## Team Organoid:

# 3D Organoid Models to Assess Safety and Effectiveness of Gene and Cell Therapy Candidates

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# Priority Areas:

**Section 4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies**

- new ways to **evaluate gene therapy and cell therapy products** developed during this period of fast-paced scientific progress.

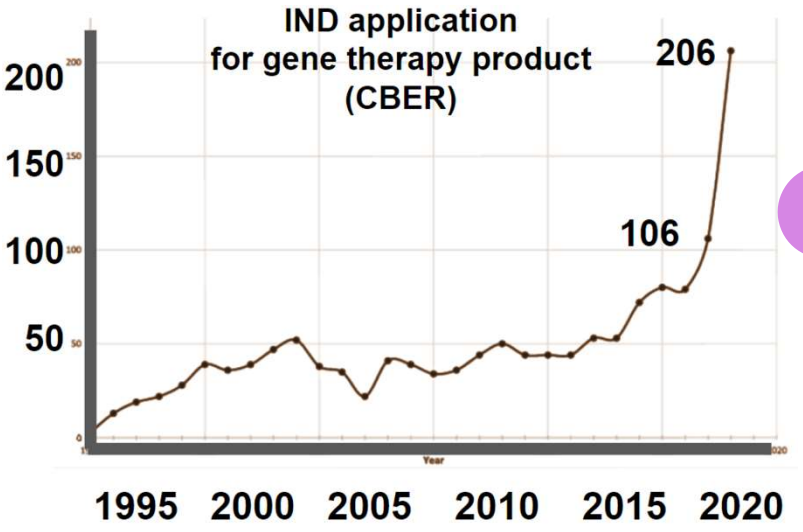
**Section 1. Modernize Toxicology to Enhance Product Safety**

- **Cell-based assays** that more accurately represent human susceptibility to adverse reactions;
- **Host genetic factors** associated with rare and unexpected adverse events ("off-target" drug effects);

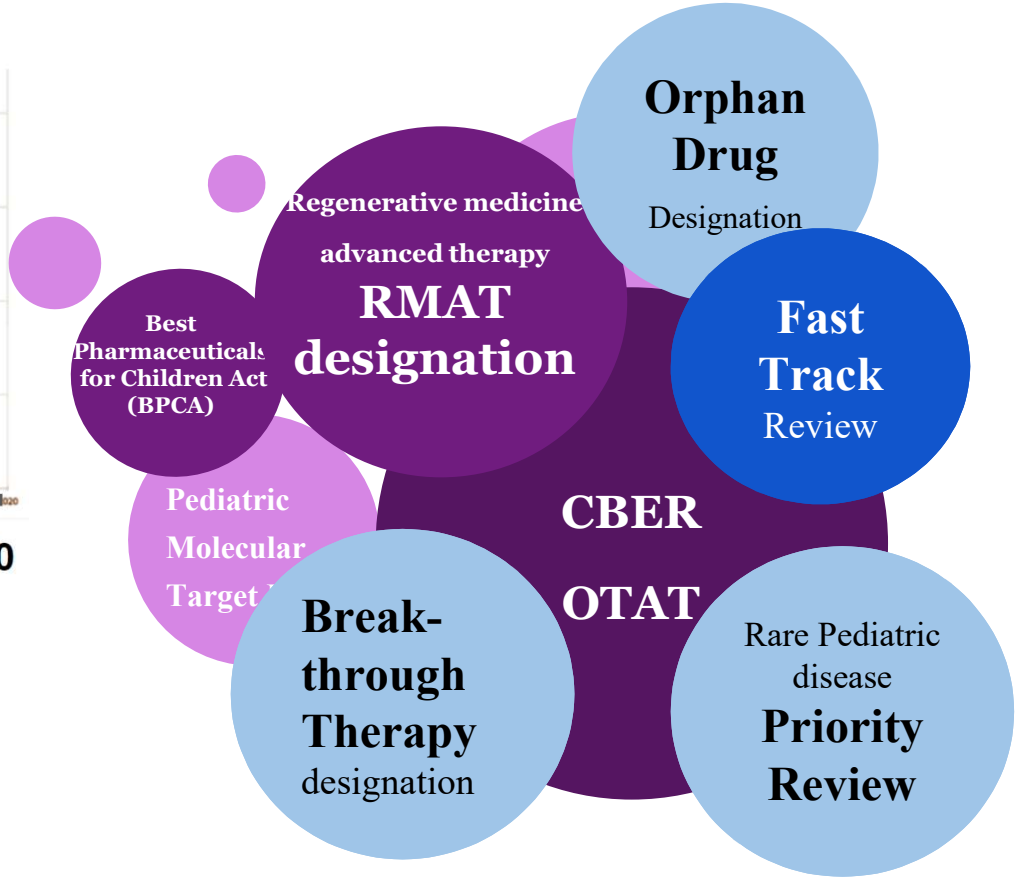
**Section 2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes**

- Promote biomarker identification, **including 'omics & high throughput methods**;
- Facilitate drug development for **special populations (such as for children and patients with rare or neglected diseases)**

# The rise of cell and gene therapy

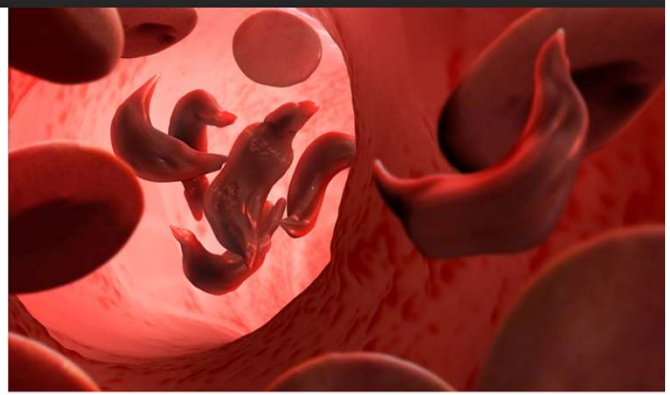



Over **900** IND applications in 2020
Expected to approve **10-25** gene therapy per year



# Evaluating unknown risk of gene therapy

Science



There are new cancer concerns swirling around a gene therapy approach designed to prevent the sickling of blood cells (above). TIM VERNON/SCIENCE SOURCE

Gene therapy trials for sickle cell disease halted after two patients develop cancer

By **Jocelyn Kaiser** | Feb. 16, 2021 , 6:15 PM

Bluebird Bio's gene therapy for **sickle cell disease**: LentiGlobin BB305

Clinical trials approved by FDA in 2014
**suspended in Feb 2021**

2 cases **linked to cancer** recently:

- Acute myeloid leukemia
- Myelodysplastic syndrome

**Better preclinical screening methods for gene therapy is needed**

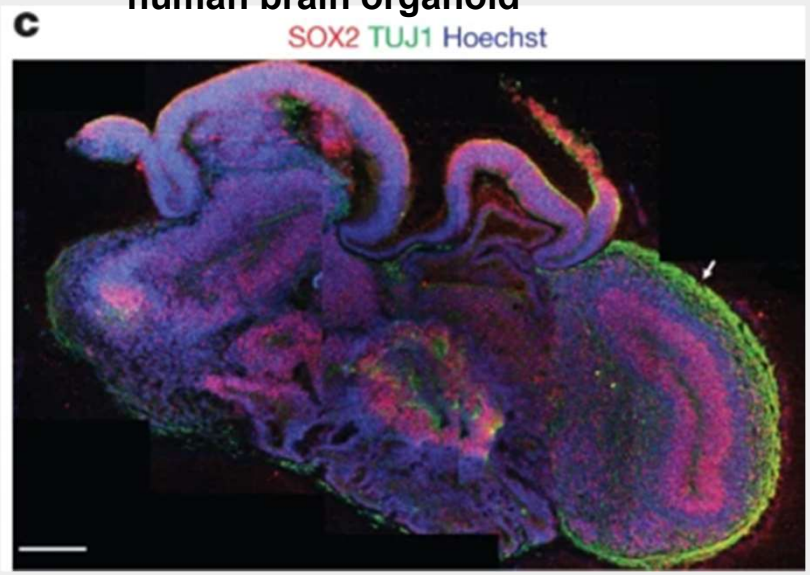
# Solution: Organoid Models to evaluate safety and effectiveness of emerging gene & cell therapies

Gene Therapy

Personalized Medicine

**Organoid models:**
recapitulate key aspects of structure and function of an organ system in vitro in 3D.

**human brain organoid**

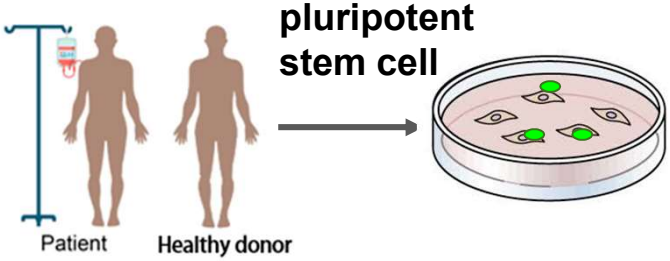



Lancaster et. al., (2013)

Cell therapy

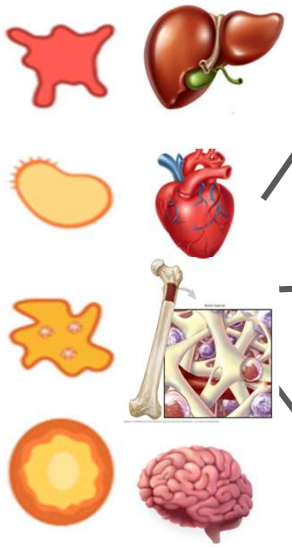
Stem Cell Technology

# Solution: Organoid models of human organs in a dish



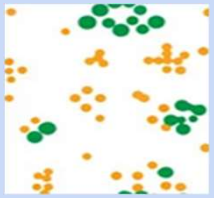

**iPSC:**
**Induced pluripotent stem cell**



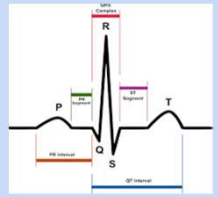


**Patient specific:**
Genetic variants
Epigenetic factors
Rare diseases

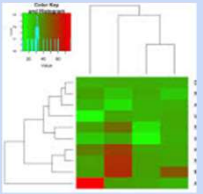
**Multiple Organ systems:**
3D Structure/function



**Protein Markers**

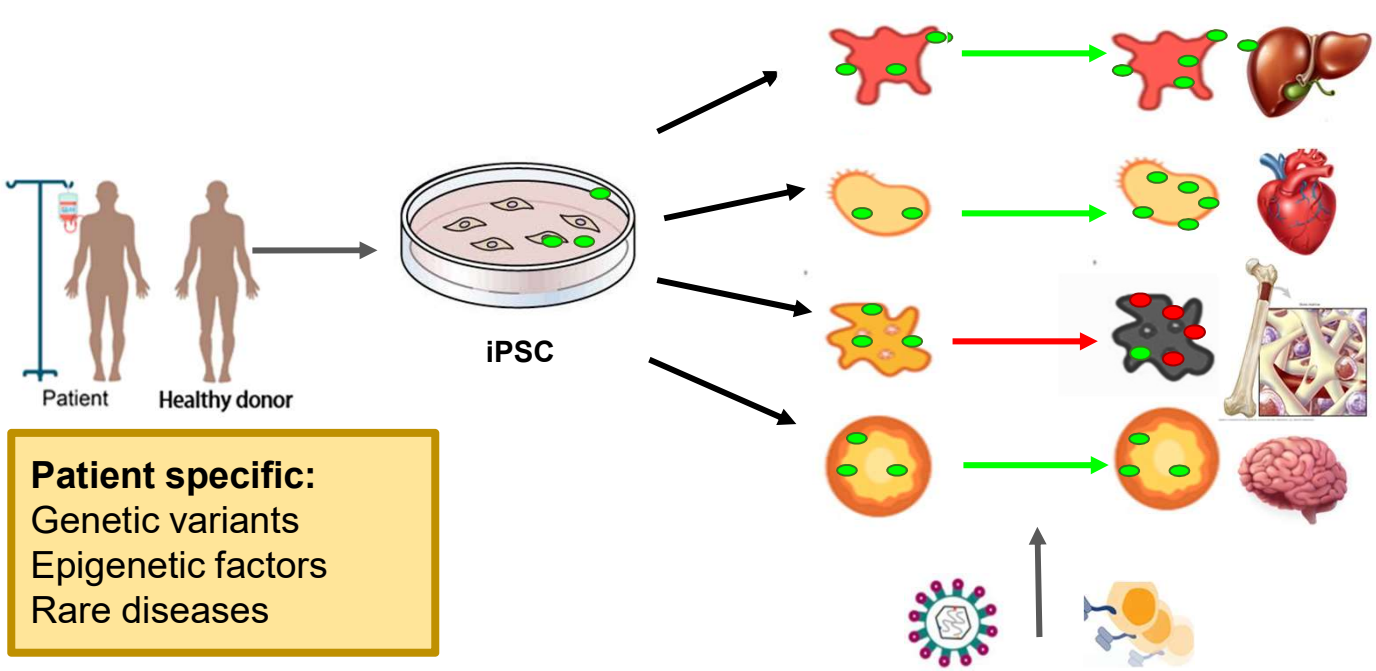



**Functional Assays**



**Single Cell Omics**

# Organoid models: testing safety & effectiveness of gene & cell therapy across multiple organ systems at once




**Patient specific:**
Genetic variants
Epigenetic factors
Rare diseases

**Gene therapy / Cell Therapy candidates**

**Safety**

**Toxicity**

**Pharmacodynamics / Pharmacokinetics**

**Cancer risk, etc**

**Effectiveness**

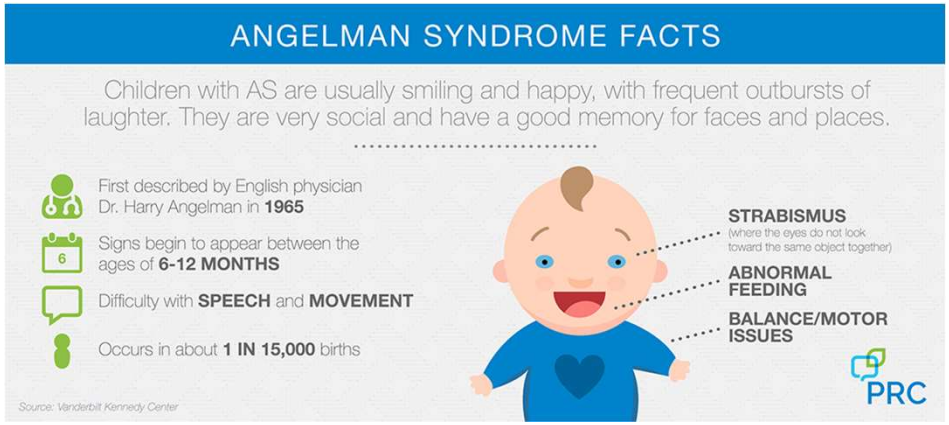
**Gene expression**

**Reporter Assay**

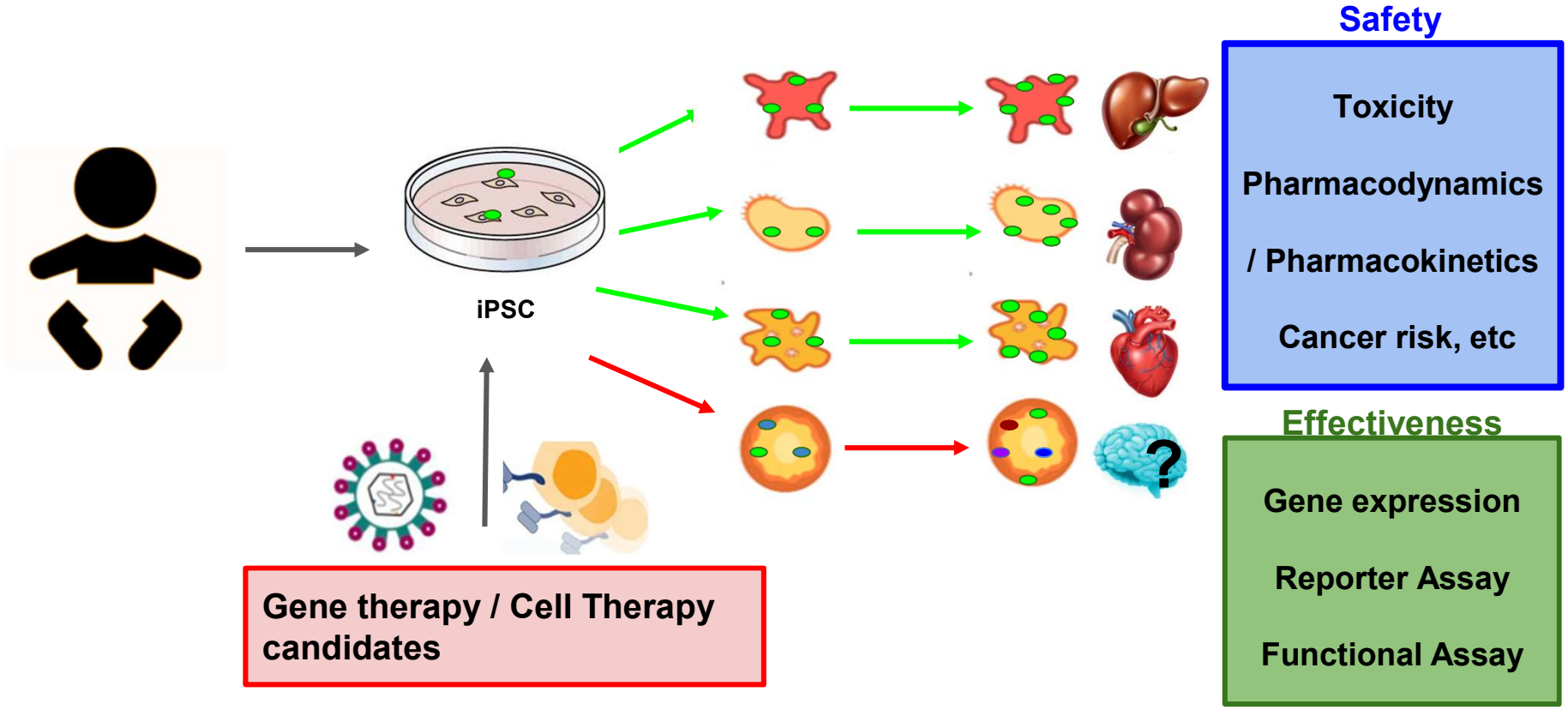
**Functional Assay**

# Example: Analyzing gene therapy candidate for Angelman syndrome using 3D organoid model

- **Rare disease** due to **genetic mutation** of UBE3A gene
- Impact **brain development** in infants
- Delayed milestones high comorbidity with Autism spectrum disorder (ASD)
- New treatment with a **CRISPR-Cas9 gene therapy** is being investigated
- **Animal models are limited** not recapitulating human brain development
- **Other unknown risk**? e.g. linked to increased Bladder cancer

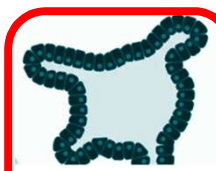


# Organoid models: testing safety gene therapy and cell therapy products during organ development



**Why Organoid 3D culture:**

Advantages of organoid systems compared to existing in vivo or in vitro systems



| | | | |
|---|---|---|---|
| **High throughput screen** | **Yes** | **Yes** | **Difficult** |
| **Single cell analysis** | **Yes** | **Yes** | **Difficult** |
| **Model human biology** | **Yes** | **Yes** | **Limited** |
| **Functional Assay** | **Limited** | **Yes** | **Yes** |
| **Model of human development** | **Limited** | **Yes** | **Limited** |
| **Complex spatial organization** | **No** | **Yes** | **Yes** |
| **Multiple Organ systems** | **Limited** | **Yes** | **Yes** |

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# Thank you!

# Questions?

## Acknowledgements


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