The Importance of the Industrial Academic Interface for Innovation in the Pharmaceutical Sector

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The pharmaceutical sector has in recent years suffered from a perceived lack of successful new drugs, especially blockbusters. There is much debate as to the causes of this, but the current regulatory and financial environment requires that the sector tackles new and innovative therapeutic targets that challenge its current science base. These new targets will continue the shift away from chemical entities (NCEs), to biologicals and in the longer term to explore all "drug space". "Drug space" that is not part of the current pharma repertoire includes higher molecular weight drugs e.g. nanomedicines, nucleic acid-based drugs[1], and "non-Lipinski" inhibitors of protein-protein interactions (Figure 1). As a result the therapeutic sector is actively looking outside its walls, taking lessons from the biotech revolution, for new thinking from academics and SMEs.

Examples from the past

Historically, industrial-academic contact in the NCE area has been, in general, limited to the education of new employees. This interface changed somewhat with the emergence of the biotech industry, largely based on the new and unexpected molecular and cell biology tools developed by the academic sector, especially in the US. These opportunities were seized by visionary entrepreneurs and despite the conservatism and scepticism of large companies, new businesses, such as Genentech and Amgen were formed and were successful. Large companies can be slow to take on transforming technologies, having evolved processes which support incremental technical improvements, with a view that they can later buy in additional required technologies. Some enterprising companies are currently trying to avoid idea stagnation by encouraging clusters of start-ups businesses - research incubators where less conventional ideas can be evaluated, or through creating smaller, devolved research groups with greater independence and autonomy.

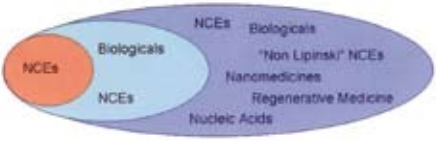

Figure 1 Diversification of "Drug Space" after the Biotech Revolution

The whole pharma sector is being squeezed by generic companies, who are predicted to have ~90% of the global market of $820bn in 2009. Many companies no longer find "me toos" commercially viable and as a result are focusing on difficult drug targets with high unmet medical need, outside the traditional pharma comfort zone. Within the non-generic market, biologicals and antibodies are competing with NCEs for market share with the expectation that within ten years they will share the revenues equally[2]. We are now seeing

the emergence of new therapeutics, occupying the last remaining untouched theoretical drug space (fig 2). Drug space can be defined by molecular size going from Aspirin (picometre) to stem cells and regenerative medicine (micrometre or larger). Early examples of larger drugs are nanoparticulates but nucleic acid-based therapeutics and regenerative medicine are just around the corner. In parallel, there are steps to broaden the market for the major drug classes, such as NCEs inhibiting protein-protein interactions and antibodies that tackle intra-cellular targets, currently the exclusive province of NCEs. Therapeutics are set to become much more eclectic with the emergence of these new modalities. These are difficult challenges and the pharma and SME sector is once again looking for inspiration from academia. It has happened before - not so long ago - and gave rise to the biotech sector. Can history repeat itself?

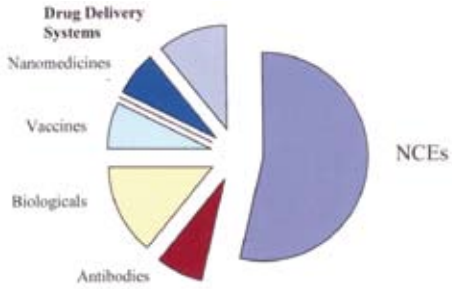

Figure 2 New Molecules Entities approved in 2008 by Class

The Communications Dilemma

A problem for both academia and industry is the lack of a common understanding of the technical issues facing drug discovery in the 21st century. Does academia, especially in Europe, have an understanding of what is required in the present pharma environment? The sides have drifted apart, perhaps due to industrial arrogance, but there is also a perception that academic freedom may be adversely impacted by working on industrial applied research. Certainly "Blue Sky" research should be encouraged - national research councils and especially the peer review system probably do not do enough to support this type of activity. However there is within Europe a considerable body of funded research that purports to be therapeutic and hence is applied research by definition. Applied research, academic freedom and "Blue Sky" are totally compatible and these seemingly different and antagonistic approaches can and must be brought together to produce radical high value new products.

How is this publicly-funded applied research strategically guided? In general it is down to the individual and the reviewer to judge whether the project objective fits into an industrial wish list. European Technology Platforms have been brought into being by the EC to advise, from an industrial perspective, how tax payers' research monies should be best spent. The Commission's objective in the therapeutics sector is both to fund academic research into new treatments and diagnostics for diseases and to support European pharmaceutical industries efforts to be more competitive. The author's experience with the ETP on Nanomedicine[3] has shown that there is a significant need for more information flow from industry to academia. Without this information, much of Europe's funded research will be non-translatable to industry, the clinic and ultimately the patient; consequently much needed new ideas will not reach the pharma sector.

The Value of Communication

Whilst academics are familiar with their departments being given a star rating by peer review, most will be unaware that industry often reviews departments and individuals independently. Industry will not only choose to work with the best scientists but also those most informed on what is needed to translate an idea to a product.

Breakthrough research requires a less conservative mentality on the part of grant reviewers. Traditionally, chemistry reviewers have strongly favoured extrapolations from the published literature. Equally it requires informed investigators to recognise where discoveries or serendipity can produce step changes for science and industry.

So we need to:

- Select fertile research areas (for industry)
- Explore good ideas or hypotheses
- Leave room for serendipity and most importantly its recognition.
- Create more academic-based key opinion leaders with industrial knowledge

What is in it for Industry?

Providing information for academic scientists is a time-consuming activity that conflicts with mounting pressures on many Business Development departments and their industrial R & D colleagues. Academics need to know whether their idea is applicable, its manufacturability and why it has not been done before. They need to understand the industrial requirements and their project's potential position in the industrial R & D process. Regrettably, much of this experience has not been published, neither is it academically accessible, and the commercial framework is changing all the time. Fortunately the traditional secrecy barriers are slowly being pulled down, as the need to search globally for ideas takes root in forward looking companies. For academia the benefits are fiscal, highly rated publications being in the driving seat for new industrial sectors and the identification of new healthcare areas which can help patients.

What is in it for Academics?

Whilst some individuals are perfectly happy to just publish their research, some departments are increasingly trying to build bridges with industry. Their aim is to increase potential funding - but also to solve real healthcare problems. There are perhaps two approaches to applied research:

- *Laissez faire* (default strategy)
- A more informed (but *not managed*) strategy.

Given that academics by and large are not familiar with the patent literature or current industrial priorities the former approach is somewhat wasteful, albeit it could produce a "Black Swan"[4], a serendipitous discovery that would produce a paradigm shift. Industrial experience is not well documented, but knowledge of it could reduce time spent on research with no possible commercial translatability. It is important that commercial information and experience is available to academics, but that no attempt should be made to impose industrial management processes. It is better to know and understand the perceived industrial roadblocks from the outset, rather than to travel hopefully.

The known obstacles to the market

Very often translatability of academic research is predictable from the outset, or if the route is not so clear then at least the road-blocks can be identified and strategies developed to overcome or bypass them. The author has come across many such predictable and manageable road-blocks[5], the following are purely illustrative!

Drug Pharmacokinetics

The importance of *in vivo* DMPK studies is often not appreciated by academics, especially those of inorganic materials that have not commonly been into man, for example silica and gold particulates. Very significant work has been done on gold imaging and therapy, but unless there are appropriate clearance studies these will remain in academic laboratories and will not be translated to the clinic. Another area requiring much more *in vivo* work is polymer therapeutics; polymer clearance being very difficult to monitor *in vivo* or in urine or faeces. Synthetic gene therapy vectors have also stagnated because of a reluctance to carry out *in vivo* studies.

Drug Stability

In the drug delivery field much effort has been expended on drug release systems exploiting the lysosome's lower pH, following endocytosis of a delivery system. Such systems often use a stabilised Schiff's base, consequently they are inherently unstable to low pH. To produce a marketed product from such a conjugate requires a simple reliable process and low exposure to water even at pH 7, to ensure that batches are analytically reproducible to regulatory requirements. The field of antibody drug conjugates has wrestled with this problem for a decade and has now adopted a manufacturable stable linkage approach - this industrial lesson has not transferred into related academic research, often with disastrous results on scale-up.

Polymer Therapeutics

The use of polymers in therapeutics is part of a multi-billion dollar sector. Aggregation of some polymers could lead to anaphylactic shock or immune responses, but polymer self-association studies are often left until the pre-clinical stage. Although nature has evolved natural polymers not to aggregate at low concentrations, commercial products are formulated at high concentrations.

Industrial Context

Often the answer as to why a concept has not been implemented before is there is no appreciation of what the advantages must be. An example here is molecular imprinting of polymers to a therapeutic target. This technology requires a substrate at a one-to-one ratio to imprint an expensive polymer. Such systems often compete with antibodies, which have much higher affinities and are cheaper and easier to scale up. Understanding the industrial context of your research is important if you are to take make the most of your efforts.

Cost

DNA cages are an interesting way to entrap a drug, which potentially could be released by a particular mRNA relevant to a

specific disease. Nucleic acids are, however, very expensive drug delivery materials when accessed by chemical synthesis. It is likely that the future of nucleic acid therapeutics lies in other directions where they are the agent rather than the formulant or drug delivery system.

Analytical Challenges

The new types of drugs being discussed throw up many analytical challenges. Analytical chemistry is often regarded as routine but with the advent of such diverse drug types it is a challenge for GMP and *in vivo* studies. It may even be a significant obstacle to progressing to development; a point that is often not appreciated by those not directly involved.

What can we do to improve industrial-academic communication?

This is a challenge which has no easy solution but it must involve more effort from the industrial sector. The following are ideas but each researcher or department should have a local strategy.

- Better industrial peer review of applied research proposals
- More effective industrial contacts with universities
- More industrialists connected with major research departments
- More sabbaticals in industry and *vice versa*
- A change in academic culture which encourages and rewards real innovation and entrepreneurship in Europe
- Each academic department developing an industrial liaison policy
- An available source of information on industrial priorities
- Industry should share its specialised technologies and expertise
- Create "reverse symposia" on what industry needs or what they do not know

Summary

For the pharmaceutical sector to survive in Europe it needs the support of academia. There is a need for more industrial experience to be available to the academic sector, which should be encouraged to find original solutions to serious healthcare problems.

Equally for academia to flourish in Europe it needs the continuation of its science based industries and a dialogue with industry.

Another question which needs answering is whether the US is better than Europe in producing translatable research? Perhaps the streak of entrepreneurship is not so evident in European culture, for cultural or fiscal reasons. This aspect will not be changed by spending yet more money on research, and it varies quite considerably between European countries. R & D is now a global activity within the industrial sector - no longer restricted to its national or continental boundaries.

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