# Can "Off-Target" become On-Target? Regulatory Science and Evaluation: from Wonderland to Oz

**The Mad Hatter: "Have I gone Mad?"**

**Alice: "I'm afraid so." "You're entirely bonkers." "But I will tell you a secret." "All the best people are."**

*Jesse L. Goodman, MD, MPH., Professor of Medicine and Infectious Diseases, Georgetown University, @Foundation Merieux, June 10, 2015*

# Overview

- Exciting potential conceptual shift, biology and observations, many opportune for definitive evaluation – as heard here in Veyrier du Lac.
- Are “off target” effects really off target?
- Generating and considering types of evidence
- Challenges, opportunities, pathways forward

# From Off-Target to On

- Off target effects of vaccines (OTEV) really are effects on true target(s), but not the one(s) that led to a product's development – some analogy in drug "repurposing" – but in this case "dual or multi-purposing"
- Analogies exist in vaccine and drug development such as extending an indication to additional, less common or later/longer-term endpoints/populations or the post-approval discovery and labeling of SAEs – and, in fact, OTEV may be harmful SAEs
- OTEV could include specific heterologous effects (e.g. reduce MS flares or RSV cases) and/or more general (e.g. reduce deaths from x diseases in y period after MVI)
  - Changes in distal outcomes are complex/multifactorial, and if not measured in RCTs, very susceptible to confounding

# From Off to Newly On-target cont…

- To consider approval or recommending new broad clinical use, such indications must be clearly defined and postulated benefits proven
- Strengths/weaknesses of study design and evidence will closely resemble those already well recognized in clinical development
- Bottom line: *Many candidate benefits/harms suggested at Annecy could be well tested in adequately controlled and powered trials for new regulatory indications*

# Generating and Considering Evidence

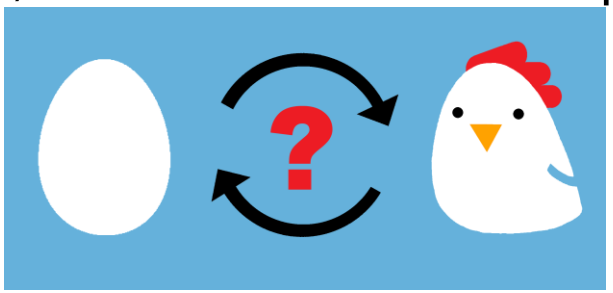
- Biology, including basic science, systems biology and immunology, biomarkers, and models – as regulatory science tools
- Observational data
- Clinical trials
- Whole of evidence approaches

# OTEV: Biology, Biomarkers and Models

- A useful biomarker will be reproducible, measurable and *causally* linked to the clinical endpoint of interest or to a phenotype or intermediate effect which is linked to the endpoint
- Current data on OTEV biology and "biomarkers" preliminary, not yet causally linked to disease phenotypes or outcomes
- Complexity of hosts, biology, candidate biomarkers and systems
- Multiple interacting host regulatory pathways and mechanisms
- Disease models could be helpful to identify both candidate mechanisms and correlates of protection or benefit
- Artificial/*in vitro* systems/network models may be particularly helpful in predicting negative OTEV, optimizing antigens/vaccines for positive ones, and in dissecting mechanisms

# Observational Studies and Causation

- Confounding (failure to recognize/account for factor(s) other than the variable of interest that can affect outcomes) – is *near universal in non-randomized clinical/health studies. Typically leads to overestimated effects.*
- **Confounding can be lead to studies with seemingly strong and reproducible, yet wrong, results**, even w/ dose-response and temporality (e.g. - presence of Starbucks in neighborhoods results in higher income)
- Studying OTEV particularly subject to unique confounding:
  - Patient/provider decisions affecting vaccination and timing may be non-deliberative, unconscious, unexpected and difficult to understand – direction of biases may not always be as intuitively predicted/modeled
  - ID susceptibility a complex, dynamic state subject to many influences
    - e.g. genetics, diet, age, sex, SES, health care, place/type of residence, geography, microbiome, environmental exposures, etc.
  - Such factors make RCTs, caution interpreting other evidence, critical
  - There are approaches in other fields, e.g. econometrics, health services, to *help* address and correct for unmeasured confounding due to unknown variables, and which could be adopted in the life sciences



# Opportunities/Risks in Big Data

- "Big data", and the bringing together of systems biology and clinical data, do create opportunities to identify and study candidate OTEV and mechanisms - just as for SAE
- Caveat - Multiplicity of measures/assays allow one to find, infer and believe in the biological "plausibility" of almost anything
- Utility will primarily be in hypothesis generation and mechanism elucidation to suggest prospective studies
- Ultimately such data systems can also facilitate large simple trials in real world settings


Sometimes I've believed as many as
SIX IMPOSSIBLE THINGS
before breakfast

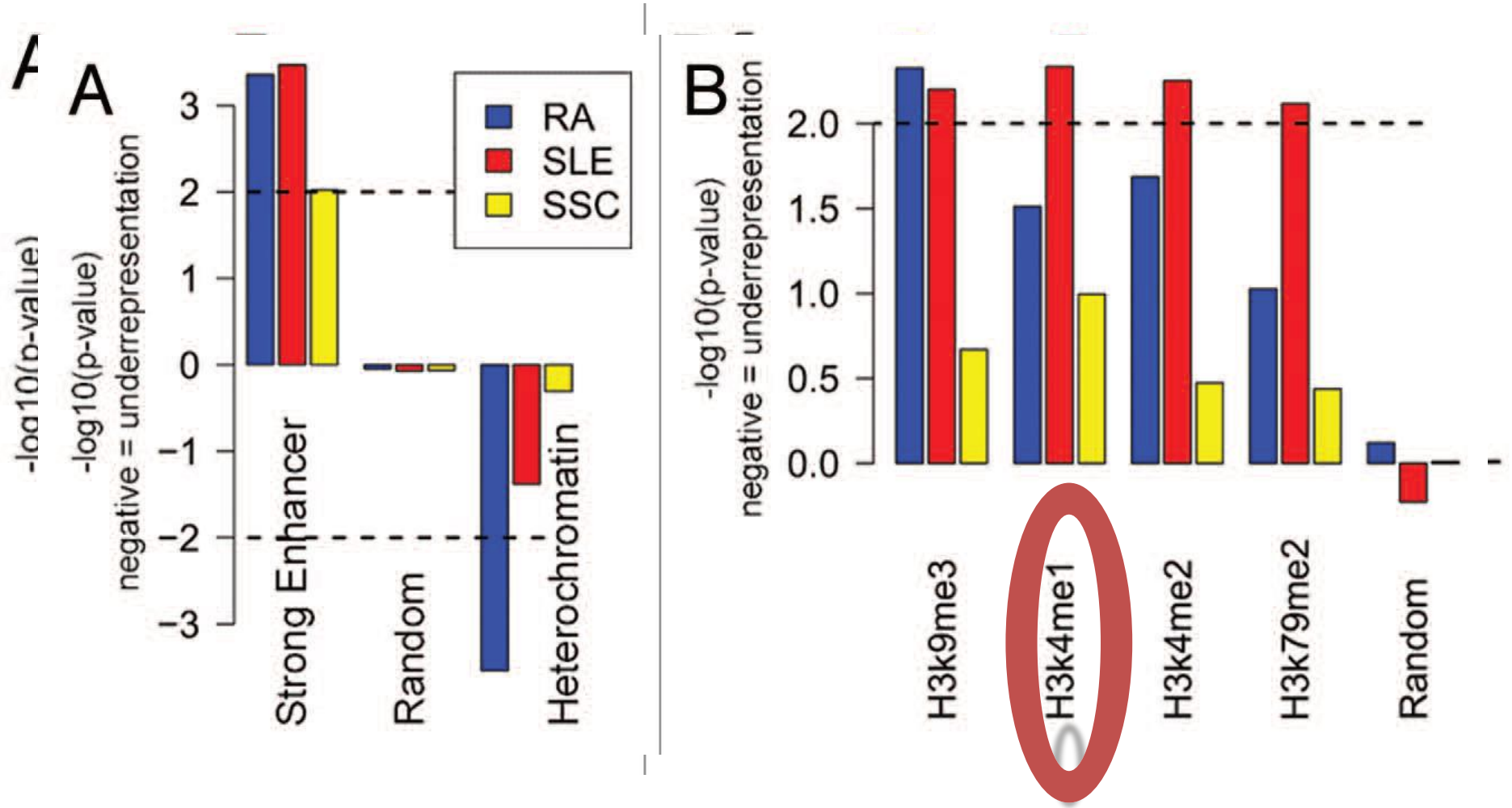
# Clinical Trials for OTEV

- Same principles and hierarchy of quality as for all medical product development; e.g. RCT >>> but other designs may be valid
- Measurable, well ascertained endpoints critical for power & accuracy
  - For multifactorial endpoints (e.g. death), specific data re: cause, temporality etc., will add to power, results interpretation, even in RCT
  - *Any prospective trial is a critical opportunity for biomarker development, specimen banking – attention to assay development, validation, core lab(s)*
  - Potential major differences in sample size needs/costs if estimates of 40-80% effects from observational data correct vs. possible lesser effects
- Given many vaccines of interest are standard of care, placebo controls may be impossible vs. designs comparing timing, vaccine sequencing
  - Cluster randomization, active controls. may be feasible, valid approaches
- Given complexity of host, disease and population factors, generalizability may be challenging, especially when biology not fully understood
  - Can address through multiple RCTs or through multi-regional approaches
  - Common protocols, endpoints, assays highly desirable
- Consult clinical trialists, statisticians, regulatory agencies early, and question all assumptions - including event rates based on historical data

# Challenges: Characteristics of Effects

- Effect size, reproducibility, clinical/public health meaning
- Population/subpopulation effects – generalizability
- Duration of benefit, and is there later reversal/catch-up?
- Specificity/unknown future benefits; e.g. can enhanced immunity provide benefit vs. future/unknown events?
- Unknown future harm: can even specific therapeutic reset(s) of immune regulation pathways be bad?
  - Example: TNF blockers (there is a reason that God, evolution, or both, devised TNF and regulates it complexly as is, witness TB/histoplasmosis)
  - Any change in regulation/development of an evolved immune response likely to have *both costs and benefits*
- Long term follow up likely important for many effects

# E.g.: in theory, could one child's salvation be another's or future epigenetic problem?




From Dozmorov et al Epigenetics 9:2; 276, 2014

# Considering Whole of Evidence

- For OTEV, “ideal” evidence may be difficult to obtain
- May be reasonable/necessary to consider composite streams of disparate types of evidence together:
  - E.g.: clear cut biology/disease models and consistent results across populations with biomarkers, combined with consistent observational data, possibly cohort studies, with at least some adequately controlled and conducted studies in representative populations, even if not “perfect”
  - As in other situations, data gaps and vulnerabilities must be recognized in policy-making and risk communication
  - Post-marketing or post-implementation studies/surveillance may be critical – *if such studies cannot be reliably conducted, and harms of existing policy unclear, policy changes may not be wise*

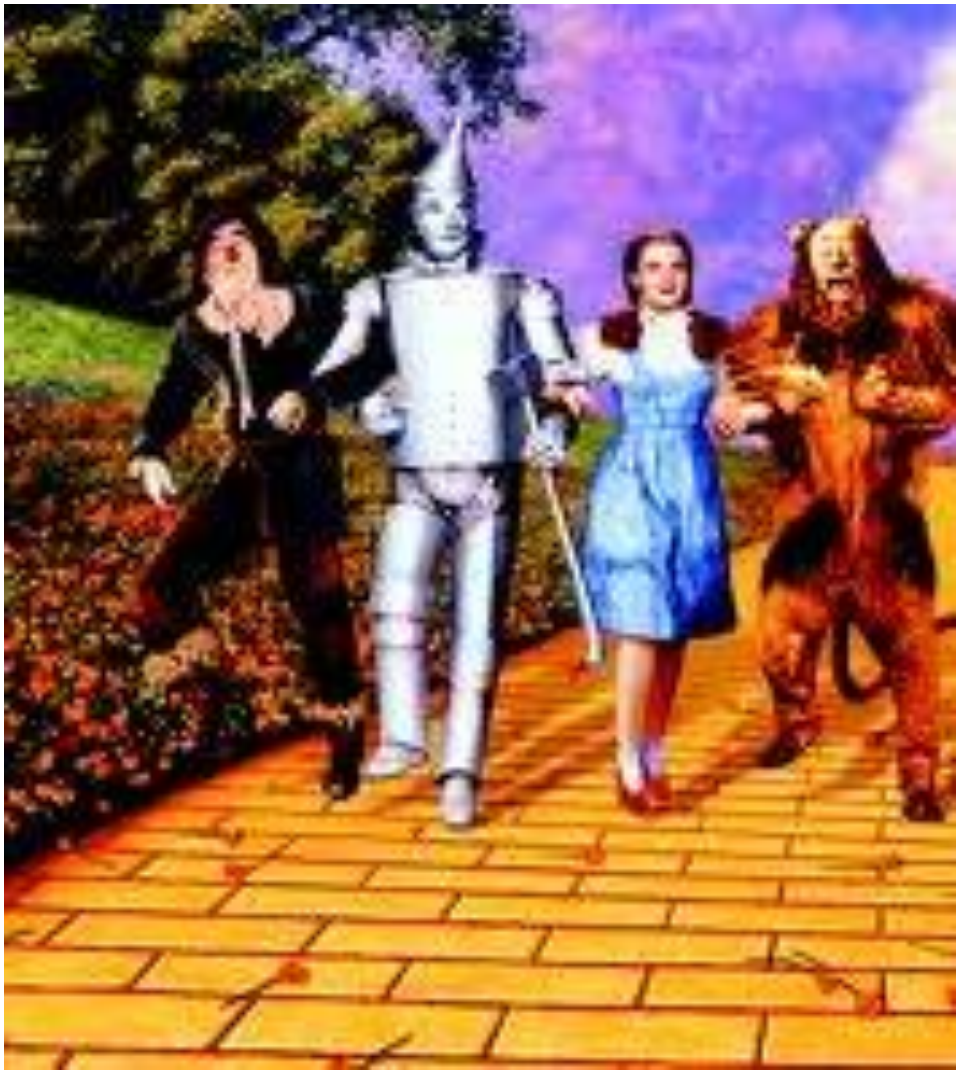

"You had good intentions. Let's find you a nice job paving roads."

# Regulatory Paths to Success for OTEV

- Focus on most important benefits/risks, unmet needs
- Plan RCT(s) with clear endpoints in relevant population
  - Critical opportunities for biomarker development, specimen/sample banking
- US mechanisms:
  - New indication for approved vaccine: clinical supplement to BLA; can rely on CMC, preclinical, safety and primary efficacy info
  - New vaccine: BLA
  - Accelerated approval: if serious and life threatening disorder, inadequate or unavailable approved therapies – can use likely surrogate marker for efficacy – requires Phase IV confirmatory clinical endpoint study

# Opportunities: Ways Forward

- Exciting to consider OTEV
- Current principles of evidence can govern development and evaluation, with flexibility as needed, weighing all data types
- High standards for evidence important given complexity of biology, data and high susceptibility to confounding and the sensitivity of immunization systems/confidence
- Building & testing the science chain from biology to biomarkers to clinical endpoints will help
- With courage, heart ***AND brains***, OTEV may lead to new uses for old vaccines or new vaccines for new uses – and basic insights - a road to Oz, so that future vaccinology may be even better
- Thanks!



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