Intracellular drug delivery technology for cancer treatment

BioMoti is a specialist pharmaceutical company investigating targeted delivery of therapeutics to the intracellular space of cancer cells, thereby dramatically increasing efficacy whilst reducing side effects. The company's oncojan technology is compatible with a range of drug classes from small molecules to larger biologicals and BioMoti's lead oncojan-based ovarian cancer candidate has shown promising potential in early preclinical studies.

BioMoti is a new company seeking to transform the treatment of cancer by targeted delivery of therapeutics to the intracellular space of cancer cells and thereby dramatically increasing efficacy whilst reducing side effects. The company's oncojan™ technology, an innovative therapeutic delivery platform, initially developed at Queen Mary, University of London, is compatible with a range of drug classes from small molecules to larger biologicals, and BioMoti has developed an oncojan-based ovarian cancer lead candidate that has shown very promising potential in early preclinical studies. The technology platform was developed from original research in the laboratories of Professor Joanne Martin at Barts and The London School of Medicine and Dentistry, which is part of Queen Mary, University of London.

Transforming cancer treatment

Oncojans are a new class of advanced therapeutic microparticles that gain entry to the interior of cancer cells where they slowly release drugs at the point of need whilst sparing healthy tissue. This has the potential to transform the clinical treatment of cancer by dramatically increasing the efficacy of cytotoxics or new chemical entities whilst reducing their devastating side effects. Early preclinical studies of BioMoti's ovarian cancer candidate compared to the current clinical standard of care have shown 65-fold reductions in tumour burden, a doubling of median survival and significant decreases in toxicity.

The delivery platform is compatible with a range of therapeutics including small molecules, peptides, proteins and nucleic acids, as it is possible to use existing and established drug carrier technologies, such as biodegradable polylactic-co-glycolic acid (PLGA), for the microparticles.

In February of this year, BioMoti completed an initial private finance round of £150,000 under the Seed Enterprise Investment Scheme (SEIS). The financing was led by the Oxford Technology OT(S)EIS Fund and an existing shareholder and will be used to progress the oncojan delivery platform towards a regulatory compliant preclinical package that will support the future clinical development of the company's ovarian cancer lead candidate.

In addition, last August BioMoti became one of the first SME recipients in a £180 million Technology Strategy Board (TSB) Biomedical Catalyst funding programme. The scheme was set up by the UK government in 2012 to provide support for the best life science opportunities arising in the UK. BioMoti is using this first TSB award to attract private risk capital and launch the commercial development of its ovarian cancer candidate. The award follows successful proof-of-concept studies within the associated academic laboratories of Professor Martin and Professor Iain McNeish (now at University of Glasgow) at Queen Mary, University of London, as well as technology validation by a major global pharmaceutical company.

"We are very excited about our lead ovarian candidate MOTI1001," says BioMoti's CEO, Dr Davidson Ateh. "Ovarian cancer is a devastating disease with a huge clinical need for efficacious therapies. Median survival is only three years and there have been no major advances in treatment for more than 20 years. After surgery, patients are generally offered a combination of paclitaxel and carboplatin, two chemotherapies with very serious side effects. However, MOTI1001 is a paclitaxel reformulation based on our oncojan technology with the potential to considerably improve the efficacy profile and reduce side effects.

Early MOTI1001 preclinical studies in relevant models compared to the current clinical standard of care formulation, Taxol, have shown remarkably good results and we are in the process of refining our regulatory compliant preclinical development plan for MOTI1001 having just completed a comprehensive market research and commercial development plan under our TSB Biomedical Catalyst project. Our main challenge is getting manufacturing to GMP standards right. This is absolutely feasible but for a complex biotherapeutic like MOTI1001 there is a higher initial cost and longer timescale than there would be for a typical small-molecule chemical production project.

"Once we raise funding, we expect to be ready for clinical trials within two years and to reach Phase 2 within another two to three years. Ideally, we would like to partner early and co-develop with an experienced pharmaceutical company, but we are gearing up to raise venture capital that will enable us to progress MOTI1001 independently to Phase 2, where succesful trials will certainly result in a very valuable asset and high return on investment."

Exploiting phagocytosis for drug delivery

Dr Ateh joined Professor Joanne Martin's laboratory in January 2005 where in addition to other topics, she was studying the phagocytic capacity of neurons. The laboratory had shown that neurons were capable of ingesting other dying neurons and very large synthetic particles (greater than 2 microns). Neuronal phagocytosis may have implications in neurodegenerative disease where healthy cells may ingest dying neighbouring cells and accelerate disease progress. Ateh joined the laboratory after completing a PhD in bioengineering and

realised the mechanism could be exploited to deliver drug-loaded microparticles to nerve cells. Martin and Ateh attracted a number of proof-of-concept grants to the academic laboratory from the Heptagon Fund, the Biotechnology and Biological Sciences Research Council (BBSRC) and the Barts and The London Charity (BtLC) to demonstrate this novel drug delivery concept.

"We quickly grew confident about the potential to commercialise the drug delivery platform and BioMoti was incorporated as a virtual entity in June 2009 after I was awarded a Royal Society of Edinburgh/BBSRC Enterprise Fellowship," says Ateh. "The Fellowship, also supported by Scottish Enterprise, enabled me to focus on commercialisation for a whole year whilst obtaining business training at the Hunter Centre for Entrepreneurship at Strathclyde Business School and accessing a significant network of bioentrepreneurs and mentors."

During proof-of-concept studies, BioMoti probed the molecular mechanisms that could increase the ability for biological cells to ingest microparticles and discovered that coating with CD95 protein dramatically increased uptake by neurons that express CD95L. CD95 and CD95L (also known as Fas and FasL or Apo-1 and Apo-1L) form a natural receptor-ligand system primarily known for the induction of apoptosis (CD95 expressing cells undergo apoptosis when bound to CD95L).

"We further discovered that the CD95-CD95L system was important in tumour biology," says Ateh. "Cancer cells can overexpress CD95L and it has been shown to be used as a mechanism to induce the apoptosis of infiltrating T-cells that express CD95, a strategy for the tumour to avoid immunesurveillance and grow unchecked. More recent data suggests that cancer cells use the CD95-CD95L system to promote tumour growth, motility and invasiveness. Indeed, pathologists have long noted that in many tumours expression of CD95L is correlated with increased malignancy and poor prognosis."

It was noted that the ability of CD95-coated particles to induce enhanced uptake in the nerve cells was replicated in cancer cells, and the mediation of this 'phagocytosis like' process was a novel and unknown property of the CD95-CD95L receptor-ligand system. "We have since focused BioMoti's activities entirely on oncology applications due to the accessibility of tumours compared to the nervous system, where there is a blood-brain-barrier, but importantly because there are more therapeutics available for cancer than the poorly understood nervous system diseases such as Alzheimer's, Parkinson's or motor neurone disease," says Ateh. "In oncology, the aim is to obliterate the tumour cells and it is always a simpler strategy to destroy rather than attempting to protect or rescue cells, as would be the case for nervous system diseases. In addition, commonly used chemotherapies have very serious and horrendous side-effects that we have the possibility to reduce with our technology by targeting the cytotoxic drugs to tumour cells whilst avoiding healthy tissues.

Davidson Ateh (centre) and his team performing cell culture work at the Blizard Institute tissue culture laboratory at Queen Mary, University of London.

"In addition to focusing on fundraising and partnering to get MOTI1001 to the clinic, we are also working on early-stage proof-of-concept for a number of follow-on candidates," he adds. "We are considering not only existing generic chemotoxins, but also new chemical entities in development that could benefit from an improved therapeutic index. BioMoti will not establish a drug discovery capability but rather aims to co-develop candidates in partnership with established drug developers such as large biotech and pharma companies."

'Semi-virtual' business model

BioMoti operates according to a 'semi-virtual' business model. The associated academic laboratory had raised just over £500,000 in proof-of-concept grants and developed 'very promising' preclinical data. In late 2011, with momentum gathering, the company appointed the experienced bioentrepreneur, Dr Keith Powell (previously CEO at Polytherics, current Chairman at Domainex and Canbex as well as on the Mayor of London's Technology advisory committee) as Chairman. BioMoti was awarded a Technology Strategy Board (TSB) Biomedical Catalyst Feasibility grant in August 2012 and closed an initial seed investment round early this year. It is now located in an office and laboratory suite at The Queen Mary BioEnterprises Innovation Centre where it carries out its core research but also works in partnership with collaborating companies and contract research organisations on defined work packages in manufacturing, preclincal studies, and regulatory and commercial strategy.

"The advantage of being semi-virtual is that we are able to keep fixed costs low and we all know how important it is to be capital efficient in the current environment," says Ateh. "Working with CROs, we are better able to plan expenditure and use the tremendous expertise available for a limited time as and when needed. Occasionally, it can be difficult for external organisations to fully understand the technology and aims of the biotech originator compared to internal staff and this may be perceived as a disadvantage. However, this can be overcome by maintaining good and regular lines of communication and further sub-dividing work packages in order to create easily understandable and achievable milestones."

Partnerships based on technological expertise

BioMoti expects to develop a number of partnerships around the oncojan technology delivering specific drug candidates to specific cancers: "We believe that due to the growing capacity of the CRO industry, we will be able to grow towards sustainability without needing to change our semi-virtual approach. However, we are a very flexible team and regularly review strategy; and we will respond as necessary to any change of circumstance and new opportunities," Ateh adds.

BioMoti's technology could potentially work as a delivery vehicle to other CD95L-expressing cells such as nerve cells. However, according to Ateh, there is still an effort to understand the basic mechanisms of a lot of neurological diseases and therefore a paucity of effective targets against which to develop drugs. "The other point is the importance of maintaining focus for success within a biotech company, and we believe the cancer segment is the right area to develop our technology as we could make a quicker

and bigger impact to patient outcomes," he says.

BioMoti's laboratory at The QMB Innovation Centre is mainly focused on molecular biology with tissue culture, small-scale protein expression and in- vitro analytical assay capabilities. Because of its proximity to Queen Mary, University of London's Barts and The London School of Medicine and Dentistry and The Royal London Hospital, the company has very good access to core facilities, for example for flow cytometry or advanced microscopy, and also contact with relevant clincal and academic experts.

"The early-stage work we do at BioMoti enables us to validate early ideas, optimise candidates and build confidence in therapeutic candidates," says Ateh. "Working with partner companies, we are then able to complete further studies such as optimising drug encapsulation with our manufacturing partner or study pharmacokinetics of our candidates with our DMPK CRO. We are able, and have already completed a successful collaboration with a major pharmaceutical company on this basis, to supply material for potential co-development partners to independently test at their laboratories or CRO of choice.

Co-developing lead candidates

"We are also actively seeking co-development partners whose candidates could benefit from oncojan delivery technology," Ateh continues. "We have already completed a successful study with a major pharmaceutical company and we are in talks with a number of organisations for further oncology development candidates. Additionally, the academic lab associated with BioMoti currently has grant funding to develop a second chemotherapy reformulation for ovarian cancer and we are always looking at grant applications to kick-start early ideas."

BioMoti aims to be a partner of choice for the co-development of cancer therapeutics with intracellular targets. Our model is based on initial low-cost feasibility studies with potential partners' active ingredients ranging from (1) formulation, (2) in vitro biological testing to (3) animal model proof-of-concept. The company offers this step-wise progression to enable potential partners to build confidence in its platform prior to engaging in (4) a long-term co-development partnership for the development of a specific candidate for a specific cancer type. "At the partnership stage we will negotiate upfront, milestone and royalty payments for the use of our technology – a typical biotech-pharma deal," says Ateh

"We are backed by private capital and intend to raise further cash so our priority is to build a sustainable company with profitable co-development deals," he adds. "This will build our value and make us an attractive acquisition target within three to five years. It is very important for us to have a defined exit strategy for our investors but even more important to build a strong and sustainable company that will offer many opportunities for a high return to investors at the right time.

The UK biotech landscape

"We are currently very optimistic about the future of the pharmaceutical sector in the UK. For context, BioMoti was formed in 2009, the middle of the economic downturn, and we were lucky along with a dose of hard work to reach a good proof-of-concept standard with non-dilutive grant funding to the academic lab originator. It should be said that beyond the economic downturn the biotech sector was in particular trouble for its own unique set of reasons including a collection of high-profile business failures and the subsequent unavailability of capital for early-stage drug discovery and development projects. Almost five years on, with a few new success stories and the realisation that later-stage assets or other health care sectors such as diagnostics and medical devices can be just as challenging an investment proposition with often much reduced multiples, there is a nascent appetite for early-stage therapeutic projects.

"We have seen the slow multiplication of venture funds dedicated to the early-stage and the expansion of corporate venturing. There has also been more grant funding available to SMEs from charities such as The Wellcome Trust and trans-governmental organisations like the EU. Encouragingly, the UK government has understood the importance of supporting the sector at an early stage and launched the Technology Strategy Board (TSB) Biomedical Catalyst scheme. This offers healthcare SMEs the opportunity to obtain grant funding prior to seeking matched private capital. BioMoti's Biomedical Catalyst award transformed our conversations with private capital providers. We were able to reduce the capital required at seed and, importantly, investor confidence was raised knowing we had undergone review by the TSB in a competitive process.

"We are ardent supporters of the scheme. It is a mechanism to encourage the return of private capital to the sector at the earliest and riskiest stages, the so-called 'valley of death'. We believe government should massively expand the budget and certainly renew the scheme to consolidate early successes and support the sector going forward. We also notice a change in global pharmaceutical companies strategies. Whereas a couple of years ago it was challenging to interest them in a non-clinical asset, this year they have been much more receptive about preclinical technologies, which is very welcome.

"We strongly believe that the small innovative biotech company is the ideal vehicle to transition academic research to major pharmaceutical companies for later-stage development and marketing. It makes great sense for each to focus on their inherent strengths in delivering health care advances to patients.

Potential for the future

"BioMoti seeks to transform the treatment of cancer and develop into a leader in the relatively new but increasingly successful area of targeted therapeutic delivery. Great success stories include the recent launch of Adcetris by Seattle Genetics and Millenium and Kadcyla by Roche on the antibody-drug conjugate front. The successful fundraising, early clinical development of BIND-014 and throng of signed partnering agreements with Amgen, Pfizer and Astra Zeneca by BIND Therapeutics on the targeted nanoparticle front is equally impressive. At BioMoti, we believe our major differentiator to antibody-drug conjugates and nanoparticles is that oncojanTM technology enables us to uniquely deliver very large drug carriers and therefore larger drug volumes to the interior of cancer cells. This means we can tailor our system for continuous and sustained drug release within the cell using established controlled release technology. Oncojans are anlogous to intracellular drug reservoirs, bunker busters if you will, that dramatically increase efficacy at targets that need constant exposure to drugs, as is the case with our lead MOTI1001 paclitaxel formulation, and therefore represent a major advance and opportunity for the development of the drugs of the future" Ateh concludes.

Further information

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