Lenti Production, Scale-up and Commercialisation
James Miskin, CTO, Oxford BioMedica

ASGCT 2017 Annual Meeting | Washington D.C.
ASGCT Clinical Trials Training Course | May 9 2017
Forward-looking statements and Disclosures

This presentation does not constitute an offer to sell or a solicitation of offers to buy Ordinary Shares (the “Securities”). Although reasonable care has been taken to ensure that the facts stated in this presentation are accurate and that the opinions expressed are fair and reasonable, the contents of this presentation have not been formally verified by Oxford BioMedica plc (the “Company”) or any other person. Accordingly, no representation or warranty, expressed or implied, is made as to the fairness, accuracy, completeness or correctness of the information and opinions contained in this presentation, and no reliance should be placed on such information or opinions. Further, the information in this presentation is not complete and may be changed. Neither the Company nor any of its respective members, directors, officers or employees nor any other person accepts any liability whatsoever for any loss howsoever arising from any use of such information or opinions or otherwise arising in connection with this presentation.

This presentation may contain forward-looking statements that reflect the Company's current expectations regarding future events, its liquidity and results of operations and its future working capital requirements. Forward-looking statements involve risks and uncertainties. Actual events could differ materially from those projected herein and depend on a number of factors, including the success of the Company's development strategies, the successful and timely completion of clinical studies, securing satisfactory licensing agreements for products, the ability of the Company to obtain additional financing for its operations and the market conditions affecting the availability and terms of such financing.

Disclosures: James Miskin is an employee of Oxford BioMedica (UK) Ltd
Introduction

• A number of very promising lentiviral vector based gene and cell therapies are in development
  • Several products are approaching commercial phase (e.g. CAR-T, primary immunodeficiency diseases, haemoglobinopathies)
  • Many products are *ex vivo* gene therapies based on T-cells or stem cells

• Oxford BioMedica (OXB) - focused on process, analytical and facility requirements to support lentiviral vector supplies for our own products and those of strategic partners
  • OXB were the first to administer lentiviral vector directly to patients (*in vivo*) (PD)
  • Followed shortly afterwards with 2nd (wet AMD), 3rd (Stargardt) and 4th (Ushers 1B) application – *insight into product manufacture and testing requirements / specification for in vivo and ex vivo*
OXB Corporate Overview

>20 years in development of lentiviral vectors
  ✓ 1st to administer in vivo (both brain and eye)
  ✓ >60 patients treated in vivo
  ✓ Four Phase I/II studies completed with encouraging safety and efficacy
  ✓ Five in-house products, available for spin out or out-licensing

• Integrated LentiVector® gene delivery platform
  ✓ IP - extensive IP comprising both patents and know-how
  ✓ Facilities – state-of-the-art bioprocessing and laboratory facilities
  ✓ Employees – Over 250 full time employees, many highly qualified and experienced
  ✓ Quality – robust quality processes for lentiviral vector production

Partnered with

Products & patents licensed to

Discussions with several other potential partners ongoing
Facilities less than 1 hour from London Heathrow Airport:

**Windrush Court**
- Corporate HQ & Laboratories
  - 71,955 sq.ft (6,684 sq.m)
- GMP Warehouse Hub
  - 2,691 sq.ft (250 sq.m)

**Harrow House & Chancery Gate**
- 19,375 sq.ft (1,800 sq.m)
- cGMP production facility
- Two clean room suites
- GMP QC microbiology laboratories
- Raw material testing
- GMP cold chain warehouse & office space

**Yarnton**
- 18,300 sq.ft (1,700 sq.m)
- cGMP production facility
- One clean room suite

Source: https://resources.oncourse.iu.edu/access/content/user/leema/profilepage/oxford.html
Cell and Gene Therapy – towards successful commercialisation

**Established mode of action**
- Rare diseases; e.g. β-Thalassaemia, ADA-SCID, haemophilia, orphan ocular
- High incidence / prevalence diseases; e.g. Parkinson’s disease, CF, cancer (e.g. CAR-T, TCR)

**Clinical proof of concept**
- Clear unambiguous clinical data in severe disease, ‘accelerated’ route to market
- Promising signs of efficacy in clinical trials, ‘traditional’ route to market?

**Manufacturing, COGs**
- Requirement for mid-to large-scale, high quality vector / cell manufacturing with ‘acceptable’ COGs (for developers and payers)

**Scaled clinical operations**
- Indication-specific
Generic “Minimal” 3rd Generation Lentiviral Vector System

Expression cassette

LTR gag pol rev tat env LTR

Psi (Ψ)

Vector Genome
Gag-Pol Packaging component
Rev expression cassette (optional)
Envelope cassette (Pseudotyping)

LTR

Gag-Pol
Rev expression cassette (optional)
Envelope cassette (Pseudotyping)
Case examples

**OXB-102 for the treatment of Parkinson’s disease**

- Direct *in vivo* administration to the brain through surgery
- Encouraging signs of efficacy from ProSavin® clinical trial in 15 patients; >7 years of safety data – no IMP or procedure related SAEs
- OXB-102 - increased potency
- Common disease in aged population

**Potential for “one off” treatment giving long-term or permanent efficacy**

**CAR-T Immunotherapy (e.g. CTL019 [Novartis])**

- *Ex vivo* autologous cell therapy
- Multiple diseases with CD19 target
- Initial Novartis target is paediatric ALL
- Manufacturing & logistics challenge for vector and cells
Clinical Lentiviral Vector Experience

- OXB’s lentiviral vector administered to >100 patients (by OXB or its partners) and cumulative patient safety data >300 years

In Vivo

- **OXB-101** - 15 patients treated via stereotactic delivery
  - Safe and well tolerated with cohort 1 out to 7 years

- **OXB-201** - 21 patients treated via subretinal delivery
  - Safe and well tolerated with cohort 1 out to 4 years
  - Protein expression from transgenes observed at latest time point (4yr)

- **SAR422459/SAR421869** – Over 20 patients treated via subretinal delivery
  - Safe and well tolerated with SAR422459 cohort 1 out to 3 years
  - Safe and well tolerated with SAR421869 cohort 1 out to 2 years

Ex Vivo

- **CTL019** – Novartis ELIANA and JULIET clinical studies
  - Ongoing safety profile is very well tolerated
  - No transgene related immune responses observed

---

1. Published in *The Lancet* January 2014 (Palfi et al.)
3. Weleber et al. Early findings in a Phase I/IIa clinical programme for Usher syndrome 1B (USH1B; MIM #276900). ARVO Meet Abstr. 2286 (B0191), 2015.
LentiVector® Platform Evidence of Long-term Duration

- Long-term four year follow up data for OXB-201
  - Dose responsive expression of proteins
  - Long term follow up continues

**Endostatin (individual)**

- Persistent expression out to >4 years so far (ongoing)

---

1 Campochiaro PA, et al. "Lentiviral vector gene transfer of endostatin/angiostatin for macular degeneration (GEM) study". Hum Gene Ther. 28 (1) 99-111, 2017
Production volume considerations

- Impact of indication and phase of development on production needs:

<table>
<thead>
<tr>
<th>Phase of development</th>
<th>‘Low demand’ indication</th>
<th>‘High demand’ indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects</td>
<td>Volume (L)</td>
</tr>
<tr>
<td>Preclinical</td>
<td>6 primates/40 rodents (10-20L)</td>
<td></td>
</tr>
<tr>
<td>Phase I/II</td>
<td>10</td>
<td>100L</td>
</tr>
<tr>
<td>Phase II</td>
<td>20</td>
<td>200L</td>
</tr>
<tr>
<td>Phase III</td>
<td>50</td>
<td>500L</td>
</tr>
<tr>
<td>Commercial</td>
<td>100’s</td>
<td>≥1000L</td>
</tr>
</tbody>
</table>

- **Conclusion** – production strategies are influenced by indication, point of process introduction etc

Assumptions:
- 1L gives approximately one dose taking into account process loses, testing etc
- Targeted USP yield improvements for later stage / higher demand
Manufacturing strategy to satisfy current / future demand

- Considerations for current and future processes (*strategy dependent on indication & phase of development*):
  - Process complexity (multiple vessels vs single)
  - Manual handling requirements vs single use closed systems (risk, COGs)
  - Reliance on raw material supply (e.g. FBS vs serum-free)
  - Output per clean room suite (COGs), number of independent suites
  - Need to support OXB and partner projects and programmes

**Overall strategy:**

- **Existing process** - ongoing supply, characterisation & validation
- **Parallel development** of future process(es)
- **Unabated progression of clinical trial(s)**
Manufacturing Process – adherent (CF10)

Process flow diagram for GMP large-scale production of drug substance

Cell build

Day 1
- Working cell bank
- Vial
- T225 Flask

Day 2
- 2-Layer Cell Factory

Day 3
- 10-Layer Cell Factory

Day 11
- Continuous source of cells for duration of campaign (rolling seed train)

Day 11 (Transfection)
- Transfection

Day 12
- Induce vector production

Day 13
- Medium exchange

Day 14
- Normal Flow Filtration
- Crude Vector Harvest (2x)
- Clarified Vector

Day 15
- Ultra/Diafiltration

Day 15
- Final Formulation

Day 15
- Vector (drug) substance

Day 15
- Chromatography

Day 15
- Hold -80°C

13
Manufacturing Process (F&F)

GMP manufacturing process for clinical supply

1. Vial to FDP: ~2000-fold volume concentration factor
2. Final volume determined by number of Ultra-diafiltered Drug Substance (UDFDS) lots and test data
OXB vector process development strategies

- Holistic view of the development of ‘next generation’ lentiviral vector manufacturing, utilising closed systems wherever possible:

**Production cells**
- Transient Plasmids
- Tfx reagent
- Short USP phase
- Stable Packaging cell line
- Producer cell line

**USP**
- Adherent Up to 72L Serum-containing
- 100% single use
- Suspension 50L – 2000L Serum-free
- 100% Single use

**DSP**
- Flexible
- Scalable
- Gentle
- 100% single use
- Rapid, optimised yield

Holistic view of the development of ‘next generation’ lentiviral vector manufacturing, utilising closed systems wherever possible:
Boosting upstream productivity

Transgene repression in vector production [TRiP] cell system

- During manufacture, transgene is normally expressed
- Can reduce vector yield activity, and impact product purity and yield
- Ideally transgene expression should be repressed to allow consistent vector production and purification, irrespective of transgene identity.
- Transgene Repression in vector Production [TRiP] cell system has been developed for the manufacture of lentiviral vectors.
- TRiP may increase production cell output and improve vector particle purity.

Potent repression of GFP transgene in cells transfected with TRiP system components

Source: Published PCT number WO 2015/092440 and 1

Cell line development – Clone screening

Manual vs. Automated Cell Screening System (ACSS)

1. Selection of parental cell line
2. Stable integration of transgene(s) into parental cell line
3. Cloning by limiting dilution in selective media
4. Screening and selection of clones
5. Expansion of clones
6. Freezing of clones

**Clones to Screening Result:** Manual
- 12 weeks
- 100-200 clones screened

**Clones to Screening Result:** Automated
- 8 weeks
- Up to 3000 clones screened

**Manual vs. Automated Cell Screening System (ACSS)**

- **Manual:**
  - 100-200 clones screened
  - 12 weeks

- **Automated:**
  - Up to 3000 clones screened
  - 8 weeks
Schematic of serum-free, suspension process (200L scale)
<table>
<thead>
<tr>
<th>Dose</th>
<th>Administration</th>
<th>3 months (UPDRS)</th>
<th>6 months (UPDRS)</th>
<th>1 year (UPDRS)</th>
<th>2 years (UPDRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, n=3</td>
<td>Original</td>
<td>27%</td>
<td>Mean 30%</td>
<td>Max. up to 30%</td>
<td>Mean 29%</td>
</tr>
<tr>
<td>2, n=3</td>
<td>Original</td>
<td>28%</td>
<td>Mean 34%</td>
<td>Max. up to 53%</td>
<td>Mean 29%</td>
</tr>
<tr>
<td>3, n=3</td>
<td>Enhanced</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Continuous process improvement

Suspension process development
GMP clean room facilities – matching capacity to demand

Flexible independent clean room suites for GMP vector manufacture, with segregated air handling, material transfer and personnel routes. Single use systems (SUS) used throughout:

- **GMP1** Grade C/D (ISO 7/8) – 4,198 sq. ft (390 sq. m) clean room suite
  - OXB’s original clean room facility, acquired in 2011
  - Planar 2D technologies e.g. CF-10, areas for cell expansion and downstream processing
  - **Operational and MHRA licenced (since 2012)**

- **GMP2** Grade C/D (ISO7/8) - 2,691 sq.ft (250 sq. m) clean room suite
  - Suspension platform 2 x 50/200L Duo SUB
  - Planar 2D technologies e.g. CF-10
  - Operational readiness **Operational and MHRA licenced (since May 2016)**

- **GMP4** Grade C/D (ISO7/8) - 6,028 sq. ft (560 sq. m) new off-site API Facility
  - Suspension platform up to 2 x 50/200L Duo SUB
  - Planar 2D technologies e.g. CF-10
  - Areas for cell expansion, media make-up, buffer preparation and downstream processing
  - **Operational and MHRA licenced (since Jan 2016)**
Analytical and development facilities

- Independent QC microbiology laboratories:
  - Primary laboratory area located in Harrow House ground floor (installed as part of Phase 1 expansion of Harrow House)
  - Yarnton (GMP4) specific QC micro laboratory located on site
- All (non-QC micro) OXB laboratories relocated to newly refurbished laboratory area in Windrush court, including process R&D and GMP analytics – MHRA licenced in Jun 2016
Concluding remarks

• Gene and cell therapy has reached the stage where several very promising therapies are reaching the commercial phase

  Strimvelis® – retroviral vector-based cell therapy product for ADA-SCID, launched summer 2016

  CTL019 - potentially the worldwide first commercial product based on lentiviral vector technology – BLA Q1 2017, “Breakthrough Status”

  Spark Therapeutics Voretigene Neparvovec: RPE65-mediated IRD – anticipate completing the BLA submission to the U.S. FDA in early 2017

• The field has been catalysed by several very promising products
• Several are for high demand indications

• Conclusion – need to continue to develop and evolve technologies and CMC strategies to support anticipated level of patient demand