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GPCR Consortium lands Novo Nordisk, Merck

By Shannon Ellis, Staff Writer

SHANGHAI – The five month old GPCR Consortium – which brings together industry and academics to explore the G protein-coupled receptors (GPCRs) family of proteins – has added two new pharmaceutical members to its fold. It now counts Novo Nordisk AS and Merck & Co. Inc. as members in addition to founding members Amgen Inc., Ono Pharmaceutical Co. Ltd. and Sanofi SA. The partners provide not just funding to the research consortium's efforts. They help ensure the basic research being conducted in the academic sites is directed to pharmaceutically relevant targets for cancer, diabetes and mental disorders.

GPCRs are complex. It wasn't until 2007 that the first high-resolution structure of a human GPCR was published. This achievement took Raymond Stevens and his team more than 19 years to accomplish. Today, there are 26 known structures, but with 826 proteins in the GPCR family, there is still a long way to go.

The goal of the consortium is to have experimental and computational models for all 826 of the GPCR in the next five years. There is also the task of determining structures for 200 of the 826 known human GPCRs, to assist in structure-based drug discovery.

Stevens, founder of the GPCR Consortium, is considered a pioneer for his work in high-throughput X-ray crystallography and recognizes better than anyone the task of getting to 826 will take substantial input from many players. The group's goal is to add three more company members.

Given GPCR's importance to drug discovery, the incentive for industry is there. Approximately 40 percent of modern drug targets are focused on GPCRs. As the signaling pathways between the cells and the environment, GPCRs account for 80 percent of all signal transduction across human cell membranes.

Understanding this signaling system on a molecular level will help pharmaceutical companies design their own molecules, tricking the system by sending signals recognized by specific GPCRs that can direct the molecular conversation to fight disease.

To come to the first structure took no less than 15 technological breakthroughs, the good news is with those now in hand, coming up with the remainder promises to be accelerated, a lower risk proposition to the companies now investing.

While pharmaceutical companies will clearly benefit from better basic research and understanding of GPCRs, a sustained two-way dialogue is also important for the researchers who need information from the drug companies.

"One of the key reasons the GPCR Consortium came together was in talking to the pharmaceutical companies about what receptor structures they would like to see and where they think the most fundamental research breakthroughs are needed in human cell signaling and drug discovery. At the same time, we communicated that we really need access to their compounds that bind different receptors," explained Stevens.

"The academic groups in the GPCR Consortium are working on the receptor protein, but what they need is access to receptor-specific compounds to stabilize the receptors in different states," he added. "By having the pharma companies provide compounds that they have a wealth of, and the academic groups working on the receptors, this is a one-plus-one-equals-four situation in regards to scientific breakthroughs and benefits."

The compounds, said Stevens, are crucial and most underestimate their role in understanding GPCR structure and function.

Beyond those original 15 breakthroughs, "the one area we do not have control over right now is understanding the relationship between a ligand stabilizing the receptor, that then allows us to form good quality crystals. This is a scientific question that technology per se cannot easily give us an answer to; it is trained chemical knowledge and insight that we need. We continue to try a lot of different compounds that bind to a specific receptor and figure out which one will lead us to getting structure and we are slowly getting better and better at knowing which combination works," explained Stevens.

PRECOMPETITIVE SPACE

A key to getting so many companies to come to the table is the notion of working in a pre-competitive space, lowering the barriers that typically stop pharma companies from working together.

"When you get to the competitive space of compounds, drug molecules being designed . . . that is being done outside of

consortia," said Stevens. "No IP is meant to be generated from the consortium."

The consortium is following a path first trod by the Structural Genomics Consortium (SGC) managed by the University of Toronto and Oxford University. The decade-long track record of the SGC has proven what is possible for academia and industry when working together, and Stevens credits SGC's success for making it easy to attract industry partners today.

A key to the consortium concept is the research findings will be made publicly available. In the case of the GPCR Consortium, the structural information generated will be made publicly available on the U.S. National Institutes of Health-funded Protein Data Bank, which is responsible for disseminating all crystallographic data throughout the world.

PACIFIC RIM CONNECTION

A sign of the times, much of the research and the partners involved in the GPCR Consortium are based in Shanghai.

"I think the China opportunity is really important to the story," said Stevens.

With the decline of funding for science research in the U.S. being almost matched by the increase of funding in China, Stevens is clearly riding an important wave. (See *BioWorld Asia,* Jan. 21, 2015.)

But his interest in China was kindled, first and foremost, by working with the Chinese scientists that he trained in his lab.

Three of them have gone to work for leading research institutes in Shanghai that are the major research sites for the consortium: Beili Wu and Zhao Qiang now at the Shanghai Institute Materia Medica (SIMM) run by the Chinese Academy of Sciences and Fei Xu of the Ihuman Institute, a part of the newly minted Shanghaitech University. Stevens is also a leading faculty member there.

Originally at the Scripps Research Institute for many years, on the U.S.-side Stevens is now also a provost professor at University of Southern California (USC), the third research site for the consortium, and credits the move in part because of the school's strategic decision to partner with Shanghai.

"USC sees it very clearly," said Stevens, "China is going to become a major contributor to global scientific data. One needs to find ways to collaborate – through the internet you can collaborate very easily – versus being your own small silo and keeping data to yourself. We really encourage and are excited about collaborations across the Pacific."

For industry partners as well, the China angle was a determining factor in joining the consortium.

"Many pharma companies are now conducting R&D in China, and are looking for ways to evaluate other opportunities in China. Two of the companies that joined the consortia are not just because of the science but because they wanted to find ways to support basic research and at the same time evaluate their own discovery needs in China," said Stevens. //