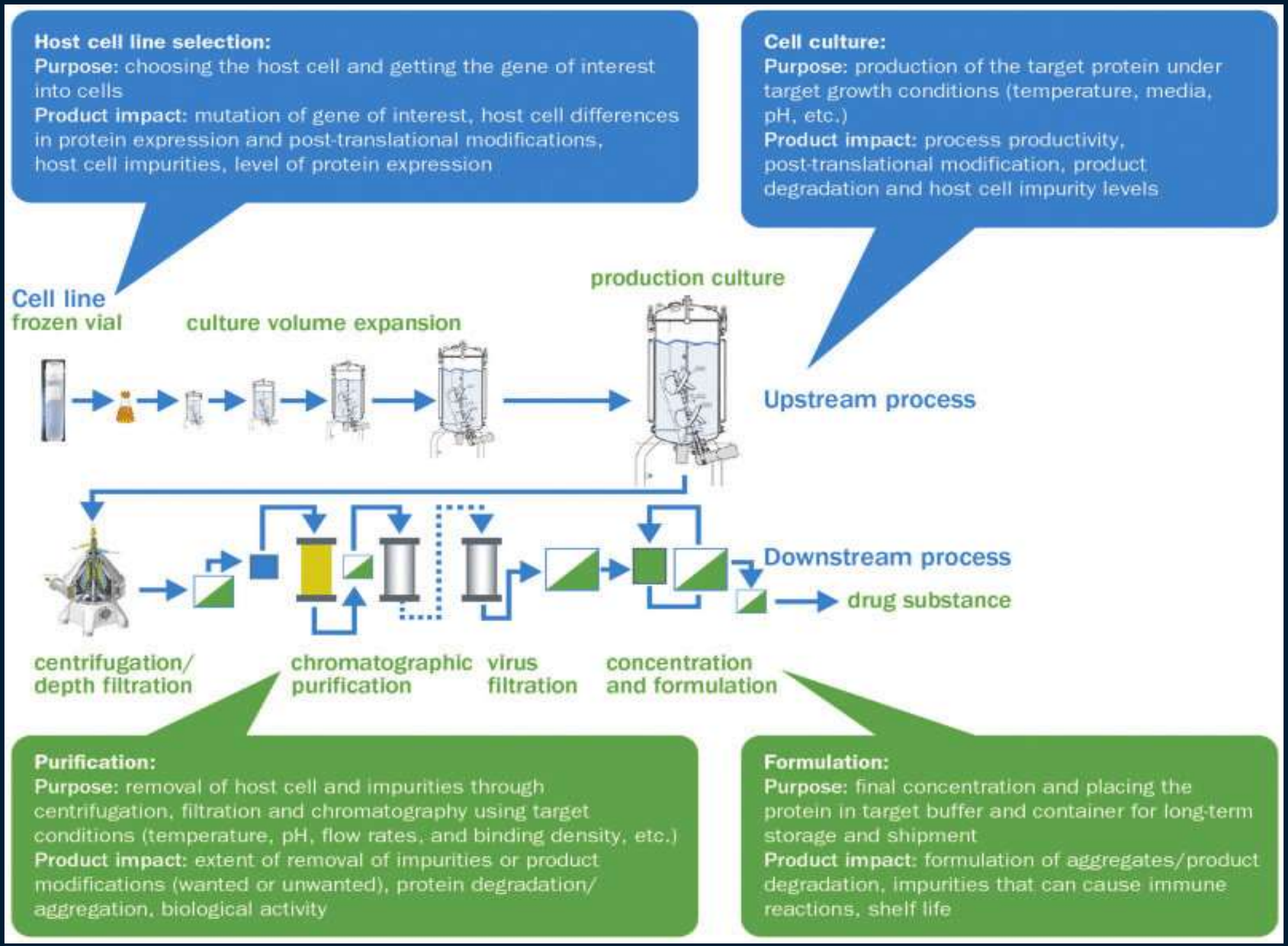
Manufacturing Systems for Vaccines and Biopharmaceuticals: *Current perspectives and future outlook*

GMP Forum 2022

John Power | 19th May, 2022

TOPICS

- Biotechnology manufacturing systems - trends
- Enabling technologies
  - Faster cell line development - Berkeley Lights Beacon
  - More robust cell culture development - ambr®250 technology
  - Lifting the bonnet of the producer strain - Systems Biology
- Regulated Manufacturing in CSIRO


Host cell line selection:
Purpose: choosing the host cell and getting the gene of interest into cells
Product impact: mutation of gene of interest, host cell differences in protein expression and post-translational modifications, host cell impurities, level of protein expression
Cell culture:
Purpose: production of the target protein under target growth conditions (temperature, media, pH, etc.)
Product impact: process productivity, post-translational modification, product degradation and host cell impurity levels
Cell line
frozen vial
culture volume expansion
production culture
Upstream process
Downstream process
drug substance
centrifugation/
depth filtration
chromatographic
purification
virus
filtration
concentration
and formulation
Purification:
Purpose: removal of host cell and impurities through centrifugation, filtration and chromatography using target conditions (temperature, pH, flow rates, and binding density, etc.)
Product impact: extent of removal of impurities or product modifications (wanted or unwanted), protein degradation/ aggregation, biological activity
Formulation:
Purpose: final concentration and placing the protein in target buffer and container for long-term storage and shipment
Product impact: formulation of aggregates/product degradation, impurities that can cause immune reactions, shelf life

Biotechnology Industry 20-year Snapshot

500 new medicines since 2000.

- **Cancer**
- **Infectious diseases**
- **Metabolic disease**
- **Cell and gene therapies**
- **Vaccines**

Maturation of single-use technology in the industry
Industry shift to smaller reactors (15kL ➔ 2kL)
Enhancement in CHO cell productivity (mAb $600 - $800 per gram)
Protein A still a relatively high portion of cost (DSP 40% of COG)
Perfusion and continuous culture modes still niche
Speed to market remains king

Microfluidics accelerates cell line development

Context: **One of the most time consuming tasks in the development of new biologicals is the time taken to generate and clone stable cell lines.**

8-12 weeks

Transfection → single cell plating → imaging → expansion → assay → scale up → select → bank

Content:

Berkely Lights BEACON

Microfluidic workflow that isolates and tracks individual cells

- Regulators expect assurance of clonality
- Over 99% assurance of monoclonality
- Acceleration of cell line development

Cell line development - *accelerated*

Sponsors are reducing the duration for cell line development from 6 to 4 months to gain advantage of speed and improved consistency in early research. The first FDA IND using Beacon has been approved.

Stability evaluation still needs to be done in real time (6-8 weeks)

Scale down to scale up

Context: **The development of manufacturing systems for biotechnology-based medicines has historically been constrained by the ability to generate sufficient data sets to support process robustness and regulatory filings**

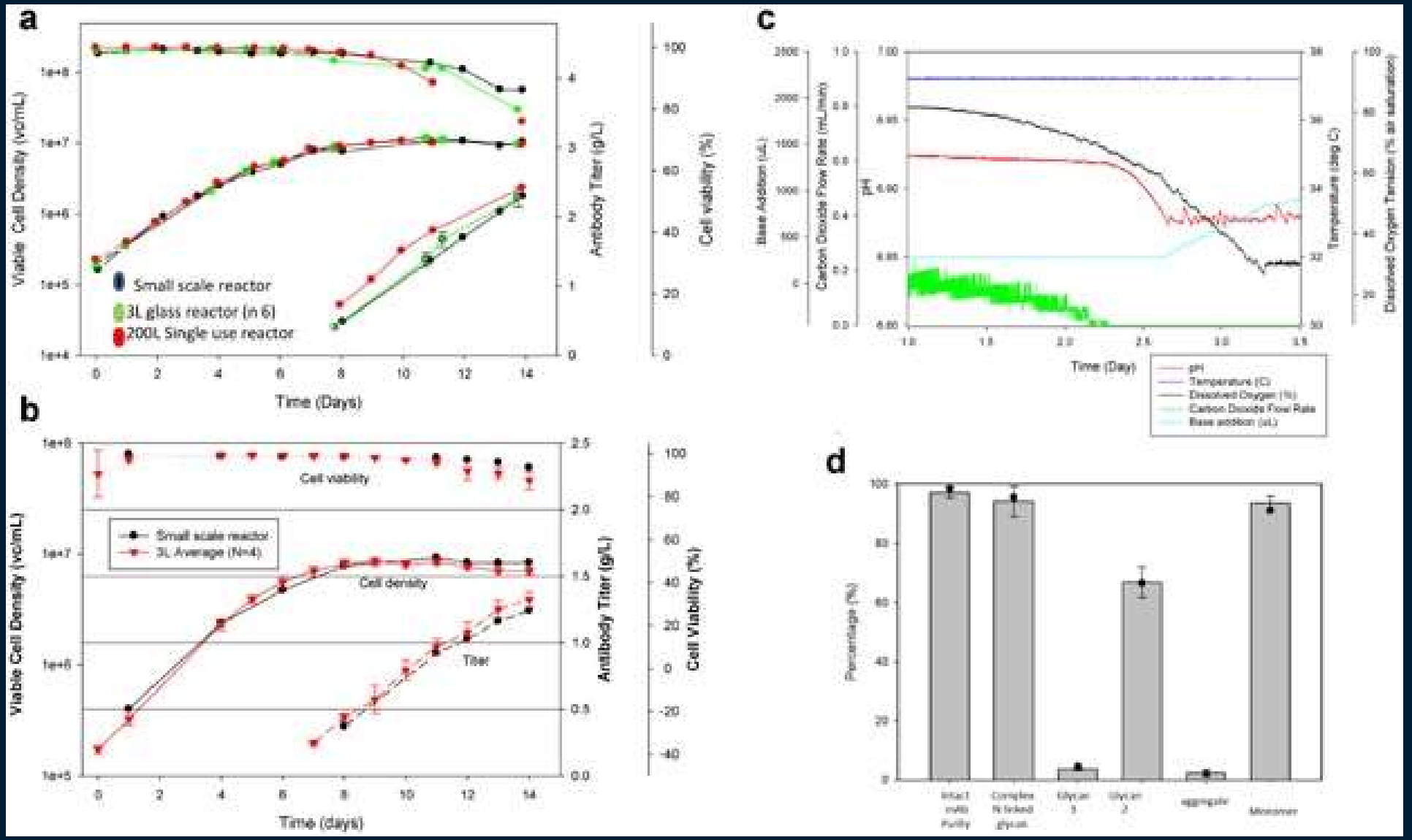
Content:

Bioreactor design has converged with new data handling capabilities to provide new options for cost-effective process development.

Sartorius ambr®250 set a new benchmark in the industry

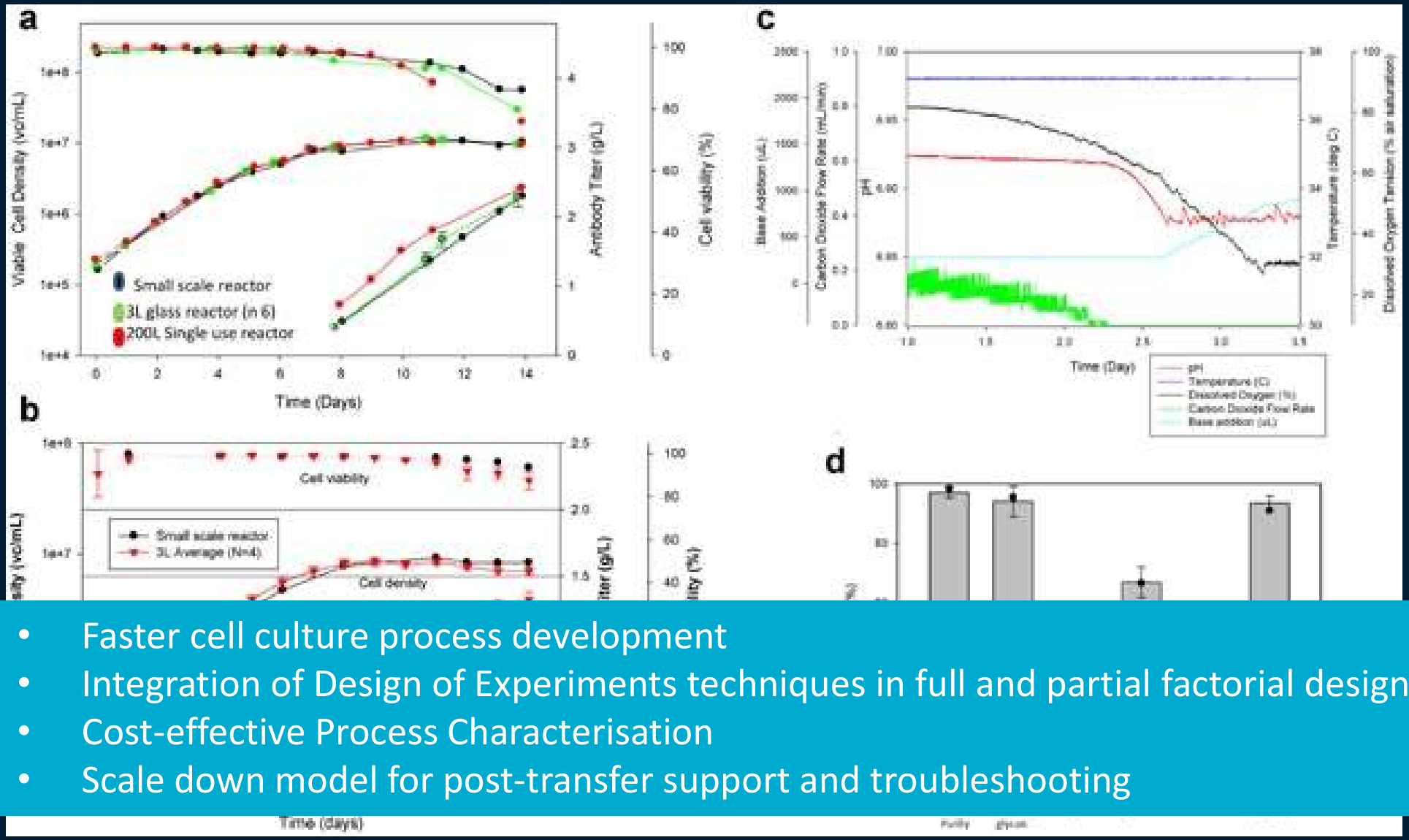
- 24-way throughput with full instrumentation
- Scaleable reactor design
- Microbial, cell culture, and microcarrier formats.
- Data integration and handling

Automated disposable reactors?



Biotechnology and Bioengineering, Volume: 110, Issue: 12, Pages: 3126-3138, First published: 15 June 2013, DOI: (10.1002/bit.24978)

Automated disposable reactors?



- Faster cell culture process development
- Integration of Design of Experiments techniques in full and partial factorial design
- Cost-effective Process Characterisation
- Scale down model for post-transfer support and troubleshooting

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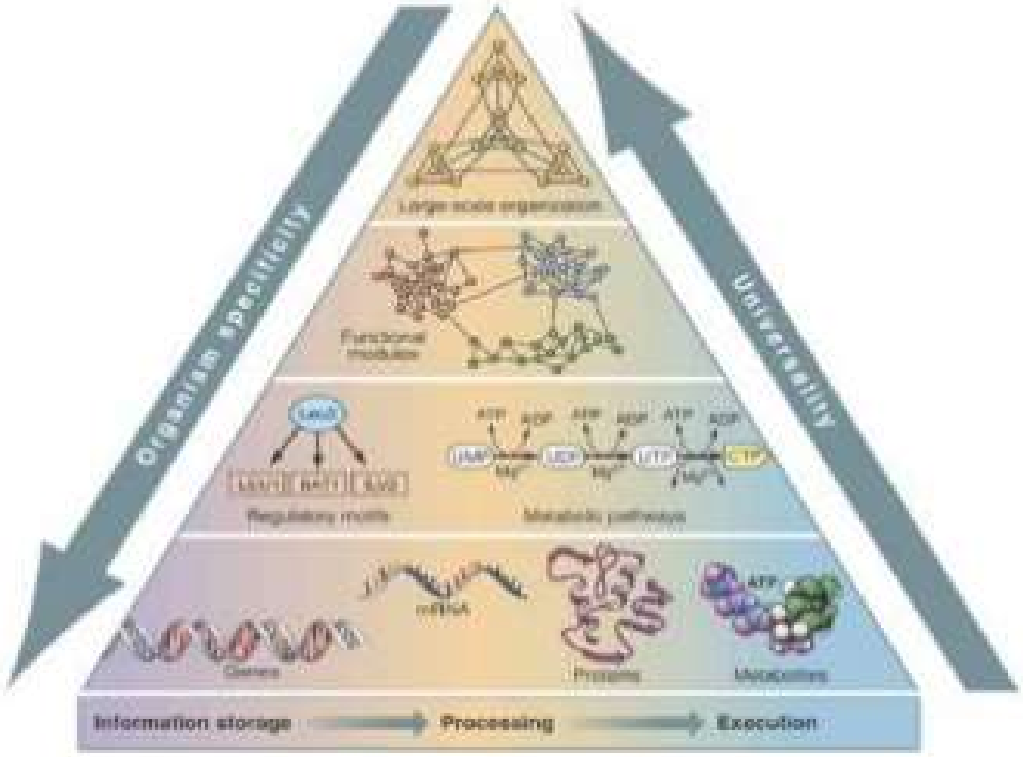
Lifting the hood on Cells: Systems Biology

What is systems biology?

- Systems biology is the study of an organism, viewed as an *integrated* and *interacting network* of genes, proteins and biochemical reactions which give rise to life.
- Networks organize and integrate information at different levels to create biologically meaningful models.
- Networks formulate hypotheses about biological function and provide temporal and spatial insights into dynamical changes.

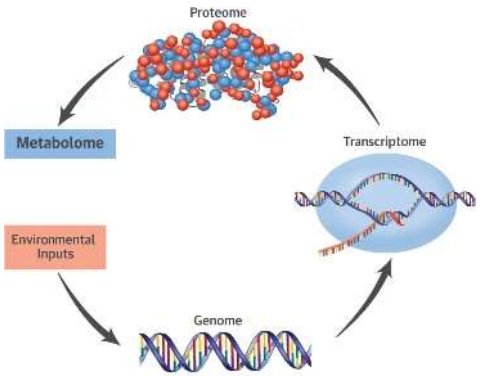


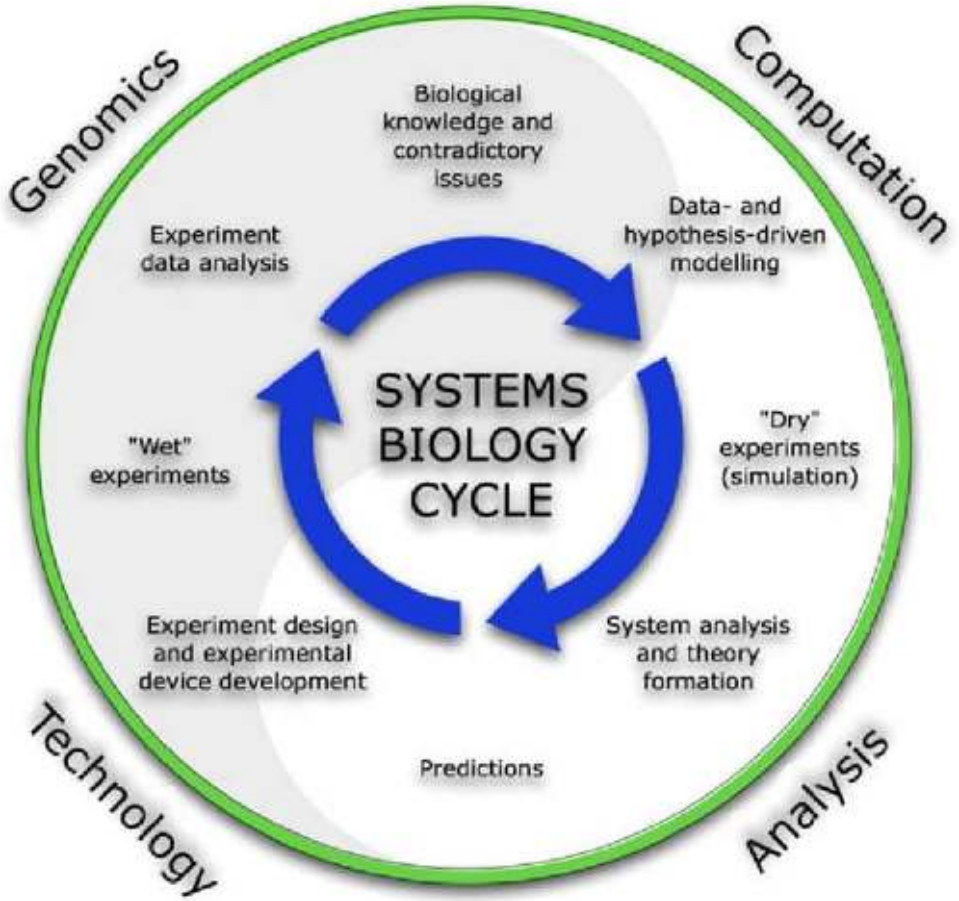
Hood and Tian, Genomics, Proteomics & Bioinformatics, 2012

Oltvai and Barabási, Science. 2002

Lifting the hood on Cells: Systems Biology

Whole genome sequence
Transcriptomics
Proteomics





Stimulus
Hi/Lo ➔

Improving clostridial toxoid production through molecular fermentation maps.
University of Queensland and Zoetis Research and Production. ARC Linkage Grant 2016 – 2019.

Lifting the hood on Cells: Systems Biology

Context:

Online CHO genome resource published 2012.

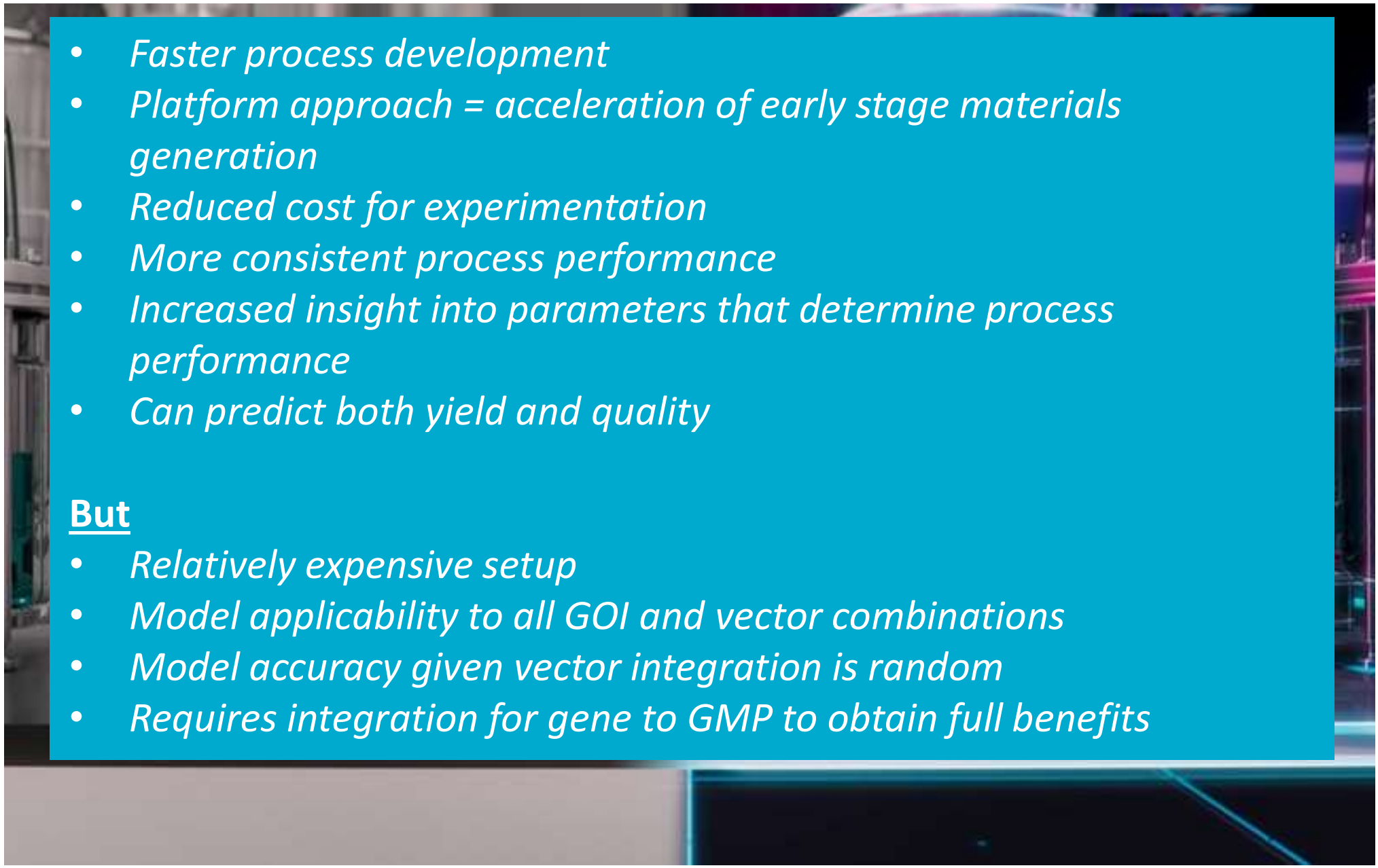
Using Genome scale and metabolic flux modelling to build a DIGITAL TWIN for CHO cell culture process optimisation.

Experimental Plan

1. Assemble CHO genome for producer strain
2. Build the metabolic flux model (flux equations)
3. Build the data to train the model
   - CHO cell culture
   - Time course Fed batch
   - Cell growth trajectory
   - Nutrient analysis (Sugars, AA, metals)
   - Metabolic profile (Lac, NH_4, OSM, pH)
4. Train the model
5. Simulate and predict (sensitivity analysis)
6. NEW OPTIMUM
7. Generate new data to test
8. (Validate what you can calculate)

insilico biotechnology

CHO Cell Digital Twin



- *Faster process development*
- *Platform approach = acceleration of early stage materials generation*
- *Reduced cost for experimentation*
- *More consistent process performance*
- *Increased insight into parameters that determine process performance*
- *Can predict both yield and quality*

But

- *Relatively expensive setup*
- *Model applicability to all GOI and vector combinations*
- *Model accuracy given vector integration is random*
- *Requires integration for gene to GMP to obtain full benefits*

Your national science agency

State-of-the-art national research infrastructure

5,500 dedicated people

Across the world including Australia, Singapore, Vietnam, US and Chile

$4.5B+ a year

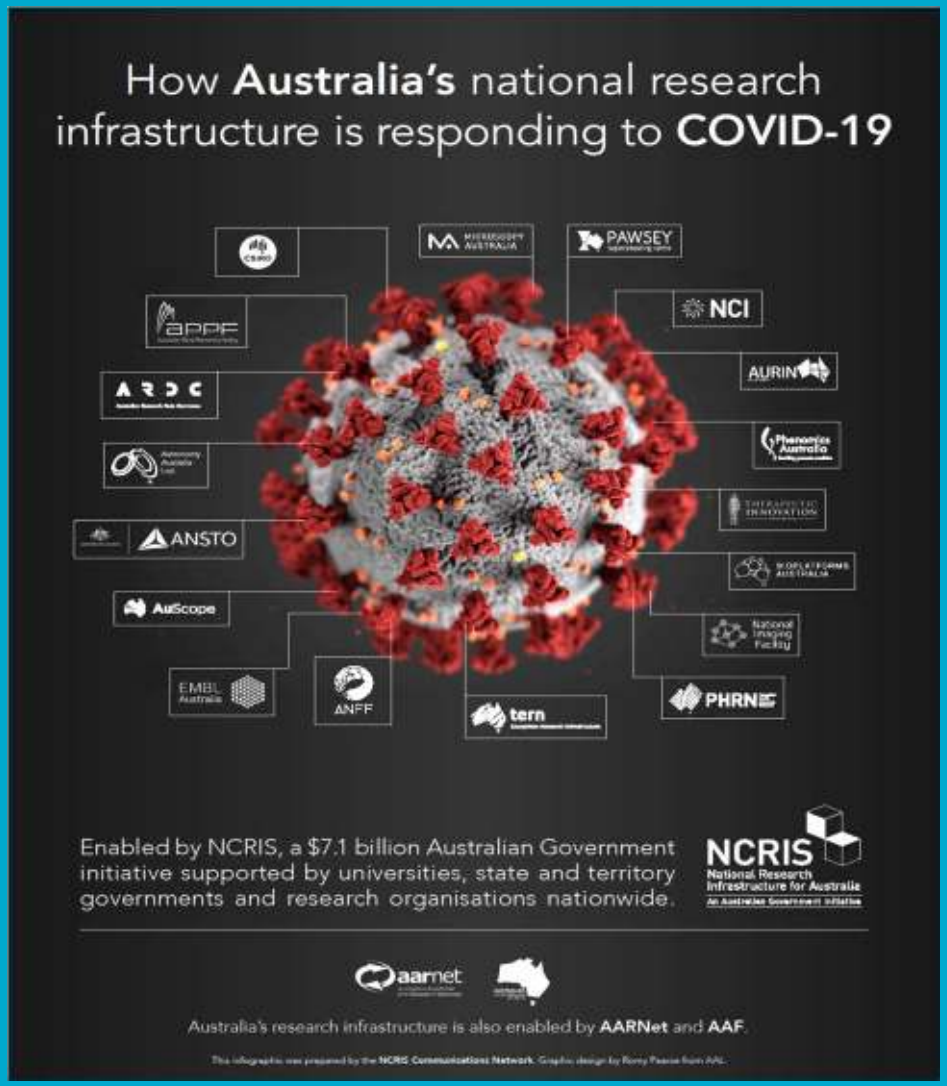
Value delivered to the Australian economy through our science and technology

57 sites

One of the world's largest multidisciplinary science and technology organisations

CSIRO Regulated Manufacturing

- Provider to the Australian research community and early-phase product sponsors.
- Manufacture of recombinant proteins and cell culture-derived products.
- Portfolio of projects for new vaccines and biotherapeutic candidates.
- Member of the National Collaborative Research Infrastructure Strategy (NCRIS)
- Member of Therapeutic Innovation Australia (TIA). Victoria node of the National Biologics Facility (NBF).



THERAPEUTIC INNOVATION AUSTRALIA

National Biologics Facility

Regulated Biologics Manufacturing

- Manufacture of Investigational Materials
- 50 and 200 L scale.
- Formulation and fill.
- Analytical Development and Testing
- Construction completion 2022.

Thank you

CSIRO Manufacturing
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Regulated Biomanufacturing

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