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ULSS3 SERENISSIMA

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ULSS4 VENETO ORIENTALE

ORDINE PROVINCIALE DEI MEDICI CHIRURGHI E DEGLI ODONTOIATRI DI VENEZIA

Federazione Nazionale
Ordine Medici Chirurghi ed Odontoiatri

Nuove tecnologie in Medicina

Giorgio Palù, MD, FESCMID, Professor
President, European and Italian Societies for Virology

22 Settembre 2018

DMM
Dipartimento di Medicina Molecolare
Università di Padova

Gene and cell therapy

Gain of function

Induced Pluripotent Stem cells

New technologies in Medicine (translation oriented)

Organoids

Vaccinology

Genome editing

Gene drives

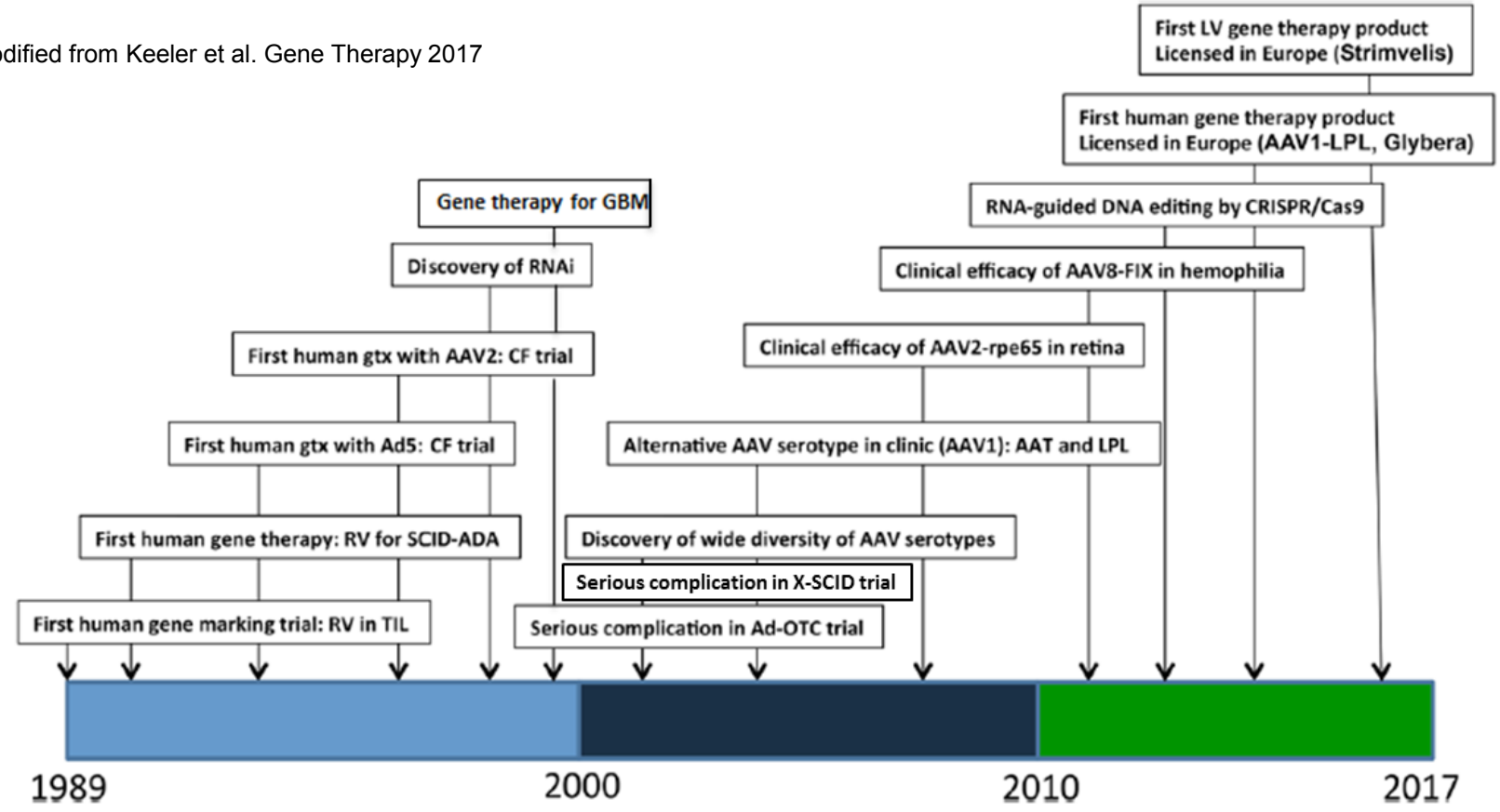
Antivirals research

GENE THERAPY

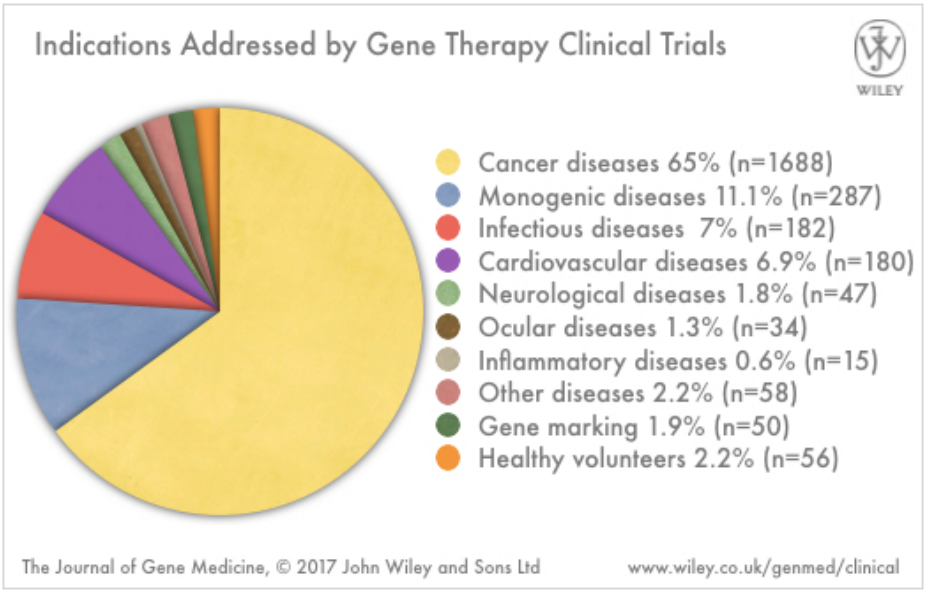
Gene Therapy

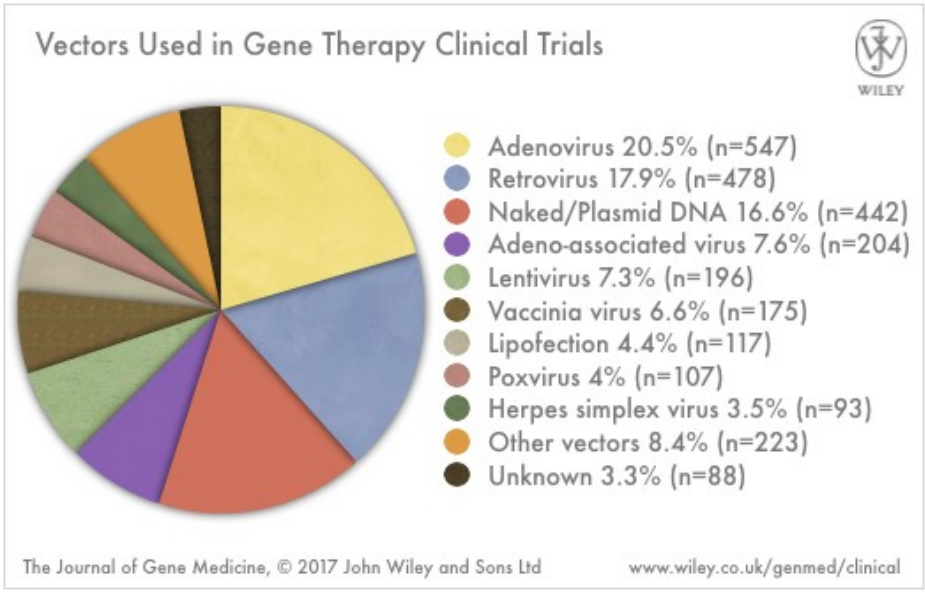
- Gene therapy is an experimental technique that **uses genes to treat or prevent a disease**. Approaches include:
- Replacing a mutated gene that causes disease with a healthy copy of the gene.
- Inactivating, or "knocking out," a mutated gene that is functioning improperly.
- Introducing a new gene into the body to help fight a disease.

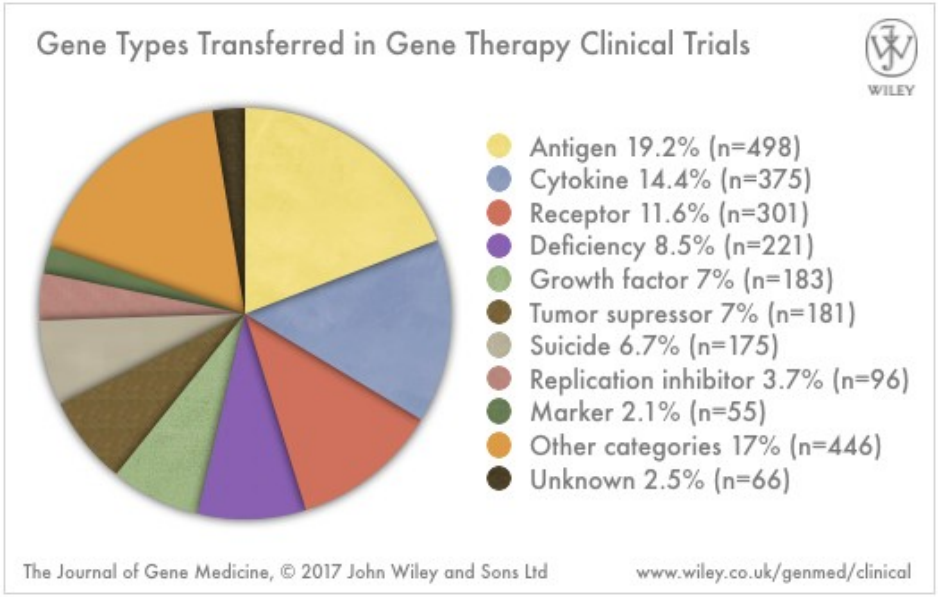
Modified from Keeler et al. Gene Therapy 2017



Gene Therapy Clinical Trials Worldwide







The NEW ENGLAND JOURNAL of MEDICINE

DMM
Dipartimento di Medicina Molecolare
Università di Padova

Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Florian Eichler, M.D., Christine Duncan, M.D., Patricia L. Musolino, M.D., Ph.D., Paul J. Orchard, M.D., Satiro De Oliveira, M.D., Adrian J. Thrasher, M.D., Myriam Armant, Ph.D., Colleen Dansereau, M.S.N., R.N., Troy C. Lund, M.D., Weston P. Miller, M.D., Gerald V. Raymond, M.D., Raman Sankar, M.D., Ami J. Shah, M.D., Caroline Sevin, M.D., Ph.D., H. Bobby Gaspar, M.D., Paul Gissen, M.D., Hernan Amartino, M.D., Drago Bratkovic, M.D., Nicholas J.C. Smith, M.D., Asif M. Paker, M.D., Esther Shamir, M.P.H., Tara O'Meara, B.S., David Davidson, M.D., Patrick Aubourg, M.D., and David A. Williams, M.D.

Gene Therapy in a Patient with Sickle Cell Disease

Jean-Antoine Ribeil, M.D., Ph.D., Salima Hacein-Bey-Abina, Pharm.D., Ph.D., Emmanuel Payen, Ph.D., Alessandra Magnani, M.D., Ph.D., Michaela Semeraro, M.D., Ph.D., Elisa Magrin, Ph.D., Laure Caccavelli, Ph.D., Benedicte Neven, M.D., Ph.D., Philippe Bourget, Pharm.D., Ph.D., Wassim El Nemer, Ph.D., Pablo Bartolucci, M.D., Ph.D., Leslie Weber, M.Sc., Hervé Puy, M.D., Ph.D., Jean-François Meritet, Ph.D., David Grevent, M.D., Yves Beuzard, M.D., Stany Chrétien, Ph.D., Thibaud Lefebvre, M.D., Robert W. Ross, M.D., Olivier Negre, Ph.D., Gabor Veres, Ph.D., Laura Sandler, M.P.H., Sandeep Soni, M.D., Mariane de Montalembert, M.D., Ph.D., Stéphane Blanche, M.D., Philippe Leboulch, M.D., and Marina Cavazzana, M.D., Ph.D.

Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B

Amit C. Nathwani, M.B., Ch.B., Ph.D., Edward G.D. Tuddenham, M.B., B.S., M.D., Savita Rangarajan, M.B., B.S., Cecilia Rosales, Ph.D., Jenny McIntosh, Ph.D., David C. Linch, M.B., B.Chir., Pratima Chowdary, M.B., B.S., Anne Riddell, B.Sc., Arnulfo Jaquilmac Pie, B.S.N., Chris Harrington, B.S.N., James O'Beirne, M.B., B.S., M.D., Keith Smith, M.Sc., John Pasi, M.D., Bertil Glader, M.D., Ph.D., Pradip Rustagi, M.D., Catherine Y.C. Ng, M.S., Mark A. Kay, M.D., Ph.D., Junfang Zhou, M.D., Yunyu Spence, Ph.D., Christopher L. Morton, B.S., James Allay, Ph.D., John Coleman, M.S., Susan Sleep, Ph.D., John M. Cunningham, M.D., Deokumar Srivastava, Ph.D., Etiena Basner-Tschakarjan, M.D., Federico Mingozzi, Ph.D., Katherine A. High, M.D., John T. Gray, Ph.D., Ulrike M. Reiss, M.D., Arthur W. Nienhuis, M.D., and Andrew M. Davidoff, M.D.

Lentiviral Hematopoietic Stem Cell Gene Therapy Benefits Metachromatic Leukodystrophy

Alessandra Biffi,* Eugenio Montini, Laura Lorioli, Martina Cesani, Francesca Fumagalli, Tiziana Plati, Cristina Baldoli, Sabata Martino, Andrea Calabria, Sabrina Canale, Fabrizio Benedicenti, Giuliana Vallanti, Luca Biasco, Simone Leo, Nabil Kabbara, Gianluigi Zanetti, William B. Rizzo, Nalini A. L. Mehta, Maria Pia Cicalese, Miriam Casiraghi, Jaap J. Boelens, Ubaldo Del Carro, David J. Dow, Manfred Schmidt, Andrea Assanelli, Victor Neduva, Clelia Di Serio, Elia Stupka, Jason Gardner, Christof von Kalle, Claudio Bordignon, Fabio Ciceri, Attilio Rovelli, Maria Grazia Roncarolo, Alessandro Aiuti, Maria Sessa, Luigi Naldini*

Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients with Wiskott-Aldrich Syndrome

Alessandro Aiuti,* Luca Biasco, Samantha Scaramuzza, Francesca Ferrua, Maria Pia Cicalese, Cristina Baricordi, Francesca Dionisio, Andrea Calabria, Stefania Giannelli, Maria Carmina Castiello, Marita Bosticardo, Costanza Evangelio, Andrea Assanelli, Miriam Casiraghi, Sara Di Nunzio, Luciano Callegaro, Claudia Benati, Paolo Rizzardi, Danilo Pellin, Clelia Di Serio, Manfred Schmidt, Christof Von Kalle, Jason Gardner, Nalini Mehta, Victor Neduva, David J. Dow, Anne Galy, Roberto Miniero, Andrea Finocchi, Ayse Metin, Pinaki P. Banerjee, Jordan S. Orange, Stefania Galimberti, Maria Grazia Valsecchi, Alessandra Biffi, Eugenio Montini, Anna Villa, Fabio Ciceri, Maria Grazia Roncarolo, Luigi Naldini

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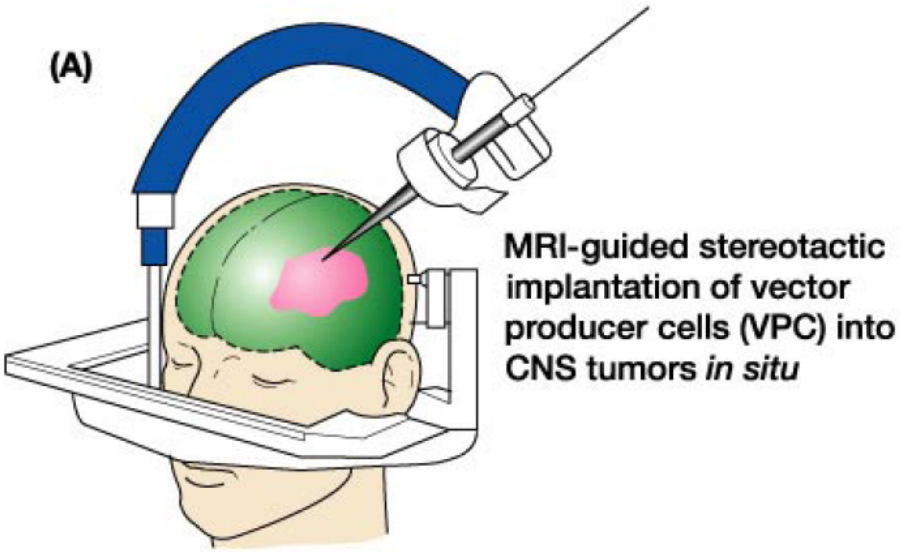
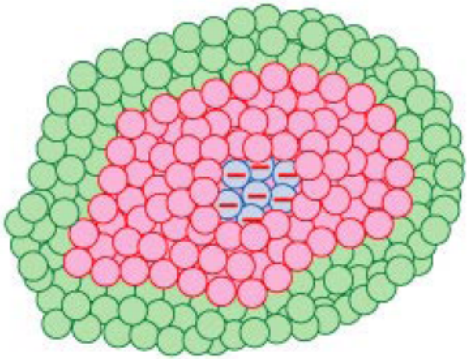
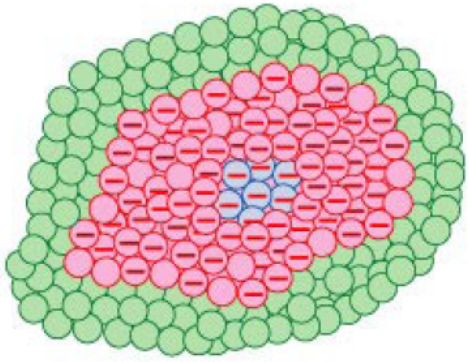
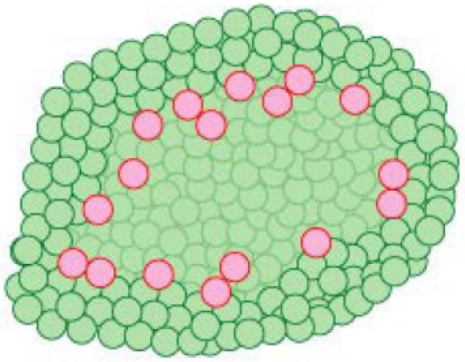
NEJM, 2018

Gene therapy of recurrent GBM



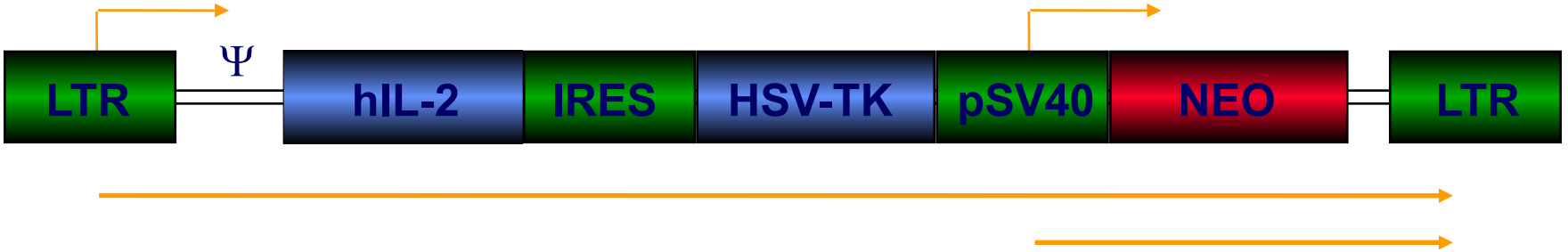






Our previous clinical experience of cancer GT in the pre-EMA era

Bicistronic Moloney-based retroviral vector expressing human *IL-2* and *HSV-TK* for gene therapy of glioblastoma multiforme and anaplastic thyroid carcinoma

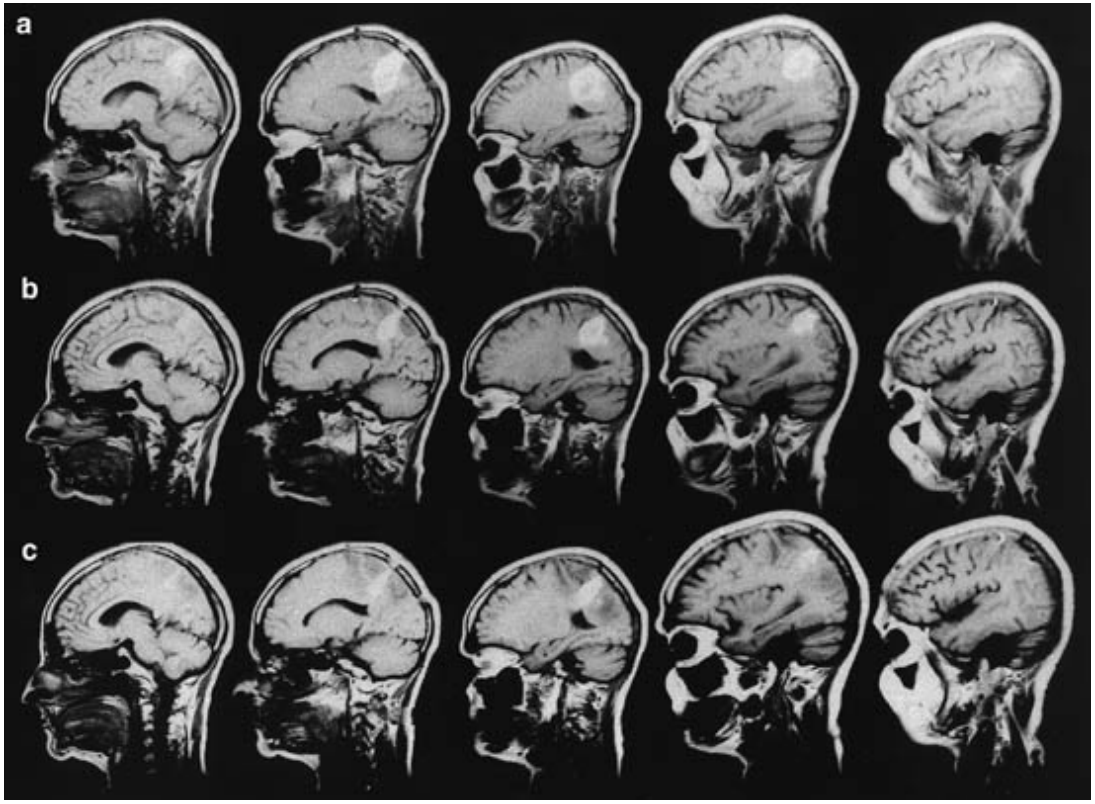


Palù et al. Ster Func Neurosurg 1997
Pizzato et al. Gene Ther 1998
Palù et al. Gene Ther Mol Biol 1999
Palù et al. Gene Ther 1999
Barzon et al. JCE&M 2002
Barzon et al. Eur J Endocrinol 2003

Barzon et al. EOBT 2004
Barzon et al. Cancer Gene Ther 2005
Colombo et al. Cancer Gene Ther 2005
Barzon et al. JCE&M 2005
Barzon et al. EOBT 2005
Barzon et al. Cancer Gene Ther 2006

Gene therapy in patients with recurrent GBM

Pt #3, F 58 yr



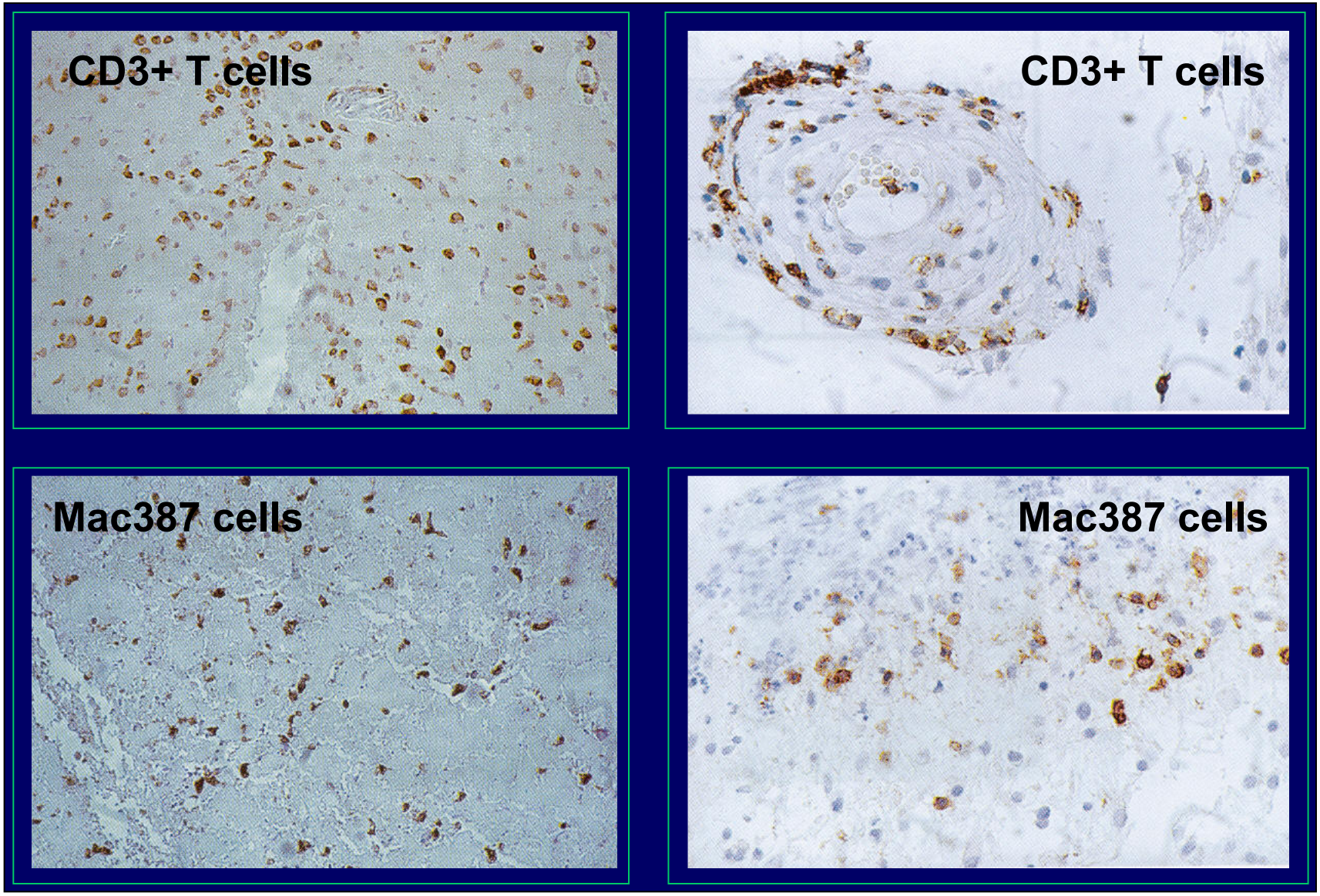
before GT

immediately after GCV

1 month after GCV

Palù G. et al. Gene Ther 1999

Gene therapy of glioblastoma multiforme: histological examination

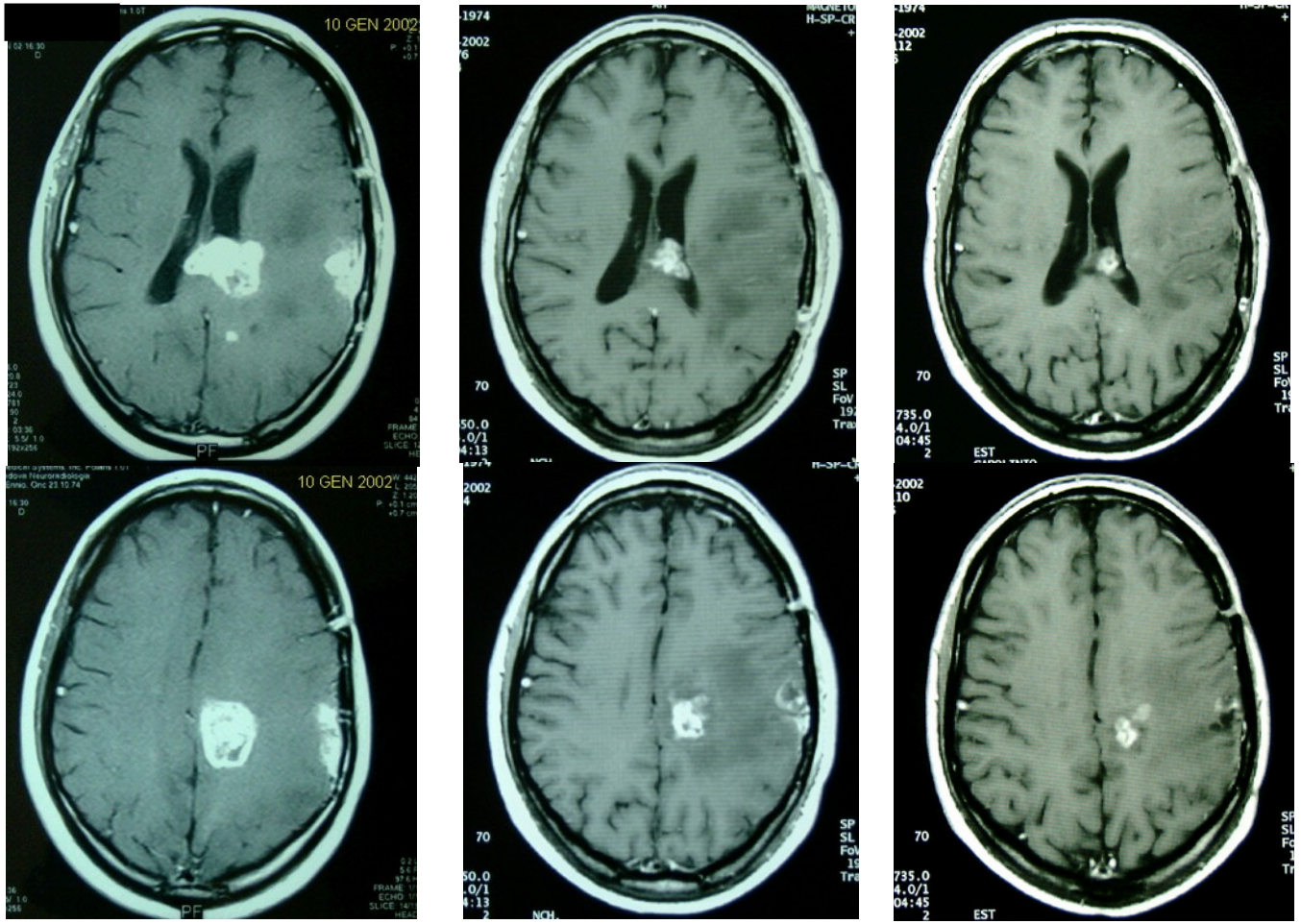


Palù G. et al. Gene Ther 1999

Gene therapy in a patient with recurrent GBM

Pt #10, M 28 yr

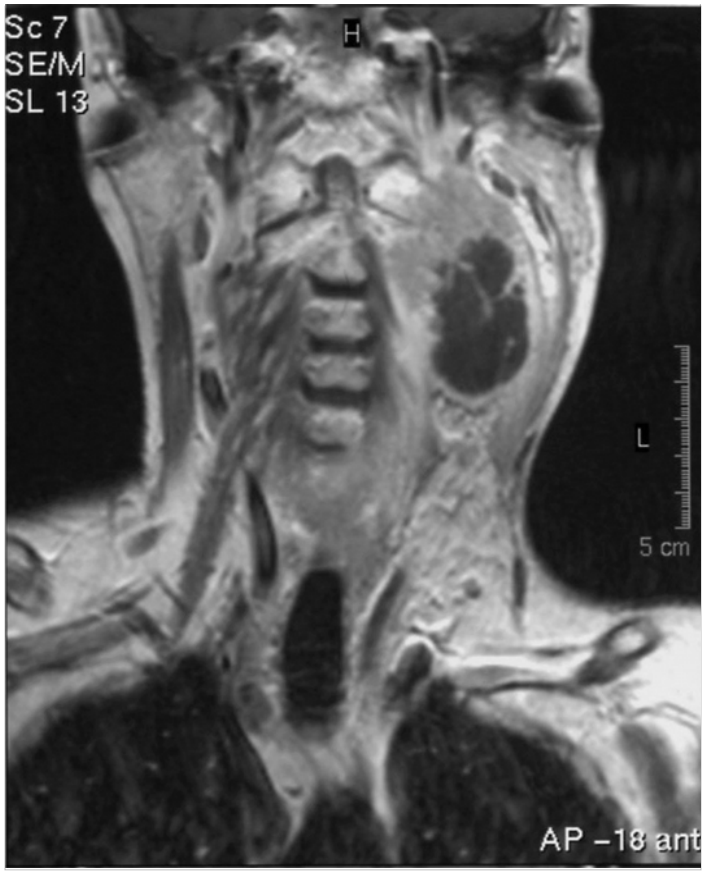
The last treated patient

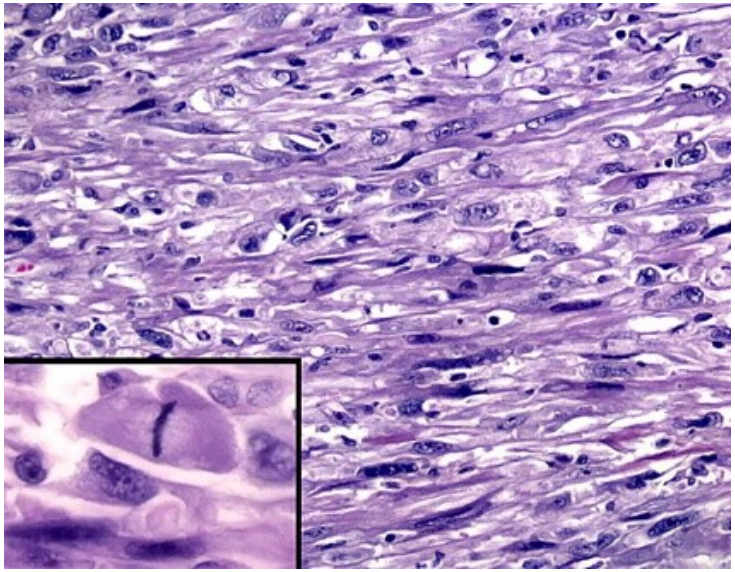


before GT | 2 mo. after GT | 8 mo. after GT

Palù G. Cancer Gene Ther 2005

Gene therapy for anaplastic thyroid carcinoma





Barzon L et al. J Clin Endocrinol Metab. (2005)

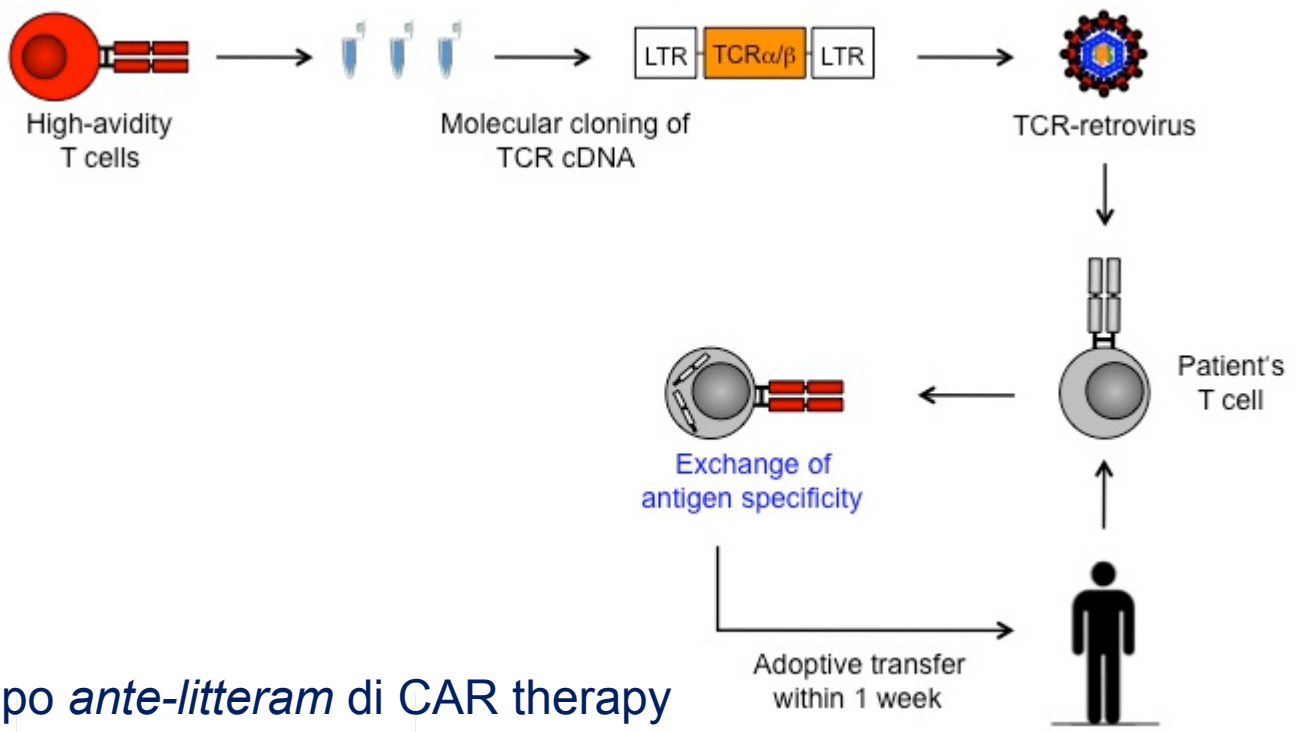
GENE THERAPY OF AIDS

Gene Therapy (2005) 12, 299–310

www.nature.com/gt

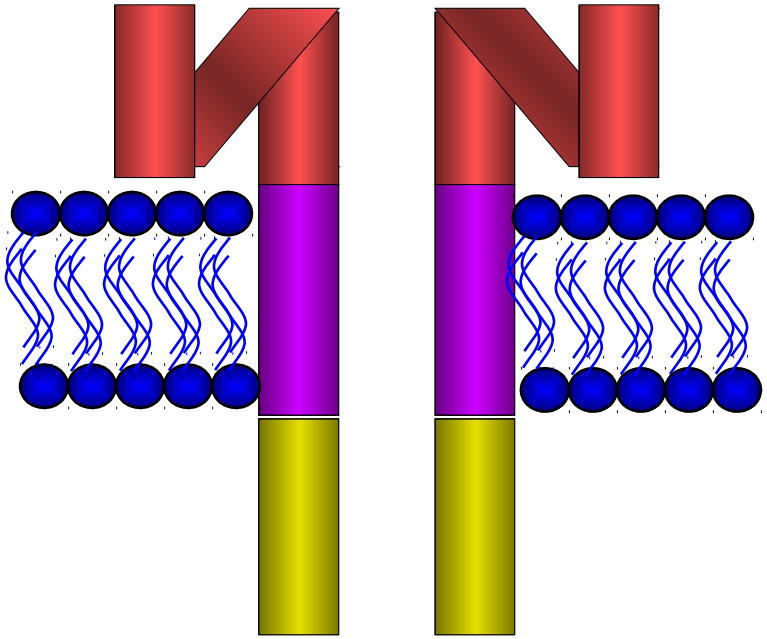
T-cell engineering by a chimeric T-cell receptor with antibody-type specificity for the HIV-1 gp120

S Masiero[1], C Del Vecchio[1], R Gavioli[2], G Mattiuzzo[1], MG Cusi[3], L Micheli[3], F Gennari[1], A Siccardi[4], WA Marasco[5], G Palù[1] and C Parolin[1]



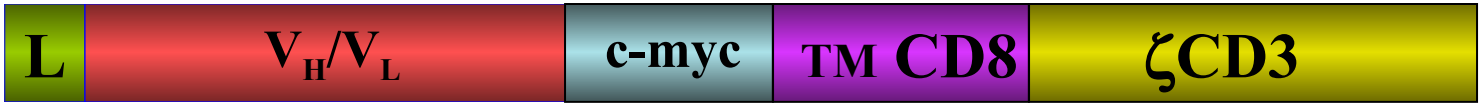
Sviluppo *ante-litteram* di CAR therapy

Recombinant TCR for cell tharapy of infectious disease and cancer

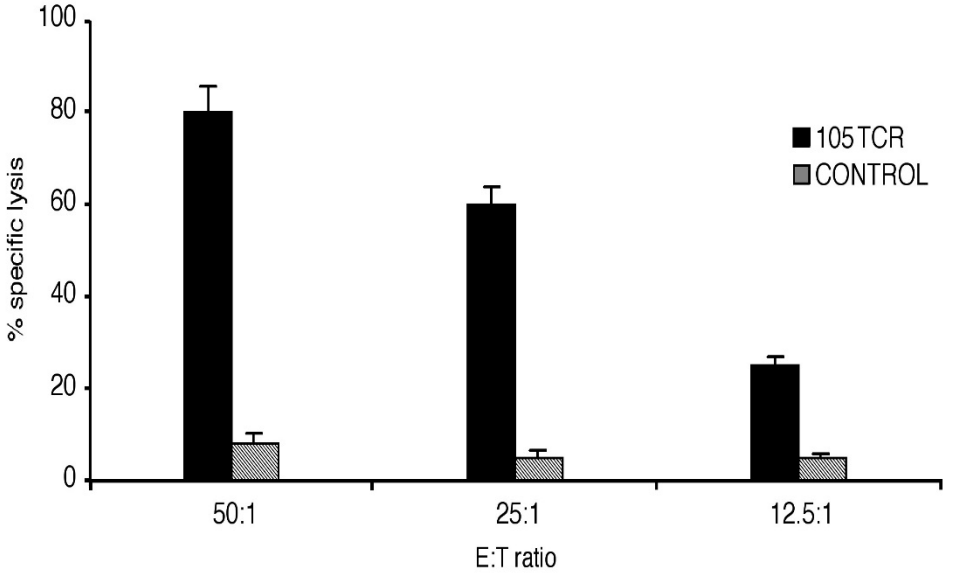


Extracellular	Antigen-specific receptor (CD4), scFv
Transmembrane	CD8, CD4, IgG hinge
Intracellular	CD3-z chain, Fc receptors

Development of TCR containing scFv of gp120/mAbF105



Lysis of HIV-1-infected CD4+ T cells by 105TCR-transduced human CD8+ T lymphocytes



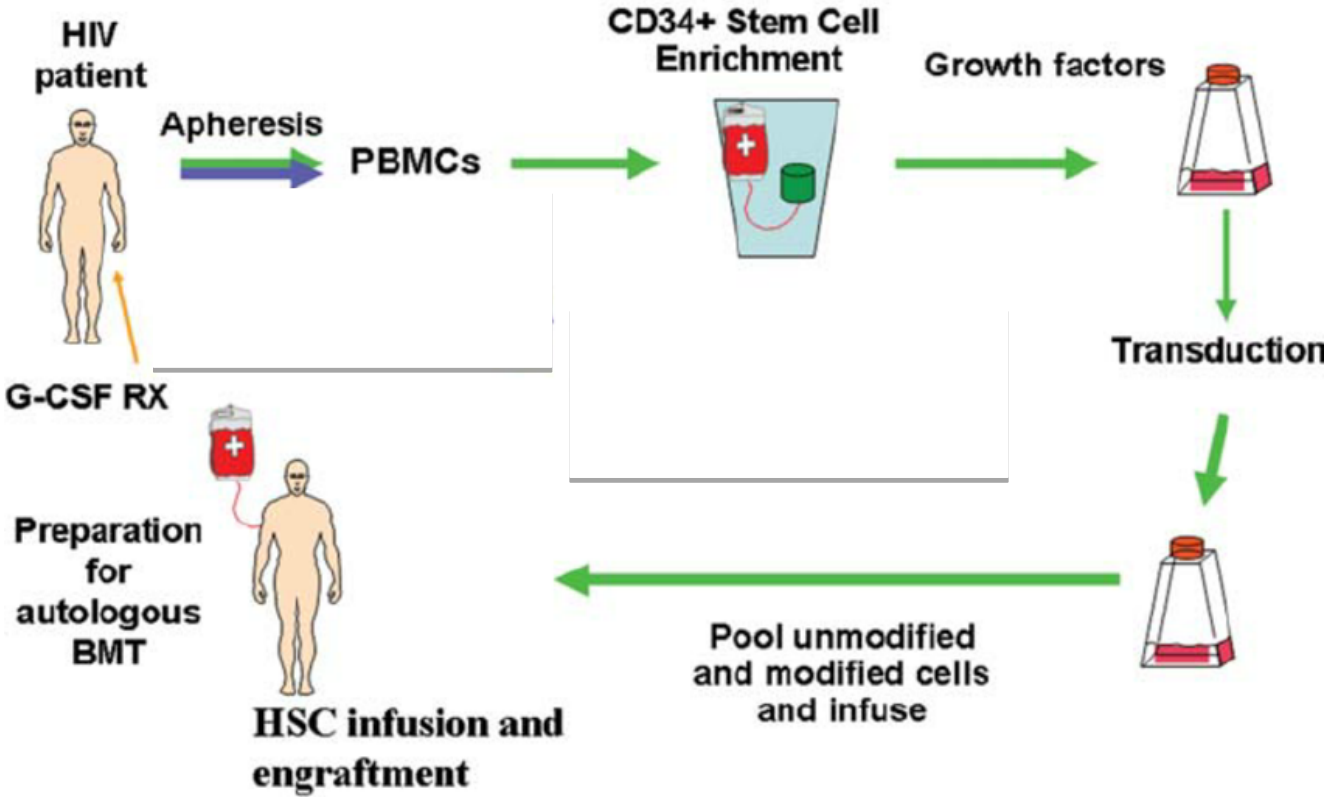
- scFv105/TCR specifically interacts with HIV-1 gp120 (immobilized or in a cellular context)
- Binding of the scFv105/TCR to the HIV-1 gp120 antigen is sufficient to trigger T cell activation

Masiero et al., Gene Ther 2005

Clinical Protocol of Gene Therapy for AIDS

Lentiviral vectors expressing anti-HIV siRNA and fusion inhibitors for transducing AIDS-related lymphoma CD34+ cells

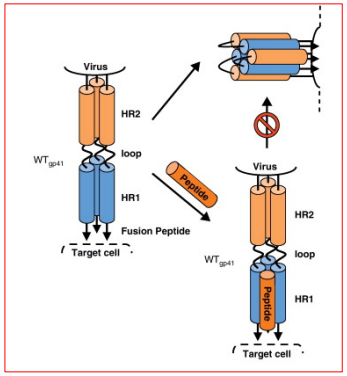
HIV patient with lymphoma



Scherer and Rossi, 2011/Parolin& Cavazzana 2016

Inhibition of HIV-1 replication in human CD4+ T lymphocytes transduced with the selected combinatorial vectors

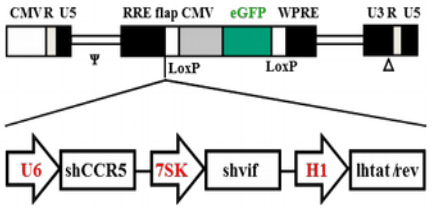
Fusion inhibitors:



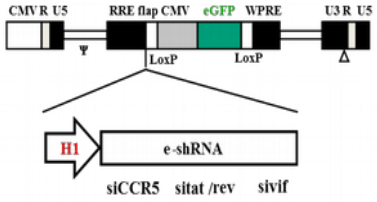
maC46

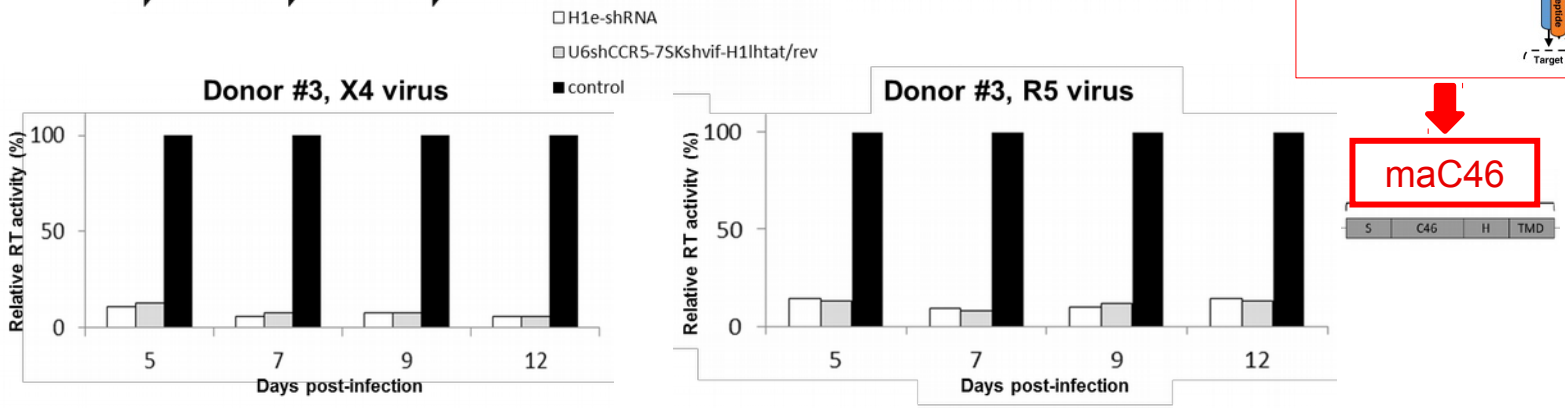
S | C46 | H | TMD

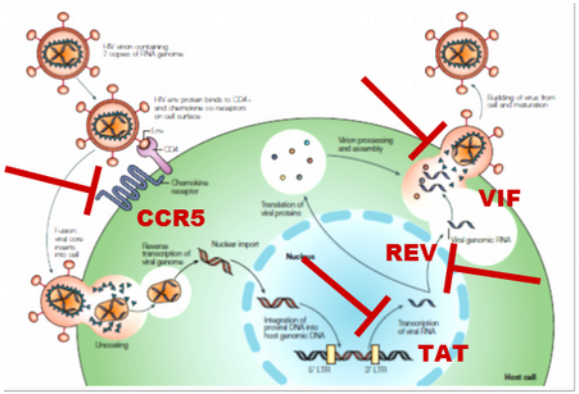
pLL3.7 U6shCCR5-7SKshVif-H1lhTat/Rev



pLL3.7 H1e-shRNA







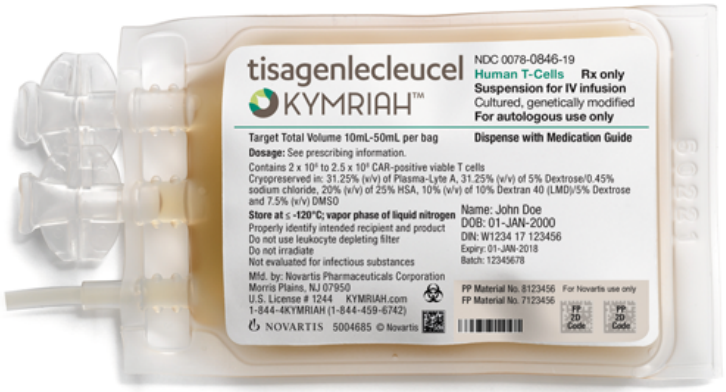
Adapted from Rambaut et al., 2004

Citation: Molecular Therapy—Nucleic Acids (2016) 5, e312; doi:10.1038/mtna.2016.24
Official journal of the American Society of Gene & Cell Therapy
www.nature.com/mtna

Development of Lentiviral Vectors Simultaneously Expressing Multiple siRNAs Against *CCR5*, *vif* and *tat/rev* Genes for an HIV-1 Gene Therapy Approach

Francesca Spanevello[1], Arianna Calistri[1], Claudia Del Vecchio[1], Barbara Mantelli[1], Chiara Frasson[2,3], Giuseppe Basso[2], Giorgio Palù[1], Marina Cavazzana[4–7] and Cristina Parolin[1]

FDA APPROVED CAR-T THERAPIES



August 2017, FDA approval

Novartis Receives Approval For Acute Lymphoblastic Leukemia

October 2017, FDA approval

Kite/Gilead Receives Approval For Diffuse Large B Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE

Roma, February 2018

First patient treated at Bambino Gesù Hospital

NETWORK L'Espresso LE INCHIESTE LAVORO ANNUNCI ASTE Accedi

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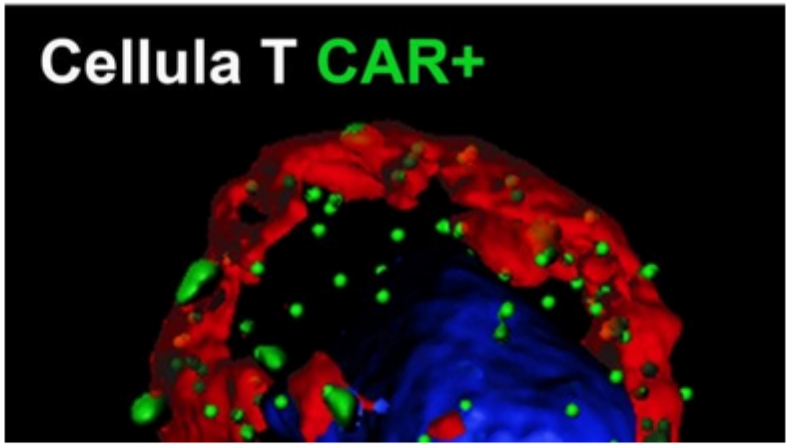
171,9mila

Leucemia, bambino curato con la terapia genica



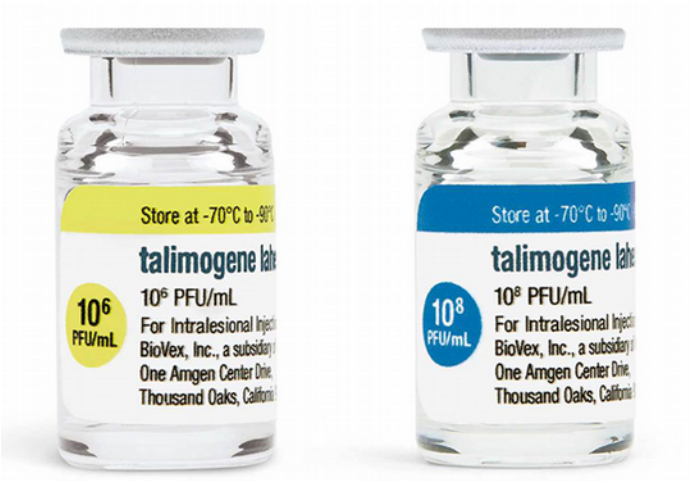
L'immunoterapia con linfociti riprogrammati comincia a dare risultati. Al Bambino Gesù di Roma trattato un piccolo di 4 anni, mentre dagli Usa arrivano i dati di efficacia a lungo termine su altri 75 pazienti

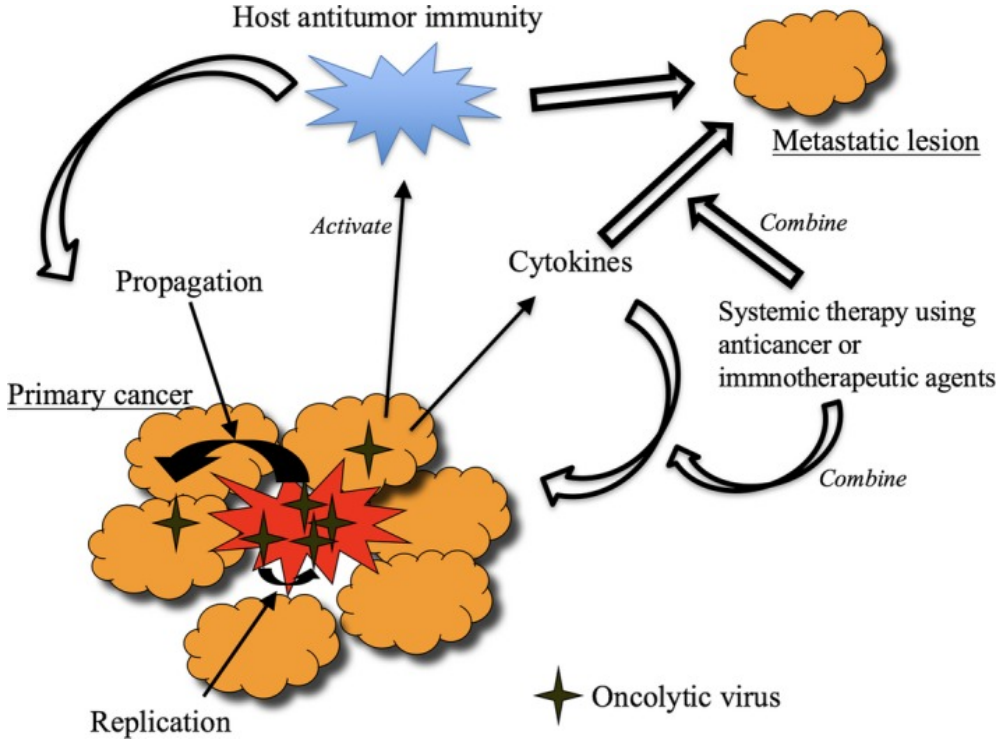
di LETIZIA GABAGLIO e TINA SIMONIELLO

Oncolytic viruses

- Viruses able to replicated in tumor cells but not in healthy cells.
- Replication of oncolytic viruses has 2 effects:
  - Kills tumor cells
  - Triggers an anti-tumoral immune responses.
- They can carry therapeutic genes in tumor cells.

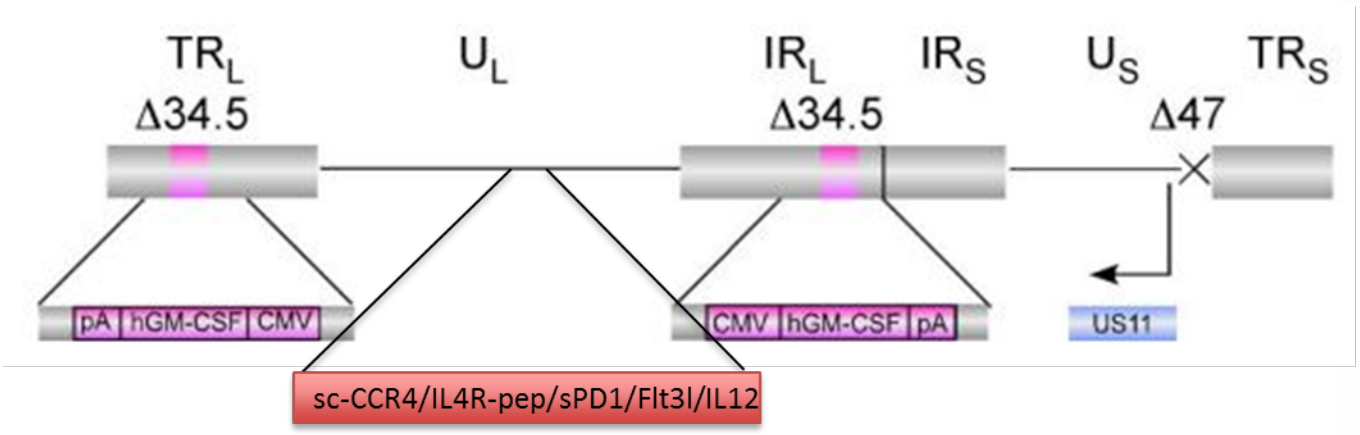
Oncolytic viruses are already in the clinic: talimogene laherparepvec (HSV-1) approved for metastatic melanoma(2016)

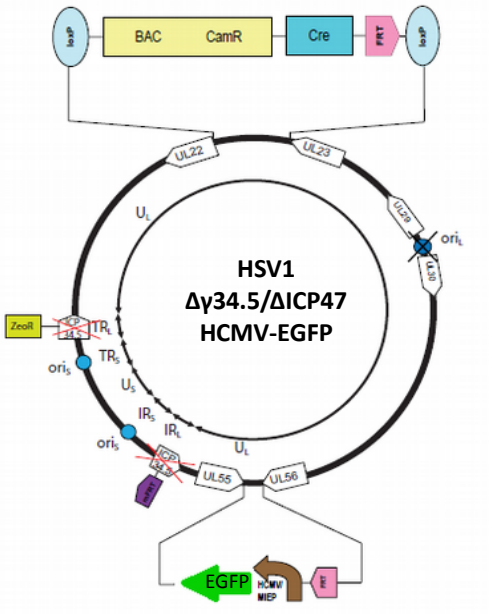




Fukuhara et al, *Cancer Science* (2016)

Generation Δγ34.5/ΔICP47 HCMV-EGFP HSV-1 BAC





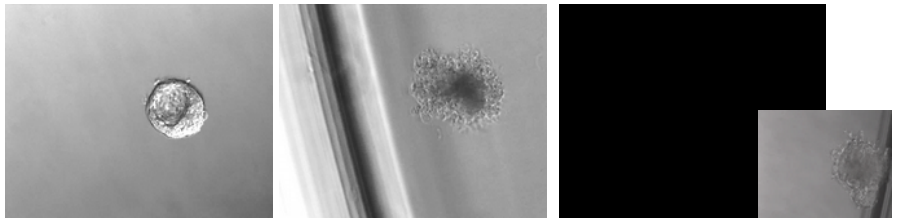
Calistri et al. 2018

wt-organoids

CTRL-mock

wt-HSV

Δγ34.5/ΔICP47
HCMV-EGFP



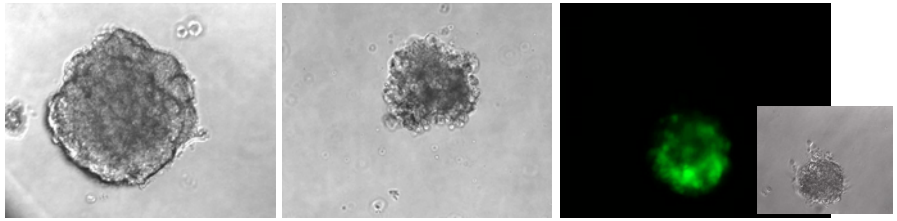
T48

tumor-organoids

CTRL-mock

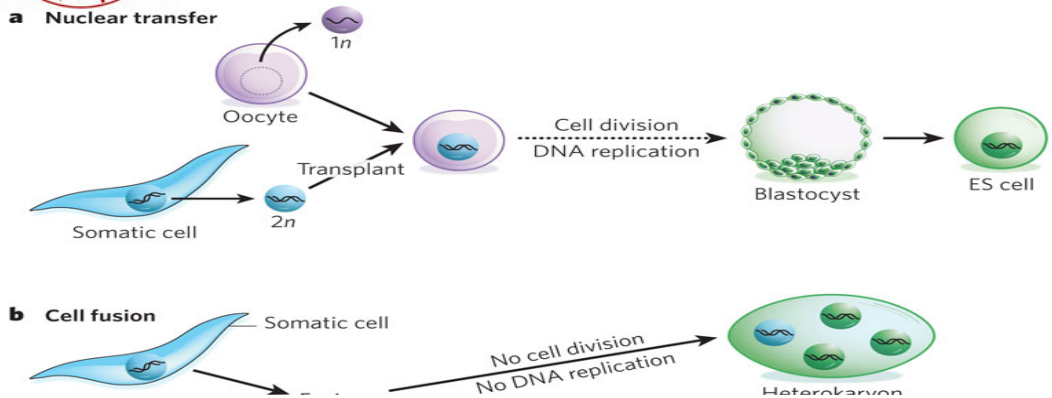
wt-HSV

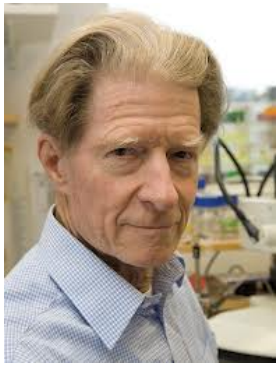
Δγ34.5/ΔICP47
HCMV-EGFP



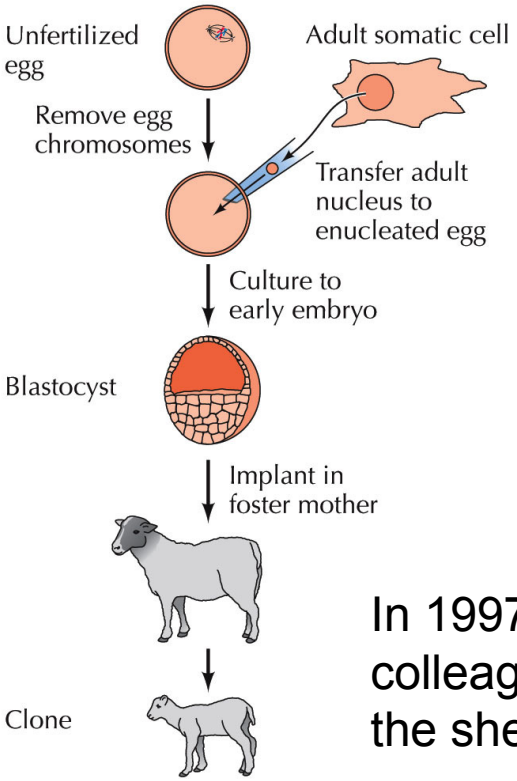
INDUCED PLURIPOTENT STEM CELLS

Reprogramming of somatic cells

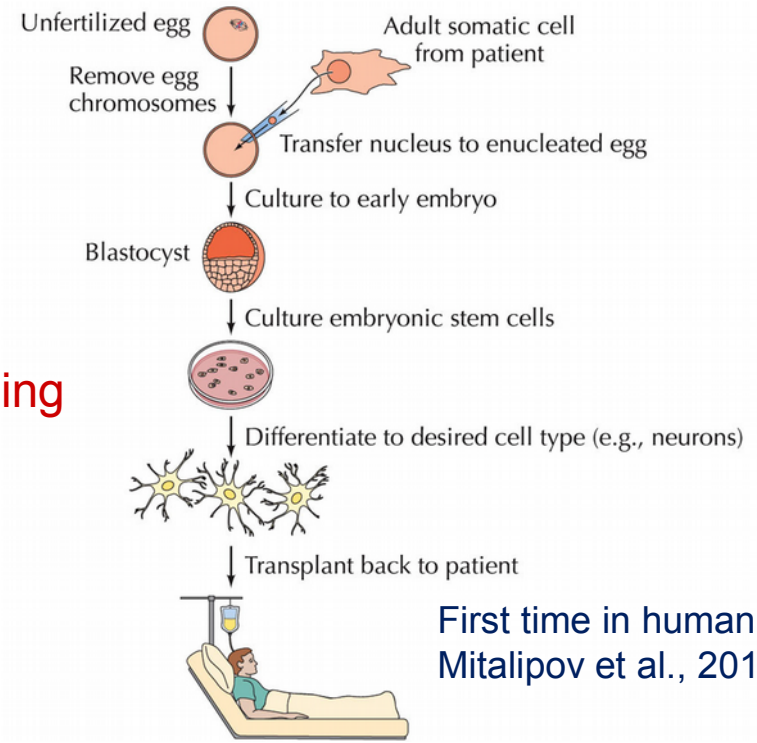




Gurdon, 1962



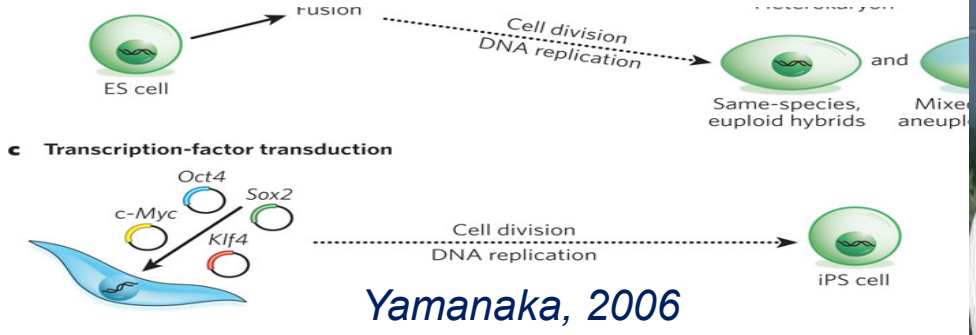
Therapeutic cloning



In 1997 Ian Wilmut and colleagues cloned Dolly the sheep.

First time in human cells
Mitalipov et al., 2013

Reprogramming of somatic cells



Yamanaka, 2006

Dr. Yamanaka

2012 Nobel Prize to **Sir John B. Gurdon** and **Shinya Yamanaka** "for the discovery that mature cells can be reprogrammed to become pluripotent."

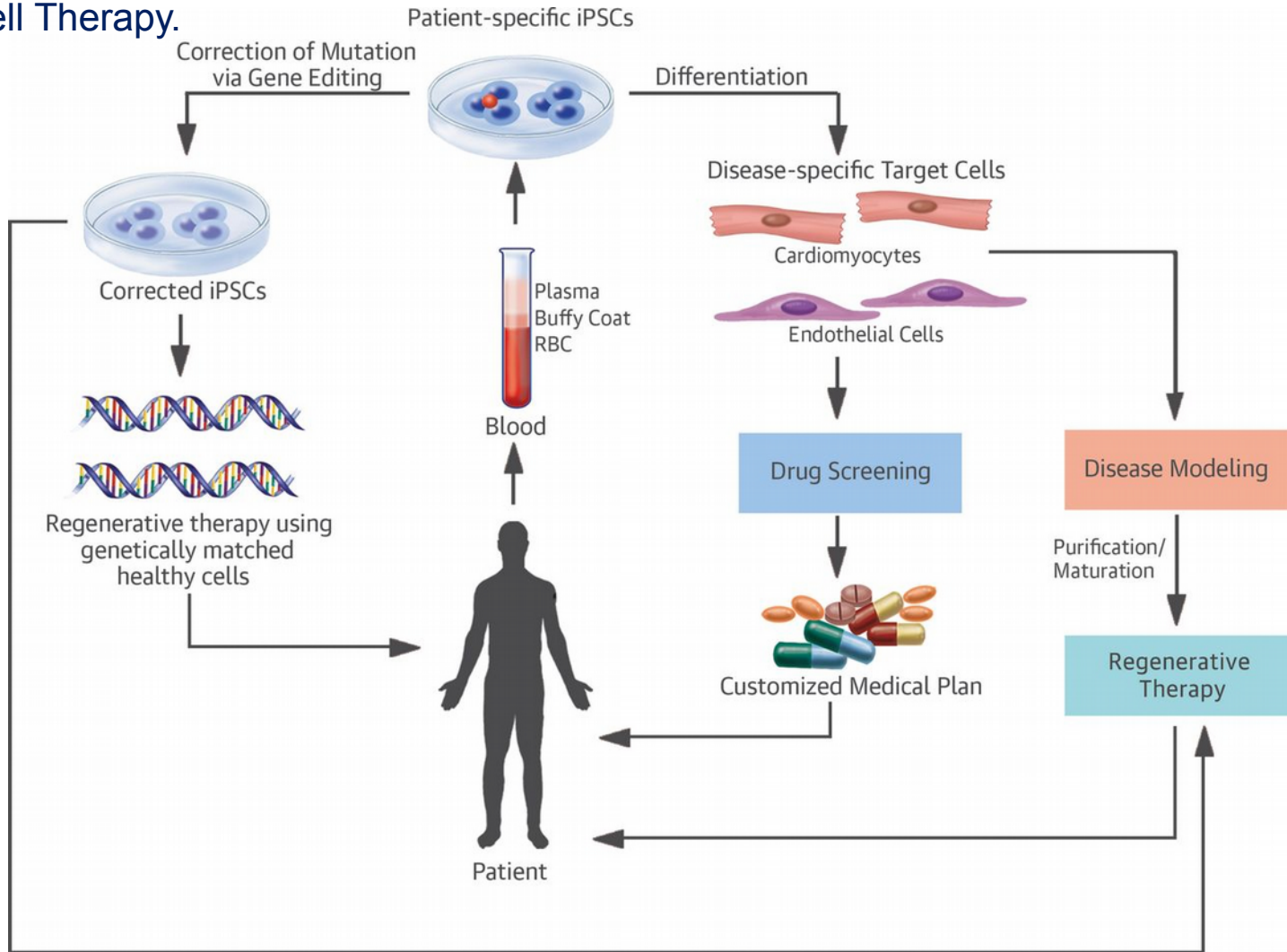
Cell

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]
[1] Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2] CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
*Contact: yamanaka@frontier.kyoto-u.ac.jp
DOI 10.1016/j.cell.2006.07.024

Induced Pluripotent stem cells: tool for….

1) Study of human development;
2) Study of pathophysiological bases of diseases;
4) Drug Screening studies;
5) Gene editing and Cell Therapy.



Sayed et al. 2016

Protocols for reprogramming: derivation of iPSCs

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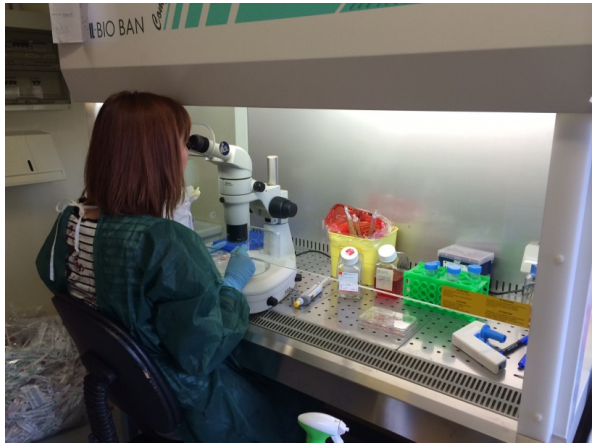
Università di Padova

Day 0 — D5 — D6 — D14 — D30

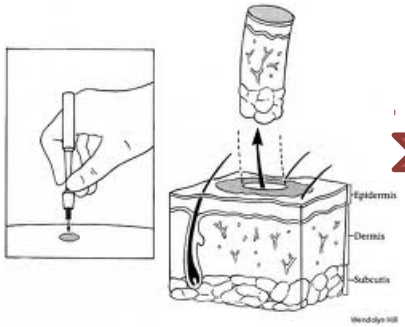
OCT4, SOX2
KLF4, MYC

Split into
plate with MEF

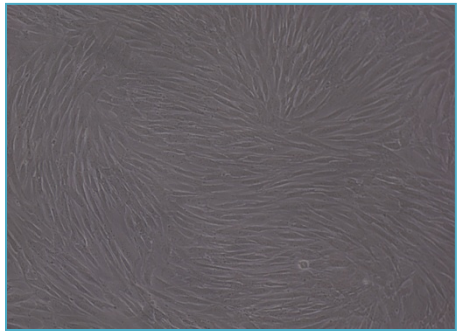
hES medium



SKIN BIOPSY

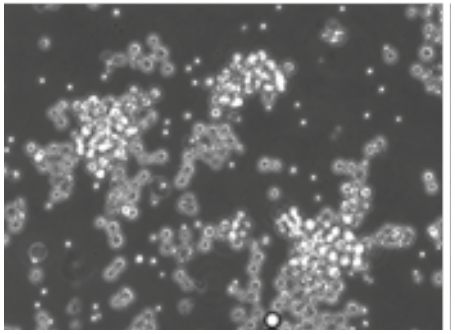


Skin fibroblasts



OCT4
Sox2
KlF4
cMyc

BLOOD SAMPLE



Erythroblasts

hiPSCs at the DMM

Stem Cell Research 28 (2018) 149–152

Contents lists available at ScienceDirect

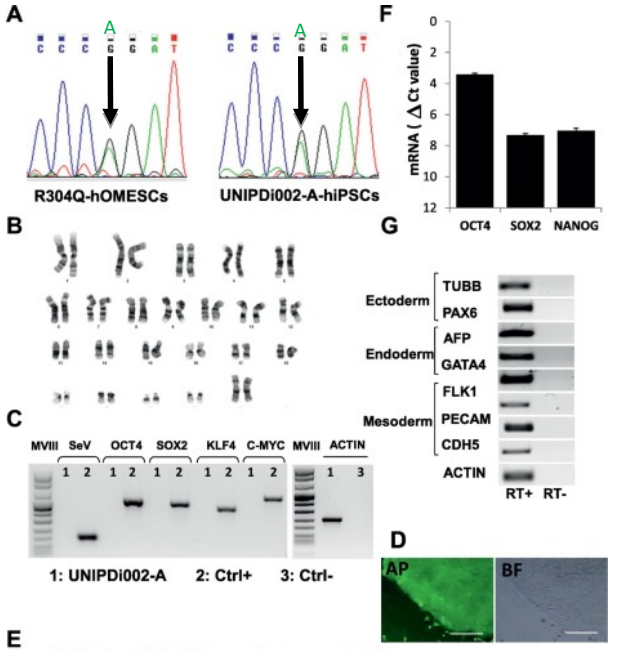
Stem Cell Research

journal homepage: www.elsevier.com/locate/scr

Lab Resource: Stem Cell Line

Generation of a transgene-free induced pluripotent stem cells line (UNIPDi002-A) from oral mucosa epithelial stem cells carrying the R304Q mutation in TP63 gene

Marta Trevisan [a,*], Vanessa Barbaro [b], Silvia Riccetti [a], Giulia Masi [a], Luisa Barzon [a], Patrizia Nespeca [a], Gualtiero Alvisi [a], Enzo Di Iorio [a], Giorgio Palù [a]

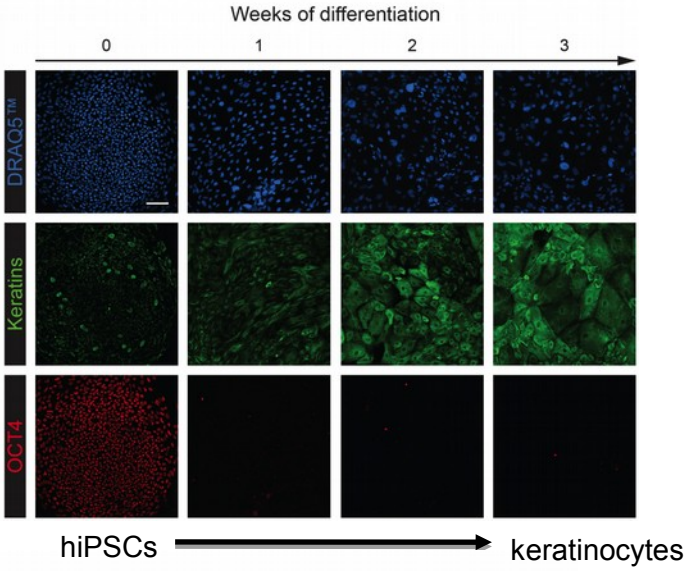


CELLULAR REPROGRAMMING
Volume 20, Number 4, 2018
© Mary Ann Liebert, Inc.
DOI: 10.1089/cell.2017.0064

Brief Communication

Oral Mucosa-Derived Induced Pluripotent Stem Cells from Patients with Ectrodactyly-Ectodermal Dysplasia-Clefting Syndrome

Marta Trevisan,[1,†] Gualtiero Alvisi,[1,†] Vanessa Barbaro,[2] Luisa Barzon,[1] Paolo Raffa,[1] Angelo Migliorati,[1] Giovanna Desole,[1] Silvia Ruzittu,[1] Giulia Masi,[1] Enzo Di Iorio,[1] and Giorgio Palù[1,*]



Stem Cell Research 28 (2018) 149–152

Contents lists available at ScienceDirect

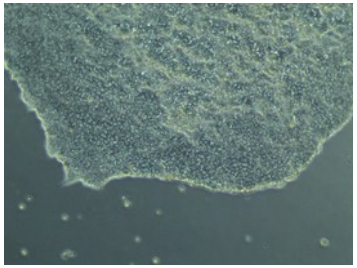
Stem Cell Research

journal homepage: www.elsevier.com/locate/scr

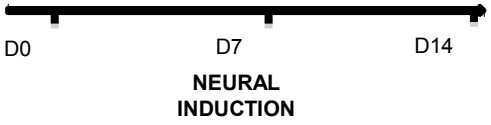
Generation of a transgene-free human induced pluripotent stem cell line (UNIPDi001-A) from oral mucosa epithelial stem cells

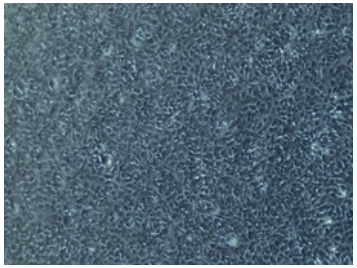
Gualtiero Alvisi [a], Marta Trevisan [a,*], Giulia Masi [a], Vanessa Canel [a], Luciana Caenazzo [a], Patrizia Nespeca [a], Luisa Barzon [a], Enzo Di Iorio [a], Vanessa Barbaro [b], Giorgio Palù [a]

Investigation of ZIKV and West Nile virus infection in hiPSC-derived neural cells

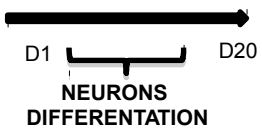


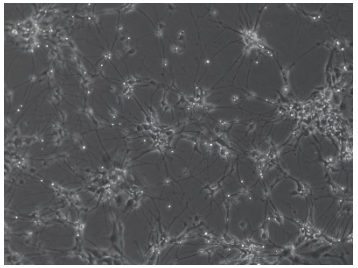
hiPSCs



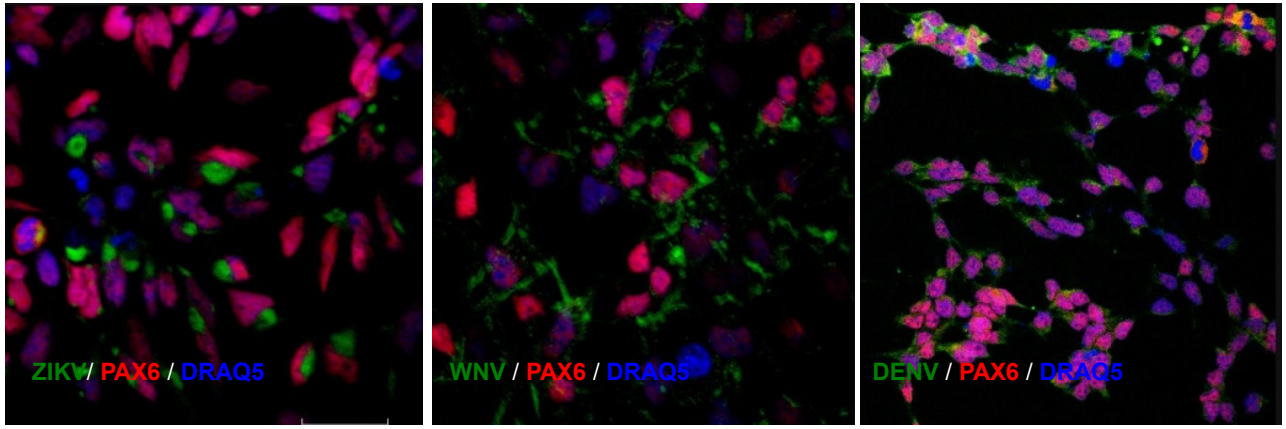


Neural Stem cells (NSCs)



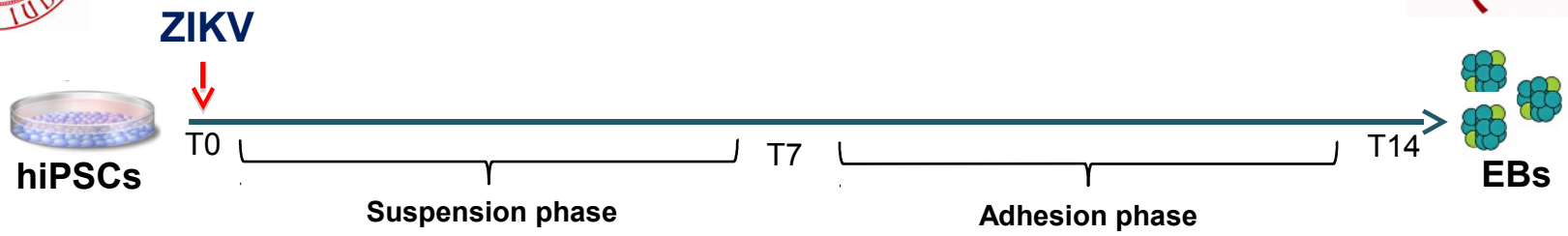


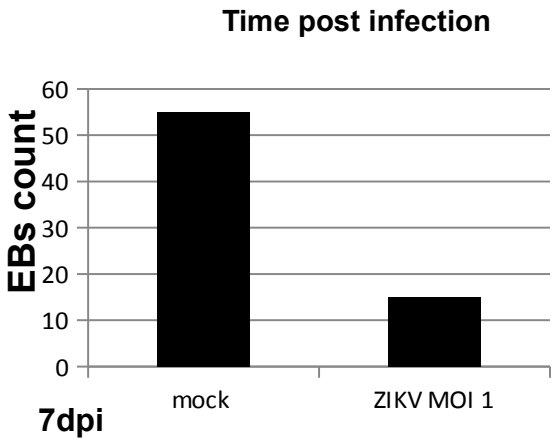
Neurons

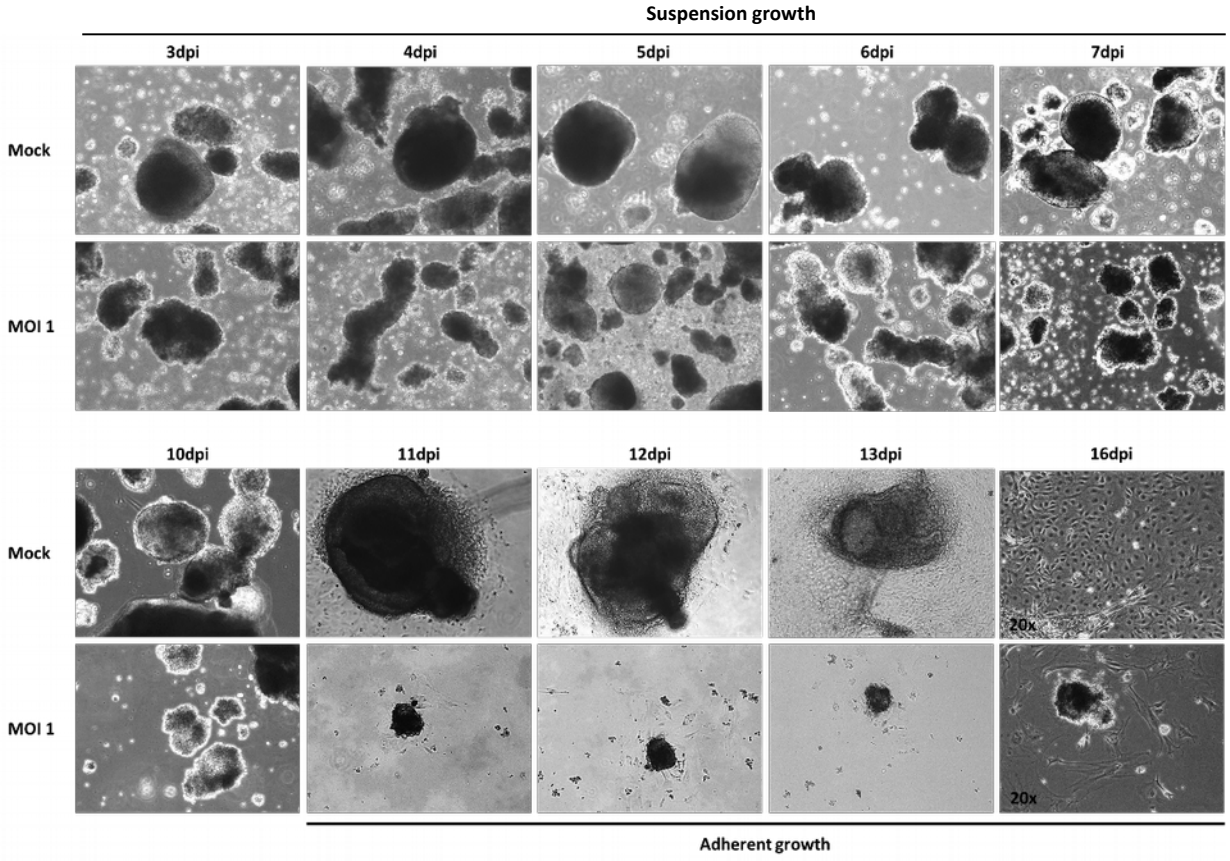


hNSCs infected with ZIKV, WNV and DENV2

ZIKV infection during embryogenesis

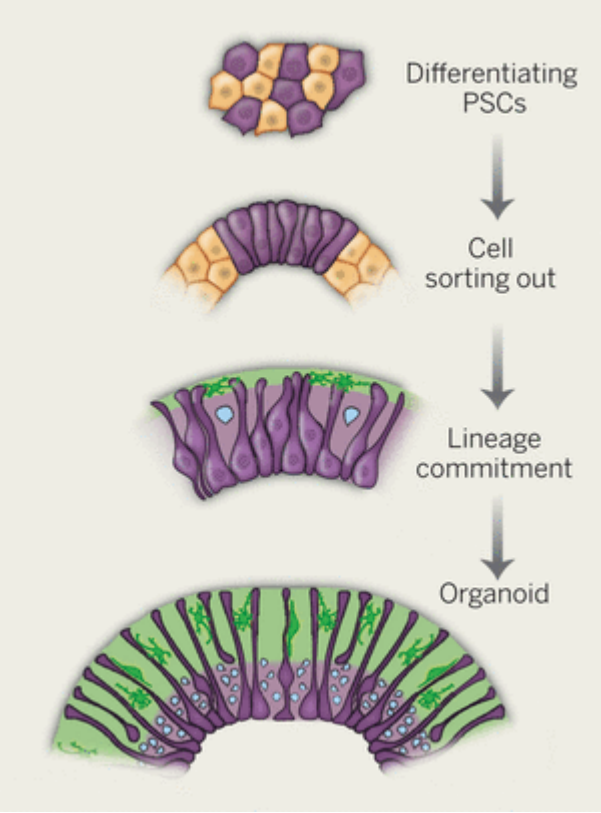


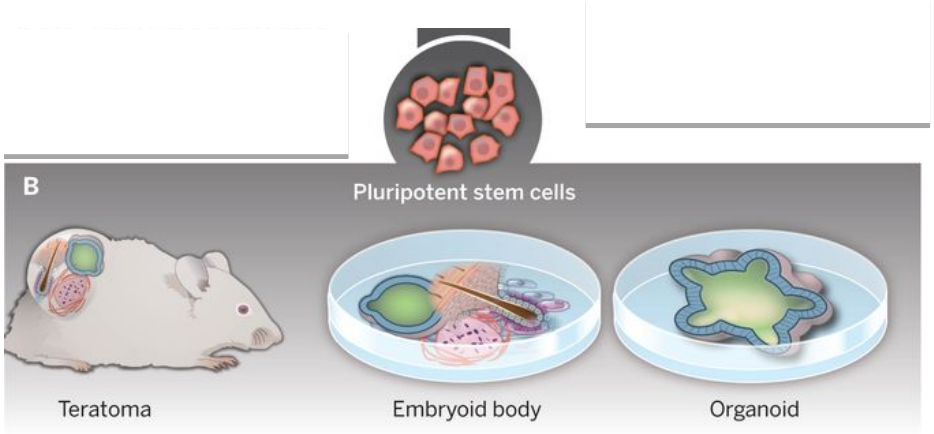




Organoids

A collection of organ-specific cell types that develops from stem cells or organ progenitors and self-organizes through cell sorting and spatially restricted lineage commitment in a manner similar to in vivo and exhibiting similar organ functionality as the tissue of origin.

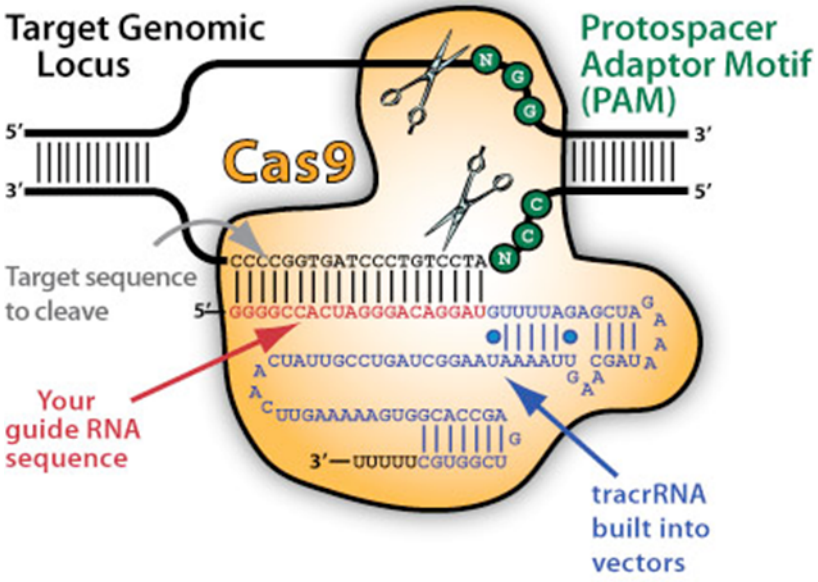




Lancaster and Knoblich, Science 2014: 345, 6194, 1247125

Genome Editing

CRISPR/Cas9: Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR associated 9

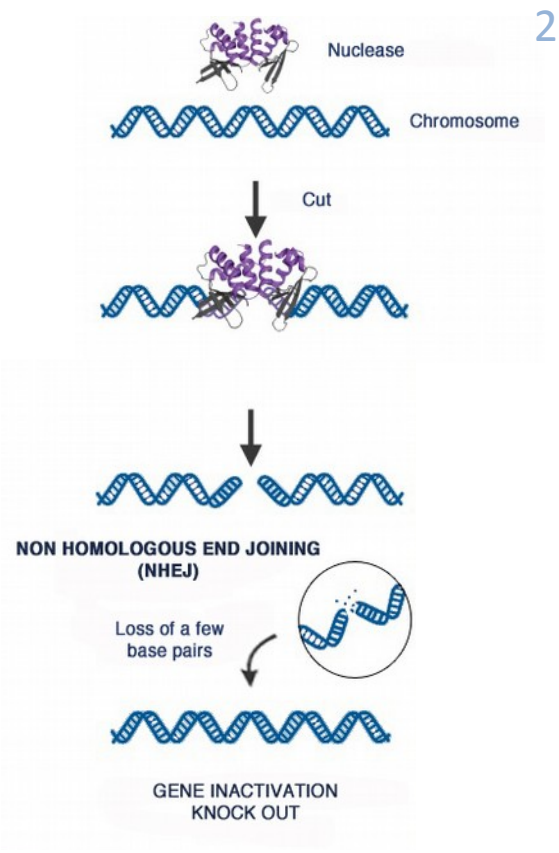


Emmanuelle Charpentier : CRISPR Therapeutics

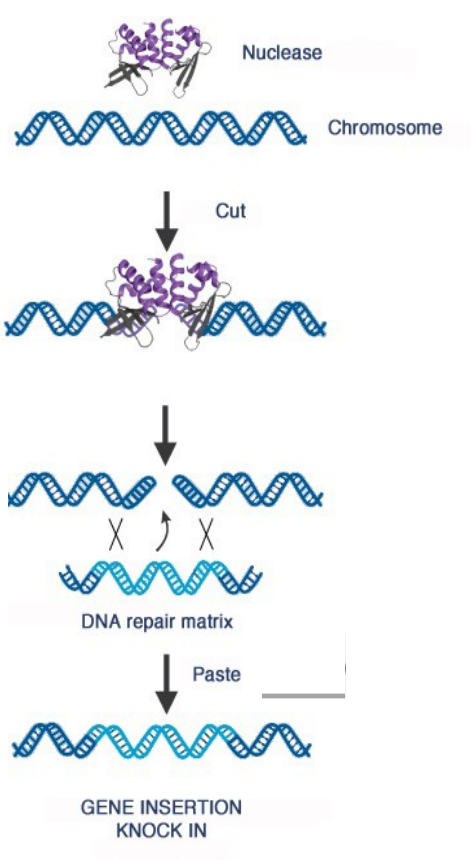
Targeted genetic modifications:

1) Gene disruption
2) Gene insertion
3) Gene correction and point mutagenesis

1)



2)



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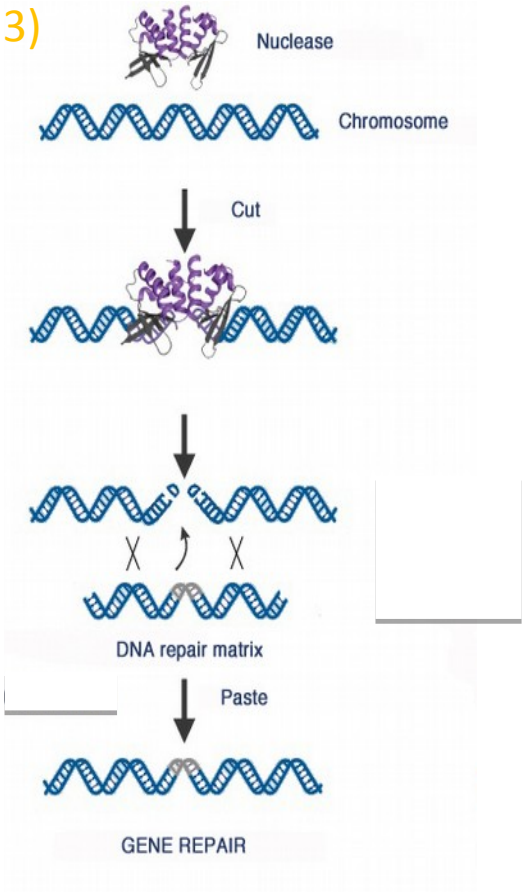
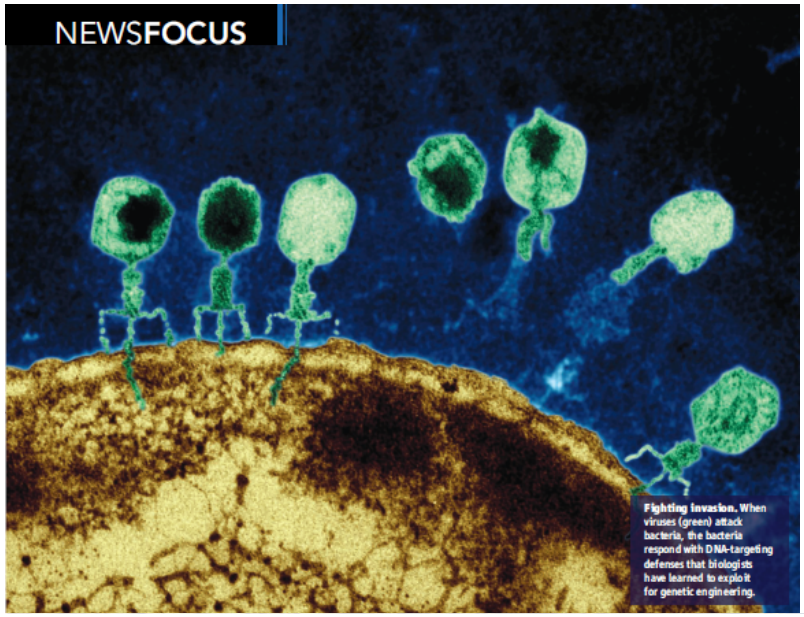


www.sciencemag.org SCIENCE VOL 341 23 AUGUST 2013



Fighting invasion. When viruses (green) attack bacteria, the bacteria respond with DNA-targeting defenses that biologists have learned to exploit for genetic engineering.

The CRISPR Craze

A bacterial immune system yields a potentially revolutionary genome-editing technique

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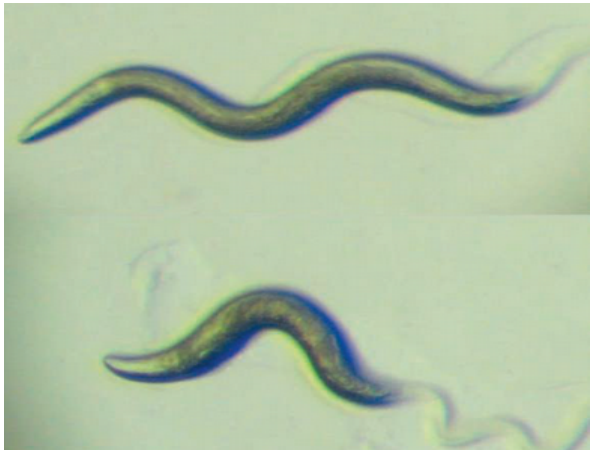
Dipartimento di Medicina Molecolare
Università di Padova

In the following 8 months, various groups have used it to **delete, add, activate, or suppress targeted genes in human cells, mice, rats, zebrafish, bacteria, fruit flies, yeast, nematodes,and crops,** demonstrating broad utility for the technique.

fruit flies with dark eyes

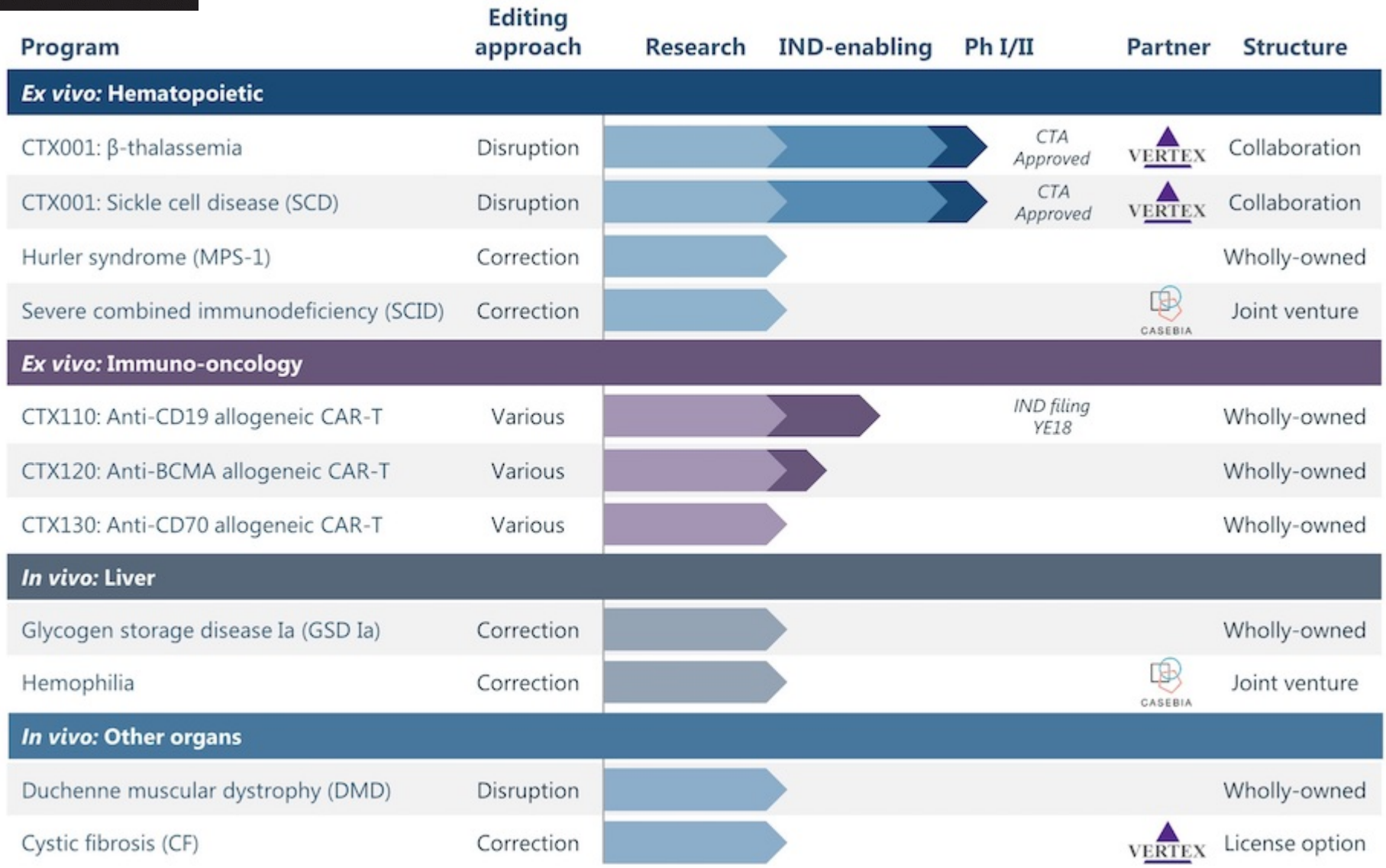


dumpier nematodes

CRISPR THERAPEUTICS

DMM Dipartimento di Medicina Molecolare Università di Padova

CRISPR is coming to the clinic this year

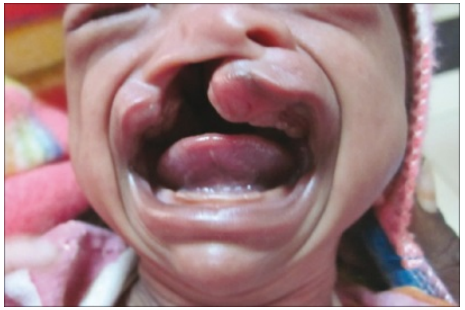


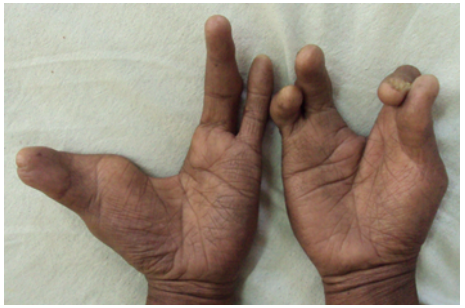
Ectrodactyly−Ectodermal dysplasia−Clefting (EEC) syndrome

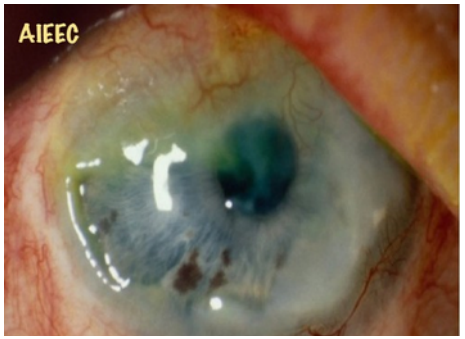
EEC is a rare autosomal **dominant inherited disease** characterized by ectrodactyly (split−hand−foot malformation), ectodermal dysplasia and cleft lip and palate.

It affects the skin, nails, hair, teeth, sweat glands and the ocular ectodermal derivatives leading to **visual impairment and blindness**.

EEC syndrome is caused by **heterozygous mutations in the p63** gene, essential for the regeneration of adult epithelia and the maintenance of the proliferative status of basal keratinocytes.

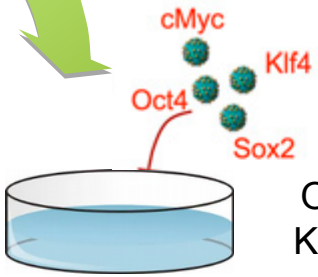




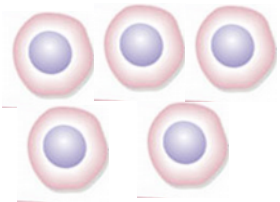


EEC-syndrome, work flow o retargeting

EEC patient

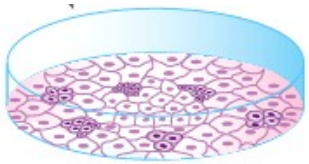


Oral mucosa Keratinocytes reprogramming



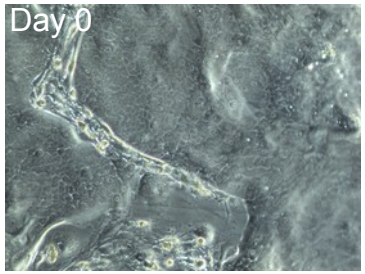
Fixed corneal epithelial cells

CRISPR Cas9 retargeting and differentiation in corneal epithelial cells

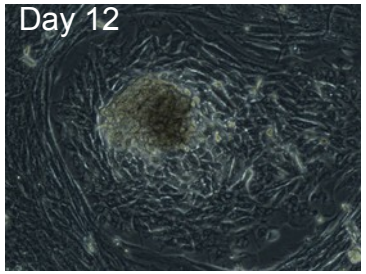


EEC-derived iPSCs → Characterization

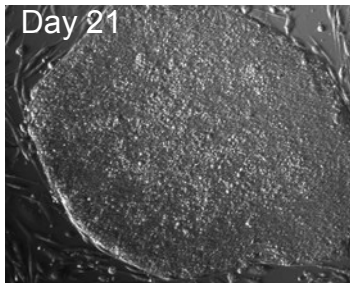
EEC-syndrome: from reprogramming to retargeting



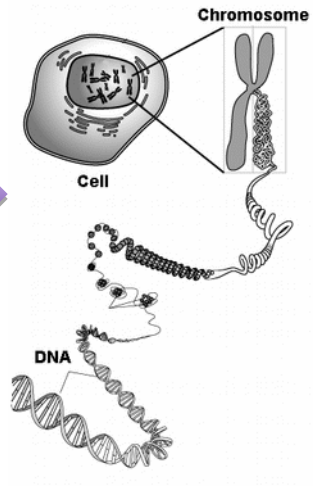
Patient's cells



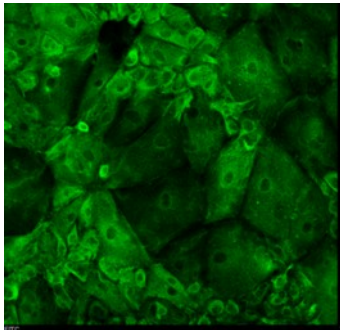
Intermediate



Patient's **stem** cells

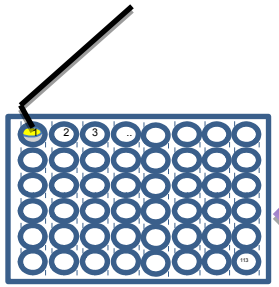


Pan Cytokeratin



Patient's **corrected** cells

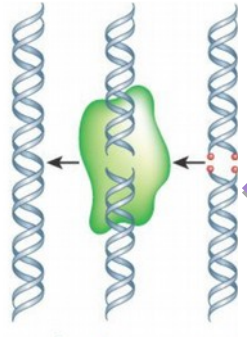
Differentiation into corneal epithelial cells

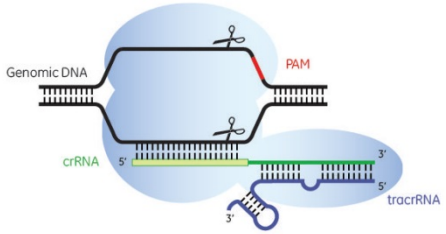


Clone selection

DNA REPAIR

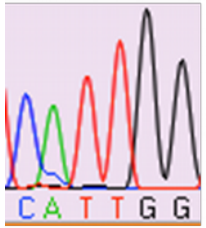
DNA double-strand breaks



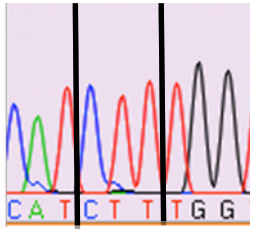


CRISPR/CAS9

Pre-editing



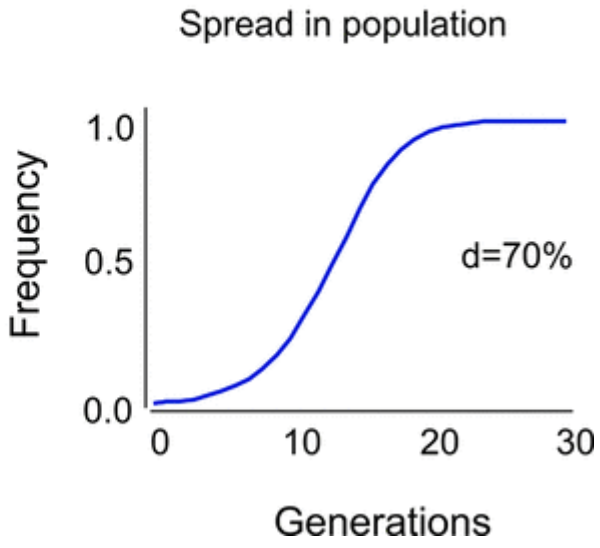
Post-editing

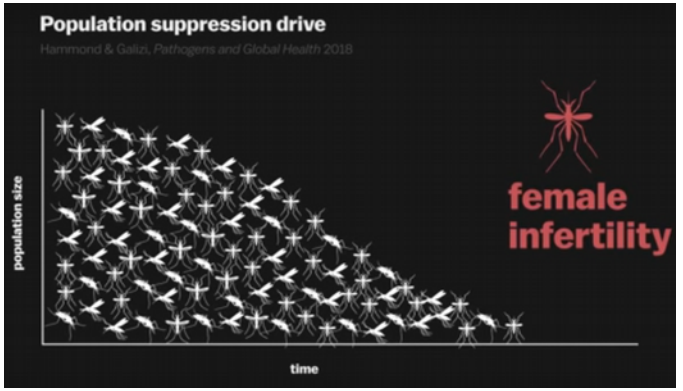


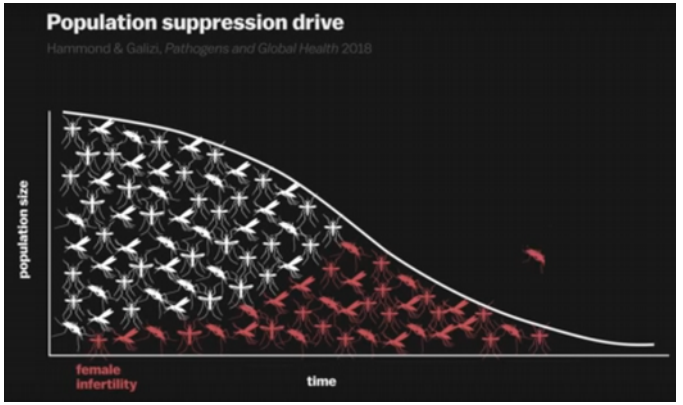
Gene correction

Gene Drive for Malaria eradication

These new types of synthetic gene drives could **alter insect populations** that spread diseases such as **malaria, schistosomiasis, dengue and Lyme**, protect at-risk ecosystems from the spread of destructive invasive species, or improve sustainability in agriculture by reducing the need for and toxicity of pesticides and herbicides.







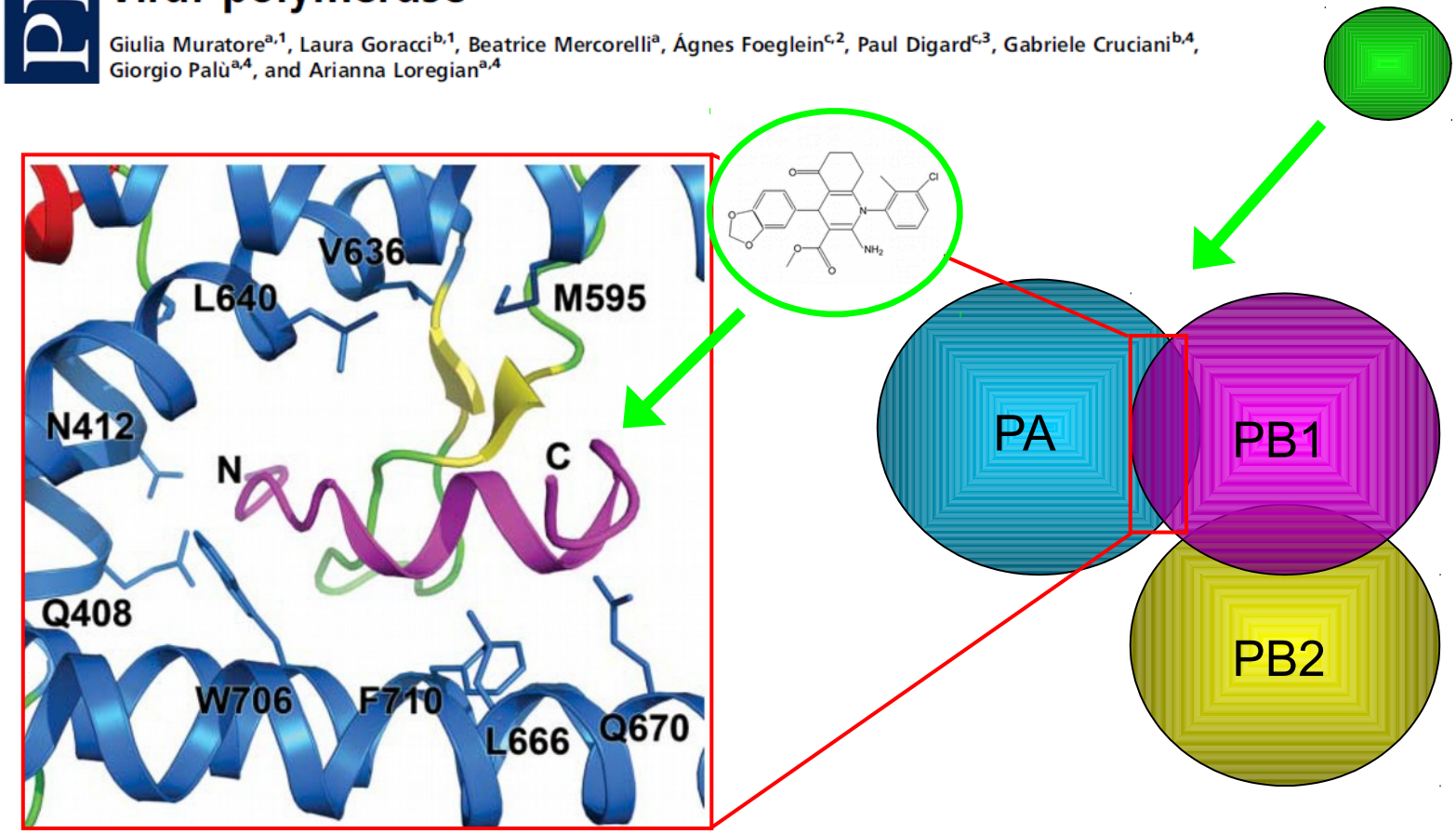
Burt and Crisanti Pathog Glob Health. 2017 Dec; ACS Chem Biol. 2018

ANTIVIRALS

PNAS | April 17, 2012 | vol. 109 | no. 16 | 6247–6252

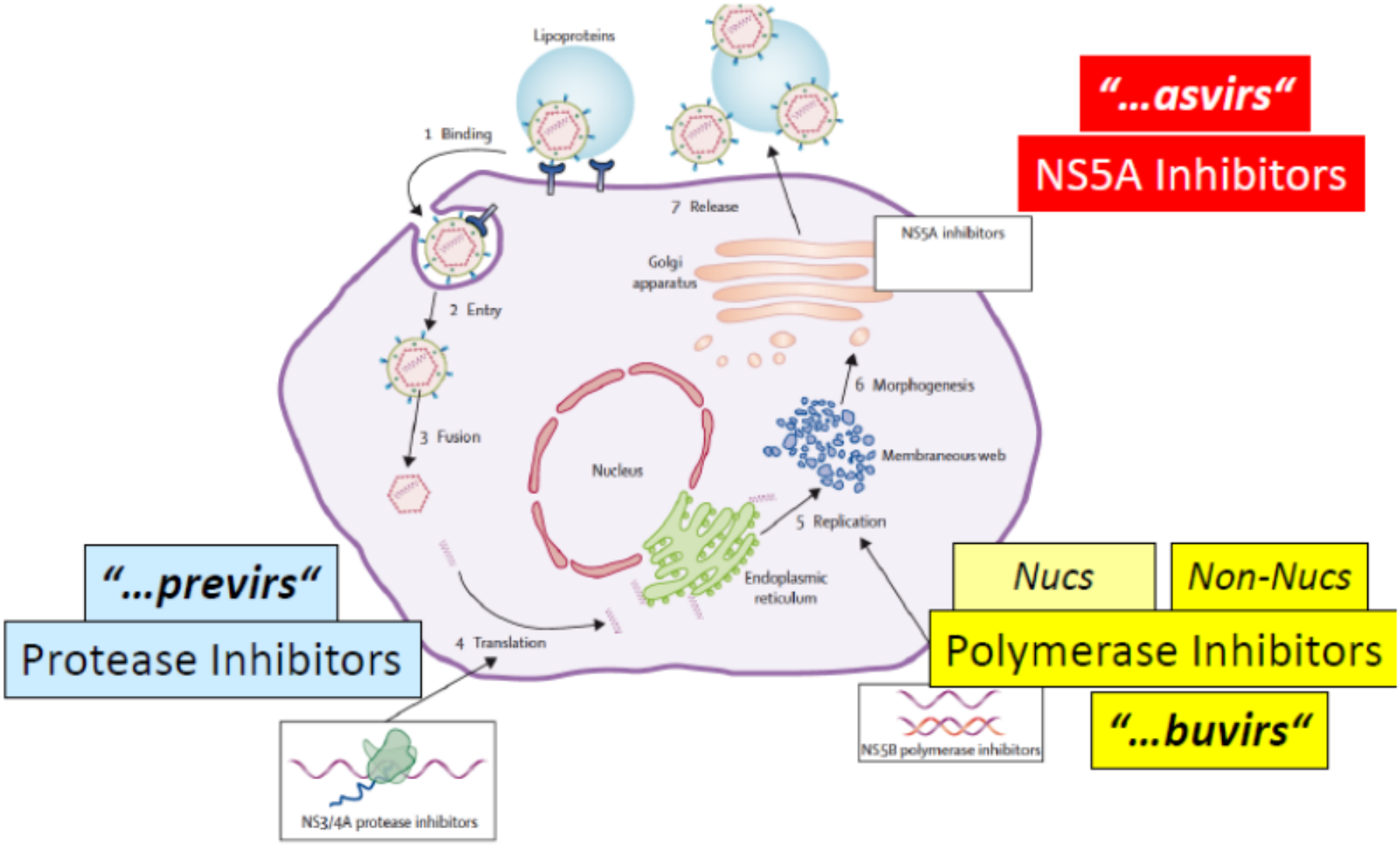
Small molecule inhibitors of influenza A and B viruses that act by disrupting subunit interactions of the viral polymerase

Giulia Muratore[a,1], Laura Goracci[b,1], Beatrice Mercorelli[a], Ágnes Foeglein[c,2], Paul Digard[c,3], Gabriele Cruciani[b,4], Giorgio Palù[a,4], and Arianna Loregian[a,4]



Loregian, A., Palù, G., Muratore, G., Cruciani, G., Tabarrini, O. “New inhibitors of influenza A and B viruses acting by disrupting PA and PB1 subunit interactions of heterotrimeric viral RNA polymerase.” **PCT/EP2012/052914**, 21 February 2012 (con finanziamento del deposito del brevetto approvato dalla Commissione Brevetti dell’Università di Padova in gennaio 2012).

Toward the eradication of HCV

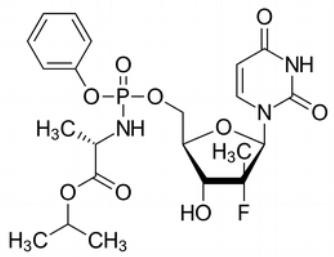


Manns, von Hahn, Nat Rev Drug Discov 2013

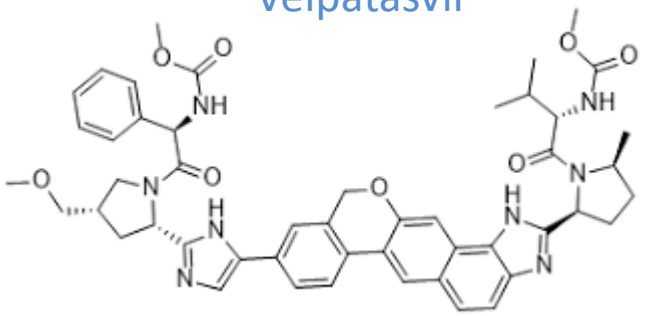
Eradication of HCV

EPCLUSA

Sofosbuvir

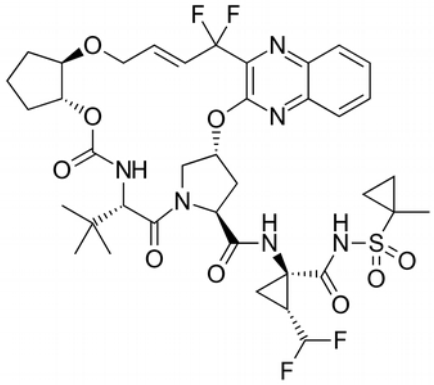


Velpatasvir

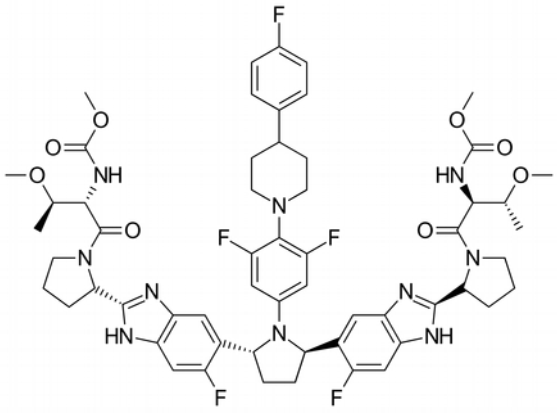


MAVIRET

Glecaprevir

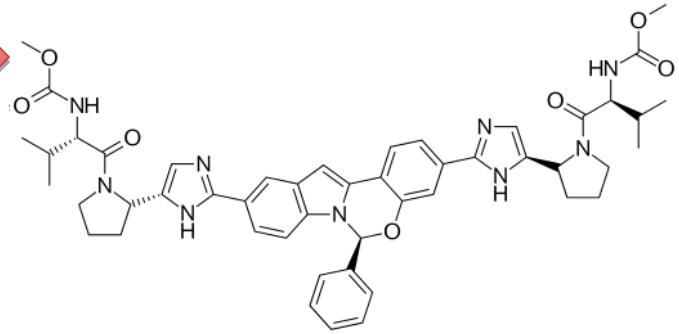


Pribrentasvir

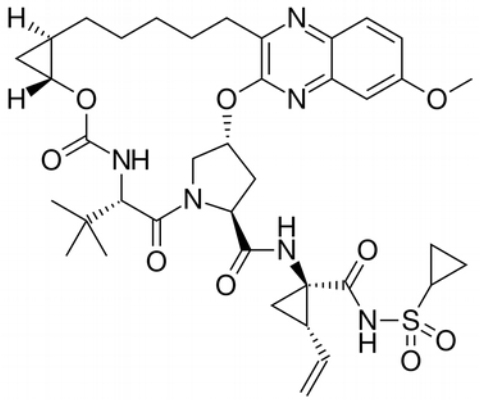


ZEPATIER

Elbasvir



Gazoprevir



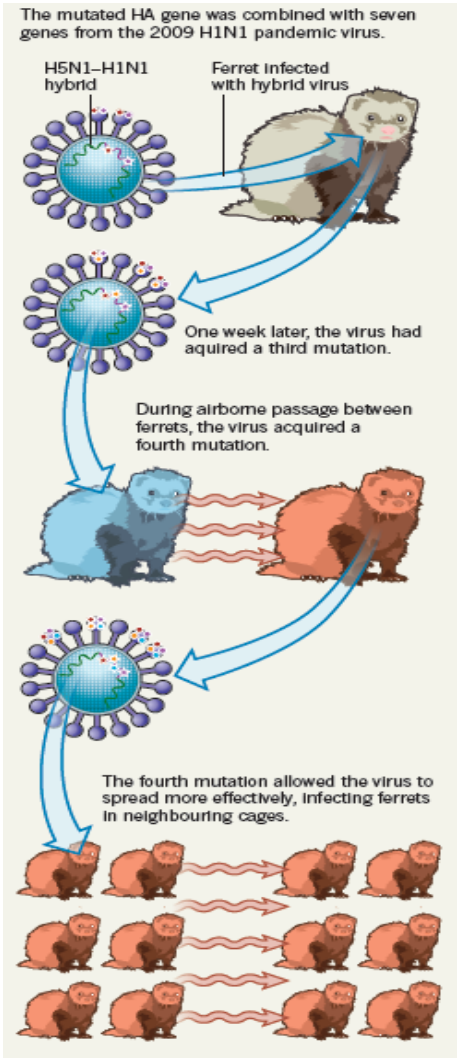
Gain of function (GOF)

Definition: a type of mutation in which the altered gene product possesses a new molecular function or a new pattern of gene expression.

GOF applied to potential pandemic pathogens is a case of potential «**Dual Use Research**»

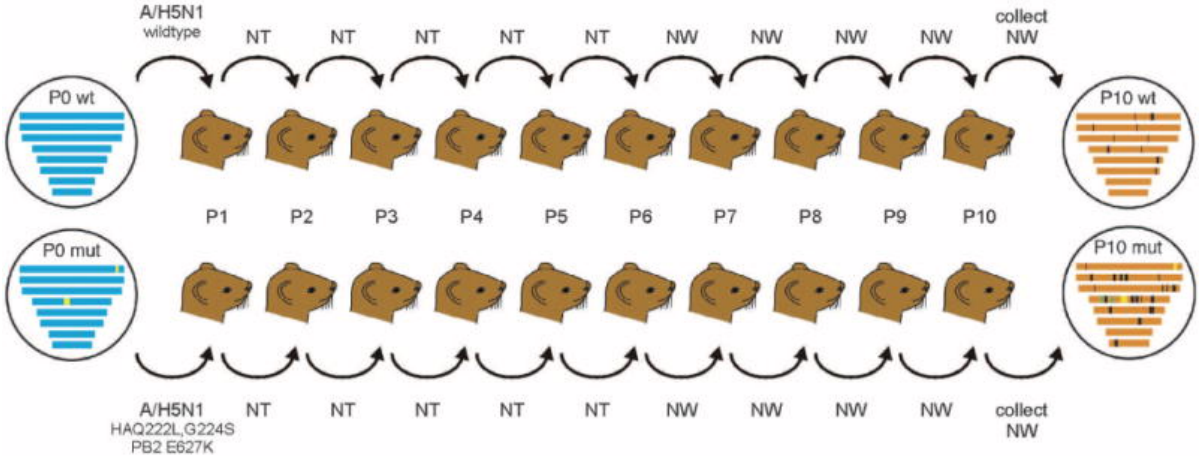
Experimental adaptation of H5N1 to mammal hosts

nature
International weekly journal of science

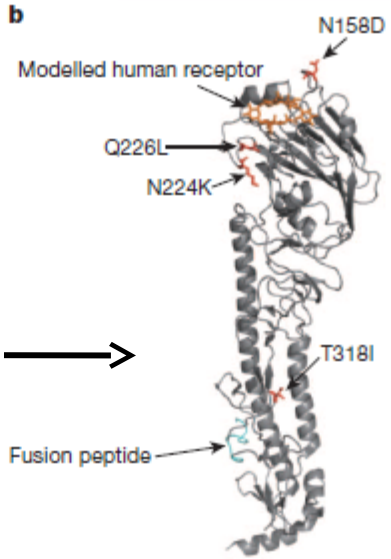


Science
AAAS

Virus passaging and airborne transmission of A/H5N1 viruses in ferrets.



Fouchier et al. Science. 2012 Jun 22; 336(6088): 1534–1541



Amino acids changes allowing an high efficient via area transmission of virus among ferrets

Kawaoka et al., N AT U R E | VO L 4 8 6 | 2 1 J U N E 2 0 1 2

Regulating dual-use research in Europe. Science. 2014 Jan 24;343(6169):368-369 Palù G.

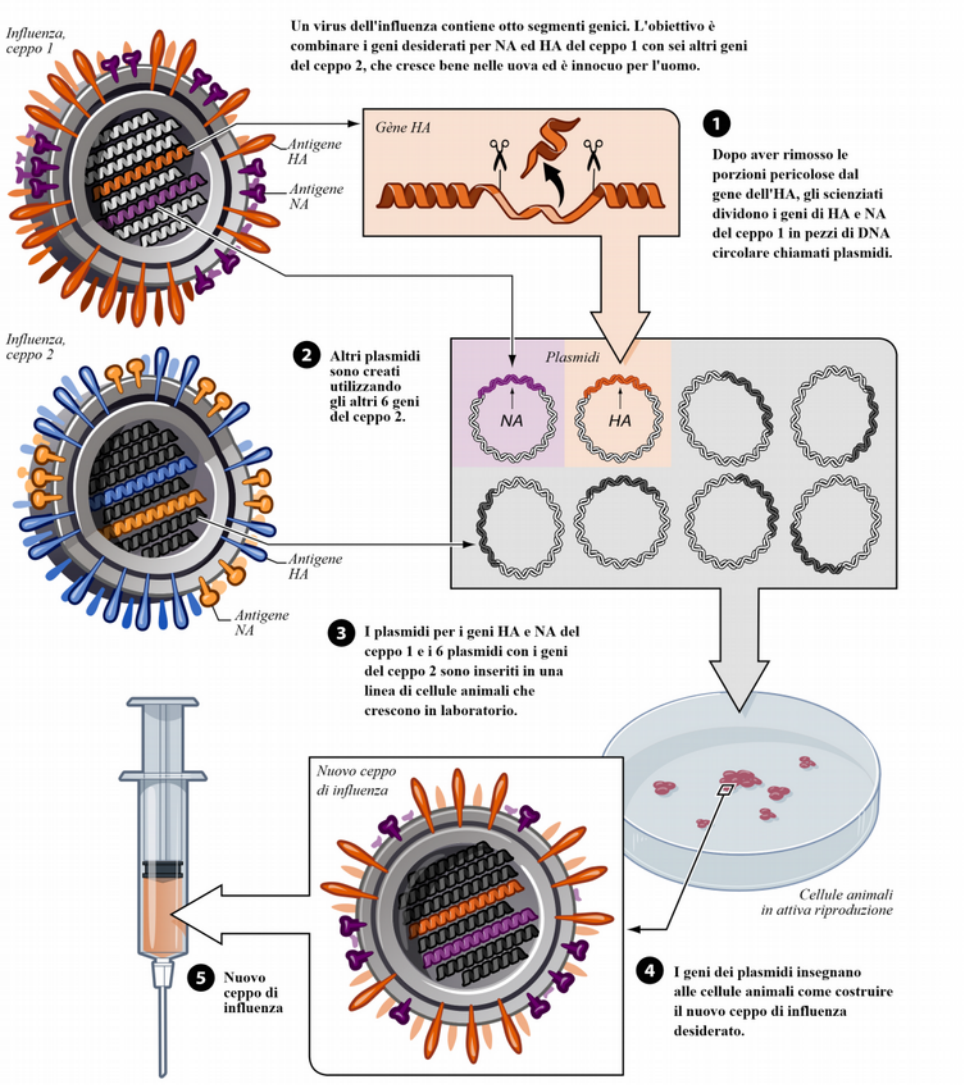
ESV's position stems from **the concern** that results from scientific work carried out in Europe on these organisms would require **an export permit before they can be published in international scientific journals.**

This prospect raises a number of serious issues. Under what circumstances should this EC regulation be applied to biomedical research? **Who is going to decide when the EC regulation does or does not apply**? What should be considered “basic scientific research,” **and who is going to judge this criterion**? (This is not a trivial question, especially in the European Union context, where, in theory, there might be 28 different interpretations of the same regulation.) Does this create the potential for discrimination among scientists working in different European States and between European scientists and those in the rest of the world? Does this decision apply only when specific results are going to be published in journals outside Europe, or does it apply universally?

It may be that controversial questions **related to this issue were ignored for too long**, allowing a precedent to be set prematurely. We are overdue for discussions on **how to regulate the dissemination of “sensitive” data in a way that does not compromise biosecurity, while maintaining the principle that acquiring important and meaningful knowledge cannot simply be stopped. ESV believes that export control does not represent the best way to deal with this issue.**

Our **intention is not to criticize or to disregard the work of jurisprudence experts.** We believe that the **European Commission should take steps to promote a common understanding of the current regulation by existing working groups or by a new advisory committee** created to deal with the dual-use research in a harmonized and balanced way throughout Europe. In the meantime, we have expressed our willingness to provide law officers with proper scientific advice, making available the expertise of our many European scientists.

Uso di GOF per allestimento vaccini ricombinanti



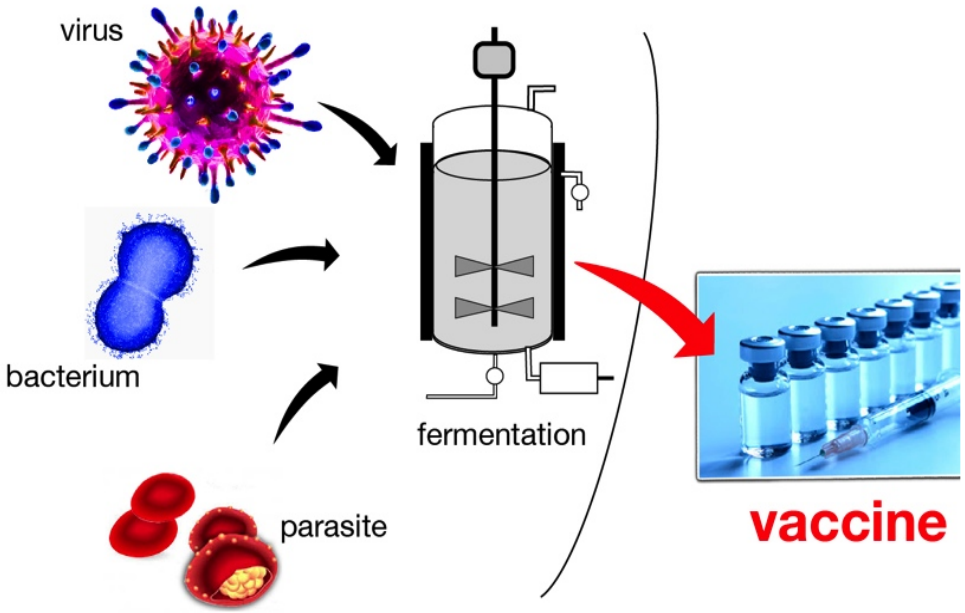
Schultz-Cherry S et al. MBio. 2014 Dec 12;5(6).

VACCINOLOGY

From Jenner to Pasteur to Hilleman

Isolate
Inactivate

CLASSICAL VACCINOLOGY
growing pathogens



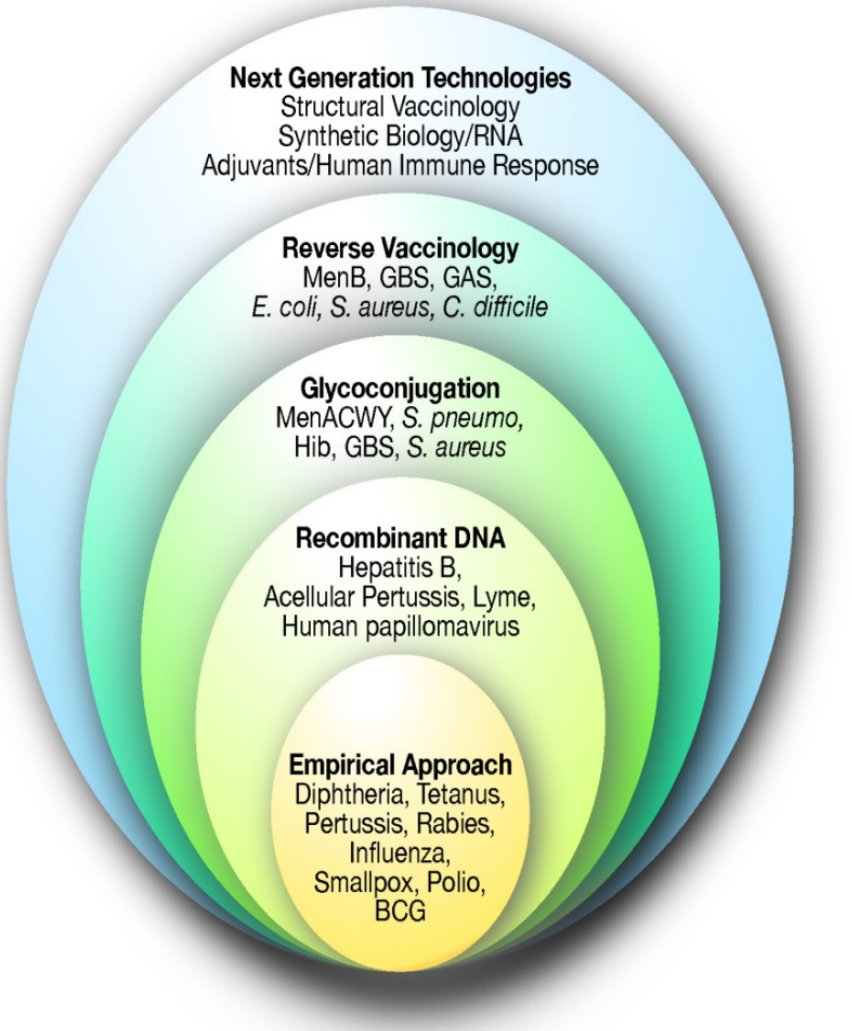

Gaston Ramon 1920


Jonas Edward Salk 1955

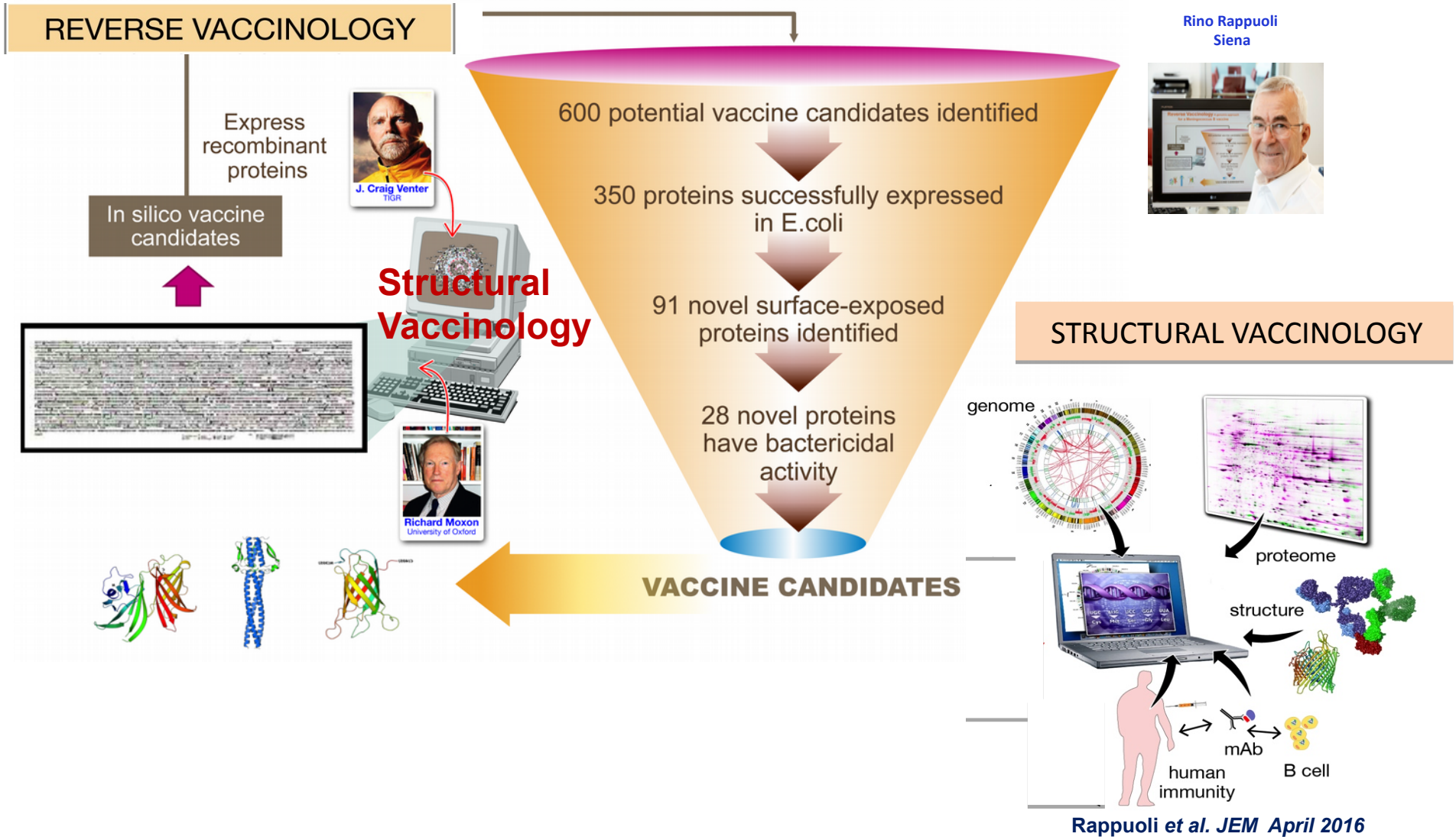

Albert Sabin 1963


Maurice Hilleman 1970

Evolution of Technologies for the development of Vaccines

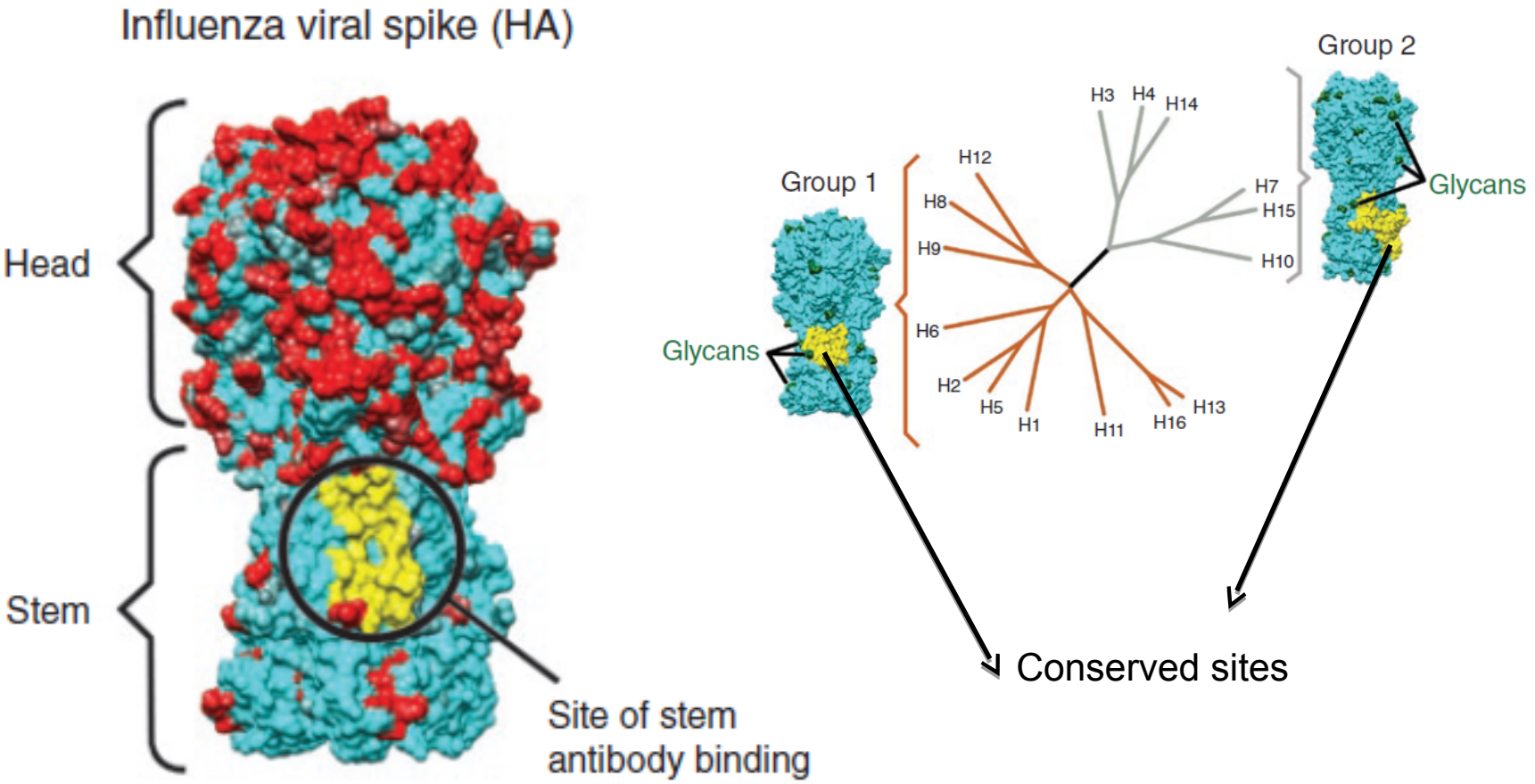


Reverse & Structural Vaccinology



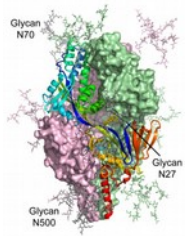
Rappuoli *et al. JEM April 2016*

Prospects for a broadly protective universal influenza vaccine

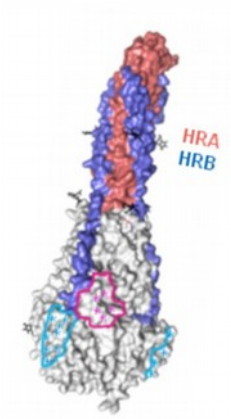


From: Nabel & Fauci, Nature Medicine (2010); Skehel et al., Cell 2016

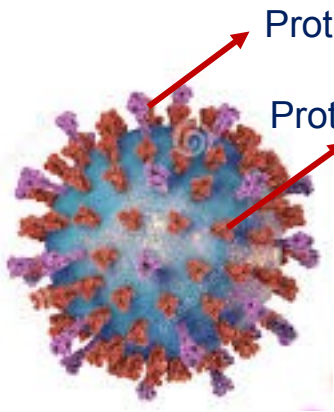
Structural Vaccinology
l'esempio di RSV

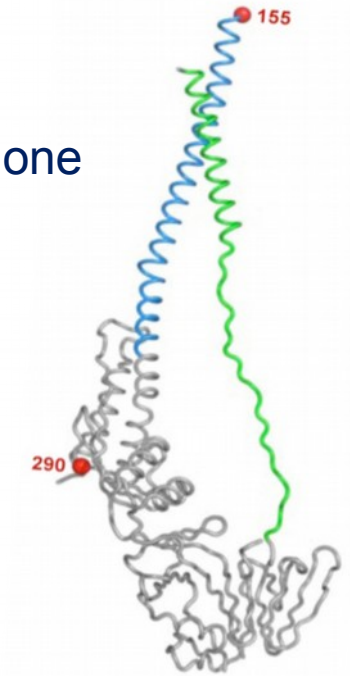


Pre-fusione

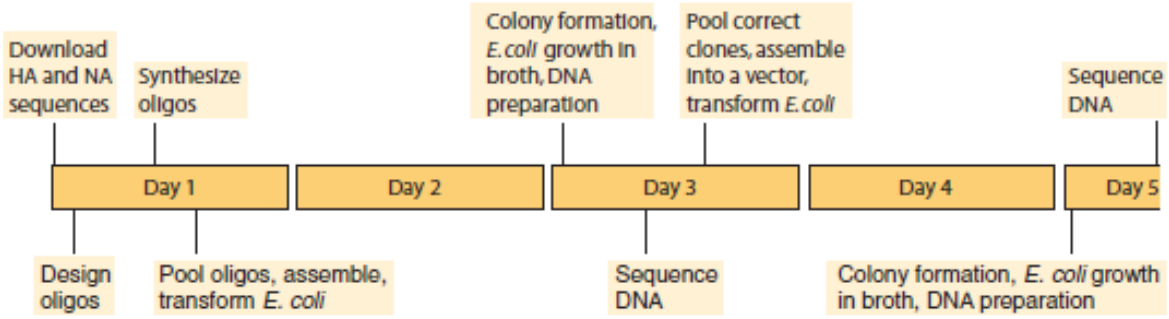


Post-fusione





Innovative approaches
Synthetic vaccinology



Dormitzer PR et al., Sci Transl Med. 2013 May 15;5(185):185ra68.

Conclusions

- Microbial products (nucleases, recombinases, repressors/promoters, vectors…) and mechanisms of gene transfer and repair in microbes made genetic engineering possible;
- Microbial and human genomes sequencing allowed to dissect the nature of many acquired and inherited diseases;
- Advanced molecular therapies based on genomic technologies are changing the face of modern medicine;
- Stem cell biology, cell reprogramming and genome editing are permitting to cure gene defects at the single nucleotide level while providing new tissues and organs;
- Refined new technologies of stem cell modifications allow to overcome many of the past ethical issues involved with manipulations of human embryos;
- New vaccines and drugs based on structural biology data are being developed to prevent and/or cure major threat like emerging infectious diseases.