Towards Industry 4.0: Development of a Smart Bioprocessing Platform Integrating Real-Time Monitoring and Advanced Process Control for Autologous Cell Therapy

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Programme Head of Digital Innovation

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Enabling the future of CGT Manufacturing

CAR-T Products

~10,000

CAR-T products manufactured/year[*1]

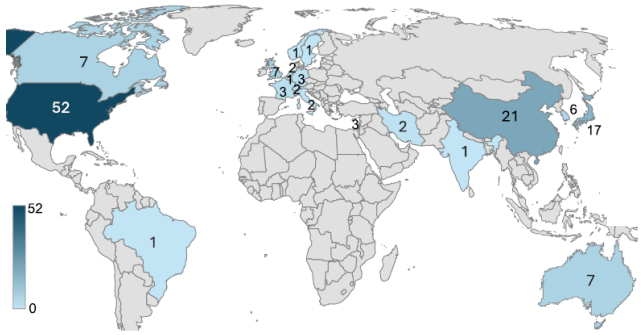
~1,894

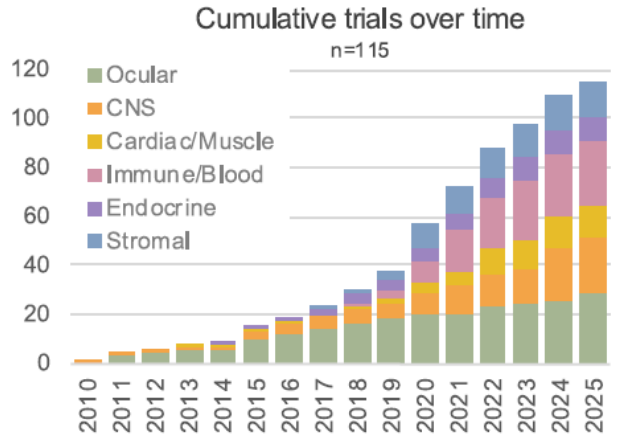
Clinical trials[*3] *underway*

2M

Hematological cancer patients eligible for CAR-T by 2029[*3]

hPSC Derived Products*[4]





- Multiple ATMPs now commercialized; strong pipeline in clinical trials
- CAR-T therapies: >$180K per dose (~$1M incl. administration) *[2]
- Industry target: ~80% margin improvement by 2030
- Allogeneic therapies: >1,200 patients, 34 indications, 190B hPSC cells + 200B platelets delivered*[4]
- **Manufacturing capacity lagging behind growing patient demand**

Digital & automation are critical to deliver long term industry success:

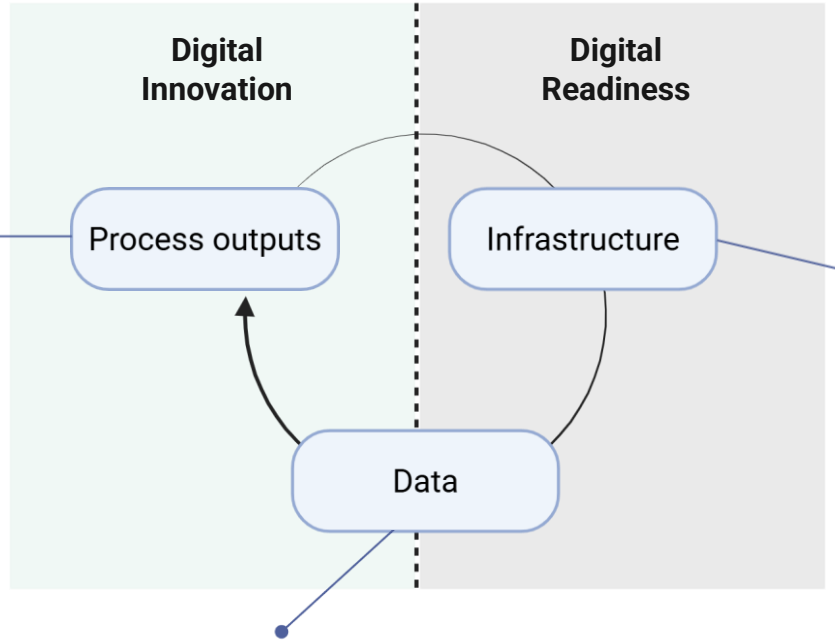
- Reducing failure rates & variability
- Reducing development timelines
- Price competitive manufacturing
- Driving improvement

*[1] Patient Access Analytics | Ori Biotech, Oribiotech (2024)
*[2] *Alliance for Regenerative Medicine Meeting at the Med 2025*
*[3] *Driving the next wave of innovation in CAR-T cell therapies.* McKinsey (2019)
*[4] Kirkeby et al., 2025, Pluripotent stem-cell-derived therapies in clinical trial: A 2025 update, Cell Stem Cell 32, January 2

Addressing sector's barriers through Digital Innovation

Scalability and supply

- Predictive analytics
- Smart bioprocessing



Digital transformation

- Digital connectivity
- Digitisation

AI-enabling Technologies

- Data architecture
- AI/ML

Building collaborations to accelerate technology advances for digital innovation

Enable greater process understanding and control for repeatable, reproducible and robust manufacturing.

PAT Consortium

>£1M

In co-investment

Aim: Technical evaluation of PATs on autologous cell therapy process.

Horizon Europe

£3.5m

Grant funding awarded

Aim: Developing first-in-class PoC "smart" bioprocessing manufacturing platform capable of analysing key biomarkers in real-time and enabling adaptive control.

Co-funded by the European Union

Innovate UK

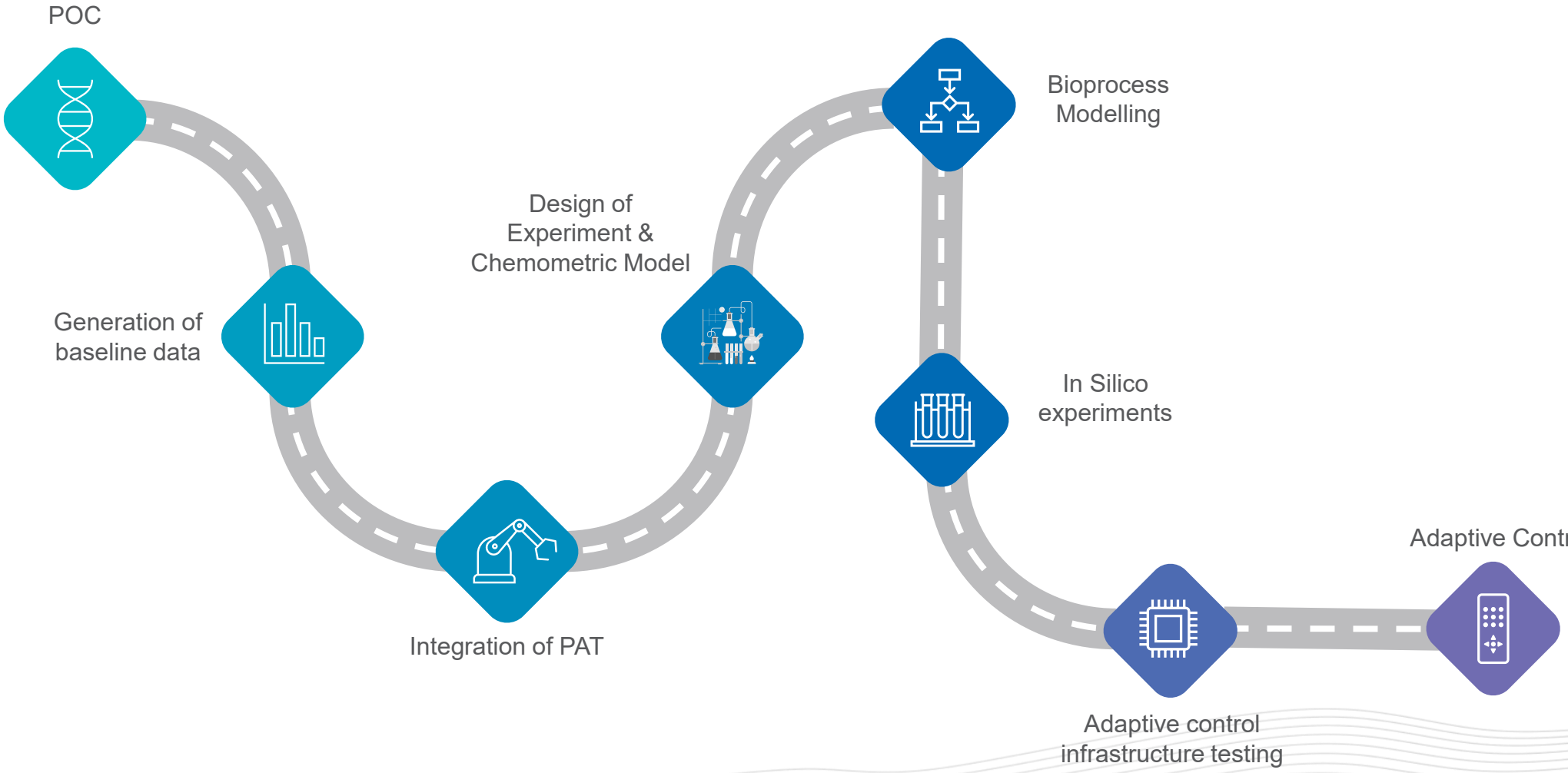
£1.1m

Grant funding awarded

Aim: Advanced process control of AAV manufacture: digitalization, PAT and automation to improve productivity, quality and consistency.

Roadmap to Digital Twins for Process Control

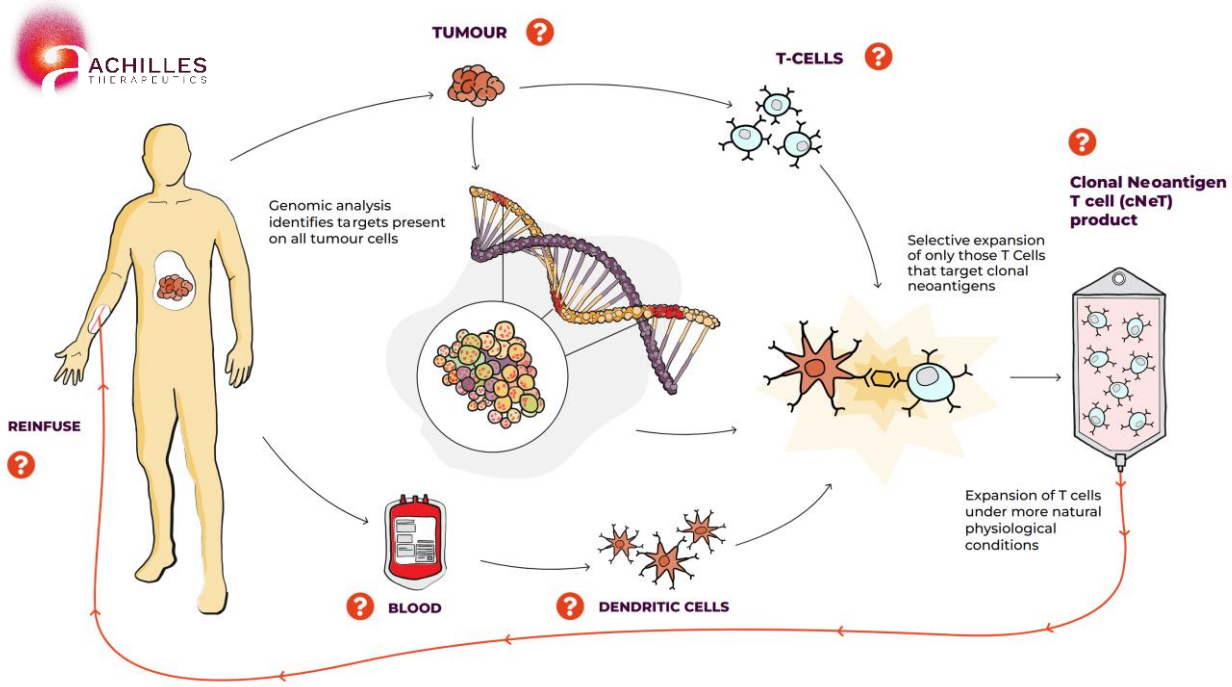
Conceptual Process Model | Digital Shadow | Digital Twin



First-generation and legacy technologies are a roadblock to scalable manufacturing

Challenge: Lack of **consistent** and **scalable** manufacturing process

1. Manual, autologous processes are **complex** and subject to **variability** and high **failure rates.**
2. **Patient variability** is a constraint to predictable outcomes and a cause of **inconsistency** in product quality.



Exemplar adoptive TIL-therapy process from Achilles Therapeutics PLC

Process Setpoint

?

G-Rex 100 (Wilson-Wolf)

Online monitoring

X

Real time process control

X

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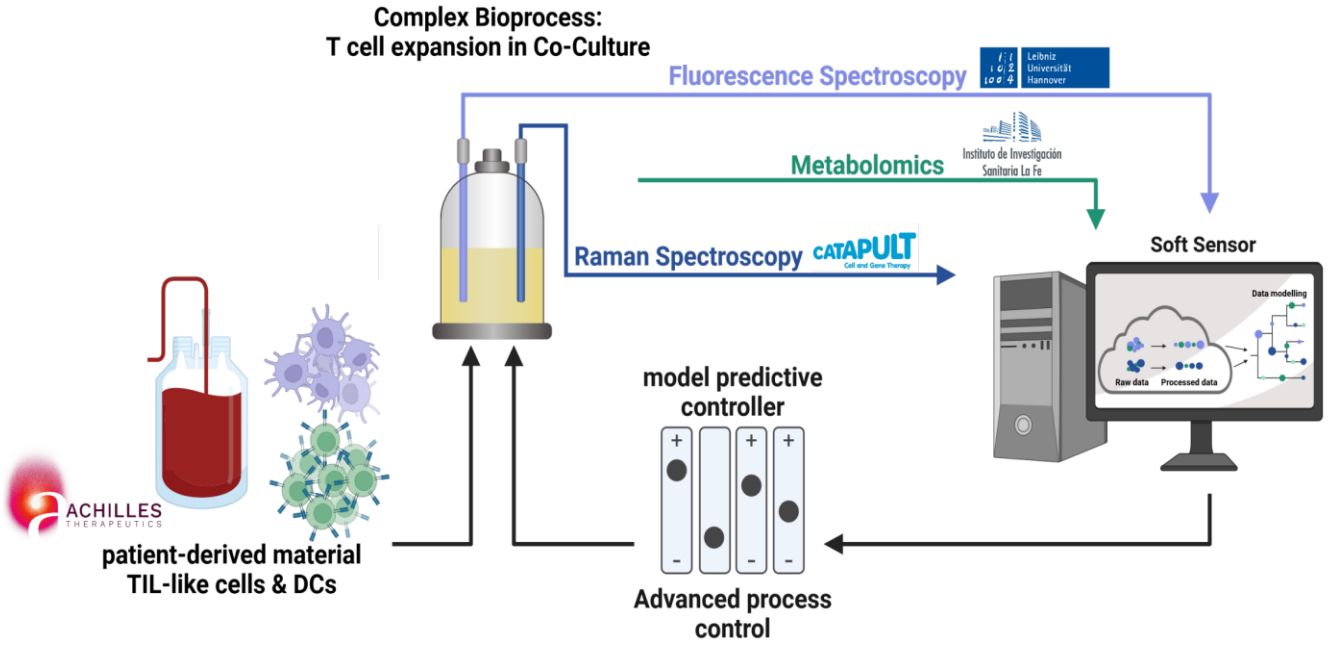


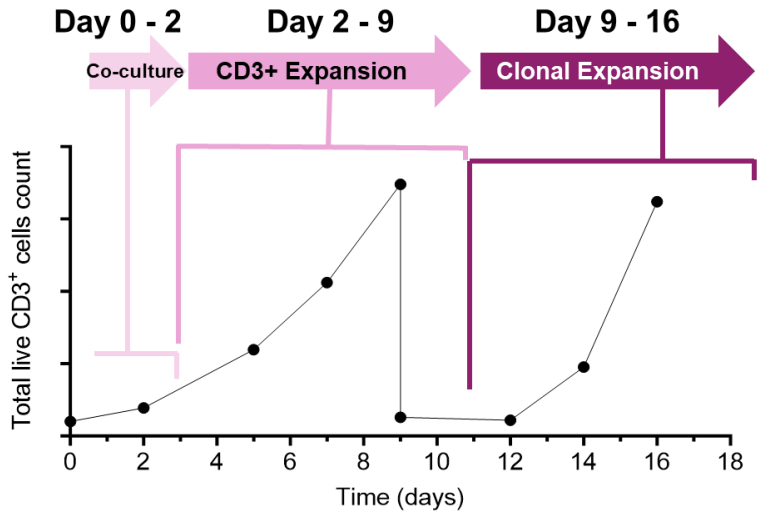
Online monitoring ✓

Real time process control ✓

Process Setpoint ✓

Adapting the TILs process from a static culture to dynamic bioreactor

Long and complex process with co-culture of TILs with dendritic cells.



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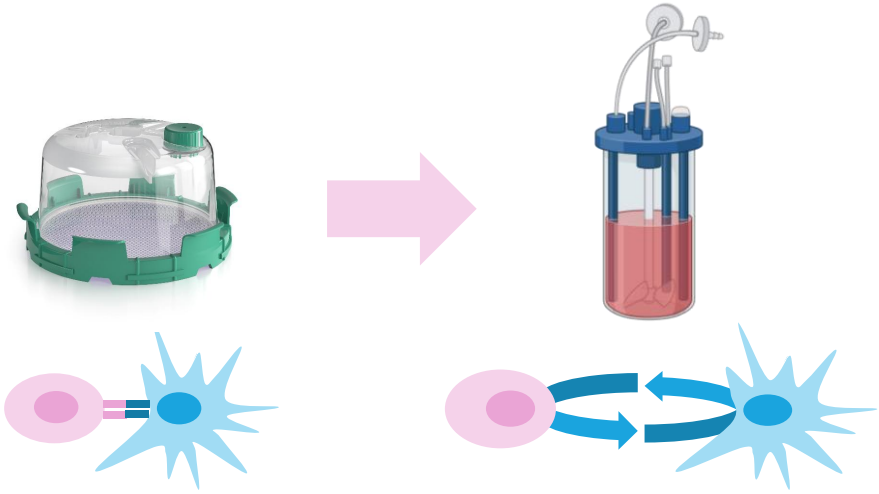


Transfer of the static G-Rex process to an agitated bioreactor optimized with **process-specific** parameters:

- Agitation speed
- Agitation intervals
- Agitation timings

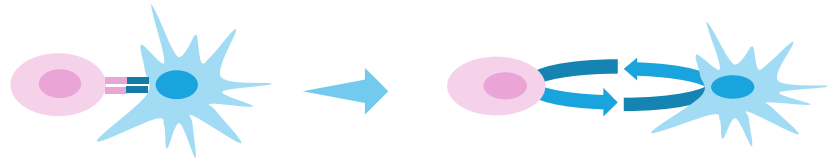
Manufacturing **critical quality attributes** used for process development evaluation in healthy donor model.

4 critical quality attributes evaluated:

- CD3+ fold expansion
- Reactive CD4+ fold expansion
- Reactive CD8+ fold expansion
- % Reactivity to the antigen

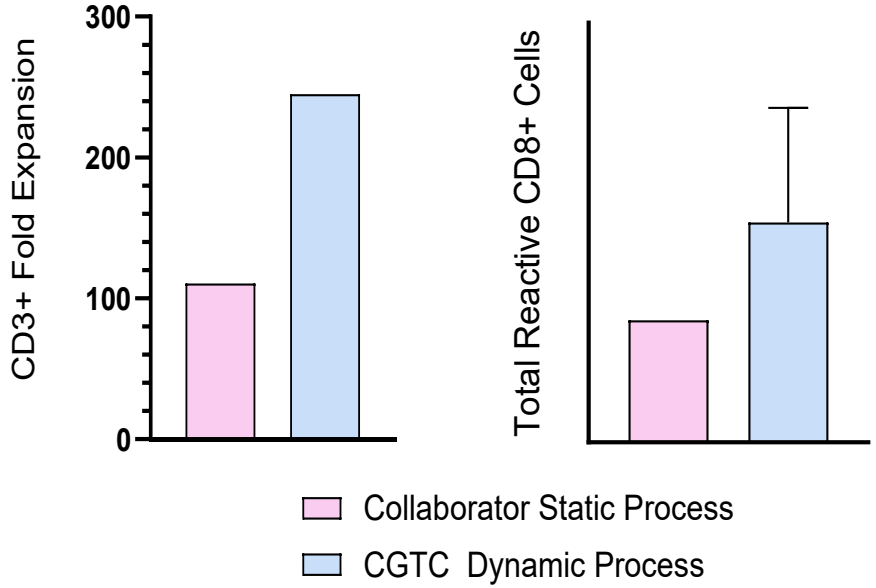
Building process understanding and optimisation

1 Adapted bioprocess from static to dynamic culture systems



Improved Yields of CD3+

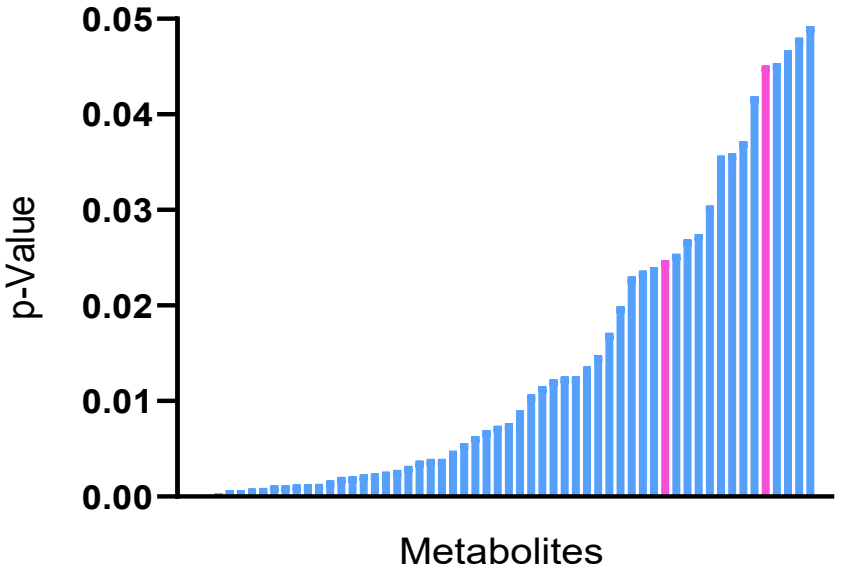
Maintenance of T-cell Reactivity to the antigen



Building process understanding and optimisation

1. Adapted bioprocess from static to dynamic culture systems

2. Identified critical process parameters (CPPs) and ~50 significantly different metabolites



3 biomarkers selected for process design space exploration

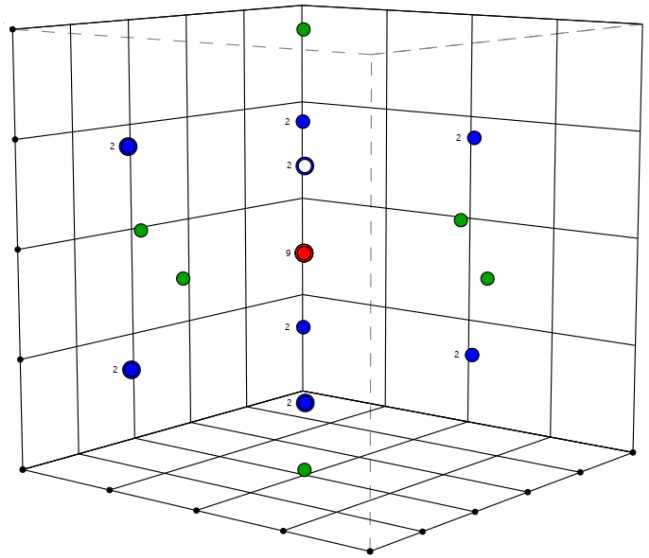
Building process understanding and optimisation

1. Adapted bioprocess from static to dynamic culture systems

2. Identified critical process parameters (CPPs) and ~50 significantly different metabolites

3. Exploring process design space through **Design of Experiment (DoE)** approaches.

   - **Screening DoE** for parameter's selection
   - **Central Composite Design** for process perturbation and optimisation



Central Composite Design DoE structure.

- ❑ Investigated 5-factors at 5-levels
- ❑ Performed 4 runs x 8 vessel
- ❑ Included Raman Spectroscopy probe for chemometric model development

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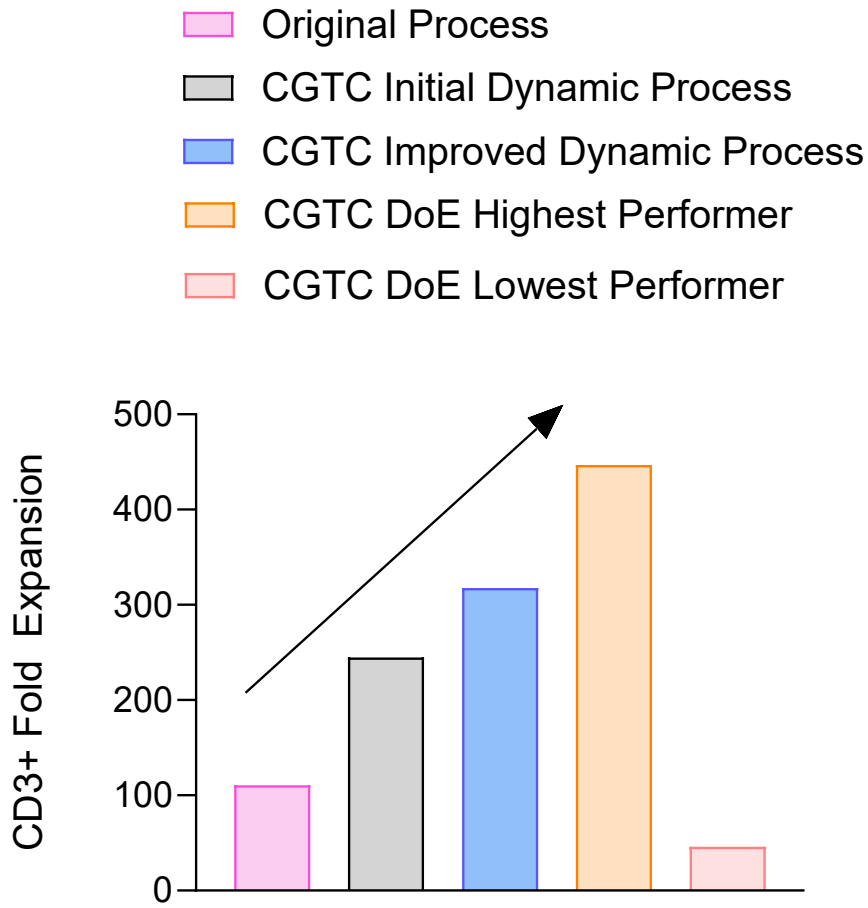
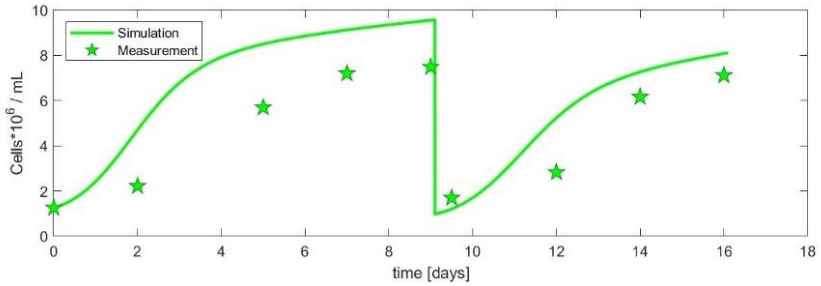
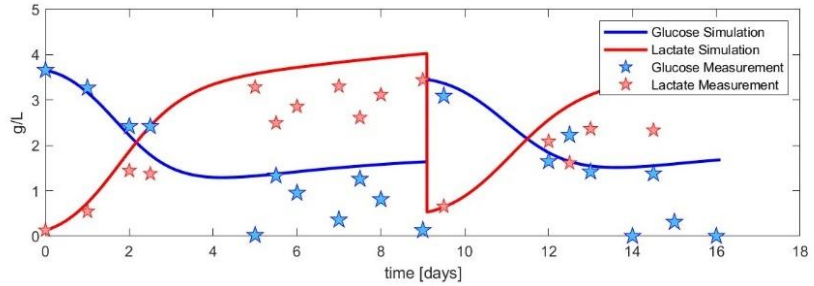
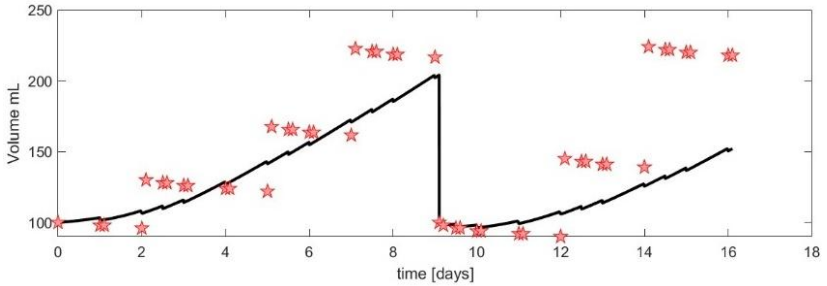


Generation of a mechanistic model based on bioprocessing data enables *in silico* process simulations

16-day process





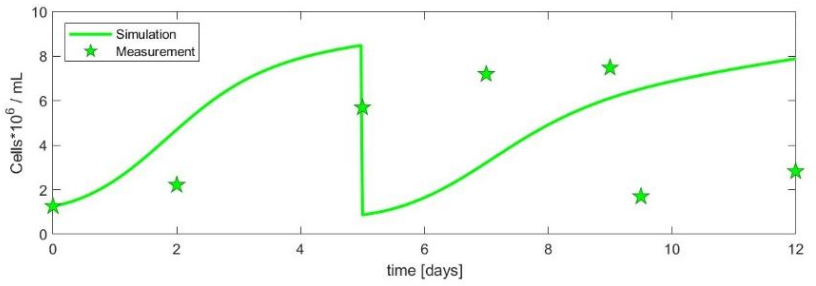


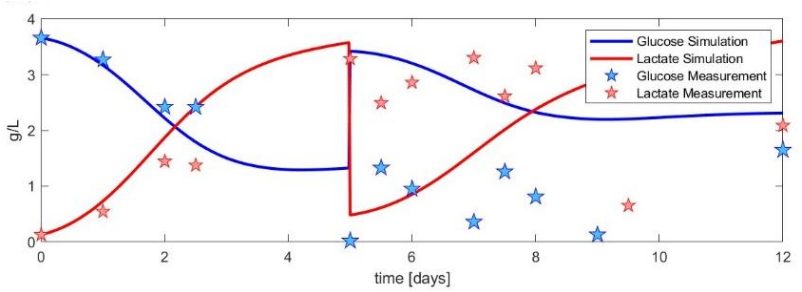
Predicted performance: Estimated total cell yield

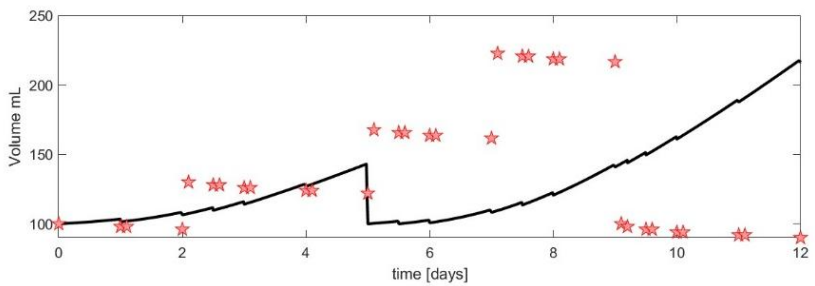
Predicted analytics: Glucose and lactate concentration model

Control Strategy: Controlled feed based on cell concentration

12-day process



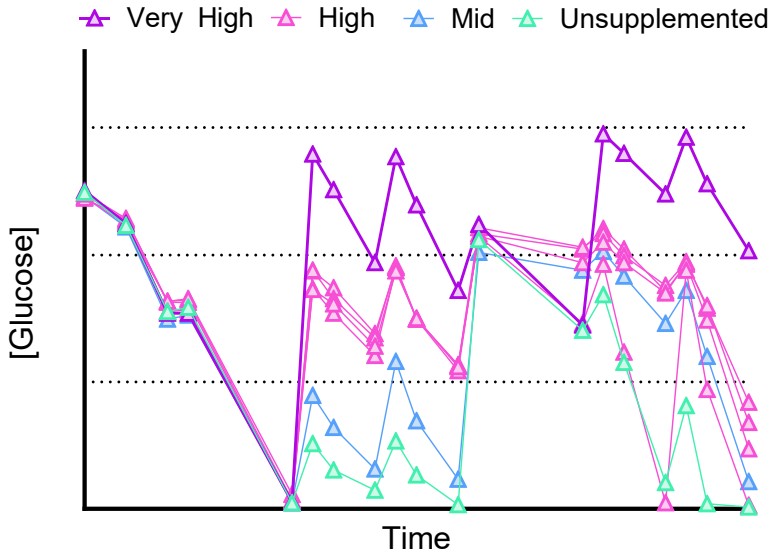




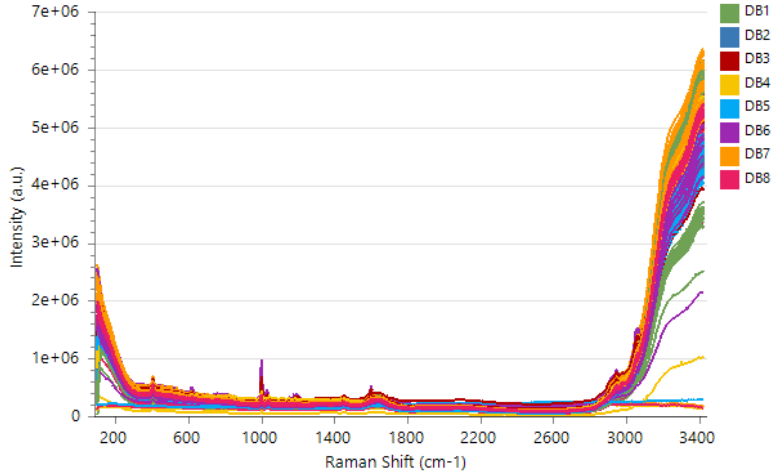
Raman spectroscopy integration to leverage culture monitoring in real-time monitoring

1. **Metabolite perturbation** in DoE studies and offline analysis enables design space definition.

2. **Variations** in the Raman spectra can be associated with variation of a given metabolite of interest.



Raw Raman spectra



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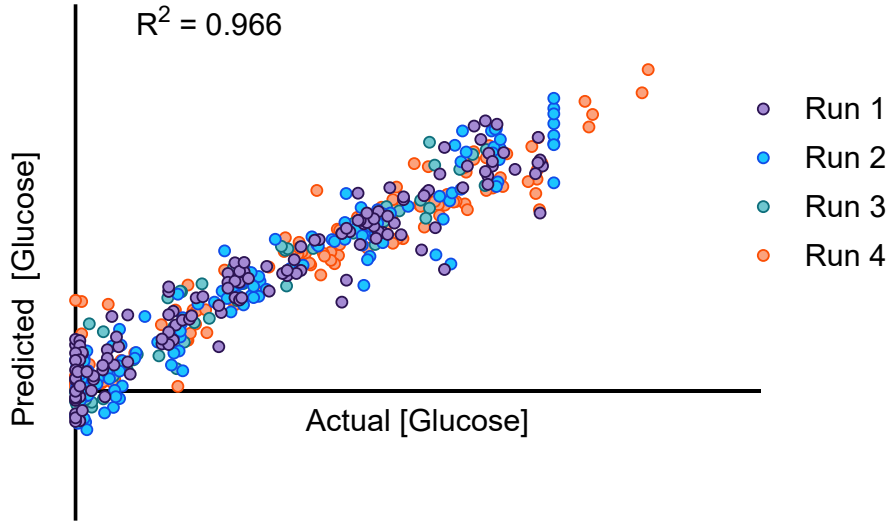

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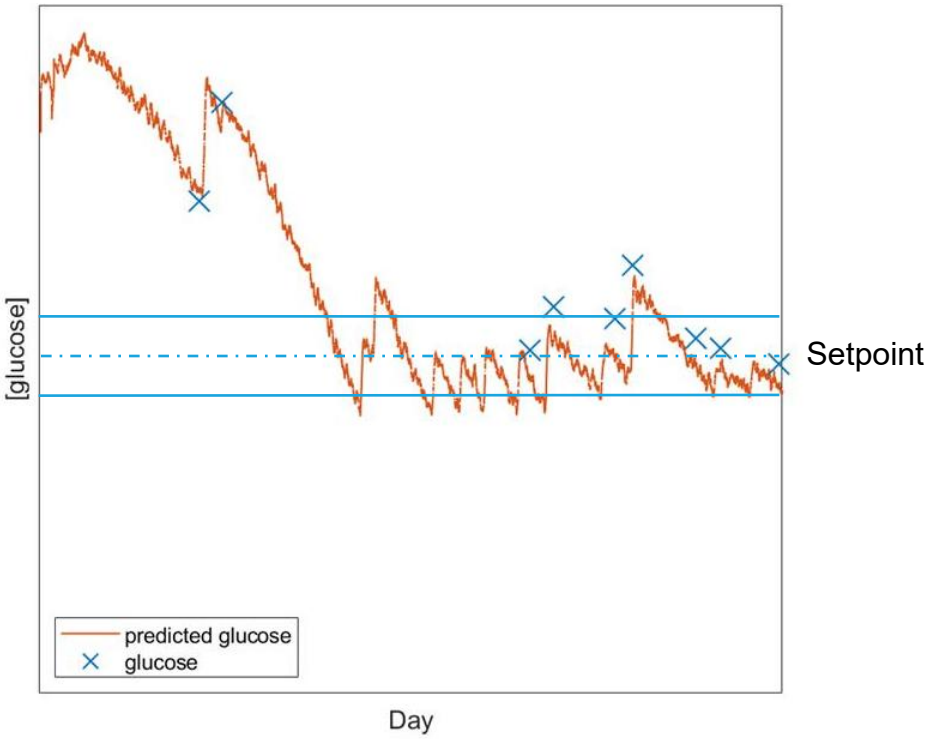
Successful glucose control within setpoint limits



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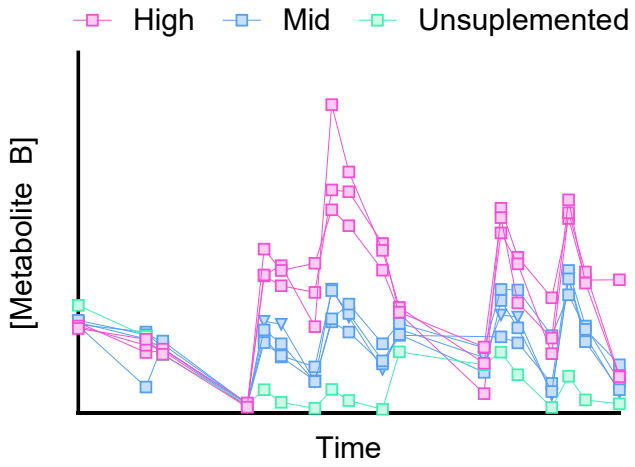
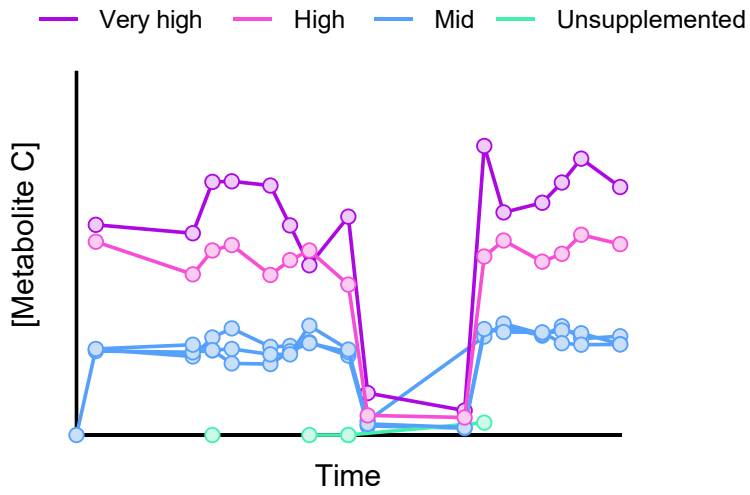
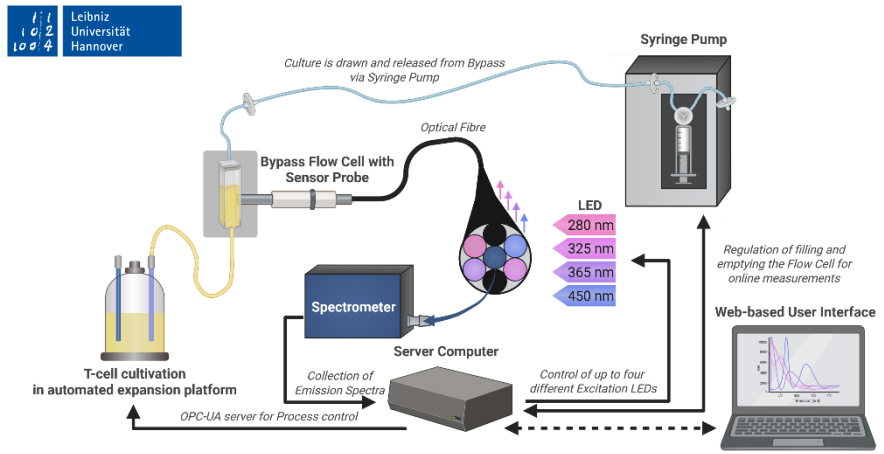
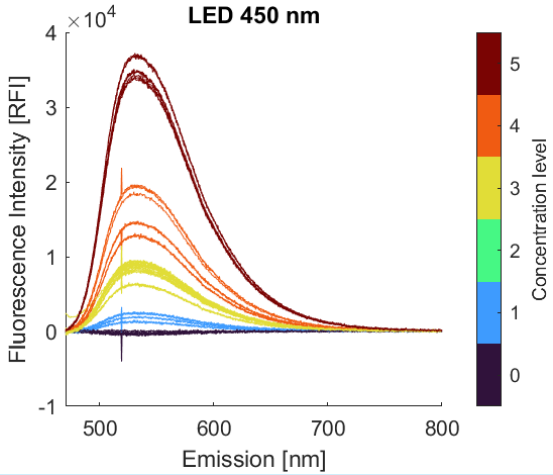
4. Two other biomarkers were not detected well by Raman and their models were not usable.

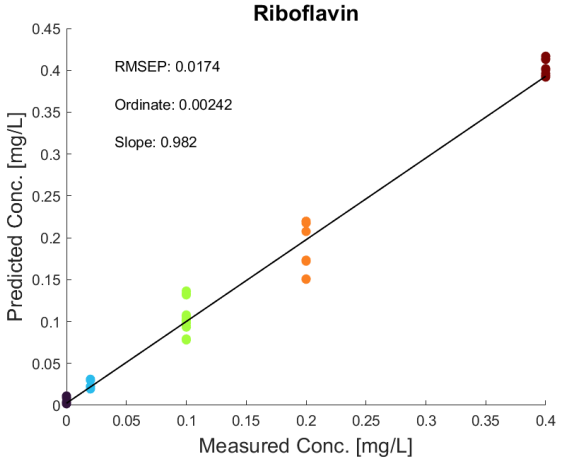




2D fluorescence integration & chemometric model development

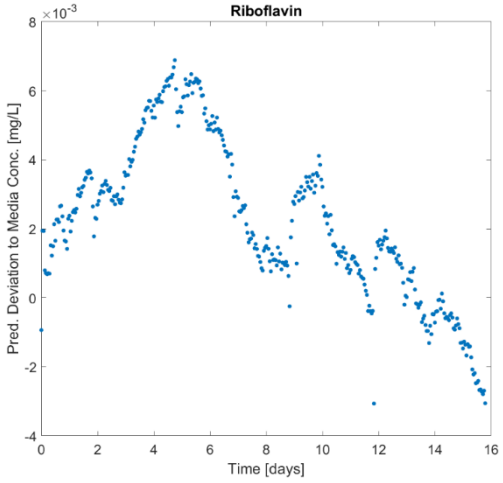






Four readouts:

- NADH
- Riboflavin
- Pyridoxine
- L-Tryptophan



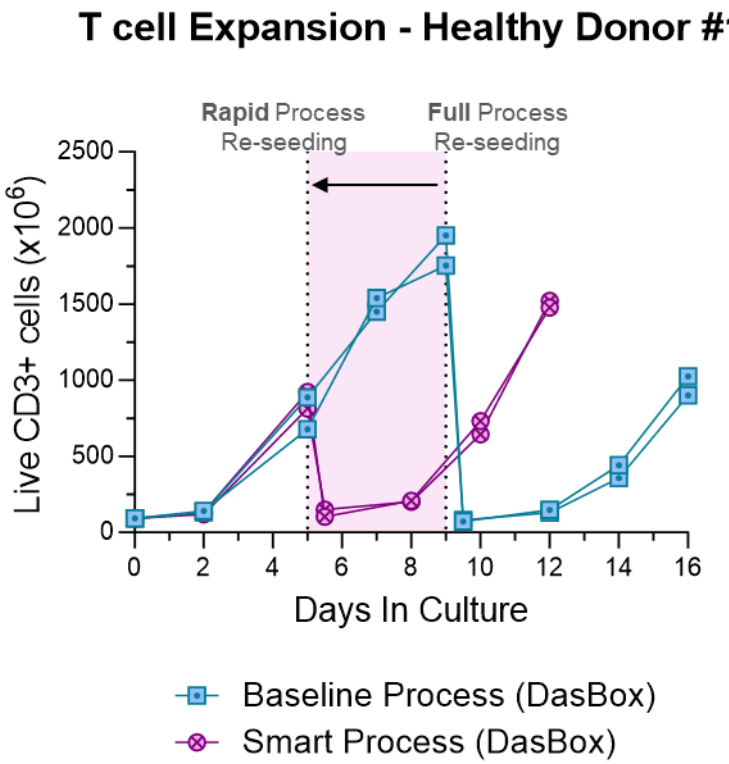
- Chemometric model based on 2D fluorescence measurements could enable **real-time monitoring of cell count**.
- **Soft sensors** development for metabolic biomarkers feeds based on cell number and estimated **consumption rates**.

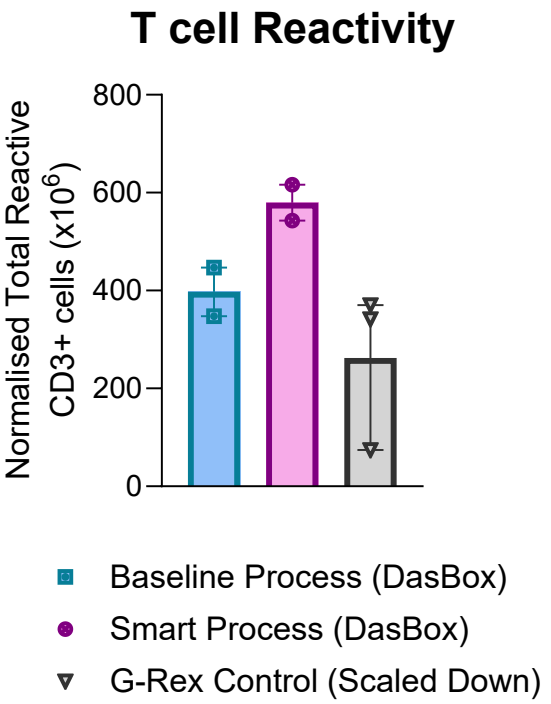
Application of the TIL smart process on healthy donors

Demonstrated on 2 healthy donors

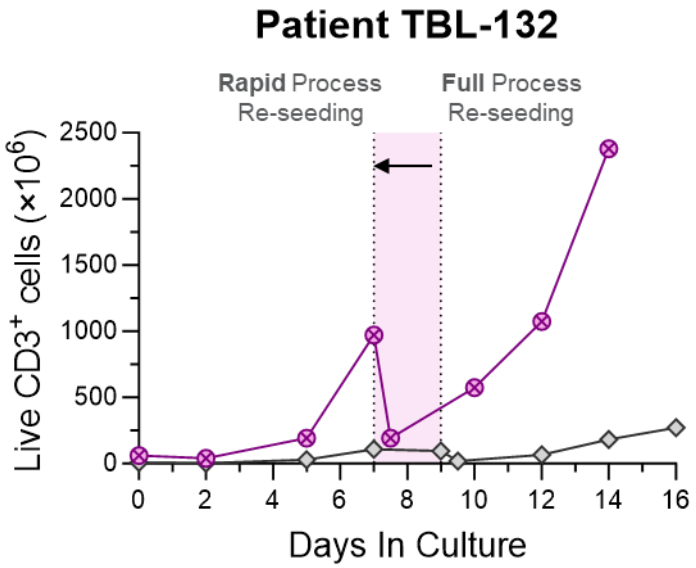
Advanced process control strategy:

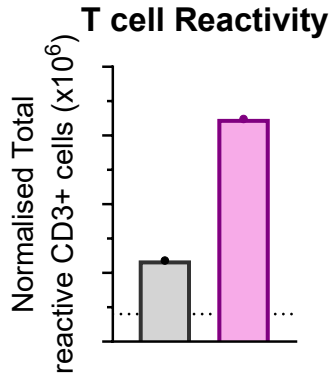
1. **Data-driven** CPP's setpoint decision (DoE optimisation)
2. **Model simulations** of a shorter bioprocess
3. **PAT integration** for Raman-based glucose control
4. **Cell-specific consumption rates** for biomarkers feeding

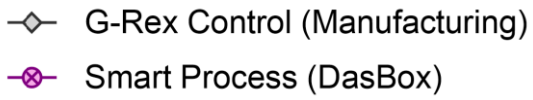


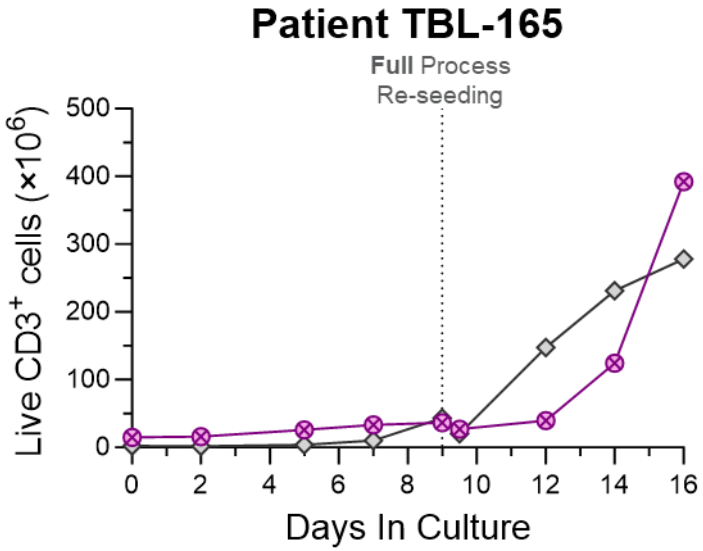


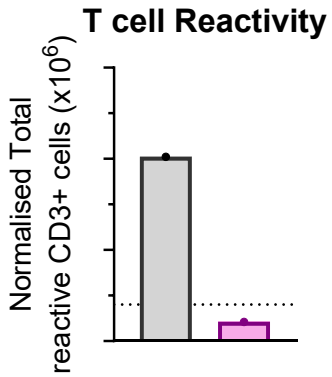
Smart process proof-of-concept on NSCLC patient's material











Considerations

- Expansion of the design space to **more donors** would enable better model generalisation
- **Donor variability** will remain a challenge
- Translation of smart process to patients is possible and may present **significant benefits**

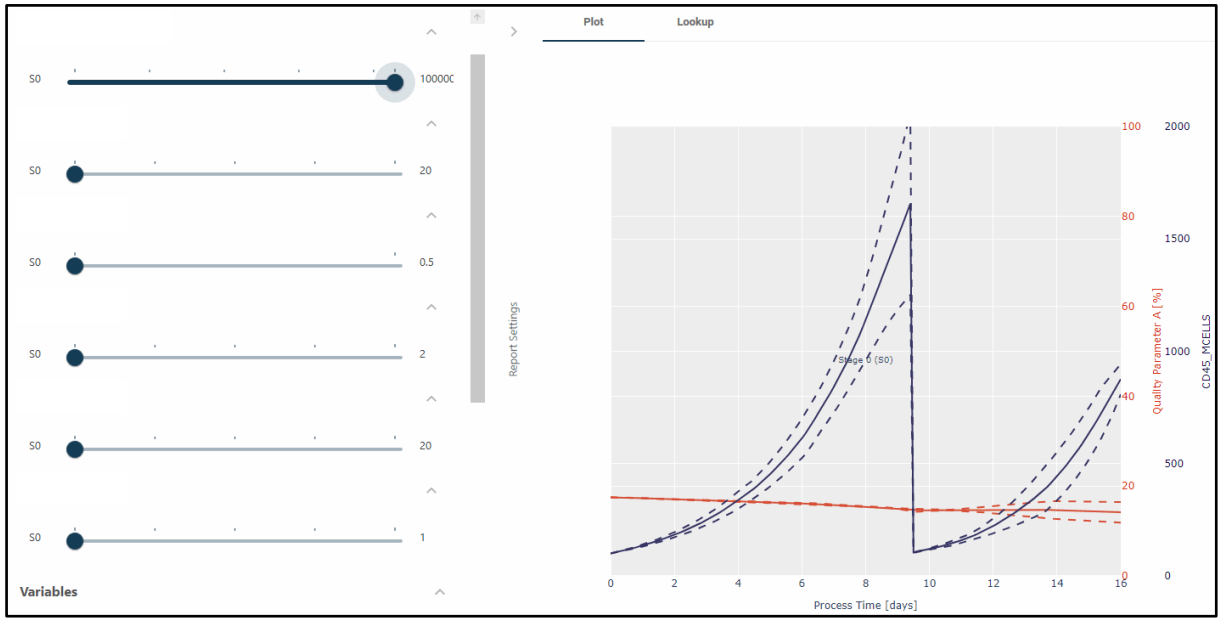
NSCLC = Non-small cell lung cancer

Towards the development of a digital twin

What this work showed so far:

- ✓ **Improving product quality**
  - Better expansion
  - Comparable/better reactivity
- ✓ **Opportunity for cost reduction as a path to better patient access**
  - Up to 4-day shorter process
  - ~15% media
  - ~32% less FTE

Future ambition



Need to overcome the complexity of CGT processes

- ❑ Understand the barriers to PAT and digital technologies adoptions
- ❑ Access to data
- ❑ Industrialise towards scalable digital & automation solutions

We are an independent innovation and technology organisation committed to the advancement of the cell and gene therapy industry

CATAPULT Cell and Gene Therapy

Our vision

A thriving industry ***delivering life-changing advanced therapies*** to the world.

Our role

Create powerful ***collaborations*** which overcome the challenges to the advancement of the ATMP sector.

How we work

We are a team of experts covering all aspects of advanced therapies.

Applying our own unique capabilities and assets, we **collaborate** with academia, industry and healthcare providers to **develop new technology and innovation**.

Scale Enabling Technologies Group Capabilities

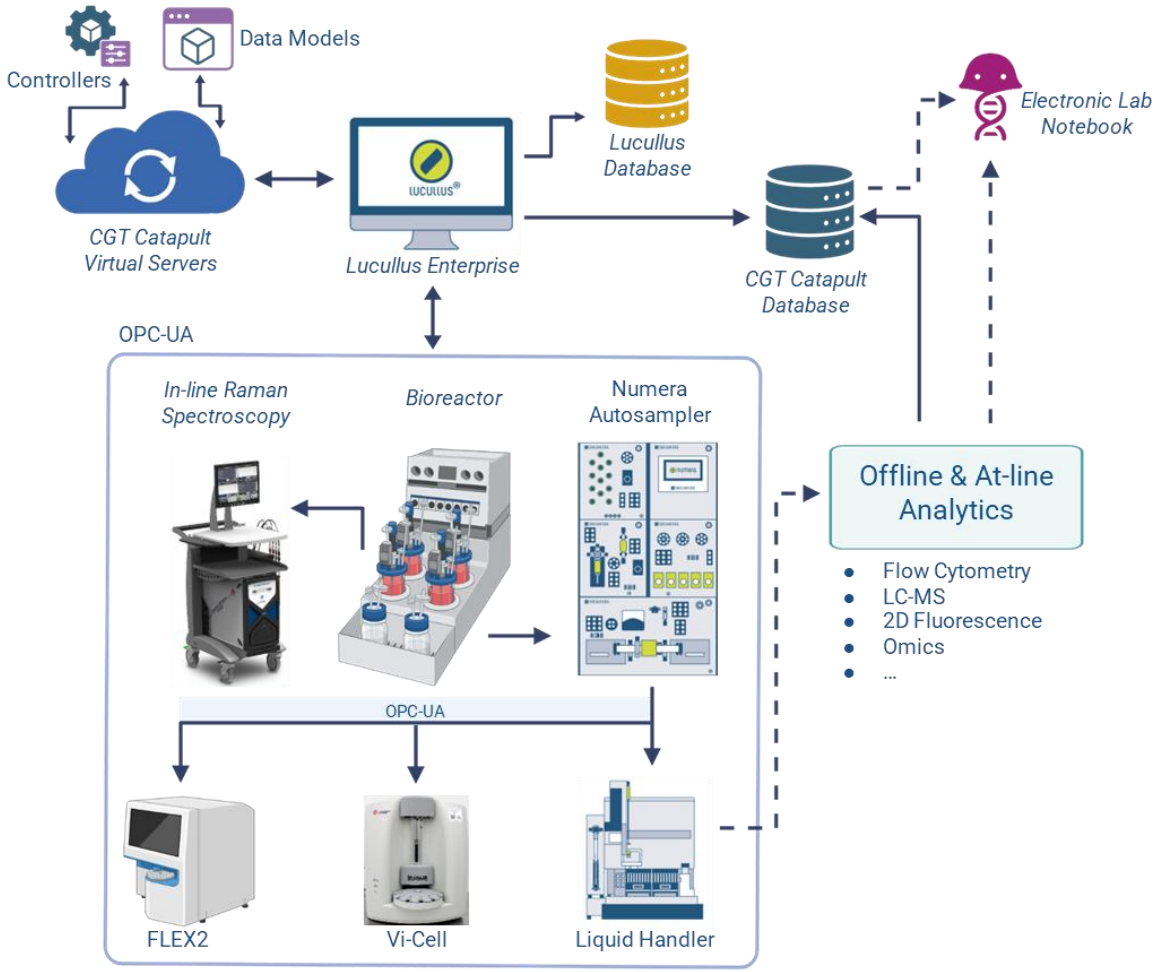
Cell & Gene Process,
USP, DSP, Analytics for release and stability
Advanced characterisation

Digital & Automation for Manufacture, Rapid Release/QC innovation

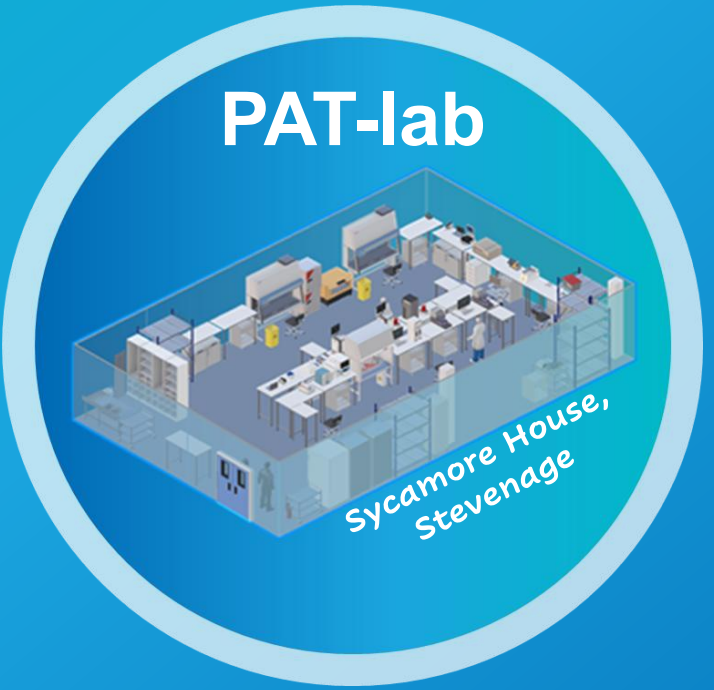
Cell Process,
Advanced Analytics
Universal Design Lab
Lab Robotics

Digital Twins & Process Models, PAT integration

CGT Catapult PAT & Biomarker Discovery Lab



PAT-lab



Designed to build **in-depth process understanding** and control through automated analytics.

Enables **advanced real-time process control** through PAT sensors and digital twins.

Lower the barrier to **access and integration** of next-generation technologies and digital solutions.

Questions?

Acknowledgements:

CGTC Team

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Consortium in Valencia (2024)

Catapult Team

https://smarter-project.eu/

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SCAN ME

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Innovate UK

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