



# Seeing the Wood and the Trees

Sitting Down With... Professor Vassilis Gorgoulis, Director of the Laboratory of Histology-Embryology, Molecular Carcinogenesis Group, Medical School, National and Kapodistrian University of Athens, Greece

Why pathology?

I realized early on that pathogenesis is the basis of medicine. Getting a clear view of the disease is vital – you can't choose the correct treatment without the correct diagnosis. In fact, pathology is a hub of many sciences; it integrates physiology, cell biology, biochemistry, embryology, immunology – even mathematics. Hence – and this is not always appreciated – while cell and molecular biologists are well aware of different “trees,” the pathologist has a clear view of the entire “wood.” You can't do decent research without pathology!

Is the importance of pathology appreciated by the broader community?

Its influence has declined, partly due to increased reliance on molecular biology, and partly due to the broad use of immunohistochemistry at the expense of traditional biochemical and experimental pathology methods. But pathologists are reclaiming their territory by introducing modern methods into standard practice; hence the emergence of the “molecular pathologist,” who integrates traditional pathology with molecular biology.

How did you come to be the first and only pathologist ever to be elected to EMBO?

If five EMBO members propose you as a candidate for membership, the EMBO community assesses your research record and votes on your proposed membership. It was a great honor to be elected, but it was the result of much effort and international collaboration – and a strong publication record – over the last 25 years.

EMBO has 1,700 members, but only one pathologist! That's not because EMBO is closed-minded; in fact, it wants to attract new disciplines. It is pathologists' responsibility to promote their speciality – but sometimes our colleagues prefer to keep within traditional boundaries! I will work hard to change this, because I believe pathology is a pillar

of modern biomedicine, and should be better represented. But we must help our own cause by generating the new breed of pathologists: molecular pathologists who integrate traditional pathology with molecular and cell biology. And that is tremendously demanding – six years of medical school, a five-year pathology residence and a three-year molecular biology PhD makes 14 years of study – but it's in our hands.

Talk us through some of the research that resulted in your EMBO election

We are best known for the “oncogene-induced DNA damage model” of cancer development (1). Our idea is that oncogene activation disrupts DNA replication, causing DNA damage that triggers a damage response pathway. Continuous activation of this pathway inactivates its downstream effectors, such as the tumor suppressor p53, and this facilitates cancer progression and further DNA damage. The cancer cell then attempts DNA repair by abnormal pathways – which are potential therapeutic targets.

Our aim is to identify and target these pathways (2). We have found that components of the cell “replication licensing” machinery, Cdc6 and Cdt1, are overexpressed in cancer, and that Cdc6 is a downstream effector of the oncogene Ras (frequently mutated in cancer). Targeting Cdc6 therefore may block the oncogenic effects of Ras. We believe this approach will result in exciting new weapons in our anti-cancer arsenal, and we are collaborating with a pharmaceutical company to develop anti-Cdc6 compounds.

Greece has been through hard times recently – how is pathology holding up?

We have very talented, internationally respected pathologists, who have developed this talent without the funding and facilities that are available to pathology departments abroad. One particular

strength of Greek pathologists is that while specializing they continue to deal with the whole spectrum of pathologies; therefore, they acquire a very good “view of the wood, not just the trees.”

That said, public and private financial resources have declined significantly since the economic crisis, which has had a negative impact on the infrastructure of our pathology departments. That in turn has dissuaded some medics from specializing in this field, and has made it more difficult to undertake systematic work programs.

But I believe there is light at the end of the tunnel; the initial shock, from 2010, is over. We are a very resilient nation; we have shown over the centuries that we can adapt, improvise and overcome, and that is what we will do. Certainly I will stay in Greece and, hopefully, continue to inspire and encourage my younger colleagues. Two senior members of my current team in fact are ex-students of mine; it has been incredibly rewarding to see them come into pathology.

If you could go back to the beginning of your career, what would you change?

Everyone makes mistakes – otherwise, you don't learn – but I would follow the same route again. And I will be very happy if I can successfully encourage the next generation of pathologists to be open-minded and non-dogmatic; it's so important to listen to new ideas, not just from lab heads but also from younger scientists and students. Once, a student had an idea about a connection between p53 and the complement system – I listened to him, and we ended up with a paper in the EMBO Journal! So you must be open-minded – the truth may lie in an unexpected part of the wood.

#### References

- 1 TD Halazonetis et al., *Science* 319, 1352-5 (2008). PMID: 18323444.
- 2 P Galanos et al., *Nat Cell Biol* 18, 777-89 (2016). PMID: 27323328.