SAN FRANCISCO COORDINATING CENTER

Translational Research Bridging the Gap

Steve Cummings, MD

Director, S.F. Coordinating Center



Outline

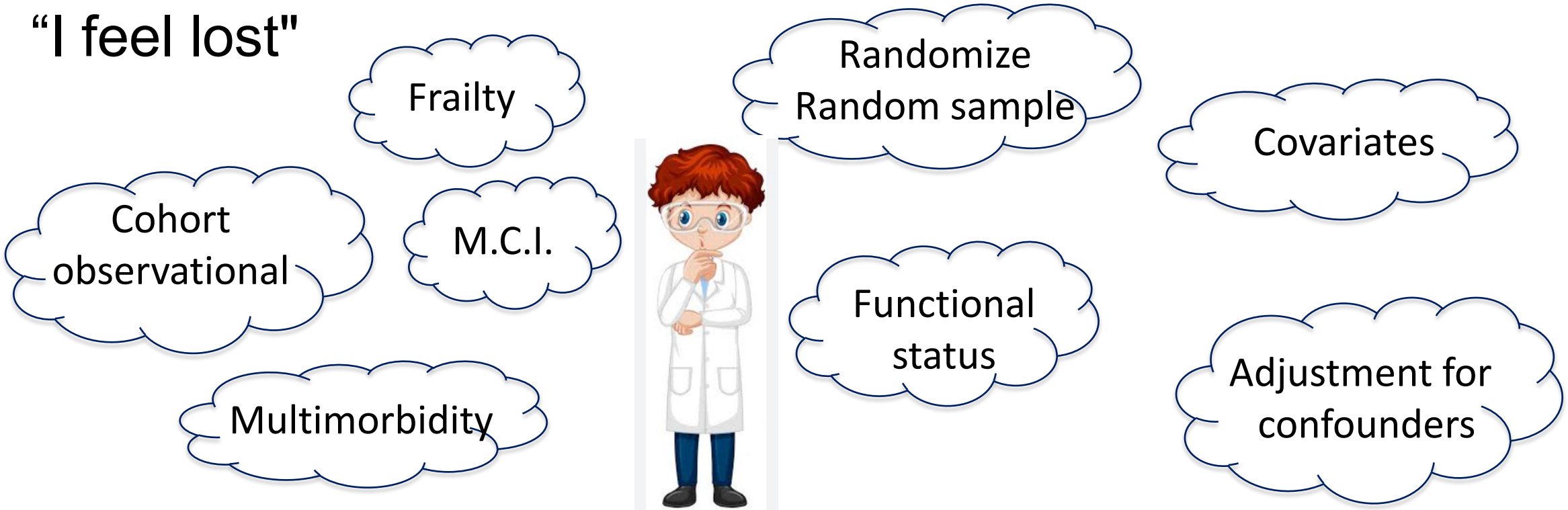
My experience from large cohort studies of aging: gaps and bridges between lab/basic and epi/clinical research

- Views of laboratory / basic scientists
- Views of epidemiologic / clinical scientists
- Differences in language, methods, organization of studies
- A few suggestions

Based on surveying a dozen lab and epidemiology and clinical investigators in aging research

Different languages

- In working with clinical scientists: “The first thing I had to learn a different language… clinical assessments, anatomy, outcomes, analyses… I didn’t know at all.”
- “I feel lost"



Different languages

- In working with lab scientists
- Numerous unfamiliar terms



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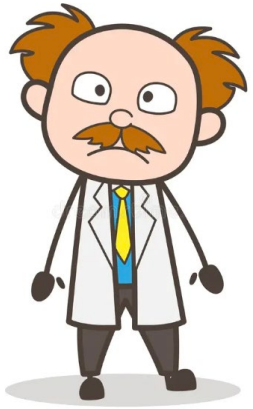
Vector

Wild type

Knockdown

Transfection

Plasmid



Repo



Vehicle control

Lysate

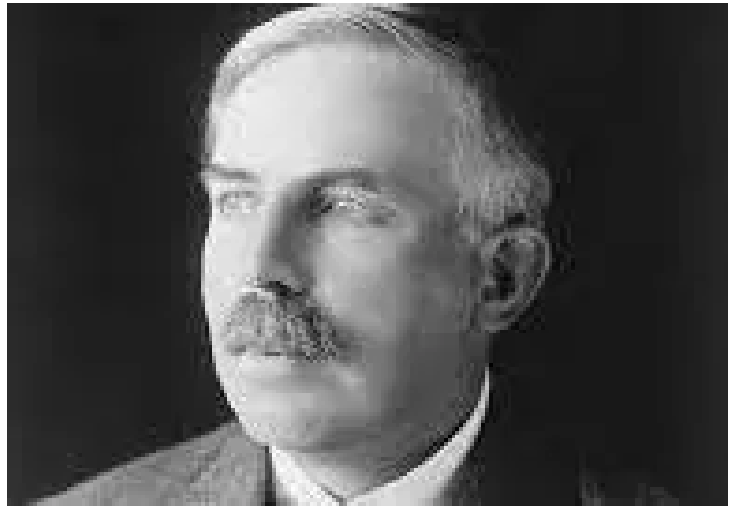
Practices that reinforce the gap

- Go to different meetings (GSA vs. Gordon Conferences vs. Endocrine Society)
- In the same meeting, go to different sessions and poster areas
- Follow news feeds & social media only within their discipline

Different methods: Sample size

- Lab studies – cells and mice – use highly standardized models, e.g. identical mouse strains decrease variance
- Experiments (e.g. knockouts) on molecules and pathways have strong effects
- Small samples reveal important effects
- With no training in statistics, refer analyses to statistician colleagues

"If your experiment needs statistics, you need to design a better experiment"



Ernest Rutherford

Different methods: sample size

Epidemiological studies

- Humans are more variable
- Measurements have variation and large sample sizes generally required to account for variance to detect effects
- Training in statistics is essential to epidemiologic research

Clash

A lab scientist view

- Epidemiologic studies are very large and too expensive
- Consume funds leaving less for real discovery science
- The results are only correlational

An epidemiologist view

- Laboratory studies involve too few observations
- Comparison of extremes are not relevant to complex human biology
- Mouse models do not represent human aging

Example: using the SOMMA biobank

- Basic scientist developed an assay for lysosomal enzymes in EVs
  - Vesicle nanoscopy: affinity isolation with super-resolution microscopy
  - Quantify LC3B & LAMP2: markers of failing autophagy?
- Limited lab time and funds
- Proof of concept in humans
- Test an association with age: 20 old vs. 20 young
  - “We are confident that this is sufficient to find important associations”
- Also correlate with VO2 peak, power, muscle mass

Review by ancillary studies committee

- Epidemiologic review: proposal rejected
  - No sample size
  - Small sample of extreme old vs. young does not allow analysis of anything else but age
  - Recommend: use a larger random sample of the cohort
    - Correlation with age & adjustments for age
- Not feasible

Finding a win-win approach

- Committed to her & novel measurement of autophagy
- Involved a biostatistician with expertise in both worlds
  - Start with *random samples* of old and younger ages (she needs as POC)
  - Add a random sample of intermediate age 20 – 10 – 20, allows exploration of other associations, adjust for age and patterns of change with age
  - For age: power 0.8 for r = 0.33 (greater than comparing means)
  - Correlations with other phenotypes provide pilot data for a grant proposal

Different study cultures

- Laboratory scientists analyze and publish their own results
- Large epidemiologic studies involve systems of analysis plans with internal reviews (including statistics) before data analyses.
- Papers undergo internal review and approval
- Frustrating and annoying for lab scientists
  - Understand the importance for collaboration
  - Provide help

Suggestions

Training and exposures

- Courses for trainees: statistics & basic research methods
- Go to meetings on the other side of the gap
  - Epidemiologists – go to Gordon Conferences
  - Lab scientists…
- In meetings: go to sessions and posters on the other side
- Try a news feeds from the other side of the gap

Engaging laboratory and epidemiologic investigators

- Study leaders recognize that it is an important issue
- Include both laboratory and epidemiologist in study leadership roles
- Offer laboratory scientists assistance with design of ancillary studies and analysis plans, including sample size!
- SOMMA: A Translational Science Interest Group – led by laboratory scientists with topics of interest – new methods
  - Epidemiology and clinical investigators encouraged to attend

Ancillary studies of large cohorts with stored biospecimens

- A good approach to translational research
- Basic scientists bring a new technology or assay
  - Expression LINE1 genes; -omics of EV contents
  - Use archived specimens, images
- Leverage data – from many humans with important outcomes – not possible for laboratory scientists
- Relatively high funding rates
- Often more important results than the Specific Aims

Ancillaries: impact on translational scientists

- Lab scientists learn clinical research concepts and statistics in preparing the proposal
- Epidemiology collaborator learns about the basic science
- They talk to each other, learning language and methods
- They present results in meetings and settings – crossing the translational gap
- The basic scientist becomes part of the study with more colleagues and, perhaps, leadership roles

Summary

- Communicate: learn the other language, translate and talk
- Cross-train in concepts and methods
- Leap across the divide
- Ancillary studies
  - Win-win opportunities to translate

Thank you

- Steve Kritchevsky
- Scientists who provided views and examples



Normal science does not aim at novelties of fact or theory and, when successful, finds none.

— Thomas Kuhn —

AZ QUOTES