Money matters

It has been calculated that to market a novel drug a pharmaceutical company has to fork out up to a staggering Euro10,000,000,000 (Source: www.forbes.com/forbes/2012/0312/strategies-pharmaceuticals-lilly-stagger-cost-inventing-new-drugs.html). It is also becoming increasingly difficult to find new moieties and this is driving the expenses further up. Furthermore, the recession does not help. However as the saying goes, necessity is the mother of invention. And one Darwinian lesson which mankind has learnt is, precisely, how to adapt. In fact pharma companies are increasingly starting to explore alternatives to increase profits. After all, profit making is a very simple formula. You either increase income from sales or decrease production costs and examples to reach these goals range from additive printing to nanotechnology to medicinal chemistry. Such techniques are being discovered or rather, rediscovered, as methods by which one can either make existing medicines cheaper, thus making them more accessible resulting in increased sales, or more effective. This editorial will discuss two novel, albeit different strategies to produce more effective medicine.

The first example revolves around Daniel Anderson, a chemical engineer hailing from the Massachusetts Institute of Technology who has recently developed a simplified, artificial version of a living cell (although without the capacity to reproduce). In the right conditions (by mixing ribosomes, DNA, a supply of raw materials and enzymes) the cell has been able to produce a green fluorescent protein. The next phase was to control the 'factory', in order to switch it on at will, and thus act only where and when needed. Thus the team enclosed the DNA in a chemical cage before encapsulating it. This cage was designed to break down when illuminated by UV light. Only once this happens can the DNA become active. This also proved to a success since mice so illuminated produced green fluorescent proteins.

The third phase involved quantifying the the yield of these tiny factories. Dr Anderson created them in a range of sizes, from 400 nanometres to 100 nanometres. The 400 nanometre version turned out an average of 190 protein molecules per vesicle whilst the 170 nanometre version managed 81 molecules. This means that the smaller the size the better the results (proportionally speaking). This also means that by making the vesicles smaller they can travel through blood capillaries more easily, and would thus be simpler to deploy. However interestingly the 100-nanometre vesicles produced no protein whatsoever. The last phase which now remains to be explored is testing the nanofactories with DNA that makes proteins which might actually act as drugs, example anticancer antibodies. Theoretically this should not pose any problems since from a ribosome's point of view, one protein is similar to another. However the challenge is the validation of the drug delivery technique. Needless to say, if successful, this will mean that a new and valuable weapon will have been added to our current armamentarium.

The second example which I am including uses the diversification strategy, by which old drugs are used for new indications. Everyone is familiar with minoxidil, first used as an antihypertensive and now used as a hair growth product, or thalidomide, first used as an anti-emetic (which the notorious phocomelia cases) and now deployed for multiple myeloma. Such switching greatly saves companies' time, as well as R&D money. Nevertheless pharma companies still have to conduct additional testing as part of such a registration process. This includes investigations as to what other proteins the drug in question is interacting with and this itself is a costly business. However a method proposed by Sivanesan Dakshanamurthy, a molecular biologist at Georgetown University in Washington, DC, is being proposed to drive such costs down.

Dr Dakshanamurthy's initial study of the method, published last August in *Medicinal Chemistry*, started from the observation that the shapes of most drug molecules are well known and publicly available. Besides there are various publicly accessible databases which are populated with information about many of the proteins found in the human body as well as what type of receptors they interact with. His team managed to build a computer model which compares information on the structures of drugs with information on the structures of human proteins, in order to find the best fit between the two. To test their model, the team used information on 3,671 drugs already approved by FDA, together with data on the structures of 2,335 proteins found in the human body. This proved to have a 91% success matching rate.

What his team are now investigating are cases where the model predicts an interaction not yet observed in clinical practice. Given the model's successful matching rate, it is hypothesised that some of these previously unknown interactions might be worth investigating. For example, the model suggests that mebendazole, currently used to combat worms, also interacts with tubulins. Since tubulins are associated with angiogenesis it might herald research on the role of mebendazole in cancer. The model also suggested that celecoxib should bind with CDH11, a protein which plays an important role in the development of both rheumatoid arthritis and metastatic breast cancer.

Nearly 27,000 molecules are approved for pharmaceutical use, and the human genome project has shown that there are at least 23,000 human proteins. Even though not all of those proteins are adequately understood to be used in the model, that still means that there are a lot of potential interactions. Furthermore screening in a computer is faster and cheaper than in a laboratory. And even if only a few new significant interactions are discovered it would have been a worthwhile exercise!

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