What Can We Expect from Integrating Precision Animal Modeling Into the Precision Medicine Paradigm?

Kent Lloyd, UC Davis
Inform, Inspire, Engage
Opportunities at Interfaces

Animal modeling researchers

- Welfare experts, ethicists
- Regulators and Safety experts
- Precision Medicine Programs
- Data aggregators & analyzers
- Patient advocates
- Advanced in vitro systems
- Global strategists
- Clinician Scientists

Global strategists
Integrating precision modeling systems into the precision medicine paradigm
“It’s far more important to know what person the disease has, than what disease the person has.”
Hippocrates 460–370 BCE
How far we’ve got to go

- Growth in “translational” research has increased incidence of poorly predictive animal models (= rigor & reproducibility)

- Modest gains in treatment successes, slow and expensive drug pipelines that fail in diverse patient populations (= valley of death)

- Genotype ➔ Mechanism ➔ Phenotype not as easy as once thought (= pleiotropy, heterogeneity, variable penetrance, sexual dimorphism, etc)

- Exponentially-increasing number of variants of unknown significance, lack of sufficient specific biomarkers of disease (= causation vs correlation, disease genes ➔ disease alleles)
Ultimate Objective of Model Organisms

Overcome bottlenecks to positive health outcomes...

Timely & accurate disease diagnosis in humans
Understanding disease mechanism at systems level
Predictable, reliable and effective therapeutic response

from “Towards Precision Medicine”, National Academies of Science, 2011
Also applicable to Veterinary Medicine

Can clinical trials on dogs and cats help people?

By David Grimm Aug. 11, 2016, 9:00 AM
Utility of Model Organism in Precision Medicine

Depends on predictive value, “proximity” to patient
How “proximate” is proximate (and is it enough)?

Undiagosed / Rare Disease (Heritable, Familial, Syndromic)

- Diagnostic odyssey
- Precision model
- Timeline:
  - History
  - Examination
  - Clinical Labs
  - WES/WGS
  - Variant call, analysis, interpretation, prioritization
  - CRISPR targeting, cohort production
  - Cohort phenotyping, data analysis

- 3 months
- 2 months
- 7 months
- 6 months

4.8 years (J Rare Disorders, 2016)
Value Proposition

(David Valle:)

Model organisms and precision medicine

- Confirm causation
- Understanding pathophysiology
- Surrogates for treatment studies
**How can model organisms improve outcomes from precision medicine?**

<table>
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<tr>
<th>Precision Medicine</th>
<th>Without modeling</th>
<th>With modeling</th>
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<tr>
<td><strong>Factors</strong></td>
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<td>Observation/Examination</td>
<td>✓</td>
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<td>Experimental Interrogation</td>
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<td>Therapeutic Intervention</td>
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**OUTCOME BETTER OUTCOME**
“Traffic” algorithm that incorporates patient-specific model organism into precision medical evaluation

Integrating diverse datasets using phenotypes to achieve a diagnosis

**Clinical**
- Physician: Patient has arachnodactyly, micrognathia, and other abnormal phenotypes; what are the possible etiologies and diagnoses?
- Patient: I have long slender fingers and toes; what are the possible diagnoses and causes?

**Basic**
- Model researcher: What are the phenotypic consequences of Ski mutation? What human diseases is Ski modeled best suited to model?
- What are the gaps in knowledge my model has the potential to address? What additional experiments would this involve?

**Translational**
- Translational researcher: What is the best model for Shprintzen-Goldberg syndrome? (zebrafish or mouse)

**Phenotype**
- Phenotype similarity
- Abnormal cranio-facial morphology

**Different communities**
- Prop-tosis
- Bulging eyes
- Micrognathia
- Small jaw
- Arachnodactyly
- Spider fingers

**Different anatomy**
- long mandible
- arachnodactyly

**Orthology**
- Shprintzen-Goldberg syndrome
- SKI (human)
- Marfan syndrome
- FBN1 (human)
- Loefs-Dietz syndrome
- TGFB1 (human)
- TGFB2 (human)
- TGF-β
- ski skib (fish)
- Ski (mouse)

**Pathways**
- Relevant models across species

**Hypothesis generation**
- What genetic tests can I order?

**Is this preliminary phenotyping complete enough for a differential diagnosis? If not, what phenotypes complete the profile? What genetic tests can I order?**
What should we expect from incorporating precision models into precision medicine?

- Disease pathogenesis, in context (patient characterization)
- Disease causation (simple [Mendelian] and complex)
- Role of environmental and other external challenges
- Relative influence and impact of behaviors and lifestyles
- An “illuminated” druggable genome
- A “diagnosed” disease network
- Targeted therapies and therapeutic effectiveness
- Improved prevention strategies: delay onset and/or progression of individual becoming a patient
**Calls to Action**

1) *Complete a comprehensive, encyclopedic functional annotation of the genome*

---it *is* data driven, but not only human data

---requires experimentation:
  - descriptive “screening” and hypothesis testing

---beyond the protein coding region:
  - non-coding variants, regulatory regions, *microRNA*

---unveil pleiotropy, sexual dimorphism, “essentiality”
2) **Formalize linkages between model organism communities and databases with precision medicine initiatives**

   --cross-talk, ontologies, and comparative phenotyping

   --model identification, nomenclature, description

   --establish formal relationship with All of Us Program
Calls to Action

3) **Enhance processes and expand availability of tools to apply comparative ontologies and develop computable phenotypes**

   --align phenotype to genotype
   
   --knowing disease genes to prioritize disease alleles
   
   --secure scientific rigor, reproducibility, reliability
   
   --ARRIVE guidelines, CAMARADES
Calls to Action

4) **Integrate animal ontologies with in vitro analyses, humans-on-a-chip, and patient data to identify knowledge gaps that propel precision modeling of specific human variants**

   --accelerate differentiation of correlated from causal factors

   --optimize selection of model organisms for analysis, including spontaneous models

   --attention to welfare issues and 3R’s

   --improve decision making, better evidence, less noise
5) Promote, incentive, and reward a culture of synergistic, clinical outcomes-focused networks and collaborations between translational researchers, clinician scientists, and patient groups

--preclinical and co-clinical trials

--work towards the “regulatory dream”

--focus on health outcomes, disease prevention
6) **Expand model organism resources and technology development for rapid assessment of variants**

   -- addn’l/enhanced “MOSC”-like, “GEMM”-like activities
   -- biorepositories, tissue/specimen banks
   -- phenotypic validation and testing capabilities
   -- anatomic, clinical, and molecular pathologies
   -- **MOD**: ‘model on demand’
   -- ensure predictive validity of models

**Calls to Action**
Calls to Action

7) Establish clinical utility of a precision modeling paradigm to advance and accelerate diagnostic decision-making, targeted therapeutic development, and predictable disease prevention strategies

8) Ensure accessibility of resources, tools, and networks of precision modelers to the global community

--transcend cultural, socio-economic divisions

--reduce and overcome disparities (access, opportunities)

--promote science education, skills training, community outreach
Advancing Disease Modeling in Animal-Based Research in Support of Precision Medicine

A Workshop of the Roundtable on Science and Welfare in Laboratory Animal Use
with support from the Office of Research Infrastructure Programs,
National Institutes of Health

October 5-6, 2017
2100 C Street NW, Washington, DC
Historic National Academies of Sciences Building
Fred Kavli Auditorium

Online participants, email questions to ilar-roundtable@nas.edu
Join the conversation on Twitter by using #ILARprecisionmedicine