IMPROVING THE TRANSLATION OF DISEASE BIOLOGY THROUGH PHENOMICS

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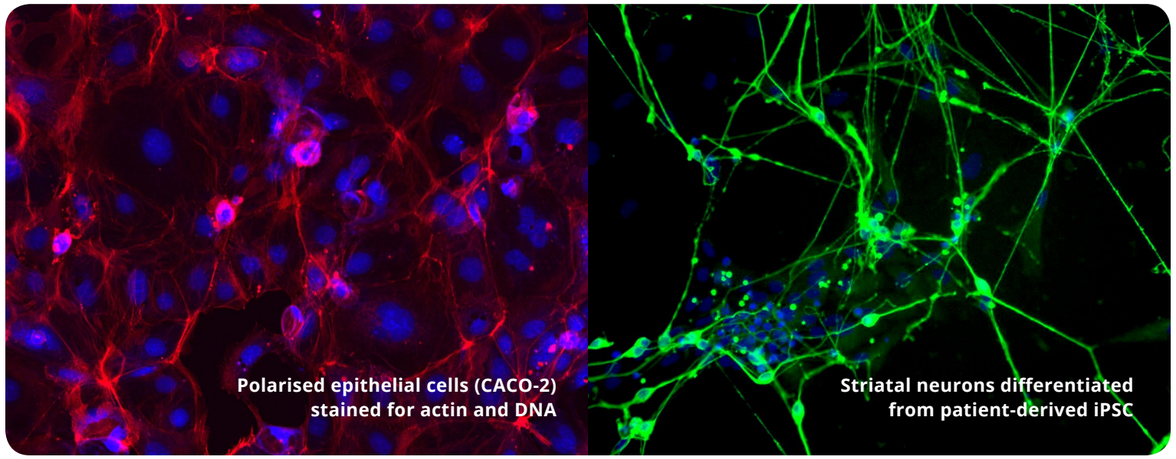
Paul holds an Honours Degree in Biochemistry and a Ph.D. in Molecular Biology from the University of Sheffield, UK and has over 25 years post-doctoral research experience encompassing biochemistry, molecular genetics, cell biology, quantitative imaging and since 2007 phenotypic drug discovery using stem cells. Paul has been working closely with the Scottish Universities Life Science Alliance and University of Oxford since 2013 to create the National Phenotypic Screening Centre, where he is now Director of Operations.

The National Phenotypic Screening Centre (NPSC) launched in 2015 after £10M of Scottish Government investment – with labs in three UK Universities renowned for their life sciences research: Dundee, Edinburgh and Oxford. NPSC's overall aim is to redress the balance in drug discovery by moving away from target-centric approaches, developing highly predictive assays and advance phenomics technologies. The driver for this is the persistent inefficiency in the drug discovery process: on average 90% of drugs fail to reach market due to failures in phase II/III clinical trials. A major contributing factor in this failure is that the traditional target-centric preclinical part of the pipeline is largely patient free, and relies on animal models of disease and toxicology, which often correlate poorly with human outcomes. The re-emergence of the phenotypic approach in drug discovery has been driven by these acknowledged shortcomings, coupled with the realisation that phenotypic approaches have historically been more successful in finding first-in-class medicines, and that before recombinant DNA technology led to target-based drug discovery domination in the 1980s, it was the way most drugs were identified. Despite great leaps in our understanding of fundamental processes in biology, we still struggle when it comes establishing the causative relationships and systems dynamics in more complex human diseases. A reductionist approach to pinpoint targets often fails to deliver when tested in the context of tissues, organs and living breathing humans. The renewed interest in more empirical strategies is partly due of the explosion in the availability of new biological tools including single cell -omics, stem cells and precision genome editing, alongside new imaging technologies and computation including machine learning and AI. The time has come for high throughput phenotypic biology to take centre stage in the hunt for new drugs.

There is a deep well of academic biology in the research community that remains somewhat untapped, for want of translational direction. We founded an industrial consortium framework called the Phenomics Discovery Initiative (PDi) that has successfully begun to address this problem by sourcing the best biology from academia and de-risking the development of more complex phenotypic assays for the industrial partner.



Polarised epithelial cells (CACO-2) stained for actin and DNA

Striatal neurons differentiated from patient-derived iPSC

The founding industrial partner is Janssen who have being working closely with NPSC staff on a wide range of assays from a highly complex air-liquid interface model of the human bronchus, to cancer stemness and immuno-oncology. PDi leverages NPSC's world class facilities, industry-standard operation and extensive global networks to either crowdsource or seek-out world-leading labs, working together to develop the best predictive biology platforms.

Developing the most patho/physiologically-relevant assay possible is often non-trivial – sometimes it may be sufficient to have a cell model growing as a homogenous monolayer but in other circumstances 3D spheroids or multicellular co-culture models, or organoids are more appropriate (though very challenging with throughput); some assays involve cancer cells, some primary cells and others iPSC/stem cell-derived with extended differentiation times, and increasingly we find assays that have used CRISPR/Cas9 engineering. At NPSC around half of our assays are image-based and "high content" whilst the other half uses flow cytometry. High content analysis (HCS) is especially powerful because it unlocks a rich source of quantitative information about single cells, groups of cells and tissues that describes their properties and responses to intrinsic cues and extrinsic perturbations. When HCS is applied to good biological assays, this so-called phenomics approach represents a powerful and highly informative first step in the drug discovery process, that should deliver more information, earlier, for medchem and safety-oriented decision-making. Phenomics is also valuable because it can extract multiscale and multiplexed data (eg probing heterogeneous cell-level behaviour and subcellular processes, or even single molecules, simultaneously) and can quantitatively measure endpoints or live events on timescales ranging from milliseconds to several days. A phenotype can be molecular or pathway-centric – examining the changes in specific proteins – or more holistically probing a multitude of readouts of cell physiology. Both approaches have value. Historically, the majority of phenotypic screens were carried out using one or two parameters, which is not as informative and risks bias towards a narrow hypothesis at the expense of understanding the wider effects that a compound has on cell behaviour. In contrast, a much more powerful approach is to extract hundreds or thousands of parameters from each experimental condition and build a phenotypic fingerprint or "phenoprint" that describes the complex responses cells have when exposed to different perturbing agents. The significance of many of these parameters may not be comprehensible to the screening scientist, but nonetheless act as signatures of underlying alterations in biology. By assembling data on the way drugs or chemical tool compounds of known target specificity perturb phenoprints, we can use machine or deep learning approaches to infer the mode of action of hits from chemical library screens. Indeed, a remarkable recent study (Semm et al, 2018), demonstrated machine learning can predict the activities of compounds in hundreds of biochemical assays from a single image-based screen. The future of phenotypic drug discovery promises to be an exciting one.

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