



# ADAPTABLE ATMP FACILITIES: DESIGN FOR AN UNKNOWN FUTURE

Howard Sneider  
ISPE BAC Product Show  
September 18, 2019  
Gillette Stadium  
Foxborough, MA

NEVER GIVE UP ON WHAT YOU REALLY  
WANT TO DO. THE PERSON WITH BIG  
DREAMS IS MORE POWERFUL THAN THE  
ONE WITH ALL THE FACTS.

/ H. JACKSON BROWN, JR.

# Agenda

## Brief overview of topics

- > Today's ATMPs
- > Current Needs
- > State of the Art Facilities
- > Tomorrow's ATMPs
- > Future Facilities
- > Bridging the Gap.

# Today's ATMP

## Types of ATMP's

- > ATMPs can be classified into three main types:
  - gene therapy (GT) medicines: active substance which contains or consists of a recombinant nucleic acid
  - somatic-cell therapy (sCT) medicines: contains or consists of cells or tissues that have been subject to substantial manipulation
  - tissue-engineered product (TEP) medicines: contains or consists of engineered cells or tissues
- > In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as combined ATMPs.
- > Except for naked nucleic acid and similar treatments, ATMP's cannot be sterile filtered.

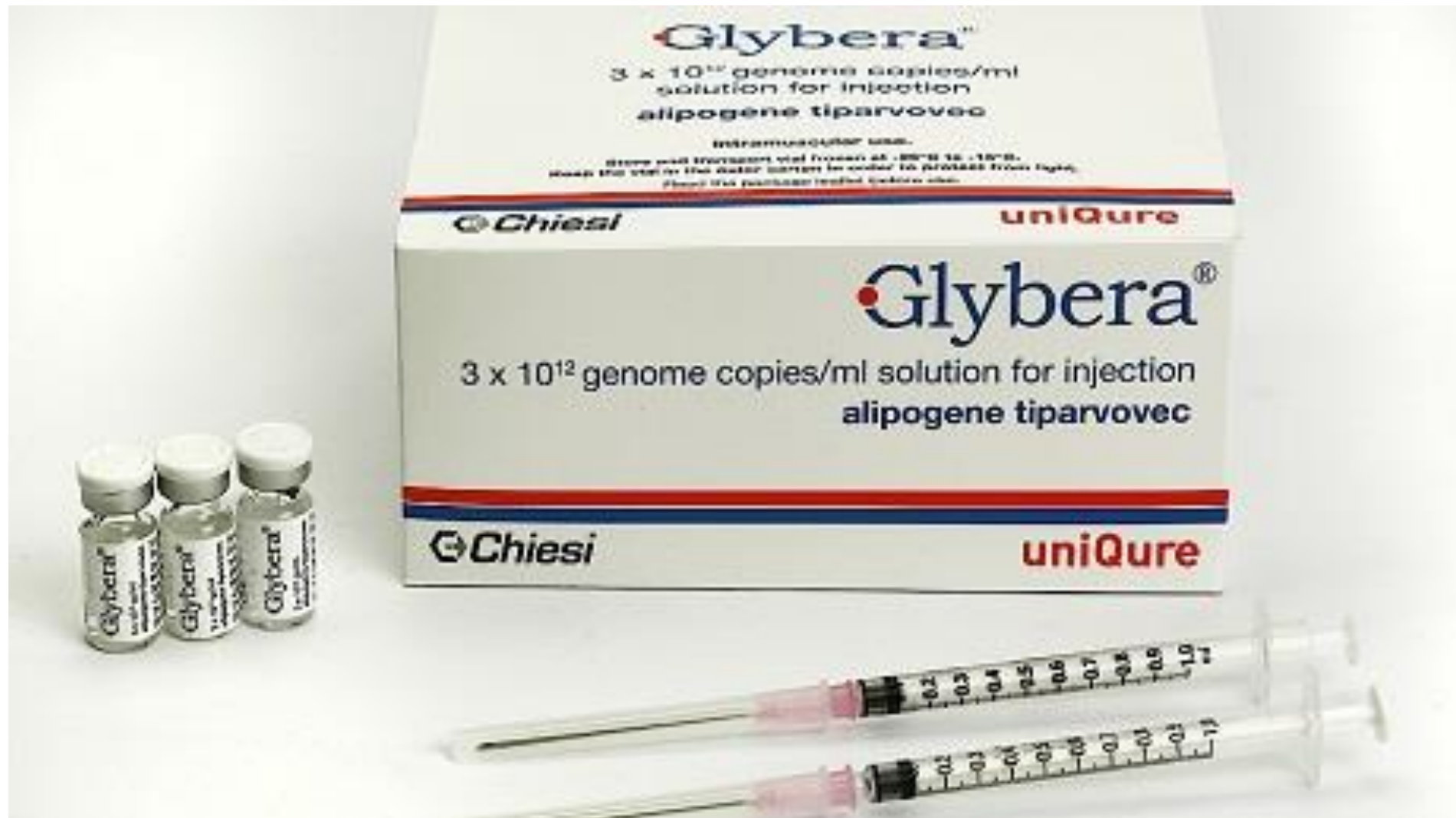
# Today's ATMP

## GT Examples

- > gene therapy (GT) medicines: active substance which contains or consists of a recombinant nucleic acid.
- > Gene based (DNA) ATMPs may treat inherited diseases, cancer, and tissue regeneration.
- > Glybera – by UniQure, in-vivo gene therapy example
  - Treatment of lipoprotein lipase deficiency
  - Replication-deficient adeno-associated viral vector designed to deliver and express the human LPL gene variant LPLS447X
  - 1<sup>st</sup> GT worldwide, approved in Oct2012 and withdrawn in Oct2017.
- > Strimvelis – by GSK, ex-vivo gene therapy example
  - CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence
  - Treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) a.k.a, “Bubble-boy disease.”
  - Only 5 sales since 2016.

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# Today's ATMP

## GT Examples





# Today's ATMP

## sCT Example

- > somatic-cell therapy (sCT) medicines: contains or consists of cells or tissues that have been subject to substantial manipulation.
- > Cell Based ATMPs may treat cartilage defects, tissue replacement, immunotherapy
- > Provenge – by Dendreon (Valeant), cell therapy example
  - Autologous peripheral blood mononuclear cells activated with PAPGM-CSF (sipuleucel-T)
  - Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer
  - approved in Apr2010. ~\$100K/treatment. First line treatment recommendation.

# Today's ATMP

## sCT Example



# Today's ATMP

## TEP Example

- > tissue-engineered product (TEP) medicines: contains or consists of engineered cells or tissues
- > Tissue Based ATMPs may treat cartilage defects, tissue replacement
- > Holoclar – by Holostem Therapie Avanzate S.R.L., tissue-engineered product example
  - Ex vivo expanded autologous human corneal epithelial cells containing stem cells
  - Treatment of adult patients with moderate to severe limbal stem cell deficiency unilateral or bilateral, due to physical or chemical ocular burns.
  - Approved in Feb2015. 1<sup>st</sup> stem cell based ATMP.

# Today's ATMP

## TEP Example

Before Holoclar®



After Holoclar®



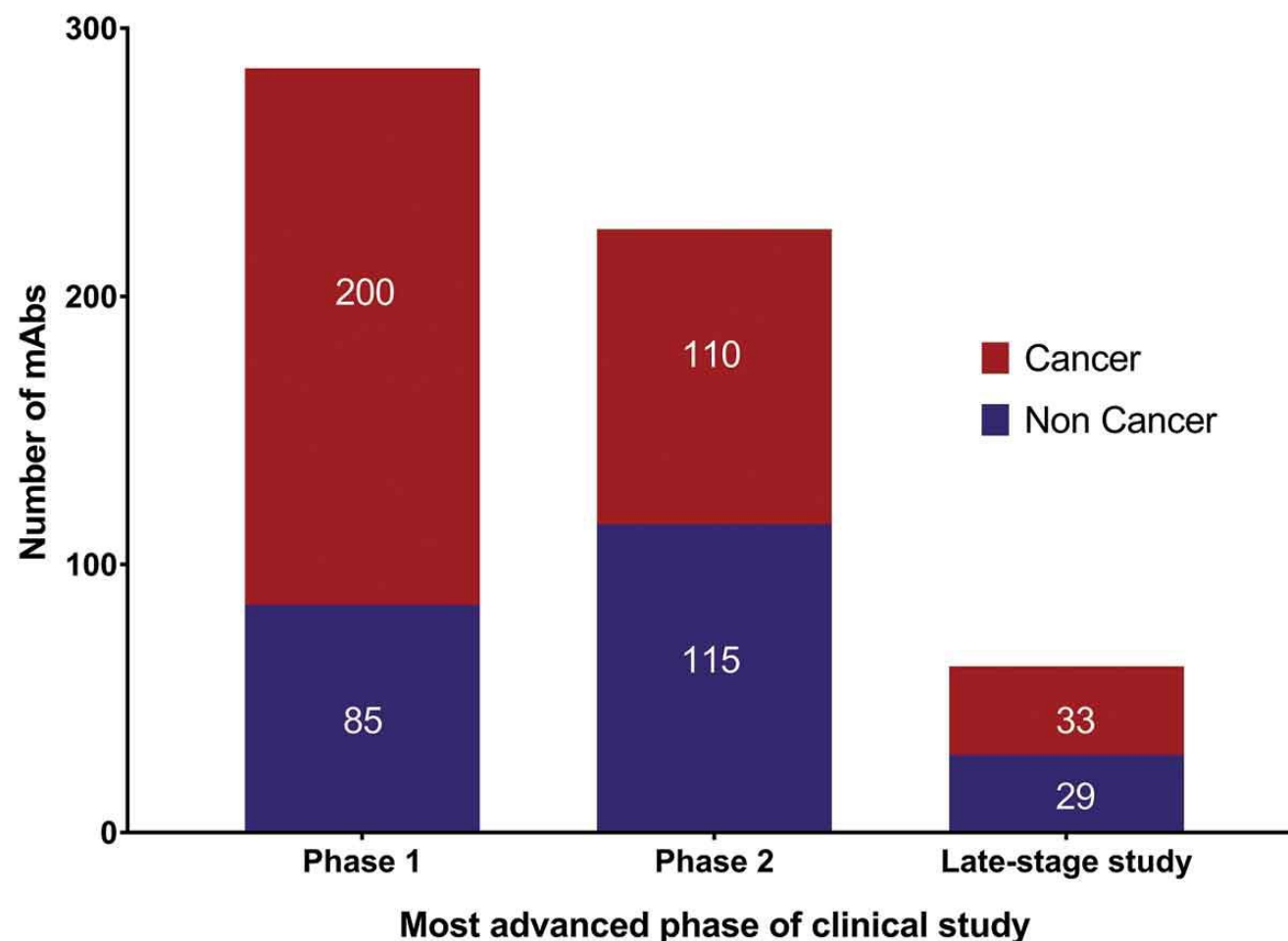
# Today's ATMP

## An explosion in research

- > Q1 2015: 466 Clinical trials underway
  - Ph. I: 150
  - Ph. II: 288
  - Ph. III: 48
- > Q1 2019: 1060 Clinical trials underway
  - Ph. I: 349
  - Ph. II: 618
  - Ph. III: 93
- > Growth rate of about 19%
- > Attrition rate consistent over 4 years
- > Data from Alliance for Regenerative Medicine (ARM), <https://alliancerm.org/>

# Today's ATMP

Comparison to mAb, Q4 2018 data



> Data as of November 2018. Totals include only antibody therapeutics sponsored by commercial firms; those sponsored solely by government, academic or non-profit organizations were excluded; biosimilars and Fc fusion proteins were excluded.

> Antibodies to watch in 2019; Hélène Kaplon & Janice M. Reichert  
<http://orcid.org/0000-0003-0400-1951>;  
<https://doi.org/10.1080/19420862.2018.1556465>

# Current Needs

## Typical ATMP production

### > Fed batch

- WCB
- Inoculum
- Scale up bioreactor
- Production bioreactor
- Harvest
- Capture chromatography
- Viral inactivation
- Polishing chromatography
- Viral filtration
- Diafiltration
- Formulation
- Lyophilization
- Packaging

### > Plasmid Manufacturing

- WCB
- Inoculum
- Scale up fermentation
- Production fermentation
- Harvest – plasmid recovery
- purification
- formulation
- Typical cold chain supply

### > Typical Viral Vector

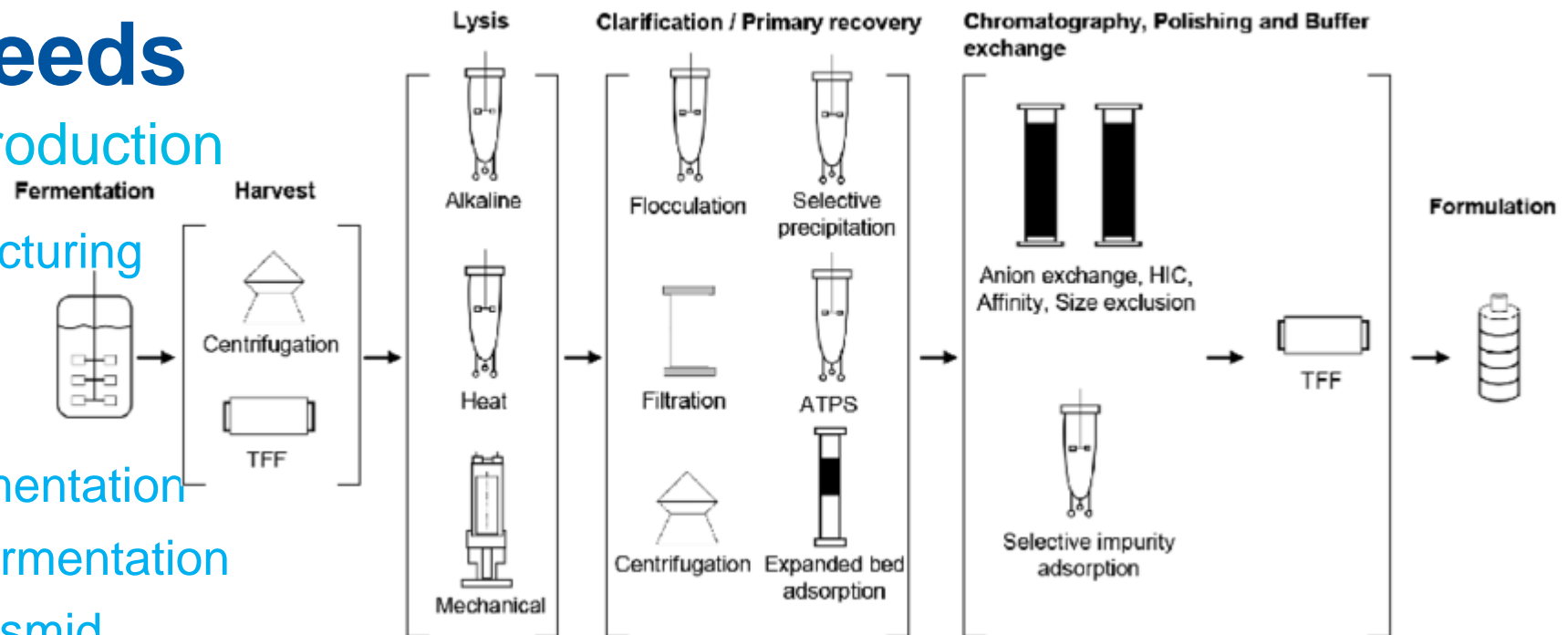
- WCB
- Inoculum
- Scale up bioreactor
- Production bioreactor
- Transduction
- Harvest
- Chromatography
- DNA removal
- Polishing chromatography
- Filtration
- Packaging
- Typical cold chain supply

# Current Needs

## Typical ATMP production

### > Plasmid Manufacturing

- WCB
- Inoculum
- Scale up fermentation
- Production fermentation
- Harvest – plasmid recovery
- purification
- formulation
- Typical cold chain supply



- > Carnes, Aaron & Williams, James. (2007). Plasmid DNA Manufacturing Technology. Recent patents on biotechnology. 1. 151-66. 10.2174/187220807780809436.



# Current Needs

## Typical ATMP production

- > Fed batch
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  - Formulation
  - Lyophilization
  - Packaging
- > Allogenic
  - WCB
  - Inoculum
  - Scale up bioreactor
  - Production bioreactor
  - Concentration
  - Formulation
  - Packaging
  - Typical Cold Chain Supply
- > Autologous
  - Patient donation
  - Formulation for transfer
  - transfer
  - Cell selection and Expansion
  - Concentration
  - Formulation
  - Packaging
  - Expedited supply
- > Scale of this process is per patient

# Current Needs

## Typical ATMP production

- > Allogenic
  - WCB
  - Inoculum
  - Scale up bioreactor
  - Production bioreactor
  - Concentration
  - Formulation
  - Packaging
  - Typical Cold Chain Supply



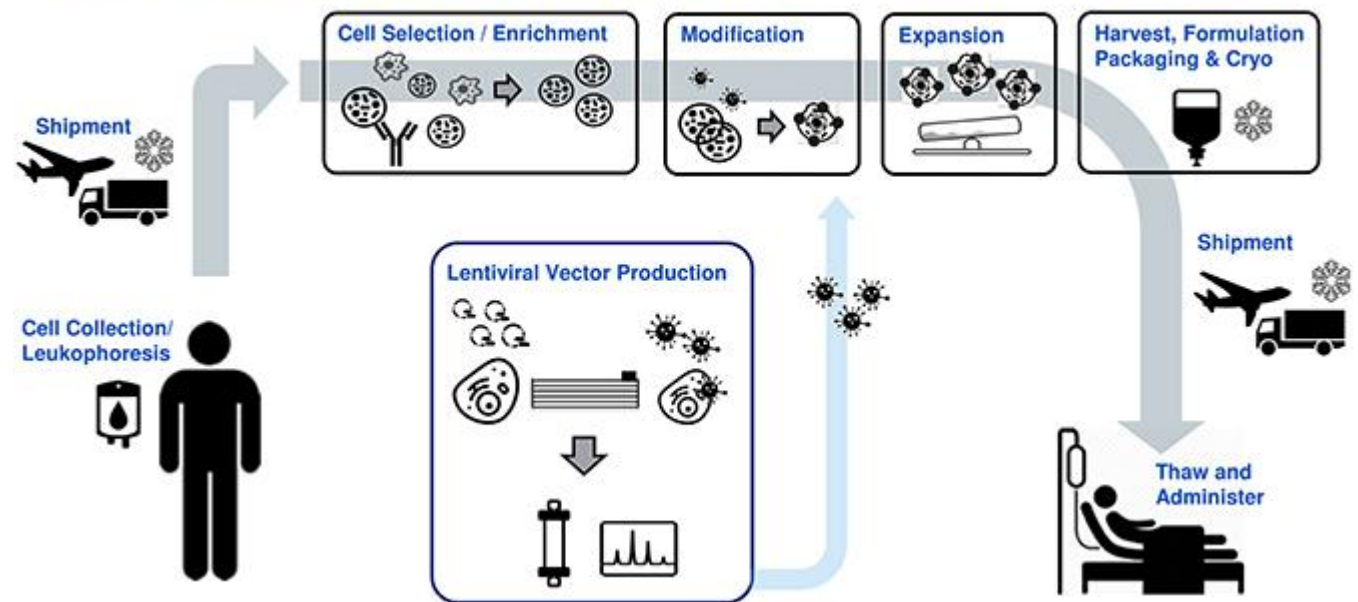
# Current Needs

## Typical ATMP production

- > Autologous
  - Patient donation
  - Formulation for transfer
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  - Formulation
  - Packaging
  - Expedited supply



### Cell-based Gene Therapy Workflow



- > Iyer Rohin K., Bowles Paul A., Kim Howard, Dulgar-Tulloch Aaron. (2018). Industrializing Autologous Adoptive Immunotherapies: Manufacturing Advances and Challenges <https://doi.org/10.3389/fmed.2018.00150>

# Current Needs

## Constraints for ATMP production

> Pharmaceuticals

> Biotech

> Gene Therapy

> Cell Therapy

> Tissue Engineering

> Medical devices

Medicinal  
Products

ATMP  
Products

Medical  
devices

Number of patients treated per  
item/batch

Difference from liquid suspension  
batch production

# State of the Art Facilities

## Gene Therapy

- > Gene Therapies are generally **viral** products:
  - Aseptic
  - **Viral segregation is critical and may segregate “ballrooms”**
  - **Higher dose per patient = lower treatments per batch**
- > In practice:
  - Open processes require Grade A conditions with the appropriate surrounding background environment (Grade B for open systems and Grade C (US) or D (EU) for isolator based systems)
  - Potential differences between development and commercial manufacturing.(e.g., CsCl ultracentrifugation versus chromatographic methods.)
  - Current process are still exploring virus production by transfection, infection, or stable producer lines that grow in either suspension or adherent conditions.

# State of the Art Facilities

## Allogenic Cell Therapy

- > Allogenic ATMP's are **living cell products**:
  - Aseptic
- > In Practice:
  - Open processes require Grade A conditions with the appropriate surrounding background environment (Grade B for open systems and Grade C or D for isolator based systems)
  - **Many therapies currently require adherent culture operations.**
  - **Workflows have high space, labor, cost, and logistic demands.**

# State of the Art Facilities

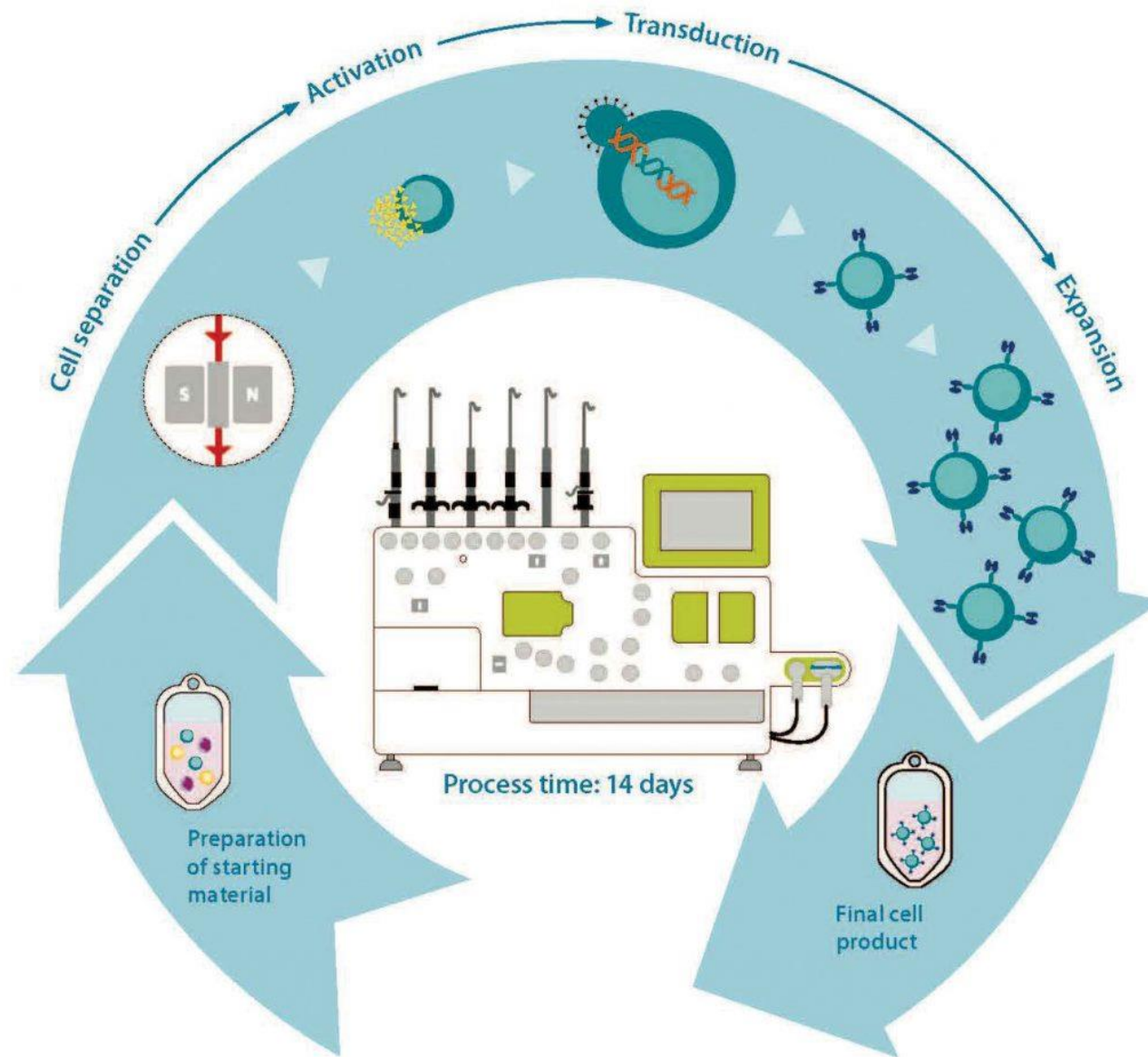
## Autologous Cell Therapy

- > Autologous ATMP's are living cell products and **personal medicine**.
  - Small volumes
  - Small batches
  - Aseptic
- > In Practice:
  - Similar to Hospital or lab compounding pharmacy but with enhanced HVAC and GMP focus
  - Open processes require Grade A conditions with the appropriate surrounding background environment (Grade B for open systems and Grade C or D for isolator based systems)
  - **Segregation for each patient-specific batch to avoid cross-contamination.**
  - Workflows have high space, labor, cost, and logistic demands.



# State of the Art Facilities

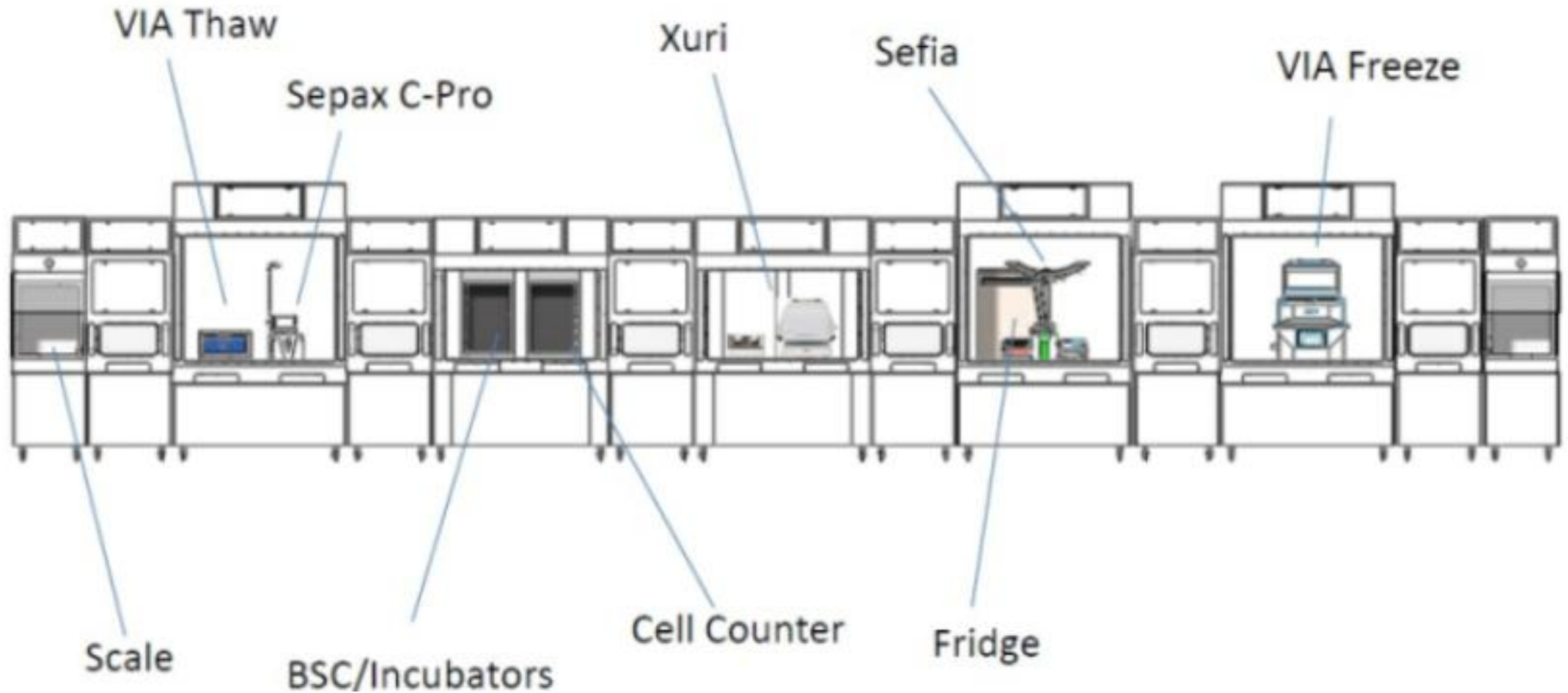
## Autologous Cell Therapy





# State of the Art Facilities

## Autologous Cell Therapy



# Tomorrow's ATMPs

## Natural Selection of ATMP production

- > Breakthrough drugs may treat large populations of incidence and prevalence.
- > Rare disease therapies will only need to treat incidence, but broad categories of treatments will be available.
- > Cell and gene therapy may become cheap and safe enough to be used on less life-threatening conditions.
- > Advanced tissue repair and surrogate tissue organ may drive adhesion based cell culture.

# Future Facilities

## Natural Selection of ATMP production

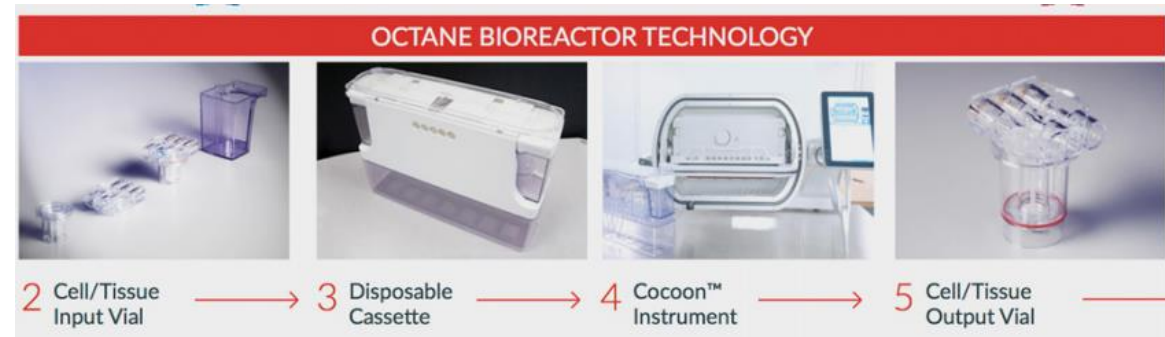
- > Technologies EVOLVE from general technologies to more specific technologies.
- > Sometimes technologies INHERIT traits from separate parent technologies.
- > The technologies that survive are the ones that are best captured by the marketplace.
- > The marketplace is best served by offerings that suit the specific needs of the customer at the lowest cost.

# Future Facilities

Tomorrow and the next few years

> TOMORROW's facility may include

- Prodigy / Cocoon
- 3DBio / Cellink
- Isolators / Clean rooms



# Future Facilities

10 to 15 years out

- > General production in a biotech environment LEADS TO
  - More technical production in a biotech environment
  - Less technical production in any environment
- > Therefore THE FUTURE facility
  - Will include technologies that we cannot recognize
  - Machines that will produce drugs without any human intervention

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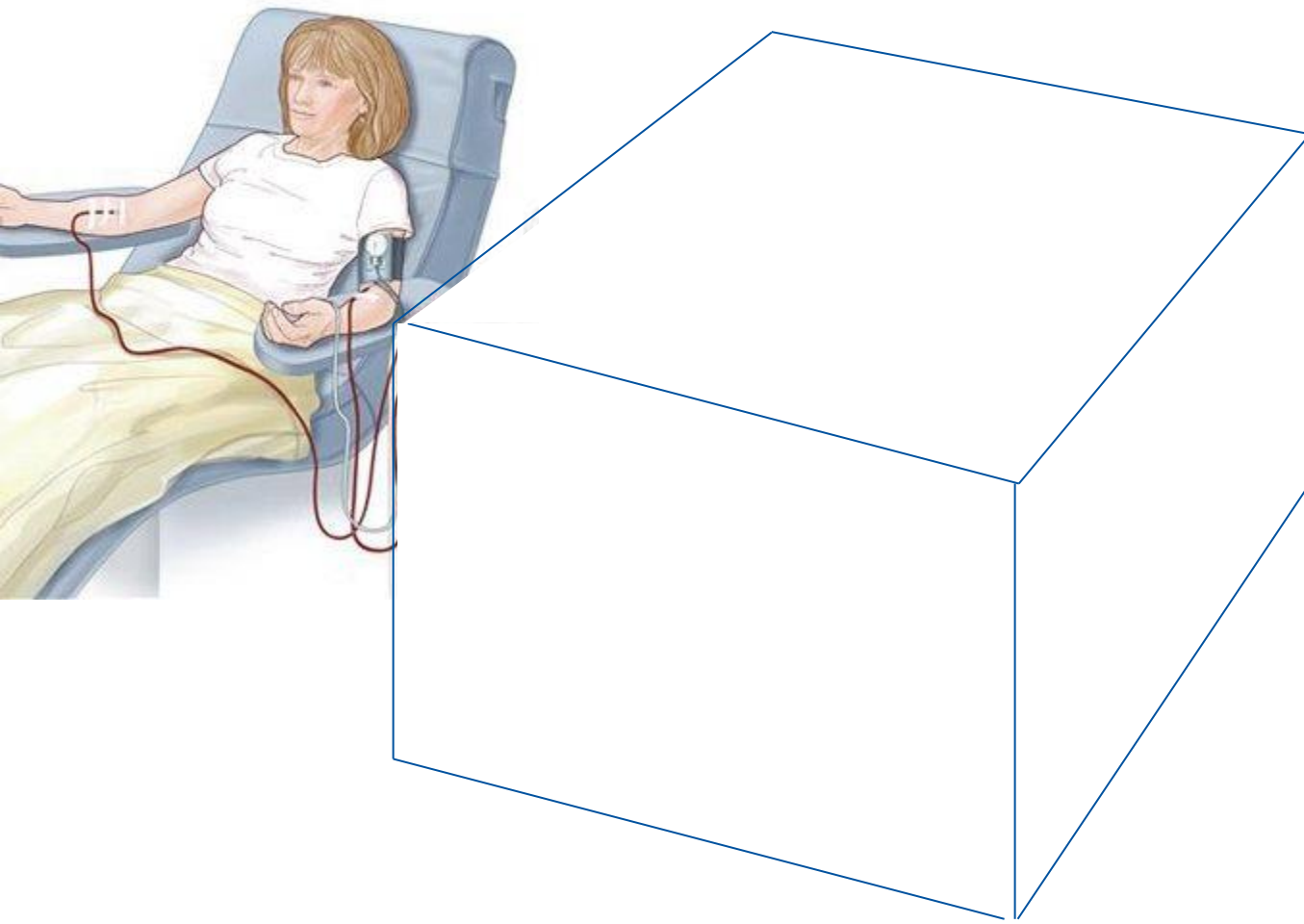
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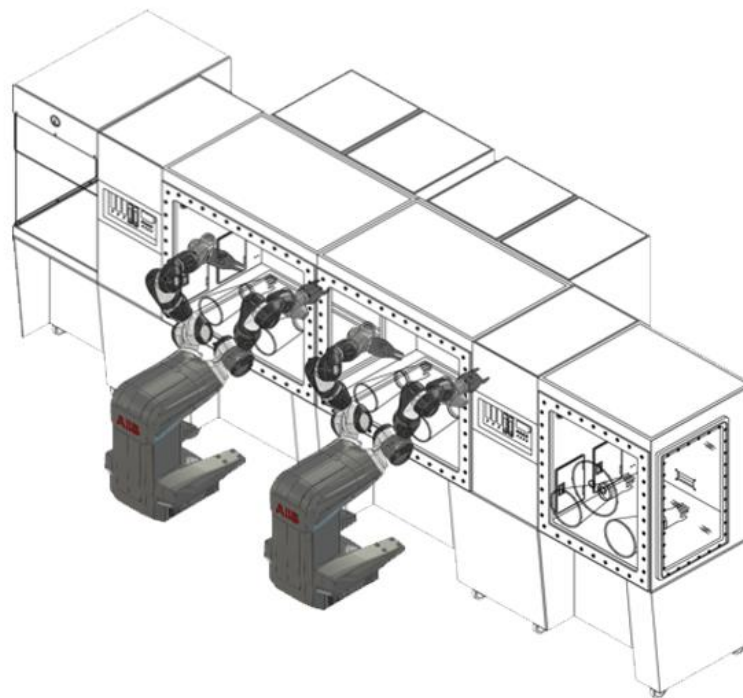
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# Future Facilities

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# Future Facilities

10 to 15 years out

- > The well established IC industry, data warehousing, and biotech will cross-pollinate and the combined industry will INHERIT traits from:
  - Mass production of cells
  - Mass Production of computer chips.
  - Mass warehousing of discrete information.
- > Therefore THE FUTURE facility
  - Will be able to provide customized therapies to large populations
  - Will have global redundant supply chains

# Future Facilities

10 to 15 years out



> GlobalFoundries Fab 8 In Malta, NY

# Bridging the Gap

3 to 10 years out

- > Be prepared for the next big thing
  - Have expert Project Management, Finance, Engineering, Quality, etc. teams
  - PD, tech transfer, manufacturing
- > Don't bank on a successful technology

QUESTIONS?

THANK YOU!