An interview with Aamir Ahmed, Head of Stem Cell and Prostate Cancer Group, Kings College London

Aamir Ahmed obtained his PhD from the **University of Dundee** where he also served as an Honorary Lecturer and Group Leader. He then joined **Yale University** as research faculty to work on ion channels.

He was awarded a Wellcome Trust Fellowship at the Department of Physiology, **University College London**, where he established his research group. This was followed by his appointment as the Head of Stem Cell Group at the **Prostate Cancer Research Centre**, also at the **University College London**. He joined the Centre for Stem Cells and Regenerative Medicine, **King's College London** in January 2015.

Aamir will be presenting an interactive post-conference workshop at SMi's 8th annual Advances in Cell Based Assays conference, taking place on 10th - 11th November 2015 in Central London.

The workshop entitled: **Latest Generation Microscopes in HTS/HCS/HCA for live cell imaging in Cells and Tissue Based Assays**, will focus upon cutting edge science and technology in cell and tissue based assays utilizing high-throughput screening (HTS), high-content screening (HCS) methods and high-content analytical (HCA) tools. We caught up with him to discuss his presen tation.

SMi: You're leading an exciting workshop featuring some cutting edge technology from Nikon? Can you enlighten us a little more about these latest generation microscopes and what new scope they're bringing in your research?

Nikon's NIS-Elements software supports total operation of high-throughput screening by integrated control of Nikon's Eclipse Ti-E motorized inverted microscope and peripheral devices such as well plate loaders and CCD cameras, to image data management. Nikon's newly developed software interface is specifically designed for imaging multiple points within a well and across a well plate, and works with dedicated automated analysis modules.

Using the JOB drag and drop approach for experiment creation it is possible to construct unique experiments per well. Image processing and analysis functions can be incorporated into the experiment design allowing the user to review data from the experiment and to make conditional imaging decisions based on 'IF THEN ELSE' logic during the experiment.

For example: IF the total number of cells identified >= 1000 THEN stop; IF a dividing cell is identified THEN zoom in and image at 40X; FIND tissue sections on a slide; THEN create an aligned tiled image at 40X

Conditional imaging is a powerful tool for reducing selection bias, increasing statistical robustness and allowing unsupervised searching and location

SMi: What special factors need to be considered in building assays that enhance the predictive quality of in vitro/ in-vivo assays? What challenges have you faced along the way?

Three R's: Robustness, reliability and reproducibility – and an unbiased, quantitative approach

SMi: In terms of off-target and on-target screening, how challenging is it in getting on-target screening results?

Pleiotropic effects are inevitable in biological systems. A validated example for preclinical screening for adverse drug effect is that of the hERG channel; other examples, if any, are few and far between. Validation of a reagent (ligand compound or an antibody) for purity is a major issue. If a reliable, validated assay reagent is available then on- and off-target outcomes could be dissected, putatively. One general problem arises from incorrect assumptions or limited knowledge that a certain molecule 'only' acts via a specific pathway or a system. The challenge sometimes is intellectual nature rather than experimental. Two major issues, in my view, are (i) in vitro assays do not reproduce the organism and (ii) in silico protocols to predict off-targets and side effects have not been, robustly, tested in clinical studies, yet and therefore not standard practice for preclinical drug development.

SMi: What combinatory approaches have been most useful in identifying novel drug targets? What can be learnt from these?

Small molecule library generation has been a staple. A long view of combinatorial drug treatments that require combinatorial drug designs suggests that it is an embryonic concept in the modern context of treating human diseases. A historical issue in this regard has been the phenotypic rather than a molecular (or even quantitative) description of the disease against which a drug needs to be designed, particularly for complex diseases such as cardiovascular and neuronal disorders or cancer. This has only been changing, rather rapidly, over the last 3 decades but we are not quite at the level of precise (or even moderately good) molecular description for many diseases. Even for a molecular description it is only very recently that we have moved from the idea of one gene, one target paradigm. Genomics, transcriptomics and proteomics (and other omics) have accelerated this process but it will be a little while before integration of these data identify novel drug targets. In my view the future is much brighter than the hyperbole that is often on display– but it will take a little time to utilize these high dimensional data capture technologies and integrate these to identify overall patterns and then drill down onto individualized treatments and targets.

SMi: What new insight does this provide about non-specific mechanisms causing collateral effects that seemingly produce action at the target site?

This is somewhat a matter of semantics that arises from the very limited knowledge we have of biological systems and how these interact; it is the interactions and consequences that produce these 'collateral effects'. To borrow a phrase, there are many unknown, unknowns in medicinal biology; fortunately these are being revealed at a much faster rate than ever before but a lot needs to be learned at the interactome level. One insight is that we observe, without bias, and keep making incremental steps towards a more comprehensive understanding how elements interact within our cells and what could be targeted, when and how. This does involve learning more and more through high-throughput analytical systems to reveal networks, pathways, localizations and interactions of many different elements that are involved in not only keeping the regular rhythm of normality but also in pathology.

SMi: What new developments do you envision for 2016? How can this be actioned sooner rather than later?

There are tremendous improvements that are likely to occur in computational power to analyse the myriad of gene and protein interactions and how these relate to physiology of organisms, and the cells that are a fundamental constituents of these. There are some exciting developments that could be expected in the imaging technologies particularly. A flavour of these will be discussed at the workshop. Awareness, training and an impetus to have these available can be instrumental in making these actioned sooner.

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8th annual Advances in Cell Based Assays conference
10th - 11th November 2015 | London, United Kingdom
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