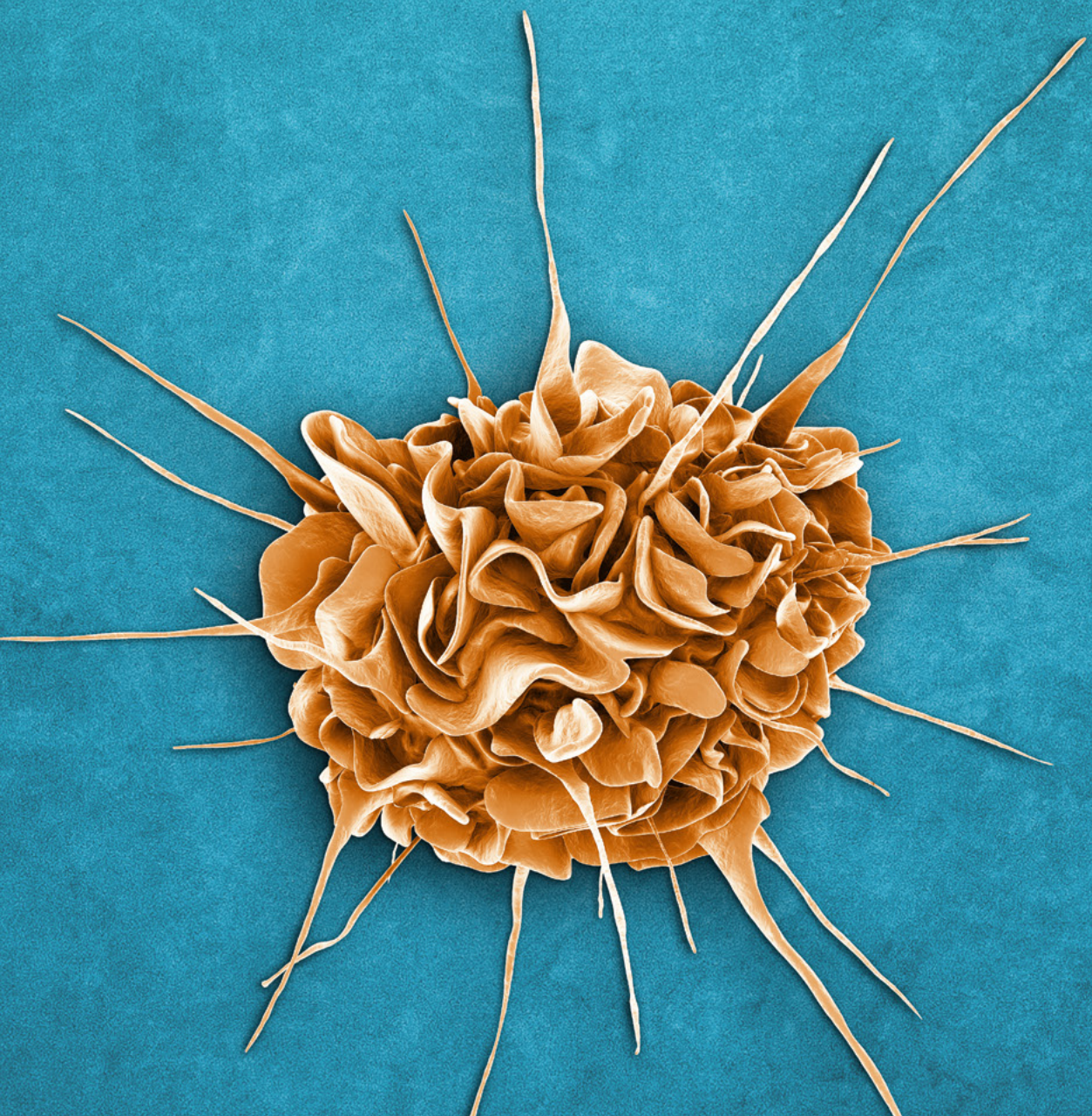
Miltenyi Biotec

Manufacturing dendritic cell products for clinical research

CliniMACS® System and MACS® GMP Products



Clinical dendritic cell research

Dendritic cell (DC)-based vaccinations in patients aim to modulate the immune response in order to enhance the immune system's ability to attack tumor while sparing the host.

In the last decade, a number of clinical studies using DCs for vaccination have been completed, largely with the easily accessible and well-characterized monocyte-derived DCs (Mo-DCs). Beneficial anti-tumor responses have been observed in some patients, illustrating the safety profile and clinical potential of this approach.[1–3] With an increasing availability of anti-cancer drugs, the role of DC-based approaches in novel combination therapies has rapidly escalated.

Today, the possibility of implementing new therapeutic protocols using primary dendritic cells grants exciting opportunities.[4, 5] Primary DC subsets have been reported to induce antigen-specific immune responses which correlated with clinical outcomes.[5–10]

This brochure provides information regarding next generation clinical-grade production of DCs that may allow optimization of cellular products for advanced clinical research on DC vaccination.





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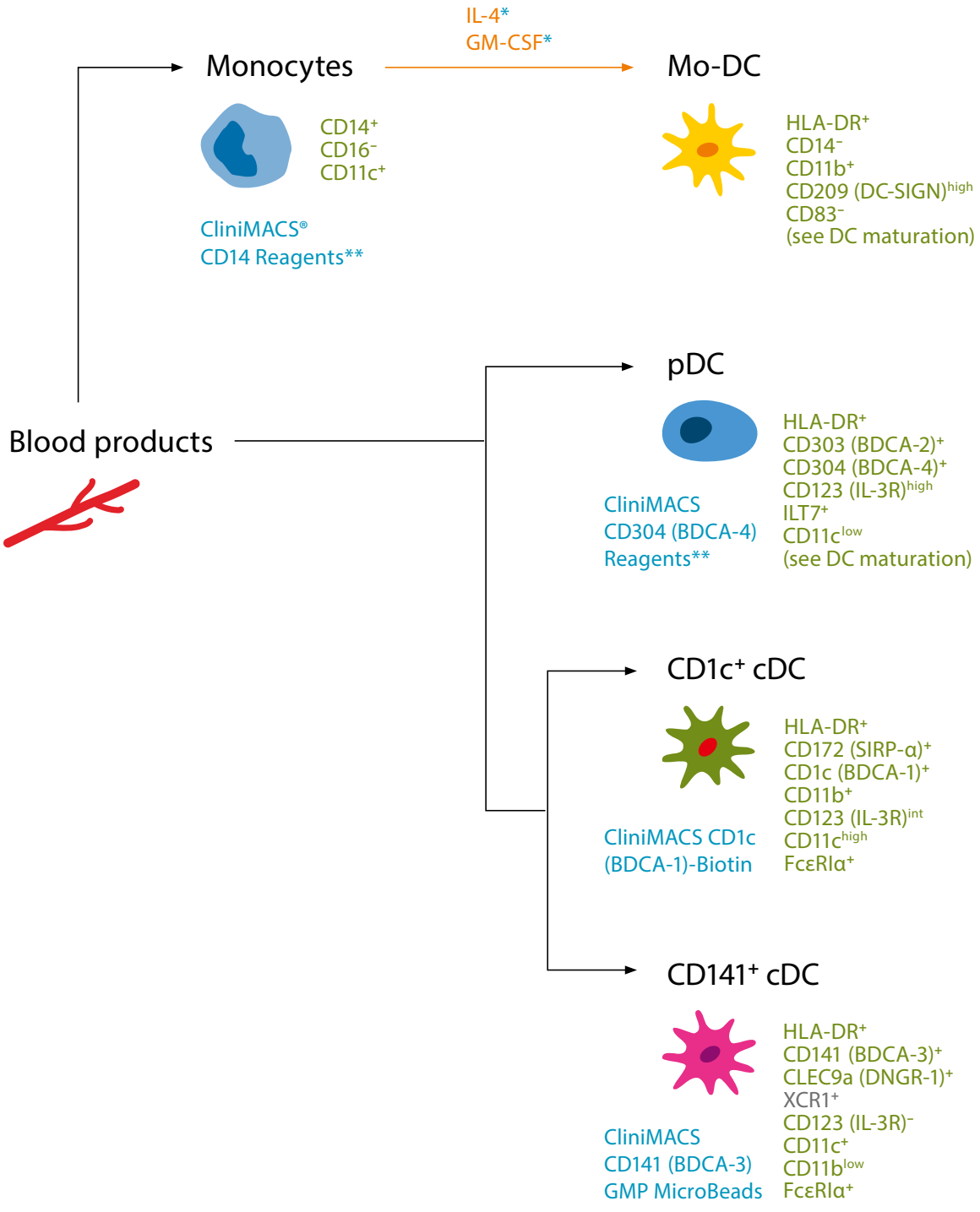
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The CliniMACS® System components, including Reagents, Tubing Sets, Instruments, and PBS/EDTA Buffer, are designed, manufactured and tested under a quality system certified to ISO 13485.
In the EU, the CliniMACS System components are available as CE-marked medical devices for their respective intended use, unless otherwise stated. The CliniMACS Reagents and Biotin Conjugates are intended for *in vitro* use only and are not designated for therapeutic use or direct infusion into patients. The CliniMACS Reagents in combination with the CliniMACS System are intended to separate human cells. Miltenyi Biotec as the manufacturer of the CliniMACS System does not give any recommendations regarding the use of separated cells for therapeutic purposes and does not make any claims regarding a clinical benefit. For the manufacturing and use of target cells in humans the national legislation and regulations – e.g. for the EU the Directive 2004/23/EC ("human tissues and cells"), or the Directive 2002/98/EC ("human blood and blood components") – must be followed. Thus, any clinical application of the target cells is exclusively within the responsibility of the user of a CliniMACS System.
In the US, the CliniMACS CD34 Reagent System, including the CliniMACS Plus Instrument, CliniMACS CD34 Reagent, CliniMACS Tubing Sets TS and LS, and the CliniMACS PBS/EDTA Buffer, is FDA approved as a Humanitarian Use Device (HUD), authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this indication has not been demonstrated. Other products of the CliniMACS Product Line are available for use only under an approved Investigational New Drug (IND) application, Investigational Device Exemption (IDE), or FDA approval. CliniMACS GMP MicroBeads are for research use and *ex vivo* cell processing only. CliniMACS MicroBeads are for research use only and not for human therapeutic or diagnostic use.
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The complete solution for clinical DC research

Over the past decades we have developed the widest portfolio of products for DC research on the market and have translated it into clinical research to enable the discovery of new therapeutic options. We now provide solutions not only for the clinical-scale separation of DCs but also a complete toolset for culturing and analyzing them. From monocyte-derived DCs to the new generation of primary DC subsets, we offer flexibility and fully automated processes to support your research effort. Our processes and clinical-grade reagents are already part of several studies.



DC maturation

Immature Mo-DC → Mature Mo-DC

IL-1β*, IL-6*, TNF-α*, CD40L

PepTivator® Peptide Pools*



$CD14^-$	$CCR7^-$
$CD80^-$	$CD1\alpha^+$
$CD83^-$	$CD209\ (DC\text{-}SIGN)^{high}$
$CD86^{low}$	$HLA\text{-}DR^+$
$CD25^-$	$HLA\text{-}ABC^+$
$CD40^+$	$CD54^{int}$



$CD14^-$	$CCR7^+$
$CD80^+$	$CD1\alpha^{int}$
$CD83^+$	$CD209^{int}$
$CD86^{high}$	$HLA\text{-}DR^{high}$
$CD25^+$	$HLA\text{-}ABC^{high}$
$CD40^{high}$	$CD54^+$

Immature pDC → Mature pDC

IL-3*, TLR 7/9 Ligands*

PepTivator Peptide Pools*



$HLA\text{-}DR^+$
$CD80^-$
$CD86^-$
$CD83^-$
$CCR7^-$
$CD303\ (BDCA\text{-}2)^+$



$HLA\text{-}DR^{high}$
$CD80^+$
$CD86^+$
$CD83^+$
$CCR7^+$
$CD303\ (BDCA\text{-}2)^{low}$

Legend

- → separation
- → differentiation (cultivation)
- ■ MACS Cell Culture and Stimulation products (RUO)
- ■ MACS Flow Cytometry products (RUO)
- * Available also as MACS GMP Product
- ** CliniMACS Reagents are available in different countries as CliniMACS Reagents and/or CliniMACS GMP MicroBeads. In this chart both will be generally referred to as CliniMACS Reagents.

DC: dendritic cell
cDC: conventional or myeloid DC
pDC: plasmacytoid DC
Mo-DC: monocyte-derived DC

- $^-$ no expression
- ^{low} low expression
- ^{int} intermediate expression
- $^+$ expression
- ^{high} high expression
- $^{+/-}$ expression dependent on subset and tissue



Clinical-scale Mo-DC manufacturing

Separation of monocytes and culture of Mo-DCs

CliniMACS CD14 Product Line*

The most widely used DC type for clinical trials are Mo-DCs. They are differentiated *ex vivo* from peripheral blood monocytes in the presence of recombinant granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin 4 (IL-4).

$CD14^+$ monocytes can be enriched *in vitro* from heterogeneous hematological cell populations with high purity and yield, using clinical-scale, magnetic cell separation systems: the CliniMACS Prodigy® LP-14 System[11] or the CliniMACS Plus Instrument[12–15] with the CliniMACS CD14 Product Line (fig. 1 and table 1). The CliniMACS Prodigy LP-14 Mo-DC System can be used for enrichment of monocytes, followed by culture for differentiation and maturation with MACS GMP Cytokines, and antigen loading with PepTivator Peptide Pools (fig. 2).

The CliniMACS CD14 Product Line has demonstrated:

- Safety and feasibility of automated, sterile, clinical scale manufacturing of monocytes and Mo-DC[16], confirmed in a number of clinical trials[1,12–14,17–21]
- High purity and recovery (also using starting cellular products with very low $CD14^+$ cell frequencies)

* In the USA, the CliniMACS Prodigy LP-14 System and the LP-14 Mo-DC System are for research use only, for complete regulatory and legal notices please refer to page 3.

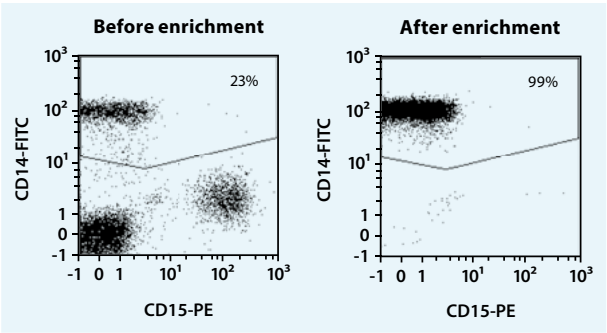


Figure 1: Clinical-scale enrichment of $CD14^+$ cells. Cells were enriched from leukapheresis products using the CliniMACS Plus Instrument with the CliniMACS CD14 Product Line. Magnetic enrichment yields a 99% pure $CD14^+$ monocyte population.

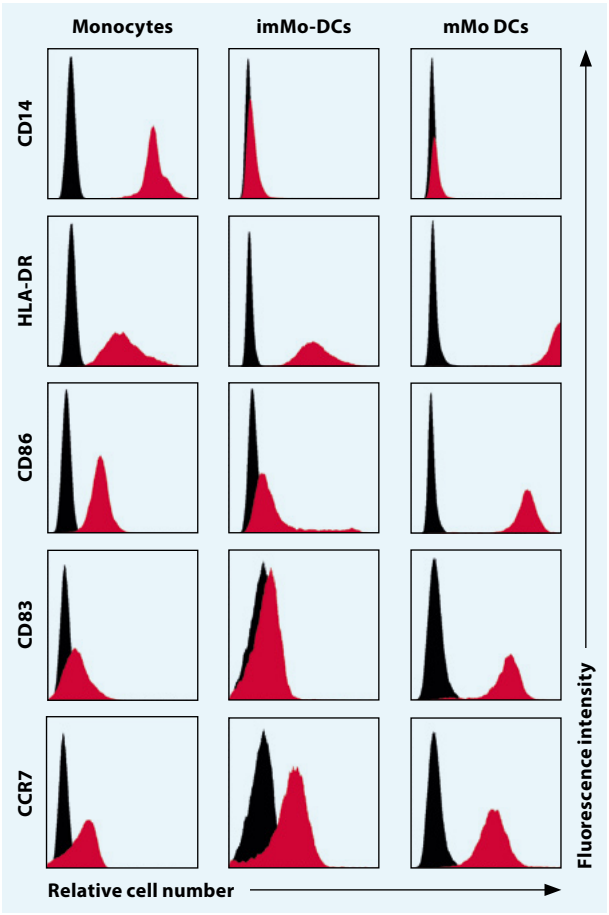


Figure 2: Immunophenotyping of monocytes, immature Mo-DCs (imMo-DC), and mature Mo-DCs (mMo-DC). Cells were labeled on days 0, 6, and 7 with antibodies specific for the respective markers and analyzed by flow cytometry. Marker-specific labeling is indicated in red, isotype controls are shown in black. The data shown here depict one representative experiment from six independent experiments.

CliniMACS CD14 System	
Capacity	4×10^9 cells from 20×10^9 total cells
Total white blood cells	20×10^9
Monocyte purity	97% (range 87–99.6)
Monocyte yield	88% (range 73–92)

Table 1: Monocyte enrichment specifications. Monocytes were enriched using the CliniMACS Prodigy LP-14 System and analyzed using the MACSQuant® Analyzer 10 (n=20).

Enrichment of primary DCs

Separation of single DC subsets from blood

CliniMACS CD1c (BDCA-1), and CD304 (BDCA-4) Product Lines*

Specific DC subpopulations can be enriched from human blood based on their expression of certain surface markers[4].

Myeloid or conventional DCs (cDCs) are comparable to Mo-DCs regarding their phenotype and function. Plasmacytoid DCs (pDCs) produce high amounts of type I interferons, thus enhancing innate and adaptive immunity in response to stimulation with ligands for toll-like or other receptors.[5, 22]



The ability of cDCs, enriched directly from the patient's blood, to induce therapeutic anti-tumor T cell responses was clinically investigated for melanoma and prostate cancer with favorable results.[7,23–27]

With the CliniMACS Plus Instrument you can enrich cDCs and pDCs separately (fig. 3 and table 2), offering the following advantages:

- **Enrichment of DC subsets directly from blood**
- **High purity of myeloid and plasmacytoid DCs**

* For complete regulatory and legal notices please refer to page 3.

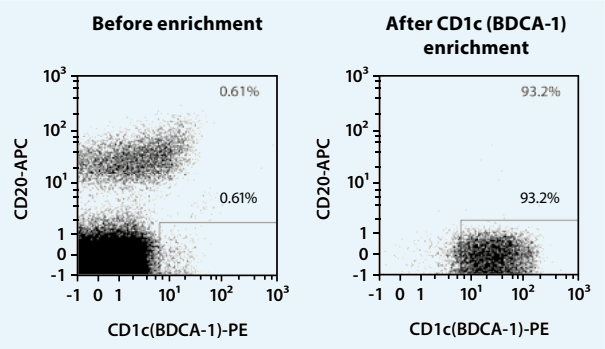
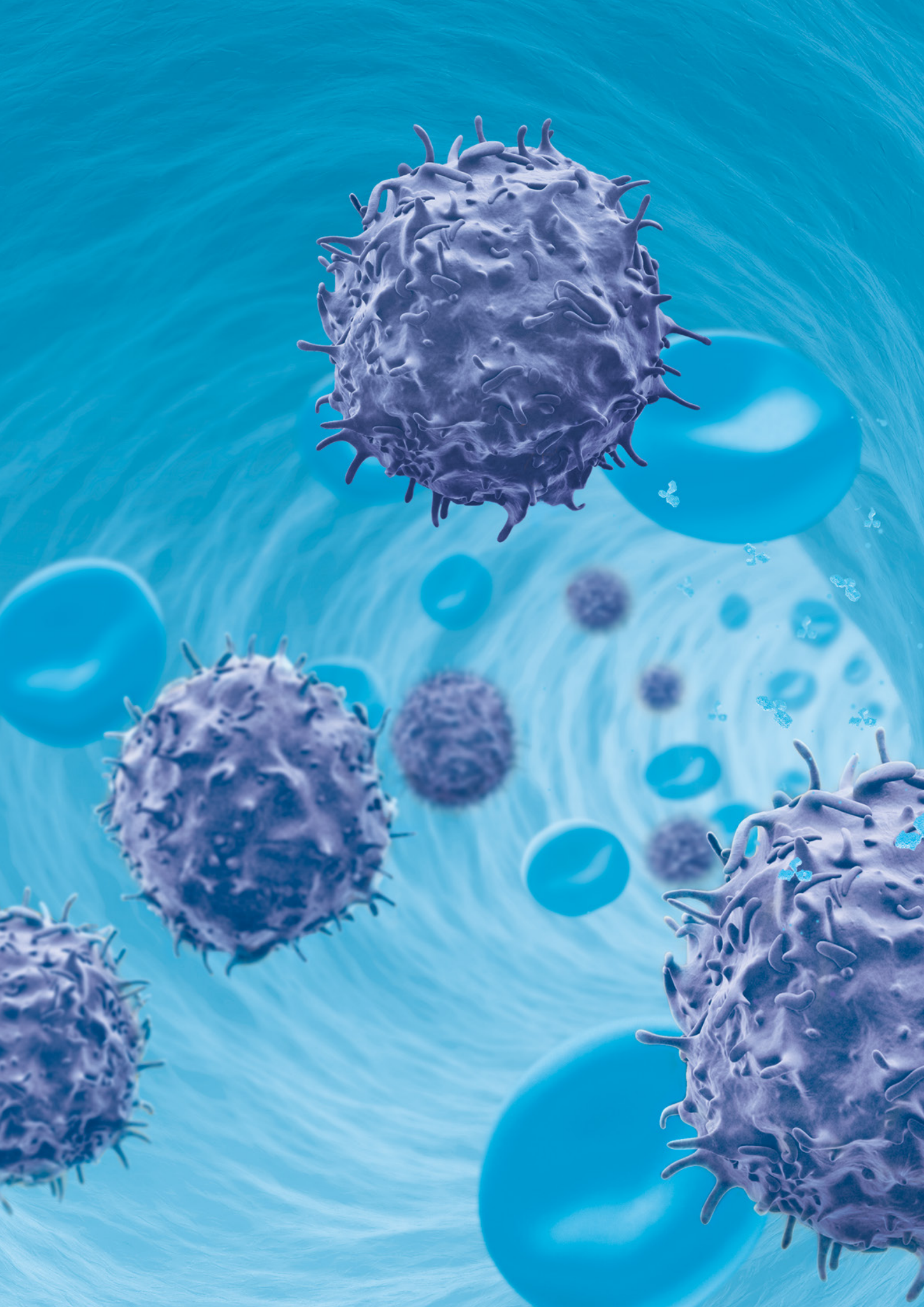


Figure 3: Clinical-scale enrichment of CD1c (BDCA-1)⁺ cells. Magnetic enrichment of CD1c (BDCA-1)⁺ cells after CD19⁺ cell depletion using the CliniMACS Plus CD1c (BDCA-1) product line yields an up to 93.2% pure cDC population.

CliniMACS CD1c (BDCA-1) System	
Capacity	0.2×10^9 from 40×10^9 total cells
Purity	95% (range 92–98.9)
Yield	50% (range 19–72)

Table 2: Myeloid DC enrichment specifications. Myeloid DCs were enriched using the CliniMACS Plus and the CD1c (BDCA-1) Product Line. Results were analyzed with the MACSQuant Analyzer 10 (n = 10).




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Co-enrichment and culture of primary DCs

Combined separation and stimulation of blood pDCs and cDCs

CliniMACS Prodigy BloodDC Systems*

Conventional DCs and pDCs recognize different stimuli and can generate non-overlapping responses. Recent reports suggest that simultaneous activation of different DC subsets may have a synergistic effect that can increase anti-tumor responses.[28]

Clinical effects of vaccination with activated pDCs or cDCs loaded with tumor-derived peptides in phase I/II studies were recently published for melanoma patients.[5,6,26] The combination of pDCs and cDCs is believed to be crucial for strong and effective anti-tumor therapy.[10]

The CliniMACS Prodigy BloodDC PreDepletion System and the CliniMACS Prodigy BloodDC Enrichment and Culture System are designed for the combined enrichment of the three DC subsets from non-mobilized apheresis products.

The CliniMACS Prodigy BloodDC PreDepletion System performs the depletion of $CD19^+$ and $CD14^+$ cells, and the labeling of $CD1c^+$ cells with biotin. Subsequently, the CliniMACS Prodigy BloodDC Enrichment and Culture System allows the enrichment of the blood DC subsets followed by stimulation and antigen loading. The combined BloodDC Systems provide:

- **Robust and efficient co-enrichment of all primary DC subsets**
- **Fully automated and flexible cultivation options for stimulation and antigen loading**

Blood DCs manufactured with the CliniMACS Prodigy BloodDC Systems effectively activate antigen-specific T cells (fig. 4). Likewise, vaccination with cDCs and pDCs manufactured with the CliniMACS Prodigy BloodDC Systems induced functional antigen-specific T cell responses against the tumor in patients with castration-resistant prostate cancer.[10]

* For complete regulatory and legal notices please refer to page 3.

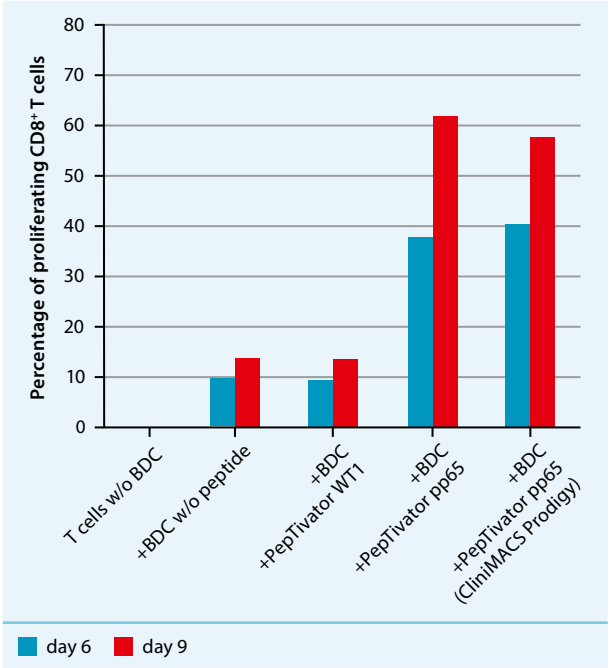


Figure 4: Blood DCs (BDCs) manufactured with CliniMACS Prodigy BloodDC Systems effectively activate antigen-specific $CD8^+$ T cells *in vitro*. BDCs manufactured with CliniMACS Prodigy BloodDC Systems, loaded with PepTivator pp65 or PepTivator WT-1 (control), were cocultured with $CD8^+$ T cells from CMV-positive donors.

CliniMACS Prodigy Enrichment and Culture System	
Capacity	0.4×10^9 (from initial 40×10^9 total cells before pre-depletion)
Purity	75% (range 58–94)
Yield	63% (range 27–93)

Table 3: Blood DC enrichment specifications. Blood DCs were enriched using the CliniMACS Prodigy BloodDC PreDepletion System and the CliniMACS Prodigy BloodDC Enrichment and Culture System and analyzed using the MACSQuant® Analyzer 10. Purity and yield were calculated for the combined fraction of plasmacytoid and cDCs together (n = 10).

The CliniMACS Instruments

Automated, standardized cellular product manufacturing

CliniMACS Prodigy*

The CliniMACS Prodigy represents the next generation in automated cell processing. This good manufacturing practice (GMP)-compliant device offers advanced integrated solutions: from cell separation to cell culture and formulation of the cell product, all in one bench-top device. The instrument provides:

- Automated cell processing
- Built-in centrifuge
- Cell separation using MACS Technology
- Cell cultivation
- Sensor-controlled processes
- Functionally closed system, reducing clean room requirements

The CliniMACS Prodigy offers the platform for an automated differentiation of Mo-DCs or cultivation of primary blood-derived DCs.

* For complete regulatory and legal notices please refer to page 3.



CliniMACS Plus Instrument

The CliniMACS Plus Instrument, in conjunction with a CliniMACS Tubing Set, a CliniMACS Reagent, and the CliniMACS PBS/EDTA Buffer, can be used to separate a variety of human cell types including monocytes and primary DCs.







Functionally closed system

The CliniMACS Prodigy is currently used in clinical trials evaluating Mo-DC and primary DCs as therapeutic options.


GMP
Compliance
Validation
Translation

MACS GMP Solutions

Optimized differentiation, maturation, and analysis of DCs

Miltenyi Biotec provides a comprehensive selection of tools for your preclinical validation and research to enable protocol optimization and standardized in-process control. With this extensive portfolio Miltenyi Biotec offers complete and innovative solutions for DC generation from monocytes and direct isolation of primary DCs enabling clinical research in a multitude of therapeutic areas.

MACS GMP Products*

The quality of starting materials dramatically influences the properties of the final cellular product. Therefore, the ultimate success of your cell product depends on the quality of the raw materials used. For the development of cell-based and gene therapy products regulatory authorities require the adherence to strict procedures in compliance with GMP. MACS GMP Products are manufactured and tested under a quality management system (ISO 13485) and are in compliance with relevant GMP guidelines. They are designed following the recommendations of USP <1043> on ancillary materials.

TexMACS™ GMP Medium*

TexMACS GMP Medium allows optimal cultivation of Blood DCs. It makes for high cell viability and consistency under serum-free conditions. Filling in flexible bags ensures reliability and sterile connection during GMP manufacturing of cellular products.

- Manufactured without animal-derived components
- Filled in flexible bags
- QC functionality test on every batch

* MACS GMP Products are for research use and *ex vivo* cell culture processing only, and are not intended for human *in vivo* applications. For complete regulatory and legal notices please refer to page 3.

MACS GMP Cytokines*

MACS GMP Cytokines are highly active and pure recombinant proteins that enable consistent cell culture results. They are lyophilized without carrier protein or preservatives. Highest product standards are ensured by aseptic filling, lyophilization, and rigorous quality control tests. Each product is supplied with a certificate of analysis that confirms the stringent specifications and states the lot-specific biological activity.

- Standardized high biological activities (IU/mg)
- Documentation of every processing step, from development to production and QC testing
- Consistent product quality

MACS GMP PepTivator Peptide Pools*

MACS GMP PepTivator Peptide Pools consist of a pool of lyophilized overlapping oligopeptides (mainly 15-mers) covering the complete sequence of the respective antigen. They have been designed for efficient *in vitro* stimulation of antigen-specific $CD4^+$ and $CD8^+$ T cells and are widely used for antigen loading of Mo-DCs and blood DCs (see p. 17 for a list of application-specific peptide pools).



Product information

CliniMACS Instruments*

Product	Content
CliniMACS Prodigy	1 unit
CliniMACS Plus Instrument	1 unit

Products for Mo-DC research*

Product	Content
CliniMACS Prodigy Tubing Set TS 510	1 set
CliniMACS Tubing Set TS	1 set
CliniMACS CD14 Reagents**	1 set
MACS GMP Recombinant GM-CSF	1 vial
MACS GMP Recombinant Human IL-4	1 vial
MACS GMP Human TNF-α	1 vial
MACS GMP Recombinant IL-1β	1 vial
MACS GMP Recombinant Human IL-6	1 vial
MC CD14 Monocyte Cocktail, human	1 vial
Mo-DC Differentiation Inspector, human	1 vial

Products for blood DC research*

Product	Content
CliniMACS Prodigy Tubing Set TS 320	1 set
CliniMACS Prodigy Tubing Set TS 510	1 set
CliniMACS Tubing Set TS	1 set
CliniMACS CD1c (BDCA-1) Biotin	1 vial
CliniMACS CD304 (BDCA-4) Reagents**	1 vial
CliniMACS CD14 Reagents**	1 vial
CliniMACS CD19 Reagents**	1 vial
CliniMACS CD141 (BDCA-3) GMP MicroBeads	1 vial
CliniMACS Anti-Biotin Reagents**	1 vial
TexMACS GMP Medium	1 bag
MACS GMP Recombinant GM-CSF	1 vial
MACS GMP Recombinant Human IL-3	1 vial
MACS GMP CpG-P	1 vial
Blood Dendritic Cell Enumeration Kit, human	1 kit

* For complete regulatory and legal notices please refer to page 3.

** CliniMACS Reagents are available in different countries as CliniMACS Reagents and/or CliniMACS GMP MicroBeads. In these tables both will be generally referred to as CliniMACS Reagents.

MACS GMP PepTivator Peptide Pools*

Product	Content	Capacity
MACS GMP PepTivator WT1	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator HCMV pp65	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator AdV5 Hexon	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator EBV BZLF1	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator EBV LMP2A	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator EBV EBNA-1	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator NY-ESO-1	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator PRAME	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator Survivin	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator MAGE A3	1 vial	60 nmol / peptide for the stimulation of 10^9 cells
MACS GMP PepTivator MUCIN-1	1 vial	60 nmol / peptide for the stimulation of 10^9 cells

MACS GMP Medium*

Product	Content	Capacity
TexMACS GMP Medium	1 bag	2000 mL

MACS GMP Cytokines*

Product	Content	Capacity
MACS GMP Recombinant GM-CSF	1 vial	25 µg
MACS GMP Recombinant Human IL-4	1 vial	250 µg
MACS GMP Recombinant Human TNF-α	1 vial	25 µg
MACS GMP Recombinant Human IL-1β	1 vial	25 µg
MACS GMP Recombinant Human IL-6	1 vial	10 µg
MACS GMP Recombinant Human IL-3	1 vial	25 µg

MACS GMP Consumables*

Product	Content	Capacity
CliniMACS PBS/EDTA Buffer	3× 1 L bag	1 L
CliniMACS PBS/EDTA Buffer	2× 3 L bag	3 L
20 mL Reagent Bag	5× 20 mL bag	20 mL



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▸ miltenyibiotec.com/dc-immunotherapy

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