Molecular biology in medical training

Department of Medical Biology

Content

Revolution in molecular biology

Revolution in molecular medicine

Our educational philosophy

Our training methods

1. Revolution in molecular biology in…

- understanding the biological processes
- the application of biological discoveries

in medicine, pharmaceutical industry, agriculture, etc.

Paradigm shift in medicine

Molecular biology vs. molecular genetics

Molecular biology

… is the branch of biology that deals with the molecular basis of biological processes. This field overlaps with other areas of biology, particularly genetics and biochemistry.

Molecular genetics

(1) A branch of biology

… examining biological processes at specific hierarchies of the biological organization. It studies the structure and expression of the genetic material and the structure and function of gene products including RNAs and proteins.

(2) A collection of techniques

… used practically, in all fields of biology.

New discoveries in the basic science

Cracking the human genome

Human variome projects

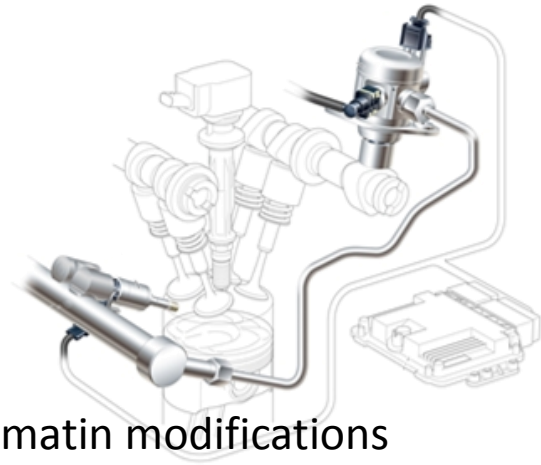
Non-coding RNAs

Gene networks control the body and mind

Phenotypic variation – regulatory variations

Surprises in epigenetic research

Technological innovations



Biotechnology

Optogenetics

Recombinant vaccines

Synthetic life

Techniques for the analysis of chromatin modifications

Metagenomics

Induced pluripotent stem cells

Nanomedicine

RNA interference

Real-time PCR

Gene therapy by viral vectors

Cloning

Chip technology

Recombinant gene technologies

3rd generation DNA sequencing

Bioinformatics – system biology

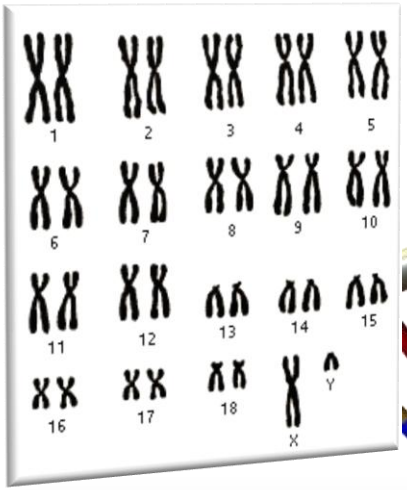
Herceptin

Conditional knock-out technologies

Genetic tools for the investigation of the structure and function of neural circuits

Genetically modified organisms: 1st, 2nd, and 3rd generations

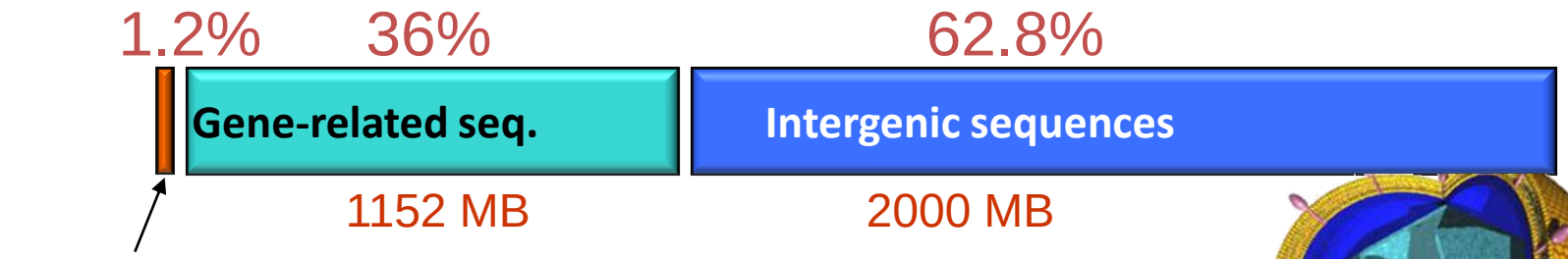
Cracking the human genome

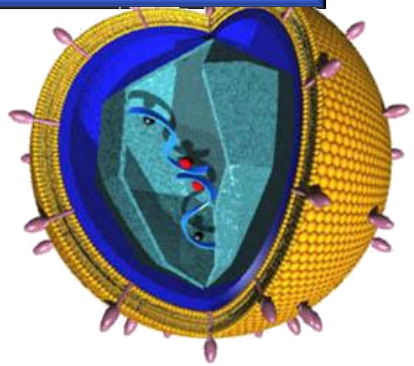


DNA: 3.2 Gbp

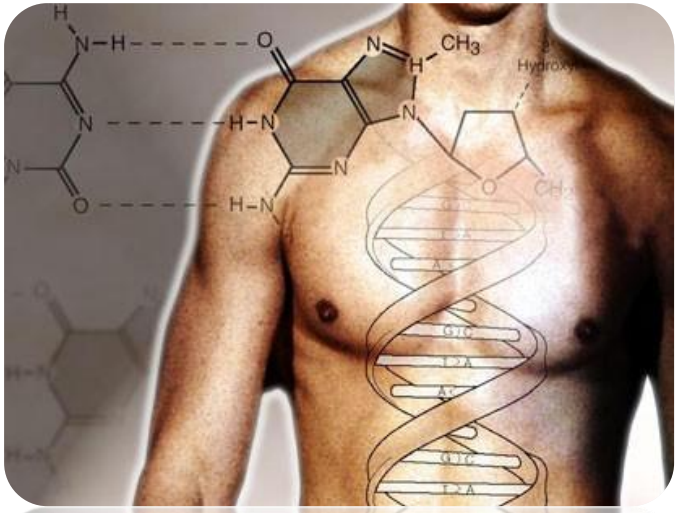
2001: draft version
2004: full version

The human genome is mostly made up of viral sequences





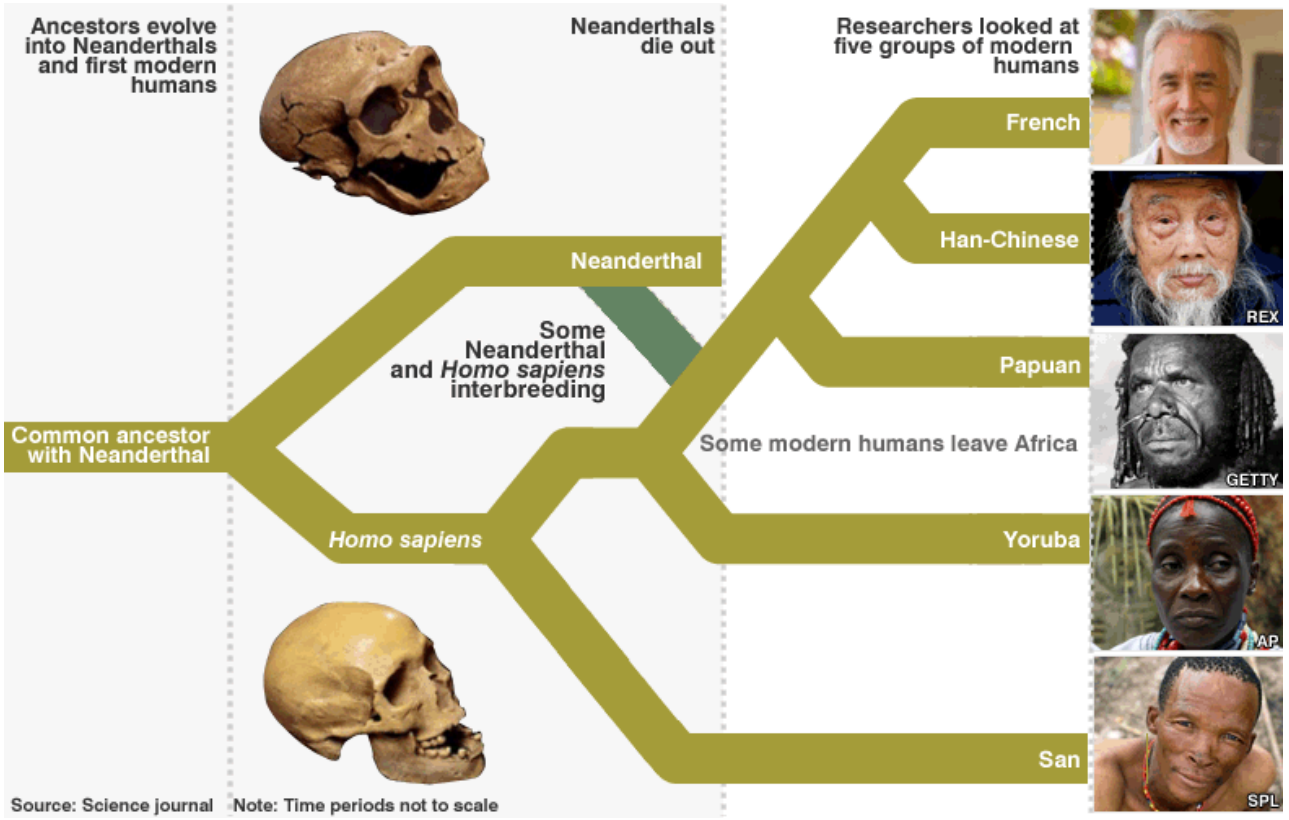
20,000 genes



Neanderthal genes

1-4% of human DNA is of Neanderthal origin

Svante Pääbo
paleogeneticist



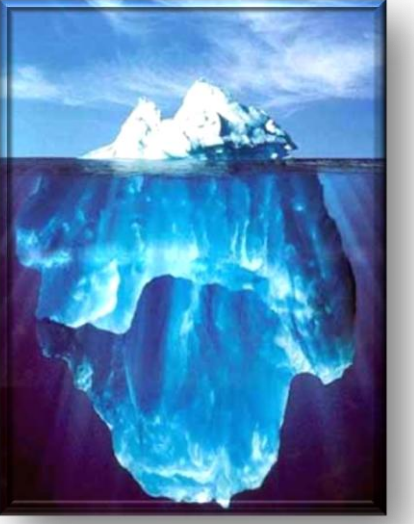
The Human Variome

1000 Genome Project
Hap Map Project
Genome-wide Association Studies
South African genomes

Comparison of individual genomes helps finding the genetic factors of common complex diseases

Personalized medicine

THE HUMAN VARIOME PROJECT



A new RNA World
- non-coding RNAs

Formerly known RNAs represent only the tip of an iceberg; new surprises are expected

(1) Discovery of entirely new RNA families– New RNA functions: regulation
(2) More than 90% of the human genome is transcriptionally active
(3) Multigenic transcription: more than one message on one mRNA strand
(4) Both DNA strands are transcribed in more than 70% of human genes
(5) Conservative non-coding regions (until now only in protein-coding genes)

The cell is an **RNA machine** rather than a protein machine

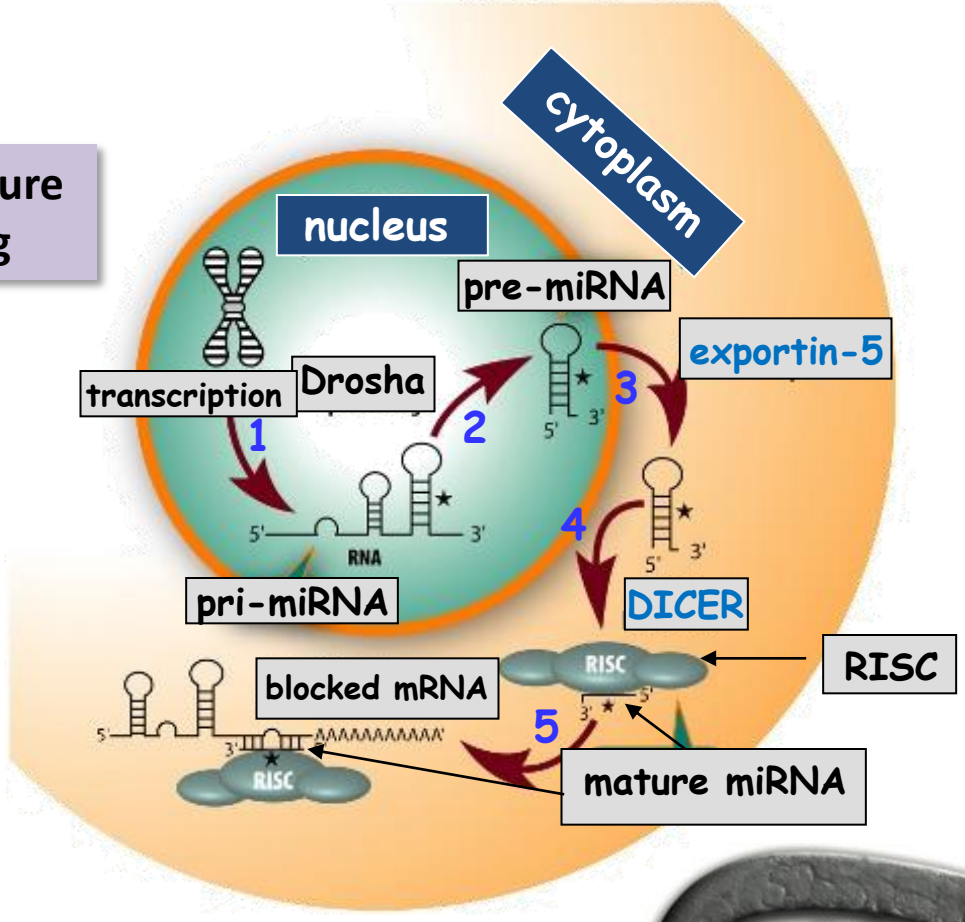
Victor Ambros

Micro RNAs

and other regulatory RNAs

Gary Ruvkun

Complementary structure
→ specific targeting



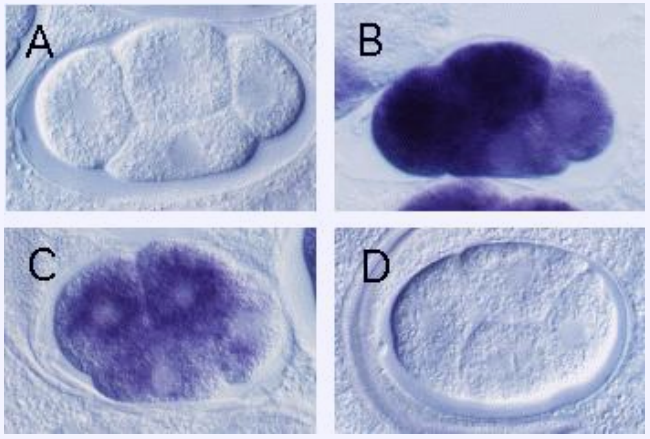
Caenorhabditis elegans

Discovered in 2000 *Lin-4 gén*


Andrew Z Fire; Craig C Mello

RNA interference

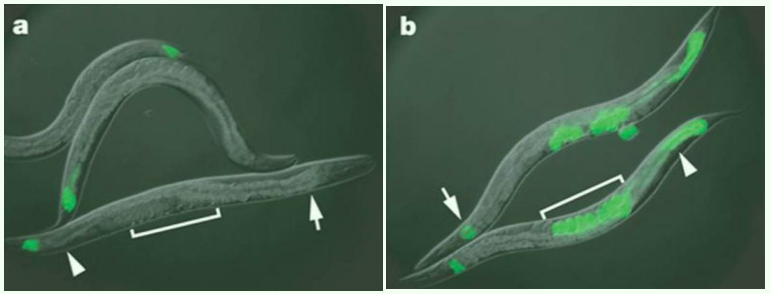
Non-stained non-injected



asRNA dsRNA

***gfp* gene** (as a transgene in E. coli)

Nutrition:
double-stranded GFP mRNA expressing E. coli

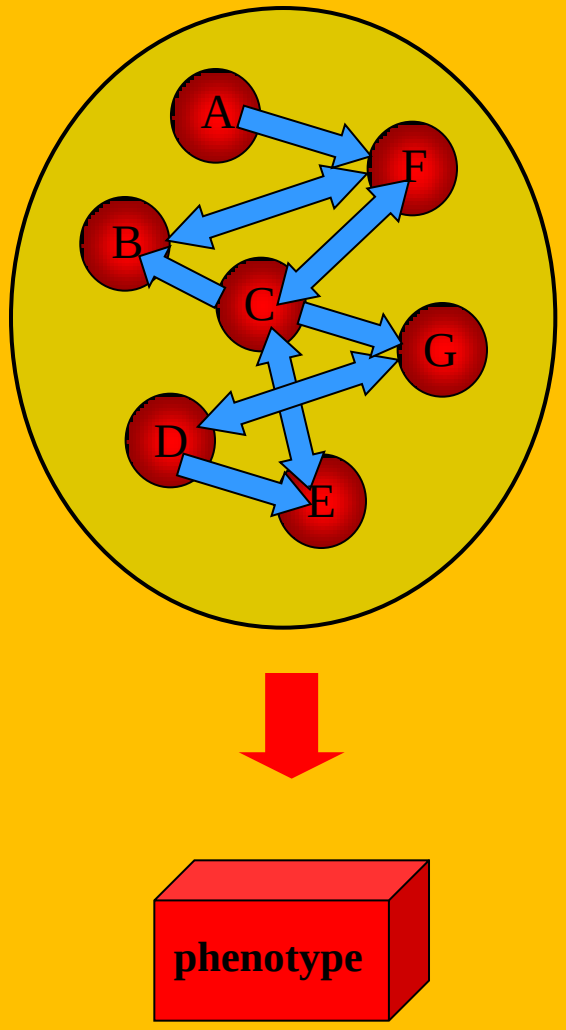


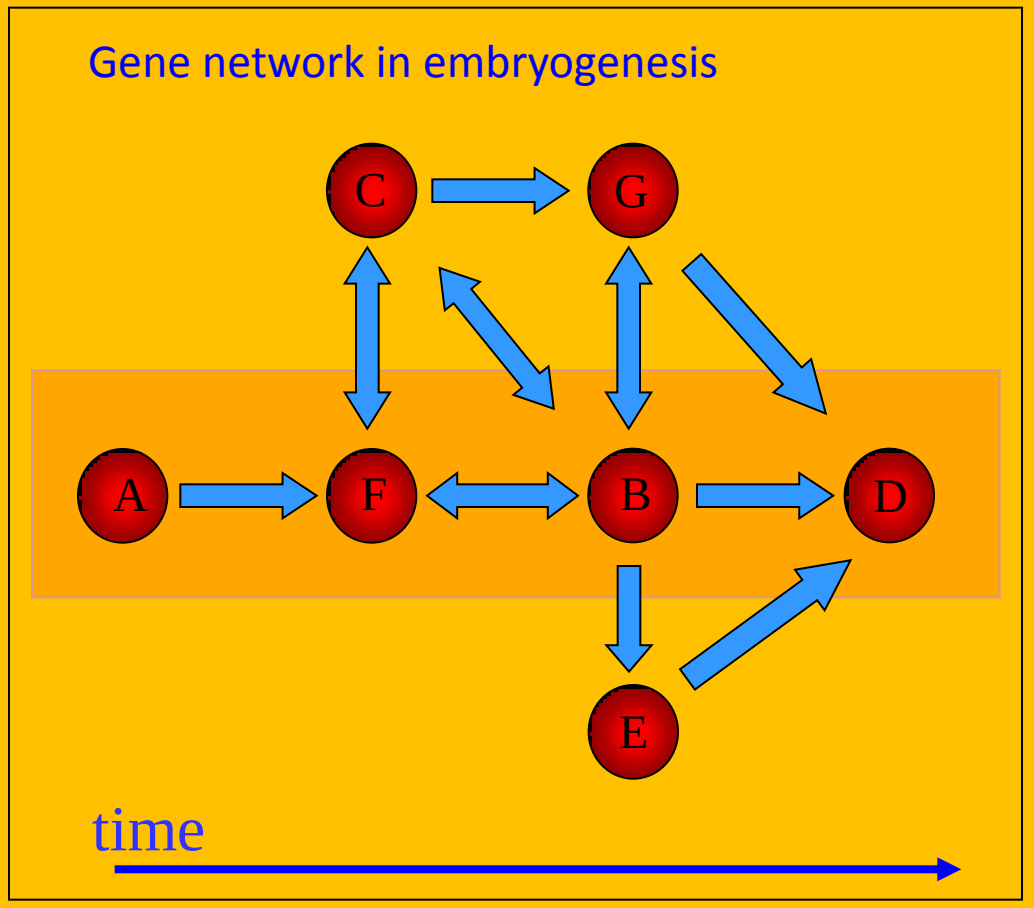
Wild type RNAi-defected strain

RNAi: degrading effect of double-stranded RNA on RNAs containing homologous sequences

Gene networks

- systems biological approach

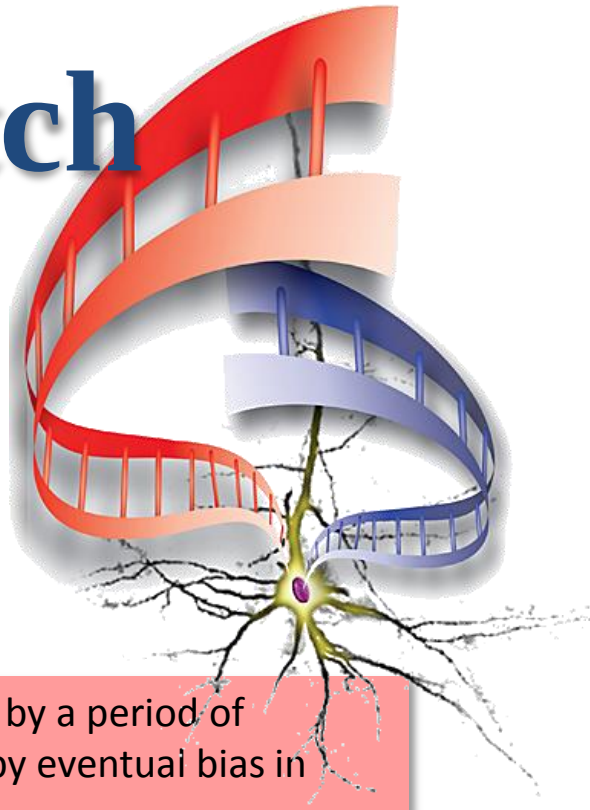




Gene network: assembly of functionally linked genes

Epigenetic switch

Epigenetic regulation & genetic imprinting



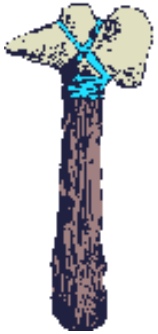
1. Genetic imprinting is wide-spread
2. Genetic imprinting is not for the whole life, it is flexible
3. Not only repression but tissue-specific gene expression
4. Differential parental effects
5. Lammarcian inheritance (?)

Maternal genes in predominate in the brain in fetal development, followed by a period of childhood where maternal and paternal genes tussle for control, followed by eventuai bias in favor of paternal genes during adulthood.

That is, sibling competition does not end at birth. It continues after birth, through competition for food, parental attention and so on -- and these behaviors are controlled by the brain.

Gene structure vs. gene regulation

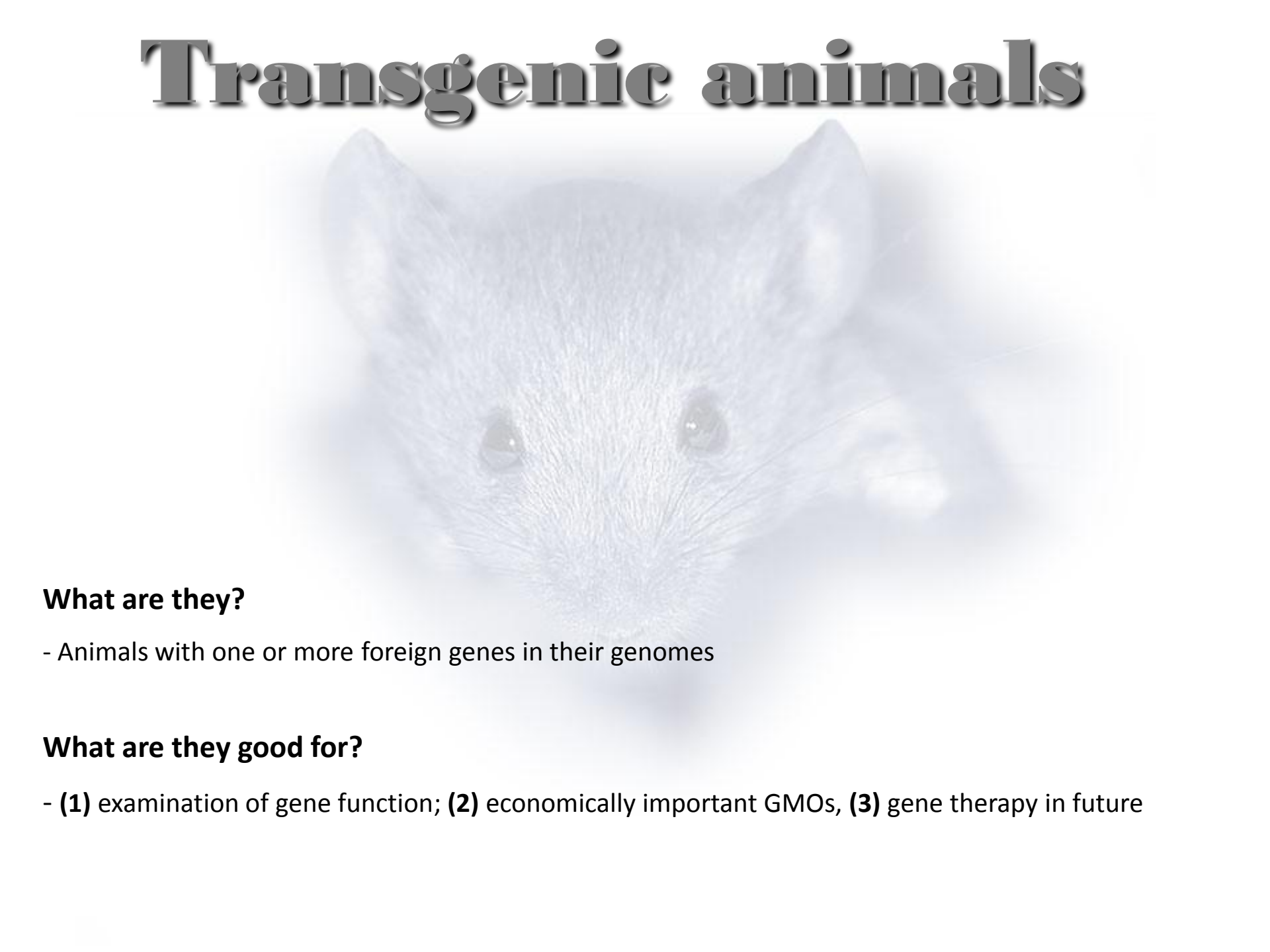
Have the genetic tools (genes) improved during evolution -or we work in a different way with the old tools?



Evolution

?

Transgenic animals



What are they?

- Animals with one or more foreign genes in their genomes

What are they good for?

- **(1)** examination of gene function; **(2)** economically important GMOs, **(3)** gene therapy in future

Knock-out animals

Investigation paradigm: the function of the knocked out gene is the reverse as the obtained phenotype

2007

Martin Evans Mario Capecchi Oliver Smithies

M. Evans: development of ES cell technology (ES cells are used for knock-out technology)

M. Capecchi & O. Smithies: homologous recombination:

- knock-out technology
- replacement of defected genes with functional ones: importance in medicine

Cloning

Reproductive cloning

Basic research: propagation of individuals with identical genotypes →
→ animals with identical genetic backgrounds provide more reliable results in scientific experiments

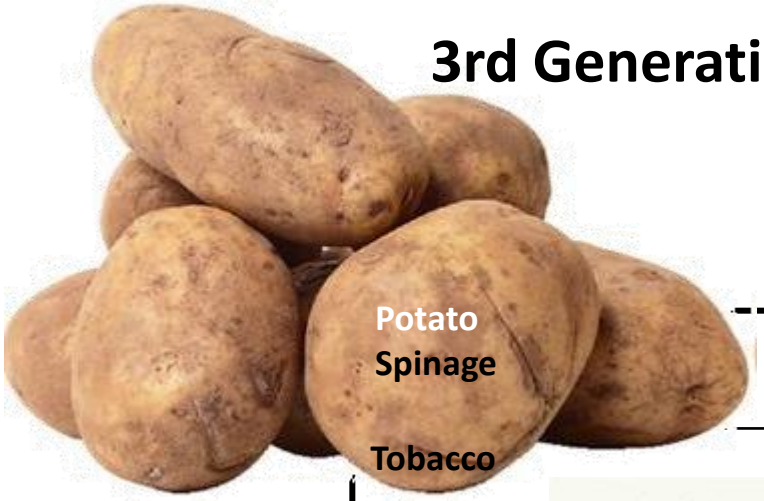
Agriculture: propagation of advantageous breeds. Danger: lack of genetic variablilty →
→ a pathogen can exterminate the entire breed or species

Therapeutic cloning

Medicine: propagation of cells identical with the donor → in the experiments we obtain useful information on the donor for his/her treating strategy (personalized medicine)

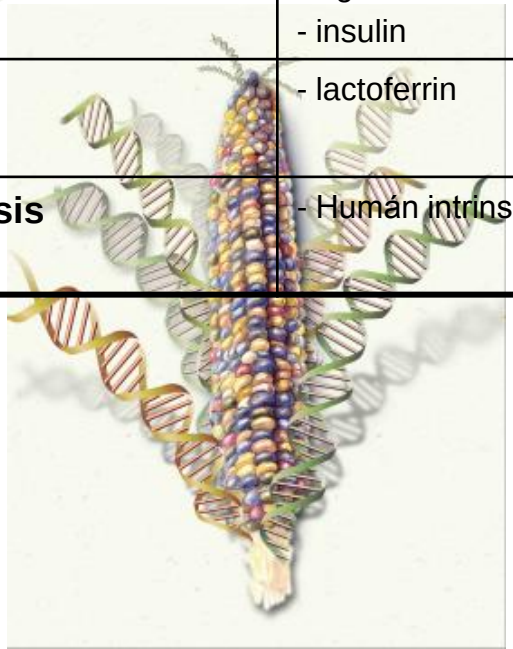
Genetically modified crops

3rd Generation GMOs: plant factories

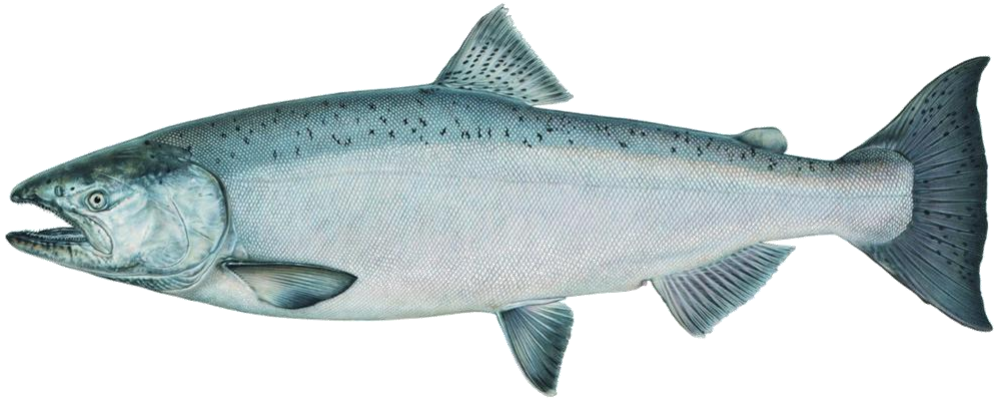


Arabidopsis

Potato Spinage	- Vaccine against hepatitis B - Vaccine against rabies
Tobacco	- Against caries - insulin
maize	- lactoferrin
Arabidopsis	- Humán intrinsic factor (against anemia)

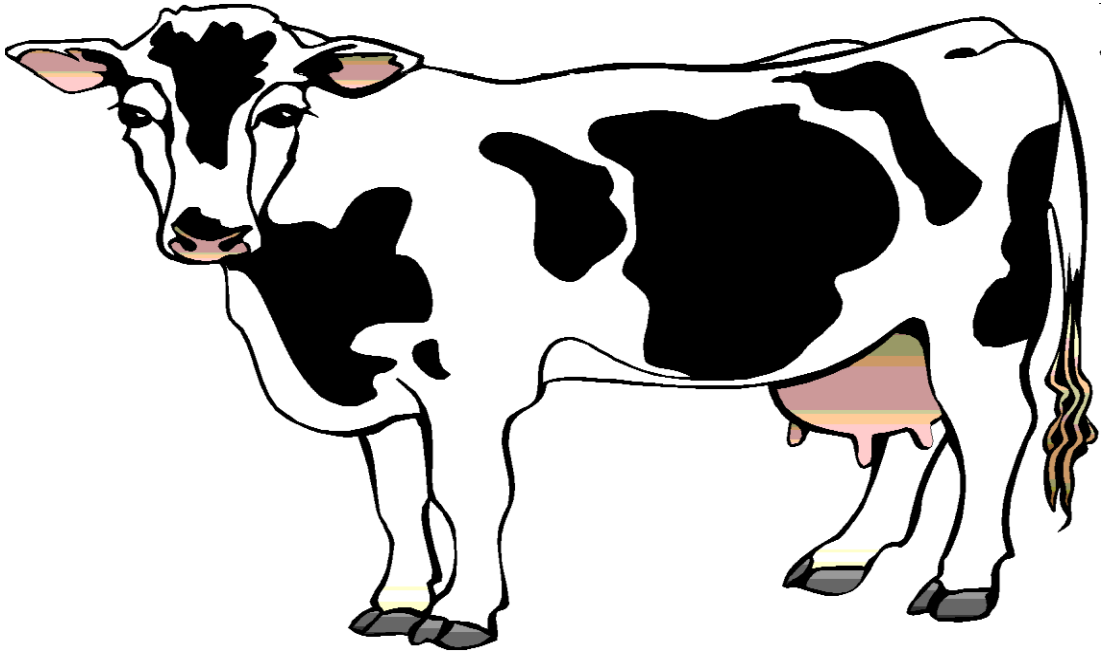


Genetically modified livestock



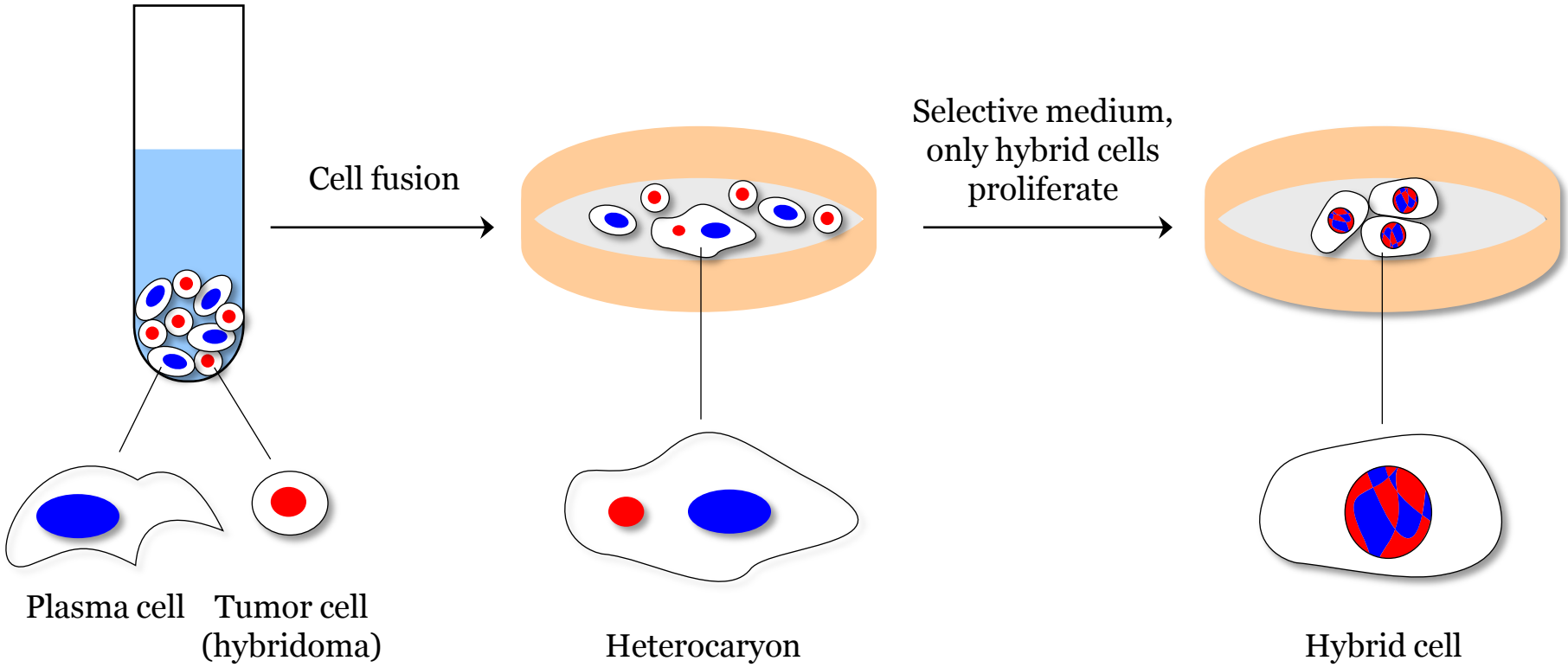
Transgenic salmon grows faster

Higher level of beta and kappa caseins in the milk of transgenic cow



Various human transgenes in pigs for transfer of liver to human

Monoclonal antibodies



2. Revolution in molecular medicine

Medical science & healing

Diagnostics

Therapy

Diagnostics

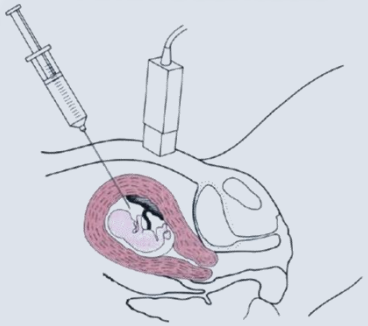
Genetic testing

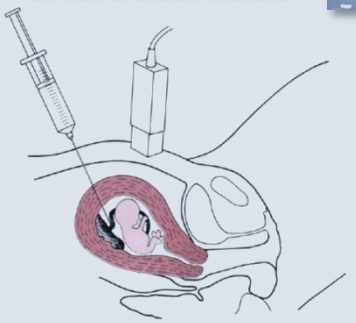
Medical genomics

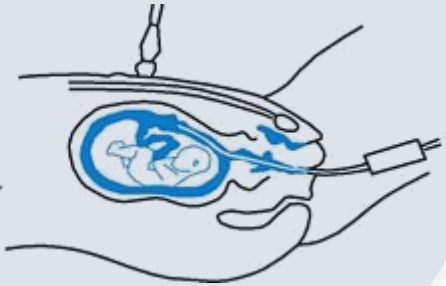
Translational medicine

Genetic testing

1. Newborn screening
2. Postconception diagnosis
   (= prenatal testing)
3. Preimplantation testing
   a. preimplantation genetic diagnosis
   b. preimplantation genetic screening
4. Carrier testing
5. Preconception testing







CVS: *chorionic villus sampling*

Medical Genomics

Genomics

1. Structural genomics
2. Functional genomics
   a. transcriptomics
   b. proteomics
3. Integrative genomics, e.g.
   a. Comparative genomics
   b. Metabolomics
   c. *In silico* genomics (bioinformatics)
   d. Pharmacogenomics
   e. Nutrigenomics
4. Epigenomics

Analysis of the structure of DNA: ascertaing of base order; mapping of SNPs and other markers, investigation of genetic disease factors

Expression of RNAs (a) or proteins (b) in a cell, tissue or organism

Associations between macromolecules **(a)** of different species; **(b)** Mapping of metabolic networks; **(c)** with bioinformatics; **(d)** or relationship between genetic variance and drug effect

Variability in DNA methylation and histon modifications between cell types at the level of whole-genome.

Trends in medical genomics

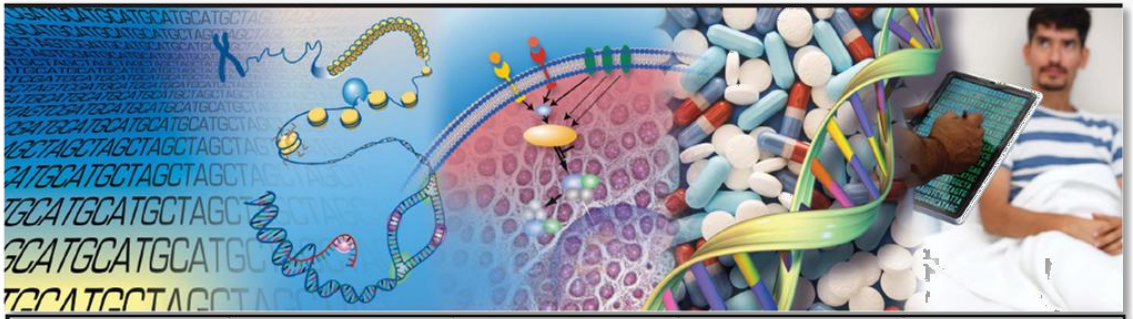
Understanding the structure of the genome

Understanding the biology of the genome

Understanding the Biology of the diseases

Advancing in the science of medicine

Improving the effectiveness of healthcare

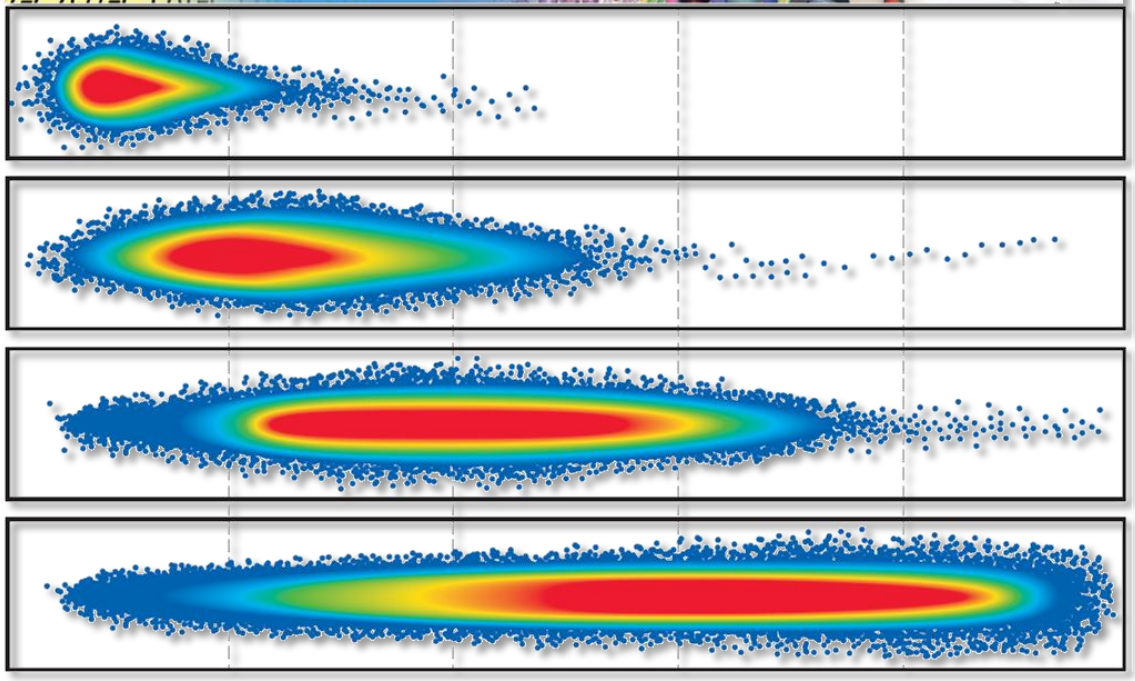


1990-2003
Human Genome Project

2003-2010

2010-2020

Beyond 2020

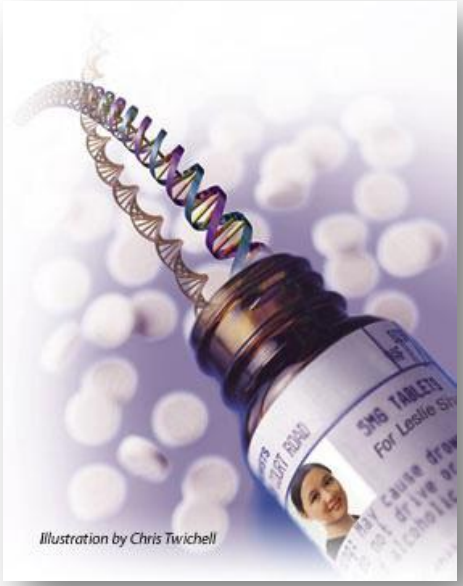


progression from base pairs to bedside

Personalized medicine

1. **Testing of traditional drugs for inidividual use**
2. **New type drugs:** DNA, RNA, proteins, antibodies, stem cells

Sequence-specific drugs:
Individual-specific

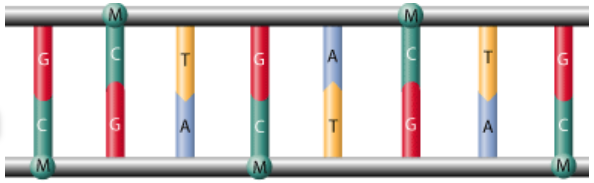


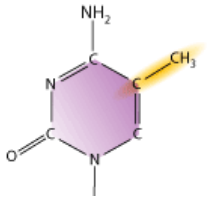
Human Epigenome Atlas

Epigenomics

Epigenomics is the fusion of epigenetics and genomics investigating genetic regulation at the level of whole gene.

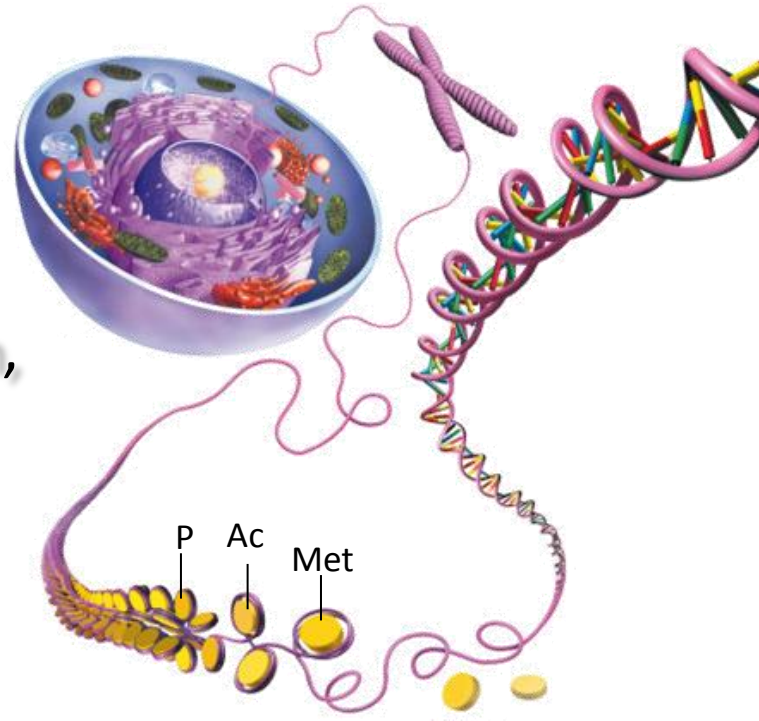
1. DNA methylation



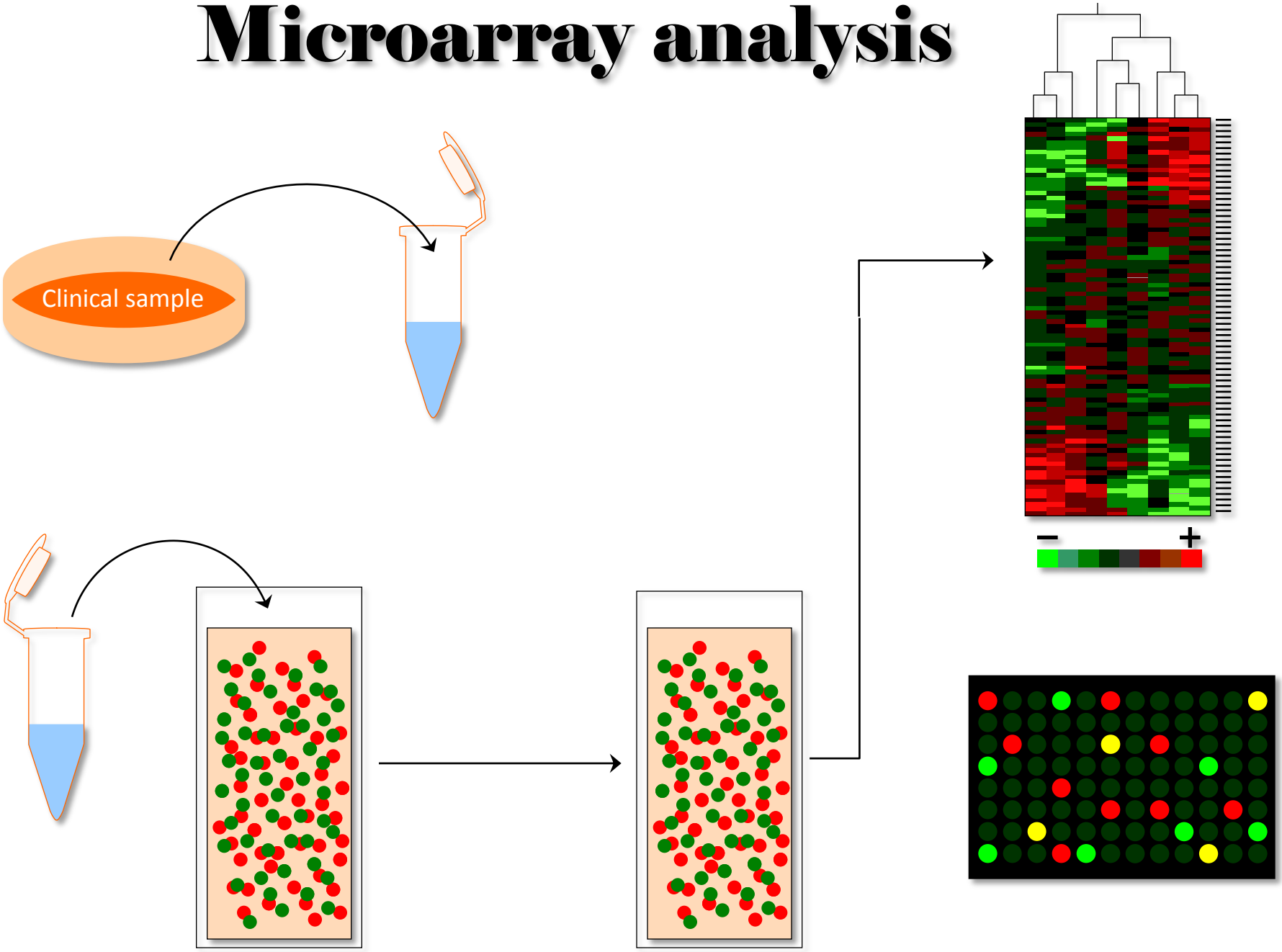


2. Histone modification:

- methylation, acetylation, phosphorylation, sumoilation



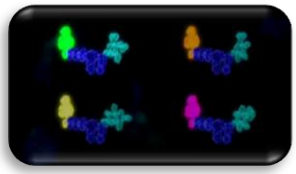
Microarray analysis



Real-Time-PCR

- Used to amplify and simultaneously quantify a targeted DNA molecule
- Detection of fluoresce at each cycle during PCR reaction → Real-Time
- No gel-based analysis at the end of the PCR reaction
- Computer based analysis of the cycle fluorescence time course

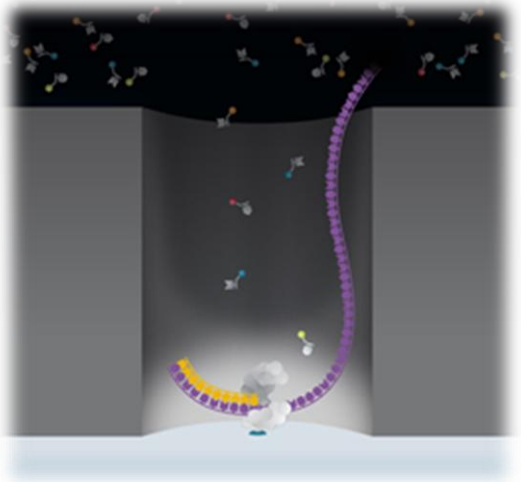
Real-Time PCR cycler



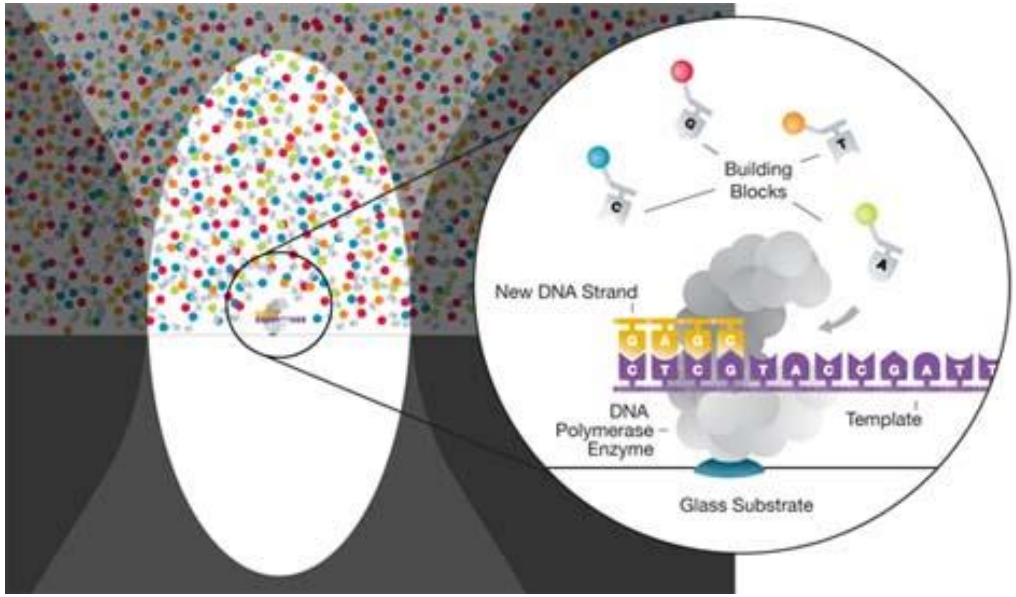
SMRT

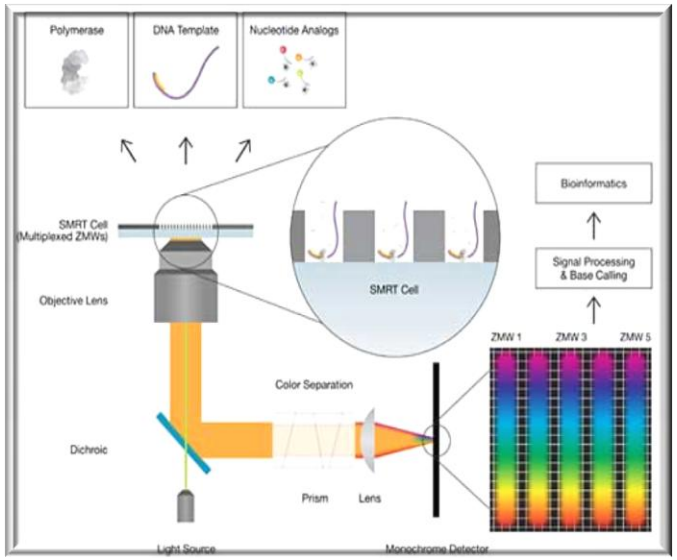
Single Molecule Real-Time Technology

Third-generation sequencing



100$/genom/~15min





Therapy

Immunotherapy

Cell replacement therapy - Regenerative medicine - stem cell technology

Nanotechnology

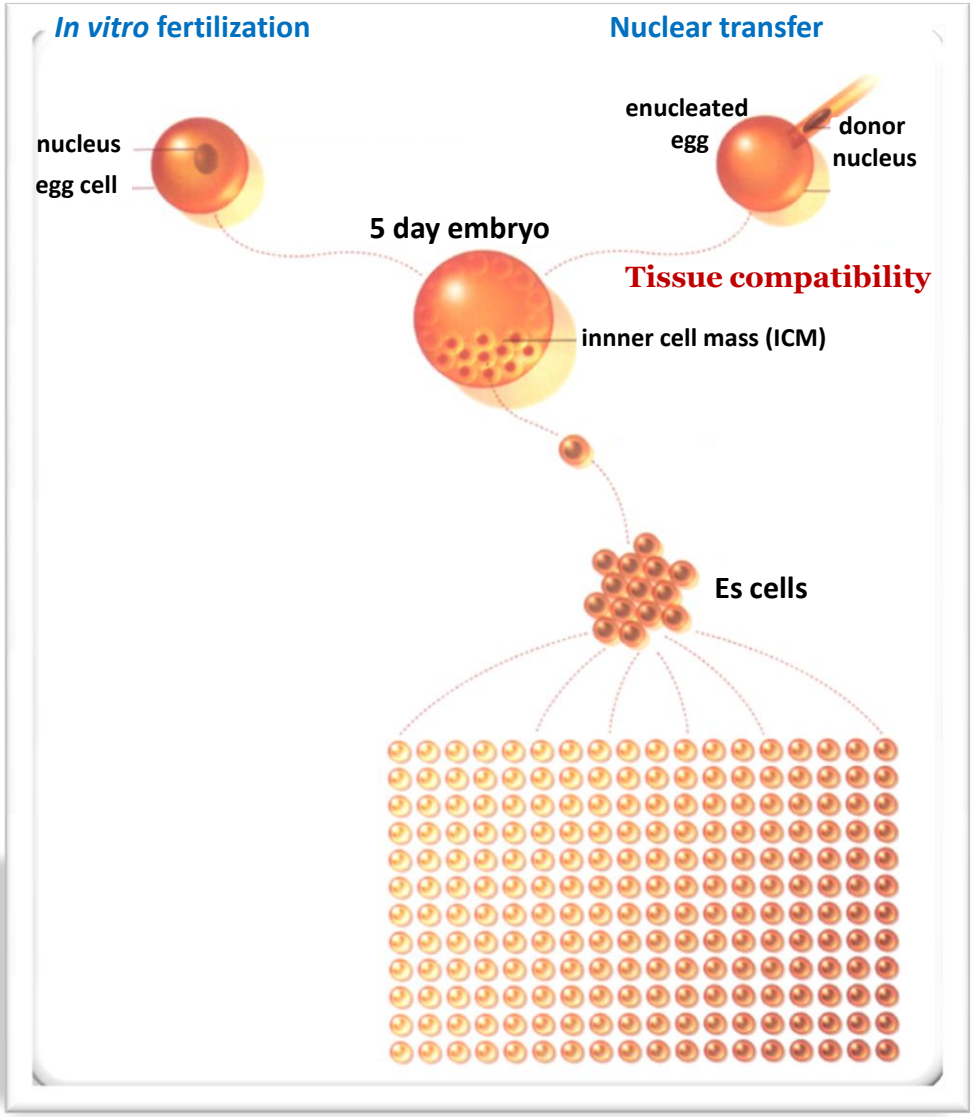
Gene therapy

Tumor therapy

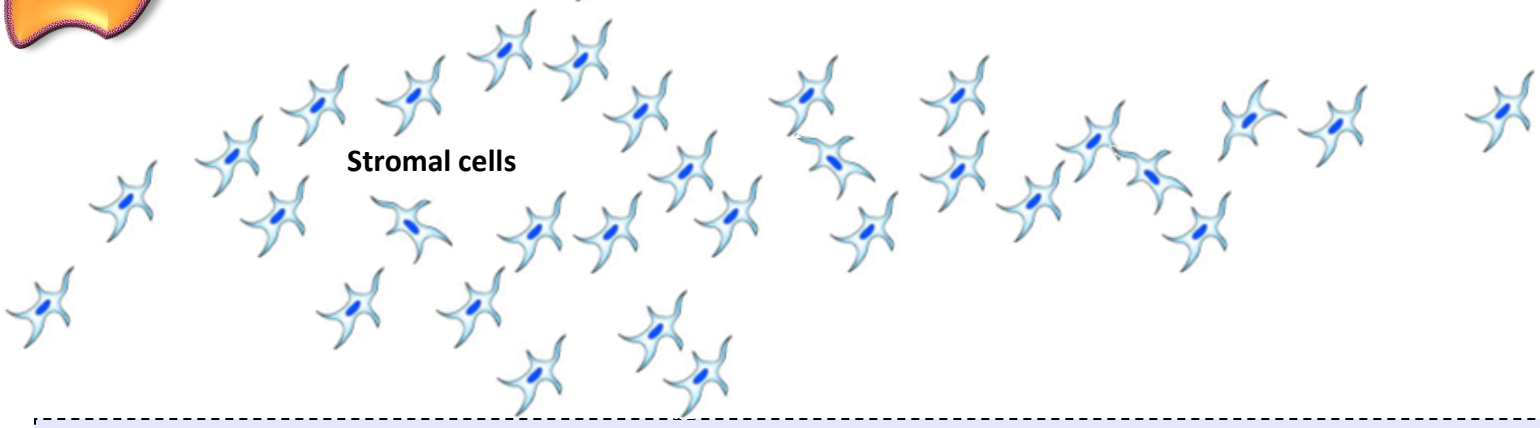
Gene therapy

1. Germline gene therapy
2. Somatic gene therapy

ES cells


In vitro fertilization
Nuclear transfer
nucleus
egg cell
enucleated egg
donor nucleus
5 day embryo
Tissue compatibility
innner cell mass (ICM)
Es cells

Adult stem cell plasticity



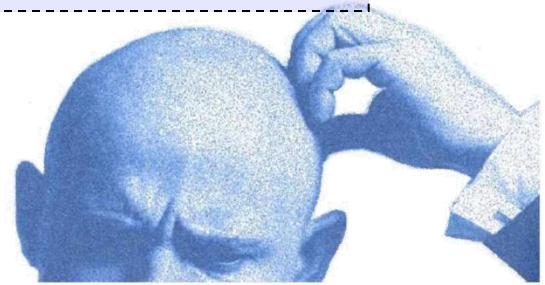
Mesenchimal stem cells (MSC; stromal stem cells)

-Not only structural role, but a role in tissue regeneration, too.

Sources:

- Bone marrow, umbilical cord blood, fat tissue

Doubts: it is possible that stromal cells only fused with other cell types instead of differentiating to other cell types.

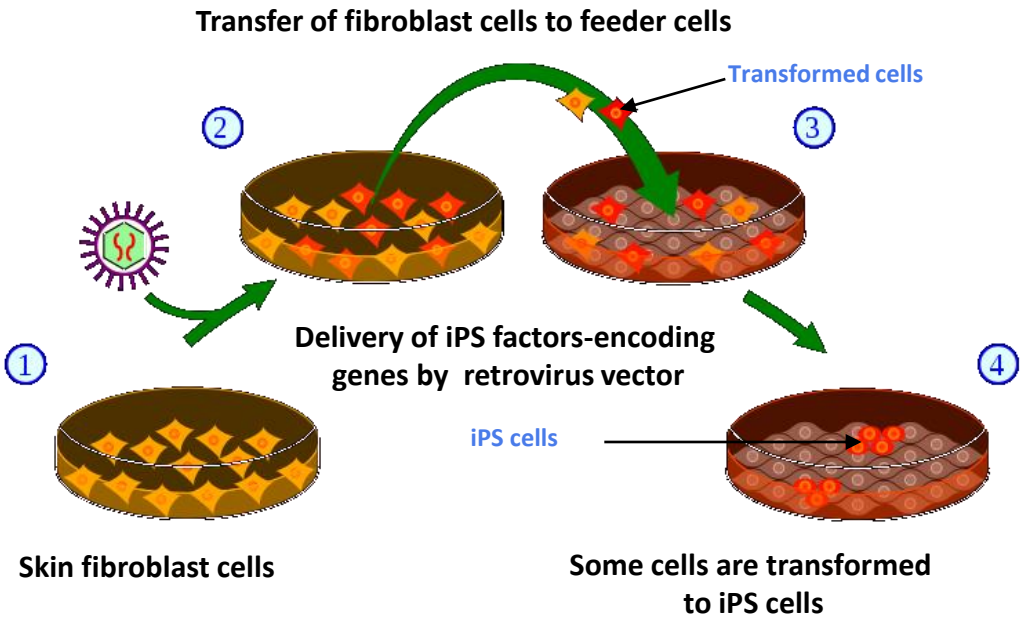


MSC: mesenchymal stem cells = marrow stromal cells

Genaration of iPS cells

- by reprogramming body cells

Cell reprogramming

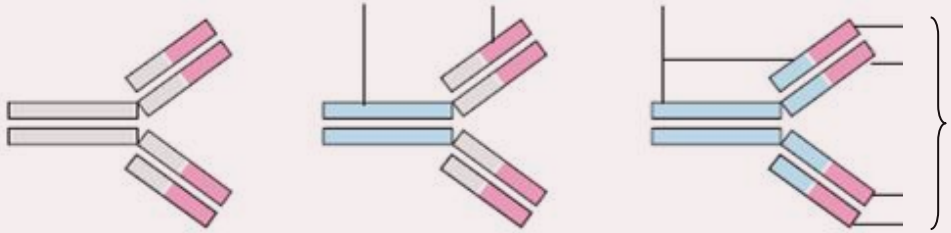


Mouse iPS cells (2005)

Shinya Yamanaka

iPSC: **i**nduced **P**luripotent **S**tem **C**ells

Antibody therapy of cancer



Herceptin

Only variable sequences are mouse

against HER2

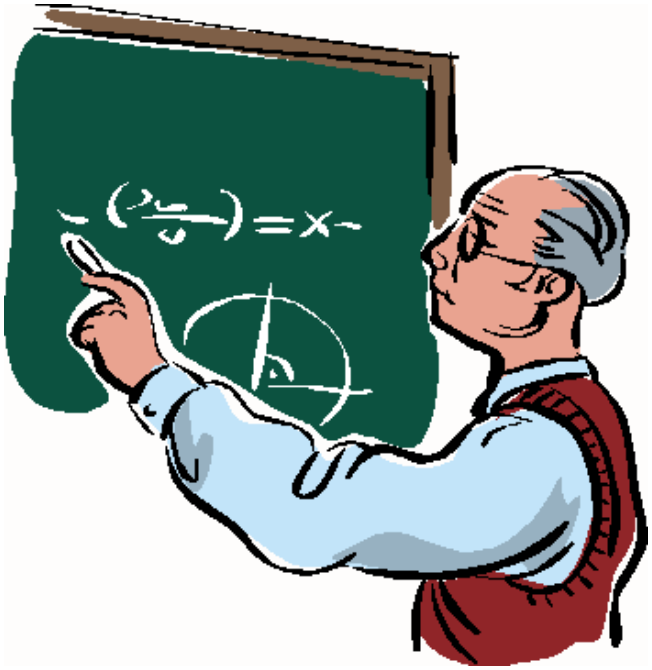
3. Our educational philosophy

Principles

1. Modern and relevant knowledge
2. Providing learning materials for the students
3. Students are treated equally and fairly
4. A professor uses his power for helping students and not for ruling over them
5. Allowing students to evaluate and give feedbacks on our work
6. Talented students and weak learners need extra attention

4. Our training methods

1. Appropriate curriculum
2. Priority of motivation over constraints
3. Two-level requirements
4. Problem-centric lectures and learning materials
5. Interactive education
6. The lecturer has to be aware the latest developments
7. Details vs. global perspectives
8. Studying facts vs. thinking in alternatives



Career opportunities for a student graduated as a medical doctor

Researchers

No. 1 Medical doctors

Medical doctors often do research

Lecturers of medicine

The importance of molecular biology for a being medical doctor

1. **Background knowledge**:

- to understand health and disease states

2. **Clinical tools**:

- in diagnostics

- and therapy

Department of Medical Biology

Our courses

Compulsory courses: Cell Biology and Molecular Genetics

Elective courses:

Basics of Molecular Biology
Frontiers of Molecular Biology
Genetic Analysis
Medical Molecular Biology and Genomics
Developmental Genetics

Cell Biology and Molecular Genetics

1st Semester

1. Origin of Life & the Basics of Cell Biology
2. DNA
3. RNAs & Proteins
4. Cell Cycle, Cytoskeleton & Cytogenetics
5. Transport Processes
6. The Human Genome
7. Genetic Regulation & Epigenetics
8. Inheritance
9. Genes and Phenotypes
10. Evolution
11. Viruses
12. Bacteria
13. Technological Arsenal of Molecular and Cell Biology
14. Selected Topics in Biology

2nd Semester

15. The Basics of Cell Communication
16. Complex Cell Signaling Pathways
17. Neural Communication*
18. Genetic Regulation of Embryogenesis
19. Immunogenetics
20. Genes and Behavior
21. Biotechnology & Recombinant Gene Technology
22. Frontiers of Molecular Biology
23. The Molecular Biology of Cancer
24. Chromosomal Disorders
25. Molecular Biology of Diseases
26. Molecular Biology of Brain and Mind Disorders
27. Molecular and Stem Cell Therapies
28. Medical Genomics

*Dentist students: Genetics of Tooth Diseases and Molecular Biology of Tooth Development

Key word: motivation

1. Interesting topics and lectures
2. Rewards, instead of penalties

Rewards:

(bonus points and other premiums)

(1) attendance at lectures
(2) attention to the lectures
(3) activity in practices and seminars
(4) good MTO grades

Penalty:

(1)failed MTO(s)

Two-level requirements

1. Basic knowledges – basic requirements

2. The newest results – extra requirements

Problem-centric lectures and learning materials

Creativity vs. swotting

Interactive education

- at the lectures, seminars and practices
- Forum