

GENETIC MODIFICATION AND DOPING IN SPORT – SCIENCE AND POLICY



AEI

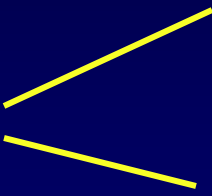
December 2008

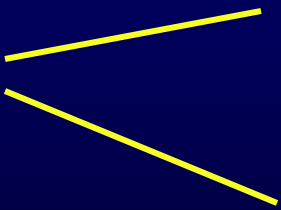


Revolutions in Sport

- Use of genetic tools to dope
- Use of genetic tools to detect doping
- Policy dilemma – control or encourage doping

I. Genetic Doping - Origins in Gene Therapy

somatic cell  therapy
enhancement

germ cell  therapy
enhancement

Extensive regulation and oversight

- Local institution biosafety, human subjects committees
- NIH Recombinant DNA Advisory Committee, FDA
- similar agencies worldwide

A difficult controversial beginning

- Early exaggerations, elevated expectations
- Highly publicized setbacks
- Severe criticism, progress too slow, not going to work

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.

Severe combined immunodeficiency diseases (SCID)

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





But a severe cost

- Immune defect corrected, children living normal childhood lives
- BUT, 5 cases of leukemia and 1 death in >30 treated children - direct result of treatment
- virus integration caused activation of quiescent cancer gene

Leber's Amaurosis

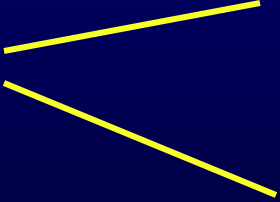
- Genetic defect in essential protein (RPE65) in photoreceptors of retina
- Childhood blindness
- AAV virus vector delivery of normal gene directly to retina
- vision



Summary

- Gene transfer for therapy is clinical reality.
- But, gene transfer technology still immature, many real and potential risks. *Reserved for serious disease*

somatic cell  therapy - **OK**
Enhancement **?**

germ cell  therapy
enhancement

Beyond Therapy - 2003 The President's
Council on Bioethics; www.bioethics.gov

*Enhancing Human Traits: Ethical and
Social Implications*, Eric Parens, ed.
Georgetown U. Press, 1998

Sport?

- Gene-b... humans... inevitab...
- Sport al... for enha... genetic



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iar area
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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

German Coach Suspected of Genetic Doping (2006)



Thomas Springsteen



Repoxygen



Regulated production
Of erythropoietin,
regulated production
of blood

II. Genetic tools for detection of doping

A new approach to doping detection

- Clever chemists change doping agents – make them invisible to testing
- Therefore, examine *EFFECTIONS* of doping agents, not agents themselves
- Methods are available to examine expression of entire human genome, distributions of all proteins in tissues and fluids



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The **WADA Informatics** infrastructure has been designed and developed to store and analyze genomic, proteomic and metabolomic data from the World Anti-Doping Agency (WADA)-sponsored research studies and from published scientific literature. This unique facility will foster a healthy cross-talk between several research groups driven by the common goal of developing tools to eliminate doping from competitive sport.

WADA Informatics also serves as a forum for the concerted and systematic understanding of the effects of performance enhancing agents based on patterns of altered genes, proteins and/or their products. Its broad aims are to identify molecular signatures following induction of cells and organisms with performance enhancing agents. Rapid advancements in science and technology will facilitate the discovery of creative outcomes in the realm of anti-doping.

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III. Policy response to doping – regulate or support?



WORLD ANTI-DOPING CODE



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International Convention against Doping in Sport 2005

Paris, 19 October 2005

Strong new cottage industry pro-doping

- Andy Miah
- Norman Fost
- John Tierney
- Nature Magazine

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HIGH-TECH HEROES

Enhanced Athletes? It's Only Natural.

By Andy Miah

Sunday, August 3, 2008; Page B01

- To ensure ability of athletes to compete on “level playing field” – everyone free to choose the enhancements that best accentuate their performance. That us what the *natural* athlete *should* look like today”.
- Enhancement includes gene doping.....”*testing is impossible*”
- Encourage drug and surgical modifications
- Invokes a model enhanced athlete – swimmer with surgical enhancement to enlarge webbing in fingers and toes,....leg extension surgery,...



- celebrate rise of new generation of genuinely superhuman athletes, rules of sports are governed by concern for *optimizing excellence*
- Steroids should still be regulated...they are *synthetic drugs that can radically alter the makeup of the body*
- But “tailor-made treatments” (genetic modifications) OK, promise *safer treatments than synthetic substances*
- We want athletes to remain extraordinary – increased use of human enhancement technology is a necessity – *even an obligation*

OPINION

LET THE DOPING BEGIN

Olympians on steroids are just giving the people what they want.

by [NORMAN FOST, MD, MPH](#) • Posted February 21, 2006 06:15 PM

The Current Issue



Anti-doping campaign ..”incoherent, hypocritical, naïve, false”.

“chicks and guys love the long ball, don’t care which performance-enhancing means used”.
Give the public what it wants (*spectacle???*)



(Viktor Koen)

John Tierney: Would legal doping level playing field?

By **John Tierney**

Published: August 12, 2008

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Commentary

Nature **454**, 692-693 (7 August 2008) |
doi:10.1038/454692a; Published online 6 August 2008

The science of doping

Donald A. Berry¹

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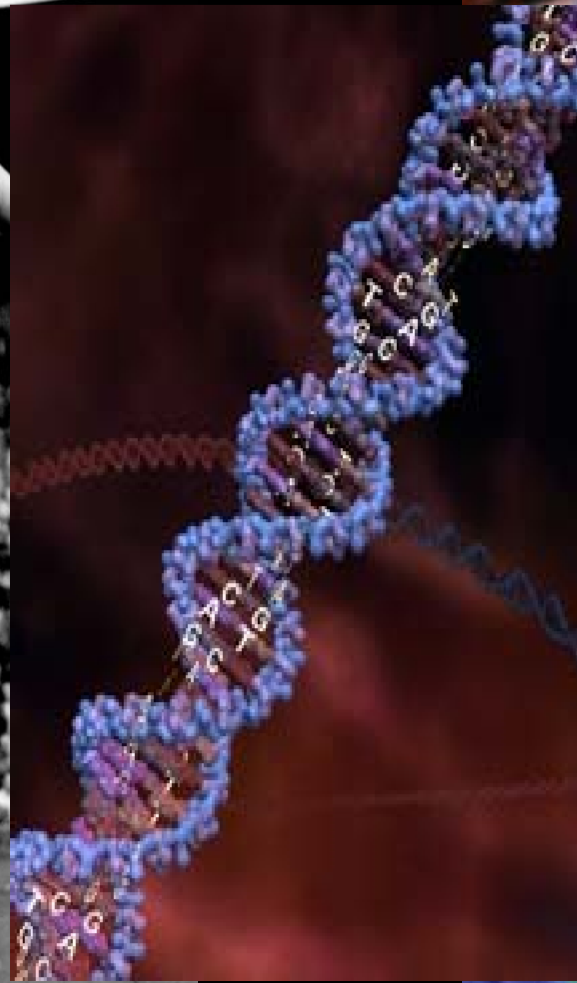
- “anti-doping authorities have fostered a sporting culture of suspicion, secrecy and fear”

- The value of sport is mostly in the spectacle
- Imperfection of testing invalidates the concept and need for anti-doping
- “extraordinary” is measured by approval of “chicks” and “guys”
- excellence is the feat- no matter how achieved – not the achievement



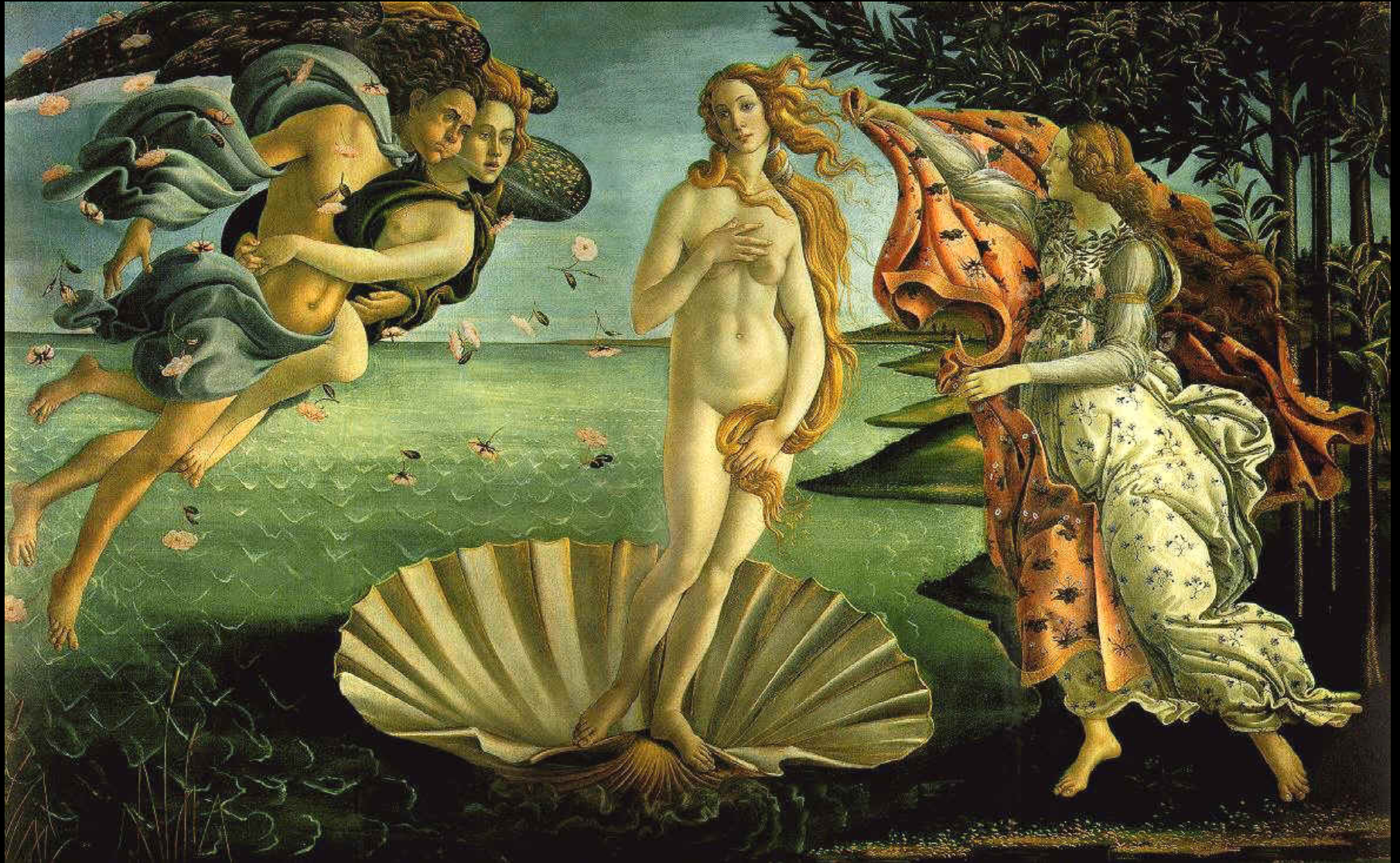
Beijing Paralympics 2008





Strong temptation for enhancement in sport

Genetic enhancement is inevitable



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

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

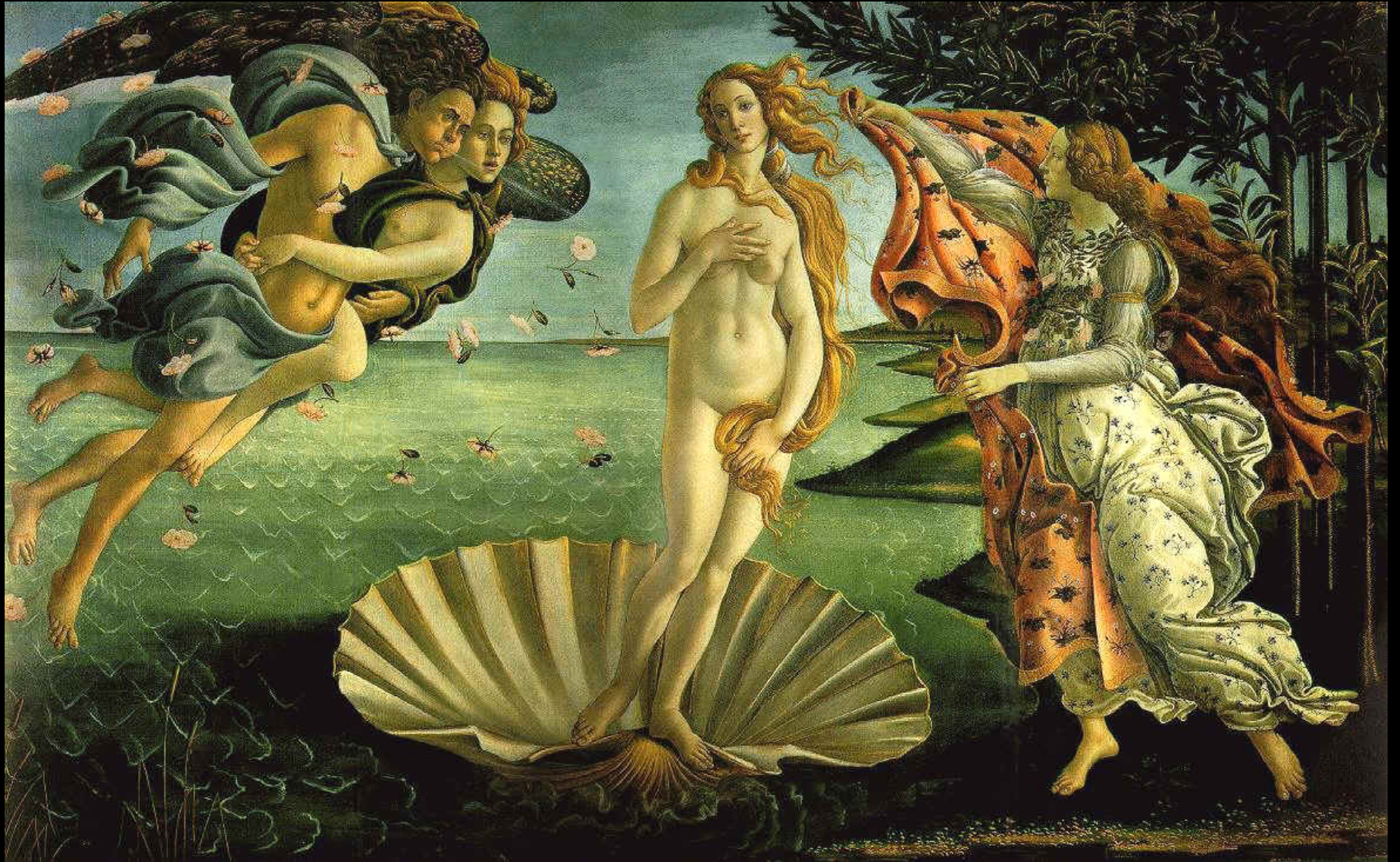
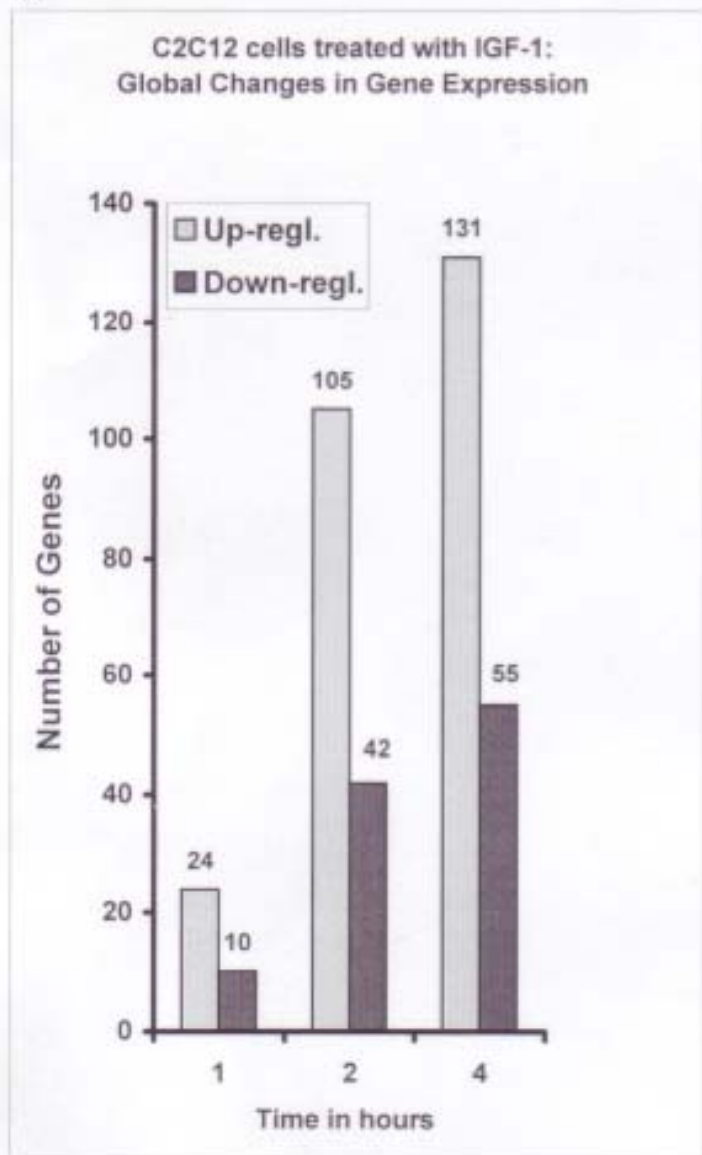
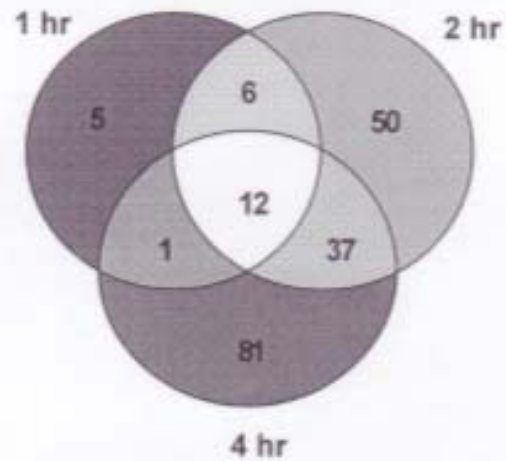


Fig. 1

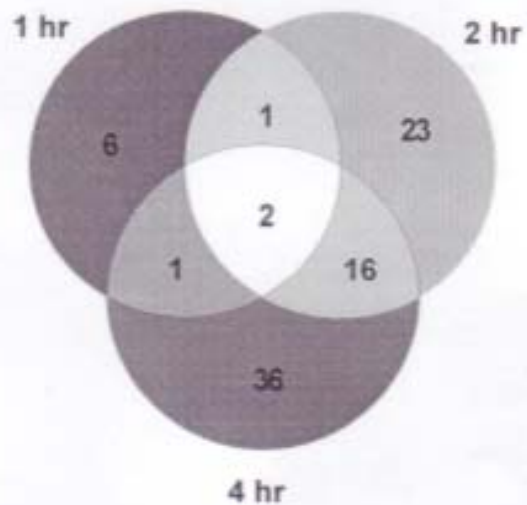
A



B Up-regulated genes

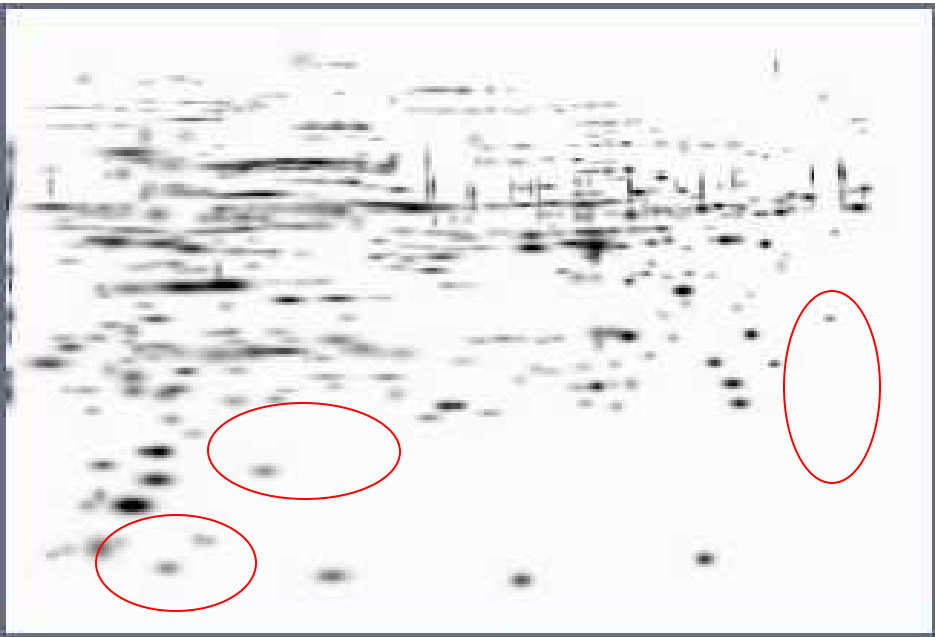


C Down-regulated genes



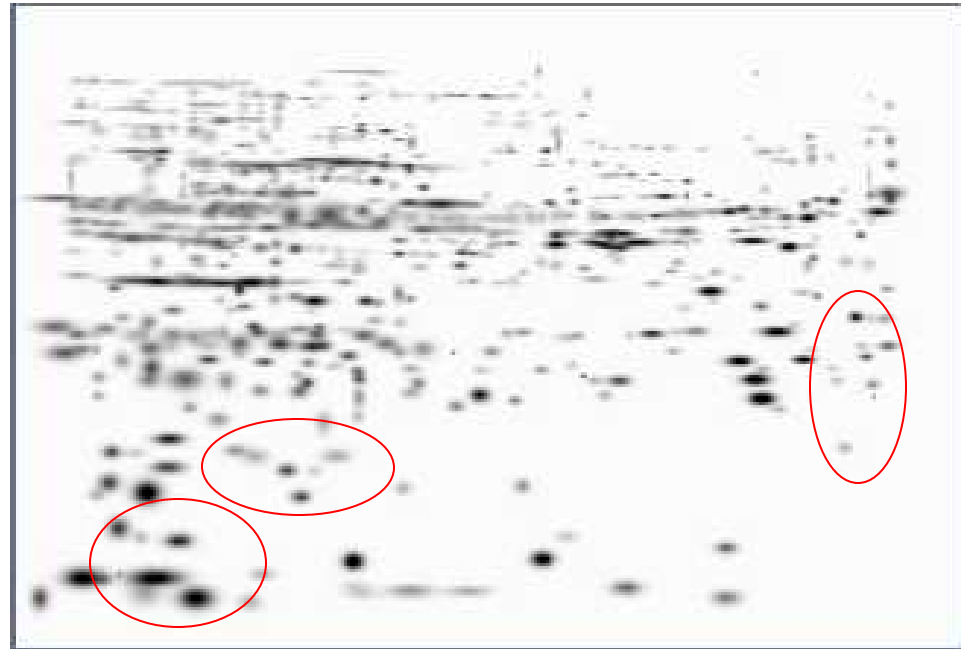
C2C12 cells treated with IGF-1 (cytoplasm)

control



1 hour

IGF-1



1 hour