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

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

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

Lancaster et. al., (2013)
Solution: Organoid models of human organs in a dish

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

**ANGELMAN SYNDROME FACTS**

Children with AS are usually smiling and happy, with frequent outbursts of laughter. They are very social and have a good memory for faces and places.

- First described by English physician Dr. Harry Angelman in 1965
- Signs begin to appear between the ages of 6-12 MONTHS
- Difficulty with SPEECH and MOVEMENT
- Occurs in about 1 IN 15,000 births

Source: VentureWell Kennedy Center
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

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<tr>
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<td>Single cell analysis</td>
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<td>Model human biology</td>
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<td>Functional Assay</td>
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<td>Complex spatial organization</td>
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Thank you!

Questions?