

Genetic manipulation in sports “Gene doping”

Peter Schjerling

Copenhagen Muscle Research Centre



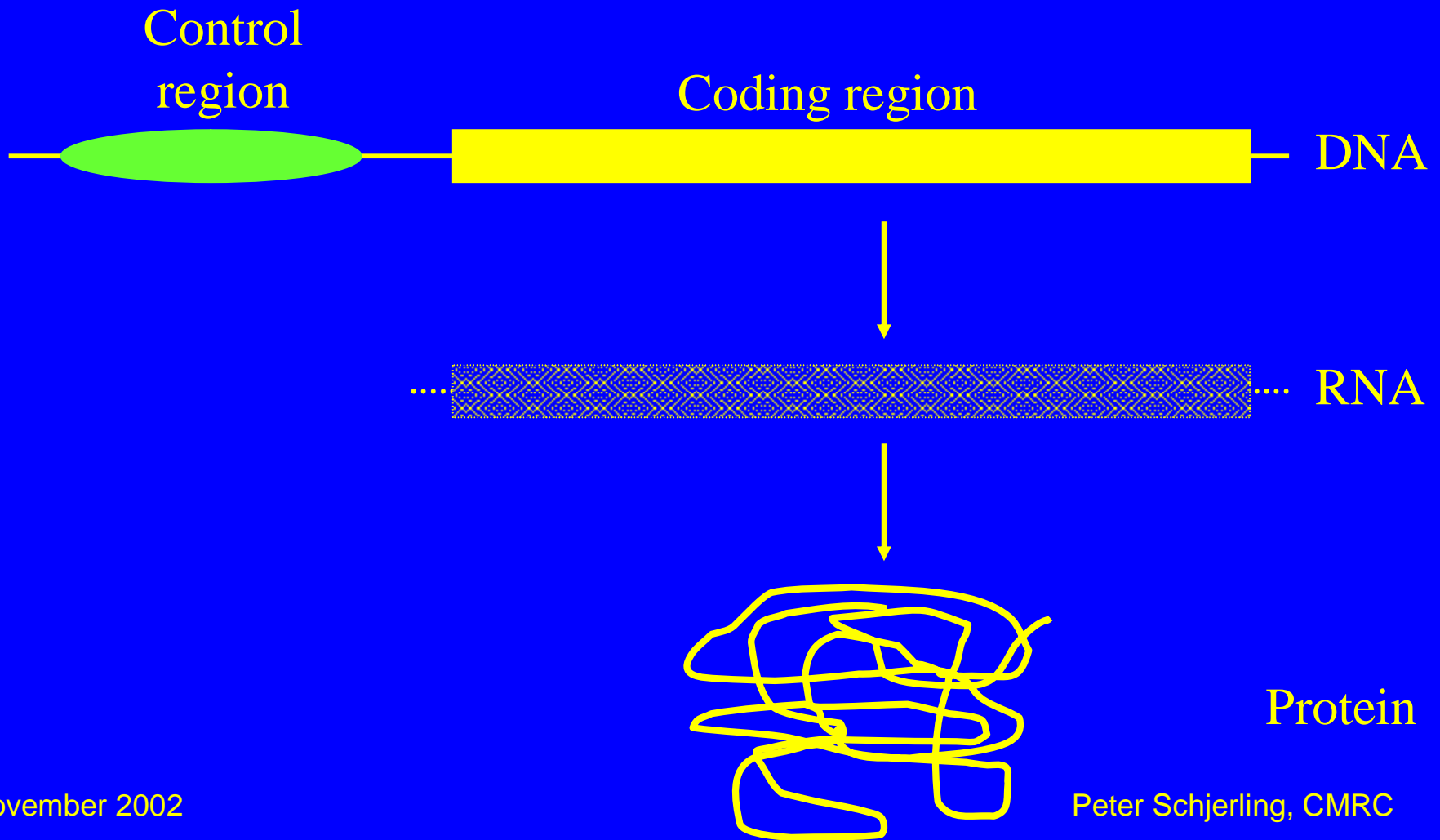
Gene doping

- Doping based on gene manipulation
- Exploitation of results in gene therapy
- A future threat in athletics?

Gene therapy

- Insertion of artificial genes in patients
- Purpose
 - To kill or weaken cancer cells
 - To enable the body itself to produce drugs that are today administered
 - To replace defect genes with healthy copies
- Problem today: lack of control over the expression of the artificial gene

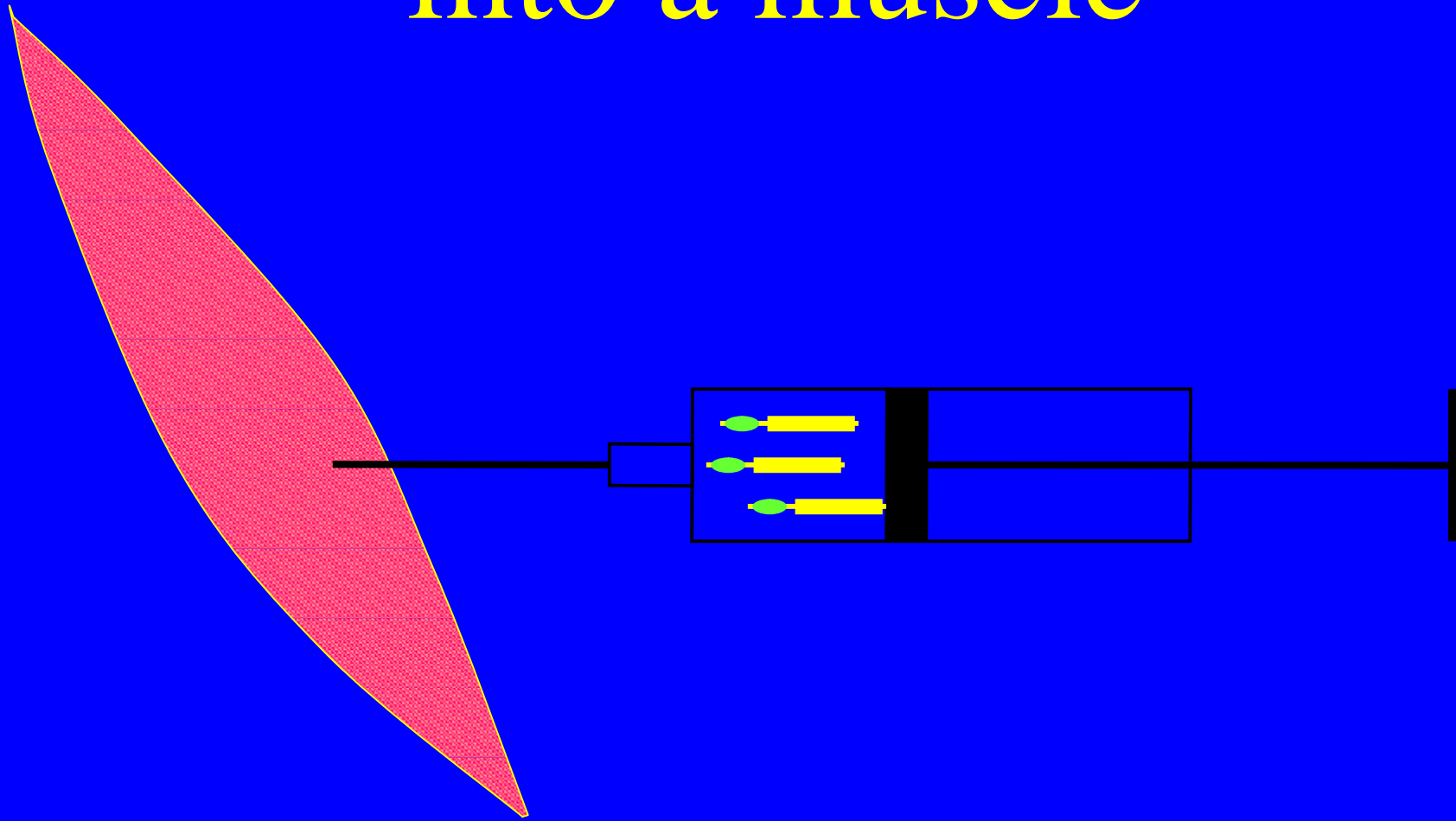
The makeup of a gene



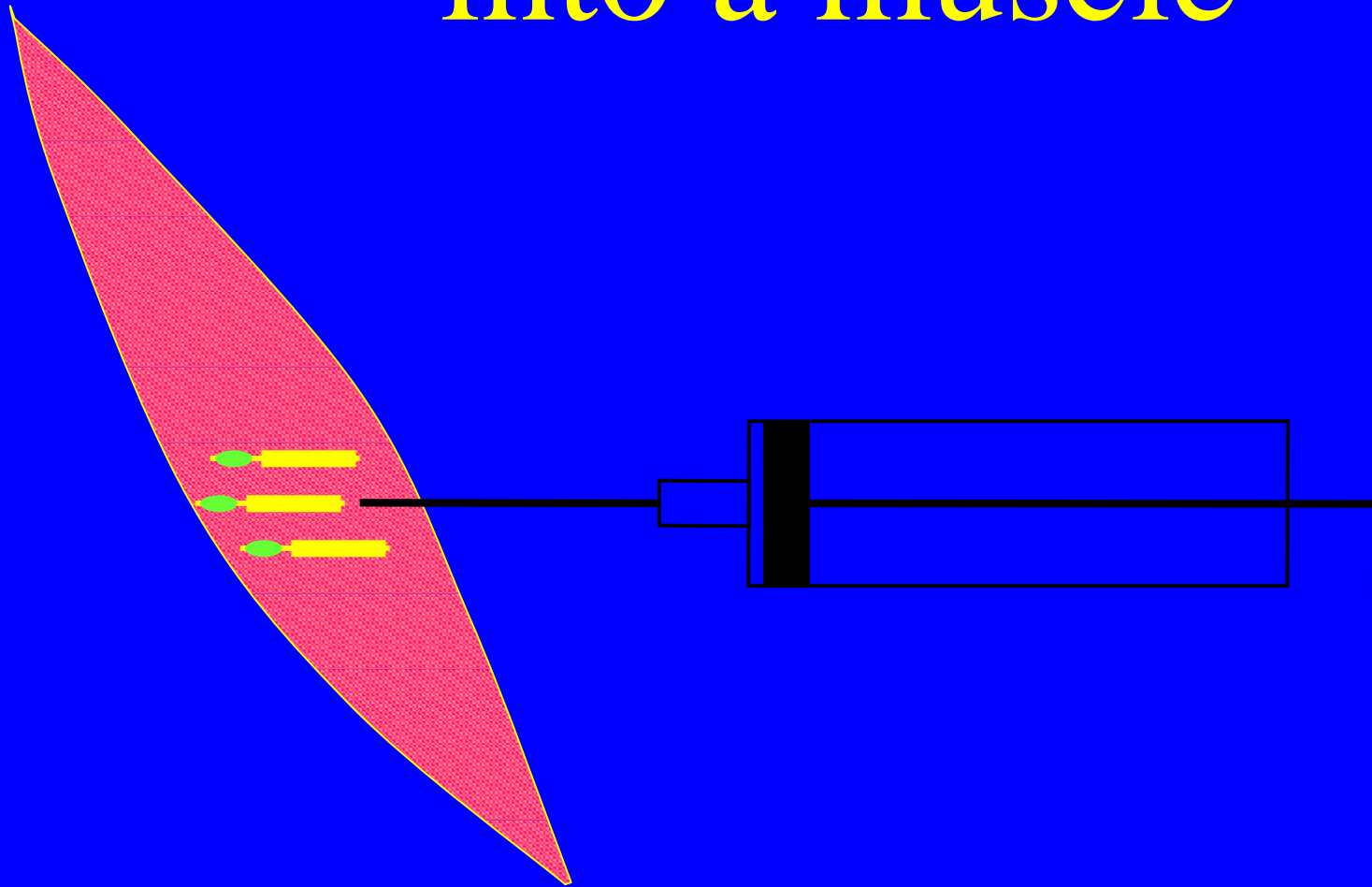
How is the artificial gene introduced?

- Direct injection of DNA into the muscles
- Insertion of genetically modified cells
- Introduction utilizing a virus

Direct injection of DNA into a muscle



Direct injection of DNA into a muscle

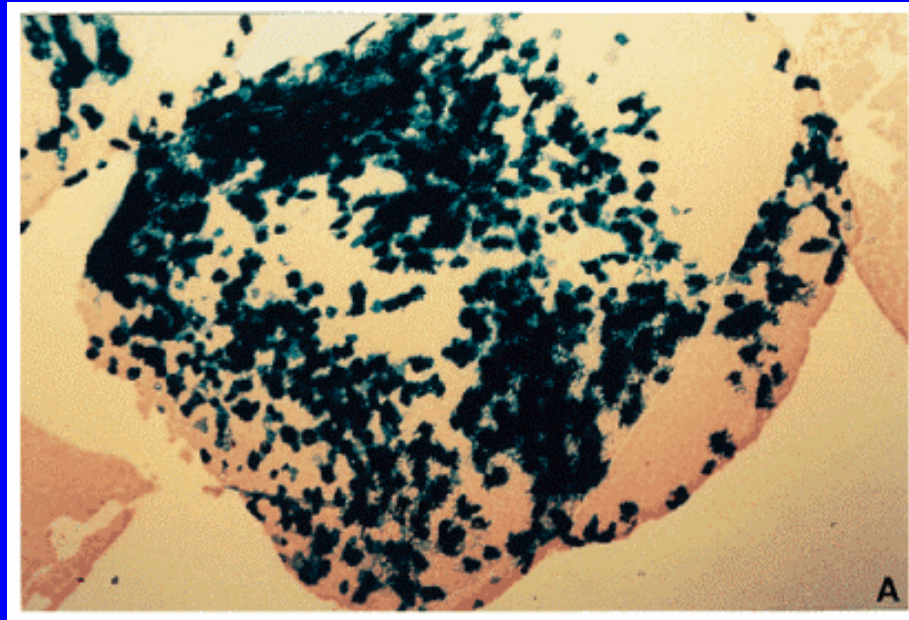


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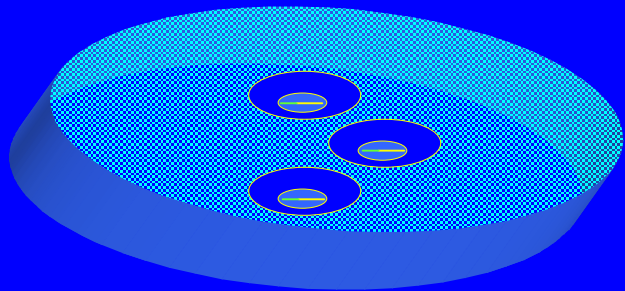
Direct injection of DNA into a muscle

Mouse quadriceps
muscle after a single
injection with a plasmid
carrying a gene giving
rise to blue color (lacZ)



Danko et al. *Human Molecular Genetics* (1997) **6**:1435-1443

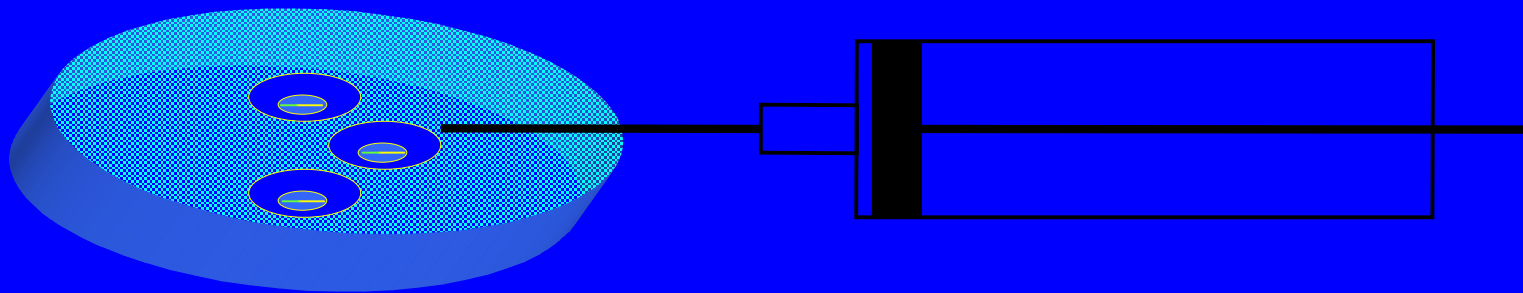
Insertion of genetically modified cells



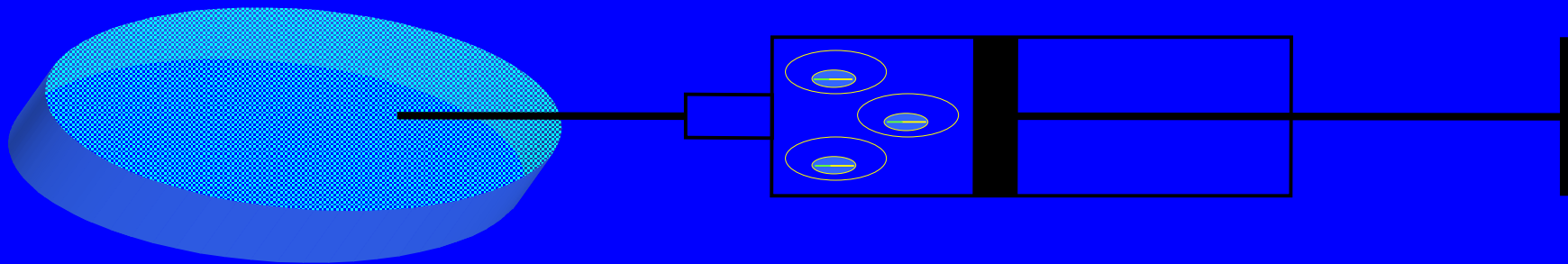
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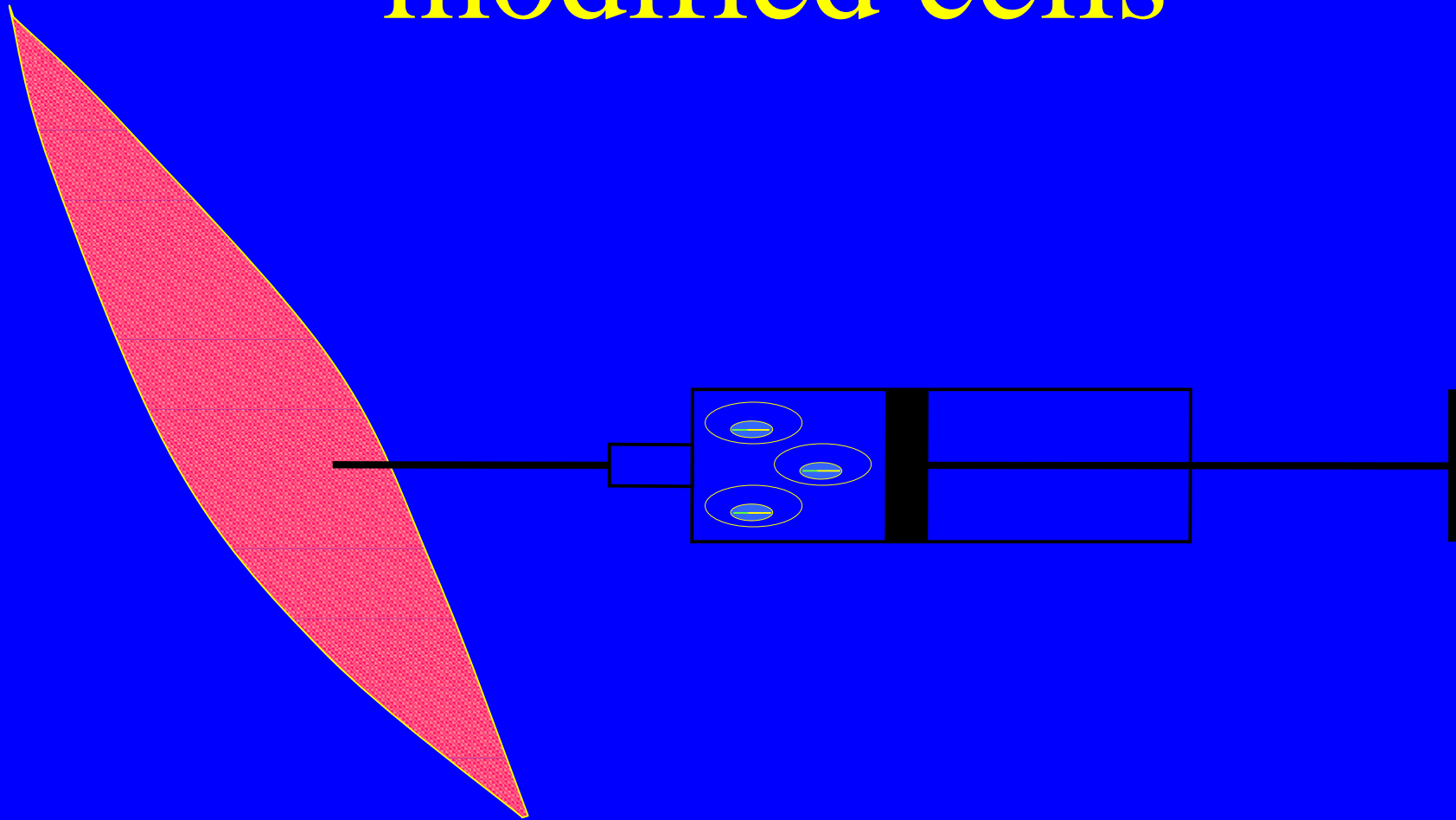
Insertion of genetically modified cells



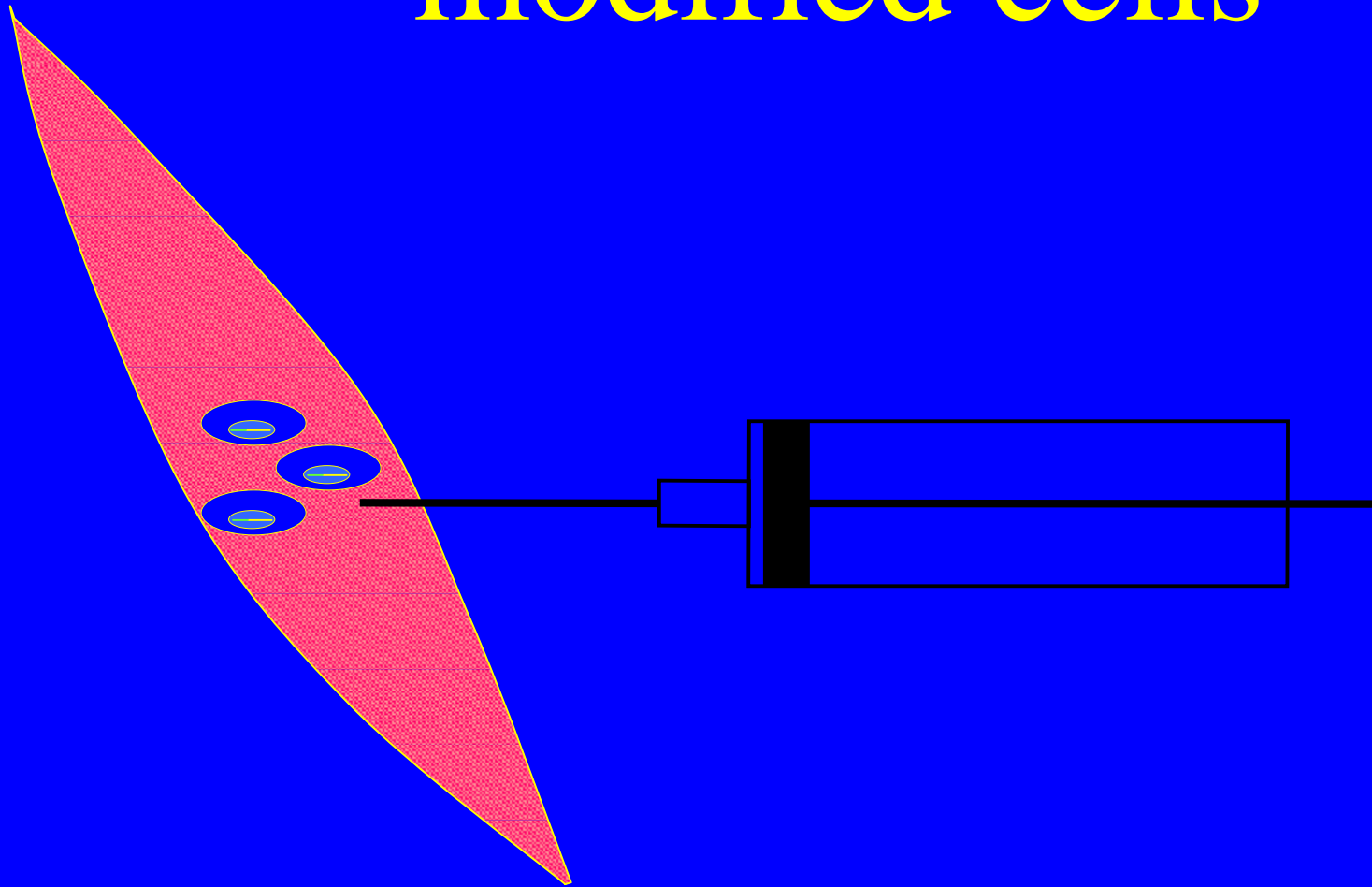
Insertion of genetically modified cells



Insertion of genetically modified cells



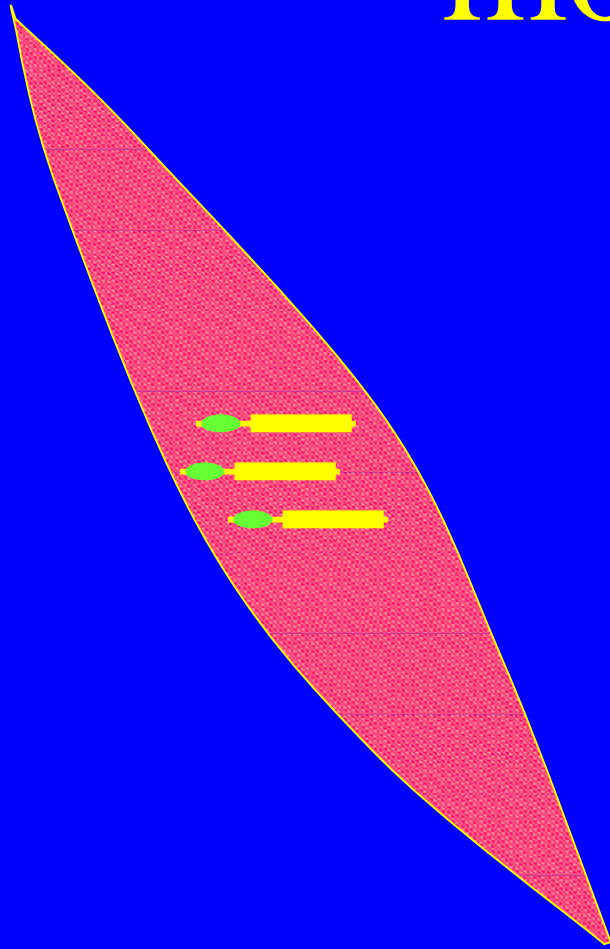
Insertion of genetically modified cells



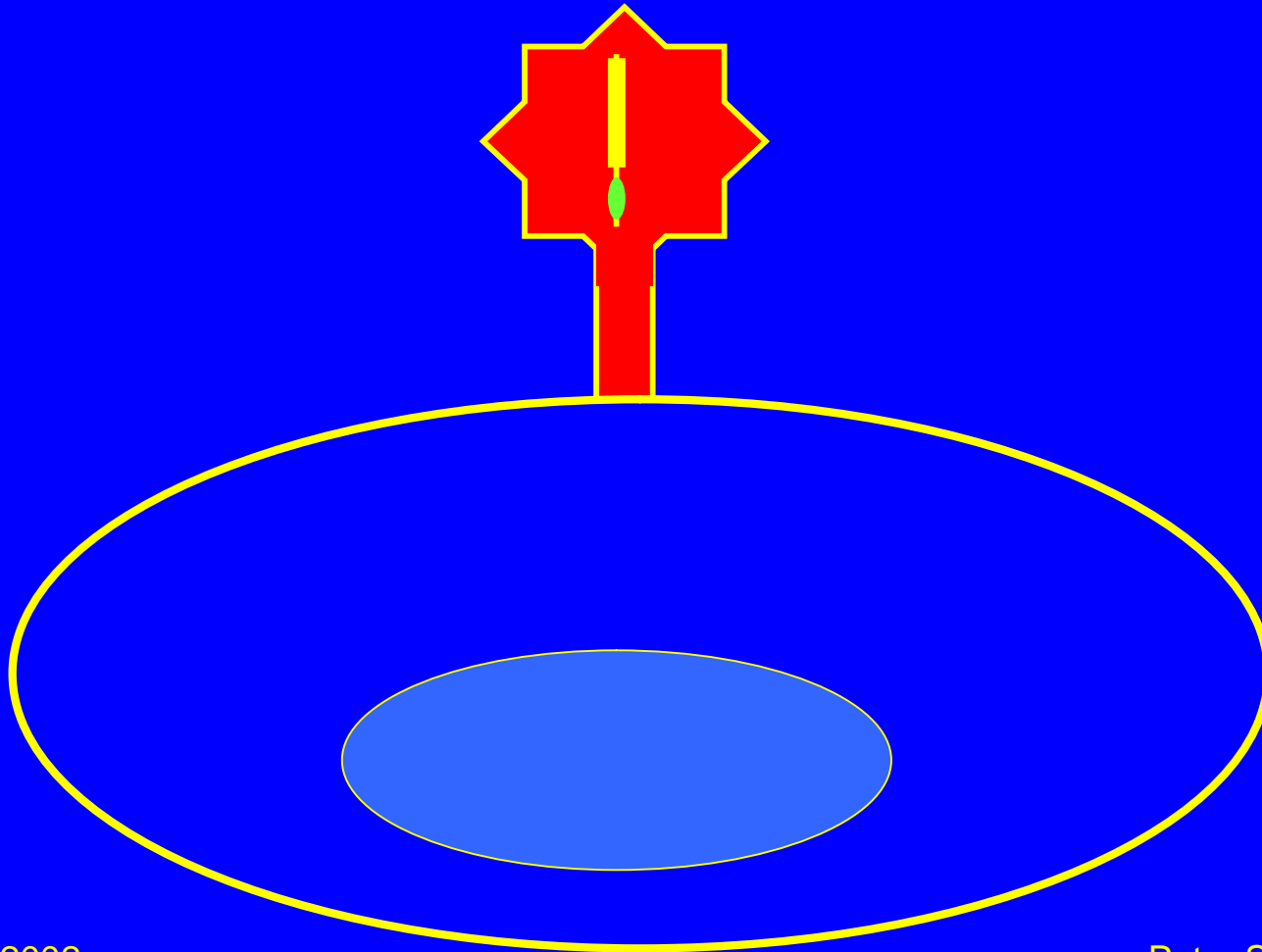
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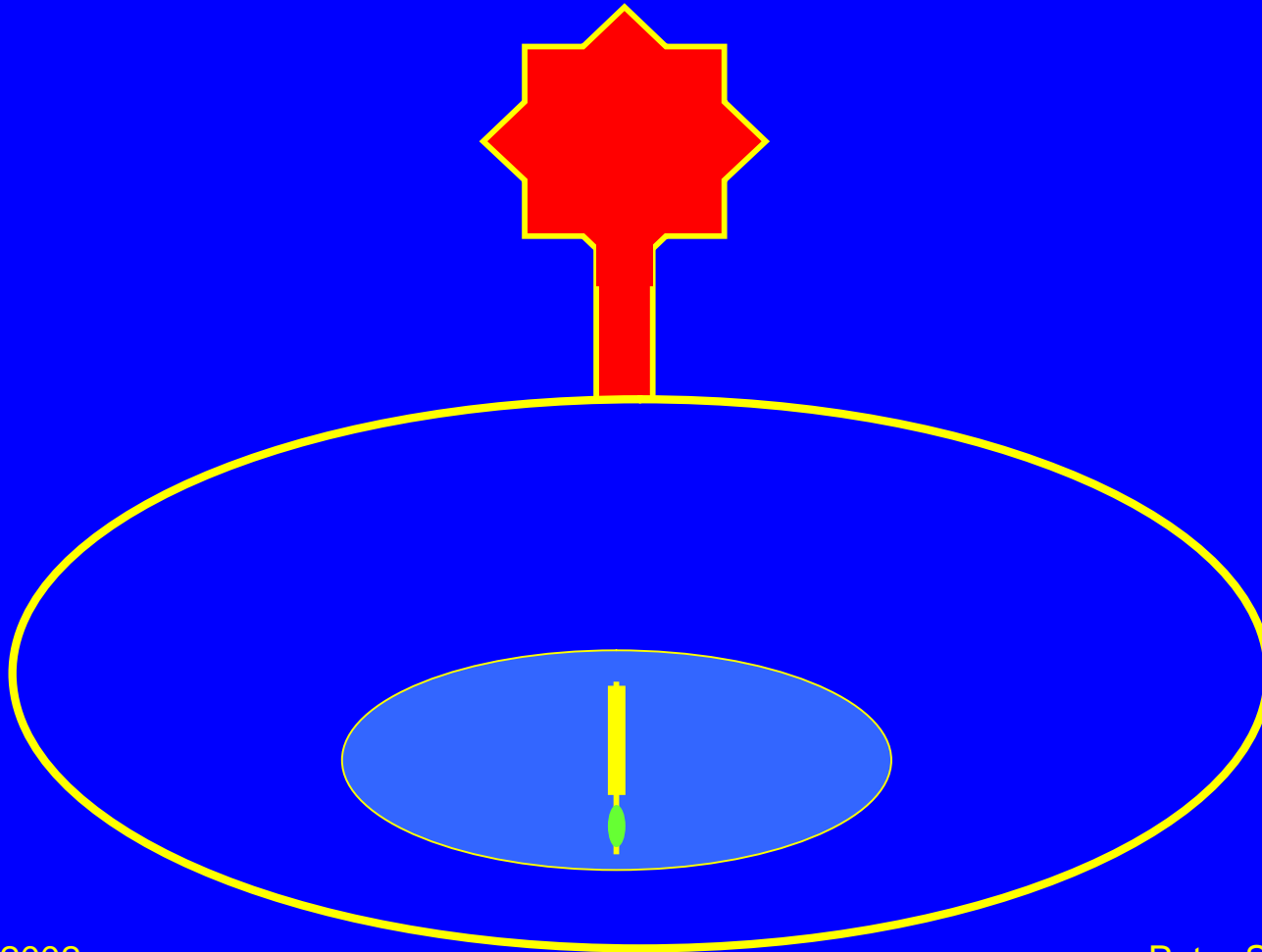
Insertion of genetically modified cells



Utilizing a virus



Utilizing a virus



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How is the artificial gene introduced?

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The "prospects" in gene doping

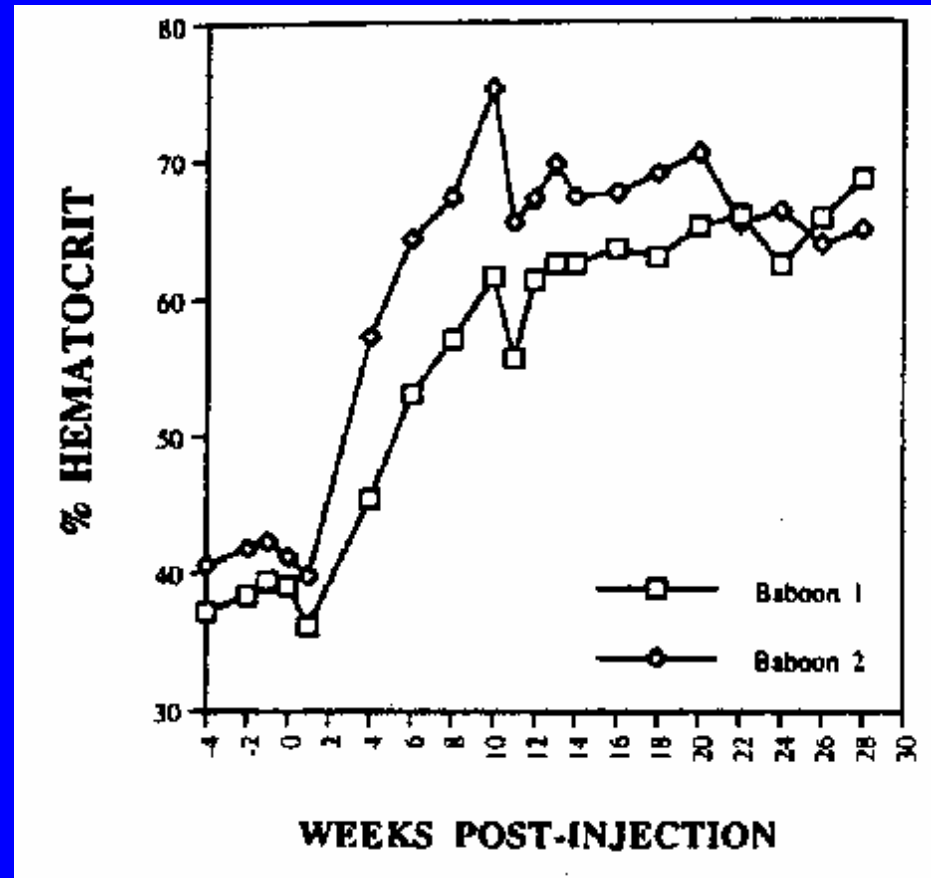
- Alternative to drugs that otherwise is administered and which the body can itself produce
- Changing the natural regulation of the genes
- Improvement of proteins within the body

Examples of the potential in gene doping

- Increase hematocrit by EPO
- Increase muscle strength by IGF-1
- Increase muscle size by removal of myostatin
- Increase blood flow by VEGF

Gene therapy with EPO

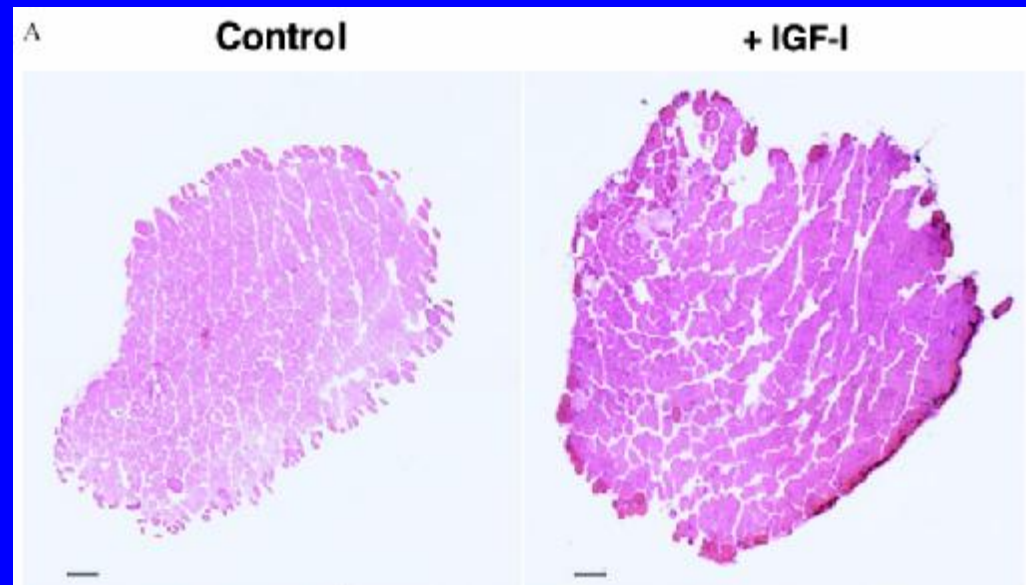
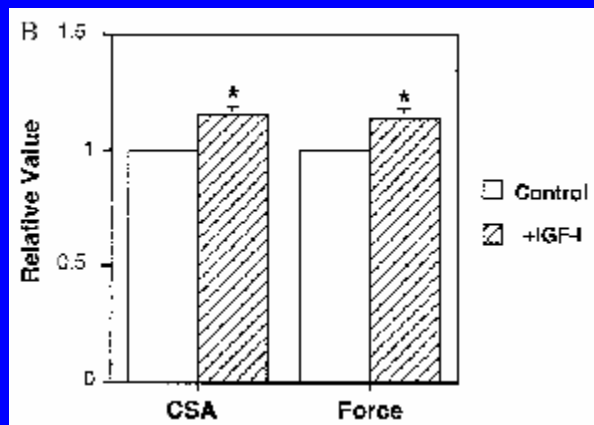
Monkeys injected with a virus carrying the gene for EPO



Zhou et al. *Gene Therapy* (1998) 5:665-670

Gene therapy with IGF-I

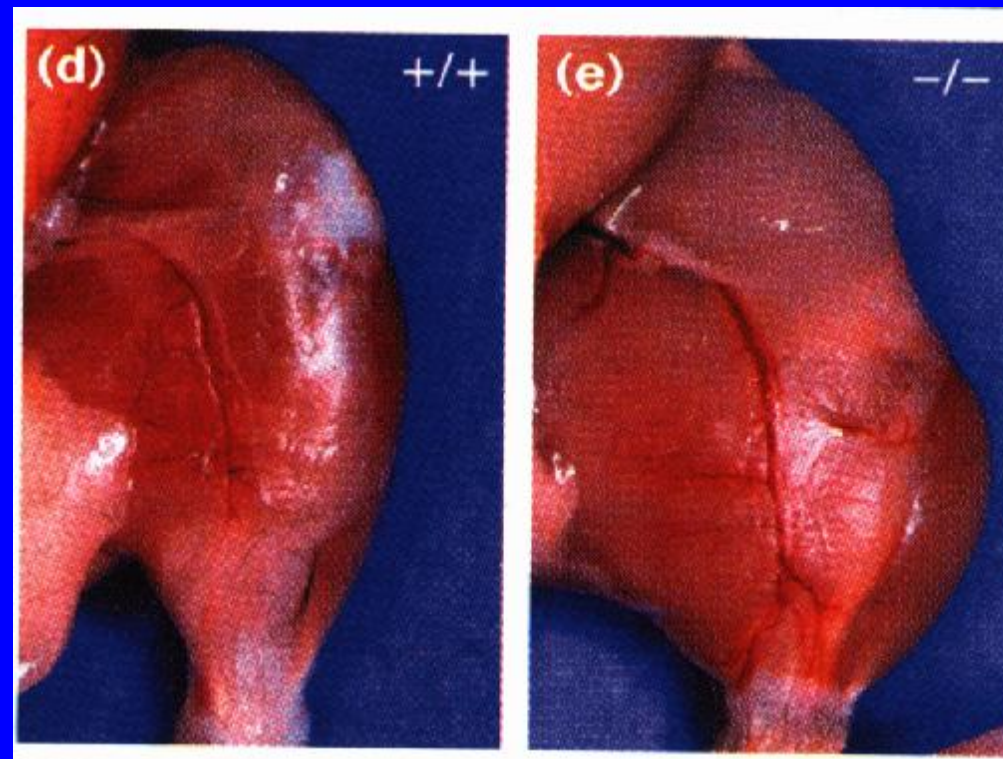
Mice injected with a virus carrying a gene for IGF-I



Barton-Davis et al. *Proc.Natl.Acad.Sci.* (1998) **95**:15603-15607

Removal of a control gene for muscle growth

Front leg of
a normal
mouse

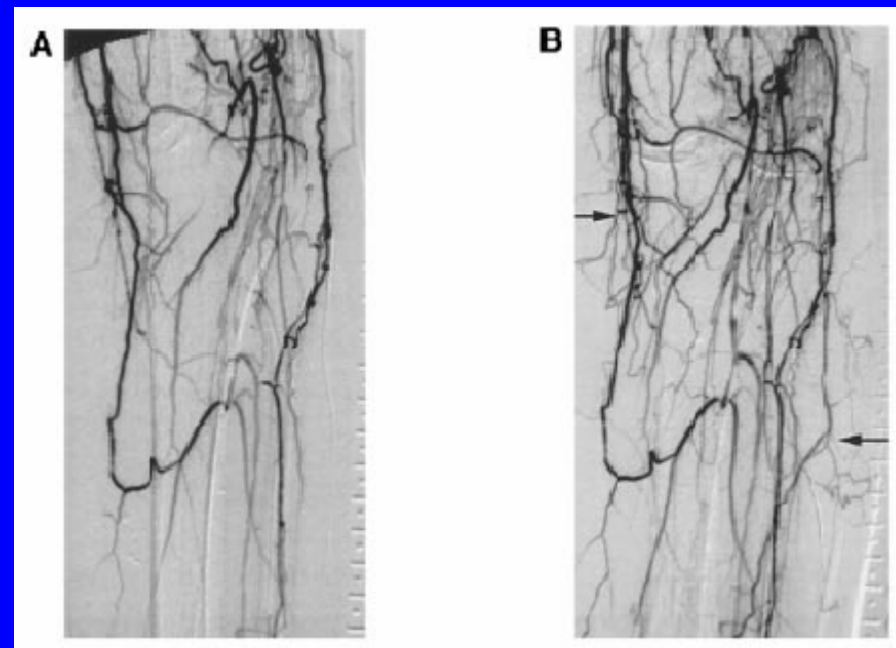


Front leg of
a mouse
lacking the
myostatin
gene

Lee et al. *Curr. Opin. Gen. Dev.* (1999) **9**:604-607

Human gene therapy with VEGF

Blood vessels in a
patient injected with a
virus carrying a gene
for VEGF



Before

After

Baumgartner et al. *Circulation* (1998) **97**:1114-1123

Can gene doping be detected?

- The protein produced is identical to the endogenous protein
- The artificial DNA is only present locally when using injection with pure DNA or genetically modified cells
- The sequence of artificial DNA has to be known to enable detection

When?

- In principle already now gene doping can be performed, however, with an extreme risk for the athlete.
- More likely when gene therapy becomes a normal procedure, a guess is 10-20 years.

Possible countermeasures

- Make gene doping illegal.
- Establish a close contact to the gene therapy society.
- Prepare DNA detection assays for known gene therapy artificial constructs.
- Develop indirect methods to detect gene doping, if possible.