Global Research Update

Progress Towards a Cure
Familial Chordoma, a Tumor of Notochordal Remnants, Is Linked to Chromosome 7q33

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Chordoma is a rare tumor originating from notochordal remnants that is usually diagnosed during midlife. We performed a genomewide analysis for linkage in a family with 10 individuals affected by chordoma. The maximum two-point LOD score based on only the affected individuals was 2.21, at recombination fraction 0, at marker D7S2195 on chromosome 7. Combined analysis of additional members of this family (11 affected individuals)
In search of cell lines
Disappointing discovery

Mouse cells

Cervical Cancer
Not Cancer

CCL3
CM319
GB60
U-CH1
U-CH2

Brachyury

β-Actin
Studying invalid cell lines doesn’t get in the way of publishing... but it does get in the way of finding a cure
» Scientific Materials
» Collaborators
» Funding
Solving those problems is critical to find a cure
» Founded: 2007 in Durham, NC

» Our mission: to improve the lives of those affected by chordoma and to lead the search for a cure.
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We seek to advance the full sequence of research needed to bring about more effective treatments for chordoma
Our Research Strategy

We marshal all of the resources needed to advance the search for a cure by:

1. Creating a vibrant research community
2. Supplying critical scientific resources
3. Strategically funding research
1. Creating a vibrant research community

» Proactively recruit talented researchers into the field

» Connect researchers through meetings and conferences

» Coordinate collaboration and data sharing
Creating a vibrant research community

Effect of Research Conferences

2011

Collaborations + 19%
Relationships + 65%

2012

Network Density + 57%
Deg. of Separation -23%

Creating a vibrant research community

Effect of Research Conferences
### Centralized Resource Repositories

<table>
<thead>
<tr>
<th></th>
<th>Acquired</th>
<th>In Dev’t/Validation</th>
<th>Goal</th>
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</thead>
<tbody>
<tr>
<td><strong>Tumor Tissue</strong></td>
<td>110 cases</td>
<td>n/a</td>
<td>250</td>
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<td><strong>Cell Lines</strong></td>
<td>7</td>
<td>9</td>
<td>10</td>
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<td><strong>PDX Models</strong></td>
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<td><strong>Genetically Engineered Mouse Models</strong></td>
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</table>
3 Strategically funding research

- Proactively fund high-priority research according to a strategic “Research Roadmap”
  - In contrast to typical reactive funding approach
- Fund the best research across the world – institution agnostic
- Require that resulting data and materials are shared quickly
- Leverage outside funding when possible
Strategically funding research

• Funded 22 research projects including:
  – Cell line and mouse model development
  – Preclinical drug screening - including all FDA approved drugs
  – Genome-wide vulnerability screen
  – Comprehensive genomic, proteomic and epigenomic analysis
  – Target validation
Discoveries published in peer reviewed publications
Brachyury: a new therapeutic target
Role of Brachyury in Chordoma

- Extra copy of brachyury causes familial chordoma
- 97% of patients with non-familial chordoma have a misspelling (a SNP) in brachyury
- 25% of chordoma tumors acquire extra copies of brachyury
- Nearly 100% of chordoma tumors highly express brachyury
- Turning off brachyury completely stops growth of chordoma cells
Unanswered Questions

• Why does the SNP in brachyury cause predisposition to chordoma?
• How does brachyury become activated in chordomas?
• How does brachyury drive chordoma?
• Can brachyury be shut off in chordoma tumors?
• Can the immune system be stimulated to destroy cells that express brachyury?
## Potential Treatment Approaches

<table>
<thead>
<tr>
<th>Therapeutic Target</th>
<th>Molecular Evidence</th>
<th>Preclinical Evidence</th>
<th>Clinical Evidence</th>
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<tbody>
<tr>
<td>Brachyury</td>
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<tr>
<td>c-MET</td>
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Next Steps
Current Research Priorities

1. Continue developing and distributing disease models and research tools

2. Refine understanding of key drivers of chordoma, including brachyury

3. Systematically test relevant existing therapies in preclinical models

4. Initiate clinical trials to test promising therapies (6 in planning)

5. Begin developing therapies targeting brachyury
New Clinical Trial

- GI-6301 yeast-brachyury vaccine
- Intended to generate immune response to cells expressing brachyury
- Phase 2 trial for 50 patients
- Radiation + vaccine vs. radiation + placebo
- Designed for patients with:
  - Newly diagnosed patients who can’t have surgery
  - Residual tumor after surgery
  - Local recurrence
Five-Year Research Investments

- Resource Dev’t: $2M
- Discovery Research: $4M
- Therapy Dev’: $3M
- Preclinical Research: $3M
- Clinical Research: $5M
- Natural History: $2.5M