Institution: EaStCHEM

Unit of Assessment: 8; Chemistry

Title of case study: Deliverics; non-viral, non-toxic DNA delivery agents for cells and tissues

1. Summary of the impact

Impact: ***Economic.*** The EaStCHEM spin-out company Deliverics has commercialised biodegradable transfection reagents for both the "research tool" and the "RNAi therapeutics" markets (globally valued at £400M and £4 billion respectively). **Beneficiaries** are the pharmaceutical and biotechnology sectors, and clinicians. The turnover since 2010/11 is £330k and the company currently has five employees.

Significance: Deliveric's agents out-perfom existing materials in term of efficacy and reduced levels of toxicity. They are not hampered by the immunogenicity, manufacturing issues, and carcinogenicity previously seen for viral vectors used as delivery agents. This presents a wide ranging ability to deliver nucleic acids into cells and tissues for biological applications.

Research; date; attribution: EaStCHEM research (2008) led by Bradley reported a family of non-viral DNA delivery agents that offered a highly-efficient and non-toxic method of delivering siRNA/DNA into mammalian cells and tissues. Development and patenting of this technology led to the spin-out of Deliverics Ltd. in 2010.

Reach: International customer base (20 research groups and 10 companies) including specially appointed distributors in Spain (Albyn Medical), South Korea (CoreSciences), and US (Galen).

2. Underpinning research

Background: The delivery of nucleic acids into cells is a requisite for numerous biological / biomedical applications, ranging from therapeutic (e.g. corrective gene therapy, gene silencing therapy, etc.) to routine *in vitro* cell-based assays. Due to the founding role of DNA and RNA molecules in all cellular processes, their transport into cells is restricted by the cell membrane. Many different physical, chemical and biological approaches have been explored for the cell delivery of nucleic acids, with viral vectors being the most efficient one both therapeutically or as a research-enabling tool. However, due to the limitations of viral agents (antigenicity, risk of mutagenesis, production costs, etc.), chemical delivery systems represent an attractive alternative but have serious toxicity issues. Most chemical transfection technologies are based on the use of large surfactants / polycationic molecules with the ability to complex nucleic acids into liposome-like particles and carry them into cells via endocytosis.

Research: Following their move to EaStCHEM in 2005, the Bradley group attracted significant support from the MRC and EPSRC (2005-2008 & 2009-2012) as well as from Scottish Enterprise (2008-2010), to develop non-toxic cationic lipids and dendrimers as DNA/RNA carriers [1]. In early development work, two families of transfection reagents, based on the rational assembly of naturally-occurring components such as amino acids, lipids and non-toxic linkers stood out.[2,3]

This novel non-viral chemical approach offered a highly-efficient and non-toxic method to:

a. **Deliver nucleic acids (**siRNA/DNA) **to a wide range of mammalian cell lines and tissues** that cannot be transfected without toxicity by existing commercial non-viral materials such as embryonic stem cells.

b. **Deliver gene therapy drugs with high efficiency**, e.g. for the delivery of RNAi-based therapeutics, an emerging application within the Bio-Pharmaceutical sector. Gene therapy drugs have not yet been approved in Europe or USA because of lack of safety and efficiency; however the in-built degradation propensity of these reagents confers upon them the ability to metabolize into natural products and enhance nucleic acid release within the cell thus improving the delivery process.

For the latter, preliminary *in vivo* assays demonstrated the ability of compounds to transfect mouse lung with no obvious signs of toxicity, attracting early interest from major market players such as Merck and Silence Therapeutics Plc. Therapeutic relevance for this is for genetic diseases such as cystic fibrosis (annual treatment cost per patient up to £160,000, 9000 sufferers in the UK, 40,000

in the US) and viral infections such as influenza (annual cost to the US economy up to £110bn, based on average 200,000 hospitalisations and 41,000 deaths).

The new series of biodegradable delivery reagents were patented in 2007 [5] and the spin-out company Deliverics Ltd created in 2010 for their commercialization. Preliminary *in vivo* assays demonstrated their ability to transfect DNA plasmids into mouse lung [2]. Improved *in vivo* biodegradable reagents were then developed in the Bradley group [3,4] and patented in 2010.[6] Their subsequent research and development led to water-based formulations (SAFEctin^{TM} product series) that allow a one-step 'mix & go' procedure. Ongoing research shows outstanding transfection performance including with difficult-to-transfect and sensitive cells. Additional *in vivo* assays have demonstrated their ability to transfect siRNA and miRNA in mouse lung and skin xerographs (unpublished data by Deliverics) with no signs of toxicity.

The unique selling points that distinguish the reagents from existing platforms, and have allowed the research commercialisation are:

in vitro

- High efficiency transfection (comparable/better than gold-standard commercial products, Lipofectamine2000 and Effectene) in a variety of mammalian cells, including stem cells.
- Non-toxic.
- Ease of use (no requirement for later removal, enabling a simple, one-step protocol).

in vivo

- Cationic lipids specifically designed to be metabolised *in vivo* rendering them non-toxic and safe for clinical applications (e.g. multiple dosing).
- The combination of reduced toxicity and increased transfection efficiency makes the compounds particularly amenable for *in-vivo* application.

Additionally, they do not incur the expensive and difficult 'Good Manufacturing Process' requirements of viral production.

Key people who led the research

Professor Mark Bradley 2005 to date (EaStCHEM); Dr A. Unciti-Broceta 2005 - 2010 (EaStCHEM).

Research team members: A. Liberska, A. Lilienkampf, L. Moggio, L. Pidgeon, A.R. Turner (EaStCHEM PhD and PDRAs) E. Holder, L.J. Jones, B. Stevenson, D.J. Porteous, A.C. Boyd, K. Dhaliwal & C. Haslett (College of Medicine and Veterinary Medicine, UoE). Our embedded business development executive Dr Keith Finlayson was involved throughout the process from application to now and continues to liaise with the company in managing the patent portfolio for both parties ensuring a productive relationship is maintained.

3. References to the research

A. Key papers: *Underpinning research has been published in international, high-quality, peer reviewed, academic journals and receives citations from across the research area:*

[1] *Tripod-like cationic lipids as novel gene carriers; A. Unciti-Broceta, E. Holder, L.J. Jones, B. Stevenson, A.R. Turner, D.J. Porteous, A.C. Boyd, M. Bradley, *J Med Chem*. **2008**, 51, 4076-4084 doi:10.1021/jm701493f. 15 cits, JIF 5.6.

[2] **Safe and efficient *in vitro* and *in vivo* gene delivery: Tripodal Cationic Lipids with Programmed Biodegradability, A. Unciti-Broceta, L. Moggio, K. Dhaliwal, L. Pidgeon, K. Finlayson, C. Haslett, M. Bradley, *J. Mat. Chem,* **2011**, 2154-2158. doi:10.1039/C0JM03241G. 5 cits, JIF 6.1.

[3] *Solid-Phase Synthesis of Arginine-Based Double-Tailed Cationic Lipopeptides: Potent Nucleic Acid Carriers. A. Liberska, A. Lilienkampf, A. Unciti-Broceta, M. Bradley. *Chem. Comm.* **2011**, 47, 12774-12776. doi:10.1039/C1CC15805H. 4 cits, JIF 6.4.

[4] A. Unciti-Broceta, J. J. Díaz Mochón, R. M. Sanchez-Martin & M. Bradley. The Use of Solid Supports to Generate Nucleic Acid Carrier, *Acc. Chem. Res.* **2012**, 45, 1140–1152. doi:10.1021/ar200263c. 5 cits, JIF 20.8.

B. Key patents:

[5] Cationic Lipids, Inventors: Unciti-Broceta A.; Bradley M.. Priority Date: 19/10/2007. Published as WO2009050483.

[6] Cationic Lipids: second generation compounds, Inventors: Unciti-Broceta A.; Liberska A.; Bradley M.. Priority date: 18/05/2010. Published as WO2011144892.

C. Key Grants:

(i) Bradley, MRC/EPSRC G0401194 'High Throughput Chemical Biology - Transfection Microarrays and Combinatorial Chemistry' £263,990 (2005).

(ii) Unciti-Broceta & Bradley, Scottish Enterprise proof-of-concept award (10-CHM-001) 'Non-Toxic DNA Delivery' £248,187 (2008).

(iii) Bradley, MRC G0801908, Multiplexed in vivo optimisation of non-toxic gene transfer agents' £646,272 (2009).

(iv) Venture funding £205K (2010).

4. Details of the impact

The new chemical reagents for transfection described and protected (above) were licenced to Deliverics, a new company which specialises in cellular delivery products and technologies, spun out of EaStCHEM in November 2010. Deliverics used the IP in both the *in vitro* reagent market as well as having longer-term interests in *in vivo* uses. These unique, chemical-based, biodegradable transfection reagents have broken into both the "research tool" (reagent) and the "RNAi therapeutics" (drug delivery) markets, delivering economic, human capital, and potential health benefits.

A. Economic: spin-out of the company Deliverics

The significance of Deliverics' commercialised biodegradable transfection reagents impacts on both the "research tool" and the "RNAi therapeutics" markets and arises from their ability to out-perform existing materials, without the immunogenicity, manufacturing issues, and carcinogenicity previously seen for current viral vectors used as delivery agents. This presents a wide ranging ability to deliver nucleic acids into cells and tissues for biological applications.[S1]

The reach of the company is international, despite its youth. It has an international customer base, including specially appointed distributors in Spain (Albyn Medical), S. Korea (CoreSciences), and US (Galen).The customer base (20 research groups and 10 companies) spans 5 countries. at Scottish Enterprise Enterpreneurial Support Manager has said, "*There is significant scope for Deliverics to expand its distribution network overseas. We're very positive about the future and looking forward to working with them as they continue to grow*."[S2]

The turnover of the new company is £330k to date.[F1]

Deliverics Ltd has so far launched the following products:[F1]

- SAFEctin™ is a biodegradable transfection kit.
- SAFEctin™-STEM is targeted at the stem cell market, a market estimated at £100M pa. This reagent offers over 90% transfection efficiency of RNA into stem cells in a simple, one-step protocol.
- New SAFEctin beta product, developed with TSB grant – out performing SAFEctin, SAFEctin STEM, HappyFect and LipoFectamine 2000 in siRNA delivery, and showing >70% transfection efficacy in notoriously difficult cell types such as human fibrosarcoma HL116, primary mouse lobular breast cancer cells, mouse embryonic limb cells and primary human monocytes.

Client testimonies:

' *[Text removed for publication].'* [S3]

'*The product that Deliverics has developed is a simple one-step protocol that is easy to perform*

and produces very high transfection efficiencies of our embryonic stem cells. During use, cells exhibited high levels of expression and remained healthy. I think this is a great product that will become market-leader over time.'[F2]

B. Human Capital:

Deliverics employs 5 people (4 PhD level).

C. Impact Development Timeline:

2008	Unciti-Broceta and Bradley awarded "Proof of Concept" grant (£250K) from Scottish Enterprise to develop patent [5] into a commercial product.
4/2010	Deliverics Ltd spun-out. Registered in Companies House, #SC377672.
11/2010	(1) University of Edinburgh licenses patents [5] and [6] to Deliverics Ltd. (2) Venture funding of £275K raised [S4]. Company valuation of £705K. (3) First product, SAFEctin Transfection Reagent, launched. (4) Dr Asier Unciti-Broceta awarded Nexxus 'Young Life Scientist of the year'.
2011	(1) Second core product, SAFEctin STEM launched.[S5] (2) Internationalisation begins: Albyn Medical S.A. appointed as distributor of Deliverics products in Spain. CoreSciences appointed as distributor of Deliverics products in South Korea. Distribution deal in the US with Galen Laboratory Supplies, giving access to the £130m US transfection reagent market, a market with 8 % annual growth.[S6] (3) Deliverics wins 'Nexxus Most Promising Young Life Science Company of the Year'[S7] (4) SE SMART: SCOTLAND Feasibility Study awarded for RNA transfection and new transfection product for stem cells (SMART ref 10-9174; £63K; 2011). (5) TSB Feasibility Study awarded to develop new protein delivery technology (TSB ref 130436 and 130436; £50K; 2011 & 2012).
2012	(1) TSB Smart PoC grant awarded (to develop *in vivo* transfection reagent prototype) (TSB ref 710195; £60K; 2012). (2) TSB Collaborative R&D Grant awarded (TSB ref 101229; £94K; 2012); TSB Collaborative R&D Grant awarded to joint consortium of AvantiCell, Deliverics, and Synpromics (£263K, 2012).[S8] (3)Deliverics CSO Dr Unciti-Broceta receives Royal Society of Chemistry Young Industrialist of the Year Award.

5. Sources to corroborate the impact

[F1] Testimony from Deliverics' CSO confirming corroboration of turnover and product range.

[F2] Testimony from Head of Production and Quality Control at R Biomedical (Deliverics customer)

[S1] Deliverics' website http://www.deliverics.com/home/index.php/aboutus.

[S2] Scottish Enterprise press release on Deliverics (quote from their Entrepreneurial Support Manager, High Growth Start-up unit on company's rate of growth).

[S3] [Text removed for publication] Deliverics customer showing efficacy of Deliverics products (results from pages 13 onwards).

[S4] The Scotsman: 'New spin-out wins early stage funding' (website tinyurl http://tinyurl.com/nzg6vzk).

[S5] Deliverics' Press release on Safectin STEM launch, Aug 2011.

[S6] Deliverics' $200M USA distribution deal, Oct 2011 (Lifescience Scotland tinyurl http://tinyurl.com/o6svk3k).

[S7] Press release on Deliverics' 2011 Nexxus Award (Scottish Life Science Business award).

[S8] Synpromics website announcing collaborative TSB award with Deliverics and Avanti (tiny url http://tinyurl.com/nd5tukc.