

OI Foundation and Children's Brittle Bone Foundation, A Winning Research Partnership

The OI Foundation and Children's Brittle Bone Foundation Boards voted together to co-fund the 2006-2008 research grants. Each organization will contribute half of the \$150,000 needed to fund three Michael Geisman Research Fellowships. The OI Foundation was founded by Gemma Giesman, whose son Michael had OI. The Children's Brittle Bone Foundation was founded by Kris and Kerry Glicken, whose daughter Ashley has OI.

This marks a welcome expansion of the OI Foundation and Children's Brittle Bone Foundation's (CBBF) research partnership that began in 1998. The two Foundations work together to advocate for increased research activity through the National Institutes of Health (NIH), increasing funding to an unprecedented \$10 million, and gaining support for scientific meetings and the Linked Clinical Research Centers. CBBF is based in the Chicago metro area.

By working together, we can fulfill the mission of each organization.

The mission of the Children's Brittle Bone Foundation is to provide funds for research into the causes, diagnosis, treatment, prevention, and eventual cure for Osteogenesis Imperfecta (OI), while supporting programs which improve the quality of life for people afflicted with OI, promote awareness and educate the public.

The mission of the OI Foundation is to improve the quality of life for people affected by OI through research to find treatments and a cure, education, awareness, and mutual support.

New grants to be co-funded are:

Role of Collagen Prolyl 3-Hydroxylation in Osteogenesis Imperfecta

Roy Morello, Ph.D.

Baylor College of Medicine, Houston

Novel High-Throughput System for Identification of Candidate Causative Genes in Bone Disorders

Bradley T. Tinkle, MD, Ph.D.

Cincinnati Children's Hospital Medical Center

Functional Characterization of Osteopotential, a Novel Transmembrane Protein Essential for Skeletal Modeling (2nd year funding)

Michael Sohaskey, Ph.D.

University of California, Berkeley

Continued grant funding:

The IBMD Study. A Proof Of Concept Study To Assess The Effectiveness Of Teriparatide (FORTEO) For Increasing Bone Mass And Improving Bone Structure In Adults Affected With Osteogenesis Imperfecta

Eric Orwoll, M.D.

Oregon Health Sciences University 

The OI Foundation and the Children's Brittle Bone Foundation work together to advocate for increased research, funding, and support for scientific meetings.

**VISIT WWW.OIF.ORG
FOR MORE DETAILED
INFORMATION ABOUT OI
RESEARCH, GRANTS AND
SCIENTIFIC MEETINGS.**

This research update provides a basic overview of the OI research projects to be funded in the next fiscal year, and information on current projects or research programs. Further information about our research program can be found online at www.oif.org/research.

2006 RESEARCH UPDATE

Research to be funded in 2007

Michael Sohaskey, Ph.D.



Dr. Michael Sohaskey is studying the effects of the absence of the Osteopotential, or Opt, gene in the newborn mouse. This gene, when defective, results in dramatically increased bone fragility that causes widespread fractures in the newborn mouse. These skeletal abnormalities bear a striking resemblance to those seen in humans who have severe forms of OI. The studies may clarify the biological mechanisms

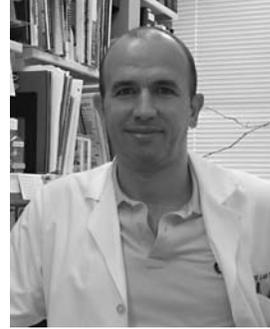
by which bone-forming cells (osteoblasts) fulfill their role in the developing skeleton and how such mechanisms become compromised in people with OI.

The research may lead to the possibility of manipulating these mechanisms to create new therapies. "A driving force in my choosing to focus my research efforts on the Opt mutant mouse is their potential contribution to designing more effective treatments and ultimately finding a cure for OI," said Sohaskey.

Dr. Sohaskey is from the Molecular and Cell Biology lab at the University of California, Berkeley.

Research to be funded in 2007

Roy Morello, Ph.D.



Dr. Roy Morello's research focuses on skeletal development and the mechanisms of cartilage and bone formation. His studies are based on the hypothesis that mutations in the CRTAP gene, a type I collagen gene, could cause recessive forms of OI.

Dr. Morello's research could improve the molecular diagnosis of recessive OI by identifying novel mutations in the CRTAP

gene. It also could improve genetic counseling for families like those where unaffected parents had recurrent pregnancies diagnosed with the lethal OI Type II form. His research could deepen the understanding of mechanisms involved in bone formation. Finally, in families where CRTAP mutations have been demonstrated to cause recessive moderate to severe OI, this research could lead to a therapeutic correction of the gene defect.

Dr. Morello is from the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, Texas.

Volunteers Participate in Research Advocacy Programs

Volunteer Heidi Wright traveled to Capital Hill to participate in the National Coalition for Osteoporosis and Related Bone Diseases Advocacy Day. Heidi met with three legislators to tell them about her experience living with OI, and to urge an increase in funding for the National Institutes of Health's medical research programs, and gain support for the Bone Research Blueprint. More than 15 Coalition volunteers visited 28 legislators to educate them and make the case for more bone research.

Volunteer Dan Mulcahy traveled to the National Institutes of Health for the National Institute of Dental and Craniofacial Research (NIDCR) Patient Advocates Forum. The NIDCR Director, Lawrence Tabak, DDS, PhD, shared information about clinical research that has the potential to treat disorders like dentinogenesis imperfecta. Exciting research developments to create new bone or to alter genes to produce new bone were discussed.

- Trials could start in humans as early as October 2006 to insert a gene into the salivary glands that will create normal salivary flow. Although still in the test tube stage, the same technique is also being used to develop nanomolecules that can be inserted to correct the dentin matrix (structure of the tooth), resulting in normal teeth.
- Materials are being developed to strengthen and restore the dentin.
- Development of "smart scaffolds," a physical framework impregnated with bone-making proteins, that would develop into a strong toothlike-structure.
- Development of biological tooth implants that would be grown just under the skin in order to maintain normal blood supply, and then implanted in the jaw.
- In addition, the Pain Coalition, which involves 21 of the National Institutes of Health is testing a pain relief gene that is delivered through gene transfer to reduce inflammation. These tests are in Phase I, which means testing on a small group of people to evaluate safety, determine a safe dosage range, and identify side effects. In one-two years, the Coalition expects to start human trials on a toxin that will selectively kill the neurons that transmit painful stimuli.

For more information, contact Heller An Shapiro at hshapiro@oif.org.

Current research

Jonathan Britton, BSc, D.D.S.



Dr. Jonathan Britton is researching the effect of the bisphosphonate alendronate (Fosomax®) on craniofacial growth in the oim mouse model for Osteogenesis Imperfecta. He is currently completing his specialty training in Orthodontics at the University of Toronto. He became interested in OI through his own family experiences; his wife and children are diagnosed with OI Type I.

“I was interested in using my background in craniofacial growth to investigate how bisphosphonate treatment impacts growth of the skull and jaws,” said Britton. “The funding [received from the OI Foundation] has allowed me to access cutting edge imaging technology to study the effects of bisphosphonate therapy in a mouse model of OI.”

Dr. Britton’s findings suggest that bisphosphonates, in addition to reducing fractures, could have positive drug effects in the skull as well. In moderate-to-severe human OI, basilar impression is a serious condition that results from progressive deformation of the weakened bone of the base of the skull. This can have devastating consequences and remains difficult to treat surgically. In our study, alendronate (third generation bisphosphonate) given to OI mice during adolescence appeared to normalize the shape of the skull where it meets the cervical spine. This appears to be as a result of improvements in bone quality in the base of the skull from drug treatment.

Dr. Britton said that although it is difficult to extrapolate these findings directly to humans, the results are encouraging and provide hope that bisphosphonates may slow the progression of skull base deformity in children with OI.

Dr. Britton is a Graduate Orthodontic Resident in the Faculty of Dentistry at the University of Toronto.

“The funding [received from the OI Foundation] has allowed me to access cutting edge imaging technology to study the effects of bisphosphonate therapy in a mouse model.”

- Dr. Jonathan Britton

Current research

Sarah K. Bronson, Ph.D.



Dr. Sarah Bronson’s research investigates whether embryonic stem cells might have a therapeutic role in treating OI, by replacing unhealthy bone cells with healthy cells cultivated from the stem cells.

Dr. Bronson has been working with mouse embryonic stem cells for 15 years, and about 6 years ago her research team developed a way to allow them to form bone nodules in a culture dish. After the initial experiments, they began to

think about whether the cells could be used therapeutically to treat disorders like OI.

“The funding that we received from the OI Foundation was absolutely critical in keeping these experiments going,” said Bronson. The OI Foundation funding also enabled her to attend the International Scientific Meeting on OI last June in Annapolis, MD, where she learned more about the possibilities of stem cell therapies for OI.

Of her work’s impact on OI, Bronson said that there is still a lot of research that needs to be done in this area, but what she has learned will help impact the next generation of scientists.

Dr. Bronson is Associate Professor of Cellular and Molecular Physiology in the Milton S. Hershey Medical Center at Penn State College of Medicine.

Current research

Eric Orwoll, M.D.

Dr. Eric Orwoll is investigating whether Forteo (a parathyroid treatment) can increase bone mass and improve bone structure in adults with OI.

He began his work with OI because he felt that there was little data to help with practical clinical decisions. He also felt that researching OI represented a fascinating opportunity to better understand bone biology.

Of the funding he receives from the OI Foundation, Orwoll said, “The dedication and resources of the OI Foundation has been very important. The funding we get is critical for our ability to better develop new treatments.”

Dr. Orwoll said that his work has positively impacted people with OI. “At OHSU we have a Bone and Mineral Clinic that provides consultative care for all kinds of metabolic bone disorders, including OI.” He said that the number of patients with OI in his clinic has considerably increased as a result of interest in his research. “Clearly there are many people with OI who are in need of skilled resources,” he said.

Dr. Orwoll is Professor of Medicine and Assistant Vice President for Research at the Oregon Health & Science University.

Fifth OI Foundation Scientific Meeting Boasted Heightened Levels of Collaboration

The fifth OI Foundation Scientific Meeting, *New Research and Clinical Strategies in OI*, was held April 26-28, 2006 in Chicago, IL. The meeting was co-chaired by Peter H. Byers, MD, Professor of Pathology and Medicine at the University of Washington; David Rowe, MD, Department of Genetics and Developmental Biology, University of Connecticut Health Center; and Michael Whyte, MD., Medical and Scientific Director of the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospitals for Children in St. Louis.



Left to Right: David Rowe, MD, Brad Buchbinder, MD, Heller An Shapiro, Michael Whyte, MD, and Peter Byers, MD. Dr. Buchbinder accepted a plaque from co-chairs Rowe, Whyte and Byers on behalf of the Buchbinder Family, the major funder for this meeting.

This was the Foundation's most exciting Scientific Meeting because the level of collaboration has grown so much since the first meeting in 1999, and continues to grow. The level of communication is growing. The base of knowledge is growing. The scope of knowledge is growing. In 1999, the first scientific meeting lasted 9 hours and involved 9 speakers and 25 participants. This meeting lasted 17 hours and involved 26 speakers and more than 50 participants. Even during breaks and meals, the discussion continued. Doctors received advice about difficult cases and shared research strategies.

Of course there is still much to learn, but what we do know has expanded tremendously since 1999. For example, the purpose of this meeting was to better understand clinical and genetic variation between all types of OI, with a special focus on Type I (mild) OI. After the April 2004 scientific meeting, which focused solely on treatments and a cure for Type I OI, similarities and differences between Type I OI and Types II-VII continued to be discovered. It is now clear that we must look at all the Types together in order to best understand each Type individually, and to understand why people with the same mutation have different degrees of severity.

Everyone agreed that in order to learn more about OI, we need larger numbers - larger numbers of people in studies, more tissue samples, more genetic information, more surgical results, and more dollars. As the OI Registry and the Linked Clinical Research Centers (LCRC) move forward toward the goal of bringing together a large pool of patients for study, this Scientific meeting showed that OI doctors are already good at working together. According to Peter Byers, MD, "These meetings break down barriers and allow for shared information. This is the soul of progress. If each of us shares, we will all do better."

Sharing information is already increasing the pace of research, with frequent interchanges of data, tissue samples, and treatment results. Doctors who are expert in a specific scientific or surgical technique share that expertise with everyone. The participants, both clinicians (who see patients and do research) and researchers (who work in the laboratory and may see a few patients), are enthusiastic and eager to learn more about OI. Applying research methods to clinical care is the only way to develop effective treatment and standards of care.

We were especially pleased to welcome representatives from OI Clinics that will become part of the LCRC, and Michael Geisman Research Fellows. The



Left to Right: Peter Byers, MD, Ken Finkel, Sandy Sandhaus, MD, PhD, Michael Whyte, MD, David Rowe, MD. Foundation Board members Ken Finkel and Sandy Sandhaus, shown here with the scientific meeting co-chairs, participated in the meeting.

See SCIENCE on next page

2006 RESEARCH UPDATE

SCIENCE from previous page

impact on these up and coming researchers was dramatic. In the words of Michael Geisman Research Fellow Michael Sohaskey, PhD, University of California, Berkeley, who is researching a cause of rare, recessive forms of OI, that may result in methods to improve bone:

"Thank you for inviting me to participate in the meeting on *New Research and Clinical Strategies in OI* last week. The meeting was an invaluable opportunity to meet and interact with other basic and clinical researchers who are thinking about many of the same issues related to skeletal development, bone quality and bone integrity. The meeting was extremely helpful in focusing my own research strategies and objectives; in particular, I look forward to pursuing a promising new strategy suggested by David Rowe, MD's presentation and our subsequent conversation. At the same time, I appreciated the diverse perspectives offered by the clinical presentations, which significantly extended and broadened my depth of understanding of OI as well as those people affected (directly and indirectly) by the disorder."

"Again, thank you for the opportunity to join a top-notch community of bone biologists working together toward finding improved treatments and, ultimately, a cure for osteogenesis imperfecta. I look forward to my continued association with the OI Foundation and to presenting my own research findings at a future meeting."

Experts in bone biology who do not routinely study OI were invited to speak at the meeting and add their perspective to the discussion. Henry Kronenberg, MD, Chief of the Endocrine Unit at the Massachusetts General Hospital and Professor of Medicine at the Harvard Medicine School said afterward "I really enjoyed the meeting and was very impressed with the community of OI investigators and how they work together."

The participation of OI Clinic Directors in this meeting is helping to make the LCRC a reality. These doctors are on the front line of clinical care. This meeting provided an opportunity for them to share their experience, and to learn cutting-edge information so they can continue to provide the best possible care for people with OI.

This meeting demonstrated an unprecedented partnership of the best minds working in OI and bone research today. Several other partnerships helped to make the meeting possible. The Children's Brittle Bone

Foundation (CBBF) is the Foundation's valued partner in OI research, working with us to make these meetings possible and initiating OI research and the LCRC. (For more about CBBF, see the article about OI research grants on page 4 of *Breakthrough*) The meeting was also sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the Office of Rare Diseases, and the Buchbinder Family.

We heard about collaborations between groups of clinicians who are sharing data to assess performance outcomes, nutrition and growth, rodding, and scoliosis. For example, the scoliosis group is comparing patients who receive corrective surgery with those who don't. The Nutrition and Growth Protocol is looking at high and low levels of nutrients and intervention for patients who are 6 months to 16 years old.

Participants got a close look at the progress in gene targeting as a therapy for OI. After looking at several options for gene therapy, the gene targeting technique appears to be the one most likely to succeed. Using a person's own stem cells, the targeting "knocks out" the mutant collagen early in the cell's collagen-making

process, so the targeted cell functions normally, producing good collagen. When the targeting is done in both the type 1 and 2 collagen genes (COL1A1 and COL1A2), the cells produce normal collagen and normal bone.

Previous studies attempting intravenous infusion of cells resulted in low engraftment. When human clinical trials begin, the targeted cells will be transplanted by direct injection, starting with a single bone, such as the humerus, and comparing it to the untreated humerus. In the lab, targeted cells are still evident in bone cells that received an injection up to 4 years ago.

Several hours were devoted to identifying the unsolved problems in OI in order to stimulate research that will find answers to these timely questions. Doctors were also asked to re-analyze their data to try to determine if responses to treatments could be correlated with genetic or Type information. In most cases, these correlations could not be made, pointing to the need for the kind of larger studies that are only possible through the LCRC, where a large pool of patients will be available for studies. According to David Rowe, MD, Medical Advisory Council Chair: "If we don't build LCRCs that can conduct research and train new doctors, we are doing a disservice to people with OI. We are grateful for the promise of long term support from the OI

**This meeting demonstrated an
unprecedented partnership of the
best minds working in OI and bone
research today.**

See SCIENCE on next page

SCIENCE from previous page

Foundation and CBBF boards of directors, which will make these Centers a reality in the near future, to start answering the unsolved problems of OI."

At the end of the meeting, Peter Byers, MD discussed goals and strategies for the LCRC and summarized what the next phase of the LCRC will look like. It is being designed to answer many of the questions raised at this meeting.

In order to improve clinical care and find treatments and a cure, we need: imagination, patients and families willing to share their medical information, expert teaching programs, more and larger animal models, interactive clinician/researcher networks, the right cells, excellent and accessible data, and open and frequent discussion, and scientific meetings. When we have these things in place, we will be able to assess the current state of care, determine the genetic and environmental influences

on response to treatment, greatly improve child and adult care, and understand the relationship between genotype (genetic information) and phenotype (symptoms). This will mean that when a child tests positive for OI, the genetic data will also provide clues to tell parents how severe the child's OI will be.

The 2007 scientific meeting will again involve the LCRC directors to build consensus on basic standards of care. Participants at this "Consensus Conference" will review research and clinical experience and develop clear guidelines that will

tell doctors how to treat OI and what data to collect.

For more information, contact Heller An Shapiro at hshapiro@oif.org.

To participate in the OI Registry or to view a summary of the Science Meeting, go to www.oif.org. 

Several hours were devoted to identifying the unsolved problems in OI in order to stimulate research that will find answers to these timely questions.

OSTEOGENESIS
IMPERFECTA

O I

FOUNDATION

JOIN US IN OUR URGENT MISSION

Supporters of the Osteogenesis Imperfecta Foundation know that continuing research can improve the lives of those who now have OI, and the children who will be born with OI. Our most generous donors are people like you who have family members with OI or have a direct connection to our cause. Foundations and corporations also provide valued support.

The Osteogenesis Imperfecta Foundation needs to raise \$433,500 by June 30, 2007 to meet our commitments to children and adults we can help through life changing research and improved clinical care. With your help we can meet this challenge.

Our friends and families deserve our best. Together we can all make a difference.

For more information, contact John O'Brien at jobrien@oif.org.