유전자 가위와 우리의 미래

송 기 원

연세대학교 생화학과

인류의 위험한 실험...신의 섭리에 도전하는 `디자인 베이비`

World's first gene-edited babies created in China, claims scientist

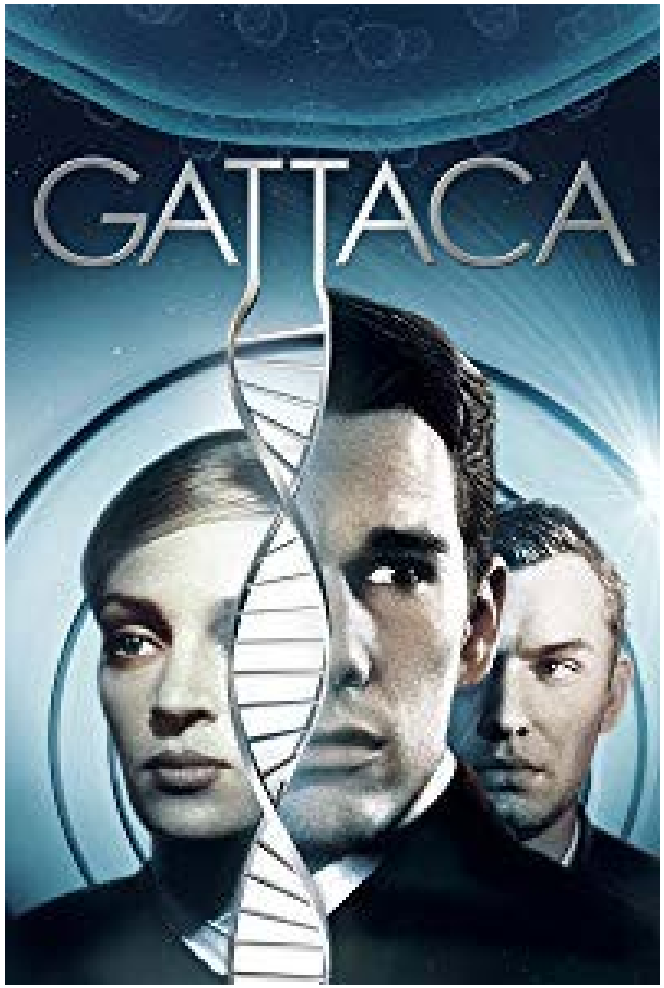
Unconfirmed scientific breakthrough sparks ethical and moral concerns

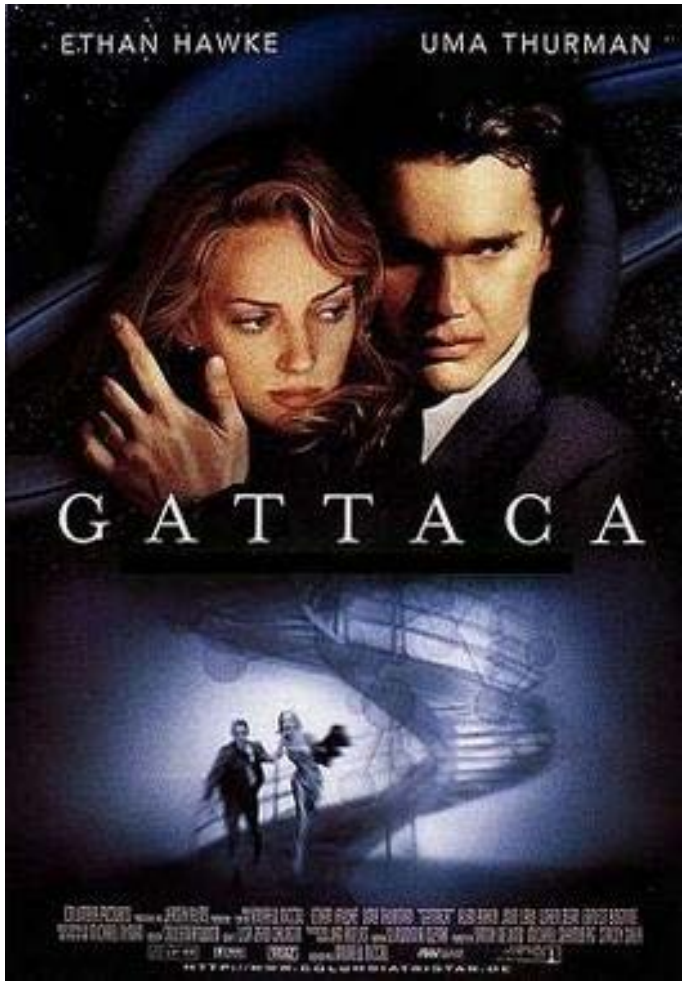
2018년 11월,

국제 인류유전자편집회의

가타카

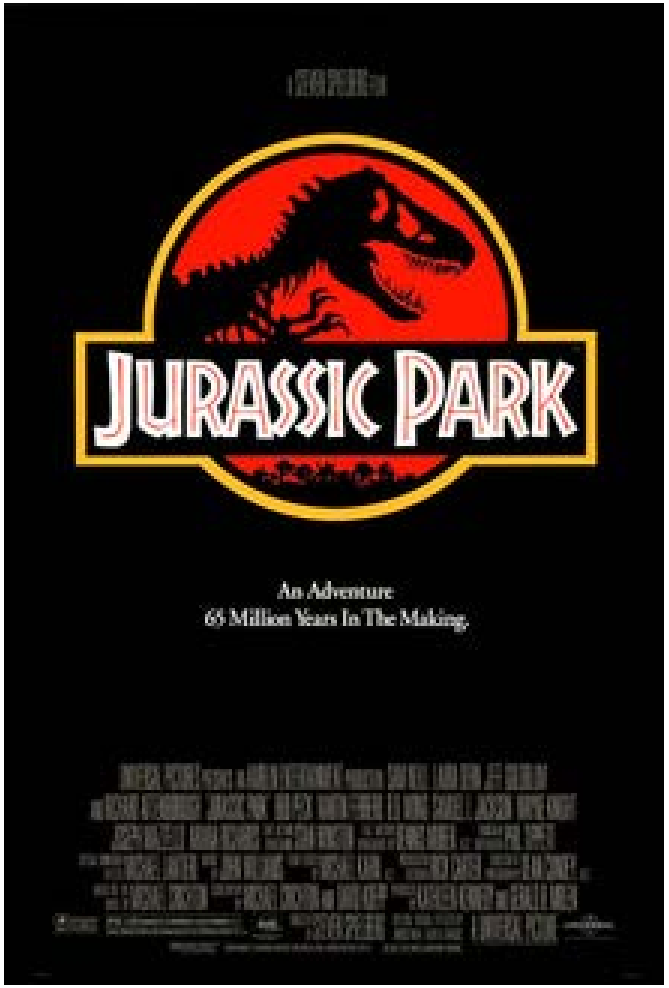
- Novel “Brave New World” in 1931 by Aldous Huxley
- Movie in 1997 by Andrew Niccol





쥬라기 공원

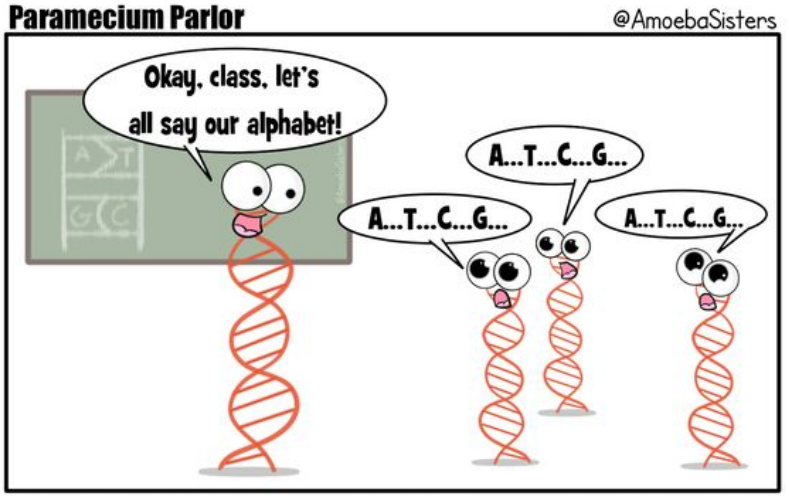
- novel in 1990 by Michael Crichton
- movie in 1993 by Steven Spielberg

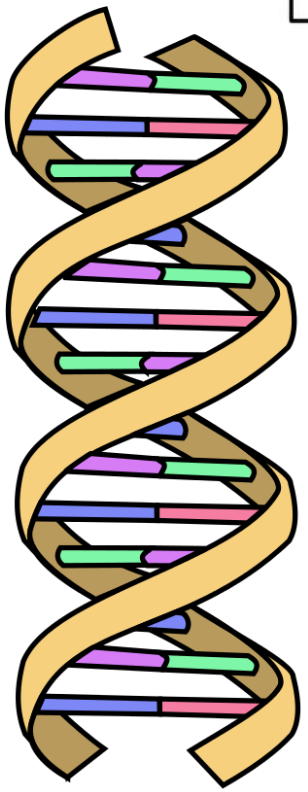


우리가 만들어 지는 정보는?

"콩 심은 데 콩 나고 팥 심은 데 팥 난다"

생명의 정보: DNA





DNA

= Adenina

= Timina

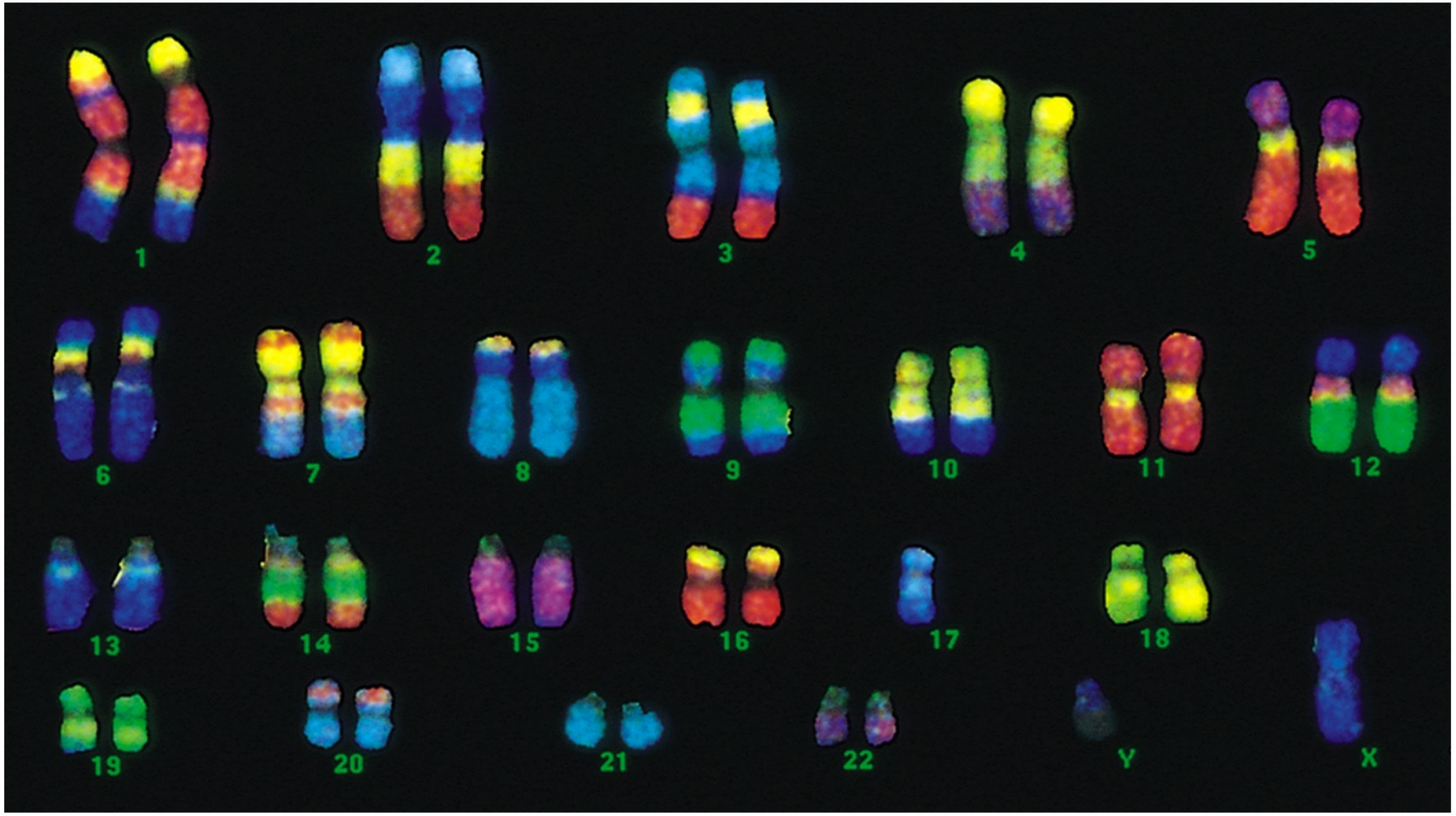
= Citosina

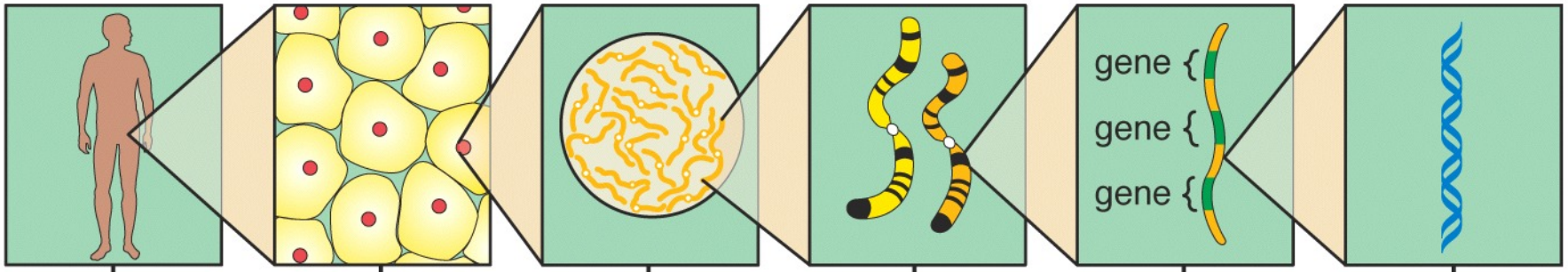
= Guanina

= Struttura laterale (gruppo fosfato e 2-deossiribosio)

1953년 DNA 이중나선 구조 발견

인간 23쌍 염색체





Organism (human)

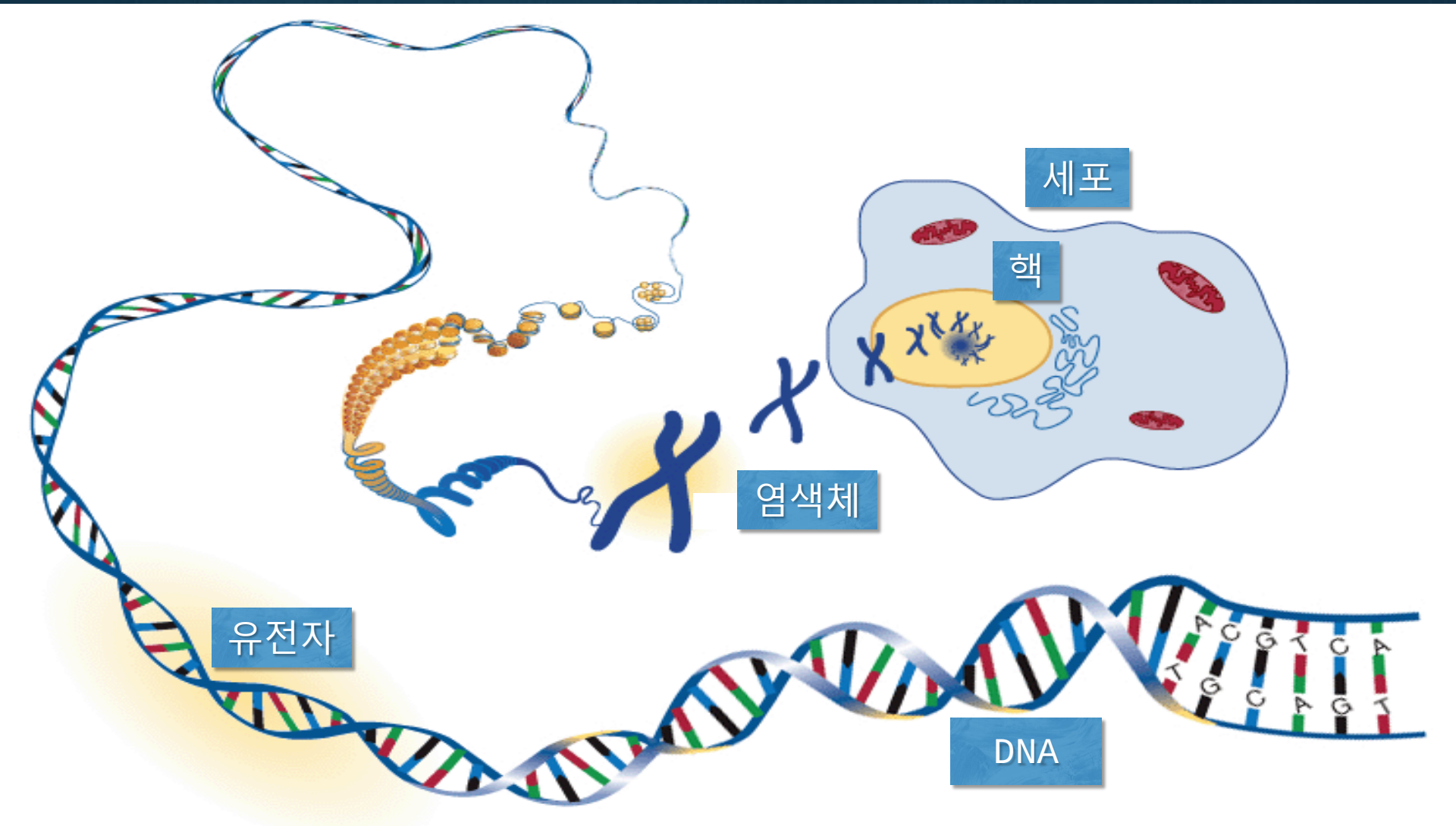
A human body is made up of trillions of cells.

Each cell nucleus contains an identical complement of chromosomes in two copies. Each copy is a genome.

One specific chromosome pair

Each chromosome is one long DNA molecule, and genes are functional regions of this DNA.

DNA is a double helix.


세포
핵
염색체
유전자
DNA

- 지구상 모든 생명체 유지의 기본 원리

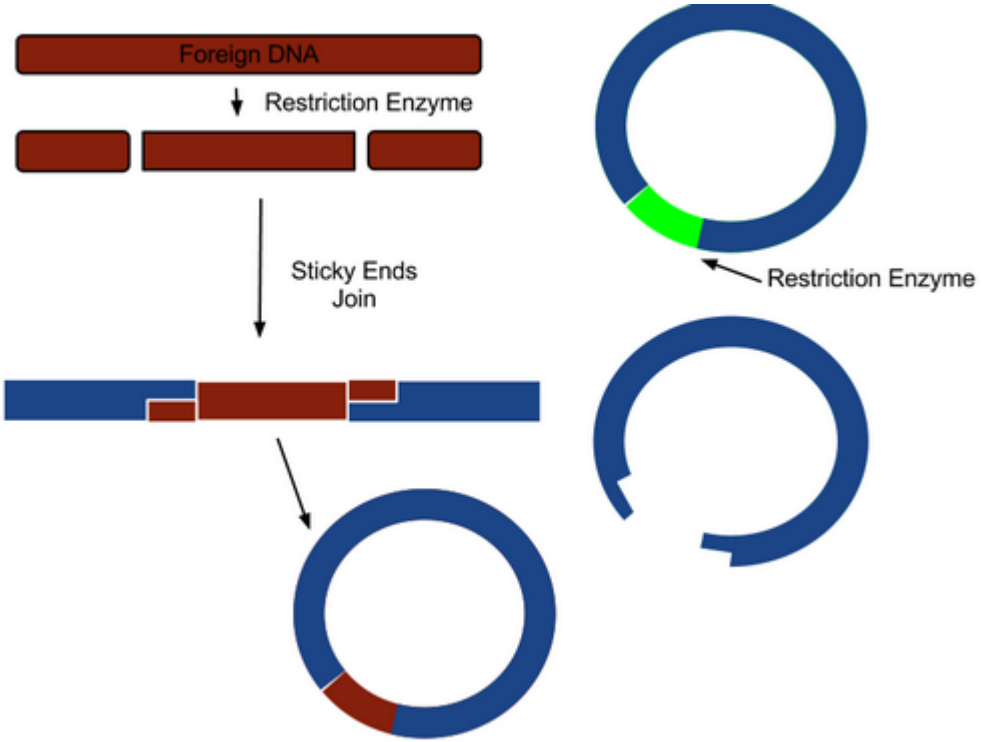
유전자

DNA ⟶ mRNA ⟶ 단백질

정보 실행자

DNA 가위와 biotechnology

- 1970년대 restriction enzyme (제한효소)의 발견 -> 유전자 재조합 (DNA recombinant technology) 가능
  - 다양한 GMO 가능한 유전공학 시대로



유전공학

값비싼 치료제를 싼 값에

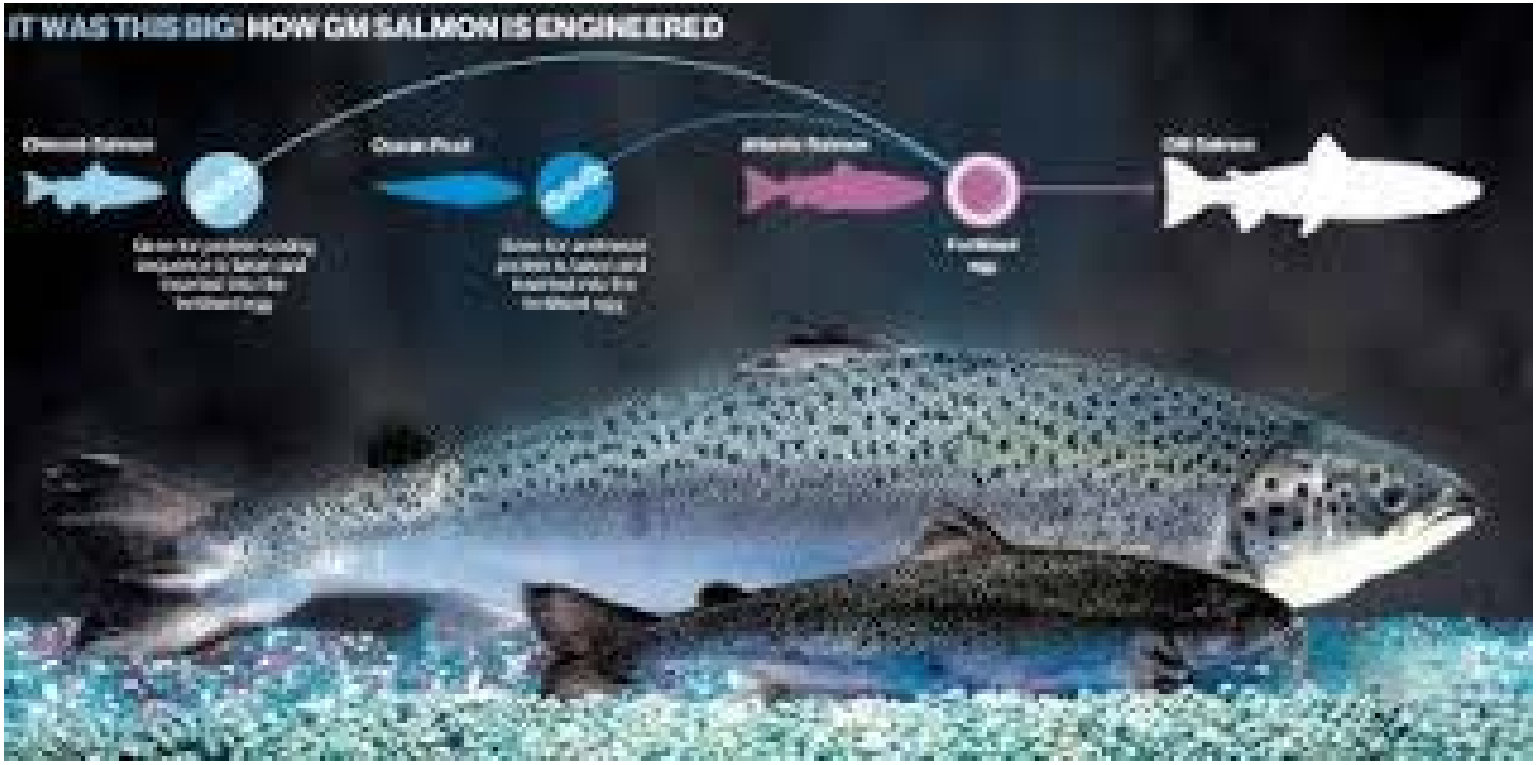
- 당뇨병 치료제 인슐린
- 항바이러스제 인터페론
- 성장촉진제
- 혈전치료제

유전자 변형 생물체: GMO

1990년대 부터 시장으로

동물 GMO 연어

2015년 11월 26일 미 FDA 최초 승인



더 많은 GMO 동물 개발 중

Heredity

Thomas Hardy
(1840-1928)

I am the family face;
Flesh perishes, I live on,
Projecting trait and trace
Through time to times anon,
And leaping from place to place
Over oblivion.

The years-heired feature that can
In curve and voice and eye
Despise the human span
Of durance -- that is I;
The eternal thing in man,
That heeds no call to die

내가 바로 가문의 얼굴이다,
육체는 슬슬 닳아버리나, 나는 살아남으니까,
불쑥 튀어나온 굴곡이며 흔적이며
까마득한 시간에서 이 근처 시간까지,
멀찍한 장소를 불쑥 건너뛰며,
망각을 훌쩍 넘으며 말이다.
세월이 유산이라고 물려준 이 관상,
휘어진 모양새나 목소리나 눈알 모양이나
인간이 헤아릴 시간의 거리를
경멸하는 게, 그게
바로 나다, 왜,
인간 속에 영원한 그것,
이제 그만 죽으라는 명령에도 아랑곳 않는
그것 말이다.

(연세대학교 영어영문학과 윤혜준 교수 번역)

인간 유전체 Human Genome 프로젝트

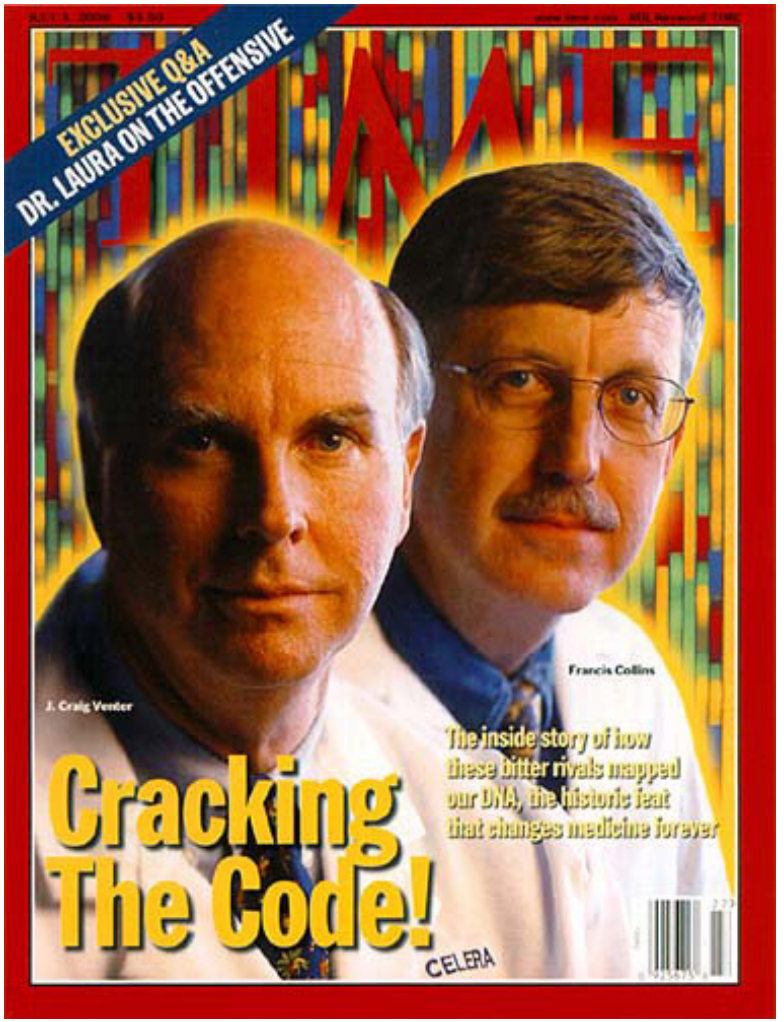
- 1990년 시작

- 초판 (Rough draft), 2001년
- 99.9% 정확도로 완성, 2003 년

- 미국 중심, UK, Japan, France, Germany, China, and India

- 30억불 (3billion dollar) project

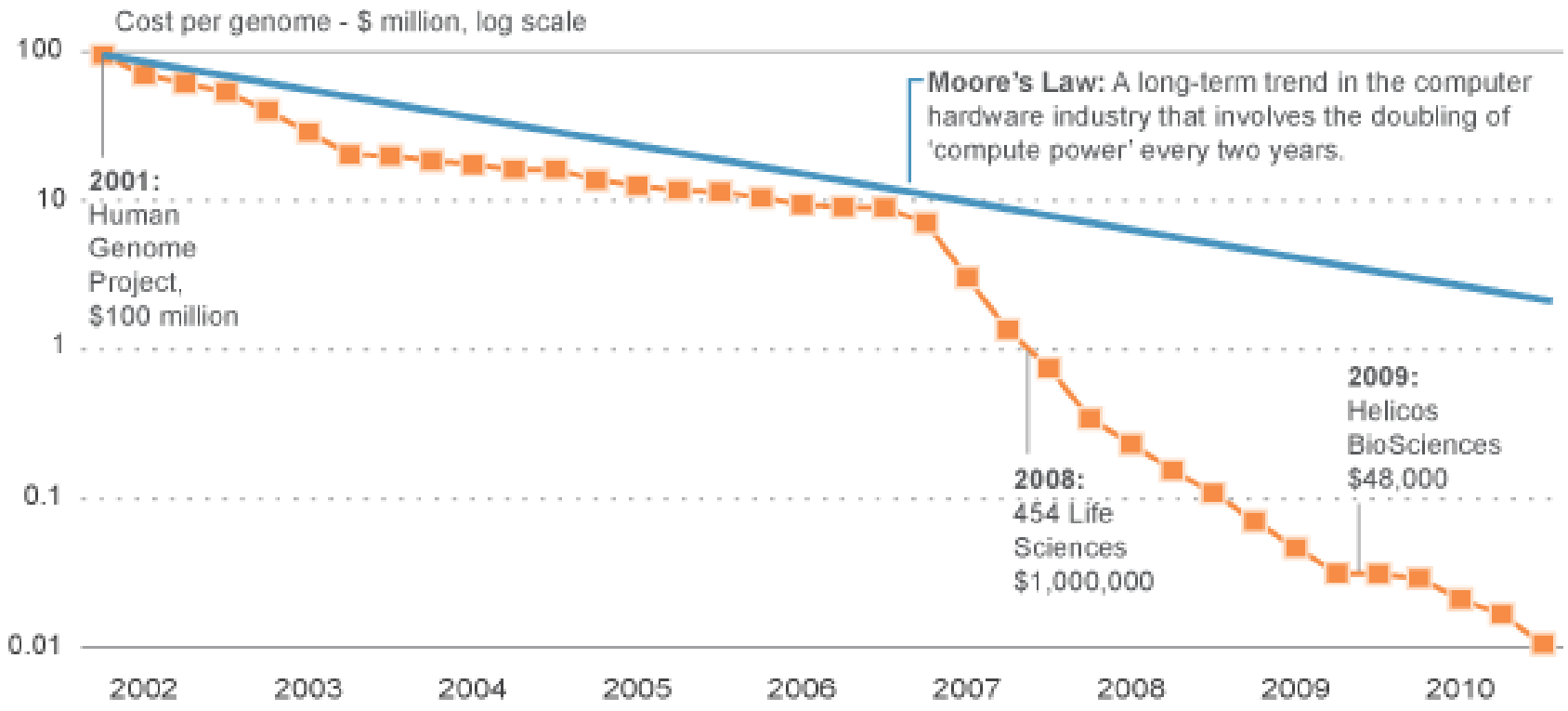
- 매 1 달러당 140 달러의 부가가치 창출



2001년 인간 유전체 정보 초판 발표

- 2003년 99.9% 정확도로 완성
- 약 30억 염기 쌍
- 약 2만3천 개의 유전자
- 모든 인간은 99% 동일
- 80% 이상은 switch
- evolutionary conserved
- 유전자 <~ 2%

DNA sequencing costs have gone down



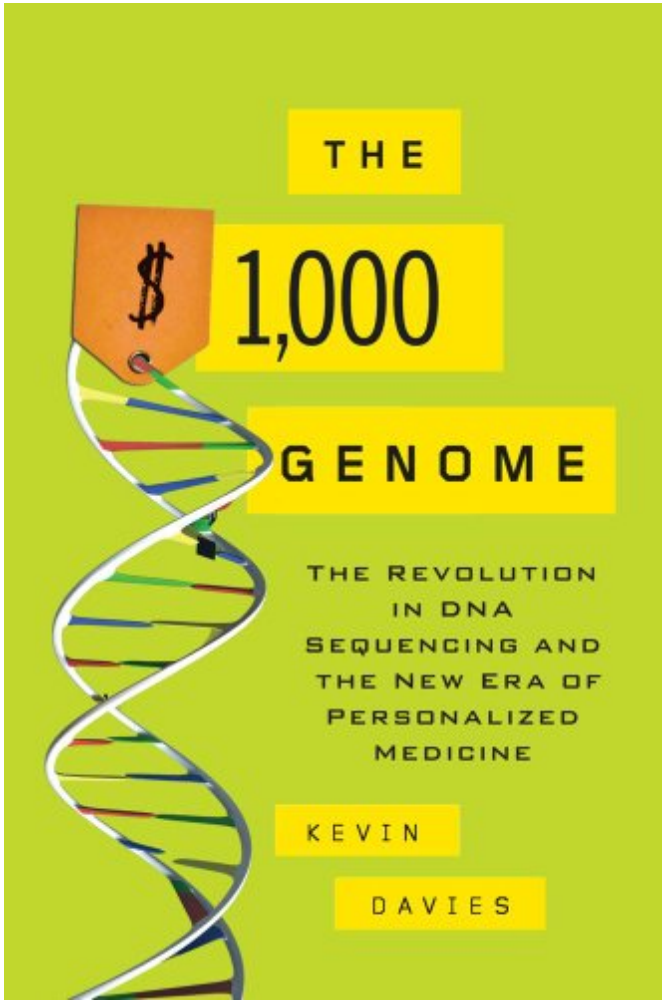
Source: National Institutes of Health

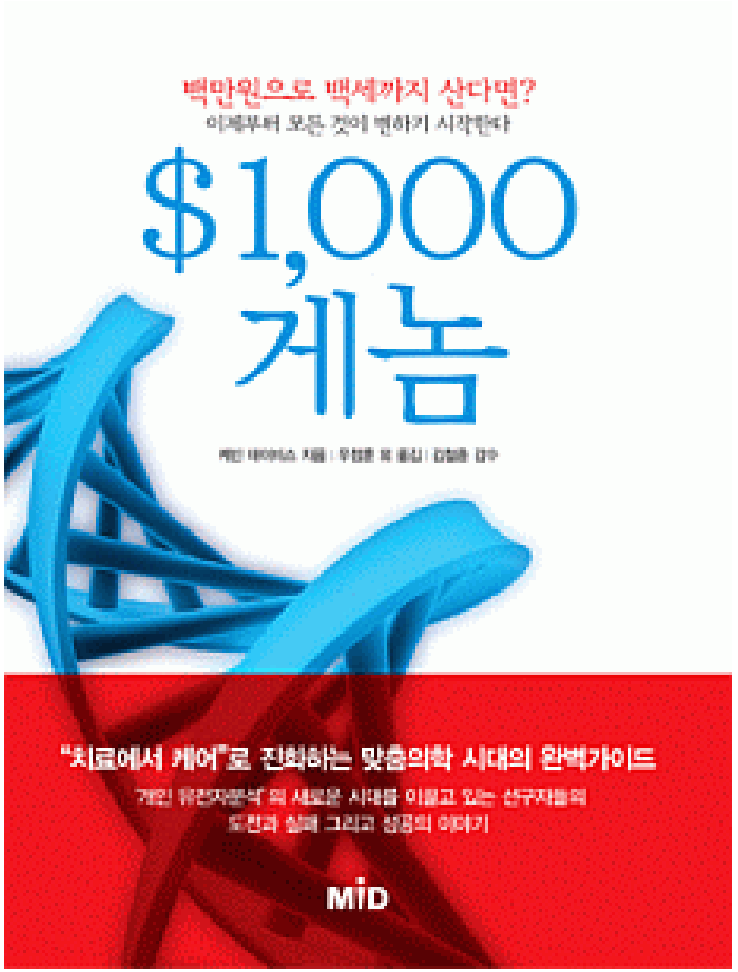
Reuters graphic/Van Tsui 05/01/12

개인 인간유전체 분석 서비스

- **2008년, 개인 유전정보 제공 서비스 시작**
  - **23 and Me : Google, Anne Wojcicki**
  - **deCODE : Amgen, Iceland genetic information**
  - **Navigenics : Life Technology**
  - **Foundation Medicine : Personalized Cancer Treatment**
- **Huge Computing Power**
- **Combining with artificial intelligence (ex, IBM's Watson system)**
- **Big data analysis 기술**
  - **삼성 SDS genome analysis software**
  - **KT Cloud Computing Infrastructure**
  - **SK chemical: DNA 분석 서비스**

백 만원 유전체 정보시대
- 2002년 Craig Venter 예견





2010

https://www.23andme.com/en-int/

autophagy AND review - Pub... | Article series : Nature Reviews... | Yonsei University Webmail | 23andMe AU, DE, FR & EU...

파일(F) 편집(E) 보기(V) 즐겨찾기(A) 도구(T) 도움말(H)

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오후 5:03
2015-11-26

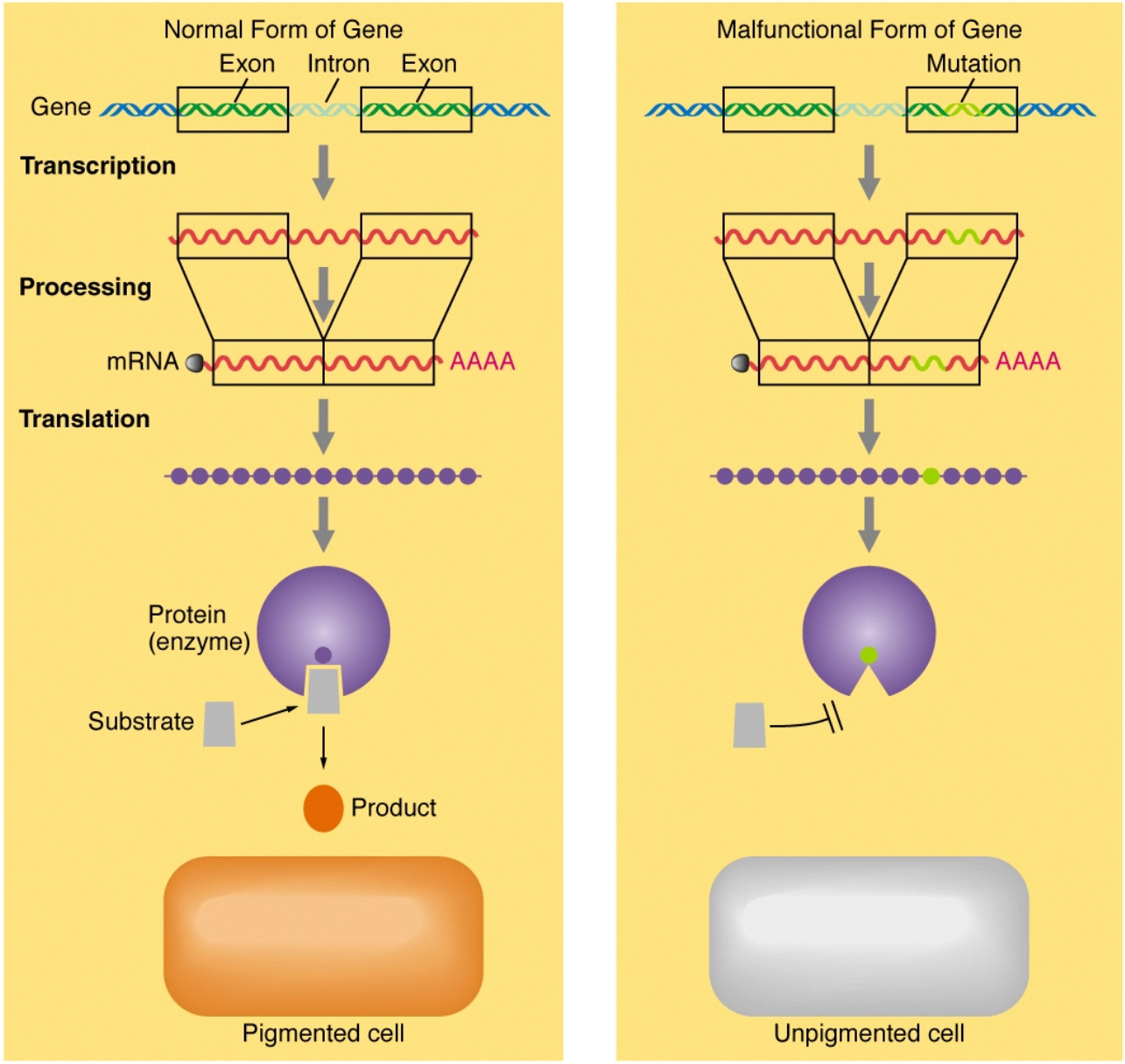
- 지구상 모든 생명체 유지의 기본 원리

유전자

DNA ⟶ mRNA ⟶ 단백질

정보 실행자

유전자 변이와 단백질 기능



많은 유전질환이 단일 유전자의 변이에 의해 발생

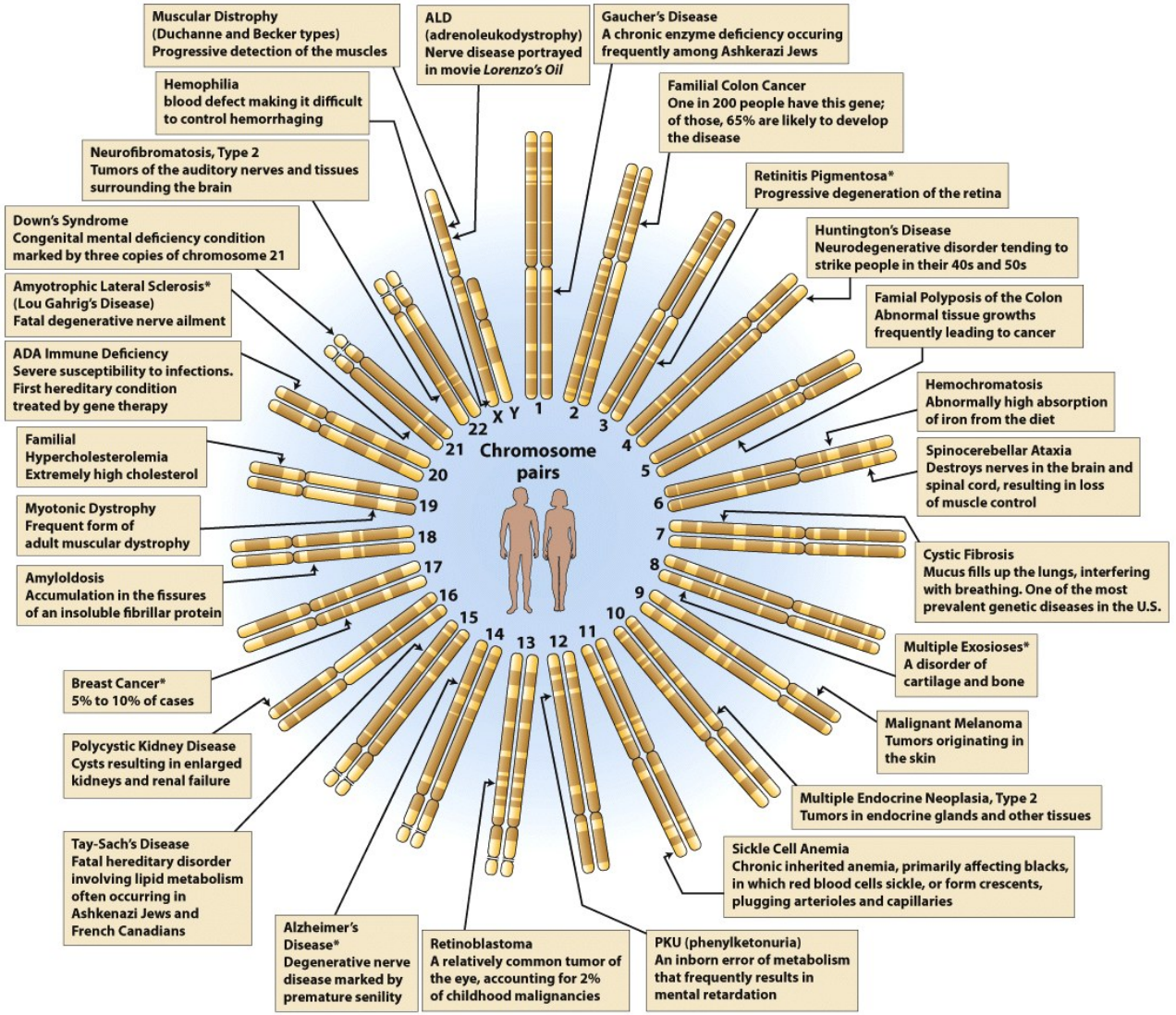


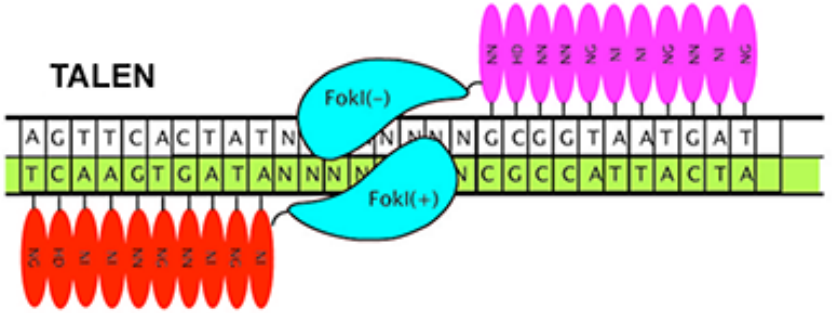
Figure 1-17
Introduction to Genetic Analysis, Tenth Edition

Desire of human for genome editing : gene therapy (유전자치료)

- ~700 genetic diseases
- mainly by a mutation of a single gene
- scissors for genome necessary

Previous scissors for DNA and genome

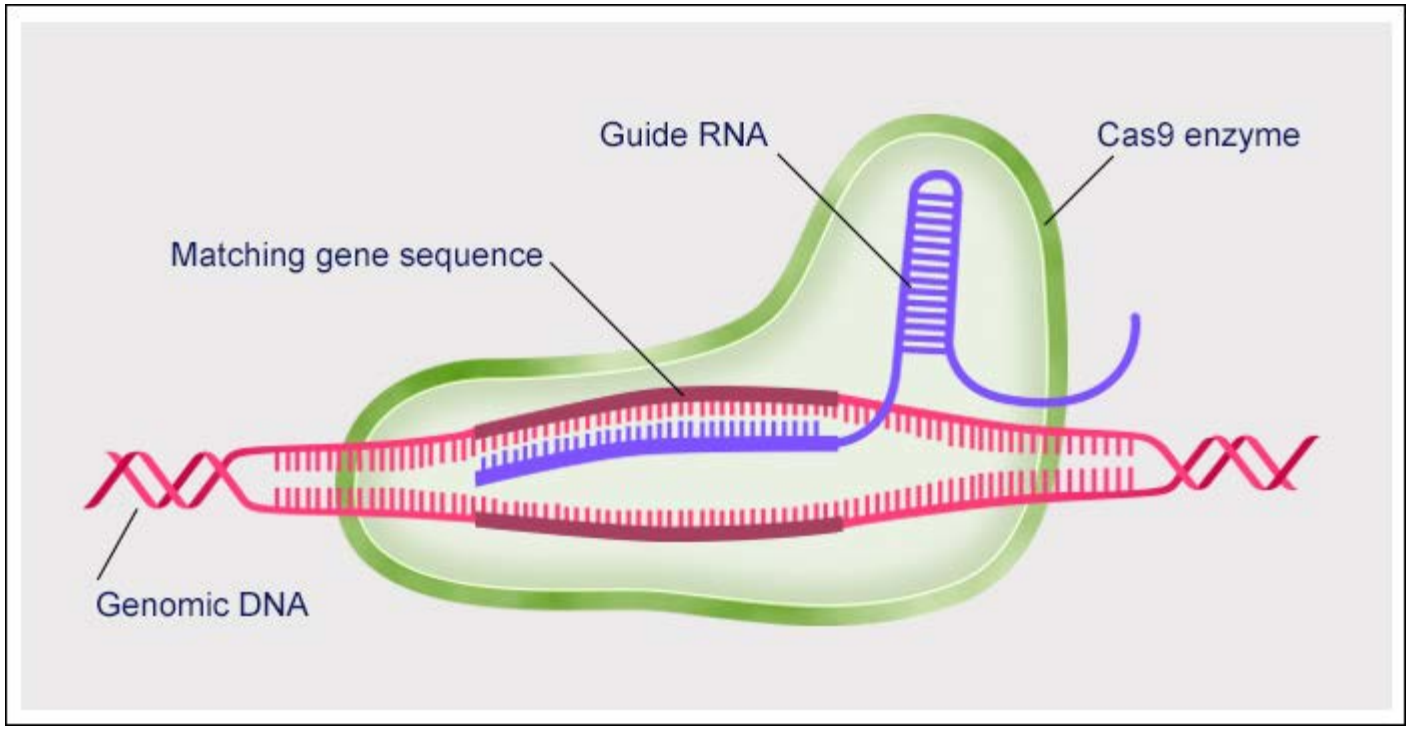
- Restriction enzyme: 4-6 nt 4^6/30억=732421 hit
- Zinc-finger nuclease (ZFN): 8-10 nt, 2861 hit
- Transcription activator-like effector nuclease (TALEN): 10-12 nt, specific sequence design



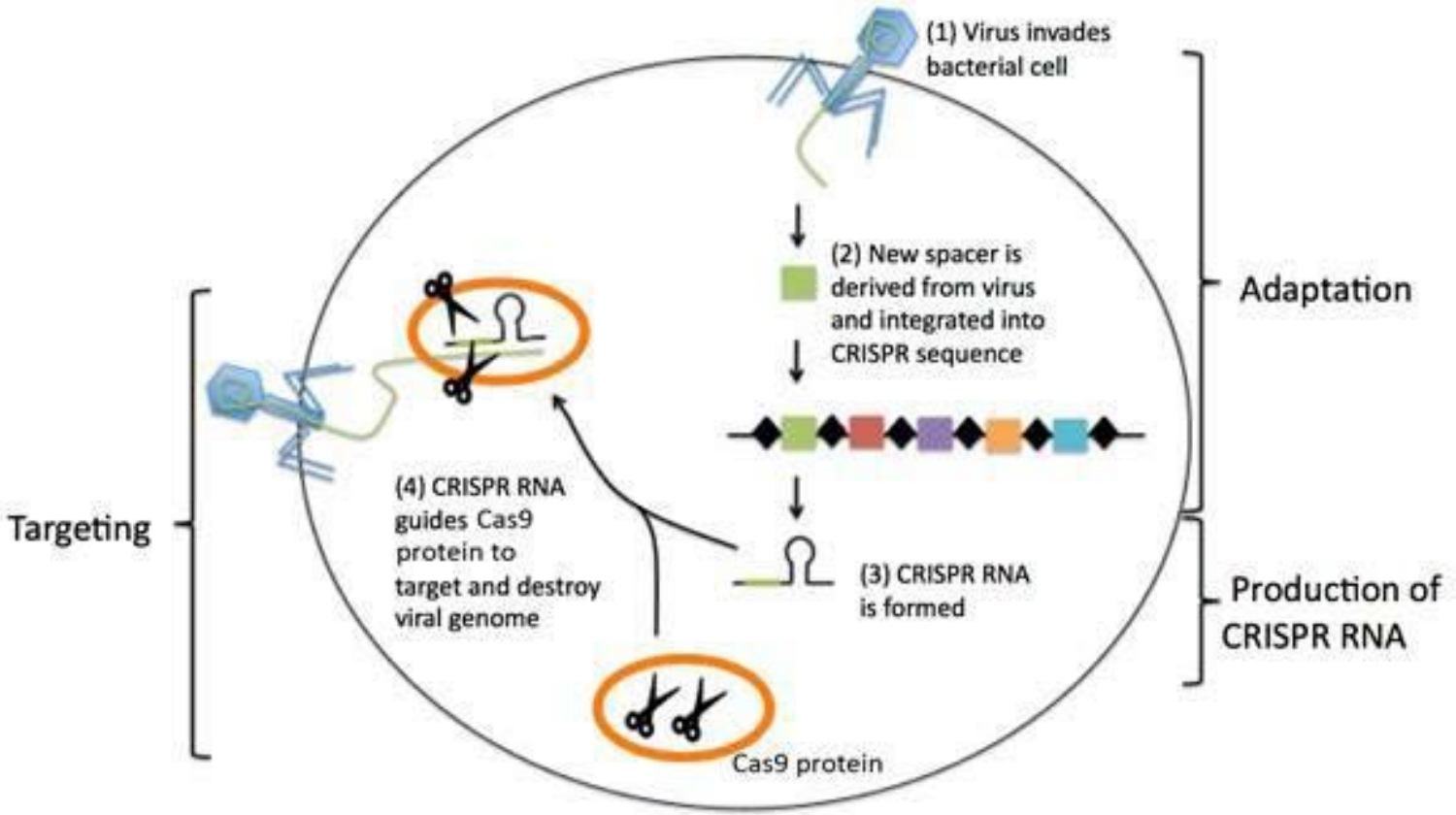
유전체편집이 가능한 새로운 ‘유전자 가위’의 등장 ; CRISPR (2013)

CRISPR

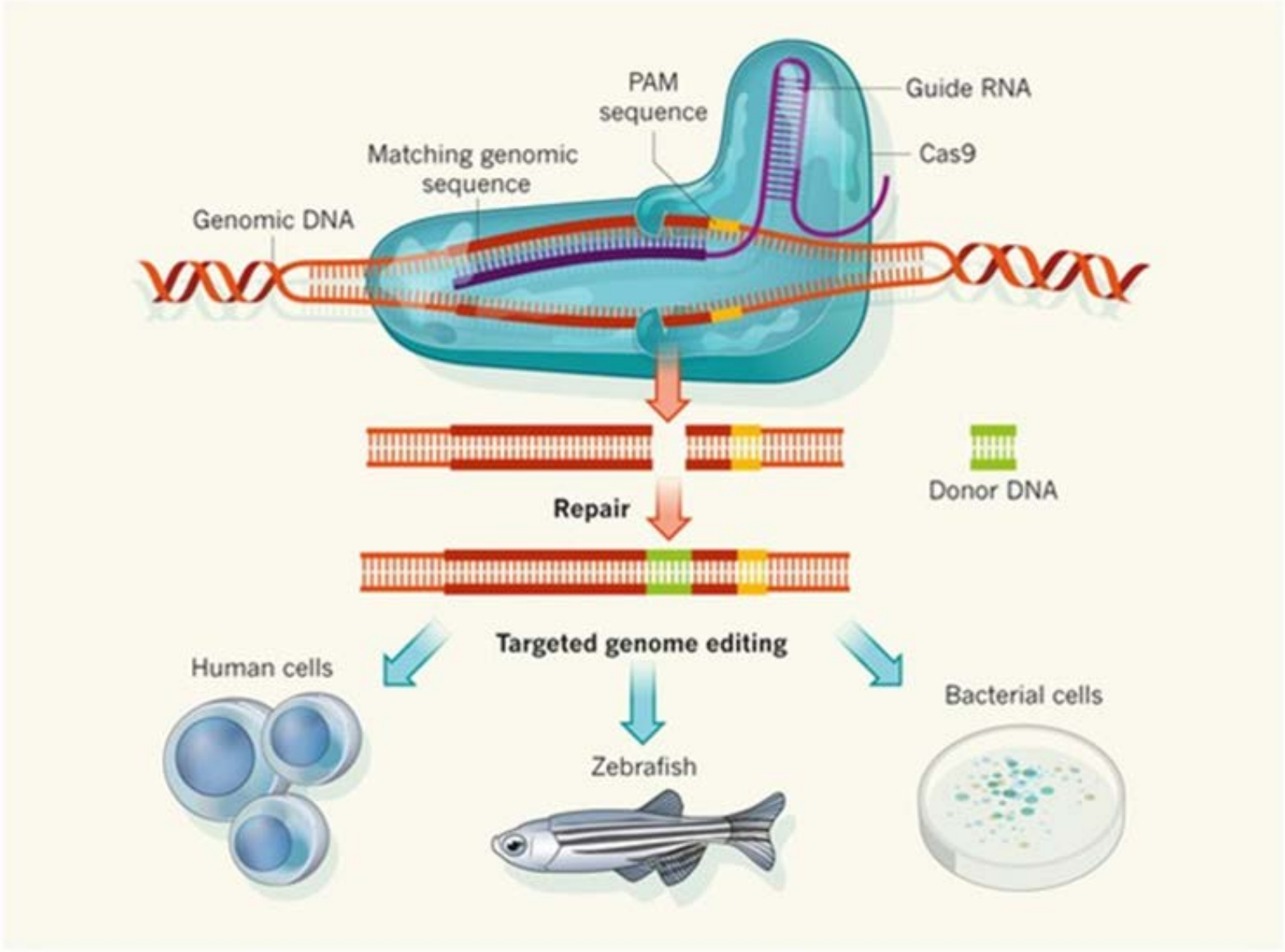
- A novel and specific scissors for genome
- CRISPR (clustered regularly interspaced short palindromic repeats) gene and Cas9 nuclease



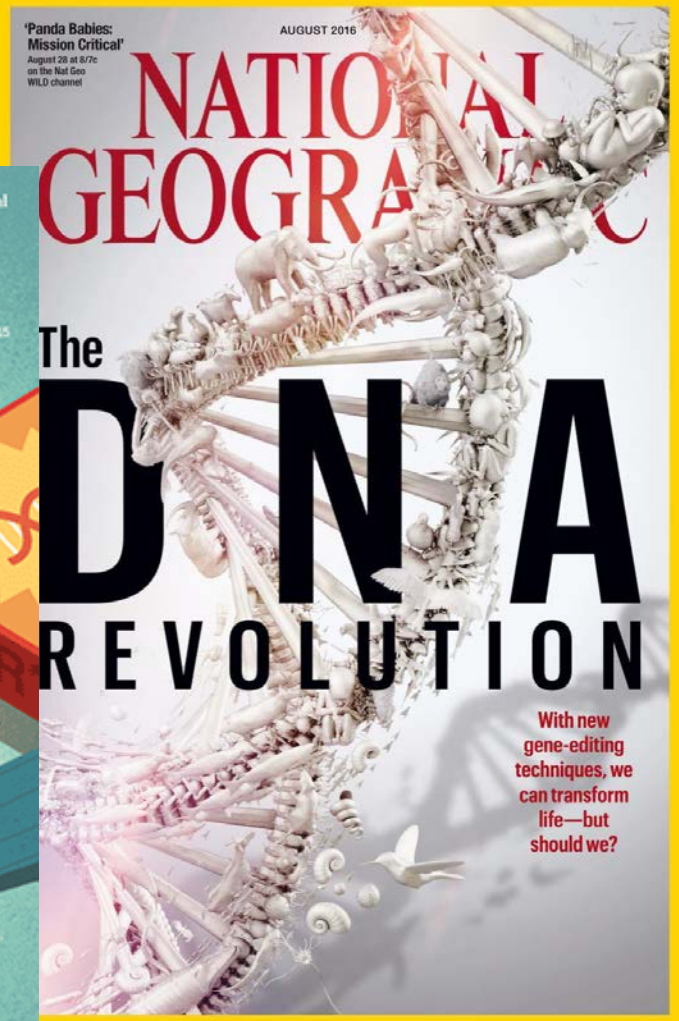
CRISPR:
Adapted immune response of bacteria



다양한 세포와 organism에서 gene editing 가능



Genome Editing Era!



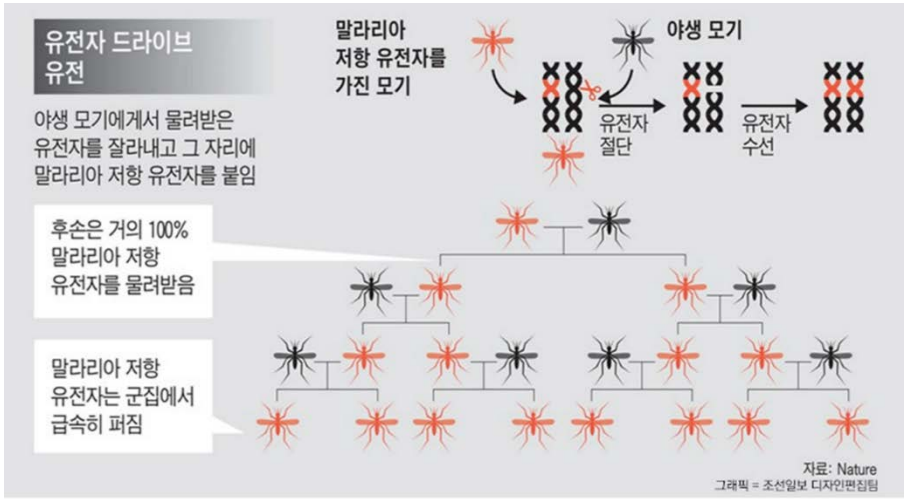
다양한 생물체 유전자 가위기술 응용

- Malaria 저항 모기 혹은 malaria 모기 인도적 멸종
- 거의 모든 생물체에 적용
- Agricultural revolution

nature biotechnology

DNA-free genome editing in plants with preassembled CRISPR-Cas9 ribonucleoproteins

Je Wook Woo[1,7], Jungeun Kim[2,3,7], Soon Il Kwon[1], Claudia Corvalán[4], Seung Woo Cho[3,6], Hyeran Kim[2], Sang-Gyu Kim[2], Sang-Tae Kim[2], Sunghwa Choe[1,4,5] & Jin-Soo Kim[2,3]




These Foods Aren't Genetically Modified but They Are 'Edited'
슈퍼 가위로 먹거리를?
크리스퍼 만찬

유전자 편집을 이용한 슈퍼 근육질 돼지, 2015년 7월

서울대학교 김진수교수 연구팀

슈퍼 가위로 이종 장기 이식을?

돼지-인간 장기 이식

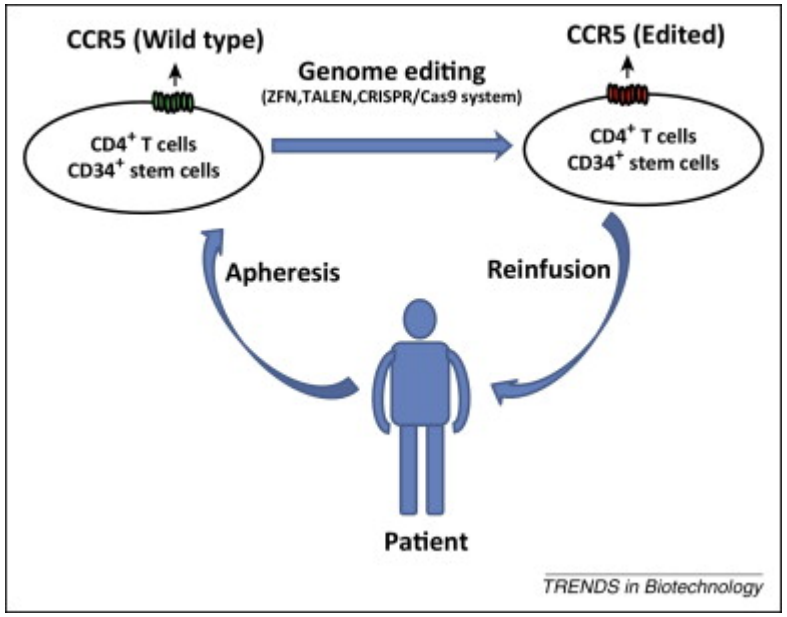
DeExtinction: Woolly Mammoth Revival Project

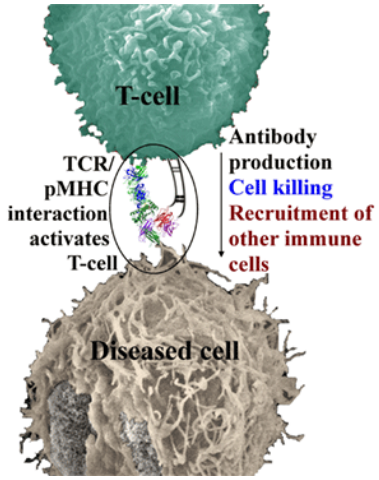
- 2015 시작
- Using DNA from a 42000 year-old frozen woolly mammoth
- 아시안 코끼리 세포의 유전체 변형을 통한 맘모스 재생
  - 유전자 가위 기술과 체세포 동물 복제 기술 적용

인체 유전자치료

- 체세포 유전자 가위기술 응용

- HIV 완치 가능성: 골수이식 때 HIV receptor CCR5 knock-out(KO) 후 이식
- Rh(+) → Rh(-) by RhD-target KO in erythrocyte
- Muscular dystrophy, cancer 등 다양한 유전병의 유전자 치료에 적용 중





유전자변형을 이용한 세포치료제 CAR-T 미 FDA 승인 (2017. 10)

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With FDA Approval for Advanced Lymphoma, Second CAR T-Cell Therapy Moves to the Clinic

Subscribe

October 25, 2017, by NCI Staff

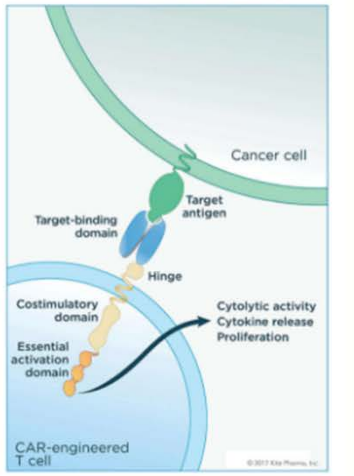
Just a month after approving the first cancer therapy that uses genetically engineered immune cells collected from patients, the Food and Drug Administration (FDA) has now cleared a second such therapy.

The approval, announced October 18, covers the use of axicabtagene ciloleucel (Yescarta™) for patients with large-B-cell lymphomas whose cancer has progressed after receiving at least two prior treatment regimens. Large B-cell lymphomas include diffuse large B-cell lymphoma (DLBCL), the most common type; primary mediastinal large B-cell lymphoma; high-grade B-cell lymphoma; and transformed follicular lymphoma.

Axicabtagene, a form of immunotherapy called CAR T-cell therapy, was initially developed at NCI by Steven Rosenberg, M.D., Ph.D., of the Surgery Branch in NCI's Center for Cancer Research (CCR), and his colleagues. It was later licensed to a private company, Kite Pharma, for further development and commercialization.

The clearance of the first CAR T-cell therapy—tisagenlecleucel (Kymriah™)—for some children and adults with advanced

ENLARGE



The engineered receptor on CAR T cells binds to an antigen on cancer cells. After binding, components of the receptor inside the T cell provide signals that activate it.

Featured Posts

Advancing Patient Care Through Focused Innovation
April 16, 2018, by Norman E. Sharpless, M.D.

Study Tests Way to Lower Dose of Prostate Cancer Drug
April 23, 2018, by NCI Staff

Cancer Immunotherapy Drug Targets Two Proteins
April 4, 2018, by NCI Staff

Categories

Biology of Cancer
Cancer Risk
Childhood Cancer
Clinical Trial Results
Disparities
FDA Approvals
Global Health
Leadership & Expert Views
Prevention
Prognosis
Screening & Early Detection

“Genetic Gold Rush”

- Partnership between pre-existing pharmaceutical companies and gene-editing start-ups

Pre-existing company	Gene-editing start-up	$ (USD)	Topic
Novartis	Intellia Therapeutics		• engineering immune cells and blood stem cells • a research tool for drug discovery
	Caribou Biosciences		
AstraZeneca	Wellcome Trust Sanger Institute		• identifying & validating new targets in preclinical models across a range of disease areas
	Innovative Genomics Initiative		
	the Broad and Whitehead Institutes at MIT		
	Thermo Fisher Scientific		
Microsoft & other patrons	Editas	) million	
Vertex Pharmaceuticals	CRISPR Therapeutics	$2.6 billion	
Bayer		$300 million	
Regeneron Pharmaceuticals	ERS Genomics		
Dupont	Lithuania’s Vilnius University & Caribou Biosciences		pplications

- Founded by Feng Zhang (Current CRISPR patent holder)
- $160 million+
- The most promising start-up

editas MEDICINE

- Founded by Caribou Biosciences & Atlas Venture
- Funded by both Atlas Venture & Novartis Institutes for Biomedical Research (NIBR)

Intellia THERAPEUTICS

- A French Biotechnology firm
- Holds a patent series, “Engineering Plant Genomes Using CRISPR/Cas Systems”

celectis

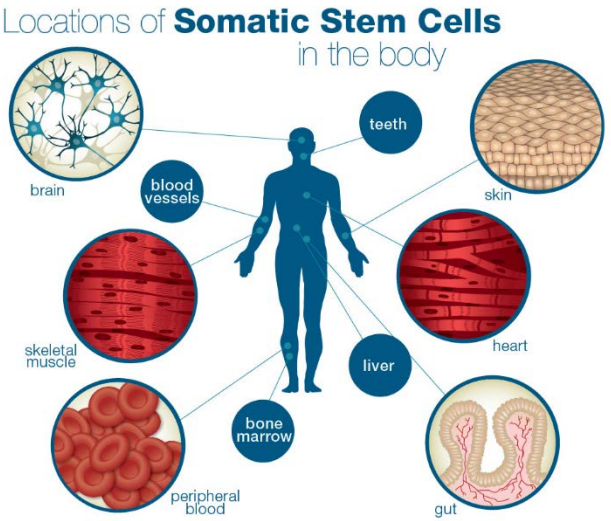
CRISPR THERAPEUTICS

- Founded by Emmanuelle Charpentier (Switzerland)
- $89million (since April 2014) + $105 million (Vertex)

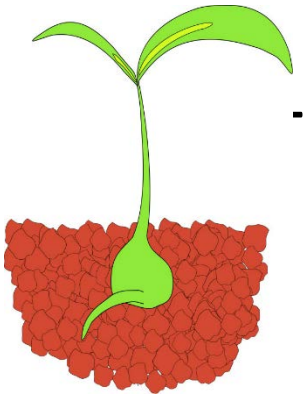
CARIBOU BIOSCIENCES

- Founded by Jennifer Doudna
- $15 million

CRISPR와 유전체 교정/편집



- 체세포
  - limitations for application
  - mainly in isolable blood cells
- 생식세포와 수정란
  - including seeds
  - efficient effect
  - unlimited inheritance



Human Embryo Editing

인간 배아 적용 논란?

Protein Cell 2015, 6(5):363–372
DOI 10.1007/s13238-015-0153-5

CrossMark Protein & Cell

RESEARCH ARTICLE

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

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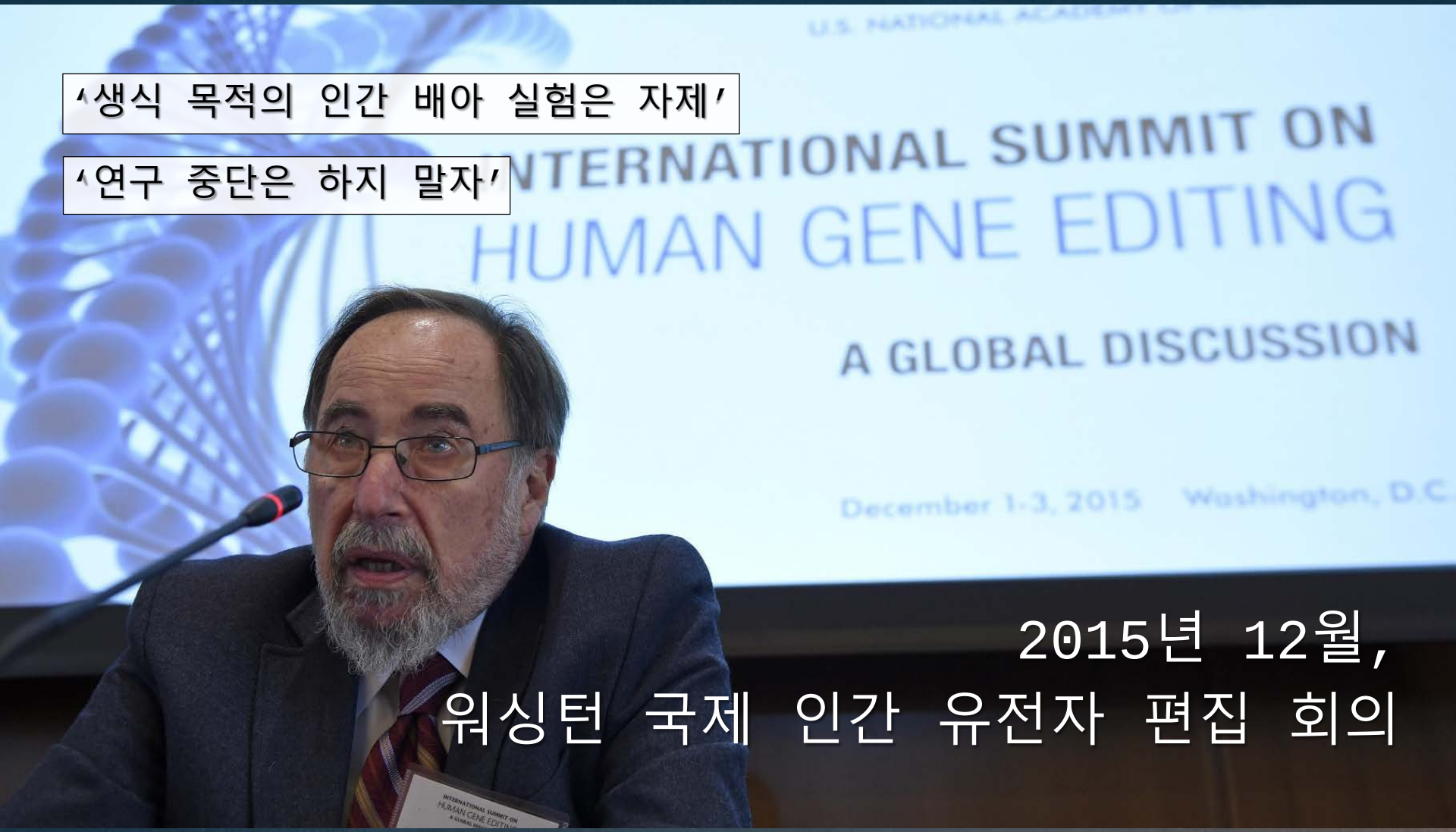
Cell

- 2015년 4월 중국 중산대 황진주 박사 연구팀 발표
- 불임치료에서 폐기된 배아를 이용
- 베타 글로빈 단백질을 부호화하는 HBB 유전자를 target으로 해서 편집 실험
- 중국에는 이런 연구를 하는 연구팀이 최소 4~5개 존재
- High off-target effect
- Low efficiency

‘생식 목적의 인간 배아 실험은 자제’

‘연구 중단은 하지 말자’



2015년 12월,
워싱턴 국제 인간 유전자 편집 회의

CRISPR 인간 배아 적용 성공 (2017)
-이미 열려버린 판도라의 상자!

ARTICLE

doi:10.1038/nature23305

Correction of a pathogenic gene mutation in human embryos

Hong Ma[1]*, Nuria Marti-Gutierrez[1]*, Sang-Wook Park[2]*, Jun Wu[3]*, Yeonmi Lee[1], Keiichiro Suzuki[3], Amy Koski[1], Dongmei Ji[1], Tomonari Hayama[1], Riffat Ahmed[1], Hayley Darby[1], Crystal Van Dyken[1], Ying Li[1], Eunju Kang[1], A.-Reum Park[2], Daesik Kim[4], Sang-Tae Kim[2], Jianhui Gong[5,6,7,8], Ying Gu[5,6,7], Xun Xu[5,6,7], David Battaglia[1,9], Sacha A. Krieg[9], David M. Lee[9], Diana H. Wu[9], Don P. Wolf[1], Stephen B. Heitner[10], Juan Carlos Izpisua Belmonte[3]§, Paula Amato[1,9]§, Jin-Soo Kim[2,4]§, Sanjiv Kaul[10]§ & Shoukhrat Mitalipov[1,10]§

Genome editing has potential for the targeted correction of germline mutations. Here we describe the correction of the heterozygous *MYBPC3* mutation in human preimplantation embryos with precise CRISPR–Cas9-based targeting accuracy and high homology-directed repair efficiency by activating an endogenous, germline-specific DNA repair response. Induced double-strand breaks (DSBs) at the mutant paternal allele were predominantly repaired using the homologous wild-type maternal gene instead of a synthetic DNA template. By modulating the cell cycle stage at which the DSB was induced, we were able to avoid mosaicism in cleaving embryos and achieve a high yield of homozygous embryos carrying the wild-type *MYBPC3* gene without evidence of off-target mutations. The efficiency, accuracy and safety of the approach presented suggest that it has potential to be used for the correction of heritable mutations in human embryos by complementing preimplantation genetic diagnosis. However, much remains to be considered before clinical applications, including the reproducibility of the technique with other heterozygous mutations.

<오레곤대학 미타리포브교수 서울대 김진수교수 연구팀 공동연구>

인류의 위험한 실험...신의 섭리에 도전하는 `디자인 베이비`

World's first gene-edited babies created in China, claims scientist

Unconfirmed scientific breakthrough sparks ethical and moral concerns

2018년 11월,

국제 인류유전자편집회의

맞춤 아기 (designer baby) 시대로?

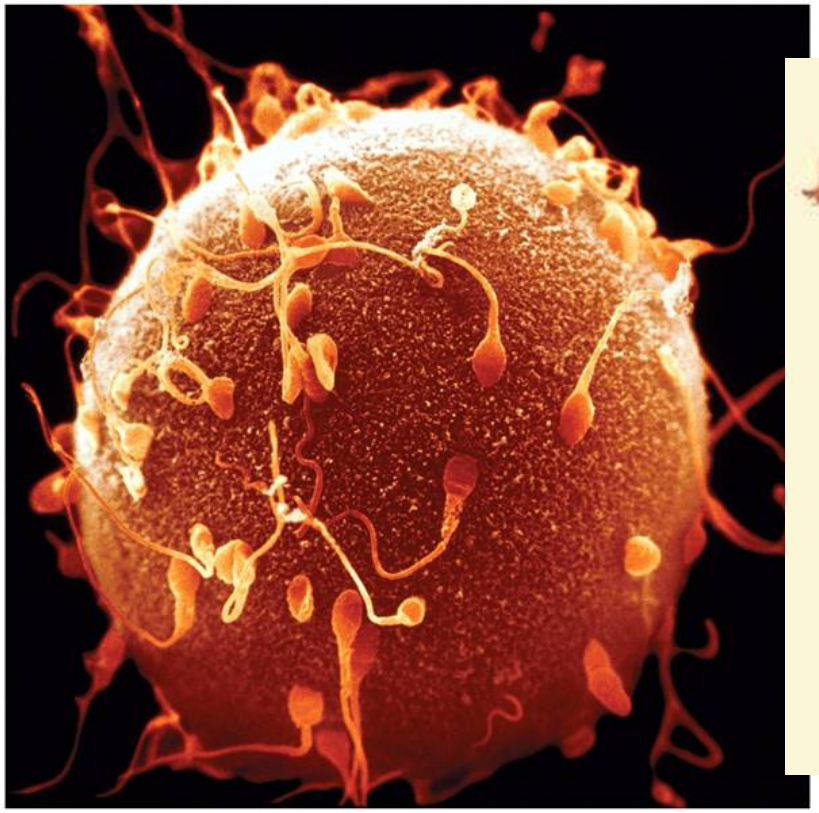
http://www.youtube.com/watch?v=lP1cCjBkWZU&feature=player_detailpage

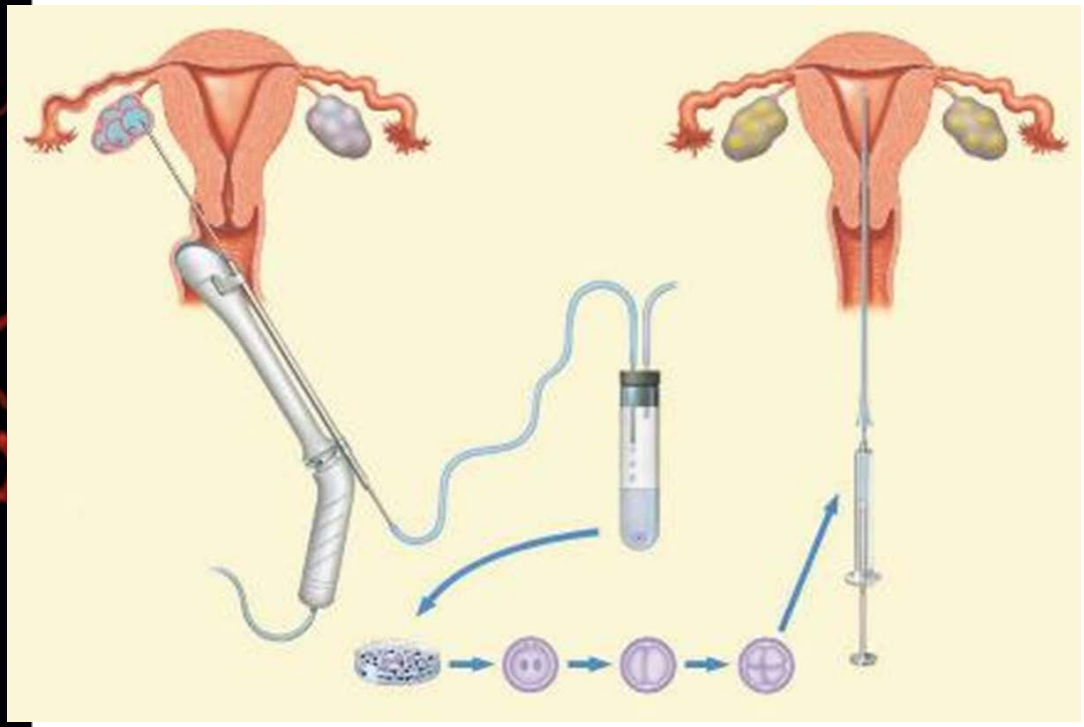
영화 <가타카 GATTACA, 1997>

유전병을 위한 배아 유전자치료

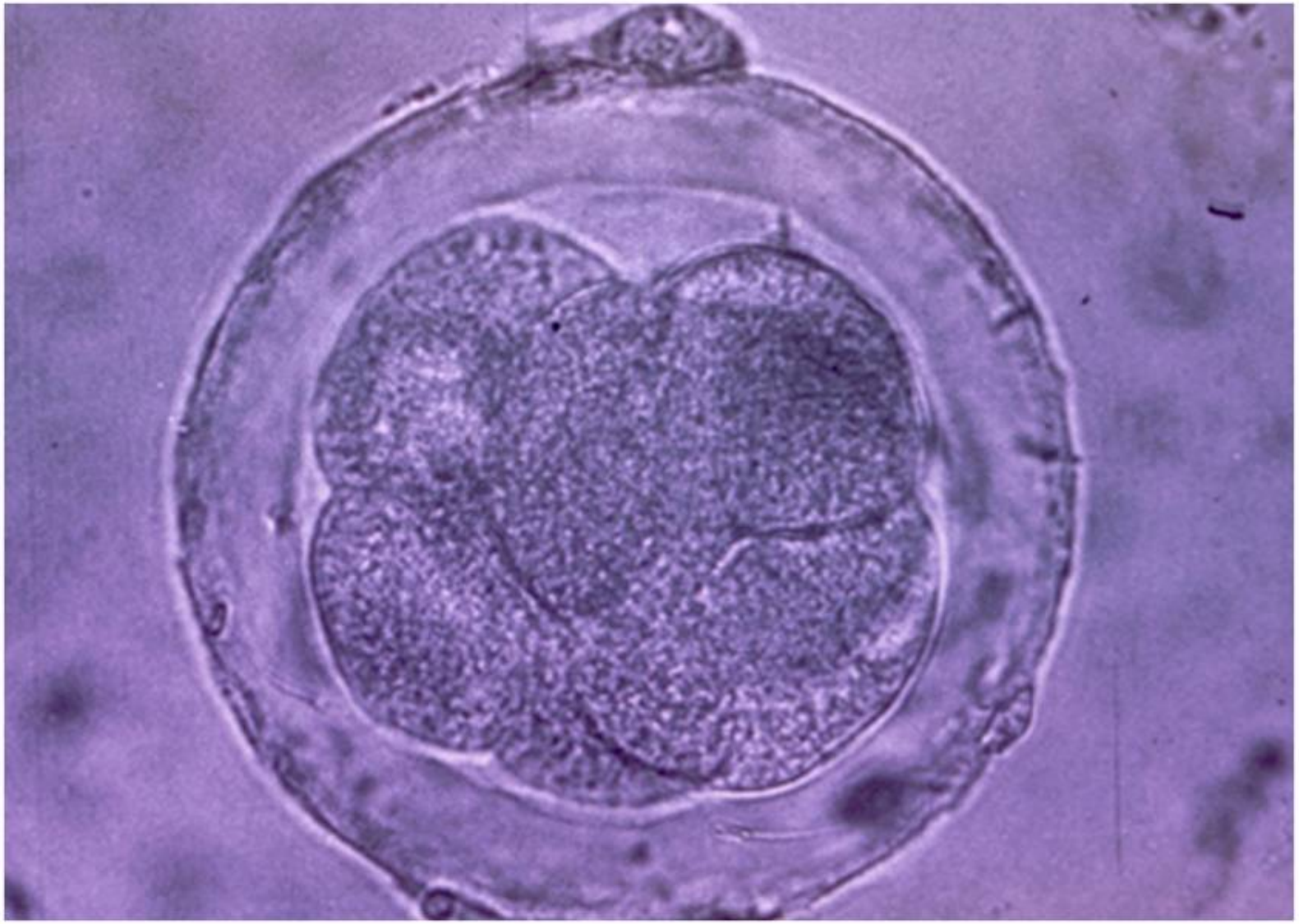
꼭 필요한가?

생명의 시작 수정란과 시험관 아기

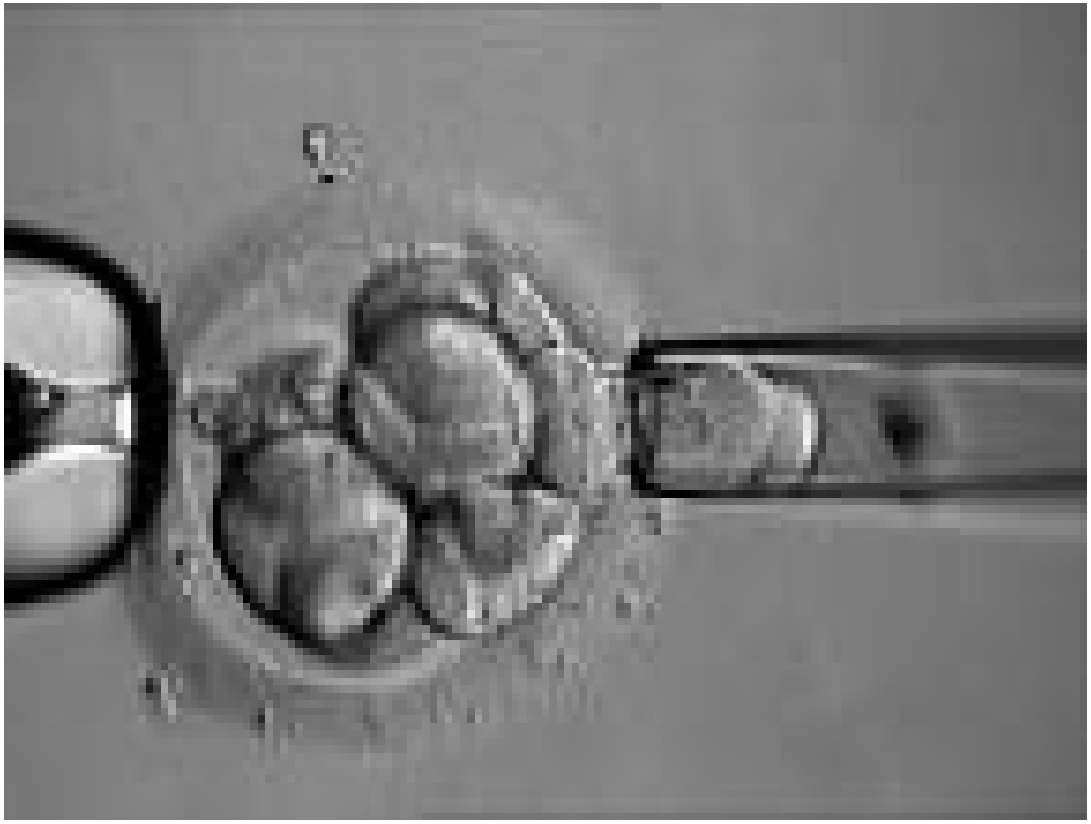




Embryonic stem cell: 배아줄기세포



Pre-implantation Genetic Diagnosis (PGD)
착상 전 태아 유전자 검사로 배아선별



Fetal genomic screening?
현재 250개 질환 유전자에 대한 서비스 가능

Issues over genome editing by CRISPR

- Ecological concerns
- Meaning of gene editing
  - 편집 혹은 교정?
  - 유전자에 가치 개념
- Regulation
  - 대상, 질환 (무엇이 질병인가?), 방법
  - 공공재: 국경을 넘는 과학
- Who are we? : 효용 vs 가치

우리 사회는 이렇게 빠르게 발전하고 있는
생명과학 기술에 의한 변화를 수용할
준비가 되어 있는가

우리는 생명과학기술과 인간에 어떤 질문을 던져야 할까?

<2018. 10>