Research Ethics

Prashant V. Kamat

Based on the lectures of

Leonard V. Interrante
Editor-in-chief, Chemistry of Materials

Presented at in the Symposium on Scientific Publishing, ACS National Meeting, Atlanta, GA March 2006

On Being a Scientist: Third Edition

Committee on Science, Engineering, and Public Policy, National Academy of Sciences, National Academy of Engineering, and Institute of Medicine
http://www.nap.edu/catalog/12192.html

Where do students learn ethical decision-making?

1. Mentor, advisor
2. Fellow graduate students
3. Family
4. Friends not in graduate school
5. Other faculty
6. Religious beliefs
7. Discussions in courses, labs, seminars
8. Professional organizations
9. Courses dealing with ethical issues

Setting off on the road to the responsible conduct of research
(From ORI http://ori.dhhs.gov/education/products/RCRintro/c02/0c2.html)

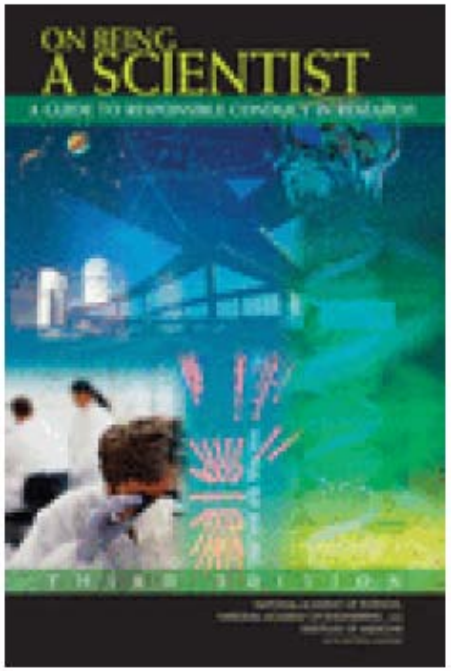
- J. P. Swazey, K. S. Louis, and M. S. Anderson, "The ethical training of graduate students requires serious and continuing attention," *Chronicle of Higher Education 9 (March 1994):B1–2; J. P. Swazey, "Ethical* problems in academic research," *American Scientist 81(Nov./Dec. 1993):542–53*.

Three sets of obligations of a researchers to adhere to professional standards.

1. An obligation to honor the trust that their colleagues place in them.

2. An obligation to themselves. Irresponsible conduct in research can make it impossible to achieve a goal.

3. An obligation to act in ways that serve the public.



On Being Scientist
http://www.nap.edu/catalog/12192.html
Available free for one download

Research Ethics

Part I. Sharing Scientific Knowledge

- Research publication
- Authorship and collaborative Research
- Scientific Misconduct –FFP & QRP
- Examples of scientific misconduct in literature

Part II Laboratory Practice and COI

- Practices of Image and Data Manipulation
- Data Ownership & Intellectual Property Guidelines
- Conflict of Interest & Commitment
- Govt. vs. Industry Sponsored Research
- Sharing the data in thesis

Who owns research data?

(From ORI http://ori.dhhs.gov/education/products/RCRintro/c02/0c2.html)

Scientific Knowledge

The object of research is to extend human knowledge beyond what is already known.

But an individual's knowledge enters the domain of science only after it is presented to others in such a fashion that they can independently judge its validity.

(NAP, "On Being a Scientist" 1995)

Sharing Scientific Knowledge

"Science is a shared knowledge based on a common understanding of some aspect of the physical or social world"

(NAP, "On Being a Scientist" 1995)

Presentations

- Social conventions play an important role in establishing the reliability of scientific knowledge

Publications in peer reviewed journals

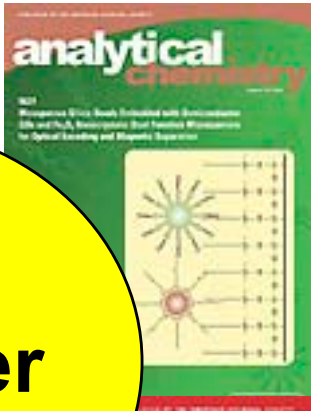
- Research results are privileged until they are published

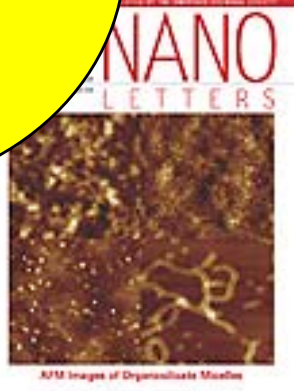
Thesis

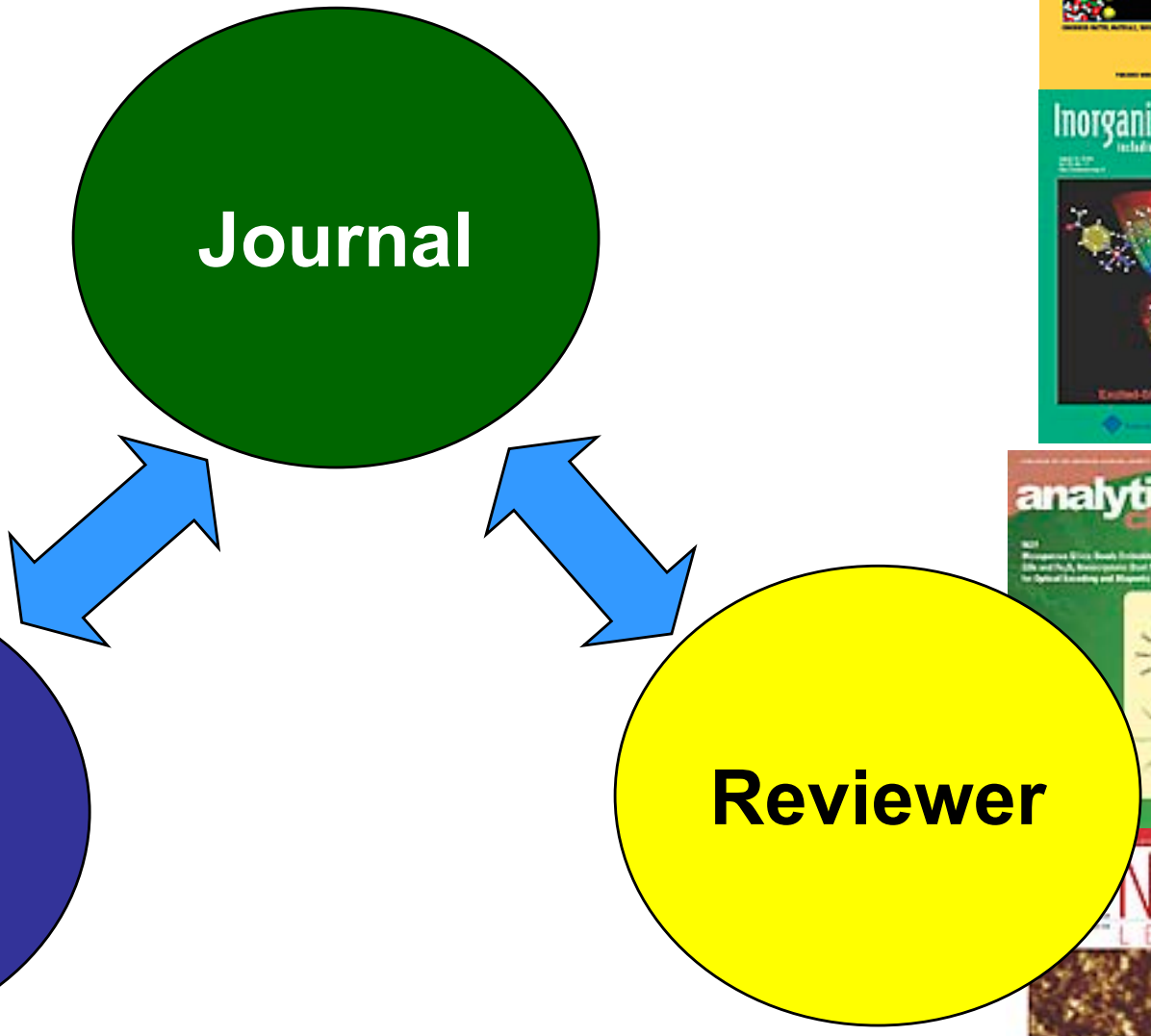
Why Publish?

- "**A paper is an organized description of hypotheses, data and conclusions, intended to instruct the reader**. If your research does not generate papers, it might just as well not have been done" (G. Whitesides, Adv. Mater., 2004, 16, 1375).
- **"if it wasn't published, it wasn't done"** - in E.H. Miller 1993

Scientific Publication is a Team Effort







ACS Journals:http://pubs.acs.org/about.html

Authorship

- The list of authors establishes accountability as well as credit.
- Policies at most scientific journals state that a person should be listed as the author of a paper only if that person made a direct and substantial intellectual contribution to the design of the research, the interpretation of the data, or the drafting of the paper.
- The acknowledgments section can be used to thank those who indirectly contributed to the work.

Including "honorary," "guest," or "gift" authors dilutes the credit due the people who actually did the work, inflates the credentials of the added authors, and makes the proper attribution of credit more difficult.
("On Being a Scientist" , NAP)

Responsible authorship?

(From ORI http://ori.dhhs.gov/education/products/RCRintro/c02/0c2.html)

Author Responsibilities

– Preparation and Submission of Manuscripts:

Follow General Rules:

- Ensure work is new and original research
- All Authors are aware of submission and agree with content and support submission
- Agree that the manuscript can be examined by anonymous reviewers.
- Provide copies of related work submitted or published elsewhere
- Obtain copyright permission if figures/tables need to be reproduced
- Include proper affiliation

What is publishable….

Journals like to publish papers that are going to be widely read and <u>useful to the readers</u>

- Papers that report **"original and significant" findings** that are likely to be of interest to a broad spectrum of its readers
- Papers that are **well organized and well written**, with clear statements regarding how the findings relate to and advance the understanding/development of the subject
- Papers that are **concise and yet complete** in their presentation of the findings

What is not acceptable…

- Papers that are **routine extensions of previous reports** and that do not appreciably advance fundamental understanding or knowledge in the area
- **Incremental / fragmentary reports** of research results
- **Verbose, poorly organized, papers** cluttered with unnecessary or poor quality illustrations
- **Violations of ethical guidelines**, including plagiarism of any type or degree (of others or of oneself) and questionable research practices (QRP)

Office of Research Integrity
US Department of Health and Human Services

http://ori.dhhs.gov/misconduct/definition_misconduct.shtml

Research Misconduct

Research misconduct means **Fabrication, Falsification, or Plagiarism (FFP)** in proposing, performing, or reviewing research, or in reporting research results.

(a) Fabrication is making up data or results and recording or reporting them.

(b) Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

(c) Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

(d) Research misconduct does not include honest error or differences of opinion.

Definitions:
Plagiarism and Self-Plagiarism

- Plagiarism: using the ideas or words of another person without giving appropriate credit (Nat. Acad. Press document)

- Self-Plagiarism: the verbatim copying or reuse of one's own research (IEEE Policy statement)

Both types of plagiarism are considered to be unacceptable practice in scientific literature

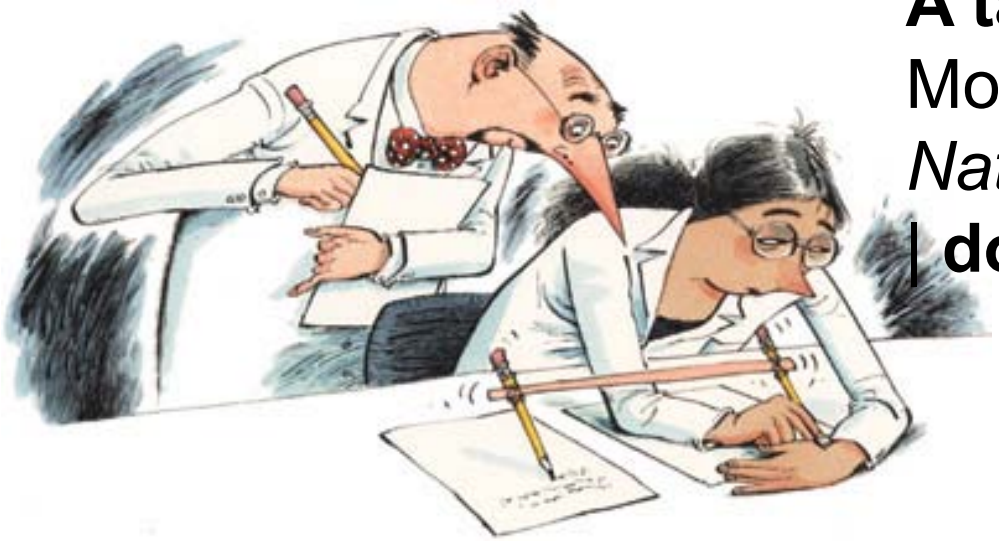
ACS Publication Policy
Plagiarism statement for Ethical Guidelines

January 2009

B. 9. It is the responsibility of the author to ensure that the submitted manuscript is original and shall not contain plagiarized material. **Plagiarism is passing off another person's work as one's own, i.e., reusing text, results, or creative expression without explicitly acknowledging or referencing the original author or publication.**

Authors should be aware this includes **self-plagiarism, defined as the reuse of significant portions of the author's own published work or works, without attribution to the original source.** Examples of plagiarism include verbatim copying of published articles; verbatim copying of elements of published articles (e.g., figures, illustrations, tables); verbatim copying of elements of published articles with crediting, but not clearly differentiating original work from previously published work; and self-plagiarism.

It is the **responsibility of the author to obtain proper permission** and to appropriately cite or quote the material not original to the author. In this context, "quote" is defined as reusing other works with proper acknowledgement. Appropriate citation applies whether the material was written by another author or the author him or herself.



A tale of two citations

Mounir Errami & Harold Garner

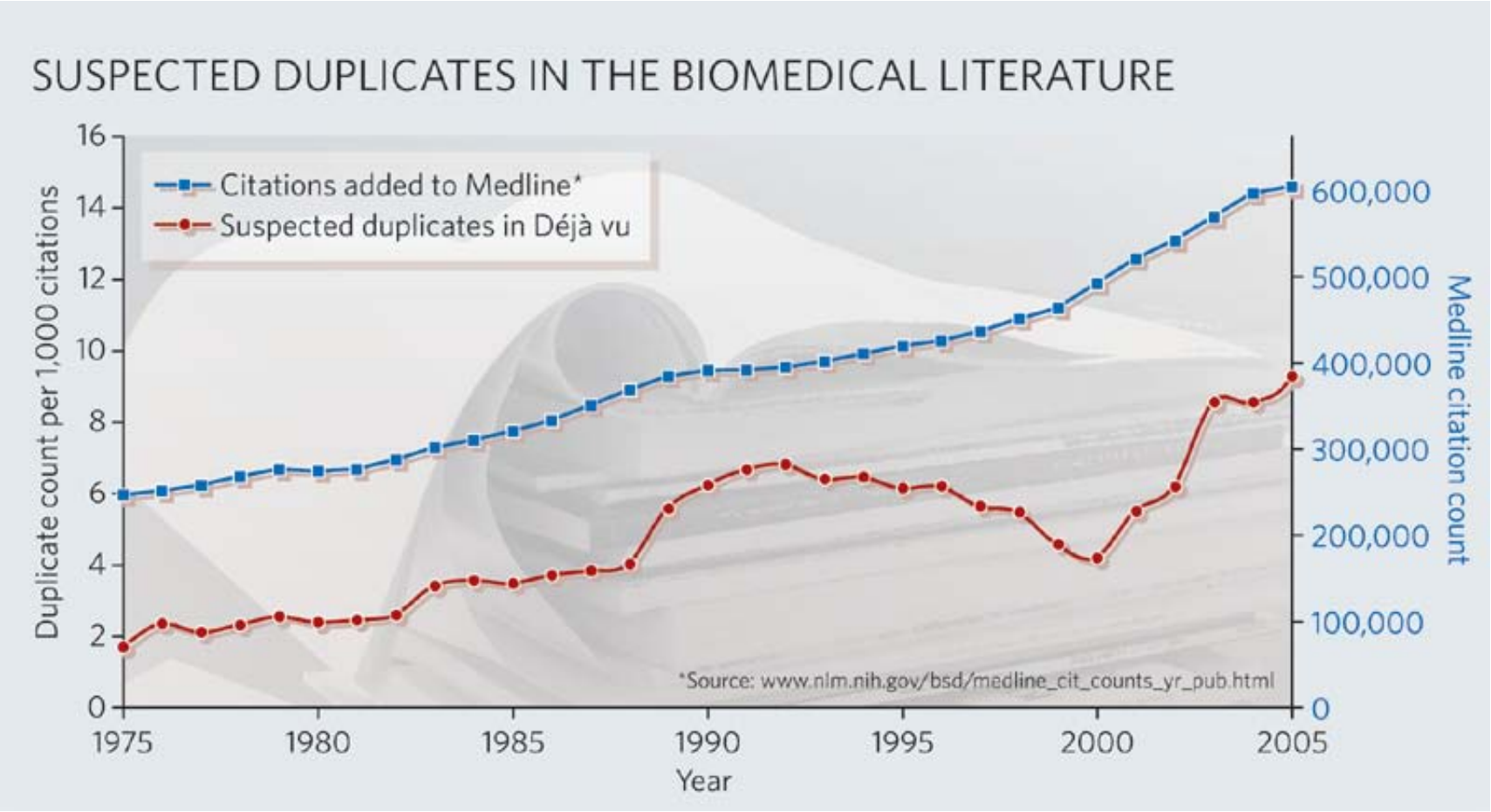
Nature **451**, 397-399 (24 Jan 2008) | **doi:10.1038/451397a**

"It is the best of times, it is the worst of times". Scientific productivity, as measured by scholarly publication rates, is at an all-time high. However, high-profile cases of scientific misconduct remind us that not all those publications are to be trusted — but how many and which papers?

The most unethical practices involve substantial reproduction of another study (bringing no novelty to the scientific community) without proper acknowledgement. If such duplicates have different authors, then they may be guilty of plagiarism, whereas papers with overlapping authors may represent self-plagiarism.

Simultaneous submission of duplicate articles by the same authors to different journals also violates journal policies.

Mounir Errami & Harold Garner
Nature **451**, 397-399 (24 Jan 2008)



China and Japan, have estimated duplication rates that are roughly twice that expected for the number of publications they contribute to Medline. Perhaps the complexity of translation between different scripts, differences in ethics training and cultural norms contribute to elevated duplication rates in these two countries.

Other Types of Ethical Violations

- Duplicate publication/submission of research findings; failure to inform the editor of related papers that the author has under consideration or “in press”
- Unrevealed conflicts of interest that could affect the interpretation of the findings
- Misrepresentation of research findings - use of selective or fraudulent data to support a hypothesis or claim

Data Manipulation

- Researchers who manipulate their data in ways that deceive others are violating both the basic values and widely accepted professional standards of science. - failure to fulfill all three obligations.
- They mislead their colleagues and potentially impede progress in their field or research.
- They undermine their own authority and trustworthiness as researchers.

(From ORI http://ori.dhhs.gov/education/products/RCRintro/c02/0c2.html)

Misleading data can also arise from poor experimental design or careless measurements as well as from improper manipulation.

When a mistake appears in a journal article or book, it should be corrected in a note, erratum (for a production error), or Additions/Corrections.

Sooner or later
……. ethical violations get exposed

Some recent examples

RESEARCH INTEGRITY

24 MAY 2002 VOL 296 SCIENCE, p 1376

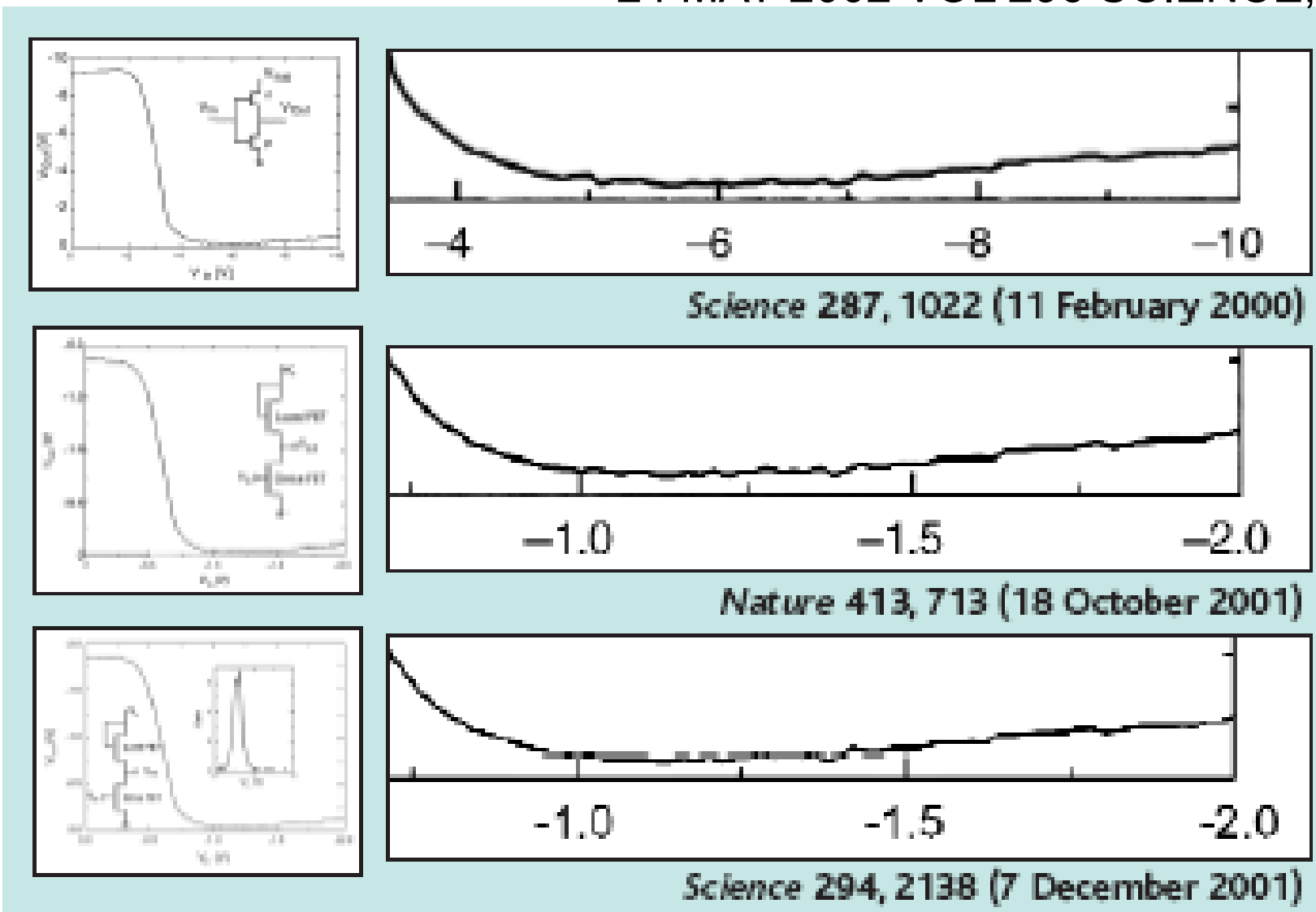
Pioneering Physics Papers Under Suspicion for Data Manipulation

Recent discoveries at Bell Laboratories—the research arm of Lucent Technologies in Murray Hill, New Jersey—said to be of Nobel quality suddenly became mired in questions last week. Outside researchers presented evidence to Bell Labs management on 10 May suggesting possible manipulation of data involving five papers published in *Science*, *Nature*, and *Applied Physics Letters* over 2 years. In response, Bell Labs officials said that they are forming a committee of independent researchers to investigate. Their conclusions may not be known for months, but scientists who have seen the data are already saying that the potential fallout from the investigation could be devastating.

The Bell Labs papers describe a series of different experiments with organic conduc-

Angeles, and director of the California NanoSystems Institute: "It's hard to understand. I know these people. Most of them are good, careful scientists." "It's a little overwhelming," adds Lydia Sohn, a Princeton University physicist who helped bring some of the discrepancies to light. "It's just disturbing, and disappointing, and sad." The noise pattern is particularly disturbing, says Charles Lieber, a chemist and nanoscience expert at Harvard University in Cambridge, Massachusetts: "It's virtually impossible for me to believe that some of this wasn't made up."

Schön himself acknowledges that the similar noise pattern is "difficult to explain." But others affiliated with Bell Labs suggest privately that a systematic artifact in the measurement equipment might account for



Striking resemblance. Published data from studies of different devices revealed a similarity in recorded "noise." Schön says the bottom figure was sent to *Science* by mistake (see correction, p. 1400).

Science

27 JULY 2007 VOL 317 SCIENCE www.sciencemag.org

Retraction

WE WISH TO RETRACT OUR REPORT "*CDX2* GENE EXPRESSION AND TROPHECTODERM LINEAGE specification in mouse embryos" (*1*). Allegations of research misconduct were received by the University of Missouri-Columbia (MU) Provost, and an investigation found that the first author (K.D.) engaged in research misconduct by intentionally falsifying and fabricating digital images in the preparation of Figs. 4I; 4N; 4S; 2G; 3, J to L; S2, V to X; and S6, I to K accompanying the *Science* article. In addition, the original raw image files for the majority of the figures in the paper have not been located (the exceptions being the confocal scanning images in Figs. S1, S3, S4, S5, and S6), raising the possibility that the data they represent may also be suspect. We have decided to withdraw the article in its entirety in view of the fact that the paper was founded at least in part on falsified or fabricated images.

The corresponding author (R.M.R.) takes responsibility for placing excessive trust in his coworker and for not assuring that a complete set of raw data existed at the time the questions first arose about the paper. We deeply regret any scientific misconceptions that have resulted from the publication of this article.

The first author resigned from MU shortly after the allegations of research misconduct were received and could not be found to sign the retraction.

R. MICHAEL ROBERTS,[1] M. SIVAGURU,[2] H. Y. YONG[3]

[1]Division of Animal Sciences, University of Missouri, Columbia, MO 65211, USA. [2]Institute for Genomic Biology, University of Illinois, Urbana-Champaign, IL 61801, USA. [3]BK21 Dental Research Institute, College of Dentistry, Seoul National University, 28 Yongun-dong, Chongno-gu, Seoul 110-749, Korea.

Reference

1. K. Deb, M. Sivaguru, H. Y. Yong, R. M. Roberts, *Science* **311**, 992 (2006).

Citations
-Read the work before you cite
-Important to cite the work correctly and completely

Paper trail reveals references go unread by citing authors

Philip Ball

Many of the references cited in scientific papers have not been read by the authors citing them, according to an analysis of how errors in citations propagate through the literature.

It isn't easy to establish directly — and truthfully — whether citations have been reference being copied from someone else's citation list. The most common misprint appeared 78 times.

Based on the number of distinct misprints, the two researchers estimate that only 22–23% of citations followed from a reading of the original paper. And they postulate that this is typical of the scientific literature as a whole.

NATURE|VOL 420 | 12 DECEMBER 20002 p 594

The Chronicle of Higher Education, August 11, 2006
Also in Wall Street Journal –today's issue
(40% students use materials downloaded from internet!)

The Plagiarism Hunter

When one graduate student went to the library, he found copycats — lots of them

By PAULA WASLEY, Athens, Ohio

In Ohio University's Library, Thomas A. Matrka takes just 15 minutes to hit pay dirt. Scattered before him on a table are 16 chemical-engineering master's theses on "multiphase flow." Identical diagrams in two theses from 1997 and 1998 strike him as suspicious. Turning a few more pages, he confirms what he suspected……..

Most of the plagiarism found at Ohio occurred in introductory chapters describing research methods and reviewing the previous literature in the field, for which there is little expectation of originality. And all but a few cases involved international students who, he says, **whether through ignorance, laziness, or cultural misunderstanding, may have either not known correct citation practices or, struggling to write** in a foreign language, been tempted to borrow another student's words.

How Journals Detect and Handle Problem Papers

- Information received from reviewers or other editors
- Literature search for related papers by the author

- Withdrawal of a paper from publication
- Banning authors from publication in the journal for 3-5 years and informing the co-authors and editors of related journals of our action
- For less serious cases, placing the author on a “watch list” for careful examination of their submissions prior to requesting reviews

A recent retraction …..

Ethical Responsibilities for Authors in *The Journal of Physical Chemistry*

I recently took the step of retracting from the scientific record a letter published in *The Journal of Physical Chemistry C*, as it is emblematic of a type of author misconduct that we as research professionals must seek to avoid if we are to uphold the integrity of the scientific literature.

The letter in question was a publication by Fang et al., *J. Phys. Chem. C* **2007**, *111*, 1065-1070. After publication of the letter, it was brought to our attention that the paper by Fang et al., as submitted and subsequently published by the journal after peer review, included a number of figures that duplicated those contained within previously published papers by other authors …….. I judged such misconduct by the authors to constitute a serious instance of plagiarism.

George Schatz
Editor in Chief
J. Phys. Chem. A/B/C

Original Paper
Oriented Assembly of Fe3O4 Nanoparticles into Monodisperse Hollow Single-Crystal Microspheres
Yu et al, *J. Phys. Chem. B* 2006, *110,* 21667-21671 (Figure 3)

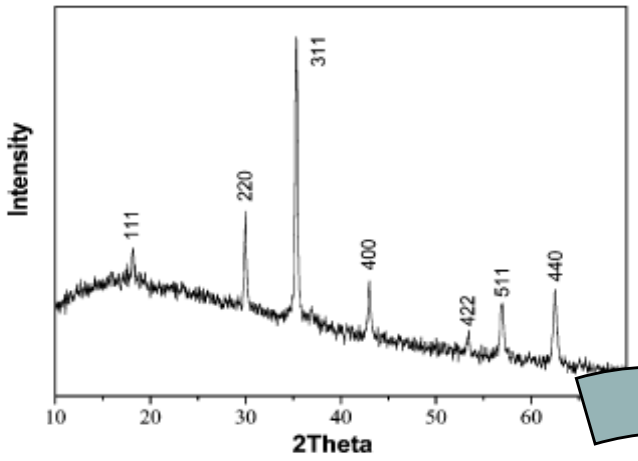
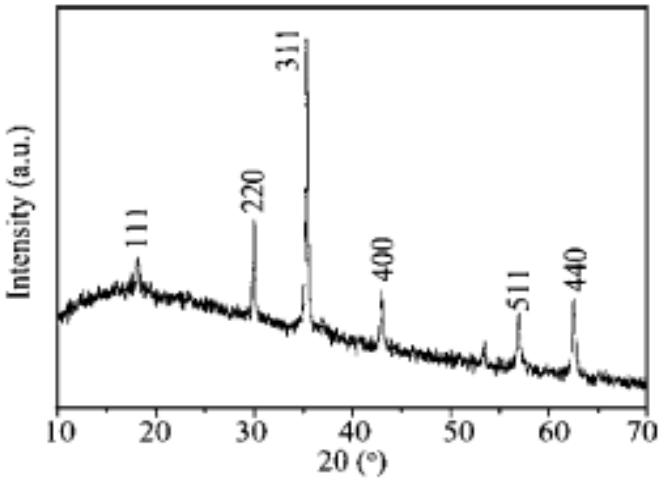
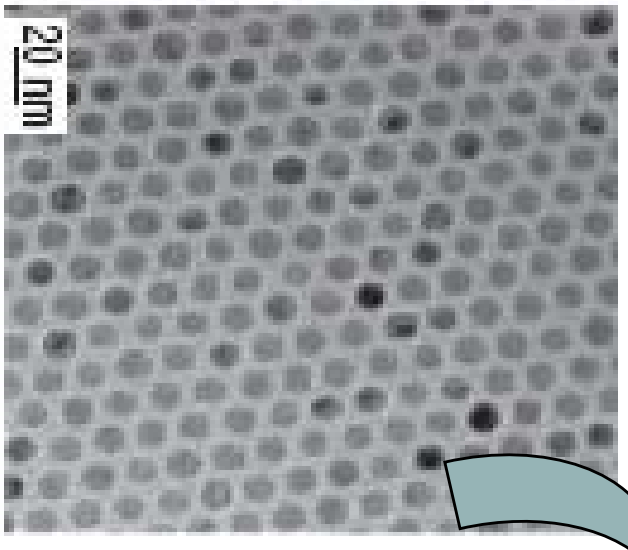


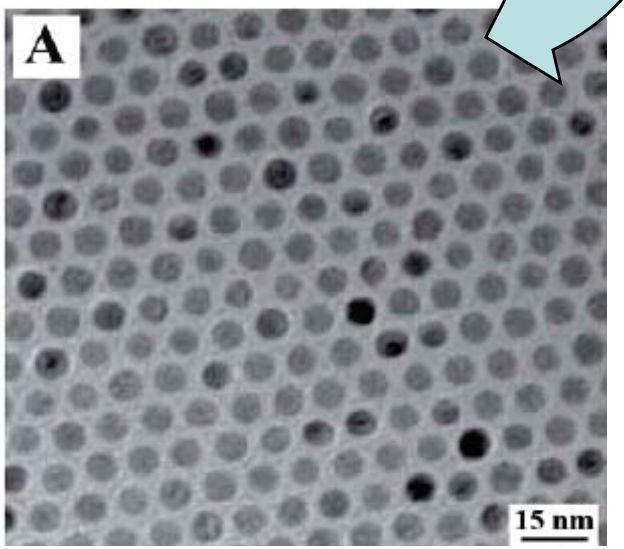
Figure 3. A typical XRD pattern of Fe_3O_4 hollow microspheres.



Plagiarized paper:
Fabrication of Monodisperse Magnetic Fe3O4-SiO2 Nanocomposites with Core-Shell Structures Hua Fang,* Chun-yang Ma, Tai-li Wan, Mei Zhang, and Wei-hai Shi J. Phys. Chem C **2007,** *111,* 1065-1070

Original paper:
Ultra-large-scale syntheses of monodisperse nanocrystals, Park et al. Nature Materials, 2004, 3, 891 (Figure 3C)





RETRACTED: Fluorescence lifetime increase by introduction of F^- ions in ytterbium-doped TeO_2-based glasses

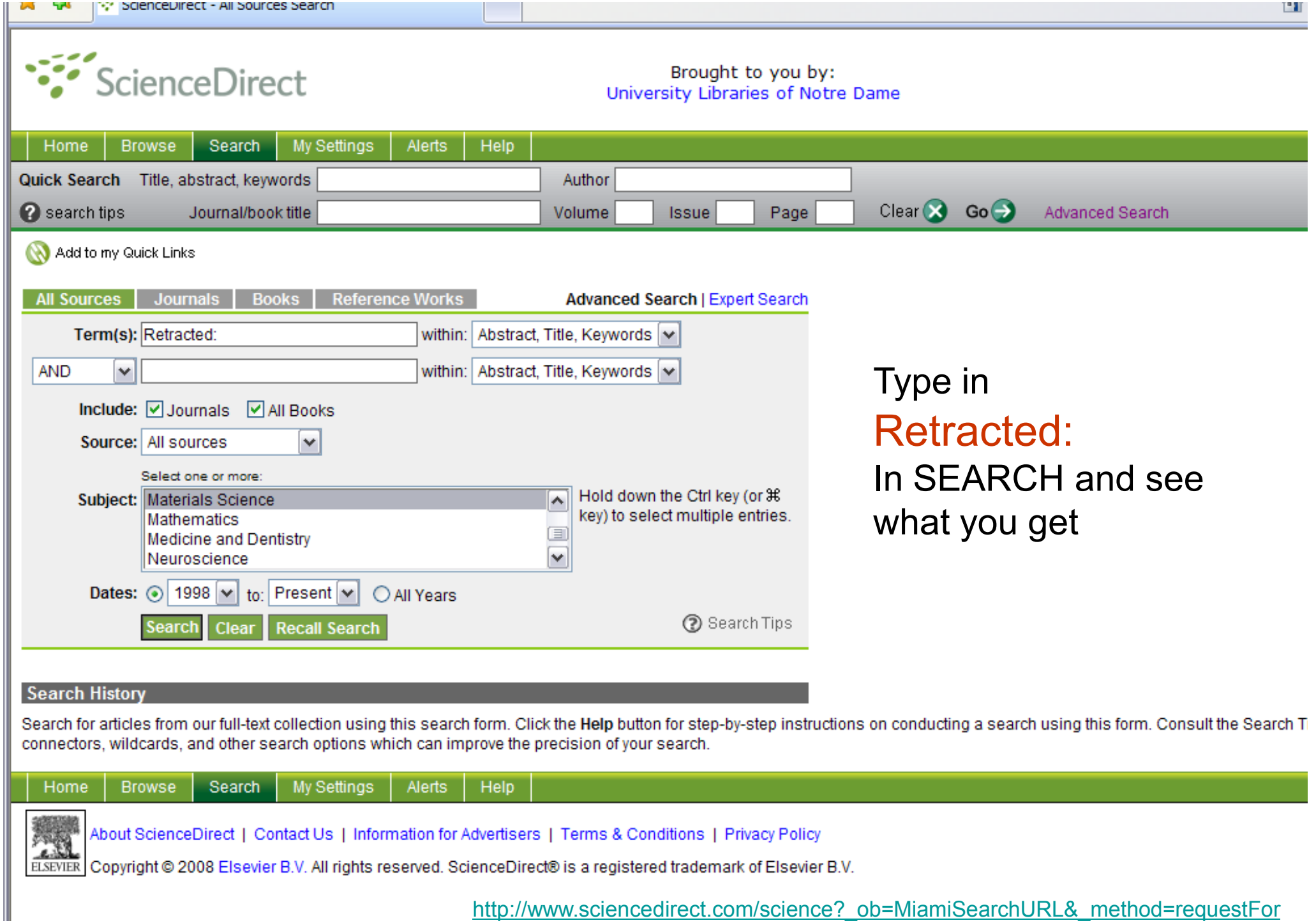
Journal of Alloys and Compounds, Volume 393, Issues 1-2, 3 May 2005, Pages 279-282

Guonian Wang, Shixun Dai, Junjie Zhang, Shiqing Xu and Zhonghong Jiang

RETRACTED: Effect of F− ions on spectroscopic properties of Yb^{3+}-doped zinc–tellurite glasses •

Journal of Physics and Chemistry of Solids, Volume 66, Issue 6, June 2005, Pages 1107-1111

Guonian Wang, Junjie Zhang, Shixun Dai, Jianhu Yang and Zhonghong Jiang



Type in

Retracted:

In SEARCH and see what you get

http://www.sciencedirect.com/science?_ob=MiamiSearchURL&_method=requestForm&_btn=Y&_acct=C000022718&_version=1&_urlVersion=1&_userid=489835&md5=ea66227488401c79ca7231fece33c1f4

1. RETRACTED: Dependence of the structural and optical properties of ZnO thin films on the substrate temperature in atomic layer deposition and post-annealing
Journal of Alloys and Compounds, Volume 449, Issues 1-2, 31 January 2008, Pages 371-374
Jongmin Lim, Chongmu Lee
Preview PDF (1478 K) | Related Articles

2. RETRACTED: Evaluation of specific properties of glass and carbon/vinyl ester composites
Composites Part B: Engineering, Volume 39, Issue 1, January 2008, Pages 27-35
Gowthaman Swaminathan, Kunigal N. Shivakumar, Mathew Sharpe
Preview PDF (1461 K) | Related Articles

3. RETRACTED: Formation of three types of ordered phases in InAlAs epilayers grown by metalorganic chemical vapor deposition
*Thin Solid Films, **In Press, Uncorrected Proof**, Available online 16 July 2007*
Dong Chan Kim, Bo Hyun Kong, Hyung Koun Cho, Sang Ouk Jun, Eundeok Sim, Won Suk Han, Sung Bum Bae
Preview PDF (1715 K) | Related Articles

4. RETRACTED: Effect of strain and nonparabolicity on electronic properties of self-assembled CdTe quantum wires grown on ZnTe buffer layer
*Solid State Communications, **In Press, Accepted Manuscript**, Available online 13 July 2007*
J.H. You, J.H. Jung, J.T. Woo, T.W. Kim, K.H. Yoo, H.S. Lee, H.L. Park
Preview PDF (478 K) | Related Articles

5. RETRACTED: On the effect of Cd doping for Ca in $La_3CaBa_3Cu_7O_y$ superconducting cuprate
*Materials Science and Engineering: B, **In Press, Uncorrected Proof**, Available online 25 May 2007*
Elsayed Kandyel, Khaled M. Elsabawy
Preview PDF (660 K) | Related Articles

6. RETRACTED: "Studies on Spray Deposited CdIn2S4 Thin Films"
*Materials Science and Engineering: B, **In Press, Uncorrected Proof**, Available online 25 May 2007*
R.R. Sawant, A.V. Kokate, K.Y. Rajpure, C.H. Bhosale
Preview PDF (872 K) | Related Articles

7. Retracted: Stress ratio and fatigue damage map study of hot rolled 7020-T6 aluminum alloy
Materials Science and Engineering: A, Volumes 454-455, 25 April 2007, Pages 552-557
Ashish Thakur, R. Raman, S.N. Malhotra
Preview PDF (1051 K) | Related Articles

8. RETRACTED: Synthesis, sinterability and ionic conductivity of nanocrystalline Sm-doped $La_2Mo_2O_9$ fast oxide-ion conductors via in situ polymerization

SCIENCE / TECHNOLOGY

FEBRUARY 18, 2008 | VOLUME 86, NUMBER 07 | PP. 37-38

A Massive Case Of Fraud

Journal editors are left reeling as publishers move to rid their archives of scientist's falsified research

William G. Schulz

A CHEMIST IN INDIA has been found guilty of plagiarizing and/or falsifying more than 70 research papers published in a wide variety of Western scientific journals between 2004 and 2007, according to documents from his university, copies of which were obtained by C&EN. Some journal editors left reeling by the incident say it is one of the most spectacular and outrageous cases of scientific fraud they have ever seen.

The culprit, sources say, is chemistry professor Pattium Chiranjeevi of Sri Venkateswara University in Tirupati, India. SVU conducted an investigation into Chiranjeevi's work after a journal editor presented evidence to university officials that the professor had plagiarized and possibly falsified several manuscript submissions. Chiranjeevi, who communicates through a wide variety of e-mail addresses, has not responded to multiple requests for comment by C&EN.

Shutte

Chiranjeevi retains his teaching position at SVU, according to a university source who has requested anonymity. "He is a permanent employee of the university, and the administration cannot fire him easily," the source says. Instead, Chiranjeevi has been barred from research and research supervision and from holding any administrative post at the university.

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Can Stem Cells Become Sperm Cells?

A Potential New Hope for Infertile Men

By RADHA CHITALE

ABC News Medical Unit

July 9, 2009

Professor Karim Nayernia, is seen at Newcastle University

Now, new research may provide a glimmer of hope that infertile men may one day be able to contribute to the gene pool.

"We have a system which enables us for the first time to produce human sperm from stem cells," said Dr. Karim Nayernia, a professor of stem cell biology at Newcastle University in the United Kingdom and the lead researcher on this study, published July 8 in the journal Stem Cells and Development.

"Studying sperm maturation is not accessible in vivo [in a body]. You cannot follow the system," Nayernia said. "Now we have a system to monitor the stages of male infertility."

Science AAAS

ScienceInsider

Breaking news and analysis from the world of science policy

July 28, 2009

Journal Editor Retracts Paper on Sperm Made From Stem Cells

The paper, published online by ***Stem Cells and Development*** **on 8 July with Karim Nayernia of Newcastle University in the United Kingdom** as the corresponding author, had already received some criticism from other experts; Dr Allan Pacey of the University of Sheffield in the United Kingdom, for example, was quoted by *The Independent* as saying: "As a sperm biologist of 20 years' experience, I am unconvinced from the data presented in this paper that the cells produced ... can be accurately called 'Spermatozoa.' "

The paper's problems soon got much worse. Graham Parker, editor-in-chief of *Stem Cells and Development*, told *Science*Insider that he received an email on 10 July from the editors of another journal, *Biology of Reproduction*, claiming that **two paragraphs from Nayernia paper's introduction were copied without attribution from a 2007 review article** by Makoto Nagano of McGill University in Montreal, Canada, that was published in their journal.

Parker says Nayernia told him the offending text was inserted by a postdoctoral fellow. But Parker says the explanation he received was not consistent with an innocent mistake. "Once I had established that the suggested reason for the text's inclusion was not being substantiated I decided to retract the paper" on 21 July, Parker says.

What are the reasons for plagiarism?

http://plagiarism-main.blogspot.com/

http://www.indiana.edu/~wts/pamphlets/plagiarism.shtml

SCIENTIFIC INTEGRITY

SCIENCE VOL 323 6 MARCH 2009, p1293

Responding to Possible Plagiarism

Documenting reactions from authors and journal editors to plagiarism may help others address the problem.

Tara C. Long,[1] Mounir Errami,[2] Angela C. George,[1] Zhaohui Sun,[2] Harold R. Garner[1,2]*

212 pairs of articles with signs of potential plagiarism were chosen for this study

86.2% -similarity between an original article and its duplicate

73.1%. the average number of shared references

Only 47 (22.2%) duplicates cited the original article as a reference.

71.4% of the manuscript pairs shared at least one highly similar or identical table or figure.

42% also contained incorrect calculations, data inconsistencies, and reproduced or manipulated photographs.

….The increasing availability of scientific literature on the World Wide Web has proven to be a double-edged sword, allowing plagiarism to be more easily committed, while simultaneously enabling its simple detection through the use of automated software.

SCIENTIFIC INTEGRITY

SCIENCE VOL 323 6 MARCH 2009, p1293

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Documenting reactions from authors and journal editors to plagiarism may help others address the problem.

Tara C. Long,[1] Mounir Errami,[2] Angela C. George,[1] Zhaohui Sun,[2] Harold R. Garner[1,2]*

The responses from duplicate authors were more varied;

- 28% denied any wrongdoing,
- 35% admitted to having borrowed previously published material
- 22% were from coauthors claiming no involvement in the writing of the manuscript.
- 17% claimed they were unaware that their names appeared on the article

93% of the original authors were not aware of the duplicate's existence.

The journal editors primarily confirmed receipt and addressed issues involving policies and potential actions.

SCIENCE VOL 323 6 MARCH 2009, p1293

Selected Responses from the authors

"There are probably only 'x' amount of word combinations that could lead to 'y' amount of statements. … I have no idea why the pieces are similar, except that I am sure I do not have a good enough
memory

"I was not involved in this article. I have no idea why my name is included."

"This article was mainly done by a young fellow Dr. [ ]. I made the corrections in text and completed the article Unfortunately Dr. [ ] has died in January this year, so we can't ask him for the reasons….."

"I am not a native English speaker so I do have problems in expressing my ideas... You and other English language speakers are lucky from this point of view…."

"To be honest with you, I was not aware of the fact that I need to take prior permission of the authors of the original article. As such I am facing many difficulties and hardships in my personal life. …"

The corresponding author has been my teacher (and a very good one at that) from whom I have learned many things. My respect for him was of the utmost level until I found that he had been plagiarizing papers from all over the world….."

There are now dozens of commercial and free tools available for the detection of plagiarism.

Perhaps the most popular programs are iParadigm's "Ithenticate" (http://ithenticate.com/) and TurnItIn's originality checking (http://turnitin.com/), which recently partnered with CrossRef (http://www.crossref.org/) to create CrossCheck, a new service for verifying the originality of scholarly content.

However, the content searched by this program spans only a small sampling of journals indexed by MEDLINE.

PubMed and other searches which, by default, return more recent articles first, ensuring that a plagiarized article will always appear higher on a list of search results than its original counterpart. As a result, citations that would have otherwise gone to an original publication are instead diverted to a plagiarized one.

Good Record-Keeping

It is your fundamental obligation to create and maintain an accurate, accessible, and permanent record of data.

Record sufficient detail for others to check and replicate the work.

> Depending on the field, it will require entering data into bound notebooks with sequentially numbered pages using permanent ink, using a computer application with secure data entry fields, identifying when and where work was done, and retaining data for specified lengths of time.

Every scientific result must be carefully prepared, submitted to the peer review process, and scrutinized even after publication.

Useful Tips to Succeed in Graduate Research

- BE SELFISH. You are working for your degree program.
- Set a weekly goal and evaluate the progress routinely.
- Minimize the time on Internet for nonscientific browsing. Just because you are sitting at your desk does not mean that your day was productive.
- HAVE FUN, BUT REMEMBER TO PUT IN A MINIMUM OF **EIGHT PRODUCTIVE RESEARCH HOURS** IN THE LAB DURING WEEKDAYS.
- IT IS YOUR PhD. IF YOU DO NOT TAKE INTEREST OR PUT HARD WORK INTO IT, NOBODY ELSE WILL!!

Note: You are a researcher and not a technician.

The role of your advisor is it guide you through your project and help you succeed in your thesis. Don't expect him/her to suggest to you experiments on a daily basis.

Get serious and take responsibility for your own project.

How to successfully complete your Ph. D.

- Complete all departmental requirements within two years.
- By the end of summer of second year, you should be able to construct a broad outline of research that you would like to pursue.
- The third year is the springboard to explore various facets of your project. You should aim to publish at least one paper (with you as the first author) by third year.
- Schedule the candidacy exam with the graduate school.
- Complete your planned experiments during the fourth and fifth years.
- Plan on publishing 3-4 papers in high impact journals (with you as the first author in at least 1or 2 papers).

  Note: Each paper can serve as the basis for writing a chapter in your thesis.

- Discuss the plan for writing your thesis with your advisor. Plan to submit the thesis during the fifth or sixth year.

This is an exciting time in your career. Make it a worthwhile effort.

To summarize …….

Research Ethics is an integral part of graduate research.

STATEMENTS, FIGURES AND TABLES

Reproduced in a Report, Presentation and/or Paper require proper citation.

Published work is protected by Copyright Law

Copyright permission is necessary if you are reproducing your work in another publication (This applies even if it is your own work).

A Call for Cooperation

"We would like to encourage the leaders of academic research groups to inform their students and research associates about the ethical responsibilities of authors of scientific publications and to insure that, when they are given the responsibility for submitting a paper, they are fully aware of the potential consequences, to themselves and to their co-authors, of violations in these ethical guidelines."

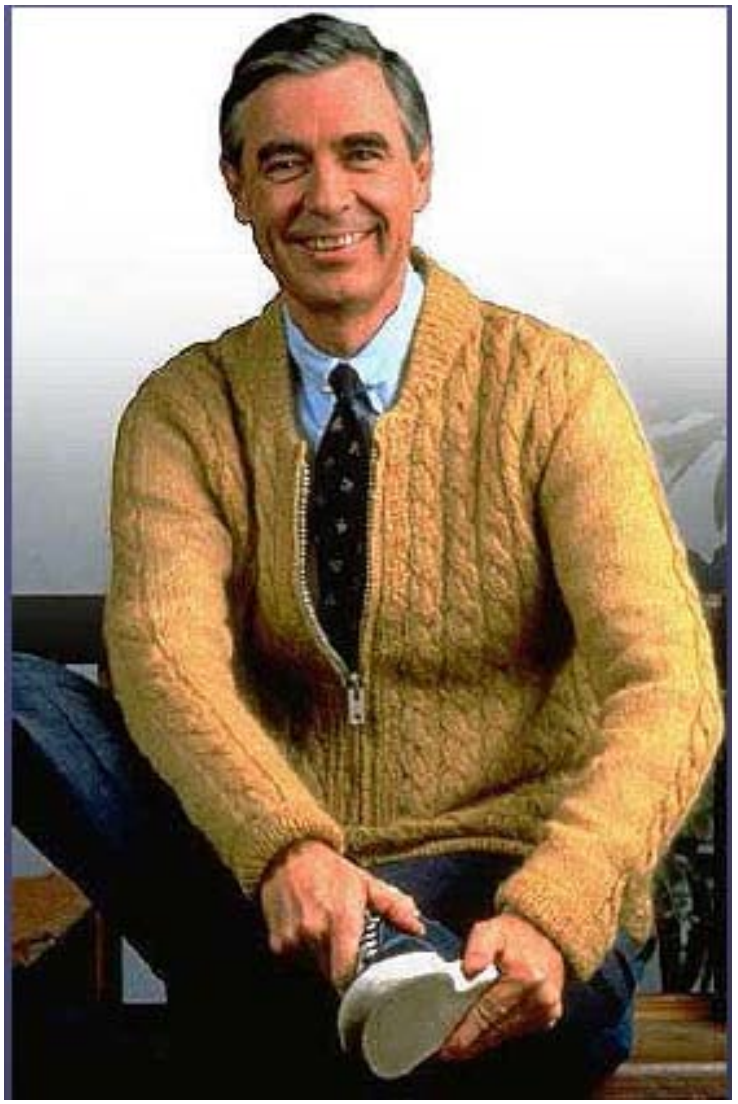
Interrante & Reichmanis,C&EN, Vol 83(6), p. 4 (2005)

“It's not the honors and the prizes and the fancy outsides of life which ultimately nourish our souls.

It's the knowing that we can be trusted, that we never have to fear the truth, that the bedrock of our very being is good stuff.”

- Fred Rogers

Commencement Address at Middlebury College May, 2001



Good Luck!


Prof Holly Goodson
Chemistry and Biochemistry
Data Ownership and Conflict of Interest

Practical Research Ethics II

Data handling, ownership and sharing
Conflicts of Interest

Research Ethics:

- Rules, expected “norms” of behavior
- What to do if the rules don’t cover the problem?
  - Good to think through the problem before you run into it!

This Discussion:

1) Data handling, ownership and sharing
2) Conflicts of interest

- Brief introduction to/reminder of key guidelines
- Specific examples
- List of resources

At the end:

- List of other Research Ethics topics
- General references for Research Ethics

Data Handling

1. **Best Practices for Record-keeping**
2. **Notes on Data analysis and presentation**
3. **Data Ownership**
4. **Data Sharing Policies from Federal Funding Agencies**

NIH Office of Research Integrity 'Best Practices' for record-keeping

http://ori.dhhs.gov/education/products/columbia_wbt/rcr_data/foundation/index.html

Raw data should be recorded and retained in indexed laboratory notebooks with permanent binding and numbered pages or in a dedicated electronic notebook. Recording should be done as soon as possible after data are collected and specific note should be made as to whether it represents the date of the recording or the date of collection, if the two are not the same. Modifications should be clearly identified and dated.

For paper records, a few pages should be kept at the front of a bound book for tables of contents.

Writing should be done in permanent ink and legibly.

Copies of original notebooks should be kept elsewhere for safekeeping.

A second loose-leaf notebook should be kept for data, such as photographs, machine printouts, questionnaires, chart recordings, and autoradiograms that cannot fit into the primary record book.

Supervisors should review and sign off on notebooks to signify their completeness and accuracy. Queries should be addressed as soon as possible and changes signed by both. Some data may need to be witnessed by a colleague. (Witnessing of data becomes important in commercial research laboratories.)

Methodology used in an experiment should be written down or a reference to how an experiment deviated from a standard laboratory technique should be explained.

Lot numbers should be recorded and special attention should be given to the hazardous-substance use.

Equipment calibrations need to be recorded.

Data should be noted directly into notebooks without putting it on scraps of paper or relying on memory beforehand.

All raw data should be included. Be honest.

Errors should be identified by crossing out the mistakes without obscuring the initial data.

Material should be logged chronologically.

Data interpretation should be carefully written.

Areas in a notebook left blank intentionally should be indicated.

Correspondence and note conversations related to experiments should be kept.

Consent forms should be kept with raw data.

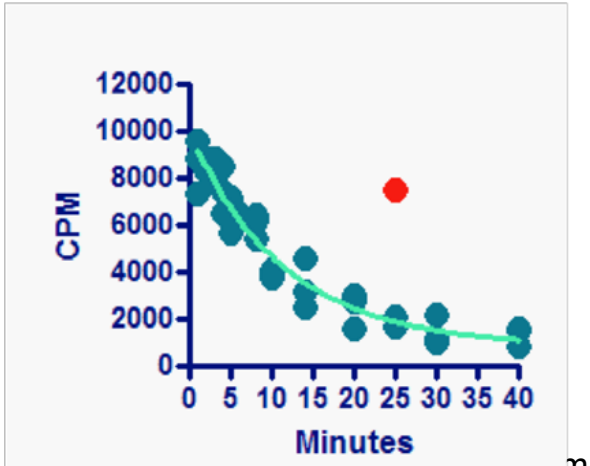
Electronic records need to be carefully monitored.

Electronic data should be backed up on a disk with a hard copy; relevant software must be retained to ensure future access, and security of data is an issue.

"How to" guides for good notebook keeping (all disciplines!)
http://www.davidpace.com/physics/graduate-school/lab-notebooks.htm
www.physics.uco.edu/wwilson/bridge09/Lab%20Notebooks.ppt

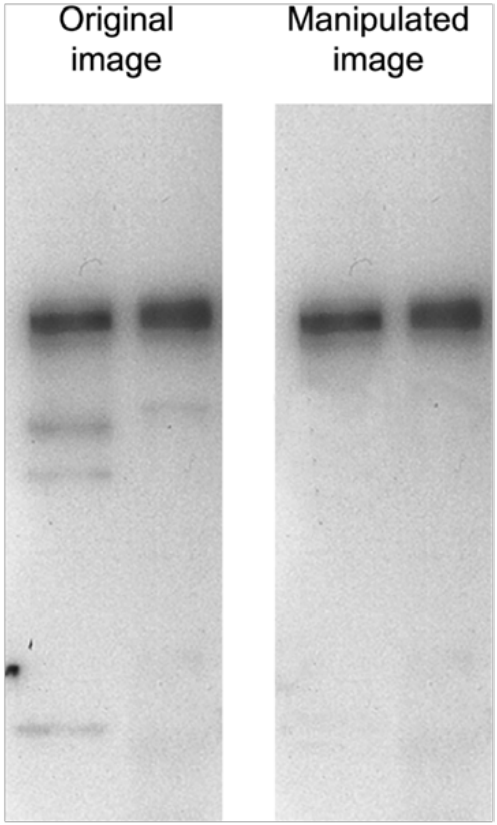
Data analysis, presentation

- Field-, analysis- specific norms
  - ↙ Understand how to handle **outliers**
  - ↙ *Understand appropriate **image manipulations!***

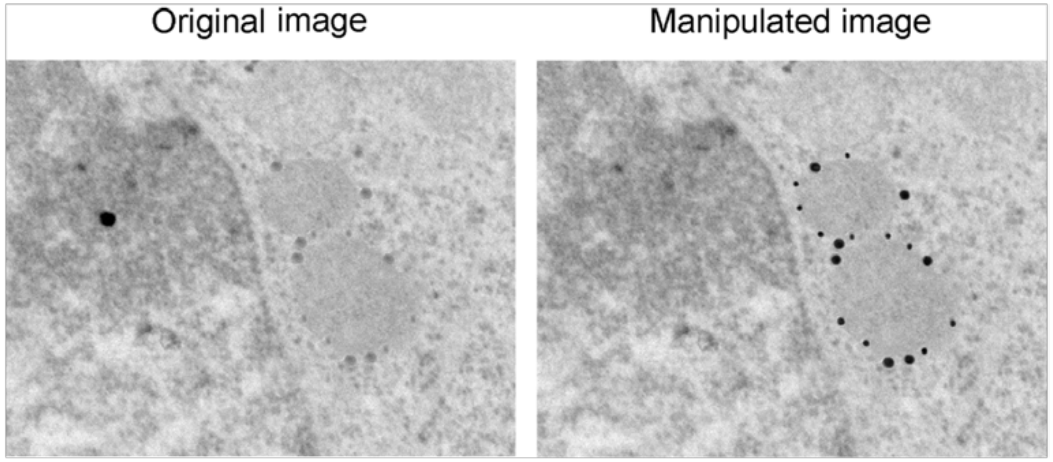


m5
http://www.graphpad.com/help/Prism5

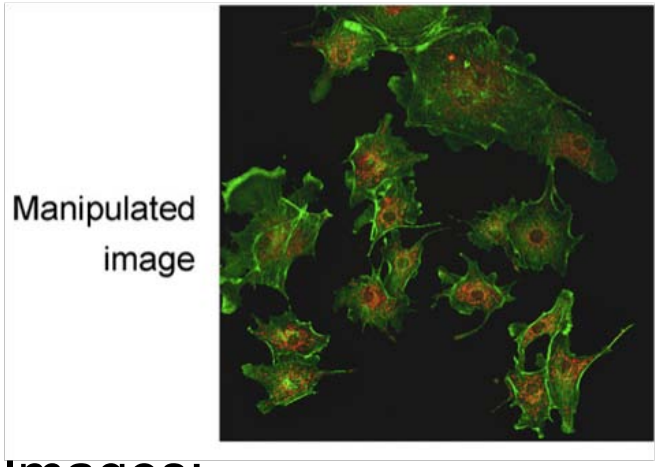
"I just wanted to clean up the background…"

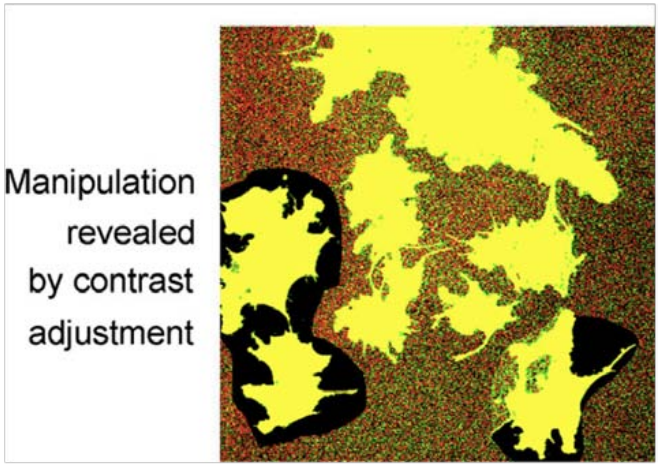


"I just wanted to emphasize the important part…



"I just wanted to present a few more of the same cells…





Some guidelines:

Nature Guide for Digital Images:

http://www.nature.com/nature/authors/submissions/images/

Examples above from Journal of Cell Biology 2004(166):14

Data Ownership

- You are getting ready to graduate and leave for a post-doc
- You are packing up your lab notebooks, and your boss tells you that you can't take them
- You insist that since it is your work, they are yours to take

↙ **Who is correct?**

Who *owns* your data??

- your notebooks
- your reagents (compounds, plasmids…)
- your ideas

↙You?

↙Your advisor/boss?

↙ NSF/NIH/DOE…

↙ ???

Federally funded research:

➲ The University owns the data

- The "principle investigator" (PI) is the *steward* of the data
  - ↙ takes responsibility for data collection, storage, publishing
  - ↙ **Data, data books** collected by undergraduates, graduates, and postdoctoral fellows on a research project belong to the grantee institution
- Graduating students can take copies of their data only with permission
- Departing faculty must negotiate with the University

➲ The University also owns the *ideas*

"It is the policy of the University of Notre Dame…that the University claims the exclusive right to all intellectual property arising from University Research"
http://www.nd.edu/~research/policies/IP.html

ND intellectual property policy:

http://www.nd.edu/~research/policies/IP.html

"It is the policy of the University of Notre Dame…that the University claims the exclusive right to all intellectual property arising from University Research"

…

PATENTS

The University owns all rights to all patentable inventions arising from University Research.

…

COPYRIGHTS

The University owns all rights to all copyrightable materials (including computer programs, software, or multi-media productions)…. the University does not normally claim ownership of works such as textbooks, articles, papers, scholarly monographs, or artistic works."

Royalty Distributions

After deductions for expenses, royalties are distributed according to a defined formula

First $100,000:

- 50% to creator
- 50% to the general fund of the University

Industry-funded research:

- Data *may* be owned by the sponsor
- Ownership/sharing of other intellectual property is negotiated
- Permission to publish *may* (or *may not*) be extended to the PI
  - ↙ the details are **negotiated** before the award
  - ↙ students need to be careful with industry-sponsored thesis work!

Resources:

Notre Dame policy on Intellectual Property:
http://www.nd.edu/~research/policies/IP.html

US PHS (NIH) Office of Research Integrity
http://ori.dhhs.gov/education/products/rcr_data.shtml

NSF policy:
http://www.nsf.gov/pubs/policydocs/papp/aag_6.jsp

Data Sharing

You've just:

- worked hard to clone a gene using NIH funds
- published a preliminary characterization
- received a request for that gene from a competitor

What should you do?

- Ignore them
- Tell them "I'm sorry, I'm still working on it"?

↗**Unique resources** produced using federal funds must be **shared**

- synthetic compounds
- organisms, cell lines, cloned DNA
- crystallographic coordinates, spectroscopic data
- computer programs
- other datasets on which publication is based

Rules for data-sharing:

NIH: NIH Grants Policy Statement
http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131

NSF: NSF GRANT GENERAL CONDITIONS (GC-1) 2009
www.nsf.gov/pubs/gc1/jan09.pdf

↙ **Specific journals:** often have additional rules

Conflicts of Interest

"…situations where researchers have interests that could interfere with their professional judgement." "On Being a Scientist," NAS 3rd Edition, p. 43

Which statement better reflects reality?

"Ethical researchers have no conflicts of interest"

"Ethical researchers recognize and manage conflicts of interest"

↗ Some conflicts of interest are **unavoidable!**

↗ **Conflicts: not only financial!**

- Time/Commitment
- Values
- Personal relationships

Financial conflicts are associated with *altered outcomes of research*

Real-life example

Stelfox et al. (1998*) reviewed the literature in 1995 and 1996 for **reports on the safety** of calcium channel antagonists (blood pressure drugs).

They classified reports as being *supportive*, *neutra*l, or *critical* of these drugs.

They found:

- Reports supportive of these drugs: 96% had financial relationships with drug companies.
- Reports critical of these drugs: Only 37% of the authors had such connections with drug companies.

**Conflict of interest in the debate over calcium-channel antagonists.* Stelfox HT, Chua G, O'Rourke K, Detsky AS. N Engl J Med. 1998 Jan 8;338(2):101-6.

When you are reading the work of another scientist, then what, if anything, do you need to know about interests/activities of that scientist that might be in conflict with a published work?

a. Financial stake (e.g., ownership, stock, stock options) in a company that markets the product discussed in the paper
b. Financial stake (e.g., ownership, stock, stock options) in a company that markets a product similar to the one discussed in the paper
c. Current or previous support (e.g., research materials, grants, or contracts) from a company that markets the product discussed in the paper
d. Current or previous role as a consultant with a company that markets the product discussed in the paper
e. Physical or psychological conditions (e.g., depression or diabetes) of the author that are also the subject of the paper

From http://research-ethics.net/topics/conflicts-of-interest/#resources

Financial Conflicts of interest are strictly regulated by Universities
Journals are beginning to ask that conflicts be disclosed
Nature: http://www.nature.com.proxy.library.nd.edu/authors/editorial_policies/competing.html

Resources:

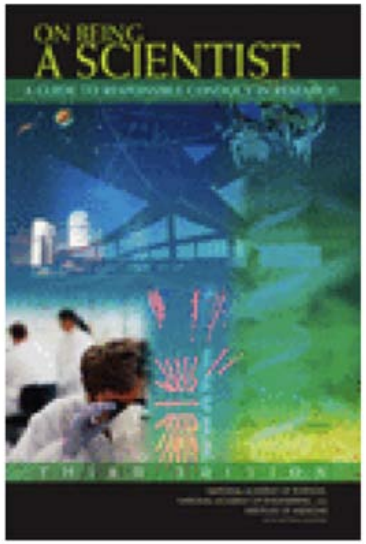
- Notre Dame Office of Research Conflicts of Interest: http://www.ndresearch.org/compliance/conflict-of-interest/
- NIH: http://ori.dhhs.gov/education/products/rcr_conflict.shtml

Handling Conflicts of Interest, Commitment, or Values

Some General Guidelines:

1. **Recognize** the conflict
2. Find out the **rules** for this type of conflict
   - ↙ some conflicts are explicitly regulated because the potential for damage is too great
     - "relationships" with students
     - financial gain
3. Try to change the situation to avoid the conflict
4. If the conflict cannot be avoided, figure out how to **manage** it.
   - ↙ **Managing** the conflict usually requires **disclosing it**
     - colleagues, lab members
     - University
     - journals
   - ↙ **Thinking** about potential conflicts before they occur leads to **clearer problem solving!**

A case study from:



A Conflict of Commitment

Sandra was excited about being accepted as a graduate student in the laboratory of Dr. Frederick, a leading scholar in her field, and she embarked on her assigned research project eagerly. But after a few months she began to have misgivings. Though part of Dr. Frederick's work was supported by federal grants, the project on which she was working was totally supported by a grant from a single company. She had asked Dr. Frederick about this before coming to his lab, and he had assured her that he did not think that the company's support would conflict with her education. But the more Sandra worked on the project, the more it seemed skewed toward questions important to the company. For instance, there were so many experiments she needed to carry out for the company's research that she was unable to explore some of the interesting basic questions raised by her work or to develop her own ideas in other areas. Although she was learning a lot, she worried that her ability to publish her work would be limited and that she would not have a coherent dissertation. Also, she had heard from some of the other graduate students doing company-sponsored work that they had signed confidentiality statements agreeing not to discuss their work with others, which made it difficult to get advice. Dr. Frederick and the company's researchers were very excited about her results, but she wondered whether the situation was the best for her.

1. Has Dr. Frederick done anything wrong in giving Sandra this assignment?
2. What potential conflicts in terms of data collection, data interpretation, and publishing might Sandra encounter as she continues with her research?

List of Research Ethics topics

"Resources for Research Ethics Education"
http://research-ethics.net/

* Animal Subjects
* Authorship
* Biosecurity
* Collaboration
* Computer Use
* Conflicts of Interest
* Data Management
* Human Subjects
* Mentoring
* Peer Review
* Publication
* Research Misconduct
* Social Responsibility
* Stem Cell Research
* Whistleblowing

NIH required topics: subset of these (next page)
NSF: similar

General Resources:

USPHS (NIH) Office of Research Integrity
http://ori.dhhs.gov/education/products/

U.S.Department of Health & Human Services www.hhs.gov Blog

ORI research integrity

Office of Research Integrity
US Department of Health and Human Services

HOME ABOUT ORI PRIVACY FOIA SITE MAP CONTACT ORI

Search ORI

Sections
- Assurance
- Conferences
- Forensic Tools
- Handling Misconduct
- International
- Policies / Regulations
- Publications
- RCR Education
- Research
- RIOs

Newsletter

Latest Newsletter (PDF)
Mar 2009

Past Issues...

Annual Report

RCR Resources - Data Management

» General » Animals » Collaboration » Conflicts » Data
» Humans » Mentorship » Misconduct » Peer Review » Authorship

Data Acquisition, Management, Sharing, and Ownership

Title	Format: HTML	PDF	VIDEO	ZIP
*Guidelines for Responsible Data Management in Scientific Research by Clinical Tools, Inc.		Go		
*Educating Clinical Staff on Clinical Research Data Collection and Data Management by St Jude Children's Research Hospital	Go			
*Data Acquisition and Management by Columbia University	Go			Go
*Data Management by Northern Illinois University	Go			Go (85MB)

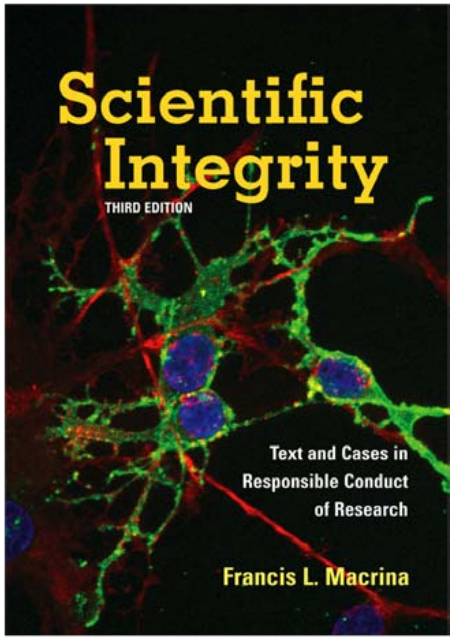
Other Resource

Title	Source	Link
Provisional Guide for Digital Images	Nature	Go
Guidelines for the Proper Handling of Digital Image Data	Journal of Cell Biology	Go
NIH Data Sharing Policy	NIH	Go

On Being a Scientist: Third Edition

Committee on Science, Engineering, and Public Policy, National Academy of Sciences, National Academy of Engineering, and Institute of Medicine

ISBN: 0-309-11971-5, 82 pages, 6 x 9, (2009)



Scientific Integrity: Third Edition
This book includes useful cases and discussions.

The online site for this book
http://www.scientificintegrity.net/
has an extensive list of websites and resources


Professor David Hyde
Biological Sciences
Stem Cell Sources and Ethics

Stem Cell Sources and Ethics

Professor David Hyde
Biological Sciences

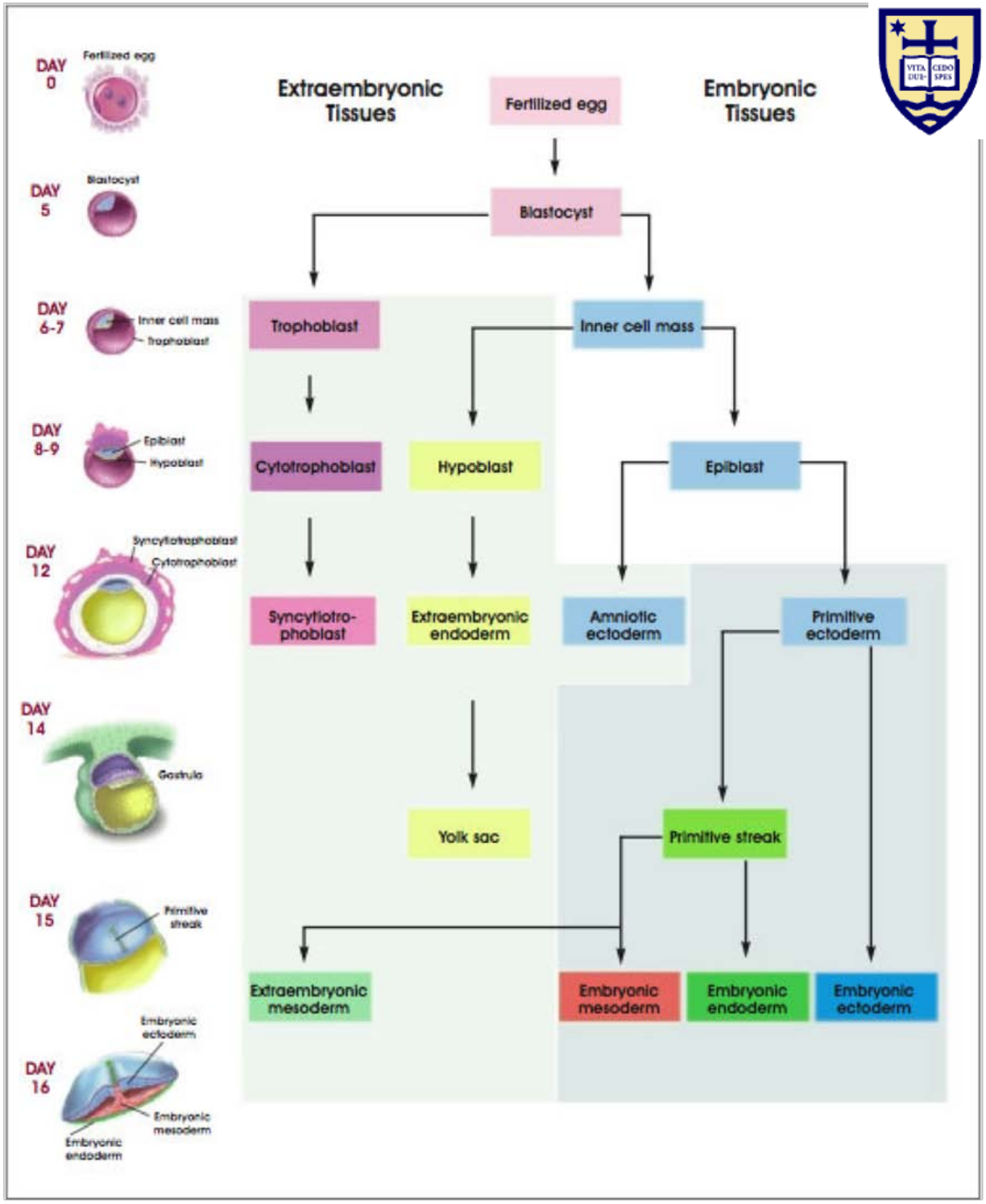
The Dream of Stem Cell Therapy

- Type 1 diabetes mellitus, where the beta cells of the pancreas have been destroyed by an autoimmune attack;
- Parkinson's disease, where dopamine-secreting cells of the brain have been destroyed;
- spinal cord injuries leading to paralysis of the skeletal muscles;
- ischemic stroke, where a blood clot in the brain has caused neurons to die from oxygen starvation;
- multiple sclerosis with its loss of myelin sheaths around axons.
- blindness caused by damage to the retina.

Human Stem Cell Therapeutic Successes

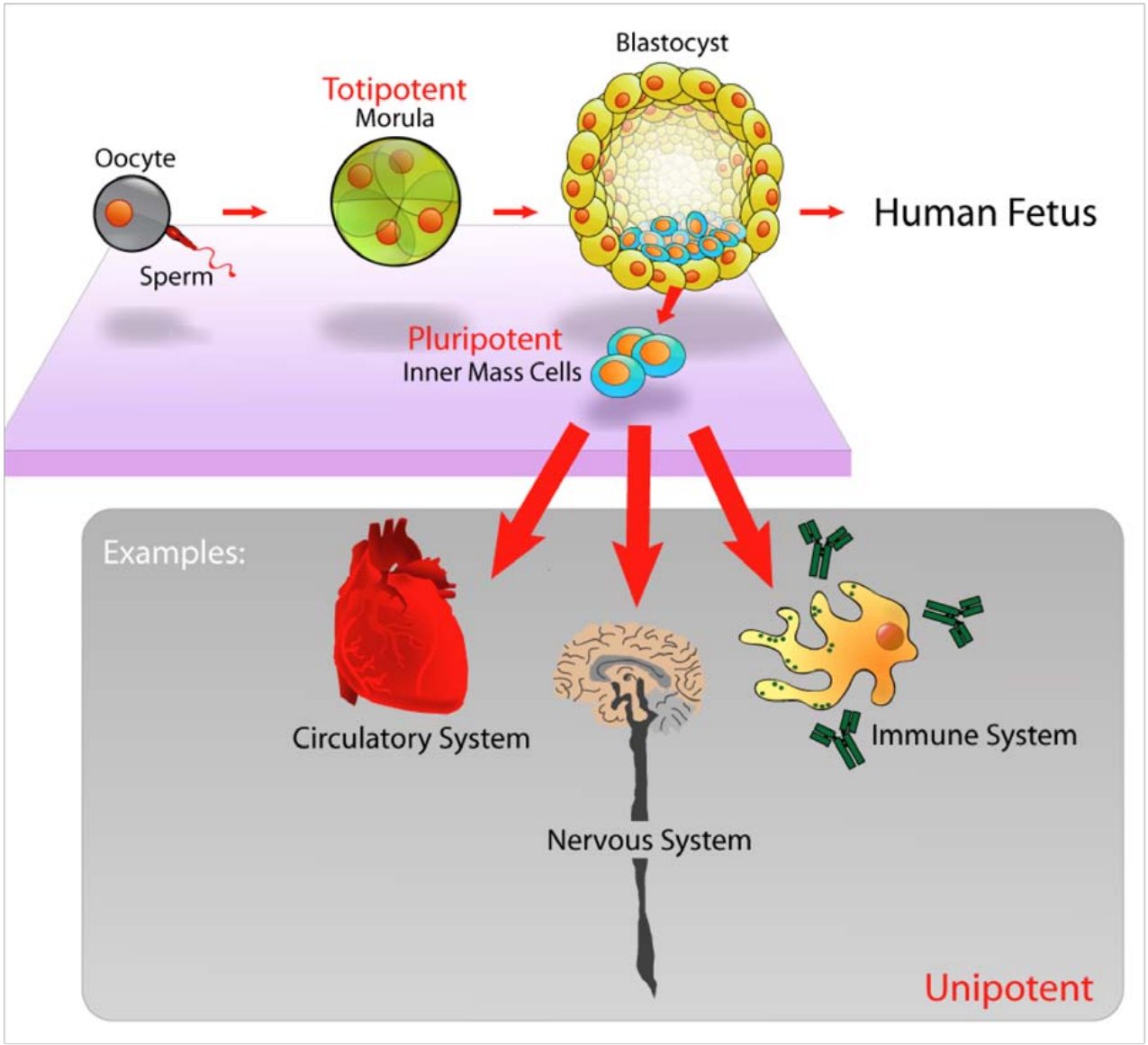
- culturing human epithelial stem cells and using their differentiated progeny to replace a damaged cornea. This works best when the stem cells are from the patient (e.g. from the other eye). Corneal cells from another person (an allograft) are always at risk of rejection by the recipient's immune system.
- the successful repair of a damaged left bronchus using a section of a donated trachea that was first cleansed of all donor cells and then seeded with the recipient's epithelial cells and cartilage-forming cells grown from stem cells in her bone marrow. So far the patient is doing well and needs no drugs to suppress her immune system.

Human Embryonic Development

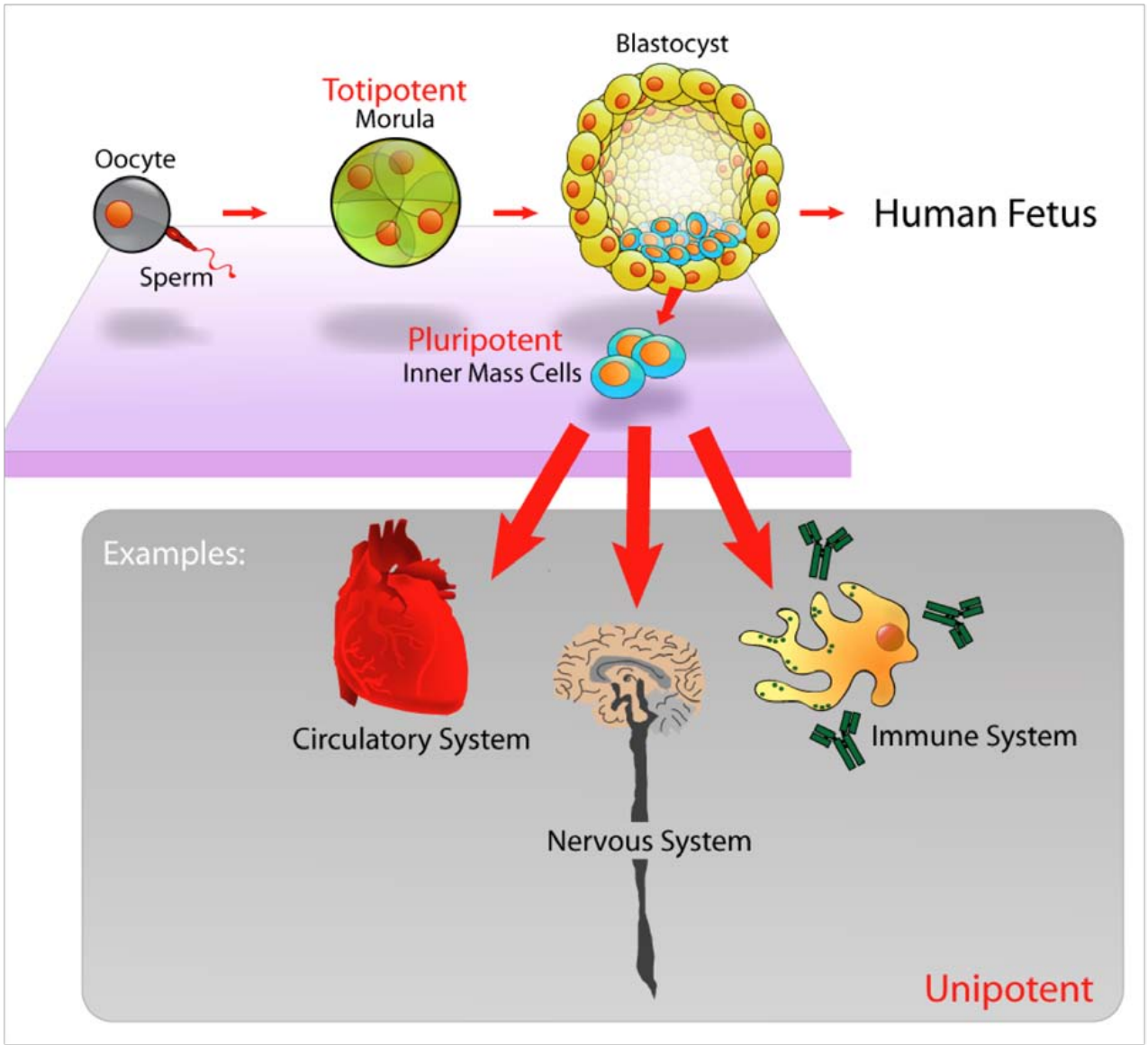


Sources of Stem Cells

- Embryonic stem cells
- Non-embryonic stem cells
- Somatic cell nuclear transfer (SCNT)
- Induced pluripotent stem (iPS) cells



Source of Embryonic Stem Cells



Embryonic Stem Cells

- Isolated from inner cell mass of blastocyst

- Embryonic Germ (EG) Cells are isolated from the precursor to the gonads in aborted fetuses

Arguments for the use of embryonic stem cells

- Embryos are not equivalent to human life while they are still incapable of surviving outside the womb (i.e. they only have the potential for life).

- More than a third of zygotes do not implant after conception. Thus, far more embryos are lost due to chance than are proposed to be used for embryonic stem cell research or treatments.

Arguments for the use of embryonic stem cells

- Blastocysts are a cluster of human cells that have not differentiated into distinct organ tissue; making cells of the inner cell mass no more "human" than a skin cell.

- Embryos are not humans, believing that the life of Homo sapiens only begins when the heartbeat develops, which is during the 5th week of pregnancy, or when the brain begins developing activity, which has been detected at 54 days after conception.

Arguments for the use of embryonic stem cells

- Roe v. Wade concluded that viability determined the permissibility of abortions performed for reasons other than the protection of the woman's health, defining viability as the point at which a fetus is "potentially able to live outside the mother's womb, albeit with artificial aid." The point of viability was 24 to 28 weeks when the case was decided and has since moved to about 22 weeks due to advancement in medical technology.

Legal definition of the beginning of life

- Before the primitive streak is formed when the embryo attaches to the uterus at approximately 14 days after fertilization, a single fertilized egg can split in two to form identical twins, or a pair of embryos that would have resulted in fraternal twins can fuse together and develop into one person (a tetragametic chimera). Since a fertilized egg has the potential to be two individuals or half of one, some believe it can only be considered a potential person, not an actual one. Those who subscribe to this belief then hold that destroying a blastocyst for embryonic stem cells is ethical.

Arguments for the use of embryonic stem cells

- In vitro fertilization (IVF) generates large numbers of unused embryos (e.g. 70,000 in Australia alone). Many of these thousands of IVF embryos are slated for destruction.

- While the destruction of human embryos is required to establish a stem cell line, no new embryos have to be destroyed to work with existing stem cell lines.

- Abortions are legal in many countries and jurisdictions. A logical argument follows that if these embryos are being destroyed anyway, why not use them for stem cell research or treatments?

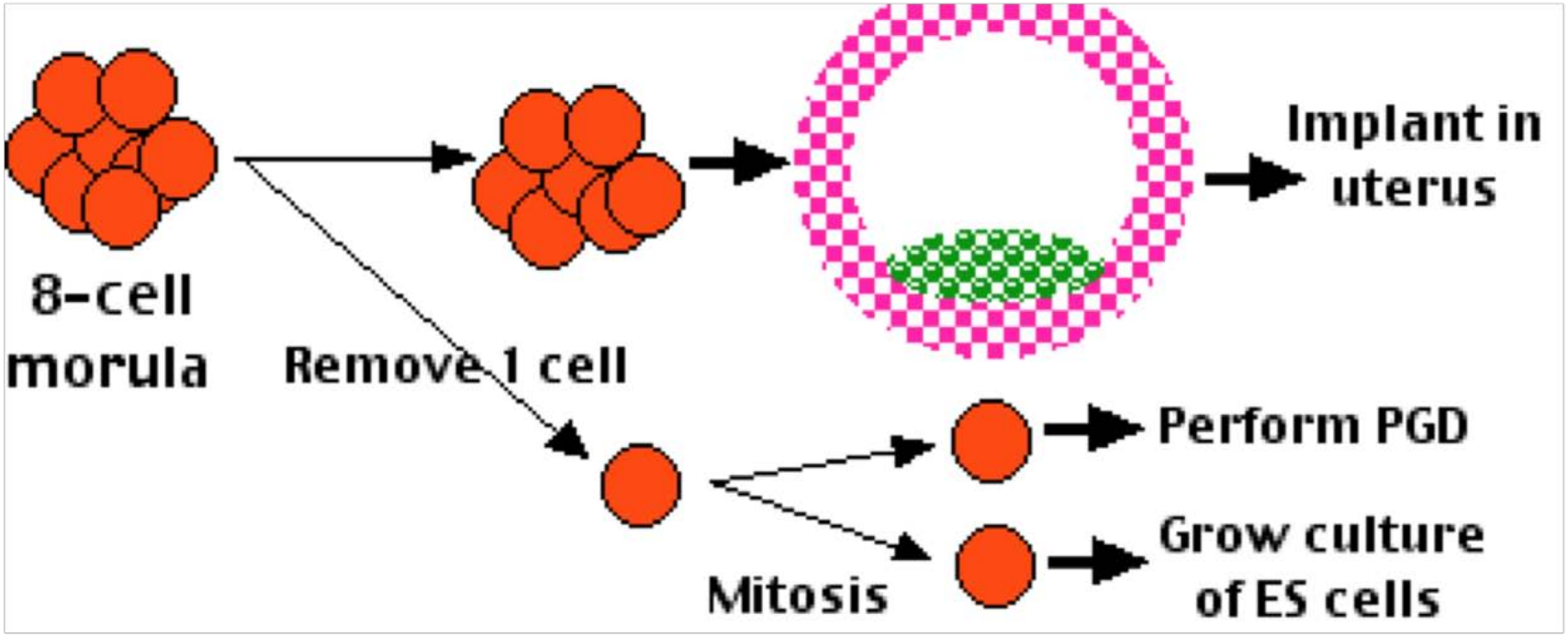
Arguments against the use of embryonic stem cells

- The deliberate destruction of a human embryo is typically interpreted as being incompatible with Roman Catholic doctrine.

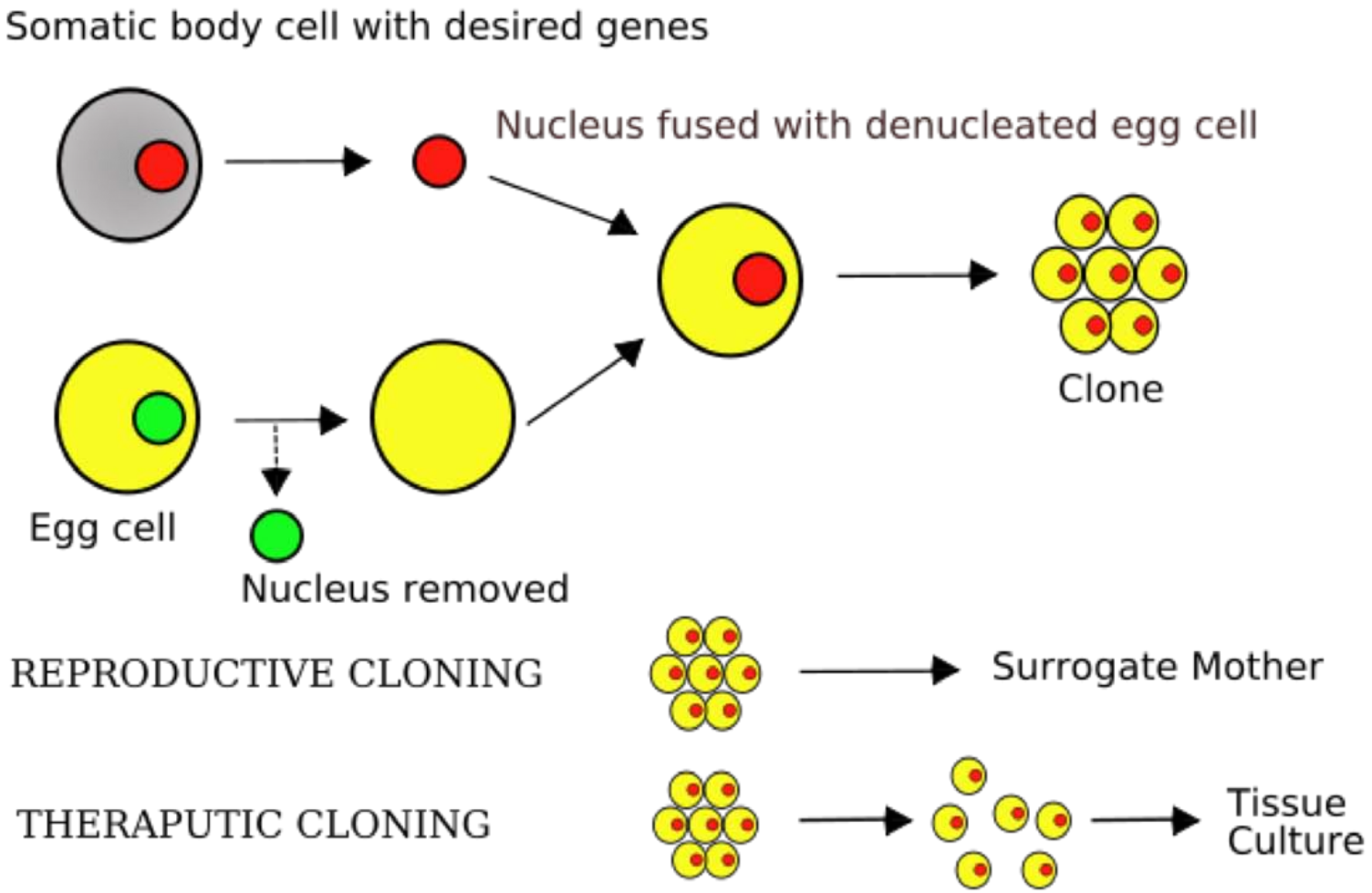
- There is no known successful therapeutic use of embryonic stem cells in humans

Morula-Derived Stem Cells

- Based on Preimplantation Genetic Diagnosis (PGD) procedure
- Isolate 1 cell from morula
- Allow cell to divide once in culture and use 1 daughter cell for PGD
- Use 2nd daughter cell as source for stem cells



Somatic Cell Nuclear Transfer (SCNT)



SCNT and Reproductive Cloning

- Dolly the Sheep
- Stresses placed on both the egg cell and the introduced nucleus are enormous, leading to a high loss in resulting cells. For example, Dolly the sheep was born after 277 eggs were used for SCNT, which created 29 viable embryos. Only three of these embryos survived until birth, and only one survived to adulthood.

SCNT and Primates

- in the 11 November 2007 issue of Science, researchers in Oregon reported success with steps 1–4 in rhesus monkeys.

1. An egg has its own nucleus removed and replaced by
2. a nucleus taken from a somatic (e.g., skin) cell of the donor.
3. The now-diploid egg is allowed to develop in culture to the blastocyst stage when
4. embryonic stem cells can be harvested and grown up in culture.
5. When they have acquired the desired properties, they can be implanted in the donor with no fear of rejection.

SCNT and Rhesus Monkeys

- removal of the spindle and thus all nuclear material from secondary oocytes at metaphase of meiosis II;
- fuse each enucleated egg with a skin cell taken from a male monkey;
- culture until the blastocyst stage is reached;
- extract embryonic stem cells from the inner cell mass;
- establish that they have the nuclear genome of the male (but mostly the mitochondrial genome of the female);
- culture with factors to encourage differentiation: they grew cardiac muscle cells (which contracted), and even neuron-like cells;
- inject into SCID mice and examine the tumors that formed. These contained cells of all three germ layers: ectoderm, mesoderm,and endoderm.
- However, all attempts to implant blastocysts in the uterus of a surrogate mother in the hope of producing a clone of adult animals genetically identical to the skin cell donor failed.

SCNT and Embryonic Stem Cells

- The SCNT can be induced to begin a developmental profile

- The resulting blastula can be used as a source of embryonic stem cells that are genetically identical to the donor individual

SCNT and Therapeutic Cloning

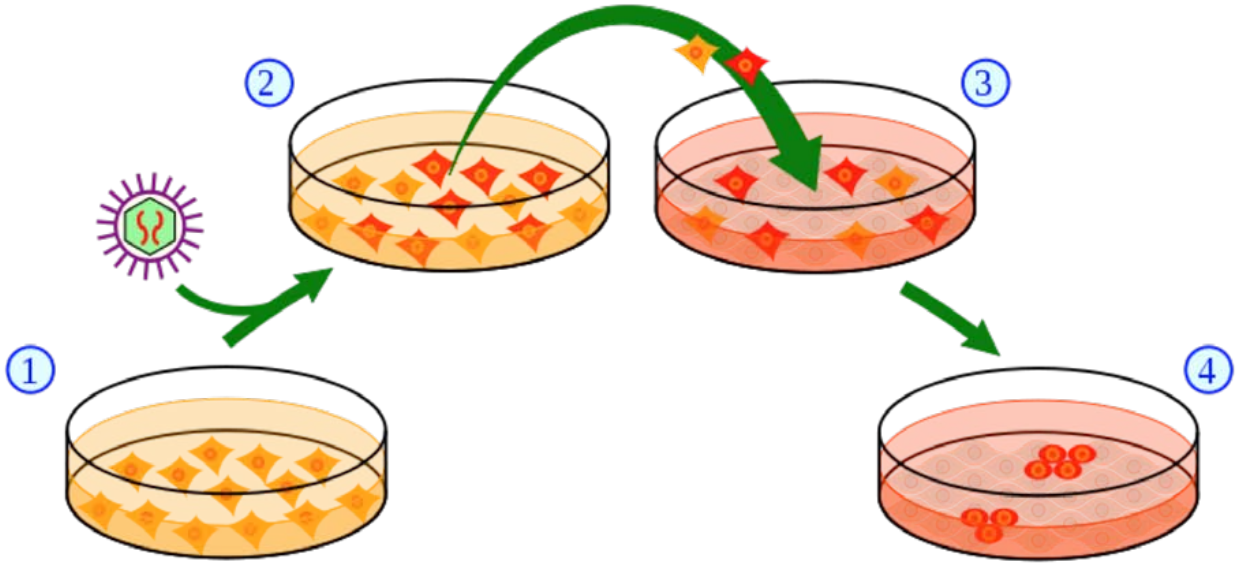
- Perform SCNT using a somatic nucleus from an individual with a disease
- The resulting pluripotent cells can be induced to differentiate in culture to generate the desired cell type to study the disease
- Alternatively, these pluripotent cells could be genetically modified and reintroduced into the patient as a potential therapy without concern for an immune system rejection

SCNT concerns

- The potential for SCNT to create human clones
- The source of the recipient eggs
  - Consequences of hormonal stimulation to induce hyperovulation
  - Payment of women for eggs
  - Number of eggs that would be required

Induced Pluripotent Stem (iPS) Cells

- first generated by Shinya Yamanaka's team at Kyoto University, Japan in 2006
- Culture differentiated cells (such as fibroblasts) from an individual
- Introduce 4 genes (Oct-3/4, SOX2, c-Myc, and Klf4) using either a retroviral vector or a transposable element (PiggyBac)
- Introduce 4 genes (SOX2, OCT4, NANOG, and LIN28) to generate human iPS cells



Definition of Pluripotent Cell

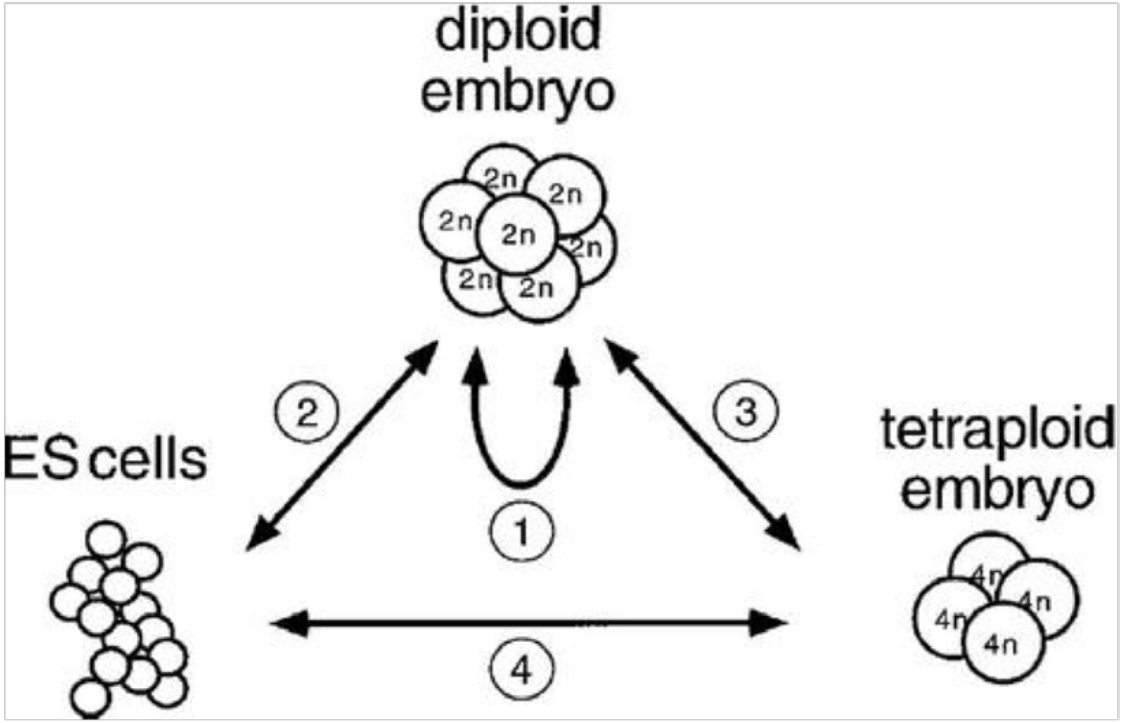
- contribute to the formation of a healthy chimeric adult when injected into a blastocyst which is then implanted in a surrogate mother;
- enter the germline of these animals; that is, contribute to their pool of gametes;
- develop into teratomas when injected into immundeficient (SCID) mice. These tumors produce a wide variety of cell types representing all three germ layers (ectoderm, mesoderm, and endoderm).

Demonstration of pluripotency of iPS cells

- Induced pluripotent stem (iPS) cells were manufactured from differentiated fibroblast by the addition of specific transcription factors. Newly created stem cells were developed into an embryo and were integrated into newborn mouse tissues, analogous to the properties of embryonic stem cells.

Tetraploid complementation

- Tetraploid cells produced by electrofusing the diploid cells at the 2-cell stage
- Mix tetraploid cells with the test cells
- Tetraploid cells can only contribute to the trophectoderm, while the pluripotent cells will be the sole source of the embryo



Multipotent Cell

- These are true stem cells but can only differentiate into a limited number of types. For example, the bone marrow contains multipotent stem cells that give rise to all the cells of the blood but not to other types of cells.

- Multipotent stem cells are found in adult animals; perhaps most organs in the body (e.g., brain, liver) contain them where they can replace dead or damaged cells. These adult stem cells may also be the cells that — when one accumulates sufficient mutations — produce a clone of cancer cells.

Arguments against the use of adult stem cells

- Embryonic stem cells make up a significant proportion of a developing embryo, while adult stem cells exist as minor populations within a mature individual (e.g. in every 1,000 cells of the bone marrow, only 1 will be a usable stem cell). Thus, embryonic stem cells are likely to be easier to isolate and grow ex vivo than adult stem cells.

- Embryonic stem cells divide more rapidly than adult stem cells, potentially making it easier to generate large numbers of cells for therapeutic means.

Arguments against the use of adult stem cells

- Embryonic stem cells have greater plasticity, potentially allowing them to treat a wider range of diseases.

- Adult stem cells from the patient's own body might not be effective in treatment of genetic disorders.

- DNA abnormalities found in adult stem cells that are caused by toxins and sunlight may make them poorly suited for treatment.

Arguments for the use of adult stem cells

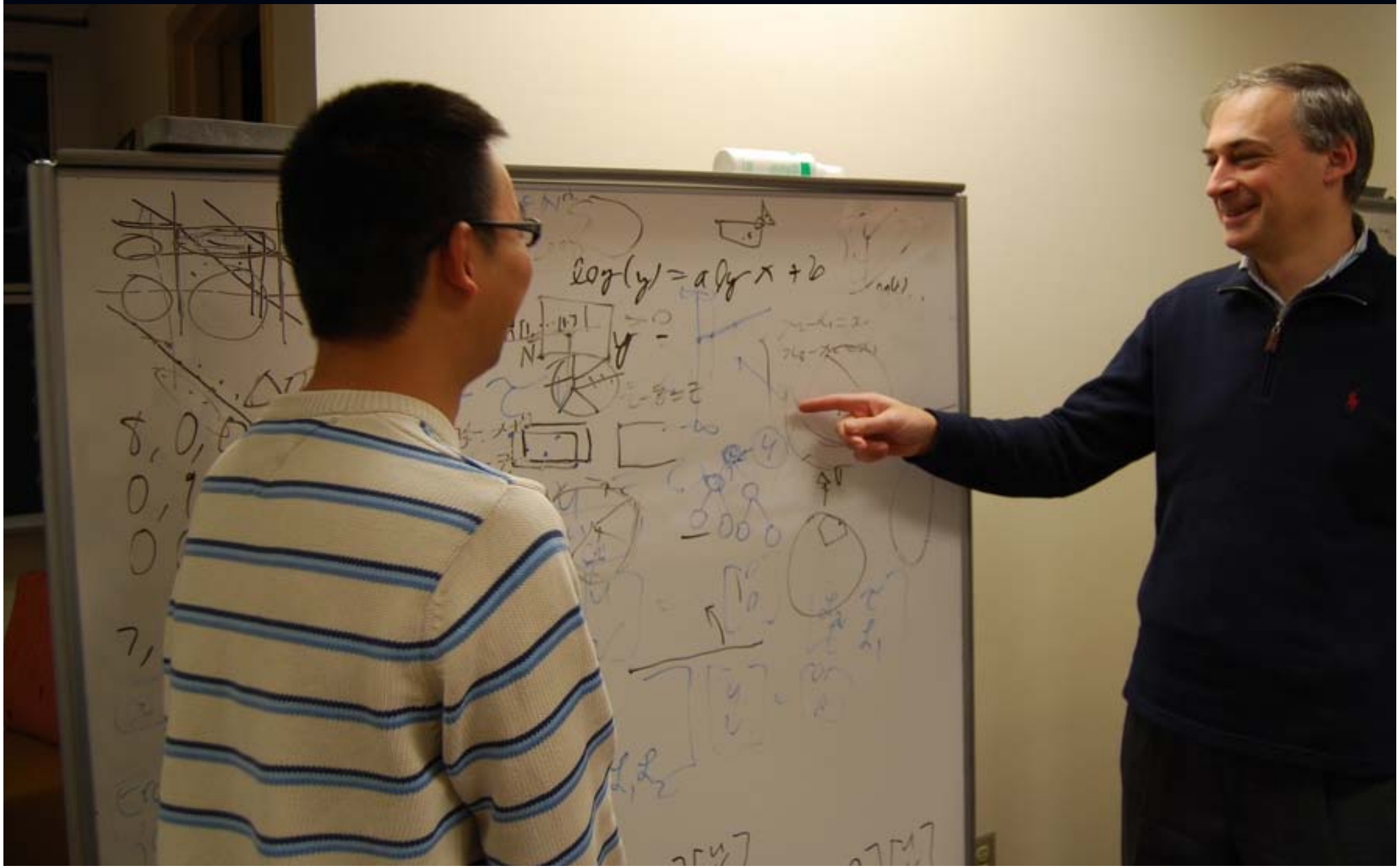
- adult stem cells from sources such as umbilical cord blood has consistently produced more promising results than the use of embryonic stem cells.

- Adult stem cells have already produced therapies, while embryonic stem cells have not.

Prof Mark Alber

Mathematics

It's All in the Numbers



It's all in the Numbers – Ethics in Mathematics and Statistics

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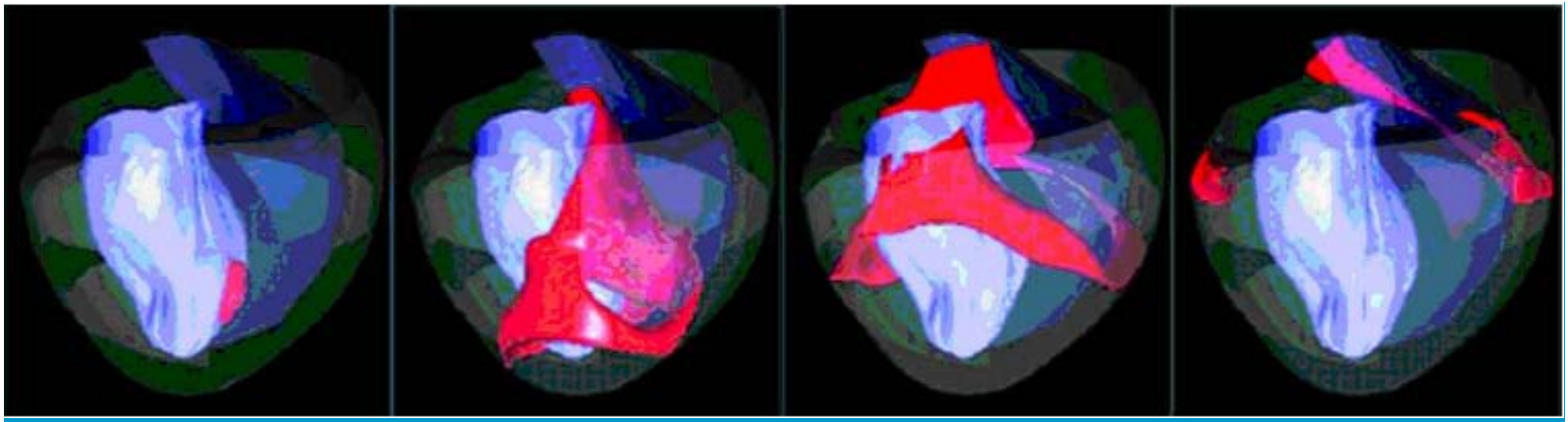
September 16, 2009



Spread of the electrical activation in an anatomically detailed cardiac model

Complex biochemically, biophysically and pharmacologically detailed mathematical models of `living cells' are being arranged in morphologically representative tissue assemblies, and, using large-scale supercomputers, utilized to produce anatomically structured models of integrated tissue and organ function. This provides biomedical sciences with a radical new tool: `*in silico*' organs, organ systems and, ultimately, organisms. *In silico* models will be a crucial tool for biomedical research and development in the new millennium, extracting knowledge from the vast amount of increasingly detailed data, and integrating this into a comprehensive analytical description of biological function with predictive power: the Physiome.

Ethics of Mathematical and Computational Modeling

The application of computational biology to clinical decision-making in human subjects is in need of a more reflective process. Modelers may be familiar with modeling applications that involve human physiology; however, their experience with research that directly involves human subjects may be limited. As the research advances and the mathematical and programming aspects of the simulation move beyond most physicians' abilities to assess correct methodology, it becomes important for modelers to consider ethical issues in human subject research.

ETHICS INVOLVED IN SIMULATION-BASED MEDICAL PLANNING, Ethics & Medicine, by Tongen, Anthony L, Adam, Mary B, 2006.

- The collaboration of modelers and physicians requires a level of trust and integrity that is similar to specialty referral in the clinical setting.
- It is imperative that the modeler and the physician understand the advantages as well as the limitations of simulations or patients' care may suffer.
- Example: The simulation of blood flow in arterial bypass grafts. The surgeon can utilize the models to choose the preferred location or positioning of the bypass graphs using simulation data calculated from the pre-operative MRI.
- A variety of potential sources of error highlight the importance of determining what margin of error is acceptable. Another source of potential error is the accuracy of the geometric model developed from MRI data. The physician needs to be assured that a given bypass graft placement site will improve blood flow in the patient and not just in the simulation.
- The biggest potential advantage is the opportunity to assist doctors in the decision-making process with pseudo-surgery that does not physically affect the patient at all.

Standards of professional and ethical conduct

- Simulations can be used as an experimental lab that may allow for innovative surgical advancement without any threat of harm to the patient. However, if physicians are to make clinical decisions based on simulations, it is of paramount importance that the simulations be carried out in a manner which maintains the highest standards of professional and ethical conduct.
- Full disclosure of assumptions and known limitations
- Specification about the conditions of applicability of models and results.
- Caution against acceptance of results without proper verification and unbiased interpretations of results.

Verification Procedure

The verifications should include, but not be limited to:

- (1) proper verification of the mathematical model,
- (2) proper understanding of the relationship between the model and actual human physiology,
- (3) proper verification of margins of error, and
- (4) proper verification of the risks and benefits of the new technology in sufficient numbers of human subjects to confirm usefulness and expose unanticipated outcome
- (5) determination acceptable margin of error

In Vivo Validation and Clinical Trials

- Mathematical models tend to be static and may not be able to adequately approximate dynamic physiological processes. By their nature, simulations can only estimate the real world setting.
- Physicians may be at risk for embracing these simulation options prior to sufficient examination. The necessary level of certainty can only be gained through extensive clinical trials.

References

- T.I. Oren. "Responsibility, Ethics and Simulation," Special Issue of Transactions of the SCS on Ethical Issues in Modeling and Simulation, 17:4 (Dec.), 165-170,2000.
- T.I. Oren. "Rationale for a Code of Professional Ethics for Simulationists," Proceedings of the 2002 Summer Computer Simulation Conference, 2002.
- T.I. Oren. M.S. Elzas, I. Smit, and L.G. Birta, "A Code of Professional Ethics for Simulationists," Proceedings of the 2002 Summer Computer Simulation Conference, 2002.
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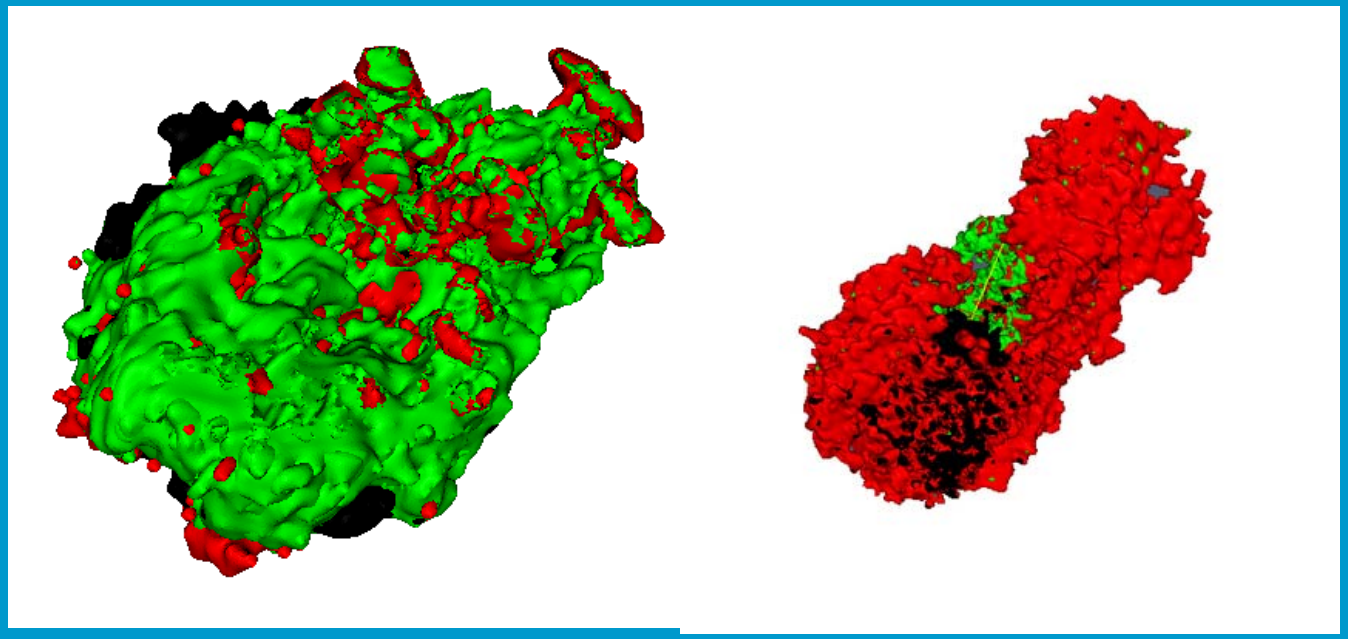
- K.W. Goodman, Ethics. Computing, and Medicine. Cambridge, 1998.

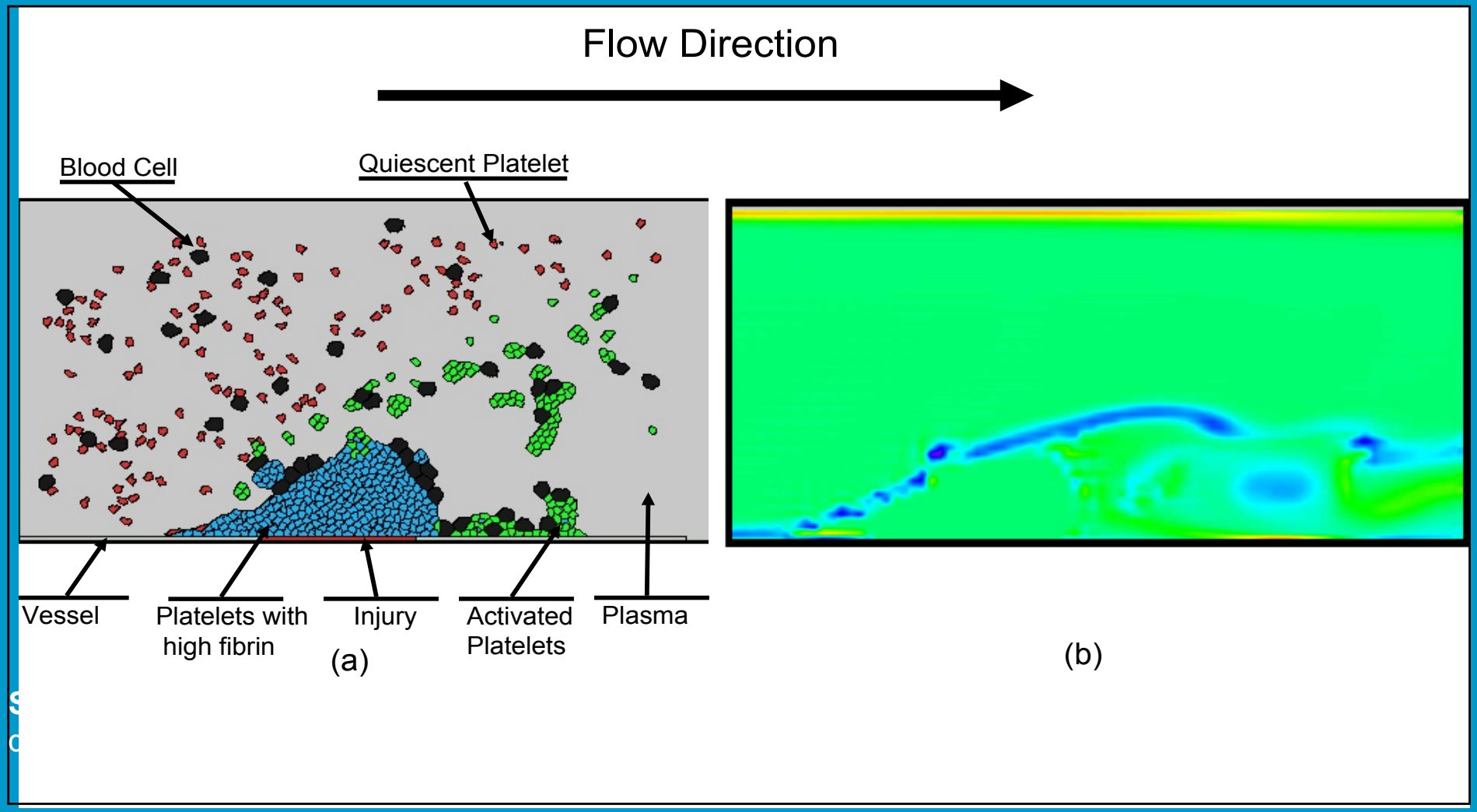
Blood Clot Physiome

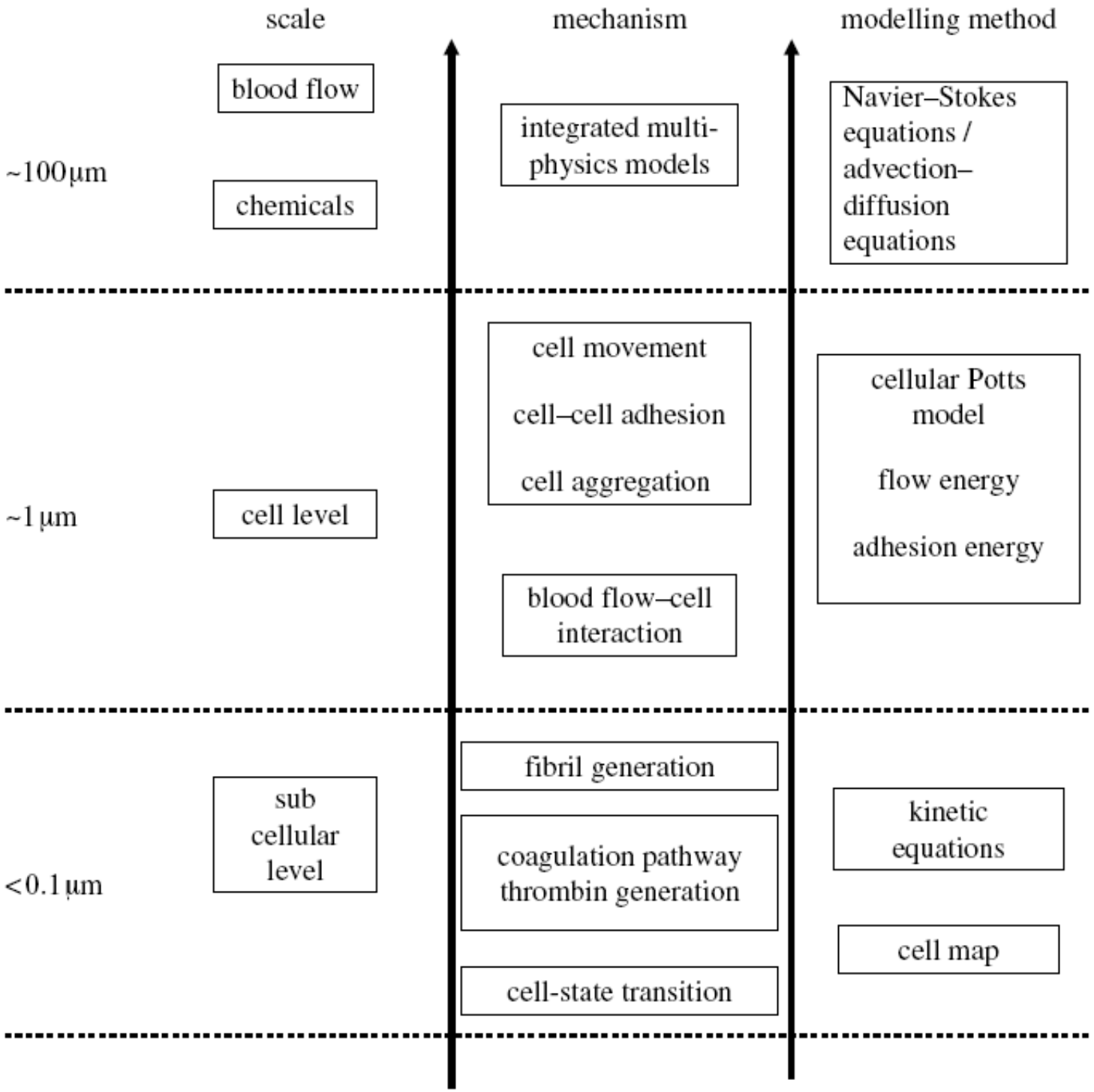
Blood Clot Formation. Fragments washed away from an unstable clot in a peripheral vein can embolize to the lungs with sometimes fatal results. The stability of the thrombus is influenced by its structural heterogeneity as the boundaries between discreet domains with different mechano-elastic properties are susceptible to fracture.



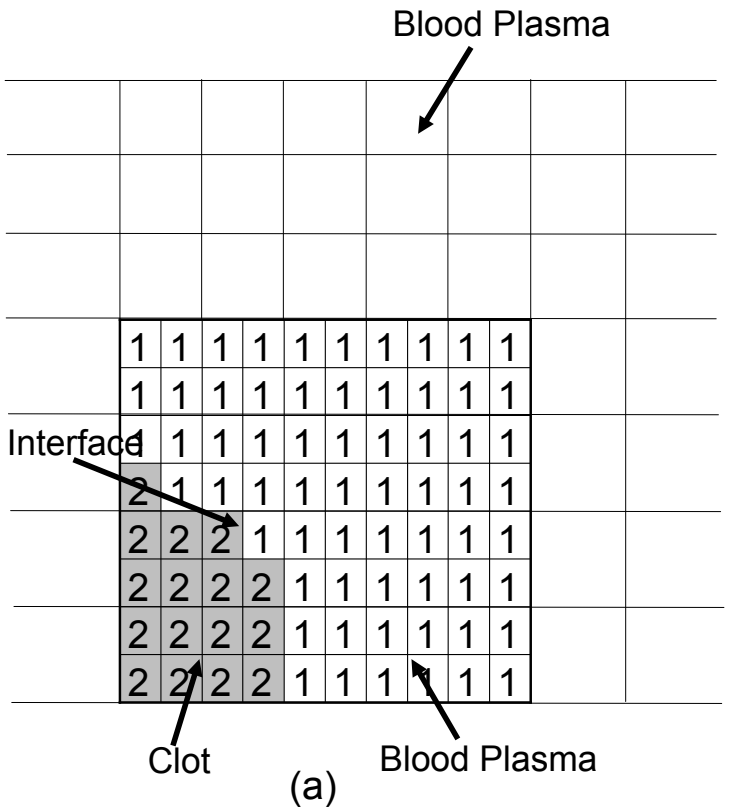
Reconstructed three-dimensional images of thrombi (clots) formed in wild type and low FVII mice.

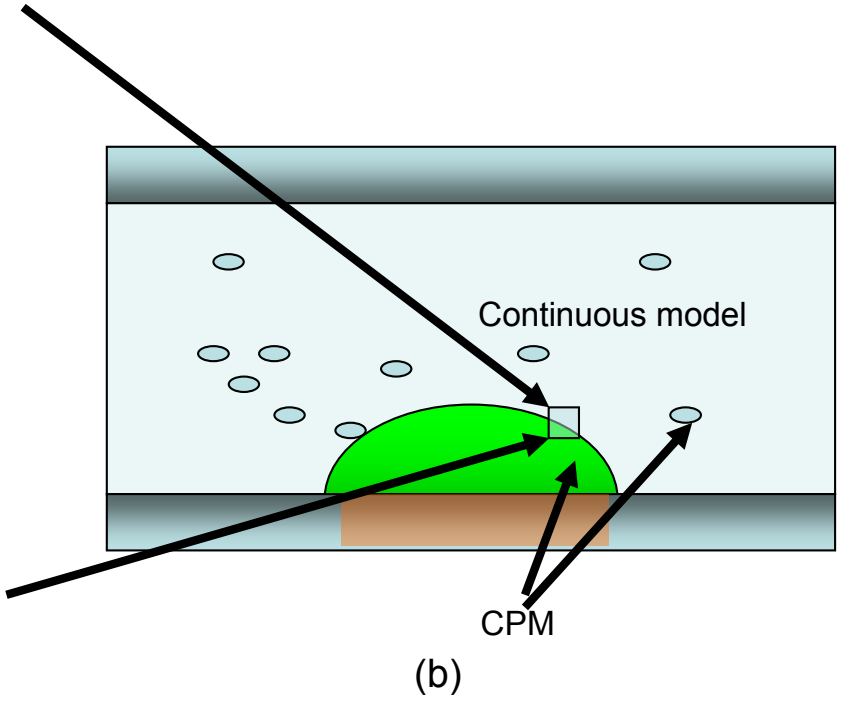
Computational Model of Clot Formation



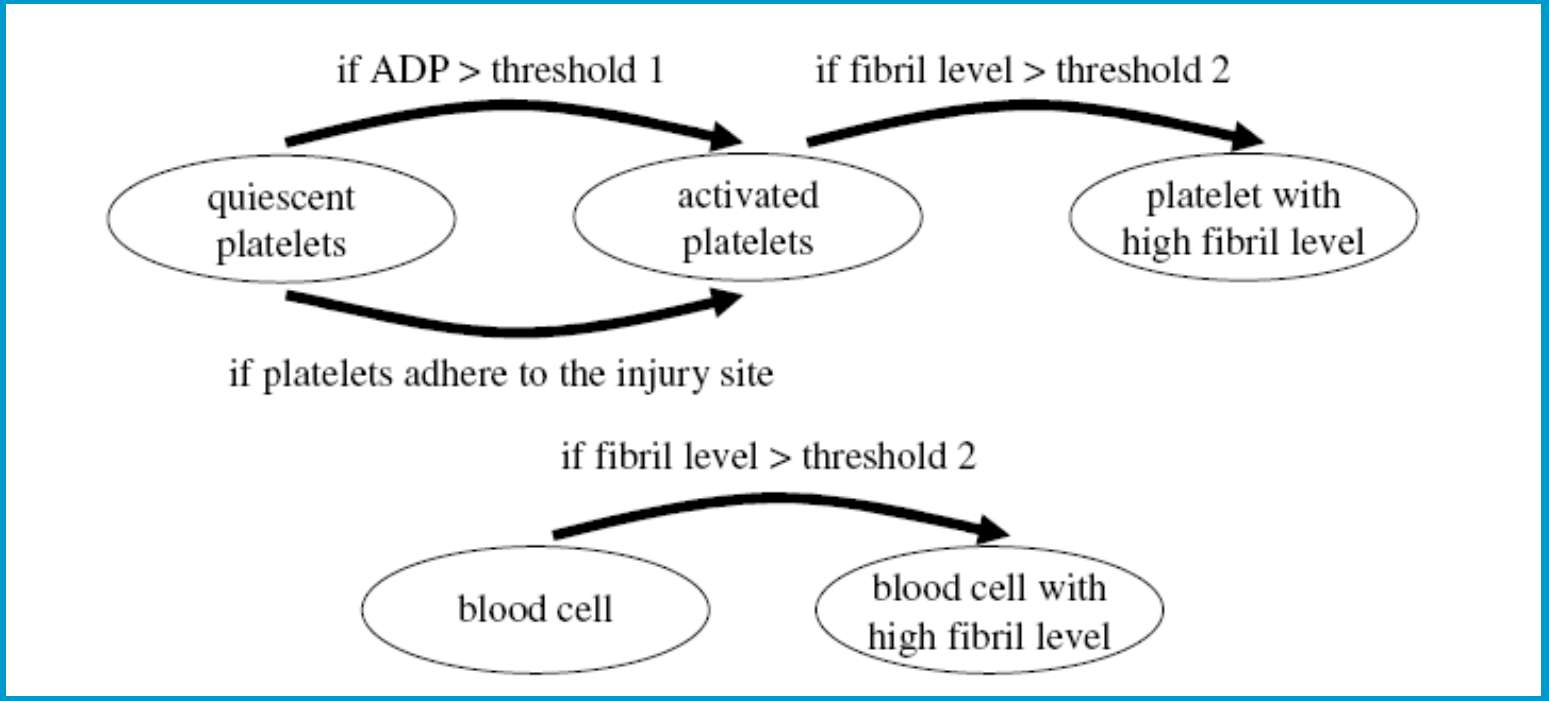

scale
mechanism
modelling method
blood flow
~100 µm
chemicals
integrated multi-physics models
Navier–Stokes equations / advection–diffusion equations
cell movement
cell–cell adhesion
cell aggregation
cellular Potts model
flow energy
adhesion energy
~1 µm
cell level
blood flow–cell interaction
fibril generation
sub cellular level
kinetic equations
coagulation pathway thrombin generation
<0.1 µm
cell map
cell-state transition

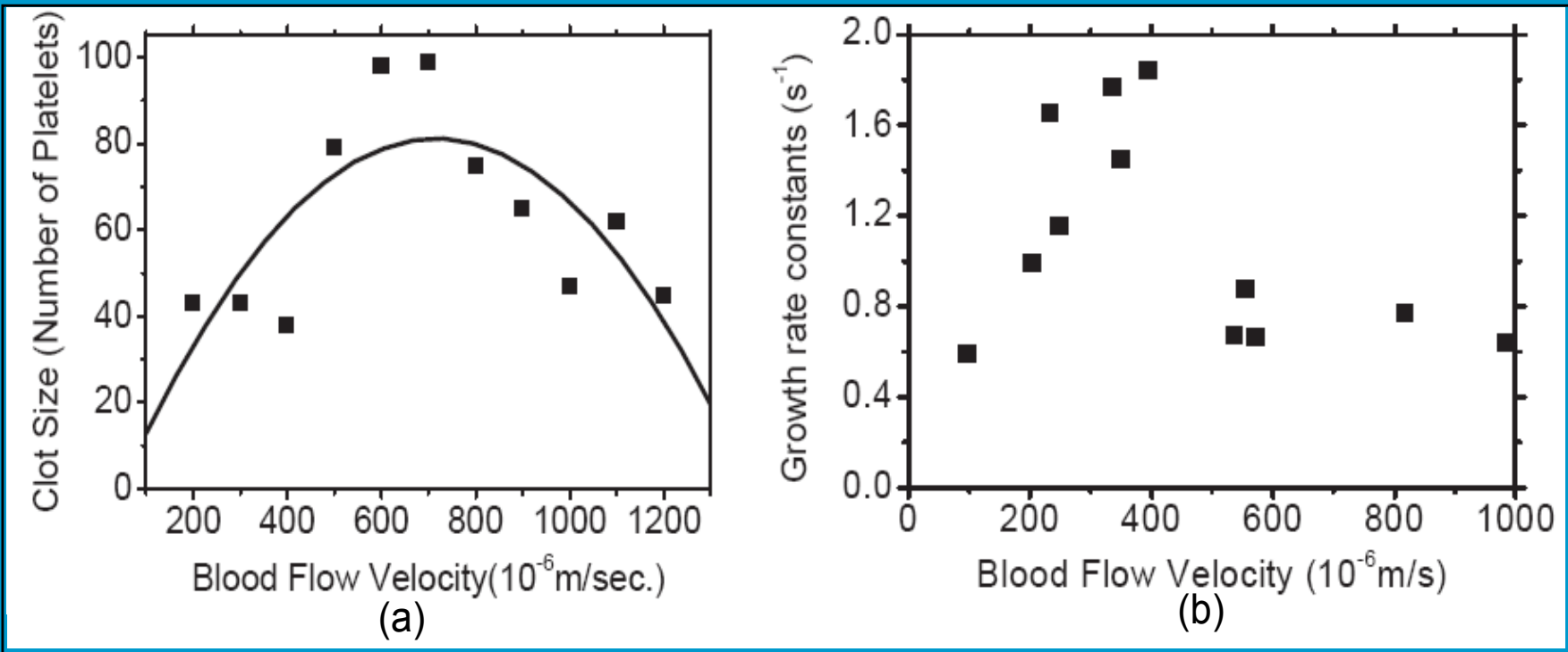
Interface


Blood Plasma
Interface
Clot
Blood Plasma
(a)


Continuous model
CPM
(b)

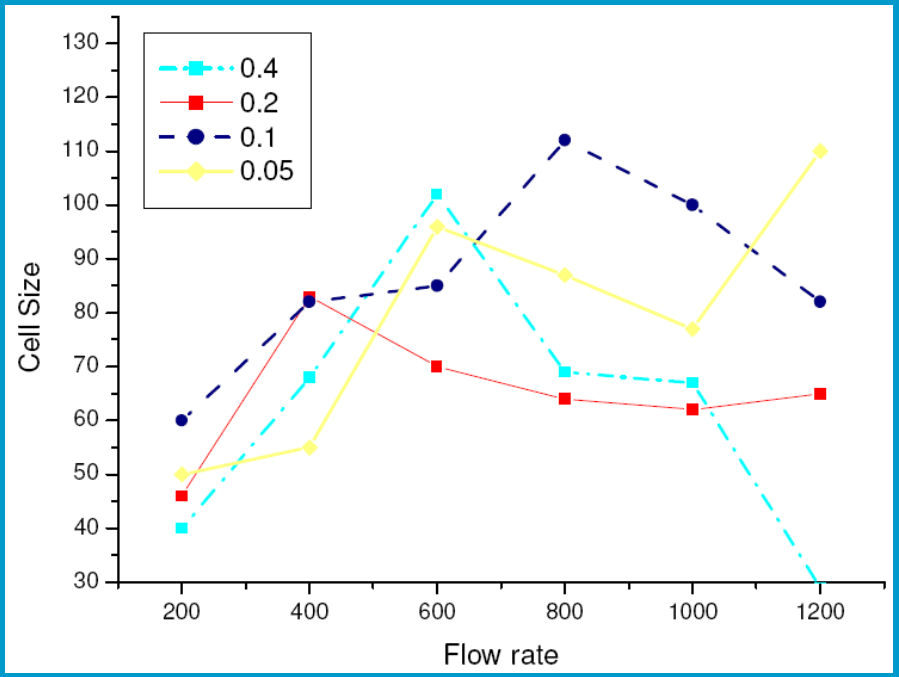
Cell-State Transition Map



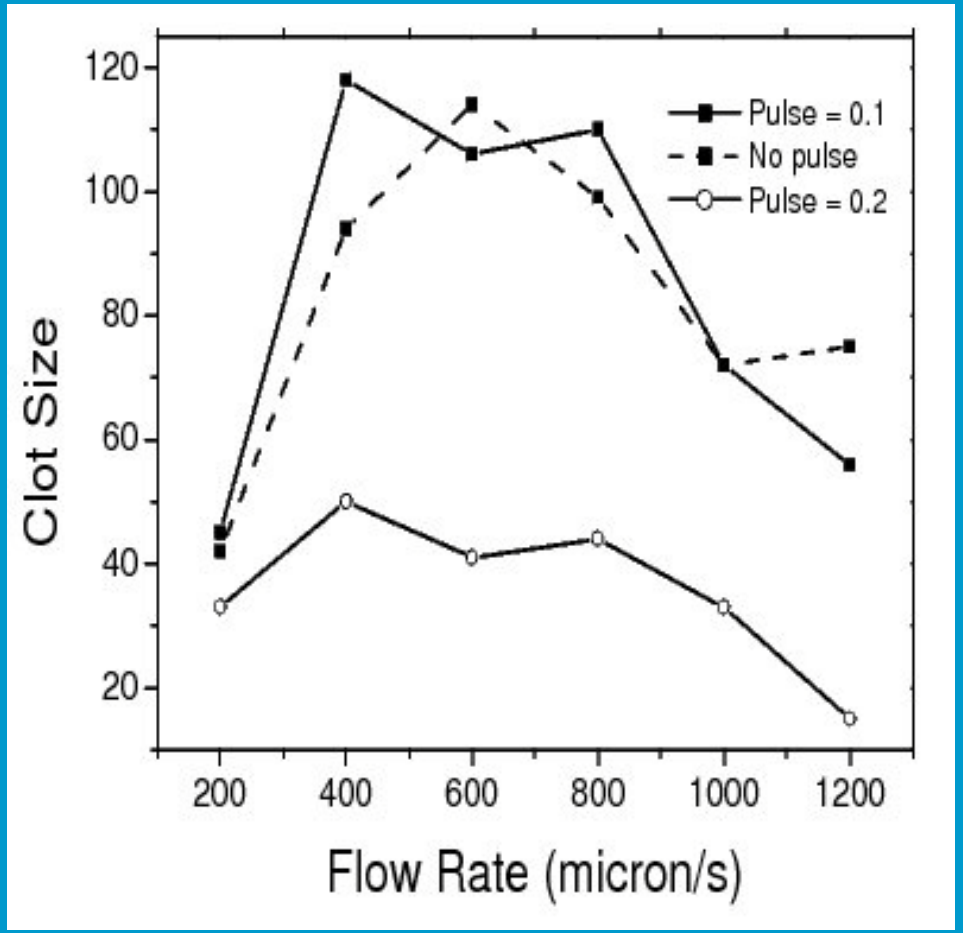


Graphs demonstrating effect of the blood flow rate on the thrombus growth.
(a) Simulation results after 20 sec; (b) Experimental data .

Different Pulse Rates



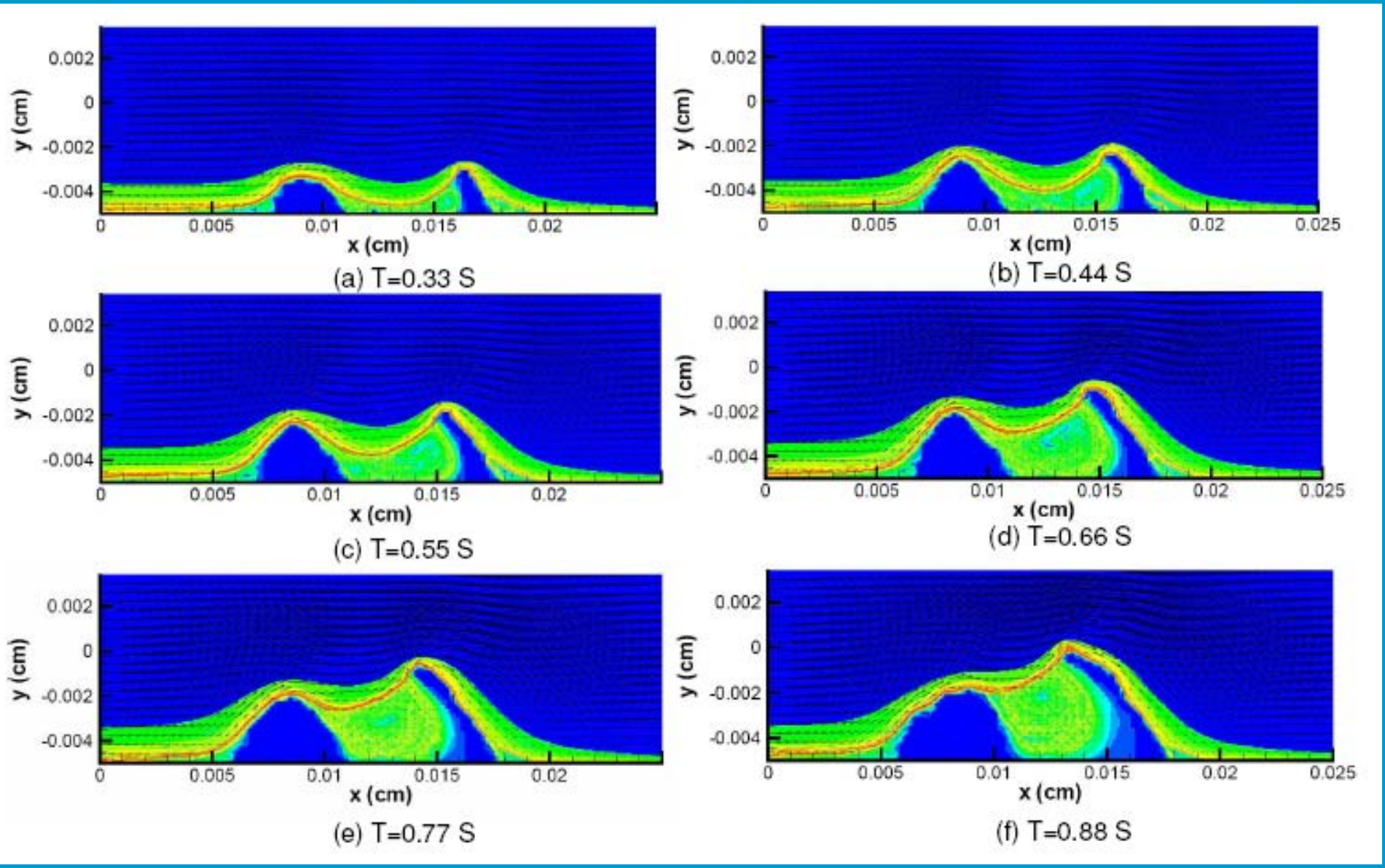
The effect of blood flow rate on the clot growth

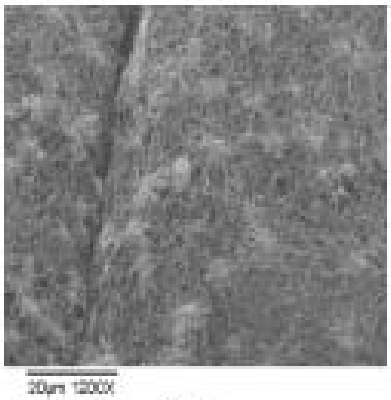


non-Newtonian flow

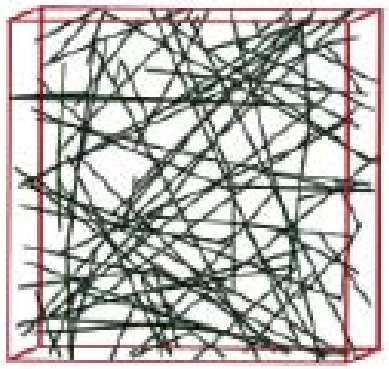
Xu, Z., Chen, N., Shadden, S., Marsden, J.E., Kamocka, M.M., Rosen, E.D., and M.S. Alber, Study of Blood Flow Impact on Growth of Thrombi Using a Multiscale Model, *Soft Matter* 5, 769–779 (2009)

Analysis of the flow near the clot using Lagrangian Coherent Structures (LCS)

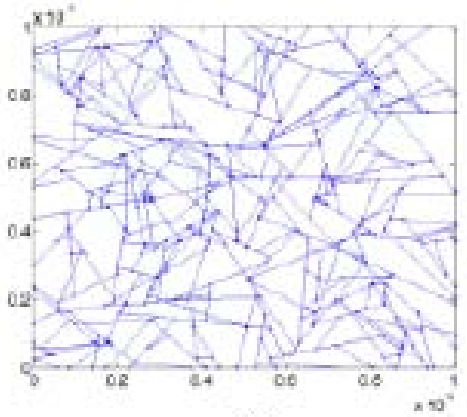




(a)



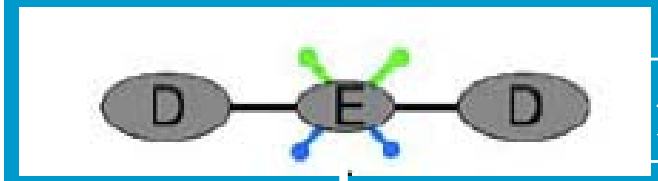
(b)



(c)

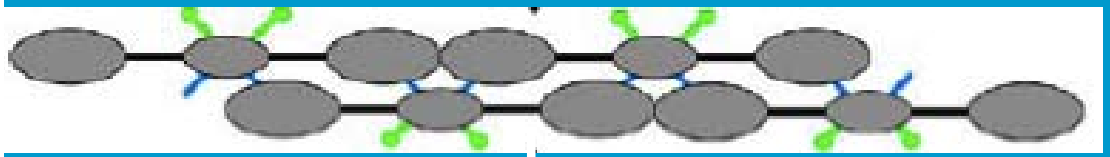
(a) Scanning electron micrographs (SEMs) of fibrin networks obtained by Dr. Wolberg lab at the University of North Carolina at Chapel Hill, (b) A brin ber network representation, (c) A 2-dimensional microscopic domain of brin network model; 500 branch points in a 100 m square domain.

Fibrin Network formation

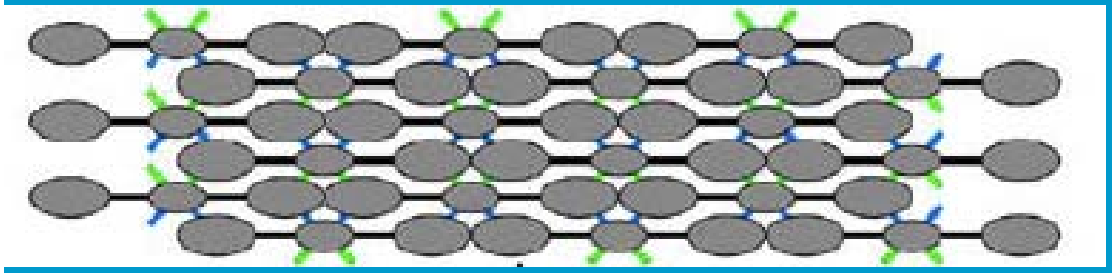


fibrinogen

thrombin



thrombin



fibrin monomer

protofibril formation

polymerization

fibrin network; cross-linking and branching

Two kinds of bonds - linear bonds and lateral bonds

Different : Thrombin kinetics, Formation/breaking rates, Response to Force

- The network consists of filaments, which are linked by crosslinks

- Each filament is an inextensible semiflexible chain, where its energy is:

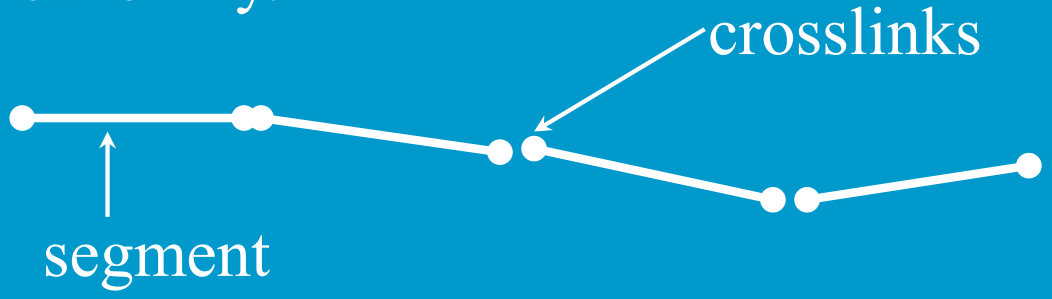
$$E = \int_0^{l_c} \left(\frac{\kappa}{2} \left| \frac{d\tau(s)}{ds} \right|^2 + \frac{f}{2} |\tau(s)|^2 \right) ds,$$

κ = bending stiffness, τ(s): tangent vector along the bond segment

f = external force

- Each filament is partitioned into segments which begin and end at a crosslink.

- Each filament can consist of many segments, but it is always a single mechanical entity.

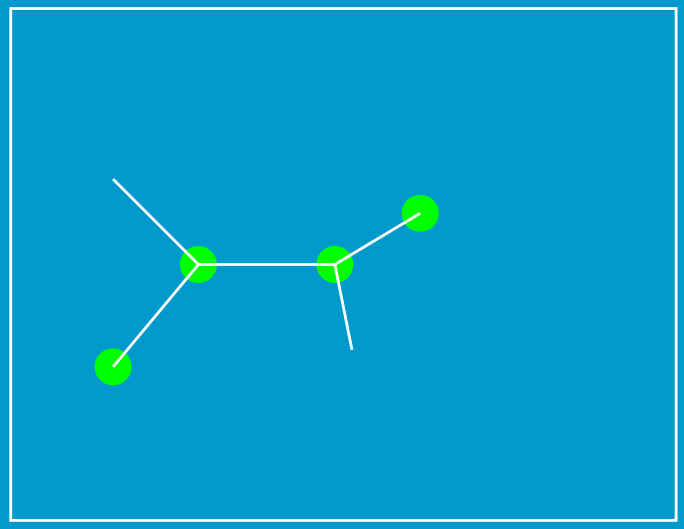


Fibrin network generation

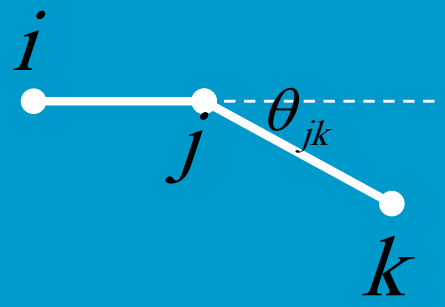
• Construct initial network by randomly placing M nodes : M depends on the concentration of fibrinogen

(coarse -grind : radius of fibrinogen ~ 4.5 nm, length ~45nm)

• Connect nodes : (1) Identify three close nodes, (2) Connect these three nodes, (3) Extend this connection to one bond at a time, (4) Repeat (1)-(3) until all nodes are fourfold connected.



Fibrin network generation algoritm



- Minimize the free energy $\text{Free Energy F} = \frac{l_p \theta_{ijk}}{l_{ij} + l_{jk}}$

l_p = Persistence length

- Monte Carlo move + local minimization

- Assign the free energy to initial network position

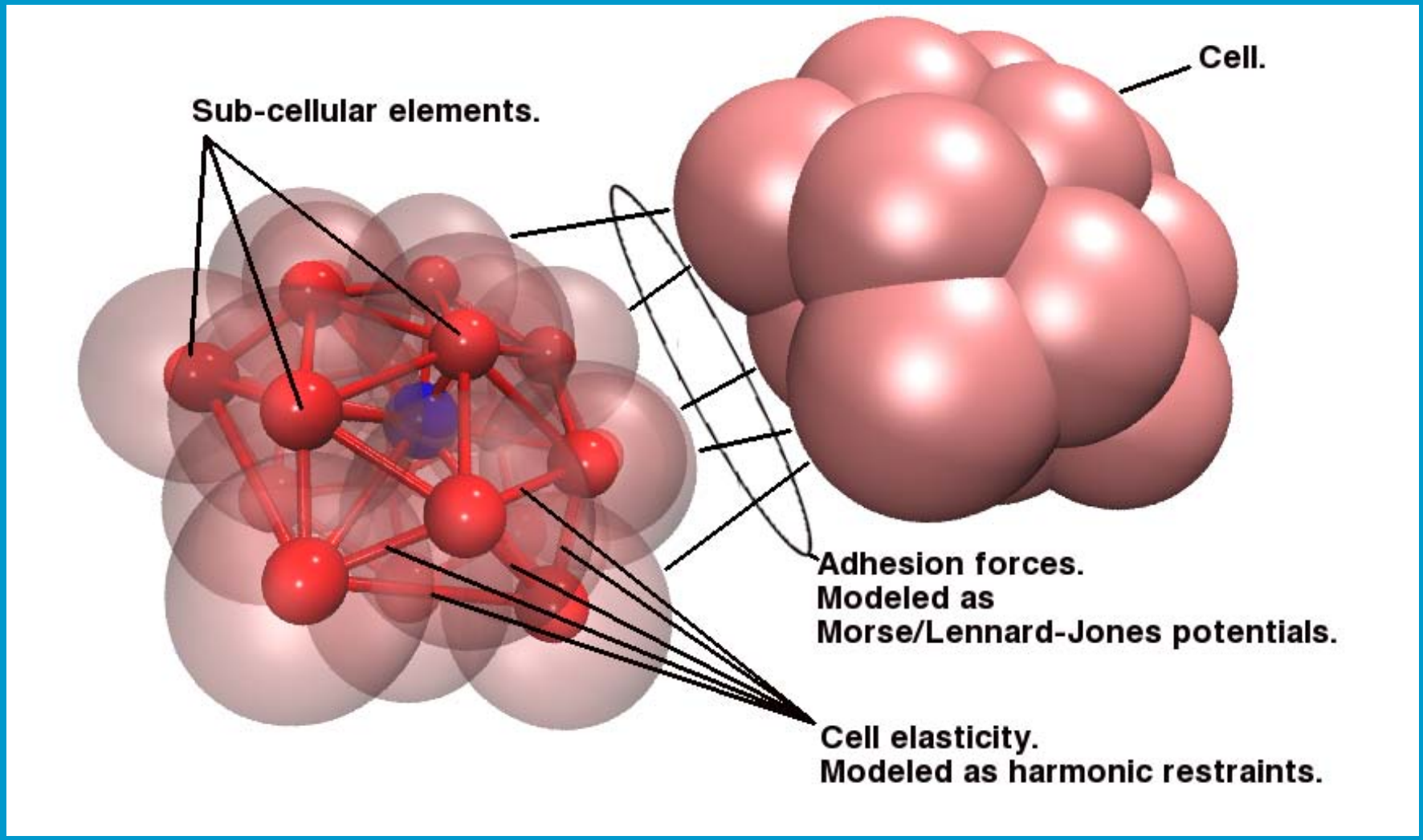
- Randomly change one of nodes in a filament

- Compute the change of the free energy

- Use Metropolis algorithm to determine (accept or reject) topological change of network

- Repeat until network free energy is minimized

Sub-cellular elements model



Zhiliang Xu, Danny Chen, Mathematics and Computer Science Department, University of Notre Dame

Elliot Rosen, Malgorzata Kamocka, Department of Medical and Molecular Genetics, Indiana University School of Medicine

NSF DMS-0800612, NSF Math Biology and NIH NIGMS

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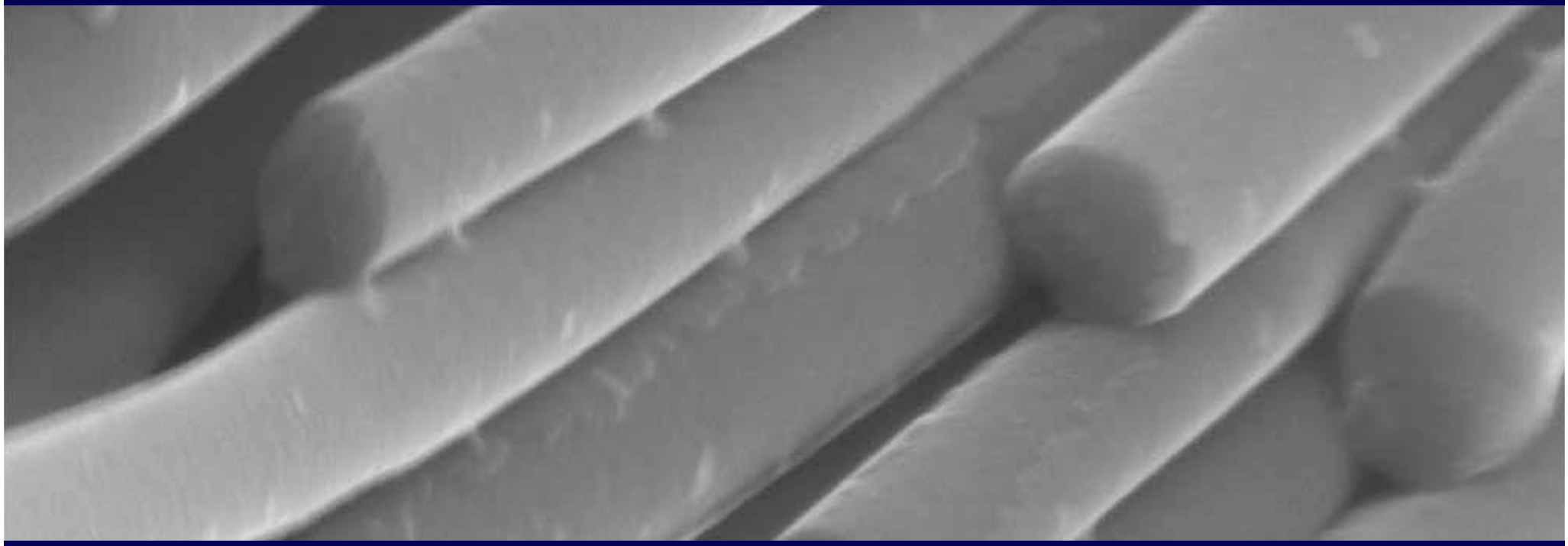
Department of Physics
College of Science
Ethics of Nano-Science & Technology

Ethics of Nano-Science and Nano-Technology:
A Scientist's Perspective



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…acknowledgements & collaborators

"Micropatterned nanotopography chips for probing the cellular basis of toxicity and biocompatibility,"
NSF NIRT Grant 2005-2010
(PIs: Hurt, Crawford, Kane, Morgan, Brown, and Sarachick)

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(Hurt) Chemical Engineering
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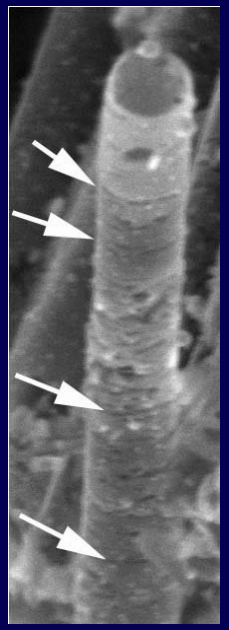
(Sarachick) EHS
(Environmental Health Safety)
Brown University

(Crawford) Physics
(College of Science)
University of Notre Dame

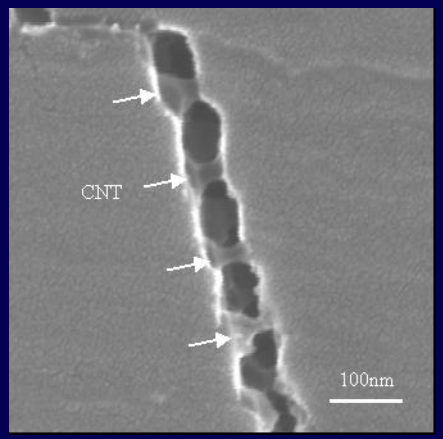
http://www.brown.edu/Administration/EHS/nanosafety/

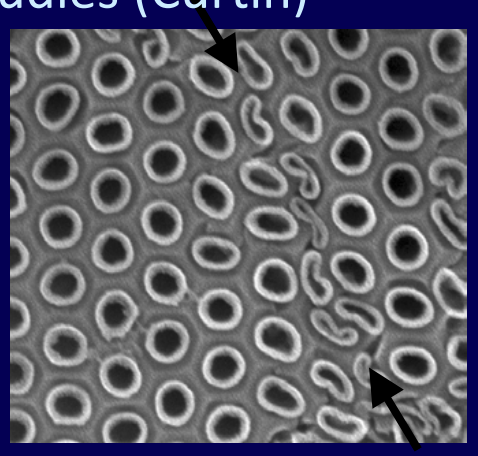
...nano-interests

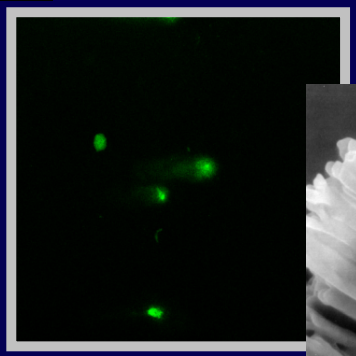
Platelet Symmetry

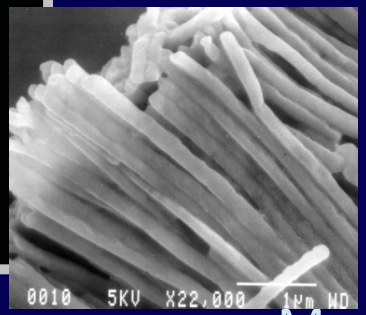


Mechanical Studies (Curtin)



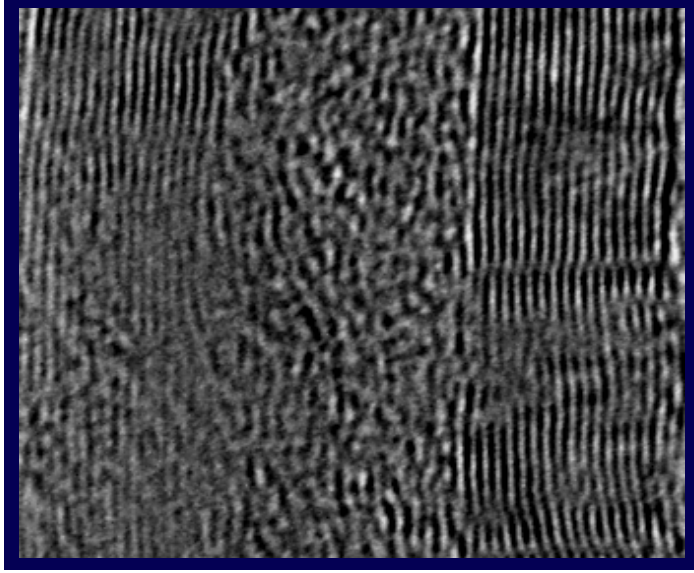




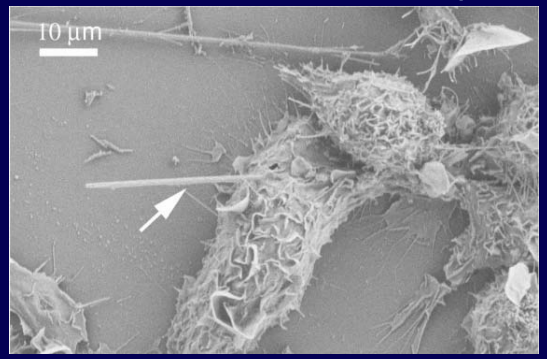


Active Sunscreen Materials (Jay)

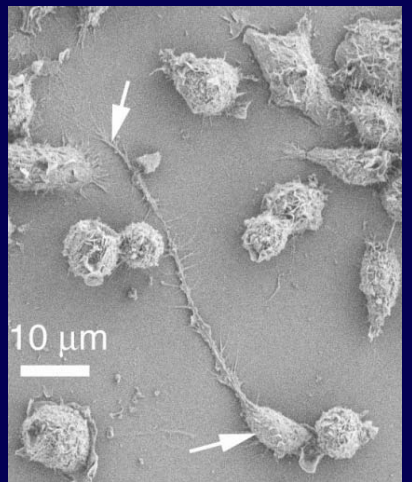
Ordering in Tubes



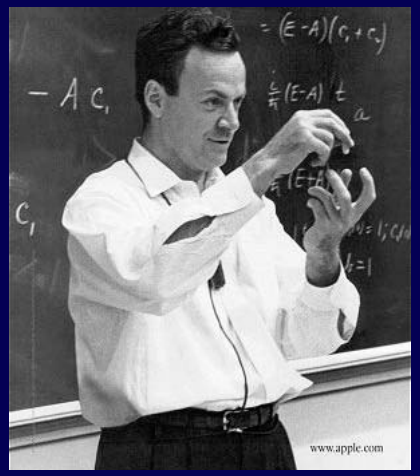
Macrophage with C-Nano-Fibers
Complete phagocytosis (Kane/Hurt)



Macrophage with Asbestos Fibers
Incomplete phagocytosis (Kane)

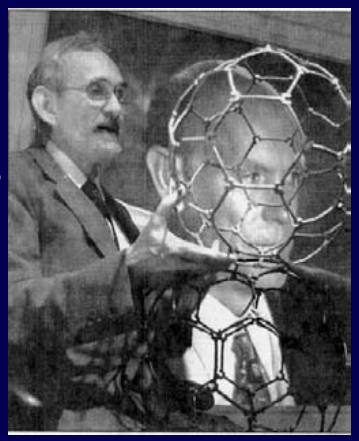


...some history of nanoscience & technology



29th December 1959

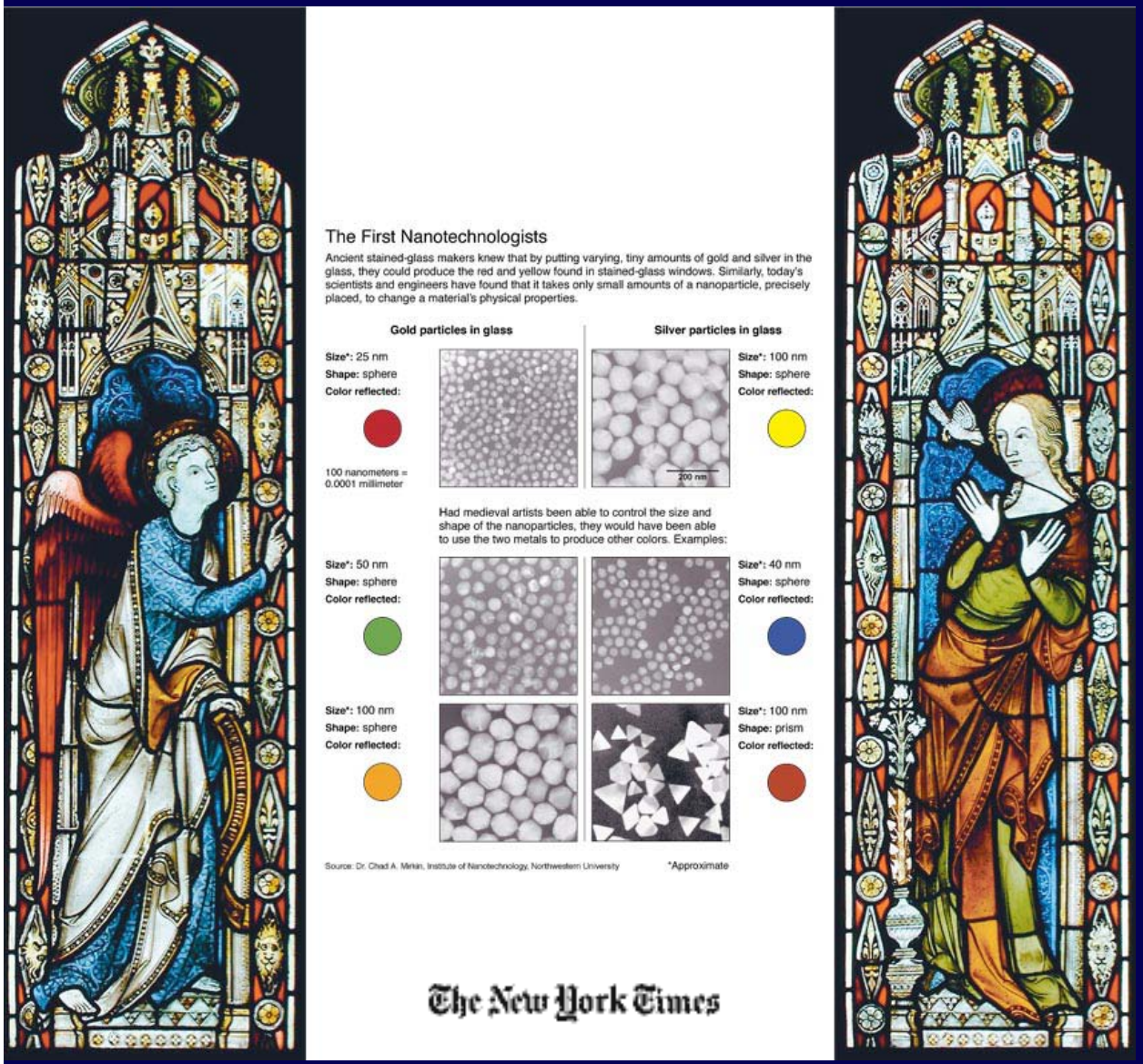
Physicist and Nobel Laureate ***Richard Feynman*** *gave a talk at the annual meeting of the American Physical Society, called "There's Plenty of Room at the Bottom"*



Richard Smalley, Robert Curl Jr. and Harold Kroto won the 1996 Nobel prize in chemistry for the discovery of C_{60}

President Bill Clinton unveiled the National Nanotechnology Initiative (NNI) at Caltech on January 21, 2000, 2001 budget doubled investment in nano-science and technology

...nano goes way back



The First Nanotechnologists

Ancient stained-glass makers knew that by putting varying, tiny amounts of gold and silver in the glass, they could produce the red and yellow found in stained-glass windows. Similarly, today's scientists and engineers have found that it takes only small amounts of a nanoparticle, precisely placed, to change a material's physical properties.

Gold particles in glass

Size*: 25 nm
Shape: sphere
Color reflected:

100 nanometers = 0.0001 millimeter

Silver particles in glass

Size*: 100 nm
Shape: sphere
Color reflected:

200 nm

Had medieval artists been able to control the size and shape of the nanoparticles, they would have been able to use the two metals to produce other colors. Examples:

Size*: 50 nm
Shape: sphere
Color reflected:

Size*: 40 nm
Shape: sphere
Color reflected:

Size*: 100 nm
Shape: sphere
Color reflected:

Size*: 100 nm
Shape: prism
Color reflected:

Source: Dr. Chad A. Mirkin, Institute of Nanotechnology, Northwestern University

*Approximate

The New York Times

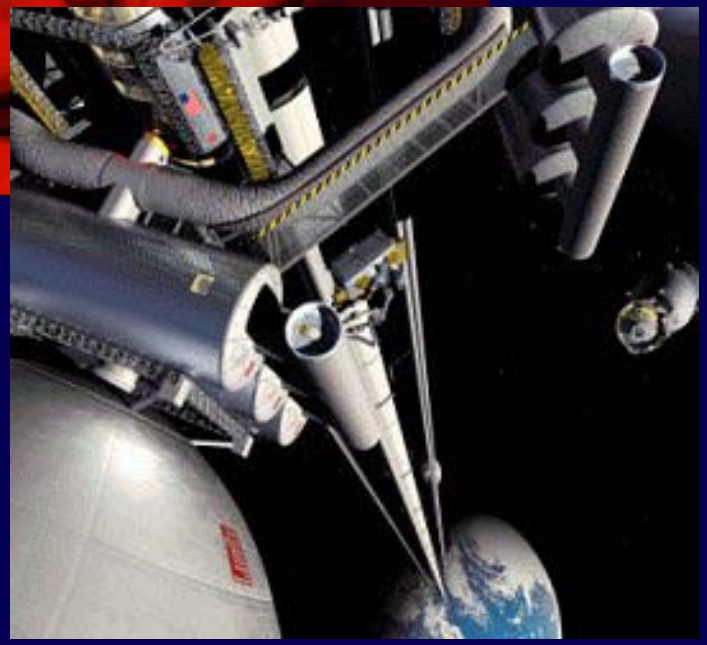
Medieval artisans unknowingly became nanotechnologists when they made red stained glass by **mixing gold chloride into molten glass**, creating tiny gold spheres, which absorbed and reflected sunlight in a way that produces a rich ruby color.

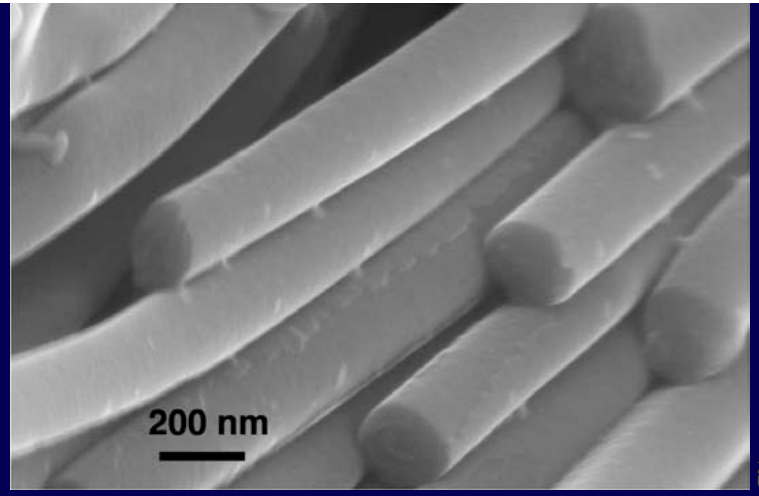
NYT, February 21, 2005

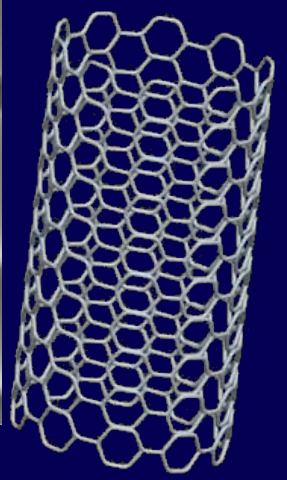
…some thoughts on nano-issues

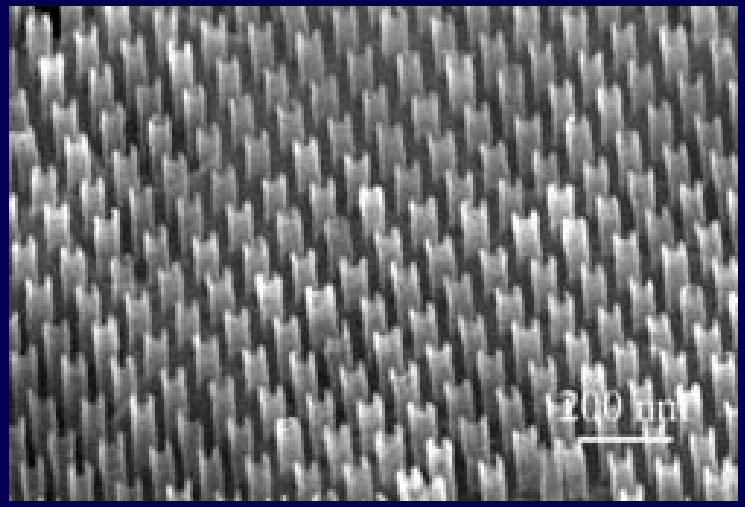
- Researcher/worker safety (precautionary);
- Environmental and health effects;
- Big investment, high stakes, public perception;
- Grey goo (nanotech taking over the world);
- The “Nano-Divide”
- Worry – military applications;
- Privacy issues
- Education Implications

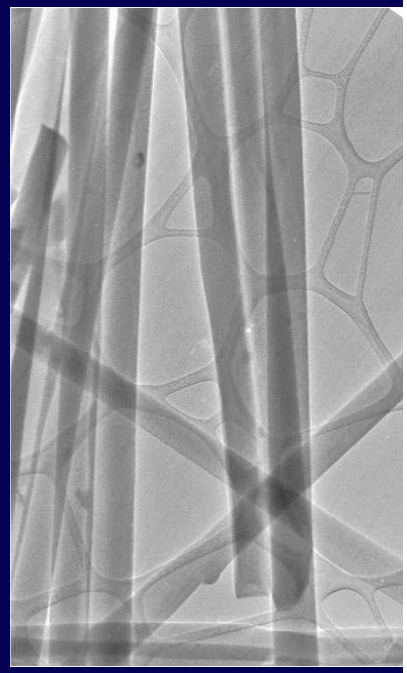
…investment to date











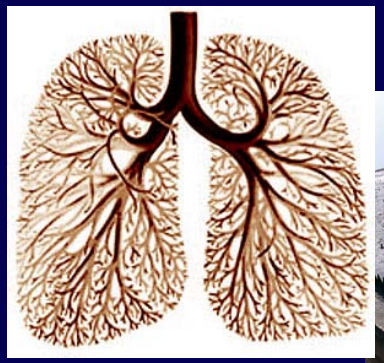
- *2007 Federal Research Dollars **$1.2 B***
- *2007 **$50 B** in manufactured Goods*
- *2011 **$15 B** in nano-enabled drugs ($3 B in 2006)*
- *Predicted Market 2014 **$2.6 Trillion***

Rapid commercialization – any nano-specific regulations?

Woodrow Wilson International Center for Scholars

…technology and society (safe)

Radioactive Materials

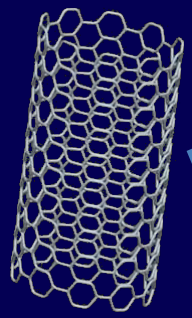


Asbestos Materials

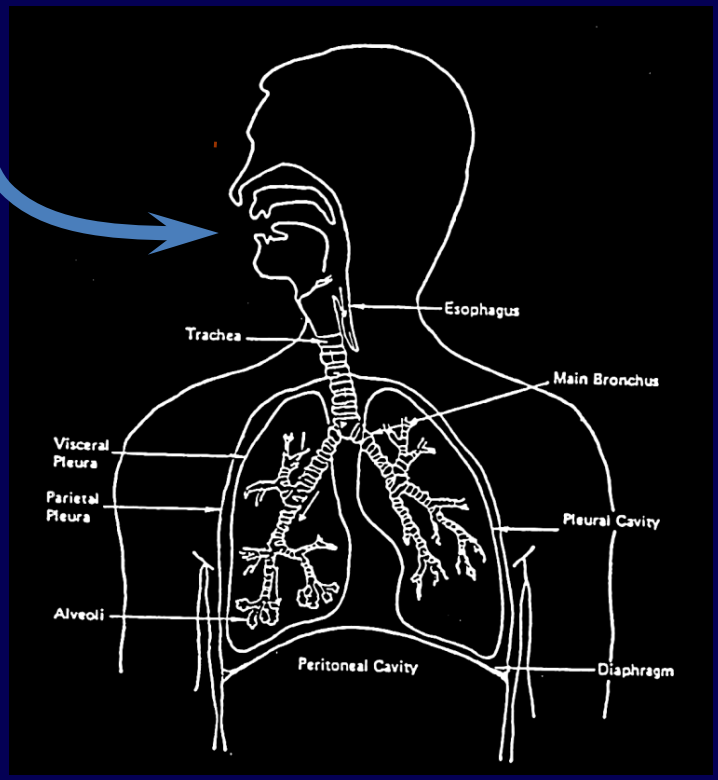
Mercury Materials

…why would they not be safe?

Toxicity Concerns ?



Nano-toxicology



Small Size

Small aerodynamic diameter

→ Deep lung penetration

High permeability in biological membranes

→ Enhanced cellular uptake
(e.g. enocytosis, phagocytosis)

High Surface Area

High Surface Activity

→ Facilitated Transport (Trojan Horse)

→ Transition metals no surface

Fibrous Morphology (Aspect Ratio)

Entanglement & airway blockage Difficulty with macrophase clearance

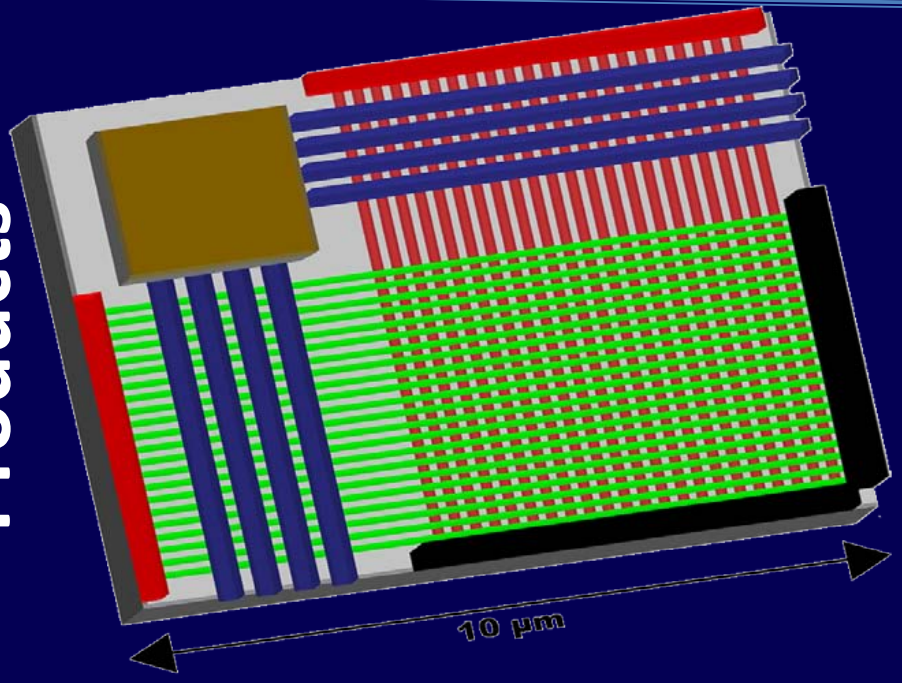
...exposure

Research

Environment

Manufacturing

Products



…nothing -- OSHA, NIOSH, FDA, or EPA

Occupational Safety & Health Administration
National Institute for Occupational Safety and Health (CDC)
Food and Drug Administration
Environmental Protection Agency

- Food Drug & Cosmetic Act [FDA] - only regulates claims made by manufacturer, no pre-manufacture review of cosmetics, no lifecycle review;
- Toxic Substances Control Act (TSCA) [EPA]- new chemical pre-manufacture notification. Some nano-materails new in size, not composition;
- OSHA- covers issues in work place, but hard to detect nano-materials;
- Woodrow Wilson Center Conference 2008 (PEW)
- Part of Stimulus Package, mandates nano-safety measures (http://www.nanotechproject.org/news/archive/7063/)

…pre-cautionary principle

Wingspread Statement

"When an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically." (Racine, WI, January 20, 1998)

- Response to uncertainty (to health/environment);
- Acting to avoid serious/irreversible potential harm, despite lack of scientific certainty as to the likelihood, magnitude, or causation of that harm.

→ Precautionary principle unknown a decade ago (US Phenomenon)
→ 2001 NYT "most influential ideas of the year"
→ June 2003, San Francisco first gov't body to make principle basis for all environmental policy
→ Integrated into many international conventions

Science and Environmental Health Network -- http://www.sehn.org/precaution.htm

…pre-cautionary principle applied to nano

- Preventative action in face of uncertainty
- Burden of protection to those responsible (e.g. manufacturers)
- Consider all alternatives to new activities and processes
- Prohibiting marketing/sale of untested and unsafe materials
- Adequate lifecycle assessment before commercialization
- Discern and use safest possible feedstock/processes

Some studies suggest some nano-materials may be harmful – many useful products, but aspect, reactivity and mobility a concern

Toxicity reliability data (?) and toxicity data in bulk (non-nano) form NOT a reliable predictor

Apply pre-cautionary principle

…what if? (this is totally fiction)

Study makes false conclusions—
(poor characterization)

→ Damage industry
→Damage investment
→ A lot of time to repair damage
→Claims, legal/health

Study turns out accurate —

→ How did we let commercialization happen?
→ Claims, legal/health

…magic nano

March 2006 – "Magic Nano" bathroom sealant released to stores in Germany

Health problems reported by 97 consumers ranging from breathing trouble to hospitalization from pulmonary edema

March 28th 2006 – product recalled by German Federal Government

Small Times, April 14th, 2006

Company scientist claims the product contains no nanoparticles!

Is existing product whose *formulation* switched from pump to spray can

Fine droplets (< 10 micrometers) form thin silica film (100 nm) that seals cracks

...toxicity and the future

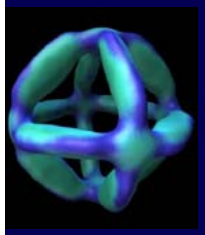
Recommended Minimum Physical and Chemical Parameters for Characterizing Nano-materials on Toxicology Studies (http://characterizationmatters.org/parameters/)
Note: This is a recommended *minimum* set of parameters,

What does the material look like? (size, shape, distribution)
What is the material made of? (composition, crystal, surface, purity levels)
What factors affect how a material interacts with its surroundings?
(surface area, reactivity, hydrophobicity, surface charge)

Characterizing engineered nano-materials in toxicity studies:
Stability—*how do material properties change with time (dynamic stability), storage, handling, preparation, delivery etc? Include solubility, and the rate of material release through dissolution.*
Context/Media—*how do material properties change in different media; i.e. from the bulk material to dispersions to material in various biological matrices? ("as administered" characterization is considered to be particularly important)*
Where possible, materials should be characterized sufficiently to interpret the response to the amount of material against a range of potentially relevant dose metrics, including mass, surface-area and number concentration.

(Woodrow Wilson International Center for Scholars, Washington DC, October 28/29, 2008)

…the "nano-divide"



Investment (research)

Knowledge

Sophisticated

Complexity

Simple

Health Care
(Global Health)

Water

Advanced Health Care
(genetics, cancer, etc.)

Military/Security

Appliances
Electronics

Toys, Gaming

Poor

Wealthy

Divide

…basic human rights

Basic Human Rights – food, water, shelter, clothing, sanitation, basic healthcare

Clean Drinking Water
Basic Need
Nano-Filtration
Should Provide

New Sunscreen
Not a Basic Need
Nano-Filtration
Cannot afford?

…problems for developing countries

Expensive Research – need to go after high-end products(?)

Potential Problems

Patents → Innovation

Excessive Patenting basic patents on nanoparticles & processes,
Products Expensive heavily propertized, difficult to create simple technology solutions (clean water) without complex legal issues

Possible Solutions - analogous to open source software, free for organizations/countries with basic needs.
Universities need to play a role here….

…military applications

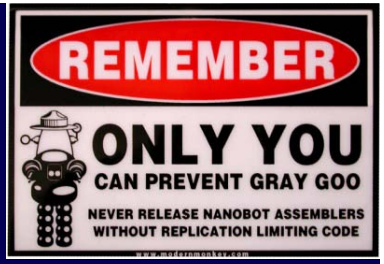
Massachusetts Institute of Technology
http://web.mit.edu/isn/

- New arms race (new competitors);
- Older war systems vulnerable;
- Evolving, untested, secret arsenals undermine confidence to retaliate/resist;
- Warning and decision times decrease;
- Covert infiltration (spying versus war);
- Actual or perceived power imbalances;
- Large scale rearmament again (before technology plateau);
- War less costly, more small wars, more police actions;
- Nano-medicine, war survival rate increases;
- Infrastructure/environmental decimation;
- Potential revolutionary NOT evolutionary developments.

Science is powerful in warfare

Incremental/transformative offensive/defensive person/group/country

…grey goo – nano-bots



Fear of runaway nanobots, or “grey goo”, is more of a public issue than a scientific problem.

Artificial replicators capable of replication in natural uncontrolled environment (?)

End products cannot/should not replicate Themselves

Bioengineered pathogens (more immediate)

http://tejiendoelmundo.files.wordpress.com/2009/01/nanobots.jpg

Computer Pathogens → Immune System Effective

Grey Goo (bad nano-bots) → Blue Goo (nano-cops)

…security implications

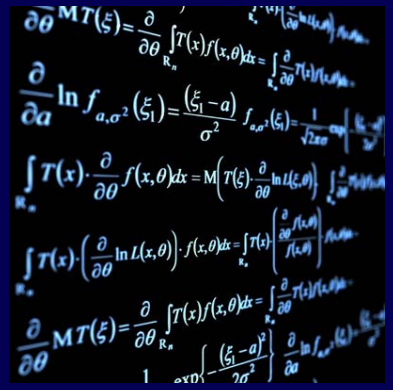
RFID – Pets, kids, products, cars (informed consent)

Shrinking electronics (nano);

“Invisible Tags” We might not know that we were sprinkled with nano-tags and are being tracked and monitored.

...interdisciplinary --- many fields converge

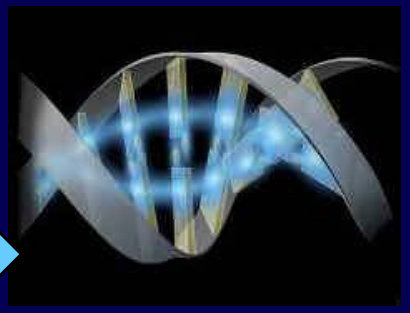
Math



Chemistry

Source:
http://home.neb.rr.com/btantra/myOwnSite/Images/Copy%20of%20chemistry.jpg

Biology



Source:
http://www.mollybish.org/dna_2.jpg

All sorts of scientists are working in these fields

Physics

Source: http://snl.mit.edu/gallery.html

Engineering

http://www.trendwaves.com/images/nano.jpg

Humanities
Social Science

…changing the way we educate

society | health | environment | globalization | energy | culture | ethics

business | humanities | law | social science | arts | architecture | languages

chemistry | physics | biology | mathematics | engineering | medicine

Adaptive Scientists (Innovators)

deep domain knowledge in core discipline

a across disciplines
across industries
across functions
across cultures
“Equals”
more experienced
more adaptive
more collaborative
more creative
solutions to big problems

…bring ethics into science (education)

- **General research ethics** (e.g. academic integrity, publication ethics, conflict of interest, conflict of commitment, legal, animal safety)
- **Bioethics for life sciences / medical researchers**
- **Need broader considerations of ethical implications in science** (e.g. nano-divide, privacy, environmental exposure)

Research at Brown – Evaluating our course:

EN092 S27 "Small Wonders: The Science, Technology and Human Health Impacts of Nanomaterials"

Professors Robert Hurt and Aggie Kane (Brown University)

Survey, Professor Phil Brown (Brown University)

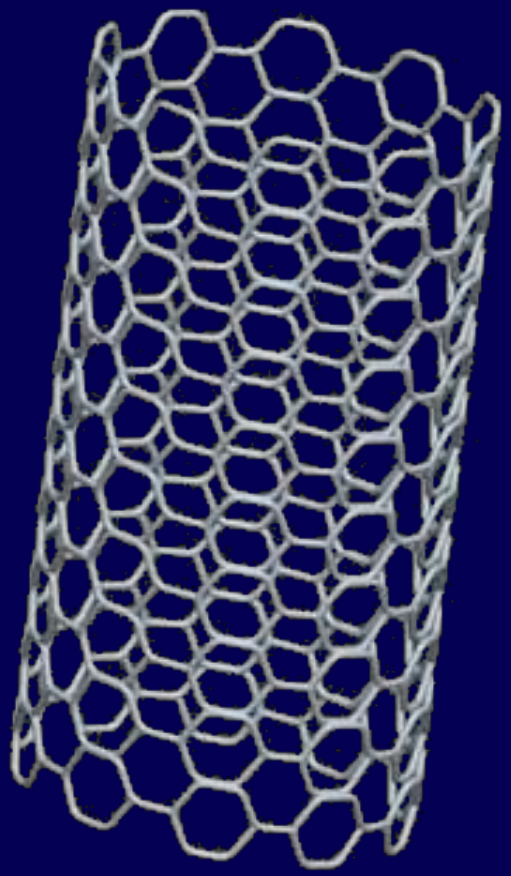
Ms. Elizabeth Hoover, Research Assistant (Brown University)

- *27 of 32 students responded to two rounds of surveys*
- 9 felt that there were greater ethical implications of nanotechnology research upon completing the course
- 6 felt risks were unaddressed prior to the course, 11 thought risks were addressed inadequately after
- 7 students felt there should be ethics training for NT researchers before course and 19 felt so after course

Survey Research at Brown:
Faculty, Postdocs, and Research Assistants

Professor Phil Brown (Brown University)

Ms. Elizabeth Hoover, Research Assistant



- *17 faculty, 22 postdoc & grad students*
- Most, especially students, have not considered ethical implications
- Most unfamiliar with Precautionary Principle, nano-divide, regulatory concerns
- Most think public is unaware of extent of NT work, and that public uniformed on risks and benefits

...summary

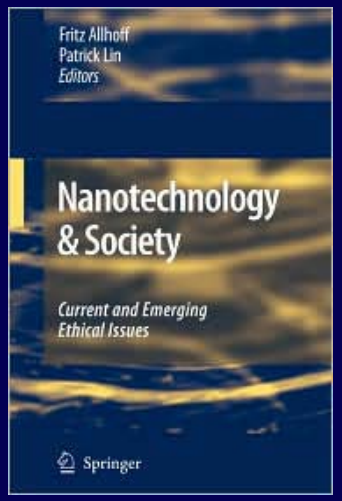
- Thank colleagues at Brown Univ (Profs. Hurt, Kane, Morgan, Brown);
- We started from pre-cautionary principle (integrate EHS);
- Problems with nano-ethics, addresses technologies not realized;
- Better to address now, even if premature, before panic;
- Novelty, continuity and risk– differentiate between different particles (some more/less dangerous than macro size), make clear to the public
- Precautionary principle needs more discussion;
- Developing technologies with public input and trust;
- Acknowledge unknowns and uncertainty;
- Toxicologists possess unique knowledge of health effects– their participation should be ensured on all levels and more nano funding should go to them;
- Interdisciplinary Education – Science & Ethics
- More and more comprehensive health studies (end-to-end):

→Two big NSF Centers (UC and Duke) Environmental Implications NT

→ **Genome**-cells-**development**-animals-environment

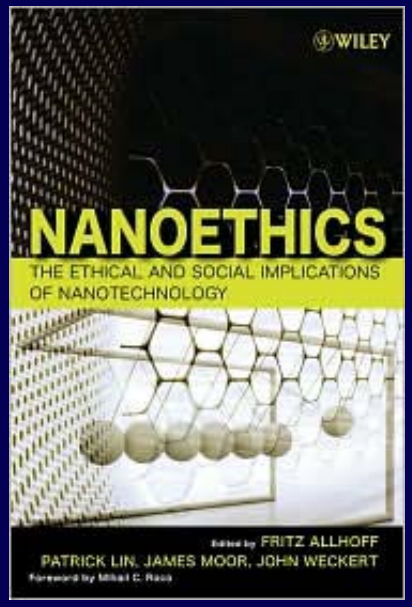
...resources

Brown University
http://www.brown.edu/Departments/IMNI/
Nanotechnology Now
www.nanotech-now.com
Center for Responsible Nanotechnology
http://www.crnano.org/
Woodrow Wilson Center, Foresight and Governance Project
http://www.wilsoncenter.org/index.cfm?fuseaction=topics.home&topic_id=1414



Collection of articles on "Ethics Web"
http://www.ethicsweb.ca/nanotechnology/

"Mind the Gap"
http://www.utoronto.ca/jcb/home/documents/nanotechnology.pdf
National Nanotechnology Initiative
http://www.nano.gov
Science and Environmental Health Network
http://www.sehn.org/precaution.htm
Massachusetts Institute of Technology
http://web.mit.edu/isn/



Nanoethics (2007, editors Allhoff, Lin, Moor, & Wechert)
The Yearbook of Nanotechnology in Society (2008, editors, Fisher, Selim, and Wetmore)

Introduction to Clinical Trials

Rudolph M. Navari, M.D., Ph.D.
Professor of Medicine and Director
Indiana University School of Medicine South Bend
Adjunct Professor of Biochemistry
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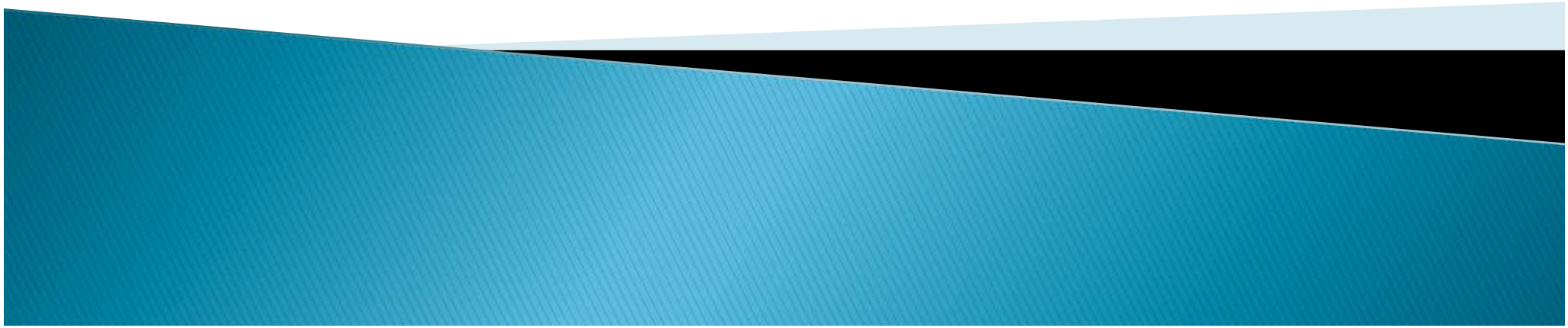
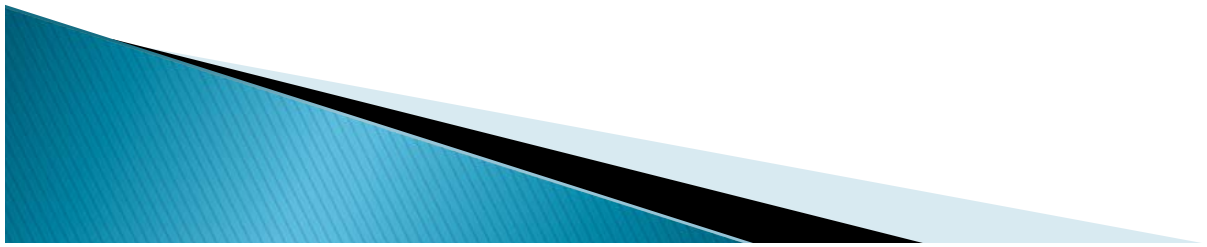


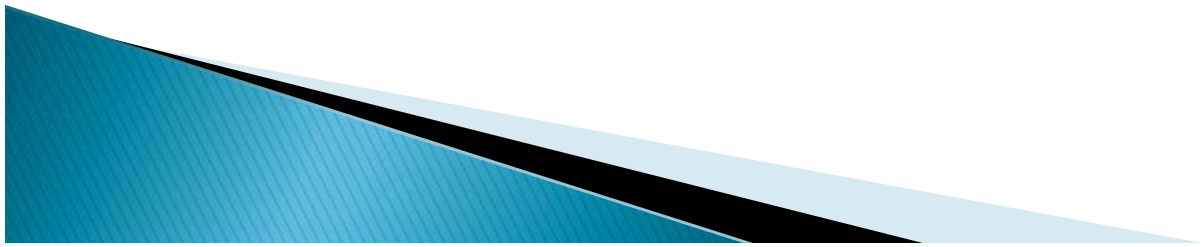
Drug Development Process

- New drug
  - 10 years in development
  - $1.5 billion; one of 10,000 candidates
- Techniques
  - Combinatorial chemistry
  - Genomics: targeted therapy
  - Biotechnology
  - High throughput screening



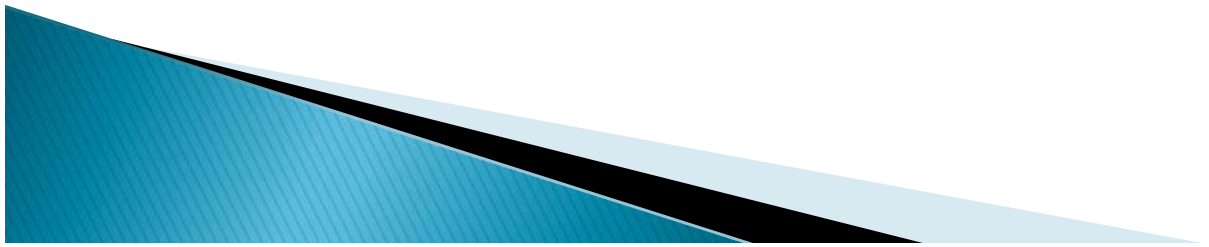
Preclinical Drug Development

- Pharmacologic evaluation
  - Activity, Potency, Target selectivity
- Biopharmaceutical evaluation
  - Bioavailability, Metabolism, Stability
- Animal testing
  - Safety, Toxicity



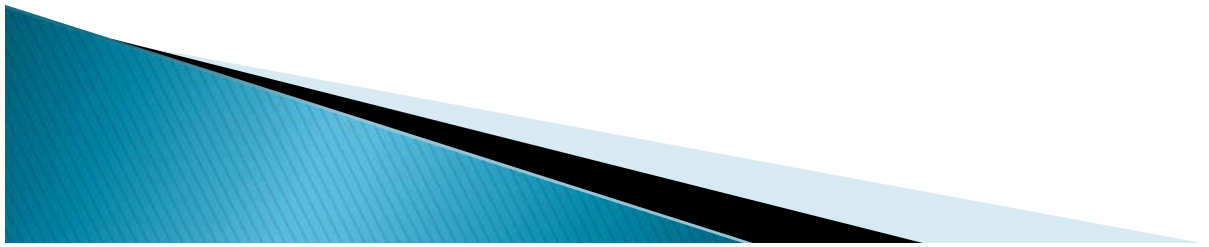
Drug Candidate

- FDA review
  - Pharmacology, Safety, Toxicity
- Clinical Trial proposal
- Institutional Review Board
  - Academic Medical Center
  - Community Hospital
  - National Clinical Trials Group
  - Independent



Institutional Review Board (IRB)

- Composition: scientist, non-scientist, laymen, religious professional, minority groups
- Review of drug protocol
- Evaluate risk to patient population
- Evaluate patient population (prisoners, children, students, minorities, poor)
- Evaluate patient incentives
- Evaluate informed consent

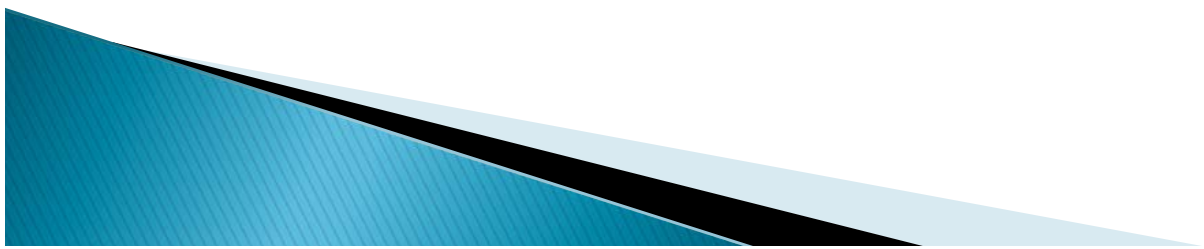


Clinical Trials – Phase I

- First introduction of drug / device into humans; Safety Data (toxicity, pharmacokinetics, maximum tolerated dose)
- Average one-year duration
- Single clinical site
- Patient volunteers; small number (20 -80)

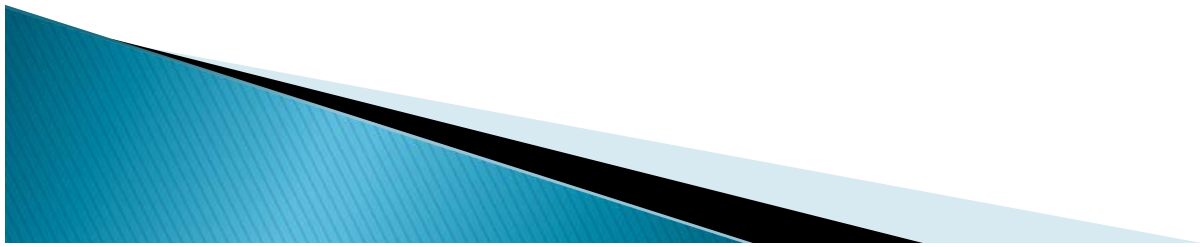
Clinical Trials – Phase II

- Evaluation of dose established in Phase I trial
- Efficacy and Toxicity evaluations
- Average 2-year duration
- Limited number of clinical sites
- Relatively small number of patients (200)
- Patients selected based on drug indication(s)
- FDA designed trial



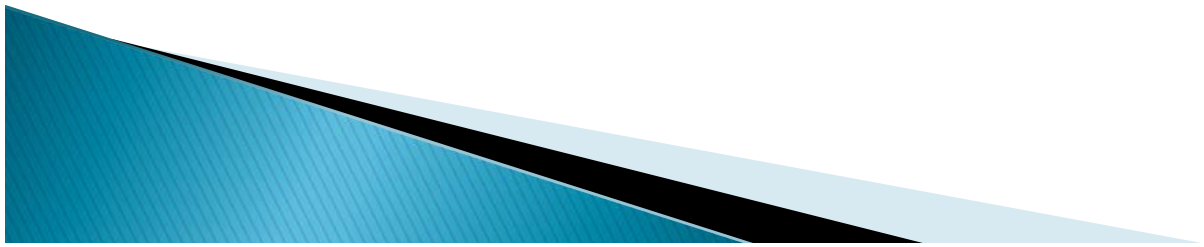
Clinical Trials – Phase III

- Comparison with standard therapy
- Efficacy and Toxicity evaluations
- Several year process
- Multiple clinical sites
- "Large" number of patients (200 – 1000)
- Patients selected based on drug indication(s)
- FDA designed trial



Clinical Trials – Phase IV

- Post-marketing study
- Monitoring of long-term issues
  - adverse events
  - risk:benefit ratio
  - dose modifications



Clinical Trial of Rezulin

- Rezulin
  - new drug
  - decreases insulin resistance
  - May permit patients with insulin dependent diabetes mellitus to reduce or eliminate insulin dose

Clinical Trial of Rezulin

- Proposed clinical trial
  - Double-blind, randomized, placebo-controlled clinical trial
  - Patients with insulin dependent diabetes
  - Patients randomized to placebo or Rezulin
  - Monitor glucose levels and insulin use

Clinical Trial of Rezulin

As an IRB member:

- Is informed consent required ?
- Is the use of a placebo ethical ?
- Is the use of a placebo harmful ?
- What other information would be useful?
- Is the trial phase I, II, III, or IV?

Rezulin

- FDA approves Rezulin for use
- At two years, liver toxicity is noted
- Liver transplants necessary in rare patients
- Drug removed from market
- IRB, FDA, Clinical Investigators,
  Pharmaceutical Co. at fault ???

Vioxx

- Second generation anti-inflammatory
- $3 Billion in annual sales for 5 yrs
- Phase IV studies suggested significant cardiac toxicity
- Drug removed from market by Merck; value of stock reduced by 35%
- What did Merck know and when did they know it? Class action lawsuits !!!


Dr. Mark Suckhow
Biological Sciences
Animal Studies, Ethics & IACUC

Introduction to Animal Studies

Ethics and the IACUC

Dr. Mark Suckhow
Biological Sciences
Director, Freimann Animal Care Facility

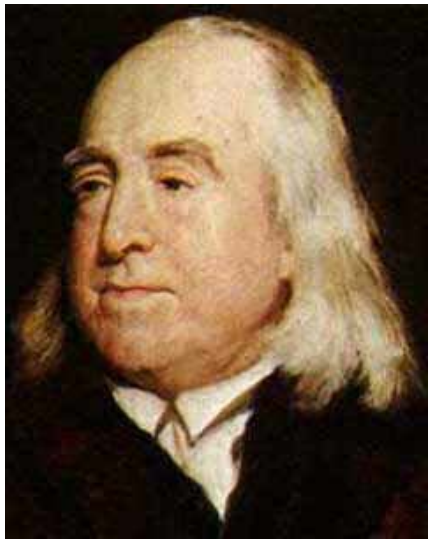
René Descartes

Animals are just
machines and thus
incapable of thinking

Philosopher & Mathematician
(1596-1650)

Jeremy Bentham

"But a full-grown horse or dog is beyond comparison a more rational, as well as a more conversable animal, than an infant of a day, or a week, or even a month, old. But suppose the case were otherwise, what would it avail? The question is not, can they reason? Nor, can they talk, but can they suffer?"



Founder of Modern Utilitarianism
1748-1832

Utilitarianism: If the good outcome exceeds the cost, then an act is acceptable

The Importance of Animals in Biomedical Research

Most of our children have not even heard of, much less know anything about, many of the diseases our ancestors experienced first-hand. Why? They have either been eradicated or can be controlled due to findings from research using animals.

Benefits of Animal Research

- Penicillin
  - Mice
- Blood Transfusions
  - Dogs
- Tuberculosis Medicine
  - Guinea pigs
- Meningitis Vaccine
  - Mice
- Kidney Transplants
  - Dogs and Pigs
- Breast Cancer Treatments
  - Mice, Rats and Dogs
- Asthma Inhalers
  - Guinea Pigs and Rabbits
- Polio Vaccine
  - Mice
- Insulin for Diabetics
  - Dogs
- Deep Brain Stimulation for Parkinson's Disease
  - Monkeys

Benefits Continued…

- Vaccine for Smallpox
- Vaccine for Anthrax
- Rabies Vaccine
- Typhoid Vaccine
- Cholera Vaccine
- Treatment for Beriberi
- Treatment for Rickets
- Corneal Transplants
- Local Anaesthetics
- Discovery of Vitamin C
- Canine Distemper Vaccine
- Coronary Bypass Operation
- German Measles Vaccine
- MMR Vaccine
- Antidepressants and Antipsychotic
- CT Scanning for Improved Diagnosis
- Chemotherapy for Leukaemia
- Medicines to Treat Ulcers
- Inhaled Asthma Medication
- Combined Therapy for HIV infection
- Medicines for Type 2 Diabetes
- Cervical Caner Antibodies
- Bird Flu Vaccine
- Malaria Vaccine
- Modern Anaesthetics
- Tetanus Vaccine
- Diphtheria Vaccine
- Anticoagulants
- Streptomycin
- Kidney Dialysis
- Whooping cough Vaccine
- Heart Lung Machine
- Hip replacements
- Cardiac Pacemakers
- High Blood Pressure Medicines
- Replacements of Heart Valves
- Chlorpromazine Psychiatric Medicine
- MRI Scanning for improved Diagnosis
- Prenatal Corticosteroids for Premature Babies
- Treatment for River Blindness
- Life Support for premature Babies
- Medicines to control Transplant Rejection
- Hepatitis B Vaccine
- Leprosy Treatment
- Oral and Inhaled Insulin for Type 1 Diabetes
- Angiogenesis Inhibitors for Cancer and Blindness
- Gene Therapy for Muscular Dystrophy
- Alzheimer’s Vaccine

US Yearly Benefits of Animal Research

- 450,000 Prescriptions for anabolic (growth) hormones[1]
- 520,000 Heart bypass operations[2]
- 1,500,000 Prescribed for Erythropoietin (for Anaemia)[3]
- 34,000,000 Anticoagulants dispensed[4]
- 95,000,000 Prescriptions for asthma[5]
- 150,000,000 Prescriptions for antibiotics[6]

1. Source: IMS Health, IMS National Prescription Audit TM, 2/2008
2. Source: IMS Health, ClinicalPlus
3. Source: IMS Health, IMS National Sales Perspectives TM, 2/2008
4. Source: IMS Health, IMS National Prescription Audit TM, 2/2008
5. Source: IMS Health, IMS National Prescription Audit TM, 2/2008
6. US Center for Disease Control and Prevention

Animal Research: Basic Reasons

- Similarities between species
- Typically precedes studies in humans; part of FDA approval process for drugs used in human and veterinary medicine.
- Can be done relatively quickly
- Relative control of genetic and environmental variables

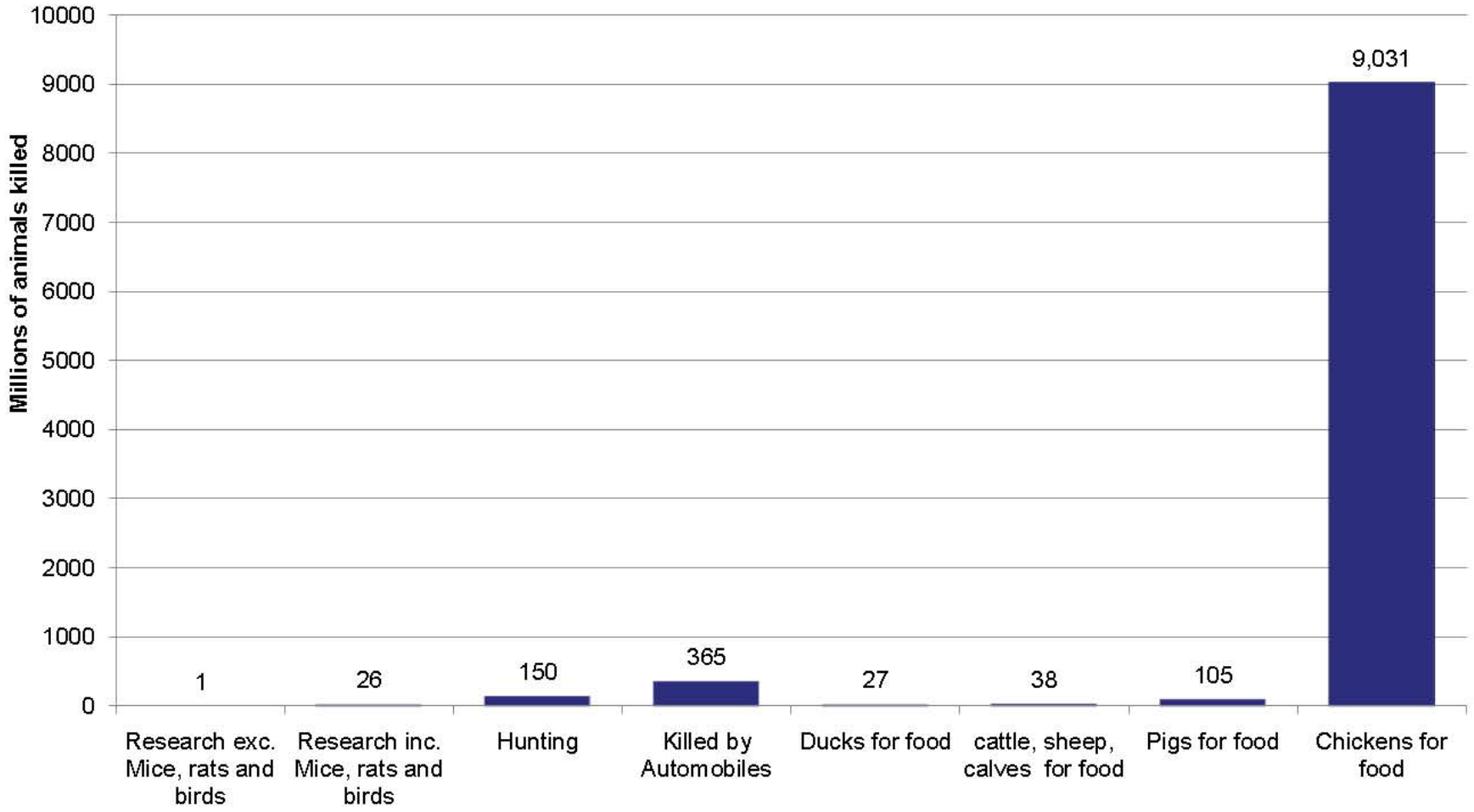
Animals Used in Research

- 97 – 98% are rodents and fish; < 1% are dogs, cats, and non-human primates.

- Most are specifically bred for research; lost or stolen pets are **not** used in research.

- Rigorous oversight to assure proper care and use. Valid scientific results *depend* on good animal care.

Numbers in Perspective



Animal Research is Heavily Regulated

- **United States Department of Agriculture** – Animal Welfare Act (Laboratory Animal Welfare Act of 1966, P.L. 89-544)

- **Public Health Service (NIH)** – PHS Policy on Humane Care and Use of Laboratory Animals; *Guide for the Care and Use of Laboratory Animals*

- **Association for Accreditation and Assessment of Laboratory Animal Care (AAALAC), International -** Voluntary accrediting body.

- **Others –** FDA, EPA, USFWS

IACUC

- Institutional Animal Care and Use Committee; mandated by all regulatory agencies and AAALAC; each institution has its own IACUC.
- Members must include a veterinarian, non-scientist, and a community representative
- Assures compliance with regulations, assures ethical treatment of animals
- **ALL** research and teaching using vertebrates must be approved by the IACUC as a written **protocol.**

IACUC Activities

- Review and approve (or not approve) animal use protocols; decisions cannot be overruled.
- Twice each year, inspect all animal facilities and labs where animals are used
- Twice each year, evaluate programs for animal care and use.

A Basic IACUC Principle: 3 Rs

- Russell and Burch, *Principles of Humane Experimental* Technique, 1959
- **Reduction** in the number of animals used
- **Replacement** of conscious, living animals with insentient material (e.g., computer and mathematical models, cell culture techniques)
- **Refinement** of methods to promote well-being of the animals

The IACUC Assures

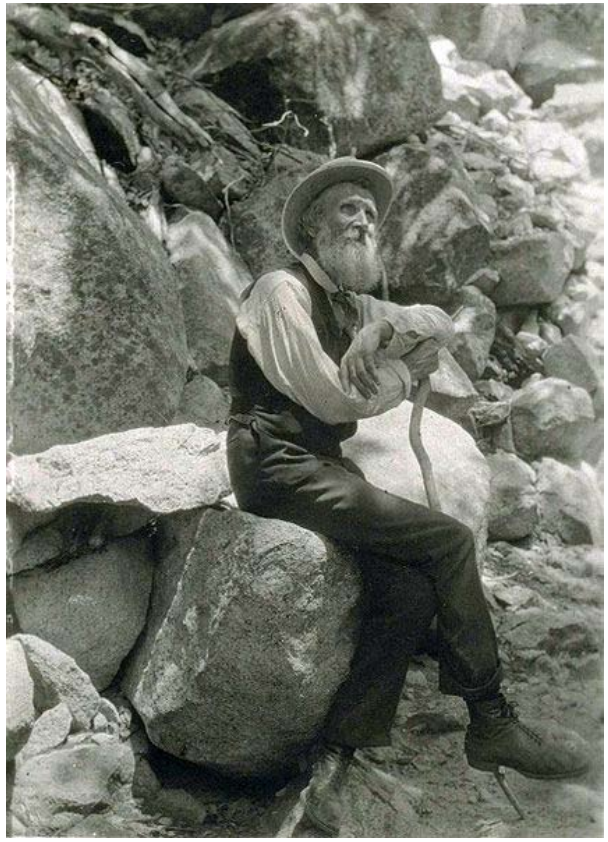
- Animals are used only when justified; minimum number used; alternative replacements have been ruled out.
- If procedures that might potentially cause pain are to be used, adequate pain-relieving medicine is used.
- Personnel working with animals are properly trained.
- Veterinary care is provided
- Animals are housed safely in clean conditions, with fresh food and water.

Questions?


Professors Jessica Hellmann and Jason McLachlan
Department of Biological Sciences
Environmental Ethics

Do Environmental Ethics have to Change in a Changing Environment?

Jessica Hellmann and Jason McLachlan, Department of Biological Sciences



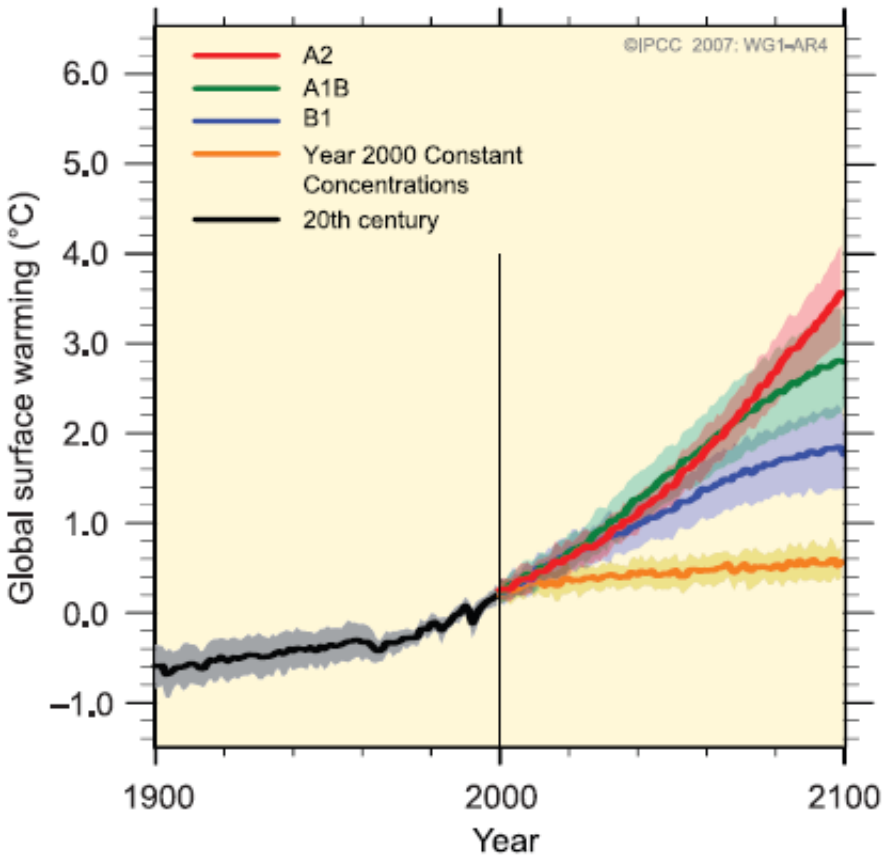
John Muir

Environmental Management options target some historical benchmark

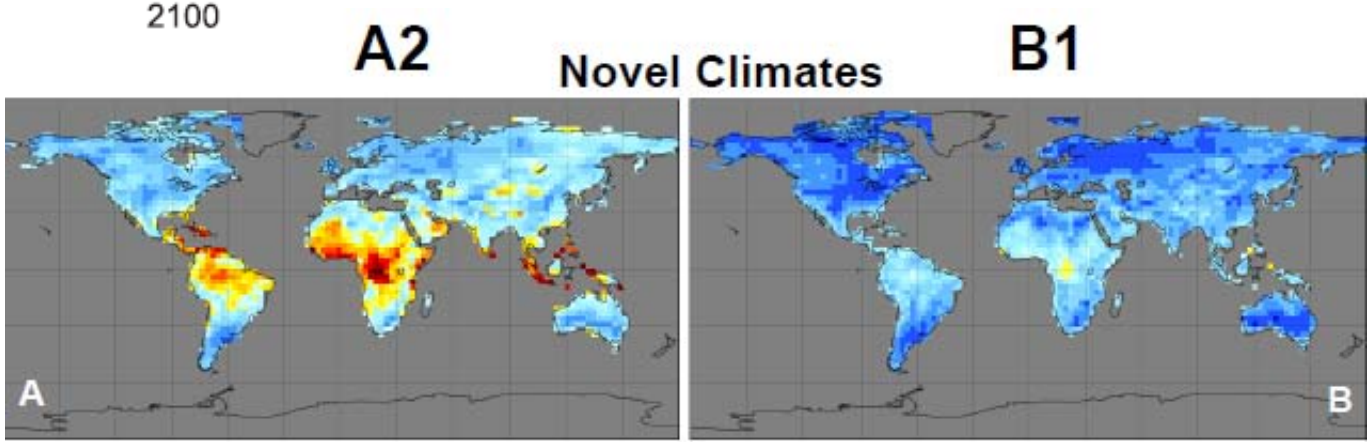
Eradicating non-native plants

Controlled burning

Climate change is shifting historical benchmarks

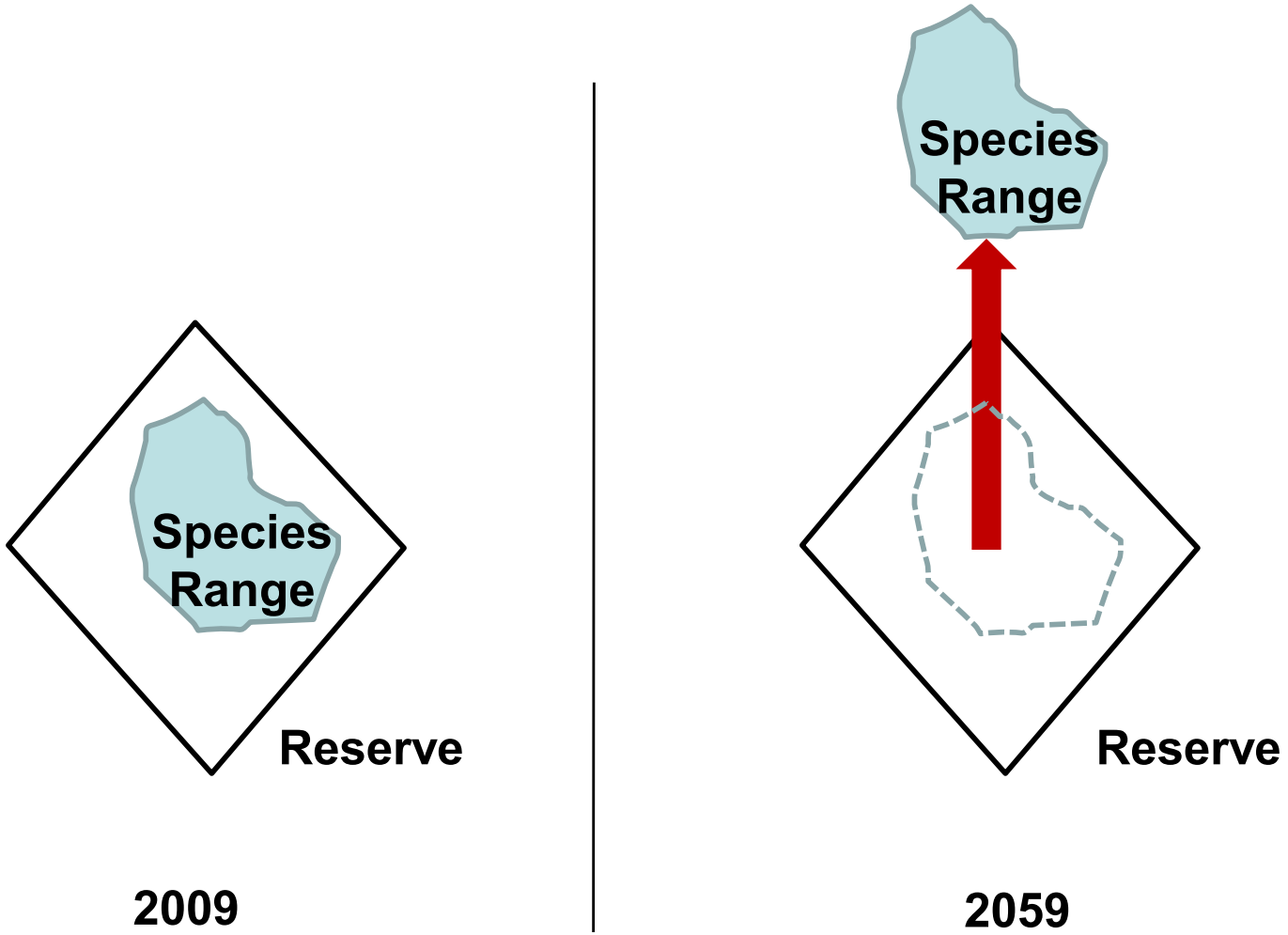


Projected warming under three carbon emissions scenarios: A2, A1B, B1 (IPCC 2007)



Expect climate surprises (Williams et al 2007)

Climate change may leave species behind



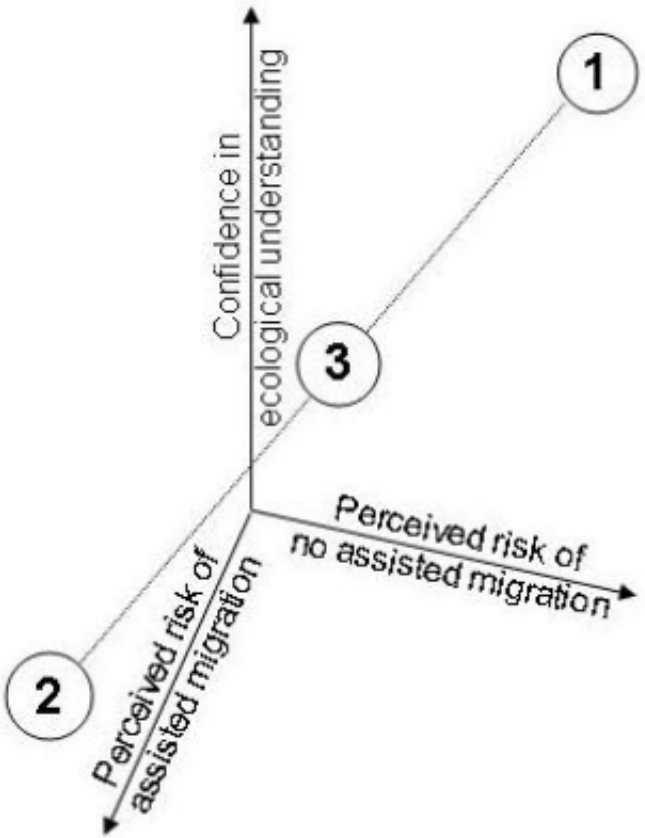
Do we need novel management strategies for novel climates?

"**Managed relocation** is an intervention technique aimed at reducing negative effects of climate change on defined biological units such as populations, species, or ecosystems. It involves the intentional movement of biological units from current areas of occupancy to locations where the probability of future persistence is predicted to be higher. The underlying motivation of MR is to reduce the threat of diminished ecosystem services or extinction from climate change."

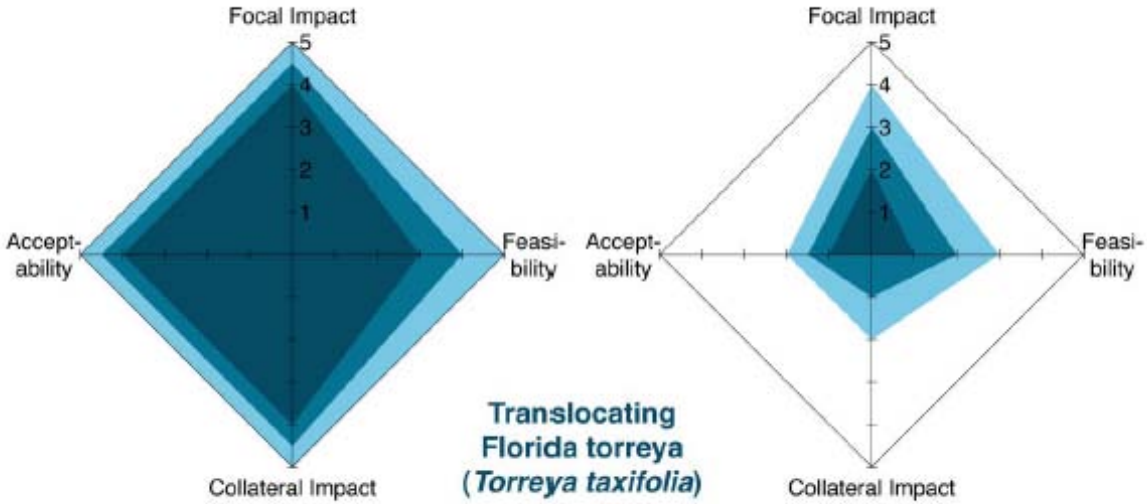
(Richardson et al 2009)

TorreyaGuardians.org

Do novel management strategies require novel ethical frameworks?



2007
McLachlan et al. (*Con. Bio.*)



2009
Richardson et al. (*PNAS*)

Integrative perspectives are needed to confront new ethical challenges

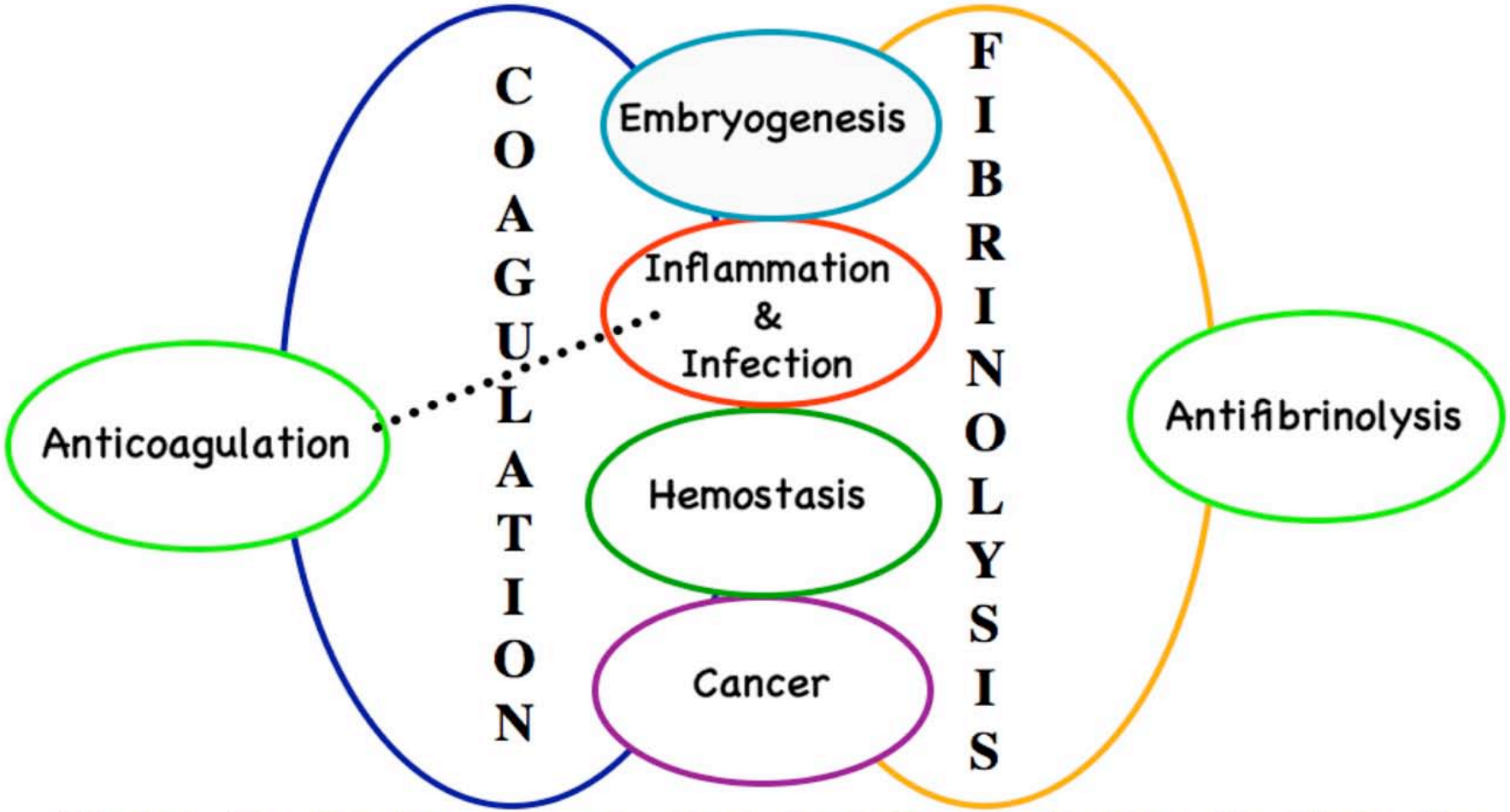
MR working group, Notre Dame Aug 2009

Boston Globe

W.M. Keck Center for Transgene Research

UNIVERSITY OF NOTRE DAME

W.M. KECK CENTER FOR TRANSGENE RESEARCH
University of Notre Dame



Mission: To develop and use gene targeting technology to study the pathophysiological roles of the genes of the blood coagulation, anticoagulation, and clot dissolving pathways in hemostasis, with associated relevance to embryonic development; cancer; and inflammatory diseases.

Transgenesis **is the process of introducing an exogenous gene - called a transgene - into a living organism so that the organism will exhibit a new property and transmit that property to its offspring.**

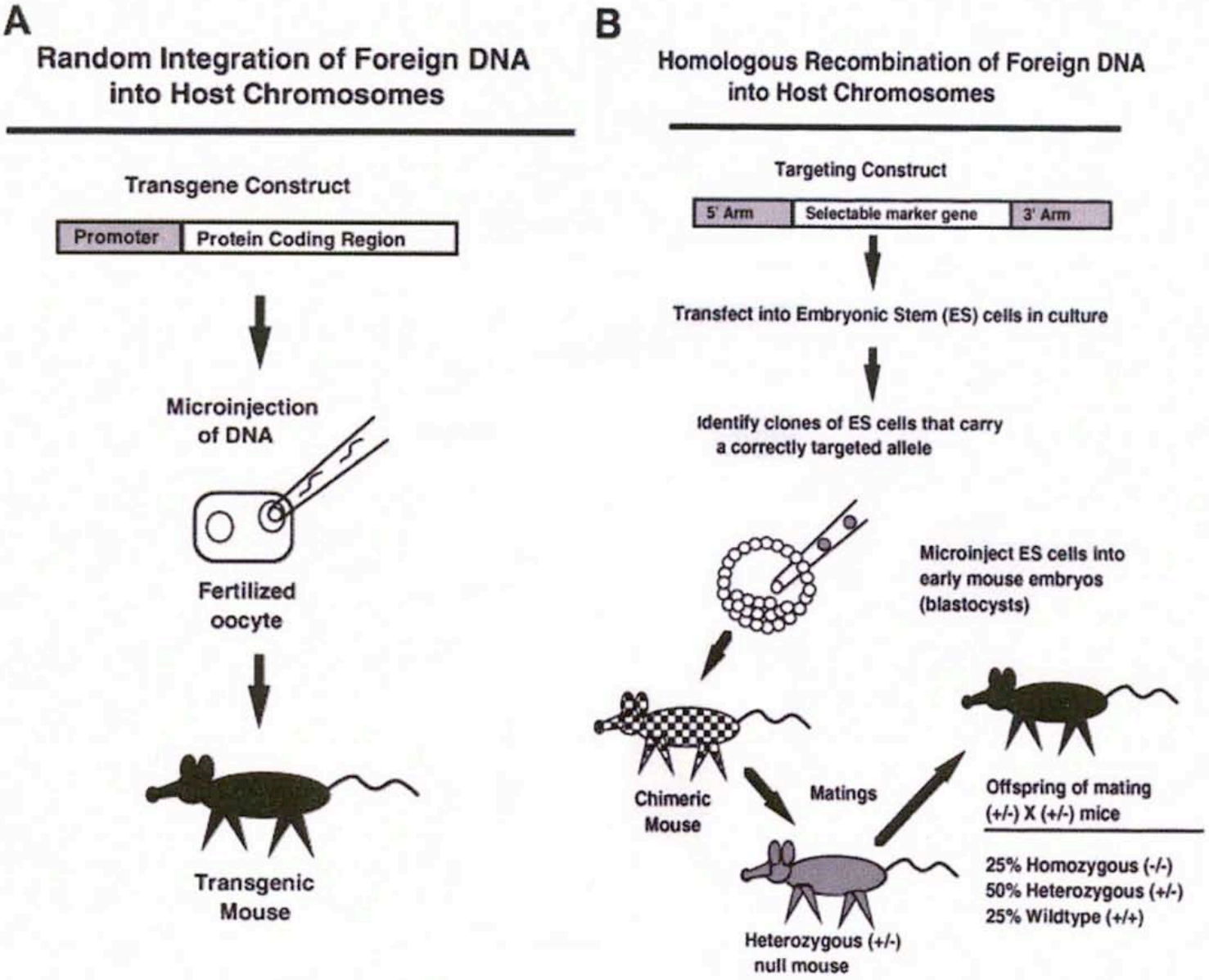
Historical Background

Before molecular genetics, studying the regulation and function of genes of organisms was by observing inherited characteristics or spontaneous mutations.

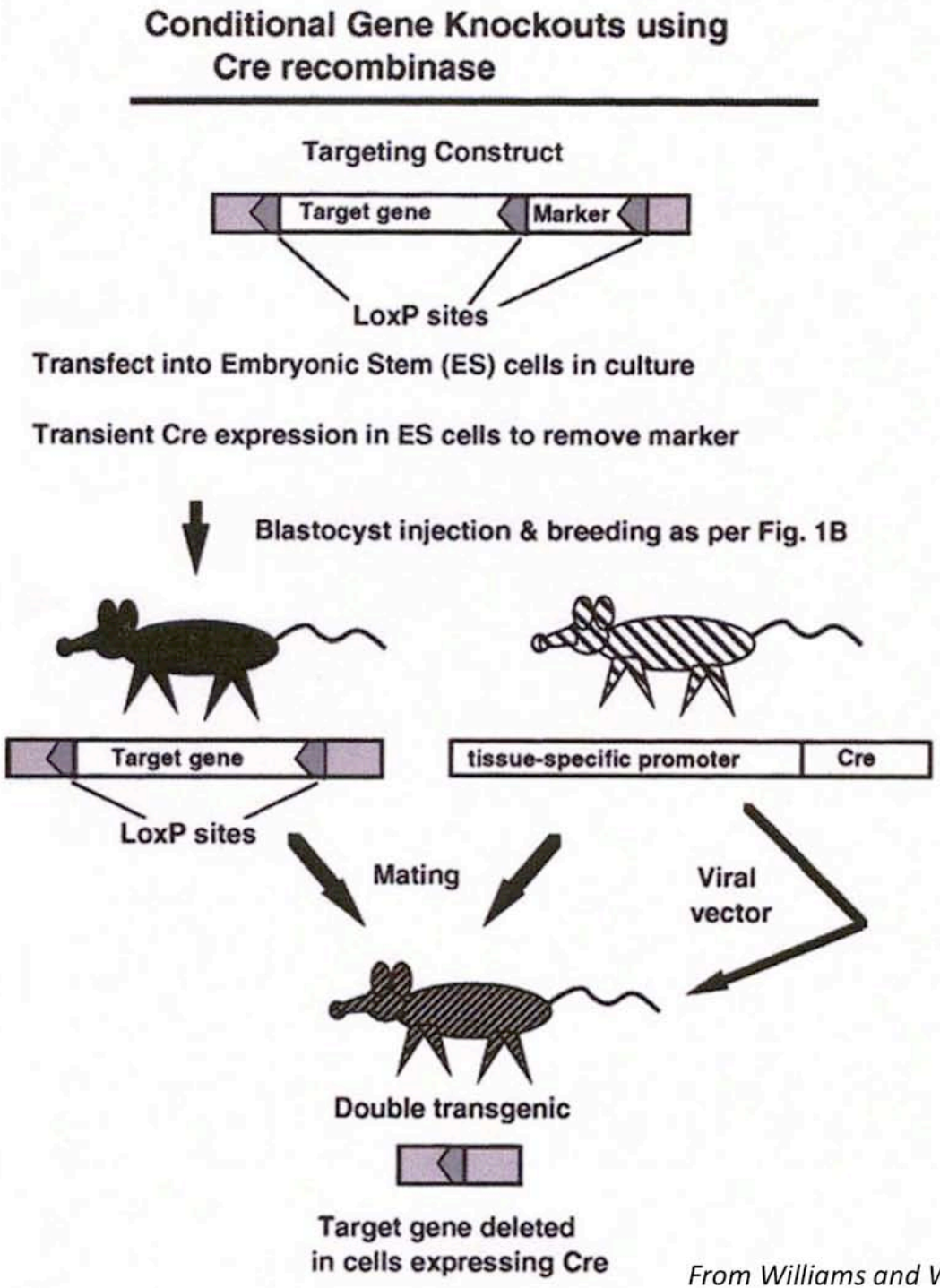
The first chimeric mice were produced in the 1970s. Cells of two different embryos of different strains were combined to form a single embryo that developed into a chimeric adult, exhibiting characteristics of each strain.

Contributions of developmental biology and genetic engineering allowed for the rapid development of techniques for creating transgenic animals.

- Retrovirus-mediated transgenesis (Jaenisch, 1976)
- DNA microinjection (Gordon and Ruddle, 1981)
- Embryonic stem (ES) cell-mediated gene transfer (Gossler et al., 1986)



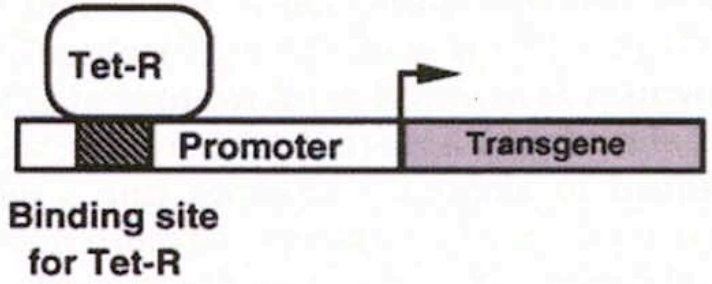
From Williams and Wagner, J. Appl. Physiol., 2000.



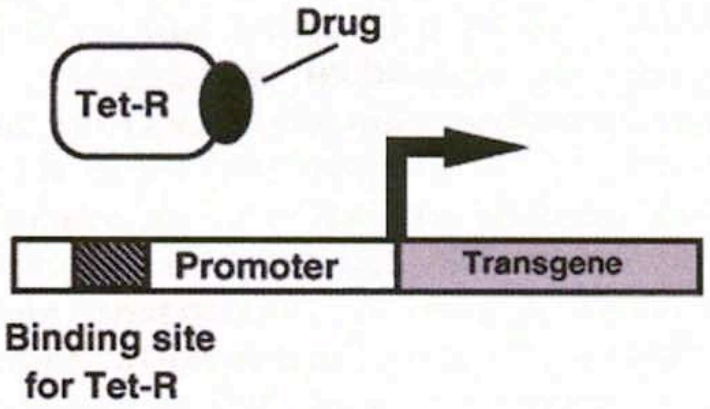
From Williams and Wagner, J. Appl. Physiol., 2000.

Drug-Regulated Expression of Transgenes

Without drug: transgene is repressed



With drug: transgene is activated



From Williams and Wagner, J. Appl. Physiol., 2000.

Early Landmarks in Transgenic Research

1982 – First transgenic animal (mice) produced
1983 – First transgenic plant expressing a gene of another specie produced
1985 – First transgenic farm animals produced (rabbits, pig, sheep)
1986 – First controlled experimental release of genetically engineered organism into the environment
1989 – US patent office announced that it would accept patent applications for genetically engineered plants and animals. First patented transgenic animal produced for pharmaceutical research – DuPont's "Oncomouse"
1995 – Genetically engineered tomato marketed in USA
1997 – Cloning of transgenic sheep in UK (Dolly)

BIOMEDICAL SUPERMODEL?

Marmoset model takes centre stage

Newly created transgenic primate may become an alternative disease model to rhesus macaques.

Japanese researchers this week report the passing of a transgene from a primate to its offspring[1,2] (see pages 515 and 523). The work could establish marmosets as a model research organism to rival the more commonly used rhesus macaque, and usher in a new era of primates as human-disease models.

Erika Sasaki and her colleagues at the Central Institute for Experimental Animals in Kawasaki injected viral vectors with green fluorescent protein (GFP) into 91 marmoset embryos, then transferred the 80 healthy transgenic embryos to surrogate mothers. Five offspring were born — including twins Kei and Kou; keikou means fluorescence in Japanese — all of which expressed the glowing transgene in some features at some point during development. Most exciting, says Sasaki, was the birth in April of a male produced by conventional *in vitro* fertilization using Kou's sperm. Since then, two more glowing second-generation marmosets have been born, although one died after being bitten by his mother.

"This is a great advancement, and it will bring more attention to primate models from people who don't normally think about primates," says Anthony Chan, a geneticist at the Yerkes National Primate Research Center of Emory University in Atlanta, Georgia.

Biomedical reseachers have long wanted primate models that can inherit and express introduced genes, as mice can. In 2001, a group led by Chan and Gerald Schatten, then at the Oregon Regional Primate Research Center in Portland and now at the University of Pittsburgh, Pennsylvania, introduced GFP into a rhesus macaque oocyte[3] and produced the animal named ANDi. In 2008, Chan reported rhesus macaques with the Huntington's disease gene[4].

"Marmosets will be better as models than rodents, but are they good enough?"

But passing transgenes to the next generation — the key to making a useful research model — had never been done. ANDi has not had any luck with natural breeding — "perhaps owing to his short stature and relatively gentle demeanour", says Schatten, who is now working instead on intracytoplasmic sperm injection and cloning techniques.

With Chan's Huntington's monkeys, all but one of the first generation died from an early and extreme manifestation of the disease. Since then, three more have been born; Chan must wait another year or two to breed them.

Sasaki's marmosets could move more quickly into disease modelling. Her first target is Parkinson's disease, but she is considering amyotrophic lateral sclerosis and Huntington's.

CENTRAL INSTITUTE FOR EXPERIMENTAL ANIMALS

Erika Sasaki (centre) with transgenic marmosets Hisui, Banko, Wakaba, Kei and Kou.

Other Japanese researchers are looking to expand on the work through the country's project in brain sciences, a 5-year programme for which 8 universities and institutes get an annual ¥600 million (US$6 million) to develop and use a "highly original model research animal". Tetsuo Yamamori, at the National Institute for Basic Biology in Okazaki, plans to introduce genes into the marmosets that control the expression of *OCC-1*, which he thinks is involved in vision.

Monkey magic?

Marmosets are small and relatively easy to handle. They reach sexual maturity in just over a year and a female can have up to 80 babies, compared with about 10 for the rhesus macaque. But the bottom line is whether marmosets can usefully model human disease. "They'll be better than rodents," says Chan. "But are they good enough?"

Marmosets, a New World monkey, are genetically further from humans than macaques. Nicole Déglon, of the French Atomic Energy Commission's Department of Medical Research in Gif-sur-Yvette, says that normal marmosets fail many cognitive ability tests that are used to judge the effects of conditions such as Alzheimer's disease. She says she stopped using marmosets because their brains are too small for positron emission tomography scans.

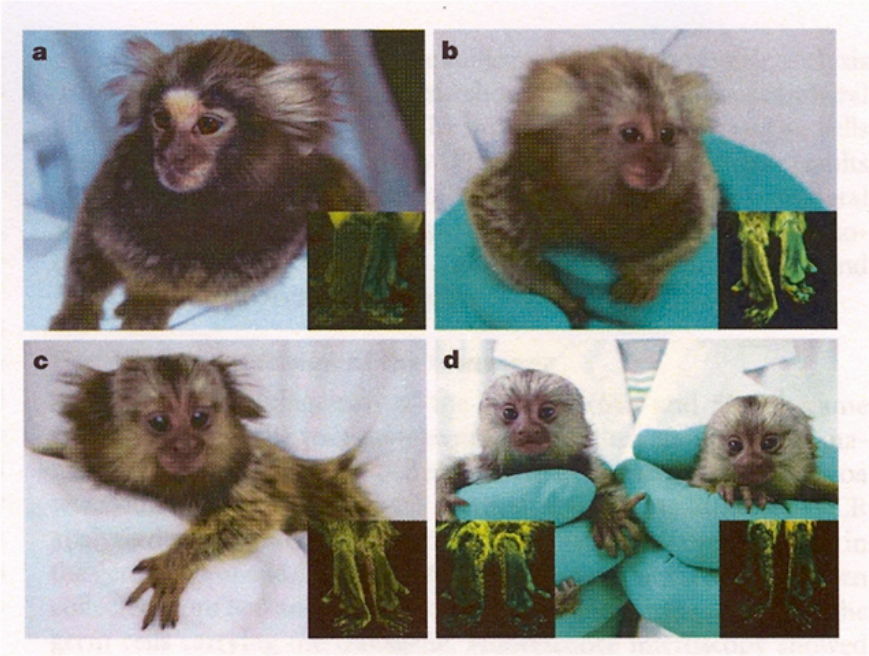
Tadashi Isa, a developmental physiologist at the National Institute for Physiological Sciences in Okazaki who is also a member of the brain-science programme, says marmoset research is likely to boom, but only as a complement to macaque research. Marmosets, he says, will be useful for studying cognitive and behavioural disorders because they share some social characteristics with humans, such as maintaining familial relationships. "But a higher brain function research paradigm has been established for things like attention and decision-making in the macaque," he says. "With marmosets, there is no history and no accumulation of knowledge."

The transgenic marmoset project is also likely to face challenges from bioethicists and animal-rights groups over creating a colony of animals born with a disease. "You must think of the cost–benefit," Sasaki responds. "If you can do it in rodents or *in vitro*, we should. But for many diseases, like Parkinson's, there is not a good model now." ■

David Cyranoski

1. Sasaki, E. *et al. Nature* **459,** 523–527 (2009).
2. Schatten, G. & Mitalipov, S. *Nature* **459,** 515–516 (2009).
3. Chan, A. W. S., Chong, K. Y., Martinovich, C., Simerly, C. & Schatten, G. *Science* **291,** 309–312 (2001).
4. Yang, S.-H. *et al. Nature* **453,** 921–924 (2008).

See Editorial, page 483, News & Views, page 515, and Article, page 523.



"To our knowledge, this is the first report of transgenic non-human primates showing not only the transgene expression in somatic tissues but also germline transmission of the transgene with the full, normal development of the embryo."

MAY 28, 2009, NATURE

Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells

Masahito Tachibana, Michelle Sparman, Hataitip Sritanaudomchai, Hong MA, Lisa Clepper, Joy Woodward, Ying Li, Cathy Ramsey, Olena Kolotushkina, and Shoukhrat Mitalipov

Oregon National Primate Research Center, Oregon Stem Cell Center, and Department of Obstetrics and Gynecology and Molecular and Medical Genetics, Oregon Health and Science Univ.

Mutations in mitochondrial DNA contribute to diverse range of currently incurable human diseases and disorders (type 2 diabetes, mitochondrial myopathies, and Leigh syndrome).

1 in 200 births is thought to have a potentially pathogenic mitochondrial DNA mutation.

Investigators were able to transfer DNA from the nucleus of rhesus macaques egg into an enucleated egg without carrying over any mitochondrial DNA.

Eggs were fertilized with sperm and implanted into females, which produced offspring that had mitochondrial DNA from one female and nuclear DNA from another.

Mito and Tracker

Ethical Concerns Surrounding Transgenesis

Should there be universal protocols for transgenesis?

Should these protocols demand that only the most promising research be permitted?

Is human welfare the only consideration? What about effects on the other life form?

Should scientists focus on in vitro (cultured in a lab) transgenic methods rather than, or before, using live animals to alleviate animal suffering?

Will transgenic animals radically change the direction of evolution, which may result in drastic consequences for nature and humans alike?

Should patents be allowed on transgenic animals, which may hamper the free exchange of scientific research?

Why Produce Transgenic Animals?

Specific economic traits

Transgenic cattle were created to produce milk containing particular human proteins, which may help in the treatment of human emphysema.

Disease models

Harvard scientists made a major scientific breakthrough when they received a U.S. patent (Dupont) for a genetically engineered mouse, called OncoMouse® or the Harvard mouse, carrying a gene that promotes the development of various human cancers.

How Do Transgenic Animals Affect the Human Condition?

Agriculture

Breeding

- Farmers use selective breeding to produce animals that exhibit desired traits (e.g., increased milk production, high growth rate).
- Traditional breeding is time consuming.
- Possible to develop traits in animals in shorter time with more precision
- Can increase yields

Quality

- Transgenic cows that produce more milk or milk with less lactose or cholesterol
- Pigs and cattle have more meat and sheep grow more wool.
- Alternative use of growth hormones leaves residue of hormones in the animal product.

Disease resistance

- Influenza-resistant pigs

Industrial Applications

Nexia Biotechnologies in Canada spliced spider genes into the cells of lactating goats. The goats began to manufacture silk along with milk and secrete tiny silk strands from their body by the bucketful. Can be used to create a light, tough, flexible material that could be used for military uniforms, medical microsutures, and tennis racket strings.

Toxicity-sensitive transgenic animals for chemical safety testing.

Microorganisms that produce enzymes that can speed up industrial chemical reactions.

Medical Applications

Xenotransplantation

- Patients die every year for lack of a replacement heart, liver, or kidney.
- Transgenic pigs may provide the transplant organ but currently xenotransplantation is hampered by a pig protein that can cause donor rejection – research underway to replace this protein with the human homologue.

Nutritional supplements and pharmaceuticals

- Insulin, growth hormones, and anti-clotting factors have been obtained from the milk of transgenic cows, sheep, and goats.
- Research is underway to manufacture milk through transgenes for debilitating diseases such as phenylketonuria, hereditary emphysema, and cystic fibrosis.

Human gene therapy

- 5,000 named genetic diseases in the human population
- Virtanene Institute in Finland produced a calf with a gene that promotes growth of red cells in humans.

PONTIFICAL ACADEMY FOR LIFE

Prospects for xenotransplantation scientific aspects and ethical considerations

Practical Guidelines:

1. Regarding the xenotransplantation of solid organs – preclinical experiments (from animal to animal) should continue until repeated positive results are obtained before trials on humans.

2. Respect rules of informed consent (host) – restricted group of patients for whom no better alternative treatment is available (wait list for allotransplantation or individual counter-indications).

3. Ensure careful and detailed monitoring of recipients – can continue throughout the life of the recipient – watch for signs of possible infection caused by known and unknown pathogenic agents.

4. Clinical trials should be carried out in highly specialized centers with a proven track record in pre-clinical (animal to animal) models.

5. Need to acquire correct information on the topics of greatest public interest identifying benefits and risks and communicated to as large a segment of public as possible.

6. Ethical commitment on the part of scientists should not neglect to explore therapeutic paths which represent alternatives to xenotransplantation, i.e., use of adult stem cells.

Pontifical Academy For Life

'Transgenesis'

"Therefore, while recognizing that transgenesis does not compromise the overall genetic identity of the mutated animal or its species, and reaffirming man's responsibility towards the created order and towards the pursuit of improving health by means of certain types of genetic manipulation ……some fundamental ethical conditions must be respected."

1. Concern for the well-being of genetically modified animals should be guaranteed so that the effect of the transgene's expression, possible modification of the anatomical, physiological and/or behavioural aspects of the animal may be assessed, all the while limiting the levels of stress and pain, suffering and anxiety experienced by the animal.

2. The effects on the offspring and possible repercussions for the environment should be considered.

3. Such animals should be kept under tight control and should not be released into the general environment.

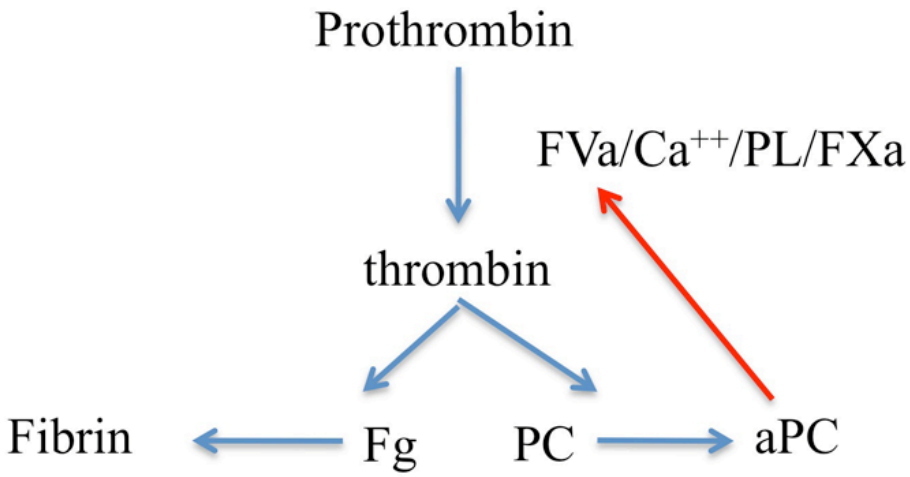
4. The number of animals used in the experiments should be kept to a bare minimum.

5. The removal of organs and/or tissues must take place during a single surgical operation.

6. Every experimental protocol on animals must be evaluated by a competent ethics committee.

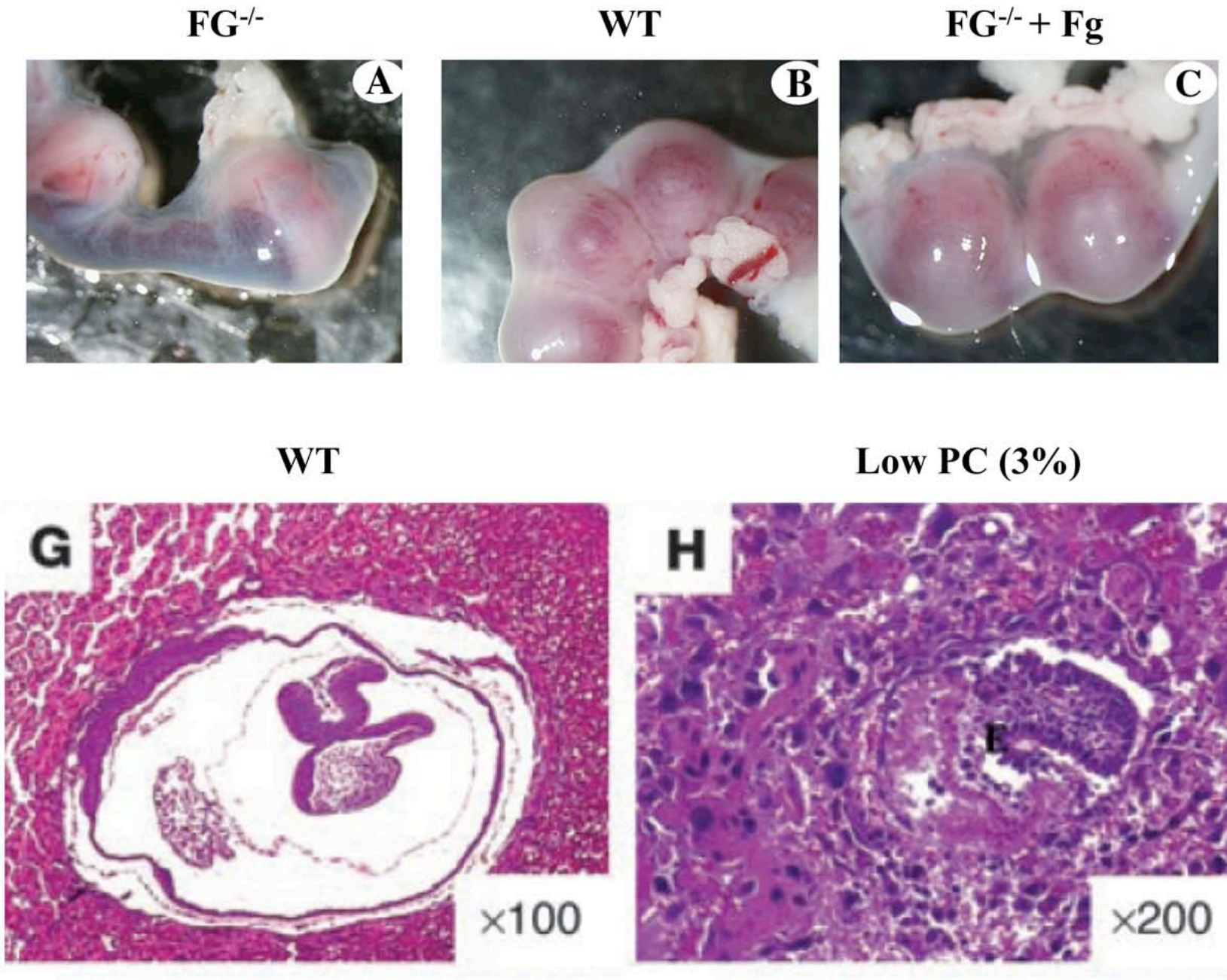
Transgenic Research at the Keck Center

Generation of 2 gene knock-out mice that regulate different stages of blood coagulation led to the discovery that these proteins, produced specifically by the mother, are critical for fetal development and survival.



$FG^{-/-}$ = no fibrin clot

$PC^{-/-}$ = too much clot?


FG-/-
WT
FG-/- + Fg
A
B
C
WT
Low PC (3%)
G
×100
H
I
×200

Downstream Ethical Considerations

Should Fg be administered to pregnant females to rescue pregnancy in women with clotting abnormalities?

Risk of maternal clotting or immune reaction to protein

Factor V Leiden is similar to a PC deficiency – Factor V insensitive to PC activity
2% occurrence in the population

Administering FV or regulating PC function have similar effects.

Genetic Regulation?

"We used to think our fate was in our stars. Now we know that, in large measure, our fate is in our genes."

Francis Crick