Name	NATHAN GOEHRING
Position	Group Leader (2nd 6)
Year joined *(Crick or founder institute)*	2013

Career History

1999-2006: Ph.D. Student, Harvard Medical School, Harvard University. Boston, MA.
2006-2013: Postdoctoral Fellow, Max Planck Institute of Cell Biology and Genetics, Dresden, Germany
2013-2020: Senior Research Associate, MRC LMCB, University College London, London, UK
2013-2015: Junior Group Leader, CRUK London Research Institute, London, UK
2015-2020: Junior Group Leader, Francis Crick Institute, London, UK
2020-present: Group Leader, Francis Crick Institute, London, UK

Major Awards, Honours and Prizes

1998-1999 Fulbright Scholar
1999-2004 Howard Hughes Medical Institute Predoctoral Fellow
2007-2009 Alexander von Humboldt Postdoctoral Fellow
2009-2011 Marie Curie International Postdoctoral Fellow

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

Theme Lead - States of Active Matter/Institute for Physics of Living Systems, UCL (2018 - current)
Advisory Board - Physics of Life Network, Imperial College (2019 - current)

Lab Name	***Polarity and Patterning Networks Laboratory***

Research programme and achievements

<u>Research Programme Summary</u>

Through their ability to link cell architecture and signalling networks, cell polarity networks play fundamental roles in the spatial regulation of intracellular processes and in so doing drive processes as diverse as cell migration, establishment of body axis, cell fate specification, and the development of tissues and organisms.

First identified in *C. elegans*, the *PAR-titioning defective* proteins make up the core of a conserved molecular network involved in polarisation of animal cells, operating from the earliest stages of cell fate specification in species from worms to human. Mutations in polarity-related molecules are linked to cancer and active programmes are in place to develop therapeutics based on manipulating the polarity-related pathways.

At the heart of this network are a set of feedback loops between PAR proteins that enables their self-organisation into discrete membrane-associated domains. Over the past decade, the field has seen a transition from genetic analysis to systems-level approaches as the dynamic and complex nature of PAR polarity has become apparent. Core questions have shifted from identification of molecules and interactions to understanding how this network of molecules generates patterns on the cell membrane.

My research programme has been at the forefront of these efforts, first as a postdoc where I first defined the intracellular mobility of PAR proteins and used this data to construct one of the first generation of mathematical models to understand symmetry-breaking and domain size control. Since starting the lab, we have expanded on this analysis of PAR protein dynamics using the *C. elegans* embryo as a model system and combining genetics, quantitative imaging and mathematical modeling. Our aims are to uncover the design principles of the PAR network that enable intracellular patterning of cells, to determine how these principles emerge from individual and collective properties of the component molecules, and to understand the consequences of these principles as they play out over embryonic development.

Since starting the lab, we have primarily focused on tackling microscale organisation of PAR proteins at the cell membrane, resolving functional complexity in the PAR network, and understanding how features of the PAR network optimise its response to developmental cues (see details in publications below). We have also developed optimised quantitative analysis and genetic techniques to set a foundation for the future.

Our work for the following period will focus on three areas which will leverage our expertise in quantitative imaging and in vivo network analysis as well as our collaborations at the physics of life interface:
- What is the molecular logic of polarity establishment by the PAR network? We will provide mechanistic insight into key feedback circuits that drive cell polarity and directly link coarse-grained network properties to molecular behaviours.

- How do polarity networks respond to developmental cues? We will explore how PAR proteins respond to developmental cues and how both the cues and the ability of the PAR network to respond to those cues is regulated during development.

- How do dynamic systems cope with energy stress? We will use *C. elegans* embryos as a model to study the nature of suspended animation and explore notions of synchrony and spatial memory as mechanisms for maintaining viability during transitions into and out of suspended states.

Research outputs

Hubatsch, L., Peglion, F., Reich, J.D., Rodrigues, N.T., Hirani, N., Illukkumbura, R., Goehring, N.W. (2019) *A cell size threshold limits cell polarity and asymmetric division potential*. Nat. Phys. 15, 1078-1085. DOI: 10.1038/s41567-019-0601-x

A key requirement for patterning networks is that the scale of pattern be appropriately matched to the size of the system to be patterned. Through a combination of theory and experiment, we show that failure of the PAR network to scale with cell size restricts stable cell polarity to a specific size range and imposes a minimum cell size threshold for polarity. Experimental alteration of cell size indicates that embryos are sensitive to this size threshold. We thus propose a general strategy by which cells can use intrinsic length scales of patterning networks to enable size-dependent decision making.

Hirani, N., Illukkumbura, R., Bland, T., Mathonnet, G., Suhner, D., Reymann, A.C., Goehring, N.W. (2019). *Anterior-enriched filopodia create appearance of asymmetric membrane microdomains in polarizing C. elegans zygotes.* J. Cell. Sci. 132, jcs230714. DOI: 10.1242/jcs.230714

This work demonstrates that filopodia-like structures form on the surface of polarising *C. elegans* zygotes. Our analysis forces a re-interpretation of prior reports of asymmetric localisation of membrane-associated molecules such as PIP2 and Rho-family GTPase to membrane microdomains. Our data indicate that these experiments simply report the localisation of filopodia (i.e. excess membrane).

Reich, J.D., Hubatsch, L., Illukkumbura, R., Peglion, F., Bland, T., Hirani, N., Goehring, N.W. (2019) *Regulated activation of the PAR polarity network ensures a timely and specific response to spatial cues*. Curr. Biol. 29, 1911-1923.e5. DOI: 10.1016/j.cub.2019.04.058

In this work, we identify a programme of PAR network activation that is repressed by the cell cycle kinases Aurora A and Polo-like kinase 1. By preventing premature responsiveness of the PAR net- work to potential symmetry-breaking cues, this regulation helps ensure that the embryo polarises along a single axis in response to the centrosome cue provided by sperm upon fertilisation.

Rodriguez, J.*, Peglion, F.*, Martin, J., Hubatsch, L., Reich, J., Hirani, N., Gubieda, A.G., Roffey, J., Fernandes, A.R., St Johnston, D., Ahringer, J., and Goehring, N.W. (2017) *aPKC Cycles between Functionally Distinct PAR Protein Assemblies to Drive Cell Polarity*. Dev. Cell 42, 400-415.e9. DOI: 10.1016/j.devcel.2017.07.007

Through the use of aPKC inhibitors and genetic mutations, we demonstrate that aPKC cycles between distinct PAR-3 and CDC-42 dependent states, which define, respectively, the ability of the aPAR network to respond to spatial cues and to displace pPAR proteins from the membrane. We further show that cue sensing depends crucially on the oligomeric nature of the PAR-3 state, that the integrity of this cycle is required for coupling of cue-sensing and effector functions of the aPAR network, and that this cycle is enforced by activity of aPKC.

Gross, P., Kumar, K.V., Goehring, N.W., Bois, J.S., Hoege, C., Jülicher, F., and Grill, S.W. (2019) *Guiding self-organized pattern formation in cell polarity establishment*. Nat. Phys. 15, 293-300. DOI: 10.1038/s41567-018-0358-7

This work combines theoretical and experimental approaches to probe the role of guiding cues in polarisation of the PAR polarity network in the *C. elegans* zygote. Notably, this work quantifies a transition point which defines the point beyond which biochemical feedback is sufficient to drive continued polarity in the absence of continued signals from the symmetry-breaking cue, highlighting the subcritical nature of the PAR feedback network and the dominant role of cues in ensuring robust polarisation.