

## Remembering Takis S Papas: A pioneer in Ets research

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This review issue of ONCOGENE is unique in that it has two important functions: To remember Takis S Papas, a year after his unexpected and sudden death, and to provide a comprehensive analysis of the current status of Ets biology. As exemplified by the review articles in this issue of ONCOGENE, the Ets field has come a long way since the discovery of Ets1 as a virally transduced oncogene over 15 years ago. We have moved from studies directed towards understanding a limited number of family members to a more complex network of nearly 30 mammalian Ets transcription factors. Animal model systems from *C. elegans*, *Drosophila*, *Xenopus*, Birds and mice are rapidly being generated to allow for a more mechanistic understanding of the family. Already, functions predicted from expression analysis of specific Ets genes are beginning to be validated by elegant gain and loss of function studies. Dysregulated Ets function is associated with human disease. In addition to affording diagnostic tools, Ets factors and the genes they control provide unique therapeutic tools. Furthermore, novel therapeutic approaches are likely to be developed, as we better define mechanisms that modulate Ets function. We now wish to highlight Takis' accomplishments and offer some personal remembrances. *Oncogene* (2000) 19, 6394–6399.

### Takis S Papas

Takis S Papas, PhD, was the Director of the Center for Molecular and Structural Biology (CMSB) at the Hollings Cancer Center and a Professor of Medicine at the Medical University of South Carolina since 1993. Dr Papas received his Bachelors and Masters degrees in chemistry and biochemistry at the University of New Hampshire and his PhD from the Marquette School of Medicine where he studied the basic molecular mechanisms of protein synthesis. He then went to the National Institutes of Health in 1970 at the National Heart, Lung and Blood Institute, joining the laboratory of Biochemical Genetics with the Nobel Laureate, Dr Marshall Nirenberg. Dr Papas led a group of scientists and physicians whose mission was and is still to conduct research that will result in new and potent anti-cancer therapies. As a cancer researcher, Dr Papas was internationally recognized as an outstanding scientific leader and among the founders of the field of Molecular Oncology. He was one of the first scientists credited with the discovery of cancer causing oncogenes. Central to this discovery was the demonstration that when critical normal genes in the cell called proto-oncogenes suffer mutations, they are transformed into oncogenes.

His scientific career spanned more than a quarter century, most of which was at the National Institutes of Health and at the National Cancer Institute (NCI). While at the NCI, he became the Chief of the Laboratory of Molecular Oncology (LMO), where he headed a group of more than 90 research scientists involved in studying the genetic basis of cancer.

Dr Papas authored over 320 research publications as well as several books. He also earned several patents. He organized and led numerous scientific meetings, both in the US and internationally and served as an Editor or Associate Editor on more than ten leading scientific journals. He was among the most sought-after lecturers in his field. Dr Papas held academic positions as a Professor of Biology at The Johns Hopkins University from 1984–1993 and as Adjunct Professor of Biochemistry at The Georgetown University School of Medicine.

Dr Papas received numerous honors and awards and was the recipient of the prestigious NIH Award of Merit in 1983 for his contributions that have led to the understanding of oncogenes. Recently, Dr Papas had received an Honorary degree in Medicine (Graudos De Doctor Honoris Causa), Universita Autonoma De Nuevo Leon, Monterey, Mexico.

Dr Papas provided advisory and academic support for research institutions in such diverse locations as



Kuala Lumpur, Crete, Shanghai and Mexico. He was a member of the scientific advisory board of the Roosevelt Foundation in Denver, Colorado, The Institute for Human Virology in Baltimore, Maryland and the Human Neurovirology Center at Allegheny University in Philadelphia, Pennsylvania. Dr Papas trained more than 200 scientists who now occupy key positions in academic and industrial laboratories throughout the world.

Dr Papas was instrumental in the discovery and systematic molecular characterization of avian leukemia virus oncogenes of the *Myc* family of viruses. He was among the first scientists to establish that viral oncogenes are sub-sets of cellular proto-oncogenes and are typically genetic chimeras with truncated, deleted or otherwise damaged proto-oncogene sequences linked to one or more retroviral essential genes. This seminal work provided the impetus to investigate the differences between proto-oncogenes and oncogenes.

Another milestone contribution by Dr Papas was the discovery of the ETS genes, showing that they exist as a large and significant gene family. Dr Papas and his team cloned, isolated and named the first five members of the family (ETS1, ETS2, ERG, ERGB/FLI1 and ERF). This family of genes are widely conserved in evolution, indicating their fundamental importance. They are required for major and diverse biological functions, such as angiogenesis, vaculogenesis, organogenesis, eye development, blood cell differentiation and cell proliferation. Dr Papas' research group have shown that the ETS genes code for transcriptional factors, i.e. genetic switches that turn genes on and off, that bind to unique DNA sequences present as control elements for the expression of many important genes. His work has opened the whole field of study into the role of these molecular switches for the temporal expression of the genetic program encoded in the chromosomes and DNA of every individual.

As the founder and director of the Center for Molecular and Structural Biology (CMSB), Dr Papas made important and fundamental discoveries on the relationship among genes and cancer. He established a Cancer Genome project in the CMSB with the emphasis on the identification of genes that play a direct role in cancer. The projects included the cloning and sequencing of candidate genes, the determination of their normal function, and how the normal function is modified in cancer. These efforts concentrated on two major classes of genes, oncogenes and tumor suppressor genes. The purpose of this Cancer Genome program continues to be to identify the genes and target a selected group of the most significant ones for the development of innovative cancer therapy. Dr Papas and his team discovered several new genes that play important roles in the cancer process. His group has also created specialized mouse strains with altered genes using state-of-the-art 'gene knockout' and 'transgenic' technologies that allow more precise study of the ways altered genes cause cancer. Together with modern biotechnology, Dr Papas created a scientific center poised to develop the molecular medicines of the 21st century.



### Personal Remembrances

I had the fortunate opportunity to know Takis for over 18 years. It is impossible to recount all of the images that have crossed my mind, as I have thought about Takis over the last year. However, Takis always encouraged me to make things simple; so, thinking of Takis makes me recall six simple but important words: Accomplishment, Family, Loyalty, Storyteller, Friend and Buddy.

### Accomplishments

Takis was a man of countless accomplishments, which can be measured in many different ways. Rather than remember his many scientific contributions, I remember Takis as a man who could achieve his goals, whatever they might be.

This ability was evident to me soon after we met in 1981, when I was looking for a position with the NCI. We had a friendly conversation/interview and, although I was quite interested in working in the Papas laboratory (he had just cloned myc, one of the first viral transforming genes), it seemed to be impossible as the government was under a hiring freeze. *No such small obstacle would keep Takis from doing what he wanted.* He found a way to create a position and offered it to me. To this day, I think I began my NCI career as a hidden exemption in the Office of Management's request for someone in a custodial or building maintenance position.

Takis' accomplishment can also be demonstrated by his ability to build groups of individuals with synergistic goals. When I began working for Takis, our lab consisted of two other Staff fellows and a technician. Within 2 years, Takis became the head of the Laboratory of Molecular Oncology. LMO grew to a team of over 80 individuals trying to understand the function of genes that were associated with cancer progression. *This achievement would perhaps satisfy most men, but not Takis.*

In 1993, new goals were set. Takis encouraged a small number of us to embark on a new mission: To

leave the intramural NIH program and join MUSC. Here, The Center for Molecular and Structural Biology was formed. Again, we started small. Not only has the Center grown to include over 50 people, Takis' goal to develop a program to promote translational research has begun. Scientists at the Center interact with many clinician/scientists in Urology, Surgery, Hematology/Oncology, GI, Pulmonary Medicine, Rheumatology, etc.

Takis was recognized internationally as a world class molecular oncologist. His network included collaborators/colleagues in Canada, throughout Europe, Australia, China, Israel, and more recently, Egypt.

### *Family*

Takis was a family man with two families. His first family included his wife, Tula and his daughters, Katie and Laura. Among my memories are stories about his family. He often recounted enjoyable times with his daughters, suggesting that my own two daughters might also enjoy similar activities. This was a very typical thing for Takis to do: Whenever he discovered something he or his family enjoyed, he wanted others to do the same thing. If he found a good buy, a comfortable pair of shoes, a new type of car, etc. he would immediately rush to tell others. He wanted to share in his happiness. *Takis always wanted to include others in the things he enjoyed.*

This is because he had a second family: His second family included nearly everyone else. He truly cared about people. He cared about the team of people at LMO and CMSB. Of course we meet frequently to discuss our work, but as family and friends do, we meet for fun as well.

### *Loyalty*

Takis was an intensely loyal man. In addition to caring for us all, he could be counted on for so many things. He was truly a generous man. Over the year, in conversations with old and new friends, a common thread keeps appearing: Takis was critical to the success of so many other people and, significantly, he did this in an unselfish way.

### *Storyteller*

Takis was a man who liked to tell stories about his vast experiences. While I was beginning to hear some of them multiple times, he still had new tales to tell. I will miss his stories.

### *Friend*

Takis was a true friend to all. While some were not always in his favor, he enjoyed people and being with friends.

### *The Buddy*

Takis was the Chief, the Director and to his closer friends, 'The Buddy'. You would always feel good when he referred to you as 'the buddy'. *However, it was Takis, who was the real buddy.* I recall two of the last times I have heard him referred to in this way. The first

of this was during our last meeting together. After offering some 'fatherly' guidance concerning my younger daughter, he referred to himself as 'the buddy'. In this case, he was expressing another goal he had set for himself and asked me what I thought about this happening to the buddy. Knowing Takis, I am confident that he would have been able to achieve this goal.

The second instance that stays with me is Tula's comment that the 'buddy' was gone. This is only true if we forget him and abandon the goals that he set for his friends. Takis, as in our games of volleyball, has served the ball; it remains for us to keep the game going.

I will miss many things about Takis. Fond memories will strengthen, but I will miss his enthusiasm and his love of life that was so contagious. He served as a catalyst to bring out the best in those around him. I will miss talking to him. I will miss seeing him come in to my lab or office, excited and telling me he had a good story or something I would find interesting or amusing. I can still hear him say: 'my door is always open'. And, I will remember him stating 'always a pleasure' or demanding to 'shake-hands' after the completion of a good talk.

We who knew and cared for Takis are forced to enter a new phase in our lives. It is my hope and belief that together we can continue towards the important goals we have set for ourselves. Using Takis' life as an example, we need to strive to achieve, while remembering the true value of family and friends.

**Dennis K Watson**

I have known Takis for more than 17 years, ever since I started my career at NIH. He was not just a mentor, and my supervisor, but one of my best friends and became like a brother to me. I truly loved him, enjoyed his friendship and will miss him very much, as will we all. I could spend a lot of time talking about Takis' accomplishments at the NIH, and most recently his work at MUSC. But that's not really what I want to talk about, we can all read about this in his bio, and his hundreds of publications.

I want to think of Takis as a warm human being. He was charmingly humorous also when he wanted to direct us towards a particular goal or project, but he was also a firm and persuasive director when we tried to deviate from the course he wanted to take. Under his guidance at NIH most of us were able to successfully go on to independent careers; and that is to his credit that he gave us the opportunity to pursue useful projects. He was a compassionate person, and always very direct. He always helped us to perform to our best capabilities and treated us and other co-workers as colleagues. He always listened to our ideas and he often praised and complimented and not put them down.

I believe that he touched the lives of hundreds of people in his contacts with them and has touched my life in many ways. The most touching and caring experience I had was when my father had a sudden fatal heart attack in 1991 at a young age. Takis at that sad time in my life gave me tremendous support when I needed it the most. My father's funeral was in

Washington DC and Takis showed up at that time, bringing almost the entire LMO lab members to the funeral home. It was a strong show of support to myself and my family, by everybody and showed me that Takis cared as a warm and compassionate human being. He went around to talk to my mother and each of my brothers and offered his sympathies. He still for every year afterwards, asked about my mother and how she was doing, showing me that he cared about us as a friend and not just a coworker.

I realized at that time he was more than just a supervisor or mentor, but also a close friend, someone I could turn to for support and confidant.

Takis was full of life and I had great time with him, especially on every trip that I traveled with him, including the Greek islands, Morocco and to Miami. A place in the sun which he loved the most, and is now resting in. Finally, I want to say that Takis was a truly good human and will be greatly missed by my family and myself, as well as all the friends that he had.

And if you take the time to read the *Bhagavad Gita*, *The Hindu Song of the Gods*, you'll find out that there are many forms of yoga besides the yoga of meditation which is the most commonly known to us in the West. But of all these forms of yoga, the Hindu teachings point out, that the greatest and most difficult one is *karma yoga*, the yoga of selfless service. When I think of Takis and what he accomplished with his life, I believe he was a real *karma yogi* and, indeed, became a kind of guru or teacher, in that domain where our work and our life and a lot of our relationships have all come and meld together. Takis Papas, my friend, a guru and a great man, was, is and will always remain, deep within my heart.

#### Arun Seth

I first met Takis S Papas in 1987 when I picked him up from the Heraklion airport in one of his first visits at the, then newly founded, Institute of Molecular Biology and Biotechnology, Heraklion, Crete, Greece. This was crucial for my future, because according to Takis 'candidate post-docs that picked him up from the airport turned out to be excellent!' It was one of his ways to compliment people in public. Amiable, in the context of a story, so will not make you feel in any way uncomfortable or embarrassed.

I joined his lab the next year and I worked under his guidance from 1988–1993 and thanks to him, this was one of the most productive periods in my scientific career. This was due both Takis the scientist and Takis the person. At that time the field on *ets* gene research was driven mostly by his lab that produced one quarter of all *ets*-related papers between 1986 and 1990 and led to the boom of the 90s. The setting was almost perfect, molecular biologists, biochemists, geneticists and virologists cooperating under his guidance, and elevating research to the highest standards. This was one of Takis' major qualities, selecting and organizing individual investigators to address a scientific question. Another major quality was to determine and recognize what was scientifically important and relevant, and steer people in this direction. His third quality was to manage a big group of intelligent and competent

people with strong personalities, in a way that minimized the inevitable conflicts and maximized efficiency. I can only indirectly conclude that his ability to conduct the lab affairs within the NCI structure was also superb, the fact that LMO was one of the labs with the top budgets within NCI, testifies to that.

He had mostly friends and that was because he was always trying to make most of the given situation. When I moved back in my home country in spite his advice to join him in his new venture at MUSC and HCC, he tried to help me to set up my lab and we kept our collaboration going. Until the last minute we were planning grand applications that would further facilitate our contact and collaboration. He was always willing to help past associates even when it was much easier not to.

As we say in his native country Greece, Takis S Papas was 'kalos anthropos'. The dictionary explanation for 'kalos' has: virtuous, useful, honest, kind, gentle, pleasant, capable, competent, powerful, energetic, gratifying, etc., and for 'anthropos': human being, gifted with intelligence and virtue. The simple translation would be a 'good person', but with the most profound meaning of the words. His loss was premature and unjust because he had much more to offer both in science and the people that knew him. The only comforting thought is that his outstanding scientific contribution and the plethora of colleagues and friends will keep his memory alive. I hope to be one of them.

#### George Mavrothalassitis

I originally met Takis in Athens, Greece in 1991, during my postdoctoral interview for a position with the Laboratory of Molecular Oncology at the National Institute of Health, where he was Chief. I joined the Laboratory of Molecular Oncology, and through the years, established a professional and personal relationship with Takis.

Takis' capability as a leader in science was truly inspiring. He demonstrated an innate ability to interpret the personalities of those around him, using this knowledge to encourage and bring out their strengths. Takis' nature in establishing personal friendships was fundamental to his ability to lead, as well as to live. He believed in friendship, and felt that through it came the richness of life. He regularly considered the well-being of those around him, and offered them encouragement, often with stories. As scientists frequently encounter peaks and valleys in their work, his favorite story provided inspiration during times of sadness or frustration. I paraphrase this story briefly: 'As scientists, we have chosen to live a life of ups and downs, and not to have routine and monotony. We have chosen a more challenging way of life, and you can be sure when you are down, that you will feel up again soon.' Takis mentioned this with hilarity in reference to those whose only care was watering their garden, and when he noticed someone feeling down, needed only to mention, 'Watering can! ...' to convey his point.

Takis was my mentor and friend. He believed in friends and the warmth and depth of the human soul.

To Takis, these were the things that mattered most in life, and he lived his life to the fullest. He instilled these convictions in those who knew him. In this way, Takis Papas continues to live on.

### Ioanna G Maroulakou

When I met Takis for the first time in the summer of 1993, he had been known to me only as a folklore-like character in the tales of those ‘oncogene guys’. Takis was about to move to Charleston, South Carolina, to start the new Center for Molecular and Structural Biology and I went to interview with him for a junior faculty position at the Center. I found him genuine and unpretentious. Without drawing any fancy vision, he put it very simply: he wanted to build a successful research program in South Carolina. He listed three most important things for this adventure: (1) We need young people; (2) We are going to make it; and (3) No bums. I was quite delighted to learn that I was not categorized as a bum. But no one had expected the institution-building business could be that hard. Straight out of the NIH environment, Takis and his gang were not used to frame their ideas in the form of grant proposals. The other junior members of the team, on the other hand, were totally oblivious to the art of grant writing. And we struggled. Although on the scientific fronts things were moving along quite nicely—projects were expanding, publications were churned out—but no one seemed able to obtain ‘real’ federal funding for the first two years. Morale was getting low and a sense of unease was creeping in. Throughout this period, from 1994 till 1996, Takis and the senior members of the core group managed to get support from various sources and kept everything afloat. Most important, Takis trusted his people. ‘We’re gonna make it, you know. It’s just a matter of time,’ he said repeatedly. He gave no threats of kicking anyone out or cutting off support if grants were not forthcoming. Instead, all he wanted to talk about was the science, about which he was quite easily excited. His tenacity paid off. When he passed away last year, the Center had expanded to 12 faculty members, from an original six, with a combined federal and private funding totaled 4 million a year and a publication record of nearly 100 since 1994. It was truly an extraordinary faith that he put in the people he brought on board. How many young careers have been wasted without such unwavering support? I know I could have been one of them.

I asked him once why he kept doing this at that stage of his career. He said he was passionate about science and he liked being around young minds. And that is the essence of Takis. In the short 6 years I had known him, what I learned—that the key to success and gaining respect is loyalty, generosity and passion—is worth a life time of experience.

### Tien Hsu

The importance of Takis’ contribution to the study of Ets genes and their roles in biology cannot be denied.

And through his efforts the retooling and ever-perfection of this study will continue long after we ourselves are gone. But, by no means was this accomplishment done alone. His recognition of the value of others was, in my opinion, his strongest suit. The joke about the Greek who was self-taught in English was one way he tried to make me aware of this point: ‘When asked by the American who taught him English, the Greek pointed with his thumb to his puffed-out chest, proudly proclaiming, “I did it, all by his self!”’

Working as an undergraduate in Takis’ lab in the late 70’s to early 80’s with Jim Lautenberger, Bob Schulz, Ken Samuel and Tom Pry, I first encountered this human side. He would have a guest, and at one point or other be kind enough to introduce the guest to us in the lab. His reference to them as ‘The buddy,’ was to me an indication of human friendship and a sharing of common goals in science. It was only later and secondary in importance when I realized that all of ‘The Buddies’ out there were acclaimed scientists. To me the human side, his focus of positive motivational energy, will be sorely missed. But as part of us is lost with the man, part of the man lives on in us.

### ΑΙΩΝΙΑ Η ΜΝΗΜΗ

As on Benjamin Franklin’s epitaph,

“The body ...  
Like the covering  
Of an old book  
Its contents torn out  
And strip of its lettering  
And gilding  
Lies here ...  
But the work  
Shall not be lost,  
It will (as he believed)  
Appear once more,  
In a new  
And more beautiful edition,  
Corrected and amended  
By the author.”

### Demetri D Spyropoulos

When I look back at my tenure at NIH, my association with Takis Papas and the work we did together is perhaps the most pleasant memory I can recall. I met Takis soon after I moved to NIH in 1978 to join the Laboratory of Cell and Molecular Biology headed by Dr Stuart Aaronson. Takis occupied the lab next door to me and was one of the first people to welcome me to Building 37 of NCI. A few days later I discovered that he lived in a house across the street from me. This proximity at work and at home created a wonderful setting for us to interact not only at a professional level but also at a personal level. It is during this time we got to know well his wife Tula and daughters Katie and Laura, who all became our close personal friends. We spent many weekdays and weekends discussing at length the emerging field of oncogenes and tumor cell

biology. Late 1970's constituted a very exciting time for retrovirologists. Relaxation of recombinant DNA guidelines allowed us to clone retroviral genes and their cellular counterparts, which led to an explosion of knowledge in this field. These studies allowed us to gain an understanding of the mechanisms associated with the activation of cellular oncogenes via retroviral transduction and the structural differences that existed between the viral and cellular oncogenes. I was in the process of cloning and sequencing several of the retroviral oncogenes when Takis proposed a collaboration to clone and sequence the *myc* and *myb* genes. This collaboration between us led to the sequence determination of *v-myc*, *c-myc* and *v-myb* sequences. Soon after, *myc* and *myb* genes occupied center stage following the delineation of their role in human cancers. This was a very exciting validation of the work carried out by many retrovirologists and Takis was instrumental in advancing this field by generously making available his *v-myc* and *c-myc* clones to all those who wanted to study this gene family. Takis later moved to the Frederick Cancer Center, where he embarked on the study of *ets* genes, which occupied the rest of his career. Interestingly, when he first started this work, many did not believe that *ets* genes were transforming genes. Takis very firmly believed that transduction of *myb* and *ets* genes by the E26

virus cannot be an accident and there has to be a selective advantage for a virus to transduce two separate genes. The systematic work of Takis along with those of several other groups around the world during the next several years clearly established the role of *ets* in oncogenesis. Takis was also the first to recognize that *ets* genes may belong to a large gene family and was instrumental in proving this theory by cloning several of the family members. Takis's success in science was not just because of his keen intellect and intuitive capabilities. He was one of the few who had little or no ego and this quality combined with his very cheerful disposition enabled him to attract talented coworkers and collaborators. Takis not only recognized that major discoveries in biology can only be made in a multi-disciplinary networking but also viewed this as an opportunity to develop lasting friendships with his fellow scientists in different disciplines around the world. His upbeat personality and warm friendship made him the most sought-after collaborator. His devotion to his friends and his love for science and his humility will be remembered and missed by all of his friends around the world for a very long time.

**E Premkumar Reddy**