Accelerating drug development for an ultra-orphan patient population

Josh Sommer
Executive Director
Chordoma Foundation
Chordoma

» Rare bone cancer of the skull and spine

» Strikes people of all ages

» 2,500 patients in the US

» High rate of recurrence after surgery & radiation

» No effective drugs
Unacceptable statistics

» 7 year median survival
Familial Chordoma, a Tumor of Notochordal Remnants, Is Linked to Chromosome 7q33

Michael J. Kelley,1,* Jeannette F. Korczak,2,* Eamonn Sheridan,3 Xiaohong Yang,4 Alisa M. Goldstein,4 and Dilyss M. Parry4

1Department of Medicine, Duke University, and Durham Veterans Affairs Hospital, Durham, NC; 2Epidemiology Section, Karmanos Cancer Institute, and Department of Internal Medicine, Wayne State University School of Medicine, Detroit; 3St. James University Hospital, Leeds; and 4Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda

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)
Serendipity

Duke oncologist, Dr. Michael Kelley, was the only federally funded chordoma researcher in the country.
In search of cell lines
Disappointing discovery

Mouse cells

CCL3
CM319
GB60
Diploid genome
CCL3
CM319
GB60
Diploid genome

HeLa

U-CH1
U-CH2

Brachyury

β-Actin
Barriers to progress

» Insufficient/invalid research tools
» Limited funding
» No collaborators
Our Mission
To improve the lives of those affected by chordoma and to lead the search for a cure
Humble beginnings
A daunting challenge

» Handful of isolated researchers
» Little known about chordoma biology
» 1 clinical trial ever conducted
» 0 companies investing in chordoma
Developing a plan

First International Chordoma Research Workshop
Bethesda, MD | March 2007
How could we hope to find new treatments with limited time and resources?
Re-engineering research

With a lot of guidance from Duke faculty…

Public Policy
Misha Angrist
Bob Cook-Deegan
Joel Fleishman
Anthony So

Law
Arti Rai

Economics
Lori Leachman

Business
Matt Nash
Howie Rhee
Bill Sax
Kevin Schulman

Medicine
Amy Abernethy
Nancy Andrews
Geoff Ginsburg
Mike Kelley
Kim Lyerly
Ralph Snyderman
Neil Spector
Sandy Williams

“Fellowship in strategic philanthropy”

SANFORD
SCHOOL OF PUBLIC POLICY

Anthony So, MD
Re-engineering research

Traditional Funders

- Passive
- Project-oriented
- Maximize investment

Chordoma Foundation

- Proactive
- Systems-oriented
- Maximize leverage
## Our research strategy

<table>
<thead>
<tr>
<th>1</th>
<th>Cultivate a capable research community</th>
<th>Researcher recruiting</th>
<th>Network development</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Develop research-enabling infrastructure</td>
<td>Resource repositories</td>
<td>Core services</td>
</tr>
<tr>
<td>3</td>
<td>Facilitate patient participation in research</td>
<td>Biospecimen donations</td>
<td>Trial participation</td>
</tr>
<tr>
<td>4</td>
<td>Marshall necessary funding</td>
<td>Direct investments</td>
<td>Leverage outside investment</td>
</tr>
</tbody>
</table>

*All are necessary; none alone is sufficient*
1 Cultivate a capable research community

6 International Research Workshops

> 400 researchers in 14 countries
1. Cultivate a capable research community

Before

- Collaborations: +19%
- Relationships: +65%
- Network Density: +57%
- Deg. of Separation: -23%

After
Develop research-enabling infrastructure

Biobank

Cell line repository

PDX repository

Drug Screening Program
**Problem**
Significant start-up time and cost makes preclinical research costly and impractical for most researchers and companies.

**Solution**
An centralized preclinical screening service offered to researchers and companies

- Screens drugs in batches to create economies of scale
- Enables fast and efficient evaluation of promising drugs
  - Reduces cost by >50%
  - Reduces time by >12 months
Facilitate patient participation in research

Problem
Small, dispersed patient population posed major barrier to trial accrual

Solution
• Patient services that build high-trust relationships
• Patient outreach
• Clinical trial education
• Tumor donation program

Patient Services
• Educational Content
• Patient Navigation Service
• Doctor Directory
• Peer Support Program
• Online Community

Online Outreach

Patient Network
>80%
Expected US Patient Population
Marshall necessary funding

- Grants
- Prizes
- Partnerships

> 35 labs funded
> $6M invested
> $20M leveraged

Funding partners

- The Mark Foundation for Cancer Research
- Canadian Cancer Society
- National Cancer Institute
<table>
<thead>
<tr>
<th>Resource Development</th>
<th>Target Discovery</th>
<th>Therapeutic Discovery</th>
<th>Preclinical Research</th>
<th>Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2007</td>
<td>Goal</td>
<td>Current</td>
<td></td>
</tr>
<tr>
<td>Tumor samples</td>
<td>0</td>
<td>250</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>Cell Lines</td>
<td>1</td>
<td>10</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>PDX Models</td>
<td>0</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>GEM Models</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Brachyury: a new cancer gene
Brachyury: a new cancer gene
Familial Chordoma

Family 1

Family 2

Family 3

Family 4

Family 6

Family 7

Family 8

Chordoma

Astrocytoma
Linkage analysis mapped disease gene locus to 6q27
T (brachyury) gene duplication confers major susceptibility to familial chordoma

Xiaohong R Yang¹, ⁶, David Ng¹, ⁶, David A Alcorta², Norbert J Liebsch³, Eamonn Sheridan⁴, Sufeng Li², ⁵, Alisa M Goldstein¹, Dilys M Parry¹ & Michael J Kelley², ⁵

Using high-resolution array-CGH, we identified unique duplications of a region on 6q27 in four multiplex families with at least three cases of chordoma, a cancer of presumed notochordal origin. The duplicated region contains only the T (brachyury) gene, which is important in notochord development and is expressed in most sporadic chordomas. Our findings highlight the value of screening for complex genomic rearrangements in searches for cancer-susceptibility genes.
Embryonic transcription factor critical for notochord formation and mesoderm development

Brachyury is highly expressed in all chordomas

- Not expressed in 323 other mesenchymal tumor samples or normal tissues
- Believed to confirm notochordal lineage of chordoma

Vujovic et al., *J Pathol* 2006
Copy number gains found in more than half of chordomas

<table>
<thead>
<tr>
<th>Classification</th>
<th>High CNG</th>
<th>Low CNG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disomy</td>
<td>78/170 (46)</td>
<td>36/92 (39)</td>
</tr>
<tr>
<td>Copy number gain (CNG)</td>
<td>92/170 (54)</td>
<td></td>
</tr>
<tr>
<td>High CNG: $\geq 4$ copies of $T$ and $CEP6$ in $&gt;40%$ cells</td>
<td>48/92 (52)</td>
<td></td>
</tr>
<tr>
<td>Polysomy (balanced): $T = CEP6$ ratio $0.8 – 1.2$</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Polysomy (unbalanced): $T &gt; CEP6$ ratio $&gt;1.2$ but $&lt;2.2$</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Amplification: $T &gt; CEP6 \geq 2.2$</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Tight clusters: ($&gt;15$ $T$ signals)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Focal amplification: ($3–11$ $T$ signals scattered)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Low CNG: $3–4$ copies of $T$ and $CEP6$ in $&lt;40%$ cells</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Polysomy (balanced): $T = CEP6$ ratio $0.8 – 1.2$</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Amplification: $T &gt; CEP6 \geq 2.2$</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Focal amplification: ($3–11$ $T$ signals scattered)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Minor allelic gain: $3–4$ copies of $T$ and $2$ copies of $CEP6$</td>
<td>8/92 (9)</td>
<td></td>
</tr>
</tbody>
</table>

Presneau et al., *J Pathol* 2010
Knockdown of brachyury induces senescence of chordoma cells

Also prevents formation of xenografts in mice

Presneau et al., *J Pathol* 2010 and Hsu et al., *J Neurosurg* 2011
Common germline brachyury SNP is strongly associated with chordoma

97% of chordoma patients have risk allele

Pillay et al., *Nature Genetics* 2012

Table 1  Summary of results for association of rs2305089 with chordoma

<table>
<thead>
<tr>
<th>Ancestry-matched cases</th>
<th>Genotype</th>
<th>Cases</th>
<th>Genotype</th>
<th>Controls</th>
<th>Allelic model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RAF</td>
<td>AA</td>
<td>GA</td>
<td>GG</td>
</tr>
<tr>
<td>Discovery</td>
<td></td>
<td>0.875</td>
<td>30</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Replication</td>
<td></td>
<td>0.825</td>
<td>15</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td>0.825</td>
<td>15</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

RAF, risk allele frequency. Total allelic counts were used to generate the combined values. *P* values were calculated using Pearson’s χ²-squared test.
Plays a role in pathogenesis of multiple carcinomas

- Over-expressed in multiple cancers (Palena et al., *Clin Cancer Res* 2007)
- Mediates invasion, metastasis, and EMT in lung and colorectal cancer (Fernando et al., *J Clin Invest.* 2010)
- Predicts poor prognosis at early stages of colorectal cancer (Kilic et al., *Eur J Cancer* 2011)
- Confers cancer stem cell characteristics on colorectal cancer cells (Sarkar et al., *Int J Cancer* 2011)
- Drives EMT, over expressed in lung cancer (Roselli et al., *Clin Cancer Res* 2012)

Up-to-date summary maintained at: [www.chordoma.org/targets/brachyury](http://www.chordoma.org/targets/brachyury)
Brachyury therapeutic discovery partners

- Koch Institute for Integrative Cancer Research at MIT
- Broad Institute
- Baylor University
- The University of North Carolina at Chapel Hill
- Massachusetts General Hospital
- UCL
- National Cancer Institute
- University of Oxford
>30 drugs and combinations tested in multiple CDX and PDX models
Moving towards genomically informed trials…

<table>
<thead>
<tr>
<th>Component</th>
<th>AMPLIFICATION</th>
<th>DRIVER MUTATIONS</th>
<th>DRIVER MUTATIONS</th>
<th>HOMOZYGOUS DELETION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brachyury</strong></td>
<td>23% Chordoma tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chromatin Regulators</strong></td>
<td>14% Models</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PI3K Pathway</strong></td>
<td>17%</td>
<td></td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td><strong>CDKN2A</strong></td>
<td>16%</td>
<td></td>
<td></td>
<td>78%</td>
</tr>
<tr>
<td>Concept</td>
<td>Initiation</td>
<td>Enrolling</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>----------</td>
<td></td>
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<tr>
<td>GI-6301 + radiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nivolumab + radiosurgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Palbociclib</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Afatinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oncolytic bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachyury vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous vaccine</td>
<td></td>
<td></td>
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</tbody>
</table>
Industry partners

Boehringer Ingelheim

Bristol-Myers Squibb

Bavarian Nordic

Biomed Valley

Pfizer
Emerging Opportunities for Target Discovery in Rare Cancers

Tanaz Sharifnia, Andrew L. Hong, Corrie A. Painter, and Jesse S. Boehm

1Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA
2Division of Hematology/Oncology, Boston Children’s Hospital, Boston, MA 02115, USA
3Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
*Correspondence: painter@broadinstitute.org (C.A.P.), boehm@broadinstitute.org (J.S.B.)
http://dx.doi.org/10.1016/j.chembiol.2017.08.002

Rare cancers pose unique challenges to research due to their low incidence. Barriers include a scarcity of tissue and experimental models to enable basic research and insufficient patient accrual for clinical studies. Consequently, an understanding of the genetic and cellular features of many rare cancer types and their associated vulnerabilities has been lacking. However, new opportunities are emerging to facilitate discovery of therapeutic targets in rare cancers. Online platforms are allowing patients with rare cancers to organize on an unprecedented scale, tumor genome sequencing is now routinely performed in research and clinical settings, and the efficiency of patient-derived model generation has improved. New CRISPR/Cas9 and small-molecule libraries permit cancer dependency discovery in a rapid and systematic fashion. In parallel, large-scale studies of common cancers now provide reference datasets to help interpret rare cancer profiling data. Together, these advances motivate consideration of new research frameworks to accelerate rare cancer target discovery.
A model for rare cancer research

### Table 1. Advances in Chordoma Research Assets

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2017</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Researcher community</td>
<td>Small, disconnected</td>
<td>&gt;300 active researchers; robust collaboration</td>
<td>International Chordoma Research Workshops; networking events</td>
</tr>
<tr>
<td>Patient community</td>
<td>None</td>
<td>&gt;1,800 patients</td>
<td>Facebook group; website; online advertising and search engine optimization; educational materials; Chordoma Community Conferences</td>
</tr>
<tr>
<td>Tumor tissue</td>
<td>Scarce, no centralized source</td>
<td>Centralized repository with tissue from &gt;200 cases</td>
<td>Tumor donation program allows patients to donate tumor from any US hospital; CF Biobank stores and distributes tumor samples</td>
</tr>
<tr>
<td>Genome characterization</td>
<td>None</td>
<td>35 cases sequenced</td>
<td>Chordoma Genome Project, in partnership with academic labs</td>
</tr>
<tr>
<td>Cell lines</td>
<td>1</td>
<td>17</td>
<td>Cell line prize; cell line validation pipeline; genomic characterization; publicly accessible cell-line repository</td>
</tr>
<tr>
<td>Patient-derived xenografts (PDX)</td>
<td>None</td>
<td>5</td>
<td>Tumor donation program coupled with rapid implantation in vivo; PDX prize; PDX validation pipeline; publicly accessible PDX repository</td>
</tr>
<tr>
<td>Small-molecule screening</td>
<td>None</td>
<td>&gt;10,000 compounds screened, including all FDA-approved drugs</td>
<td>Collaboration with NIH Chemical Genomics Center; grants to academic investigators; collaborations with industry</td>
</tr>
<tr>
<td>Functional genomic screening</td>
<td>None</td>
<td>Genome-wide CRISPR/Cas9 screens; targeted shRNA screen</td>
<td>Grants to academic investigators</td>
</tr>
<tr>
<td>In vivo evaluation</td>
<td>None</td>
<td>&gt;20 drugs evaluated</td>
<td>CF drug screening pipeline provides in vivo evaluation as a service to academic and industry collaborators</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>1 completed clinical trial</td>
<td>Pipeline of 7 new clinical trials</td>
<td>Clinical trials program supports trials with: funding, trial design, patient education, and outreach</td>
</tr>
</tbody>
</table>
Looking ahead

RESEARCH to find better treatments

ENGAGES PATIENTS IN FINDING SOLUTIONS

CONNECTS PATIENTS WITH RELEVANT STUDIES

PATIENT SERVICES to create better experiences

PATIENT-CENTERED

ENABLES THE DELIVERY OF BETTER CARE

HEALTHCARE IMPROVEMENT to drive better care

DRIVES REFERRALS TO QUALIFIED SPECIALISTS

DEFINES THE TREATMENT GUIDELINES THAT UNDERPIN PATIENT EDUCATION

Fosters patient participation in research.
# Looking ahead

<table>
<thead>
<tr>
<th>Program Area</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research</strong></td>
<td>- Discover therapies that target brachyury</td>
</tr>
<tr>
<td></td>
<td>- Apply immunotherapy advances to chordoma</td>
</tr>
<tr>
<td></td>
<td>- Accelerate clinical evaluation of promising therapies</td>
</tr>
<tr>
<td><strong>Healthcare Improvement</strong></td>
<td>- Identify clinical correlates of patient outcomes</td>
</tr>
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<td></td>
<td>- Update and disseminate treatment guidelines</td>
</tr>
<tr>
<td><strong>Patient Services</strong></td>
<td>- Provide more personalized educational resources</td>
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<tr>
<td></td>
<td>- Scale-up and enhance patient navigation offerings</td>
</tr>
<tr>
<td></td>
<td>- Facilitate more peer support &amp; knowledge sharing</td>
</tr>
</tbody>
</table>
Looking ahead

Achieving our goals will require investing $16M by 2020
Thank You

Josh Sommer
josh@chordoma.org
@sommerjo