Università di Pisa

Centro 3R

African Biomedical Engineering Consortium
Innovation through Education

Ethics in Biomedical Research

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Ethics in biomedical research

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Study 1

- Subject wrapped in neoprene and immersed in cold water (5°C) till loss of life.
- Aim: evaluate the performance of military clothing

Study 2

- Subject administered an intravenous drug every 3 days. After 30 days the subject is euthanised to inspect tissue damage.
- Aim: to evaluate the side effects of an anti-cancer drug.

Study 3

- Eye drops are administered to the subject twice a day for 10 days.
- Aim: evaluate the irritancy and toxicity of mascara.

What is ethics?

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- **Ethics** and **morals** relate to “right” and “wrong” conduct. While they are sometimes used interchangeably, they are different: **ethics** refer to rules provided by an external source, e.g., codes of conduct in workplaces or principles in religions. **Morals** refer to an individual’s own principles regarding right and wrong.
- **The two may be in conflict.**
- **Society generally agrees that consensual sex before marriage is acceptable. However my mother thinks it is immoral.**
- By these definitions of the terms, my mother’s *morality* contradicts the *ethics* of the community.

But what does ethics have to do with research?

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Many researchers think that the pursuit of knowledge is above ethics and morals

They think it only applies to the application of results and so is a technology and political issue.

$E=mc^2$

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Biomedical research

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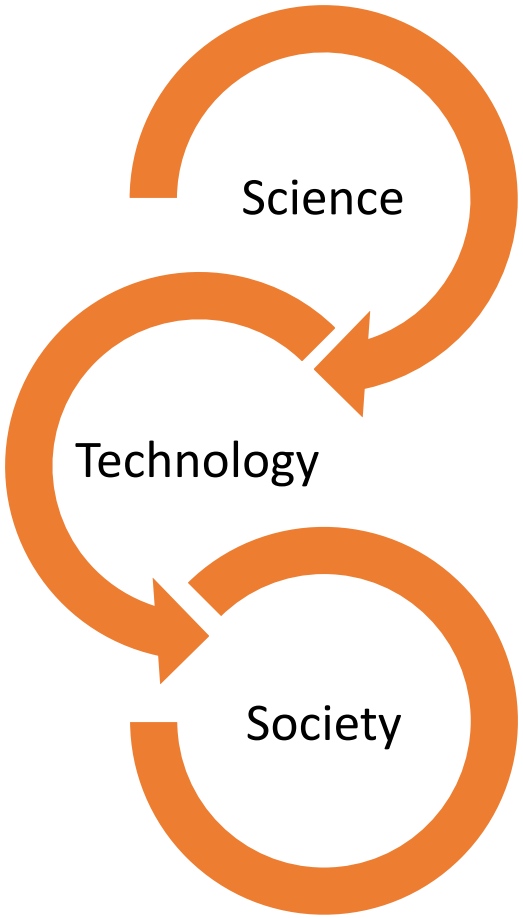
- **Biomedical Science:** Science applied to health.
- **Biomedical Engineering**: Application of engineering principles to human health



Ethics in biomedical research

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- Professional conduct

- Use of living beings

The 7 rules of professional conduct

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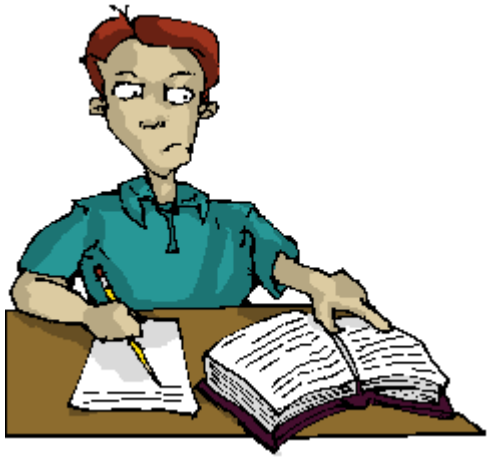

- Do not copy data and texts from others (do not commit plagiarism)
- Do not manufacture and falsify data
- It is incorrect to not publish some data
- Improper data collection procedures are incorrect
- Improper procedures for storing and storing data are incorrect
- The non (or incorrect) -recognition of contributions by others in the research is misconduct.
- It is incorrect to use improper publication methods

Similar rules apply when reviewing and proposing results

8

Falsifying data

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Nature retracts controversial stem cell papers

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By Dennis Normile | 2 July 2014 10:30 am | 2 Comments

TOKYO—*Nature* today published a retraction of two controversial papers that had reported a new, astoundingly simple way of generating pluripotent stem cells. The retraction notice—for an article and a letter written by Haruko Obokata of the RIKEN Center for Developmental Biology (CDB) in Kobe, Japan, and colleagues there, at other institutions in Japan, and at Brigham and Women's Hospital in Boston, an affiliate of Harvard Medical School—had been expected for some time.

The two papers reporting the stimulus-triggered acquisition of pluripotency (STAP) phenomenon appeared online on 29 January. Questions about the papers arose almost immediately, leading to an investigation by RIKEN, the headquarters of the network of the nationally funded laboratories that is based in Wako near Tokyo. Investigators documented several instances of fabrication and falsification in the papers and concluded that some of these constituted research misconduct on the part of Obokata.

Japanese media recently reported that authors had agreed to retract the papers but were discussing the wording of the notice. In the note that appeared today, the authors point to

The Japanese boss committed harakiri after a month

Not acknowledging others

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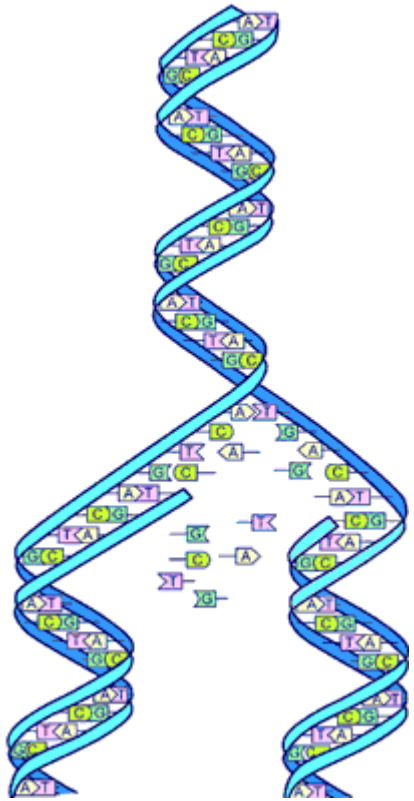

- Watson and Crick, with Wilkins won the Nobel Prize (1962) for deducing the structure of DNA. They used data from a researcher (Rosalind Franklin) to do it, but Franklin was never recognized

Plagiarism☹

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- Self plagiarism==Rehashing
- Copying bits of text or results from others
- Using ideas without reference or acknowledgement

"Your work is both good and original. Unfortunately the parts that are good are not original, and the parts that are original are not good".

Ethical conduct and living beings

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- Human beings

- Animals

Humans in biomedical research

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In the past:

- War prisoners and refugees (1941-1946)
- Tuskegee scandal (1932-1972)
- Vipeholm experiments (1945-1955)

More recent

- Helsinki declaration, ethical principles for human medical experimentation: (1975, 1996, 2000)
- Informed consent and patient protectiom.

Informed consent

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- Informed Consent is the decision, which must be written, dated and signed, to take part in a clinical trial or medical experiment, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.
- **Minors: parents.**
- **Dead persons: next of kin**

Informing is crucial

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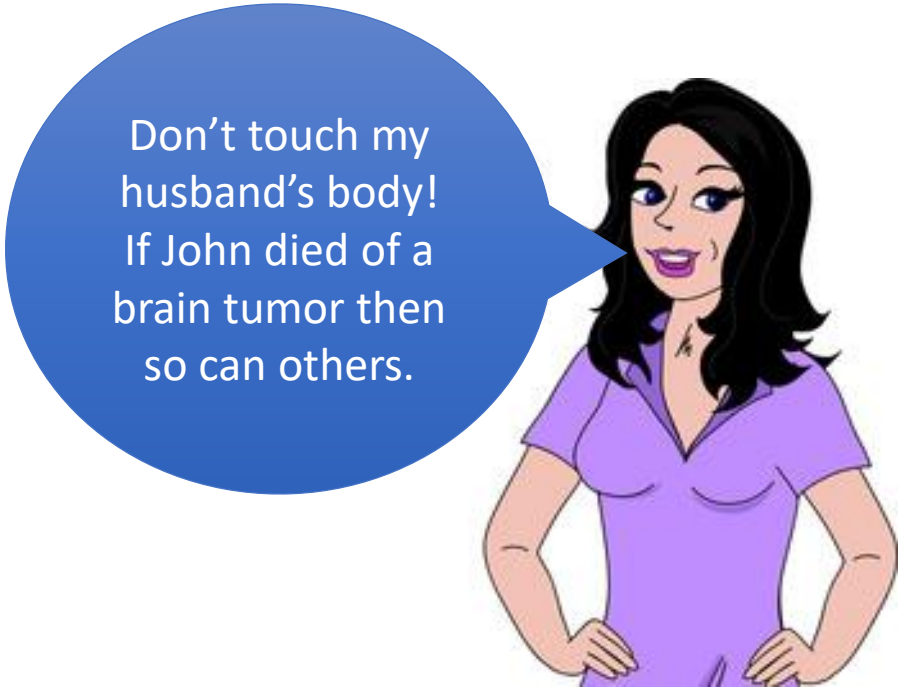

Ethics and research: animal experimentation

Animal models: genetic similarity

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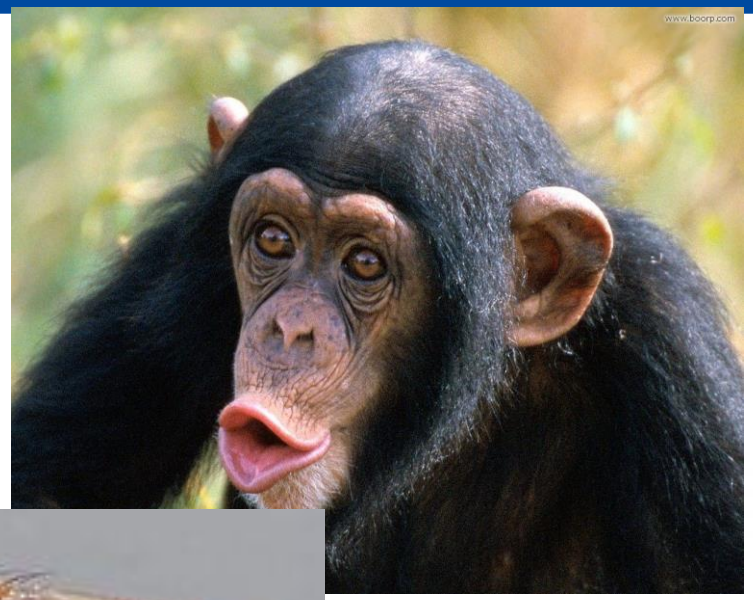

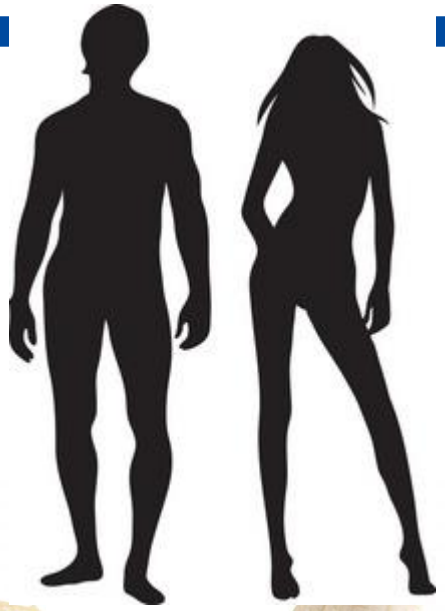

Chimpanzee: 96%
Cat: 90%
Cow: 80%
Mouse: 75%
Drosophila: 60%
Banana: 50%

Debate for and against animal research

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- Would you give your child a medicine which has not been tested?
- Why should an animal not be allowed to give consent?
- The animal dies for a greater good
- A human is not a 70 kg rat
- Animal research has helped save lives
- 92% of drugs fail after clinical trails
- Animal research has led to great discoveries
- ……..

The 3Rs Principles

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- In 1959, Rex Burch and William Russell proposed a principle for humane animal experimentation (Russell, Burch, The principles of humane experimental technique, 1959).
- The 3R principles refers to three fundamental concepts: replacement, reduction and refinement.
- Replacement: replace the animal model with an alternative model;
- Reduction: reduce the number of individuals used in a certain experimental protocol as much as possible;
- Refinement: to refine, or improve, the experimental conditions to which animals are subjected.

Europe's legislation on animal testing (EC Directive 2010/63)

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- In Europe, the law prohibits the sale of cosmetic products tested on animals (since March 2013 in absolute terms and since 2009 in large part).
- In Italy the use of primates in laboratories is prohibited.
- However, drugs must (by law) undergo different stages of experimentation:
- At least 2 live animal species
- At least one must be non-rodent

- In other countries (USA, Japan, India, China) laws are less stringent

Biomedical research: replacement

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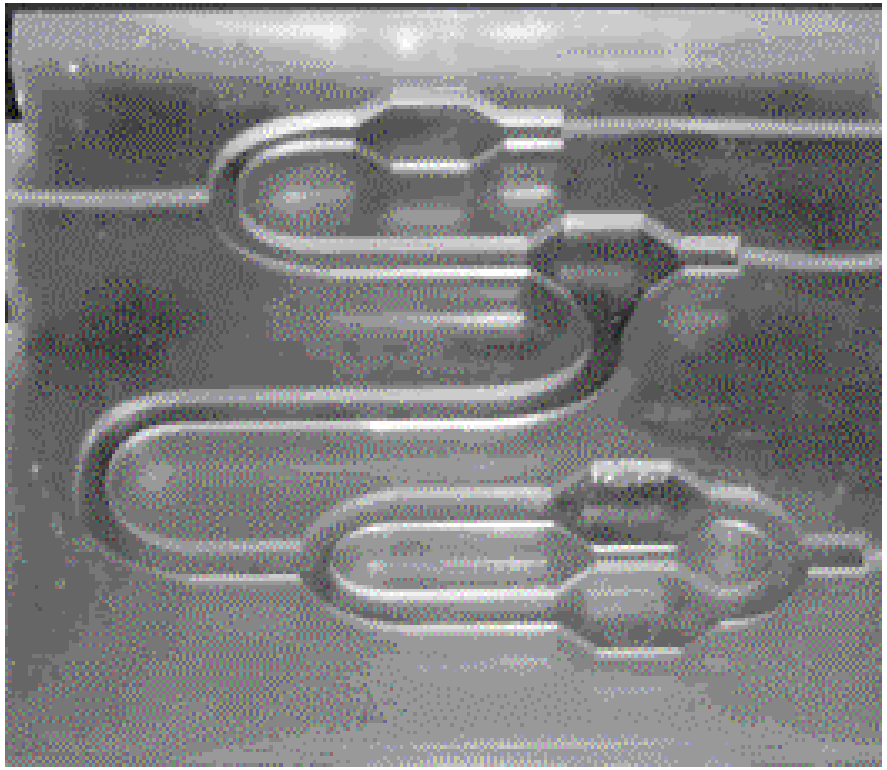
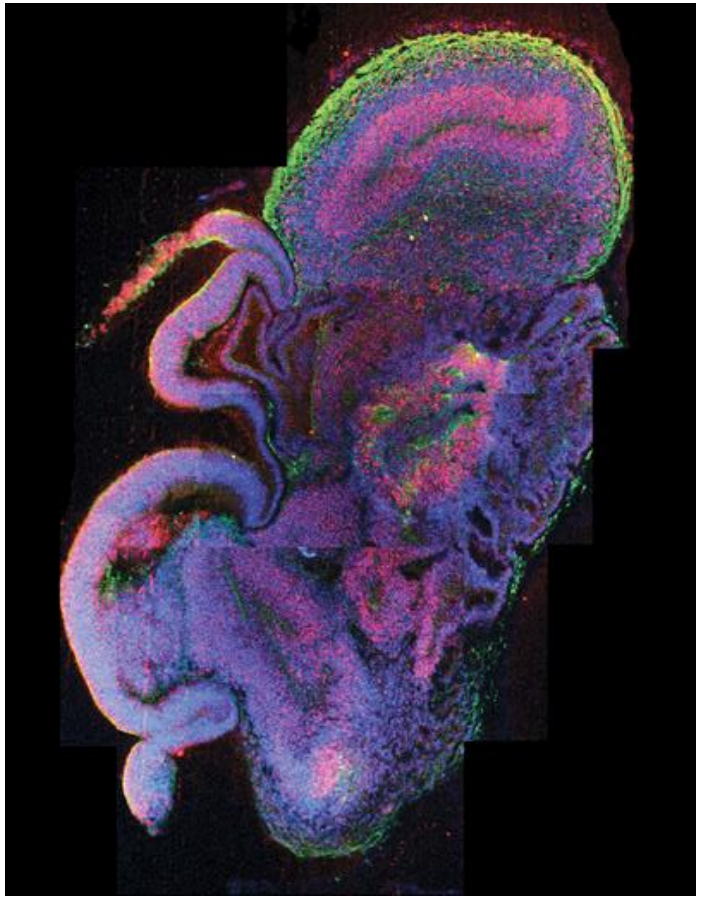


Pancreas

Liver

Blood vessels



Replacement

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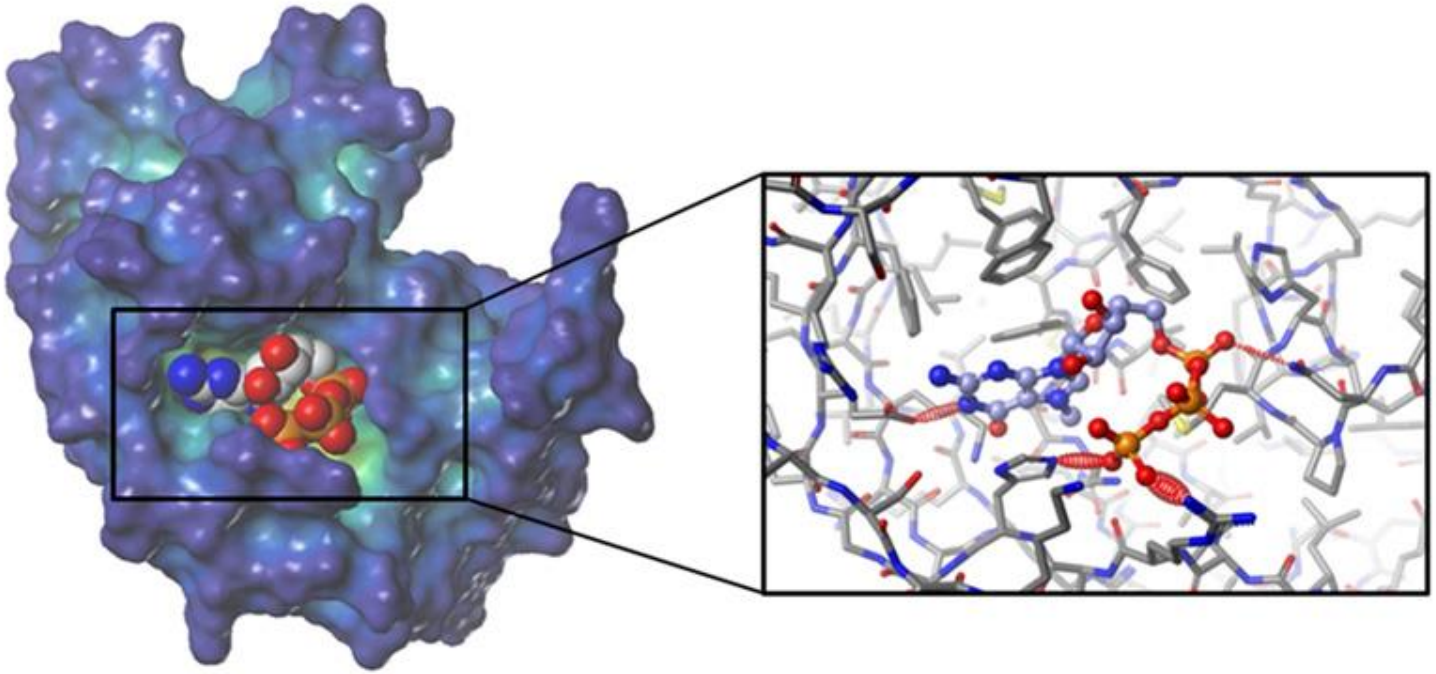
In vitro methods
- Organ-on-a-chip
- Body-on-a-plate

- In silico methods



The animal model in medical device testing

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- Safety testing
  - biocompatibility
- Perfomance testing for pre-clinical assessment
  - Complex anatomies
  - Complex physiological responses
- Quality control
  - test for absence of pyrogens in the infusional/implantable devices

Biocompatibility

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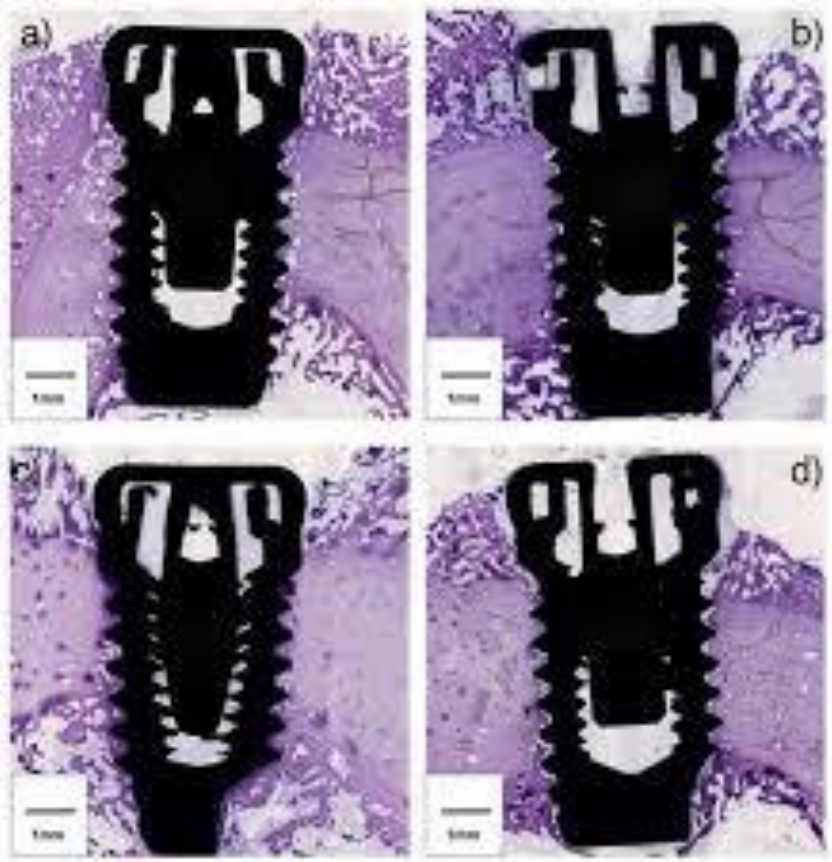
- Blood compatibility
- Local and systemic toxicity
- Irritation, sensitization
- Local effects at implants
- Genotoxicity and reproductive/ developmental toxicity

Skin irritation test



Bone to implant contact is a great parameter to evaluate how well the implant is healed

Device Categories		Examples
Surface devices	Skin	Electrodes, external prostheses, fixation tapes, compression bandages, monitors of various types
	Mucous membrane	Contact lenses, urinary catheters, intravaginal and intraintestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices, IUDs
	Breached or compromised surfaces	Ulcer, burn, and granulation tissue dressings or healing devices, occlusive patches
Externally communicating devices	Blood path indirect	Solution administration sets, extension sets, transfer sets, blood administration sets
	Tissue/bone/dentin communicating	Laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials, skin staples
	Circulating blood	Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialyzers, dialysis tubing and accessories, hemoadsorbents and immunoadsorbents
	Tissue/bone Implant devices	Orthopedic pins, plates, replacement joints, bone prostheses, cements and intraosseous devices, pacemakers, drug-supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, ligation clips
	Blood	Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug-delivery catheters, ventricular-assist devices

Performance testing

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- Compatibility with blood flows
  - For example: haemolysis of haemo-dializers capiliaries
  - For example: calcification of heart valves
- Bone- implant interactions for osteointegration
  - For example: dental implant osteointegration over time, capability to sustain the load
- Bio- resorbable implants: time of healing, time of resorbtion, drug cinetics
  - For example: bone fillers, soft tissue fillers
  - For example: antiobiotated bone cement
- Fatigue
  - For example: hip implants; heart valves

Replace

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- In vitro methods for pyrogen testing
- Simulators
  - For example: organoids for local pharmaco-kinetics and toxicology
  - For example: artificial skin for sensitization effects
  - For example: FEA simulations for fatigue of nitinol stents
  - For example: dummies for implants and for invasive devices
  - For example: rhythm simulators for ECG
- Cadaver labs
  - For example: For fine-tuning of surgical procedures

Simulators

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- ecg

Less than 1000 euros... All the simulated pathological ECGs you may need

- Anatomical settings
- Ultrasound compatible
- Generic healthy anathomy for CVC placement

Still can not reproduce a complex system such as a living organ system

Cadaver lab is an ethical and technological challenge

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- Complex anatomies

Nasal endoscopy can ensure correct intubation

- Complex ethics

Not really saving lives…. Just testing dental implants for asthetic results

Reduce

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- New ISO 10993 standard for biocompatibility
- Reduces overall number of animals by requesting preliminary physico-chemical assessment
  - Of material
  - Of extractables and leachables
- Some test for sensitization, irritation, toxicity may be waived

Refine

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- Choose the correct model!
  - Sometimes the big animal model is the most appropriate
- specific animal- model protocols with multiple observation end points
  - Local effects at implant + osteointegration
  - Haemocompatibility and long term implant effects for systemic toxicity
- specific animal- model protocols, control groups from veterinary clinical medicine

A heart-warming example: test for pyrogens

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1941 to late 1980

Rabbit model

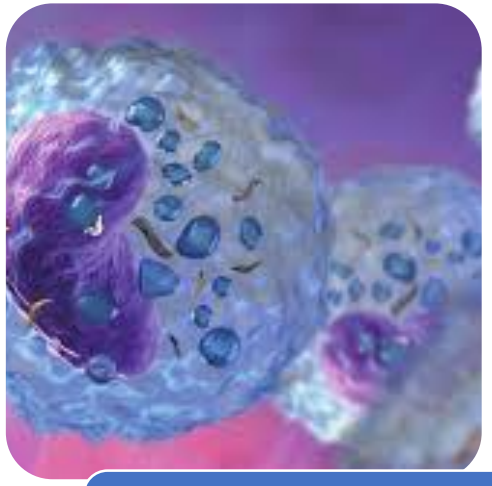
Multiple injections in caged mammals

State of the art

Gel clot model LAL

Blood sampling of crabs, non-life threatening

Under validation



In vitro MAT test

In vitro Test on monocytes

Questions

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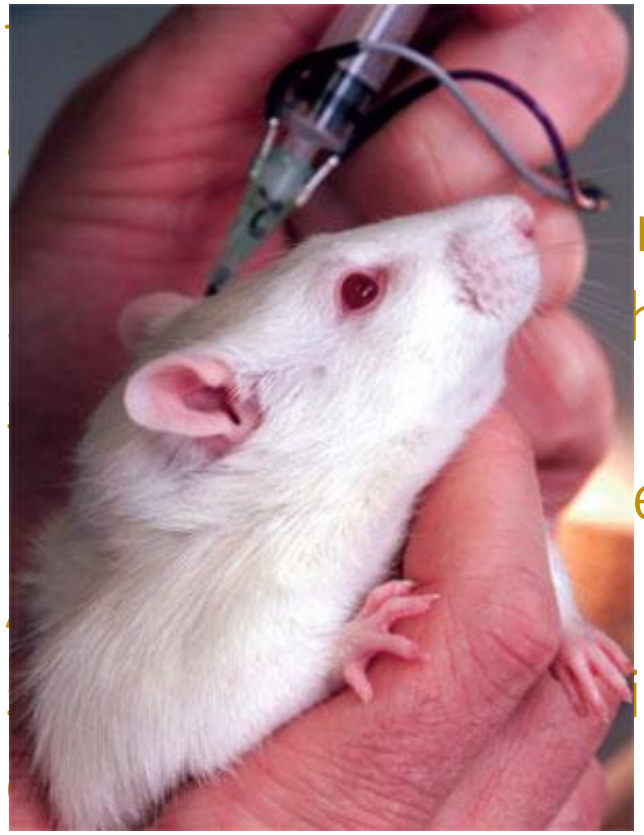
Study 1

1941, Dachau

Study 2

-
-



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2014, Italy

Study 3

Banned in Europe since 2013

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Thank You!

Arti Ahluwalia

Centro E. Piaggio
bioengineering and robotics research center

African Biomedical Engineering Mobility

Scholarships for:

Master's-level courses & short research visits for women only:
Host universities: Kenyatta University and Addis Ababa University
Home universities: universities in any African country excluding Ethiopia

PhD-level courses & short research visits for women and men:
Host universities: Kenyatta University and Cairo University
Home universities: universities in any African country excluding Ethiopia

Staff (academic, research, administrative) visits for women and men:
Host universities: any of the partner universities
Home universities: any of the partner universities

The call is informed by the profile of our past scholarship awardees, and aims to balance the country and gender profile of our combined cohort of awardees.

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