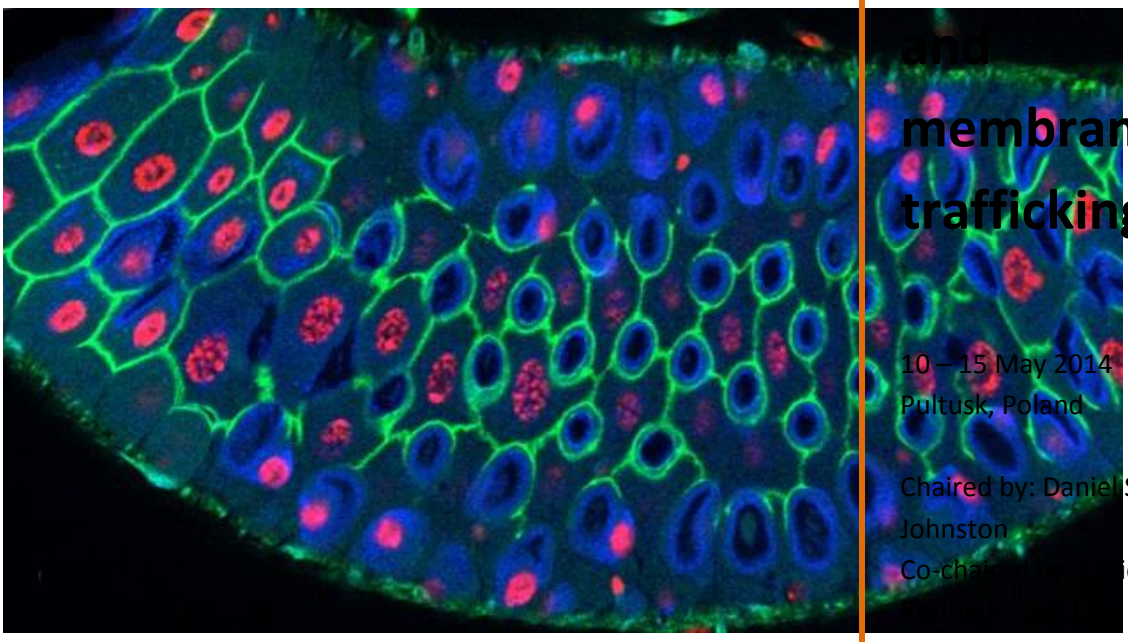
RESEARCH CONFERENCES

ESF-EMBO Conference

Cell polarity and membrane trafficking



10 – 15 May 2014
Pultusk, Poland

Chaired by: Daniel St Johnston
Co-chaired by: [illegible]ique

http://cellpolarity.esf.org/

Highlights & Scientific Report

Conference Highlights

Please provide a brief summary of the conference and its highlights in non-specialist terms (especially for highly technical subjects) for communication and publicity purposes. (ca. 400-500 words)

The ESF/EMBO conference on cell polarity and membrane trafficking brought together more than 120 researchers from five different continents to discuss recent advances in how cells become polarised (i.e. make one side different from the other) and how this relates to the trafficking of membrane vesicles to and from the appropriate side of the cell. The conference got off to an excellent start with a key note address from Alan Hall, who gave a fascinating historical perspective on the discovery of Rho GTPases as key regulators of cell shape and his more recent work on the role of the role of the tumour suppressor and Rho GTPases in the formation of the tight junctions that form the seal a the apical surface of sheets of epithelial cells. The first full day of the conference focused on the signals that direct membrane proteins to the correct compartment of the cell, and how different types of cells become polarised. Amongst the highlights were the beautiful movies from Dr Franck Perez (Institut Curie) showing secreted cargoes moving to the cell surface in different types of vesicle and from Dr Gillian Griffiths (University of Cambridge) revealing how an activated T-cell moves its nucleus to polarise towards a target cell that it is about to kill. The main topic of the third morning was how epithelial cells become polarised, with Keith Mostov providing an elegant story of how the binding of integrins to the extracellular matrix induces MDCK cells in three dimensional culture to reverse their polarity, and Eli Knust illustrating the multiple roles of the "apical determinant" Crumbs in trafficking and cytoskeletal organisation. This was followed by several talks on how cell shape affects polarity including some beautiful work from Manuel Thery (CNRS, Grenoble) on cells spinning on artificial substrates. The last two days of the conference concentrated on the role of cell polarity factors in cancer, with exciting new results on the ability of polarity mutants to synergise with classical oncogenes (Patrick Humbert, Peter MacCallum Cancer Centre, Australia) and new pathways that control metastasis (Eric Sahai: London Research Institute). Finally , the conference ended with an inspiring keynote address from Scott Emr describing his pioneering work on endocytosis and how the ESCRT complex deforms membranes to bud vesicles into the interior of multivesicular bodies.

Several factors made this a particularly successful conference. Firstly, the talks selected from the submitted abstracts were of a unusually high standard, including two excellent presentations by graduate students. Second, there was extensive discussion after each talk, largely because almost all of the speakers presented new, unpublished work. Third, almost all of the participants of the meeting presented their research, either as a talk or a poster, and this helped engage everyone in the lively discussions. Last but not least, the conference saw the emergence of multidisciplinary work at the interface between the two topics of the meeting, cell polarity and membrane trafficking, showing that these meetings have catalysed a cross-fertilisation between the two fields.

X	I hereby authorise ESF – and the conference partners to use the information contained in the above section on 'Conference Highlights' in their communication on the scheme.

Scientific Report

Executive Summary

(2 pages max)

The conference ran very smoothly thanks to the expert support from Marie-Laure Schneider and Sophie Gablin, who worked tirelessly to manage all of the complex arrangements for organizing and running the meeting, and I am very grateful for all of their outstanding help.

Extra support was obtained from eLife (€7,000), The Foundation for Polish Science (€5,000), Abcam (£3,000), and The Company of Biologists (£1,000). This was used to support the travel costs and registration of fees for Alan Hall, who gave the opening keynote lecture (eLIFE) , to provide free beer and wine for the poster sessions and to increase the number of grants to cover the registration fees for junior researchers and people from less well-off countries. The funds from the Foundation for Polish Science covered the full registration costs of six Polish students and postdocs and half the registration fee for two others. In total, we managed to support 40 participants with conference and travel grants, as well as covering most of the travel costs of the non-EU based speakers. We also used the external funding to provide two €100 poster prizes. These were awarded to Dr Andrew Porter (CRUK, Manchester Institute) and Alvaro Roman-Fernandez (CBMSO, Madrid), and they also received a year's free subscription to F1000 prime provided by Faculty of 1000.

The gender balance of the invited speakers was only 24% women (4 women:13 men), partly because I got confused about the gender of one of the invited speakers from Japan and because two of the invited speakers declined the invitation. We also discovered that one of the invited speakers who accepted the invitation had been found guilty of scientific misconduct that led to the retraction of several papers and loss of their University position. He originally insisted that he would still like to present his results at the meeting, but I eventually persuaded him not to attend. 7 of the short talks selected from the abstracts were given by women compared to 14 by men (33%; to give 29 % women speakers overall).

78% of the participants came from Europe (19 different countries), with the highest representation for the UK (22), France (15), Poland (12), and Germany (10). The remaining 22% came from 14 different countries with the highest proportion from the US (5), India (3), Japan (2) and Mexico (2). There were slightly fewer participants than last time, which may reflect the limited advertising of the conference, which was only promoted through the ESF website and emails to past participants (no poster and no announcements in journals). The smaller size of the meeting enhanced the opportunities for interactions between participants, particularly between studnts and postdocs and established PIs.

The organization of the conference was modified in a number of ways compared to last time, and these changes generally appeared to work well.

1) The Invited speakers were given 30 minutes for their talks plus 10 minutes for questions rather than 25 +5 minutes as last time, and this helped generate good discussions after each talk.

2) Ten of the invited speakers were asked to act as poster judges and this ensured that all of the

students and postdocs presenting posters got a chance to talk to a number of more senior members of the field about their work, which they greatly appreciated

3) We used the sponsorship funds to provide free beer and wine during the poster sessions, which ensured that they were very well attended

4) We kept the posters up throughout the meeting. A number of people took advantage of this to catch up on posters that they didn't have time for during the sessions. Several presenters also invited people to discuss their posters in the free evenings.

5) We used a home-made traffic light system to warn the speakers when they were running out of time. None of the speakers ran over, which allowed plenty of time for discussion.

Scientific Content of the Conference

(1 page min.)

- *Summary of the conference sessions focusing on the scientific highlights*
- *Assessment of the results and their potential impact on future research or applications*

The meeting started with an excellent plenary lecture on the first evening from Alan Hall, who described how he discovered the roles of Rho, Rac and Cdc42 in actin organization, before describing in more detail the functions of Rho and Cdc42 in the formation of the apical domain in epithelia and the effectors through which they each act.

The next morning's session entitled "**Polarised Secretion and trafficking"** started with a talk from Fernando Belmonte describing the Zebrafish intestinal tract as a new model for epithelial polarity. His group has identified the Occludin-related protein, PLLP, as a key regulator of apical endocytosis and he presented evidence to support a model in which PLLP facilitates the recycling of SNARE proteins from late endosomes to the apical recycling endosomes. He was followed by Frank Perez (Paris) who presented a series of impressive movies of different labelled cargoes moving from the Golgi to the plasma membrane after synchronous release. This revealed that distinct cargoes travel at very different speeds and in different shaped vesicles. This was followed by a short talk from Akiko Satoh who described an elegant screen for mutants that affect the polarised secretion of Rhodopsin in the *Drosophila* that identified Rab6 as necessary for transport from the Golgi to the recycling endosome and Myosin V for transport from the recycling endosome to the apical membrane. Significantly, Eye shut, which is secreted to the marginal zone on either side of the rhabdomere shares the first step but not the second, providing the first demonstration that multiple secretory pathways deliver cargoes to distinct apical regions. Other highlights in the session included evidence that apical cell extrusion upon activation of the Ras/MAPK pathway requires the proteolytic cleavage of Cadherin (Catherine Rabouille; Utrecht), a new model for the trafficking of large cargoes through the Golgi (Gregoire Lavieu; Yale) and results showing a role for GM130 in activating Cdc42 at the Golgi (Hesso Farhan;).

The afternoon session began with two talks on the polarisation of non-epithelial cells with Alfredo Cacares (Buenos Aires) discussing microtubule organisation by Golgi outposts in neurons and Gillian Griffiths describing the parallels between how cytotoxic T lymphocytes polarise towards their targets and cilia formation. Elena Taverna (Dresden) continued the theme of Golgi positioning, reporting differences in the behaviours of the centrosome and Golgi between apical and basal neural progenitor cells. Barry Thomson (London) then presented his model for epithelial polarity and

highlighted the partially-redundant role played by the cortical spectrin cytoskeleton in localising the apical determinant Crumbs and in regulating cell growth through the Hippo pathway. The remarkable way that pathogens hijack polarity systems was the focus of Roland Thenauer's short talk, which described how the LecB lectin of Pseudomonas triggers endocytosis when applied to the apical side of epithelial cells by activating Akt to produce PIP3, but triggers a complete loss of polarity when applied basally by inducing Integrin internalisation. The session ended with an excellent talk from Eurico Morais de Sá (Porto) on how Aurora A regulates the lateral polarity factor Lgl during mitosis and how this is important for normal cell division in epithelia.

The third session of the meeting addressed polarity in insect and mammalian epithelia. Keith Mostov (USCF, USA) presented a detailed model for how integrin adhesion induces the reversal of polarity in MDCK cysts and the role of classical protein kinase C in moving the apical protein Podocalyxin from one side of the cell to the other. Elisabeth Knust then described the multiple roles of Crumbs in the eye and the embryo and the function of the Moesin-binding domain in morphogenesis. Francois Schweisguth (Paris) next presented the interesting case of the *Drosophila* sensory organ precursors, where the planar cell polarity system directs the localisation of the apical polarity protein Bazooka (Par3) to orient an asymmetric cell division. This was followed by Enrique Rodriguez-Boulan who discussed the roles of AP-1A and AP-1B in secretion to the basolateral domain of epithelial cells, and their different sites of action at the trans Golgi and recycling endosome respectively. The short talks in this session discussed the role of Par-1 in controlling the unusual polarity of hepatocytes, which remodel their apical surfaces to form lateral caniculi (Sven van Ijzendoorn; Groningen, Netherlands) and the function of microtubules in delivering E-cadherin to the adherens junctions (Antoine Guichet, Paris).

The session on Monday afternoon covered the relationship between polarity and cell shape, and kicked off with an excellent talk from Yoshihisa Oda (Tokyo) on how microtubules are remodelled in plant xylem cells to trigger changes in the cell wall. This was followed by an entertaining presentation from Manuel Thery (Grenoble) in which he used micro-patterned substrates to determine how cell shape and contractility influence the positioning of the centrosome and Golgi with respect to the nucleus. Next, Stefano De Renzis (EMBL) reported his results on how the phosphoinositides, PIP2 and PIP3, control furrow invagination during cellularisation in *Drosophila* by regulating the contractility of the actomyosin network, with PIP2 promoting contractility and PIP3 inhibiting it through the cellularisation factor, Bottleneck. Daniel St Johnston (Cambridge) followed with an account of how a polarised microtubule network is established in the *Drosophila* oocyte to define the anterior-posterior axis of the embryo and the central role of the spectraplakin, Shot, in anchoring microtubules to the cortex. The session ended with short talks from Carine Rosse(Paris) on the role of aPKC in matrix metalloprotease secretion from invadosomes and Ceniz Zihni (London) on Dbl3, which localises apically in epithelial cells and activates Cdc42 to control the size of the apical domain.

The topic for Tuesdays session was cell polarity and cancer, and Cayetano Gonzales (Barcelona) started things off by describing the behaviour of the centrioles during the asymmetric divisions of the Drosophila neuroblasts, which can produce tumours if they divide symmetrically. The daughter centriole remains anchored apically during interphase and may provide the primary cue for the polarity during mitosis, whereas the mother centriole moves around the cell until just before mitosis.

This difference in their behaviour depends on the localisation of Centrobin specifically to the daughter centriole. Holly Lovegrove (Cambridge) then discussed whether mis-oriented mitotic spindles in epithelial cells could give rise to cells above or below the epithelium that contribute to the formation of cancers. Surprisingly, she found that spindle orientation was not important in most *Drosophila* epithelia because the misplaced cells rapidly reintegrate into the epithelium. Ian Macara (Vanderbilt, USA) discussed the role of the mouse PAR3 paralogue, PAR3L, in mammary gland development ,where it is required for stem cell survival and regeneration, probably through a role in repressing LKB1. Patrick Humbert (Melbourne, Australia) followed with an account of the role of the lateral polarity factor Scribble in tumorigenesis and its ability to synergise with activated Ras in promoting anchorage independent growth, a property it shares with a number of other polarity and spindle orientation factors. The final short talk in the session form Sandra Iden (Cologne) returned to the topic of Par3, this time in the skin, where its removal leads to premature ageing and a non-autonomous increase in melanocyte proliferation.

The last day of the meeting started with a session on endocytosis and polarity. Thomas Vaccari (Milan) described a new tumour suppressor that his group has characterised that contains two SNARE domains and appears to function to repress the release of exosomes from autophagosomes. Anne Spang (Basel) discussed the function of N-linked glycosylation in the polarisation of the *C. elegans* embryo and described the role of SAND, Vps33 and the CORVERT complex in controlling endosome maturation. She was followed by Alexander Ludwig (Singapore) who presented some beautiful biochemical and structural data on how Caveolin and Cavin induce the membrane invaginations of caveolae. Ulrich Tepass (Toronto) continued with the theme of the role of Crumbs with his presentation on genetic interactors of the *crumbs* and the role of Crumbs phosphorylation by aPKC in controlling its endocytosis. The session ended with two short talks on polarity factors in *C. elegans*. Thijs Koorman (Utrecht) presented the results of a large scale two hybrid screens that identified many new interactions, and Josanna Rodriguez (Cambridge) reported that inactive aPKC fails to become restricted to the anterior cortex of the zygote and instead shows a uniform cortical localisation that depends on Cdc42.

The last session of the meeting on polarised cell migration started with a presentation for Sandrine Etienne-Manneville (Paris) on the role of specific isoforms of Cdc42 and Scribble in astrocyte migration. Eric Sahai (London) then followed with a report of a computational model for the factors that determine whether cancer cells migrate by blebbing or with lamellipodia, and the identification of FAM40 as a key factor in the collective migration of *Drosophila* border cells and human cancer cells. The session ended with two short talks. Gregoire Michaux (Rennes) describes a screen in C. elegans for factors required for Cadherin secretion that identified many known factors, as well as the AP1-binding protein HEAT200, and Varun Chaudhary (Heidelberg) who presented evidence that Wingless (*Drosophila* Wnt) must be secreted apically to be able to signal to nearby cells.

The last talk of the meeting was given by Scott Emr (Cornell University, USA) who gave some inspiring advice to the younger scientists before presenting his latest results on how proteins in the plasma membrane are selected for endocytosis and how the ESCRTIII proteins assemble into helical

filaments to drive the invagination of endocytic vesicles into multivesicular bodies.

Forward Look

(1 page min.)

- *Assessment of the results*
- *Contribution to the future direction of the field – identification of issues in the 5-10 years timeframe*
- *Identification of emerging topics*

The ESF questionnaire sent to all participants will probably provide a more objective assessment of the success of the conference, but my view as organizer is that it went very well. Almost all of the invited speakers presented largely unpublished data, which gave participants a chance to see the directions of new research in this field. The submitted abstracts were of a high standard and the selected talks were uniformly excellent. The meeting also provided an excellent opportunity for PhD students to meet potential postdoctoral supervisors, and I am aware of a number of students who have now applied for positions with invited speakers from the conference.

Several themes emerged from the meeting, which are likely to become major topics for research over the next few years:

1) Although the prevailing view from review articles is that the same small set of polarity proteins acts in the same way to polarize many different types of cell, results presented at the meeting are beginning to challenge this view in two ways. Firstly, polarity factors are remodeled in some cell types to perform new functions or to drive changes in cell shape. Secondly, some cells appear to polarize independently of the canonical PAR proteins, indicating that there are other, as yet undiscovered mechanisms for generating cellular asymmetries.

2) There are generally considered to be two destinations for polarized secretion in epithelial cells: to either the apical or basolateral domain. Results presented at the meeting by Frank Perez and Akiko Satoh now challenge this view by revealing that there are multiple routes and at least two distinct sites for apical secretion. Unravelling the complexity of secretory pathways will be a major topic for future research.

3) The trafficking of specific exocytic or endocytic cargoes is rarely completely blocked in mutants that disrupt a specific sorting or transport pathway, and instead the cargoes are often routed into an alternative pathway. This complicates the analysis of mutant phenotypes, and it will be important in future to develop the tools to measure the flux through different pathways in a quantitative manner.

4) The fields of membrane trafficking and cell polarity may soon be revolutionized by the development of super-resolution microscopes that can image living cells in real time. For example, most exocytic and endocytic vesicles are of the order of 100nm in diameter, which is below the resolution of traditional light microscopes. If live super-resolution imaging makes it possible to track the movement and behavior of these vesicles, it will make a huge difference to our ability to analyse intracellular vesicular trafficking pathways. This is therefore likely to be major topic for future conferences.

- Is there a need for a foresight-type initiative?

Could be

Business Meeting Outcomes

- *Election of the Organising Committee of the next conference*
- *Identified Topics*
- *Next Steps*

Dr Fernando Martin-Belmonte (Universidad Autónoma de Madrid) and Dr Gillian Griffiths (Cambridge Institute for Medical Research) were unanimously elected as organisers of the next meeting and both have accepted. Since the ESF will probably not be supporting conferences in three years time, the most likely sponsor would be EMBO, but other possibilities will be considered.

Contributors to the discussion expressed enthusiasm for the continuation of the meeting as it has proved a very effective mechanism for bringing the cell polarity and membrane trafficking fields together, has promoted a number of new collaborations, and has facilitated the exchange of techniques and ideas between groups.

One suggestion was to include some talks on mathematical modelling of polarity systems in the next conference.

Atmosphere and Infrastructure

- *The reaction of the participants to the location and the organisation, including networking, and any other relevant comments*

The participants found the conference site difficult to reach, but were otherwise very happy with the location and organisation. One advantage of the remoteness of Pultusk is that almost everyone stayed for the complete conference and spent any free time talking to the other participants. This fostered a very open and interactive atmosphere, and a number of people commented on the extensive and friendly discussions after each talk.

The staff were all extremely helpful and accommodating and the food was good, if a bit heavy. There were only two complaints about the facilities. The first concerned the quality of the projector, which was weak and had a poor colour balance. The second was about the slow internet access and patchy WiFi signal. As the meeting organiser, I was pleased that the WiFi in the conference hall was poor, as this prevented people from reading their email etc. during the talks, but it would have been nice to have had afaster connection in the bedrooms.

Sensitive and Confidential Information

This report will be submitted to the relevant ESF Scientific Review Group for review.

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Date & Author: Dr. Daniel Johnston	