Cell and gene therapy GMP manufacturing in the UK

Capability and capacity analysis
November 2018

CATAPULT
Cell and Gene Therapy

Contents

1 Executive summary

The Cell and Gene Therapy Catapult conducted the fifth annual survey on the status of the UK's MHRA MIA and MIA(IMP) licensed ATMP manufacturing facilities. This survey report is designed to provide an overall picture of the capability and capacity of MHRA-licensed cell and gene therapy manufacturing facilities in the UK, covering early-stage translational centres in the academic and public sector, through to industrial centres, including CDMO's and facilities for in-house product manufacture The first review was published in 2014 and has been repeated yearly following a House of Lords Committee's recommendation of an annual stocktake into Regenerative Medicine manufacturing to inform decisions on infrastructure investments by the UK government, ATMP developers and other investors. Previous years' reports can be viewed at https://ct.catapult.org.uk/manufacturing-survey and we remain grateful of the support of all participating centres.

2018 has marked the fourth consecutive year of increases in cleanroom operational footprint within the UK's MHRA-licensed GMP manufacturing facilities, as manufacturers try to keep pace with high global demand. Substantial new manufacturing space was added this year by the opening of the Cell and Gene Therapy Catapult manufacturing centre, creating additional capacity for growing and established companies looking to develop their own products in a collaborative GMP environment. The academic and public sector is as busy as ever, with the CDMO industry also actively expanding. Of significance is the further increase in product-pipeline manufacturing space, operated by seven cell and gene therapy companies. At the Cell and Gene Therapy Catapult facility, Adaptimmune, Autolus, Cell Medica and Freeline are producing their own products whilst Oxford Biomedica, MeiraGTx and TC Biopharm operate stand-alone facilities for their own pipelines. This continued growth in industrial scale facilities, is built upon the foundational investments in translational and collaborative manufacturing spaces.

The addition of the Cell and Gene Therapy Catapult manufacturing centre, expansion of the pre-existing facilities of Cobra Biologics and the new flagship building of the Scottish National Blood Transfusion Service has driven growth in the total building footprints and cleanroom footprints by (60%) and (28%) respectively. During 2019, it is expected that there will be an additional (~1500 m^2) of cleanroom footprint from 6 x 185 m^2 cleanrooms coming on-line at the Cell and Gene Therapy Catapult facility, expansion at Cobra Biologics and new facilities operated by Advent BioServices and Kings College London. In addition to IMP licences, two facilities (Oxford BioMedica and Cell and Gene Therapy Catapult) have commercial licenses, demonstrating that the UK is well placed to service the growing cell and gene therapy pipeline, strengthening its global position in this complex and technically challenging area.

The total number of UK licensed facilities has increased to 25, with the addition of the Cell and Gene Therapy Catapult manufacturing centre, MeiraGTX and TC Biopharm. The Wolfson Gene Therapy Unit, London, has transitioned to MeiraGTx who have obtained MIA (IMP) and MS Licenses recently for manufacturing their own pipeline of gene therapy viral vectors. This network of facilities, operated by 21 organisations, comprises 15 dedicated cell therapy sites, 6 dedicated gene therapy sites and 4 multifunctional sites. More than 45% (~ 3016 m^2) of the total cleanroom operational space is dedicated to gene therapy whilst the dedicated cell therapy footprint is 27% (~ 1745 m^2). Multi-functional facilities manufacturing both cell and gene therapies comprise 27% (~ 1795 m^2). Over 85% of the gene therapy capacity is commercially owned space. The remainder of the gene therapy cleanroom space is distributed between UK academia and the NHS with 8 cleanrooms per site being the median.

National booked capacity is running at 81%, compared to 77% for 2017. With 80% utility generally accepted as full, this trend again shows that global demand is outstripping supply for 2018 and into 2019/20 for certain Centres, due to the rapidly increasing pipeline of advanced therapies, as shown in

the Alliance for Regenerative Medicine Q3 2018 Data Report. With increased production comes an additional burden on analytical services, required to service this increase in the number of batches manufactured. The limited availability of capacity for relatively small, viral vector manufacturing is considered by the UKs academic community to be a rate limiting step for therapies in early development. However, this may be eased by the opening of the new Kings College London, Rayne facility which will approximately double its capacity.

The network of facilities employs over 500 people full-time, an increase of ~ 40% from last year. In March 2018, the ATMP Apprentice programme was launched with 8 organisations employing 17, Level 5, apprentices. These individuals will gain knowledge of the industry, hands on manufacturing skills whilst studying for an ATMP Foundation degree at the University of Kent. This is the first of several industry specific programmes designed to support and grow the cell and gene therapy UK workforce.

This major investment in facilities and manufacturing capacity, together with the associated investment in new jobs will result in significant growth in manufacturing capability in the UK, which is essential if the UK is to continue to fulfil its potential in cell and gene therapy, within a competitive global market place. Clearly a burgeoning sector and with the commercial side growing quickly, the Cell and Gene Therapy Catapult shall continue to evaluate and reflect on this growth in future reports.

2 Introduction and methodology

As more and more cell and gene therapy products undergo transition from pre-clinical promise to clinical reality, there is an increasing demand for facilities that offer GMP manufacturing services for these advanced therapies. The Industry-led Advanced Therapy Manufacturing Taskforce published an Action plan in 2016 listing actions that the UK should consider taking in order to capture manufacturing in the UK. The document highlights the important opportunity cell and gene manufacturing affords to UK economic growth.

Through conducting a UK-wide GMP manufacturing survey, national resource (facilities and workforce) and spare manufacturing capacity can be identified and used as a basis for future infrastructure and investment decisions. With this in mind, the Cell and Gene Therapy Catapult performed an initial review of the capacity and capability of the cell and gene therapy manufacturing base within the UK in April 2013. A report based on these data was published in April 2014 and has been subject to annual review every successive year since.

The aim of the report is to collect and summarise information on each of the MHRA-licensed cell and gene therapy manufacturing sites in the UK with GMP capacity accessible to the market for collaboration. Amongst other elements, the report includes:

- An analysis of the overall capacity and capability for cell and gene therapy manufacture within the UK. The analysis highlights the distribution of the capabilities on the basis of the geographical location of the facilities (London, South England (non-London), Midlands and North and Scotland), product type (cell therapy, gene therapy or multifunctional) and track record of experience (types of cells and/or viral vector/plasmid DNA and manufacturing processes).
- A profile of the MHRA-licensed cell and gene therapy manufacturing organisations. Each profile provides a brief overview of the organisation, the geographic location of their facilities, and an overview of the technical and quality capabilities, alongside predictions of the available operational capacity at the facilities.

To conduct the 2018 annual review, new facilities and all facilities listed in the preceding report were contacted in September 2018 and asked for updates with regards to their capability and capacity. Changes made to the facility listings since November 2017 are documented in Table 1, including the addition of the Cell and Gene Therapy Manufacturing Centre, MeiraGTx and TC Biopharm and expansion of pre-existing facilities at Cobra Biologics and Scottish National Blood Transfusion Service.

This year's report does not account for data from The Wolfson Gene Therapy Unit (WGTU) as the facility has transitioned to Meira GTx who have recently obtained MIA (IMP) and MS Licenses. Meira GTx and TC Biopharm are dedicated to the production of their proprietary pipelines.

	Organisation/facility name
New listing	
1	Cell and Gene Catapult manufacturing centre
2	Meira GTx
3	TC BioPharm
Expansions	
4	Cobra Biologics
5	Scottish National Blood Transfusion Service (SNBTS)
Other facilities	
6	BioReliance
7	Immetacyte Ltd (formerly Cellular Therapeutics Ltd)
8	Cancer Research UK Biotherapeutics Development Unit (CRUK)
9	University College London, Great Ormond Street Hospital Cellular Therapy Laboratories (GOSH)
10	Biomedical Research Centres GMP Unit at Guy's and St Thomas' (GSTT BRC)
11	Imperial College London, John Goldman Centre for Cellular Therapy
12	Moorfields Eye Hospital, Cells for Sight Cell Research Unit
13	Newcastle University, Newcastle Cellular Therapy Facility
14	NHS Blood and Transplant (NHSBT) Birmingham
15	NHSBT Filton
16	NHSBT Langford
17	NHSBT Speke
18	Oxford BioMedica, Harrow House manufacturing facility
19	Oxford Biomedica, Yarnton manufacturing facility
20	King's College London, Rayne Cell Therapy Suite (RCTS) and The Wellcome Trust / BRC Clinical Research Facility and Cell Therapy Unit (CTU)
21	RoslinCT
22	Royal Free Hospital London, Centre for Cell and Gene Tissue Therapeutics
23	University of Birmingham, Advanced Therapies Facility
24	The University of Manchester Cleanroom Facility
25	University of Oxford, Clinical BioManufacturing Facility (CBF)

Table 1 MHRA-licensed Facilities in the 2018 UK GMP Manufacturing Capability and Capacity Report

3 National picture of cell and gene therapy manufacture

Geographic locations

The map below (Figure 1) highlights the diverse geographical spread of sites across the UK, with a clear cluster around the Greater London area (six facilities). MHRA licensed facilities specialising in cell therapy manufacture are shown by blue markers; gene therapy manufacture by pink markers and both cell and gene therapy manufacture by green markers. It should be noted that, King's College RCTS and King's College CTU are combined for analysis throughout this review.

Figure 1: Location of MHRA-licensed cell and gene therapy manufacturing sites within the UK

The infographic on the following page (Figure 2) shows a snapshot of overall capabilities for cell and gene therapy manufacture within the UK. Table 2 provides details of the total cleanroom footprint and the distribution of the number of cleanrooms nationwide by region; London, South England (non-London), Midlands and Northern England and Scotland. The median number of cleanrooms per site is 5 and average booked capacity for 2019 is already at 64%. South England (non-London) hosts 43% of the total UK footprint and Scotland has increased its footprint to 29% in the last year. The cleanroom footprint for the Midland and Northern regions are comparable to London which retains a relatively large number of early translational facilities. Commercially focussed facilities are generally larger in footprint and have a several fold increase in staff numbers, compared to earlier translational centres. Figure 3 provides a more detailed breakdown of the total cleanroom footprint within the UK with respect to both cell and gene therapy manufacture. It should be noted that, for this analysis, cleanroom footprint is defined to include essential personal airlock (PAL) and material airlock (MAL) areas.

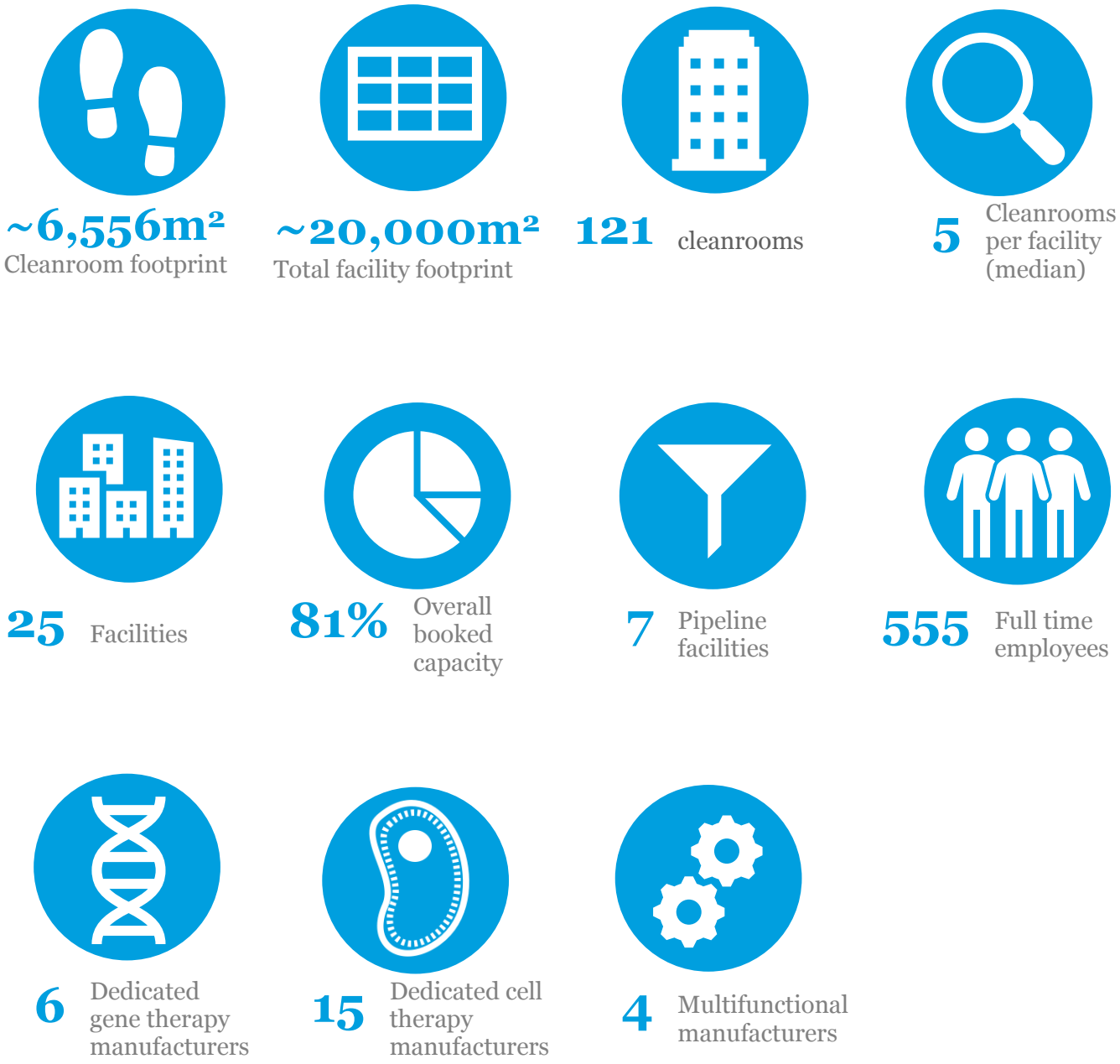
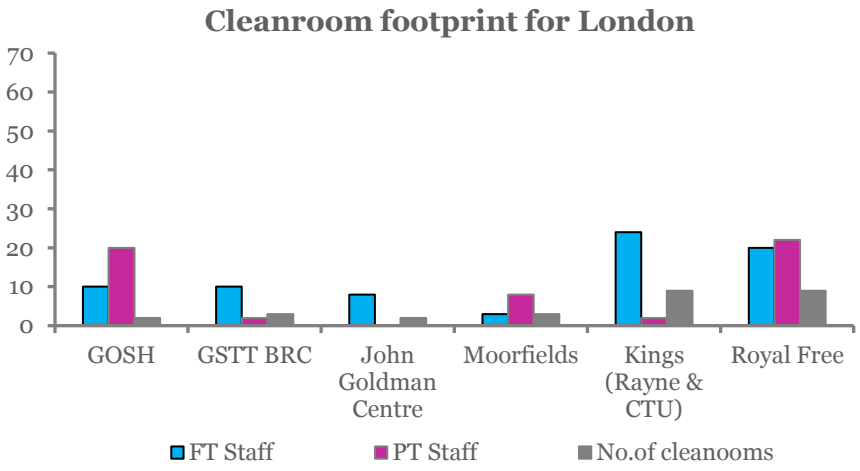
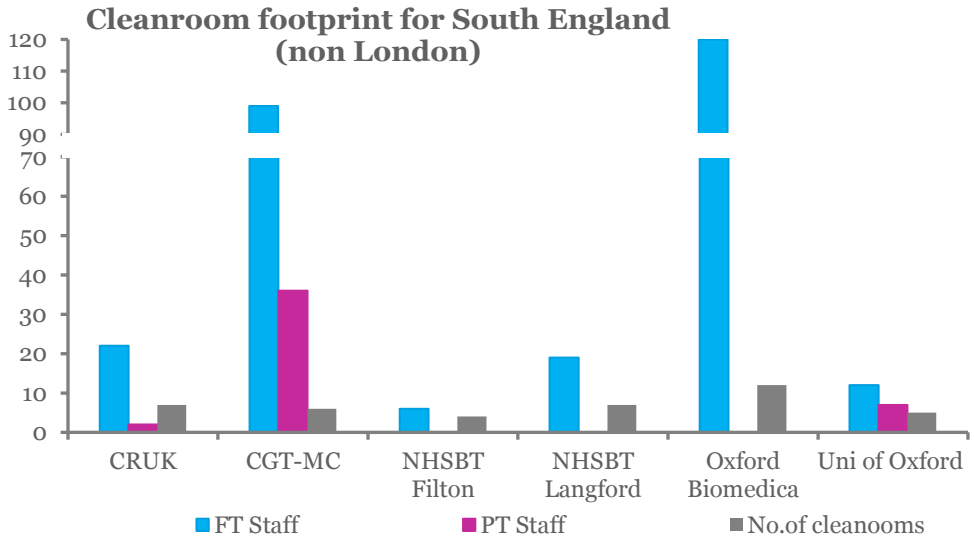


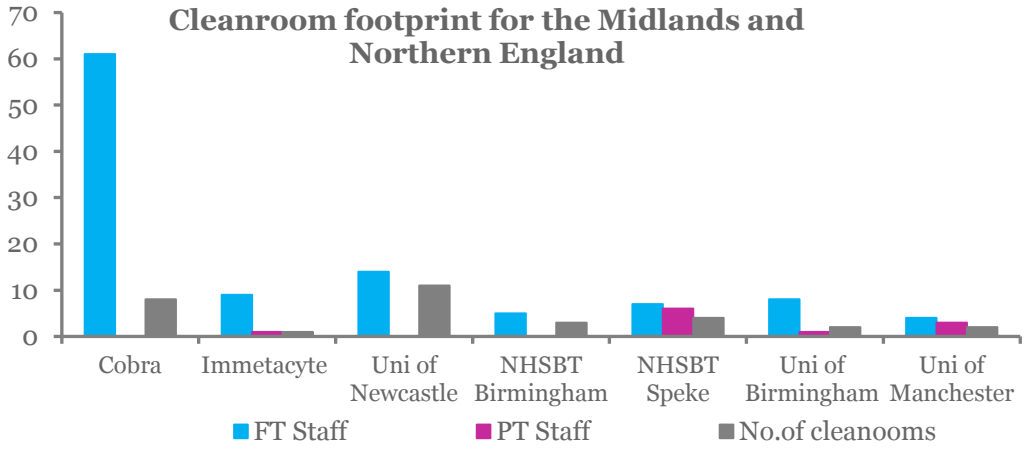
Figure 2: Snapshot of cell and gene therapy facilities in the UK

UK Location	Cleanroom Footprint (m²)	FT Staff	PT Staff	No. of cleanrooms
London	806.5	75	67	28
South England (non- London)	2787.1	231	45	41
Midlands and North	1071.5	108	11	31
Scotland	1891	94	1	21
UK Total	6556.1	555	111	121

Table 2: Cleanroom footprint in the UK for cell and gene therapies







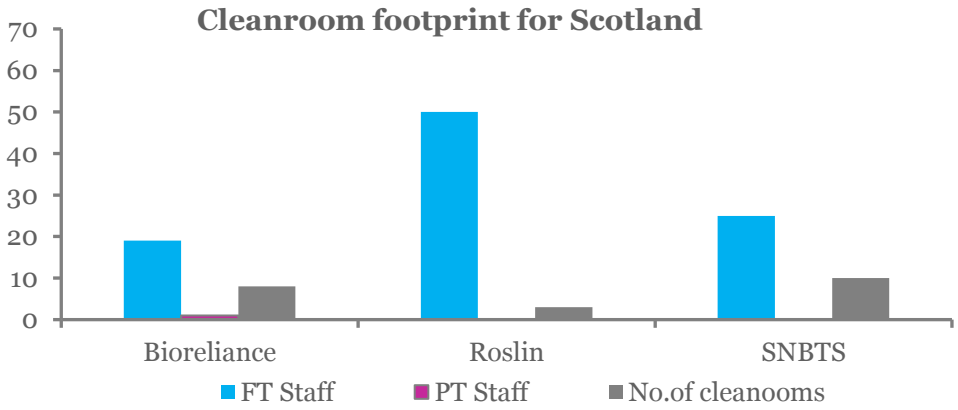


Figure 3: Distribution of cleanroom number and staff across the facilities in London, South England (non-London), Midlands and North England and Scotland (these charts incorporate cell therapy sites, gene therapy sites and multifunctional sites).

Key: FT = full time, PT = part time

N.B For the purpose of this figure, Oxford Biomedica's two sites have been incorporated together.

3.1 Cell therapy manufacture

A snapshot of the nation's GMP cell therapy manufacturing resource for 2018 is captured in Figure 4. A network of 19 facilities are in place, 4 of which have multifunctional cell and gene therapy production capabilities. The facilities supply approximately 3,540m² of licensed total cleanroom space between them for the manufacture of cell therapies. Over 61% expansion in cell therapy cleanroom footprint has taken place over the last year via the addition of the new CGT Catapult manufacturing centre facility and expansion of the SNBTS facility. The sector has an extremely positive outlook with numerous planned expansion projects on the horizon. The extensions, scheduled to come online before the end of 2019 (detailed in section 4), aim to increase current licensed cleanroom space by approximately 1,500m². The figures in this report do not include these as they are yet to be licensed facilities. The figures below combine the dedicated cell therapy manufacturing sites with multifunctional facilities.

Figure 4: Snapshot of cell therapy facilities in the UK

The current UK capability covers the whole technology sphere of expected manufacturing requirements. The figure below shows a breakdown of the types of processes and cell types that the various organisations have dealt with in the past or are currently working with. This section of the analysis includes the 4 multifunctional sites (King's College, CRUK, the University of Oxford's CBF site and the CGT Catapult Manufacturing Centre, which are capable of viral vector manufacture.

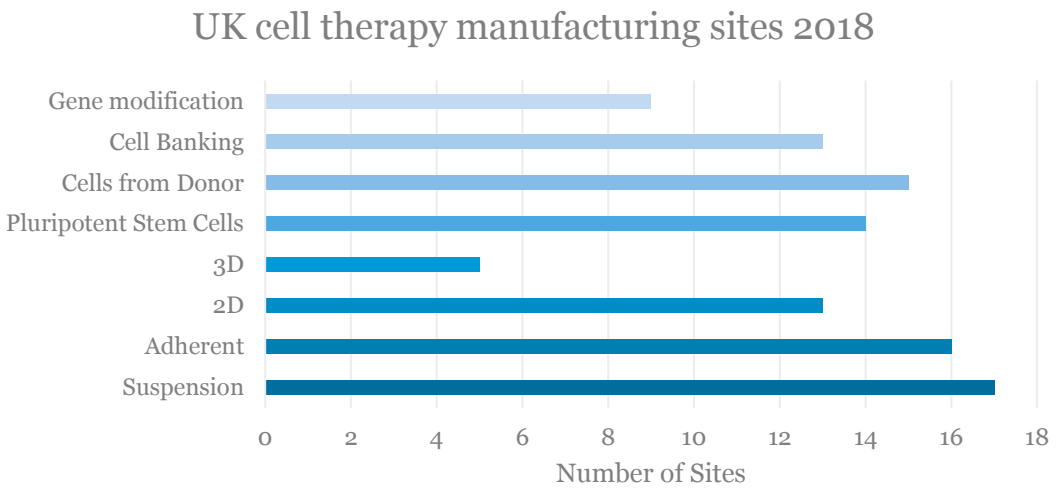
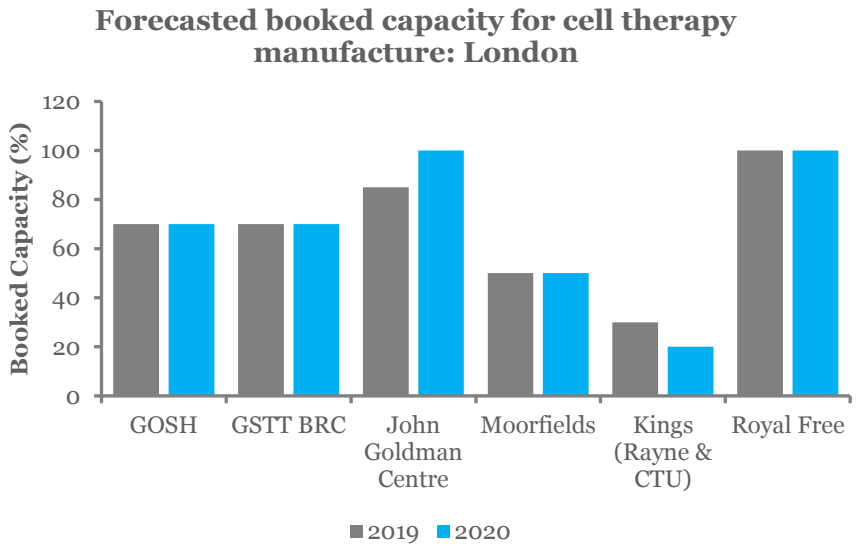
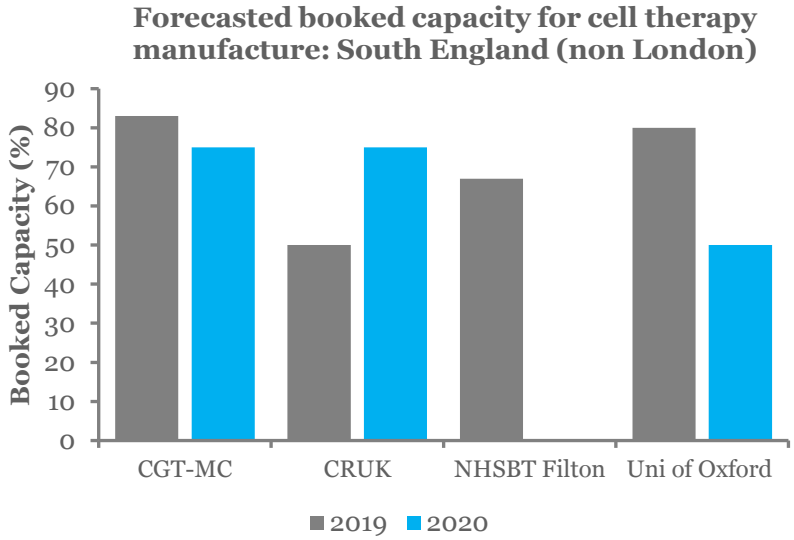


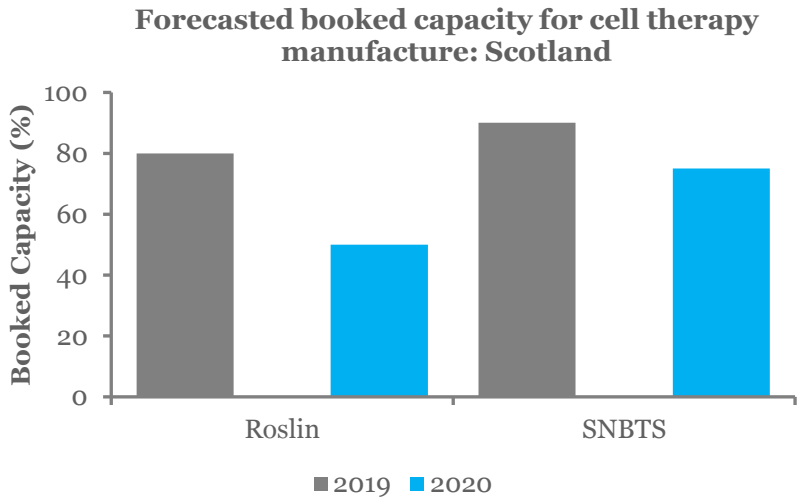
Figure 5: Summary of cell therapy process capability in the UK

Key: *Gene modification – ex vivo modification of cells to be used as a medicinal product; Cell banking – laying down of master cell banks and working cell banks including any necessary testing; Cells from donor – handling primary tissues and cells; pluripotent stem cells – culture of induced pluripotent stem cells from donor tissue or culture of human embryonic stem cells from donor tissue; 3D – culture of cells in a 3D environment; 2D – culture of cells in a 2D environment; Adherent – culture of anchorage dependent cells; Suspension – culture of anchorage independent cells. N.B. regarding pluripotent stem cells, 7 sites have capability to culture hESCs and 5 sites have capability to culture iPSCs.*

Figure 6 highlights the projected booked capacity for cell therapy manufacture from 2019 and 2020 in in the UK regions. Whilst limited capacity is available in 2019 and 2020 across the UK, the size of facility and cleanroom needs to be considered together with the technical expertise available; a more detailed breakdown is shown in Table 3, highlighting the strong and diverse manufacturing base in the UK for clinical development. Some spare capacity is predicted in 2019 and this is indicative of project cycles ending and contracts yet to be finalised.







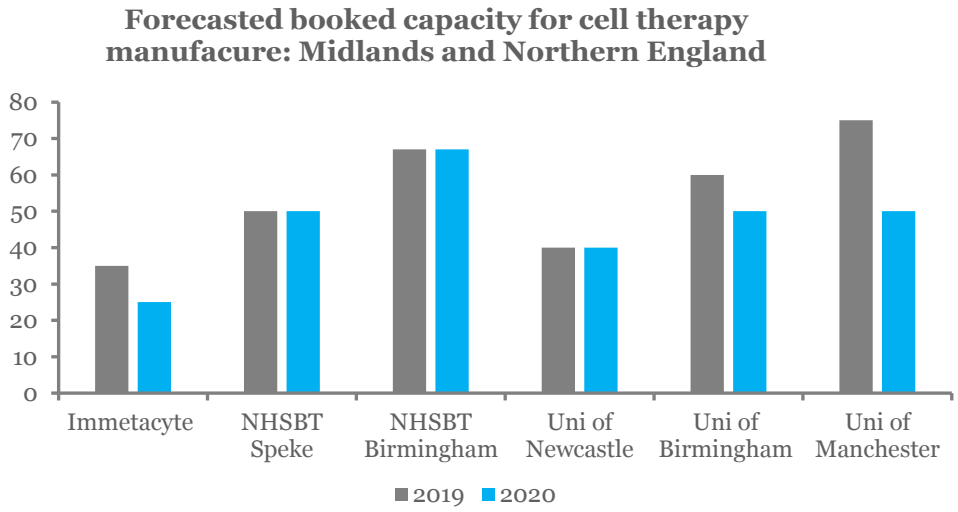


Figure 6: Forecasted booked capacity for cell therapy manufacture in London, South England, Midlands and Northern England and Scotland

Organisation	Parallel products (open/closed)	Capability										Availability 2019 (%)
		Auto suspension	Auto adherent	Allo suspension	Allo adherent	2D	3D	Human ES	iPS	Cells from donor	Other	
CGT -MC	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	CB, GM	17
CRUK	2			✓	✓			✓		PE	CB	50
Immetacyte	6 (4/2)	✓	✓	✓	✓					✓	GM	65
GSTT BRC	4 (1/1)*	✓	PE	✓	PE	PE	PE	PE	PE	PE	GM (PE of CB)	30
John Goldman Centre	4 (4/0)	✓	✓	✓	✓	✓				✓	CB	15
Kings (Rayne & CTU)	4	✓		✓	✓				✓	✓	CB, GM	70
NHSBT Speke	2 (1/1)	✓	✓	✓	✓	✓	✓			✓	CB, GM	50
NHSBT Filton	2	✓		✓		✓				✓		33
Roslin	4	✓	✓	✓	✓	✓		✓	✓	✓	CB, GM	20
SNBTS	DoP	✓	✓	✓	✓	✓		✓	✓	✓	CB	10
GOSH	5	✓	✓	✓		✓				✓	GM	30
Moorfields	2		✓		✓	✓	✓	✓		✓	CB	50
Uni of Newcastle	9	✓		✓	✓	✓		✓		✓	CB	60
Uni of Oxford	DoP			✓	✓							20
Royal Free	7 (7/0)	✓	✓	✓	✓	✓	✓	✓	✓	✓	CB, GM	0
Uni of Birmingham	3-5 DoP	✓	✓	✓	✓	✓				✓	CB	40
Uni of Manchester	2-3 DoP	✓	✓	✓	✓	✓		✓	✓	✓	CB, GM	25
NHSBT Birmingham	3	✓	✓	✓	✓	✓	✓			✓	CB	33

Table 3 GMP Cell Therapy capability and availability summary at UK organisations for 2018

*Key: PE – Key staff have previous experience but not at this organisation; DoP – Dependent on Process; CB – Cell Banking; GM – Gene Modification; * remaining parallel products can be open or closed.*

3.2 Gene therapy manufacture

Licensed facilities specialising in the manufacture of viral vectors and/or essential plasmid DNA for *in vivo* or *ex vivo* cell modification were again tracked this year. Figure 7 gives a snapshot of the gene therapy manufacturing facilities in the UK. Whilst the number of dedicated gene therapy facilities has remained at six (through the repurposing of the Wolfson Gene Therapy Unit for a dedicated commercial pipeline supply, the total cleanroom footprint for gene therapy manufacture has increased significantly by the expansion at Cobra and opening of the multifunctional Cell and Gene Therapy Catapult manufacturing centre and MeiraGTx.

Figure 7: Snapshot of gene therapy facilities in the UK

Figure 8 shows a breakdown of the types of plasmid, vector and cell producer systems in which facilities with gene therapy capabilities are experienced. This includes dedicated manufacturers (NHSBT Langford, Cobra Biologics, Oxford Biomedica Yarnton site, Oxford Biomedica Harrow site and Bioreliance) and multifunctional gene therapy facilities (CRUK, Kings College, The University of Oxford and the CGT-MC). There is broad coverage of capabilities, from supporting plasmid DNA through to GMP-grade manufacture of lentivirus and gamma-retrovirus, two of the main viral vectors used in *ex vivo* gene modification processes. On the other hand, the supply of AAV used predominantly for *in vivo* gene modification is severely restricted. This lack of viral vector manufacturing has been identified by the Advanced Therapy Manufacturing Task Force and was a key recommendation to Government in its 2016 published action plan as an important opportunity for the UK. With the announced £18M investment by Cobra Biologics for its UK manufacturing operations and the expansion of the Kings College London RCTS facility, the situation should start to improve. In addition, 6 x 185m² flexible modules are available through the CGT-MC in 2019.

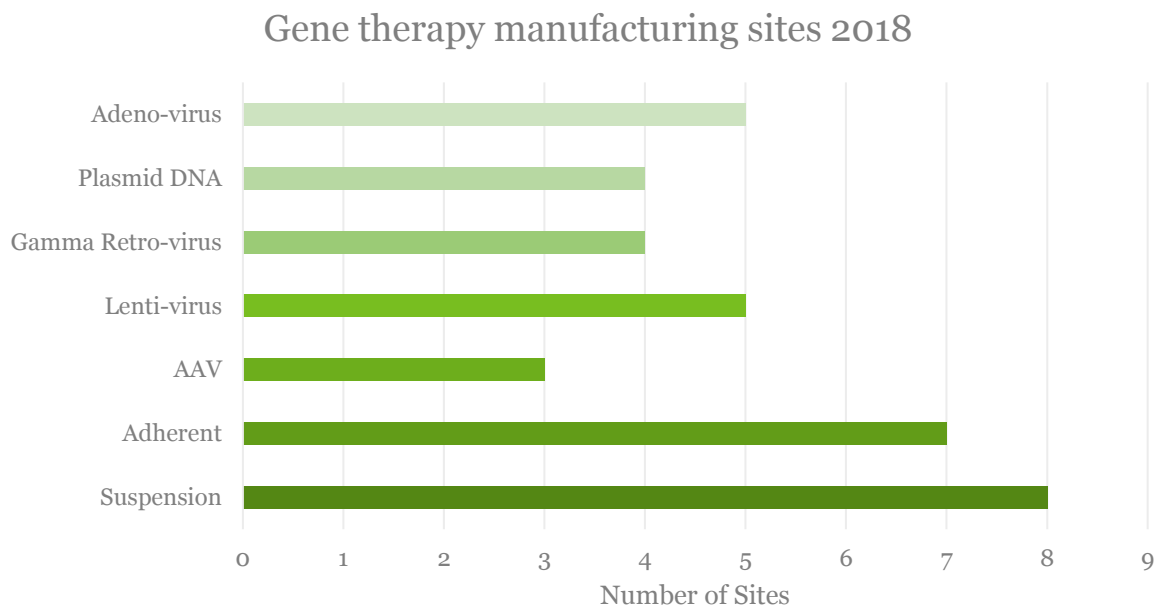


Figure 8: Summary of gene therapy activities across UK facilities

Key: Plasmid DNA – material used directly as IMPs and/or starting material used for transient infection to enable manufacture of viral vectors; Adenovirus/Gamma Retrovirus/Lentivirus/Adeno-associated virus (AAV) – key types of viral vectors used directly as IMPs and/or starting material used for transduction of cells ex vivo; Adherent – culture of anchorage dependent cells; Suspension – culture of anchorage independent cells.

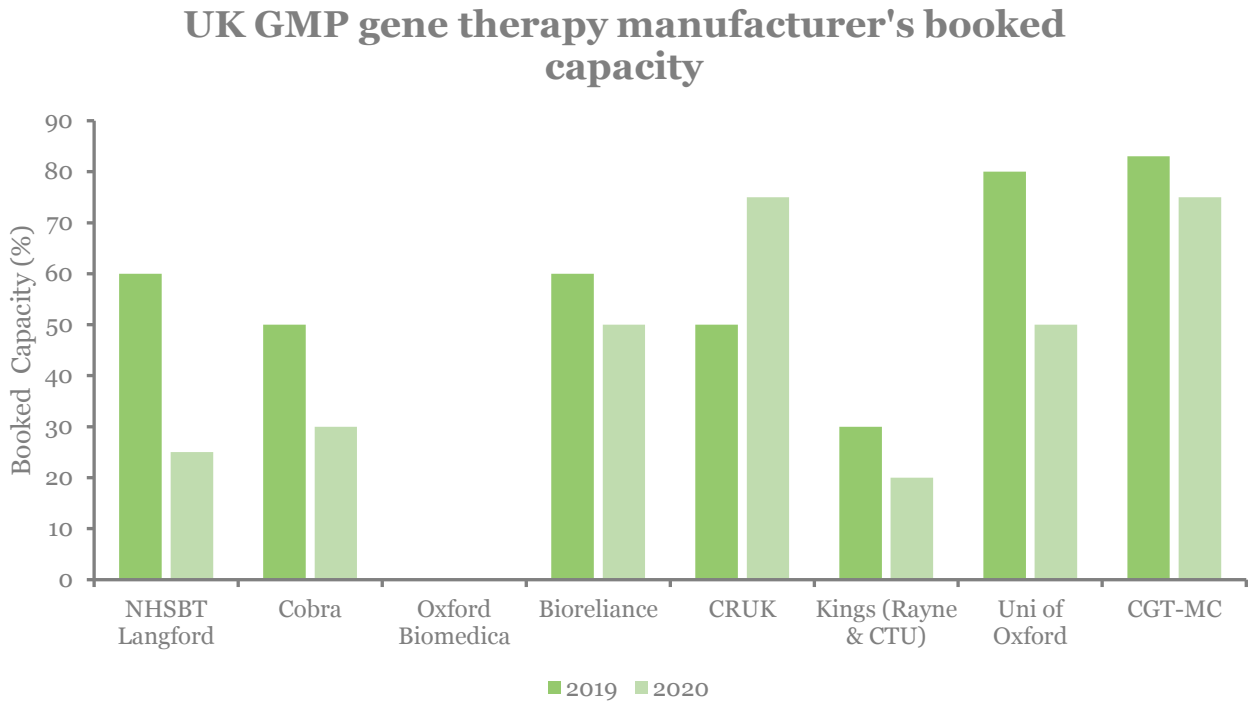


Figure 9: Predicted booked capacity for gene therapy manufacturing facilities in the UK

Table 4 shows a summary of the capability and availability at all the gene therapy production centres. Spare capacity at the manufacturing centres is essential for prospective growth within the UK gene therapy sector. Again, pipelines are very full, with small amounts of spare capacity only at some centres. The opening of the second phase of the Cell and Gene Therapy Catapult Manufacturing Centre in 2019, will further enhance the existing viral vector manufacturing network and facilitate the largescale manufacture and initial commercial supply of gene therapies.

Organisation	Capability									Availability 2019
	Parallel products	Suspension	Adherent	AAV	Lenti-virus	Gamma retro-virus	Plasmid DNA	Adeno-virus	HTA License	
CGT Catapult	✓	✓	✓	✓	✓	✓	✓	✓		17
CRUK	2	✓	✓	✓	✓		✓	✓		50
Kings (Rayne & CTU)	4	✓	✓		✓	✓			✓	70
NHSBT Langford	2	✓					✓			40
Uni of Oxford	DoP	✓	✓		PE	PE		✓		20
Cobra	DoP	✓	✓	✓	✓		✓	✓		50
Oxford Biomedica	DoP	✓	✓		✓	✓				Unavailable
Bioreliance	8	✓	✓	PE	PE	✓		✓		40

Table 4: Gene therapy capability and capacity for 2019

Key: DoP – dependent on process; PE – previous experience

N.B For the purpose of this figure, Oxford Biomedica's two sites have been incorporated together.

3.3 Multifunctional facilities

Four facilities are multifunctional with cell and gene therapy production capabilities. Summary data from the 4 facilities; Cancer Research UK, King's College London (Rayne and CTU), University of Oxford CBF and the CGT Catapult Manufacturing Centre are shown in Figure 10. These facilities, identified in this report as cell therapy production sites, offer additional resources which can be deployed to gene therapy production and further strengthen the UK gene therapy industry. See section 5 of this report for more detailed information on these multifunctional facilities respectively.

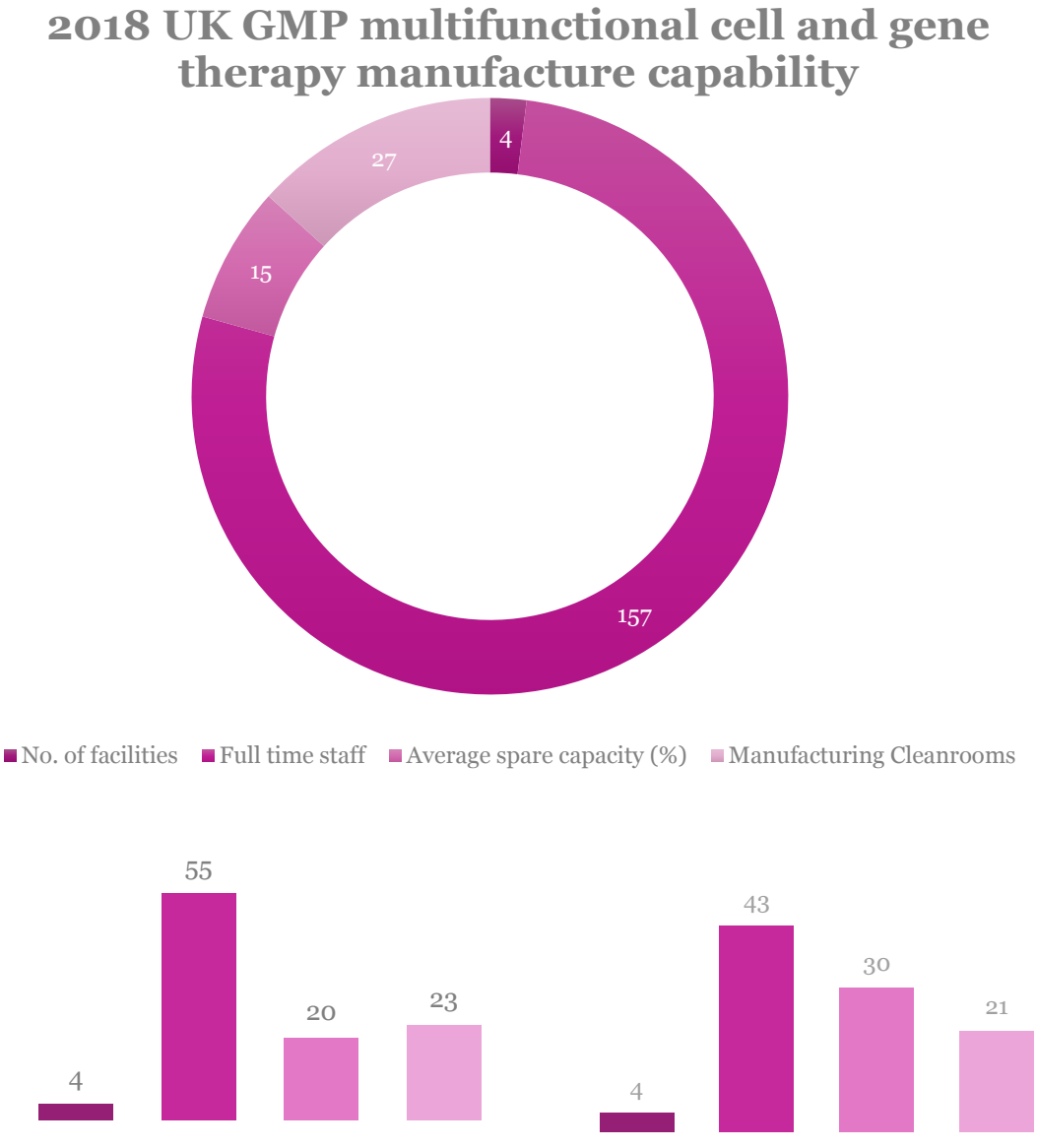


Figure 10 Summary Data for Multifunctional Cell and Gene Therapy Facilities 2018 (2016 & 2017 data inset)

4 Future capacity and expansion

Annual reviews of the UK manufacturing landscape are important to identify facility expansions, increase in personnel numbers and track records and the opening of new facilities. As a forward-looking statement, a description of upcoming expansions of existing facilities or newly licensed sites has been outlined below:

- Phase 1 of Advent Bioservices' own new facility in Cambridgeshire, is due to be licensed and operational from Q3 2019 and includes two completed suites (185m² each), comprising B, C and PD/QC labs, offices and storage space. This facility is due to bring to market 199 m² of cleanroom footprint (including MAL & PAL areas) in its first phase. However, the site has capacity for a further ~7,500 m² of additional development.
- Phase 2 construction of the Cell and Gene Therapy Catapult Manufacturing Centre was started in Q1/Q2 2018 to fit out the already constructed space on the second floor of the existing building with six additional cleanrooms (185 m² each) and offices. This project is expected to be completed in 2019.
- The Rayne Cell Therapy Facility at King's College London is in the process of building a new suite of cleanrooms, which will boost vector production capacity by 50%. The additional ~60m² of cleanroom space is scheduled to be available in 2019 following completion of qualification procedures.
- Expansion is also underway at Cobra Biologics to increase the Company's viral vector and DNA plasmid production platforms for clinical and commercial supply. Phase I of the construction will create an additional 95 m² of cleanroom space for the UK industry and is scheduled to be available in 2019.
- Oxford BioMedica announced the further expansion of its manufacturing capabilities with a new significant facility of approx. 7,800 m² scheduled to be ready in Q1 2020. Planned Phase I and Phase 2 expansion will fit out around 4,200 m² with four GMP clean room suites and two fill and finish suites as well as offices, warehousing and QC laboratories, with space available for future expansion. The facility is scheduled to be ready for GMP manufacture in Q1 2020 which will more than double the group's bioprocessing capacity.
- Expansion plans remain at Cellular Therapies, Great Ormond Street to significantly extend manufacturing cleanroom space. Seven new cleanrooms will occupy the top floor of the Zayed Centre for Research and allow multi-product processing. Construction started in Q1/Q2 2016 and completion will be at the start of 2020, creating an additional 697 m² of space for the organisation.
- Expansion plans are also on the horizon for the University of Oxford CBF and RoslinCT. In addition, NHSBT Birmingham plasmid manufacture will move to Filton and double its capacity in 2020. Further details regarding these expansion projects will be provided when available in the 2019 review.

To our knowledge no other new MHRA-licensed cell or gene therapy manufacturing sites are due to come online in 2018/2019, which offer collaborative potential. However, please contact gmp@ct.catapult.org.uk if you have any information regarding new facilities of which we are not aware.

5 Manufacturing organisations

Advent Bioservices

Room 1/458, 1st Floor
Royal Free Hospital
Pond Street
London
NW3 2QG

Vision Centre
A1301 Sawston Bypass
Cambridgeshire
CB22 3JG
(Under development)

Tina Crombie
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tcrombie@adventbio.uk
0203 627 9960/ 07905 658843

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Chief Operations Officer
ppire@adventbio.uk
0203 627 9960

Facility

Advent Bioservices Ltd is a cell therapy Contract Manufacturing Organisation currently operating from the CCGTT, an ATMP manufacturing unit owned and operated by the Royal Free London NHS FT, under the CCGTT licences. The facility consists of GMP laboratories, two quarantine goods stores, two released goods stores, and male/female changing rooms, two Quality Control labs, one GMP Process Development lab and staff offices as well as RFH/UCL biobank cryogenic cell repository.

The CCGTT GMP suite comprises grade D laboratories (including a lab for in-process QC accessible from D and B laboratories), grade C laboratories for long-term "closed" cell expansion and grade B laboratories with individual grade B gowning compartments to prevent cross-contamination. One of the grade B laboratories is dedicated to handling GM products under negative pressure within a positive pressure background.

Phase 1 of Advent Bioservices' own new facility in Cambridgeshire includes two completed suites (185m² i.a. each) comprising B, C and PD/QC labs, offices and storage space. Following revised business plans, application for MHRA/ HTA license will be Q3 2019. The facility has infrastructure in situ and capacity for 7,566m² additional development.

Sawston Vision Centre external

Sawston Vision Centre QC lab showing pass through from B lab

Licence

CCGTT MHRA MA(IMP) MS 11149 / HTA licence 11016

Track record and experience

Allo/Auto	Suspension	Adherent	2D	Cells from tissue	Cell banking
✓	✓	✓	✓	✓	✓

Personnel

- GMP Team of 6
- Quality Team 2
- QP through CCGTT

Capacity

Biomedical Research Centres (BRC) GMP unit at Guy's and St Thomas'

Advanced Therapy Manufacturing (GMP) Unit
NIHR Guy's and St Thomas' Biomedical Research Centre Clinical Research Facility
15th Floor, Tower Wing
Guy's Hospital
Great Maze Pond
London SE1 9RT

Laura Fry
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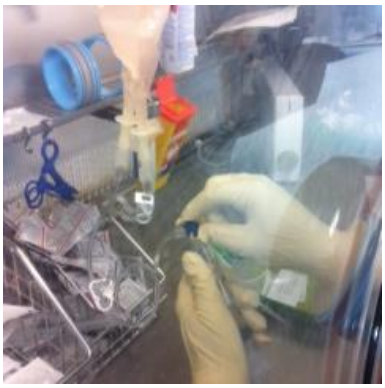
Facility

Guy's and St Thomas' BRC Advanced Therapy Manufacturing (GMP) Unit is a 125m² facility located on the 15th floor of Guy's Hospital Tower Wing. The main manufacturing area houses three grade D clean rooms which are in total 95m². Closed processing occurs within the clean rooms and each is equipped with an isolator for open processing.

Processing equipment	Analytical equipment
3 x Rigid four-glove Grade A isolators	Scepter cell counter
Incubators	Inverted microscopes
Controlled-rate freezer	MACS Quant Flow Cytometer
Centrifuges	FORTESSA Flow Cytometers
CliniMACS Plus, CliniMACS Prodigy cell isolators	7900 HT quantitative PCR
Sepax and SynGenX1000 cell isolators	
MACS Quant Tyto FACS cell isolator	
Xuri Bioreactor	
GentleMACS tissue processor	



Example of clean rooms at Guy's and St Thomas'

Licence

MHRA licences for IMPs and Specials; HTA licence for procurement, donor testing and processing.

Track record and experience

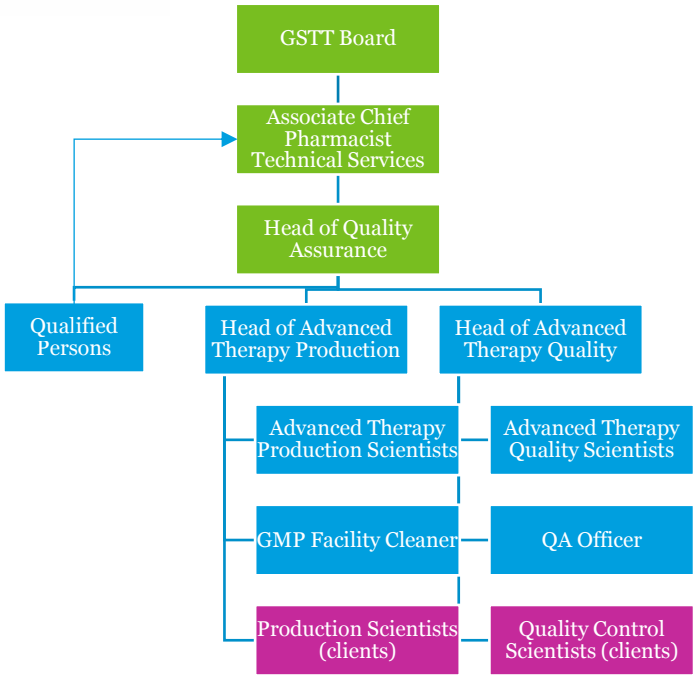
Experience with autologous T cells and autologous T-Reg cells at the facility.

	Suspension	Adherent	2D	3D
Auto	✓			Previous experience
Allo	✓	Previous experience	Previous experience	

Human ES Cell	iPS Cell	Cell isolation from donor tissue
Previous experience	Previous experience	Previous experience

Personnel

Two members of staff are permanently employed in the Unit to oversee the quality management system; a Head of Advanced Therapy Production and a Head of Advanced Therapy Quality. Two contract QPs are used for batch release. Five Advanced Therapy Production Scientists, two Advanced Therapy Quality Scientists and a Quality Assurance Officer are employed to assist with projects being undertaken within the unit. Client-teams of up to four operators may work in a hotel-like system, trained by the Unit to work in production and analytical roles.



Capacity

Guy's and St Thomas' CRF has indicated that it would be possible for them run up to five open and 10 closed projects per year.

BioReliance Ltd

Merck BioReliance® Services
Todd Campus
West of Scotland Science Park
Glasgow
G20 0XA

Susan Livingston
0141 576 2462
susan.livingston@bioreliance.com

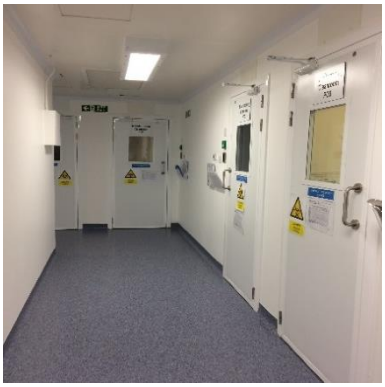
Angela Waugh
0141 946 9999

Facilities

BioReliance® Services has a long established facility for:

- Mammalian/ Insect Cell and Viral Banking
- Bulk Viral production
- Investigational Medicinal Products manufacture

BioReliance® Services has 8 cleanrooms on the Glasgow site. These are EU grade B with grade B and D change areas. Each cleanroom has a separate air handling system supplying HEPA filtered air and a local EU Grade A Laminar flow hood where open manipulations are carried out. On-site in Glasgow there are local Facilities Management, Validation and Equipment Support staff. The site also has a full service biosafety testing operation where cell banks, viral seeds, clinical lots and commercial lots can be rapidly tested and released to clients.



Merck BioReliance ® Services Glasgow facility

Licence

- MHRA MIA(IMP) licence no.: 22774 (Site 4473)
- FDA Facility establishment Identifier: 3005343934

Track record and experience

Experienced manufacturing team for handling a wide variety of cell types and culture platforms.

Cell culture technology and expertise;

- culture condition optimisation
- cell line adaptation to serum free
- optimising MOI and infection strategy

- stability studies
- long-term storage

Significant collective experience in mammalian and insect cell banking; established viral manufacturing experience producing viral vectors and vaccines (viral clinical trial batches in addition to virus seed stocks). Culture systems in flat and suspension stock (T flasks; shaker & spinner flasks; cell factories/ cell stacks and wave bioreactors). Downstream purification methods used include ultracentrifugation (including density gradient), TFF/UFF, chromatography methods and filtration.

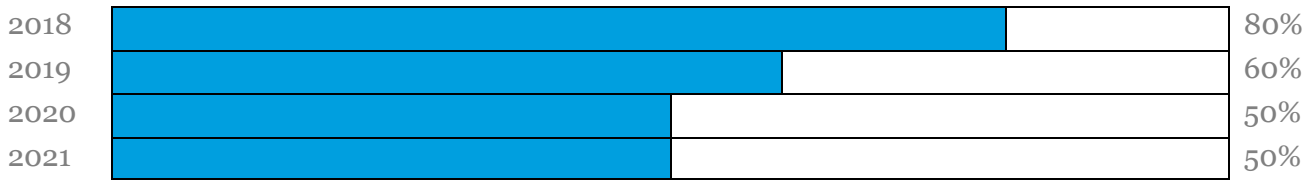
Personnel

The Manufacturing Manager (Angela Waugh) reports directly to the Director of Operations for the Manufacturing facility. Angela has been a member of the BioManufacturing team since 2001 and has been leading cell and virus manufacture, supporting client campaigns from initial cell banking right through to commercial approval. Running a facility with routine FDA and MHRA inspections, she has significant expertise in compliance requirements in relation to both the productions and the manufacturing facility.

Our manufacturing manager has a team of highly experienced scientists running our client projects supported by a wider team of experienced cleanroom personnel. Senior scientific staff liaise with clients to define the scope of the project and coordinate the work with the processing team. Average tenure amongst our senior scientific staff is over 12 years.

In addition to the manufacturing team, Merck BioReliance® Services allocates a dedicated Programme Manager to each production to ensure smooth running of the projects. The site also has dedicated QA resource ensuring approval of manufacturing documentation prior to processing and subsequent batch record review and a consultant QP for release of material to our clients.

Capacity



Cancer Research UK Biotherapeutics Unit

Clare Hall Laboratories,
Blanche Lane,
South Mimms,
Potters Bar,
Hertfordshire EN6 3LD

Alison Niewiarowska
alison.niewiarowska@cancer.org.uk
0203 4695755

Facility

Manufacturing suites

- Two segregated manufacturing suites each with grade C clean rooms for closed processing and a separate 6-glove isolator for aseptic filling.
- Grade B clean room operation has been successfully qualified
- HVAC is fully segregated between suites allowing multi-product manufacture. Areas are all designed for cat II containment.

Cell culture processing and analytical equipment	Other processing equipment
Various Microbiological Safety Class II and Laminar Air Flow Cabinets	Millipore Mobius Disposable Mixer System
Static and Shaking Incubator with CO_2 control, some with humidity control	Disposable TFF System
AppliFlex Bioreactor 20L and 50L (disposable)	AKTA Explorer, AKTA Pilot and AKTA Ready (Disposable) Chromatography Controller
Single-use Bioreactor (SUB Hyclone) 50L, 100L, 250L	Maxcyte for electroporation
NucleoCounter, Vi-Cell for automated cell counting	
FacsLyric (BD) for immunophenotyping	
CubiAnalyzer for metabolite analysis	
CellMetric Clone Image	
Sterile filling equipment	**Analytical equipment**
Flexicon FP50 Filling Machine	UV/VIS Spectrophotometers
Two 6-Glove Isolators	Plate Readers (visible light only - can be upgraded to bioluminescence or fluorescence)
	HPLC
	FTIR
	TOC Analyzer
	Q-PCR
	FACS
	Zetasizer Nano SP

	Stability Cabinets
	Sterility Test Isolator


Example photos of CR UK BDU facility

Licence

MHRA licence for IMPs has been granted and includes cell therapy products. The site does not have an HTA licence.

Track record and experience

The main experience to date has been with biologics production (recombinant proteins, monoclonal antibodies, DNA and viruses etc.). Adherent and suspension cell cultures have therefore been used for this purpose (CHO, A549, various Hybridoma cell lines). Technology transfer of a manufacturing process for expansion of human embryonic stem cells and their differentiation into dendritic cells has been completed successfully. Two GMP manufacture campaigns were completed successfully in 2017 and 2018 and drug product has been released for a CR-UK Phase I clinical trial. A further GMP manufacturing campaign is currently in progress and will finish in Dec 2018. A summary of staff experience can be found in Table 5.

The organisation has experience with the manufacture of cell and virus banks and has established cell line development technology for generating high yielding, recombinant cell lines for antibody and protein production using a commercial proprietary expression system.

The organisation has experience of large (250L) scale, disposable stirred tank and rocking bioreactors. A 70L CIP/SIP vessel is available for microbial fermentation.

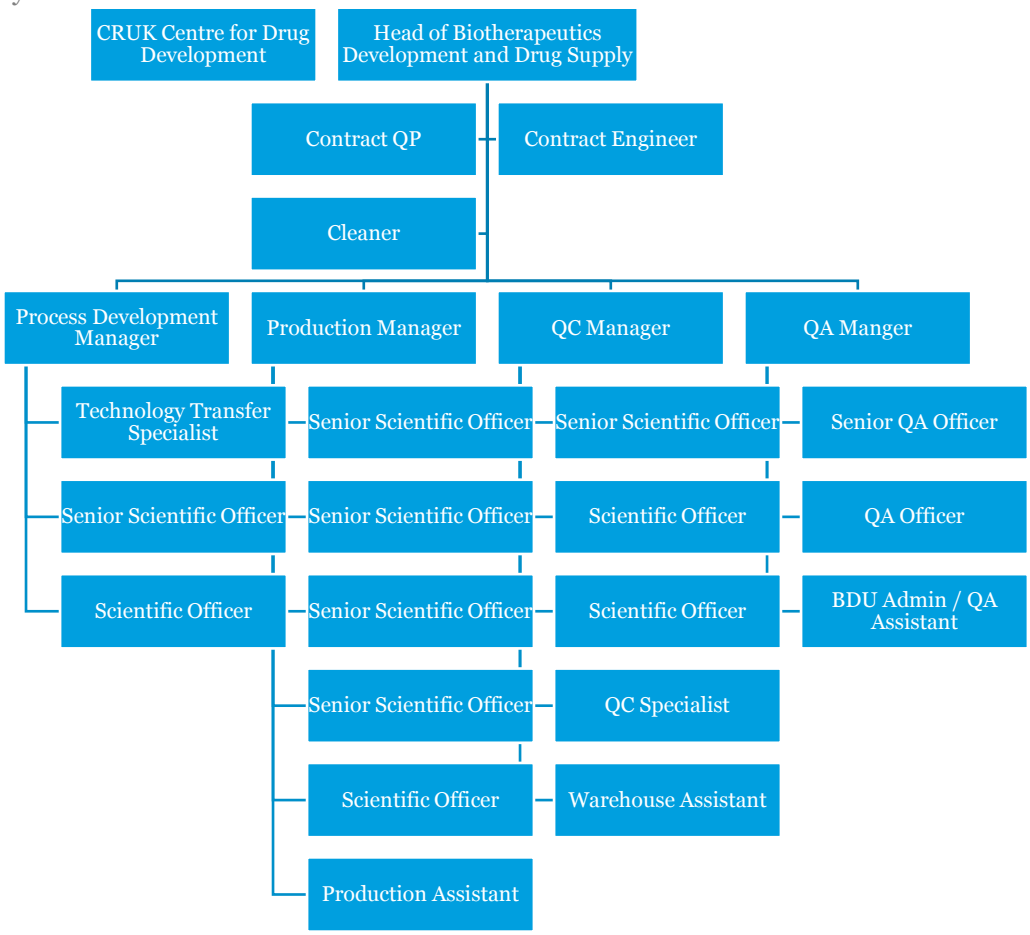
	Suspension	Adherent	2D	3D
Auto				
Allo	✓	✓		

Human ES Cell	iPS Cell	Cell isolation from donor tissue
✓		Previous experience

Personnel

In total there are 22 members of staff working within the facility supported by a contract QP for drug product certification and a contract engineer looking after maintenance of the plant. Staff are deployed where necessary but strict controls are in place to prevent staff working on multiple different product

streams. Main areas of experience have been focused on production of biologics from various cellular expression systems.



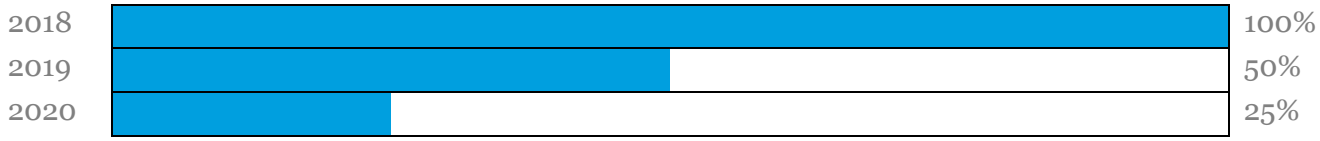
Capacity

CR UK BDU indicated that they could run up to three projects per year on the assumption that each would require lengthy tech transfer activities prior to GMP manufacture. The multiple GMP suites with separate air handling, personnel, material and waste segregation would enable up to two simultaneous production campaigns.

The main bottleneck limiting further increases in capacity appear to be staff numbers. A second bottleneck defined as space within process development labs to run through the process prior to GMP manufacture was also identified.

A concept design study was completed in 2015 to evaluate potential plans for facility expansion.

Standard methodology to plan capacity and occupancy are used and updated monthly.



Cell and Gene Therapy Catapult manufacturing centre

Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2FX

Sharon Brownlow PhD
Head of Collaboration
sharon.brownlow@ct.catapult.org.uk

Facilities

The Cell and Gene Therapy manufacturing centre opened in April 2018 and is a state-of-the-art MHRA MIA and MIA (IMP) licensed and GMP-compliant facility based within the Stevenage Bioscience Catalyst (SBC) campus, Hertfordshire. The phase I build (Figure 1) consists of 7,200 m² of shell and core construction with 3,405 m² of fitted-out clean module, warehouse, QC, business and support spaces.

The centre's unique operating model allows collaborator companies to manufacture their therapies at scale, all to GMP standards and underpinned by end-to-end expertise and practical support from CGT Catapult experts across scientific research, manufacturing, supply and regulation. Collaborators can have access to and control of one or more cleanroom modules to perform their own processes with their own staff and equipment without the capital investment of an own build. The collaborator personnel are supported by core CGT Catapult manufacturing centre teams such as QA, QC, warehouse and engineering allowing them to focus on their core manufacturing activities without the constraints of managing a GMP site on their own.

The phase 2 build will fit out the already constructed space on the second floor of the existing building with additional cleanroom modules and offices. The phase 2 project was started in Q1/Q2 2018 with completion expected in 2019.

Manufacturing modules

The phase 1 build includes 6 x 100 m² grade B or C modules consisting of 2 production rooms (87 m² and 16 m²) with single pass heating, ventilation, and air conditioning (HVAC) connected and dedicated to each module. All the modules are pre-qualified and licensed for ATMP and viral vector manufacturing. Technical corridors between the modules and a walk on ceiling (interstitial space) allow access to attend to maintenance, reducing the need for cleanroom re-instatement post maintenance activity.

The flow of materials and personnel into the production areas follows a unidirectional pathway. Separate dedicated pathways are established and utilized to prevent cross contamination between materials and people. Personnel enter the controlled environment via the main changing area, where outdoor clothes are removed, and scrubs are worn before entry into the controlled non-classified corridor (CNC) and D/C PALs. Sterile gowning is donned in the D/C PALs and module PALs before

entry into the production modules. Materials enter the CNC corridor via the material and product lobby (adjacent to the warehouse) and are passed through the D/C MALs, grade C corridor and module MALs before entry into the production areas. The material surfaces are cleaned by a validated spray and wipe method or by the removal of a single outer bag (or wrap) in lieu of the cleaning procedure at the material and product lobby (M&PL) or MALs.

Each module and associated PALs and MALs are dedicated to a single collaborator while the main changing area, CNC corridor, D/C MALs and PALs and grade C corridor are shared. Upon leaving the production area, gowning is removed in the module MAL out or PAL out to prevent cross contamination in the shared areas. In addition, negative pressure sinks on all module entry and exit routes allow containment in the processing areas. Temporal segregation of the shared areas ensures confidential control of intellectual property in the multi-collaborator and multi-product facility.

The manufacturing modules are designed to flex to an autologous, allogeneic or viral vector process and can be adapted to support any cell and gene therapy company seeking to develop new market ready GMP processes. Companies currently developing their manufacturing processes in the modules are:

Adaptimmune – viral vector manufacturing
Autolus – semi-automated cell manufacturing process
Cell Medica – cell therapy manufacturing
Freeline Therapeutics – viral vector manufacturing

Warehouse

The warehouse is used for storage of collaborator raw materials and consumables, intermediates and finished products. The following storage facilities are available:

- Segregated multi temperature storage (room temperature (15°C to 25°C), 2-8o°C, -20o°C, -80o°C, short-term cryostore and controlled rate freezer)
- Two quarantine goods stores and two released goods stores
- Raw material sampling facilities
- Access to the on-site ThermoFisher European Cryohub, for the storage and distribution of starting and finished materials.

The warehouse is access controlled, restricted to CGT Catapult manufacturing centre warehouse personnel. Validated electronic tools for inventory management and materials requisition called Warehouse Management System (WMS) and VSR+ are employed at the CGT Catapult manufacturing centre to ensure end-to-end traceability in the manufacturing process. Warehouse staff are responsible for the receipt of goods into the warehouse, issue of materials from the warehouse, and inventory management. CGT Catapult manufacturing centre staff deliver the materials to Collaborators at the handover point in the D/C MALs.

Quality control labs

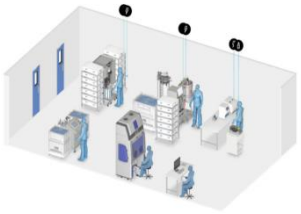
The QC laboratory complex comprises four central CGT Catapult manufacturing centre labs and three collaborator dedicated labs with grade D air cleanliness. The CGT Catapult manufacturing centre QC service provision includes:

- Environmental monitoring (viable and non-viable particulate monitoring) in the modules, outside of the manufacturing space and QC labs.
- Training and qualifying collaborator personnel in gowning and de-gowning procedures
- Microbiological testing (Bioburden and sterility, mycoplasma and endotoxin testing)

- Raw material testing
- Bioanalytics (in-vitro cell culture, qPCR, flow cytometry, ELISA and western blotting)

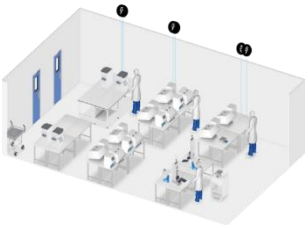
QC Processing Equipment:	QC Analytical Equipment:
Biological Safety Cabinets	Air Samplers
CO2 incubators	Air Particulate Counter (non-viable particles)
Sampling booth	Biolog Gen III Microstation System
Lightbox	Endosafe System (LAL)
	Celsis Accel System
	BACT/Alert BioMerieux
	ViCell XR Cell Counter
	EVOS Microscope
	AutoMate Express Nucleic Acid Extraction System
	Veriti Thermocycler
	Autopol VI Polarimeter
	Raman Spectrometer – Nanoram Pacer
	HIAC
	Micro Digital Osmometer
	Karl Fischer
	Hach HQ440D Multi-parameter meter
	SDS PAGE / CE
	SEC
	Nanodrop 8000
	Multi Spec Reader
	FACSCelesta BVR Flow Cytometer
	CytoFlex F low Cytometer

Grade B/C module 'as built'

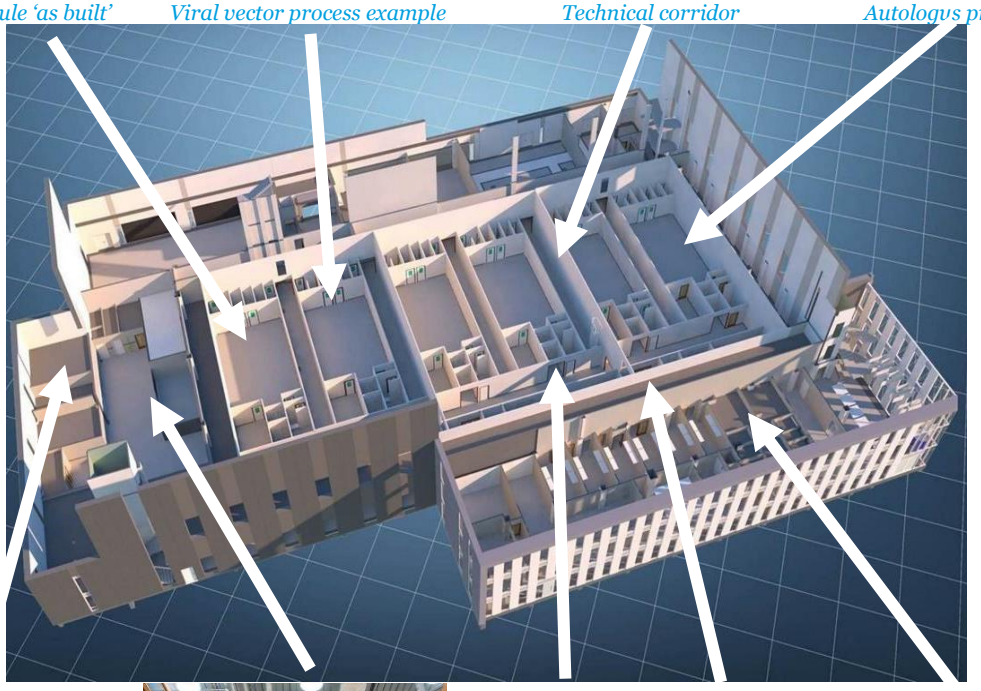


Viral vector process example

Technical corridor



Autologus process example



Grade D QC labs (second floor)

Warehouse

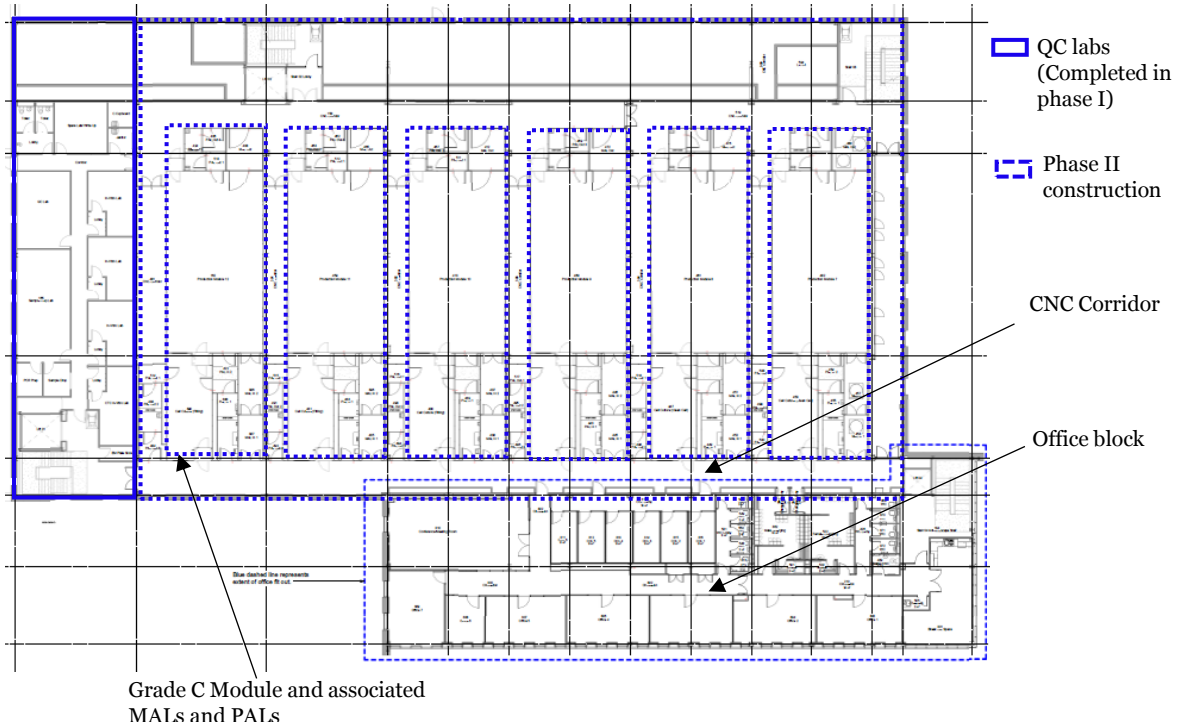
Grade C corridor

CNC corridor

Office areas

Phase 2 construction

Phase 2 involves the construction of six additional cleanroom modules (130m²) in the already constructed space on the CGT Catapult manufacturing centre's second floor. Each module will contain 2 grade C cleanrooms (106m² and 25m²) both with their own dedicated access airlocks. This increase in footprint and room flexibility, plus the inclusion of additional transfer hatches and fumigation chambers, will deliver a step-change in productivity increase for collaborator companies.



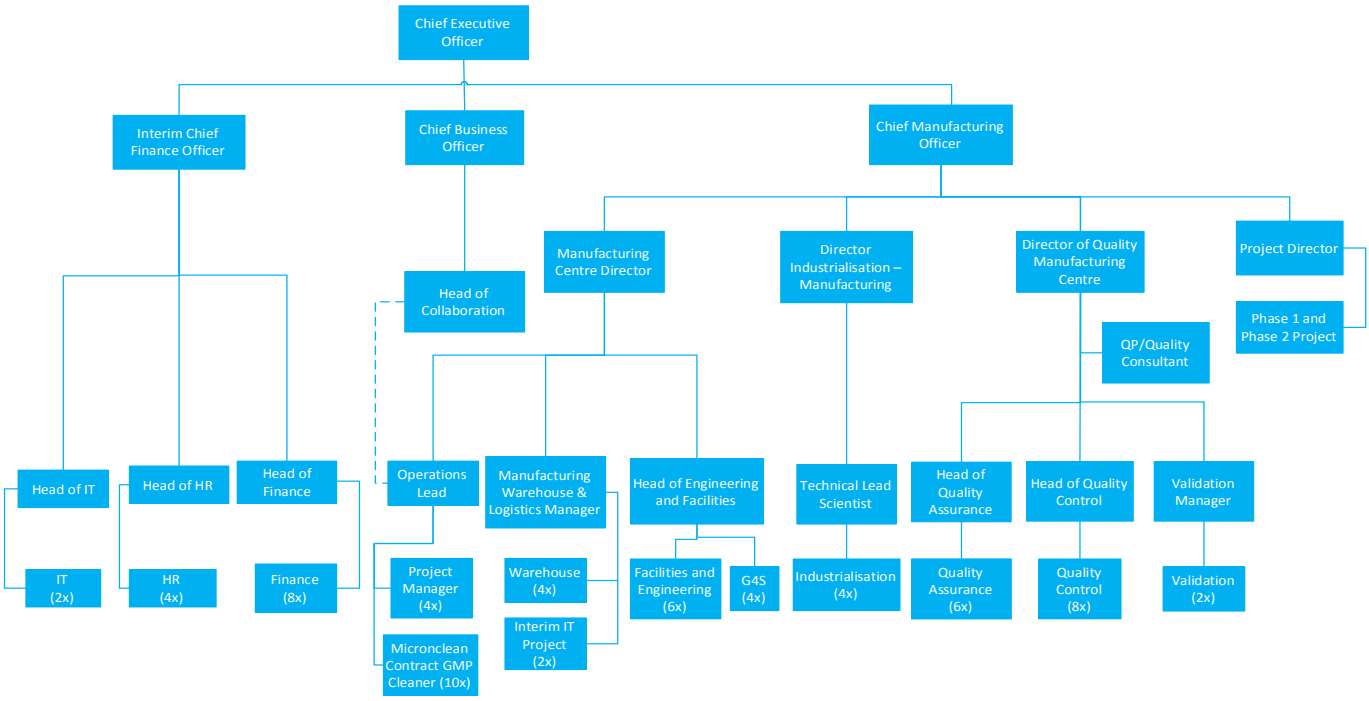
Phase 2 construction on the second floor of the CGT Catapult manufacturing centre

Licence

The CGT Catapult holds 2 manufacturing MHRA licenses (MIA # 48152 and MIA (IMP) # 48152), which are supported by a full quality management system (QMS). Each collaborator will manufacture their own products within their manufacturing module in accordance with their own QMS and will be responsible for obtaining their own Marketing Authorisation (MA) and/or Clinical Trials Authorisation (CTA) licenses for their products.

Personnel

CGT Catapult manufacturing centre staff provide end-to-end expertise and practical support to collaborators across quality assurance, quality control, operations, validation, finance and supply chain management. A top-level organogram for the organisation as of October 2018 is shown in Figure 3.



Capacity

Collaborating companies

Adaptimmune

Vector manufacturing is one crucial element of Adaptimmune's integrated manufacturing process. This project with CGT Catapult will enable them to have their own dedicated vector manufacturing capability in the UK.

Autolus

Autolus have developed their own proprietary viral vector and semiautomated cell manufacturing processes. The CGT-MC is allowing Autolus to grow their manufacturing capacity as well as access a range of services provided at the Centre.

Cell Medica

The CGT-MC is enabling Cell Medica to establish their cell therapy manufacturing and have more control over their manufacturing activities, working in a purpose-built, cost-effective, collaborative facility.

Freeline Therapeutics

Freeline Therapeutics are collaborating at the CGT Catapult manufacturing centre to further develop proprietary viral vector manufacturing technology. The CGT-MC will ensure rapid and secure manufacturing of these vectors.

Cobra Biologics

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Steve Garland
Director of Operations
+44 1782 714 181

Facilities at Cobra Keele & Matfors

Cobra is a Contract Development and Manufacturing Organisation (CDMO) producing materials for pre-clinical, Phase I/II/III clinical trials and in-market products with over 160 employees (100 based in UK). The company routinely produces a wide range of advanced therapy medicinal products (ATMPs) ranging from HQ plasmid DNA, GMP plasmid DNA, viral vectors, and microbiota. Cobra is currently undergoing a £15m phased expansion plan, supporting the company's R&D expertise in developing rapid and cost effective viral vector and DNA plasmid production platforms for clinical and commercial supply. Commercial supply of plasmid DNA and viral vectors will be available in 2019.

Licence

All of Cobra's facilities are cGMP licenced under the EU clinical trials directive and inspected on a regular basis; MHRA and MPA licence for IMPs for the respective country locations. Cobra has a QP employed at each of its manufacturing sites.

Track record and experience

Cobra has over 20 years of experience as a CDMO providing services for gene therapy and immuno-oncology therapies with viral vector and DNA production. In the UK the advance therapy site is designed for BLS-2 handling. The company has worked with over 50 customers and produced 200+ GMP batches for customers in Europe, North America and Asia in Phase I to Phase III clinical trials.

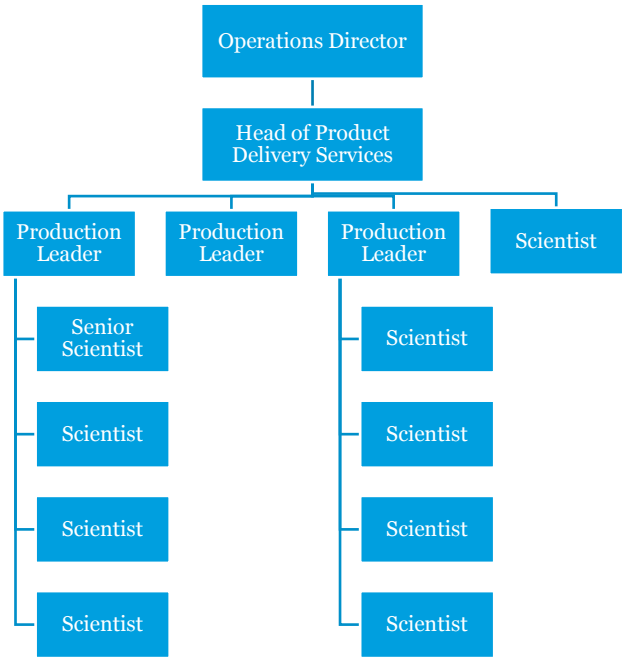
Over the last 20 years Cobra has developed a number of platform services key in helping their gene therapy customers:

- Platform process for GMP adenovirus production
- Platform process for GMP lenti viral vector production
- Platform process for GMP DNA production for Phase I-III
- Platform process for HQ DNA requiring traceability for AAV and lentivirus production

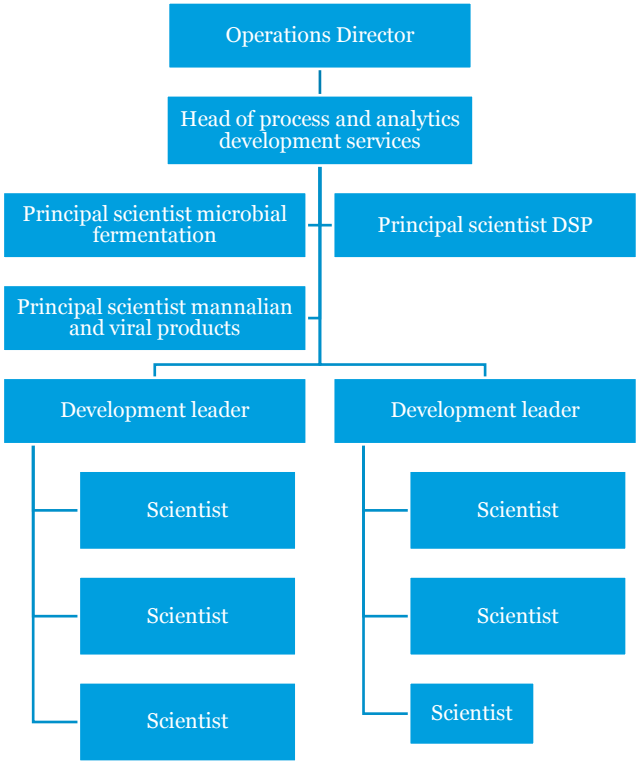
An AAV production process is currently being developed to meet the demands of the ATMP market.

Personnel

Key production personnel:



Key analytical personnel:



Capacity

Great Ormond Street Hospital

Details

Cellular Therapies
Great Ormond Street
London WC1N 3JH

Barry Flutter
Barry.Flutter@gosh.nhs.uk
0207 905 2830

Facility

There are two suites within Cellular Therapies. The first consists of a grade C clean room with a grade A positive isolator for aseptic processing. The second suite has a grade C preparation room and aseptic processing with two grade A negative isolators. The facility is licenced for gene and cell therapy products by the MHRA (MIA (IMP) and MS 17328). There is an adjacent stem cell facility for routine cell manipulation licensed by the HTA.

Processing equipment	Analytical equipment
Centrifuges (various)	Nikon stereoscopic and inverted microscopes
Incubators (various)	
Plasmatherms	
Tube welders and sealer and bag sealers	
Dynal ClinExVivo (magnetic particle concentrators for removal of beads)	
CliniMACS cell separator	
Wave Bioreactors	
CliniMacs Prodigy	

Example of clean room at GOSH Cellular Therapies

License

MHRA licence for IMP and specials. The facility is also licenced by the HTA.

Track record and experience

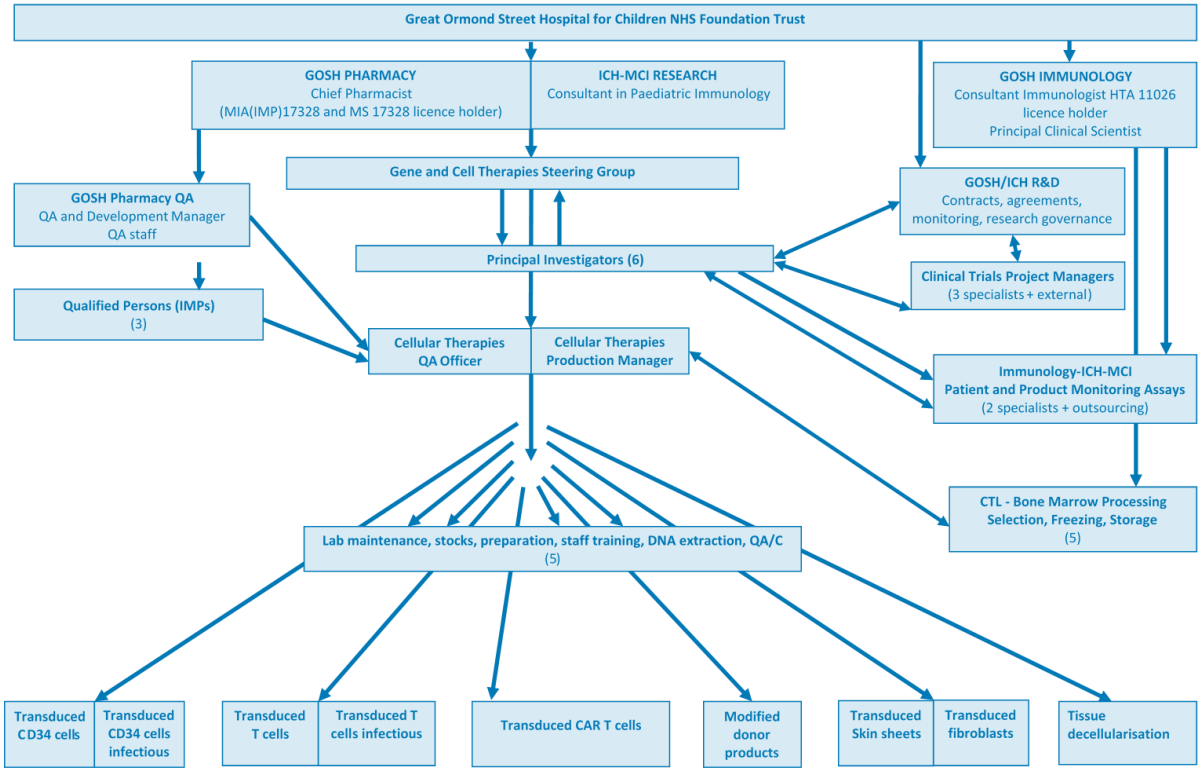
The facility has the experience of manufacturing gene and cell therapy products for Phase I / II trials. In total around 10 products have been manufactured for clinical trials and another 10 are in progress.

	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	
Allo	✓		✓	

Human ES Cell	iPS Cell	Cell isolation from donor tissue
		✓

Personnel

The unit is organised under a chief pharmacist with an aseptic services manager, a quality assurance manager and a contract QP.



Capacity

The facility has indicated that it is capable of manufacturing up to 50 products per year in the facility. The facility will be expanding from January 2020 to around 140 products / year.

Immetacyte Ltd

(formerly Cellular Therapeutics Ltd)

Cellular Therapeutics
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Manchester
M13 9XX

info@cellulartherapeutics.co.uk

0161 606 7278

Facility

This facility comprises of one large multiproduct manufacturing suite (grade D) with three isolators (grade A) and associated transfer hatches (grade B). Each open product is incubated within a product specific secondary containment system to avoid cross contamination.

Processing equipment	Analytical equipment
Process development laboratory	Flow cytometer
Environment Monitoring System to log parameters (particle count, pressures, temperature etc) from the isolators, incubators and storage locations.	Microbiology QC
CliniMACS – bench top platform enabling the separation of different cell types within a closed system using magnetic bead conjugates.	GMP and process development assays
Automated closed system to aseptically concentrate and wash cells.	
Standard incubators for static cell culture	
Bag/closed vessel centrifuge and 'bag squeezer' (to remove supernatant).	
Perfusion bioreactors for actively managed cultures (10L scale)	
Cryopreservation	

Figure 1 Example of clean room at the Cellular Therapeutics Unit

Licence

CTL holds MHRA Authorisation for Investigations Medicinal Products (IMPs) and Manufacturing Specials (MS) (#44168).

HTA licence (#22657).

Track record and experience

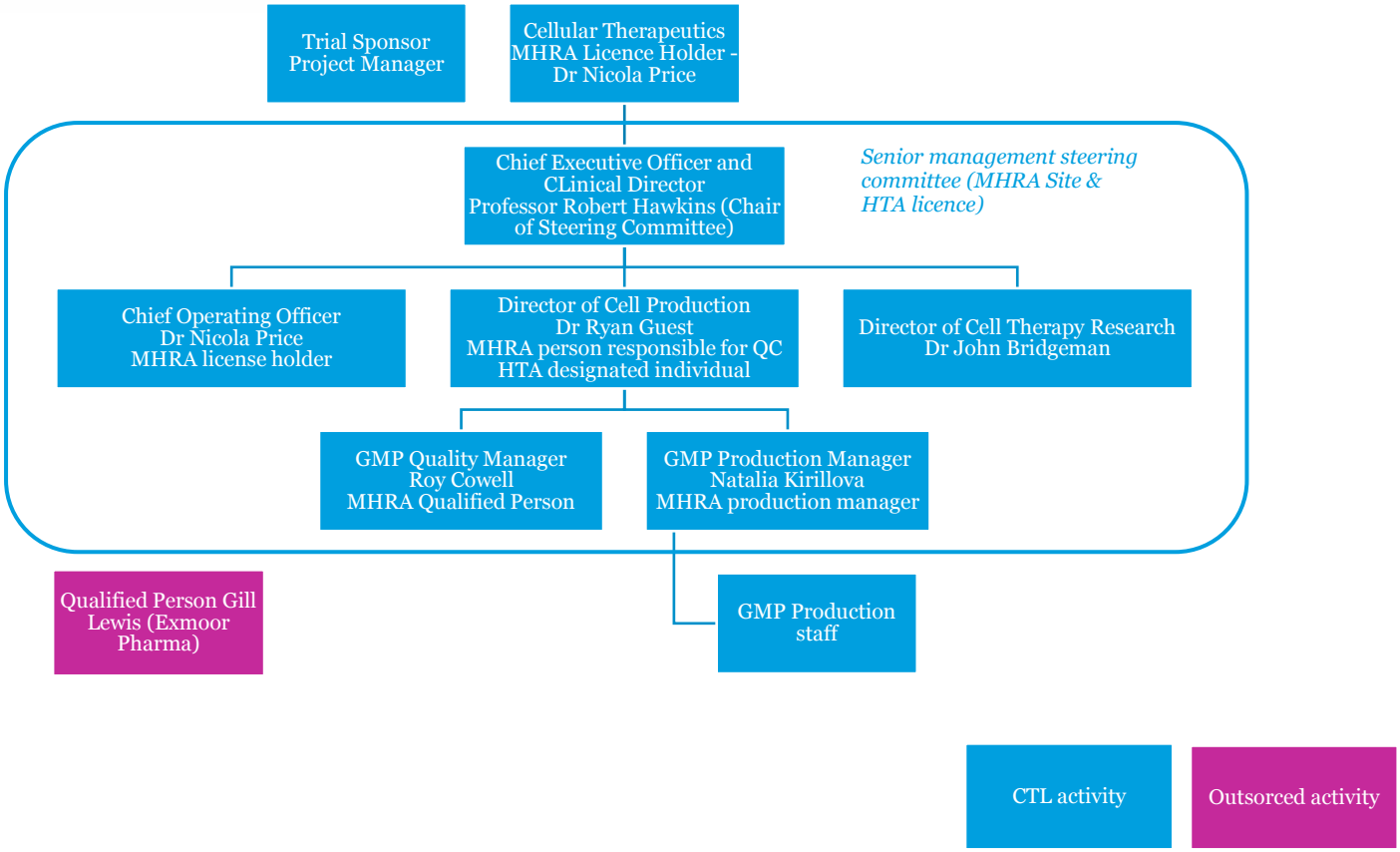
CTL has experience of manufacturing both closed and open cell therapy products, manufacturing gene modified T cell (viral vectors) and Tumour Infiltrating Lymphocyte products: having completed two cell therapy trials; four trials ongoing; and further trails in the pipeline.

	Suspension	Adherent	2D	3D
Auto	✓	✓		
Allo	✓	✓		

Human ES Cell	iPS Cell	Cell isolation from donor tissue
		✓

Personnel

An organogram for CTL can be found below. The unit operates under the CTL Board which is responsible for determining the direction and oversight of products in the pipeline and in process. There are individual board members responsible for finance and contracts; production and quality and process translation, scientific review; and GMP research and development. Within the facility we have access to consultant qualified personnel and dedicated product management and production staff.



Capacity

Cellular Therapeutics have the capability to manufacture six different products simultaneously with a current maximum of four open processes at any one time. This assumes a manufacturing cycle of two to three weeks per product.

This allows us to manufacture between 60 and 100 complex ATMP products per year.

Imperial College London, John Goldman Centre for Cellular Therapy

Catherine Lewis Building,
Hammersmith Hospital,
Ducane Road,
LONDON
W12 0HS

Sandra Loaiza
Sandra.Loaiza@nhs.net
0203 313 2056

The centre is equipped with two independent clean room suites. Each suite has two grade B rooms for processing and a grade C room for preparation. Class II MBSCs provide grade A environments for open processing. One of the suites is designed to work with GMO level 2 material (for example for gene replacement work). Work with genetic modification would require an update to the IMP Licence however.

Processing equipment	Analytical equipment
Class II ducted cabinets	Flow Cytometer
Laminar airflow stations (LAF)	Bench top centrifuges
Cell separators e.g. Cobe 2991	Pharmacy grade fridge
Immunoselection devices e.g. Miltenyi CliniMacs, Miltenyi Prodigy	
Tubing heat sealers	
Automated Cell washer – Sepax 2	
Sterile Docker – Terumo SCDC	
Tissue Culture incubators	
Vacuum wrapping device	
Pharmacy grade fridge/freezer	
Controlled rate freezer	

Licence

MHRA Licences to manufacture IMPs and Specials. HTA licences have also been awarded for various operations. The centre is also JACIE accredited.

Track record and experience

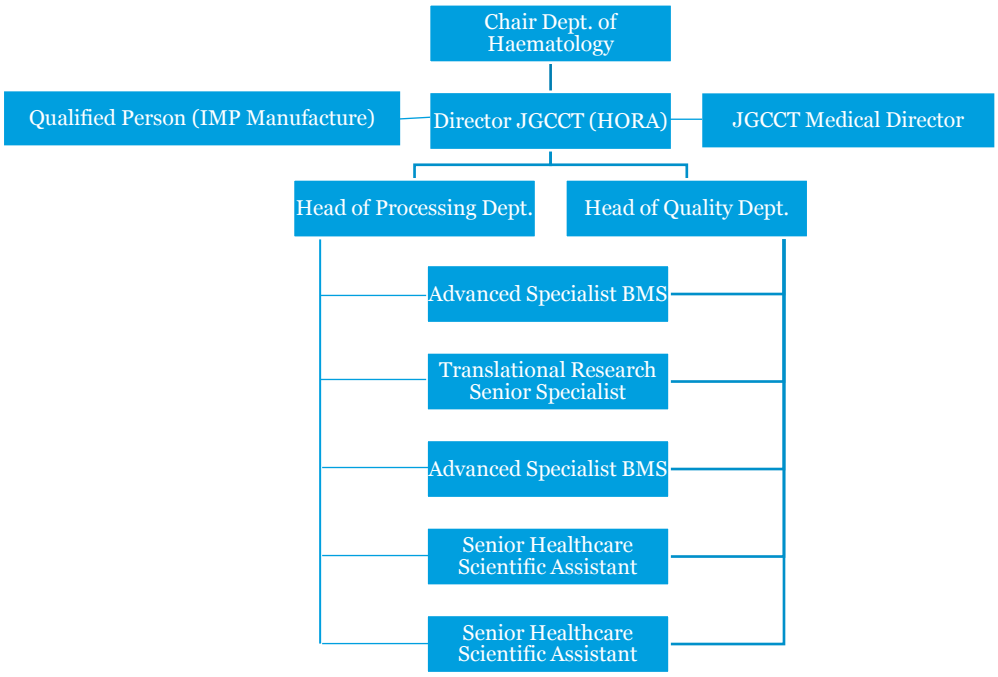
The centre has a long history of experience immune-selection and separation (CD34+) using devices such as the CliniMACS. The centre has experience with Haematopoietic Progenitor Cells and T lymphocytes for both autologous and allogeneic use. The laboratory generates antigen-specific donor derived T-cells for the treatment of opportunistic infections post allogeneic HSCT using the Miltenyi Prodigy device. The centre also grows autologous and allogeneic derived Mesenchymal stromal cells from bone marrow for the treatment of Graft versus Host Disease and other indications.

	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	
Allo	✓	✓	✓	

Human ES Cell	iPS Cell	Cell isolation from donor tissue
✓		✓

Personnel

Key personnel at the centre include a Head of Operations and Regulatory Affairs, a Medical Director, consultant QP, Head of Processing and a Head of Quality.



Capacity

The centre has two independent suites each with two grade B rooms enabling up to four simultaneous projects. The spare capacity over the next few years is indicated below.

Meira GTx

Britannia Walk
Hoxton
London
N1 7NF

James Christie
James.Christie@meiragtx.com

Facilities at Meira GTx

MeiraGTx is a vertically integrated, clinical stage gene therapy company with four ongoing clinical programs and a broad pipeline of preclinical and research programs. MeiraGTx has core capabilities in viral vector design and optimization and gene therapy manufacturing, as well as a potentially transformative gene regulation technology.

Completed in early 2018, Meira GTx's 2694 square metre cGMP manufacturing facility located in central London was designed to operate as a flexible and scalable manufacturing hub, housing two cell production suites and three separate viral vector production suites, offering production of multiple product candidates in parallel, as well as sequentially at different scales. The facility also incorporates an integrated analytical department, an in-house analytical tool kit, and a dedicated product fill-and-finish suite. MeiraGTx's facility has been designed to meet MHRA, European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) regulatory standards.

Personnel

The company's manufacturing team consists of more than 30 highly trained multidisciplinary staff with backgrounds in manufacturing, managing and delivering gene therapy products.

License

The company was granted an MHRA MIA license for IMPs (# 45522) in June 2018.

Moorfields Eye Hospital, Cells for Sight Cell Research Unit

UCL Institute of Ophthalmology
11-43 Bath Street
London,
EC1V 9EL

Julie Daniels
j.daniels@ucl.ac.uk
0207 608 6893

Facility

The manufacturing facility is a cleanroom suite that includes two Grade B processing laboratories (2 Person Lab and 3 Person Lab), a Grade B Lab Airlock, a Grade C Prep Area, a Grade D Change Room and an unclassified Vestibule. A schematic representation of the manufacturing facility is shown in Figure 1. The different areas of the manufacturing facility are used for the following purposes:

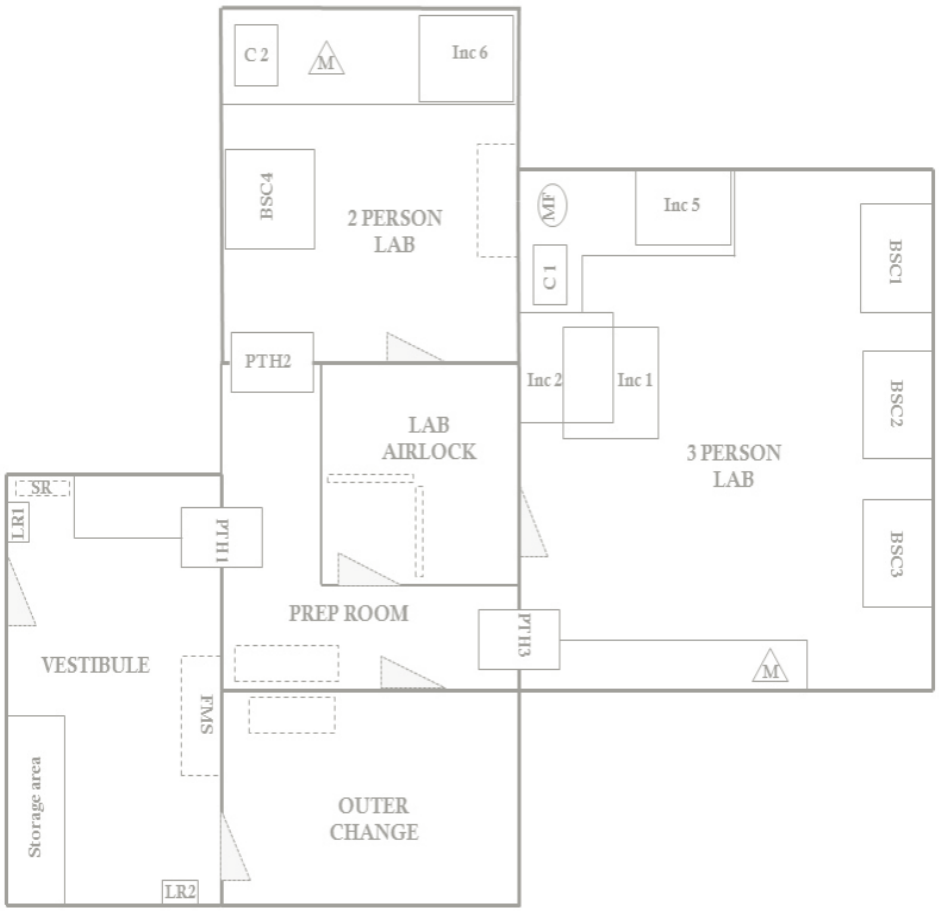
The Vestibule is the initial point of entry into the facility, where cells, reagents and consumables are transferred into, and out of, the graded areas via a transfer hatch (PTH1). The Vestibule also serves as the control centre for the unit because it houses Magnahelic gauges that monitor differential pressures between the rooms, a computer that displays the status of parameters monitored by the continuous monitoring system installed within the facility, and a CCTV camera display that relays images from the Grade B laboratories.

Entry into the graded areas is initially via the Change Room (Grade D/C), where outdoor clothes are removed and cleanroom undergarments are donned.

The Prep Area (Grade C) is where items are collected from the transfer hatches to be passed into or out of the facility. This area could also serve as an initial processing preparation area if required.

Within the Lab Airlock (Grade B), cleanroom garments are donned over the undergarments before entering the labs.

Finally, all tissue-processing operations are performed within the class II Biological Safety Cabinets (Grade A) in either the 2 Person Lab or 3 Person Lab (both Grade B).



BSC: Biological Safety Cabinet

SR: Shoe Rack

MI: Mini-incubator

I: Incubator

LR: Labcoat Rack

S: Shelves

C: Centrifuge

MF: Microfuge

M: Microscope

PTH: Pass Through Hatch

FMS: Facility Monitoring System

Processing equipment	Analytical equipment
Validated continuous monitoring system to log all parameters associated to the facility and equipment within it (particle counts, pressure differentials, fridge and freezer temperatures, incubator CO2, RH, O2 and temperatures etc.)	2 x Nikon inverted light Microscopes
4 x Class II BSCs	3 x Microbiological incubators
3 x CO_2 incubators	Access to licensed QC labs for outsourced testing activities
1 x multigas incubator	Also available on-site for early stage development work (not to GMP grade):
1 x mini incubator	– FACS
4 x Fridges	– Q-PCR
4x Freezers	– HPLC
1 x -80°C freezer	– Plate readers
2 x Bench-top Centrifuges (600 ml max capacity)	– Spectrophotometer
1 x Microfuge	– Confocal microscopes
Potential for GMP cell cryopreservation	– Transmission Electron Microscope
	– Cell sorting and separating facilities
	– Multiplex Reader- cytokine and chemokine assays

Example of clean room at Cells for Sight

Licence

The facility has an MHRA licence for MIA (IMP) manufacture, a Specials licence (MS) and a HTA licence.

Track record and experience

Cells for Sight have extensive experience as a cell therapy manufacturer working alongside both academic and commercial partners. The Cells for Sight Stem Cell Therapy Research Unit was established in 2005 and was the UK's first Medicines and Healthcare products Regulatory Agency (MHRA) accredited cultured stem cell facility. The team consists of a highly experienced, multi-skilled personnel and has a proven track record as:

a) Contract manufacturer, including the compilation and independent quality review of GMP documentation

b) Tech transfer activities, including the translation of research based protocols to GMP and subsequent validation of protocols at GMP

c) Early stage product development helping define the GMP process for future potential cell therapy products.

We have a wealth of expertise in the culture of both allogeneic and autologous limbal epithelial stem cells on tissue engineered scaffolds, for transplantation to patients (Specials). Within the stem cell field, we have experience of culturing limbal epithelial stem cells, buccal mucosal stem cells, corneal stromal stem cells, keratocytes and mixed population cells.

Our team have also been responsible for, and been involved in the development of, two tissue engineered scaffolds, fibrin gels and collagen gels (RAFT). We have recently cultured epithelial cells on the fibrin scaffold for patients affected with Limbal Stem cell deficiency ('Specials').

We also recently manufactured a pioneering human embryonic stem cell based IMP for Pfizer Neusentis and The London Project. Our team was involved with process development for the product from its infancy all the way to clinical manufacture and product release. This involved development meetings, protocol writing, material risk assessments, equipment/process validations, training, and the successful continuous cell manufacture lasting many months.

The team are due to begin training for processing and labelling of blood products and for manufacture of cell banks, for other projects.

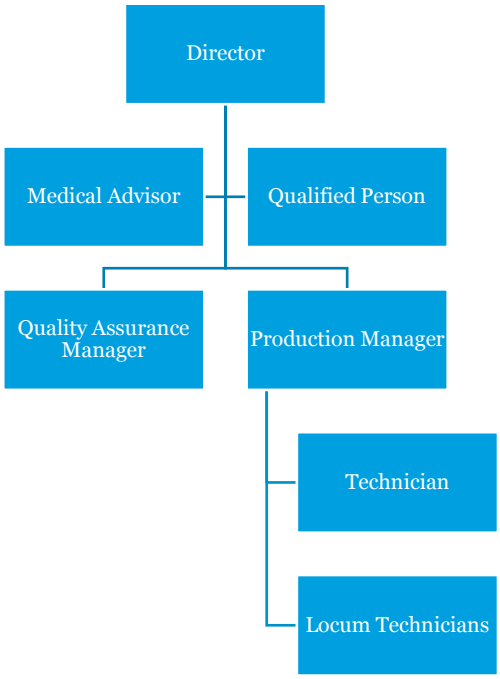
	Suspension	Adherent	2D	3D
Auto		✓	✓	✓
Allo		✓	✓	

Human ES Cell	iPS Cell	Cell isolation from donor tissue
✓		✓

Table 21 Summary of experience for Cells for Sight

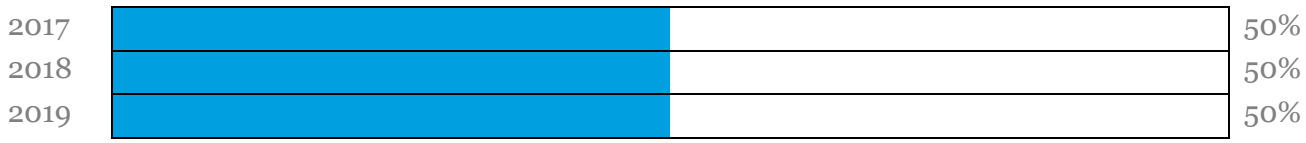
Personnel

- Key personnel include the Director (DI/licence holder), Production Manager, Quality Assurance Manager and one Research Assistant.
- A contract QP is available for consultations, regular audits and batch release.
- The Medical Advisor is available for consultations, clinical feedback and care of patients
- Additional staff may be supplied by the client, if required.



Capacity

Depending upon the nature of the campaign, two different projects can be delivered concurrently at any one time in each grade B room. Different projects are run on a campaign basis with validated decontamination procedures in between each product type.



Newcastle Cellular Therapy Facility

Newcastle Cellular Therapies Facility
Newcastle University
3rd Floor, West Wing
Bioscience Centre
Times Sq
Newcastle University NE1 4EP

Anne Dickinson
Facility Director
anne.dickinson@ncl.ac.uk
0191 208 6794

Dean Bradley
Quality Assurance and Quality Control Manager
dean.bradley@ncl.ac.uk
0191 282 4062

Kay Carruthers
Production Manager
kay.carruthers@ncl.ac.uk
0191 282 4062

Facility

The facility contains two suites one with four grade B clean rooms and a second with five grade B rooms. These processing labs are supported by two grade C preparation rooms that also provide access to the rooms.

Processing equipment	Analytical equipment
MBSC (Class II)	Microscope
CO_2 incubators	FACS analysis
Miltenyi Biotec CliniMACS® Plus	PCR Thermocycler
Miltenyi Biotec Prodigy®	
Planer controlled rate freezer	
Refrigerated centrifuges	
TerumoBCT COBE® 2991 cell processor	
Water baths	
Blood warmer	



Example of clean room at Newcastle Cellular Therapy Facility

Licence

MHRA licence for manufacture of IMPs and “Specials”. The Facility also has a HTA licence for Human Tissues and Cells for Patient Treatment.

Track record and experience

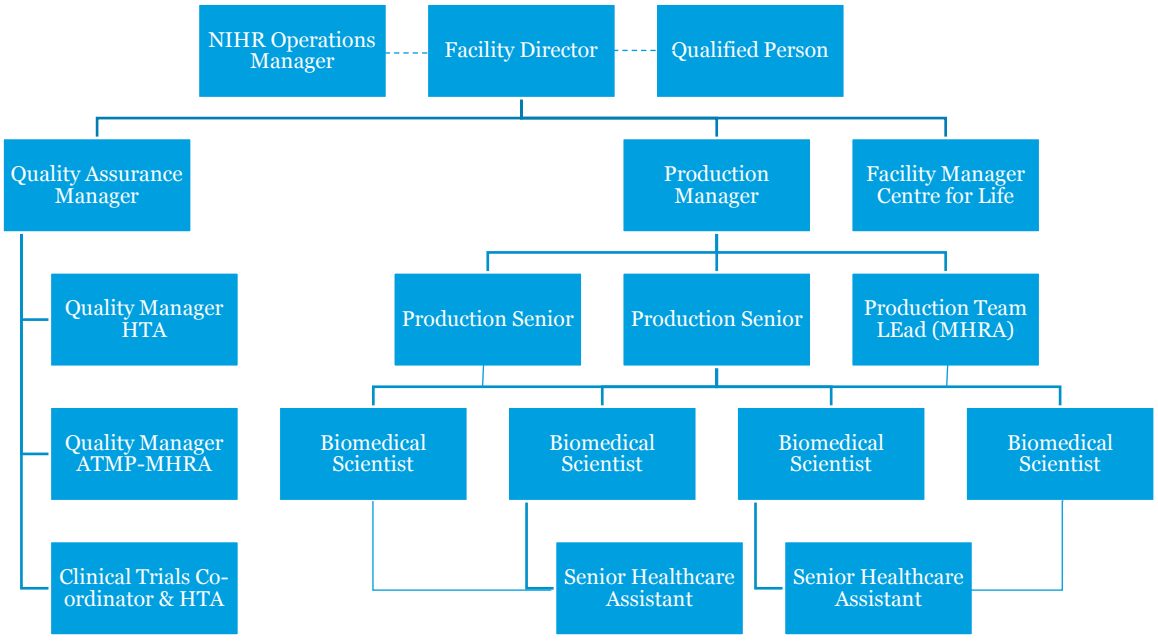
The Facility has experience with stem cell cryopreservation using controlled rate freezing, cell manipulation using COBE 2991 (separation of blood and bone marrow) and isolation of sub-populations using a CliniMACS. Development and culture of dendritic cells and mesenchymal stem cells, limbal stem cells and tolerogenic dendritic cells for ATMP clinical trials. Processing engineering experience and contract manufacture.

	Suspension	Adherent	2D	3D
Auto	✓		✓	
Allo	✓	✓		

Human ES Cell	iPS Cell	Cell isolation from donor tissue
✓		✓

Personnel

The Facility employs 14 staff, including one QA/QC manager, production manager and one QP. An organogram for the company can be found below. **Error! Reference source not found.**



Capacity

The Facility has nine separate clean rooms and depending on the demand per project, it currently runs up to 5-6 separate projects during any one year. The predicted available capacity at the facility for the next four years is listed below:

NHS Blood and Transplant

NHS Blood and Transplant (NHSBT) has four sites with MHRA Manufacturer's Authorisation for IMPs covering cellular and molecular therapies. In addition, there are a further four laboratory sites with HTA licences.

NHS Blood and Transplant
Advanced Therapies Unit
14 Estuary Banks
Estuary Commerce Park
Speke
Liverpool L24 8RB

Dr Vivien Hanson
Head of Laboratory
vivien.hanson@nhsbt.nhs.uk
0151 268 7200

NHS Blood and Transplant
Clinical Biotechnology Centre
Langford House
Lower Langford, near Bristol
BS40 5DU

Dr Paul Lloyd-Evans
Head of Laboratory
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0117 928 9388

NHS Blood and Transplant
Advanced Therapies Unit
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Birmingham
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Dr Phil Jenkin
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0121 278 4147

NHS Blood and Transplant
Advanced Therapies Unit
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Northway
Filton
Bristol BS34 7QH

Dr Laurence Pearce
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0117 912 5700

Dr Jonathan Caddick
Business Development Manager
jonathan.caddick@nhsbt.nhs.uk
07471 147804

Dr Jon Smythe
Head of Cellular and Molecular Therapies
jon.smythe@nhsbt.nhs.uk
01865 38 7967

Facilities at Speke

The NHSBT Speke facility has two grade B rooms currently dedicated to the manufacture of cell therapies. There are also additional grade B and grade C rooms shared with the NHSBT Tissue Services department. The department also has a dedicated QC laboratory.

Processing equipment	Analytical equipment
Class II cabinets	Haematology analyser
Bioreactors	Flow cytometer
CO_2 incubators	
Sterile connecting devices	
Controlled rate freezers	
Liquid nitrogen bulk supply tank supplying liquid nitrogen storage vessels	
Dry Shippers and Ships Logger devices	
Centrifuges	
Orbital shaker	
4°C storage pharmacy fridges	

-20°C storage freezer	
Peristaltic pump	
Filter integrity tester	
Endosafe PTS	
Cytospin	
Line sealers	
Microscopes	

Figure 2 Example of clean room at NHSBT (Speke site)

Licence

The Speke site has a MHRA licence for IMPs and a HTA licence.

Track record and experience

The ATU has experience of the genetic manipulation of T cells, cell selection and depletion protocols and broad cell culture knowledge. The unit also has experience of the isolation and culture of mesenchymal stem cells from bone marrow and umbilical cord plus peripheral blood stem cells for clinical trials. The laboratory has prepared master and working cell banks under GMP.

	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	✓
Allo	✓	✓		

Human ES Cell	iPS Cell	Cell isolation from donor tissue
		✓

Personnel

The NHSBT site in Speke has six dedicated staff for IMP manufacture and a further 3 staff for the broader workload.

Capacity

Facilities at the Clinical Biotechnology Centre, Langford

The NHSBT Clinical Biotechnology Centre has four grade D rooms and three grade C rooms. One grade C room is dedicated to the aseptic filling of products in a pharmaceutical grade positive pressure isolator with a state of the art closed-vial sterile filling station. Class II MBSC or laminar flow cabinets are present in the other rooms dedicated to the manufacture of gene therapy and biotechnology products.

Processing equipment	Analytical equipment
HVAC System	UV / Visible spectrophotometer
Class II cabinets / laminar flow hoods	Filter integrity tester
Pharmaceutical grade positive pressure isolator with VHP generator capabilities	Endosafe PTS
Fermentation systems	Microplate plate reader with fluorescence capability
AKTA chromatography equipment	Osmometer
Highly purified water plant	pH & Conductivity meter
Incubators and shaker incubators	Turbidity meter
Freezers, fridges and storage areas including liquid nitrogen storage vessel	PCR equipment
Centrifuges	HPLC
Peristaltic pumps	Electrophoresis equipment
GMP grade Autoclave	Gel analysis and documentation system
Laboratory grade dishwasher	Access to DNA capillary sequencer
Emulsiflex high pressure homogeniser	Environmental testing equipment
Aseptic Technologies Crystal M1 closed-vial sterile filling station for dispensing of products	

Examples of clean rooms and equipment at NHSBT (CBC site)

Licence

The CBC site has a MHRA licence for the manufacture and importation of molecular IMPs.

Track record and experience

The facility has experience in the manufacture of plasmid DNA vectors as direct vaccines or for use in viral vector manufacture and the production of recombinant proteins including conjugation of antibodies for therapy. To date the facility has manufactured over 50 plasmid DNA vectors, five recombinant proteins and been involved in over 14 clinical trials since 2001 (with over 400 patients treated). The CBC has developed an expertise in the manufacturing and testing of DNA plasmids to current regulatory requirements.

Personnel

The NHSBT site in Langford has 15 dedicated staff for IMP manufacture and a further 4 development staff at NHSBT Filton.

Capacity

CBC can process two products in parallel with a capacity of up to 20 products per year, depending on scale. NHSBT is planning to significantly expand CBC capacity from 2020 at a new facility at NHSBT Filton.

Facilities at Birmingham

The NHSBT Birmingham facility has three grade B rooms with Class II MBSC dedicated to the manufacture of cell therapies. The department also has dedicated closed system processing, QC and development laboratories.

Processing equipment	Analytical equipment
Class II cabinets	Haematology analyser
CO_2 incubators	Flow cytometers
Hypoxic incubator	
Bioeactors	
Sterile connecting devices	
Controlled rate freezers	
Dry Shippers & Ships Logger devices	
Liquid nitrogen bulk supply tank supplying	
Liquid nitrogen storage vessels	
Vacuum Sealers	
Centrifuges	
Gambro 2991 cell washer / processor	
4°C storage blood / pharmacy fridges	
-30°C storage freezers	
-80°C storage freezer	
Miltenyi CliniMACS immunomagnetic cell selector / depletor	
Endosafe PTS	
22°C microbiological plate incubator	
35°C microbiological plate incubator	
Hand held non-viable particles counters	
Static non-viable particles counter	
Hand held viable particle counter	
Line sealers	
Sepax 2 cell processor	
Video / Light Microscopes	

Licence

The Birmingham site has a MHRA licence for IMPs and an HTA licence.

Track record and experience

The Birmingham ATU has experience of cell selection and depletion protocols and broad cell culture knowledge. The unit also has experience of the isolation and culture of mesenchymal stromal cells from umbilical cord tissue for clinical trials. The unit has experience of Treg isolation under GMP for clinical use.

Personnel

The NHSBT site in Birmingham has 5 dedicated staff for IMP manufacture plus another 17 staff for the broader workload including processing for bone marrow transplantation.

Capacity

Examples of clean rooms and equipment at NHSBT (Birmingham site)

Facilities at Filton

The NHSBT Filton facility has four grade B rooms, three with Class II MBSC and one with an isolator dedicated to the manufacture of cell therapies. The department also has dedicated closed system processing, QC and development laboratories.

Processing equipment	Analytical equipment
Class II cabinets	Haematology analyser
Isolator	Flow cytometers
CO2 incubators	
Hypoxic incubator	
Terumo Sterile connecting devices	
Controlled rate freezers	
Dry Shippers & Ships Logger devices	
Liquid nitrogen bulk tank supplying	
Liquid nitrogen storage vessels	
Vacuum Sealers	
Centrifuges	
Gambro 2991 cell washer / processor	
4°C storage blood / pharmacy fridges	
-80°C storage freezer	
Miltenyi CliniMACS immunomagnetic cell selector / depletor	
Endosafe PTS	
22°C microbiological plate incubator	
35°C microbiological plate incubator	
Ice machine	
Hand held non-viable particles counters	
Static non-viable particles counter	
Hand held viable particle counter	
Line sealers	
Sepax 2 cell processor	
Video / Light Microscopes	

Licence

The Filton site has a MHRA licence for IMPs and a HTA licence.

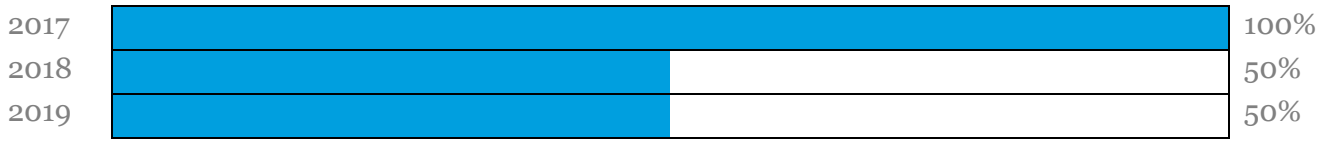
Track record and experience

The Filton ATU has experience of a range of cell selection and depletion protocols and broad cell culture knowledge. The unit also has experience of culturing red cells from stem cells under GMP and the isolation and culture of saphenous vein cells under GMP.

Personnel

The NHSBT site in Filton has 6 dedicated staff for IMP manufacture and a further 7 staff for the routine workload.

Capacity



Therapeutic Apheresis Service

NHSBT offers apheresis services supporting the provision of raw material e.g. leucapheresis for autologous cell therapies. These services are available at a number of locations across England.

Oxford BioMedica

Harrow House manufacturing facility
Oxford BioMedica (UK) Limited
Harrow House
Transport Way
Oxford
OX4 6LX

Yarnton manufacturing facility
Oxford Biomedica (UK) Ltd
Unit 5 Oxford Industrial Park
Yarnton
Oxford
OX5 1QU

Jason Slingsby
enquiries@oxb.com
+44 (0) 1865 785300

Facilities at Oxford BioMedica

Oxford BioMedica is a leading gene and cell focused biopharmaceutical company specialising in lentiviral based vectors for gene and cell therapy. Oxford BioMedica has a platform of technologies, intellectual property including know-how for underpinning the design, development and manufacture of unique gene-based medicines.

Oxford BioMedica has capabilities encompassing the full range of GMP manufacturing and analytical activities to support pre-clinical, research and bioprocessing development through to clinical and commercial GMP manufacture.

The company currently has three independent cleanroom facilities totalling 1200 m^2/12917 ft^2 of cleanroom area spread over two sites in and around Oxford, with additional facilities planned for 2020. Each cleanroom suite/facility is configured with dedicated Upstream, Downstream, and media processing rooms, and utilise single use consumables for the entirety of the processes. The company's third facility (GMP2), became operational in April 2016 and was designed and built around a novel serum-free suspension lentiviral vector process. The facility incorporates a 50L/200L Single Use Bioreactor skid enabling routine GMP manufacture of 200 L sized batches. Both the GMP2 and Yarnton (GMP4) facilities can be configured to run adherent or suspension processes.

Each manufacturing site is operated independently, thereby providing a robust dual supply strategy for both Oxford BioMedica's own products and those of their partners. Adjacent to the production cleanroom areas are an additional ~1100 m^2/11840 ft^2 of space providing warehouse, QC microbiology, offices and utilities.

In September 2018 Oxford BioMedica announced the further expansion of its manufacturing capabilities with a new facility of approx. 7,800 m^2 (84,000 ft^2). The Group's planned Phase 1 and Phase 2 expansion will fit out around 4,200 m^2 (45,000 ft^2) for four GMP clean room suites and two fill and finish suites as well as offices, warehousing and QC laboratories, with space available for future expansion. Once open, the facility will more than double the Group's bioprocessing capacity, with the additional GMP suites being scheduled to be ready in Q1 2020.

Processing equipment	Analytical equipment
CO_2 incubators (static and shaker)	HPLC System
Microbiological Safety Cabinets	Flow cytometer
Pallet tank mixers	Micro Plate Reader
50L/200L dual Single Use Bioreactor skid	Automated nucleic acid extraction systems

Peristaltic pumps	qPCR instruments
Clarification rigs	UVP Biospectrum 500 gel documentation system
Filter integrity testers	Class II Biological Safety cabinets
ÄKTA Ready liquid chromatography systems	UV/Vis Spectrophotometer
Centrifuges	Cell culture equipped containment level 3 laboratories
-150°C, -80°C and -20°C freezers	Cell counters
	Microscopes
	Centrifuges (floor and bench-top)
	Temperature mapped CO_2 incubators
	4°C storage pharmacy fridge
	Temperature mapped -80°C and -150°C freezers
	pH meter
	Electrophoresis equipment
	LAL endotoxin reader
	TOC analyser

GMP manufacturing is supported by a comprehensive array of validated analytical methods all housed within the companies new Windrush Court laboratory complex. The total laboratory space covers 2136 m²/22992 ft², of which 470 m²/5059 ft² comprises of GMP analytical lab space; the facility has 3 dedicated CAT3 suites for performing critical RCL testing.

An example cleanroom at Oxford BioMedica is shown below.

Example cleanrooms at Oxford BioMedica

Licence

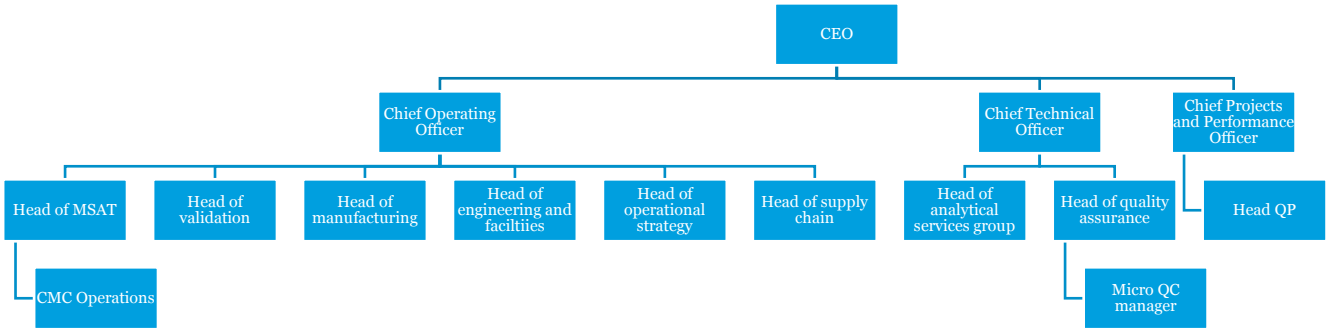
Oxford BioMedica has Manufacturer's Authorisations covering all sites for the manufacture, testing and release of both commercial products (MIA) and Investigational Medicinal Products (MIA [IMP]). All sites are also registered with the US FDA and have been inspected in support of commercial product license applications with successful outcomes.

Track record and experience

Oxford BioMedica does not operate as a traditional contract manufacturing organisation (CMO). Instead Oxford BioMedica is a platform and product development company with a unique combination of technical expertise, vector-related intellectual property, a proprietary LentiVector® platform coupled with process development and in-house GMP manufacturing/analytical testing services and clinical & regulatory expertise. Multiple facilities that can be independently operated allows for the production of lentiviral based vector products for Phase I/II, Phase III clinical trials, and to support commercial market supply.

Personnel

The manufacturing department currently consists of >50 biotechnologists who are supported by a process compliance team, warehouse, engineering, QC micro and MSAT functions. QC release testing is performed by the Analytical Service Group (ASG) overseen by the Chief Technical Officer (CTO). Batch certification and release is performed by the Qualified Person (QP) team.



Capacity

Capacity is 1200m² of cleanroom processing space.

Rayne Cell Therapy Suite (RCTS) and The Wellcome Trust / BRC Clinical Research Facility and Cell Therapy Unit (CTU) at King's College London

Cell and Gene Therapy at King's (CGT-K)
King's College London,
The Rayne Institute,
123 Coldharbour Lane,
London SE5 9NU

Farzin FARZANEH
Farzin.farzaneh@kcl.ac.uk
+44(0) 7848 5902/2900

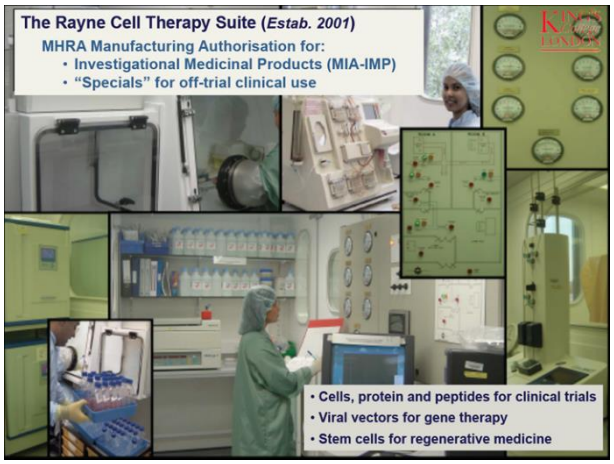
Facility

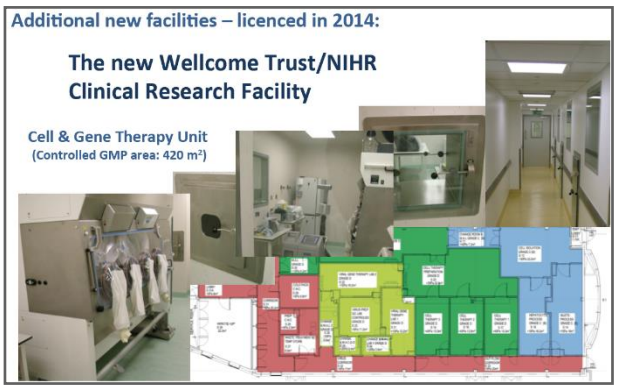
The Rayne Cell Therapy Suite (RCTS) premises contain 40 m² of grade D clean rooms with two grade A isolators. This facility has operated as a GMP facility for the production of cell and gene therapy-based investigational medicinal products since 2001.

The Cell Therapy Unit (CTU) facility has a floor area of 420 m² and is separated into 7 clean rooms. The Cell and Gene Therapy at King's (CGT-K) suite contains two independent grade D areas complete with isolators. Each area is designed to handle separate products. Production runs in the CGT-K are conducted on a campaign basis with a "deep clean/decontamination" between the manufacture of different products. The Cell Isolation Suite has two grade C areas with Class II MBSC (Microbiological Safety Cabinet) for initial isolation of the starting material from donor tissue. The final steps of processing are carried out in an isolator in the same grade C background. Although the grade C areas in this suite are declared as such they are designed to function as Grade B rooms.

Processing equipment	Analytical equipment
Cell Culture Incubators.	4 x Microscope – inverted.
CO^2 Incubators.	2 x Microscope – fluorescent.
Centrifuges.	5 x Microscope – upright.
Cryovial Filler/Capper.	Multi laser/colour FACSCanto and LSR Fortesa Analysers.
Controlled-Rate Freezer.	FACSAria cell sorting.
2 x Plasmatherm.	
Micro-Encapsulator.	
2 x CliniMACS Cell Processing Systems.	
Plasma Expressor.	
Sepax Cell Separation System.	

As well as access to a range of other analytical and imaging techniques through the CRUK Cancer Centre and the NIHR Biomedical Research Centres at King's College London, Guys and St Thomas' Trust, and King's College Hospital NHS Trusts.



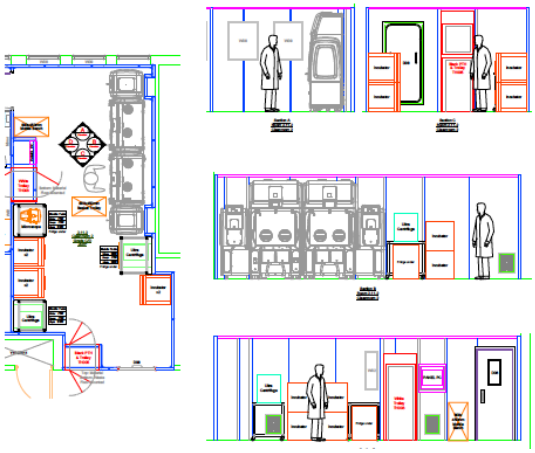


Example of clean room at The Rayne Cell Therapy Suite (RCTS)

Construction of New GMP Facility

Summer 2017 the building of a new GMP suite, close to the RCTS facility, was initiated. This new facility will be completed in November 2018 and is expected to begin GMP manufacture after the completion of qualification procedures in 2019.

With a floor area of 80 m², plus additional QC and GMP Storage rooms, the new facility will comprise, 2 grade D clean rooms housing isolators, incubators, centrifuges etc. for open and closed processing, a grade D Preparation Room used to service the isolator rooms, an outer lobby separating the clean rooms from the general corridor, and separate personnel airlocks between the Preparation Room and the isolator rooms.



Plan of new CGT-K manufacturing suite

Licence

The RCTS facility holds MHRA Manufacturing Authorisation for Investigational Medicinal Products (MIA(IMP)) and a "Specials Manufacturer's" (MS) licence for the production of cell and gene therapy products for their off-trial clinical use. In addition it also has a HTA licence for the procurement,

testing, processing, storage, distribution and/or import and export of tissues and/or cells intended for human applications. These licences cover the activities in both the RCTS and CGT-K facilities.

Track record and experience

The organisation has experience with dendritic cells for a variety of different indications (including an FDA approved Phase-III clinical trial), donor Natural Killer (NK) cells, mesenchymal stem cells and haematopoietic stem cells. They also have extensive experience with the manufacture of gene therapy products such as retrovirus and lentivirus vectors. This experience includes the manufacture of the largest number of retro- and lenti-virus based vectors for regulatory approved clinical trials in Europe and the manufacture of IMPs for a range of academic and industry sponsored Phase-I through to Phase-III clinical trials. The GMP production of AAV vectors is expected to become available in 2019.

	Suspension	Adherent	2D	3D
Auto	✓			
Allo	✓	✓		

Human ES Cell	iPS Cell	Cell isolation from donor tissue
	✓	✓

Personnel

There are ten permanent members of staff at the RCTS and the CGT-K component of the Cell Therapy Unit. The current list of staff include:

Rebecca PRU
Head, Quality

Sabine DOMNING
Senior GMP Production Manager

Aisha SATNEY
Quality Officer

To be appointed
Head, Manufacture

To be appointed
Deputy Quality Manager

To be appointed
Senior GMP Production Scientist

Emeliano RAKAJ
Senior Specialist Technician (GMP Materials)

Katarzyna WOLANSKA-HAJDUK
Quality Control Scientist

Joel POPE
Quality Assistant

Ziyadur RAHMAN
GMP Technician

Cameron BROWN
GMP Production Scientist

Meghan MADIGAN
GMP Production Scientist

Manisha GURUNG
GMP Production Scientist

Shahed MIAN
GMP Production Scientist

David George HULLAH
GMP Production Scientist

Safiya MORRISON
GMP Production Assistant

Ravin KHINDER
GMP Production Assistant

X 2 To be appointed
GMP Technician

David DARLING
Senior Staff Scientist – R & D

Glenda DICKSON
Senior Research Fellow – R & D

Carlo SCALA
Senior Research Fellow – R & D

Anil CHANRASHEKRAN
Senior Research Fellow – R & D

Nahid ZAREIAN
Senior Research Fellow – R & D

To be appointed
Senior Research Fellow – R & D

To be appointed
Senior Research Fellow – R & D

David BUSATO
Research Associate – R & D

Ruby QUARTEY-PAPAFIO
Research Associate – R & D

Wendy COLLICOTT
External QA/QC (Pharma-Resolution)

David FARRER
External QP (Pharma-Resolution)

Felix MUNKONGE
Manager, Projects

Faith GREEN
Programme Development Manager

Farzin FARZANEH
Internal QP/PI/ Director

Capacity

The RCTS and the CGT-K components of the CTU can handle four separate GMP manufacturing runs at any time. In the current manufacturing campaigns the production of each batch of cell therapy product takes one to two weeks and the manufacture of each batch of gamma retrovirus or lentiviral vectors between 2 to 8 weeks.

The new GMP manufacturing suite will provide a 50% increase in production capacity, allowing the production of up to 40 batches of viral vectors in 2019/2020.

Roslin CT

RoslinCT's manufacturing facility is situated within the Scottish Centre for Regenerative Medicine (SCRM) based at the Edinburgh BioQuarter. The company also has established cell and gene therapy process development facilities.

The manufacturing facility was specifically designed for the development and manufacture of cellular therapies / Advanced Therapy Medicinal Products (ATMPs) and contains three separate suites served by a dedicated air handling unit.

NINE Edinburgh BioQuarter
9 Little France Road
Edinburgh
EH16 4UX

Sue Bruce
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0131 658 5359

Janet Downie
Chief Executive Officer
janet.downie@roslinct.com
0131 658 5182

Facilities at RoslinCT

Product Types

Advanced Therapy Medicinal Products (ATMPs)
Allogeneic and autologous cell therapies
iPSCs
hESCs

Manufacturing

Clean rooms
Grade B processing rooms with Grade A MSCs and Grade C processing room. Further clean rooms in expansion phase.

Quality Control

RoslinCT has an established GMP Quality Control department providing in house testing. In addition RoslinCT is located close to a number of GMP contract testing facilities with a full range of testing capabilities.

Processing equipment:	Analytical equipment:	Cell/product storage:
Cell culture incubators	Real Time PCR system	Vapour Phase LN_2 Storage Vessels
Centrifuges	Thermal cycler	Mechanical -150 °C Freezers
Controlled rate freezers	Flow cytometers	
Analytical balance / precision balance	Plate readers	
Closed system cell processing	Spectrophotometers	
Cell selection and cell processing systems	Filter integrity tester	
Portable ice-free cooling systems	Haematology analyser	
Dry block heaters	Automated cell counters	
Closed filtration system for large-scale media production	Endotoxin and mycoplasma testing equipment	

Electroporators		
Automated cell counters		
Microscopes		
Automated filling equipment		

Example of cleanroom at RoslinCT

Cell Therapy Process Development

RoslinCT's cell therapy process development laboratories mirror the manufacturing facility in terms of equipment. The laboratories offer flexibility and expertise required to optimise processes for GMP manufacturing.

- Cell selection and cell processing systems
- Bioreactors
- Tissue culture and associated equipment
- Quarantine lab (primary cultures)
- Microscopy suite
- Flow cytometers
- Controlled rate freezers
- qPCR / molecular suite and associated equipment
- Gel tanks
- UV doc
- Mediboxes / dry shippers (for control temp shipment)
- Cryopreservation suite
- Electroporators

Example of equipment in process development laboratories

Licences

RoslinCT holds an HTA licence, MHRA MIA (IMP) and Manufacturer's Specials licences for the facility.

Track record and Experience

RoslinCT – Contract Manufacturing

The team at RoslinCT has extensive cell therapy expertise and a wealth of experience to ensure projects progress to the highest quality from the very beginning, in a timely and cost effective manner.

The GMP team has many years' experience in the production and testing of cell therapies/ATMPs and GMP pluripotent stem cell banks. These include:

- Manufacturing drug substance cell banks for neuronal and retinal cell products
- Manufacturing drug product from drug substance cell banks for use in clinical trials
- Manufacturing final product batches of pluripotent cell based products
- Producing clinical grade cell banks of pluripotent stem cells
- A range of adherent cell based products
- Gene edited cell products

They are experienced in the practicalities of technology transfer of cell therapy/ATMP processes. The team has also performed the manufacture of some of the leading cell therapy clinical trials within the UK, including manufacturing for ReNeuron and Pfizer Neusentis.

RoslinCT – Cell Therapy Process Development

The Cell Therapy Development team have many years of experience of translating cell therapy protocols to GMP, process development and the associated documentation required for GMP manufacturing. Specific services provided by the Cell Therapy Development Department include;

- Transfection/transduction capability
- iPSC generation
- PSC culture
- Process scale up and automation
- Generation of cellular material for toxicology and engraftment study
- Cell characterisation
- Cell growth parameter optimisation
- Cell banking
- Gene editing
- GMP translation
- Assay design and qualification
- Process design, gap analysis, streamlining and qualification
- Differentiation strategy optimisation
- Final formulation optimisation
- Cryopreservation strategy optimisation
- Cold chain logistics and dispatch optimisation
- Reinfusion optimisation and logistics (clinical site)

Personnel

RoslinCT currently has 50 employees with the core team organised into 4 departments; Production, Quality Control, Quality Assurance and Cell Therapy Development.

Capacity

Expansion underway, please enquire: enquiries@roslinct.com

Royal Free Hospital London

Royal Free Hospital
Pond Street
London
NW3 2QG

Professor Mark Lowdell
Director of Cell Therapy & Qualified Person
020 7830 2183

Dr Owen Bain
Head of QC
020 7794 0500 x33140

Facility

The CCGTT is an ATMP manufacturing unit owned and operated by the Royal Free London NHS FT providing a core facility for the manufacture and storage of all three types of ATMP to full GMP compliance under licences from the MHRA (MIA IMP / MS) and the HTA. It consists of a suite of 10 GMP laboratories with 5 associated support rooms (two Quarantine Goods stores, two Released Goods stores and male/female changing rooms) on the lower ground floor at RFH plus two Quality Control labs, three GMP Process Development labs and three staff offices on the first floor together with the RFH/UCL biobank cryogenic cell repository on the first floor.

The suite consists of 4 grade D laboratories (including a lab for in-process QC accessible from D and B labs), 1 large grade C laboratory for long-term “closed” cell expansion and 5 individually isolated grade B labs with individual grade B gowning compartments to prevent cross-contamination. One of the grade B labs is dedicated to handling GM products under negative pressure within a positive pressure background.

Each B lab is maintained at +50Pa to atmospheric air pressure and there is a 10-15Pa air cascade through each grade of laboratory and there is no air recirculation; fresh air enters each laboratory through a terminal Hepa filter and is removed via a low level extract. Air change rates vary from 70 AC/H in the B labs to 28 AC/H in the D labs. Continuous particle monitoring is provided in each of the class II microbiological safety cabinets and the QUBE isolator which provide the grade A environments.

Each laboratory can be completely isolated from the others for fumigation with vapourised hydrogen peroxide.

GMP Manufacturing facility at CCGTT

Licence

MHRA MA(IMP) MS 11149 / HTA licence 11016

Track record and experience

The CCGTT has the skills and resources to undertake GMP conversion of almost any process for any type of ATMP and has taken multiple somatic cell therapies and now three tissue-engineered 3-D structures to clinical use. They have QA and QC skills and a QP in-house to release ATIMPs. They can draft IMPDs, IBs, PSFs, SOPs and BMRs and manage them within their in-house document control system. The CCGTT can train staff to work in a GMP compliant manner and have routinely done so. These resources are largely provided by the core NHS staff and the facility currently has no excess capacity.

The CCGTT has successfully supported 5 commercial clinical trials and has a number under negotiation at present.

- Pre 2001-83-EC
  - Autologous IL-2 primed NK cells in AML
  - Autologous TIL in RCC

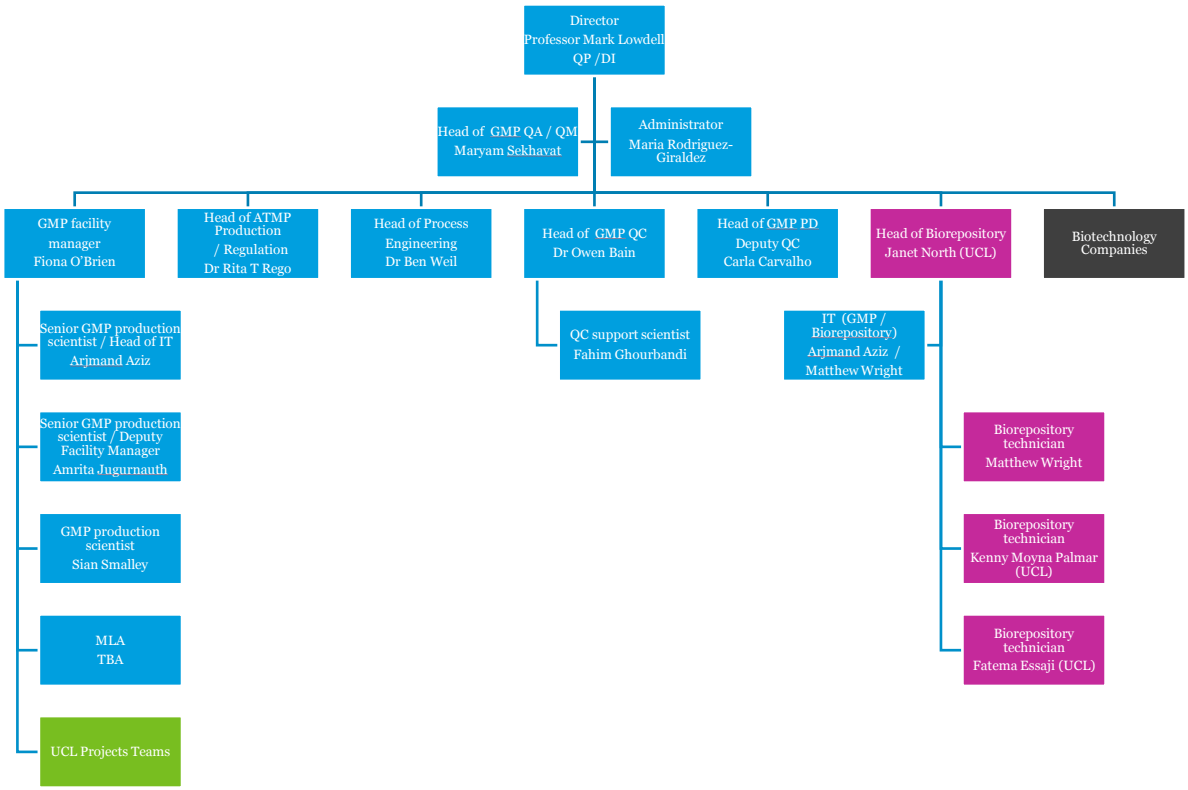
- Autologous LAK in Ca Ova
- Allogeneic NK in AML
- DC primed sib allo CMV-specific T cells

- Post 2001-83-EC
  - Sib allo CMV T cells by IfnG catch
  - DC-Vax in glioma
  - HuESC retinal epithelia – PhI commercial
  - Allogeneic NK cell therapy for AML – PhI/IIa PhII commercial
  - Two, matched allogeneic anti-viral T cell products - PhI/IIa commercial
  - Autologous stem cell seeded cadaveric tracheal tissue engineered products
  - Autologous stem cell-derived cell seeded biocompatible tissue structure tissue engineered products
  - Autologous stem cell seeded cadaveric laryngeal tissue engineered products
  - Large scale MCB and WCB of allogeneic MSC carrying a single gene insertion (lentiviral)
  - Large scale closed-system MSC manufacture and banking
  - Intermediate scale human ES expansion and differentiation
  - Autologous iPS cells
  - Autologous bone marrow MSC
  - Autologous adipose MSC
  - Autologous CAR-T manufacture (intermediate scale closed system)

	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	✓
Allo	✓	✓	✓	

Human ES Cell	iPS Cell	Cell isolation from donor tissue
✓	✓	✓

Personnel



Capacity

TC Biopharm

Maxim Park
Parklands Way
Holytown
Scotland
ML1 4WQ

info@tcbiopharm.com

Facilities at TC Biopharm

TC BioPharm (TCB) is a biopharmaceutical business currently developing the closest to market drug candidate in Gamma Delta T (GDT) cell therapies. The company has a strong focus on chimeric antigen receptor (CAR) modified GDT cells with the aim of treating cancer and major viral diseases. We have a unique technology with a demonstrable safety profile and established intellectual property rights for the entire GDT-based platforms - ImmuniCAR® and OmmniCAR®. This negates increasing concerns over the safety of current alpha beta CAR-T cell therapy approaches.

The company operates a 465 square metre GMP cell therapy manufacturing facility in Central Scotland where our products are manufactured. All regulatory, clinical and quality functions are performed in-house.

License

TCB received an MIA (IMP) license and MS licence (# 42803) from the MHRA to produce human cell therapy products at its clinical manufacturing facility in Lanarkshire.

Scottish National Blood Transfusion Service (SNBTS)

SNBTS has manufacturing facilities in Edinburgh based at the Jack Copland Centre (JCC) and Scottish Centre for Regenerative Medicine (SCRM).

These facilities were specifically designed for the development and manufacture of cellular therapies/ATMPs and contain a total of 10 classified cleanroom areas of various grades, served by dedicated air handling units.

SNBTS Jack Copland Centre
Research Avenue North
Heriot Watt University Research Park
Riccarton
Currie
Edinburgh
EH14 4AP

SNBTS Cellular Therapy Facility
Scottish Centre for Regenerative Medicine
5 Little France Drive
Edinburgh BioQuarter
Edinburgh
EH16 4UU

Prof. John Campbell
Associate Director, Tissues, Cells and Advanced Therapeutics
johncampbell3@nhs.net
0131 314 5677

Dr Neil McGowan:
Head of Manufacturing, Tissues, Cells and Advanced Therapeutics
neil.mcgowan@nhs.net
0131 314 5659

Facilities at SNBTS

Manufacture:

- 4 Grade B cleanrooms with a minimum of 2 Grade A MSCs in each.
- 4 Grade C cleanrooms with Grade A MSCs and/or isolators (n=3) – tissues and closed processes.
- Grade D manufacturing areas (3 enclosed rooms and extensive manufacturing 'pods').
- Extensive Grade C support space, VHP transfer hatches at both sites for sanitisation of materials.
- Dedicated AHU with fumigation modes and 2 dedicated VHP generators.
- Irradiators and sterilising autoclaves.

Characterisation & QC:

- GMP cell analysis, including Flow Cytometry, Sorting and Cell enumeration.
- Extensive in-house testing facilities (virology, bacteriology and endotoxin).

Equipment	Analytical equipment	Cell/product storage
2x GE Excellerex 10L bioreactor	2x FACS Canto II, 1x MACSQuant 10, 2x MACSQuant Vyb, 1x BD Fortessa (16 colour)	Extensive -80°C and Vapour Phase LN_2 Storage
2x CliniMACS plus	Sysmex haematology analysers	
4x CliniMACS prodigy	Evos imaging microscopes (x4)	

>10 Cell culture CO_2 incubators	MACsQuant Tyto GMP Cell Sorter	
>10 Centrifuges		
5x Controlled rate freezer (Planers)		
Various closed system cell processing equipment – TSCD		
Tube sealers		

Licence

SNBTS holds an HTA licence and MHRA MIA (IMP), MS, BEA and WDL.

Track record and Experience

SNBTS has experience in the manufacture of a range of cellular therapy products, under appropriate HTA, MHRA specials or MIA(IMP) licences. These include CD133+ autologous stem cells, EBV-specific cytotoxic T cells, corneal epithelial stem cells and cell banking (iPSC).

This is in addition to the provision of blood products, tissues (bone, tendons, heart valves, skin) and well-established cell therapy products (haematopoietic progenitor cells and pancreatic islet cells for the treatment of a range of haematopoietic malignancies and diabetes respectively).

SNBTS also has extensive cell therapy translational research laboratories at SCRM and JCC which are involved in novel process development through to the final translation of several other novel cell therapy products.

Personnel

SNBTS employs 25 full time team members in the GMP manufacture of tissues and cellular therapies and receives extensive R&D and QA support from wider SNBTS.

Capacity

University of Birmingham

GMP Manufacturing Facility
Advanced Therapies Facility
College of Medical and Dental Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT

Dr Stuart Curbishley
s.m.curbishley@bham.ac.uk
07887 515001

Dr Jane Steele
j.c.steele@bham.ac.uk
0121 414 7668

Professor Phil Newsome
p.n.newsome@bham.ac.uk

Facility

The facility houses two grade B cleanroom suites (one GMO compliant) and each contains a biological safety cabinet (BSC, Grade A), change room (Grade B/C) with pressure sink to containment suite, preparation room (Grade C), change room (Grade C/D) and an unclassified store room, office, lobby and locker room. There is a separate QC laboratory, freezer room and cryostore containing liquid nitrogen storage and a controlled rate freezer.

The GMP manufacturing facility is joined onto the adjacent NIHR/Wellcome Trust Clinical Research Facility, under the governance of University Hospital Birmingham NHS Foundation Trust, where manufactured products can be administered to patients in an appropriately staffed and monitored environment.

During 2019 we are hoping to install a Miltenyi Biotec Tyto GMP cell sorter.

Processing equipment	Analytical equipment
Environment Monitoring System	MACSQuant analyser
Temperature Monitoring System (Tutela) for Fridges, Freezers, Incubators	Endosafe PTS Endotoxin Detector
CliniMACS Plus	TECAN Infinite Spectrophotometer
CliniMACS Prodigy	Microbiology QC
4 x standard CO2 incubators	GMP and process development assays
1 x hypoxic incubator	
Tube sealers, centrifuge, microscope	
Terumo Quantum	

Licence

MHRA licence for IMPs and an MS specials licence. An application for an HTA licence has been reviewed and the facility is awaiting a licencing inspection.

Track record and experience

Production for the first clinical trial commenced in June 2016 with the manufacture of autologous dendritic cells from patients with hepatocellular carcinoma. The site functioned as a partner for phase I/II trial preparing stem cells for release to patients with Acute Respiratory Distress Syndrome. In Q1

2018 the facility was part of a Birmingham lead bid for Innovate UK funded Advanced Therapy Treatment Centres and was named as the lead organisation within the Midlands-Wales ATTC (Director, Prof Newsome). As part of the ATTC program, the facility is integrating a manufacturing team from a clinical stage biotech to deliver mesenchymal stromal cells in a phase II basket trial. In addition, a new phase II dendritic cell study will be delivered based on fully automated isolation and differentiation of circulated DC.

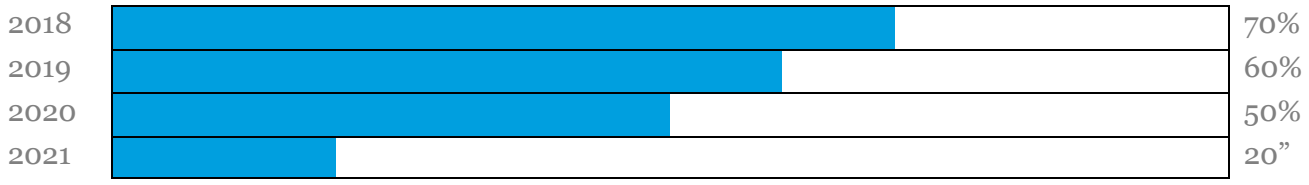
Personnel

An organogram can be seen below. The facility is regulated by the Advanced Therapies Facility Management Committee which oversees the direction, management, governance and finances.

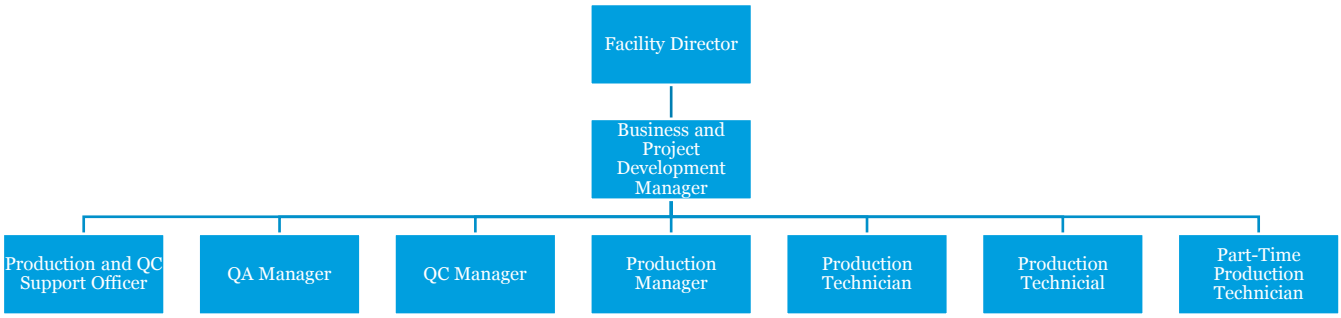
There is a full time New Business and Project Development Manager, Production Manager, Quality Control Manager, Quality Assurance Manager, Production support officer and two production technicians plus one part time technician on site maintaining the Cell Therapy Suite – further technical and production staff is employed on a project by project basis as required. The unit sub contracts a Qualified Person for batch release.

Capacity

The Cell Therapy Suite at the University of Birmingham has the capability to manufacture 3-5 different products simultaneously depending upon the timings and complexities of manufacturing protocols.



Organogram



University of Manchester

Core Technology Facility
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M13 9NT

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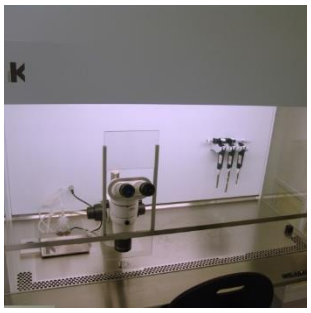
0161 275 6773

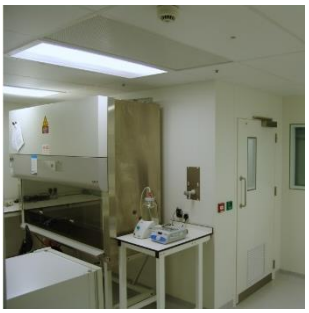
Joan Benson
joan.benson@manchester.ac.uk
0161 275 7436

Facilities

The facility houses two grade B processing areas each containing 2 x Class II MBSCs; the grade B rooms each has a grade C support/preparation area. A QC testing laboratory is available for environmental monitoring and sterility testing.

Processing equipment	Analytical equipment
CO_2 Incubators	Automated rapid sterility testing (BacT/ALERT® 3D Signature)
Class II MBSCs	Microbiological and physical environmental monitoring
Centrifuges	
Microscopes	
Heat blocks	
Water baths	
Analytical balance	
LN_2 storage	
Controlled rate freezer	
Controlled temperature storage: ambient to -80°C	


Licence

MHRA licence for manufacture of IMPs and a Specials licence. The facility also has HTA and HFEA licences.

Track record and experience

The University of Manchester Cleanroom Facility provides researchers with the ability to translate their research from basic studies and pre-clinical work, to clinical trials, by providing the capacity to generate clinical grade Investigational Medicinal Products (IMPs), Advanced Therapy Medicinal Products (ATMPs) and Specials.

GMP derivation of hES cell lines

hESCs differentiated to Chondrocytes, for repair of Osteoarthritis

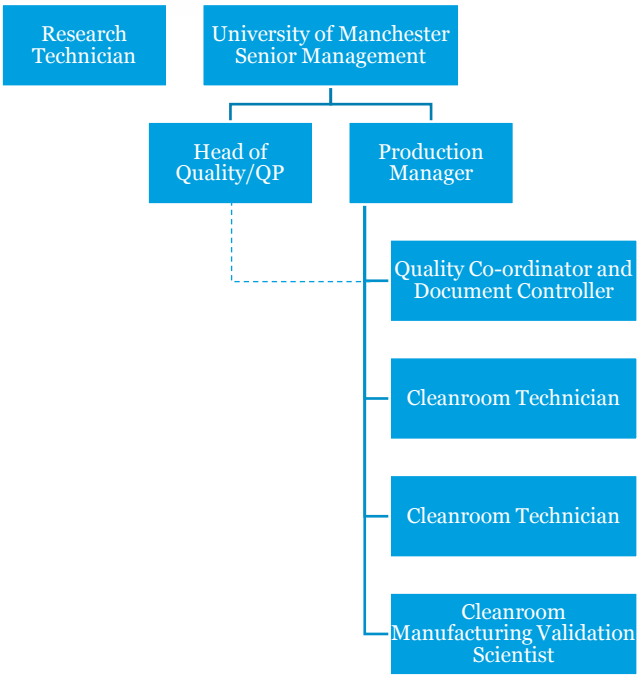
Development of a cell/gene therapy treatment for Duchenne Muscular Dystrophy Translation of a novel synthetic polymer nerve conduit for Peripheral Nerve Regeneration.

	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	
Allo	✓	✓	✓	

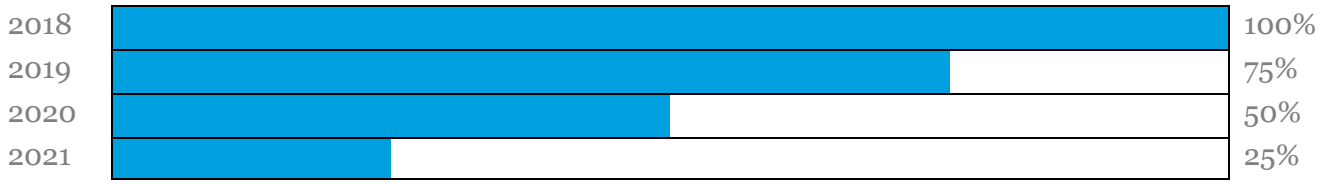
Human ES Cell	iPS Cell	Cell isolation from donor tissue
✓	✓	✓

Personnel

The facility is headed by a University of Manchester professor who acts as senior management, the cleanroom has 6 staff and 1 consultant QP.



Capacity



University of Oxford Clinical BioManufacturing Facility

Clinical BioManufacturing Facility
University of Oxford
Old Rd
Headington
Oxford OX3 7JT

Emma Bolam
Emma.bolam@ndm.ox.ac.uk
01865 611356/744845

Facility

Manufacturing suites

- Five grade C rooms in total: one large 51m² room with two MBSCs, two rooms (23m² and 11m²) with one MBSC each, as well as two rooms with isolators: a smaller room of 10m² with a two-port isolator and a larger room of 17.4m² with a 4 glove isolator currently used for fill/finish but could also be used for manufacture.
- One grade D area 22.9m² for preparation, staging and inspection and a through wall pharmaceutical autoclave.

Processing equipment	Analytical equipment
2 x CO_2 shaking incubators	Endotoxin measurement
2 x static CO_2 incubators	Sterility check
4 x Class II MBSCs	DNA and protein quantification
4-glove isolator	Access to FACS analysis
2 glove isolator	Molecular Biological Capabilities (QPCR, PCR, enzyme restriction analysis, sequencing)
2 ultracentrifuges	Analytical QC testing for viral vector applications
3 low speed centrifuges	Analytical QC testing for residuals
AKTA pilot	Other QC testing can be outsourced to approved sub-contractors

Figure 3 Example photos of Oxford CBF facility

Licence

An MHRA MIA (IMP) licence has been granted which authorises cell therapy products, gene therapy products and many additional manufacturing capabilities. The facility does not currently have an HTA licence. The CBF has prior experience importing IMPs from outside the EU and certifying these to clinical trial in the EU.

Track record and experience

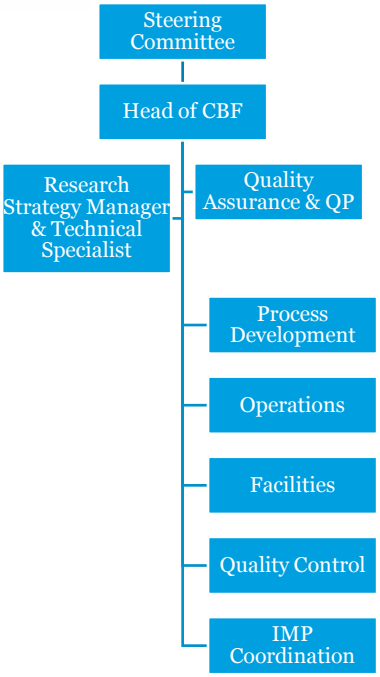
The facility has a great deal of experience with biologics production (recombinant proteins and viruses etc.). Adherent and suspension cell cultures have therefore been used for this purpose. Key staff have experience during previous employment with cell therapy manufacture (including viral transduction). A summary of their experience can be found below. Personnel at the Oxford CBF have a large degree of experience with viral vector manufacture which is a key component of gene modified cell therapies.

	Suspension	Adherent	2D	3D
Auto				
Allo	✓	✓		

Human ES Cell	iPS Cell	Cell isolation from donor tissue
		Previous experience

Personnel

In total there are 19 members of staff are working within the facility. The site has two permanent QPs onsite and three named contract QPs on their licence.



Capacity

The facility is currently working at capacity with respect to manufacturing work. The facility has plans for expansion which would mean a greater degree of capacity in the future.

6 Appendix

6.1 Glossary of terms

AAV – Adeno-associated virus

CMO – Contract Manufacturing Organisation

CoG – Cost of Goods

DoP – Dependent on Process

FT – Full Time

PT – Part Time

HTA – Human Tissue Authority

IMP – Investigational Medicinal Product

GMO – Genetically Modified Organism

GMP – Good Manufacturing Practice

MBSC – Microbiological Safety Cabinet

MHRA – Medicines and Healthcare Products Regulatory Agency

MIA(IMP) – MHRA manufacturing authorisation licence for Investigation Medicinal Products

QA – Quality Assurance

QC – Quality Control

Auto – Autologous, patient is treated with their own cells (i.e. each patient requires their own product)

Allo – Allogeneic, all patients are treated with cells derived from one donor (i.e. one product for all patients)

PE – Previous experience; meaning that key staff have experience in a particular technique or cell therapy manufacturing process but not at their current organisation.

Thank you to the UK cell and gene therapy manufacturing community for supporting the delivery of this publication: