Leading the Search for a Cure

AGENDA
• Background
• Research Strategy
• Research Progress
• Next Steps
OUR MISSION

To improve the lives of those affected by chordoma and lead the search for a cure

THE PROBLEM

Chordoma is poorly controlled with current treatments

- Disease-free: 40%
- Stable local disease: 11%
- Progressive local disease: 6%
- Stable metastatic disease: 11%
- Progressive metastatic disease: 32%

THE PROBLEM

Patients experience a multitude of health effects that diminish quality of life

- Chronic pain
- Depression or severe anxiety
- Difficulty walking
- Chronic fatigue
- Difficulty sleeping
- Balance impairment
- Double vision
- Limited mobility
- Sexual dysfunction
- Hearing loss
- Chronic sinus problems
- Urinary incontinence
- Urinary retention
- Bowel obstruction
- Fecal incontinence
- Speech impediment
- Other vision problems
WHAT PATIENTS NEED

• Treatments that:
  – Improve quality of life
  – Reduce recurrence
  – Stop progression
  – Cure the disease

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PATH TO BETTER TREATMENTS

1. Repurposing existing 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

2. Discovering new therapies
PATH TO BETTER TREATMENTS

1. Repurposing existing therapies
   - Both paths depend on understanding the biology of the disease
   - Then, scientists can come up with ideas for how to treat it
   - Those ideas could point to existing therapies or new therapies that need to be developed

2. Discovering new therapies

OUR RESEARCH STRATEGY

- We lead the search for a cure by advancing a comprehensive research roadmap that spans every stage of the treatment development process
- Within each stage, we set goals and develop plans with guidance from our Scientific and Medical Advisory Boards
OUR RESEARCH STRATEGY

Proactively Drive Research

Streamline the Research Process

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Our Research Strategy:

- We lead the search for a cure by advancing a comprehensive research roadmap that spans every stage of the treatment development process.
- Within each stage, we set goals and develop plans with guidance from our Scientific and Medical Advisory Boards.
- Progress is regularly measured and evaluated.
- Plans are continually updated as discoveries are made and new needs and opportunities arise.

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Scientific Advisory Board
- David Drewry, PhD
  University of North Carolina
- Adrienne Flanagan, MD, PhD
  University College London
- Fran Hornicek, MD, PhD
  Massachusetts General Hospital
- Michael Kelley, MD
  Duke University
- Paul Melzner, MD, PhD
  National Cancer Institute
- Deric Park, MD
  National Cancer Institute

Medical Advisory Board
- Tom Delaney, MD
  Massachusetts General Hospital
- Hans Gelderblom, MD, PhD
  Leiden University Medical Center (Netherlands)
- John Kelley, MD
  Johns Hopkins
- Mitali Gaurav, MD
  Memorial Sloan Kettering
- Chris Henry, MD
  Memorial Sloan Kettering
- Fran Hornicek, MD, PhD
  Massachusetts General Hospital
- Shreya Patel, MD
  MD Anderson
- Chandra Sen, MD
  New York University
- Silvia Stacchiotti, MD
  Instituto di Caringi, Milan (Italy)
- Katie Thornton, MD
  Johns Hopkins
- Josh Y赞美, MD
  Memorial Sloan Kettering

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12/7/15
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STREAMLINING RESEARCH

NETWORK DEVELOPMENT
• Proactively recruit researchers into the field
• Hosted 4 international research conferences
• Built a network of over 300 researchers worldwide
CENTRALIZED REPOSITORIES

We supply researchers with easy access to critical scientific resources through centralized repositories of:

- Tumor Tissue
- Cell Lines
- Mouse Models

DRIVING RESEARCH
**RESOURCE DEVELOPMENT**

- **Key resources**
  - Cell Lines
  - Tumorgraft Mouse Models
  - Genetically Engineered Mouse Models

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**Strategy**

- Grants
- Prizes
- Contract Research
- Independent Validation

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**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

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**TARGET DISCOVERY**

- **Approaches** (partial list)
  - Genome sequencing
  - Epigenomic analysis
  - Proteomic analysis
  - Loss of function screens
  - Chemical screens
  - Super-enhancer analysis
  - Antigen profiling

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TARGET DISCOVERY

• Targets discovered

Therapies Exist (partial list)
- CDKs
- EGFR
- L-MAK
- FGFR
- HDAC
- Hypoxia
- mTOR
- PDL/PD1
- PI3K
- SWI/SNF

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

THERAPEUTIC DISCOVERY

• 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

**Strategy**

- **Grants and Partnerships**
  - Tested all FDA-approved drugs in chordoma cell lines, identified ~20 promising drugs
  - Tested 15 promising drugs in mouse models
  - Identified several drugs that inhibit tumor growth in mice

**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

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12/7/15
PRECLINICAL RESEARCH

• CF Drug Screening Pipeline
  – Experiments with first 5 drugs started in Sept ’15
  – 10 more drugs vetted
  – Next 5 will start in Q1 ’16
  – Capacity to test ~15 drugs per year (requires $400K)

CLINICAL RESEARCH

• Key goals
  – Launch 10 clinical trials by 2020
  – Create patient registry to systematically track patient outcomes

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

CLINICAL RESEARCH

• Progress
  ✓ Started phase 2 trial of brachyury yeast vaccine at National Cancer Institute in April ’15
  ✓ Prioritized new trial concepts in July ’16
    • MAB and SAB reviewed 18 concepts
    • Identified 3 with potential clinical value
SUMMARY OF RESEARCH INVESTMENTS

- Invested $4M in research
- Funded 25 research grants
  - Broad Institute, Duke, Istituto dei Tumori, Johns Hopkins, Mass General, Memorial Sloan Kettering, University College London, University of Florida, University of Maastricht (Netherlands), etc.
- Initiated >90 research partnerships leveraging millions of external research dollars

DISCOVERIES PUBLISHED IN PEER REVIEWED PUBLICATIONS

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<th>Therapeutic Target</th>
<th>Molecular Evidence</th>
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2016 RESEARCH PRIORITIES

- Continue developing, validating and distributing preclinical models - $200K
- Invest in projects to (i) understand brachyury’s role in chordoma and (ii) discover new targets for immune therapy - $400K
- Invest in projects to identify ways to target brachyury - $250K
- Test 15 drugs in Drug Screening Pipeline - $400K
- Initiate and support three clinical trials - $600K

Total - $1.85M

Questions?