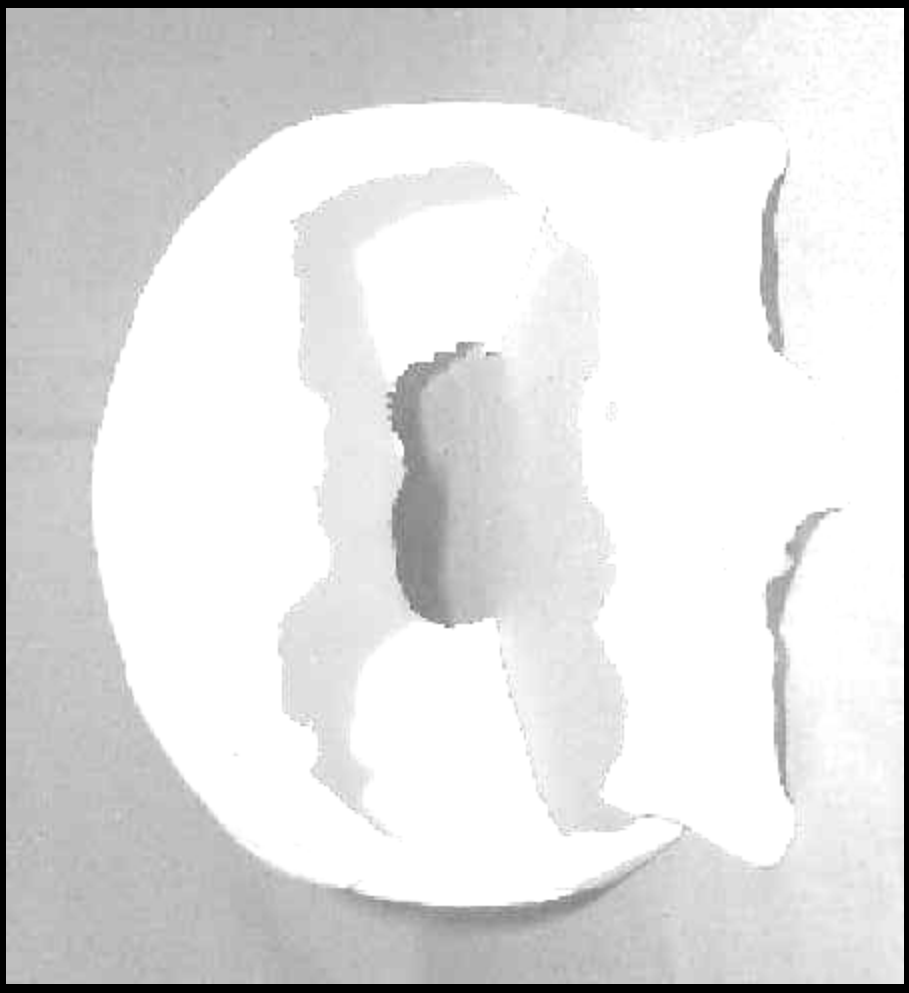
Nanosystems in regenerative medicine

Jöns Hilborn
Materials Chemistry
The Ångström Laboratory
Uppsala University
Sweden



Outline

- Motivation for tissue regeneration
- Cell based approaches
- Material based approaches

Drug Biologic Device

• Drug (21 USC 201(g)) - Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and…to affect the structure or any function of the body of man or other animals

• Biologic (42 USC 351(i)) - Virus, Therapeutic Serum, Toxin or Antitoxin, Vaccine, Blood, Blood Component or Derivative, Allergenic Product , Protein (except any chemically synthesized polypeptide), or Analogous Product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings

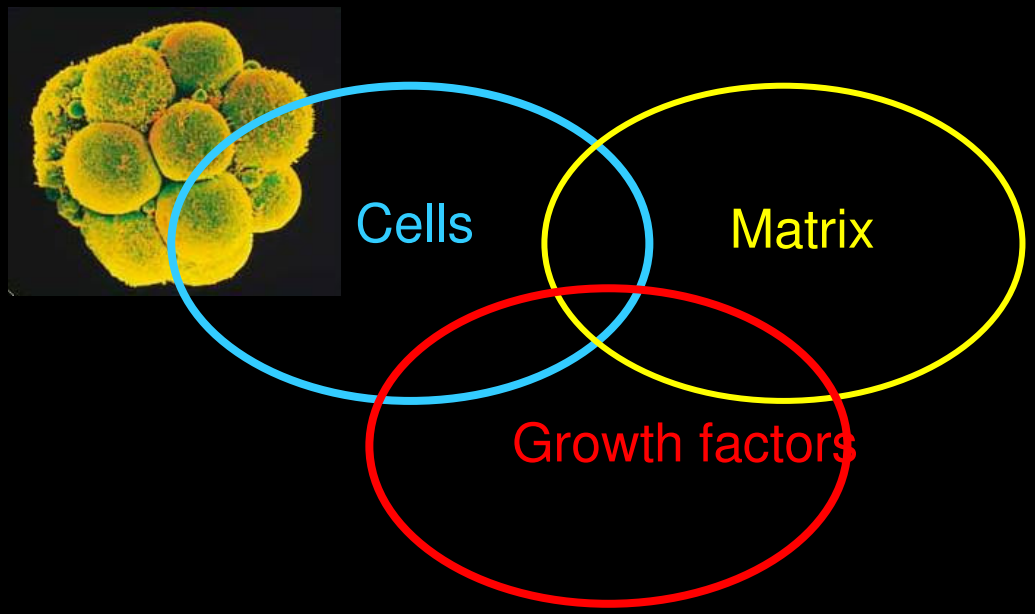
• Device (21 USC 201(h)) - An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article which is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or… to affect the structure or any function of the body of man or other animals; And does not achieve its primary intended purposes through chemical action within or on the body of man and is not dependent on being metabolized to achieve its primary intended purposes

Pharma's Developing Interest in Stem Cells

Clinical Phase[a]	Cell-Based Therapies	Company-Sponsored Therapies	Proportion of Company-Sponsored Therapies (%)	Large Company-Sponsored Therapies
Phase I	38	35	92	0
Phase II	24	22	92	3 (Teva, Baxter, Genzyme)
Phase III	6	5	83	0
Total	68	62	91	3 (5%)
Disease-Specific View[b]				
Disease	Trials	Company Sponsored Trials	Proportion of Company Sponsored trials (%)	Large Companies
Cardiac Disease	117	24	20	1 (Baxter)
Autoimmune Disorders	60	6	10	1 (Genzyme)
Endocrine/Metabolic	43	11	26	1 (Genzyme)
CNS	43	7	16	0
Total	263	48	18%	1%

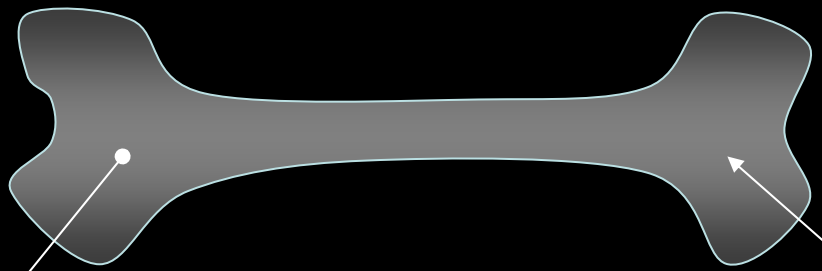
Cell Stem Cell, Volume 6, Issue 6, 4 June 2010, Pages 517-520

The three components



Challenges: Scar formation & vascularization

Traditional approach

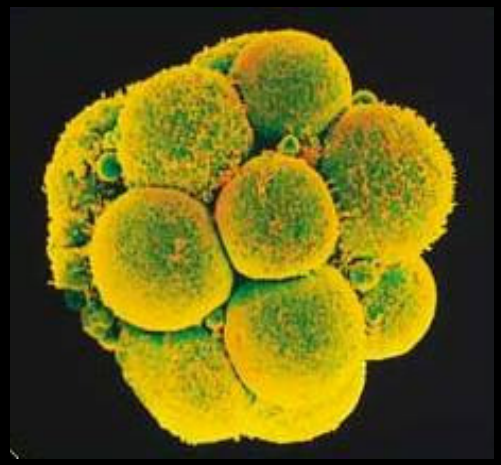


Harvest – isolate – expand – differentiate – seed on scaffold - implant

Stem Cells

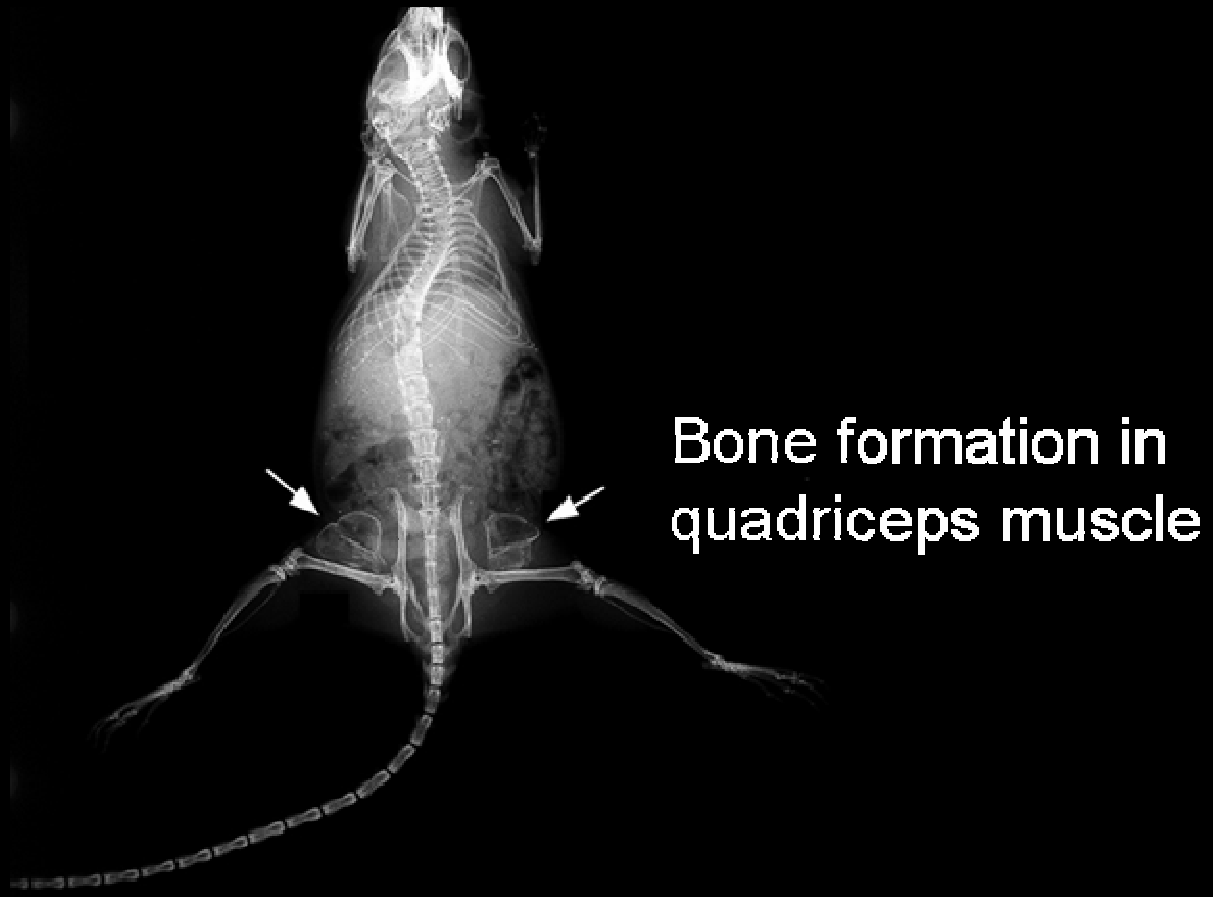
- hEMCs (derived from blastocysts)
- Haematopoetic progenitors / stem cells (HSCs)
- Mesenchymal/stromal stem cells (MSCs)
- Tissue specific progenitors (tissue turnover and renewal)

Implanted cells without nutrient supply die

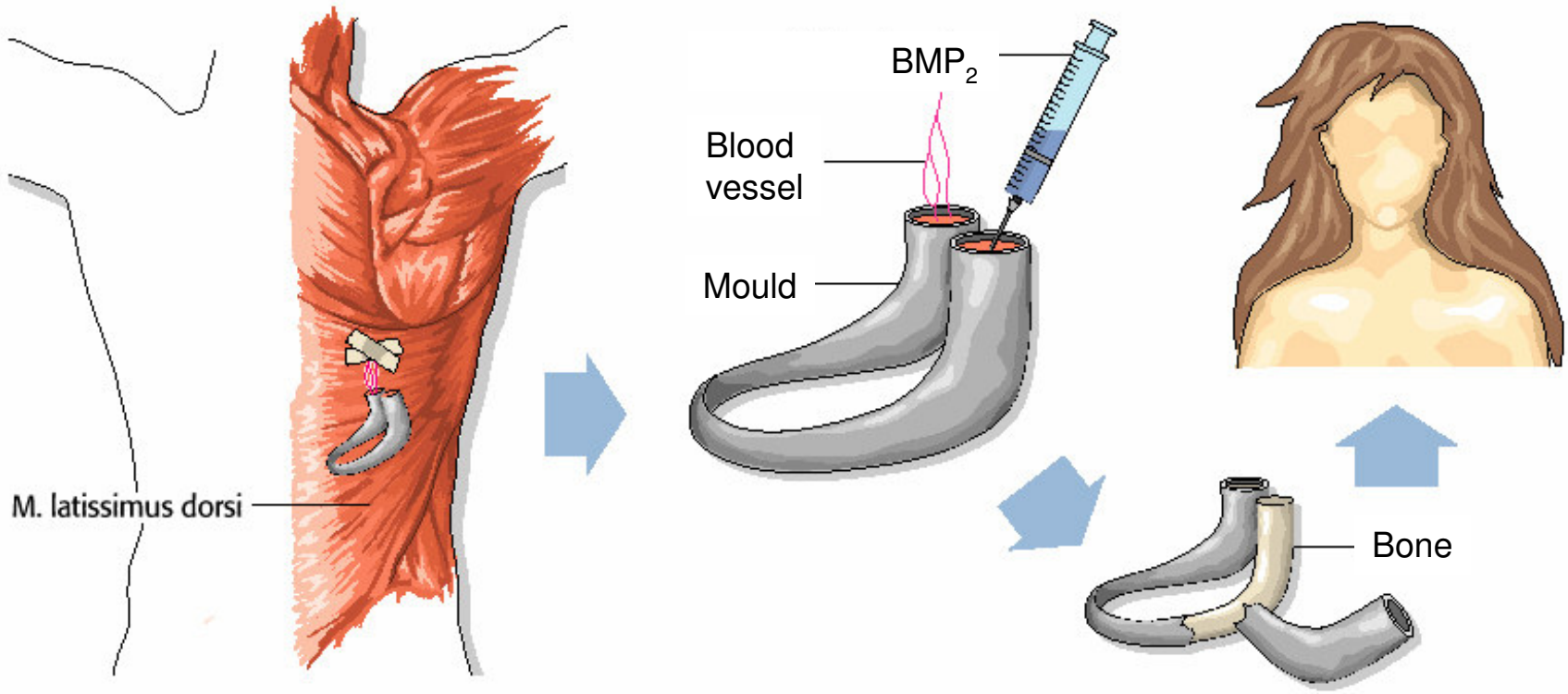


1. Bone formation by collagen and BMP-2 (mg)

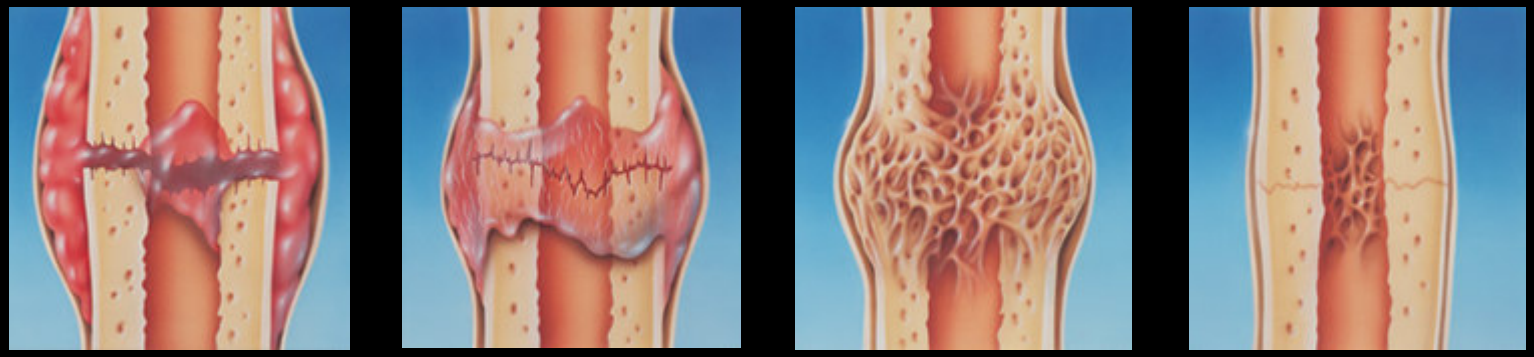
- Collagen/heparin



Bone fabricated from a muscle



MiraGel™
shortens healing time and regenerates tissue



TIME

Stem Cell Quality

- Complex mixture
- Should be well defined & characterized
- ESC and iPS should be lineage comitted (teratoma)

From harvest to use

- Origin, sampling procedure – markers
- Reprogramming (iPS)
- Expansion supporting undifferentaited cells
- In vitro differentiation
- Select intended biologically active population

Characterization

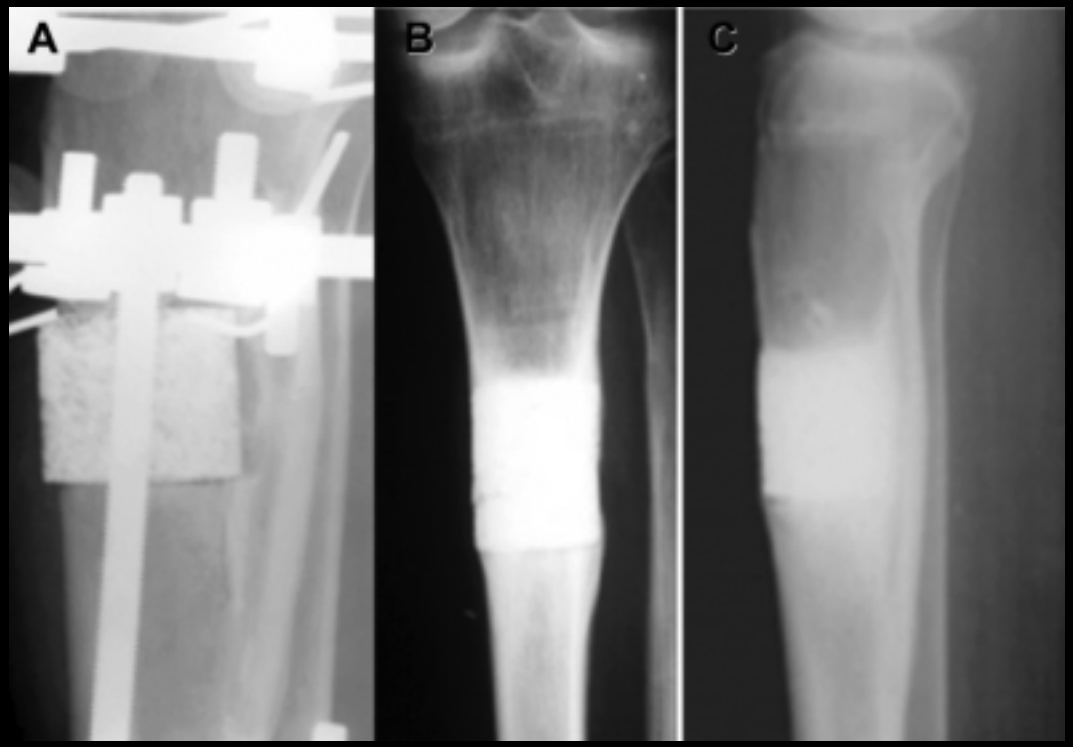
- Identity
- Purity
- Potency
- Tumourigenicity

Non-clinical

- Animal models
- Biodistribution niche
- Tomourigenicity and genomic stability
- Differentiation in vivo
- Immune rejection & persistence

Clinical considerations

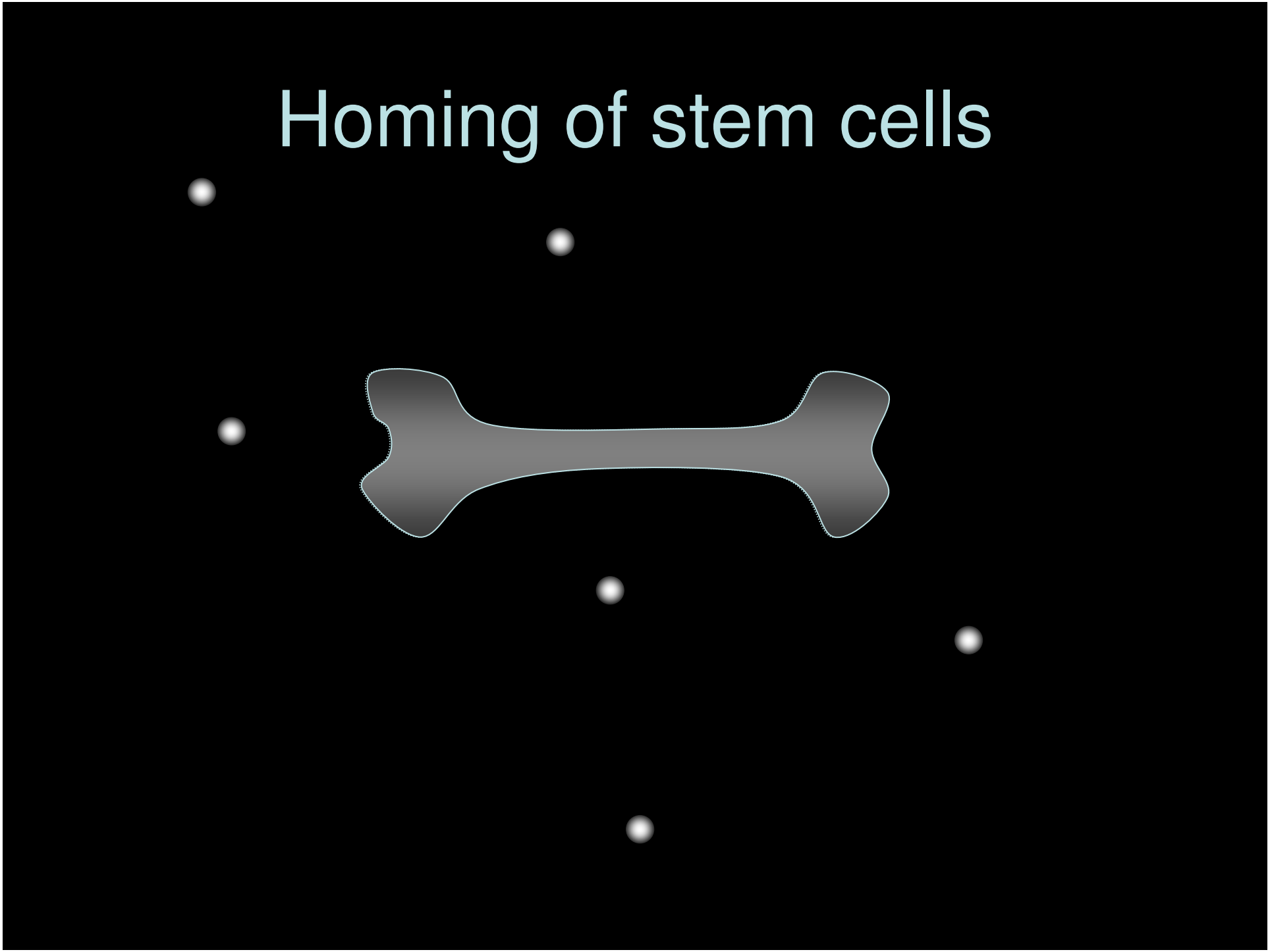
- Pharmacodynamics
- Pharmacokinetics
- Dose finding studies
- Clinical efficacy
- Clinical safety



Orthodontics & Craniofacial ResearchVolume 8, Issue 4, pages 277–284, November 2005

Mastrogiacomo, A Muraglia, V Komlev, F Peyrin, F Rustichelli, A Crovace, R Cancedda

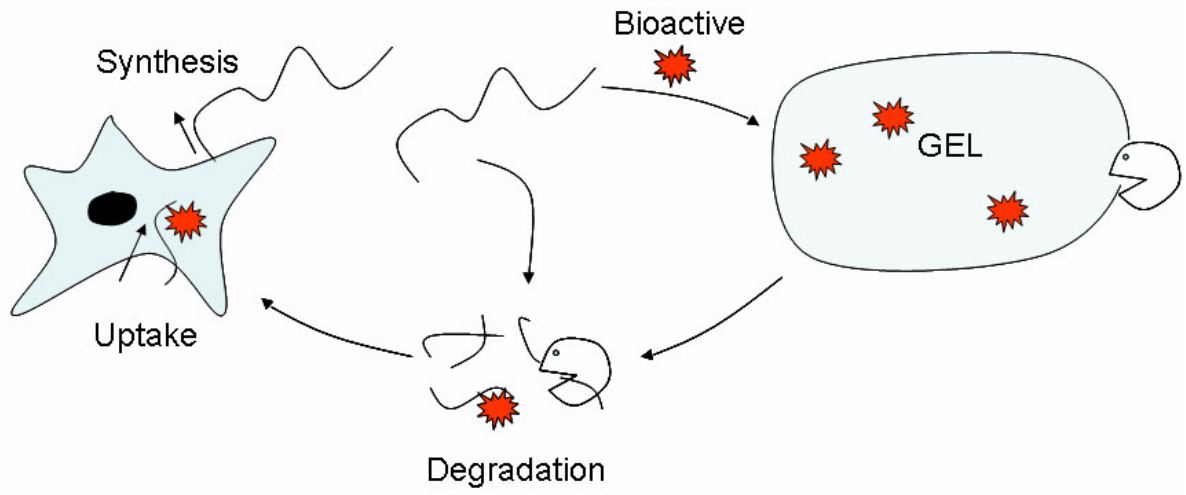
Homing of stem cells



Hyaluronan is a safe biopolymer

- Identical in all vertebrates
- Water soluble with short in-vivo life time
- Long tested biocompatibility
- Can be derived from animals or produced in culture
- Biologically active
- Contains functional groups allowing modification

Borrowed from Nature



-CHO

-$NHNH_2$

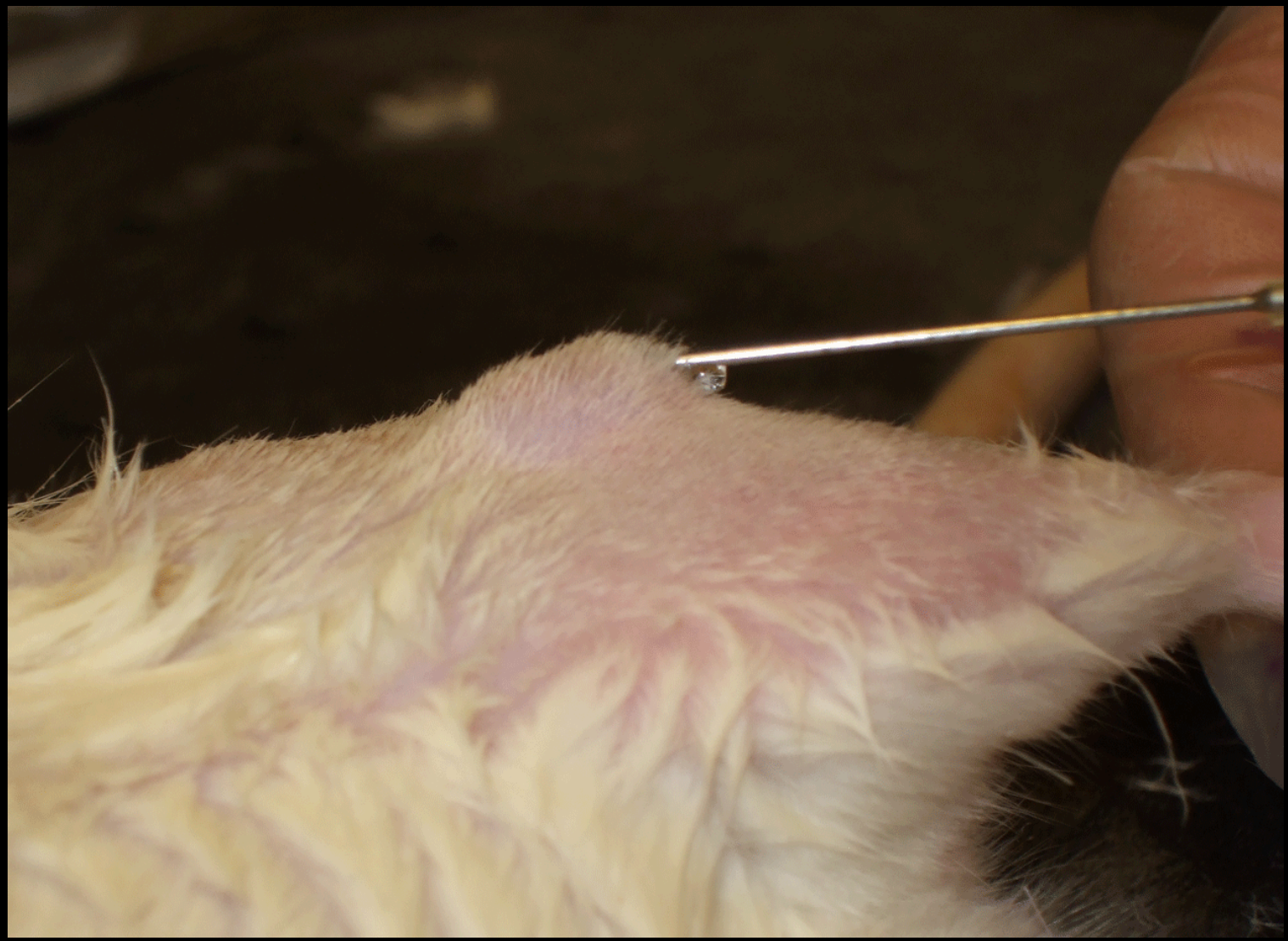
PBS, 37C

Medical device
Functionalized turns it into a drug

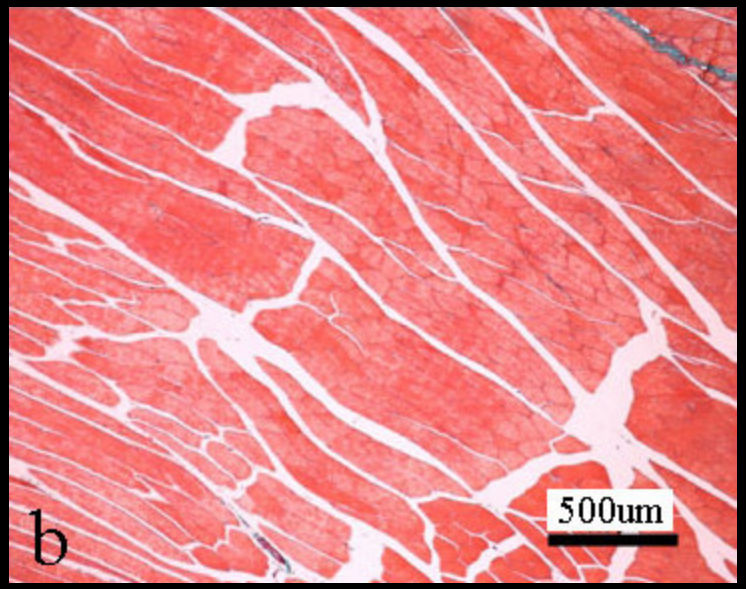
Cross-linking *in situ*

Gel formation < 1 min

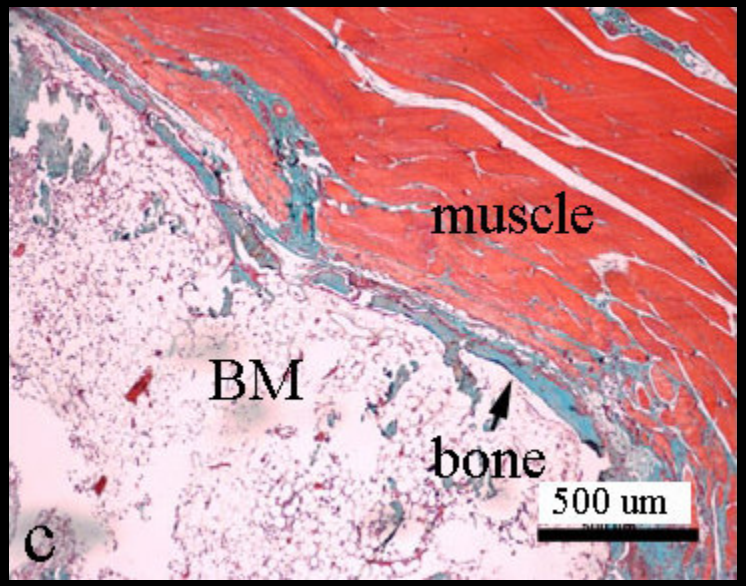
Gel formation in 30-40 seconds



The matrix shows complete degradation, no inflammation and efficient bone formation in the rat model

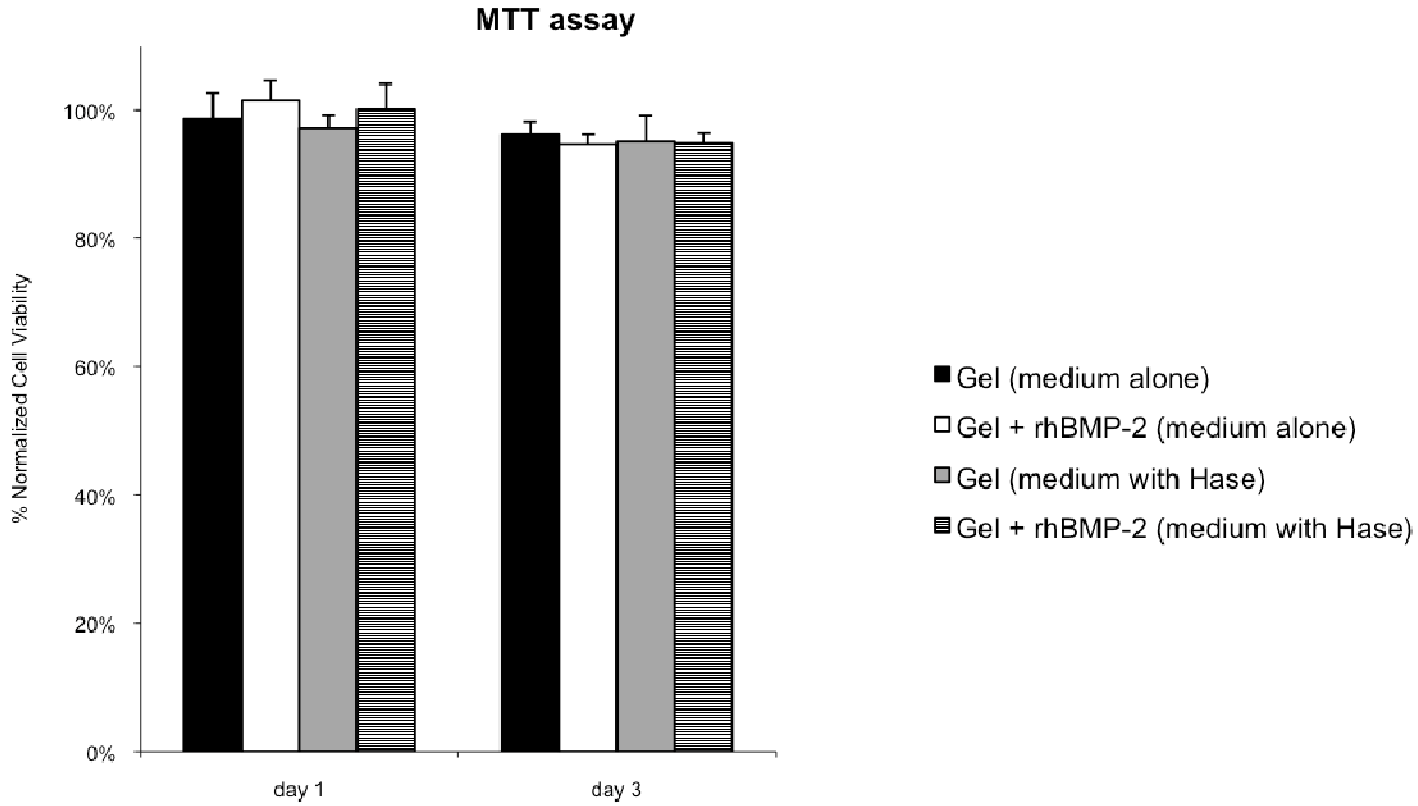


Gel 4 weeks



Gel + 50µg BMP2 4 weeks

Analysis of cytotoxicity



Active growth factor release

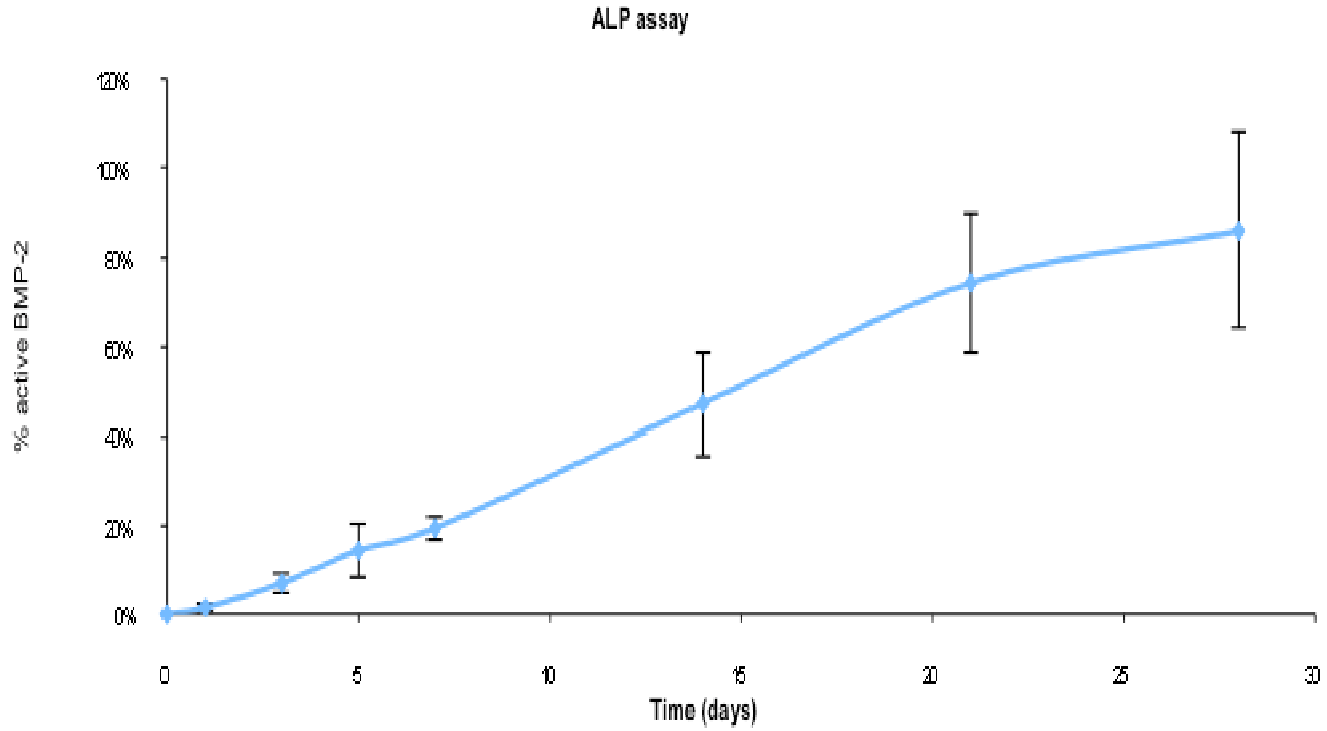


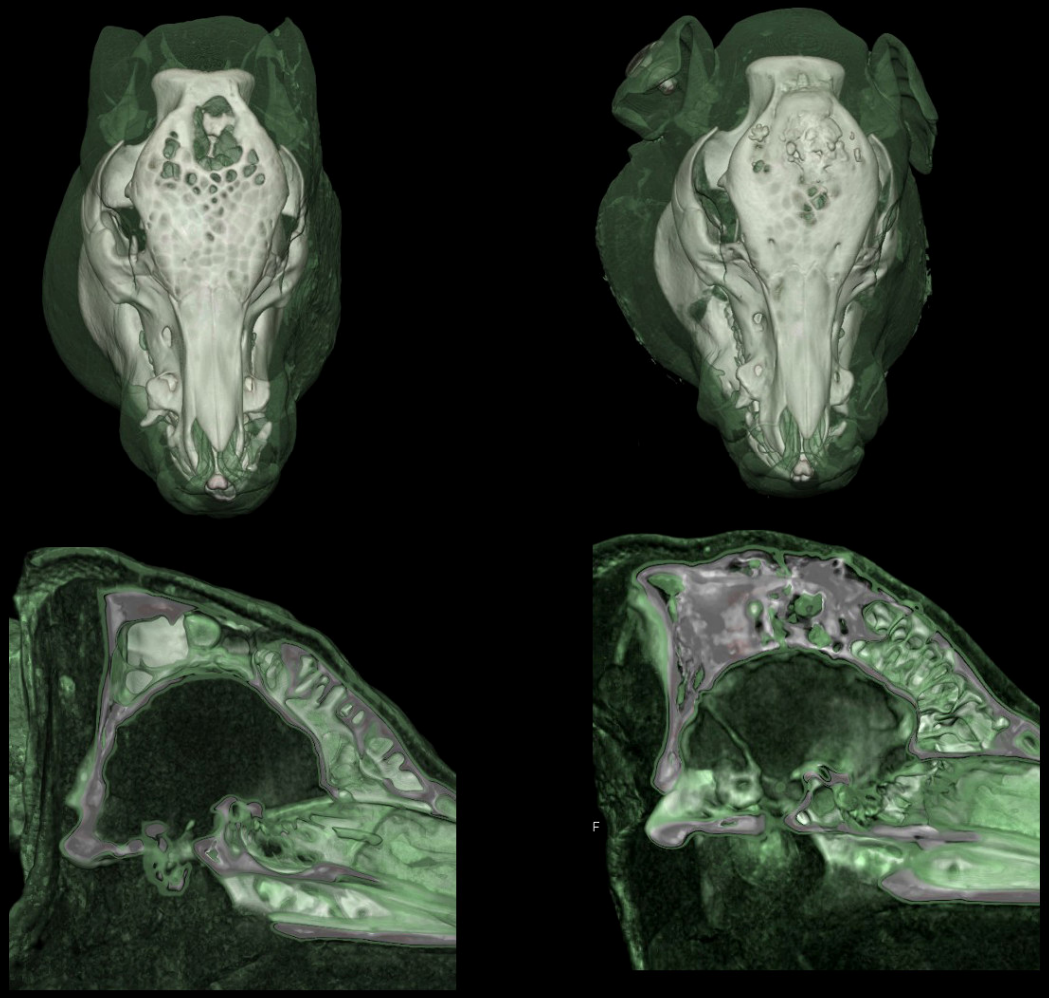
Fig 5. Release profile of active rhBMP-2 from cross-linked hydrogels up to 28 days of incubation *in vitro*. ALP activity of cells cultured in presence of cross-linked hydrogels were immersed for different time points up to 28 days revealed a continuous and prolonged active rhBMP-2 release.

Bone grafts

- 2.2 million grafts per year
- 2.5 billion USD cost
- Major problem is donor site morbidity
- Costs: Open surgery, hospitalization

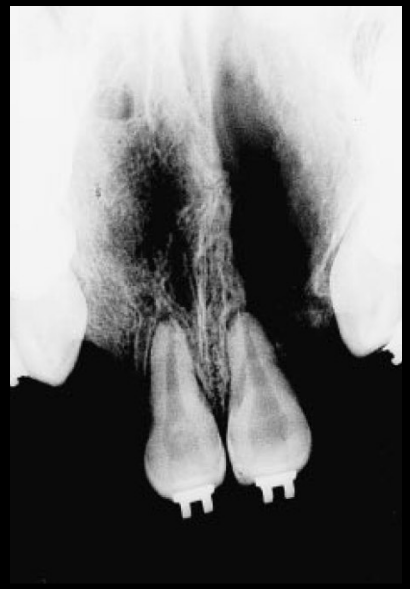

m
1
2
3
4
5
6
7
8

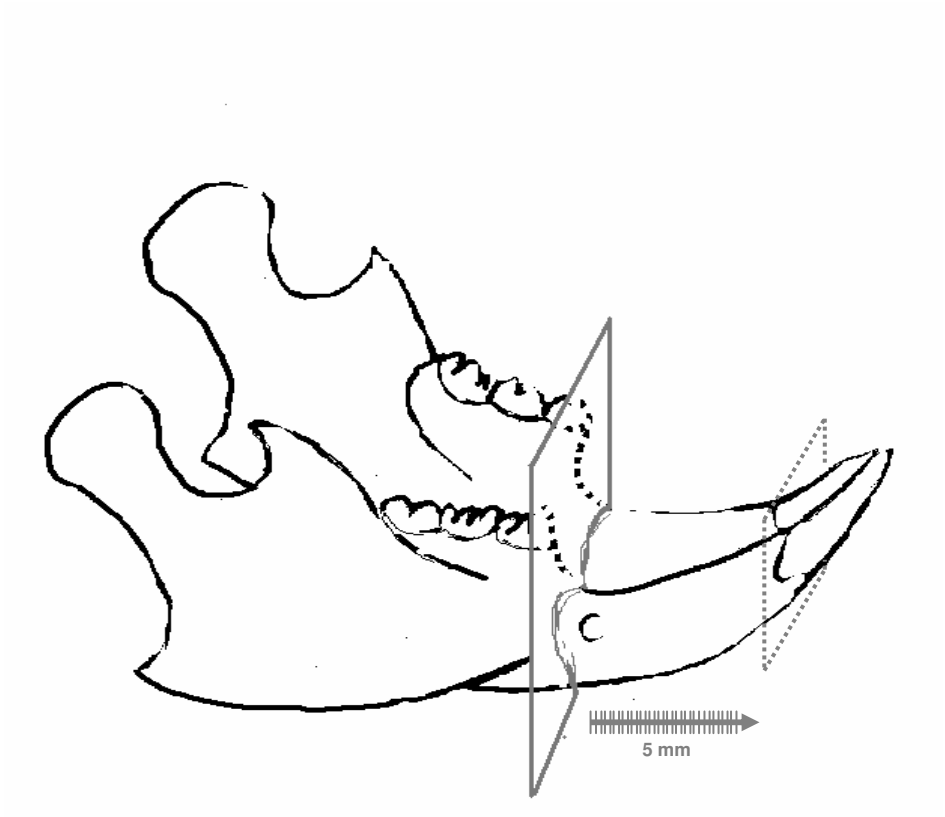
Cranial repair in the pig model



Clinical trials

1. Repair of alveolar clefts
2. Craniotomy




5 mm

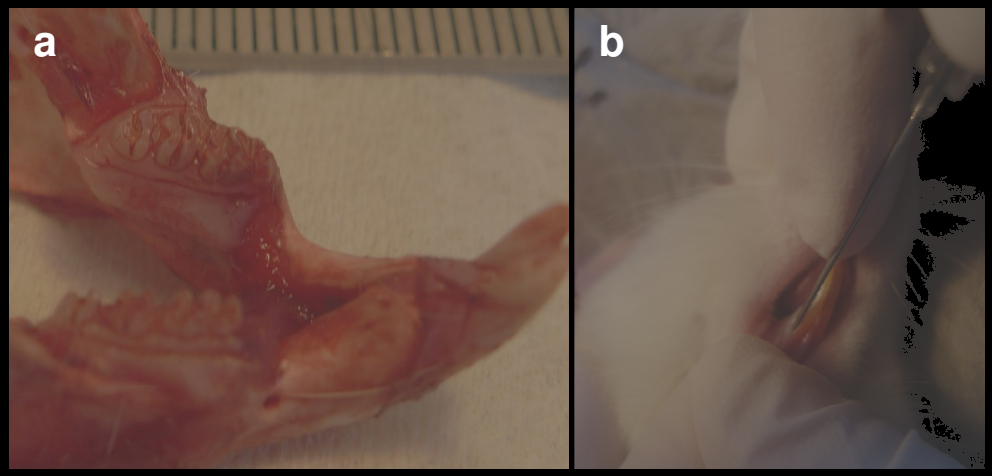
Sub periostal tunneling

Aim:

To replace open surgery by injection

Model:

Rat (na=26)



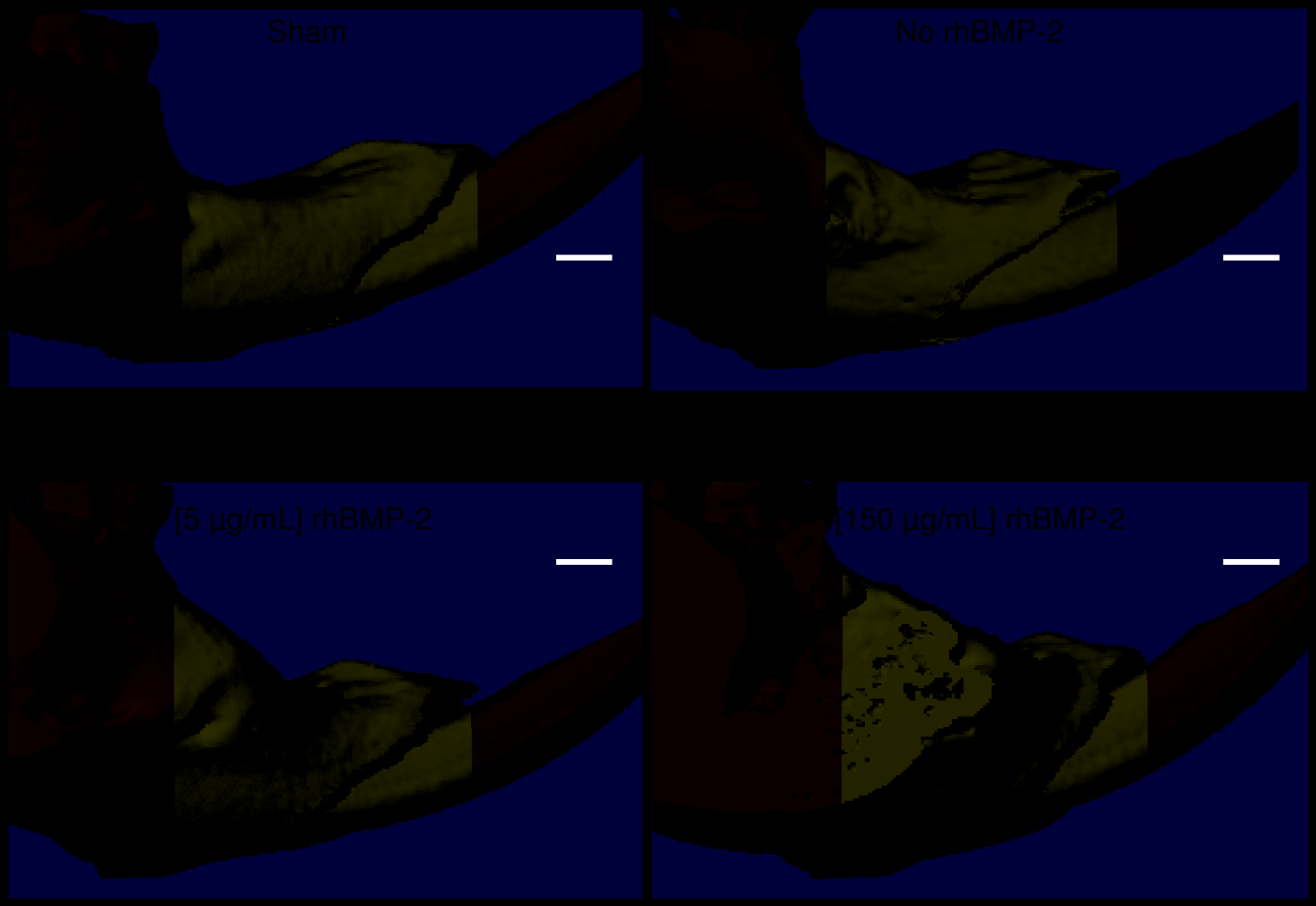
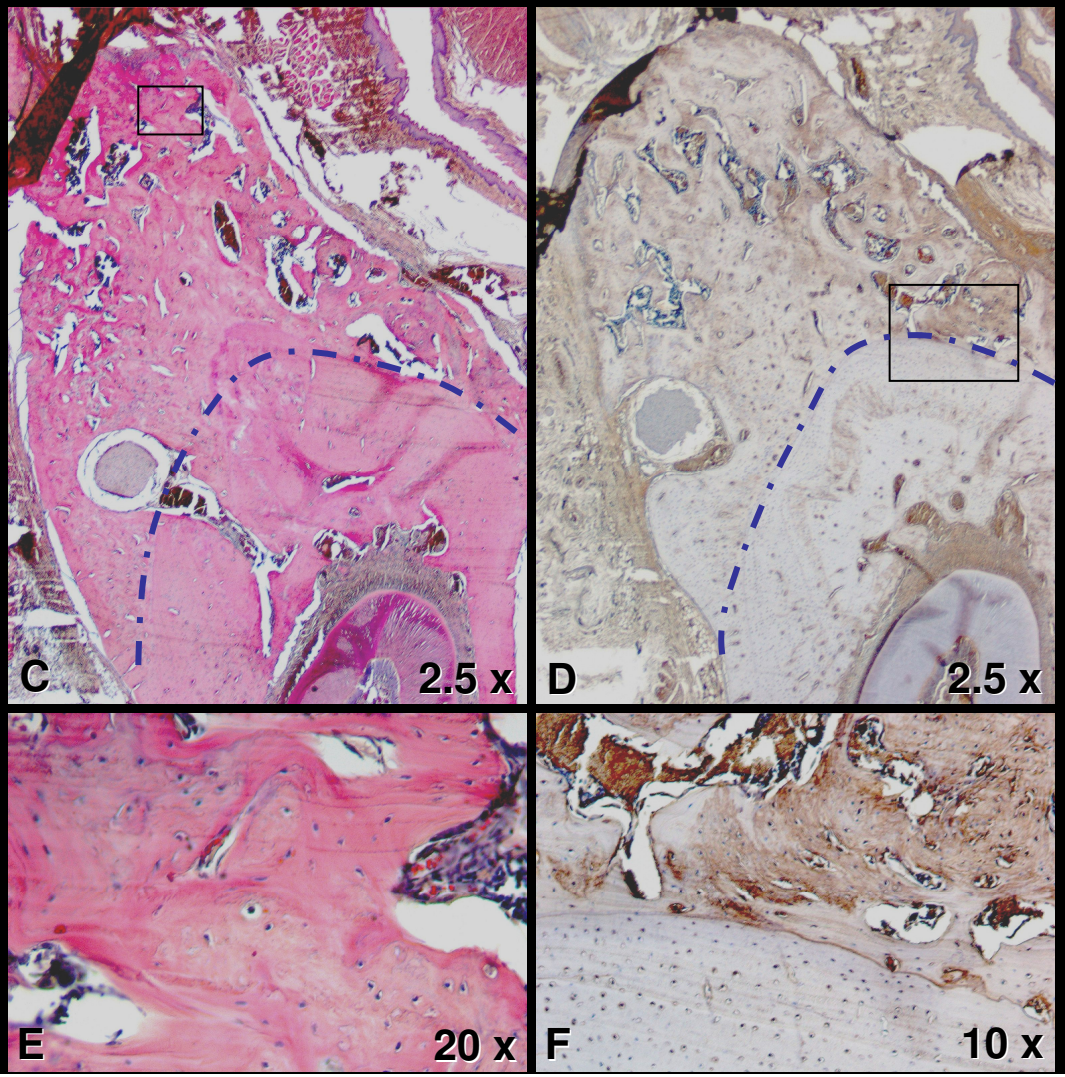
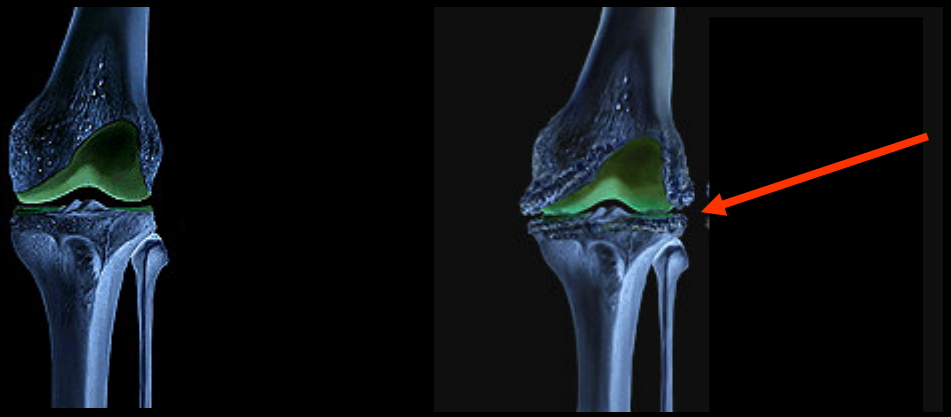


Fig 8. Representative 3D reconstruction images from miro Computed Tomography (µCT) of hemimandibles of each experimental group after 8 weeks. (a) sham injected hemimandible (b) Superiosteal injection of hydrogel + HAp without rhBMP-2. (c) Subperiosteal injection of hydrogel + HAp+ [5 µg/mL] rhBMP-2 (d) Subperiosteal injection of hydrogel + HAp+ [150 µg/mL] rhBMP-2. Scale bars: 1 mm

Successfully augmented bone is firmly linked to existing bone

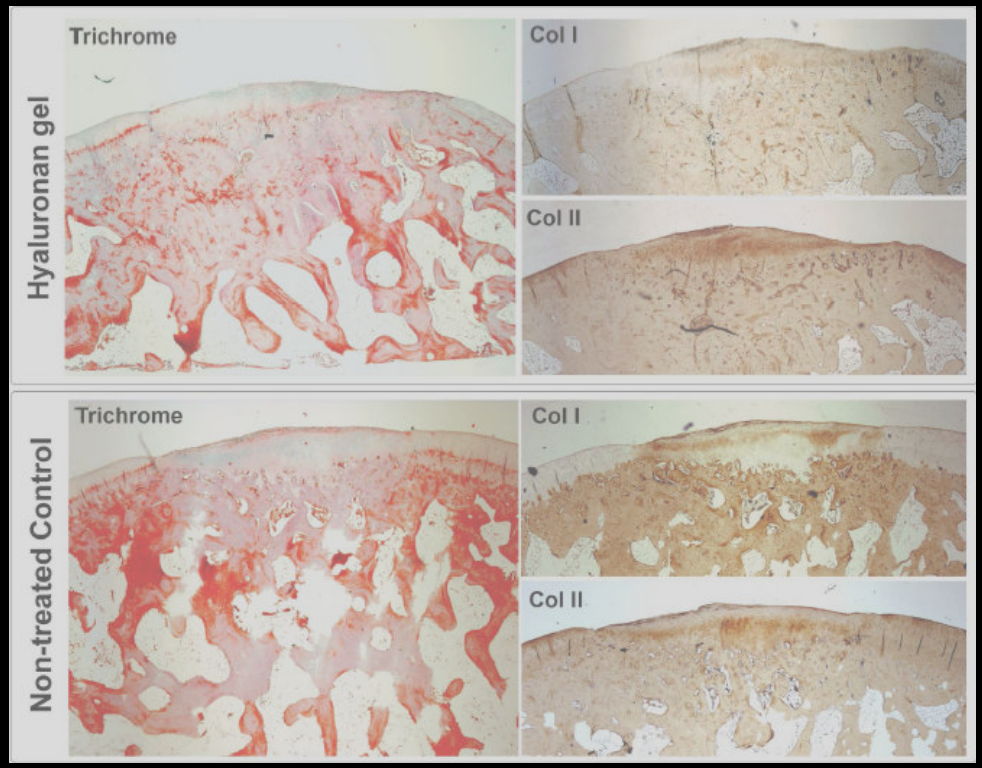


Future product for Arthritis



- US expentitures for arthritis 2005 was $353 billion USD
- 19 million people affected in US alone
- 40% expected growth in number of patients until 2030

Regenerates healthy cartilage to potentially treat arthritis



Rabbit model: Collagen type II shows healthy cartilage while collagen type I is a sign of fibrotic cartilage

Product definitions

Combination Product (21 CFR 3.2 (e)(1)) - A product composed of two or more components which would normally be regulated under different regulatory authorities (e.g., biologic + device, biologic + drug) that are physically, chemically, or otherwise combined or mixed and produced as a single entity

Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps) 21 CFR 1271.3 d): Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation,

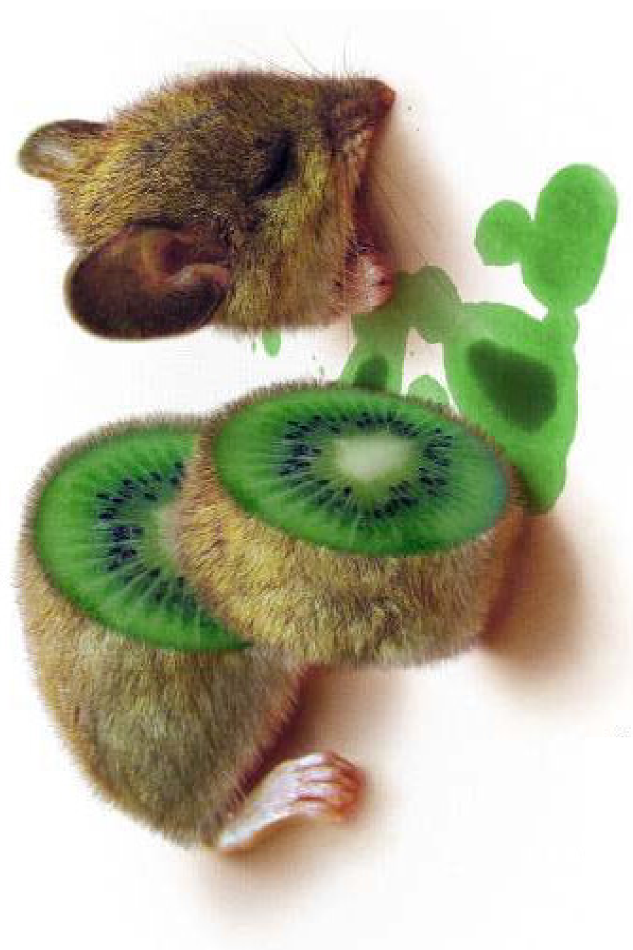
Evolution of Stem Cell field

Evolution of Stem Cell Field:

✓ Cell therapy and gene therapy products –and therefore stem cell products-- do not lend themselves to a “one size fits all” concept of product development and regulation.

✓ Regulations set framework of criteria that must be fulfilled: safety, identity, purity, potency, and clinical efficacy

✓ Flexibility in how to fulfill the criteria



Summary

- Tissue Engineering & Regenerative Medicine holds enormous potential
- Safety & Efficacy are key issues for both cell based and material based approaches
- We will see new approaches using other stimuli