NOVADISCOVERY
THE EFFECT MODEL COMPANY

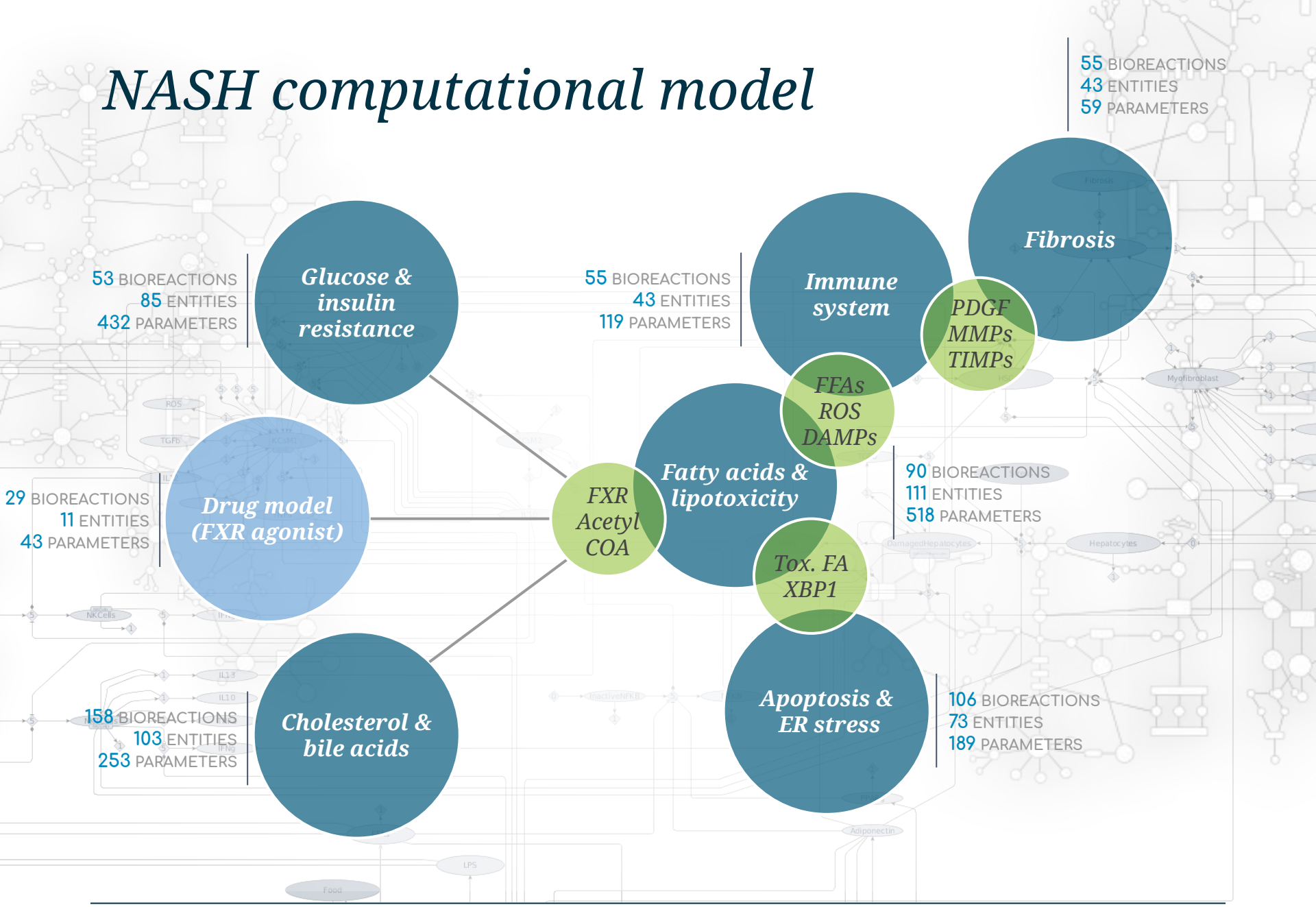
“The in silico paradigm:
understanding the potential of mechanistic models and their limitations,
adapting organizations and building the necessary expertise

EUFEMED conference 2019

Characteristics of mechanistic models

- What
  - The computational modeling of diseases, drugs and patients
  - A multiscale representation of the disease of interest
  - Consisting in a collection of pathophysiological submodels
  - From target site to clinical endpoint
- How
  - Knowledge extracted from scientific articles to map all biological entities and their functional relationships
  - Data to calibrate then validate the model
- Why
  - Failure of the trial-and-error drug R&D paradigm
  - Intrinsic complexity of human biology
  - Limits of data-heavy models

NASH computational model



Use cases

- Neuroprotective agents in acute stroke
  - Failure of animal-to-man translation could have been avoided
- Target combination exploration in immuno-oncology
  - 6,000 trials necessary to explore the entirety of potential pairwise combinations
- Rare diseases and virtual patients
  - Reach statistically significant study populations with virtual patients
- Repurposing in cardiovascular diseases
  - Shorten development time by skipping a Phase 2

Trend towards smaller trials focused on responders

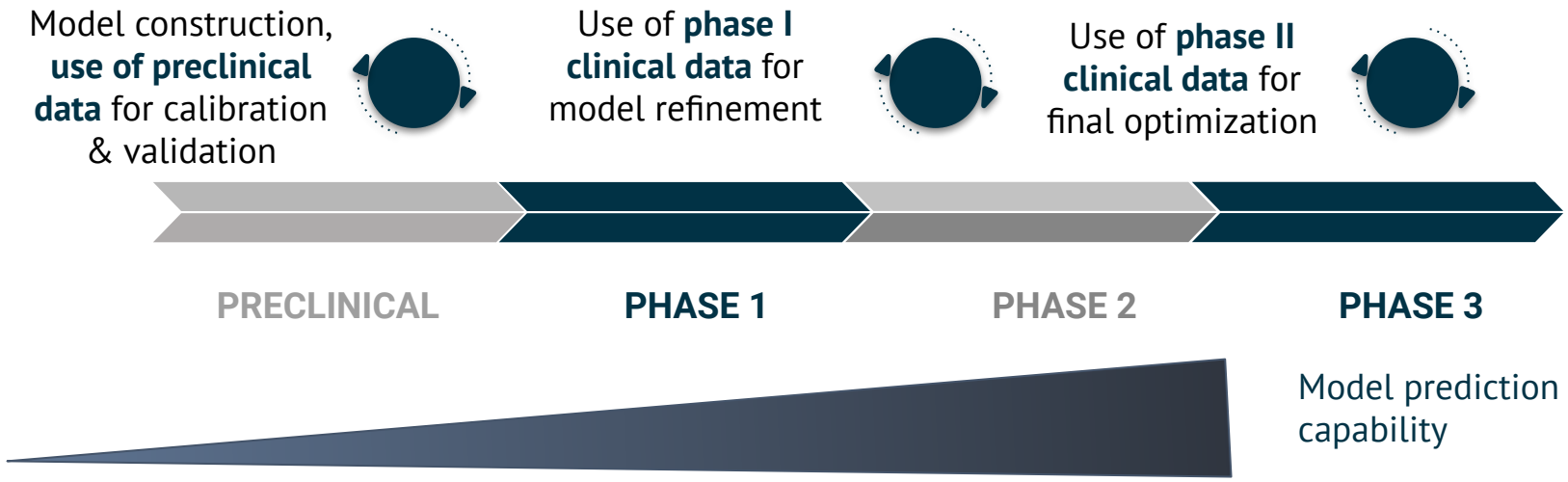
Benefits of the in silico R&D paradigm

Establish in silico as the 3rd pillar of drug R&D in support of in vitro and in vivo trials

- **Learn & confirm**
  Optimize *in vitro* & *in vivo* assays
  Elucidate MoA
- **Reduce time and costs**
  Explore assumptions cheaper/faster
- **De-risk decisions**
  Assess consequences in terms of clinical benefit before trials on humans
- **Run more ethical trials**
  Select best responders

Limitations

- Bad scoping of the model > **iterate with experts**
- Knowledge gaps > **generate additional insights**
- Unreliable knowledge > **apply curation model**
- Improper validation > **follow the guidelines**



Adapting organizations & bringing necessary expertise

- How is big pharma currently approaching the problem
  - Centralized/siloed modeling groups serving all R&D programs in a provider/customer relationship
  - Modeling project budget taken out of R&D program P&L
- What will work
  - Embedded multidisciplinary teams, i.e. modeling experts form an integral part of the R&D team
  - Blend expertise in biology, medicine, clinical pharmacology, applied mathematics, data science, artificial intelligence and software development
- An interesting development in the smaller biotech space
  - An increasing number of venture capital funds are imposing in silico clinical trials as a funding milestone in lieu of less value-accretive milestones (e.g. first patient enrolled)