The Transition from Pre-Clinical to Clinical Application of Safety Related Genomics

IOM/FDA Emerging Safety Science Workshop

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What Are the Relevant Questions?

- Can we identify better (genomic or other) biomarkers that accurately predict the risk of drug-induced toxicity?

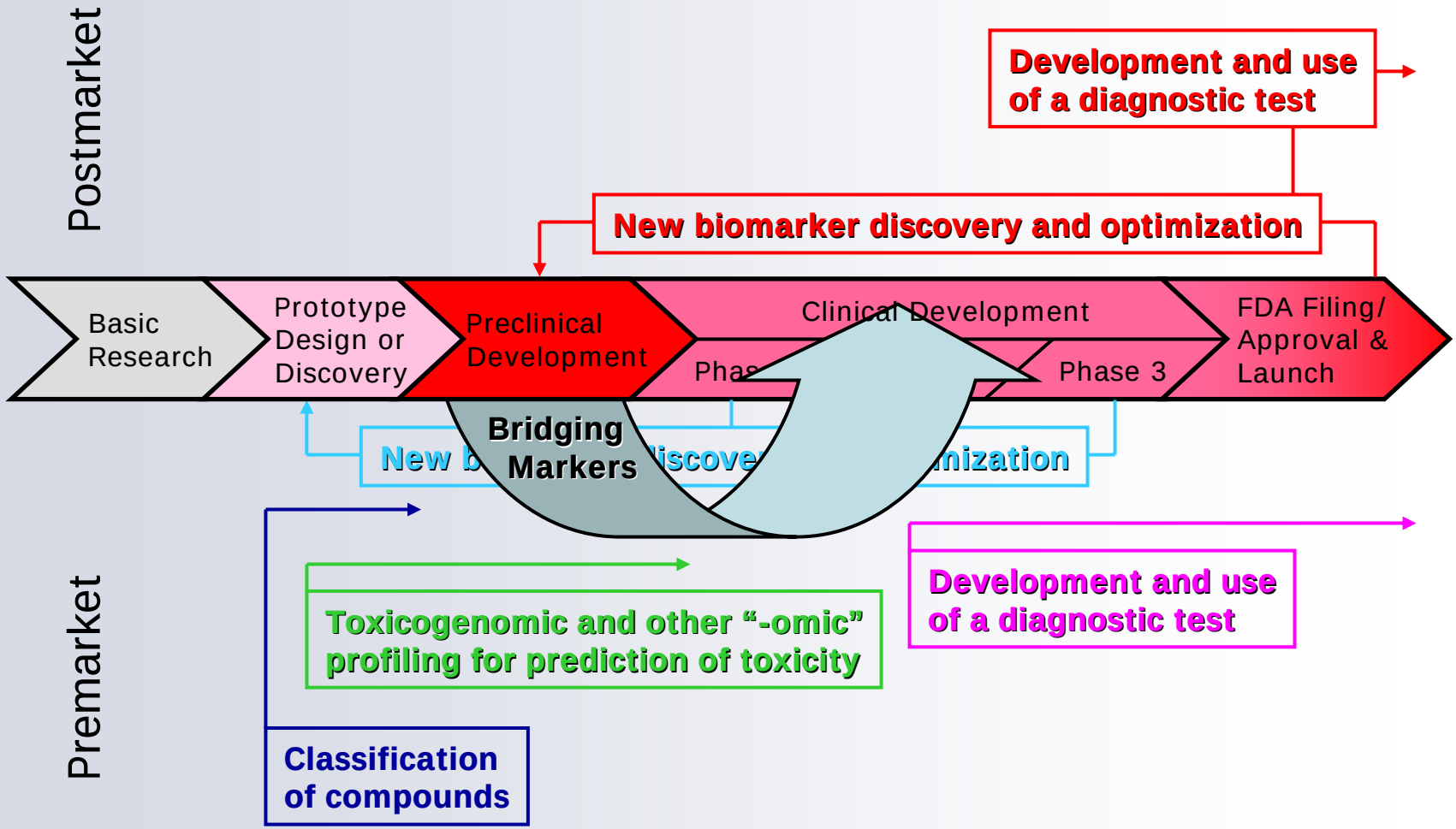
More specifically:

- Can we develop *pre-clinical* tests to screen out compounds that have the potential to induce toxicity in man?

and:

- Can we develop *clinical* tests (diagnostics) that measure the probability of drug-induced toxicity?

What I Want to Talk About: Pre-Clinical and Clinical Safety as a Continuum



Non-Clinical Test Systems to Assess Safety

- Animals (including transgenic animals)
- Tissue slices
- Cell cultures
- In silico models

- How good are these systems, i.e.
  - can these non-clinical test systems predict what will happen in man?
    - Yes, but not always – although such models provide useful information, for some classes of drugs the models are poor predictors of human response
  - Then there is also the issue of time:
    - The time it takes to run these tests
    - The “toxicity state” at which these systems pick up a signal

The Problem and a Potential Solution

- Traditional markers are often not useful for early detection of toxicity
  - For example, blood urea nitrogen (BUN) or creatinine are not measurable until 50-75% of the nephrons have been destroyed – obviously, a more sensitive marker that picks up renal toxicity *before* nephrons are being affected is desirable
- Toxicogenomics (and other –omics technologies) promise to detect toxicity earlier because they measure the molecular changes that later lead to toxicity
- The biomarkers developed using these technologies represent, in a way, surrogates for the toxic endpoint of interest

How To:
A Straightforward Concept

- Expose test system to known toxicants and known non-toxicants
- Collect serum and tissue(s) of interest
- Verify toxicological effect via traditional methods, e.g. histopathology
- Compare gene expression (or other) pattern of toxicants with non-toxicants
- Create a “fingerprint” for the known toxicants studied

- Once a comprehensive amount of structurally diverse compounds that all lead to the same toxicity have been tested and the biomarker picks up all of these compounds as toxicants, we can feel certain that the biomarker is based on the mechanism(s) responsible for this particular toxic event
- It is therefore reasonable to assume that a new compound will produce the same fingerprint should the compound have the potential to lead to the toxicity for which this signature is representative

What We Aim For

- Biomarkers to predict the potential for toxicity with a high specificity and sensitivity:
  - I.e. to be 100% sensitive and 100% specific, the marker must cover all possible pathways that lead to the toxicity for which the marker has been qualified

- How can we be sure?
  - Absence of evidence is not equal to evidence of absence:
    - The biomarker is a characteristic identified and qualified using a series of known toxicants; but those are not the compounds we are continuing to measure – our interest is in classifying a new, uncharacterized compound
  - The more diverse known toxicants are available to create the fingerprints, the higher the sensitivity and specificity of the marker will be

Where Are We Today ?

- ✓ Compound classification markers:
  - Several studies demonstrate that it is possible to create a signature for certain classes of compounds, e.g. PPARα agonists, AhR agonists, and others
  - Large public (e.g. ArrayExpress, CEBS, GEO) and private (Gene Logic, Iconix) databases have been created based on this concept (and many pharmaceutical companies started to create their own databases as well)
  - None of these new markers have been validated (although it's fair to say that there are many "probable valid" markers out there)
  - These markers may work well for compound selection and early characterization,
    - but they are not necessarily characteristic for a toxic event (but they can be), i.e. they are not designed to close the gap between pre-clinic and clinic

What do we need ?

1. Pre-clinical to clinical bridging markers
2. Markers to pick up idiosyncratic events

1. Bridging Biomarkers

- What are bridging biomarkers:
  - Biomarkers that are of the same type in pre-clinical models and humans and represent quantifiable indicators of normal biologic processes, pathophysiological states and response to therapeutics
- Studies to identify and validate bridging biomarkers are underway (e.g. for nephrotoxicity – Predictive Safety Testing Consortium, PSTC)

- Potential bridging application: exploratory IND
  - If indeed these markers are more sensitive, signals should be detected early (i.e. before harm to organs occur) and at low doses
  - The availability and measurement of a variety of bridging markers in this setting could result in the creation of a new “Phase 0 safety package”

2. Idiosyncratic Events: Learning “after the fact”

- Idiosyncratic events are random, unexpected, often dose-independent
  - Caused likely by a combination of the properties of the drug in combination a (genetic?) predisposition of the patient
- Drugs withdrawn from the market due to rare serious adverse events
  - Should not have been on the market in the first place so that the patients harmed could have been spared from harm
  - Pose a problem for (the many more) patients that are not at risk and benefit from treatment
  - Negatively affect the companies that make the drugs
- So what can we do?
  - Develop processes and invest in research that lead to a reduction in adverse events (serious and non serious)

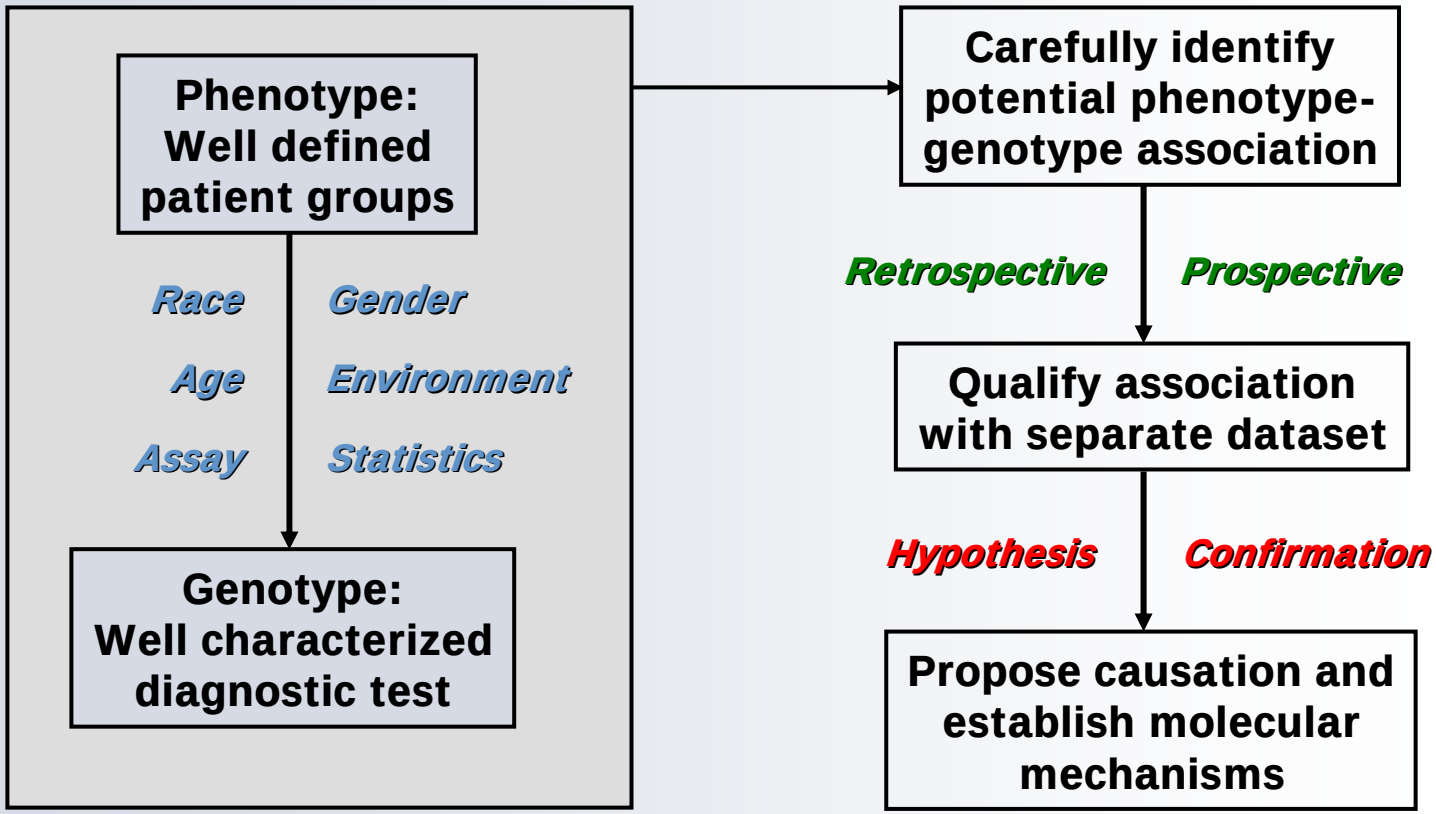
Example: Drug-Induced Long QT Syndrome

- Idiosyncratic, rare adverse event
- Next to hepatotoxicity reason #1 for drug withdrawals
- Reversible, but can lead to TdP, which can be fatal (i.e. not all QT prolongation leads to TdP, but we cannot predict when a prolongation will lead to TdP)
- Occurs in a wide variety of structurally diverse compounds (i.e. a “class prediction” would not work here!)
- Besides drug-induced LQT, a congenital form of LQT exists and several genes have been identified causing QT prolongation – the line between the drug-induced and the congenital form from a genetic perspective continues to remain blurry
  - Generally believed that the drug’s potential to block KCNH2 (HERG) leads to QT prolongation, but other factors such as DME to play a role as well (e.g. CYP2D6 PM can lead to higher levels of thioridazine, which can lead to TdP)
  - Not all KCNH2 blockers lead to QT prolongation (e.g. verapamil leads to a shortening of the QT interval)

Example: Drug-Induced Long QT Syndrome, cont'd

- So, how do we design a study that identifies new (genetic) biomarkers to determine whether a drug has the potential to cause QT prolongation and TdP, and/or which patients are at risk?
- The study needs to consider:
  - Influence of other external factors, including co-medications
  - Genetic predisposition to congenital LQT – but the same mutation does not mean the same phenotype: the same mutation can lead to
    - QT prolongation in absence of drugs
    - QT prolongation only in presence of a drug ("forme fruste") – responsible for about 10% of cases of drug-induced QT prolongation
  - Other relevant genotypes (e.g. CYP2D6 and other DMEs)
- Therefore, most likely only a genome-wide SNP analysis conducted in a large number of patients using a variety of different drug classes can help us to better understand the risk factors for drug-induced QT prolongation and TdP
  - (Next question: what are we going to do with this information?)

Framework for Genomic Association Studies



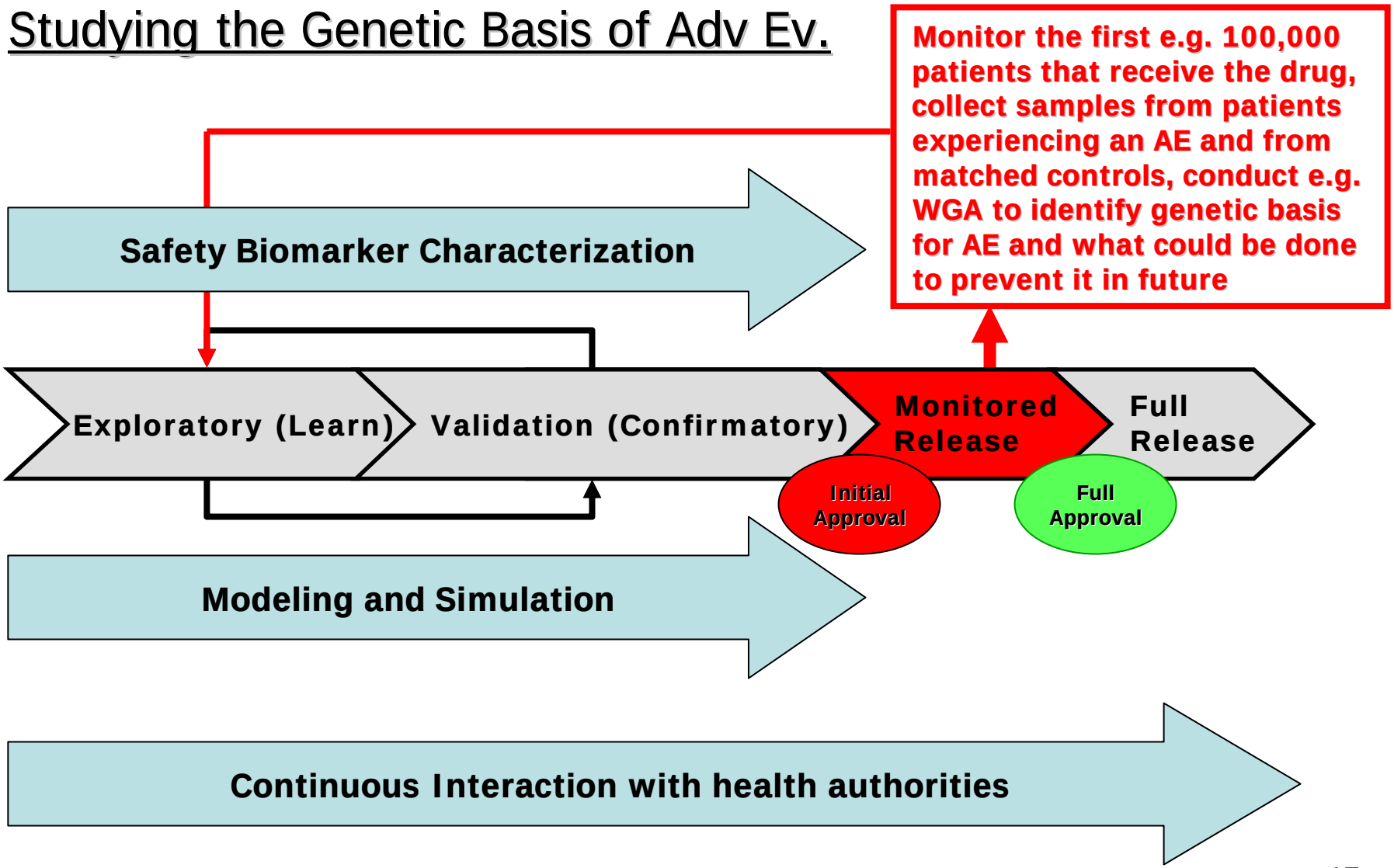
So we solved it all ?

- Not quite:
  - The fact is that we will never know for sure whether a drug is entirely safe when it gets to the market
- A main problem persists: access to the samples and to data that could help us to study rare adverse events:
  - Usually, the size of safety databases that are generated during drug development are too small to do a good job in picking up rare safety events
  - The largest safety information is produced when a drug is on the market
    - Our current tools do not allow us to effectively capture this information and capitalize on its potential

Size of Safety Database

- Typical size of clinical trials:
  - Phase 1: tens
  - Phase 2: tens – hundreds
  - Phase 3: hundreds – thousands
- What happens if an adverse event occurs 1:5,000 ?
  - We will likely miss the event because the size of the safety database is too small.
- How could we create a larger safety database before a drug is fully launched?
  - We create a system that looks something like this:

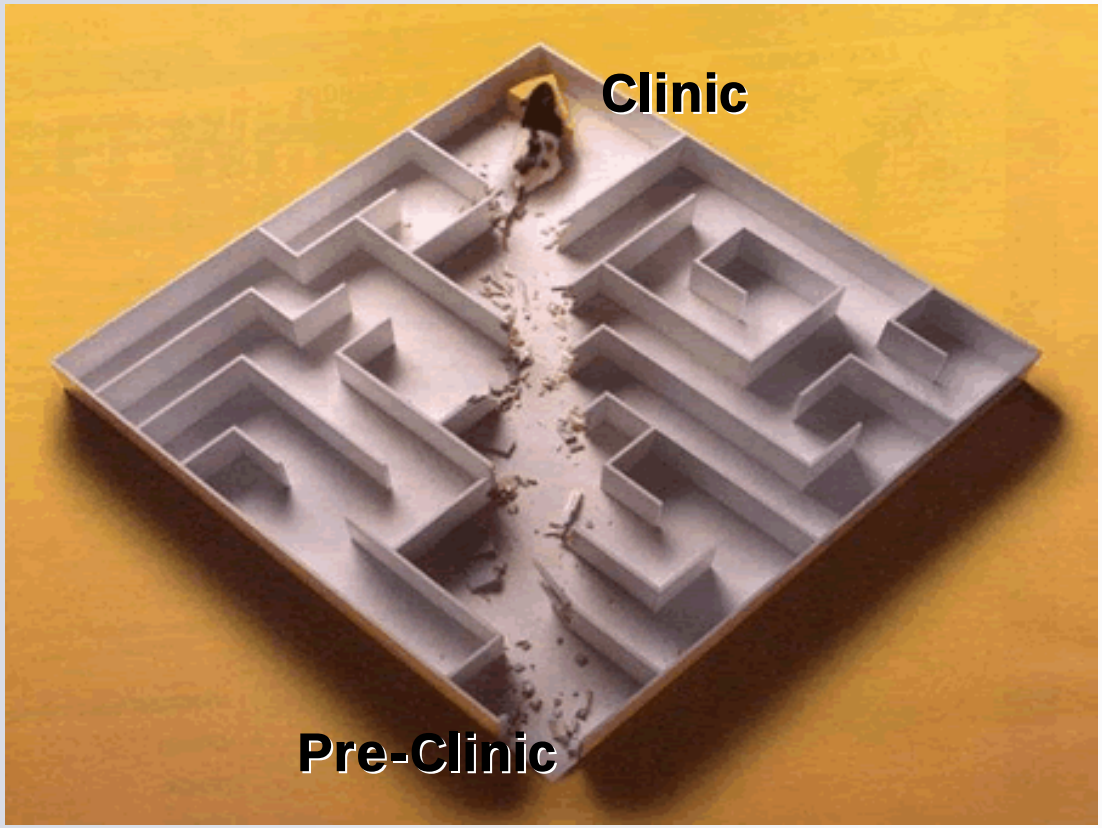
A Proposal to Significantly and Effectively Increase the Size of Drug Safety Databases and to Enable Studying the Genetic Basis of Adv Ev.



Conclusions

- The emergence of new molecular biomarkers for drug safety will allow us to better bridge the safety gap between the pre-clinic and the clinic – we hope that eventually there will be a true continuum
- Safety cannot be “proven”, i.e. we will continue to rely on the absence of a signal
- The better characterized the toxicity, the better a marker for this toxicity will be – this requires an interdisciplinary approach
- New (genomic and other) technologies have already enabled us to better classify compounds, what we now need are qualified markers for bridging studies and markers to address idiosyncratic events
- New bridging markers will be submitted to the FDA for review this year and a process to review these markers is being set up
- Genomic association studies (incl. e.g. whole genome SNP scanning) have the potential to identify markers for rare adverse events, but access to well characterized samples remains a problem
- New mechanisms and processes to study clinical (incl. postmarket) safety should be explored

Think Different !



Thank You !

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