Canadian Chemical Biology Network: biochemistry back to the future

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When the Canadian Society of Biochemistry was founded 50 years ago, there was a profound interest in the chemical principles that underpinned biology. Pauling and Corey had proposed alpha-helical and beta-sheet structures. Watson and Crick had just solved the structure of the DNA double helix and there was considerable excitement about how macromolecules would interact with small molecules. Studies of the action of small molecule hormones and second messengers in cells by the likes of Earl Sutherland captured the imagination of a generation of Biochemists. Work by Kendrew and Perutz on the structures haemoglobin and myoglobin were driven by a deep fascination for their interactions with oxygen and carbon monoxide. Meanwhile, isopropyl-thio-β-D-galactoside (IPTG) was the product of elegant investigations done in part by Monod and Jacob in *Escherichia coli* where a variety of synthetic galactosides were systematically tested for activity as either substrates or inducers of the *lac* genes for lactose utilization. The latter highlights the use of small molecules to perturb biological systems, that is the basis for renewed research efforts at the interface of chemistry and biology.

Small molecule-macromolecule interactions range from the exquisitely stringent, such as the biotin-avidin interaction, to the modestly specific, such as the interactions of penicillin with penicillin-binding proteins, to the non-specific, such as the effects of detergents on cellular membranes. Unlike genetic manipulations, small molecules can exert their effects in a time scale of seconds or less and be added or removed from the system at will. Thus small molecules are exquisite probes of biology. Despite these advantages, efforts to discover new small molecules with biological activity have largely been limited to the private sector, where the goal is drug discovery, not new reagents to probe complex biology. Only relatively recently has small molecule screening emerged as a tool in academic biological research, and happily Canadian biochemists, molecular biologists and cell biologists are leading the charge.

The Canadian Chemical Biology Network (CCBN) is an expanding collection of chemists and biologists from across Canada who are working to develop a network in support of small molecule screening. These researchers recognize the value of small molecules as probes of complex biology and have taken on the challenge of setting up pharma-style facilities for systematically screening tens of thousands of small molecules. They include principals with screening operations at the University of British Columbia, the Samuel Lunenfeld Research Institute, McMaster University, McGill University and the Université de Montréal. In 2005, the CCBN was founded with a grant from the Canadian Institutes of Health Research to support the purchase of a national chemical library of 30,000 compounds, now housed, curated and distributed by the McMaster High Throughput Screening (HTS) Laboratory. Also supported is a grass-roots effort to amass a library of Canadian-synthesized molecules to be included in this national collection. Most recently, the CCBN has launched an informatics effort to network screening activities across the country. Here the focus is the Canadian Chemical Biology Database, (http://www.ccbn-rcbc.ca/), to analyze, store and integrate results of CCBN screening activities. The web-accessible database

is open to all network participants and anyone with an interest in screening should join! The national database will house both curated screening data and up-to-date fully annotated descriptions of CCBN compound libraries.

Will the CCBN and similar efforts in other countries in fact lead to new drugs? The sceptics reasonably advance two main arguments. The first, and seemingly overwhelming argument that is the most widely discussed, is that the cost of development of a new drug is estimated to be more than $800 million. The second is that medicinal chemistry is weak in academia. There is considerable dispute about the real costs of the research component of drug development but it is certain that drug development is an expensive process. However, many drugs that are in clinical use were discovered in universities: the *Vinca* alkaloids and 3TC are two good Canadian examples to add to our national protein, insulin. There is also an innovation deficit in large pharma resulting in a dearth of new drugs. Also there are few incentives to work on orphan and neglected diseases, but these impart enormous health burdens on individuals and society. The medicinal chemistry and knowledge of drug development question is being addressed by biopharmaceutical companies, but innovative solutions to this rate-limiting step are also being explored by diverse initiatives across Canada. While it will be a challenge to bring to bear necessary resources in academe to the goal of discovering drugs, it is nevertheless clear that initiatives like the CCBN will take us some considerable steps closer.

So it seems that biochemistry may have found its roots again in the CCBN. At the interface of chemistry and biology, small molecule screeners across Canada will be searching for new probes with unique biological activity. And some of these molecules will surely have the right stuff to serve as leads for new efforts in therapeutic drug discovery. At a time when biochemists, molecular and cell biologists are working hard to have their academic research efforts recognized as relevant to economic and health agendas the CCBN provides a special and exciting opportunity.

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