



UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Telmo Pievani

Department of Biology

dietelmo.pievani@unipd.it

Università degli studi di Verona

**Cerimonia di Proclamazione
dei Dottori di Ricerca**

30 Settembre 2016

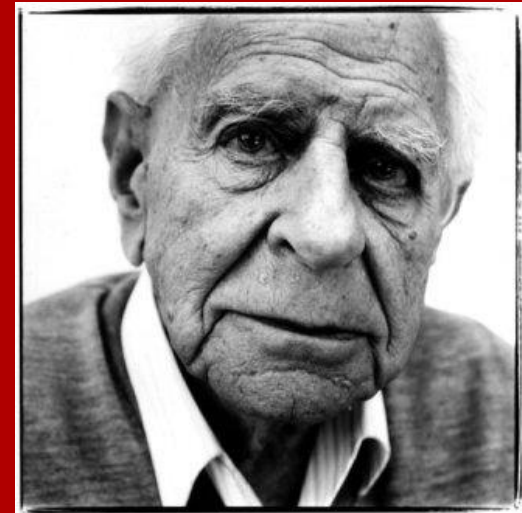
Scienza e Democrazia:

libertà di ricerca, responsabilità e nuove sfide

When I speak of reason or rationalism, all I mean is the conviction that we can learn through criticism of our mistakes and errors, especially through criticism by others, and eventually also through self-criticism. A rationalist is simply someone for whom it is more important to learn than to be proved right. The genuine rationalist does not think that he or anyone else is in possession of the truth; nor does he think that mere criticism as such helps us achieve new ideas. But he does think that, in the sphere of ideas, only **critical discussion** can help us sort wheat from chaff. He is well aware that acceptance or rejection of an idea is never a purely rational matter; but he thinks that only critical discussion can give us the maturity to see an idea from more and more sides and to make a correct judgment of it.

Karl R. Popper, *All Life is Problem Solving* (1994)

**Science and democracy:
handy analogy?**



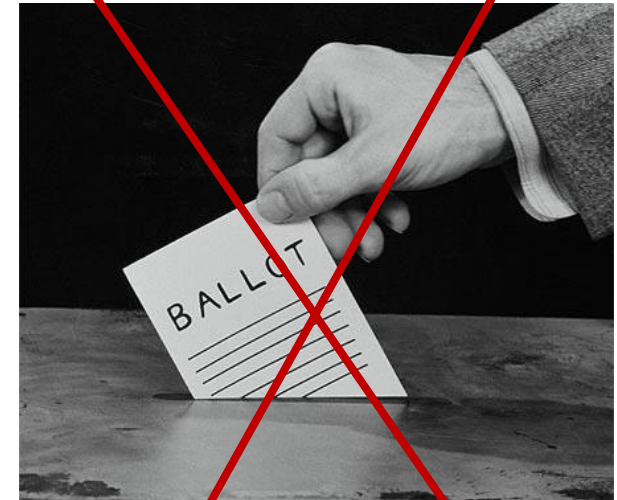


UNIVERSITÀ
DEGLI STUDI
DI PADOVA

What science and democracy do not share




1) Scientific results are not decided by majority or referendum

- Cross-checking and peer-review
- Experimental proofs
- Past experience and reputation



Origin of Humans

Which of these statements comes closest to your own point of view regarding the origin and development of human beings on earth?

	CANADA 	UNITED STATES 	GREAT BRITAIN 
Evolved over millions of years	61 %	35 %	68 %
Created within 10,000 years	24 %	47 %	16 %
Not sure	15 %	18 %	15 %

Angus Reid Poll, 2010



2) Scientific consensus has not the same weight as the opinion of single scientists

- The state of the art as a constraint
- Divisions between scientists must be supported by evidence and argued
- Science is not a TV talk-show





What science and democracy do not share

3) Advanced science and technology (have been and) are possible in countries with oppressive regimes.

- The worst expressions of totalitarianism have been in Europe and after the Scientific Revolution

- More science and technology = more democracy? (ex. “science” on the web)



War time great scientists



Fritz Haber (1868-1934)

«During peace time a scientist belongs to the World, but during war time he belongs to his country».

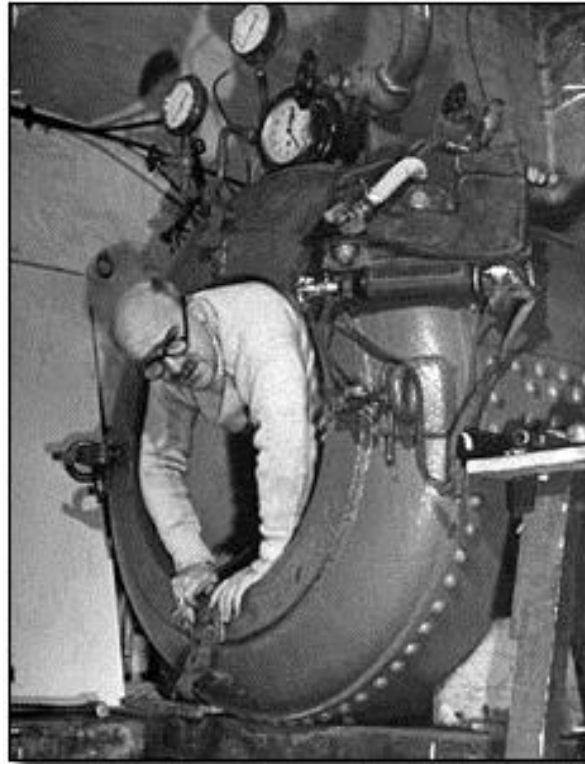


Wernher von Braun (1912-1977)

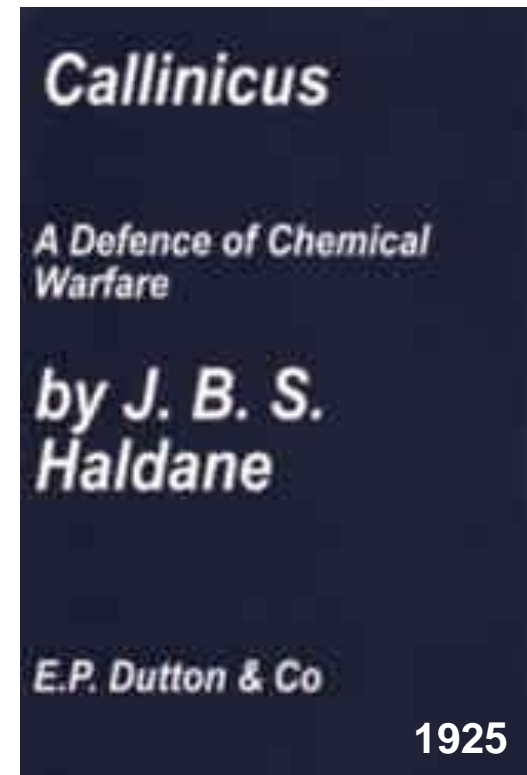


Edward Teller (1908-2003)

J.B.S. Haldane testing poison gas chambers...



- Societal consequences?
- Responsibility of the scientist?
(molecular biology has become the most
disputed research field by the public)
- How to avoid potential misuses? **THE
OTHER SIDE OF THE PARALLEL...**



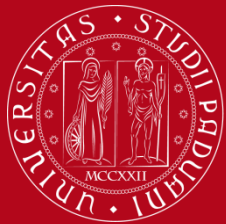


UNIVERSITÀ
DEGLI STUDI
DI PADOVA

What science and democracy do share

- 1) **Self-correction through critical discussion**
- 2) **Freedom of criticism (rational argumentation)**
- 3) **The value of dissent (with the burden of proof)**



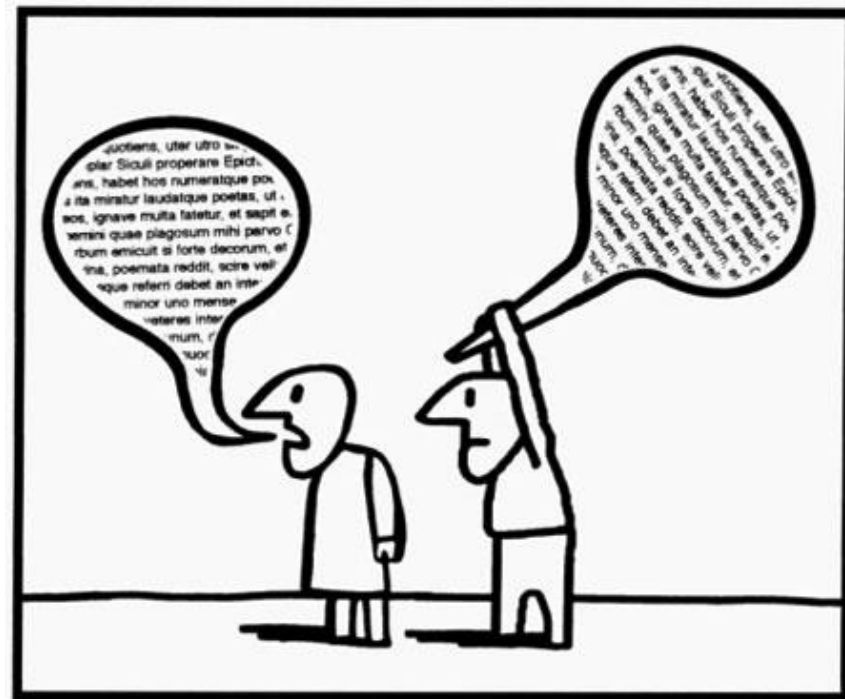


4) No absolute authorities

5) Universal language

6) Ethics of communication
(transparency)

(and) the Kantian Principle: science
(as any creative human activity) is for
people, and not people for science.





UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Science and democracy: our debt to Henrietta



Henrietta Lacks
Death: October 4th, 1951





U 53
HENRIETTA LACKS
(1920-1951)

Born in Roanoke on 1 Aug. 1920, Henrietta Pleasant lived here with relatives after her mother's 1924 death. She married David Lacks in 1941 and, like many other African Americans, moved to Baltimore, Md. for wartime employment. She died of cervical cancer on 4 Oct. 1951. Cell tissue was removed without permission (as usual then) for medical research. Her cells multiplied and survived at an extraordinarily high rate, and are renowned worldwide as the "HeLa line," the "gold standard" of cell lines. Jonas Salk developed his polio vaccine with them. Henrietta Lacks, who in death saved countless lives, is buried nearby.

DEPARTMENT OF HISTORIC RESOURCES, 2010



The restitution of memory



“It is a non-sense: if our mother’s cells have done so much for medicine, how comes that her family cannot pay the doctor’s visits?” (Deborah Lacks)

The Genomic and Transcriptomic Landscape of a HeLa Cell Line

Jonathan J. M. Landry,^{*1} Paul Theodor Pyl,^{*1} Tobias Rausch,^{*} Thomas Zichner,^{*} Manu M. Tekkedil,^{*} Adrian M. Stütz,^{*} Anna Jauch,[†] Raeka S. Aiyar,^{*} Gregoire Pau,^{*2} Nicolas Delhomme,^{*3} Julien Gagneur,^{*4} Jan O. Korbel,^{*} Wolfgang Huber,^{*5} and Lars M. Steinmetz^{*5}

^{*}European Molecular Biology Laboratory, Genome Biology Unit, 69117 Heidelberg, Germany, and [†]University Hospital Heidelberg, Institute of Human Genetics, 69120 Heidelberg, Germany

ABSTRACT HeLa is the most widely used model cell line for studying human cellular and molecular biology. To date, no genomic reference for this cell line has been released, and experiments have relied on the human reference genome. Effective design and interpretation of molecular genetic studies performed using HeLa cells require accurate genomic information. Here we present a detailed genomic and transcriptomic characterization of a HeLa cell line. We performed DNA and RNA sequencing of a HeLa Kyoto cell line and analyzed its mutational portfolio and gene expression profile. Segmentation of the genome according to copy number revealed a remarkably high level of aneuploidy and numerous large structural variants at unprecedented resolution. Some of the extensive genomic rearrangements are indicative of catastrophic chromosome shattering, known as chromothripsis. Our analysis of the HeLa gene expression profile revealed that several pathways, including cell cycle and DNA repair, exhibit significantly different expression patterns from those in normal human tissues. Our results provide the first detailed account of genomic variants in the HeLa genome, yielding insight into their impact on gene expression and cellular function as well as their origins. This study underscores the importance of accounting for the strikingly aberrant characteristics of HeLa cells when designing and interpreting experiments, and has implications for the use of HeLa as a model of human biology.

KEYWORDS

genomics
transcriptomics
HeLa cell line
resource
variation

Nature News:

“Steinmetz’s team confirmed that HeLa cells contain one extra version of most chromosomes, with up to five copies of some. Many genes were duplicated even more extensively, with four, five or six copies sometimes present, instead of the usual two. Furthermore, large segments of chromosome 11 and several other chromosomes were reshuffled like a deck of cards, drastically altering the arrangement of the genes”.

Good models for human cell biology? Are they still “HeLa”? Are they really “immortal”? Who has the rights? Are they “natural”? Tissues banks, a “limbo situation”.

HeLa publication brews bioethical storm

Genome of controversial cell line no longer public, but another sequence is in the works.

Ewen Callaway

27 March 2013

When Lars Steinmetz and his team published the genome of the world's most famous human cell line earlier this month¹, they did not imagine that the work would become a bioethical lightning rod. He and his group at the European Molecular Biology Laboratory in Heidelberg, Germany, saw the HeLa cell genome as a helpful resource for their work examining how gene variants influence basic biological functions, and for the countless other scientists studying the same cell line.

But the descendants of Henrietta Lacks — whose cervical tumour gave rise to HeLa cells — saw otherwise, as did other scientists and bioethicists. They have criticized the decision to publish the sequence, noting that the HeLa cell line was established without Lacks's consent (around the time she died in 1951) and that aspects of what Steinmetz and his team have published may disclose genetic traits borne by surviving family members.

In response, Steinmetz and his team pulled the genomic data from public databases. "We were surprised, we did not expect this to happen at all," Steinmetz says. "We wanted to respect the wishes of the family, and we didn't intend to cause them any anxiety by the publication of our research."

Swirling questions

Scientists and bioethicists say that this fast-moving debate has opened up a morass of unresolved bioethical issues surrounding HeLa cells as well as genetic privacy and the use of archival tissue samples in genomic studies.

"My hope is that the major outcome of this is that it's going to force a top-to-bottom re-think" in how genetic data are handled, says John Stamatoyannopoulos, a genomics researcher at the University of Washington in Seattle (UW).



OBSTETRICS & GYNAECOLOGY/SPL

The descendants of Henrietta Lacks have objected to the publication of her tumour cells' genome.

Print

National Institutes of Health, August 2013, an unprecedented agreement:

A) No economical compensations and it cannot constitute a precedent.

B) Family agrees on publication but with privacy guaranteed. **(but is it possible to keep genetic data secret in Internet era?)**

C) Two representatives of the family in Ethical Committees.

- **A progressive agreement or the outcome of sense of guilt (and fear of precautionary suspensions of HeLa use)?**
- **How to keep privacy and scientific transparency together?**
Two contradictory and equally worthy values.



Francis Collins



EDITORIAL

Phillip A. Sharp

Phillip A. Sharp is Institute Professor at the Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA.
10.1126/science.1120820

*T. M. Tumpey et al., *Science* 310, 77 (2005). †J. Taubenberger et al., *Nature* 437, 889 (2005). ‡S. Salzberg, *Nature* 10.1038/nature04239 (2005).

1918 Flu and Responsible Science

The influenza pandemic of 1918 is estimated to have caused 50 million deaths worldwide; 675,000 in the United States. The reconstruction of the 1918 virus by the synthesis of all eight subunits and the generation of infectious virus are described on p. 77 of this issue,* and the sequences of the final three gene segments of the virus are described in a concurrent *Nature* paper.† Predictably, but alarmingly, this virus is more lethal to mice than are other influenza strains, suggesting that this property of the 1918 virus has been recovered in the published sequence. The good news is that we now have the sequence of this virus, perhaps permitting the development of new therapies and vaccines to protect against another such pandemic. The concern is that a terrorist group or a careless investigator could convert this new knowledge into another pandemic.

Should the sequence of the 1918 virus have been published, given its potential use by terrorists? The dual-use nature of biological information has been debated widely since September 11, 2001. In 2003, a committee of the U.S. National Academies chaired by Gerald Fink considered this issue, weighing the benefits against the risks of restricting the publication of such biological information. They outlined the tradeoff between erring on the side of prudence, thus potentially hindering the progress of critical science, and erring on the side of disclosure, thus potentially aiding terrorists. The U.S. National Science Advisory Board for Biosecurity (NSABB) was established to advise governmental

**Knowledge is
always better
than ignorance.**



I firmly believe that allowing the publication of this information was the correct decision in terms of both national security and public health. It is impossible to forecast how scientific observations might stimulate others to create new treatments or procedures to control future pandemics. For example, in the *Nature* article, sequence comparisons

Herfst *et al.*, *Science*, 22 June 2012

Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets

Highly pathogenic avian influenza A/H5N1 virus can cause morbidity and mortality in humans but thus far has not acquired **the ability to be transmitted by aerosol or respiratory droplet (“airborne transmission”) between humans**. To address the concern that the virus could acquire this ability under natural conditions, **we genetically modified A/H5N1 virus by site-directed mutagenesis and subsequent serial passage in ferrets**. The genetically modified A/H5N1 virus acquired mutations during passage in ferrets, ultimately becoming airborne transmissible in ferrets. None of the recipient ferrets died after airborne infection with the mutant A/H5N1 viruses. Four amino acid substitutions in the host receptor-binding protein hemagglutinin, and one in the polymerase complex protein basic polymerase 2, were consistently present in airborne-transmitted viruses. The transmissible viruses were sensitive to the antiviral drug oseltamivir and reacted well with antisera raised against H5 influenza vaccine strains. **Thus, avian A/H5N1 influenza viruses can acquire the capacity for airborne transmission between mammals without recombination in an intermediate host and therefore constitute a risk for human pandemic influenza.**



Ron Fouchier
(Erasmus Medical
Center – Rotterdam)

Russell *et al.*, *Science*, 22 June 2012

Report

The Potential for Respiratory Droplet–Transmissible A/H5N1 Influenza Virus to Evolve in a Mammalian Host

Avian A/H5N1 influenza viruses pose a **pandemic threat**. **As few as five amino acid substitutions, or four with reassortment, might be sufficient for mammal-to-mammal transmission through respiratory droplets.** From surveillance data, we found that **two of these substitutions are common in A/H5N1 viruses**, and thus, some viruses might require only three additional substitutions to become transmissible via respiratory droplets between mammals. We used a mathematical model of within-host virus evolution to study factors that could increase and decrease the probability of the remaining substitutions evolving after the virus has infected a mammalian host. These factors, combined with the presence of some of these substitutions in circulating strains, **make a virus evolving in nature a potentially serious threat.** These results highlight critical areas in which more data are needed for assessing, and potentially averting, this threat.

DUAL-USE RESEARCH
(future vaccines – potential bioweapons)

A bioethical conundrum

- **How to keep biosecurity (warning about biological weapons) and scientific transparency (open access) together?**
- **Academic freedom (in the International competition) or public regulations?**
- **Moratorium? How to have them respected worldwide?**
- **Prior-reviews? How to forecast future scientific results? (intended and unintended consequences)**
- **External regulations (legislative measures to control or even ban dual use research) or internal awareness and enhanced sense of responsibility in the scientific community?**

Two contradictory and equally worthy values

science & society

science & society

The responsibility of the scientist

What can history teach us about how scientists should handle research that has the potential to create harm?

Peter Herrlich

Three proposals:

- 1) **Advisory scientific committees about dual use research**
- 2) **Statements of the scientific Institutions (for exclusively pacific aims)**
- 3) **Total transparency of funding and open access to all research data.**



Are we in the same situation?

NO:

- 1) Current scientists actively started discussions on biosecurity;
- 2) They had no intention to weaponize their research;
- 3) They live in much more liberal and open countries.

YES:

- 1) Despite the potential for misuse of their work, they still published it (pressing to publish);
- 2) They both originally sought to serve the public good.



UNIVERSITÀ
DEGLI STUDI
DI PADOVA

New challenges

COMMENT

EQUALITY Family policies are necessary, but not sufficient **p.471**

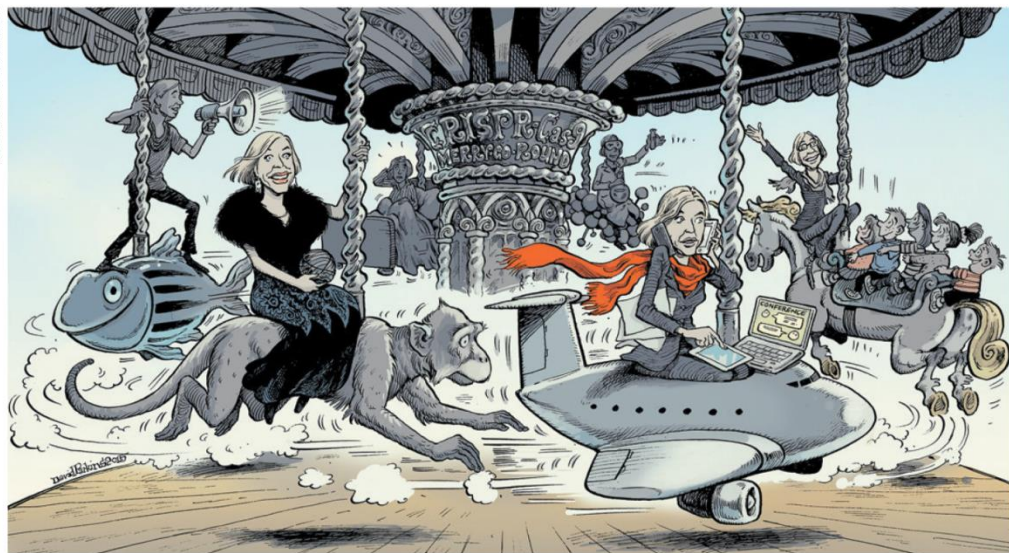


ECOLOGY George Schaller, pioneering field biologist, in conversation **p.474**

CULTURE On the beautiful relationship between mathematics and art **p.476**

OBITUARY Maurice Strong, architect of UNEP, remembered **p.480**

ILLUSTRATION BY DAVID PARKINS



My whirlwind year with CRISPR

Jennifer Doudna, a pioneer of the revolutionary genome-editing technology, reflects on how 2015 became the most intense year of her career — and what she's learnt.



Emmanuelle Charpentier and Jennifer Doudna



BIOTECHNOLOGY

A prudent path forward for genomic engineering and germline gene modification

A framework for open discourse on the use of CRISPR-Cas9 technology to manipulate the human genome is urgently needed

By David Baltimore,¹ Paul Berg,² Michael Botchan,^{3,4} Dana Carroll,⁵ R. Alta Charo,⁶ George Church,⁷ Jacob E. Corn,⁴ George Q. Daley,^{8,9} Jennifer A. Doudna,^{4,10*} Marsha Fenner,⁴ Henry T. Greely,¹¹ Martin Jinek,¹² G. Steven Martin,¹³ Edward Penhoet,¹⁴ Jennifer Puck,¹⁵ Samuel H. Sternberg,¹⁶ Jonathan S. Weissman,^{4,17} Keith R. Yamamoto^{4,18}

ture developments. The meeting identified immediate steps to take toward ensuring that the application of genome engineering technology is performed safely and ethically.

The promise of so-called “precision medicine” is propelled in part by synergies between two powerful technologies: DNA sequencing and genome engineering. Advances in DNA sequencing capabilities and genome-wide association studies have

CURRENT APPLICATIONS. The simplicity of the CRISPR-Cas9 system allows any researcher with knowledge of molecular biology to modify genomes, making feasible experiments that were previously difficult or impossible to conduct. For example, the CRISPR-Cas9 system enables introduction of DNA sequence changes that correct genetic defects in whole animals, such as replacing a mutated gene underlying

1 – SLIPPERY SLOPE: from disease-curing applications towards uses with less compelling or even troubling implications.

2 – RUNAWAY EVOLUTION: a technology with direct evolutionary effect (germline modifications).

3 – RESPONSIBLE USE: the potential for unintended consequences of heritable germline modifications, because there are limits to our knowledge of human genetics, gene-environment interactions, and the pathways of disease (off-target alterations + on-target events with unintended results)

April 22, 2015

«Chinese scientists genetically modify human embryos.

Rumours of germline modification prove true — and look set to reignite an ethical debate”.

Nature, David Cyranosky and Sara Reardon



«Genome editing» in abnormal human embryos with CRISPR/cas9 method (Junjiu Huang, Sun Yat-sen University in Guangzhou; about beta-thalassaemia).

- a) **IMMATURE TECHNIQUE:** The researchers say that their results reveal serious obstacles to using the method in medical applications. A warning to any practitioner who thinks the technology is ready for testing to eradicate disease genes.
- b) **OFF-TARGET MUTATIONS,** in surprising number.
- c) **READY-TO-USE:** ubiquitous access and simplicity of the method; such experiments are now possible everywhere.

Feb. 2016, Human Fertilisation Authority UK: permission for F. Crick Institute (Kathy Niakan)

The Economist

How Russians cope with recession
No-go for NGOs in China
Islamic State's taste for slavery
Commodities: the binge, the hangover
India's poet-politicians

AUGUST 22ND - 28TH 2014

Economist.com

Editing humanity

The prospect of genetic enhancement



INSIDE THIS WEEK: A 16-PAGE SPECIAL REPORT ON WATER

The Economist

The battle of Bangkok
America's surprising primaries
Does Facebook know too much?
Labour after Gordon Brown
How to plug an oil well

AUG 22ND - 28TH 2014

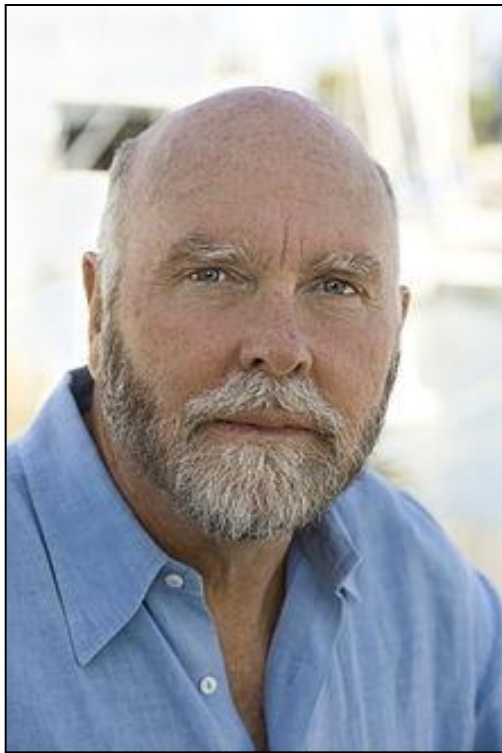
Economist.com

And man made life

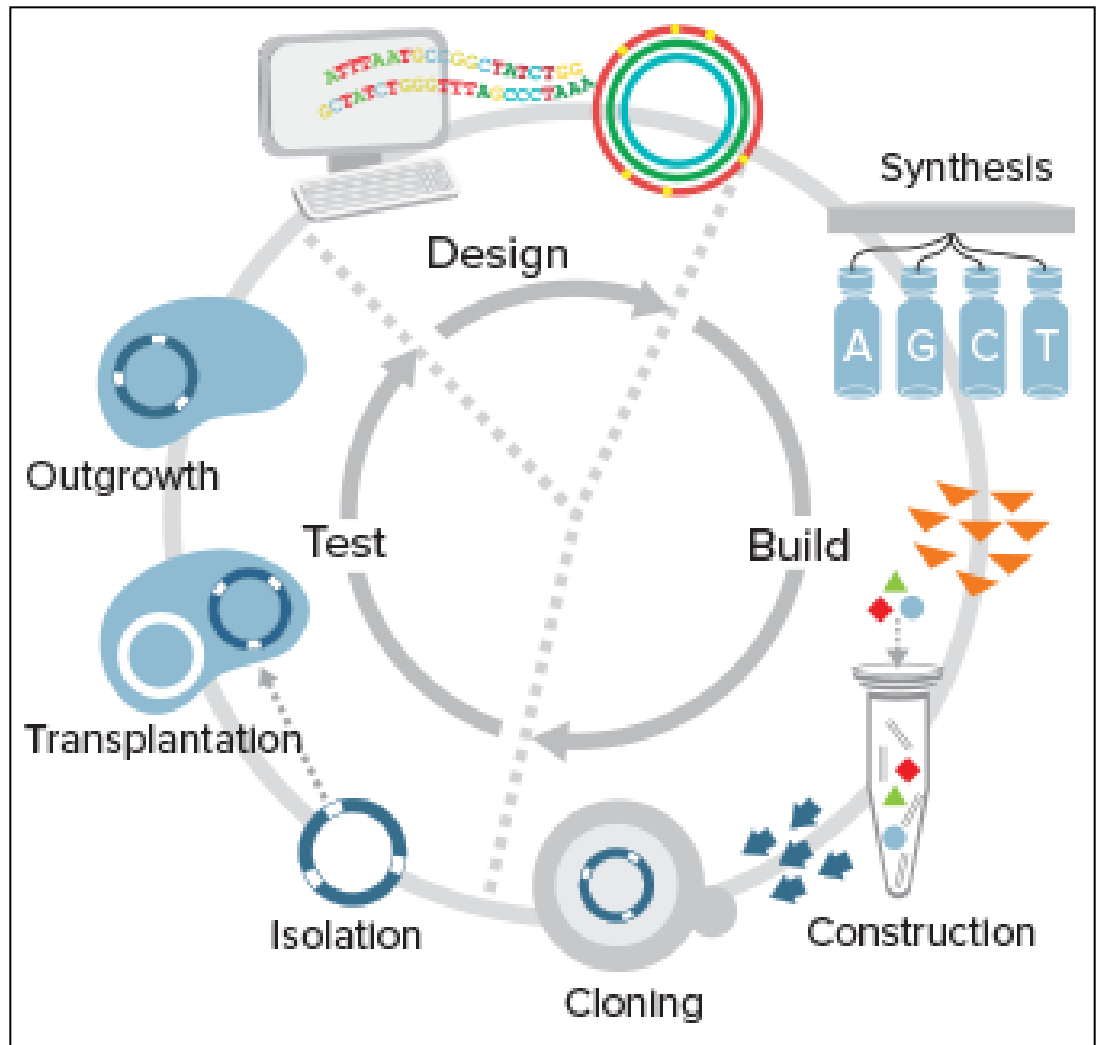


MINIMAL CELL

JCVI-SYN3.0 | FIRST MINIMAL SYNTHETIC BACTERIAL CELL



Craig Venter



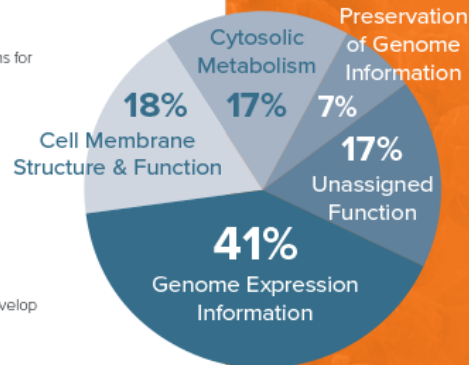
MILESTONES IN JCVI SYNTHETIC BIOLOGY RESEARCH AND POLICY

- **1995-99** **Minimal Genome Project Begins**
 Mycoplasma genitalium genome sequenced and minimal genome project begins. Ethical review of work is published in Science in 1999.
- **2004** **PhiX Synthesized**
 Venter team publishes PhiX174, the synthesized version of this was the first step in the team's goal of constructing a fully synthetic organism.
- **2005** **Synthetic Genomics, Inc. Formed**
 SGI formed to commercialize advances in synthetic biology.
- **2007** **Bacterial Genome Transplantation**
 JCVI synthetic genomics team makes breakthrough in transforming one bacterial species into another through genome transplantation.
- **Synthetic Genome Policy Paper**
 JCVI-led team publishes major policy report outlining options for governance of synthetic genomics.
- **2008** **First Synthetic Bacterial Genome**
 JCVI scientists construct first synthetic bacterial genome.
- **2010** **First Self-replicating Synthetic Cell**
 Synthetic bacterial cell constructed by JCVI researchers.
- **SGVI formed**
 Synthetic Genomics Inc. and JCVI form new company to develop next generation vaccines.
- **2013** **Synthetic Influenza Vaccine**
 Research team publishes new methods for synthetic generation of influenza vaccines.
- **2014** **Leader in Synthetic Biology Policy**
 JCVI-led policy group publishes report on challenges and options for oversight of synthetic biology technologies.
- **2015** **Efficient Synthetic Biology Methods**
 Scientists at the J. Craig Venter Institute Publish Paper Outlining Efficient Synthetic Biology Methods to Genetically Engineer Microalgae. Results have important implications in developing algae-based products such as biofuels and chemicals.
- **DNA Synthesis and Biosecurity Paper**
 JCVI Policy Group Releases New Report: "DNA Synthesis and Biosecurity: Lessons Learned and Options for the Future" which reviews how well the Department of Health and Human Services guidance for synthetic biology providers has worked since it was issued in 2010.
- **2016** **First Minimal Cell Published**

○ JCVI ○ JCVI & Partner

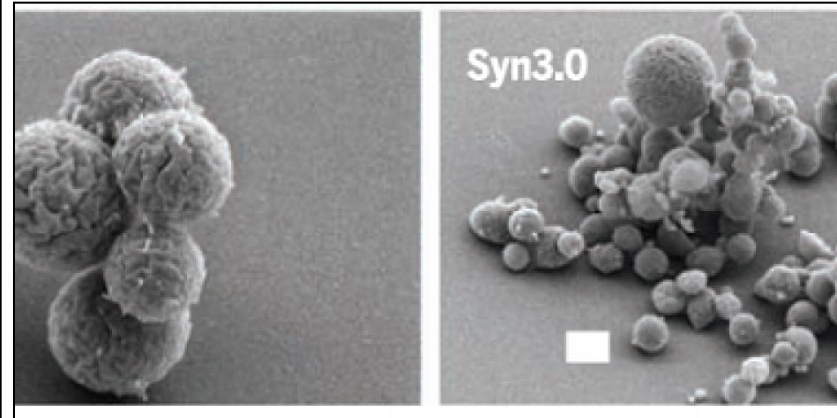
MINIMAL
CELL
473
GENES

CELL MAKE UP



531,560
BASE
PAIRS

149 GENES
OF UNKNOWN
FUNCTION





UNIVERSITÀ
DEGLI STUDI
DI PADOVA

What science and democracy definitely share

Science and democracy are imperfect, open, vulnerable. They both are counter-intuitive human achievements.

Then they need continuous vigilance (early education; communication; public sharing).



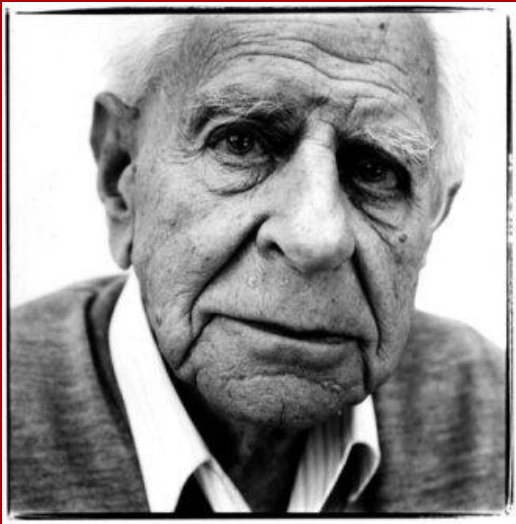


UNIVERSITÀ
DEGLI STUDI
DI PADOVA

What science and democracy
definitely share

Counter-intuitive rules and concepts are particularly at risk in countries with weak public scientific culture and low awareness about the social role of science, like Italy.





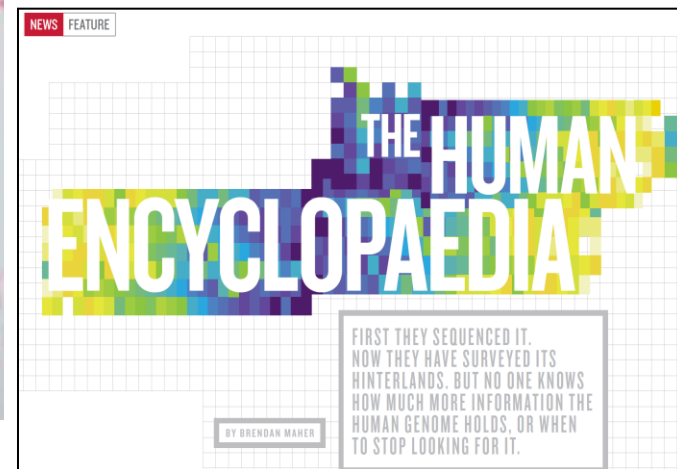
True ignorance is not the absence of knowledge, but the refusal to acquire it. The history of science, like the history of all human ideas, is a history of irresponsible dreams, of obstinacy, and of error. But science is one of the very few human activities — perhaps the only one — in which errors are systematically criticized and fairly often, in time, corrected. This is why we can say that, in science, we often learn from our mistakes, and why we can speak clearly and sensibly about making **progress** there.

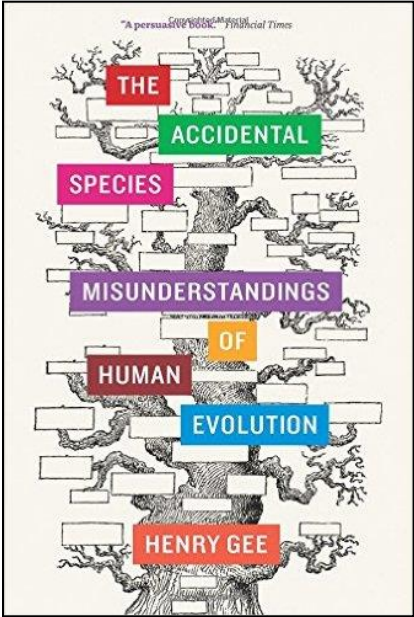
Karl R. Popper, *Conjectures and Refutations* (1963)

From Junk DNA to Jungle DNA

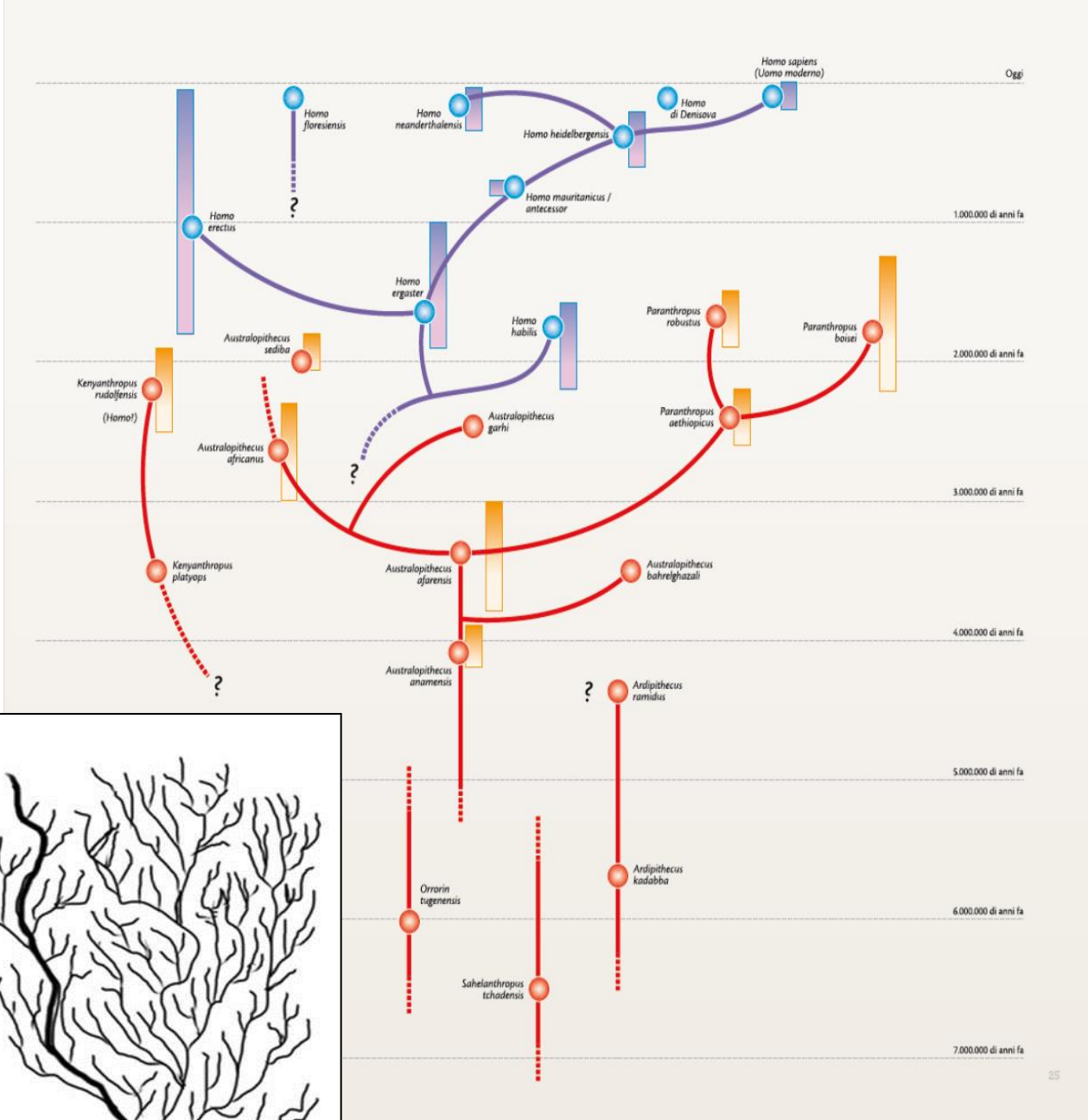
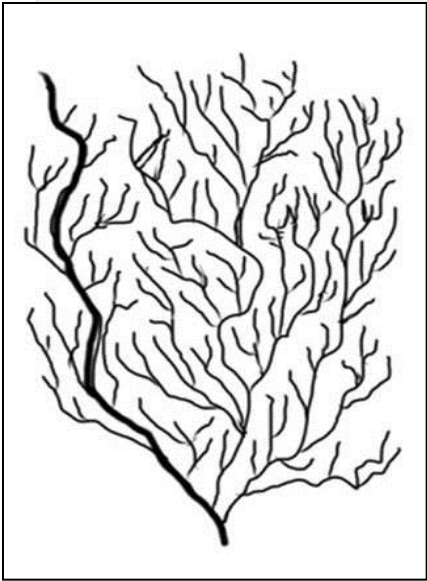
«Quello a cui somiglia il genoma è un'autentica giungla, una foresta fitta, una muraglia di elementi attraverso la quale bisogna aprirsi il passaggio. Cerchi di squarciare la via per raggiungere una certa posizione e non sei veramente sicuro di dove sei. Ho reso l'idea? E' abbastanza facile sentirsi perduti lì dentro»

(Ewan Birney, 2012)





Fossils do not speak for themselves (they need interpretation, and interpretations are made of theories, frames, expectations, story-telling, etc.)



Missing links? Ancestors?

HENRY GEE

LA SPECIE IMPREVISTA

Fraindimententi sull'evoluzione umana

Presentazione di
Telmo Pievani

il Mulino

**Science is not about truth, but
doubt, not about knowledge but
ignorance, not certainty but
uncertainty.**

**We know that there are things we
do not know. But there are also
things that we do not know we do
not know.**

**And this is the only way we have
to fight against any kind of
fundamentalism.**



**Having your work
much to do with
democracy and public
debates... you have a
social responsibility:**

Good luck!