The rise and rise

of Cobra Biologics

Julian Hanak
COMMERCIAL DIRECTOR AT COBRA BIOLOGICS

COBRA BIOLOGICS WAS FORMED ON KEELE UNIVERSITY SCIENCE AND BUSINESS PARK (KUSBP) MORE THAN 20 YEARS AGO. THROUGH GRANTS AND USING KUSBP'S POSITION AS AN IMPORTANT PART OF THE NORTH WEST BIOTECH CLUSTER – THE THIRD LARGEST BIOMEDICAL NETWORK IN THE UK, GENERATING £5 BILLION ANNUAL SALES – COBRA HAS GROWN FROM ONE OFFICE TO A MULTINATIONAL COMPANY. JULIAN HANAK, COMMERCIAL DIRECTOR AT COBRA BIOLOGICS, DISCUSSES THE PROGRESS AND RESEARCH OF THE BIOPHARMACEUTICALS COMPANY.

When we formed Cobra Biologics in 1992, the company took up just one room in the building that it now completely fills. At this time, biotechnology was seen as a niche and pioneering area within the pharmaceutical industry. By using the position KUSBP holds as part of the North West Biotech Cluster, as well as its research community and expert business advice on hand we have won grants and become a major part of the biotechnology industry, which generated $100 billion of revenue in 2013.

My vision, 'the cell as the bioreactor', was to engineer cells and organisms used for production and customise them to perform new functions. Thanks to our position on KUSBP we have collaborated with top universities, including Keele and Manchester, to increase our chances of receiving funding as well as benefiting from expertise to fulfil our ambitions.

Upstream processing at Cobra Biologics... 50L Microbial fermentor

One partnership with the University of Oxford, alongside grants from the UK Department of Trade & Industry SMART and SPUR, has seen the launch of an antibiotic-free maintenance system; Operator Repressor Titration technology (ORT). ORT produces plasmid DNA without antibiotics, antibiotic resistance genes or any other selectable markers in *E. coli*.

Before the creation of ORT, the isolation of bacterial transformants and subsequent stable plasmid maintenance was traditionally accomplished using plasmid-borne selectable marker genes. The marker genes typically encode resistance to an antibiotic such as ampicillin, or alternatively encode an essential gene that complements a host cell deficiency (auxotrophy).

ORT enables:

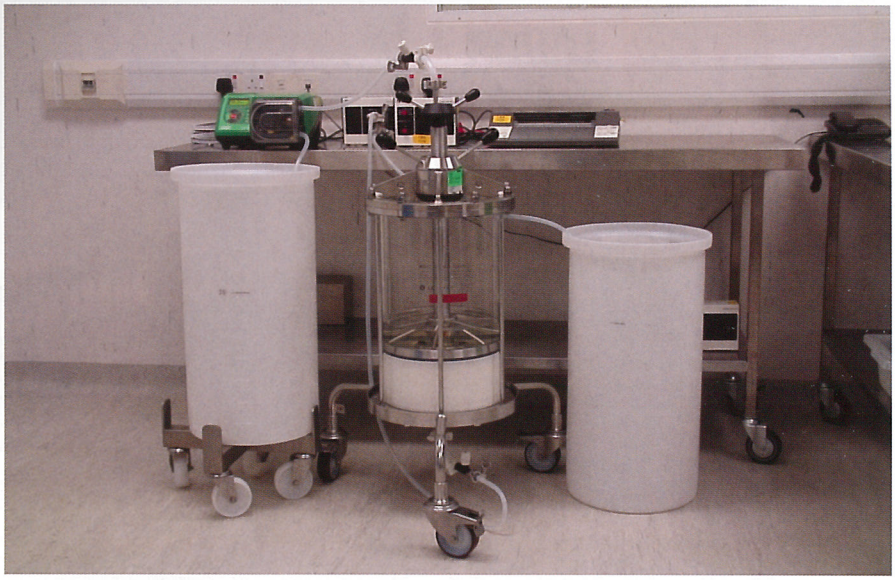
- Smaller plasmids to be produced for improved antigen gene delivery in DNA vaccines
- A plasmid backbone with an improved safety profile to maximise the efficiency of therapeutic gene delivery when administering gene therapy
- Antibiotic-free fermentation with potential for enhanced product yields through enhanced stability

ORT was first administered by Prof A. McMichael of Oxford University during a clinical trial in an International AIDS Vaccine Initiative (IAVI) project in July 2000. From that moment Cobra and ORT were heavily involved in collaborative projects to develop a vaccine for HIV and AIDS. This work, also supported by the South African AIDS Vaccine Initiative (SAAVI), was at the forefront of the fight against HIV and AIDS. The project has seen us work with the University of Cape Town for Phase I and II clinical trials, as well as GlaxoSmithKline and IAVI for process development and manufacturing of two further HIV vaccine candidates for evaluation in clinical trials.

However, ORT is not the only success story from Cobra's grant funded research. Also as part of our Keele University location, we have established a strong track record of gaining value from grants.

Funding for other major collaborative projects has come from the European Commission Framework Programmes for Research and Technological Development, better known as the Fifth, Sixth and Seventh Network Programmes. Through this we took bacterial strains (*Bacillus subtilis*) used for industrial enzyme production, for example biological washing powders, and genetically engineered them to be suitable for biopharmaceuticals production. We did this by removing the host's 'feeding' proteases (which would otherwise digest the product) and spore-forming functions (making it easier to use in a modern multi-product manufacturing facility). The platform, termed BacilXpress, was developed in collaboration with The Defence Science and Technology Laboratory (Dstl) and Newcastle University.

This funding has also aided us in getting our MaxXpress[1] (Maximum Protein Expression) technology, enabling the rapid production of recombinant proteins from mammalian cells, off the ground, and the Technology Strategy Board (now InnovateUK) Knowledge Transfer Partnership fund has been crucial in launching a variety of other customer-focused technologies.



Downstream processing... Chromatography column

With the success of our research, our reputation grew and with the help of the TSB grants, we were able to found spin-out company Prokarium, a biotech company based on our Keele University Science and Business Park site. Prokarium's vision is that all protein vaccines can be delivered orally. It uses its own Vaxonella platform, designed to take antigens from gene sequence to immune response with a standardised production process, regardless of the type of antigen used. By making vaccines that can be delivered orally they are more accessible to travellers and people living in rural and resource-poor areas, as well as reducing costs and time for vaccine manufacture.

This vaccine is expressed in attenuated strains of *Salmonella enterica* which have been proven to be safe in clinical trials. With this orally delivered version, the bacteria are ingested, pass through the stomach and then traverse the lining of the small intestine via M cells into lymphatic nodules called Peyer's patches; there they are phagocytosed by antigen-presenting cells (APCs), such as macrophages. The antigens are then processed and presented by the APCs to stimulate humoral and cellular immune responses. Salmonella is a potent immunostimulator, so no additional adjuvant is needed to elicit a strong, protective immune response.

Our latest initiative, as a result of funding from the network programmes, is the ELIMOX project[2]. This seeks to develop a bacterial pharmaceutical therapy for the treatment of Primary Hyperoxaluria, a severe and debilitating inherited disease which is present at birth. Most patients develop kidney stones and nephrocalcinosis at very young ages (usually under the age of 10) and progression of renal failure is followed by systemic deposition of CaOx and premature death. The ELIMOX Consortium has three SME-partners; Cobra Biologics, Oxthera[3], project co-ordinator based in Sweden, SymbioPharm[4], based in Germany, and nine Research, Technology & Development (RTD) partners.

The project approach is to use the metabolic potential of a naturally occurring microbe, *Oxalobacter formigenes*, to eliminate toxic compounds from the blood. To achieve our aims we started manufacturing the anaerobic bacterial product for administration in the gut. The

Cobra Biologics microbial and virus production facility at Keele University Science and Business Park

consortium developed analytical tools to verify the quality, delivery and activity of the bacterial product. Finally, the clinical development of the bacterial product was initiated to verify clinical efficacy and safety.

As part of the North West Biotech Cluster we are afforded access to collaborations with multinational companies. Astra Zeneca, Bristol-Myers Squibb, Lilly and Actavis – as with us – have all been integral to the research and development work of the cluster and a combined £5 billion of annual sales. In support of AstraZeneca's programmes for the identification and evaluation of conventional drug targets Cobra supplied know-how and licences to its DNA manufacturing technology. Our expertise in DNA manufacture was recognised by John Stageman, former Vice President, Enabling Science, Technology & Information for AstraZeneca, citing Cobra's expertise having a "direct benefit to our (AstraZeneca's) discovery programmes".

Cobra has been able to build a stable base at Keele; a crucial factor when considering the incredibly high standards required to become, and continue to be, a Medicines and Healthcare Products Regulatory Agency (MHRA) licenced manufacturing facility. But research does not stop now. Current projects, spearheaded by the newly appointed Chief Scientific Officer Dr Daniel Smith, are looking to enhance our capabilities in Adeno Associated Virus (AAV) production, the development of a new plasmid DNA production and purification process, enhancing our DNA offering and, as part of our ongoing collaboration with the UK academic science base, using KTPs to focus on the fermentation development and optimisation for the expression of microbial proteins.

The Keele University Science and Business Park environment, facilities and location as part of the North West Biotech Cluster, on a University campus, has given us the ability to attract high-profile collaborators and funding to grow. By continuing to expand, we will be able to complete further research, and with further grants and help increase not only Keele University's reputation as a thriving biotech research hub, but also the UK's.

References:

1 http://www.cobrabio.com/Services/Technologies/Maximum-Protein-Expression-(MaxXpress)/Features-and-benefits

2 http://elimox.se

3 http://www.oxthera.com

4 http://symbiopharm.de/en/home.html

www.cobrabio.com