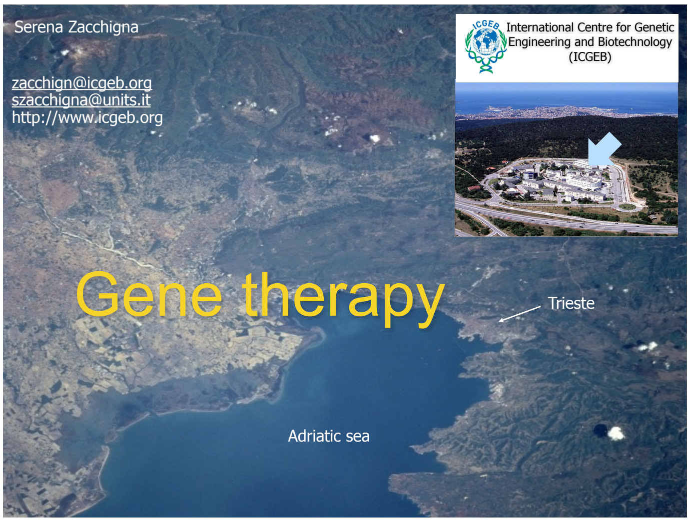
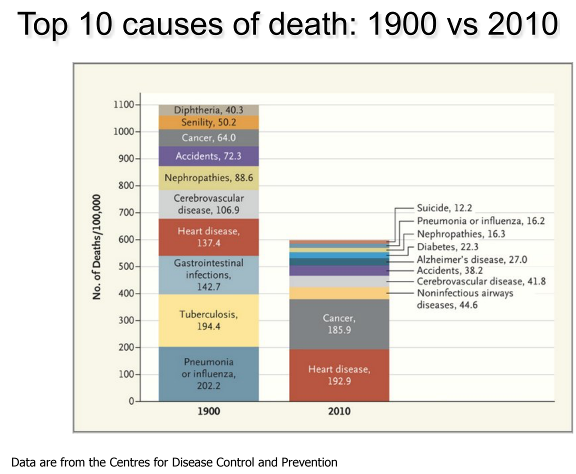


Serena Zacchigna

zacchign@icgeb.org
szacchigna@units.it
http://www.icgeb.org

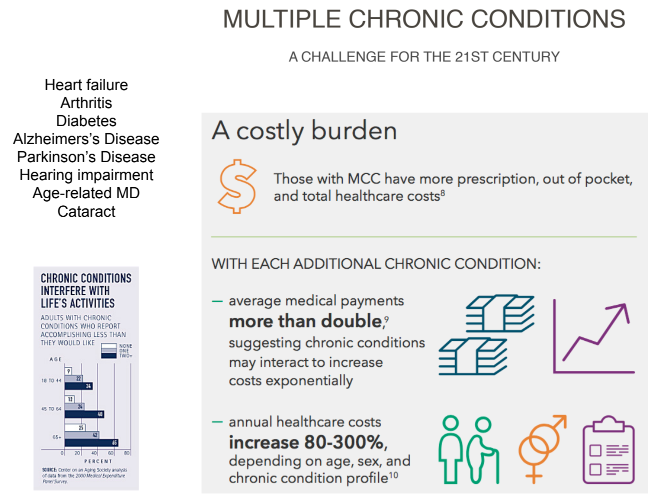
International Centre for Genetic Engineering and Biotechnology (ICGEB)

Gene therapy



Top 10 causes of death: 1900 vs 2010

Data are from the Centres for Disease Control and Prevention



MULTIPLE CHRONIC CONDITIONS

A CHALLENGE FOR THE 21ST CENTURY

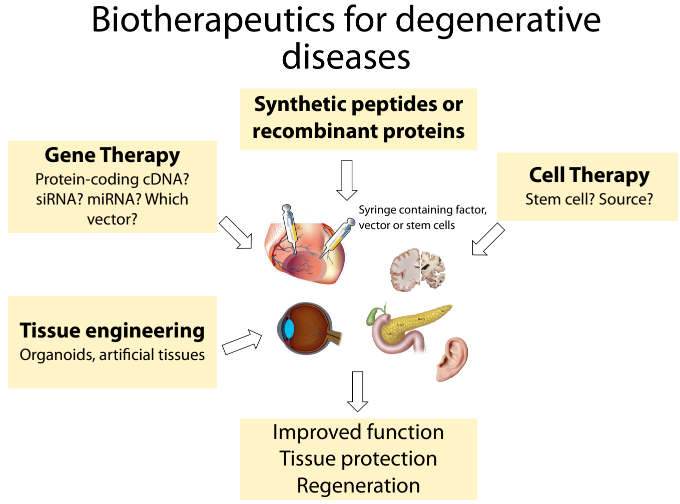
Heart failure
Arthritis
Diabetes
Alzheimers's Disease
Parkinson's Disease
Hearing impairment
Age-related MD
Cataract

A costly burden

Those with MCC have more prescription, out of pocket, and total healthcare costs[8]

WITH EACH ADDITIONAL CHRONIC CONDITION:

- average medical payments **more than double**,[9] suggesting chronic conditions may interact to increase costs exponentially
- annual healthcare costs **increase 80-300%**, depending on age, sex, and chronic condition profile[10]



Biotherapeutics for degenerative diseases

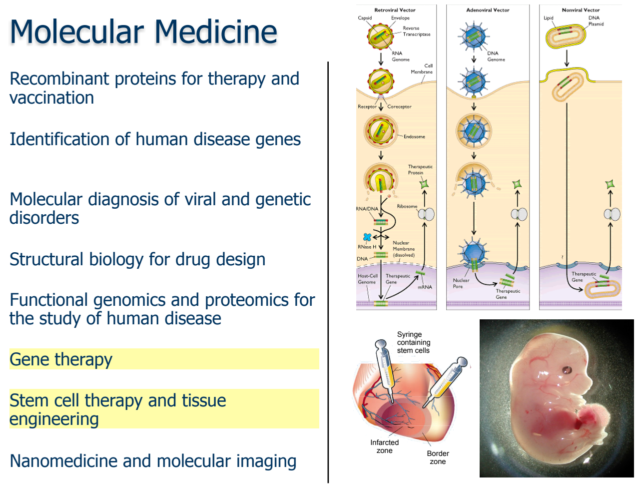
Synthetic peptides or recombinant proteins

Gene Therapy
Protein-coding cDNA? siRNA? miRNA? Which vector?

Cell Therapy
Stem cell? Source?

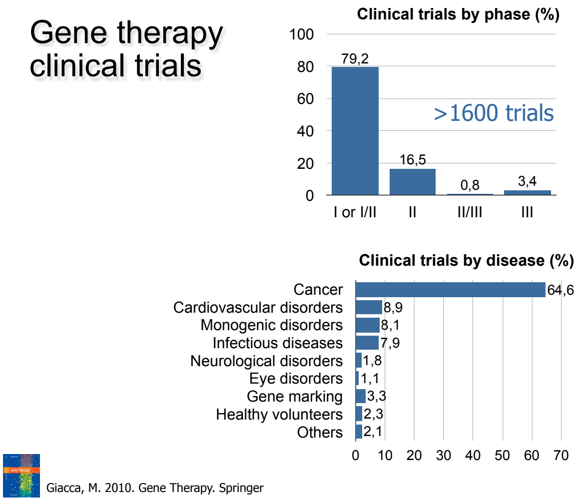
Tissue engineering
Organoids, artificial tissues

Improved function
Tissue protection
Regeneration



Molecular Medicine

- Recombinant proteins for therapy and vaccination
- Identification of human disease genes
- Molecular diagnosis of viral and genetic disorders
- Structural biology for drug design
- Functional genomics and proteomics for the study of human disease
- Gene therapy
- Stem cell therapy and tissue engineering
- Nanomedicine and molecular imaging



Gene therapy clinical trials

Giacca, M. 2010. Gene Therapy. Springer

Gene Therapy

Genetic modification of human somatic cells via transfer of nucleic acids

European Guidelines for the Production of
Gene Therapeutics, 1994

Therapeutic nucleic acids

Protein-coding cDNAs

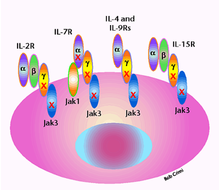
Proteins replacing missing cellular functions

Burden of genetic disease

Disorder type	Population %
Single gene	2
Congenital abnormalities	3
Chromosomal abnormalities	0.5
maternal age >35	4
Behavioral & CNS	10
Adult onset multifactorial	60

Gene therapy of monogenic inherited disorders

e.g.
Immunodeficiencies (ADA, SCID-X1)
Hemophilia
Leber's congenital amaurosis
Muscular dystrophy
Cystic fibrosis
Lysosomal storage disease
.....
several others



Therapeutic nucleic acids

Protein-coding cDNAs

Proteins replacing missing cellular functions
Proteins modulating cellular functions
Proteins regulating cell survival

Gene therapy for neurodegenerative or traumatic disorders

Clinical trials of growth factors for neurological disease

Ref	Disease	Growth factor
45–47	Amyotrophic lateral sclerosis	CNTF, BDNF, CNTF + BDNF, GDNF, IGF-1
48	Spinal muscular atrophy	BDNF
49	Alzheimer's disease	NGF
50–53	Peripheral neuropathy	NGF, BDNF, NT-3
54	Stroke	FGF-2

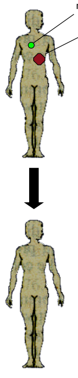
CNTF=ciliary neurotropic factor; BDNF=brain-derived neurotropic factor; GDNF=glial cell line-derived neurotropic factor; IGF-1=insulin-like growth factor 1; NGF= nerve growth factor; NT-3=neurotropin 3; FGF-2=fibroblast growth factor 2.

Therapeutic nucleic acids

Protein-coding cDNAs

Proteins replacing missing cellular functions
Proteins modulating cellular functions
Proteins regulating cell survival
Proteins activating the immune system
Antibodies and intracellular antibodies

Anti-tumor vaccination



Tumor-Associated Antigens (TAA)

Normal proteins overexpressed (PSA, HER2/Neu, MUC-1)

Oncofetal antigens (CEA, AFP)

Differentiation antigens (Melan A/MART-1, tyrosinase, gp100)

Cancer-testis antigens (members of the MAGE, BAGE, GAGE, NY1-ESO-1 families)

Tumor-Specific Antigens (TSA)

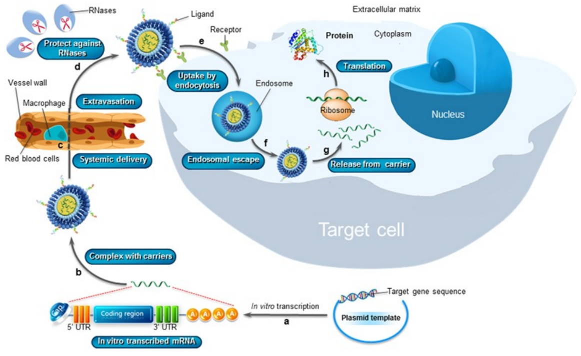
Antibody or TCR idiotypes

Mutated cellular proteins (eg. p53, p21)

Viral poteins (HPV E6 and E7, EBV EBNA-1)

Therapeutic nucleic acids

Protein-coding modRNAs



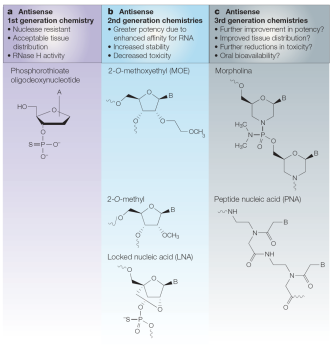
Therapeutic nucleic acids

Protein-coding cDNAs

Proteins replacing missing cellular functions
Proteins modulating cellular functions
Proteins regulating cell survival
Proteins activating the immune system
Antibodies and intracellular antibodies

Small, non-coding DNAs and RNAs

Oligonucleotides and modified oligonucleotides
- Phosphorothioate oligonucleotides
- Oligonucleotides modified in 2' ribose
- Locked Nucleic Acids (LNA) and Ethylene Bridged Nucleic Acids (ENA)
- Morpholino (PMO)
- Peptide Nucleic Acids (PNA)



Chemical modifications to modify in vivo pharmacokinetics of oligonucleotides
Gleave et al. Nat. Rev. Cancer 2005

Therapeutic nucleic acids

Protein-coding cDNAs

Proteins replacing missing cellular functions
Proteins modulating cellular functions
Proteins regulating cell survival
Proteins activating the immune system
Antibodies and intracellular antibodies

Small, non-coding DNAs and RNAs

Oligonucleotides and modified oligonucleotides
- Phosphorothioate oligonucleotides
- Oligonucleotides modified in 2' ribose
- Locked Nucleic Acids (LNA) and Ethylene Bridged Nucleic Acids (ENA)
- Morpholino (PMO)
- Peptide Nucleic Acids (PNA)

Cancer gene therapy clinical trials using oligonucleotides

ODN	Chemistry	Target gene	Gene function
G3139 (Oblimersen)	Phosforothioate	Bcl2	Apoptosis inhibitor
OGX-011	Phosforothioate, 2'-methoxyehtyl	Clusterin	Protein chaperon
ISIS 3621	Phosforothioate	Protein kinase C alpha	Signal transduction
LY2181308	Phosforothioate, 2'-methoxyehtyl	Survivin	Apoptosis inhibitor
LR3001	Phosforothioate, 2'-methoxyehtyl	Myb	Oncogene, transcription factor
AEG35156	Phosforothioate, 2'-methoxyehtyl	XIAP	Apoptosis inhibitor
OGX-427	Phosforothioate, 2'-methoxyehtyl	Hsp27	Heat shock protein
ISIS 345794	Phosforothioate, 2'-methoxyehtyl	STAT-3	Transcriptional activator

---

Therapeutic nucleic acids

Protein-coding cDNAs

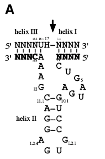
Proteins replacing missing cellular functions
Proteins modulating cellular functions
Proteins regulating cell survival
Proteins activating the immune system
Antibodies and intracellular antibodies

Small, non-coding DNAs and RNAs

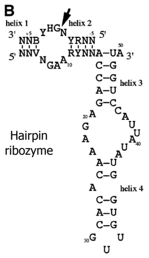
Oligonucleotides and modified oligonucleotides
- Phosphorothioate oligonucleotides
- Oligonucleotides modified in 2' ribose
- Locked Nucleic Acids (LNA) and Ethylene Bridged Nucleic Acids (ENA)
- Morpholino (PMO)
- Peptide Nucleic Acids (PNA)

Catalytic RNAs and DNAs (ribozymes and DNAzymes)

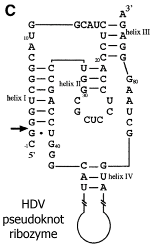
Small catalytic RNAs



Hammerhead ribozyme



Hairpin ribozyme



HDV pseudoknot ribozyme

Therapeutic nucleic acids

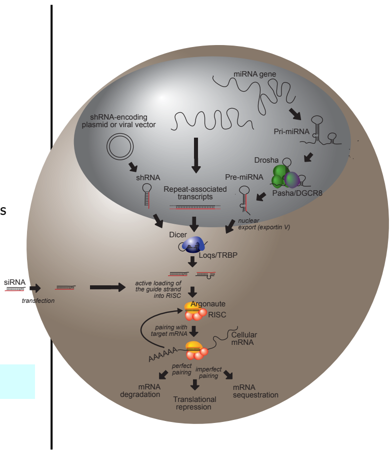
Protein-coding cDNAs

Proteins replacing missing cellular functions
Proteins modulating cellular functions
Proteins regulating cell survival
Proteins activating the immune system
Antibodies and intracellular antibodies

Small, non-coding DNAs and RNAs

Oligonucleotides and modified oligonucleotides
- Phosphorothioate oligonucleotides
- Oligonucleotides modified in 2' ribose
- Locked Nucleic Acids (LNA) and Ethylene Bridged Nucleic Acids (ENA)
- Morpholino (PMO)
- Peptide Nucleic Acids (PNA)

Catalytic RNAs and DNAs (ribozymes and DNAzymes)
Small regulatory RNAs (siRNAs, shRNAs, microRNAs)



Therapeutic nucleic acids

Protein-coding cDNAs

Proteins replacing missing cellular functions
Proteins modulating cellular functions
Proteins regulating cell survival
Proteins activating the immune system
Antibodies and intracellular antibodies

Small, non-coding DNAs and RNAs

Oligonucleotides and modified oligonucleotides
- Phosphorothioate oligonucleotides
- Oligonucleotides modified in 2' ribose
- Locked Nucleic Acids (LNA) and Ethylene Bridged Nucleic Acids (ENA)
- Morpholino (PMO)
- Peptide Nucleic Acids (PNA)

Catalytic RNAs and DNAs (ribozymes and DNAzymes)
Small regulatory RNAs (siRNAs, shRNAs, microRNAs)

Therapeutic approaches using siRNAs

Condition	Disease	Target gene
Hereditary and multifactorial disorders	Familial hypercholesterolemia (FH)	Apolipoprotein B
	Age-related macular degeneration (AMD)	VEGF, VEGFR1, RTP801
	Lateral amyotrophic sclerosis (LAS)	SOD1
	Spinocerebellar ataxia	Ataxin 1
	Alzheimer's disease	Tau, APP
	Parkinson's disease	-sinucleina
Cancer	Several cancers	Bcl-2
	Acute myeloid leukemia (AML)	AML1/MTG8
	Chronic myelogenous leukemia (CML)	BCR-Abl
	Glioblastoma	MMP-9, uPAR
Infectious disorders	Hepatitis B	HBsAg
	Hepatitis C	NS3, NS5B, E2
	Influenza	Nucleoprotein, polymerase
	HIV-1	Different viral genes
	HSV-1	Glicoprotein E
	RSV	Genes P, N and L

Therapeutic nucleic acids

Protein-coding cDNAs

Proteins replacing missing cellular functions
Proteins modulating cellular functions
Proteins regulating cell survival
Proteins activating the immune system
Antibodies and intracellular antibodies

Small, non-coding DNAs and RNAs

Oligonucleotides and modified oligonucleotides
- Phosphorothioate oligonucleotides
- Oligonucleotides modified in 2' ribose
- Locked Nucleic Acids (LNA) and Ethylene Bridged Nucleic Acids (ENA)
- Morpholino (PMO)
- Peptide Nucleic Acids (PNA)

Catalytic RNAs and DNAs (ribozymes and DNAzymes)
Small regulatory RNAs (siRNAs, shRNAs, microRNAs)
DNA and RNA decoys
Aptamers

Age-related macular degeneration (AMD)

Most frequent cause of blindness
>30% of people +75 y

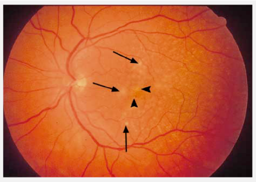


Figure 2. Early Age-Related Macular Degeneration, Characterized by Large Drusen (Arrows) and Clumps of Pigment (Arrowheads) in the Macula.

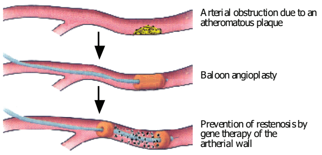
This eye has normal visual acuity but is at risk for late age-related macular degeneration and loss of vision.

Gene therapy of AMD

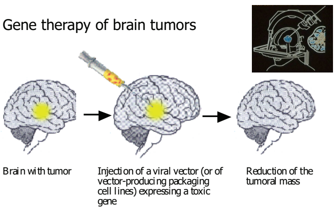
Anti-VEGF antibodies (bevacizumab, ranibizumab)
Soluble VEGFR (VEGF Trap-Eye)
Anti-VEGF aptamer (pegaptanib)
Anti-VEGF siRNA (bevasiranib)

In vivo gene therapy

Prevention of restenosis after angioplasty

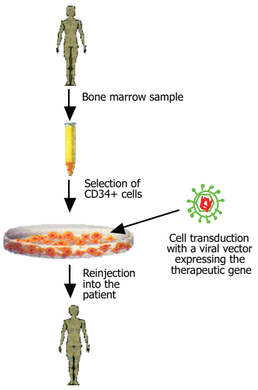


Gene therapy of brain tumors



Ex vivo gene therapy

Gene therapy of hematopoietic stem cells



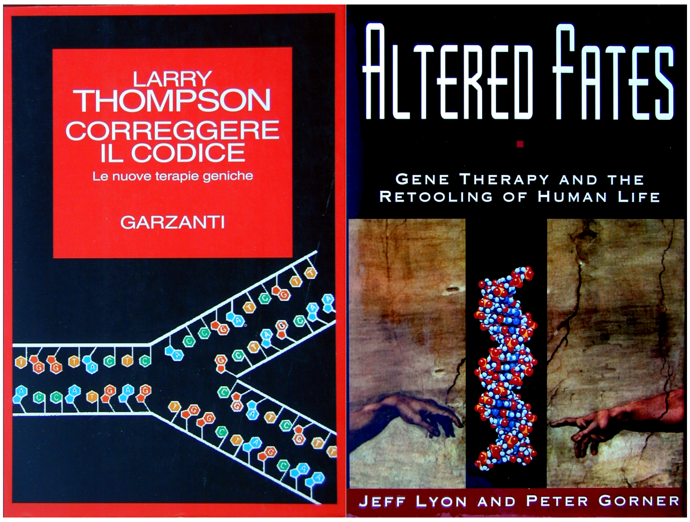
Somatic gene therapy: appropriate candidate genetic diseases

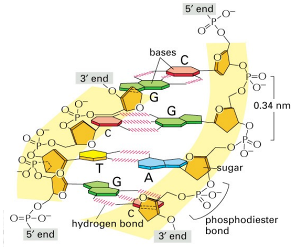
Single-gene disorder, recessive or X-linked inheritance

Significant morbidity or mortality

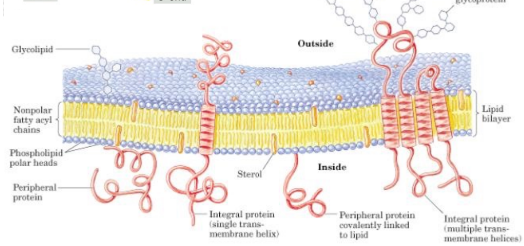
Current therapy inadequate or unavailable

Accessible cellular site of genetic defect causing phenotype





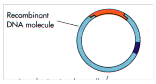
The plasma membrane is an impermeable barrier to large polyanions such as DNA



Delivery systems for gene therapy

I. Naked DNA or RNA

Direct uptake of plasmid DNA



- limited to muscle cells and APCs
- very low efficiency

Uptake of oligonucleotides, siRNAs and other small RNAs

- very low efficiency

Delivery systems for gene therapy

I. Naked DNA or RNA

II. Physical methods

Electroporation
- skeletal muscle and skin mainly

Bombardment with DNA-coated gold microparticles ("gene gun") and **jet injection**
- limited to the skin

High hydrodynamic pressure
- usually very invasive

Ultrasound and **microbubble-aided ultrasound**
- difficult to standardize
- vascular or perivascular applications

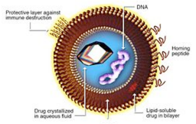
Delivery systems for gene therapy

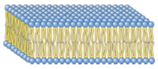
I. Naked DNA or RNA

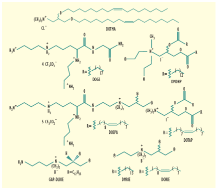
II. Physical methods

III. Chemical methods

Liposomes and cationic lipids
Lipid nanoparticles (LNPs)







Delivery systems for gene therapy

I. Naked DNA or RNA

II. Physical methods

III. Chemical methods

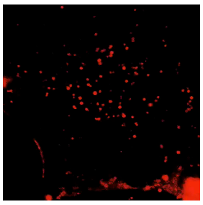
Proteins

To induce passage through membranes (e.g. HIV-1 Tat, Antennapedia, VP22)

To confer cell targeting (e.g. asialoglycoproteins, transferrin. RGD peptide, antibodies)

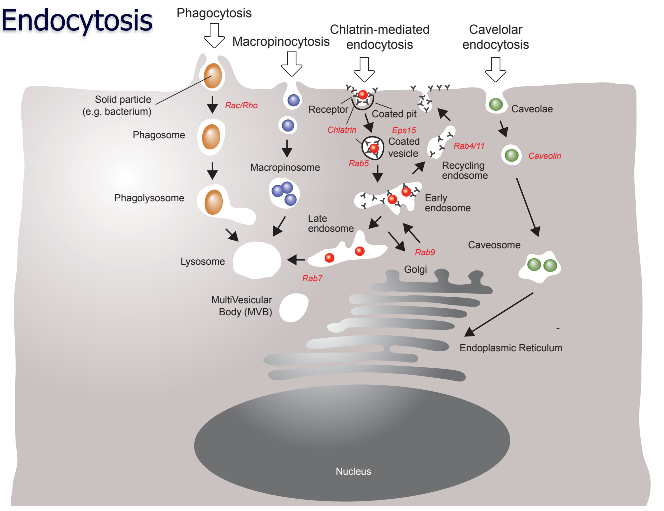
To induce DNA condensation (e.g. protamine, histones, poly-L-lysine)

To promote endosomal escape (e.g. influenza hemoagglutinin, Ad capsid)



HIV-1 Tat-rhodamine in endosomes

Endocytosis



Delivery systems for gene therapy

I. Naked DNA or RNA

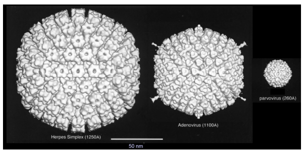
II. Physical methods

III. Chemical methods

IV. Viral vectors

Gammaretroviruses
Lentiviruses
Adenovirus
Adeno-associated virus (AAV)
Herpes simplex virus type 1

Vaccinia (for genetic vaccination)



Viruses do it better

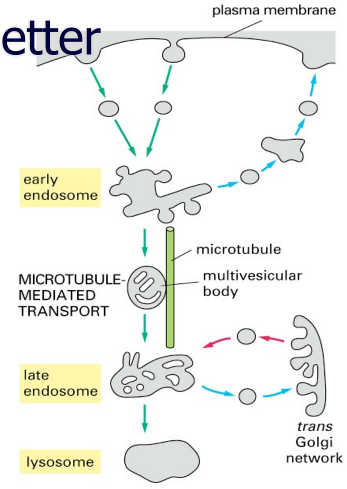
Targeting to specific receptors

Direct fusion of envelope at the cell membrane or escape from endosomes

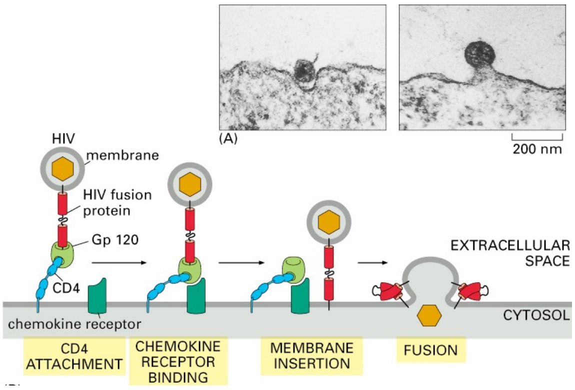
Transfer of nucleic acids to the nucleus

Protection of nucleic acids from degradation

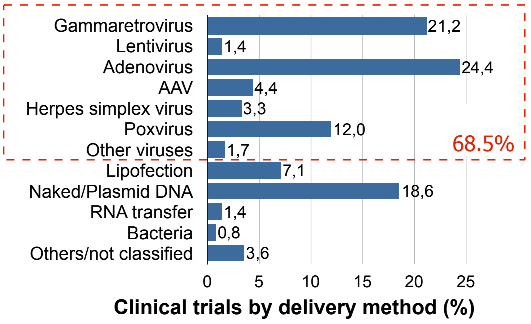
Prolonged (permanent) expression of therapeutic gene



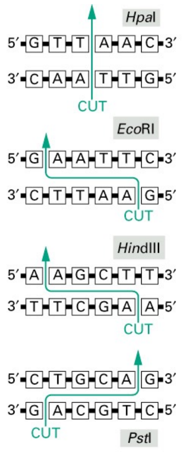
Retrovirus internalization by fusion at the plasma membrane



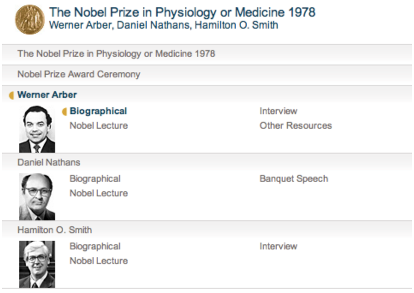
Gene therapy clinical trials by delivery method



Giacca, M. 2010. Gene Therapy. Springer



Restriction enzymes


The Nobel Prize in Physiology or Medicine 1978
Werner Arber, Daniel Nathans, Hamilton O. Smith

The Nobel Prize in Physiology or Medicine 1978

Nobel Prize Award Ceremony

Werner Arber

Biographical	Interview
Nobel Lecture	Other Resources

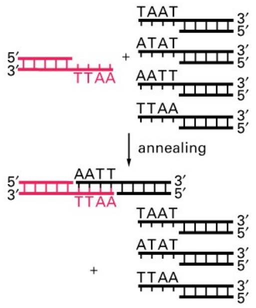
Daniel Nathans

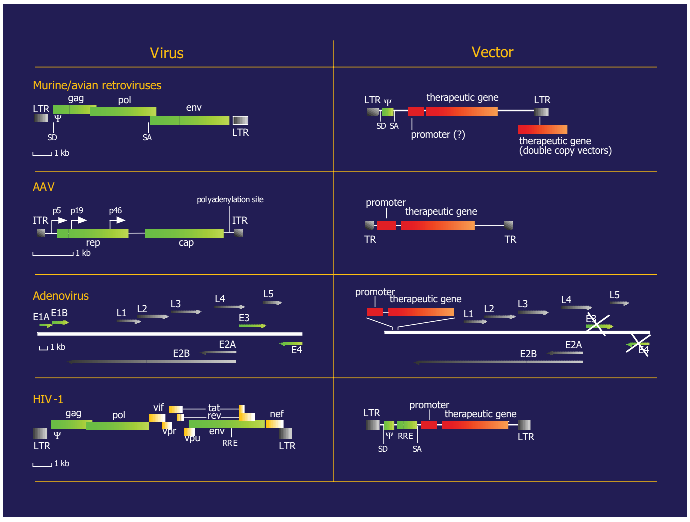
Biographical	Banquet Speech
Nobel Lecture	

Hamilton O. Smith

Biographical	Interview
Nobel Lecture	

Recombinant DNA molecules






MEDICINA. È esplosa la polemica sulle speranze suscitate dalla ricerca di frontiera

Terapia genica , un bluff?

Ha cominciato il *New England Journal of Medicine* mettendone in forse la validità. La polemica poi è rimbalzata sulle più importanti testate internazionali, da *Newsweek* all'*Independent*. La terapia genica non sembra mantenere le promesse: finora non ha guarito nessuno. «Dateci tempo» dice Claudio Bordignon, autore di una sperimentazione clinica italiana svolta su due «bubble boys», i bambini costretti a vivere in ambiente sterile.

CRISTIANA PULCINELLI

■ Sarà colpa dei giornalisti che, come al solito, mettono troppa enfasi nei titoli, ma fino a qualche settimana fa sembrava che la terapia genica avrebbe presto risolto tutti i nostri problemi di salute. Il principio su cui si basa, in effetti, è semplice e affascinante: hai una malattia? Scopri qual è il gene difettoso che la determina e poi sostituiscilo con un gene «sano».

Poi, d'improvviso, la bastonata: ma quale rivoluzione, finora non è si è visto un risultato positivo. Mentre i soldi, quelli sì, sono piovuti a palate su chi si occupa di questo settore. Il dubbio si insinua: forse anche in futuro non si riuscirà a fare un granché con questa tecnica. L'attacco arriva dalle più prestigiose testate internazionali: «Promesse, promesse» titola il settimanale americano *Newsweek*, e il quotidiano britannico *The Independent* rincalza pochi giorni dopo: «Cura miracolosa o mera illusione?». Ma non sono i giornalisti a dubitare per primi, le riviste scientifiche hanno dato il via al ripensamento.

I giornali scientifici

Tutto è cominciato con un editoriale comparso sul *New England Journal of Medicine* il 28 settembre scorso. L'autore prendeva spunto da un lavoro sulla fibrosi cistica che aveva ottenuto risultati negativi per chiedersi: «Ci troviamo di fronte ad un altro esempio di quella enfatizzazione che affligge molte imprese scientifiche, come la fusione fredda? Dobbiamo abbandonare il nostro entusiasmo?». La risposta è no, tuttavia, «sarebbe bene riconsiderare gli obiettivi iniziali della terapia genica». *Nature Medicine* rincarava la dose pochi giorni dopo: «Grandi ostacoli restano da superare perché la terapia genica diventi una realtà». «La polemica che ne è scaturita - dice Claudio Bordignon, responsabile del progetto "Terapia genica" dell'Istituto scientifico San Raffaele di Milano - si è svolta proprio un mese prima che *Science* pubblicasse i due lavori più vecchi in questo campo: quello cominciato nel 1990 negli Stati Uniti e quello nostro, partito nel 1992. Bisogna tener presente una cosa: una sperimentazione clinica negativa si può pubblicare rapidamente. Se invece lo studio presenta un qualche risultato positivo i tempi di pubblicazione si allungano. Facciamo un esempio: se il ricercatore vede che le cellule modificate geneticamente sopravvivono a distanza di tre mesi, il direttore della rivista chiederà di vedere che cosa succede dopo sei mesi, o un anno». Così, dice Bordignon, si è parlato di disfatta troppo presto: guardiamo i risultati prima di buttarli dalla finestra.

E guardiamo, allora, questi risultati. Le due ricerche riguardano i «bubble boys», i bambini nella bolla, quelli cioè affetti da immunodeficienza grave combinata, una malattia provocata dalla carenza di adenosina deaminasi (ADA) che costringe chi ne è colpito a vivere in un ambiente sterile. I ricercatori statunitensi hanno trasferito il gene dell'ADA nei linfociti T di due bambine. Il numero dei linfociti si è normalizzato così come la risposta immunitaria. Le bambine stanno bene, insomma, anche se continuano a prendere un farmaco (che, secondo quanto riferito da *Newsweek*, costa la bellezza di quasi 400 milioni l'anno) il cui compito è proprio quello di normalizzare la risposta immunitaria.

Cosicché le acque si confondono: si può dire che le bambine siano state «guarite» dalla terapia genica? No, e infatti gli autori scrivono: «si conclude che la terapia genica per alcuni pazienti può affiancarsi in modo efficace e sicuro al trattamento convenzionale».

Nello studio italiano, finanziato con 640 milioni di lire in due anni da Telethon, il gene dell'ADA è stato trasferito nelle cellule del midollo osseo e nei linfociti del sangue periferico di due piccoli pazienti che non rispondevano più al trattamento convenzionale. Dopo due anni si è ottenuta la sopravvivenza a lungo termine delle cellule corrette geneticamente e il ripristino della risposta immunitaria (cosicché sembrerebbe che le cellule «buone» rimpiazzino a poco a poco quelle «cattive»), benché non sia stata interrotta la somministrazione del farmaco.

Uno su cento ce la fa

Risultati parziali? Forse, ma le due ricerche dimostrano indubbiamente la «fattibilità» di applicazioni di questo genere. «Nei nostri lavori - ribadisce Bordignon - una risposta immune c'è. Bisogna vedere, ovviamente, su quanti pazienti funzionerà. Ma dateci tempo. Lei sa quanto ci vuole a portare un antibiotico sul mercato, dopo la sua scoperta? Dieci anni. Come è pensabile che una disciplina che 10 anni fa non esisteva dia risultati eclatanti? Anche perché stiamo parlando di una disciplina rivoluzionaria, nel senso che produce tecnologie che prima non esistevano. Noi lavoriamo così: per una cosa che funziona, ne buttiamo via cento».

C'è comunque un ostacolo teorico alla possibilità di curare un largo spettro di malattie con la terapia genica. Ce lo spiega Giorgio Morpurgo, docente di genetica all'università di Perugia. Morpurgo è convinto che in capo a una decina d'anni la terapia genica otterrà discreti successi. E i rischi diminuiranno. Tuttavia, le malattie che si potranno curare in questo modo rimarranno un numero limitato. «Alcune malattie ereditarie saranno guarite fenotipicamente, cioè la persona non sarà più malata ma continuerà a trasmetterla. Altre no, perché sono troppo complesse. Se la malattia non è causata da un unico gene difettoso, ma da più geni, e se poi anche l'ambiente svolge il suo ruolo nel determinarne la comparsa, le prospettive di curarla in questo modo si allontanano di molto». Questo mette in crisi anche il «progetto genoma umano»? «Esistono altri progetti genoma che si occupano di organismi molto più semplici e che daranno senz'altro informazioni interessanti. Per dar vita al Progetto genoma umano si doveva aspettare per lo meno la fine di questi lavori. Fatto così questo progetto non servirà a nulla e costerà una quantità di soldi indescrivibile». Il business dunque sta dietro le nuove frontiere della genetica? Negli Stati Uniti sono oltre 100 le sperimentazioni cliniche in corso. In Italia meno di dieci. Ma tutte sono molto costose. Sarà per questo che chi paga vuole vedere risultati fortemente visibili e in tempi brevi. Purtroppo, invece, i tempi della tecnologia medica, oggi, sono lunghi.

L'Unità, 4 novembre 1995

CLINICAL RESEARCH

Gene Therapists Celebrate a Decade of Progress

It has taken many years, but researchers may have reached a prized goal in gene therapy: lowering the risk of uncontrolled bleeding in patients with hemophilia. At a meeting last week, researchers reported that six patients who received a virus engineered to carry a gene for a blood-clotting protein called factor IX needed fewer transfusions of the protein for as long as 18 months; some didn't require any transfusions. One patient developed an immune response to the viral vector, but this side effect was successfully treated with drugs.

Some researchers say these results mark a watershed for the long-struggling field. At the meeting at the U.S. National Institutes of Health (NIH) in Bethesda, Maryland, gene therapy researchers summarized progress on several fronts. They said they have proved that they can treat at least a half-dozen rare genetic diseases (see table), and that early trials are beginning to find benefits for common diseases as well, including HIV, leukemia, and heart disease.

Most important, gene therapy seems to have overcome a reputation for recklessness it acquired a decade ago after an 18-year-old, Jesse Gelsinger, died in a trial. "It's a different day now," says meeting attendee Theodore Friedmann of the University of California (UC), San Diego, who has followed the field since the 1970s: People recognize that "it really is the right thing to do for some diseases."

To be sure, enthusiasm is not what it was 20 years ago when NIH last held a similar symposium. That event attracted nearly twice as many speakers and attendees (21 speakers and about 400 registrants came this time), noted R. Jude Samulski of the University of North Carolina, Chapel Hill, president of the American Society of Gene and Cell Therapy (ASGCT), a meeting co-sponsor. Back then, "excitement clearly exceeded any of the data," Samulski said at the meeting. After the Gelsinger incident, U.S. regulators put many trials on hold; others were canceled.

But in the early 2000s, teams in Paris and Milan demonstrated the first clear-cut benefits from gene therapy, treating children with two different forms of severe combined immunodeficiency disorder (SCID), which make the patient highly vulnerable to infection. Last year, researchers reported success in two patients with another immune disorder, Wiskott-Aldrich syndrome; like SCID patients, they were treated by adding a curative gene to blood stem cells. By now, about 86 patients with these immune deficiencies have been helped this way, Donald Kohn of UC Los Angeles said at the NIH meeting.

Last year also brought good news in a new area: Gene therapy researchers published the first success in treating a patient with β-thalassemia, a blood disorder that is relatively common in South Asia and the Mediterranean region. Eight centers are now setting out to expand on this result, noted Michel Sadelain of Memorial Sloan-Kettering Cancer Center in New York City.

These trials were not without problems, however. In some the viral vector, a retrovirus, which can insert unpredictably in DNA, turned on an oncogene, increasing the risk of cancer. Nine patients, including three with chronic granulomatous disease, another immune disorder, who initially seemed cured by gene therapy later developed a leukemia-like disease, Kohn noted. In response, a U.S.-European consortium has developed alternative "self-inactivating" retroviral vectors that are less likely to turn on other genes. All new trials treating blood cells are using these vectors.

It's a sign of the field's overall health that researchers are going beyond safety testing now. The San Raffaele Telethon Institute for Gene Therapy in Milan, for example, will soon apply to European regulators to conduct a phase III trial needed for regulatory approval of a plan for treating adenosine deaminase deficiency–SCID. Last year, that institute struck a deal with pharmaceutical giant GlaxoSmithKline to commercialize gene therapies for seven disorders. "Gene therapy for rare genetic diseases is really a mature field now," Telethon Institute immunologist Maria-Grazia Roncarolo said at the NIH meeting.

Eye diseases are another success story. In three trials that are "kind of biblical in impact," Friedmann says, eyesight improved, sometimes dramatically, in 28 of 30 patients with Leber's congenital amaurosis, a type of inherited blindness, after gene therapy using an adeno-associated virus (AAV) to deliver a curative gene to the retina. The Children's Hospital of Philadelphia (CHOP) plans to apply this fall to the U.S. Food and Drug Administration to conduct a phase III trial for this treatment. Gene therapy trials for two other blindness diseases are under way. "In the next year and a half, there's going to be a boatload coming out," says Stephen Rose, chief research officer for Foundation Fighting Blindness.

Gene therapy is working for neurologic diseases, too. The San Raffaele Telethon Institute has treated four patients with a devastating brain disorder called metachromatic leukodystrophy, following a report published in 2009 from a team in France that used a similar strategy to halt the progression of a related disease, adrenoleukodystrophy. So far the treatment seems safe and the patients' blood cells are producing the corrected enzyme, Roncarolo reported.

The path to better health has been long and winding for hemophilia B patients. A trial in the early 2000s led by Katherine High of CHOP and Stanford University's Mark Kay resulted in only brief gene expression; patients developed an immune response that destroyed cells with the corrected gene. This trial used AAV to deliver a factor-IX clotting factor gene to the liver. But a new trial led by Amit Nathwani of University College London and Andrew Davidoff of St. Jude Children's Research Hospital in Memphis, Tennessee, has overcome earlier immune problems. These researchers used a different AAV that can be delivered intravenously and may be less likely to trigger an immune reaction. As

Some Gene Therapy Successes

Disorder	Disease type	Patients benefiting	First publication
X-SCID	Immunodeficiency	17/20	2000
ADA-SCID	Immunodeficiency	26/37	2002
Adrenoleukodystrophy	Neurologic	2/4*	2009
Leber's congenital amaurosis	Blindness	28/30	2008
Wiskott-Aldrich syndrome	Immunodeficiency	8/10	2010
β-thalassemia	Hemoglobinopathy	1/1	2010
Hemophilia	Coagulation	6/6	2011?

*Includes a patient treated too recently to see benefit

TABLE SOURCES: D. KOHN, N. CARTIER-LACAVE, U. REISS, W. HAUSWIRTH, NIH GENE THERAPY SYMPOSIUM, 26 SEPTEMBER, 2011; LANCET 374, 1597 (2009); NEJM 358, 2231 (2008); NATURE 467, 318 (2010)

Published by AAAS