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Stem Cell-derived Medicinal Products:

Cellular Engineering to Address Manufacturing and Regulatory Concerns

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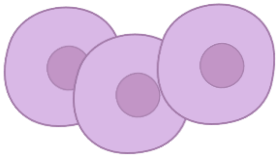
FIRST PRINCIPLES OF CELL THERAPY DEVELOPMENT

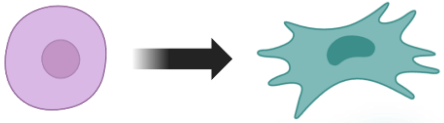
Stem/progenitor cells



Biological **substrate** for cell-based medicines

- Cell sources of origin
- Expansion potential
- Differentiation capacity

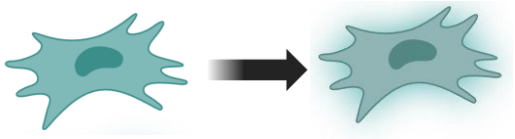
Differentiation



Transform into relevant therapeutic cell states

- Differentiated phenotypes
- Engineering intrinsic prop's
- Scalability of manufacturing

Augmented function



Engineer intrinsic traits to enhance cell **potency**

- Prolonged persistence
- Stabilization of phenotype
- Enhanced expansion *in vivo*

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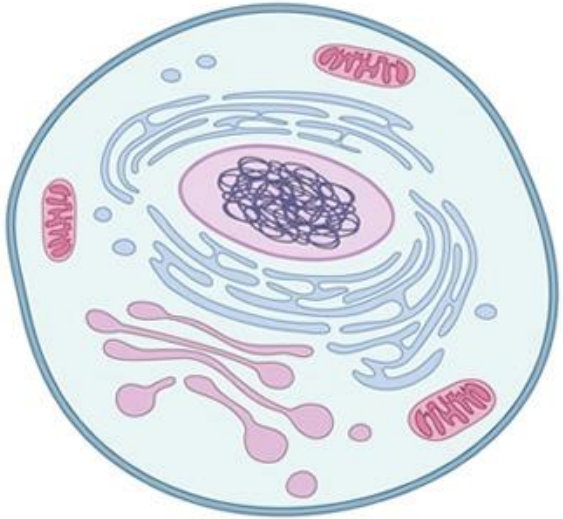
EVOLUTION OF THERAPEUTIC CELL ENGINEERING

Surface properties
(*present day*)

- Antigen recognition
- Immune evasion
- Synthetic receptors
- Cytokine signaling



Cell phenotype
(*near term*)

- Intracellular organelles
- Enhanced cell robustness
- Immunosuppressant secretion

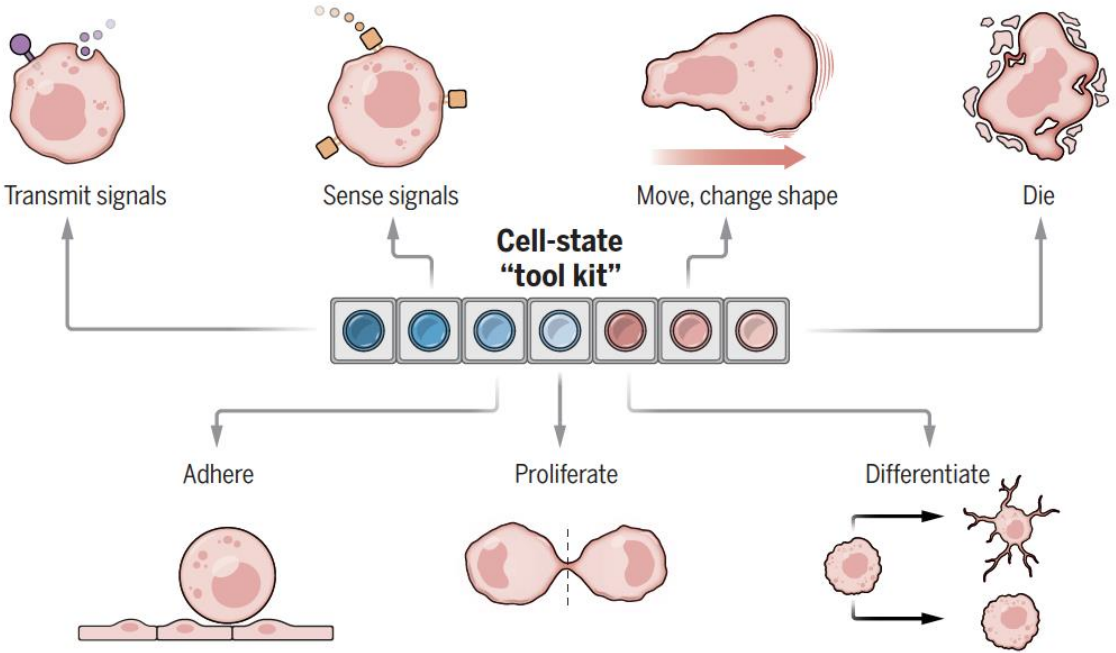
Cell manufacturing

Enhanced function
(*longer term*)

- Stimulus-responsive, on-demand
- Overcome *in vivo* obstacles
- Impart cells with novel capabilities

FUNDAMENTAL CELLULAR RESPONSES

- **Conserved genetic programs** enable cells to execute a diverse array of activities in response to external stimuli
- **Modular units** formulate the basis of a fundamental “tool kit” that can be employed to control cellular state(s)
- Engineering of input stimuli and/or functional response(s) enables **novel cell behaviors**



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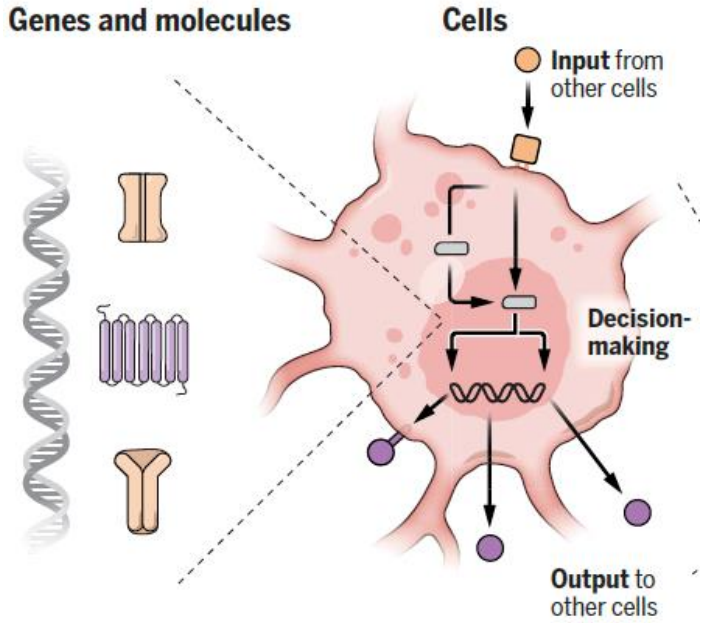
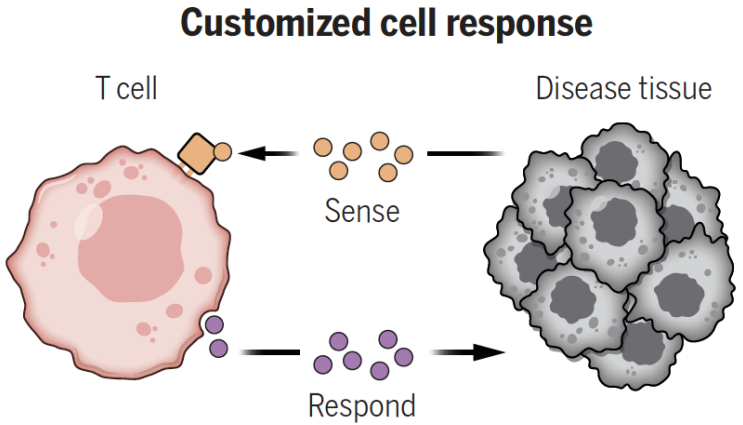
CELLULAR SYSTEMS PROCESSING



- Re-engineer endogenous signaling pathways to elicit desirable therapeutic outcomes

- Example: engineer T cell potency in response to specific pathobiology molecular stimuli



- Recognize disease tissues
- Migrate to disease sites
- Launch local therapeutic responses

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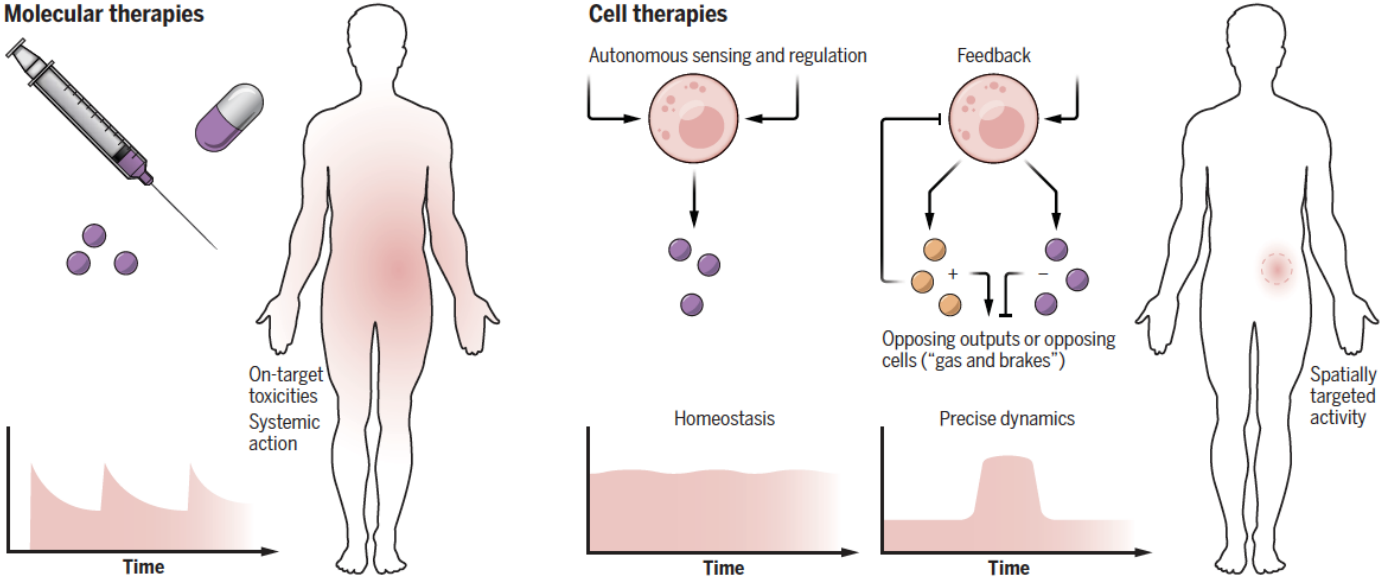
ADVANTAGES OF CELL-BASED MEDICINES



- Systemic exposure vs. localized mechanism(s) of specific activity
- Finite drug dose per administration vs. continuous production *in situ* (w/ cells)
- Prescribed drug dosing regimens vs. on-demand molecular release

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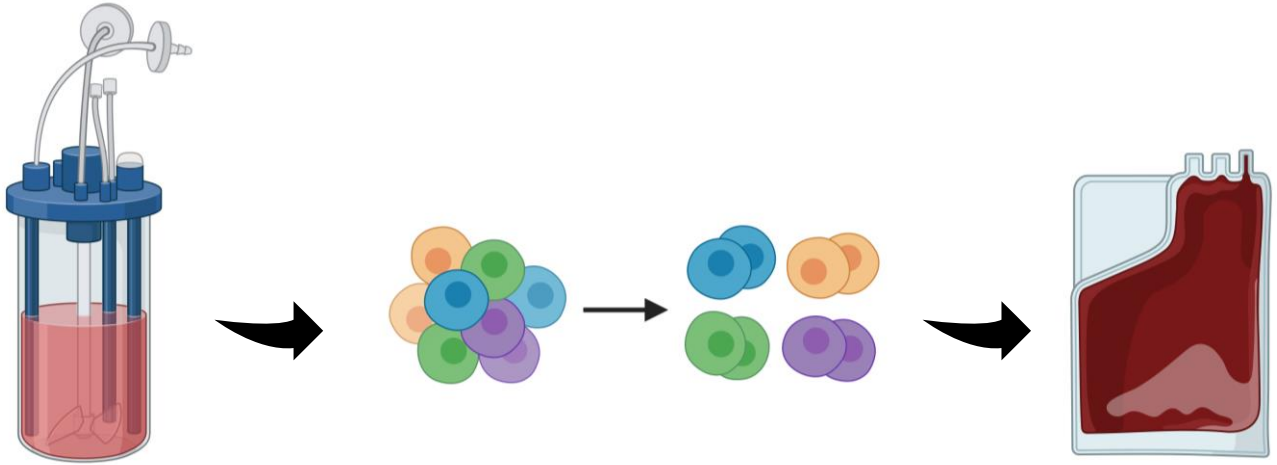
INTRINSIC vs. EXTRINSIC CONTROL OF CELL MFTG

- Classically, process development relies upon systematic optimization of **extrinsic control parameters** to yield consistent CGT products
- Engineering **intrinsic cell properties** to address specific manufacturing challenges represents a new paradigm for process development
- Examples of engineering cellular traits to address mftg challenges:
  - Attenuate adverse responses (knock-down/knock-out relevant genes)
  - Augment critical cellular needs (knock-in of relevant genes/constructs)
  - Re-wire endogenous pathways (introduce synthetic biology elements)
- Create cell lines that are better suited to handle the stresses imposed by specific stages of manufacturing pipelines → **safety & consistency**

CELL MANUFACTURING CHALLENGES



Cell expansion

- Cell density (metabolics)
- Reagent consumption
- Waste by-products

Cellular heterogeneity

- Promote cell survival
- Prevent phenotype emergence
- Control cell proportions

DP formulation

- Cell density (fill conc.)
- Cryopreserve tolerance
- Post-thaw recovery

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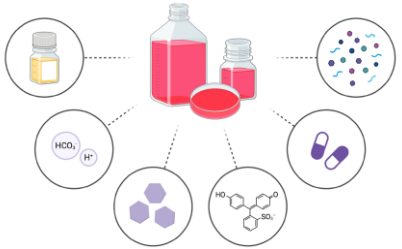
CELL ENGINEERING FOR COGs REDUCTION



- Prevailing assumption that CoGs will be reduced by scaling-up
  - fixed costs (labor, facilities, etc.) may be reduced by dose
  - largest contributor to CoGs are materials/reagents for mftg

- Dependent relationship between cell quantity and mftg costs
  - decreased #'s of cells/dose one route to reduce costs
  - enhanced functional performance (per cell) to reduce dose

- Assessing cell quality requires **better cell potency assays**

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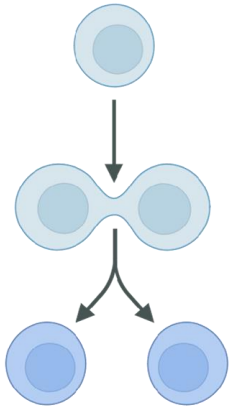
CELL EXPANSION *in vivo*

- Minimize mftg time for cell engineering (e.g., T-charge™)
  - reduce time and CoGs to produce therapeutic dose
  - preserve less differentiated (more potent) cell phenotype

- Rely upon cell expansion *in vivo* to achieve efficacious dose
  - harder to accurately define the dose in individual patients
  - ability to trigger expansion at desired site of action



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PHENOTYPIC STABILITY

- Cell phenotypes are impacted by exposure to extrinsic (host) factors
  - systemic (humoral) factors presented globally
  - local microenvironmental parameters at site of intended action

- Employ strategies to de-sensitize cells to extrinsic factors
  - remove the ability to respond (e.g., knock-out strategies)
  - redefine the response to stimuli (likely requires knock-in)

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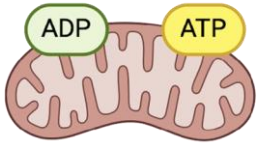
METABOLIC REPROGRAMMING

- Metabolic function
  - common underlying quantitative metric of cell potency
  - highly variable amongst individuals & over time



- Potential strategy to extend therapeutic window of activity
  - enhance survival and persistence of cells after administration
  - accelerate the therapeutic mechanism of activity

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SUMMARY & CONCLUSIONS

- The rapid development of genome/epigenome editing tools permits novel opportunities to modify and equip cells with non-native functional traits
- The regulatory acceptance of genetically engineered cells enables new strategies to develop manufacturing processes for cell therapies
- Engineering cells for manufacturing challenges could result in enhanced scalability, greater consistency & comparability, and reduction of CoGs

THANK YOU

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PRIORITIZATION CRITERIA FOR CELL THERAPIES

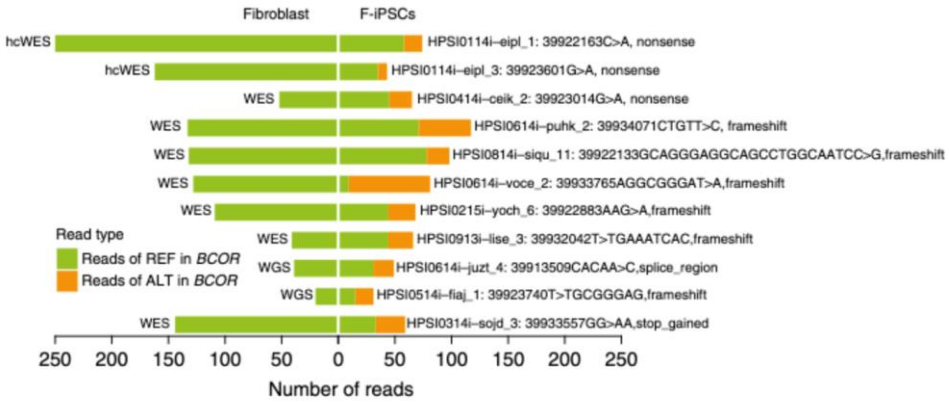
- Alternative therapeutic modalities?
    - recruitment of endogenous cell populations (e.g., bi-specific Abs)

- Route of administration?
    - technology and expertise needed to deliver cell therapies
    - supporting infrastructure to deploy broadly with consistency

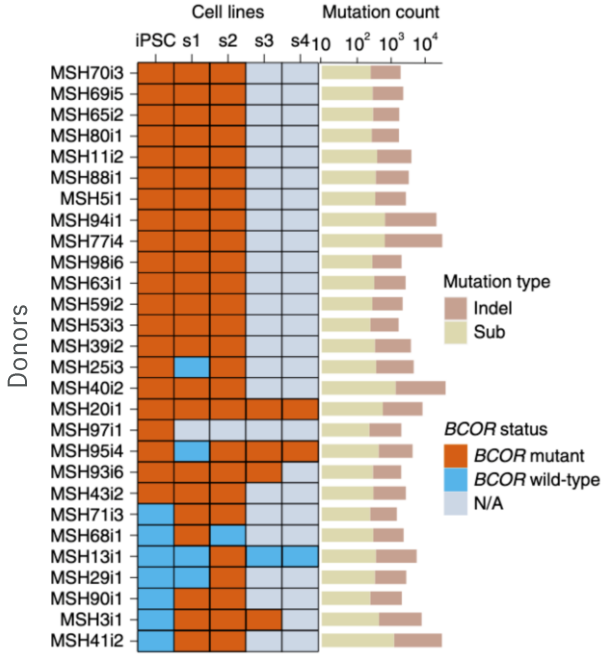
- Potential opportunity to treat multiple indications?
    - significant investment in technology & mftg to make a single cell type
    - Broaden the potential impact by equipping with multiple targets

HUMAN iPSC GENOMIC INTEGRITY

- Frequency of **BCOR mutations** in human iPSC lines



- 72% of fibroblast-derived iPSCs had UV-related mutations
- Pathogenic BCOR mutations were **not found to be present** in parental fibroblast lines prior to iPSC reprogramming



- 27% of blood-derived iPSCs had pre-existing BCOR mutations or **acquired de novo** during iPSC expansion

Rouhani *et al.*, Nature Genetics 2022

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