Harvard-MIT Division of Health Sciences and Technology
HST.535: Principles and Practice of Tissue Engineering
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PRINCIPLES AND PRACTICE OF TISSUE ENGINEERING

"GENE TRANSFER WEDDED TO TISSUE ENGINEERING"

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WHY THIS MARRIAGE?

INEFFICIENCIES OF PROTEIN DELIVERY

- SHORT BIOLOGICAL HALF-LIFE
- LOCALISATION DIFFICULT
- RAPID EGRESS FROM APPLICATION SITE
- VERY LARGE DOSES REQUIRED
- SIDE EFFECTS
- COST

ADVANTAGES OF GENE DELIVERY

- SUSTAINED, REGULATED, ENDOGENOUS SYNTHESIS OF GENE PRODUCT
- LOCALIZATION FEASIBLE
- GREATER BIOLOGICAL POTENCY (?)
- MULTIPLE GENES MAY BE TRANSFERRED AND INDEPENDENTLY REGULATED
- ADVANTAGES OF COST AND EFFICIENCY

GENE TRANSFER TO HEAL ORTHOPAEDIC TISSUES

- BONE
- ARTICULAR CARTILAGE
- MENISCUS
- INTERVERTEBRAL DISC
- LIGAMENT and TENDON
- MUSCLE

PRACTICAL ISSUES

- SIMPLICITY
- ECONOMY

  (*in situ* delivery; minimal scaffolds)
- ADAPT STANDARD ORTHOPAEDIC PROCEDURES

FACTORS INFLUENCING CHOICE OF VECTORS

- Long term transgene expression not needed. (Big advantage)
- No need for integrating vectors.(Safer)
- Adenovirus vectors may be adequate for tissue engineering purposes:
  - Easy to construct and produce
  - High levels of transgene expression
  - In vivo delivery possible
  - Immune/inflammatory problems????

Adenoviral Vectors Used in 25% of Gene Therapy Clinical Trials

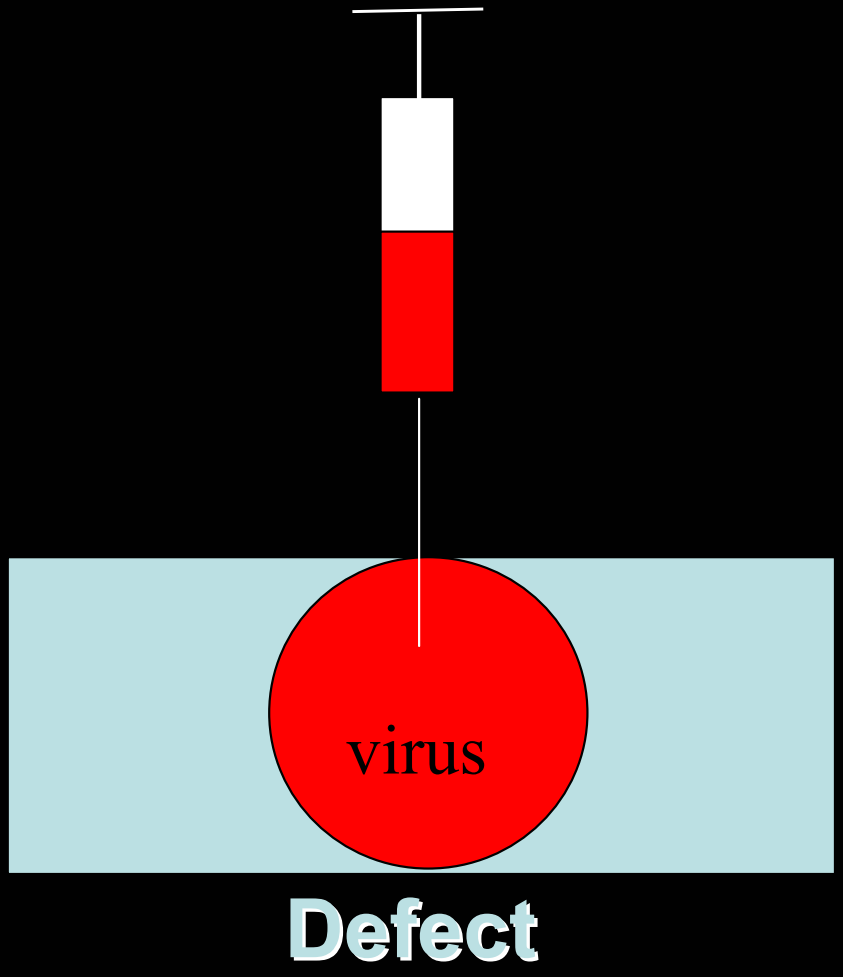
Properties

- Common respiratory virus
- Vector deleted of genes essential for viral replication
- Non-integrating virus
- Efficiently infects most tissues
- Stably produced in high titers
- Relatively large packaging capacity

BONE HEALING

A MINIMALLY INVASIVE,GENE-BASED APPROACH

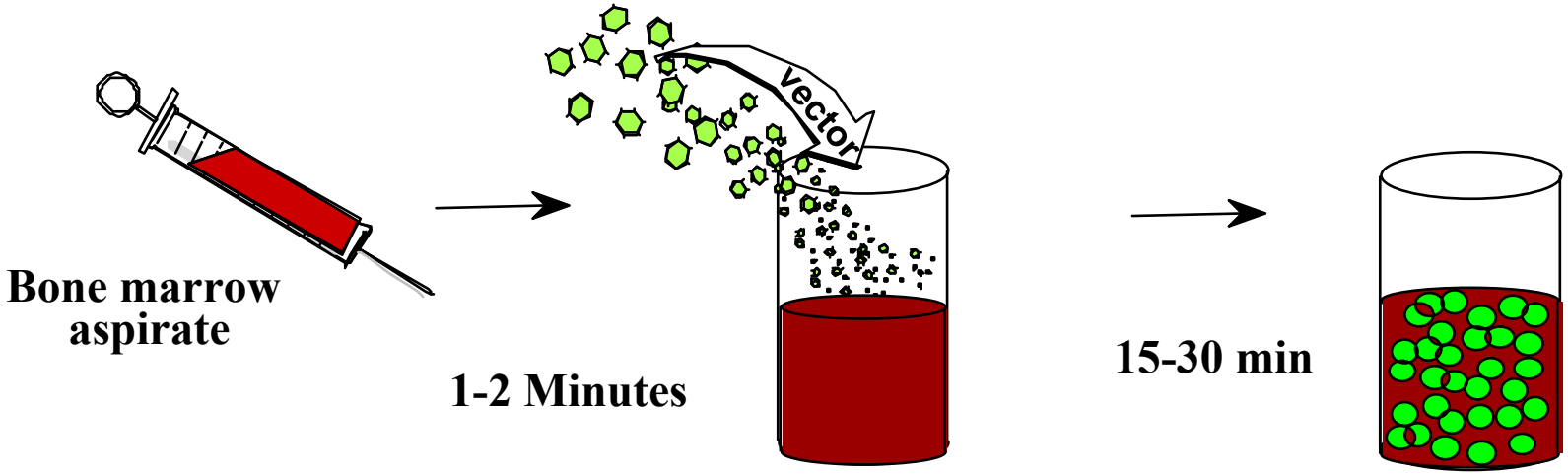
Direct injection of adenovirus-BMP-2



Photos of surgical procedure and results removed for copyright reasons.

GENE TRANSFER TO CARTILAGE DEFECTS

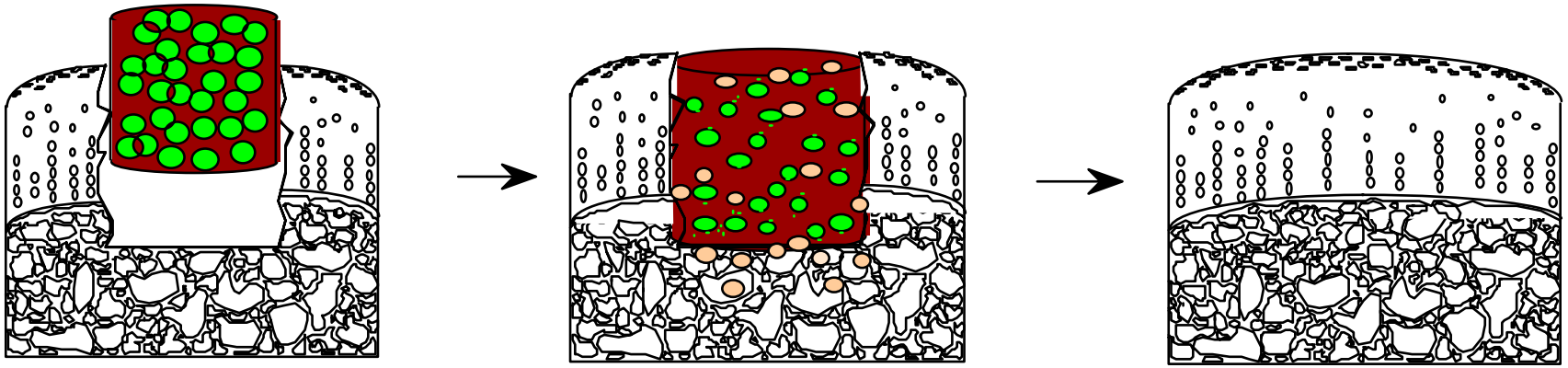
Abbreviated Ex Vivo Gene Delivery To Osteochondral Defects



Blood clot+ modified BMCs

Localized transgene expression and containment of free vector

?



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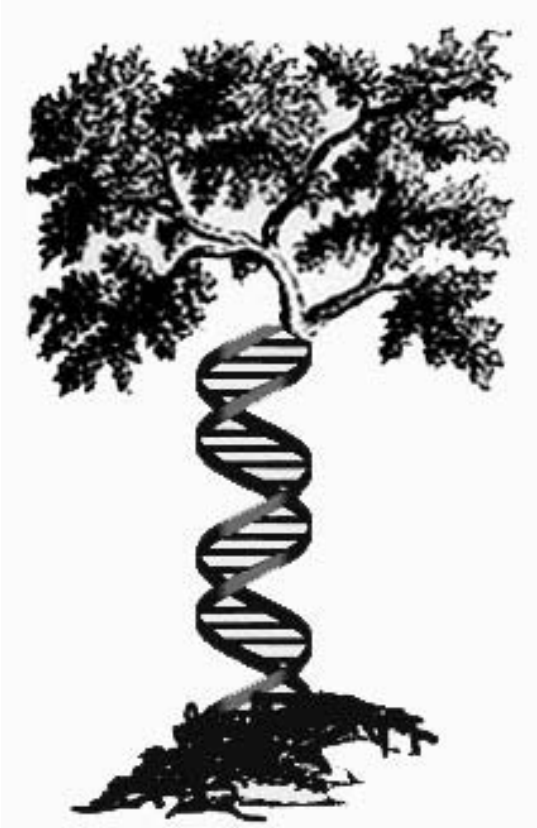
GENE PLUGS PROVIDE

- NATURAL, RESORBABLE MATRIX
- VECTOR DELIVERY SYSTEM
- IMMEDIATE SOURCE OF PROGENITOR CELLS
- SIMPLICITY---NO NEED FOR CELL CULTURE, SCAFFOLDS etc.
- GOOD PHYSICAL PROPERTIES; MOULDABLE
- SINGLE, INTRAOPERATIVE PROCEDURE



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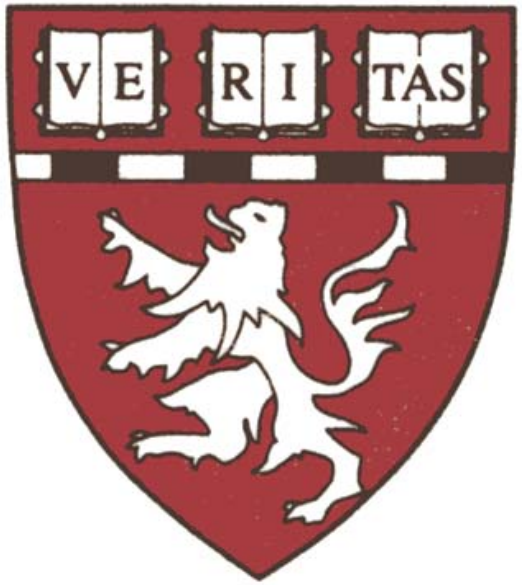
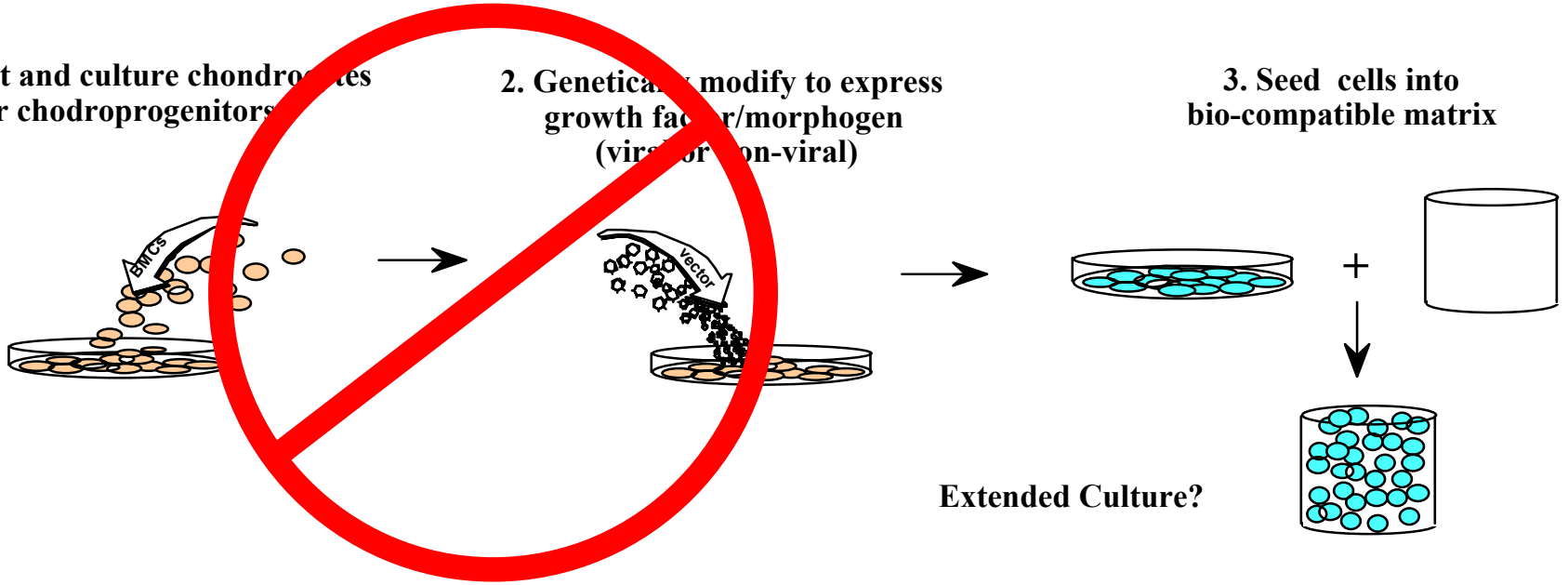


Genetically Enhanced Repair of Osteochondral Defects

1. Harvest and culture chondrocytes or chodroprogenitors

2. Genetically modify to express growth factor/morphogen (viral or non-viral)

3. Seed cells into bio-compatible matrix



Extended Culture?

4. Surgically implant matrix + cells

5. Secreted proteins stimulate implanted and infiltrating chondroprogenitors

6. Regeneration of normal cartilage?