The Sheffield spin-off experience

Asterion

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Early in the Spring of 2000, I attended a series of increasingly animated and exciting meetings with Richard Ross, a clinician with a passion for research specializing in endocrinology, and Pete Artymiuk, an equally enthusiastic structural biologist working in Sheffield University’s Krebs Institute.

The two made an unlikely pair, Richard, the besuited, confident and learned medical man, and Pete, a rather less fashion-conscious figure, mostly found peering at crystal structures on a computer screen. I had known Pete since the early 1990s, even before I had moved from Bangor to Sheffield University Medical School to take up a lectureship in the area of polygenic disorders in 1995. To borrow an image from Monty Python, a vague vision of John Cleese’s deceased parrot flashed through my mind, but, I guessed that that could not be right, as the lectureship was at Sheffield Medical School. So I looked up a few polygenic disorders and applied for the job. Somehow, 5 years later, here I was with Sheffield’s answer to Walter Matthau and Jack Lemon’s odd couple.

Richard and I had met briefly when we were both new boys on the block in 1995. We got to know each other’s work at the water-cooler level of detail, but, as we were based at different hospitals, we did not really have much chance to interact. My head of department, Professor (now Sir) Gordon Duff encouraged basic scientists and clinicians to talk to each other as much as possible and had suggested that Richard tell me (a biochemist/molecular biologist) in more detail about his work on growth hormone (GH).

A crash course in endocrinology

Richard had made some very interesting clinical observations regarding patients with an unusual resistance mechanism to the action of GH, and soon the three of us were discussing how we might be able to collaborate. Richard explained that GH is a cytokine hormone released by the pituitary. It circulates in the bloodstream, but has a very short serum half-life, as it is a relatively small non-glycosylated protein. It has to bind simultaneously to two identical receptors on the cell surface in order for signal transduction to occur, leading eventually to cell division and growth. The GHR (GH receptor) chains must bind to opposite sides of the asymmetric GH molecule in order to undergo the required conformational change needed to activate the cytoplasmic domains of the juxtaposed GHR chains.

A deficit in functional GH signalling leads to short stature, a disorder that is usually treated by daily injections of GH. At first, GH was purified from cadavers, but, after the tragedies resulting from the administration of CJD (Creutzfeldt-Jakob disease)-contaminated material, Genentech introduced Protropin, a recombinant GH, in 1985, following on from their pioneering biotechnological production of insulin. This pathogen-free therapeutic protein heralded the era of billion-dollar blockbuster treatments. Although a deficit of GH is undesirable, a surfeit results in increased morbidity and mortality. High levels of GH result in acromegaly and can lead to gigantism when onset is pre-pubertal. When onset occurs later, the result is often manifest as obvious thickening of the fingers, brows and jaw, leading to disfigurement and, if untreated, premature death. Once again, recombinant DNA technology has been applied to the problem. Pfizer’s Pegvisomant, a GHR antagonist, offers effective, if expensive, treatment and requires chemical modification with poly(ethylene glycol) to increase the protein’s size and give it a workable serum half-life.

Figure 1. (A) GH (pink oval) binds to two identical molecules of the GHR (blue), bringing the intracellular domains (green ovals) together. (B) Asterion’s chimaeric GH linked by a polypeptide linker (grey) to the extracellular domain of GHR could theoretically exist in the forms shown, depending on the flexibility and design of the linker. (C) If locked in the intramolecular ligand-receptor form, this chimaera could act as an antagonist (left), meanwhile a flexible chimaera acts as an agonist (right).
Too good to be true

Richard had identified a mutation that inactivated the cytoplasmic domain of GHR, leading to restricted growth, even in patients with one normal copy of the GHR allele (Laron’s syndrome). Thus the mutant allele acted as a dominant-negative, probably by forming a 1:1:1 complex with GH and the normal GHR chains. This resulted in children with the unusual phenotype of normal levels of GH, but an impaired ability to respond to the circulating hormone.

We discussed ways of making long-acting GH antagonists, employing my knowledge of recombinant DNA technology with Richard’s expertise in clinical endocrinology and Pete’s structural insights. Lots of (mostly) wild suggestions were considered until we came up with possible approaches. During one of these brainstorming sessions when the brainwaves were particularly high, I even managed to invent an antagonist by mutating the weaker of the two GHR-binding sites on GH so that the modified GH would only bind to one receptor on the cell surface, mimicking Richard’s clinical observation. It would give a similar 1:1:1 dominant antagonist. A brilliant design! Sadly, Richard pointed out that ‘my’ brilliant invention had already been invented by John Kopchick a few years earlier and his company had been acquired by Pfizer for close to US$50 million. I had reinvented Pegvisomant. Great idea Dr Kopchick.

In a way, that rather comical experience (looking at the structure on Pete’s computer, coming up with Kopchick’s idea and getting very excited thinking ‘hey, this must work’), fanned our flames of optimism: maybe the three of us could come up with new ideas that would work. After all, we had lots of ideas, and surely at least one would work? Even a broken watch is right twice a day. If we thought of enough ideas, we might be able to get one with both properties and have that essential element: a patentable invention.

The Big Idea

Could we use Richard’s mechanistic insight into Laron’s to design a new therapy? Pete showed us the crystal structure of GH bound to GHR and explained the intricacies of three-dimensional structure and how the GH ligand stuck to its receptor. The concept of fusing GH to the soluble domain of its receptor soon emerged from these discussions. Depending on how we constrained such fusions, the chimaeric molecules might be able to fold up on itself so that the receptor domain bound its covalently attached ligand. This might mimic the rare dominant-negative phenotype seen in Laron’s syndrome and provide a way of blocking excess GH in acromegaly. Long serum half-life is necessary for a GH antagonist for use in acromegaly: GH is released in regular pulsatile bursts, so that any antagonist is in direct competition with the natural hormone for the cell-surface receptor. Thus the antagonist needs to be in excess if it is going to block signalling effectively. Our ligand–receptor fusion would be significantly bigger than GH alone and would have increased serum half-life, owing to its larger size.

The fusions could be produced simply, using standard recombinant DNA technology, with no requirement for chemical modifications. GH normally circulates with its binding protein GHBP (GH-binding protein), a soluble form of its receptor. GHBP is the cleaved extracellular domain of the normal cell-surface receptor. Thus, if we made our fusions with enough conformational freedom, for example by using Jim Huston’s flexible linkers based on polyglycine–serine peptides, perhaps our fusions might mimic this natural state of affairs.

More ideas

Naturally, we were quite excited. Of course we thought of possible problems. Would we be able to make the fusion proteins, and, even if we could, would they fold up properly? How would we purify and test the chimaeric proteins we wanted to make? Putting these questions aside, we began to think of applying the fusion idea to other cytokine hormones. Excitement grew, and our meetings threw up a number of alternative strategies and new targets. We gradually realized that our ideas might form platform technologies, potentially applicable to a wide range of cytokines, a wider range of disorders.

The funding problem

Our meetings could not continue like this for much longer, even though most of the ideas we generated foundered on the rocks of prior art, other people’s patent applications or
some other impracticality, a small proportion of our ‘inventions’ seemed to stand up to a little scrutiny. We also needed to stop thinking and get testing. As academics, the first thing we thought of was to write a grant application. We had lots of ideas, little experience of making proteins like the ones we were designing on the computer and, most importantly of all, not much in the way of resources to get started. At this point, the grim reality of our situation hit us. No pilot data, no history of collaboration and unproven concepts equals 3–6 months of waiting for the rejection letter from the funding body.

The commercial viability audit

Sheffield University, under Vice Chancellor Sir Gareth Roberts, had an enlightened and encouraging attitude to translational research. We filled in a form on the Sheffield University Enterprise Limited (SUEL) website. They would assess the commercial potential and help us file patents and commercialize our ideas should they stand up to scrutiny. We waited a few days and became impatient; Richard pestered David Catton, head of SUEL. The three of us talked with David. We were enormously enthusiastic about recombinant this, that and the other, platforms and diseases, the hundreds of possible products and how we could become the next AstraZeneca. In response, he asked us about development costs, markets, timelines and what patents we had filed. We were pretty clueless really. He must have thought that the three of us were naïve, stupid or, most probably, both.

The wonderful world of patents

Slightly deflated, we waited for SUEL to have our ideas evaluated by ‘one skilled in the art’. Now there is a phrase that we were to become familiar with. It is patent agent’s patter for an expert in everything relevant to any particular application. David’s background was in engineering (Xerox) and he initially seemed somewhat less excited than we were, but Richard’s endless energy and charm persuaded David that we should get Rob Docherty, a patent agent, to see whether we had anything. He would evaluate the prior art. Not just the academic literature, but also the patent databases. Rob gave SUEL the good news that he thought there was something worth filing and he proceeded to translate our ideas into another complex and at times obtuse language, that of the patent application. We wrote methods explaining how to make our ‘target molecules’; he spoke of making ‘enabling disclosures’. We discussed our initial results while he asked us to provide patent exemplification. He was (and remains) very patient with us, constantly explaining the finer points of phrases such as ‘consisting of’ and ‘comprising’, introducing us to the concepts of exemplification, claims, divisional filings, examiners reports, category B citations, inventive steps and generally providing us with ongoing tuition in the language of patents and intellectual property.

Making the pitch

Academic grant applications usually consist of various forms, cases for support and costings. We were used to writing that kind of thing, but David asked us to write something called a business plan. He advised us how to put it together, and, when we were happy with it, the plan was to go before the funders.

Long before the TV show ever rented that old factory that they use for the set of Dragons’ Den, we had to make our pitch to the Board of the White Rose Seedcorn Fund (WRSF). The WRSF is an early-stage fund, which invests in exciting new technology emerging from the Universities of York, Leeds and Sheffield. It consisted of high-flying businesspeople rather than academics. We were nervous, and, if we had known how the would-be tycoons would be treated in the Dragons’ Den, we would have been petrified. Richard and I wore suits and Pete even put on a jacket, and we persuaded them to give us a loan to get started. WRSF support, and later that of BioFusion, has enabled our company to stay afloat ever since.

Our first major shock came when the cheque arrived. One small catch: we had to start a spin-out company, and the founding shareholders would need to put in cash and become directors before the cheque could be banked. The term director is a much misunderstood and improperly used term. Directors have fiduciary responsibilities and have to consider the good of the company, stakeholders such as shareholders, creditors and employees alike. Most importantly, directors carry the can if things go wrong. So,
after lots of legal documents were signed, agreements on patent transfers were enacted, visits to see the Notary Public were executed and we put in our own cash, a new star in the biotechnology sky sparked into life. Pete Artymiuk had come up with the name Asterion and a logo that was soon trademarked. He chose the name because our company was based on ligand–receptor fusions or chimaeras, and Asterion was a chimaera: part man part bull, the star at the centre of the labyrinth on Cretan coins. Websites were claimed, articles of incorporation were written and 288a forms signed and filed. The last are the documents sent to Companies House declaring our status as directors of the company along with Company Secretary, Richard Birtles.

**Exemplifying the patents**

So all we needed to do now was to make the purified fusion protein and then see whether it blocked GH signalling and, hey presto, Translational Research here we come! I have often heard academics espouse the view that getting the funding is usually more difficult (and certainly less enjoyable) than doing the science. Not quite so for us. Possibly because the process of presenting our business plan to the WRSF Board was such a novelty to us, we very quickly had to get on with producing results to support our patent applications; no long months of waiting for us this time. In order to make the best use of our newly acquired funding, we decided to operate the company on a virtual model. The founders were seconded part-time to Asterion and took on the roles of MD and Chief Scientific Officer. We would use our limited resources to set up a research contract with the University and the lab team, Dr Ian Wilkinson and Dr Sarb Pradhananga, were soon busy in the laboratory. Despite their hard work and dedication, progress in the laboratory was steady, but not spectacular, at first. Undaunted, they plugged away, gathering experience and gradually solving the problems that arose along the way. Ian and Sarb began to make the molecules that we had designed on paper, but our backers were sometimes less than completely impressed with our progress than we were.

**Funding squeeze**

Soon the money that we had raised was running out, so we went on the VC roadshow. VC in this case stands for venture capitalists. The VC is out to get a serious return from their investment. We talked to all sorts of possible investors. Rich Americans, investors who slept through our presentation, investors who said we had too many ideas and needed to focus, others said we hadn’t got enough vision and were blinkered. Some liked our GH ideas, other hated them. In fact, most potential investors had their own pet target proteins and diseases. If we suggested a target such as a new-generation erythropoietin (the biggest selling biotech drug to date), they said the market was crowded. If we suggested something less well known than a current blockbuster, we were told that there was no proven market. Some showed up only to tell us that “we are not investing in biologics” or “we only invest when you have Phase II clinical trial data”. We were focused on biologics and had neither Phase II data nor Phase I. Come to think of it, despite a lot of hard work in the laboratory, we had few data of any sort at the time. It seemed like we could not win. To be fair, the period following 9/11 was a hard time in which to raise VC money. So, after some pretty gruesome ordeals in the VC arena, we gave up trying to raise fresh investment capital. Our business advisors said we were unworldly and naïve in the ways of business. There were rumours that we should be wound up. We almost ran out of funds, and the Asterion star seemed to be fading away.

**A biotechnological entente cordiale**

In the nick of time, Richard’s contacts in the pharmaceutical industry agreed to meet us. Peter Grant of BioFusion [an AIM (Alternative Investments Market)-quoted company set up to commercialize University of Sheffield intellectual property] had joined us acting as a CEO. He understood our science and had a background in biotechnology. Peter led us down to the swanky head office of a pharmaceutical company in a part of London where an academic’s salary wouldn’t be enough to buy a small parking space. We
presented our ideas to the men from big pharma, and Peter Grant must have felt that keeping us in order was like trying to herd cats. He was instrumental in our initial success, helping Asterion strike a joint research and development deal. However, that in itself turned out to be heralded in a much more dramatic manner than we would have liked. The signed agreement arrived by fax late on a Friday night preceding a public holiday. In fact, it arrived so late we thought that our French pharmaceutical collaborators had pulled out of our lifeline deal. We had a miserable few days, thinking how we would break the news to our faithful researchers, but, eventually, we found the fax, and the deal marked the start of a truly collaborative and very enjoyable relationship. More patents were filed, and David Catton chaired our Board, tactfully hid his frustration at our constant excursions into academic territory, while transparently beaming his approval at the way we worked together to achieve milestones and generated (too) many new ideas. Business advisors came and went. David steered Asterion with good humour and enthusiasm. Sometimes he even succeeded in making us act like a real company directors. So much so, that, in recent years, we have suggested that the Company might consider actually paying us.

**Academic indifference**

In the early days, some of our academic colleagues were a little scornful of our foray into the world of commerce. Our work was viewed by some as contract research, to them the academic equivalent of selling one’s body for physical gratification. We certainly had an overhead-bearing contract to fund research, but they were our research ideas, and the University was a shareholder in Asterion as well. There is no doubt that, while we filed patents and pitched for funding, we could not put all our effort into academic matters, but we all continued to run reasonably successful research groups outside our Asterion-related projects and contributed to administration and teaching. We dropped no academic commitments and worked on Asterion mostly in our own time.

**Publish or patent?**

Academics are often concerned that commercializing their work might stop them publishing. Although it is true that we didn't publish academic papers on the Asterion work very quickly, the reason for this had nothing to do with secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial. The programmes we had embarked on represented secrecy; we simply wanted to publish something substantial.

**Asterion today**

Through it all, the three founders have remained friends and our collaboration has intensified. Sometimes we see eye-to-eye immediately, sometimes after a few (metaphorical) punches have been exchanged. It has been very hard work, but it has also been a truly enlightening and, at times, frightening few years. Above all, the spin-off experience has been a hell of a lot of fun and I am sure that will help us get through the huge challenges and changes that lie ahead for Asterion. Richard Birtles as Company Secretary is now ably assisted by Ross McMaster, who keeps an eye on our budget. Our current Chairman, Kevin Bryett, non-executive director David Lawrence and CEO Ray Barlow are relatively recent supporters of the Asterion cause. They bring new skills and experience to add to the founders’ enthusiasm and curb their academic tendencies. Our early ideas are now embodied in AFT™ and ProFuse™ technologies. No doubt there will be many more presentations to snoring VCs and discussions which are really fishing trips in the Asterion pond, but we hope that one or two of these will help to take Asterion forward, and maybe some day we might even get paid for all our work! I am often asked if I would recommend setting up a spin-out company. The Asterion experience has been hard work, educational, frustrating and incredibly exciting. Would I recommend the spin-out route? Yes, I think I probably would.

Jon Sayers trained in synthetic nucleic acid chemistry with the Stan Jones/Dick Walker group in Birmingham in the early 1980s and moved to Fritz Eckstein’s Max Planck group in Göttingen, Germany, in 1986. Leaving Germany in 1991, he took up a New Blood Lectureship in the Biochemistry Department, University College of North Wales, Bangor, where he developed interests in proteins secreted by human pathogens. He then moved to Sheffield Medical School in 1995. Together with Richard Ross and Peter Artymiuk, he founded Asterion Ltd, a biotechnology spin-out, in 2000. He holds a personal chair and is Head of Infection and Immunity, Sheffield University Medical School.

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