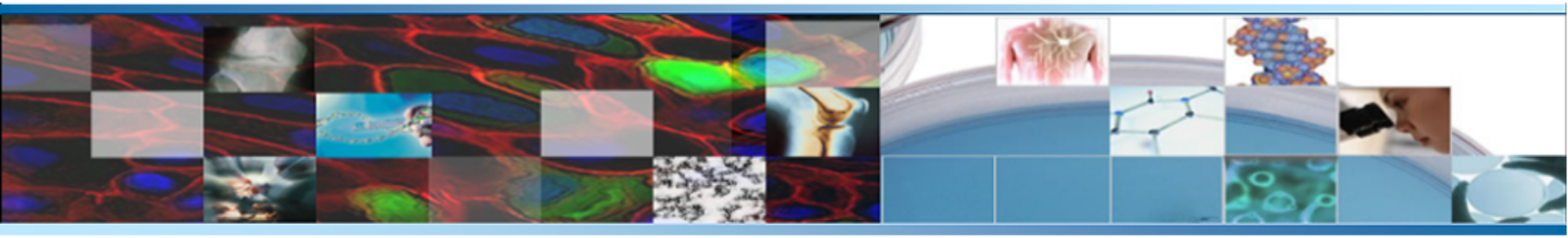


Human Gene Transfer Protocol: #0912-1016

A Phase II Study to Determine the Safety & Efficacy of TG-C in Patients with Grade 3 Chronic Degenerative Joint Disease of the Knee

NIH RAC MEETING

March 11, 2010

Presentation Outline

1 TG-C Technology

2 Preclinical Results

3 Phase I Results

4 Phase II Protocol

5 Q&A

TG-C Product Overview

TG-C harnesses the regenerative capabilities of TGF-β1 to repair damaged cartilage

Untransduced Chondrocytes (hChonJ)

- Primary human chondrocytes
- Bulk material to fill defect site
- Target cells for expressed TGF-β1

Transduced Chondrocytes (hChonJb#7)

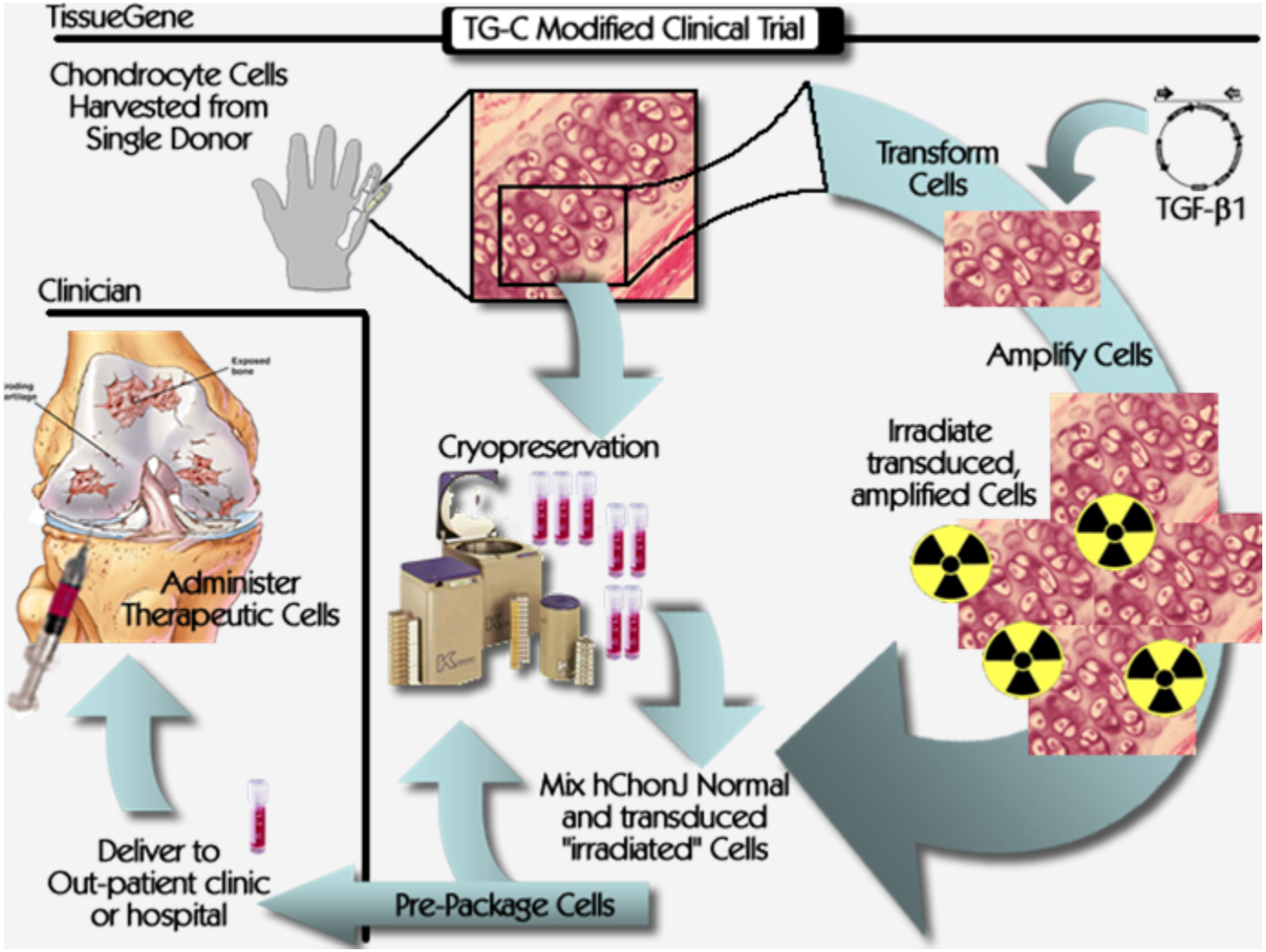
- hChonJ cells expressing TGF-β1
- Induce hChonJ & host chondrocytes to form cartilage via paracrine effects

TG-C

- hChonJ & hChonJb#7 mixed in 3:1 ratio
- Direct injection of TG-C into knee joint
- Optimal regeneration of hyaline cartilage

Developed to treat severe degenerative arthritis of the knee

TG-C Product Development



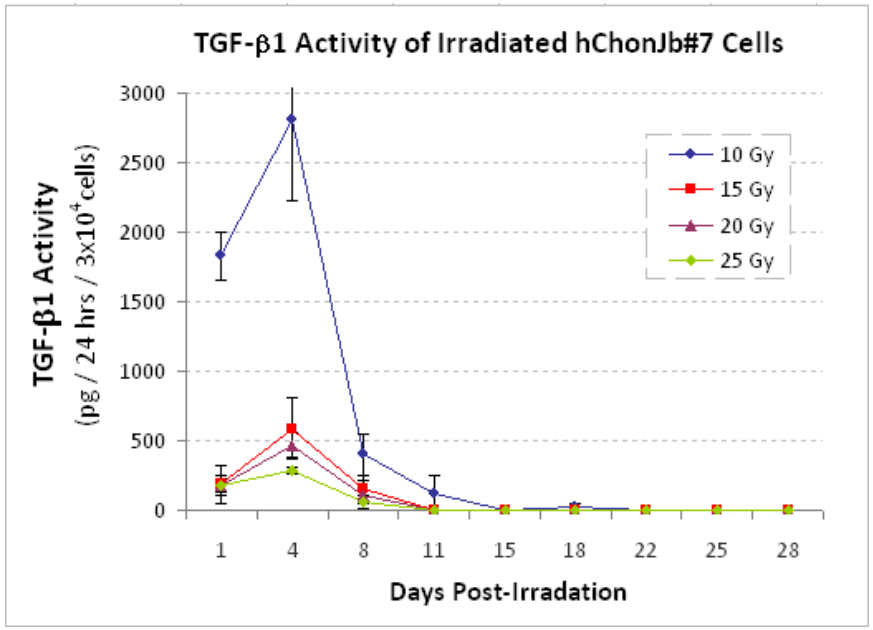
Transduced Cell Characterization & Irradiation

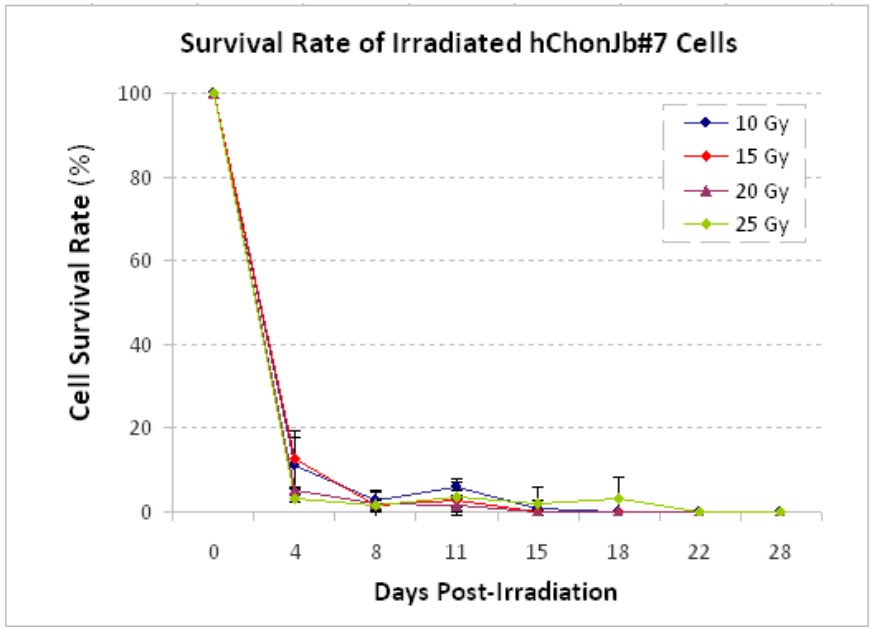
hChonJb#7 Cell Characterization

- Negative for HLA type-A antigen
- Single-clone isolation via limiting dilution
- Stable transfection, insertion site analysis
- Negative for gag, pol, env gene expression

Irradiation of hChonJb#7 at 15 Gy

- Render cells replication incompetent
- TGF-ß1 activity continuous for 11 days
- Cells disappeared after 14 days





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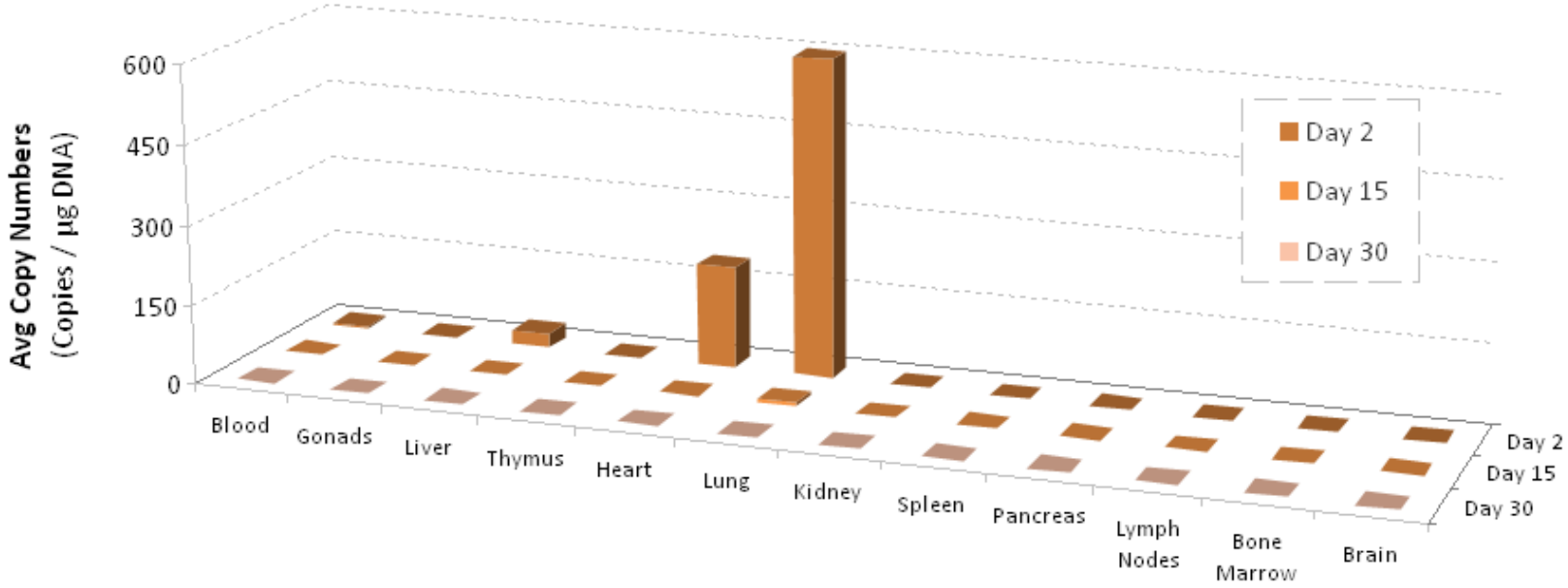
Biodistribution in SCID Mice

90-Day Biodistribution Study of TG-C in SCID Mice

- Single intravenous administration of TG-C in SCID mice
- TG-C doses range: $1x10^5$ - $4x10^6$ cells/animal
- Maximum tolerated dose (MTD): $1x10^6$ cells
- TG-C detected in blood, liver, heart, & lung at day 2
- TG-C found in 1 animal lung at day 15, cleared by day 30

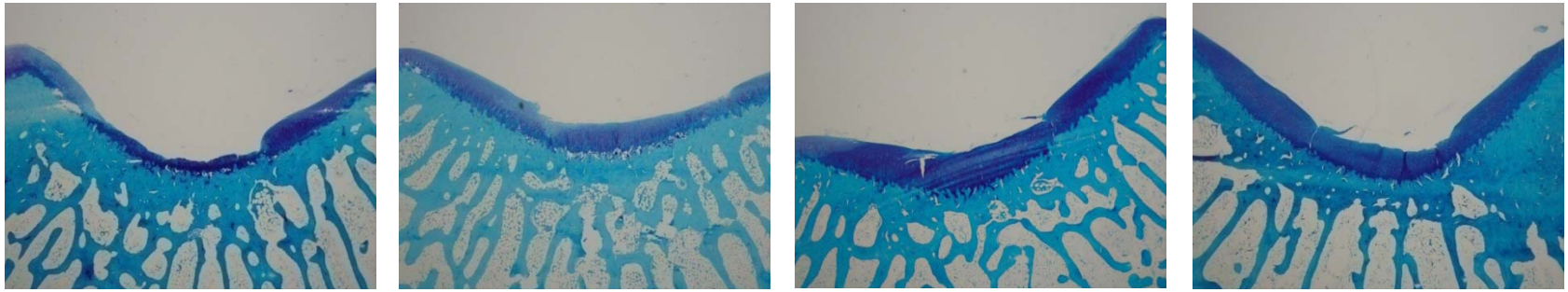


Safety & Efficacy in Rabbits

90-Day & 6-Month Study of TG-C in Rabbits

Study Design	• 90-Day (80 rabbits), 6-Month (40 rabbits) • Surgically induced partial cartilage defect • Single intra-articular injection of TG-C	• Group 1 (control), Group 2 (1.8×10^5 cells) • Group 3 (1.8×10^6 cells), Group 4 (9.0×10^6 cells)
Safety Results	• No treatment-related mortality • No dose-related toxicity • No abnormal clinical observations	• No changes in pathology or antibody analysis • No TG-C detected in blood or tissues at day 30
Efficacy Results	• Greater efficacy observed in higher doses compared to low dose TG-C & control • Most extensive & consistent hyaline cartilage formation in higher dose groups	

Histological Results in Rabbits 30-Days Post-Dosing of TG-C



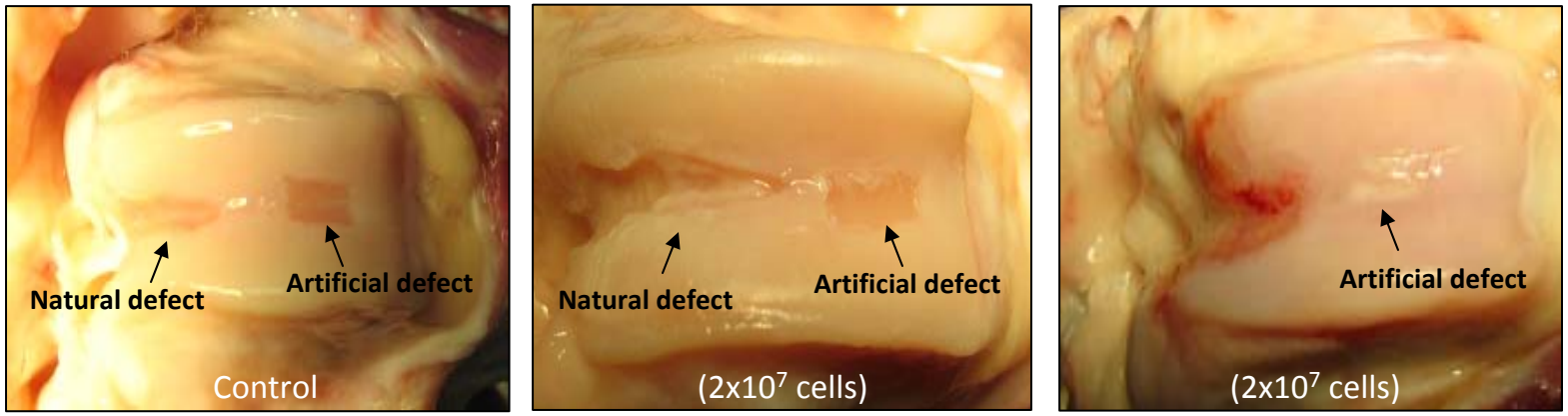
Control | Low Dose (1.8×10^5 cells) | Mid Dose (1.8×10^6 cells) | High Dose (9.0×10^6 cells)

Safety & Efficacy in Goats

8-Week Pilot, 1-Year Single-Dose, 1-Year Multiple-Dose Study of TG-C in Goats

Study Design	• Artificial full-thickness cartilage defects • Single & multiple intra-articular injections • 8-Week (control, $1x10^6$ & $2x10^7$ cells)	• 1-Yr Single-Dose (untreated, control & $3x10^7$ cells) • 1-Yr Multi-Dose (control, $1x10^7$ & $5x10^7$ cells) • 3 injections compared to 1 injection & control
Safety Results	• No treatment-related mortality • No dose-related toxicity • No abnormal clinical observations	• No WBC increase due to multiple doses • No TG-C detected in blood or tissue at week 8
Efficacy Results	• Chondrocyte proliferation, Type II collagen deposition, & hyaline cartilage formation observed at high doses of TG-C at 8-weeks • Greater cartilage formation observed in TG-C treated groups than control at 1 year	

8-Week Pilot Study of TG-C in Goats



Summary of Preclinical Safety Results

Biodistribution	• TG-C did not adversely distribute or persist following systemic administration to SCID mice or following intra-articular injection in either rabbits or goats.
Safety Results	• TG-C found to be well-tolerated in rabbits & goat preclinical studies • No evidence of treatment-related mortality or dose-related toxicity • High doses of TG-C shown to be safe at 42x the initial TG-C dose for Phase I
Efficacy Results	• TG-C effectively promotes regeneration of hyaline cartilage in goats & rabbits • Efficacy observed at doses equivalent to 85% and 420% of Phase II TG-C dose

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U.S. Phase I Protocol Synopsis

U.S. PHASE I PROTOCOL FOR TG-C	
Study Design	• Multi-center, placebo-controlled, single-blind, dose-escalating, & randomized
Study Population	• 12 adults with refractory degenerative joint disease (DJD) of the knee • Scheduled for total knee replacement 1 month following dosing
Administration	• Single intra-articular knee injection of TG-C or placebo
Dose Levels	• Dose level 1: $3x10^6$ cells/joint (N=3) or placebo (N=1) • Dose level 2: $1x10^7$ cells/joint (N=3) or placebo (N=1) • Dose level 3: $3x10^7$ cells/joint (N=3) or placebo (N=1)
Evaluation Schedule	• During screening, prior to dosing, & 2 hrs post-dosing • Days 3, 7, 11, 28, & 29 following treatment • Month 3, 6, 9, & 12 following treatment

U.S. Phase I Safety Results

Summary	• All 12 patients have completed 9-month follow-up without any safety concerns • TG-C well-tolerated at all dose levels, with no treatment related SAEs or AEs

U.S. Phase I Safety Results for TG-C	
SAE & Toxicity	• No treatment-related SAEs or dose-limiting toxicity • No changes in clinical chemistry, hematology, or urine analysis.
Adverse Events	• No treatment-related AEs
PK	• No confirmed increase in TGF-β1 levels of TG-C treated patients • No vector DNA or RCR detected by PCR
Histology & MRI	• No evidence of abnormal tissue growth

Korea Phase I Protocol Synopsis

KOREA PHASE I PROTOCOL FOR TG-C	
Study Design	• Single-center, open-label, dose-escalation study
Study Population	• 12 adults with refractory degenerative joint disease (DJD) of the knee
Administration	• Single intra-articular knee injection of TG-C
Dose Levels	• Dose level 1: $3x10^6$ cells/joint (N=4) • Dose level 2: $1x10^7$ cells/joint (N=4) • Dose level 3: $3x10^7$ cells/joint (N=4)
Evaluation Schedule	• During screening, prior to dosing, & 2 hrs post-dosing • Week 1, 2, 3, & 4 following treatment • Month 3, 6, 9, & 12 following treatment

Korea Phase I Safety Results

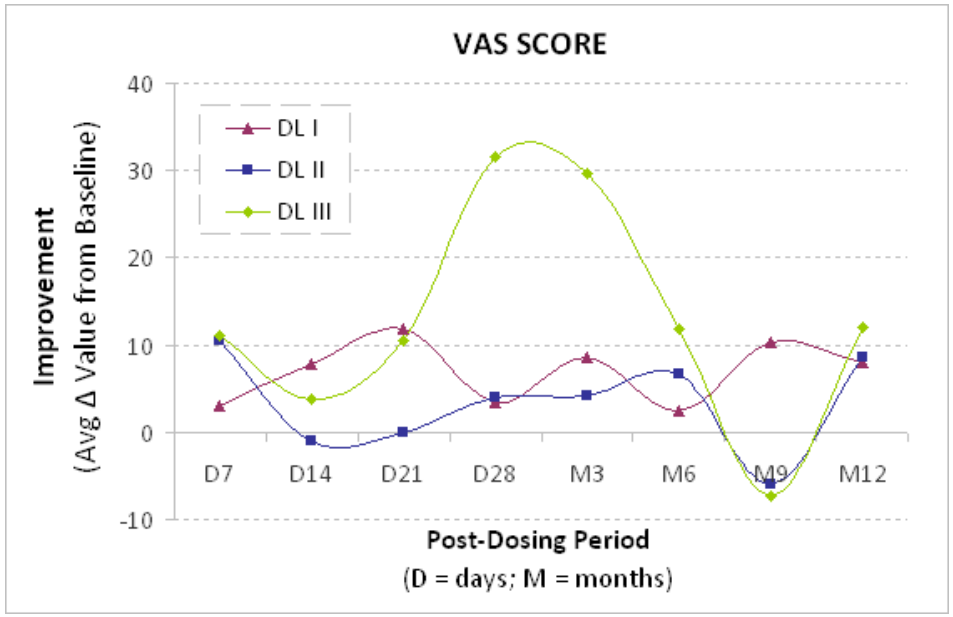
Summary	• All 12 patients have completed 12-month follow-up without any safety concerns. • TG-C well-tolerated at all dose levels, with only minor injection site reactions observed

Korean Phase I Safety Results for TG-C	
SAE & Toxicity	• No treatment-related SAEs or dose limiting toxicity • No clinical deviations in lab safety parameters, vital signs, or physical exams
Adverse Events	• Edema (swelling), effusion & minor localized reactions observed • Edema typically observed 1-3 days post-dosing & disappeared within 2 days • No adverse effects observed in laboratory safety parameters evaluated
PK	• No elevated TGF-β1 levels detected by ELISA • No vector DNA or RCR detected by PCR
Histology & MRI	• No evidence of abnormal tissue growth

Evidence of Symptomatic Improvement (Korea)

Summary

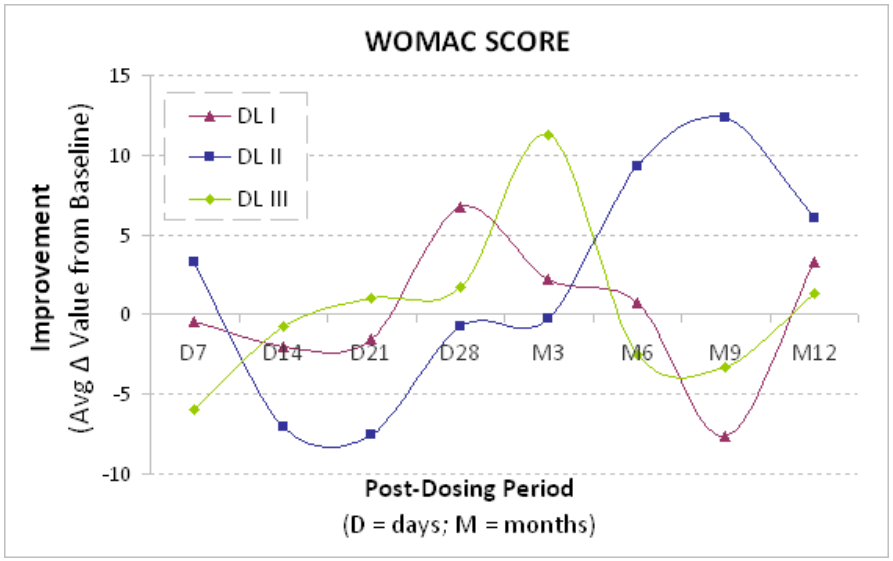
- 3 scoring systems used to evaluate symptomatic improvement: VAS, WOMAC, & KSCRS
- Suggest trend towards dose-dependent improvement of TG-C in patient symptoms

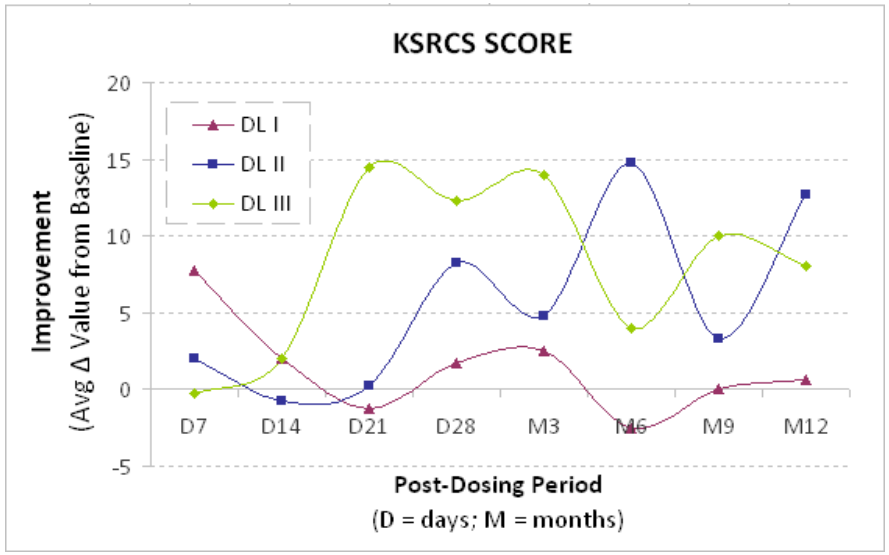


Visual Analog Scale (VAS) Pain Index

- Pain intensity measured along 100mm line
- Decrease in pain observed in all 3 dose levels
- Dose level 3 improved from baseline to M3

Evidence of Symptomatic Improvement (Korea)





WOMAC Osteoarthritis Index

- Evaluates pain, disability, & joint stiffness
- Decrease in score = symptomatic improvement
- 7 of 12 patients improved from baseline to M6
- Early improvement observed in dose level 1 & 2

Knee Society Clinical Rating System (KSCRS)

- Evaluates pain, range of motion, & joint stability
- Increase in score = symptomatic improvement
- 10 of 12 patients improved from baseline to M6
- Dose level 2 & 3 improved from baseline to M12

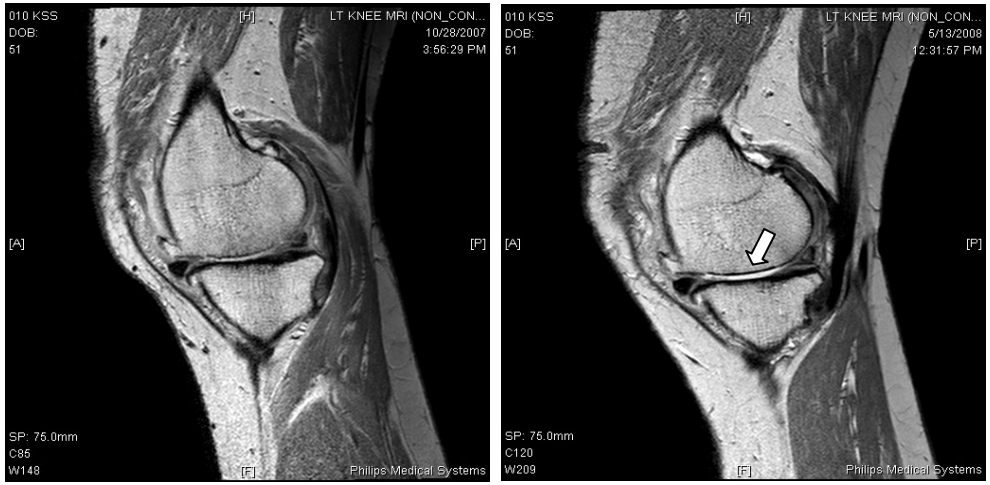
Evidence of Cartilage Regeneration (Korea)

New cartilage formation observed at the lateral epicondyle.

Baseline **6-months post-dosing**

Patient #007:
Dose Level 2
Proton Density
Coronal MRI

New cartilage formation observed at the lateral epicondyle.



Baseline **6-months post-dosing**

Patient #013:
Dose Level 3
Proton Density
Sagital MRI

Summary of Phase I Results

Phase I Overview	• Total of 21 patients treated with TG-C in Phase I trials (U.S. & Korea) • 12 patients treated in Korea & 9 patients treated in the U.S.
Safety Results	• TG-C well-tolerated at all dose levels with no treatment-related SAEs. • No elevated TGF-β1 levels, vector DNA, or RCR detected. • No AEs observed in the U.S. with AEs in Korea primarily transient injection site reactions
Efficacy Results	• Symptomatic improvement & cartilage regeneration assessed in Korea • Suggest dose-dependent improvement in arthritic symptoms & cartilage regeneration

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Korea Phase IIa Protocol Synopsis

KOREA	A Phase IIa Study to Determine the Safety and Efficacy of TG-C in Patients with Grade 4 Chronic Degenerative Joint Disease (DJD) of the Knee
Study Design	• Multi-center, randomized, escalating dose-response
Study Population	• 28 adults with Grade 4 (ICRS) chronic knee DJD
Administration	• Single intra-articular injection to the damaged joint area
Dosage Levels	• Low dose: $6x10^6$ cells/joint (N=14) • High dose: $1.8 x10^7$ cells/joint (N=14)
Evaluation Schedule	• During screening & prior to dosing • Week 2 & 4 and Month 3 & 6 following treatment

Korea Phase IIa Safety & Efficacy Endpoints

Current Status	• All 28 patients have been dosed as of Dec 30, 2009 with no SAEs reported

Korean Phase IIa Endpoints for TG-C	
Safety Endpoint	• Incidence & severity of AEs, injection site irritation, or other abnormalities • Incidence & severity of inflammation measured by ESR & CRP • Changes in physical examination & laboratory tests
Primary Efficacy	• Changes in arthritic symptoms, pain & knee functionality • Assessed by International Knee Documentation Committee (IKDC)
Secondary Efficacy	• Changes in symptoms, pain & knee functionality (WOMAC & VAS) • Regeneration of hyaline cartilage via 3D MRI analysis (0.5mm)
PK	• TGF-β1 levels detected by ELISA • Vector DNA & RCR detected by PCR

U.S. Phase II Protocol Synopsis

U.S.	A Phase II Dose Response Study to Determine the Safety and Efficacy of TG-C in Patients with Grade 3 Chronic Degenerative Joint Disease (DJD) of the Knee
Study Design	• Multi-center, comparator-controlled, randomized, elective crossover
Study Population	• Adults with Grade 3 (Kellgren & Lawrence) chronic knee DJD
Sample Size	• 100 patients: A sample size of 100 patients (67 TG-C & 33 control) is needed to see at least a 25% difference from the control group with alpha=0.05
Administration	• Single intra-articular injection to the damaged joint area
Dosage Levels	• Dose level: $3x10^7$ cells/joint (N=67) • Control: Single hyaluronan injection (N=33)
Evaluation Schedule	• During screening, prior to dosing, 24 hr post-dosing • Months 1, 3, 6, 12, 18 & 24 post-dosing

U.S. Phase II Efficacy Endpoints

Current Status

- Phase II protocol submitted to the FDA in Sept 2009 & received no comment
- Phase II protocol approved by the Sinai Hospital IRB

	EFFICACY CRITERIA	EVALUATION METHOD
Primary Endpoint	• Articular knee cartilage damage • Knee symptoms, pain & functionality • Need for total knee arthroplasty	• Lysholm Knee Scale • Knee Injury & Osteoarthritis Outcome Score (KOOS) • Election to undergo total knee arthroplasty (TKA)
Secondary Endpoint	• Cartilage regeneration • Pain reduction • Inflammation • Knee functionality	• 3T MRI (baseline to month 3, 6, 12, & 24) • VAS, questionnaires, analgesia (incidence & dose) • Anti-inflammatory medications (incidence & dose) • Lower Extremity Functional Scale (LEFS)

U.S. Phase II Safety Endpoints

Current Status	• Phase II protocol submitted to the FDA in Sept 2009 & received no comment • Phase II protocol approved by the Sinai Hospital IRB

U.S. Phase II Safety Endpoints for TG-C		
Safety Endpoint	• Adverse events (incidence & severity) • Injection site irritations • Other abnormalities	• Changes in physical exams • Clinical chemistry analysis • Hematology & urinalysis tests
PK	• TGF-β1 levels detected by ELISA	• Vector DNA & RCR detected by PCR
Immune Response	• C-reactive protein (CRP) • Interferon-gamma (IFN-γ)	• White blood cell count (WBC) • Erythrocyte sedimentation rate (ESR)

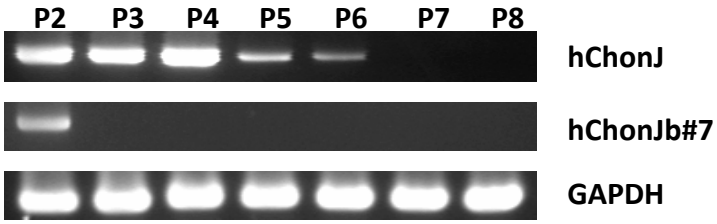
Stop Criteria	• Temporary suspension of dosing & review by IDMC & regulatory authorities will occur for: • Any serious adverse event attributed to TG-C administration • A Grade 3 or two persistent Grade 2 events due to TG-C (NCI CTCAE Classification)

Cell-Mediated Immune Response Considerations

TG-C Characteristics Reducing Immunogenicity

- Knee joint immuno-privileged location
- HLA type-A antigen negative
- Chondrocytes immunosuppressive

RT-PCR Analysis of HLA Type-A Antigen



No Previous Evidence of TG-C Immunogenicity

- No WBC increase in goat multi-dose study
- No WBC increase in Phase I (US & Korea)
- No SAEs reported in Phase IIa (Korea)
- 49 total patients safely treated with TG-C

U.S. Phase II Assessment Methods

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- White blood cell count (WBC)
- Interferon-gamma (IFN-γ)

Concluding Remarks

1 TG-C Technology Review

2 Preclinical Review

3 Phase I Review

4 Phase II Protocol

5 Q&A