CLOVES SYNDROME COMMUNITY

RESEARCH ROUNDTABLE PRESENTATION SIMPLIFIED

DATE: 27 January 2022

1st Presenter: Dr. Ralitsa R. Madsen (UCL Cancer Institute, London, UK)

Dr. Ralitsa R. Madsen is an independent research fellow, physically based at UCL Cancer Institute in Prof Bart Vanhaesebroeck's group, with Prof Alex Toker (Beth Israel Deaconess Medical Centre / Harvard Medical School) as her secondary research sponsor. Previously, Dr Madsen obtained her PhD at the University of Cambridge, UK, under the supervision of Prof Robert Semple. Her work focuses on fundamental principles of information transmission within the so-called PI3K signaling pathway, which is the prime target of the *PIK3CA* mutations found in PROS (including CLOVES) and cancer. Through a better understanding of how cellular information transmission is corrupted by *PIK3CA* mutations, she hopes to contribute to the design of more effective, future therapeutic strategies for diseases of activating *PIK3CA* mutations.

Research Simplified Summary:

Dr. Madsen presented her recent progress on a complex gene engineering project that will ultimately allow her to establish human cells with and without a PIK3CA mutation. The key to her new system is the ability to distinguish normal from mutant cells by simultaneously tagging them with proteins of different colors. This option enables advanced, so-called single-cell studies that shed light on how exactly PIK3CA-mutant cells may crosstalk and reprogram their normal counterparts. Understanding this phenomenon is important in PROS given the mosaic nature of the diseases, with PIK3CA-mutant and normal cells living side-by-side in the affected tissue(s). The new system that Dr. Madsen is setting up also allows a researcher to control the dose of the PIK3CA mutation, which is relevant for understanding the basic principles of information transmission within the PI3K signaling pathway, which underpins the ability of our cells to distinguish important signals in the body from each other.

2nd Presenter: Dr. Emily C. Erickson (Beth Israel Deaconess Medical Centre / Harvard Medical School, Boston, U.S.)

Dr. Emily C. Erickson recently completed her PhD with Prof Alex Toker (Beth Israel Deaconess Medical Centre / Harvard Medical School). Before her PhD, Dr. Erickson obtained her MPhil at Cambridge University under the direction of Prof Christine Watson and completed her BS at Purdue University. Her work has focused on targeting AKT using small molecule degraders (or PROTACs) and using these tools to better understand the role of AKT in PI3K pathway signaling with the ultimate goal of improving therapeutic strategies for diseases with hyperactive PI3K

signaling. Dr. Erickson is now working at Blueprint Medicines in Cambridge, Massachusetts, where she continues to focus on therapeutic targeting of protein kinases.

Research Simplified Summary:

Dr. Erickson presented work on a novel drug that targets and inactivates a critical component, known as AKT, in the PI3K signaling pathway. Like PIK3CA, mutations in AKT cause a developmental overgrowth disorder known as Proteus Syndrome. AKT-targeting agents have also been evaluated in PROS. The new drug, developed in Prof Toker's laboratory in collaboration with Prof Nathaniel Gray at Stanford University, works by removing AKT from the cell and is known as an "AKT degrader". Dr. Erickson has performed extensive characterization of its actions, mainly in breast cancer cells for now, and together with computational analyses performed by Dr. Madsen, their work has demonstrated that the AKT degrader outperforms some of the best-in-class conventional AKT-targeting drugs currently available. This work has also identified biomarkers that predict which breast cancer cells may be most sensitive to AKT degradation. Moving forward, one could envisage similar studies of AKT degradation in PROS-relevant cell models, to determine whether this drug and its mechanism of action may have therapeutic potential in this context.