Good Laboratory Notebook Practices

Background

- You have discovered a new lead compound and have tested it in animal models to prove it has therapeutic effect in treating prostate cancer.

- After many months of thorough testing of this compound and numerous analogs *in vivo*, you submit a paper for publication describing your research findings.
- Several months later, your article publishes.

Protecting your invention

- You hear a talk from the Innovations group explaining the importance of disclosing your invention, how to fill out an invention disclosure form, and the impact of publication on patenting
  - Outside the U.S. publishing before patenting = forfeiting of patent rights
  - In the U.S., there is a 1-year grace period in which to file a patent application after public disclosure or publication (whew!)

Protecting your invention

- You file an Invention Disclosure Form, submit it with Innovations, and provide a copy of the publication
- Innovations files a patent application before the 1-year deadline – the technology is licensed to a pharmaceutical company (your 'Partner') for commercialization

The patent process

- About a year or so after your patent application is filed, Innovations makes you aware of a U.S. patent application filed by a smallish Japanese pharma company that has just published – claiming the same genus of compounds
  - Patent applications in the U.S. publish about 18 months after filing
- Some digging reveals that the patent application was licensed exclusively to Large Pharma
  - This is slightly peculiar, because Large Pharma just entered the market with a strong selling prostate cancer drug with respectable, but not terribly inspiring efficacy
- Six months later (the 18th month mark), your patent application publishes

The controversy

- The U.S. Patent Office notices that your patent application and the one licensed to Large Pharma cover the same subject matter, and it declares an **Interference**.
- Innovations explains that the application licensed to Large Pharma predates your filing date by six months
  - The U.S. has a “first to invent” system, not a “first to file system like the rest of the world, so there is still a chance you can prevail in the U.S.
  - No chance outside the U.S., due to the first to invent system, but
  - If you can show that you conceived the invention before the Japanese pharma company, you get the patent over them!!!

The lab notebook

- You bring out your lab notebooks, which memorialize your conception of the invention
- You recall from the notes, and from other events that occurred at that time, that you conceived the invention about 8 months before the Large Pharma patent application date
  - You should be good to go

Technicalities

- Unfortunately, the USPTO (or a court, in similar scenarios) is unable to consider your notebook as evidence of the point of first conception
  - The notebook is not dated
  - The notebook is not witnessed by others
  - Therefore, there is **no corroboration**

The ramifications

- The Clinic loses the patent to Large Pharma, and loses out on licensing revenue – it gets screwed
- Your Partner is pretty upset about the results, and about losing its monopoly on the compound, losing its freedom to operate, and therefore losing the last 2+ years of development activity and the corresponding $10M – it get screwed
- The inventors lose out on a potentially sizable royalty stream – they get screwed
- Large Pharma does not develop the compound, since their current product has dominant market share – people with prostate cancer lose out on a better therapeutic – millions get screwed

Corroborating Evidence

But let's not lose sight of the big picture ……..

Our scientific obligation

- Allows your work to be **reproduced** faithfully
  - By yourself
  - By others - Science must be reproducible!!!
- Facilitates accurate reporting & publication
- Organizes how you do Science
  - Formulate ideas clearly
  - Specify materials & methods
  - Plan experiments well
  - Obtain maximum value from data
- Protects intellectual property
- Supports future clinical development

Our moral obligation

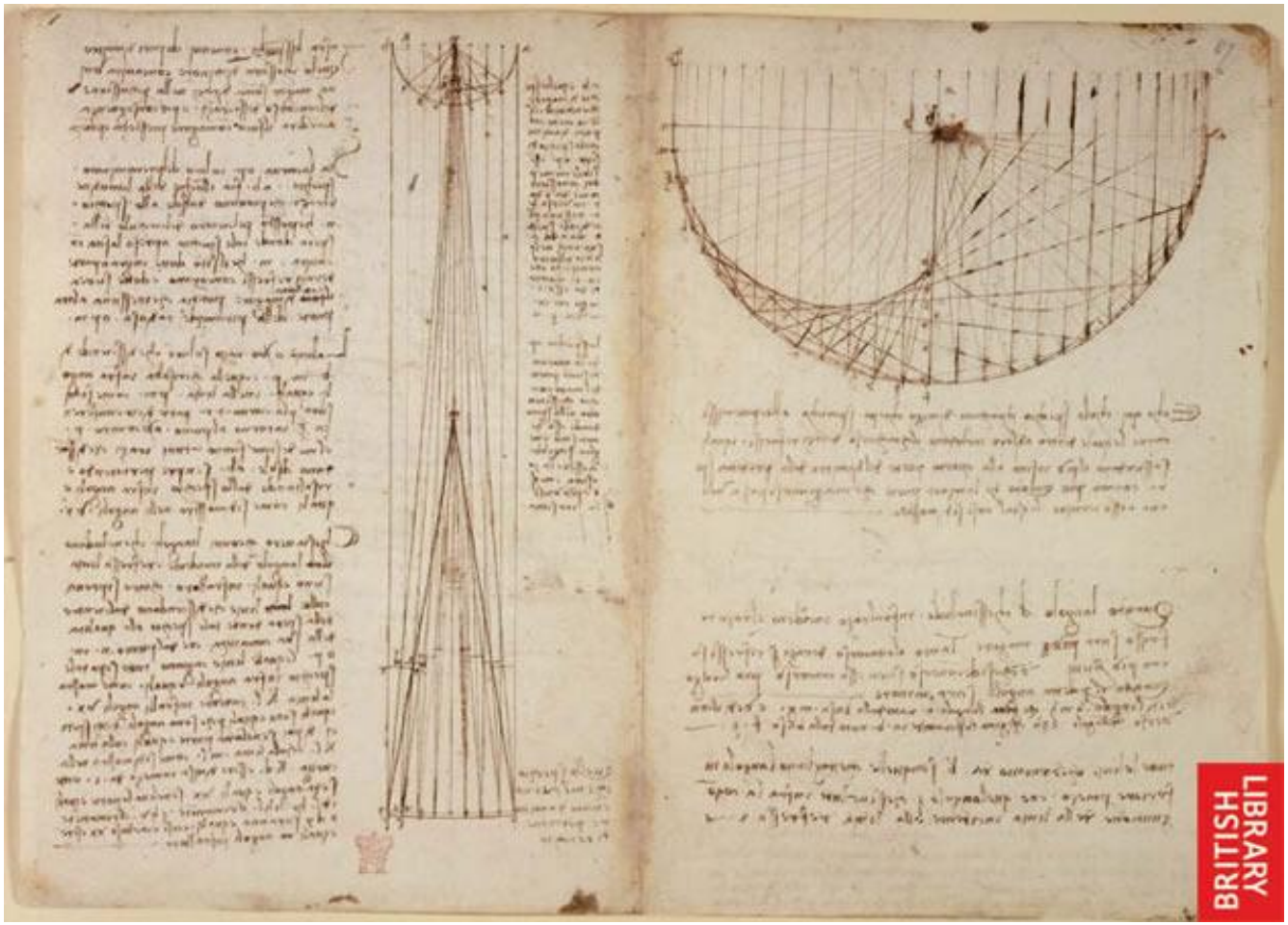
- A major goal of the Clinic is to translate our research into the development of new technologies and therapies that will help patients

We have a moral and legal obligation to patients and to those who provide funds for our work to maintain accurate, complete records, and to protect the Clinic's intellectual property

Surely nobody of any import bothered with the lab notebook…

I can think of a few

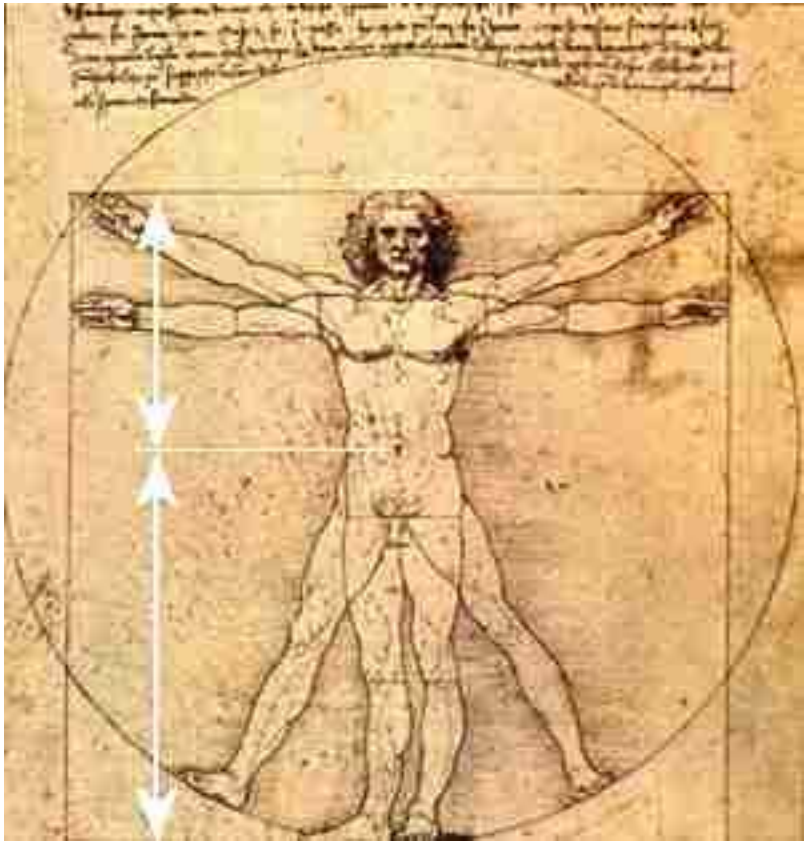
Leonardo da Vinci's notebook



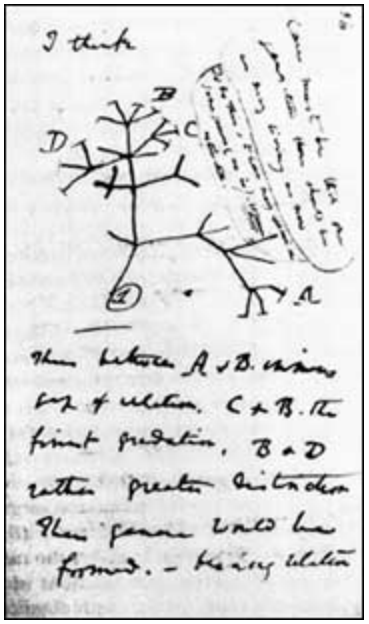
Studies of reflections from concave mirrors. Italy, probably Florence, from 1508.
British Library Arundel MS 263, f. 86v-87

We can read and understand Leonardo's notebooks from 500 years ago

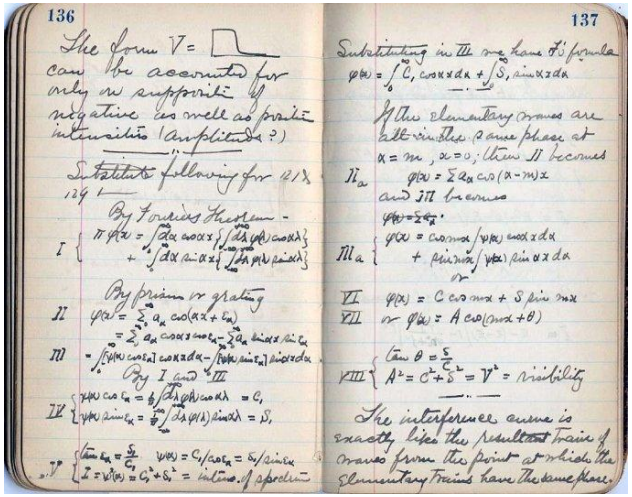
Leonardo da Vinci's Notebook



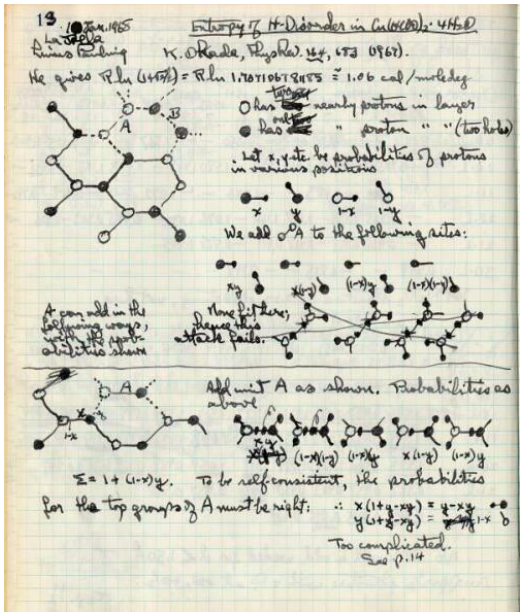
Darwin, Einstein, and Pauling



Darwin

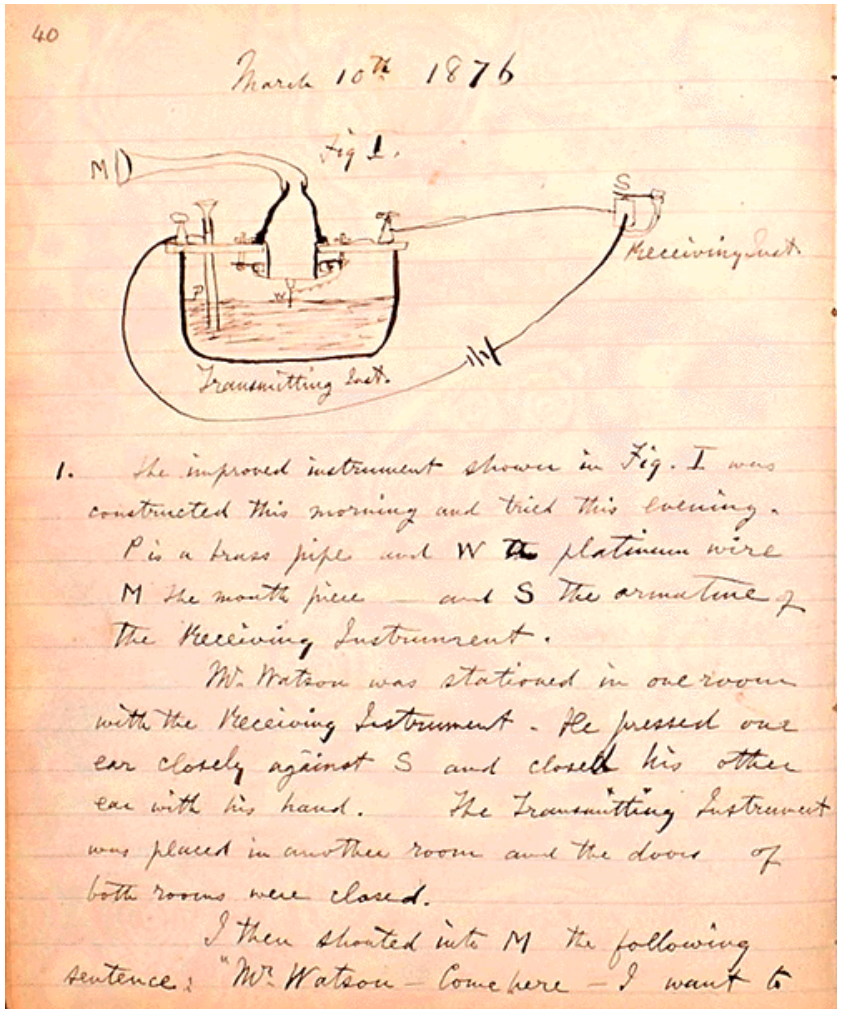


Einstein



Pauling

Alexander Graham Bell's notebook



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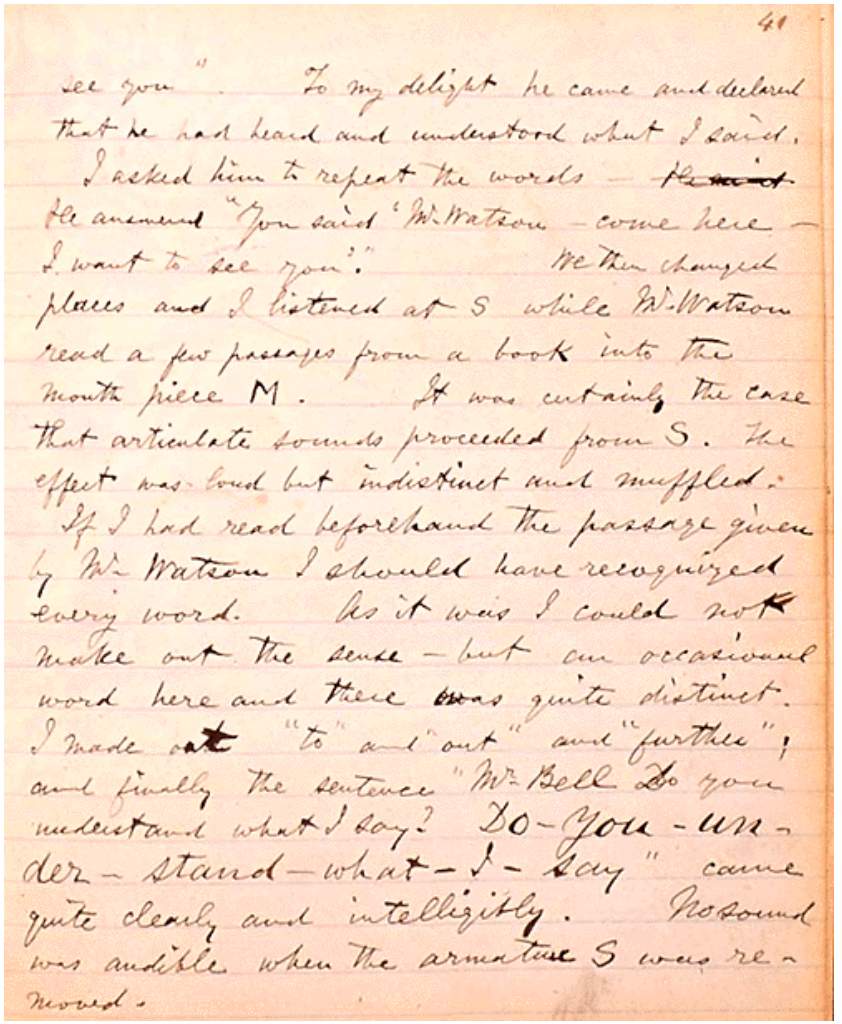
March 10th 1876

Fig 1.

1. The improved instrument shown in Fig. I was constructed this morning and tried this evening. P is a brass pipe and W the platinum wire M the mouth piece — and S the armature of the Receiving Instrument.

Mr. Watson was stationed in one room with the Receiving Instrument. He pressed one ear closely against S and closed his other ear with his hand. The Transmitting Instrument was placed in another room and the doors of both rooms were closed.

I then shouted into M the following sentence: "Mr. Watson — Come here — I want to



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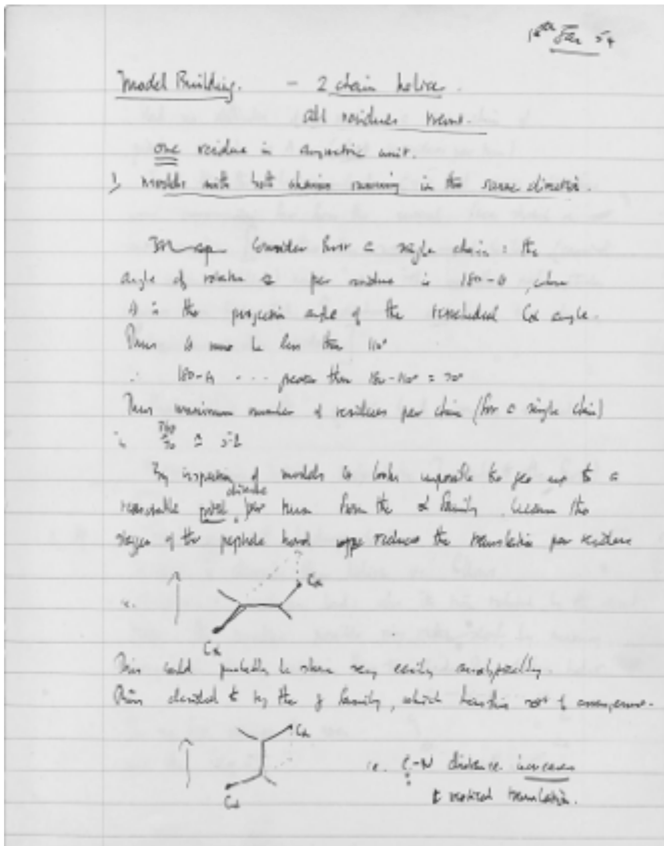
see you". To my delight he came and declared that he had heard and understood what I said.

I asked him to repeat the words — ~~He said~~ He answered "You said 'Mr. Watson — come here — I want to see you'." We then changed places and I listened at S while Mr. Watson read a few passages from a book into the mouth piece M. It was certainly the case that articulate sounds proceeded from S. The effect was loud but indistinct and muffled.

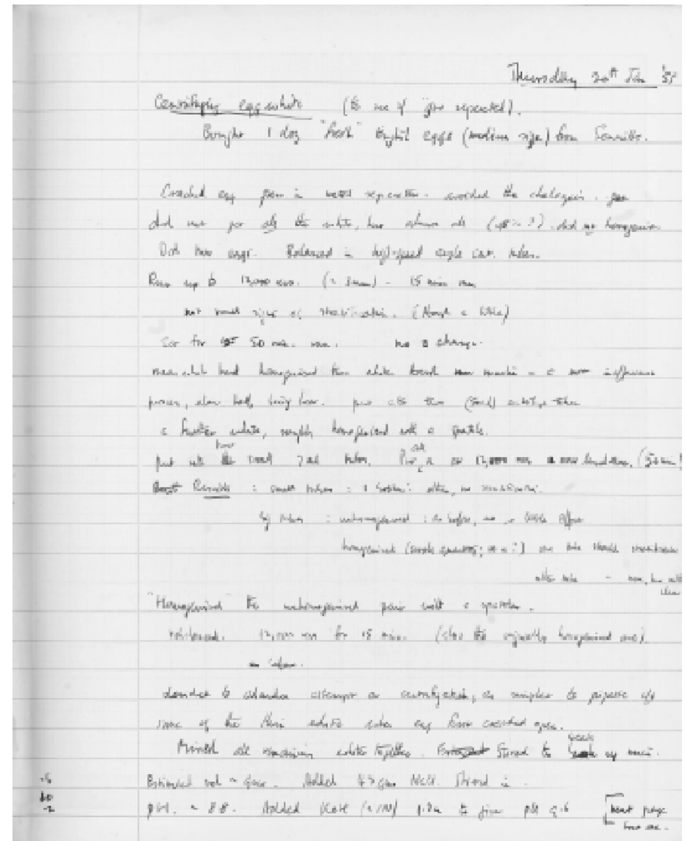
If I had read beforehand the passage given by Mr. Watson I should have recognized every word. As it was I could not make out the sense — but an occasional word here and there was quite distinct. I made out "to" and "out" and "further"; and finally the sentence "Mr. Bell Do you understand what I say? DO-YOU-UN-DER-STAND-WHAT-I-SAY" came quite clearly and intelligibly. No sound was audible when the armature S was removed.

March 10th 1876: "Mr. Watson – Come here – I want to see you".

Francis Crick's notebook



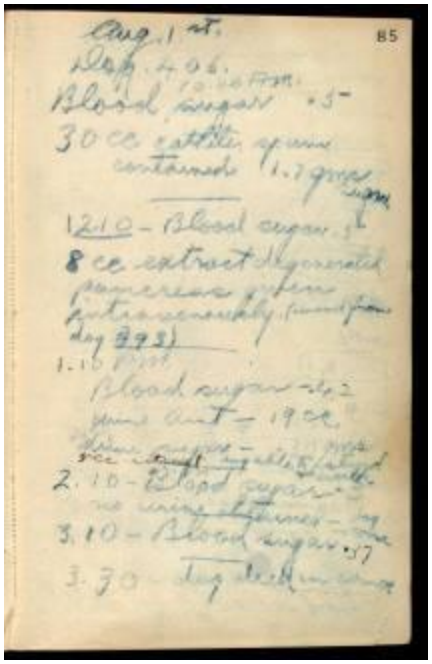
Model building



Centrifuging egg white

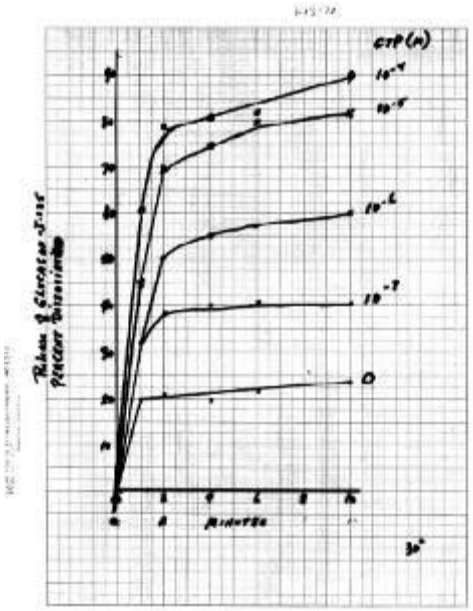
Methods set forth clearly

Results in Nobelists' notebooks



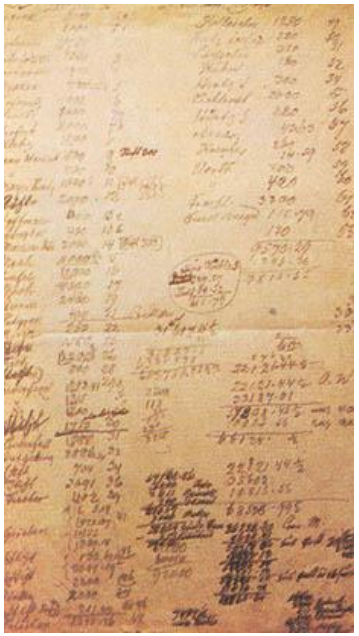
C. H. Best –
Blood sugar

S. Luria –
Bacteriophage growth

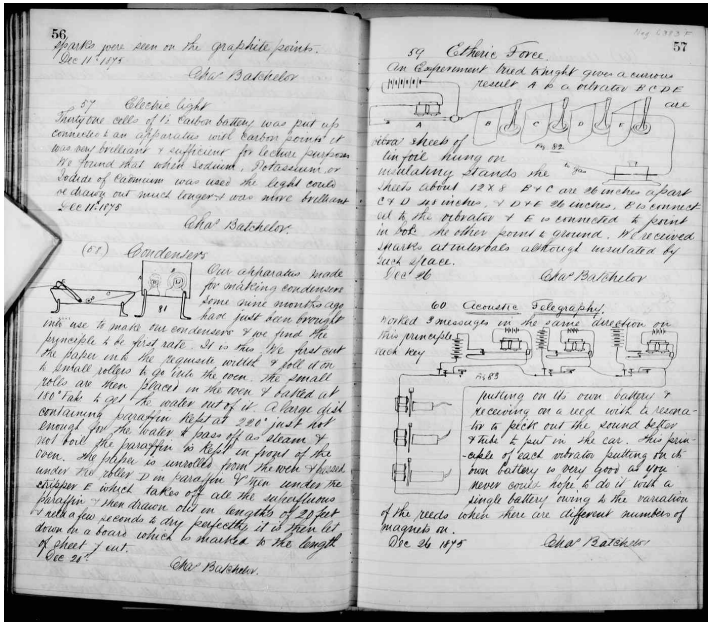


M. Rodbell –
Glucagon release

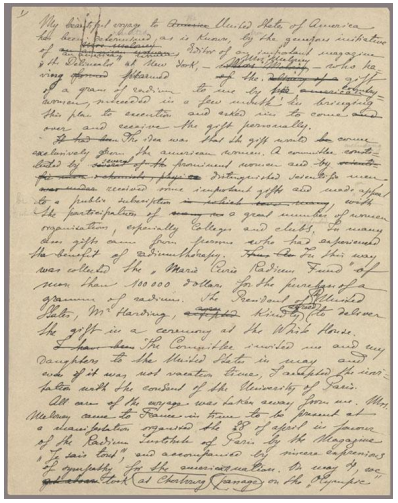
Mendel, Edison, and Curie



Mendel



Edison



Curie

Laboratory Notebook

- A chronological record of an individual's work- the primary document in a research laboratory.
- Notebook is a legal document
- Your data may have to be explained, defended, reconstructed or repeated without your assistance, so others must be able to understand what you did.

Laboratory Notebook Rules

- The notebook should have permanently bound pages which are consecutively numbered and should be used by a single scientist.
- Ideas, calculations and experimental results should be entered into the notebook ***as soon as possible***, preferably the same date they occur, so that the laboratory notebook becomes a daily record of the inventor's activities. Recopying can cause errors.

How do you record the data?

- Directly into the notebook; not on post-its, paper towels, scraps of paper, etc.
- In black or blue, indelible ink; no gel pens
- Make entries only in the ruled areas of the numbered pages
- Unnumbered pages can not be used
- Only one experiment per page
- Attach forms or printouts

Laboratory Notebook Rules

- Notebook entries should be made without skipping pages or leaving empty spaces at the bottom of a page.
- To start an entry on a new page, draw a line through any unused portion of the previous page.
- Never tear out or remove a page from the notebook.

Laboratory Notebook Rules

- Each page should be signed with the inventor's full name and dated.
- All photos, charts or computer printouts pertinent to the project should be permanently put in the notebook with your initials and date over the tape.
- No entry should be changed or added to after signature by a witness.
- If the inventor has any additional information or corrections, a new entry should be made.

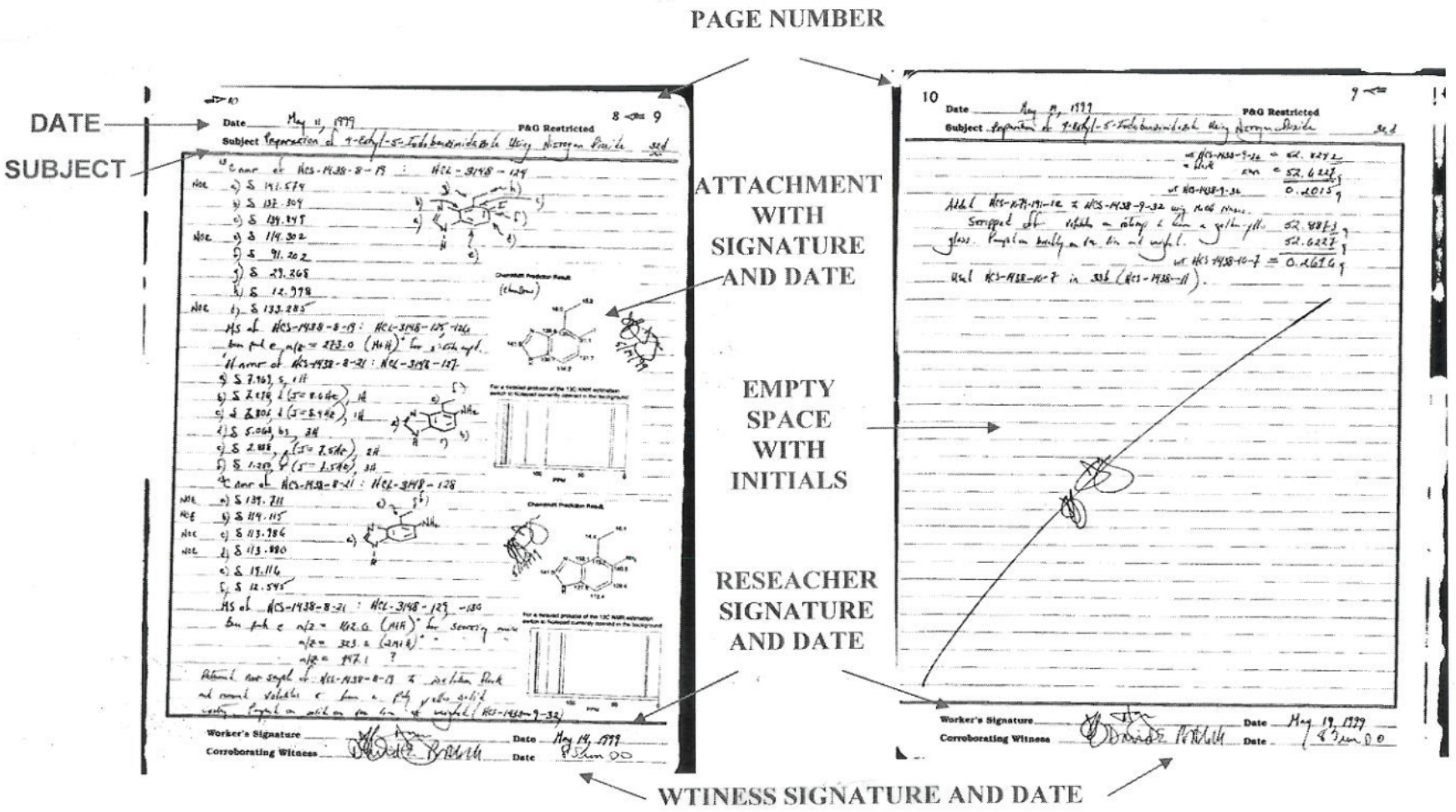
Mistakes?

- Never use white-out
- Never erase
- Never write-over
- Never discard or replace attached supplementary data
- Always record a defensible reason for the correction/edit
- Always circle the reason
- Always add your dated initials to the corrected/edited data after the circled reason

Laboratory Notebook Rules

- Store the lab notebook in a safe location in the lab.
- In a company or university lab, the lab notebook belongs to the company or university, and should NOT be removed from the premises.
- The old notebooks should stored following the company's record retention and destruction policy for such documents.

EXAMPLE NOTEBOOK PAGES



[redacted]

* Formatted and Resubmitted PLoS CPP paper with [redacted], discussed additional / future projects

2-Jun-2011

Taking a break from PEM DB generation script for today – will work on figuring out MPI-BLAST on HPC[2] clusters for nematode project.

New genome assembly, 74.94% of RNA-Seq reads map with at least 1 reported alignment → that's up ~2% from the old abyss_n10_k40 assembly (see: 18-May-2011)
– Also in light of Li et al. Science Express paper (1-Jun-2011), this seems very reasonable and I feel like the assembly using all data is better than previous assemblies.

Also, need to re-run PHOBOS on this data for updated microsatellite analysis.
generated phobos_new.out → need to perform analysis...

Also, examined PEAKS and Sieve software [redacted] → both available through Thermo and integrate with Proteome Discoverer, both seem to have "cluster" versions but unclear exactly what → PEAKS is for de novo sequence identification as opposed to DB search while Sieve does differential expression analysis (control vs. treatment, etc.) → may want to check for open source alternatives...

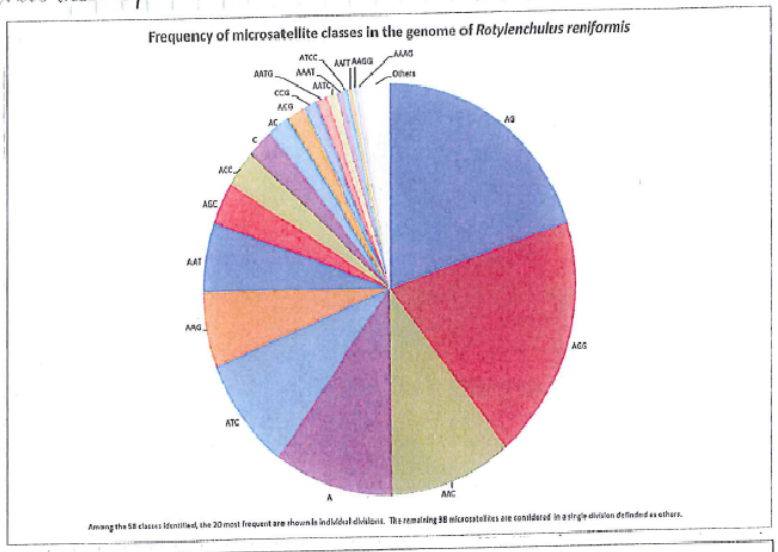
Also, the PEAKS (Bioinformatics Solutions) software webpage provides some insight into using multiple peptide identification strategies (multiple algorithms, i.e. X!Tandem, Sequest, MASCOT, etc.) to increase peptide coverage of identified proteins → may want to investigate this for Book Chapter and proteotypic peptide observability followup paper.

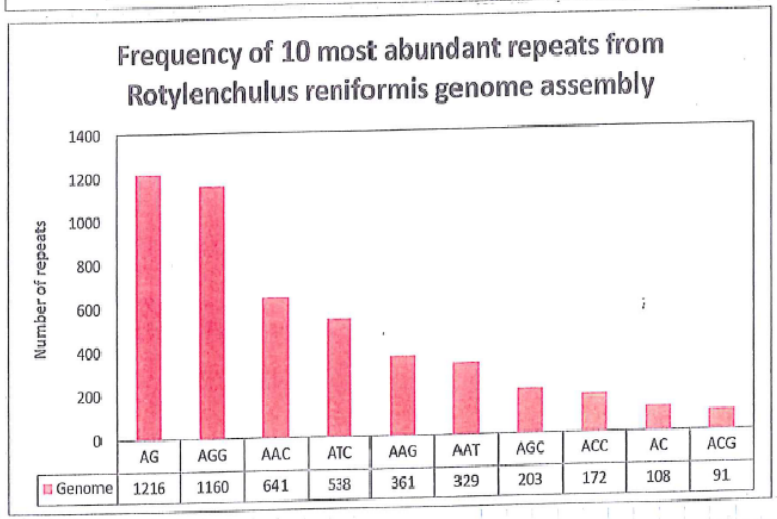
PHOBOS Output on Newest Genome Assembly—
① run PHOBOS, pipe output to file. ② download file, run micro_stats.pl ③ run frequency.pl on micro_stats.pl output file.

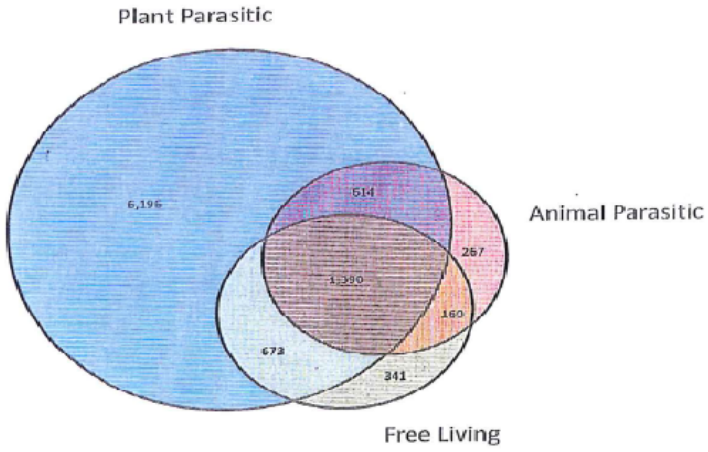
	R. reniformis' [redacted]
Sequence analyzed (bp)	139,677,102
GC Content (in %)	40.16
Number of microsatellite loci	6,055
Average density of loci (no./MBp)	43.35
Total length of microsatellites (bp)	106,630
Coverage (length in bp/MBp)	763.40
Genome content (in %)	0.08

MOTIF LENGTH	1	2	3	4	5	6
No	771	1,334	3,583	335	29	3
No. /MBp	6.41	11.08	29.77	2.78	0.24	0.02
%a	12.73	22.03	59.17	5.53	0.48	0.05
Length (bp)	10,358	26,228	61,226	7,906	814	98
Bp/Mbp	86.05	217.89	508.64	65.68	6.76	0.81

Microsatellite #'s for this assembly seem relatively inline w/ the previous assembly → also [redacted] mentioned that the genome assembly alignment to the reniform ESTs seems comparable to the previous assembly.







- From [redacted] analysis of reniform transcriptome against all the available nematode seqs he was able to identify, download, and classify.

[redacted] needed help with multidimensional sorting in Perl; sent him some example code.

Read up on GIT version control system [redacted]

28-July-2011

[redacted] is going back through the GO Output provided by [redacted], and going to send the GO Group a cutoff of ~e-5 based on a [redacted] recommendation instead of ~e-30 isn based on F recommendation. ** MAY WANT TO CONSIDER SPEAKING AGAIN WITH [redacted], POS GETTING THE DATA FILTERED AT [redacted] CUTOFF ** ~E-15 selected after further di

29-July-2011
(w. [redacted] in Lab)
- Reniform Sample, 33-Cotton Samples ; QuantIt kits [molecule probes] (Invitrogen Quant-IT)
checking concentration w/ fluorescence (Qubit) - Invitrogen Qubit fluorometer

measure quantity of dsDNA before sending it off...>

Cotton to Opcon
Reniform to Roche/454 } Reniform & Cotton within Range for Assay

References

- **GLP Recordkeeping** http://users.stlcc.edu/departments/fvbio/Lab_Practices_GLP_STLCC.htm
- **Good Laboratory Notebook Practice** http://www.mddionline.com/article/good-laboratory-notebook-practice-0
- **Laboratory Notebook Guidelines** http://www.bookfactory.com/special_info/lab_notebook_guidelines_A4.html
- **Advice on keeping a laboratory notebook** http://www.swarthmore.edu/NatSci/cpurrin1/notebookadvice.htm
- **Guidelines for Keeping a Laboratory Record** http://www.ruf.rice.edu/~bioslabs/tools/notebook/notebook.html#entry