INTERNATIONAL SOCIETY FOR
ISMRM
MAGNETIC RESONANCE IN MEDICINE

Declaration of Conflict of Interest or Relationship

Speaker Name: Richard G. Spencer

I have no conflicts of interest to disclose with regard to the subject matter of this presentation.

Toronto!

Unmet Needs for MR in the Unsolved Problem of Tissue Engineering:

Not just one problem, not just one solution

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ISMRM Toronto, 2008

Definition of Tissue Engineering:

"…an interdisciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function."

Langer and Vacanti, 1993

Tissue Engineering

Includes:

- Implanted cellular constructs designed in the lab
  --off-the-shelf cartilage, pancreas, liver,…
- Implanted cells which will develop function in vivo
  --stem cells for MI or stroke repair
  --cartilage matrix from implanted cells
- Implanted acellular scaffolds
  --bioactive bone graft scaffold

Excludes:

- Organ transplants
- Artificial mechanical organs
- Metal joints
- Hemodialysis, external blood oxygenators,…

Motivation for TE

Limitations of non-biologic repair:

- Duration < longevity of patient
  (metal implants)
- Highly invasive
  (hemodialysis)
- Typically, no growth or adaptation
  (c.f. advantage of demand pacemakers)

Funding Opportunities

NIH: regenerative medicine funding 2008--
US$575 M (approx. 2% of NIH budget)

DoD: Armed Forces Institute of Regenerative Medicine (AFIRM), April, 2008:
US$265 M over 5 years

Other: NIST, NSF, Arthritis Foundation, Musculoskeletal Transplant Foundation…

The product list is limited but active

- *Medtronic: INFUSE bone grafts*

- *RESTORE small intestine submucosa (duPont)*

- *Apligraf skin patch (Organogenesis)*

- *Cord blood stem cell banking*

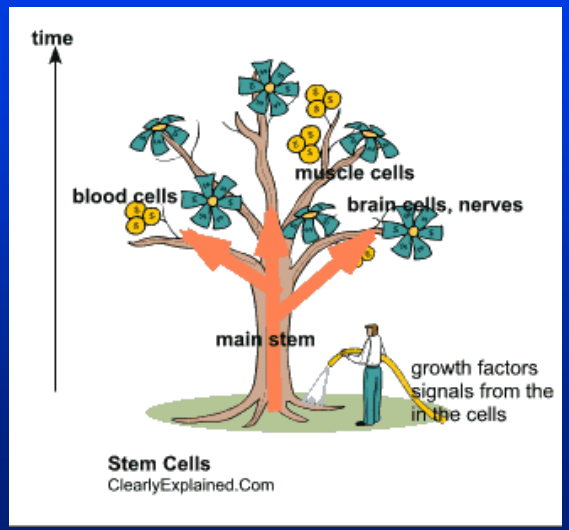


Table 3. Commercial Products (Rounded Totals; $ [Millions])

Commercial products	*2007 sales*	*Cumulative patients*
Bioactive bone grafts	$700	170,000
Regenerative biomaterials (SIS)	$240	750,000
Cord stem cells	$270	*
LSE and cartilage	$90	250,000

LSE: Living skin equivalent.
*Cord stem cell donors are not classified as patients.

Lysaght, Tissue Engineering, 2008

Private sector activity, 2007 (worldwide)

of firms or business units > 50

# of employees > 3000

Annual sales > US$1.3 billion

# of patients treated > 1M

products in preclinical stages > 50

Lysaght, Tissue Engineering, 2008

What Can MRI and MRS Contribute?

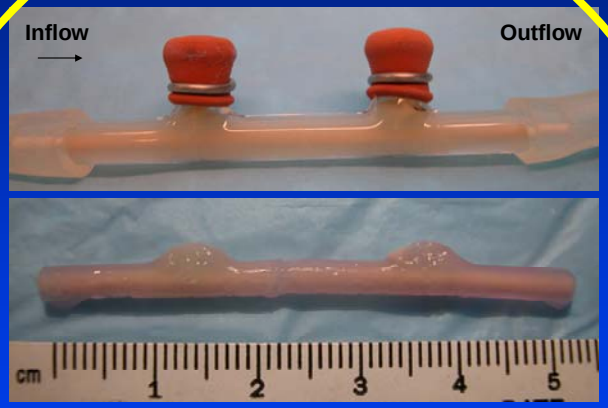
Non-invasive Monitoring after Implantation

- Positional stability
- Integration with surroundings
- Metabolic activity
- Need for and response to ongoing intervention

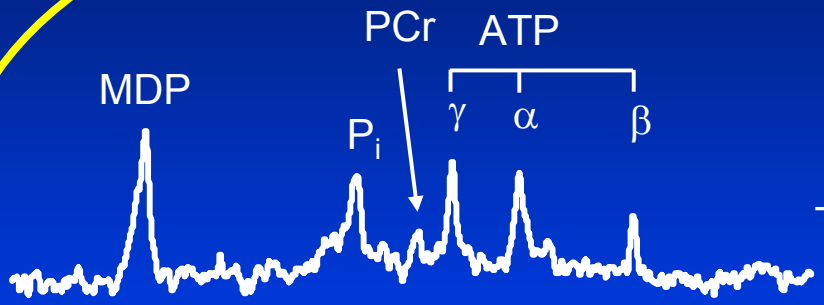
"Structural imaging" may be less important than other capabilities of MR, such as more specific microstructural and molecular analyses, and metabolic analysis

Examples of Current MR/TE Studies

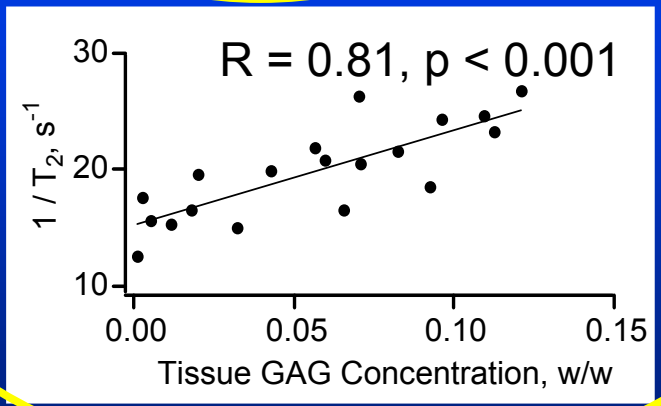
TE Cartilage Development in Hollow-fiber Bioreactor



Bovine neocartilage developing from chondrocytes



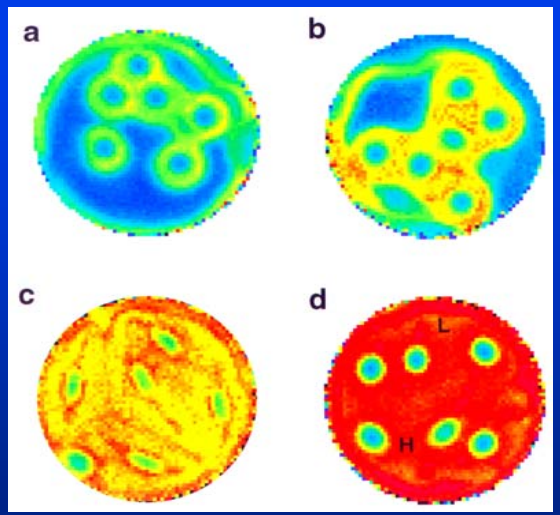
^{31}P spectrum of avian neocartilage



MT of TE Cartilage

1 week

2 weeks

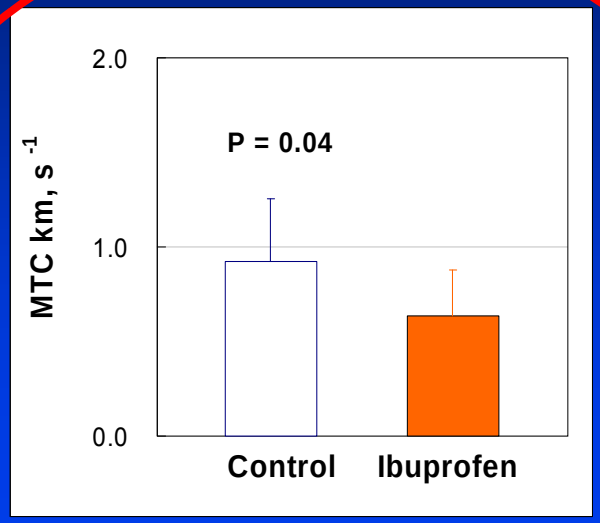


3 weeks

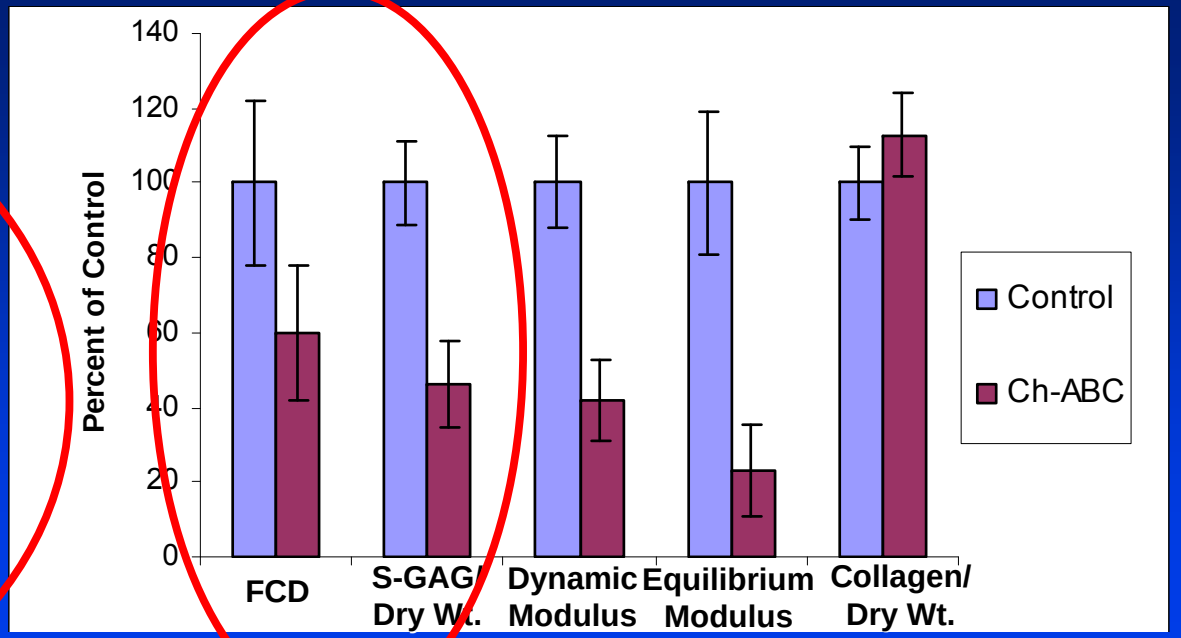
4 weeks

Blue: MT< 0.4 Red: MT> 0.8

Neocartilate in Bioreactor

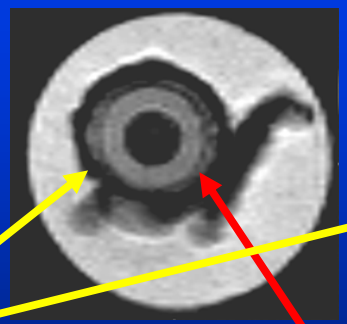


Effect of ibuprofen on developing cartilage

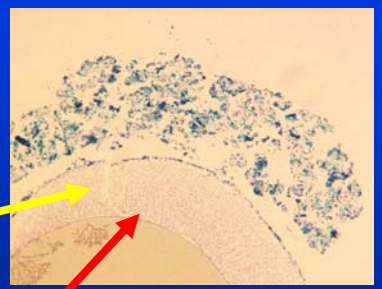


Effect of chondroitinase on developing cartilage

MR Image



Prussian blue stained section



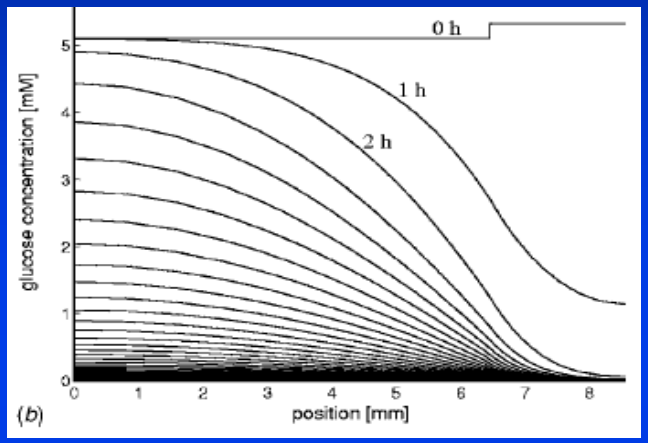
Matrix containing iron-labeled cells

Non-labeled matrix

Day 14

Non MRI: Model Based Estimates

(Sengers B. G. et al. JBME 2005)



Computed spatial glucose concentration

Fick's law

$$\frac{\partial n^f c^\beta}{\partial t} - D\frac{\partial^2 c^\beta}{\partial x^2} = q^\beta,$$

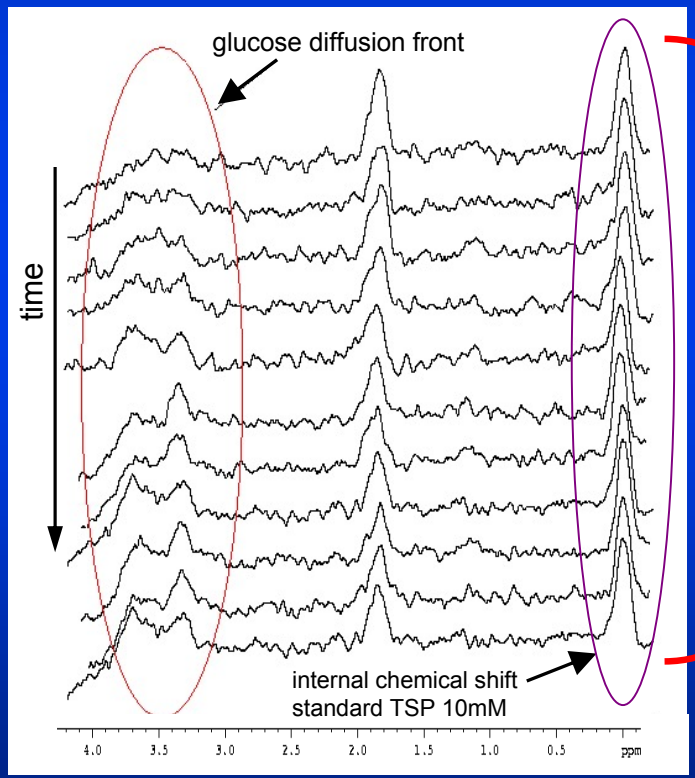
Michaelis-Menten

$$q^{glc} = -\frac{V^{glc} c^{glc}}{K_m^{glc} + c^{glc}} \rho^{cell},$$

Metabolic Mapping in TE cartilage

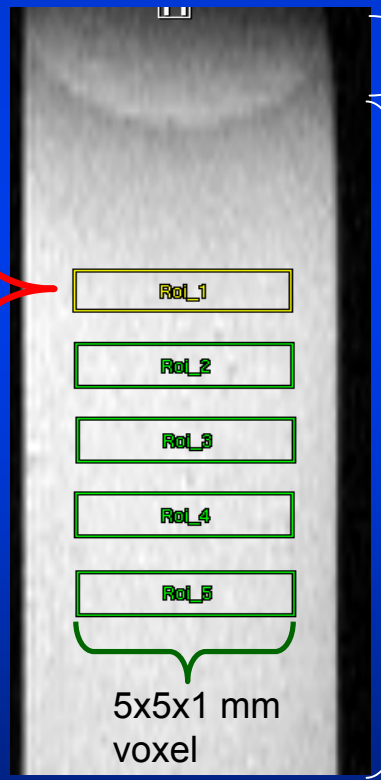
^{1}H Localized Spectroscopy in Collagen I Constructs

Time course of glucose diffusion into ROI_1



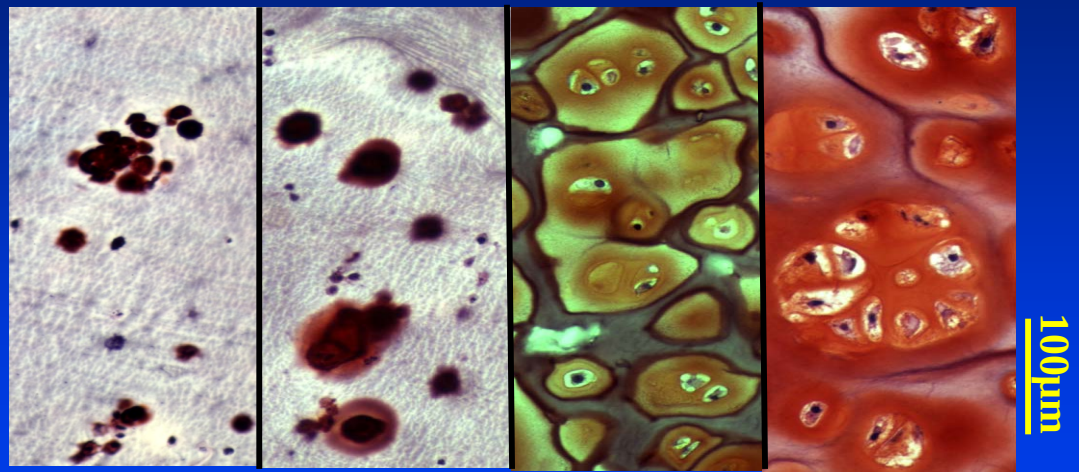
Direct measurement of spatial glucose concentration

Reference geometry of collagen I gel



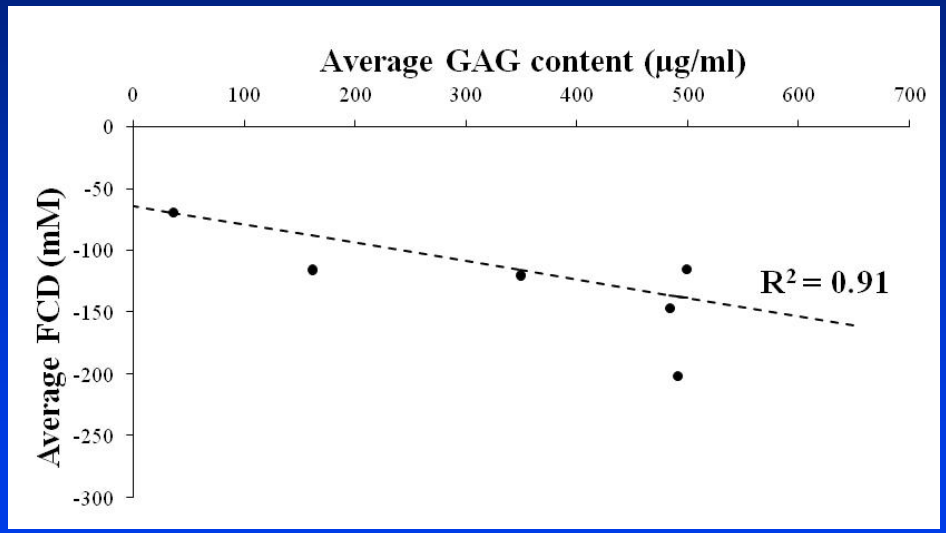
Courtesy David Reiter

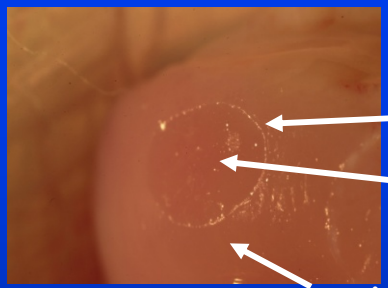
Cartilage/Hydrogel Studies

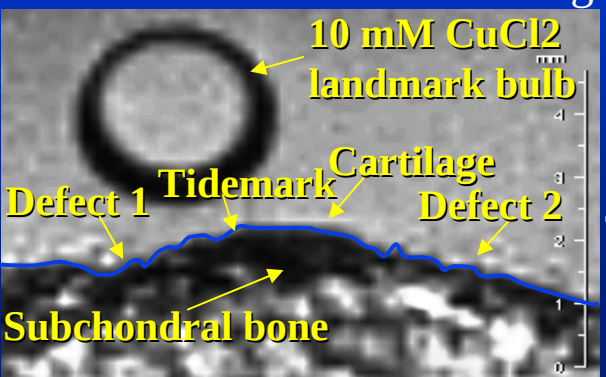


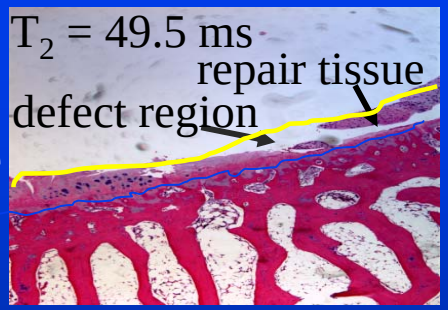
9 days 21 days 28 days 43 days

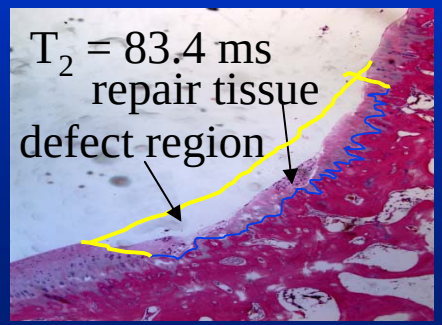
Cartilage in hydrogel
Biochem vs MRI



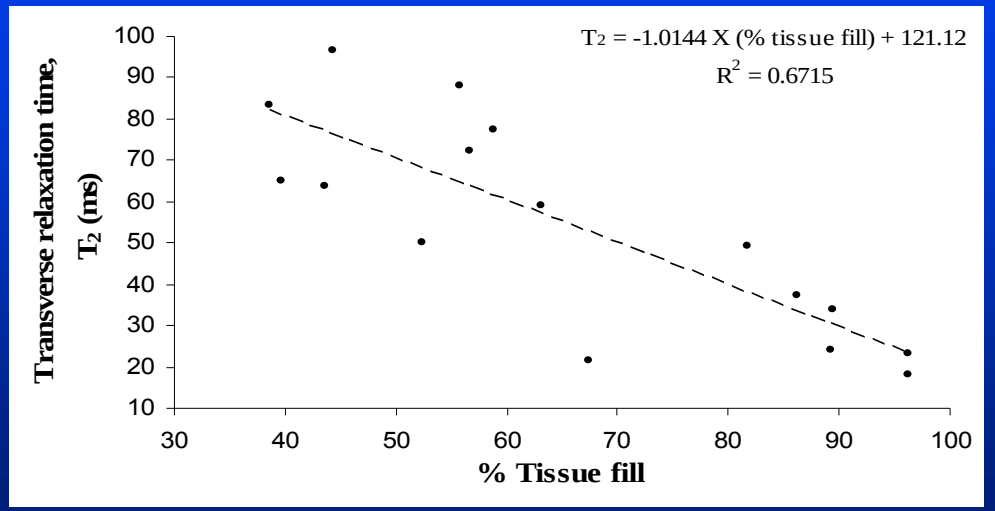








Hydrogel defect repair in rabbit
Histology vs MRI

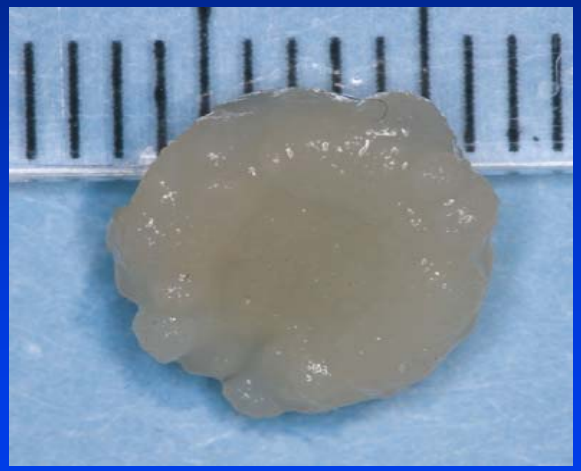


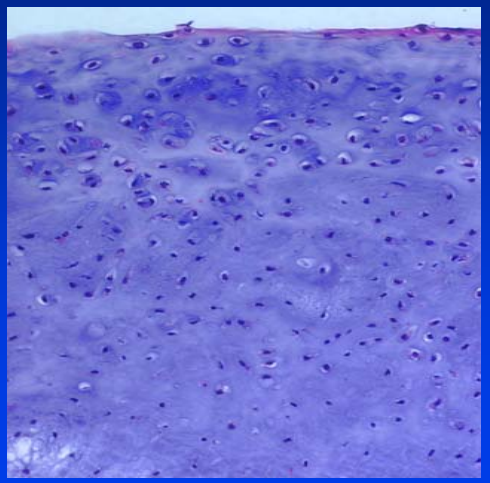
Courtesy S. Ramaswamy, Bioengineering, Univ of Pittsburgh

Asssessment of Cartilage formed in Self-Aggregating Suspension Culture

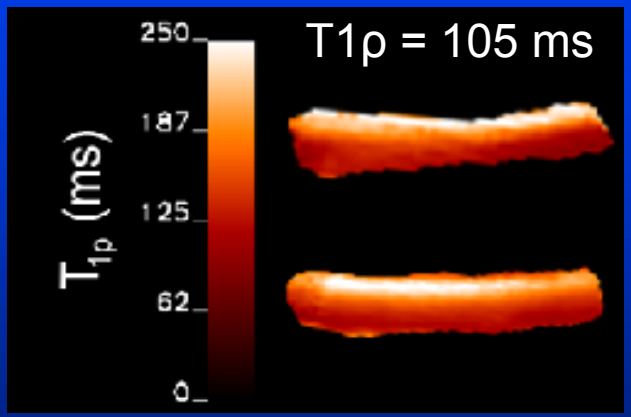
Characteristics of Culture Model

- **Grows in suspension at high density (1-2 X10^7 cells/ml)**
- **Forms a mass quickly (1→10 weeks mass >6 fold)**
- **Maintains cartilage phenotype (cartilage specific ECM, no Coll I)**

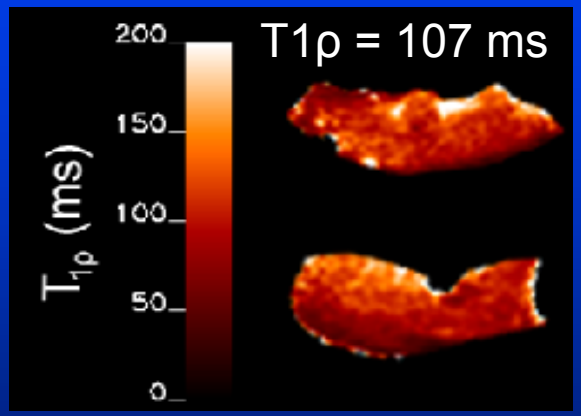




Bovine patellar cartilage



Engineered cartilage



Previous studies:
Direct correlation of T1ρ MR measurements with FCD and PG in cartilage

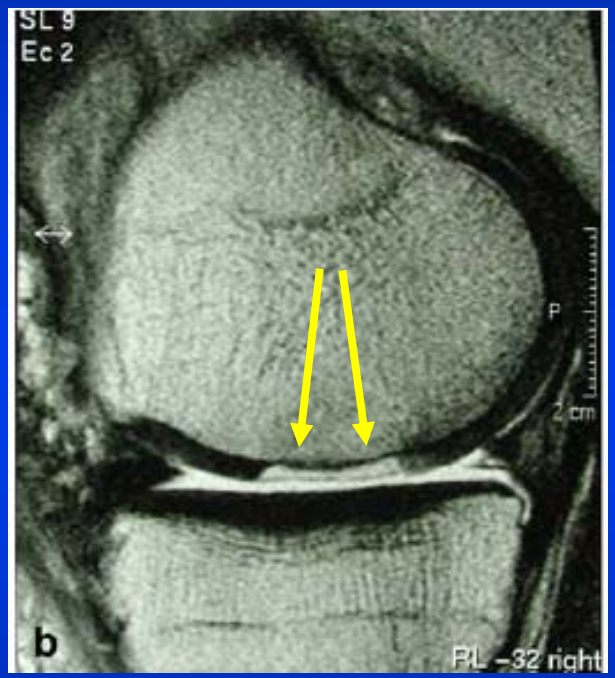
MR-based methods offer advantages of providing noninvasive, nondestructive, and quantitative surrogate measures of material properties.

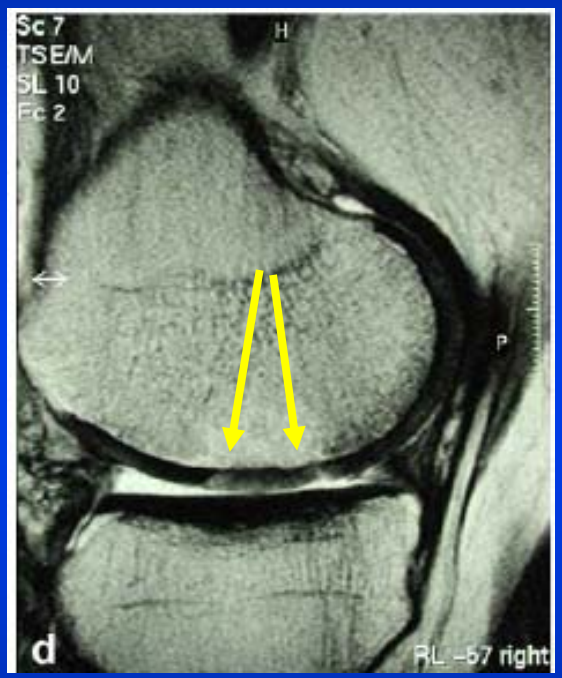
Courtesy of George Dodge
Bone & Cartilage Research Lab, Nemours Biomedical Research

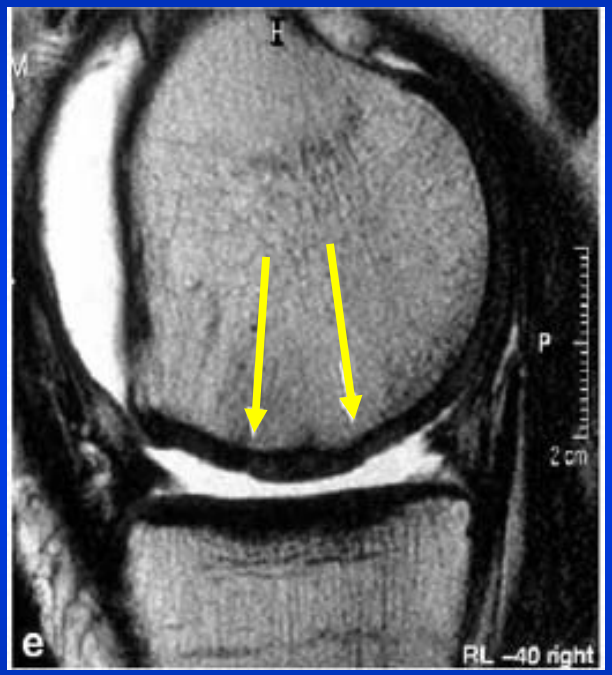
Nemours | Alfred I. duPont Hospital for Children
Nemours Children's Clinic

MRI Following Matrix-assisted Autologous Chondrocyte Transplantation

T_2-weighted fast spin echo images reveal longitudinal changes in repair zone containing implanted chondrocytes







4 Weeks Post-Surgery:

Fluid-like contrast in repair zone

24 Weeks Post-Surgery:

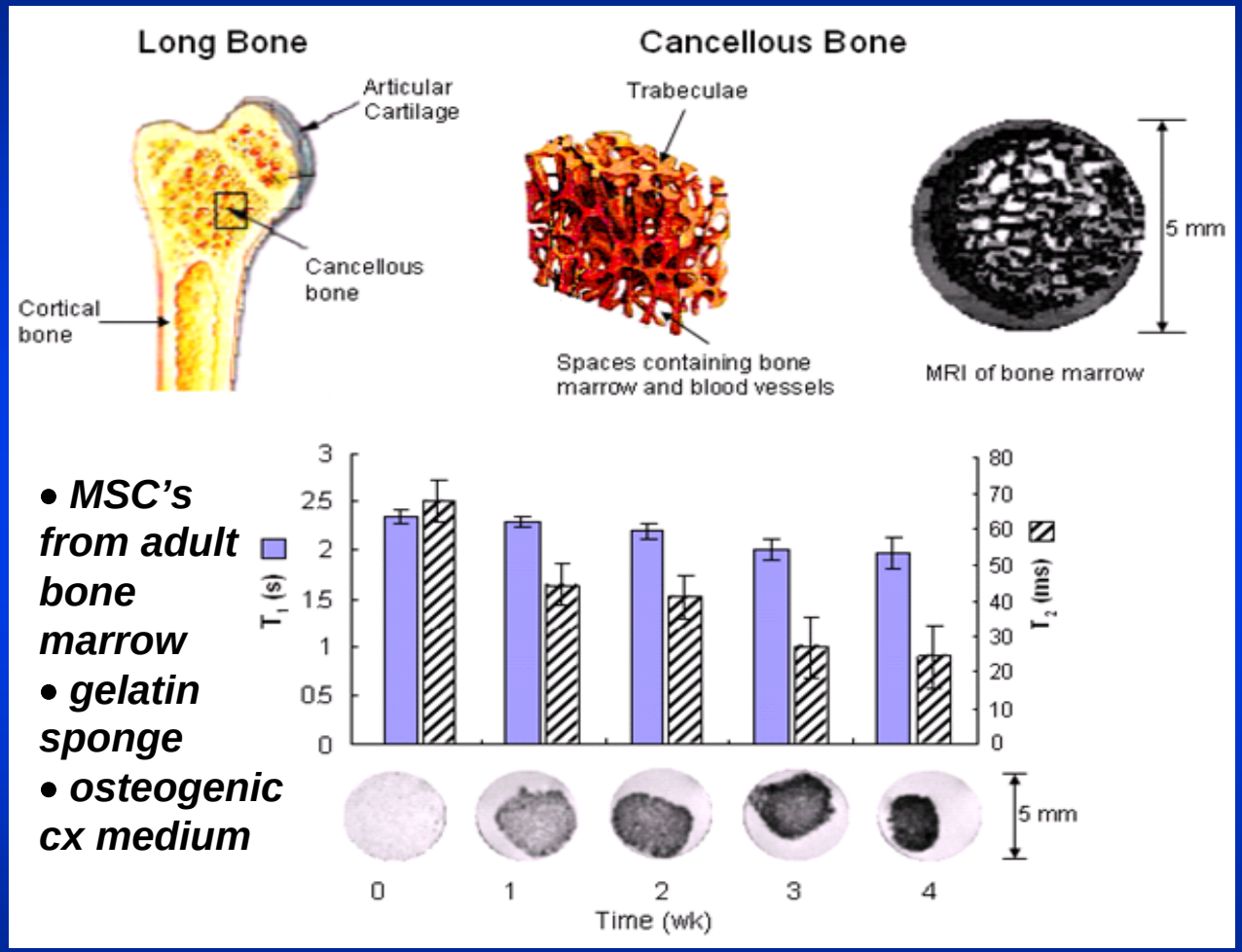
Heterogeneous contrast

52 Weeks Post-Surgery:

Repair zone isointense with native cartilage

Source: Trattnig et al., 2007

Ostogenesis in a Tissue Engineered Construct



← T_1 weighted image of osteochondral plug

← T_1 and T_2 values for developing TE bone

Conclusion: T_2 is an effective marker for ossification

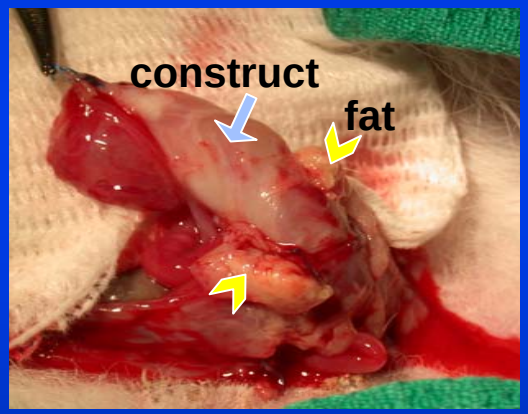
11.7 T SE; TE/TR=1000/30

Courtesy Richard Magin, UIC

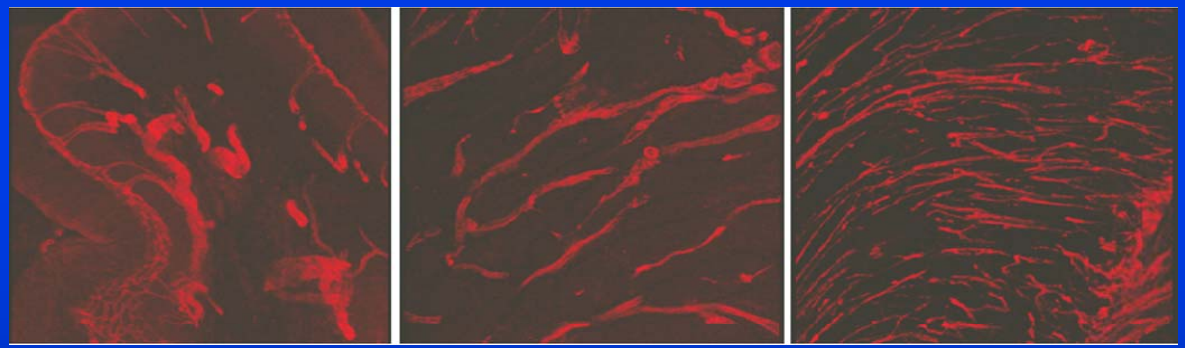
Non-invasive MRI of tissue-engineered bladder construct

Major challenge to successful regeneration: creating immediate angiogenesis
Role for imaging: non-invasive quantitative assessment of angiogenesis

Exposed bladder



Angiogenesis at different VEGF levels
CD31-immunostaining



VEGF → microvessel density

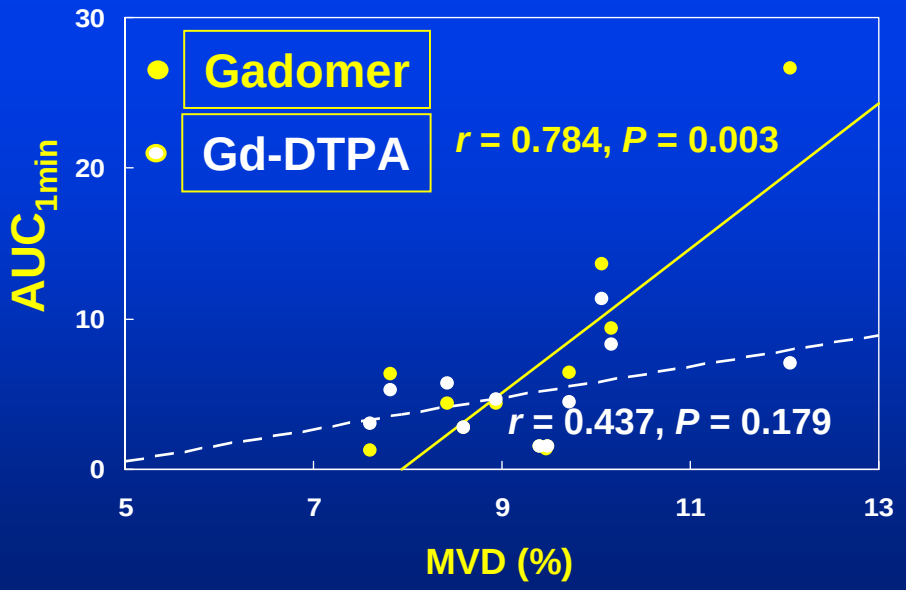
Courtesy of Hai-Ling Margaret Cheng, PhD
The Hospital for Sick Children and University of Toronto

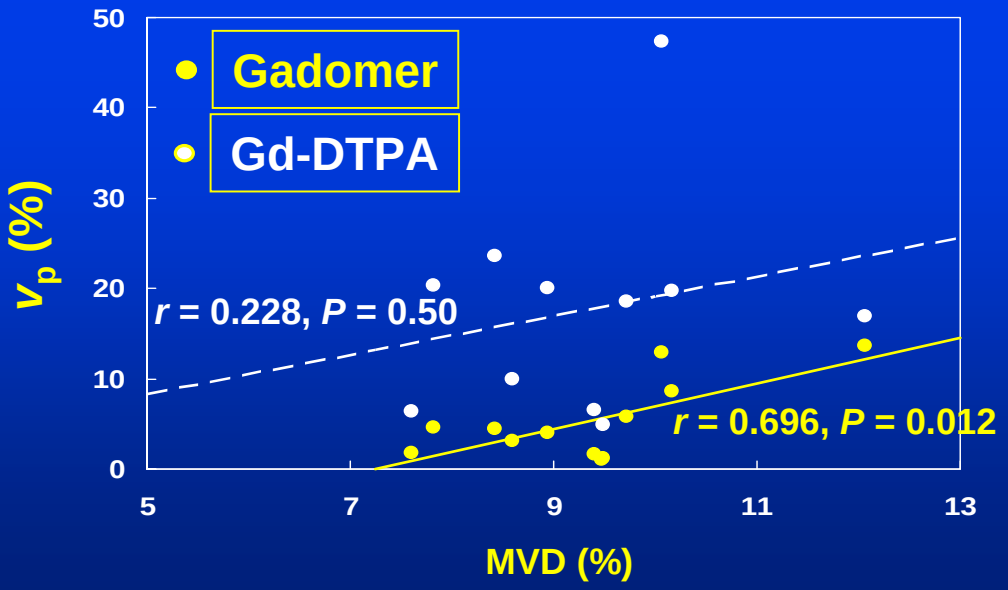
Tissue-engineered bladder construct

Gadomer (blood pool cx agent): correlation with microvessel density (MVD) through either fractional plasma volume (vp) or area under uptake curve (AUC);
➔ *superior to Gd-DTPA*

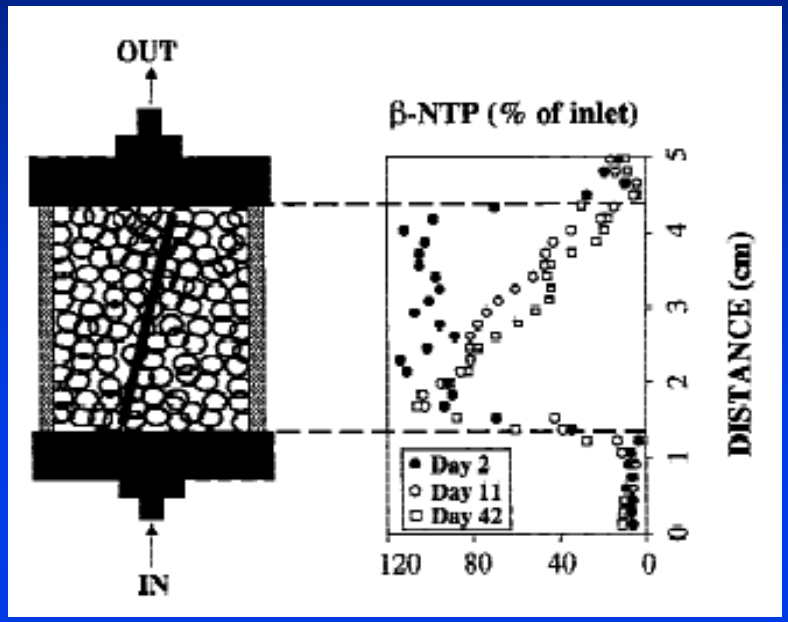
Gd-DTPA (extracellular cx agent): correlation with MVD is best obtained with AUC

SIGNIFICANCE: ***MRI measurement of absolute blood volume is feasible in therapeutic angiogenesis paradigms***



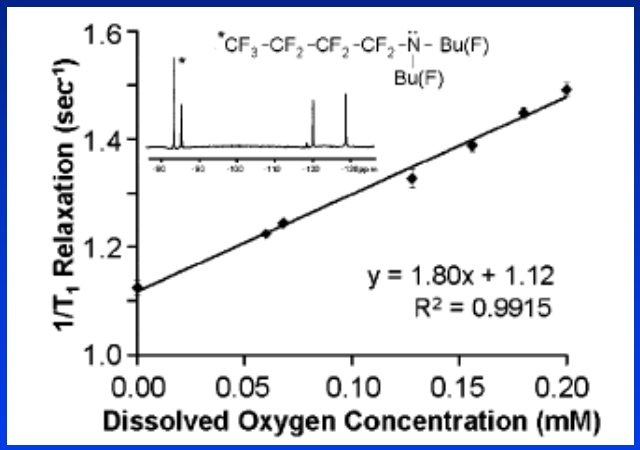


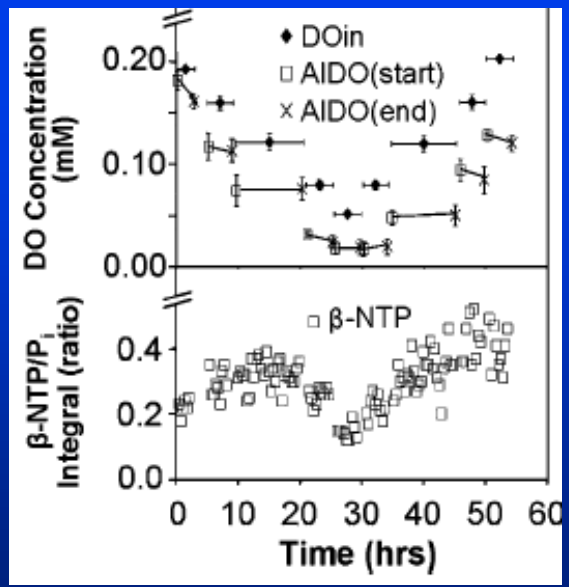
MR Monitors Viable Cell Number, Bioenergetics and Oxygen Distribution for Mouse Insulinoma βTC Cells in Tissue-Engineered Pancreas



^{31}P 1D CSI yields bioenergetic data **with both spatial and temporal resolution**.

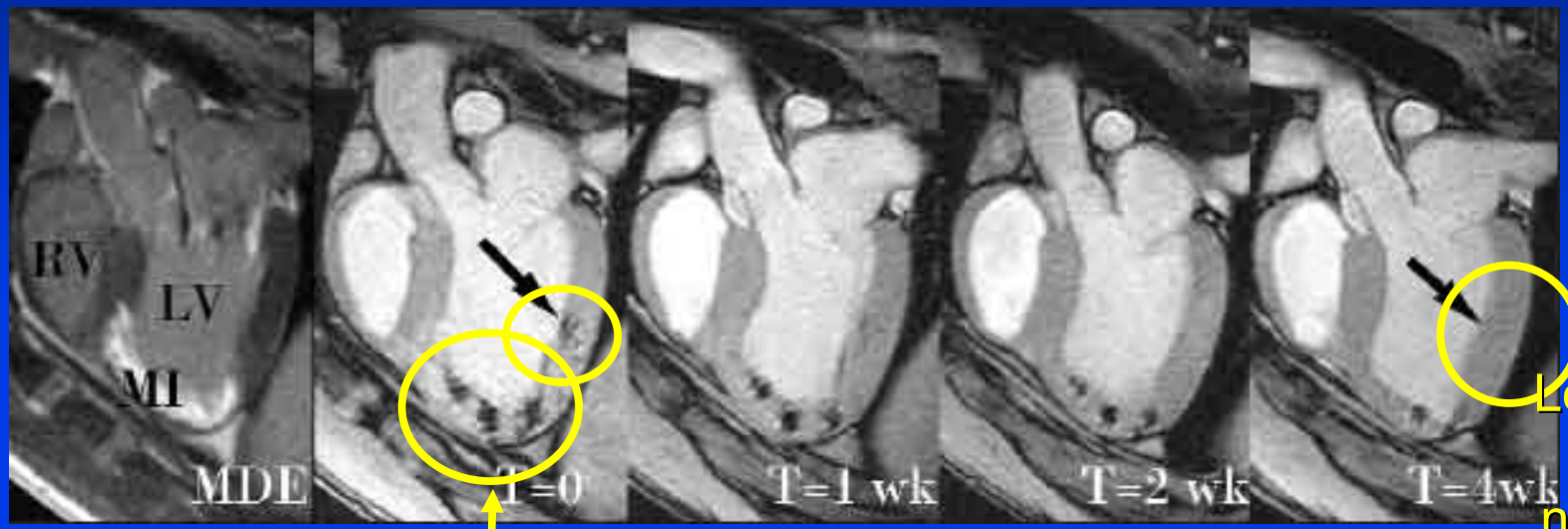
T_1 of ^{19}F PFTBA shows changes in **dissolved oxygen content** during hypoxic intervention.





Constantinidis et al.

Stem Cell Therapeutics—Cell Persistence



Loss of cells from noninfarcted tissue

Hypointense regions showing sites of mesenchymal stem cell injection

D. Kraitchman--JHU

Tissue properties can often be evaluated by highly *sensitive* but *invasive* techniques

- *Gene expression analysis* for genotype and tissue quality
- *Electron microscopy* for microstructure
- *Histology* for exquisite structural detail
- *Immunohistochemistry* for protein expression
- *Optical spectroscopy* for more specific matrix components
- *Microelectrodes / biochemical analysis* for metabolic analysis
- *Mechanical testing* for functional support properties

Unmet Needs

Replacement of gold-standard techniques with non-invasive versions

- Molecule-specific MR:
  example: molecular imaging for collagen I vs collagen II
- Mechanical measurements:
  example: bone/cartilage elastography; strain measurements
- Sequences and analyses more specific to tissue components
  example: water compartment analysis; multiparametric approaches
- Functional analysis (esp. metabolism)
  example: localized spectroscopy for cell number and viability
- Histologic-like resolution
  example: microscopy

Opportunities Abound!

Caveat:

Capital value of publicly traded TE companies:

2007: $4.7 billion US

2000: $2.5 billion US

2003: $300 million US

Lysaght, Tissue Engineering, 2008

Conclusions

- Tissue engineering is currently in a growth phase
- Fundable through several sources
- There is a substantial market presence *(contrast gene therapy)*
- MR can actually contribute to further progress
- *Come to the educational session in Hawaii!*