nature chemical biology

Chemical biology on the brain

A two-day symposium on chemical neurobiology revealed an open frontier for researchers at the interface of chemistry and neuroscience.

In an article entitled "The impact of molecular biology on neuroscience," Francis Crick outlined how "molecular biology will provide new tools for characterizing both the structure and the function of neurobiological systems" and encouraged greater cross-disciplinary dialogue between neuroscientists and molecular biologists (*Phil. Trans. R. Soc. Lond. B* **354**, 2021–2025, 1999). In the intervening years, new postgenomic technologies have provided substantial insights into neurobiology through an enhanced capability to observe and perturb the human brain at the molecular level. Although Crick's musings centered on molecular biology, his ideas are strikingly relevant to the emerging field of chemical biology. In this spirit, the second *Nature Chemical Biology* symposium, "Chemical Neurobiology," highlighted how chemical biology is providing new chemical tools and molecular insights that are advancing the frontiers of neuroscience.

The *Nature Chemical Biology* symposium series was designed to facilitate interactions among scientists working at the interface of chemistry and biology. Our "Chemical Neurobiology" symposium focused on the intersection of chemistry with neuroscience (www.nature.com/natureconferences/nchembio2008). The conference was co-organized with The New York Academy of Sciences and was held on 22–23 February 2008 at the Academy's new World Trade Center location in New York City. Surrounded by breathtaking views, an international group of chemists and neurobiologists enjoyed seminars and lively discussion centered on frontier areas in chemical neurobiology—from "chemical sensing" to "synapses and signaling", and "synthetic neurobiology" to "brain matters"—and a keynote address from Linda Buck (Fred Hutchinson Cancer Center), winner of the 2004 Nobel Prize in Physiology or Medicine for her work on olfactory sensing.

The conference highlighted a particular forte of chemical biology: its ability to create new chemical tools for probing biological systems. For instance, Hagan Bayley (Oxford University) reported new technologies for creating and screening arrays of membrane channel proteins. Engineering approaches—including the use of microfluidics to probe oxygen sensing in *Caenorhabditis elegans* (Cori Bargmann, Rockefeller University) and materials engineering to improve neuronal stem cell culture (David Schaffer, University of California, Berkeley)—show great promise for understanding neurobiology.

Several investigators described new pharmacological and chemical-genetic approaches for probing and modulating neuronal function. From a drug discovery perspective, Frank Walsh (Wyeth) reported on a new class of neuroregenerative compounds based on the natural product rapamycin. The power of chemical genetic screens for identifying modulators of neuronal processes such as circadian rhythms (Steve Kay, University of California, San Diego), neuronal stem cell development (Peter Dirks, University of Toronto) and the regulation of lifespan in *C. elegans* (Linda Buck) highlighted chemical biology's growing impact on current neurobiological research.

A series of talks highlighted molecular approaches for understanding the chemical mechanisms of neuronal function. David Julius (University of California, San Francisco) provided insights into mechanisms of pain sensation mediated by natural products and environmental toxins. Jeffrey Kelly (The Scripps Research Institute) challenged prevailing models of protein misfolding in neurodegenerative diseases and suggested alternative mechanisms for realigning natural protein homeostasis. In the ion channel arena, Ehud Isacoff (University of California, Berkeley) showed how single-molecule microscopy and electrophysiology could be applied to aid understanding of the mechanism of unusual voltage-sensing channels.

Throughout the conference participants were reminded of the inescapable complexity of neurobiology. For example, Dana Small (Yale University) described functional magnetic resonance imaging studies that showed how brain signals impinge upon human perceptions of chemical inputs. Ralf Heinrich (University of Göttingen), reporting on pathways that influence song generation in grasshoppers, showed that this complexity extends across all levels of biology. Dennis Dougherty (California Institute of Technology), who described the application of physical organic chemistry to understand neurotransmitter binding to nicotinic receptors, pointed out that such complexity translates down to the biochemical level. Yet, complex systems also can be inspiring, as indicated by Eric Anslyn (University of Texas, Austin), who applied principles of neuronal sensing to create 'artificial tongues' based on synthetic organic receptors.

The ability to visualize and map the connections between neurons, which Crick referred to as "architectonics," is essential for a complete understanding of neurobiology. Several seminars emphasized the central importance of imaging technologies for understanding complex neurobiological systems. Karl Deisseroth (Stanford University) highlighted recent applications of light-activated proteins for modulating and visualizing neuronal processes. Atsushi Miyawaki (RIKEN) described the application of fluorescent proteins to look at neural progenitor cell proliferation in brain slices. Finally, Jeff Lichtman (Harvard University) illuminated Crick's 'architetonics' concept with Technicolor clarity using "Brainbow," a technique that permits differential fluorescent labeling of individual neurons and provides a tool to understand the 'connectomics' of the brain.

The *Nature Chemical Biology* symposium highlighted the importance of enhanced interactions between neurobiologists and chemical biologists. Given the breadth and complexity of the unanswered questions in neurobiology, chemical biologists still have much to contribute. "After all," stated Crick, "exactly how our brains work is of vital interest to us all, so why shilly-shally." ■