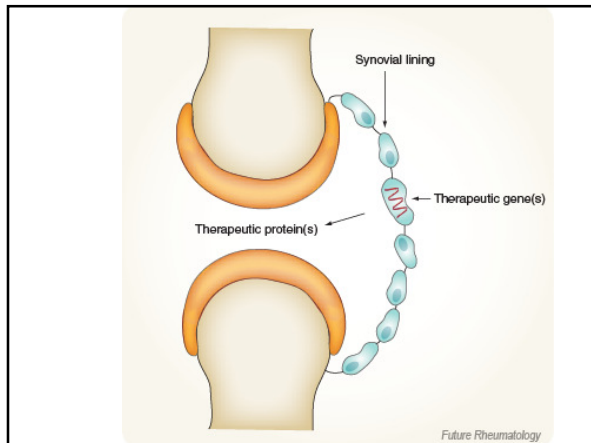
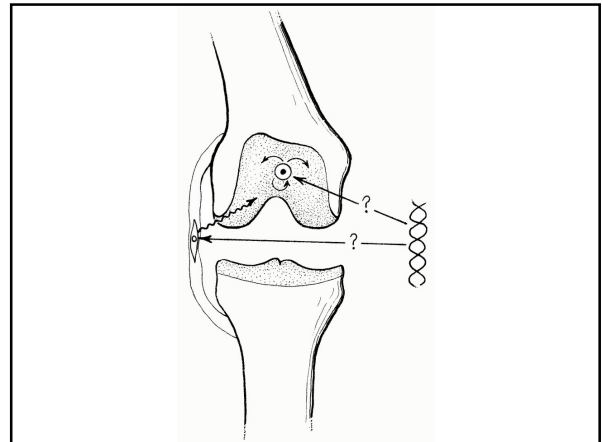


## YEAR IN REVIEW UPDATE ON REGENERATIVE MEDICINE AND OA BY GENE THERAPY



*Chris Evans,  
Centre for Molecular Orthopaedics  
Harvard Medical School*



## UPDATE VECTORS

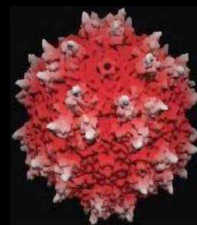
Adeno-associated virus (AAV) is emerging as the vector of choice for clinical application:

- Perceived to be safest viral vector
- Improved AAV technology
- Non-viral vectors remain inefficient

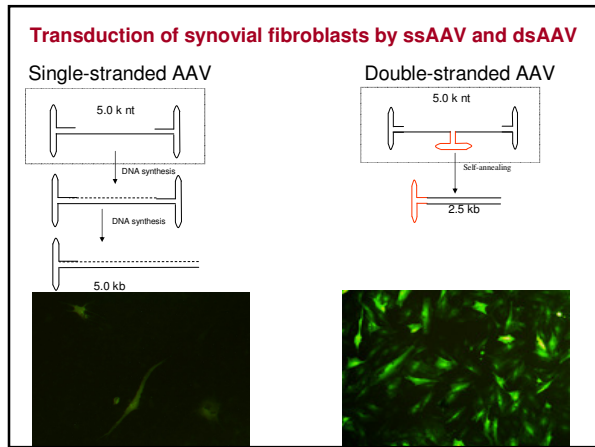
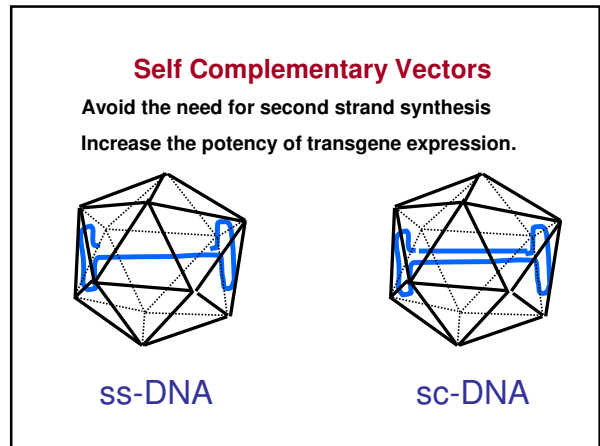
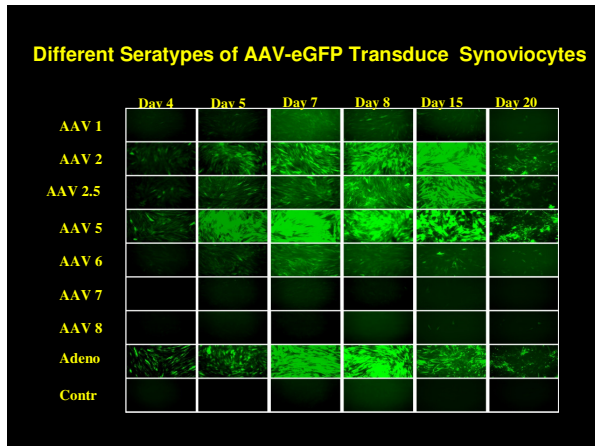
## RECENT IMPROVEMENTS IN AAV TECHNOLOGY

- Improved production technologies
- Identification and modification of novel serotypes
- Development of recombinant, double-stranded (self-complementary) DNA genomes

## AAV Serotypes

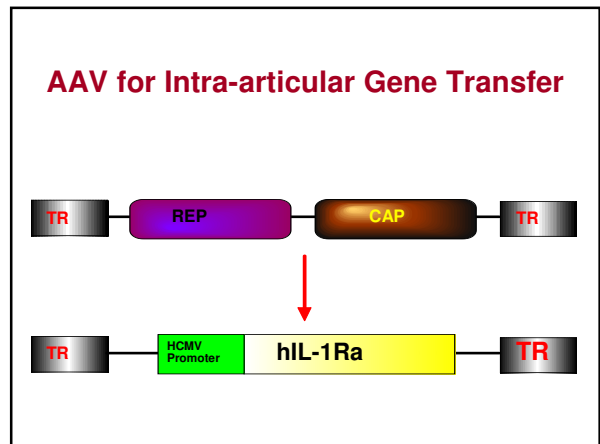


AAV1  
AAV2  
AAV3  
AAV4  
AAV5  
AAV6  
AAV7  
AAV8  
AAV9  
AAV2.5



- USE OF rAAV IN HUMAN GENE THERAPY TRIAL FOR RA**
- Sponsor: Targeted Genetics Corp.
  - AAV-etanercept (single stranded)
  - Injected i.a. into symptomatic RA joints
  - Phase I and Phase I/II trials
  - N=130
  - Suggestion of symptomatic improvement in some subjects.
  - One death!

- July, 2007 death in RA gene therapy clinical trial using AAV**
- 36 year old ♀; 15 year history of RA
  - Humira, prednisone, methotrexate,
  - i.a. steroid for symptomatic knee
  - Died ~1 month after receiving a 2<sup>nd</sup> i.a.injection of AAV.etanercept into knee
  - Cause of death: histoplasmosis-retroperitoneal haematoma
  - FDA has allowed trial to continue



## PHASE I CLINICAL TRIAL OA OF THE KNEE (NIH funded)

- Knee joints with mild to moderate OA
- In vivo delivery – scAAV
- IL-1 Ra as the transgene
- Dose-escalation; 9 subjects
- Primary outcomes: safety and IL-1Ra expression
- Secondary outcomes: WOMAC; MRI

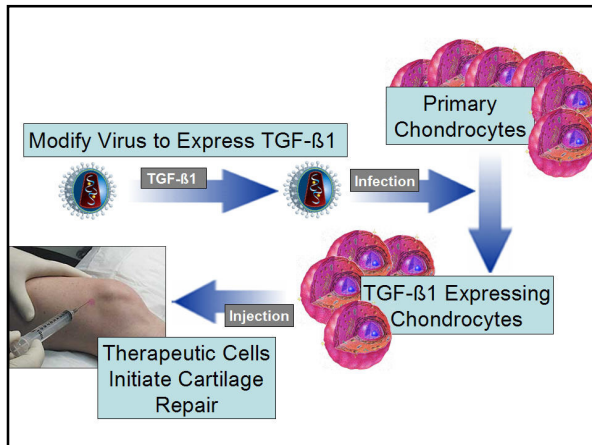
## CLINICAL TRIALS IN OA GENE THERAPY

### SPONSOR

USA -TissueGene Inc. (Rockville, MD)  
Korea – Kolon Life Sciences

### DISCLOSURE

CHE is on the SAB of Tissuegene



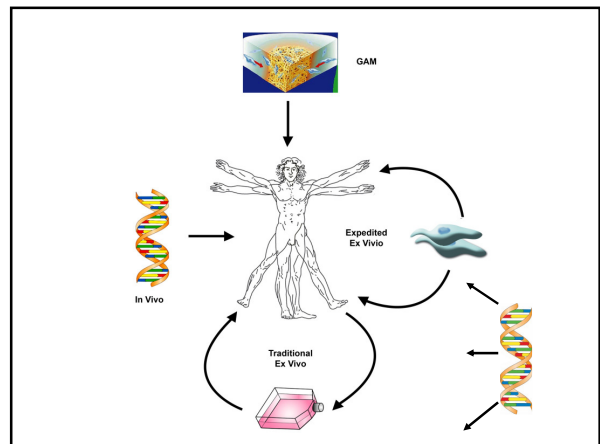
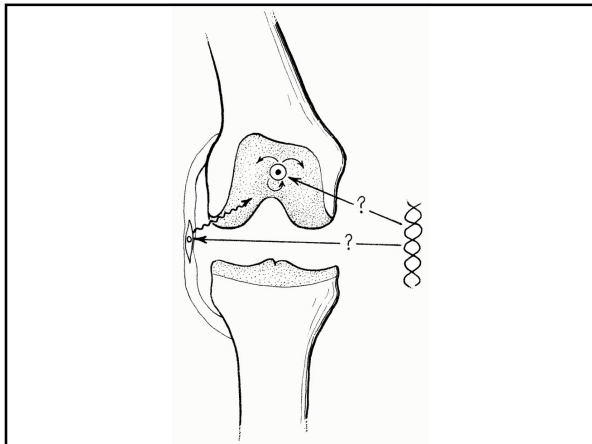
## CLINICAL TRIAL IN OA GENE THERAPY

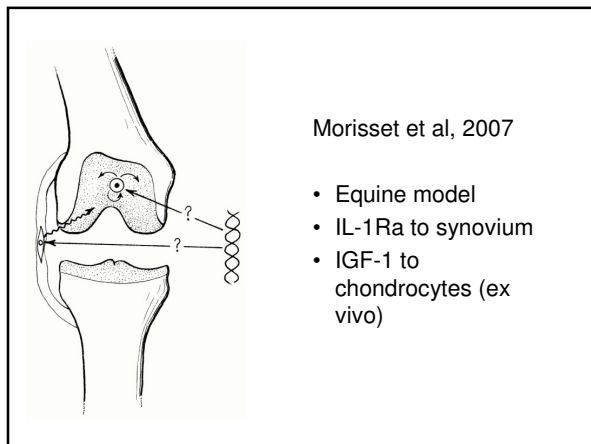
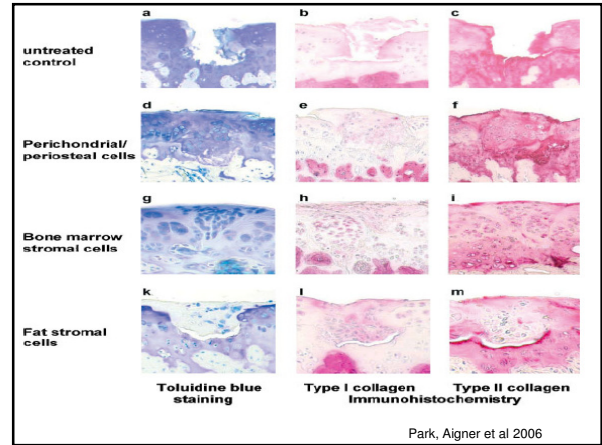
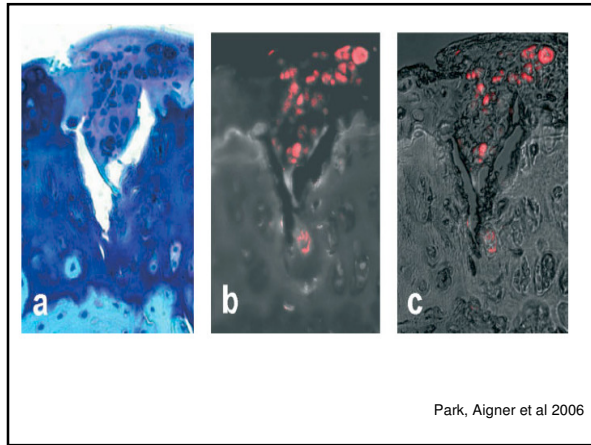
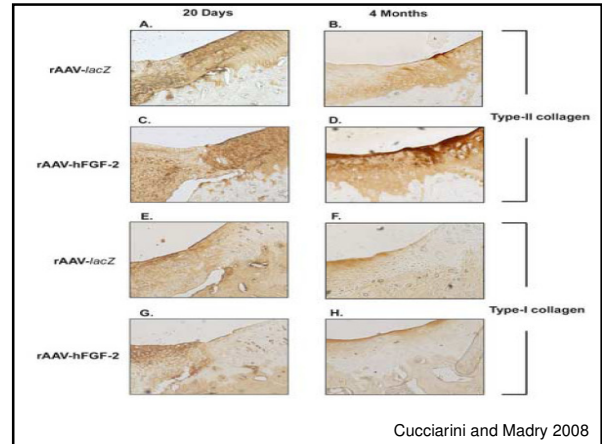
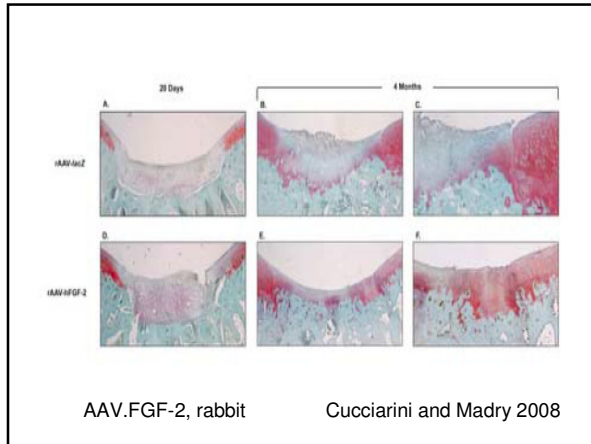
### STATUS

12 Subjects treated in Korea; 4 in US

### RESULTS

No elevation of TGF- $\beta_1$  in serum  
2 subjects presented with synovial effusion  
8 subjects reported "symptomatic improvement"  
MRI evidence of cartilage regeneration





## SUMMARY

- Continued accumulation of promising, but preliminary, pre-clinical data using gene transfer to promote cartilage repair (but using injury models, not OA)
- Two Phase I clinical trials using *ex vivo*, retroviral delivery of TGF- $\beta_1$  to joint
- One Phase I clinical trial using *in vivo*, AAV delivery of IL-1Ra in development