

Fraunhofer Institute for  
Production Technology IPT

**Simon Hort, M.Sc.**

Sep 6th 2023 | *Advanced Therapies Europe, Estoril, Portugal*

# How can digitalisation and AI improve CAR-T cell manufacturing?



Grant Agreement No. 101016909  
Programme H2020-DT-2020-1

# AIDPATH



Drive the creation of an AI-driven automated ATMP manufacturing platform forward to guarantee a future with equitable and affordable access to advanced therapies.



VISION

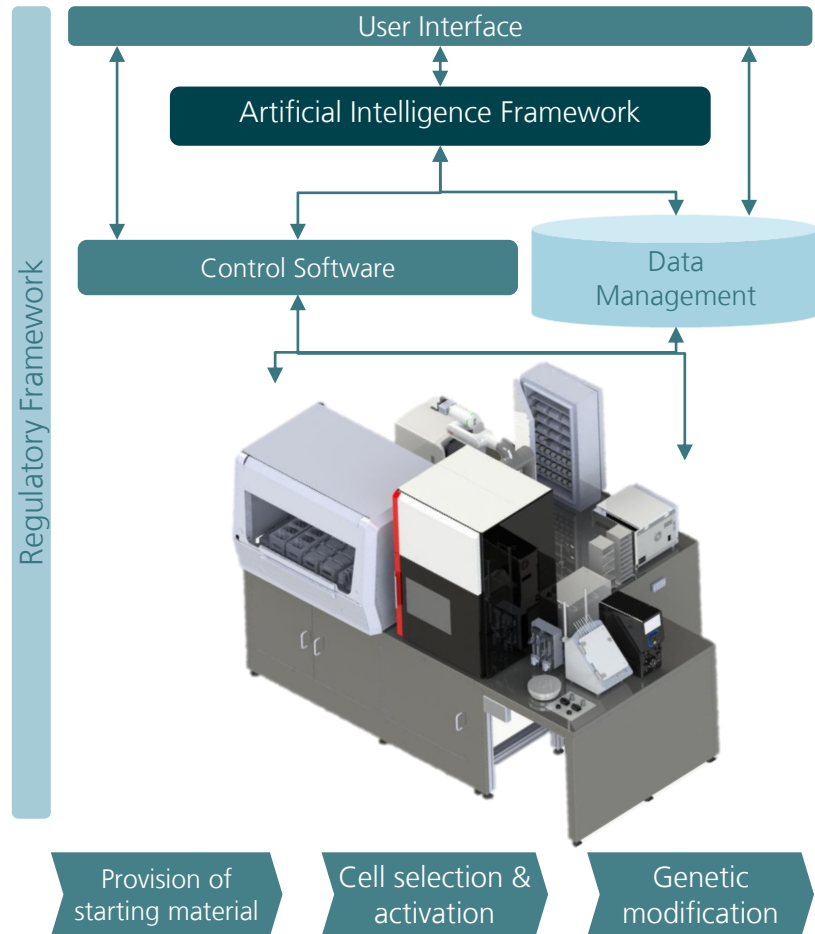


MISSION

Deliver an adjustable AI driven manufacturing platform for ATMP based on the AIDPATH set of modular software and hardware tools.

# Big Picture AIDPATH

January 1st 2021 – December 31st 2024



## DIGITALISATION

- Execution of process protocols
- Centralized control of all devices
- Patient and manufacturing data management
- AI-driven decision making

## AUTOMATION

- Modular and manufacturer-independent
- Parallelized manufacturing
- Automated quality control
- Fluidic and robotic automation

## AI use cases



AI-powered digital cell twin



Reactive online process control



Production scheduling



Resource management

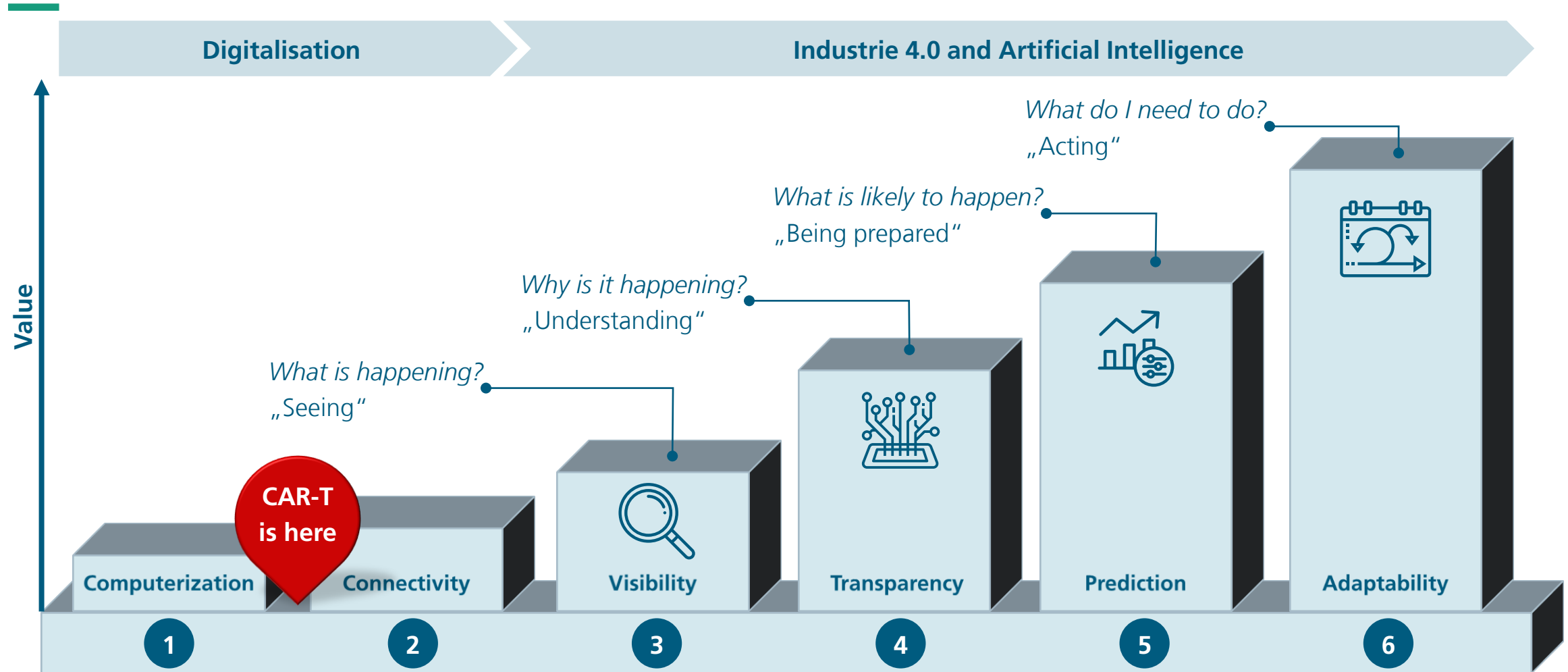


Clinical decision support

[1]

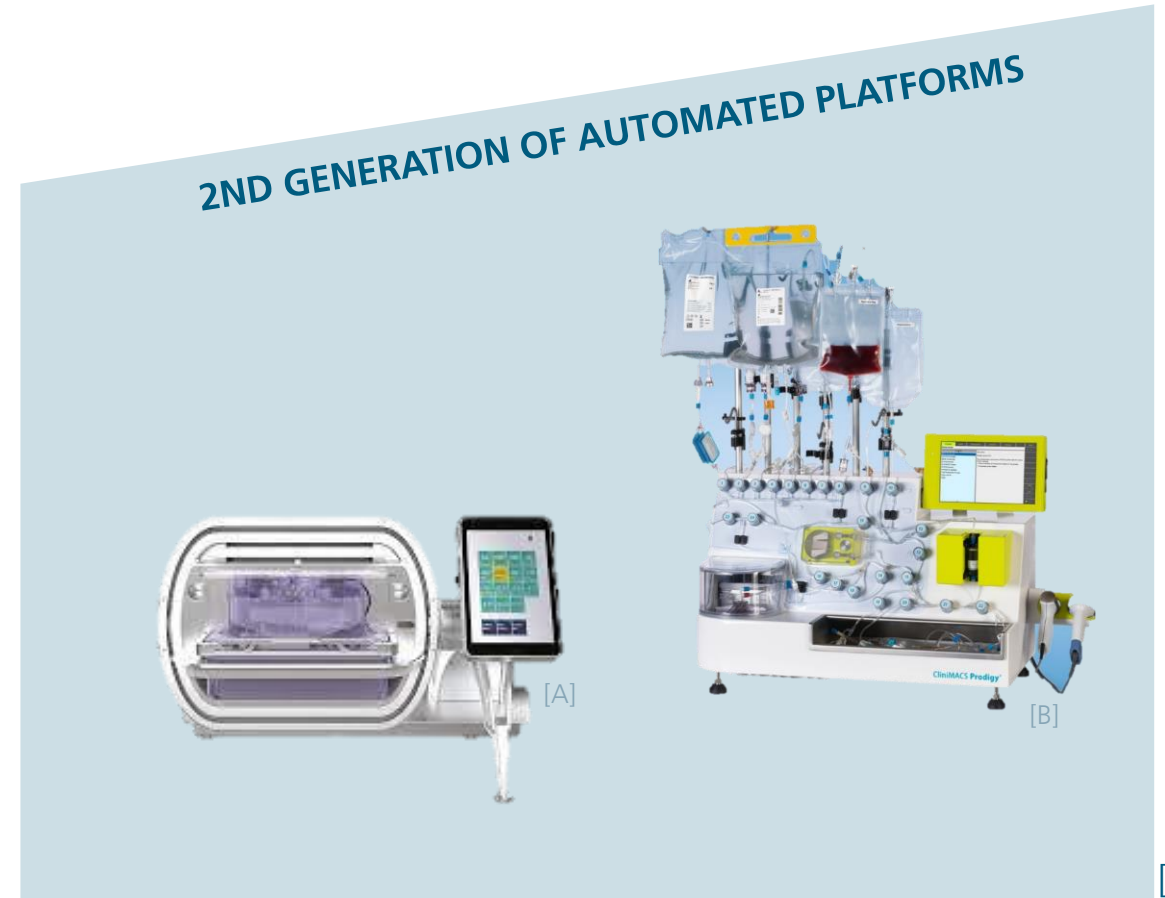
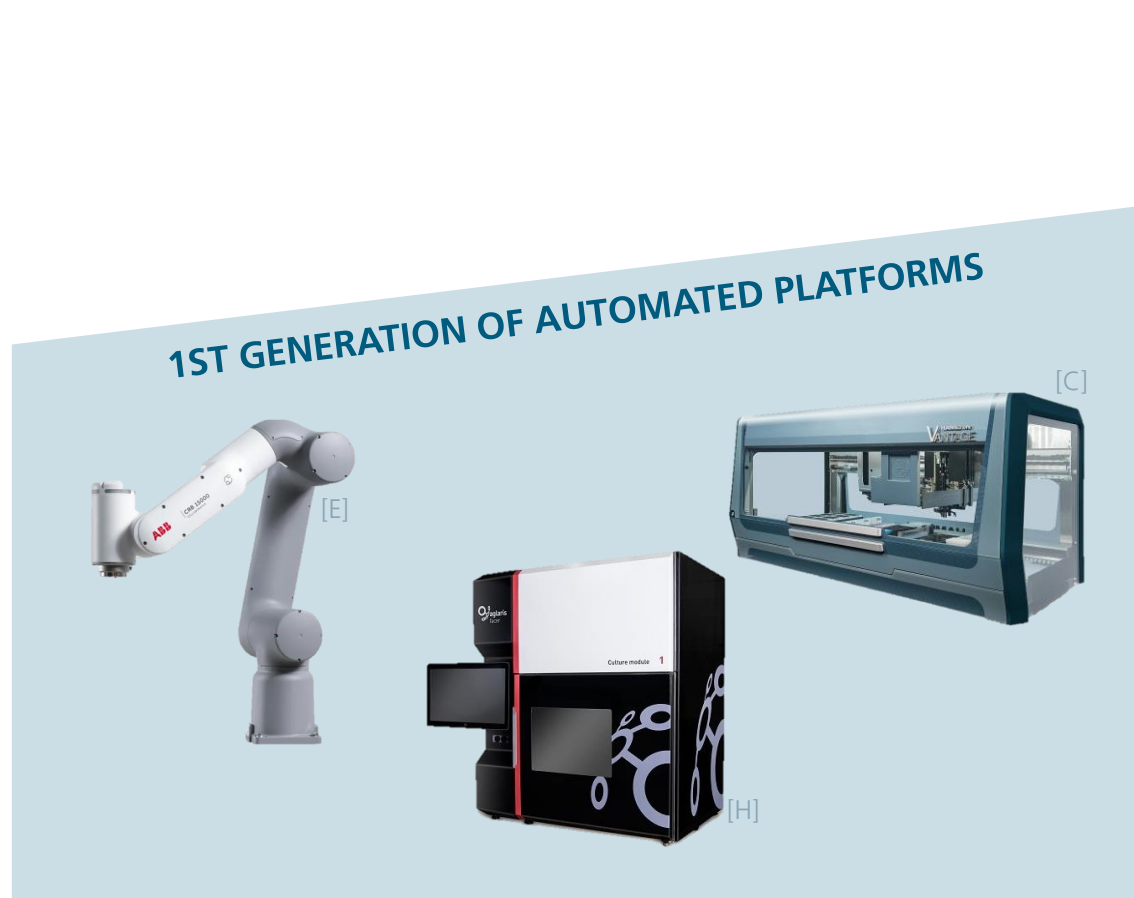
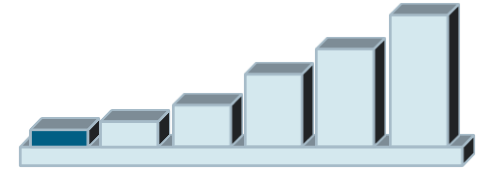
# How can digitalisation and AI meet the challenges of CAR-T?

Industry 4.0 maturity model<sup>[2]</sup>



# 1 | Computerization

Stand-alone machines and computers for automated execution



## 2 | Connectivity

COPE – Flexible Control Software for cell and gene manufacturing

13 controlled platforms  
10+ years experience  
70+ device integrations

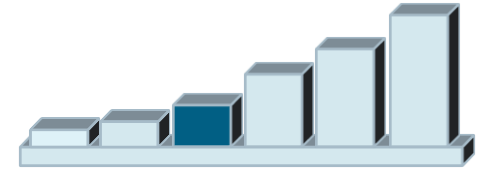
The COPE logo features a stylized 'C' with a green dot and a line extending from it, followed by the letters 'OPE' in a bold, sans-serif font.

- Manufacturer-independent Plug&Produce machine and device integration
- Creation and Execution of Protocols via Drag&Drop
- Adaptive event handling
- GAMP guidelines



# 3 | Visibility

What is happening?

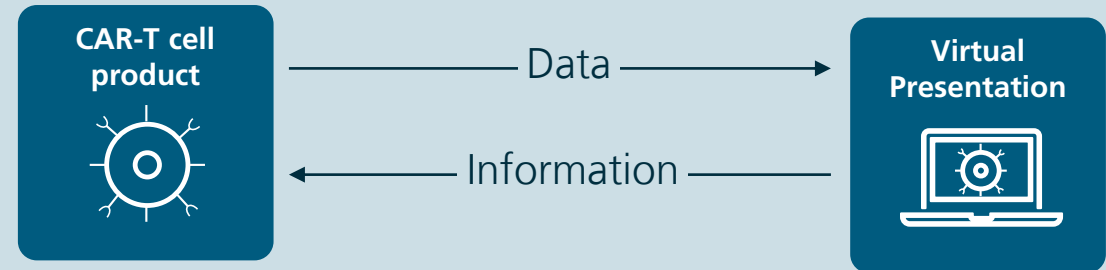


## AUTOMATED QUALITY CONTROL



## DIGITAL CAR-T CELL TWIN

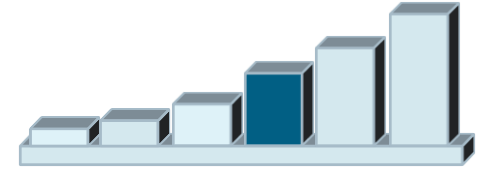
COPE



- Virtual presentation for storing, retrieving and processing large amount of data
- Valuable process insights and continuous monitoring
- Automated quality assurance and documentation

# 4 | Transparency

Why is it happening?



*Why are certain patients responding well to a CAR-T cell therapy and others not?*



*Why are different patient's T cells behaving in a certain way?*

## GAIN PROCESS INSIGHTS

AIDPATH



*Detecting deviations in optimal expansion process for assessing diminished cell quantity and viability*

Critical Quality Attributes

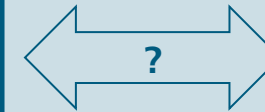
Safety

Identity

Content

Purity

...



Critical Process Parameters

Transduction method

Cell selection

Activation efficiency

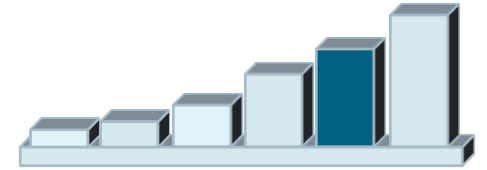
Seeding density

...



# 5 | Prediction

What is likely to happen?



**How** will the patient respond to a certain CAR-T cell product?



**How** will the cells react to certain manufacturing steps?

## AI IN CAR-T CELL THERAPY



CAR-T cell design



Disease and adverse reactions



Cell Expansion

[6,7,8]



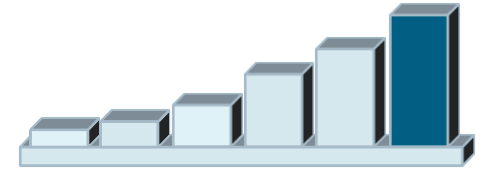
*Real time predictions of T-Cell growth using online sensors of glucose and lactate.*




Aglaris Facer [H]

# 6 | Adaptability

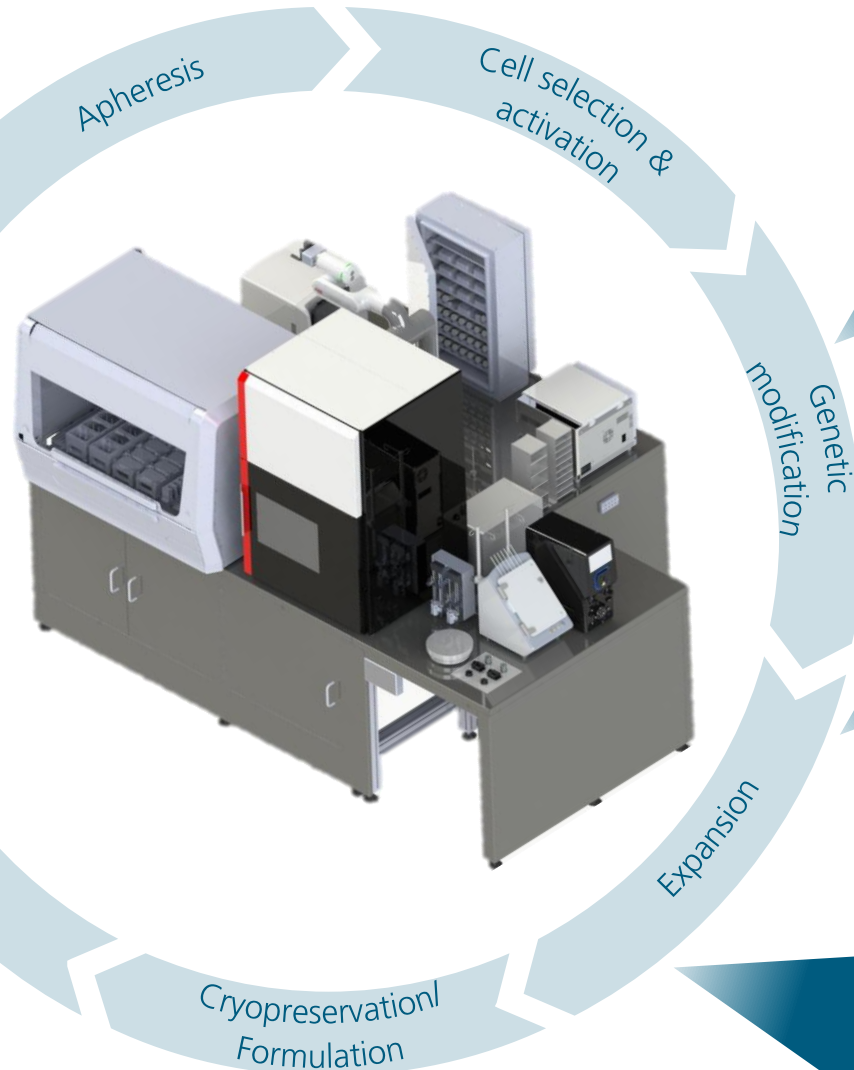
What do we need to do?



  
Increase of overall efficiency with scheduling, resource planning and decision support



*Patient*



Decision on viral transduction



Perfusion start point based on dissolved oxygen



Expansion end point based on cell density

[9,10]



QC releases based on viability



## Events in 2023

### Phacilitate

Sep 7th 10:30  
Laura Herbst

Automation in Cell and  
Gene Therapies – Drivers  
and Economy of Scale

### Medica

Nov 13th – 16th  
Düsseldorf, Germany

Join us at our booth in Hall  
12!

Stay in touch!

[www.aidpath-project.eu](http://www.aidpath-project.eu)



### Contacts

Simon Hort, M.Sc.  
+49 241 8904 251  
[simon.hort@ipt.fraunhofer.de](mailto:simon.hort@ipt.fraunhofer.de)

# References

## Figures

- [A] <https://www.weichilab.com/upload/files/202205061446007847.pdf>
- [B] <https://www.miltenyibiotec.com/DE-en/products/clinimacs-prodigy.html>
- [C] [https://www.trillium.de/fileadmin/user\\_upload/F-2010-03\\_NGS-VANTAGE-Flyer.pdf](https://www.trillium.de/fileadmin/user_upload/F-2010-03_NGS-VANTAGE-Flyer.pdf)
- [D] <https://www.fishersci.de/shop/products/11790829/11790829>
- [E] <https://new.abb.com/products/robotics/de/roboter/kollaborative-roboter/crb-15000>
- [F] <https://www.beckman.com/resources/reading-material/application-notes/cell-counting-performance-of-vi-cell-blu>
- [G] <https://www.beckman.de/flow-cytometry/research-flow-cytometers/cytoflex-s>
- [H] <https://cordis.europa.eu/article/id/430106-smart-cell-manufacturing-for-therapeutic-applications/de>

## Publications

- [1] Hort S, Herbst L, Bäckel N, Erkens F, Niessing B, Frye M, König N, Papantoniou I, Hudecek M, Jacobs JIL and Schmitt RH (2022) Toward Rapid, Widely Available Autologous CAR-T Cell Therapy – Artificial Intelligence and Automation Enabling the Smart Manufacturing Hospital. *Front. Med.* 9:913287. doi: 10.3389/fmed.2022.913287
- [2] Schuh, G., Reiner, A., Dumitrescu, R., Krüger, A., Hompel, M. ten, 2020. Industry 4.0 Maturity Index: Managing the Digital Transformation of Companies. *acatech Studie - Update 2020*. <https://www.acatech.de/publikation/industrie-4-0-maturity-index-update-2020/download-pdf/?lang=en> .
- [3] Moutsatsou P, Ochs J, Schmitt RH, Hewitt CJ, Hanga MP. Automation in cell and gene therapy manufacturing: from past to future. *Biotechnol Lett.* 2019 Nov;41(11):1245-1253. doi: 10.1007/s10529-019-02732-z. Epub 2019 Sep 20. PMID: 31541330; PMCID: PMC6811377.
- [4] <https://www.ipt.fraunhofer.de/en/offer/special-machines/laboratory-automation/laboratory-automation-software.html>
- [5] Alliance of Regenerative Medicine (Hrsg.): A-Cell. A case study-based approach, 2022
- [6] Lee, M., Lee, Y.-H., Song, J., Kim, G., Jo, Y., Min, H., Kim, C.H., Park, Y., 2020. Deep-learning-based three-dimensional label-free tracking and analysis of immunological synapses of CAR-T cells. *eLife* 9.
- [7] Mösch, A., Raffegerst, S., Weis, M., Schendel, D.J., Frishman, D., 2019. Machine Learning for Cancer Immunotherapies Based on Epitope Recognition by T Cell Receptors. *Frontiers in genetics* 10, 1141.
- [8] Dannenfelser, R., Allen, G.M., VanderSluis, B., Koegel, A.K., Levinson, S., Stark, S.R., Yao, V., Tadych, A., Troyanskaya, O.G., Lim, W.A., 2020. Discriminatory Power of Combinatorial Antigen Recognition in Cancer T Cell Therapies. *Cell systems* 11 (3), 215-228.e5.
- [9] Iyer, R.K., Bowles, P.A., Kim, H., Dulgar-Tulloch, A., 2018. Industrializing Autologous Adoptive Immunotherapies: Manufacturing Advances and Challenges. *Frontiers in medicine* 5, 150.
- [10] Klarenbeek, S.E., Weekenstroom, H.H.A., Sedelaar, J.P.M., Fütterer, J.J., Prokop, M., Tummers, M., 2020. The Effect of Higher Level Computerized Clinical Decision Support Systems on Oncology Care: A Systematic Review. *Cancers* 12 (4).