Moving towards personalized care

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Precision medicine and chordoma

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Outline

• What is precision medicine and how does it work?

• Types of genomic profiling tests

• Practical considerations for chordoma patients

• How is research advancing the outlook for precision medicine in chordoma?
What is personalized or “precision” medicine?

• Match the right patient with the right drug

• Considers the **molecular profile** of cancers to be of key importance, rather than their tissue of origin

• Typically utilizes **genomic profiling** to identify biomarkers for targeted therapy or immunotherapy
Precision oncology: birth of the “magic bullet” era

Established a new paradigm focused on understanding the range of DNA mutations responsible for cancer growth, and developing drugs targeted against each mutation.
The promise of precision oncology

38-yo metastatic melanoma patient

Oncogenic BRAF mutation detected

BRAF inhibitor

Genetic profiling

Adapted from Wagle et al., J Clin Oncol, 2011
2010s: Genomics-guided precision oncology comes of age

...and more
Approaches to DNA (genomic) profiling

Gene A
Gene B
Gene C
Gene D
Gene E

Recurrently mutated in cancer X
Recurrently mutated in cancer Y
Comparison of genomic profiling approaches

<table>
<thead>
<tr>
<th></th>
<th>Targeted</th>
<th>Whole-exome</th>
<th>Whole-genome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage (breadth)</td>
<td>~500 genes analyzed</td>
<td>~20,000 genes analyzed</td>
<td>Full genome</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>~2 weeks</td>
<td>~2 weeks</td>
<td>weeks to months</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Very high</td>
<td>High</td>
<td>Decent</td>
</tr>
</tbody>
</table>

- Targeted profiling panels are *limited* and *biased* in their gene coverage, and are typically optimized for a few common cancer types.

- Due to differences in disease biology, targeted panels can miss potentially actionable mutations.

- **Whole-exome** profiling provides more information, and has become increasingly economical and practical in recent years.
Practical considerations for chordoma patients

1. Who should consider tumor profiling?
   - Chordoma patients in need of systemic therapy should consider whether testing is right for them
   - Discussing the pros and cons with your oncologist can help you make the best decision for your individual situation
   - New or archival tumor samples can be used (surgery, biopsy)
2. Are test results needed for enrollment in clinical trials?

- Circumstantial – it depends on the trial (check eligibility criteria)
- Results can help point to personalized clinical trial, off-label, or compassionate use opportunities
- Precision oncology trials: NCI-MATCH, TAPUR
- “Basket” trials

H West, JAMA Oncol, 2017
Practical considerations for chordoma patients

3. Are the test results guaranteed to identify a biomarker for personalized therapy?
   - Oftentimes no currently-actionable mutations are found
   - Actionable mutations but inaccessible therapies (e.g. ineligibility for clinical trial)
   - What works for some people doesn’t work for others (i.e. response rate < 100%)
Most chondoma patients have not benefitted from genomics-guided precision oncology.

- **Chordoma**
  - Targetable mutations: 12%
  - Undruggable mutations: 88%

- **Lung cancer (non-small cell)**
  - Targetable mutations: 30%
  - Undruggable mutations: 70%

*FDA levels of evidence 1-3
AMP/ASCO/CAP levels A-C
FDA-approved or investigational therapies for specific alteration in any cancer type*
How can research maximize the number of chordoma patients that benefit from personalized medicine?

Grow our understanding of chordoma biology through:

- Identifying new types of targetable vulnerabilities
- Predicting actionability of mutations in cancer-related genes
- Defining mechanisms of therapy response and resistance
Predicting the actionability of mutations in cancer-related genes

- Through the lens of current genomic profiling tests, well-validated therapeutic biomarkers are rare in chordoma
- In the absence of recognized biomarkers, **potentially actionable alterations** or **variants of unknown significance (VUS)** in cancer-related genes can suggest possible therapeutic opportunities based on emerging science
- These are typically listed near the end of the report and should be discussed with your oncologist
Predicting the actionability of mutations in cancer-related genes

Now up to 40% of patients may benefit from genomics-guided precision oncology when including reported actionable mutations + potentially actionable/VUS in cancer-related genes.
SMARCB1/INI1 mutations create a targetable Achilles’ heel

- Drug Screening Program collaboration with Dr. Greg Cote at MGH identified vulnerability created by mutations in SMARCB1/INI1 gene
- Important to repeat this experiment in more chordoma models, plus complementary experiments in our new lab
- Extending these observations to related genes to understand if more chordoma patients could benefit

Tumors in 3 out of 7 mice disappeared completely
Multiple integrated systems contribute to tumor biology

Geography

Biology

Opportunities for personalized medicine exist within each layer; combining more layers provides fuller picture

Source: usgs.gov
Identifying responders to EGFR inhibitors
Identifying and validating new types of therapeutic vulnerabilities

Target Discovery Initiative

Systematically uncovering chordoma’s most promising vulnerabilities

The new paradigm of precision oncology relies on the identification of specific molecular features in cancer cells that are essential to their growth and survival, called “therapeutic targets.” Hence, finding effective treatments for chordoma depends first and foremost on illuminating such vulnerabilities. These targets could be, for example, certain proteins upon which tumor cells are uniquely dependent for survival, processes that are inappropriately activated in tumor cells, or signaling cascades of tumor cells to which therapies can be directed.

Our Target Discovery Initiative aims to systematically uncover the most promising therapeutic targets in chordoma among the vast number of possible therapeutic targets that exist within tumor cells. The initiative is guiding the redirection of existing treatments to chordoma (drug repurposing) or, if necessary, the development of new drugs against currently inaccessible targets.

Strategy

The Chordoma Foundation is supporting a broad portfolio of projects employing cutting-edge technologies to uncover aspects of chordoma biology that could serve as therapeutic targets. Key areas of focus include:

- Mapping the spectrum of chordoma dependencies: creating a deep understanding of the genes and proteins upon which chordoma cells depend for growth or survival.
- Conducting multi-omic analyses: characterizing alterations in genes (genome), gene expression (epigenome), proteins (proteome), and additional “omes” to paint a comprehensive, multi-layered picture of chordoma biology.
- Understanding the chordoma microenvironment: learning how chordoma interacts with immune cells and surrounding tissues.
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Target Discovery Initiative, e.g., SMARCB1 project, e.g., EGFR project
Thank you

Questions?