Chemistry Skills for Drug Discovery

A Royal Society of Chemistry Position Paper

Chemistry expertise is critical to technical success across the spectrum of innovative medicines R&D. This position paper describes the changes that have taken place in the drug discovery sector and the challenges this presents in terms of ensuring chemistry, as the key enabling science, continues to deliver the essential translation of biological opportunity into clinical application.

Background

Over recent years, the model for pharmaceutical R&D within the UK has undergone a transformation from the integrated approach, largely contained within large pharma through to an ecosystem of collaborative research partners across small and large pharma, SMEs, academia, health charities and the NHS, each contributing complementary skills and expertise.[i]

As a result of these changes, there has been a shift in the way chemistry expertise is brought to bear on drug discovery programmes. For example, the more routine aspects of chemical synthesis and analysis are now often outsourced to contract research organisations and many of the new emerging drug discovery technologies are being pioneered by medicinal chemistry experts within the academic sector and small biotech companies. These include, amongst others, chemical biology to support target validation and biotherapeutics; new classes of therapeutics (e.g. polynucleosides); analytical method development; computational modelling.

However, the inventive design of small molecules in the context of lead discovery, lead optimisation and clinical candidate nomination has largely been restricted to industrial organisations and has been a major strength of medicines research in the UK. Furthermore, the movement of trained experts from large pharma to smaller biotechs has been an important mechanism for building drug discovery expertise within the SME sector. This core enabling capability is now under threat as the industry in the UK contracts and fragments, with the number of RSC members engaged in pharmaceutical research dropping by 20% over the last three years. Unless positive action is taken now, there is a real risk that key areas of expertise will be irrevocably lost; in particular the ability to design high quality tools that build confidence in new mechanistic approaches and the invention of safe and effective medicines that deliver benefit to patients.

Training capacity and mobility

Training programmes for existing and future medicinal chemists will be essential to ensure UK-based drug discovery scientists can maintain their worldwide leadership. Within the academic/SME sector, where the infrastructure to deliver in-house training is largely lacking, there is a pressing need to provide specific training/CPD in drug discovery. Furthermore, as new technologies are developed, particularly within the academic sector, there is an ever-increasing need to train new and established drug discovery scientists in these emerging areas.

The IMI Education and Training initiative EMTRAIN will provide a valuable resource (*on-course*®) for capturing the available training/CPD opportunities but this will only be effective if it is populated with high quality, up-to-date

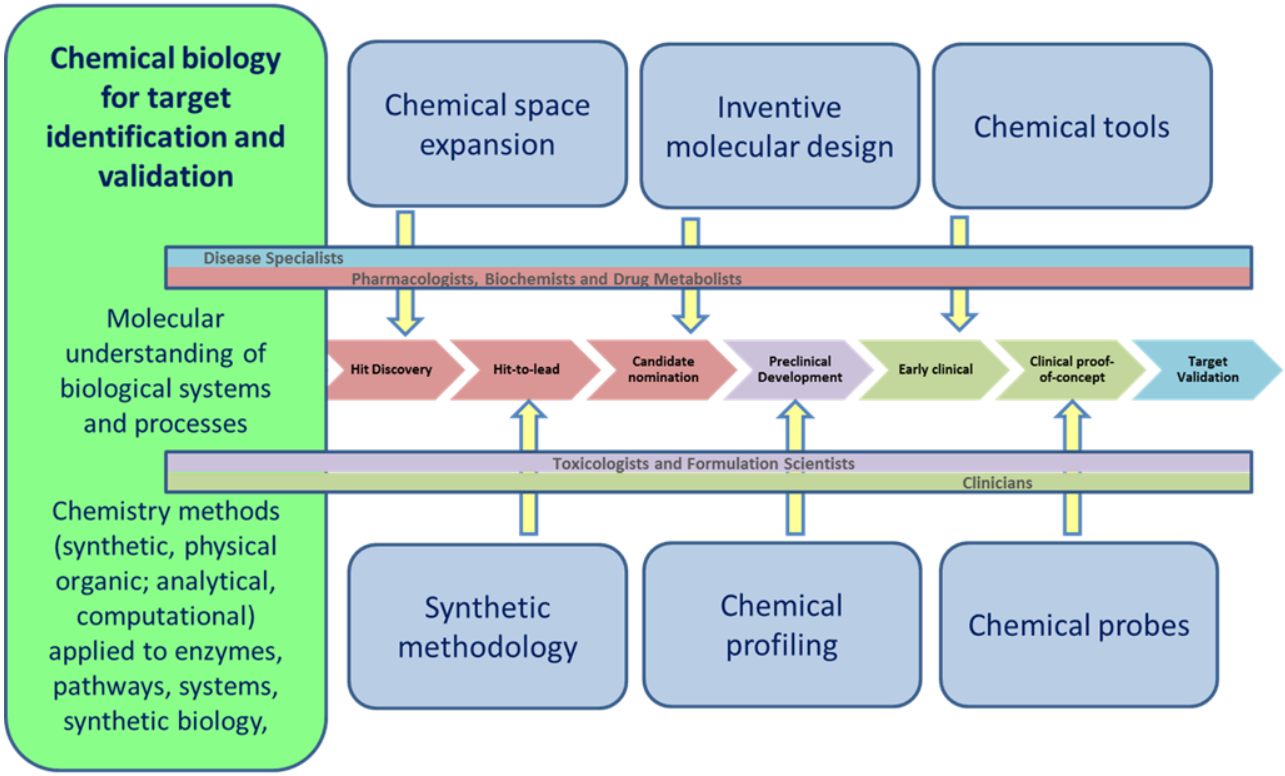
programmes. Opportunities need to be provided for budding drug discovery scientists to work alongside drug discovery experts, academic and industrial chemists and scientists from aligned disciplines. This will serve the needs of the medicines research community on a number of levels:

- **Immediate term:** Enable existing portfolios of drug discovery programmes to benefit from academic/industry partnerships, bringing to bear complementary capabilities and expertise.
- **Mid-term:** Build a cross-disciplinary network across academia/Pharma/biotech to provide a means for training, guidance and mentorship for the next generation of drug discovery scientists. This will help to cultivate a research environment that supports cross sector/cross disciplinary exchange. (e.g. through academies for medicines research, doctoral training centres, in partnership with industry).
- **Long-term:** Create an environment where clusters/centres of excellence emerge (incorporating universities, institutes and biotechs) based on scientific opportunity and bottom-up proposals. Populate these clusters with the next crop of drug discovery scientists who are expert in the latest developments in their field whilst also able to combine mobility and partnership-building skills.

Key skills and capabilities for drug discovery chemists

Core **discipline skills** underpin the contribution of medicinal chemistry and chemical biology to drug discovery. At the early phase of target identification and validation, this involves developing a molecular understanding of biological systems and processes through application of synthetic, physical, analytical and computational methods. Further downstream, there is a greater emphasis on inventive design of biologically active molecules to generate high quality probes and drug candidates that minimise attrition risks.[ii]

- **Synthetic chemistry:** synthesis to support the iterative design and evaluation of biologically active compounds. Access to new areas of chemical space and so provide chemical enablement of new target classes (e.g. glycosides, nucleosides, RNA). Examples include: green chemistry; catalysis; flow technologies; alternative feedstocks; biocatalysis; chemical manipulation (e.g. phosphorylation, conjugation, rigidification) of biological systems (e.g. enzymes,



antibodies, RNA) to modulate function, stability, physical properties; understanding of coordination chemistry to develop tools and to gain new insights into protein structure and function.

- **Computational chemistry/chemo-informatics/physical organic chemistry**: to enable a molecular understanding of biological mechanisms and to model molecular interactions with biological systems and processes; to develop predictive models for synthetic chemistry, toxicology and drug metabolism.

- **Analytical chemistry**: to facilitate investigation of biological targets and drug metabolism; to provide new insights into how molecular properties affect biological profile, to underpin biotherapeutic approaches (e.g. purification, quality assurance). Techniques for biomarker identification and detection and probe design (mass spectrometry, PET, SPECT, MRI, labelling). Biophysical techniques for screening and target validation.

Beyond this, as the science of medicines R&D develops, so the skills and capability requirements evolve. To be successful, chemists need to have a broader working knowledge of **aligned disciplines**, to enable them to understand the wider aspects of drug discovery whilst still maintaining their core discipline expertise to ensure scientific rigour.

These additional disciplines are increasingly becoming core areas of knowledge, in particular within the context of chemical biology and include:

- computational methods, predictive models and systems;
- data manipulation, visualisation and analysis and proficiency with open-source databases;
- design of experiments and statistics;
- target identification methods;
- biomarker and probe technologies;
- tissue engineering and remodelling;
- synthetic biology;
- pharmacology, drug action and assay formats;
- drug metabolism and pharmacokinetics;
- methods to support diagnostics, imaging and patient stratification;
- intracellular pathways and transporters;
- intellectual property: patentability and freedom-to-operate;
- formulation and delivery technologies;
- molecular basis of toxicology.

In terms of **transferable skills**, the following are essential in a dynamic, unpredictable and complex environment.

- Use of fundamentals to solve new problems
  - problem- and context-based learning;
  - confidence and competence in mathematics.

- Able to reinforce ideas through practical experimentation.
- Promoting and engaging in scientific challenge across disciplines.

- Resilience and leadership:
  - energised by change.

- Continually building on existing knowledge base and skill-set:
  - learning skills, reflective learning;
  - self-driven learning and development.

- Developing partnerships and collaborations (cross-discipline, cross-cultural, multi-centred)
  - understanding of the external landscape of expertise, capability/collaboration partners and able to facilitate partnership through networks;
  - basic understanding of R and D financing models, value creation, risk, return on investment, licensing models, project management;
  - work effectively in geographically fractured teams with complex cultural elements. Use of state of the art communication/inform-ation sharing technology.

- Mobility
  - able to seize opportunities for exchange/secondment to build knowledge and understanding of adjacent disciplines and establish effective networks spanning industry/academia.

Conclusion

From target selection and compound design through to informing the design of clinical studies, chemistry has a vital role to play in driving the future success of drug discovery and, more broadly, the pharmaceutical sector as a whole.

A major stumbling block for the industry over recent years has been the unacceptably high level of Phase 2 attrition resulting from poor target selection. It is essential to embed chemistry at the earliest stages of drug discovery as well as within the clinical setting, to help develop a more thorough molecular understanding of disease pathways and to inform target selection.

Equally important is the need to safeguard the skills, knowledge and expertise that are necessary to translate biological opportunities into safe and effective therapeutic agents. As the capacity within UK-based industry to develop these skills amongst drug discovery chemists diminishes, an alternative model for training must be established if the UK is to maintain its global competitiveness in the sector.

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[i] For recent articles in *Research Fortnight*, see:

- Phillips, David, Big Pharma Is Broken, How Can We Fix It?, 29 February 2012 [http://www.researchresearch.com/index.php?option=com_news&template=rr_2col&view=article&articleId=1167132]
- Fox, David, Keep Making the Tablets, 16 May 2012 [http://www.researchresearch.com/index.php?option=com_news&template=rr_2col&view=article&articleId=1190844]
- Downs, Mark, Drug discoverers must adapt to a more complex world, 30 May 2012 [http://www.researchresearch.com/index.php?option=com_news&template=rr_2col&view=article&articleId=1195611]

For a recent article in *Chemistry World*, see:

- Campbell, Simon, Protecting patients at all costs, 23 August 2012 [http://www.rsc.org/chemistryworld/2012/08/protecting-patients-all-costs]

[ii] For more details, see

- Chemistry for Better Health – A White Paper from the Chemical Sciences and Society Summit (CS3) 2011 [http://www.rsc.org/images/Chemistry-for-better-health-cs3-white-paper_tcm18-222884.pdf]

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