Pioneering Cell Therapies for the Next Generation

ISPE Boston Product Show

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Speakers

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Advanced Manufacturing Lead

VERTEX

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Technology

ARCADIS

Agenda

Vertex Pharmaceuticals Mission

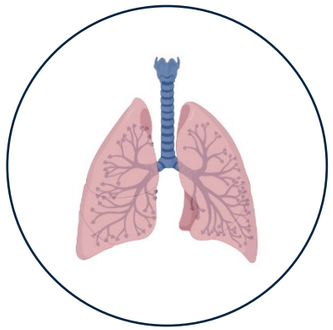
Cell Therapy Discussion

Scale Up Considerations

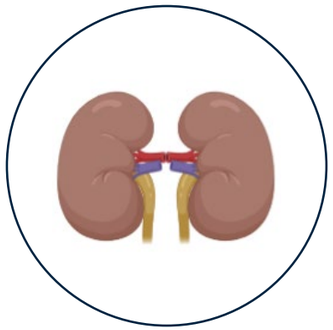
Facility Design Case Study

Vertex Pharmaceuticals Mission

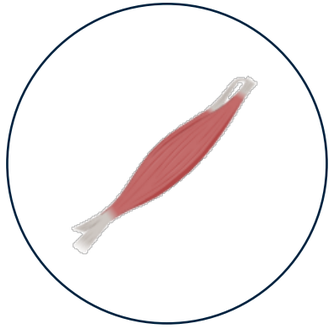
At Vertex, we invest in scientific innovation to create transformative medicines for people with serious diseases with a focus on specialty markets.



Cystic Fibrosis

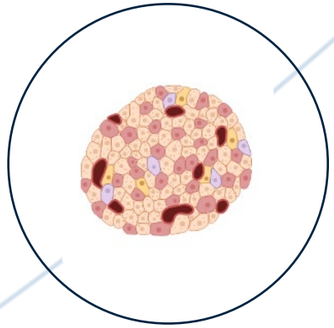


APOL-1 Mediated Kidney Disease



Duchenne's Muscular Dystrophy

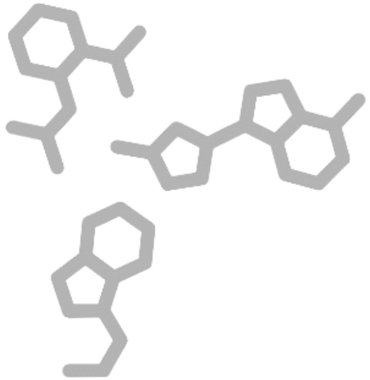
Sickle Cell Disease



Type 1 Diabetes

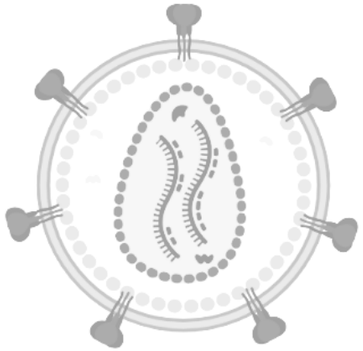
Vertex Pharmaceuticals Pipeline Approach

Multiple medicines, multiple modalities

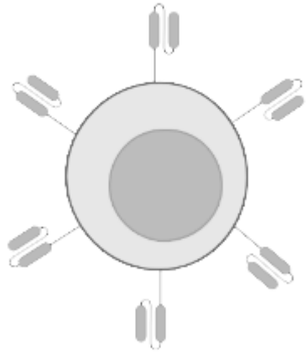


Small Molecule

Gene Editing



Gene Therapies



Cell Therapies

Vertex Pipeline:
Cell Therapy, Two Different Approaches

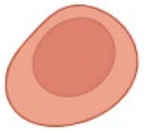
Approach 1:
Autologous Cell Therapy

Patient
Stem
Cells

RNP
Complex

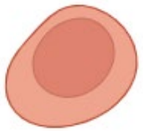
CRISPR/Cas9
Gene Editing

Patient
Stem
Cells
(edited)



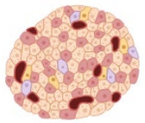
Approach 2:
Allogeneic Cell Therapy

Donor
Hematopoietic
Stem Cells



Differentiation

Pancreatic
Islet
Cells



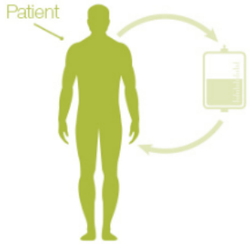
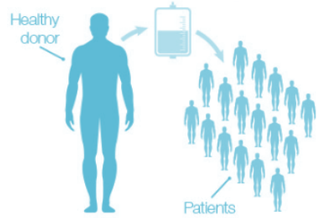
Vertex Pharmaceuticals Mission

Cell Therapy Discussion

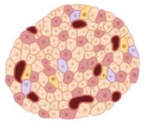
Scale Up Considerations

Facility Design Case Study

Cell Therapy Primer, Autologous vs Allogeneic

	Autologous	Allogeneic
		
Cell Source:	Patient Specific	Healthy Donor
Scaling Strategy:	Scale “Out”	Scale “Up”
Delivery Timeframe:	Weeks – Months	Days
Safety Profile:	CRS, Neurotoxicity	Risk of GvHD
Cost:	$$$$	$$$

Vertex Pipeline:
Cell Therapy, Two Different Approaches

	Approach 1: Autologous Cell Therapy		Approach 2: Allogeneic Cell Therapy
Indication:	Sickle Cell Anemia 	Transfusion-dependent Beta Thalassemia 	Type 1 Diabetes 
Prevalence (US):	70,000 - 100,000	>100,000	1.5 million
Technology:	“ex vivo” CRISPR/Cas9 gene-edited cells		fully-differentiated insulin-producing cells

Gene Editing 101

- Ability to add, delete, or alter, genes at a **precise** location
- Viral, non-viral approaches available for delivery
- Used in combination with cell therapy for “ex vivo” applications

Vertex Pharmaceuticals Mission

Cell Therapy Discussion

Scale Up Considerations

Facility Design Case Study

Scale Up Considerations

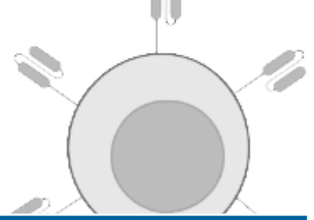
technology platform	cell expansion*	Cell Processing	Filling[3]
“Scale Out” Autologous Cell Therapy[1]	Maintenance		
“Scale Up” Allogeneic Cell Therapy[2]			

1 Gene editing step is unique per product
2 Media, Media, Media
3 Critically connected to cold transport

Autologous Scale Up Considerations

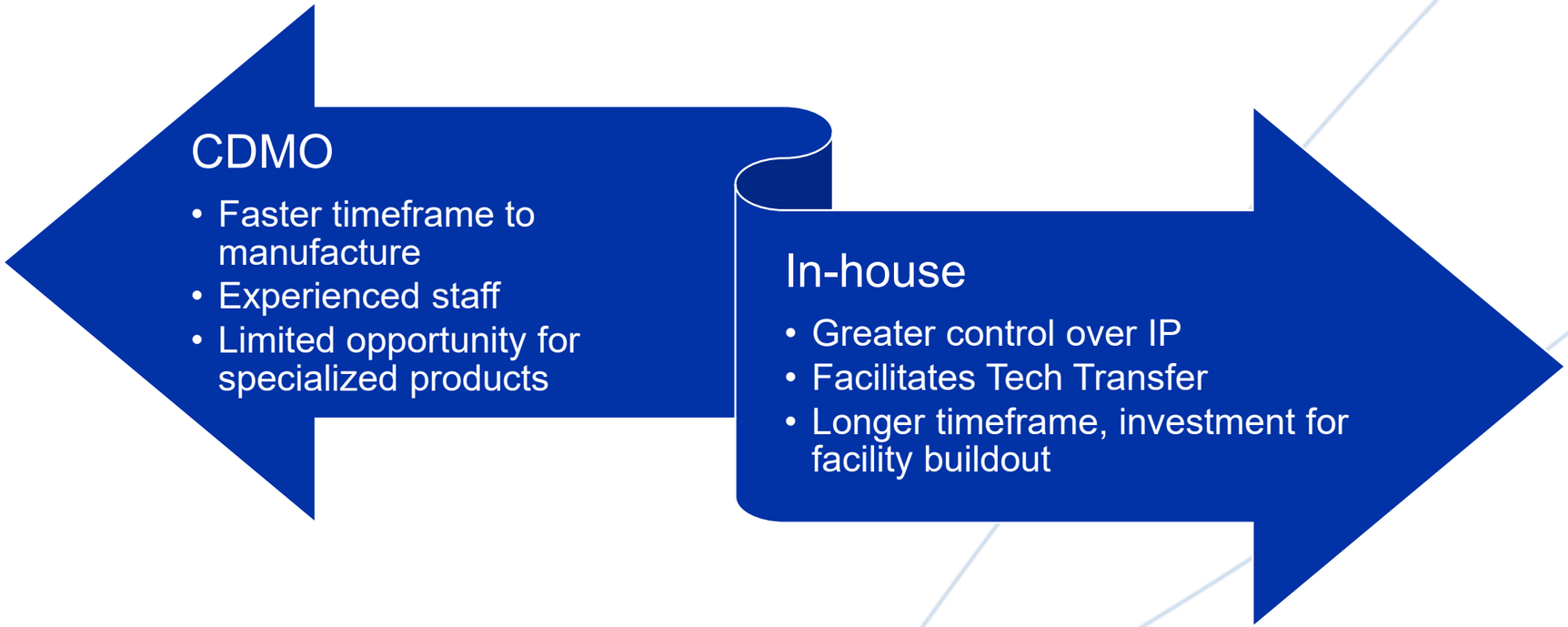
Lifecycle stage	Process Description	Room Grades	Facility Throughput
FIH / Phase 1 “1 patient”	Laboratory GMP Process Very manual Very “open”	Entirely Grade B Ballroom style	1 Train Increase throughput by Maximizing equipment up-time until bottlenecked
Phase 2 / 3 “Scale Out”	Process improvements (e.g. yield) “Closing” process steps Less manual	Reduced Grade B Some Grade C B/C operations grouped around open-processing steps	Multiple Trains Added equipment to relieve bottlenecks. Filling likely becomes permanent bottleneck.
Late Phase / Commercial “More Scale Out”	Continuation of above	Majority Grade C B space minimized Room setup dictated by personnel/material flows	Continuation of above Throughput significantly effected by site layout

Allogeneic Scale Up Considerations



Lifecycle stage	Process Description	Room Grades	Facility Throughput
FIH / Phase 1 “1 patient”	Laboratory GMP Process Very manual Very “open”	Entirely Grade B Ballroom style	1 Train Throughput from staggered runs limited by differentiation reactor duration
Phase 2 / 3 “Scale Out or Scale Up”	Process improvements (e.g. yield) “Closing” process steps Less manual	Seed only Grade B Grade C operations either ballroom or suite style	Multiple Trains Dependent on # of incubators & bioreactors
Late Phase / Commercial “Scale Up”	Continuation of above Bulk media/factor preps (SU vs SS)	No change	Continuation of above Throughput significantly effected by site layout

Scale Up Considerations: CDMO vs In-house Manufacturing

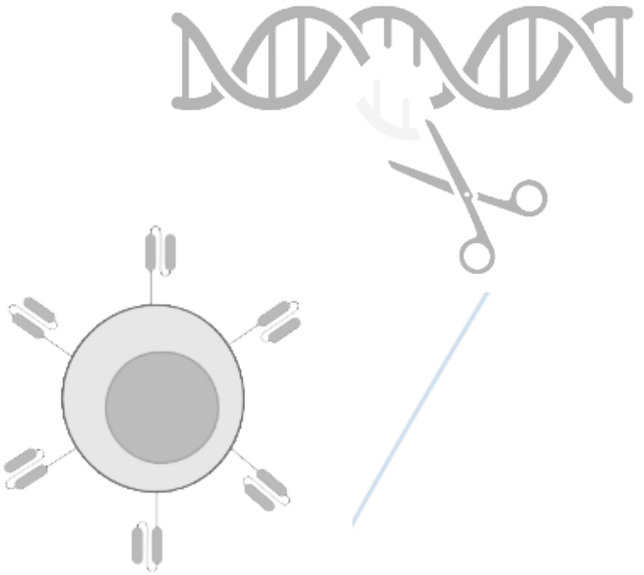


Scale Up Summary

How do we as engineers plan & build a manufacturing facility for producing at-scale for an unknown process 2-3 years in the future?

Distill process to fundamentals and understand:

- Autologous & allogeneic scale differently
- Every process is unique: review N=1 process for scalability & closure
- Allogeneic scale-up similar to traditional biologics
- Autologous at scale requires dynamic analysis of personnel/material flows
- Drug delivery method impacts facility design & throughput
- Control of DP after filling is key input to facility design
- CDMOs limited operator experience vs in-house manufacturing



Questions for peers

- can OEMs create modular equipment for autologous scaling-out
- Method for concurrent autologous DP fills

Vertex Pharmaceuticals Mission

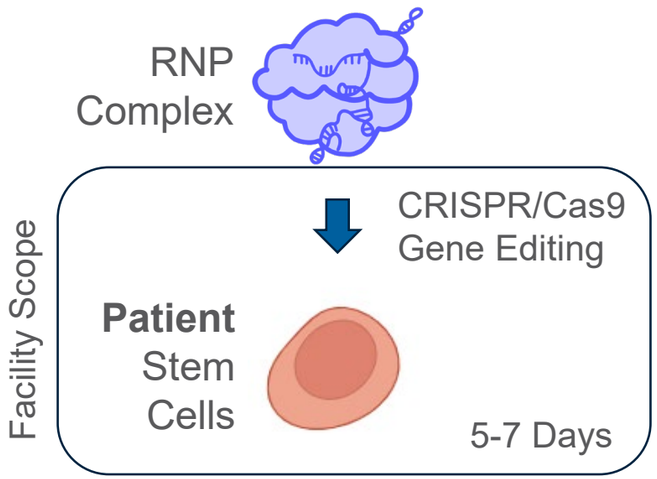
Cell Therapy Discussion

Scale Up Considerations

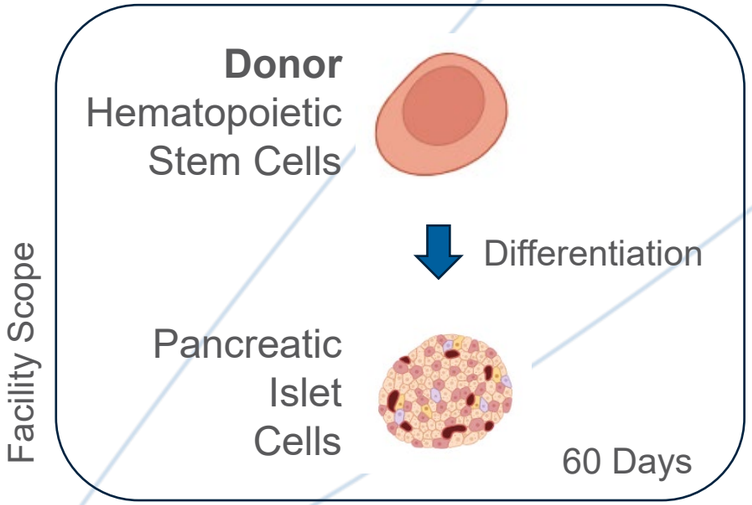
Facility Design Case Study

Facility Design Case Study: Two Different Products, Two Different Facilities

Approach 1: **Autologous** Cell Therapy



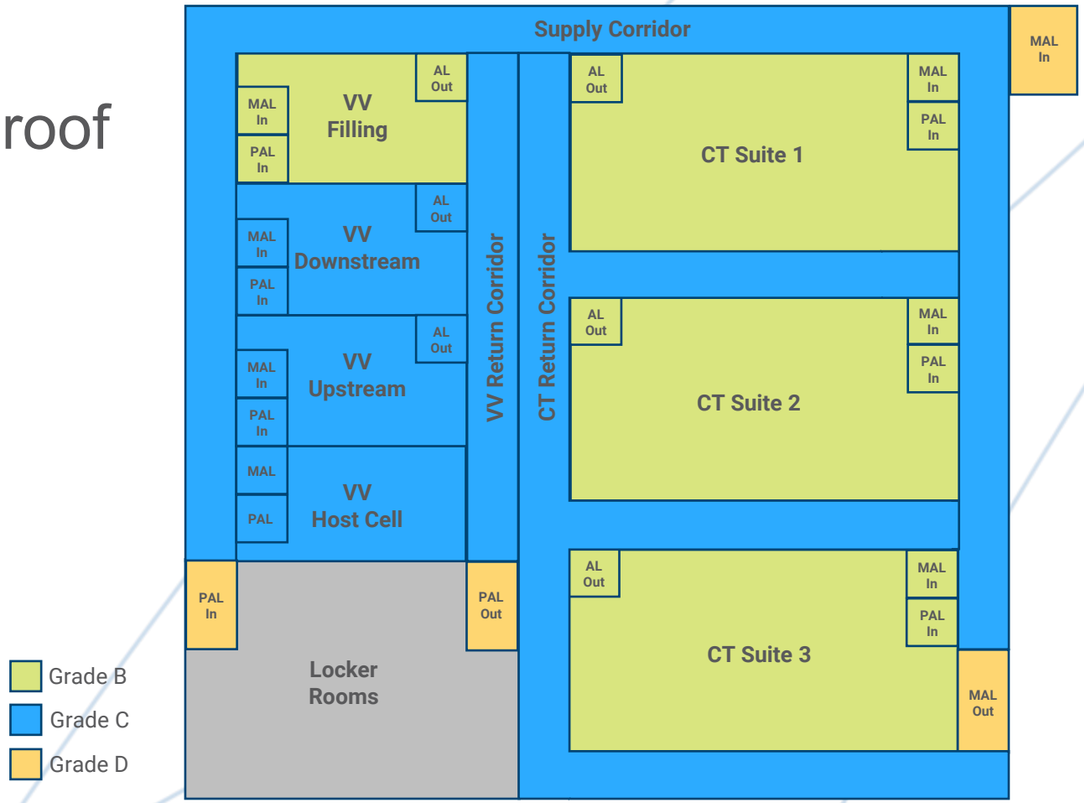
Approach 2: **Allogeneic** Cell Therapy



Facility Design Case Study: Autologous Cell Therapy Facility

Facility Highlights:

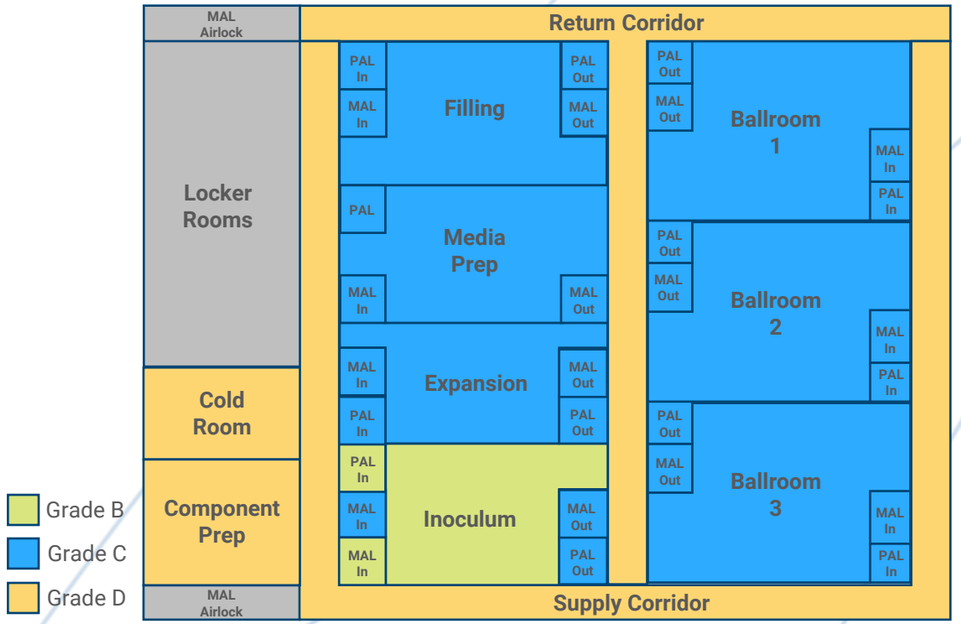
- Gene therapy + cell therapy under one roof
- Grade C corridors
- Grade B CT Suites, VV filling
- Shared locker rooms
- Uni-directional GMP flows



Facility Design Case Study: Allogeneic Cell Therapy Facility

Facility Highlights:

- Cell therapy - scale up to 2000L bioreactors
- Media Prep in-house vs. pre-purchased
- Grade D corridors
- Uni-directional GMP flows



Facility Design Case Study: Facility Metrics Comparison

	Approach 1: **Autologous** Cell Therapy	Approach 2: **Allogeneic** Cell Therapy
Scale:	Individual Patient	Up to 2000L Bioreactors
Patient Population:	~500 PPY	>10,000 PPY
Facility Square Footage:	50,000 ft2	100,000 ft2
Manufacturing Duration:	5-7 Days	60 Days
Final Product Format:	Cryopreserved	Fresh – Three Day Window

Summary

Multiple modalities are being pursued to develop therapies for a given indication

Scale up to allogeneic production has limited equipment options, equipment closure is key to downgrading cleanrooms

Autologous production is more conservative due to inherent risks with multiple products within the same facility

Allogeneic production can scale to >2000L to address large patient populations, although primarily theoretical in nature