Modeling Chemicals' Adverse Effects
by high-throughput transcriptomics

Stefano Monti
Division of Computational BioMedicine, BU School of Medicine
Department of Biostatistics, BU School of Public Health
Bioinformatics Program, Boston University

Exposures and Latent Disease Risk: Session IV - Moving Forward
Sponsored by: NIEHS Superfund Research Program

Outline

Overview of the experimental and computational approaches we have developed and applied to model environmental chemicals and to predict their long-term adverse effects from short-term transcriptomics assays.

Vignettes from two studies

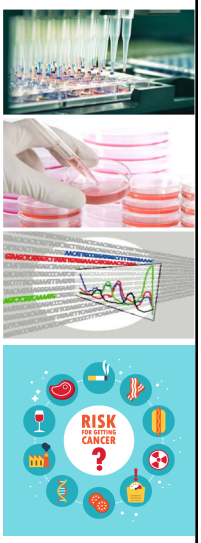
- ***The Carcinogenome Project***: Predicting Long-Term Chemical Carcinogenicity and Genotoxicity from Short-Term Assays.
- ***The Adipogenome Project***: Genomics Characterization of Adipocyte Dysregulation by Environmental and Therapeutic Perturbagens.

Challenges and lessons learned.

Modeling
Chemical Carcinogenicity

Development of
analytical/experimental framework to

predict long-term cancer risk
from exposure to chemical compounds
using genomic assays and computation



Cancer Prevention

Modeling
Chemical Adverse Effects

Development of
analytical/experimental framework to

predict long-term disease risk
from exposure to chemical compounds
using genomic assays and computation

Disease Prevention

Chemical Exposure Understudied



- Constant exposure to pesticides, industrial pollutants, consumer products and drugs — **~ 85,000**
- Less than 2% of all chemical compounds have been systematically tested — **~ 1,500**
- Mixtures of compounds challenging to evaluate — **~ 10^9–10^{12}**

Carcinogenicity Testing
approaches

Epidemiology studies

- ✓ **observational**, not randomized trial
- ✓ incomplete/unstandardized exposure data
- ✓ difficult to control for **confounders**

Carcinogenicity Testing
approaches

Epidemiology studies

- ✓ **observational**, not randomized trial
- ✓ incomplete/unstandardized exposure data
- ✓ difficult to control for **confounders**

In vivo assays

- ✓ two year rat bioassay ("gold standard")
- ✓ **time and resource consuming**
- ✓ Imperfect **mapping to human** carcinogenicity

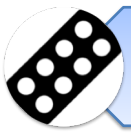
Carcinogenicity Testing
approaches

Epidemiology studies

- ✓ **observational**, not randomized trial
- ✓ incomplete/unstandardized exposure data
- ✓ difficult to control for **confounders**

In vivo assays

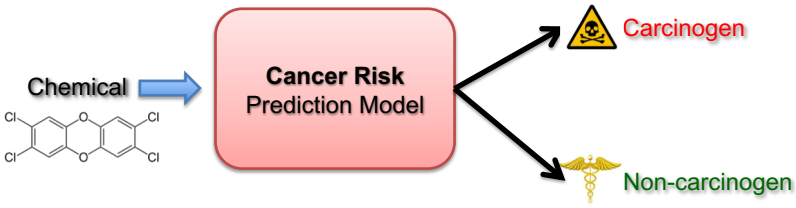
- ✓ two year rat bioassay ("gold standard")
- ✓ **time and resource consuming**
- ✓ Imperfect **mapping to human** carcinogenicity



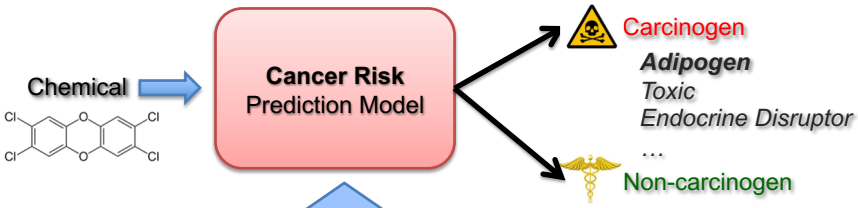
In vitro assays

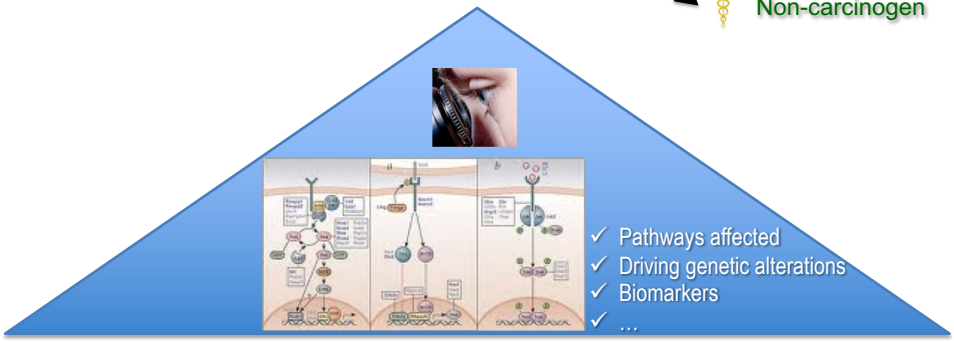
- ✓ human cell lines
- ✓ less time and resource consuming
- ✓ allows large sample size of chemical perturbations
- ✓ **Challenge: translation to in vivo relevance**

The Quest for
a Chemical Carcinogenicity "Crystal Ball"



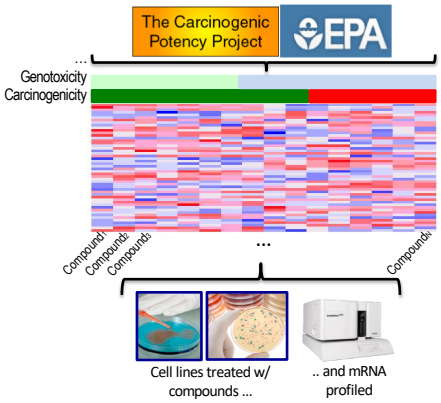
The Quest for
a Chemical Carcinogenicity "Crystal Ball"



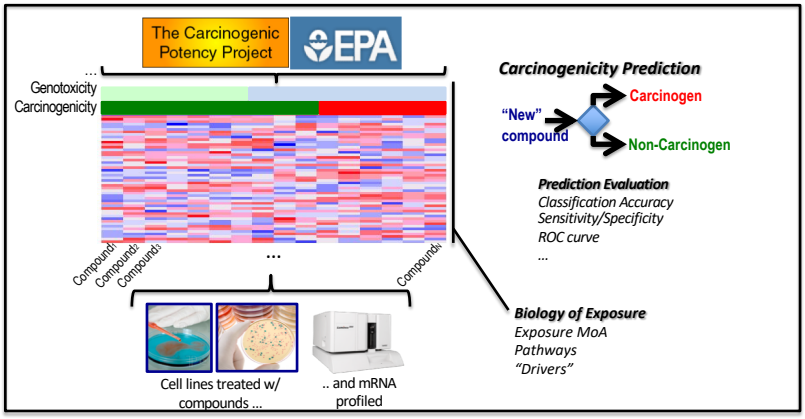


Understand Why

Experimental Design Overview

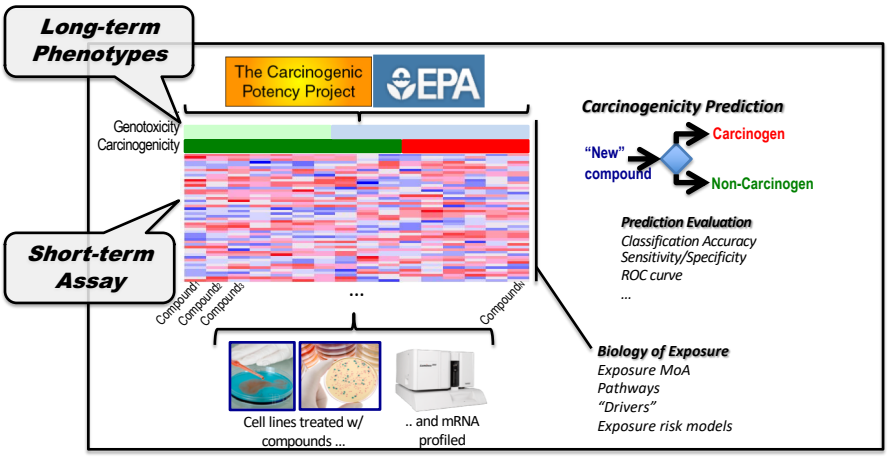


Experimental Design Overview



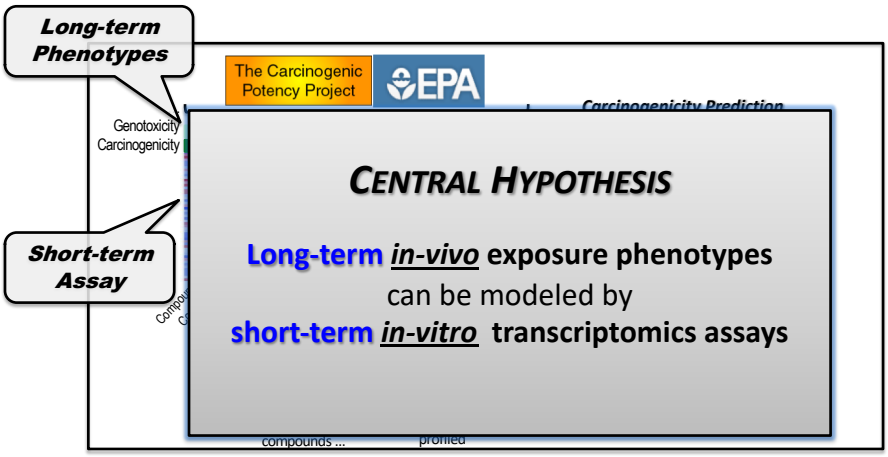
Project relies on high-throughput, cost-effective gene expression assays
Luminex-1000 (L1000) @ Broad Institute
(or highly multiplexed RNA-sequencing)

Experimental Design Overview



Project relies on high-throughput, cost-effective gene expression assays
Luminex-1000 (L1000) @ Broad Institute
(or highly multiplexed RNA-sequencing)

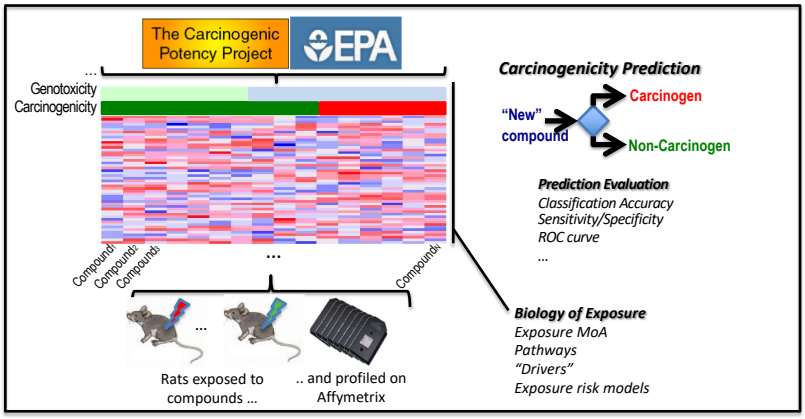
Experimental Design Overview



Project relies on high-throughput, cost-effective gene expression assays
Luminex-1000 (L1000) @ Broad Institute
(or highly multiplexed RNA-sequencing)

Can Carcinogenicity be Predicted from GEP?

the answer from short-term in-vivo (rat-based) assays



DrugMatrix NIEHS TG-GATEs NIBIO

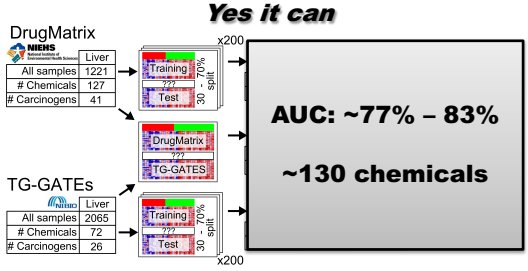
1000s of profiles, 100s of chemicals

Gusenleitner et al., 2014

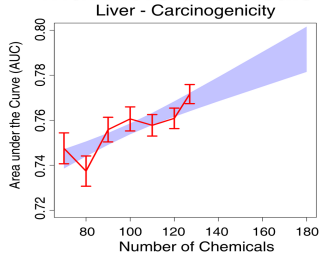
Can Carcinogenicity be predicted from GEP?

The DrugMatrix/TG-GATEs answer

Yes it can



Prediction can be improved with more chemicals



Helps elucidate modes of action

MoA's

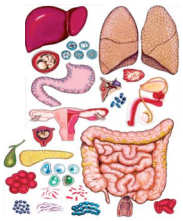
- **DNA damage**
- **Oxidative Stress**
- **Altered metabolism**
- **Proteasome**
- **...**

Gusenleitner et al., 2014

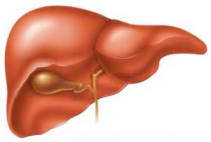
Carcinogenicity Prediction
is tissue-specific

Classification Results

Tissue Agnostic
***AUC:* 65%**



Tissue Specific (Liver)
***AUC:* 77–83%**



Gusenleitner et al., 2014

Home About Contact

https://carcinogenome.org

The Carcinogenome Project

Chemical Carcinogenicity Screening using high-throughput transcriptomics assays

Project	Cell line	Description
Liver Carcinogenicity	HEPG2	This experiment uses 330 selected chemicals for in-vivo liver carcinogenicity testing, including 128 liver carcinogens, 168 non-carcinogens, and 34 miscellaneous chemicals (e.g. nuclear receptor ligands). Chemical carcinogenicity and genotoxicity annotations are based on the Carcinogenicity Potency Database (CPDB), which is the result of tissue-specific long-term animal cancer tests in rodents. In the liver carcinogenome project, HepG2 (liver) cells are exposed to each individual chemical for 24 hours and their gene expression is profiled on the L1000 platform. Each chemical is assayed at 6 doses (2 fold dilutions starting from the highest concentration of 40uM or 20uM) with triplicate profiles generated for each dose...
Breast Carcinogenicity	MCF10A	This experiment uses 345 selected chemicals for breast carcinogenicity testing, including 120 breast carcinogens, 114 non-carcinogens, and 68 miscellaneous chemicals (e.g. nuclear receptor ligands, BU SRP chemicals, lung carcinogens). Chemical carcinogenicity and genotoxicity annotations are based on the Carcinogenicity Potency Database (CPDB), which is the result of tissue-specific long-term animal cancer tests in rodents, or breast carcinogens published from Rudel et. al., 2007. In the CRCGN project, MCF10A (breast epithelial) cells are exposed to each individual chemical for 24 hours and their gene expression is profiled on the L1000 platform. Each chemical is assayed at 3 doses (3 fold dilutions starting from the highest concentration of 100uM, with the exception of selected BUSRP chemicals...

The Carcinogenome Project: Developed by Monti Lab at Boston University
2017

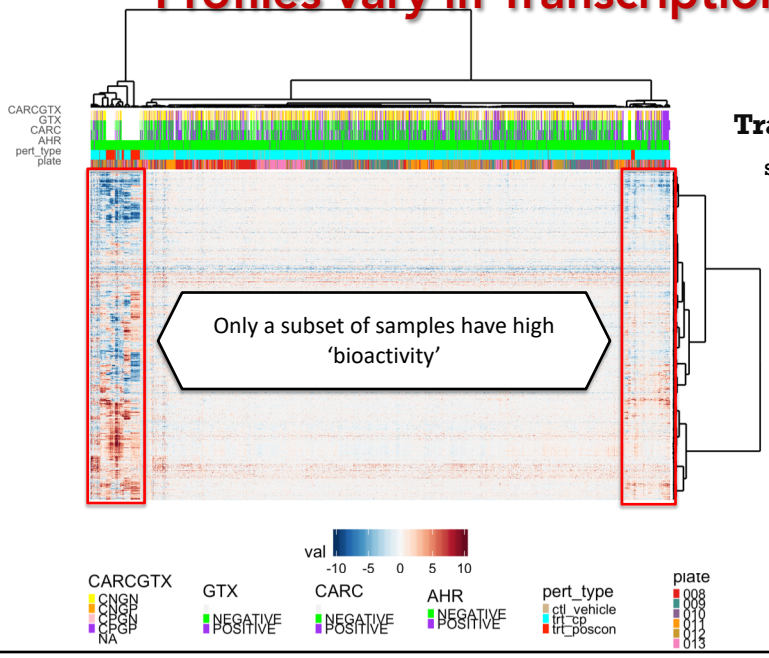
The Carcinogenome Project

In-vitro Carcinogenicity Profiling

Profiled >330 chemicals (~6,000 profiles) in liver cell lines with "liver-specific" carcinogenicity annotation

	Cell line	Chemical Type	# Chemicals	# Profiles
24h *6 doses 3 replicates 1 cell type*	HEGP2	Liver carcinogens	131	2358
		Non-carcinogens	172	3096
		Others (BUSRP)	33	594
		Total	336	6048
24h *3 doses 3 replicates 2 cell type*	MCF-10A, MCF-10A P53-	Breast carcinogens	120	2160
		Non-carcinogens	114	2052
		Others (BUSRP)	68	1224
		Total	302	5436
	MCF10A & HEPG2	breast carcinogens + others	115	2070

Profiles vary in Transcriptional Bioactivity



Transcriptional Activity Score (TAS)

summary of signature strength (SS_{ngene}) and replicate correlation (CC_{q75})

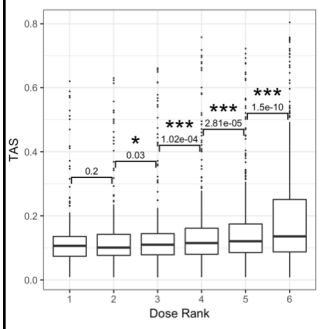
$$\frac{\text{Signal Strength}}{\text{Replicate Reproducibility}}$$

adapted from Lev Litichevskiy @ Broad

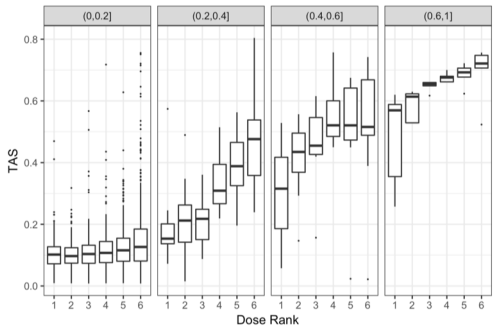
Bioactivity *vs.* Carcinogenicity

no significant association

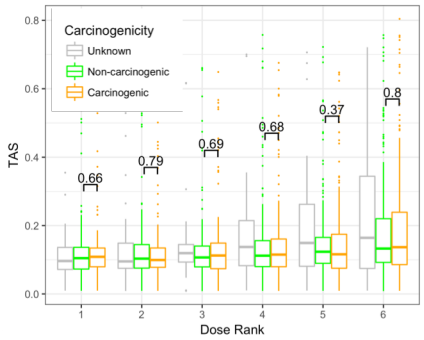
Bioactivity (TAS) increases with Dose



Dose response steeper with higher Bioactivity (TAS)



Carcinogenicity not associated with Bioactivity (TAS)



Difference between Acute *vs.* Chronic Response

short-term chemical perturbation with minimal transcriptional response cannot be assumed "safe"

Carcinogenicity Prediction

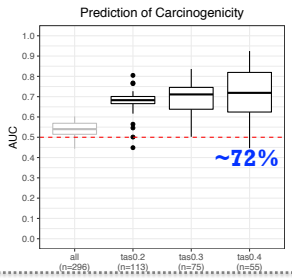
accuracy improves with higher bioactivity

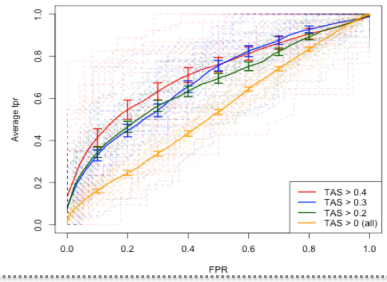
Carcinogenicity Prediction

accuracy improves with higher bioactivity

Carcinogenicity

Carcinogenicity AUC			
data	median	mean	se
all	54	53.9	0.9
tas > 0.2	68.3	66.9	1.6
tas > 0.3	71.1	69.1	1.8
tas > 0.4	71.9	72.2	2.7



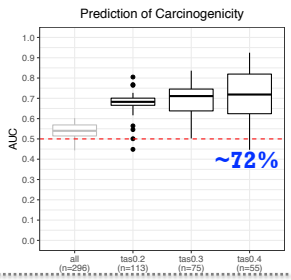


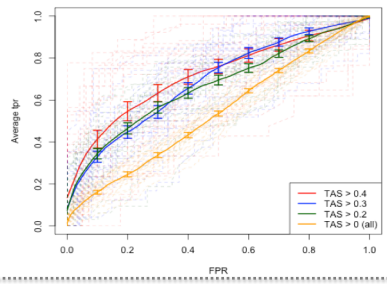
Carcinogenicity Prediction

accuracy improves with higher bioactivity

Carcinogenicity

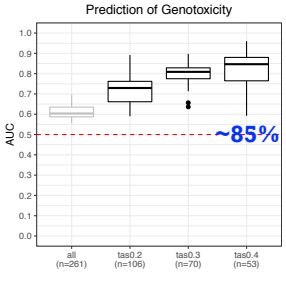
Carcinogenicity AUC			
data	median	mean	se
all	54	53.9	0.9
tas > 0.2	68.3	66.9	1.6
tas > 0.3	71.1	69.1	1.8
tas > 0.4	71.9	72.2	2.7

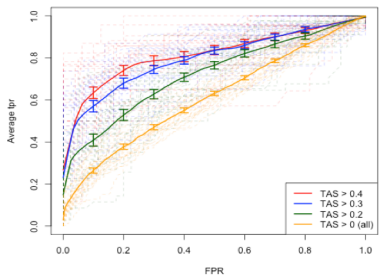




Genotoxicity

Genotoxicity AUC			
data	median	mean	se
all	60.3	61.3	0.7
tas > 0.2	72.9	72.4	1.5
tas > 0.3	80.9	80.1	1.3
tas > 0.4	84.7	82.3	1.7





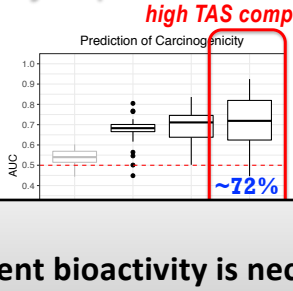
Carcinogenicity Prediction

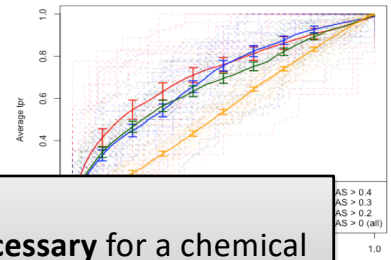
accuracy improves with higher bioactivity

high TAS compounds

Carcinogenicity

Carcinogenicity AUC			
data	median	mean	se
all	54	53.9	0.9
tas > 0.2	68.3	66.9	1.6
tas > 0.3	71.1	69.1	1.8
tas > 0.4	71.9		

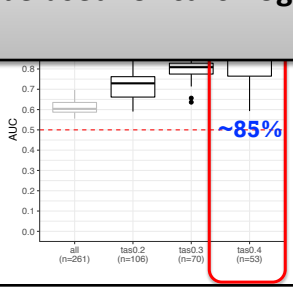


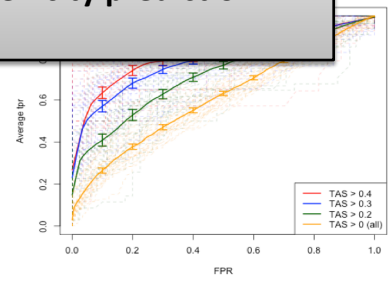


sufficient bioactivity is necessary for a chemical to be used **for carcinogenicity prediction**

Genotoxicity

Genotoxic			
data	median	mean	se
all	60.3	61.3	0.7
tas > 0.2	72.9	72.4	1.5
tas > 0.3	80.9	80.1	1.3
tas > 0.4	84.7	82.3	1.7





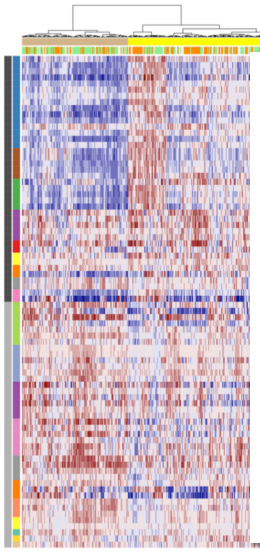
Chemicals' Modes of Action

by GeneSet Projection

Immune response (IFN signaling)
DNA repair
Cell cycle progression
Oxidative Stress

Phase II xenobiotic metabolism (conjugation)
Hormone biosynthesis
Cell-cell junction
Cell-cell communication
ECM organization

Chemicals' Modes of Action
by GeneSet Projection



Key Characteristics of Human Carcinogens

Key characteristic:	
1. Is Electrophilic or can be metabolically activated	✓
2. Is Genotoxic	✓
3. Alters DNA repair or causes genomic instability	✓
4. Induces Epigenetic Alterations	✓
5. Induces Oxidative Stress	✓
6. Induces chronic inflammation	✓
7. Is Immunosuppressive	✓
8. Modulates receptor-mediated effects	
9. Causes Immortalization	
10. Alters cell proliferation, cell death, or nutrient supply	✓

Evidence that these characteristics are observed, especially in humans or as intermediate biomarkers in human specimens can provide biological plausibility for epidemiological findings and/or early warning if no epidemiology exists

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ and K Straif. *Env Health Persp.*, 124(6), 713, 2016.

adapted from M. Smith

esponse (IFN signaling)
DNA repair
cycle progression
Oxidative Stress

enobiotic metabolism
(conjugation)
mone biosynthesis
ell-cell junction
cell communication
M organization

Home About Contact

The Carcinogenome Project

Chemical Carcinogenicity Screening using high-throughput transcriptomics assays

https://carcinogenome.org

Project	Cell line	Description
Liver Carcinogenicity	HEPG2	This experiment uses 330 selected chemicals for in-vivo liver carcinogenicity testing, including 128 liver carcinogens, 168 non-carcinogens, and 34 miscellaneous chemicals (e.g. nuclear receptor ligands). Chemical carcinogenicity and genotoxicity annotations are based on the Carcinogenicity Potency Database (CPDB), which is the result of tissue-specific long-term animal cancer tests in rodents. In the liver carcinogenome project, HepG2 (liver) cells are exposed to each individual chemical for 24 hours and their gene expression is profiled on the L1000 platform. Each chemical is assayed at 6 doses (2 fold dilutions starting from the highest concentration of 40uM or 20uM) with triplicate profiles generated for each dose...
Breast Carcinogenicity	MCF10A	This experiment uses 345 selected chemicals for breast carcinogenicity testing, including 120 breast carcinogens, 114 non-carcinogens, and 68 miscellaneous chemicals (e.g. nuclear receptor ligands, BU SRP chemicals, lung carcinogens). Chemical carcinogenicity and genotoxicity annotations are based on the Carcinogenicity Potency Database (CPDB), which is the result of tissue-specific long-term animal cancer tests in rodents, or breast carcinogens published from Rudel et. al., 2007. In the CRCGN project, MCF10A (breast epithelial) cells are exposed to each individual chemical for 24 hours and their gene expression is profiled on the L1000 platform. Each chemical is assayed at 3 doses (3 fold dilutions starting from the highest concentration of 100uM, with the exception of selected BUSRP chemicals...

The Carcinogenome Project: Developed by Monti Lab at Boston University
2017

Gusenleitner et al., *PLoS One* 2014
Mulas et al., *BMC Bioinformatics* 2017
Li et al., *Environmental Health Perspective* 2019

Outline

Overview of the experimental and computational approaches we have developed and applied to model environmental chemicals and to predict their long-term adverse effects from short-term transcriptomics assays.

Vignettes from two studies

- ***The Carcinogenome Project***: Predicting Long-Term Chemical Carcinogenicity and Genotoxicity from Short-Term Assays.
- ***The Adipogenome Project***: Genomics Characterization of Adipocyte Dysregulation by Environmental and Therapeutic Perturbagens.

Challenges and lessons learned.

Adipocytes Function

…

Maintaining Energy Homeostasis

"Obesity is a disorder of the energy homeostasis system, rather than just a passive accumulation of adipose, and **that environmental factors, including chemicals, confer obesity risk**."
– Endocrine Society's latest scientific statement

	Brown	*White*	*Brite/beige*
Primary Function	Thermogenesis Endocrine	Energy storage Endocrine	Thermogenesis? Endocrine?

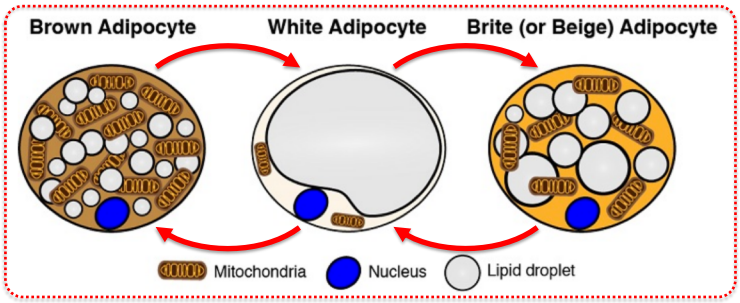
adapted from Guertin Lab @ UMass

Adipocytes Function

How is it affected by Exogenous Compounds?

Chemical Exposure

Disruption of Metabolic Balance?

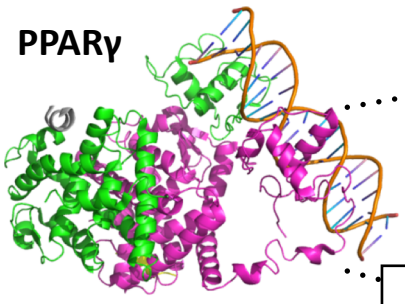


	Brown	White	Brite/beige
Primary Function	Thermogenesis Endocrine	Energy storage Endocrine	Thermogenesis? Endocrine?

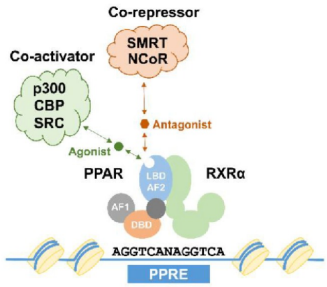
adapted from Guertin Lab @ UMass

Adipogens

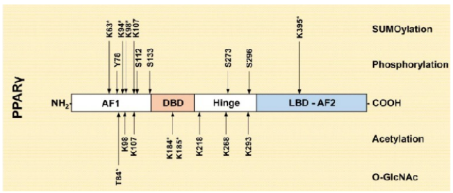
PPARγ Activity Modifying Compounds



Ligand Binding



Post-translational Modification



Int J Mol Sci. 2018 Jun; 19(6): 1738.
Published online 2018 Jun 12. doi: 10.3390/ijms19061738

The Adipogenome Project

Adipogens

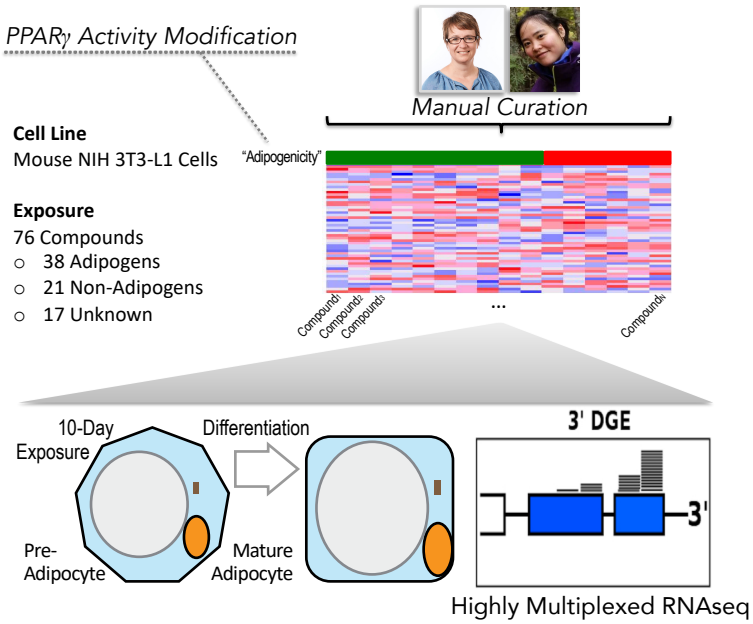
Exogenous compounds that directly alter white adipocyte function via **modification of PPARγ activity**

Project Goals

1. Create a ***Classifier*** to identify novel candidate adipogens
2. Create a ***Taxonomy*** to group chemicals based on their effects on PPARγ's transcriptome and downstream metabolic functions

Kim et al., *Arch Tox* 2018
Kim, Reed, et al., *bioXiv 519629* (under 2nd review at EHP)

Experimental Design



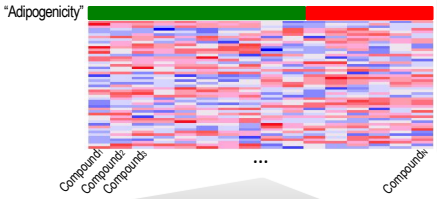
Highly Multiplexed RNAseq

Experimental Design

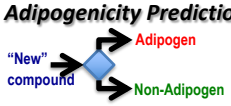
Manual Curation

Cell Line
Mouse NIH 3T3-L1 Cells

Exposure
76 Compounds
- 38 Adipogens
- 21 Non-Adipogens
- 17 Unknown

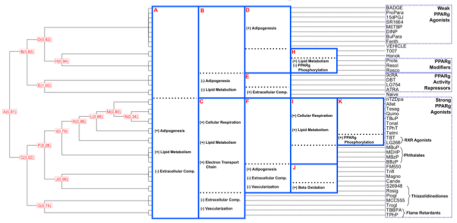


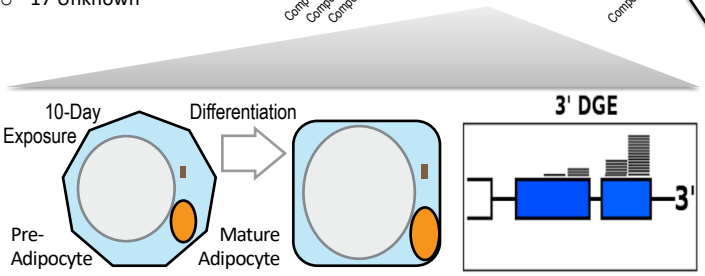
Adipogenicity Prediction



Prediction Evaluation
Classification Accuracy
Sensitivity/Specificity
ROC curve
...

Data-Driven Chemical Taxonomy





Highly Multiplexed RNAseq

New Machine Learning (ML) Algorithms

tailored to the experimental design (multiple replicates/condition)

Novel ML Approaches

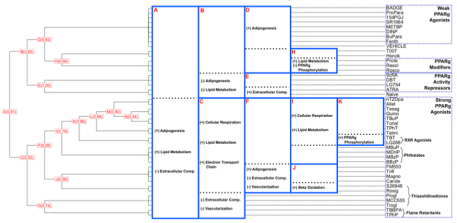
Amended Random Forest

Adipogenicity Prediction

Prediction Evaluation
Classification Accuracy
Sensitivity/Specificity
ROC curve
...

K2 Taxonomer

Data-Driven Chemical Taxonomy



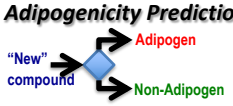
New Machine Learning (ML) Algorithms

tailored to the experimental design

Novel ML Approaches

Amended Random Forest

Adipogenicity Prediction



Prediction Evaluation
Classification Accuracy
Sensitivity/Specificity
ROC curve
...

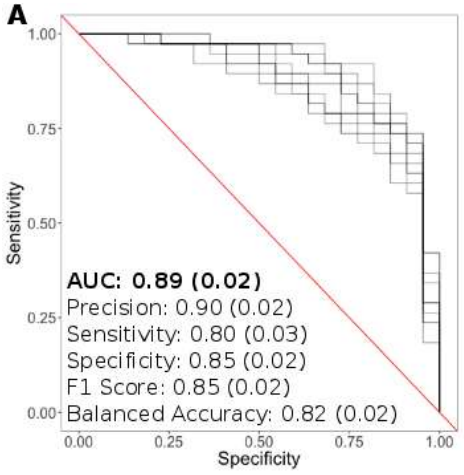
K2 Taxonomer

Data-Driven Chemical Taxonomy

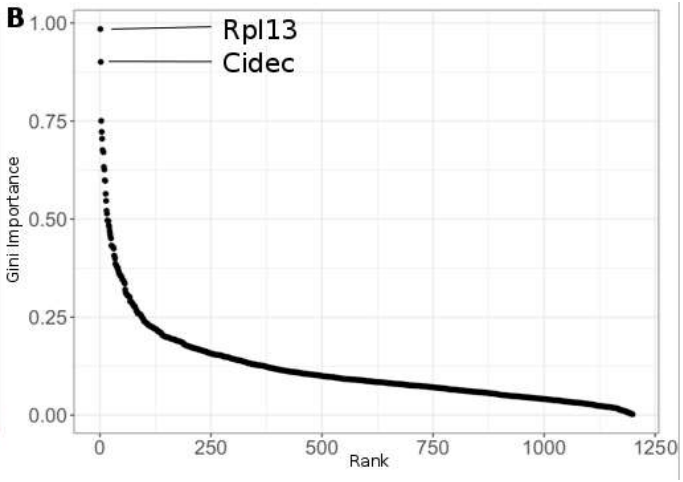
PPARγ Activity Modifier Classification Results

by *Amended Random Forest*

Predictive Accuracy



Gene "Importance"



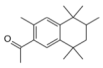
PPARγ Activity Modifier Classification Results
of 17 unknown compounds

Final Prediction Results

Chemical Name	Abbreviated Name	Known Source/Use	PPARg Modifier Voting	
d-cis,trans-Allethrin	Allethrin	Insecticide	0.91	High Confidence Adipogens
Tonalid	Tonalid	Musk (fragrance)	0.90	
Quinoxyfen	Quinoxyfen	Fungicide	0.90	
Fenthion	Fenthion	Insecticide	0.88	
2,4,6-Tris(tert-butyl)phenol	TTBP	Antioxidant (industrial)	0.80	
Prallethrin	Prallethrin	Insecticide	0.78	
Tebuconazole	Tebucon	Fungicide	0.78	
Fludioxonil	Fludiox	Fungicide	0.77	
Tris(1,3-dichloro-2-propyl) phosphate	TDCPP	Flame retardant	0.76	
Cyazofamid	Cyazofamid	Pesticide	0.72	
Perfluorooctanoic acid	PFOA	Fluorosurfactant	0.59	
Triphenyl phosphite	Triphen_Phosphite	Pesticide	0.57	
Tris(1-chloro-2-propyl) phosphate	TCCP	Flame retardant	0.54	
Triphenylphosphine oxide	Triphen_Phox_Ox	Crystallizing aid, byproduct	0.49	
Diphenyl phosphate	DPP	Metabolite of TPhP	0.47	
Dioctyl sulfosuccinate sodium	DOSS	Surfactant	0.41	
Perfluorooctanesulfonic acid	PFOS	Fluorosurfactant	0.40	

PPARγ Activity Modifier Classification Results
novel adipogens that favor white adipogenesis

Tonalid (Fragrance)



- (Reiner and Kannan, 2006)
  - 48% of perfumes
  - 29% of body lotions/creams,
  - 75% of deodorants
  - 14% of shower gel/shaving creams
  - 33% of hair products
  - 31% of sanitation products

Quinoxyfen (Fungicide)

- Fortress™, Orka™, Legend™, Quintec™
  - Grain, Hops, Grapes
  - Low Residue
  - Bioaccumulates in Fish

Functional analyses confirmed that Quino and Tonalid **induce white, but not brite, adipogenesis** in both mouse and human preadipocyte models

The Adipogenome Project

Adipogens

Exogenous compounds that directly alter white adipocyte function via **modification of PPARγ activity**

Project Goals

1. Create a ***Classifier*** to identify novel candidate adipogens

2. Create a ***Taxonomy*** to group chemicals based on their effects on PPARγ's transcriptome and downstream metabolic functions

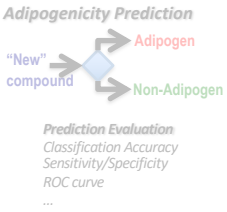
Kim et al., *Arch Tox* 2018
Kim, Reed, et al., *bioRxiv 519629* (under 2nd review at EHP)

New Machine Learning (ML) Algorithms

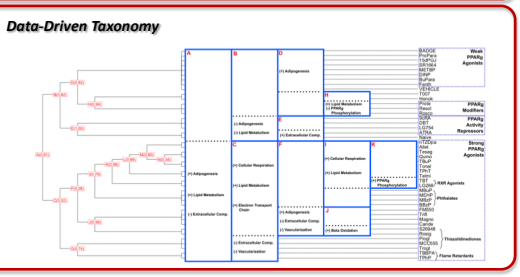
tailored to the experimental design

Novel ML Approaches

Amended Random Forest



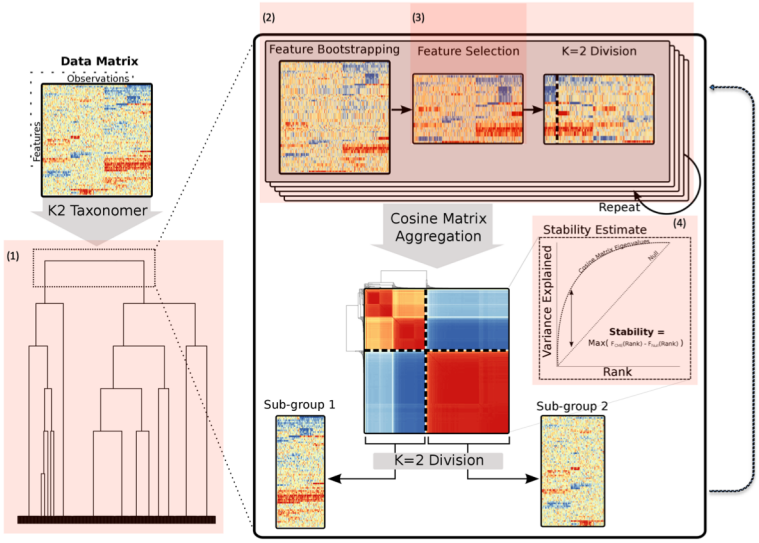
K2 Taxonomer



K2 Taxonomer

hierarchical taxonomy discovery from (transcript)omics data

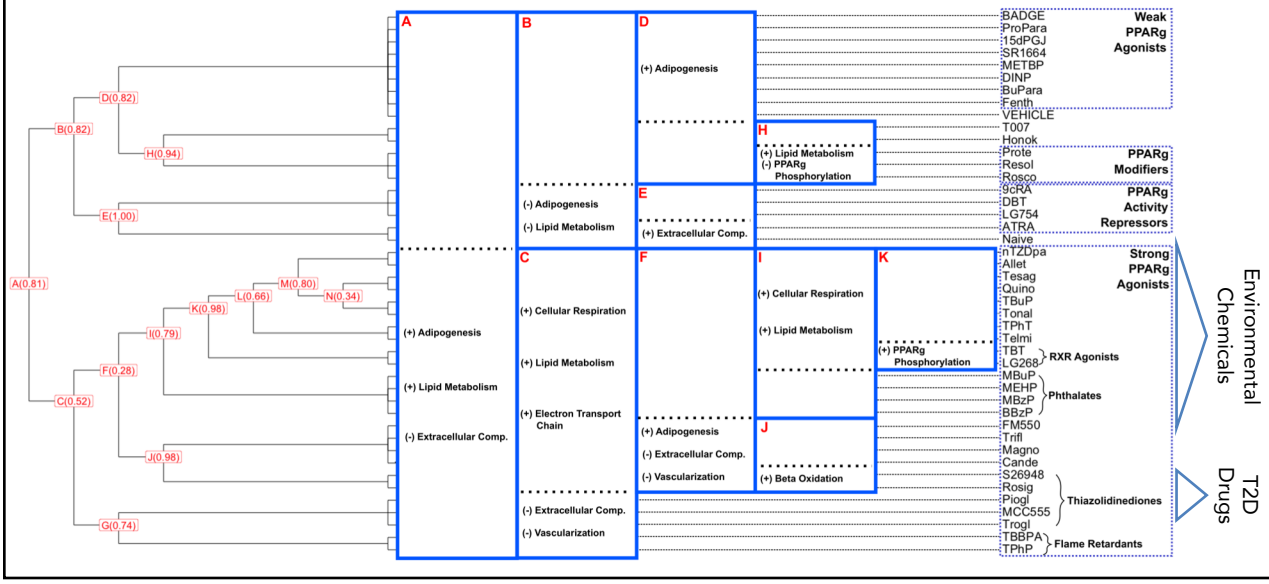
1. Top-down (Divisive) Clustering
   - ✓ *Unsupervised Decision Tree*
2. Aggregation of repeated perturbations
   - ✓ *Generate robust subtypes*
3. Feature selection for each split
   - ✓ *Hierarchical clustering algorithms use one set of features*
4. Robustness assessment
   - ✓ Based on eigendecomposition of aggregate cosine matrix



Reed et al., Manuscript in Preparation

A Data Driven Adipogen Taxonomy

identifies subgroups of PPARγ ligands/modifiers



In-Silico Validation of (mouse-based) Taxonomy

confirms its human relevance

Signature Projection
onto
METSIM

subcutaneous adipose tissues
770 subjects
12 clinical measurements

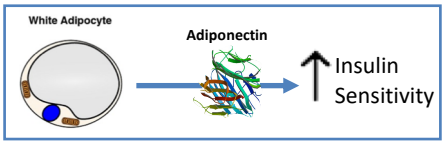
In-Silico Validation of Human Relevance

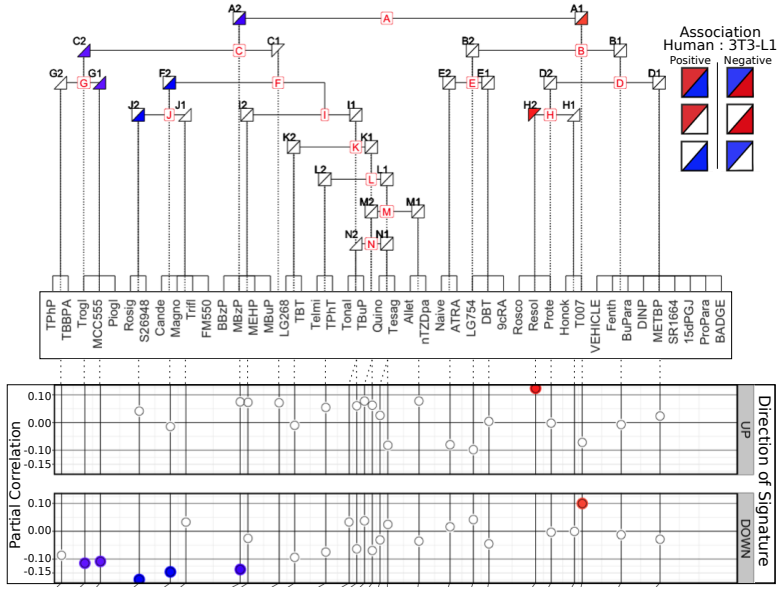
in-vitro signatures significantly associated with clinical endpoints in primary tissues

Signature Projection
onto
METSIM

subcutaneous adipose tissues
770 subjects
12 clinical measurements

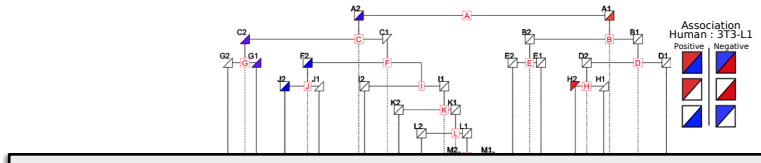
association with
Plasma Adiponectin



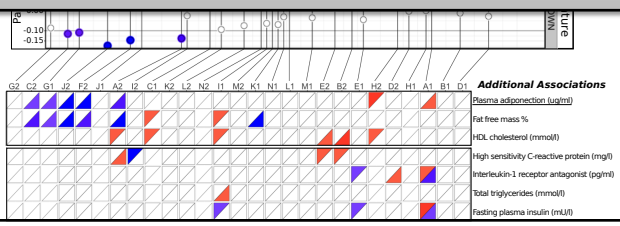


In-Silico Validation of Human Relevance

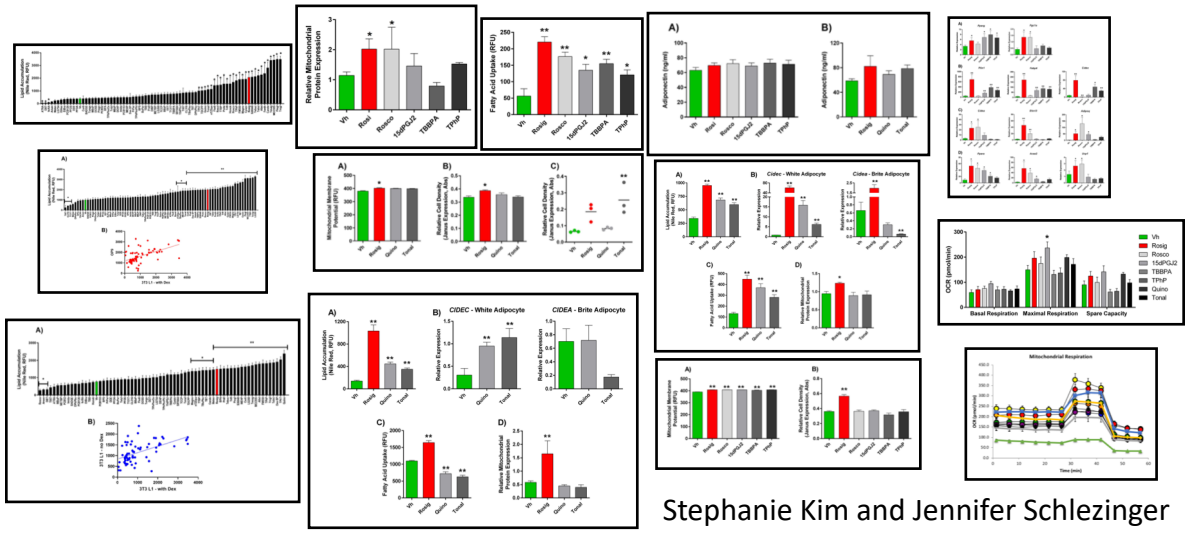
in-vitro signatures significantly associated with clinical endpoints in primary tissues



Mouse-based, in vitro-derived signatures
capture salient functional aspects of
healthy and unhealthy metabolic functions in human subjects

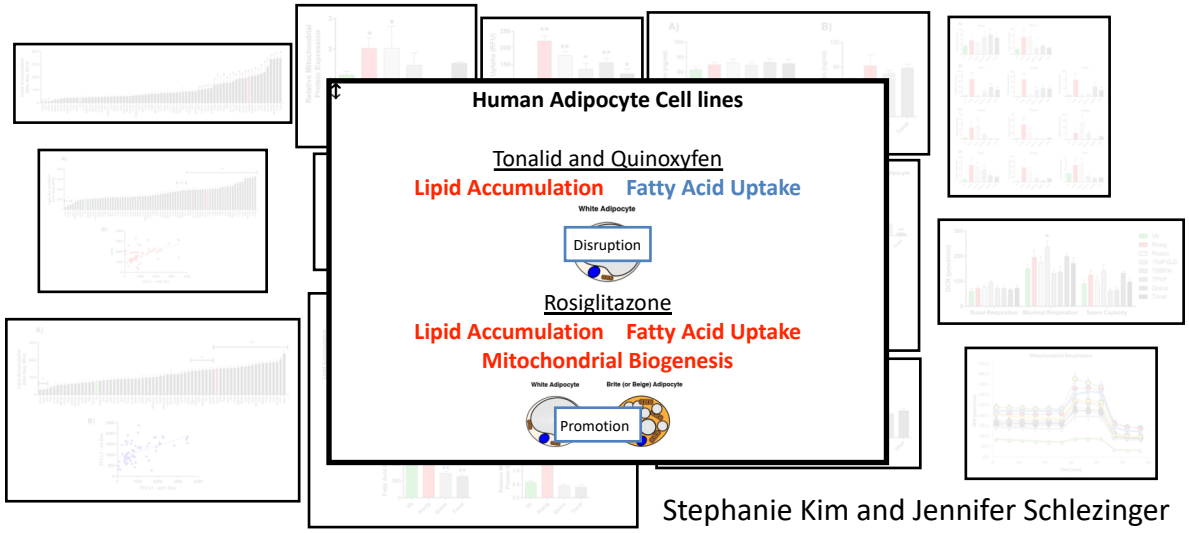


Experimental Validation



Stephanie Kim and Jennifer Schlezinger

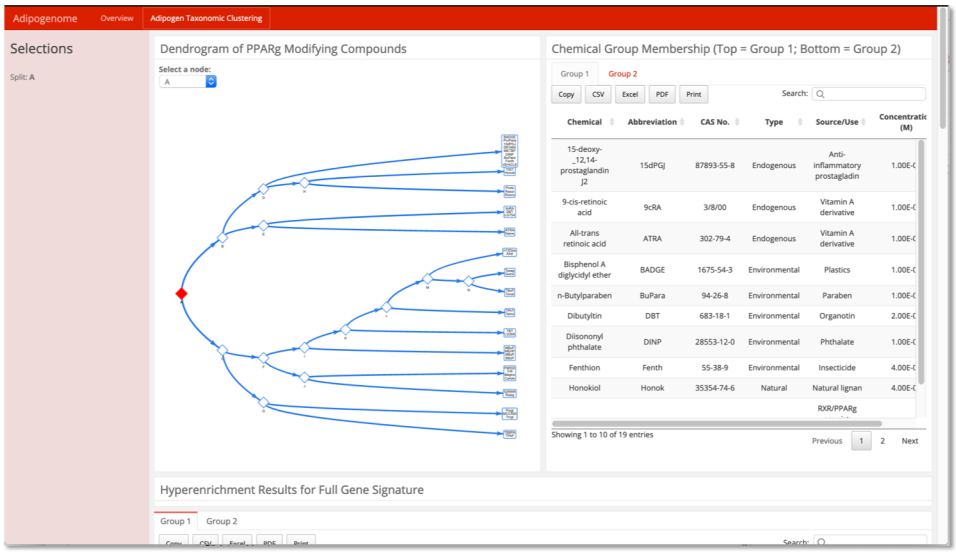
Experimental Validation



Stephanie Kim and Jennifer Schlezinger

The Adipogenome Portal

https://montilab.bu.edu/adipogenome



Summary

- Identified (new) PPARγ agonists/modifiers
- Sorted agonists into likely white or brite adipogens
- Developed new classification and taxonomy discovery methods
- Computational & Experimental framework with general applicability to the classification of as-yet uncharacterized chemicals

Kim et al., *Arch Tox* 2018
Kim, Reed, et al., *bioRxiv 519629* (under review at EHP)

Bringing it altogether: The Xposome Portal

https://montilab.bu.edu/Xposome

(under construction)

Carcinogenome **Adipogenome**

National Institute of Environmental Health Sciences
Superfund Research Program

The Xposome Project

Chemical Screening using high-throughput transcriptomics assays

Home About Contact Sign In

Project	Cell line	Description
Liver Carcinogenicity	HEPG2	This experiment uses 330 selected chemicals for in-vivo liver carcinogenicity testing, including 128 liver carcinogens, 168 non-carcinogens, and 34 miscellaneous chemicals (e.g., nuclear receptor ligands). Chemical carcinogenicity and genotoxicity annotations are mainly based on the *Carcinogenicity Potency Database* (CPDB), which is the result of tissue-specific long-term carcinogenicity tests in rodents. In this study, HepG2 (liver) cells were exposed to each individual chemical for 24 hours and their gene expression profiled on the L1000 platform. Each chemical was assayed at 6 doses (2-fold dilutions starting from the highest concentration of 40uM or 20uM) with triplicate profiles generated for each dose...
Breast Carcinogenicity	MCF10A	This experiment uses 345 selected chemicals for breast carcinogenicity testing, including 120 breast carcinogens, 114 non-carcinogens, and 68 miscellaneous chemicals (e.g., nuclear receptor ligands, BUSRP chemicals, lung carcinogens). Chemical carcinogenicity and genotoxicity annotations are based on the *Carcinogenicity Potency Database* (CPDB), which is the result of tissue-specific long-term carcinogenicity tests in rodents, or breast carcinogens from [Rudel et al., 2007]. In this study, MCF10A (breast epithelial) cells were exposed to each individual chemical for 24 hours and their gene expression profiled on the L1000 platform. Each chemical was assayed at 3 doses (3-fold dilutions starting from the highest concentration of 100uM, with the exception of selected BUSRP chemicals)...
Adipogenicity	3T3-L1	This experiment uses 3T3-L1 cells differentiated in the presence of 77 chemicals, comprising 38 known PPAR_ ligands or modifying compounds, 22 negative controls, and 17 suspected PPAR_ ligands/modifiers. 3' digital gene expression profiling was performed on mouse NIH 3T3-L1 pre-adipocytes exposed to each of the chemicals over a 10-day period during differentiation...

TG-GATEs NIBIO DrugMatrix NIEHS National Institute of Environmental Health Sciences ...

with Oregon State University

Lessons Learned and Challenges

- "Logistics" (chemical procurement, profile generation, etc.)
- Dose for hazard determination: high enough to elicit "bioactivity"
- Acute vs. Chronic exposure
  - ✓ Low transcriptional response cannot be assumed "safe"
- Models more adequate for hazard prediction than MoA's
  - ✓ However, rich MoA information can still be parsed from data
- Wealth of results not adequately sharable through publications
  - ✓ Interactive online Portals a necessary complement
- Difficulty in funding these efforts
  - ✓ "hypothesis testing" bias
  - ✓ misplaced request for "in vivo validation" of results

Acknowledgements

Monti Lab
Amy Li
Eric Reed
Anthony Federico
Reina Chau
Adam Gower
Adam Labadorf

BU SPH
David Sherr
Jennifer Schlezinger
Stephanie Kim
Elizabeth Stanford

Broad Institute
Aravind Subramanian
Xiaodong Lu
Ted Natoli
Todd Golub
Josh Bittker

NTP/NIEHS
Scott Auerbach
Rick Paules
Ray Tice

BU Superfund
Mark Hahn
Jed Goldstone
John Stegeman
et al.

Tufts Medical
Paola Sebastiani
Gail Sonenshein
Charlotte Kuperwasser

NIH LINCS PROGRAM
NIH National Institute of Environmental Health Sciences Superfund Research Program
FIND THE CAUSE Breast Cancer Foundation
Evans Center For Interdisciplinary Biomedical Research
Boston University Superfund Research Program

Acknowledgements

NIH National Institute of Environmental Health Sciences
Superfund Research Program

Boston University
Superfund Research Program

THE END