Clinical Program Review: Oncology

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Diverse Clinical Stage Portfolio

- Neurologic Disorder / Injury: 13%
- Ophthalmology: 9%
- Hematology: 15%
- Infectious Disease: 5%
- Oncology - hematological malignancies: 17%
- Ophthalmology: 9%
- Hematology: 15%
- Cardiovascular: 9%
- Bone & Cartilage: 7%
- Metabolic: 2%
- Other: 6%

43 Clinical Trials (38 active)
8 Preparing IND
10 Active Oncology Clinical Trials
Oncology Clinical Trials

Therapeutic Modality

- 6 Cell Therapy
- 3 Biologic
- 1 Small Molecule
Tumor growth is fueled by small numbers of self-renewing CSC

- CSC are resistant to radiation and chemotherapy and can re-grow the tumor and drive relapse after remission
- Explains why tumors recur after initially successful therapy
- CSC can spread to distant sites and drive metastases
- **CSC must be eradicated to achieve a cure**
Evolution of Cancer Treatment

20th Century

- Radiation Chemotherapy
  - Kill dividing cells
  - Kill cancer and some normal cells

Late 1990’s

- Targeted Therapies
  - More cancer-specific
  - Less toxic

21st Century

- Immunotherapy
  - Co-opts immune system
  - Specific, powerful
    - Checkpoint inhibitors
    - Engineered CAR-T cells
    - 2017, Kymriah for ALL
## Active Clinical Trials

### Hematological Malignancies

<table>
<thead>
<tr>
<th>Indication</th>
<th>Investigator / Organization</th>
<th>Phase</th>
<th>Status</th>
<th>Targeted Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Myeloma</td>
<td>Spear/Poseida</td>
<td>Phase 1</td>
<td>Enrolling</td>
<td>40</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>Chao/Forty Seven Inc.</td>
<td>Phase 1b</td>
<td>Enrolling</td>
<td>96</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>Kipps/UCSD</td>
<td>Phase 1b/2a</td>
<td>Enrolling</td>
<td>56</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>Finnegan/Angiocrine</td>
<td>Phase 1</td>
<td>Initiating</td>
<td>12</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>Delaney/Nohla</td>
<td>Phase 2</td>
<td>Initiating</td>
<td>220</td>
</tr>
<tr>
<td>Immunosuppressed patients with persistent viral infections</td>
<td>Pulsipher/CHLA</td>
<td>Phase 1/2</td>
<td>Initiating</td>
<td>60</td>
</tr>
</tbody>
</table>
## Active Clinical Trials

### Solid Tumors

<table>
<thead>
<tr>
<th>Indication</th>
<th>Investigator / Organization</th>
<th>Phase</th>
<th>Status</th>
<th>Targeted Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Glioma</td>
<td>Brown/COH</td>
<td>Phase 1</td>
<td>Enrolling</td>
<td>100</td>
</tr>
<tr>
<td>Synovial Sarcoma and Advanced tumors</td>
<td>Ribas/UCLA</td>
<td>Phase 1</td>
<td>Initiating</td>
<td>12</td>
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<tr>
<td>Colorectal cancer and solid tumors</td>
<td>Chao/Forty Seven Inc.</td>
<td>Phase 1b/2a</td>
<td>Enrolling</td>
<td>112</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>Slamon/UCLA</td>
<td>Phase 1</td>
<td>Enrolling</td>
<td>84</td>
</tr>
</tbody>
</table>
Immunotherapy: CAR-T for Malignant Glioma

Rationale

- Malignant glioma is a highly lethal disease with low survival rates
- Engineered CAR-T-cells are a promising strategy to treat cancer
- Developed a CAR-T cell therapy targeting IL-13 receptor alpha 2 (IL13Rα2) expressed on malignant glioma cells
- CAR-T cell persistence is critical for durable effect
- Use stem cell memory T-cells which have stem cell-like properties i.e. self-renew and differentiate – drive long-term persistence
- Progression from earlier CIRM grant

Goal and Design

- Phase 1 trial of stem cell memory CAR-T cells targeting IL13Rα2 for patients with malignant glioma
- Objectives: Safety and Efficacy, Route of delivery and Dose

Status

- Enrolling patients
Rationale

• Multiple myeloma (MM) is an incurable and ultimately fatal disease
• BCMA (B-Cell Maturation Antigen) expressed on MM cells is an attractive target for a CAR-T approach
• Using autologous *stem cell memory T-cells* designed to increase T-cell persistence

Goal and Design

• Phase 1 FIH clinical trial of stem cell memory CAR-T cells targeting BCMA
• Objectives: Safety and Efficacy

Status

• Initiating trial
Rationale

• NY-ESO-1 is a tumor antigen expressed in many advanced cancers including synovial sarcomas
• T-cells engineered to target NY-ESO-1 have shown remarkable antitumor efficacy BUT the T-cells don’t persist and patients relapse
• Approach: engineer both T-cells and stem cells and co-administer
• T-cells provide immediate effect while engrafted stem cells will provide a renewable source of engineered T-cells

Goal and Design

• Phase 1 clinical trial of dual cell therapy combining stem cells and T-cells engineered with an NY-ESO-1 TCR
• Objectives: Safety, Feasibility, Efficacy

Status

• Initiating trial
CD47 Blockade: Novel Immunotherapy Approach

- CD47 is over-expressed on cancer and csc and is an important mechanism for immune evasion from macrophages
- CD47 blockade takes the brakes off macrophages and enables them to eliminate cancer and csc
- CD47 blockade is a novel Immunotherapy approach with broad applications spanning multiple tumor types
CD47 Blockade Development History

Preclinical Evidence for csc-targeting
- CD47 blockade prevents transfer of human AML by eliminating csc
- CD47 blockade prevents tumor growth and metastasis of solid cancers in mice

Investigator:
Mark Chao, MD, PhD

Company:
Forty Seven Inc.

2 Active CIRM2.0 CLIN2 Trials

2010
Disease Team 1
Research Concept → IND

2014
Disease Team 3
Phase 1 solid tumor trial in US
AML trial in UK

2016
Phase 1b in AML
• High-risk patients
• Combo with chemotherapy

Phase 1b/2a Colorectal Cancer
• Combination with cetuximab
CSC-Targeted Therapies

Investigator:
Thomas Kipps, MD, PhD

Institution:
UCSD/Oncternal

Investigator:
Dennis Slamon, MD

Institution:
UCLA

Rationale
• Biologic or small molecule targeting pathways important for csc
• Prevent transfer and propagation of human cancers in mice by eliminating csc
• Progressions from DT1 and DT3

Goal and Design
• Kipps: Phase 1b/2a trial in CLL testing cirmtuzumab in combination with ibrutinib
• Slamon: Phase 1 trial in advanced solid tumors

Status
• Initiating/in progress
Cord Blood Expansion Cell Therapies

**Investigator:**
Colleen Delaney, M.D., MSc

**Institution:**
Nohla Therapeutics

**Investigator:**
Paul Finnegan, M.D., M.B.A.

**Institution:**
Angiocrine Bioscience

**Rationale**
- Cord blood expansion cell therapies –stem and progenitor cells
- Designed to improve/provide immune reconstitution after high-dose chemotherapy

**Goal and Design**
- Nohla: Phase 2 clinical trial in AML patients
- Angiocrine: Phase 1 trial in hematological cancers

**Status**
- Initiating trial
Oncology Clinical Trials Summary

- Diverse oncology portfolio
- Majority cell therapies
- Cutting edge immunotherapy approaches
- Cancer-stem cell targeted therapies
- Programs funded by CIRM from inception
COURAGEOUS

Karl Trede

Diagnosed with throat cancer, then later lung cancer, for which there was no effective treatment

Every Moment Counts