



Second International Chordoma Research Workshop Summary

Agenda

On April 3-5, 2008 the Chordoma Foundation co-hosted the Second International Chordoma Research Workshop along with the National Cancer Institute and NIH Office of Rare Diseases. The 2 ½ day meeting, held at the NIH Neurosciences Conference Center in Bethesda Maryland, included over twenty plenary presentations highlighting new data, as well as poster presentations, and three working-group break-out sessions.

The three breakout groups focused on:

- **Mechanisms of Disease** – Understanding the molecular, genetic, epigenetic, and micro-environmental factors that cause the development and progression of chordoma.
- **Therapeutic Development** – Identifying strategies for screening, selecting, and testing new drugs to treat chordoma.
- **Clinical Management.** – Developing consensus regarding the optimal treatment of chordoma patients, and the role of research in clinical care.

Participants

A diverse group of eighty outstanding physicians and scientists from eight countries (US, Canada, England, China, India, Germany, Italy, Japan) and thirty-two institutions attended the second ICRW. Participants included basic scientists, medical and surgical oncologists, and experts in drug development. Nearly half of the participants were new to the field of chordoma research, and were invited based on their relevant expertise or overlapping research interests. Notably, four leading members of the Sarcoma Alliance for Research through Collaboration (SARC) presented new pre-clinical and clinical findings that could impact how chordoma patients are treated. In addition, eight members of the chordoma patient community were represented at the ICRW, five of whom were themselves physicians or scientists. The entire group was remarkably eager to collaborate, and many new research partnerships were formed within and between institutions.

Scientific Highlights

- **Model Systems**
 - Access to well characterized cell lines and animal models remains a significant barrier to research, and the need to develop such models was reinforced. Several research groups are now actively pursuing the development of cell lines, xenografts, and genetically engineered animal models of chordoma.

- Brian Harfe, PhD, a developmental biologist from the University of Florida, presented elegant data showing for the first time individual notochordal cells in the vertebrae of mice. Dr. Harfe hypothesizes that chordomas arise from this population of cells, and is attempting to induce chordomas in mice by knocking out specific genes in these notochordal cells. Dr. Harfe's findings caused excitement among all the participants because they could pave the way for creating a genetic mouse model of chordoma.
 - The Foundation announced the launch of the Chordoma Foundation Cell Line Panel, which will include 10-15 well characterized chordoma cell lines. The morphology, gene expression, genotype, of each cell line in this panel will be analyzed to ensure that they are derived from chordoma tissue and are valid models of the disease.
 - The Foundation will award \$25,000 grants for the development and characterization of model systems.
- **Chordoma Genomics**
 - At the first ICRW participants agreed on the importance of surveying the chordoma genome for alterations that could lead to an understanding of the genetic events responsible for the development and progression of chordoma. Information gleaned from these studies could indicate potential therapeutic strategies.
 - The Chordoma Foundation continues to work with Dr. Paul Meltzer to collect tissue for the Chordoma Genomic Profiling project which will analyze 100 chordoma specimens using multiple genomic platform technologies to characterize genomic alterations responsible for chordoma.
 - Since the first workshop several groups have performed high-resolution copy number and loss of heterozygosity (LOH) analysis on small samples of chordoma tumors. This analysis has identified several recurring deletions in genes known to be involved in tumor progression. In particular the CDKN2A (p16), a tumor suppresser commonly lost in multiple tumor types, was confirmed in multiple labs to be deleted in most chordomas.
 - The need for cross-platform validation and comparison of genomic, transcriptomic, and proteomic data was emphasized, and it was felt that this comparison would be more valuable if it occurred across the same set of tissue samples.
 - **Signaling Pathways**
 - Several groups independently confirmed using different techniques that mTOR (mammalian target of rapamycin) appears to be activated in nearly all chordomas. This has the potential to quickly impact the way chordomas are treated since mTOR inhibitors are already on the market. In several other tumor types, blocking the mTOR pathway has resulted in tumor regression, or increased sensitivity to other therapies.
 - Based on findings regarding mTOR, oncologists from Milan have begun treating chordoma patients who do not respond to Gleevec with Sirolimus (rapamycin).

Preliminary findings presented at ASCO indicate that the combination of Sirolimus and Gleevec caused a response in several patients who did not respond to Gleevec alone.

- Data was presented indicating an important role for several receptor tyrosine kinases (RTKs), particularly PDGF, in the growth and survival of chordomas. In the past several years numerous targeted drugs have been approved to inhibit various RTK's, and two of these targeted small molecules – Imatinib, and Sunitinib – have been tested in clinical trials for chordoma patients.
- Several groups are actively analyzing tractable signaling pathways in order to identify potential therapeutic approaches.
- **Drug Screening**
 - Chris Austin, MD, director of the NIH Chemical Genomics Center, presented preliminary data from high throughput screening of the 2500 compound FDA-approved library against the U-CH1 chordoma cell line. This screening has identified several molecular “hits” that warrant further investigation.
 - Researchers at Dana Farber and Pittsburgh also presented data from pre-clinical compound screening against U-CH1 and primary chordoma tumor cultures

Clinical Highlights

- The workshop was attended by senior radiation oncologists from three leading proton therapy centers in the US and carbon ion facilities in Germany and Japan. Significant time was devoted to understanding the role of radiation in the treatment and management of chordoma patients. In particular, vigorous discussion relative advantage of protons vs carbon ions. Beginning in November, 2008 the new Heavy Ion Therapy Center will open at the University of Heidelberg, Germany. This new center will be the only facility in the world treat with both carbon ions and protons, and researchers at Heidelberg plan to conduct a clinical trial to compare the efficacy of the two modalities in treating chordoma.
- The importance of making an accurate pathological diagnosis for chordoma was discussed at length. The Chordoma Foundation worked with three expert pathologists to help craft draft consensus statement for the diagnosis of chordoma. This consensus statement was presented by Andrew Rosenberg, from Massachusetts General Hospital – one of the world’s leading chordoma pathologists.
- Fran Hornicek, MD, PhD announced the beginning of an effort to create clinical management guidelines for chordoma with the aim of eventually having these guidelines adopted by the National Comprehensive Cancer Network (NCCN). Some basic recommendations were made by the Clinical Management working group:

- Early referral to experienced surgeons
 - Aggressive surgery to achieve maximal resection
 - Multidisciplinary care involving surgeons, radiation oncologists, radiologists, and medical oncologists
- The entire group reached consensus regarding the importance of prioritizing new clinical trials. The group also agreed on the importance of encouraging chordoma patients to participate in clinical trials, as this is the most direct and effective way to determine which drugs work.

Chordoma Foundation Announcements

New Chordoma Foundation Cell Line Panel

Cell lines are live tumor cells grown perpetually in a laboratory that are used to model the behavior of human tumors. They are a critically important tool for modern cancer research because they allow scientists to manipulate live cancer cells and observe the biological processes that cause them to grow.

Before any experiments or drug testing can be performed, cell lines must be extensively studied and characterized to ensure that they are a realistic model of actual chordoma tumors. Unfortunately, several purported chordoma cell lines that were created turned out not to be chordoma – this is a rampant problem in cancer research not unique to chordoma. Studying these invalid lines would lead to invalid data and would waste precious time and resources. To ensure that published data is not contaminated, and that research dollars are spent the Chordoma Foundation will create and distribute a panel of at least ten well-characterized and validated chordoma cell lines, each of which faithfully represents the biology of the tumor from which it was derived.

The panel will include cell lines representing the diverse clinical spectrum of the disease, including chordomas of the skull-base and spine from primary, recurrent, and metastatic tumors in adults and pediatrics. Cell lines in the panel will be distributed by the Chordoma Foundation to research labs across world and data generated on each cell line will be aggregated in a centralized database, allowing results from the same cell line in multiple labs to be directly compared. By enabling all researchers to study the same set of high-quality cell lines, the Chordoma Foundation Cell Line Panel will make the entire field of chordoma research more efficient and effective, and will accelerate the pace of discovery.

New grants available for the development and characterization of model systems

Currently, access to valid model systems is a major barrier for chordoma research and treatment development. To overcome this barrier the Chordoma Foundation seeks to create and distribute well-characterized model systems including cell lines, xenografts, and genetic animal models of chordoma that faithfully represent the biology of human chordomas. One-year grants of up to \$25,000 each will be awarded for projects to create and characterize relevant models of chordoma.

Co-funding grants with Liddy Shriver Sarcoma Initiative

The Chordoma Foundation has partnered with the Liddy Shriver Sarcoma Initiative to fund cutting edge chordoma research. All chordoma-related grants that are recommended for funding by Liddy Shriver Sarcoma Initiative reviewers will be forwarded to the Chordoma Foundation Board of Directors to be considered for co-funding.

Prizes for validated chordoma cell lines

The Chordoma Foundation will award up to ten (10) \$5,000 unrestricted prizes to the laboratory of any investigator who submits a cell line that is selected for inclusion in the Chordoma Foundation Cell Line Panel. This award is meant to encourage novel and creative approaches to establishing chordoma cell lines. It is also intended to promote biological diversity and avoid homogeneity among the set of cell lines in the panel. ALL investigators, including recipients of Chordoma Foundation research grants, are eligible to receive up to five (5) \$5,000 awards.

Outcomes & Next Steps

In all, the First and Second International Chordoma Research Workshops have brought together over 100 scientists and physicians from around the world, many of whom had not previously studied chordoma, forging literally thousands of new relationships and collaborations. These researchers shared nearly the sum-total of knowledge about chordoma, and together came up with a comprehensive plan to uncover the mysteries of chordoma and develop improved therapies for treating it. Now, for the first time ever a chordoma research community has formed, and is progressing with great momentum down a clear path towards new treatments. The major next steps for chordoma research are clear:

- 1) **Model Systems:** develop valid and well characterized models of chordoma and make these models freely available to researchers across the globe
- 2) **Chordoma BioBank:** collect high quality chordoma tissue, matched normal DNA, and clinical data in a centralized repository; distribute this tissue to be studied by multiple investigators, and aggregate data generated using this tissue to allow for cross-lab and cross-platform validation
- 3) **Chordoma Genomics Project:** perform a comprehensive cross-platform genomic and proteomic analysis of 100-200 chordoma tumors to uncover the genetic underpinnings of chordoma and identify hypotheses about potential therapeutic approaches
- 4) **High throughput screening:** use model systems such as cell lines and animal models to perform high throughput screening of compound libraries, and genome-wide RNA interference studies
- 5) **Functionalize data:** use information generated from screening the model systems, and the outcome of the Chordoma Genomics Project to test rational treatment strategies in model systems and ultimately in clinical trials

In tandem with advances in chordoma research and treatment development, progress must be made with respect to the clinical management of chordoma. The Chordoma Foundation will continue to work with expert physicians to form clinical guidelines for the optimal diagnosis and treatment of chordoma patients.

The next international research workshop will be held in the spring of 2010. Until then the Chordoma Foundation will remain steadfastly committed to driving these projects forward. Completion of these projects should, for the time, put effective treatments for chordoma patients within reach.

In order to accomplish the goals above and provide funding to chordoma researchers, the Chordoma Foundation aims to raise \$1.5 million by the end of 2008 and \$3 million by the end of 2009. Researchers at the Second ICRW lamented that the current funding climate is extremely challenging, and that without funding from the Chordoma Foundation many researchers who are beginning to study chordoma will be forced to turn towards projects on other diseases which have a higher likelihood of getting funded by the NIH or other foundations. With adequate funding, however, the potential for progress is limitless. This is a truly exciting time as Chordoma Research stands at a tipping point: the goal has been set, team has been assembled, the plan has been crafted – now it's up to the Chordoma Foundation to execute, and we need the support of the entire Chordoma Community to succeed.