Latest Happenings

Ashok Venkitaraman is a scientific trailblazer

An interview with the DITL director, Ashok Venkitaraman by Jill Arul from Asian Scientist – an award-winning science and technology magazine that highlights R&D news stories. Please click on the link below for Prof Ashok's insightful comments and vision for scientific advances within DITL and Singapore.

Asia's Scientific Trailblazers: Ashok Venkitaraman - Asian Scientist Magazine

2021 A*STAR Career Development Fund (CDF) recipients

Congratulations to Yuri Frosi and David Koschut, who were awarded 2021 A*STAR Career Development Fund (CDF) in the latest competition, in which 64 awardees were chosen from over 300 eligible applicants. With this honour, Yuri and David join Teresa Ho who is an A*STAR Scholar as well as a current Career Development Award (CDA) and Young Individual Research Grant (YIRG) recipient within DITL.

A Novel Discovery Platform to Identify First-in-Class Druggable Targets for Human Diseases

The pathways that control the behaviour of diseased cells involve complex interactions between large molecules like proteins. Protein-protein interactions (PPIs) represent a vast repertoire of potential targets for new drugs against human diseases. But not all PPIs are suitable as drug targets, and many hundreds of thousands of PPIs occur in human cells. As such, identifying the right PPI target for the development of next-generation drugs is oftentimes akin to looking for a needle in a haystack. Finding better, more efficient ways to discover druggable PPI targets is therefore critical to expand the number of first-in-class drugs for human diseases.

Ashok Venkitaraman's laboratory has developed a novel approach to PPI target discovery, termed Protein-interference or Protein-i, whereby a library of biologically derived, short, stable peptides is used to hunt for ligands that can disrupt therapeutically important and potentially druggable PPIs. Their study, published in the journal Cell Chemical Biology, illustrates a complete blueprint for Protein-i based drug discovery – from the use of genetic screens to identify potential PPI targets, to their biological validation and structural characterization, and to the subsequent development of small-molecule leads against the PPI target. Using this methodology, the team has identified drug-like small molecules that reactivate via nuclear relocalization the tumour suppressor protein FOXO3a, which is more frequently inactivated by post-translational modification rather than mutation, thereby offering the potential development of additional therapeutic tools targeting this important pathway. More generally, this work opens up a new approach for targeting the estimated 300,000 binary PPIs involving human proteins using an efficient genetic screening technology.

Prof. Venkitaraman, lead author of this study said,

"I am excited to report the development of Protein-i as a new approach for the discovery of druggable PPI targets for human diseases. Protein-i enables the rapid identification of potential sites for the development of first-in-class drugs that target PPIs, including peptides, macrocyclics or small-molecules. I am delighted that the Protein-i approach has been successfully spun-out into industry through the founding of PhoreMost, a start-up biotech based in Cambridge, where it is fuelling new drug discovery by several pharma partners."

A Novel Discovery Platform to Identify First-in-Class Druggable Targets for Human Diseases – Cancer Science Institute of Singapore (CSI)

Reversing Cancer-Causing Faults in the Breast Cancer Gene BRCA2.

Inherited faults ('mutations') in the breast cancer gene, BRCA2, can lead to cancers of the breast, ovary or other organs. BRCA2 codes for a protein containing 3,418 building blocks (called 'amino acids') in human cells. Surprisingly, certain BRCA2 mutations that cause cancer affect just a single building-block out of over three thousand.

Ashok Venkitaraman's laboratory has discovered how such a subtle change in BRCA2 might cause cancer, and also how this effect might be reversed. Instead of traveling to the cell nucleus, where they normally repair damage to our DNA and safeguard the information encoded in our genome, these mutations make BRCA2 proteins accumulate in the cytoplasm. Interestingly, these effects can be reversed by another protein, called DSS1, which acts as a chaperone for mutant BRCA2 and helps it to reach the cell nucleus and work correctly again. These findings hold out the future hope of designing drugs that mimic the chaperone protein, to prevent or delay cancer in patients who inherit certain faults in BRCA2.

The team's findings were published in the journal *Nucleic Acids Research* on 12 May 2021.

Prof. Venkitaraman said,

"It is very rewarding to have discovered how certain types of mutations affecting the BRCA2 breast cancer gene may cause cancer, and more importantly, to see how we might use this new information to develop drugs that prevent or delay cancer in families who are unfortunate enough to inherit faulty BRCA2. I am very grateful to the Gray Foundation in New York for having supported our research."

Reversing Cancer-Causing Faults in the Breast Cancer Gene BRCA2. – Cancer Science Institute of Singapore (CSI)

Novel First-in-Class Drug Discovery Approach is Breaking New Ground in Anti-Cancer Therapeutics

ATP-hydrolyzing enzymes like protein kinases are major drug targets for oncology. Drugs that inhibit these enzymes typically engage their ATP-binding (active) sites to inhibit catalysis. However, these active sites are structurally similar to one another, especially in enzymes belonging to the same family, making it difficult to develop drugs that are highly selective with reduced off-target effects.

Ashok Venkitaraman's laboratory has systematically developed a different approach to this problem – termed 'allo-targeting'. 'Allo-targeting' seeks to create first-in-class drugs that target enzymes outwith their active domains, by modulating regulatory protein interactions or allosteric (regulatory) sites that are unique to that particular enzyme. Over the years, their work has successfully exemplified 'allo-targeting' to create novel inhibitors against important anti-cancer targets like the polo-like kinases (PLKs) (Narvaez et al., Cell Chem Biol (2017)) and the BRCA1 E3 ligase (Periasamy et al., Cell Chem Biol (2018)). Their PLK1 inhibitor has been licensed to industry, and is expected to reach human clinical trials in 2022.

Dr. Venkitaraman' s lab, in collaboration with their colleagues from multi-disciplinary fields at the University of Cambridge, now reports novel inhibitors of the ATP-hydrolyzing DNA repair enzyme, RAD51, that target the regulatory protein-protein interaction between BRCA2 and RAD51 (Scott et al., Cell Chem Biol (2021)), disrupting DNA repair in cells and thereby potentiating DNA-damage-induced cell death. They used a structure-guided approach based on their original structural analysis of the BRCA2-RAD51 complex (Pellegrini et al., Nature (2002)) to create the novel RAD51 inhibitor. This new compound termed CAM833 promises to be of great value not only in dissecting the mechanisms by which DNA repair pathways contribute to genome instability in cancer, but also to seed the future development of anti-cancer drugs that target these pathways.

Dr. Venkitaraman, one of the corresponding authors of this study said,

"My colleagues and I are excited to report our latest progress in creating next-generation inhibitors of enzymes involved in human diseases like cancer via a new approach of targeting the protein-protein interactions that regulate enzyme activity. We believe that this approach, termed 'allo-targeting', could lead to new drugs that are more selective and safer than current drugs that bind to the active sites of enzymes."

Novel First-in-Class Drug Discovery Approach is Breaking New Ground in Anti-Cancer Therapeutics – Cancer Science Institute of Singapore (CSI)

USD 45M Series B Funding for UK-Based Biopharmaceutical Company's Drug Discovery Programmes

The pathways that control the behaviour of cells are complex, non-linear and highly redundant. As such, identifying the right molecular target for the development of next-generation drugs is oftentimes akin to looking for a needle in a haystack.

Ashok Venkitaraman's laboratory developed a novel approach termed "Protein-interference" or "Protein-i" to hunt for new drug targets, which was spun out in 2016 by University of Cambridge into the biotech company PhoreMost, with Dr. Venkitaraman as co-founder. Since then, the value of Protein-i has been rapidly demonstrated through serial deals between PhoreMost and major pharmaceutical partners including Boehringer-Ingelheim, Otsuka, Novartis and Plexxicon.

In March 2021, PhoreMost crossed another major milestone through a Series B fund-raise of >USD$45M with a group of international investors. This funding will empower PhoreMost to advance its pipeline of novel therapies for cancer – including the PLK inhibitor program first begun in Dr. Venkitaraman's academic lab – and diseases of ageing, as well as to develop novel drugs that enable targeted protein degradation, termed 'Protacs'.

Dr. Venkitaraman added,

"It has been very exciting to co-found PhoreMost and be involved in its rapid growth with the successful application of the 'Protein-i' technology in multiple partnerships with major pharma. I am delighted that our original academic research has fuelled commercial developments in this way, and hope that the new drugs developed by PhoreMost and its partners will help to alleviate the burden of human diseases like cancer."

USD 45M Series B Funding for UK-Based Biopharmaceutical Company's Drug Discovery Programmes – Cancer Science Institute of Singapore (CSI)