Systems biology

The application of systems-oriented approaches has become increasingly common in drug discovery in recent years. This month, two researchers who have been working in the field since its inception discuss their career paths.

Malcolm Young, Ph.D.

CEO, e-Therapeutics, Newcastle, UK.

The past decade in drug discovery has been dominated by a target-focused approach in which molecules are sought that specifically affect a particular protein with a link to disease. However, there has been growing appreciation of the limitations of this approach and a concomitant increase in interest in strategies that could allow more effective therapeutic intervention based on a systems-oriented understanding of disease biology and drug response.

Among the companies that focus on such strategies is e-Therapeutics, founded by systems biology researcher Malcolm Young in 2001. "The core technical capability is an ability to evaluate the impact that a molecule will have on any cell for which we have data, on the basis of the set of proteins for which it has affinity — not just affinity for a single protein target," he explains. "If the cell is pathogenic or pathological we can gain insight into efficacy, and if the cell is a normal one, we can gain insight into safety and tolerance."

Young's laboratory, initially at the University of Oxford, and then at the University of Newcastle, UK, began developing approaches to understanding complex biological networks in 1991, and focused on applying these tools to investigate the organization of the brain. "The core attraction to me of informatics and systems-level approaches is that, in my experience, they give much better insight into the systems being studied than reductionist approaches," he says.

By 2000, this neuroinformatics approach had matured to the extent that it was possible to successfully predict from network data where particular types of physiological function would occur in the brain. An unexpected visit from a pharmaceutical researcher shortly after publication of this research then provided the stimulus for the foundation of e-Therapeutics. "The suggestion was that if we could predict the effects of multiple interventions on complex brain networks, then we should be able to do the same for macromolecular interaction networks in cells, and in that way develop a drug discovery platform," recalls Young.

Successfully realizing this goal has presented a range of challenges. "First, we had to build large protein-interaction and chemoproteomics databases from multiple, often inconsistent and always differently formatted sources, which we were able to successfully validate retrospectively by 2004," Young says. "But having a platform that predicts drug efficacy and safety much better than chance still doesn't constitute a business, and it took some time to work out where the best commercial opportunities for this capability lay."

In this respect, the company has focused on applying its technology to reposition drugs for specific premium clinical niches. "Accurate assessment of efficacy and safety can be applied to reposition compounds, rapidly, at low cost, and these candidates can often leap straight into Phase II trials," says Young. Several such compounds are now progressing in Phase II clinical trials. "At the outset, I had the ambition that the company might help make just one patient better. The most rewarding feature so far has been the fact that our drugs have now done this for patients in multiple clinical settings," he concludes.

Hiroaki Kitano, Ph.D.

Director, Sony Computer Science Laboratories, and President of the Systems Biology Institute, Tokyo, Japan.

For Hiroaki Kitano, a chance encounter provided the catalyst for his transition from studying artificial intelligence to the emerging field of systems biology. He focused on artificial intelligence during his Ph.D. in computer science, which he gained while working in software engineering at NEC Corporation in Tokyo and later also as a visiting researcher at the Center for Machine Translation, Carnegie Mellon University, USA, before joining Sony Computer Science Laboratories as a researcher in 1993. "Coincidentally, in 1994, I met Susumu Tonegawa [who won the Nobel Prize in 1987 for his discovery of the genetic principle for the generation of antibody diversity], and we discussed the possibility of computer simulation of biological systems," recalls Kitano. "He said it seemed too far-fetched, which triggered me to investigate biology in depth to see if computer science could add something."

"Soon, I found out that quantitative and systems aspects were largely missing, which I believed to be essential to understand biological systems, not just each gene or protein," says Kitano. "And as I spent more time on biological problems, I confirmed my initial intuition that a lot can be done with a computational systems-oriented approach. This triggered me to use the term 'systems biology' around 1996–1997 and to keep working on it."

Now, Kitano is Director of Sony Computer Science Laboratories, a unit of ~30 researchers that is a 100% subsidiary of Sony, but covers a wide range of research fields that are not confined to the company's current business, such as systems biology, neuroscience, economics, computational geometry, electrical engineering, human–computer interactions and sustainability. "We recommend challenging research and do not need to worry about peer-review, which is a solid system, but which may risk filtering out truly original, and often crazy, thoughts," says Kitano. "I love science and playing with new ideas, so this situation is ideal."

Kitano is also President of the Systems Biology Institute, a non-profit private research organization that he established in 2000 with the aim of promoting systems biology research and its application to medicine and global sustainability. He is fully responsible for the operation and fund raising, as well as the research.

In both roles, as well as needing management skills, Kitano feels that a key requirement is to be open to challenging, new ideas, to create and develop a vision, and to have the passion to make it reality. He also highlights the value of gaining experience in fields that might not be directly associated with one's core interest, as he has found that this later became very useful or even essential in his career. "After I joined NEC Corporation in 1984, I developed commercial software for 4 years and I thought it was remote to my research," he says. "However, this experience is now essential for developing and maintaining high quality, industrial-strength software, such as CellDesigner, which is used by thousands of researchers today."

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Career snapshots: http://www.nature.com/naturejobs/magazine/career_snaps.html