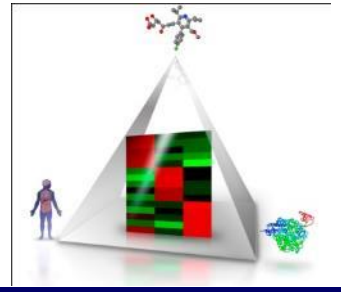
# Artificial Intelligence in Drug Discovery 2022 – Aspects of Validation, Data, and Where We are on the Hype Cycle

Andreas Bender, PhD
Natural Philosopher for Molecular Informatics
Department of Chemistry, University of Cambridge

Chief Scientific Officer, Terra Lumina, Berlin

Co-Founder of Healx, Ltd. and PharmEnable, Ltd.

UNIVERSITY OF CAMBRIDGE



Any statements made during this talk are
in my capacity as an academic

Further reading: Artificial Intelligence in Drug Discovery – What is Realistic, What are Illusions? (Parts 1 and 2)

Andreas Bender and Isidro Cortes-Ciriano

*Drug Discovery Today* 2021

# Contents

1. Current state of AI in drug discovery

2. How do we know that a method *works*? What is ‘validation’?

3. The Achilles heel of AI in drug discovery: data & proxy assays

4. Psychology, the hype cycle & the translational gap of methods

5. OK… and now?

# 1. Current state: The 3rd wave of computers in drug discovery (80s, 2000, today) – time for realistic assessment has come

Fortune cover 1981

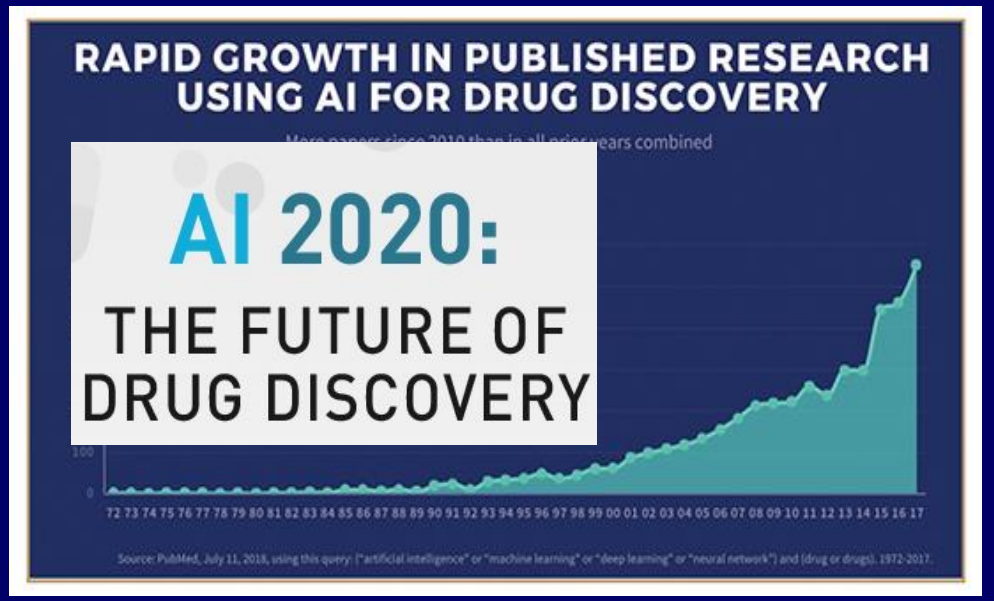

Recent headlines (2018-2020)

SPOTLIGHT · 30 MAY 2018

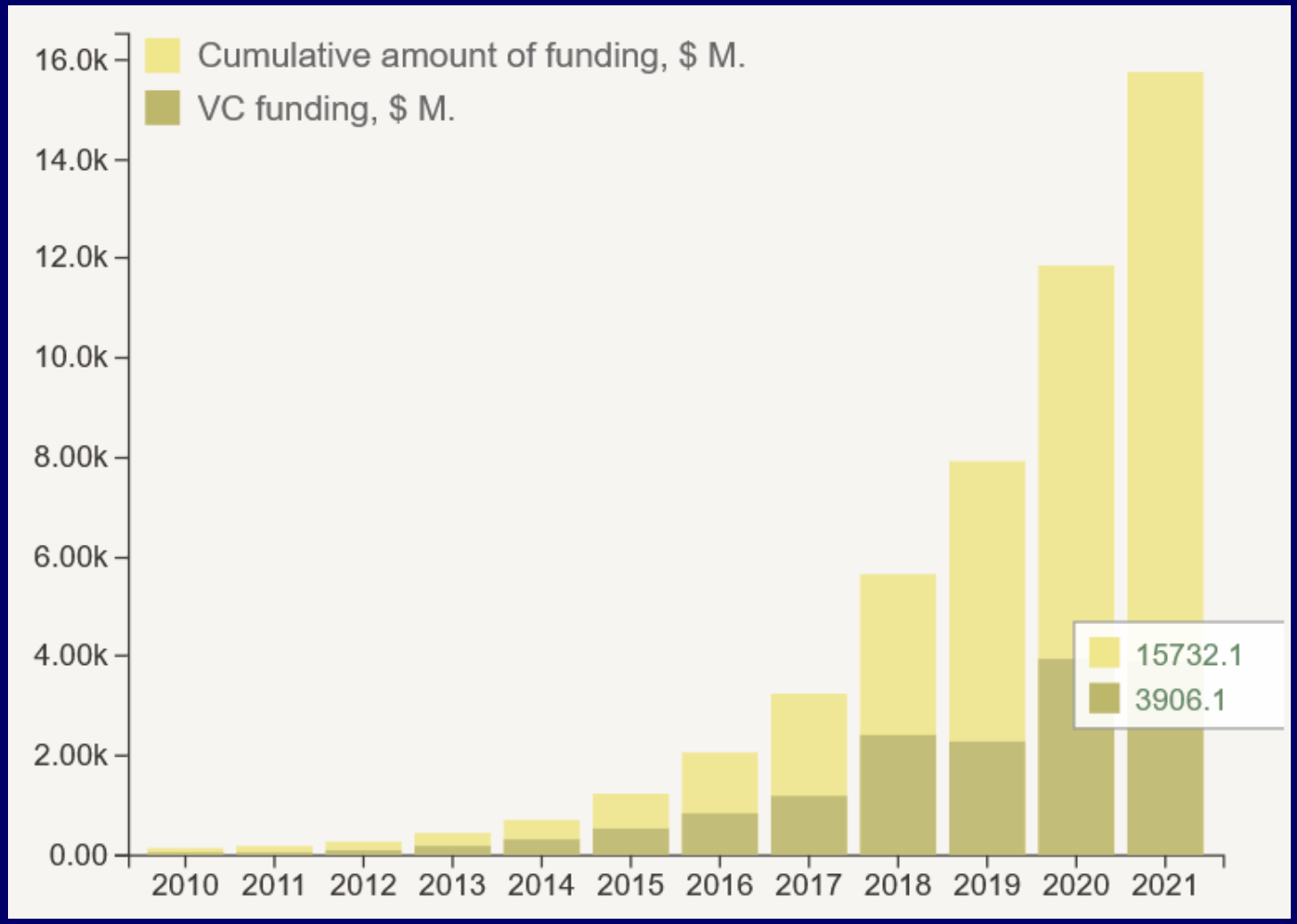
**How artificial intelligence is changing drug discovery**

World first breakthrough in AI drug discovery

By **Emma Morriss** - January 30, 2020



# Funding going into AI in drug discovery until 2021: ~$4bn VC funding, $16bn total (*very approx.)*



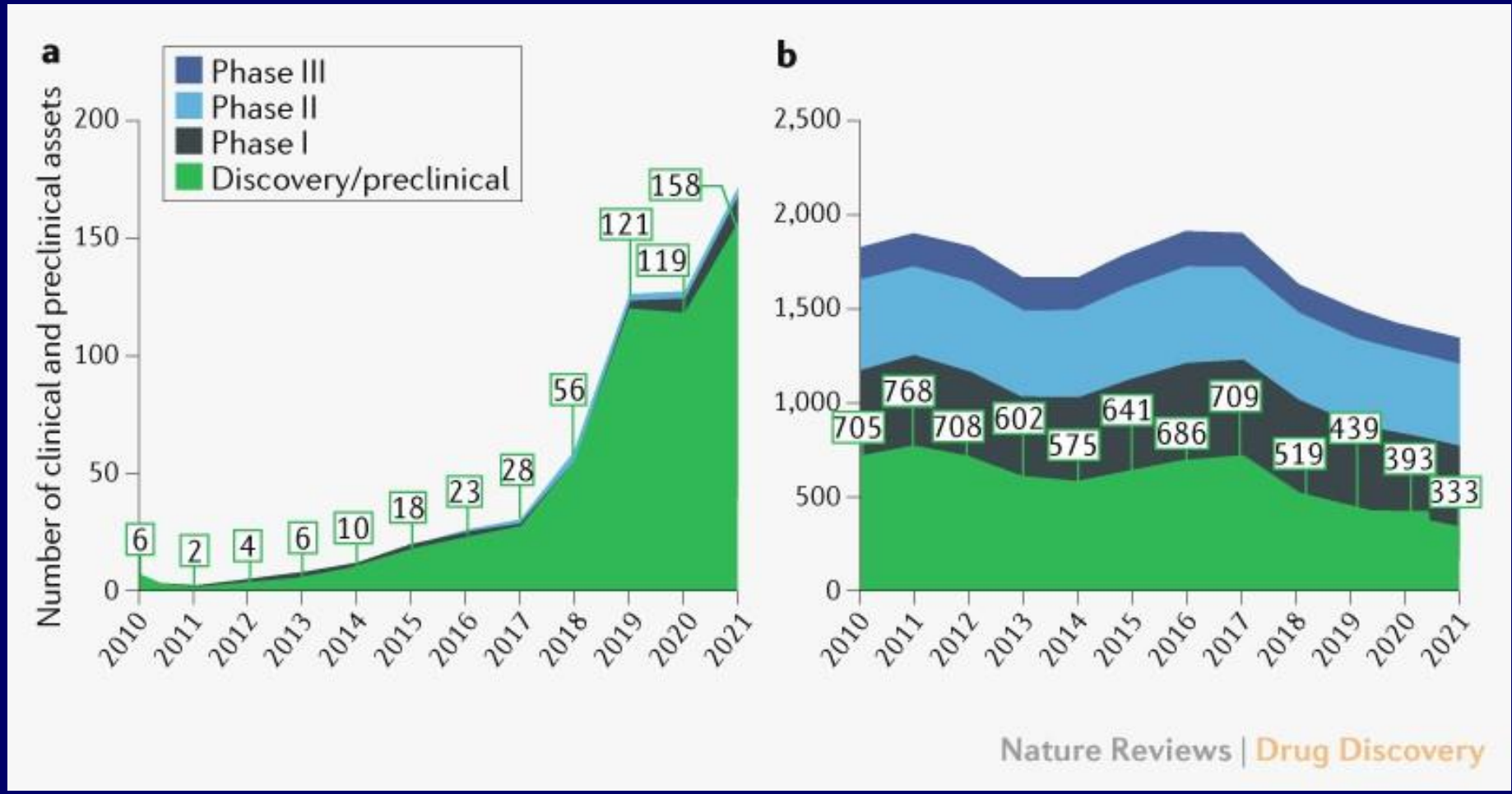

https://www.biopharmatrend.com/post/397-pharmaceutical-artificial-intelligence-in-2021-key-developments-so-far/

# Current discovery pipeline: AI-based start-ups vs big pharma

‘AI-native companies’ Top 20 pharma

Significant *number* of *discovery/ preclinical* programs of AI companies (~160 vs ~330)

Very little Phase 1, less Phase 2, no Phase 3



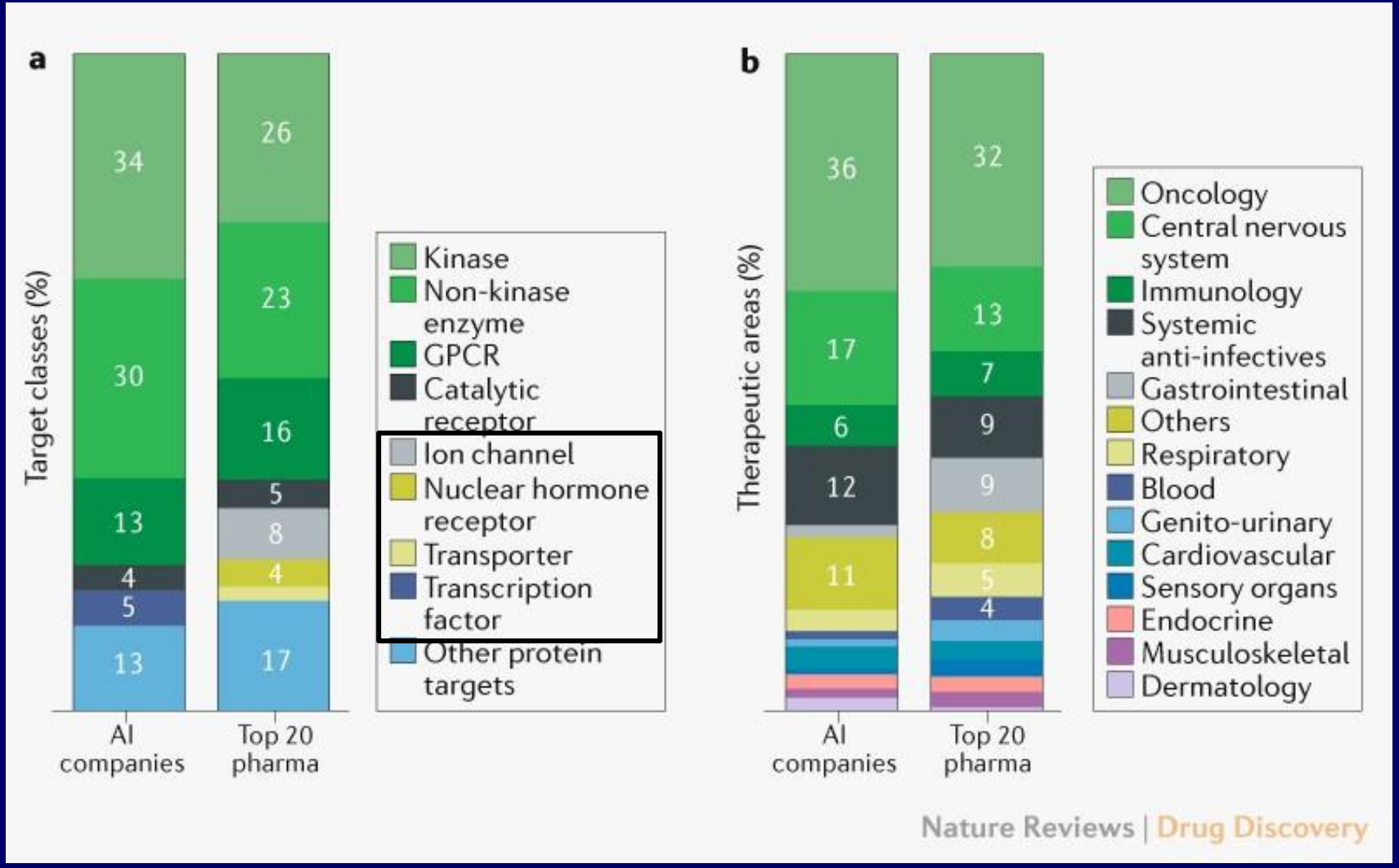

-> Little *in vivo* safety (Phase 1) data *yet*; virtually no *in vivo* efficacy (Phase 2/3) data *yet*

Jayatunga et al., AI in small-molecule drug discovery: a coming wave? *Nature Reviews Drug Discovery* 7 Feb 2022

# Distribution of target profile similar, but focus on areas of more data, less complex target pharmacology

More kinases and enzymes in AI-driven companies:
(a) Quite *data-rich*
(b) Less complex pharmacology than other target classes

+ Transcription factors
- No ion channels, NHRs and transporters




Jayatunga et al., AI in small-molecule drug discovery: a coming wave? *Nature Reviews Drug Discovery* 7 Feb 2022

# Conclusion about the world as it is

- Lots of activity in early stage pipeline of AI-first companies, but often already explored targets, close analogues
- Appropriate question to ask: Where is the novelty?
- Data is often limiting factor – in both chemical and target space (leads to work on well-explored targets, with more data, less complex pharmacology)

- Is *input* (e.g. funding) success, or *output*?
- The first ‘AI-designed drug’ will be celebrated by the media, but…

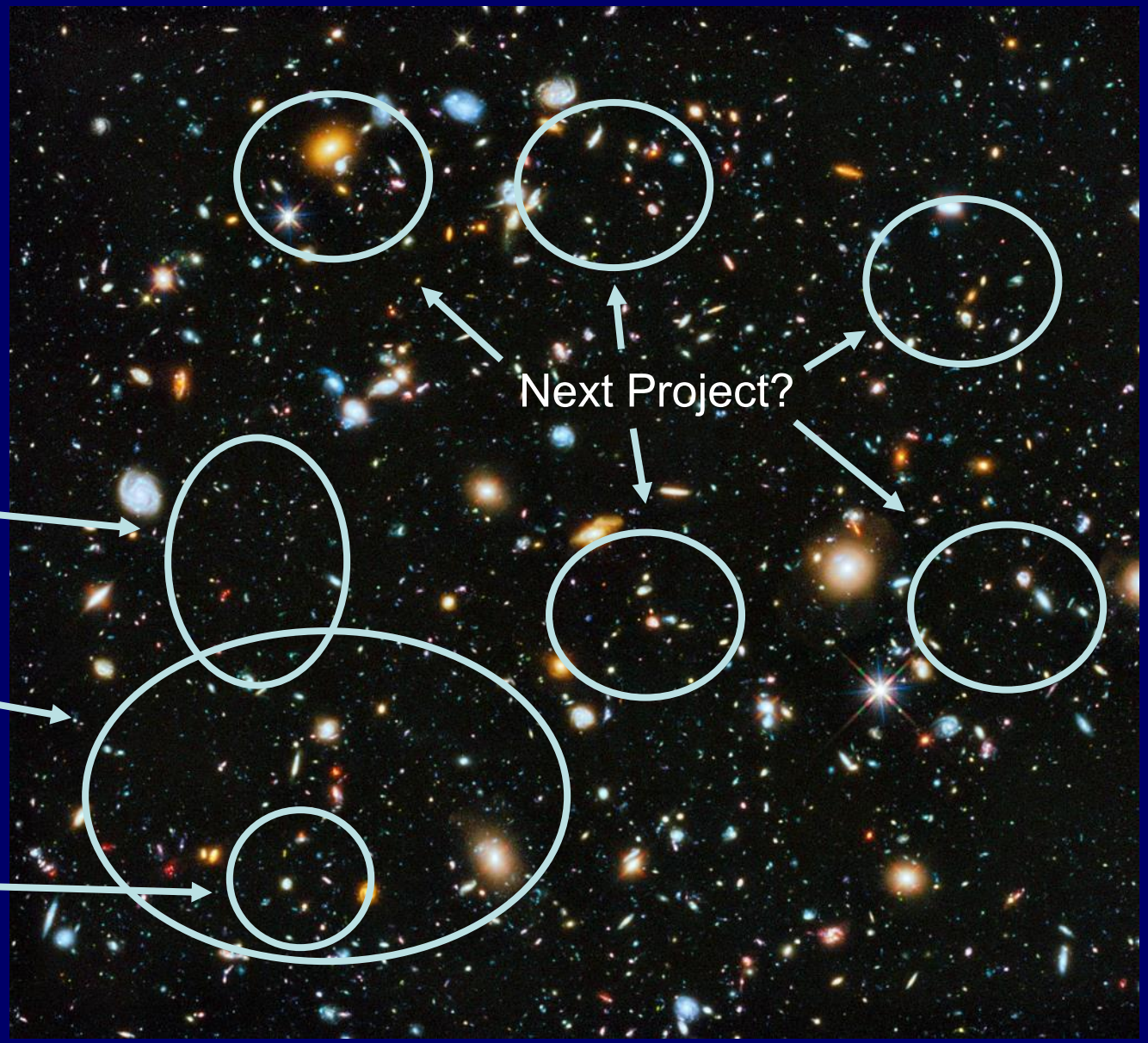
… tens of billions went into funding AI in drug discovery, so even the null model would lead to an expected tens of approved drugs

# 2. How do we know that something *works*? What is ‘validation’?

- Core question in science, core question for start-ups
- In *theory* we establish a method, use a benchmark, and know how well the method works
- In *practice* this doesn’t really work in *drug discovery* –
  - Labels are either mostly only *in vitro*-relevant, or conditional (‘depend’ on dose, *etc*)
  - Validation is costly (phase II studies for efficacy; *plus controls*), so *little prospective data*
  - Difficult to sample distribution in chemistry/’project’ space well (diversity, number), so performance *depends heavily on test set*
- Retrospective validation is (nearly) equally futile (no prospective discovery, predictivity for future projects unknown, all behave differently)

- *Core reasons for problem: In chemical space proper sampling impossible, underlying distribution unknown; conditionality of in vivo data*

# Why ‘validation’ of a model has little value: You get the numbers you want (depending on the question you ask/data set you use)




- Chemical space is large; data sets are small
- Model is unable to generalize to unseen spaces

- ***Numerical distances mean something different in different areas of chemical space***

- *‘If you go **10m (Tc, model score)** from **a bridge (active compound[s])**, you… can be in lots of different places!’*
- “Every model is a local model”

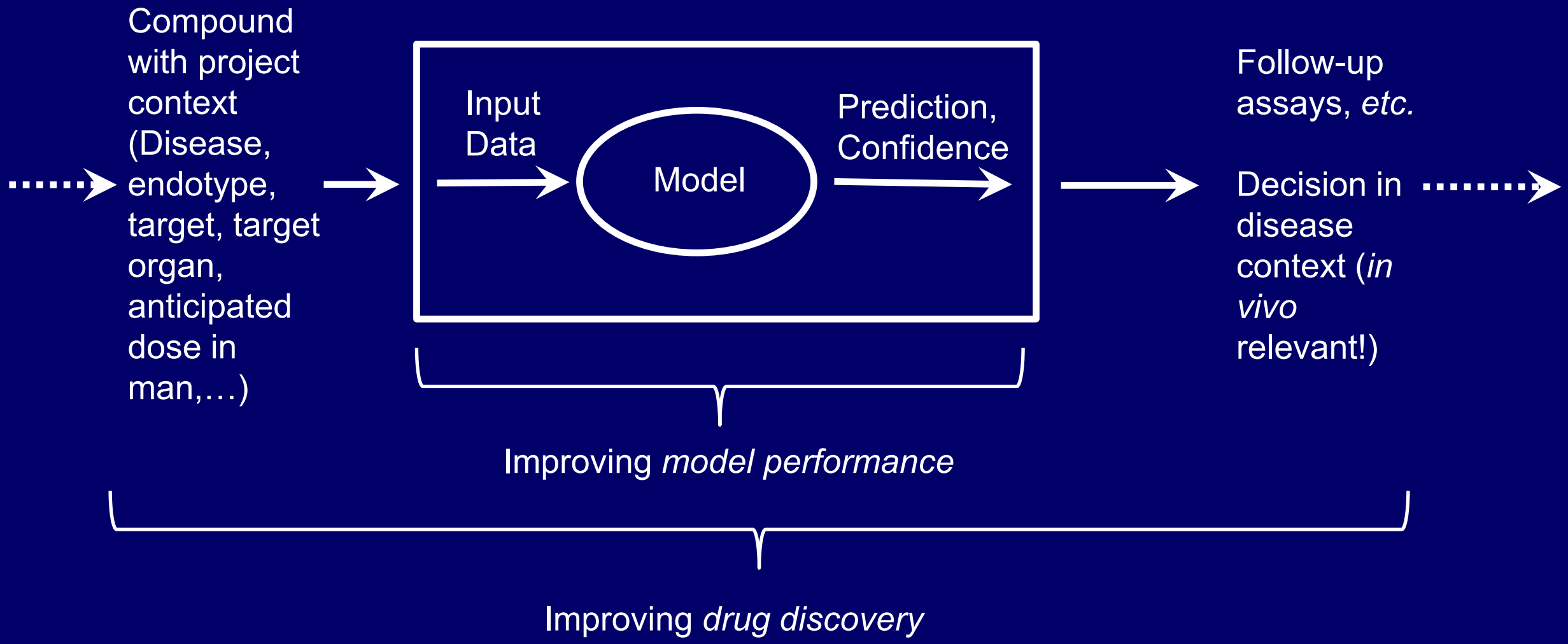
# What to watch out for in validation – and why the model, *embedded into the process* matters

- ‘Proof by example’ abounds, without baseline
- Irrelevant endpoints abound (numerical improvements, endpoints that don’t directly translate into *in vivo*-relevant decision making)

- *Validation that matters* includes the *process and not only the model* in the validation (!)
- Related: What is the role of the human in the process? Hardly ever properly described in press releases/related material

- Further discussion of model validation in my blog:
  http://www.DrugDiscovery.NET/HowToLie
- Nature Reviews Chemistry article on ‘validation’ appearing shortly

# Model validation vs process validation (e.g. ligand structure-based property predictions)



# Conclusion: So *did* AI contribute something to drug discovery?

- Probably in some areas yes (e.g. target prediction, digital pathology, …), but very difficult to quantify related to *process*
- After ~$20bn VC funding into AI in drug discovery we *better see some successes*!

… always good to ask this crucial question:

"It works in practice, but does it work in theory?"

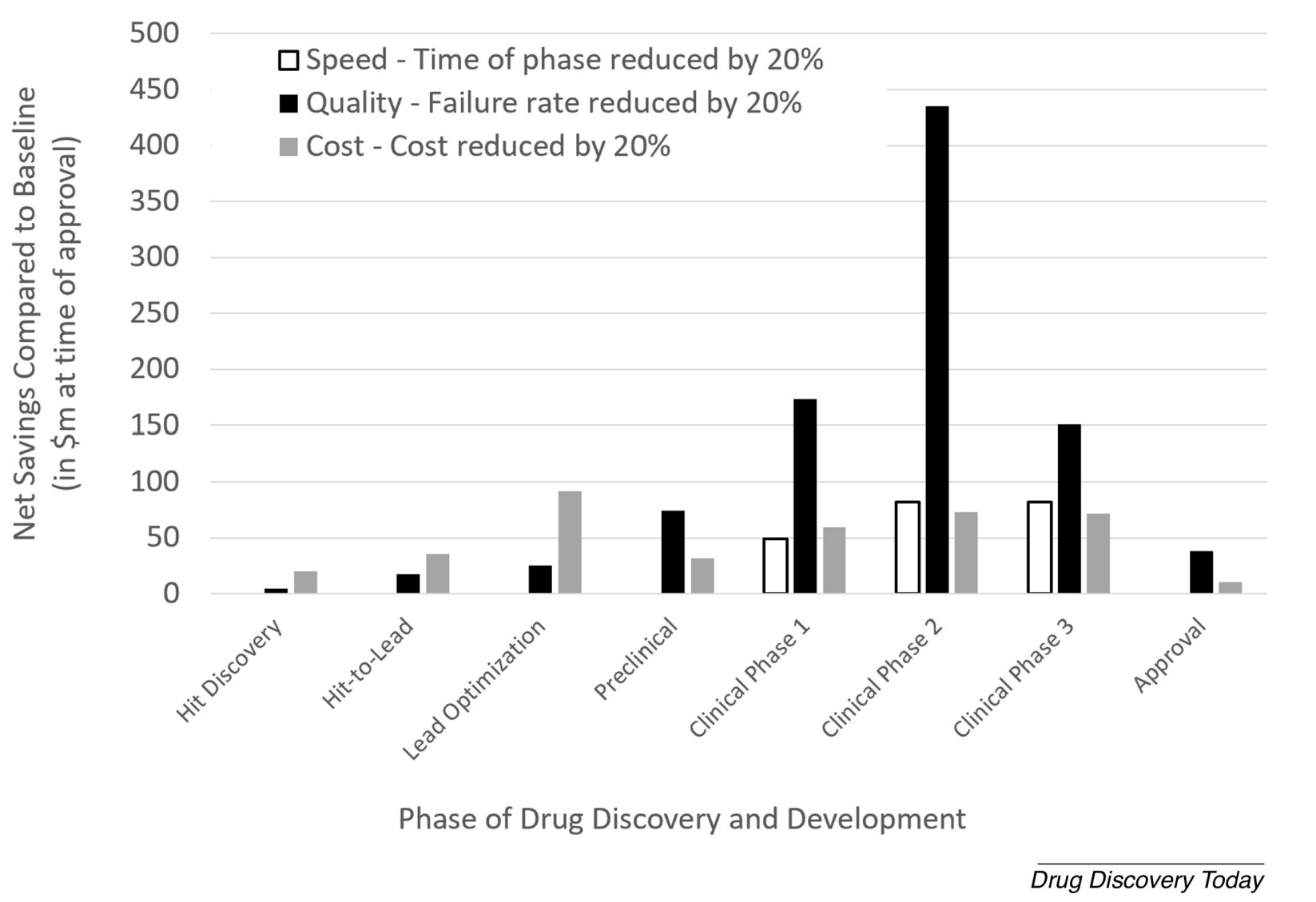
… but of course, the wise (wo)man knows:

"The difference between theory and practice is bigger in theory, than in practice"

# 3. The Achilles heel of AI in DD: Data and proxy assays

*“…it’s the data, stupid!”*

# The *quality* of *in vivo-relevant* decisions matters more than *speed* and *cost*!



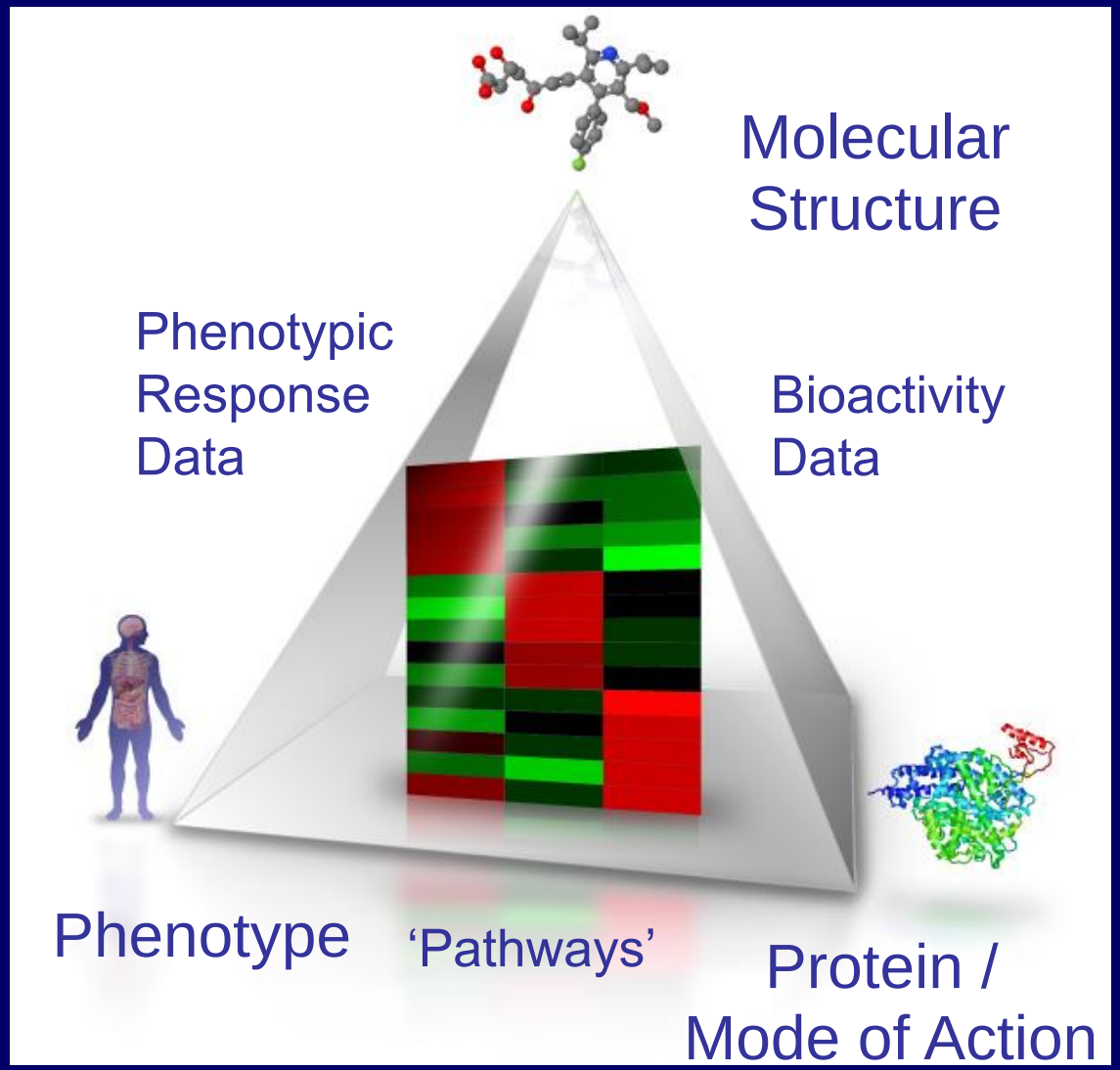

Bender and Cortes, Drug Discovery Today 2021

# *In vivo*-relevant decisions matter most!
# But… is this where our *data* for models is?

- Chemical and biological data: The flat-earth (~‘in vitro’) view
  - And where a flat earth is great!
- Chemical and biological data: The round-earth (~’in vivo’) view
  - Drug discovery data and its complexity (... the elephant in the room…)

- Why algorithms from image and speech recognition don’t really translate to *drug* discovery

# A simple view on the world: Linking Chemistry, Phenotype, Targets / Mode of Action (myself, until *ca.* 2010)




a.k.a. "The world is flat"

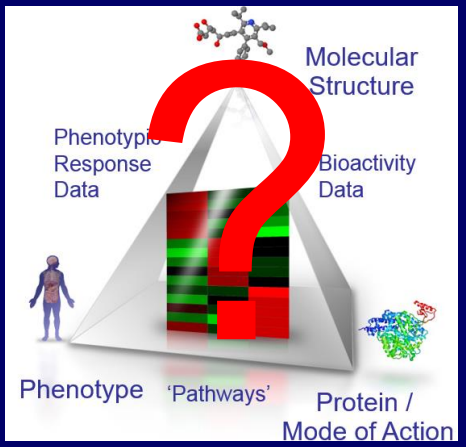
= "We believe our labels"

"Compound A is toxic",
"Compound B binds target X",
"Compound C treats disease Y", …

Works in cases where data is large-scale, and homogenous, and we have meaningful labels

Does not consider data conditionality, e.g. dose, PK, translatability from model system to *in vivo* setup, endotype, genotype, *etc. etc.*

# BUT…The world is not flat. What now?




- Links between drugs/targets/diseases are quantitative, incompletely characterized
- Subtle differences in eg compound effects (partial vs full agonists, off-targets, residence times, biased signalling, etc.)
- 'Pathways' from very heterogenous underlying information; dynamic elements not captured etc.
- Effects are state-dependent (variation between individuals, age, sex, co-medication…) – PK is often rather neglected in AI approaches
- Phenotyping is sparse, subjective (deep phenotyping?)
- We don't understand biology ('the system'), we don't know what we *should* label, and measure, hence …
- We label what we *can* measure: 'T*echnology push*' vs '*science pull*' (!)
- **Are our labels – 'drug treats disease X', 'ligand is active against target Y', … - meaningful?**
- **Conditionality: Causality, confidence, quantification, ….?**
- **Computer science is tremendously powerful… but is our data?**

# Example of conditional labels: adverse reactions

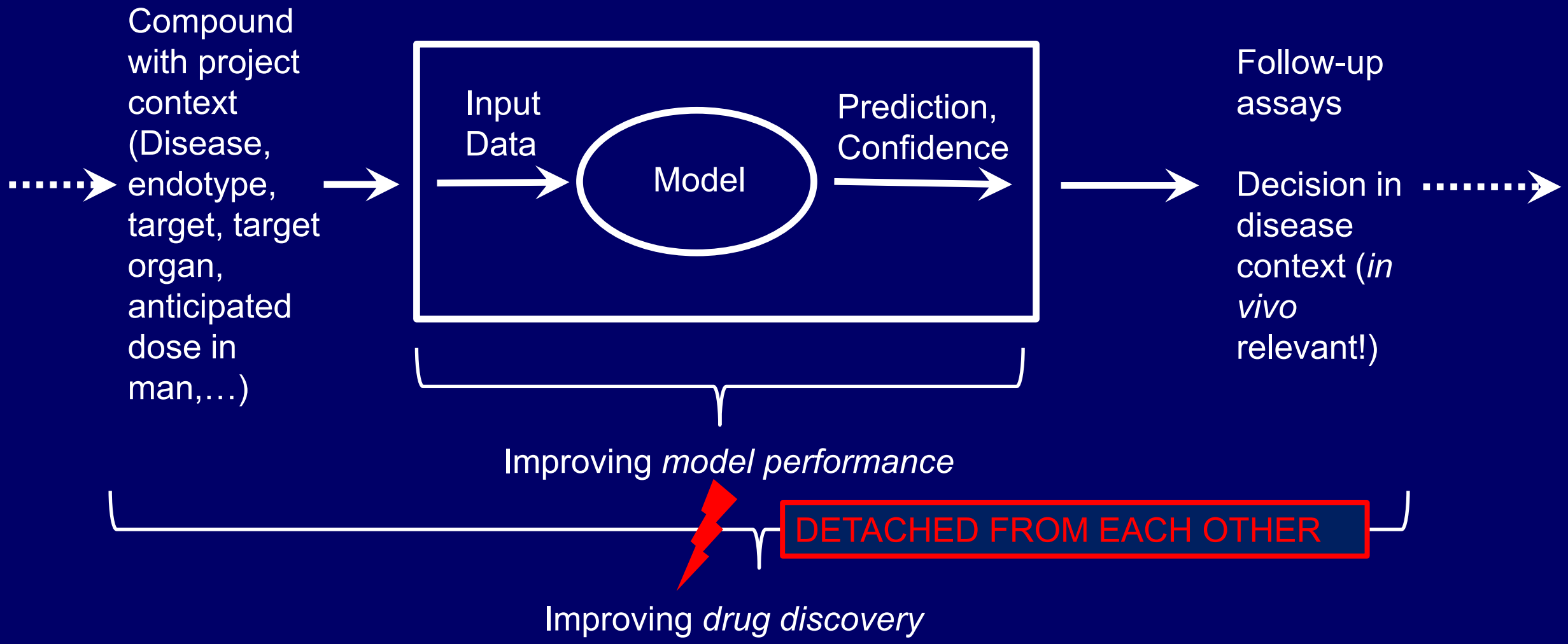
- **“*Does* drug Y cause adverse reaction Z? Yes, or no?”**
- Pharmacovigilance Department: Yes, *if* we have…
  - A patient with this *genotype* (which is generally unknown)
  - Who has this *disease endotype* (which is often insufficiently defined)
  - Who takes *dose X* of *drug Y* (but sometimes also forgets to take it)
  - With known targets 1...n, but also unknown targets (n+1…z)
  - Then we see *adverse reaction (effect) Z* …
  - But only in x*% of all cases* and
  - With *different severity* and
  - *Mostly if co-administered with a drug from class C*, and then
  - More frequently in *males* and
  - Only *long-term*
  - (Etc.)
- **So – does drug Y cause adverse event Z?**

# Much of the data we have has been generated with proxy assays. Why is this a problem for AI in drug discovery?

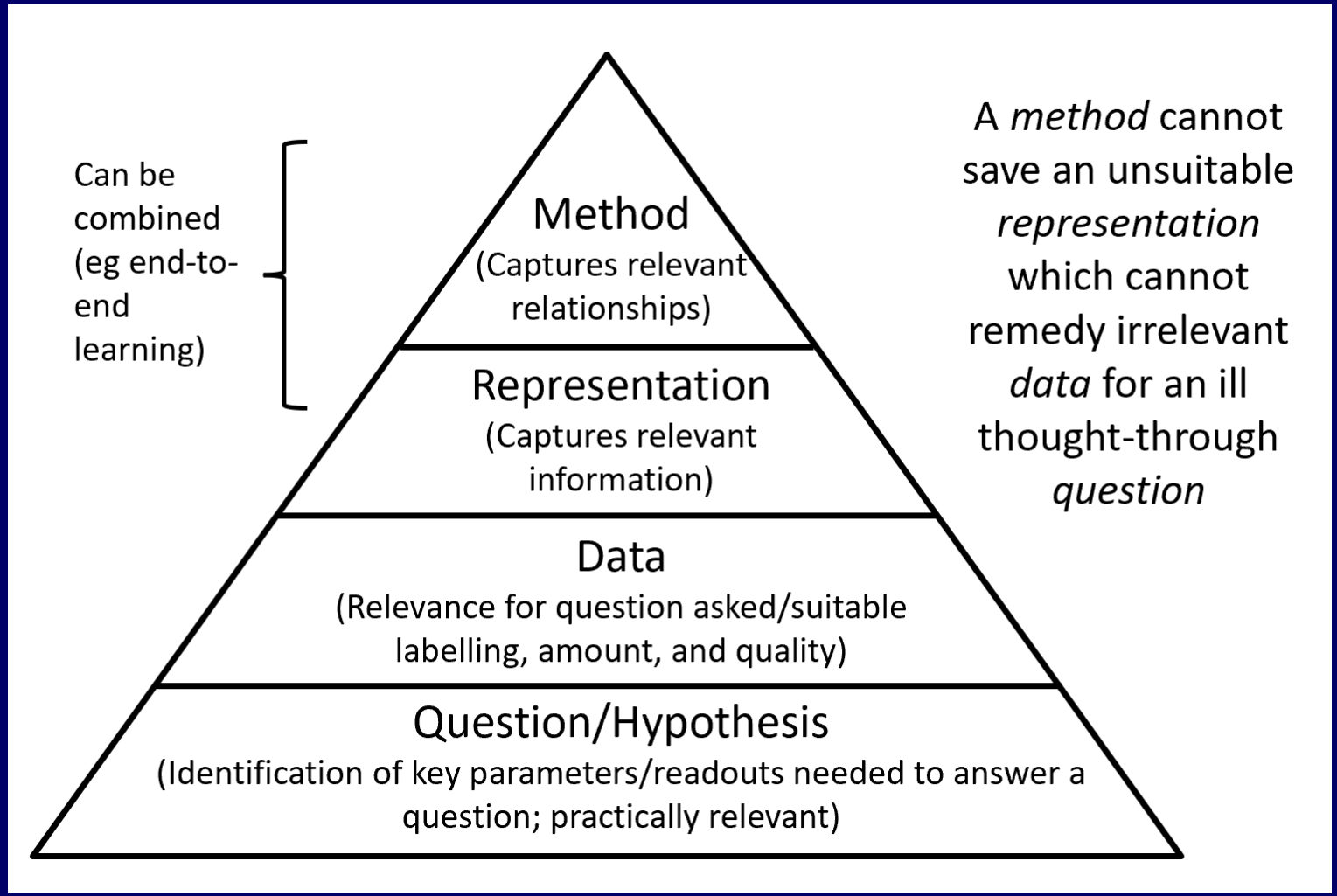
- There is *what we are really interested in* - say, mitochondrial safety, Drug-Induced Liver Injury (DILI), …
- And there is what we *measure as an assay endpoint* – say, cytotoxicity in a Glu/Gal (differential cytotoxicity) assay to *approximate* mitochondrial safety; Bile Salt Export Pump (BSEP) inhibition to *approximate* DILI, …

- Take-away: ‘Proxy’ assays measure only part of reality, in a particular assay, with particular conditions
- Not to be confused with property itself!!!
- Problem: Proxy endpoint (a) taken as ‘ground truth’ in AI in drug discovery, (b) embedding into project context neglected

# Why meeting the proxy endpoint (and any derived models) is neither sufficient (nor necessary!) for success in a drug discovery project



# The *question* needs to come first… and then the data, then the representation, and then the method
# http://www.DrugDiscovery.NET/HowToLie




Lots of attention currently here…

But we need to care more about this

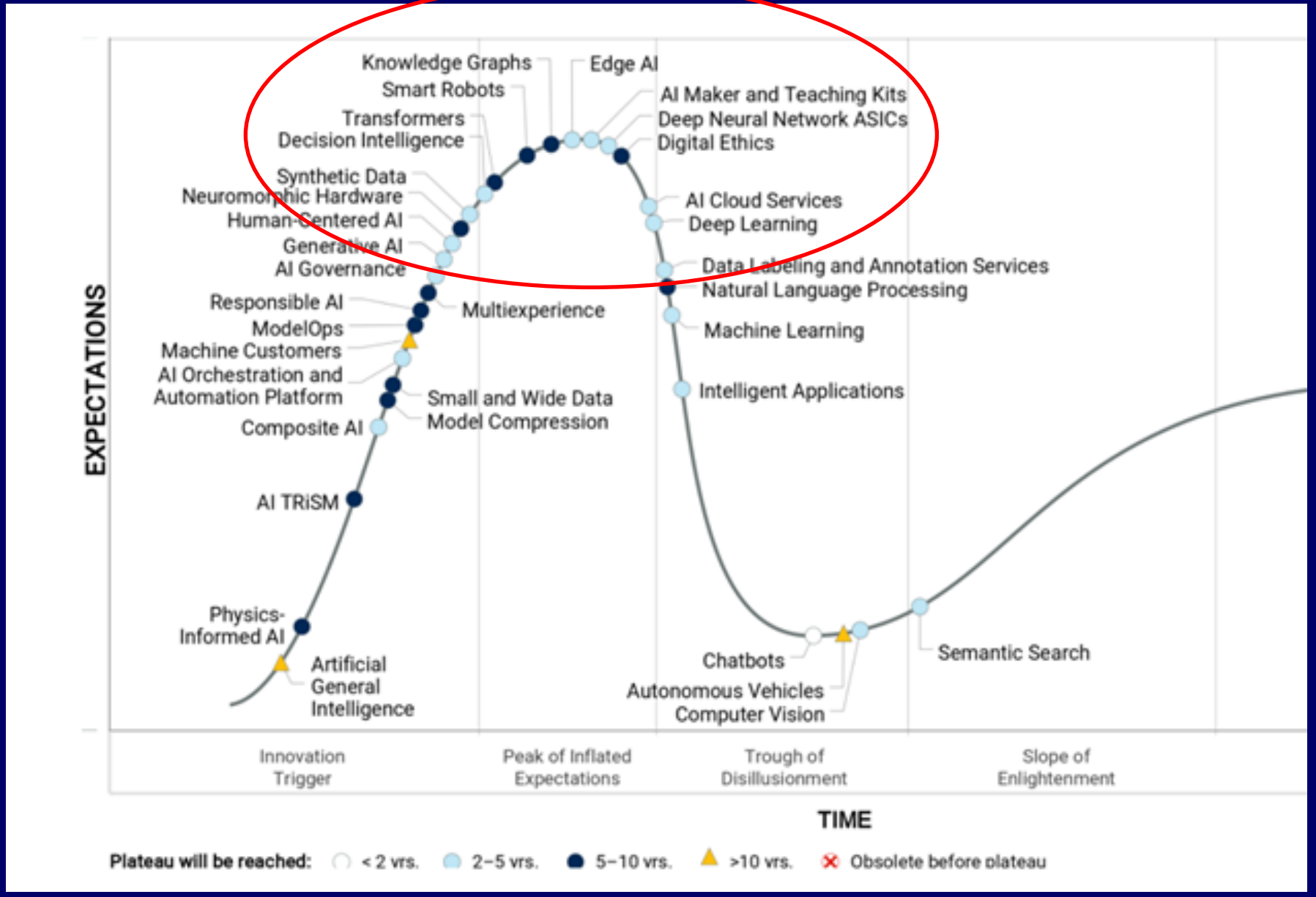
Bender and Cortes, Drug Discovery Today 2021

# 4. Psychology, the hype cycle and a methods translational gap

# The bigger picture: ‘AI’ is where it is due in no small part due to human psychology

- Hype brings you money and fame – realism is boring
- FOMO (‘the others also do it!’) and ‘beliefs’ often drive decisions (‘maybe they *really* have the secret sauce?’)
- Beware of the ‘hot air strategy’ of start-ups.. (*hot air + FOMO -> perception of ‘secret sauce’*)!
- ‘Everyone needs a winner’ (‘*after investing X million we need to show success to the CEO/VP/our investors/…’)*
- Selective reporting of successes leads to everyone declaring victory (but in reality no one knows what’s actually going on)
- Difficult to really ‘advance a field’ (or admit defeat!) with little real comparison of methods… *we cannot even properly measure progress!*

# AI on the Hype cycle (Gartner, 2021)




Notes:

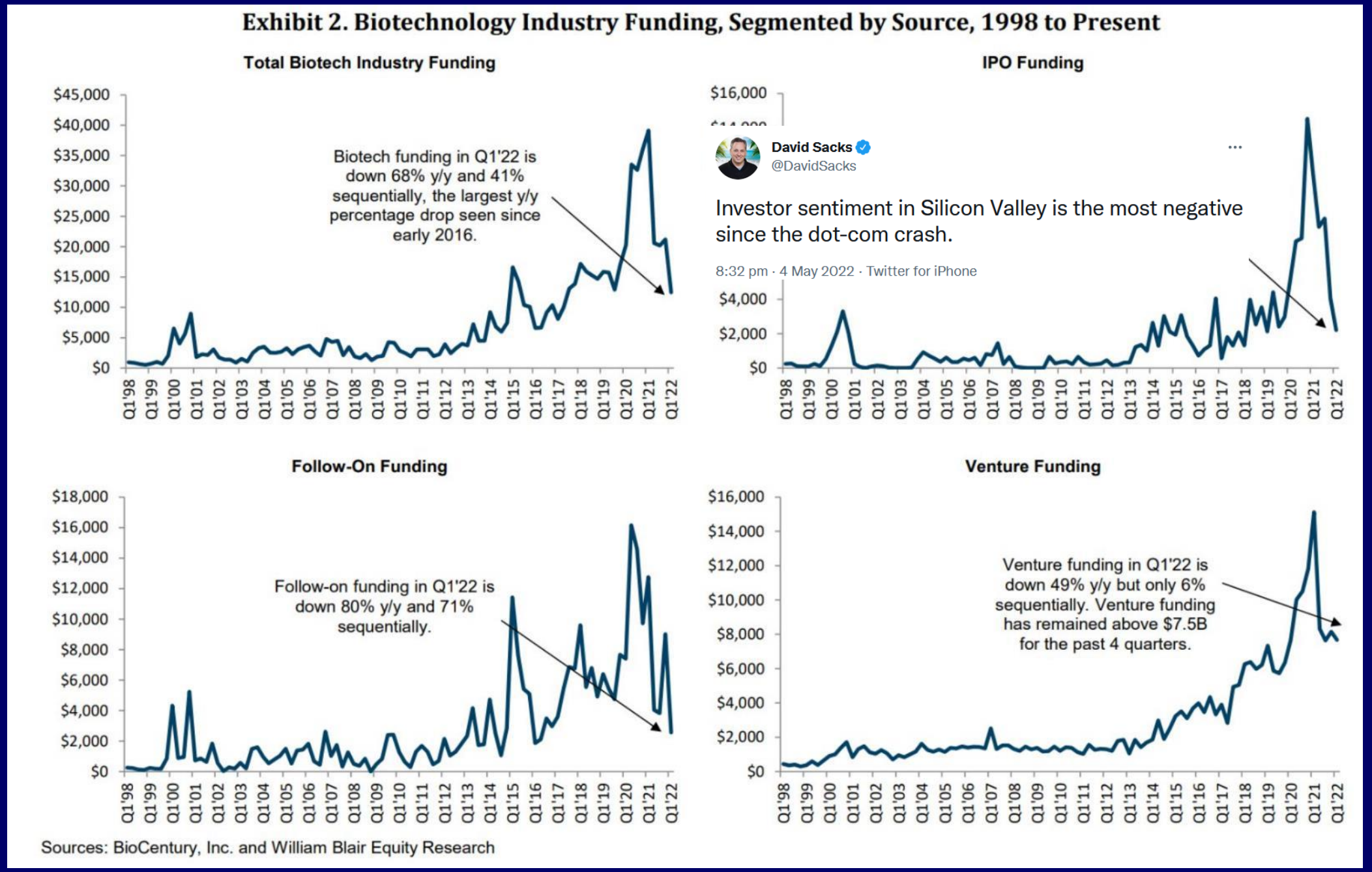
- Y axis are expectations, not ‘results’
- *Does not exist in this form*, only in *perception*, *with huge spread in the details*
- Agree with general place; *but aspects* clearly working (DL for images, ML for target prediction, cloud services useful in practice, etc etc.)
- Near future will further explore applicability of given method in a given context

# My look into the crystal ball (unchanged from 26 Feb 2022)

- Q1/2022: Inflation increasing (e.g. UK in 2021 5.5%)
- Central banks increase interest rates (money gets more expensive); pressure on asset prices; Ukraine war; …
- Return of the safe haven (gold etc.) within 1-3 (?) years

-> Less VC money available in the system

- *AI in drug discovery needs to deliver soon (in the next ~2-3 years?)*
- If you are a start-up, get funding into place soon




# Update 5/2022:

# It's hitting the fan…

https://twitter.com/paras_biotech/status/1519867841469718528
https://twitter.com/DavidSacks/status/1521905564967612416

# 5. Ok… and now?

- We need *relevant* data (predictive for the *in vivo* situation), which is *possible to generate large-scale*
  - ‘omics data: *Yes, but* experimental conditions (e.g. cell line)/dose/time point often don’t extrapolate to relevant situations
  - Cellular morphology data: *Yes, but* we need to understand better what the applicability domain is/which interventions are visible in the readout (HESI consortium, etc.)
  - Organ-on-a-chip: *Yes (!), but* still under heavy development, details to be seen

- Probably industry-wide precompetitive consortia *involving experimental design and data generation* needed to establish best-in-class approaches across endpoints
- Required due to (a) large size of chemical/mode of action space, (b) high number and dimensionality of readouts that can be generated, and (c) large number of *in vivo* endpoints we are interested in

# When you see ‘success stories’, remember…

… there are always multiple ways to claim a ‘win’:

- Scientifically (broad, *meaningful* benchmarking);
- Using individual success cases; or
- Economically (‘See, I found someone who bought my stuff!’… which is mostly psychology)
- …

# One activity if you are interested in ML/life science data expertise: AI in Drug Discovery Institute in Cluj, Romania

- Largest Computer Science Department in the country; houses Research Institute on Artificial Intelligence, Virtual Reality and Robotics
- Second specialization in medicine
- Cluj home to Bosch Engineering Centre; large number of CS companies
- InfoBioNano4Health Research Infrastructure
- Etc.

UBB BECOMES A ROMANIAN ARTIFICIAL INTELLIGENCE HUB FOR THE AMERICAN COMPANY SAS

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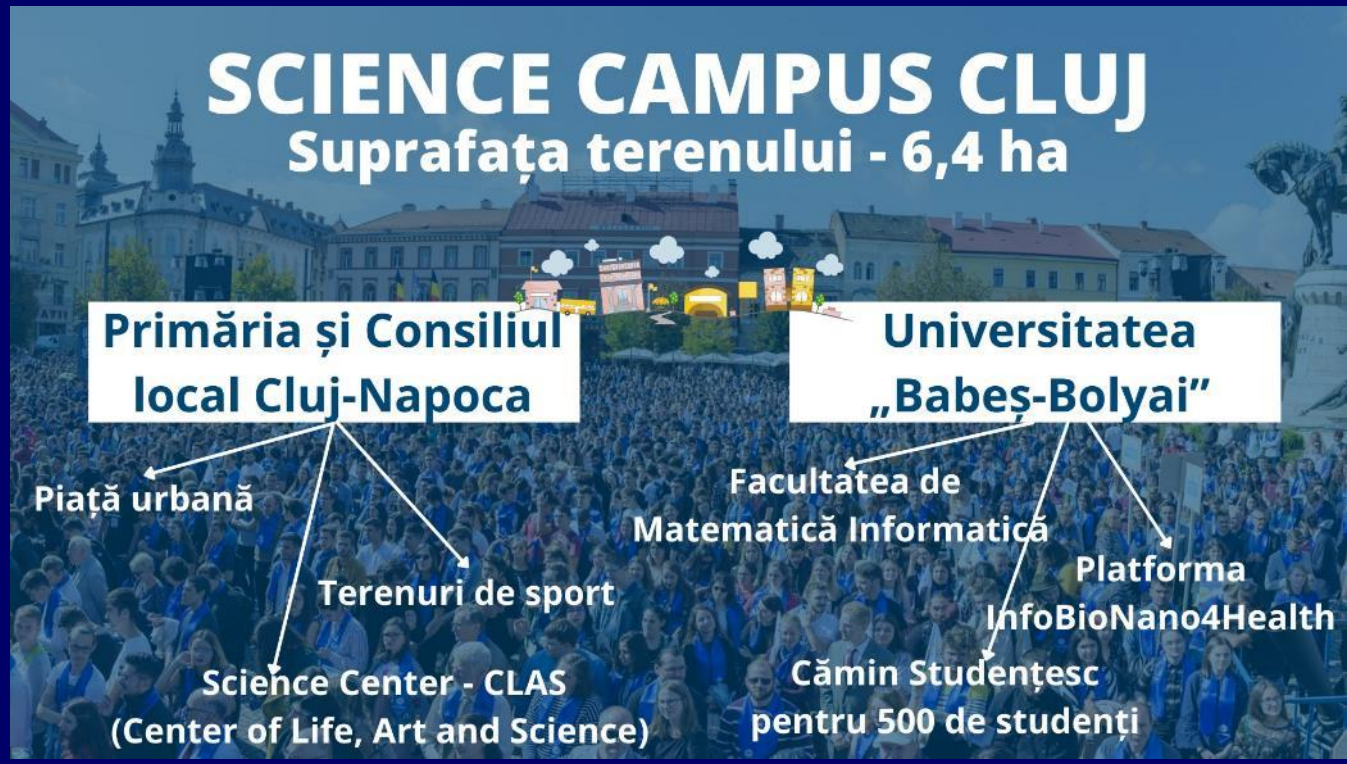
UBB OUTLINES THE PAN-EUROPEAN COMPETITIVE ADVANTAGE FOR CLUJ THROUGH INFOBIONANO4HEALTH

The *SMART InfoBioNano4Health&Innovation* project proposed by UBB in partnership with the Cluj-Napoca Town Hall, with a budget of €45 mil., was awarded first place in the competition for defining the RIS3 smart specialisation in the North-West region. The purpose of the competition was to identify smart specialisation and endorse it for its successful implementation during 2021-2027.

# Science Campus Cluj

- 35m EUR from EIB; 6.5ha
- Government/University co-sponsored Science Campus




2021

2023 onwards

# In planning:
# AI in Drug Discovery Institute, start 10/2023

- Leader (funded), support staff (funded), 3+ permanent research staff
- 10+ PhD students on continuous basis (currently 50% funded)
- Excellent *potential* for *talent!*

- Start 10/2023
- Flexible IP arrangements possible
- Core areas of expertise:
  - Image analysis (cellular, organ); Multi-Omics Data Analysis
  - Causal Modelling; Combining Knowledge and Data; Computational Safety

- EUR 400k/year for 5 years (2m EUR in total) external funding sought
- **Looking for talent / resources in ML/drug discovery area? Let me know!**
- 1 Company as anchor /1 lead already committed – looking for additional partners

# Summary

- We need to analyse our data (as we did for many years before), absolutely!
- ‘AI’ *is a valuable tool* in the toolbox
- The *real* game changer for translation to patients will come only once we understand biology/biological data better (and generate it, and encode it, and analyse it)
- From the data side, consortia on even larger scale are needed (for targeted data *generation*, not just sharing what is there already)
- Methods need to *translate into reality*, we need to go *from model validation to process validation*

Thank you for listening!
Any questions?

Contact: ab454@cam.ac.uk
Personal email: mail@andreasbender.de
Web: http://www.DrugDiscovery.NET
Twitter: @AndreasBenderUK