Flagship Pioneering

Pioneering Life Science Platforms and Their Challenges

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VIRTUAL WORKSHOP ON TECHNICAL AND REGULATORY BARRIERS TO INNOVATIONS IN PHARMACEUTICAL MANUFACTURING

June 3, 2020

The Current Flagship Ecosystem

FLAGSHIP LABS

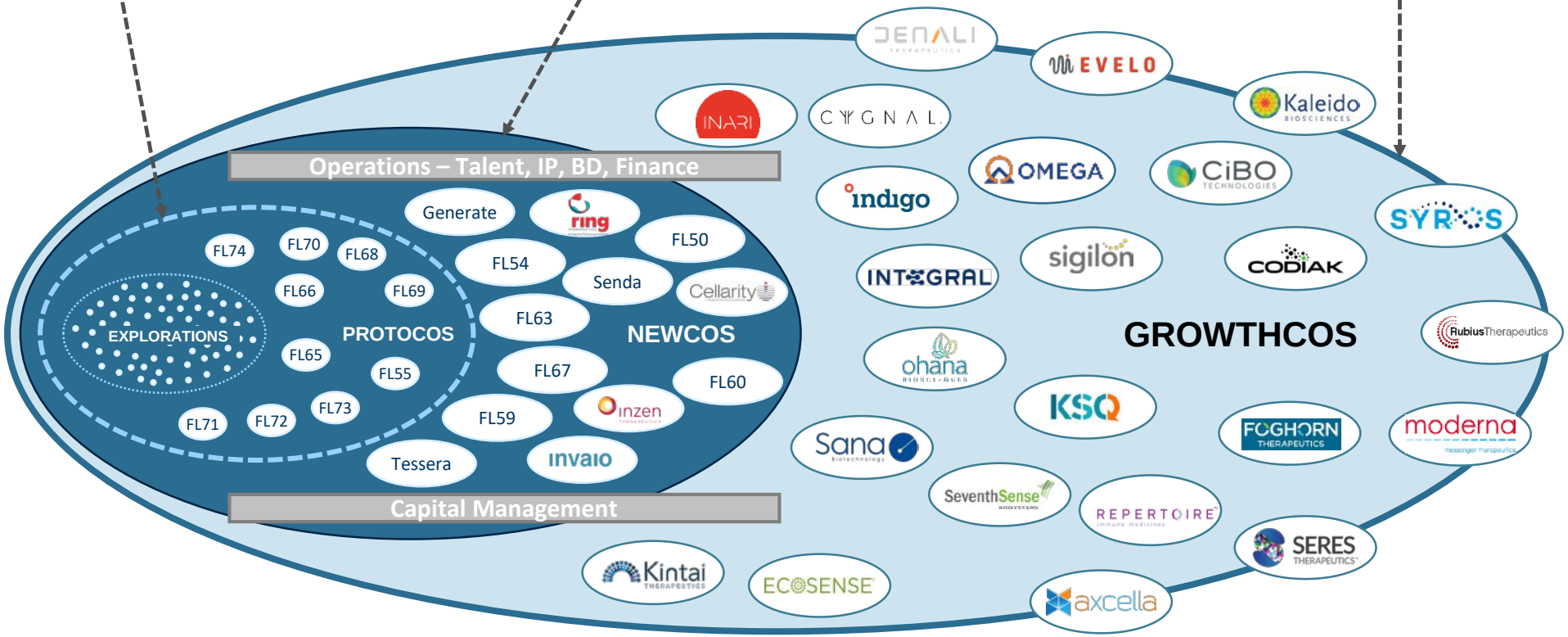
Experienced scientists, entrepreneurs and operational executives providing economies of scale to the creation and growth of our companies – Exploration and ProtoCompanies (>135 members)

FLAGSHIP PIONEERING ENTERPRISE

Includes wholly owned companies conceived by Flagship Labs team and led by Flagship executives during first 2-3 years (350+ members, $200M+ annual R&D and 250K sq. ft. space)

FLAGSHIP PIONEERING ECOSYSTEM

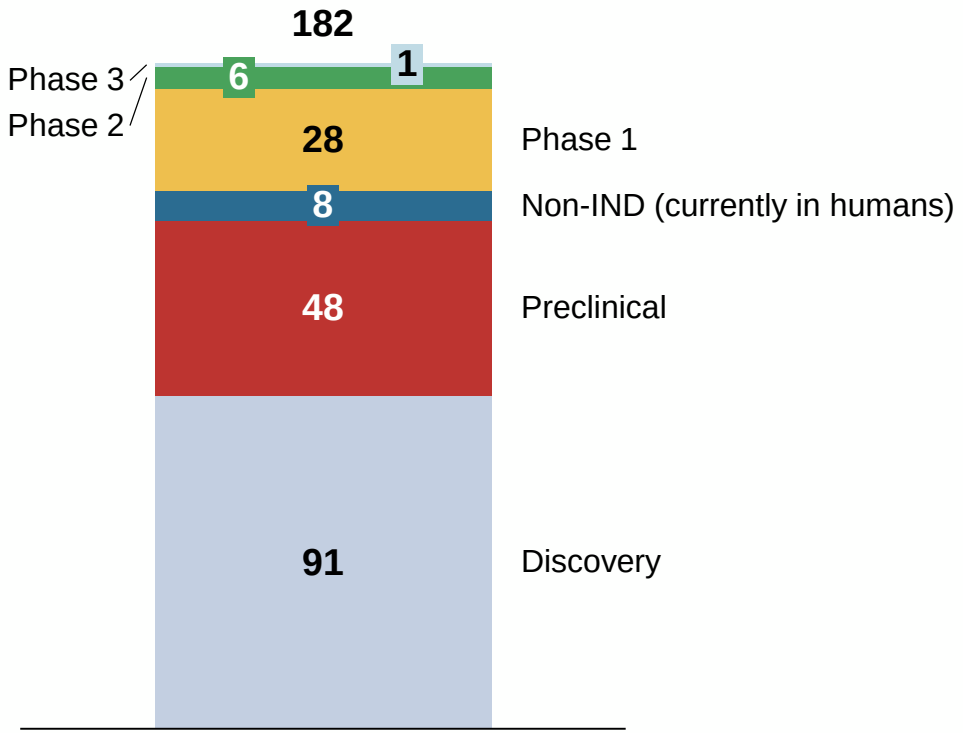
Includes growth-stage companies spun-out of Enterprise (3500+ members, $1.5B in annual R&D and 1.3M sq. ft. space)



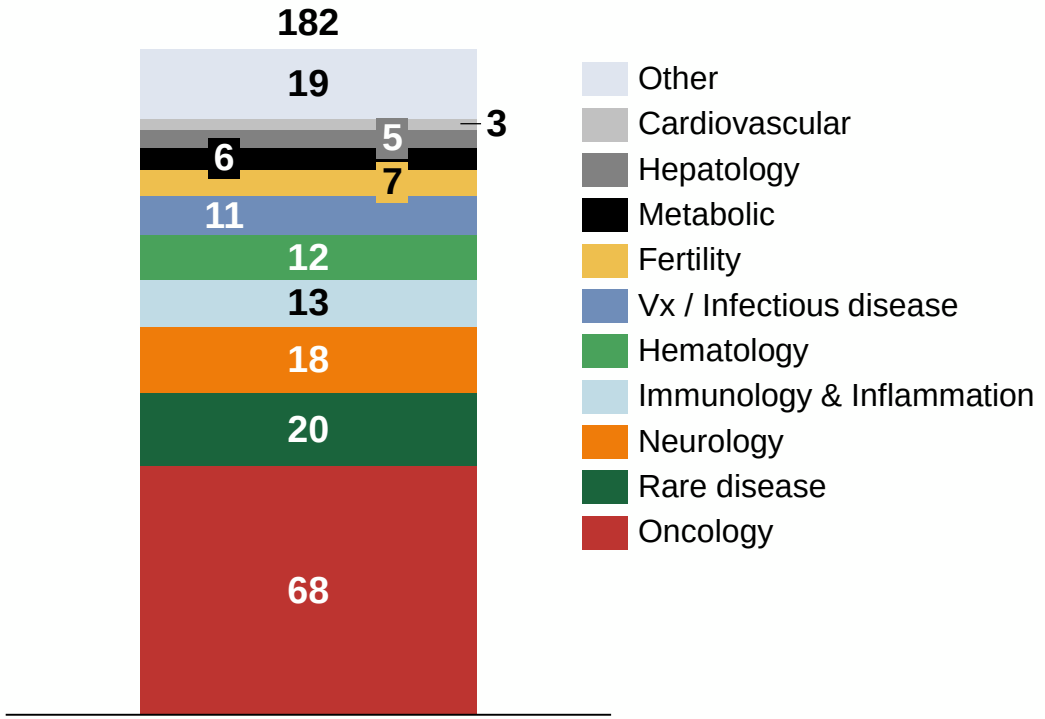
Flagship Pioneering

Flagship ecosystem portfolio by phase and therapeutic area

By development phase



By therapeutic area

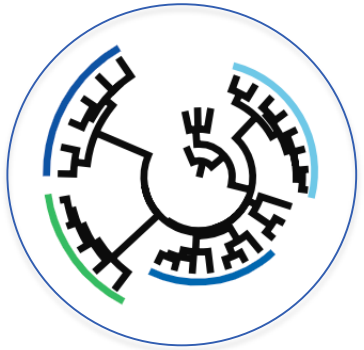


Source: Flagship Ecosystem company pipeline data as of year-end 2019

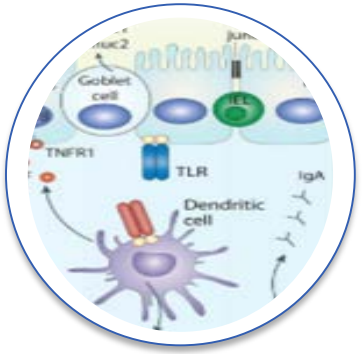
Flagship Pioneering

Seres Therapeutics is developing a novel drug modality that modulates the gut microbiome

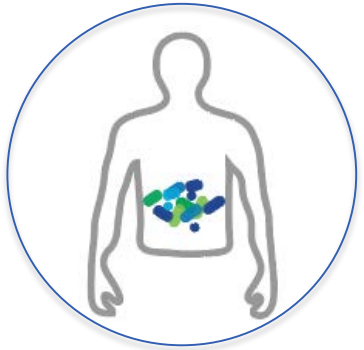
Ecobiotic® Live Microbiome Biotherapeutics are encapsulated consortia of bacteria with specific pharmacologic properties



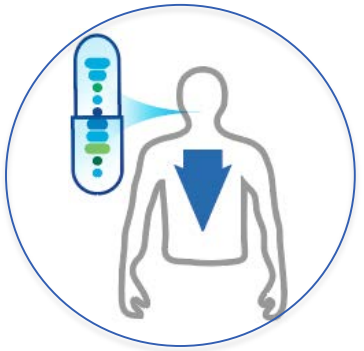
Consortia capture **breadth of phylogenetic & functional diversity** in gut



Designed to **target inflammatory & immunological** disease pathways simultaneously



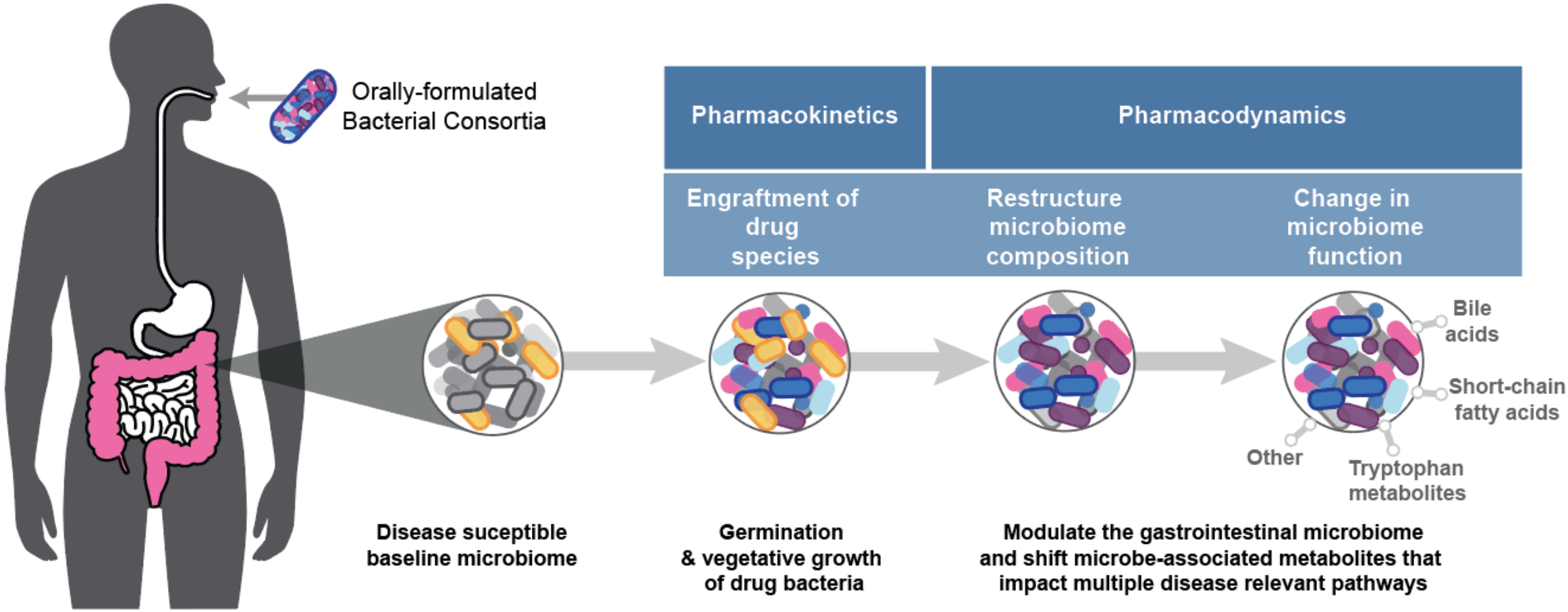
Mechanisms includes microbial **engraftment in GI tract** to restructure the microbiome



Formulated for **oral delivery** using current Good Manufacturing Practices (cGMP)

SERES THERAPEUTICS™

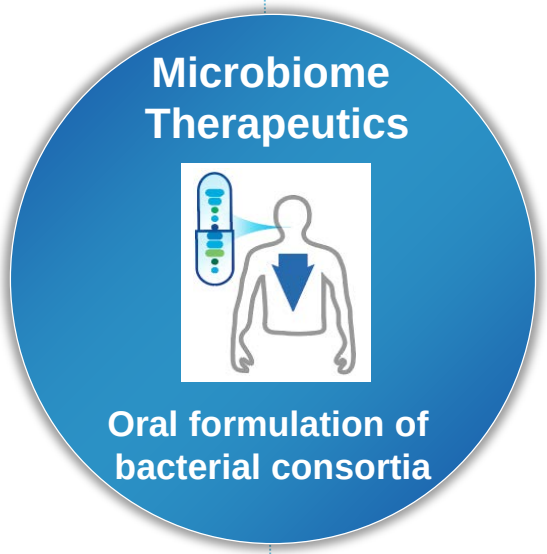
Seres microbiome therapeutics are designed to rapidly restructure the microbiome and modulate disease relevant pathways



SERES THERAPEUTICS™

Unique features for GMP manufacturing and quality control of microbiome therapeutics

- **Gut microbes have limited-to-no industrial pharmaceutical experience**
  - Generally anaerobic
  - Often not aerotolerant
  - Many are spore-formers
- **Manufacturing Issues to Solve:**
  - Multiplicity of organisms in a product
  - Diversity of organisms and their culture behaviors
  - Stable preservation, oral (targeted) delivery
  - Analytical characterization of microbial mixtures
  - cGMP supply chain



- **Safety**
  - Genome sequencing, characterization for Abx resistance/ mobile elements, (pro)phage, toxins
- **Identity**
  - Genome sequencing
  - Functional/phenotypic characterization
- **Strength**
  - CFU assays optimized for species detection in mixtures
  - Potency assay for activity
- **Purity**
  - USP <61>/<62> not useful for commensals and mixtures; optimize to suppress product background while maintaining sensitivity to pathogens
  - Expectation of contaminant minimization, even in non-sterile oral dosage forms
  - Process (bio)chemical residuals
- **Quality (Pharmaceutical)**
  - Formulation excipients, moisture content, disintegration, container closure, etc.

SERES THERAPEUTICS™

SER-109: A novel biologically-derived product adapted from proven approaches

Well-established Inactivation Paradigm, Validated by Pathogen Challenge Studies

Multi-Component, High Potency Active analogous to other natural biologics: IVIG, Premarin®, Otosporin®

Highly Stable Spore Drug Product

Donor Collection | **Pathogen Inactivation** | **Spore Purification** | **Drug Substance** QC | **Formulation & Encapsulation** | **Drug Product** QC | **Packaging & Distribution**

Follow Blood, Urine, and Tissue Product Paradigms

Conventional, Simple, Well-Understood Purification Steps

Off the Shelf Formulation and Capsule Packaging

Room Temp storage

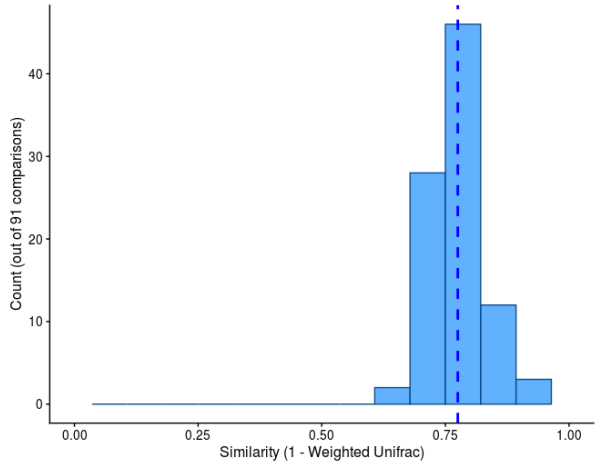
Straightforward Production Elements

- Individual operations and their features are well-established
- Modest production scales
- Hard shell capsule delivery enables standard processing, storage, distribution

Live vaccine-like product

- Provide small, potent spore dose, using the human gut as a bioreactor to amplify
- Modest donor program scale
- Results in a consistent product

Weighted UniFrac comparison of SER-109 lot composition

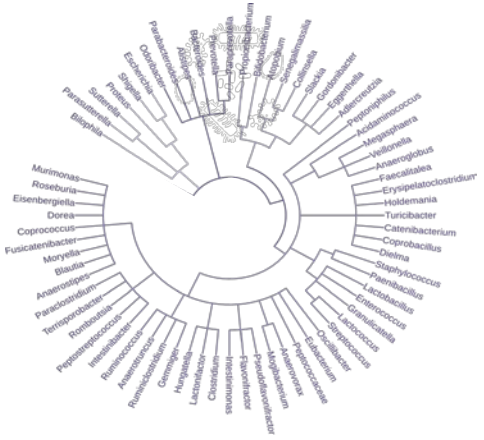


SERES THERAPEUTICS™

Evelo's integrated platform efficiently selects and develops candidates

SOURCE	SELECT	DEVELOP	
MICROBIAL LIBRARY	ASSAYS & BIOLOGY	PROCESS DEVELOPMENT & MANUFACTURING	FORMULATION

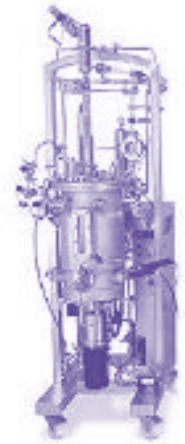
Proprietary strains from healthy and diseased tissue



Match activity in human *in vitro* and mouse *in vivo* assays

- *In vitro* Human Assays
- Animal Models
- Computational Biology

In-house pilot scale fermentation and lyophilization



Delivering pharmacologically active monoclonal microbes

Manufactured and formulated for optimized pharmacology

Integration of microbiology, immunology, computational biology

Developing monoclonal microbials into a new class of therapy requires significant CMC advancements beyond current practices

Extensive characterization of target microbes for safety assessment and activity

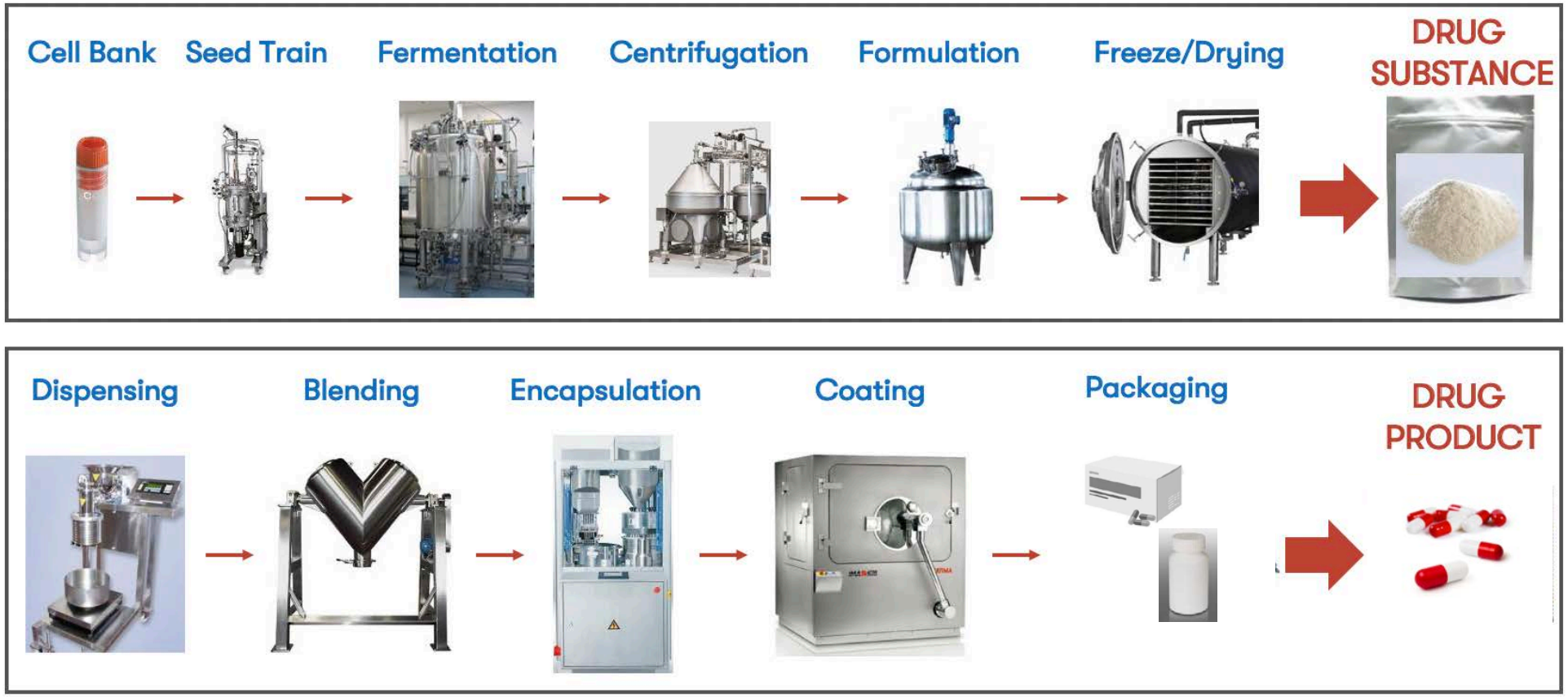
Developing novel formulations to achieve optimal release profile and room temperature storage

Developing robust and high yield processes for novel microbes with limited literature or industrial experience

Scaling up under strict anaerobic conditions from vial thaw to drug substance

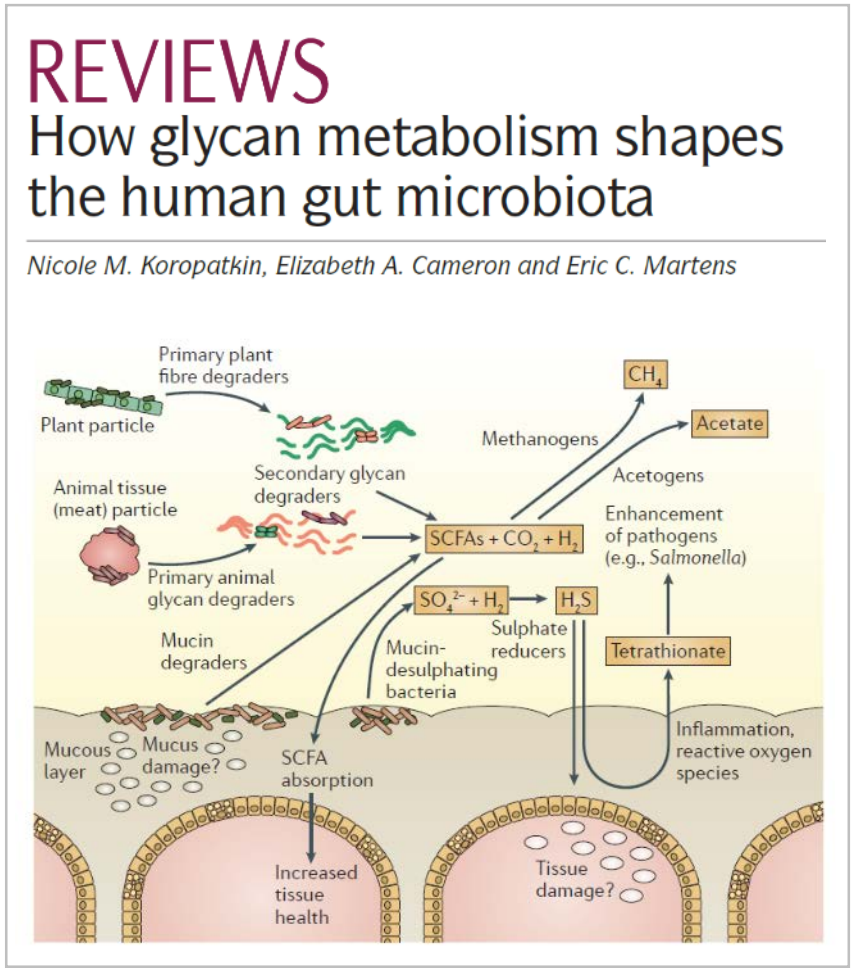
Understanding impact of process conditions on microbe's efficacy

Evelo's proprietary methods enable scalable manufacture of pharmacologically active monoclonal microbials

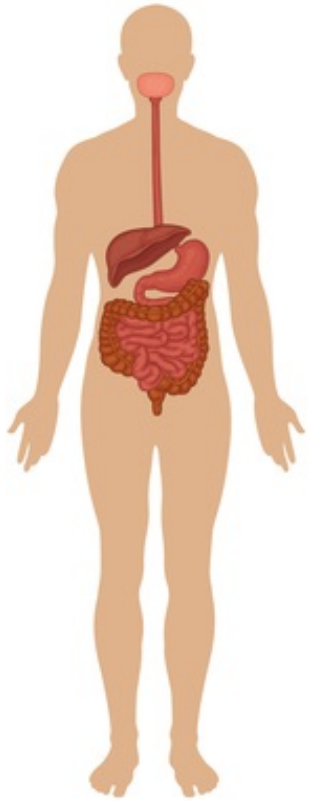


Monoclonal microbials are isolated, fermented, and purified in a manner analogous to the manufacture of pharmaceutical drugs

Glycans Play a Major Role in Shaping the Gut Microbiome and Drive Metabolites that Modulate Disease Pathways



Natural glycans from multiple sources e.g. plant, mucus, meat, microbial, milk



Humans:
17 glycosidases

Microbiome:
>3000 glycosidases

Advancing Chemistry to Create Novel Synthetic Glycans Targeted at Multiple Pathways

Source: Koropatkin et al., *Nature Reviews Microbiology*, 10, 323–335 (2012)

Kaleido is applying novel chemistry to modulate the entire metabolic profile of the microbiome

Microbiome Metabolic Therapies (MMTs) are complex oligosaccharides metabolized by the microbiome to systematically drive its metabolic outputs

Kaleido BIOSCIENCES

Kaleido's chemistry insight: catalysts that normally degrade glycans can synthetize them instead if we reverse the reaction

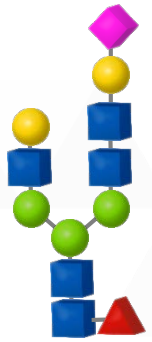
Sugar monomers

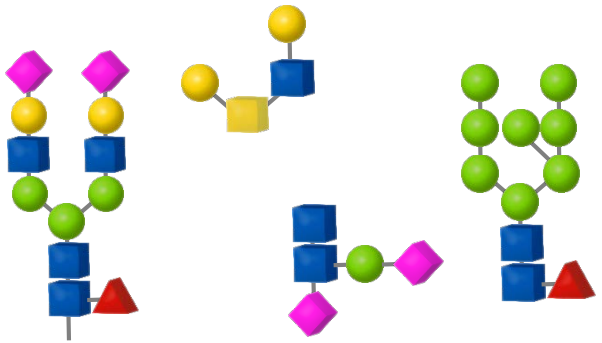
Proprietary catalysts

Proprietary catalysts and enzymes generate diverse glycans with controlled or diverse composition

Tailored molecules

Structures with controlled bonds





Novel mixtures

Drives diversity of novel structures

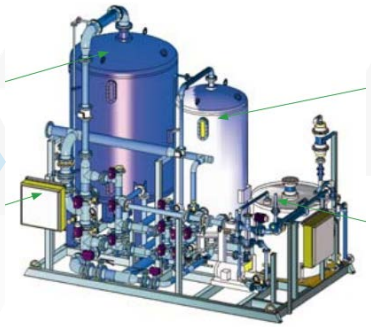
Kaleido BIOSCIENCES

Kaleido's platform allows for multiscale synthesis, rapid formulation, and can easily scale to 1,000kg+

Our platform enables multiscale synthesis

We can produce many diverse glycans using small batch synthesis and our glycans are easily scalable to 1,000kg+

2g scale



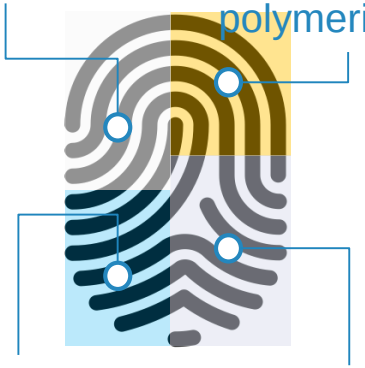
1,000kg+ scale

We have a strong analytical pipeline

Kaleido's platform integrates multiple analytical methodologies for structural characterization of our oligosaccharides

IAC: Monomer content

SEC: MW and Degree of polymerization

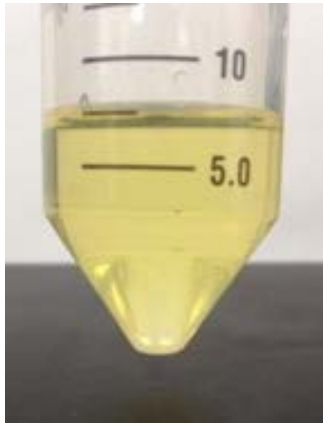


HSQC NMR: α-/β-distribution & substructure

GC-MS: Degree of Branching & Linkage

Our glycans are easily formulated

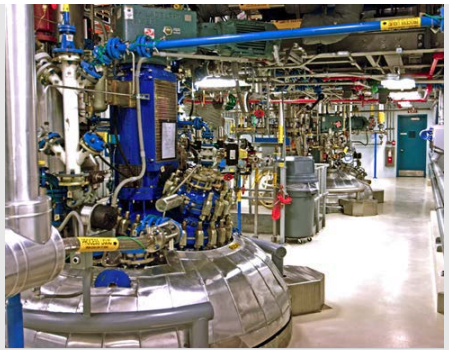
Our glycans are highly soluble (~650g/kg+) and can be easily formulated to be bioavailable to the microbiome



A 80% w/v solution of Kaleido glycan

Manufacturing is a Core Strategic Advantage: Small-molecule like, Efficient and Scalable Cost-Effective Process

Proprietary Methods
Standard Small Molecule
Unit Operations
Scalable and Transferable



Internal Manufacturing

Production for *ex vivo*, toxicology, and human clinical studies

3rd Party Manufacturers

Large scale production for clinical trials and future commercial supply (Thermo Fisher Scientific)

- Efficient and scalable process
- Internal capability to manufacture 12 MMTs per year; potential to double in 2020
- Completed tech transfer to Thermo Fisher in ~6 months, scaled to 1,000 kg with capability to increase by >40X
- KB195 manufactured for Phase 2 trial and toxicology

Exosomes: “Nature’s Drug Delivery Vehicles”
A New Class of Targeted Biologic Medicines

Exosome Therapeutics

Exosome basics

- 30-200nm lipid/protein nanoparticle
- Transfer and protect macromolecules for intercellular delivery
- Alter biological functions of recipient cells

Body’s “Fed Ex” system for packaging and delivery

Allogeneic, off-the-shelf, immune silent drug delivery

Engineered cell tropism for selective targeting

Broad combinatorial therapeutic spectrum

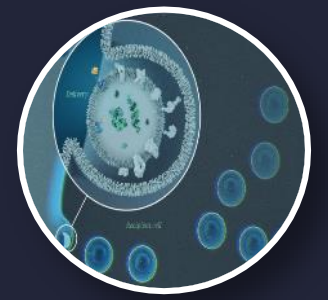
Natural Exosome Function

Cell Tropism/
Membrane Signaling

Cancer Sci. 2019, 110(7):2119
Nature. 2018, 560(7718):382

Intracellular
Payload Delivery

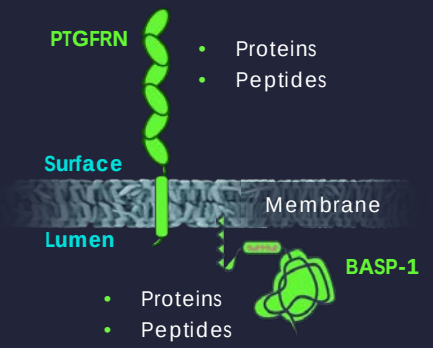
Nat Cell Biol. 2007, 9(6):654
Cancer Immunol Res. 2018, 6(8):910



Creating Customized Exosomes with the engEX Platform: Packaging and Addressing

engEx CELL-ENGINEERING

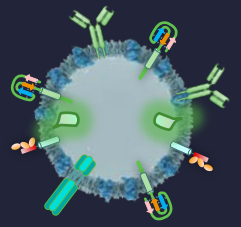
Exosome bioengineering



Plasmid

Targeted integration

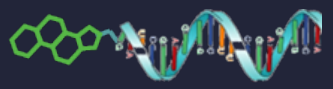
Surface or lumen protein engineered exosomes



engEx EXOSOME-LOADING

Small molecule

Oligonucleotide

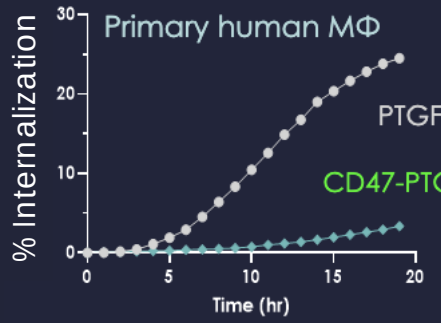


Peptide or protein

Creating the package

engEx EXOSOME-TROPISM

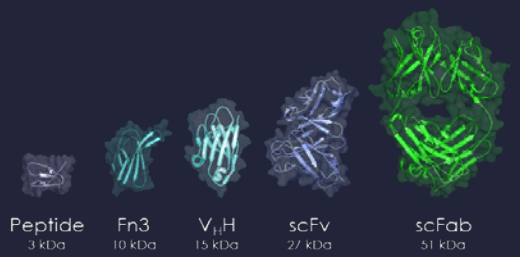
Engineered macrophage (MΦ)tropisms



Enhanced MΦ tropism
- PRGFRN

Reduced MΦ tropism
- CD47

Engineered cell specific routing



- B cells: CD40L
- T cells: anti-CD3
- mDC cells: anti Clec9A
- Neurotropic peptides
- Cancer neoantigens

Addressing the package

Successful Industrialization of Exosome Manufacturing

Human clonal cell line engineered to secrete custom exosomes

2,000L fed-batch or 500L perfusion operation

Proprietary centrifuge-free purification

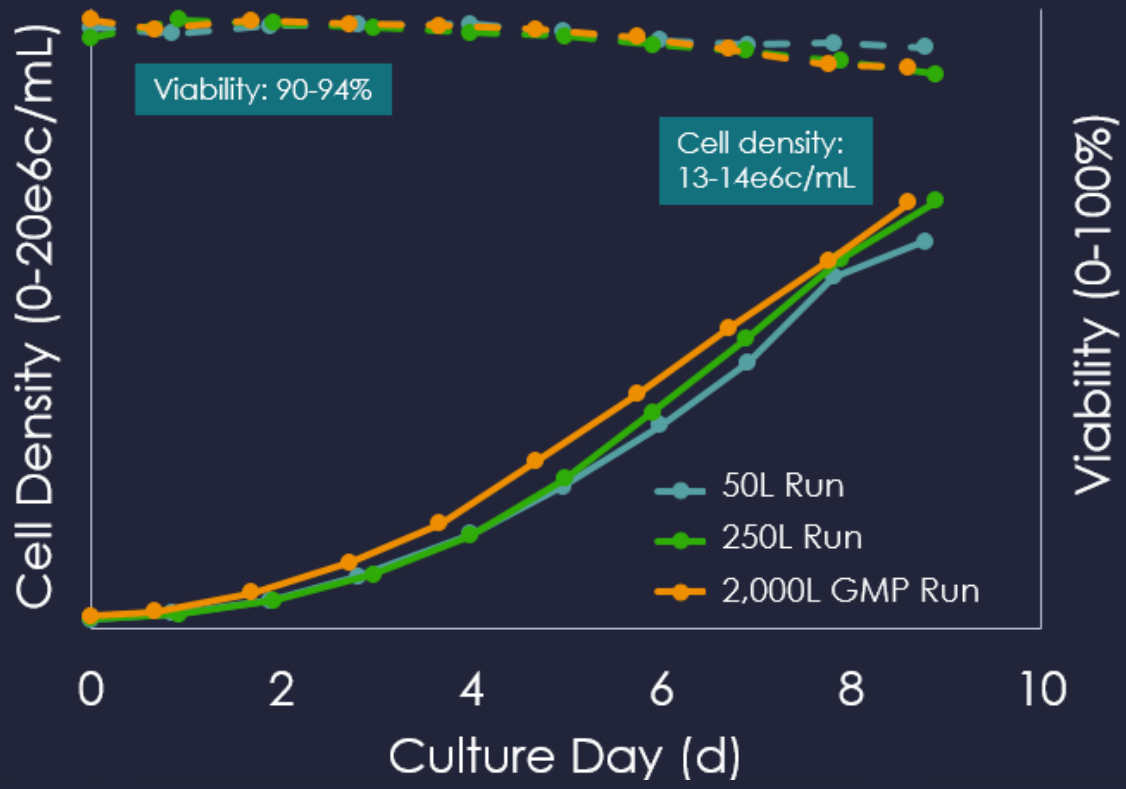
Large scale sublots of highly purified exosomes

Supply to support large patient populations

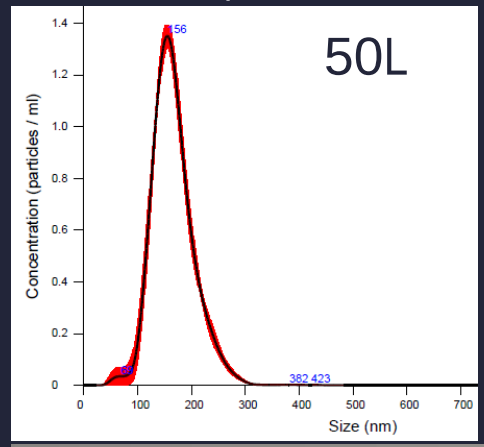
Proprietary portfolio of GMP analytical methods to confirm product quality, potency and consistency

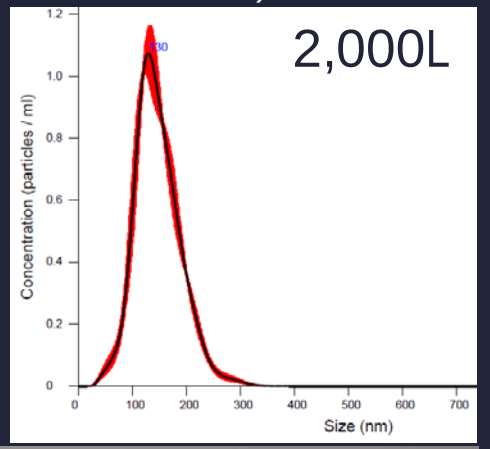
- Largest scale GMP production completed for exosome therapeutics
- Codiak Clinical Manufacturing Plant available summer 2020

Reproducible Operation Up to 2,000L Scale Under GMP



High & consistent quality of purified product
(NTA exosome size distribution)

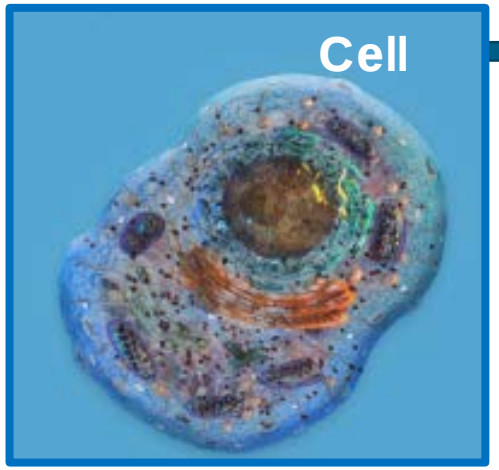




- Successful scale up 50L > 250L > 2,000L
- High degree of reproducibility at all scales

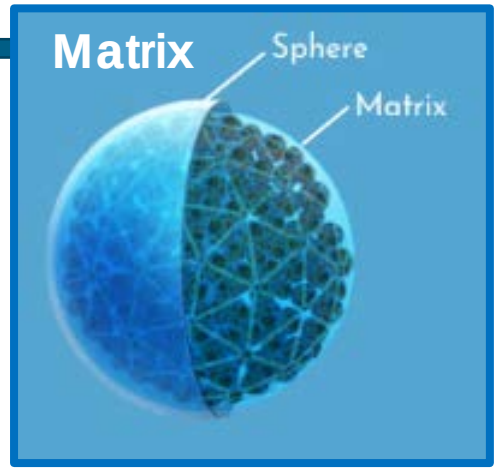
The SLTx™ Product Platform:
From Cell Function to Functional Cure

Shielded Living Therapeutics™ - IP across the platform



Human cell lines selected for safety, durability, efficacy

- Engineered to express high levels of desired protein
- Straightforward to manufacture



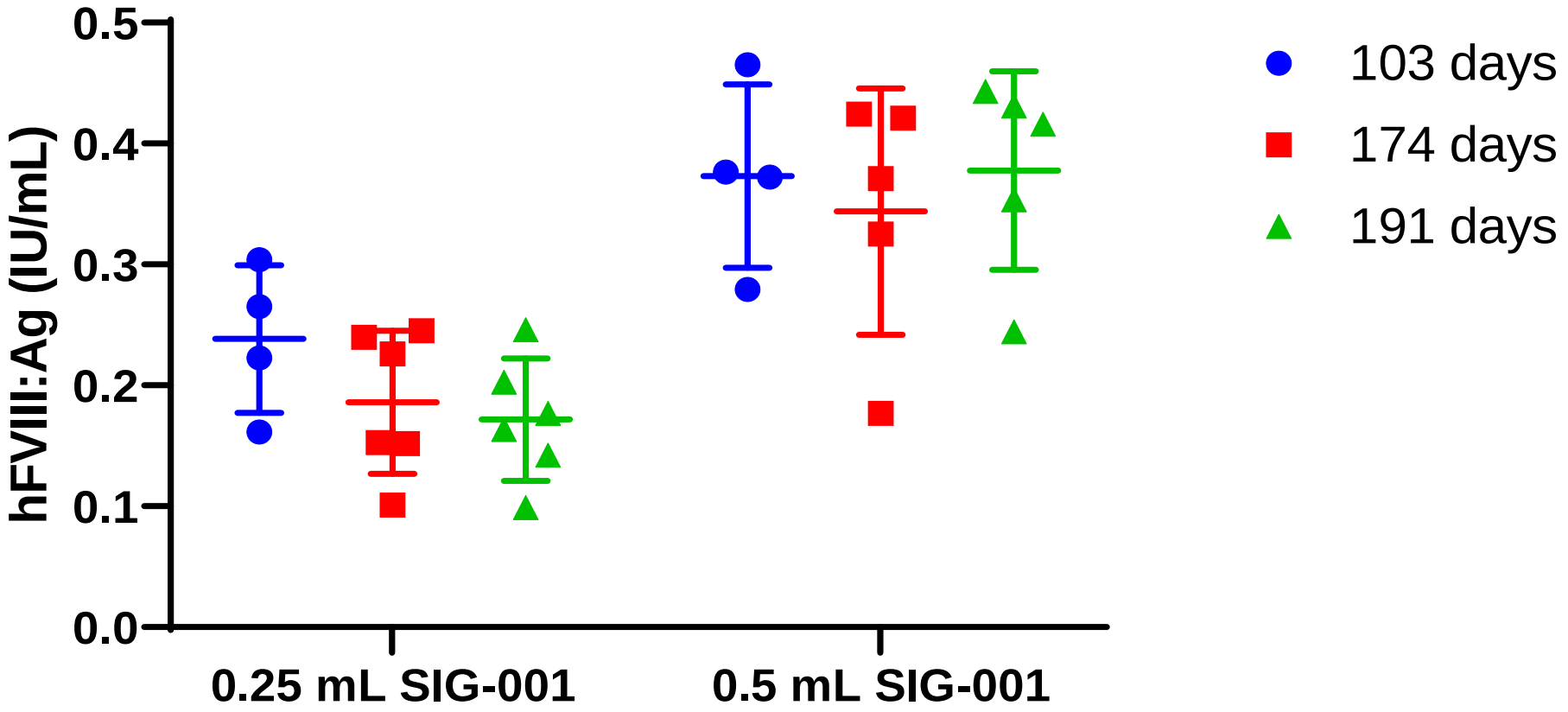
Biocompatible matrix

- Afibromer™ hydrogel shields cells from immune attack and fibrosis
- Allows oxygen & nutrients in; therapeutic proteins out

sigilon therapeutics

Unprecedented Durability:

Demonstrated 6 Months of human factor VIII (hFVIII) Plasma Levels in Mice



sigilon therapeutics

SLTx™ is a Modular Platform:
Rapid Transit from Concept to Clinic

1 2

2 years

Stable characterized cell line

Sphere components optimized

Manufacturing standardized

Platform optimization

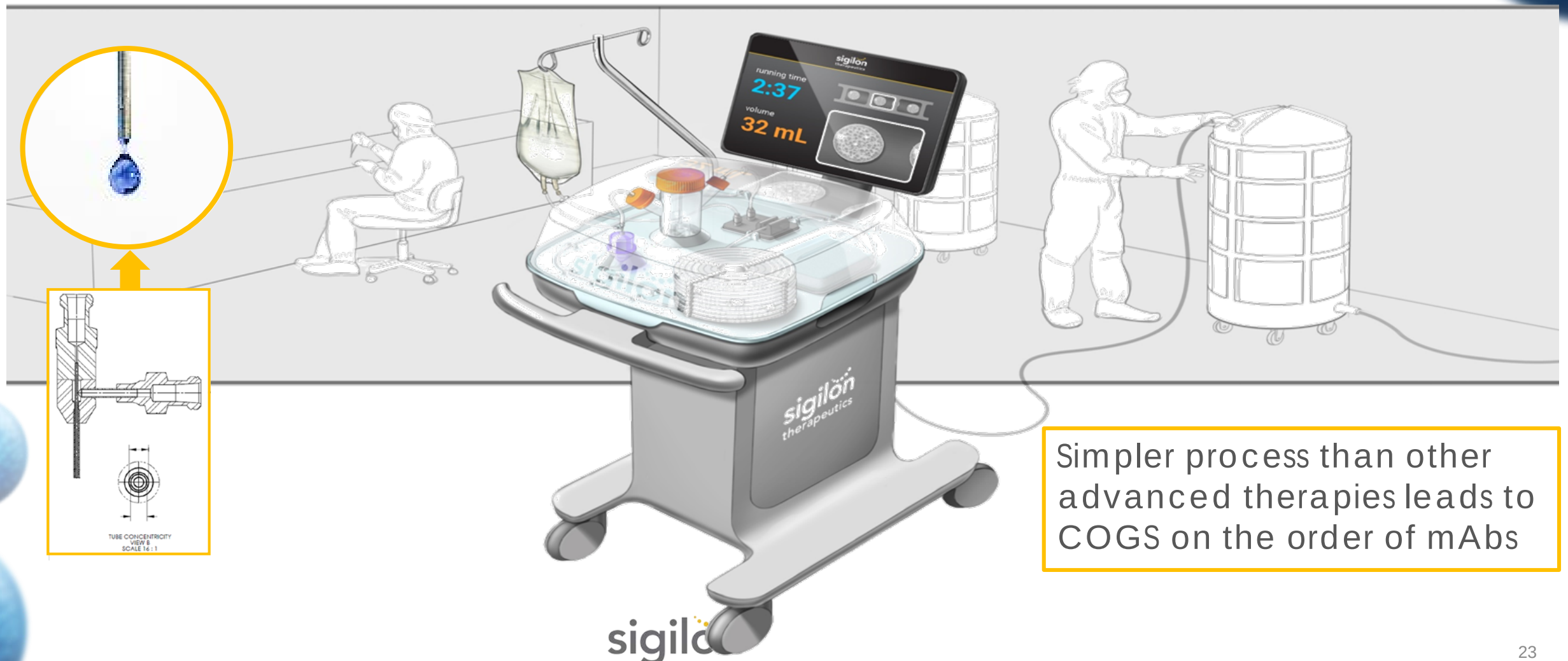
Platform validation
cell, sphere, manufacture

"Plug & play"
Cell engineering approaches

IND/FIH

sigilon therapeutics

Pioneering an Innovative and Scalable Automated Encapsulation System



Simpler process than other advanced therapies leads to COGS on the order of mAbs

sigilon therapeutics

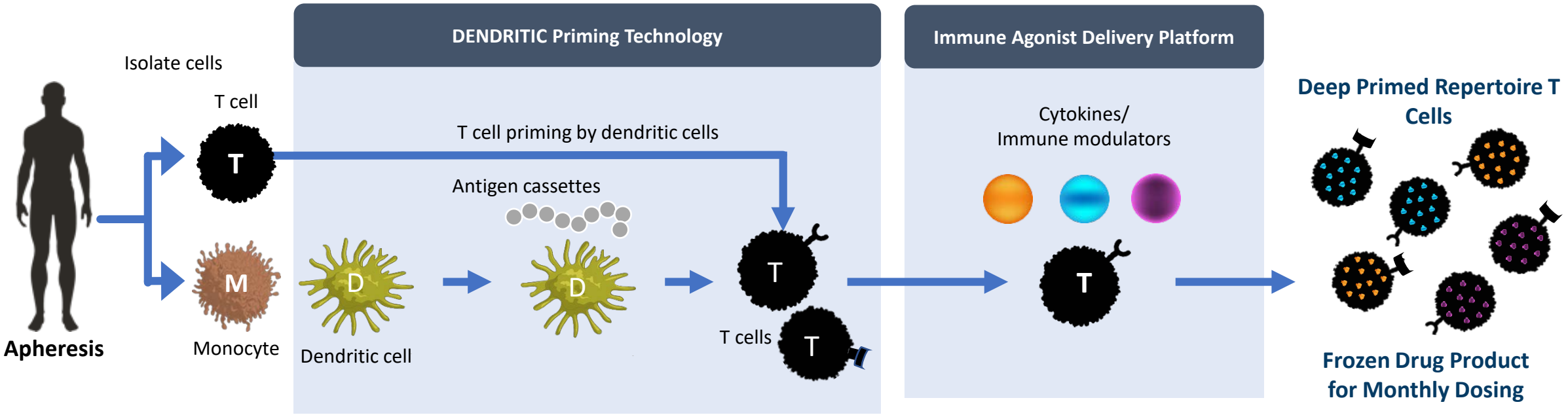
Functional Cure To Patients With Chronic Diseases

Shielded Living Therapeutics™

- **Unique approach to treating chronic disease**
- **Extensive validation and direct translation to the clinic**
- **Cost effective to scale**
- **Initiating our first in human trial in Q3 20**

sigilon therapeutics

Adoptive Cell Therapy: Dendritic Priming of Autologous T Cells



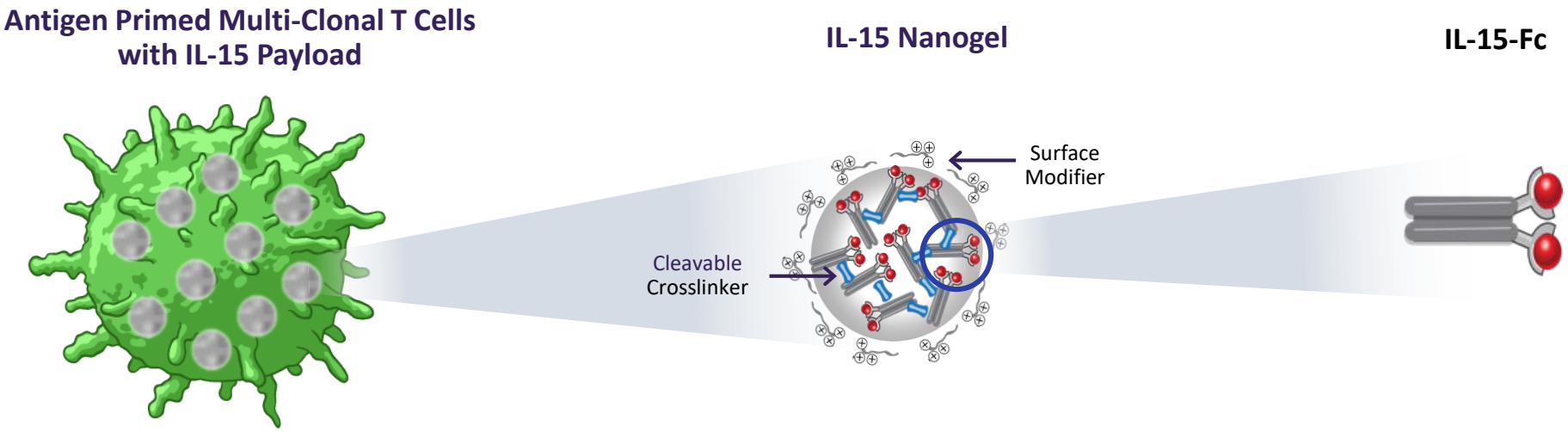
Single In Vivo Process Enables Repetitive Dosing

- **Proprietary Enhanced T cell Activation Process** – Broad T cell repertoire against multiple antigens, optimized T cell phenotypes
- **Surface Anchoring of Immune modulators** – Targeted delivery of potent immune agonists to tumors
- **Single, high yielding platform** – No genetic engineering, cost efficient, scalable

Novel First Products in Cellular Therapeutics: PRIME IL-15

PRIME IL-15 T CELLS

Delivering a Cytokine Directly to a Tumor Using the Intrinsic Homing Ability of the T Cell



NOVEL DESIGN

- Designed for slow, consistent release by hydrolysis
- Highly precise and reproducible IL-15 loading on T cells
- Slow IL-15 release stimulates the T cell for 2+ weeks

HIGHLIGHTS

- T cells proliferate *in vivo* for an extended periods of time
- No associated toxicity enables outpatient-dosing
- Killing is limited to tumor tissues

Novel First Products in Cellular Therapeutics: PRIME IL-12

IL-12 PRIMED T CELLS

Delivering a Potent Immunomodulator to Engage a Broad Immune Response

NOVEL DESIGN

- Developed releasable tethering to enable paracrine activity
- Engineered for cellular hitchhiking
- Optimized for directed, controlled and local activation of immune cells

HIGHLIGHTS

- Enhances T cell activity
- More efficacious than T cells alone
- No associated toxicity issues
- Killing of diseased tissues

Product Tailored to Manufacture the Right T Cell Clones for the Right Patient at the Right Dose

INITIAL

Common Tumor Associated Antigens

Cassette 1	Tumors
TAA 1	Melanoma
TAA 2	NSCLC
TAA 3	Bladder
TAA 4	Head and Neck
TAA 5	RCC
	DLBCL
	Sarcoma
	Ovarian

GEN 1 PRIMING

Manufacturing and Priming Improvements (IND Amendment)

- Increased antigen reactivity
- Higher cell doses
- Addition of virus-specific T cells
- Continued escalation including 1.5 – 2 Billion T cells per dose
- >100M reactive cells per dose

REFINED

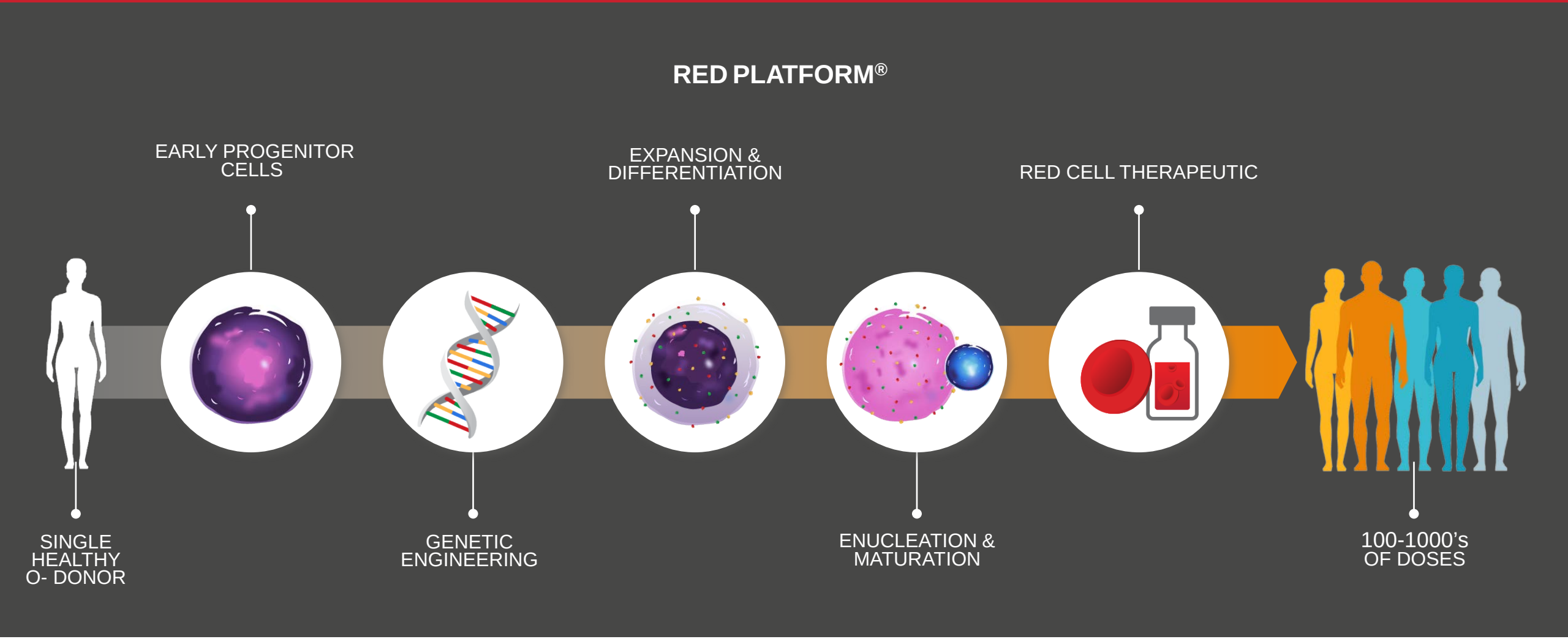
Viral (Driver Ag) Cassette/Tumors

Cassette 2	Tumors
TAA 1	Head and Neck
HPV E6	Cervical Cancer
HPV E7	Anal Cancer
TAA 2	Other HPV-associated cancers
TAA 3	

GEN 2 PRIMING

Ongoing Refinement of Both Antigens in Each Cassette and Included Patient Population

The Promise of Red Cell Therapeutics™: Highly Potent, Allogeneic and Off-the-Shelf



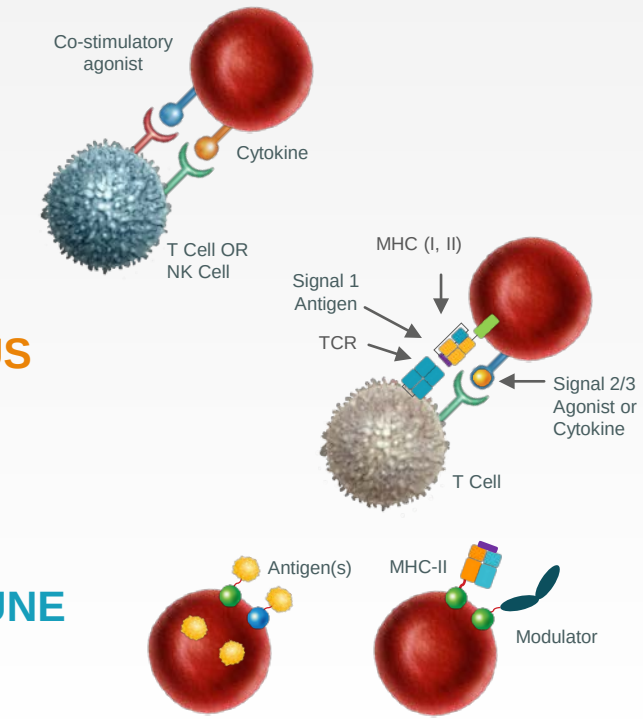
Rubius Engineering Red Cells To Drive Unique Biology Across Multiple Therapeutic Areas

TRANSFORMATIONAL SCIENCE

CANCER

CANCER / INFECTIOUS DISEASE

AUTOIMMUNE DISEASES



UNIQUE BIOLOGY

Combination immune cell agonists with native synergy safely delivered

Potent, targeted T cell responses by mimicking natural APC-T cell biology

Tolerance induction for suppression that is disease- or antigen-specific

Rubius RCT Process resembles Biologics process

Biologics

Cell Bank

Seed Train → Bioreactor → Purification → Formulation → Frozen/ Liquid Fill(s)

- Cell Bank
- Well defined platform
- High productivity
- COGM/dose low

RUBIUS RCTs

Donor

Collection / Enrichment / Cryo-preservation

Seed Train → Bioreactor → Cell Recovery → Formulation → Frozen/ Liquid Fill(s)

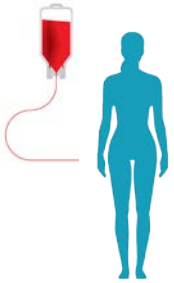
- **One donor, many doses**
- **Safety stock**
- **Select donors, lower starting material variability**
- **COGM/dose lower**
- **Labor contribution smaller**

AUTOLOGOUS

Patient

Collection / Bio-preservation

Selection → Transduction → Expansion → Formulation → Cryo-preservation



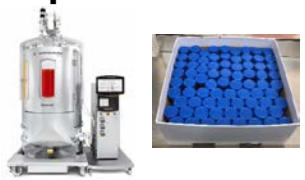
- One patient, one lot
- No safety stock, no errors
- Starting material variability
- Speed is critical
- COGM/dose high
- COI
- Labor intensive

Rigorous Approach To Technical Innovation And Supply Continuity Initiatives – Focus Areas

Process Definition

- **Achieve significant improvements in volumetric productivity**
  - Incorporate new technologies and analytical platforms
  - Optimize transduction efficiency, media, recovery operations
  - Decouple Drug Substance and Drug Product with a Freezing Step

Operations



- **Lower operational costs and support an expanding pipeline**
  - Incorporate automation and enabling PAT technologies
  - Rapid Safety Testing Technologies
  - Scale-up the process similar to biologics with disposables (50L to 200L to 1000L scale up)

Sourcing

- **Raw Materials for ensuring safety and supply continuity for pipeline**
  - Enhance apheresis network and CD34+ cell supply
  - Reduce animal derived RMs and move to chemically defined

Media, Transduction, Feed, Process, Analytical, PAT Innovation

Separation, Concentration, Rapid Safety & Release Testing, PAT Innovation

Flagship Pioneering