

# International Chordoma Research Workshop 2007

## Speaker Abstracts and Bios

### **Francis Hornicek, *Clinical Overview***

Dr. Francis Hornicek is Chief of the Orthopaedic Oncology Unit at Massachusetts General Hospital and an Associate Professor in the Department of Orthopaedic Surgery at Harvard Medical School. Dr. Hornicek received his M.D. from the University of Pittsburgh School of Medicine and his Ph.D. from Georgetown University School of Medicine.

### **Mary McMaster, *Overview: Epidemiology of Chordoma***

Dr. Mary McMaster trained in internal medicine and medical oncology at Vanderbilt University. After developing an interest in cancer genetics, she then accepted a postdoctoral position in the laboratory of Dr. Bernard Weissman at the University of North Carolina Lineberger Comprehensive Cancer Center, where she studied the Wilm's tumor gene, WT1, using a microcell hybrid approach. In 1996, she came to the National Institutes of Health and completed the National Human Genome Research Institute's Medical Residency in Clinical Genetics. She subsequently moved to the Division of Cancer Epidemiology and Genetics in the National Cancer Institute, where she continues to work with Dr. Dilys Parry investigating the epidemiology of chordoma and the genetic basis of susceptibility to familial chordoma. In today's presentation, Dr. McMaster will provide updated epidemiological data on chordoma from the SEER (Surveillance, Epidemiology and End Results) program of the National Cancer Institute.

*Because chordoma is rare, it has been difficult to obtain population-based data about it. In 2003, we published the first large descriptive epidemiological study of chordoma, based on data for 400 cases collected over 23 years (1973-1995) by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. SEER has recently expanded its registry coverage, which, combined with the accumulation of nearly another decade of case reporting and follow-up, has resulted in the addition of a substantial number of chordoma cases to its database (total ~800). We decided to update our descriptive analysis to reflect these larger numbers, which are likely to result in more stable rate estimates. Methods: We used data from the 9 original SEER registries, (1973 - 2003) to calculate incidence rates of microscopically-confirmed chordoma and data from 17 registries to derive information regarding case distribution and to calculate survival rates. Results: The age-adjusted chordoma incidence rate (IR) was stable at 0.08 per 100,000. Incidence was age-dependent, more common in males (IR 0.11) than females (IR 0.07) and rare among patients < 40 years and blacks. Within the axial skeleton, 39.9% of cases were cranial, 29.1% spinal and 31.1% sacral. Young age ( $p < 0.005$ ) and female sex ( $p < 0.025$ ) were associated with greater likelihood of cranial presentation. Overall median survival (without stratification by treatment) was 7.17 years; 5- and 10-year relative survival rates were 70.3% and 48.1%, respectively. Conclusions: This study provides data supporting previous estimates of incidence and survival patterns of chordoma in the U.S. Additional epidemiologic studies are required to elucidate the genetic and environmental determinants underlying this rare, distinctive neoplasm.*

## **Rose Yang, *Linkage Analysis to Map Major Susceptibility Genes for Familial Chordoma***

Dr. Rose Yang received a B.S. and M.S. in cell biology in Beijing Normal University before she came to the States. She received a Ph.D. in physiology from the Lombardi Cancer Center, Georgetown University in 1999 and then switched her research interest from lab-based approaches to studying genes, exposures, and gene-environment interactions in human populations. Dr. Yang joined the Genetic Epidemiology Branch, Division of Cancer Epidemiology & Genetics, at NCI in 2000 as a fellow. While getting hands-on experiences in genetic and epidemiological research, she also obtained formal training in epidemiology by receiving a MPH degree from Johns Hopkins University School of Public Health in 2003. She became a tenure track investigator in the Genetic Epidemiology Branch at NCI in 2006. Dr. Yang's research interests include identification of genes for familial chordoma and melanoma. She is also interested in assessing etiologic heterogeneity of breast cancer using tissue microarray analysis of molecular markers involved in hormone-mediated pathways.

*R.X. Yang*<sup>1</sup>, *M.J. Kelley*<sup>2</sup>, *D. Ng*<sup>1</sup>, *N.J. Liebsch*<sup>3</sup>, *E. Sheridan*<sup>4</sup>, *A.W. Bergen*<sup>1</sup>, *M. Beerman*<sup>5</sup>, *A.M. Goldstein*<sup>1</sup>, *D.M. Parry*<sup>1</sup>

1. DCEG, NCI, NIH, DHHS, Rockville, MD; 2. Dept. of Medicine, Duke Univ., Durham, NC; 3. Dept. of Radiation Oncology, Mass. General Hospital, Boston, MA; 4. St. James Univ. Hospital, Leeds, UK; 5. CGF, NCI, NIH, DHHS, Gaithersburg, MD.

*Chordoma is a rare tumor believed to develop from notochordal remnants. Six chordoma families with two or more affected individuals have been described, suggesting a genetic predisposition. We previously reported significant evidence for linkage to chromosome 7q33 ( $Z_{max} = 4.78$ ) with a minimal disease gene region of 11 cM in three multiplex chordoma families. Subsequently, we evaluated a new chordoma family from Italy; linkage analyses of 7q markers ruled out 7q linkage in this family. In addition, sequencing candidate genes on 7q failed to identify a chordoma susceptibility gene(s) in the first three families. These findings motivated us to analyze data from an independent genome-wide scan of high-density SNPs in all four families to further investigate the evidence for 7q linkage and genetic heterogeneity and to identify new linkage regions. The four families (16 affected individuals) were genotyped for 2.2k SNP markers (Illumina II SNP linkage panel). We conducted both parametric and non-parametric linkage analyses. Initial results confirmed linkage to 7q33 in the three original families and genetic heterogeneity in the fourth family. Currently we are genotyping additional highly informative STR markers in several other regions that show suggestive evidence for linkage in some families. Although our linkage analyses have provided promising findings, our ability to narrow the disease gene region and examine genetic heterogeneity has been limited by the small number and size of the studied families. Inclusion of more chordoma families is essential to accelerate identifying susceptibility genes for familial chordoma.*

## **Paul Meltzer, *Mapping a Candidate Region for Chordoma***

Dr. Paul Meltzer is Chief of the Genetic Branch of the National Cancer Institute's Center for Cancer Research at the National Institutes of Health.

## **Vijaya Ramesh, *Understanding the Role of TSC/mTOR Pathway in Sporadic Chordomas***

Dr. Vijaya Ramesh is an Associate Professor of Neurology (Genetics) at Harvard Medical School and an Associate Neurologist at MGH. She obtained her Ph.D. from University of Madras, India and completed postdoctoral training in the laboratories of James Gusella (MGH) and Dr. Vivian Shih (MGH). She is a member of the Molecular Neurogenetics Unit and the Center for Human Genetic Research at MGH. She also directs a Monoclonal Antibody Core.

Dr. Ramesh's laboratory investigates tumor suppressor genes and their functions, particularly tumor suppressors related to Neurofibromatosis 2 (NF2) and Tuberous Sclerosis 1 and 2 (TSC). The NF2 protein merlin is a cytoskeletal-associated protein with a variety of functions. Her laboratory is working on understanding merlin's functions through two of its interacting partners, NHERF and Magicin. NHERF is a multifunctional adaptor protein that links various ion channels and receptors to the actin cytoskeleton through merlin and its related family members Ezrin, Radixin and Moesin (ERMs). Magicin, a novel cytoskeletal protein that we have isolated recently appears to have an essential role in signaling to the actin cytoskeleton as well as in transcription regulation.

Tuberous sclerosis complex (TSC), an autosomal dominant disease caused by mutations in either TSC1 or TSC2, is characterized by the development of hamartomas in a variety of organs. We have shown distinct activation of Akt/MAPK pathways in the CNS tumors of TSC patients, which may contribute to some of the neurological manifestations seen in TSC. Our most recent work documents the binding of TSC2 protein tuberin with Pam, a huge protein originally identified as associated with c-My. Dr. Ramesh's laboratory is investigating whether Pam function as an E3 ubiquitin ligase, regulating the stability of the TSC proteins and other key signaling molecules in neurons, thus playing a role in synaptic plasticity.

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*Chordomas are rare tumors that originate from notochordal remnants along the axial skeleton in the sacrococcygeal/sacral, sphenoccipital/clivus, and spinal regions. They are characterized by slow growth, local destruction of bone, extension into adjacent soft tissue and, rarely, distant metastatic spread. The incidence of chordomas in tuberous sclerosis complex patients (TSC) has been described, however, the role of the TSC1 and TSC2 genes at the somatic level in these tumors remained unclear. We identified earlier two TSC patients with coexisting chordomas. In a collaborative study performed with Lee-Jones and Sampson of UK, we have provided the first evidence of a pathogenic role played by the TSC genes in sacrococcygeal chordomas (Lee-Jones, et al., 2004). TSC proteins, tuberin and hamartin function together to inhibit mTOR signaling, which regulates protein synthesis and cell growth. Inactivation as well as downregulation of TSC proteins result in aberrant hyperactivation of mTOR signaling. Since our earlier study suggests a possible role for the TSC genes in the pathogenesis of sporadic chordomas, we have undertaken an effort to examine whether the TSC genes could be inactivated in adult as well as pediatric cases of sporadic chordomas. As a first step, we have examined the aberrant activation of mTOR signaling in these tumors, by performing staining for the downstream targets of mTOR, such as phospho-S6K and phospho-S6. Preliminary results obtained show positive staining of p-S6K and p-*

*S6 in tumor cells, suggesting a possible activation of mTOR signaling pathway in adult sporadic chordomas examined.*

### **Marnie Halpern, *Genetic Regulation of Notochord Development***

Dr. Marnie Halpern is a staff member in the Department of Embryology at the Carnegie Institution of Washington and an Adjunct Professor at Johns Hopkins University. Dr. Halpern received her Ph.D. from Yale University.

### **Cristina Antonescu, *Pathology, Gene and Protein Expression, Cell Surface Antigens***

Dr. Cristina Antonescu is Associate Attending and Associate Member at Memorial Sloan Kettering Cancer Center. Dr. Antonescu received her M.D. from Carol Davila School of Medicine in Bucharest, Romania.

*By the WHO classification, chordoma is regarded as a low to intermediate grade malignant tumor, accounting for 1-4% for all primary malignant bone neoplasms. Chordomas typically arise in the sacrococcygeal and spheno-occipital regions of the axial skeleton, most commonly after age 30. Grossly, chordomas frequently extend beyond the skeletal boundaries, having a lobulated growth within surrounding soft tissues, ranging from mucogelatinous to dark-hemorrhagic appearance. Microscopically, most tumors have a lobular architecture, in which cells are arranged in sheets, cords, or float singly in an abundant myxoid stroma. There is variable degree of nuclear pleomorphism, but mitoses are rare. Their cytoplasm may have a vacuolated ("physaliphorous cells"), clear, dense eosinophilic (oncocytic-like), or signet-ring (mimicking lipoblasts) appearance. In 5% of cases progression from a conventional morphology to a high grade spindle cell sarcoma (dedifferentiated component) is noted. Immunohistochemical (IHC) studies show consistent expression for keratins, EMA, S100 protein and vimentin. Ultrastructurally, tumor cells show epithelial features, such as microvilli, intracytoplasmic lumina, tonofilaments and well-formed desmosomes. In addition, pools of glycogen and mitochondria-RER complexes are often noted. In the base of skull location, chondroid variants of chordoma are described, showing variable degree of hyaline or myxoid cartilage matrix. Although the presence of chondroid differentiation has been noted since its first description of chordoma by Virchow in 1857 in the spheno-occipital site, this concept has been long controversial, not only as to its existence, but also to its improved prognosis. Subsequently, several studies have proven the validity of chondroid chordoma diagnosis by demonstrating keratin and EMA expression, which distinguishes them from chondrosarcomas. Most recently, T Brachyury, a transcription factor known to be involved in notochord development, has emerged as a sensitive and specific marker for chordomas. The transcriptional signature of chordoma includes in addition to T Brachyury, CD24 and Keratin 8,13,15,18 and 19. In a recent gene expression profiling analysis, conventional chordomas shared a similar gene expression profile of up-regulated extracellular matrix genes with a group of chondrosarcoma tumors. Notably, CSPG4 stood out as a promising therapeutic target, already extensively used in melanoma immunotherapy. IHC with CSPG4-specific mAb revealed positivity in 62% of chordomas tested. Flow cytometry using CSPG4-specific mAb showed staining of human chondrosarcoma and chordoma cell lines. These findings suggest that targeting cell-matrix interaction might be a promising therapeutic strategy, to replace the ineffective cytotoxic chemotherapy. Interestingly, chordoma is the most common bone tumor in ferrets, with significant morphologic and immunohistochemical overlap with both classic and chondroid chordoma in humans. As such, ferret chordoma*

*may serve as a potential animal model for the human counterpart, which may be used to test various targeted therapeutic agents, such as CSPG4.*

### **Adrienne Flanagan, *Brachyury expression in chordomas and other neoplasms-possible insights into the pathogenesis of the chordomas***

Dr. Adrienne Flanagan trained as a Surgical Histopathologist in London, UK directly after which she undertook a PhD in experimental pathology when her main focus became the regulation of osteoclast formation. She is professor of musculoskeletal pathology at University College London, and Clinical Lead and consultant histopathologist for the London Bone & Soft Tissue Sarcoma Unit which is based across two sites the Royal National Orthopaedic Hospital in Stanmore, just outside central London and University College Hospital. Dr. Flanagan was involved in a large scale gene microarray gene study of a variety of sarcomas and found that brachyury was highly expressed in these chordomas. She followed this up on an immunohistochemistry analysis of several hundred tumours and showed that brachyury is an exceptionally useful diagnostic marker for chordomas. She has subsequently found that so called "extra-axial chordomas" expressing brachyury occur at extra axial sites.

### **Takehiko Yamaguchi, *Chordomas arising from benign notochordal cell tumors***

Dr. Takehiko Yamaguchi graduated from Dokkyo University School of Medicine, Tochigi, Japan in 1986. He completed his postgraduate work at Dokkyo University School of Medicine in 1992 after an internship as an orthopedic surgeon at Dokkyo University School of Medicine. Dr. Yamaguchi was a Research Fellow at the Hospital for Special Surgery at the Cornell University School of Medicine as well as at Montefiore Medical Center, Albert Einstein School of Medicine. Dr. Yamaguchi is currently Associate Professor in the Department of Surgical Pathology at Sapporo Medical University School of Medicine.

*Any histologically confirmed cases of chordoma arising from notochordal vestige have never been documented although chordomas have been believed to develop in residual notochordal tissue. Most notochordal vestiges are found in the intervertebral discs of neonates, however, notochordal cells are rarely seen in the adult intervertebral discs. Meanwhile, benign notochordal cell tumor (BNCT) is a recently recognized intraosseous benign neoplasm of notochordal origin (the subjects will be discussed in poster session). This condition seems to be different from notochordal tissues in the fetal intervertebral discs microscopically and immunohistochemically.*

*I experienced a clinical case of chordoma arising from BNCT and found two autopsy cases of BNCT with malignant transformation. Furthermore, I recently encountered a clinical case of BNCT transforming into chordoma that were confirmed on imaging study. Based upon their clinicopathological findings, chordoma in adult patients seems to arise from intraosseous BNCT. It may not develop in notochordal remnants in the intervertebral discs. BNCT is usually depicted as an intraosseous sclerotic lesion without bone destruction. Osteolytic changes associated with intraosseous osteosclerosis may be a major important imaging finding.*

### **Amin Kassam, *Future Advances in Surgical Techniques***

Dr. Amin Kassam, completed his medical and undergraduate education at the University of Toronto and his residency and fellowship training at the University of Ottawa. Dr. Kassam pursued additional post-graduate training in epidemiology and clinical outcomes. Dr. Kassam joined the faculty of the Department of Neurological Surgery at the University of Pittsburgh in February of 1998. He spent the next year focusing on microvascular surgery. Dr. Kassam has performed over 1,000 microvascular decompression procedures for cranial nerve neuropathy and has provided a unique perspective by using the endoscope to visualize and enhance difficult regions. Since his appointment, he has also focused on building a collaborative center to provide comprehensive care for complex pathology of the skull base. This center builds on the strength of combining the talents of surgeons from multiple specialties. This allows for the use of proven conventional approaches in conjunction with new minimally invasive endoscopic approaches to provide safe and effective treatment for patients. This has culminated in the development of the multidisciplinary Minimally Invasive Neurosurgical Center (MINC). Dr. Kassam along with Carl Snyderman, MD, and Ricardo Carrau, MD, were directly involved with the development of the Expanded Endonasal Approach (EEA). This approach represents an entirely new paradigm to remove complex lesions of the skull base and brain without incisions. The center, under the direction of Dr. Kassam, has pioneered and developed much of the technology and instrumentation used during the EEA surgeries. With continued research and experience, he now uses the EEA surgery for most tumors affecting the skull base. Dr. Kassam has performed over 3,000 neurosurgical procedures including over 700 minimally invasive endoscopic procedures. Dr. Kassam remains active in cerebrovascular surgery and has helped to develop a program to better understand the genetic alterations that lead to the development of intracranial aneurysms. In July 2006, Dr. Kassam was named Interim Chairman of the Department of Neurological Surgery. Since then he has focused on increasing interdisciplinary activities between neurosurgery and radiology, medical, radiation and surgical oncology, anesthesiology, neurology, and otolaryngology. It is hoped that these cooperative ventures will lead to new innovations in care for patients with a variety of neurologic abnormalities. Dr. Kassam has over 80 peer reviewed publications, an additional 11 book chapters currently published or in press, and is funded by both industry and the NIH. He lectures extensively nationally and internationally on surgery of the cranial nerves, skull base and on minimally invasive endoscopic techniques.

### **Thomas DeLaney, *Radiation Treatment***

Dr. Thomas DeLaney is Medical Director, Francis H. Burr Proton Therapy Center, Massachusetts General Hospital (MGH), Boston. He also is Co-Director of the Sarcoma Center at the hospital, and Associate Professor of Radiation Oncology, Harvard Medical School. His primary areas of clinical and research interest include bone and soft tissue sarcomas and charged-particle (proton) radiation therapy.

Dr. DeLaney obtained his B.A. degree in history at Harvard College in 1978 and his medical

degree from Harvard Medical School in 1982. Herman Suit, MD, D.Phil., who was chief of Radiation Oncology at MGH while Dr. DeLaney was a Harvard medical student, was a major influence in his decision to enter the field of radiation oncology. After completing his internship at the Yale-New Haven Hospital in general surgery, Dr. DeLaney took three years of residency training at MGH in radiation oncology, completing training in 1986. He then spent six years as a senior investigator at the National Cancer Institute in Bethesda MD, where his interests were in the treatment of adult and pediatric sarcomas and translational research in photodynamic therapy with light-activated dyes. He returned to Boston in 1992 to become chief of radiation oncology at Boston University Medical Center, where he also established a joint residency program in conjunction with MGH. He returned to MGH to head the sarcoma service in the Department of Radiation Oncology in 2000, and became medical director of the Francis H. Burr Proton Therapy Center in 2001. He and Hanne Kooy, Ph.D. are editors of the book Proton and Heavier Charged Particle Radiotherapy (Lippincott, 2007).

*Of chordomas, 49% occur at the sacrococcygeal region, and 30% occur at the sphenoccipital region, with nearly all of these occurring at the clivus. Vertebral chordomas account for only 15% of total chordomas and occur in the lumbar, cervical, and thoracic regions in descending order of frequency. They present formidable surgical and radiation challenges. Gross total resections can be achieved for lesions arising below S3 and occasionally for the vertebral lesions; they are rarely possible for the sacrum or skull base. Recurrences or progression after surgery alone are frequent; these can occur years after the initial surgical procedure. Local recurrences of tumor are generally associated with very significant morbidity. The efficacy of conventional radiation therapy is limited because critical adjacent normal tissues constrains the dose that could be delivered to the entire tumor to < 60 Gy. Protons and heavier charged particles, which deliver physically and biologically higher doses, do appear to improve local control after surgery and have been able to control unresected tumors in some patients for very long periods of observation. Newer radiation modalities such as stereotactic radiotherapy or intensity modulated radiation therapy also allow higher radiation doses and data from the use of these techniques is emerging and will need to be compared to that achieved with charged particles.*

### **Soldano Ferrone, *The human high molecular weight-melanoma associated antigen (CSPG4) as a target of antibody-based immunotherapy***

Dr. Soldano Ferrone is a member of the Roswell Park Cancer Institute. Dr. Ferrone has focused his research program on the development and application of antibody-based immunotherapy targeting the human high molecular weight-melanoma associated antigen (HMW-MAA). He has shown that HMW-MAA-specific antibodies have an anti-tumor effect both in animal model systems and in patients with melanoma.

*The human high molecular weight-melanoma associated antigen (HMW-MAA) as a potential target for antibody-based immunotherapy in chordoma. This presentation will review the characteristics of HMW-MAA which is expressed in at least 50% of surgically removed chondroma and chondrosarcoma lesions. This antigen has a restricted tissue distribution and limited inter- and intra-lesional heterogeneity in its expression. This antigen is also expressed on activated pericytes; therefore immunotherapeutic strategies targeting HMW-MAA may have an anti-tumor effect not only by a direct effect on tumor cells but also by inhibiting neoangiogenesis. The results which indicate the anti-tumor effects of HMW-MAA-specific antibodies in animal model systems and in patients will be reviewed.*

## **Paolo Casali, Chemotherapy: *Imatinib clinical trial and the PDGF pathway in chordoma***

Dr. Paolo Casali is a medical oncologist and head of the Adult Sarcoma Medical Treatment Unit, Cancer Medicine Department, Istituto Nazionale Tumori, Milan, Italy. He is also Secretary of the Italian Sarcoma Group, and coordinator of the Italian Network on Rare Tumors.

*The first advanced chordoma patient in Milan was treated with imatinib mesylate as from August 2002. Difficulties with tumor response assessment delayed appraisal of drug's antitumor activity in the disease. The first 6 patients on compassionate treatment were reported preliminarily at CTOS in 2003, and then in a paper journal in 2004. The expanded series of 18 patients was reported at ASCO in 2005, encountering problems thereafter with publication in journals, the tumor being rare and the research being judged of "retrospective" nature. A total of 29 patients have now been treated with imatinib on a compassionate basis in Milan. A Phase II study was conducted in Italy and Switzerland on 55 patients, and preliminary results will be reported soon. Major problems with tumor response assessment in such a multi-institutional collaborative framework were encountered. A total of 10 patients with secondary progression after imatinib have continued receiving the drug with the addition of cisplatin. Early results have been reported at CTOS in 2006 and will be expanded soon.*

*On the basis of what observed so far, one may conclude that:*

- 1. Imatinib has antitumor activity in most patients with advanced chordoma.*
- 2. Tumor response with imatinib alone is generally a non dimensional,  $i; \frac{1}{2}$ tissue response $i; \frac{1}{2}$ , as for other solid tumors undergoing molecular targeted therapies, with decrease in tumor density on CT scan as its hallmark. PET scan is consistent with CT scan.*
- 3. This pattern of tumor response results in subjective improvement in most responsive patients with symptoms at baseline.*
- 4. Duration of response to imatinib in the advanced disease is in the one-year range, although continuation of the drug may still slow down progression.*
- 5. Addition of cisplatin has resulted in some dimensional responses in patients progressing on imatinib alone.*

*In the meantime, a comprehensive molecular/biochemical analysis of PDGFRB, PDGFRA, and KIT was carried out in a series of 31 chordoma patients from Milan (whether treated or not with imatinib). PDGFRB was found to be highly expressed and phosphorylated, whereas PDGFRA and KIT were less expressed but phosphorylated, in the face of lack of gain-of-function mutations, presence of cognate ligands, lack of gene amplification.*

*In prospect, we plan: to formally review all treated patients, in order to provide the most detailed results as possible for each case; to accurately review the data from the Phase II study results; to explore the value of imatinib plus cisplatin in the localized disease amenable to surgery, with a focus on pathologic response and resectability. Regulatory perspectives are under discussion, while the drug is largely unavailable at the moment for most chordoma patients all over the world.*



## **Mike Kelley, *Approaches to development of therapeutics for chordoma***

Dr. Michael Kelley is a graduate of University of Michigan School of Medicine (MD, 1985). He completed Internal Medicine Residency training at Duke University (1988), and completed training at National Cancer Institute including post-doctoral work in the laboratory of Stuart Aaronson and a clinical fellowship in Medical Oncology. He is currently Associate Professor of Medicine at Duke University and Chief of Hematology/Oncology at the Durham Veterans Affairs Hospital. Dr. Kelley's primary research interest is development of molecularly targeted agents for prevention and treatment of cancer, especially in lung cancer. His interest in chordoma began more than a decade ago in collaboration with Dilys Parry and others in pursuit of familial chordoma gene(s).

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*Chordoma is a rare tumor thought to arise from notochordal remnants with about 300 incident cases per year in the US. Only one prospective clinical study of systemic therapy for chordoma has been published in the English language. To develop the framework for drug development for chordoma, we obtained the UCH1 cell line and performed expression analysis, which confirmed its likely origin from chordoma including high level expression of brachyury. Three approaches are being pursued. (1) In vitro drug sensitivity testing using 14 standard agents was performed in a 96 hour growth assay using the MTS reagent. The chordoma cells were sensitive to four agents at clinically achievable concentrations in the 96-hour MTS assays: doxorubicin, topotecan, SN-38, and fludarabine. There was evidence of schedule dependency on 48-hour assay with topotecan, fludarabine, and, to a lesser extent, SN-38. Imatinib showed no activity. Screening of additional agents in this and other cell lines is planned. (2) Pathway activation signatures. RNA expression profiles from 8 sporadic chordoma tumors and 2 chordoma cell lines are available. These data are being examined for pathway activation signatures of more than 10 pathways implicated in oncogenesis including p53, ras, myc, E2F2, src, and PI3K. (3) Selected gene analysis. Based on its high expression level in chordoma and known anti-apoptotic activity, brachyury is being targeted by RNAi to determine its role in chordoma. Techniques and reagents being developed to examine brachyury can be applied to additional selected target genes. The rarity of chordoma will require non-traditional approaches to drug development including more comprehensive pre-clinical investigation of potential therapeutic agents using approaches such as those described here.*

## **Neil Spector, *Rational development of targeted therapies: ErbB receptors in IBC and potential candidates for chordoma***

Board Certified in Hematology, Medical Oncology; Fellowship at Harvard Medical School (1986-1989); Faculty: Dana-Farber Cancer (1989-1993), U. Miami School of Medicine (1993-1998); UNC-Chapel Hill (Adjunct Appt. 2000-2006); Duke University (2006-Present). Director of Translational Oncology Research and program leader for lapatinib (Tykerb) and Nelarabine (1998-2006).

*The ErbB (HER) family of transmembrane receptor tyrosine kinases (ErbB2 or EGFR; ErbB2 or HER2; ErbB3 or HER3; ErbB4 or HER4) are widely expressed in epithelial cells and play pivotal roles in regulating cell growth, survival particularly during embryogenesis. In solid tumors, deregulation of ErbB receptors promotes the growth and survival of tumor cells and has been associated with resistance to hormone, chemotherapy, particularly in breast cancer where ErbB2 protein overexpression or gene amplification predicts for a poor clinical outcome. Consequently, ErbB2 has become an attractive therapeutic target illustrated by the development of anti ErbB2 antibodies, small molecule tyrosine kinase inhibitors, hsp90 antagonists, and immunotherapeutics. ErbB receptors form dimers-homo- or heterodimers-with ErbB2/ErbB3 heterodimers representing the most potent signaling ErbB receptor signaling complex. Although ErbB2 lacks an exogenous ligand, it is the preferred heterodimeric partner, itself transactivated through its heterodimeric partner. Formation of ErbB receptor heterodimers induces autophosphorylation of conserved tyrosine residues within the cytoplasmic domain of the receptor that serve as docking sites for adaptor proteins linking the activated receptor to downstream signaling networks that regulate tumor cell growth and survival (e.g., MAPK-Erk and PI3K-Akt). Unfortunately, in carcinomas of the breast and other solid tumors, ErbB2 protein overexpression or gene amplification is not sufficient to predict for response to ErbB targeted therapies. In our studies of lapatinib (GW572016), an oral small molecule reversible inhibitor of EGFR and ErbB2 tyrosine kinases, we found that ErbB2+ inflammatory breast cancer (IBC) cell lines and in patients, were highly sensitive to the pro-apoptotic effects of lapatinib. IBC, which occurs in 1-6% of breast cancers in the U.S. and 20% in parts of North Africa, is one of the most aggressive sub-types of breast cancer. In an attempt to understand the mechanism responsible for the sensitivity of these tumors to lapatinib, we found that the growth and survival of ErbB2+ IBC were more likely to be dependent upon ErbB2 mediated signaling compared with ErbB2+ non-inflammatory breast cancer. The sensitivity of these tumors may in part be related to the presence of activated ErbB2/ErbB3 heterodimers, which appear to be activated in an autocrine or paracrine loop by heregulin, the ligand for ErbB3. Interestingly, chordoma also express ErbB receptors, making them or the downstream signaling network they regulate, potential therapeutic targets. Here we show that ErbB2, ErbB3, and EGFR are present in UCH1 chordoma cells, although in a hypophosphorylated state. Treating UCH1 cells with the proteasome inhibitor bortezomib, reduces ErbB2 and ErbB3 protein and inhibits activated p-Akt, a key regulator of tumor cell survival and mediator of resistance to chemotherapy. In contrast, p-Erk was not as sensitive to bortezomib. Importantly, treatment with bortezomib resulted in marked tumor cell death. In contrast, small molecule inhibitors of ErbB tyrosine kinases were less effective at inhibiting p-Akt and at inducing an anti-tumor response. Therefore, Akt and upstream regulators of Akt are potential tractable targets for therapeutic development in chordoma.*

### **Josh Sommer, Simone Sommer, *The Chordoma Foundation: Coordinating Collaborative Projects to Rapidly Improve Patient Outcomes***

*Simone Sommer, M.D., MPH*

Dr. Simone Sommer is the President and treasurer of the Chordoma Foundation, which she formed after her son and best friend, Josh, was diagnosed with a chordoma in 2006. Dr. Sommer is dedicated to improving the quality of lives of people affected by chordomas, and has devoted her full-time efforts to bringing about effective treatments, and ultimately a cure for this disease. Under her direction, the Chordoma Foundation has initiated numerous collaborative research projects with scientists and physicians at institutions across the world. Dr. Sommer's goal is to serve as the focal point for a coordinated international chordoma research effort.

Dr. Sommer received her M.D. from George Washington School of Medicine and her masters degree in public health in epidemiology from the University of North Carolina School of Public Health. She was formerly Associate Clinical Professor at the University of North Carolina, Department of Family Medicine and previously served as Medical Director of the Guilford County Health Department Chronic Disease prevention Program. She is past president of Sommer Health Services of Greensboro, North Carolina, which delivered comprehensive on-site corporate health promotion, disease prevention and targeted interventions for self-insured companies.

### *Josh Sommer*

Josh Sommer is vice president of the Chordoma Foundation, which he co-founded along with his mother, Dr. Simone Sommer, after he was diagnosed with a clival chordoma in 2006. He believes that patients should play an active role in bringing about treatments for their own conditions, and that patients represent a largely untapped source of funding, energy, and know-how in the treatment development process. Josh is currently a sophomore at Duke University where he is a Trinity Scholar. Josh is conducting research in the lab of Dr. Michael Kelley at Duke to understand the unique biology of chordoma, and search for therapeutic targets. His investigations include gene-expression microarray analysis, candidate gene knockdown using RNAi, in vitro drug screening, and analysis of known oncogenic pathways in chordoma. In high school Josh received numerous honors and awards including the USA Today All-USA Academic First Team Award, Prudential Spirit of Community Award, Coca-Cola Scholarship, and AXA Achievement National Award.

*The goal of the Chordoma Foundation is to rapidly move chordoma from a poorly characterized disease with few treatment options and relatively poor prognosis, to a treatable, and ultimately curable, condition. We are promoting a strategic and holistic research agenda, directing resources to all stages of the treatment development process - from basic science to clinical applications. Our strategy is to engage researchers with varied expertise and bring them together to collaborate on specific projects that fit logically into the larger coordinated research effort. The Chordoma Foundation will serve a central role in these projects by providing easy access to biological material, connecting researchers, providing logistical support, and acting as an interface between patients and researchers. These functions will help catalyze new projects, and streamline the discovery and translation process. Furthermore, by promoting patient participation and investment in research, the Chordoma Foundation hopes to tap into the determination of patients and their families, and instill a sense of urgency and focus into the treatment development process. We anticipate that this model will speed research advances, and will generate results for patients in the form of treatments within the next several years, rather than decades.*

### **Eric Green, *Mechanisms of Disease***

Eric D. Green, M.D., Ph.D. is the Scientific Director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH) in Bethesda, Maryland, a position he has held since 2002. In addition, he serves as Chief of the NHGRI Genome Technology Branch (since 1996) and Director of the NIH Intramural Sequencing Center

(since 1997). Dr. Green received his B.S. degree in Bacteriology from the University of Wisconsin-Madison in 1981, and his M.D. and Ph.D. degrees from Washington University in 1987. Since the early 1990s, Dr. Green's research program has been at the forefront of efforts to map, sequence, and understand eukaryotic genomes. His work included significant, start-to-finish involvement in the Human Genome Project. More recently, Dr. Green established a program in comparative genomics that involves the generation and comparative analyses of sequences from targeted genomic regions in multiple evolutionarily diverse species. His laboratory has directly utilized its own mapping and sequence data to identify and characterize several human disease genes, including those implicated in certain forms of hereditary deafness, vascular disease, and inherited peripheral neuropathy.

### **Ziya Gokaslan, *Future Clinical Management***

Dr. Ziya L. Gokaslan completed his medical education at the Medical Faculty of Istanbul University. In 1984, Dr. Gokaslan returned to the U.S. and worked as the Clinical Director of Sleep Disorders Center of the Department of Psychiatry for 1 ½ years. He then entered General Surgery Residency under Dr. Michael E. DeBakey in 1985. After one year of internship, he joined Department of Neurosurgery of Baylor College of Medicine as Clinical Neurotrauma Research Fellow. In 1988, he became a Neurosurgery Resident under Dr. Robert G. Grossman and completed his training at the Baylor College of Medicine in Houston in 1993. He was, then, accepted into Orthopaedic Surgery Fellowship Training under Drs. Paul Cooper and Thomas Erric at the New York University Medical Center in New York. After the completion of his Fellowship Training in Spinal Surgery, Dr. Gokaslan returned to Houston and joined the faculty of Department of Neurosurgery as Assistant Professor at the University of Texas, MD Anderson Cancer Center under Dr. Raymond Sawaya. That is where Dr. Gokaslan specialized in the surgical treatment of spinal neoplasms, published extensively on the topic and developed novel surgical approaches in managing these tumors. In 2000, Dr. Gokaslan became the Director of Neurosurgical Spinal Oncology Section and, in 2002, he was appointed as Deputy Chairman of the Department of Neurosurgery and was promoted to Associate Professor. In 2002, Dr. Gokaslan was recruited to Johns Hopkins University, Department of Neurosurgery and became the Director of the Spine Division, Vice-Chairman, and Professor of Neurosurgery, Oncology, and Orthopaedic Surgery under Dr. Henry Brem. Later that year, he was awarded the Donlin M. Long Professorship at Johns Hopkins. Dr. Gokaslan's clinical practice focuses on the radical surgical treatment of both primary and metastatic spinal tumors, sacral neoplasms and spinal cord tumors. He developed many novel approaches for resection of pancoast tumors, spinal neoplasms, as well as sacral tumors, including total sacrectomy and complex spinal and pelvic reconstruction. His basic research focuses on the development of new animal models to study the pathophysiology of neoplastic spinal cord compression and to define the roles of proteolytic enzymes in tumor invasion and to devise novel therapeutic approaches to spinal tumors.

## **Francis Collins, *An Action Plan for Chordoma Research***

Francis S. Collins, M.D., Ph.D., is the director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH). He led the successful effort to complete Human Genome Project (HGP), a complex multidisciplinary scientific enterprise directed at mapping and sequencing all of the human DNA, and determining aspects of its function. A working draft of the human genome sequence was announced in June of 2000, an initial analysis was published in February of 2001, and a high-quality, reference sequence was completed in April 2003. From the outset, the project ran ahead of schedule and under budget, and all the data is now available to the scientific community without restrictions on access or use.

Dr. Collins received a B.S. from the University of Virginia, a Ph.D. in Physical Chemistry from Yale University, and an M.D. from the University of North Carolina. Following a fellowship in Human Genetics at Yale, he joined the faculty at the University of Michigan, where he remained until moving to NIH in 1993. His research has led to the identification of genes responsible for cystic fibrosis, neurofibromatosis, Huntington's disease and Hutchison-Gilford progeria syndrome. He is a member of the Institute of Medicine and the National Academy of Sciences.