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IN SUCCESS

AGENDA
Cryogenic Solutions Distributor Meeting

Springfield, Missouri, USA

23 – 25 April, 2024

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WELCOME TO
SPRINGFIELD

DATE:

Tuesday 23 – Thursday 25 April, 2024

LOCATION:

Hotel Vandivort. Springfield, Missouri, USA

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SPRINGFIELD
FUN FACTS

04

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04

If you have a cassette tape, it was likely made at ***National Audio Company here in Springfield.***

This is the ***only producer of magnetic tape for cassettes in the United States****, and one of just a handful of cassette manufacturers left in the country.*

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03

*Depending on your google results, Springfield is home to **the world's largest (or second largest) fork!***

*Perhaps bested in size in 2022, but at **35 feet tall**, it's still very large – and unique, paying homage to **Springfield's exciting dining scene.***

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02

Did you know Springfield is considered the ***birthplace of Route 66****?*

As a result, the Queen City is a popular destination for history-buffs and classic car enthusiasts.

Hosting the ***Route 66 Festival each August,*** *events center around the* ***History Museum on the Square, original Steak ‘n Shake drive-in with curbside service,*** *and Route 66 Rail Haven motel* ***where Elvis once stayed.***

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01

*The **nation's first one-on-one quick draw duel** took place on Springfield's town square between J.B. "Wild Bill" Hickok and Davis K. Tutt, on July 21, 1865.*

*What began as an argument over gambling debts turned into a **dual to the death**, when Tutt seized a prize watch of Wild Bill's as collateral during one of their card games.*

At around 6pm, the two men went for their guns, aimed at each other, and fired. Tutt missed. Hickok didn't.

With You This Week – The Azenta Team

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Robin Vacha
SVP, Global Operations

Gil Edwards
Sr. Director, Cold Storage

Amy Kuhn
Director, Channel Sales

Brian Gleason
Channel Manager, Cold Storage

Sean Cantrell
Director, Automation Engineering

Brandon Courtois
Senior Operations Manager

Olga Bukatova
Assoc. Director, Business Dev., Cell & Gene Therapy

Erica Waller
Sr. Product Manager, Cryogenic Storage & Automation

Charlie Knowles
Sales Applications Engineer

Caroline Mackinnon
Sr. Commercial Marketing Manager

Erik Rapp
Sr. Account Executive, Digital Sample Management Solutions

Tuesday 23 April

*Subject to change

TIME	AGENDA	SPEAKER	LOCATION
01:00 – 02:00 PM	*Arrival & Welcome Lunch*	-	*Hotel Vandivort, Cornerstone*
02:00 – 02:45 PM	Introduction to Azenta	Robin Vacha	
02:45 – 03:30 PM	Introduction to Cryopreservation	Gil Edwards	
03:30 – 04:30 PM	Application/Market Spotlight – Cell and Gene Therapy	Olga Bukatova	
Evening Reception **Gates open 05:05PM* **Game starts 06:05PM*	*Let's Play Ball…* MiLB: Springfield Cardinals v Arkansas Travellers	Hammons Field ***We look forward to hosting you in Suites 29 & 30, at Hammons Field. Please pick up your ticket from Caroline ☺*** *Access is via Gate 3. The ballpark is a 20minute walk from Hotel Vandivort.* *All-American ballpark food & drinks will be provided within our exclusive suites, as we enjoy the baseball game.* Hammons Field is a CASHLESS venue, and operates a CLEAR BAG policy. *Check out: Know Before You Go*	

Wednesday 24 April

**Subject to change

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TIME	AGENDA	SPEAKER	LOCATION
08:00 – 08:15 AM	Day One Review & Discussion	Brian Gleason	Hotel Vandivort, Cornerstone
08:15 – 10:35 AM	Product Line Training: • High-Efficiency Freezers & Product Updates • Automated Freezers • CryoPod & Filling Station	Gil Edwards, Brian Gleason, Sean Cantrell Erica Waller, Charlie Knowles	
10:35 – 10:45 AM	*Break*	-	
10:45 – 11:15 AM	Cryo Software Demonstration	Charlie Knowles	
11:15 – 11:45 AM	FreezerPro Integration	Erik Rapp	
11:45 – 12:20 AM	*Lunch*	-	
12:20 – 12:50 PM	Liquid Nitrogen Supply Systems	Gil Edwards	
12:50 – 01:20 PM	Racking Systems, Bags, Cassettes & Frames	Zach Carlson, Brooklyn Tool	
01:20 – 01:30 PM	*Refresh*	**Transport is organized to the Springfield Facility at 01:30 PM prompt.*	

Wednesday 24 April

**Subject to change

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TIME	AGENDA	GROUP LEADERS	LOCATION
01:30 – 06:00 PM	Manufacturing Site Facility Tour Hands-On Training & Demonstrations • High-Efficiency Freezers • Automated Freezers • CryoPod & Filling Station • Troubleshooting & Repair	• Gil Edwards, Brian Gleason • Erica Waller, Erik Rapp • Charlie Knowles • Brandon Courtois	Azenta Life Sciences **Transport is organized to the Springfield Facility at 01:30 PM prompt.*
GROUP 1	**Start with HE Freezers*	Jeff Kadyk, Daniel Morris, James Meggs, Ralph Bell, Brent Kokhede, Robin Vacha	
GROUP 2	**Start with Automated Freezers*	Patrick McCann, Bob Wood, James Martell, Carleton Sherman, Steven Fyfe, Caroline Mackinnon	
GROUP 3	**Start with CryoPod & Filling Station*	Larry Morgan, Tony Gandy, Steve Ivie, Alexander Lima, Rebecca Ginther, Juan Bello	
GROUP 4	**Start with Troubleshooting & Repair*	George Koutris, Rod Harnden, Kelly Grimmett, Zach Carlson, Amy Kuhn, Olga Bukatova	
06:00PM	Mill Tour & Evening Dinner	The Ozark Mill **Transport is organized to the Ozark Mill, with return to Hotel Vandivort post-dinner.*	

Thursday 25 April

*Provisional agenda, subject to change

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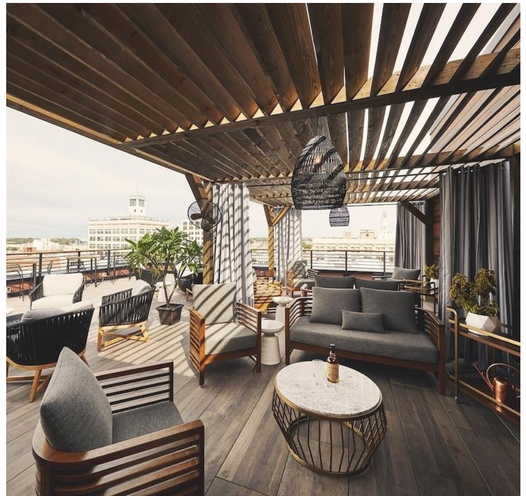
TIME	AGENDA	SPEAKER	LOCATION
08:00 – 08:15 AM	Day Two Review & Discussion	Brian Gleason	Hotel Vandivort, Cornerstone
08:15 – 08:45 AM	Independent Monitoring – Set-up & Operation	Gil Edwards, Sean Cantrell	
08:45 – 09:30 AM	Value Propositions, Competitor Analysis & Differentiators	Gil Edwards, Erica Waller, Charlie Knowles	
09:30 – 10:15 AM	Lead Finding & Qualification – Target Customers, Personas & Demographics	Gil Edwards, Erica Waller, Charlie Knowles	
10:15 – 10:45 AM	Target Market Focus – Translation & Transfusion	Gil Edwards	
10:45 – 11:30 AM	Grow Together – Business Reviews, Resources, Tools & Collateral	Amy Kuhn, Caroline Mackinnon	
11:30 – 11:45 AM	Summary & Review	Gil Edwards, Amy Kuhn, Brian Gleason, Charlie Knowles	
11:45 – 12:45 PM	*Closing Lunch*		


The
OZARK
MILL


Springfield




BIRTHPLACE
OF
ROUTE
66
SPRINGFIELD
MISSOURI
★ USA ★

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Welcome and Azenta Overview

Robin Vacha
SVP, Global Operations
April 2024

OUR PURPOSE

Enabling Breakthroughs Faster

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AT A GLANCE

A Well-Established Global Life Sciences Leader

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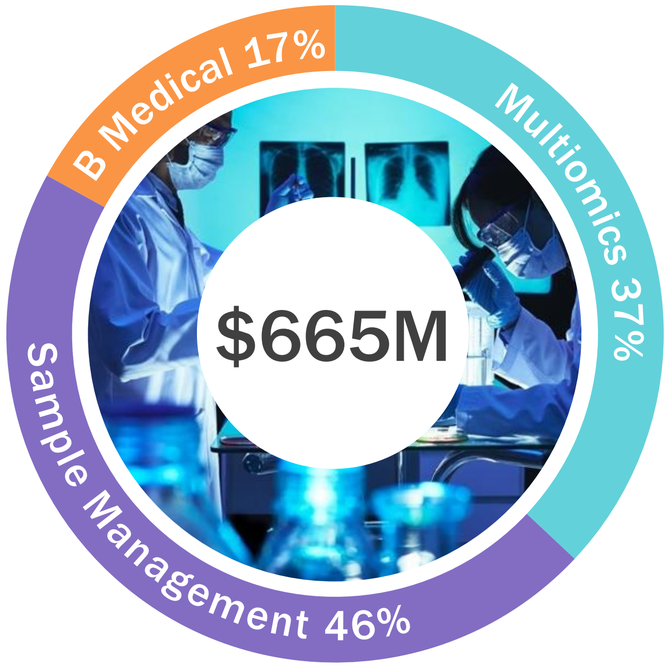
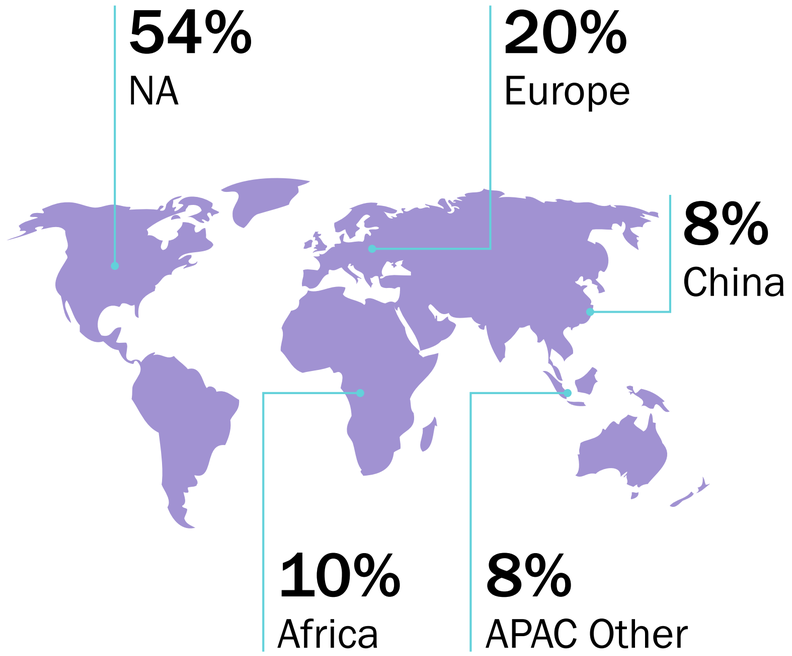
FY'23 Revenue by Segment



Revenue by Region



Key Metrics

- **~13,000** Customers
- **20 of 20** Top Pharma/Biotech
- **>150** Countries
- **1 in 3** employees is a scientist/engineer
- **1 Billion +** Samples Supported

Data as of FY'23 (12 months ended 9/30/23)

Portfolio Offering Examples

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Automated Stores

SampleStore™

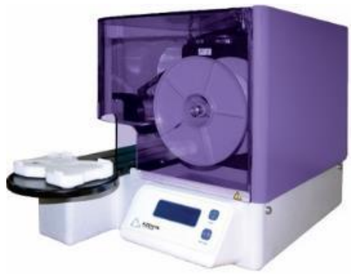
BioStore™

BioStore™ III Cryo

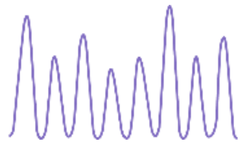
Sample Repository Solutions

B Medical Systems

Consumables & Instruments



Genomic Services



Sanger Sequencing

Gene Synthesis

Next Generation Sequencing

10+ Years Building a Leading-Edge Life Sciences Company

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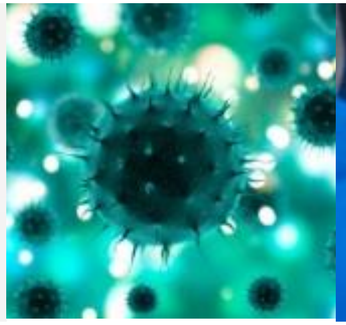

2013-2014
- Matrical
- BioCision 1

2015-2016
- FluidX
- BioStorage Technologies

2017-2018
- BioCision 2
- PBMMI
- FreezerPro
- 4titude Ltd.
- BioSpeciMan

2019-2020
- GENEWIZ
- RURO
- Trans-Hit Biomarkers

2021
- Abeyance

Azenta Life Sciences Launch

2022-2023
- Barkey
- B Medical
- Ziath

Automated Stores *Consumables & Instruments* *Sample Repository Solutions* *Genomics Services* *Temperature-Controlled Storage Solutions*

Highly Differentiated Sample Management Portfolio Provides Comprehensive End-to-End Solutions

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Sample / Patient

Find

Sample Sourcing

Format

Consumables & Instruments

Store / Manage

Storage, Automation and Logistics

Measure

Genomics and Analytical Services

Inform

Data and Informatics

Drug Development / Physician

ENABLING BREAKTHROUGHS FASTER

Our Customers are at the Forefront of Scientific Breakthroughs from Discovery to Delivery

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33
Nobel laureate labs use Azenta

27,500
Citations in scientific journals

20 of 20
Top pharma / biotech served by Azenta

33 of 50
Top customers purchase across multiple business lines

13,000+
Total customers served by Azenta

Academic / Other

HARVARD UNIVERSITY
UNIVERSITY OF CAMBRIDGE
CHDI FOUNDATION
VANDERBILT UNIVERSITY
biocentre
NIH
CORNELL UNIVERSITY FOUNDED A.D. 1865
LUPUS RESEARCH ALLIANCE

Pharma / Biotech

GSK
Catalent
AskBio
sanofi
AGC Biologics
BIOMARIN
AstraZeneca
ENDPOINT HEALTH™
cytiva
iSPECIMEN

Healthcare / Clinical

Dana-Farber Cancer Institute
MAYO CLINIC
Children's Hospital of Philadelphia
Mount Sinai
Boston Children's Hospital
Cleveland Clinic

Meaningful Discoveries in Life Sciences Start with High Quality Samples. Billions of them…

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Our Opportunity

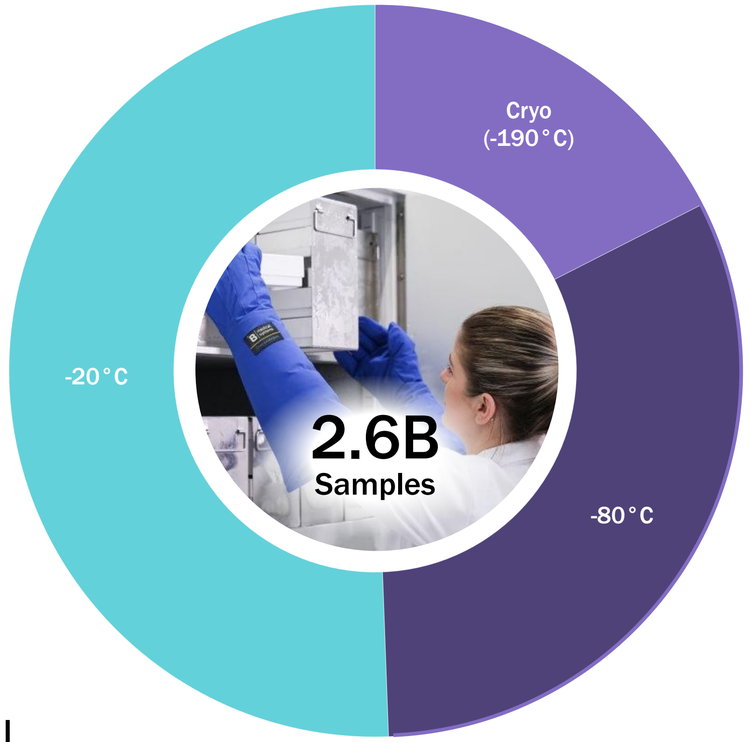
~24 Billion samples are stored cold globally

~1 Million upright manual freezers

~2.6 Billion samples are generated each year that must be stored cold

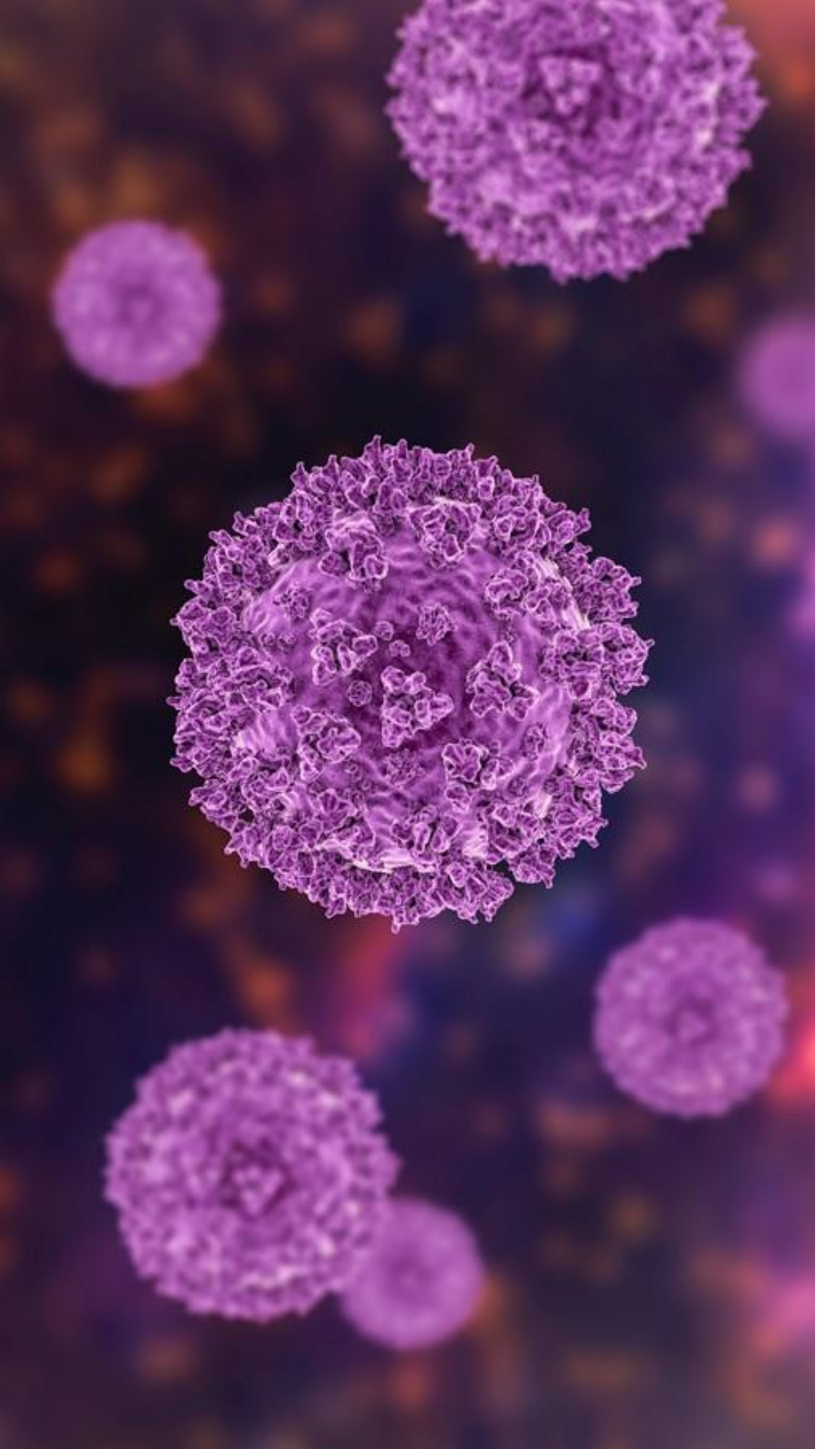
~50% or ~1.3B of Samples Generated Each Year Require Ultracold Storage

Samples Generated per year by Storage Temperature



~50%
or ~1.3B

Note: Metrics include research and clinical trial samples only
Source: ClearView and Company analysis



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Q&A

Azenta – A Leading, Differentiated Life Sciences Company

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Portfolio Positioned to Capitalize on Market Trends

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Trend Toward Outsourcing R&D

>50%

Biopharma R&D outsourced today

Quality Sample Collections are Essential

2X

Growth expected in outsourced samples in 5 years

Demand for Automated Temperature Control

>45%

2023 FDA drug approvals require temp. control

Cell & Gene Therapy, the Next Frontier

~2K

Cell & Gene Therapy active trials today

Novel Modalities Driving Demand for Sample Products & Services

>20%

Growth expected in patients treated by cell therapies

~$11B TAM Provides Significant Opportunity

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Total Addressable Market

The Near-Term Opportunity

~$11B Market
- Large, diverse market

<10% Market Share
- Small share in a large market

Low-Single Digit
- Market growth rate FY'23-26

WE EXPECT TO OUTGROW THE MARKET IN ANY ENVIRONMENT

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Introduction to Cryopreservation

North America Distributor Meeting. April 2024

Gil Edwards, Sr. Director, Cold Storage

Cryo-preservation

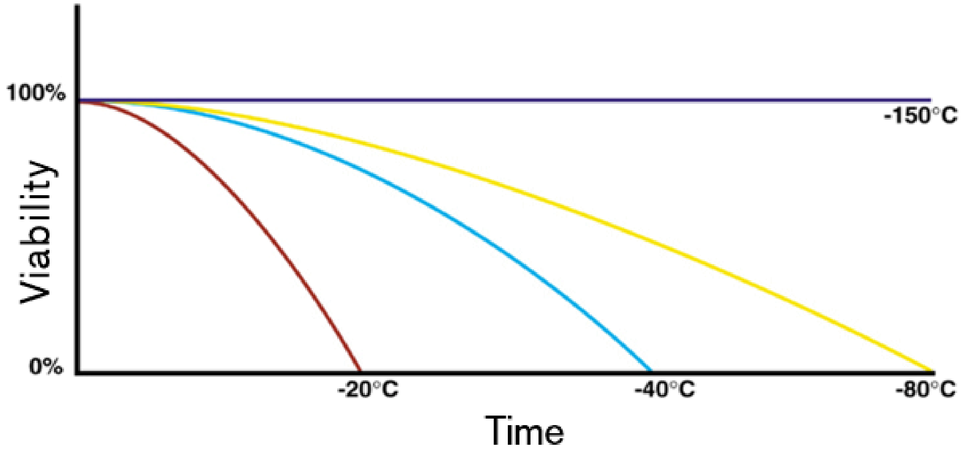
Principles and importance

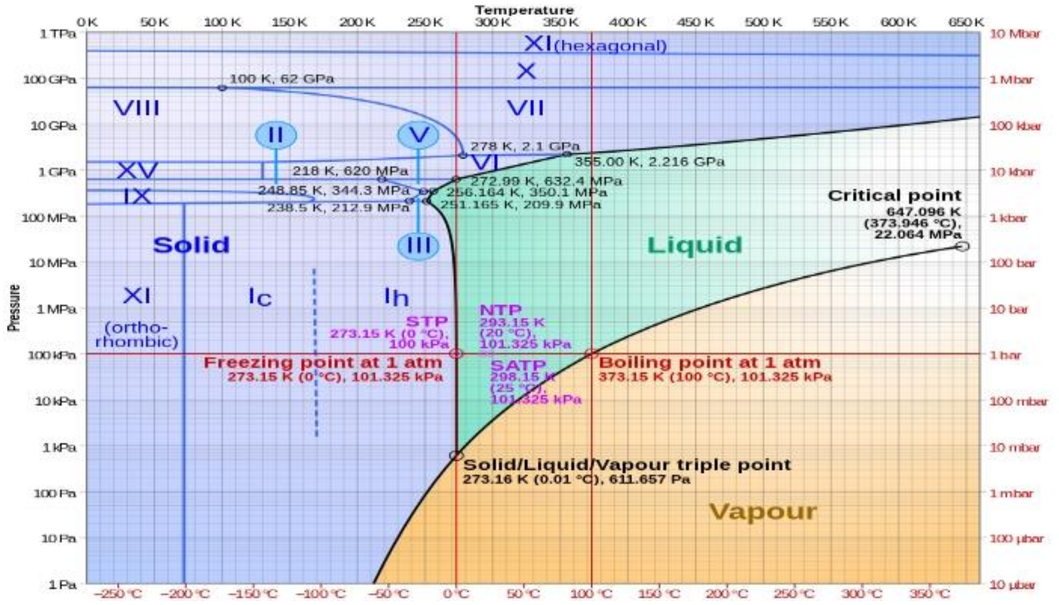
PRESERVATION OF LIVING CELLS AND TISSUES AT VERY LOW TEMPERATURES FOR AN EXTENDED DURATION OF TIME.

- Glass Transition temperature (Tg) = -135 °C
- Liquid nitrogen (LN2) provides cooling to -196 °C
  - Cryo-preservatives (CPAs) used for sample protection at low temperatures.
- Typical samples: Blood cells, stem cells, oocytes, sperm, embryos, forms of medication

Significance

- Sample quality for pharmaceutical research, biotechnological industries or in medical transplantation
- **Sample recovery and viability is imperative**





Transient warming and Sample Viability

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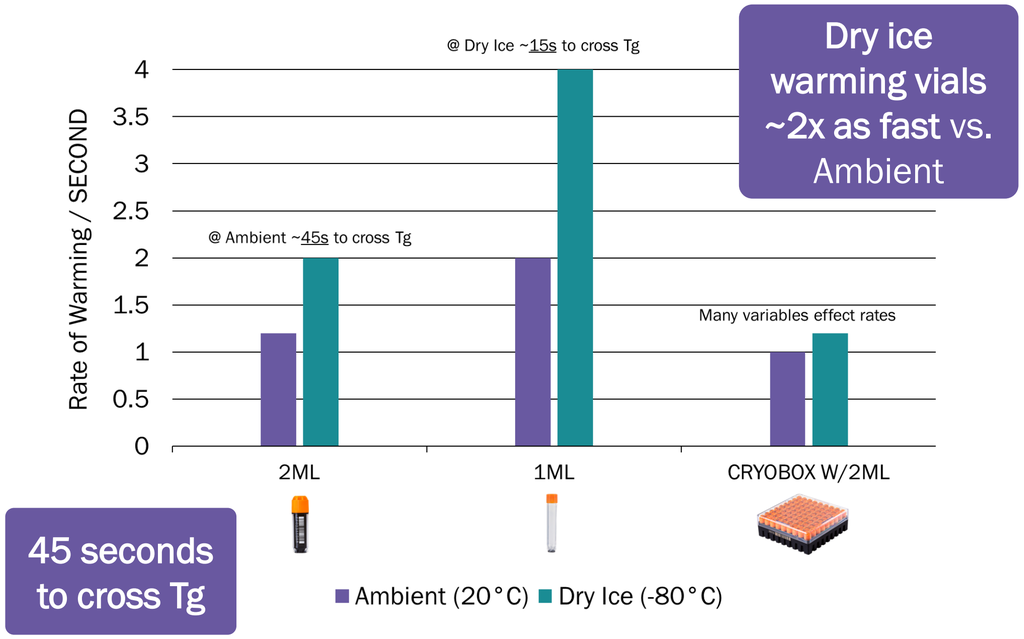
A BRIEF EXPOSURE OF CRYOPRESERVED PRODUCT TO TEMPERATURES ABOVE THE CRITICAL STORAGE TEMPERATURE.

How quick do samples warm? How long is 'Transient'?

- **Conduction and Convection**

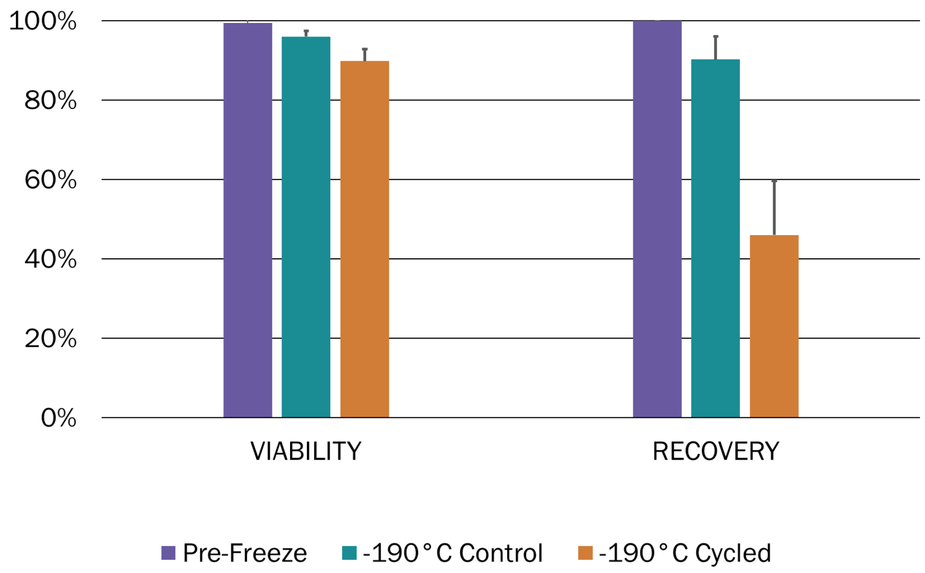


Viability and recovery of mesenchymal stem cells pre-freeze and post-thaw

Control pre-storage at cryo temperatures

3 months at -190°C with no exposures

3 months at -190°C with 20 exposures to -110 °C



Liquid Nitrogen (LN_2)

The “Fuel” for cryogenic refrigeration

Liquid nitrogen is consumed as it “cools” the freezer

- The more heat you put into the system, the more LN2 is consumed
- Biggest source of heat is incurred during sample access
- Other sources include ambient heat through convection, conduction, radiation

Liquid nitrogen comes from the air we breathe

- Atmosphere is composed of 78% Nitrogen, 21% oxygen, 1% other stuff
- LN2 is a byproduct of the production of those “Other” gasses
- Because it’s a byproduct, it’s economical to use as a consumed refrigerant

When used properly, LN2 is safe

- Proper monitoring, training, PPE critical
- LN2 cannot be liquid at room temperature
- At 1atm, LN2 is at -196C and has an expansion ratio of almost 800:1

Liquid Nitrogen (LN_2)

How much nitrogen is consumed?

All sources of LN2 consume it naturally

- Freezers typically consume 7-15% of stored LN2 naturally
- Liquid cylinders typically consume 3-5% of LN2
- Bulk tanks consume 1-3% of their capacity

Transfer Losses can be a substantial contributor to LN2 consumed

- Because LN2 is stored pressurized (22-35psi) it is at a warmer temperature
- The higher the pressure, the warmer the temperature
- LN2 at 50psi is ~-185C and must re-saturate when entering the freezer

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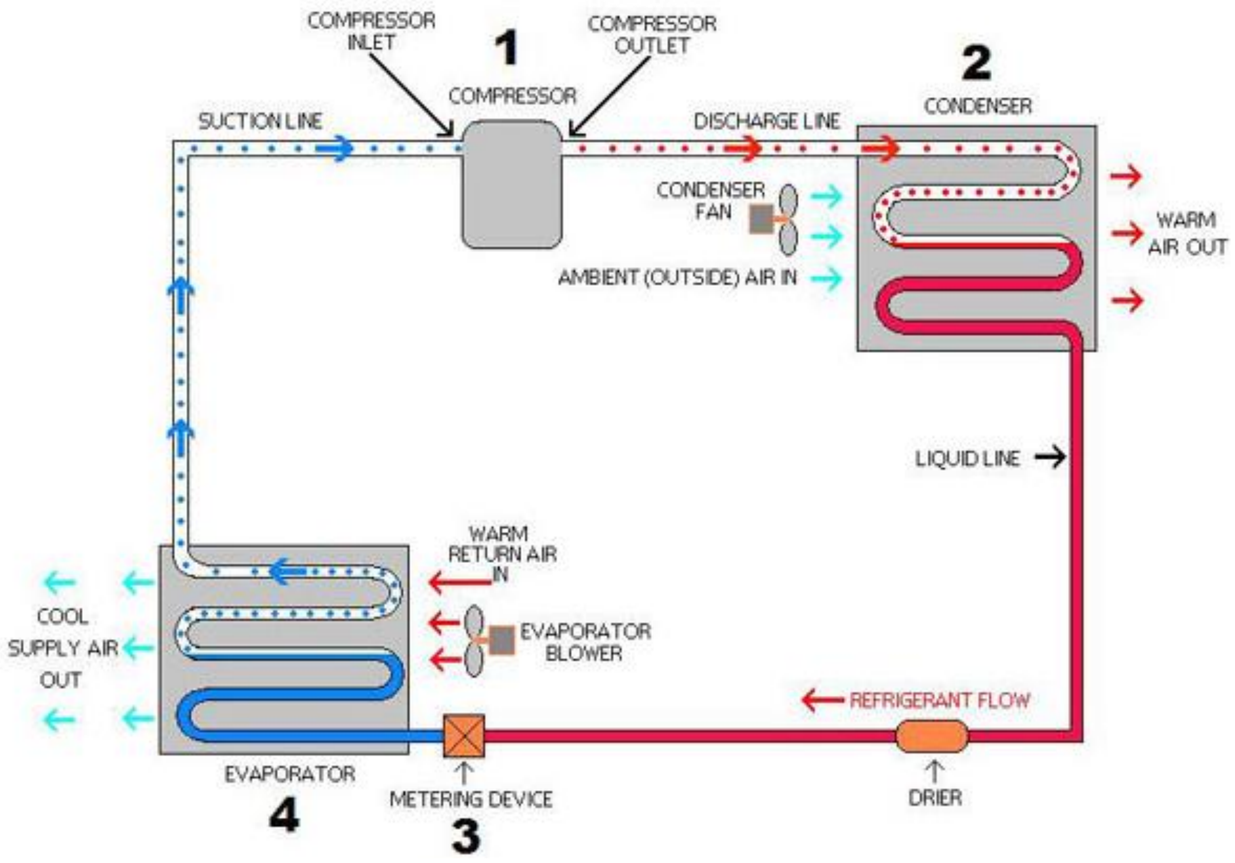
Liquid Nitrogen Usage Calculator

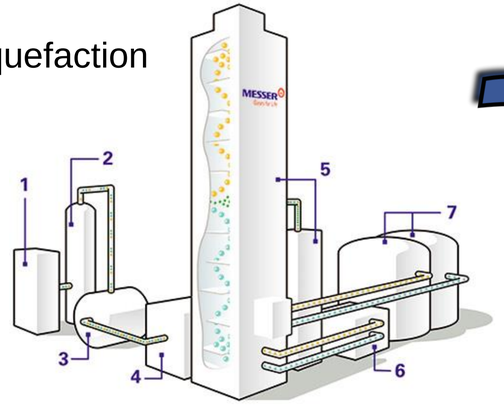
Model	NER	inches/ day	Fill Freqeuncy (Days)	Liters per Fill	Transfer Losses	Total Usage per fill	Usage per year	Usage per month	Usage per week
A220/E264	6.4	0.5	4.0	25.4	8	33	3013	251	58
A440/E528	9.1	0.4	5.0	45.4	14	59	4308	359	83
A700/E840	10.5	0.3	6.7	70.2	21	91	4996	416	96
A1000/E1200	20.0	0.4	5.0	99.8	30	130	9471	789	182

Liquid Cylinder	NER (%/day)	Usage	Usage per Year	Usage Per Month	Usage per week
180	5	9	3285	274	63
230	5	12	4198	350	81
450	5	23	8213	684	158

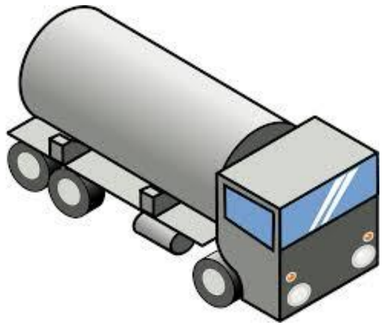
Closed vs Open Loop Refrigeration



Air Liquefaction Plant



Transport



On-site Storage

Cryo Freezer is analogous to the evaporator in a closed loop system

Heat Transfer and Insulation

Heat is transferred in 3 ways:

- **Conduction**

- Through physical contact; electric burner on a stove heating a pan
- Minimize metal contact and heat path between inner and outer vessels

- **Convection**

- Through movement of a fluid (gas/liquid); forced-air furnace, weather systems
- Vacuum between vessels removes molecules and heat path

- **Radiation**

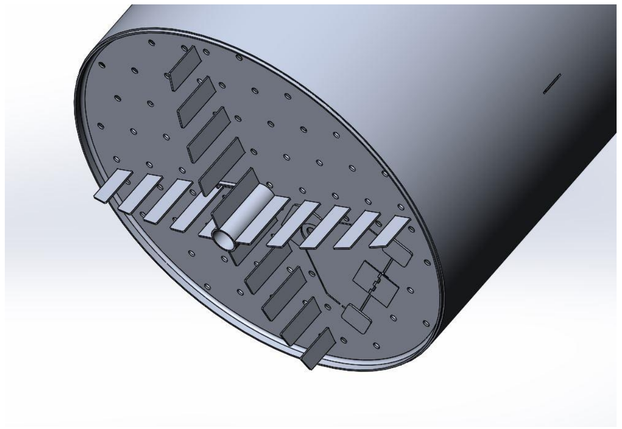
- Sun warming the Earth, microwaves, infrared, body heat
- Super insulation wrap lengthens heat path from 1” between the vessels to over 1 mile.
- Heat must follow full length of insulation wrap to reach inner vessel

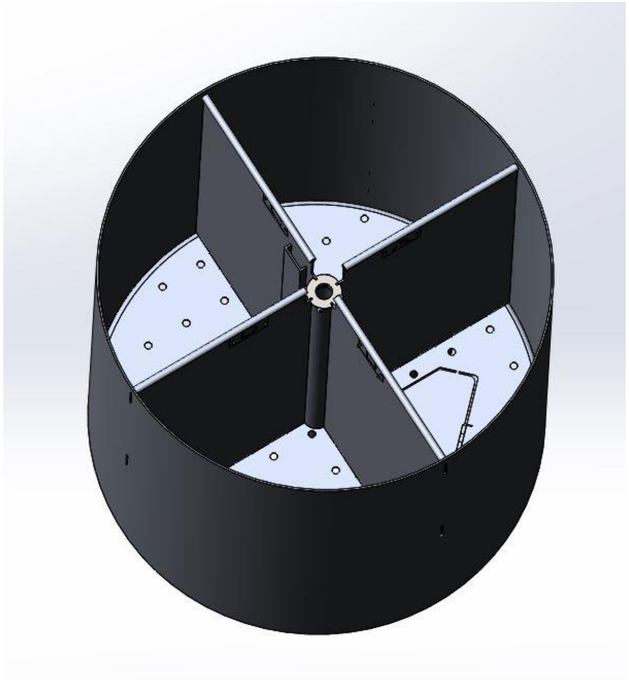
Goal is to keep as much heat out of the freezer as possible

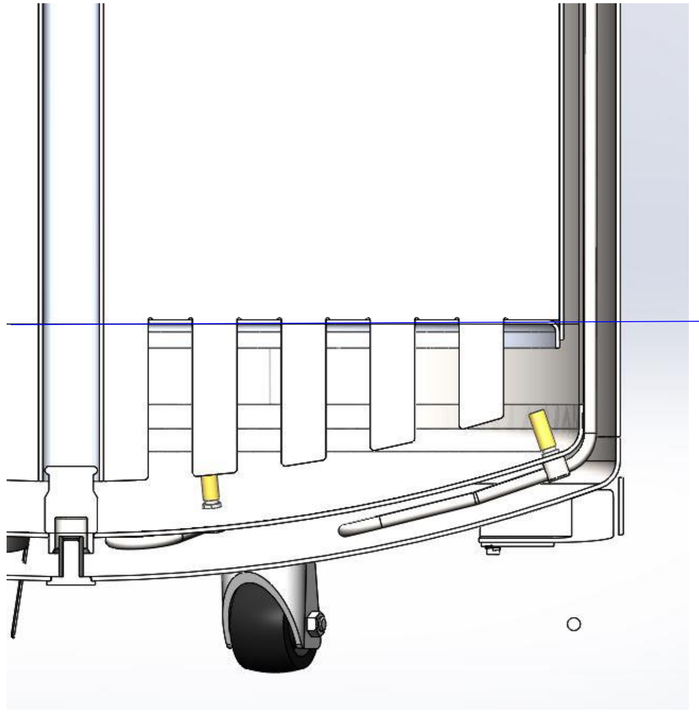
Turn Tray Fingers

Extension of aluminum dividers below the turntray floor to carry heat from samples in the turn tray to the LN2.

Current art has a shell around the outside of the turntray that touches the LN2 but it does not extend into the dish of the bottom head and as such loses contact sooner. This design improves on that by having the extensions reach deeper and also be directly connected to the interior dividers of the turn tray thus pulling heat from the samples and into the LN2







Cryopreservation Summary

Goal is to preserve sample potential for successful use in the lab or clinic

Samples preserved by reducing temperature below where:

- Enzymatic activity slows to a stop
- Molecules completely frozen and solidified

Scientific basis for selecting temperature:

- Sample type, end-use application, and duration

Cryo applications in life science research, therapies, diagnostics, and drug development

Cryo freezers are open loop refrigeration systems

- LN2 is a consumed refrigerant produced industrially through air separation
- Cryo freezers cold because of LN2 vaporization inside super insulated vessel
- Cryo freezers must be refilled to maintain cooling function

Double-walled, vacuum insulated freezers minimize the 3 forms of heat transfer:

- Conduction, convection and radiation
- Maintain low, stable temperature with extended hold times

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Market spotlight: Cell and Gene Therapy

Olga Bukatova, April 2024

What do we know about CGT?

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What do we know about CGT?

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TIME

HEALTH • DRUGS

The World's Most Expensive Drug Is Now a $4.25 Million Gene Therapy

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Girl with deadly inherited condition is cured with gene therapy on NHS

Teddi Shaw, from Northumberland, first recipient on health service of Libmeldy, world's most expensive drug

Teddi Shaw is 'walking, running, a chatterbox,' says her mother, Ally. Photograph: PA

A girl born with a rare and deadly genetic condition is expected to live a long and normal life after becoming the first person to be cured on the NHS with the help of a revolutionary gene therapy.

First patients of pioneering CAR T-cell therapy 'cured of cancer'

Cancer-killing cells still present 10 years on, with results suggesting therapy is a cure for certain blood cancers

Doug Olson still has cancer-killing cells 10 years after infusion. Photograp

The cancer cell therapy Carvykti dramatically outperformed standard drugs in a late-stage clinical trial testing its use in earlier treatment of the blood cancer multiple myeloma, according to data from a study abstract that was briefly posted online Tuesday.

The abstract showed Carvykti, which is made by Johnson & Johnson and Legend Biotech, reduced the risk of disease progression or death by 74% compared to standard of care — a degree of benefit that analysts who viewed it described as "stellar" and "highly encouraging."

Biopharma Dive, 2023
J&J study data show dramatic benefit to multiple myeloma cell therapy

However, historically, marketing gene therapy products has been led by large pharmaceutical companies, and with high development costs, the price per therapy has been high. In the U.S., on average, cell therapies are priced at around $500K per treatment course, and gene therapies at around $1M per treatment course (mercer.us, 2021).

Medium, 2022
Trends and Pricing Models for Cell and Gene Therapy

Agenda

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01 CGT Basics

02 State of CGT industry

03 Cryo Cold Chain in CGT

04 Conclusions

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CGT BASICS

01

Cell and Gene Therapy
Ex-vivo and in-vivo Gene Transfer

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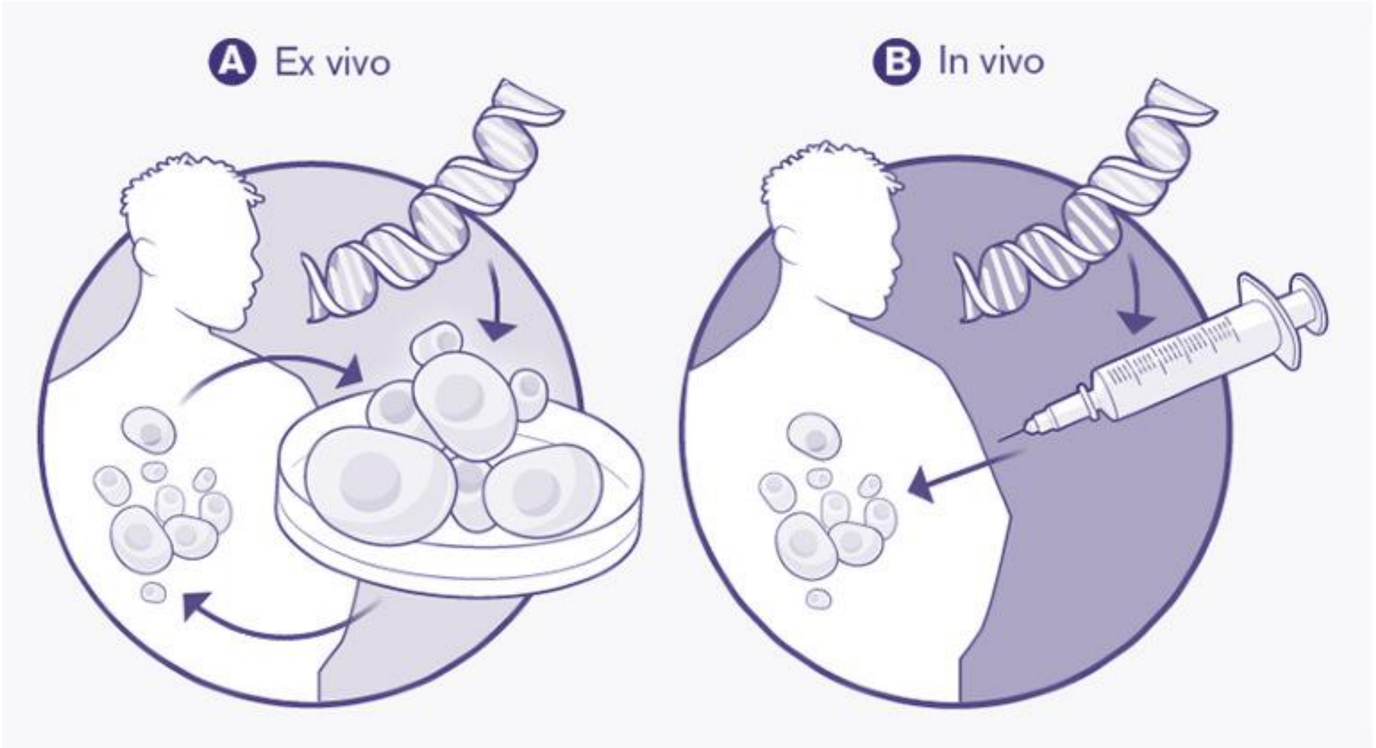
Cell therapy involves injection of living cells into the patient for curative purpose. The cells can be derived from the patient (autologous cell therapy) or from a donor (allogeneic cell therapy).
Example: iPSC-based cell therapy for cardiac regeneration

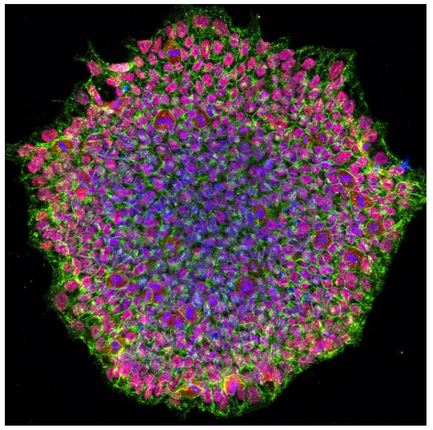
Gene therapy involves introducing, removing, or changing genetic material to alter how a protein or group of proteins is produced in a cell, to alleviate or cure a disease.
Example: Luxturna, AAV-based gene therapy for inherited retinal disease

Combination: Cell and gene therapy approaches are combined for **gene-modified cell therapy**
Example: Kymriah, Carvykti, ex-vivo chimeric antigen receptor (CAR) T-cell therapy.



Visual from The Definition of Gene Therapy Has Changed,
Esther Landhuis, Nature, 2021

Which cells for cell therapy?
Cell types

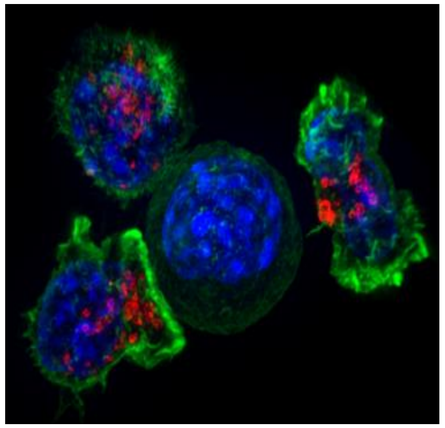


Stem cells

- pluripotent stem cells (PSCs): induced pluripotent stem cells (iPSCs), derived from direct reprogramming of postnatal/adult somatic cells in vitro (biologically equivalent to Embryonic Stem Cells). Other application: Disease modeling, Drug Screening. Organoids!

- adult stem cells (ASCs): hemopoietic stem cells (HSCs), skin stem cells (SSCs), neural stem cells (NSCs), mesenchymal stem cells (MSCs)

Image credit: National Eye Institute/NIH,
A human induced pluripotent stem cell colony from OCA1A patient



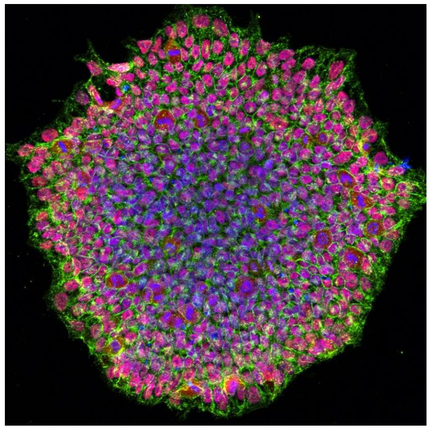
Non-stem (somatic) cells

- fibroblasts, chondrocytes, keratinocytes, hepatocytes, pancreatic islet cells

- immune cells: T cells, dendritic cells (DCs), natural killer (NK) cells, macrophages (“Adoptive cell therapy”, “Cell-based immunotherapy”, “Cellular immuno-oncology”)

Image credit: Alex Ritter, Jennifer Lippincott Schwartz and Gillian Griffiths,
National Institutes of Health, Killer T cells (green and red) surround a cancer cell (blue, center).

Which cells for cell therapy? Cell types



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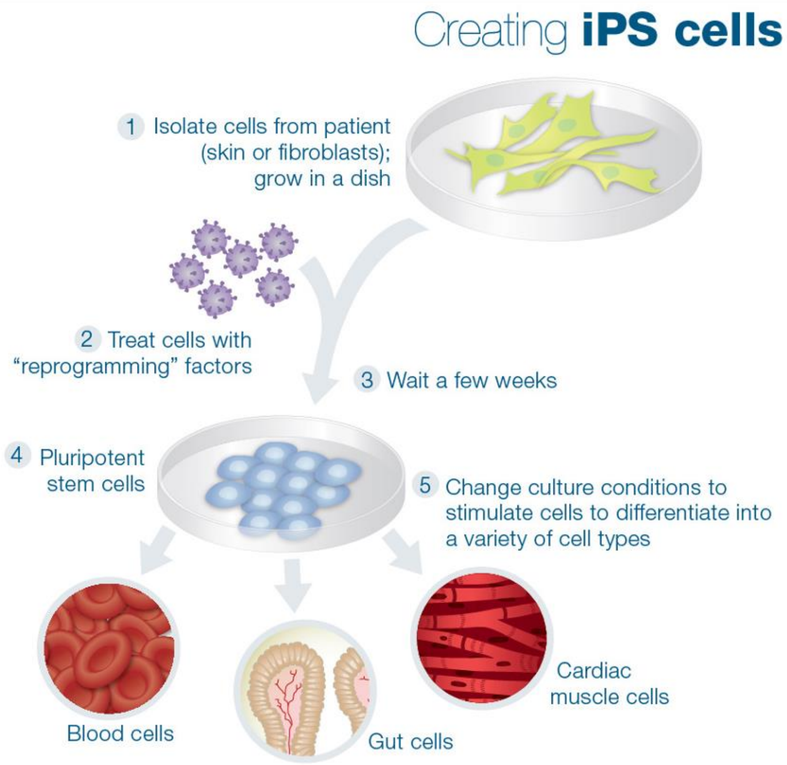
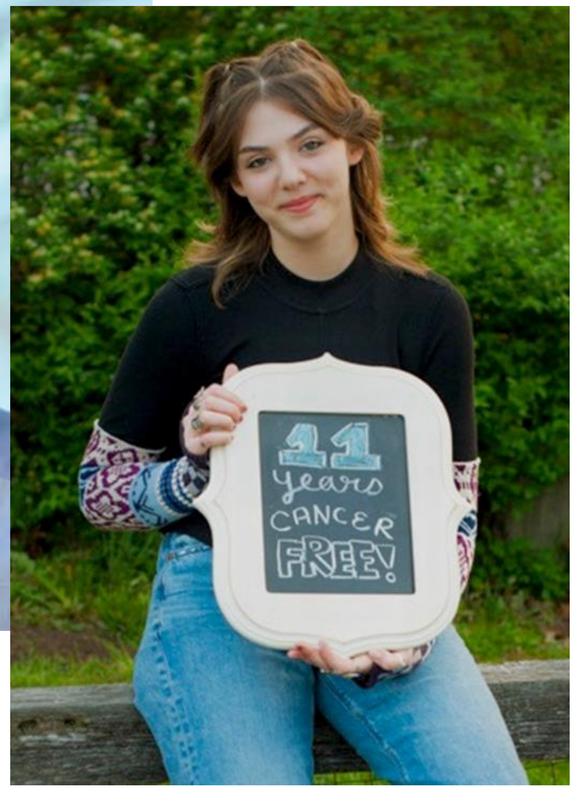


Shinya Yamanaka

Which cells for cell therapy?
Cell types

Carl June



Emily Whitehead

Jennifer Doudna, Emmanuelle Charpentier

Image credit: Dan David Prize,
Emily Whitehead Foundation

Image credit: Miguel Riopa/Agence France-Presse,
MRS Bulletin

PRODUCT	BY
GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)	Organogenesis Incorporated
MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)	Vericel Corp.
RETHYMIC (allogeneic processed thymus tissue – agdc)	Enzyvant Therapeutics GmbH
STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts)	Stratatech Corporation
LAVIV (Azficel-T)	Fibrocell Technologies
LANTIDRA (donislecel)	CellTrans Inc.
CASGEVY (exagamglogene autotemcel [exa-cel])	Vertex Pharmaceuticals Incorporated
LYFGENIA (lovotibeglogene autotemcel [lovo-cel])	bluebird bio, Inc.
LENMELDY (atidarsagene autotemcel)	Orchard Therapeutics (Europe) Limited
SKYSONA (elivaldogene autotemcel)	bluebird bio, Inc.
ZYNTEGLO (betibeglogene autotemcel)	bluebird bio, Inc.
ALLOCORD (HPC, Cord Blood)	SSM Cardinal Glennon Children's Medical Center
CLEVECORD (HPC Cord Blood)	Cleveland Cord Blood Center
Ducord, HPC Cord Blood	Duke University School of Medicine
OMISIRGE (omidubicel-onlv)	Gamida Cell Ltd.
HEMACORD (HPC, cord blood)	New York Blood Center
HPC, Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Ba
HPC, Cord Blood - MD Anderson Cord Blood Bank	MD Anderson Cord Blood Bank
HPC, Cord Blood - LifeSouth	LifeSouth Community Blood Centers, Inc.
HPC, Cord Blood - Bloodworks	Bloodworks
PROVENGE (sipuleucel-T)	Dendreon Corp.
ABECMA (idecabtagene vicleucel)	Celgene Corporation, a Bristol-Myers Squibb Company
BREYANZI (lisocabtagene maraleucel)	Juno Therapeutics, Inc., a Bristol-Myers Squibb Compar
CARVYKTI (ciltacabtagene autoleucel)	Janssen Biotech, Inc.
TECARTUS (brexucabtagene autoleucel)	Kite Pharma, Inc.
YESCARTA (axicabtagene ciloleucel)	Kite Pharma, Incorporated
KYMRIAH (tisagenlecleucel)	Novartis Pharmaceuticals Corporation
AMTAGVI (lifileucel)	Iovance Biotherapeutics, Inc.
ADSTILADRIN (nadofaragene firadenovec-vcng)	Ferring Pharmaceuticals A/S
ELEVIDYS (delandistrogene moxeparvovec-rokl)	Sarapeta Therapeutics, Inc.
HEMGENIX (etranacogene dezaparvovec-drlb)	CSL Behring LLC
IMLYGIC (talimogene laherparepvec)	BioVex, Inc., a subsidiary of Amgen Inc.
LUXTURNA (voretigene neparvovec-rzyl)	Spark Therapeutics, Inc.
ROCTAVIAN (valoctocogene roxaparvovec-rvox)	BioMarin Pharmaceutical Inc
VYJUVEK (beremagene geperpavec)	Krystal Biotech, Inc.
ZOLGENSMA (onasemnogene abeparvovec-xioi)	Novartis Gene Therapies, Inc.

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LYFGENIA (lovotibeglogene autotemcel [lovo-cel])	bluebird bio, Inc.	Gene-edited cell therapy
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ALLOCORD (HPC, Cord Blood)	SSM Cardinal Glennon Children's Medical Center	Hematopoietic stem cell transplant (HPSCT)
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HPC, Cord Blood - Bloodworks	Bloodworks	Hematopoietic stem cell transplant (HPSCT)
PROVENGE (sipuleucel-T)	Dendreon Corp.	Immunotherapy: dendritic cells
ABECMA (idecabtagene vicleucel)	Celgene Corporation, a Bristol-Myers Squibb Company	Immunotherapy: T-cell therapy: CAR T
BREYANZI (lisocabtagene maraleucel)	Juno Therapeutics, Inc., a Bristol-Myers Squibb Company	Immunotherapy: T-cell therapy: CAR T
CARVYKTI (ciltacabtagene autoleucel)	Janssen Biotech, Inc.	Immunotherapy: T-cell therapy: CAR T
TECARTUS (brexucabtagene autoleucel)	Kite Pharma, Inc.	Immunotherapy: T-cell therapy: CAR T
YESCARTA (axicabtagene ciloleucel)	Kite Pharma, Incorporated	Immunotherapy: T-cell therapy: CAR T
KYMRIAH (tisagenlecleucel)	Novartis Pharmaceuticals Corporation	Immunotherapy: T-cell therapy: CAR T
AMTAGVI (lifileucel)	Iovance Biotherapeutics, Inc.	Immunotherapy: TIL
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Cryopreserved

ULT storage

FDA

Anticipated CGT approvals

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PRODUCT	BY	TYPE
Fidanacogene Elaparvovec	Pfizer	Gene therapy
Pz-cel	Abeona Therapeutics	Cell therapy
Kresladi	Rocket Pharmaceuticals	Gene therapy
Afami-cell	Adaptimmune Therapeutics	Cell therapy
Human Acellular Vessel	Humacyte	Cell therapy/Tissue engineering
Obe-cel	Autolus Therapeutics	Cell therapy
RP-L102	Rocket Pharmaceuticals	Gene therapy
Upstaza	PTC Therapeutics	Gene therapy
Tab cel	Atara Biotherapeutics	Cell therapy
Giroctocogene fitelparvovec	Pfizer	Gene therapy
Remestemcel-L	Mesoblast	Cell therapy

Anticipated CGT approvals

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Gene delivery
Viral vectors

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Adeno-Associated Viral Vectors

- Small DNA packages or genes
- In-vivo therapies
- Do not integrate to cell's genome
- Limitations: innate immunity and single dose

Adenoviral Vectors

- x8 times larger packages
- In-vivo therapies
- Do not integrate to cell's genome
- Limitations: strong immune response

Lentiviral + Retroviral Vectors

- Large packages
- Ex-vivo therapies
- Integrate to cell's genome

Which cells for cell therapy? Autologous and allogeneic

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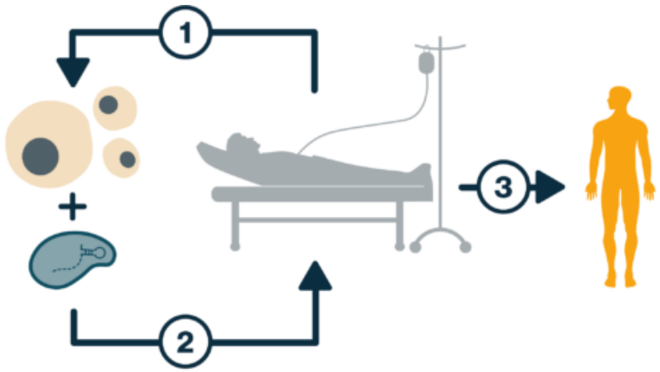
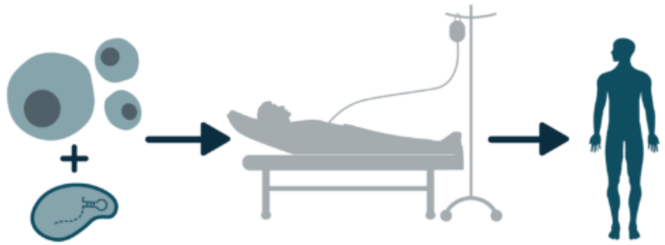
Autologous

The patient's own cells are extracted, edited (1), returned to the patient (2) for curative effect (3)



Allogeneic

Donor cells are edited, infused to the patient for curative effect



Lower cost	On-stock	Long lived	Consistent quality	Immune tolerance
		X		X
X	X		X	

Credit: Cell therapies and ex vivo genome editing, Tyler Ford, Mammoth Biosciences blog

Auto or allo reality for cell-based immuno-oncology?

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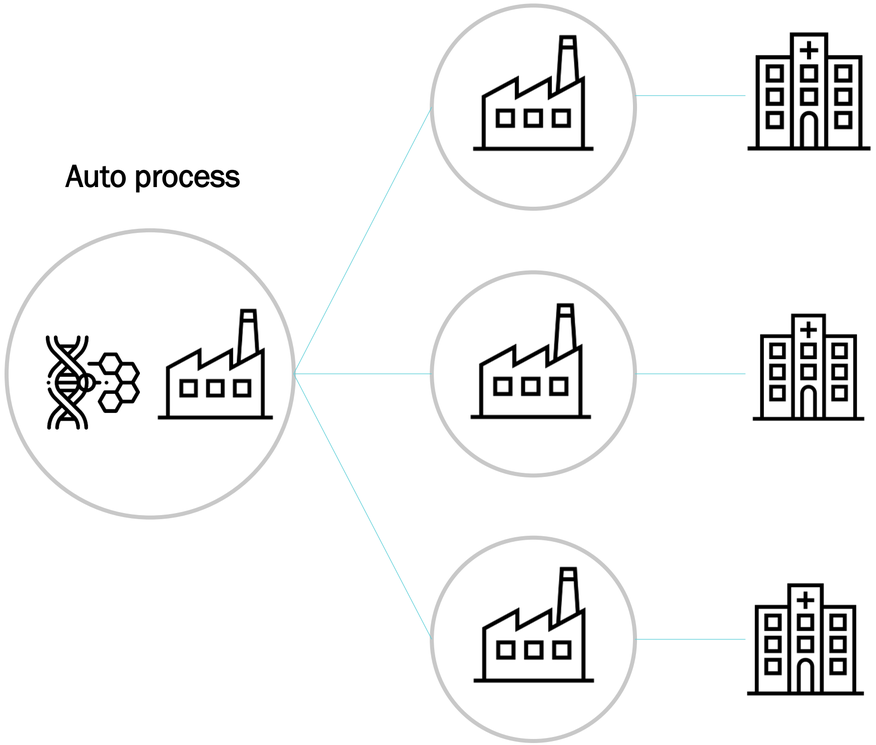
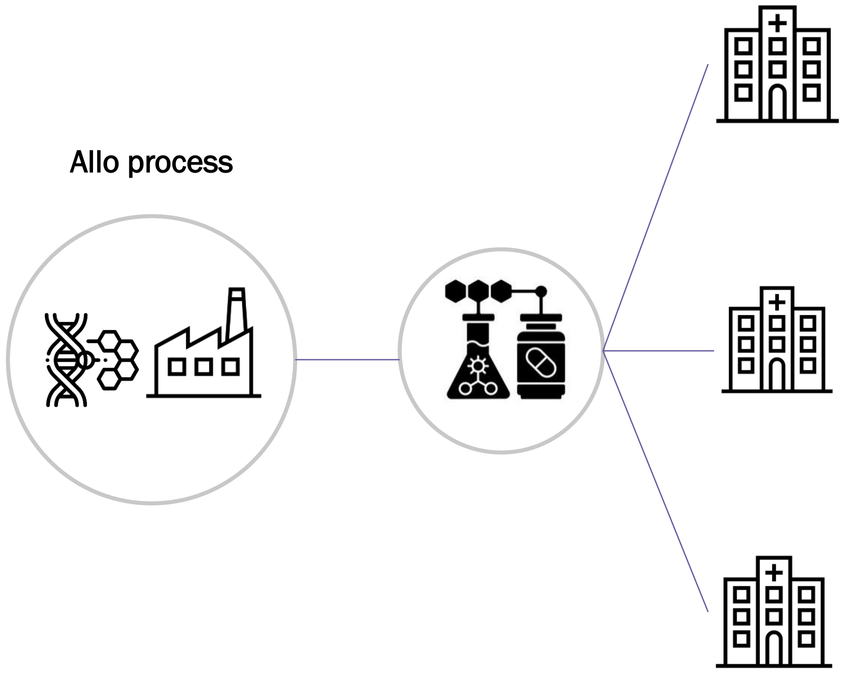
	Autologous	Allogeneic
Principle	Fully **personalized medicines**, the patients own cells are used	**Off-the-shelf medicine,** the healthy donor-cell derived
Performance challenges	**Important vein-to-vein intervals:** Collection, complex logistics and manufacturing steps can take up to 30 days **Starting material quality / quantity:** Patients medical history (immune suppression)	**Immune compatibility:** Graft-versus-host (GVHD) disease due to antigen mismatch, shorten cell-persistence **Lack of in vivo activity control:** Impact of mis-edited cells, risks of continuous cell proliferation
Manufacturing challenges	Can **only scale-out:** 1 batch per patient, numerous manual processes, complex release documentaton **Consistency:** variability of product due to the lack of control over cell collection processes, lack of adaptability to the „out of specification“ cells lots	**Scalining-up:** Challenges of yield in large bioreactors, fill&finish and freezing bottlenecks **Dependance of the donnor** starting material: Limitations to cell expansion – limiatations on drug doses per cell collection
Approvals to date	**7 T cell based therapies**, numerous products in the pipeline for both liquid and solid tumours	A couple of allogeneic cell transplants, only **1 T cell based therapy** approved in EU

Auto- and allo- strategy





63% cell therapy professionals are working on both autologous and allogeneic platforms

Allogeneic and Autologous Cell Therapies Report 2022
Survey by Informa and Catalent, 2022

Indication
Addressable patient population

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Orchard therapeutics™

LENMELDY (LIMBELDY)

Early-onset Metachromatic Leukodystrophy

400 - 1,700

pediatric patients worldwide

IOVANCE BIOTHERAPEUTICS

AMTAGVI

Advanced melanoma

15,000

new patients in US only, yearly

CGT therapies target various diseases with various patient population to be addressed

Manufacturing capacity is designed accordingly

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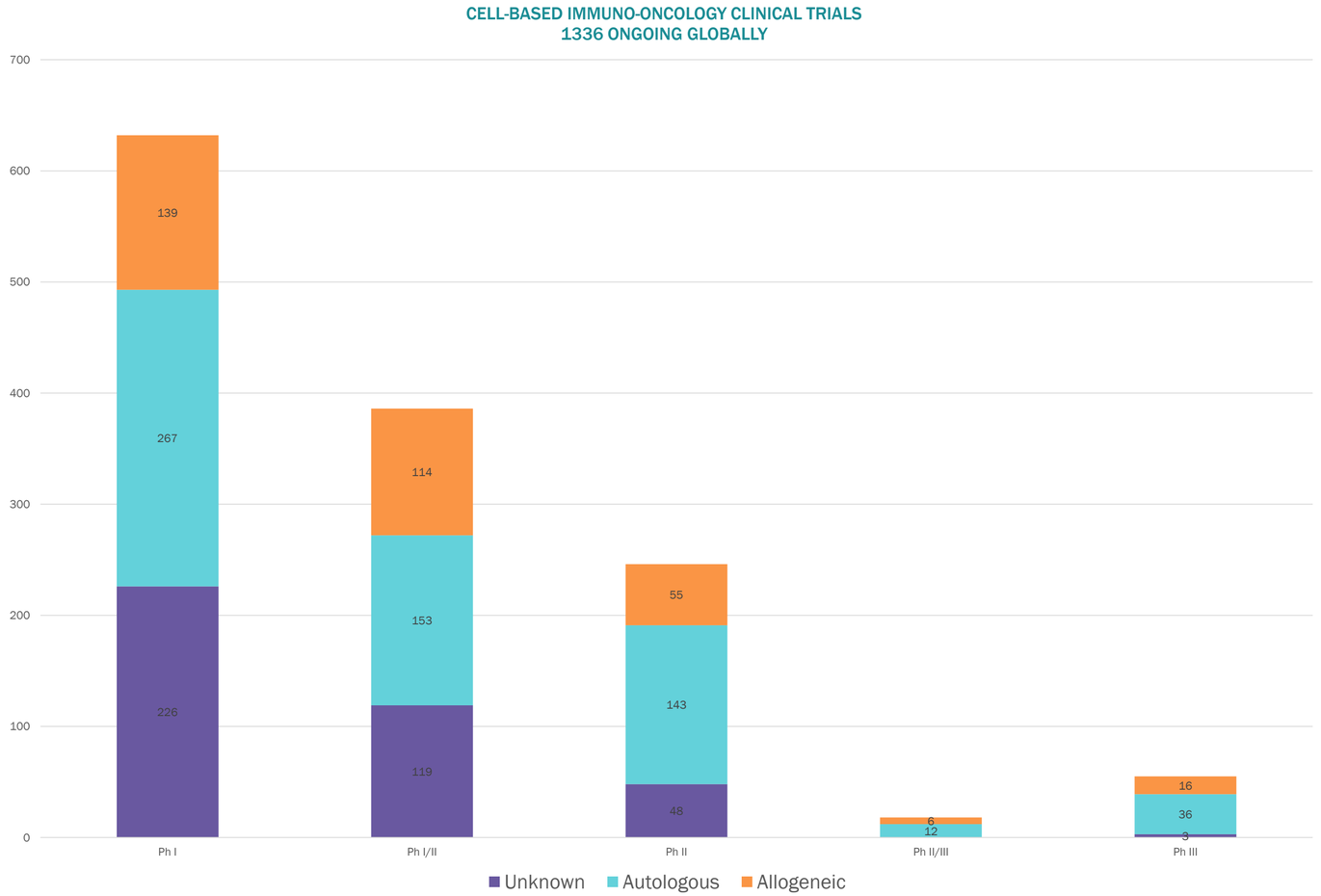
STATE OF CGT INDUSTRY

02

Auto or allo reality for cell-based immuno-oncology?



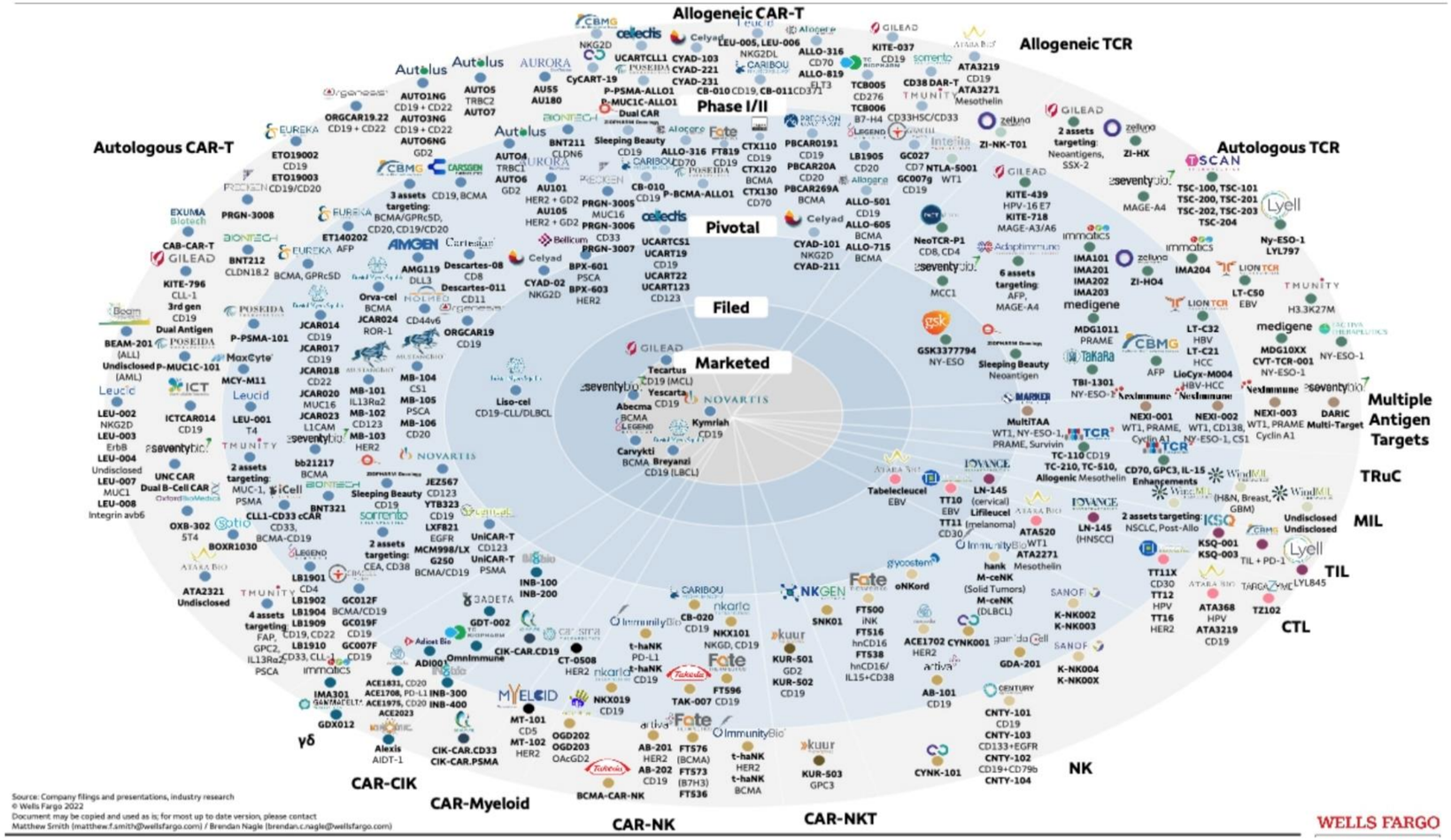
Sector Snapshot, April 2024
ARM

60%

CGT product pipeline foreseen to be allogeneic by 2030

Source: DHC presentation at ATW24

Clinical trial landscape
Cell-based immuno-oncology



Cell-based immune-oncology remains the biggest focus area

- Market estimated $34.69B by 2030
- CAGR of 20.4% (InsightAce Analytic, 2022)

Cell therapy clinical landscape 2024

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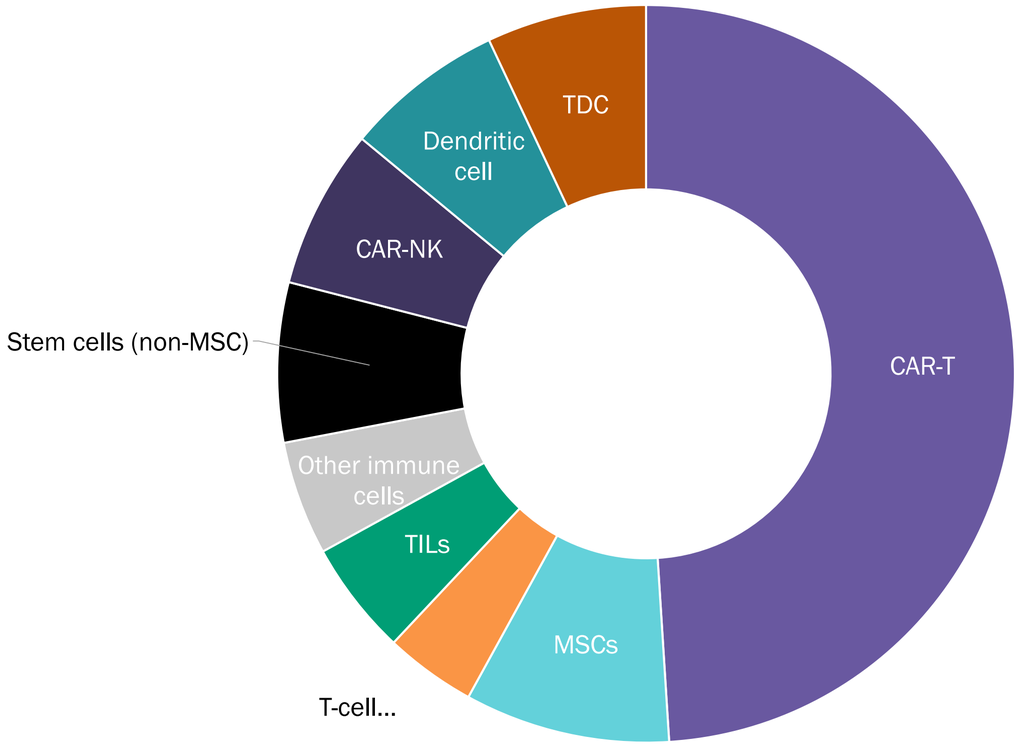
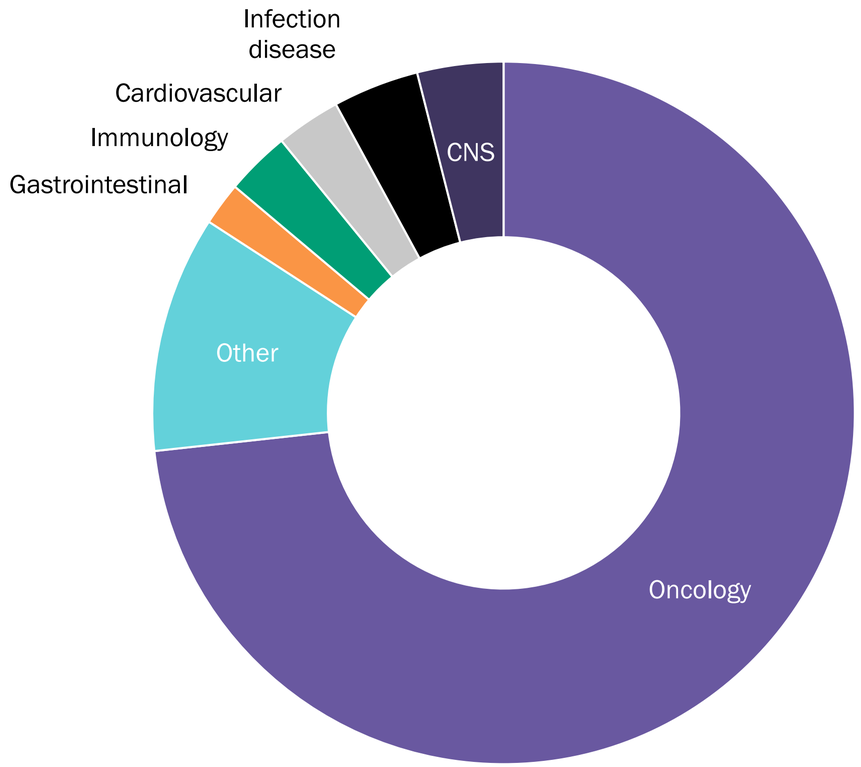
CELL TYPE USED



CLINICAL FOCUS



Cell-based immuno-oncology as the dominant field

Sector Snapshot, April 2024
ARM

Current adoption rate of the cell-based immuno-oncology

Remains „**boutique therapy**“: despite approvals, only around 35K patients recieved the CAR T cell therapy

Challenge for the healthcare systems: first line treatment for liquid tumors would exceed in the US 35B USD

Complex

- large vein-to-vein intervals
- high COGs:
  - long and „manual“ manufacturing
  - cryo cold chain

Image credit: EWF, Emily Whitehead, the first paediatric CAR T patient, celebrates with her family and friends 10 years cancer free, 2022

CGT Manufacturing & Distribution

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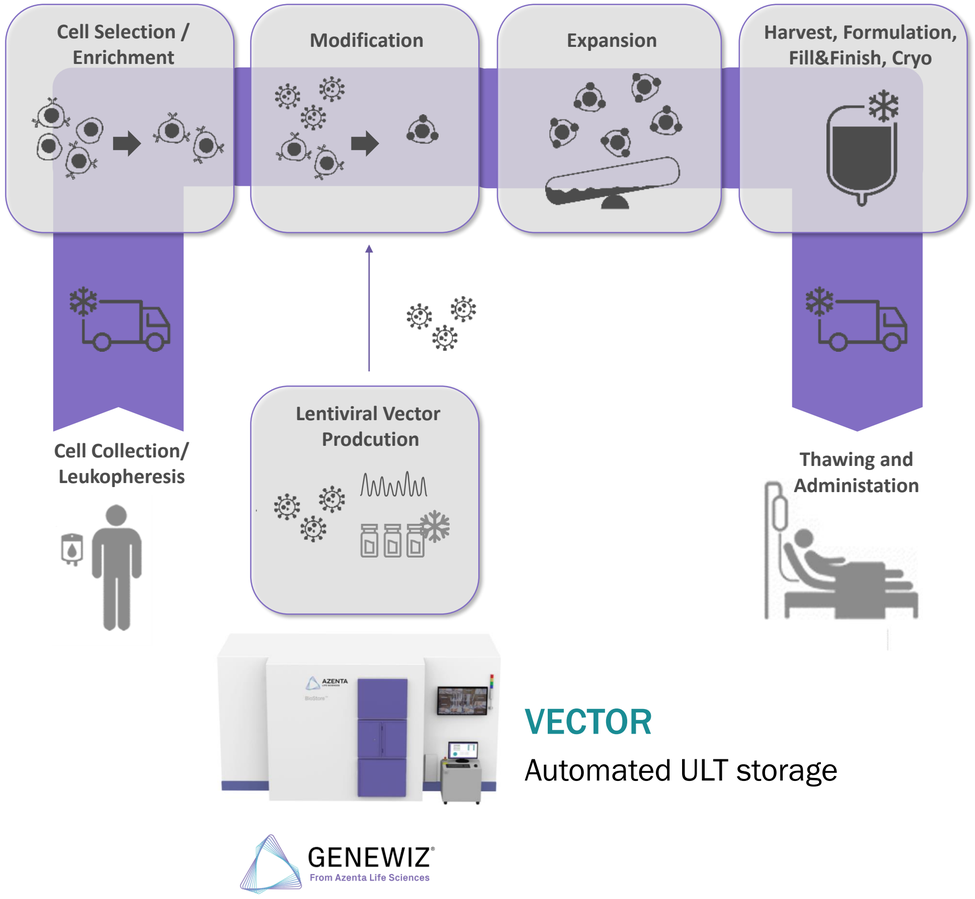
Gene-modified cell therapies require multiple cryopreservation-thawing processing steps that must be controlled

STARTING MATERIAL

Automated cryostorage

Controlled on-site handling

Controlled thawing in GMP environment



VECTOR

Automated ULT storage

GENEWIZ From Azenta Life Sciences

QC SAMPLES, DRUG PRODUCT

Automated cryostorage

Controlled on-site handling

Controlled thawing of QC samples

DRUG PRODUCT AT POC

Compact automated cryostorage

Controlled on-site handling

Controlled thawing at the point-of-care

Case study: T cell therapy

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Autologous

CARVYKTI

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

LEGEND BIOTECH

Manufacturing:

Continuous

Own manufacturing facility J&J in Raritan, NJ in Ghent, Belgium, in China

Starting material:

70 ml apheresis in cryobags

Batch size: < 10 cryobags / patient

QC samples: up to 6

Drug product: 30 ml or 70 ml in cryobag

Allogeneic

EBVALLO

ATARA BIO®

Manufacturing:

In campaigns

Own manufacturing facility Thousand Oaks, CA – sold to FujiFilm (exclusive agreement)

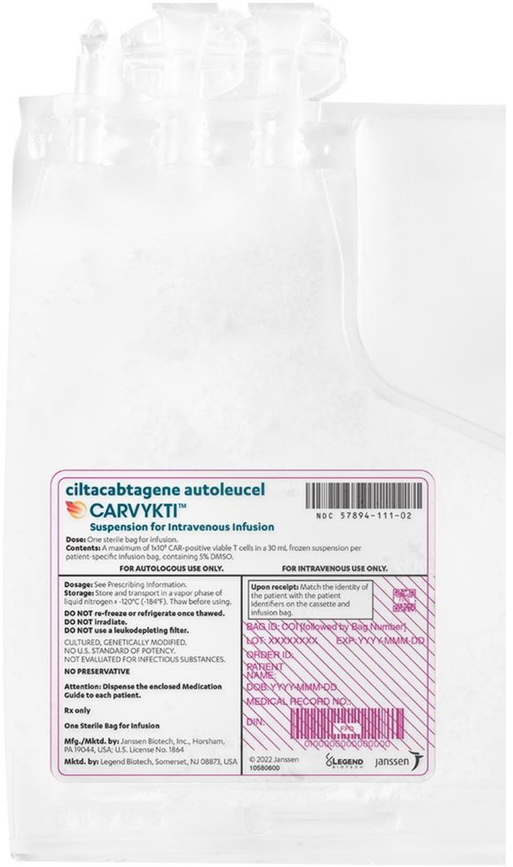
Starting material:

T-cell bank in low volume cryovials

Batch size: several thousands - up to 20000 doses / batch

QC samples: up to hundred

Drug product: 2 ml AT-Closed Vial



Lifecycle of CGT product

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GCP

Clinical site

Clinical site

Clinical site

CRO/Supplier

GCP

Approved Therapy Center

BASIC RESEARCH
Proof of concept

PRE-CLINICAL
Thera. candidate
IND

PHASE I
Safety

PHASE II
Efficacy

PHASE III
Larger cohort

COMMERCIAL

Process open/locked

GLP

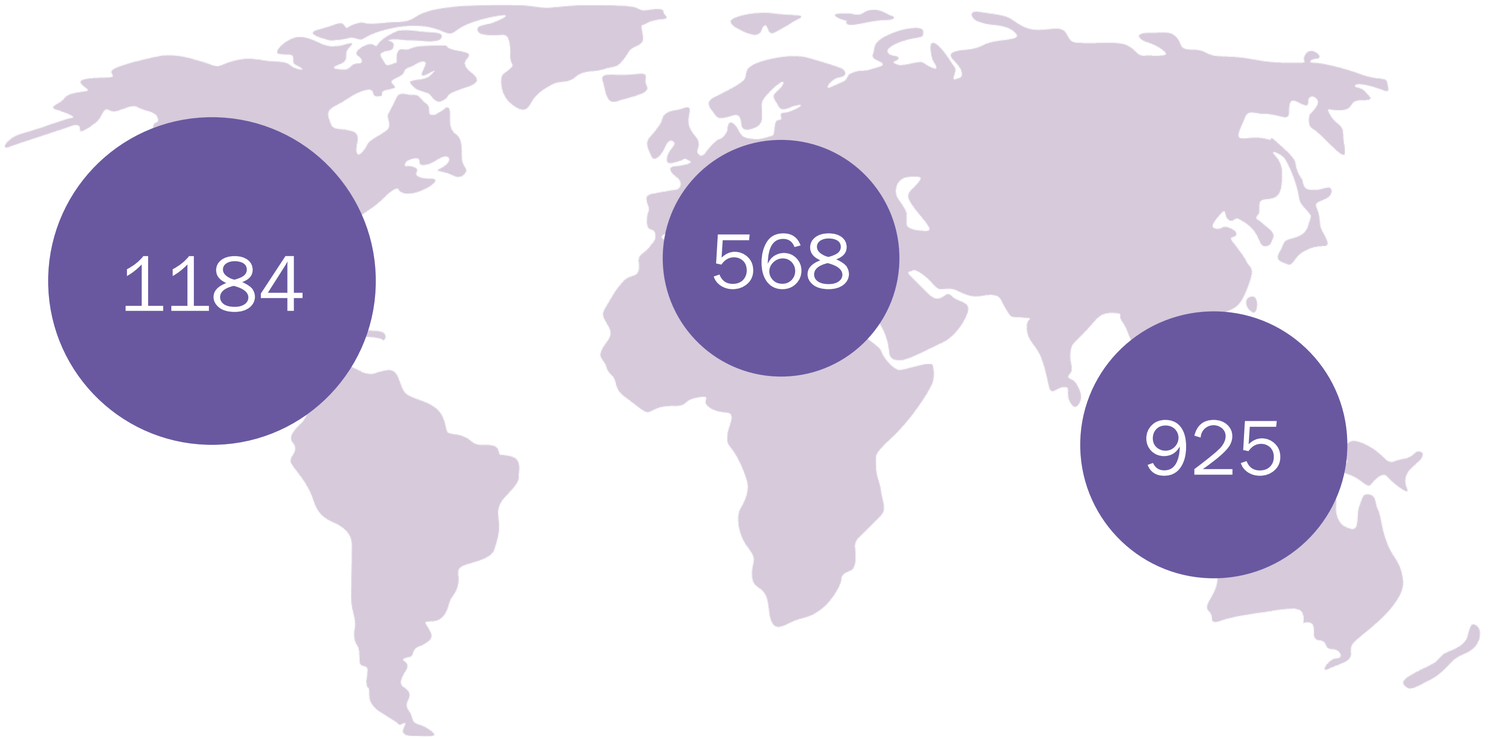
Academia

Developer

GMP
GLP

CDMO

CGT landscape 2024



2762

CGT developers

Cell And Gene Therapy Sector Data Q4 2023
ARM

Case-study: Project Actors

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sanofi

KNK-003 (SAR-445419)

ALLOGENEIC NK CELL-BASED PRODUCT

The therapeutic candidate comprises of natural killer cells and is being developed based on K-NK platform. Is under development for the treatment of chronic myelocytic leukemia (CML), relapsed and refractory acute myeloid leukemia and myelodysplastic syndrome.

Process Development:

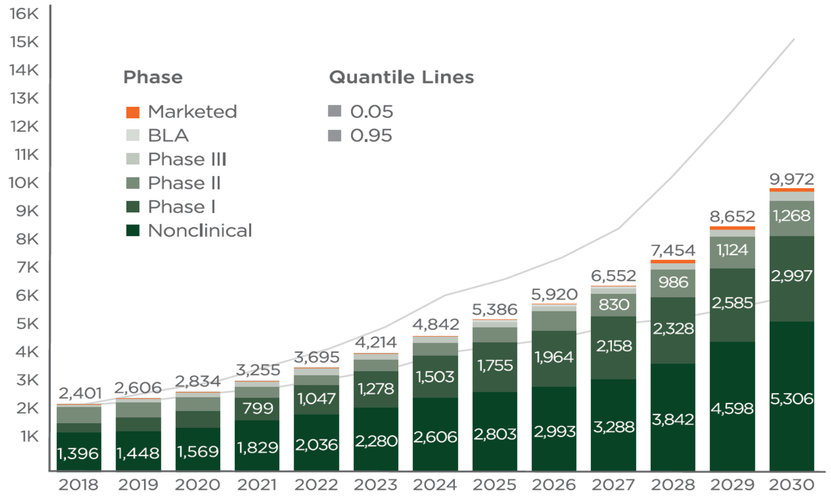
- Waltham, MA
- Amsterdam, NL

Manufacturing:

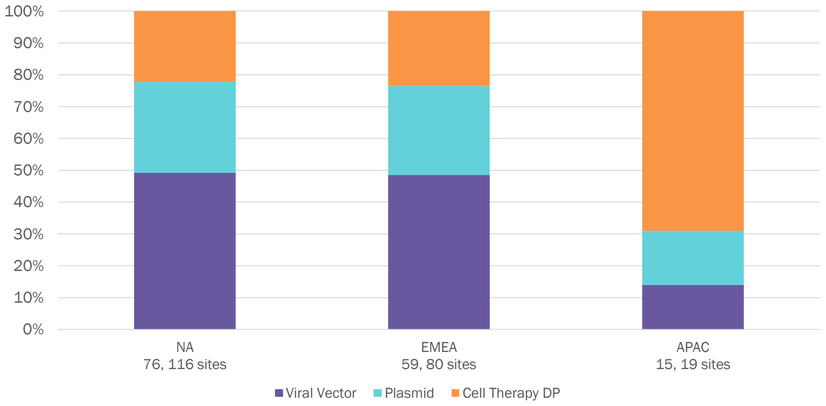
- Framingham, MA
- Milano, IT (AGC Biologics)

CGT state of industry 2024

Number of CGT products*



CGT CDMO landscape*



By 2030:

54–74

cumulative US product approvals

93 000

patients treated

$24.4B

a mean list price product revenues generated**

* Dark Horse Consulting
**Tufts Medical Center

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Key figures

- “17 approvals anticipated for 2024
- Over 2500 CGT developers globally (ARM), CGT market will double by 2030 (DHC)

Hot topics:

- The FDA safety advisory on the risk of T-cell malignancies vs Advancements of CAR T in treatment line in both US and EU
- Approval of the first CRISPR therapies (large patient population, bluebird bio, Vertex/CRISPR Tx)
- Approval of the first TIL therapy (Iovance Biotherapeutics)
- Anticipated approvals of first TCR therapy and allogeneic T cell therapy

CGT CDMO spotlight
USA footprint: 116 sites

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Lonza

WuXi ADVANCED THERAPIES 药明生基

药明康德 WuXi AppTec

Catalent BIOLOGICS

ThermoFisher SCIENTIFIC

charles river

FUJIFILM Diosynth biotechnologies

Center for Breakthrough Medicines

RESILIENCE

MINARIS REGENERATIVE MEDICINE

elevatebio

AGC Biologics

FORGE BIOLOGICS

CELLARES

LYKAN BIOSCIENCE

Andelyn BIOSCIENCES Reliably Expert. Purposefully Driven.

Cellipont BIOSERVICES

Theragent

RoosterBio

CGT trends

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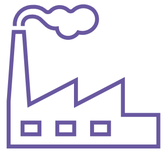
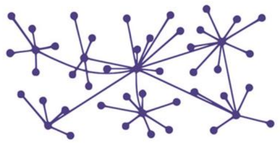
Identified and highlighted from discussions during industry events in 2024



CDMO

Further consolidation



Decentralized

manufacturing model

Emerging markets

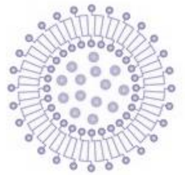
First CGT approval

Big pharma

Further involved: AZ

Allogeneic raise

Is actually happening



Non-viral gene delivery

tech raising

CGT trends (details)

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TREND	DETAILS	WHAT'S IN IT FOR US?
CDMO further consolidation	Forge Biologics - Ajinomoto deal USD 620 Mio, 3rd largest CGT CDMO deal in history, after BrammerBio ThermoFisher (USD 1.7B), Cognate-Charles River Labs (USD 875Mio)	Investment in technology and capabilities, need to differentiate and develop specific competitive advantages
Decentralized manufacturing	Includes point-of-care CGT production. Development of dedicated platforms. Bottleneck is the product release, a lot of digital solutions are developed in-house	Co-existence of fresh and cryo pathways
Emerging markets CGT efforts	The 1st CAR-T approved in India. ImmunoACT, spin-out of IIT Bombay. Cost USD 41K	Anticipation of the dedicated "cost-effective" products
Big pharma getting more involved	CGT assets are anticipated to become the "CEO level topic". Pharma dominates M&A and partnerships.	AstraZeneca: acquisition Neogene and Gracell, Pfizer gene therapy assets, Quell and Cellectis collaboration and investment agreement
Allogeneic raise	DHC at ATW24 suggests that by 2030, 60% CGT product pipeline will be allogeneic. DeciBio still considers 5-10 years domination of autologous platforms.	<10 fill&finish companies addressing CGT needs. Only 3 vial types available. Besides Aseptic Technologies and Biolife, the suppliers process CZ vials by West and currently target vectors and plasmids.
Non-viral gene delivery	Switch to non-viral delivery technologies (DNA, mRNA, LNP) forecasted for next 5 years with 70% adoption rate	The storage temperature needs for vectors and in-vivo product will get diversified: from room/refrigerated to -80C

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CRYO COLD CHAIN IN CGT

03

Pharmaceutical Process Development
Basic requirements

- Scalability
- Consistency
- Reproducibility
- Robustness
- Transferability
- Compliance
- Flexibility
- Reduction of COGs

Out and Up

Subject to qualification / validation

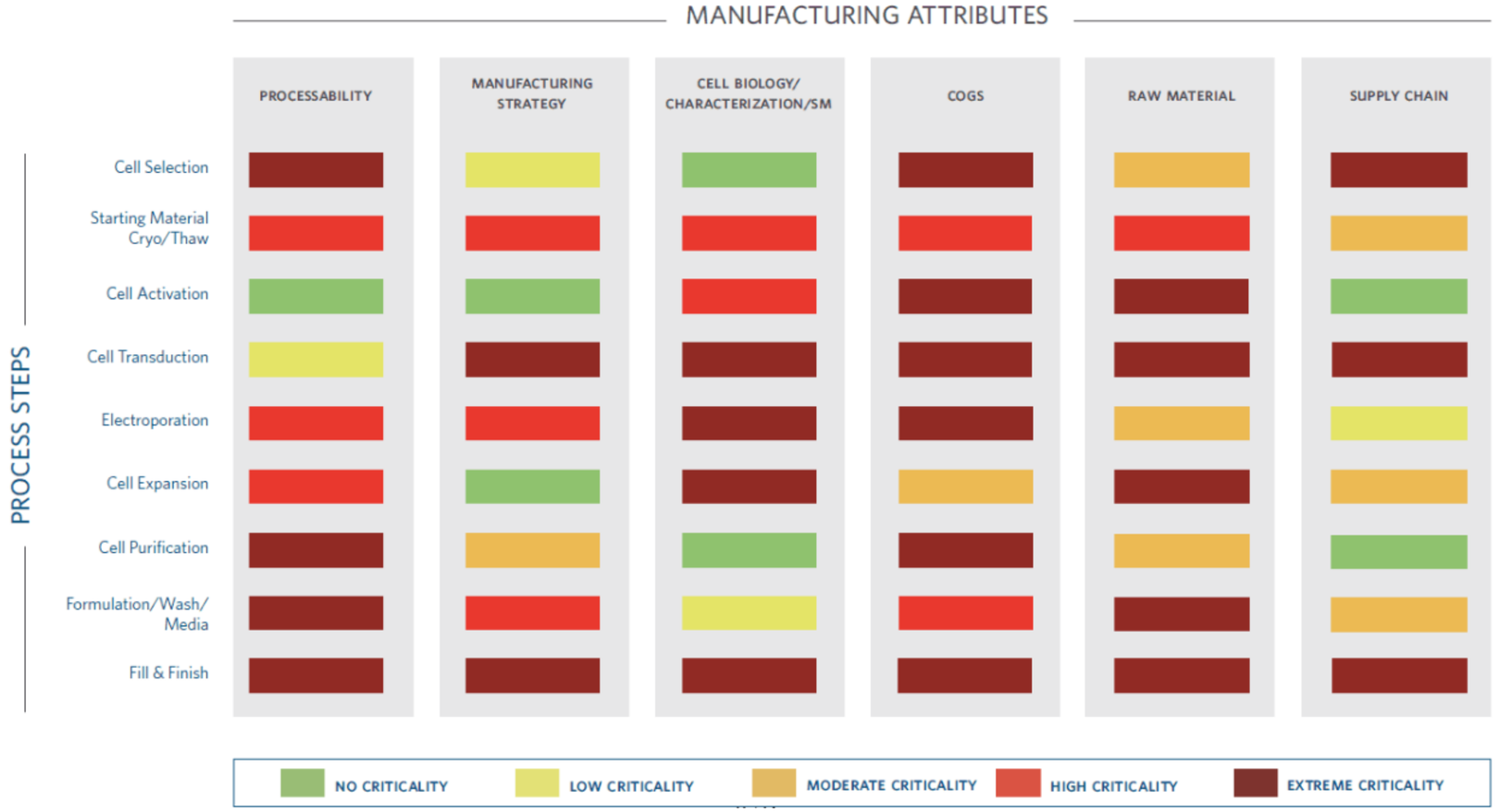
Tech transfer: site to site, to CDMO

GMP, 21 CFR Part 11

Standardized flows

Optimized use of space, less manual interventions

CGT process heat map



Highlights

- Starting Material **Cryo/Thaw process is identified as highly critical** for Processability, Manufacturing Strategy, Cell Biology, COGs, Raw Material manufacturing attributes
- Fill & Finish process is identified as highly critical for all manufacturing attributes. Besides it impacts the choice of the **Drug Product container** and by consequence, its cryologistics, thawing and patient administration procedure.

Cell Therapy Process Heat Map
Allogeneic cell therapies: Efficient Commercial Manufacturing Readiness using “Manufacturing by Design” Methodology, white paper by Catalent, 2020

General cryo cold chain considerations for CGT

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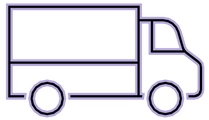
CRYOPRESERVATION

Controlled Rate Freezing
Cryoprotectant agents
Primary packaging



STORAGE AND SHIPPING

Temperature
Secure long-term storage, shelf-life
Primary packaging

THAWING

Controlled thawing
Maintenance of cell viability, efficacy, and potency

SUBJECTS OF CRYO COLD CHAIN in CGT: apheresis / cellular Starting Material, QC samples, Drug Product

CGT primary packaging needs

Cryovial

Cryobag
OriGen
Charter
Miltenyi

CellSeal
Biolife

Dedicated Vials
AT-Closed Vial, AT
Crystal Zenith, West

CGT primary packaging needs

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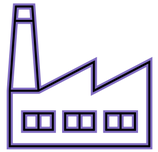
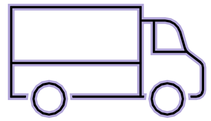
Several factors are considered during choice of primary container for CGT DP or key intermediate products

Cryopreservation
Volumes / cell concentration
Cryoprotecive agent
Container closure integrity
Identification



Processability
Fill & finish process
Scalability / automation
Connections – open/closed
Visual inspection



Cryologistics
Space
Fragility when frozen

DP administration
USP / Eph requirements:
- materials,
- bacterial endotoxins,
- sterility,
- particles,

User-friendly in clinic
Dosing - multiple

Platforms and solutions handling various types of container systems allow standardization and minimize COGs

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CONCLUSIONS

04

Conclusions

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Rapid growth – High product value – Cryopreservation is critical part of the workflow

- Various types of CGT products, main cellular immuno-oncology, developed ex-vivo
- Subjects of cryopreservation in CGT are Starting Material (apheresis), QC samples, Drug Product, filled in cryovials, cryobags, vials of various volume (1 ml and less to 500 ml)
- Autologous and allogeneic therapies require different manufacturing considerations, including quantity of samples (products) to store, scalability. Current CGT pipeline is already almost 50/50
- CGT projects involve multiple actors: Developers, CDMOs, Clinical sites, therapy centers, on multiple sites, in multiple geographies
- Cryo cold chain and cryo/thaw process are identified as critical for ensuring the CGT product quality
- US CGT market is leading by number of actors, investment, CDMO concentration

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Thank you

Feel free to connect on LinkedIn and reach out to

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