Spring 2005

Cell and Developmental Biology Annual Symposium Joint with the BSCB

6th-9th April, Warwick University, UK

BSDB Organisers: Alfonso Martinez-Arias and Phil Ingham

Cell & Developmental Biology Annual Symposium

6th - 9th April 2005
University of Warwick

An Extravaganza of Cell & Developmental Biology

Organisers: Phil Ingham, Alfonso Martinez-Arias & Jordan Raff

Plenary Speakers

Cori Bargmann
Matt Scott

Symposia

mRNA localisation; Regeneration & Wound Healing; Systems Biology
Neural Stem Cells; Polarised Secretion; Development of Marine Animals
Neuronal Transmitters; Asymmetric Cell Division; Space & Time in Health & Disease
Cell Biology of Behaviour; Micro RNAs; Epithelial Migration
Regulation of Cell Death; Mitosis; Guidance Systems

Symposium Speakers

Detlev Arendt
David Baulcombe
Hamid Bolouri
Bruce Bowerman
Simon Bullock
Folma Buss
Philippe Chavrier
Steve Cohen
Daniel Chourrout
Kim Dale
Graeme Davis
Ilan Davis
Mario de Bono
Denis Duboule
Suzanne Eaton
Anne Ephrussi
Mike Fainzilber
Jean-Francoise Ferveur
Charles ffrench-Constant
Cayetano Gonzalez
Darren Gilmore
Bruno Goud
Pierre Gönczy
Magdelena Gotz
Doug Green
Gillian Griffiths
Wieland Huttner
Tony Hyman
Antonio Jacinto
Ray Keller
Juergen Knoblich
Guido Kroemer
Ulrike Kutay
Ruth Lehmann
Patrick Lemaire
Chris Lowe
Paul Martin
Alfonso Martinez Arias
Pascal Meier
Ira Mellman
Luis Miguel Martins
Nick Monk
Stephen Nurrish
Ronald Plasterk
Jordan Raff
Freddy Radtke
Eres Raz
Giampietro Schiavo
Francois Schweisguth
Luis Serrano
James Sharp
Robert Singer
Kate Storey
Elly Tanaka
Guy Tear
Derek van der Kooy
Xiadong Wang
Cornelius Weijer
Magda Zernicka-Goetz
Yixian Zheng

Plus….
Beddington,
Hooke,
& Waddington
Medal Lectures

Plus…..
Special Symposium on "Women in Biology"

For further information and online registration please visit:
www.bsdb.org

Abstract Submission and Registration Deadline –
29th January 2005

BSDB/BSCB Annual Spring Symposium

Warwick, 2005

The following are reports of selected sessions at the recent Spring Symposium.

Neural stem cells

The neural stem cell session was opened by Charles ffrench-Constant (University of Cambridge, UK) who gave an overview of how integrins and their ligands in the extracellular matrix regulate growth factor signalling to provide precise temporal and spatial control within the stem cell niche. He also described how in tenascin-C deficient mice, neural stem cells show reduced sensitivity to FGF-2 and enhanced activity to BMP-4. He illustrated the expression of laminins within the neural niche and demonstrated their roles in maintenance.

Jun-An Chen (Wellcome/CRUK Gurdon Institute, Cambridge, UK) described a novel cell type-specific cyclin (cyclin Dx) that is required for maintaining ventral neuronal progenitors in the spinal cord. He suggested that motor neuron progenitors differentiate prematurely when the concentration of cyclin Dx falls. These results support the hypothesis that the coordination of cell proliferation and cell fate determination is regulated by cell cycle components.

It was a pity that Magdelena Gotz (Max Planck Inst Neurobiology, Germany) was ill and could not come to this meeting. However, a post-doc from her lab presented evidence of how Pax6 plays a master role in the control of neurogenesis. He showed that neurogenesis becomes fully Pax6-dependent in the neurosphere culture system, independent of the region of origin, and that Pax6 overexpression is sufficient to direct almost all neurosphere-derived cells towards neurogenesis.

Kate Lewis (University of Cambridge, UK) described the advantages of using zebrafish to study ventral interneuron specification and patterning. Many of the transcription factors (Evx1, Eng1b, Chx10) implicated in interneuron specification in amniotes are also expressed in the embryonic zebrafish spinal cord, suggesting that the mechanisms of interneuron specification are conserved across vertebrate species. She also showed a transgenic line of zebrafish in which GFP is expressed in cells that express Pax2, a ventral interneuron transcription factor. This tool will be very useful for future functional studies.

Derek van der Kooy (University of Toronto, Canada) showed how primitive neural stem cells are formed directly from single ES cells in a manner dependent on exogenous LIF and endogenous FGF. Embryonic stem cells quickly acquire neural identity and give rise to neurons and glia in minimal culture conditions. Moreover, experiments in vivo with mouse chimeras reveal that these primitive ES-derived neural stem cells have a broad range of neural and non-neural lineage potential. These results support a model whereby definitive neural stem cell formation is proceeded by a primitive neural stem cell stage during neural lineage commitment.

Finally, Wieland Huttner (Max Planck Institute, Dresden, Germany) demonstrated how is it possible to distinguish between proliferating and neuron-generating neuroepithelial cells using the anti-proliferative gene TIS21. Using time-lapse microscopy of neuron-generating divisions of neuroepithelial cells in a transgenic TIS21-GFP mouse embryo reveals the existence of a novel neuronal progenitor dividing at the basal side of the neuroepithelium. In addition, he described using prominin-1 to define the symmetric and asymmetric distribution of apical plasma membrane during proliferating and neuron-generating divisions of neuroepithelial cells.

Jun-An Chen, Gurdon Institute and Department of Zoology, University of Cambridge

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Polarized secretion of endocytic organelles

One of the fantastic things about the BSDB/BSCB Spring meeting is the broad range of topics covered and the opportunities this presents to discover (or rediscover) exciting areas of research that unfortunately one never seems to have the time to keep up with. Thursday presented me with such an opportunity and also a dilemma: which session should I choose? Finally plumping for “Polarized secretion of endocytic organelles”, I headed over to social sciences to see what I could learn.

The session was chaired by Gillian Griffiths (University of Oxford, UK) who kicked off with a fantastic account of how T lymphocytes achieve polarized secretion, allowing them to kill target cells. Brilliantly, Griffiths has been able to exploit clinical samples to get a handle on the process. She outlined both what this had taught us about players in the biological processes and the understanding this conferred of clinical aspects of the syndromes, highlighting how much can be gained by the availability of clinical samples to the research community. In a short talk, Alistair Hume (London, UK) then gave us a summary of the melanocyte assay he has been using for his research and the insights it has provided into the role of melanophilin in melanosome transport. Next, Phillipe Chavrier (Paris, France) gave an excellent account of his work on membrane delivery to the cell surface during phagocytosis and of the interplay of formins and arp2/3 in actin dynamics. G. Michaux followed with a brief outline of his functional analysis of P-selectin trafficking in endothelial cells.

After a coffee and biscuit pit-stop, I heard Susan Eaton (Dresden, Germany) address a packed audience. She spoke of how gradients of lipid-linked morphogens are achieved during *Drosophila* development. I was intrigued by her research on argosomes – membranous particles that may play a role in the process. These particles sounded fantastic – a novel solution to an old question. Eaton went on to present progress she is making in dissecting the argosome, which highlighted just how difficult some questions are to address and yet how, with some ingenuity and determination, we can move forwards. Last, but definitely not least, was Ira Mellman (New Haven, USA) who wowed us with some fantastic images of endocytosis in action. She demonstrated that with careful analysis of such data we can get a crucial understanding of the processes in question.

"As the session ended, I reflected on the fantastic opportunity I had been afforded."

As the session ended, I reflected on the fantastic opportunity I had been afforded. I had hoped to get an insight into this topic unfamiliar to me and had been lucky enough to spend the afternoon listening to cutting edge research by world class scientists. Not something I have the luxury of doing everyday!

Nina Peel, Gurdon Institute, Cambridge

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Asymmetric cell division

The session on asymmetric cell division was chaired by Jürgen Knoblich (IMP, Vienna), who started by talking about polarization of recycling endosomes during asymmetric cell division in the *Drosophila* nervous system. The hallmark of asymmetric cell division is segregation of cell fate determinants, the first of which to be identified was Numb. In the endocytic pathway, recycling endosomes are generated and accumulate around the centrosome of only one of the daughter cells. Rab11 is the marker for these recycling endosomes and is suppressed in cells that do not inherit Numb. Rab11 binds Nuf, a centrosomal protein that binds and accumulates on only one of the centrosomes. Nuf and Numb act redundantly in asymmetric cell division.

"[The] spatial arrangement of individual 4-cell stage [mouse] blastomeres and the order in which they are generated correlate with blastocyst pattern in the mouse embryo."

Rita Sousa-Nunes (King's College, London) described a mutant obtained in a screen to identify new genes involved in the asymmetric division of the *Drosophila* neuroblast. This mutant has the intriguing phenotype of enhanced detection of centrosomal Miranda. Continuing the studies on *Drosophila*, François Schweisguth (Ecole Normale Superieure, Paris) spoke about Neuralized, which, along with Numb, regulates Notch-mediated binary fate decisions. Bearded is a partner of Neuralized; overexpression and deletion experiments suggest that negative regulation of Neuralized by Bearded is at least partly responsible for the spatially restricted distribution of Delta (a Notch ligand).

Arwen Wilcock (School of Life Sciences, Dundee) outlined a strategy to build extensive maps of cell lineage using electroporation of the spinal cord of chick embryos with GFP tubulin, followed by time-lapse 3D imaging. After the coffee break, Pierre Gönczy (ISREC, Switzerland) described the importance of G protein signalling pathways for asymmetric cell division in *C. elegans* embryos.

Finally, Magda Zernicka-Goetz (Gurdon Institute, Cambridge) presented a non-invasive lineage tracing study of the early mouse embryo. The aim is to determine whether development of blastocyst pattern shows any correlation with the orientation and order of the second cleavage divisions that result in specific positioning of blastomeres at the 4-cell stage. The results suggest that the spatial arrangement of individual 4-cell stage blastomeres and the order in which they are generated correlate with blastocyst pattern in the mouse embryo.

Teresa Barros, Gurdon Institute, University of Cambridge

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Micro RNAs

The micro-RNAs session was devoted to small, non-coding RNAs that regulate gene expression at the post-transcriptional level. It was opened by Steve Cohen (EMBL, Heidelberg), who described a combined experimental and computational approach to study genome-wide micro-RNA functions. Given the large number of micro-RNA-encoding genes (over 100 in *Drosophila*), the time that would be required for functional analysis by genetics alone has prompted the use of computational methods to infer potential roles for these genes. Although the variability in base pairing makes it hard to predict the identity of candidate targets for micro-RNAs, Steve described how comparisons between known micro-RNA targets reveal that base pairing is more consistent at the 5' end and this "seed" region appears to contain most of the important information, whilst the targeting of micro-RNAs to a suite of genes with related functions facilitates functional annotation. Jan Rehwinkel (EMBL, Heidelberg) then described a genome-wide analysis of RNAs regulated by Drosha and Argonaut proteins in *Drosophila*, using microarray expression profiles. Of the various transcripts upregulated when these proteins were depleted, most were known to be involved in axon guidance, cell adhesion, organogenesis or apoptosis (including the validated micro-RNA targets hid and reaper).

The role of RNAi in transposon silencing was explored by Ron Plasterk (Hubrecht Laboratory, Utrecht), who pointed out that even though there are multiple copies of transposons in the Caenorhabditis elegans genome, none of these are mobile in the germline. However, in “mutator” mutants (which lose the activity of genes owing to the aberrant activation of a subset of transposons in the germline), it was found that RNAi was also defective, suggesting that RNAi might protect the genome against transposon activity. Describing RNAi as the “immune system of the genome”, Ron pointed out how the amplification of RNAi signals might be compared to clonal selection, given that a brief episode of RNAi activity may lead to stable germline gene silencing that is heritable over 30 generations! Changing track, Ron then highlighted how the sequencing of micro-RNAs from a host of primates might facilitate the discovery of new micro-RNA genes through “phylogenetic shadowing” and described ongoing functional studies of micro-RNAs in zebrafish development.

The role of micro-RNAs in C. elegans development was picked up by Eric Miska (Gurdon Institute, Cambridge), who described a combined functional genomics approach involving GFP expression studies and the generation of knockout mutants. In this way, the lin-4 micro-RNA and four members of the evolutionarily conserved let-7 family were shown to yield heterochronic phenotypes in mutants. Eric then described the downregulation of micro-RNAs in primary human tumours. The session was concluded by David Baulcombe (Sainsbury Laboratory, Norwich), whose presentation focused on the role of siRNAs in chromatin silencing in Arabidopsis. He related how enhanced and reduced silencing phenotypes were observed in a host of mutants for homologues of RNA processing enzymes, presumably by affecting the turnover of RNA sequences entering the RNA silencing pathway and their subsequent direction of sequence-specific epigenetic modifications.

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BSDB

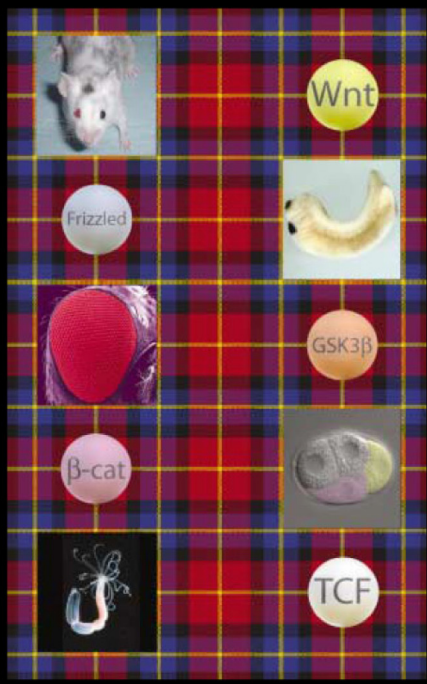
BSDB Autumn Meeting 2005

Wnt signalling in Development, Disease and Cell Biology

14th-16th September 2005

Speakers
Mariann Bienz
Alan Clarke
Hans Clevers
Trevor Dale
Bob Goldstein
Barry Gumbiner
Thomas Holstein
Rik Korswagen
Alfonso Martinez Arias
Pierre McCrea
Randall Moon
Inke Näthke
Roel Nusse
Patricia Salinas
David Strutt
Jean-Paul Vincent

Organisers
Stefan Hoppler
Jonathan Pettitt
Adrian Harwood
Pip Francis-West



Early registration and abstract deadline: 1st July 2005

For registration and more information, visit:
http://www.abdn.ac.uk/cdb/wntmeeting2005.htm

1495 UNIVERSITY OF ABERDEEN

BSDB Autumn Meeting

Aberdeen, 2005

Wnts and all

It sometimes seems that you can't do anything in developmental biology without running into Wnts. For the uninitiated help appears to be at hand with the constant stream of review articles describing a linear pathway of protein interactions that lead from Wnt ligand-receptor binding to increased β-catenin concentrations and subsequently altered gene expression. However anyone who stops to consider Wnt signalling soon realizes that the questions far outweigh our current understanding. Our attempts to find answers brought together an exciting mix of over 200 developmental biologists, cell biologists and biomedical researchers. for the BSDB Autumn meeting on "Wnt signalling in development, disease and cell biology" at the University of Aberdeen.

There are multiple Wnt proteins, which fall into families that are conserved throughout the animals; for example, sea anemones have 11 of the 12 Wnt sub-families, including WntA, which is not present in mammals. This level of complexity occurs throughout the Wnt signalling. There are at least two other signal pathways in addition to regulation of β-catenin: one controlling cell and tissue polarity, the other mediating calcium signalling. This generates a two-tier problem of identification of which pathway is active in a particular circumstance and then to explain how specificity is maintained and different pathways insulated from each other. This second problem is exacerbated by the presence of paralogues and parallel signalling for many of the pathway components and potential cross over into other signalling pathways.

Part of the answer lies in the cell biology of Wnt signalling cells. Cell surface interactions control the delivery of Wnt proteins to cells, then internalization and subcellular compartmentalization control protein interactions within the cell. Kinetics is also clearly important and rapid Wnt mediated changes in cytoskeletion and cell adhesion are distinct from those mediating gene expression. Signalling pathways may assemble over time to first establish and then maintain cellular states such as cell polarity. Wnt signalling must also be considered in the overall signal network. A case in point is the interaction of Wnt and Notch in formation of colon crypts – this offers alternative approaches to suppressing aberrant Wnt signalling in colon cancer.

Discussion of the imperfections in our understanding of this apparently well-known signalling pathway provided more than enough material for a fascinating and intellectually lively Autumn meeting. It raised as many questions as it answered, a sign of an exciting field, and invigorated our research. It has long been our ambition to hold a meeting in the UK and we are extremely grateful to the BSDB for their support. We hope that this is the beginning of a series of Europe based meetings.

Adrian Harwood, Cardiff University

Note added by Editor: We should add that the meeting proved to be very popular – with twice as many delegates as originally intended. The organisers are due our thanks for adapting the meeting to this and still managing to produce a highly successful meeting.