KXTbio's founder wins GSK award

UNC researchers win drug-discovery awards from pharmaceutical giant GSK

Nov. 2013 – GlaxoSmithKline drug-discovery competition winners aim to find a new cancer therapy and a novel way to regulate male fertility, projects spearheaded by scientists at the UNC School of Medicine.

CHAPEL HILL, N.C. – Reproductive biologist Deborah O'Brien, PhD, and biochemist John Sondek, PhD, have uncovered potential targets for therapies that could have major implications for men's health and cancer treatment. Now, thanks to the GlaxoSmithKline Discovery Fast Track competition, they will work separately with GSK scientists to quickly screen millions of compounds to see if any show promise for regulating male fertility or for cancer treatment.

O'Brien and Sondek, both members of Lineberger Comprehensive Cancer Center, were two of eight GSK awardees out of 142 candidates in the United States and Canada. Without the award or collaboration with a drug company in general, the researchers would have access to just a small fraction of the millions of compounds that could be screened to identify leads for drug development.

O'Brien, a professor in the Department of Cell Biology and Physiology in the UNC School of Medicine, studies the regulation of sperm production and function. Her lab found that a sperm-specific enzyme called GAPDHS is essential for the production of ATP – the energy of the cell that allows sperm to move. But other cells throughout the body have a similar, but not identical, enzyme called GAPDH. The trick for O'Brien is to find a compound that selectively modulates the GAPDHS pathway so that only the metabolism of sperm is inhibited or activated. Otherwise, many cells throughout the body could be affected.

Through collaborations with BRITE's drug discovery center at NC Central University and the UNC Center for Integrative Chemical Biology and Drug Discovery in the UNC School of Pharmacy, O'Brien screened about 90,000 compounds. She identified compounds that inhibit GAPDHS activity and sperm motility but do not have sufficient strength or selectivity for drug development.

"Finding a compound that can become a drug requires a partnership with a pharmaceutical company," O'Brien said. A typical high-throughput screen at GSK involves about 1.8 million compounds. "But they have new technology that we will use," O'Brien said, "and that will allow screening of several billion compounds." GSK's screen will allow O'Brien to see results by the middle of 2014.

To earn his GSK fast track award, John Sondek, a professor in the Department of Pharmacology in the UNC School of Medicine, created an assay to find compounds that inhibit a protein called Rac1, which is the third most-frequently mutated active protein in melanoma, a kind of skin cancer. Of the two other commonly activated proteins, one of them – Ras – has failed as a drug target.

"But Rac1 mutations are fundamentally different and involve totally different mechanistic aspects of the protein's regulation," Sondek said. "What's interesting is that several different Ras-driven cancers *need* Rac1. So if we knock down the expression of Rac1, then we could interfere with tumor growth."

His assay could help GSK find compounds to treat lung, prostate, breast, and skin cancers.

Prior to winning a Drug Discovery Fast Track award, Sondek also worked with BRITE to screen about 80,000 compounds. "We got hits," he said. "Getting hits isn't the problem. The problem is figuring out if the hits – the compounds that seem to inhibit Rac1 – are any good. But the hits from this compound library weren't good enough." For instance, the BRITE screen found compounds that altered Rac1 but didn't stop it in its tracks, which is a prerequisite for a drug company to spend time and resources creating a drug for clinical trials.

"Without the GSK award, that would've been the end of the line for our screen of Rac1," Sondek said. "Now we'll be able to screen 1.7 million compounds at one time."

He should find out what the GSK screen reveals by the middle of 2014.

GSK's inaugural Discovery Fast Track competition, designed to translate academic research into starting points for new potential medicines, attracted 142 entries across 17 therapeutic areas from 70 universities, academic research institutions, clinics, and hospitals in the United States and Canada.

The selected scientists will collaborate with GSK's Discovery Partnerships with Academia (DPAc) team. The winning investigators could be offered a DPAc partnership to further refine molecules and assess their potential as new medicines. Since its inception in 2010, Glaxo's DPAc team has initiated nine collaborations with academic researchers in Great Britain, France, the U.S., and Canada.