Name	CAROLINE HILL
Position	Senior Group Leader Assistant Research Director
Year joined *(Crick or founder institute)*	1998

Career History

1981–1984: University of Cambridge, BA (First class honours), Natural Sciences
1985–1989: University of Cambridge, PhD in Biochemistry
1989–1991: Department of Biochemistry, University of Cambridge, Postdoc,
1991–1995: Imperial Cancer Research Fund, London, Postdoc,
1995–1998: Head of the Laboratory of Transcriptional Regulation, Ludwig Institute for Cancer Research, UCL Branch and holder of a Royal Society University Research Fellowship.
1998–present: Imperial Cancer Research Fund (Tenure May 2002), London Research Institute, Francis Crick Institute
2018–present: Assistant Research Director, Francis Crick Institute

Major Awards, Honours and Prizes

2002 Elected Member of EMBO
2013 Elected Member of Academia Europaea
2015 Elected Fellow of the European Academy of Cancer Sciences
2019 Elected Fellow of the Academy of Medical Sciences

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

Advisory Boards
2009-present: Member of Scientific Advisory Board for Centre for Interdisciplinary Research in Biology (CIRB) at Collège de France, Paris, France
2014–2018: Member of the Scientific Advisory Board for the EU FP7 Collaborative Project "HumEn" coordinated by Prof Henrik Semb
2014-present: Member of PLoS Biology Advisory Board
External committees
2015–2018: Member of EMBO Membership Committee
Journal Editor
2020-present: Editor of *Journal of Cell Science*
Conference organisation
2016 Joint organiser of Biochemical Society Focused Meeting on BMP signalling in Cancer, Cambridge, UK
2017 Joint organiser of the Francis Crick Institute and Dundee University Life Sciences Joint Symposium "Signal transduction in health and disease"
2019 Organiser of EpiGeneSys – The Journey Continues, London, UK.

2019 Joint organiser of Biochemical Society Focused Meeting on BMP signalling in Cancer II, Oxford UK

Lab Name	***Developmental Signalling Laboratory***

Research programme and achievements

The fundamental biological problem I want to solve is how cells use signal transduction pathways to communicate with each other in the context of whole organisms to regulate new programmes of gene expression and induce new behaviours in their neighbours. This is important, as cell communication is fundamental to the decision-making processes that orchestrate embryonic development, thereby determining how tissues and organs of the appropriate size develop in the right place at the right time. Furthermore, mis-regulation of developmental signalling pathways results in severe human diseases, like cancer.

To understand how intercellular signalling functions in embryonic development and disease, my lab focuses on the TGF-β family of ligands, a group of highly evolutionarily-conserved growth and differentiation factors that signal through serine/threonine kinase receptors and the SMAD transcription factors. These ligands play essential roles in the very earliest processes of germ layer specification and patterning, and perturbation of their activity leads not only to cancer, but to a plethora of other disorders, including the Marfan-related syndromes. Our goal is to unravel mechanistically how dynamic spatial and temporal patterns of signals are established, then transduced from receptors to the nucleus, and how this leads to new programmes of gene expression. Furthermore, we want to understand how signalling by TGF-β family ligands functionally cooperates with other signalling pathways to pattern tissues, and to determine how mis-regulation of TGF-β family signalling leads to human pathologies.

A theme that unites the entire programme is the issue of how spatial and temporal information is ‘encoded’ in TGF-β family signalling pathways and interpreted at both the cellular level and more broadly, at the level of tissues and organisms. We take the distinctive approach of studying the pathways in the context of both normal development and disease, which allows us to take fundamental insights from our developmental work and apply them to our studies of deregulated signalling in disease contexts. Working on the diseases in turn uncovers mechanisms relevant for normal physiology.

Our major achievements in the last quinquennium have been to decipher the mechanism underlying how signal duration affects output, and to determine how TGF-β family signals drive dynamic transcriptional programmes, leading to different cell behaviours. In this context, we have uncovered the mechanism whereby domains of BMP and Nodal ligand activity are established in early zebrafish embryos and are functionally interpreted. Furthermore, we have demonstrated how Nodal signalling acts in an incoherent feedforward loop with the FGF pathway to specify mesoderm and endoderm. Importantly, insights from our developmental work on Nodal signalling and the unexpected behaviours we discovered for TGF-β, prompted us to rethink the role of TGF-β family signalling in tumourigenesis, and has led to a major translational project, developing a potential cancer therapeutic. We have also discovered a new mechanism of receptor activation in TGF-β family signalling that we have now shown to be relevant for aberrant Activin

signalling in the diseases Fibrodysplasia Ossificans Progressiva and Diffuse Intrinsic Pontine Glioma.

Our goal in the next five years is to exploit this new knowledge and expertise in a fully integrated project with three main aims:
1. To dissect the function of TGF-β family signalling in cell fate decision making over time. We particularly want to solve the mystery of why only a subset of cells in the first two cell tiers of the blastula stage zebrafish embryo are specified to become endoderm progenitors, whilst the adjacent cells, which experience an almost identical environment, become mesodermal progenitors.
2. To determine the mechanisms by which cells read time to monitor signalling duration and strength in health and disease. From our previous work we hypothesise that this occurs primarily at the level of receptor trafficking. We are therefore focusing on developing new methods for tracking individual receptors and thus defining trafficking routes and dynamics.
3. To unravel the consequences of deregulated TGF-β family signalling in disease. We want to understand the role of aberrant TGF-β family signalling in cancer, in particular in modulating the tumour microenvironment, and are actively developing a potential therapeutic that we hypothesise will act synergistically with immune checkpoint therapies. We are also focused on understanding the molecular mechanisms underlying Marfan-related syndromes, which arise as a result of point mutations in core components of the TGF-β family pathways.

Research outputs

van Boxtel, A. L., Chesebro, J. E., Heliot, C., Ramel, M. C., Stone, R. K., and Hill, C. S. (2015) *A temporal window for signal activation dictates the dimensions of a Nodal signaling domain*. Dev Cell 35, 175-185. DOI: 10.1016/j.devcel.2015.09.014
This paper shows how temporal information in the zebrafish embryo is transformed into a spatial pattern. We demonstrate how the Nodal signalling gradient is formed in the early zebrafish embryo and show that its size and shape are determined by a temporal signal activation window created by a microRNA-mediated delay in the translation of Lefty, a Nodal antagonist. This paper was important as it not only challenged the long-held view in the field that the Nodal gradient was formed by a reaction–diffusion mechanism, but highlighted the importance of signalling duration in gradient formation.

Coda, D. M.*, Gaarenstroom, T.*, East, P., Patel, H., Miller, D. S. J., Lobley, A., Matthews, N., Stewart, A., and Hill, C. S. (2017*) Distinct modes of SMAD2 chromatin binding and remodeling shape the transcriptional response to NODAL/Activin signaling*. Elife 6, e22474. DOI: 10.7554/eLife.22474
This paper explains how SMAD2, the downstream signal transducer of the NODAL/Activin pathway, regulates transcription. We defined the sequence of events that occur from SMAD2 binding to transcriptional activation, and the mechanisms underlying them, thereby establishing new paradigms for signal-dependent transcriptional regulation.

Ramachandran, A., Vizán, P., Das, D., Chakravarty, P., Vogt, J., Rogers, K. W., Müller, P., Hinck, A. P., Sapkota, G. P., and Hill, C. S. (2018) *TGF-β uses a novel mode of receptor activation to phosphorylate SMAD1/5 and induce epithelial-to-mesenchymal transition*. Elife 7, e31756. DOI: 10.7554/eLife.31756

This paper describes a new mechanism for receptor activation, which we believe may be widespread among TGF-β family members. It also demonstrated for the first time the importance of combinatorial signalling via both SMAD pathways for a functional TGF-β response.

van Boxtel, A. L., Economou, A. D., Heliot, C., and Hill, C. S. (2018) *Long-range signaling activation and local inhibition separate the mesoderm and endoderm lineages*. Dev Cell 44, 179-191 DOI: 10.1016/j.devcel.2017.11.021
This work represents a major step forward in deciphering the organising principles underlying early embryonic patterning. It revises the view that tissues are patterned through a simple long-range morphogen gradient, and instead reveals the importance of feedforward and feedback loops involving multiple signalling pathways.

Miller, D.S.J., Bloxham, R.D., Jiang, M., Gori, I., Saunders, R.E., Das, D., Chakravarty, P., Howell, M., Hill, C.S. (2018) *The dynamics of TGF-β signaling are dictated by receptor trafficking via the ESCRT machinery*. Cell Rep 25, 1841-1855.e5. DOI: 10.1016/j.celrep.2018.10.056
This work revealed for the first time how receptor trafficking shapes signalling dynamics. Using whole genome siRNA screening, we demonstrated that TGF-β receptors are targeted for degradation by the ESCRT machinery. Inhibiting ESCRT components upregulates long-term TGF-β signalling and enhances functional outputs of the pathway to sensitise cells to low levels of ligand in the microenvironment, which we show could be relevant in cancer.