# Post-Genomic Partnership for Chemistry and Biology

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by Gary Burd
(Executive Editor)

Biology and Chemistry Departments have traditionally occupied separate buildings on campus — at one time in the not too distant past, few universities managed to encourage mingling. A one-day symposium, organized by the UKLSC and RSC, aimed to address some of the issues involved in convincing biologists that chemistry is invaluable, and *vice versa*. The presentations demonstrated how a mixture of disciplines can achieve impressive results in the new post-genomic proteomic era.

Steven Neidle (Institute of Cancer Research), the chairman of the morning session, began by questioning what chemical biology actually means. Can it even be defined? The difficulty in pigeonholing this combination of disciplines has arisen solely because of the elucidation of the human genome, which has "propelled chemistry into the forefront of biology". All of the speakers detailed the technology of their respective companies and showed that both chemistry and biology are vital if we are to glean information from the genome.

David Bailey (De Novo Pharmaceuticals) was given the formidable task of commenting on the future challenge that faces chemists now that the human genome sequence is available for data mining. He predicted that genomics and proteomics would be continuing themes into the 21st century, but that eventually, cellomics would emerge as the leader. David defined cellomics as the complex (cellular pathways) molecular interactions and pathways within cells. "The key technology drivers have been DNA sequencing, bioinformatics, protein chemistry, mass spectrometry and NMR," he says. "In the future, they will be cell biology, gene expression, chemoinformatics, structural biology and population genetics."

Data acquisition is currently a dominating force in the field of biological chemistry. "We now need ways of focusing these data," says David. "The avalanche of data is clearly seen in the growth of the sequence database. New tools are needed for the chemoinformatic investigation of the data, as we try to capture the value in the human genome.

"Pharmaceutical companies are driving chemical biology," claims David. "Only they have the resources to tackle the numbers of molecules involved in this field." The current drug targets are a starting point, and homologues to hydrolases, kinases, receptors, transcription factors and ion channels are under investigation. But: "History has shown us that there can be 10 years between the discovery of an active molecule and a drug in the clinic," says David, stating HIV as an example.

De Novo Pharmaceuticals can help with the design of algorithms to test lead drugs. "A lead drug is not a candidate drug, and the cost of failed drugs makes it difficult for pharmaceutical companies to survive," says David. De Novo uses a technique that it calls 'Virtual Screening' where a drug's potential is assessed using molecular modelling techniques. This, David hopes, will reduce the critical time to novel lead molecule. The importance of biological chemistry research in this field is clear: "New technologies are needed," concludes David.

François Natt (Novartis) emphasizes that in the post-genomic era, we mustn't forget about RNA. "With chemistry the analytical tools gave the needed boost. Now, in functional genomics, with a notable contribution from oligonucleotide approaches, biology is facing the same type of revolution."

At Novartis, anti-sense oligonucleotides are being used for functional analysis. Anti-sense RNA binds to the mRNA and prevents formation of the protein. In this way, the involvement of a particular protein in a bio-

Left to right: Charles Wilson (Archemix) and Matthew Shair (Harvard, US)

Left to right: François Natt (Novartis) and Peter Stockley (Professor of Biological Chemistry, University of Leeds)

logical response can be characterized.

François detailed a high throughput oligonucleotide synthesis and reporter gene assay technique utilized at Novartis that allows the rapid screening of anti-sense oligonucleotides. "This has been integrated as a technology platform at Novartis," says Francois. "It rapidly provides anti-sense inhibitors as tools for gene analysis." Clearly, there is potential, for example, for products such as a 'Gene Family Inhibitor Plate' which can maximize disease analysis, and this in turn can lead to novel validated targets for drug discovery.

Charles Wilson (Archemix) continued the RNA theme, discussing evolved RNA biosensors for use in the drug discovery and drug development processes. "The genome sequence is only a starting point, as it provides limited functional information," explains Charles. "We are limited by the tools for looking at functionality. Therefore, we need to be looking at proteins, and at Archemix, we apply evolved nucleic acids."

Archemix core technology is based on the ability to engineer allosteric ribozymes, i.e. enzymes whose activity is switched on or off by the presence of a specific target. Allosteric ribozymes act as reporter molecules in that they directly couple molecular detection to the triggering of a chemical reaction. "These RiboReporters therefore couple molecular recognition to signal generation, making them powerful tools for a wide range of applications. They can be used to detect all molecular species, function both *in vitro* and *in vivo*, and in solution or on chips. In this way, they can be used to measure the level and function of any protein as a function of tissue type, disease state, environmental stress, etc. Clearly, they also have application in molecular profiling arrays, high throughput screening, cell-based assays and animal models," concludes Charles.

Yeast proteomics is now heavily studied as the genome sequence of *Saccharomyces cerevisiae* has become available. Mike Washburn (Syngenta) described a technique called MudPIT (multi-dimensional protein identification technology), which he is using to mine even more protein data than are available with more traditional techniques. 2D-PAGE followed by MS is the most widely used method of protein resolution and identification. However, "Portions of proteomes such as proteins with extremes in isoelectric points and molecular weight, low-abundance proteins and membrane-associated proteins are rarely seen in a 2D-PAGE study," says Mike.

"The MudPIT technique is a method for rapid and large-scale proteome analysis by multi-dimensional liquid chromatography, tandem mass spectrometry, and database searching by the SEQUEST algorithm." Mike went on to present results from application of the method to the yeast genome, revealing a total of 1484 proteins.

"The MudPIT method gives a greater throughput, and proteins of lower abundance are detected. Furthermore, the insoluble portion can be analysed to allow visualization of membrane proteins," says Mike.

The final speaker discussed the future as he saw it. Matthew Shair (Harvard, US) asked "what are the methods to convert genomic sequences into a better understanding of basic cell biology?". According to Matthew, the way to do this is to use the resources around us — natural products — and accelerate the synthesis of structural mimics. "What we need to do is devise a new form of organic synthesis starting from basic natural product backbones, and creating multiple molecules at each stage," says Matthew. His method is called 'diversity-oriented synthesis' and enables the construction of libraries of complex molecules. His lab is currently focused on biomimetic reactions since these often result in products that have significant increases in molecular complexity and they occur under mild conditions. Matthew thinks that the resultant molecules may target some of the proteins that do not interact with known natural products. He collaborates with colleagues both inside and outside Harvard to test the libraries in a variety of high-throughput biological screens.

"To carry out this work, Harvard established the Harvard Institute of Chemistry and Cell Biology (ICCB)," explains Matthew. "Founded in 1997, as a collaboration between the Faculty of Arts and Sciences and the Faculty of Harvard Medical School, it created a space to study the new field of chemical genetics, where small molecules are used to explore the cellular and physiological function of proteins. ICCB embodies several concepts that are essential for success in this endeavour: chemists and cell biologists work side by side, and visiting scientists from our corporate partners work with ICCB researchers and are thus able to collaborate on projects and exchange ideas".

The audience agreed that collaboration between biologists and chemists was the future, but what was needed was special funding to set up centres like the one at Harvard. Until one of the Research Councils has the desire to provide the funding, it was felt that Britain would always be lagging behind the Americans in biological chemistry research.