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Doctorate in Professional Studies by Public Works

Institute for Work Based Learning

Middlesex University

From Cancer Researcher to Opinion Leadership and Advocacy in Translational Medicine

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Disclaimer: The views expressed in this context statement are mine and are not necessarily those of my supervisory team, of the examiners, nor of Middlesex University.

Dedication

I want to dedicate this book to my father, who fought so heroically against Rommel in World War II as an Officer of the Greek Army with the Western Allies, including the British Commonwealth Forces. My father influenced my attitudes towards the sanctity of life and our duty to help other people, even if that means sacrifice, and to never give up.

Acknowledgements

I want to thank my beloved daughter, wife, father and mother for their continuous encouragement, support, inspiration and understanding which has been characterized by great patience for all the time that I have spent away from them through my work and more recently in the extra time needed for writing up this critique of my work.

I want to thank my adviser, Dr Kate Maguire, to whom I am incredibly grateful for her continuous academic advice, support, guidance and encouragement.

GLOSSARY

AACR	American Association of Cancer Research
ACAMP	Apoptotic Cell Associated Molecular Pattern
ASCO	American Society of Clinical Oncology
BBC	British Broadcasting Corporation
BES	British Endocrine Societies
Big Pharma	A collective term used to describe the largest pharmaceutical companies
BMI1	Polycomb Ring Finger Oncogene
Ca	Cancer
CD44	Receptor for Hyaluronic Acid
CEO	Chief Executive Officer
CIN	Cervical Intraepithelial Neoplasia
CME	Continuing Medical Education
CMV	Cytomegalovirus
CSC	Cancer Stem Cells
DCA	Dichloroacetic Acid
DNA	Deoxyribonucleic Acid
EACR	European Association of Cancer Research
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
ESGO	European Society of Gynecological Oncology
FDA	Food and Drug Administration
FECS	Federation of European Cancer Societies
HER2/neu	Human Epidermal Growth Factor
HISMGM	Hellenic & International Society of Molecular & Genomic Medicine
HPV	Human Papillomavirus
HRBC	Hormone Refractory Breast Cancer
IGCS	International Gynecologic Cancer Society
IP	Intellectual Property
ISGIO	International Society of Gastrointestinal Oncology
JAMA	The Journal of the American Medical Association
KRAS	Kirsten Ras Proto-oncogene
MDR-1	Multidrug Resistance Protein 1
mHRBC	Metastatic Hormone Refractory Breast Cancer
miRNA-373	MicroRNA-373
MIT	Massachusetts Institute of Technology
MTCT	Molecular Tumor Cell Targeting

NDDS	Nanoparticle Drug Delivery Systems
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OSCC	Oropharyngeal Squamous Cell Carcinoma
P53	Tumor Suppressor Protein 53
PBS	Pharmaceutical Benefits Scheme
PCD	Programmed Cell Death
PCM	Personalized Cancer Medicine
Pgp	Permeability Glycoprotein 1
PMA	Personalized Medicine Approaches
Rb	Retinoblastoma
R&D	Research and Development
RNA	Ribonucleic Acid
SCLC	Small Cell Lung Carcinoma
siRNA	Small Interfering Ribonucleic Acid
SMM	Systems Molecular Medicine
T _c	Transition Temperature
TM	Translational Medicine
UCLA	University College of Los Angeles
UCSF	University of California San Francisco

1. Overview of Learning

I am a cancer researcher and a translational medicine practitioner. This doctorate has been a challenging journey for me in many ways, not least the requirement to put myself at the centre of the work which, for a scientist, is an anathema – or so I thought. To explore in this way has itself been a profound learning experience and one I am already disseminating in the training of new doctors.

The doctorate has required of me an exploration of my motives, my way of dealing with opposition and how I learn. It has led to me exploring my values and thinking about concepts like altruism. I always saw myself as altruistic; now I might describe myself as ethically motivated. I have been able to see that my work in today's complex society requires me to be more than a researcher and how much I have needed to improve my knowledge and skills in different areas like political lobbying, media, politics and public health. The learning threads I have extracted through exploring a selection of my public works all relate to some form of transformation or indeed translation. I am a cancer researcher and a translational medicine practitioner. The term 'translational medicine' reflects the complexities that face the movement of what is known in the laboratory to practical application in the clinic. The process is long, frustrating and sometimes quite disheartening and the core skill that is required is an understanding of and movement between different areas of practice. When I look back to the beginning of this doctoral process I see that I had a particular way of dealing with the translation, a more battle-focused stance. Now that I have taken the time to stand back I believe I have widened my view and see the way forward as collaborating with other ethically motivated people and learning more about the agendas of other stakeholders and how to deal with them productively.

So this journey is one of transformation and translation – negotiating understanding, changing attitudes and mobilizing actions in oneself and in others. I have spent my life researching cancer treatments. I have selected four examples (see Introduction) from several dozen to illustrate best the major challenges facing cancer researchers in translating their work from the laboratory to the clinic and the changes that have been required in me as a professional. They are also the ones that demanded of me the greatest challenge: to change the way I was approaching the obstacles or risk becoming marginalized as a brilliant, but possibly mad, scientist.

The following is a summary of my thinking and development to act as a guide through the context statement.

Scientific obstacles to translation from research to optimal clinical efficacy

Response: to develop

1. Personalized treatments
2. Inhibitors of resistance
3. Delivery systems.

Professional learning threads:

From laboratory to clinic.

Environmental obstacles to translation from laboratory to cancer patients

Response: to tackle the environmental obstacles more efficiently

1. The monopoly of the Big Pharma
2. To share knowledge with practitioners
3. To convince practitioners of the efficacy through knowledge and training
4. To convince the media through sound research and lobbying
5. To collaborate not just on the science but on lobbying through knowledge, persuasion and outcomes
6. To lobby decision makers at the highest level to rethink current methods of translation and criteria for trials, etc.

Personal learning threads:

From sole campaigner to president of a new association and a new journal.

Personal obstacles to transformation

1. Challenge the seductive power, for me, of 'the loneliness of the long-distance runner'
2. Reflect on the 'doing' with passion and on the personal is political, the personal is universal
3. Giving myself time to reflect on the cost of the drive to save lives in time
4. Recognizing that 'the good and the bad' duality thinking avoids complexity
5. Transforming opposition into effective strategies
6. Transforming the energy of the revolutionary into collaborative leadership with others.

2. Introduction

The science context

In my roles of hospital translational medicine practitioner, cancer researcher and President of the Hellenic, European and International Society of Molecular and Genomic Medicine and Research, I take novel treatments from the laboratory to the clinic. This is done mainly through presenting tailored molecular targeting therapeutic approaches, based on -omics that analyse the interactions of biological information objects in various omes including genome, proteome, metabolome, expressome, and interactome, in plenary sessions or invited lectures of international medical congresses. Presenting at congresses is a political statement as well as a scientific one that I explain more later, but briefly one does so to contribute to open knowledge and thus gives up the patent rights – but no-one else can own them either, including the pharmaceutical companies.

In my field, congresses are the highest level of peer review since work is accepted and approved by elite professionals and academics in the field of clinical oncology and translational cancer medicine. Congresses are the source of cutting-edge medical information for new treatments that are then published in the summit's proceedings on which regulatory agencies base their approvals. This is the ultimate in medical communication because it offers the most recent advancements in oncology to participants who can ask questions or may ask for future collaborations. Furthermore, by the time a new treatment is published in peer reviewed journals it will be out of date, for by then congresses will have already published further advances. In addition, medical doctors and oncologists who attend these congresses, auspiced by medical universities, earn continuing medical education credits that they need for renewing their medical licence.

I have presented papers more than 2,500 times and have received more than 150 international awards in personalized medicine. I have become one of the recognized pioneers of the last two decades in aiming to eradicate fatal tumours from the start by inducing apoptosis, otherwise the tumours become chemo/radio resistant, leading to lethal metastasis.

This congress approach is to ensure independence of research. In my field we know that the current approaches by the large pharmaceutical companies known as the Big Pharma tend to focus on the 'one size fits all', but cancer researchers know this is inappropriate and that symptom management only uses a small part of the knowledge we have and could go forward with. Finding a cure for cancer or effective treatment leading to its eventual eradication is not only within our grasp but can be part of a successful business model. This

may sound dramatic, but this journey through my work may offer some important information and insight into the world my colleagues and I function in daily.

As a researcher and advocate of individualized treatment, after decades of stagnation in the development of effective approaches to cancer treatment my role and goal is to discover novel molecular approaches to eradicate tumours and to bring them into clinical use. I have to concern myself with where to find funding for clinical research free from conditions of patent rights. This is looked at in more detail later.

Personalized Medicine uses what we call pharmacogenomics. Treatments like chemotherapy are administered to all patients without taking into consideration molecular level differences, which are addressed by genomics technologies. Chemotherapy can create resistant tumour types that proliferate in an unconstrained way due to an enhanced rate of DNA repair, activation of drug-efflux pumps and genetic, epigenetic and generally -omic alterations that inhibit induction of apoptosis. Furthermore, these conventional chemotherapies are extremely toxic, exerting severe side effects because they disrupt cellular proliferation and DNA metabolism in fast-growing cells of the human body, including those of bone marrow, the gastrointestinal tract and hair follicles. Some severe side effects of chemotherapy include cancer such as leukemia due to massive DNA damage; chemobrain that involves brain damage and memory loss, impaired orientation, brain shrinkage, deterioration of cognitive function and vision problems; systemic toxicity including infections due to immunosuppression, toxicity in the liver, kidney, heart and lungs, anemia, appetite and metabolic changes leading to cachexia and blood clots.

<http://www.medicinenet.com/script/main/art.asp?articlekey=21716>
http://www.cancervic.org.au/about-cancer/types-treatmentstrials/chemotherapy/side_effects_of_chemotherapy.html <http://canceraustralia.nbcc.org.au/breast-cancer/treatment/side-effects-of-chemotherapy>,
http://www.rethinkingcancer.org/resources/magazine-articles/7_1-2/chemotherapy-side-effects.php
<http://www.telegraph.co.uk/health/healthnews/6690767/Woman-died-after-cancer-drug-side-effects-were-ignored.html>

I have given a lecture at the Annual Meeting of the Surgical Society of Oncology in the United States proving that, after surgery to cut out the organs affected by cancer, we have enhanced angiogenesis and subsequent metastasis in cancer patients. In addition, radiation is as toxic as chemotherapy, enhancing synergistically the risk of developing secondary tumours by approximately 300 per cent. A publication in *The Lancet* by German epidemiologist Dr Ulrich Abel from the Oncology Clinic of University of Heidelberg has confirmed some of my published results from 1994 to the present, based on exhibition of mechanisms of novel therapeutic approaches,¹ stating that chemotherapy for advanced

epithelial cancer is a 'scientific wasteland' because there is no scientific evidence to demonstrate that conventional chemotherapy can extend the survival rate of cancer patients suffering from the most common epithelial cancers. He had previously made a comprehensive review and analysis of every major study and clinical trial of chemotherapy ever carried out which he published in *The Lancet* in 1991, stating that the overall worldwide success rate of chemotherapy was 'appalling' because there was simply no scientific evidence available anywhere that chemotherapy can extend in any appreciable way the lives of patients suffering from the most common organic cancers, emphasizing that chemotherapy can rarely improve the quality of life.

<http://cancertutor.com/ChemoSp,heill/deathbydoctoring4.htm>
<http://www.karinya.com/chemotherapy.htm>
<http://just-say-no-to-chemo.blogspot.gr/2011/07/battle-against-cancer-industry.html>
<http://icurecancer.ning.com/profiles/blogs/the-battle-against-the-cancer>

Furthermore, he states that at least 80 per cent of chemotherapy administered throughout the world is worthless and is akin to the 'emperor's new clothes' (<http://www.mnwelldir.org/docs/fraud/chemo.htm>) – neither doctor nor patient is willing to give up on chemotherapy even though there is no scientific evidence that it works. Surviving does not prove that it was due to the chemotherapy, as there are so many other factors and variables to consider. Furthermore, a survey of oncologists at McGill University Cancer Center has reported that 75 per cent of them would refuse any type of chemotherapy, citing the 'ineffectiveness of chemotherapy and its unacceptable degree of toxicity', according to Philip Day's, *Cancer: Why We're Still Dying to Know the Truth* (Credence Publications, 2000).

<http://www.curenaturalcancro.com/2-physicians-refuse-chemo.html>
<http://www.cancernetwork.com/display/article/10165/66128>
<http://cancercommonsense.com/#/statistics/4538345819>
<http://eclinik.wordpress.com/health-tips/why-you-should-refuse-chemotherapy/>
http://hfs1.com/DOCTORS_ON_CANCER_CURE.php
<http://curezone.com/blogs/fm.asp?i=967954>
<http://www.scam.com/showthread.php?t=34028>
<http://curezone.com/forums/am.asp?i=1284922>
<http://www.curenaturalcancro.com/2-physicians-refuse-chemo.html>
<http://salonesoterica.wordpress.com/2007/12/01/why-75-of-doctors-would-refuse-chemotherapy-on-themselves/>
http://www.naturalnews.com/036054_chemotherapy_physicians_toxicity.html

A study published in 2005 by Professor Michael Morgan, Chief of Medical Oncology at Australia's Royal Prince Albert Hospital, reports that, despite the use of new and expensive single and combination anticancer agents, the contribution of chemotherapy to five-year survival in adult cancer patients was 2.1 per cent in the United States and 2.3 per cent in Australia (<http://www.icnr.com/articles/ischemotherapyeffective.html>).

Another researcher, Professor Hardin Jones from the University of California,² has concluded that the survival rate of untreated cancer patients who had refused conventional cancer treatments including chemotherapy, radiation and surgery, was enhanced four-fold compared to cancer patients who had undertaken these treatments. In addition their quality of life was better. Although this finding is quite surprising to the general public, it is not considered so by many in my profession, given that our knowledge is greater than that communicated to the public through a variety of channels. In my research I have proved scientifically the disadvantages of conventional chemotherapy by exhibiting molecular mechanisms based on signalling pathways using advanced and state of the art -omic technologies. I have been very outspoken at medical congresses about these issues and am supported by sound knowledge and research.

I ensure that I have all the scientific facts for explaining and supporting my research work on novel molecular treatments tailored to each patient's genomic. An example of pharmacogenomics in the oncology sector consists of the FDA's decision to revoke its approval of Avastin for use in metastatic breast cancer due to severe side effects including internal bleeding, blood clots, heart failure and colon perforation. One of my previous research works included the exhibition of VEGF165b as a resistant mechanism for Avastin. I presented this in the 2008 Gastrointestinal Cancer Symposium of the American Society of Clinical Oncology (Giannios, 2008). Personalized anticancer treatment is completely tailored to the requirements of the individual cancer patient using pharmacogenomics (Hu et al., 2005) or even molecular testing for stratifying cancer patients with shared biological characteristics to the most efficient treatment by using one or few molecular biomarkers (Jorgensen et al., 2007; Trusheim et al., 2007).

Another drug, the antidiabetic Avandia, is still on the market with the FDA's permission despite exhibiting serious side effects. Avandia is a drug for type-II diabetes belonging to the family of thiazolidinediones. Since its approval in 1999 it has killed about 100,000 diabetic patients from heart attacks, strokes and liver problems and still continues to cause more than 500 heart attacks and subsequent deaths per month, according to the US Senate Finance Committee report.

http://www.cbsnews.com/8301-504763_162-20009124-10391704.html

<http://www.chicagoinjurylawblog.com/cat-pharmaceutical-litigation.html>

<http://www.politicalnews.com/fda-keeps-avandia-for-gsk-profits/>

<http://www.worldwidehealth.com/health-article-Avandia-is-Killing-Americans-FDA-Negligence-Comes-Front-and-Center.html>

<http://www.youhavealawyer.com/avandia/lawsuit-claim/> <http://www.bloomberg.com/news/2011-05-04/glaxo-is-poised-to-settle-about-1-000-suits-over-avandia-drug-lawyer-says.html>

<http://www.prweb.com/releases/2012/4/prweb9403970.htm>

<http://www.dailyfinance.com/2010/07/13/glaxosmithkline-settles-avandia-lawsuits-fda/>

<http://www.businessweek.com/news/2012-02-14/glaxo-settles-20-000-lawsuits-over-avandia-lawyer-says.html>
<http://www.fiercepharma.com/story/gsk-resolves-20k-more-avandia-lawsuits-lawyer-says/2012-02-02>
<http://www.adrugrecall.com/avandia/lawsuit.html>
<http://www.drugwatch.com/avandia/lawsuit.php>
<http://www.resource4thepeople.com/defectivedrugs/avandia.html/> <http://avandia.legalview.com/>

According to the report, two US senators, Max Baucus and Charles Crassley, even accused the company of intimidating physicians, misrepresenting findings and exerting pressure on medical researchers to stop publishing the side effects. The New England Journal of Medicine published an article in 2007 linking Avandia to a 43 per cent enhanced ischemic cardiovascular risk.

<http://www.rightinginjustice.com/news/2010/02/22/senators-ask-why-dangerous-avandia-was-not-pulled-from-market/>
<http://www.avandia-legal.com/page/2/?s>
<http://www.nejm.org/doi/full/10.1056/NEJMoa072761>

The Wall Street Journal reported that Avandia (rosiglitazone) was allowed to continue its sales.³ However, in November 2011 the pharmaceutical company involved was ordered to settle all the cases and, to date in 2012, it has settled some 25,000 (<http://www.businessweek.com/news/2012-02-14/glaxo-settles-20-000-lawsuits-over-avandia-lawyer-says.html>).

Issues such as these undermine confidence in the Big Pharma.

A further concern that intensifies doubts about trustworthiness is the Big Pharma's increasing outsourcing policies in the Third World, where people participate in low-cost trials and increase further the difficulties in replicating or challenging the findings. According to Dr Light's findings⁴ presented in Atlanta at the 105th Annual Meeting of the American Sociological Association on 17 August, 2010, the phenomenon of enhancing the number of patients taking new drugs characterized by low effectiveness and high risks of adverse effects is called 'risk proliferation syndrome'. The Big Pharma argue that the benefits of their drugs outweigh their risks, making them valuable treatment options. If the only source of funding is the Big Pharma, then many doctors and researchers may believe that something is better than nothing in fighting any kind of serious illness, and if they do not bring in funding they may not be able to progress in their work and careers. Moreover, if they go against the accepted practice for treatment and suggest alternatives they could be sued for malpractice in that they did not follow conventional treatment and thus have endangered patients' lives. This is a professional risk few are willing to take.

I and many of my colleagues wonder why the drug regulators, advocacy groups, politicians, the legal system and especially the media do not pay more attention to many of these issues

and do something about them. In particular, they could inform people of options through creating reliable sources of information to help them make the best choices when faced with serious illnesses. For my part, what I have managed to do is to publish many of my novel molecularly targeted anticancer treatments, educating the public about the advantages of personalized medicine compared to the disadvantages of conventional treatments.⁵

I have been fighting for the last two decades as an opinion leader in international oncology, cardiology, diabetic and other medical congresses for the establishment for personalized medicine which, in my opinion, is the best solution for the rational use of drugs where anticancer agents will be prescribed, based on pharmacodiagnostic results.

However, before we are able to target drugs for each unique genetic profile (Langreth & Waldholz, 1999), we must establish stratification of patients who share biological characteristics by using pharmacodiagnostic testing to divide patients into biological subgroups to be targeted with more effective drugs that exert reduced systemic toxicity. Then we can fully move into the realm of personalized medicine to establish a more targeted drug therapy, minimizing medication error and high costs to treat drug-related adverse effects. In addition to a much more cost-effective drug therapy for patients, personalized medicine will be able to reveal mechanisms of the pathogenesis of different diseases and their response to drug therapy (Woodcock, 2007) tailored to the individual biology and pathophysiology of each patient. This will mean the end of the 'one treatment fits all' approach that expects the same drug to work in the same way for each patient, because a pharmacodiagnostic test will select the drug for each individual.

By individualized drug treatment tailored to every patient's unique biology, we will be able to administer the right drugs to the right patients with the use of molecular methods such as genomics, metabolomics and proteomics. These are affected by genetic variations including germline-alterations such as hereditary mutations and somatic ones such as non-hereditary mutations. These will improve drug efficacy and minimize side effects in diseases like cancer, cardiovascular conditions, infectious diseases, psychiatric illness and respiratory diseases currently being treated with a blanket approach in which some patients gain a few benefits but most gain little or have added problems (Jorgensen et al., 2007). With the new molecular diagnostic methods, we will be able to improve medical treatment in all disease areas by achieving the best possible health outcome for each individual. Generally, the drug treatments that must be individualized in association with pharmacogenomics in the future are the ones characterized today by unmet medical needs such as oncology, infection and cardiovascular medicine. Although Sikora (2007) believes the personalized medicine approach will significantly reduce the potential subsequent profits for a given drug due to market segmentation, the development of pharmacodiagnostics can compensate partially for

profit losses and can also cause a reduction in the size of clinical trials that the Big Pharma perform for the development of a new drug by minimizing the number of patients who fail to respond to a specific therapy (Woodcock, 2007). Thus, the efficiency of any novel therapeutic agent can be improved significantly during clinical development with the use of predictive biomarker tests, because pharmacodiagnosics may identify those responsive to therapy subgroups by reducing the variability of chemosensitivity, especially in cancer where chemoresistance is the greatest problem (Hortobagyi, 2004).

Throughout the last two decades I have seen in the struggle with the Big Pharma over the establishment of personalized medicine in oncology that the greatest supporters of the idea of individualized medicine are patient advocacy groups, academic groups, some health authorities and, surprisingly, some of the health insurance companies that are increasingly aware that they pay huge amounts of money for cancer treatments that often fail to work. Furthermore, they have to pay for the treatment of the side effects caused by these cancer treatments. In addition, health authorities are interested in saving money by moving from a blanket drugs approach to new targeted therapies administered in association with pharmacodiagnostic tests that will ensure that these novel personalized drugs will be administered only to cancer patients with a reasonable chance of being chemosensitive to this particular treatment.

After many years of pressure, regulatory agencies like the FDA have started to support the idea of personalized medicine with the formation of initiatives such as the Critical Path⁶ because they have come to realize that only personalized medicine can improve the efficacy, safety and cost-effectiveness of drug therapy (Lesko, 2007). Not since 2005 have they issued guidelines from their concept paper on how future drug diagnostic co-development should be used for new targeted drugs.

The principle of personalized medicine has started to spread worldwide, including Australia, New Zealand, China, Japan and Europe. In the United States the non-governmental Personalized Medicine Coalition (PMC) was formed in 2004 and very active, with members from academic medical centers, universities, trade associations, industry such as diagnostic companies excluding the Big Pharma, patient advocacy groups, healthcare providers, information technology companies, venture companies, health insurance companies and government officials. All are all focusing on the understanding, and adoption of personalized medicine.

Cancer researchers like myself have contributed to this shift, but there is still a long way to go. I have emphasized in my published work that this transition shan't be easy. The pharmacogenomic methods that must be developed in parallel with the novel drugs for

targeting disease mechanisms must be characterized by very high standards of predictive performance. This is based on the analysis of genes expressing the targets of drugs including signal peptides, proteins, enzymes, non-coding-RNAs, and so on, for the identification of responsive biological subgroups and ultimately chemosensitive individuals, about whose pathophysiology we must know as much as possible at the molecular level (Trusheim et al., 2007).

Although the personalized pharmacogenomic transition can minimize drug development time and subsequent costs for the Big Pharma, it will reduce its huge profit from the blanket treatment. It will also require division into smaller units and separation of sales and marketing from research and development, which will depend upon the acquisition of specialized biotech companies. All these will bring unavoidable changes to how future drugs will be developed, marketed and prescribed. However, society must be ready for this new system of healthcare by creating a flexible pricing and reimbursement system (Garrison & Austin, 2006). Thus, the science behind personalized medicine must be associated with pharmacogenomics, politics and adaptable regulatory legislation.

All the works that I have chosen to reflect upon for this doctorate are examples of novel therapeutic approaches based on personalized medicine. The method is to aim to eradicate chemo/radioresistant tumours with molecular targeting that minimizes systemic toxicity, and not to make tumours more resistant to treatment with associated severe side effects, perhaps involving subsequent treatments that might lead to deaths.

By critiquing my work I hope to uncover and develop other aspects of this translational process that I can contribute to more effectively. These include forming and participating in more advocacy groups, deepening knowledge of political and social issues, developing better communication skills, encouraging more collaboration and lobbying regulatory and legislative bodies. This will more effectively and persuasively bring about a successful transition from the 'blockbuster' drug era to personalized cancer medicine.

I must find the most appropriate way to deal with the media, regulation, legislation and advocacy. But that is the role of the relatively new profession of translational medicine practitioners. I am a scientist, but if we are to get what we know in the laboratory into the clinic, it requires the scientist to enter that arena and learn how to change what needs to be changed. I have picked up some skills on the way, but this is the first time that I have given myself the opportunity to step back and see how I can be better.

3. Positioning Myself and My Work

I had never looked too deeply into why I do what I do until I embarked on this doctorate. My focus, my obsession even, has been for many years the application and ongoing development of my knowledge in the field of cancer research to save lives. This does fit well with my values regarding truth and rights.

I originally applied for this doctorate to explore my work to see if I could be more effective in challenging the old paradigm and bringing the new one into centre stage. However I soon found myself questioning my own motives, values and beliefs and, through that, realizing that efficacy begins with a research on self.

Before setting out on this critique of my learning through my chosen public works, three questions were already at the fringes of my thinking, at the fringes because I am, I believe, a man who defines himself by doing, by action in the Nietzschean sense of having a 'why'. By taking this particular doctoral journey, I believed I might stand still long enough to reflect on 'why' – why do I do what I do? – in the hope that it may reveal to me the answer to the second and third questions: what keeps me doing it, and how can I do it better? I believe the answers to these three questions need to be brought more centrally into my professional life and, by critiquing my work through this lens, I will be able to reframe the steps that I will take in the future to counteract the substantial obstacles to achieving the aims of my personal and professional life, informed by my values and my epistemological stance.

I live and work in Athens. I was brought up in a family whose values derive from very hard work, education and honesty. I loved literature and was quite good at it but I chose science, particularly cancer research, which has a lot to do with my father with some influence from my grandfather. During my years of elementary school I was raised by my grandfather. He was a lawyer. I was fascinated by his wisdom and his compassion for other people. He taught me that I should help people by any means when they need it. He didn't just talk. He was a living example in his guidance to me. He used to help poor people on legal matters with no payment. I saw the respect and love that these people had for him. That looked to me even at that young age as an excellent reward for kindnesses given. Then when I began high school I went to live with my father, who used to work in the Bank of Greece. I remember he used to become depressed when a relative or colleague died from cancer. He always used to try and help them in any way he could. Not being a doctor himself he often ended up frustrated and angry because he could not save them. I later came to understand that, as a young man serving with the allies in North Africa during the war, he had killed to save others, others had died to save him and some he could not save. This experience

influenced his approach to life. His frustration and agony at the death of others affected me deeply, making me feel extremely scared and helpless at those times. I remember the terrible nightmares I had as a child because I was afraid that my family might get some cancer at some time, and I would lose them forever.

I could not live with this fear for the rest of my life. I promised myself that I would do anything to avoid this. The only way to achieve this was by educating myself. Therefore, even when I was in high school I used to buy and read medical and oncology books. On high school courses like biology, biochemistry, physics and chemistry I used to get straight A+. Then I realized that I also had to learn very good English to be able to read the international bibliography. This subsequently opened my scientific horizons, because I knew exactly which subject I would like to pursue for the rest of my life so I could help people in the best way possible.

I did not know it would be my own father who would put my skills to an early test and, in fact, directly influence the path I now follow. He developed lung cancer and, according to his physician who also happened to be his sister, he was destined to die from it. I used what skills I had and developed more as I was determined to find a therapeutic solution for my father to keep him alive as long as possible. I analysed his tumour genotype and phenotype on which I tailored a molecular targeting therapy. This is when I observed that his chemoresistant mechanisms were circumvented, leading to eradication of his NSCLC cells. If he had gone through the conventional treatments offered by the Big Pharma he would not have survived because of the systemic toxicity, immunosuppression and activation of cancer stem cells, leading to metastasis. When my father had another serious cancer recently, diagnosed as hormone refractory prostate cancer, I achieved its eradication by radiation therapy. First, however, I circumvented radioresistant mechanisms caused by overexpressed antiapoptotic oncogenes and silenced tumour suppressor genes by using antisense molecules, antibodies and demethylating agents.

That is what I have done since. I am the assigned Head of Cancer Research, Molecular and Genomic Oncology, and Translational Cancer Medicine in one of the biggest oncology hospitals in Europe (Erasinio Hospital) that I have made an International Anticancer Center of Excellence even before its opening by developing novel anticancer therapies. These are presented and published in international oncology congresses from which I have obtained many awards by acting as an opinion leader among my peers.

I have always been interested in philosophy, more as something to do for pleasure and, as for my values, I have carried these within me, never questioning where they came from, never seeing the need to. Now I do. Strangely perhaps for a Greek, I did not immediately

turn to Greek thought in my enquiry into myself but to the Italian philosopher Antonio Gramsci, whose words come closest to how I might describe myself – the pessimism of the intellect and the optimism of the will. ‘I’m intellectually a pessimist, but an optimist because of will’, will as in will to action. Gramsci wrote these words in a letter from prison during his incarceration by Mussolini’s Fascist regime (Gramsci, 1971). Professionally, I feel like I am in a state of imprisonment in the middle of a crisis caught between two paradigms, where the old, risky and increasingly ineffective ‘blockbuster’ drug cancer policy is dying out and the new policy of personalized medicine cannot be born. In fact, like all old paradigms it fights harder, knowing its days are numbered. Thus, in the interregnum, a great variety of morbid symptoms appear. In the more poetic words of Gramsci, the old world is dying away and the new world struggles to come forth: now is the time of monsters like doubt, resistance, uncertainty and fear.

I can also relate to Gramsci on another two levels. Firstly, he was a man of great courage who suffered ill health and continued to write through his pain. I meet great courage every day in cancer sufferers that motivates me to do what I do. Secondly, he was driven by his beliefs and ideals which were, like mine, an obsession. He was held a prisoner by the Fascist regime of Italy and the only way his work could reach the public was secretly, subversively. I ask myself why we have to be subversive about what is evidenced, ethical and can save lives and be forced to behave as prisoners in a domain owned by the multinational pharmaceutical companies, with only occasional day release. Like Gramsci, I am a multidirectional thinker who fights the current paradigm of cancer treatment with evidenced knowledge. I am also energized by this fight. Through a long, painstaking period of cancer research I have recognized my own semiotic technologies for making scientific meanings that can overturn the present paradigm by dissolving the usual boundaries between the rational and irrational, in the Lacanian sense, and taming the beast.⁷

I have attempted this, which I will demonstrate in greater detail in critiquing my learning through each of my selected works, by establishing myself as an advocate for personalized cancer medicine. I need to know how to get better at this. In line with Haraway’s aim for science, which is to reveal the limits and the impossibility of its objectivity offering inventive analogies that reveal whole new vistas and possibilities for investigation (Elkins, 1990), during the last decade of the twentieth century and the first decade of the twenty-first century I have been concerned with the production of scientific knowledge through cancer research. I have acted on that knowledge by aiming to transform the present status of the healthcare system against cancer. But scientific knowledge is not enough.

As Gramsci has contributed much needed insights and correctives to current cultural and political work, I try to do the same in influencing significant and crucial changes in the current

healthcare approach to cancer. This has proven to be extremely inefficient and, in my opinion, is victimizing human lives. Of course, this will never parallel the contributions of Gramsci to European political thought, but his work has helped me to position this paradigm struggle into a political frame to understand better its complexities, in particular his insights into the capitalist formation of the pharmaceutical industry, 'the contradictory positions that constitute subalternity and the importance of arriving at a sense of the multivalent relations between economic, cultural and political phenomena'.⁸

The agenda of critical theory, especially that of poststructuralist writing over the past few decades, has been to address the ways in which modernity and subjectivity are interconnected and are crucial to understanding the persistence of certain modes of thought and behaviours such as resistance to change. Lacanian theory has complicated the issue of ideology in particular, moving it away from notions of false consciousness.⁹ For instance, my ideology and that of several like me involves protection of the lives of cancer patients unmotivated by profit. Many colleagues therefore may not be 'profit' motivated, but they are forced by the old paradigm to be 'funding' motivated. There is also the right of the people to receive the best that the most advanced knowledge can offer when their lives are at stake. Increasingly in the modern global economy, excessive profit for individuals has become a right, a kind of ideology that is fought for and protected and is divorced from responsibilities to the communities from which this profit is extracted.

The Althusserian focus on ideology¹⁰ has allowed a more complex entry into the difficult question of the persistence of dominant ideological practices, a requisite for Marxist thinking and for exploring connections between economics, politics and culture reconfiguring traditional notions of base and superstructure. It even calls into question distinctions between ideology and science. Like Gramsci, Althusser¹¹ insisted on the need to disarticulate prevailing and totalizing sociological notions concerning base and superstructure.

In his theorizing about hegemony, however, Gramsci offers more flexible, less monolithic and less stratified insights into how the relation of state and civil society produces forms of consensus and coercion. Also, borrowing from Gramsci's notion of cultural hegemony, Poulantzas saw a capitalist class that in this case I see represented by the profits of conventional anticancer treatment.¹²

My ontological position is that continuation with practices involving conventional treatment in the face of known advances is anti-knowledge. The fascism that imprisoned Gramsci was also anti-knowledge. Ideologically, I can also relate to Althusser, who has been known as a theorist of ideology especially with his 'Ideology and Ideological State Apparatuses: Notes

Toward an Investigation'.¹³ I agree with Althusser's view on Freud's and Lacan's concepts of the unconscious and mirror-phase, describing respectively the structures and systems that enable the concept of the self. For Althusser, these structures are both agents of repression and inevitable.

Thus, for myself as a cancer researcher the scientific knowledge I learned made two impossibilities for me. The first was to support the existing paradigm and the second was to ignore what is best for the cancer patient, resulting in me pursuing it no matter what the consequences for my personal and scientific life. At this point I have to declare a bias for Althusser, who is one of my favourite thinkers because he has examined the contributions of the ancient Greeks, Thales on mathematics and Galileo on physics. As Socrates said: 'Life unexamined is not worth living'.

I do not support Heidegger's approach to technology with neither praise nor blame – neither as an optimist nor pessimist or, in Gramsci's terms, a pessimism of intellect (Rodriguez, 2010). Taking action is the optimism of will¹⁴ and I am optimistic that personalized cancer medicine will take its place in the future.

However, I do agree with Heidegger that technology's essence is not technological, but a system. As such, technology involved in cancer medicine can be dangerous because it can lead to the transformation of the human being by which human actions and aspirations are fundamentally distorted. Medical technology can enter the innermost recesses of human existence, transforming the way we know and think and will. In my opinion, medical technology as a system should be used exclusively for the benefit of the patient and never for the profit of big multinational pharmaceutical companies.

The Hippocratic oath taken by medical practitioners solemnly swears them to practice ethically and to save lives. It is an oath that I believe should be extended to and bind all who have direct dealings with the translation of scientific findings, from the laboratory to the clinic. In today's world of complex technologies and multidisciplinary we can no longer look to doctors as being the only people to be bound by such an oath, but to all members of the system, as medicine today is without doubt a system with many stakeholders.

This intersection of rights, ideologies and economic structures requires a look at Hegel for a frame through which to view them. My situation resembles aspects of his *Difference Essay* (<http://socserv.mcmaster.ca/econ/ugcm/3ll3/hegel/1015.pdf>), where Fichte failed in the project of systematizing. The conventional 'one size fits all' treatment will fail in the future due to the difference that personalized medicine will bring. Like Hegel, I remain in the remnants of the Platonistic idea of a search for ahistorical truths that, combined with his works like the *Science of Logic* (<http://plato.stanford.edu/entries/hegel/>), can support the idea of personalized

cancer medicine. Based on what we know now, the future is in personalized approaches in medicine, particularly in cancer and, once the new paradigm can be allowed to function without obstacles, it will be profitable and make economic sense. There are, of course, other obstacles such as lack of training and equipment that I will deal with in subsequent chapters.

I also have been inspired by Hegelianism, which offers a metaphysico-religious view of God qua or Absolute Spirit (<http://escholarship.org/uc/item/3qs0713v#page-4>) as the ultimately reality that can be known through pure thought processes alone. Like Hegel's, my philosophy is derived from a more religious conception than the critique of pure reason of Kant (<http://www.highbeam.com/doc/1G1-276808891.html>). I mention religion, because my Christian upbringing has always privileged the notion of recognition of pain in others and being motivated to action to resolve it. Other Christian perspectives may try to make meaning out of pain and see it as some kind of cathartic endurance that expiates sins. I do not. I see it as everyone's responsibility to alleviate pain. I feel pain when I see it in others. If I alleviate theirs, I alleviate my own. Thus, with the Absolute Spirit I am trying to introduce an effective and life-saving approach of personalized cancer medicine by pure thought processes alone ignoring the profitable aspects of this strategy. I support Hegel's form of idealism that lies in the idea that the mind of God becomes actual only through its particularization in the minds of his finite material creatures, which consist of simple people and not systems such as our industrial ones. So I can personally and professionally relate to his notion that individuals in their consciousness of God, serve to realize God's selfconsciousness. Translated into my world and manifested, this is the search for fair treatment for suffering fellow persons who have cancer.

Despite this dominant theological theme, I believe more in existentialism and that everyone has the right to try to prolong their existence. That is part of the motivation for what I do.

It is obvious from my perspective that the old paradigm has not supported nor believed that it should support the Hegelian philosophy of 'ethical life'. 'Ethics' is commonly used interchangeably with 'morality', and sometimes it is used more narrowly to mean the moral principles of a particular tradition, group, or individual (Deigh, 1995). I can see some resonance with what we are trying to do as cancer researchers with Hegel's philosophy, which represents civil resolution or, that will continue to prove that the current paradigm for cancer treatment is not only wrong, but dangerous.

However, this has required sacrifices: professional alienation, marginalization, financial sanctions, personal relational sacrifices that I and others like me have felt throughout these years. I believe they are motivated by altruism but, as my life has been so defined by this fight, I need to get inside what altruism is. My fear is that if I start to deconstruct too much

what drives me, it may result in my being less driven or vulnerable. In a fight, if a soldier stops to think and reflect it is like taking off the armour that protects him and provides the courage to stay in the battle.

Am I then the altruist, and does it matter? There are many philosophical and psychological aspects of altruism that motivate my struggle against this dominant: evolutionary, developmental, psychological, social, cultural, political, and religious aspects. I would subscribe to the notion that there is no such thing as pure altruism. We all get something out of what we do for others, and this motivates us to do it. Perhaps it is in many cases a way to respond to fear of uselessness, fear of being a nobody, fear of not belonging, fear of being ordinary, and fear of death. I know one day that, through the efforts of many good people, altruists or not, we will beat cancer. I hope that my optimism is not Panglossian. I always ask myself what assumptions am I making and how do I know what I know? The answer is then simple, because I look back to my previous cancer research experience and it is about knowledge and transparency. I am known in my field as an opinion leader and that has considerable ethical responsibilities. I am uncompromising in my support for evidence-based practice, innovative anticancer scientific evidence that can withstand scrutiny. This has been recognized globally by the International Oncological and Medical Society especially the International Translational Cancer Medicine Society where I am a practitioner.

Returning to Gramsci, this optimism of will, I think, is what gives me the courage to attempt difficult or impossible tasks like fighting the old Pharma paradigm. I believe that my will can overcome the odds if I can encourage a collective will. If I did not, I should not have come this far. For me, research leads to knowledge but it requires evidence, transparency, honesty and criticality not only in carrying out that research but in bringing it into usefulness. There is no value in research without that:

All sciences are now under the obligation to prepare the ground for the future task of the philosopher, which is to solve the problem of value, to determine the true hierarchy of values. (Friedrich Nietzsche)¹⁵

4. Selected Public Works

The four works I have selected from more than 2,000 that I have presented in international medical congresses represent evidence of my contribution to oncology, how the findings from one influence the direction and development of the next treatment and illustrate the challenges I have had to overcome progressively to arrive at a new way of dealing with both the scientific and socio/political obstacles. They represent a process of transformation as I increased and widened my skills. This process of reflection itself has tied everything together resulting in not only changes in myself but culminating in the founding of the Hellenic and International Society of Molecular and Genomic Medicine and Research. My presidency is in recognition of the contribution of my work and advocacy by my peers. This Society will mark its arrival in Greece in October this year with an international conference. I now no longer feel I am on my own, and neither do the members.

Although I lose my intellectual property rights after I publish my work at international congresses, independent from any conflict of interest, by acting as an opinion leader I influence other researchers to use my novel therapeutic approaches for cancer patients' welfare and take it through all the required clinical stages for achieving regulatory approval. This transmission of state of the art and cutting-edge knowledge of novel therapeutic approaches such as mine against incurable tumours may spread as a chain reaction in the cancer research establishment. Furthermore, this work has been used by cancer advocacy groups and even an organization for psychological support for cancer patients. All these have numerous implications concerning medical, social, economical, political and regulatory issues.

The work for each novel treatment was deeply challenging because I had to play the main role in discovering each one of the new treatments, during which my learning was enhanced not only in the usual way for science research in that one discovery leads on to another, but in ways I neither expected nor set out to achieve. In science terms the innovations came together to offer solutions to many unsolved problems in oncology. I am presenting the first one with a summary of technical details. For those remaining, I have put the technical details in the appendices.

4.1 Public Work 1

A novel combined and multitargeted therapeutic strategy of chemoradio-immunotherapy based on a pharmacogenomic approach against advanced and metastatic breast cancer (for more technical details see Appendix 1A, and for associated public works see Appendix 2A).

This work was undertaken because hormone refractory breast cancer that metastasizes to the lungs, livers and bones is incurable. This is due to overexpressed oncogenes or inactivated tumour suppressor genes that are controlled by epigenetic mechanisms such as methylation, acetylation, histone variants and so on. I have recently written a book (Giannios, 2011) about these. They cause potent chemo and radioresistance, inhibiting programmed cell death mechanisms such as type-I or apoptosis. These mechanisms make this tumour type incurable and lethal, especially due to metastasis where we have more than a hundred heterogeneous tumours.

As Head of Translational Medicine and Cancer Research of Erasimio Oncology Hospital¹⁶ and now as the President of the Hellenic and International Society of the Molecular and Genomic Medicine, I believe it is an imperative of these positions to try always to find therapeutic solutions to incurable cancers like the metastatic hormone refractory breast cancer. This is currently incurable with conventional therapeutic regimens, which complicates the situation by exerting lethal systemic toxicity and creating potent chemo/radioresistant mechanisms while activating metastatic mechanisms such as angiogenesis or cancer stem cells (Giannios, 2010).

I presented this work firstly in 2004 at the 18th Annual Meeting of the European Association for Cancer Research (EACR) of which I am a founding member. It is a pan-European organization representing cancer researchers and belongs to the Federation of European Cancer Societies (FECS). This is a Brussels-based organization representing more than 18,000 cancer professionals in Europe. This work was selected as the best of the congress for publication. It was given to the international medical media¹⁷ to inform different societies that a combined anticancer therapeutic approach against metastatic breast cancer can circumvent resistance to treatment mechanisms leading to the eradication of tumour cells by induction of apoptosis. This therapeutic approach was translated into many different languages from the electronic media. Furthermore, the Greek press, television and radio announced this treatment as a medical breakthrough that might save many breast cancer patients in the future.

Since then, I have extended this therapeutic approach to other metastatic cancers, such as pancreatic cancer, periampullary cancer, non-small cell lung carcinoma (NSCLC), endocrine

tumours such as anaplastic thyroid cancer. These works were presented in congresses including ASCO, British Endocrine Societies (BES), ESGO, ISGIO and others.¹⁸ Furthermore, they were published in many specialized medical journals such as the International Journal of Gastroenterology and Hepatology.¹⁹ This work, since its presentation and publication, has been followed up by many other researchers who have taken it to multicentre clinical trials for many cancers including pancreatic adenocarcinoma, periampullary carcinoma and other cancers.²⁰

This novel therapeutic approach emphasizes the importance of combination therapy under a personalized cancer medicine approach with molecular targeting. I was both the innovator and project leader, with a number of collaborators and a team of assistants. The role of each collaborator or assistant was designed by me to cover each part of the research. They are the co-authors of each of my publications and congress presentations. Such co-authorship is one of the protocols that I have established for the Hellenic and International Society of Molecular and Genomic Medicine where all its members can collaborate to achieve publishable results that can benefit cancer patients in the future until regulatory approval is granted. It is multidisciplinary research under systems molecular medicine (SMM), the science of combining systems biology with molecular analysis and intervention to address clinically relevant questions.

I had concluded that since cancer is an extremely heterogeneous and complex disease, especially in metastasis that consists of more than a hundred different tumour types, we have to fight it on many different fronts. In this particular case of incurable advanced and metastatic breast cancer, I had to detect the chemoresistant mechanism to inactivate conventional chemotherapy that exerted only systemic toxicity destroying normal cells. Thus, with multitargeted combination therapy using immunotherapy, radiotherapy and genetically based antisense therapy, I targeted these chemoresistant mechanisms to circumvent them, allowing the conventional chemotherapeutic agent to exert its cytostatic action inducing apoptosis and led to the eradication of tumour cells by a bystander killing effect. This novel multimodal anticancer therapy should be applied in the future for treating advanced or metastatic breast Ca or other incurable cancers.

This novel combined treatment establishes the foundations of a new era of translational cancer medicine in which pharmacogenomics are employed to tailor a molecular therapeutic approach to chemoresistant and radioresistant metastatic breast cancer patients.

Furthermore, this approach allows conventional chemotherapy to exert its antitumour effect enhancing therapeutic index and reducing systemic toxicity. One of the main roles of this innovative therapeutic approach consists of providing one more proof that cancer research changes the face of oncology by emphasizing the significance of functional tumour cell

profiling on which a personalized treatment can be tailored. I have proved that targeting one pathway may not be as effective as targeting multiple pathways in a cancer cell. Finally, I have proved that when novel therapeutic agents are combined with existing ones they target the tumour more effectively by acting synergistically.

The key for a successful anticancer treatment is the circumvention of chemoresistance or radioresistance and effective molecular targeting using nanomedicine and ligands such as antibodies that can bind onto specific overexpressed oncogenic receptors, such as HER2/neu or EGFR.

Public Impact:

Some of the implications of my work have been described in the Introduction and have been referenced with the related websites. This public work brought me into more direct contact with the media and I found myself wanting to become a journalist to explain better the potentials of my work and its implications for cancer treatment. This critical reflection has given me the space, in a sense, to be the journalist. How might I explain it to as many stakeholders as possible, including the public at large so they can understand? Like this?

In their attempts to transmit information to the public, the media have found cancer to be a complex disease. The complexity is the key to the approach. It needs to be attacked on many fronts. This novel treatment is a combined one, targeting the right drug to the right tumour phenotype with the use of pharmacogenomics. This means fewer treatment failures leading to cheaper clinical programs and subsequently cheaper drugs. Otherwise, the rise in the number and cost of new anticancer drugs will lead to discrimination in treatment: the poor will be left to die. My work sets priorities for funding the right combined treatments based on a personalized approach.

Cancer is an enormous socioeconomic problem because conventional treatment, depending on the stage of the disease, is mostly ineffective due to complications such as drug resistance or acquired mutations after initial therapy. Thus, a novel and drastic multimodal anticancer treatment like this, consisting of personalized therapeutic approaches combined with conventional anticancer agents is desperately needed to combat cancer especially the metastatic type. This could save tax-payers' money for cancer care.

I began to look more closely at how cancer issues are reported and found a number that were good examples, not because they fitted with my views but because I could see how persuasion with scientific evidence, bringing in economic issues supported by facts and figures and having a non-aggressive style, was more effective in changing mind-sets. I liked the following example.

James Gallagher, health reporter for BBC News, published a Lancet Oncology report in 26 September 2011 stating that most developed countries dedicate up to 7 per cent of their healthcare budgets to dealing with cancer. However, few treatments or tests are clear clinical winners, with many falling into the category of substantial cost for limited benefit.²¹ Furthermore, lead author Professor Richard Sullivan told the BBC that it is not just pharmaceuticals. Biomarkers, imaging and surgery are all getting through with very low levels of evidence, because the hurdles are set too low. There is also criticism of futile care using expensive chemotherapy with no medical benefit in the last few weeks of a patient's life. The issue that concerns economists and policymakers is not just the amount of money spent on healthcare, but also the rate of increase in healthcare spending or what has become known as the cost curve. The report says the UK's total spend on breast cancer has increased by about 10 per cent in each of the past four years. Also, it says that the number of cancer patients and the cost of treating each one is increasing. A group of 37 leading experts from around the world say the burden of cancer is growing and becoming a major financial issue because about 12 million people worldwide are diagnosed with cancer each year. That figure is expected to reach 27 million by 2030. The cost of new cancer cases is already estimated to be about £185bn (\$286bn) a year.

Personalized cancer medicine might circumvent some of these issues because all cancers are not the same; not even all breast or lung cancers are the same. Thus, it is hoped that better pharmacogenomic testing will bring about this new era of 'personalized cancer medicine', meaning drugs can be tailored to specific cancers. For instance, testing for the KRAS gene in colorectal cancer patients before deciding whether to use a cancer drug saves £32m per year in Japan.²²

This approach might reduce DALYs. This measure has been developed by the World Health Organization (WHO), and it is the most common yardstick of the cancer burden of mortality and disability. One DALY represents one lost year of healthy life, and the burden of disease as a measurement of the gap between actual health status, and an ideal situation where everyone lives into old age free of disease and disability. Cancer may account for many million DALYs lost in the European countries.²³

I have learned from such journalistic writing and have realized that I have targeted for years only my medical peers, but I need to work with others to persuade different target audiences to act through finding a way to communicate stem knowledge effectively to those outside of the field, but who can nonetheless impact that very field to change. I had once believed that the only way to change something was from within. This is not the case. One needs to do both.

This personalized cancer medicine breakthrough in breast cancer treatment described in this public work might improve health cost minimization, benefits, effectiveness and utility. This will exert political pressure for implementation of new governmental guidelines for reduction of delays and improvements on the development of more effective medical therapies like this which create the political challenge of ensuring equal access to innovative anticancer treatments for women from deprived backgrounds.

A medical challenge is also posed to select or stratify the patients who are most likely to benefit from this combined multitargeted treatment through molecular profiling. Innovative anticancer therapies should be analysed through macroeconomics, the study of the sum of individual economic decisions for establishing social benefits through distribution and consumption, because cancer has surpassed heart disease as the leading cause of death for persons younger than 85.²⁴ The Massachusetts Institute of Technology (MIT) issued a report in 2011 stating that cancer recently has replaced heart disease as the leading cause of death in the United States.²⁵ Thus, the public impact of this treatment is extremely important because the proven activity of many anticancer drugs that have been approved by regulatory agencies have little to do with curing heterogeneous chemo and/or radioresistant cancers since they are based on finding the tiniest improvement instead of genuine medical breakthrough.

It is like a Greek tragedy where the Fates predetermine the outcome. The worst tragedy is that there is a shortage of good ideas on solving the problem of metastasis. This kills breast cancer patients because, by the time a tumour is diagnosed, there is extensive metastasis to bones, liver, lungs, brain or other vital organs that is sometimes detectable only with –omics’ technologies, meaning large-scale studies of bio-molecules to allow us thoroughly to investigate diseases with the goal of identifying underlying molecular networks and new druggable targets.²⁶

The Big Pharma focuses on devising drugs that shrink tumours without eradicating them. Therefore, the system will remain inefficient, unresponsive, and unduly expensive without major changes unless the Big Pharma shifts its focus from incremental improvement to developing and producing the new generation of anticancer agents that are based on molecular multiple targeting. Combined with traditional chemotherapy, these may eradicate metastatic mutant cells by attacking them on multiple fronts.

However, these treatments are derived from pharmacogenomics where genetic analysis may predict drug efficacy or toxicity. Complex bureaucratic and regulatory constraints in Europe from agencies such as European Medicines Agency (EMA) need to be simplified for such treatments like mine that aim to circumvent chemoresistance and radioresistance. I

think the American Food and Drug Administration (FDA) models such as the Critical Path Initiative that helps streamline drug testing and review, and sharpens its focus on methods of efficiently identifying and resolving drug safety issues, can ‘fast track’ designation where the FDA meets with the sponsor allowing for accelerated approval designation that allows approval of the drug based on a surrogate endpoint, such as shrinking tumours and priority review.²⁷

Does it always have to be about the money?

I believe that part of the communication of our stem knowledge is about accepting the economic realities and making an economic as well as a social case. This is part of the art of persuasion, as James Gallagher so clearly demonstrated. I really do not want to own the intellectual property rights for this therapeutic innovation, because I strongly believe that market and knowledge monopolies may hinder the advancement and clinical adoption of personalized cancer medicine. Besides, freely accessible innovations may promote further innovations.

Although my work is self-financed and I could have made a substantial amount of money by selling these novel anticancer treatments, I lose the right to patent them after I present them in oncology congresses. I do this because I want to act as an opinion leader, educating my peers about these innovations. They can modify them according to their patients’ needs or even improve them. This creates a chain reaction, spreading the word that there is hope for a cancer cure if the cancer policy changes from the ‘blockbuster’ one to the personalized cancer medicine. The latter uses pharmacogenomics on which molecular targeting is tailored according to the genomic characteristics of each individual tumour.

I have been able, on the whole, to self-finance much of my work although it has put considerable strain on me and my family. I know many potential innovators are not in a position to self-finance but, if we could work together to shift our thinking away from intellectual property (IP) and money to sharing knowledge, then the effect could cascade.

For example, when breast cancer patients learn through the media about novel combined anticancer treatments consisting of potential multiple targeted agents and conventional chemotherapeutic agents, they will be keener to participate in clinical studies. Enhancing participation rates will lead to faster and cheaper testing of anticancer combinations. A mass media information flow on cancer-related issues and such innovations may induce significant changes in health services through planned campaigns and unplanned coverage. Also, the manner in which the media portray the issue of any work as hope for the future for breast cancer patients may have significant implications on the public’s participation in rationing on healthcare resources. Furthermore, the media may suggest the need for a legitimate and fair

approach to priority setting for breast cancer patients with innovative personalized approaches. Moreover, the media coverage of these may act as a catalyst between interdependent external factors like politicians, industry and patient advocacy to change delivery of healthcare exerting pressure which influences the decisions of regulatory authorities like NICE and EMEA and authorities of anticancer drug funding.

After the media presented my work, I was approached by interdependent external factors such as patient groups, industry and even politicians to commercialize my novel anticancer therapy so it could reach the market. The pharmaceutical industry wanted the IP of my treatment for profit, the politicians for votes and the metastatic breast cancer patients for saving their lives which were in jeopardy.

The blunt, 'one size fits all' approach to cancer treatment is giving way to the individualized approach based on theranostics, which uses testing to diagnose a given disease, chooses the correct treatment regimen and dose and monitors the patient response to therapy on an individualized basis. It is sensible, logical and evidenced in the laboratory yet, like others in my position, I am still struggling to complete the regulatory requirements of this treatment because: there is a lack of interest in predictive tests from the drug industry due to fear of loss of profits; the complexity and monopoly of funding mechanisms; and entrenched physician behaviour and unfamiliarity with concepts of genetic factors that influence response to drugs. I try to circumvent all these barriers by giving lectures in medical congresses.

The slow pace of translating research discoveries to the clinical arena, combined with lack of funding from granting agencies for true translational research, is deeply frustrating and one of the few ways left is by applying to European Union grants as a translational medicine practitioner. Premium behaviour was not invented by the Big Pharma, it already exists in human beings: to pay a premium for what they most desire. It is a question of exploiting the situation when what you most desire is your life, or the life of those you care about.

However, when the Big Pharma is left out of these new therapeutic innovations, they have the means to erect obstacles. These include lack of financial resources for scientific attacks at medical congresses in the form of questioning by experts representing the interests of the Big Pharma. The discussion often reveals their ignorance on the specific theme especially when it comes to the molecular aspects of the novel treatment on which mechanisms are based. This is something that the Big Pharma lacks because they base their treatments on survival rates and not mechanisms. Treatments like mine may enhance the quality of healthcare that might increase the number of healthy people and reduce mortality, and subsequently improves labour productivity.

Reflections:

It makes me feel great when my hard work can result in potential cures for incurable cancers like the metastatic breast cancer. A therapy like this is also very constructive for my professional status as an opinion leader in oncology and cancer research. It gives me prestige and recognition among my peers. Finally, it gives me public recognition. These things mean more to me than money. This public work in which there is so much interest presents me with many issues about media and effective use of media, communicating to different audiences. In turn, this raised issues of ethics of trials, ethics of withholding and ethics of marketing. I realized I needed to get to know how the media works and how to persuade them to publish more about the alternatives to the approach of the Big Pharma and so on.

Finally, this work which is a part of my continuous struggle to establish the approach of personalized cancer medicine. It has influenced the establishment of the personalized cancer medicine era. In the last Annual Meeting of ASCO, its President, Dr George Sledge, after addressing thousands of cancer professionals from around the world, talked about the impact of the forthcoming era of personalized medicine.²⁸

I am proud to be playing a part in this through my scientific skills and my values. Through this reflective journey I think my efficacy will increase by communicating it out there in a way that influences people's attitudes and behaviour, which is a core driver of change.

4.2 Public Work 2

The invention of a formulation composed of pegylated liposomal anti-eif3c shRNA-vinorelbine, named after my daughter, Sevina.

This has led to the eradication of chemoresistant and hormone refractory breast cancer (mHRBC) cells by inhibiting oncogenic protein translational initiation and oncogene addiction inducing type-I PCD or apoptosis, type-II or autophagy, type-III or necrosis and antimetastatic anoikis. This work, still going through the regulatory stages, was carried out by me while Head of Translational Cancer Medicine and Cancer Research of Oncology Unit of the General State Hospital of Athens.

The significance of this novel research work, a further development of my previous work, was selected by the scientific committee (which includes Nobel Laureates in Medicine such as Dr Murad) of the International Modern Drug Discovery and Development Congress (28–30 November 2007, San Francisco, California), as the best of Congress. It was the first

award consisting of an honorary certificate (see Appendix 2B) and a cheque that I invested in my next cancer research project.

The scientific mechanism of this Public Work 2 is included in Appendix 1 B.

In my previous work I wrote about the media. Public perception is controlled by the media and academic perception by academic journals, conferences and congresses. In my discussions in this section I draw supporting evidence from the Internet. Many people involved in cancer research now publish more through this medium than any other. What is challenging for the public is who or what to believe when faced with so many points of view.

I discuss my learning from this public work towards the end of the chapter. At this point I would say that it demonstrates my ongoing learning about the power of the media to bring about a change in public perception that in turn can influence both the science and policies to take a different direction. Not everyone is invested in the space programme, but everyone is or should be invested in cancer. It helped me to think about what could be done to help the public differentiate between fact and fiction, reality and hype. This public work also emphasized the personal and professional cost of working from within to try to bring about a paradigm shift and the power of the Big Pharma, and how there are plenty of challenges on the web to the Big Pharma but few changes. Through trawling the websites I became more aware of these interfaces of finance, science, politics and public health in a way that went beyond the usual concerns of cancer researchers which is in finding funding to progress research.

Cancer science, the Big Pharma and the media

A full description of how and why I developed this novel anticancer treatment is as follows: Firstly, the 'why' has been described clearly by many experts such as Morgan et al. (2004), who state that conventional chemotherapy has not been proven to be generally effective. They cite the overall contribution of curative and adjuvant cytotoxic chemotherapy to five-year survival in adults was estimated to be 2.3 per cent in Australia and 2.1 per cent in the United States. Although by 2009 the total spent on cancer care, treatment and research exceeded **\$305 billion** per year, according to the British Medical Journal, 28 August 2009, the five-year survival rate from hepatoma, pancreatic, lung (NSCLC, SCLC), osteosarcoma, advanced hormone refractory breast cancer and other solid tumours remains virtually the same as it was 25–30 years ago (McColl, 2009). Most cancer patients in the United States die of chemotherapy.²⁹ As a result at present there are more than 568,668 cancer deaths per year there alone (Kochanek et al., 2011). It is a scientific fact that when chemotherapy is administered blindly it does not eliminate metastatic tumours such as colon, lung, or breast cancer. Chemotherapists are aware of this. In 2002, the Journal of the American Medical

Association reported that, in the previous year, the average oncologist had made \$253,000 of which 75 per cent was profit on chemotherapy drugs administered in his or her office. However, surveys of oncologists by the Los Angeles Times and the McGill Cancer Center in Montreal show that from 75 per cent to 91 per cent of oncologists would refuse chemotherapy as a treatment for themselves or their families. Why? It's too toxic and not effective. Yet, 75 per cent of cancer patients are urged to take chemo by their oncologists.³⁰ Serious complications with conventional chemotherapy have been associated with a weakened immunity system and an enhanced risk of secondary cancers. It is a fact that chemotherapy is only rarely curative in solid malignancies, particularly advanced solid malignancies. In this kind of environment, the media focus on public figures such as Jacqueline Kennedy Onassis and Betsy Lehman, an award-winning health columnist for the Boston Globe, and the role of chemotherapy in their deaths. Ralph Moss, the former Director of Information for Sloan Kettering Cancer Research Center, said that 'chemotherapy is basically ineffective in the vast majority of cases in which it is given'.³¹ Dr Ralph Moss in 2006 reported in *Curezone*³² that an important paper had been published in the journal *Clinical Oncology* (Morgan et al., 2004) by three Australian oncologists:

Lead author Associate Professor Graeme Morgan is a radiation oncologist at Royal North Shore Hospital in Sydney; Professor Robyn Ward is a medical oncologist at University of New South Wales/St. Vincent's Hospital. The third author, Dr. Michael Barton, is a radiation oncologist and a member of the Collaboration for Cancer Outcomes Research and Evaluation, Liverpool Health Service, Sydney. Prof. Ward is also a member of the Therapeutic Goods Authority of the Australian Federal Department of Health and Aging, the official body that advises the Australian government on the suitability and efficacy of drugs to be listed on the national Pharmaceutical Benefits Schedule (PBS) – roughly the equivalent of the US Food and Drug Administration.

The meta-analysis of the Australian oncologists was, 'the Contribution of Cytotoxic Chemotherapy to 5-year Survival in Adult Malignancies was set out to accurately quantify and assess the actual benefit conferred by chemotherapy in the treatment of adults with the commonest types of cancer'. This peer-reviewed article (<http://www.ncbi.nlm.nih.gov/pubmed/15630849>) suggests that the 'chemo program has been a total failure, a fact which has been difficult for the oncology profession to admit'. Although this paper attracted significant attention in Australia, 'it has been greeted with complete silence on the other side of the world' (University of California, San Francisco).³³ As oncologist Glen Warner said before his death in 2000, after forty years of oncology practice:

We have a multi-billion dollar industry that is killing people, right and left, just for financial gain. Their idea of research is to see whether two doses of this poison are better than three doses of that poison'. This occurs because 'chemotherapy is an incredibly lucrative business for doctors, hospitals, and pharmaceutical companies. The medical establishment wants everyone to follow the same exact protocol. They don't want to see the chemotherapy industry go under, and that's the number one obstacle to any progress in oncology.³⁴

I have presented and published in the Annual Meetings of the International Society of Gastrointestinal Oncology (ISGIO), and the American Society of Clinical Oncology (ASCO) that conventional chemotherapy may activate cancer stem cells and angiogenesis inducing chemoresistance and metastasis (Giannios, 2010). The severe systemic toxicity caused by chemotherapy can cause more harm than good according to Dr Alan Nixon, the past president of the American Chemical Society, who in 1998 also asked the obvious and logical question of how oncologists can ignore this clear evidence (<http://www.cancer-treatment-tips.com/chemotherapy.html>). A study published on 23 May, 2011 in the Archives of Internal Medicine (Duke et al., 2011) revealed the average number of different side effects for each drug is 70, with more commonly prescribed drugs having around a hundred. It has been reported that 522 different side effects were reported for just one drug. How in reality can any physician know what are the interacting side effects in a patient who is taking five or ten prescribed medications simultaneously? Even worse, there are patients who are taking more than 15 medications at once.³⁵

Concerning the term oncologist, it is actually an improper title because it implies an understanding of the physiology of tumours. The more accurate nomenclature should be chemotherapist.

Obstacles from research to application

From our position within the field as cancer researchers and translational medicine practitioners dedicated to getting knowledge from the laboratory to the clinic, it is part of our work to explore what blocks and what facilitates that route. Passions run high and there are many ideas on why knowledge appears to be being blocked.³⁶

Economics

The economics of cancer treatment deserve further exploration and to be brought more prominently to the public's attention. The real economics of cancer treatment are exorbitant and astounding. Cancer treatment expenditures, for treatment and research, are close to \$100 billion (\$100,000,000,000) per year. The chemotherapy part of that figure, in 1995, was approximately, \$8.5 billion. These numbers have reached much higher levels today.

Cancer deaths are not widely advertised, but are definitely increasing despite some fluctuations that prompt media outlets to claim cancer is declining. Thus, cancer has overtaken heart disease as America's number one killer. In spite of the best therapy that conventional medicine has to offer, over 650,000 Americans suffer and die from cancer every year.³⁷

Conflicts of interest

There is also the issue of overlapping interests, which are actually conflicts of interests as they can compromise independence. One pharmaceutical company owns 12 of the 40 patents of FDA approved chemotherapy drugs. Senior members of its board past and present also hold positions on the board of a cancer centre. This compromises the ethical integrity of the centre. This is happening because the boundaries between academic medicine—medical schools, teaching hospitals, and their faculty—and the pharmaceutical industry have been dissolving since the 1980s, and the important differences between their missions are becoming blurred. Medical research, education, and clinical practice have suffered as a result, according to a report entitled 'Big Pharma, Bad Medicine'. This report was published in Boston Review last year by Marcia Angell who delivered a talk at Harvard University about ethics describing how corporate dollars corrupt medical research and education.³⁸

Conventional cancer treatment is not addressing the underlying causes of cancer.³⁹ Dr John Diamond MD has said that finding a cure for cancer is absolutely contraindicated by profits.⁴⁰

Sometimes cancer is treated with the risk of developing secondary tumours, according to a study which reports that there is an enhanced risk of leukemia in breast cancer patients who take drugs to get a boost in white blood cell growth in order to tolerate more aggressive chemotherapy treatments, leading to some speculation about Amgen's Neulasta and Neupogen.⁴¹

Also, antagonists of estrogen receptor such as tamoxifen which are used to prevent the recurrence of breast cancer may enhance the risk of developing uterine cancer by 30 per cent.⁴²

German investigators from Friedrich-Schiller University in Jena have shown that paclitaxel (taxol), the gold standard of chemo, causes a massive release of tumour cells into circulation resulting in extensive metastasis many months or even years later, long after the chemotherapy could be suspected to be the cause of the spread of the cancer. This little known horror of conventional cancer treatment should be spread far and wide, but it is not even listed in the side effects of paclitaxel.⁴³ Thus, sometimes conventional cancer chemotherapy may prove to be worse than the disease.⁴⁴ This observation is confirmed by

Dr Allen Levin of University College of San Francisco (UCSF), who states that most cancer patients in America die of chemotherapy that does not eliminate metastatic solid tumours such as breast, colon or lung cancers. Although this fact has been well documented for over a decade, still physicians still use chemotherapy for these tumours.⁴⁵

Why nothing changes despite the evidence

The problem is that conventional chemotherapy suppresses cancer symptoms temporarily often converting cancer into a chronic disease. This is then supported by more drugs that do not eliminate recurrence or eradicate the root of the tumour, such as cancer stem cells, that can be activated by chemotherapy and induce metastasis. I spoke about this in a lecture in the plenary session of the Annual Meeting of the International Society of Gastrointestinal Oncology in 2010 that took place in the United States (Giannios, 2010).

A devastating blow to the current cancer establishment was exerted by the legendary cancer researcher Ralph W Moss PhD, who concluded that conventional chemotherapy is simply ineffective in the vast majority of human cancers.⁴⁶ Also, Dr Martin Shapiro of University College of Los Angeles (UCLA) has stated that cancer researchers, medical journals, and the popular media have contributed to a situation in which many people with common malignancies are being treated with drugs not known to be effective.⁴⁷ A report in the website CancerResearchInformation.com states that anti-cancer chemotherapy does not work, it is costly, it has adverse effects, and it kills cancer patients. Also, this report demonstrates the passion and anger felt by many people. There is no-one who is not touched in some way by cancer in their lives, either themselves, a relative or friend, or a colleague. It states that 'chemotherapy and radiation which share the same resistant mechanisms are very much part of conventional medical protocols to "treat" cancer today'. However, they are hideous crimes against humanity, and in the near future, humankind will look back on these medical Dark Ages and wonder how such brutal and savage methods could ever have passed off as 'cancer treatments'.⁴⁸

Quoting Benjamin Disraeli, Prime Minister of Britain, Mark Twain wrote there are three kinds of lies in the world: 'lies, damned lies, and statistics'. That statement is even more true (and dangerous) when applied to medical studies concerning chemotherapy.⁴⁹ All the research papers relating to chemotherapy and efficacy over a 14-year period have been cited in the meta-analysis published in the Australian Journal Clinical Oncology entitled 'The Contribution of Cytotoxic Chemotherapy to 5-year Survival in Adult Malignancies' mentioned earlier. This excellent study was based on an analysis of the results of all the randomized, controlled clinical trials (RCTs) performed in Australia and the United States. It measured statistically the five-year survival rate from the use of conventional chemotherapy in adult

malignancies. The survival data was drawn from the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) registry, and the Australian cancer registries, analysing the period between January 1990 and January 2004. For the authors to be more than fair, wherever and whenever data was uncertain, they deliberately erred on the side of over-estimating the benefit of chemotherapy. Even so, this meticulous study concluded that, overall, chemotherapy contributes approximately just 2 per cent to improved five-year survival in cancer patients. Despite the mounting evidence for chemotherapy's lack of effectiveness in prolonging survival, chemotherapists continue to present chemotherapy as a rational and promising approach to cancer treatment that is false.⁵⁰

Evidence to support alternatives

Dr Gregory Foltz discovered that oncologists have been targeting the wrong cells in the treatment of cancers such as brain cancer. Cancer stem cells cause the growth of cancer cells, and stem cells resist chemotherapy. Dr Foltz explains that this is why 'standard cancer treatments so often fail: those therapies target the wrong cells'. He has created the Center for advanced Brain Tumor Treatment at the Swedish Medical Center of Seattle where I have given numerous lectures about novel personalized cancer treatments. There he tries, like me, to design pioneer and novel personalized treatments for glioblastoma patients. He follows my approach, offering to cancer patients the possibility of tailoring their anticancer treatment based on their unique genetic makeup of their tumour.⁵¹

I also have carried out a great deal of research concerning cancer stem cells.⁵² I have proved for the first time that chemotherapy may activate cancer stem cells, inducing tumour relapse after enhancing angiogenesis and subsequent metastasis in solid tumours.⁵³ The new biotech companies recognize that conventional chemotherapy treatments do not work. The researchers are starting to 'think outside the box', shifting to a systems approach to solve the cancer problem. Why wasn't this shift made years ago, after the failure of chemotherapy was first observed?

Reflections on my efforts

I can research and invent. This is what I do best. But research and development need funding and the complexities of ownership, patenting, trials which are prohibitively expensive, and need to be confronted and negotiated. The only group that can afford them easily is the Big Pharma. This has strong partnerships and contracts and so on with governments, universities and health authorities all over the world. It also has very powerful marketing and lobbying groups.

Some important innovations and discoveries are being accomplished by 'independents' like myself. The way we circumvent our work being bought up by the Big Pharma and possibly

shelved or developed for huge profit is to go to or be invited to speak at international congresses so that the knowledge is shared and can be used, but not patented by anyone. So far I have been able to defend my work through knowledge. I took this novel treatment to the International Modern Drug Discovery and Development Congress as mentioned above. Over the years I have built up a reputation at major congresses such as the American Society of Clinical Oncology (ASCO), International Society of Gastrointestinal Oncology (ISGIO), European Society of Gynaecological Oncology (ESGO), American Association of Cancer Research (AACR) and many others for sound scientific research and, in more recent years, also for my stance against the Big Pharma's approach. I am now seen as an opinion leader. This is not my natural arena, but looking at how important this novel treatment is and the difference it can make to lives, I believe I can do more to get our work from the laboratory to the clinic. I have still much to learn.

Inside

I have tried to convince chemotherapists to tailor molecular targeting approaches under a personalized therapeutic strategy for incurable cancers like HRBC by detecting chemoresistant mechanisms with pharmacogenetics. These must be circumvented by inhibiting the dominant signalling pathways that activate them. This is done with genetic-based therapeutic approaches like the antisense therapy to allow the conventional standard chemotherapeutic agents like vinorelbine to exert their cytostatic action. This way we can begin to challenge the existing policies of the the Big Pharma with evidence clearly demonstrating by comparison just how unnecessary these harmful and distressing adverse (side) effects are under their protocols, which cause systemic toxicity and secondary tumours.

The obstacles to the scientifically sound approach that I and others advocate continue to be significant. Many obstacles have been put in the way of this progress. Like many independents, I have suffered periods of scientific isolation with obstruction of financial resources, regulatory pressures and a continuous painstaking struggle to complete my research work while I hold down the demands of my official roles.

Circumventing the obstacles

My understanding of the opposition to my work, shared by many colleagues in the cancer research field, is that it is down to the profit from the massive sales of the drugs all over the world. This public work is self-financed. How doctors attending my lectures are awarded Continuing Medical Education (CME) credits is that congresses like the Annual Meetings of ISGIO are under the auspices of American Universities such as the Medical School of the University of Nebraska.

The funding issues were extremely challenging and this work was an individual effort. The Big Pharma are aware that after I publish my new treatments in medical congresses I have no rights to their intellectual property (IP). I publish them because I want to prove my scientific point, that personalized cancer medicine is much more effective than the drug policy of the pharmaceutical industry for eradicating chemoresistant and radioresistant tumour cells exhibiting molecular mechanisms and not just survival rates. The Big Pharma knows that without huge financial investment these treatments cannot get through the regulatory process. However, by making them known to academics in congresses a change in drug policy can be induced that has a chain reaction, spreading the idea of personalized cancer medicine to all associated sectors.

All the novel cancer treatments originate from the cancer researcher and then it is up to the translational medicine practitioner to take it from bench to clinic through all the stages of the required regulatory process, leading to the drug being approved. This procedure is extremely expensive. After this point, the chemotherapists can use this drug on a routine basis. Translational medicine practitioners have established a new regulatory tool called Phase 0 and this can save a great deal of time and money in drug development.

The most evidenced impact of translational medicine at the moment is educational, keeping chemotherapists up to date with what is possible. In cancer research, we move faster than regulation hence experience frustration in trying to get anything from the laboratory to the clinic. We know things work and will save lives, but we are held up by a complex arena of regulation, stakeholders, old paradigms and the required funding that depends upon the control of a triad of pharmaceutical companies, government/regulation and cancer fundraising organizations that rarely fund independent research. A serious issue that should be circumvented is that if a compound is not patentable such as dicholoacetate (DCA) it shan't be accessible to cancer patients, even if it is effective in deadly tumours such as glioblastoma. This is simply because the Big Pharma sees relatively little money in developing it. Regulatory agencies such as FDA, instead of helping its development process for being accessible to glioblastoma patients who really do not have many therapeutic options, they create obstacles such as trying to stop DCA being sold.⁵⁴ These complications should be prevented in the future by political intervention that can be motivated by advocacy action. In the case of DCA, the local town raised money for the clinical trials.

With novel molecular targeting therapeutic approaches like mine, the public impact is significant because chemotherapists and radiation oncologists in the future will learn how to practise personalized cancer medicine. This is radically more efficient than the conventional treatments: It provides better differentiated therapeutic solutions and improves the medical outcomes, saving the lives or improving the quality of life of many cancer patients who now

are destined to die. Treatments like this are set to motivate regulatory authorities like EMEA or FDA to be supportive, accelerating their drug approval process, because innovative therapeutic methods like personalized medicine may take us in the direction of safer and more effective cancer treatment. After regulatory approval, these targeted therapies would be widely adopted by chemotherapists and radiation oncologists, because they are extremely effective in eradicating tumour cells in a specific subpopulation of cancer patients using -omic approaches.

A better economic argument

There is also the issue of common sense economics. For instance, by dramatically improving the efficacy of cancer treatments and minimizing systemic toxicity, personalized cancer medicine may circumvent the enormous problem of non-compliance. Many cancer patients at the present time do not adhere to their prescribed drugs due to severe adverse effects. This wastes many millions of pounds for healthcare systems like the NHS, for example. It will enhance compliance rates of cancer patients to their prescribed medications, for instance chemoradioimmunotherapy such as the one that I presented at the 18th Annual Meeting of the European Association of Cancer Research in July 2004. It was reported as a breakthrough treatment, giving hope to the future treatment of advanced breast cancer, in the cancer/oncology category of the Medical News Today website.⁵⁵ This work was selected as the most significant of the EACR congress by the whole Federation of European Cancer Societies (FECS), the Brussels-based organization that represents the interests of almost 18,000 cancer professionals in Europe. FECS promotes the multidisciplinary aspect of cancer care through scientific activities. At that time I was Head of the Radiotherapeutic Cancer Research at IASO Hospital, Athens.

With this successful, and novel, therapeutic technique I managed to kill metastatic breast cancer cells by circumventing their chemo- and radioresistant mechanisms (Giannios, 2004). Therapeutic approaches like this one may save huge amounts of money because cancer patients will have more trust in something that is tailored particularly for their cancer type at the molecular level, targeting their individual phenotype and will be more compliant. Furthermore, the financial burden of conducting clinical trials will be decimated, significantly accelerating the drug development process because clinical trials will be smaller, targeting smaller cancer populations. With these tailored drugs, we will get positive results within weeks or months instead of years since we will be able to exclude the non-responsive type cancer types from clinical trials. We will be able to identify responders by using biomarkers. This will allow chemotherapists and radiation oncologists to take a more rational and selective approach to their therapeutic decisions.

With the new generation of personalized treatments that aim to tailor drugs, specifically targeting cancer patients who are likely to respond positively to these specific treatments, we can circumvent the presently existing trial and error approach to cancer treatment which is associated with high cost, high risk and low efficacy. Thus, by blocking the growth and spread of incurable cancers by interfering with specific molecules involved in oncogenesis and tumour proliferation, we can save the lives of cancer patients and avoid the huge financial waste of 'one size fits all' drugs. Furthermore, these treated patients will be able to boost the economy by staying in work. This helps society. Standards of social life will be greatly upgraded by reaching an optimal level of health. Providers and hospital groups will become much more efficient from a welfare perspective. Deficits will be reduced and politicians will be more efficient and popular by investing more money in other social needs. The pharmaceutical companies will have to learn to accept the end of an era that has been financially very successful for them in its 'one size fits all' policy, because there are many more treatment options for an individual cancer patient.

Such innovative cancer research like personalized medicine will hopefully or could already be influencing medical bodies, health authorities and even pharmaceutical companies to focus on grouping disease by mechanisms of action and not to group disease by symptoms. It also indicates very clearly to them that they must be prepared to invest money on research. This is still needed for the future development of drugs to target oncogenic mechanisms instead of organ types, shifting to a horizontal mechanism of action from a vertical organ-specific view. With the development and use of pharmacogenetic tests, they will be able to accelerate pharma R&D, minimizing financial costs for clinical design and the time to market for their innovative products of personalized treatment that will be characterized by enhanced efficacy. Taking this particular public work as an example, my research that produced the novel treatment indicates that apoptotic cells may be used as targets for specific delivery of novel anticancer agents, instead of the blind survival rates that the Big Pharma currently uses without knowledge of any mechanism for cytotoxic action. In this way, clinical trials may be more efficient and effective, influencing positively the regulatory authorities for accelerating their approval because apoptosis is the ultimate end result for individualized cancer treatment.

Personalized Cancer Medicine is a new medicine in the context of healthcare delivery and will be very competitive in the future. It will require close and productive collaboration between diagnostic and pharmaceutical companies, offering many new jobs that will help society. Molecular diagnostics will guide the practice of personalized medicine by targeting the right drug to the right patient. Companies must learn that they can capture value by delivering value. They must focus on developing innovative medically differentiated cancer

products for surviving in the future. I am one of the many scientists and cancer researchers who have fought the 'one size fits all' anticancer policy of the Big Pharma for more than a decade by presenting in International congresses works like the one mentioned above, and acting as an opinion leader regularly presenting research work with novel therapeutic strategies of personalized cancer medicine. The resistance of the big multinational pharmaceutical companies has been extremely strong because they fear that personalized healthcare would undercut their revenues. Time will prove them wrong and hopefully soon, because cancer patients should be respected and supported to the highest degree possible with no compromises involved.

This work in cancer research has had positive and negative influences on my life and my professional development. It requires a patience that can quickly turn to frustration and anger when I have to wait for my novel molecularly targeted drugs to be available to cancer patients after the procedures of patenting and licensing have been completed. The enhanced scientific experience from my recognized work gives me better potential to continue with more strength to give lectures in oncology congresses educating colleagues about the benefits of personalized medicine for cancer patients. Furthermore, initiating collaboration improves my research work, discovering new therapeutic strategies for cancer especially metastasis which is very chaotic. In addition, with this international award, one of many that I have received, I can influence the Big Pharma to be more interested in the personalized healthcare that I strongly believe can offer many more benefits to desperate cancer patients, their relatives and to society in general compared to the existing conventional 'blockbuster' policy. As I always learn from each of my novel anticancer works, so can other cancer co-researchers using this knowledge to improve the treatments or use them as the basis to develop better treatments or improve their already developed treatments. This will make them more advanced and efficient against advanced tumours that are currently incurable under the conventional 'one size fits all' anticancer policy.

This work of personalized medicine that uses pharmacogenetics to develop safer, cheaper and more effective anticancer drugs, from bench to clinic, as a translational medicine approach may contribute to the developing area of sociology of socio-technical expectations by creating new technological visions. In itself this will be a challenge to the 'one size fits all' approach.

Fear

When I trawled the web in a more systematic way I was overwhelmed by what I found, and as an insider I already knew a considerable amount. I now more than ever know that to bring the new paradigm in we need to all work together and to develop a high level research

journal and web presence where people can access evidenced findings from oncologists, cancer researchers and translational medicine practitioners.

If I was overwhelmed, then what must it be like for relatives of sufferers trying to find the best treatment, a cure even? There are so many charlatans waiting to take advantage of them. It was at this stage that I decided that this should be for me a primary goal. It is not only the patient who suffers, but all those friends and relatives who care and feel powerless, plus all the scientists who know they have the answers to many of the problems but can't get it to them. My thinking began to be around an association, a journal and a website.

One very positive aspect of our era is that informative dissemination of medical knowledge is rapid and widespread due to the existing technological advancements. This can mediate cutting-edge medical education of health professionals, cancer patients and their families, advocacy groups, policy makers, journalists and society in general that may lead to radical policy changes in the way that cancer is tackled in the future. So that people know who and what to believe it is vital that cancer researchers and translational medicine practitioners can lobby and convince governments of their case which at least gives some seal of approval.

4.3 Public Work 3

Therapeutic genetic vaccine for HPV 16(+) cervical cancer and oropharyngeal (OSCC) cancer

My novel therapeutic anticancer genetic vaccine, presented at the Annual Meeting of the American Society of Clinical Oncology in 2009 under the category of Developmental Therapeutics: Immunotherapy-subcategory: Vaccines and citation: *J Clin Oncol* 27: 15s, 2009 (suppl: abstr 3062) is as follows:

Effect on humoral and cellular immunity and on apoptosis in CIN2, CIN3, and HPV16+ cervical cancer of therapeutic divalent genetic vaccination with CMV replicon system (CRS) delivering HPV16 recombinantly mutated E6 and E7 viral oncogenes targeting p53 and Rb, respectively.

The technical aspects of this work are described in Appendix 1C. Other anticancer vaccines I have developed and presented in oncology congresses are in Appendix 2C.

This work demonstrates what is possible if one is highly motivated and dedicated. Cancer has to be managed in a multipronged approach: science, trials, individual and team effort and dedication, the media, policies, funding. The science carried out by individuals and teams provides the evidence and trials to establish its efficacy and feedback information on such things as optimum delivery and counterindications, dosages and exclusions. This

combined evidence needs to be made known to both the general public and decision makers like government bodies and funders. Training has to be carried out to help practitioners in cancer understand the delivery of the treatment and its combination array to optimize impact. This work was motivated not only by the science but by a social conscience. Cancer treatment as it exists today has great disparity but if it continues with the Big Pharma controlling both doctors and the price of drugs, it will be disastrous for people in the lower income groups.

Description: This therapeutic genetic vaccine against HPV 16(+) derived cancers is the only one that exists in medical oncology.

Its therapeutic significance is substantial because it is independent from chemoresistant and radioresistant mechanisms. HPV is the most common sexually transmitted infection in the world. HPV type 16 can cause cervical and oropharyngeal squamous cell cancers(OSCC), such as soft palate, tonsillar and tongue cancers that rise rapidly with an overall five-year survival of about 25 per cent. Other tumour types that HPV 16 causes include anus, vagina, vulva and penile cancer. None of the vaccines to date actually treat cancer. The vaccines which are used today are only preventive vaccines fighting viral agents that are capable of causing cancer. This therapeutic cancer vaccine is an emerging experimental type of treatment designed to stimulate the humoral and cellular immune system that are the body's natural defences for finding and fighting cancer cells. This therapeutic vaccine can be combined with other cancer treatments including chemotherapy, radiation, surgery, antiangiogenesis drugs, and so on. This therapeutic vaccine targets certain molecules such as antigens on the surface of tumour cells, never expressed by healthy cells. Thus, this therapy circumvents systemic toxicity. For the development of this novel therapeutic vaccine which is one of a kind, I have developed a cytomegalovirus (CMV) replicon system (CRPs) for the efficient delivery of the HPV16 recombinantly mutated E6 and E7 genes replacing part of the CMV genome for the HPV genes which were genetically altered to block binding sites for tumour suppressor gene p53 and oncogene Rb. The replicon vectors infected and co-transfected CIN and cervical cancer cells derived from HPV16 (+) tumours. After vaccination with a needleless injection system the viral E6 oncogene did not degrade apoptotic p53 and it blocked activation of telomerase. This induced type-I PCD or apoptosis and DNA repair in cervical intraepithelial neoplasia (CIN) and cervical cancer cells. This vaccination led to scheduled cell cycle entry, genetic stability and mortalization of tumour cells. Cellular and humoral immune responses were exhibited which led to irreversible D2 apoptotic stage of apoptosis or type-I PCD leading to a bystander killing effect of intraepithelial neoplasia, and cervical cancer cells. BrdU and MTT analysis exhibited inhibition of DNA synthesis and metabolic activity of vaccinated tumour cells compared to

controls. This genetic vaccine coding for E6 and E7 mutations designed to prevent p53 and Rb binding sites, activating humoral and cellular immune responses leading to eradication of cervical intraepithelial neoplasia (CIN2, CIN3) and cervical cancer cells via induction of irreversible D2 apoptosis to give a bystander killing effect. This therapeutic vaccine has tremendous potential to stimulate humoral and cellular immunity against HPV16 (+) derived tumours.

My role in it: I was the innovator and developer of this pioneer work. The idea was mine and I achieved its realization, although it was painstaking work at considerable expense to my personal time and at high risk due to the need to use live human tumour cells from metastatic patients. I also was exposed to the carcinogenic HPV(+) 16 virus with which I could have been infected at any time, causing me cancer. Of course all the required measures were taken according to the guidelines of good laboratory practice (GLP) and good clinical practice (GCP). However, accidents can always occur that carry some risks. I do not take unnecessary risks in my work but I think take a balanced view. The outcomes are so important that some things are worth the risk, but it is always professional to minimize the risk as much as is humanly possible. So yes, I have exposed myself to such risks to discover a therapeutic solution to these chemoresistant incurable tumours that kill people whose only mistake was to have unprotected sexual intercourse or the wrong blood transfusion. Like the other public works, this was presented at international oncology congresses where my lectures are approved by the scientific committees and colleagues have the chance to ask questions. This is the best way for them to learn that there are therapeutic solutions available to patients with incurable cancer but which need to go through procedures to arrive in the clinic.

Public impact: The human benefits of developing cancer vaccines will be of great importance – for millions of patients cured, to billions of pounds saved. Unfortunately, so far we have only vaccines that offer prophylaxis for the development of cervical cancer. To date, none of these approved vaccines actually treat patients who have developed cancer. The vaccines that I have developed and have been accepted for presentation in oncology congresses prove that gene modified cellular vaccination can be personalized against various types of advanced chemo- and radioresistant tumours, leading to apoptosis. Furthermore, these genetic vaccinations can be used synergistically with conventional chemotherapy under a personalized cancer medicine approach with vaccines derived from an individual cancer patient. Analysis of the therapeutic divalent genetic vaccine with CMV replicon system that I have developed against chemoresistant HPV16+ cervical cancer is facilitated by the intratumoural delivery of HPV16 recombinantly mutated E6 and E7 viral oncogenes that target tumour suppressor genes p53 and RB, as follows:

It is well known that there is a huge increase of HPV(+)¹⁶ derived cancers that can be fatal due to the increased incidence of infectious blood transfusions and unprotected sexual activity. I must emphasize that although this project was self-financed, as I declared officially in the disclosure form of the Annual Meeting of American Society of Clinical Oncology, I have completely waived my IP rights so future massive production of my therapeutic vaccine can be as economical as possible and be available in the future to deprived cancer patients. This production should be by a governmental, not a for-profit, facility. This will benefit society. Since the rapid increase in cervical cancer incidence worldwide requires improved healthcare access to under-served areas, my affordable HPV therapeutic vaccine aims to overcome the socioeconomic barriers associated with this fatal disease, and the other HPV(+) derived cancers that spread worldwide, especially in the developing countries where there is no available screening.

The social macroeconomic benefits can be very significant. Society will benefit from better health and lower public expenditures for treatment that can be reallocated to other productive uses such as pharmacogenomics. The great utility of this therapeutic approach is that it is much more effective than conventional anticancer treatment because it may circumvent resistant antiapoptotic mechanisms with fewer adverse effects. Immunological analysis after vaccination exhibited significant antibody and antigen specific T-cell immune responses that were induced against the target E6 and E7 proteins. This led to the apoptotic eradication of cervical or vulvar intraepithelial neoplasia, limiting adverse events and injection site reactions to mild or moderate that need no treatment. That has a huge clinical impact because it can substitute chemotherapy with its associated tremendous systemic toxicity, chemoresistance, and development of secondary tumours. The public impact might spread worldwide because cervical cancer kills million of women every year, making it the second biggest cause of death among female cancer patients globally, according to WHO,⁵⁶ because HPV is carried by approximately 450 million people.

Since HPV is the most common sexually transmitted infection in the world, a genetic therapeutic vaccine like mine is a distinctive kind of biotechnological agent, invoking notions of containment and contagion. Thus, politics can shape every aspect of the biotechnological and/or pharmaceutical life-course consisting of the way of production, use and so forth. Therapeutic vaccines like mine may instigate political struggles and social change because by curing HPV(+) derived cancer, it embodies the dream of hygienic containment by transforming bodies, practices, and institutions. The high-quality healthcare provided by this vaccine means that providers can manage a population's healthcare by timely, skillful application of advanced therapeutic technology in a culturally sensitive manner within the available resource constraints. Policy interventions can be derived from this novel

therapeutic genetic vaccine that can lead to a higher quality process of care and rapidly improve a population's health outcome, which can be cost effective in the long run.

The news media comprise the channel for making this potential treatment known to the public so cancer patients may exert pressure on policymakers, physicians and guideline panelists (who define acceptable standards of care) for the immediate development, approval and availability of this vaccine. It can save lives and money by substituting toxic chemotherapy and/or radiotherapy. When this therapeutic option is known to cancer patients, it can circumvent the moral hazard where patients purchase drugs and services differently when they have insurance, based on the differences in value decisions and costs. Chemotherapy with all its supplementary drugs may be much more expensive than this vaccine. Subsequently, it can cut direct costs of cancer care, such as biochemical diagnostic tests associated with chemotherapy, hospital and physician fees, and mainly the cost of drug therapy paid by the government and other public and private insurers.

The money saved can be used for other social priorities. For this to take place, new legislation should eliminate treatments that are not reasonable and necessary for the treatment of cancer. A therapeutic vaccine like this can go against the larger economics of the chemotherapeutic policy because, in a private system, investors such as pharmaceutical and biotechnology companies or venture capital investors must seek a positive financial return for shareholders for their drug development investment regardless of the quality of healthcare that they provide to cancer patients. Thus, policymakers must maintain an appropriate balance between responsibility for public and private healthcare programs and incentives for investments in future health innovations like mine. They should circumvent disparities in cancer care where individuals from lower socioeconomic groups, and specific racial or ethnic minorities who are characterized by enhanced cancer risk and worse cancer-related outcome must have free access to innovative, revolutionary and novel treatments, like my therapeutic vaccine. This is not easy because the causes for these disparities are complex and include economic, cultural and social factors. Even the risk of uninsurance reaches the highest levels among those in lower income brackets. This should be immediately corrected. The social macroeconomic benefits of my therapeutic vaccine can be of huge importance because it can make healthier populations in societies that can increase tremendously the levels of human capital by enhancing the capacity to generate wealth. Higher quality of healthcare provided by a therapeutic vaccine like mine can increase society's human capital by reducing the number of deaths from cancer, and the amount of disability, improving worker productivity. In addition, providers and insurers may benefit by avoiding unnecessary or inappropriate healthcare such as 'blockbuster' chemotherapy. Thus, society may benefit from better health, and cost effectiveness for treatment. Thus,

novel therapeutic interventions like mine that can improve quality have an especially high social value. This may lead to public dissemination by motivating managers and providers to undertake changes that will improve the delivery of healthcare. This vaccine might bring a new era of therapeutic genetic vaccination against cancer that may bring real value in healthcare, overturning today's situation where cancer patients are left to settle for a market that has sub-optimal equilibrium and a poor quality of healthcare, like the conventional 'blockbuster' chemotherapy. I strongly believe that novel anticancer approaches like my therapeutic genetic vaccine may improve tremendously the provider–patient interaction by increasing the overall value of healthcare.

All involved parties in cancer treatment including Big Pharma must understand that the field of personalized medicine is rapidly expanding even in the sector of genetic vaccination against tumours with viral origin (ie HPV16+), such as cervical intraepithelial neoplasia (CIN) 2–3, or cervical cancer. The more we learn about the genetic mechanisms of cancer growth and cause, the more we can harness this knowledge to improve survival rates, and improve quality of life for cancer patients by circumventing unnecessary side effects at affordable financial terms.

My work offers new genetic clues about the effectiveness of therapeutic cancer vaccines based on genetics. The development of biotechnological advancements like this genetic vaccination against cervical cancer is feasible because it greatly reduces biotechnological development costs, ensuring that a high proportion of derived products make it through all the phases of development, and subsequently onto the health market. It is a fact that genomics-related technology (GRT) mediates the removal of unfavourable biotechnological products at the very early stages of development. The current advancements in genomics that reveal the detailed molecular basis of cancer may allow cost benefits to be passed onto the government agencies that fund healthcare, and cancer patients.

A very serious ethical issue that I want to emphasize is whether the genomic medicine revolution will ever reach the healthcare system in developing countries that cannot afford even the cheapest of anticancer treatments already available to their poor and immunosuppressed patients due to malnutrition. To be honest, I do not think these treatments will ever reach cancer patients in the Third World and this worries me considerably. My belief has been confirmed by the WHO, which emphasizes that global inequalities are widening in the availability and subsequent use of anticancer treatments based on pharmacogenetics including molecular profiling, proteomic profiling, genetic testing, and metabolomic analysis.

For instance 90 per cent of the global health research expenditure is directed at diseases that affect only 10 per cent of the world's population. Thus, we must stop the divide growing between the rich and poor concerning availability of cutting-edge anticancer treatments. Only with intensive scientific effort from cancer researchers like myself and political effort, the major anticancer advances derived from genetic research will be able to save millions of lives, especially in the developing world. Scientific evidence of genomic cancer medicine derived from oncology congresses have started to influence policy debates, mainly between cancer researchers who invent novel treatments that are followed by chemotherapists, radiation oncologists, regulators and company representatives. Only with the positive collaboration among them will all these new anticancer treatments be translated from bench to clinic, especially for sexually transmitted viruses that may cause malignant tumours, such as cervical cancer and oropharyngeal carcinoma (OSCC).

Influence on my professional life/development: The innovation of this therapeutic genetic vaccine opens many doors for me in academia, research and industry. As a matter of fact, after this development and presentation I was proposed as Global Vice-President for Lilly Oncology in the United States, a position that I turned down. It is more important for me to remain independent and this vaccine also enforces my position as a pioneer cancer researcher, and gives me the pleasure in persuading and educating my peers about this therapeutic option. However, my greatest reward is that this vaccine can really help cancer patients in the future, improving their quality of life.

All my works evoke the same issues about increasing my community of practice's awareness, that of my field, public awareness and that of the media. And I learned from this. Until then I had been opposing them, both of us keeping to different sides of the table, they trying to undermine me in congresses and me fighting them, primarily with my scientific skills and knowledge and often feeling quite isolated. However, this time the approach was at a higher level, the offers at a higher level, the techniques persuasive rather than oppositional. I decided then that I could learn from this. I needed to be persuasive rather than oppositional, I needed to develop a way to impact the media and to influence the Big Pharma's practice through public and expert opinion which could only be achieved through not standing alone but through collaboration and our own association.

4.4 Public Work 4

Nanomedicine - Formulation SEVIN-A composed of Pegylated-Nanoparticles of CDP bound to multitargeted siRNA molecules against BMI1 and Survivin conjugated with miR-373 which targets CD44 overexpressing cancer stem cells (CSCs) of metastatic ovarian carcinoma induces Apoptosis/PCD type-I (D2 Stage) circumventing potent Chemoresistant-Multifactors caused by Vinorelbine.

This work was presented at the plenary session of the 8th Ovarian Cancer Research Symposium at the University Hospital of Seattle in Seattle, Washington, 28–29 October, 2010.

This novel treatment received a distinction from the congress committee.

This novel treatment exhibited eradicating results due to induction of D2 irreversible stage of type-I PCD or apoptosis in chemo and radioresistant cancer stem cells of advanced ovarian cancer.

For the technical aspects of this public work, see Appendix 1D. For a list of all associated works developed from this and put into the public domain, see Appendix 2D.

As a cancer researcher I have to keep up to date with the very latest developments in science, to know every part of the body and its functions and to be an expert in genetics if I am to find new treatments, and new ways to deliver our treatments that do not damage the patient further. In addition, I must learn about particular delivery systems that can bypass the brain barrier and to negotiate the complex world of media, finance and politics. This work demonstrates my learning at the scientific edge and its application in my field of cancer research. In a sense, the good cancer researcher never sleeps. But what is the use of all of these novel treatments if we cannot get them to the patients? This work, at the cutting edge, confirmed for me that as a group we could be more powerful, more vocal and, most importantly, more organized. At one time the doctor and the specialist were highly respected; now we are treated like cogs in a wheel of big finance, increasingly separated from our patients and indirectly colluding with unethical practices. I no longer need to go on proving myself as a scientist, I am a good one: I just need to use the reputation I have built up to be more effective in the public arena and this time I do not go into it alone, or even thinking I am alone.

Nanomedicine has great potential for breakthroughs in basic, applied and clinical sciences, leading to more efficient and targeted diagnosis, treatment and monitoring of diseases like cancer. In my pioneering work I have used colloids, which are lipid-based liposome nanoparticles and niosomes. I use high Tc phospholipids which are combined with cholesterol which are located between acyl chains for enhancing stability when the nanoparticles interact with the biological milieu. For circumventing opsonin adsorption I

pegylate the surface, making it more hydrophilic. This way the nanoparticles carrying therapeutic molecules can circumvent elimination by the Reticulo-Endothelial System (RES) that consists of the macrophages (Kupffer cells) of the liver and spleen. With these nanoparticles I can target specific tumour cells characterized by chemoresistance due to overexpressed drug efflux genes such as MDR-1 that encode protein Pgp, which acts as a pump by binding drug molecules to its ATPase chains. Molecular Tumor Cell Targeting (MTCT) is achieved by linking antigens or other biosensors such as RNA strands to the surface of the nanoparticles that detect specialized properties of the tumour cell walls delivering their cargo of therapeutic molecules intracellularly by endocytosis circumventing chemoresistant efflux pumps. Only then can personalized medicine, which is molecularly targeted, be achieved for individual cancer patients by tailoring the treatment specifically to their tumour phenotypes.

Once the target tumour cells have been identified – in my therapy they are the cancer stem cells (CSCs) that overexpress CD44 – and they have been activated by the chemotherapeutic agent vinorelbine, the nanoparticles that I have designed with high Tc phospholipids and pegylation to enhance hydrophilicity and lead to the circumvention of biological milieu interactions will bind with the conjugated miR-373 onto the CD44 of tumour cells. This will cause the entrance of tumour cells via endocytosis, releasing the therapeutic siRNA molecules intracellularly for downregulating BMI1 and survivin and inhibit downstream signalling pathways that lead to induction of type-I PCD or apoptosis (D2 irreversible stage) and activate a bystander killing effect. The siRNA molecules were protected and their life was prolonged during delivery with nanoparticles. Otherwise, the RNA strands would be destroyed by cellular mechanisms before reaching their targets.

Furthermore, specific molecular targeting will aid in the treatment of late phase metastasized cancers and hard-to-reach tumours like breast and ovarian tumours. Also, nanoparticles will circumvent tumour chemoresistance by overpassing Pgp drug efflux pump. These nanoparticles will treat only the tumour, without damaging adjacent healthy tissue. They dissolve intracellularly in the endosome, releasing their therapeutic siRNA cargo that eradicates endodyploid cancer stem cells after downregulation of Aurora-B. The bottom-up construction of these nanoparticles takes advantage of molecular self-assembly for building specific structures, based on Watson-Crick DNA base pairing, for building nucleic acids of defined structure that will be used for personalized medicine involving molecular targeting. The benefits of nanoparticle delivery are extremely significant because they improve bioavailability of entrapped therapeutic molecules by targeting specific organs, tissues and mainly tumours, providing the highest dose of the therapeutic agent directly and with precision where it is needed, in our case to the cancer stem cell that causes metastasis. This

will reduce waste and cost due to breakdown prior to the drug binding to its target.

Nanomedicine is a relatively new area of biotechnology, but the possibilities for novel therapies to treat advanced and metastatic cancers seems endless, as you can see from my novel anticancer therapies using nanoparticles, as included in the appendices.

I was the innovator of this novel nanotechnology-based anticancer therapy, targeting cancer stem cells that cause metastasis. This work is of importance for the future of nanomedicine because currently there are no approved nanotechnology-based drugs or therapies on the market. Thus, I have learned to design, manufacture and manipulate biocompatible nanomaterials with a molecular understanding of tumour cell function and disease development. This way I can target cancerous tissue for transporting drugs into tumour cells to induce apoptosis. The main thing is that I prepare them with biocompatible phospholipid molecules that are not immunogenic, and intracellularly they are biodegradable.

Nanomaterials are of great value in oncology and other medical applications because they improve the efficacy of cancer treatment tremendously. With the design and use of nanosomes I have managed to reduce adverse side effects of chemotherapy, overcome biological barriers such as the blood–brain barrier, and circumvent chemoresistant mechanisms, thus enhancing the therapeutic index of anticancer agents and reducing systemic toxicity.

I always use drug delivery systems in my novel anticancer therapies, because they concentrate the therapeutic molecules in cancerous tissue and significantly reduce the collateral damage caused by chemotherapy. Another driver is the low solubility of many anticancer agents that prevents their formulation as drugs. I also have extended the life cycle of an anticancer agent by using reformulation. Furthermore, I have managed to make these nanoparticle drug delivery systems (NDDS) cost effective. My main concern is to deliver the right drugs with nanosomes to the right cancer patients, under a personalized medicine approach using molecular targeting.

Public impact:

The impact of nanomedicine will revolutionize health. The following is a summary; for a fuller account, see Appendix 4. Nanomedicine will improve healthcare in future. It is taking place now and in conjunction with the personalized treatment –omics approach it poses the most major challenge yet to the Big Pharma ‘blockbuster’ policy. The Big Pharma do not possess the know-how to produce products based on nanomedicine and must rely on merging with biotech companies or buying patents related to nanomedicine. Either way, the group has no control over this technology, and it can prove to be extremely costly. Novel nanotechnology-based therapy will introduce a new market segment that will be established by focusing on a

more individualized or personalized medicine using tailored molecular targeting that will be developed, and marketed, by medium-sized pharma companies. Nanotechnology can add new functionality to anticancer agents, making them more competitive. For instance, nanosomes can inhibit chemoresistance by circumventing P-gp (MDR-1) polymorphism C3435T, especially in West Africans and African Americans characterized by overexpression of this multiple drug resistance gene, according to an article published in *The Lancet*.⁵⁷ Furthermore, they can enhance therapeutic index of entrapped drugs and reduce their systemic toxicity. This is the reason that drug delivery systems currently represent the largest market in the pharmaceutical industry. There are no general scientific hurdles that block nanomedicine products, such as nanoenabled drugs that, combined with pharmacogenomics, could change disease costs.

Commercialization of these products depends upon external factors such as the availability of capital, technology transfer management by universities, regulatory issues, and the IP landscape. These are complex and fragmented aspects because nanosomes studies have a multidisciplinary nature consisting of physics, chemistry, and biology that makes categorization difficult. The commercialization of nanoenabled drugs needs companies to finance clinical trials for novel drugs and provide the distribution network. However, these products are associated with personalized medicine mediated by molecular targeting. These mean fewer failures, cheaper clinical programs and potentially cheaper drugs, leading to more affordable, high-quality cancer care. Nanotechnology in oncology is seen as an area in which there is significant potential for delivering health gain.

Reflections:

I started to write this as a scientist, describing accurately the scientific process of arriving at this innovation. I then wrote about my role in it. But when it came to public impact and potential for the future, I found I could not stop writing. I wrote so much I have had to put a large section in the Appendices. This reflects who I am. I am determined, I am angry, I am passionate and energetic, and fundamentally I am an optimist. I could not have done what I have done without that attitude to life. This optimism is built on the shoulders of the peoples of our recent past who sacrificed so much, so that my generation could be free. I have no hesitation in sacrificing things in my life so the next generation will benefit and to derive satisfaction at the same time, something our war generations could not do as the loss of life had been so great.

This wonderful coalescence of different science disciplines is resulting in new ways of thinking and doing things in the world. It fundamentally challenges this insidious movement towards the wealthy of access to medicine and appropriate life saving treatments. It also

moves us closer to cures, rather than profiting by inhibiting cures by promoting symptom management. This coalescence has become a constant inspiration to me to, in a sense, to mimic it. I can be a vehicle for achieving a similar coalescence of practitioners from the many different areas of cancer medicine and delivery. We can work together to change the policies, perceptions and misinformation that are standing in the way of the progress of our science. The Big Pharma can resist individuals working alone or in niche groups, it can marginalize them; but it cannot resist a huge groundswell of scientifically and strategically informed agendas that place human life and values such as social responsibility at the core of its activity.

5. From Reflection to Action

I have said at the outset that this doctoral journey has to be more than a critique of my work. It has to be a critique that has purpose. I have hoped that through this critical journey I can become a more informed and more effective advocate in my field of translational cancer medicine. I am aware that I am regarded as passionate and, some would say, even obsessive. Passion needs to be harnessed by objectivity achieved through evidence and insight for holding particular views and challenging the dualistic thinking of good and evil, which is seductive but intellectually lazy. In my busy life in pursuit of bringing laboratory research to the clinic, I have been in the past been seduced into such thinking, but this journey has helped me take a step back, and may make me more effective rather than less.

Recently there has been the case of reviving the old tricyclic anti depressant clomipramine (Parker & Pilkington, 2006) with laboratory evidence and anecdotal evidence to support its efficacy in killing brain tumour cells. Brain tumours pose the greatest challenge to researchers and clinicians as so many treatments cannot cross the brain barrier and debulking of the tumour can cause disabilities.

In the last year I have been working on a delivery system that can pass through the brain barrier and my work is about to be published next year as a part of a book involving epigenetic cancer medicine. The researchers and clinicians involved⁵⁸ have been unable to get funding from the Big Pharma, because the drug is already very cheap and available. Clinical trials will now be funded by an independent brain tumour trust. A year ago I would have been angry and seen this as just another example of the Big Pharma controlling everything. Now I can step back and look at how we can encourage more private and charity funding of independent research, as in the case of DCA⁵⁹ that is funded entirely by the public and directly to the researchers in the United States and how cancer specialists can be brought more closely together, not only through congresses but through an association. In 2011, I received judicial approval for inaugurating the activities of the Hellenic and International Society of Molecular and Genomic Medicine that now has more than a hundred subscribed members, so that we can not only share knowledge and agree on a strategy for the acceleration of individualized treatments, but be able to present united and rigorously examined areas of research to be presented to independent funding bodies. It will be officially launched at its first conference in October 2012.

More Effective Advocacy for personalized cancer medicine (PCM)

Good and Evil?

Personalized cancer medicine targeted with pharmacogenomics and pharmaco-epigenetics has been established by cancer researchers and translational medicine practitioners with resistance from the Big Pharma. This resistance is mostly manifested in the refusal of funding and in the practice of conditional funding in which every discovery is patented to the Big Pharma. The way that supporters have counteracted this resistance has been through public sharing of medical knowledge through congresses where a number of figures, including myself, act to change the attitudes and stimulate positive action to advance the progress of discoveries from laboratory to clinic.

When you are part of this oncology world, as in all sub-cultures one is privy to knowledge that may enrage you. When related to outsiders, they could be forgiven for believing one is suffering from some form of paranoia. For example, there are things that happen at all levels of a university's infrastructure that would not be believed. The same is true for anybody in government departments, mental health hospitals or banks. Therefore, it will be no surprise to me if readers construe some of what I say as a touch paranoid.

The Big Pharma's 'race for cancer cure' could be seen as a major sociomedical misrepresentation, because its administrators establish cancer non-profit groups but put their own executives on their administration boards. It is therefore difficult to assess whether all decisions by these cancer non-profit groups are independent of the interests and direction of the Big Pharma or whether such groups are inadvertently subsidizing Big Pharma lobbying and drug campaigns and whether their research efforts are not fully accountable. Such groups depend upon donations by ordinary citizens who deeply believe that all their donations are being used responsibly to find cures for the various cancers that have often affected members of their own families or friends. For instance, take the non-profit American Cancer Society:

http://www.tbyil.com/ACS_Problems_Part3.htm

<http://www.articlesbase.com/cancer-articles/asbestos-mesothelioma-the-questionable-ethics-of-the-american-cancer-society-do-you-trust-them-2126581.html>

<http://www.chelationtherapyonline.com/PreventCancer/index.html>

This organization has millions of dollars in cash, a fleet of luxury cars, multimillion-dollar real estate and many hundreds of millions of dollars in other assets, while its CEO has an annual salary of about a million USDs. The Big Pharma publicity indicates that the only obstacle to a cure is money. It is left to extraordinary individuals suffering from cancer like David Schreiber

(who recently lost his fight against brain cancer) to spread the word about prevention of cancer through books like his best-selling *Anticancer* (http://en.wikipedia.org/wiki/David_Servan-Schreiber).

Unfortunately, cancer has been transformed by the Big Pharma into a market-driven industry that has a high yield for corporate sponsors, instead of financially supporting independent research groups to find innovative strategies for treating cancer. I myself would have no issue with the Big Pharma if it devoted much more funding to the development of beneficial molecular targeting therapeutic approaches on a personalized basis, using epigenetic and genetic treatments establishing circumvention of chemo/radioresistant mechanisms, supporting clinical delivery training and guaranteeing that these treatments will be available at reasonable prices. However, due to a lack of investment, these PMA approaches are currently specialized knowledge that the Big Pharma does not possess. The group has recently been trying to fuse or purchase biotech companies to address that deficit.

Another success for the Big Pharma monopoly of cancer is their influence on legislation. It is now illegal to claim anticancer effects by nutritional therapies, medicinal herbs, chemical detoxification, and so on. For instance, alternative cancer clinics have been made illegal in Western countries, including the United States, where federal criminal law with imprisonment applies to these cases. The reasons given are to protect the public from exploitation. Thus, everything that is not controlled by conventional cancer medicine is discredited as quackery, dictating that conventional doctors disregard all supporting scientific evidence of PMA that could show the 'blockbuster' drug policy of the Big Pharma as inefficient and dangerous. Cancer patients receiving chemotherapy are required to avoid antioxidant nutraceuticals on the grounds that they interfere with the drug treatments, while in reality they protect normal cells from the chemotherapeutic systemic toxicity that may cause immunosuppression, heart failure, brain, liver and kidney damage and even secondary tumours. In these circumstances one might be forgiven for thinking that conventional 'blockbuster' cancer medicine does not aim to eradicate tumours, but to convert cancer into a chronic disease dependent on drugs that suppress only the symptoms of cancer and never the disease itself.

In nothing we do in the congresses and through no strategy developed in our association or publications do I want to contribute to repeating the approach of the Big Pharma, not least in failing to educate the public in what is possible and what could be available through PMA based on -omics, which might actually eradicate tumours. There is no excuse for keeping people in ignorance, particularly in today's global village. It is very hard to censor all information in a modern environment, but there are forms of censoring knowledge such as buying up patents and therefore preventing their development or, most importantly, the timing of their development. To a small team or an individual researcher, the cost to patent findings these days is financially prohibitive.

Cancer cure is the holy grail of medicine. I ask myself often if that is what drives me, to be that person or one of those people that 'finds' the cure. I firmly believe that no single person will do this, but that the future is in prevention and eradication brought about by individuals and teams openly sharing knowledge. I have saved people through my work and lost people. It is a humbling experience and at my age I want to contribute to the creating of conditions that will support a new way of thinking and save more lives. I regret every day the lives of those lost under my care and I am fully aware that it is at those times easier to blame something like the Big Pharma than myself or the randomness of life.

But I also believe, and have and can evidence, the substantial obstacles the Big Pharma impose and the powerful monopoly they have in this arena. This prevents a new paradigm that can be objectively assessed as more efficient, fairer, sustainable and visionary than what we have now. At the moment the patient has no choice but to follow conventional treatment. To oncology scientists, that is like cutting off a leg without anaesthetic when we know anaesthetic will work yet is not allowed, while the patient does not even know it exists. It is like condemning a person to a wheelchair when there are amazing prosthetics, yet the company who makes them has set the price too high, or well-publicized incidents even within conventional cancer treatments when a patient is denied a treatment because it is too expensive yet the clinicians know it will prolong life. If a cancer cure was actually discovered, the cancer 'blockbuster' policy of the Big Pharma would no longer be the second most profitable industry after the petroleum industry. The majority of cancer patients die from permanent organ damage caused by conventional chemotherapy (<http://realhealthtalk.com/chemotherapy.html>). I make no apologies as an insider for my anger.

The future

One of the biggest challenges for the health sector in the twenty-first century will be to develop personalized therapeutic agents specifically tailored to individual cancer patient's biology and pathophysiology. This change from the 'blockbuster' cancer medicine (BCM) to personalized cancer medicine (PCM), initiated by cancer researchers like myself globally during the last decade of the twentieth century, will influence the development, marketing and prescription of advanced cancer drugs such as epigenetic inhibitors that can be delivered on an individualized basis with nanotechnology. These changes could lead to major changes in cancer treatment, such as the stratification of cancer patients into biological subgroups with the utilization of pharmacoepigenomics and pharmacogenomics, leading to the development of tailor-made personalized treatments for individual cancer patients. It would involve the molecular targeting that has been established and presented in oncology congresses by cancer researchers.

However, the materialization of personal cancer medicine practice requires the support of advocacy groups to influence political decision makers. Thus, advocacy strategies for being productive and efficient must focus on a well-conceived advocacy plan for the successful monitoring, implementation and evaluation of this change in cancer control policy. Advocacy efforts must aim to activate social mobilization through the media and support coalition building for a sustained fight against the resistance of the current paradigm. Public assistance, including groups and organizations, can influence national and international leaders who, in turn, can exert pressure on ministries of health and local authorities to adopt new comprehensive cancer control policies or programmes.

Yet it is up to cancer researchers like myself to prove with publications and lectures at international oncology congresses the superior medical advantages of the new personalized approach against cancer compared to the old one. This way, the advocacy groups can use the medical evidence to engage the support of regulatory authorities in establishing this new era of cancer control policy. Thus advocacy groups can put cancer control knowledge into action by turning authorities such as health ministries into advocates for influencing other regulatory bodies and planners.

The establishment of a successful and effective advocacy action requires devotion and the commitment of a great deal of time, however. Knowledge provided by health experts such as cancer researchers will define the current cancer situation by analysing in great depth the scientific barriers and opportunities of cancer control; professional advocacy skills are needed for careful planning and productive collaboration to achieve a sustained strategy. Pie in the sky? A dream too far? As the anthropologist Margaret Mead⁶⁰ said, even a small group of thoughtful, committed citizens can change the world, especially when their advocacy strategies are carefully tailored to the cultural, social, economic and political milieu.

Dr Martin Luther King⁶¹ said that ‘radical and breakthrough change towards social benefit does not roll in on the wheels of inevitability but comes through continuous and painstaking struggle against all fronts.’ The fact is that this new paradigm of personalized cancer medicine has unfortunately to pass through three stages, according to German philosopher Arthur Schopenhauer (1788–1860). He said that ‘all truth passes three stages: First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as self-evident.’

<http://paganpressbooks.com/jpl/DEFENCE.HTM>
<http://plato.stanford.edu/entries/schopenhauer/>

As Clarence Darrow (1857–1938) said, ‘I will chase after the truth like all hell and I will free myself, even though I never touch its coat-tails’ (<http://www.informationphysics.com/truth>).

International bodies and effecting change

The guide for effective programmes of cancer control focusing on policy and advocacy published by WHO at the end of 2008 has clearly identified barriers to and opportunities for comprehensive cancer control and advocacy that must be considered in the planning of advocacy strategies in order to establish a personalized cancer policy. The barriers that must be circumvented include lack of political will and leadership for developing cancer control under a public health approach that could be influenced by the Big Pharma and the reliance on symptom control over effective treatment approaches, prevention and early detection. Social barriers that must be circumvented include cultural taboos or myths, stigma, religious attitudes to cancer and limited understanding or poor need for cancer advocacy and mainly lack of advocacy skills. Only if we achieve the implementation of the six basic components of cancer control: prevention, early detection, diagnosis, treatment, survivorship and palliative care, can we circumvent and cure most of the cancers that currently kill approximately ten million people per year.

I want to emphasize how important is advocacy support in improving the new challenge of cancer survivorship care, because currently there are many deficits in cancer care: patients become long-term survivors. According to the Continuing Medical Education (CME) course at Harvard Medical School on Cancer Survivorship Care, there are four essential components that should be improved. They include prevention of recurrent or new cancers plus other late effects derived from cancer; organized and effective coordination of oncology specialists and primary care providers; intervention for cancer control and its sequelae; surveillance of cancer and effective assessment of medical and psychosocial late effects (Rowland et al., 2006; Hewitt et al., 2006). This oncology challenge of cancer survivorship, up to now was quite unexplored and underestimated, covers the period of time from the onset of cancer diagnosis through the remainder of one's lifespan. More narrowly, it covers the period of time after the current forms of cancer treatment that can leave people more disabled than they were before diagnosis, exposing them to long-term complications such as chemobrain, vital organ dysfunction due to irreversible damage, functional disorders and potentially lethal secondary tumours (Horning, 2008; Gilbert, 2008). Thus, cancer survivors of current conventional chemotherapeutic agents face potentially disabling physical, mental and social complications. All would be improved or circumvented by the introduction of the personalized cancer medicine (PCM) approach that can be facilitated by strong advocacy action.

Generally, for implementing improvement of the six basic components of cancer control, we must educate policy makers and programme managers on how to advocate, plan and implement efficient programmes that are able to control cancer and reduce its incidence,

mortality or morbidity, and improve the quality of life for cancer patients, especially in late stage IV. This needs to be done by establishing a systematic implementation of evidence-based interventions for the five basic components of cancer that apply to my selected works for the DProf. So what I have done now and will carry into the future is:

1. I will go on researching into cancer and safe and effective modes of delivery
2. I will launch the Hellenic Association this year and work with my colleagues to bring about change based on good science, ethics and values which support social responsibility. This association will:
 - a. form a powerful lobby group on policy
 - b. educate the media
 - c. produce collaborative papers
 - d. advocate for social responsibility and all medical practitioners to subscribe to the equivalent of the Hippocratic oath.

There is strength in numbers. We have been fighting and been marginalized as individuals for years. I have myself have gone from being an idealist to being a realist. I have gone from revolutionary to pragmatist.

The most important thing I have learned by going through this laboratory to clinic process was to be sound in knowledge, patient and diplomatic. What I have learned going through this doctoral process is how to be more effective, more persuasive and less dualistic in my thinking, that is, we are good and they are bad. I have found a way to gather the independents together for a unified voice and to form stronger lobbying. I needed to bring cancer researchers and translational practitioners into some organization or body that will give their work prominence and recognition. This is not about making money, but doing what may seem old fashioned – doing what is right.

My own learning edge – the art of translation

It is easy to say what needs to be done and what I will do. I have the skills to do some of this, but my learning edge is in knowing how to communicate effectively with different stakeholders, particularly those who are outside my normal domain of practice, the general public, advocacy groups and the media. I need to find out how to manage communication more effectively with those I have seen until now as obstacles that need to be circumvented like those doctors who work for the Big Pharma and whom I have termed chemotherapists. In this sense, my journey in translational medicine is in its early stages, but I have been taking rewarding steps in the right direction and can see how effective this is. For example,

as a cancer researcher and translational medical practitioner I believed myself to have all the technological and scientific knowledge of importance to the patient. I never gave particular attention to the nurses who look after patients and their families, and who have the primary relationships with the patient. If I were to caricature myself it would be the scientist who walks into the room and, although I care deeply and do not want the patient to die and devote all my professional life to finding away to keep them alive, that is not what comes out of my mouth. I tend to talk the science. What has been so helpful is talking to the nurses, explaining the issues to them and listening to their advice about how to communicate that to the patient. Similarly, if a doctor at a congress challenged me, I would respond by using my knowledge almost like a weapon. In this way, a skirmish might be won but I lost the battle. Now, instead of doing that, I ask if they would like to consider joining my association or whether there is a way I can help to elucidate the science. I realize now that before this doctorate it was my lack of flexibility in communication style behind the lack of progress in getting people on my side.

If I can learn from my own scientific training, then practice is the answer. First, however, I need to become familiar with the language and communication styles of the different stakeholders who are part of this translational process from bench to clinic, defining exactly the reason for our communication, and what we should discuss at a specific time. If I can't do that, I need to have people who can. These stakeholders consist of my own field that I am already familiar with (see Introduction and the role of congresses, and whose proceedings are translated to the media) and the various governmental and non-governmental groups that impact on public opinion and with whose language I am less familiar. They include:

- a. regulatory officials
- b. government officials, parliament representatives
- c. all the professionals dealing with the healthcare
- d. patient groups
- e. external players such as the media.

I will be initiated into this process of communication very soon, as I have been invited to give a lecture in the World Antibody Drug Conjugate (ADC) taking place in San Francisco this year on 23–25 October (<http://adc-summit.com/speakers>), where all the major stakeholder groups necessary for establishing the Personalized Cancer Medicine paradigm will be present. I have come to realize that I need to have a strategy for communicating and thereby collaborating with this range of stakeholders. It will include an analysis of each group of stakeholders, their perspectives, their questions and the content that may both answer their questions and at the same time offer them a little more to think about.

The challenge, of course, in establishing an effective communication strategy for each group is to distinguish the main characteristic differences between them. From an intensive Internet search I have found the following considerations that apply to different stakeholder groups. They have been written by Suzane McDonald from Ireland and Ann-Elisabeth Hammer from Norway (http://www.hma.eu/fileadmin/dateien/HMA_joint/02-_HMA_Topics/02-HMA_Strategy_Paper/Index/Section_III_01_Stakeholders.pdf). I have modified them to the particular context of my drive to establish a new paradigm in how we respond to cancer. Common to all is to do what we say and say what we do.

- a. communicating with cancer patient groups and the general public requires consideration of timing (eg in relation to events in the media, government policies, etc), appropriate language, clarity, being concise, non-sensational, non-trivial, relevance to audience, actions very clearly defined and feasible and contacts provided.
- b. communicating effectively with healthcare professionals involves considering the role of each professional, their concerns and contexts in which they have to operate as they will have their own cultures, timely access, clear recommendations for action, a clear understanding of what is feasible, collaboration opportunities and contacts provided.
- c. communicating with peers internally requires establishing confidentiality, pre-action discussion with relevant colleagues, clear understanding of the vision and purpose, a persistent and consistent message and circulation or notification of medical information.
- d. communicating with regulatory officials requires having confidentiality assured, thorough knowledge of regulation and why it is the way it is, evidence-based recommendations, persuasive argument,
- e. communicating with government officials for political action requires accurate information, meaningful language and contextual/background information and economic advantages.

I also have to improve my communicative skills to establish effective media relations, which is an extremely important issue. Handling this requires sensitivity to and understanding of the social and political aspects of public health and how words can be taken out of context.

If any government is to take action to make novel treatments more accessible to the public, then it is public pressure that can make it happen. This requires us as the scientists to ensure effective information and collaborative communication to shift them towards the new paradigm that aims to protect public health. A major step is the engendering of trust through the association's being independent, not for profit, transparent and thorough in its research

and having at its core the principle of social responsibility. If we are to establish confidence and trust between society and our association that may lead to strong advocacy action for the benefit of public health, we have to get our message across effectively. As Aristotle (384–322 BC), Plato's student and teacher of Alexander the Great, said: 'if communication is to change behavior, it must be grounded in the desires and interests of the receivers'. We are helped in this by the Internet and its use in disseminating accurately and quickly medical information-sharing across all the stakeholder groups, leading to the appropriate decision-making required for the establishment of personalized cancer medicine.

The art of translation in teaching

I have recently been engaged to design and deliver Masters in translational medicine and in pharmacogenomics and pharmacoepigenetics. I can teach the science but I can become more skilled in teaching what 'translational' means and the skills of negotiation with different stakeholders. To help in this I want to explore taking a PG Higher Education teaching certificate if I am to be successful in persuading future doctors to challenge dominant paradigms and the Big pharma from a position of knowledge of the complexities as well as the specifics.

To more effectively communicate with the advocacy groups and with the media, I need to find a way to translate the complex into the simple in the way that distillation is simple which is not the same as simplistic which I now realize is patronizing. For this reason I think that our new association will need to look at guest speakers and co authors who are experts in lobbying, public relations, public health to better support the shifts for many of us from cancer research to translational medicine which is a relatively new discipline. I need to find associates and people I know in the press to help me with my presentation skills. When I am in my comfort zone which is populated with science and scientists I can face people head on and draw confidence from my subject knowledge. When I am not in my comfort zone and faced with people who do not know my field but whose lives, or the lives of their relatives depend on them understanding what I am saying, I lack confidence and fall back into the science which is not helpful.

I have never been asked to give an account of my work other than in the scientific sense and neither have I ever been asked to give an account of myself. I found it challenging and turned to philosophy to help me to begin to position my thinking, emotions and behaviours, as philosophy is close to science. But now I see philosophy as cognitive and a necessary step for someone like me to begin to cross that more difficult bridge of relating. In my experience with the nurses, I saw that relating for me has to have a purpose, an outcome. In talking further with them, the impact of my science was more effective through them being

translators or helping me to translate. I do not think I am going to make some giant leap or have an epiphany that will transform me into some highly relational being. I believe it will be through a process of collaboration, having more conversations and less didactic encounters, recognizing that extensive knowledge of a discipline does not make you superior, especially if you cannot communicate it effectively to achieve a successful translation from bench to clinic. If cancer researchers like me want to be successful translational practitioners, we need to learn the art of translation and be guided by those who have mastery in such skills.

Hippocrates was an able translator and distilled from his extensive learning a simple oath that everyone can understand. It is my aim to encourage all health practitioners in cancer-related practice to study this oath and undertake it, and for members of our new association to build on it together, as translational practitioners of the future.

I swear... that I will fulfill according to my ability and judgment this oath and this covenant:

To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and if he is in need of money to give him a share of mine, and to regard his offspring as equal to my brothers in male lineage and to teach them this art – if they desire to learn it – without fee and covenant; to give a share of precepts and oral instruction and all the other learning to my sons and to the sons of him who has instructed me and to pupils who have signed the covenant and have taken the oath according to medical law, but to no one else.

I will apply dietic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice.

I will neither give a deadly drug to anybody if asked for it, nor will I make a suggestion to this effect. In purity and holiness I will guard my life and my art.

I will not use the knife, not even on sufferers from stone, but will withdraw in favor of such men as are engaged in this work.

Whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relations with both female and male persons, be they free or slaves.

What I may see or hear in the course of treatment or even outside of the treatment in regard to the life of men, which on no account one must spread abroad, I will keep myself holding such things shameful to be spoken about.

If I fulfill this oath and do not violate it, may it be granted to me to enjoy life and art, being honoured with fame among all men for all time to come; if I transgress it and swear falsely, may the opposite of all this be my lot.⁶²

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APPENDIX 1 PUBLIC WORK SUMMARIES

1A] SCIENTIFIC MECHANISM OF PUBLIC WORK 1

This novel therapeutic strategy constitutes a cornerstone in cancer research, because my novel chemoradioimmunotherapeutic approach developed as a personalized cancer medicine approach consisting of chemotherapy, radiation therapy and immunotherapy in one. The chemotherapy component consisted of cytostatic vinorelbine tartrate, used in the treatment of breast and other cancers, the radiotherapy component was provided through the addition of high-energy radioisotopes, while the immunotherapy aspect was achieved by attaching scFv antibody specific to HER2/neu oncogene onto radioisotopes as well as through the inclusion of a separate 21-nucleotide double stranded siRNA generated against hypermethylating gene DNMT1 that constituted the genetically based antisense treatment.

The main problem of advanced and metastatic breast cancer is chemoresistance and radioresistance caused by hypermethylation of CpG islands due to upregulated genes such as DNMT1 that inactivate tumour suppressor genes responsible for induction of apoptosis. In just 24 hours after treatment the novel treatment regime achieved effective targeting of the tumour cells by blocking the genetic mechanisms that protect the tumour cells from conventional treatment, thus allowing the chemotherapy and radiation therapy components to exert their cytostatic and cytotoxic effects. This led to activation of caspases 3 and 9 that induced the irreversible D2 stage of apoptosis, with a subsequent bystander killing effect leading to the eradication of tumour cells, according to transmission electron microscopy results (TEM). This effect is caused when apoptotic bodies are phagocytosed by adjacent tumour cells.

Several diagnostic tests were employed as a pharmacogenomic approach for determining the genetic basis for the observed success of the molecularly targeted multimodality treatment. This targets multiple pathways in the tumour cells, including the downstream signalling pathways. These tests tailored the molecular targeting approach against oncogenes essential to the propagation and perpetuation of the tumour cells. Since cancer is a complex disease, it needs to be attacked on many fronts. Thus, my multimodal treatment worked synergistically against tumour cells by downregulating oncogene HER2/neu as a consequence of the antagonizing action of antiHER2-scFv antibody by re-expressing the apoptotic tumour suppressor gene BRCA1 as a consequence of the inhibition of the DNMT1 mRNA, and finally by breaking the DNA strand of tumour cells irreversibly leading to induction of type-I programmed cell death (PCD) or apoptosis. This combined treatment has proved that, if we target resistant to treatment mechanisms such as antiapoptotic oncogenes and re-express silenced tumour suppressor genes by inhibiting methylation of the CpG islands with genetically based antisense treatment against methylating genes, we can allow chemotherapy to exert its cytotoxic and/or cytostatic action eradicating advanced and even metastatic tumour cells which are characterized by extreme heterogeneity. Downregulation of oncogenes such as HER2/neu might inhibit the dominant oncogene effect that depends on a complex system of downstream signalling pathways.

Furthermore, administration of radiation by linking the radioisotopes to the anti-HER2 antibody proved to be much more efficient than conventional external beam radiotherapy, because the radiation is targeted specifically on those breast cancer cells that overexpress HER2/neu and leave normal cells unaffected, thereby reducing systemic toxicity. This, in synergy with the improved therapeutic index of the chemotherapeutic agent, inhibited DNA synthesis and metabolic activity, leading to eradication of tumour cells. These results opened up the possibility of challenging and circumventing the policy of the Big Pharma by combining targeted immunotherapy with chemotherapy and radiation therapy for the

successful eradication of resistant to treatment tumour cells under a stratified or personalized cancer medicine approach.

I have applied this approach to other types of cancer characterized by hypermethylation of tumour suppressor genes and overexpression of dominant oncogenes such as HER2/neu and bcl-2 that activate antiapoptotic downstream signalling pathways. For instance, the same treatment with combined antisense gene treatment achieved the eradication of radio- and chemoresistant metastatic non-small cell lung carcinoma (NSCLC), which is a currently incurable and lethal tumour, proving once more that under a personalized cancer medicine approach chemoresistant mechanisms can be circumvented, allowing conventional chemotherapeutic agents to exert their cytostatic or cytotoxic actions inducing apoptosis. In contrast, the 'one size fits all' approach of the Big Pharma exerts the opposite effect in cancer treatment.

1B] SCIENTIFIC MECHANISM OF PUBLIC WORK 2

My novel treatment of Public Work 1 aims to circumvent chemoresistance after its mechanisms have been detected with the use of pharmacogenetics, enabling me to use the appropriate molecular targeting strategy under a personalized cancer medicine approach. This leads to the eradication of tumour cells by induction of Programmed Cell Death, after elimination of the oncogenic antiapoptotic downstream signalling pathways that were activated by the phenomenon of oncogene addiction. This Work includes a novel drug delivery system based on nanomedicine which, with the proper composition of high Tc phospholipids and Chol, has protected the therapeutic molecules from biological milieu interactions such as opsonin adsorption that might lead to RES elimination. This results in the enhancement of therapeutic index and reduction of systemic toxicity. The novel genetic-based therapeutic antisense agent (anti-eIF3c shRNA) has enabled the chemotherapeutic agent vinorelbine tartrate to exert its cytostatic action by circumventing antiapoptotic mechanisms such as oncogene bcl-2, which was phosphorylated, leading to the upregulation of tumour suppressor gene beclin-1 that led to autophagy. Other anticancer effects observed were anoikis and necrosis. Finally, the induction of irreversible D2 stage of apoptosis led to a bystander killing effect, eradicating the chemoresistant tumour cells of hormone refractory breast cancer. My work suggests that, although no single drug is likely to eradicate cancer, combinations of tailored therapeutic agents that target specific multiple sites in the oncogenic biochemical pathway signalling cascade may induce apoptosis even in chemoresistant tumour cells. Furthermore, the therapeutic index may be improved with the use of drug delivery systems such as colloidal nanoparticles that can mediate molecular targeting.

1C] SCIENTIFIC MECHANISM OF PUBLIC WORK 3

This therapeutic genetic vaccine against HPV 16(+) derived cancers is the only one that has ever existed in medical oncology. Its therapeutic significance is great because it is independent from chemoresistant and radioresistant mechanisms. HPV is the most common sexually transmitted infection in the world. HPV type-16 can cause cervical and oropharyngeal squamous cell cancers (OSCC), such as soft palate, tonsillar and tongue cancers that rise rapidly, with an overall five-year survival of about 25 per cent. Other tumour types that HPV 16 causes include anal, vaginal, vulval, and penile cancer. To date, none of the vaccines actually treat cancer. Those used today are only preventive vaccines, fighting viral agents that are capable of causing cancer. This therapeutic cancer vaccine is an emerging experimental type of treatment designed to stimulate the humoral and cellular immune systems that are the body's natural defences for finding and fighting cancer cells. It can be combined with other cancer treatments including chemotherapy, radiation, surgery, anti-angiogenesis drugs, and so on. This therapeutic vaccine targets certain molecules such

as antigens on the surface of tumour cells, and they are never expressed by healthy cells. Thus, this therapy circumvents systemic toxicity. For the development of this novel therapeutic vaccine, which is one of a kind, I have developed a cytomegalovirus (CMV) replicon system (CRPs) for the efficient delivery of the HPV16 recombinantly mutated E6 and E7 genes replacing part of the CMV genome for the HPV genes that were genetically altered to block binding sites for tumour suppressor gene p53 and oncogene Rb. The replicon vectors infected and co-transfected cervical intraepithelial neoplasia (CIN), and cervical cancer cells derived from HPV16 (+) tumours. After vaccination with a needle-less injection system, the viral E6 oncogene did not degrade apoptotic p53 and it blocked activation of telomerase. This induced type-I PCD or apoptosis and DNA repair in CIN and cervical cancer cells. It led to scheduled cell cycle entry, genetic stability and mortalization of tumour cells. Cellular and humoral immune responses were exhibited that led to irreversible D2 apoptotic stage of apoptosis or type-I PCD, leading to a bystander killing effect of intraepithelial neoplasia and cervical cancer cells. BrdU and MTT analysis exhibited inhibition of DNA synthesis and metabolic activity of vaccinated tumour cells compared to controls. This genetic vaccine coding for E6 and E7 mutations designed to prevent p53 and Rb binding sites activated humoral and cellular immune responses, leading to eradication of cervical intraepithelial neoplasia (CIN2, CIN3) and cervical cancer cells via induction of irreversible D2 apoptosis that led to a bystander killing effect. This therapeutic vaccine has tremendous potential to stimulate humoral and cellular immunity against HPV16 (+)-derived tumours.

1D] SCIENTIFIC MECHANISM OF PUBLIC WORK 4

Nanomedicine has great potential for breakthroughs in basic, applied and clinical sciences, leading to more efficient and targeted diagnosis, treatment, and monitoring of diseases like cancer. In this novel public work I have used colloids, which are lipid-based liposome nanoparticles, and niosomes. I use high Tc phospholipids, which are combined with cholesterol, located between acyl chains for enhancing stability when the nanoparticles interact with the biological milieu. To circumvent opsonin adsorption I pegylate the surface to make it more hydrophilic. This way the nanoparticles carrying therapeutic molecules can circumvent elimination by the Reticulo-Endothelial System (RES) consisting of the macrophages (Kupffer cells) of the liver and spleen. With these nanoparticles I can target specific tumour cells characterized by chemoresistance due to overexpressed drug efflux genes such as MDR-1 that encode protein Pgp that acts as a pump by binding drug molecules on its ATPase chains. Molecular Tumor Cell Targeting (MTCT) is achieved by linking antigens or other biosensors such as RNA strands to the surface of the nanoparticles that detect specialized properties of the tumour cell walls, delivering their cargo of therapeutic molecules intracellularly by endocytosis circumventing chemoresistant efflux pumps. Only then can personalized medicine, which is molecularly targeted, be achieved for individual cancer patients by tailoring the treatment specifically to their tumour phenotypes. Once the target tumour cells have been identified, where in my therapy they are the cancer stem cells (CSCs) that overexpress CD44, and they have been activated by the chemotherapeutic agent vinorelbine, the nanoparticles that I have designed with high Tc phospholipids and pegylation for enhancing hydrophilicity that leads to the circumvention of biological milieu interactions will bind with the conjugated miR-373 onto the CD44 of tumour cells. This causes entrance of tumour cells via endocytosis, releasing the therapeutic siRNA molecules intracellularly for downregulating BMI1 and survivin inhibiting downstream signalling pathways that led to induction of type-I PCD or apoptosis (D2 irreversible stage) activating a bystander killing effect. The siRNA molecules were protected and their life was prolonged during delivery with nanoparticles, otherwise the RNA strands would be destroyed by cellular mechanisms before reaching their targets. Furthermore, the specific molecular targeting will aid the treatment of late-phase metastasized cancers and hard to reach tumours like breast and ovarian tumours. Also, nanoparticles will circumvent tumour

chemoresistance by overpassing Pgp drug efflux pump. These nanoparticles will treat only the tumour, without damaging adjacent healthy tissue. They dissolve intracellularly in the endosome, releasing their therapeutic siRNA cargo that eradicates endodyploid cancer stem cells after downregulation of Aurora-B. The bottom-up construction of these nanoparticles takes advantage of molecular self-assembly for building specific structures based on Watson-Crick DNA base-pairing for building nucleic acids of a defined structure that will be used for personalized medicine using molecular targeting. The benefits of nanoparticle delivery are extremely significant because they improve bioavailability of entrapped therapeutic molecules by targeting specific organs, tissues and mainly tumours, providing the highest dose of the therapeutic agent directly and with precision where it is needed. In our case this is to the cancer stem cell that causes metastasis, reducing waste and costs due to breakdown prior to a drug binding on its target. Nanomedicine is a relatively new area of biotechnology, but the possibilities for novel therapies to treat advanced and metastatic cancers seems endless, as you can see from my novel anticancer therapies using nanoparticles, attached.

I innovated this novel nanotechnology-based anticancer therapy for targeting cancer stem cells that cause metastasis. I repeatedly have used nanosomes for molecular targeting of nanoscale therapeutic antisense nucleic acids, DNA, proteins and chemotherapeutic molecules that can circumvent chemoresistant mechanisms, leading to the eradication of metastatic tumour cells, as you can see in Appendix 2D where I have developed novel anticancer treatments that have been accepted by the scientific committees of international congresses for presentation. This work is of huge importance to the future of nanomedicine, because currently there are no approved nanotechnology-based drugs or therapies on the market. Thus, I have learned to design, manufacture and manipulate biocompatible nanomaterials with a molecular understanding of tumour cell function and disease development. This way I can target cancerous tissue for transporting drugs into tumour cells for induction of apoptosis. The main thing is that I prepare them with biocompatible phospholipid molecules that are not immunogenic, and intracellularly they are biodegradable. Nanomaterials are of great value for oncology and other medical applications because they improve the efficacy of cancer treatment tremendously. With the design and use of nanosomes I have managed to reduce adverse side effects of chemotherapy, overcome biological barriers such as the blood–brain barrier and circumvent chemoresistant mechanisms, enhancing the therapeutic index of anticancer agents and reducing systemic toxicity. I always use drug delivery systems in my novel anticancer therapies because they transport selectively and safely the therapeutic molecules in the targeted cancerous tissue, and significantly reduce the collateral damage caused by chemotherapy. Another driver is the low solubility of many anticancer agents that prevents their formulation as drugs. I have also extended the life cycle of an anticancer agent by using reformulation. Furthermore, I have managed to make these nanoparticle drug delivery systems (NDDS) cost effective. My main concern is to deliver the right drugs with nanosomes to the right cancer patients under a personalized medicine approach using molecular targeting.

APPENDIX 2 SELECTED PAPERS AND AWARDS

2A] SELECTED PAPERS ASSOCIATED WITH PUBLIC WORK 1

I have extended the therapeutic approach of Public Work 1 in other cancers including pancreatic cancer, periampullary Ca, non-small cell carcinoma, endocrine-tumours such as anaplastic thyroid Ca. These works were presented in annual congresses of medical societies including American Society of Clinical Oncology (ASCO) as follows:

Giannios, J., Antisense chemoradioimmunotherapy consisting of anti-IGF-1/HGF bs-scFv linked onto high-energy radioisotopes and TFO targeted to DNMT1 and conjugated to vinorelbine induce ADCC, apoptosis and anoikis in metastatic NSCLC characterized by radio and chemoresistance. Meeting: 2006 Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology (ASCO).

Additional presentations include societies such as British Endocrine Societies (BES), International Society of Gastrointestinal Oncology (ISGIO), European Gynecological Society (ESGO) and many others. Furthermore, related papers were published by myself in many specialized medical journals such as the International Journal of Gastroenterology and Hepatology, The Journal of Breast Cancer Research of impact factor 5.79, etc. This work since its presentation and publication has been followed by many other researchers who have taken it to multicentral clinical trials for many cancers including pancreatic adeno Ca, periampullary Ca, B-lymphomas etc.

2B] AWARD OF PUBLIC WORK 2



2C] SELECTED PAPERS ASSOCIATED WITH PUBLIC WORK 3

Other anticancer vaccines that I have developed and presented in oncology congresses are as follows:

Multi-vaccine SEVINA Composed of Vinorelbine Apoptotic Tumour Cell Lysate (VATCL), Cationic Colloidal 25 mer ISS CpG Oligonucleotide (ODN) Adjuvant and Recombinant Chaperone GRP94/gp96+HER2 Differentiation Antigen Vaccine Induces Formation of Exosomes from APCs and Humoral Cellular Immune Responses Leading to Vaccine Induced Apoptosis (VIA) in Chemoresistant Distal Breast, Lung, Prostate and Ovarian Cancer.

This was published in the Journal of Immunotherapy: November/December 2005, 28(6), 655-656.

Abstracts: Abstracts for the 20th Annual Scientific Meeting of the International Society for Biological Therapy of Cancer: TURNING IMMUNIZATION INTO TUMOR REGRESSION: OBSTACLES AND STRATEGIES.

This work was presented in the plenary session of the ISBTC Congress in Washington DC, USA.

Effect of gene modified cellular vaccine (GMCV) composed of autologous adipose-derived mesenchymal stem cells (AADMSCs) transfected with lipid-cation Hsp70 on innate and adaptive immunity after targeting primary and metastatic breast Ca cells inducing secondary-necrosis and lethal bystander effect, while injured cells were renewed.

This work was presented in the 2009 Breast Cancer Symposium of the American Society of Clinical Oncology (ASCO).

Gene modified cellular vaccine (GMCV) composed of autologous adipose-derived mesenchymal stem cells (AAD-MSCS) transfected with lipid-cation Hsp70 activated innate and adaptive immunity after targeting metastatic pancreatic Ca cells.

Speaker/Presenting Author: John N Giannios,^{1*} Translational Cancer Medicine, Erasimio Oncology Hospital, Athens, Greece.

This work was presented at the Congress of the British Society of Gastroenterology (BSG) in 2011 as an oral presentation under the category of Neoplasia and Cancer Pathogenesis BSG11-ABS-2453.

Humoral and cellular immunity induces apoptosis in CIN2-3, HPV16+ cervical Ca after genetic vaccination with CRS targeting p53 and Rb.

This work was presented in the Congress of International Gynaecological Cancer Society (IGCS) in 2010.

Gene-Modified Cellular Vaccine (GMCV) Transfected with Lipid-Cation Hsp70 Activates Innate and Adaptive Immunity in Primary and Metastatic Gastric Cancer Cells.

This work was presented as a lecture in the Annual Meeting of the International Society of Gastrointestinal Oncology (ISGIO) in USA.

Gene Modified Cellular Vaccine of Autologous Adipose-derived Mesenchymal Stem Cells transfected with lipid-cation Hsp70 activates innate and adaptive immunity in metastatic ovarian Ca.

This work was presented in the meeting of the European Society of Gynaecological Oncology where I am a founding member in Italy (2009).

Eradication of unresectable chemo/radioresistant hilar cholangiocarcinoma with gene-modified cellular vaccine (GMCV) composed of autologous adipose-derived mesenchymal stem cells (AADMSCs) which was transfected with lipid-cation Hsp70 activated innate and adaptive immunity, and induced secondary-necrosis leading to a lethal bystander effect.

This work was presented in the plenary session and received a grant award of the Annual Meeting of the International Society of Gastrointestinal Oncology (ISGIO) in 2011 in USA.

Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces PCD and ADCC in chemoresistant gastric carcinoma (GC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, TSGs, invasion/metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes.

This work was presented in the session of Cancers of the Esophagus and Stomach (Upper GI Cancer) of the 2004 Gastrointestinal Cancers Symposium (Abstract 81) of the American Society of Clinical Oncology (ASCO).

Two more works selected from the many developed by myself on immunostimulation against various incurable cancers are as follows:

Eradication of osteolytic and osteoblastic metastases of breast cancer inhibiting proliferation of tumour associated (TAEC) and bone microvascular endothelial cells (BMEC) inducing antibody dependent cellular toxicity (ADCC), antibody mediated phagocytosis, and D2 stage of PCD type-I/apoptosis.

This work was presented in the session of New Systemic Agents---New drugs and targets (includes antiangiogenics) of the 2007 Breast Cancer Symposium (Abstract No: 170) of the American Society of Clinical Oncology ASCO).

This last work is very important because it shows of how immunotherapy can act synergistically with conventional chemotherapy to circumvent antiapoptotic mechanisms, while it enhances therapeutic index minimizing systemic toxicity.

Immunochemotherapy consisting of rhuMAb HER-2/neu, docetaxel and vinorelbine eradicates aneuploid metastatic breast carcinoma (MBC) from sentinel lymph nodes (SLN) overexpressing cyclin D1, HER-2/neu and Ras via ADCC, CMC, anoikis, PCD and inhibition of angiogenesis.

This work was presented in the Sub-Category: Molecular/Ligand Targeted Therapies of Category: Biologic and Targeted Therapies of the 2002 American Society of Clinical Oncology (ASCO) Annual Meeting. Citation: Proc Am Soc Clin Oncol 21: 2002 (abstr 1913).

2D] SELECTED PAPERS ASSOCIATED WITH PUBLIC WORK 4

The novel treatment of Public Work 4 also exhibited eradicating results due to induction of D2 irreversible stage of type-I PCD or apoptosis in chemo and radioresistant cancer stem cells of advanced breast cancer, entitled: 'Effect of pegylated-nanoparticles of CDP bound to multitargeted siRNA molecules against BMI1 and survivin conjugated with miR-373 (termed as SEVIN-A), which targets CD44 overexpressing cancer stem cells (CSCs) of advanced breast cancer (ABC) on apoptosis and circumvention of chemoresistant multifactors caused by vinorelbine- tartrate.'

This work uses combined nanomedicine with antisense gene therapy to circumvent tumour igenesis induced by cancer stem cells activated by conventional chemotherapy, and was presented in the Sub-category: Novel Targets – Category: Prevention, Survivorship & Health Policy in the Meeting: 2010 Breast Cancer Symposium of the American Society of Clinical Oncology. It was reported as Abstract No: 231 in the proceedings of the congress, and it was granted an exception in accordance with ASCO's Conflict of Interest Policy because this work was self-financed, with absolutely no commercial attachments. Thus, it was designated with a caret symbol (^) in the print version.

ANTISENSE TREATMENT WITH PEGYLATED LIPOSOMAL-OVARIAN TUMOR MULTITARGETING WITH MABS AGAINST GP38, MUC1, AND TAG72 ON PEGYLATED APOPTOSIS NANODELIVERY PLATFORM OF CYLD AND RIP-1 LEADS TO NECROPTOSIS.

MULTITARGETED SIRNA AGAINST UBCH5, C-SRC, AND HSP90 COMBINED WITH BEVACIZUMAB ERADICATED HORMONE REFRACTORY BREAST CA (HRBC) BY INDUCTION OF APOPTOSIS/PCD TYPE-I

PEGYLATED-NANOPARTICLES OF CDP BOUND TO MULTITARGETED SIRNA AGAINST BMI1 AND SURVIVIN CONJUGATED WITH MIR-373 (SEVIN-A) ERADICATES METASTATIC OVARIAN CARCINOMA

IMMUNOCHEMOGENIC TREATMENT WITH STEALTH – NANOPARTICLE FORMULATION CONSISTING OF CLAMP PNA AGAINST MRNA-FOXC2, ANTI-CD44 CHIMERIC-MAB, AND TAXOTERE ERADICATED ADVANCED OVARIAN EPITHELIAL CA

LNA MODIFIED OLIGONUCLEOTIDES TARGETING MRNA-DICER IN PEGYLATED COLLOIDAL NANOPARTICLES WITH LINKED ABS AGAINST CD44 ERADICATE OVARIAN CANCER STEM CELLS (OCSCS)

ADMINISTRATION OF GENE-MODIFIED-CELLULAR-VACCINE COMPOSED OF AUTOLOGOUS-ADIPOSE-DERIVED MESENCHYMAL-STEM-CELLS TRANSFECTED WITH LIPID-CATION-HSP70 ACTIVATES INNATE AND ADAPTIVE IMMUNITY ERADICATING METASTATIC OVARIAN CA

COLLOIDAL-CDNA ENCODING RECOMBINANT PROTEINS-RMDVA COMPRISING DISINTEGRIN/CYSTEINE-RICH-DISULFIDE BOND 2RGD, AND C-TERMINAL DOMAIN, METALLOPROTEASE-DOMAIN, AND DIMERIC DISINTEGRIN/MLD-VGD DOMAIN (VADD) INDUCED APOPTOSIS IN OVARIAN CA

APPENDIX 3 Curriculum Vitae

Name: JOHN N. GIANNIOS

Translational medicine practitioner, cancer researcher, molecular oncologist and genetic counsellor

President of the Hellenic and International Society of Molecular and Genomic Medicine and Research (HISMGMR)

Editor of the official journal of the Hellenic and International Society of the Molecular and Genomic Medicine and Research

Head of the Department of Personalised Cancer Medicine, Head of Department of Translational Cancer Medicine and Cancer Research, Head of Regenerative Medicine, Erasimio Oncology Hospital, Athens, Greece

Translational Cancer Medicine Practitioner, Molecular Oncologist, Cancer Researcher and Genomic/Epigenomic Counsellor in the Dept of Clinical Oncology, General State Hospital of Athens with the Head of the Department, Dr E Michailakis

Translational Cancer Medicine Practitioner, Genetic Counselor, and Head of Cancer Research and Molecular Oncology in the Dept of Clinical Oncology of St Andreas Hospital, Patras

Translational Medicine Practitioner and Genetic Counselor in Immunology dept, Mediteraneo Hospital, Athens

Translational Medicine Practitioner and Genetic Counselor in the Dept of Gynecologic Surgery in Lito and Mitera Hospital with gynaecological surgeon Dr J Peristeris

Translational Cancer Medicine Practitioner, Molecular Oncologist, Cancer Researcher and Genetic Counsellor in the Dept of Clinical Oncology with director Dr G Samelis of Hippokration Hospital, Greece

Translational Cancer Medicine Practitioner, Molecular Oncologist, Cancer Researcher, and Genetic Counsellor in the Dept of Radiotherapeutic Oncology and Gynecologic Surgery in IASO Hospital, Athens

President of Medical Biomics, Balkan Cancer Research Center

Additional institutions:

American College of Physicians

American Society of Internal Medicine

Albert Einstein College of American College of Physicians-American Society of Internal Medicine

Albert Einstein College of Medicine

University of Alabama School of Medicine

University of Wisconsin, Madison Medical School

Jefferson Medical College

University of Kentucky Medical Center

University of Michigan Medical School

Beth Israel Medical Center

Academy Medicine of New Jersey

John Hopkins Medicine

Loyola University Chicago

Stritch School of Medicine

Mount Sinai School of Medicine

University of Arizona, Health Sciences Center

University of Iowa, College of Medicine

School of Medicine, Case Western Reserve University

Northwestern University Medical School

Penn State College of Medicine

American School of Oncology

Medical College of Wisconsin

Univ. of Rochester School of Medicine

Baylor College of Medicine

The University of Chicago, School of Medicine

Wayne State University, School of Medicine

American Academy of Family Physicians

American Society of Nuclear Medicine

American College of Chest Physicians

The University of Texas-Health Science Center at San Antonio

Accreditation Council for Continuing Medical Education (ACCME)

Seton Hall University

University of Minnesota

The University of Miami-School of Medicine

Postgraduate Institute for Medicine

Baylor College of Medicine

American Society of Critical Care Medicine

NIH/FAES

The University of Louisville, Health Sciences Center

American Pain Society

The Finch University of Health Sciences/The Chicago Medical School

American Medical Association

NEOUCOM (Northeastern Ohio Universities College of Medicine)

European Board and College of Obstetrics and Gynaecology

Degrees, Certificates, Fellowships and Memberships

Diploma in English (New York University, USA)

BSc in Chemistry and BSc in Biology, American University in Athens, Greece

Certificate in Oncology/Hematology (American College of Physicians)

Certificate with Distinction in Good Clinical Practice (UK), Postgraduate Diploma in Translational Medicine with Distinction (A3) at the Medical School of University of Edinburgh

Postgraduate Certificate in Translational Medicine with Distinction (A3) of the Medical School of the University of Edinburgh

MSc in Translational Medicine of the Medical School of University of Edinburgh. Grade 71

Completion of four years (120 credits) of Professional Pharmacy Degree in New York, School of Pharmacy (LIU)

Postgraduate Cancer Research in University of London

Completion of 78 online medical courses in Medical School of Harvard University

Founding and active member of 183 American and European Professional Oncology and Medical Societies or Associations

Completion of more than 2000 Continuing Medical Education Credits after passing exams above 75% online

Genetic Counselor creating the new guidelines of perioperative medicine genomics in the Dept of Breast Surgery, Kapodistriakon University of Athens, collaborating with Professor Zografos

Medical Awards:

First Poster Award at 3rd Annual Modern Drug Discovery and Development Summit (M3D), 28-30 November, 2007, San Francisco, CA., from Nobel Laureate F. Murad

Awards from 2000 to present at ISGIO Congresses in USA

Awards from 2002 to present at International Ovarian Ca Congresses in Seattle from the Swedish Medical Center and the University of Seattle

Certificate of Award for Ovarian Ca, National Institute of Health, 1995, USA

First research prize of the Fourth International Conference on Small Cell Lung Cancer, Ravenna, 25-26 April, 1996

Young Scientist Award of the First Balkan Congress of Oncology, Athens, 3-7 July, 1996

Best Research Prize of the First Balkan Congress of Oncology, Athens, 3-7 July, 1996

First Research Award of the 16th Annual Hellenic Gastroenterology Congress, Athens, 12-16 October, 1996

Best Cancer Research Study Award of the International Congress on Cancer Research in the year 2000, Athens, May 6-10, 1997

First Research Prize, International Laser Congress, Athens, 25-28 September, 1996

Brupbacher Young Investigator's Award, Third Scientific Symposium of Novel Approaches to Cancer Therapy, Zurich, 13-14 March, 1997

Best Cancer Research Study Award of the International Congress on Clinical Advancements of Cancer Research, Athens, 2-5 May, 1997

First Research Prize, 23th Annual Hellenic Medical Congress with International Participation, Athens, 13-17 May, 1997

Award of Highest Grading in Medical Research Study, 23th Annual Hellenic Medical Congress, Athens, 13-17 May, 1997

First Research Prize, 6th Annual Hellenic Congress of Clinical Oncology with International Participation, Athens, 3-5 April, 1997

First Research Prize, 6th International Congress of the Hellenic Society for Breast Cancer Research, Alexandroupolis, 12-15 June, 1997

Laudation for the Best Research Study of the 9th Hellenic Oncology Congress, 12-15 November, 1997

Highest Scientific Award in Breast Cancer, International Congress of IABCR and HSBCR, Thraki, 12-16 June, 1997

Lecture of Distinction in the Frontiers of Gynaecological Cancer, Figo, Copenhagen, 1997

Best Cancer Research Award, 8th International Congress on Anti-Cancer Treatment, Paris, February, 1998

First Research Award of the 18th Annual Hellenic Gastroenterology Congress, Athens, 25-28 November, 1998

Poster of Distinction selected from more than 3000 submitted by the Scientific Committee for presentation during the 7th United European Gastroenterology Congress (UEGW) Rome 1999

First Cancer Research Award of the 7th Hellenic Congress of Mastology with International Participation, Athens, 16-19 March, 2000

Selected inclusion in the prestigious registry of the 6th Edition of Marquis Who's Who in Science - The Definite Register of Outstanding Scientific Professionals

Selection as one of the 2000 Outstanding Intellectuals of the 21st Century, 2nd Edn-Honours List from the International Biographical Centre, Cambridge, England

Election as Deputy Director General of the International Biographical Centre, Cambridge, England

Honorary position on the distinguished Research Council of IBC

Invited lecturer at plenary session of the ASCO Molecular Therapeutics Symposium (Educational Program) Angiogenesis Section, 2001, chimeric antibodies targeting the SH2 domain of Grb2 and p85a of PI3-K linked on ILD induced ADCC, ADMC, complement-fixation

Reviewer of Medical Congresses for Current Drugs Ltd. Universal Award of Accomplishment, American Biographical Institute Inc, ABI, 11 October, 2002

Selection by the Board of American Biographical Institute as one of the 500 Leaders of Science for achievements during the 20th and 21st centuries, 27 September, 2002

Selection in the book of *Living Legends* edited by the International Biographical Centre, Cambridge, England, celebrating its fortieth anniversary

Award (\$1000) for the best lecture in UEGW 2002, 10th United European Gastroenterology Congress and the Annual Congress of the European Society of Gastroenterology, Swiss Society of Gastroenterology Professionals, European Association of Gastroenterology and Endoscopy, European Association for the Study of the Liver, European Pancreatic Club, European Society of Gastrointestinal Endoscopy, European Society for Paediatric gastroenterology, Hepatology and Nutrition, International Society of Digestive Surgery (European Chapter, European Society of Gastro-Intestinal and Abdominal Radiology, European Digestive Surgery, European Association for Endoscopic Surgery, European Society of Neurogastroenterology & Motility, European Society for Primary Care Gastroenterology, 'Replication-incompetent AdvCMV-Smad4, vinorelbine tartrate and docetaxel reconstitute transcriptional response of TGF- β and phosphorylate bcl-2 inducing apoptosis in chemoresistant pancreatic ductal adenocarcinoma (PDAC)'

Invitation to submit medical articles in BioMed Central

Invitation as an author of leading scientific research for BIOSIS

Fellow of the International Biographical Association, Cambridge

Invited lecturer in ASCO International Symposium in Old Quebec, 19-21 November, 2002

Invited lecturer in the 1st Interamerican Breast Cancer Conference, 25-27 July, 2002, Cancun, Mexico

Invited lecturer at plenary session of 55th Annual Cancer Symposium of the American Society of Surgical Oncology, March 14-17, 2002, Breast Cancer Session, 'Metastatic tumour growth inhibition after open surgery in patients with primary infiltrating ductal breast carcinoma (IDBC) by adenoviral transfection against VEGFmRNA'

Selection and inclusion in the book *Great Minds of the 21st Century*, by the American Biographical Institute

Invited lecturer at the Annual Congress of the American Association for the Study of Liver Diseases, American Gastroenterological Association, American Society for Gastrointestinal Endoscopy, Society for Surgery of the Alimentary Tract, 19-22 May, 2002, San Francisco, California, USA, Pancreatic Cancer: Bench to Bedside, 'Eradication of chemoresistant aneuploid pancreatic adenocarcinoma characterised by overexpression of K-Ras and hypermethylation of CpG islands of p16 (INK4a) after chemogene treatment with vinorelbine, docetaxel and recombinant adenoviral type 5 transfection'

Invited lecturer at the World Conference in Breast Cancer, Victoria, BC, Canada, Victoria Conference Centre, 4-8 June, 2002, 'Combined chemogenetic treatment of cyclinD1 antisense ORN(SV-22), vinorelbine and docetaxel eradicates by PCD chemoresistant aneuploid metastatic breast carcinoma (MBC) over-expressing Ras and HER-2/neu'

Invitation to join the Science Advisory Board, an international group of more than 10,000 life science and medical professionals, as a Scientific and Medical Expert

Invited lecturer at plenary session of the 55th Annual Cancer Symposium of the American Society of Surgical Oncology, 14-17 March, 2002, Breast Cancer Session, 'Metastatic tumour growth inhibition after open surgery in patients with primary infiltrating Ductal Breast Carcinoma (IDBC) by adenoviral transfection against VEGF mRNA, Denver, Colorado, USA

Elected member of MEG/AACR 'The molecular epidemiology working group of the American Association for Cancer Research'

Invited lecturer at 3rd Congress of Clinical Oncology, 10 Feb 2002, Greece, 'Immunochemogene treatments against solid and hematologic malignancies'. Elected Faculty Member of the Center for Biomedical Continuing Education (CBCE) accredited by the Accreditation Council for Continuing Medical Education (ACCME)

Nomination as International Scientist of the Year 2002, by the International Biographical Centre, Cambridge, England

Invited lecturer at the Breast Cancer Treatment in the 12th International Congress on Anti-Cancer Treatment, 4-7 February, 2002, 'Synergistic antiangiogenic and antitumour activity inducing ADCC, CMC, anoikis and PCD after immunochemogene treatment consisting of vinorelbine combined with pegylated colloidal complex (SEVINA) of anti EGFR Mabs and bcl-2 antisense oligonucleotides in chemoresistant metastatic breast carcinoma (MBC)

Invitation to publish my research work in BioMed Central's online journals

Invited lecturer at Congress of GI, Malignancies can be prevented and treated: from the bench to the bedside, Meeting in Israel, 17-18 January, 2002 'Eradication of chemoresistant gastrointestinal stromal tumour (GIST) cells and lymphatic/vascular endothelial cells by induction of D2 apoptotic stage leading to bystander killing effect (BKE) after treatment with rhu Mab KDR/Fik-1 (VEGFR-2) linked onto pegylated liposomal vinorelbine tartrate (PLVT)'

International Biographical Institute, UK

Invitation to International Order of Merit between 500 personalities worldwide

Selection in the International Register of Profiles, 12th edition, IBC, Cambridge

Invited lecturer at ASCO PAN Asia cancer conference (A-PACC), 21-23 September 2001, New Delhi, India, 'ILT induces ADCC, ADMC, complement-fixation, anoikis and apoptosis in chemoresistant metastatic breast carcinoma (MBC)'

Nomination to ABI's distinguished Research Board of Advisors

Honorary position seat on board International Panel of American Biographical Institute

Nomination for the United Cultural Convention's (UCC) International Peace Prize

Received the International Biographical Centre Lifetime Achievement Award from the International Biographical Centre, Cambridge, England

First Award, Annual Meeting of the International Society of Gastrointestinal Oncology, 2004, Washington, USA

First Award, Annual Meeting of the International Society of Gastrointestinal Oncology, 2005, Washington, USA

Active Involvement in Cancer Congresses:

President of the 1st Panhellenic Congress of the Hellenic and International Society of Molecular and Genomic Medicine and Research, 'From basic research to clinical practice in Melanoma, Lung Cancer, Gastrointestinal Tumors, and Breast Cancer, 12-14 October, 2012, Volos, Greece

President of Organizing Committee of International Congress on Cancer Research in 2000, Athens, 6-10 May, 1997

President of Organizing Committee of World Congress on Clinical Advancements in Cancer, Athens, 2-5 May, 1997

Invited Commentator in the Meeting of International Association for Breast Cancer Research (IABCR), Thraki, 12-16 June, 1997

President of Scientific Committee, First European Congress of Oncology (Multimodality Treatment in Malignancies), Athens, October, 1997

Member of Scientific Committee, International Congress of the Hellenic Society for Breast Cancer Research, Greece, 12-16 June, 1997

Panelist in Satellite Update on Hepatobiliary, Pancreatic and Gastric Cancer, International Conf. of Gastro-Surgical Club and WHO, Athens, 5-7 December, 1996

Invited author for Recent Results in Cancer Research Journal

Invited lecturer for the section New Frontiers in Oncology, 4th Postgraduate Course in Hepatobiliary, Pancreatic and Gastric Diseases, Athens, 5-7 December, 1996

Invited lecturer at plenary session of Frontiers in Gynaecological Cancer, Figo, Copenhagen, 1997

Invited lecturer at Novel Approaches in the Treatment of Gynaecological Cancers, 10th Seminar of Gynaecological Cancer, University of Patras, Greece, 3-5 October, 1997

Invited lecturer at plenary session of the Scientific Program of the 10th International Meeting of Gynaecological Oncology, Coimbra, 26 April-1 May, 1997

Invited lecturer at plenary session, Antioncogene Therapy of Pancreatic Cancer, 6th UEGW Birmingham, 1997

Invited lecturer at plenary session of 2nd International Congress on Lung Cancer, Greece, 9-15 November, 1996

Invited lecturer at plenary session of 7th International Congress On Anticancer Treatment, Paris, 3-6 February, 1997

Invited speaker in plenary session of International Congress on Cancer Research, Athens, 6-10 May, 1997

Invited speaker at plenary session of Clinical Advancements in Cancer Research, Athens, 2-5 May, 1997

Member of Scientific Committee of 22nd International Congress of IABCR, Athens, 25-28 September, 1998

Invited lecturer at two main plenary sessions of 22nd Congress of the International Association for Breast Cancer Research, Athens, 25-28 September, 1998

Member of Scientific Committee, 2nd Mediterranean Congress of International Diagnosis and Treatment for Thoracic Diseases, Athens, 26-30 November, 1997

Invited lecturer at two main plenary sessions of 22nd Congress of the International Association for Breast Cancer Research, Athens, 25-28 September, 1998

Member of Scientific Committee, 2nd Mediterranean Congress of International Diagnosis and Treatment for Thoracic Diseases, Athens, 26-30 November, 1997

Invited Speaker at the plenary Session of 18th Annual Congress of Panhellenic Gastroenterological Association, Athens, 26-28 November, 1998

Invited speaker at plenary session of 7th Hellenic Congress of Breast Cancer with International Participation, Athens, 16-19 March, 2000

Member of the Scientific Committee of 7th Panhellenic Congress of Breast Cancer with International Participation, Athens, 16-19 March, 2000

Invited speaker at 9th International Congress on Anticancer Treatment, Paris, February 1999

Invited speaker at 10th International Congress on Anticancer Treatment, Paris, February 2000

Invited speaker at Eurogin 2000 Congress, Global Challenge of Cervical Cancer Prevention Human Papillomavirus & Genital Ca

Invited lecturer at the Symposium on Diagnostic and Therapeutic Advancements in Oncology, Patras, 3-4 February, 2001

Invited lecturer and member of the Scientific Committee of 8th Panhellenic Congress of Breast Cancer with International Participation, Salonika, 7-10 March, 2002

Invited author, examiner and contributor for editorials in peer-review medical journals such as Clinical Lung Cancer Journal

Tumour Targeting, EJC, Archives of Hellenic Medicine, Gene Therapy & Immunotherapy, European Journal of Gynaecological Oncology, etc

Invited author for Recent Results in Cancer Research Journal

Lecturer at plenary session of the 5th International Conference on Head and Neck Cancer, San Francisco, 29 July-2 August, 2000

Lecturer at plenary session of XXXII World Congress of the International College of Surgeons, 8-12 October, 2000, Singapore

Lecturer at plenary session of 1st Multidisciplinary Colorectal Cancer Congress, 17-20 April 2001, Netherlands

Lecturer at plenary session of 11th International Congress on AntiCancer Treatment, Paris, February 2000

Lecturer at plenary session of ESSO 2000-FECS Conference, Brussels, Belgium

Invited lecturer and member of Scientific Committee, 8th Panhellenic Congress of Mastology with International Participation, 7-10 March 2002, Thessaloniki

Invited lecturer and coordinator of Round Table of Genetics in Breast Cancer, 1st Congress of the World Society for Breast Health, 22-26 September, 2001, Istanbul, Turkey

Lecturer in the Annual Meeting of the American Society of Surgical Oncology

Award candidate and published work in the Annals of Surgical Oncology, 14-17 March, 2002, Denver, USA

Invited teaching lecturer in Oncology Congress of Clinical and Molecular Foundations in the Prognosis and Therapy of Lung Cancer, Patras, 2001

President of Frontiers of Novel Targets in Molecular Oncology, UICC, 2004

Fellow of Research Council of International Biographical Centre, Cambridge

Induction in the American Hall of Fame, 19 December, 2003, American Biographical Institute

Member of International Who's Who of Professionals, 20 February, 2004

Advisor to the Research Board, American Biographical Institute

American Medal of Honor, 9 May, 2003

Leading Intellectuals of the World, American Biographical Institute

International Biographical Centre, Lifetime of Scientific Achievement Award

The order of International Fellowship, IBC

2000 Outstanding Intellectuals of the 21st Century, Cambridge, England

World Medal of Honor, American Biographical Institute, ABI

Inclusion in the Contemporary Who's Who, USA, 24 January, 2003

Nomination for the Governor's Award, American Biographical Institute

Vice-Consul, International Biographical Centre, Cambridge, England

International Order of Merit, International Biographical Centre

The Presidential Seal of Honor, American Biographical Institute, 29 August, 2003

International Biographical Centre Living Legends, Cambridge, England

Invited lecturer at 16th Asia Pacific Cancer Conference, Manila, Philippines, 18-21 November, 2001

Invited lecturer and Session Chairman in ten international oncology congresses in China

Teaching Experience in Molecular Oncology:

From 9 February 1996 to the end of 1998: I taught medical oncologists PCD in the Oncology Hospital, St Anargiri, as an appointed Scientific Advisor. This included all aspects of chemo- and radio-resistant mechanisms in cancer and their circumvention, molecular diagnosis, gene therapy, immunotherapy, biological therapy, chemotherapy and innovative approaches of developmental cancer therapeutics such as ECT and. Also, I established a Cancer Research Center at the hospital that, under my supervision, gained cancer research awards from oncology congresses. I taught lectures concentrating in gynaecological cancers in Mitera Surgical Center. Until 1999 I was project leader in cancer research and experimental cancer therapeutics in Department of Gynaecology, Medical School University of Patras where I delivered many lectures when the Chairman was Professor Tsigounis. I acted as Scientific Advisor and Head of Cancer Research in the oncology clinic of St. Andreas Hospital, where I have given many oncology lectures. I was invited by the

International Academy of Cytology as a cytopathology cancer expert for the people's mission to China.

1994-1998: I attended in Metaxa Oncology - Surgical procedures for Lung Cancer in the Lung Surgical Oncology Dept of Dr Antypas where lung with cancer lesions were removed surgically or photodynamic treatment or surgical laser was performed. Furthermore, I led research protocols which were presented at Int Medical Congresses. Also, at that time I led research projects in St Anargiroi Hospital, teaching all the Clinical Oncologists and those from other hospitals about molecular oncology principles every Thursday for five hours.

1999-2009: General State Hospital of Athens - I contributed as a cancer research consultant in the Clinical Oncology Hospital of Dr Michailakis E where chemotherapies on a personalized basis were performed. Also during that time I contributed as a research consultant in IASO Radio-Oncology Dept of Dr Maragudakis where radiotherapeutic procedures were performed on a personalized basis, and in the Dept of Dr Xepapadakis and Dr J Peristeris where breast and gynaecological surgical procedures were performed with perioperative genomics. Also perioperative medicine aspects have been described in my article of the official journal of the Hellenic and International Society of Molecular and Genomic Medicine and Research, where I am the President and Editor.

APPENDIX 4 Other Supporting Evidence

Publications, Presentations in Oncology Congresses, and Online Exam Passes on Medical Courses, Earning Continuing Medical Education Credits

I have presented lectures in oncology congresses and published work in cancer research. Many have been selected by Internet search engines such as Medline, Pubmed, Yahoo, Google Scholar, and so on.

1. [Effect of stem cell therapy with mesenchymal stem cells on apoptosis in inflammatory breast cancer, and effect of vinorelbine on epithelial mesenchymal transition and metastatic spread – ASCO](#)

Abstract 2009 Breast Cancer Symposium – Category: Treatment - Other: Treatment

Background: Inflammatory breast carcinoma is a lethal variant of locally advanced breast Ca with no specific clinical treatments available at the present time.
Methods: We obtained IBC cells from patients with FNA biopsy, and we developed animal..

2. [Effect of vinorelbine on chemoresistant cancer stem cell renewal in colorectal cancer \(CRC\) and on metastasis. - ASCO](#)

Abstract 2010 Gastrointestinal Cancers Symposium - Category: Cancers of the Colon and Rectum - Translational research

Background: Vinorelbine, which is an anticancer cytostatic agent, may shrink tumors but it stimulates production of more cancer stem cells, which then metastasize as a way to survive the cytostatic action of this drug. Colorectal Ca

3. [Use of liposomal siRNA against Msi1 combined with docetaxel to eradicate advanced gastric adenocarcinoma after inhibition of angiogenesis, proliferation, migration, invasion, and metastasis of cancer stem cells, cancer progenitor cells, and tumor cells. - ASCO](#)

Abstract 2010 Gastrointestinal Cancers Symposium - Category: Cancers of the Esophagus and Stomach - Translational research

Background: We aim to eliminate metastatic recurrences of the advanced gastric adenocarcinoma by eradicating cancer stem cells with antisense molecular targeting, while with conventional chemotherapy we aim to eradicate tumor cells.

4. [Use of induced pluripotent stem cells \(iPSCs\) encoded with anti-GRP78 shRNA, which induces apoptosis after a gene-silencing bystander to circumvent vinorelbine induced angiogenesis, and metastatic spread in advanced gastrointestinal stromal tumors \(GIST\). - ASCO](#)

Abstract 2010 Gastrointestinal Cancers Symposium - Category: Cancers of the Esophagus and Stomach - Translational research

Background: Vinorelbine in advanced GIST cells induces tumor relapse with enhanced angiogenesis and metastasis by inducing an innate cancer cellular stress response, which enhances the expression of GRP78 that blocks cell death O. . .

- 5 . [Antisense immunochemogene therapy \(AICT\) composed of siRNA targeting angiostatic VEGF-A165b mRNA \(SEVINA-VI\), antiVEGFMab \(bevacizumab\), and vinorelbine inhibited VEGF mediated desmoplastic response, angiogenesis, and lymphangiogenesis inducing maturation of DCs, ADCC, CMC, autophagy, and apoptosis in PDAC cir](#)

Abstract 2008 Gastrointestinal Cancers Symposium - Category: Pancreas, Small Bowel, and Hepatobiliary Tract - Translational research

Background: In pancreatic ductal adenocarcinoma, the desmoplastic response is predominant. VEGF-A165b causes resistance to bevacizumab. Methods: We established a clinically relevant model of PDAC in animals by orthotopically inoculating human PDAC ce. . . (More)

- 6 . [Eradication of metastatic breast cancer resistant to trastuzumab and cetuximab following immunochemogene treatment with SV-IV, a stealth nanoparticle formulation composed of clamp PNA against mRNA of sGCa1/b1, vinorelbine, and antiMUC1 chimeric MAb - ASCO](#)

Abstract 2008 Breast Cancer Symposium - Category: Treatment - New Systemic Agents – New drugs and targets (includes anti-angiogenics) - Other

Introduction: The unmet medical need for metastatic breast cancer (Ca) is very high because of potent chemoresistance. We aim to circumvent these resistant factors. Methodology: We obtained surgically tumor cells from patients with stage IV breast

- 7 . [Use of pegylated liposomal multitargeted siRNA against UbchH5, c-Src, and HSP90 combined with bevacizumab and vinorelbine-tartrate to circumvent oncogene addiction, transactivation, and acquired resistance due to VEGFR ubiquitination, and mutations/deletions in the kinase domain of VEGFR inducing apoptosis in m](#)

Abstract 2009 Genitourinary Cancers Symposium - Category: Genitourinary Cancers - Bladder

Introduction: Metastatic transitional cell carcinoma (mTCC) of the bladder can develop resistance to bevacizumab. We aim to circumvent this resistance and eradicate mTCC with vinorelbine (VRL). Methods: mTCC cells were obtained from patients with meta. . . (More)

- 8 . [Cetuximab combined with multi-targeted siRNA against HSP90, UbchH5, and c-Src circumvented oncogene addiction, transactivation, and acquired resistance as a result of EGFR ubiquitination, and mutations/deletions in the kinase domain of EGFR in mCRC. - ASCO](#)

Abstract 2008 Gastrointestinal Cancers Symposium - Category: Colon and Rectum

- Translational research

Introduction: CRC cells develop resistance to cetuximab through insertion mutations at exon 20, ubiquitination, and c-Src which activates EGFR in the absence of ligand despite treatment with cetuximab. We aim to circumvent this acquired resistance.

- 9 . [LIP-rMDVA+VRL composed of liposomal cDNA encoding recombinant multimodular proteins rMDVA comprising disintegrin/cysteine rich disulfide bond 2RGD, and C-terminal domain \(ammodystatin\), metalloprotease-domain \(ammodylisin\), and dimeric disintegrin/MLD-VGD domain \(VADD\) isolated vipera ammodytes with VRL e](#)

Abstract 2009 Genitourinary Cancers Symposium - Category: Genitourinary Cancers - Early/Localized disease, Locally Advanced/Recurrent/Advanced disease, and Biology

Introduction: We investigate if venom proteome of vipera ammodytes can induce apoptosis in HRPC. Materials and Methods: We developed a large scale expression system with prostate cell line (PCL), which we modified genetically by..

- 10 . [\(AS-CRI\) antisense chemoradioimmunotherapy consisting of anti-CaSm scFv linked onto high-energy radioisotopes, vinorelbine and 21 nucleotide double stranded siRNA targeted to DNMT1 induce apoptosis \(PCD\) in pancreatic and periampullary Ca characterised by hypermethylated tumour suppressor RASSF1A, RAR-b2. B](#)

Abstract 2005 Gastrointestinal Cancers Symposium - Category: Pancreas, Small Bowel, and Hepatobiliary Tract - Multidisciplinary Treatment

Introduction: Failure of tumour cells to undergo PCD cause resistance to chemoradiological therapies due to overexpression of oncogenes and transcriptionally repressed apoptotic TSGs due to methylation. Methods: We obtained surgically 19 pancreatic Ca.

- 11 . [Effect on humoral and cellular immunity and on apoptosis in CIN2, CIN3, and HPV16+ cervical cancer of therapeutic divalent genetic vaccination with CMV replicon system \(CRS\) delivering HPV16 recombinantly mutated E6 and E7 viral oncogenes targeting p53 and Rb, respectively. - ASCO](#)

Abstract 2009 ASCO Annual Meeting - Category: Developmental Therapeutics: Immunotherapy - Vaccines

Background: Prophylactic vaccines have no therapeutic capacity for all the women who are already infected with HPV16 and have developed cervical intraepithelial neoplasia (CIN) or cervical cancer. Approximately 300 million women with CIN ..

- 12 . [Effect of LNA-modified oligonucleotides targeting mRNA of DICER in pegylated colloidal nanoparticles with linked abs against CD44 on prostate cancer stem cells \(PCSCs\) and hormone-refractory prostate cancer cells \(HRPC\): Role of induction of PCD after inhibition of oncomir machinery leading to downregulation o](#)

Abstract 2010 Genitourinary Cancers Symposium - Category: Prostate Cancer: Early/Localized disease, Locally Advanced/Recurrent/Advanced disease, and Biology - Prostate Cancer: Early/Localized disease, Locally Advanced/Recurrent/Advanced disease, and Biology

Background: HRPC is incurable due to chemoresistance caused by cancer stem cells due to overexpression of oncomirs which upregulate oncogenes and hypermethylation in CpG islands which inactivates tumour suppressor genes.

- 13 . [RhuMAb Anti-HER2/Neu Peglyated Immunoliposomes with Incorporated Vinorelbine Tartrate Induces P53 Independent PCD and ADCC in Chemoresistant NSCLC \(Meeting abstract\). - ASCO](#)

Abstract 1999 ASCO Annual Meeting - Category: Lung Cancer - Lung Cancer

At diagnosis NSCLC are usually resistant to apoptosis or PCD after chemotherapy due to overexpression of HER-2/neu protooncogene. Tumour cells were derived by FNA from a patient with advanced stage IV NSCLC. Tumour cells were paraffin ..

- 14 . [Paclitaxel exacerbates doxorubicin induced cardiac mitochondrial dysfunction leading to apoptosis of human cardiomyocytes. - ASCO](#)

Abstract 2002 ASCO Annual Meeting - Category: Clinical Pharm- Clinical Pharm

There is high incidence of congestive heart failure after combined administration of doxorubicin and paclitaxel. Doxorubicinol (dxol) is the major metabolite formed in cancer patients' hearts who are treated with doxorubicin. Enzymatic reduction at t.

- 15 . [Effect of gene modified cellular vaccine \(GMCV\) composed of autologous adipose-derived mesenchymal stem cells \(AADMSCs\) transfected with lipid-cation Hsp70 on innate and adaptive immunity after targeting primary and metastatic breast Ca cells inducing secondary-necrosis and lethal bystander effect, while injur](#)

Abstract 2009 Breast Cancer Symposium - Category: Treatment - Other: Treatment

Background: Metastatic breast Ca leads to fatalities due to resistance in conventional anticancer therapies. Methods: Animal models characterized by metastatic breast Ca refractory to conventional treatment were developed and

- 16 . [Pegylated liposomal anti-eIF3c shRNA-vinorelbine tartrate formulation \(SEVINA-V\) inhibits oncogenic protein translational initiation, and oncogene addiction inducing PCD type-I, II, and III in NSCLC chemoresistant to taxanes. - ASCO](#)

Abstract 2008 ASCO Annual Meeting - Category: Lung Cancer--Metastatic Lung Cancer - Metastatic Lung Cancer

Background: eIF3c is required for the initiation of protein translation, and directly interacts with mTOR activating eIF4e, which is overexpressed in NSCLC. mTOR activates the PI3K/AKT signal transduction pathway, which mediates cell proliferation through. . . (More)

- 17 . [Effect of vinorelbine on chemoresistant cancer stem cell renewal . . .](#)

Virtual Presentation 2010 2010 Gastrointestinal Cancers Symposium - Track: Cancers of the Colon and Rectum - Session: General Poster Session C Cancers of the Colon and Rectum (General Poster Session)

2010 Gastrointestinal Cancers Symposium Presentation. Session: General Poster Session C Cancers of the Colon and Rectum (General Poster Session).

- 18 . [Effect of pegylated-nanoparticles of CDP bound to multitargeted . . .](#)

Virtual Presentation 2009 2010 Breast Cancer Symposium - Track: Systemic Therapy - Session: General Poster Session D (General Poster Session)

2010 Breast Cancer Symposium Presentation. Session: General Poster Session D (General Poster Session).

- 19 . [Effect on humoral and cellular immunity and on apoptosis in CIN2 . . .](#)

Virtual Presentation 2009 2009 ASCO Annual Meeting - Track: Developmental Therapeutics - Session: Developmental Therapeutics Immunotherapy (General Poster Session)

2009 ASCO Annual Meeting Presentation. Session: Developmental Therapeutics Immunotherapy (General Poster Session).

- 20 . [Use of liposomal siRNA against Msi1 combined with docetaxel to . . .](#)

Virtual Presentation 2010 2010 Gastrointestinal Cancers Symposium - Track: Cancers of the Esophagus and Stomach - Session: General Poster Session

- 31 . [ASCO Speaker](#)

- 32 . [ASCO Speaker](#)

- 33 . [ASCO Speaker](#)

- 34 . [Chimeric Antibodies Targeting the SH2 Domain of Grb2 and p85a of PI3-K Linked on PEG-SUVs with Entrapped Vinorelbine Induced ADCC, ADMC, Complement Fixation, Anoikis, Apoptosis and Inhibition of Ras/Raf/MEK/MAPK and PI3K/AKT Pathways in Chemoresistant Breast Ca Overexpressing HER-2/neu. - ASCO](#)

Abstract 2001 ASCO Annual Meeting - Category: Immunobiology and Biologic Therapy - Gene Therapy

Breast cancer cells with high HER-2/neu expression use Grb2 to transduce signals to MAPK and AKT via binding of pTyr to SH2 domain propagating mitogenic signals. Breast tumour cells characterised by overexpression of HER-2, Ras and Akt were obtained . . . (More)

35 . [Reception and General Poster Session B: Prostate Cancer - ASCO](#)

Chair: Alan Pollack, MD, PhD; Chair: Howard I. Scher, MD; Presenter: Sheila M. J. Aubin, Ph. D; Presenter: John R. Day, Ph. D.; Presenter: Jacek K. Pinski, MD, PhD; Presenter: Shreya K. Shah, MD; Presenter: Jack Groskopf, Ph. D; Presenter: David G. McGowan, MB. ChB, FRCPC; Pres: Karim Fizazi, MD, PhD;

Meeting Session 2010 Reception and General Poster Session B: Prostate Cancer (General Poster Session)2010 Genitourinary Cancers Symposium - Track: Prostate Cancer: Epidemiology, Risk factors, Prevention, and Health Services Research

|PRESENTATION 1: Fellows Poster Walk. |PRESENTATION 2: Fellows Poster Walk. |PRESENTATION 3: Urine measurement of *TMPRSS2:ERG* for the early detection of significant prostate cancer. |PRESENTATION 4:. . . (More)

36. Presenter: Austin Duffy, MD; Presenter: Robert R McWilliams, MD; Presenter: Cristina Ferrone, MD; Presenter: Christopher Aoki; Presenter: Jessica Hwang, MD, MPH; Presenter: Jessica P Simons, MD; Presenter: Mitsuo Shimada, MD, PhD; Presenter: Kashif Ahmed, MD; Presenter: Charles C Hsu, PhD; Pres: V J Pi

Meeting Session 2008 General Poster Session C (Poster Presentation)2008 Gastrointestinal Cancers Symposium - Track: Colon and Rectum

|PRESENTATION 1: Pancreatic adenocarcinoma (PAC) in a younger patient population: 10-year experience at Memorial Sloan Kettering Cancer Center (MSKCC). |PRESENTATION 2: *CFTR* mutations and risk for pancreatic adenocarcinoma.

37 . [Evaluation of an antisense antibody drug conjugate \(SEVINA\) co-administered with gamma-irradiation \(IR\) for the treatment of HMTV and HERV \(+\) advanced breast Ca](#)

Abstract 2007 Breast Cancer Symposium - Category: Treatment - New Systemic Agents---New drugs and targets (includes antiangiogenics)

Introduction: HMTV viruses cause tumors by insertional mutagenesis in patients with breast Ca. Also, HERV viruses exist in the 2. 9 billion base pairs of silent regions in breast Ca cells. Methods: HMTV and HERV at the latent form were detected in 96%.

38 . [Antisense chemoradioimmunotherapy eradicates metastatic pancreatic CCa characterised by hypermethylation of oncosuppressor genes and overexpression of antiapoptotic oncogenes - ASCO](#)

Abstract 2006 Gastrointestinal Cancers Symposium - Category: Pancreas, Small Bowel, and Hepatobiliary Tract - Translational research

Introduction: Metastatic pancreatic Ca is resistant to almost all cytotoxic drugs and radiation making it one of the most aggressive malignancies in human with the worst mortality. Materials and Methods: We obtained surgically 96 metastatic

39 . [Bispecific nanobody targeting DNMT1 and SHH conjugated to vinorelbine inhibit DNA methylation, hedgehog-patched \(PCTH\) receptor signaling protein smoothed and hTERT expression leading to re-expression of apoptotic tumor suppressor genes and inductio - ASCO](#)

Abstract 2007 Prostate Cancer Symposium - Category: Locally Advanced/Recurrent/Advanced Disease - Developmental therapeutics (molecular therapeutics, immunotherapy, cytotoxic chemotherapy)

Introduction: HRPC is incurable due to continued evolution of the cancer stem cells (CSC) which give rise to metastatic cells and further drug resistance. Stem cell self renewal and survival requires signaling from molecules which we aim to..

- 40 . [Liposomal vinorelbine with linked PyMT MAbs inhibited VEGF-mediated human telomerase reverse transcriptase \(hTERT\), c-Src, Ras, PI3K, VEGF-A, MMP-2, and integrins \$\alpha\$ 1, 2, 6 inducing apoptosis in pancreatic cancer - ASCO](#)

Abstract 2006 Gastrointestinal Cancers Symposium - Category: Pancreas, Small Bowel, and Hepatobiliary Tract - Translational research

Pancreatic Ca cells from a metastatic patient were obtained and they were treated with liposomal vinorelbine tartrate with linked PyMT Mabs. Staining of tumor cells with β -galactosidase was used a marker of cell senescence. Flow...

- 41 . [Eradication of osteolytic and osteoblastic metastases of breast cancer inhibiting proliferation of tumor associated \(TAEC\) and bone microvascular endothelial cells \(BMEC\) inducing antibody dependent cellular toxicity \(ADCC\), antibody mediated phagocyt - ASCO](#)

Abstract 2007 Breast Cancer Symposium - Category: Treatment - New Systemic Agents---New drugs and targets (includes antiangiogenics)

Introduction: Bone metastasis is a complication of breast Ca for which only palliative treatment is available. We aim to inhibit the cycle between tumor cells and the bone microenvironment, which results in increased tumor burden and bone destruction. . .

- 42 . [Pegylated colloidal anti-eIF3c shRNA-vinorelbine formulation \(SEVINA-V\) inhibited oncogenic protein translational initiation, and oncogene addiction inducing apoptosis in HRPC chemoresistant to taxanes. - ASCO](#)

Abstract 2008 Genitourinary Cancers Symposium - Category: Genitourinary Cancers - Prostate

Introduction: eIF3c is required for the initiation of protein translation, and interacts with mTOR activating eIF4e, which is overexpressed in HRPC. Bcl-2 overexpression inhibits apoptosis causing oncogene addiction, and chemoresistance. Materials and .

- 43 . [Multi-vaccine \(SEVINA\) composed of vinorelbine-apoptotic tumour cell lysate \(VATCL\), cationic colloidal 25 mer ISS CpG oligonucleotide \(ODN\) adjuvant and recombinant chaperone GRP94/gp96+HER2 differentiation antigen vaccine induces formation of exosomes from APCs and humoral cell immune responses I](#)

Abstract 2006 Gastrointestinal Cancers Symposium - Category: Pancreas, Small Bowel, and Hepatobiliary Tract - Translational research

Introduction: In this study, we try to eradicate chemoresistant metastatic tumours by activating immune responses of the host. Materials & Methods: We established growth of distal tumours after injection of chemoresistant human pancreatic tumour

- 44 . [Diabody vinorelbine conjugate \(DVC\) composed of vinorelbine-tartrate conjugated to anti-DNMT1/SHH di-diabody induce ADCC, CDC, AMP and inhibit DNA methylation. - ASCO](#)

Abstract 2007 ASCO Annual Meeting - Category: Breast Cancer--Metastatic Breast Cancer - Metastatic Breast Cancer

Background: Hormone refractory breast cancer (HRBC) is incurable due to malignant stem cells, which represent a potential nidus for the recurrent cancer that arises after treatment failure. Methods: From 126 metastatic HRBC patients, we obtained CSCs

- 45 . [Chimeric LNA/DNA antisense oligonucleotides against DNA MeTase and vinorelbine-tartrate encapsulated in pegylated liposomes induce apoptosis in chemoresistant advanced colon carcinoma characterised by 5'CpG island methylation of RUNX3, MLH1, MGMT, p16INK4A, CDH1, LKB1, HIC1, CDX1, FHIT and RAR-β2 genes. - ASC](#)

Abstract 2004 Gastrointestinal Cancers Symposium - Category: All - Colon and Rectal Cancers

Colon cancer is a leading cause of death in developing countries. Mortality is high because the majority of colon tumours have already at the time of diagnosis. The available drug therapies for colon cancer are largely ineffective due to.

- 46 . [Combined administration of hydrophilic antimitotic desoxyepothilone B and vinorelbine induce PUMA, suppression of microtubule dynamics, development of hypodiploidy and multinucleation, cell cycle perturbation at G2/M and apoptosis in advanced breast carcinoma \(ABC\) characterised by MDR-1 \(Pgp\), bcl-2 and mutant](#)

Abstract 2004 ASCO Annual Meeting - Category: Developmental Therapeutics - Cytotoxic Chemotherapy - Drug Resistance

Introduction: Low aqueous solubility of VRL is a high substrate for ATP dependent drug efflux proteins such as MDR-1(Pgp) and MRP2(ABCC2) inserted in plasma membrane of tumor cells. Furthermore, b-tubulin mutations are cross-resistant to VRL. Methods: . . . (More)

- 47 . [Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single-chain Fv molecules \(bs-ScFv\) and encapsulated vinorelbine induces PCD and ADCC in chemoresistant gastric carcinoma \(GC\) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers](#)

Abstract 2004 Gastrointestinal Cancers Symposium - Category: All - Upper GI Cancer (Esophageal and Gastric)

Gastric carcinoma is one of the most aggressive type malignant tumors. Failure to trigger apoptosis due to changes in DNA methylation and histone acetylation causes chemoresistance in gastric malignancies. DNMT1 interacts with HDAC2

- 48 . [Antisense chemoradioimmunotherapy consisting of anti-IGF-I/HGF bs-scFv linked onto high-energy radioisotopes and TFO targeted to DNMT1 and conjugated to vinorelbine induce ADCC, apoptosis and anoikis in metastatic NSCLC characterised by radio and chemoresistance. - ASCO](#)

Abstract 2005 ASCO Annual Meeting - Category: Lung Cancer - Non-Small Cell Lung Cancer

Introduction: Metastatic NSCLC is resistant to almost all cytotoxic drugs and radiation. Materials and Methods: We obtained surgically 132 metastatic NSCLC specimens from patients. MS-PCR exhibited hypermethylation of oncosuppressors VHL, p63, p53, IGF. . . (More)

- 49 . [Biology of the estrogen receptor, GPR30, in triple-negative breast cancer. - ASCO](#)

Abstract 2010 Breast Cancer Symposium - Category: Prevention, Survivorship & Health Policy - Novel Targets

Background: Triple-negative breast cancer currently has no targeted therapy because the growth signals are poorly understood. One theory is that a non-classical ER receptor is present in some tumors, driven by estrogen in premenopausal women. GPR 30, . . . (More)

- 50 . [General Poster Session B - ASCO](#)

Presenter: William Fraser Symmans; Presenter: Sherene Loi; Presenter: Joseph A Sparano; Presenter: Allen S Melemed; Presenter: Guillermo L Lerzo; Presenter: Stacy L Moulder; Presenter: John W Smith; Presenter: Rupert Bartsch; Presenter: Lee S Schwartzberg; Presenter: Cathy Van Poznak; Presenter: Jose J Illarramen

Meeting Session 2007 General Poster Session B (General Poster Session) 2007 Breast Cancer Symposium - Track: Treatment

|PRESENTATION 1: A 200-gene endocrine sensitivity index (SET) predicts survival for patients who receive adjuvant endocrine therapy, but not for untreated patients. |PRESENTATION 2: Gene expression profiling identifies potential therapeutic ta. . .

- 51 . [General Poster Session C: Cancers of the Colon and Rectum - ASCO](#)

Presenter: Kavitha P Raj, MD; Presenter: Sarah Kraus, PhD; Presenter: Stephen C Lloyd, M. D., Ph. D. ; Presenter: Kueiyu Lin, MD, MPH; Presenter: Kathleen Mary Wesa, MD; Presenter: Ticiana A. B. Leal, MD; Presenter: Inna Naumov, MSc; Presenter: Winson Y. Cheung, MD, MPH; Presenter: Michel Houde, PhD; Aude

Meeting Session 2010 General Poster Session C: Cancers of the Colon and Rectum (General Poster Session)2010 Gastrointestinal Cancers Symposium - Track: Cancers of the Colon and Rectum

|PRESENTATION 1: Role of dietary polyamines in a phase III clinical trial of DFMO and sulindac for prevention of metachronous colorectal adenomas: A potential target for colon cancer chemoprevention. . |PRESENTATION 2: Use..

52 . [Immunobiology and Biologic Therapy : Immunobiology and Biologic Therapy ASCO](#)

|ABSTRACT 1: Immunotherapy of Multiple Myeloma Using Idiotype-Loaded Dendritic Cells (APC8020). . |ABSTRACT 2: Immunologic Gene Therapy of Melanoma: Phase I Study of Therapy with Autologous Dendritic Cells Transduced with Recombinant Adenoviruses En. . . (More)

53 . [Immunobiology and Biologic Therapy - ASCO](#)

Presenter: Abraham Mittelman, MD; Presenter: Alfredo Velasco, MD; Presenter: Andrea L. Veatch, MD; Presenter: Antoine Yver, MD; Presenter: Antoni Ribas, MD; Presenter: Ben Guo, MD; Presenter: Candelaria Gomez-Manzano, MD; Presenter: Carsten Nieder, MD; Presenter: Charles S. Hesdorffer, MD; Presenter: Christine Od

Meeting Session 2001 Immunobiology and Biologic Therapy (General Poster) 2001 ASCO Annual Meeting - Track: General Oncology

|PRESENTATION 1: A Human Blood Dendritic Cell Purification Platform For Clinical Applications . |PRESENTATION 2: A Phase I And Pharmacokinetic Study Of Intravenous (iv) P53 Gene Therapy With Rpr/ingn-201 In Patients (pts) With Advanced Cancer. . . (More)

54 . [Cancers of the Esophagus and Stomach - General Poster Session - ASCO](#)

Presenter: Aldo Iop, MD; Presenter: Ayumu Hosokawa; Presenter: Bach Ardalan; Presenter: Barbara Burtness, MD; Presenter: Charles Blanke, MD; Presenter: Dana E Rathkopf, MD; Presenter: Desiree Pantalone, MD; Presenter: Esther Chuwa; Presenter: eva galizia; Presenter: Giannios N John; Presenter: Hiromichi Ito, MD;

Meeting Session 2004 Cancers of the Esophagus and Stomach - General Poster Session (Poster Presentation)2004 Gastrointestinal Cancers Symposium - Track: 2004 Gastrointestinal Cancers Symposium

|PRESENTATION 1: A phase I/II study of epirubicin, cisplatin, high dose 24-hour infusion 5-fluorouracil and sodium folinate (ECSF) for advanced gastroesophageal carcinoma. . |PRESENTATION 2: A phase I/II trial of docetaxel, capecitabine, and ..

55 . [ASCO Speaker](#)

56 . [Effect of temsirolimus on the growth inhibitory effect of trastuzumab in HER2-positive breast cancer cell lines. - ASCO](#)

Abstract 2010 Breast Cancer Symposium - Category: Prevention, Survivorship & Health Policy - Novel Targets

Background: The mammalian target of rapamycin (mTOR) is a central regulator of G1 cell cycle protein synthesis that precedes commitment to normal cellular replication. Temsirolimus binds to the immunophilin FK506/rapamycin-binding..

57 . [Cancers of the Colon and Rectum - General Poster Session - ASCO](#)

Presenter: Adrian G Dan; Presenter: Alok Khorana, MD; Presenter: Barbara Jung, MD; Presenter: Barry Mirtsching, MD; Presenter: Bruce J Giantonio, MD; Presenter: C. Richard Boland; Presenter: Carol Townsley, MD; Presenter: Cheryl Ho, MD; Presenter: Claus-Henning Kohne; Presenter: Derek J Jonker, MD; Presenter: Dom

Meeting Session 2004 Cancers of the Colon and Rectum - General Poster Session (Poster Presentation)2004 Gastrointestinal Cancers Symposium - Track: 2004 Gastrointestinal Cancers Symposium

|PRESENTATION 1: A multicenter phase II study of 'adjuvant' irinotecan following resection of colorectal hepatic metastases. . |PRESENTATION 2: A proposed mechanism for the induction of chromosomal instability (CIN) by JC virus (JCV) . . .

58 . [Biologic and Targeted Therapies : Molecular/Ligand Targeted Therapies - ASCO](#)

|ABSTRACT 1: KIT mutational status predicts clinical response to STI571 in patients with metastatic gastrointestinal stromal tumors (GISTs). |ABSTRACT 2: A rationally designed, targeted tumor treatment approach: a phase II study of imatinib mesylate . . (More)

59 . [Inhibition of AKT- and VEGF-signaling pathways by targeting both VEGF-R and ErbB-2 in breast cancer cell lines. - ASCO](#)

Abstract 2010 Breast Cancer Symposium - Category: Prevention, Survivorship & Health Policy - Novel Targets

Background: Deregulation of PI3K/AKT pathway occurs commonly in breast cancer, and is associated with ErbB-2 amplification as well as activating PI3K mutations. Trastuzumab have potent antiproliferative effects in ErbB-2-positive human breast tumors . . . (More)

60. Basic science and Bench to bedside (lab) (Abstract No. 43-74) Ann. Onc., Oct 2002; 13: 13 - 20. solid tumors Christopher Souder (1), John H. Marx (1), Kim Leitzel (1), Suhail. . . Hochhauser (2), Berend Tolner (2), John Hartley (2) (1) Royal Marsden Hospital. . . overexpressing EGFR, Ras, MDR-1 & PGE2 JohnGiannios (1), Emmanuel Michailakis (1) (1.

61. CANCER THERAPEUTICS: POSTER PRESENTATIONS: Pegylated liposomal anti-eIF3c shRNA-vinorelbine formulation (SEVINA-V) inhibits oncogenic protein translational initiation and oncogene addiction inducing apoptosis in HRBC chemoresistant to taxanes John Giannios and P. Ginopoulos AACR Meeting Abstracts, Nov 2007; 2007: C26.

First AACR Centennial Conference on Translational Cancer Medicine-- Nov 4-8, 2007; Singapore John Giannios, P.

Ginopoulos GSHA, Athens, Greece, IH, Athens, Greece C26
Introduction: eIF3c is required for the initiation.

62. ANTIANGIOGENIC/ANTIVASCULAR AGENTS: POSTER PRESENTATIONS:
Antisense immunochemogene therapy (AICT) composed of siRNA targeting VEGFA-165b mRNA (SEVINA), bevacizumab, and vinorelbine inhibited VEGF mediated desmoplastic response, angiogenesis, lymphangiogenesis, and osteoblastic/osteolytic skeletal metastasis inducing maturation of DCs, ADCC, CMC, autophagy, and apoptosis in HRBC, circumventing Trousseau's syndrome.
JohnGiannios, E. Michailakis, and N. Alexandropulos
AACR Meeting Abstracts, Oct 2007; 2007: A9.
63. AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics-- Oct 22-26, 2007; San Francisco, CA **JohnGiannios E. Michailakis N. Alexandropulos** GSHA, Athens, Greece, IH, Athens, Greece A9 Background:. Bevacizumab blocks. [Find more like this.](#) .
64. EGFR/HER2/RAS/RAF/MAPK PATHWAYS: POSTER PRESENTATIONS: Multi-targeted siRNA against c-Src, and HSP90 combined with Cetuximab circumvented oncogene addiction, transactivation, and resistance due to mutations, and deletions in the kinase domain of EGFR in mCRC.
JohnGiannios and Emmanuel Michailakis AACR Meeting Abstracts, Oct 2007; 2007: B126.
. AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics-- Oct 22-26, 2007; San Francisco, CA **JohnGiannios Emmanuel Michailakis** GSHA, Athens, Greece B126 Introduction: CRC cells can develop resistance to Cetuximab through.
65. CANCER INITIATING CELL THERAPEUTIC POTENTIAL: POSTER PRESENTATIONS:
(BNT) Bispecific nanobody targeting DNMT1 and SHH conjugated to vinorelbine-tartrate (anti-DNMT1/SHH bsNAb-VRL) inhibit DNA methylation, Hedgehog(HH)-Patched(PCTH) receptor signaling protein smoothed (SMO) and hTERT expression leading to re-expression of apoptotic tumor suppressor genes and induction of type-I, II, III PCD in HRBC stem progenitor cells (CSCs).
JohnGiannios, Esmeralda Seraj, Philip Lambrinos, and Nick Alexandropulos AACR Meeting Abstracts, Apr 2007; 2007: 1334. [Find more like this](#)

66. **Announcements** [PDF](#)
Cancer Res. Apr 1997; 57: 1400 – 1402 . . Resort, Palm Springs, CA Chairpersons **John C. Reed**, La Jolla, CA Vishva M. Dixit. . . Athens Hilton, Greece. Contacts: Dr **JohnGiannios**, Congress Secretariat, Triaena Congress. . . previously listed as July 1997), St. **John's** College, Cambridge, United Kingdom. [Find more like this](#)
67. **Announcements** [PDF](#)
Cancer Res. Mar 1997; 57: 1213 - 1215.
. Resort, Palm Springs, CA Chairpersons **John C. Reed**, La Jolla, CA Vishva M. Dixit. . . Athens Hilton, Greece. Contacts: Dr **JohnGiannios**, Congress Secretariat, Triaena Congress. . . International Seminar, July 20?'23, 1997, St. **John's** College, Cambridge, United Kingdom. [Find more like this](#)
68. EXPERIMENTAL AND MOLECULAR THERAPEUTICS 52: [Abstract](#)
PREDICTION OF DRUG SENSITIVITY AND RESISTANCE: [Find more like this](#)
Combined administration of antisense chemoradioimmunotherapy (ACRIT) consisting of antiHER2 scFv linked onto high-energy radioisotopes and triplex forming oligonucleotides (TFO) targeted to DNMT1 and conjugated to vinorelbine-tartrate induce apoptosis in metastatic breast Ca (MBC) characterized by hypermethylated oncosuppressor genes VHL, p53, p16, RASSF1A, RAR-b2, TIMP3, PTEN, H-cadherin, BRCA2, p14ARF and overexpression of HIF-1, VEGF, MMP-2, MMP-9, Glut-1, IGF1R, bcl-2, cdc25c, Raf1, TGFa, UPAR, c-Met and EGFR
John N. Giannios, Philip Lambrinos, Emmanuel Michailakis, Nick Alexandropoulos, Evangelos Maragudakis, and Nick Pergandas AACR Meeting Abstracts, Apr 2005; 2005: 1398.
. 9, Glut-1, IGF1R, bcl-2, cdc25c, Raf1, TGFa, UPAR, c-Met and EGFR [Proc Amer Assoc Cancer Res, Volume 46, 2005]
John N. Giannios Philip Lambrinos Emmanuel Michailakis Nick Alexandropoulos Evangelos Maragudakis Nick Pergandas GSHA
69. DEVELOPMENTAL THERAPEUTICS: CYTOTOXIC CHEMOTHERAPY: [Abstract](#)
Combined administration of hydrophilic antimetabolic desoxyepothilone B and vinorelbine induce PUMA, suppression of microtubule dynamics, development of hypodiploidy and multinucleation, cell cycle perturbation at G2/M and apoptosis in advanced breast carcinoma (ABC) [Find more like this](#)

characterised by MDR-1 (Pgp), bcl-2 and mutant b-tubulin
John NGiannios, E. Michailakis, S. Konstandinidou, G. Xepapadakis, N. Alexandropoulos, and T. Kononas
ASCO Meeting Abstracts, Jul 2004; 22: 2087.

. and apoptosis in advanced breast carcinoma (ABC)
characterised by MDR-1 (Pgp), bcl-2 and mutant b-tubulin G.
N. **John J. Giannios E. Michailakis S. Konstandinidou G. Xepapadakis N. Alexandropoulos T. Kononas** GSHA,
Athens, Greece; BC.

70. EXPERIMENTAL AND MOLECULAR THERAPEUTICS 35: [Find more like this](#)
PRECLINICAL MODELS/PHARMACOLOGY/MECHANISMS: [Abstract](#)
Pegylated colloidal with linked anti-DNMT1/HDAC2 bispecific
single-chain Fv molecules (bs-ScFv) and encapsulated
vinorelbine induces apoptosis in chemoresistant infiltrating
ductal carcinoma of the breast (IDC) characterized by
HDAC2 overexpression and 5'CpG island hypermethylation
of growth regulators, signal transducers, tumor suppressor
genes, invasion/metastasis suppressor genes, DNA repair
genes, hormone and kinase receptors, angiogenesis
inhibitors, tumor antigens, GTP proteins and apoptotic genes.
John N. Giannios
AACR Meeting Abstracts, Mar 2004; 2004: 883 - 884.
71. Renaissance Esmeralda Resort, Palm Springs, CA [PDF](#)
Chairpersons **John C. Reed**, La Jolla, CA **Vishva M. Dixit**,
Ann Arbor, MI **ANGIOGENESIS**. . . May 6?'10, 1997, Athens [Find more like this](#)
Hilton, Greece. Contacts: Dr **JohnGiannios**, Congress
Secretariat, Triaena Congress, 24 Har Trikoupistr.
72. NOVEL DRUG TARGETS, AGENTS, AND MECHANISMS: [Find more like this](#)
POSTER PRESENTATIONS - PROFFERED ABSTRACTS:
SEVINA-V composed of pegylated liposomal anti-eIF3c
shRNA and vinorelbine inhibits oncogenic protein
translational initiation, and oncogene addiction inducing type-
I, II PCD in HRBC.
JohnGiannios, Emmanuel Michailakis, Esmeralda Seraj,
and Nick Alexandropulos
AACR Meeting Abstracts, Apr 2008; 2008: 2819.

. . and oncogene addiction inducing type-I, II PCD in HRBC.
99th AACR Annual Meeting-- Apr 12-16, 2008; San Diego,
CA **JohnGiannios Emmanuel Michailakis Esmeralda**
Seraj Nick Alexandropulos GSHA, Athens, Greece, IH,
Athens, Greece 2819.

73. APOPTOSIS AND AUTOPHAGY: POSTER PRESENTATIONS: [Find more like this](#)

Cetuximab and pegylated bispecific disulfide linked Fv(sdFv) targeting epitopes of PTHrP, and RANKL conjugated covalently with SATA to vinorelbine eradicated osteolytic, and osteoblastic metastases of breast Ca inhibiting proliferation of tumor associated, and bone microvascular endothelial cells inducing ADCC, AMP and type-I, II, III PCD.

JohnGiannios and Panagiotis Ginopulos

AACR Meeting Abstracts, Oct 2007; 2007: A38. AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics-- Oct 22-26, 2007; San Francisco, CA

JohnGiannios Panagiotis Ginopulos PHSA, A., Greece
A38 Objective: Bone metastasis is a common complication of breast Ca.

TUMOR BIOLOGY AND HUMAN GENETICS:

Diabody vinorelbine conjugate (DVC) composed of vinorelbine-tartrate conjugated to anti-DNMT1/SHH diabody induce ADCC, CDC, AMP and inhibit DNA methylation

JohnGiannios, E. Seraj, G. Kanelopulos, P. Ginopulos, and N. Alexandropulos

ASCO Meeting Abstracts, Jun 2007; 25: 11503.

vinorelbine-tartrate conjugated to anti-DNMT1/SHH diabody induce ADCC, CDC, AMP and inhibit DNA methylation G. N. **John J. Giannios** E. Seraj G. Kanelopulos P. Ginopulos N. Alexandropulos PHSA, Athens, Greece; IH, Athens, Greece 11503.

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Pegylated trispecific disulfide linked Fv(sdFv) targeting epitopes of EGFR, PTHrP and RANKL conjugated covalently with SATA to vinorelbine eradicated osteolytic and osteoblastic metastasis of breast Ca inhibiting proliferation of tumor associated and bone microvascular endothelial cells inducing ADCC, AMP and type-I, II, III PCD.

JohnGiannios, Philip Lambrinos, Esmeralda Seraj, Nick Alexandropulos, and Evangelos Maragudakis

AACR Meeting Abstracts, Apr 2007; 2007: LB-267.

endothelial cells inducing ADCC, AMP and type-I, II, III PCD.
98th AACR Annual Meeting-- Apr 14-18, 2007; Los Angeles, CA **JohnGiannios Philip Lambrinos Esmeralda Seraj Nick Alexandropulos Evangelos Maragudakis** PHSA, Oncology Athens

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ABSTRACT: Cancer vaccination Ann Onc., Jan 2000; 11: 41 - 43. . . . ILV) with linked antiHER2 MAb ECD IgG1 eradicates metastatic breast Ca cells overexpressing HER2 via PCD and ADCC. **JohnGiannios**. Emmanuel Michailakis Depl of Oncology, General Hospital of Athens, Athens, About 50% women with breast

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LUNG CANCER: Antisense chemoradioimmunotherapy consisting of anti-IGF-I/HGF bs-scFv linked onto high-energy radioisotopes and TFO targeted to DNMT1 and conjugated to vinorelbine induce ADCC, apoptosis and anoikis in metastatic NSCLC characterised by radio and chemoresistance **Giannios N. John, E. Michailakis, E. Maragudakis, N. Alexandropoulos**, Meeting Abstracts, Jun 2005; 23: 7194. apoptosis and anoikis in metastatic NSCLC characterised by radio and chemoresistance G. N. **John E. Michailakis E. Maragudakis N. Alexandropoulos J. Giannios** GSHA, Athens, Greece; IASO, Athens, Greece; IH, Athens, Greece 7194 Introduction.

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INDEXES: author index Ann. Onc., Jun 2006; 17: vi109 - vi119. . . vi43 Gheta C P-224, vi86 Giacomi N P-162, vi71 **Giannios J** P-118, vi60 **Giannios J** P-119, vi60 Giaquinta S P-268, vi97 Gibbs J P. . . S P-256, vi94 Jo H P-192, vi79 Joe H P-232, vi88 **John A** P-104, vi56 Johnson C P-010, vi34 Johnston P P-056.

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ABSTRACTS: posters Ann. Onc., Jun 2006; 17: vi32 - vi108.

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. P-104 UTILITY OF CA 19 9 IN DENOVO ARISING CHOLANGIOCARCINOMAS **John A**, Haghighi K, Taniere P, Esmat E & Bramhall S Queen Elizabeth. . . TARTRATE (EVT) (UNDER PATENT) INDUCES APOPTOSIS IN PANCREATIC CA **Giannios J** 1, Lambrinos P 2 & Alexandropoulos N 3 1ACR, Oncology; 2PF.

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John Giannios, Emmanuel Michailakis, Esmeralda Seraj, and Nick Alexandropoulos
SEVINA-V composed of pegylated liposomal anti-eIF3c shRNA and vinorelbine inhibits oncogenic protein translational initiation, and oncogene addiction inducing type-I, II PCD in HRBC. AACR Meeting Abstracts, Apr 2008; 2008: 2819. [Meeting Abstract](#)

CANCER INITIATING CELL THERAPEUTIC POTENTIAL: POSTER PRESENTATIONS:

John Giannios, Esmeralda Seraj, Philip Lambrinos, and Nick Alexandropoulos
(BNT) Bispecific nanobody targeting DNMT1 and SHH conjugated to vinorelbine-tartrate (anti-DNMT1/SHH bsNAb-VRL) inhibit DNA methylation, Hedgehog(HH)-Patched(PCTH) receptor signaling protein smoothened (SMO) and hTERT expression leading to re-expression of apoptotic tumor suppressor genes and induction of type-I, II, III PCD in HRBC stem progenitor cells (CSCs). AACR Meeting Abstracts, Apr 2007; 2007: 1334.

EXPRESSION PROFILING OF TUMOR PROGRESSION AND METASTASIS: POSTER PRESENTATIONS - LATE-BREAKING ABSTRACTS:

John Giannios, Philip Lambrinos, Esmeralda Seraj, Nick Alexandropoulos, and Evangelos Maragudakis
Pegylated trispesific disulfide linked Fv(sdFv) targeting epitopes of EGFR, PTHrP and RANKL conjugated covalently with SATA to vinorelbine eradicated osteolytic and osteoblastic metastasis of breast Ca inhibiting proliferation of tumor associated and bone microvascular endothelial cells inducing ADCC, AMP and type-I, II, III PCD.
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EXPERIMENTAL AND MOLECULAR THERAPEUTICS 52: PREDICTION OF DRUG SENSITIVITY AND RESISTANCE:

John N. Giannios, Philip Lambrinos, Emmanuel Michailakis, Nick Alexandropoulos, Evangelos Maragudakis, and Nick Pergandas
Combined administration of antisense chemoradioimmunotherapy (ACRIT) consisting of antiHER2 scFv linked onto high-energy radioisotopes and triplex forming oligonucleotides (TFO) targeted to DNMT1 and conjugated to vinorelbine tartrate induce apoptosis in metastatic breast Ca (MBC) characterized by hypermethylated oncosuppressor genes VHL,

p53, p16, RASSF1A, RAR-b2, TIMP3, PTEN, H-cadherin, BRCA2, p14ARF and overexpression of HIF-1, VEGF, MMP-2, MMP-9, Glut-1, IGF1R, bcl-2, cdc25c, Raf1, TGFa, UPAR, c-Met and EGFR
 AACR Meeting Abstracts, Apr 2005; 2005: 1398.

EXPERIMENTAL AND MOLECULAR THERAPEUTICS 35: PRECLINICAL MODELS/PHARMACOLOGY/MECHANISMS:

John N. Giannios

Pegylated colloidal with linked anti-DNMT1/HDAC2 bispecific single-chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant infiltrating ductal carcinoma of the breast (IDC) characterized by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, tumor suppressor genes, invasion/metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumor antigens, GTP proteins and apoptotic genes.

AACR Meeting Abstracts, Mar 2004; 2004: 883-884.

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Janet Sawicki • Lankenau Institute for *Medical Research*. Activation of NF-κB signaling by IKKβ . . . *John Giannios* • Erasinio *Oncology Hospital* (Greece) . . .
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Esophageal *Cancer*

από GY Yang, *John Giannios*. Head, *Cancer Research*, Erasinio *Oncology Hospital*, Athens, Greece Department of *Medical Oncology*, Kidwai Memorial Institute of *Oncology*, . . .
www.ncbi.nlm.nih.gov › . . . › v. 2(5 Supplement 3); Sep–Oct 2008 - Παρόμοιες

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...gatherings of scientists engaged in *cancer research* worldwide. . . . This July the AACR and the American Society of *Clinical Oncology*. . . Contacts: Dr *John Giannios*, Congress.

Secretariat, Triaena Congress, 24 Har Trikoupistr, 10079 Athens, . . . Academy of Postgraduate *Medical Education and Research*, Alser Strasse 4, . . . cancerres.aacrjournals.org/content/57/7/1400.full.pdf

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International Congress on AIDS and *Cancer Research* in the Year 2000, 10 May, 1997, Athens Hilton, Greece. Contacts: Dr *John Giannios*, Congress . . . cancerres.aacrjournals.org/content/57/6/1213.full.pdf

Περισσότερα αποτελέσματα από cancerres.aacrjournals.org

H. Lee Moffitt Cancer Center & Research Institute - H. Lee Moffitt . . .

Contact Dr *John Giannios*, Congress Secretariat, Triaena Congress, . . . Contact Office of Continuing *Medical Education*, University of Minnesota, . . . 38th Annual Meeting of the British Association of *Cancer Research*, London, United Kingdom. . . . Contact European School of *Oncology*, Via Ripamonti 66, 20141 Milan, Italy. . . . www.moffitt.org/. . . /ccj/. . . /calender.html -

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CALENDAR - Future Medicine-Home

American Association for *Cancer Research*. (AACR) 99th Annual Meeting. San Diego, CA, USA. . . . *Oncology*. Achaia, Greece. Contact: Dr John Giannios. . . . www.futuremedicine.com/userimages/ContentEditor/. . . /FON0402.pdf

Cancer vaccination

από JML Vega - 2000
Medical Oncology, Hospital Nuestra. Senora del Carmen-Alarcos, Ciudad Real; 3. . . . some clinical activity (funded by Spanish *research* project 98/0662). . . . *John Giannios*. Emmanuel Michailakis Dept of *Oncology*, General Hospital . . . annon-c.oxfordjournals.org/content/11/suppl_4/41.full.pdf

Use of induced pluripotent stem cells (iPSCs) encoded with anti . . .

ASCO - The American Society of Clinical *Oncology* (ASCO) is the world's leading professional . . . Category: Cancers of the Esophagus and Stomach - Translational *research*. . . Effect of vinorelbine on chemoresistant *cancer* stem cell renewal in . . . Presenter: *John Giannios*, MD, PhD. Session: Reception and General Poster . . . www.asco.org/. . . /Abstracts?&. . . 72. . . - Προσωρινά αποθηκευμένη

Combining targeted immunotherapy with chemotherapy and radiation . . .

. . . cancer cells by circumventing their chemo and radioresistant mechanisms was by presented by Dr *John Giannios*, Head of Radiotherapeutic *Cancer Research*. . .
www.news-medical.net/. . . /3112.aspx -

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www.ams.ac.ir/AIM/08112/0027.htm -

Layout 1

από GY Yang

John Giannios, Head, *Cancer Research*, Erasinio Oncology Hospital, . Athens, Greece
Department of *Medical Oncology*, Kidwai Memorial Institute of . . .
www.ncbi.nlm.nih.gov/pmc/articles/PMC2663375/pdf/gcr2_5ap0002.pdf

Combined administration of antisense chemoradioimmunotherapy (ACRIT . . .

από JN Giannios - 2005

Molecular *Cancer Research* · Cancer Prevention Research . . . *John N. Giannios*, Philip Lambrinos, Emmanuel Michailakis, Nick Alexandropoulos, . . . GSHA and IASO, Athens, Greece, *Oncology*, PF, Athens, Greece, GSHA, Athens, Greece, IH, . . .
www.aacrmeetingabstracts.org/cgi/content/abstract/2005/1/1398

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2008 ISGIO Conference - International Society of Gastrointestinal . . .

Promoting Excellence in Education, *Research*, and Patient Care in the Rapidly Evolving Management of . . . 2008 Gastrointestinal *Oncology* Conference September 25-27, 2008 . . . *John Giannios*. Session 4: Hepatobiliary *Cancer*. Proffered Papers . . .
www.isgio.org/. . . /program.html - Προσωρινά αποθηκευμένα - Παρόμοιες [PDF]

Gynaecological Gynaecological Gynaecological Gynaecological *Cancer*. . .

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Medical Oncology Group of Australia (MOG) Annual Scientific Meeting . . . Thorne, *Research* Dept, Peter MacCallum *Cancer* Centre, Locked Bag 1 . . . Frontiers of Novel

Targets in Molecular Oncology. *John Giannios*, GHA, Sarantaporou-3, . . .
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[rosscommunications. net/newsletters/GIONC_6_3. pdf](http://rosscommunications.net/newsletters/GIONC_6_3.pdf)

AnnOnc13_S5 Sym pp. 1-200

από RMM Medeiros - 2002

(1) Institute of *Cancer Research*, *Cancer Research UK Centre* for *John Giannios* (1), Emmanuel Michailakis (1). (1) GSHA, Dept. of Oncology, Athens, Greece (1) Hospital Ciudad de Jaén, *Medical Oncology Department*.
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Pegylated liposomal anti-eIF3c shRNA-vinorelbine tartrate . . .

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Failure to trigger PCD due to changes in DNA methylation and histone acetylation is a contributing factor in chemoresistance of IDC. DNMT1 interacts with HDAC2 causing gene silencing which interferes with therapeutic and diagnostic procedures. Our cohort consists of 126 samples . . . P-341 Immunochemotherapy consisting of vinorelbine and IFNa2b induced synergistic TRAIL-mediated apoptosis with caspase-3 release after activation . . .

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Breast cancer constitutes one of the most lethal malignancies due to limited effects of chemotherapy, radiotherapy and immunotherapy. A high metastatic chemoresistant human breast cell line has exhibited overexpression of MDR-1 and MRP mRNA by both RT-PCR. .
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Targeted Therapy: Magic Bullet. . . or Shot in the Dark Tim Eisen. Royal Marsden Hospital, London, United Kingdom. We entered the era of targeted therapies some years ago. However, many questions remain as to how best to develop these therapies. In this talk I . . .

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P-340 Immunochemotherapy consisting of vinorelbine encapsulated in pegylated liposomes with linked anti EGFR chimeric Mabs (SV/22/00) exert ...

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Combined administration of antisense chemoradioimmunotherapy (ACRIT) consisting of antiHER2 scFv linked onto high energy radioisotopes and triplex forming ...

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Introduction: Metastatic breast Ca (MBC) is resistant to almost all cytotoxic drugs and radiation making it one of the most aggressive malignancies in human with the worst mortality. The failure of tumour cells to undergo apoptosis cause resistance to chemoradiological therapies . . .

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Catalytic cleavage of HER2mRNA induces D2 stage of PCD into chemoresistant ESCC after recombinant defective adenovirus mediated transfer of ...

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Combined administration of hydrophilic antimitotic desoxyepothilone B and vinorelbine induce PUMA, suppression of microtubule dynamics, development of ...

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Diabody vinorelbine conjugate (DVC) composed of vinorelbine-tartrate conjugated to anti-DNMT1/SHH di-diabody induce ADCC, CDC, AMP and inhibit DNA ...

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May 24-25, 2008 Kastro Kyllinis, Greece Contact: Dr **JohnGiannios** Tel:
69-74-711-158 E-Mail: jng@otenet.gr 18th Annual Anatomic Pathology ...
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14-3-3-s (stratifin), HIC1 and MDG1 Tumour Suppressor Genes **Giannios**, GSHA, Athens . .

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JohnGiannios Tel: 69-74-711-158 E-Mail: jng@otenet.gr 9TH ...
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metastases within 5 years after primary treatment. Early ...
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Introduction: Metastatic NSCLC is resistant to almost all cytotoxic drugs and radiation.
Materials and Methods: We obtained surgically 132 metastatic NSCLC specimens from
patients. MS-PCR exhibited hypermethylation of oncosuppressors VHL, p63, p53, IGFBP4,
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Contact Dr **JohnGiannios**, . . . Contact Office of Continuing **Medical** Education, University of Minnesota, Radisson Hotel Metrodome, . . . c/o Institute of **Oncology**, . . . www.moffittcancercenter.com/moffittapps/ccj/v4n2/ca. . . - Cached

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8. Esophageal Cancer

JohnGiannios Head, Cancer Research, Erasimio **Oncology** Hospital, Athens, Greece . . . Department of **MedicalOncology**, Kidwai Memorial Institute of **Oncology**, Bangalore, India, www.ncbi.nlm.nih.gov/pmc/articles/PMC2663375

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WASHINGTON, DC— The International Society of Gastrointestinal **Oncology** (ISGIO) played host to more than 500 of the world's top researchers and physicians from 14 . . . www.isgio.org/newsletters/GIONC-2-3.pdf

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. . . **medical** industry professionals and women patients together, . . . **JohnGiannios**, head of Radiotherapeutic Cancer Research at the IASO Hospital, Athens, Greece, . . . Gynecological **Oncology** www.obgyn.net/newsheadlines/womens_health-Breast_Cancer. . . - [Cached](#)

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Victor Levenson • Rush University **Medical** Center . . . **JohnGiannios** • Erasimio **Oncology** Hospital (Greece) 4:30: Closing Remarks. Site Map Contact Us www.marsharivkin.org/events/symposium_agenda.html - [Cached](#)

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Medical Fields . . . **Oncology** . . . technique to kill metastatic breast cancer cells by circumventing their chemo- and radioresistant mechanisms was by presented by Dr **JohnGiannios**, Head . . . www.brightsurf.com/search/r-a/Tumour_Suppressor/1/Tumour. . . - [Cached](#)

14. [Chemoradioimmunotherapy for advanced breast cancer: hope for . . .](#)

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. . . between genetic markers and **oncology** patient quality of life (QOL) . . . versus A and cyclophosphamide (C) as primary **medical** therapy (PMT) in women with breast cancer **meeting**. ascopubs.org/content/vol22/14_suppl - Cached

21. American Society of Clinical **Oncology** 2007

Evaluation of local control in patients with non-metastatic Ewing sarcoma of the bone: A report from the Children's **Oncology** Group. S. G. DuBois, . . .

www.mindcull.com/preview/ASCO_2007.php - Cached

22. Annals of **Oncology** - October 2002, Volume 13, Issue

Are you affiliated with a leading **medical** or academic institution? . . . Annals of **Oncology**. Current Issue . . . **Giannios, John** 1; Michailakis, Emmanuel 1

pt.wkhealth.com/pt/re/anon/toc.00002352-200200005-00000. . . - Cached

BRITISH SOCIETY OF GASTROENTEROLOGY

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS

We are pleased to inform you that your paper has been accepted for **oral presentation** at this meeting. Below you will find instructions regarding your presentation.

Details of your presentation are as follows:

Title: GENE MODIFIED CELLULAR VACCINE (GMCV) COMPOSED OF AUTOLOGOUS ADIPOSE-DERIVED MESENCHYMAL STEM CELLS (AAD-MSCS) TRANSFECTED WITH LIPID-CATION HSP70 ACTIVATED INNATE AND ADAPTIVE IMMUNITY AFTER TARGETING METASTATIC PANCREATIC CA CELLS

BSG11-ABS-2453

Programme Number:	OC-042
Session:	NEOPLASIA & CANCER PATHOGENESIS FREE PAPERS
Date and time of presentation:	Tue 15. 03. 2011 15:30
Place of presentation:	Hall 6
Length of Presentation:	<i>10 minutes presentation + 5 minutes discussion</i> <i>IT IS THEREFORE IMPORTANT THAT YOU REHEARSE YOUR PAPER TO KEEP TO THIS</i>
Presentation Order	5
Speaker guidelines:	See below

Presenting Author: John Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: BIOLOGIC ANTICANCER ACTIVITY OF DESIGNED ANKYRIN REPEAT PROTEINS (DARPINS) TARGETED AGAINST DNMT1 AND CONJUGATED TO DOCETAXEL LEADS TO ERADICATION OF CHEMORESISTANT MUTATED SQUAMOUS CELL EPISPHAGEAL CANCER STEM CELLS.

BSG11-ABS-2388

Programme N°:	PTU-102
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09.30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: APOPTOTIC EFFECT OF PEGYLATED-NANOPARTICLES OF CDP BOUND TO MULTITARGETED SIRNA MOLECULES AGAINST BMI1 AND SURVIVIN CONJUGATED WITH MIR-373 (TERMED AS SEVIN-A) WHICH TARGET GASTRIC CANCER STEM CELLS (GCSCS) OVEREXPRESSING CD44 AFTER CIRCUMVENTION OF CHEMO

BSG11-ABS-2376

Programme N°:	PTU-101
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John N Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: ANTISENSE CHEMORADIOIMMUNOTHERAPY CONSISTING OF ANTI-CASM SCFV LINKED ONTO HIGH ENERGY RADIOISOTOPES, DOCETAXEL, AND 21 NUCLEOTIDE DOUBLE STRANDED SIRNA TARGETED TO DNMT1 INDUCE APOPTOSIS/PCD TYPE-I IN PANCREATIC AND PERIAMPULLARY CARCINOMA

BSG11-ABS-2419

Programme N°:	PTU-104
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: TUMORIGENIC EFFECT OF VINOURELBINE ON CHEMORESISTANT CANCER STEM CELL RENEWAL IN COLORECTAL CANCER (CRC) AND ON METASTASIS.

BSG11-ABS-2428

Programme N°:	PTU-105
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: USE OF INDUCED PLURIPOTENT STEM CELLS (IPSC) ENCODED WITH ANTI-GRP78 SHRNA INDUCES APOPTOSIS/TYPE-I PCD AFTER A GENE-SILENCING BYSTANDER EFFECT FOR CIRCUMVENTION OF VINOURELBINE INDUCED ANGIOGENESIS, AND INHIBITION OF METASTATIC SPREAD IN ADVANCED GIST

BSG11-ABS-2399

Programme N°:	PTU-103
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: ANTISENSE IMMUNOCHEMOGENE THERAPY COMPOSED OF SIRNA TARGETING VEGF-A165B MRNA, ANTIVEGFMAB, AND TXT INHIBITED VEGF MEDIATED DESMOPLASTIC RESPONSE, ANGIOGENESIS, AND LYMPHANGIOGENESIS INDUCING MATURATION OF DCS, ADCC, CMC, AUTOPHAGY, AND PCD IN PDAC

BSG11-ABS-2518

Programme N°:	PTU-108
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: ERADICATION OF METASTATIC GASTRIC CA OF THE ANTRUM RESISTANT TO TRASTUZUMAB AND CETUXIMAB FOLLOWING IMMUNOCHEMOGENE TREATMENT WITH SV-IV, A STEALTH NANOPARTICLE FORMULATION COMPOSED OF CLAMP PNA AGAINST MRNA OF SGCA1/B1, DOCETAXEL, AND MUC1 CHIMERIC MAB

BSG11-ABS-2536

Programme N°:	PTU-109
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: CHEMOGENE TREATMENT CONSISTING OF RECOMBINANT ADENOVIRAL TRANSFECTION OF P16CDNA (SVN-22/3), AND DOCETAXEL ERADICATES CHEMORESISTANT ANEUPLOID PANCREATIC ADENOSQUAMOUS CA CHARACTERISED BY OVEREXPRESSION OF K-RAS AND HYPERMETHYLATION OF CPG ISLANDS OF P16

BSG11-ABS-2591

Programme N°:	PTU-110
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John Giannios

BSG ANNUAL MEETING 14 - 17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted for **poster presentation** at this meeting. Below you find instructions regarding necessary preparation. The details of your presentation are as follows:

Title: LIP-RMDVA COMPOSED OF LIPOSOMAL CDNA ENCODING RECOMBINANT MULTIMODULAR PROTEINS RMDVA COMPRISING DISINTEGRIN/CYSTEINE RICH DISULFIDE BOND 2RGD, C-TERMINAL DOMAIN, METALLOPROTEASE-DOMAIN, AND DIMERIC DISINTEGRIN/MLD-VGD DOMAIN ERADICATED CRC

BSG11-ABS-2592

Programme N°:	PTU-111
Date of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

Presenting Author: John Giannios

BSG ANNUAL MEETING 14-17 MARCH 2011

ICC Birmingham

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted as a **poster** at this meeting. Furthermore, we have the pleasure to inform you that your poster is among the 10% best posters. It is therefore classified as a

Poster of Distinction and will be highlighted with a rosette at the meeting to make sure it gets the appropriate attention. Your abstract will also be highlighted as a 'poster of distinction' in the abstract book. The details of your presentation are as follows:

Title: CETUXIMAB COMBINED WITH MULTI-TARGETED SIRNA AGAINST HSP90, UBCH5, AND SRC CIRCUMVENTED ONCOGENE ADDICTION, TRANSACTIVATION, AND ACQUIRED RESISTANCE AS A RESULT OF EGFR UBIQUITINATION, AND MUTATIONS/DELETIONS IN THE KINASE DOMAIN OF EGFR IN COLORECTAL CA

BSG11-ABS-2500 12 January 2011

Dear John GIANNIOS,

We are pleased to inform you that your abstract has been accepted as a **poster** at this meeting. Furthermore, we have the pleasure to inform you that your poster is among the 10% best posters. It is therefore classified as a

Poster of Distinction and will be highlighted with a rosette at the meeting to make sure it gets the appropriate attention. Your abstract will also be highlighted as a 'poster of distinction' in the abstract book.

The details of your presentation are as follows:

Title: LNA-MODIFIED OLIGONUCLEOTIDES TARGETING MRNA OF DICER IN PEGYLATED COLLOIDAL NANOPARTICLES WITH LINKED ABS AGAINST CD44 ERADICATE ESOPHAGEAL CANCER STEM CELLS (ECSC) BY INDUCTION OF PCD AFTER INHIBITION OF ONCOMIR MACHINERY.

BSG11-ABS-2509

Programme N°:	PTU-107
Date and time of poster presentation:	Tue 15. 03. 2011
Time of poster round:	Please stand next to your poster board between 12:30 and 14:00
Place of poster presentation:	Poster Area
Hanging of poster:	09. 30 on the morning of the presentation day
Removal of poster:	Before exhibition close on the same day
Poster Board size:	2m wide by 1m high (landscape format)

PL07 Plenary Session**ADVANCES IN THE TREATMENT OF ANEURYSM / THORACIC AORTIC PATHOLOGY**

GENE REPLACEMENT THERAPY INDUCES DEVELOPMENT OF NEW CORONARY ARTERIES CIRCUMVENTING CORONARY ARTERY DISEASE

J. Giannios, N. Liasis, N. Alexandropoulos, Erasimio Hospital, Athens, Greece

[15th World Congress on Heart Disease - Advance Program](#)

26 Jul 2010 . . . **International Academy of Cardiology** Awards REGENERATION OF INFRACTED MYOCARDIUM WITH NUTRITIONALLY MODIFIED CARDIAC **STEM CELLS**.
. . by **JOHN GIANNIOS**



13th Biennial Meeting of the International Gynecological Cancer Society
Prague, October 23-26, 2010

Dear John Giannios

1. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0003-00178 entitled '**COLLOIDAL-CDNA ENCODING RECOMBINANT PROTEINS-RMDVA COMPRISING DISINTEGRIN/CYSTEINE-RICH-DISULFIDE BOND 2RGD, AND C-TERMINAL DOMAIN, METALLOPROTEASE-DOMAIN, AND DIMERIC DISINTEGRIN/MLD-VGD DOMAIN (VADD) INDUCED APOPTOSIS IN OVARIAN CA**' has been accepted for **POSTER PRESENTATION** at the *13th Biennial Meeting of the International Gynecological Cancer Society (IGCS 2010)*. Details of your schedule can be found below. In addition, please refer to the IGCS 2010 [scientific program](#) and [instructions for presenters](#) for more information.
2. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0003-00175 entitled '**ADMINISTRATION OF GENE-MODIFIED-CELLULAR-VACCINE COMPOSED OF AUTOLOGOUS-ADIPOSE-DERIVED MESENCHYMAL-STEM-CELLS TRANSFECTED WITH LIPID-CATION-HSP70 ACTIVATES INNATE AND ADAPTIVE IMMUNITY ERADICATING METASTATIC OVARIAN CARCINOMA**' has been accepted for **POSTER PRESENTATION** at the *13th Biennial Meeting of the International Gynecological Cancer Society (IGCS 2010)*. Details of your schedule can be found below. In addition, please refer to the IGCS 2010 [scientific program](#) and [instructions for presenters](#) for more information.
3. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0003-00174 entitled '**LNA MODIFIED OLIGONUCLEOTIDES TARGETING MRNA-DICER IN PEGYLATED COLLOIDAL NANOPARTICLES WITH LINKED ABS AGAINST CD44 ERADICATE OVARIAN CANCER STEM CELLS (OCSCS)**' has been accepted for **POSTER PRESENTATION** at the *13th Biennial Meeting of the International Gynecological Cancer Society (IGCS 2010)*. Details of your schedule can be found below. In addition, please refer to the IGCS 2010 [scientific program](#) and [instructions for presenters](#) for more information.
4. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0003-00162 entitled '**IMMUNOCHEMOGENIC TREATMENT WITH STEALTH NANOPARTICLE FORMULATION CONSISTING OF CLAMP PNA AGAINST MRNA-FOXC2, ANTI-CD44 CHIMERIC-MAB, AND TAXOTERE ERADICATED ADVANCED OVARIAN EPITHELIAL CA**' has been accepted for **POSTER PRESENTATION** at the *13th Biennial Meeting of the International Gynecological Cancer Society (IGCS 2010)*. Details of your schedule can be found below. In addition, please refer to the IGCS 2010 [scientific program](#) and [instructions for presenters](#)

5. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0003-00161 entitled '**PEGYLATED-NANOPARTICLES OF CDP BOUND TO MULTITARGETED SIRNA AGAINST BMI1 AND SURVIVIN CONJUGATED WITH MIR-373 (SEVIN-A) ERADICATES METASTATIC OVARIAN CARCINOMA**' has been accepted for **POSTER PRESENTATION** at the *13th Biennial Meeting of the International Gynecological Cancer Society* (IGCS 2010). Details of your schedule can be found below. In addition, please refer to the IGCS 2010 [scientific program](#) and [instructions for presenters](#) for more information.

6. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0006-00177 entitled '**ANTISENSE TREATMENT WITH PEGYLATED LIPOSOMAL MULTITARGETED SIRNA AGAINST UBCH5, C-SRC, AND HSP90 COMBINED WITH BEVACIZUMAB ERADICATED HORMONE REFRACTORY BREAST CA(HRBC) BY INDUCTION OF APOPTOSIS/PCD TYPEI**' has been accepted for **POSTER PRESENTATION** at the *13th Biennial Meeting of the International Gynecological Cancer Society* (IGCS 2010). Details of your schedule can be found below. In addition, please refer to the IGCS 2010 [scientific program](#) and [instructions for presenters](#) for more information. Session title: **Poster Session I**
Session date: **Saturday, October 23 - Sunday, October 24, 2010**

7. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0006-00167 entitled '**LIPOSOMAL TAXOTERE WITH LINKED-PYMT-MABS INHIBITED VEGF-MEDIATED-HUMAN-TELOMERASE-REVERSE-TRANSCRIPTASE (HTTERT), C-SRC, PI3K, VEGF-A, MMP-2, AND INTEGRINS- A1-2-6 INDUCING APOPTOSIS IN HRBC**' has been accepted for **POSTER PRESENTATION** at the *13th Biennial Meeting of the International Gynecological Cancer Society* (IGCS 2010). Details of your schedule can be found below. In addition, please refer to the IGCS 2010 [scientific program](#) and [instructions for presenters](#) for more information. Session title: **Poster Session I**
Session date: **Saturday, October 23 - Sunday, October 24, 2010**

8. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0001-00166 entitled '**HUMORAL AND CELLULAR IMMUNITY INDUCES APOPTOSIS(PCD) IN CIN2-3, HPV16+ CERVICAL CA AFTER DIVALENT GENETIC VACCINATION WITH CRS TARGETING P53 AND RB**' has been accepted for an **oral presentation** in a **FREE COMMUNICATION SESSION** at the 13th Biennial Meeting of the International Gynecological Cancer Society.
Session title: **Free Communication Session: Cervical, Vulvar, and Vaginal Cancer**
Session date: **Monday, October 25, 2010**
Session time: **08:00 – 10:00** Abstract Presentation Notification

9. On behalf of the Scientific Program Committee, we are pleased to inform you that your abstract A-214-0003-01402 entitled '**OVARIAN TUMOR MULTITARGETING WITH MABS AGAINST GP38, MUC1, AND TAG72 ON PEGYLATED NANODELIVERY PLATFORM OF CYLD AND RIP-1 LEADS TO NECROPTOSIS/ APOPTOSIS**' has been accepted for an **oral presentation** in a **FREE COMMUNICATION SESSION** at the 13th Biennial Meeting of the International Gynecological Cancer Society. Details of your schedule can be found below. In addition, please refer to the IGCS 2010 [scientific program](#) and [instructions for presenters](#) for more information.

Session title: **Free Communication: Young Investigator Oral Presentations**
 Session date: **Monday, October 25, 2010**
 Session time: **08:00-10:00**

Chemoradioimmunotherapy for advanced breast cancer: hope for the future?

7 July, 2004

A successful, and novel, technique to kill metastatic breast cancer cells by circumventing their chemo- and radioresistant mechanisms was presented by Dr John Giannios, Head of Radiotherapeutic Cancer Research at the IASO Hospital, Athens, Greece at the 18th Annual Meeting of the European Association of Cancer Research today (Tuesday 6 July 2004).

Advanced breast cancer, with metastases to lung and bone, has a very poor prognosis and current treatment protocols for this stage of disease generally result in survival periods of less than two years. One of the reasons for this poor prognosis is that metastatic cancer cells are less responsive to treatment than primary tumour cells.

This is partly caused by the fact that the normal cell death process (apoptosis) is repressed by the overexpression of oncogenes such as bcl-2, HER-2, Raf-1 and cdc25c (these oncogenes are expressed more strongly in metastatic tumour cells), which means that the cells fail to die following treatment with chemotherapy drugs and radiation therapy.

Using metastatic tumour tissue taken from a patient with advanced breast cancer, Giannios's team analysed the cells to determine if known oncogenes were being overexpressed. In addition to finding overexpression of the oncogenes bcl-2, HER-2, Raf-1 and cdc25c they also detected overexpression of DNMT1 (a DNA methyltransferase, involved in DNA replication during cell division, and implicated in cancer development) and they also detected methylation of BRCA1 promoter (a process implicated specifically in the development of breast cancer tumours).

The experimental treatment, termed 'chemoradioimmunotherapy', combined chemotherapy, radiation therapy and immunotherapy in one. The chemotherapy component consisted of vinorelbine tartrate (a cytotoxic drug used in the treatment of breast (and other) cancers), the radiotherapy component was provided through the addition of high-energy radioisotopes, whilst the immunotherapy aspect was achieved by attaching an antibody specific to HER-2 to those radioisotopes, as well as through the inclusion of a separate 21-nucleotide double stranded siRNA ('small interfering RNA') generated against DNMT1.

It was hoped that the novel treatment regime would effectively target the tumour cells by blocking the genetic mechanisms that protect the cells from conventional treatment thereby allowing the chemotherapy and radiation therapy components to exert their cytotoxic effects.

By 24 hours post-treatment there was clear evidence that the treated tumour cells were undergoing significantly greater apoptosis than the untreated controls.

Apoptosis was confirmed by the detection of activation of caspase-3-9 (an enzyme involved in apoptosis), inhibition of DNA synthesis and metabolic activity in the tumour cells and the formation of apoptotic bodies. These apoptotic bodies were seen to be phagocytosed (absorbed) by adjacent tumour cells, which resulted in the subsequent apoptosis of the tumour cells through a 'bystander' killing effect.

Several diagnostic tests were employed to determine the molecular basis for the observed success of the chemoradioimmunotherapy treatment. The tests proved that the novel regimen had specifically impacted on the identified oncogenes that are essential to the propagation and perpetuation of the tumour cells. Evidence was found to show 1) there was clear downregulation of HER-2 as a consequence of the action of antiHER-2 scFv antibody; 2) there was re-expression of the tumour suppressor gene BRCA1 as a consequence of the inhibition of the DNMT1 mRNA and; 3) the radioisotopes had induced DNA double strand breaks in the tumour cells.

The combination of these molecular actions was responsible for circumvention of chemo- and radioresistant mechanisms in the tumour cells, allowing them to be effectively targeted and damaged by the chemotherapy and radiation therapy components leading to induction of apoptosis.

According to John Giannios, 'This technique will be very applicable in a clinical setting where treatment difficulties will be limited because, as a tailored and targeted anti-cancer treatment, the treatment will reduce systemic toxicity whilst enhancing the therapeutic index.

'Introducing the radiation by linking the radioisotopes to the anti-HER-2 antibody is more efficient than conventional external beam radiotherapy because the radiation is targeted specifically to those breast cancer cells that over-express HER-2/neu, leaving normal cells unaffected and thereby reducing system toxicity', he added.

'These results open the possibility of combining targeted immunotherapy with chemotherapy and radiation therapy to successfully kill metastatic tumour cells', said Dr Giannios.

'Theoretically this novel technique should be as effective in other types of cancer that are characterised by hypermethylation of tumour suppressor genes and the overexpression of oncogenes such as HER-2 and bcl-2. Our next step will be to develop the treatment in patients, and on a bigger scale, in a Phase I clinical trial'.

Note: The Federation of European Cancer Societies (FECS) is the Brussels-based organisation that represents the interests of almost 18,000 cancer professionals in Europe. FECS promotes the multidisciplinary aspect of cancer care through political and scientific activities.

The European Association for Cancer Research (EACR) is the pan-European organisation representing the scientists and researchers involved in the basic science and research in the field of oncology.

Contact: Stuart Bell

stuart@fecsb.be

00-32-0-495-27-2838

Federation of European Cancer Societies

Article URL: <http://www.medicalnewstoday.com/articles/10412.php>

Main News Category: Cancer/Oncology

Plenary Session-Award 1500 USD

Formulation SEVIN-A composed of Pegylated-Nanoparticles of CDP bound to multitargeted siRNA molecules against BMI1 and Survivin conjugated with miR-373 which targets CD44 overexpressing cancer stem cells (CSCs) of metastatic ovarian carcinoma induces Apoptosis/PCD type-I (D2 Stage) circumventing potent Chemoresistant-Multifactors caused by Vinorelbine

John Giannios • *Erasinio Oncology Hospital (Greece)*



In addition to those listed below are many new, unmentioned presentations in oncology congresses:

Giannios, J. et al., Induction of PCD in ALL cells after combined wtp53 lipofection vinorelbine treatment and radiation, 40th Annual American Society of Hematology Meeting, 4-8 December, 1998, Miami Beach, Florida.

Giannios, J. et al., Eradication by ADCC and p53 indept. PCD of chemoresistant esophageal squamous cell carcinoma (ESCC) overexpressing c-erbB2 after adm. of vinorelbine encapsulated in pegylated immunoliposomes consisting of Mab-antiHER2/neu and hexadecyl-PC, downregulating c-erbB2, (Immunobiology and Biologic Therapy Session) 36th ASCO Annual Meeting, 20-23 May, 2000, New Orleans, Louisiana.

Giannios, J., Immunochemogene Tx consisting of recombinant adenovirus transfection of wt PTEN/MMAC1/TEP1 and PEGylated liposomal transfer of vinorelbine with linked anti-HER2/Neu Mabs induced ADCC, complement dept. cytotoxicity and PCD in breast Ca overexpressing AKT2 and HER2/neu (Experimental/Molecular Therapeutics), 92nd AACR Annual Meeting, March 24-28, 2001, New Orleans, LA, 42, March 2001.

Giannios, J. et al., Chimeric antibodies targeting the SH2 domain of Grb2 and p85a of PI3-K linked on PEG-SUVs with entrapped vinorelbine induced ADCC, ADMC, complement fixation, anoikis, apoptosis and inhibition of Ras/Raf/MEK/MAPK and PI3K/Akt pathways in chemoresistant breast Ca overexpressing HER-2/neu, Proceedings of American Society of Clinical Oncology, Volume 20, Part 1, 37th Annual Meeting, 12-15 May, 2001, San Francisco, CA.

Giannios, J. et al., RhuMAb anti-HER-2/neu pegylated immunoliposomes with incorporated vinorelbine tartrate induces p53 indept. PCD and ADCC in chemoresistant NSCLC, ASCO, 18, 1999.

Giannios, J. et al., HMG-CoA inhibitor lovastatin sensitizes highly aggressive breast carcinoma to PCD induced by vinorelbine, upregulating BAX, p53 and downregulating RhoA-GTPase, bcl-2, ECCO 10, 12-16 September. 1999, Vienna.

Giannios, J. et al., A phase II study with vinorelbine, gemcitabine and cisplatin in the treatment of patients with stage IIIb-IV NSCLC, *Lung Cancer*, 23(1999), 31-37.

Giannios, J. et al., Carcinoembryonic antigen and CA19-9 expression in primary and metastatic histological specimens of colorectal cancer, Annual Panhellenic Oncology Congress, 1999.

Giannios, J. et al., Paclitaxel and carboplatin in advanced NSCLC: a phase II study, *Eur. J. Oncol.*, 4(1), 15-20, 1999.

Giannios et al., ScFv antibody fragments directed against intracellular HER-2/neu has blocked synthesis of membrane HER-2/neu (c-erbB2) proto-oncogene product p185 leading to induction of PCD, International Conference on Advances in Cancer Immunotherapy, New Jersey, March 4, 2000.

Giannios et al., Induction of PCD in human chemoresistant breast carcinoma after combined adm. of Gene and Cytotoxic treatments, 10th International Congress on Senology (Breast diseases) of the Senologic International Society (S. I. S.), 31 May-4 June 1998, Oporto, Portugal.

Giannios, J. et al., Induction of PCD in chemoresistant NSCLC after combined adm. of cytostatic paclitaxel, cytotoxic etoposide and colloidal plasmid pCB6+wtp53, 17th International Cancer Congress, UICC, Rio de Janeiro, Brazil, 24-28 August, 1998.

Giannios, J. et al., Combined adm. of vinorelbine, wtp53cDNA and mitoxantrone treatment induces PCD in chemoresistant cervical carcinoma, *Pharmacology and Experimental Therapeutics*, AACR, April 1, 1998.

Giannios, J. et al., Apoptotic-induced vinorelbine delivery (AIDD) mediated by electrochemotherapy (ECT) under hyperthermic conditions and radiation induced apoptosis (RIA) caused by IR (x-ray) enhanced wtp53 cDNA gene-transfer (REGT) and subsequent ROS formation by p53 induced genes (PIGs) eradicated radioresistant advanced breast Ca (aBRCa) with mutant p53, III International Symposium: Changes in the Treatment of Breast Cancer, 2-4 June, 1999, Madrid, Spain.

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Giannios, J. et al., Chemogene treatment consisting of cyclinD1 antisense ODN, docetaxel and vinorelbine eradicates chemoresistant human metastatic breast carcinoma overexpressing ER, N-Ras and HER-2/neu, Endocrine Treatment & Prevention of Breast and Gynaecological Cancers, 29-30 November and 1 December, 2001, Brussels, Belgium.

Giannios, J. et al., rhuMAb KDR/Fik-1 (VEGFR-2) conjugated to pegylated liposomal docetaxel (ALD) induce ADCC and PCD in endothelial cells and human ovarian carcinoma cells (OCC), Fourth International Symposium on Anti-Angiogenic Agents, Recent Advances and Future Directions in cell Biology and Clinical Research, 11-13 January, 2002, Dallas, Texas.

Giannios, J. et al., Recombinant replication defective adenovirus-p27wt (ARDN/22/76), docetaxel and vinorelbine induce PCD in chemoresistant aneuploid metastatic breast carcinoma (MBC) characterised by overexpression of cyclin D1, N-Ras and Her-2/neu, 93rd Annual Meeting of American Association for Cancer Research, 6-10 April, 2002.

Giannios, J. et al., Bystander killing effect of chemoresistant NSCLC overexpressing HER-2/neu, K-Ras and bcl-2 after induction of ADCC, CMC, anoikis and PCD by immunochemogene treatment consisting of docetaxel and vinorelbine combined with pegylated colloidal complex (SEVINA-00) of anti HER-2/neu Mabs and K-Ras antisense oligonucleotides, Second World Conference on Clinical Cooperative Research for Lung Cancer, Brussels, 7-9 March, 2002.

Giannios, J. et al., Fab fragments of rhu Mab VEGFR-2 conjugated to pegylated colloidal docetaxel (PCD) induce ADCC and apoptosis in endothelial cells and ovarian carcinoma, 1st International Conference on Clinical Gene Therapy, 24-26 January, 2002, University Hospital Groningen, The Netherlands.

Giannios, J. et al., Induction of ADCC and D2 apoptotic stage with subsequent bystander killing effect in medullary breast carcinoma (MBC) cells and lymphatic/vascular endothelial cells after treatment with rhuMAb KDR/Fik-1 (VEGFR-2) linked onto pegylated liposomal vinorelbine tartrate (PLVT), 3rd European Breast Cancer Conference, Federation of European Cancer Societies, 19-23 March 2002, Spain.

Giannios, J. et al., Cyclin D1 antisense ODN, docetaxel and vinorelbine eradicates chemoresistant human metastatic breast carcinoma (MBC) overexpressing ER, N-Ras and HER-2/neu., 3rd European Breast Cancer Conference, Federation of European Cancer Societies, 19-23 March 2002, Spain.

Giannios, J. et al., Combined chemogene treatment consisting of recombinant replication defective adenovirus-p27 (ANST/26/7/64), docetaxel and vinorelbine induces apoptosis in chemoresistant aneuploid metastatic NSCLC characterised by overexpression of cyclin D1, K-Ras and HER-2/neu (c-erbB2), 3rd International Symposium on Genetic Anticancer Agents, 28 February-2 March, 2002, Amsterdam, The Netherlands.

Giannios, J. et al., Eradication of chemoresistant aneuploid metastatic colon carcinoma overexpressing cyclin D1, K-Ras and HER-2/neu after chemogene treatment consisting of recombinant replication defective adenovirus p-27, docetaxel and vinorelbine, 43rd Annual Clinical Conference on Drug Discovery and Clinical Evaluation in the 21st Century, January 16-18, 2002, The University of Texas, MD Anderson Cancer Center, Houston, Texas, USA.

Giannios, J. et al., Eradication of chemoresistant NSCLC overexpressing HER-2/neu, K-Ras and bcl-2 after induction of ADCC, CMC, anoikis and PCD by immunochemogene treatment consisting of docetaxel and vinorelbine combined with pegylated colloidal complex (SEVINA-00) of antiHER-2/neu Mabs and K-Ras antisense oligonucleotides, 43rd Annual Clinical Conference on Drug Discovery and Clinical Evaluation in the 21st Century, January 16-18, 2002, The University of Texas, MD Anderson Cancer Center, Houston, Texas, USA.

Giannios, J. et al., Chemogene treatment consisting of recombinant replication defective adenovirus-p27, docetaxel and vinorelbine induces apoptosis in chemoresistant aneuploid metastatic colon carcinoma characterised by overexpression of cyclin D1, K-Ras and HER-2/neu (c-erbB2), Second Int Conf on High Dose Chemotherapy, INNOVATION and EVOLUTION, 9-12 April 2002, Alberta, Canada.

Giannios, J. et al., Synergistic antiangiogenic and antitumour activity inducing ADCC, CMC, anoikis and PCD after immunochemogene treatment consisting of vinorelbine combined with pegylated colloidal complex (SEVINA-00) of anti HER-2/neu Mabs and K-Ras antisense oligonucleotides in chemoresistant NSCLC, CELL SIGNALING, TRANSCRIPTION AND TRANSLATION AS THERAPEUTIC TARGETS, 30 January-2 February, 2002 (European Conference Center-Luxembourg).

Giannios, J. et al., Induction of ADCC and D2 apoptotic stage with subsequent bystander killing effect in mucinous breast carcinoma (MBC) cells and lymphatic/vascular endothelial cells after treatment with rhu Mab KDR/Fik-1 (VEGFR-2) linked onto pegylated liposomal vinorelbine tartrate, 12th Int Congress on Breast Diseases-SIS, 3-8 November, 2002, Jerusalem, Israel.

Giannios, J. et al., Paclitaxel and not vinorelbine exacerbates doxorubicin induced cardiac mitochondrial dysfunction leading to irreversible apoptotic D2 stage of human cardiomyocytes after alteration of transcripts encoding tissue specific genes and pro-apoptotic genes, 17th Meeting of AACR and 9th Congress of ASEICA, 8-11 June, Granada, Spain.

Giannios, J. et al., Paclitaxel exacerbates doxorubicin induced cardiac mitochondrial dysfunction leading to irreversible apoptotic D2 stage of human cardiomyocytes, 18th International Cancer Congress of UICC, 30 June-5 July, Oslo, Norway.

Giannios, J. et al., Immunochemotherapy consisting of IFNa2b and vinorelbine induced synergistic trail-mediated apoptosis leading to a bystander killing effect of hepatocellular cell carcinoma (HCC), 94th Annual Meeting, American Association for Cancer Research, 5-9 April, 2003, Toronto, Ontario, Canada.

Giannios, J. et al., Chemogene treatment consisting of docetaxel, adenovirus type 5 transfecting p16cDNA and diclofenac induce anoikis, apoptotic-D2 stage and bystander killing effect in chemoresistant pancreatic adenosquamous carcinoma characterised by hypermethylation of CpG islands of p16 (INK4a) and overexpression of bcl-2, K-Ras and PEG2, Eleventh International Conference on Gene Therapy of Cancer, 12-14 December, 2002, Sidney Kinnel Cancer Center, San Diego, California.

Giannios, J. et al., Ad5CMVp53 and vinorelbine decreases MAP4mRNA and VEGFmRNA, suppresses spindle microtubule polymerization, induces NK-cell mediated lysis, CD95L overexpression, neutrophil infiltration, JNK/SAPK activation, bcl-2 phosphorylation, cytochrome-c release, micronucleation, oncosis, apoptosis and bystander killing effect in advanced ovarian carcinoma characterised by missense classII mutations, 11th International

Conference on Gene Therapy of Cancer, 12-14 December, 2002, Sidney Kimmel Cancer Center, San Diego, California.

Giannios, J. et al., Synergistic antiangiogenic and antitumour activity inducing ADCC, CMC, anoikis and PCD after immunochemogene treatment consisting of docetaxel combined with pegylated colloidal complex (SEVINA-3/22) of anti HER2/neu Mabs and K-Ras antisense oligonucleotides in chemoresistant NSCLC, Eleventh International conference on Gene Therapy of Cancer, 12-14 December, 2002, Sidney Kimmel Cancer Center, San Diego, California.

Giannios, J. et al., Chimeric antibodies targeting the SH2 domain of Grb2 and p85a of PI3-K linked on colloidal docetaxel (ILD) induced ADCC, ADMC, complement-fixation, anoikis, apoptosis and inhibition of Ras/Raf/MEK/MAPK and PI3K/Akt pathways in chemoresistant metastatic breast carcinoma overexpressing HER-2/neu, ASCO Molecular Therapeutics Symposium (Educational Program), Angiogenesis Section, Fall, 2002, San Diego, California, USA.

Giannios, J. et al., Induction of PCD in chemoresistant aneuploid pancreatic adenocarcinoma with overexpression of K-Ras and hypermethylation of CpG islands of p16 (INK4a) after chemogene treatment composed of vinorelbine, Docetaxel and recombinant adenoviral type 5 transfection of p16cDNA(SV/22-3/00), ASCO Molecular Therapeutics Symposium (Educational Program), Targeting Molecules Section, Fall, 2002, San Diego, California.

Giannios, J. et al., Overexpression of MAP4 enhances docetaxel's action on microtubule polymerization and bundling, interphase-mitosis (G2/M) arrest, centrosome-damage, JNK/SAPK activation, bcl-2 phosphorylation, cytochrome-c release, kinetochore (+) micronucleation, oncosis and p53 independent apoptosis in metastatic breast carcinoma from SLN characterised by missense class-II p53 mutations, 14th International Congress on Anticancer Treatment, 1-4 February, 2003, Paris, France.

Giannios, J. et al., Combined chemogene treatment of cyclin D1 antisense ORN (SV-22), vinorelbine and docetaxel eradicates by PCD chemoresistant aneuploid metastatic breast carcinoma (MBC) overexpressing Ras and HER-2/neu, 14th International Congress on Anticancer Treatment, 1-4 February, 2003, Paris, France.

Giannios, J. et al., Vinorelbine and doxycycline activate mitochondrial pathway, DR-5 and Fas, downregulate EGFR, MMP, bFGF and bFGF, reduce CA15-3, CEA, Ca⁺⁺, hydroxyproline and hyaluronidase including apoptosis in stage-IV metastatic breast carcinoma metastasized to proximal end of femur, 14th International Congress on Anticancer Treatment, 1-4 February, 2003, Paris, France.

Giannios, J. et al., Fab fragments of the Mab KDR/Flk-1(VEGFR-2) conjugated to pegylated liposomal docetaxel induced ADCC and apoptosis in endothelial cells and ovarian carcinoma cells, 44th Annual Clinical Conference on Molecular Therapeutics for Cancer Metastasis, 18-21 March, 2003, MD Anderson University Hospital, Houston, USA.

Giannios, J. et al., Gene therapy consisting of adenoviral transfection against VEGF mRNA inhibits metastatic tumour growth of infiltrating ductal breast carcinoma after open surgery, 44th Annual Clinical Conference on Molecular Therapeutics for Cancer Metastasis, March 18-21, 2003, MD Anderson University Hospital, Houston, USA.

Giannios, J. et al., Vinorelbine and doxycycline activate mitochondrial intrinsic apoptotic pathway, DR-5, p53, mtCLIC and Fas, downregulate EGFR, MMP, bFGF, bcl-2mRNA and bFGF, reduce CA15-3, CEA, AP, Calcium, hydroxyproline and hyaluronidase inducing PCD in stage-IV metastatic breast carcinoma metastasized to proximal end of femur, 44th Annual Clinical Conference on Molecular Therapeutics for Cancer Metastasis, March 18-21 March, 2003, MD Anderson University Hospital, Houston, USA.

Giannios, J. et al., Combined adm. of vinorelbine, fostriecin, genistein and celecoxib induced anoikis and PCD leading to bystander killing of chemoresistant advanced lung adenocarcinoma (NSCLC) overexpressing EGFR, Ras, MDR-1 and PGE-2, 27th ESMO Congress Nice, France 18-22 October, 2002.

Giannios, J. et al., Combined adm. of docetaxel, EGFR AS-ODN and celecoxib inhibit angiogenic growth factors cytokines, MMPs, PGE2, actin, tubulin, KSP, catenin, Wnt and Bcl-2 inducing TCR-AICD, mitotic-catastrophe and apoptosis in chemoresistant pancreatic carcinoma overexpressing EGFR, Educational Project sponsored by Astra Zeneca, UEGW, 21-23 October, 2002, Geneva, Switzerland.

Giannios, J. et al., Chimeric antibodies targeting the SH2 domain of Grb2 and p85A of PI3-K linked on PEG-SUVs with entrapped docetaxel induced ADCC, ADMC, complement fixation, anoikis, apoptosis and inhibition of Ras/Raf/MEK/MAPK and PI3K/Akt pathways in chemoresistant gastric carcinoma, Educational Project sponsored by Astra Zeneca, UEGW, 21-23 October, 2002, Geneva, Switzerland.

Giannios, J. et al., Replication-incompetent AdvCMV-Smad4, vinorelbine-tartrate and docetaxel reconstitute transcriptional response of TGF- β and phosphorylate bcl-2 inducing apoptosis in chemoresistant pancreatic ductal adenocarcinoma (PDAC), Lecture in Educational Project sponsored by Astra Zeneca, UEGW, 21-23 October, 2002, Geneva, Switzerland.

Giannios, J. et al., Interferon- α 2b and doxycycline activate mitochondrial pathway, Dr-5 and Fas, downregulate EGFR, MMP and bFGF, reduce CA15-3, CEA, AP, Ca, hydroxyproline and hyaluronidase including apoptosis in stage-IV metastatic breast carcinoma metastasized to proximal end of femur, 8th European Winter Oncology Conference, Flims, Switzerland, 19-24 January, 2003, Federation of European Cancer Societies.

Giannios, J. et al., Overexpression of MAP4 enhances docetaxel's action on microtubule polymerization and bundling, interphase-mitosis (G2/M arrest), centrosome-damage, JNK/SAPK activation, bcl-2 phosphorylation, cytochrome-c release, kinetochore (+) micronucleation, oncosis and p53indep. apoptosis in metastatic breast carcinoma from SLN characterised by missense class-II p53 mutations, 4th Annual Lynn Sage Breast Cancer Symposium, 1-3 November, 2002, Chicago.

Giannios, J. et al., Induction of PCD in acute promyelocytic leukemia (APL) after combined administration of chemogene treatment consisting of recombinant PML adenovirus and docetaxel, Leukemia 2002 Congress, towards the cure, 19-22 September, 2002, Miami, FL, USA.

Giannios, J. et al., Eradication of chemoresistant aneuploid metastatic pancreatic carcinoma overexpressing cyclinD1, K-Ras and HER-2/neu after chemogene treatment consisting of recombinant replication defective adenovirus-p27 and docetaxel, Journal of Immunotherapy, Society for Biological Therapy's 17th Annual Meeting, 7-10 November, 2002, San Diego, California, USA.

Giannios, J. et al., Interferon- α 2b and doxycycline activate mitochondrial pathway, DR-5 and Fas, downregulate EGFR, MMP, bFGF and VEGF, reduce S-100B, TA-90, AP, Ca, hydroxyproline and hyaluronidase inducing apoptosis in stage IV malignant melanoma metastasized to proximal end of femur, Journal of Immunotherapy, Society for Biological Therapy's 17th Annual Meeting, 7-10 November, 2002, San Diego, California, USA.

Giannios, J. et al., Interferon- α 2b exhibits pleiotropic immunomodulatory and antitumour effects in metastatic melanoma leading to apoptosis, Journal of Immunotherapy, Society for Biological Therapy's 17th Annual Meeting, 7-10 November, 2002, San Diego, California, USA.

Giannios, J. et al., rhuMAbHER-2/neu and docetaxel eradicates aneuploid and chemoresistant NSCLC overexpressing cyclinD1, HER-2/neu and Ras via ADCC, CMC, anoikis, PCD and inhibition of angiogenesis, 1st International Symposium on Signal Transduction Modulators in Cancer Therapy, 24-25 September, 2002, Amsterdam, The Netherlands.

Giannios, J. et al., Chemogene treatment consisting of cyclinD1 antisense ODN and docetaxel eradicates chemoresistant human metastatic breast carcinoma overexpressing ER, N-Ras and HER-2/neu, Dept. of Defense, USA, Breast Cancer Research Program Meeting, 25-28 September, 2002, Orlando, Florida.

Giannios, J. et al., Combined adm. of antimicrotubule-vinorelbine, NSAID-diclofenac and retinoic-isotretinoin form RAR-RXR heterodimer, activate PPAR, transactivate RARE, stimulate TIL and NK, release IL-2, IFN- γ and TNF- α , phosphorylate bcl-2, inhibit EGFRvIII, Grb2, Raf, MAPK/ERK, AP-1, VEGF, PEG-2, COX-2 and MMP1-3, induce p21Waf1, inhibit kinetochore attachment to spindle poles, disrupt MT dynamics and block cell cycle at G2/M leading to anoikis, apoptotic stage-D2 and bystander killing effect in chemoresistant HNSCC overexpressing bcl-2, PEG-2 and EGFRvIII, Sixth Research Workshop on the Biology, Prevention and Treatment of Head and Neck Cancer, 9-13 October, 2002, McLean, Virginia, USA, American Society of Head and Neck Cancer.

Giannios, J. et al., Overexpression of MAP4 enhances docetaxel's action on microtubule polymerization and bundling interphase-mitosis (G2/M) arrest, centrosome-damage, JNK/SAPK activation, bcl-2 phosphorylation, cytochrome-c release, kinetochore (+) micronucleation, oncosis and p53 indept. apoptosis in NSCLC characterised by missense class-II p53 mutations, H. Lee Moffitt Cancer Center and Research Institute, NCI Comprehensive Cancer Center, 'Molecular Targets for Cancer Therapy:Second Biennial Meeting, 11-15 October, 2002, University of South Florida-College of Medicine.

Giannios, J. et al., Fab fragments of rhuMAb KDR/Fik-1 (VEGFR-2) conjugated to pegylated liposomal vinorelbine (ALV) induce ADCC and apoptosis in ovarian carcinoma cells and activated vascular and lymphatic endothelial cells, 3rd Annual International Conference on Ovarian Cancer, University of Texas MD, Anderson Cancer Center in Houston, Texas, 25-28 September, 2002.

Giannios, J. et al., Combined adm. of vinorelbine-Ad5CMVp53 decreases MAP4mRNA and VEGFmRNA, suppresses spindle microtubule polymerization, poleward tubulin flux and dynamic instability, induces NK-cell mediated lysis, CD95L overexpression, neutrophil infiltration, JNK/SAPK activation, bcl-2 phosphorylation, cytochrome-c release, micronucleation, oncosis, apoptosis and bystander killing effect in advanced ovarian carcinoma characterised by missense class-II mutations, 3rd Annual International Conference on Ovarian Cancer, University of Texas MD, Anderson Cancer Center in Houston, Texas, 25-28 September, 2002.

Giannios, J. et al., Chemogene treatment consisting of vinorelbine and Ad5CMVp53 decreases MAP4mRNA and VEGF mRNA, suppresses spindle microtubule polymerization, induces NK-cell mediated lysis, CD95L overexpression, neutrophil infiltration, JNK/SAPK activation, bcl-2 phosphorylation, cytochrome-c release, micronucleation, oncosis, apoptosis and bystander killing effect in advanced ovarian carcinoma characterised by missense classII mutations, The 3rd World Congress on Controversies in Obstetrics, Gynecology and Infertility-COGI Washington D. C., USA, 20-23 June 2002, The American College of Obstetricians and Gynecologists.

Giannios, J. et al., rhuMAb HER-2/neu, vinorelbine and docetaxel eradicates aneuploid and chemoresistant NSCLC overexpressing cyclinD1, HER-2/neu and Ras via ADCC, CMC, anoikis, PCD and inhibition of angiogenesis, 18th UICC International Cancer Congress, 30 June-5 July, 2002, Oslo, Norway.

Giannios, J. et al., Immunochemotherapy consisting of vinorelbine and IFN- α 2b induced synergistic TRAIL-mediated apoptosis with caspase-3 release, PARP cleavage and internucleosomal DNA fragmentation after activation of DR-5(TRAIL-R2), downregulation of bcl-2, inhibition of endocytosis and signalling of ligand bound-EGFR leading to a bystander killing effect of hepatocellular cell carcinoma (HCC), Gastrointestinal Cancer Research Conference 2002, November 21-3, 2002, Orlando, Florida, Organised by the University of Texas, MD Anderson Cancer Center.

Giannios, J. et al., Induction of apoptosis in chemoresistant pancreatic carcinoma with methylated death receptors and overexpressed bcl-2 after treatment with procanamide and docetaxel, Gastrointestinal Cancer Research Conference 2002, November 21-23, 2002, Orlando, Florida, Organised by the University of Texas, MD Anderson Cancer Center.

Giannios, J. et al., Eradication of chemoresistant gastrointestinal stromal tumour (GIST) cells and lymphatic/vascular endothelial cells by induction of D2 apoptotic stage leading to bystander killing effect (BKE) after treatment with rhu Mab KDR/Fik-1(VEGFR-2) linked onto pegylated liposomal docetaxel (PLD), Gastrointestinal Cancer Research Conference 2002, November 21-23, 2002, Orlando, Florida, Organised by the University of Texas, MD Anderson Cancer Center.

Giannios, J. et al., Combined adm. of vinorelbine, genistein and celecoxib inhibit tyrosine phosphorylation in EGFR, Ras, Raf/MEK/MAPK, PI3K/Akt, STAT3, VEGF, topoisomerase II, PGE-2, COX-2, MMP2, cyclin-B, cdk2, bcl-2, ATP and MDR-1, hyperphosphorylate p53, induce chk2, p27Kip1 and p21Waf1, activate TIL, TIB and NK, release IL-2, IFN-g and TNF- α , inhibit attachment of kinetochores to spindle poles, disrupt MT dynamics and block cell cycle at G2/M leading to anoikis and D2-apoptosis with subsequent bystander killing of pleiotropic chemoresistant advanced lung adenocarcinoma (NSCLC), 8th (CELCC) Central European Lung Cancer Conference (Vienna, Austria, September 1-4, 2002).

Giannios, J. et al., Vinorelbine and doxycycline activate mitochondrial pathway, DR-5 and Fas, downregulate EGFR, MMP, bFGF and VEGF, reduce CA15-3, CEA, AP, Ca, hydroxyproline and hyaluronidase inducing apoptosis in stage-IV metastatic breast carcinoma metastasized to proximal end of femur, 2nd European Conference of Perspectives in Breast Cancer and 1st European Conference of Perspectives in Gynecologic Oncology, 8-9 November, 2002.

Giannios, J. et al., Vinorelbine and ubiquitin-26s proteasome inhibitor deoxyspergualin inhibit NF-kB, TNF- α , IL-8, bcl-2, MDR-1, VEGF, MMP-9, IAPs, CCAAT enhancer-binding proteins and IL-6 with its downstream signaling pathways(Ras/MEK /MAPK, JAK/STAT, PI3-K/Akt), disrupt MT dynamics, include interphase-mitosis (G2/M) arrest and interoligonucleosomal

cleavage of DNA leading to D2-apoptotic stage with subsequent bystander killing of chemoresistant metastatic breast carcinoma, 2nd European Conference of Perspectives in Breast Cancer and 1st European Conference of Perspectives in Gynecologic Oncology, 8-9 November, 2002.

Giannios, J. et al., Concomitant chemoradiotherapy consisting of radiosensitizer vinorelbine, tyrosine-kinase inhibitor (TKI) genistein and X-radiotherapy (XRT) induce apoptosis and bystander killing effect in chemoresistant advanced squamous cell carcinoma of the head and neck (SCCHN), ESTRO, Prague, 17-21 September, 2002.

Giannios, J. et al., Metastatic tumour growth inhibition after open surgery in patients with primary Infiltrating Ductal Breast Carcinoma (IDBC) by adenoviral transfection against VEGFmRNA, Breast Cancer Session of the 55th Annual Cancer Symposium of the American Society of Surgical Oncology, 14-17 March, 2002, Denver, Colorado, USA.

Giannios, J. et al., Eradication of chemoresistant aneuploid pancreatic adenocarcinoma characterised by overexpression of K-Ras and hypermethylation of CpG islands of p16(INK4a) after chemogene treatment with docetaxel, vinorelbine and recombinant adenoviral type 5 transfection, DDW 2002, Pancreatic Cancer Session, 19-22 May, 2002, San Francisco, California, USA.

Giannios, J. et al., Chimeric antibodies targeting the SH2 domain of Grb2 and p85a of PI3-K linked on PEG-SUVs with entrapped vinorelbine induced ADCC, ADMC, complement-fixation, anoikis, apoptosis and inhibition of Ras/Raf/MEK/MAPK and PI3K/Akt pathways in chemoresistant breast carcinoma overexpressing HER-2/neu, Annual Congress of American Society of Clinical Oncology, 2001, USA.

Giannios, J. et al., Concomitant chemoradiotherapy consisting of radiosensitizer vinorelbine, tyrosine kinase inhibitor (TKI), genistein and X-radiotherapy (XRT) induce apoptosis and bystander killing effect in chemoresistant advanced squamous cell carcinoma of the head and neck (SCCHN), 21st Annual ESTRO Meeting, Praha, Czech Republic, 17-21 September 2002.

Giannios, J. et al., Combined chemogene treatment of cyclin D1 antisense ORN (SV-22), vinorelbine and docetaxel eradicates by PCD chemoresistant aneuploid metastatic breast carcinoma (MBC) overexpressing Ras and HER-2/neu, World Conference in Breast Cancer, Victoria Conference Centre, Canada, 4-8 June, 2002.

Giannios, J. et al., Induction of ADCC and D2 apoptotic stage with subsequent bystander killing effect in infiltrating ductal breast carcinoma cells (IDBC) and Lymphatic/vascular endothelial cells after treatment with rhuMAb KDR/FLK-1 (VEGFR-2) linked onto pegylated liposomal vinorelbine tartrate (PLVT), Lecture in the 3rd Annual International Congress of American College of Physicians and American Society of Internal Medicine, Pennsylvania Convention Center in Philadelphia, PA, 11-14 April, 2002, USA.

Giannios, J. et al., Recombinant replication defective adenovirus p27, docetaxel and vinorelbine induces apoptosis in chemoresistant aneuploid metastatic NSCLC overexpressing cyclin D1, K-Ras and HER-2/neu, 3rd International Symposium on Genetic Anticancer Agents, NDDO Oncology, 28 February-2 March 2002, Amsterdam, The Netherlands.

Giannios, J. et al., Immunoliposomal taxol (ILT) induces ADCC, ADCC-complement fixation, anoikis and apoptosis in chemoresistant metastatic breast carcinoma (MBC) overexpressing HER-2/neu, Lecture in ASCO-PACC Congress, India, February 2002.

Giannios, J. et al., Bystander killing effect of chemoresistant NSCLC overexpressing HER-2/neu, K-Ras and bcl-2 after induction of ADCC, CMC, anoikis and PCD by immunochemogene treatment consisting of docetaxel and vinorelbine combined with pegylated colloidal complex (SEVINA-00) of anti HER-2/neu Mabs and K-Ras antisense oligonucleotides, Second World Conference on Clinical Cooperative Research for Lung Cancer, European Lung Cancer Working Party, Session: Therapeutic Clinical Investigation for Lung Cancer, 8-9 March, 2002, Brussels, Belgium.

Giannios, J. et al., Eradication of human epidermoid lung carcinoma (ELC) and lymphatic/vascular endothelial cells by induction of D2 apoptotic stage and ADCC. After treatment with rhu Mab KDR/Flk-1(VEGFR-2) linked onto pegylated liposomal vinorelbine tartrate (PLVT), Second World Conference on Clinical Cooperative research for Lung Cancer, European Lung Cancer Working Party, Session: Therapeutic Clinical Investigation for Lung Cancer, 8-9 March, 2002, Brussels, Belgium.

Giannios, J. et al., Eradication of chemoresistant NSCLC overexpressing HER-2/neu, K-Ras and bcl-2 after induction of ADCC, CMC, anoikis and PCD by immunochemogene treatment consisting of docetaxel and vinorelbine combined with pegylated colloidal complex (SEVINA-00) of anti HER-2/neu Mabs and K-Ras antisense oligonucleotides, 43rd Annual Clinical Conference Drug Discovery and Clinical Evaluation in the 21st Century, The University of Texas, MD Anderson Cancer Center, Houston, Texas, 16-18 January, 2002.

Giannios, J. et al., Eradication of chemoresistant aneuploid metastatic colon carcinoma overexpressing cyclin D1, K-Ras and HER-2/neu after chemogene treatment consisting of recombinant replication defective adenovirus-p27, vinorelbine and docetaxel, 43rd Annual Clinical Conference Drug Discovery and Clinical Evaluation in the 21st Century, The University of Texas, MD Anderson Cancer Center, Houston, Texas, 16-18 January 2002.

Giannios, J. et al., Synergistic antiangiogenic and antitumour activity inducing ADCC, anoikis and PCD after immunochemogene treatment consisting of vinorelbine combined with pegylated colloidal complex (SEVINA) of anti EGFR Mabs and bcl-2 antisense oligonucleotides in chemoresistant metastatic epidermoid/squamous lung carcinoma (NSCLC), II European Spring Oncology Conference (ESOC), Latest Advances on Anticancer Drugs in Clinical Development, Organized by AACR, ESMO, EORTC and Society for Translational Oncology, Marbella, Malaga, Spain, 12-15 June 2002.

Giannios, J. et al., Expression status of p53 in association with cytochrome P450 (CYP3A4) affects metabolism and concentration of vinorelbine in NSCLC, II European Spring Oncology Conference (ESOC), Latest Advances on Anticancer Drugs in Clinical Development, Organised by AACR, ESMO, EORTC and Society for Translational Oncology, Marbella, Malaga, Spain, 12-15 June 2002.

Giannios, J. et al., Alkylating agent cisplatin, antitumour antibiotic-doxorubicin and anti-metabolite fluorouracil repress transcriptionally MAP4 after induction of wtp53 enhancing sensitivity to vinorelbine in metastatic breast carcinoma (MBC), II European Spring Oncology Conference (ESOC), Latest Advances on Anticancer Drugs in Clinical Development, Organised by AACR, ESMO, EORTC and Society for Translational Oncology, Marbella, Malaga, Spain, 12-15 June 2002.

Giannios, J. et al., Combined chemogene treatment consisting of recombinant replication defective adenovirus-p27(ANST/26/7/64), vinorelbine and docetaxel induces apoptosis in chemoresistant aneuploid metastatic NSCLC characterised by overexpression of cyclin D1, K-Ras and HER-2/neu(c-erbB2), 3rd International Symposium on Genetic Anticancer Agents, Feb 28-March 2, 2002, Amsterdam, The Netherlands.

Giannios, J. et al., Chemogene treatment consisting of recombinant adenoviral transfection of p16cDNA (SVN-22/3), vinorelbine and docetaxel eradicates chemoresistant aneuploid pancreatic adenocarcinoma characterised by overexpression of K-Ras and hypermethylation of CpG islands of p16(INK4a), 38th Annual Meeting of American Society of Clinical Oncology, 18-21 May, 2002, Orlando, Florida, USA.

Giannios, J. et al., Immunochemotherapy consisting of rhuMAbHER-2/neu, vinorelbine and docetaxel eradicates aneuploid metastatic breast carcinoma (MBC) from sentinel lymph nodes (SLN) overexpressing cyclin D1, HER-2/neu and Ras via ADCC, CMC, anoikis, PCD and inhibition of angiogenesis, 38th Annual Meeting of American Society of Clinical Oncology, 18-21 May, 2002, Orlando, Florida, USA.

Giannios, J. et al., Paclitaxel exacerbates doxorubicin induced cardiac mitochondrial dysfunction leading to apoptosis of human cardiomyocytes, 38th Annual Meeting of American Society of Clinical Oncology, 18-21 May 2002, Orlando, Florida, USA.

Giannios, J. et al., Chemogene treatment consisting of recombinant replication defective adenovirus p27, vinorelbine and docetaxel induces apoptosis in chemoresistant aneuploid metastatic colon carcinoma characterised by overexpression of cyclinD1, K-Ras and HER-2/neu(c-erbB2), University of Calgary, EBMT Alberta Cancer Board, 2nd International Conference on High Dose Chemotherapy: Innovation and Evolution, Banff, Alberta, Canada, 9-12 April, 2002.

Giannios, J. et al., recombinant replication defective adenovirus-p27 and vinorelbine induces PCD in chemoresistant aneuploid metastatic colon carcinoma characterised by overexpression of cyclinD1, K-Ras and HER-2/neu(c-erbB2), Second International Conference on High Dose Chemotherapy, Innovation and Evolution, April 9-12th 2002, Banff, Alberta, CANADA.

Giannios, J. et al., Overexpression of MAP4 enhances docetaxel's action on microtubule polymerization and bundling, interphase-mitosis (G2/M) arrest, centrosome-damage, JNK/SAPK activation, bcl-2 phosphorylation, cytochrome-c release, kinetochore (+) micronucleation, oncosis and p53 indept. apoptosis in metastatic breast carcinoma from SLN characterised by missense class-II p53 mutations, 4th Annual Lynn Sage Breast Cancer Symposium, 2002 November, Chicago, USA.

Giannios, J. et al., Eradication of chemoresistant aneuploid metastatic pancreatic carcinoma overexpressing cyclinD1, K-Ras and Her-2/neu after chemogene treatment consisting of recombinant replication defective adenovirus-p27, vinorelbine and docetaxel, 17th Meeting of the European Association for Cancer Research, Granada, Spain, 8-11 June, 2002.

Giannios, J. et al., Eradication of chemoresistant aneuploid pancreatic adenocarcinoma characterised by overexpression of K-Ras and hypermethylation of CpG islands of p16 (INK4a) after chemogene treatment with vinorelbine, docetaxel and recombinant adenoviral type 5 transfection, Session: Pancreatic Cancer-Bench to Bedside, DDW, San Francisco, California, 19-22 May, 2002.

Giannios, J. et al., Combined administration of vinorelbine, genistein and celecoxib inhibit tyrosine phosphorylation in EGFR, Ras, Raf/MEK/MAPK, PI3K/Akt, STAT3, VEGF, topoisomerase II, PGE2, COX-2, MMP2, cyclin-B, cdk2, bcl-2, ATP and MDR-1, hyperphosphorylate p53, induce chk2, p27KIP1 and p21Waf1, activate TIL, TIB and NK, release IL-2, IFN-g and TNF-a, inhibit attachment of kinetochores to spindle poles, disrupt MT dynamics and block cell cycle at G2/M leading to anoikis and D2 –apoptosis with subsequent bystander killing of pleiotropic chemoresistant advanced lung adenocarcinoma (NSCLC), 8th Central European Lung Cancer Conference, 1-4 September, 2002, Vienna, Austria.

Giannios, J. et al., Concomitant chemotherapy consisting of radiosensitizer vinorelbine, tyrosine-kinase inhibitor (TKI), genistein and x-radiotherapy (XRT) induce apoptosis and bystander killing effect in chemoresistant advanced squamous cell carcinoma of the head and neck (SCCHN), 21st Annual ESTRO Meeting, 17-21 September, 2002, Praha.

Giannios, J. et al., Fab fragments of rhuMab VEGFR-2 conjugated to pegylated colloidal docetaxel (PCD) induce ADCC and apoptosis in endothelial cells and ovarian carcinoma, 1st International Conference on Clinical Gene Therapy, Groningen, 24-26 January 2002, University Hospital Groningen, Groningen, The Netherlands.

Giannios, J. et al., Eradication of human epidermoid lung carcinoma (ELC) and lymphatic/vascular endothelial cells by induction of D2 apoptotic stage and ADCC after treatment with rhu MAb KDR/Fik-1 (VEGFR-2) linked onto pegylated liposomal vinorelbine tartrate (PLVT), Second World Conference on Clinical Cooperative Research for Lung Cancer, Brussels, March, 2002.

Giannios, J. et al., Bystander killing effect of chemoresistant NSCLC overexpressing HER-2/neu, K-Ras and bcl-2 after induction of ADCC, CMC, anoikis and PCD by immunochemogene treatment consisting of docetaxel and vinorelbine combined with pegylated colloidal complex (SEVINA-00) of anti HER-2/neu Mabs and K-Ras antisense oligonucleotides, Second World Conference on Clinical Cooperative Research for Lung Cancer, Brussels, March, 2002.

Giannios, J. et al., Synergistic antiangiogenic and antitumour activity inducing ADCC, CMC, anoikis and PCD after immunochemogene treatment consisting of vinorelbine combined with pegylated colloidal complex (SEVINA-00) of anti HER-2/neu Mabs and K-Ras antisense oligonucleotides in chemoresistant NSCLC, 'Cell Signaling, Transcription and Translation as Therapeutic Targets', 30 January-2 February, 2002, European Conference Center-Luxembourg.

Giannios, J. et al., rhuMab KDR/Fik-1(VEGFR-2) conjugated to pegylated liposomal vinorelbine (PLV) induce ADCC and PCD in endothelial cells and human ovarian cancer cells (OCC), 4th International Symposium of Anti-angiogenic Agents, Recent Advances and Future Directions in Cell Biology and Clinical Research, January 11-13, 2002, Dallas, Texas, Organised by the University of Arizona, College of Medicine, University of Toronto, Indiana University Cancer Center, National Cancer Institute and The University of Texas, MD Anderson Cancer Center.

Giannios, J. et al., Recombinant replication defective adenovirus p27wt (ARDN/22/76), vinorelbine and docetaxel induce PCD in chemoresistant aneuploid metastatic breast carcinoma (MBC) characterised by overexpression of cyclinD1, N-Ras and HER-2/neu, 93rd Annual Meeting, 6-10 April, 2002, San Francisco, California, 43, March, 2002.

Giannios, J. et al., Combined administration of vinorelbine, fostriecin, genistein and celecoxib induced anoikis and PCD leading to bystander killing of chemoresistant advanced lung adenocarcinoma (NSCLC) overexpressing EGFR, Ras, MDR-1 and PGE-2, 27th ESMO Congress, 18-22 October 2002, Nice, France.

Giannios, J. et al., Synergistic antiangiogenic and antitumour activity inducing ADCC, CMC, anoikis and PCD after immunochemogene treatment consisting of vinorelbine combined with pegylated colloidal complex (SEVINA) of anti EGFR Mabs and bcl-2 antisense oligonucleotides in chemoresistant metastatic breast carcinoma (MBC), 12th International Congress of Anti-Cancer Treatment (SOMPS), 4-7 February, 2002, Paris, France, An International Congress endorsed by ASCO.

Giannios, J. et al., Combined chemogene treatment of cyclinD1 antisense ORN (SV-22) and vinorelbine eradicates by PCD chemoresistant aneuploid NSCLC overexpressing K-Ras and HER-2/neu after their DNA pattern changes to diploid, 12th International Congress of Anticancer Treatment (SOMPS), 4-7 February, 2002, Paris, France, an International Congress endorsed by ASCO.

Giannios, J. et al., Eradication via PCD of chemoresistant pancreatic carcinoma after combined administration of vinorelbine-tartrate and pH sensitive DOPE liposomes which convert to hexagonal phase at tumour micromilieu of pH 6. 8 delivering antisense oligonucleotides against bcl-2mRNA (SV-22-00), 12th International Congress of Anticancer Treatment (SOMPS), 4-7 February, 2002, Paris, France, an International Congress endorsed by ASCO.

Giannios, J. et al., Eradication of chemoresistant aneuploid pancreatic adenosquamous carcinoma characterised by overexpression of K-Ras and hypermethylation of CpG islands of p16(INK4a) after chemogene treatment with vinorelbine, docetaxel and recombinant adenoviral type 5 transfection of p16cDNA termed as SEVINA-22/3, DDW2002, USA.

Giannios, J. et al., Eradication of chemoresistant gastrointestinal stromal tumour (GIST) cells and lymphatic/vascular endothelial cells by induction of D2 apoptotic stage leading to bystander killing effect (BKE) after treatment with rhuMAbKDR/Fik-1 (VEGFR-2) linked onto pegylated liposomal vinorelbine-tartrate (PLVT), GI Malignancies can be Prevented and Treated:From the bench to the bedside, International Congress, Israel, 17-18 January, 2002.

Giannios, J. et al., Induction of ADCC and PCD with subsequent bystander killing effect in infiltrating lobular breast carcinoma cells (ILBC) and lymphatic/vascular endothelial cells after treatment with rhuMAb KDR/Fik-1(VEGFR-2) linked onto pegylated liposomal vinorelbine tartrate (PLVT), Flemish Gynaecological Oncology Group (FGOG), Endocrine Treatment and Prevention of Breast and GynaecologicalCancers, 3rd Biennial International Meeting of the Flemish Gynaecological Oncology Group, 29-30 November and 1 December 2001, KBC Building, Brussels, Belgium.

Giannios, J. et al., Chemogene treatment consisting of cyclinD1 antisense ODN, vinorelbine and docetaxel eradicates chemoresistant human metastaticbreast carcinoma overexpressing ER, N-Ras and HER-2/neu, Flemish GynaecologicalOncology Group (FGOG), Endocrine Treatment and Prevention of Breast and Gynaecological Cancers, 3rd Biennial International Meeting of the Flemish Gynaecological Oncology Group, 29-30 November and 1 December, KBC Building, Brussels, Belgium.

Giannios, J. et al., Induction of ADCC and PCD with subsequent bystander killing effect in infiltrating lobular breast carcinoma cells (ILBC) and lymphatic/vascular endothelial cells after treatment with rhuMAb KDR/Fik-1 (VEGFR-2) linked onto pegylated liposomal

vinorelbine tartrate (PLVT), Flemish Gynaecological Oncology Group (FGOG), Endocrine Treatment and Prevention of Breast and Gynaecological Cancers, 3rd Biennial International Meeting of the Flemish Gynaecological Oncology Group, 29-30 November and 1 December, KBC, Brussels, Belgium.

Giannios, J. et al., Gene therapy consisting of adenoviral transfection against VEGF mRNA inhibits metastatic tumour growth of infiltrating ductal breast carcinoma after open surgery, 11th Congress of the European Society of Surgical Oncology (ESSO), 17-20 April, 2002, Lille, France.

Giannios, J. et al., Immunoliposomal taxol (ILT) induces ADCC, ADCM, complement – fixation, anoikis and apoptosis in chemoresistant metastatic breast carcinoma (MBC) overexpressing HER-2/neu, ASCO PAN-ASIA Cancer Conference (A-PACC), 21-23 September 2001, New Delhi, India.

Giannios, J. et al., Combined chemogene treatment of cyclinD1 antisense ORN (SV-22) and vinorelbine eradicates by PCD chemoresistant aneuploid NSCLC overexpressing K-Ras and HER-2/neu after their DNA pattern changes to diploid, ICACT 2002, February 6-7, 2002, Paris, France.

Giannios, J. et al., Eradication via PCD of chemoresistant pancreatic carcinoma after combined adm. of vinorelbine-tartrate and pH sensitive DOPE liposomes which convert to hexagonal phase at tumour micromilieu of pH 6.8 delivering antisense oligonucleotides against bcl-2 mRNA (SV-22-00), ICACT 2002, February 6-7, 2002, Paris, France.

Giannios, J. et al., Synergistic antiangiogenic and antitumour activity inducing ADCC, CMC, anoikis and PCD after immunochemogene treatment consisting of vinorelbine combined with pegylated colloidal complex (SEVINA) of anti EGFR Mabs and bcl-2 antisense oligonucleotides in chemoresistant metastatic breast carcinoma (MBC), ICACT 2002, 6-7 February, 2002, Paris, France.

Giannios, J. et al., Chemogene treatment consisting of docetaxel, adenovirus type 5 transfecting p16cDNA and diclofenac induce anoikis, apoptotic D2 stage and bystander killing effect in chemoresistant pancreatic adenocarcinoma characterised by hypermethylation, International Conference on Gene Therapy of Cancer, Coronado, California, 12-14 December, 2002.

Giannios, J. et al., Synergistic antiangiogenic and antitumour activity inducing ADCC, CMC, anoikis and PCD after immunochemogene treatment consisting of docetaxel combined with pegylated colloidal complex (SEVINA-3/22), International Conference on Gene Therapy of Cancer, Coronado, California, 12-14, December, 2002.

Giannios, J. et al., AdCMVp53 and vinorelbine decreases MAP4 mRNA and VEGF mRNA, suppresses spindle microtubule polymerization, induces NK-cell mediated lysis, CD95L overexpression, neutrophil infiltration, JNK/SAPK activation, bcl-2 phosphorylation, cytochrome c release, International Conference on Gene Therapy of Cancer, Coronado, California, 12-14 December, 2002.

Giannios, J. et al., Immunochemogene treatments against solid and hematologic malignancies, 3rd Congress in Diagnostic and Therapeutic Developments in Oncology, Greek Ministry of Health Society of Pathologists and Oncologists, Radiotherapeutic Society, 9-10 February, 2002, Patra.

Giannios, J. et al., Eradication of chemoresistant Gastrointestinal Stromal Tumour (GIST) cells and lymphatic/vascular endothelial cells by induction of D2 apoptotic stage leading to bystander killing effect (BKE) after treatment with rhuMAb KDR/Fik-1 (VEGFR-2) linked onto pegylated liposomal vinorelbine (PLV), European Organization for Research and Treatment of Cancer Pharmacology and Molecular Mechanisms Group, 24th Winter Meeting of the EORTC-PAMM Group, 5-8 February, 2003, Florence, Italy.

Giannios, J. et al., Immunochemotherapy consisting of vinorelbine and IFN α 2b induced synergistic trail-mediated apoptosis after activation of DR-5 (TRAIL-R2), down-regulation of bcl-2 and inhibition of signalling of EGFR leading to a bystander killing effect of chemoresistant hepatocellular carcinoma, DDW, AASLD, AGA, ASGE, SSAT, 17-22 May, 2003, Orange County Convention Center, Orlando, FL, USA.

Giannios, J. et al., Adenoviral transfection against VEGFmRNA inhibits metastatic tumour growth of infiltrating ductal breast carcinoma after open surgery, The American Society of Breast Surgeons, 4th Annual Scientific Meeting, The Grand Hyatt Atlanta in Buckhead, 1-4 May, 2003, USA.

Giannios, J. et al., Interferon- α 2b exhibits pleiotropic immunomodulatory and antitumour effects in metastatic malignant melanoma leading to apoptosis, 2003 Annual Meeting of ASCO, 31 May-3 June, 2003, Chicago, Illinois.

Giannios, J. et al., Antimitotic vinorelbine combined with PKC and NF- κ B inhibitor staurosporin induce apoptotic DNA fragmentation in ER(-) advanced breast carcinoma (ABC) overexpressing EGFR, 2003 Annual Meeting of ASCO, 31 May-3 June, 2003, Chicago, Illinois.

Giannios, J. et al., Adenoviral transfection against VEGFmRNA inhibits metastatic tumour growth of infiltrating ductal breast carcinoma after open surgery, The American Society of Breast Surgeons, 4th Annual Scientific Meeting, The Grand Hyatt Atlanta in Buckhead, 1-4 May, 2003.

Giannios, J. et al., Immunochemotherapy consisting of vinorelbine and IFN- α 2b induced synergistic trail-mediated apoptosis after activation of DR-5 (TRAIL-R2), downregulation of bcl-2 and inhibition of signalling of EGFR leading to a bystander killing effect of chemoresistant hepatocellular carcinoma, DDW, AASLD, AGA, ASGE, SSAT, Turning Science into Medicine Orange County Convention Center, Orlando, Florida, USA.

Giannios, J. et al., Vinorelbine and ubiquitin-26S proteasome inhibitor deoxyspergualin inhibit NF- κ B, TNF- α , IL-8, bcl-2, MDR-1, VEGF, MMP-9, IAPs, CCAAT enhancer-binding proteins and IL-6 with its downstream signalling pathways (Ras/MEK/ MAPK, JAK/STAT, PI3-K/AKT), disrupt MT dynamics, induce interphase-mitosis (G2/M) arrest and interoligonucleosomal cleavage of DNA leading to D2 apoptotic stage with subsequent bystander killing of chemoresistant metastatic breast carcinoma, 13th International Meeting of the European Society of Gynaecological Oncology (ESGO), Congress Palace, Brussels, Belgium, 6-10 April, 2003.

Giannios, J. et al., Eradication of chemoresistant Gastrointestinal Stromal Tumour (GIST) cells and lymphatic/vascular endothelial cells by induction of D2 apoptotic stage leading to bystander killing effect (BKE) after treatment with rhuMAb KDR/Fik-1 (VEGFR-2) linked onto pegylated liposomal vinorelbine (PLV), European Organization for Research and Treatment of Cancer (EORTC), Pharmacology and Molecular Mechanisms Group, 24th Winter Meeting of the EORTC-PAMM Group, 5-8 February, 2003, Florence, Italy, Convitto delta Calza.

Giannios, J. et al., Immunochemotherapy consisting of vinorelbine encapsulated in pegylated liposomes with linked anti-EGFR chimeric Mabs (SV/22/00) exert antiangiogenic action and induce ADCC, CMC, anoikis and PCD in chemoresistant metastatic epidermoid/squamous lung carcinoma (NSCLC), 10th World Conference on Lung Cancer, International Association for the Study of Lung Cancer, 10-14 August, 2003, Vancouver, Canada.

Giannios, J. et al., IFN- α 2b in metastatic malignant melanoma (MMM) exerts antiangiogenic, immunoregulatory and antitumour effects leading to PCD with a bystander killing effect, 9th World Congress on Cancers of the Skin, 7-10 May, 2003, Sevilla, Spain.

Giannios, J. et al., Adenoviral-(wt) apaf-1 and vinorelbine induces apoptosis via the caspase-3 pathway in chemoresistant metastatic malignant melanoma characterised by bcl-2 overexpression and mutated Apaf-1 gene, 9th World Congress on Cancers of the Skin, 7-10 May, 2003, Sevilla, Spain.

Giannios, J. et al., Recombinant replication defective adenovirus-p27 and vinorelbine induces apoptosis in chemoresistant aneuploid metastatic NSCLC characterised by overexpression of cyclinD1, K-Ras and HER-2/neu (c-erbB2), International Association for the Study of Lung Cancer, 10th World Conference on Lung Cancer, 10-14 August, 2003, Vancouver, Canada.

Giannios, J. et al., Combined chemogene treatment of cyclinD1 antisense ORN (SV-22) and vinorelbine eradicates by PCD chemoresistant aneuploid NSCLC overexpressing K-Ras and HER-2/neu after their DNA pattern changes to diploid, International Association for the Study of Lung Cancer, 10th World Conference on Lung Cancer, 10-14 August, 2003, Vancouver, Canada.

Giannios, J. et al., Vinorelbine, fostriecin, genistein and celecoxib induced anoikis and PCD leading to bystander killing of chemoresistant advanced lung adenocarcinoma (NSCLC) overexpressing EGFR, Ras, MDR-1 and PEG-2, International Association for the Study of Lung Cancer, 10th World Conference on Lung Cancer, 10-14 August, 2003, Vancouver, Canada.

Giannios, J. et al., Immunochemotherapy consisting of vinorelbine and IFN α 2b induced synergistic TRAIL-mediated apoptosis with caspase-3 release after activation of DR-5 (TRAIL-R2) and downregulation of bcl-2 and EGFR leading to a bystander killing effect of chemoresistant NSCLC, International Association for the Study of Lung Cancer, 10th World Conference on Lung Cancer, 10-14 August, 2003, Vancouver, Canada.

Giannios, J. et al., rhuMAb HER-2/neu and vinorelbine eradicates aneuploid and chemoresistant NSCLC overexpressing cyclinD1, HER-2/neu and Ras via ADCC, CMC, anoikis, PCD and inhibition of angiogenesis, International association for the Study of Lung Cancer, 10th World Conference on Lung Cancer, 10-14 August, 2003, Vancouver, Canada.

Giannios, J. et al., Induction of apoptosis in chemoresistant pancreatic carcinoma with methylated death receptors and overexpressed bcl-2 after treatment with procanamide and vinorelbine, 3rd Circulating Nucleic Acids Plasma/Serum Conference, John Wayne Cancer Institute, The Sidney Kimmel Comprehensive Cancer Center at John Hopkins and Division of Genetics, Tufts-New England Medical Center, Loews Santa Monica Beach Hotel, California, USA, 17-19 March, 2003.

Giannios, J., Immunochemotherapy consisting of IFNA2B and vinorelbine induced synergistic trail-mediated apoptosis leading to a bystander killing effect of hepatocellular cell carcinoma (HCC), 94th Annual Meeting, 5-9 April, 2003, Toronto, Ontario, Canada.

Giannios, J., Immunochemotherapy consisting of vinorelbine and IFNA2B induced synergistic Trail-mediated apoptosis after activation of DR-5(TRAIL-R2), downregulation of bcl-2 and inhibition of signalling of EGFR leading to a bystander killing effect of chemoresistant hepatocellular carcinoma, DDW 2003.

Giannios, J., Immunochemotherapy consisting of vinorelbine-tartrate and IFN-a2b induced synergistic TRAIL mediated apoptosis with caspase-3 release after activation of DR-5(TRAIL-R2) and downregulation of bcl-2 and EGFR leading to a bystander killing effect of chemoresistant advanced breast carcinoma, ESEC2003, 19-22 June 2003, UK.

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant infiltrating (or invasive) ductal carcinoma of the breast (IDC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, TSG, invasion/metastasis suppressors, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, Lynn Sage Breast Cancer Symposium, 18-21 September, 2003, Chicago.

Giannios, J., Pegylated liposomal formulation of chimeric LNA/DNA antisense oligonucleotides against DNA MeTase and vinorelbine induces apoptosis in infiltrating ductal carcinoma (IDC) characterised by 5'CpG island methylation of the FHIT gene, Second Annual Future of Breast Cancer, July 31-August 3, 2003, Canada.

Giannios, J., Synergistic action of vinorelbine, sodium phenylbutyrate and 5-azacytidine eradicates breast cancer cells characterised by epigenetic alterations such as DNA methylation and histone deacetylation, Second annual Future of Breast Cancer, July 31-August 3, 2003, Canada.

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single-chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant infiltrating ductal carcinoma (IDC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of the FHIT, RAR-b2, BBRCA-1, APC, p16(CDKN2A), RASSF1A, CDH1(E-cadherin), 14-3-3- σ (stratifin), HIC1 and MDG1 tumour suppressor genes, Second International Congress on Targeted Therapies in Cancer, 2003, 29-31 August, Washington, USA.

Giannios, J., Synergistic action of vinorelbine and 5-azacytidine against breast cancer using epigenetic alterations consisting of DNA methylation and histone deacetylation as biomarkers, The 20th IATMO Conference, Tumor Markers in Cancer Diagnosis and Therapy, 21-25 June, 2003, Siena, Italy.

Giannios, J., Immunotherapy consisting of vinorelbine encapsulated in pegylated liposomes with linked antiEGFR chimeric Mabs (Sv/22-00) exert antiangiogenic action and induce ADCC, CMC, anoikis and PCD in chemoresistant metastatic choroidal melanoma, 18th Annual Meeting of the iSBTc, 30 October-2 November, 2003, Bethesda.

Giannios, J., Peg-liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated VRL induces ADCC and apoptosis in advanced breast Ca (IDC) characterised by HDAC2 overexpression and 5'CpG island

hypermethylation of TSGs, 18th Annual Meeting of the iSBT, 30 October-2 November, 2003, Bethesda.

Giannios, J., Pegylated colloidal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant prostate carcinoma (Pca) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, TSGs, invasion suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, European School of Urology, 2nd European Urological Winter Escape Meeting, Tenerife, Spain, 30 November-3 December, 2003.

Giannios, J., antiEGFR chimeric Mabs linked on pegylated liposomal vinorelbine exert antiangiogenic action and induce ADCC, CMC, anoikis and PCD in chemoresistant prostate Ca, European School of Urology, 2nd European Urological Winter Escape Meeting, Tenerife, Spain, 30 November-3 December, 2003.

Giannios, J., Induction of apoptosis of chemoresistant pancreatic carcinoma after combined administration of vinorelbine tartrate and pH sensitive DOPE liposomes which convert to hexagonal phase at tumour micromilieu of pH 6. 8 delivering antisense oligonucleotides against bcl-2 mRNA (SV-22-00), The 3rd International Conference on Tumour Microenvironment:Progression, Therapy and Prevention, Prague, Czech Republic, 12-16 October, 2004.

Giannios, J., Immunochemotherapy consisting of vinorelbine and IFNa2b induced synergistic TRAIL mediated apoptosis with caspase-3 release after activation of DR-5 (TRAIL-R2) and downregulation of bcl-2 and EGFR leading to a bystander killing effect of chemoresistant NSCLC, World Conference on Lung Cancer, Canada, 2003.

Giannios, J., Combined chemogene treatment of cyclin D1 antisense ORN (SV-22) and vinorelbine eradicates by PCD chemoresistant aneuploid NSCLC overexpressing K-Ras and HER-2/neu after DNA pattern changes to diploid, World Conference on Lung Cancer, Canada, 2003.

Giannios, J., Immunochemotherapy consisting of vinorelbine encapsulated in pegylated liposomes with linked anti EGFR chimeric Mabs (SV/22/00) exert antiangiogenic action and induce ADCC, CMC, anoikis and PCD in chemoresistant metastatic epidermoid/squamous lung carcinoma (NSCLC), IASL, World Conference on Lung Cancer, 2003.

Giannios, J., Eradication of chemoresistant breast carcinoma with methylated death receptors and overexpressed bcl-2 after treatment with procanamide and vinorelbine, Lecture, XVII FIGO World Congress of Gynecology and Obstetrics, 2-7 November, 2003, Santiago, Chile.

Giannios, J., Eradication of metastatic orbital rhabdomyosarcoma characterised by hypermethylation of CpG islands of p16(INK4a) after chemogene Tx with vinorelbine and recombinant adenoviral type 5 transfection of p16cDNA termed as SV-22/0, 12th Int. Conference on Gene Therapy of Cancer, 11-13 December, 2003, San Diego, California.

Giannios, J., Pegylated colloidal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant infiltrating ductal carcinoma of the breast (IDC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers,

tumour suppressor genes, metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, 12th Int Conf on Gene Therapy of Cancer, 11-13 December, 2003, San Diego, California.

Giannios, J., Peg-liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated VRL induces ADCC and apoptosis in advanced breast Ca (IDC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of TSGs, the International Society for Biological Therapy of Cancer, 18th Annual Meeting, 30 October-2 November, 2003, Bethesda, Maryland, USA.

Giannios, J., Immunotherapy consisting of vinorelbine encapsulated in pegylated liposomes with linked antiEGFR chimeric Mabs (Sv/22-00) exert antiangiogenic action and induce ADCC, CCMC, Anoikis and PCD in chemoresistant metastatic choroidal melanoma, iSBTc 18th Annual Meeting, 30 October-2 November, 2003, Bethesda, Maryland, USA.

Giannios, J., Eradication of chemoresistant aneuploid metastatic pancreatic carcinoma overexpressing cyclinD1, K-Ras and HER-2/neu after chemogene treatment consisting of recombinant replication defective adenovirus p-27 and vinorelbine, 11th United European Gastroenterology Week –UEGW 2003, Madrid, Spain, 1-5 November 2003.

Giannios, J., Ppeglylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant prostate carcinoma (Pca) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, TSG, metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, The 5th World congress on Urological Research, 24-27 September, 2003, London, UK.

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces ADCC and apoptosis in chemoresistant acute myelocytic leukemia (AML) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, TSGs, metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, cell cycle regulators, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, Lynn sage breast Cancer Symposium, Chicago, 19-21 September, 2003.

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant gastric carcinoma (GC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of the FHIT, TRAIL, p16(INK4A/MTS1/CDKN2), ARHI, E-Cad, hMLH1, p15, MGMT, DAPK1, MINT2, GSTP1, RIZ1, HLTF, PLA2G2A, LOX, HRASLS, Thrombomodulin, FLNc, HAND1, DFNA5, SOCS-1, BACE2, NFYA, PRKCBP1, MBP, RBICCI, TIMP3, THBS1, TP53 and APC genes, 4th ESH-UT MD Anderson Cancer Center, Int. Conf on Mechanisms of Cell Death and Disease:Advances in Therapeutic Intervention, 14-17 November 2003, Mexico.

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces ADCC and apoptosis in chemoresistant acute myelocytic leukemia (AML) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, tumour suppressor genes, invasion/metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, cell cycle regulators, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, 4th ESH-UT MD Anderson Cancer Center, Int.

Conf on Mechanisms of Cell Death and Disease:Advances in Therapeutic Intervention, 14-17 November 2003, Mexico.

Giannios, J., PEG-liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated VRL induces ADCC and apoptosis in advanced breast Ca (IDC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of TSGs, International Society for Biological Therapy of Cancer (iSBT), 18th Annual Meeting, 30 October-2 November, 2003, Bethesda, Maryland, USA.

Giannios, J., Immunotherapy consisting of vinorelbine encapsulated in pegylated liposomes with linked antiEGFR chimeric Mabs (Sv/22-00) exert antiangiogenic action and induce ADCC, CMC, anoikis and PCD in chemoresistant metastatic choroidal melanoma, International Society for Biological Therapy of Cancer (iSBT), 18th Annual Meeting, October 30-Nov 2, 2003, Bethesda, Maryland, USA.

Giannios, J., Eradication of chemoresistant breast carcinoma with methylated death receptors and overexpressed bcl-2 after treatment with procanamide and vinorelbine, Lecture, XVII FIGO World Congress of Gynecology and Obstetrics, Santiago, Chile, 2-7 November, 2003.

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant prostate Ca (PCa) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, TSGs, invasion/metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, Lecture, The 5th World Congress on Urological Research Congress Secretariat, 2003, London.

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Giannios, J., Immunochemoconjugate of anti-DNMT1/HDAC2 bispecific F(ab02-bsAb linked with cleavable disulfide to vinorelbine (I-VRL) induces apoptosis in chemoresistant infiltrating ductal carcinoma (IDC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of the FHIT, RAR-b2, BRCA-1, APC, p16(CDKN2A), RASSF1A, CDH1(E-cadherin), 14-3-3-s(stratifin), HIC1 and MDG1 TSGs, Third International Congress on Monoclonal Antibodies in Cancer, Quebec, Canada, 14-17 August 2003.

Giannios, J., Combined immunochemogene treatment with adenoviral (wt)Apaf-1, Interferon a2b and vinorelbine induces apoptosis pathway in chemoresistant metastatic malignant melanoma characterised by bcl-2 overexpression and mutated Apaf-1 gene, First International Melanoma Research Congress, 21-24 June, 2003, Pennsylvania, USA.

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single-chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant epithelial ovarian carcinoma (EOC) characterised by HDAC2 overexpression

and 5'CpG island hypermethylation of growth regulators, signal transducers, tumour suppressor genes, invasion/metastasis suppressors, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, 4th Annual Int Conference on Ovarian Cancer, 11-13 September, 2003, New York.

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Giannios, J., Pegylated liposomal formulation of chimeric LNA/DNA antisense oligonucleotides against DNA MeTase and vinorelbine induces apoptosis in NSCLC characterised by 5'CpG island methylation of the FHIT gene, Fourth International Lung Cancer Congress, Maui, Hawaii, 25-28 June, 2003.

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Giannios, J., Immunochemogene treatment consisting of vinorelbine combined with pegylated colloidal complex (SEVINA) of anti EGFR Mabs and bcl-2 antisense oligonucleotides induces ADCC, anoikis and PCD in chemoresistant metastatic breast carcinoma (MBC), The 19th Annual Meeting on Oncogenes-Cancer Biology and Therapeutics, 18-21 June, 2003, Hood College frederick, Maryland.

Giannios, J., IFN-a2b in metastatic melanoma exerts antiangiogenic, immunoregulatory and antitumour effects leading to PCD with a bystander killing effect, 9th World Congress on Cancers of the Skin, 7-10 May, 2003, Sevilla, Spain.

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Giannios, J., Combined administration of antimitotic vinorelbine tartrate and sulfatase inhibitor danazol induces apoptosis in chemoresistant prostate Ca characterised by overexpression of AR, ARSC and bcl-2, 13th European Urological Winter Forum, Davos, Switzerland, 14-18 February, 2004.

Giannios, J., Genetically engineered VRL-loaded endothelial cells expressing FGFR1/TRAIL/Apo-2L caused apoptotic-induced drug delivery (AIDD) leading to bystander killing effect in chemoresistant prostate carcinoma characterised by overexpression of MDR-1 and bcl-2, 13th European Urological Winter Forum, Davos, Switzerland, 14-18 February 2004.

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant prostate carcinoma (PCa) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, tumour suppressor genes, invasion/metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, 13th European Urological Winter Forum, Davos, Switzerland, 14-18 February 2004.

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Giannios, J., Anastrozole, 5-deoxy-azacytidine and vinorelbine tartrate induce apoptosis in advanced breast infiltrating ductal carcinoma characterised by overexpression of bcl-2, CpG island hypermethylation of aromatase (CYP19) gene and ER, The 4th Genolier –Geneva-MSKCC Cancer Conference Optimizing Cancer Chemotherapy and Hormonal Therapy: The key role of supportive agents, 2004.

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Giannios, J., Photodynamic treatment with porfimer sodium associated LDL and vinorelbine tartrate exert synergistic MT depolymerizing action, antiangiogenicity and induction of D2 apoptotic stage in chemoresistant breast carcinoma overexpressing bcl-2 and MDR-1, American Society of Laser Medicine Society, 2004.

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Giannios, J., Genetically engineered VRL loaded FGFR1/TRAIL/Apo-2L expressing endothelial cells caused apoptotic-induced drug delivery (AIDD) leading to bystander killing effect in chemoresistant stromal breast carcinoma characterised by overexpression of MDR-1 and bcl-2, 1st ISC Int. Conf on Cancer Therapeutics, Molecular Targets, Pharmacology and Clinical Applications, 19-21 February, 2004, Florence.

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Giannios, J., Combined adm. of indomethacin, anastrozole and vinorelbine exert antiangiogenic, antimetabolic and antiaromatase action against invasive ductal Ca (IDC) metastasized to axillary lymph nodes of a postmenopausal patient characterised by overexpression of HER-2/neu, COX-2, Ras, bcl-2 and ER, 5th Int. Symposium on Women's Health and Menopause Endocrine Treatment and Prevention of Breast Cancer, Florence, Italy, 15-17 January, 2004.

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Giannios, J., Vinorelbine and anastrozole induce apoptosis and anti-angiogenesis in breast desmoplastic stromal carcinoma postmenopausal patients characterised by overexpression of ER and ECM proteins fibronectin (FN) and tenascin (TN), 11th World Congress of Gynecological Endocrinology, 26-29 February 2004, Florence, Italy.

Giannios, J., Epigenetic alterations consisting of DNA methylation and histone deacetylation are used as cancer molecular markers for breast cancer treated with vinorelbine and 5-azacytidine, 3rd International Meeting on Cancer Molecular Markers: from discovery to clinical practice, 18-20 April, 2003, Brussels, Belgium.

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Giannios, J., Eradication of chemoresistant breast Ca with methylated death receptors and overexpressed bcl-2 after treatment with procanamide and VRL, XVII FIGO 2003, Lecture, World Congress of Gynecology and Obstetrics.

Giannios, J., Second line treatment composed of trichostatin, anastrozole and vinorelbine tartrate induce apoptosis in post-menopausal patients with TAM resistant breast cancer depleting mRNA and protein levels of HDAC, HER2/neu, AIB1(SRC-3), PI3-K/AKT/NFkB, MAPK, CYP19, Era, bcl-2, c-Raf-1, MAP-1, MMP-2(gelatinaseA) and upregulating p21Waf1 and p27KIP1, 5th Int. symposium on Women's Health and Menopause, New findings, New Strategies, Improved Quality of Life, Florence, Italy, 21-24 April, 2004.

Giannios, J., Photodynamic treatment with porfimer sodium associated LDL and vinorelbine cause eradication of chemoresistant breast carcinoma overexpressing bcl-2 and MDR-1, Breast Cancer Session, European Society of Surgical Oncology, ESSO 31-March-3 April, 2004, Budapest, Hungary.

Giannios, J., PDT with porfimer sodium associated LDL and vinorelbine exert synergistic microtubule depolymerization, antiangiogenicity and induction of D2 apoptosis in chemoresistant Breast Carcinoma overexpressing bcl-2 and MDR-1, 24th Annual Meeting of the American Society for Laser Medicine and Surgery, April 2004, Dallas, Texas (lecture).

Giannios, J., Pegylated liposomal formulation with linked anti-DNMT1/HDAC2 bispecific single chain Fv molecules (bs-ScFv) and encapsulated vinorelbine induces apoptosis in chemoresistant prostate carcinoma (PCa) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, TSGs, invasion/metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GGTP proteins and apoptotic genes, European

Association of Urology, 13th European Urological Winter Forum in Davos, 15–17 February, 2004.

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Giannios, J., Combined administration of antimitotic vinorelbine tartrate and sulfatase inhibitor danazol induces apoptosis in chemoresistant prostate Ca characterised by overexpression of AR, ARSC and bcl-2, 13th European Urological Winter Forum in Davos, 15-17 February, 2004.

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Giannios, J., Genetically engineered endothelial cells expressing VRL-loaded FGFR1/TRAIL/Apo-2L caused apoptotic-induced drug delivery (AIDD) leading to bystander killing effect in chemoresistant stromal breast carcinoma characterised by overexpression of MDR-1 and bcl-2, 1st conference on Cancer therapeutics-Molecular Targets, Pharmacology and Clinical Applications, February, 2004, Florence, Italy.

Giannios, J., Combined adm. of hydrophilic antimitotic desoxyepothilone b and vinorelbine induce PUMA, suppression of MT dynamics, development of hypodiploidy and multinucleation, cell cycle perturbation at G2/M and apoptosis in advanced NSCLC characterised by MDR-1(Pgp), MRP1/ABCC1, bcl-2 and mutant b-tubulin, 1st Conference on Cancer Therapeutics-Molecular Targets, Pharmacology and Clinical Applications, 19-21 February, 2004.

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Giannios, J., Anastrozole, 5-deoxy-azacytidine and vinorelbine tartrate induce apoptosis in advanced breast infiltrating ductal carcinoma characterised by overexpression of bcl-2, 5'CpG island hypermethylation of aromatase (CYP19) gene and ER, The 4th Genolier-Geneva-MSKCC Cancer Conference:Optimizing Cancer Chemotherapy and Hormonal Therapy:The Key Role of Supportive Agents, 5-6 February 2004.

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carcinoma (IDC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of the FHIT, RAR-b2, BRCA1, APC, p16(CCDKN2A), RASSF1A, CDH1(E-Cadherin), 14-3-3-s(stratifin), HIC1 and MDG1 tumour suppressor genes, ASCO 2004, American Society of Clinical Oncology, annual meeting.

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Giannios, J., Pegylated liposomal formulation with linked antiDNMT1/HDAC2 bispecific single chain Fv molecules ((bs-ScFv) and encapsulated VRL induces PCD and ADCC in chemoresistant gastric carcinoma (GC) characterised by HDAC2 overexpression and 5'CpG island hypermethylation of growth regulators, signal transducers, TSGs, invasion/metastasis suppressor genes, DNA repair genes, hormone and kinase receptors, angiogenesis inhibitors, tumour antigens, GTP proteins and apoptotic genes, 2004 Gastrointestinal Cancers Symposium, san Francisco, CA 22-24 January, 2004.

Giannios, J., Chimeric LNA/DNA antisense ODN against DNA MeTas and VRL encapsulated in pegylated liposomes induce apoptosis in chemoresistant advanced colon Ca characterised by 5'CpG island methylation of RUNX3, MLH1, MGMT, p16INK4A, CDH1, LKB1, HIC1, CDX1, FHIT and RAR-b2 genes, 2004 GI Cancers Symposium, ASCO.

...and many more publications and lectures in molecular targeting, and tailored treatment with -omics in all types of metastatic and radio/chemoresistant cancer presented in American and European oncology congresses and journals.
