

Gene-Based Enhancement in Sport

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higher, faster, stronger - bioengineering or sport? What is feasible? Why do we care?

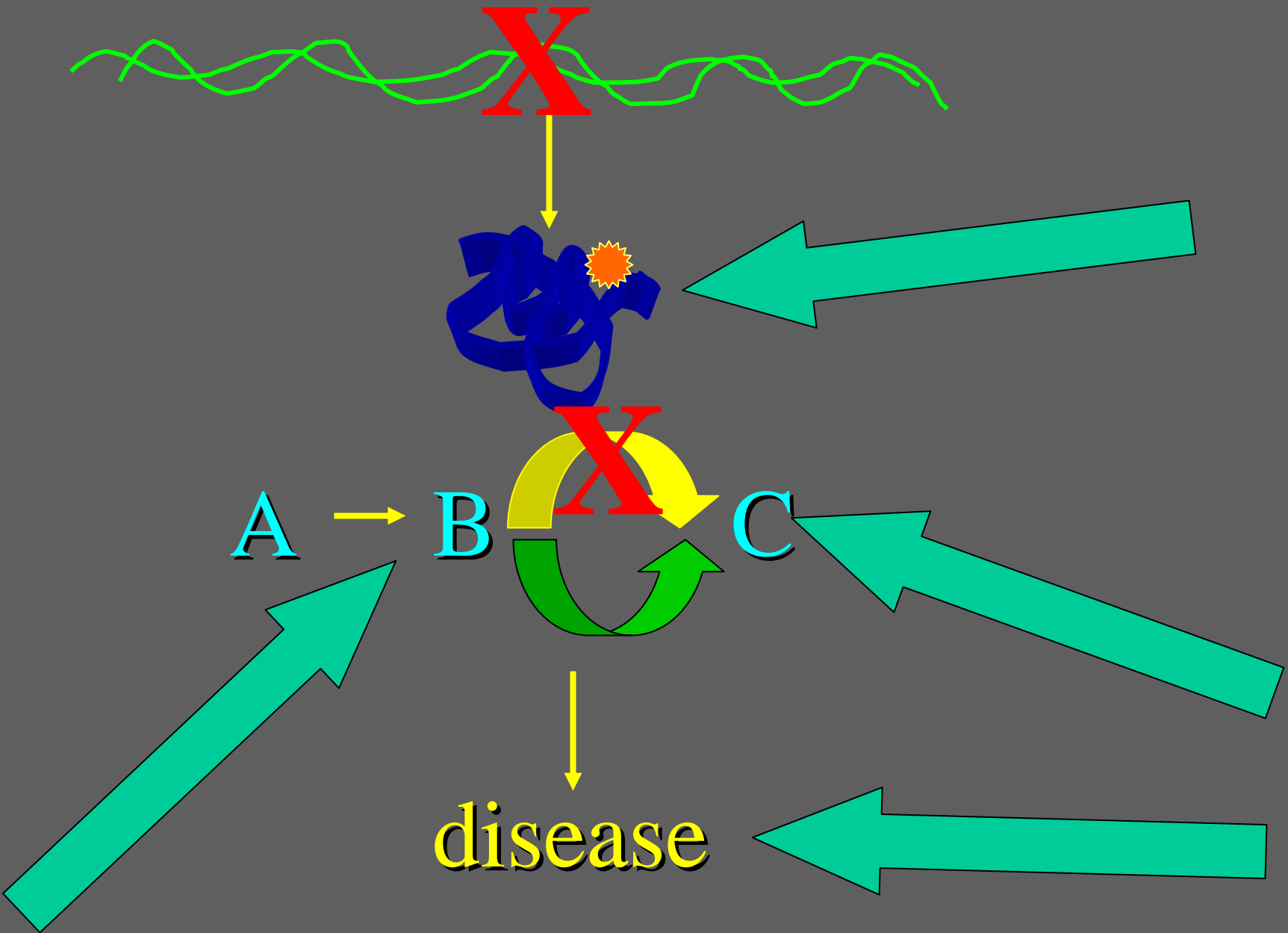
What's the issue, where does it come from and why does it matter?

Advances in human gene therapy

- methods are becoming available for genetic modification of human beings for treatment of disease - a recent therapeutic success
- the same methods will be used to enhance non-disease traits.

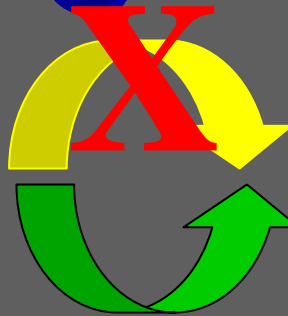
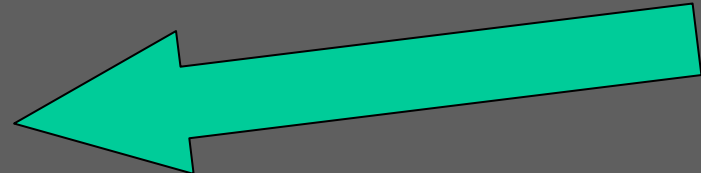
Advances in human gene therapy

- sport offers unique opportunities for gene-based enhancement - enormous financial and political pressures from high school sport to elite sport
- rampant drug-based enhancement at all levels of sport.
- is gene-based approach less tolerable? If drugs, why not genes? Why do we care so much?





X

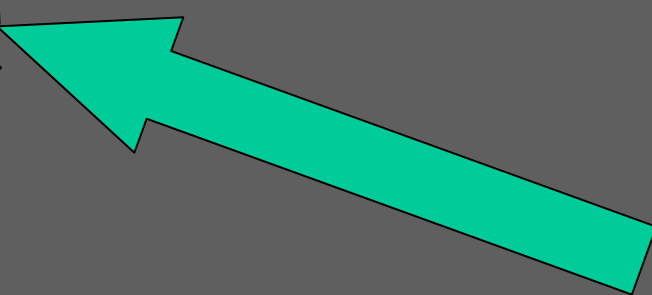


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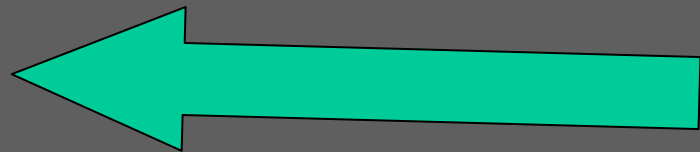


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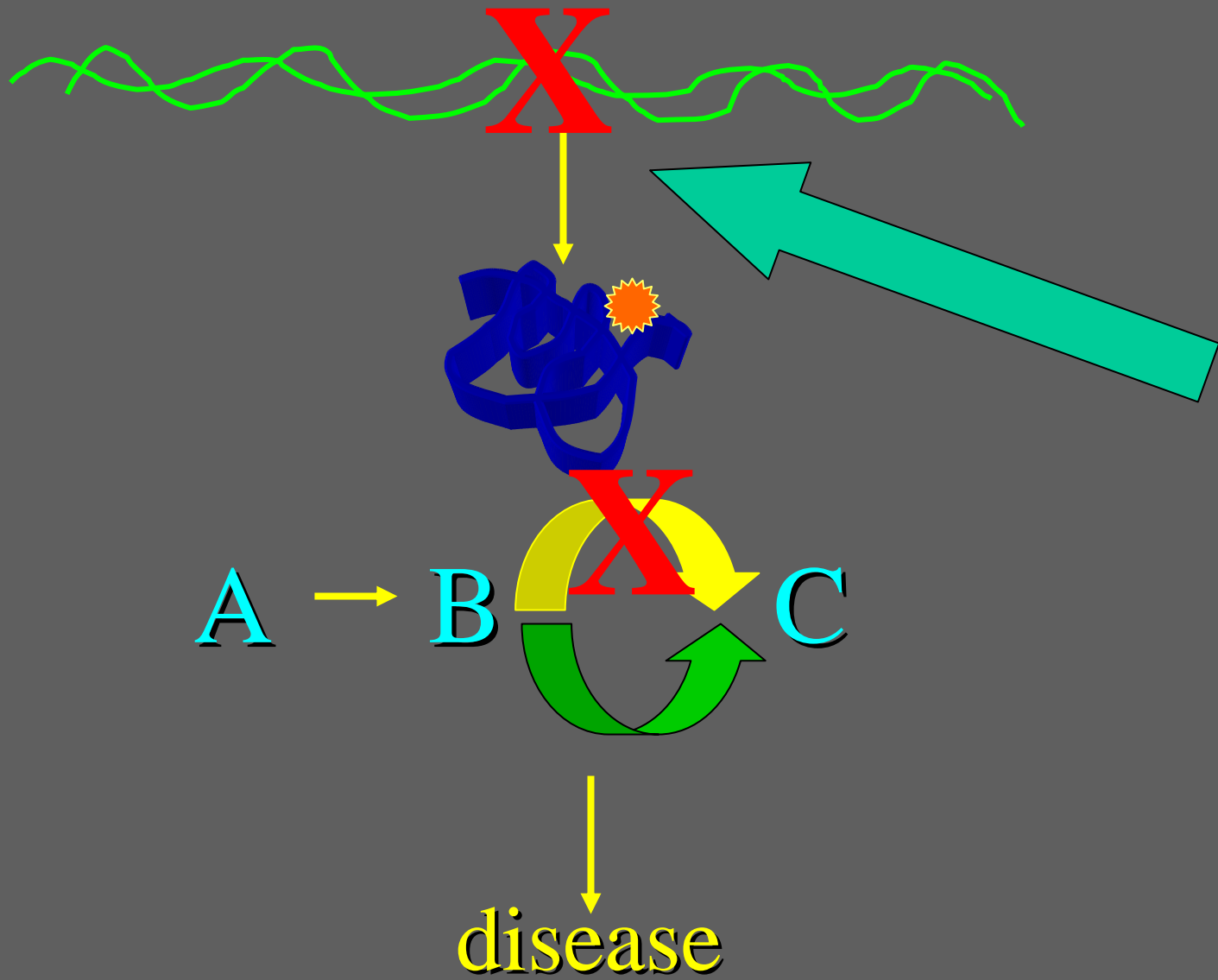
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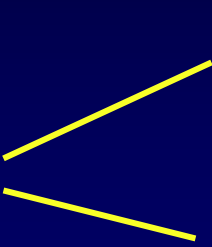


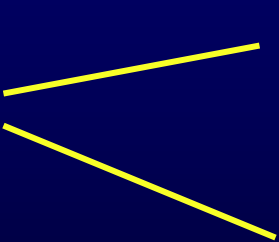
disease



What's wrong with this picture?



somatic cell  therapy
enhancement

germ cell  therapy
enhancement

human gene transfer studies - 2005

- more than 800 clinical studies world-wide since 1990 - many thousands of patients
- most for serious, life-threatening disease (cancer, heart disease, etc.)
- rigorous local and national review and regulation - FDA, NIH/RAC
- most have been “unsuccessful” or exceedingly inefficient



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Sustained Correction of X-Linked Severe Combined Immunodeficiency by ex Vivo Gene Therapy

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ABSTRACT

Background X-linked severe combined immunodeficiency due to a mutation in the gene encoding the common γ (γ_c) chain is a lethal condition that can be cured by allogeneic stem-cell transplantation. We investigated whether infusion of autologous hematopoietic stem cells that had been transduced in vitro with the γ_c gene can restore the immune system in patients with severe combined immunodeficiency.

ARTICLE

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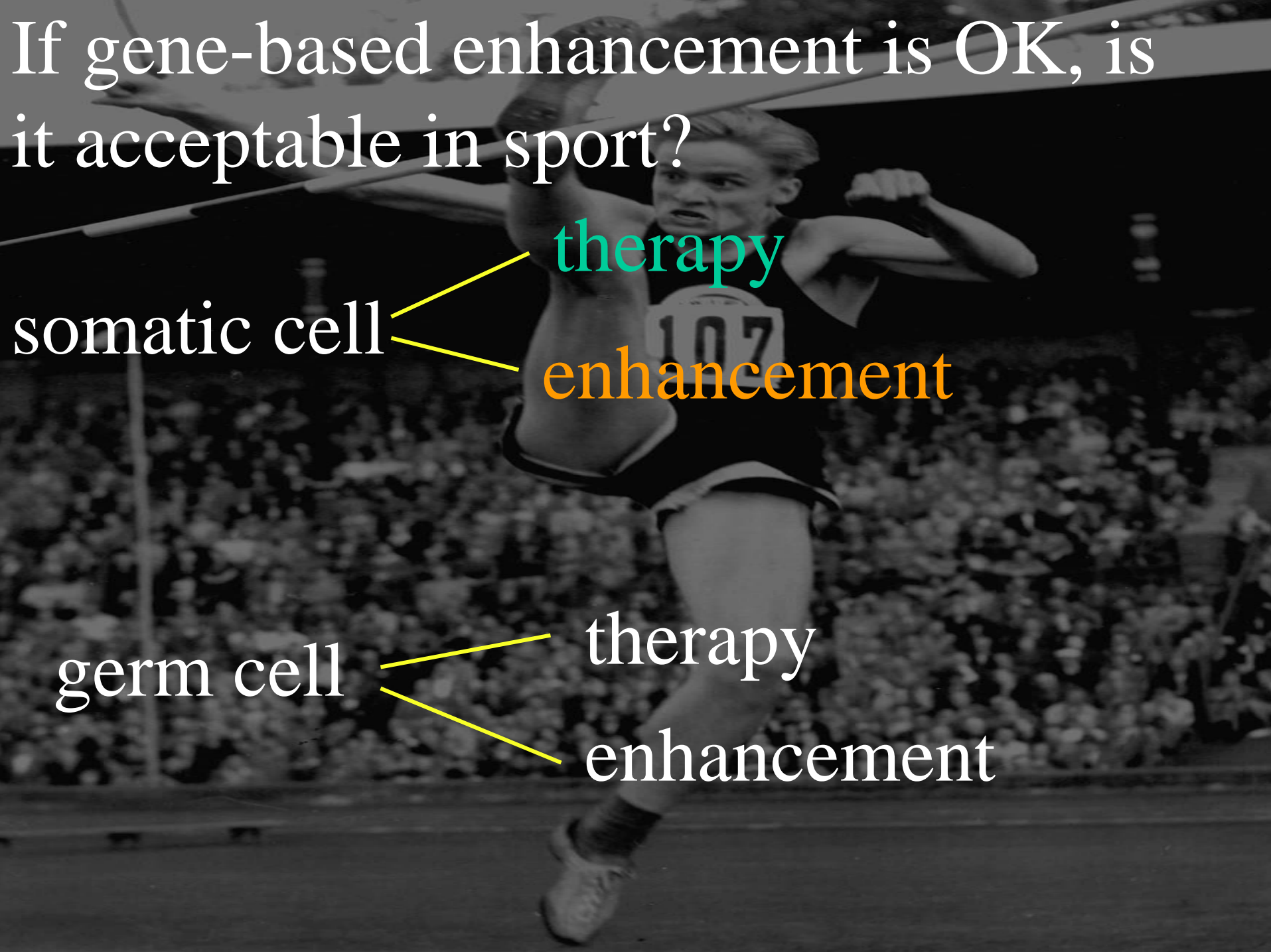
.....but at a cost

- current methods very immature and inefficient, but also potentially hazardous
- at least two treatment-caused deaths, three cases of leukemia, other probable adverse events in gene therapy studies
- need for continued oversight and regulation of the technology, even for life-threatening disease

If gene-based enhancement is OK, is it acceptable in sport?

somatic cell therapy
enhancement

germ cell therapy
enhancement



Enhancement in modern society

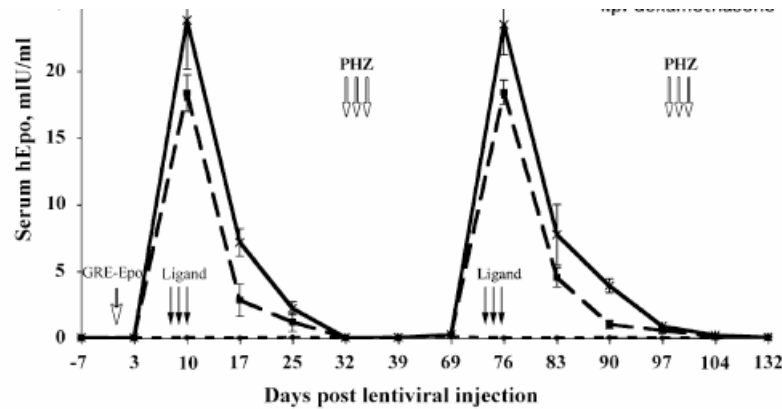
- our society encourages and accepts many forms of enhancement - cosmetic surgery, psychoactive drugs, life-style drugs, etc.
- if drug-based enhancement is acceptable in general, why not gene-based enhancement?
- if drug-based enhancement is acceptable, why not for sport? We know that drug-based enhancement is common in sport - why not genes?
- if not, what are we trying to protect?

development of genetic enhancement

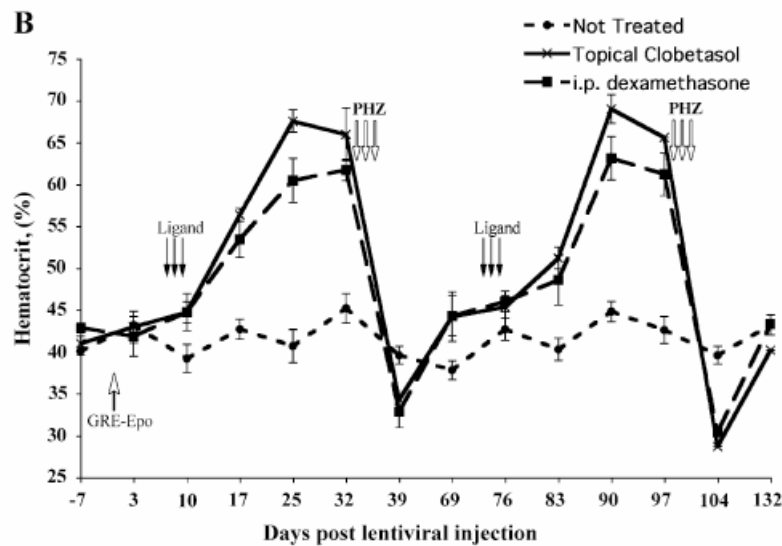
- direct outcome of therapeutic methods - muscular dystrophy, anemias in patients with cancer, chronic kidney disease

Sport-relevant functions easily enhanced by genetic manipulation

- muscle bulk, strength, force of contraction
- increased red blood cell production for enhanced oxygen delivery to exercising muscle



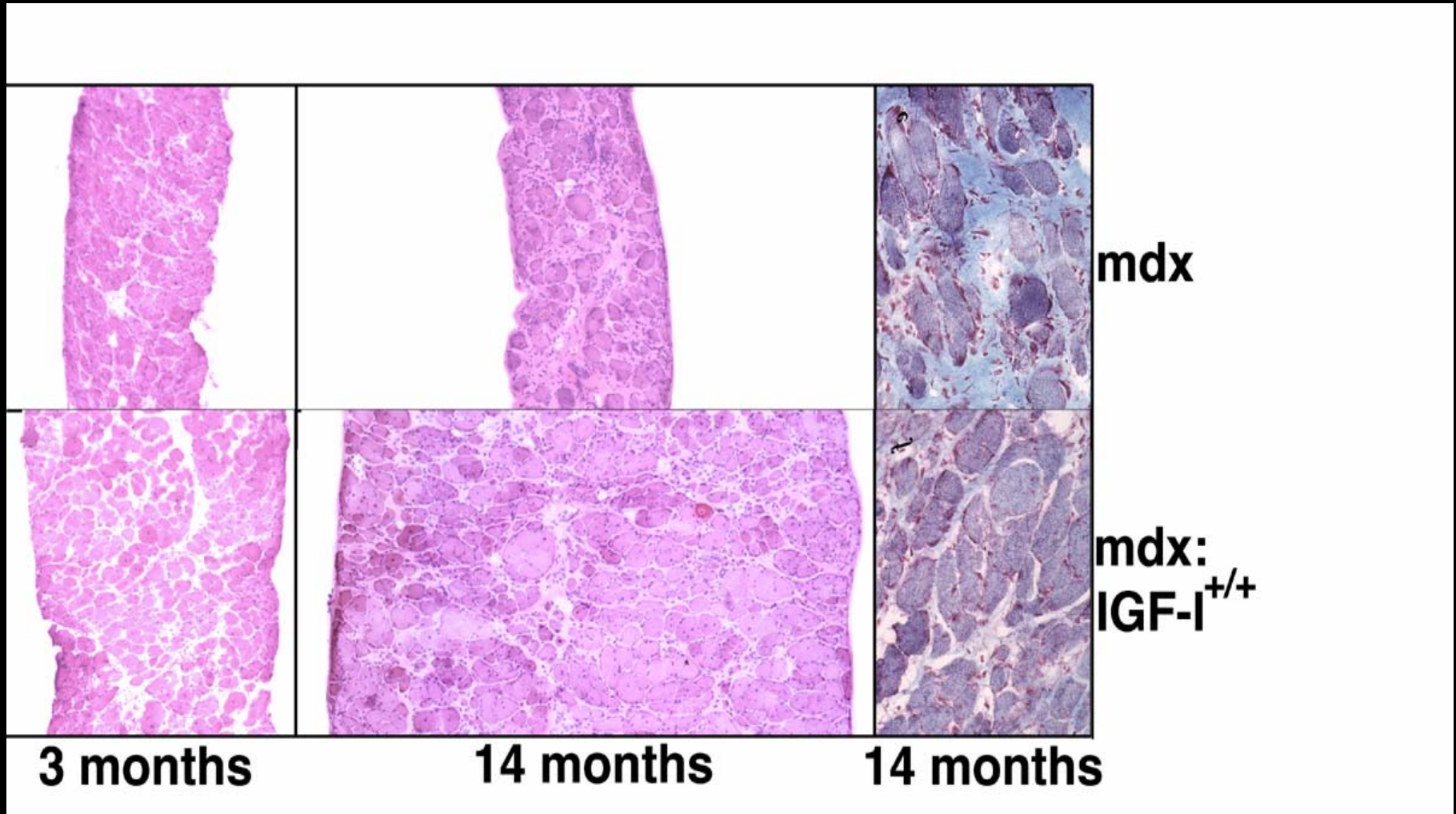
tions of the ligand: topical clobetasol or i.p. injection of 50 μ g dexamethasone (closed arrows). Hemolysis to lower hematocrit was induced experimentally with three i.p. injections of 60 mg/kg PHZ starting at day 34 and 99, as indicated (open arrows) ($n = 5$).



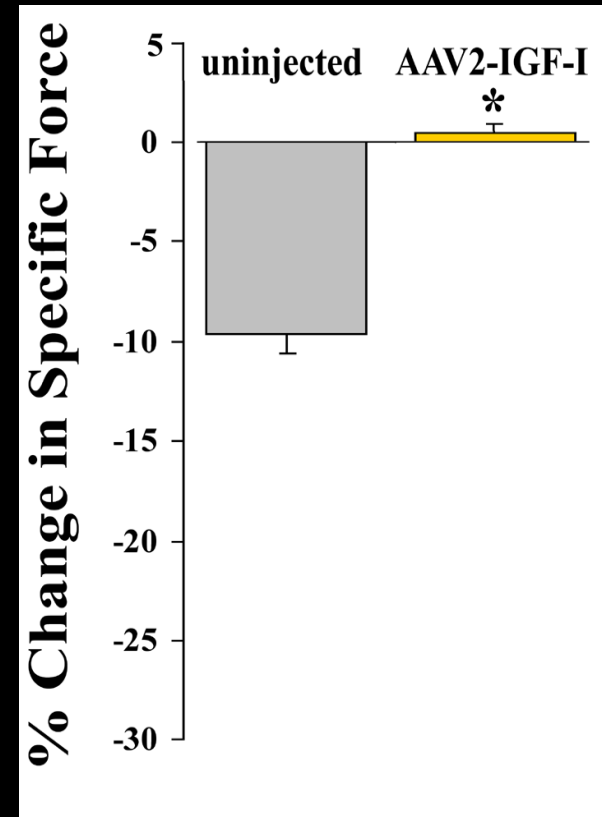
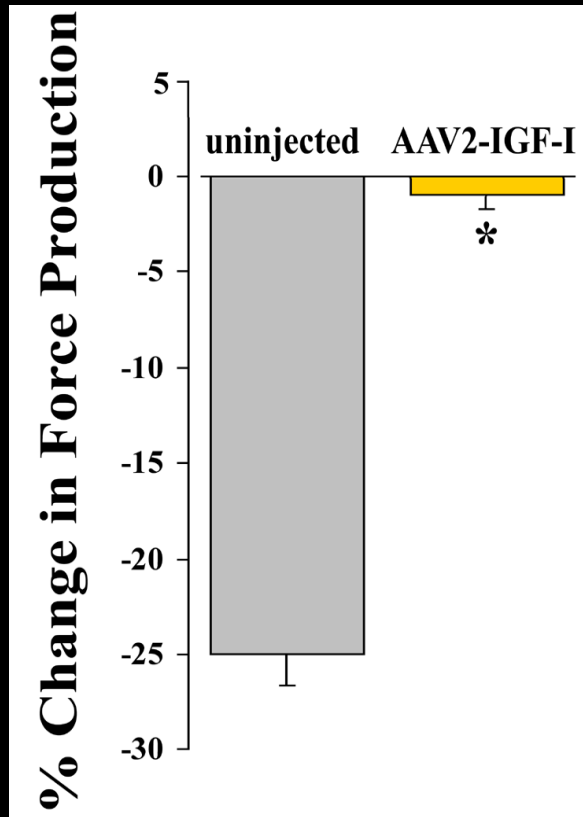
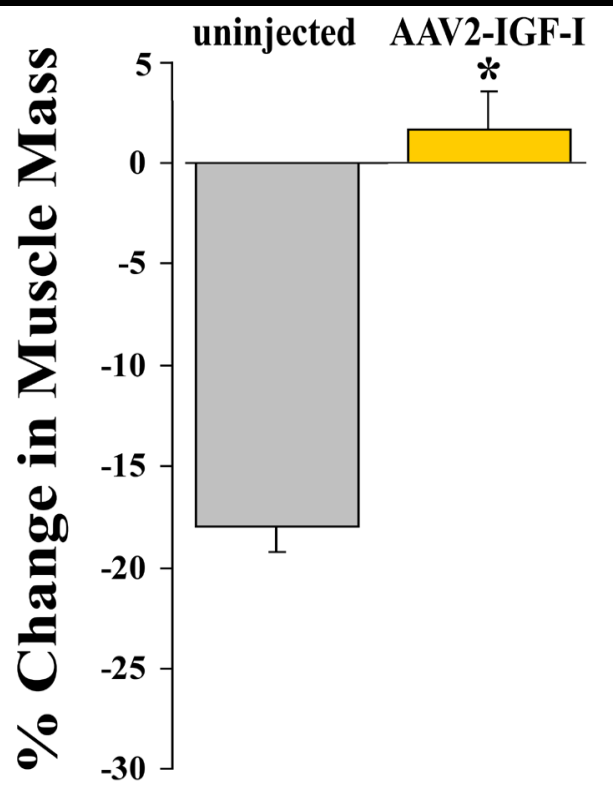
therapeutic gene. To do this, we used the GRE-Epo vector. We measured hematocrit and serum Epo concen-

cations or i.p. doses of 50 μ g dexamethasone 1 week after virus injection. A rapid increase in hematocrit was

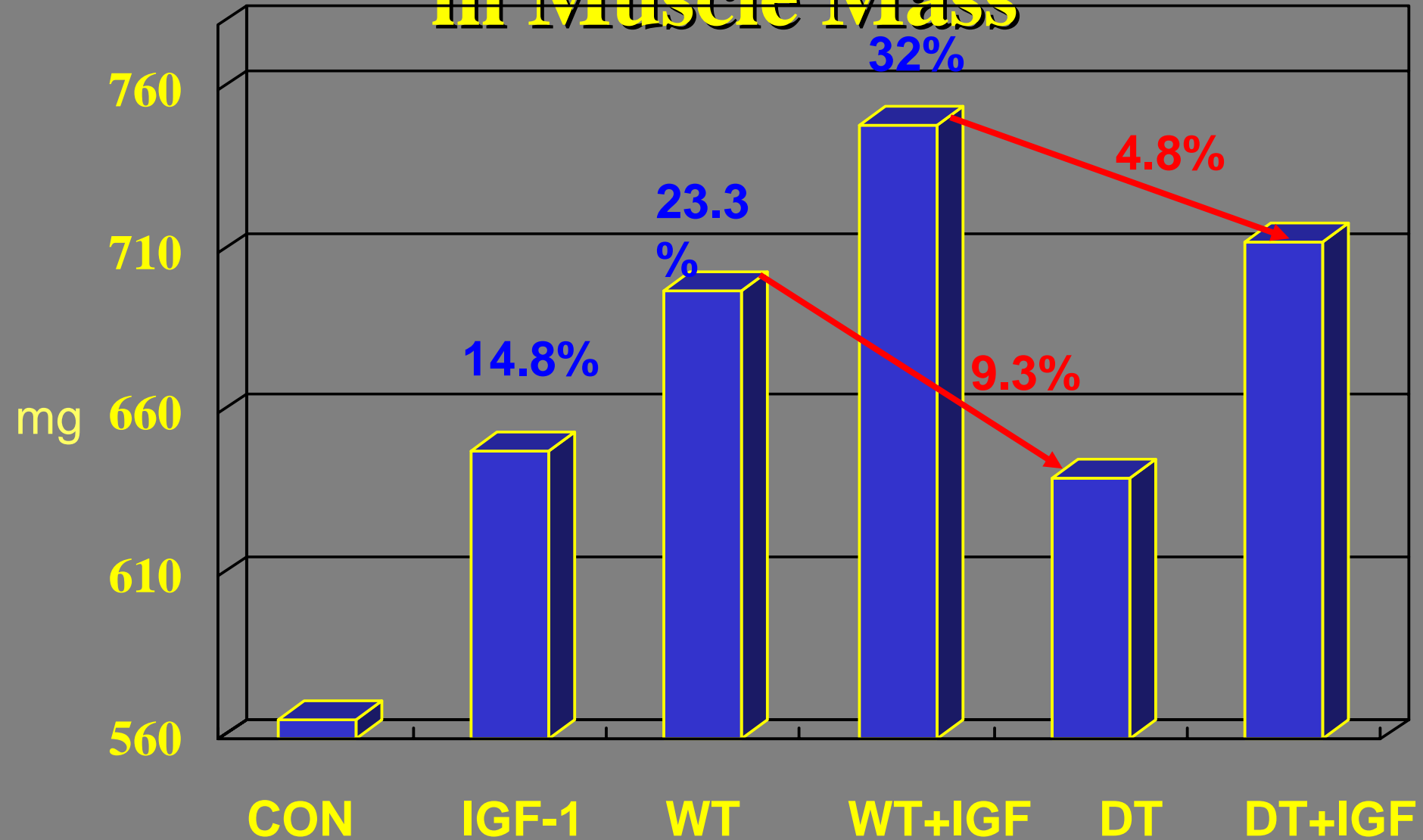
Overt disease - IGF-I produces hypertrophy in the mdx diaphragm



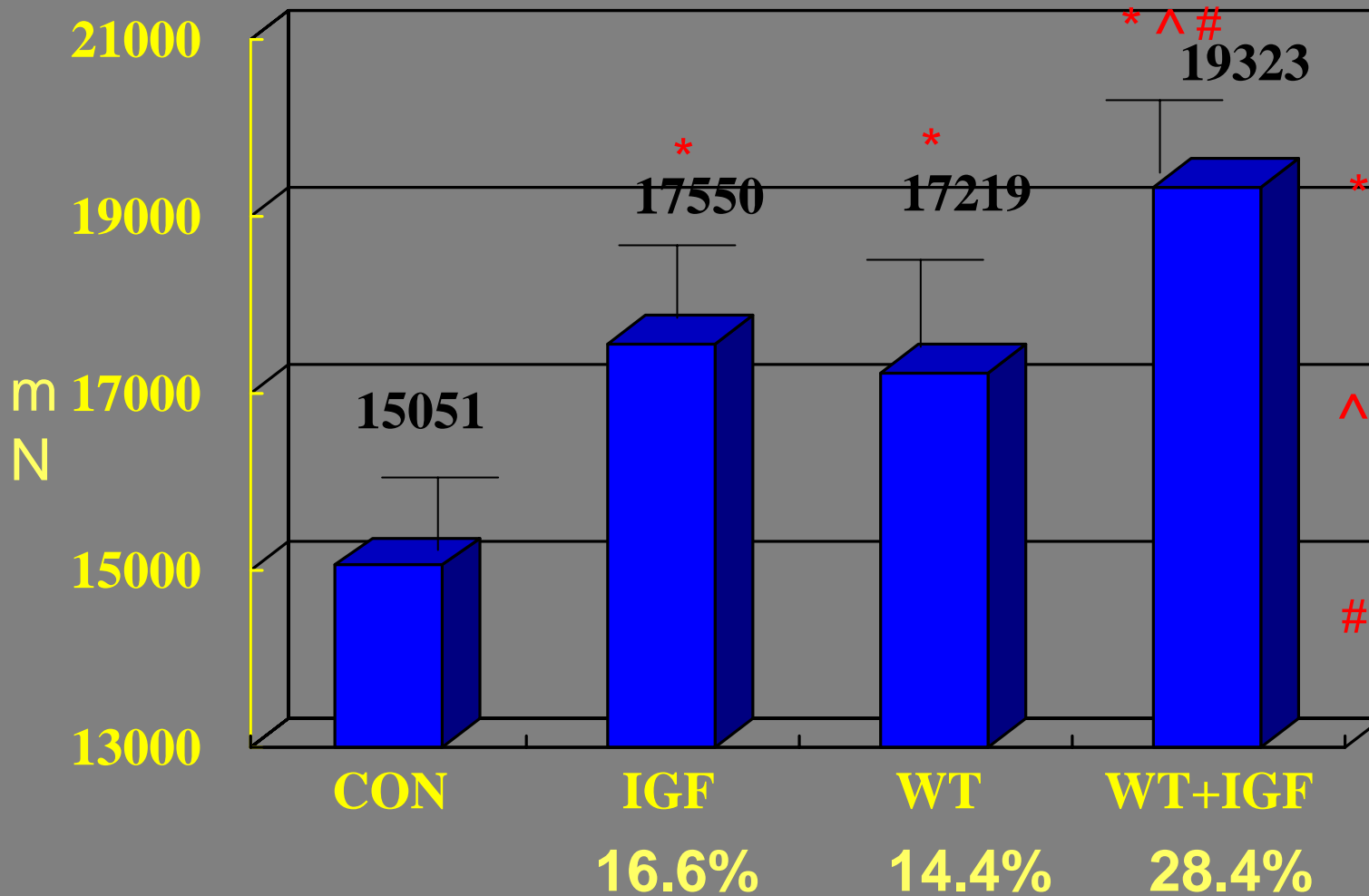
Human aging (disease?/enhancement) IGF-I expression in adult mice prevents age-related muscle atrophy



Sports enhancement - Changes in Muscle Mass



Maximal Force Production



Conclusions

- gene-based “enhancement” is going to become feasible
- sport is one of the most “attractive” areas for application
- with current gene transfer methods, application even for life-threatening disease is potentially hazardous but justified on risk-benefit basis
- therefore, with current methods, technology too immature to justify use in non-disease settings, including sport

Conclusions

- rogue application in sport will not conform to standards of review and regulation and will not be consistent with ethical standards - informed consent, human experimentation (Nuremberg, Helsinki, Inuyama, NIH, etc.)
- any attempts at genetic manipulations in athletes that circumvent review and regulation standards should be considered malpractice, professional misconduct and, where appropriate, illegal.

What else should be done?

- more communication with athletes, scientific and policy and ethics communities
- clear policy positions by gene therapy and medical professional societies
- more forceful policies from athletic communities
- greater public education

San Francisco Chronicle

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Genome Discovery Shocks Scientists

Genetic blueprint contains far fewer genes than thought — DNA's importance downplayed

By Tom Abate

CHRONICLE STAFF WRITER

Deepening the mystery of what makes us human, two scientific teams will publish the first maps of the human genome this week, revealing that the human genetic blueprint contains only a third as

many genes as had been supposed.

The publication of the maps is a milestone in the decade-long, multibillion-dollar effort to decipher the DNA that carries the set of instructions, passed on from parents to children, for making a human being.

Until recently, scientists had expected to find as many as 100,000 genes in the genome. But the two scientific teams, reporting their findings this week in the journals *Science* and *Nature*, independently found only about 30,000 genes.

The paucity of genes left scientists

struggling to understand how humans could be so much more complex than other animals with essentially the same number of genes.

"We have only 300 unique genes in the human (genome) that are not in the mouse," said Craig Venter, president of Celera

Genomics, the Maryland firm that led one of the mapping teams. "This tells me genes can't possibly explain all of what makes us what we are."

Francis Collins, leader of the U.S. contingent to the Human Genome Project, a consortium of publicly funded scientists from

around the world, said the findings will force scientists to look for other factors to explain many aspects of health, disease and behavior.

"We had a hard time explaining the (genetic) control mecha-

► **GENOME:** Page A17 Col. 1

Scientists' Discovery Casts Doubt on Importance of Genes

► **GENOME**

From Page 1

nism when we thought there were 100,000 (genes)," Collins said. "Now we have only a third as many."

Celera and the public scientists of the Human Genome Project have been rivals in the race to map the genome. In June, the two teams announced at a White House ceremony that they had read most of the 2.91 billion chemical letters found in each strand of human DNA.

This week, in dozens of articles in the journals *Science* and *Nature*,

instructions for making one or more of the proteins constitute the body's chemical workforce.

But genes are few and far between. Less than 1.5 percent of the genome seems to code for proteins, Lander said. Scientists thought it was twice as much before the map was done.

Both scientific teams painted the genome as a landscape of vast dark stretches of repetitive chemical letters, interspersed with genes that seem as rare as city lights seen from an airplane at night.

"The good news is that these two papers, which are the result of different approaches, offer pretty

Understanding the Human Genome

Geneticists have found about 30,000 genes in the human genome — only a third as many as had been thought.



■ What is DNA?

Found in every living cell of every living thing, DNA is the instruction

process. All of this suggests, as Collins put it, "that some of our junk isn't junk after all."

■ **Men, women and mutations:** Public gene mappers made one finding that could thrust the genome into the battle of the sexes.

The public scientists theorize that men pass on mutations to their offspring twice as often as women. They surmised this by comparing the genetic sequences of the X and Y chromosomes. Women have two Xs, men an X and a Y. The scientists analyzed the repeat elements on the Y chromosome and measured how

the proteins in other organisms we've studied," said Mark Adams, vice president for genome research at Celera and a co-author on Venter's paper. "They are capable of more interactions, they do more things."

This is important because molecular biologists see the human body as a machine, in which proteins serve as the gears, motors and (pulleys that perform every task from flexing muscles to firing nerve synapses. Before the mapping project, genes were considered the control software in this analogy. But now that metaphor seems dated.