NA-ATTC Pathways from Translational Research to Industrialisation

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Funded by UK Research and Innovation

Coordinated by CATAPULT Cell and Gene Therapy

The Northern Alliance Advanced Therapy Treatment Centre (NA-ATTC), formally established in March 2018, is a consortium of twenty industry, NHS and academic organisations led by The Newcastle upon Tyne Hospitals NHS Foundation Trust and the Scottish National Blood Transfusion Service (SNBTS).

NA-ATTC's vision is to increase patient access to advanced therapy medicinal products (ATMPs) regionally and nationally by growing a cost-effective clinical delivery pathway which meets the needs of the providers of such products. The Centre has a patient reach of ~15 million spanning Scotland and the North of England, working across two healthcare systems.

The Centre focuses on all elements of the clinical delivery pathway from procurement of starting materials, centralised and near to patient GMP manufacturing, distribution and administration, through to delivery of clinical trials culminating in adoption and reimbursement across a range of indications. This will entail the participation and collaboration of nurses, clinicians, hospital pharmacists, NHS managers, clinical commissioners and industrial partners.

Synopsis

The field of ATMPs is rapidly evolving. These novel products are being increasingly used to treat complex diseases and conditions for which there were previously limited therapeutic options.

The manufacturing of these living therapies is considerably more complex than that for currently marketed products such as small molecules and biotherapeutics, and falls under different regulatory procedures. The journey from concept to Marketing Authorisation may take longer, and have different clinical trialling requirements, compared to (bio) pharmaceuticals.

Initial development of new treatments frequently begins in an academic research setting.

Translation to clinical application means navigating a complex set of regulatory guidelines, involvement of multiple collaborators and ultimately, commercial investment.

This document highlights exemplar ATMPs which have undergone this process, moving fully to marketing authorisation or currently in late phase clinical trial.

Introduction

The development of ATMPs is more complex than for traditional therapies. Translation from a basic research concept to industrial realisation can be captured using Technology Readiness Levels (TRLs).
In 2009 Professor Chris Mason captured these levels for cellular therapeutics, which provided a useful guide for developers of advanced therapies (Fig. 1).

Fig. 1. TRLs in CBT manufacturing development; adapted from [1,2]

Technology readiness level	TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8	TRL 9
Milestone	Basic idea	Concept development	Experimental proof of concept	Process validated in laboratory	Process validated on production equipment	Process capability validated on production equipment	Capability validated on economic runs	Capability validated over range of parts	Capability validated on full range of parts over long periods
Drug development pipeline	Basic research		Preclinical research		Late preclinical research		Phase I	Phase II	Phase III/IV

TRL1 to 2

Common to academic research projects and often involving an element of animal-based cell and/or tissue work before 'translation' to human cells and tissues.

This is typically the stage of most flexibility and innovation due to less stringent regulatory constraints and greater experimental freedom. This can uncover new concepts to fuel transition to other TRLs. However, researchers need to be aware of potential translational limitations in later stages of the development process.

Points for consideration:

- Will findings from animal studies translate to humans (early stage translation) i.e. do similar cell identification markers exist and what is the availability of reagents/consumables to investigate this?
- Access to technology and resources to enable development past the initial concept e.g. availability of GMP-grade versions of reagents and consumables.
- Initiation of academic-industry collaborations early to ensure a clear path for ATMP development through the translational process.

TRL3 to 4

Often a bottleneck, TRL3-4 considers what is possible with available technology and whether there are any significant challenges to scale up and robustness of the process. Processes are critically examined with substitution of research reagents and techniques for those suitable for ATMP manufacture.

Points for consideration:

- Rigorous validation of research methods to give confidence in the reproducibility and consistency of processes for routine use.
- Additional costs of GMP-grade reagents and consumables compared to research-grade.
- Requirement for risk assessment of all reagents with a particular focus on those not available at GMP-grade or as xeno-free products.
- Life cycle of the product including frozen stability and requirement for development of an extensive QC portfolio.

TRL5 to 7

To continue its progress to the clinic, the manufacturing of the ATMP must be sufficiently validated to compile an Investigative Medicinal Product Dossier and gain Clinical Trial Authorisation which is essential for entry into Phase 1 clinical trial. In addition, this stage must consider a number of factors relating to future manufacturing ability, logistics and cost. This can often be overlooked in the drive to make a clinical breakthrough, but can hamper future scale-up.

Points for consideration:

- Does the process design take into account future scalability?
- Is the process commercially viable, taking into account staff, materials, equipment etc?
- Labour-intensive production versus partial or complete automation.
- Does the technology implemented account for automation in future where this may be needed for manufacture at commercial scale?
- Defining manufacturing specifications – can these be met at scale consistently and reproducibly?
- Regulatory requirements in different geographical areas - USA versus Europe versus Asia e.g.:
    - o CE certification for Europe
    - o 'GMP' grade reagents to cover global manufacture
- Health economic analysis – consider cost:benefit when determining reimbursements.

TRL7 to 9

Serious consideration must be given to future scale-up and commercial manufacture. Industrial partners typically possess the financial capacity to support all elements of expansion of the production cycle from Phase I through to commercial manufacture.

Points for consideration:

- Scale-out (multiplexing and ultimately moving to multiple sites) versus scale-up: Growth in the ATMP field, driven by CAR-T and other individualised cellular products, had triggered great interest in scale-out as the route to commercialisation. Scale-up remains a goal for "many from one" pluripotent cell-based therapies.
- Single versus multicentre manufacturing.
- Complex contracts (Supply and Quality Agreements) required with suppliers to ensure continuity of supply of materials.
- Timelines associated with construction and qualification of bespoke facilities.
- Will the planned facilities be able to meet commercial demand following initial and further reporting of phase I/II/III/IV data?
    - Promising results may lead to a rapid rise in demand
    - Will the planned processes allow for a rapid increase in capacity if necessary?
    - Additional staffing and training requirements.
    - Alignment of multi-centre facilities – manual manufacturing processes can complicate translation of the production processes between sites for qualification and eventual release.

Concluding remarks

The journey of any therapy from concept to commercialisation is a complicated one - ATMPs are no exception.
Even at the conceptual stage in academic settings, careful consideration for future development is vital to identify and address potential bottlenecks when transitioning between TRLs. Addressing these issues early in the process can mitigate potential delays and financial burdens, bringing these much-needed therapies to patients as fast as possible.

Exemplars of approved and pending ATMPs

The following tables showcase exemplars of ATMPs that have been approved for use in patients or are working towards this.

Key for all subsequent Exemplars (Colour indication)

Funding	Academic innovation and discovery
	Public-private collaborations
	Industry

Kymriah® Novartis

Year	Learning	Reference	Technology Readiness Level (TRL)
1997	CD3/CD28-bead costimulation for CD4+ T cells	Levine at al. JI 159:592	2
1998	Large scale production of CD3/CD28 costimulated CD4+ T cells	Levine et al. J Hematotherapy 7:437	2
2000	CD4 and CD8 respond differently to CD3/CD28 costimulation; double positives sign of immuno senencensce	Laux et al. Clin. Immunol. 96:187	2
2002	Adoptive transfer of CD3/CD28 costimulated CD4	Levine et al. Nat. Med. 8:47	3
2003	GMP Bioreactor-based process for autologous T cell therapy	Hami et al. BioProcess J 2: 23 (Xcyte Therapies)	4
2004	CML remission post CD3/CD28 costimulated autologous T cells	Rapoport et al. BM Transplantation 33:53.	4
2006	DLI with allo donor cells expanded with CD3/CD28 costimulation; CD14 depletion >20% monos	Porter et al. Blood 107:1325	4
2011	Autologous CAR+ T cells for anti-leukemic memory	Kalos et al. Sci Transl. Med 3:1	4
2011	CAR+ T cells in CLL	Porter et al. NEJM 265:725.	3
2012 - 2014	Tech transfer from UPenn to Novartis	Novartis documents	6
2014	Adaptation of UPenn process (A) to Novartis process (B)	Novartis documents	6
2015	Morris Plains clinical manufacturing	Novartis documents	7
2016	Process characterisation phase 1	Novartis documents	7/8
2017	Process characterisation phase 2	Novartis documents	8
2017 - 2018	Commercial manufacturing readiness	Novartis documents	9

Exemplars of approved and pending ATMPs

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Strimvelis® Orchard Therapeutics

Year	Learning	Reference	Technology Readiness Level (TRL)
1991	Selective advantage for transduced T-cells	Ferrari et al Science 1991	1
1995	PB lymphocytes and BM cells without conditioning	Bordignon et al, Science 1995	1
2000	Pilot studies; BM CD34+ cells with non-myeloablative conditioning	Aiuti et al, Science 2002	2
2002 - 2009	Phase I/II pivotal study; BM CD34+ cells with non-myeloablative conditioning	Aiuti et al, NewEngLJMed 2009	2 - 3
2005	EMA orphan drug designation		4 - 5
2004	How I treat ADA deficiency	Gaspar et al, Blood 2009	4 - 5
2009	FDA orphan drug designation	Porter et al. Blood 107:1325	5 - 6
2010	GSK, Telethon and OSR Alliance; Compassionate use programme and Named patient programme		6 - 7
2015	GSK filing MAA		7 - 8
2016	GSK receives positive CHMP opinion	Circalese, Ferrua et al, Blood 2016	8
2016	Strimvelis Approval in EU		8
2018	GSK signs strategic agreement to transfer rare disease gene therapy portfolio to Orchard Therapeutics		9

Key

OSR - Ospedale San Raffaele

MAA - Market Authorisation Application

CHMP - Committee for Medicinal Products for Human Use

Exemplars of approved and pending ATMPs

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	Public-private collaborations
	Industry

ORBCEL-C® Orbsen Therapeutics

Year	Learning	Reference	Technology Readiness Level (TRL)
2009	Allogeneic human MSCs can restores normal fluid balance in an ex vivo perfused human lung injured by E. coli endotoxin.	Lee JW et al., Proc Natl Acad Sci U S A. 2009 Sep 22;106(38):16357- 62.	1
2012	MSC therapy enhances lung repair following VILI via a paracrine mechanism	Curley GF et al., Thorax. 2012 Jun;67(6):496-501	1
2012	Human placenta is an abundant source of multipotent stem cells that are promising candidates for cell-based therapies	Nazarov I et al., Stem Cells Transl Med. 2012 May;1(5):359-72	2
2014	Proof of principle that MSCs can restore alveolar fluid clearance in human lungs rejected for transplantation.	McAuley, D F et al., Am J Physiol Lung Cell Mol Physiol. 2014;306: L809–L815.	3
2014	ORBSEN THERAPEUTICS LTD (IE) patented The MEDICAL USE OF SYNDECAN-2 (CD362)	Patent Application WO/2014/170411; Oct 2014	3
2015	hMSC therapy decreased E. coli induced pneumonia injury and reduced lung bacterial burden	Devaney J, et al., Thorax . 2015 Jul;70(7):625-35.	3
2016	Novel mechanism for the antimicrobial effect of MSC in ARDS	Jackson MV et al., Stem Cells 2016;34:2210-2223.	3
2017	Human umbilical cord MSC option for clinical trials in ARDS.	Curley GF. et al., Crit Care Med. 2017;45: e202–e212.	4
2016 - 2017	Technology transfer to NHSBT for GMP manufacturing of REALIST ORBCEL-C		4/5
2017	Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST)- clinical trial submission.	Clinical trial identifier: NCT03042143	5
2017	Manufacture REALIST ORBCEL-C to GMP standards for the REALIST trial. Protocol, IB, IMPD finalised		6

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ORBCEL-C® Orbsen Therapeutics

Year	Learning	Reference	Technology Readiness Level (TRL)
2018 - 2019	Trial received ethics approval from the REC. Phase 1 clinical trial to assess safety and maximum tolerated dose. Patient recruitment stopped due to some issues and MHRA advise to halt trail	Gorman E, et al., Trials. 2020 Jun 3;21(1):462.	6/7
2019- 2020	REALIST Phase 1 open label dose escalation study of REALIST ORBCEL-C in patients with ARDS completed	Gorman E, et al., Trials. 2020 Jun 3;21(1):462.	7
2020	REALIST Phase 2 trial as a COVID-19 specific trial. Urgent Public Health status was awarded by the NIHR	Gorman E, et al., Trials. 2020 Jun 3;21(1):462.	8
2020	The efficacy of CD362+ UC-hMSCs.	Horie, Shahd et al., Stem Cell Res Ther. 2020; 11: 116	4/5

References

1. Mason C. Adapted from written evidence from Professor Chris Mason. Presentation outlining the vision for a Cell Therapy TIC, May 2011, US Department of Defense: Technology Readiness Assessment Strategy for Regenerative Medicine Technology Readiness Assessment (TRA) Deskbook 2009.
2. House of Lords Science and Technology Committee. First Report: Regenerative medicine (HL Paper 23). Chapter 3: The current landscape. London, UK; printed 26 June 2013. [cited 2020 Feb 10] **https://publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/23.pdf.**