

# GENETICS FOR DOPING AND DOPING



WADA



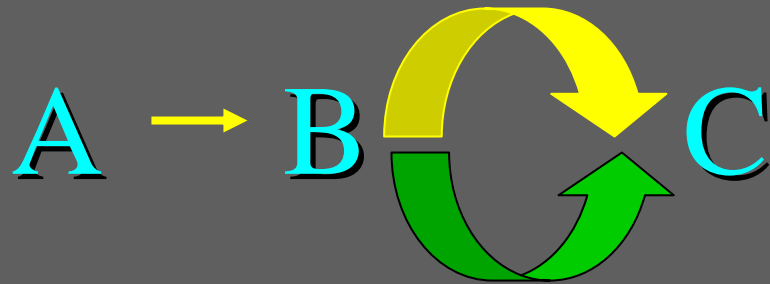
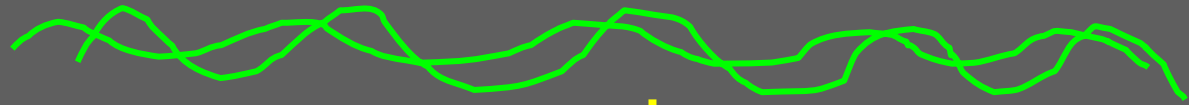
# GENETICS FOR DOPING AND DOPING



WADA



# Origins in Gene Therapy





A

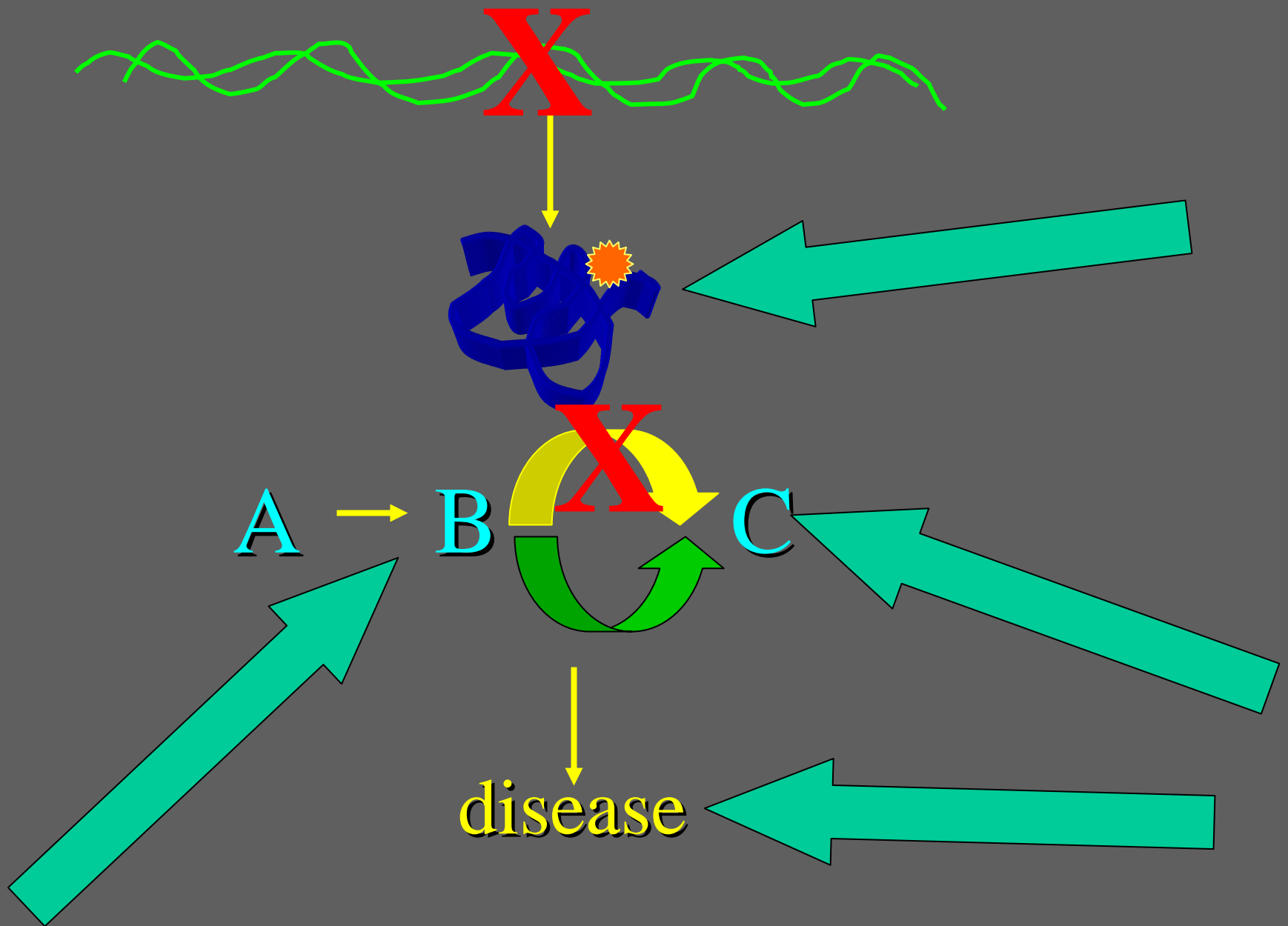


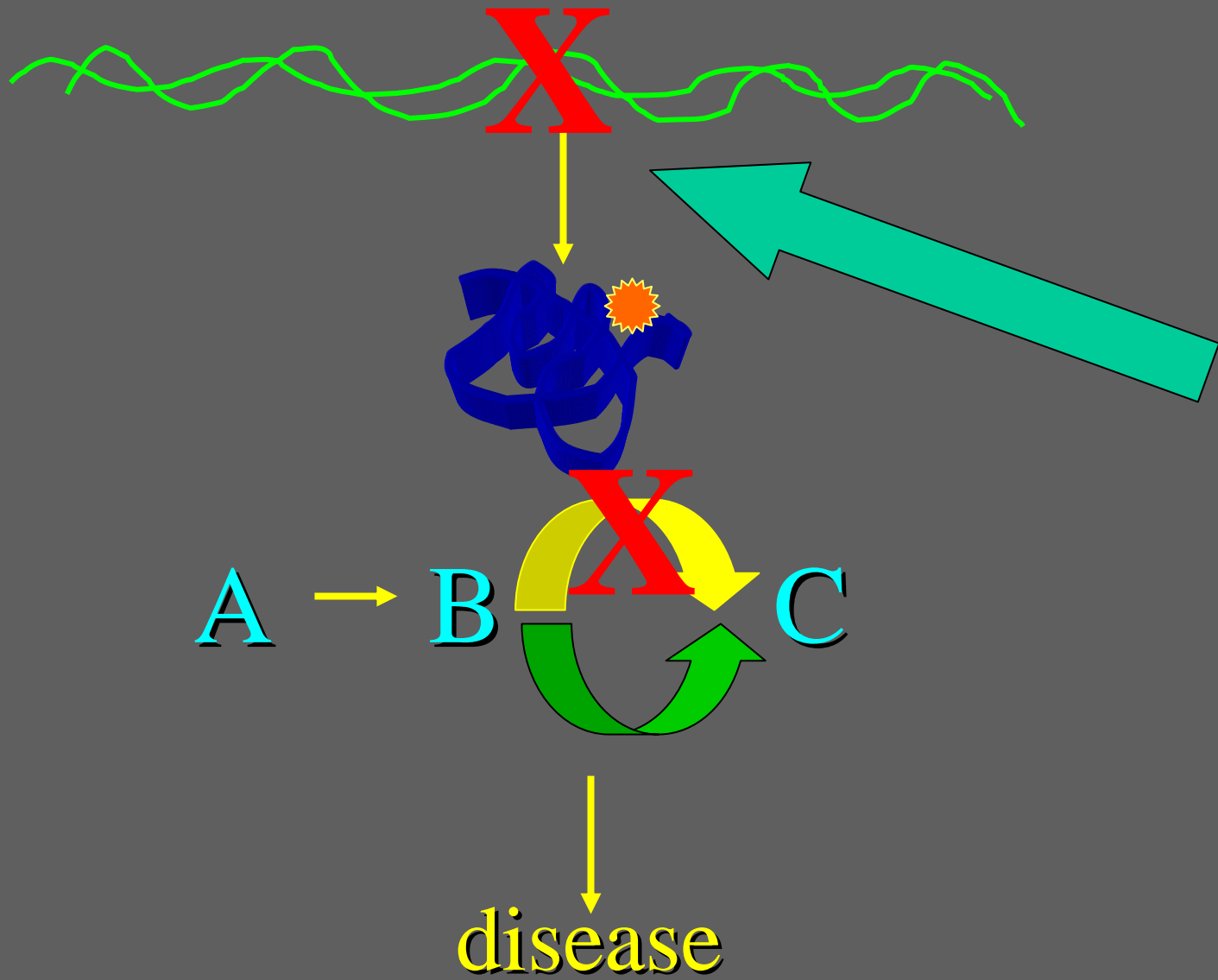
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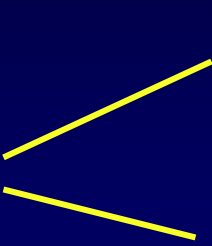
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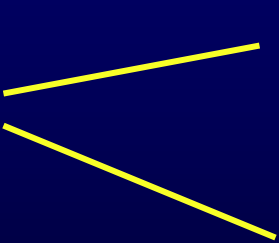


disease





somatic cell  therapy  
enhancement

germ cell  therapy  
enhancement

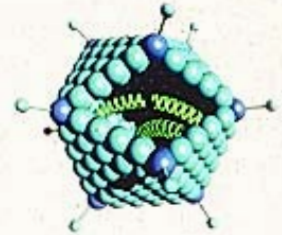
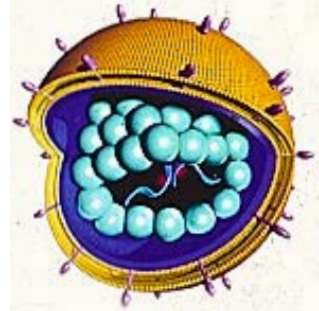
retrovirus 1981-2 random  
integration, insertional mutagenesis?

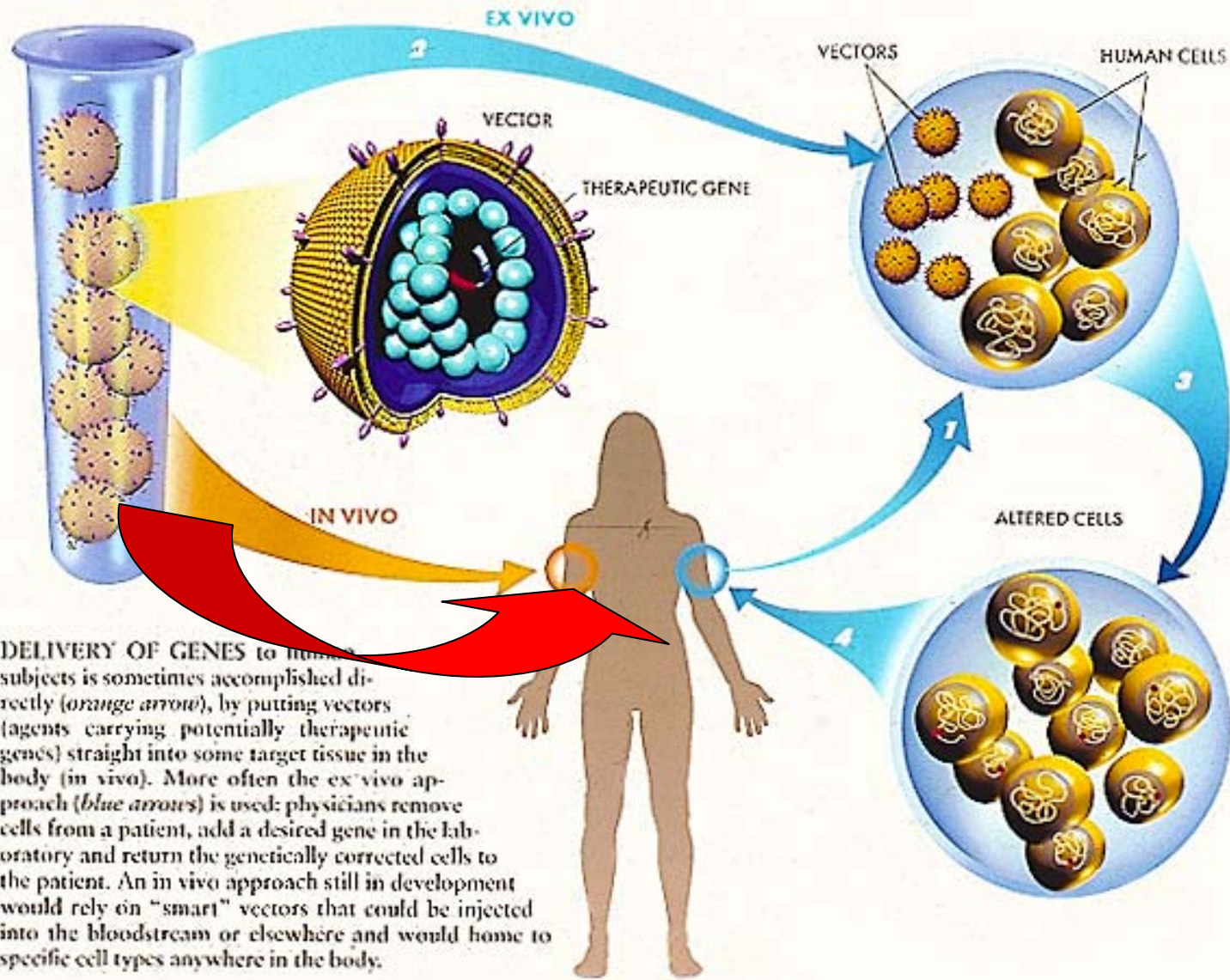
adenovirus

adeno-associated virus

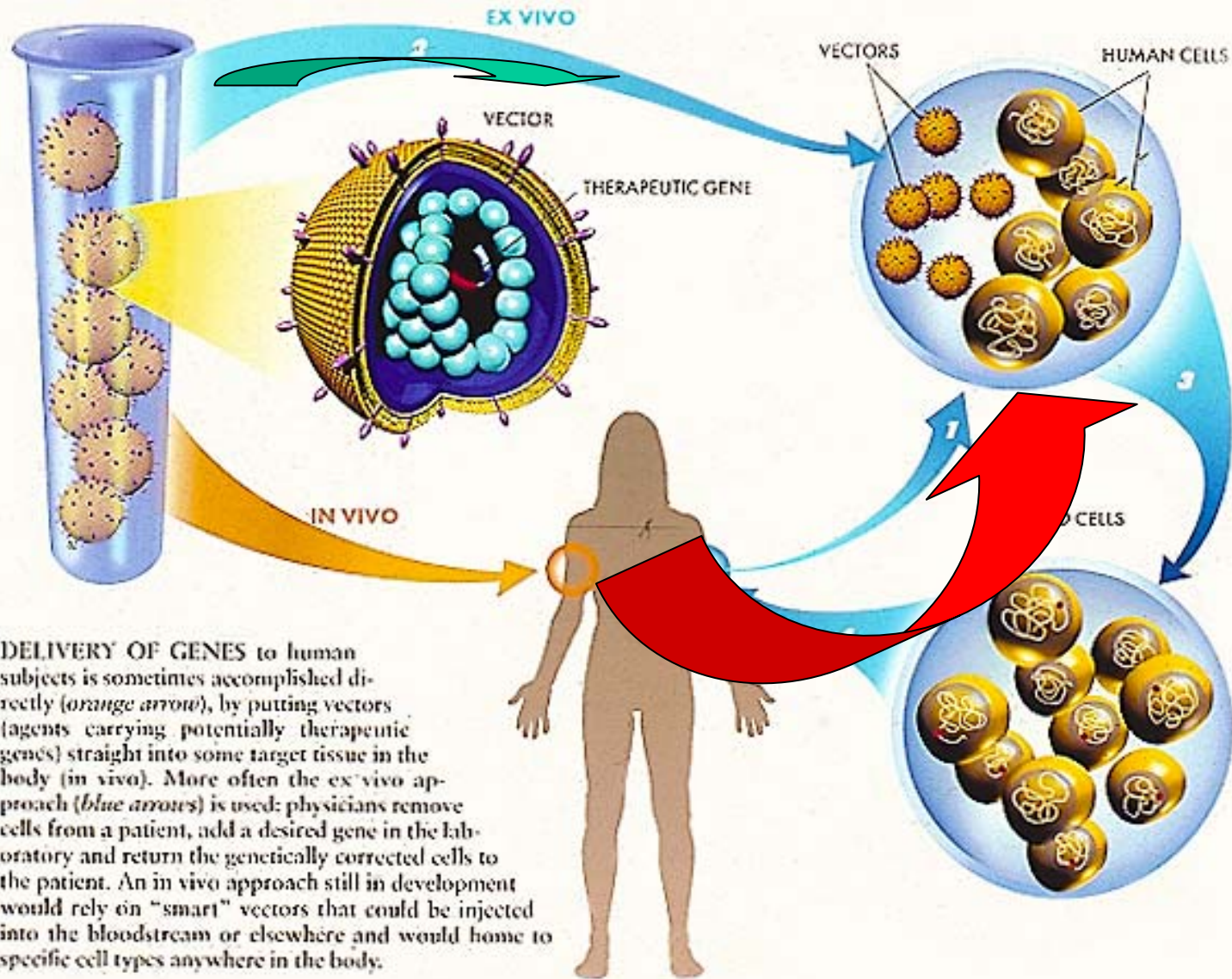
liposomes

naked DNA

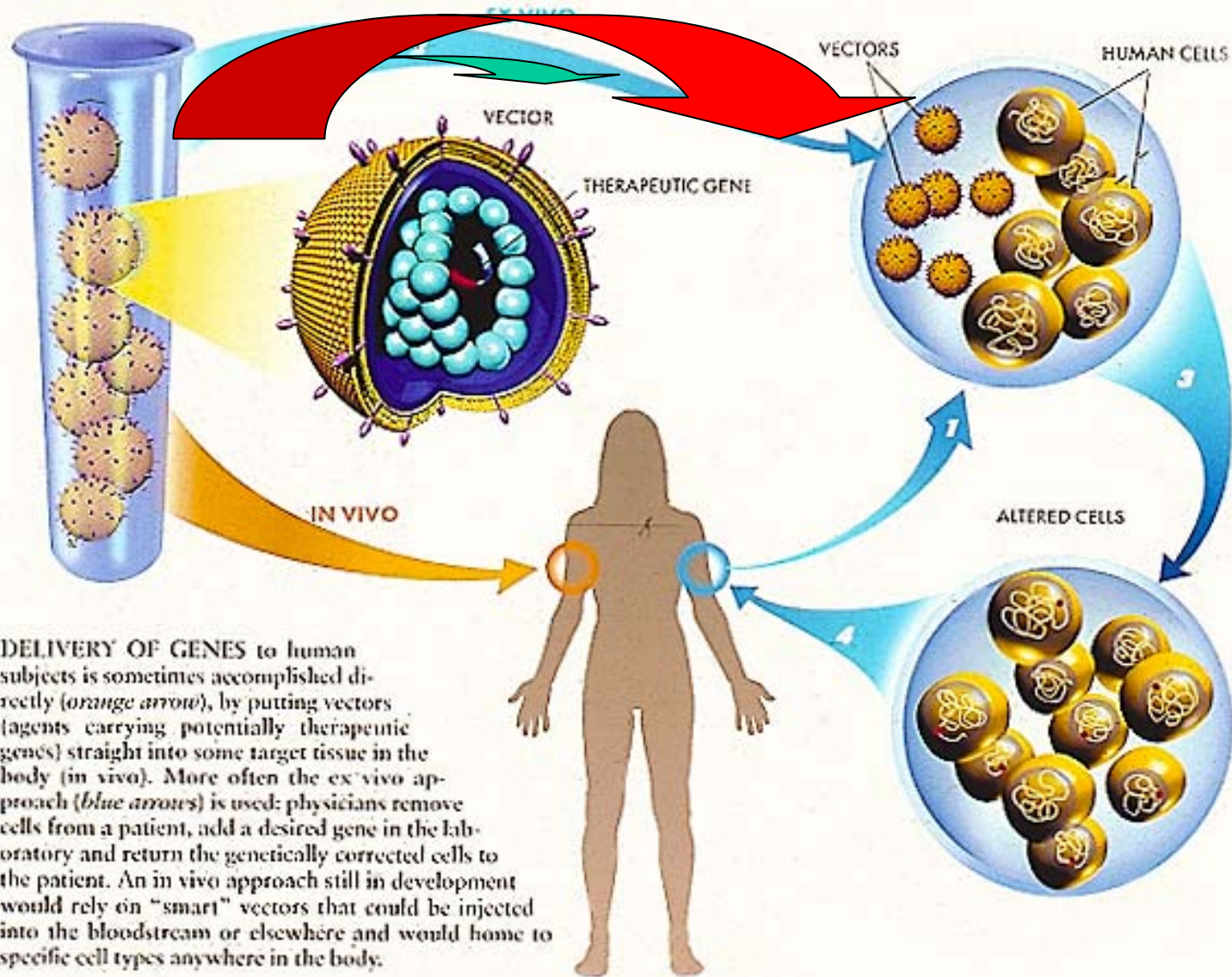




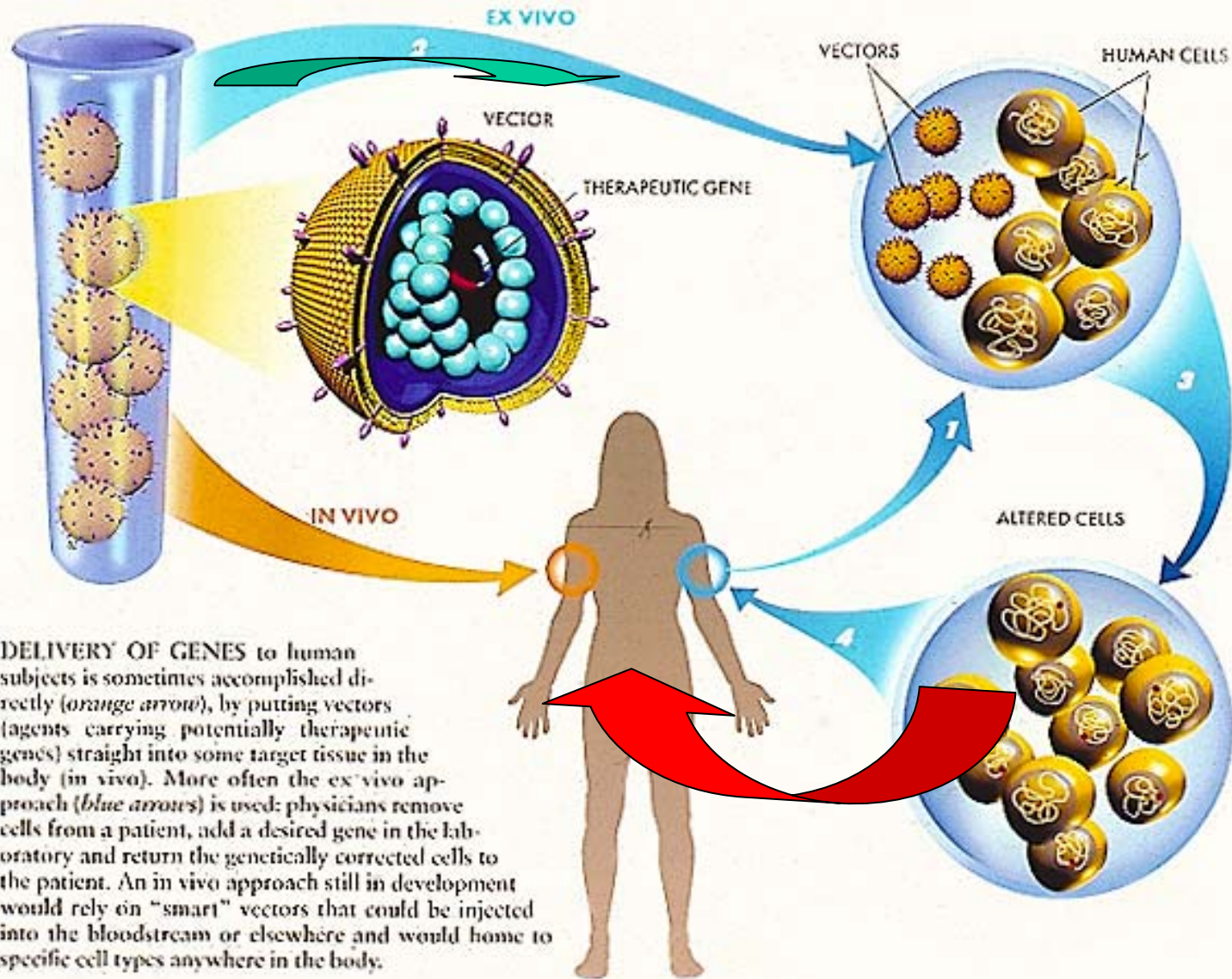
**DELIVERY OF GENES** to human subjects is sometimes accomplished directly (*orange arrow*), by putting vectors (agents carrying potentially therapeutic genes) straight into some target tissue in the body (*in vivo*). More often the *ex vivo* approach (*blue arrows*) is used: physicians remove cells from a patient, add a desired gene in the laboratory and return the genetically corrected cells to the patient. An *in vivo* approach still in development would rely on "smart" vectors that could be injected into the bloodstream or elsewhere and would home to specific cell types anywhere in the body.



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# A difficult controversial beginning

- Early exaggerations, elevated expectations
- Highly publicized setbacks
- Progress “slow”.

# The reality

- Gene transfer for therapy - concept now clinical reality.
- Gene transfer technology still immature, many real and potential risks. Reserved for serious disease
- Pace of progress, adverse events and setbacks typical for new therapeutic technology.

# Clinical studies

- 19 years
- 700-800 studies, several thousand patients
- Target diseases - cancer, cardiovascular, neurological disease, muscular dystrophy, metabolic disease (hemophilia, enzyme deficiencies, hypercholesterolemia, etc)
- Generally safe, but with increasing efficiency come increasing toxicities

# Extensive regulation and oversight for all human gene transfer studies

- Local institution biosafety, human subjects committees
- NIH Recombinant DNA Advisory Committee
- FDA
- Similar requirements worldwide

**Striking successes**

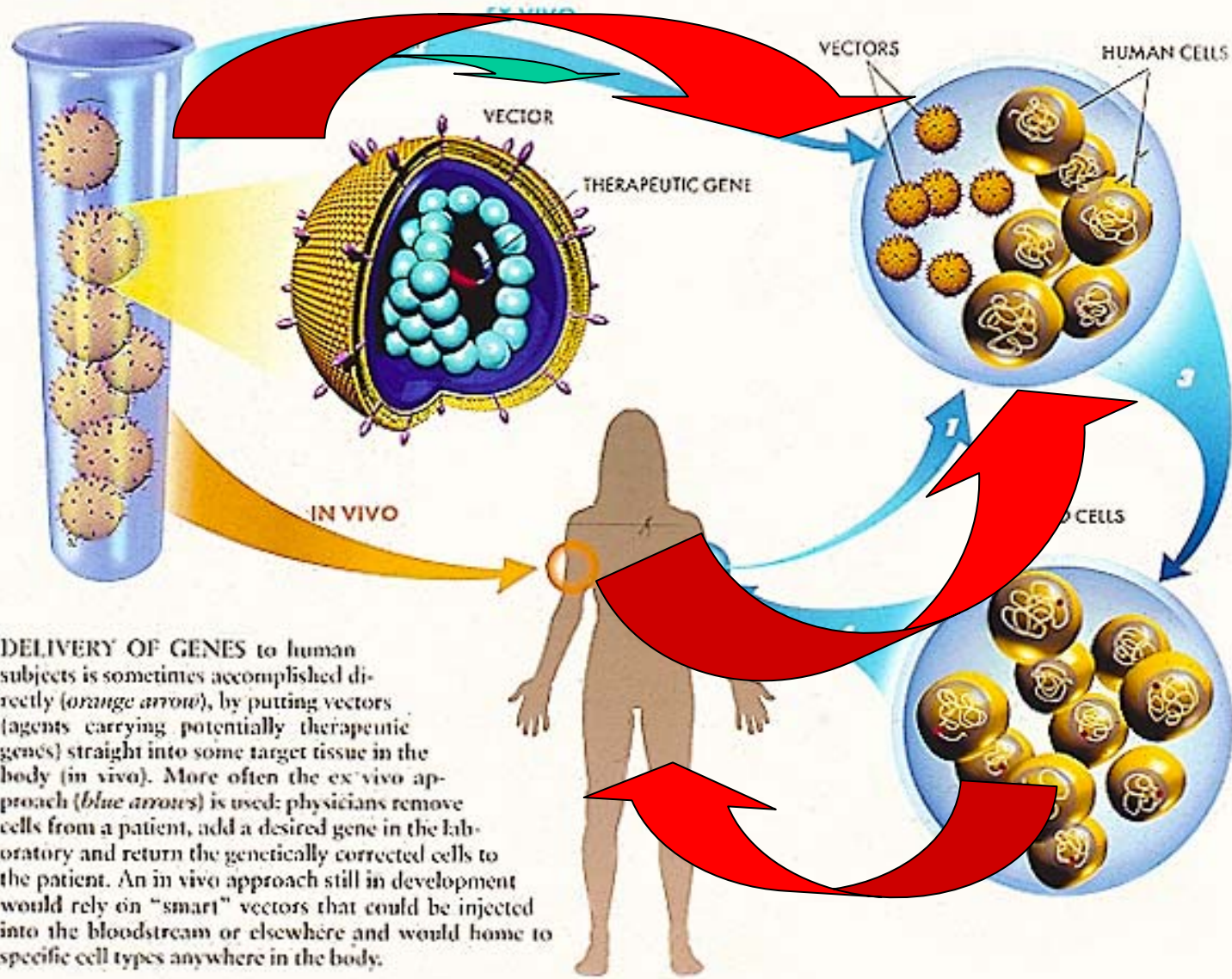
# Severe combined immunodeficiency diseases (SCID)

- Genetically-caused absence of immune system
- Traditional therapy - isolation, bone marrow transplantation, antibiotics. Inadequate.
- Death in childhood from infections



## David Vetter - “Texas Bubble Boy”

- Born 1971 - prenatal diagnosis of SCID
- Lived in isolation bubble 12+ years
- Died at age 12 - infection following failed bone marrow transplant



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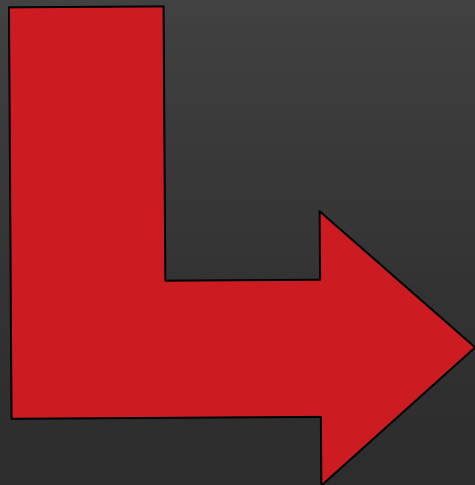
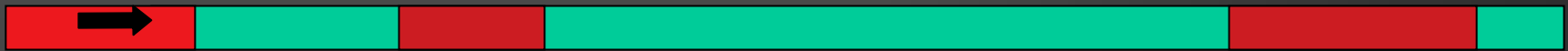
## But a severe cost

- Immune defect corrected, children living normal childhood lives
- BUT, 5 cases of leukemia and 1 death in ~ 21 treated children - direct result of treatment
- virus integration caused activation of quiescent cancer gene

# Integration into a cancer gene



LMO2 - known oncogene



Cell overgrowth,  
cancer

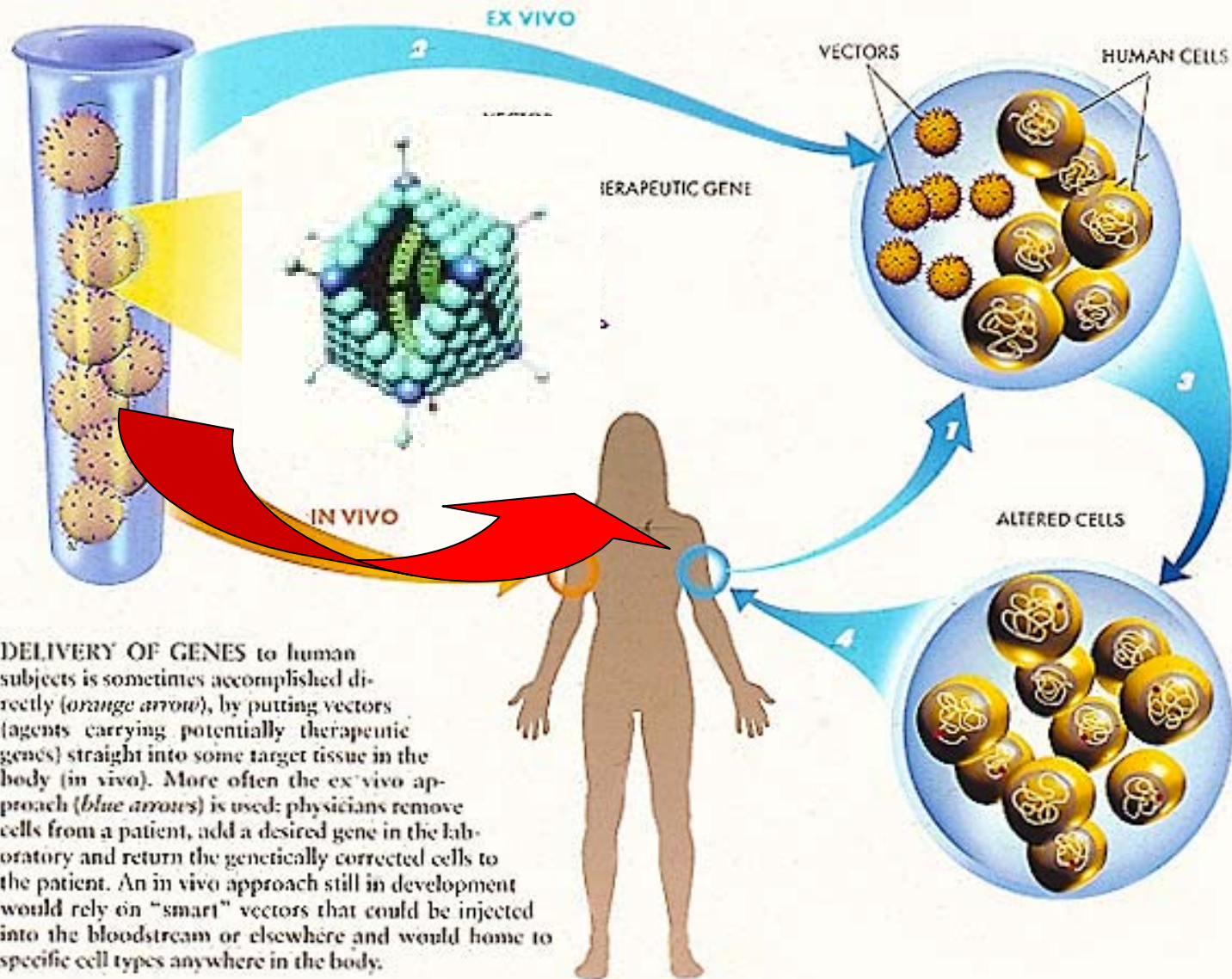
## Additional successes in gene therapy

- Cancer - vaccine approach to enhance anti-cancer response - melanoma, neuroblastoma, head and neck cancer, brain cancer (glioblastoma)
- Blindness - restored vision in genetic form of retinal degeneration and blindness in children (Leber's amaurosis in children)

# Leber's Amaurosis

- Genetic defect in essential protein (RPE65) in photoreceptors of retina
- Childhood blindness
- AAV virus vector delivery of normal gene directly to retina
- vision





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# First commercial product - SiBiono

## China approves first gene therapy

China became the first country to approve the commercial production of a gene therapy, and it is due to hit the market in early January. Despite technical hurdles and the wary attitude of regulatory authorities outside China, other countries are expected to soon follow suit.

On October 16, 2003, Shenzhen SiBiono GenTech (Shenzhen, China), obtained a drug license from the State Food and Drug Administration of China (SFDA; Beijing, China) for its recombinant Ad-p53 gene therapy for head and neck squamous cell carcinoma (HNSCC)—a cancer that accounts for about 10% of the 2.5 million annual new cancer patients in China. Sold under the brand name Genticine, the world's first commercial gene therapy uses an adenoviral vector and cost the company more than RMB 80 (\$9.6) million to develop in addition to research grants they received from government.

"We have had more than five years of clinical trials, and the only side effect of Genticine is self-limited fever," says Zhaohui Peng, chairman and CEO of SiBiono. After eight weeks of a joint treatment of radiotherapy and weekly gene therapy injections, 64% of late-stage HNSCC tumors experienced complete regression and 32% experienced partial regression.

"SiBiono's approach is not a trivial one," Jean-François Carmier, CEO of Transgene (Strasbourg, France) comments. "Introgen has been using a similar strategy for head and neck cancer and their product is showing encouraging results in Phase 3 trials" (see Table 1).

The success of SiBiono was in overcoming difficulties in developing the right system for delivering its adenoviral vector—considered an effective way of introducing a gene into tumor cells—without integrating the gene in the host cells' chromosomes and creating genetic alterations. SiBiono has addressed safety concerns by carefully dosing the injection (injecting a weekly dose of  $1 \times 10^{12}$  viral particles) and closely monitoring reactions of participants during the clinical trials and subsequently following up with them for one to five years, according to Peng.

So why did the first commercial gene therapy treatment get produced and approved in China? "In China, where hundreds of thousands die of diseases such as cancer without access to the clinical options available to patients in the US and Europe, the potential for a one-time treatment that is relatively simple to administer



Zhaohui Peng receives an approval certificate issued by China's State Food and Drug Administration for Genticine, the world's first commercial gene therapy.

is very appealing," says Mark Kay, a director of the human gene therapy program at Stanford University (Stanford, CA, USA). Size matters as well. "Due to its large population, the Chinese can recruit enough patients for a trial in a short time and can therefore generate statistically significant amounts of clinical data very rapidly," says Carmier.

And because China has not been blighted by failure—as happened in the United States with the death of Jesse Gelsinger of an inherited nitrogen metabolism disorder

# Intra-Tumoral Administration and Clinical Response - Ad p53

Before



Cycle 3



Dr. Jack Roth - MD Anderson Cancer Center

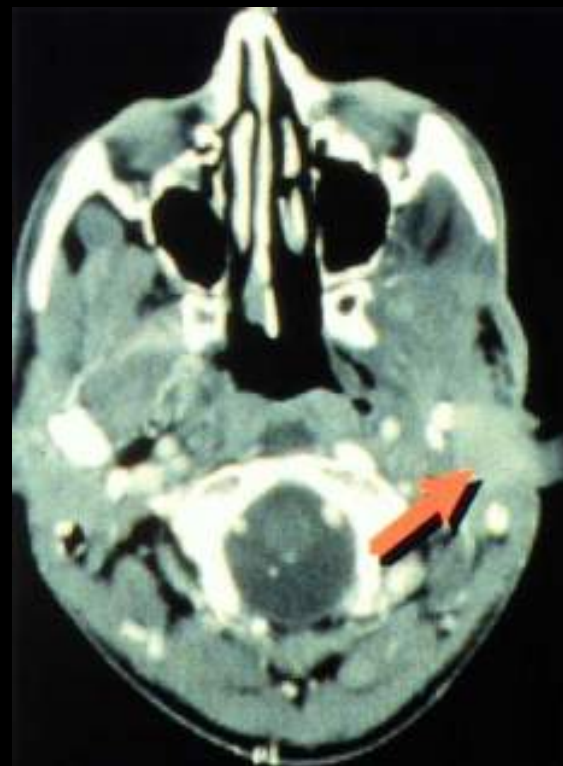
# Response After Ad-p53 Treatment (Monotherapy) in Head & Neck Cancer

**Before**



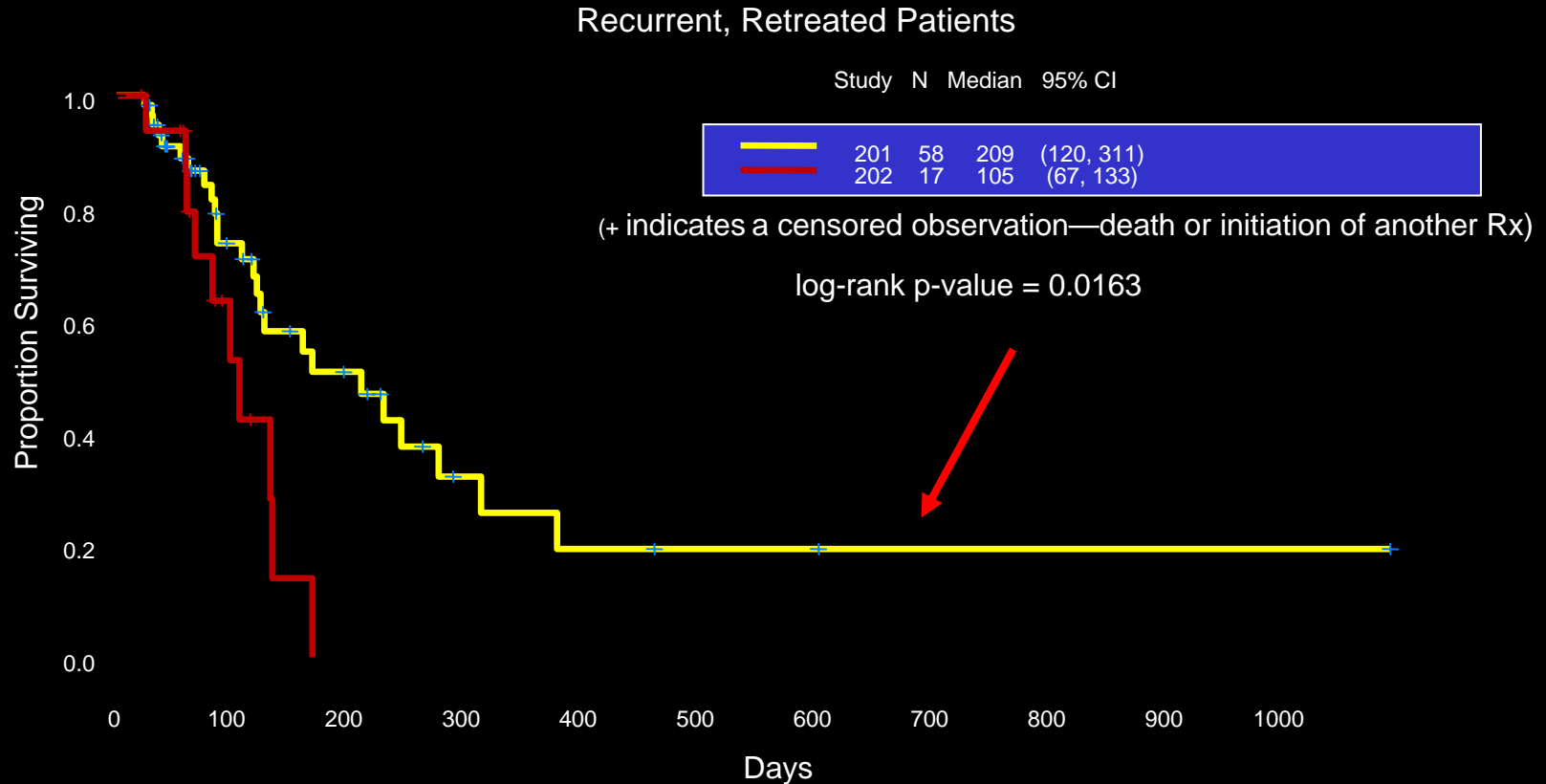
**Refractory to surgery, chemotherapy  
and radiation therapy**

**After**

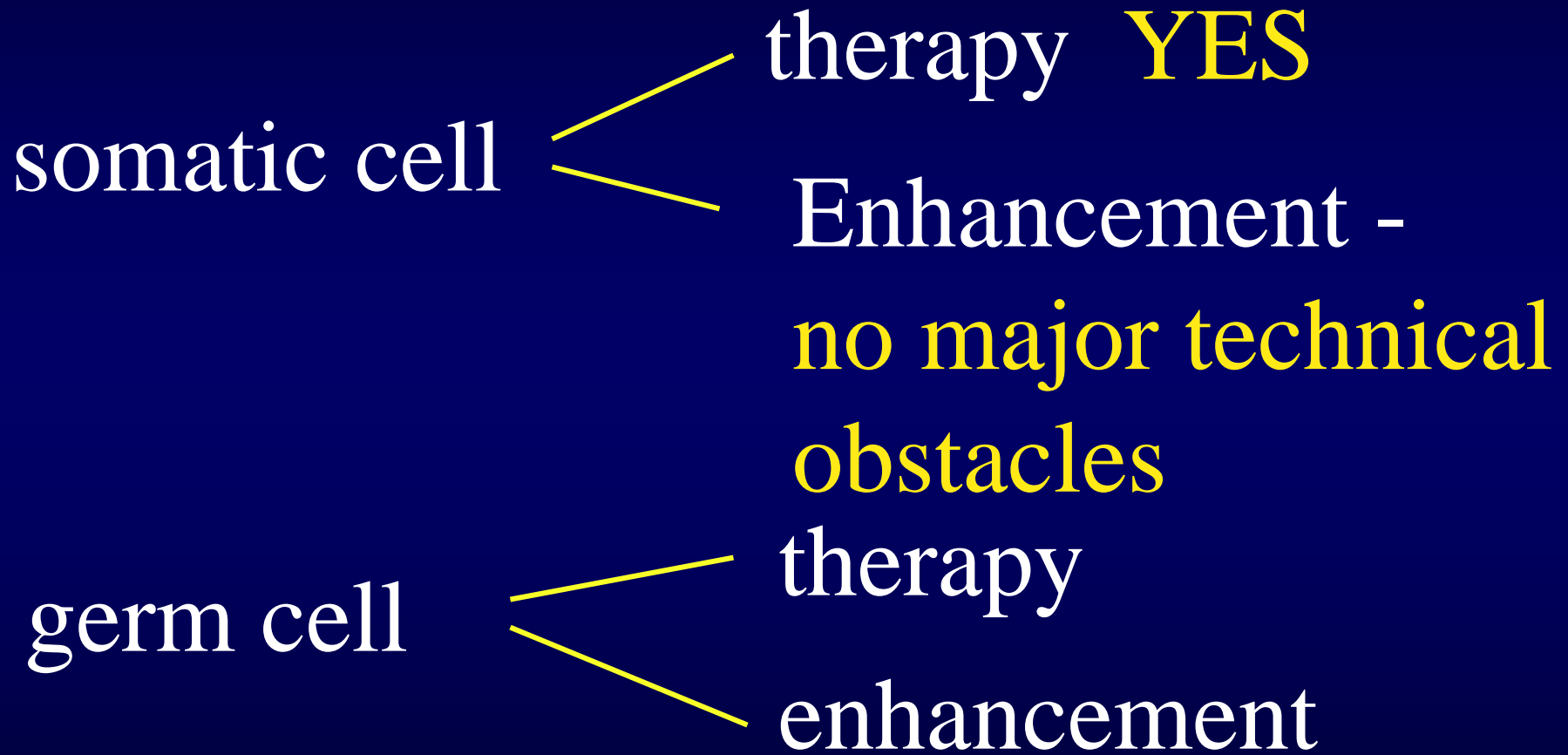


**80% regression**

# Ad-p53 Phase 2 Head and Neck Data Increased Survival



T201 – High Dose; T202 - Low Dose



How might one apply genetic  
modification in Sport?

# General approaches

- Add new foreign genes - “transgenes”
- Use drugs to modify function of existing endogenous cellular genes

# Which functions might be modified in Sport enhancement?

- Muscle - size, strength, more rapid recovery from injury
- Blood-formation - increase blood flow to exercising tissues
- Production and use of metabolic energy

# Which genes?

- Muscle size, strength - growth hormone, IGF-1, myostatin
- Increase blood production - erythropoietin gene
- Metabolic regulator genes - PPAR delta - increases efficiency of calorie utilization and increases type I (slow) twitch muscle fibers

# Introduce foreign “transgenes”

- Construct virus vector that expresses Epo gene only when needed - low oxygen concentration in tissues (e.g., Repoxygen)
- Inject into muscle - produced epo will enter blood stream, stimulate bone marrow to produce more red blood cells - delivery oxygen more effectively to tissues

# German Coach Suspected of Genetic Doping (2006)

QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

Thomas Springsteen



Repoxygen



Regulated production  
Of erythropoietin,  
regulated production  
of blood

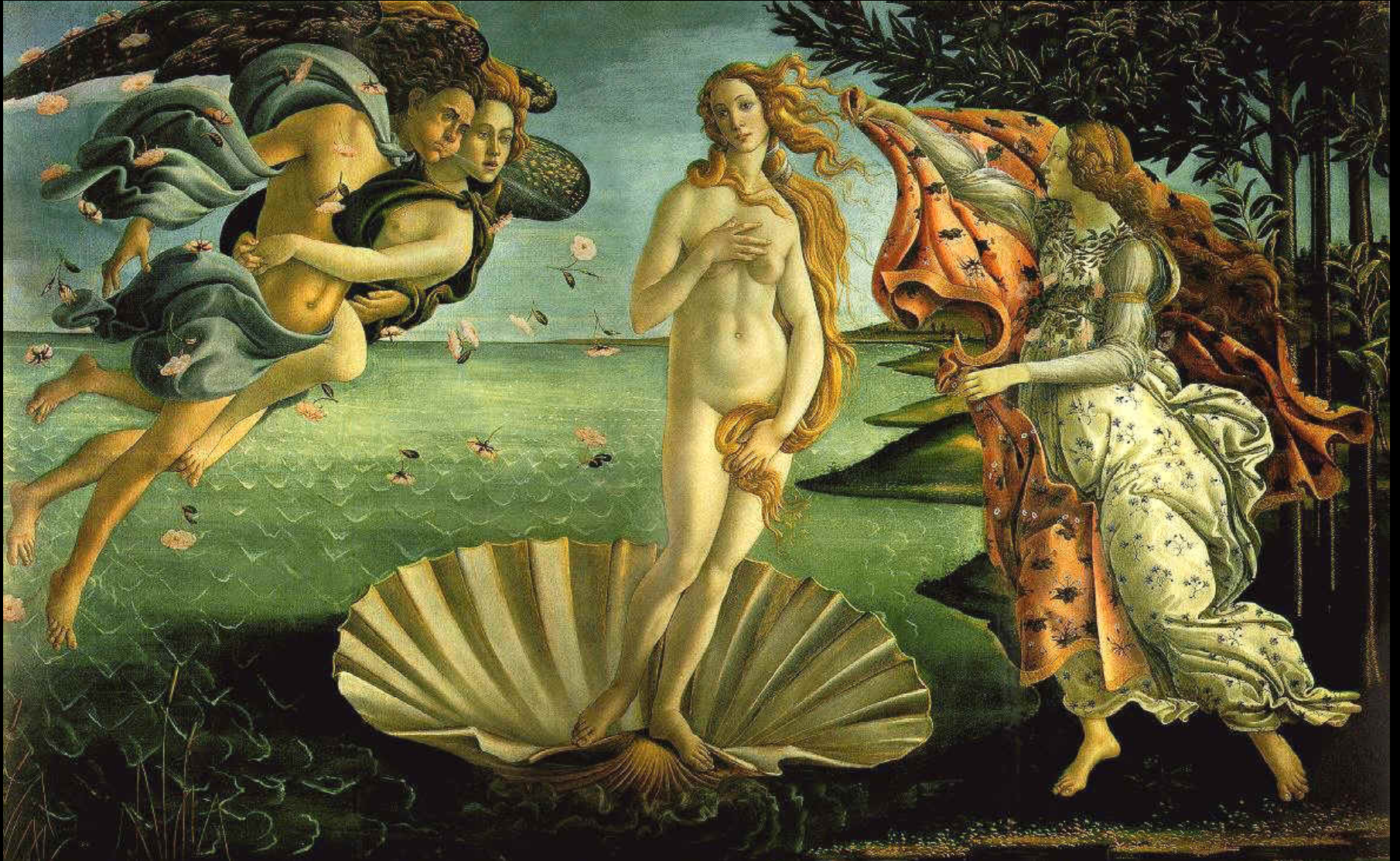
# If true, unethical and professional misconduct

- threat to health of athletes, known dangers of technology
- unlikely to comply with regulatory oversight, full disclosure, informed consent - unethical human experimentation
- violation of WADA Code

# Drugs to modify expression of endogenous genes

- inhibit expression of myostatin
- regulate expression of PPAR $\delta$  - make calorie utilization more efficient, regulate ratio of slow/fast muscle fibers. Drugs already in clinical trials for obesity.

# The semantic problem - where is the boundary between therapy and enhancement?



# Summary

- Gene transfer for therapy is clinical reality.
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- Gene transfer for therapy is clinical reality.
- But, gene transfer technology still immature, many real and potential risks. Reserved for serious disease
- Inevitable application of identical methods for enhancement - Sport obvious early area of application

