NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

VIRTUAL BIOLOGY COLLOQUIUM

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Hosted by A/P Liou Yih-Cherng

Translating erythroid terminal development to cell therapy with tens of million dollars venture investments

By **Shi Jiahai**

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About the Speaker

Dr. Shi has 20 years' experience in the development of bio-therapeutics . He participated in vaccine development against hepatitis E virus (HEV), causing a type of viral hepatitis. The vaccine was commercialized under the trade name 益可宁Hecolin in 2012. During his PhD studies under Dr. Song Jianxing, Dr. Shi developed novel strategies for drug development against Severe Acute Respiratory Syndrome (SARS) coronavirus (SARS-CoV), by targeting its main protease (SARS-CoV Mpro). He demonstrated that the dimerization interface at the extra helical domain of SARS-CoV Mpro is an attractive drug targeting pocket. As this pocket is far from the active site of Mpro, drugs targeting this pocket will have minimum off-target effects to other human proteases. Given the similarity between SARS-CoV Mpro and COVID-19-CoV Mpro, such an approach might also be attractive for COVID-19.

When he was at the Lodish lab, Dr. Shi co-invented a new technology for engineering red blood cells as carriers for a wide range of therapeutic cargoes, particularly for therapeutic proteins. This invention led to the establishment of Rubius Therapeutics, which went public in 2018 and reached a market capitalization of almost 2 billion USD.

After setting up his own lab, Dr. Shi is focused on the development of novel therapeutics, including cell and gene therapy, genome editing and antibody therapy. Working with his collaborators, Dr. Shi engineers red blood cell extracellular vesicles (RBCEV) as a non-viral gene delivery vehicle and invents a second-generation engineered RBC therapy. Again, these innovations have led to the establishment of two spin-offs. The first biotech company, now based in Cambridge, Massachusetts, is Carmine Therapeutics, co-founded with Harvey Lodish, Minh Le and EVX Venture. And the second biotech company is Carcell Biopharma, now based in Shanghai and Singapore, co-founded with EVX Venture.

Red blood cells (RBCs) are the most abundant cell in our body, accounting for more than 80% of cells. RBCs are differentiated from hematopoietic stem and progenitor cells (HSPCs), followed by erythroid specific lineages, including colony forming unit erythroid (CFU-E). And all RBCs enucleate eventually. We build the first-generation engineered RBC (eRBC) therapy derived from HSPCs for protein and single domain antibody delivery, leading to the establishment of a Nasdaq listed company Rubius Therapeutics. Rubius utilizes eRBC to treat cancers and autoimmune diseases. However, the first-generation eRBC therapy demands huge costs with a difficult manufacturing process. Thus, we develop a second-generation eRBC therapy using mature RBCs with cost reduction and easier manufacturing, but with less therapeutic areas. And we build a shark single domain antibody discovery platform from a small and economical shark locally for eRBC surface antibody discovery. To further improve eRBC therapy by creating an erythroid progenitor cell line that enucleates lastly, we study the regulatory mechanism of genes, WD Repeat Domain 26 (Wdr6) and Spleen Tyrosine Kinase (Syk), in erythroid terminal development including erythroid enucleation. We demonstrate that, as part of the glucose-induced degradation-deficient (Gid) ubiquitin ligase complex, Wdr6 regulates the ubiquitination and degradation of nuclear proteins in differentiating erythroblasts. Deficiency of Wdr26 blocks nuclear condensation and enucleation. Moreover, we demonstrate that Syk plays an essential role in terminal erythropoiesis. Loss of Syk leads to severe anemia in mouse embryos, and chronic anemia in adult mice with extramedullary erythropoiesis in the enlarged spleen. Syk deficiency disturbs defective erythropoiesis in fetal livers and adult erythropoiesis in bone marrow in vivo and impairs terminal development of erythroid progenitors ex vivo. Taken together, our study reveals the essential role of SYK during terminal erythropoiesis. Our study advances the knowledge of regulation mechanism governing erythroid terminal development and enucleation, and incubates new generation engineered RBC platform technology for innovative therapies against cancers and other unmet clinical needs. Our pioneering work integrates basic cell research and venture building as a new model of biotech entrepreneur and benefits regional and global economy.

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