International Chordoma Community Conference
Our mission is to improve the lives of those affected by chordoma and lead the search for a cure
Research is a Team Sport
A Vibrant Research Community

Before

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

After
A Different Way of Doing Research
PATH TO A CURE

We lead the search for a cure by advancing a comprehensive research roadmap that spans every stage of treatment development.

There are two potential routes to better treatments for chordoma:

1. Repurposing existing therapies
2. Discovering new therapies

Both depend on understanding the biology of the disease: what drives it and what its weaknesses are. Then, scientists can come up with ideas for how to treat it. These ideas could point to existing therapies or the need to discover new therapies.

Purpose

- Create the biological materials, disease models, and tools needed for research
- Uncover characteristics of and vulnerabilities in chordoma tumors that could be targets for treatment
- Discover new therapies that could more effectively treat chordoma than any existing therapy
- Test therapies in cell and animal models to predict their efficacy in chordoma patients
- Conduct research involving chordoma patients to test promising therapies and treatment protocols

Within each stage, goals are:
- Developed with guidance from scientific and medical thought leaders
- Regularly measured and evaluated
- Continuously updated to address new needs and opportunities

Together, we will cure chordoma. Visit chordoma.org
We lead the search for a cure by advancing a comprehensive research roadmap that spans every stage of treatment development.

- Research at each stage is important, but alone is not sufficient to deliver better treatments to patients.
- Progress must be made across the entire treatment-development continuum to achieve the outcome we desire.
There are two potential routes to better treatments for chordoma:

1. Repurposing existing therapies
2. Discovering new therapies

- There are over 150 cancer drugs already on the market, and over 1,000 more in development
- Different types of cancer often share common underlying biology, making them susceptible to the same treatments
- The majority of cancer treatments are approved for more than one type of cancer

Both depend on understanding the biology of the disease: what drives it and what its weaknesses are. Then, scientists can come up with ideas for how to treat it. Those ideas could point to existing therapies or the need to discover new therapies.
• The only way to know whether a treatment works is to test it in patients
• But all therapies carry risks and a limited number of therapies can feasibly be tested in patients due to scarce resources and small patient population
• Therefore, we must have convincing evidence that a therapy is likely to be effective in order to justify exposing patients and investing in clinical research
Within each stage, we set specific goals with input from our research network and Medical and Scientific Advisory Boards. Goals are continually updated as discoveries are made and new opportunities arise.
Scientific Advisory Board

» David Drewry, PhD
   GlaxoSmithKline

» Adrienne Flanagan, MD, PhD
   University College London

» Fran Hornicek, MD, PhD
   Massachusetts General Hospital

» Michael Kelley, MD
   Duke University

» Paul Meltzer, MD, PhD
   National Cancer Institute

» Deric Park, MD
   University of Virginia

Medical Advisory Board

» Tom DeLaney, MD
   Massachusetts General Hospital

» Hans Gelderblom, MD, PhD
   Leiden University Medical Center (Netherlands)

» Ziya Gokaslan, MD
   Johns Hopkins

» Mrinal Gounder, MD
   Memorial Sloan Kettering

» Chris Heery, MD
   National Cancer Institute

» Fran Hornicek, MD, PhD
   Massachusetts General Hospital

» Shreyas Patel, MD
   MD Anderson

» Chandra Sen, MD
   New York University

» Silvia Stacchiotti, MD
   Istituto dei Tumori, Milan (Italy)

» Katie Thornton, MD
   Johns Hopkins

» Josh Yamada, MD
   Memorial Sloan Kettering
Create the biological materials, disease models, and tools needed for research

Uncover characteristics of and vulnerabilities in chordoma tumors that could be targets for treatment

Discover new therapies that could more effectively treat chordoma than any existing therapy

Test therapies in cell and animal models to predict their efficacy in chordoma patients

Conduct research involving chordoma patients to test promising therapies and treatment protocols
## RESOURCE DEVELOPMENT

### Key resources

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>Goal</th>
<th>Current</th>
<th>In Dev’t</th>
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</tbody>
</table>

### Strategy

- Grants
- Prizes
- Contract Research
- Independent Validation
- Centralized Repositories
TARGET DISCOVERY

• Key goals
  – Discover molecular drivers
  – Uncover vulnerabilities
  – Identify unique characteristics

Strategy

✓ Grants awarded to:
  – Broad Institute of Harvard and MIT (2)
  – Johns Hopkins University (3)
  – Maastricht University, Netherlands
  – Massachusetts General Hospital (3)
  – Memorial Sloan Kettering (3)
  – Sanger Institute, UK
# TARGET DISCOVERY

## Approaches (partial list)

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Genome sequencing</td>
<td>Complete</td>
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<tr>
<td>Epigenomic analysis</td>
<td>Ongoing</td>
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<tr>
<td>Proteomic analysis</td>
<td>Ongoing</td>
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<tr>
<td>Loss of function screens</td>
<td>Ongoing</td>
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<tr>
<td>Chemical screens</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Super-enhancer analysis</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Antigen profiling</td>
<td>Planned</td>
</tr>
</tbody>
</table>
TARGET DISCOVERY

• Targets discovered

1. Therapies Exist
   (partial list)
   ▶ CDKs
   ▶ EGFR
   ▶ c-Met
   ▶ FGFR
   ▶ HDAC
   ▶ Hypoxia
   ▶ mTOR
   ▶ PD1/PDL1
   ▶ PI3K

2. New Therapy Required
   ▶ Brachyury
     • 97% of chordoma patients have inherited SNP in brachyury
     • Inherited extra copy of brachyury causes familial chordoma
     • Activated in all chordomas
     • Essential for chordoma cell survival
TARGET DISCOVERY

• Targeting brachyury
  – Determine how brachyury drives chordoma
    • What turns it on?
    • What other factors does it require to operate?
    • What genes does it activate?
    • What genes does it suppress?
    • How does the chordoma-associated SNP affect brachyury function?

Strategy

✓ Seed grant awarded to University of Toronto
• Additional investments needed
  – Pending funding commitment
**Key goals**

- Discover therapies that directly or indirectly block brachyury

**Strategy**

- Seed grant awarded to MGH (Sept ’15)
- Additional investments needed
  - Pending funding commitment
PRECLINICAL RESEARCH

• Key goals
  – Test all approved drugs and libraries of experimental therapies in chordoma cell lines
  – Test promising therapies in mouse models
PRECLINICAL RESEARCH

Strategy

✅ Grants awarded to:
  - Johns Hopkins (2)
  - Massachusetts General Hospital

✅ Drug screening partnerships established with:
  - NIH
  - Sanofi
  - Novartis
  - Broad Institute
PRECLINICAL RESEARCH

• **Initial results**
  – Tested all FDA-approved drugs in chordoma cell lines, identified ~20 promising drugs
  – Tested 12 promising drugs in mouse models
  – Identified several drugs that inhibit tumor growth in mice

![Graph showing tumor growth over time with Erlotinib compared to a negative control.](image)
PRECLINICAL RESEARCH

Strategy

✓ Grants awarded to:
  – Johns Hopkins (2)
  – Massachusetts General Hospital

✓ Drug screening partnerships established with:
  – NIH
  – Sanofi
  – Novartis
  – Broad Institute

✓ Launched CF Drug Screening Pipeline (Aug ‘15)
PRECLINICAL RESEARCH

• CF Drug Screening Pipeline
  – A centralized drug screening service offered to the entire research community
  – Enables fast and efficient evaluation of promising drugs proposed by researchers, companies or SAB
  – Reduces cost by 40-50%
  – Reduces time by 60-70%

  • Eliminates 12-18 months of start-up time
  • Eliminates 12-24 years of publication delay
PRECLINICAL RESEARCH

• CF Drug Screening Pipeline
  – Tested 12 drugs and combinations
  – More drugs being prioritized today
  – Capacity to test ~15 drugs per year (requires $400K)
CDK4/6 Inhibitor

Tumor Volume (Mean ± SEM)
00-2015-ST001, 10-1-2015

Cubic Millimeters

Day

0 14 28 42

Control Palbociclib
EGFR Inhibitor

Tumor Volume (Mean ± SEM)
00-2015-ST001, 10-1-2015

- Black line: Control
- Red line: Sapitinib
EGFR Inhibitor

Tumor Volume (Mean ± SEM)
00-2015-ST001, 10-1-2015

Control

Cetuximab

Cubic Millimeters

Day
Key goal: launch 10 clinical trials by 2020

Clinical Trials Strategy
- Carefully vet and prioritize trials with MAB and SAB
- Provide MAB and patient input on trial design
- Assist in trial site initiation
- Provide grants for non-drug costs
- Educate and notify patients and physicians
RESEARCH:
CLINICAL RESEARCH

• Progress
  ✓ Started phase 2 trial of brachyury yeast vaccine at NCI in April ’15
  ✓ Prioritized new trial concepts in July ’15
    • MAB and SAB reviewed 18 concepts
    • Identified 3 with strong rationale
  ✓ Drug committed by companies
  ✓ Protocols developed
  ✓ Reviewing 8 more trial concepts today
## Clinical Trials Pipeline

<table>
<thead>
<tr>
<th></th>
<th>Planning</th>
<th>Protocol Approved</th>
<th>Recruiting</th>
<th>Enrollment Complete</th>
<th>Trial Complete</th>
<th>Results Available</th>
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<tr>
<td><strong>Clostridium Novyi</strong></td>
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## 2016 Research Priorities

<table>
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<th>Priority</th>
<th>Budget</th>
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<tbody>
<tr>
<td>Continue developing, validating and distributing preclinical models</td>
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<tr>
<td>Invest in projects to (i) understand brachyury’s role in chordoma and (ii) discover new targets for immune therapy</td>
<td>$400K</td>
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<tr>
<td>Invest in projects to identify ways to target brachyury</td>
<td>$250K</td>
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<tr>
<td>Test 15 drugs in Drug Screening Pipeline</td>
<td>$400K</td>
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<tr>
<td>Initiate and support two clinical trials</td>
<td>$600K</td>
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