Name	KATIE BENTLEY
Position	Physical Science Group Leader (King's)
Year joined *(Crick or founder institute)*	2018

Career History

2006: PhD Computer Science University College London, UK
2006 - 2009: Postdoctoral Fellow Biomolecular Modelling Laboratory (Bates Lab) LRI, Cancer Research UK
2009 - 2013: Postdoctoral Fellow, Vascular Biology Laboratory, Cancer Research UK, LRI, London (in Holger Gerhardts Lab). Funding: Leducq Fondation
2010: Visiting postdoc to Weilan Ye's Vascular Biology Lab, Genentech, CA, USA (2 weeks)
2010: Visiting postdoctoral fellow to Prof. Luisa Iruela-Arispe's Vascular Biology Laboratory, UCLA, CA, USA (1 month).
2011: Visiting postdoctoral fellow to Profs. Michael Simons and Anne Eichmann's Vascular Biology Laboratories, Yale, CT, USA (1 month).
2013 - 2017: Staff Scientist, Pathology Department, Center for Vascular Biology Research, Beth Israel Deaconess Medical Center, MA USA
2013 - 2017: Faculty Member: Harvard Medical School Systems Biology PhD Program Boston, MA USA
2014 - 2017: Assistant Professor of Pathology, Harvard Medical School, Boston MA USA
2015 - present: Assistant Professor, Immunology, Genetics and Pathology Department, Uppsala University, Sweden
2017- present: Research Assistant Professor, Biomedical Engineering Department, Boston University, MA, USA

Major Awards, Honours and Prizes

2010: Poster Prize, North American Vascular Biology Organization, CA, USA

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

2018 – Fight for Sight Grant Assessment Panel
2018 – EMBL Barcelona new group leader search committee and panel member
2014-2018: elected member of the board for International Society of Artificial Life
2016 ERC consolidator grants Ad hoc reviewer
2014-2016 The Research Foundation – Flanders (FWO) Belgium. Expert reviewer for: New research project proposals and Marie Sklowdoska-Curie/other postdoctoral fellowships
2016 BSF (US – Israel Binational Science Foundation) Grant Ad hoc Reviewer
2014-present: Invited Editorial Board Reviewer for Frontiers in Computational Intelligence Journal.
2015-2016 KU Leuven Research Council Grant Ad hoc Reviewer

Lab Name	*Cellular Adaptive Behaviour Laboratory*

Research programme and achievements

We use simulations integrated with experiments to explore how cells choose their behaviour at a given moment in time, and how their local environment and neighbouring cells influence them to either help the tissue (adaptive behaviour) or help a pathogen/disease condition persist (maladapted behaviour).

We developed a novel, time-based formulation of endothelial cell behaviour during angiogenesis and through our collection of recent integrated in silico/in vivo studies we have demonstrate that various alterations to cell or tissue conditions act to locally adapt the timing of collective cell decisions and behaviours, impacting when certain cells decide to move, and generating a different spacing of vessel branches in the growing network. We are calling these ‘temporal regulators’ or ‘temporal adaptors’ of blood vessel branch spacing and they represent an exciting potential to externally modulate vessel branching under different conditions. As such we are now investigating them further and their potential as therapeutic targets to normalize vessel growth in disease.

Our most recent studies in this area have focused on an unexpected role for actin-based filopodia protrusions as an aid to making quick collective decisions on which cell will be the “tip cell” and lead a new blood vessel sprout. We propose they are a basal form of cognition - a form of “active perception” or sensorimotor feedback – as their movement alters sensory input and vice versa leading to enhanced (faster) tip decisions. Our simulations predict they confer positive feedback to sensing which generates a bistable switch property to speed up the otherwise slow process of notch lateral inhibition. We are currently finalising the first proof of concept paper laying out this theory and plan to perform the full investigation, validation and characterisation of the mechanism while at the Crick with integrated in vitro micropatterning and simulation studies together with our in vivo (zebrafish) collaborator Shane Herbert Manchester University.

We also work on understanding pathological vessel growth, in particular how changes to cell shape and signalling dynamics contribute to vascular abnormalities. Eye diseases affect millions of people worldwide and can have devasting effects on people’s lives. Vascular anomalies are central to many retinopathies. To find new treatments, scientists need to understand more about how these diseases arise and how they progress. This is challenging and progress has been held back by limitations in current techniques for looking at the eye. We recently showed that light-sheet fluorescent microscopy (or LSFM for short) can quickly produce highly detailed, three-dimensional images of mouse retinas, from the smallest parts of cells to the entire eye. The technique also identified new features in a well-studied mouse model of retina damage caused by excessive oxygen exposure in young mice. Previous studies of this model suggested the disease caused blood vessels in the eye to balloon, hinting that drugs that shrink blood vessels would help. But using LSFM, we revealed that these blood vessels actually take on a twisted, knotted and swirled shape. This suggests that treatments that untangle the vessels rather than shrink them may be more effective.

We also recently identified that timing of notch patterning, key in tip cell selection, abnormally oscillates in retinopathy conditions – so we are actively engaged now in both developing new sophisticated computer modelling methods to better capture the complex 3D shapes and cross-talking signalling driving abnormal knotted vessel growth in

retinopathy as well as performing cutting edge 3D/4D imaging and analysis of the tufts in retinas from Crick colonies as well as our collaborator Claudio Franco (IMM Lisbon) to better characterise this newly identified knotted morphology. Overall we aim to discover how they form and predict new ways to therapeutically untangle them.

We are also actively collaborating with software engineers to develop a biologist friendly programming language to aid wider adoption of predictive simulations in biology as they have been instrumental for our research in uncovering hidden counter-intuitive dynamics and could help many other labs understand how non-linear dynamics and unconventional algorithmic cross-scale or cell shape/signalling mechanisms could be contributing to their cell system's behaviour.

Research outputs

Claudia Prahst*, Parham Ashrafzadeh*, Thomas Mead* (co-first), Ana Figueiredo, Karen Chang, Douglas Richardson, Lakshmi Venkatraman, Mark Richards, Ana Martins Russo, Kyle Harrington, Marie Ouarne, Andreia Pena, Dong Feng Chen, Lena Claesson-Welsh, Kin-Sang Cho, Claudio Franco, Katie Bentley. (2020) *Mouse retinal cell behaviour in space and time using light sheet fluorescence microscopy*. ELife 9:e49779. DOI: 10.7554/eLife.49779
We successfully performed the first lightsheet 3D/4D imaging of mouse retinas (focussing on vessels and neurons) and demonstrated that current confocal methodss distorted vessel tissue. This brings a much improved way to observe and quantify the devastating changes to vessels and neurons in retinopathy mouse models. The work also solidified our lab as multidisciplinary performing our own mouse experiments and imaging as well as computer modelling.

Page, Donna, Thuret, Raphael, Venkatraman, Lakshmi, Takahashi, Tokiharu, Bentley, Katie*, Herbert, Shane P* (co-last). (2019) *Positive feedback defines the timing, magnitude, and robustness of angiogenesis*. Cell Reports 27(11) 3139-3151.e5. DOI: 10.1016/j.celrep.2019.05.052
Collaborative project proving in vivo (zebrafish) validation of our simulation model predictions that positive feedback alters the timing of the important tip cell selection step in blood vessel branching. We also identify a previously unappreciated time window for selection in vivo.

Bentley, Katie, and Shilpa Chakravartula. (2017) *The temporal basis of angiogenesis*. Philosophical Transactions of the Royal Society B: Biological Sciences 372, 1720. DOI: 10.1098/rstb.2015.0522
Perspective piece detailing my theory that many "temporal regulators" exist to modulate and adapt the timing of tip cell selection during angiogenesis in order to fine tune the vessel branch spacing of new blood vessel networks.

Ubezio, B., Blanco, R.A., Geudens, I., Stanchi, F., Mathivet, T., Jones, M.L., Ragab, A., Bentley, K*. and Gerhardt, H* (co-last). (2016) *Synchronization of endothelial Dll4-Notch dynamics switch blood vessels from branching to expansion*. Elife 5:e12167. DOI: 10.7554/eLife.12167
In vivo validation of simulation predictions, and further simulation studies, showing that pathologically high VEGF in tumours and retinopathy cause synchronised Notch oscillations among endothelial cell collectives in growing blood vessels and demonstration that this synchrony contributes to vessel expansion rather than branching in pathological vessels.

The culmination of ten years work when my simulations first predicted patholgical oscillations.

Bahti Zakirov, Georgios Charalambous, Raphael Thuret, Irene M. Aspalter, Kelvin Van-Vuuren, Thomas Mead, Kyle Harrington, Erzsebet Ravasz Regan, Shane Paul Herbert, Katie Bentley. (2021) *Active Perception during Angiogenesis: Filopodia speed up Notch selection of Tip cells in silico and in vivo*. Philosophical Transactions B of the Royal Society 376, 1821. DOI: 10.1098/rstb.2019.0753

Our work addresses Notch mediated tip cell selection preceding angiogenesis. Although the molecular players surrounding this process are well characterized, we have discovered an unexpected role for filopodia (fingerlike, actin-rich cell membrane protrusions) in regulating the timing of Notch patterning. We argue that the filopodia are used by the cells to actively sense morphogens in the environment- thus speeding up patterning decisions. This feeds into the theory that the topology of vascular networks created by angiogenesis is regulated by the timing of Notch patterning, and represents a step towards understanding complex, adaptive morphogenesis in terms of collective cell behaviour and communication.