Genetic Interventions: Therapy and Enhancement

Phil/Biol 2510, Spring 2009
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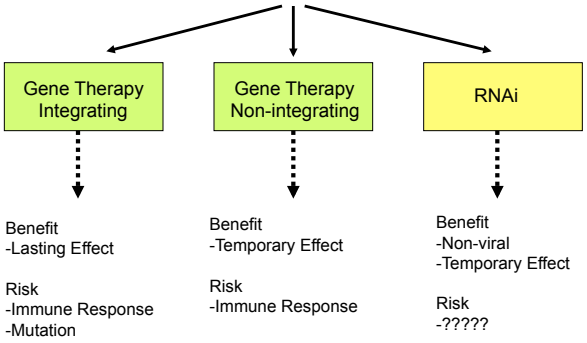
Outline

- Genetic Therapy & RNAi
  - Benefits and Risks
  - Somatic vs Germline Modifications
- Therapy vs. Enhancement
  - What is the distinction?
  - Is it a useful distinction?
- IGF-1 Case

Genetic Interventions



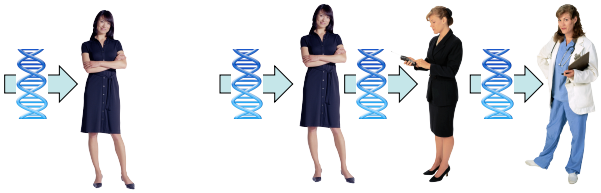
What cells should gene therapy be used on?

Somatic Cells

- Genetic modification effects only individual, or part of individual.

Germ Cells

- Genetic modification effects future generations.



Somatic vs. Germline

Somatic Cells

- Genetic modification effects only individual, or part of individual.
- Currently Permitted and largely considered ethical

Germ Cells

- Genetic modification effects future generations.
- Currently Prohibited and largely considered unethical

What purposes should gene therapy be used for?

Therapy vs. Enhancement?

- **Therapy** includes those procedures used for purposes of returning an individual to a state of health or back to normalcy.
- **Enhancement** includes those procedures used for increasing an individual's abilities beyond the normal range or beyond what they would have achieved if not used.

Erythropetin (EPO)

EPO is a natural hormone that regulates red blood cell production, and thus influences the oxygen carrying capacity of the blood.

- Therapy: EPO is used in therapeutic context to treat cancer patients for anemia caused by chemotherapy.
- Enhancement: But EPO can be (and is) taken by endurance athletes to improve their oxygen carrying capacity.

EPO

http://www.nrk.no/sport/annan_idrett/4988390.html

Lance Armstrong 7 time champ (took EPO for chemotherapy induced anemia)


http://instantpundity.blogspirit.com/archive/2005/09/index.html

David Millar banned for 2 years

Why celebrate Armstrong but dismiss Millar?

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Why celebrate Armstrong but dismiss Millar?

An Argument:

- Armstrong used EPO for legitimate medical purposes, to treat a health condition (anemia) as a result of cancer treatment.
- Millar did not use EPO for a legitimate medical purpose, but rather to (unfairly?) enhance his competitive athletic performance.

Argument 1

- Gene therapy should be used only for legitimate medical purposes, returning individuals to health or normalcy.
  - Enhancement distorts the traditional goals of medicine.
  - Enhancement leads to the 'medicalization' of the human condition – makes normality pathological

Therapy vs. Enhancement

Argument 1

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Counter-Argument 1

- An very narrow view of what are "legitimate medical purposes".
  - If goals of medicine are to make people better, but that could include enhancement (e.g., cosmetic surgery, Lazik…)
  - People regularly "enhance" without the risk of medicalizing human condition. (e.g., Coffee, diet, education, etc.)

Argument 2

- Enhancement is unfair to other individuals (in competitive sports).
  - It fails to value the natural limits and abilities that prompt standards of athletic excellence. (E.g., the enhanced athlete wasn't successful because of his/her own natural talents or efforts.)
  - It was against the rules.

Therapy vs. Enhancement

Argument 2

- Enhancement is unfair to other individuals (in competitive sports).
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  - It was against the rules.

Counter-Argument 2

- "Fairness" only applies to contexts in which rules are agreed upon. (Outside competitive sports?)
  - Difficult to divide natural and unnatural/artificial, even in sports. Also, highest levels of athletes are already genetic elites/freaks.
  - Rules can be changed.

A Twist…

1991 paper* describes a Finnish family with a mutation that makes them hypersensitive to EPO…

"The erythrocytosis has not had any obvious effect on the health or life-span of the affected individuals. Many of them have reached an advanced age, and one of the affected family members has won several Olympic gold medals and world championships in endurance sports."

*Autosomal Dominant Erythrocytosis Caused By Increased Sensitivity to Erythropoietin. By Eeva Juvonen, Eero Ikkala, Frej Fyhrquist, and Tapani Ruutu *Blood*, Vol 78, No 11 (December I), 1991

Question:

Should the Finnish family members be barred from competing in competitive endurance sports?

– Do they have an <u>unfair</u> advantage?

– How is this case different from Millar's or Armstrong's use of EPO?

An Ethical Distinction?

Does it captures a morally relevant distinction between good and bad practice?

Therapy is Good!

and

Enhancement is Bad!

Useful Distinction?

"In evaluating the ethical aspects of any particular genetic intervention, we should ask not whether it is therapy or enhancement but whether the intervention poses significant risks, offers significant benefits, violates or promotes human dignity, is just or unjust, and so on."

(Resnik, p. 374

Dual-use Dilemma, again?

Perhaps the distinction between therapy and enhancement is best understood as a variant of the dual-use dilemma, in which a technology developed for medical therapy may also have applications outside that original medical/therapeutic context. If so, then we need to assess the ethics of that use, independent of its origin.

"The first efforts to enhance human genetic traits may well take place in athletics. Athletes' willingness to accept risks in order to win makes them good candidates for gene modifications aimed at improving performance. The intense commitment that many parents now bring to a child's athletic career suggests that some parents may be willing to cooperate [or pay large amounts of money] with reproductive specialists to increase their chances of bringing a future sport champion into the world."

Ronald M. Green, *Babies by Design: The Ethics of Genetic Choice* (Yale Press, 2007)

IGF-1 Case

- H. Lee Sweeny (U. Penn) sought was to combat the wasting effects of muscular dystrophy and aging (how muscles waste away).
  - Knew that insulinlike growth factor 1 (IGF-1) naturally multiples cells responsible for growth of muscle tissue.
  - Knew that injecting IGF-1 into muscle tissue helped grow muscle tissue, but dissipated in hours.

IGF-1 Case

- Sweeny's team isolated gene that manufactures IGF-1 and inserted into a virus.
  - Exposing mice to virus with IGF-1 gene, resulted in mice with muscles 15-30% greater than normal, even though mice were sedentary.
  - Exposing virus to middle-aged mice resulted in mice living to old age without any noticeable muscle weakness.

IGF-1 Case

- Colleagues of Sweeny altered gene sequences in early-stage mouse embryos producing line of mice that overexpressed IGF-1 in skeletal muscles.
  - Produced "Schwarzenegger mice" that developed normally, but were 20-50% larger than normal.
  - IGF-1 levels were increased in muscles, not bloodstream removing risk of cardiac problems and increased cancer risk.

IGF-1

- Soon after story broke in the news, Sweeney and his colleagues were swamped with calls from coaches and athletes around the country/world.
  - Could not be detected by current anti-doping tests (that has changed, now).
  - Demonstrates the desire to "enhance"
  - Potential use in engineering children…?

IGF-1

- Should Sweeney's rDNA use of IGF-1 be available for human use, outside of its potential application to MD or muscle waste in the aged?
  - What questions should you ask to determine the answer?
  - Ethics Framework…

Some Questions

- What are the risks of enhancement?
- Who will be affected by the risks/benefits of enhancement (who bears the risks/benefits)?
- What is fair or unfair about the use of IGF-1 rDNA technology for enhancement?

Epilogue

CASE 1a: Achondroplasia

A newborn child is diagnosed with achondroplasia – the most common form of dwarfism – caused by a mutation in the FGFR3 gene, which controls bone growth. The mutation causes a decrease in the rate at which cartilage turns into bone during development and particularly affects long bones, thus people with achondroplasia typically have average sized torso with disproportionately short limbs and slightly enlarged head with prominent forehead. Gene therapy could be used to add a normally-functioning copy of the FGFR3 gene to the child's bone cells.

80% of the time, achondroplasia is the result of a new mutation, not inheritance. Inherited forms are autosomal dominant.

CASE 1b: Short Stature

A couple have a healthy newborn who is in the lowest 10% of height for his age. The parents worry that since they are short in stature, that there child is likely to be short too. But they don't want him to suffer the disadvantages they have experienced. So, the parents decide to use growth hormone treatment (e.g., humatrope) and consider using gene therapy to provide a more permanent solution to short stature.

CASE 1c: Future Hopes

A couple who are fans of basketball plan to have a baby. They would like their child to tall and extremely muscular by the time he is 16 years old. This should give him an improved chance to develop an NBA career. Height is a polygenic trait that can be influenced by human growth hormone. Gene therapy could also be used to add multiple genes that control height and muscle growth in the embryo or newborn.

Genetic Intervention Punnett Square

	Treatment	**Enhancement**
Somatic Modification	Somatic Treatment	Somatic Enhancement
Germline Modification	Germline Treatment	Germline Enhancement

Genetic Intervention Punnett Square

	Treatment	**Enhancement**
Somatic Modification	Somatic Treatment (X-SCD gene therapy)	Somatic Enhancement (Gene doping in sports)
Germline Modification	Germline Treatment (Removing disease from family line)	Germline Enhancement ("Superathletes")

Genetic Intervention Punnett Square

	Treatment	**PREVENTION**	**Enhancement**
Somatic Modification	Somatic Treatment (X-SCD gene therapy)		Somatic Enhancement (Gene doping in sports)
Germline Modification	Germline Treatment (Removing disease from family line)		Germline Enhancement ("Superathletes")

CASE 2a: SCID

A newborn is diagnosed with Severe Combined Immune Deficiency (SCID), a genetic disorder that affects B and T lymphocyte production in the body. Because people with SCID lack the necessary immune response, many die within the first year of life as a result of complications from illnesses. Current treatment includes bone marrow transplants, monthly injections of antibodies, and also gene therapy to add a functioning gene responsible for producing T and B lymphocytes.

CASE 2b: Immunity

Firemen, emergency technicians, police, doctors, nurses, dentists, and other health care workers are constantly exposed to infectious diseases while transporting and caring for sick or hurt people. These diseases range form minor to life threatening and are obvious a concern for all involved. Gene therapy could be used to enhance these people's immune system so they have a more robust immune response to potential infections.

Problems with the distinction?

- No clear distinction between therapy and enhancement.
  - Vaccines? Corrective glasses?
  - What technology or social environment is available?
- Only assumes enhancement is wrong (or suspect) without providing justification…

Some Arguments

- Health and Disease
- Goals of Medicine
- Human Dignity
- Eugenics

Health and Disease

- Statistical normality
- Functional normality

Goals of Medicine

- Enhancement distorts the traditional goals of medicine.
- Enhancement leads to the 'medicalization' of the human condition?
  - makes normality pathological

Human Dignity

- Enhancement is unnatural
  - Alternatively: against God's law.
- It fails to value the given limits and natural abilities that prompt standards of human flourishing.
- It expresses a desire for mastery or perfectionism that is destructive of human dignity
  - a *Brave New World* dystopia

Eugenics

- Enhancement leads down a slippery slope to eugenic actions and policies
  - Also, consider genetic disparities
- Enhancement places improper emphasis on genetics as the locus of human value
  - Also medicalization

Useful Distinction?

Depends on other moral considerations (e.g., ethics framework):

"In evaluating the ethical aspects of any particular genetic intervention, we should ask not whether it is therapy or enhancement but whether the intervention poses significant risks, offers significant benefits, violates or promotes human dignity, is just or unjust, and so on."

(Resnik, p. 374)

Use of Distinction?

Also, expresses concerns about the meaning of the technology: ends and means

"…biotechnology is also a *conceptual and ethical outlook*, informed by progressive aspirations. In this sense, it appears as a most recent and vibrant expression of the technological spirit, a desire and disposition rationally to understand, order, predict, and (ultimately) control the events and workings of nature, all pursued for the sake of human benefit."

(*Beyond Therapy*, p. 1)

Summary

- Safety Concerns with Gene Therapy
  - Immune response and tumors
  - Gelsinger and Mohr
- Therapy vs. Enhancement
  - Arguments and counter-arguments
  - Uses of distinction

Bioconservatives vs. Transhumanists

- Hold to notion of natural and important limits to human genetic modification
- Ethical limits about commodification and hubris

- Hold no natural or unnatural limits to human modification
- Ethical issues about individual autonomy and pushing the limits of human possibility