A 21st Century Paradigm: Immunogenicity Assays Are Biomarker Assays

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Overview

- Reasoning by Analogy vs First Principles Thinking
- Perspective on Immunogenicity Guidance
- What have we learned?
- What we need - 21st Century Paradigm
- Patient perspective
- Conclusions

Reasoning by Analogy is a slippery slope

dangerous, lazy and wrong

Reasoning by Analogy…

- Building knowledge and solving problems based on prior assumptions and beliefs, and perceived ‘best practices’
- Basically, a comparison:
  - You draw a conclusion on an unknown based on its similarity to a known
  - The analogy makes the assumption that since the unknown is like the known in some ways, it must also be similar in other ways

Not Science

Seductive

Feels like knowledge & experience

Don’t stop thinking here!

Reasoning by Analogy…

Or you risk getting it wrong…

Two cars are the same make, model and year; therefore, they must also be the same color.

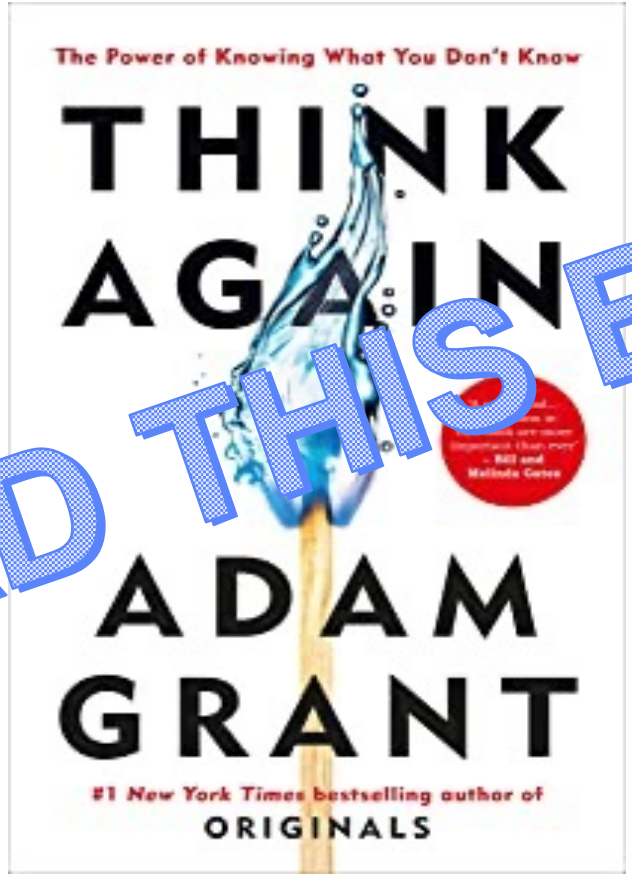
REMEMBER There are *always* differences between the unknown and the known – the closeness of fit between your model and your unknown is what counts

And determining the closeness of fit requires…

First Principles Thinking…

- Actively questioning everything you think you know (or assumptions you have) about a given problem and then creating new knowledge and solutions from the ground up
- Requires willingness to rethink – ensures that you evaluate the differences between the unknown and the known before determining best course

= Doing Science



READ THIS BOOK

Rethinking can be uncomfortable…

Preacher

Protecting our sacred beliefs

Prosecutor

Looking for flaws in others' arguments to prove them wrong

Politician

Lobbying for support

"We get so busy preaching that we are right, prosecuting others we believe are wrong and politicking for support, that we don't bother to rethink our views"

Enter the hero scientist

If you're a scientist by trade…

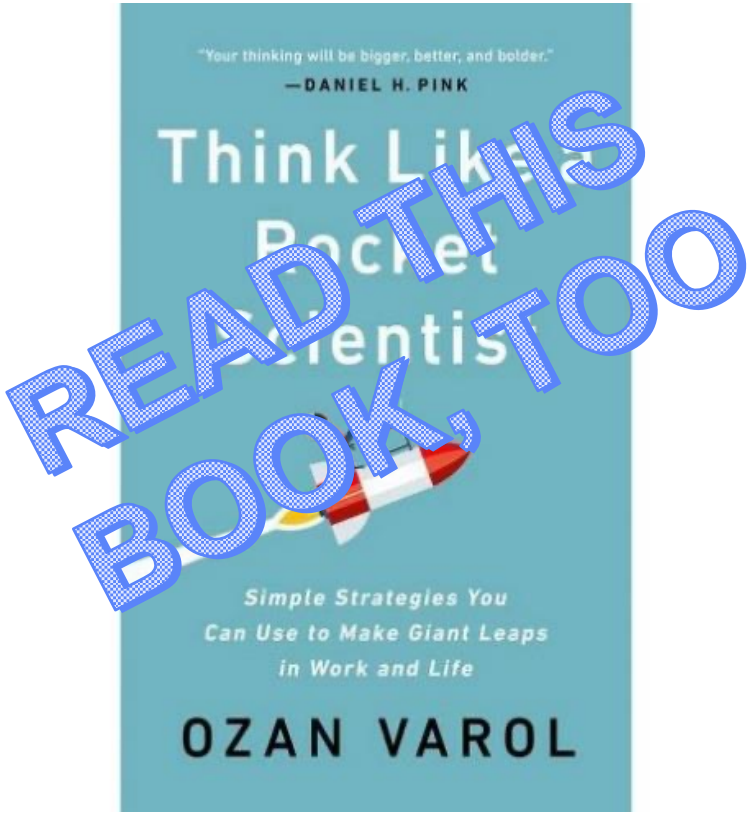
- Rethinking is fundamental to your profession
- You're paid to be constantly aware of the limits of your understanding
- You're expected to doubt what you know, be curious about what you don't know and **update your views based on new data**

- It's not about being right, it's about being incrementally less wrong over time
- Frame of mind = truth seeking
- And it's why we are all here today!

Reasoning by analogy is our

It cripples our critical thinking

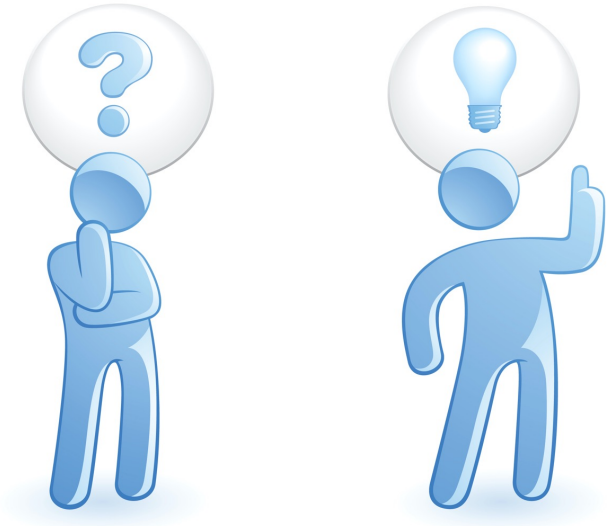
More slippery slopes…



Three key themes

- First Principles Thinking (think like scientist) vs Reasoning by Analogy
- Invisible rules that constrain us (that's how we've always done it) – pot roast
- Nothing fails like (apparent) success
  - Space Shuttle Challenger O-rings
  - Space Shuttle Columbia foam insulation
  - The guidance has worked well so far…

First Principles Thinking



Immunogenicity is a biomarker!

Biomarker Definition

- According to BeST a biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions

- Immunogenicity is a biological response to a therapeutic intervention = **BIOMARKER**

And what do we know about biomarker assays?

We need to understand Context of Use!

Biomarker contexts of use….

Relative quantification assay able to detect 2-fold changes in Biomarker X

Relative quantification assay able to detect 10% changes in Biomarker X

ADA Assay for high-risk protein therapeutic

Qualitative assay to detect trends in levels of Biomarker X

PK Assay
(biomarker of drug administration)

Historical Perspective on Guidance – when we didn’t know what we didn’t know

Immunogenicity Guidance in Context

- More than 2 decades ago…
  - Biotherapeutics were simpler in structure and complexity (e.g. mAbs and recombinant proteins), yet less human(ized)
  - Drug administration was primarily systemic
  - The relative clinical impact of immunogenicity incidence vs magnitude of immunogenicity response was not known
  - It was not well understood what would truly differentiate high vs low risk – manufacturing processes, drug MOAs, etc.
  - Assays were rudimentary, technology platforms developing
  - Alarming safety events had occurred associated with high-risk molecules (EPO)
- Therefore, an approach to sensitively detect and characterize anti-drug immune responses was desirable
- Guidance was written to address this high risk COU – because we didn't know what we didn't know

Immunogenicity Guidance in Context

- The 3-tiered ADA testing paradigm originated from a time where an absence of data necessitated extreme caution

- BUT…historical best effort with limited data does not equate to best practice for all time

#BeAScientist

You're expected to doubt what you know, be curious about what you don't know and **update your views based on new data**

Guidance today reflects history…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2017
EMEA/CHMP/BMWP/14327/2006 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Immunogenicity assessment of therapeutic proteins

The scope of this guideline covers a wide applicability. Thus, the concepts might have to be adapted on a case-by-case basis to fit an individual development programme.

FDA

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2019
Pharmaceutical Quality/CMC

Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection

This guidance may also apply to some peptides, oligonucleotides, and combination products on a case-by-case basis.

Scope of Current Guidance

Even with subsequent revisions, limitations on intended scope are evident

- EMA
  - The Applicants need to demonstrate that the ADA assays are applicable for the demonstration of **clinical correlations of ADAs**.
  - The goal of immunogenicity studies is to investigate presence of an immune response to the **therapeutic protein** and its **clinical impact**. Thus, the evaluation of immunogenicity should be based on **integrated analysis** of immunological, pharmacokinetic, pharmacodynamic, as well as clinical efficacy and safety data.
- FDA
  - This guidance provides recommendations to facilitate industry's development and validation of assays for assessment of the immunogenicity of **therapeutic protein products during clinical trials**.
  - For the purposes of this guidance, immunogenicity is defined as the propensity of a **therapeutic protein product** to generate immune responses to itself and to related proteins or to induce immunologically related **adverse clinical events**.

- Focus is on **therapeutic proteins** and understanding **clinical impact**

But what happened….

- Guidance accepted as gospel and presumed best practice for all contexts
- All therapeutics effectively treated as high risk
  - Everything automatically goes to 3-tiered analysis
  - So-called risk assessments focused on Nabs (thanks to ERG)
  - Nab assays for all assets – not a matter of if, but when
- Additional scope creep
  - Preclinical studies [illegible] alities, including some non-biologics!
  - Blanket application of 3-tiered approach for modalities, questions and goals that guidance was never intended to address
- Believing (or hiding behind) ‘It’s the only guidance we have, so we have to follow it’
- Driven by fear, not science

Reasoning by Analogy

Rethinking - What have we learned? (what we now know)

Reasoning by Analogy has been costly

Treating everything like it is high risk and blindly applying, misapplying, over-applying the 3-tiered approach has resulted in…

- High sensitivity assays developed in instrument noise – screen and confirm CPs lower than assay analytical variability – many believing more sensitive assay = better assay
- High incidence of detection of low-level ADA that do not correlate with clinical impact
- Excessive testing (screen, confirm) in preclinical studies to detect ADA that do not meaningfully inform interpretation of data
- Time, money and resources to develop and validate Nab assays for **all programs** even when clinical impact of Nab was non-existent or detectable by other means
- Expectations from regulators focused on set criteria (sensitivity, drug tolerance) regardless of context
  - e.g. PMRs for assay 'improvements' even when the study results and interpretation will not change
  - High cost for the drug program without value added for patients

Not Good Science

Reasoning by Analogy has been costly

MORE TIME

- Spent educating leaders and BODs who fear immunogenicity incidence and don't consider clinical impact
- Spent with sponsors who want to discard study data and retest with a 'new assay' to eliminate low positives with no clinical impact

MORE MONEY

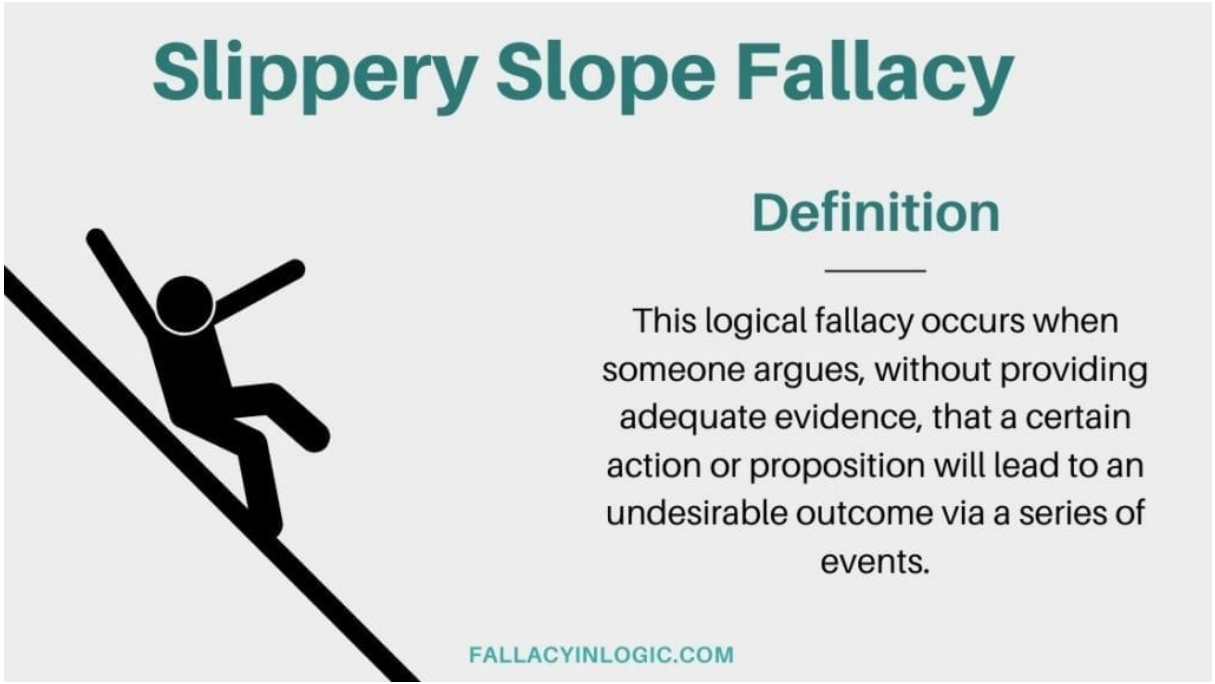
- Spent on experts who propagate the fear – "Regulators expect…"
- Spent on different experts to dispel the fears (but still being afraid)
- Spent on analyses that do not add value

MORE RESOURCES

- Scientists afraid to think like scientists – internal and external backlash
- Even worse - Scientists not taught to be scientists, but
  - To follow guidance without thinking
  - To believe that expertise = knowing how to do things, not why
- = Lost resources

Another (tough) lesson learned…

The slippery slope fallacy is real…



…but it is not Science

It's for patient safety!

It's in the guidance!

We've always done it this way!

We need to see more data!

It's for patient safety! But I can't explain how it will affect any patient level decisions or outcomes.

It's in the guidance! But I have no scientific rationale to support it.

We've always done it this way! But we never asked why.

We need to see more data! But we don't know how much.

Some critical things we now know

- Even for traditional protein therapeutics, the 3-tiered approach does not provide commensurate value for low vs high risk molecules
  - Risk assessment should determine which evaluations will provide value
  - Do not add tiers if commensurate value is not added
- ADA testing in preclinical studies should be implemented on a case-by-case basis
- Confirmation tier is not orthogonal – its value is therefore limited
- Titer and S/N correlate (and we should not assume the former is better than the latter)
- More sensitive assay ≠ better assay
- Assay that reliably detects clinically meaningful responses = better assay
- PC ≠ individual ADA response (Biomarker assay reference material ≠ endogenous analyte)
- Drug tolerance needs to be understood in context
- Applying current guidance to new modalities is misapplication and risks not delivering the data sets required to address critical questions

Good Science

Rethinking: Let’s Be Scientists!

A 21st Century Paradigm…

- Needs to address…traditional modalities, new modalities and yet to be imagined modalities
- Must robustly evaluate risk – not assume everything is high risk
  - High risk, low risk, no risk…
  - e.g. Peptide drug with 30-minute half life
- Focus on clinical impact and value add
  - What would the clinical impact of immunogenicity look like?
  - What is the most effective way to evaluate that impact?
  - How will any patient level outcomes or drug development decisions change?
- Must have the flexibility to address new questions
  - e.g. When immunogenicity is a ‘good’ thing for therapeutic efficacy
- In short, it must be able to accommodate ever-expanding COUs

Immunogenicity assay contexts of use….

Detection of pre-existing ADA to viral capsid

Detection of ADA to transgene product

Detection of ADA that affects drug exposure levels

Detection of ADA/Nab that cross-reacts with endogenous counterpart of Tx

Detection of ADA to vector that enhances delivery to target

Detection of very low levels of ADA with no clinical impact?

How do we approach this new paradigm?

Lessons from biomarkers

#BeAScientist – starts with an open mind

- First Principles - imagine a world where there is no existing guidance
- Imagine a risk-based thought framework that is flexible enough to capture countless COUs
  - Focus on key questions, understand your COU, design your assays to address that COU
- Some starter questions – to ensure you're adding value
  - What is the risk of your drug from perspective of **clinical impact** of immunogenicity?
  - What do you need to understand and why? Is it about safety, or efficacy, or something else?
  - What would the clinical impact of immunogenicity look like?
  - What is the most effective means to evaluate/measure that impact?
  - What other data sets (e.g. exposure, PD) will inform your understanding?
  - How will the impact be mitigated, if needed, and when?
  - How will any drug development decisions or patient level outcomes change?
- Build your assay or suite of assays to address these questions (COU)
- Accept that there is no single, magic approach to suit all COUs – thinking is requisite
- *'Better to be uncomfortably uncertain than comfortably wrong'* – Ozan Varol

Remember the patients

What do patients need?

- Beyond the 3 R's (Replacement, Reduction, Refinement)
- 4th R - ROI for patients
  - Everything we do (industry and regulators alike) should be justifiable to a patient
  - Without value added, doing more ≠ better or safer
  - All of the time, money and resources we expend on non-value-added efforts = wasted time, money and resources
  - The 21st Century Cures Act insists we do better – bring life-saving/life changing therapies to patients efficiently and cost effectively
- 5th R – Rethink Regularly

Historical best effort with limited data ≠ best practice for all time

What do patients deserve?

#BeAScientist

Conclusions

- Guidance and 3-tiered approach was established to address one COU (high risk protein therapeutics)
- Reasoning By Analogy is our kryptonite
- Rethinking is requisite = First Principles
- Immunogenicity is a biomarker!
  - Immunogenicity assays are biomarker assays
  - Know your COU
- Avoid misguided guidance – a paradigm for the 21st century requires a Thought Framework
- Patients need and deserve heroes

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Thank you!

IMMUNOLOGIX

LABORATORIES

Designed by Scientists, Run by Scientists

backup

How Science Works...

We did not get from flat earth to round earth by round earth demonstrating flatness

Instead, we just continued moving forward…and didn't fall off

Flat earth may have seemed to get the job done for small journeys (= limited data set)

But there were journeys flat earth never imagined

Don't settle for small journeys

Dare to imagine, rethink, and even understand, what we may not yet see

#BeAScientist