OSTEOGENESIS IMPERFECTA OI FOUNDATION

RESEARCH UPDATE
FROM THE OSTEOGENESIS IMPERFECTA FOUNDATION, SPRING 2007

OI Foundation and Children's Brittle Bone Foundation, Advancing Research

The OI Foundation and Children's Brittle Bone Foundation Boards voted to co-fund six 2007-2008 research grants. Each organization will contribute half of the $309,999 needed to fund four Michael Geisman Research Fellowships, one seed grant, and renewal funding for one Michael Geisman Memorial Fellowship. The outstanding progress made by Dr. Roy Morello, Ph.D. in the first year of his Fellowship is a great example of how this funding impacts people with OI. Dr. Morello's research resulted in the discovery of a new recessive form of OI. This discovery will greatly improve OI diagnosis and family counseling for people with a family history of Type II, III or VII OI.

A record number of research grant proposals were received this year:

- 8 Michael Geisman Research Fellowship Proposals
- 6 Seed Grant proposals
- 2 Clinical Seed Grant proposals
- 2 Second year fellowship proposals

These proposals represent nearly three times the number of OI Foundation proposals received last year. "The increase in proposals is due to the decrease in available federal funds and the Foundation's consistent funding levels in recent years." Said Heller An Shapiro, Executive Director. "Our partnership with our donors, and the Children's Brittle Bone Foundation, ensures that we can move research forward."

A personal letter from the Foundation requesting your support for these critically needed projects will arrive in your mailboxes in June. With your contribution, doctors and researchers can continue to increase their understanding of the causes and mechanisms behind OI, leading to better care, more effective treatments, and potentially, a cure.

New Grants to be co-funded are:

Renee Bargman, M.D.
NYPH-Weill Cornell Medical Center
Award: Michael Geisman Research Fellowship
Topic: *Direct comparison of RANKL blockade and bisphosphonate therapy in OI*
Description: This is an exciting opportunity to test an important new Osteoporosis drug in mice with OI. The drug, RANKL, will be compared to bisphosphonate drugs. Bisphosphonates slow resorption (bone breakdown), and RANKL works on both sides of the equation, slowing resorption and increasing remodeling (bone building). This balanced approach may be beneficial for OI.

Dale L. Bodian, Ph.D.
Stanford University
Award: Michael Geisman Research Fellowship
Topic: *Predicting genotype-phenotype relationships in osteogenesis imperfecta*
Description: This study will create a publicly available collagen database. The data will be used to create models for predicting OI severity and to learn about collagen structure and function.

Dale L. Bodian, Ph.D.

Charlotte L. Phillips, Ph.D.
University of Missouri-Columbia, Department of Biochemistry
Award: Seed Grant
Topic: *Myostatin inhibition: A potential therapeutic strategy to enhance bone quality and strength*
Description: This study will look at whether a new drug that increases muscle mass will also increase bone mass and strength in OI. The therapy is already in clinical trials for diseases that affect the muscles, such as muscular dystrophy. This is the first time it will be tested in OI.

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2007 Research Update

Our Research Mission

Since 1970, the OI Foundation has doubled funding for research every five years, for a total investment of more than $2 million. That commitment to research continues to grow; the Foundation recently committed more than $400,000 to fund research during this fiscal year. Funding is available for postdoctoral fellowships to encourage new investigators to begin a career in OI research, and seed grants for preliminary research. The potential for results in OI research is growing, with recent advancements in gene therapy, drug therapies, and bone marrow transplant strategies currently under study.

Michael Geisman Research Fellowship Doubles the Reward

A Michael Geisman Research Fellowship gave Christopher Niyibizi, Ph.D. the funding he needed to study stem cells and their potential for treating OI.

Now, Dr. Niyibizi is mentoring another Michael Geisman Research Fellow. Feng Li, MD, PhD responded to an advertisement to work in Dr. Niyibizi's laboratory to study stem cells and skeletal repair and regeneration. "Dr. Li wanted to learn about skeletal diseases and use of stem cells for potential treatment. Upon joining my laboratory, he developed an interest in OI and the potential for treatment with cell and gene therapies."

Dr. Niyibizi explains: "As Dr. Li's interest in OI research grew, I encouraged him to apply for an OI Foundation/Children's Brittle Bone Foundation Michael Geisman Research Fellowship. I know this will be a stepping stone for establishing himself in OI research, just as it was for me."

After getting his start in OI research as a graduate student in OI Foundation Medical Advisory Council member Darwin Prockop, M.D., Ph.D's Biochemistry lab. Dr. Niyibizi's Michael Geisman Fellowship research led him to additional funding through the Children's Brittle Bone Foundation's *Brittle Bone Treatment Challenge* award. "This allowed me to continue the studies on OI and potential treatment using marrow derived stem cells. With the combination of the two Foundation grants, Dr. Niyibizi was able to produce enough data to obtain a grant from the National Institutes of Health. "This grant allowed me to continue studies on bone regeneration and repair using marrow derived stem cells and OI animal models. This line of research remains a major focus of my research interest."

From one Michael Geisman Research Fellow to another, the promise of gene and stem cell therapies for OI continues to grow. Dr. Li will learn from Dr. Niyibizi and together they will identify the strategies needed to use cell based gene therapy to improve engraftment of bone forming cells in bone.

Science Meeting Summary

Historic Sixth Annual Scientific Meeting Will Improve Medical Care

The Foundation's sixth annual scientific meeting, *Clinical Care Strategies in Osteogenesis Imperfecta,* exceeded its goals. Prior to the meeting, working groups met to develop recommendations for quality medical care for people with OI of all ages and types. During the meeting, more than 60 clinic directors and researchers discussed and finalized the recommendations. Several local families shared their personal experiences with medical care. The dialogue was productive, focusing on defining the best medical care for people with OI. When the recommendations are completed and published in a few months, people with OI will be able to receive evidence-based quality care, instead of "best guess care."

"I thought the meeting was very rewarding, with excellent discussion. It should be a very nice starting point for a lot of positive collaboration. The bottom line is how can we make things better for the kids and their families. Take care."

Paul Esposito, MD
Orthopedic Surgeon
Omaha Children's Hospital and Univ. of Nebraska

One of the most valuable results that comes from holding annual scientific meetings is improved collaboration and communication between many of the best minds working in OI and bone research today. An essential part of this meeting occurred when participants met in small groups to share their most difficult cases. Everyone learned from the discussion and suggestions that were made.

The Foundation's Linked Clinical Research Centers (LCRC) took a big step forward as standard intake forms were developed and criteria for becoming a Center was agreed on. A pilot test linking the first four Centers is expected to begin in Fall 2007. Sponsored by the OI Foundation and the Children's Brittle Bone Foundation, the LCRC will improve the quality of life and lifespan of adults with OI by defining the standard of care for people with OI, developing a means by which people with OI in different parts of the U.S. all have access to the highest standard of care, and advancing the standard of care and improving potential for a cure through patient related research.

"I thought the meeting in Chicago was provocative to say the least...I always come home from these gatherings excited to try a new approach."

Gayle Tyerman, MD
Head of Pediatrics
Shriners Hospitals for Children, Los Angeles

Major support for this meeting was provided by the Buchbinder Family Foundation. The Buchbinder Family Foundation pledged $250,000 over five years to make future annual meetings possible. Now Clinic Directors and Researchers can plan to collaborate and work together annually to improve care and speed up research for people with OI.

"Thank you for giving me the opportunity to attend the recent scientific meeting on clinical care for OI. I found it informative and interesting. It was likewise a privilege to witness the growth of the OI Foundation, which represents the reflection of all the effort that various individuals have expended in their effort to help children with OI. Certainly they have much greater opportunity to lead productive lives now than when the Foundation was founded."

Edward R. Millar, MD
Past Medical Advisory Council Chair
Chief of Staff, Emeritus
Shriners Hospitals for Children, Chicago

"I offer my thanks to the entire OI Foundation for putting on a wonderful meeting. There was frank discussion but within an atmosphere of collegiality that was quite beneficial. There is a lot of work to do but I have witnessed great progress in the two years that I have been participating in these meetings."

Charles P. McKay, M.D.
Pediatric Nephrology
Carolinas Medical Center

Orthopedic Surgeons at the Clinical Care Strategies in Osteogenesis Imperfecta, scientific meeting share ideas about surgical technique in OI. Standing from left to right: Laura Tosi, MD; Children's Hospital National Medical Center; Peter Smith, MD; Shriners Hospital for Children, Chicago; Paul Esposito, MD; Omaha Children's Hospital and Univ. of Nebraska Medical Center Metabolic Bone Diseases Clinic; Cathleen Raggio, MD; Hospital for Special Surgery and Center for Skeletal Dysplasias & OI Clinic, New York; Fred Shapiro, MD; Children's Hospital, Boston. Seated from left to right: Francois Fassier, MD; Shriners Hospital for Children, Montreal; Paul Sponseller, MD; OI Clinic at the Kennedy Krieger Institute, Baltimore.

What does the Recessive Gene Discovery Mean for Me?

OI can be inherited in a recessive or dominant form. Different genes are involved with each type of inheritance.

Understanding how OI is inherited

- Every person has two copies of almost every gene.
- They get one copy from their mother and one copy from their father.
- Some functions in the body require two normal copies of a gene. Other functions only need one normal copy of the gene.
- Often changes occur in genes near the time of conception.
- Changes to the genes, called "mutations," cause genetic disorders such as OI.

Dominant OI

- Dominant inheritance means that only one copy of the mutation-carrying gene is necessary for the child to have OI.
- Most cases of OI (85-90%) are caused by a dominant mutation in a gene for type 1 collagen. These genes are called COL1A1 and COL1A2.
- The child receives this gene from one parent who has OI or as the result of a spontaneous mutation.
- Dominantly inherited OI does not "skip a generation."
- Each person who has a dominant form of OI has a 50 percent chance with each pregnancy they are part of to pass on the OI gene to their children.
- Siblings of a person who has a dominant form of OI, who do not have OI themselves, can not be carriers of the OI gene.

Recessive OI

- Recessive inheritance means that two copies of the mutation-carrying gene are necessary for the child to have OI.
- The child receives one copy of the mutation-carrying gene from each parent.
- Approximately 10-15 percent of cases of OI are the result of recessive mutations to genes that influence collagen production. These genes are called CRTAP (cartilage-associated protein) or LEPRE1.
- The parents do not have OI, but both carry the mutation for it in their genes.
- The parents function normally with only one normal copy of the gene.
- Each person who has a form of OI caused by a recessive mutation will pass on the mutation to all of their children.
- These children will be carriers of the gene for recessive OI. Whether or not any of them will have OI depends on the genes they receive from their other parent.
- Recessively inherited OI can "skip a generation."
- Siblings of a person who has a recessive form of OI have a 50 percent chance of being carriers of the recessive gene.

For more information, contact Mary Beth Huber, Information and Resource Director, mhuber@oif.org

Buchbinder Family Pledges Continued Support of Scientific Meetings

The Buchbinder Family generously pledged $250,000 over the next five years to support an annual Scientific Meeting. The 2007 meeting which took place in Chicago, IL, focused on establishing standards of care for OI.

Parents Henry and Gilda, and siblings Leslie and Brad, supported the past three scientific meetings and are thrilled with how successfully these meetings foster collaboration and communication between doctors and their commitment to improving care for people with OI.

Thirteen year old Hannah Buchbinder has Type I OI and was the impetus for the family's funding of the *Mild forms of osteogenesis imperfecta (OI): Molecular basis, natural history, and treatment* Scientific Meeting in 2004.

The OI Foundation is extremely grateful for the support and commitment of the Buchbinder Family. "Henry and Gilda's concern for their granddaughter resulted in leadership giving that allows the Foundation to achieve a higher level of medical research collaboration between researchers and clinicians. This moves research faster and improves medical care." said Heller An Shapiro, Executive Director.

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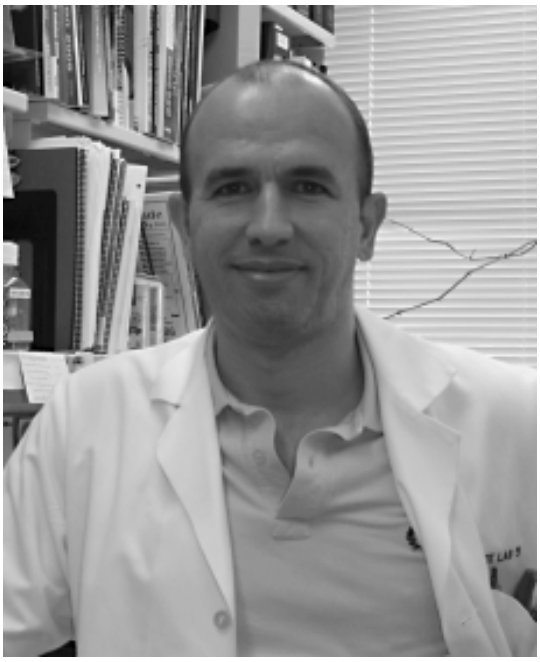
Arabella I. Leet, M.D.
Johns Hopkins University
Award: Michael Geisman Research Fellowship
Topic: *The effect of bisphosphonates on human osteoblasts and mouse bone marrow stromal cells*
Description: This study will try to better understand how bisphosphonates slow the growth of osteoblasts (bone building cells), and try to find a way to reverse this.

Arabella I. Leet, M.D.

Feng Li, MD, Ph.D.
Penn State College of Medicine, Department of Orthopaedics and Rehabilitation
Award: Michael Geisman Research Fellowship
Topic: *Engraftment and differentiation of human mesenchymal and embryonic stem cells in developing immunodeficient mice*
Description: This study will test the ability of human mesenchymal stem cells and embryonic stem cells to form osteoblast (bone building) cells in mice. The focus will be on finding strategies to enhance engraftment of these bone forming cells.



Roy Morello, Ph.D.

Roy Morello, Ph.D.
Baylor College of Medicine, Houston
Award: Second Year Michael Geisman Research Fellowship
Topic: *Role of collagen prolyl 3-hydroxylation in Osteogenesis imperfecta*
Description: In the first year of this study, Dr. Morello proved that Crtap and P3H1 cause recessive forms of types II, III and VII OI. A blood test is now available to identify these recessive forms. A paper about the discovery was published in a peer reviewed journal (Cell) in October 2006. In the second year, Dr. Morello will continue to build on the first year progress by studying the effects of Crtap on cartilage development and the growth plate. He will also develop a mouse model for recessive OI, that will allow future researchers to better understand the impact of P3H1 on severity of OI.

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.

Gene Targeting: Possible Treatment or Cure for OI

David Russell, MD, PhD, Professor of Medicine and Biochemistry at the University of Washington School of Medicine in Seattle, published an article in 2004 in Science, a peer-reviewed journal. The article described how his work in gene targeting could potentially treat or cure OI. The following interview, excerpted from the Winter, 2007, issue of Breakthrough, describes Dr. Russell's progress since 2004.

OI Foundation: We know gene targeting has great potential to eventually cure OI. What is gene targeting?

Dr. Russell: Gene targeting is the process of introducing genetic changes at a specific chromosomal gene in a cell. Using mesenchymal stem cells (MSCs), we used gene targeting to knock out the mutant collagen gene early in the cell's collagen-making process, so the targeted cell functions normally, producing good collagen.

OI Foundation: How did you develop the gene targeting technique?

Dr. Russell: Our lab developed the gene targeting technique as a way to precisely manipulate human chromosomes. It turns out that OI is the perfect candidate for treatment through gene targeting because in most cases, the OI mutation is dominant, so it can't be treated by adding more of the normal gene. Rather, we need to disrupt the mutant gene.

> Funding for all types of OI research will give us the data we need when we're ready to put it to use. The OI Foundation's annual scientific meetings are helping us to find partners and learn about new possibilities. The Linked Clinical Research Centers are putting a network in place that will allow us to test our methods as they are developed. But when we do move into the clinic, the costs and preparations will increase, and we'll have to raise a lot more money.

We started by obtaining pieces of bone from teens and kids with OI who were undergoing surgery. Using mesenchymal stem cells from these bone fragments, we were able to successfully target the mutant collagen and knock it out.

One of the exciting things about this technique is that we can use cells from the patient's own body (autologous cells). This means we will target a person's own cells and implant the corrected cells back into that person. So there won't be any problems with autoimmune reactions.

OI Foundation: What's happened since you published the Science paper in 2004?

Dr. Russell: We've targeted OI cells and made them produce normal collagen and bone. But we don't know how long this normal collagen production will last. We also can't yet prove that we've made normal bone that is also better bone. So we searched for bigger animal models that could provide larger bones to study.

OI Foundation: Now that you've developed a successful technique for knocking out the OI mutation in collagen genes, what's the next step?

Dr. Russell: This is an exciting time because we are moving out of the test tube and into living bone. The next step is to develop techniques for returning targeted cells to living bones. Using autologous cells, we are testing three different gene delivery methods in rabbits: surgical insertion, intravenous injection, and pretreating the bone to improve engraftment. Over the next few years we expect to be able to accumulate all the pieces of data we need to move into human clinical trials.

Of course, we adhere to the Animal Welfare Act, National Research Council Guide for the Care and Use of Laboratory Animals, and all appropriate U.S. Department of Agriculture and National Institutes of Health regulations and standards for animal research.

We expect to have good luck with direct surgical injection because it has been shown to be more efficient in other animal models, but the studies will determine this for sure.

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OI Foundation: If direct surgical injection is effective, then how will that apply to people?

Dr. Russell: If the animal studies are successful, the next step is to design a clinical trial (testing in people). We would probably start with the weight bearing bones, and initially just one bone on one side, so we could compare it to the bone on the other side. We expect to be able to treat each bone through the skin (percutaneously) with local anesthesia. If it works, I think we could go after all the important bones pretty easily, even if it meant a fairly extensive set of injections.

OI Foundation: It's truly exciting to think about being able to inject corrected cells back into the bone to cure OI. But we have to ask, what could go wrong?

Dr. Russell: Based on what we know now, there are very few things that could go wrong and cause harm to people. We will be using a person's own cells and creating a very narrowly defined genetic change. We don't expect any inflammation because there are no new antigens (a substance that stimulates antibodies) involved. One real possibility is that the cells won't survive after injection, but this shouldn't be dangerous.

OI Foundation: Who will be most likely to benefit from gene targeting?

Dr. Russell: We really can't say at this stage. Adults could benefit, and we will probably start with them. However, kids might do better because of their higher bone turnover and growth rate.

If we find that the targeted cells are remodeling the bone, then perhaps proper exercise and therapy would make the bone remodel into a normal shape. Remodeling could also cause improvements in adults.

OI Foundation: It sounds like you're covering all the bases. You've done your research into past experiments, you're collaborating with others, and thinking through potential problems in advance. What do you need right now to move this research forward faster?

Dr. Russell: Funding for all types of OI research will give us the data we need when we're ready to put it to use. The OI Foundation's annual scientific meetings are helping us to find partners and learn about new possibilities. The Linked Clinical Research Centers are putting a network in place that will allow us to test our methods as they are developed. But when we do move into the clinic, the costs and preparations will increase, and we'll have to raise a lot more money.

Breakthrough Society Supporting Research

The Breakthrough Society honors those making annual or lifetime gifts of $100,000 and up. These gifts represent a new level of involvement, which helps bridge the gap between the increasing needs in the OI Community and the services available to meet them.

During Fiscal year 2007, the following donors, foundations, and corporations made research their top priority. They represent the Foundation's highest Giving Society. We are extremely grateful for their leadership giving and commitment.

The Buchbinder Family Foundation
The Charitable & Research Foundation, Inc.
Kroger Food Stores
Frank and Denise Quattrone Foundation
S.C.P.I Charity Association

2007 Research Update

Your Gift to Research is Worth Twice as Much!

The Frank and Denise Quattrone Foundation and The Buchbinder Family Foundation challenge the OI Community. These generous foundations will match 1:1 the first $105,000 raised before December 31, 2007.

Money raised from this match will establish Research Fellowships which will increase and facilitate research through development of career research investigators. Fellowships also encourage these investigators to enter and stay in the field of OI Research. You can make your gift online at www.oif.org or through the research appeal mailing you receive.

"This is a tremendous opportunity to increase the pace of OI research", said Richard Wenstrup, MD, Chair of the OI Foundation Medical Advisory Council "I hope this challenge inspires our donors to respond and maintain their level of generosity"

Money raised from this match will establish Research Fellowships which will increase and facilitate research through development of career research investigators.

The OI Foundation would like to thank the Quattrone and Buchbinder Family Foundations for giving us the opportunity to issue this Research Challenge. Meeting the fundraising challenge enables the OI Foundation to maintain momentum that will move us closer to better treatments and a cure for osteogenesis imperfecta.

OSTEOGENESIS IMPERFECTA FOUNDATION

Join Us In Our Urgent Mission

Donors to the Osteogenesis Imperfecta Foundation know that research is the best way to 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 $500,000 by June 30, 2008 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.