Name	VENIZELOS PAPAYANNOPOULOS
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2012

Career History

1994- 1998: undergraduate degree, Rutgers university. In parallel worked for 2 years with Kenneth Irvine as an undergraduate student/technician on Notch signalling in tissue patterning.
1998- 2005- 2006: PhD, University of California San Francisco -Tetrad programme. advisor: Wendell Lim.
2006- 2011: Postdoctoral fellowship, Max Planck Institute for Infection Biology. Advisor: Arturo Zychlinsky.
2011: Greek army compulsory military service
2012- 2017: Programme leader track and group leader, MRC Mill Hill and The Francis Crick Institute.
2018- present: Senior Group Leader, The Francis Crick Institute.

Major Awards, Honours and Prizes

2014. MRC centenary award.

Membership of external committees, editorial boards, review panels, SABs etc

I have not been a member of any such committees other than organising the 2021-22 Myeloid Cells Keystone conference. In 2017 I had been invited to observe the MRC Infection and Immunity board, to which I am currently applying for 2021.

Lab Name	***Antimicrobial Defence Laboratory***

Research programme and achievements

Neutrophils are key antimicrobial cells that were once only appreciated for the their antimicrobial properties, which were thought to be implemented via a single antimicrobial programme. The discovery of a defence strategy called NETosis which promotes the release of neutrophil extracellular traps (NETs) raised the possibility that these cells may selectively implement their antimicrobial strategies. Furthermore, it remained unclear whether neutrophils could minimise their destructive effects on tissues. Finally, the role of neutrophils as regulators of inflammation remained unclear.

In 2014 we showed that neutrophils could sense microbe size and release NETs selectively in response to pathogens that are too large to be phagocytised. This discovery inspired subsequent work that highlighted the role of NETs as a strategy to counter large fungi, parasites and bacterial aggregates. It also led to the discovery of a mechanism that allow neutrophils to tune inflammation and swarming according to the size of the microbes they encounter, by sensing the localisation of reactive oxygen species (ROS) generation. This was the first example of ROS localisation being able to influence cellular signalling. This work uncovered mechanisms for intelligent tuning of inflammation.

We also discovered a novel mechanism that allows neutrophils to drive sterile inflammation in atherosclerosis by priming macrophages for the production of pro-inflammatory cytokines via NET-mediated signalling. These studies exemplified the role of neutrophils as regulators of inflammation.

Furthermore, we showed that NET-mediated signalling is driven by NET histones via synergy with NET DNA. This work highlighted a new role for extracellular DNA as a regulator of the cellular localisation of immune receptors and provided the first mechanistic basis for synergy between putative TLR-agonists by showing they trigger sequential distinct functions.

We also contributed to collaborative work that implicated NETs in *Mycobacterium tuberculosis* pathology and allergic airway hypersensitivity as well as gut barrier destruction in Inflammatory bowel disease.

Finally, we uncovered a novel mechanism that promotes neutrophil dysfunction during sepsis and we are investigating how these mechanisms promote severe Covid-19 symptoms. Based on this unpublished work we have established the phase II COVASE clinical trial for Covid-19 patients with the aim of reducing the severity of symptoms by treating immune pathology using a repurposed Dornase alpha therapy.

We are currently expanding our studies of the mechanisms regulating the production of neutrophils with alternative properties and understand their contribution to human diseases such as cancer and atherosclerosis particularly at the pre-clinical stage. We are also continuing work on the mechanisms of NET formation and immunomodulatory properties of NETs.

Research outputs

Warnatsch, A., Ioannou, M.,Wang, Q. and Papayannopoulos V. (2015) *Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis*. Science 349 (6245), 316-320. DOI: 10.1126/science.aaa8064
The priming signals in sterile chronic inflammatory diseases remained elusive. Moreover, NETs were mostly thought to serve as an antimicrobial defence mechanism. This work showed that NETs are proinflammatory and provide the priming signals for inflammation in atherosclerosis. It has important implications for our understanding of the mechanisms driving many inflammatory conditions and the important amplification mechanisms involving neutrophil-macrophage crosstalk.

Warnatsch A., Tsourouktsoglou D., Branzk N., Wang Q., Reincke S., Herbst S., Gutierrez M., Papayannopoulos V. (2017) *Reactive oxygen species localization programs inflammation to clear microbes of different size*. Immunity 46(3):421-432. DOI: 10.1016/j.immuni.2017.02.013
How inflammatory programmes are tuned to recruit sufficient numbers of neutrophils to clear microbes of different size remained unknown. Furthermore, neutrophils were not thought to serve as major regulators of inflammation in vivo. We showed that reactive oxygen species localisation allows neutrophils to regulate their own recruitment by setting the appropriate level of cytokine production.

Tsourouktsoglou T.D., Warnatsch A., Ioannou M., Hoving D., Wang Q., Papayannopoulos V. (2020) *Histones, DNA, and Citrullination Promote Neutrophil Extracellular Trap Inflammation by Regulating the Localization and Activation of TLR4*. Cell Rep. 31(5):107602 DOI: 10.1016/j.celrep.2020.107602
This paper uncovered the role of NET histones as major proinflammatory signalling molecules of NET-mediated pathology. It addresses longstanding questions about how cytotoxic chromatin can signal without killing macrophages and changes the way we think about the signaling properties of extracellular DNA. It also answers another longstanding question about the mechanistic basis of synergy between putative TLR agonists. It also offers the first genetic mouse model to interrogate the proinflammatory role of histones *in vivo*. We are building on this story and I think with time, the mechanistic details here will have a great impact on PAMP-induced signaling.