Solving the structures of life

A Swedish-Anglo-Canadian collaboration is leading the world in determining the shape of protein structures relevant to human health and disease.

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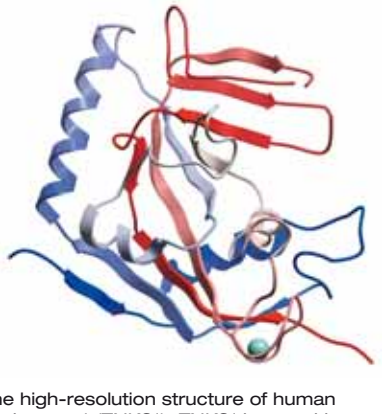
Every year, approximately USD$1.5-2 billion of the world's annual public-sector research budget is dedicated to structural biology – the effort to determine the shapes of biological molecules. This core component of basic and applied research is used both by scientists to understand biological function, and by pharmaceutical companies to expedite drug development. It is widely acknowledged that using the three-dimensional (3-D) image of the therapeutic target in early stage drug development can reduce the time to develop a new medicine by years. Solving the 3-D structures of medically-relevant proteins and releasing the information into the public domain without restriction is the mission of the Structural Genomics Consortium (SGC).

Formed in 2004, the SGC is a public-private partnership operating out of the Universities of Toronto, Oxford, and Karolinska Institutet (KI). The SGC focuses on solving the structures of human proteins – the majority of which have application in common diseases such as cancer and diabetes, but also expends considerable effort in studying proteins from human parasites, such as the ones that cause malaria.

The consortium receives funding from thirteen international sources, including one of the world's largest medical charities – the Wellcome Trust in the UK; in Canada, Genome Canada through the Ontario Genomics Institute (OGI), the Canadian Institutes of Health Research (CIHR) and Ontario's Ministry of Research & Innovation (MRI); three "top ten" global pharmaceutical companies (GlaxoSmithKline, Novartis and Merck); and a consortium of Swedish sponsors including the Knut and Alice Wallenberg Foundation, the Swedish Governmental Agency for Innovation Systems, the Swedish Foundation for Strategic Research and KI.

Dr. Johan Weigelt, Chief Scientist of the SGC.



The high-resolution structure of human Tankyrase-1 (TNKS1). TNKS1 is a positive regulator of telomerase and is an interesting drug target for various cancers.

Sweden's role

Originally, a collaboration operating out of the Universities of Oxford and Toronto, the SGC added a Swedish site at KI in 2005. Since that time, the KI node has played a unique role in making the consortium a truly world-class international scientific collaboration.

"The KI site has been instrumental in enhancing the consortium's international profile," explains Dr. Aled Edwards, the SGC's Chief Executive, who oversees the project from Toronto. "In two years since they joined the SGC, the KI lab has grown to become world leaders in the areas of nucleotide metabolism, RNA helicases and poly ADP-ribose polymerases. The lab has also become a dominant force in European science. The twenty five or so scientists at the KI have alone produced roughly 15% of all of the new human protein structures in Europe in each of the past two years."

The decision to include a Swedish site to the SGC was a natural move, due in large

part to the country's strong track record in advanced protein chemistry and structural biology. Beyond the scientific credentials however, the Swedes have also influenced the project in other areas.

"There are several examples of Stockholm-based approaches that have been adopted at the Oxford and Toronto sites," explains Dr. Johan Weigelt, the SGC's Chief Scientific Officer at KI. "For example, we've implemented a programme to involve the local scientific community in our protein target selection process which has allowed us to identify important under-explored target areas for study. Overall, it's helped the project progress, and everyone involved is proud to be part of an important international effort."

Professor Jan-Carlstedt Duke, Dean for Research at KI views the institution's involvement in the project as a positive development for Swedish science. "Participation in projects like the SGC is important for Sweden to stay at the forefront of protein science, with implications for competitiveness and training of skilled researchers," he notes. "We are extremely proud of being part of the SGC. The freely available data generated by the public-private partnership is crucial to answer fundamental biomedical questions and is a valuable resource to other scientists at KI."

Fundamental science

One of the philosophies driving the SGC's work is that the information it discovers is fundamental to human beings and should be available for all to use. This idea is rooted in the Human Genome Project (HGP), which was one of the first major international scientific efforts to adopt this principle. Projects like the HGP and SGC operate under the belief that the understanding and discovery of human biology is – in essence – the discovery of what it means to be human and as such should not be bought or sold for private gain. In the case of the SGC, this means the consortium does not seek to patent its results or focus on commercialisation efforts. Once the SGC solves a structure, it gets deposited into the publicly accessible Protein Data Bank – a central repository of 3-D structural data of proteins and nucleic acids.

"The SGC was not formed to publish papers or patent results," explains Edwards. "Because of the fundamental nature and importance of the information we discover, we place our results immediately and without restriction into the public domain, allowing commercial efforts and academics elsewhere to access and utilise the data freely and without any delay."

Though commercial opportunities and patenting results are not the consortium's focus, there is still a great deal of industrial value in the structures the SGC discovers. It has been estimated that the information found in a protein structure – routinely uncovered in the SGC's work – can reduce early-phase drug discovery time by as much as 18 months. In addition to this, the SGC delivers structures at roughly 1/3 to 1/8 less cost than traditional academia and industry, making the consortium's efforts both timely and cost-effective. Perhaps most remarkable of all however, is the SGC's output. The consortium has produced approximately one-fourth of the new human protein structures in the world for the past two years making it far and away the world's leading structural biology project focused on human proteins.

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Dr. Aled Edwards, Chief Executive of the SGC.

Phase II and beyond

During its first phase of operation, the SGC was mandated to produce 386 structures, selected by the consortium's funding partners and scientific committee. Having met and exceeded this goal ahead of schedule and below budget, the SGC was approved for a second four-year phase of operation this past July. Expectations are that the SGC will determine the structures for over 1,000 proteins by the end of this phase in 2011. 'Phase II' will also see the SGC tackle new projects, such as a concerted effort towards solving integral membrane proteins relevant to human health (the consortium hopes to determine at least eight structures of this variety during the Phase), as well as a recently-launched Visiting Scientists Programme which encourages and facilitates researchers from other institutions to collaborate with the SGC.

Edwards is quick to point out however that the real foundation for the SGC's future lies in the people at the consortium's three sites. "For a project of this size and complexity, finding the right people to participate has been important to us from the beginning. The extremely talented and cooperative group of scientists at our Toronto, Oxford and Stockholm sites is at the core of the SGC's success," he explains. "And I'm confident that our team will continue to drive the SGC forward during our next Phase of operation and beyond." ✣