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Selected references

CliniMACS Prodigy® Platform

Scientific publications

CAR T cells

Bozza, M. *et al.* (2021) A nonviral, nonintegrating DNA nanovector platform for the safe, rapid, and persistent manufacture of recombinant T cells. Sci. Adv. 7: eabf1333.
https://doi.org/10.1126/sciadv.abf1333
The CliniMACS Prodigy TCT Process was used to manufacture CAR T cells at clinical scale and subsequently anti- tumor activity *in vitro* and *in vivo* of CAR T cells was demonstrated.

Maschan, M. *et al.* (2021) Multiple site place-of-care manufactured anti-CD19 CAR-T cells induce high remission rates in B-cell malignancy patients. Nat. Commun. 12: 7200
https://doi.org/10.1038/s41467-021-27312-6
At two disparate clinical sites, Moscow (Russia) and Cleveland (USA), CAR19 T cells were successfully manufactured with the CliniMACS Prodigy TCT Process under cGMP conditions.

Mougiakakos, D. *et al.* (2021) CD19-targeted CAR T cells in refractory systemic lupus erythematosus. N. Engl. J. Med. 385: 567–569.
https://www.doi.org/10.1056/NEJMc2107725
CAR T cells were successfully generated with the CliniMACS Prodigy Instrument and used for the treatment of a patient with the autoimmune disease SLE.

Ortíz-Maldonado, V. *et al.* (2021) CART19-BE-01: A multicenter trial of ARI-0001 cell therapy in patients with CD19^{+} relapsed/refractory malignancies. Mol. Ther. 29: 636–644.
https://doi.org/10.1016/j.ymthe.2020.09.027
In the course of a clinical trial the authors perform CAR T cell manufacturing with the CliniMACS Prodigy and use the cell product for adult and pediatric patient treatment.

Palen, K. *et al.* (2021) Manufacturing chimeric antigen receptor T cells from cryopreserved peripheral blood cells: time for a collect-and-freeze model? Cytotherapy 23: 985–990.
https://doi.org/10.1016/j.jcyt.2021.07.015
CAR T cells were manufactured from cryopreserved cell product using an 8-day process on the CliniMACS Prodigy.

Alzubi, J. *et al.* (2020) Automated generation of gene-edited CAR T cells at clinical scale.
Mol. Ther. Methods Clin. Dev. 20: 379–388.
https://doi.org/10.1016/j.omtm.2020.12.008
TCR^{-} CAR^{+} T cells were engineered using the CliniMACS Prodigy T Cell Engineering Process. Hereby, the TCR was knocked out by transferring specific TALENs via electroporation and the CAR construct was integrated with viral transduction.

Castella, M. *et al.* (2020) Point-of-care CAR T-cell production (ARI-0001) using a closed semi-automatic bioreactor: Experience from an academic phase I clinical trial. Front. Immunol. 11: 482.
https://doi.org/10.3389/fimmu.2020.00482
The authors' results demonstrate the feasibility of clinical-grade production of CAR T cells for heavily pre-treated patients using the CliniMACS Prodigy Instrument and show that the obtained products meet the current quality standards of the field.

Jackson, Z. *et al.* (2020) Automated manufacture of autologous CD19 CAR T cells for treatment of non-Hodgkin lymphoma. Front. Immunol. 11: 1941.
https://doi.org/10.3389/fimmu.2020.01941
The authors show that point of care manufacturing of CAR T cells on the automated CliniMACS Prodigy Instrument allows reproducible and fast delivery of cells for the treatment of patients with NHL in a phase I/II clinical study.

Loff, S. *et al.* (2020) Rapidly switchable universal CAR-T cells for treatment of CD123-positive leukemia. Mol. Ther. Oncolytics 17: 408–420.
https://doi.org/10.1016/j.omto.2020.04.009
GMP-equivalent manufactured UniCAR T cells were produced according to the protocols of the automated CliniMACS Prodigy Platform.

Ran, T. *et al.* (2020) Cost of decentralized CAR T-cell production in an academic nonprofit setting. Int. J. Cancer. 147: 3438–3445.
https://doi.org/10.1002/ijc.33156
A scenario cost analysis was performed for potential centralized CAR T cell manufacturing site according to the standard CliniMACS Prodigy TCT Process and protocol.

Shah, N. N. *et al.* (2020) Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: A phase 1 dose escalation and expansion trial. Nat. Med. 26: 1569–1575.
https://doi.org/10.1038/s41591-020-1081-3
In a 14-day process bispecific CAR T cells were successfully manufactured on the CliniMACS Prodigy and used in a phase I dose escalation and expansion trial.

Aleksandrova, K. *et al.* (2019) Functionality and cell senescence of CD4/CD8-selected CD20 CAR T cells manufactured using the automated CliniMACS Prodigy Platform. Transfus. Med. Hemother. 46: 47–54.
https://doi.org/10.1159/000495772
Six CliniMACS Prodigy TCT Processes were completed using starting material from healthy donors to expand CD20 CAR T cells.

Fernández, L. *et al.* (2019) GMP-compliant manufacturing of NKG2D CAR memory T cells using CliniMACS Prodigy. Front. Immunol. 10: 2361.
https://doi.org/10.3389/fimmu.2019.02361
Authors prove feasibility and reproducibility of clinical-grade NKG2D CAR memory T cell manufacturing with the CliniMACS Prodigy.

Vedvyas, Y. *et al.* (2019) Manufacturing and preclinical validation of CAR T cells targeting ICAM-1 for advanced thyroid cancer therapy. Sci. Rep. 9: 10634.
https://doi.org/10.1038/s41598-019-46938-7
Here the authors report the use of the CliniMACS Prodigy TCT Process to automatically manufacture CAR T cells targeted to ICAM-1. Thawed leukopaks were rested overnight before starting the TCT process involving lentiviral transduction on days one and two.

Blaeschke, F. *et al.* (2018) Induction of a central memory and stem cell memory phenotype in functionally active $CD4^+$ and $CD8^+$ CAR T cells produced in an automated good manufacturing practice system for of $CD19^+$ acute lymphoblastic leukemia. Cancer Immunol. Immunother. 67: 1053–1066.
Partly automated, GMP-compliant manufacturing of CAR T cells from critically small blood samples was feasible with a new stimulation protocol that leads to high functionality and expansion potential, balanced CD4/CD8 ratios and a conversion to a Tcm/Tscm phenotype.

Castella, M. *et al.* (2018) Development of a novel anti-CD19 chimeric antigen receptor: A paradigm for an affordable CAR T cell production at academic institutions. Mol. Ther. Methods Clin. Dev. 12: 134–144.
https://doi.org/10.1016/j.omtm.2018.11.010
The CliniMACS Prodigy TCT Process was used to translate the authors CAR T cell research to clinical-scale in an academic institution. Robust and reliable manufacture of CAR T cells was obtained.

Zhang, W. *et al.* (2018) Characterization of clinical grade CD19 chimeric antigen receptor T cells produced using automated CliniMACS Prodigy system. Drug Des. Devel. Ther. 12: 3343–3356.
https://doi.org/10.2147/DDDT.S175113
Automated closed-system production of clinical-grade CAR T cells was performed by the CliniMACS Prodigy. The final CAR T cell product was functional with minimal expression of exhaustion cell surface markers.

Zhu, F. *et al.* (2018) Closed-system manufacturing of CD19 and dual-targeted CD20/19 chimeric antigen receptor T cells using the CliniMACS Prodigy device at an academic medical center. Cytotherapy 20: 394–406.
https://doi.org/10.1016/j.jcyt.2017.09.005
The CliniMACS Prodigy Instrument tubing set TS520 and TCT software allow CAR T cells to be manufactured in a closed system at the treatment site without need for clean-room facilities and related infrastructure.

Lock, D. and Mockel-Tenbrinck, N. *et al.* (2017) Automated manufacturing of potent CD20-directed chimeric antigen receptor T cells for clinical use. Hum. Gene Ther. 28: 914–925.
https://doi.org/10.1089/hum.2017.111
Automated cGMP-compliant process on the CliniMACS Prodigy reliably produces a therapeutic dose of anti-CD20 specific CAR T cells, starting from healthy or patient material and independent of operator or device.

Mock, U. *et al.* (2016) Automated manufacturing of chimeric antigen receptor T cells for adoptive immunotherapy using CliniMACS Prodigy. Cytotherapy 18: 1002–1011.
https://doi.org/10.1016/j.jcyt.2016.05.009
The feasibility of CliniMACS Prodigy for TCT is demonstrated with automated generation of $CD19\text{-}CAR^+$ T cells in clinically relevant doses, including studies on the confirmation of *in vitro* and *in vivo* efficacy of the product.

Priesner, C. *et al.* (2016) Automated enrichment, transduction and expansion of clinical-scale $CD62L^+$ T cells for manufacturing of GTMPs.
Hum. Gene Ther. 27: 860–869.
https://doi.org/10.1089/hum.2016.091
Proof of principle in clinical-scale selection, stimulation, transduction and expansion of T cells using the automated closed CliniMACS Prodigy Instrument.

Engineered T cells / HIV

Schwarze, L. I. *et al.* (2021) Automated production of CCR5-negative $CD4^+$ T cells in a GMP-compatible, clinical-scale for treatment of HIV-positive patients. Gene Ther. 28: 572–587.
https://doi.org/10.1038/s41434-021-00259-5
The CCR5 in T cells could be successfully knocked out in a closed and automated fashion employing the CliniMACS® Electroporator together with the CliniMACS Prodigy.

Li, H. *et al.* (2020) Preclinical development and clinical-scale manufacturing of HIV gag-specific, lentivirus-modified CD4 T cells for HIV functional cure. Mol. Ther. Methods Clin. Dev. 17: 1048–1060.
https://doi.org/10.1016/j.omtm.2020.04.024
The CliniMACS Prodigy TCT Process successfully performed clinical-scale manufacturing of HIV-specific $CD4^+$ T cells in terms of immunotherapy development for HIV disease.

Virus- / Antigen-specific T cells

García-Ríos, E. *et al.* (2022). Isolation of functional SARS-CoV-2 antigen-specific T-cells with specific viral cytotoxic activity for adoptive therapy of COVID-19. Biomedicines, 10: 630.
https://doi.org/10.3390/biomedicines10030630
The CliniMACS Prodigy Instrument was used to for automated T cell isolation following specific SARS-CoV-2 peptide stimulation.

Cooper, R. S. *et al.* (2021). Rapid GMP-compliant expansion of SARS-CoV-2-specific T cells from convalescent donors for use as an allogeneic cell therapy for COVID-19. Front. Immunol. 11: 598402.
https://doi.org/10.3389/fimmu.2020.598402
The publication describes a process that starts with the enrichment of virus-specific T cells (VSTs) using the CliniMACS Cytokine Capture System. After enrichment of IFN-gamma–secreting cells a culturing step is added to increase the harvest of VSTs. According to the authors the final products can be provided within a biobank.

Leung, W. *et al.* (2020). Rapid production of clinical-grade SARS-CoV-2 specific T cells. Adv. Cell Gene Ther. 3: e101.
https://doi.org/10.1002/acg2.101
Authors describe a process for flexible and rapid manufacturing of VSTs once a donor is available. This procedure uses the CliniMACS Cytokine Capture System.

Suarez, L. *et al.* (2020) AIM Platform: A novel nano artificial antigen-presenting cell-based clinical system designed to consistently produce multi-antigen-specific T-cell products with potent and durable anti-tumor properties. Transfus. Med. Hemother. 47: 464–471.
https://doi.org/10.1159/000512788
Here, the CliniMACS Prodigy Instrument is used as manufacturing platform of antigen-specific CD8$^+$ T cells. Due to the highly controllable, closed, automated, and scalable nature of the process, the authors use the platform for the production of two phase 1/2 clinical trial material.

Tasnády, S. *et al.* (2020) Identification of the best-suited donor for generating virus-specific T cells. Vox Sang. 115:18–26.
https://doi.org/10.1111/vox.12857
Administration of virus-specific T cells from third-party donors using the CliniMACS Prodigy Instrument is a potentially effective antiviral treatment option after allogeneic HSCT.

Kállay, K. *et al.* (2018) Early experience with CliniMACS Prodigy CCS (IFN-gamma) System in selection of virus-specific T cells from third-party donors for pediatric patients with severe viral infections after hematopoietic stem cell transplantation. J. Immunother. 41: 158–163.
https://doi.org/10.1097/CJI.0000000000000197
Virus-specific T cell therapy implemented by the CliniMACS Prodigy CCS (IFN-gamma) System is an automated, fast, safe, and probably effective way to control resistant viral diseases after pediatric hematopoietic stem cell transplantation.

Kim, N. *et al.* (2018) Robust production of cytomegalovirus pp65-specific T cells using a fully automated IFN-γ Cytokine Capture System.
Transfus. Med. Hemother. 45: 13–22.
https://doi.org/10.1159/000479238
The findings reported here suggest that the IFN-γ CCS by the CliniMACS Prodigy is a simple and robust approach to produce CMV-CTLs, which may be applicable for the treatment of clinically urgent CMV-related diseases.

Pello, O. M. *et al.* (2017) BKV-specific T cells in the treatment of severe refractory hemorrhagic cystitis after HLA-haploidentical hematopoietic cell transplantation. Eur. J. Haematol. 98: 632–634.
https://doi.org/10.1111/ejh.12848
Use of products enriched with BKV-specific T cells generated using CliniMACS Prodigy and the Cytokine Capture System is safe and efficient in HLA-haploidentical HCT where BKV cystitis can be a serious complication.

Priesner, C. *et al.* (2016) Comparative analysis of clinical-scale IFN-γ-positive T cell enrichment using partially and fully integrated platforms. Fron. Immunol. 7: 393.
https://doi.org/10.3389/fimmu.2016.00393
The manufacturing process on the CliniMACS Prodigy saved development and hands-on time due to its higher process integration and ability for unattended operation.

Bunos, M. *et al.* (2015) Automated isolation of primary antigen-specific T cells from donor lymphocyte concentrates: results of a feasibility exercise. Vox. Sang. 109: 387–93.
https://doi.org/10.1111/vox.12291
The CCS protocol on CliniMACS Prodigy is unrestrictedly functional. It runs fully automatically beyond set-up and thus markedly reduces labor. The quality of the products generated is similar to products generated with CliniMACS Plus. The automatic system is thus suitable for routine clinical application.

Kumaresan, P. *et al.* (2015) Automated cell enrichment of cytomegalovirus-specific T cells for clinical applications using the cytokine-capture system. J. Vis. Exp. 104. (Video)
https://doi.org/10.3791/52808
The goal of this protocol is to manufacture pathogen-specific clinical-grade T cells using a bench-top, automated, second generation cell enrichment device that incorporates a closed cytokine capture system and does not require dedicated staff or use of a GMP facility. CD34$^+$ and CD45RA$^+$ cells

CD34$^+$ cells

Pello, O. M. *et al.* (2020) Optimal large-scale CD34$^+$ enrichment from a leukapheresis collection using the CliniMACS Prodigy Platform. Clin. Case Rep. 8: 2650–2653.
https://doi.org/10.1002/ccr3.3232
Optimization of hematology patient's treatment: It is possible to obtain a 100% CD34$^+$ recovery after CD34$^+$ selection using the CliniMACS Prodigy.

Mueller, N. *et al.* (2018) Generation of alloreactivity-reduced donor lymphocyte products retaining memory function by fully automatic depletion of CD45RA-positive cells. Cytotherapy 20: 532–542.
https://doi.org/10.1016/j.jcyt.2018.01.006
The novel, closed, fully GMP-compatible process on CliniMACS Prodigy generates highly CD45RA-depleted cellular products predicted to be clinically meaningfully depleted of GvH reactivity.

Bateman, C. *et al.* (2017) Results of using automated CliniMACS Prodigy for CD34 selection from mobilized peripheral blood stem cell products. Blood 130: 3201.
http://www.bloodjournal.org/content/130/Suppl_1/3201
Results suggest that the CliniMACS Prodigy can be used for the routine clinical application of CD34 selection to HSCT products.

Hümmer, C. *et al.* (2016) Automation of cellular therapy product manufacturing: results of a split validation comparing CD34 selection of peripheral blood stem cell apheresis product with a semi-manual vs. an automatic procedure. J. Transl. Med. 14: 76.
https://doi.org/10.1186/s12967-016-0826-8
The CliniMACS Prodigy is shown to be suitable to perform CD34 selection to validation products met a pre-defined specification.

Ishida, T. *et al.* (2016) Multiple allogeneic progenitors in combination function as a unit to support early transient hematopoiesis in transplantation. J. Exp. Med. 213: 1865–80. *https://doi.org/10.1084/jem.20151493*
The CliniMACS Prodigy, an all-in-one cell-processing instrument, efficiently harvested viable mononuclear cells (MNCs) after protocol optimization, and viable CD34$^+$ cells as well from frozen UCB cells.

Stroncek, D. F. *et al.* (2016) Preliminary evaluation of a highly automated instrument for the selection of CD34$^+$ cells from mobilized peripheral blood stem cell concentrates. Transfusion 56: 511. *https://doi.org/10.1111/trf.13394*
CD34$^+$ cells can be effectively selected from mobilized PBSC concentrates with the CliniMACS Prodigy.

NK cells
Fernández, A. *et al.* (2021) Optimizing the procedure to manufacture clinical-grade NK cells for adoptive immunotherapy. Cancers 13: 577. *https://doi.org/10.3390/cancers13030577*
Optimization of a GMP-compliant manufacturing method using the CliniMACS Prodigy to obtain activated and expanded NK cells with feeder cells suitable for clinical use.

Oberschmidt, O. *et al.* (2019) Development of automated separation, expansion, and quality control protocols for clinical-scale manufacturing of primary human NK cells and alpharetroviral chimeric antigen receptor engineering. Hum. Gene Ther. Methods 30:102–120. *http://doi.org/10.1089/hgtb.2019.039*
Manufacturing and clinical-scale expansion of primary human NK cell using the CliniMACS Prodigy. Three runs using peripheral blood leukapheresis products resulted in high NK cell purities (median 99.1%) and approximately 4.2–8.5-fold NK cell expansion rates.

Klöß, S. *et al.* (2017) Optimization of human NK cell manufacturing: fully automated separation, improved *ex vivo* expansion using IL-21 with autologous feeder cells, and generation of anti-CD123-CAR-expressing effector cells. Hum. Gene Ther. 28: 897–913. *https://doi.org/10.1089/hum.2017.157*
Fully automated one-step separation of NK CD56$^+$CD3$^-$ cells using the CliniMACS Prodigy is shown, starting with approximately 1.2×10^9 leukocytes collected by small-scale lymphapheresis or from buffy coats.

Granzin, M. *et al.* (2015) Fully automated expansion and activation of clinical-grade natural killer cells for adoptive immunotherapy. Cytotherapy 17: 621–31. *https://doi.org/10.1016/j.jcyt.2015.03.611*
The automation of the entire NK cell expansion process presented in the present report represents a novel procedure with the use of a single instrument that allows for the efficient production of clinical-grade NK effector cells.

Dendritic cells
Erdmann, M. *et al.* (2018). Automated closed-system manufacturing of human monocyte-derived dendritic cells for cancer immunotherapy. J. Immunol. Methods 463: 89–96. *https://doi.org/10.1016/j.jim.2018.09.012*
The authors compared the CliniMACS Prodigy Instrument with their manual standard process for dendritic cell generation. They found that the device offered the same product quality, but with simplified training requirements, 50% reduced hands-on time and reduced cleanroom requirements from complex class A into class C.

Regulatory T cells
Marín Morales, J. M. (2019) Automated clinical grade expansion of regulatory T cells in a fully closed system. Front. Immunol. 10: 38. *https://doi.org/10.3389/fimmu.2019.00038*
Authors show results from their approach to translate manual Treg manufacturing to the fully closed automated CliniMACS Prodigy Instrument reducing contamination risk, hands-on time, and quality variation from human intervention.

Mesenchymal stem cells
Vieira, C. P. *et al.* (2021). Novel methods to mobilize, isolate, and expand mesenchymal stem cells. Int. J. Mol. Sci. 22: 5728. *https://doi.org/10.3390/ijms22115728*
The authors used the CliniMACS Prodigy Instrument to collect, culture, and expand mobilized equine MSCs from peripheral blood. They show that the CliniMACS Prodigy Adherent Cell Culture Process can be used to produce cells with surface markers phenotypically considered as MSCs.

Miscellaneous
Fraser, A. R. *et al.* (2017) Development, functional characterization and validation of methodology for GMP-compliant manufacture of phagocytic macrophages: a novel cellular therapeutic for liver cirrhosis. Cytotherapy 19: 1113–1124. *https://doi.org/10.1016/j.jcyt.2017.05.009*
Large-scale, GMP-compliant, autologous macrophage cell therapy product for the potential treatment of cirrhosis.

Skorska, A. *et al.* (2017) GMP-conformant on-site manufacturing of a CD133$^+$ stem cell product for cardiovascular regeneration. Stem Cell Res. Ther. 8: 33. *https://doi.org/10.1186/s13287-016-0467-0*
Automatic manufacturing of a CD133$^+$ cell product within few hours in compliance with EU guidelines for Good Manufacturing Practice.

Reviews

Roddie, C. *et al.* (2019) Manufacturing chimeric antigen receptor T cells: issues and challenges. Cytotherapy S1465-3249(18)30701–1. *https://doi.org/10.1016/j.jcyt.2018.11.009*

Tarnowski, J. *et al.* (2017) Delivering advanced therapies: the big pharma approach. Gene Therapy 24: 593–598. *https://www.nature.com/articles/gt201765*

The key to unlocking CARs. Editorial (2017) Nature Biotechnology 35: 889. *https://www.nature.com/articles/nbt.3993*

Levine, B. L. *et al.* (2016) Global manufacturing of CAR T cell therapy. Mol. Ther. Methods Clin. Dev. 4: 92–101. *https://doi.org/10.1016/j.omtm.2016.12.006*

Walker, A. *et al.* (2016) Commercialization of cellular immunotherapies for cancer. Biochemical Society Transactions 44: 329–332. *https://doi.org/10.1042/BST20150240*

Wang, X. *et al.* (2016) Clinical manufacturing of CAR T cells: foundation of a promising therapy. Molecular Therapy – Oncolytics 3. *https://doi.org/10.1038/mto.2016.15*

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130-132-515.04