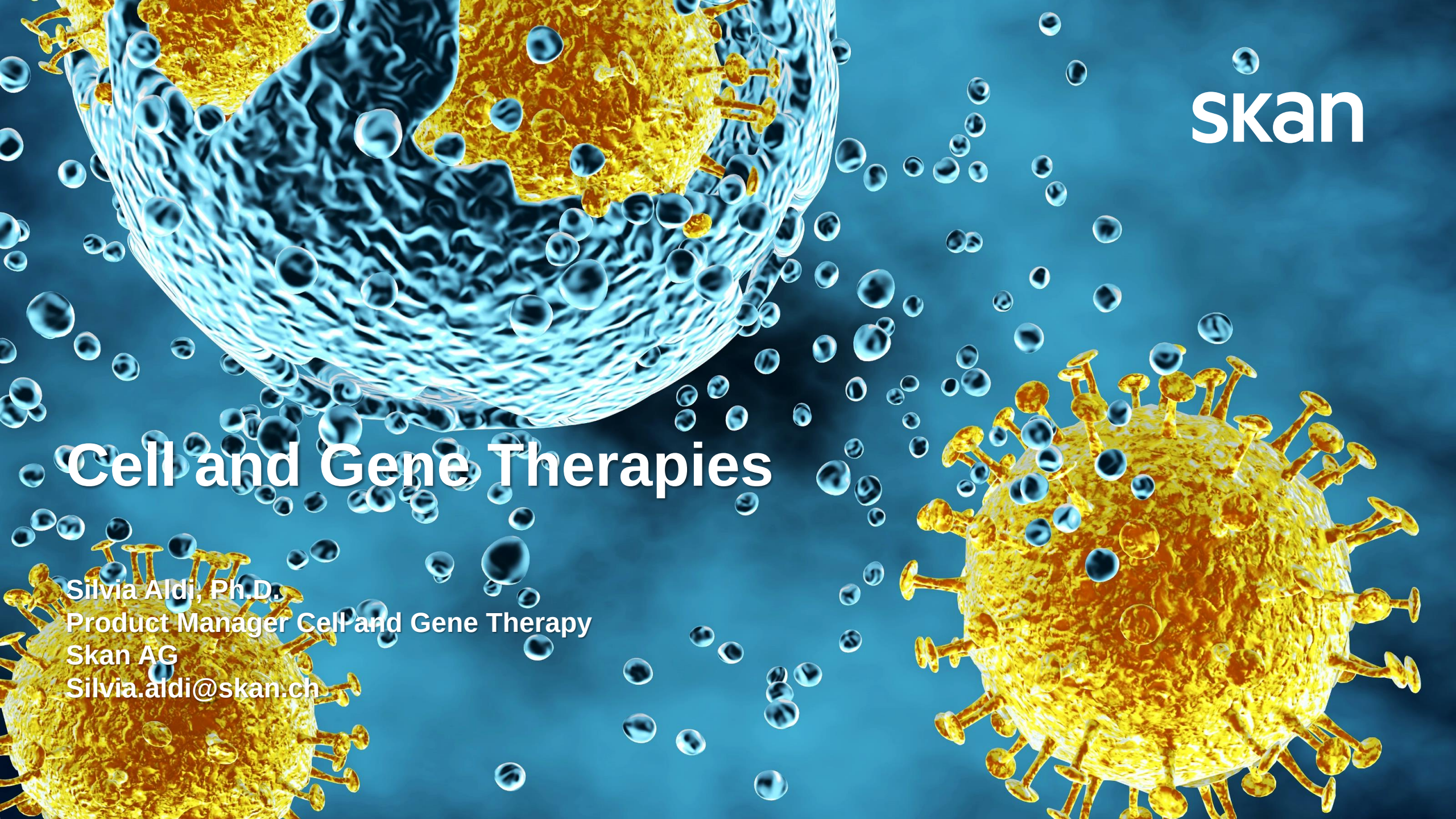

Cell and Gene Therapies

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1. Introduction to ATMPs
2. ATMP manufacturing
3. Case study I: Mesenchymal stem cell-based therapy
4. Case study II: CAR T-cell therapy
5. Fill and finish options for cell and gene therapy products
6. Summary and Conclusions

Regenerative medicine and advanced therapies financing has soared to new heights so far this year

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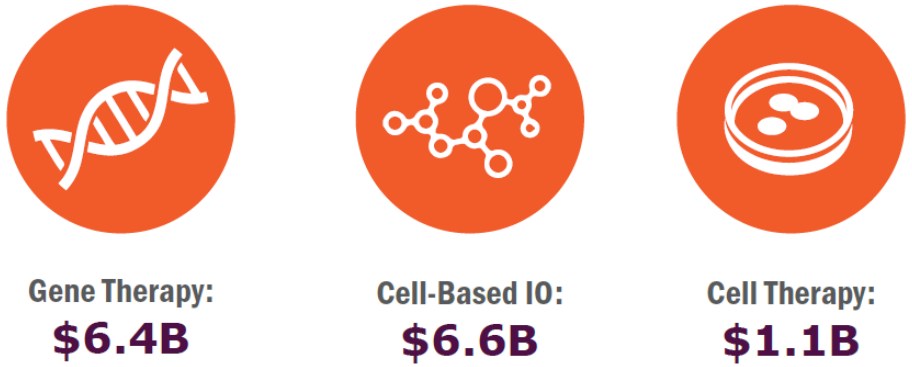

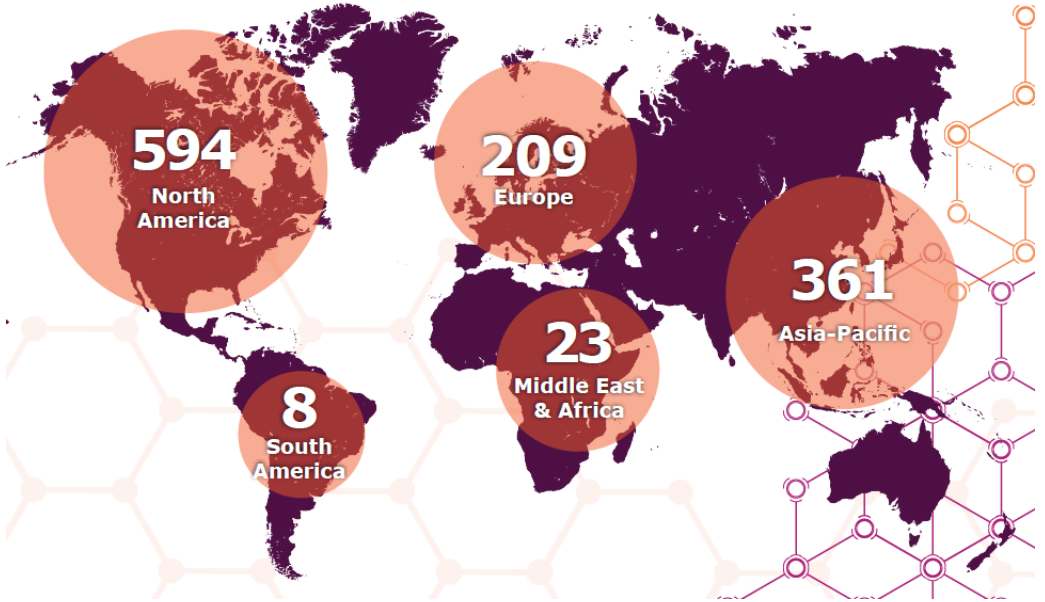

$14.1B raised in H1 2021, a 35% increase from H1 2020

Alliance for Regenerative Medicine H1 2021 report. http://alliancerm.org/wp-content/uploads/2021/08/ARM-H1-2021-Report.pdf

Record Product Approvals Incoming

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- Decisions are expected on 18 regenerative medicine products across 6 geographies
- Bristol Myers Squibb's Breyanzi, bluebird bio and BMS' Abecma, and Mallinckrodt's Stratagraft, all approved by the FDA, and bluebird's Skysona, approved in Europe
- Breyanzi, Abecma, and Skysona, are gene therapy/gene-modified cell therapies, which means 2021 is likely to be a record year for new approvals of this category of products
- Decisions are expected this year on four more gene therapy/gene-modified cell therapy products, with the possibility of seven total approvals which would more than double the previous record of three in 2017

Alliance for Regenerative Medicine H1 2021 report. http://alliancerm.org/wp-content/uploads/2021/08/ARM-H1-2021-Report.pdf

Cell & Gene Therapies: ATMPs

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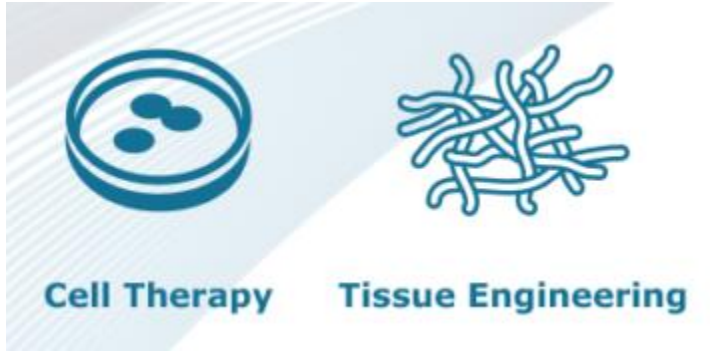
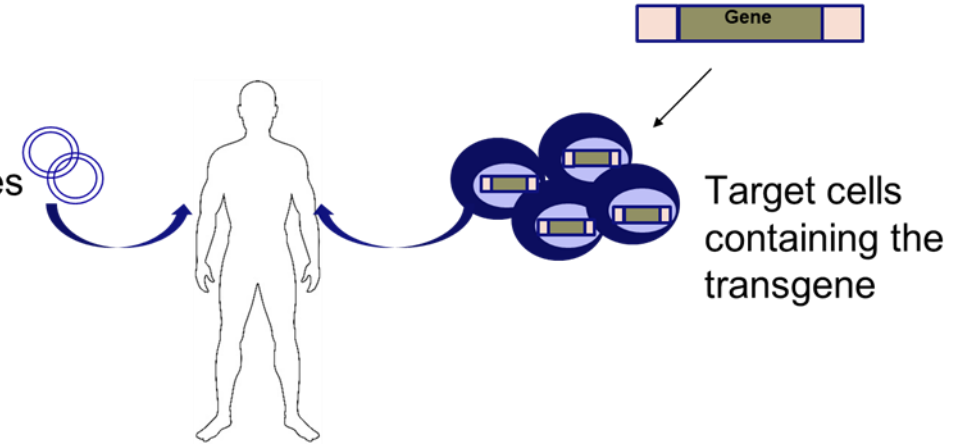
Advanced Therapy Medicinal Products (ATMPs) are medicines that are based on genes, tissues or cells. They represent groundbreaking new opportunities for the treatment of diseases and injuries



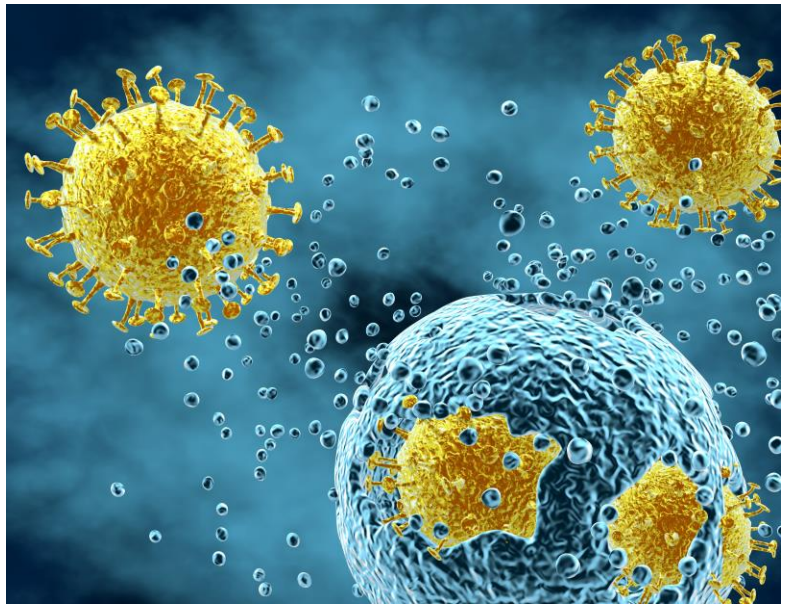
***In vivo gene* editing:** direct delivery to patients:

- Viral vector
- Lipid nanoparticles
- Polymers
- Peptides

***Ex vivo* gene editing:** transgenes are delivered to cells in vitro and gene edited cells are injected into patients



Types of Therapies



- Autologous medicinal products
- Allogeneic medicinal products

- CAR T-cell therapies
- Mesenchymal stem cells-based therapy (MSCs)
- Viral vectors production

- Recombinant proteins/vaccine production
- Monoclonal antibodies/vaccine production

New Therapies

- CAR NK-cell therapies
- Induced pluripotent stem cells-based therapy (iPSCs)

- mRNA-based therapies (not only vaccine)
- Plasmid DNA-based therapies
- Extracellular vesicles, Exosomes

ATMPs developmental manufacturing process

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Starting materials
- ⟶ Patient/donor sample
- ⟶ Viral particles
- ⟶ Bacteria

Upstream process
- ⟶ Cell prep
- ⟶ Cell expansion
- ⟶ Gene editing

Downstream
- ⟶ Cell washing
- ⟶ Cell separation
- ⟶ Final formulation

Final Fill and finish
- ⟶ Fill in final container (glass vials, AT-closed vials, CZ vials, IV bags, bulk and nested)

ATMPs manufacturing

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Final Fill and finish
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Target to bring any open process into ISOLATORS

Novel therapies: manufacturing challenges

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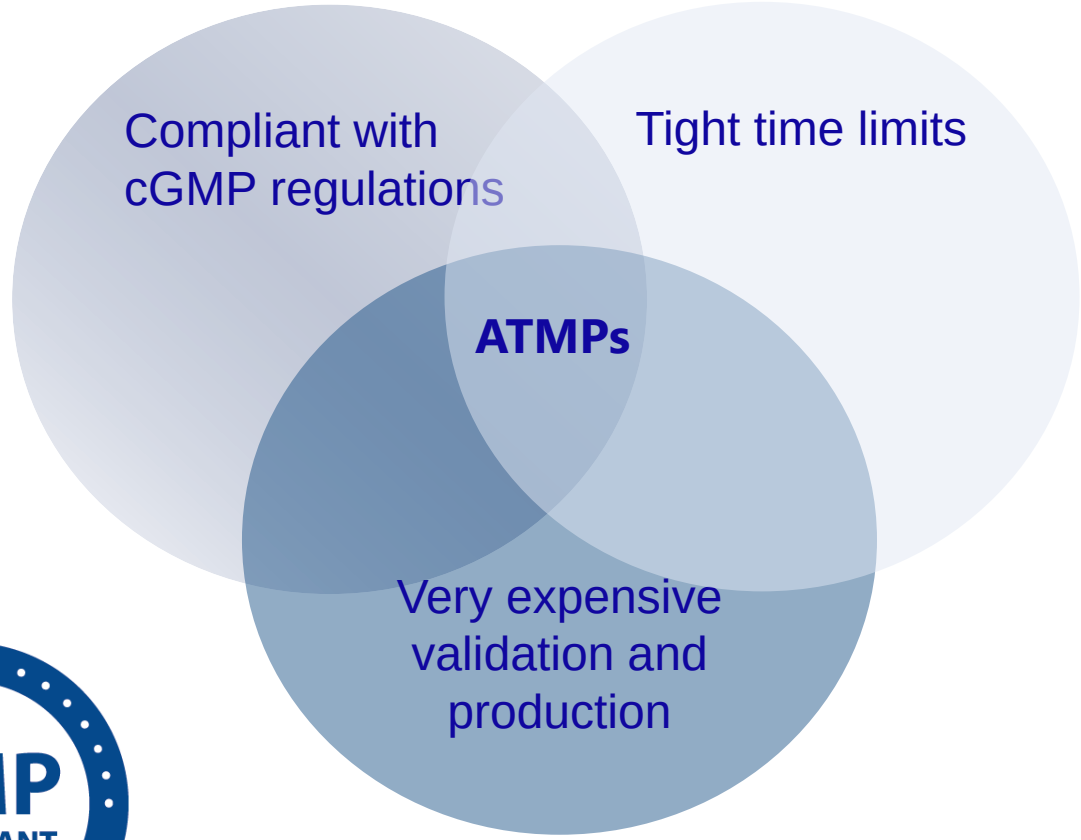
- Methodology transfer from biosafety cabinets to high aseptic work environments (isolators)
- Many different manufacturing processes/methodologies
- Wide variety of lab equipment
- Cell Therapies cannot be sterilized – high risk of contamination by open operations and growth promoting media
- Short delivery times
- Scaling-up/Scaling-out
- Stringent regulatory requirements



The complexity of Up- and Down-stream Laboratory Equipment

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Up-stream equipments:

- Automated cell thawing system
- Centrifuge
- CO2 incubator
- Inverted Microscope
- Electroporator
- Plasma extractor
- Rocking incubator/Bioreactor
- Tubing Welder
- Tubing sealer
- Orbital shaker
- Weight balance scale

Down-stream equipments:

- ⟶ Automated closed systems for cell processessing
- ⟶ Tangenzial flow filtration TFF
- ⟶ Immunomagnetic beads separation
- ⟶ Isolators for aseptic filling

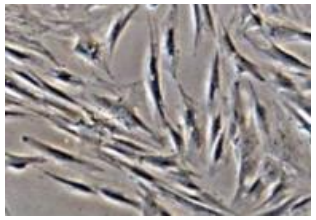
Customers’ needs

- Aseptic controlled environment to process autologous and allogeneic therapeutics for pre-clinical and human clinical use with highest sterility assurance
- Fast transfers of biological materials in various containers (cell culture flasks, conical tubes, cryovials, bags, etc.)
- Gene manipulation by viral transduction / electroporation
- Fast and ultra-rapid decontamination cycles
- Operator and patient safety
- Acceptance from cGMP regulatory authorities (US FDA, EU EMA and other global agencies)

Examples of Cell and Gene Processes produced with isolator technology

Case Study I

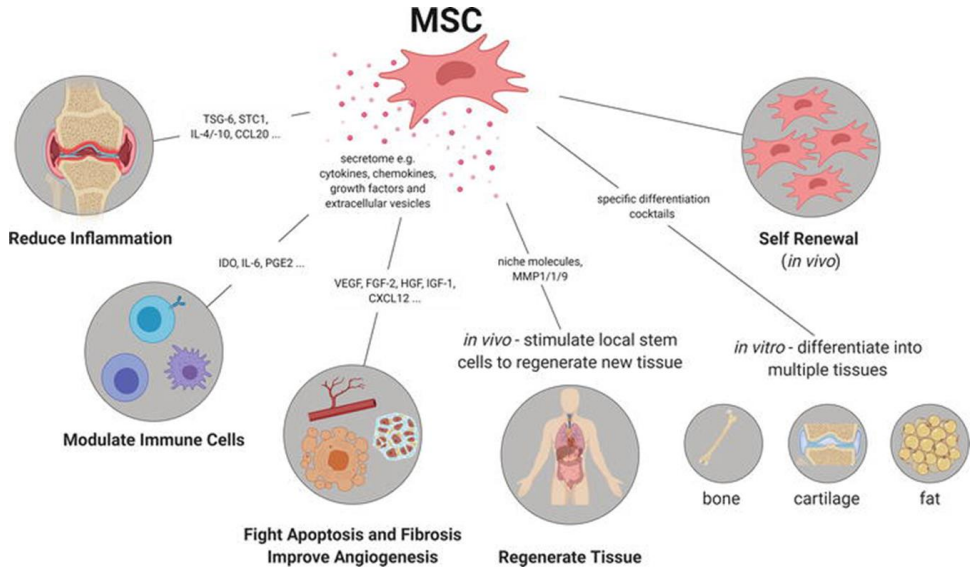
Example of mesenchymal stem cell (MSCs)-based therapy



MSC

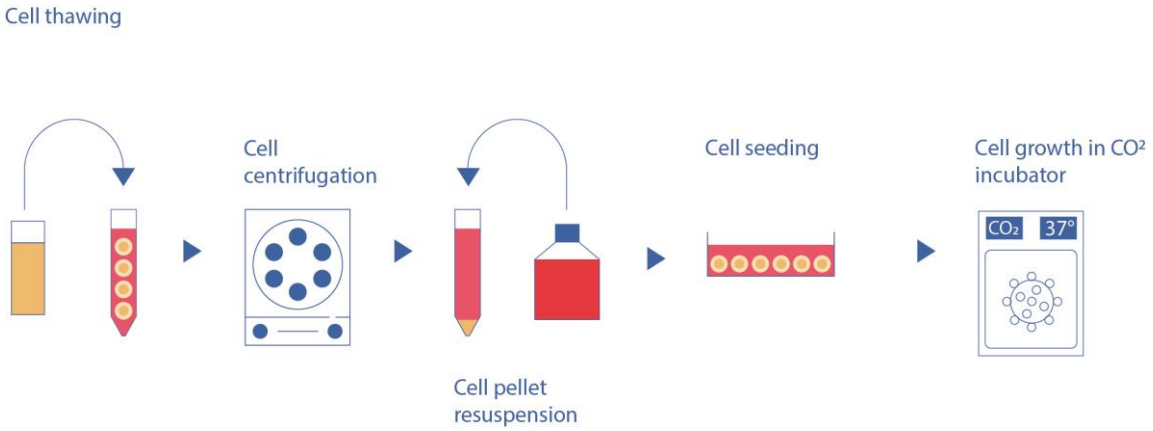
Origin: bone marrow, adipose tissue, umbelical cord

Clinical Use: for treatment of immune disorders (post-transplantation immune responses), tissue repair (damaged by stroke), cardiovascular disorder (induced ischemia), neurological and rheumatological disorders (multiple sclerosis and osteoarthritis)

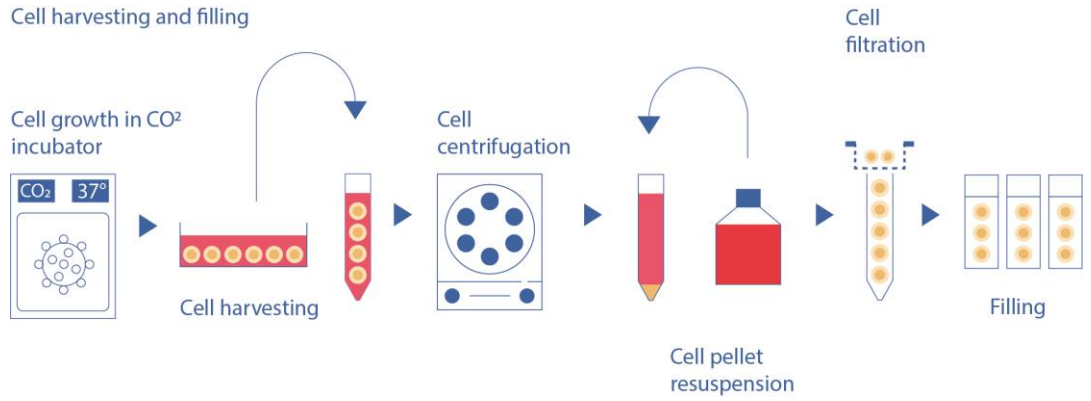


https://www.intechopen.com/chapters/69881

Inoculum Cell Culture



Cell Harvesting



Lab equipment integration and isolator design

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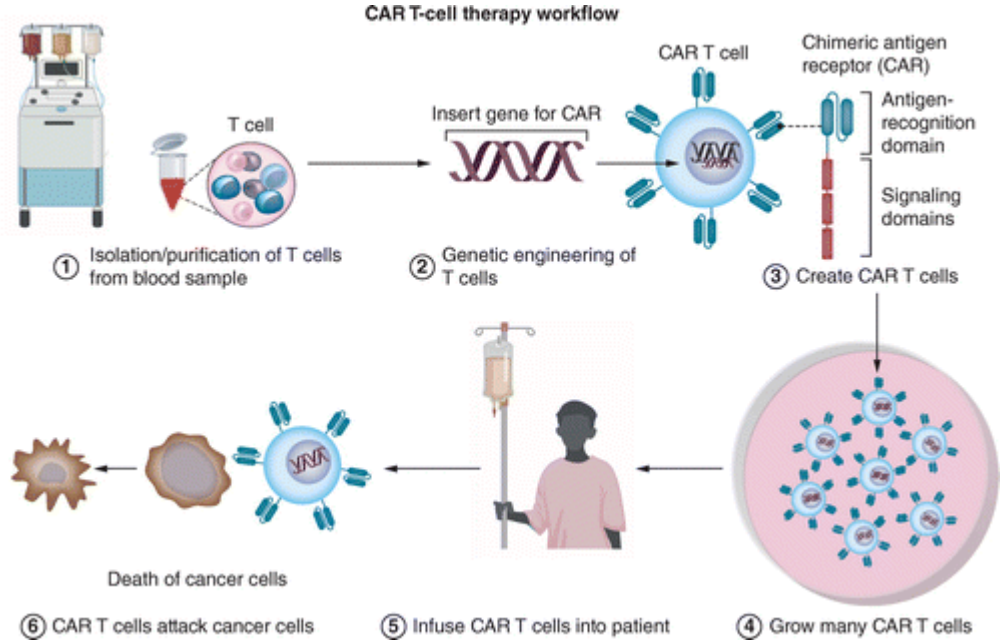
Cellana-M solutions

- Rapid Transfer Airlock
- Customized fast decon cycles
- CO_2 Incubator
- Centrifuge
- Customized shelves

Case Study II

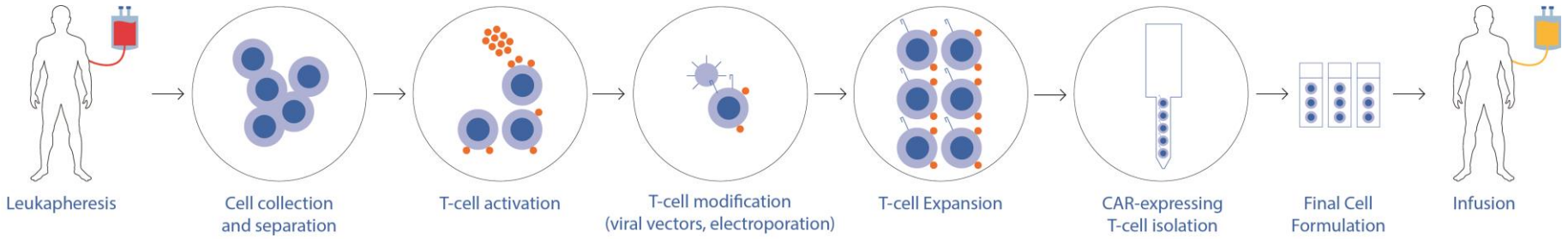
Case Study II
Chimeric Antigen Receptor (CAR) T-Cell Therapy: Process Overview

- **Origin**: T-cells are specific immune cells floating in the blood (cells develop in the thymus gland, T-cells)
- From donors (**allogeneic**) or patients (**autologous**)
- **Biological specifications**: Chimeric Antigen Receptor (CAR) T-cells are genetically manipulated *in vitro* to target specific cancer antigens expressed on cancer cells to treat lymphomas, leukemia

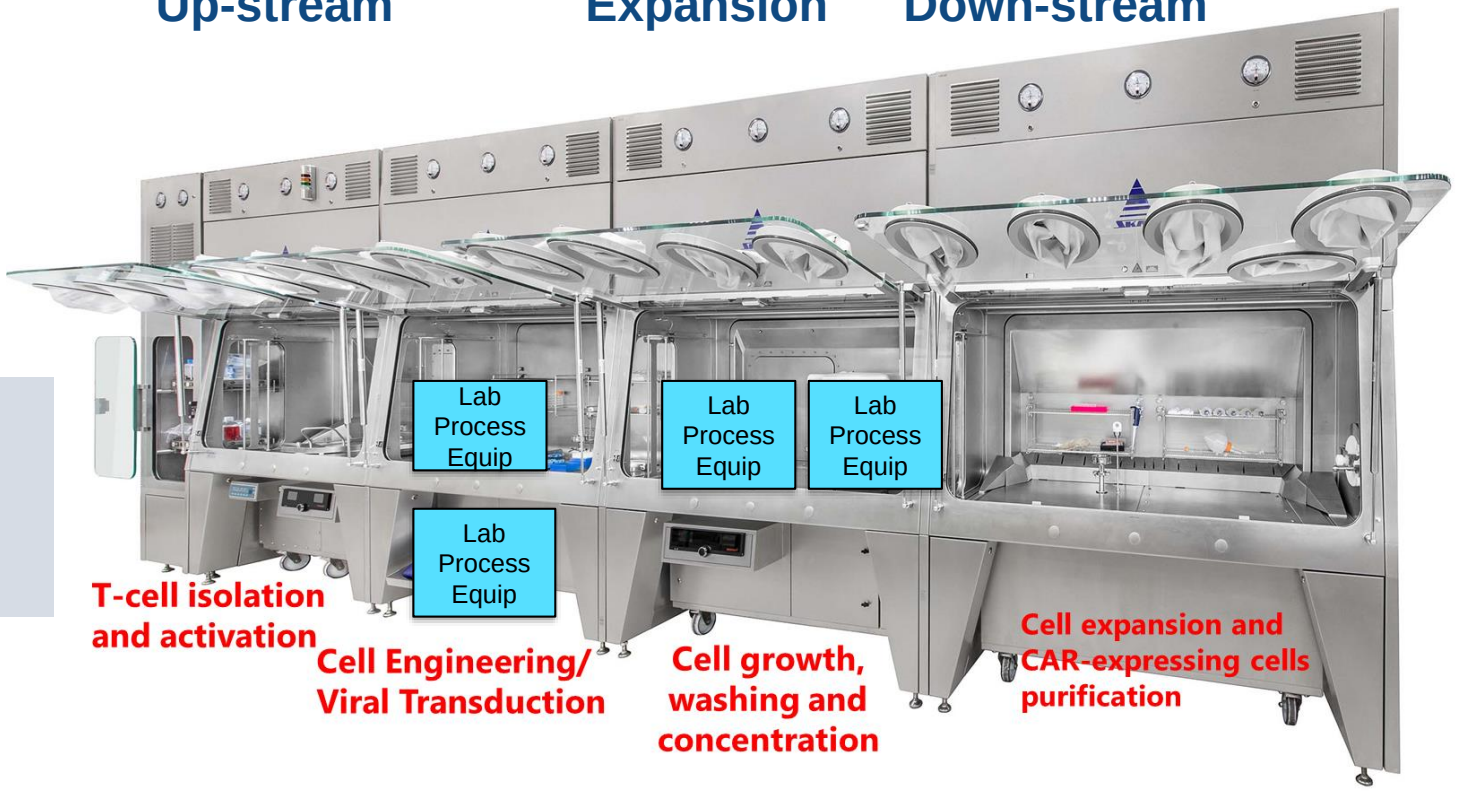


https://www.nature.com/articles/s41434-021-00246-w.pdf

CAR T-cell Manufacturing Process in Isolator



Up-stream **Expansion** **Down-stream**



Cellana-L

- High Flexibility
- Interchangeable modules
- Scalability and Versatility

Automated or Manual ATMPs filling

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Key features

- Filling technology minimizing the contamination risks
- Containers must be resistant to cryopreservation agent (DMSO)
- For safe cryogenic storage at -80°C and in the nitrogen liquid tank

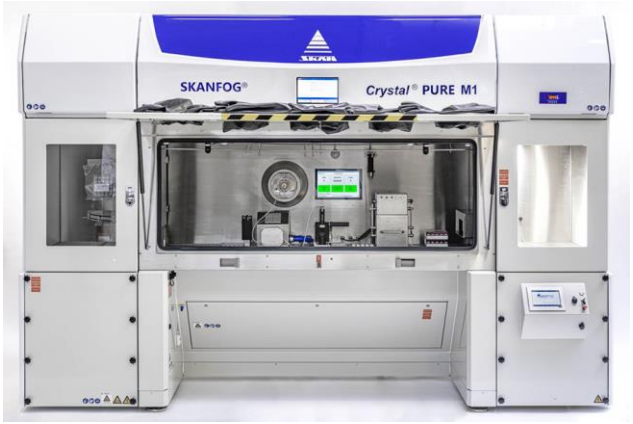
AT-Closed Vial® Technology

ASEPTIC TECHNOLOGIES

https://www.aseptictech.com/

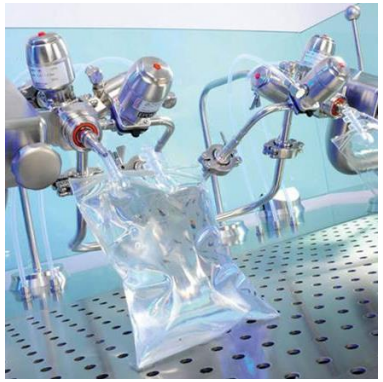
- ⟶ Ready-to-fill closed vial
- ⟶ Scalable filling equipment
- ⟶ Full validation package
- ⟶ Particularly suitable for Cell and Gene Therapies

Crystal PURE M1



Cell and Gene Isolators

Cellana Crystal L-1



IV Bag Filling-small scale

Summary and Conclusions

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- As lab-based processes are introduced for clinical and GMP production, increased controls are required
- Isolator technology is a natural next step to increase process and quality control
- Challenges in ergonomics and transfers must be addressed, including deco. practices and equipment integration
- End goal is not necessarily perfection, but improved quality

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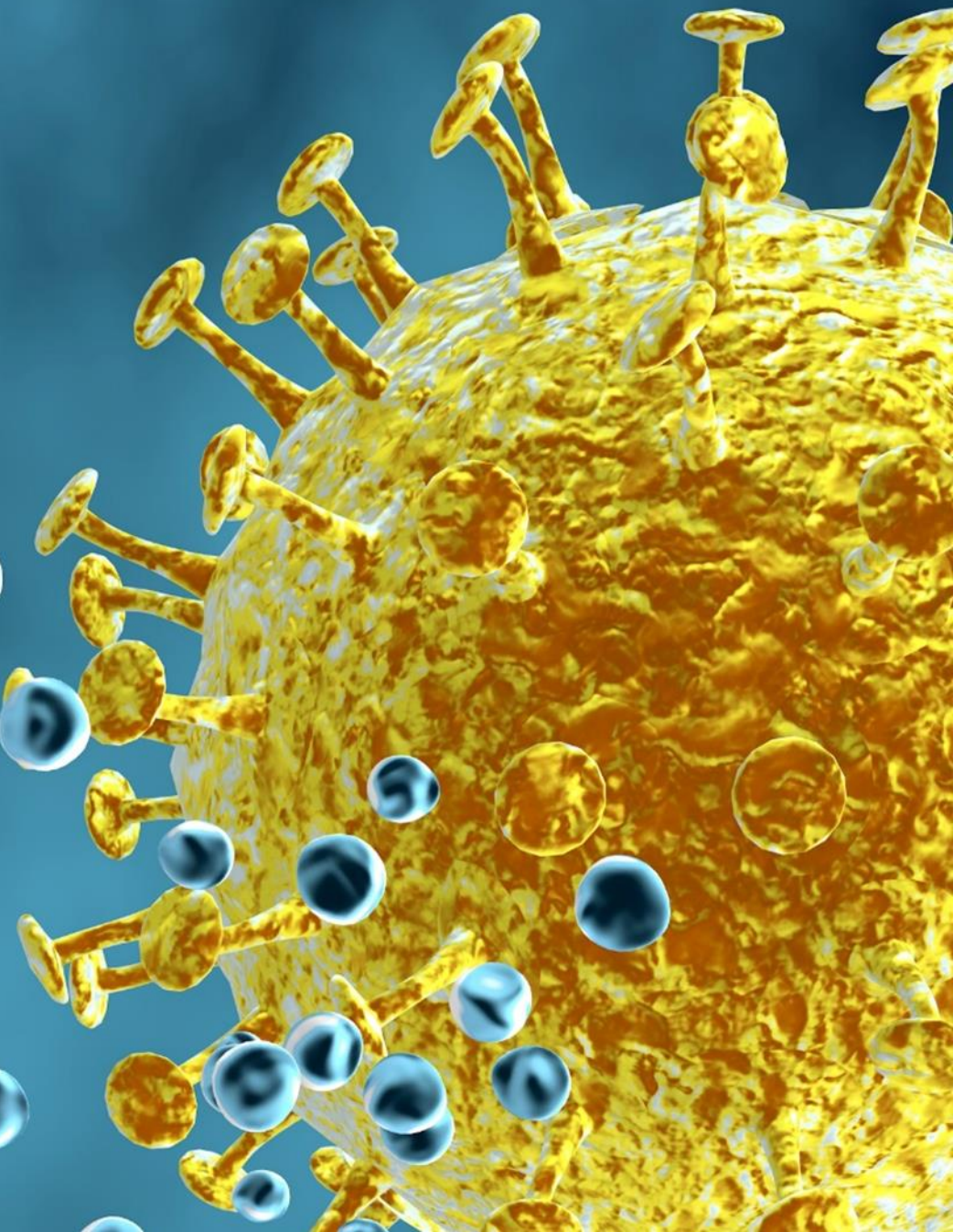
Thank you for your time!



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