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The Lilly Perspective: *Challenges We Face & Tools We Need*

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Part I: Challenges

The Lilly Perspective: Challenges We Face & Tools We Need

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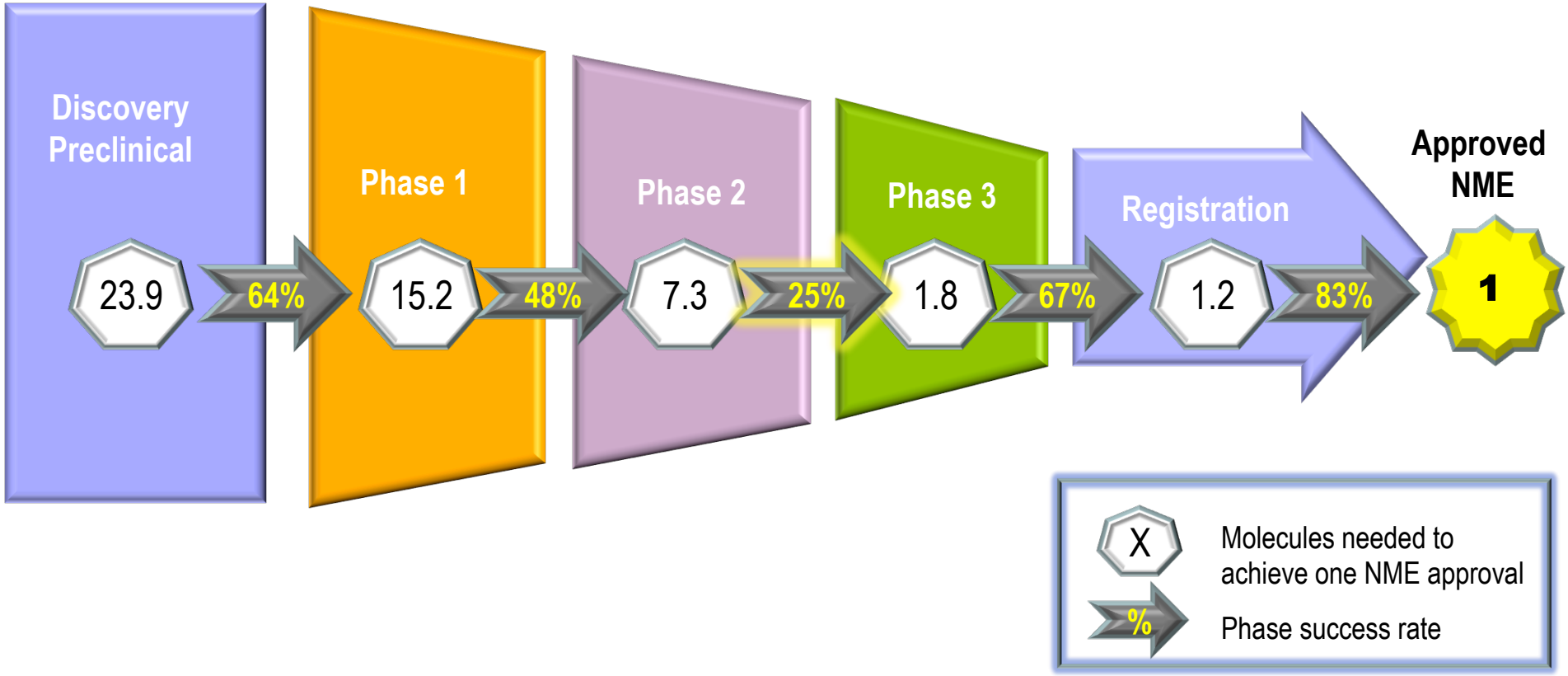
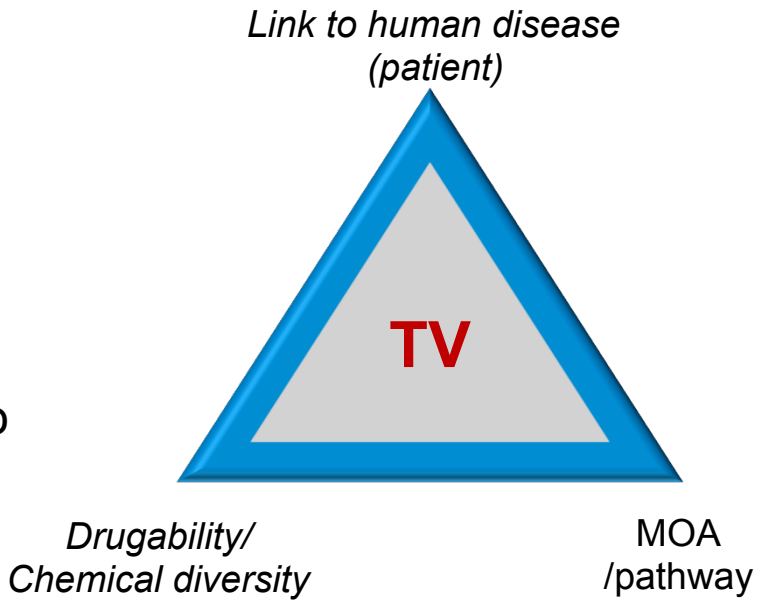
Part I: Challenges
The Drug Discovery & Development Process



Data from Bunnage, *Nature Chemical Biology*, **2011**, *7*, 335.

Part I: Challenges
Target Validation Remains Critical

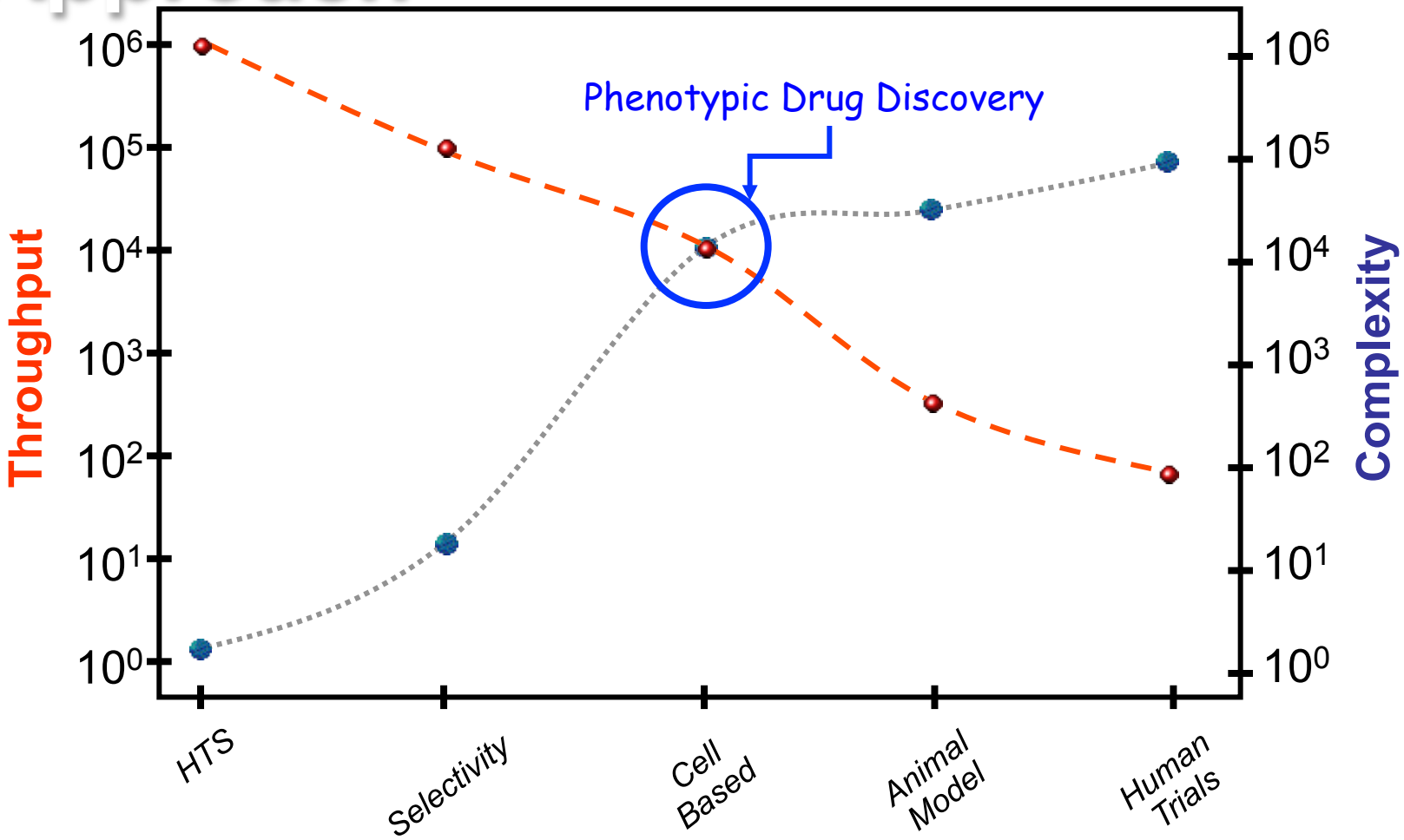
- Despite huge increases in R&D investment, wealth of scientific and technological advances, the output of new drugs has not increased.
- Not all biological insights lead to effective drug targets, and focusing on the wrong target can result in clinical failures costing time, money, and ultimately, not helping patients.
- Developing a new drug — from early discovery to approval — takes well over a decade and has a failure rate of more than 95 percent.



Thus, it is critical to do a better job in identifying the right biological targets early in the process.

The global biomedical research community and the public have a common interest in compressing timelines, reducing costs, and increasing success rates of new targeted therapies. Is there a pre-competitive opportunity to collaborate to identify human relevant targets worth investing further?

Part I: Challenges
Allure of the Phenotypic Approach



Part I: Challenges
Target *vs* Phenotypic Approaches

- Target Approach
  - Target-centric, pick “best” target hypothesis
  - biochemical criteria prioritize compounds for evaluation in cell
  - Cell-based assays Provide a “Physiological” Context

- Phenotypic Approach
  - R&D Conducted Using Complex, Disease-Relevant *In Vitro* Models
  - Does Not Require Identification of Target(s), Does Not Preclude It
  - Complements and Supports Target-Based Discovery
  - May Increase p(TS)

Part I: Challenges
The Price of Going Phenotypic

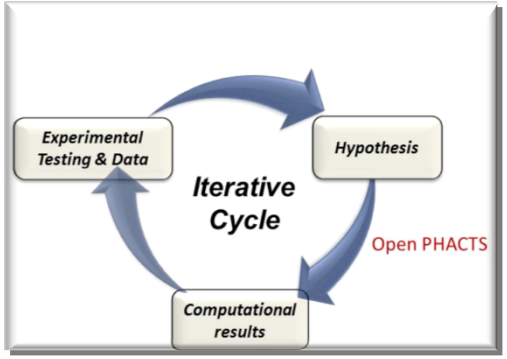
- Offers an empirical approach to identify novel targets linked to human disease.
- Unbiased approach for increasing understanding of a pathway
- It could lead to multiple target opportunities (single or polypharmacology)

Key challenges:

- ❑ Data deconvolution (complex and lengthy) leading to target-hypothesis
- ❑ Identification of key experiments to confirm target hypothesis (who has expertise; timelines)
- ❑ Chemoproteomic approaches to confirm target engagement in different species (probe design)
- ❑ Internal level of interest/buy-in (really early drug discovery/exploratory)
- ❑ Needs to focus on a few key areas/pathways (due to complexity/resources)

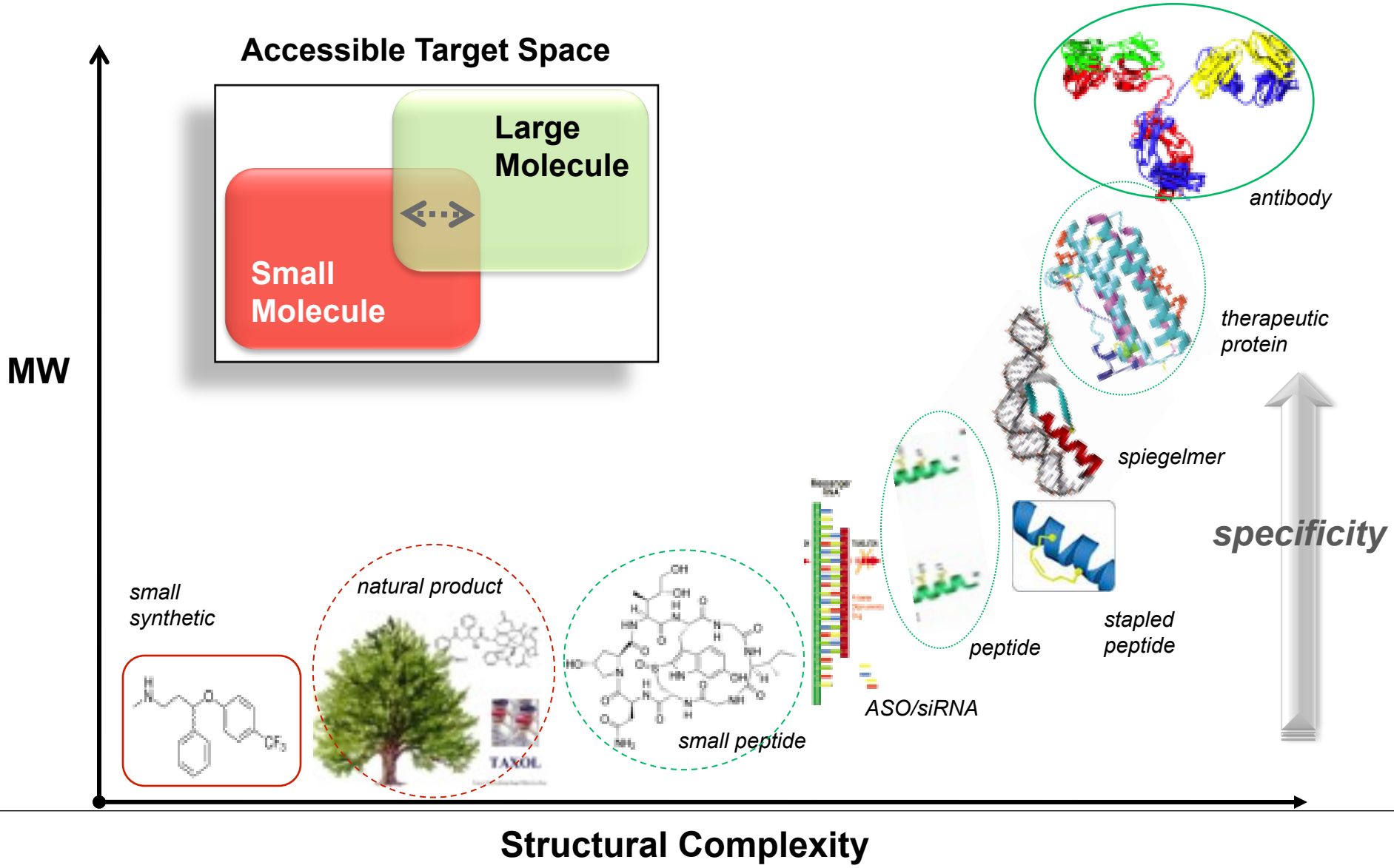
Part I: Challenges
Data Analysis & Deconvolution

Once some hypotheses had been generated (e.g. 5 key targets), what are the key experiments that can feed the data pool, validating or discarding some hypothesis:



- Do clinical biomarkers/database exist for this target or disease?
- Can a selective and potent compound tested in human tissue?
- Level of expression in different human tissues (isoforms) – is this data available in any database?
- Interpretation of pathway MOA – up or downregulation, compensation mechanisms, disease state
- Integrate data with known target population/patients (known mutations, resistance….)
- Confirm or generate a database of human genotypes with associated medical records and a target safety review portal
- Do KO experiments/data exists in preclinical species ?
- In depth review of each target and iterative data update (data curation)
- Do we have a high quality tool/compound?

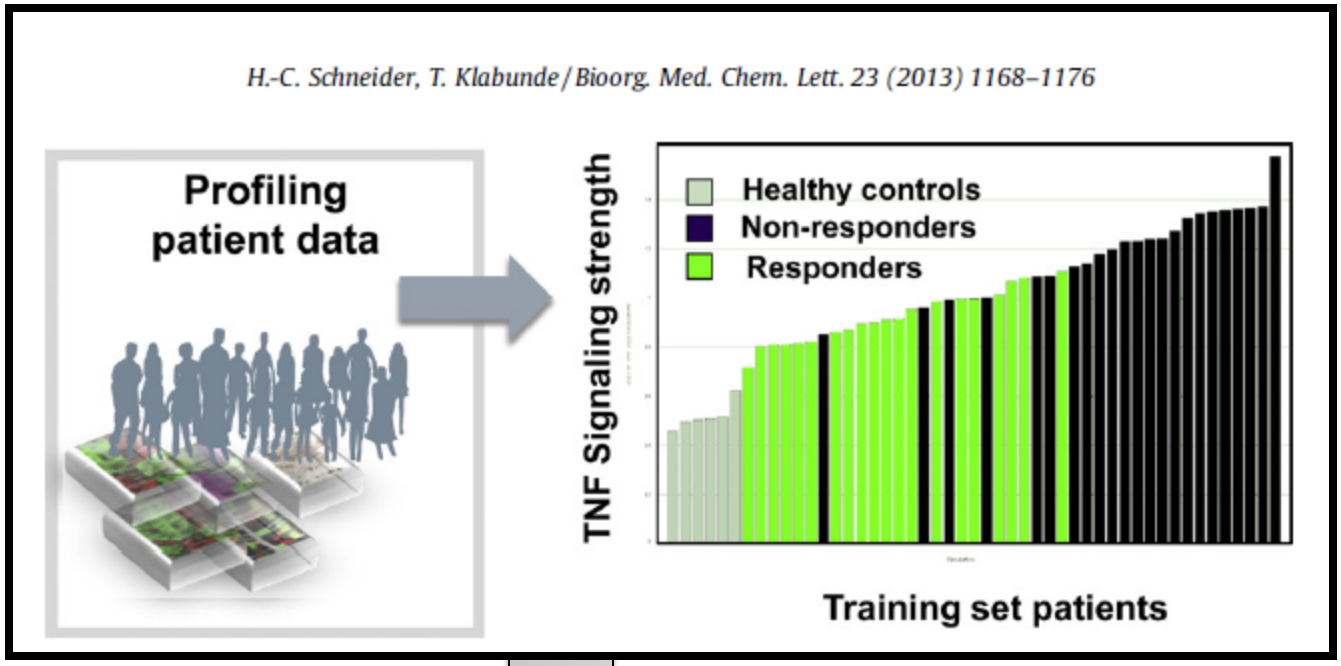
Part I: Challenges
Chemical Space Complexity



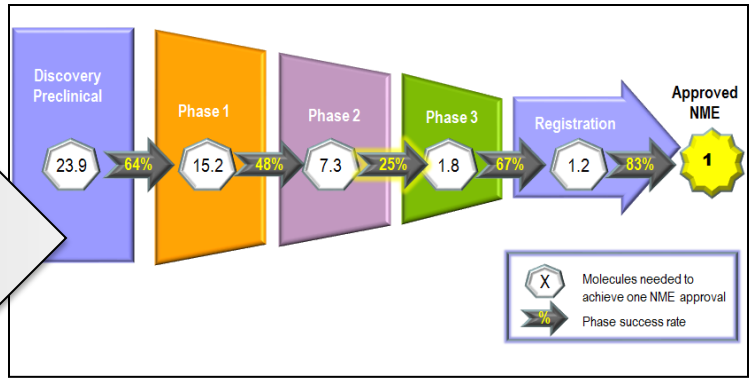
Part I: Challenges
Impact on Lead Generation

- Improving target selection might be key to reduce attrition in phase 2
- There is a need to expand druggability of novel biological targets *e.g. epigenetics, protein-protein interactions….*
- Lead Generation plays a critical role to identify starting points for those novel targets
- Identification of <u>novel chemical space</u> relies on:
    - Structure-based drug design, biophysical methods
    - Expansion of chemical diversity and topology
    - Moving beyond “Rule of Five” small molecule
    - Computational methods

Part I: Challenges
Integrating Clinical Learnings



Data Integration
& Into
Lead Generation
Strategies



Part II: Tools

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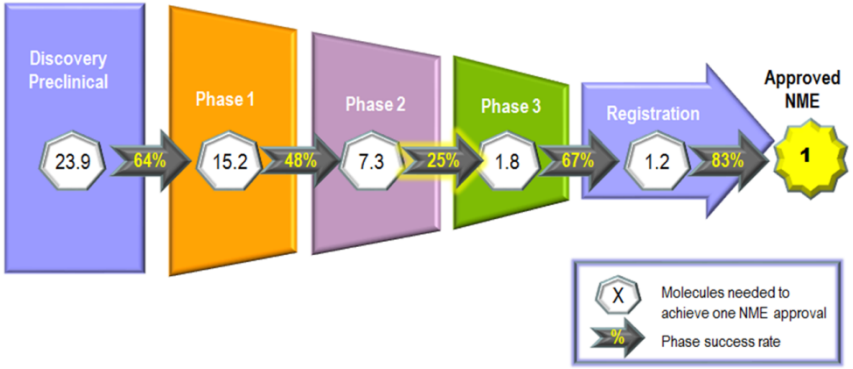
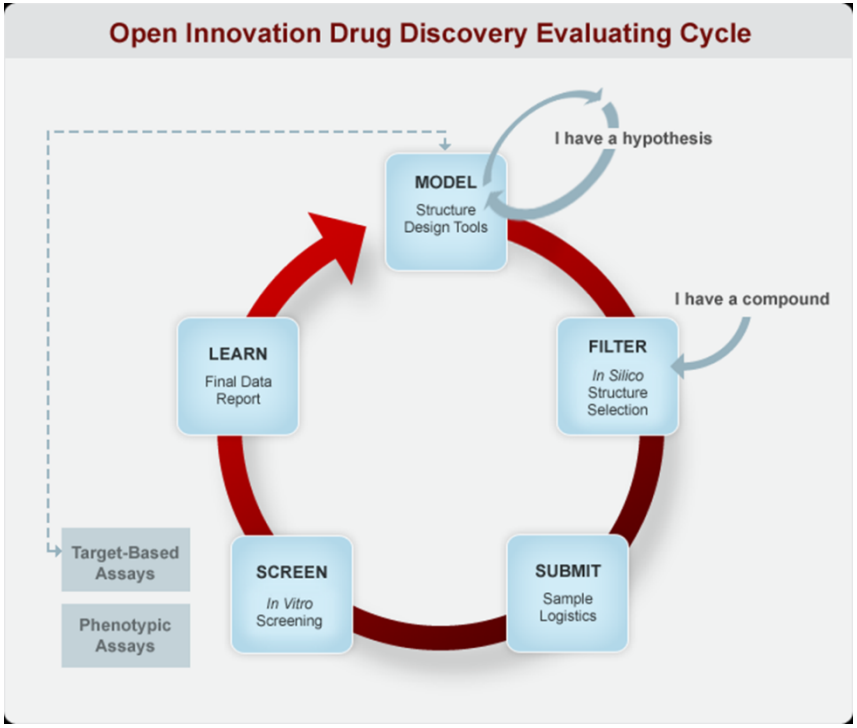
Part II: Tools
The Rocket vs The Wheel

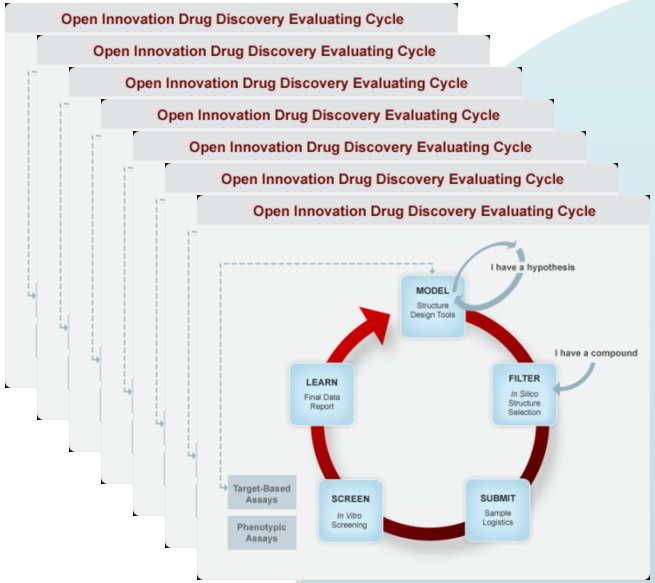
In early Discovery, it's not a rocket….



…but an infinite cycle of learning



Part II: Tools
What The Process Is Really Like…



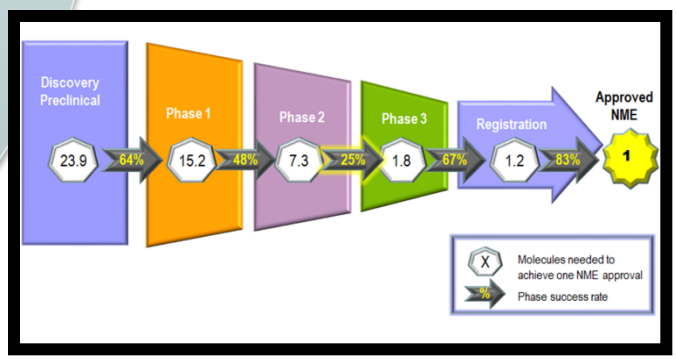
TOI & Lead Generation Space

Hypothesis

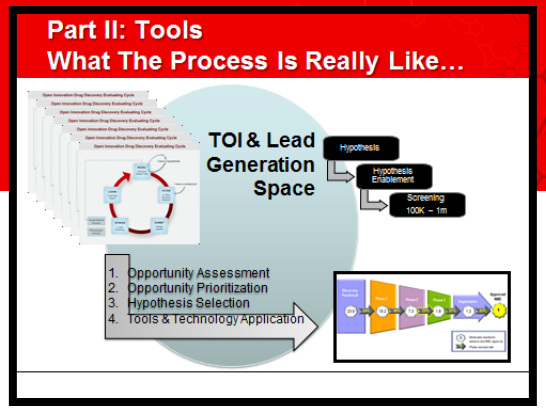
Hypothesis Enablement

Screening
100K – 1m

1. Opportunity Assessment
2. Opportunity Prioritization
3. Hypothesis Selection
4. Tools & Technology Application



Part II: Tools
TOI & Lead Generation Space



- Biological Understanding
  - Tools & Technologies - Applicability
  - Chemical Space – Availability
  - Rapid-Fire Learning – Remove Uncertainty ASAP
- Data Analysis
  - Multiple Scaffolds – Prioritization
  - Large Data Sets – Relevance
  - Multi-Parameter Evaluation - Visualization
- Resourcing
  - How much $$$/Effort?
  - Is this a good bet? How do we know it is? Rabbit hole?
  - Opportunity cost: while we do this, what are we missing?

Part II: Tools

Pre-Competitive Space Offers Complementarity of Strengths

ACADEMIC/GOV'T Presence/Focus Continuum **INDUSTRY**

ASKING WHY: Hypothesis

- Explore, experiment, refine, test limits,
- Data to support and define NEXT experiment
- When to stop trying?

ASKING WHAT: Proof-of-Concept

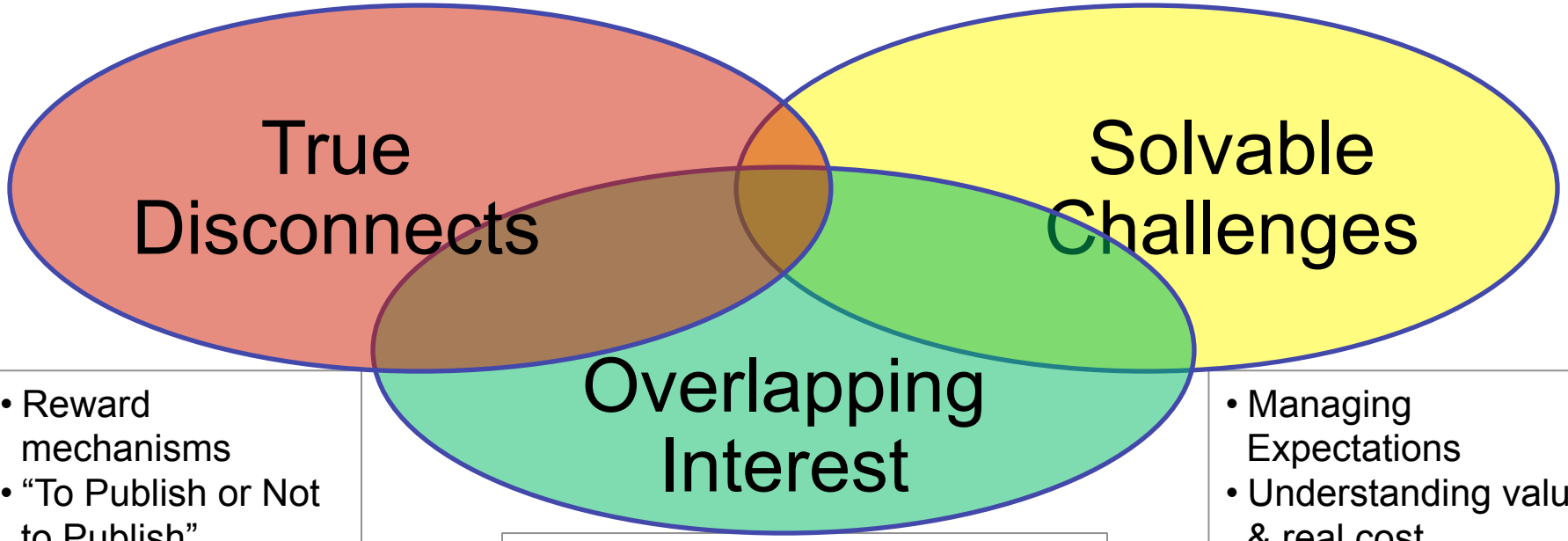
- Defining experiments, provide definitive data package
- Comfortable level of uncertainty

ASKING HOW: R&D Portfolio

- Is this worth further investment?
- Information for decision-making: Brevity, contextual

Part II: Tools

Pre-Competitive Space Offers Come With Its Own Set of Issues

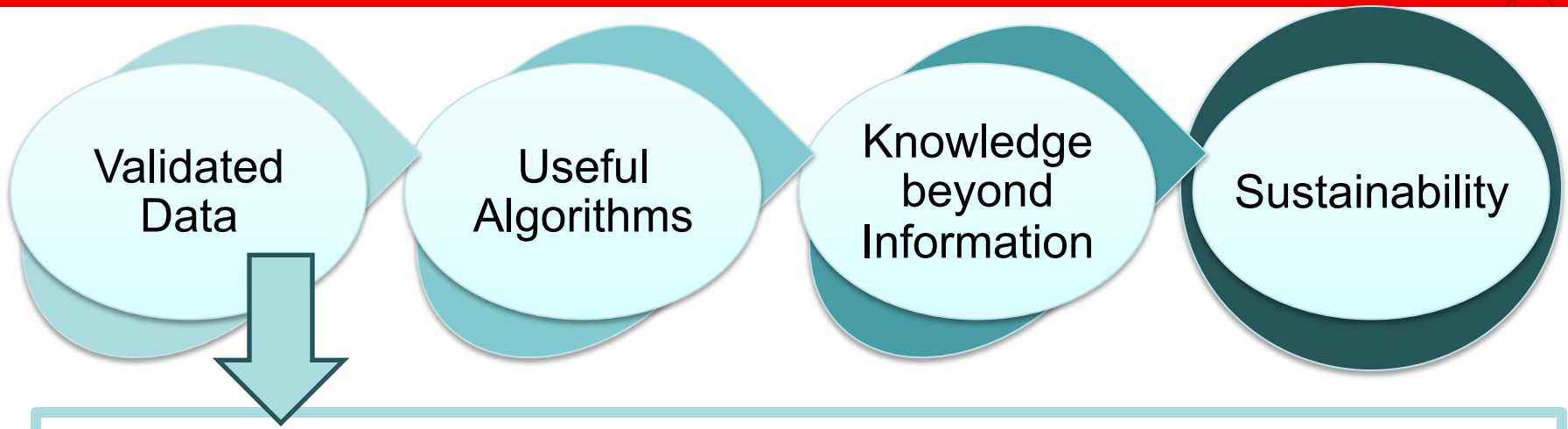


- Reward mechanisms
- "To Publish or Not to Publish"
- IP considerations
- Who's paying here?

- Validated data packages
- Knowledge vs information: what does this mean?
- What else is out there?
- How do I know what's known?

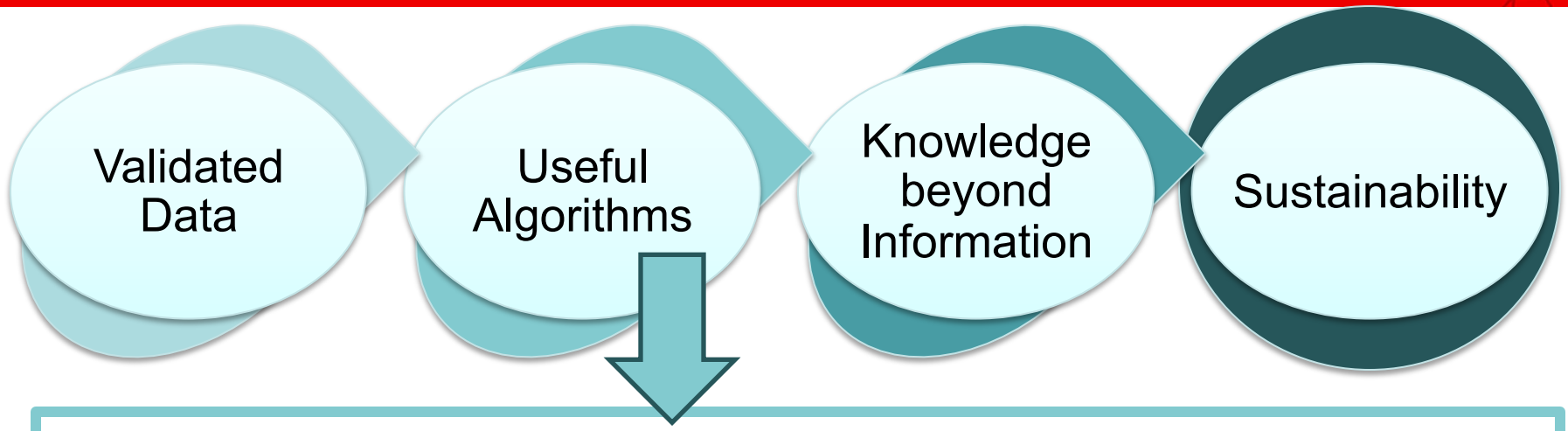
- Managing Expectations
- Understanding value & real cost
- Approaching the problem (neat science vs relevant & applicable)
- Who are the right partners? Choosing better

Part II: Tools
What Do We Build Next?



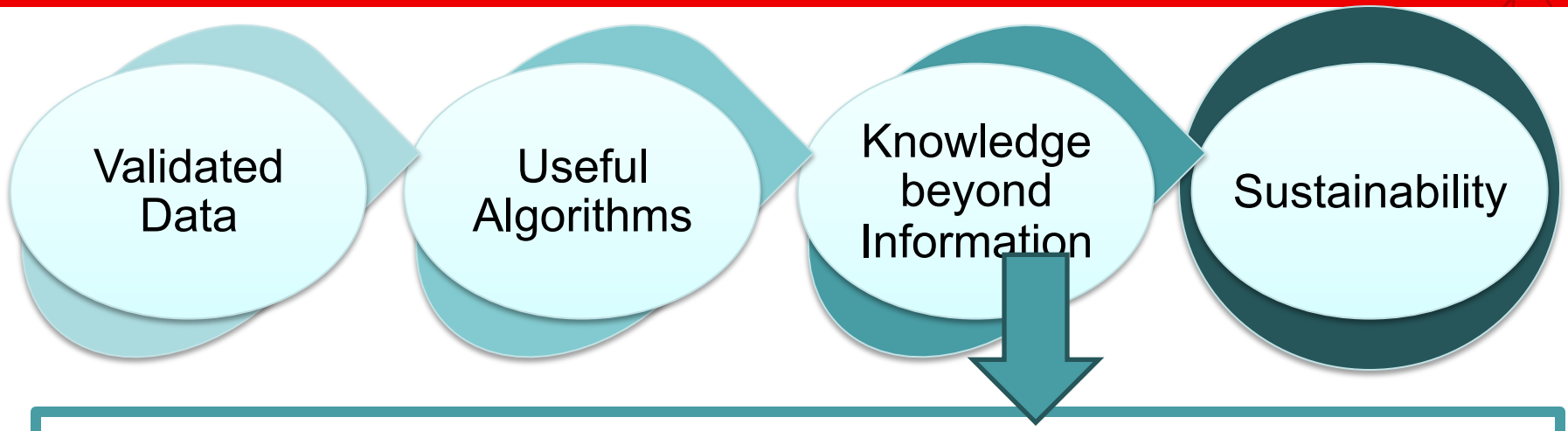
- Data validation, lit issues – recent statistics point of irreproducibility
- Think about:
  - Format
  - Quality
  - Gatekeeping (refute/purge)
- Feeding the algorithms: selecting from ever-growing data sets
- Experimental validation => example of Org Syn Prep – possible reward system? Go CRO and crowdsourcing

Part II: Tools
What Do We Build Next?



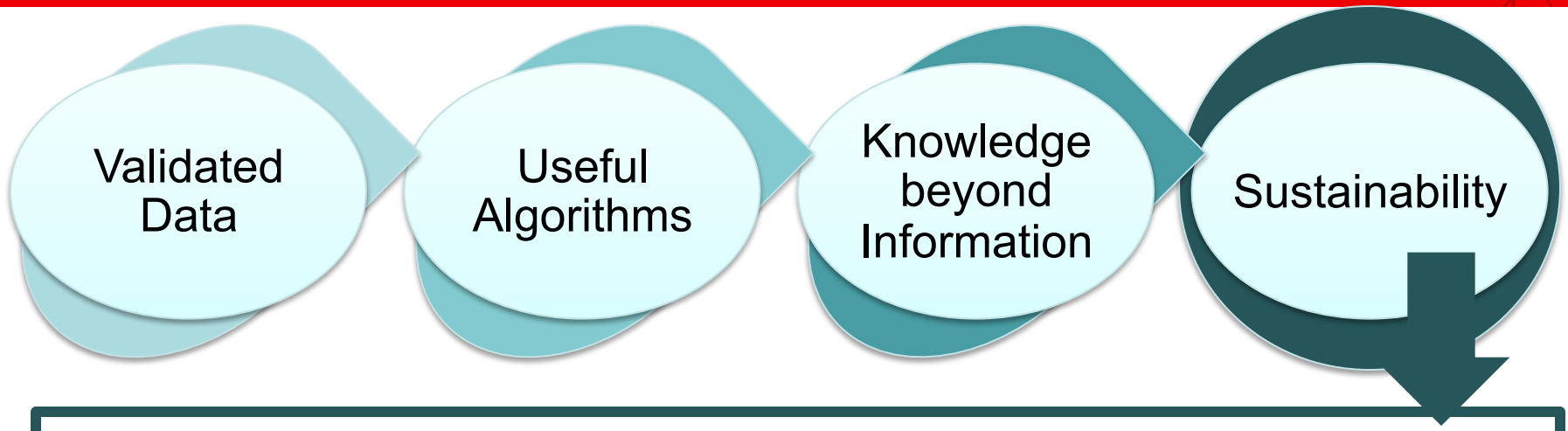
- Connect-the-dots: provide information within context
- How do I found a NOVEL idea?
- Complicated pathways: what's out there relevant to my question? Prioritize my answers
- Where do I look? How do I integrate?
- Alert me: give me partners, technologies, competitive space
- Feedback incorporation: machine learning (means) & human learning (end)

Part II: Tools
What Do We Build Next?



- Understanding requires interpretation => opportunity for academia
- What's next – integrating information provenance & relevance: think amazon.com vs google => becoming the supplier
- What does this mean? Incorporation of cross-functional learning
- Avoiding the "Expertise syndrome" => insular/isolated views
- Visualization tools; "Analysis for dummies" at the service of <u>opportunity identification</u>

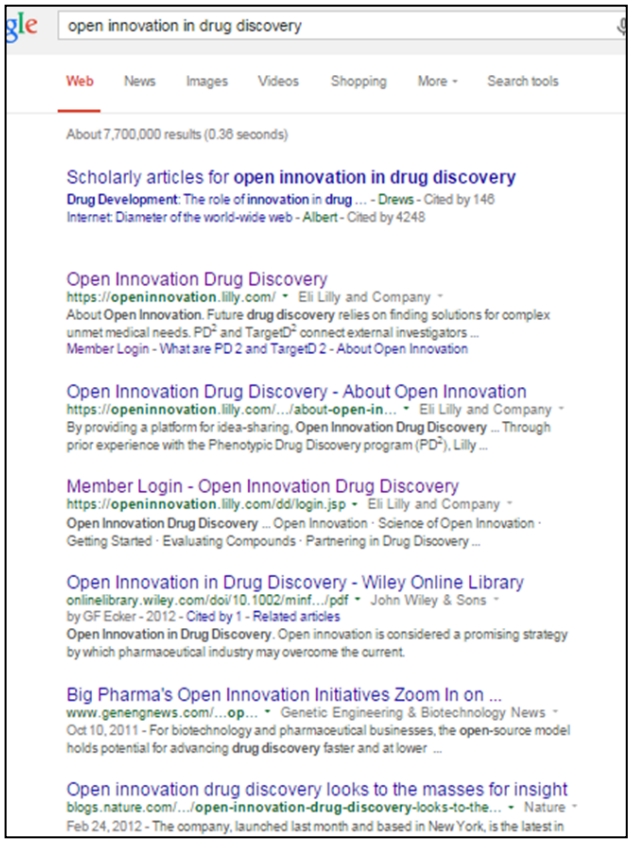
Part II: Tools
What Do We Build Next?



- Think Habitat for Humanity – need to pay for yourself!
- What's your ROI? => you need to keep your stakeholders happy (think Washington DC museums – all free)
- The "How" matters: user interfaces, presentation
- What do we have already? What do we need to build?
- Dealing with "NIH Syndrome" and "WIIFM"
- The ultimate value proposition for this exercise is to achieve incorporation of translational science, i.e. patient data

Think Amazon vs Google

Known Unknowns



Unknown Unknowns