Jorge Alegre-Cebollada

Moral dilemmas in scientific research

Disclosure: you're going to hear about my opinions

You're more than welcome to share yours!

Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III

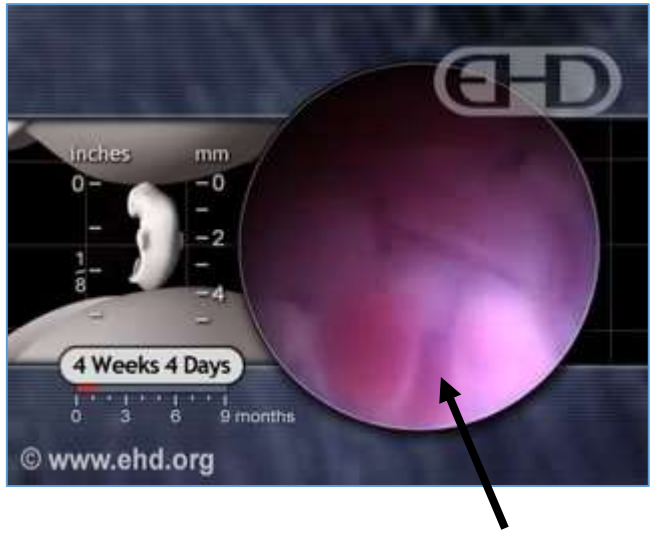
NIAIA
Formación e Investigación en la Resolución de Problemas Morales

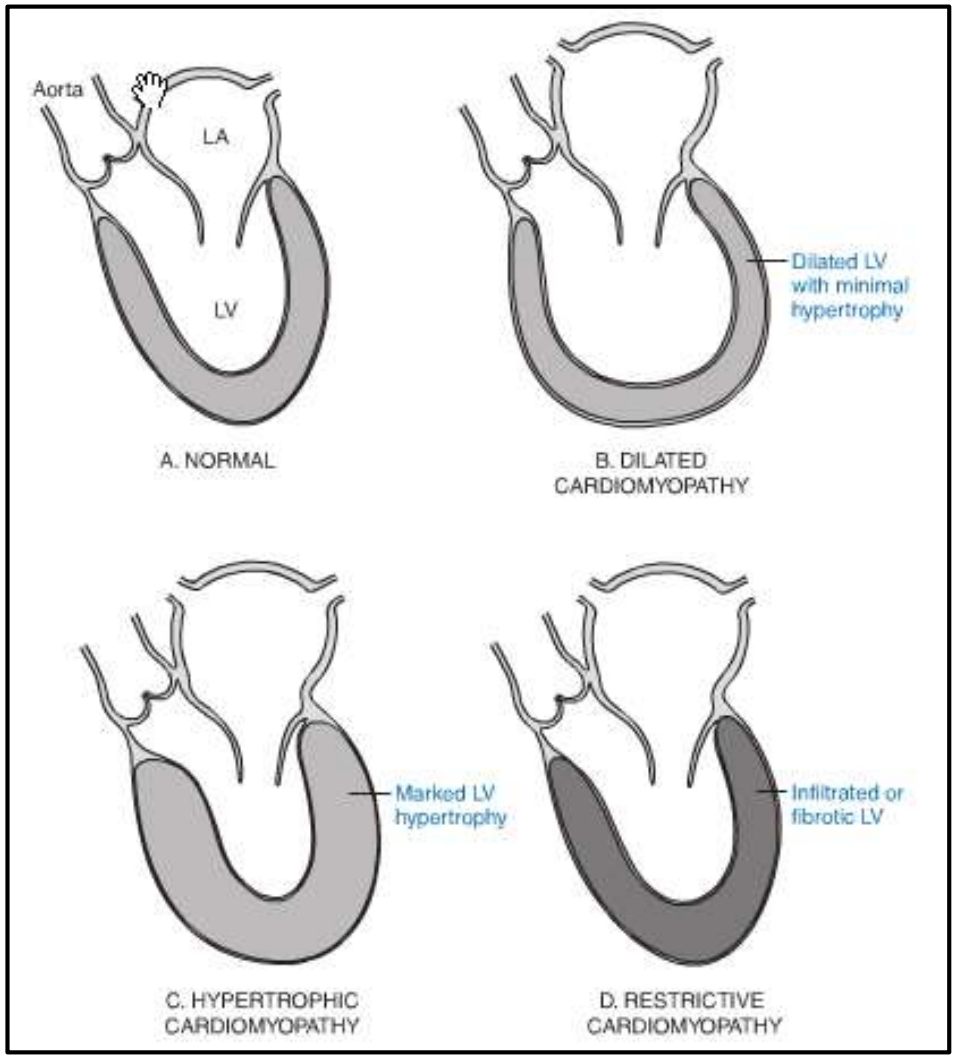
Single-molecule Mechanobiochemistry

Cristina Sánchez, Diana Velázquez, Carla Huerta, Carmen Suay, Elías Herrero-Galán

Collaborators: P. García (*Hospital Puerta de Hierro*); Health in Code (*A Coruña*); J. Delgado, L. Serrano (*CRG*); J. Vázquez's lab (*Proteomics, CNIC*); M.A. del Pozo's lab (*CNIC*); R. Pérez-Jiménez's lab (Nanogune)

Altered mechanical properties of the heart cause disease… why?

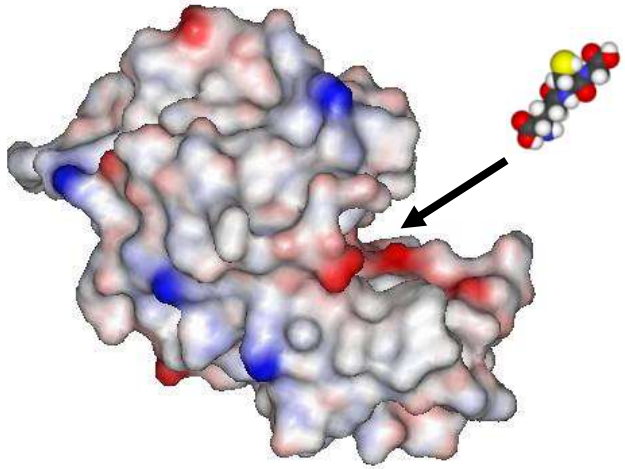




Why do we want to know?

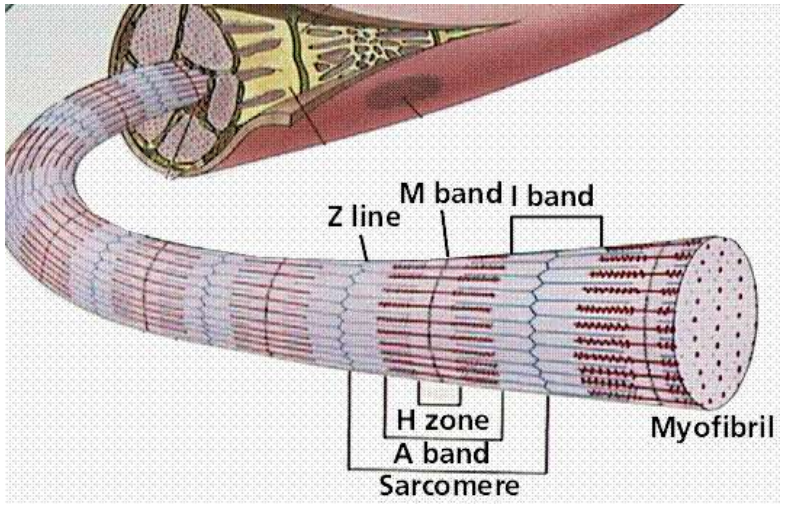
Diagnosis

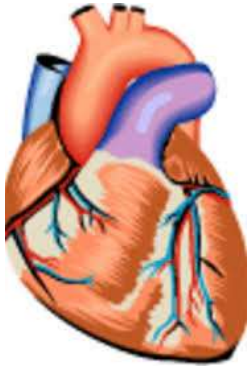
Therapy



The sarcomere is the functional unit of striated muscle

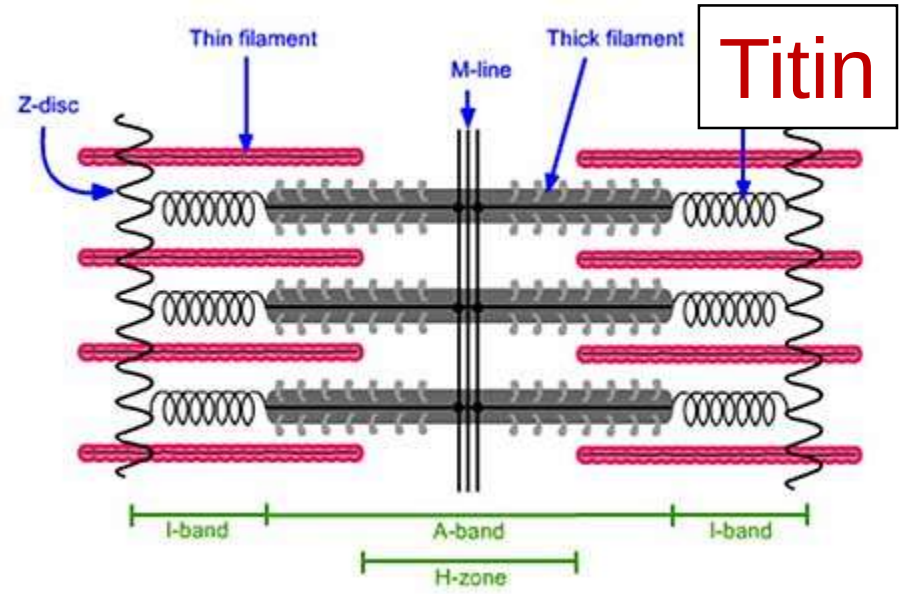
Skeletal muscle





Cardiac muscle

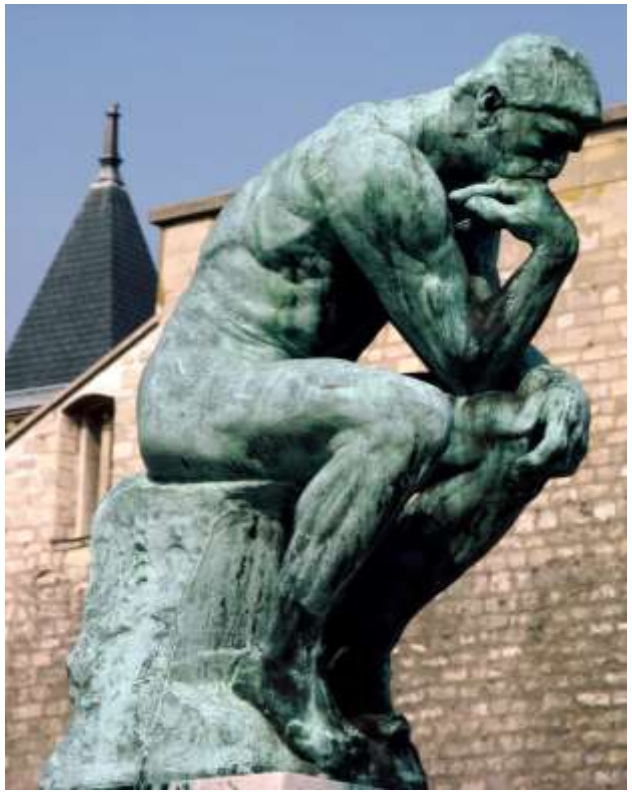
Sarcomere



In which ways being a researcher brings moral dilemmas?

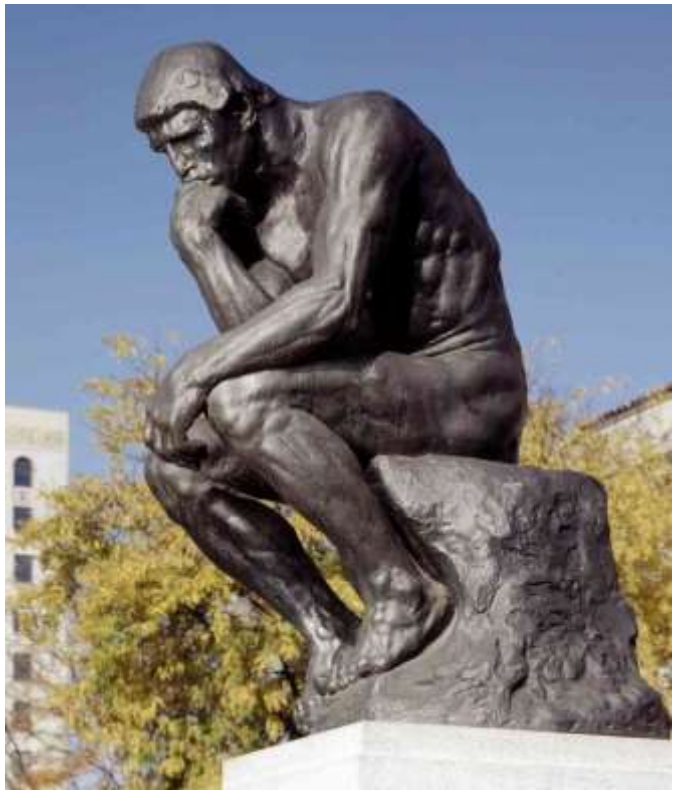
Scientific activity is usually considered to show high ethical standards, but…

Are my products morally acceptable?



Are the tools that I use morally acceptable?

Is my activity morally acceptable?

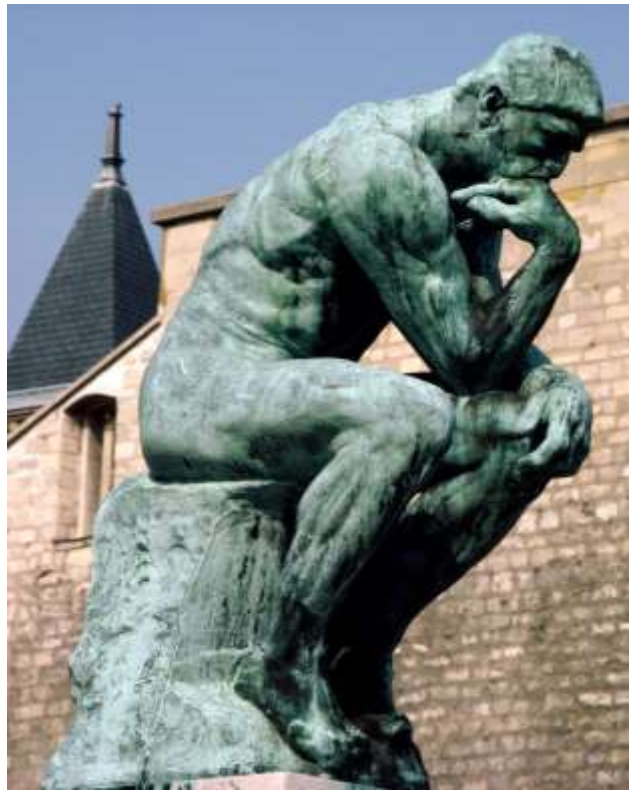


Why should we care at all?

Science is supported by society

Science provides products but does not define their use

Are my results morally acceptable?



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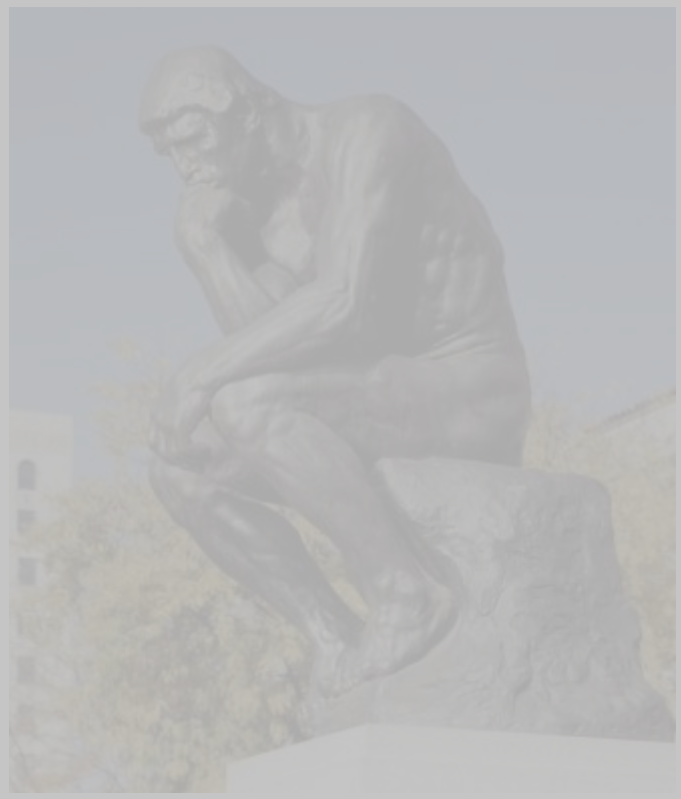
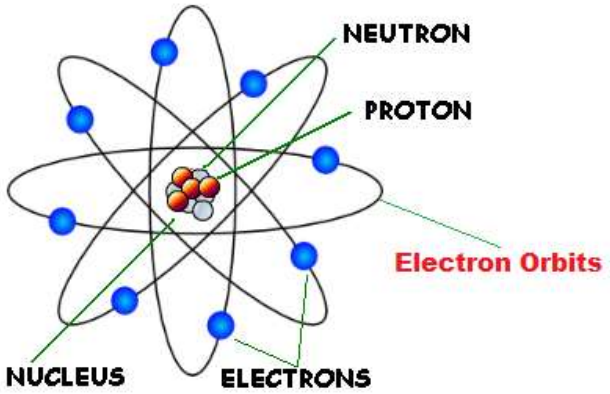


The development of nuclear physics

Ernest Rutherford
Pioneer of nuclear physics



Rutherford's
Atomic Model
(1910's)

Nuclear Weapons
(1940's)

Manhattan Project for the development of nuclear weapons

Albert Einstein
Old Grove Rd.
Nassau Point
Peconic, Long Island

August 2nd, 1939

F.D. Roosevelt,
President of the United States,
White House
Washington, D.C.

Sir:

Some recent work by E.Fermi and L. Szilard, which has been communicated to me in manuscript, leads me to expect that the element uranium may be turned into a new and important source of energy in the immediate future. Certain aspects of the situation which has arisen seem to call for watchfulness and, if necessary, quick action on the part of the Administration. I believe therefore that it is my duty to bring to your attention the following facts and recommendations:

In the course of the last four months it has been made probable - through the work of Joliot in France as well as Fermi and Szilard in America - that it may become possible to set up a nuclear chain reaction in a large mass of uranium,by which vast amounts of power and large quantities of new radium-like elements would be generated. Now it appears almost certain that this could be achieved in the immediate future.

This new phenomenon would also lead to the construction of bombs, and it is conceivable - though much less certain - that extremely powerful bombs of a new type may thus be constructed. A single bomb of this type, carried by boat and exploded in a port, might very well destroy the whole port together with some of the surrounding territory. However, such bombs might very well prove to be too heavy for transportation by air.

-2-

The United States has only very poor ores of uranium in moderate quantities. There is some good ore in Canada and the former Czechoslovakia, while the most important source of uranium is Belgian Congo.

In view of this situation you may think it desirable to have some permanent contact maintained between the Administration and the group of physicists working on chain reactions in America. One possible way of achieving this might be for you to entrust with this task a person who has your confidence and who could perhaps serve in an inofficial capacity. His task might comprise the following:

a) to approach Government Departments, keep them informed of the further development, and put forward recommendations for Government action, giving particular attention to the problem of securing a supply of uranium ore for the United States;

b) to speed up the experimental work,which is at present being carried on within the limits of the budgets of University laboratories, by providing funds, if such funds be required, through his contacts with private persons who are willing to make contributions for this cause, and perhaps also by obtaining the co-operation of industrial laboratories which have the necessary equipment.

I understand that Germany has actually stopped the sale of uranium from the Czechoslovakian mines which she has taken over. That she should have taken such early action might perhaps be understood on the ground that the son of the German Under-Secretary of State, von Weizsäcker, is attached to the Kaiser-Wilhelm-Institut in Berlin where some of the American work on uranium is now being repeated.

Yours very truly,

(Albert Einstein)

Oppenheimer, after the first successful atomic test:
“I am become Death, the destroyer of worlds” (Bhagavad-Guita)

Fritz Haber (1868-1934)

"During peace time a scientist belongs to the world, but during war time he belongs to his country"

Synthesis of ammonia

$$N_2(g) + 3H_2(g) \leftrightarrow 2NH_3(g)$$

- Production of fertilizers
- It has enabled to feed the whole world population
- Nobel Prize in Chemistry (1918)

Development of chemical weapons (1915)

Scientists borrow tools from nature

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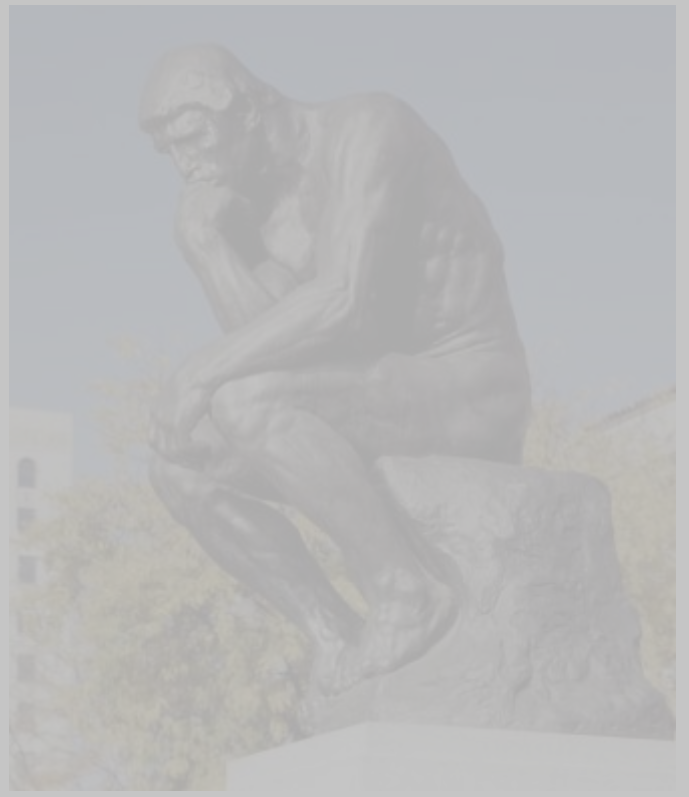
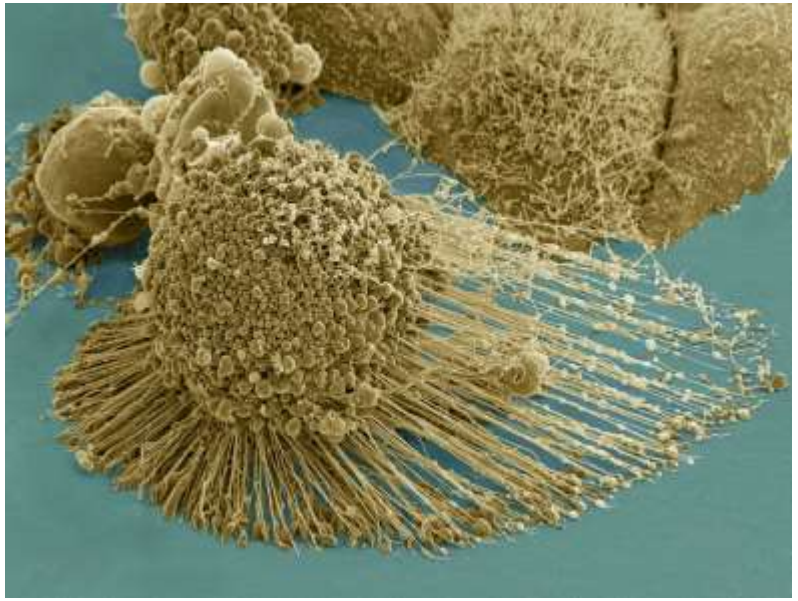
Is my activity morally acceptable?



HeLa cells

Henrietta Lacks

- HeLa cells were obtained from Henrietta Lack's cervical tumor in 1951. Cells were obtained and distributed without consent. Neither Henrietta or her family knew that her cells would be used for scientific research
- It was the first immortal cell line, which made them an ideal research tool
- They were used to develop the first polio vaccine
- 11.000 patents are based on HeLa cells
- The use of HeLa cells is still common in many laboratories around the world



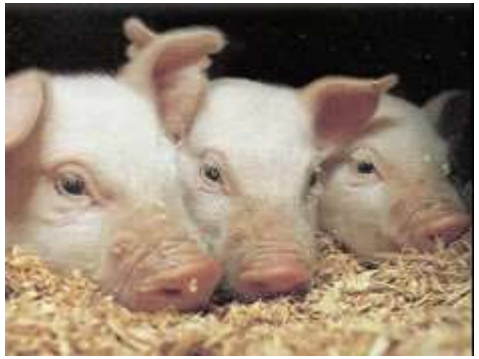
Contemporary human subject research

The Declaration of Helsinki (1964, latest amend in 2013) sets the basic rules that most countries follow. Some of its key points:

- While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
- The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The research protocol must be submitted [...] to the concerned research ethics committee before the study begins
- Every precaution must be taken to protect the privacy of research subjects.
- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary.

Research with animals

Only in the EU, 11 million animals are used in research every year



Scientific activity provides general rules of how things work

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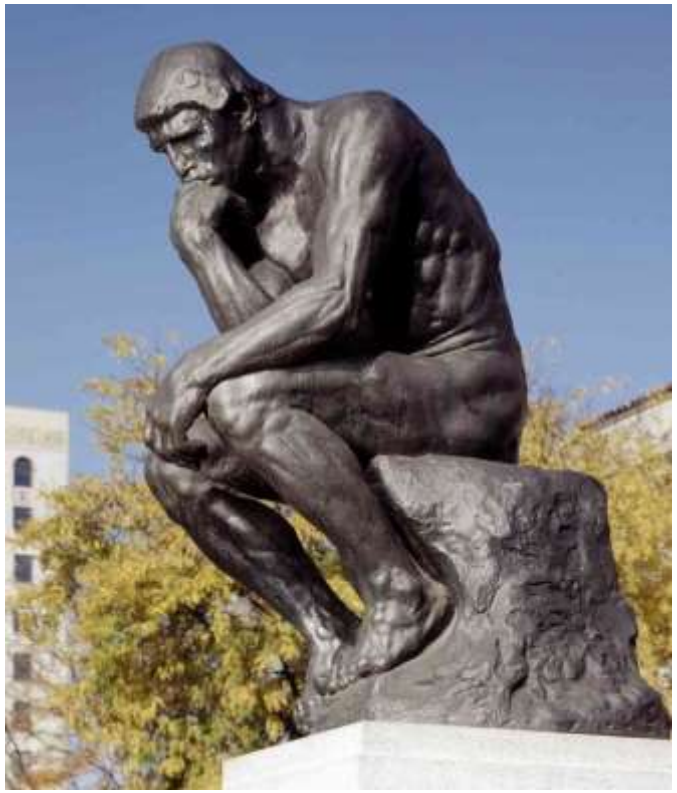
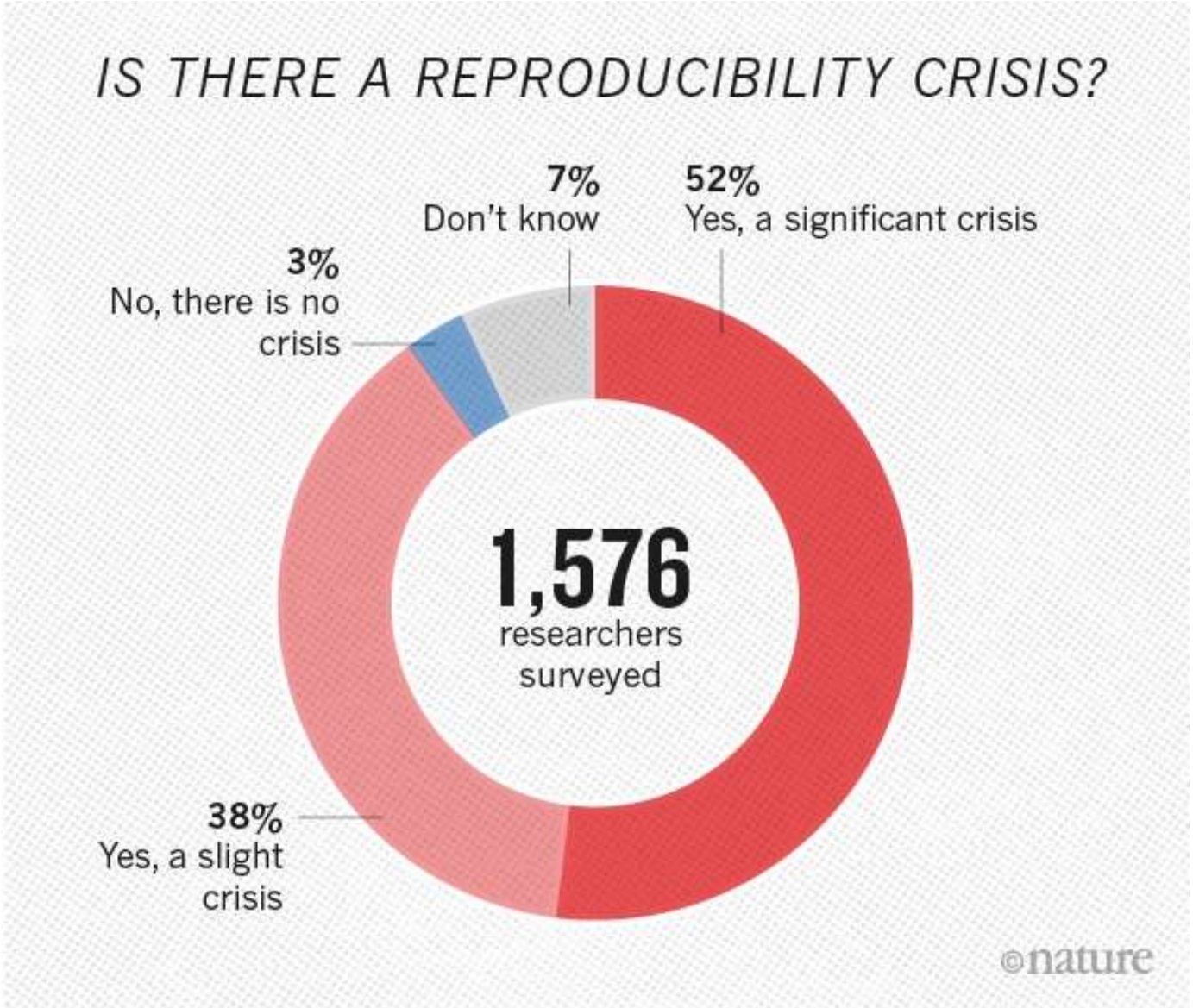


A reason for concern

La investigación es fundamental para lograr mejores resultados en la lucha contra el cáncer. Por ello, la investigación contra el cáncer es uno de los pilares de actuación de la aecc, que promueve y financia proyectos de investigación biomédica y social.

More than 70% of papers in the cancer field published in the most prestigious journals cannot be reproduced…

Begley and Ellis (2012) **Nature** 483, 531



Nature 533, 452 (2016)

First indications that society may stop trusting science?

The Economist | World politics | Business & finance | Economics | Science & technology | Culture

Unreliable research

Trouble at the lab

Scientists like to think of science as self-correcting. To an alarming degree, it is not

Oct 19th 2013 | From the print edition | Timekeeper | Like 22k | Tweet 2,274

"There are errors in a lot more of the scientific papers being published, written about and acted on than anyone would normally suppose, or like to think."

CDB

RIKEN Kobe since 2000

Questions have dogged the STAP technique—which the researchers claimed could make all the cell types in a mouse fetus—from the start.

Nature retracts controversial stem cell papers

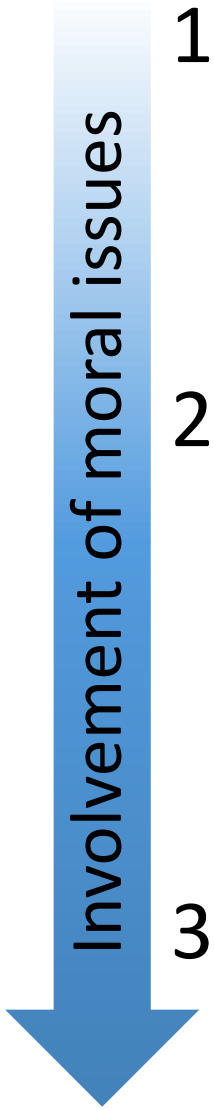
How Japan's stem cell study became a scandal

Pioneering research on stem cells in Japan took a series of bizarre turns.

Senior RIKEN scientist involved in stem cell scandal commits suicide

Tweet 36 | Share 435 | G+1 16

Sources of irreproducibility



1. Stuff is difficult

   Researching the unknowns is difficult and brings multiple challenges: it is virtually impossible to control all variables that contribute to the result of an experiment

2. Sloppy research and malpractice

   An example: when publishing a paper is more important than the scientific discovery. “I know that our experimental design is problematic but I will describe it in such a way that the reviewer won’t be able to catch it”
   In many instances, a problem derived from lack of training

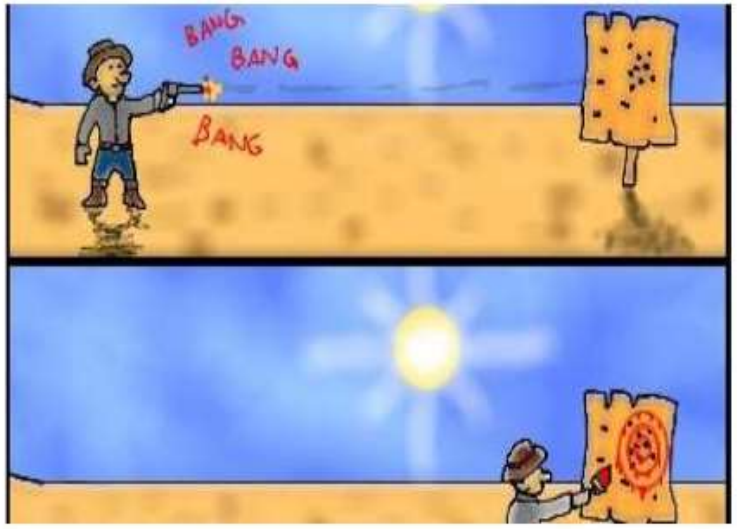
3. Fraud

   Unethical actions that take advantage of the fragility of the system for the own benefit

Solutions:

1. If the stuff is difficult, improve methods section, and make raw data available
2. To avoid sloppy science: we must identify sloppy practices

Texas Sharpshooter Fallacy



"Data don't make any sense,
we will have to resort to statistics."

How to fight sloppy research

- Scientific community has to realize that sloppy research is probably its main enemy
- Critical thinking. Scientists must be their most critical reviewer and have to be as critical with themselves as with other fellows
- Science is about discussing data and ideas. Scientist have to ask questions and raise concerns if necessary in seminars, conferences, etc.
- Improvements of the peer review system: publication of reviewing reports, post-publication review (PubPeer)
- Don’t get carried away by competition. “Losing” is way better than producing sloppy science.
- Tell your trainees about sloppy research and how to avoid it

Some factors that can worsen the impact of irreproducibility on the society

- The problem of irreproducibility is worsened because the career of the professional scientist is unknown for the society

- Current science system generates expectations that are not realistic

Evolution of professional scientists

Lavoisier

1700’s

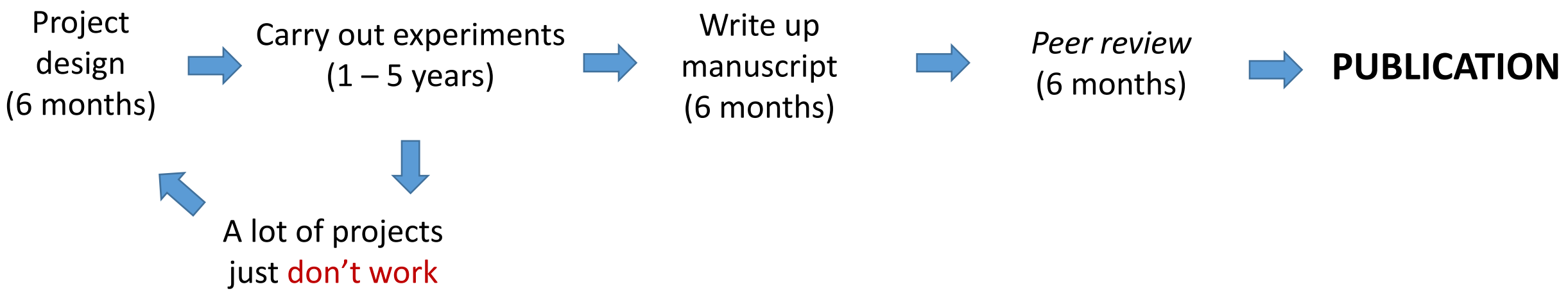
- Aristocrats
- Self-funded

2000’s

- Professionals
- Public funds

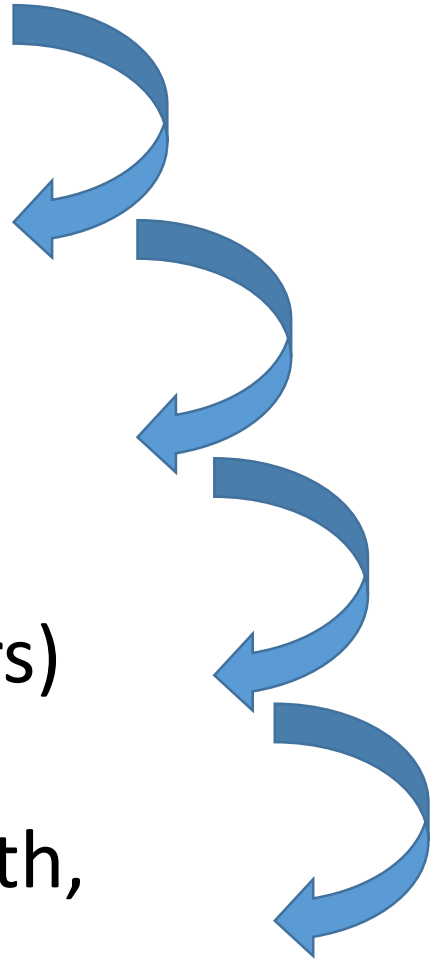
Goals of the professional scientist

- Make discoveries
- Publish papers



The career of a scientist

- Master
- PhD (4-5 years)
- Postdoc (4-8 years)
- Junior group leader (5-10 years)
- Senior group leader (until death, or retirement, do us part…)



Grades

Publications

Publications

Publications

Conflict of interest

Received 29 May 2014 | Accepted 8 Oct 2014 | Published 2 Dec 2014

DOI: 10.1038/ncomms6515

Mybpc3 gene therapy for neonatal cardiomyopathy enables long-term disease prevention in mice

Giulia Mearini[1,2,*], Doreen Stimpel[1,2,*], Birgit Geertz[1,2], Florian Weinberger[1,2], Elisabeth Krämer[1,2], Saskia Schlossarek[1,2], Julia Mourot-Filiatre[1,2], Andrea Stoehr[1,2], Alexander Dutsch[1,2], Paul J.M. Wijnker[1,2], Ingke Braren[1,2,3], Hugo A. Katus[4,5], Oliver J. Müller[4,5], Thomas Voit[6], Thomas Eschenhagen[1,2] & Lucie Carrier[1,2]

Competing financial interests: L.C., T.E., T.V., O.J.M., G.M., D.S. and J.M.-F. are co-authors of a provisional European Patent Application No. EP13164212, filed 17 April 2013, 'Gene-therapy vectors for treating cardiomyopathy', followed by a provisional international Patent Application No. PCT/EP2014/057984, 17 April 2014. The remaining authors declare no competing financial interests.

The existence of a conflict of interest is not negative *per se*. The problem is when the conflict is not declared or when it interferes with scientific judgement

Conflict of interest

A not-so-obvious example: a physicist studying how grasshopers jump

Should there be a statement of conflict of interest in every single paper? Or should we just be open about it?

Peer review system

1. Authors submit manuscript to a scientific journal

2. Editor evaluates whether the topic is suited for the journal

3. Editor send the manuscript to 2-5 expert reviewers for evaluation of the article. Reviewers are scientists who do not receive any reward or compensation for reviewing manuscripts

4. Reviewers write a evaluation report that is sent to the editor

5. According to the reviewer's comments and her own judgemente, the editor makes the decision to accept, reject or suggest resubmission with minor/major changes (going back to point 3)

The system of peer review is fragile and presupposes honesty

AMERICAN SCIENTIFIC PUBLISHERS
Journal of Computational Intelligence and Electronic Systems
Phone: +86-24-83958379-807 Email: asp.jcies@gmail.com

July 23, 2014

Acceptance Letter

Dear Margaret Simpson, Kim Jong Fun,Edna Krabappel,

Congratulations! As a result of the reviews and revisions, we are pleased to inform you that your following paper has been formally accepted for publication in Journal of Computational Intelligence and Electronic Systems (http://www.aspbs.com/jcies/).

- The text was randomly generated by a computer
- Article was accepted in two journals

The extent of fraud can be minimized but not avoided

Some examples of fraud:

- Piltdown man (1912): a human skull + an orangutan jawbone
- Hwang Woo-Suk (2004-2005): embryonic stem cells from adult tissues. Data were not true.
- Jan Hendrik Schön (2002): many results about organic semiconductors were fake.

Potential consequences of scientific fraud

CHARLIE NEIBERGALL/AP/PA

Dong-Pyou Han (centre) confessed to fabricating and falsifying data on an HIV vaccine.

RESEARCH MISCONDUCT

Uneven response to scientific fraud

The case of jailed US vaccine researcher Dong-Pyou Han shows up inconsistent nature of penalties.

BY SARA REARDON

Rare is the scientist who serves time on charges of research misconduct. But on 1 July, Dong-Pyou Han, a former biomedical scientist at Iowa State University in Ames, was sentenced to 57 months in prison for fabricating and falsifying data in HIV vaccine trials. Han has also been fined US$7.2 million and will be subject to three years of supervised release after he leaves prison.

His case had a higher profile than most, attracting interest from a powerful US senator. Han's harsh sentence raises questions about how alleged research fraud is handled in the United States, from decisions about whether to prosecute to the types of punishment imposed by grant-making agencies.

Han was forced to resign from Iowa State in 2013, after the university concluded that he had falsified the results of several vaccine experiments supported by grants from the US National Institutes of Health (NIH). In some cases, Han spiked rabbit blood samples with human HIV antibodies so that the vaccine seemed to have caused the animals to develop immunity to the virus.

In a confessional letter sent to the university just before its investigation concluded, Han said that he began the subterfuge to cover up a sample mix-up that he had made years before.

The US Office of Research Integrity (ORI), which oversees investigations into alleged misconduct involving NIH funds, barred Han from receiving federal grants for three years — the maximum penalty that it generally imposes on junior investigators. The case probably would have ended there had it not drawn the attention of Senator Charles Grassley (Republican, Iowa), who has a history of investigating misconduct in the biomedical sciences.

This story is the first in an occasional series on research misconduct in the United States.

"This seems like a very light penalty for a doctor who purposely tampered with a research trial and directly caused millions of taxpayer dollars to be wasted on fraudulent studies," Grassley wrote in a February 2014 letter to the ORI. The office can issue lifetime funding bans,

Nature
July 2015

DO NOT EVER, EVER CHEAT!!!

How do I convince society I'm worth of being funded?

1953

Watson and Crick conclude their seminal work about the structure of DNA in Nature by saying:

"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material"

Scientific conclusion

2015

Conclusion of a random paper published also in Nature in 2015.

"In summary, the structure of the F-actin-tropomyosin complex shows how F-actin filaments are stabilized in health and destabilized in certain diseases"

Conclusion has social impact

Where is the balance?

A research system based on public funding

European Union. H2020 program.

H2020 promises more breakthroughs, discoveries and world-firsts by taking great ideas from the lab to the market.

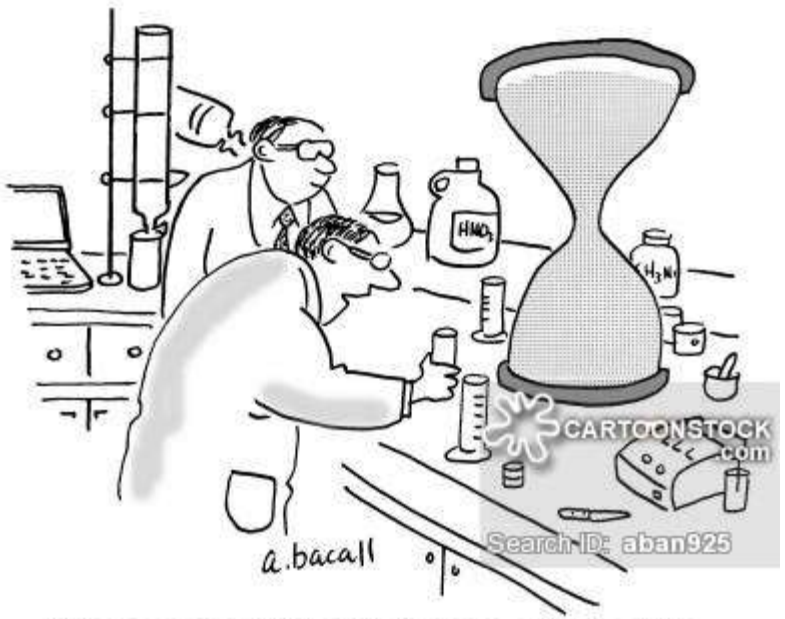
United States. National Science Foundation (NSF)

We are tasked with keeping the United States at the leading edge of discovery in areas from astronomy to geology to zoology

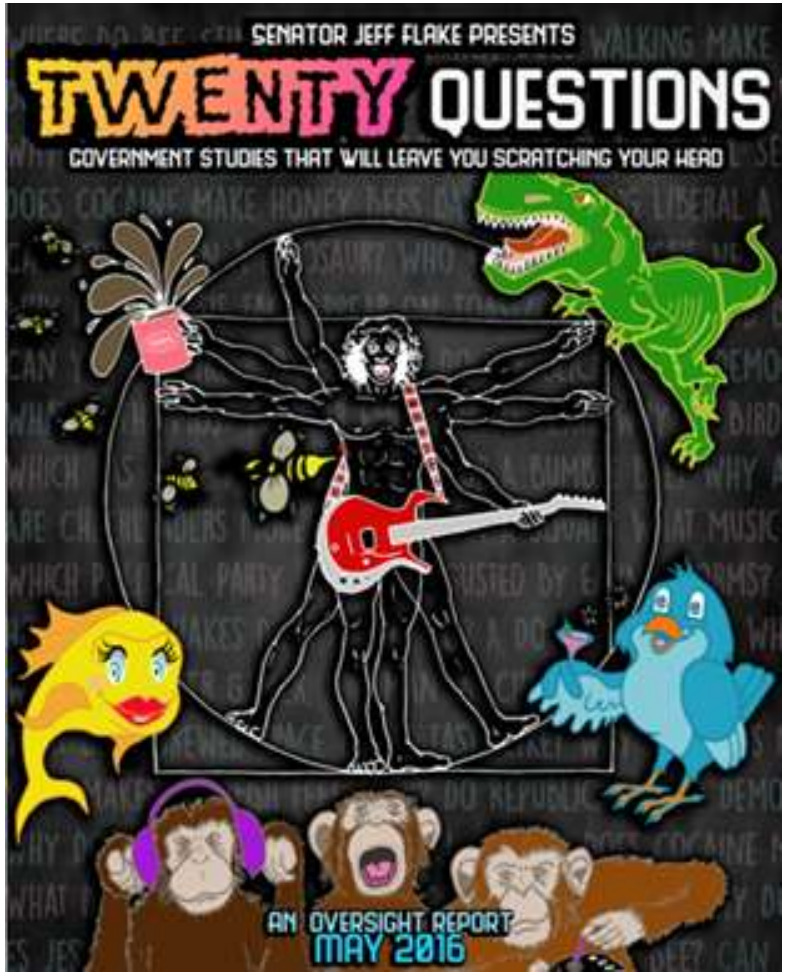
United States. National Institutes of Health (NIH)

NIH is the nation's medical research agency—making important discoveries that improve health and save lives.

Funding bodies are increasingly expecting immediate and useful results



"It's a one-year timer. It gives an added sense of urgency to my research grant."

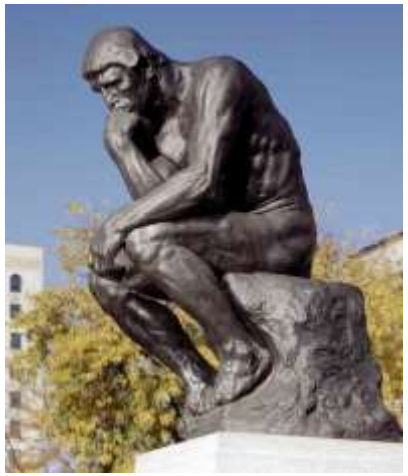


… so what do we do now?

- Science is vocational and as such it self-regulates. Web sites: Retraction watch, PubPeer
- Reach out to society to explain the career of a professional scientist to avoid deceit.
- Lower expectations regarding future impact. **The usefulness of science is shown by past successes but not by future developments.**
- Science police?

- A balance between critical evaluation of results and presumption of innocence
- We have to talk about all these issues and punish severealy those who cheat. However, how much effort de we need to invest to find out whether there has been fraud or not?

Take-home messages



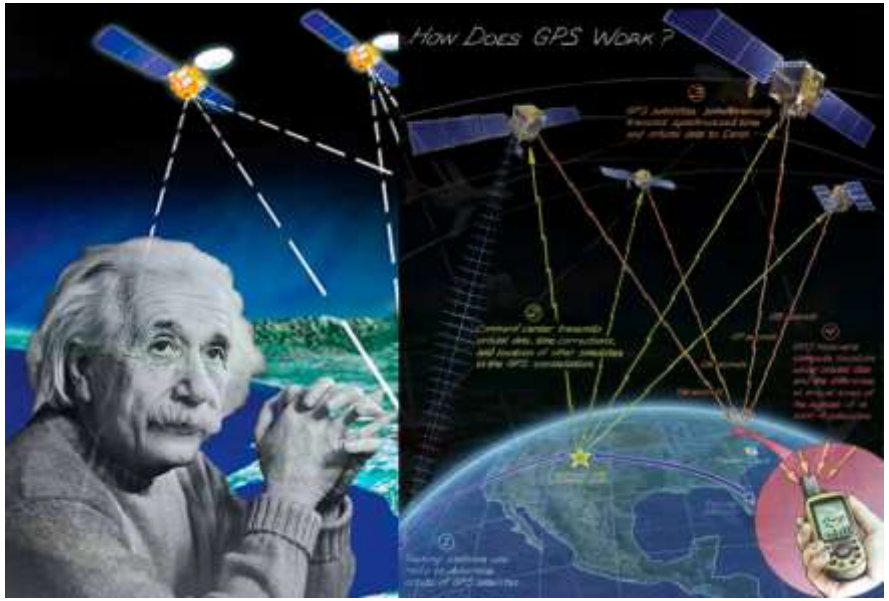
Scientific activity generate plenty of moral dilemmas since:

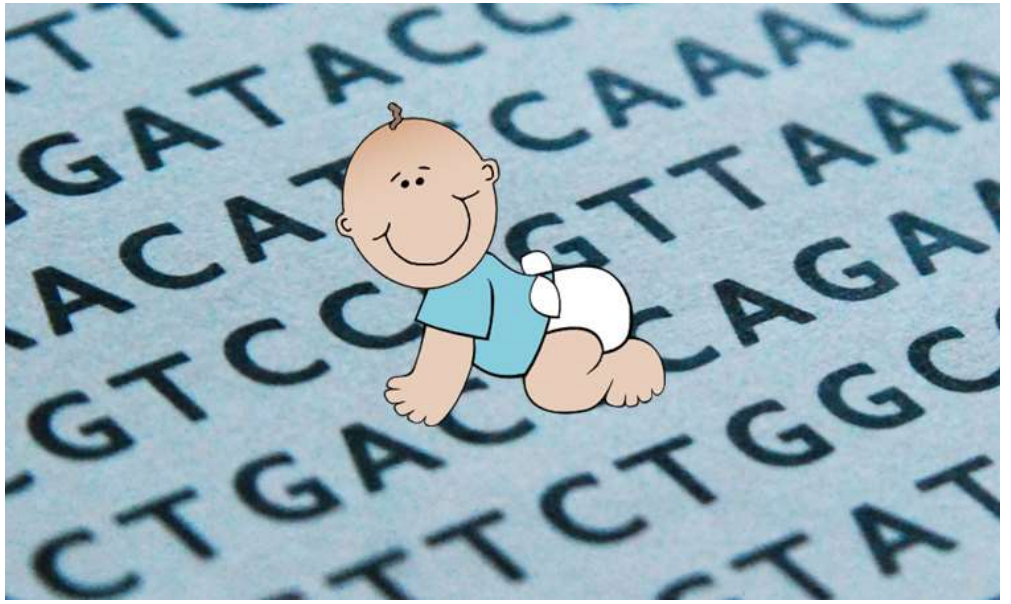
- It provides general rules of how things work
- It provides products but does not define their final use
- it borrows tools from nature

To keep the good image of scientific activity:

- Raise awareness among the scientists that Science has a moral dimension that we need to take care of
- Critical thinking, discussion, training, etc.
- Outreach to society

Yes, the scientific endeavor faces some problems but...





Your project may end up here

Further reading

- Irreproducibility in Science. Editorial article in biofisica.info: http://biofisica.info/articles-4-2/irreproducibility-in-research-what-can-we-do-about-it/

- "Fooling ourselves", **Nature** 526, 182 (2015)... An interesting article on tricks used by our brain for self-deception.

- Lawrence P.A. "The Last 50 Years: Mismeasurement and Mismanagement Are Impeding Scientific Research". **Current Topics in Developmental Biology** 116, 617 (2016)

Many thanks for your comments and suggestions!

jalegre@cnic.es

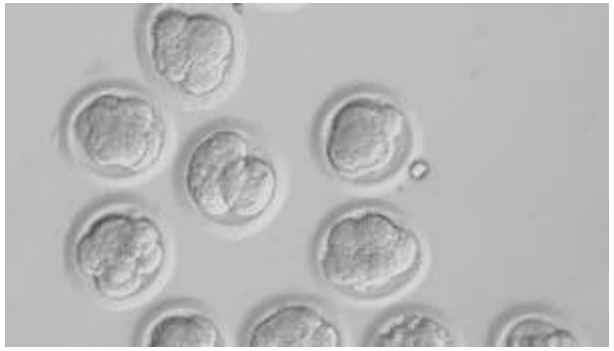
Jorge Alegre-Cebollada

Moral dilemmas in scientific research

Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III

NIAIA
Formación e Investigación en la Resolución de Problemas Morales

Genetics and eugenics



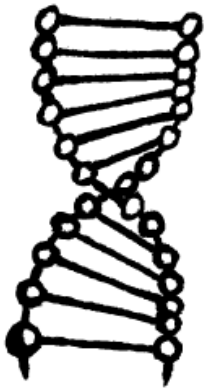
Embryo selection
to avoid genetic disease

Kids with three progenitors
(legal in the UK from 2015)

CRISPR/Cas9 and gene editing in embryos

Should We Move Forward With Human Germline Genome Modification?

48%	52%
No	**Yes**
Germline editing may lead to a world against nature	**You can't stop the advancement of science**
We do not know enough about gene regulation and interactions, balanced polymorphisms, epigenetics, etc	We should allow it with responsible oversight
Designer babies and other eugenic issues cannot be overseen.	It is up to the scientists to push back on the science fiction thinking and push forward the science that can cure disease!
For the same reasons that we don't recommend most drugs to be used during pregnancy	You can take a pill or have a surgical procedure and die. In both cases, risks are clearly communicated to the patient and they have the choice of going forward.

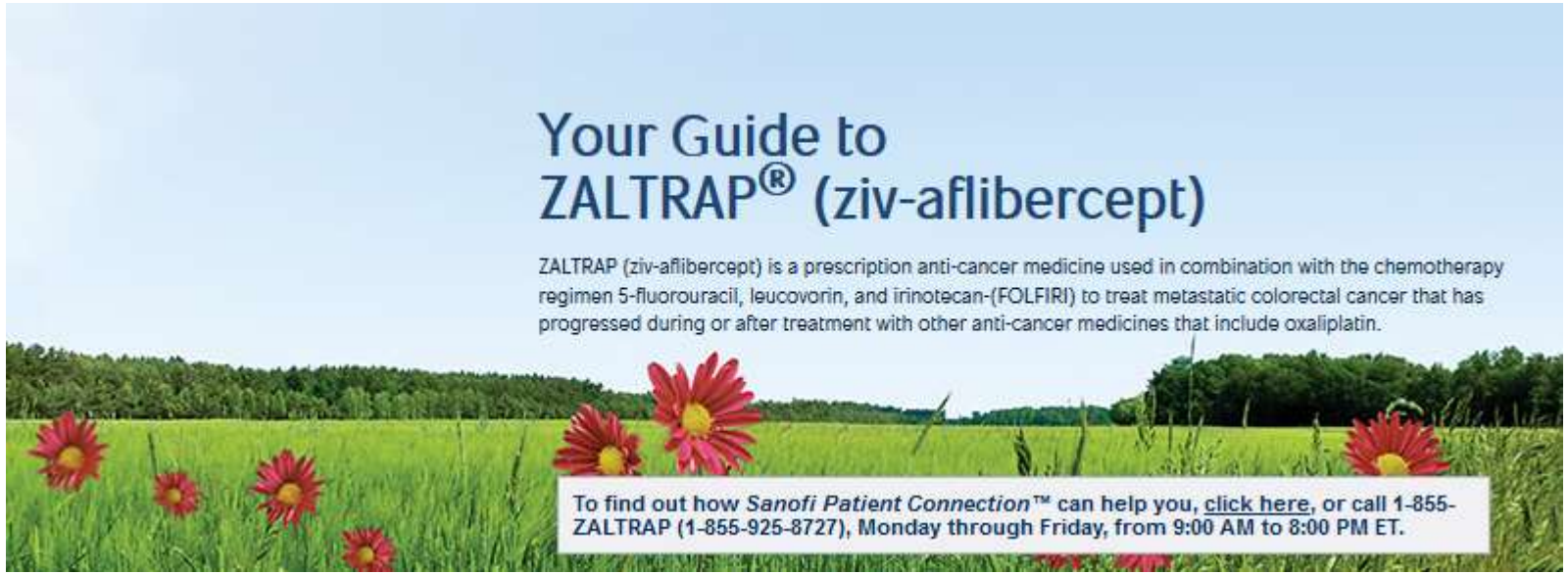


The Science Advisory Board

The Voice of The Scientific Community

*These comments do not represent the views of The Science Advisory Board.
They are redacted excerpts of a discussion between scientists hosted on the ScienceBoard website.

Development of expensive medical treatments



- Zaltrap is a drug for patients with metastatic colon cancer
- The cost of the treatment is more than $10,000 per month
- On average, the drug incresases survival by 1.5 months

Nazi experiments with human subjects

Dilemma: what to we do with data obtained in experiments that are ethically unacceptable?

Are we demanding too much of our scientists? Researcher rehab

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