



Biochemistry Skills for Drug Discovery

A Biochemical Society position statement | February 2014

In this paper we seek to identify and discuss some of the most significant topics in modern drug discovery where young biochemists can have a major impact.

We identify some critical areas for instruction and training that will equip a new generation of biochemistry graduates to have a real impact on drug research and development and therefore on human health.

Introduction

Modern drug design and development is a complex process that brings together numerous chemical, biological and clinical disciplines. This includes a wide range of biomolecular science and as such there are many roles suited to scientists whose background, training and expertise lies in biochemistry. These range from early involvement in the identification and validation of potential molecular targets for new drug projects, to key roles in assay design, troubleshooting and implementation throughout the screening and optimization stages of both traditional small molecules and biopharmaceutical products. In the last case, expertise in molecular immunology, genetic manipulation, protein chemistry and synthetic biology have been crucial and provided new directions for drug discovery. At a later stage in new drug research, biochemical assays are needed to evaluate disease models and to drive biomarker analysis in translational medicine and clinical research.

Throughout the discovery process, biochemical skills are required for monitoring routes of drug metabolism, for pharmacokinetic analysis and safety testing. At a more biophysical level, biochemists may contribute significantly to computational chemistry and structural analysis, such as crystallography or other methods employed to demonstrate drug-binding modes and to predict potential modifications and improvements of lead compounds.

With the current growth in bioinformatics, proteomics and genomics, there is even more scope for researchers with biochemical expertise, including emergent areas of carbohydrate diversity and glycomics or in lipidomics and lipid biology. New drug opportunities provided by various nucleic acid-based disease interventions, including gene replacement, use of micro RNA gene silencing or exploitation of other novel methods for controlling gene expression may draw more biochemistry graduates into pharmaceutical and drug discovery careers.

Key knowledge, skills and capabilities for biochemists

Any list of key knowledge, skills and capabilities is inevitably dynamic. Nonetheless, there are clearly identifiable core requirements for biochemists that are unlikely to change rapidly while other, new skill requirements will emerge as technology advances and knowledge grows, requiring any syllabus to be continuously reviewed and updated.

Biochemical basics

These should be central to all undergraduate courses in biochemistry. However, as the field grows new discoveries may tend to displace the traditional topics that were taught. This can leave newer generations of students struggling with some basic concepts. We must never lose sight of the fundamental topics that underpin understanding of more complex biological process.

Analytical skills

Accurate identification and precise measurements of biochemical entities supports many aspects of the life sciences, none more so than in drug design. Understanding of key principles of analytical science allows new assays to be developed and refined, many of which make use of biochemical systems (e.g. ELISA and its newer homogenous formats) as well as hardware-centred techniques such as HPLC, LC-MS, and robotic systems for high-throughput screening or bioimaging assay formats.

The last of these, imaging and high-throughput microscopy, is an area of growth and rapid change that offers novel approaches to drug screening and creates high content assay formats that the industry is adopting so researchers with specific training in these areas will be needed. Elsewhere, the shifting emphasis towards the use of biomarkers to inform personalized healthcare and in translational science will provide more opportunities for biochemists in the future.

Assay design and statistics

Young scientists need to be able to design their own experimental protocols with a clear understanding of how to ensure they generate data that are fit-for-purpose. At different stages in drug research, the types of experimental design may change (e.g. high-throughput screening might be less rigid than pre-clinical studies). A good grounding in assay design

is important, including appreciation of the roles and value of controls, reference substances and statistics such as Z -factors, t tests, analysis-of-variance and P values.

Our graduates should be conversant with data analysis and aware of the importance of understanding data distribution and the differences and relevance of arithmetic and geometric means and how to use these calculations appropriately.

Enzymology and receptor theory, including rate kinetics and thermodynamics

A fundamental need is for fluency in the concepts and analysis of intermolecular interactions, whether the formation of a macromolecular complex or binding between a protein and its ligand. The relationships and importance of different ways of quantifying binding interactions and their affinities from concentration/effect curves, kinetic rate constants or thermodynamic measurements can each have a role in characterizing drug–target interactions when the biochemists studying these parameters are well informed. Enzymology, and in particular principles relating to the observation and analysis of enzyme inhibition, should be taught at a level similar to that seen with receptor theory, agonism and antagonism in pharmacology courses.

There are many underlying elementary principles that are common to these two protein types and students should appreciate their similarities and differences. We should promote the most up-to-date techniques for quantifying ligand binding, substrate turnover, inhibitor characterization or agonist and antagonist responses using non-linear parametric or non-parametric statistically robust curve fitting as well as traditional linear graphical representations of data. The nature and impact of rate constants (particularly dissociation rates) on assay design, the data produced and its interpretation should all be represented in the core knowledge set.

Signalling

Signalling events lie at the heart of physiological control in health and disease, influencing biology from the cellular to the organismal level and directing wholesale changes in cellular biochemistry. Frequently, faults or imbalances in a signalling process drive disease pathology. Manipulation of such pathways has resulted in many examples of successful drug development, for example by targeting G-protein-coupled receptors, ion channels or protein kinases and has benefited from the molecular level of analysis that biochemists have contributed. A sound knowledge of the messengers and sometimes complex pathways and networks involved will continue to be one of the most important topics for young scientists to grasp as they move into careers in medical and drug research.

Molecular pathology

Understanding the biochemical basis of disease pathology is one of drug discovery's main challenges and we might anticipate thorough education and training in the techniques and principles that can be employed will be a cornerstone of drug discovery skills training. In addition to traditional methods for biochemical dissection of pathological processes, we must not neglect more modern approaches and should remain dynamic and responsive to the appearance of novel technologies and assay platforms that can be applied to understand biochemical pathology.

Pharmacokinetics and drug metabolism

Evaluation of drug metabolism requires biochemists who are conversant with some of the most elementary skills in isolating and identifying reaction products and blood-borne metabolites. Increasingly, pharmacokinetics has moved from a dependence on *in vivo* studies to *in vitro* experimentation and predictive techniques. This requires considerable skill in designing suitable assays and interpreting their output, but offers greater opportunity for small drug discovery units to provide predictive data about the likely fate of their products *in vivo* without recourse to animal experimentation.

Toxicology

Toxicity or other safety issues are a leading cause of attrition at all stages of the drug discovery process, but can sometimes be predicted using biochemical toxicology tests, leading to the selection of better drug candidates. At the early stages of discovery, the cytotoxicity of potential therapeutics can be assessed against a range of cell types, including hepatocyte toxicity and phospholipidosis potential or monitoring interactions with hERG channels. Biochemical skills are also important when examining drug-drug interactions.

Bioinformatics, 'X-omics' and 'Big data'

Activities such as the human genome project, genome-wide association studies and informatics have identified very many potential biochemical targets for new drugs; elucidating which of these offer authentic potential is an emerging modern challenge. Indeed, poor target validation is often quoted as a reason for attrition during drug development, input from a range of biomolecular specialities can be used to support clinical target validation or to set up suitably rigorous model systems to allow robust choices to be made. In particular, it seems timely for graduates to be able to understand the outlines of analytical approaches and the types of visualization available for such analysis. We have moved into an era where enormous datasets can be generated from genomic and

proteomic experimentation or from automated high-throughput and high-content assays. Young researchers need the skills to effectively analyse these datasets.

Systems biology

Most of the diseases for which new treatments are now sought are multi-factorial and medication is often with drug combinations. The underlying cellular systems of signalling and metabolism are networks with multiple inputs and outputs, as well as many interconnected internal routes. The net behaviour of these systems is too complex to be understood intuitively, arising as it does from non-linear interactions between multiple components. Systems biology applies mathematical analysis and computational modelling to determine the responses to alterations in the activities of various components, offering improved potential to identify the most effective molecular targets. Models can also function to integrate diverse experimental information, including high-throughput data, enzyme kinetics, inhibition constants and pharmacokinetic data, as well as cell-based assays, animal experimentation and biomarker measurements. This mathematical modelling is based on prior identification of the components and their interactions and needs to be informed by sound biochemical and biophysical principles, as well as quantitative measurements. It may also need to take into account the spatio-temporal concentrations and compartmentalization of the relevant components. Simply measuring the concentration of individual analytes is unlikely to provide useful information if the biochemical pathways and networks are not adequately understood. Systems biology requires a team approach where skills of practical and theoretical biochemistry combine in creating and testing of models. New researchers are needed who understand these opportunities and are able to apply techniques and principles of pathways analysis and systems biology to decide which new targets might be given priority.

Structural biochemistry, crystallography and other physical techniques to derive structural information, including molecular modelling

Advances in high-throughput crystallography and other biophysical techniques for the determination of biomolecular 3D structures has enabled structure-based drug design to emerge from an area of great potential in the 1980s to its present role as a powerful contributor to lead compound discovery and optimization.

Where experimentally derived 3D models are not available, molecular modelling techniques may be used to generate them from knowledge of homologous proteins. Experimental and modelled protein structures are now routinely used alongside computational docking in virtual screening of chemical libraries to accelerate the search for new drug molecules.

Bioinformatics, data mining, systems biology and structural biology are all dependent on considerable mathematical ability and advanced computing skills. Although these may be beyond the interests or capability of some researchers, they will all, undoubtedly, need to interact with professionals using these techniques and we should seek to equip future biochemists with knowledge that enables them to communicate effectively in these disciplines. There is little doubt, biochemistry underpins *in silico* approaches to drug discovery and development that are likely to contribute significantly to the therapeutic portfolio of our pharma industry over the coming years.

The nature and challenges of biological therapies

The fastest growing sector within the pharmaceutical industry is biologics. Antibody-based therapies in particular have seen huge growth in the last decade and some predictions suggest they will soon dominate drug sales. Biochemistry graduates need to have an understanding of how these agents are discovered and produced. This would include a working knowledge of monoclonal antibodies and how they are produced. It is important to have a clear understanding of why these types of molecule offer distinct opportunities, as well as the challenges in modifying them into therapeutic agents.

Antibody engineering is of particular importance in creating effective, safe biologic therapies so it may be envisaged that questions of humanization and other forms of protein modification to address pharmacokinetics, immunogenicity and stability should become widely understood among biochemists. Virtually all biologic drugs are glycoproteins and graduates are sorely needed with glycoscience skills in order to accelerate progress in biologic drug R&D.

Practices in outsourcing

The use of external collaborations and contract research organizations has grown within the industry; in some cases to the extent that models similar to many start-up companies where all research activities are outsourced now operate within major pharmaceutical firms. Many biochemists entering the industry will need to be familiar with these business models, either because they will seek employment within companies offering services to industry or they will be working with groups that seek to outsource some of their own studies.

Training in practice

Ideally, we should create opportunities for students at undergraduate, graduate or post-doctoral levels to participate in placements, training programmes, workshops or lecture courses delivered by experienced scientists who are actively involved in drug discovery projects within industrial as well as academic environments. This may serve to allow students to make well-informed career decisions and ensure graduates have more rapid impact when they move into drug discovery roles.

Concluding remarks

Throughout the drug discovery process; from building our understanding of the cellular processes that drive disease, through initial identification of novel molecular targets and chemical entities with the ability to modulate their activity, to monitoring pathological changes in disease and during drug treatment, biochemistry has a central role to play alongside other important disciplines.

Rising costs in drug discovery, coupled with high attrition rates throughout the pipeline, particularly during clinical trials, have been a major cause for concern within the drug industry in recent years. Skilful application of traditional and modern techniques in biochemistry and molecular biosciences have the capacity to play a pivotal role in reducing attrition by providing better target selection, more suitable chemical choices and improving success in translational research and clinical development.

This will require excellent knowledge transfer between scientists with industrial experience and young researchers, such that lessons that we have already learned are passed on and the science of drug discovery can develop and grow to the benefit of patients.

Practices and structures within the industry are in a constant state of flux. Although we may promote specific business aspects, our graduates need to appreciate they are not universal, however, the underlying principles can be widely applied. Most important is that we furnish graduates with a sound understanding of the basic scientific principles so that they have a secure platform upon which individual R&D organizations or academic units can themselves add specific training.

Our list is, inevitably, incomplete, but already the wide-ranging influence of biochemical sciences is likely to mean that no single biochemistry course, run in one academic institution could hope to adequately cover all of the potential specialities and areas of expertise. Indeed, there is probably more than enough material relevant to drug discovery to offer entire degree courses concentrating on this subject. So, we might anticipate certain key areas will be widely taught to a high level with other more specialized topics included in some courses depending on local research interests and the availability of suitable lecturers and facilities. Let us not lose sight of the fact that a strong basic training in the fundamental elements of our subject is the essential foundation on which to build this knowledge and expertise for drug discovery.

Biochemistry encompasses a broad syllabus with technical relevance to many biological disciplines and several that might traditionally be considered chemistry. Biophysical techniques in particular have potential for much greater impact on the design and optimization of new chemical entities. It is important that scientists in any specific discipline have a working knowledge of other key disciplines. Interaction and close cooperation with those working in different subject areas is vital in order to facilitate effective meaningful exchange of data and information so that everyone may contribute to intelligent decision-making within the drug design and development process.

It is imperative that techniques taught in drug discovery are relevant to the practices most widespread in commercial drug discovery so that graduates have good employability. The needs of the pharmaceutical industry, large pharma, smaller R&D companies, the biotech sector, start-up companies and contract research organizations must be met by the training of young scientists and should enable graduates to function in all of these environments. However, if we are to equip graduates now to enter the industry in 4–7 years' time, they also need to have an appreciation of where new therapies will come from. This might include gene therapy, tissue repair and regeneration and include stem cell technology and novel forms of drug delivery, as well as the traditional approaches. Graduates need to have their horizons broadened beyond what the industry currently does.

Finally, it is crucial that the pharmaceutical industry, in all of its guises, endorse and embrace these initiatives and recognize their value. It is, therefore vital that our education practices should be forward thinking and carefully tailored to the emerging requirements of a very dynamic industry.

This document was created in February 2014 and will be reviewed regularly.

The Biochemical Society exists for the **advancement of the molecular and cellular biosciences**, both as an academic discipline and to promote its impact on areas of science including biotechnology, agriculture, and medicine.

We achieve our mission through our publications and journals, scientific meetings, educational activities, policy work, awards, and grants to scientists and students.

Education Team

Tel: +44 (0)20 7685 2454

Email: education@biochemistry.org

Policy Team

Tel: +44 (0)20 7685 2453

Email: policy@biochemistry.org

General Enquiries

Tel: +44 (0)20 7685 2400

Email: genadmin@biochemistry.org

www.biochemistry.org



@BiochemSoc



Biochemical Society



Biochemical Society
Advancing Molecular Bioscience

Registered charity No. 253894