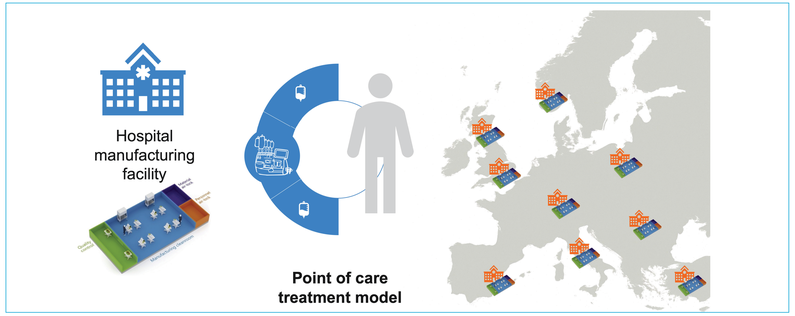
Point of Care Automated Manufacturing Enables Rapid Translation of Both Novel TCR-T Cell Therapies as well as Conventional CAR T Cell Therapies into the Clinic

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Introduction

Although cell and gene therapies are showing impressive efficacy, a number of serious barriers to widespread patient access remain, including manufacturing logistics, manufacturing upscaling and the cost of the therapies themselves. One possible solution to reduce costs and improve patient access is to manufacture using a local point of care (PoC) model.
Using closed, GMP-compliant, automated manufacturing systems, it is possible to standardize ATMP manufacturing procedures to greatly accelerate and simplify the translation of novel therapies into the clinic. To illustrate this, one approach is described to accelerate the transfer of 2 novel TCR-modified T cell therapies into the clinic with different manufacturing protocols using the CliniMACS Prodigy® at a PoC clinical manufacturing site in the Netherlands. A complementary strategy is also presented which is focused less on novel therapies but on more established approaches using CAR T cells. A concept has recently been implemented to supply "blueprints" for manufacturing and quality control along with GMP-quality reagents, consumables, GMP lentiviral vector encoding a selection of clinically-relevant CAR constructs as well as regulatory documentation packages to academic clinical centers. This approach has enabled rapid establishment of PoC manufacturing either for early-phase CAR T cell clinical trials or for treatment of patients under hospital exemption.



Results

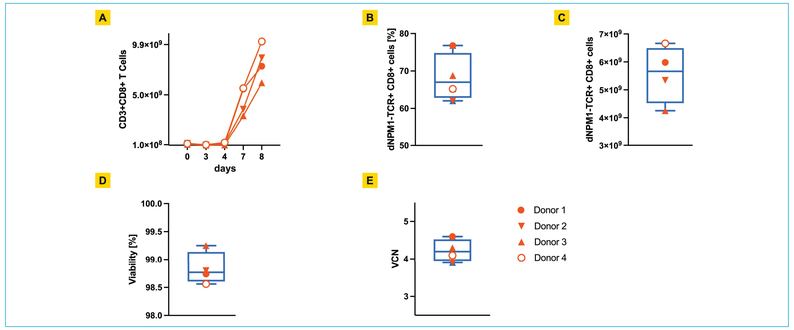
1 Establishment of PoC GMP manufacturing of novel TCR-T therapies

Two different manufacturing protocols for generating TCR-modified T cells were established on the CliniMACS Prodigy at a PoC clinical manufacturing site in the Netherlands. The first of these was a T cell Transduction large-scale (TCT-LS) 8-day protocol to generate T cells modified with a lentiviral vector encoding an HLA-A*02:01 restricted recombinant ΔNPM1 neoantigen-specific TCR[1] to be used in a clinical trial targeting relapsed or refractory AML. The second was a standard scale (TCT) 6-day shortened protocol to enable expression of an HLA-B*07:02 restricted recombinant BOB1-specific TCR[2], which will be used in a trial for treatment of relapsed or refractory B-cell malignancies. BOB1 is a B-cell lineage-specific transcription coactivator shown in studies to be essential for survival of certain B cell malignancies and therefore provides an attractive novel target.

Method transfer and process establishment was simplified due to a high level of automation. As all processes are performed at the clinical site and a fresh product is infused into the patient, a short vein-to-vein time is readily achievable. The ΔNPM1-TCR trial is currently recruiting patients in the Netherlands (NCT06424340) while the BOB1-TCR trial is in preparation.

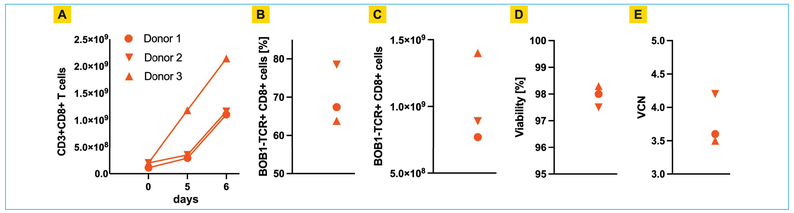
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2 Manufacturing of ΔNPM1-TCR-modified CD8+ T cells



After 8 days of manufacturing using the TCT-LS process in the CliniMACS Prodigy, up to 1E10 CD8+ T cells were generated from 4 cryopreserved healthy donor apheresis samples (A) of which a mean of 68.2 ± 6.4% expressed the ΔNPM1-TCR (B) with a yield of 5.6E9 ± 1E9 ΔNPM1.TCR+CD8+ T cells (C) with viability > 98% (D) and less than 5 viral vector genome integrations (E).

3 Manufacturing of BOB1-TCR-modified CD8+ T cells

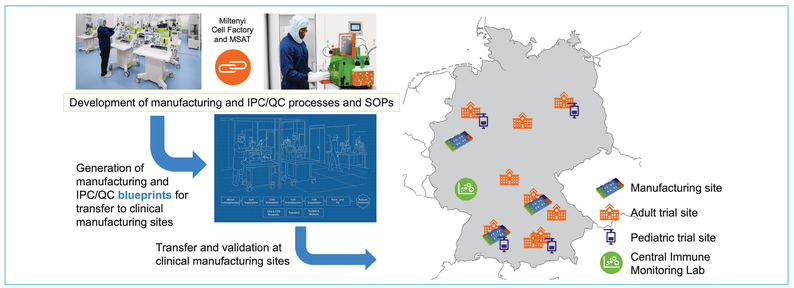


A standard CliniMACS Prodigy TCT process using the Tubing Set 520 was implemented at the clinical manufacturing site. Starting from fresh apheresis (donor 3), cryopreserved apheresis (donor 1) or frozen CD8+ T cells (donor 2), up to 2e9 CD8+ T cells were generated by harvest on day 6 of the process (A; mean of 1.5E9 ± 0.58E9) of which 69.9 ± 7.7% expressed the BOB1-specific TCR (B). 1.0E9 ± 0.32E9 BOB1.TCR+CD8+ T cells could be harvested (C) with viabilities > 97.5% after formulation (D) and VCN < 5 (E).

4 Establishing a multi-center clinical trial with a decentralized and PoC manufacturing concept

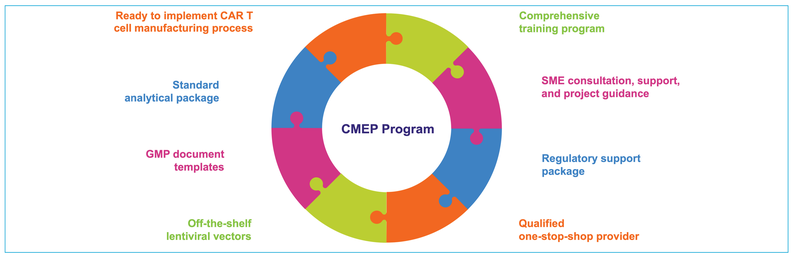
How best can decentralized manufacturing for a multi-center clinical trial be established? In 2017, Miltenyi Biotec, and subsequently Miltenyi Biomedicine, started to establish a first-in-human Phase 1 clinical study to assess the safety and preliminary efficacy of a CD19-directed CAR (4-1BBz) gene-modified, autologous T-cell immunotherapy (MB-CART19.1) in relapsed/refractory B cell malignancies (NCT03853616) within Germany. During this trial, 3 manufacturing sites were established in 3 different German federal states. In addition to a central manufacturing approach at Miltenyi Biotec's Cell Factory in Bergisch Gladbach, cell products were manufactured in an academic PoC setting (Erlangen and Tübingen) while both the industrial and academic manufacturing facilities supplied numerous additional treatment sites for adult and pediatric patients in a decentralized manner in Münster, Berlin, Göttingen, Würzburg, Regensburg and Munich. Investigational Medicinal Products were manufactured for 41 patients: 11 at the CliniMACS Cell Factory in Bergisch Gladbach, 8 in Tübingen and 22 in Erlangen. 37/41 patients (90.2%) received fresh products manufactured according to clinical trial specifications. One patient passed away prior to infusion.
Using expertise built up in the Research and Development department, the Miltenyi Cell Factory manufacturing facility and the Manufacturing Science and Technology (MSAT) team, detailed documentation and protocols were established to ease transfer of the manufacturing, in-process controls and release testing procedures to the different manufacturing sites. Detailed support was provided for the application of local manufacturing licences and to ensure comparability of on-site assay performance. Drug product quality was overseen by a central Qualified Person and a central immune monitoring lab (CIML) was implemented to analyse patient samples to determine outcomes.

From the knowledge gained during this endeavour, detailed manufacturing and IPC/QC blueprints were generated which have been used to further establish PoC manufacturing for independent academic studies at varied sites around the world.Recent publications highlight the establishment and implementation of the CliniMACS Prodigy TCT manufacturing around the world in a PoC and decentralized approach using the CART19.1 lentiviral vector in Vellore, India[3,4], Bangkok, Thailand[5] and Cleveland and St. Louis, USA[6].



5 Accelerating transfer of automated manufacturing and quality control to PoC sites

To accelerate transfer of essential technologies to areas where there is still great unmet patient need, the methodology and documentation to enable transfer of this robust and automated manufacturing technology has been further refined into a commercial offering: a Cell Manufacturing Enabling Package (CMEP). This package provides detailed blueprints for CAR T cell manufacturing and quality control, equips the customer with knowledge and support necessary to achieve a validated CAR T cell manufacturing and analytics process and integrates clinical instruments, MACS GMP reagents, MACS GMP consumables, and lentiviral vectors encoding various CAR constructs that have already been clinically evaluated.



Summary and Outlook

- Point of care manufacturing was established for two novel TCR-based autologous T cell therapies targeting ΔNPM1 and BOB1 respectively in Leiden, the Netherlands
- Manufacturing for a multi-center Phase 1 CD19-CART study was established combining central with decentral and PoC manufacturing with central QP oversight and immunomonitoring.
- Learnings from these activities have enabled the development of detailed blueprints to accelerate transfer of automated CGT manufacturing to a PoC setting
- The Cell Manufacturing Enabling Package (CMEP) is now available as a commercial offering to support establishment of T cell immunotherapies
- Advantages of PoC and decentralized manufacturing:
- Foster innovation
- Faster and better patient access
- Increased flexibility of scheduling
- Higher control by treating physician

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