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Opinion
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Why Bother?

Colin Suckling*

University of Strathclyde, Department of Pure & Applied Chemistry, Scotland

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***Corresponding author:** University of Strathclyde, Department of Pure & Applied Chemistry, Scotland; Tel: (44) 141 548 2271; Fax (44) 141 548 5743; Email: c.j.suckling@strath.ac.uk

Opinion

Although a nihilistic title, this opinion piece is an encouragement to positive thinking and action in the fields of chemical biology and medicinal chemistry. So I'll take two challenges: why bother to teach chemistry and why bother to carry out academic research into drug discovery.

Should We Bother To Teach Chemistry Any More?

I don't think that the media in general give chemistry a fair press. The word 'chemical' through misunderstanding and misuse has acquired a pejorative tone, something that I've observed develop over the course of my career as an academic. Moreover chemistry is a mature scientific discipline and does not necessarily attract the interest of fashionable new fields of science. But this is to miss the point. It is true that the core components of the subject like thermodynamics, kinetics, functional group chemistry, and the chemistry of the elements are more or less constant. I checked and looked at my old lecture notes, which I still have. But almost everything else has changed. Substantial fields of chemistry that commanded much interest and argument when I was an undergraduate no longer have a place in the curriculum. This is as it should be. One of the characteristics of the omitted material was that it was very inward looking. To put it another way, it was chemistry that interested the chemist but didn't really do anything, or to use my favourite phrase from my old graduation speeches it didn't 'make things possible'. This encapsulates the major philosophical change that has taken place over the last half century in chemistry courses. Upon the same solid foundation of the core science as before, today we must show our students what we can do with chemistry, we must make connections for them with other conventional scientific disciplines, especially adjacent fields of biology, physics, and engineering. We must help them to become creative.

For my own students, some knowledge of biochemistry and pharmacology has been particularly important because of my field of research, medicinal chemistry and chemical biology. For some colleagues, it is spectroscopy and quantum physics that are important. The chemistry that we carry out in our laboratories produces new compounds and new materials that make a difference and make things possible for others. This echoes Berthellot's famous remark that 'chemistry creates its own object'; so much the better if that object has properties of practical value like a new drug, which brings me to the question of academic research in drug discovery.

Should We Bother To Research Into Drug Discovery In Academic Laboratories?

In principle any topic should be open to genuine academic research in a free society, although there are always limitations associated with funding, human and physical resources, and public policy. A better case for a project can be made if the researcher can explain simply and clearly why it is worth the investment in terms of its future intellectual or practical impact. Drug discovery in the academic environment can easily support both types of impact and thereinlies a powerful justification as I shall explain.

Some people say that we have such a well-resourced global pharmaceutical industry full of some of the best scientists in the world that there is no point in attempting to compete from an academic laboratory. Paradoxically this statement is correct. If all that the academic laboratory did was to reproduce on a smaller scale what big pharma does it would indeed be pointless. On the other hand, whilst holding to the goal of finding new drugs to treat unmet clinical need, if the academic laboratories do different things from big pharma they are creating opportunity. To those of us committed to such research this answer is so obvious that it's hardly worth stating. However to the wider world some justification is needed. I will give several examples, all deliberately taken from my own working neighbourhood in Scotland; other views and examples can also be drawn in support.

A senior executive of the former Wyeth Company once said to the Scottish science community that industry could not do

everything; despite its size it still faced competition for resource and had to make choices recognising the immense downstream costs of drug development. He came to Scotland to encourage research into new druggable biological targets. This approach has led to many opportunities that have migrated from the academic laboratory to the small pharma company. One recent case connected with my University is Mironid, which has a focus of activity in phosphodiesterases as targets and the associated modulation of cellular activity in disease states (http://www.mironid.com). There are hundreds more round the world which would not have been there but for academic research.

Another differentiator that can be used positively in academic research is the extent to which commercial pressures are key drivers. Big pharma has condensed because of commercial pressures for growth and revenue, a phenomenon that left an opportunity for small pharma and biotech industries. Clinical needs without strong commercial benefit are also of low interest to big pharma, which creates another opportunity niche. Again from Scotland, a prime example is the Drug Discovery Unit at the University of Dundee (http://www.drugdiscovery.dundee.ac.uk/) which is probably one of the biggest university based drug discovery organisations in the world. Established in 2006 it states that it targets 'diseases of the developing world' which are less commercially attractive to big pharma and, as in the Mironid example, has an 'innovative targets portfolio'.

I like to look at things more widely still and bring in the intellectual and philosophical side to academic drug discovery. Our drug discovery projects at the University of Strathclyde couple active research into the related chemical biology with designing, synthesising, and evaluating new molecules. In particular I think it is a good idea to approach the drug discovery process with a different paradigm from the standard in industry, namely single drug, single target, single effect. Whilst recognising the challenges for big pharma and their constraints, I would say that the industrialisation of drug discovery has also industrialised thinking. Adopting a different paradigm is liberating from constraints and has contributed to our choice of projects, two of which I'll mention.

In collaboration with the University of Glasgow we have designed, synthesised, and evaluated some novel immunomodulatory compounds based upon the properties of a protein, known as ES-62, secreted by a parasitic worm. ES-62 is known to have multiple targets and produces multiple effects molecular effects but is very good at treating inflammatory diseases such as asthma, rheumatoid arthritis, and lupus. Our small molecule analogues do the same and are highly effective in animal models of such diseases [1].

Looking at the same philosophy another way, our anti-infectives programme has DNA as its molecular target. Whilst the challenges for selectivity with DNA as a target are obvious, in a therapeutic field where the evolution of resistance to drugs is critical to their long term effectiveness and more broadly to public health, a drug molecule that touches down on many sites of an infectious organisms DNA is likely to be highly resilient to the evolution of resistance. This is exactly what we have found in our antibacterial compounds being developed by our partner company, MGB Biopharma (http://www.mgb-biopharma.com). We've not been able to generate resistance in one of our target pathogens, the bacterium *Staphylococcus aureus*, despite hundreds of consecutive challenges. Moreover we know that our drug causes many different biochemical effects when it kills S. aureus. So we have single drug, multiple targets (all on DNA, of course), and multiple effects [2].

And Good Value In the Co-Products (Not By-Products)

Returning to the teaching theme again, outputs of practical use are one thing. Another, arguably as important, is the range of skills that a good chemistry curriculum provides, analytical, conceptual, practical, mathematical, and many more. Add this to the range of knowledge and connections with other fields and the value of a chemistry degree stands out. I'm sure that one reason why many of my later PhD students found no problem in getting jobs was their comfort in interdisciplinary science together with their practical skills and underlying chemical competence. Graduates with a good chemistry degree are valuable, versatile people. This is especially true in fields such as medicinal chemistry and chemical biology, which are intrinsically multidisciplinary.

Will modern studies of particle physics will directly affect our daily lives? Perhaps they will and I think it's good to know more about the fundamental properties of matter anyway. Simply understanding more subtle details about biology won't on its own make something useful happen although it can make an opportunity. We need that key translational component, chemistry, the science that can create the objects in the form of new molecules that make the difference. What other science has room for discovery, creativity, and applicability? As the former chancellor of the University of Strathclyde and Nobel Prize winner, the Lord Todd put it at a meeting that I organised many years ago, 'Chemistry is the Queen of Sciences. Get your chemistry right and everything else follows'.

References

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2. Colin Suckling is a research professor in the Department of Pure & Applied Chemistry at the University of Strathclyde, Glasgow, Scotland, which is part of the West CHEM research school.

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