Biomedical Tissue Engineering-Where We Go in the Future

Chair: Lynda Bonewald

Interim Vice Chancellor for Research

Goal for Session

- Present Biomedical and Tissue Engineering in our area
- Showcase successful collaborations
- Provide ideas for products and applications
- Establish academic/business partnerships

Panelists

- **Mark Johnson** -Role of Genetics
- **Delbert Day** -How to be successful as an entrepreneur.
- **Michael Detamore** -Moving biomaterials into applications.
- **Marco Brotto** -Potential therapeutics for muscle wasting.
- **Daniel Leon–Salas** -Biomedical devices for bone, muscle, heart.

New Insights Revealed by Genetic Studies and the Future of Treating Bone Health Related Issues

Mark L. Johnson, Ph.D.
Department of Oral Biology
UMKC School of Dentistry

Genetics of Bone

- 20-70% of the variation in bone properties are estimated to be inherited
- During the past 15 years there have been a number of major efforts to identify genes underlying bone traits
- While it was originally thought (hoped) that a few major effect genes would underlie various bone traits; current results indicate dozens, perhaps hundreds of genes may be involved.

Osteoporosis

The Osteoporosis Epidemic

- 30-40% increase in population over 50 years of age by 2020
- If nothing changes 50% of population over 50 years will have osteoporosis and or low bone mass
  - Osteoporotic fractures annually exceed the combined numbers of heart attacks, strokes and breast cancer
  - ~50% of women who suffer an osteoporotic hip fracture will die within 1 year.
- Increase in health care costs predicted to be as high as $200 billion

Genetic Dissection of Bone Traits

- Candidate gene studies (CGS)
- Genome wide association studies (GWAS)
- Gene expression profiling (GEP)

Dr. H.-W. Deng

- Single gene trait segregating in families
  - Dr. Y. Ueki (*SH3BP2*, Cherubism)
  - Dr. M.L. Johnson (*LRP5*, HBM)

Genes Identified/Confirmed from Genome Studies

Gene	Signaling Pathway	Study Design
LRP5	Wnt/β-catenin	Human family linkage GWAS, CGS Mouse genetics
SOST	Wnt/β-catenin	Human family linkage GWAS
sFRP4	Wnt/β-catenin	GWAS, CGS Mouse genomics and genetics
ALOX 12/15	Arachidonic acid metabolism	Mouse genomics and genetics GWAS, CGS
BMP2	BMP signaling	GWAS, CGS Mouse genomics and genetics
VDR	Transcriptional regulation	CGS, GWAS
ESR1/ESR2	Transcriptional regulation	CGS, GWAS
STAT1	Transcriptional regulation	GEP, CGS Mouse genetics
Col1A1	Extracellular matrix	CGS GWAS

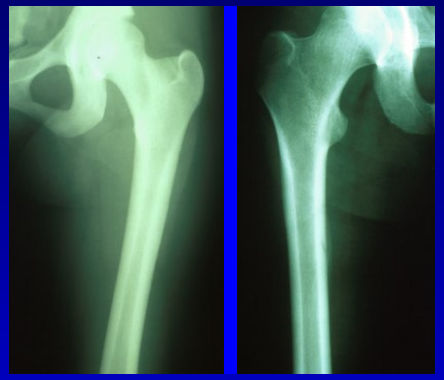
GWAS: genome-wide association study; CGS: candidate gene study; GEP: gene expression profiling

Johnson, et al. Genome Med. 2009 Sep 7;1(9):84

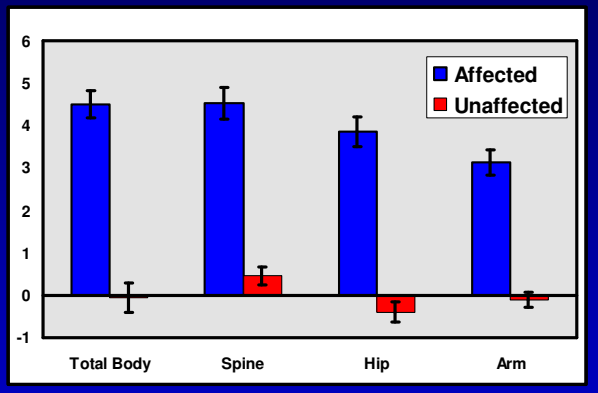
Impact of Bone Gene Identifications

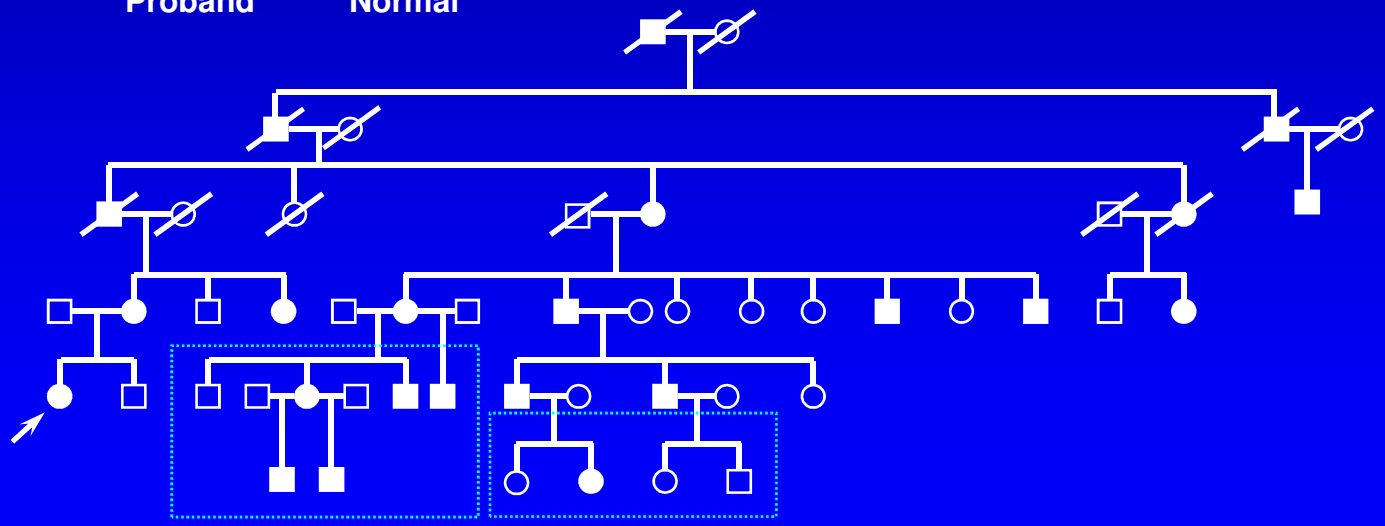
- Revealed new pathways important in bone biology (ex: Wnt/β-catenin signaling)
- Generated new targets for drug development for treating diseases of bone
- Placed us on the threshold of personalized bone treatments/therapies

High Bone Mass Kindred

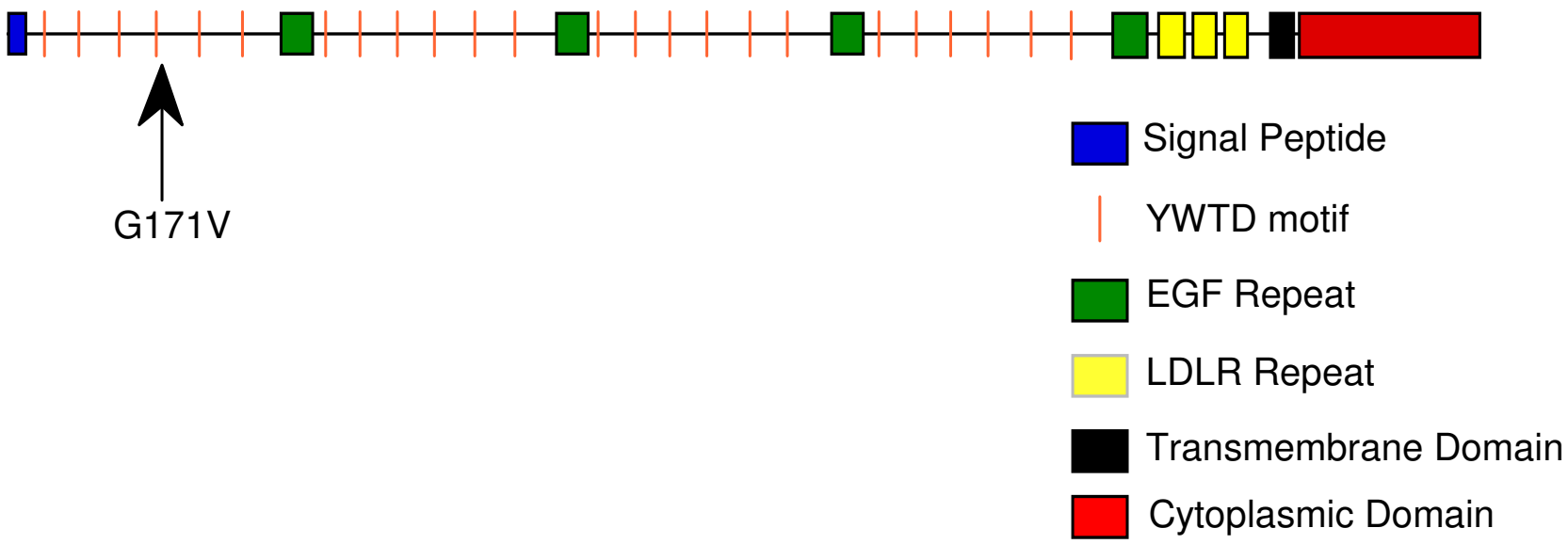


Proband Normal





Structure of LRP5 and HBM Mutation



Little et. AJHG 70:11-19, 2002

Sclerosteosis/Van Buchem Diseases

- Sclerosteosis: mutation in the *SOST* gene
- Van Buchem: large deletion of the promoter region of the *SOST* gene
- *SOST* gene encodes the protein sclerostin

LRP5 and Sclerostin

- LRP5 is a co-receptor (along with frizzled) for the Wnt proteins and this binding activates Wnt/β-catenin signaling pathway.
- Sclerostin binds LRP5 and prevents Wnt proteins from binding, thereby inhibiting the Wnt/β-catenin signaling pathway.

Wnt/β-catenin Signaling Pathway as a Drug Target

- Sclerostin antibody (Amgen)
- Diphenylsulfonyl sulfonamides (target sFRPs) (developed by Wyeth)
- GSK-3β inhibitors (several groups)
- Sclerostin Inhibitors (OsteoGeneX Inc., KC)

New Biology Revealed by Studying the Role of Wnt/β-catenin Signaling in Bone

- Better understanding of how bone responds to mechanical loading (exercise) and the role of various bone cells in the bone regulation process – Dr. L. Bonewald, Dr. S. Dallas, Dr. M.L. Johnson (UMKC)
- Means to identify other factors produced by bone cells that regulate bone formation and new assays for monitoring bone formation – Dr. J. Gorski (UMKC)
- New targets for therapy – Dr. D Ellies (OsteoGeneX, Inc.)
- New paradigm for treating bone diseases such as osteoporosis; i.e. perhaps we can develop agents that will enhance the skeleton's ability to respond to mechanical load and thereby use the natural mechanisms intrinsic in bone to treat diseases such as osteoporosis

Future of Bone Scaffolds and Bone Tissue Engineering

- Creating better scaffolds
  - Ultimately we want to achieve scaffolds that are indistinguishable from bone
- Bone tissue engineering
  - Growing new bone from an individual's MSCs (personalized therapy).

Future of Bone Scaffolds and Bone Tissue Engineering

- These efforts need to incorporate a full understanding of basic bone biology; including an understanding of the pathways that regulate normal bone formation.
- Genetic studies have revealed a number of important pathways and potential targets for treating bone diseases and likewise revealed biology needed to support scaffold and bone tissue engineering development.

Personalized Therapy for Treating Bone Diseases

The identification of genes underlying various bone traits and understanding how these contribute to both variation in the general population and basic bone biology will be key steps towards developing therapeutic approaches that are customized on an individual by individual basis.

Work Supported by

U.S. Department of Health and Human Services

Supported by the
National Institutes of Health

RO1 AR053949
PO1 AR46798

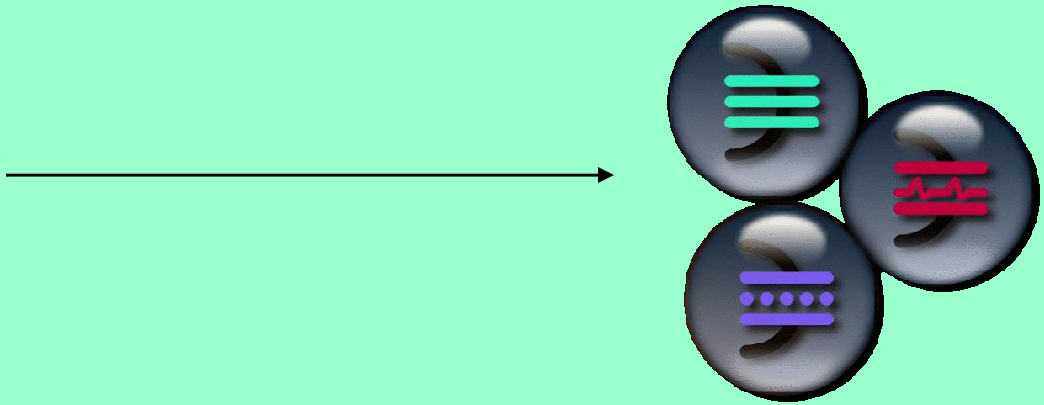
MLSRB
MISSOURI LIFE SCIENCES RESEARCH BOARD

Missouri Life Sciences Summit
Panel on Biomedical Tissue Engineering
9 March 2010

CREATING A HEALTH CARE BUSINESS FROM UNIVERSITY RESEARCH

BY

Delbert E. Day
Missouri University of Science and Technology
&
MO-SCI CORP.



Consortium for Bone and Tissue Repair and Regeneration (CBTRR)

Joint MS&T/UMKC center to research and develop advanced biomaterials, biosensors, and biointerfaces for the repair and regeneration of traumatized bone and tissues

MISSOURI S&T

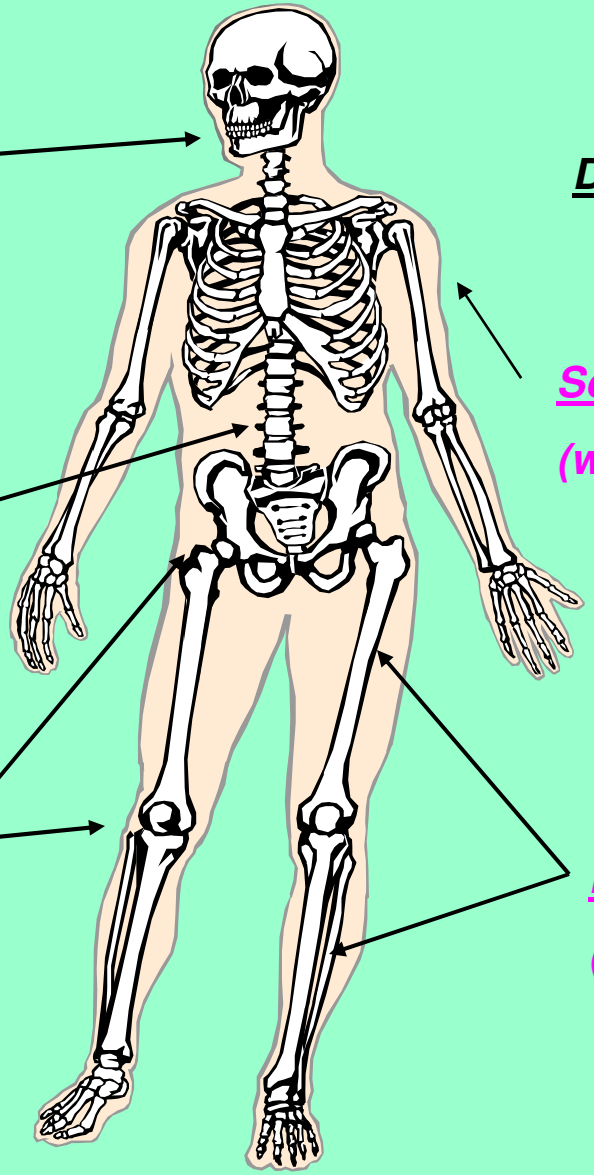
UMKC
UNIVERSITY OF MISSOURI
KANSAS CITY
SCHOOL OF DENTISTRY

Uses of Bioinert, Bioactive & Biocompatible Glasses

Dental Implants/Repair

(caps, crowns, veneers)

Drug Delivery



Soft Tissue Repair

(wounds, clotting)

Destroying Malignant Tumors

(liver, kidney, brain, other)

Joint Repair/replacement

(hip, knee)

Bone Repair

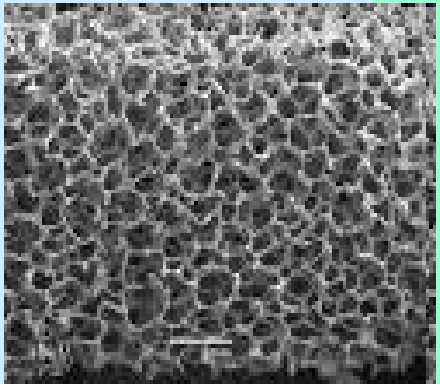
(trauma, disease)

The Magic of Bioactive Glass

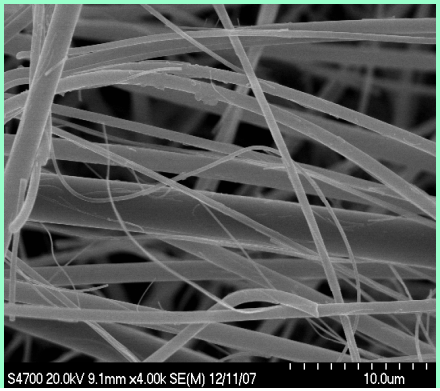
Bioactive glass reacts in the body and bonds strongly to hard and soft tissue

Powders

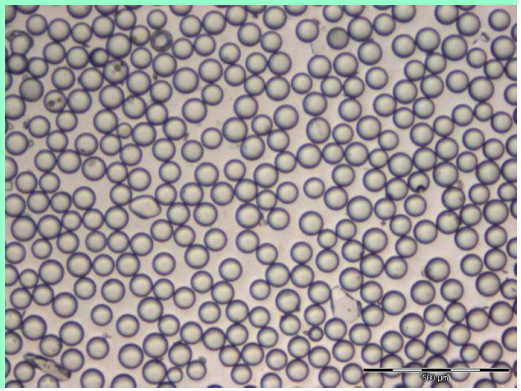
Scaffolds



Fibers



Microspheres/beads



University of Missouri
Four Missions

- *Teaching --- transfer of knowledge*
- *Research --- discovery of new knowledge*
- *Service --- helping others*
- *Economic development --- creating wealth from knowledge*

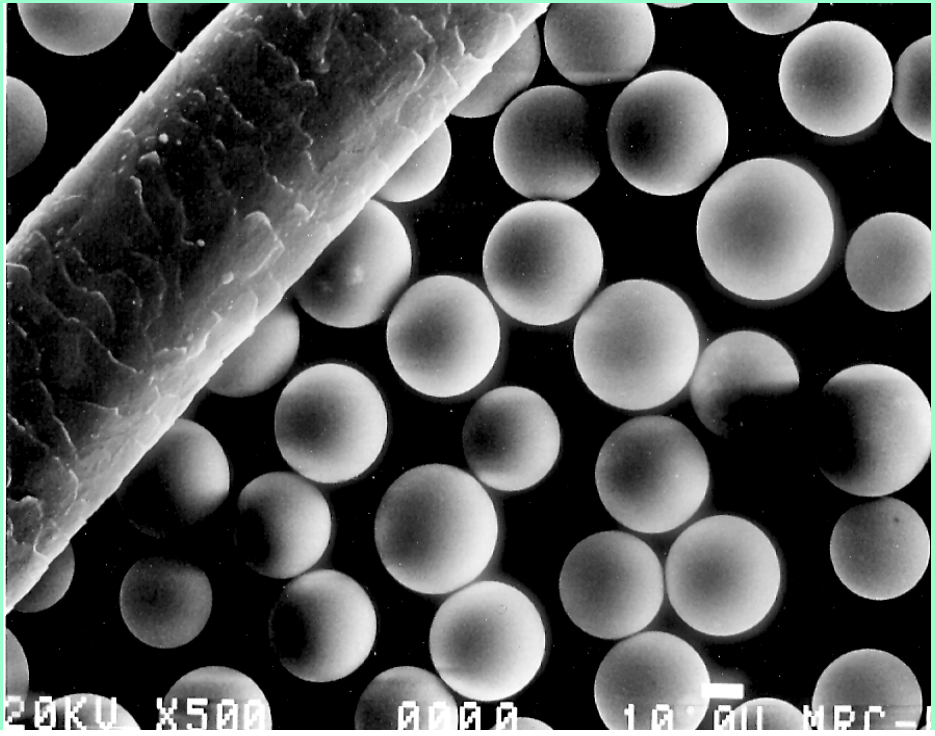
A Case Study

Factors and events that were important to creating a successful business from life science technology that was spun off from university research--

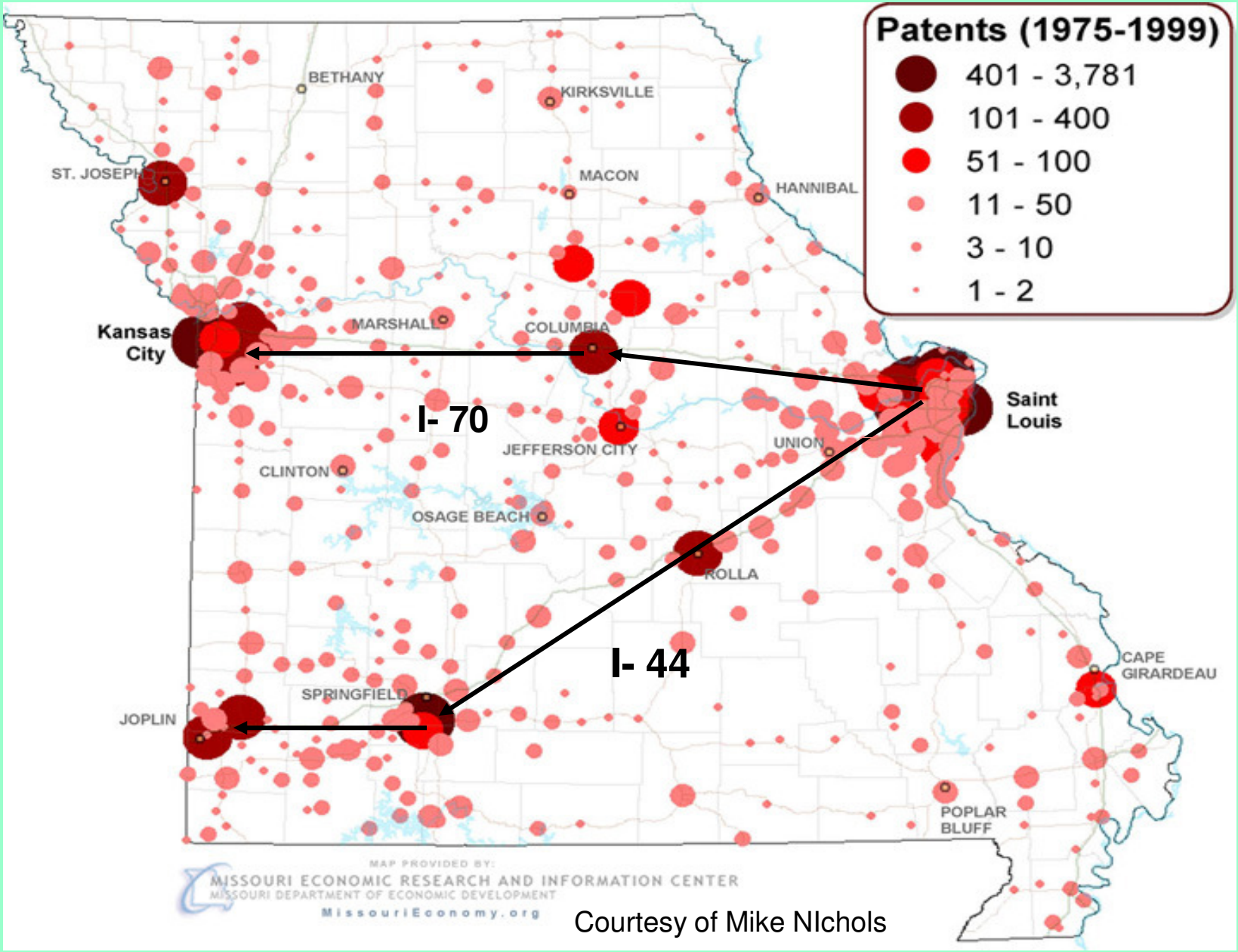
MO-SCI Corp----founded in 1984, Rolla MO

Created to manufacture products for the health care industry---

glass microspheres for treating liver cancer
TheraSphere™



Patents issued in Missouri



Courtesy of Mike NIchols

Factors important to the formation and early survival of MO-SCI Corp.

- State funded incubator program----shared facilities reduces start up expense
- University (MS&T)----receptive to aiding industry, fosters economic development by encouraging spin offs, labs & needed equipment available
- Available personnel & surroundings receptive to entrepreneurs
- Small Business Innovative Research (SBIR) program----important source of income

Profiles of Entrepreneurs in Incubators*

Personal traits	Male, 35-40 yrs old, 17 yr of formal education
Location of business	Near personal and family ties: lived in area for 17 yr
Source of financing	>75% from personal funds, mortgage, borrowed from friends & family; <25% from banks or venture capital
Business Experience	No formal training or experience; no written business plan
Marketing	Done by owner, "seat of pants" analysis
Government assistance	Wary; too much paper work

* J.R. Mullin and J.H. Armstrong, "Profile: Prospective Tenants for Business Incubators," Landuse, Inc. Hadley, Ma, 1987

INGREDIENTS FOR A SUCCESSFUL START UP

Supportive environment for entrepreneurs

Private Sector---Government---University

Everyone has a financial stake

Founders---University---Others

Plan for generating income

Dedication

hard work---long hours---luck

Being an entrepreneur can be a lot of fun

Hdqs of MO-SCI Corp in Rolla MO

- A new company
- 35 new jobs
- More than 950 customers in 40 countries
- Direct economic benefit to MO
  - >>> royalties paid to UM
  - >>> irradiation fees paid to UM
  - >>> new research dollars to MO
  - >>> new healthcare products produced in MO

Health care products made by MO-SCI

--- TheraSphere™
--- microspheres for blood typing
--- glass fillers for dental composites
--- bioactive glasses for bone repair
--- antimicrobial glasses for catheters

The Federal SBIR Program

- Established to help small businesses compete for government research funds
- Federal agencies must set aside a part of their research budget for small business
- Agencies request proposals from small businesses---competitive awards
- Phase I, 6 to 9 months, $60K to $100K
- Phase II, up to 2 yrs, $200K to $300K/yr
- Phase III, commercialization

Benefits of SBIR Program to MO-SCI

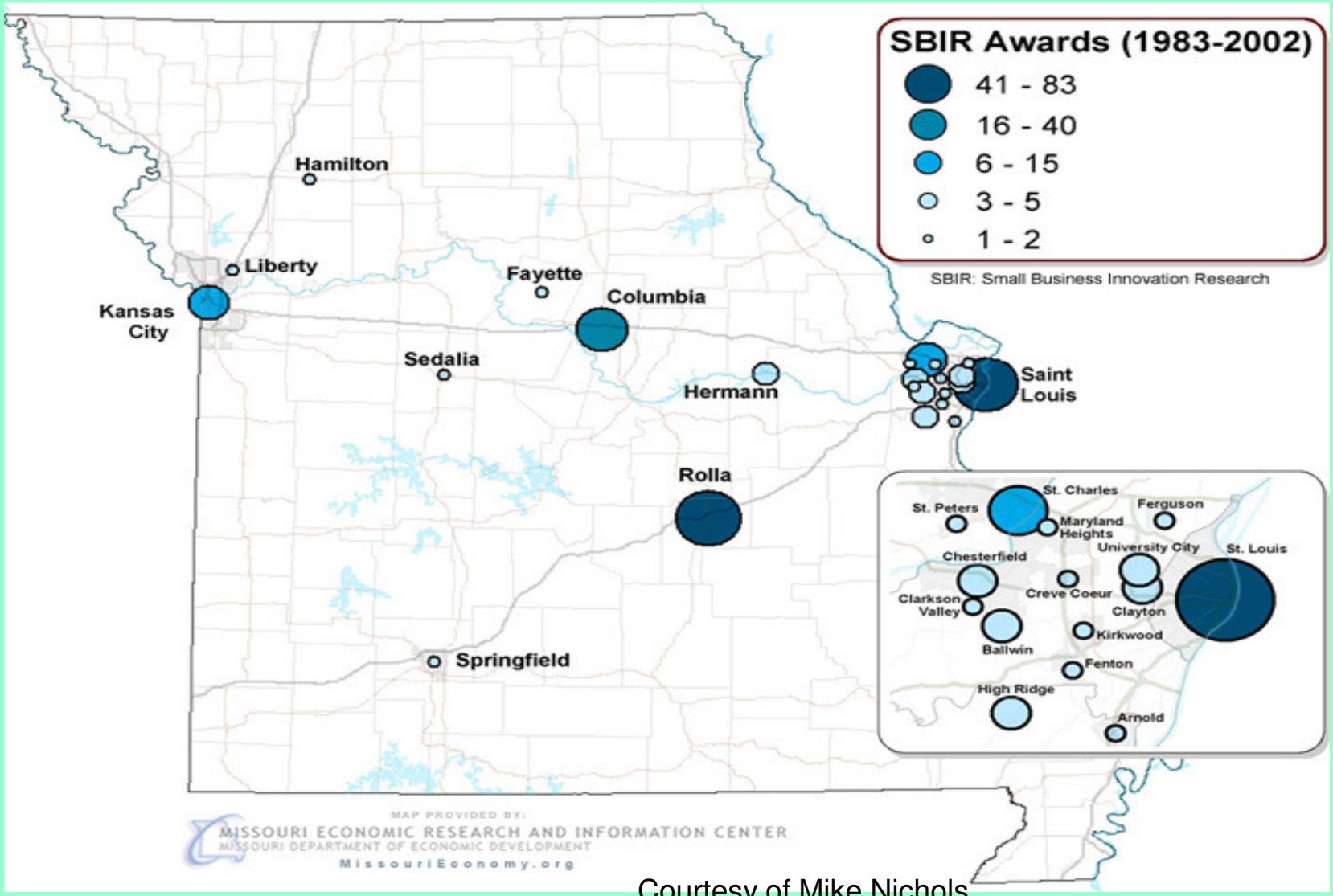
Provided a important source of income during initial start up (financially difficult period).

Enabled MO-SCI to perform important research/acquire equipment that otherwise couldn't be afforded.

Research performed under the SBIR Program has/is leading to new products.

Kept research an important business interest.

Small Business Innovation Research (SBIR) Awards in Missouri—1983-2002



Courtesy of Mike Nichols

Orthopedic Tissue Engineering

Michael Detamore, Ph.D.

Associate Professor of Chemical & Petroleum Engineering

University of Kansas

March 9, 2010


KU

What does my group do?

- Tissue Engineering
- Biomaterials
- Stem Cells

Tissues of Interest

- Temporomandibular Joint
- Intervertebral Disc
- Knee (osteochondral)*
- Cranium*
- Trachea*
- Liver*
- Cochlea*

*KUMC collaborator

Biomaterials Strategies

- Microsphere-based gradient scaffolds
- Colloidal gels
- Electrospinning
- IPN hydrogels

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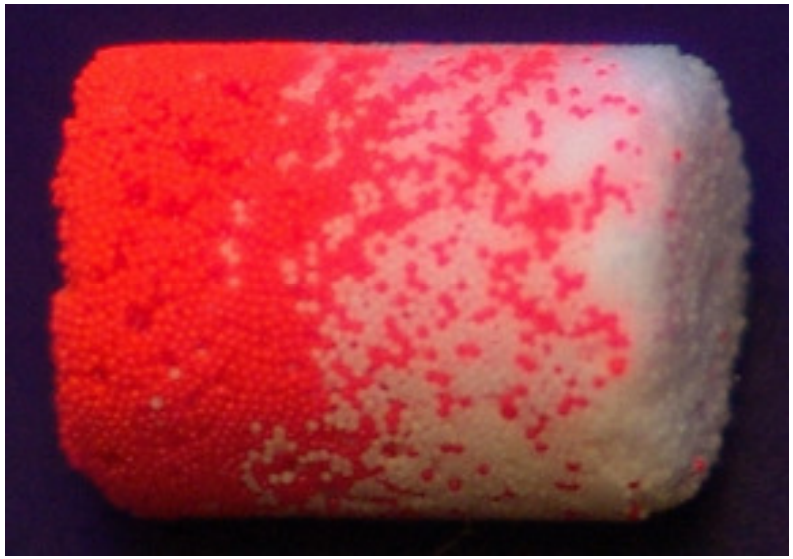

Biomaterials Strategies

- Microsphere-based gradient scaffolds
- **Colloidal gels**
- Electrospinning
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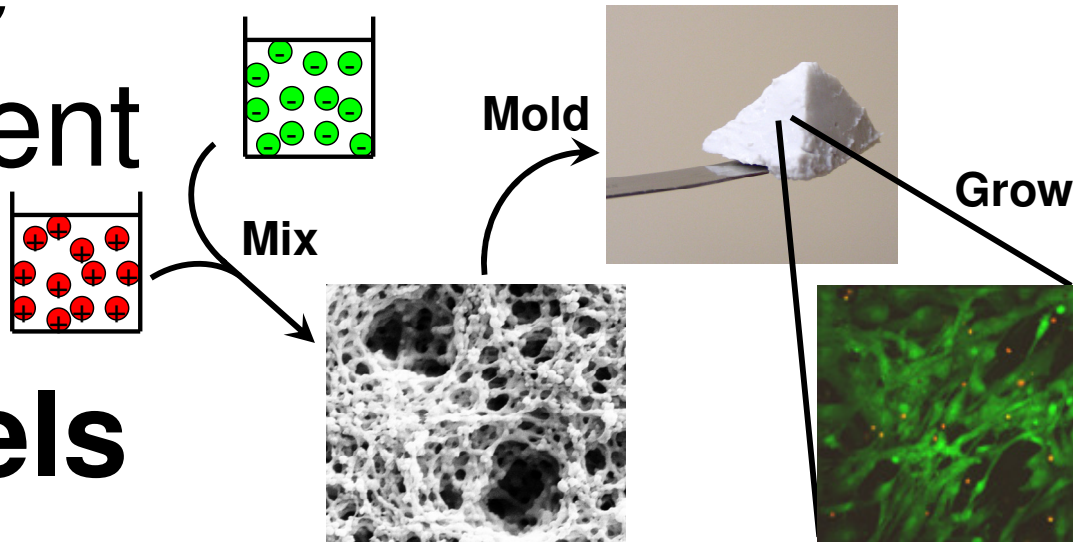

Biomaterials Strategies

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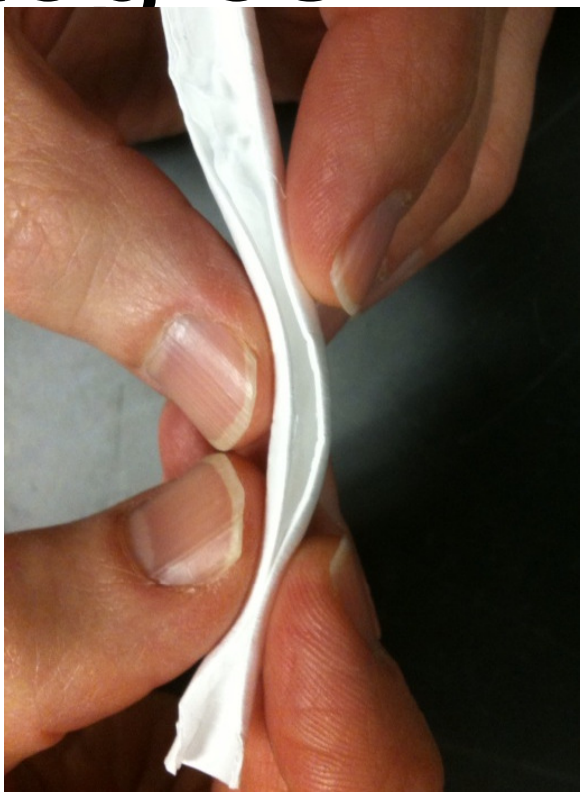
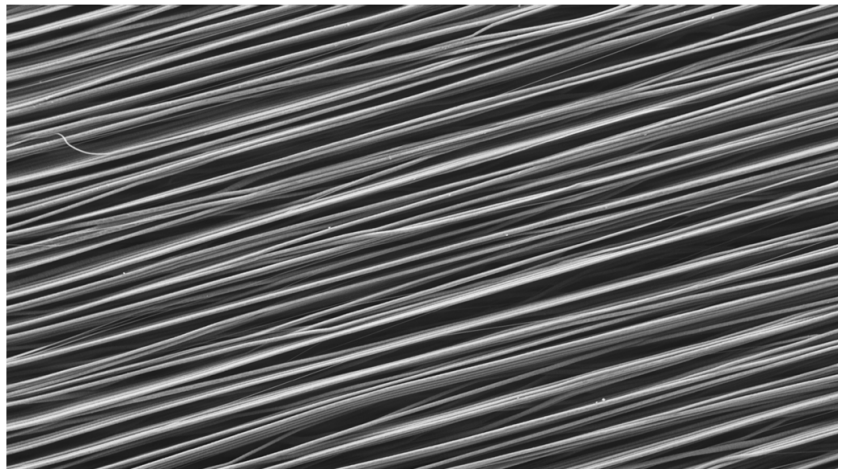




Biomaterials Strategies

- Microsphere-based gradient scaffolds
- Colloidal gels
- Electrospinning
- **IPN hydrogels**

Umbilical cord stromal cells

- Not cord blood, not HUVECs
- Combine with biomaterials
- Signaling strategies
- Comparisons to BMSCs

Collaborations & Commercialization

- Currently working with scientists, engineers, and surgeons
- Patents pending on gradient and IPN designs
- Interested in talking to entrepreneurs

Collaborations Across State Lines

- UMKC Dental School (bone biology)
- Children's Mercy (ENT, orthopedics)
- Sinclair Research Center (*in vivo*)
- UM-Columbia (*in vivo*)

Questions?

ARTHRITIS FOUNDATION®
Take Control. We Can Help.™

Oral and Maxillofacial Surgery Foundation
Leading the specialty through support of research and education

NSF

NATIONAL INSTITUTES OF HEALTH

NIGMS

K-INBRE
Kansas IDeA Network of Biomedical Research Excellence

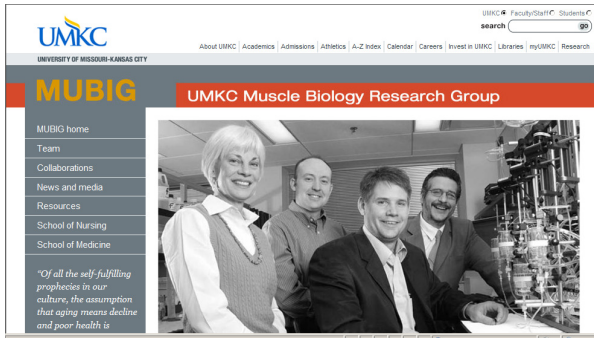
NIBIB

KU THE UNIVERSITY OF KANSAS
The Institute for Advancing Medical Innovation

National Institute of Dental and Craniofacial Research

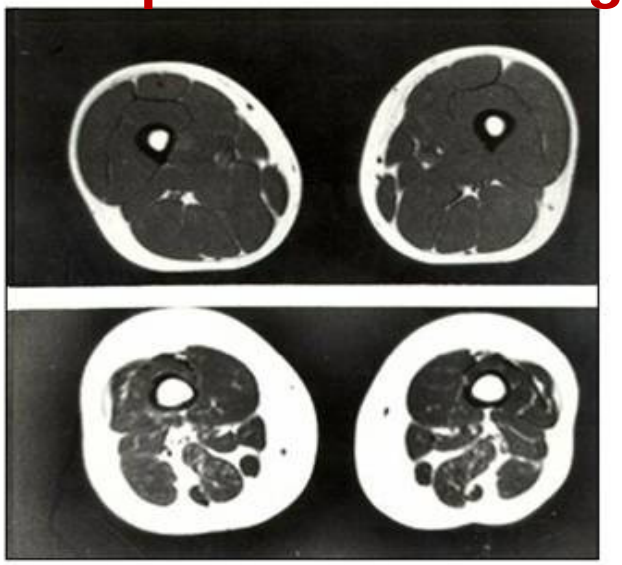
Muscle Aging Sarcopenia is a FACT!
What are we going to do about it?

Marco Brotto, *B.S.N., M.S., Ph.D.*
Associate Professor of Nursing, Medicine & Biological Sciences,
International Visiting Professor, Brazilian Council of Research
Director, Muscle Biology Group-MUBIG
University of Missouri-Kansas City



But, what is sarcopenia?

The power of an image



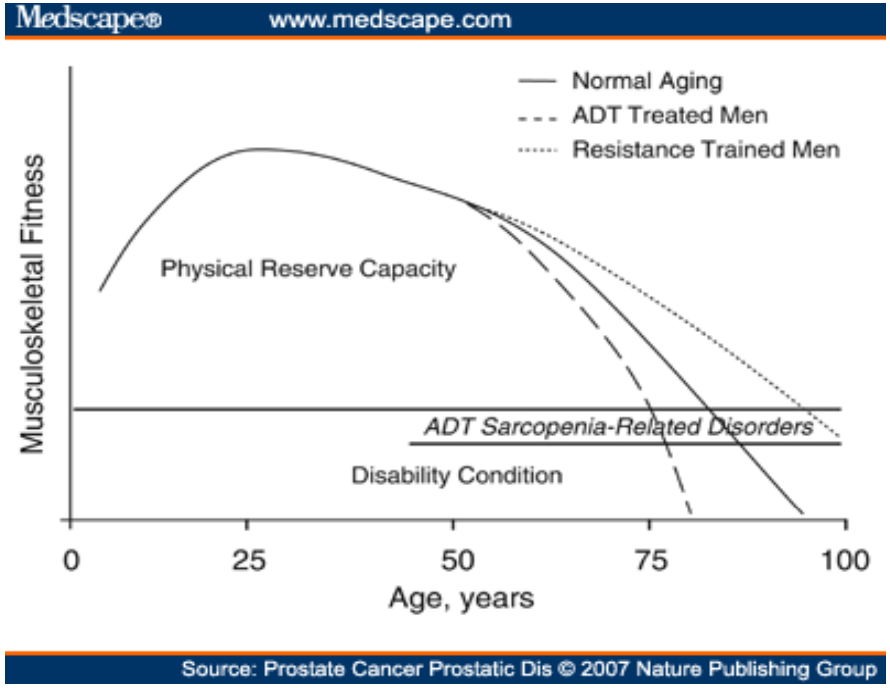
Age-related changes in muscle mass in thigh cross-sectional area of two people with similar BMI

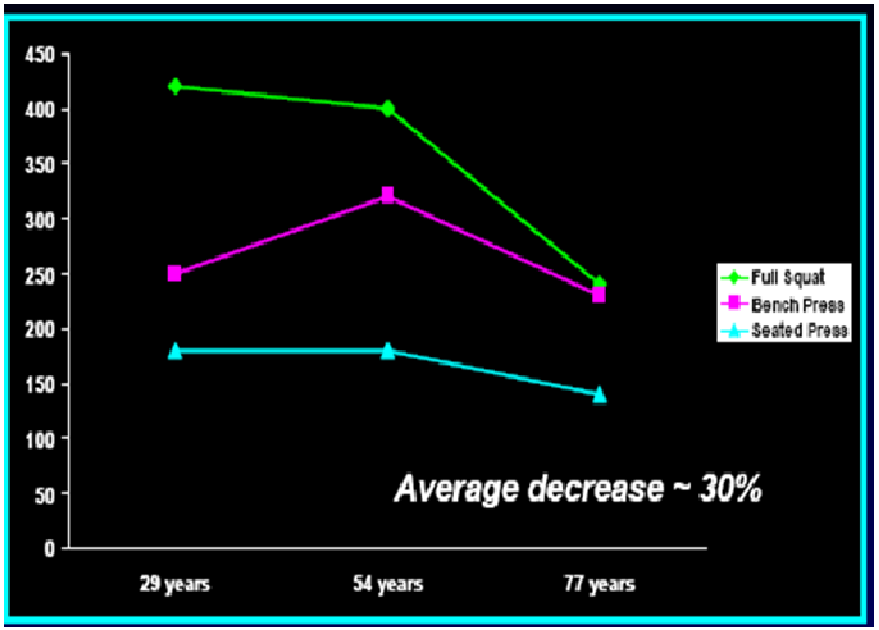
Beginning in the fourth decade of life, adults lose 3% to 5% of muscle mass per decade, a rate of decline that increases to 1% to 2% per year after the age 50 years.

Loss of skeletal muscle mass and strength is associated with declining health.

The cost of sarcopenia is in the hundreds of billions in the US and trillions in the world!

The devastating consequences of sarcopenia!





Surprisingly, there is an almost universal lack of awareness of

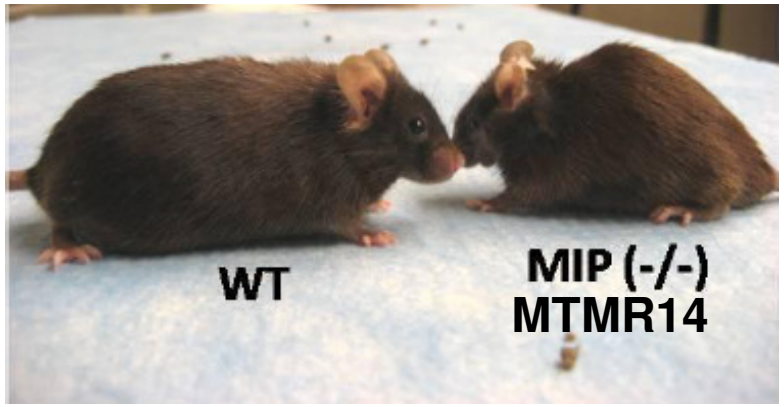
sarcopenia, its consequences, and working to delay it or

reducing its effects.

What can we do about?

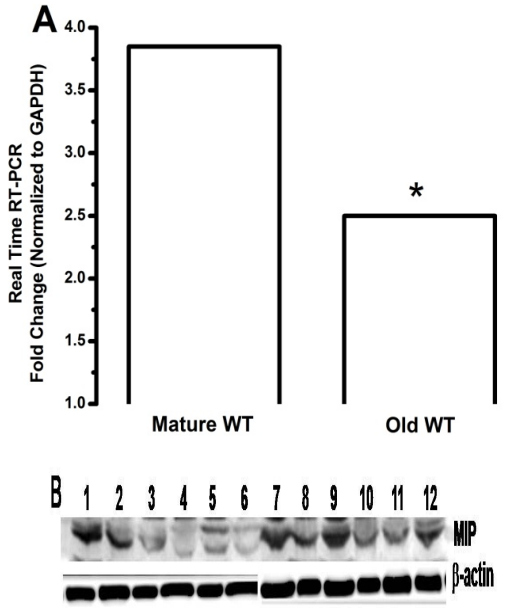
While these measure help, unfortunately they are still NOT enough

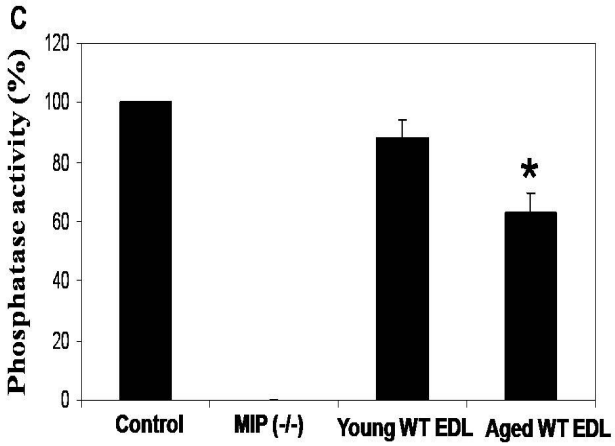
Our Innovative Research has Potential to Help



We have discovered that during aging disruption of intracellular calcium homeostasis develops, particularly compromised SOCE.

Using animal models of muscle research, we have discovered key genes (mg29, sarcalumenin, mg53, mip) that are important for muscle function. Some of these genes are down regulated during aging





Expression of MIP increased with muscle fiber formation and differentiation. MTMR14 is a phosphatidylinositol-3-phosphatase that dephosphorylates PtdIns(3,5)P2, an essential second messenger! Mutations in MIP associated with muscle myopathies in humans

What else can we do?

The MIP-PI(3,5)P2 is a novel pathway that is essential for muscle development, fo and muscle function. Clinically relevant also. How about we partner to develop ne to modulate this pathway? Gene therapy?

Following role models: Drs. Jianjie Ma and Noah Weisleder, MG53, and Trimedic
http://www.trim-edicine.com/About_Us.html

How about a blood diagnostic test for early detection of sarcopenia and aging frailty?

I really think that I have a great for such a test!

What else can we do?

The UMKC Muscle Biology Group recently discovered that hyperthermia induces hypertrophy in cardiac, smooth and skeletal muscle cells, alters calcium homeostasis, and activates a complex network of genes, including a pathway

We could partner to explore the healing effects of hyperthermia.
New devices could be developed

Bones & Muscles talk to each other:
Muscle Biology Research Group & the Bone Biology Research Group

Muscles need activity:
Most of us are exercising less. Many can't even exercise!

In collaboration with Dr. Leon-Salas, we are developing a new device for dual Electrical and electromagnetic stimulation of muscles and bones!
And you will see in Dr. Salas presentation, we already have some exciting data!

We are very thankful for

Support

- Missouri Life Sciences Research Board
- UMKC Center of Excellence of Mineralized Tissue
- National Institutes of Health
- American Heart Association
- Schools of Nursing, Medicine, Computer & Engineering, Dentistry

Outside Collaborators:

C-K Qu, Case Western Reserve University

Thomas Nosek, Case Western Reserve University

Hector Valdivia, University of Wisconsin

Jianjie Ma, Robert Wood Johnson Medical School

Hiroshi Takeshima, Tohuko University, Japan

University of Sciences & Technology, Salvador, Brazil

UMKC Collaborators

Lynda Bonewald

Mark Johnson

Walter Leon-Salas

MUBIG

NOT KNOWING IT WAS
IMPOSSIBLE,
WE COMPLETED THE MISSION!

Marco Brotto

Missouri Life Sciences Summit

March 8,9 2010

Collaboration Opportunities between Biological Scientists and Electrical Engineers

Daniel Leon-Salas

Assistant Professor

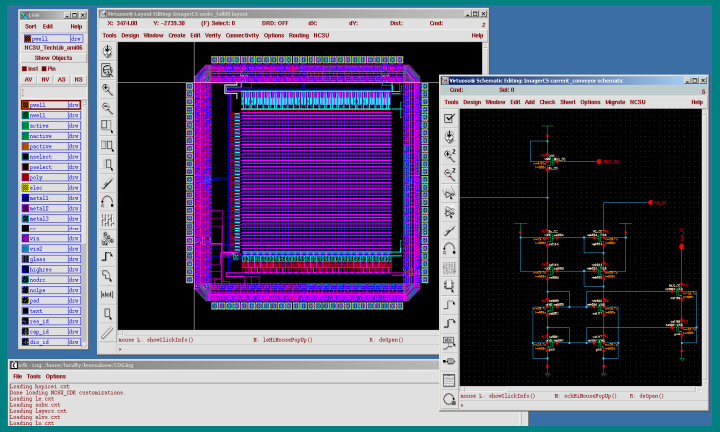
Computer Science Electrical Engineering Dept.

Outline

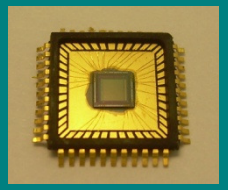
- Opportunities for collaborative work
- Case 3: Smart Stent
- Case 2: Cell Stimulator
- Future Work
- Questions

We great expertise on

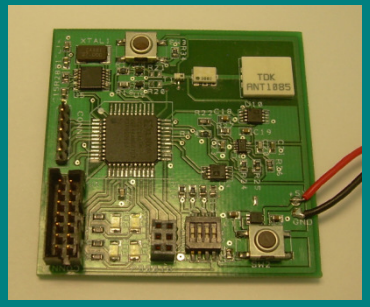
Integrated Circuits and Electronic Systems Design



CAD Software



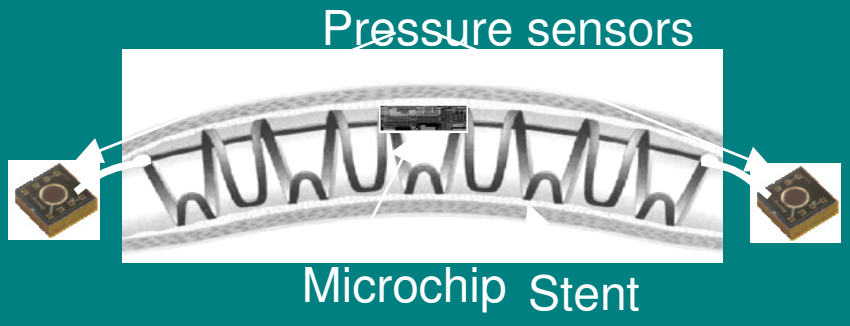
Fabricated chip

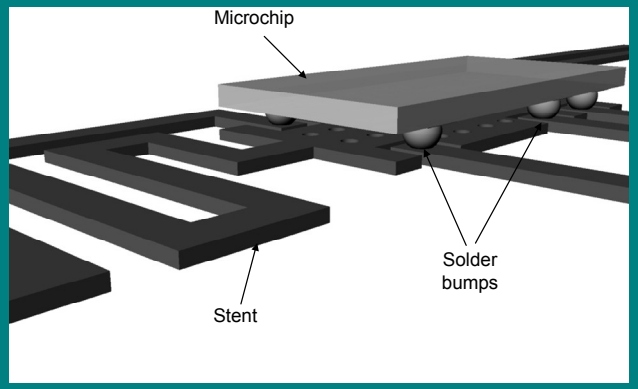


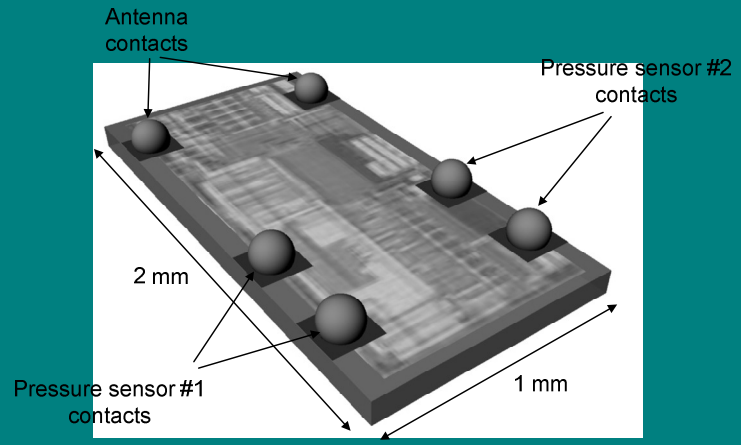
Printed circuit board

Smart Stent

Sensor laden stent to assess the effects of in-stent restenosis





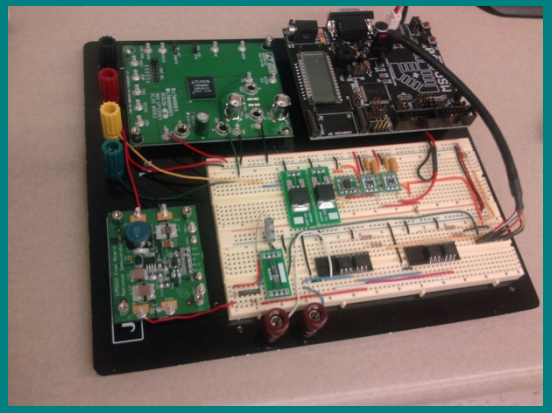


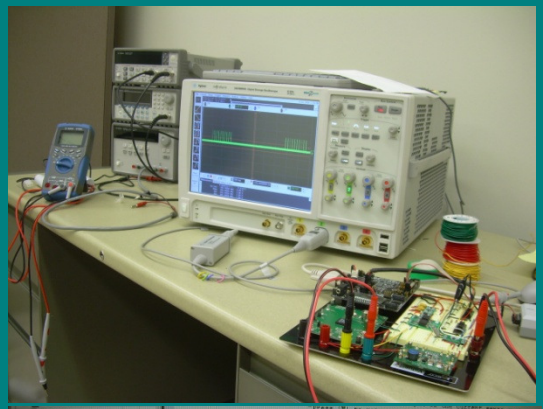
Restenosis simply is the recurrence of stenosis, the narrowing of vessels.

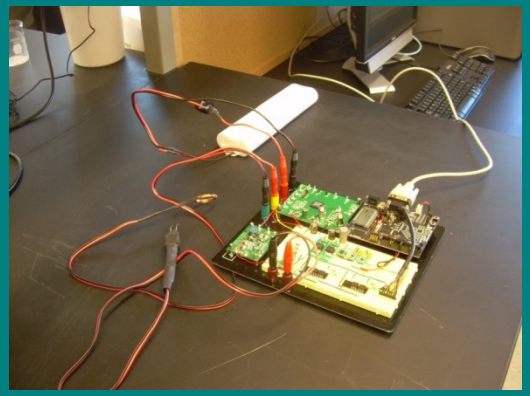
It occurs in 25-30% of patients with stents

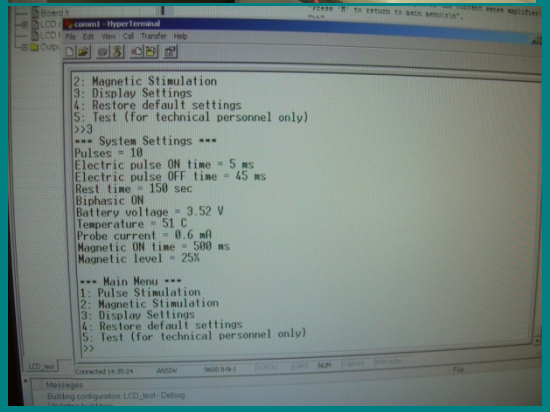
A smart stent could help reduce restenosis and health care costs

Electro-Magnetic Cell Stimulator







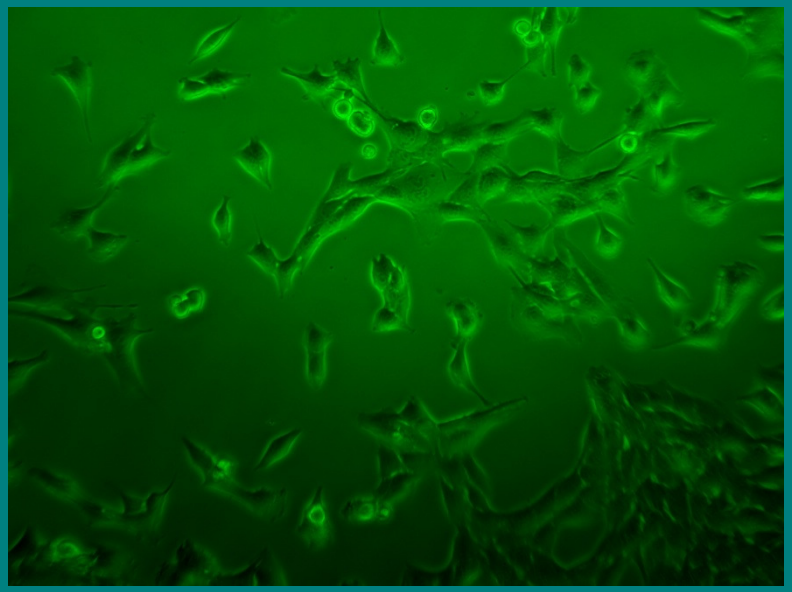


Why?
We know that electrical stimulation is good for muscles; clinically used to prevent muscle wasting.
We also know that electromagnetic stimulation is excellent for healing of bone fractures and prevention of bone wasting

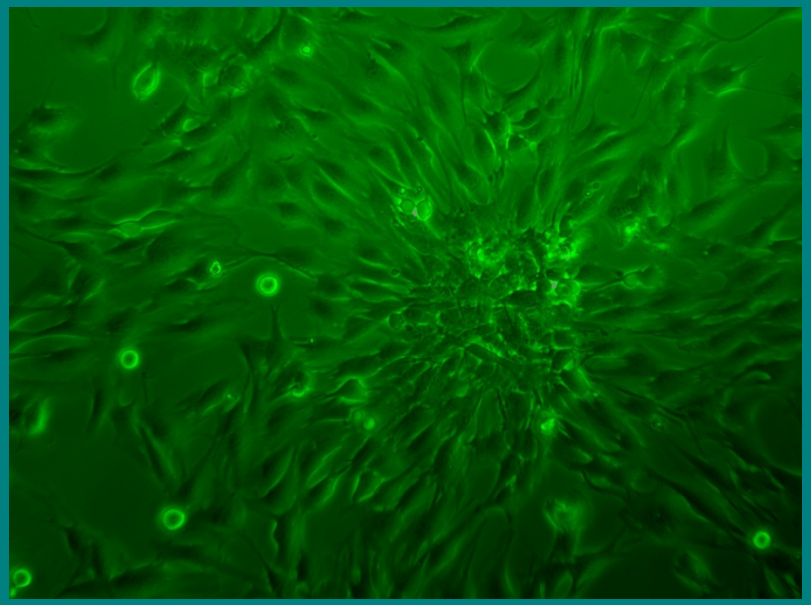
Thus, we created the first Dual stimulation device

And look at the effects in myoblasts

Control



Dual Stimulation



This is very exciting because suggests that our device can enhance Cell-cell communication, necessary for muscle repair/regeneration

We now want to move forward -Partners are welcomed

- We want to make a prototype to be tested in animals
- We want to make prototype to be tested in humans
- We predict that such a device if properly adapted for animals and humans could be highly beneficial in the treatment and prevention of muscle wasting and osteoporosis

Thank you

Time for Questions