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| **Name** | JAMES BRISCOE |
| **Position** | Senior Group Leader<br>Assistant Research Director |
| **Year joined *(Crick or founder institute)*** | 2000 |

**Career History**

1992 -1996: PhD. King's College, London/Imperial Cancer Research Fund, London.
1996 –2000: Postdoctoral Research. Columbia University, New York, USA.
1996-1998: HFSP Long Term Fellowship

**Major Awards, Honours and Prizes**

1991: Celltech Prize for Undergraduates
1996: Human Frontiers Science Program Long Term Fellowship
1998: Young Investigator (British Society for Developmental Biology)
2001: EMBO Young Investigator
2008: EMBO Gold Medal
2009: EMBO Member
2019: Fellow of the Academy of Medical Sciences
2019: Fellow of the Royal Society

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

Editor-in-Chief, Development
Editorial Board Membership: PLoS Biology, Developmental Biology
Roslin Institute Scientific Advisory Board 2014-
MRC-Harwell Scientific Advisory Board 2013-
EMBL Scientific Advisory Council 2017-
TIFR, Mumbai, India. Institute review committee 2018
Institut de Biologie du Développement de Marseille. Institute review committee 2017
EMBO Long Term Fellowship Committee 2015-
Wellcome International Scholars Panel 2017
Director, International Society for Differentiation 2017-
Chair, Developmental Biology Gordon Research Conference 2019-2021
School Governor, Regent High School - Inner London Secondary School 2013-

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| **Lab Name** | ***Developmental Dynamics Laboratory*** |

**Research programme and achievements**

How are the right types of cells produced in the right place, at the right time, in the right amounts in a developing tissue? In broad terms, initially uncommitted progenitors acquire their fate in response to signals that control transcriptional programmes. These gene regulatory networks (GRNs) determine the spatial and temporal succession of states that progressively define cell identity.

To understand the structure, function and logic of GRNs, we use an experimentally tractable system – the vertebrate spinal cord. We take an interdisciplinary approach combining *in vivo* developmental biology with molecular, genomic and computational methods. Our work has identified mechanisms by which the spatiotemporal pattern in the neural tube is generated, established design principles of the GRN architecture that interpret graded morphogen signalling, and provided insight into the coordination of growth and patterning in the developing neural tube. The work reconciles mechanisms of morphogen activity based on spatial or temporal gradients and provides evidence for how opposing gradients generate and maintain precise patterns in a growing tissue.

Our current directions are driven by three recent advances in the lab. First, we have developed *in vitro* differentiation systems using mouse and human embryonic stem cells that accurately recapitulate developmental processes *ex vivo*. Second, we have embraced new technologies that provide unprecedented ability to manipulate and assay single cells. These include state of the art genomic, genome engineering and imaging methods. Finally, we have embedded collaborations with physicists and computer scientists to develop computational tools and construct data driven mathematical models. Together with our established embryological expertise, this is allowing us to establish a platform for manipulating and analysing the molecular and cellular mechanisms by which cell fate is acquired and tissues organised.

These studies advance beyond qualitative explanations to a dynamic and quantitative understanding of how tissues are patterned and how GRNs operate. We will identify the rules by which cells make decisions and we will define the design logic and network architectures that lead to distinct cell fate choices. The ability to: (i) follow the trajectory of a cell as it transitions to a specific neuronal subtype i*n vivo*; (ii) manipulate the process *in vitro* and *in vivo*; and (iii) model it *in silico*, offers a unique system for understanding organogenesis. By bridging scales - from molecules to cells to tissues – we aim to explain the generation of specific cell types and how a functional, well organised neural tube is assembled. Understanding this will provide insight into the mechanisms that produce and organise cells in complex tissues and establish the foundations for rational, predictive tissue engineering.

## Research outputs

**Rayon T, Stamataki D, Perez-Carrasco R, Garcia-Perez L, Barrington C, Melchionda M, Exelby E, Tybulewicz V, Fisher EMC, Briscoe J. (2020) *Species-specific pace of development is associated with differences in protein stability*. Science 369(6510) Article number eaba7667. DOI: 10.1126/science.aba7667**
Despite evolutionarily conservation of molecular mechanisms, the speed of development varies substantially between species. Using *in vitro* directed differentiation of embryonic stem cells to motor neurons, we show that the programme of motor neuron differentiation runs twice as fast in mouse as in human. We provide evidence that a two-fold increase in protein stability and cell cycle duration in human cells compared to mouse can account for the slower pace of human development, indicating that global differences in kinetic parameters play a major role in interspecies differences in developmental tempo. This study establishes a new experimental system in which to address fundamental questions.

**Delile J, Rayon T, Melchionda M, Edwards A, Briscoe J, Sagner A. (2019) *Single cell transcriptomics reveals spatial and temporal dynamics of gene expression in the developing mouse spinal cord*. Development 146 (12): dev173807. DOI: 10.1242/dev.173807**

We used single cell mRNA sequencing to generate a molecular atlas of the mouse neural tube between embryonic days 9.5-13.5. The analysis documented gene expression profiles of developing spinal neurons, but also highlighted a previously underappreciated temporal component to the mechanisms generating neuronal diversity. The data offer insight into the mechanisms responsible for neuronal specification, and provide a compendium of gene expression for classifying spinal cord cell types that will support future studies of neural tube development, function and disease. With ASF, we established 10X Genomics methods at the Crick and also implemented and developed the associated computational methods for data analysis.

**Metzis V, Steinhauser S, Pakanavicius E, Gouti M, Stamataki D, Ivanovitch K, Watson T, Rayon T, Mousavy Gharavy SN, Lovell-Badge R, Luscombe NM, Briscoe J. (2018) *Nervous System Regionalization Entails Axial Allocation before Neural Differentiation*. Cell 175(4):1105-1118. DOI: 10.1016/j.cell.2018.09.04**

The prevailing view of neural induction in vertebrate embryos had been that cells are initially induced with anterior (forebrain) identity and then caudalising signals convert a proportion to posterior fates (spinal cord). Using chromatin accessibility, to define how cells adopt region-specific neural fates, combined with genetic and biochemical perturbations, we found that contrary to the established model, cells commit to a regional identity before acquiring neural identity. These findings prompt a revision to textbook models of neural induction. The study illustrates our adoption of new genomic methods (ATACseq) to address long-standing questions, and our capacity to productively collaborate with computational biologists.

**Gouti, M; Delile, J; Stamataki, D; Wymeersch, FJ; Huang, Y; Kleinjung, J; Wilson, V and Briscoe, J. (2017) *A gene regulatory network balances neural and mesoderm specification during vertebrate trunk development*. Developmental Cell 41, 243-261. DOI: 10.1016/j.devcel.2017.04.002**

Here, we reverse-engineered the transcriptional network controlling bipotent neuromesodermal progenitors (NMPs) that fuel embryo elongation by generating spinal cord and trunk mesoderm tissue. We used single-cell transcriptomics to identify the molecular signature of NMPs and together with genetic perturbations, delineated the architecture of a regulatory network architecture that balances the generation of different cell types from bipotential progenitors. The study is an example of our use of stem cell methods and data driven mathematical modelling to address developmental questions.

**Zagorski, M; Tabata, Y; Brandenberg, N; Lutolf, MP; Tkačik, G; Bollenbach, T; Briscoe, J and Kicheva, A. (2017) *Decoding of position in the developing neural tube from antiparallel morphogen gradients*. Science 356, 1379-1383 DOI: 10.1126/science.aam5887**

Like many developing tissues, the vertebrate neural tube is patterned by antiparallel morphogen gradients. Using quantitative gene expression and signalling measurements we derived and validated a characteristic decoding map that relates morphogen input to the positional identity of neural progenitors. This revealed a strategy that minimises patterning errors in response to the joint input of noisy opposing gradients. The study illustrates how we integrate quantitative data, developmental and microfluidic experiments with phenological and mechanistic models.