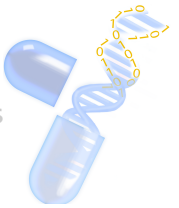
Bioinformatics and
Computational Genomics
Laboratory

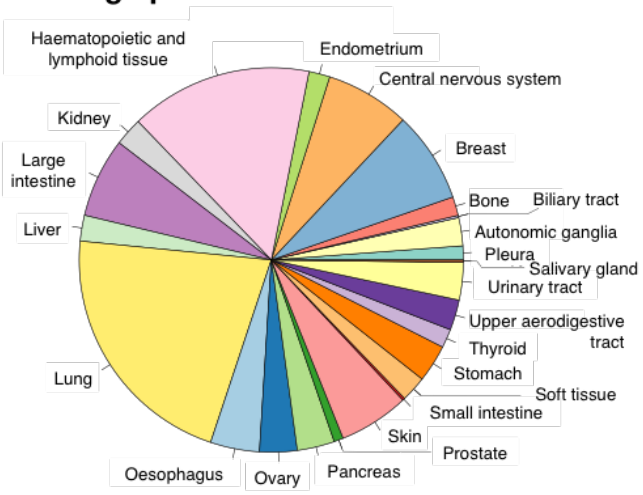


PharmacoGx: Analysis of High Throughput Pharmacogenomics Studies

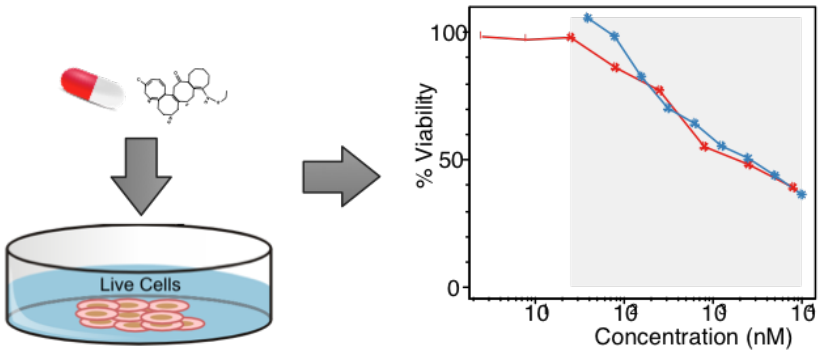
Petr Smirnov

Benjamin Haibe-Kains Lab
Department of Medical Biophysics,
University of Toronto &
Princess Margaret Cancer Centre
University Health Network

Large panel of cancer cell lines

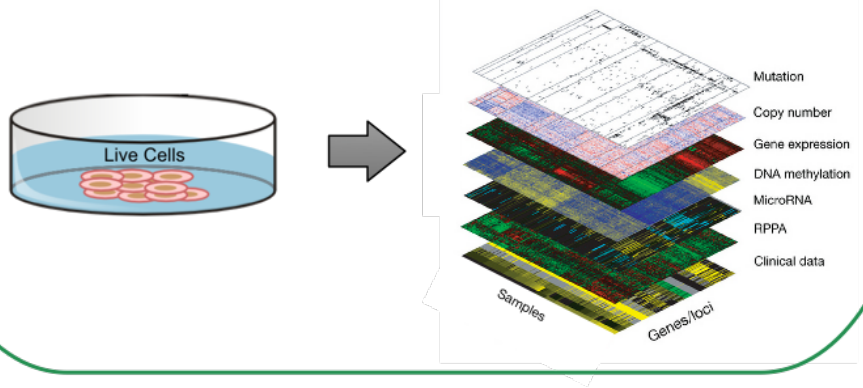


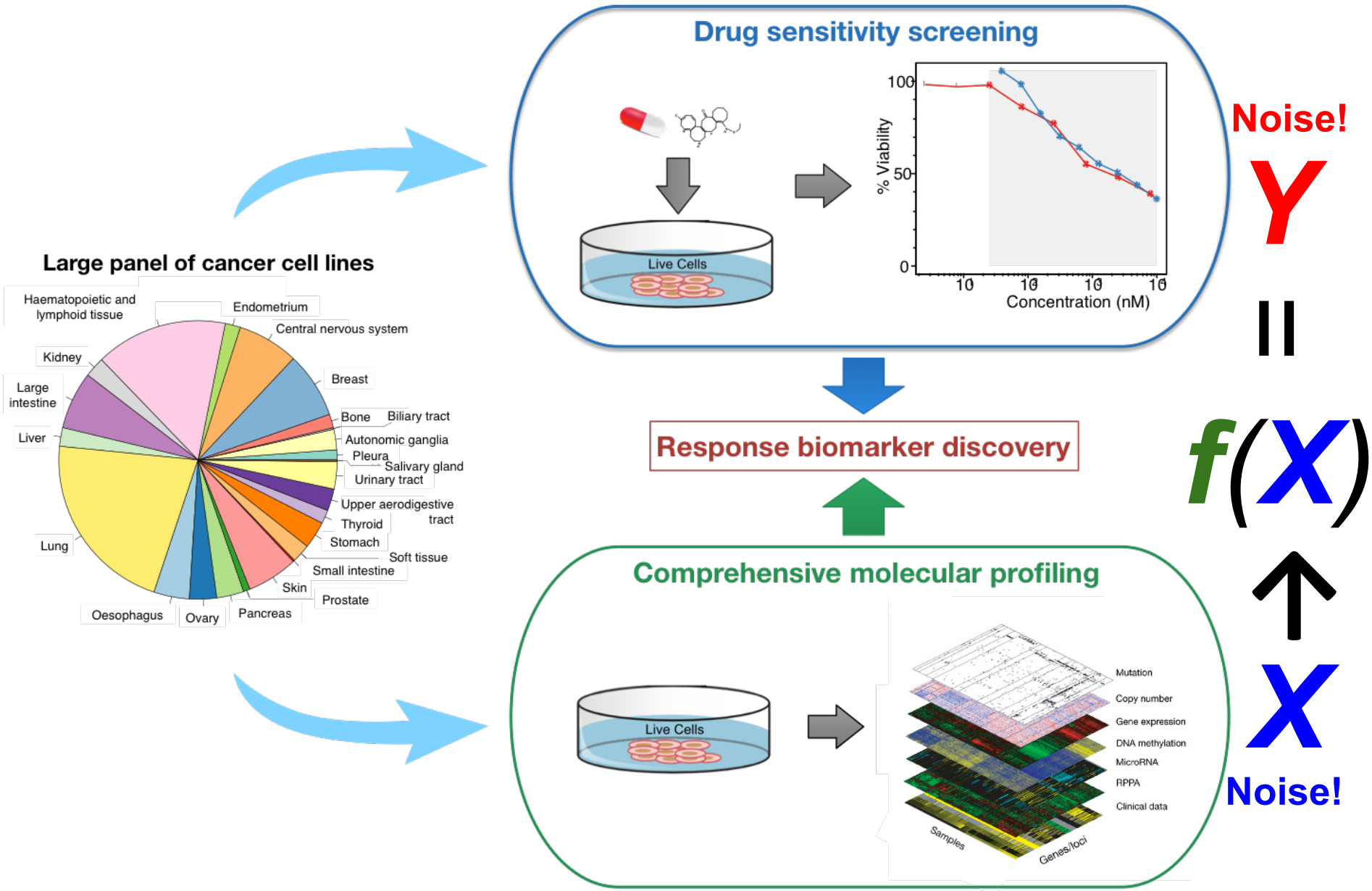
Drug sensitivity screening



Response biomarker discovery

Comprehensive molecular profiling




Large panel of cancer cell lines
Haematopoietic and lymphoid tissue
Endometrium
Central nervous system
Kidney
Breast
Large intestine
Bone
Biliary tract
Liver
Autonomic ganglia
Pleura
Salivary gland
Urinary tract
Upper aerodigestive tract
Thyroid
Stomach
Lung
Soft tissue
Small intestine
Skin
Prostate
Oesophagus
Ovary
Pancreas
Drug sensitivity screening
Live Cells
% Viability
100
50
0
10
Concentration (nM)
Response biomarker discovery
Comprehensive molecular profiling
Live Cells
Mutation
Copy number
Gene expression
DNA methylation
MicroRNA
RPPA
Clinical data
Samples
Genes/loci
Noise!
Y
=
f(X)
X
Noise!

Pharmacogenomic datasets must be curated

(Meta)data is scattered across
data portals and journal websites

Mismatched Identifiers
→ Tedious process of curation and annotation

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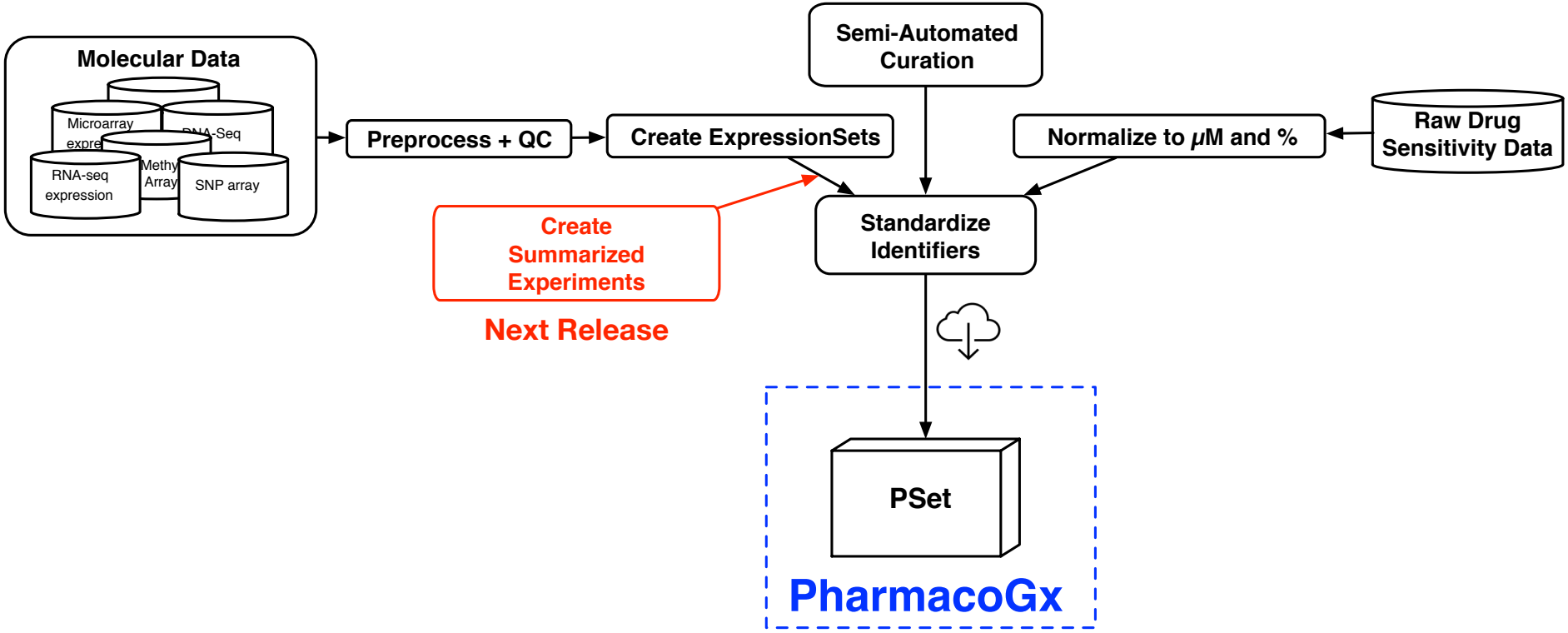
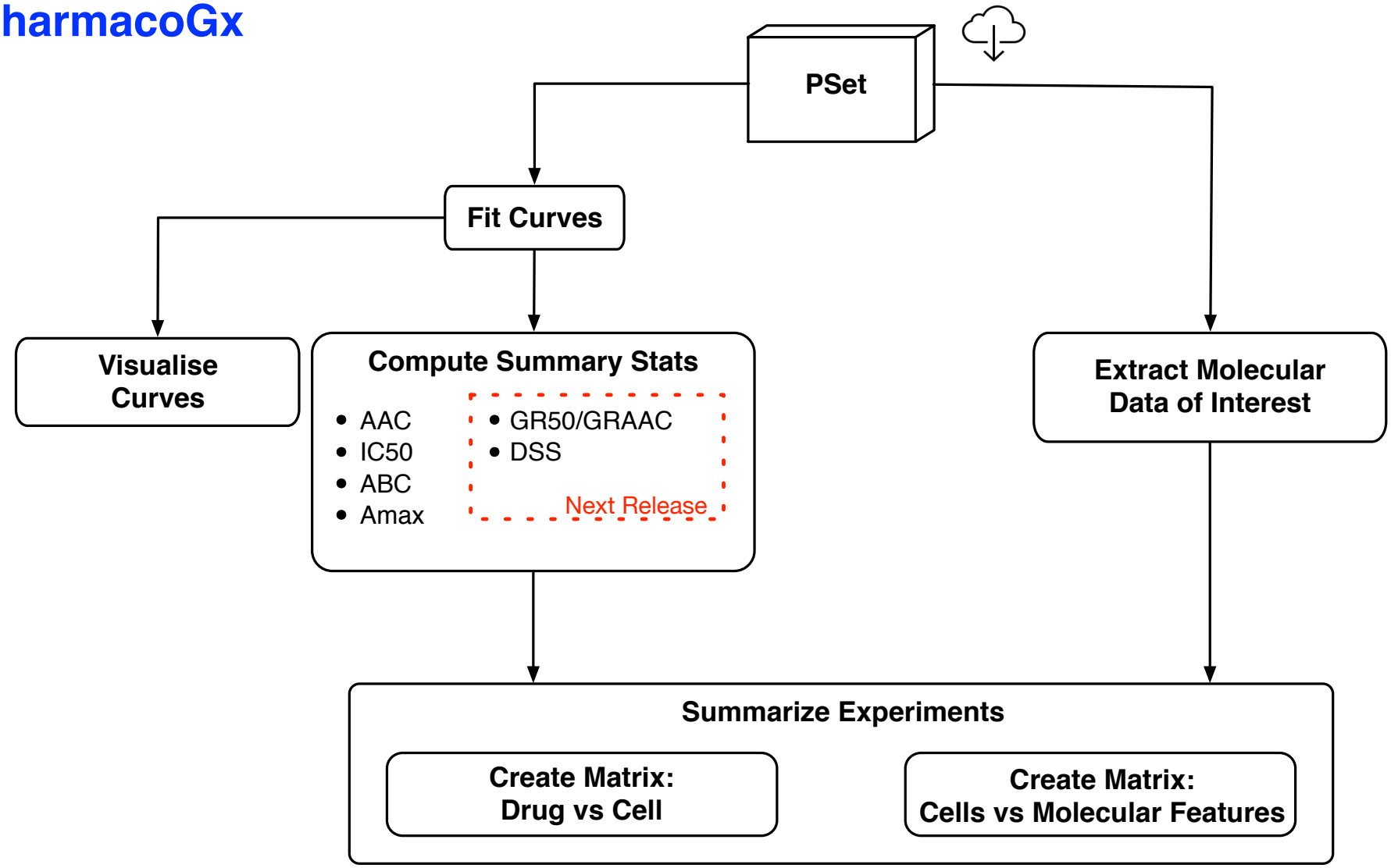
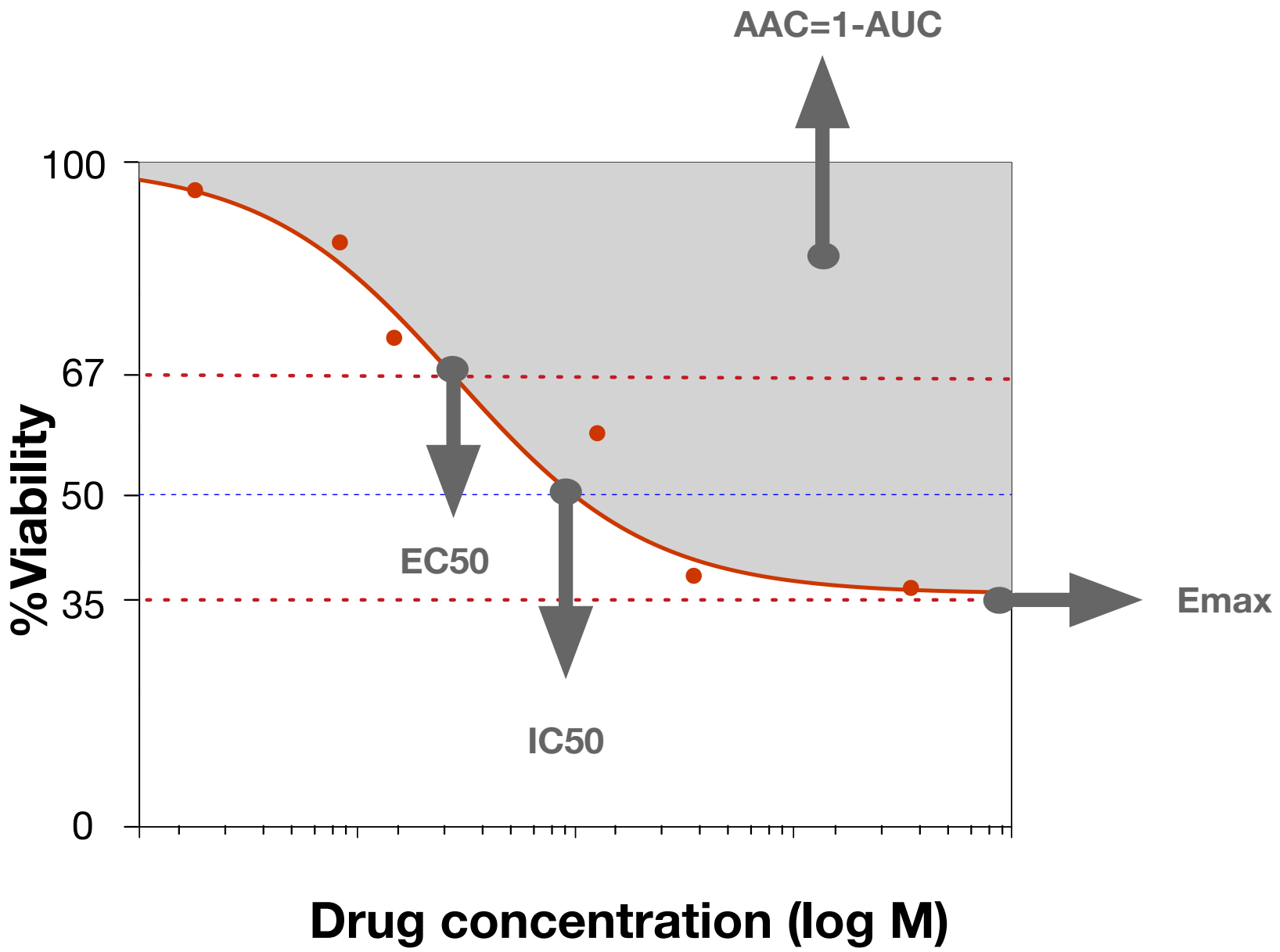
Develop **PharmacoGx** to empower data use for:
→ Hypothesis generation and validation
→ Comparative and integrative studies
→ Method development for Biomarker Discovery and Predictive Oncology


Molecular Data
Microarray expression
RNA-Seq
RNA-seq expression
Methy Array
SNP array
Preprocess + QC
Create ExpressionSets
Semi-Automated Curation
Normalize to μM and %
Raw Drug Sensitivity Data
Create Summarized Experiments
Next Release
Standardize Identifiers
PSet
PharmacoGx

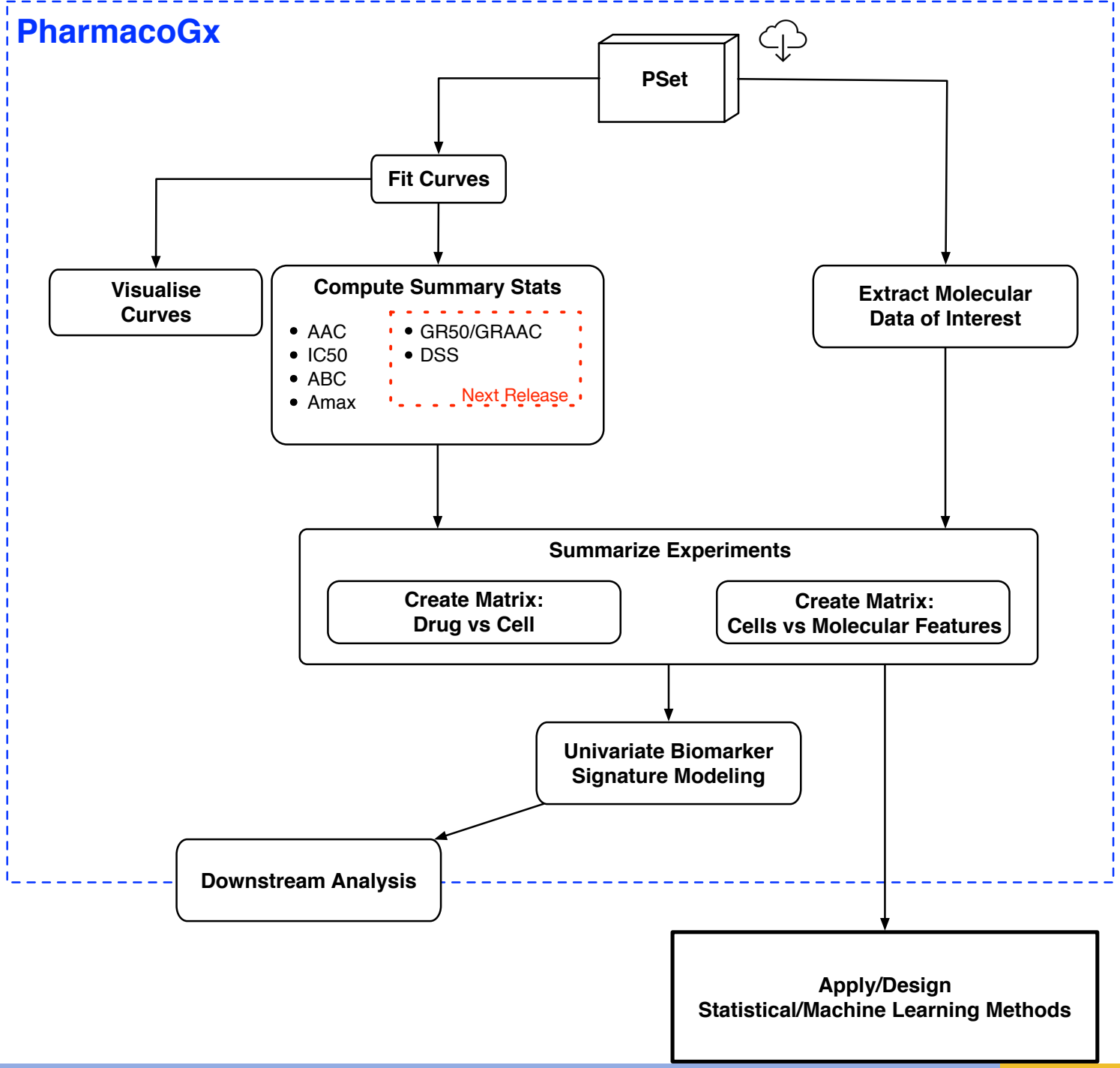
PharmacoGx

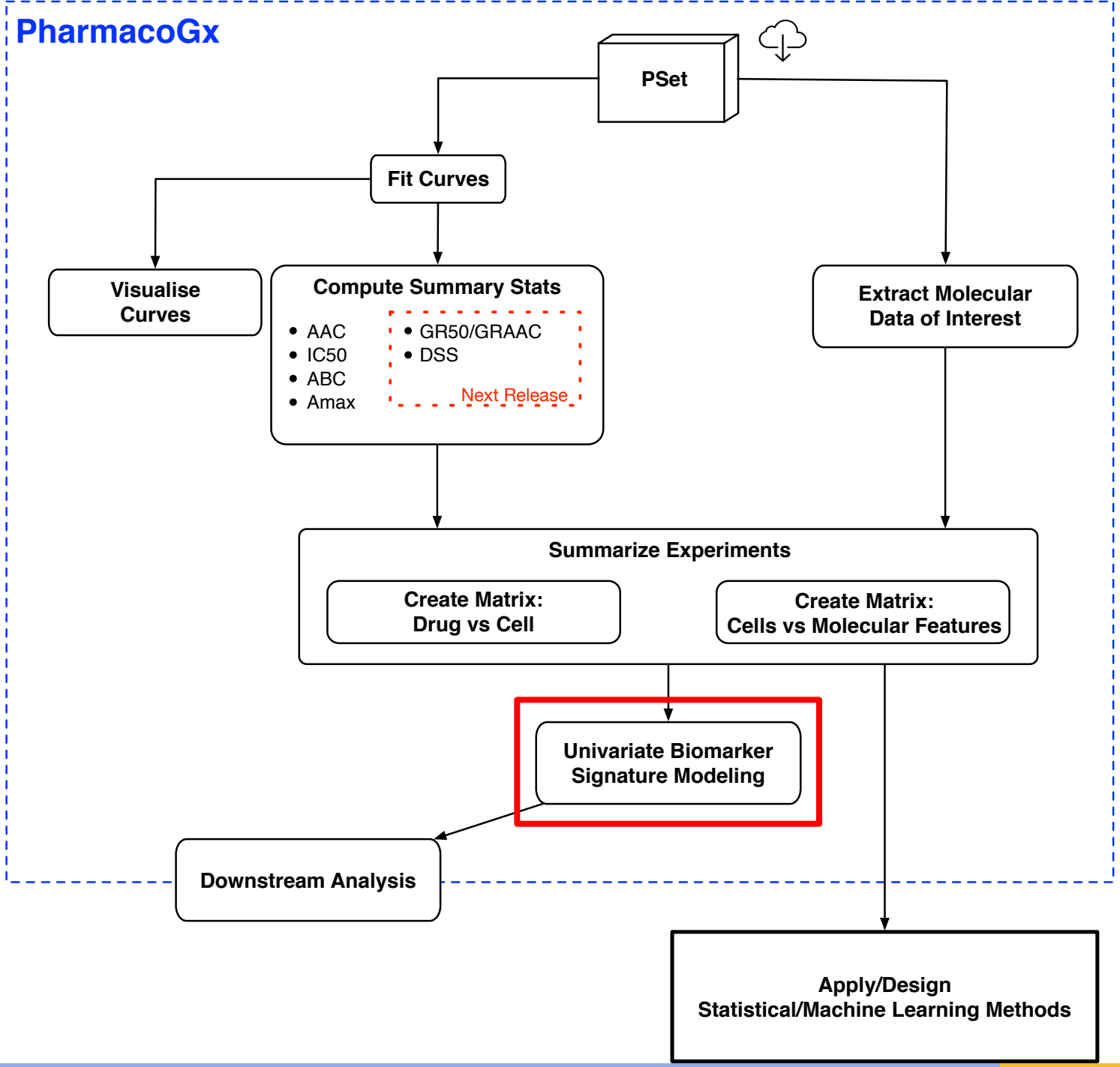


$$Y = f(X) \leftarrow X$$



Per Drug – Cell Pair


PharmacoGx
PSet
Fit Curves
Visualise Curves
Compute Summary Stats
AAC
IC50
ABC
Amax
GR50/GRAAC
DSS
Next Release
Extract Molecular Data of Interest
Summarize Experiments
Create Matrix: Drug vs Cell
Create Matrix: Cells vs Molecular Features
Univariate Biomarker Signature Modeling
Downstream Analysis
Apply/Design Statistical/Machine Learning Methods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Univariate Biomarker Discovery

$$Y = \beta_0 + \beta_i G_i + \beta_t T + \beta_b B$$

Y = AAC /IC50

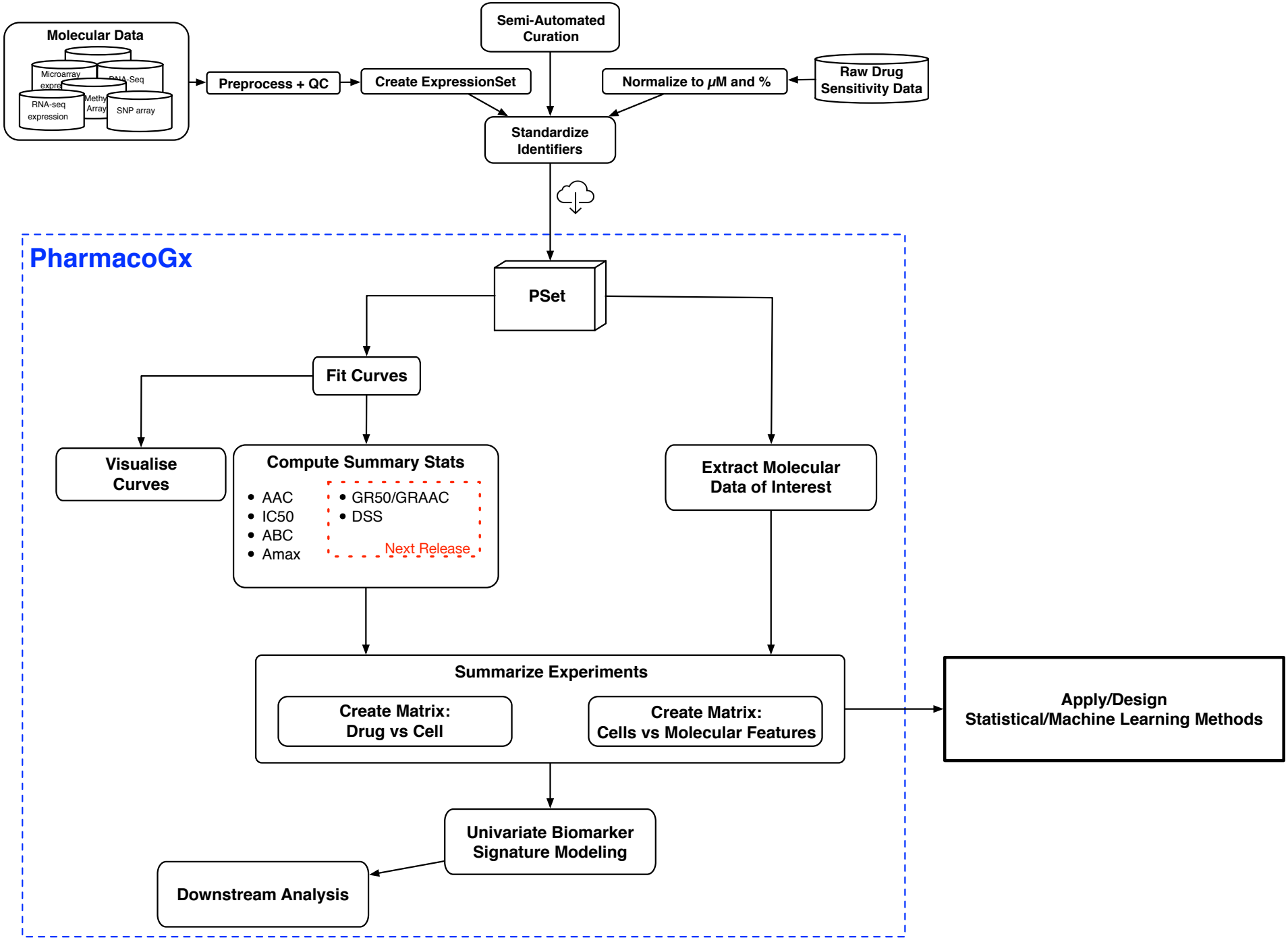
G = Molecular Feature

T = Tissue of Origin

B = Batch

Top molecular features associated with response to AZD6244

Feature Type	Gene ▲	Dataset ▲	Stat ▲	Standardized Coefficient ▲	Nominal ANOVA p-value ▼
mRNA	SPRY2	CCLE	AAC	0.42	2e-18
mRNA	LYZ	CCLE	AAC	0.38	8e-17
mRNA	SPRY2	FIMM	AAC	0.29	3e-14
mRNA	ZFP36L2	FIMM	AAC	0.27	6e-13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Next Steps

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Integrate with standard Bioconductor data objects

→ SummarizedExperiment & MultiAssayExperiment

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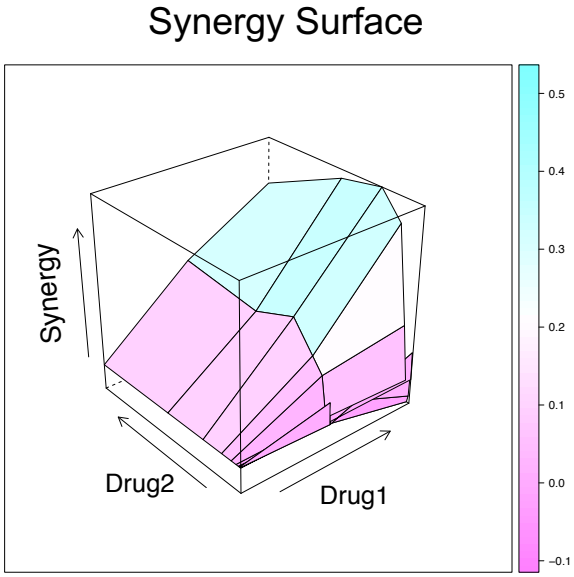
Drug Combinations



Next Steps

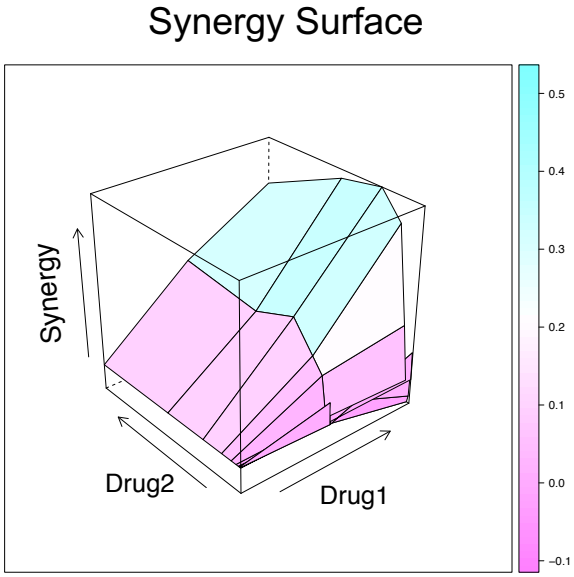
Integrate with standard Bioconductor data objects

→ SummarizedExperiment & MultiAssayExperiment

Drug Combinations

Time Dimension

→ IncuCyte



Search, Visualize, Export

https://pharmacodb.pmgenomics.ca

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- → Fupan Yao

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- → Anna Goldenberg
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- → Andrew Beck
- → Hugo Aerts

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- → Lillian Siu
- → David Cescon
- → Ming-Sound Tsao
- → Fei-Fei Liu
- → Scott Bratman
- → Carl Virtanen
- → …

Canadian Cancer Society

OICR

NSERC CRSNG

CIHR IRSC

The Cancer Research Society

The Princess Margaret Cancer Foundation UHN

Thank you!

PharmacoGx:
https://bioconductor.org/packages/release/bioc/html/PharmacoGx.html

PharmacoDB:
http://pharmacodb.pmgenomics.ca

Github:
https://github.com/bhklab