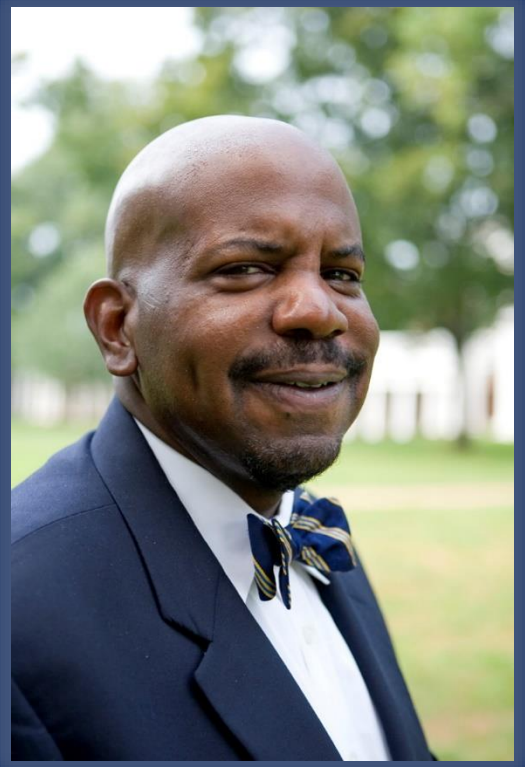
Regenerative Engineering



Cato T. Laurencin, M.D., Ph.D.

University Professor

Albert and Wilda Van Dusen Distinguished Endowed Professor of Orthopaedic Surgery
Professor of Chemical and Biomolecular Engineering
Professor of Materials Science and Engineering
Professor of Biomedical Engineering
The University of Connecticut

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Disclosures

Johnson and Johnson
Globus Medical
Healing Orthopaedic Technologies
Soft Tissue Regeneration/Biorez
Biobind
Mimedx
Alkermes

Regenerative Engineering

14 NOVEMBER 2012, VOL. 4, #160

Special Issue: Biomaterials

EDITORIAL

Regenerative Engineering

The future of tissue regeneration lies in “regenerative engineering,” with biomaterials playing a key role.

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14 NOVEMBER 2012, VOL. 4, #160

Special Issue: Biomaterials

EDITORIAL

Regenerative Engineering

The future of tissue regeneration lies in "regenerative engineering," with biomaterials playing a key role.

COMMENTARY

Regulatory Challenges in Biomaterials Translation

Thought leaders comment on what they perceive to be the greatest barriers to clinical translation of biomaterials.

PERSPECTIVE

Building Vascular Networks

Vascularization of biomaterials will enhance survival of engineered tissues.

PERSPECTIVE

Dynamic Microenvironments: The Fourth Dimension

Four-dimensional cell matrices better recapitulate tissue and organ function in 3D space and over time.

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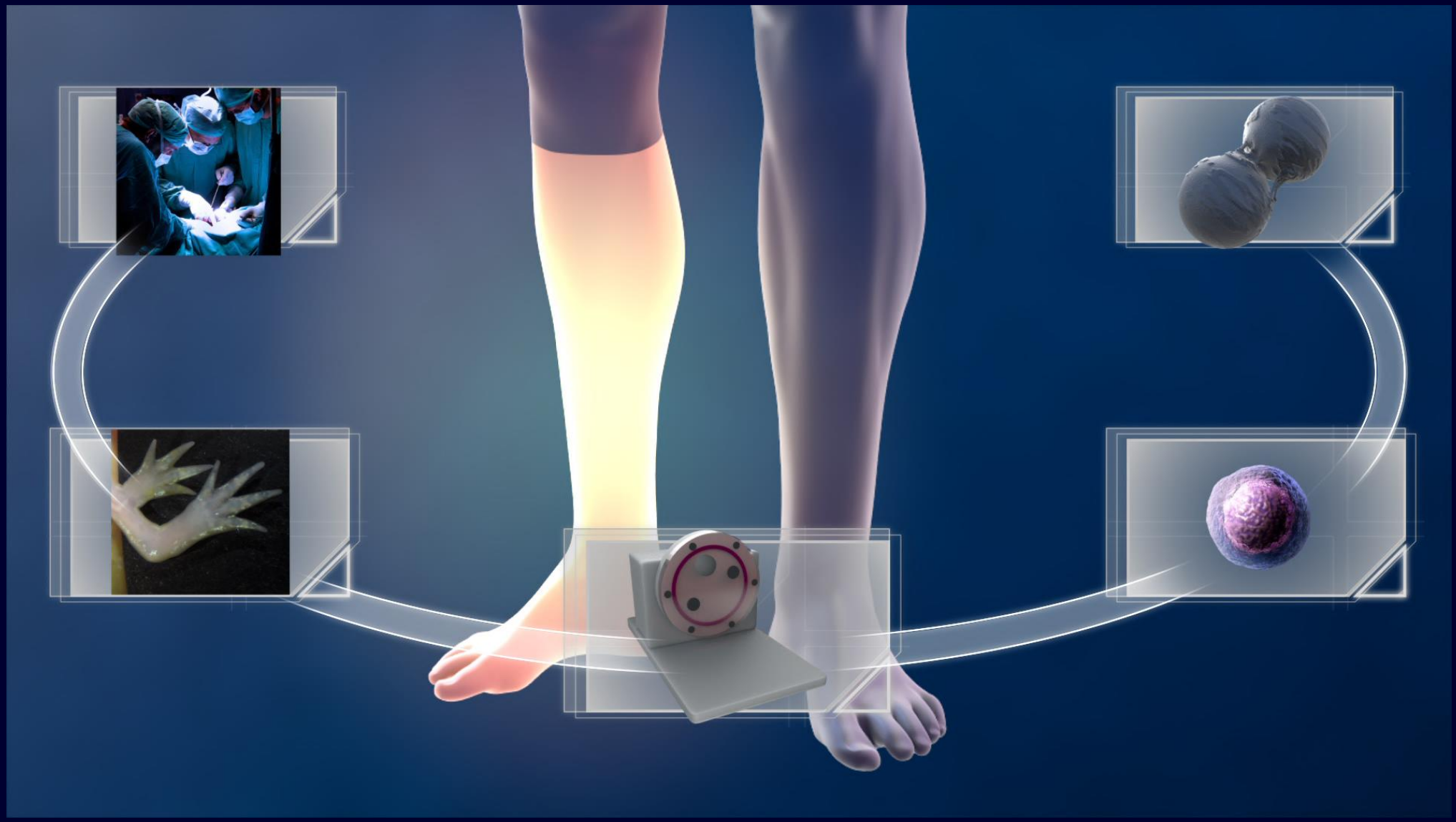
Regenerative Engineering

“The Convergence of advanced materials science, stem cell science, physics and developmental biology

And clinical translation toward the regeneration of complex tissues, organs, or organ systems.”



Convergence

“The coming together of Insights and Approaches from Originally Distinct Fields”

Regenerative Engineering

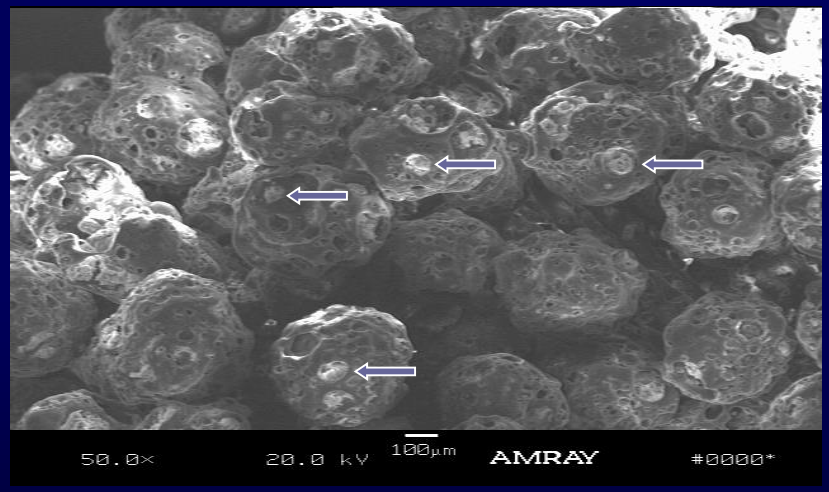
In Action

Inductive Materials

Candidate Materials

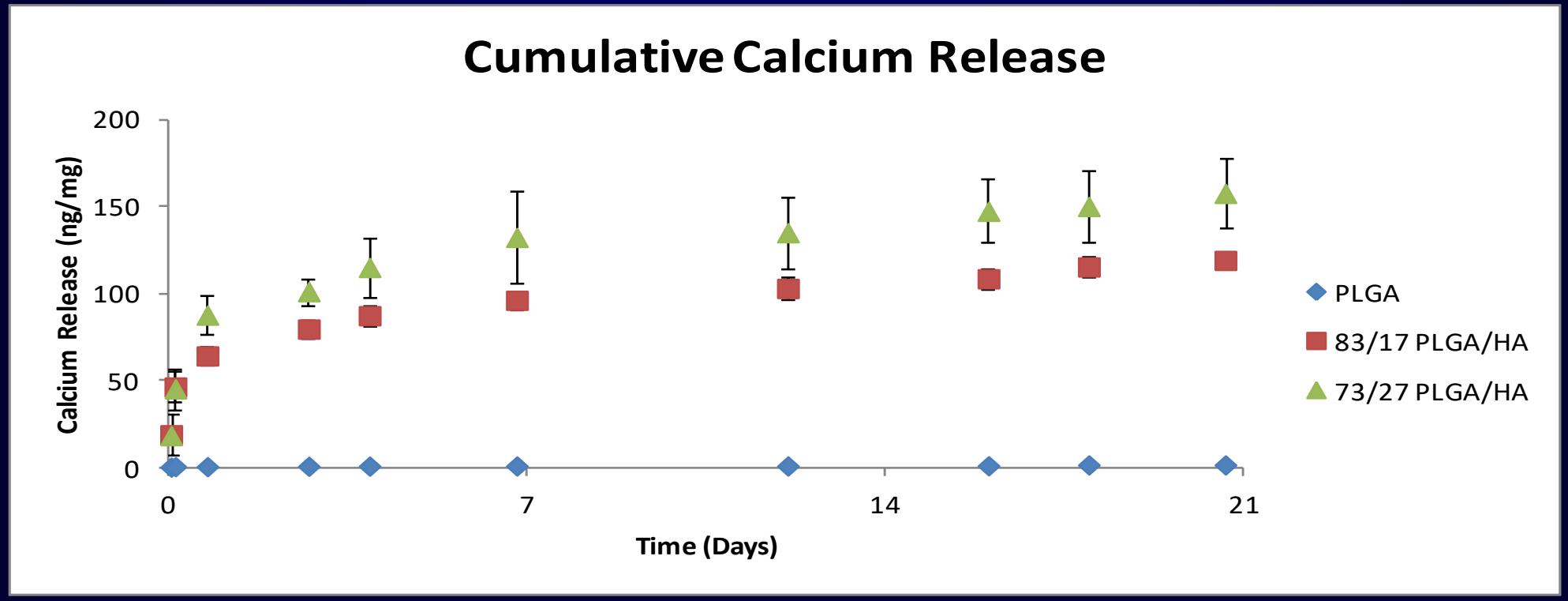
POLYMER (PLAGA)
Strength, formability, ease of use, biodegradable
Limited osteoconductivity, osteogenicity and bioactivity

CERAMIC (CaP)
Bioactive, osteointegrative, osteoconductive
Brittle in failure, poor formability, slow degradation



POLYMER/CERAMIC COMPOSITE
Biodegradable, formable, osteoconductive, osteointegrative material

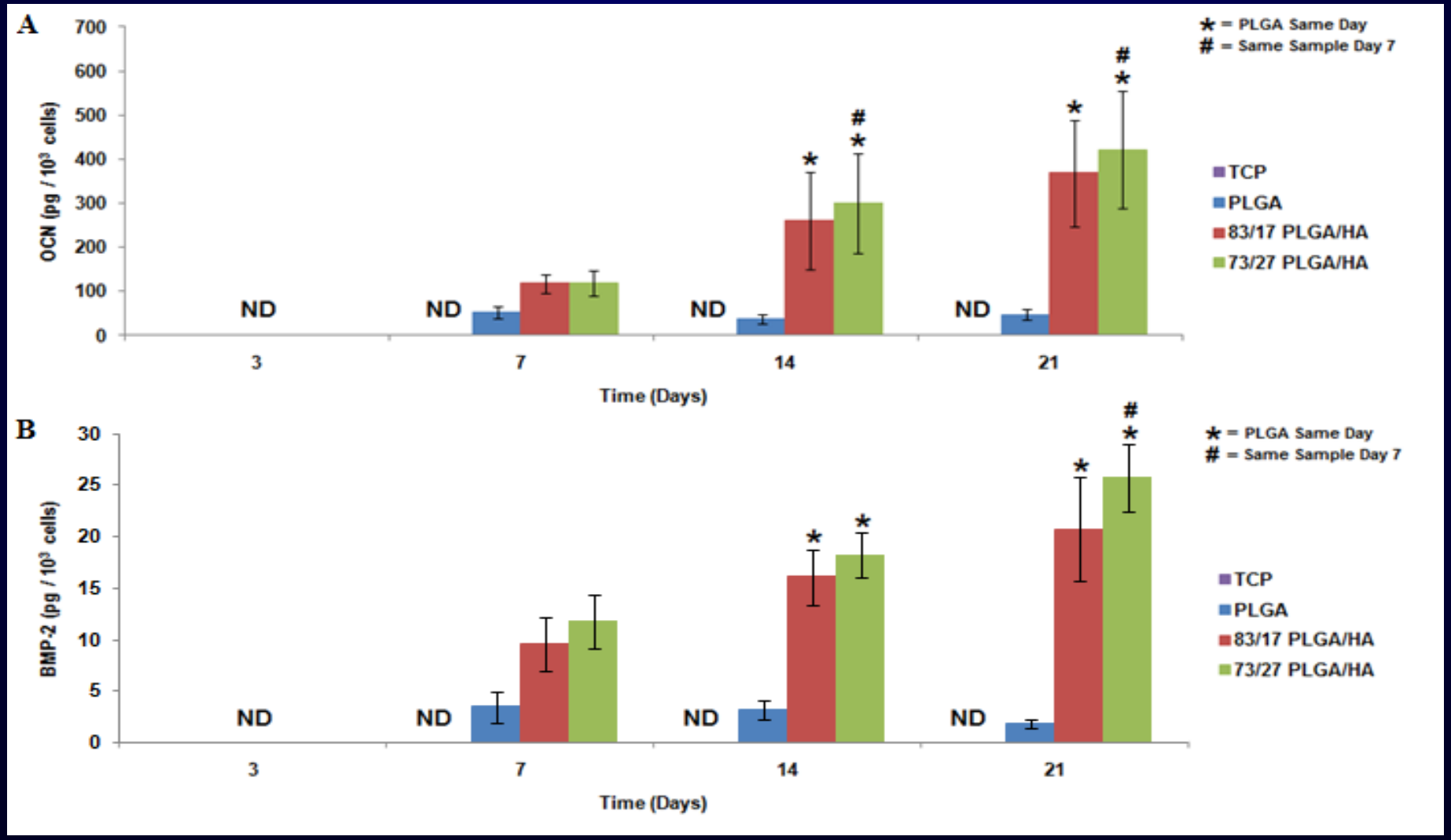
Calcium Ion Release



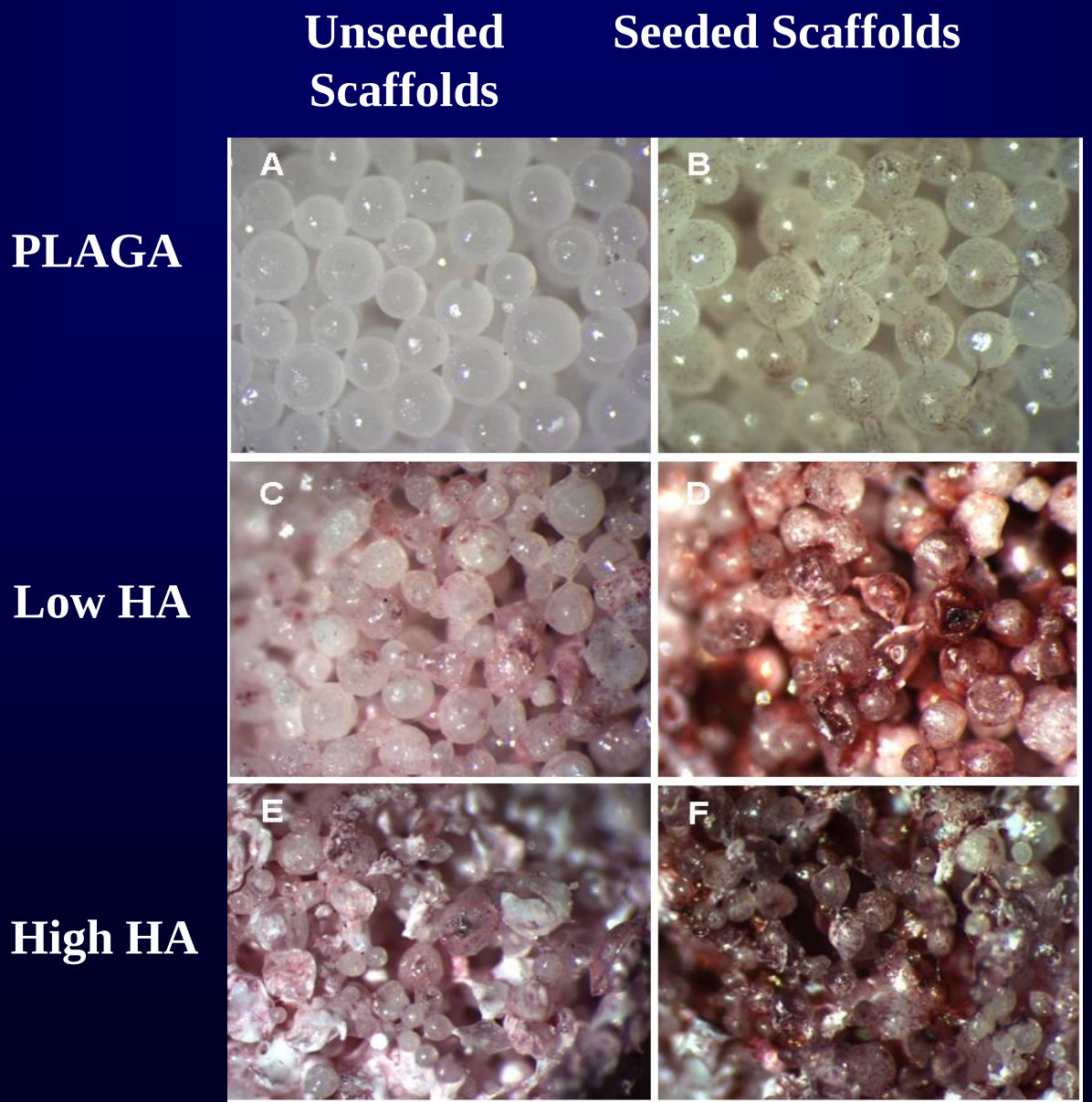
- PLAGA scaffolds showed no calcium ion release

- High HA released more calcium ions as compared to Low HA

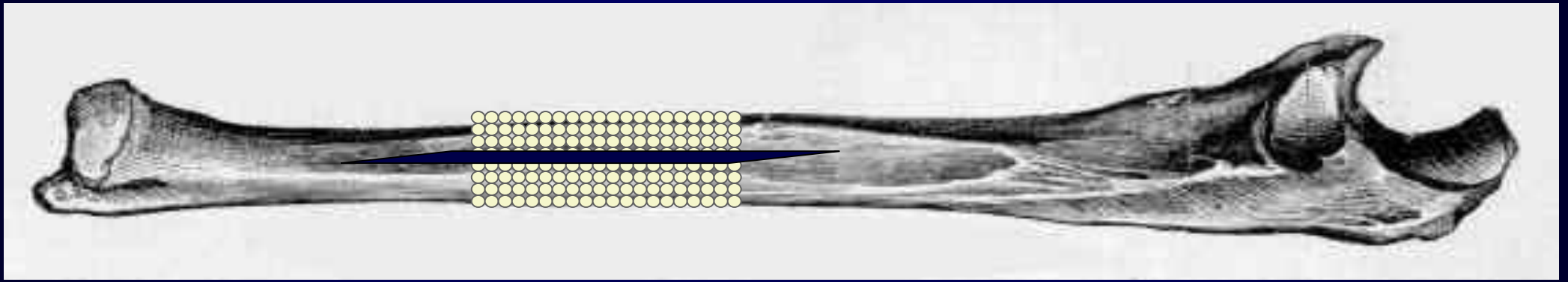
Secretion of Osteogenic Markers

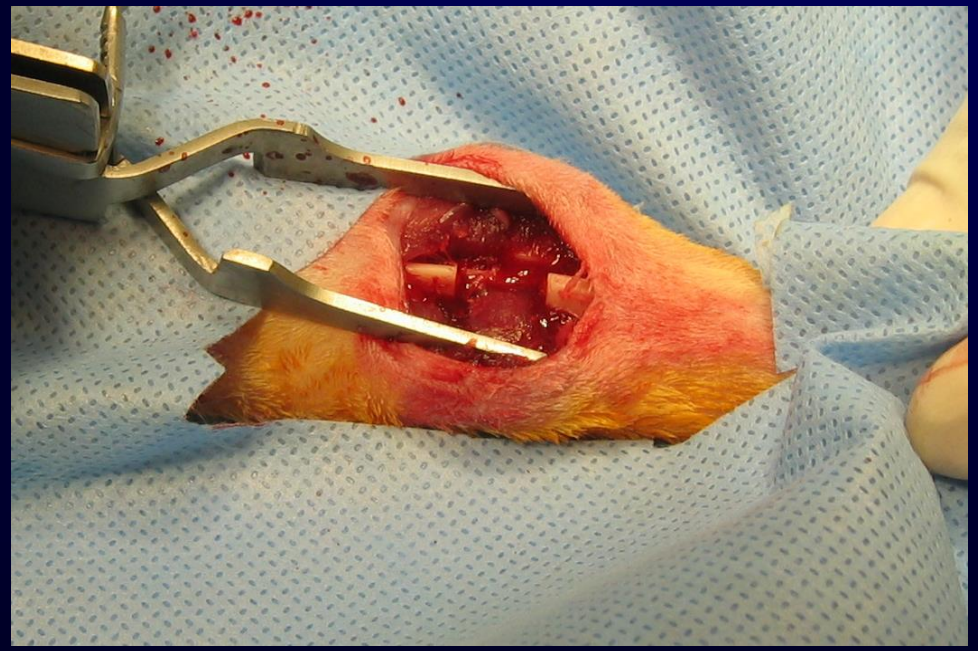


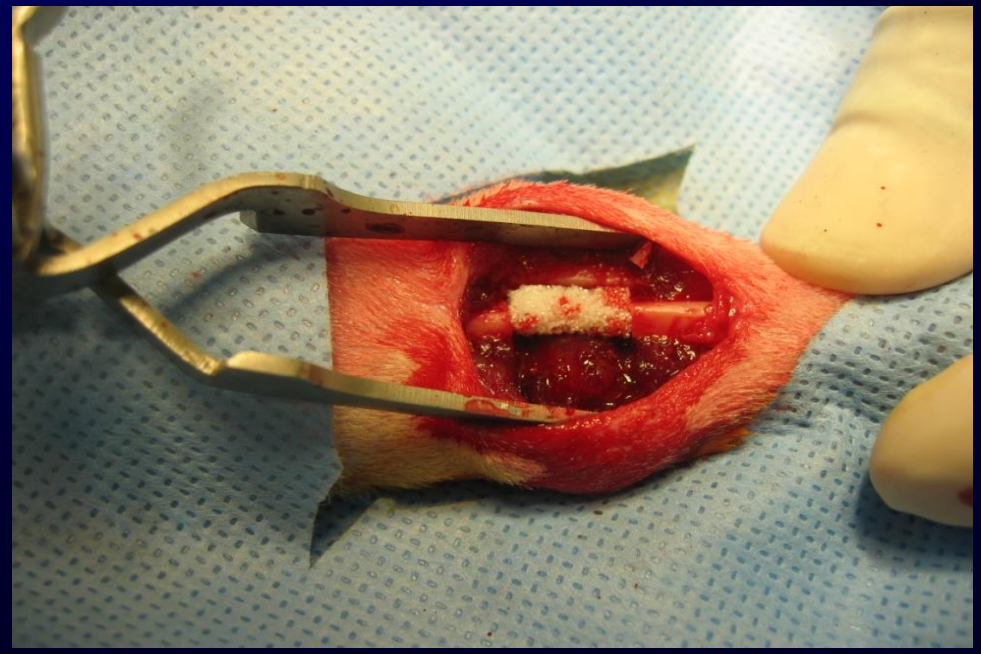
In Vitro Mineralization



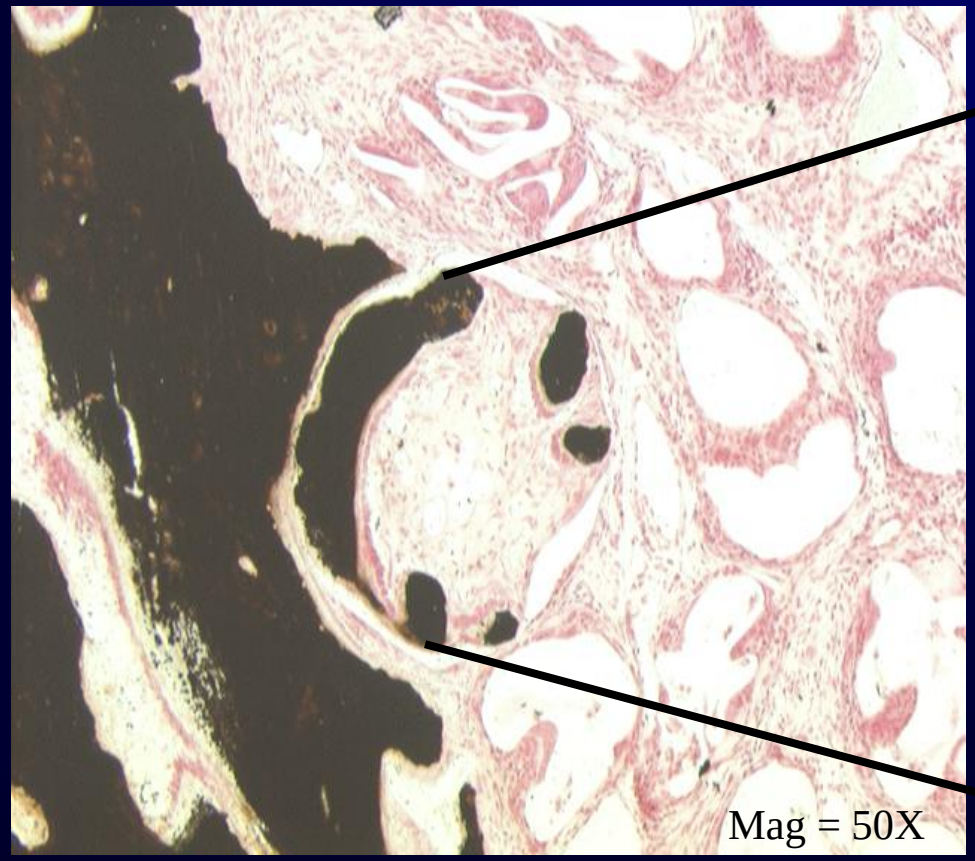
In Vivo Evaluation

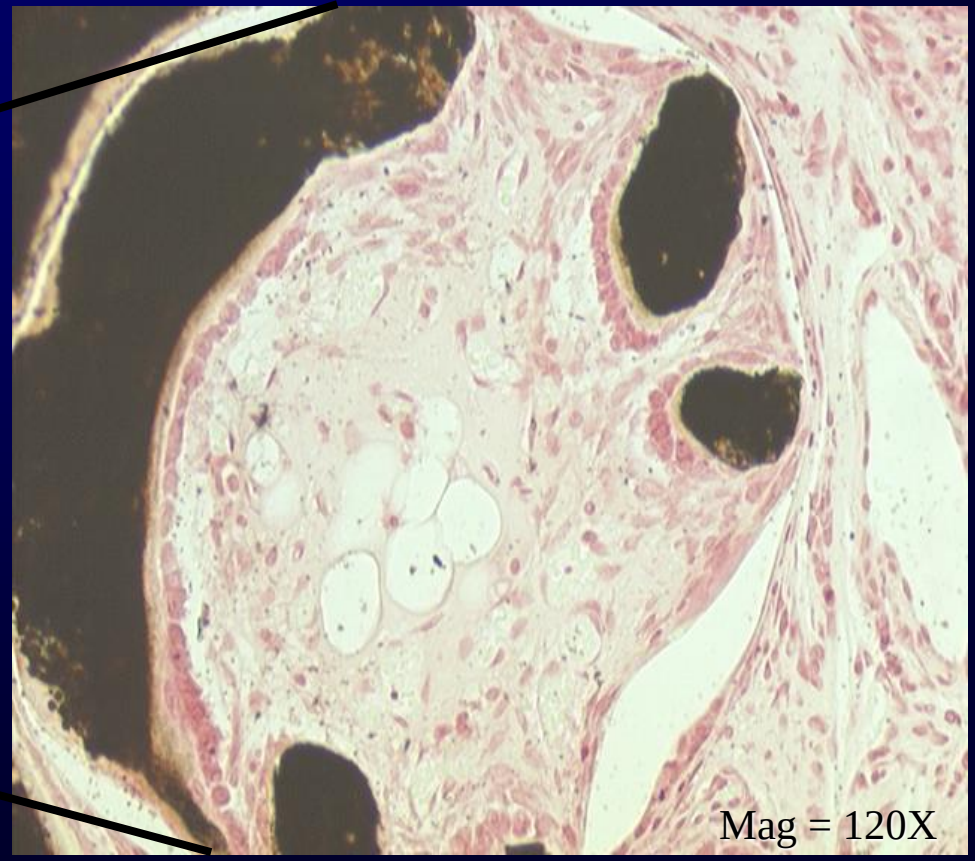


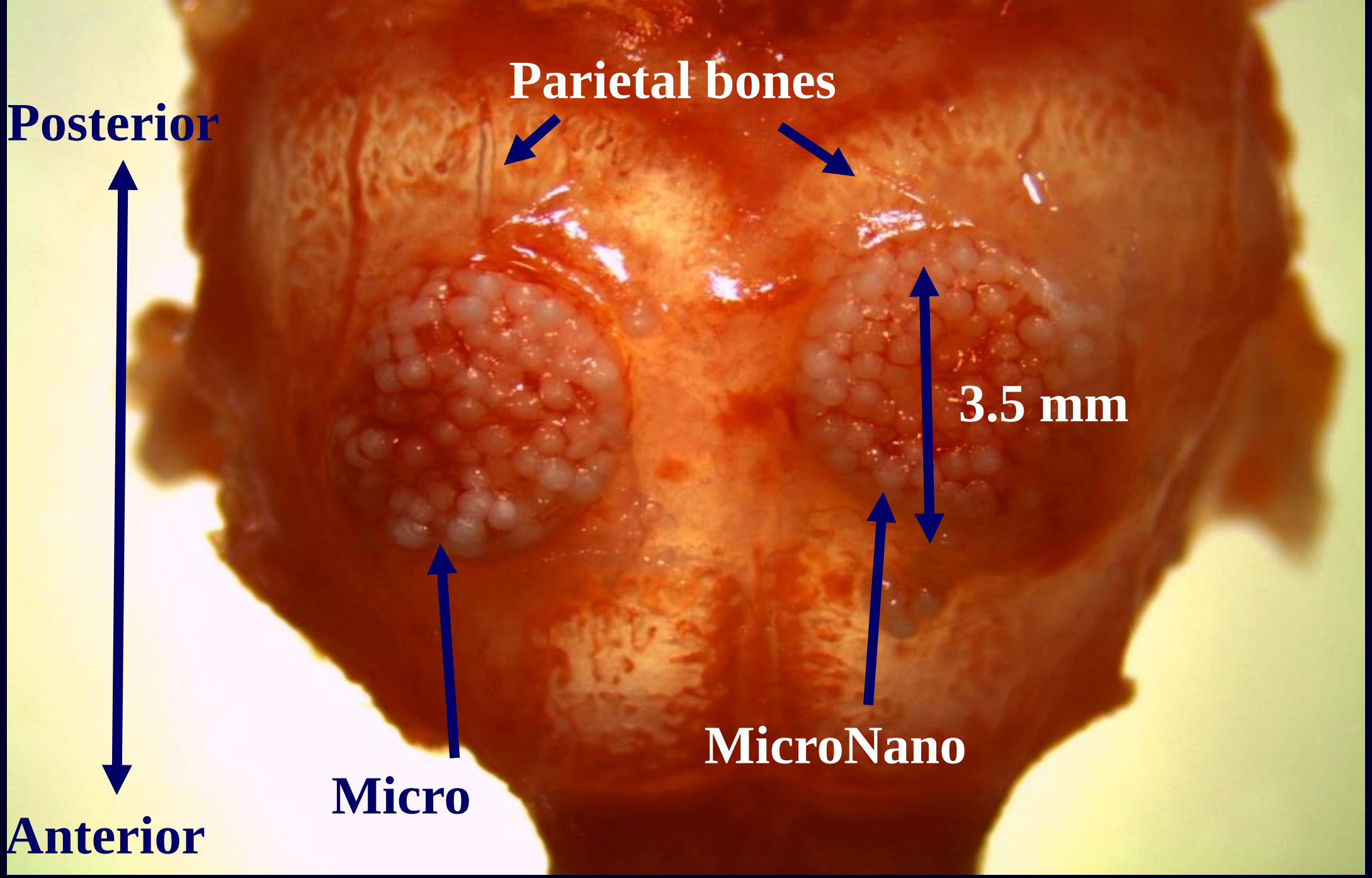




Composite Eight Week Healing






Parietal bones
Posterior
3.5 mm
Micro
MicroNano
Anterior

In vivo

Low Crystalline Hydroxyapatite

- Critical sized cranial defect in mice
  - Rigorous

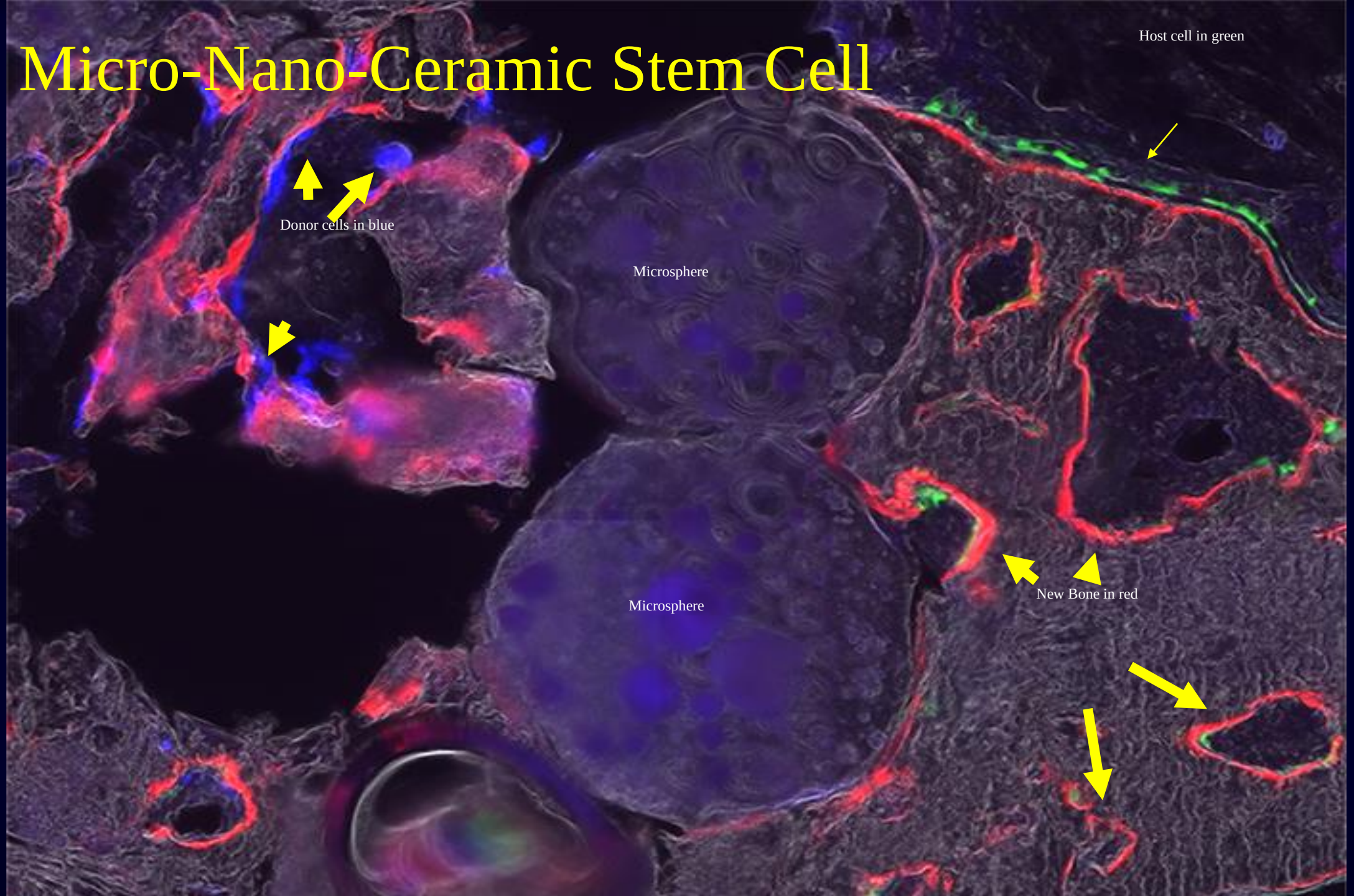
- Bilateral defects
    - Micro and Micro/Nano matrix in each animal

In vivo - Cell Matrix

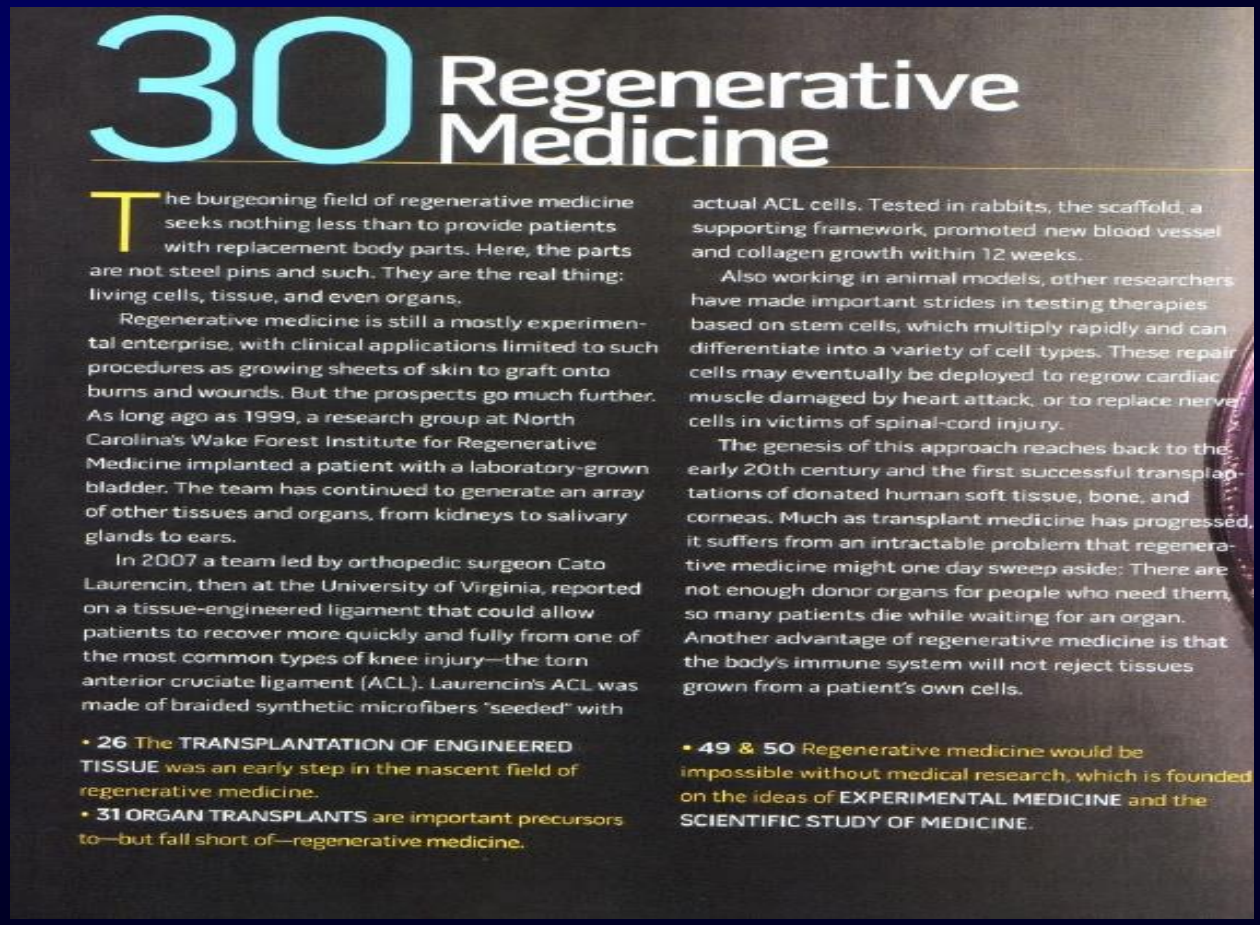
- 10^6 donor BMSCs seeded onto each scaffold

- Transgenic mouse host and donor
  - **Topaz** reports **host** collagen production
  - Cyan reports **donor** collagen production

Micro-Nano-Ceramic Stem Cell



Laurencin Soft tissue Regeneration highlighted by National Geographic Magazine.



30 Regenerative Medicine

The burgeoning field of regenerative medicine seeks nothing less than to provide patients with replacement body parts. Here, the parts are not steel pins and such. They are the real thing: living cells, tissue, and even organs.

Regenerative medicine is still a mostly experimental enterprise, with clinical applications limited to such procedures as growing sheets of skin to graft onto burns and wounds. But the prospects go much further. As long ago as 1999, a research group at North Carolina's Wake Forest Institute for Regenerative Medicine implanted a patient with a laboratory-grown bladder. The team has continued to generate an array of other tissues and organs, from kidneys to salivary glands to ears.

In 2007 a team led by orthopedic surgeon Cato Laurencin, then at the University of Virginia, reported on a tissue-engineered ligament that could allow patients to recover more quickly and fully from one of the most common types of knee injury—the torn anterior cruciate ligament (ACL). Laurencin's ACL was made of braided synthetic microfibers "seeded" with actual ACL cells. Tested in rabbits, the scaffold, a supporting framework, promoted new blood vessel and collagen growth within 12 weeks.

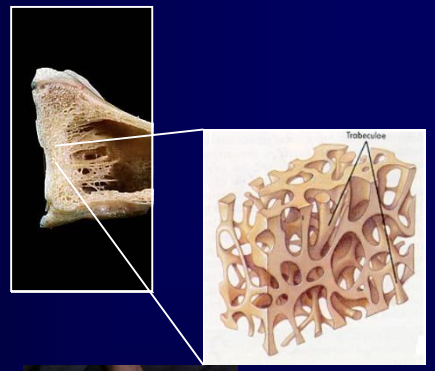
Also working in animal models, other researchers have made important strides in testing therapies based on stem cells, which multiply rapidly and can differentiate into a variety of cell types. These repair cells may eventually be deployed to regrow cardiac muscle damaged by heart attack, or to replace nerve cells in victims of spinal-cord injury.

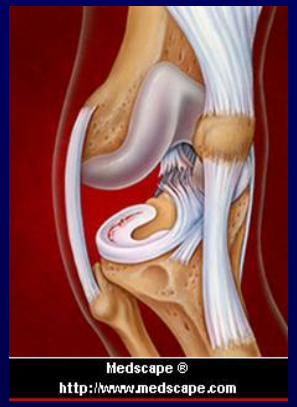
The genesis of this approach reaches back to the early 20th century and the first successful transplantations of donated human soft tissue, bone, and corneas. Much as transplant medicine has progressed, it suffers from an intractable problem that regenerative medicine might one day sweep aside: There are not enough donor organs for people who need them, so many patients die while waiting for an organ. Another advantage of regenerative medicine is that the body's immune system will not reject tissues grown from a patient's own cells.

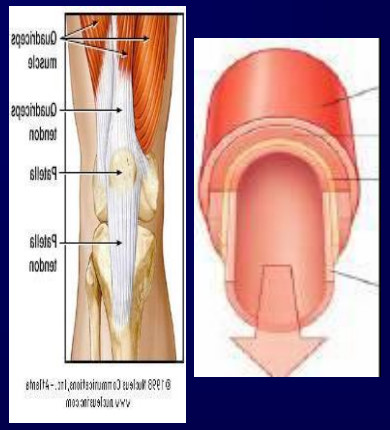
• **26** The **TRANSPLANTATION OF ENGINEERED TISSUE** was an early step in the nascent field of regenerative medicine.
• **31 ORGAN TRANSPLANTS** are important precursors to—but fall short of—regenerative medicine.

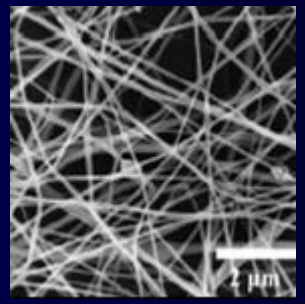
• **49 & 50** Regenerative medicine would be impossible without medical research, which is founded on the ideas of **EXPERIMENTAL MEDICINE** and the **SCIENTIFIC STUDY OF MEDICINE**.

Regeneration of Musculoskeletal Tissues

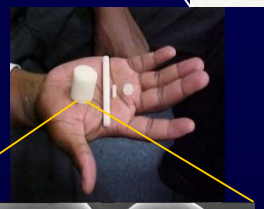


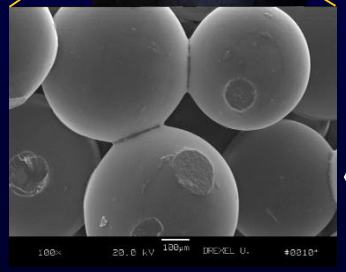


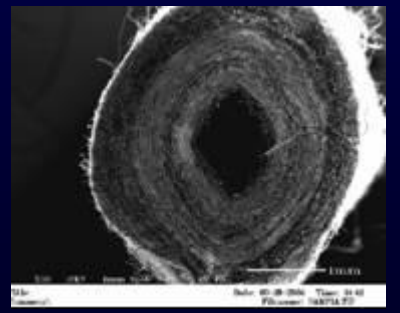




Skin





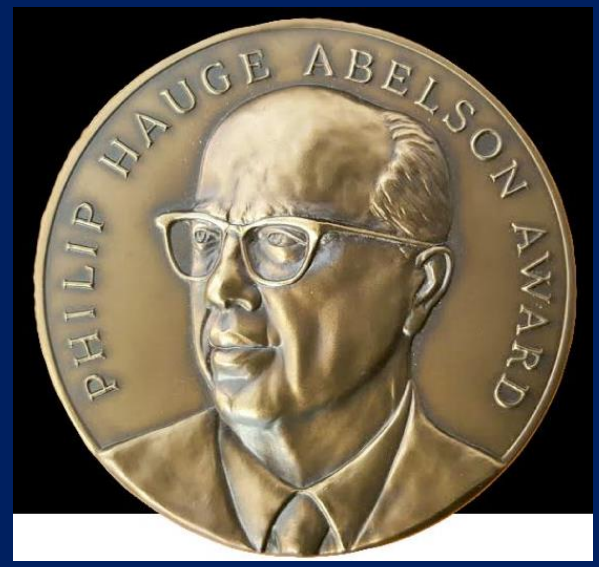


Cartilage

Bone

Ligament/Tendon, Blood Vessel, Nerve

The Work has resulted in singular honors in Medicine, Engineering, Science and Technology



Medicine Engineering Science

Walsh McDermott Medal
National Academy of Medicine

Simon Ramo Founders Award
National Academy of Engineering

“For fundamental, critical, and groundbreaking scientific advances in the engineering of tissues, guiding technology and science policy, and promoting diversity and excellence in science.”

Philip Hauge Abelson Prize

American Association for the Advancement of Science

“For signal contributions to the advancement of science in the United States.”


NATIONAL MEDAL OF TECHNOLOGY AND INNOVATION

10th Anniversary *Regenerative Engineering*

14 November 2022

14 NOVEMBER 2012, VOL. 4, #160

Special Issue: Biomaterials

EDITORIAL

Regenerative Engineering

The future of tissue regeneration lies in "regenerative engineering," with biomaterials playing a key role.

EDITORIAL

BIOMATERIALS INNOVATION

Regenerative Engineering

THIS YEAR MARKS THE 25TH ANNIVERSARY OF THE FIELD OF TISSUE ENGINEERING. The bioengineer Y. C. Fung first proposed the term at a 1987 meeting of the National Science Foundation's Director for Engineering, Bioengineering and Research to Aid the Handicapped Program. Great interest in the field heightened with the paper by Langer and Vacanti in *Science* (*1*), which described it as "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ." Laurencin further defined it as "the application of biological, chemical and engineering principals towards the repair, restoration, or regeneration of living tissue using biomaterials, cells, and factors alone or in combination" (*2*).

Over the past 25 years, advances have been made in biomaterials-based tissue engineering research to repair organ systems. In the past decade, three areas of technology have emerged and have added to the "toolbox" available to biomaterials scientists and engineers, presenting exciting possibilities to moving beyond maintaining or repairing tissue to regenerating them. First, our appreciation of phenomena taking place in the nano-regime gained appreciation in the late 1990s and ushered in nanotechnology as a tool for engineering tissues, and advances in materials science have allowed us to harness those tools. Second, stem cell science has matured to where the use of stem cells is an everyday tool. We now have a deeper understanding of both adult and embryonic stem cells, and have developed and characterized induced pluripotent stem cells. Third, we have gained a more sophisticated understanding of developmental biology mechanisms in the salamander and the newt, and the role of the blastema in regeneration which has furthered our efforts in wound repair and regeneration. Each of these scientific advances has matured to the extent that they are now regarded as tools rather than simply concepts and ideas. It is with this in mind that we believe the future of tissue engineering lies in what can be termed "regenerative engineering."

We define regenerative engineering as the integration of tissue engineering with advanced material science, stem cell science, and areas of developmental biology. Regenerative engineering will harness and expand these newly developed tools toward the regeneration of complex tissues (*3*). Whereas tissue engineering sought to encourage interdisciplinary teams from the fields of engineering, science, and medicine, we see regenerative engineering as an expansion of this approach—a "convergence" (*4*) of tissue engineering with the three distinct fields above, to move beyond interdisciplinary scientific teams with siloed expertise toward an era in which scientists, engineers, physicists, and clinicians will have integrated training that spans these disciplines.

Dr. Cato T. Laurencin is the Van Dusen Distinguished Professor of Orthopaedic Surgery and the Director of both the Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences, and the Institute for Regenerative Engineering at the University of Connecticut. E-mail: laurencin@uchc.edu

Dr. Yusuf Khan is a member of the Institute for Regenerative Engineering and an Assistant Professor in the Department of Orthopedic Surgery at the University of Connecticut.

Citation: C. T. Laurencin, Y. Khan, Regenerative engineering, *Sci. Transl. Med.* **4**, 160ed9 (2012).

10.1126/scitranslmed.3004467

ADVANCED BIOMATERIALS SCIENCE

Tissue engineering has largely focused on the restoration and repair of individual tissues and organs, but over the past 25 years, scientific, engineering, and medical advances have allowed us to start considering the regeneration of complex tissues and biological systems. For instance, the traditional tissue engineering approach has used biomaterials from a limited pool of biodegradable and nondegradable polymers and ceramics to form three-dimensional structures to facilitate repair. The choice of biomaterials, however, has increased over the past 25 years to include polymers that can be designed with a range of mechanical properties, degradation rates, and chemical functionality. The polyphosphazenes are one good example. These and other advanced materials support a greater diversity of applications because their chemical versatility allows the polymer to be designed for a specific tissue or application rather than relying on extant materials repurposed as biomaterials.

Nanoscale control over scaffold architecture has led to a greater understanding of cellular sensitivity to topography. These tools are now being used to selectively control cell behavior—a potentially valuable resource when the inclusion of proteins and growth factors is not clinically possible and a requisite tool to move beyond single-tissue repair to complex multitissue regeneration. Biomaterials-based tissue engineering has also historically included the use and delivery of signaling molecules, such as growth factors, generally

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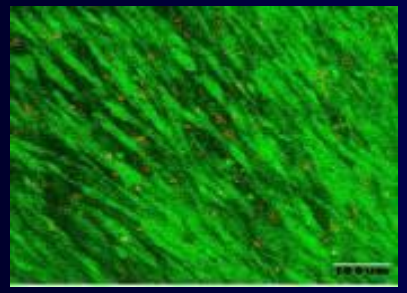
The Regenerative Engineering Society

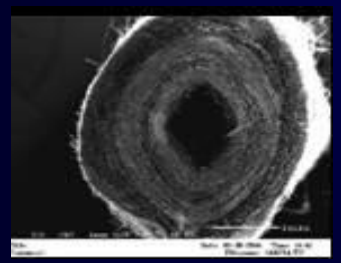
(The First Society Built Upon Convergence in Humans)

Cato T. Laurencin Regenerative Engineering Founder's Award

Convergence Approach towards Regeneration

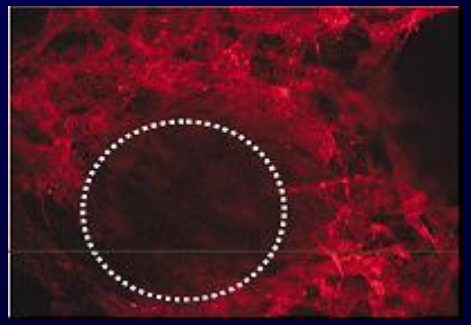


Skin, fascia



nerve, vascular
tissue, tendon

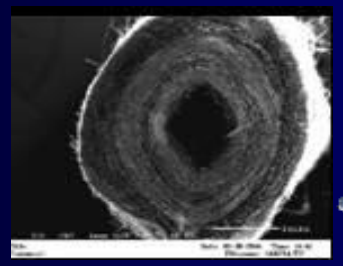
Bone

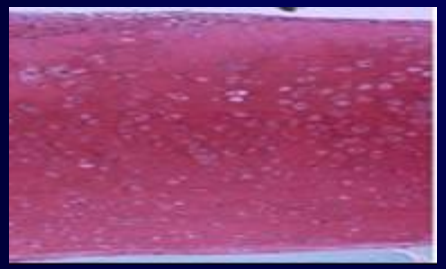


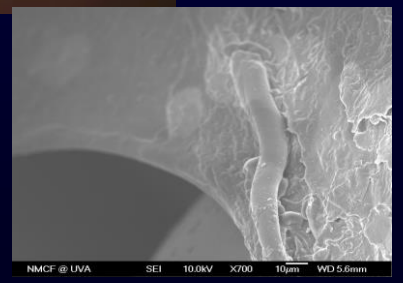
ligaments, muscle

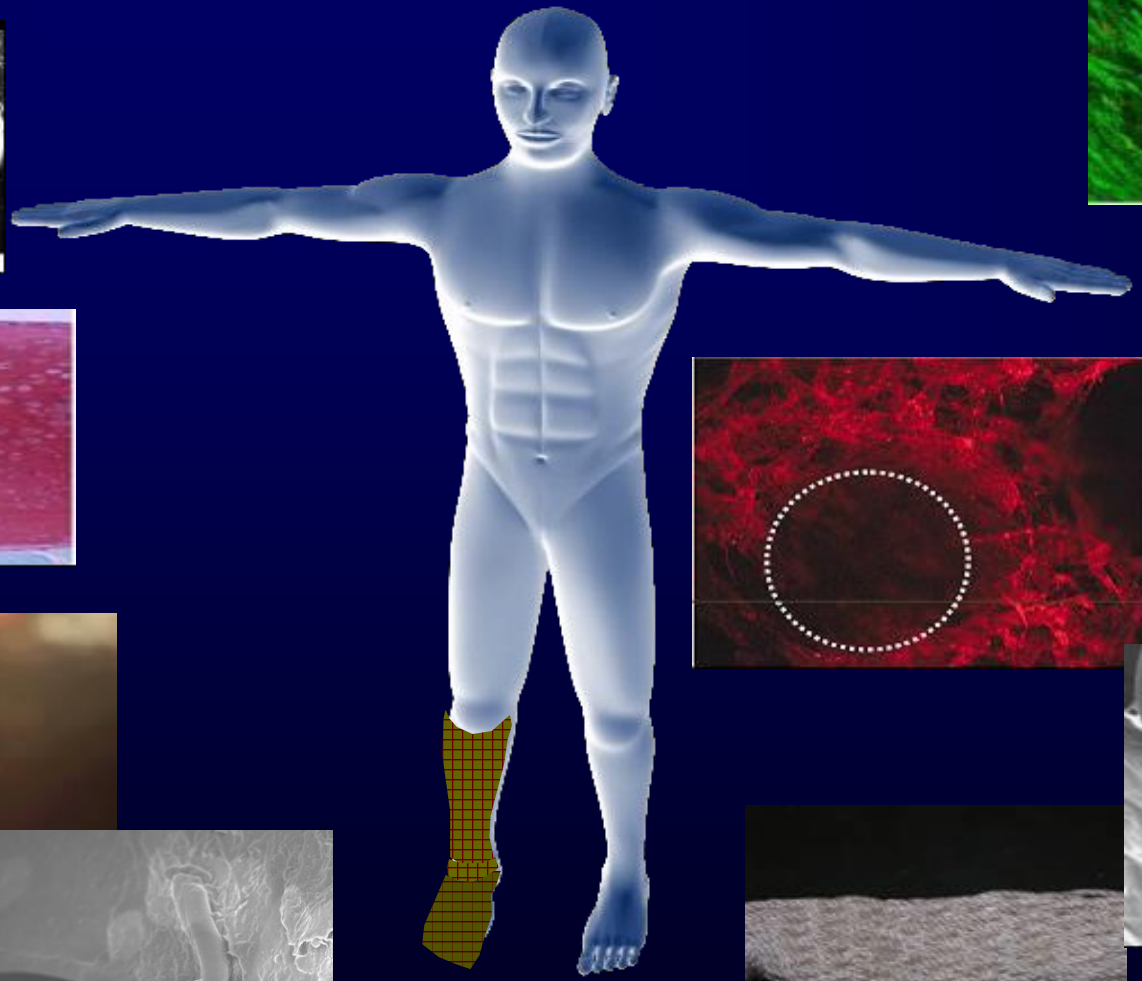
Cartilage

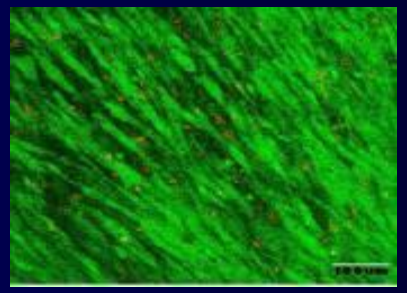
What's Next: Limb Regeneration

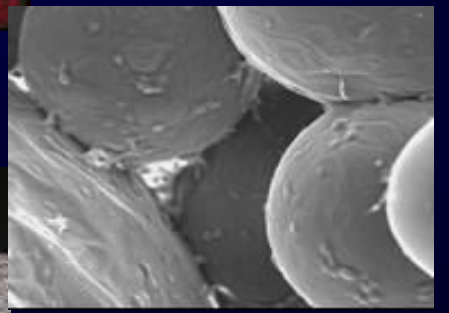












In 2017, **57.7 million people** were living with limb amputation due to traumatic causes worldwide.

Leading causes falls (36.2%), road injuries (15.7%), other transportation injuries (11.2%), and mechanical forces (10.4%).

*Global prevalence of traumatic non-fatal limb amputation

Prosthet Orthot Int 2021 Apr 1;45(2):105-114.

http://wnpr.org/post/hartford-ambitious-goal-regenerate-lost-limbs-humans#stream/0

Laurencin, Cato T. - Outlook W... | In Hartford, an Ambitious G...

In Hartford, an Ambitious Goal to Regenerate Lost Limbs in Humans

By PATRICK SKAHILL • 11 HOURS AGO

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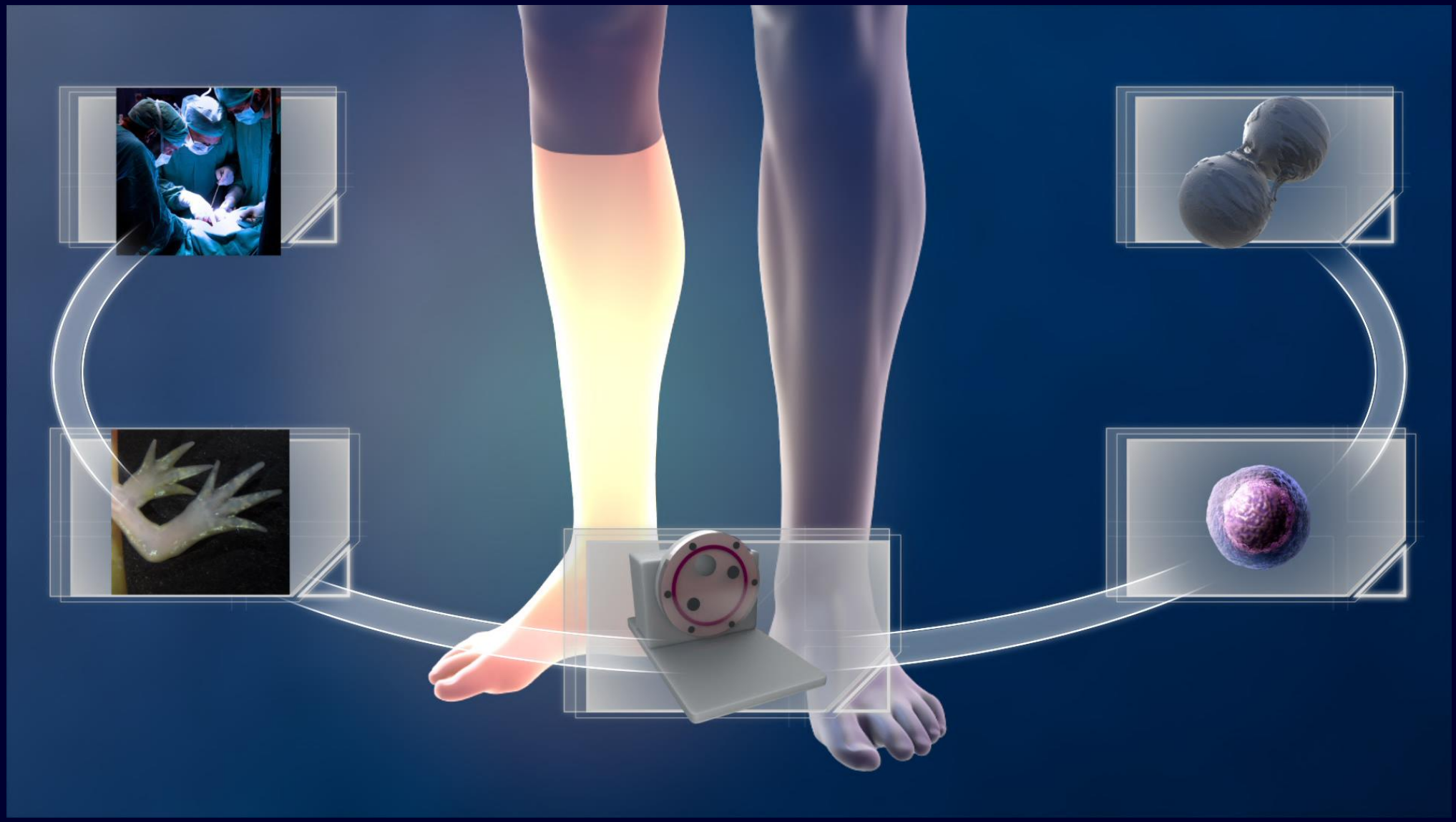
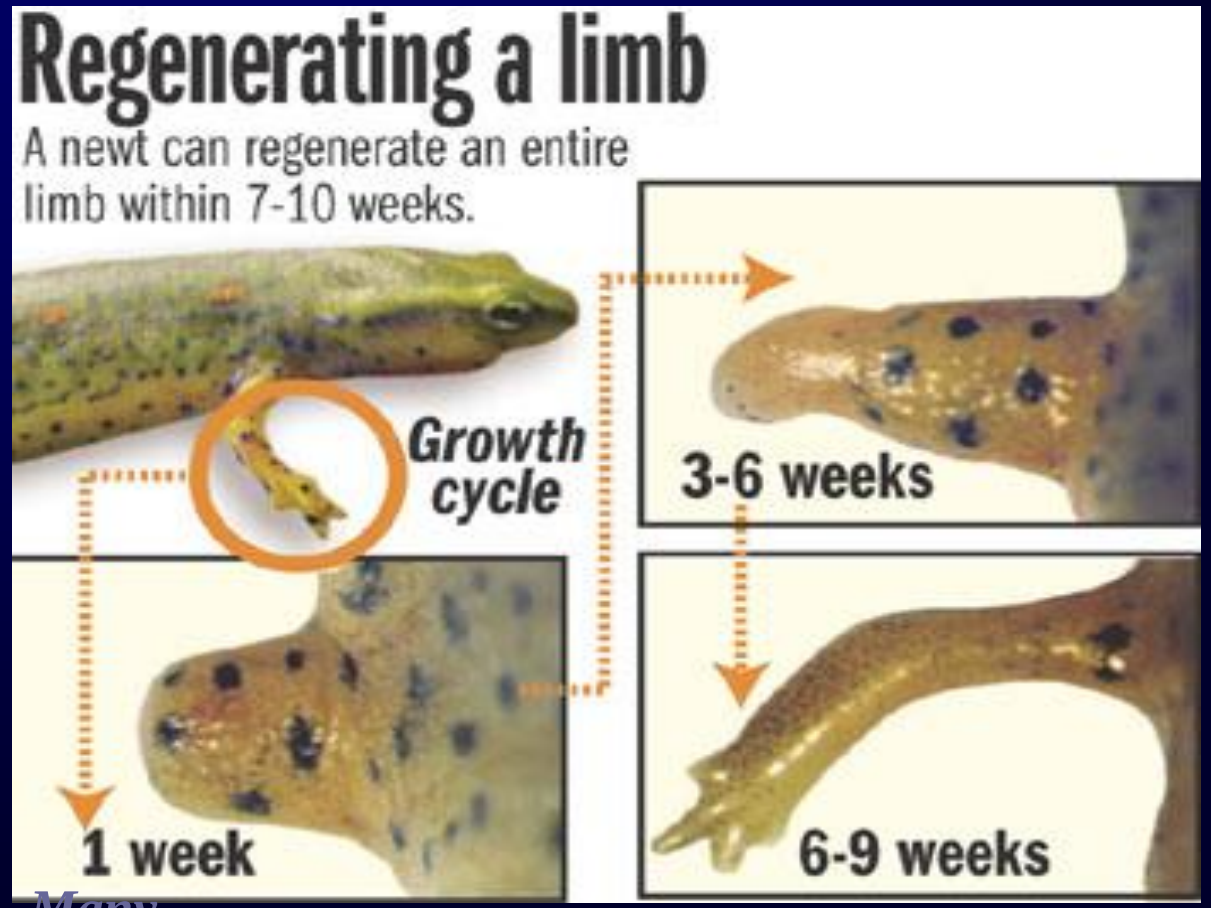
Hartford Engineering A Limb



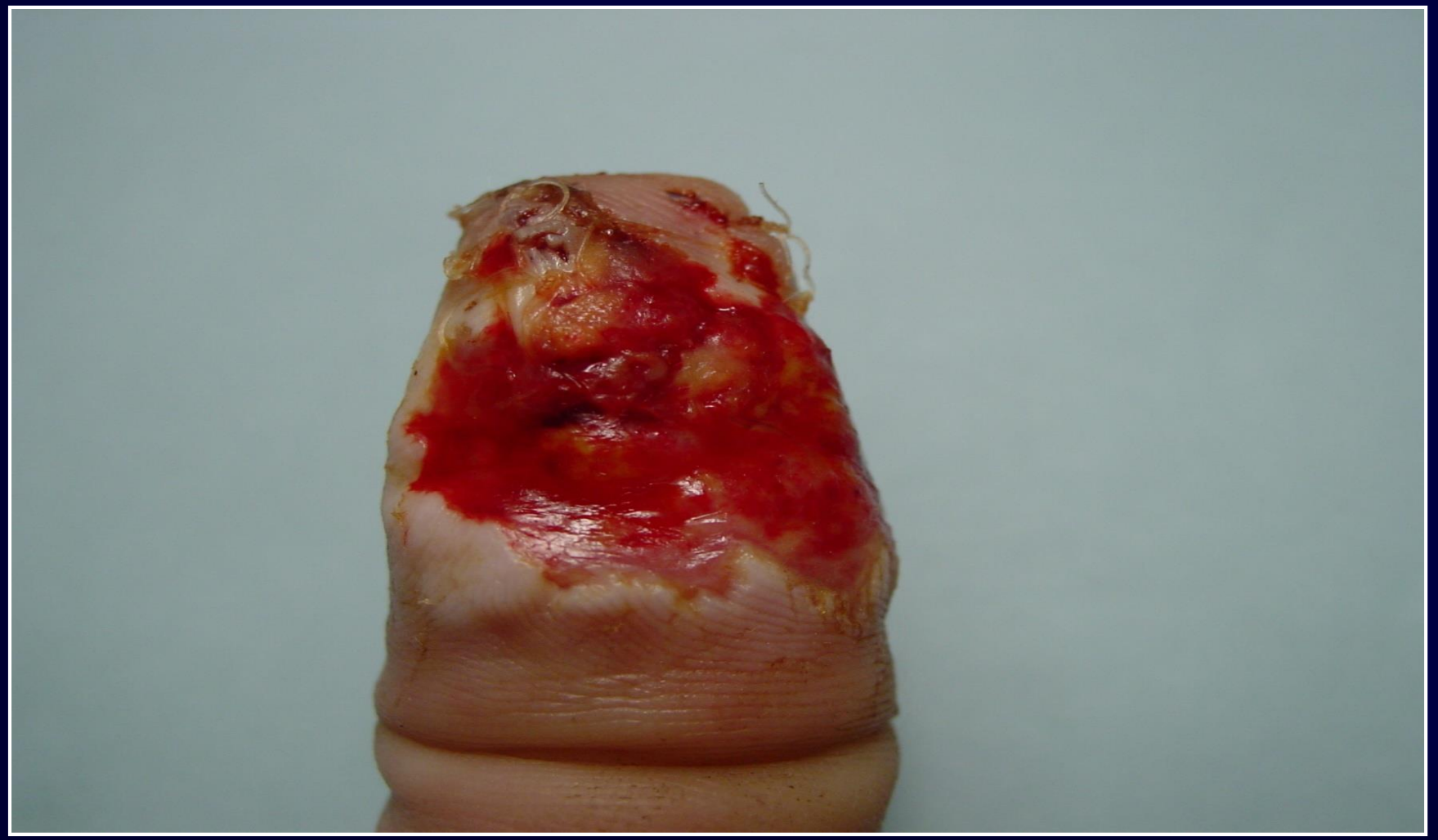
Convergence: Learning from Animals that Regenerate

- Bottom Up Approach
  - Tissues assembled from the cellular scale and up to produce fully intact tissue structures
- Blastema

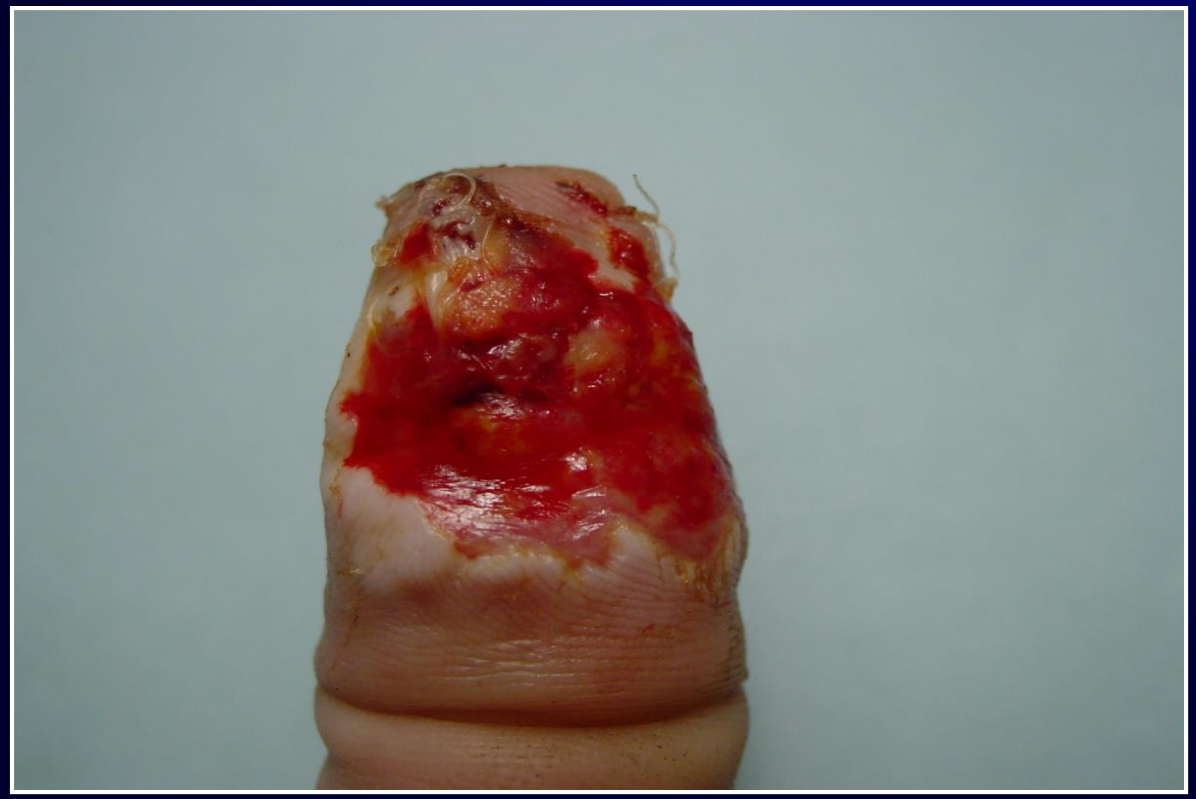


Translational Challenges –Many,

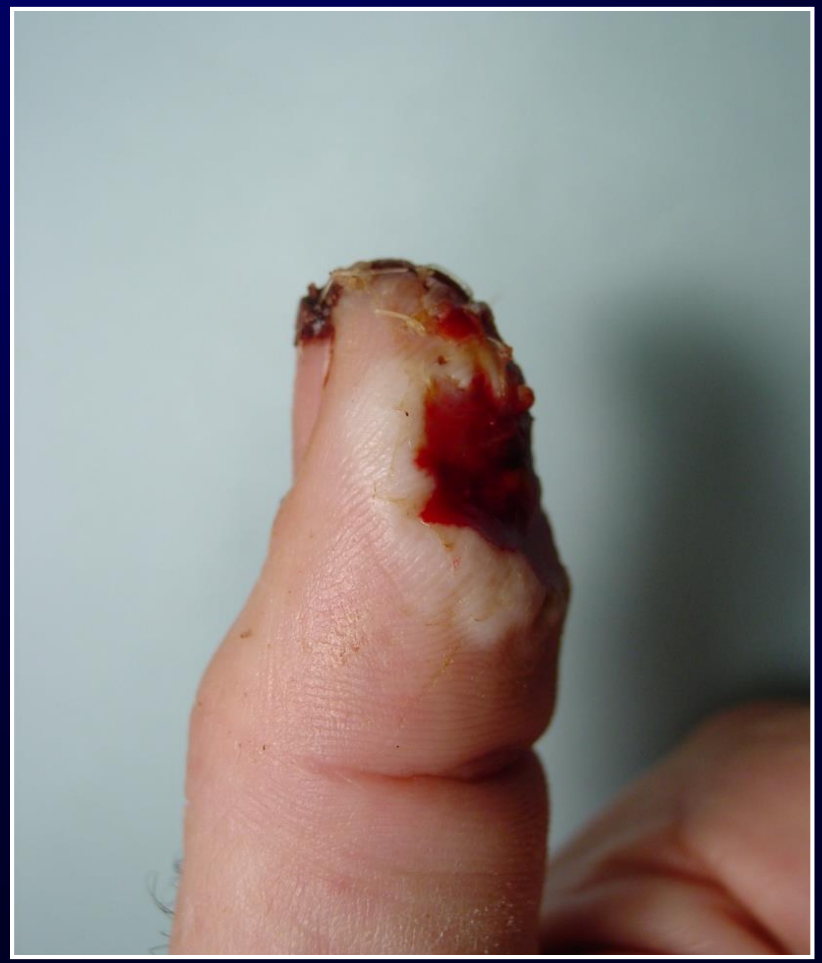
but must be part of the arsenal.



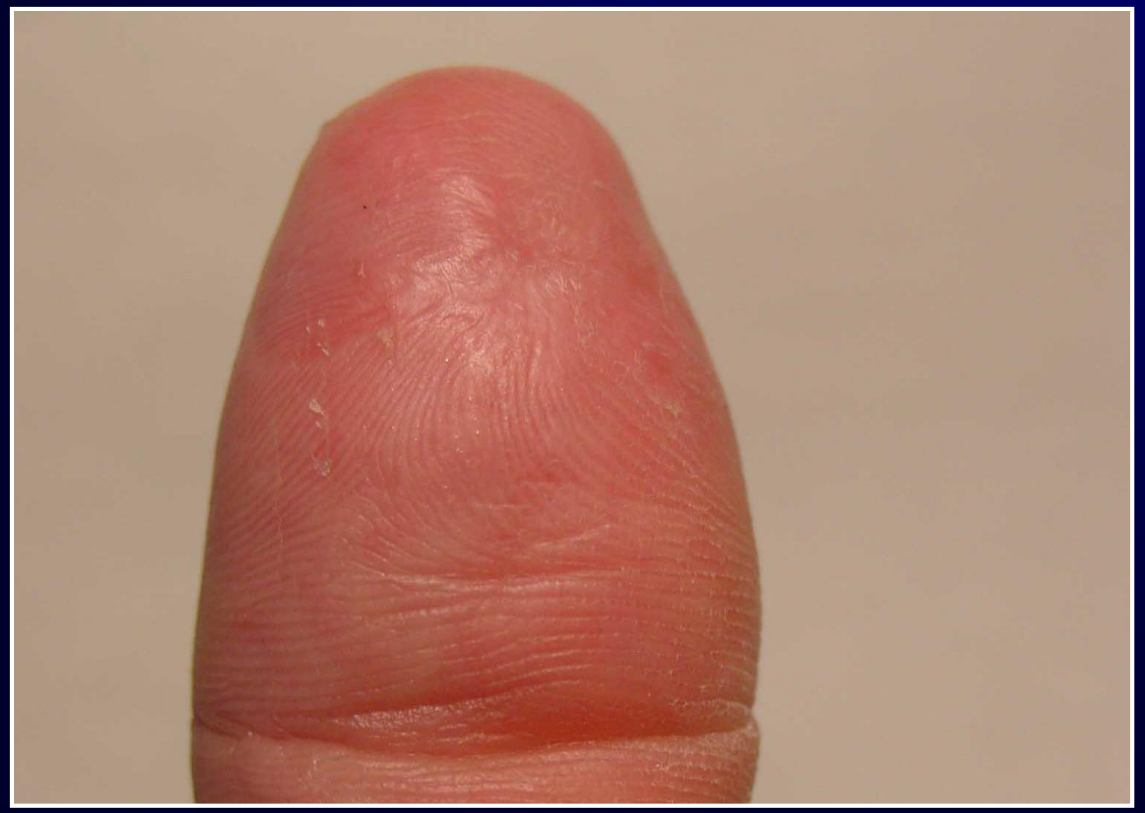
Non-operative Treatment



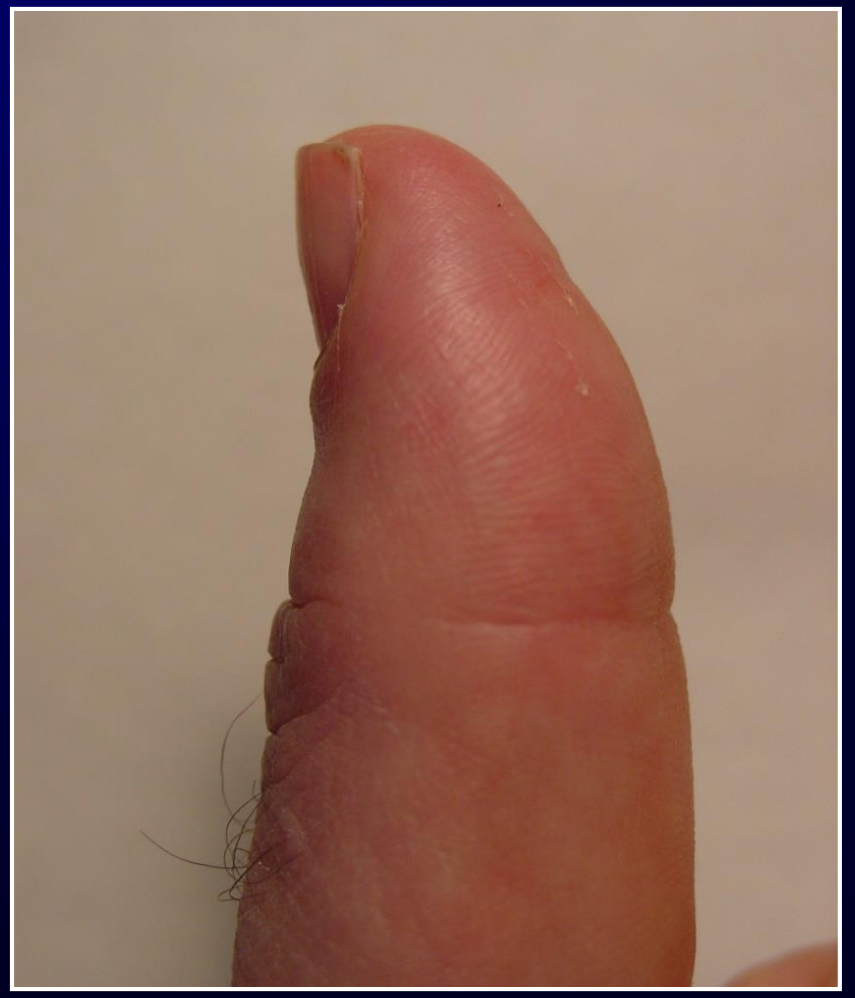
1 week post saw injury



Non-operative Treatment



8 weeks post saw injury

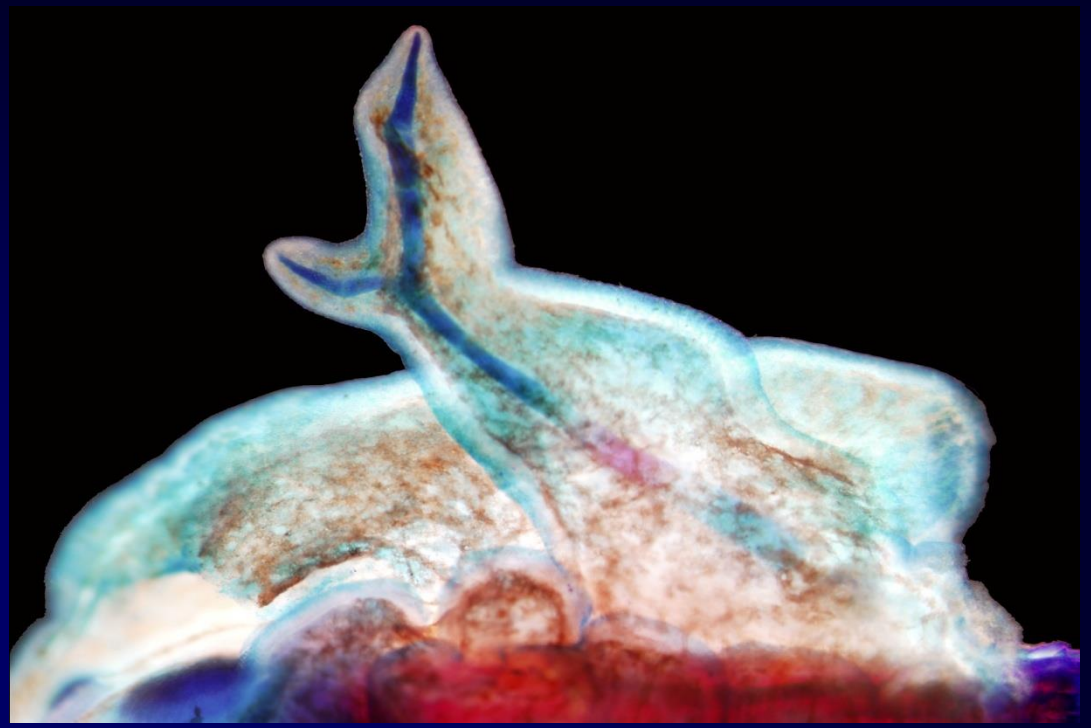


Regenerative Engineering: A New Therapeutic Strategy

- **Regenerative Engineering**
  - –Harnessing the ‘Newt in Us’

Cato T. Laurencin MD. Ph.D.

“We have made a “LIMB FROM SCRATCH” with PURFIED GROWTH FACTORS (FGSs and BMPs) combined with PURIFIED HSPG (heparan sulfate proteoglycan) from a mammal.”



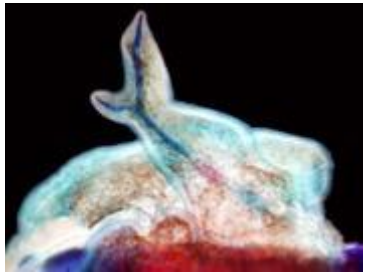
“just because you do not see a regenerative response does not mean that regeneration cannot happen”

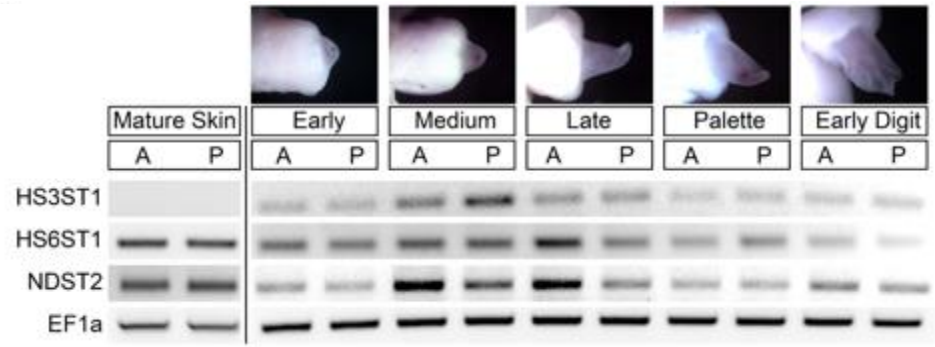
David Gardiner, Ph.D.

Heparan Sulfate (HS) may Hold a Key to Control Pattern Formation

- Heparan sulfate (HS) can bind to lots of morphogens and cytokines to mediate these signaling pathways e.g. FGFs, BMPs, Wnts, shh
- HS is a glycosaminoglycan (GAG) chain located cell surface and extra cellular matrix (ECM)

- HS can induce ectopic pattern formation in axolotl limb.
- Some sulfotransferases are differentially expressed in blastema

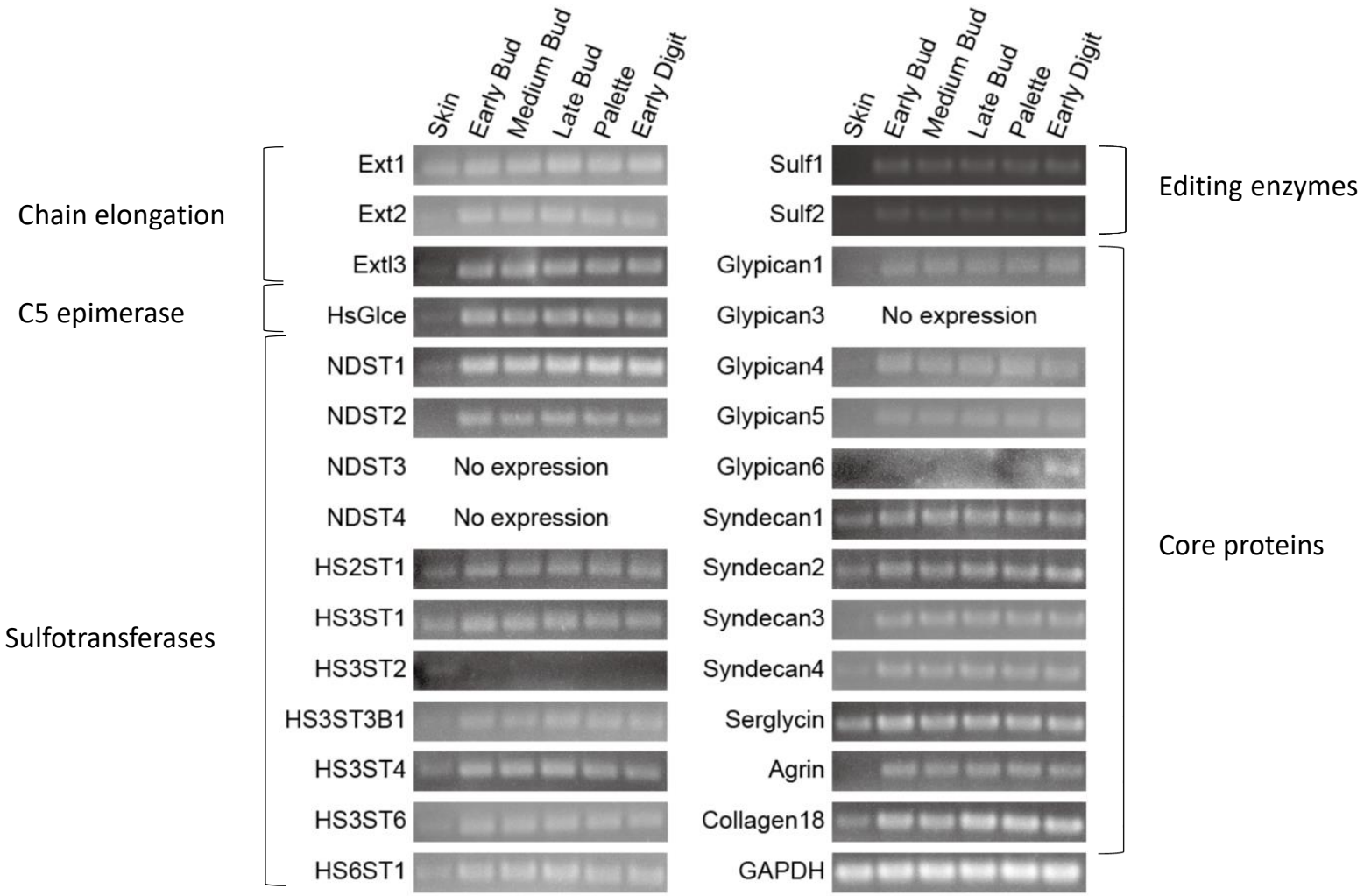




- Phan, A et al. Regeneration (2015)

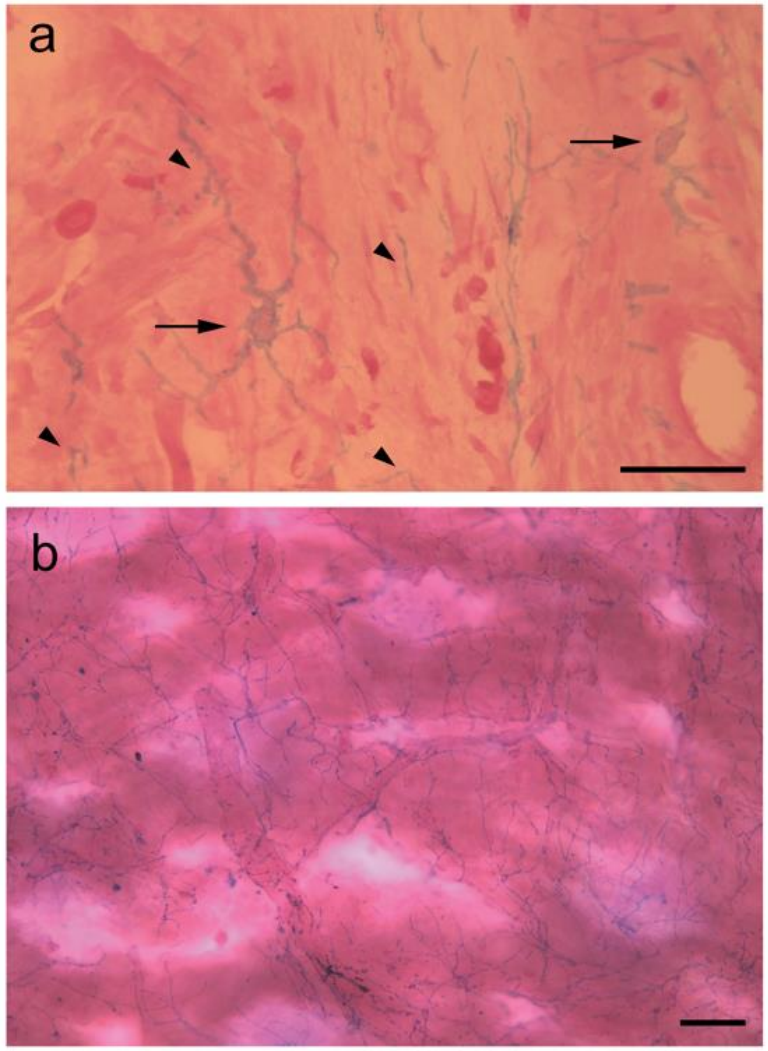
This project focused on the presence of pattern forming cells in limb.

Various HS-related Genes Upregulation during Limb Regeneration



- Laurencin, C. T. et al. Regen. Eng. Transl. Med. (2020)

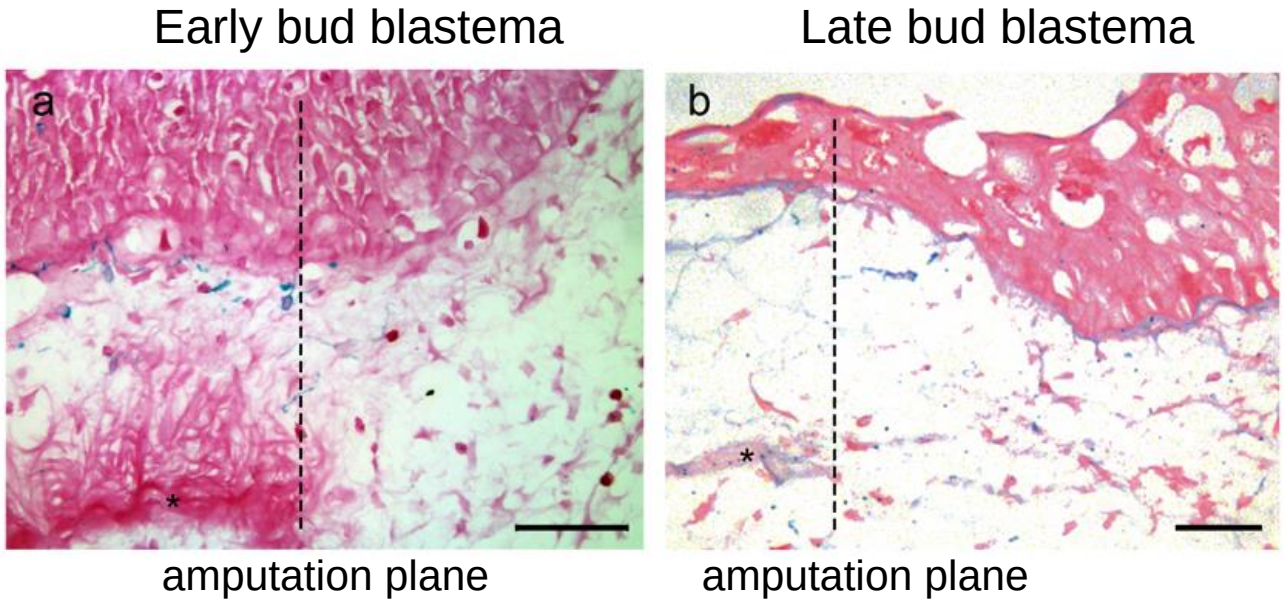
Identification of Pattern Forming HS-rich Cells in Axolotl Dermis



- HS-rich cells possessed multiple branching cell processes
- These cells were arranged in a grid and their multiple cellular processes overlapped with processes.
- We termed these cells as positional information GRID (Groups that are Regenerative, Interspersed and Dendritic) cells

- Laurencin, C. T. et al. Regen. Eng. Transl. Med. (2020)

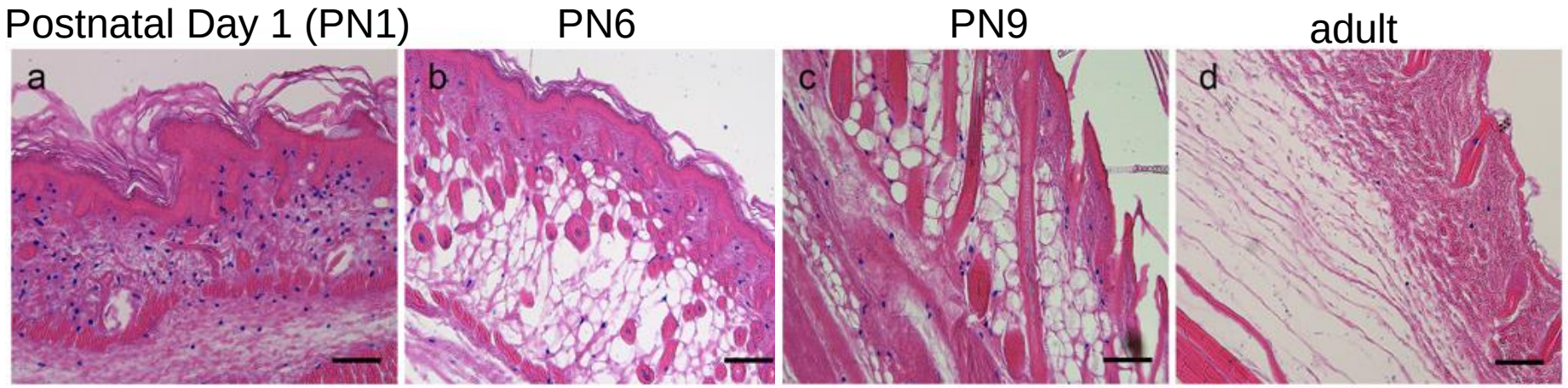
The Distribution of GRID cells during Regeneration



- Laurencin, C. T. et al. Regen. Eng. Transl. Med. (2020)

- GRID cells were not evident at the early stage of blastema formation distal to the amputation plane.
- At later stage of blastema, GRID cells reappeared distal to the amputation plane, but not distal tip.

Abundance of Mammalian GRID Cells in Neonatal Mice Skin



- Laurencin, C. T. et al. Regen. Eng. Transl. Med. (2020)

- GRID cells were also identified in mouse limb skin.
- The abundance of GRID cells change ontogenetically.

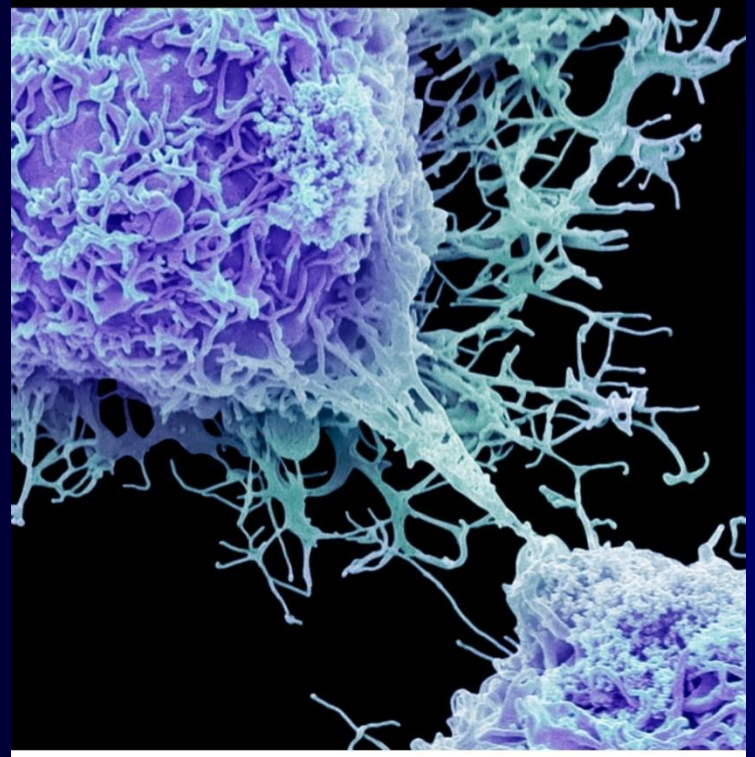
Summary

- The unique cell population was identified in both axolotls and mice
  - The cells have stellate morphology with long projection and show network (axolotl).
  - The cells show ontogenetical decrease after birth (mice).

- GRID cells are candidate for pattern forming cells.
  - Further characterization (such as gene expression profile) will be required.
  - The investigation of mouse GRID cells during limb development will provide further understanding.

- GRID cells hold a potential to provide positional information and enhance regeneration in mammals.

AMERICAN Scientist



Fixing Joints That Appear Beyond Repair

BY CATO THOMAS LAURENCIN, DEBOLINA GHOSH

AMERICAN Scientist

Fixing Joints That Appear Beyond Repair

BY CATO THOMAS LAURENCIN, DEBOLINA GHOSH

A lunchtime sketch of an engineered ligament helped launch a revolution in sports medicine.

MEDICINE · TECHNOLOGY

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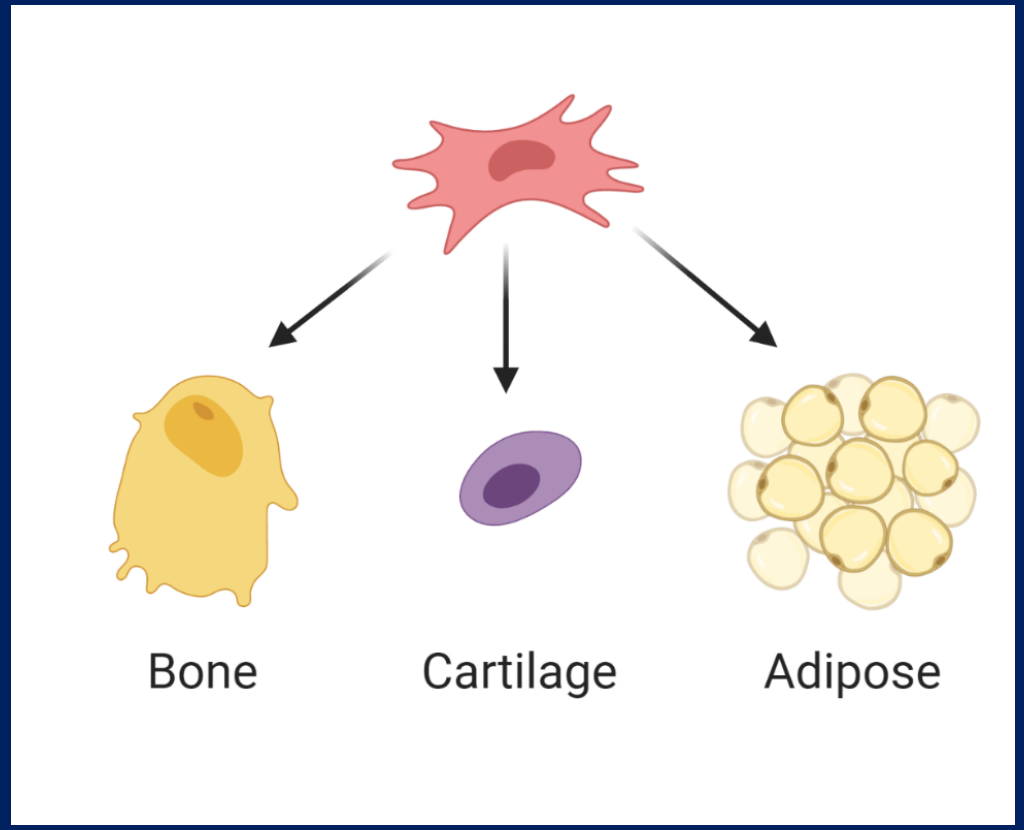
The Synthetic Artificial Stem Cell:

A New Paradigm for Regenerative Engineering

SASC

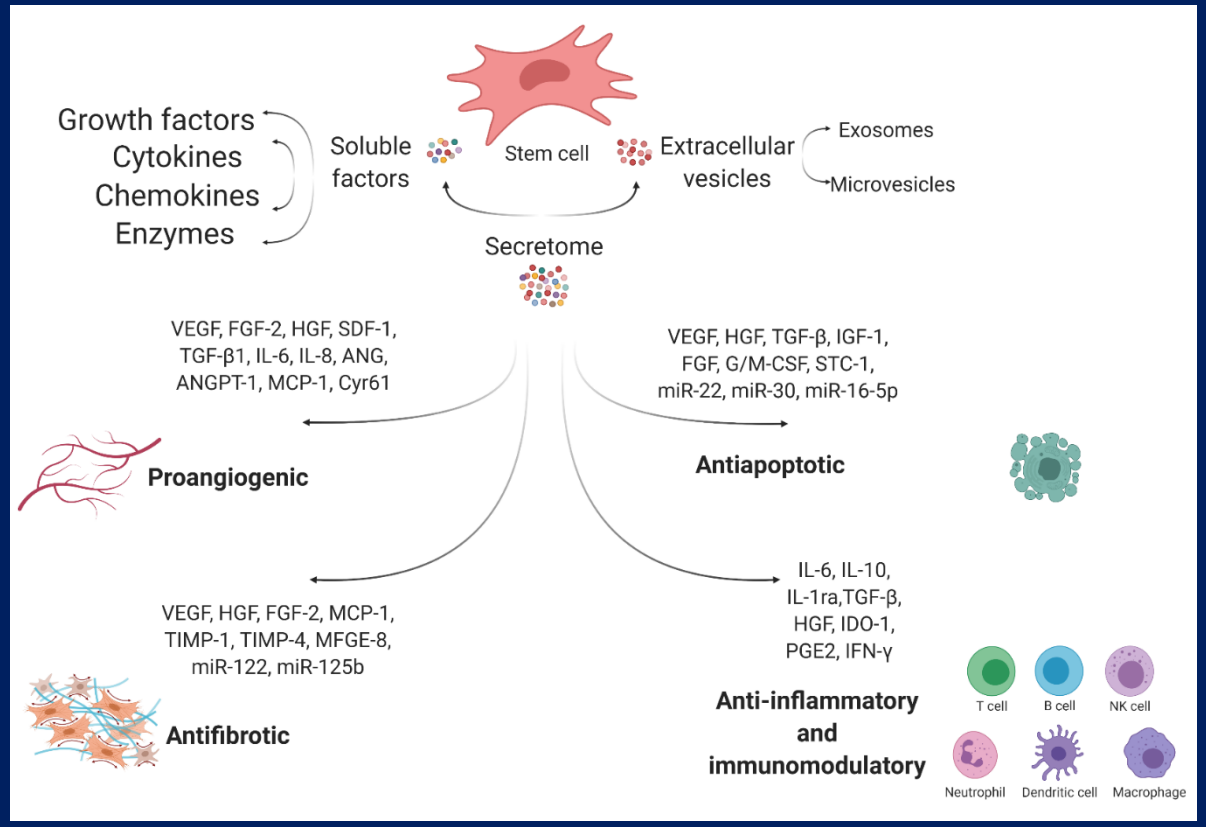
Stem Cells as Drivers for Regeneration

1. Multipotent Differentiation to Repair Injured Tissue



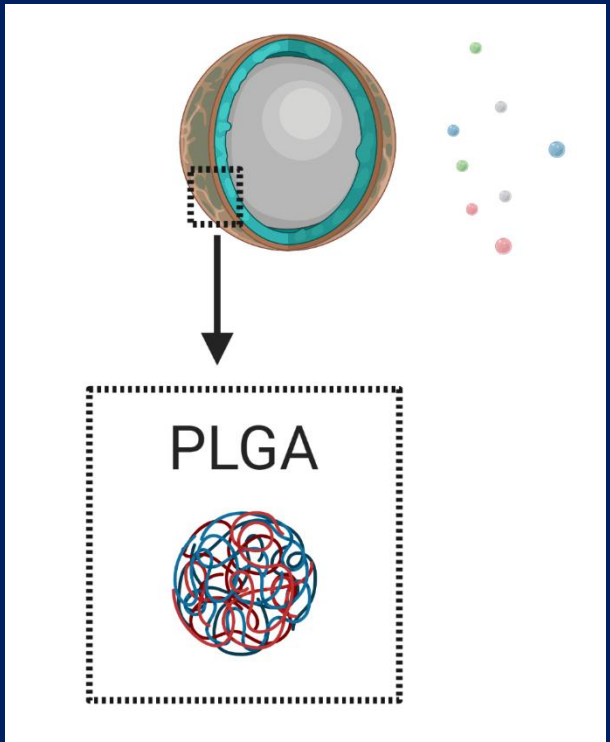
Stem Cells as Drivers for Regeneration

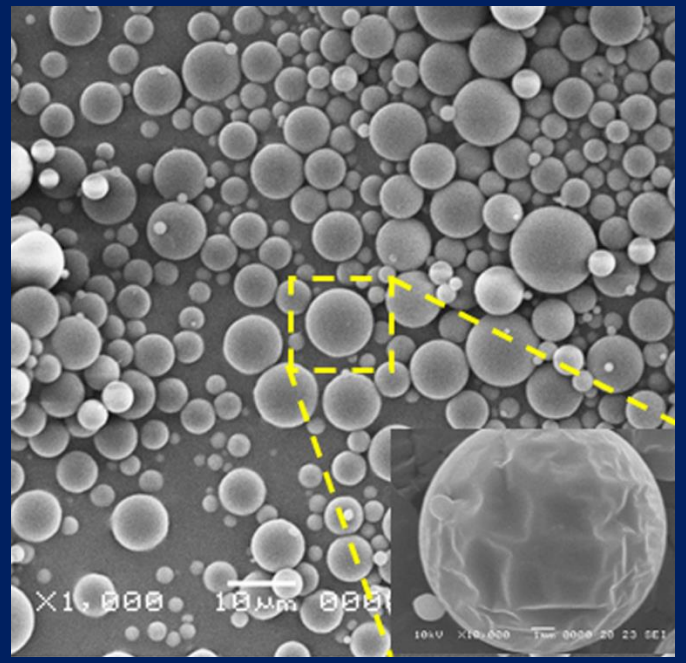
2. Release of biological factors (**The Secretome**) to signal tissue repair



Can we channel these paracrine factors into a tailored and translatable regenerative technology?

The Synthetic Artificial Stem Cell (SASC)





- Paracrine effect
- Tailored composition
- Controlled, targeted therapy

Looks like and acts like a stem cell.

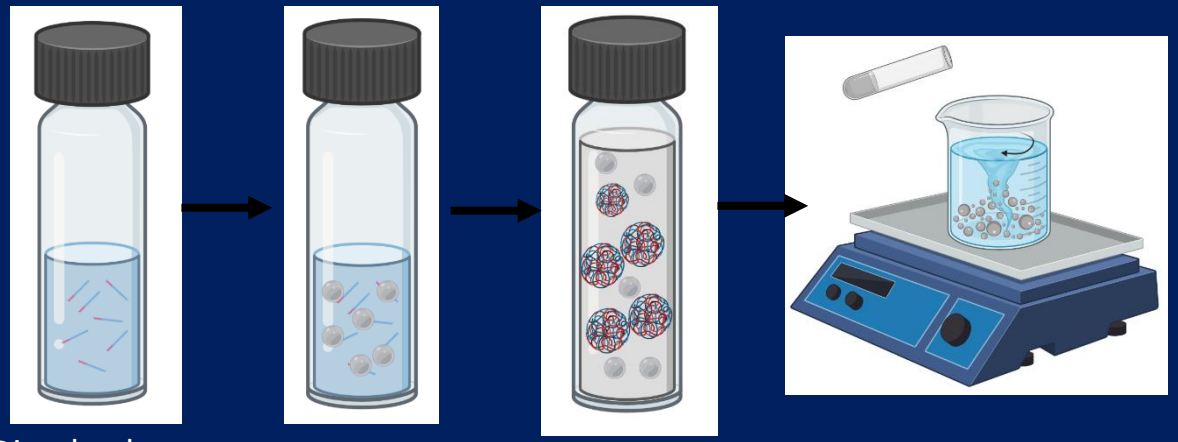
Osteoarthritis (OA) Treatment

A Tailored Composition to Target OA: A Systematic look in the Literature

Insulin-Like Growth Factor 1 (IGF-1) • Stimulates proteoglycan production • Decrease Matrix Catabolism	**Transforming Growth Factor β1 (TGF-β1)** • Stimulates ECM synthesis • Decreases catabolic activity of IL-1 and MMPs • Additive effect with IGF-1
Human Growth Hormone (HGH) • Stimulates native stem cell proliferation • Indirect anabolic effect by IGF-1 signaling	**Fibroblast Growth Factor 18 (FGF-18)** • Increases chondrocyte proliferation • Selectively stimulates ECM in injured joints

A Modular Approach to Formulate SASC

Load each factor into microsphere using double emulsion method



Dissolved Polymer PLGA 85:15

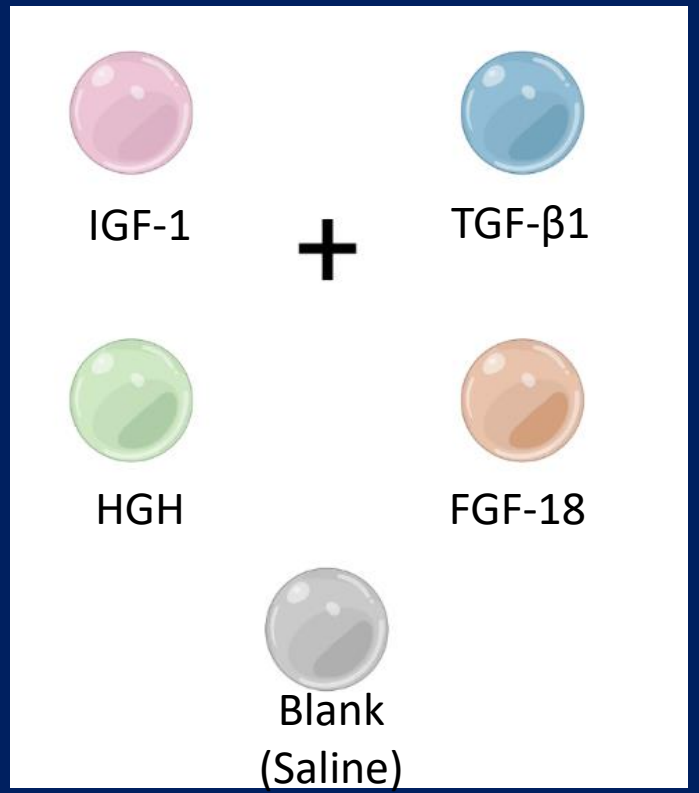
Primary Emulsion

Secondary Emulsion

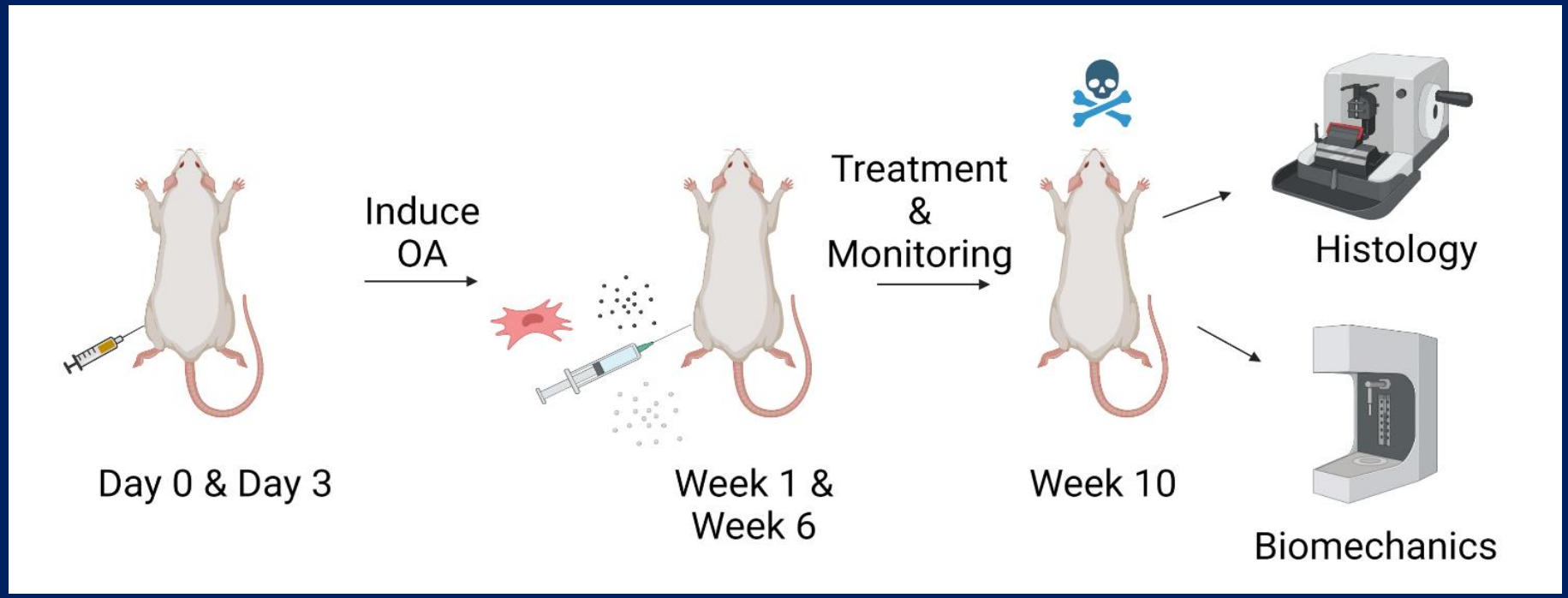
Solvent Evaporation

0.01 µg growth factor / mg Polymer

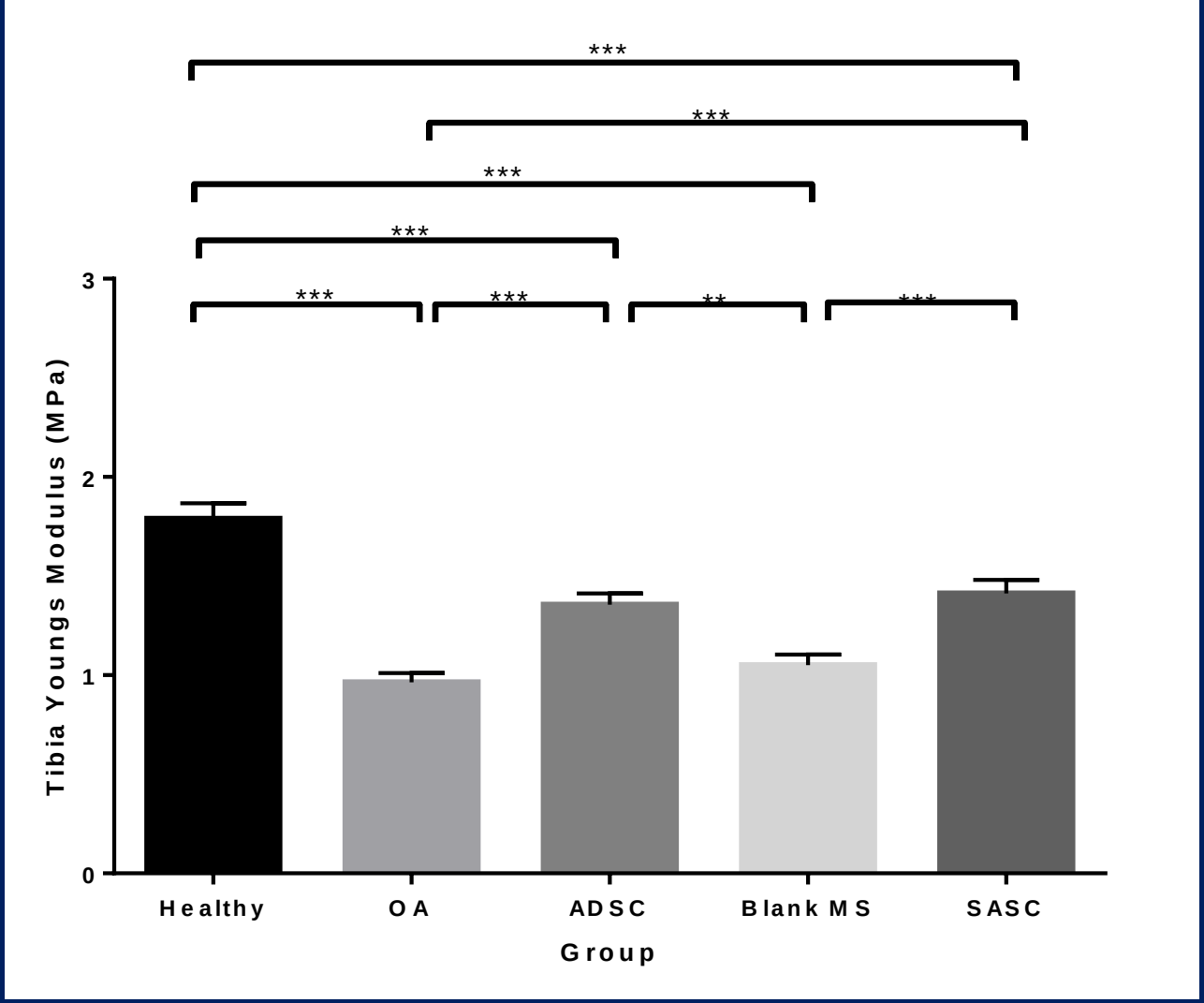
Mix batches in equal weight %



In Vivo Collagenase Induced OA Model



SASC Recovers Tibia Young's Modulus

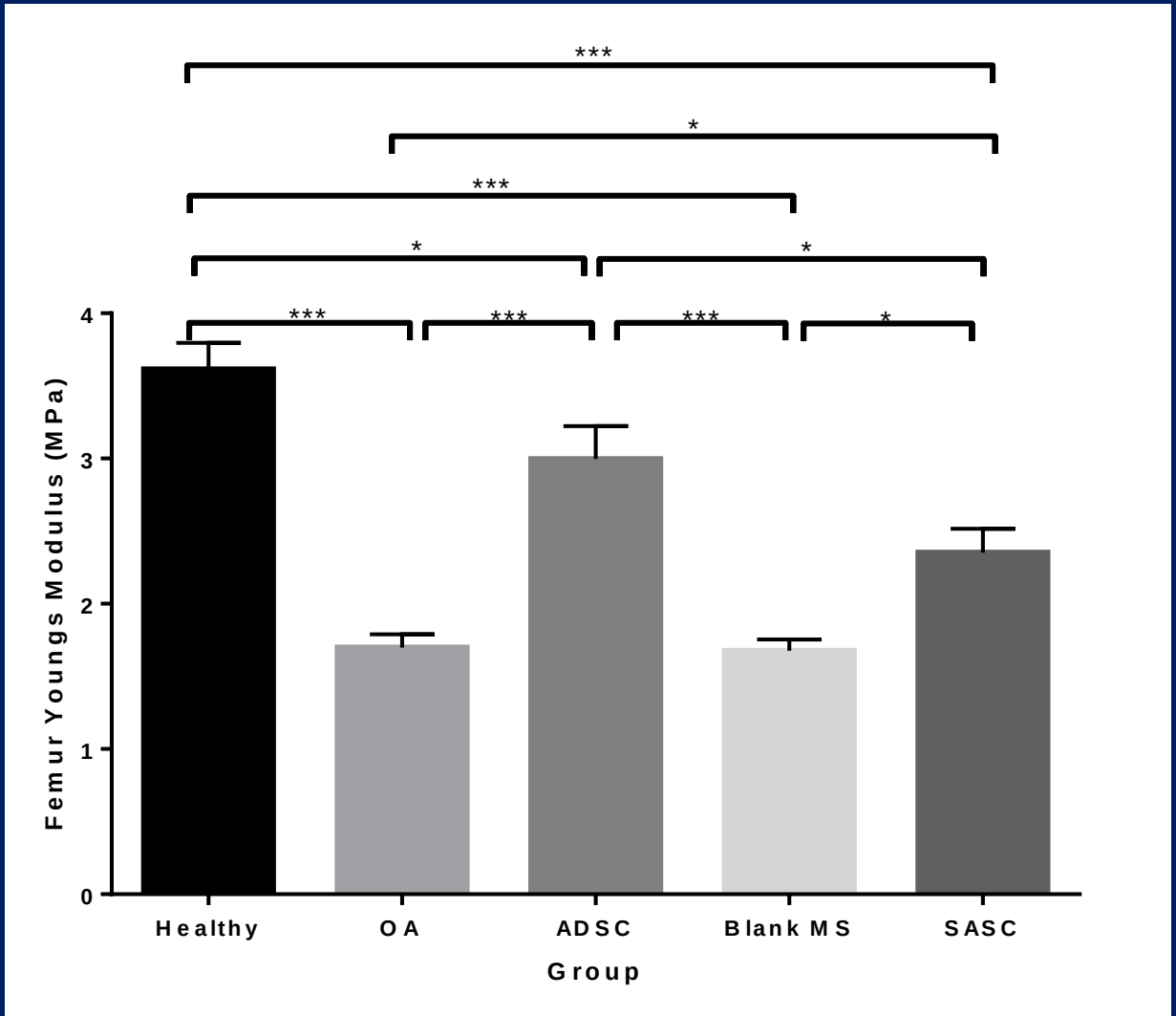


After 9 Week Treatment

- ADSC and SASC recover modulus ($p<0.001$)
- Neither SASC nor ADSC recover to a fully healthy modulus ($p<0.001$)
- SASC and ADSC have similar modulus

* $p<0.05$
** $p<0.01$
*** $p<0.001$
**** $p<0.0001$

SASC Recovers Femur Young's Modulus

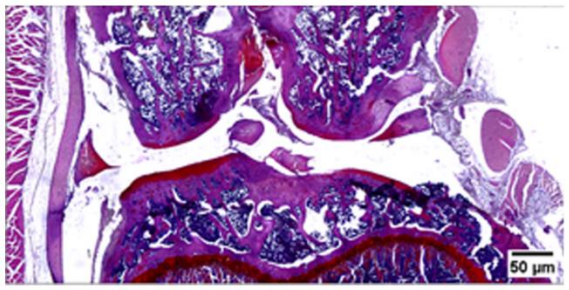


After 9 Week Treatment

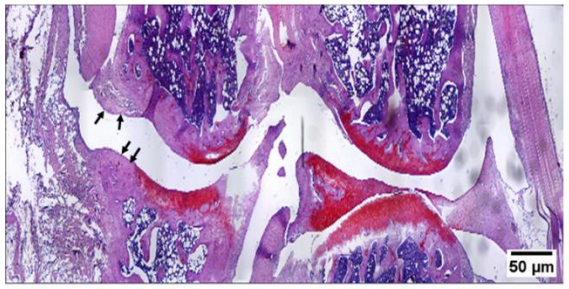
- ADSC and SASC recover modulus ($p<0.001$)
- Neither SASC nor ADSC recover to a fully healthy modulus ($p<0.001$ and $p<0.05$ respectively)
- ADSCs modulus higher than SASC ($p<0.05$)

* $p<0.05$
** $p<0.01$
*** $p<0.001$
**** $p<0.0001$

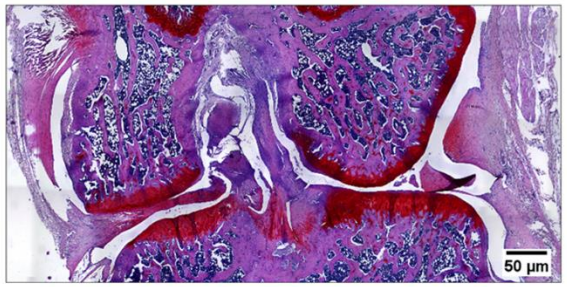
SASC Cells Regenerate Knee Joint Cartilage



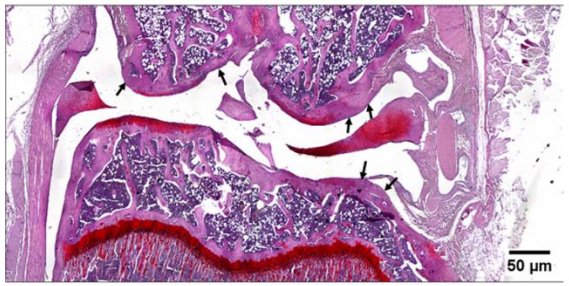
Healthy



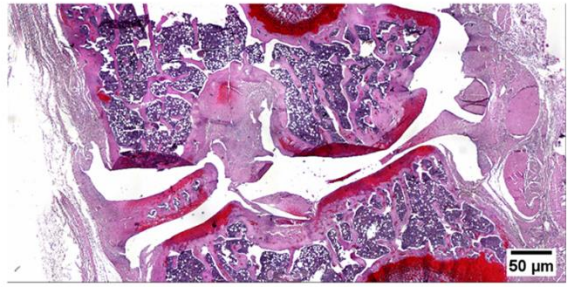
OA



ADSC



Blank Microspheres



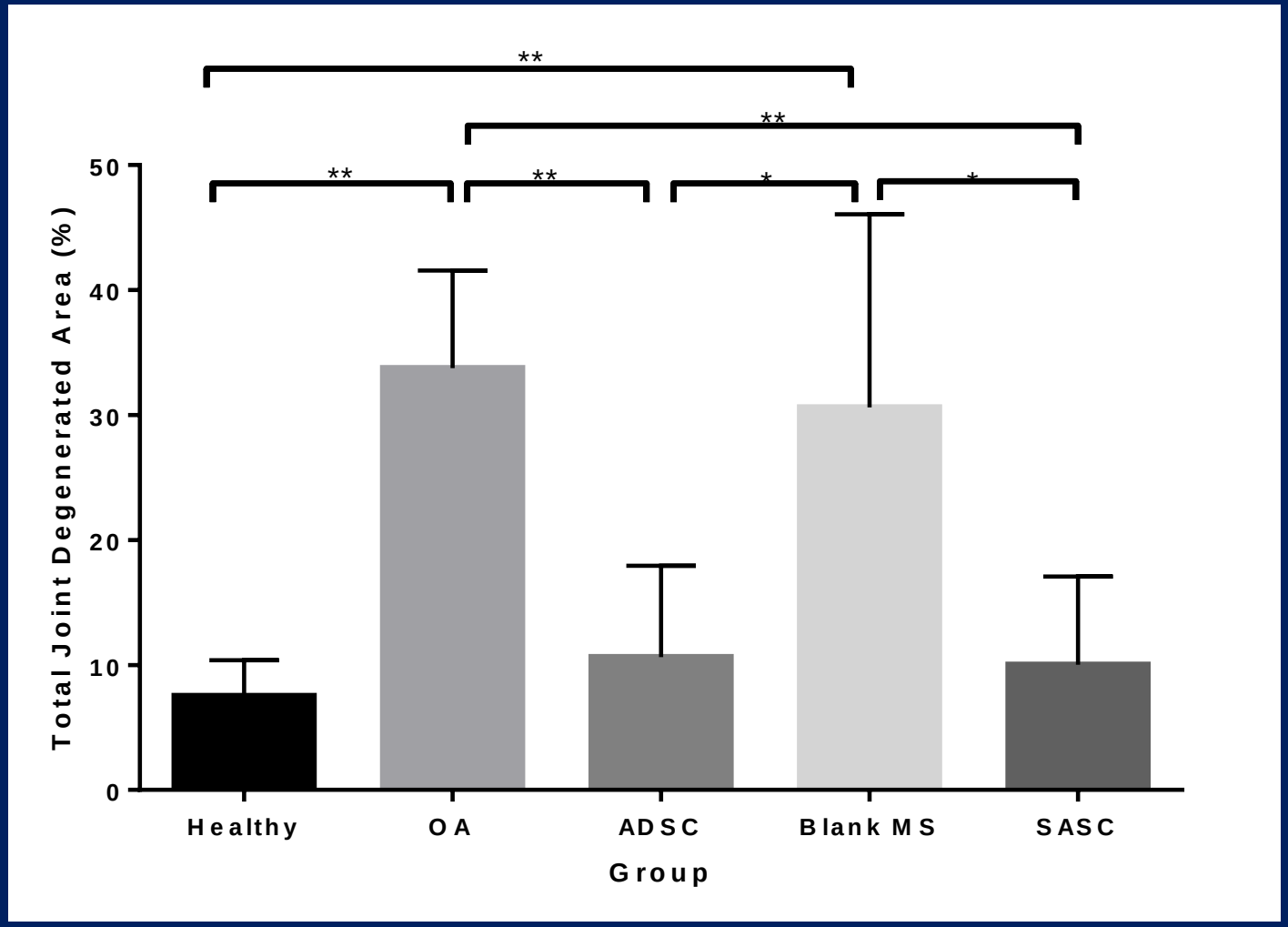
SASC

- Frontal Sections
- Staining on 4 articular surfaces (Medial and Lateral Surfaces of each bone) indicate healthy cartilage
- Arrows point to areas of degeneration. No staining

- Image analysis software (ImageJ) used to quantify Total articular surface area and degenerated surface area (area where no red staining visible)

$$\%\ Degeneration = \frac{\sum Degenerated\ Areas}{\sum Theoretical\ Healthy\ Articular\ Surface\ Area} * 100$$

SASC Regenerates Knee Joint Cartilage



After 9 Week Treatment

- ADSC and SASC similar to Healthy ($p<0.01$)
- OA and Blank have significant degeneration

n=5

* $p<0.05$

** $p<0.01$

*** $p<0.001$

**** $p<0.0001$

Conclusions

- SASC has comparable anti-inflammatory and chondroprotective effects to ADSC
- SASC and ADSC recovered biomechanical properties to similar extent
- SASC successfully stopped OA mediated cartilage degeneration and regenerated the joint.

Synthetic Artificial Stem Cells (SASC): A new dimension in stem cell therapy: the ability to tailor the paracrine response to a targeted tissue.

PNAS Proceedings of the National Academy of Sciences of the United States of America

The synthetic artificial stem cell (SASC): Shifting the paradigm of cell therapy in regenerative engineering

Shiv Shah[a,b,c], Caldon Jayson Esdaille[a,b], Maumita Bhattacharjee[a,b], Ho-Man Kan[a,b], and Cato T. Laurencin[a,b,c,d,e,f,g,h,1]

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Regenerative Engineering

A Convergence Discipline Focused on Humans Throughout the World


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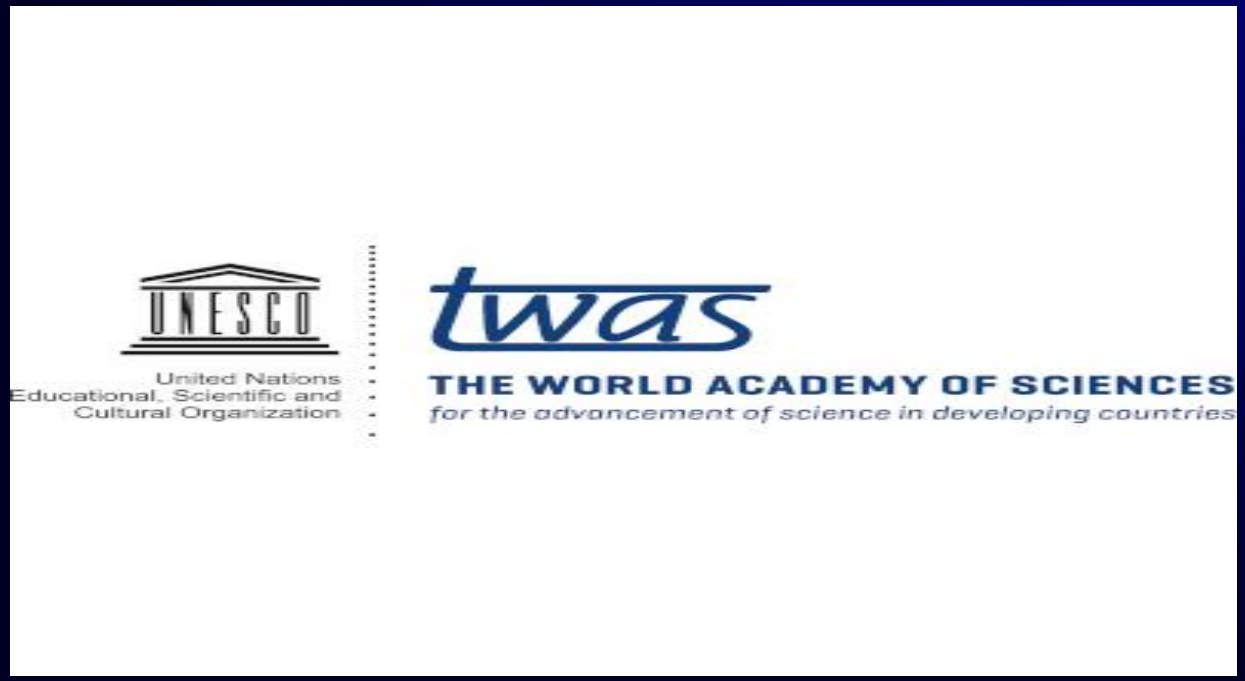
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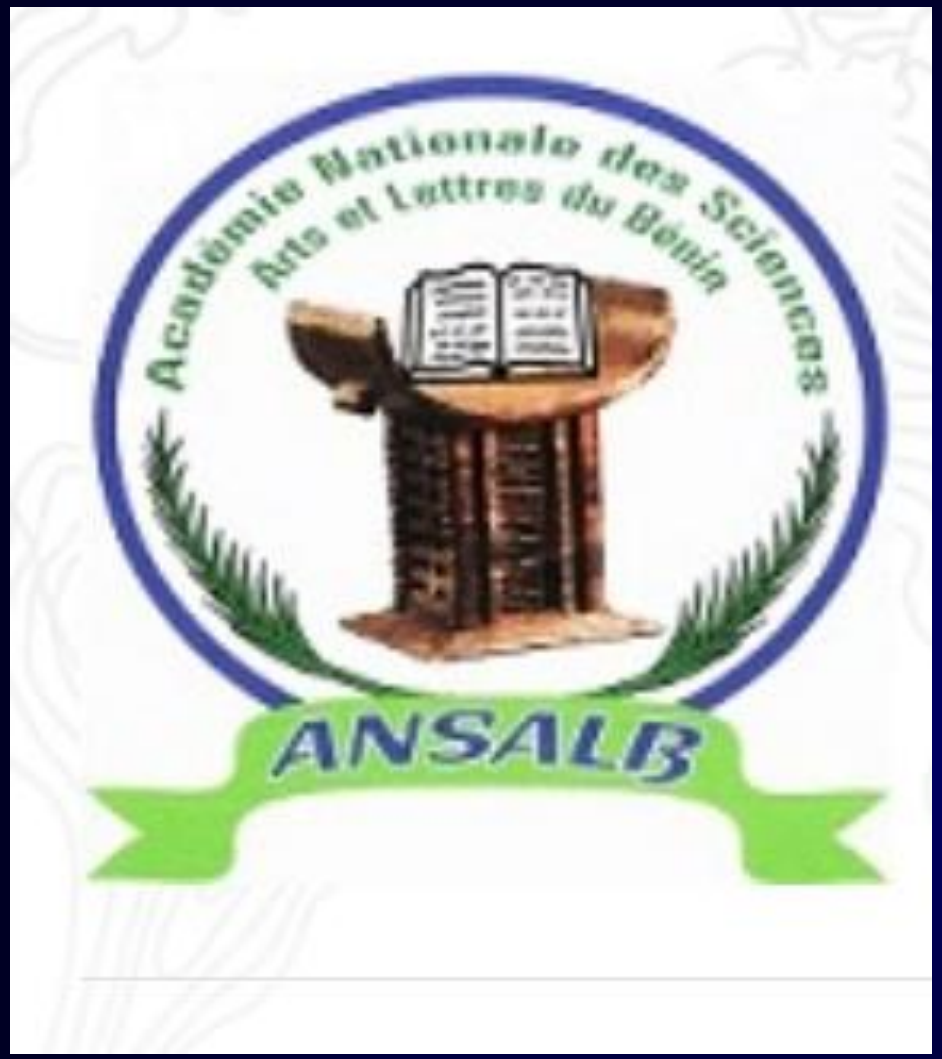

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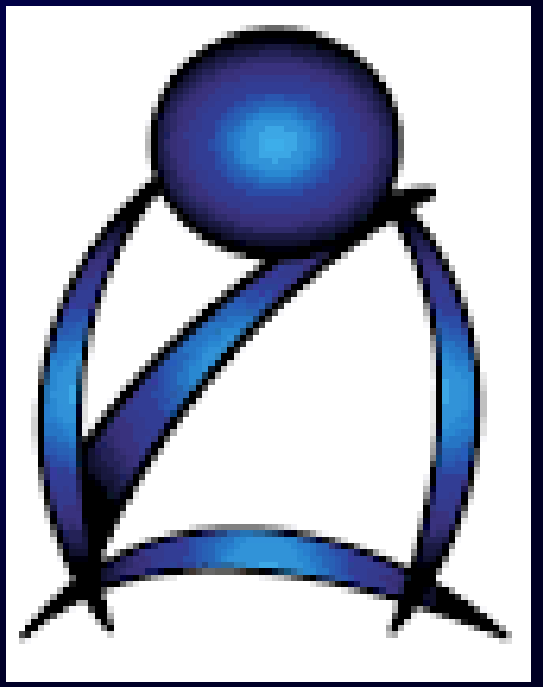

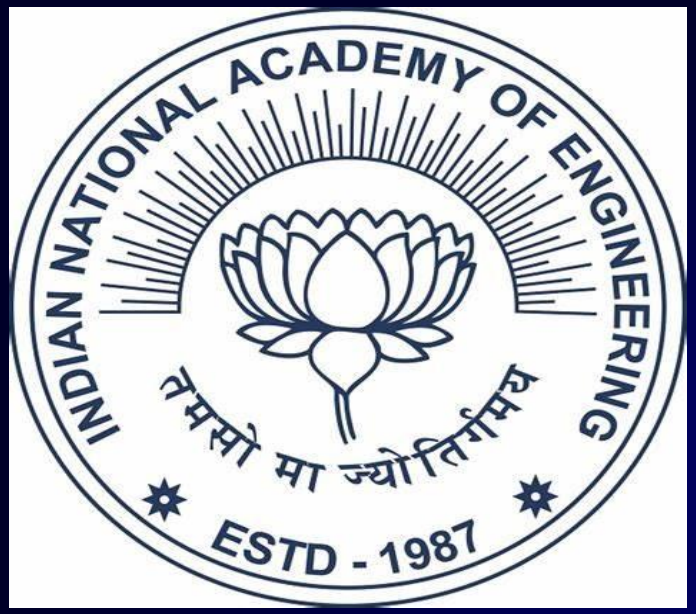
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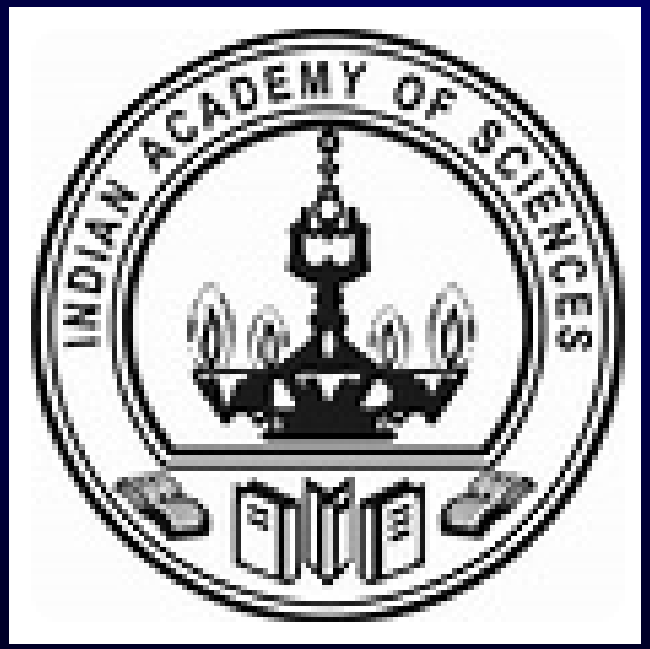
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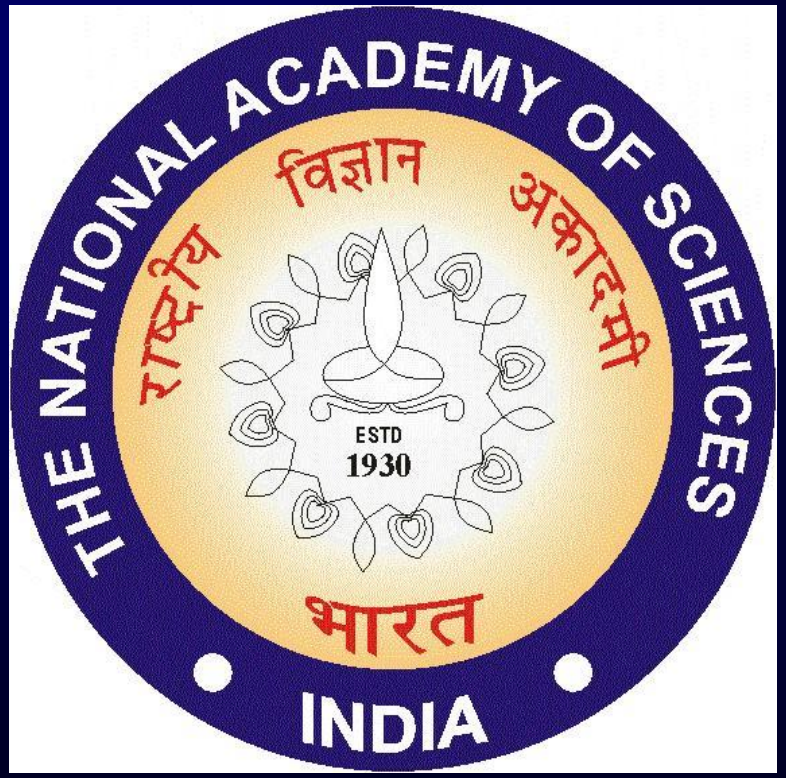
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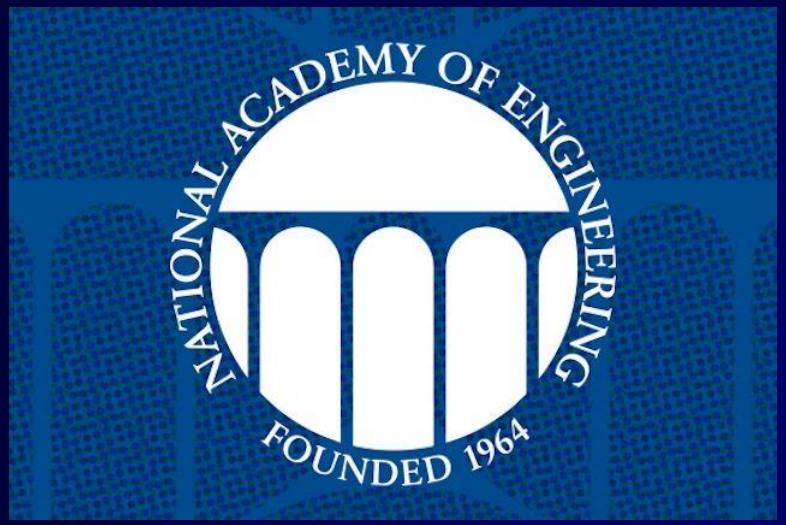
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