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## In Memoriam

### Dr. Panagiotis (Takis) Tsonis: A man for all seasons

*“In girum imus nocte et consumimur igni”*

Risk taking and the strength to stomach failure used to broadly characterize the way scientists solved complex problems in biology. How success is measured today, wittingly or not, has launched a process of domestication that prevents our ranks from being populated by mavericks willing to buck trends and challenge assumptions. The untimely death of Dr. Panagiotis (Takis) Tsonis stresses not only how few non-conformist scientists remain among us, but also how little we seem to be doing to robustly promote their regeneration today. Dr. Tsonis' work and intellect were and will continue to be constant reminders that there is not a single formula to do great science, that diversity of opinions, thoughts, inclinations, approaches and experiences are needed, indeed, are indispensable to shed light onto the complex fabric of nature, the great charge we biologists are entrusted with. We are all, therefore, collectively impoverished by his absence.

Dr. Tsonis was a Professor from the Department of Biology, University of Dayton. Dr. Tsonis held the title of Director of the Center for Tissue Regeneration and Engineering at Dayton and was an adjunct Professor of the Sanford Burnham Medical Research Institute, in La Jolla, CA.

Dr. Tsonis was world-renowned for his work in regenerative biology, especially in the areas of lens and limb regeneration using salamander models. He published well-over 100 peer-reviewed papers on regeneration, and also published several books as author and editor. His 1996 book entitled “Limb Regeneration” is an invaluable resource for those that study regeneration, and it is accessible to those that are simply curious about the regenerative potential of salamanders. Dr Tsonis's work concerning lens regeneration was continuously supported since 1995 by the National Eye Institute at NIH, and over the years various other grants from NIH and the Arthritis Foundation supported his research on topics ranging from chondrogenesis to micro-RNA function.

To honor Takis' memory, we aim to paint a picture of this great man, and our respective stories, like a triptych, are hinged together by the generosity, wisdom and profound insights that Takis shared so freely with all of us.

#### Panel I: András Simon

Takis passed away almost exactly ten years after I first met him at an EMBO conference. I can still see him standing outside of the lecture hall intently talking to a colleague. I approached him to congratulate him on his paper he published one year earlier in *Nature* on lens regeneration in newts. His team defined molecular components involved in transdifferentiation of pigmented epithelial cells into lens and also showed which molecular manipulations were sufficient to confer regenerative traits to a normally non-regenerative tissue. This highly original paper inspired me, and of course several others too, in many ways. The study was very important not the least because it highlighted that, although newts are genetically not easily tractable species, with innovative approaches, perseverance and dedication one can defy the obstacles and reach mechanistic understanding of the regeneration process at the molecular level. We started chatting, and at some point, I asked him what will be the topic of his presentation. He looked at me smiling and told he still had two days until the presentation to figure it out. “Plenty of time”, he added and smiled even bigger. This was such a quintessentially Takis kind of answer. For me, as a starting PI and relative novice in the field, who would give my first long talk at a major conference his response appeared first as quite an attitude. But I soon realized it actually meant the opposite and represented one of the many important things I learnt from Takis during the years: scientific meetings should be fun, we should not complicate things, at a conference we are together to enjoy each other's company without worries. And of course, his presentation was great - a refreshing mixture of intriguing data, far reaching conclusions and teasing jokes. I feel fortunate that I had the chance to attend several other conferences together with him. Two years later we were co-organizers together with Enrique Amaya and Daniel Bachiller of the subsequent EMBO regeneration conference in Mallorca. That was the period I had the most frequent interactions with Takis. He had strong opinions and could be very persuasive with arguments. Then under the palm trees of Mallorca he also introduced me into Greece's quite complicated political traditions and told me wonderful stories from his time in Japan where he was working with Goro Eguchi. We did not cease to interact after the conference in Mallorca and regularly talked over the phone to share the latest in newt regeneration. In a small field like ours, one is so dependent on collegiality and lack of antagonisms. Takis represented both. His forward looking and optimistic attitude meant a lot to me in days of anguish when I asked myself why I chose to work with such an experimentally challenging model organism. He was always encouraging and never let me be discouraged by any hurdle. Takis was a dear colleague who constantly looked on the bright side, seeing the glass always half full.

#### Panel II: Randal Voss

Dr. Tsonis led an interesting life, and in fact his CV shares some of the content that you would expect in the CV of the most interesting man in the

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world. No he didn't scale Everest, but he grew up in Greece and after receiving his undergraduate degree, gained a fellowship to complete MS and PhD degrees in the Institute of Molecular Biology, Nagoya University. Takis took pride in the fact that he was the first Greek Citizen to receive a PhD from a former Imperial Japanese University. Dr. Tsonis completed post-docs in the San Diego/La Jolla area before taking a faculty position at Indiana University, before settling down in Dayton in 1989. He is perhaps best known for his work concerning mechanisms of cellular transdifferentiation associated with lens regeneration, however his contributions spanned many different regeneration paradigms, including recent discoveries of age/developmental changes in mechanisms of salamander lens and limb regeneration. He had boundless energy and was one of the salamander communities' greatest spokesmen through NIH committees and editorial work for major scientific journals, and through his public addresses.

It was great working with Takis over the last 8 years. Dayton, OH and Lexington, KY are close enough that we got together 1–2 times a year to chat about life and science. It was through these meetings that I learned of his love of family which included his identical twin brother and equally famous regenerative biology spouse Katia, although he would joke that it was he who was riding her coat-tails to fame. I learned of his commitment to undergraduate teaching and research (*e.g.*, he wrote a Molecular Biology textbook for the course he taught), and the quality graduate students and post-docs he trained. I also grew to appreciate his love for poetry, reading, and of course, regeneration! I came to the field of regenerative biology late in my career. Looking back, I probably would have stayed on the sidelines, content to be a genomics person and not fully embraced the field, had not Takis taken the time to share his knowledge and views. As András and Alejandro echo in their sections, Takis was very generous with his time and inclusive to all that would genuinely listen and exchange ideas. He was a master at motivating young and old minds to think and do science.

When we first started to collaborate, he intimidated me, partly because my knowledge of regenerative biology was nowhere near his, but also because he was always challenging me to do what hadn't been done before. For example, even though he knew relatively little about genomics he peppered me with questions and kept pushing me to think about ways to explore the structure and function of large salamander genomes, and in particular the newt genome. At the time, again 8 years ago, I told Takis that it was not realistic to sequence and assemble the newt genome, nor was it rationale to direct effort toward making the newt a genetic model....it takes newts a very long time to reach maturity and they are not easy to breed in the lab. Takis didn't want to hear such defeatist talk as he was very loyal to the newt and thought it a much better model of adult-stage regeneration than the paedomorphic axolotl that I was developing. Although a man of short stature, his will was stronger than mine, and he held the purse strings, so not surprisingly one of the first studies we published was a comparison of genomic segments harboring newt Hox genes to orthologous vertebrate genomic segments. Surprisingly after this body of work, Takis recognized that axolotl research resources were maturing quickly and in the end game, the axolotl would become a more practical genetic model than the newt. During the last few years of his life he generously supported collaborative work that led to an initial axolotl genome assembly. I am deeply saddened that he passed away before we could finish our work. My hope is that someone will someday write a review article acknowledging the pioneers and forward thinkers in the regenerative biology field, scientists like Takis, on whose shoulders we currently rest.

### Panel III: Alejandro Sánchez Alvarado

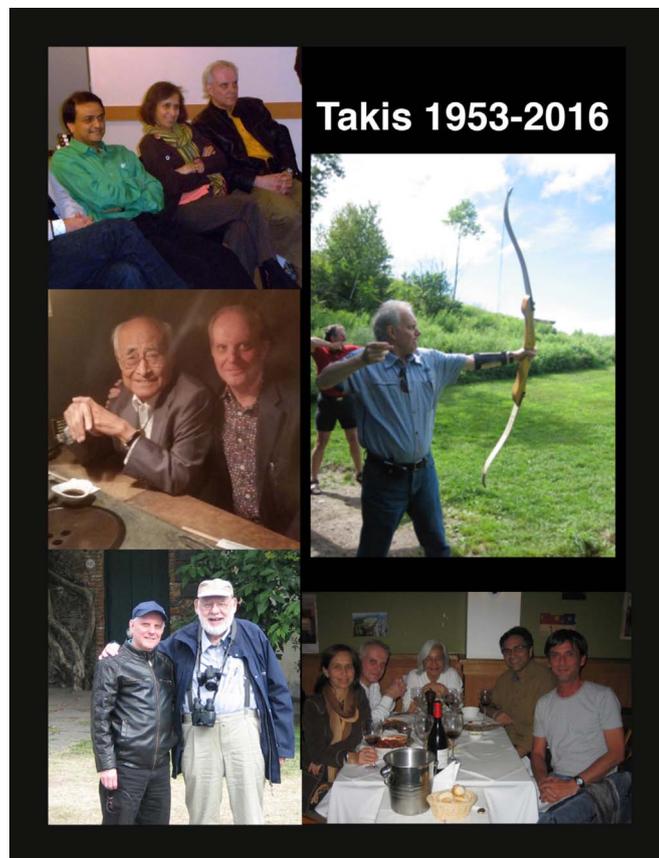
“As per our discussions about your ideas, I think you should go ahead and give it a try. You have the intellect and the stamina to do this. Don't worry about possible difficulties. They are always there anyway and I am sure you will overcome them.”

Takis

I first met Takis and his long-time collaborator and wife (and now dear friend) Dr. Katia Del Rio-Tsonis standing in front of my poster during a meeting at the University of Cincinnati College of Medicine. It was 1991. I was a graduate student at the time working on the *in vitro* differentiation of mouse embryonic stem cells into embryoid bodies in the laboratory of Dr. Jeffrey Robbins. At the time, I had no idea how that initial interaction would ripple across my life in the years to come. Takis, in usual form, not only bombarded me with questions, but also suggested new perspectives and interpretations of my work, all of which we discussed and argued about vigorously. I am not sure he actually called me “young man” back then, (one of the monikers he preferred to address me by), but I still can hear his voice as he told me then: “...keep up the good work!” We politely said goodbye to each other and parted ways. I would not have remembered this encounter, and it would have easily slipped into the drawer of vague memories like many such encounters at meetings and conferences, had it not been the case that in 2002 I would not only run into Takis again, but that he also remembered me and the work I was doing when we first met. That was classic Takis. On that occasion, he said something along the lines that I had finally seen the light and “...decided to leave stem cells behind to study regeneration!” To this day, I consider this re-encounter at the 2002 EMBO meeting on regeneration at El Ciocco in Castelvécchio Pascoli, Italy, as the true beginning of both our robust scientific exchanges and our profound friendship, both cut impossibly short by his untimely death.

In 2005, Takis and I decided to write a review for *Nature Reviews Genetics*, in which we tried to integrate the many observations and results that had been accrued until then about animal regeneration. The field was starting its present upward trajectory and Takis felt it was necessary to attempt an effort at integrating the many bodies of knowledge emerging from laboratories around the world working in a delightfully diverse set of research organisms. Takis was particularly interested in understanding why there is such a wide gamut of regenerative capacities in the vertebrates. Salamanders and newts fascinated him, and the various modes of regeneration such as dedifferentiation, transdifferentiation, tissue remodelling and the activation of adult stem cells displayed not only by these animals, but also by other vertebrates like fish and mice were a constant preoccupation for him. I discovered this first hand when we set out to write the review and recall fondly the many arguments, discussions, agreements and disagreements we had as we crafted the manuscript. I soon learned that working with Takis was akin to a Socratic exercise in logic, and ultimately an inspiring and invigorating experience. I know he was very proud of our review because he would, out of the blue, pepper my e-mail account and our frequent phone conversations with citation statistics for this article.

When my father passed away on April 20th, 2009, I was devastated. In June of that same year, I had agreed earlier to participate in a meeting in Greece, a trip I was going to cancel. Takis insisted that I should not and that I should come to Greece and travel with him after the meeting. I credit Takis with ultimately helping me overcome the grief I experienced for losing my father so abruptly. We crossed the Ionian sea from Corfu to Igoumenitsa, and travelled by bus to Ioannina, Trikala, and all the way down south to Athens. All our conversations centered around regeneration in particular and science, history and the arts in general. We contemplated the remnants of Byzantine and Ottoman cultures in Ioannina, a city Takis considered the birthplace of Greek Enlightenment. We walked through its palaces while discussing the works of the Greek poet Aristotelis Valaoritis



**Fig. 1.** Left column (Top): Nipam Patel, Katia Del Rio-Tsonis and Takis; (Middle): With Professor Goro Eguchi; (Bottom): With the late Walter Gehring. Right column (Bottom): Katia, Takis, Ida Chow, Alejandro Sánchez Alvarado and Richard Behringer.

(whose poetry he had just completed translating into English), and deliberated the nexus between science and the arts. We climbed the hills of Meteora while debating the intricacies of regenerative capacities in the animal kingdom. We discussed evolution as we contemplated the rugged terrain of the Greek countryside. We discussed Greek philosophy, mythology, and the scientific method on the terrace of an Athenian café overlooking the Parthenon, while -unbeknownst to us- the famed Greek actress Irene Papas -sitting at a table right behind us- listened intently to our entire conversation. When we decided to leave, she acknowledged us with a deferential gesture and imagine our surprise (and faces) when we recognized her!

Takis was a man for all seasons and the full measure of this man is hard, perhaps impossible to truly arrive at. Takis' wit, knowledge and erudition on many aspects of science, literature and music were always a source of joy and amazement to all who knew him. Take for instance the opening quote to this piece: a palindrome he used in a posthumously published autobiographical collection of poems (Tsonis, 2016). A palindrome that takes us back to where we started. A riddle for all to figure out in their own respective terms. And here is Takis' most enduring contribution to developmental biology: the fact that he never ceased to ask questions and that he was rarely satisfied with the answers. His perseverance, his constant curiosity, and his intellect will inspire us and those we teach for years to come (Fig. 1).

## Reference

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