

## Profiles and Legacies

# The Cancer Story

### Demetrios A. Spandidos

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As I am looking back on 35 years of my career I come to the conclusion that science is for long distance runners. I also think that Max Planck was right in saying that an important scientific innovation rarely makes its way by gradually winning over and converting its opponents. What does happen is that its opponents gradually die out and that the growing generation is familiarized with the idea from the beginning.

I was born in Agios Constantinos a little village in the slopes of mount Taygetos near Sparta, Greece. As a youngster I had to walk long distances to go to school, forming a habit that I still keep up. During my undergraduate studies at the Department of Chemistry, University of Thessaloniki, Greece, I was fortunate to meet my first mentors Professors John Georgatsos and Joyce Taylor-Papadimitriou. My first article<sup>1</sup> with them on interferon published in *Biochemical and Biophysical Research Communications* in 1971, while I was still an undergraduate student, was seminal in my future experiments on gene transfer since I had first hand experience of the precipitation of DNA at certain concentrations of calcium. The work was carried out at the laboratories of Biochemistry and Virology at the Theagenion Cancer Institute of Thessaloniki where I was first introduced to cancer research in 1970.

After I got my degree in Chemistry I did my Ph.D. in Biochemistry at McGill University in Montreal, Canada (where my two older sisters and brother lived as landed immigrants) with Professor Angus F. Graham on the genetics and transcription control of human reoviruses. During those studies I also had the opportunity to discover the first avian reovirus.<sup>2</sup> I am still in touch with Professor Angus F. Graham who retired nearly 20 years ago, however his thoughts continue to be as solid as a rock.

My main interest still remained in cancer research, which is why I had chosen for post doctoral work the laboratory of Professor Louis Siminovitch in Toronto, Canada where I had the freedom to do whatever I thought was of great importance. There, when I started working on the gene transfer of dominant markers in somatic cell cultures I got the idea that cancer cells would carry genes which I called cancer genes and that these genes would act dominantly in the cells. So, if these genes could be transferred from cancer cells to normal cells then they could be eventually isolated. Thus, I envisaged an ideological and methodological approach to study cancer and identify cellular cancer genes, the so-called oncogenes. The idea and the methodology were very provocative at the time. First, because oncogenes were supposed to exist only in viruses and cellular cancer genes to act recessively, as had been hypothesized by the work in cell hybrids, the idea seemed improbable. Second, the calcium phosphate technique of F. Graham and A. Van der Eb had predicted a frequency for transfer of cellular markers (genes) of  $10^{-9}$ , so it was not feasible to select for the transfer any marker with existing techniques. However, for reasons that we still not quite understand and to the surprise of Frank Graham who visited me in the lab in Toronto it turns out that transfer of biochemical and cancer markers using total cellular DNA or chromosomes works with a frequency of  $10^{-6}$  making it possible.<sup>3,4</sup> These theoretical and practical advances produced by me later made possible the cloning of the first human oncogene (the H-ras1) from a bladder carcinoma cell line by the groups of R. Weinberg at MIT, M. Wigler at Cold Spring Harbor Laboratory and M. Barbacid at NIH.

The identification of cellular oncogenes has probably been the most important discovery in modern cancer research. Prior to their isolation and identification as cellular homologues of retroviral transforming genes, many scientists believed that highly transforming retroviruses and their oncogenes were experimental artifacts irrelevant to human cancer. Since then an explosion of work has demonstrated the direct relevance of cellular oncogenes to cancer development, diagnosis and treatment dependent on technical and conceptual advances in the identification of cellular oncogenes and analysis of their role in multistage carcinogenesis.<sup>5</sup> My discoveries have made extremely important and perhaps unique contributions in these fields.



## ABOUT DR. SPANDIDOS

Demetrios A. Spandidos is Professor of Virology (since 1988) at the Medical School, University of Crete, Director of Clinical Virology Laboratory (since 1990) at the University Hospital in Heraklion, Crete and he was Research Professor and Director of the Laboratory of Molecular Oncology and Biotechnology (1988–1998) at the Institute of Biological Research and Biotechnology at the National Hellenic Research Foundation in Athens, Greece. He is the founder and Editor of the *International Journal of Oncology*, *Oncology Reports* and *International Journal of Molecular Medicine*.

Dr. Spandidos obtained his B.Sc. in Chemistry from the University of Thessaloniki, Greece in 1971, a Ph.D. in Biochemistry from McGill University in Montreal, Canada in 1976 and a D.Sc. in Genetics from the University of Glasgow, UK in 1989. He is Fellow of the Royal Society of Health (1994) London, UK, Fellow of the Royal College of Pathology (1997) London, UK and corresponding Member of the Academia Nacional de Medicina de Buenos Aires, Argentina (1999). He has received the degrees of doctor honoris causa from the Universities of Bucharest (2002) and Cluj-Napoca (2004) Romania.

He was an MRC of Canada post-doctoral Fellow at the Department of Medical Genetics at the University of Toronto in 1976–1978, an Assistant Professor (Epimelitis) at the Hellenic Anticancer Institute in Athens in 1978–1979, an MRC of Canada Centennial Fellow at the Beatson Institute for Cancer Research in Glasgow in 1979–1981 and a member of the Senior Scientific Staff at the Beatson Institute for Cancer Research from 1981–1989 when he took up his present appointments in Greece.

Dr. Spandidos was the first scientist in the field of oncology to develop and apply the gene transfer technique, which has become a most potent tool to investigate oncogenes. Thus, his work assisted in development of the gene transfer technology that has been of paramount importance in revealing new oncogenes, as well as implementing the molecular understanding of oncogenes and how the normal proto-oncogenes become activated into their malignant transforming cognates. This field has expanded tremendously over the past twenty years and Dr. Spandidos has

continued to contribute actively, playing a major role in his scientific investigations on the ras oncogene. While at the Beatson Institute for Cancer Research in Glasgow he performed notable and important investigations on the nature of transformation of normal cells by introduction of single ras genes using retroviral LTRs and other strong promoters.

Dr. Spandidos has organized 27 international meetings on a variety of areas of oncology and molecular medicine and he has served on the Editorial Boards of a number of journals and he is an Honorary Member of several societies. Dr. Spandidos has authored more than 420 publications, 640 communications and invited talks at international conferences and his work has received over 6700 citations. Dr. Spandidos is the most highly cited scientist in all sciences of the Balkan countries for work carried out in Greece. Although actively occupied in fundamental studies in cell and molecular oncology he has always been ready to explore the medical implications of his work with colleagues in the pathological and clinical sciences and has stimulated work in many different laboratories throughout the world. Part of his efforts has been to establish a scientific tradition in biomedical sciences in Greece, including the successful creation of a school of talented scientists with international recognition. A result of Dr. Spandidos efforts has been to put Greece on the map of biomedical research and cancer research in particular at an international level. For full details of Professor D.A. Spandidos's achievements and a list of publications see [www.spandidos.com](http://www.spandidos.com).

My initial discovery immediately attracted a lot of interest, created unusual science politics and made it very difficult for a foreign young post-doctoral fellow like me inexperienced in science politics to handle it. So I returned to my homeland Greece for a year, but with the first opportunity I came back to competitive science at the Beatson Institute for Cancer Research in Glasgow, Scotland where under the patronage of its director Dr. John Paul (a man with principles and guts) I achieved the transfer of cloned human globin genes into hemopoietic cells, a rather difficult task at the time.<sup>6</sup> Then my wish to return to cancer research led me to a second significant discovery concerning the mechanism of carcinogenesis: This was the demonstration that a single overexpressed mutant H-ras gene can convert a normal primary cell into a tumor cell.<sup>7</sup> While at the Beatson Institute a collaboration with Professor Andrew Wyllie, who had taken a sabbatical from the University of Edinburgh to work with me in Glasgow resulted in the first demonstration of the involvement of myc in apoptosis.<sup>8</sup>

Some other ideas of mine were very provocative at the time such as the dual function of ras genes as oncogenes and onco-suppressors<sup>9,10</sup> which have now proven to be correct.<sup>11</sup> Among my most significant work apart from that mentioned above is the involvement of ras genes in colon tumours<sup>12</sup> and the role of c-myc<sup>13</sup> and p53<sup>14</sup> in head and neck carcinomas.

In 1988, I was elected Professor in the Medical School University of Crete, Heraklion and the same day Director of Research at the National Hellenic Research Foundation in Athens. I held the parallel positions for ten years. Since 1999 I am exclusively professor at the University of Crete.

Apart from lack of funding, the most important hindrance to do research in Greece is the lack of modern scientific tradition. So my aim has been to establish scientific tradition in biomedical research

in modern Greece by creating a functional laboratory which maintains links with advanced institutes abroad and to be productive, by organizing international conferences which allow personal interactions between scientists from all over the world and by establishing quality scientific journals. I am satisfied to see that significant progress has been made in the past twenty years.

My journey in science has not been an easy one, but rather reflects a real scientific Odyssey. My straightforward Spartan character is not ideal for today's success in science and Academy. As much as I abhor low level science politics, I am certain that the journey is the ultimate reward as the Alexandrian poet of Greek origin C.P. Cavafy (1863–1933) suggests in his poem entitled *Ithaka*:

As you set out for Ithaka  
 hope your road is a long one,  
 full of adventure, full of discovery.  
 Laistrygonians, Cyclops,  
 angry Poseidon—don't be afraid of them:  
 you'll never find things like that on your way  
 as long as you keep your thoughts raised high,  
 as long as a rare excitement  
 stirs your spirit and your body.  
 Laistrygonians, Cyclops,  
 wild Poseidon—you won't encounter them  
 unless you bring them along inside your soul,  
 unless your soul sets them up in front of you.  
 Hope your road is a long one.  
 May there be many summer mornings when,  
 with what pleasure, what joy,  
 you enter harbours you're seeing for the first time;  
 may you stop at Phoenician trading stations  
 to buy fine things,  
 mother of pearl and coral, amber and ebony,  
 sensual perfume of every kind—  
 as many sensual perfumes as you can;  
 and may you visit many Egyptian cities  
 to learn and go on learning from their scholars.  
 Keep Ithaka always in your mind.  
 Arriving there is what you're destined for.  
 But don't hurry the journey at all.  
 Better if it lasts for years,  
 so you're old by the time you reach the island,  
 wealthy with all you've gained on the way,  
 not expecting Ithaka to make you rich.  
 Ithaka gave you the marvellous journey.  
 Without her you wouldn't have set out.  
 She has nothing left to give you now.  
 And if you find her poor, Ithaka won't have fooled you.  
 Wise as you will have become, so full of experience,  
 you'll have understood by then what these Ithakas mean.

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