

Chordoma Foundation Update

December 2015

Better treatments. Better medical care. A better experience for chordoma patients and their families. In 2015, we made encouraging progress on each of these fronts. Through new and enhanced **Patient Services**, we are now offering those affected by chordoma a place to turn for comprehensive information, guidance, and support throughout their journey with the disease. With new **Healthcare Improvement** initiatives, we are helping to raise the standard of care doctors provide to chordoma patients. And, eight years of strategic investments in **Research** are paying off with a wave of promising new treatments moving toward clinical trials. As the year draws to a close, we are excited to share this update on the key achievements of 2015 in each of the Foundation’s three program areas, as well as a preview of what’s ahead.

Contents

Patient Services	2
Healthcare Improvement	3
Research	4
Resource Development.....	4
Target Discovery	5
Therapeutic Discovery.....	7
Preclinical Research.....	7
Clinical Research	8
Looking Ahead	11

PATIENT SERVICES

The Chordoma Foundation's (CF) mission has always been to improve the lives of those affected by chordoma today while leading the search for better treatments in the future. While we have made significant progress in research over the past eight years, there remains much more that can and, we believe, must be done to help patients who are dealing with chordoma right now. As a first step toward meeting that need, last year, we worked with our [Medical Advisory Board](#) (MAB) and Education and Outreach Committee to develop a comprehensive strategy for serving the chordoma patient community. We identified five key needs of those affected by chordoma, designed a suite of programs to meet those needs, and developed a plan for expanding our service offerings to the chordoma community. In 2015, we began bringing that plan to life.

Thanks in part to a grant from the pharmaceutical company, Celgene, we started by hiring the Foundation's [first Patient Services Manager](#), Shannon Lozinsky, to run and professionalize our services for the chordoma community. A social worker by training, Shannon has experience working in social service organizations, as an educator, and in private counseling practice. With Shannon on board, we made significant headway in 2015 toward expanding and enhancing our services for the patient community in the following ways:

- **Launched a Patient Navigation Service**

This is a new service that provides one-on-one support and guidance to patients and families dealing with chordoma. For example, we provide referrals to qualified doctors, information about treatment options and clinical trials, and assistance in finding local resources to help with travel and accommodations. Since starting this service earlier this year, we have served 278 families facing chordoma in 37 countries. In the year ahead, we aim to increase utilization to 400 families.

- **Enhanced our Doctor Directory**

This year, we implemented new criteria for membership in our [Doctor Directory](#) recommended by our MAB. With these new criteria in place, we began the process of updating and vetting all the profiles in the directory. In the year ahead, we plan to vet 120 recently-identified specialists in the U.S. and abroad. In preparation for this expansion, we upgraded the technology that powers the directory to improve the user experience and make it easier to keep records up to date and accurate.

- **Created New Educational Materials**

We created a new, easy-to-understand [booklet](#) for chordoma patients and caregivers with evidence-based recommendations for the diagnosis and treatment of chordoma. It faithfully summarizes guidelines published this year in *The Lancet Oncology* by an international group of chordoma experts, and provides commentary from CF to help interpret and act upon the expert recommendations. Thus far, we have translated it into Italian and we plan to translate it into four additional languages. Next, we aim to develop a series of guides tailored to patients at each stage of the disease.

- **Hosted Three Chordoma Community Conferences**

In 2015, we brought together over 220 chordoma patients and family members for [Chordoma Community Conferences](#) in Los Angeles, New York, and Milan, Italy. These events provided a unique opportunity to learn about the latest treatment approaches from expert physicians, hear about cutting edge research, and develop meaningful connections with fellow members of the community. Furthermore, the New York and Los Angeles conferences were live-streamed to over 1,000 viewers across the world. [Video from these conferences](#) is now available on the Foundation's [YouTube channel](#). Going forward, as resources permit, we plan to continue hosting regional conferences in partnership with leading medical centers to reach more patients and families in communities across the world.

HEALTHCARE IMPROVEMENT

Until this year, there was no consensus among doctors about how to best treat chordoma. As a result, there was a great deal of inconsistency in care provided to chordoma patients in different hospitals and too many patients received suboptimal treatment. As a first step to address that problem, in 2013 we partnered with the European Society of Medical Oncology (ESMO) to convene a multidisciplinary group of more than 40 expert physicians to come to consensus on evidence-based recommendations for the diagnosis and treatment of chordoma. This year, their recommendations were published in *The Lancet Oncology* — the highest profile journal in clinical oncology, read by tens of thousands of physicians around the world. [The paper](#) was co-authored by CF MAB member Dr. Silvia Stacchiotti, a medical oncologist at the Istituto Nazionale dei Tumori (INT) in Milan, and CF Executive Director Josh Sommer, on behalf of the global consensus group. It is intended as a reference for medical professionals, particularly those outside of referral centers who are most likely to first encounter new chordoma patients.

Because the first treatment for chordoma is the most important and has the biggest effect on a patient's outcome, this consensus statement focused on the diagnosis and primary treatment of the disease. Addressing how to manage recurrences — which are all too common for chordoma patients — was left unresolved after the first consensus meeting, requiring further data and further debate. Thus, in November 2015, along with ESMO and INT, we convened a second consensus group meeting in Milan to develop recommendations for treating recurrences. Over 60 physicians from the US, Europe, and Japan participated and 15 groups presented unpublished data about their experience with recurrent chordoma. Through a day of constructive debate and discussion, the group came to agreement on many key principles and produced an early draft of a consensus statement. In the months ahead, we will continue working with the consensus group to refine and vet these recommendations, with the goal of submitting a second manuscript for publication before the end of 2016. We also need to disseminate the consensus recommendations more broadly so that anywhere chordoma patients are likely to present, physicians are aware of the most appropriate ways to manage the disease, including referring patients to more experienced specialists and our Patient Navigation Service.

RESEARCH

In 2015, we made progress across all five stages of our Research Roadmap. We continued our ongoing investments in Resource Development, Target Discovery, and Preclinical Research that have uncovered solid rationale for well more than a dozen new treatment approaches. And, based on that strong evidence, for the first time, we began investing in Therapeutic Discovery and Clinical Research projects.

RESOURCE DEVELOPMENT

We continued working to provide the research community with easy access to high-quality tumor tissue and disease models needed for research:

- **Tumor Tissue**

Through our [Tumor Donation Program](#), we helped 30 chordoma patients undergoing surgery to contribute their tumor tissue to research. With these new donations, our Biobank inventory grew to 133 tumors. We are currently performing quality control checks on these samples in preparation for distributing samples next year. This year, we also implemented new procedures to use tumor tissue collected through our Tumor Donation Program to develop mouse xenograft models of chordoma — critical tools needed for evaluating new drugs. Going forward, we aim to increase participation in our Tumor Donation Program and grow our Biobank through greater marketing and outreach to the chordoma patient community.

- **Cell Lines**

This year, we distributed chordoma cell lines to 37 labs, enabling a wide variety of experiments aimed at identifying new therapeutic targets and evaluating new therapies. Since beginning our [Cell Line Repository](#) in 2008, we have provided cell lines to 92 research groups and companies across the world, leveraging millions of dollars of outside investment in chordoma research.

We also continued to expand our Cell Line Repository to ensure that researchers have access to models that represent all clinical and biological subtypes of chordoma. After four years of offering a [prize](#) to incentivize researchers to develop new cell lines, this year we were pleased to see the multi-year efforts of several researchers pay off. In all, we received eight new submissions for our cell line prize, six of which passed our validation tests. This brings the total number of validated chordoma cell lines to 12 — surpassing our initial goal of ten lines. As of year-end, we deposited three of these lines into the [chordoma collection at ATCC](#) (the world's largest public cell line repository), and awarded prizes to the creators. Additionally, one cell line that we previously deposited in ATCC finished the yearlong accessioning process, bringing the total number of chordoma cell lines now available through ATCC to four. We plan to continue offering prizes for additional cell lines in order to develop a panel of cell lines that represent all clinical

presentations of the disease — including tumors of all anatomic locations, from males and females, young and old, as well as primary and advanced tumors.

- **Xenograft Mouse Models**

This year, we inaugurated our much-awaited Xenograft Repository. As of year-end, we have two patient derived xenograft (PDX) models and two cell-line based xenograft models banked and available for use. Attempts are ongoing to establish two more PDX models received from collaborators, and five additional cell line-based xenografts.

Additionally, as described above, this year, we established and piloted a protocol to create PDX models from fresh tumor contributed through our Tumor Donation Program. We succeeded in engrafting live tissue from six surgeries into mice, and we will know within a year whether these tumors can be serially transplanted and expanded for use in drug screening experiments.

What's more, we collaborated with Dr. Michael Lim at Johns Hopkins University to develop of the first "humanized" chordoma xenograft mouse model. These mice are populated with a human immune system, which enables them to serve as models for evaluating immune therapies – one of the most promising emerging areas of cancer treatment. Over the course of the year, we contracted with the Jackson Laboratory (JAX) to supply the Lim Lab with 45 of these humanized mice for in-vivo drug testing experiments. Through JAX we can now make these models available to the broader research community as well.

- **Genetically Engineered Mouse (GEM) Models**

Previously funded GEM model development projects at Duke and JAX continued to make progress. We also initiated a long-term research collaboration agreement with JAX to systematically attempt to develop a chordoma GEM model based on new discoveries about chordoma biology. As a first step in this collaboration, JAX began engineering two new mouse strains that we believe will be important for the eventual development of a GEM model. Going forward, we plan to sponsor a series of attempts by JAX to use these strains to develop a GEM.

Additionally, we worked with our colleagues at Duke to deposit a [new mouse strain](#) into the JAX public mouse repository, making this resource freely available to the research community.

TARGET DISCOVERY

We continued investing in a variety of approaches to identify new therapeutic targets for chordoma through new and ongoing grants to support the following projects::

- Vulnerability Discovery**

Dr. Stuart Schreiber and colleagues at the Broad Institute of Harvard and MIT (Broad) employed three complementary approaches to identify vulnerabilities in chordoma that could be targets for therapy. These included super-enhancer analysis to identify genes that are critical to the identity of chordoma cells, a small molecule chemical screen to identify novel druggable targets, and a genome-wide CRISPR loss of function screen to systematically identify all genes upon which chordoma depends for survival. Early results have pointed to a class of proteins called transcriptional cyclin dependent kinases (CDKs) as potentially promising therapeutic targets for chordoma. To follow up on this finding, we awarded an additional grant of \$160,000 over two years to the Schreiber Lab. We also worked with the Broad chordoma team to test a CDK inhibitor that they identified in our Drug Screening Pipeline (explained below). A manuscript is being prepared describing preliminary results of this study.
- Proteomic Analysis**

Dr. Yasin Temel and colleagues at Maastricht University in the Netherlands continued to perform proteomic analysis to identify patterns of protein expression that differentiate chordoma from its normal counterpart, notochord. They also began experiments to determine how loss of brachyury changes the proteomic profile of chordoma cells. A manuscript is being prepared describing results of this study.
- Epigenetic Analysis**

Dr. Cameron Brennan and colleagues at Memorial Sloan Kettering continued epigenetic analysis of chordoma tumors. They have identified unique epigenetic profiles that differentiate chordoma from other tumors and normal tissue. A manuscript is being prepared describing results of this study. To complement this work, we awarded the Brennan Lab an additional \$100,000 grant to perform a shRNA loss of function screen of the druggable genome and epigenetic pathways. In addition to potentially identifying new therapeutic targets, this shRNA screen will replicate a portion of the Broad CRISPR screen, thereby providing real-time independent validation of results.
- Evaluating Mechanisms of Immune Evasion**

Dr. Joe Schwab and Dr. Soldano Ferrone at Massachusetts General Hospital (MGH) continued their collaboration to evaluate the integrity of the antigen presentation machinery in chordoma tumors in order to determine potential routes of immune evasion. A manuscript is being prepared describing results of this study.
- Brachyury Binding Partner Discovery**

Dr. Jack Greenblatt's group at the University of Toronto concluded a pilot project to detect protein-protein interactions of brachyury — a key insight that could point to new ways to disrupt brachyury. In a carcinoma cell line, they found two novel protein-protein interactions with brachyury. Next they plan to validate these findings in chordoma cell lines. Working through a contract lab, we grew large quantities of chordoma cells

required for this experiment and provided these cells to the Greenblatt Lab. Results from this experiment could provide important insights about how brachyury functions and could reveal new targets for therapy. If potentially druggable protein-protein interactions are identified in chordoma cells, we plan to support follow-up studies to evaluate and validate these new targets.

THERAPEUTIC DISCOVERY

Because brachyury activation plays a central role in driving the development and proliferation of chordoma, we aim to discover drugs that can block the effect of brachyury in chordoma cells.

As a first step toward discovering new drugs that can inhibit brachyury activity, we awarded a \$56,000 seed grant to Dr. Slim Sassi at MGH to evaluate and optimize a new brachyury activity reporter assay — a test that can be used to screen large libraries of compounds to detect agents that inhibit the function of brachyury. With this grant, Dr. Sassi, will perform a medium throughput small molecule screen as an initial attempt to identify inhibitors of brachyury, and to further evaluate the performance of the assay. Furthermore, we have negotiated options to license the assay from MGH for use in other larger-scale chemical screens, should it perform as planned.

Going forward, as funding becomes available, we plan to invest significantly more in additional projects to discover therapies that target brachyury. In the year ahead, we plan to release a request for proposals and run a peer review cycle to identify the most promising projects to fund.

PRECLINICAL RESEARCH

After two years of development, this fall we were pleased to launch our Drug Screening Pipeline — a program that enables us to systematically evaluate promising drugs in preclinical models of chordoma through a contract research lab. Each year, we will have the ability to test approximately 15 drugs, selected with input of our MAB and [Scientific Advisory Board \(SAB\)](#). In December, we completed experiments testing the first five drugs. Four of the five significantly shrunk or reduced the growth of the tumors in mice. These included a CDK4/6 inhibitor and three different EGFR inhibitors. These results provide strong rationale for pursuing clinical trials with agents in both classes. Looking ahead, we have already vetted and prioritized a list of more drugs to test as funds become available.

In 2015, we also continued grant support for several preclinical research projects:

- **In-vivo evaluation of combination therapies**

Dr. Gary Gallia at Johns Hopkins continued testing combinations of targeted therapies in PDX models of chordoma. With a prior grant from CF, the Gallia Lab published results showing that EGFR inhibitors significantly reduce growth of chordoma PDX models. With

continued support from the Foundation, this year, his work revealed a new class of drugs that inhibits growth in PDX models as well as combinations that may be synergistic. A second manuscript is being prepared describing recent results of this project.

- **In-vivo evaluation of immune therapies**

We awarded a \$30,000 seed grant to Dr. Michael Lim at Johns Hopkins to evaluate immune therapies in combination with radiation in a new humanized xenograft mouse model of chordoma. This work is based on findings from a previous grant to Dr. Lim, which resulted in a publication in the *Journal of Neuro-Oncology* in January 2015. To make this project possible, we facilitated and funded a collaborative effort between the Lim Lab and JAX to develop the first humanized chordoma mouse model. In the year ahead, as funds become available, we plan to continue investing in Dr. Lim's efforts to identify promising new immune therapies for chordoma.

- **In-vitro evaluation of epigenetic inhibitors**

Dr. Greg Cote at MGH concluded his pilot project to evaluate a panel of epigenetic modulating agents in chordoma cell lines. The results were unremarkable in chordoma cell lines from conventional chordomas; however, the defect targeted by these drugs appears to only occur in dedifferentiated chordomas, arguing for the need to develop cell lines and mouse models of dedifferentiated chordoma.

Going forward, we plan to consolidate our investment in Preclinical Research through our Drug Screening Pipeline. This will provide the ability to quickly and efficiently test nearly any drug from any lab or company at a fraction of the cost and time of the traditional approach of awarding grants to academic labs. Furthermore, by working through a contract lab, we avoid lengthy IP and data sharing negotiations that are commonplace for collaborations between researchers at different universities or companies. This significantly lowers the barrier for any researcher to propose and test new treatment ideas. Working with a contract lab also allows us to share results much more quickly and more broadly prior to publication.

CLINICAL RESEARCH

CLINICAL TRIALS

In 2015, we reached several important milestones toward our goal of initiating 10 proof of concept clinical trials by 2020. Early in the year, we worked with investigators at the National Cancer Institute to [launch the first of those trials](#), which is testing whether a therapeutic vaccine called GI-6301 can improve the effectiveness of radiation for controlling tumor progression for patients with inoperable or partially resected tumors. This vaccine works by stimulating the immune system to mount a response to cells that express brachyury – a protein that is present in chordoma, but not in normal tissue. In addition to providing input into the trial design, we helped the study team develop easy-to-understand educational materials about the trial and

disseminated that information to the chordoma patient community, as well as to treating physicians.

Additionally, we turned to the global chordoma research community to put forward new ideas for promising treatments to test in clinical trials. We were tremendously pleased to receive 18 proposed trial concepts from researchers in seven countries. In July, our MAB and SAB reviewed and vetted these ideas in the context of everything known about chordoma and identified three treatment approaches for which there is strong scientific and clinical rationale. We have now begun working with leading treatment centers in the US and Europe to design and imitate clinical trials testing two of these approaches:

- **Second-generation EGFR inhibitor**

EGFR is a cell surface receptor that is overactive in many types of cancer and drives cancer cells to grow and multiply uncontrollably. Targeted therapies that block this protein — called EGFR inhibitors — are approved for the treatment of cancer (e.g., lung, head, neck, colon). Data from multiple labs clearly shows that EGFR is activated in most chordomas, and that chordoma cells are highly sensitive EGFR inhibitors. Previous work by Dr. Gary Gallia at Johns Hopkins funded by CF showed that clinically available EGFR inhibitors can slow the growth of chordoma tumors in mouse models. What's more, there are multiple case reports in the literature and unpublished anecdotes of chordoma patients responding to treatment with EGFR inhibitors. Given the weight of this evidence, investigators at University College London (UK), University of Leiden (NL) and Istituto Nazionale dei Tumori (IT) each independently proposed this approach. We brought all three groups together and they are now jointly designing a multi-site trial in Europe, with the goal of enrolling patients beginning in the first half of 2016.

- **Checkpoint inhibitor + hypofractionated radiation**

This trial is intended to harnesses the power of the body's own immune system to more effectively fight chordoma. In order for the immune system to destroy cancer cells it must both recognize the cancer as a threat, and be able to mount an effective attack. However, data from laboratory studies funded by CF at Johns Hopkins and MGH suggests that chordoma cells evade the immune system both by hiding and by expressing proteins that neutralize any immune response. Thus, for the immune system to control chordoma, it must overcome both of these defense mechanisms. Drugs called checkpoint inhibitors, recently approved for several other cancers (e.g., melanoma, lung, kidney), block a key mechanism by which cancer cells rebuff attack by the immune system. High dose, hypofractionated (delivered over a small number of sessions) radiation focused on the tumor causes tumor cells to expose their abnormal contents to the immune system, thus stimulating a heightened immune response to the tumor. Multiple ongoing clinical trials are testing checkpoint inhibitors in combination with radiation for other tumor types. Preliminary results from some of these studies have demonstrated impressive results, including examples of complete responses. Researchers at Johns Hopkins and at Memorial Sloan Kettering independently proposed applying this approach to chordoma.

We brokered a collaboration between these groups and they are now working together to design the trial.

Both trials will involve drugs that are already on the market, meaning that, if successful, patients could benefit from these drugs very quickly. Each trial will involve 20-40 patients. For both trials, the drugs will be donated by their respective manufacturers. However, additional non-drug costs of the trials (approximately \$300,000 per trial) will need to be funded by CF. A major priority now is raising funds needed for these trials as soon as possible.

The third trial concept endorsed by the MAB and SAB involves a drug that is in clinical development and not yet on the market (until the trial is given approval to proceed by the FDA, details about the treatment are confidential). The company developing this drug has written a trial protocol for chordoma patients, which will be reviewed in detail by our MAB in early 2016. Once the protocol is approved by our MAB, we will work with the company to identify and recruit trial sites, and, eventually, to generate awareness about the trial among patients and physicians. The pharmaceutical company will sponsor the trial, and we do not expect that it will require financial support from CF.

What's more, several other companies approached us this year interested in pursuing clinical trials in chordoma. Executives at two companies said the way in which we have organized the chordoma physician and patient communities makes chordoma an attractive disease to pursue for drug approvals compared to most other rare cancers. As ideas for additional trials are already accumulating, we plan to conduct another trial concept review in 2016 to evaluate new proposals and identify the next set of trials that we will support.

REGISTRY

Our MAB continues to strongly recommend developing a prospective registry for chordoma for several reasons: (i) to identify patterns of response to off-label use of systemic therapies, (ii) to uncover treatment approaches or decisions associated with better or worse outcomes, (iii) to better define the typical course the disease takes, and (iv) to more precisely identify candidates for upcoming clinical trials. In preparation for launching this program, we studied registries of several peer organizations and professional societies this year. Through this process, we identified key elements important for a chordoma registry, such as ways to collect data both directly from patients and from healthcare providers, ways to minimize the burden of data collection, and ways to ensure participation and buy-in from leading medical centers. Through this benchmarking exercise, we determined that creating such a registry will require an investment of approximately \$1.5-2M over the first five years. Significant federal funding is available to support this type of program in the long run through the recently formed Patient Centered Outcomes Research Institute. Our plan is to raise the first \$1M from private sources to pilot the program and build a track record that would make us competitive for PCORI funding.

LOOKING AHEAD

Building on the progress of 2015, in the next one to two years, we will focus on the following key initiatives:

PATIENT SERVICES

- Fill remaining gaps in our Doctor Directory in the U.S., expand list in Europe, and eventually beyond
- Increase capacity and utilization of our Patient Navigation Service and our Peer Support Program
- Continue developing better Educational Materials; create an “Expert Answers” video series, develop information sheets for key aspects of treatment, create comprehensive guides tailored to patients at different stages of the disease
- Create an online chordoma community to facilitate knowledge sharing among chordoma patients and caregivers

HEALTHCARE IMPROVEMENT

- Publish second consensus paper addressing management of recurrent disease
- Disseminate consensus papers through relevant professional societies, conferences and advertising
- Contribute to the second edition of the book *Chordomas and Chondrosarcomas of the Skull Base and Spine*

RESEARCH

- Continue developing new preclinical models of chordoma, and expanding the Foundation’s repositories of tumor tissue and models
- Continue investing in research to identify new therapeutic targets; in particular, elucidate how brachyury drives chordoma, and search for chordoma-specific cell-surface antigens
- Invest in projects to discover therapies that block the function of brachyury
- Evaluate the preclinical efficacy of more drugs through our Drug Screening Pipeline
- Initiate and support ten clinical trials by 2020, including three in 2016
- Establish a prospective chordoma registry to systematically track outcomes of chordoma patients
- Continue expanding and strengthening chordoma research network through biennial research conferences, ongoing networking, and, eventually, an online research community