



# Example for IMPACT Curriculum

**IMPACT Program Curriculum**



# Example of Statement, Storyline, Case

We've shown some examples along the way of statements, storyline, and parts of a case related to the problem of evaluation of osteoarthritis. These are put together here in one place for you to see the progression. In reality, getting to these final products would take much back and forth!



# Monitoring changes in cartilage composition in early osteoarthritis

## IMPACT STATEMENT

### Version 1:

Pharmaceutical researchers can now test the efficacy of therapies which might prevent or reverse the effects of osteoarthritis with our MRI technique which images the concentration of the critical glycosaminoglycan molecules in cartilage.

### Version 2:

Biologists and physiologists can now monitor the degeneration and repair of intact cartilage under conditions of metabolic and mechanical stress with our developed magnetic resonance imaging technique, which images the concentration of the critical glycosaminoglycan molecules in cartilage.

### Poor version1:

We are using T1 maps after IV GdDTPA administration to provide an image of GAG concentration; this should enable an earlier detection of OA.

### Poor version 2:

We are developing MRI techniques for early detection of OA.



# Monitoring changes in cartilage composition in early osteoarthritis : IMPACT STORYLINE

Osteoarthritis is a debilitating disease whose current “cure” is total joint replacement surgery.

2. Pharmaceutical therapies have been suggested as means of delaying or preventing the development of arthritis, however it has been difficult to evaluate the effectiveness of these therapies.
3. In order to enable evaluation of these therapies in clinical trials, our goal was to develop a method to measure the concentration of macromolecules which are lost early in the disease process. In particular, we wanted to measure the concentration of glycosaminoglycans (GAG).
4. We proposed a method based on the fact that GAG have a net negative bound charge, and this charge is balanced by the free ions in the tissue. Therefore the concentration of positively charged free ions will be higher in cartilage with low GAG than in healthy cartilage, and this is the basis for histology stains such as Toluidine Blue<sup>+</sup>
5. One of the commonly used MRI contrast agents (molecules that are injected into the body and can be imaged with standard MRI techniques), is Gd-DTPA<sup>2-</sup>, and has a negative charge. We hypothesized that Gd-DTPA<sup>2-</sup> will distribute in lower concentration in diseased cartilage depleted of GAG. We called this proposed technique delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC).
6. Our goals were to: (1) Validate this technique ex-vivo, (2) Demonstrate the feasibility in vivo, and (3) Monitor GAG in patients in situations which might be early OA.
7. We first demonstrated that by imaging excised cartilage samples in Gd-DTPA<sup>2-</sup> and imaging with MRI, the “GAG map” matched that of standard GAG histology.
8. In the second set of experiments, by injecting this contrast agent intravenously and giving it time to penetrate cartilage, imaging the knee, and then obtaining histology of the cartilage after total knee replacement surgery, we validated that we can image the distribution of GAG in cartilage in patients.
9. Pilot clinical studies demonstrated that not only is there GAG loss in otherwise apparently “healthy” cartilage in patients with early OA, but GAG loss was reversible.
10. With this information, we are able to design clinical trials; in particular, we will enroll patients immediately after ligament tears of the knee, and monitor cartilage status within the first 2 years after injury, with comparison of different physical therapy and pharmacologic therapies.



# Monitoring changes in cartilage composition in early osteoarthritis

Deborah Burstein, Martha Gray

Osteoarthritis is a debilitating disease whose current “cure” is total joint replacement surgery.

Pharmaceutical therapies have been suggested as means of delaying or preventing the development of arthritis, however it has been difficult to evaluate the effectiveness of these therapies.

In order to enable evaluation of these therapies in clinical trials, our goal was to develop a method to measure the concentration of macromolecules which are lost early in the disease process. In particular, we wanted to measure the concentration of glycosaminoglycans (GAG).

We proposed a method based on the fact that GAG have a net negative bound charge, and this charge is balanced by the free ions in the tissue. Therefore the concentration of positively charged free ions will be higher in cartilage with low GAG than in healthy cartilage, and this is the basis for histology stains such as Toluidine Blue<sup>+</sup>

One of the commonly used MRI contrast agents (molecules that are injected into the body and can be imaged with standard MRI techniques), is Gd-DTPA<sup>2-</sup>, and has a negative charge. We hypothesized that Gd-DTPA<sup>2-</sup> will distribute in lower concentration in diseased cartilage depleted of GAG. We called this proposed technique delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC).

Our goals were to: (1) Validate this technique ex-vivo, (2) Demonstrate the feasibility in vivo, and (3) Monitor GAG in patients in situations which might be early OA.



We first demonstrated that by imaging excised cartilage samples in Gd-DTPA<sup>2-</sup> and imaging with MRI, the “GAG map” matched that of standard GAG histology.

In the second set of experiments, by injecting this contrast agent intravenously and giving it time to penetrate cartilage, imaging the knee, and then obtaining histology of the cartilage after total knee replacement surgery, we validated that we can image the distribution of GAG in cartilage in patients.

Pilot clinical studies demonstrated that not only is there GAG loss in otherwise apparently “healthy” cartilage in patients with early OA, but GAG loss was reversible.

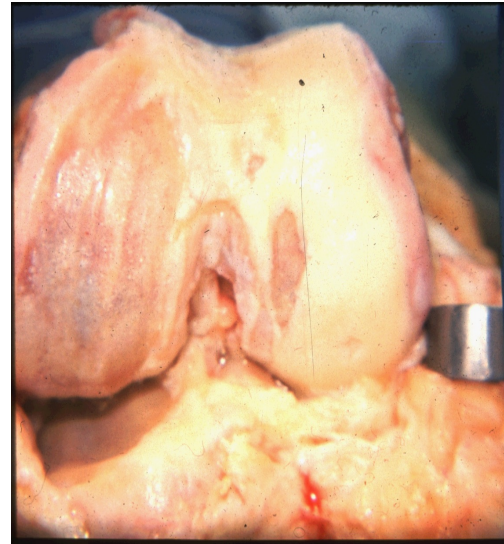
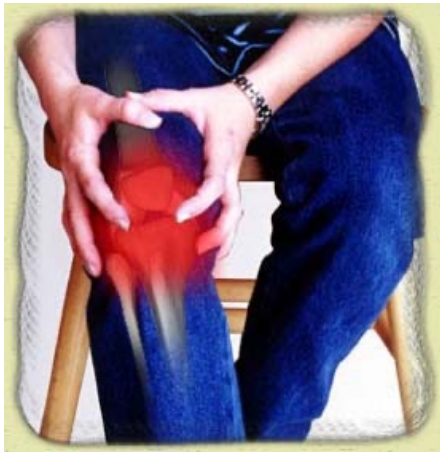
With this information, we are able to design clinical trials; in particular, we will enroll patients immediately after ligament tears of the knee, and monitor cartilage status within the first 2 years after injury, with comparison of different physical therapy and pharmacologic therapies.

# Cartilage injury and repair after ligament tears of the knee

*Deborah Burstein, Ph.D.*  
*Martha Gray, Ph.D.*



Osteoarthritis (OA) is a debilitating disease,  
whose current "cure" is total joint replacement



# Challenge to assess therapeutic approaches

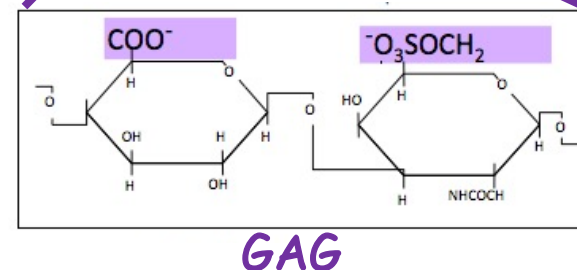
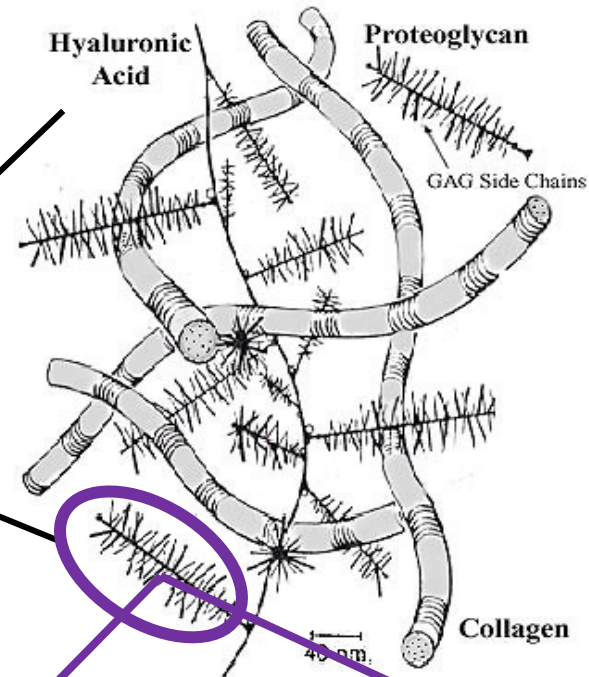


- Various pharmaceutical therapies have been suggested as a means of delaying or preventing OA development.
- Can't "see" if cartilage is getting "better" or "worse" in standard imaging tests

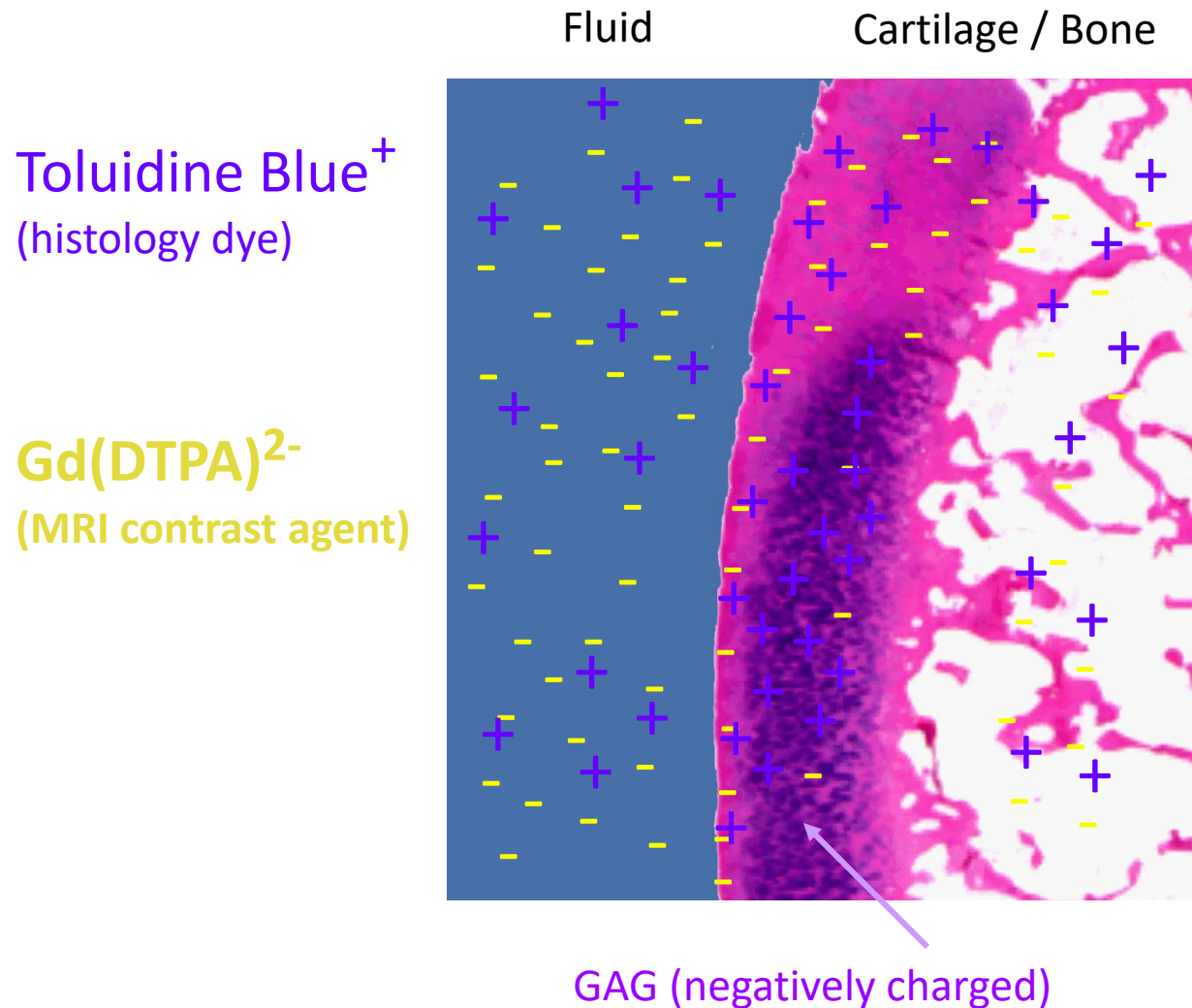
# Potential diagnostic: Measurement of the Concentration of Glycosaminoglycans (GAG)



Critical macromolecules in cartilage lost early in OA



# Delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC)



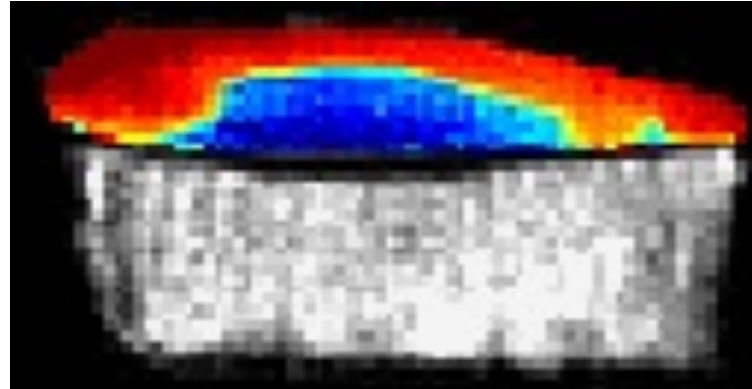
## Goals:

- (1) Validate this technique ex-vivo,
- (2) Demonstrate the feasibility in vivo, and
- (3) Monitor GAG in patients in situations which might be early OA.

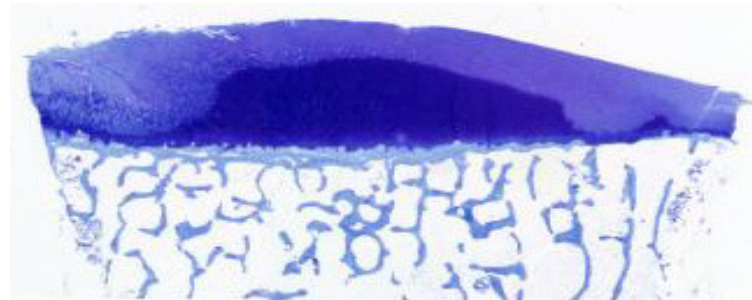


# Excised human tissue

dGEMRIC



Histology



# dGEMRIC: In vivo protocol



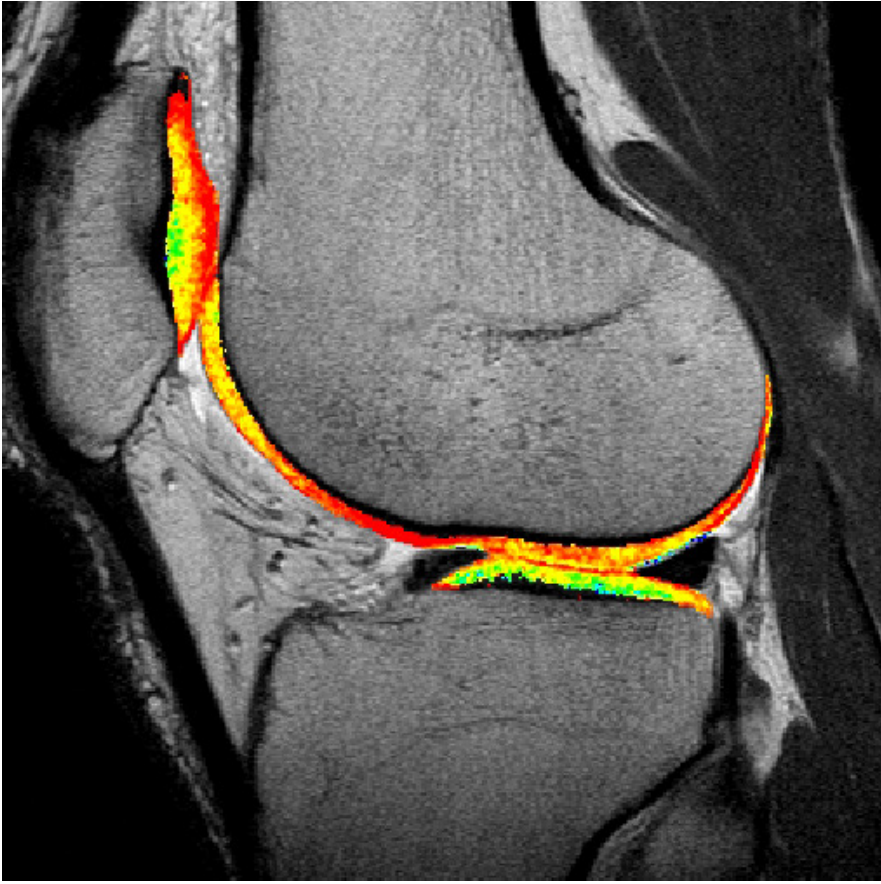
Inject  $\text{GdDTPA}^{2-}$   
intravenously



Move joint for  
10 minutes



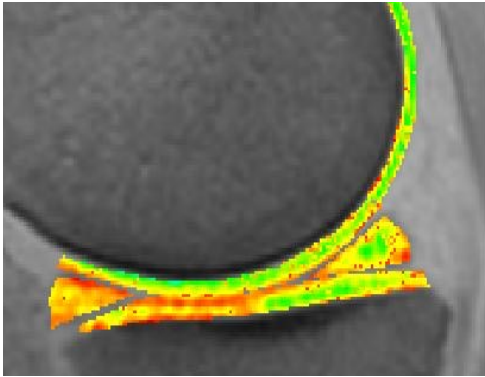
Image 90 minutes  
after injection



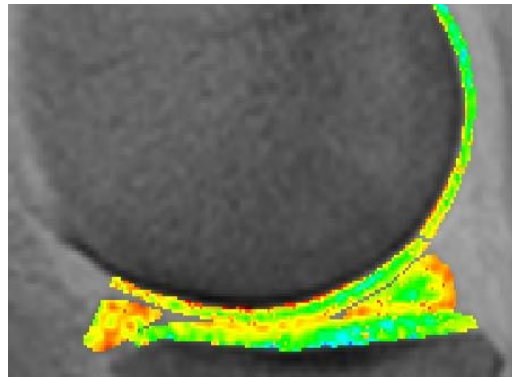
# Injury and Spontaneous Repair

## Evidence for the potential of therapeutics

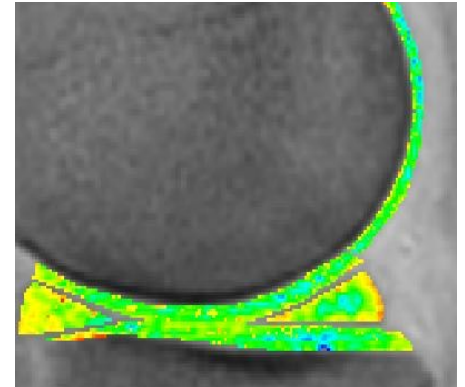
Baseline



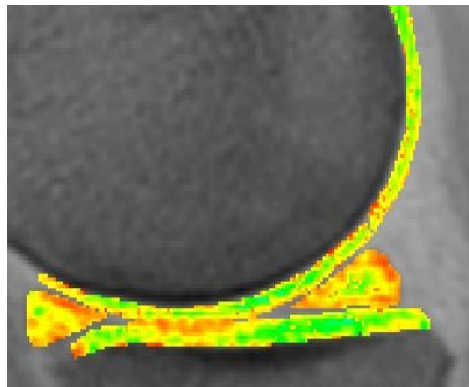
3 months



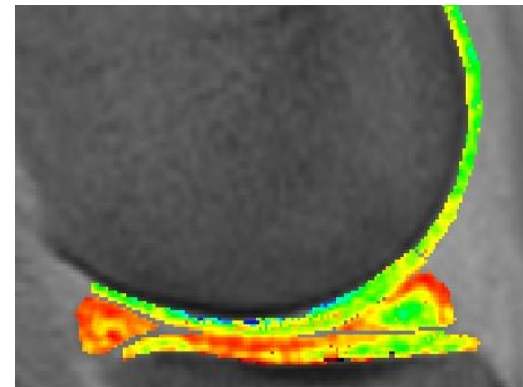
6 months



1 year



2 years



# Path to impact

Design clinical trials;

- patients immediately after ligament tears of the knee,
- monitor cartilage status within the first 2 years after injury,
- comparison of different physical therapy and pharmacologic therapies.