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Jürgen Drews discusses the future of the industry

Interviewed by Rebecca N. Lawrence

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What do you see as the key research bottleneck and how would you optimize the discovery process to increase the success of development candidate identification?
We now have relatively easy and abundant access to gene sequences and to proteins. Hence, we can identify targets, but only on a hypothetical basis and targets really need validation to be useful.

Everyone has a rather different idea about what validation really means – it means to increase the credibility of a target in the context of drug therapy for a particular disease using a stepwise process. In other words, you postulate that a particular gene product contributes to a particular disease phenotype. This is not so difficult. However, showing that a hypothetical target is indeed a good target can be difficult and can require some very complex biology. So far, this area has only partially benefited from techniques of automation and robotics, so the throughput is still relatively low. Even if you start with a huge number of potential targets, it is not easy to validate even a few of them to such a degree that they can be used for identifying novel compounds and for developing these compounds in preclinical and then clinical models.

There are several techniques to try to get around this: we can use genetic techniques (e.g. knockins and knockouts), developmental biology (Exelixis is trying to do this), or more conventional animal models. Unfortunately, these techniques are all quite complex and involved, corresponding to the nature of the problem. However, it is essential to validate these targets first before we throw lots of money at them and build a complete chemical program around them. This is one of the things that companies struggle with.

I also think that the conventional ways of using combinatorial chemistry by many people has been rather thoughtless. They did not think much about the validity of each target but rather nominate many targets and then throw huge numbers of compounds at each of these targets and identify hits. If they confirm the hits (which is not always the case), they then start to think about the particular compound in question and optimize the result to develop a lead. But the combinatorial chemistry that has been used is not very targeted and is really just diverse chemistry. A study by Bohacek and colleagues[1] showed that if you synthesize all the compounds that contain just the elements that are the main building blocks of drugs (C, N, O, H, Ph, S,Cl, Br and F), keep the MW below 500, and only synthesize stable compounds, you can still produce an astronomically large number of possibilities (10^{62}–10^{63}). This figure is totally out of proportion with the number of compounds we actually know (a few thousand). It is like comparing one proton to the mass of the sun.

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I guess the trend that can now be observed in the biotechnology industry is to concentrate on 5000–10,000 interesting protein targets. Once we know what these targets are, and have a certain degree of validation for each one, then we should use combinatorial chemistry in a much more targeted way within the confines of the structure of the particular target. It is certainly not easy to find the right ligand and to understand the structure and function of so many proteins, but at least it is a task that is within the scope of what the industry or the academic community can do. It is probably much bigger than the Human Genome Project but with the right technology and the right coordination between institutions, the task can be accomplished within a couple of decades. This seems to me the new thrust in biotechnology.

There are many companies that are concentrating on the three-dimensional structure of proteins instead of the structure of genes. We are using many chemical tools that have been developed rather quietly, such as better methods for X-ray crystallography and for molecular modelling to tailor-make compounds. Alternatively, bioinformatics (e.g. Physiome) can be used to simulate biological cascades and regulatory pathways that have an influence on selected parameters (e.g. blood pressure), and alter components of these cascades *in silico* and see what happens to the parameter. Targets are then identified that make the most sense to be studied in more detail.

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For the past decade, 'hot new technologies' have promised to revolutionize the drug discovery process, but these benefits have not materialized. Why should we therefore believe that the 'hot new technologies' of the present will do any better?
I guess whenever something new comes up, a new perspective is gained and some people (usually those that do not understand the complexity of the biology and of drug discovery) get totally hyped up. They just think that this is a new way of doing things that will make everything easier, and that if only we just follow these new paradigms, we will be hugely successful. Anybody who has studied the history of drug discovery and other fields of biology and medicine knows that breakthroughs do happen. The elucidation of the human genome, for example, will certainly be classified as such a breakthrough. However, breakthroughs not only make certain new things possible, but also show where the limits are. Things

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have to be added to these breakthroughs to make them really productive.

The main mistake people made when genomics came along was to say the following: we will know all the genes and will have combinatorial chemistry, so let us play a 'big numbers' game with all the potential targets (instead of validated targets) instead of trying to understand everything. This approach was then expected to result in leads and developmental compounds by purely empirical methods and thus to increase productivity. That has not played out as expected. We have increased our raw data numbers by orders of magnitude: numbers of a typical screening programme for a large company have risen from ~250,000 data points per year in the early 1990s to 60–100 million now. However, this has not led to a corresponding increase in productivity because most hits are meaningless. I therefore think people have now understood that you need a better understanding of things first, which is why structural genomics, proteomics, X-ray crystallography and molecular modelling are now coming to the fore. They are being used to narrow the number of possibilities to really play this game in a more intellectual and more thoughtful way.

Even if we can develop discovery technologies that really do increase the production of new chemical entities for the clinic, more time and money is wasted here than anywhere else. How would you suggest we solve this problem?

I am actually very enthusiastic about some of the new methods of pharmacogenomics. Single nucleotide polymorphisms (SNPs) have been around for years now. This method was devised by Daniel Cohen at Geneset who suggested measuring SNPs in individual genomes and establishing genomic patterns that correlate with good and untoward drug responses. This is a very crude and general method that will not work as originally designed, as there are too many SNPs in the human genome. However, if you take 20–30 genes that appear to be related to certain pathways of a particular disease and look for polymorphisms and their arrangement within these genes, then you come up with much more narrowly defined patterns that can really be correlated to drug responses in a more effective way.

For example, a recent paper from Genaissance (New Haven, CT, USA) found that responses to HGM-CoA reductase inhibitors are highly dependent on the number of polymorphisms in about five genes. They also showed that a small part of the population responds negatively (~6%). If these individuals could be genetically defined using a simple test, then you could remove the patients that have an untoward response from the trial group, and reduce the number of people required to prove efficacy of the drug from say 3000 to 700. If this is the case, then development costs could reduce by 60–70%, lowering the hurdle for development decisions in companies. Of course, this would constrain the patient population for which a drug is developed. In this way, drug therapy will become much more targeted, precise and predictable, and will move away from the blockbuster mentality. At the same time, it opens up perspectives for making the development much cheaper and for increasing compliance and acceptance.

One of the real shortcomings that I am afraid of lies in the changing roles between basic research and applied research.

Do you think the knowledge of disease-related defective genes will shift the work in industrial R&D towards prophylactic medicine?

Yes, definitely. Through genomics, and especially pharmacogenomics, it will become more diagnostic because eventually we will be able to recognize disease dispositions from individual genomes. This is never 'black' or 'white' (probably only for some monogenetic diseases), but you can say that the chances are high above the average that an individual will acquire a disease. Genetic components cannot usually be altered, especially if they are represented by several genes, but you can adapt the environment to minimize the possibility of acquiring the disease. So I guess medicine is becoming more causal, i.e. it will attack the causes rather than the symptoms.

Do you think the industry is giving enough money and time to drug delivery research (e.g. brain delivery)?

It is very difficult to say enough or not enough. The proper answer to that question implies that you know how it is going to work and that there is a correlation between the number of experiments you are doing and the outcome. I am not sure whether there is not some basic understanding that is still lacking that one needs to attack in a convincing way.

One of the real shortcomings that I am afraid of and that should be looked at lies in the changing roles between basic research and applied research. The ideal configuration would be to have institutions in both areas close to each other so that they live together in the spirit of scientific exchange and communication. But it is a serious mistake to try to influence the agenda of basic research by needs that come from the practical arena – that is not the way science progresses. Science has always progressed by finding its own problems and going from problems or questions to answers. That is the algorithm in which nature discloses itself to us. All the serendipitous and all the interesting and totally unexpected possibilities can then be exploited by more applied researchers such as physicians or drug researchers.

The only thing that I think we could and should do is to maintain the principle of having basic research institutes within the network of big companies. The important thing is to have basic research being conducted within the confines of a large company and to establish good communications between basic and applied scientists. This requires the right people. People who are interested in what others are doing, even if it is outside their own field, who will talk to each other and who will communicate. Consequently, interesting new projects will develop. We are probably doing enough research in the blood–brain barrier field in quantitative terms but not in qualitative terms.

The large companies, especially the very large ones, are not the best environment for R&D and their potential to really innovate is poor.

Do you believe that the industry can achieve the R&D productivity increases that are being demanded of it by shareholders?

If you demand something, it does not mean that what you demand is going to occur. Most companies have understood that there is an innovation deficit and that they have to do something about it. In the

past, they have responded to this mainly by trying mergers and acquisitions. In other words, if they were not productive enough to have products on their own, they would just buy other people's products and then cut down the overall organization to achieve a good balance between product portfolio, revenues, profits and costs. But in doing so, they have not really taken great care in increasing the productivity of the newly resulting R&D organizations. These mergers always occur under great time pressures and the portfolios and the projects of the acquired company rarely get the attention and scrutiny from both sides to make them stronger than what either of the two merging companies had before.

Better pharmacoeconomics could help to detect targets and to solve problems in a better way.

I would guess that this happens in 90–100% of all cases and therefore, companies that have undergone such metamorphosis are likely to be in the same position again if they cannot increase their productivity by other means. These means can only be provided by the biotechnology industry and by academic research. The large companies, especially the very large ones, are not the best environment for R&D and their potential to really innovate is poor. The smaller companies that are driven by certain scientific ideas and that are motivated by entrepreneurial spirit (e.g. Genentech and smaller similar companies) are much more innovative. Merging and acquiring is not the answer: you can do it once perhaps and try to eliminate some weaknesses. Eventually you will have to generate new ideas yourself, build up networks and develop certain skills within these networks to make sure that some of the good ideas and good projects come your way.

Do you think pharmacoeconomics is a pre-requisite for a pharmacogenetic lead discovery and development programme?
Yes, of course it is important, especially for development. There might be other forms of treatment evolving and there could be certain demographic changes that will have an impact on the morbidity and therefore change the economics. These tools have not been traditionally developed within the pharmaceutical industry. There are some companies that are quite good but, in general, better pharmacoeconomics could help to detect targets and to solve problems in a better way.

Do you think the pricing of drugs will alter in the future, especially with increasing lack of funds from Governments to pay for these new expensive treatments?
There will be limits to everything – it is quite obvious that not everything can be paid for. Therefore, there must be priorities and I just hope that the priorities will be set in such a way that the most innovative techniques and drugs will be generously funded with respect to drug prices. I find it much more acceptable that new drugs that do not represent a major or even modest advance but are nevertheless launched do not enjoy any price benefits and will be under price pressure right from the beginning of their existence. As long as regulatory authorities and governments, with the help of experts, distinguish between a truly valuable innovative achievement and something that is not, we can have a price bonus for important and progressive techniques. In such a way, innovative companies could secure the funds that they need to carry out their research.

What alternative pricing strategy do you think is required for third-world countries?
I have just visited a company in Argentina that has enjoyed the absence of patents (Argentina had a patent law that did not include drugs since 1880). They could therefore produce compounds such as recombinant proteins (e.g. GCSF, IFN) at a very high quality and very fast and build a market of their own that today is very valuable. These compounds have been sold with great success in Latin America and in second- and third-world markets. It might not look very pretty in the eyes of the US, European and Japanese authorities but, from a worldwide perspective, this company is rendering a great service to their society.

Now that they have a patent law that does cover drugs (since 1995), the company selects drugs that have run off patents and makes them at a quality that is comparable to what western companies manufacture. I expect that an industry of its own will develop for these markets, at lower price levels (10–20% or sometimes even 50% less), working beside the large pharmaceutical and biotechnology companies in the industrialized world. One can find regulations and trade policies to stop pharmaceutical warehouses from buying these cheap drugs and undercutting the western suppliers. It is important that these prices are not used to undermine the markets in the industrialized markets because these countries will have to pay for the research.

R&D in pharmaceutical companies is getting too much under the control of marketing people who interpret the current and future needs from marketing and sales figures of the past.

Do you think the recent problems experienced by venture capitalists in dot-com companies are likely to deter their future support of new biotech start-ups?
I do not think so because, according to my experience as an investor or as an investment manager in biotechnology, the industry is much more substantive than the dot-com industry. Even if there are not yet many products and some new methods are not as great as their inventors say, biotechnology companies have created better and more consistent value than what has been done in the dot-com field. We must expect volatility for the biotechnology companies, but I do not expect anything nearly as volatile as in the dot-com arena.

Furthermore, the biotechnology industry is not there all by itself: it relates very strongly to the AgBio, pharmaceutical and food industries. Biotechnology is clearly emerging as the discovery arm of these more established industries, as well as the 'brain' and deliverer of new concepts. While many of the biotechnology companies that appeared and disappeared do not qualify, the industry as a whole is an important intellectual and experimental foundation for many other established industries. Therefore, in the long run, this industry shows a more stable performance on the markets than other NASDAQ companies, for instance dot-coms.

What is your greatest worry/concern about current/future research?
R&D in pharmaceutical companies is getting too much under the control of marketing people who interpret the current and future needs from marketing and sales figures of the past. They extrapolate the past into the future and think that this is what is going to happen. Of course that is the only thing that will definitely not happen. The future is very open and multifaceted. By assuming that it will be a linear continuation of the past, one is making an assumption that is wrong almost by definition. And to put a future-orientated activity like research under such false premises is a fundamental mistake that has contributed very seriously to the decline in productivity of the pharmaceutical industry.

Where do you think the next major change in drug discovery will be?
I would expect the real new breakthroughs in cancer and CNS, in that order.

What do you think the next type of start-up company might be?
Structural genomics, molecular modelling and X-ray crystallography, computer simulation, and combinations between bioinformatics and genomics.

What would you like to have achieved by the end of your career?
I would like to have made a contribution to our understanding of how science works, in particular, how basic and applied research relate to each other. In my view, it is important to find better ways to exploit the results of science, basic and applied, for the progress of medicine.

Reference

1 Bohacek, R.S. *et al.* (1996) The art and practice of structure-based drug design: A molecular modeling perspective. *Med. Res. Rev.* 16, 3–50

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