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Advancing the Next Generation of Risk Assessment

NexGen

A Community of Practice Discussion

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The purpose of this talk is to:

- Review the NexGen Program
- Discuss and get feedback on potential implications for risk assessment

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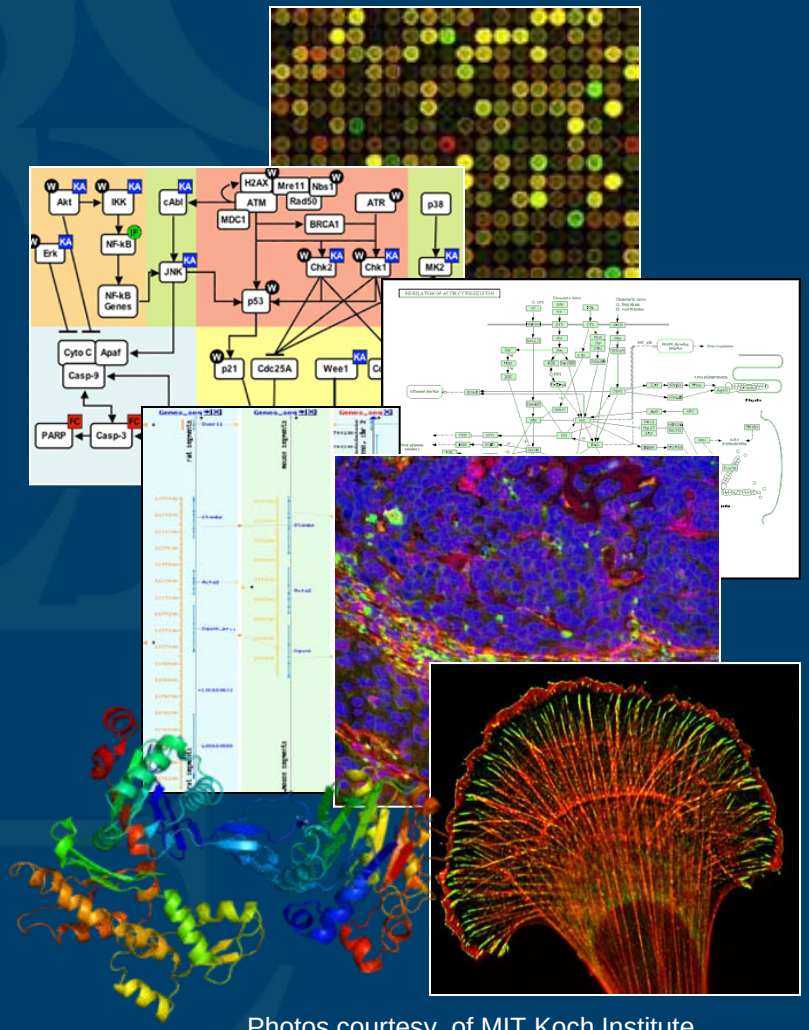
What is NexGen??

Program Goal:

To advance risk assessment science via incorporation of recent progress in molecular systems biology



Photos courtesy of MIT Koch Institute

NexGen Partners

- US Environmental Protection Agency, Office of Research and Development
- National Institutes of Environmental Health Sciences & National Toxicology Program
- Centers for Disease Control & Agency for Toxic Substances and Disease Registry
- NIH Chemical Genomics Center
- California's Environmental Protection Agency, Office of Environmental Health Hazard Assessment
- FDA National Center for Toxicological Research
- Department of Defense
- European Chemical Agency & Joint European Commission Joint Research Center

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Drivers for Change

- Scientific revolution in biology – most is not used in risk assessment
- In the European Union –
  - REACH ~ 120,000 chemicals
  - Emphasis on “non-standard” data for risk assessment
  - 40,000 dossiers in near future
- In the United States –
  - Several NRC reports and workshops
  - Tox21 – 10,000 chemicals tested in biotech assays the next few years

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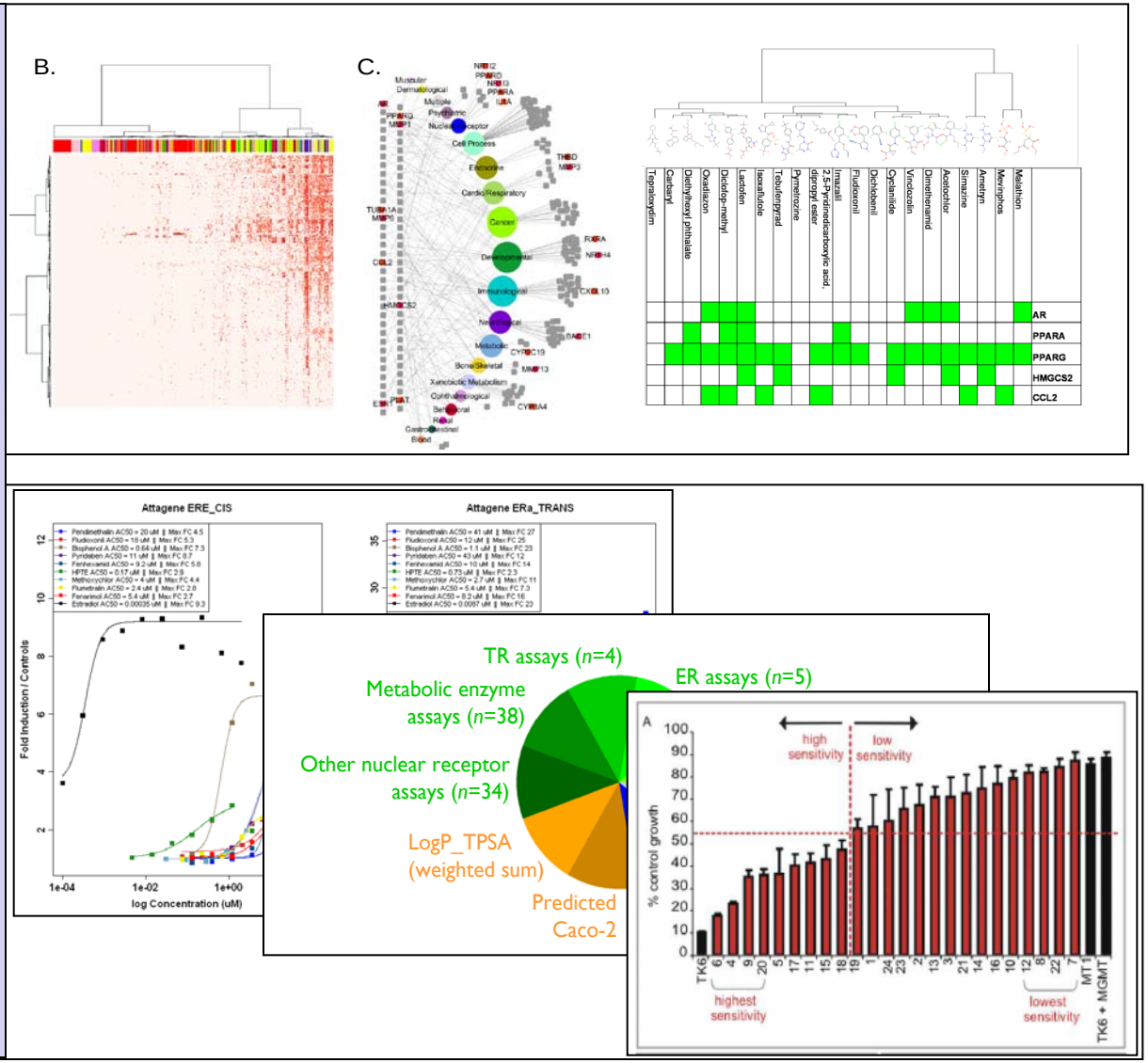
Objectives of NexGen

- Pilot a NexGen Framework that considers at how new types of data fits in with other types of data used in risk assessment
- Refine bioinformatics systems for knowledge mining and creation to serve risk assessment.
- Develop prototype health assessments
  - ✓ Elucidate proof of concept, value of information, & decision rules
  - ✓ Refine through discussions with scientists, risk managers, and stakeholders

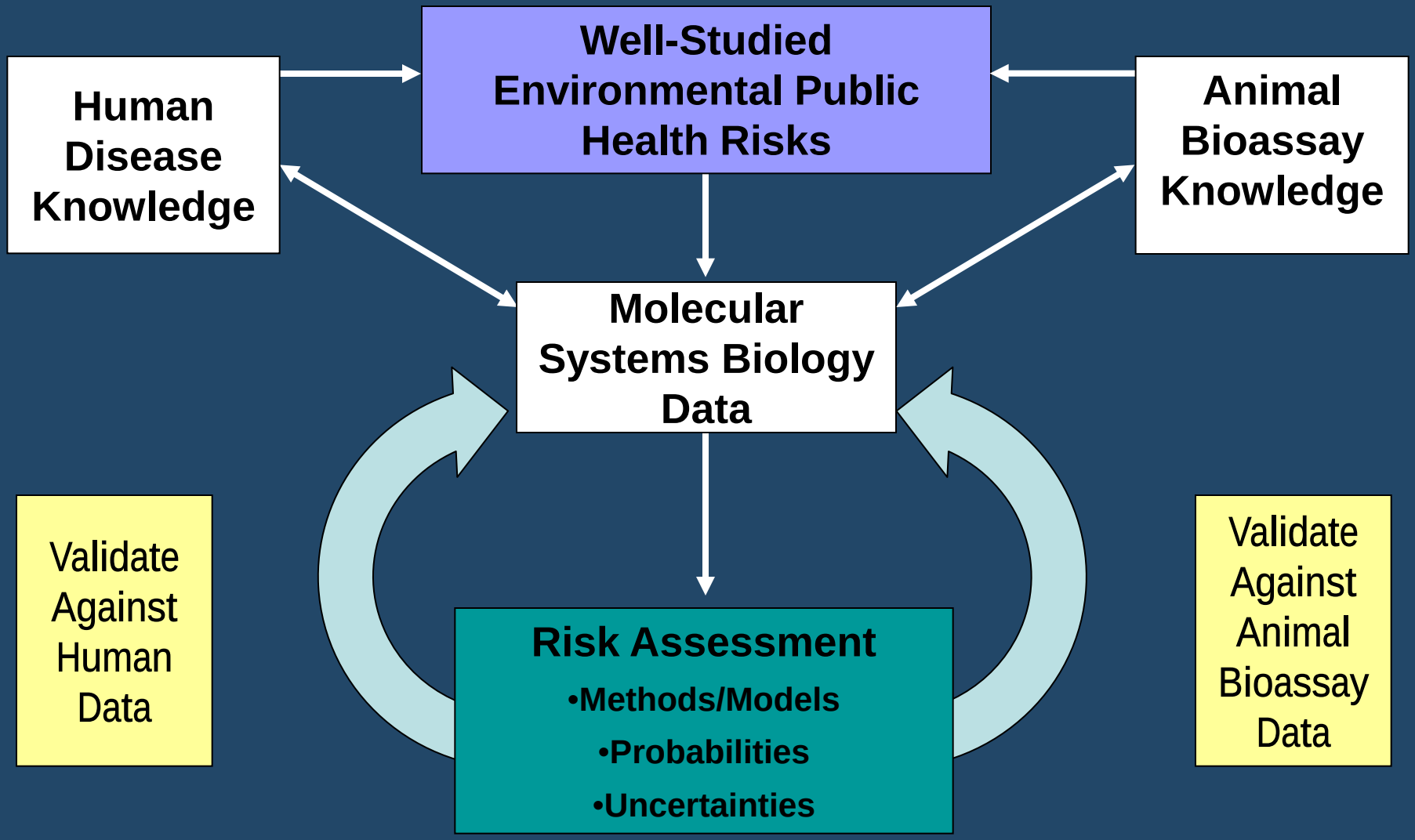
Risk Assessment Questions

- Identify potential adverse health effects?
- Inform dose-response?
- Link dose to exposures?
- Address issues:
  - –Low-dose response?
  - –Sensitive subpops?
  - –Relevance of non-human species?
  - –Mixtures/stressors exposures?
- Better characterize human risks?

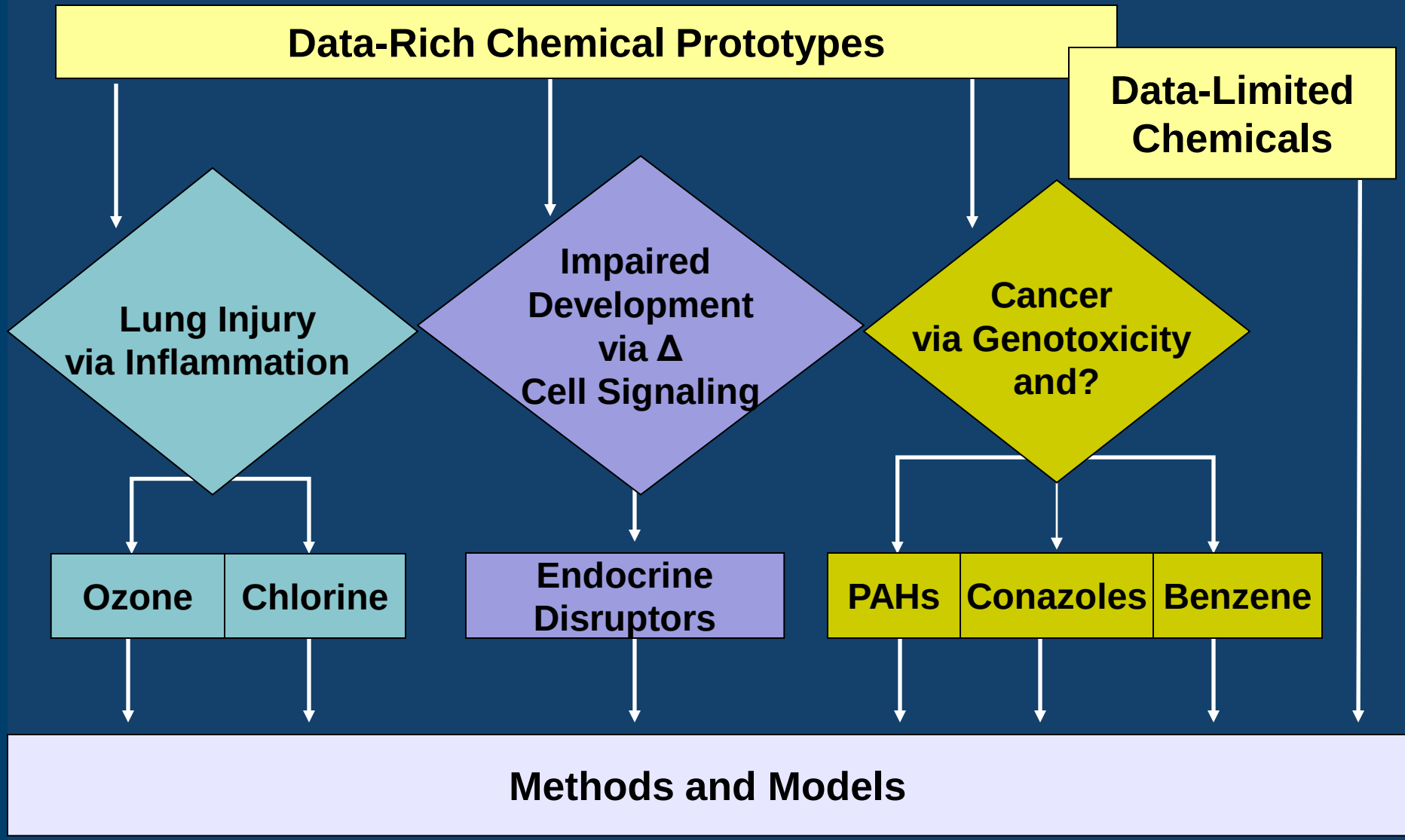


General Prototype Approach

Reverse Engineer



Overview of Projects



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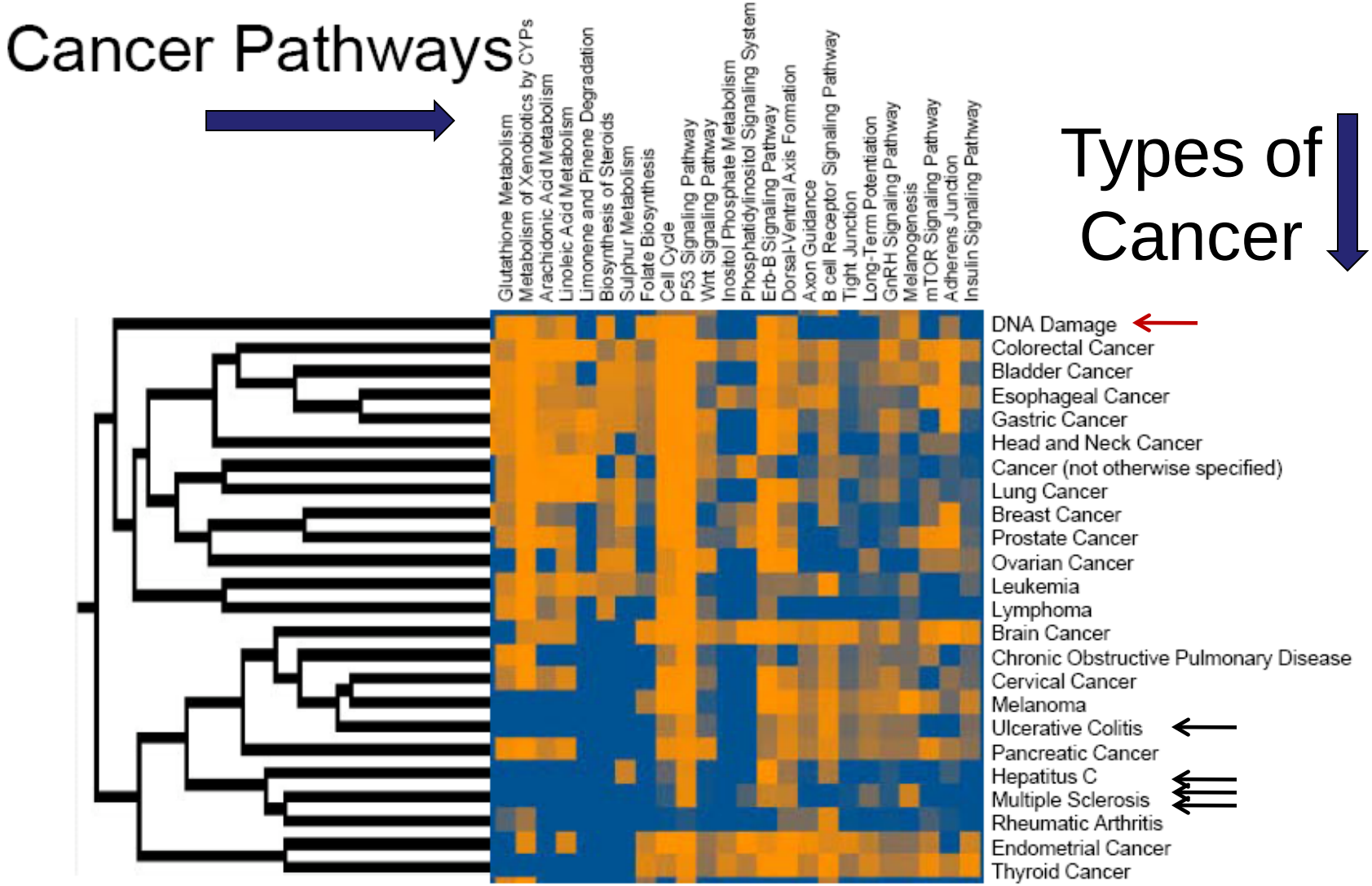
Hazard Id: Can We Identify Specific Adverse Effects Using Omics?

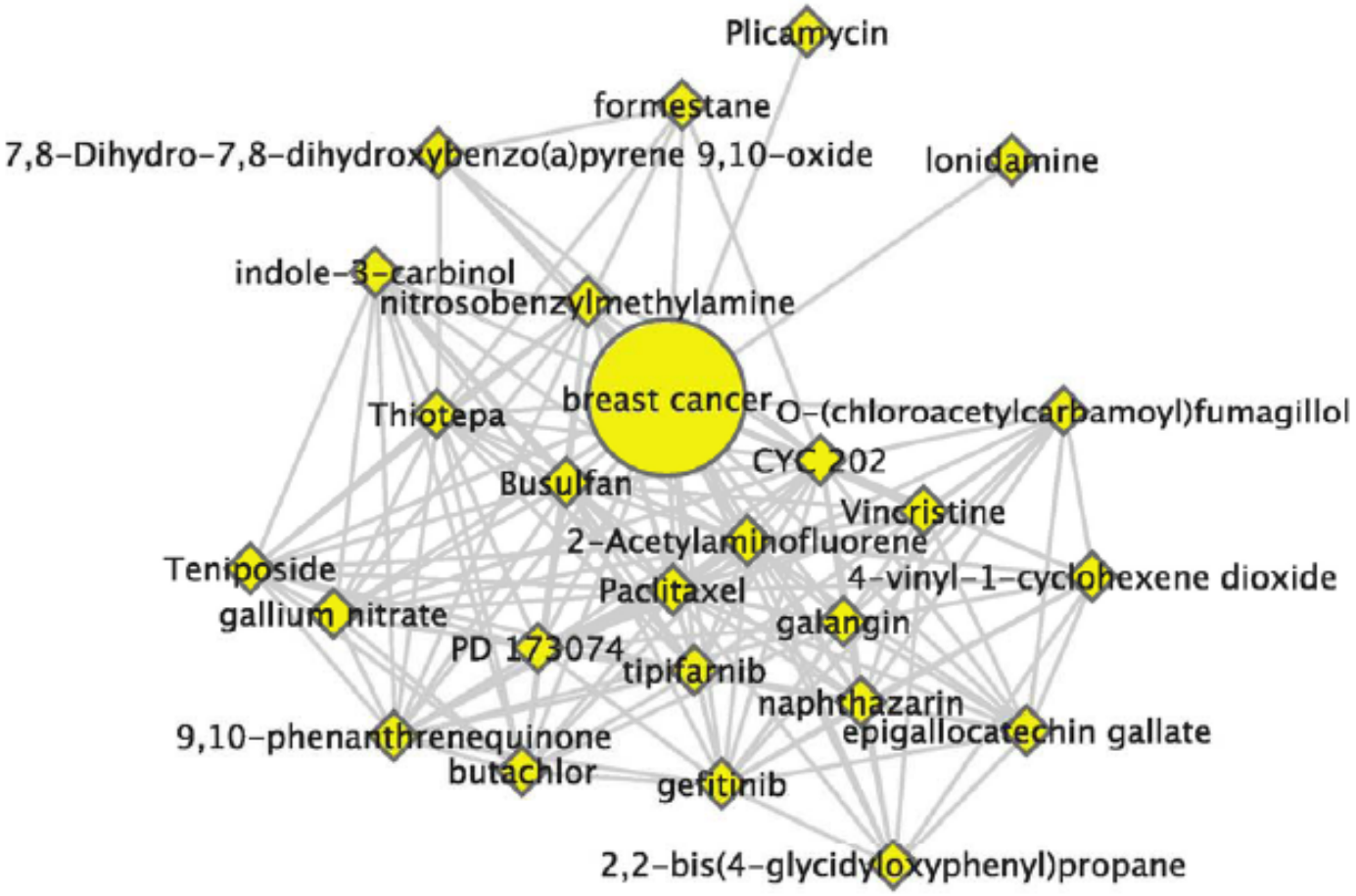
Hazard Id: Can We Identify Specific Adverse Effects

- I think yes.
- It seems like we are beginning to identify causal mechanism or molecular patterns that make one chemical more likely to produce a specific effect than another.
- The “answer” will, for the foreseeable future, be a probability vs. yes/no answer about cause and effect.
- Knowledge of single events or linear MOAs, in general, is not insufficient – **Think Networks**
- Some illustrations follow….

From Chris Portier



Chemicals linked to breast cancer



from Chris Portier

Hazard Id: Issues

So we are beginning to identify hazards with omics, BUT its complicated….

- Omic patterns change with dose and time.
- Metabolism still matters.
- High throughput cell line assays can only tell us about molecular/cellular mechanisms.
- Specific phenotypic outcome depend on both tissues/organism level integration, and lifestage; examples follow

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Hazard Identify: Issues

Common Pathway/Different Disease

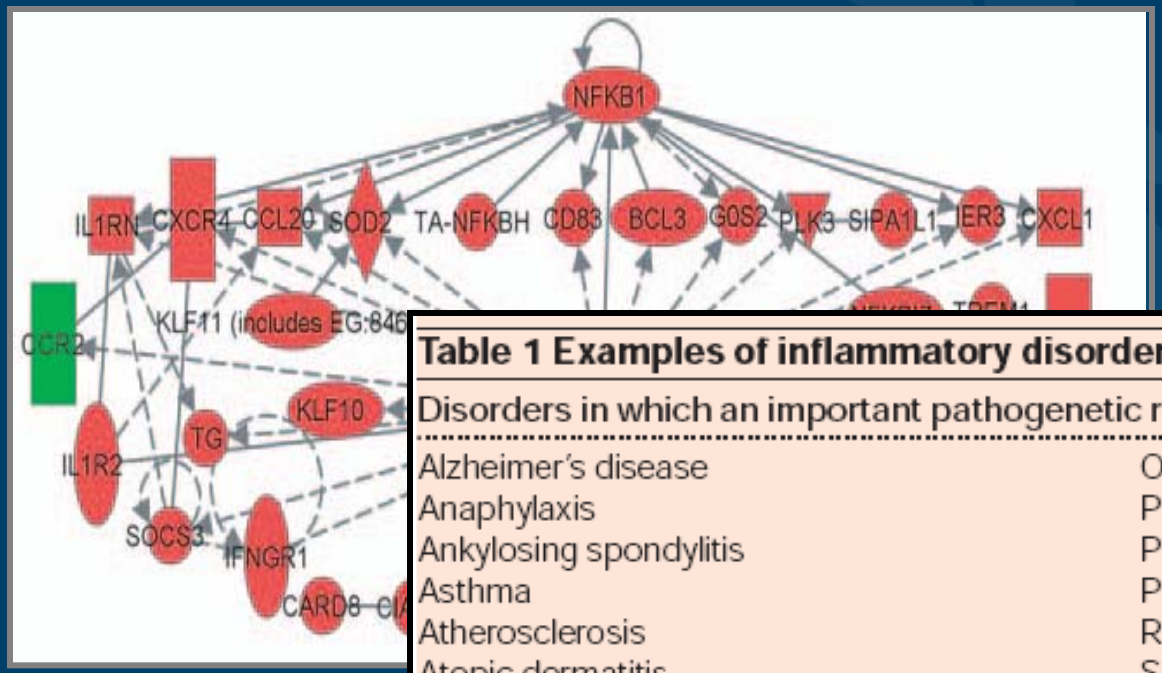


Table 1 Examples of inflammatory disorders

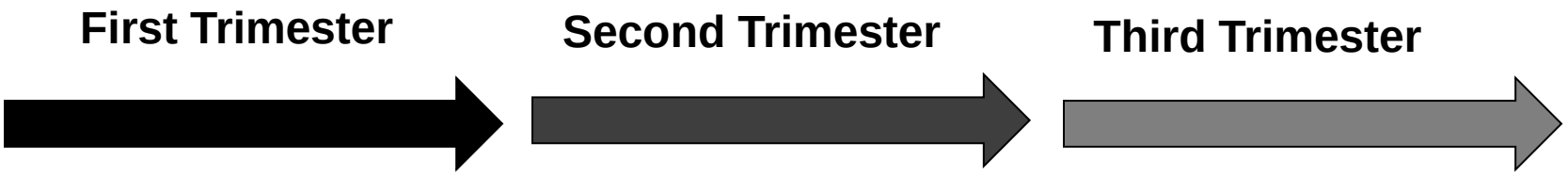
Disorders in which an important pathogenetic role is assigned to inflammation	
Alzheimer's disease	Osteoarthritis
Anaphylaxis	Pemphigus
Ankylosing spondylitis	Periodic fever syndromes
Asthma	Psoriasis
Atherosclerosis	Rheumatoid arthritis
Atopic dermatitis	Sarcoidosis
Chronic obstructive pulmonary disease	Systemic lupus erythematosus
Crohn's disease (regional enteritis)	Type I diabetes mellitus
Gout	Ulcerative colitis
Hashimoto's thyroiditis	Vasculitides (Wegener's syndrome, Goodpasture's syndrome, giant cell arteritis, polyarteritis nodosa)
Ischaemia-reperfusion injury (occlusive and embolic stroke and myocardial infarction)	Xenograft rejection
Multiple sclerosis	

Hazard Identify: Issues

Common Mechanism/Different Diseases

Lifestage Dependency

Environmental Stressor > Δ DNA Methylation > Δ Increased Disease



- ✓ CV Disease
- ✓ Hypertension
- ✓ Dyslipidemia
- ✓ Obesity

- ✓ Pulmonary Disease
- ✓ Renal Disease

- ✓ Diabetes
- ✓ Depression
- ✓ Schizophrenia
- ✓ Anti-Social Personality Disorder

From Robert Lane,
UT Dept Neonatology

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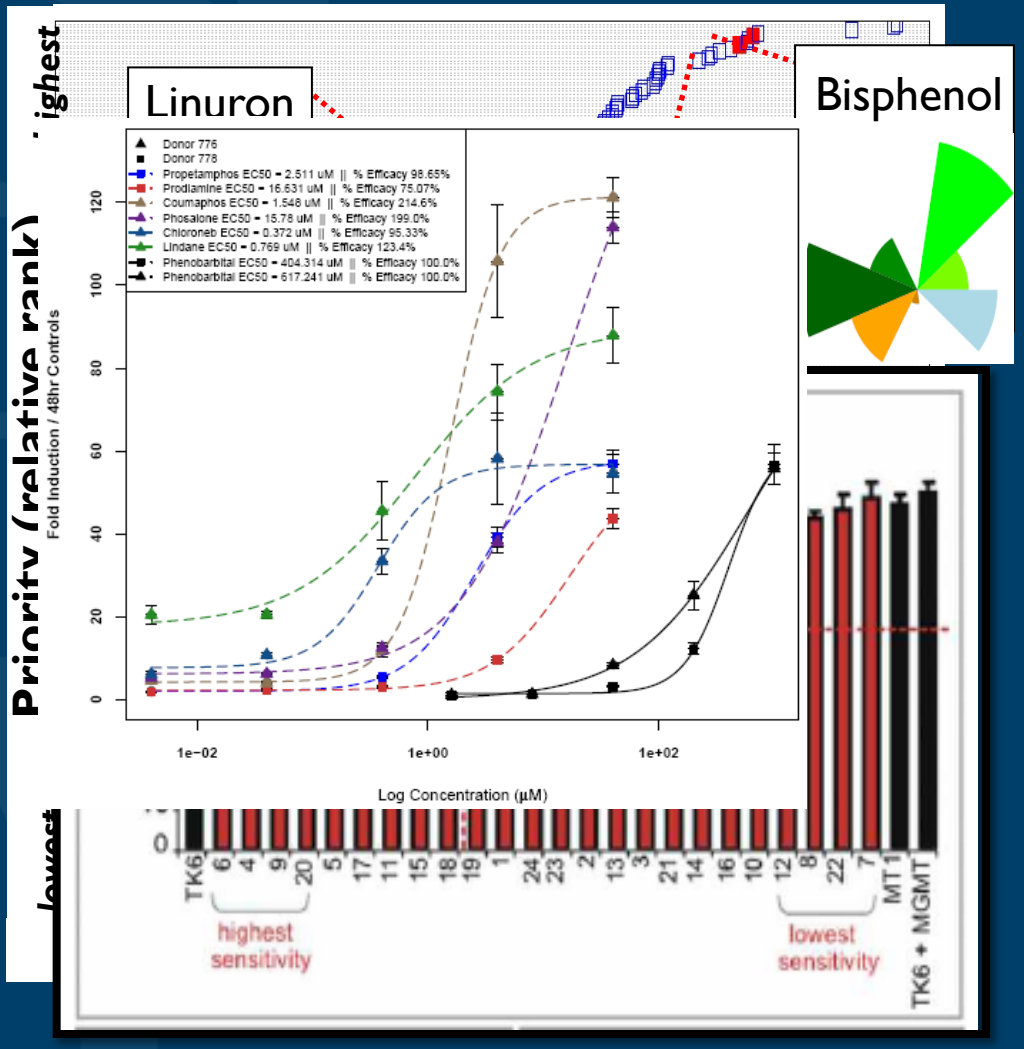
Dose – Response: At what concentrations do effects occur?

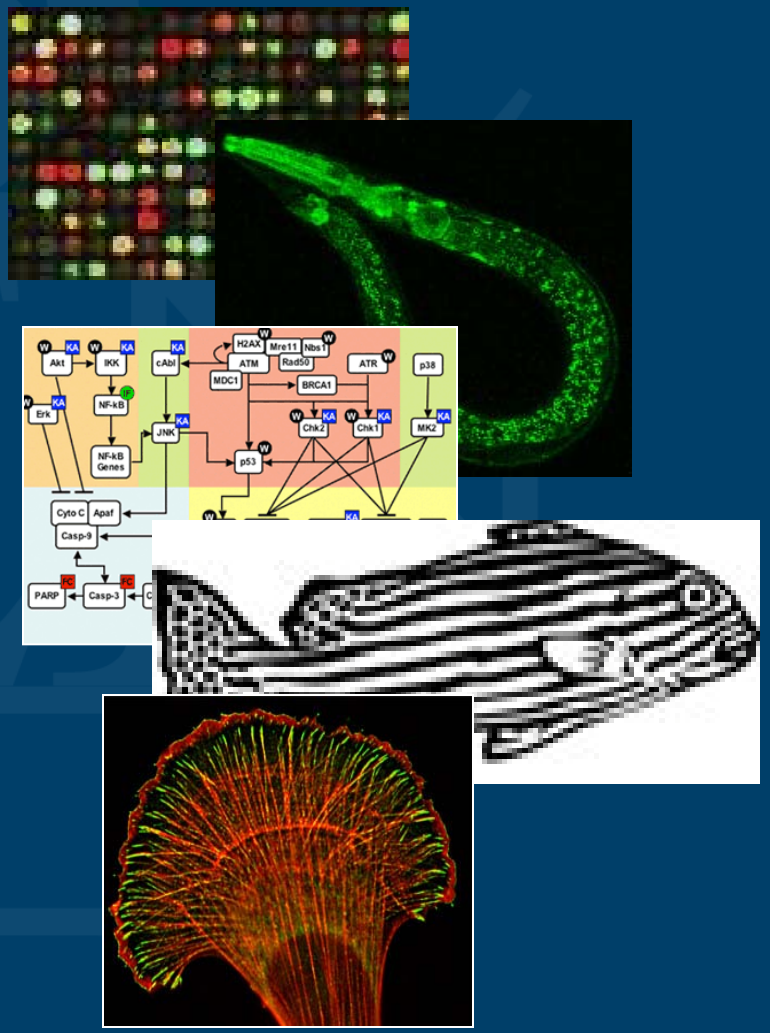
Dose – Response Tier 1

- Lots of nice dose-response data, collected over a wide range
- Must integrate various pathway data
  - Use LOEL or slope estimate of molecular data
  - Number of pathways impacted
- Must incorporate variability as feasible
- Yields relative potencies of chemicals to induce molecular/cellular mechanisms
- Use experimental data, don't extrapolate

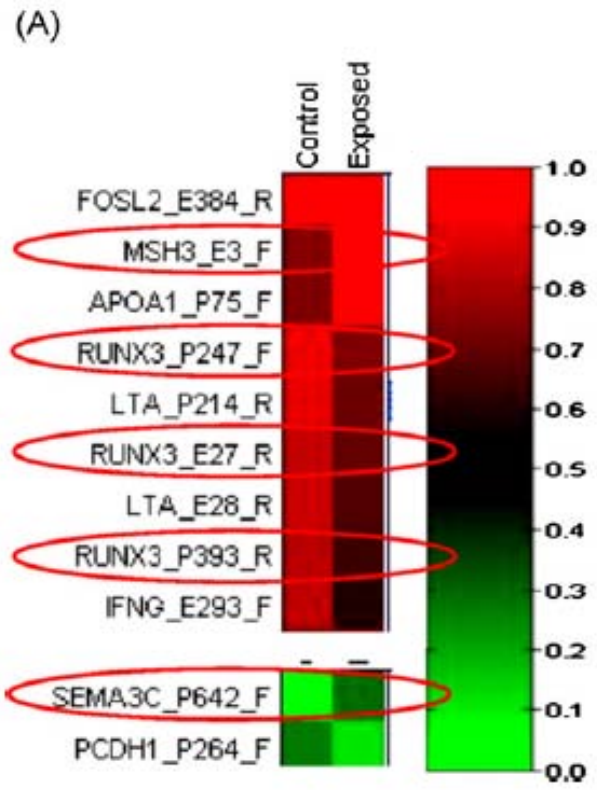


Dose – Response –Tier 2

- Similar to Tier 1 but using high & medium test systems that yield more direct insights into risks by including tissue/ organism level integration and metabolism.
- Examples include: virtual tissue modeling, tissue, culture, alternative species of Tier 2 include.



Dose – Response: Tier 3



Heat map of DNA methylation patterns in in vivo benzene exposed and control humans. Red is methylated. Green is unmethylated. Zhang et al. 2010

- Human biomarkers of effect and exposures
- Estimation of risks vs. relative potencies
- Interaction of background and chemically induced events leading to disease
- Think in terms of biasing the population toward or away from disease.
- Risk assessments will focus on shifts in population distribution

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Summary

- Proof of concept, value of information and decision rules are being developed.
- New types of data (e.g. omics) can be used to identify the likelihood of adverse effect outcomes and estimate relative potencies and human risks.
- Weight of evidence varies depending on the type of data

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Summary

- Think in terms of networks and pattern recognition:
  - –Phenotypically similar diseases can be induce by perturbation in different parts of the network.
  - –A specific pattern of disruption can result in several different diseases depending on species, tissue and life stage.
- Risk will best be characterized as distributions that incorporate variability.

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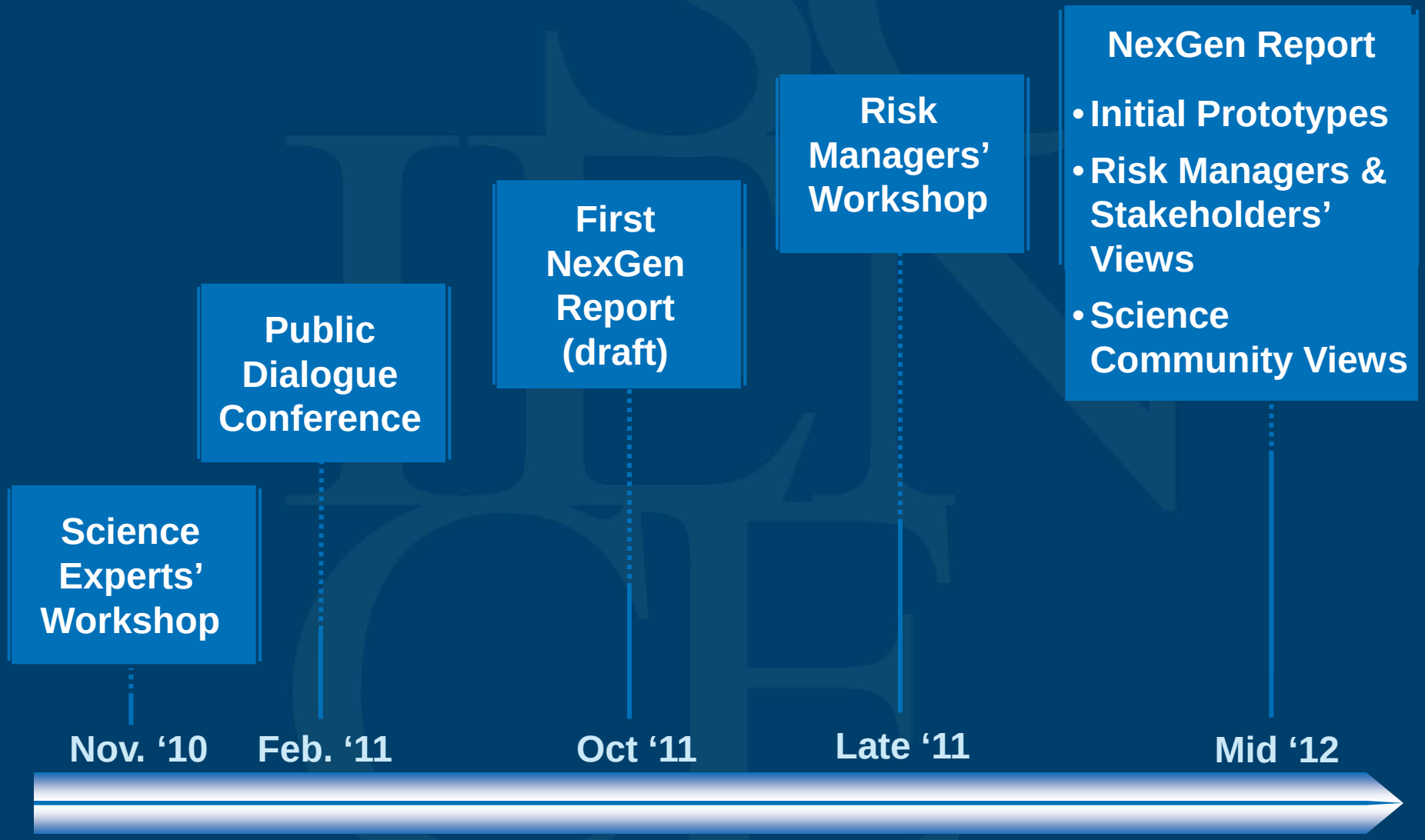
NexGen Health Assessment Timeline



Acknowledgements

Paul Anastas
Becki Clark
Peter Preuss
James Avery
Stan Barone
Weihsueh Chiu
Kathleen Deener
Rob DeWoskin
Lynn Flowers
Kate Guyton
Annie Jarabek
Kathleen Raffaele
Jason Lambert
David Miller
Debra Segal
Bob Sonowane
David Bussard
Abdel Kadry
Robert Kavlock
David Dix
Richard Judson
Tom Knudsen
David Reif
Matt Martin
Imran Shah
John Wambaugh
Lyle Burgoon
Robert Devlin
Stephen Edwards
Mary Gilbert
Julian Preston
Woody Setzer
Hal Zenick
Linda Sheldon
Annette Gatchett
John Vandenberg
Martyn Smith
Ken Ramos
Linda Birnbaum
Ray Tice
Mike Devito
Kris Thayer
Chris Austin
James Inglese
Chris Portier
Bruce Fowler
Rusty Thomas
Peter McClure
Dale Hattis
Dan Krewski
Doug Crawford-Brown
Greg Paoli
Lauren Zeiss
Martha Sandy
Brenda Foos

And ~ 50 other people

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Please visit EPA's NexGen Web site for more information:

www.epa.gov/risk/nexgen

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Assays & Assessments

Tier 1 10,000s of chemicals	Tier 2 1000s of chemicals	Tier 3 100s of chemicals
High Throughput **Molecular Mechanisms of Action**	***+High Content/Med Throughput*** **Adds Tissue/Organism Level Integration**	***+High Content, Med/Low Throughput*** **Adds Most Realistic Scenarios**
• In vitro only bioassay batteries (~73-500 assays) ✓Network/disease pattern recognition ✓Metabolism or surrogates ✓QSAR • Anchored to in vivo data • Bioinformatic data integration	• Short-term in vivo exposures with in vitro assays ✓Mammalian species ✓Alternative species • Primary tissue culture • In silico virtual tissues • In vivo or anchored to in vivo data • Bioinformatic data & knowledge integration	• Mo/ecular epidemiology & clinical Studies • Molecular biology + traditional animal bioassay • Environmental exposures • Upstream & phenotypic outcomes • Mechanism of action for multiple stressors • Knowledge integration

Screening/Ranking

Limited decision-making

Regulatory decision-making

Increasing Weight of Evidence