Miltenyi Biotec

Selected references

CliniMACS Prodigy®

Scientific publications

CAR T cells

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 T Cell Transduction processes were completed using starting material from healthy donors to expand CD20 CAR T cells.

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 T Cell Transduction (TCT) process to automatically manufacture CAR T cells targeted to ICAM-1. Thawed and rested leukopaks were rested overnight before starting the TCT process involving lentiviral transduction on days one and two. This data supports further study to evaluate the safety and efficacy.

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 T Cell Transduction 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.

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 the treatment of CD19$^+$ acute lymphoblastic leukemia.
Cancer Immunol. Immunother. 67: 1053–1066.
https://doi.org/10.1007/s00262-018-2155-7
Partly automated GMP-generation 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.

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 device, 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. & 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.

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 system.

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 T cell transduction is demonstrated with automated generation of CD19-CAR$^+$ T cells in clinically relevant doses, including studies on the confirmation of *in vitro* and *in vivo* efficacy of the product.

Virus- / Antigen-specific T cells

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 system 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.

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.

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.

CD34$^+$ and CD45RA$^+$ cells

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.

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.

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.

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

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.

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® system reducing contamination risk, hands-on time, and quality variation from human intervention.

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

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

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

Wang, X. *et al.* (2016) Clinical manufacturing of CAR T cells: foundation of a promising therapy.
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https://10.1038/mto.2016.15

Tarnowski, J. *et al.* (2017) Delivering advanced therapies: the big pharma approach.
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Nature Biotechnology 35: 889.
https://www.nature.com/articles/nbt.3993

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https://10.18609/cgti.2017.070

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Autologous CAR T cell manufacturing: current standing and future directions. (2017) GEN.
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http://www.genengnews.com/gen-news-highlights/point-of-care-gene-therapy-is-out-of-the-box/81253344

A critical look at CAR T therapeutics. (2016) Phacilitate SIG.
https://phacilitate-sig.com/a-critical-look-at-car-t-therapeutics/

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https://newsroom.mcw.edu/news-articles/cart-cell-immunotherapy-clinical-trial-cancer-patient-in-remission

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https://www.autolus.com/news-and-events/press-releases/autolus-and-miltenyi-biotec-sign-strategic-supply-agreement

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