

Quality Control in Research Laboratories: The Need for Standardization

Yasemin Uçal, Ph.D

Acibadem Mehmet Ali Aydınlar University

School of Medicine, Department of Medical Biochemistry

XXVII. Balkan Clinical Laboratory Federation Meeting BCLF 2019
XXX. National Congress of the Turkish Biochemical Society TBS 2019
October, 29th 2019



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Content

- Background Information
- Validity and Reliability of Research Data
- Any Standards for Research Laboratories?
- Challenges
- Potential Solutions
- Example from Our Research Laboratory
- Can There be any Community Standards?



What is Research?



- **Process of systematic inquiry**

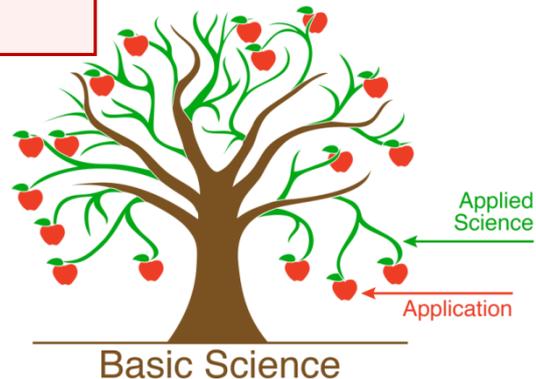
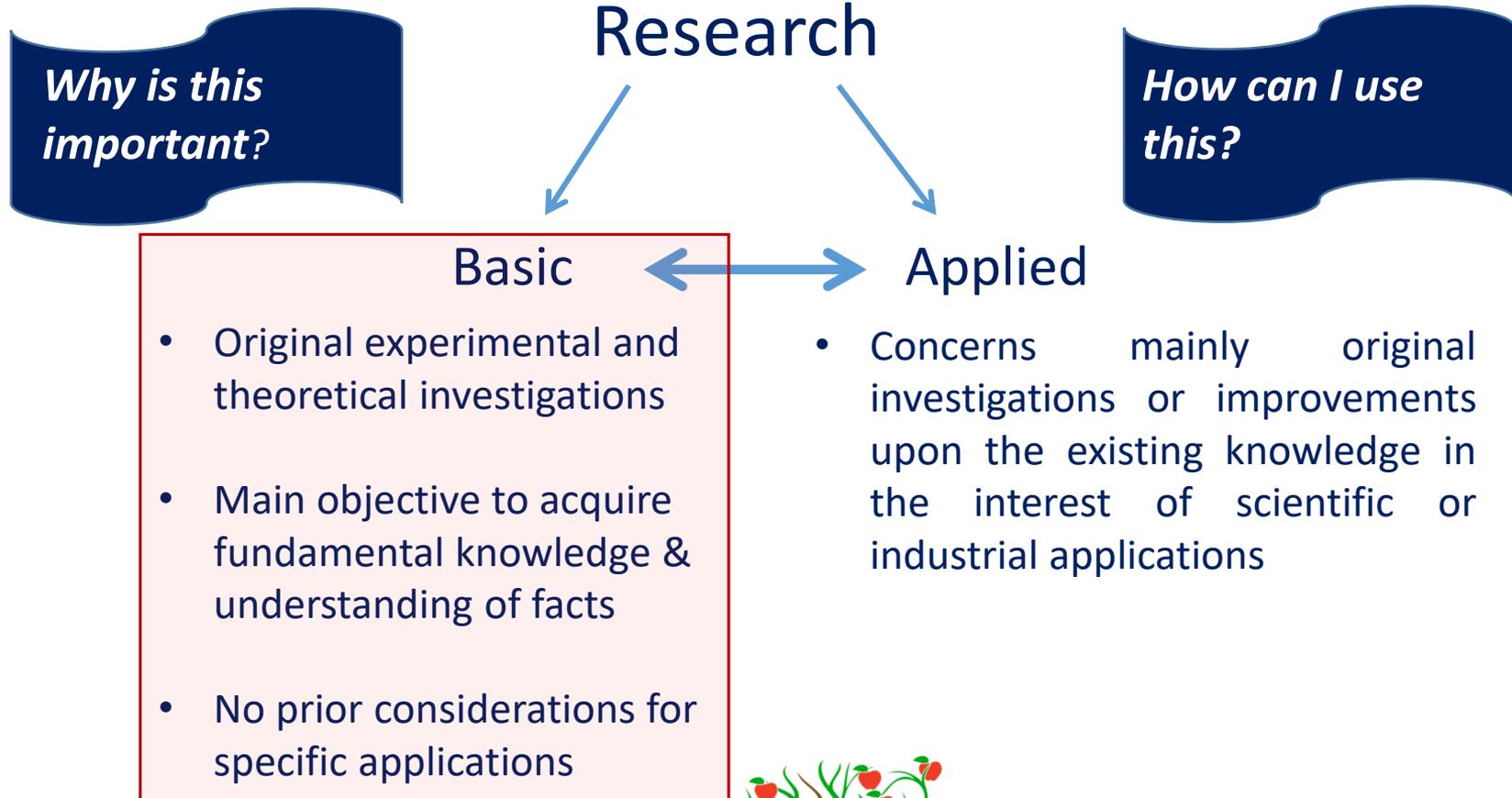
- defining problems, formulating hypothesis
- collection of data
- analysis and interpretation of the data

By using suitable methodologies

- **Performed by wide range of scientists or researchers with different education and training.**



Classification



How important is basic research?

Clinical research builds upon the findings of basic research.

E.g. Translation of the scientific knowledge into the development of potential treatments.



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Validity and Reliability of Data in Research Laboratory

- Validity and reliability in a simple context:



An alarm clock ringing at 7:00 each morning, but is set for 6.30.

Alarm clock is **reliable** → consistently rings the same time each day

But not **valid** → not ringing at the desired time



Are Research Data Valid and Reliable?

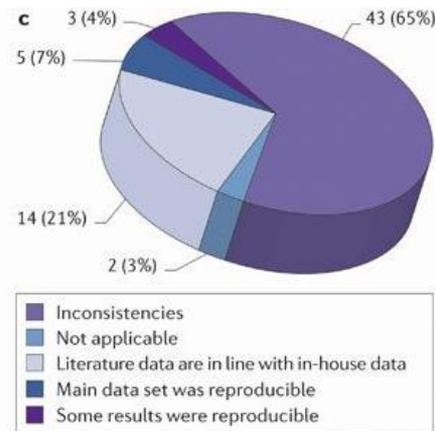
Examples from various sources



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Research on Drug Targets

- Researchers at Bayer could **NOT** reproduce **43 of 67** oncological and cardiovascular findings reported in academic publications.
 - Published in Nature Reviews Drug Discovery, 2011.



- Researchers at Amgen could **NOT** reproduce **47 of 53** landmark oncological findings for potential drug targets.
 - Published in Nature, 2012

Journal impact factor	Number of articles
>20	21
5-19	32



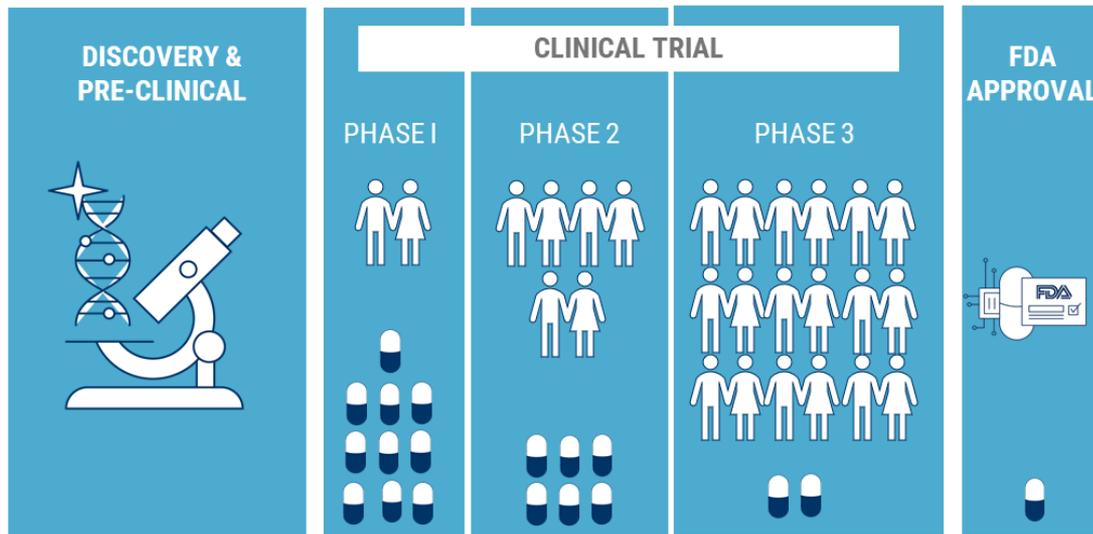
Clinical Trials Perspective

- Success rates for new development projects in Phase II trials have fallen from **28% to 18%** in recent years.
 - Published in Nature, 2011

Insufficient efficacy being the most frequent reason for failure

Limitations of the predictivity of disease models ?

Validity of the targets being investigated ?

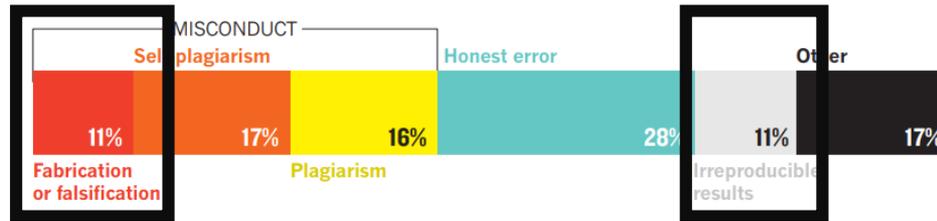
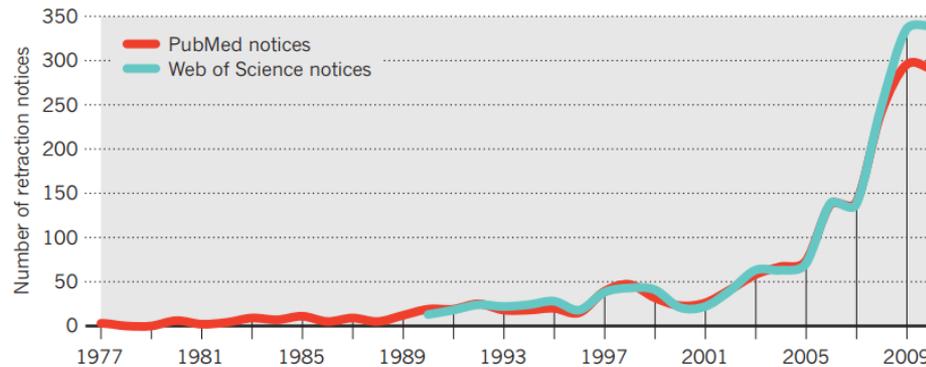


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Rise of the Retractions



- Definition of **retraction**; An act of taking back, withdrawing



- In surveys, approximately 1-2% of scientists admit to having fabricated, falsified or modified data or results at least once.

Van Noorden R (2011). Science publishing: the trouble with retractions. Nature, 478, 26-28.

Fanelli D (2009). How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. PLOS ONE



Attention in the Media

THE TRUTH WEARS OFF

Is there something wrong with the scientific method?

By **Jonah Lehrer** December 5, 2010

the Atlantic

Lies, Damned Lies, and Medical Science

Much of what medical researchers conclude in their studies is misleading, exaggerated, or flat-out wrong. So why are doctors—to a striking extent—still drawing upon misinformation in their everyday practice? Dr. John Ioannidis has spent his career challenging his peers by exposing their bad science.

DAVID H. FREEDMAN NOVEMBER 2010 ISSUE

IN 2001, RUMORS were circulating in Greek hospitals that surgery residents, eager to rack up scalpel time, were falsely diagnosing hapless Albanian immigrants with appendicitis. At the University of Ioannina medical school's teaching hospital, a newly minted doctor named Athina Tatsioni was discussing the rumors with colleagues when a professor who had overheard asked her if she'd like to try to prove whether they were true—he seemed to be almost daring her. She accepted the challenge and, with the professor's and other colleagues' help, eventually produced a formal study showing that, for whatever reason, the appendices removed from patients with Albanian names in six Greek hospitals were more than three times as likely to be perfectly healthy as those removed from patients with Greek names. "It was hard to find a journal willing to publish it, but we did," recalls Tatsioni. "I also discovered

On September 18, 2007, a few neuroscientists, psychiatrists, company executives gathered in a conference room in Brussels to hear startling news. It had to do with a class of drugs known as atypical or second-generation antipsychotics, which came on the scene in the early nineties. The drugs, sold under names such as Abilify, Seroquel, and Zyprexa, had been tested on schizophrenics in large clinical trials, all of which had demonstrated a dramatic decrease in subjects' psychiatric symptoms. As it turned out, Zyprexa had become one of the fastest-growing classes. By 2001, Eli Lilly's Zyprexa



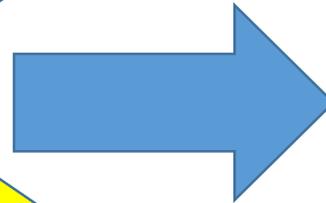
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The Major Issue in Research Laboratories

**Many of the
published
methods do NOT
work in other
labs!**



**Problems in
Reproducibility**



Issues Causing a Lack of Reproducibility in Research Labs

Poor study design

Poor statistical practices

Inadequate reporting of results

Poor training

Problems with quality control (QC)

Temporary Staff
(incl. Graduate students,
visiting scholars)

Immature research culture

Pressure on publication

Quality Control

However, in research laboratories the culture regarding quality control is immature!

Any standards for Research Labs?

- Started with → to implement existing QA applications to non-routine analytical work

*widely argued that non-routine work **does not fit easily** into a highly documented and formalized quality system*

- A guide was produced in **1998** by a **EUROCHEM** and **CITAC** working group to promote QA applications in **R&D** and **non-routine analysis**.

Quality Assurance for
Research and Development
and Non-routine Analysis

Eurachem  *A FOCUS FOR
ANALYTICAL CHEMISTRY
IN EUROPE*

CITAC 

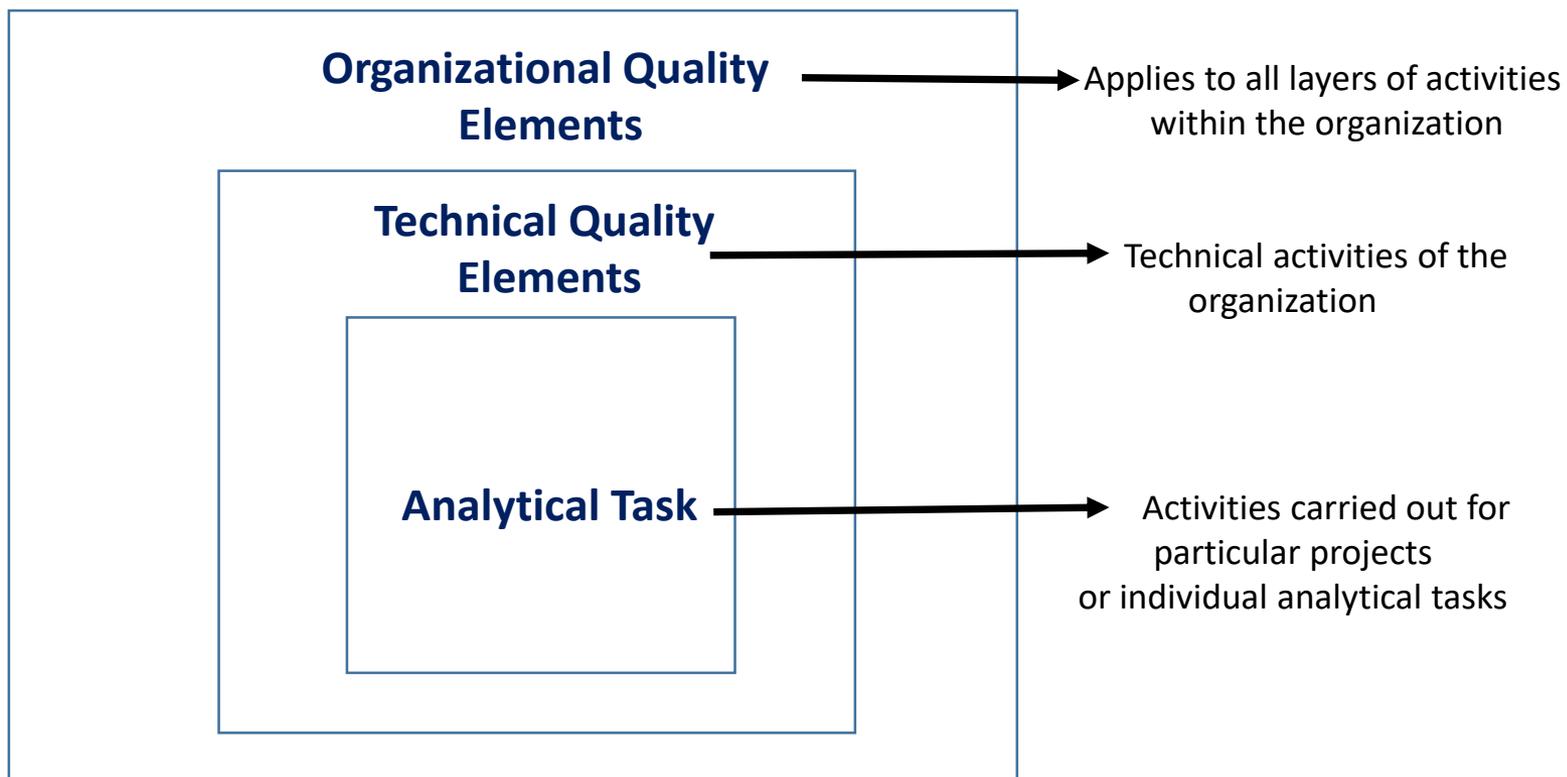
Co-Operation on International Traceability in Analytical Chemistry



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Structure of this guide:

- Activities are listed in a **nested structure**
 - Structure within a structure



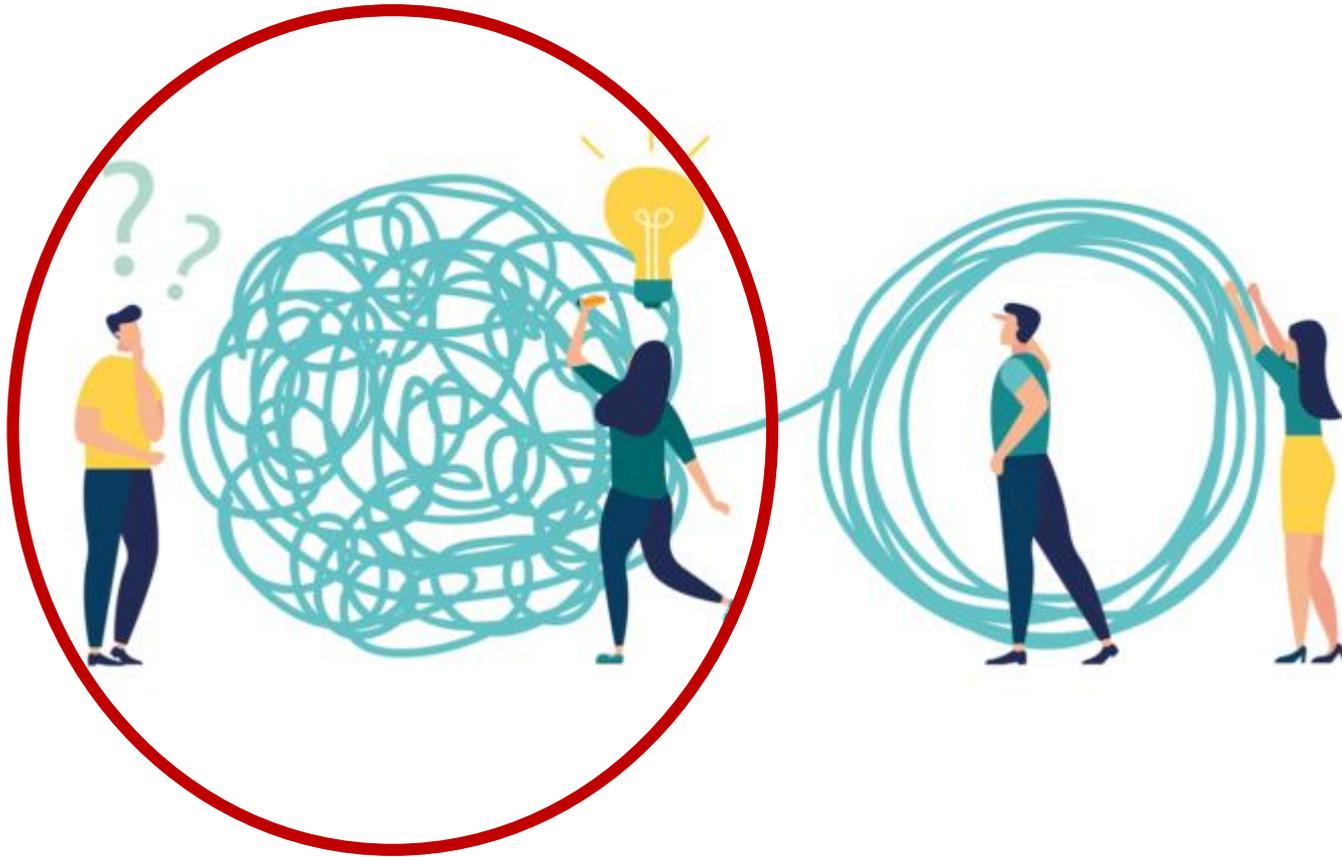
Conclusions of this guide:



1. No single method of assessment stands out as being the most suitable for monitoring the quality of non-routine and R&D work.
2. Informal verification principles (self assessment, peer review, visiting groups etc) could be made more formal if required.
3. Research workers must have an appreciation of the quality requirements of clients and quality must be designed into every process.



The Challenges





Alan G. MacDiarmid

Professor at the University of Pennsylvania,
Philadelphia, USA.

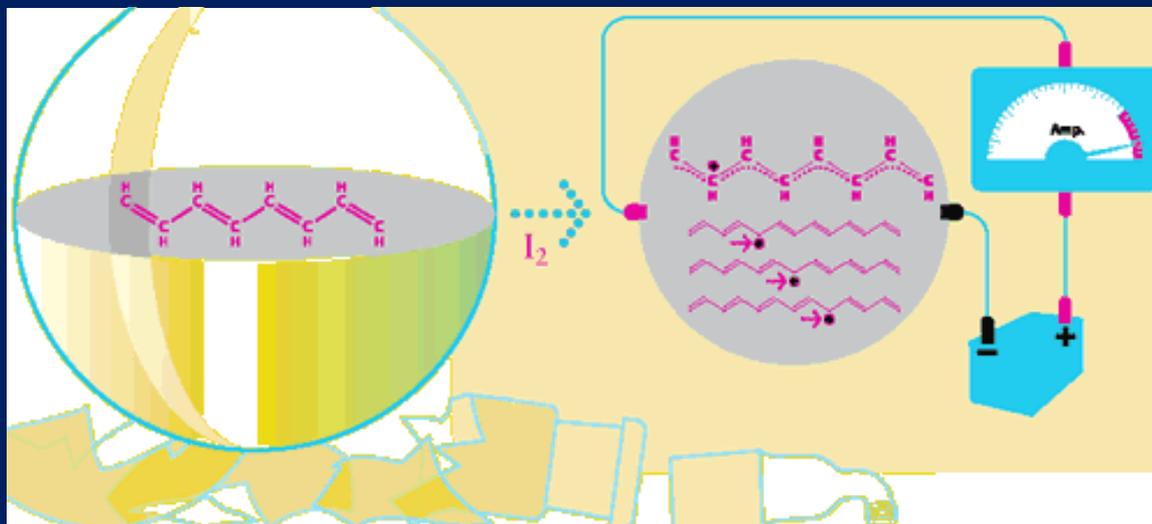
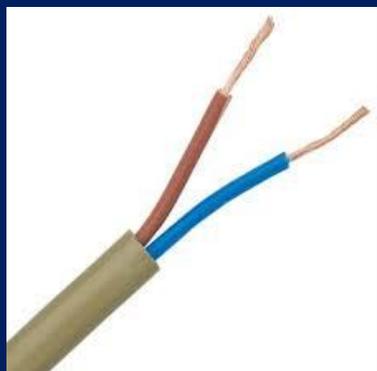
Hideki Shirakawa

Professor Emeritus,
University of Tsukuba, Japan.

Alan J. Heeger

Professor at the University of California
at Santa Barbara, USA.

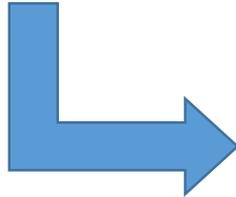
In 2000 MacDiarmid, Heeger, and Shirakawa received the Nobel Prize in Chemistry for the *“discovery and development of conductive polymers”*.



Challenge: research environment

- **Beliefs in research community**

- Such a quality system can restrict the freedom of research and motivation of researchers



The idea should be:

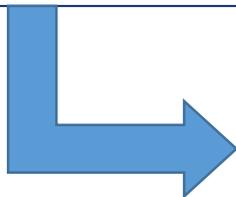
- Add approved tools and techniques
- Improve existing research approaches.
- Merge quality assurance tools and techniques with research
- Gain benefits and BUT not adversely affect the research.

Symbiosis: the art of living together



- **Complexity of the research**

- Simple exploration of ideas
- Investigate specifically defined problems



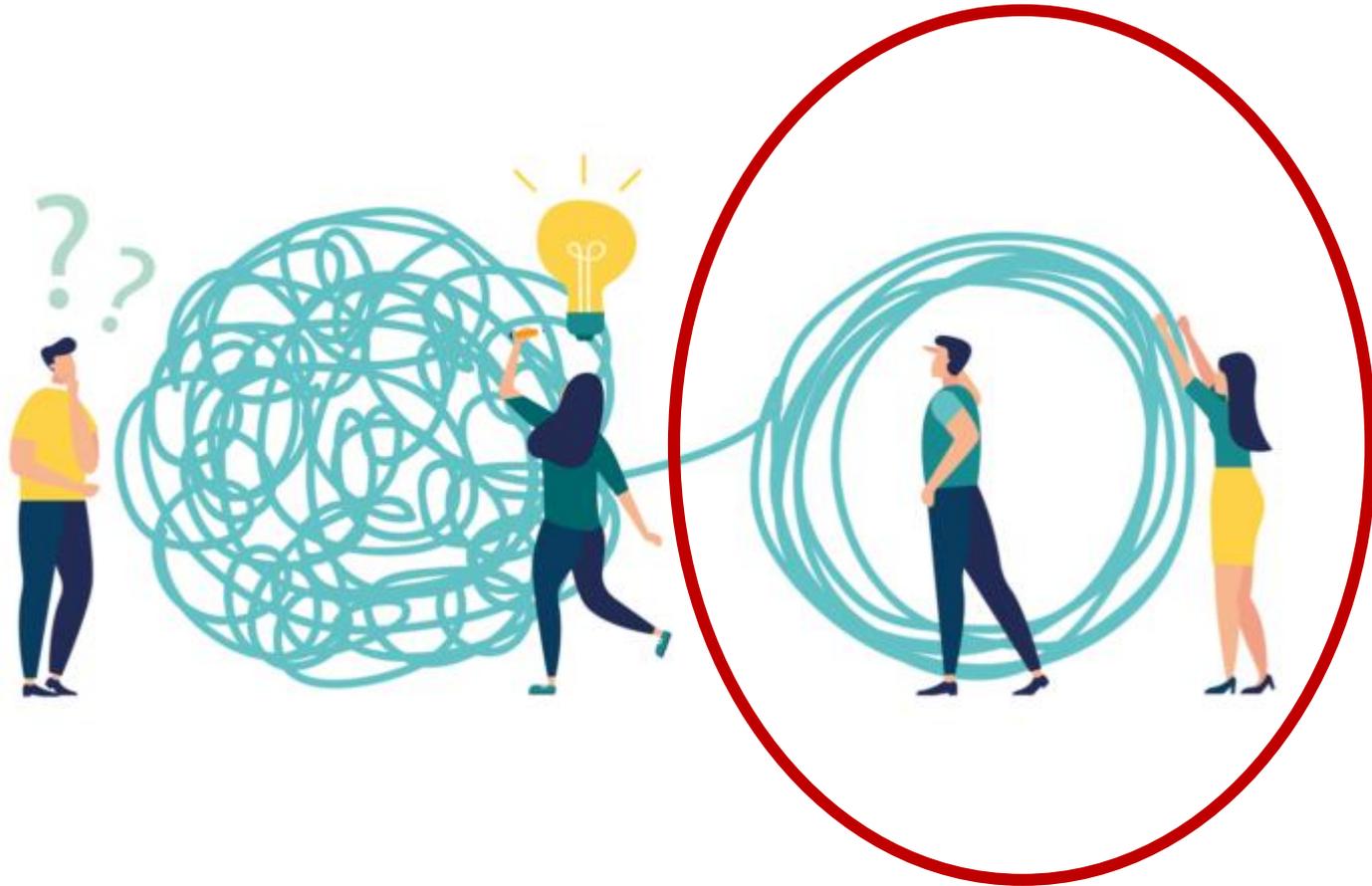
There is somebody asking for the investigations and using the results of these investigations.

Challenge : Many academics in research are NOT familiar with guidelines

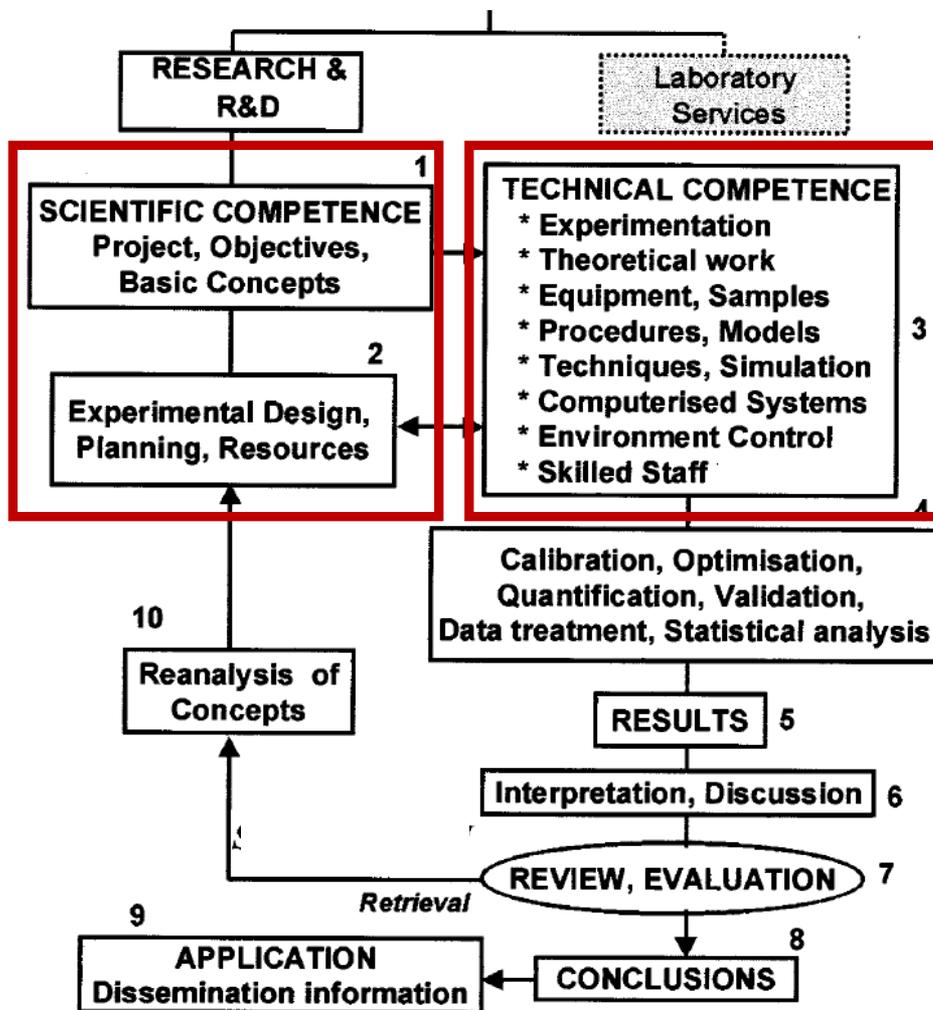
If academics do not know it, they **cannot** teach it!



The Potential Solutions



Different stages of a research project



Although the stages remain valid for research; it is subjected to change based on

- the diversity of the procedures/methods,
- extent of activities,
- nature of the objectives



Integrating quality into research

1. Quality of the objective
2. Quality of the research approach

4 Quality Criteria:

1. Reliability
2. Repeatibility
3. Reproducibility
4. Monitoribility

3. Quality of the results/scientific output
4. Quality of the researchers



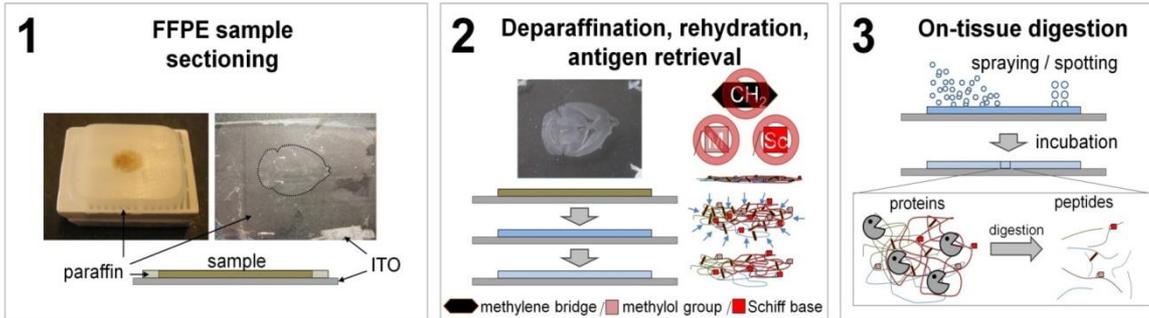
What are we dealing with in our lab?



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MALDI-Mass Spectrometry Imaging (MALDI-MSI)

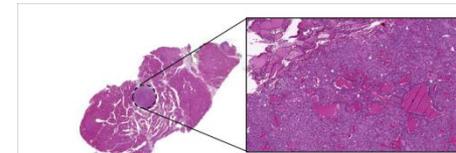
MALDI: Matrix-assisted laser desorption/ionization



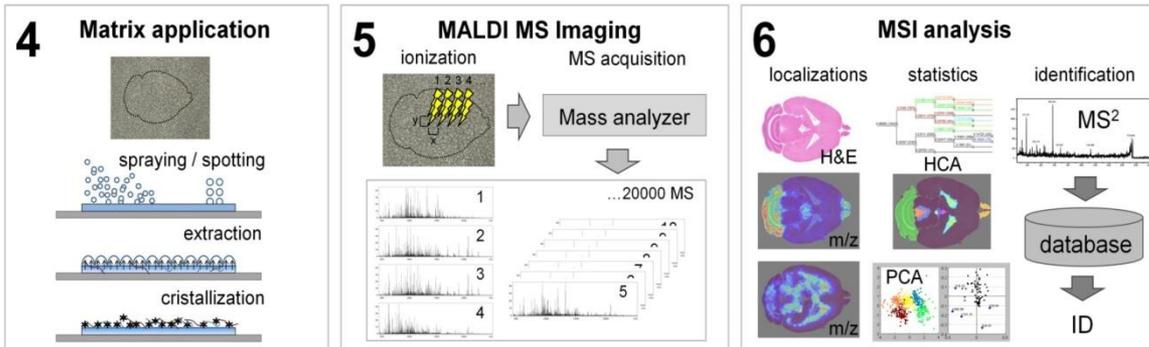
THYROID
Volume 00, Number 00, 2019
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2018.0392

Peptide Profile Differences of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features, Encapsulated Follicular Variant, and Classical Papillary Thyroid Carcinoma: An Application of Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging

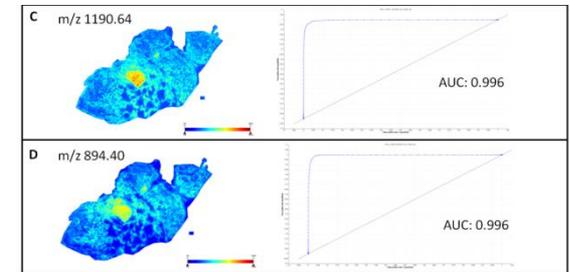
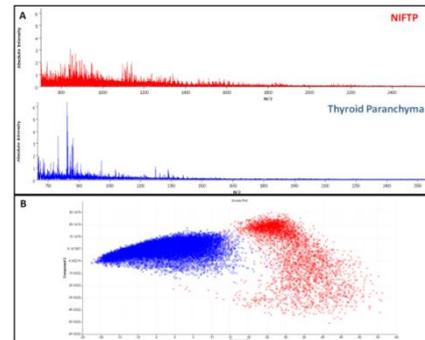
Yasemin Ucal,¹ Fatma Tokat,² Mete Duren,³ Umit Ince,² and Aysel Ozpinar¹



Representative thyroid tissue section



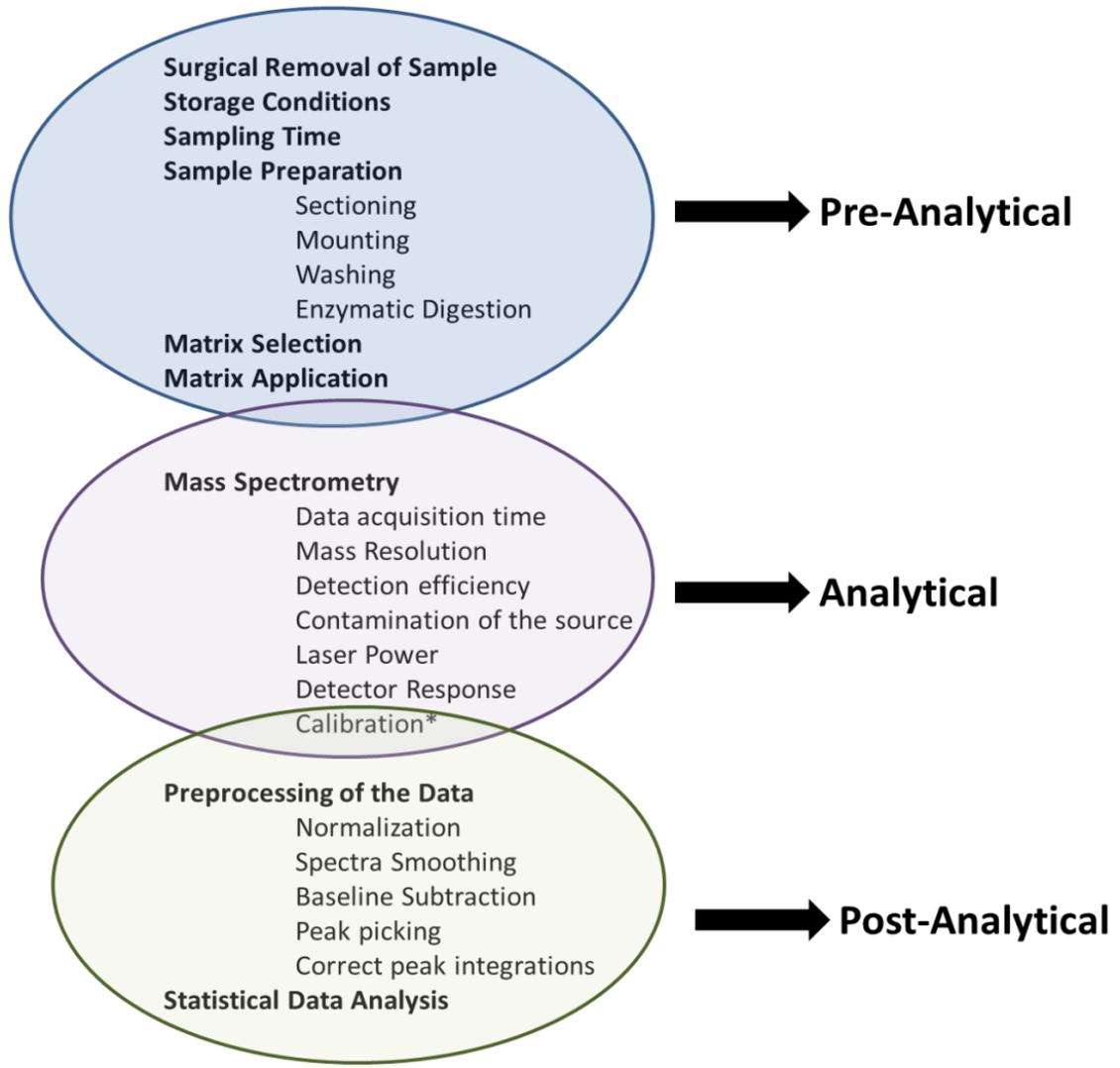
MALDI MSI of representative NIFTP lesion. (A) Tryptic peptide profile of representative NIFTP lesion (up, red), and its neighbor normal thyroid parenchyma (bottom, blue).



(C) Representative ion image of m/z 1190.64 and its corresponding ROC curve (AUC = 0.99).
(D) Representative ion image of m/z 894.40 and its corresponding ROC curve (AUC = 0.99)

Quality Control in MALDI-MSI

There are:
pre-analytical,
analytical,
post-analytical phases
that are responsible for
different results generated
in MSI applications.



What else?

- **Lab books and protocols** → **DOCUMENTATION**
understandable by others, ensure monitorability of samples, methods, results..
- **Working duplicates/triplicates**
- **Technician vs Young researcher, Senior researcher vs Young Researcher** → Comparison of results
- **Use QC samples**
- **Choose suitable QC samples** → simple peptide mixture from a single protein digest (e.g., bovine serum albumin (BSA), enolase, cytochrome c) for MS-based applications



What else? (cont'd)

- **Lab instruments and devices**
 - Internal/external service
 - Calibration
 - Performance tests
 - Keep logbooks



More things to add:

There are some areas of research where community standards could provide a straightforward way to assess some issues associated with reproducibility.



Data Sharing

1. Data need to be monitorible and accessible
- 2. Set as a requirement in publication**
3. Peer review of the article can also take account of the dataset
4. Data Journals are gaining attention (Data in Brief, Scientific Data....)

Many leading journals are now working to adopt policies to make public deposition of data and protocols a prerequisite for publication



Reward System for Reproducibility

- Research designs can be supported and rewarded (at funding or publication level, or both)
 - has careful documentation
 - allows testing of repeatability and reproducibility, datasets being made available to research groups that are independent of the original group.

Funders should increase attention towards quality and enforce public availability of raw data and analyses



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Standardized Reagents and Materials in life science research

- The **Global Biological Standards Institute (GBSI)** advances life science standards to enhance global health.

- Cell Line Authentication

‘Since the 1960s, more than 400 widely used cell lines worldwide have been shown to have been misidentified’

- Antibody Validation

- Antibody Validation Initiative



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Initiatives....

- Open Science Movement → conduct freely available, reproducible, and reliable science that results in fewer erroneous science.
- Reproducibility Initiative (<http://validation.scienceexchange.com>)



Reproducibility Project: Cancer Biology

About

The Reproducibility Project: Cancer Biology is a collaboration between the Center for Open Science and Science Exchange to examine the replicability of cancer biology studies.

The key experimental findings from each of the [50 most impactful cancer biology studies](#) published between 2010-2012 are being replicated by experts from the [Science Exchange](#) network, according to best practices for replication established by the [Center for Open Science](#).

The experimental protocol, materials, data, and results are being made openly available on each study's project page on the [Open Science Framework](#).



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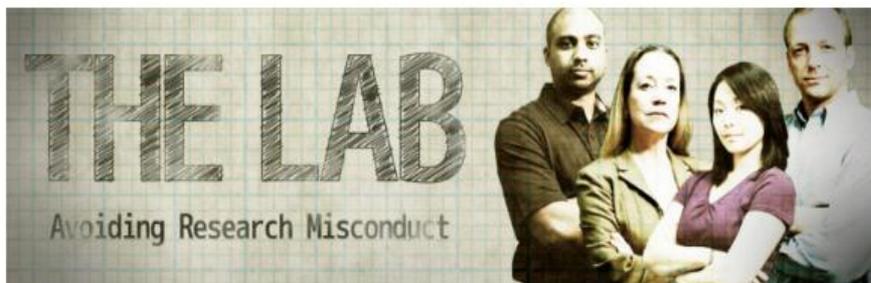
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Interactive Movie on Research Misconduct

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Sep-17 8 Research on Research
Integrity Grants Awarded

Sep-17 ORI Awards 5 Conference
Grants



On-Going Education

- Continuing education of researchers at all career levels
 - Trainings regarding specific issues related to quality in research
- Symposiums, e-learning tools, training courses for researchers
 - Laboratory leadership, mentoring
 - Good research practice
 - Data management, data presentation....





**Quality starts in the
mind!**



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Thank you for your
attention!



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