OxfordBioMedica

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

OxfordBioMedica

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

OxfordBioMedica

>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

NOVARTIS

IMMUNE DESIGN

Green Cross LabCell

Orchard therapeutics

Discussions with several other potential partners ongoing

Products & patents licensed to

SANOFI

gsk GlaxoSmithKline

Oxford BioMedica Facilities in the UK

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

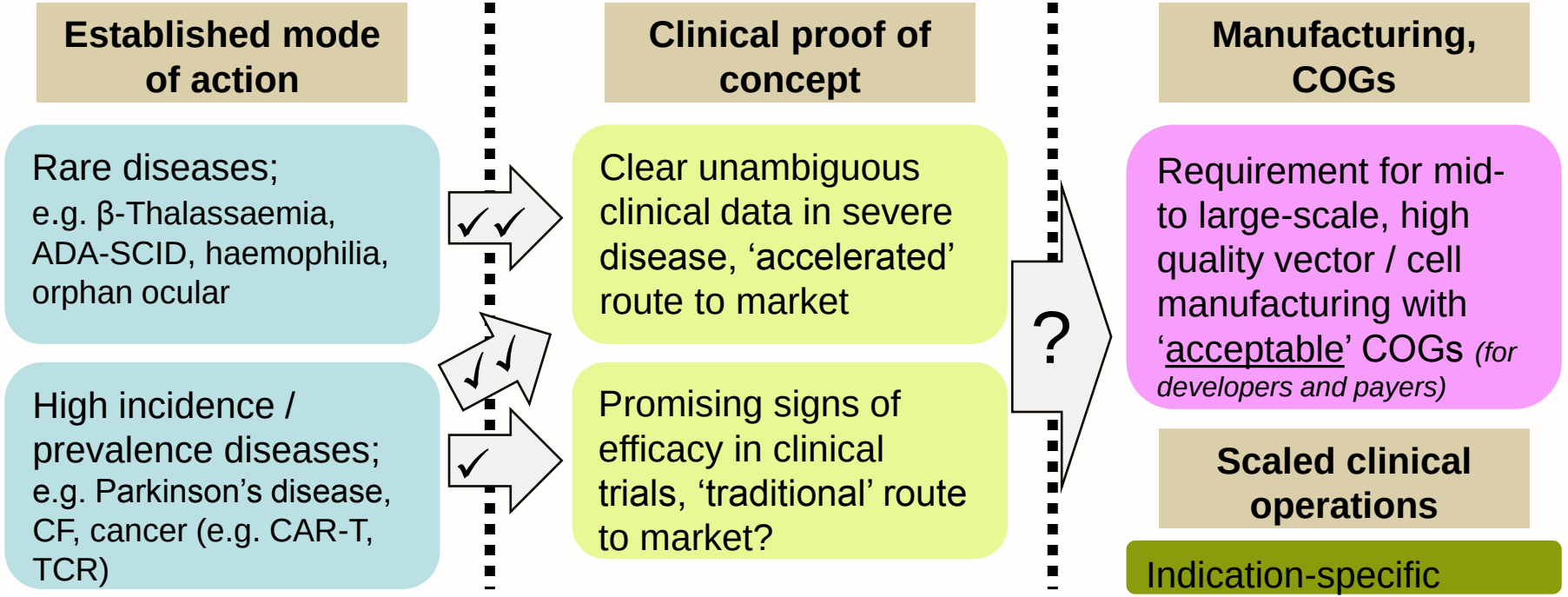

Yarnton

18,300 sq.ft (1,700 sq.m)

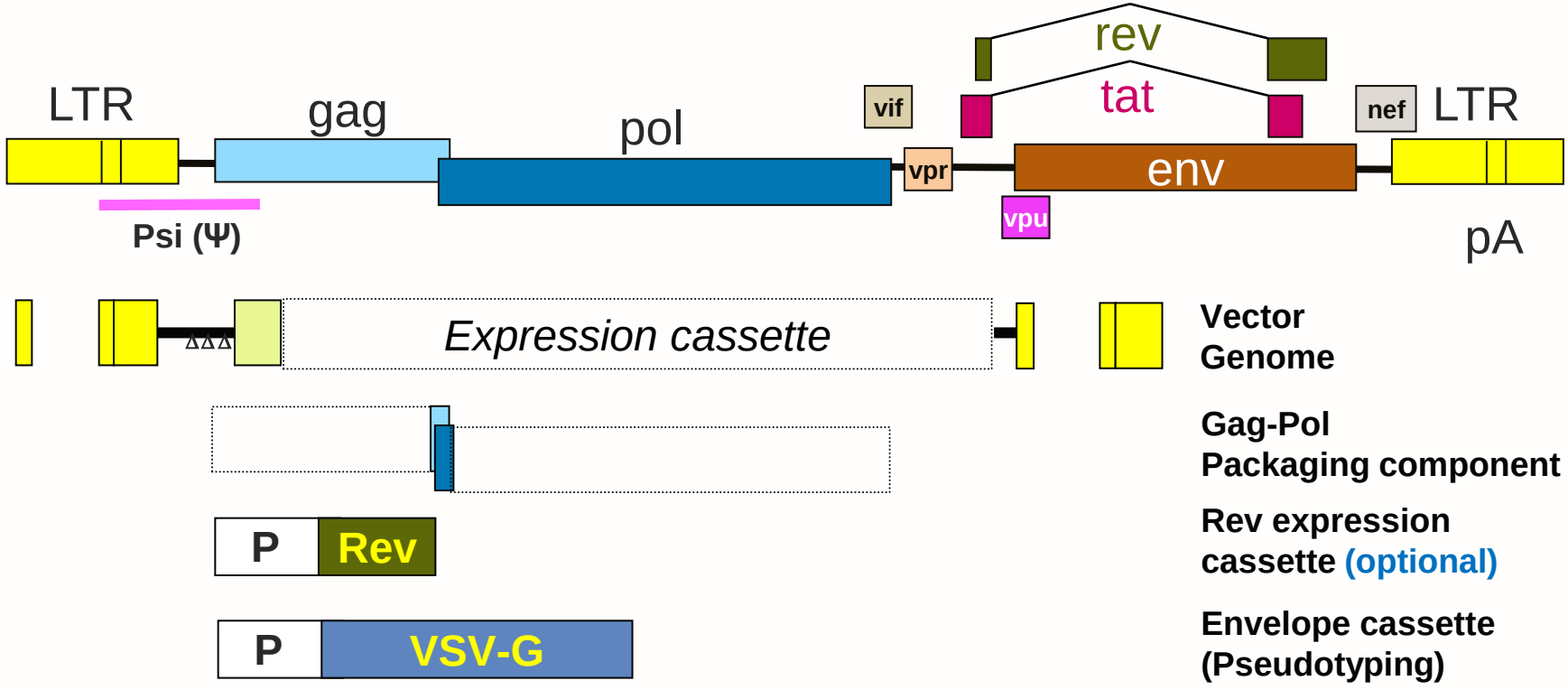
- cGMP production facility
- One clean room suite


Source: https://resources.oncourse.iu.edu/access/content/user/leema/profilepage/oxford.html

Cell and Gene Therapy – towards successful commercialisation



Generic "Minimal" 3rd Generation Lentiviral Vector System



Vector Genome

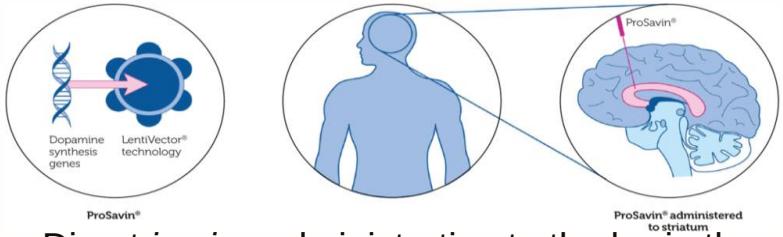
Gag-Pol Packaging component

Rev expression cassette (optional)

Envelope cassette (Pseudotyping)

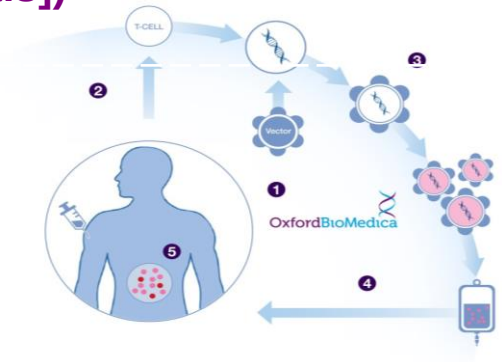
Case examples

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

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

Potential for "one off" treatment giving long-term or permanent efficacy

Clinical Lentiviral Vector Experience

OxfordBioMedica

- 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[1]
  - 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[2]
  - Safe and well tolerated with SAR421869 cohort 1 out to 2 years[3]

Ex Vivo

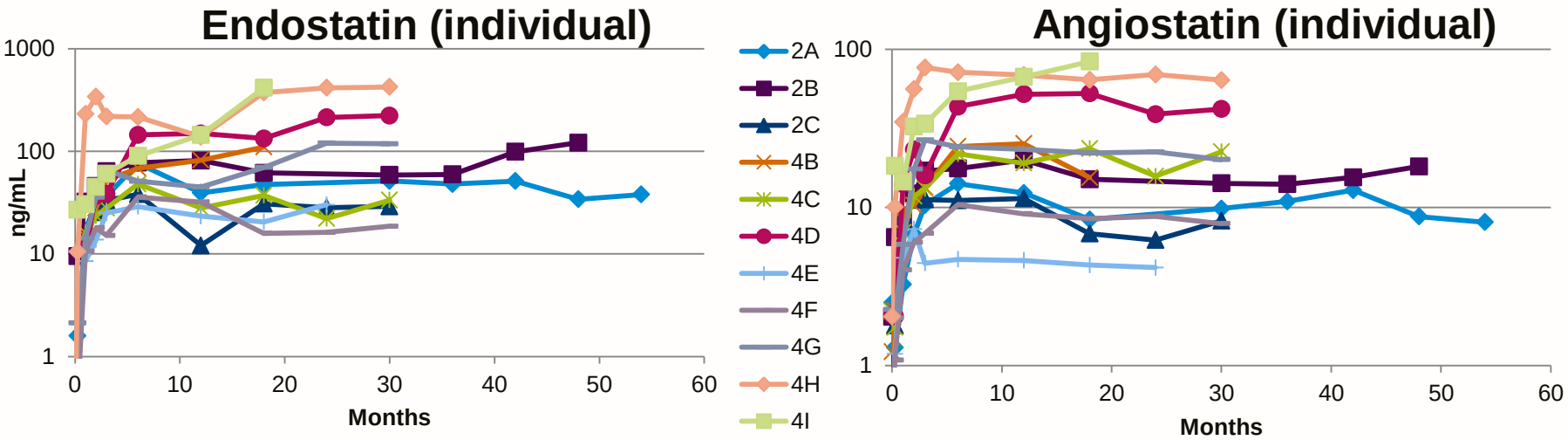
- CTL019 – Novartis ELIANA and JULIET clinical studies
- Ongoing safety profile is very well tolerated
- No transgene related immune responses observed

1 Published in *The Lancet* January 2014 (Palfi *et al.*)
2 Binley et al. Transduction of Photoreceptors With Equine Infectious Anemia Virus Lentiviral Vectors: Safety and Biodistribution of StarGen for Stargardt Disease. IOVS 54 (6): 4061-4071, 2013
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

OxfordBioMedica

- Long-term four year follow up data for OXB-201[1]
  - Dose responsive expression of proteins
  - Long term follow up continues



- **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:

Phase of development	'Low demand' indication		'High demand' indication	
	No. of subjects	Volume (L)	No. of subjects	Volume (L)
Preclinical	6 primates/40 rodents (10-20L)			
Phase I/II	10	100L	10-20	100-200L
Phase II	20	200L	50-100	500-1000L
Phase III	50	500L	100-500	1000L-5000L
Commercial	100's	≥1000L	>1000's	>10,000L

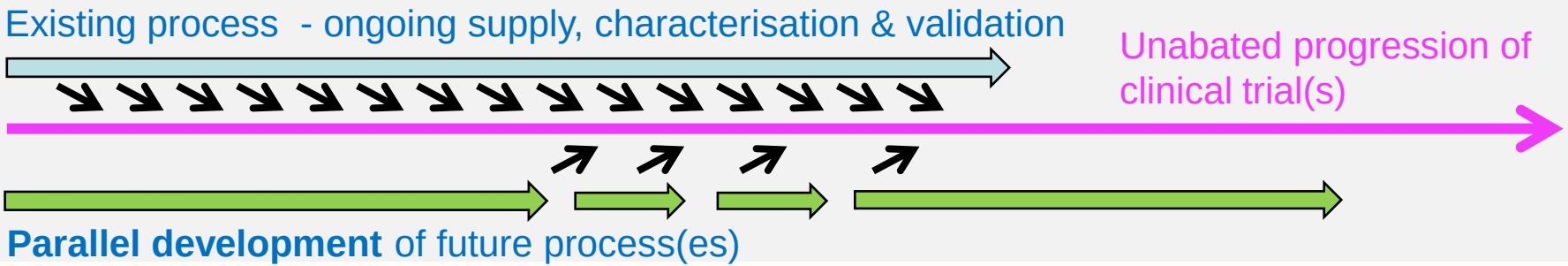
- ***Conclusion*** *– production strategies are influenced by indication, point of process introduction etc*

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

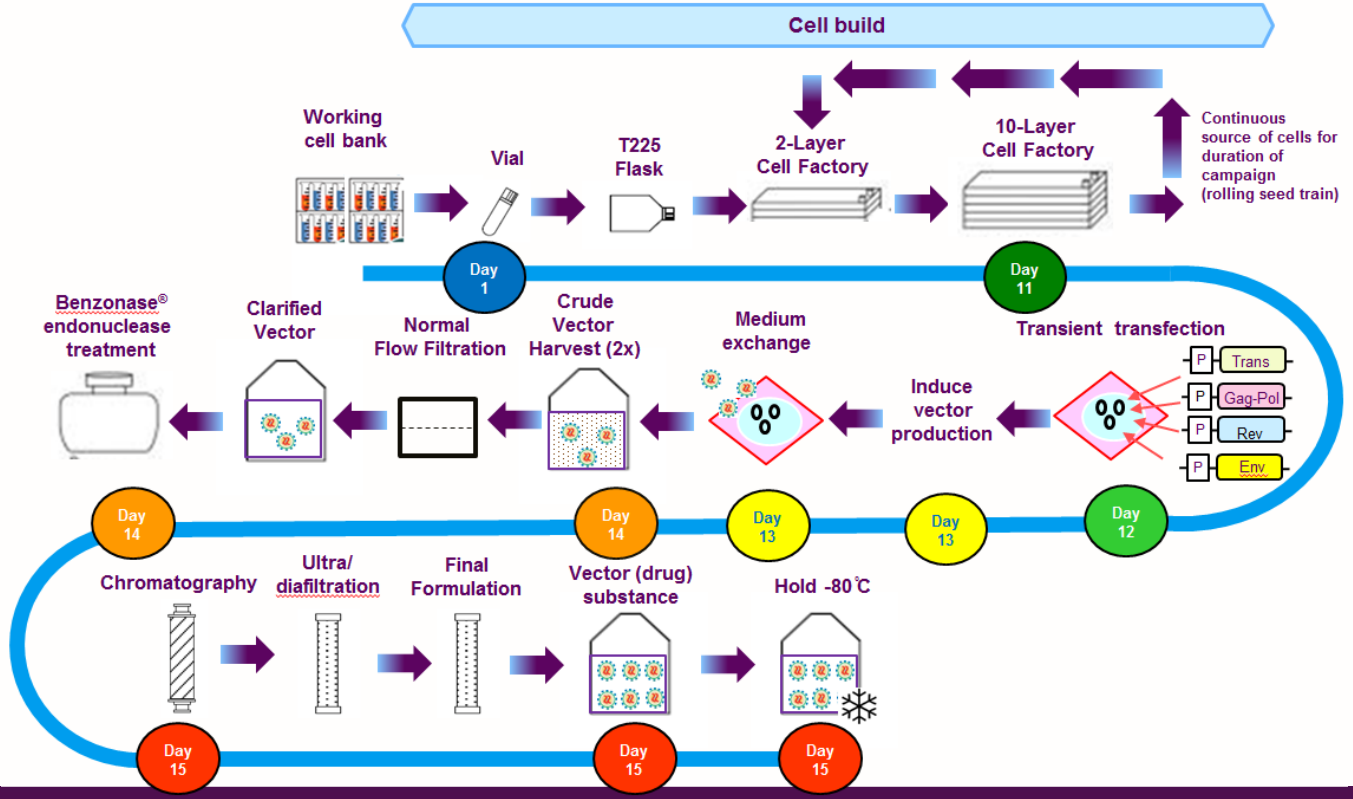
Overall strategy:



Manufacturing Process – adherent (CF10)

OxfordBioMedica

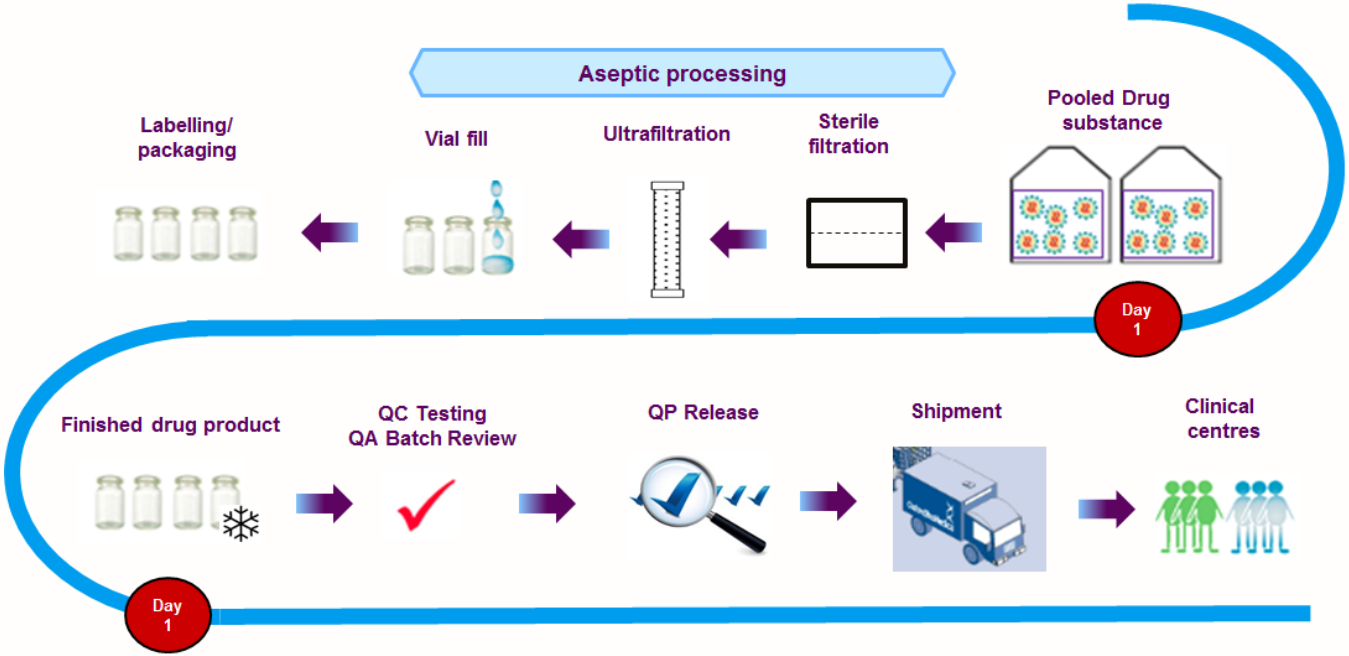
Process flow diagram for GMP large-scale production of drug substance



Manufacturing Process (F&F)

OxfordBioMedica

GMP manufacturing process for clinical supply



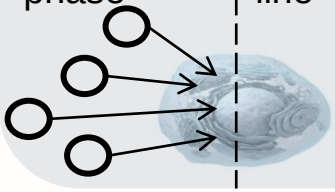
1. Vial to FDP: ~2000-fold volume concentration factor
2. Final volume determined by number of Ultra-diafiltered Drug Substance (UDFDS) lots and test data

OXB vector process development strategies

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

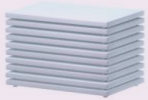
Production cells

Transient	Stable
Plasmids Tfx reagent Short USP phase	Packaging cell line Producer cell line



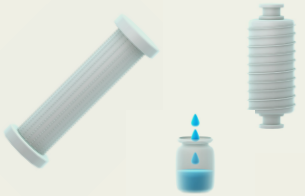
USP

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



DSP

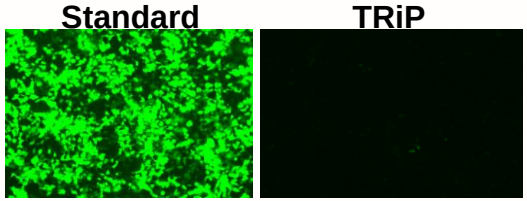
Flexible
Scalable
Gentle
100% single use
Rapid, optimised yield



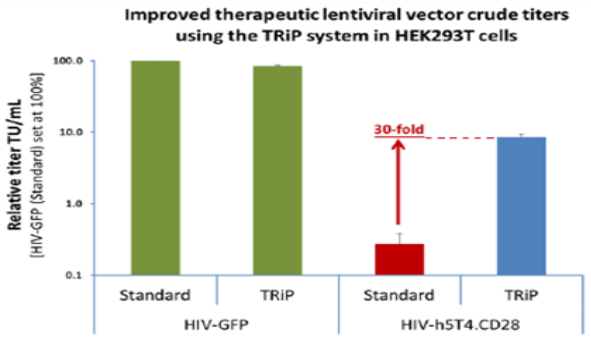
Boosting upstream productivity

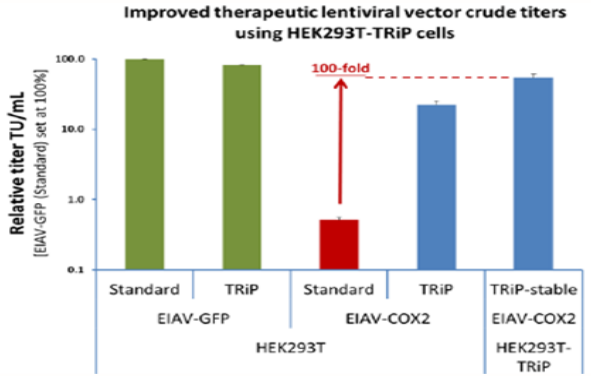
Transgene repression in vector production [TRiP] cell system

- 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]

[1] Maunder, H.E. et al, Enhancing titres of therapeutic viral vectors using the transgene repression in vector production (TRiP) system. Nat Commun. 2017; 8: 14834.

Cell line development – Clone screening

OxfordBioMedica

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

'Bottle neck' in terms of time and number of clones that can be screened

Clones to Screening Result: Manual

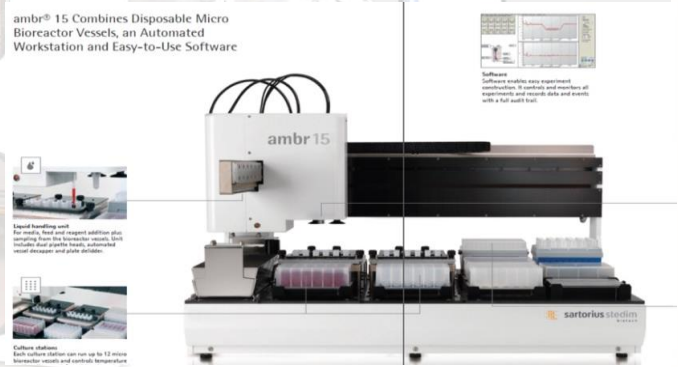
12 weeks

100-200 clones screened

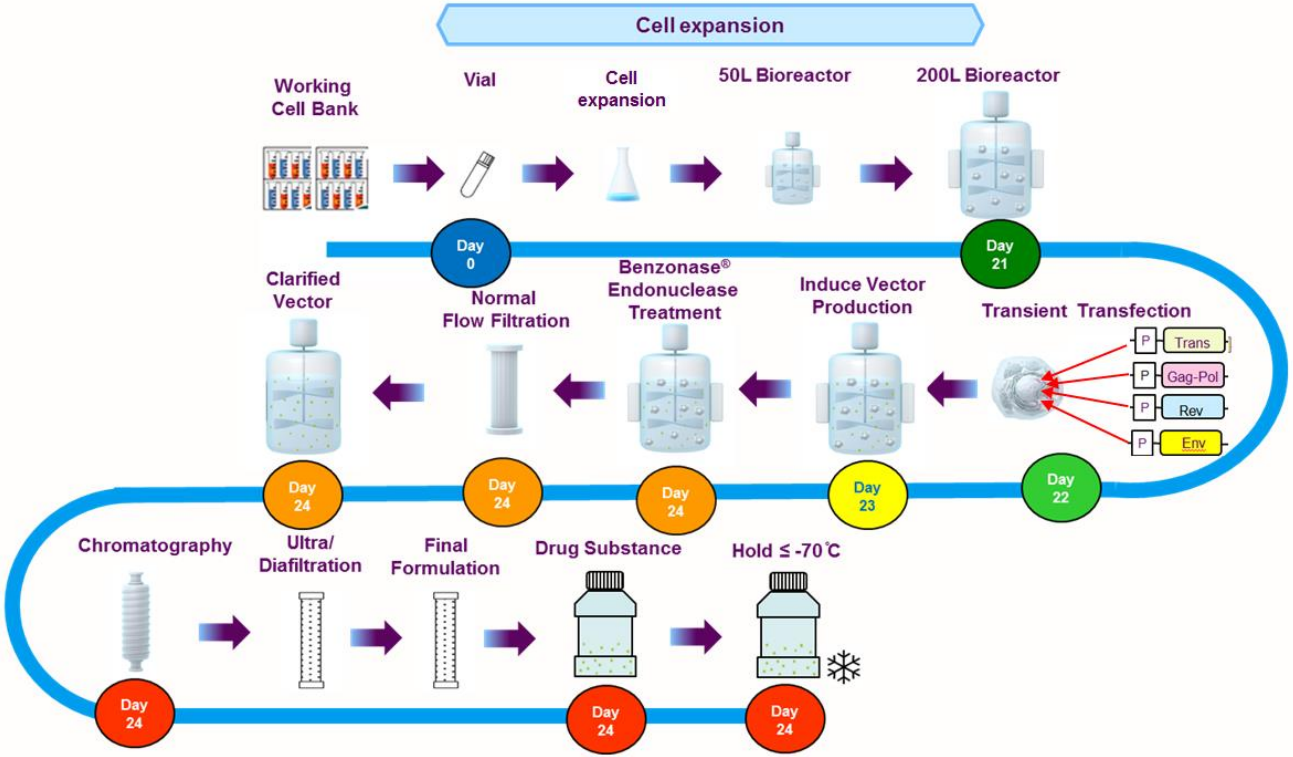
Clones to Screening Result: Automated

8 weeks

Up to 3000 clones screened

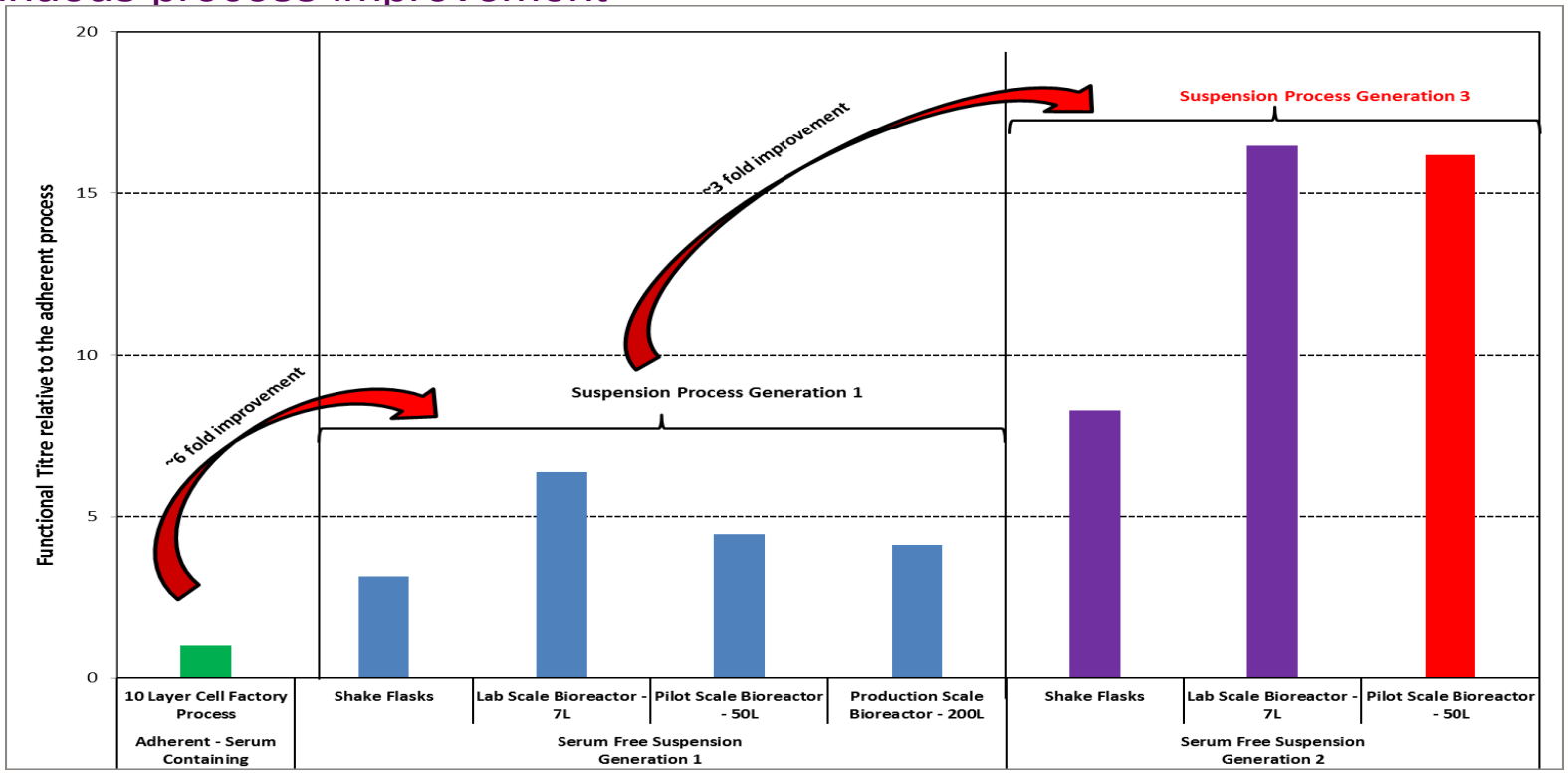


Schematic of serum-free, suspension process (200L scale)



Suspension process development

Continuous process improvement



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*

Contact us

James Miskin
Chief Technical Officer

+44 (0) 1865 783 000
j.miskin@oxfordbiomedica.co.uk

Further information:
http://www.oxfordbiomedica.co.uk/