

“UGA’s Cancer Center: A Nexus for Oncological Research”

Eileen Kennedy, Georgia Athletic Association Professor of Pharmacy and Director, UGA Cancer Center

Eugene Douglass, Assistant Professor, College of Pharmacy

Natarajan Kannan, Professor and Georgia Cancer Coalition Distinguished Scholar, Franklin College of Arts & Sciences Department of Biochemistry & Molecular Biology

Shaying Zhao, Professor and Georgia Cancer Coalition Scholar, Franklin College of Arts & Sciences Department of Biochemistry & Molecular Biology

April 12, 2024

Research Live



UNIVERSITY OF
GEORGIA

Organizational Structure



Director
Eileen Kennedy

Executive Committee



Eugene Douglass
PBS



Natarajan Kannan
BCMB



Corey Saba
Vet Med



Shaying Zhao
BCMB



Cancer Center Composition

- Over 40 members from diverse departments across campus
 - Animal and Dairy Science
 - Biochemistry and Molecular Biology
 - Bioinformatics
 - Cellular Biology
 - Chemistry
 - Clinical and Experimental Therapeutics
 - Complex Carbohydrate Research Center
 - Engineering
 - Environmental Health Science
 - Family and Consumer Sciences
 - Genetics
 - Microbiology
 - Molecular Medicine
 - Pharmaceutical and Biomedical Sciences
 - Public Health
 - Regenerative Bioscience
 - Statistics
 - Veterinary Medicine



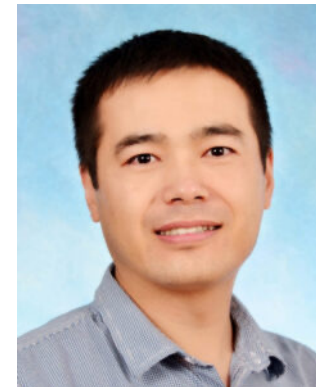
New Members in FY23-24



Karin Allenspach Jorn
Vet Med



Tim Bolger
Molecular Biology



Wentao Li
Env. Health Science



Aditya Mishra
Statistics



Jon Mochel
Vet Med



Yaguang Xi
Pharm & Biomed Sci



Areas of Research

- Six primary areas of research:
 - Cancer genetics, epigenetics, cancer biology
 - Cancer detection
 - Targeting cancer motility/signaling pathways
 - Cancer cell surface targeting
 - Clinical strategies for therapeutic development
 - Prevention/Epidemiology



Student Related Activities

- UGA Cancer Center has its own interdisciplinary group for student recruiting through ILS
 - Approximately 150 applicants for Fall 2024 cohort
 - Approximately 20% of the incoming class has a declared interest in Cancer Biology
- Placement opportunities for undergraduate research



Recent Cancer Center Activities: 2023 UGA-Emory Joint Cancer Center Retreat

- Joint symposia with Emory-Winship Cancer Center in July 2023 (UGA College of Pharmacy)
 - Keynote: Dr. Nicole Lopanik (American Cancer Society)
 - 4 faculty talks (2 per university)
 - 4 student talks (2 per university)
 - 50 posters, 100 participants
 - 2 poster awards given to students/postdocs



Recent Cancer Center Activities: 2023 UGA-GCC Joint Cancer Center Retreat

- Joint symposia with Georgia Cancer Center (Augusta University) in December 2023 (Augusta University)
 - Keynote speaker: Maureen Murphy (Wistar Institute)
 - 8 faculty talks (4 per university)
 - 70 posters, 150 participants
 - 3 poster awards given to students/postdocs



Recent Cancer Center Activities:

Cancer Center Seminar Series 2023-2024

Fall 2023

- **Biao He**, GRA Distinguished Investigator, Vet Medicine, “PIV5-Based Cancer Therapy”
- **Aditya Mishra**, Assistant Professor, Statistics, “On Integrative Statistical Learning Approach for Cancer Genomics and Microbial Science”
- UGA Office of Business Engagement (**Richard Potter**), “Business Engagement Toolkit for Faculty”
- **Karin Allenspach and Jon Mochel**, Professor, Vet Medicine, “Using Spontaneous Animal Disease Models to Improve Clinical Outcomes in Man and Man’s Best Friend”

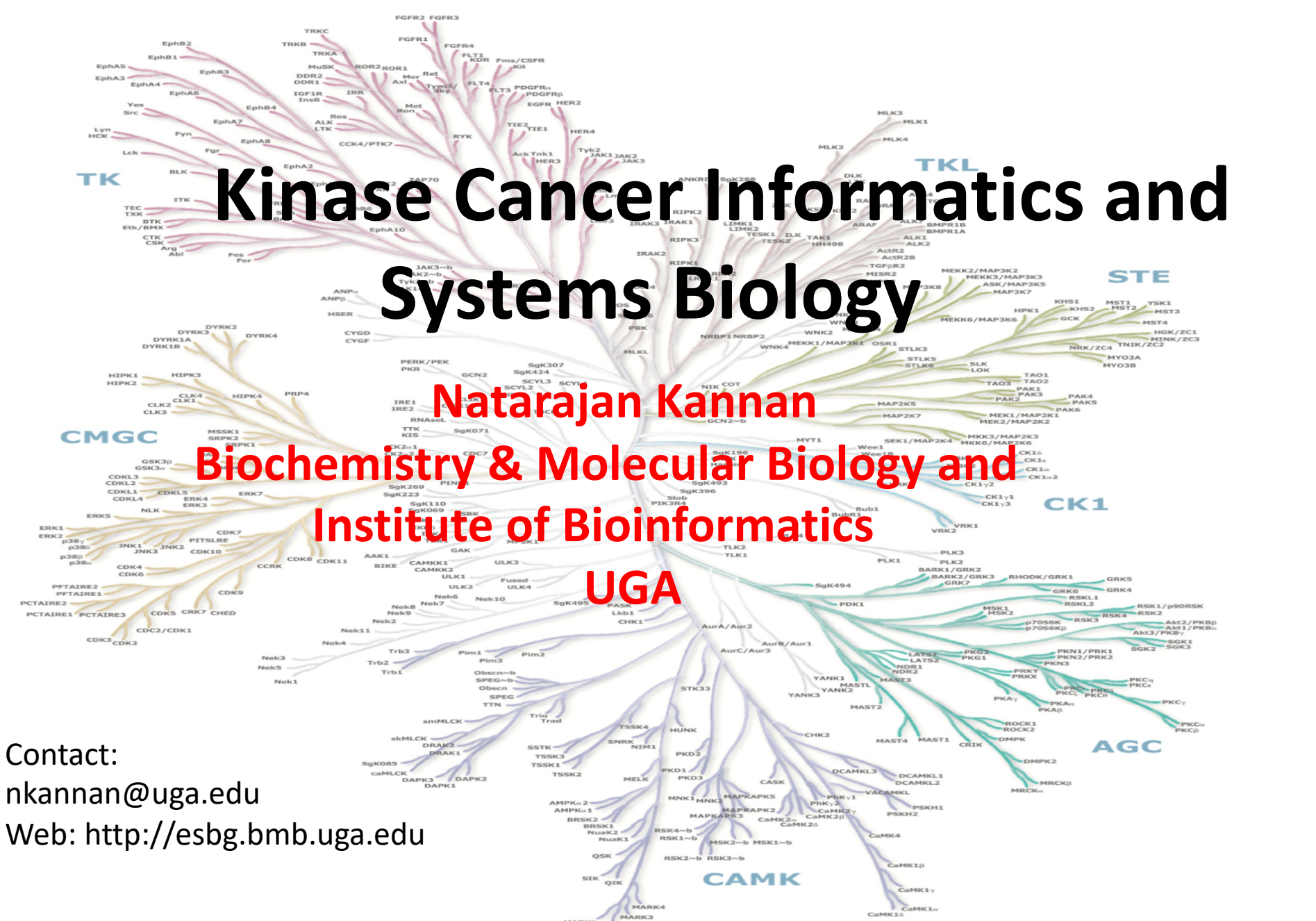


Recent Cancer Center Activities: Cancer Center Seminar Series 2023-2024

Spring 2024

- **Kosuke Funato**, Assistant Professor, Biochemistry,
"Dissecting the Heterogeneity of Pediatric Brain Tumor Using Human Embryonic Stem Cell-Based Models"
- **Vivian Lui**, Associate Professor, GCC,
"Targeting Head and Neck Cancer with Genomic Understanding"
- **Darby Arakelian**, Command Strategies,
"Cancer Research Programs at CDMRP"



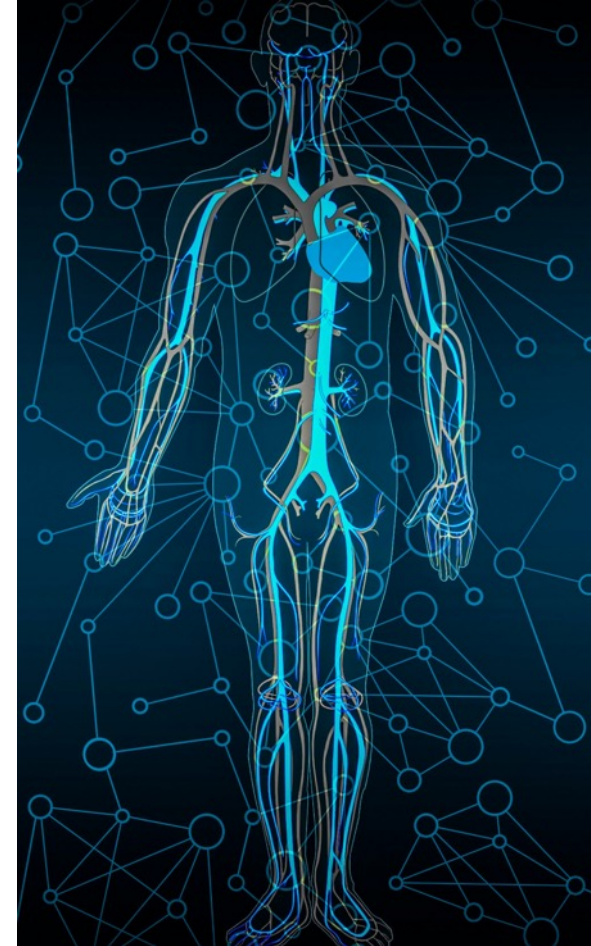
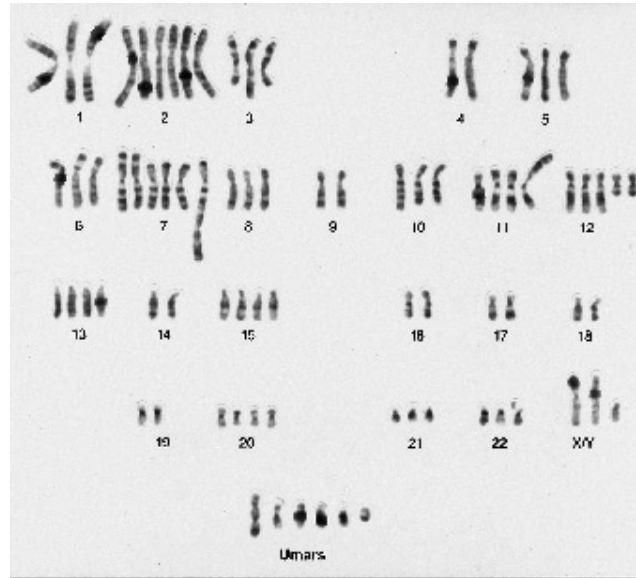
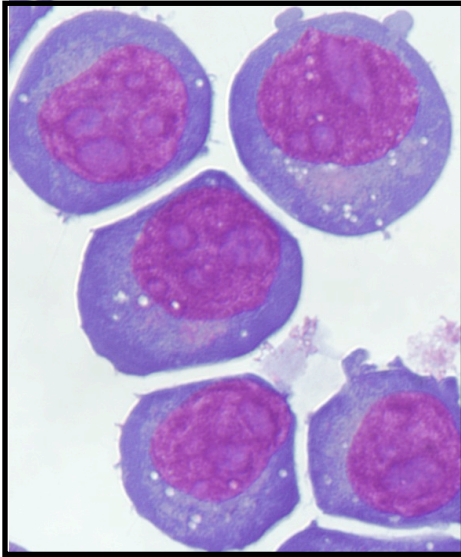


Kinase Cancer Informatics and Systems Biology

Natarajan Kannan
Biochemistry & Molecular Biology and
Institute of Bioinformatics
UGA

Contact:
nkannan@uga.edu
Web: <http://esbg.bmb.uga.edu>

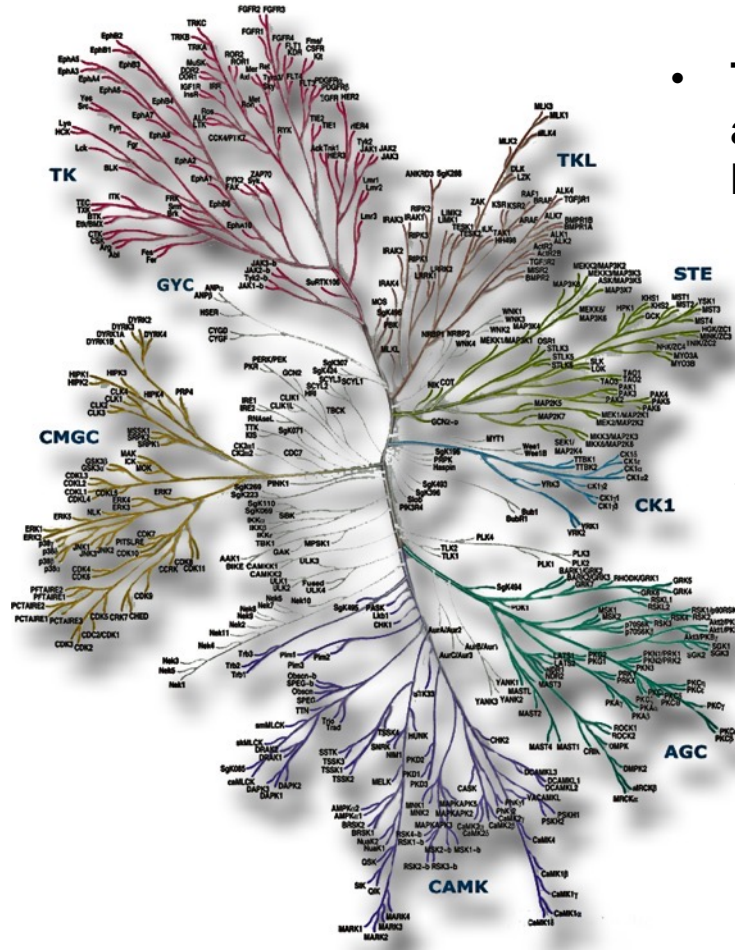
Cancer: A Disease of the Genome



Challenges in Cancer Treatment:

- Every tumor is different
- Every cancer patient is different
- Complexity of cellular signaling networks

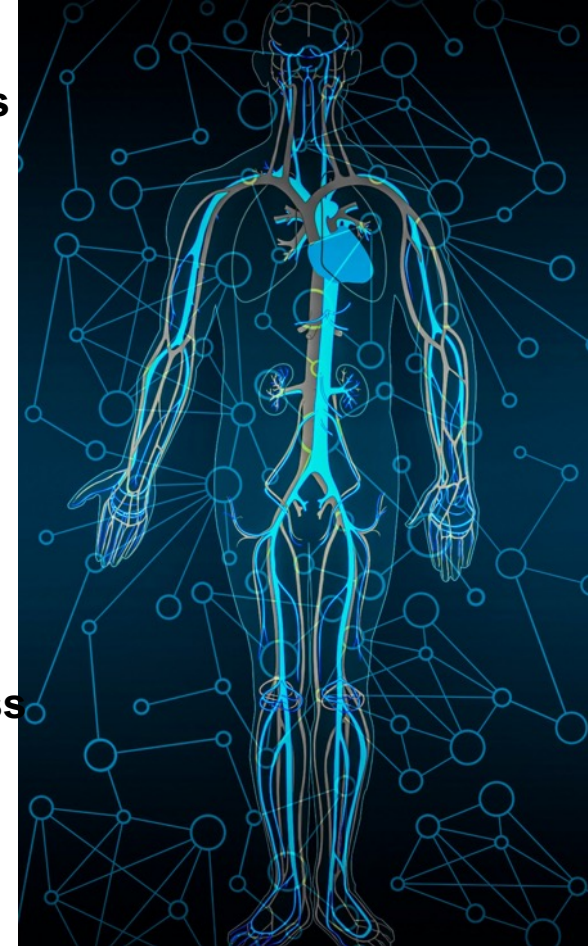
The human kinome is a major target for personalized cancer therapy



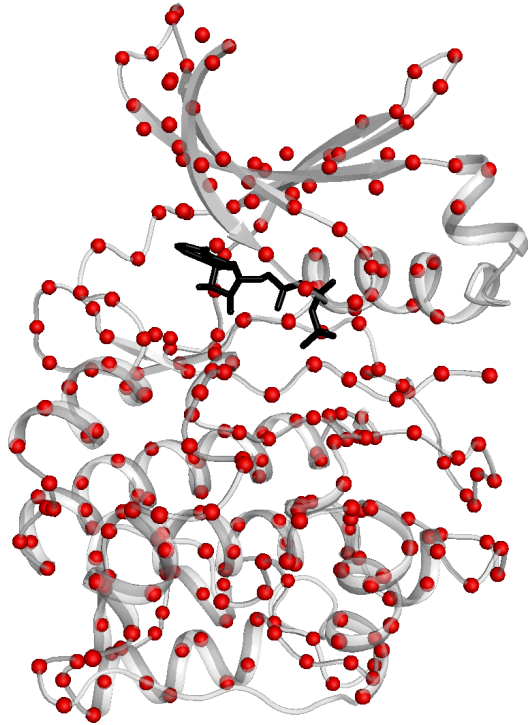
- The 518 protein kinase genes are frequently mutated in human cancers



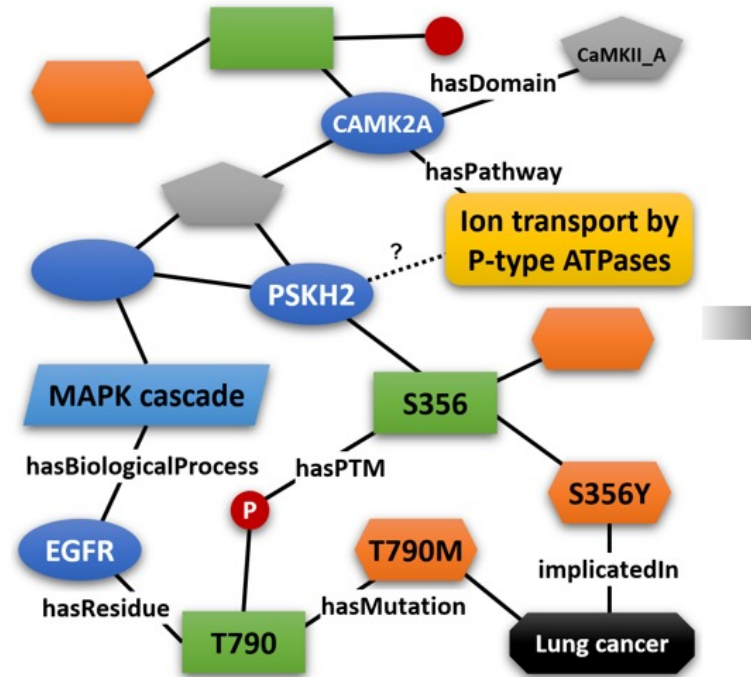
- They regulate all known signaling pathways through phosphorylation of proteins, lipids and metabolites
- They are a druggable class of proteins with many FDA approved drugs



Effectively mining the cancer kinome is a challenge

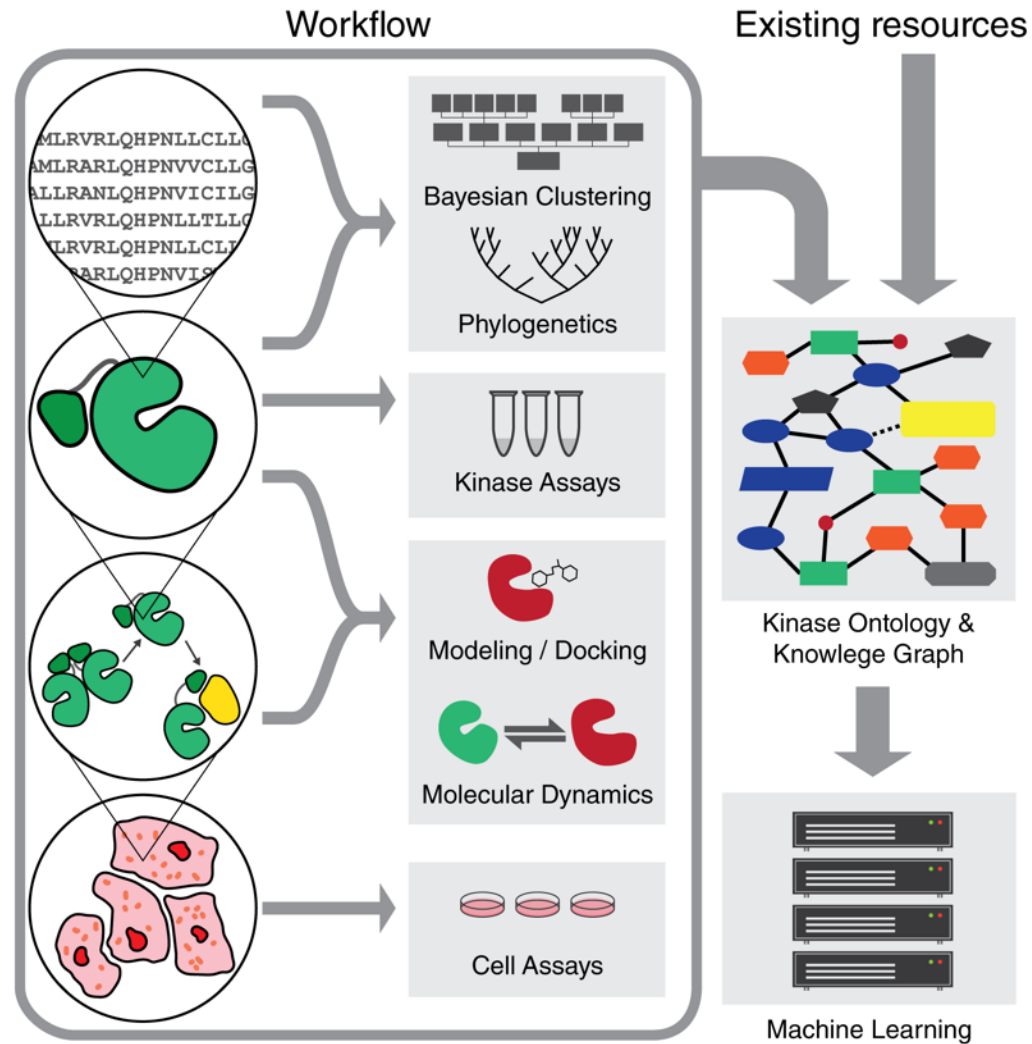


EGFR

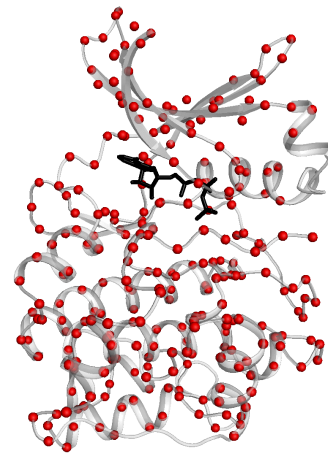
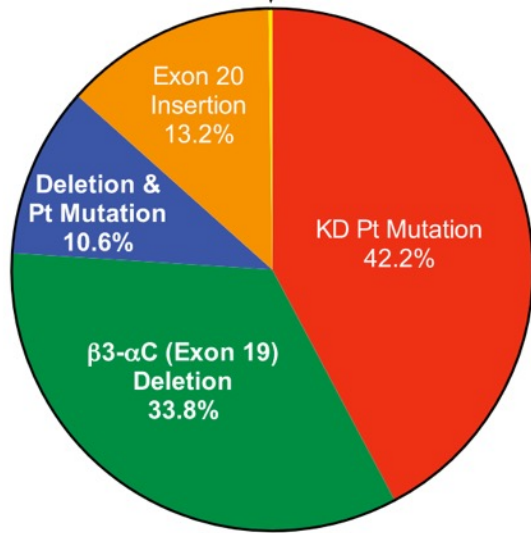


Predicting and prioritizing oncogenic mutations requires structural and biological context

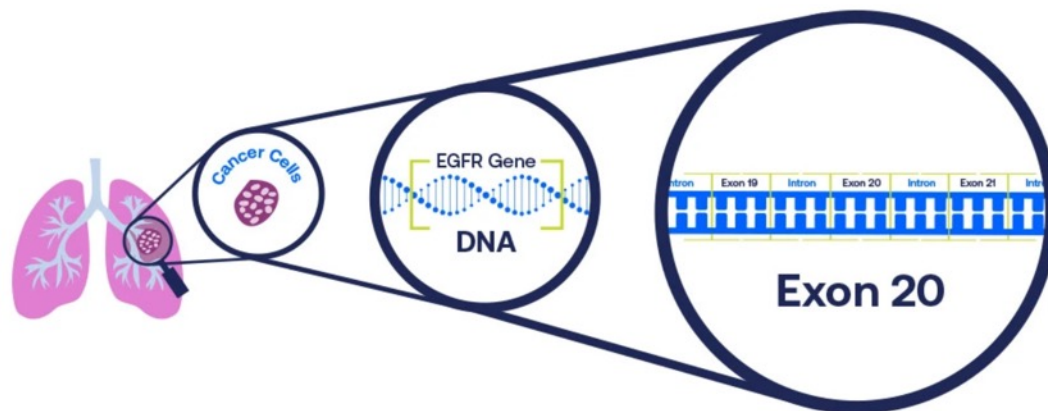
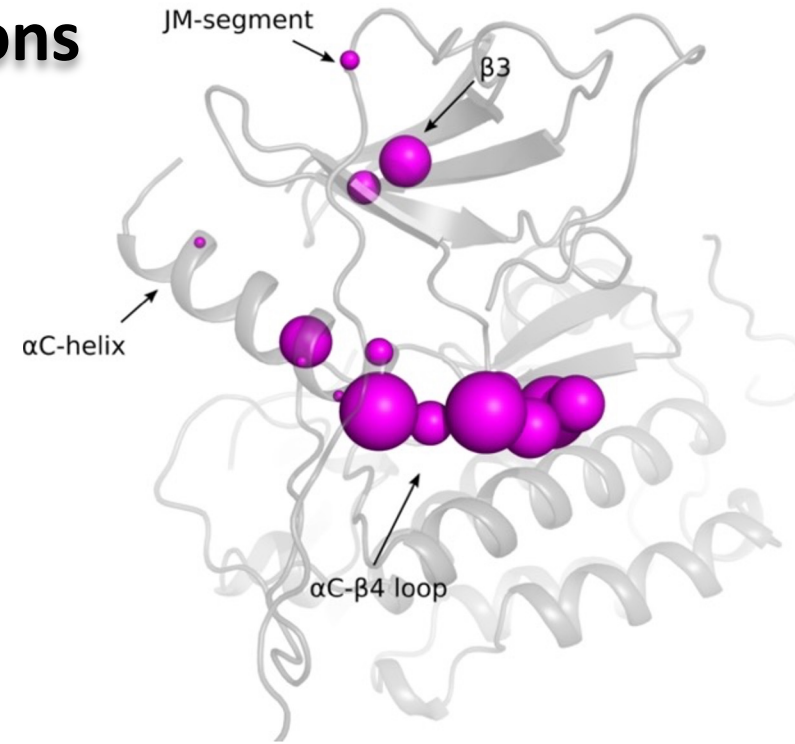
Systems and data-driven approaches to investigate oncoproteins



EGFR Exon 20 insertion mutations in lung cancer

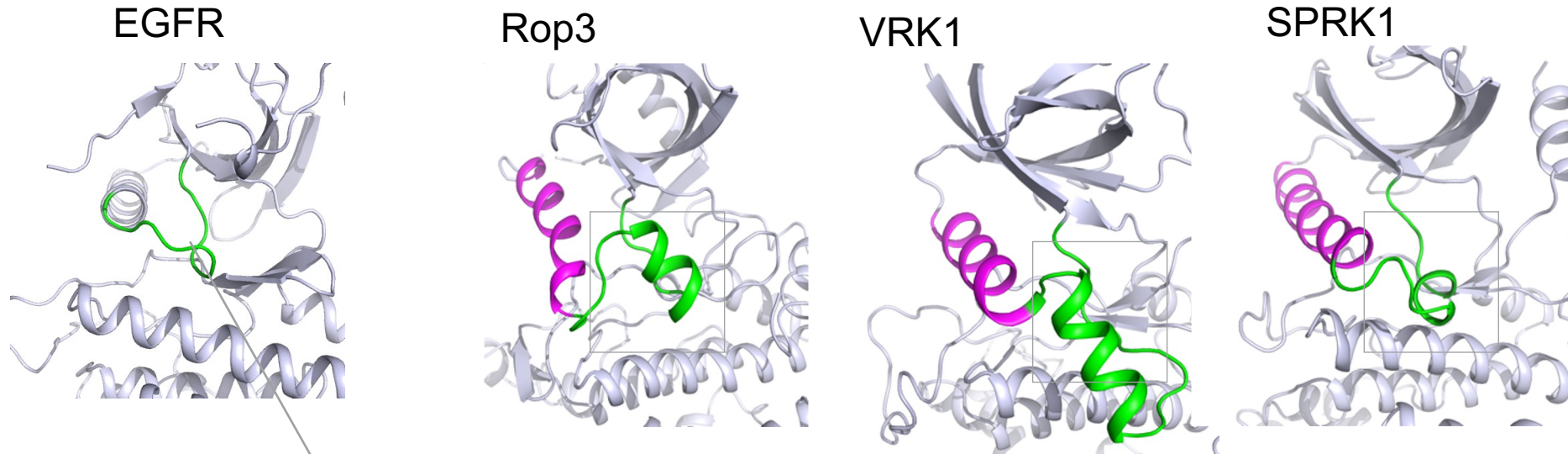


EGFR



- The median overall survival is 5 months for patients with exon 20 insertion mutations compared to 16.1 months for patients with EGFR TKI-sensitizing point mutations
- The structural and functional impact of these mutations is poorly understood (Yasuda et al, *Sci Transl Med* 2013)

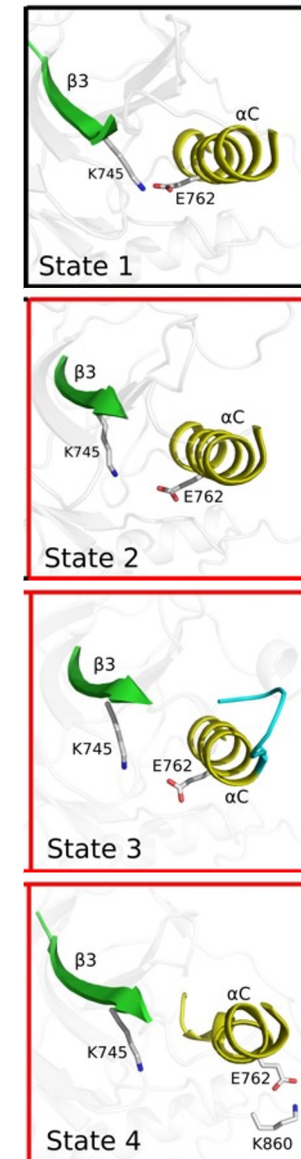
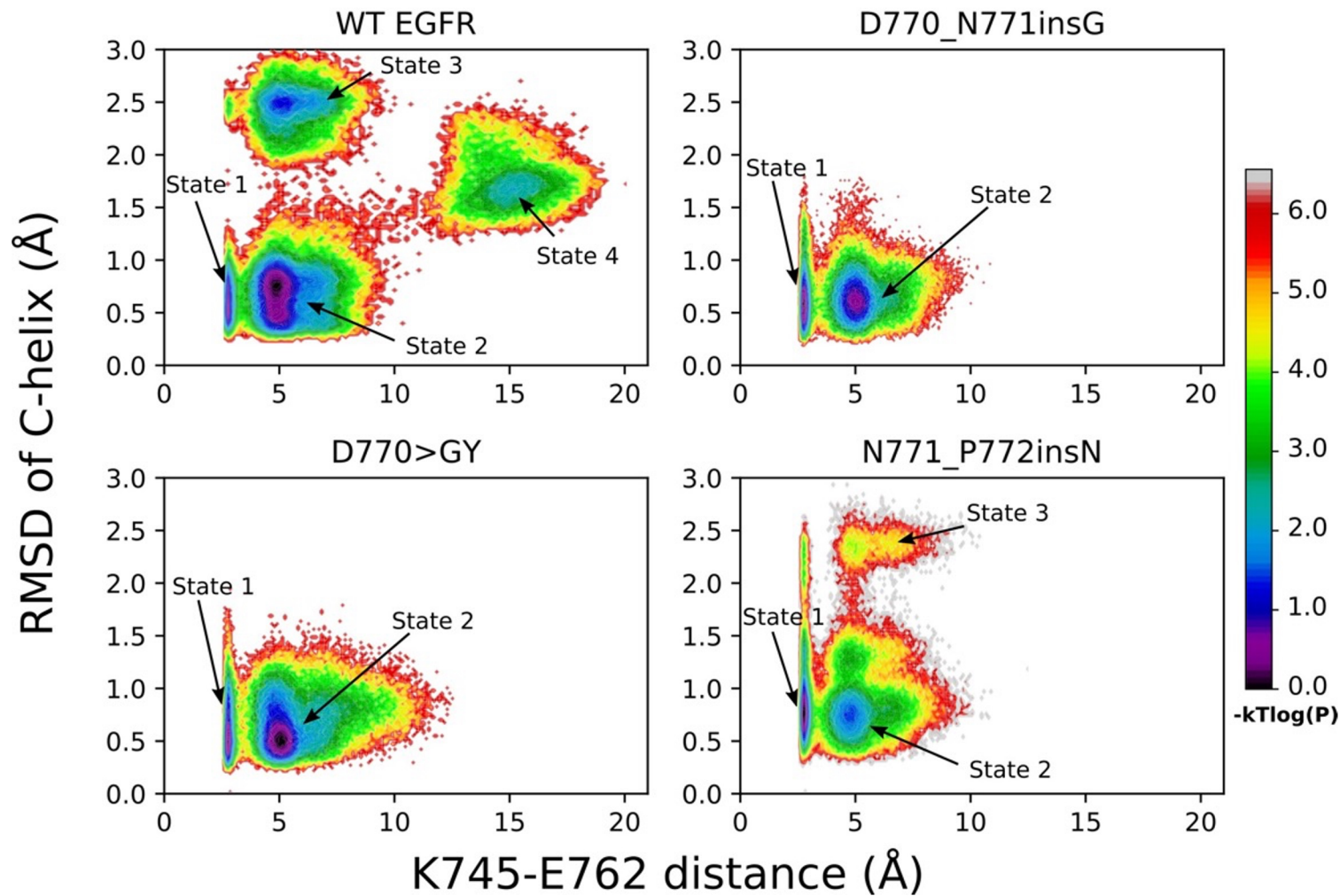
Deep evolutionary comparisons across the kinome provide insights into exon 20 insertion mutations



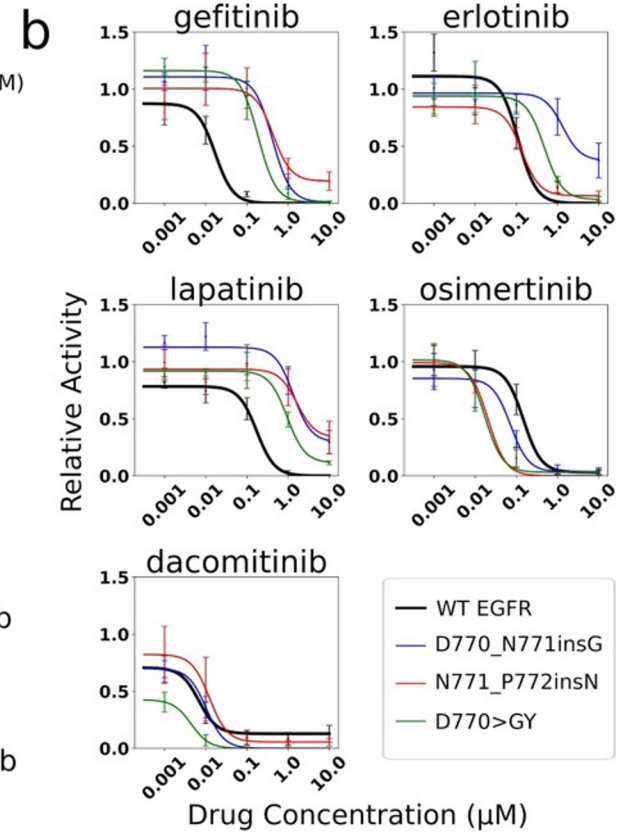
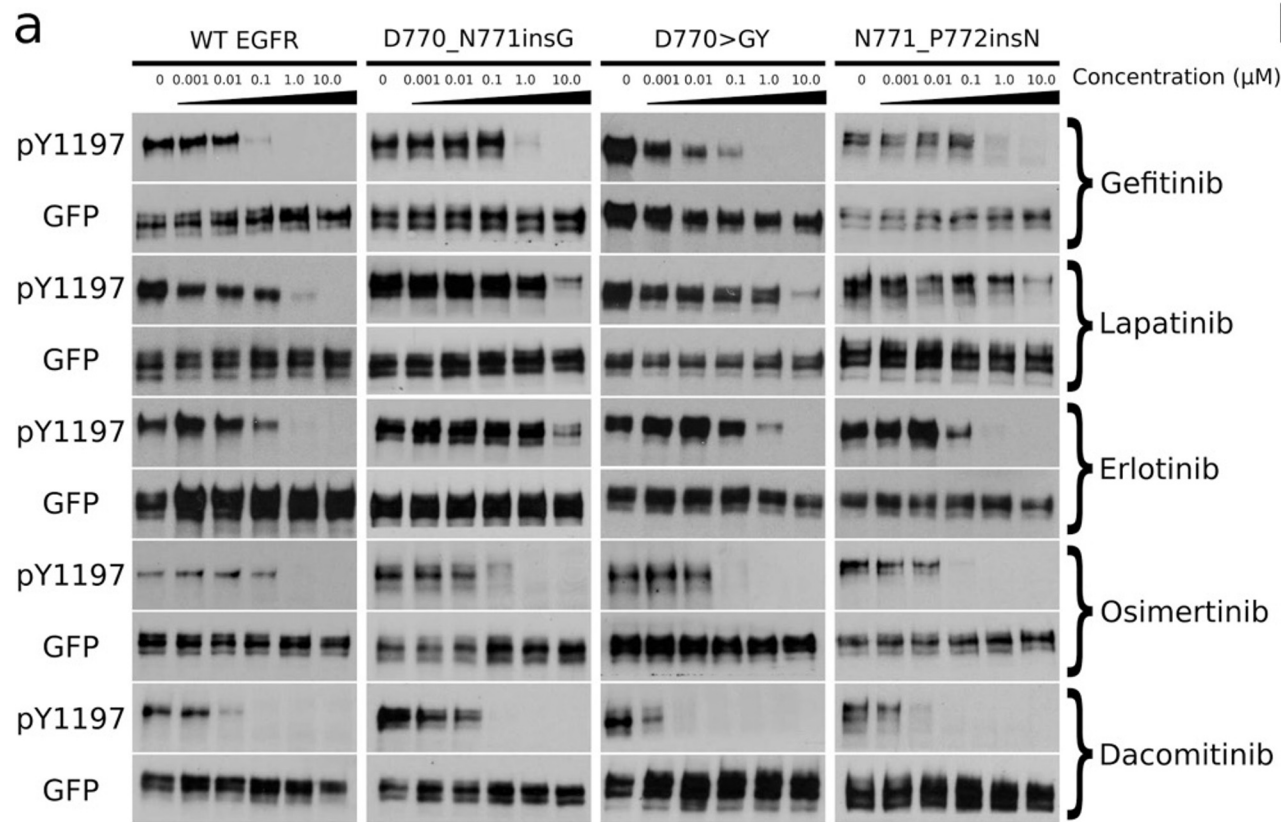
	αC	αC - $\beta 4$ loop	$\beta 4$
WT	oooooo		→
D770_N771insG	EAYVMASVD	...NPHVCRL	LLGI
N771_P772insN	EAYVMASVDG	...NPHVCRL	LLGI
N771_P772insH	EAYVMASVDN	...NPHVCRL	LLGI
P772_H773insPR	EAYVMASVDNP	.RPHVCRL	LLGI
V774_C775insHV	EAYVMASVDNP	.HVHVCRL	LLGI
H773_V774insAH	EAYVMASVDNP	.HAHVCRL	LLGI
H773_V774insPH	EAYVMASVDNP	.HPHVCRL	LLGI
H773_V774insNPH	EAYVMASVDNPN	PHVCRL	LLGI
H773_V774insH	EAYVMASVDNP	..HHVCRL	LLGI
V769_D770insASV	EAYVMASVASVDN	PHVCRL	LLGI
D770_N771insSVD	EAYVMASVDSVDN	PHVCRL	LLGI
N771_P772>SVDNR	EAYVMASVDSVDNR	RHVCRL	LLGI
D770>GY	EAYVMASVGY	..NPHVCRL	LLGI

Hypothesis: Exon 20 insertion mutations impact catalytic activity by altering kinase conformational regulation

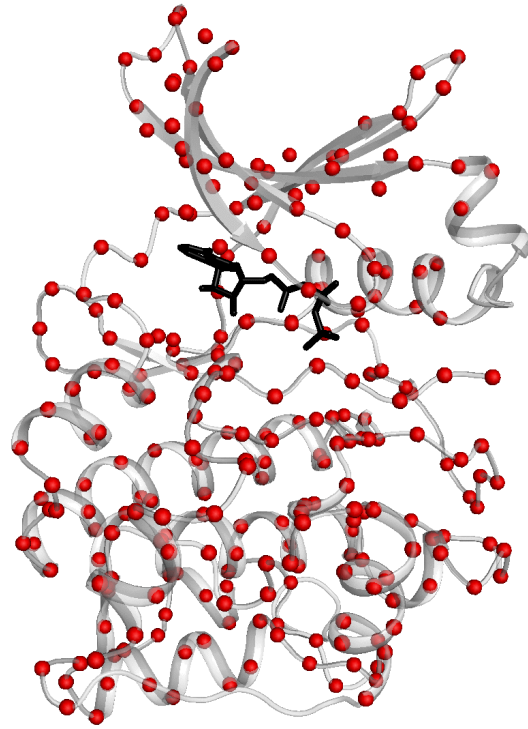
Activating mutations restrict conformational freedom to active-like states



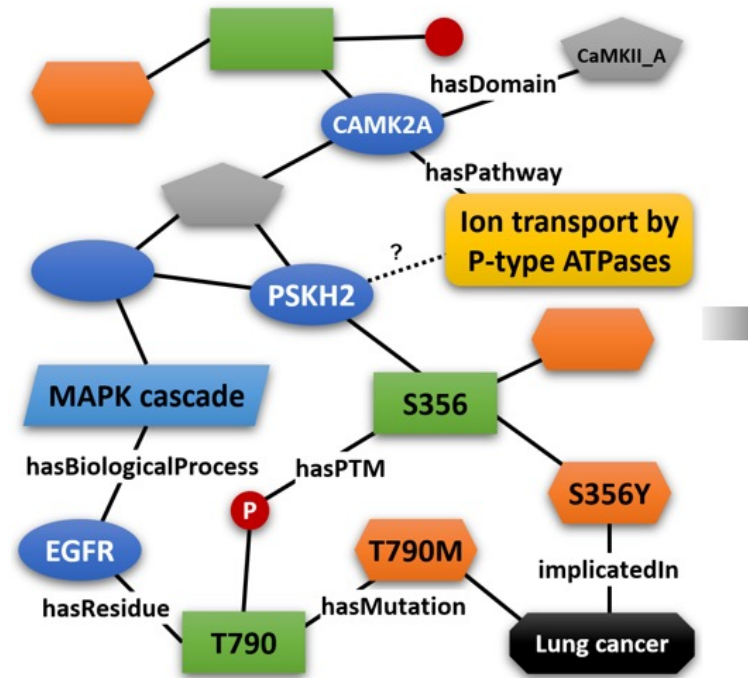
Insertion mutations display differential sensitivity to second-generation EGFR inhibitors



Effectively mining the cancer kinome is a challenge

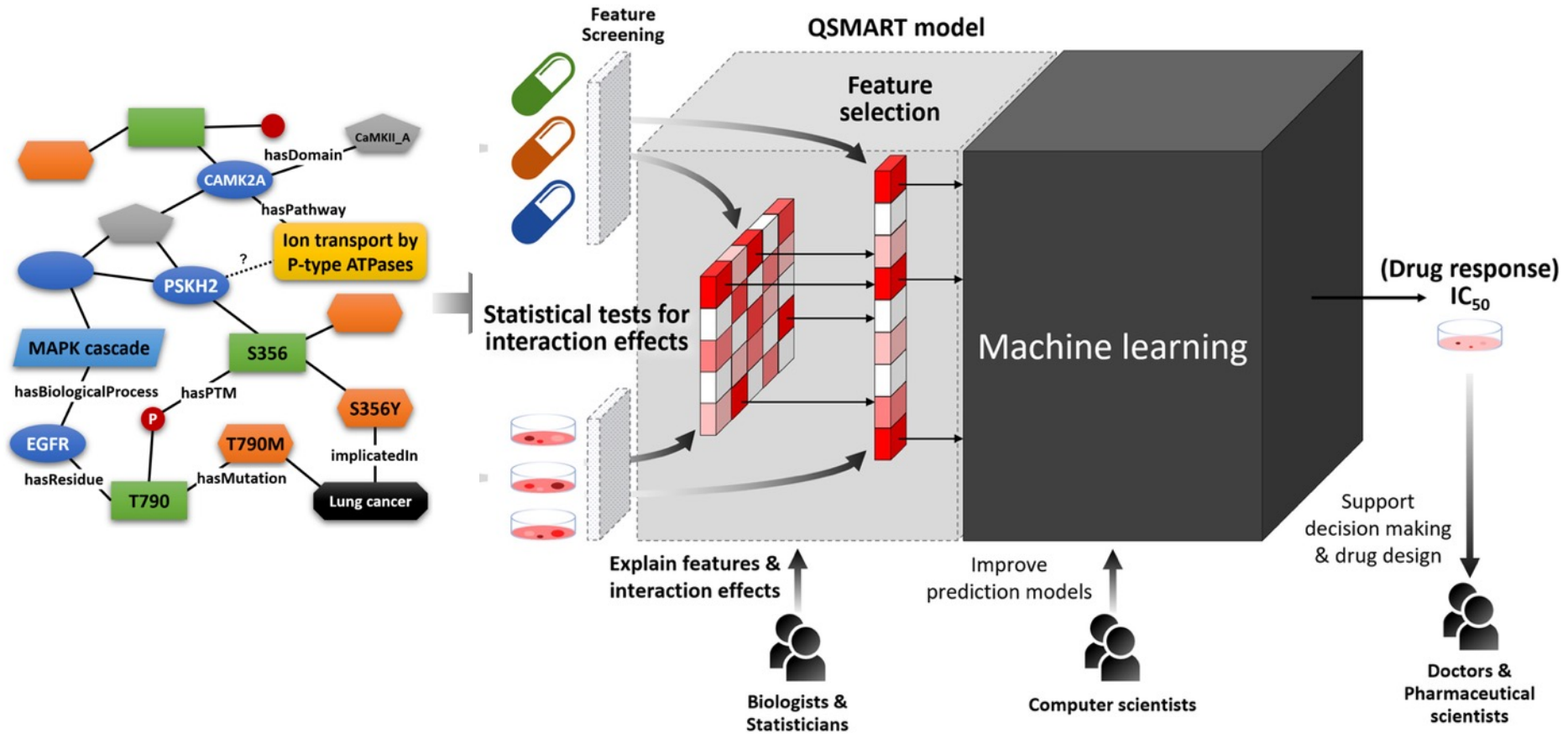


EGFR



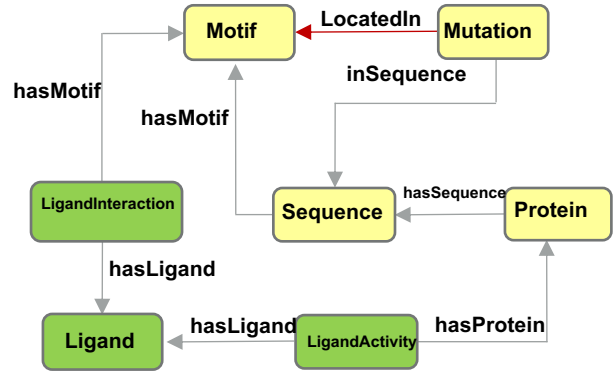
Predicting and prioritizing oncogenic mutations requires biological context

Explainable machine learning models for predicting mutant kinome drug response

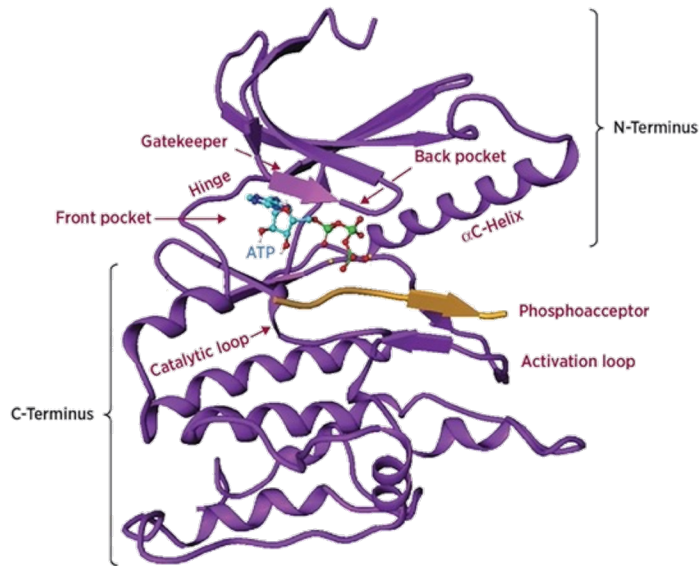
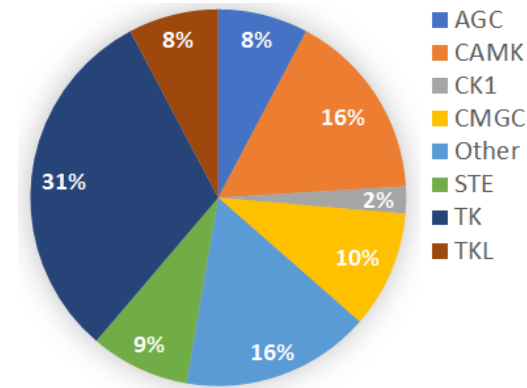


[QSMART: BMC Bioinformatics](#) volume 21, Article number: 520 (2020)

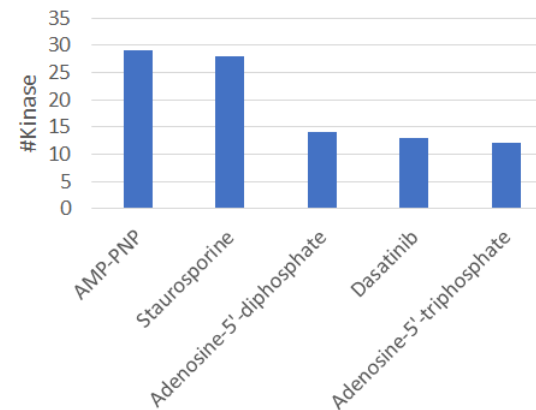
Hypothesis generation using knowledge graph mining



Q1: #Kinases with mutation in the gatekeeper position?



Q2: #Ligands interacting with gatekeeper residue?



- Huang LC et.al. Sci Rep. 2018 Apr 25;8(1):6518.
- Hu J. et. al. MCB. 2015;35(1):264-76.

- Bailey FP et.al. Biochem. J. 2015;465(2):195-211
- McClendon CL et.al. PNAS. 2014;111(43):E4623-31.

ProKinO is open-source and widely used



ProKinO



Protein Kinase Ontology (ProKinO)

The Protein Kinase Ontology (ProKinO) is an ontology and knowledge graph, which provides a controlled vocabulary of terms, their hierarchy, and relationships unifying sequence, structure, function, mutation and pathway information on kinases. The conceptual representation of such diverse information in one place enables not only rapid discovery of significant information related to a specific protein kinase, but also enables large scale integrative analysis of the protein kinase family.

ProKinO Browser

You can use this ontology browser to quickly query, navigate, and explore the knowledge graph including the sequence, structure, function, disease, pathway, and ligand information on kinases.

Launch

KinView

The Kinome Viewer (KinView) can be used as a comparative tool to identify differences and similarities in natural variation, cancer variants and post-translational modifications between kinase groups, families and subfamilies.

Launch

Downloads

To download a version of the ontology, or an offline version of the KinView, you can visit the Downloads page.

Launch

19/SEP/2021 — 14/JUL/2022

Unique Visitors

5,992

Requested Files

4,830

Total Requests

77,440

Valid Requests

77,438

<https://prokino.uga.edu/>

Acknowledgements

Kannan ESG Lab



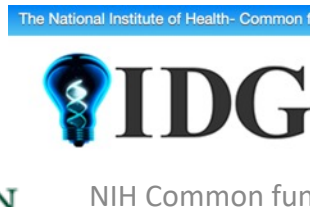
Lab members

Wayland Yueng (Bioinformatics)
Nathan Gravel (Bioinformatics)
Dr. Samiksha Katiyar (Biochemistry)
Liang-Chin Huang (Bioinformatics)
Saber Soleymani (Computer Sci.)
Abbas Keshavarzi (Computer Sci.)
Safal Shresta (Bioinformatics)
Rahil Taujale (Bioinformatics)
Aarya Venkat (Biochemistry)
Brady O' Boyle (Biochemistry)
George Bendzunas (Biochemistry)

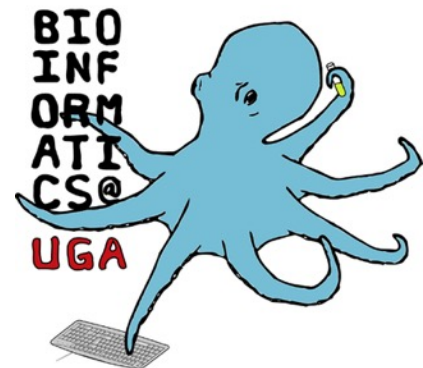
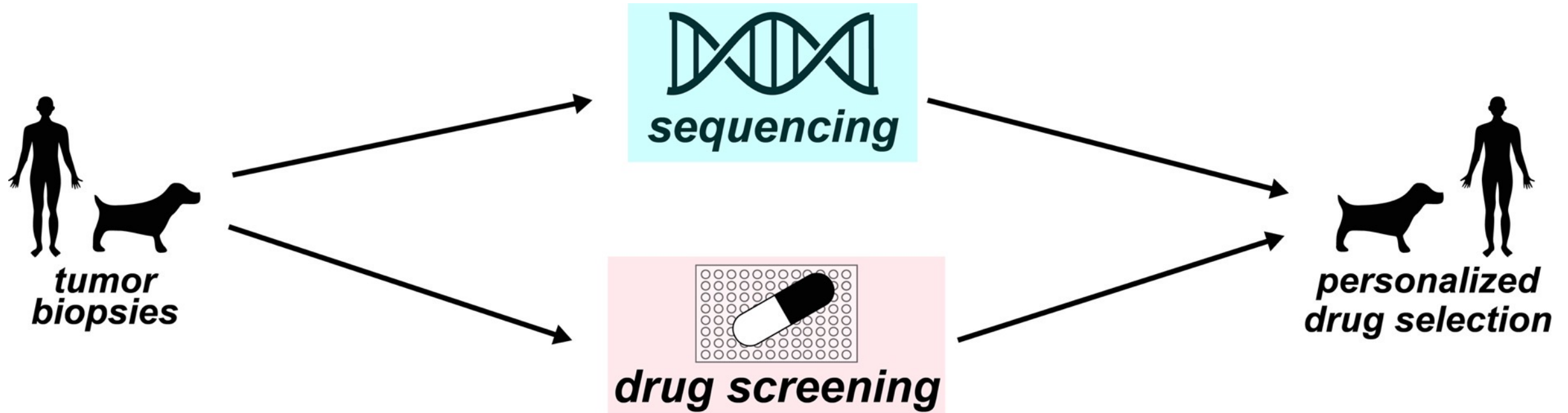
Collaborators

Eileen Kennedy (Pharmacy, UGA)
Krystof Kochut (Computer Sci.)
Sheng Li (Computer Sci.)
Patrick Eysers (U. Liverpool)
PDBe-KB team (EBI)
IDG Consortium (NIH, UNC Chapel Hill)

Funding



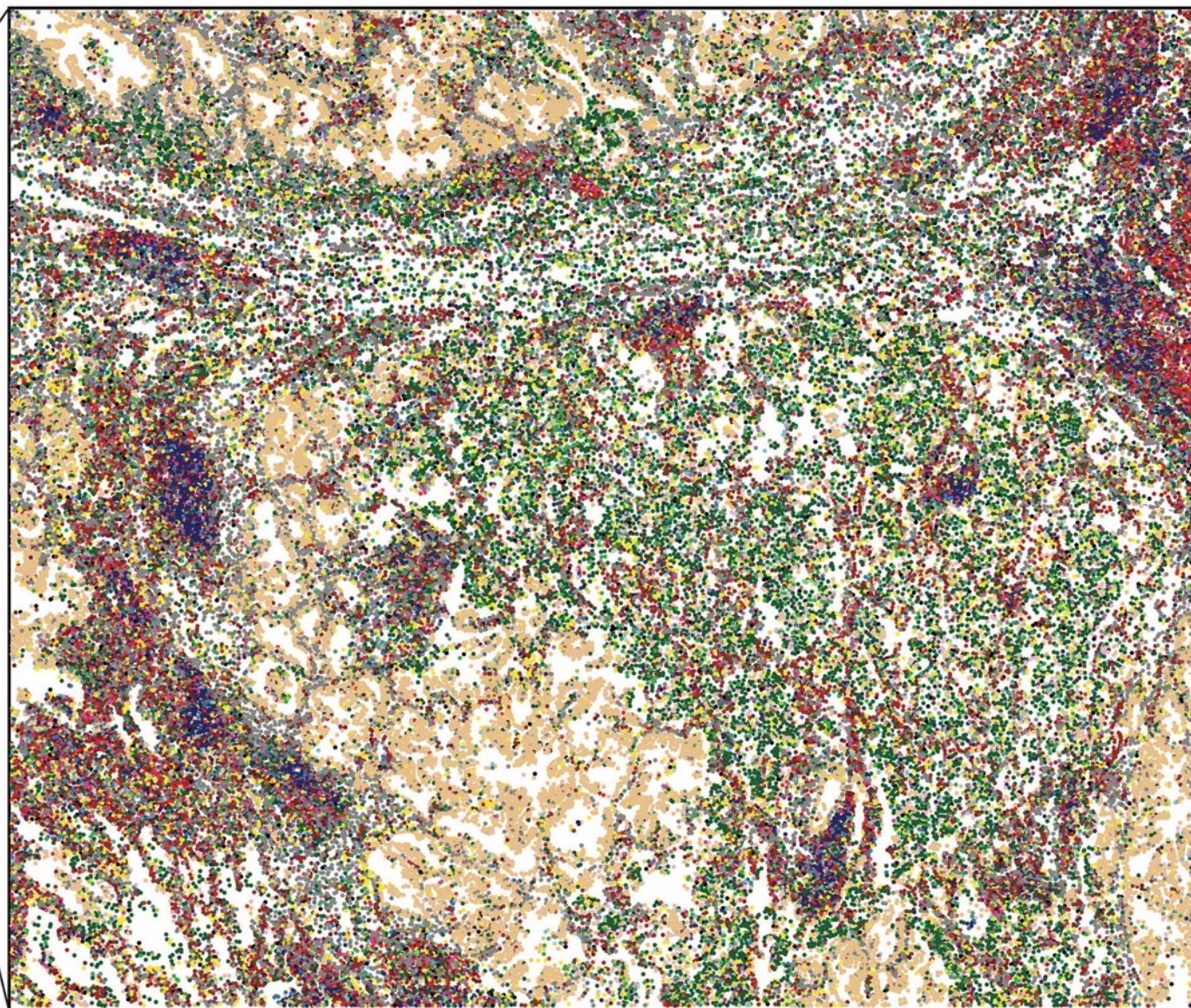
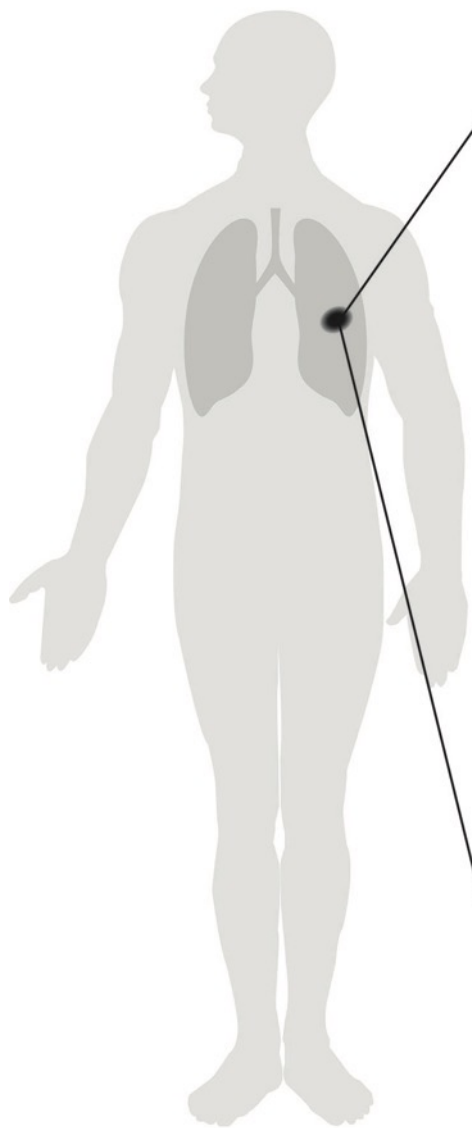
Douglass Lab: #1 genomic diagnostics #2 drug-screening




FFPE tissue:
lung cancer

Spatial transcriptomics (CosMx SMI):
99,803 individual cells x 960 genes/cell


sequencing




B-cell
8,839


Mac
14,179


neutrophil
2,709


CAF
20,488


cancer
17,170

Need different “weapons” for different battles



Immune-Inflamed: open warfare

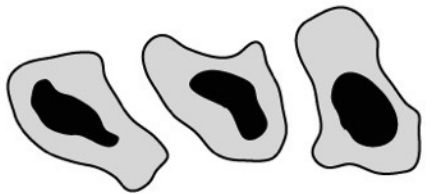
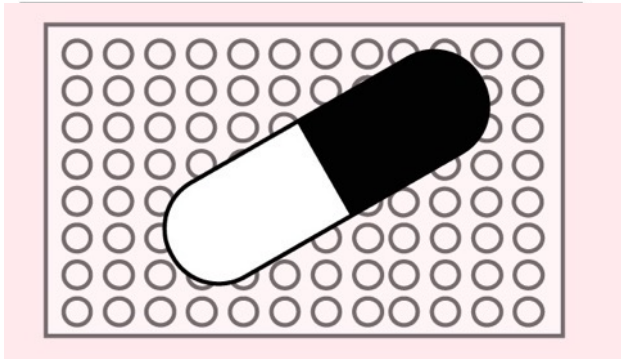


Immune-Excluded: siege of castle



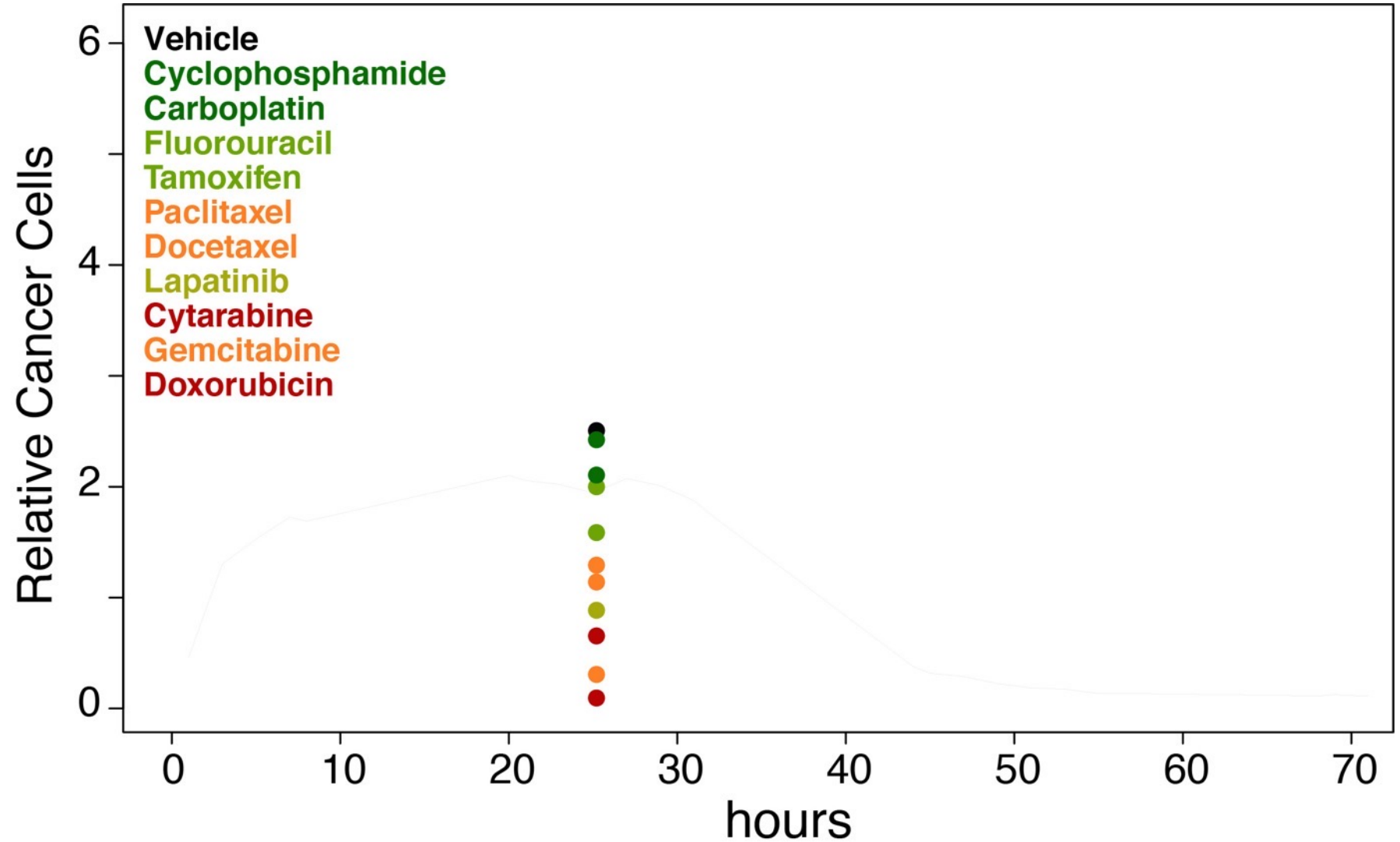
Traditional Drug-Screening Platforms: 24 hour time point

UGA Screen Platform



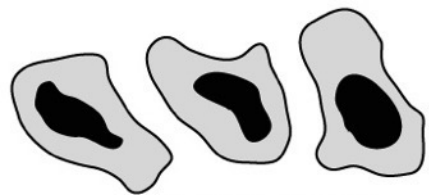
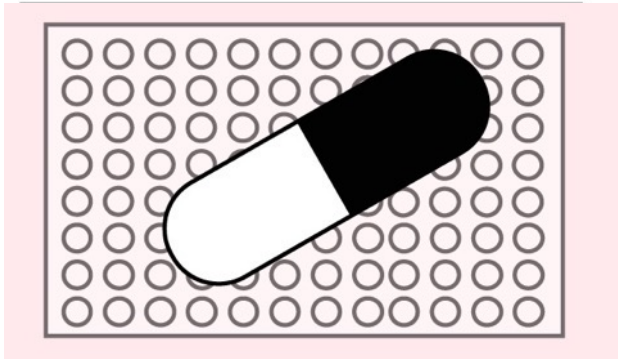
NALM6

(leukemia cell-line)



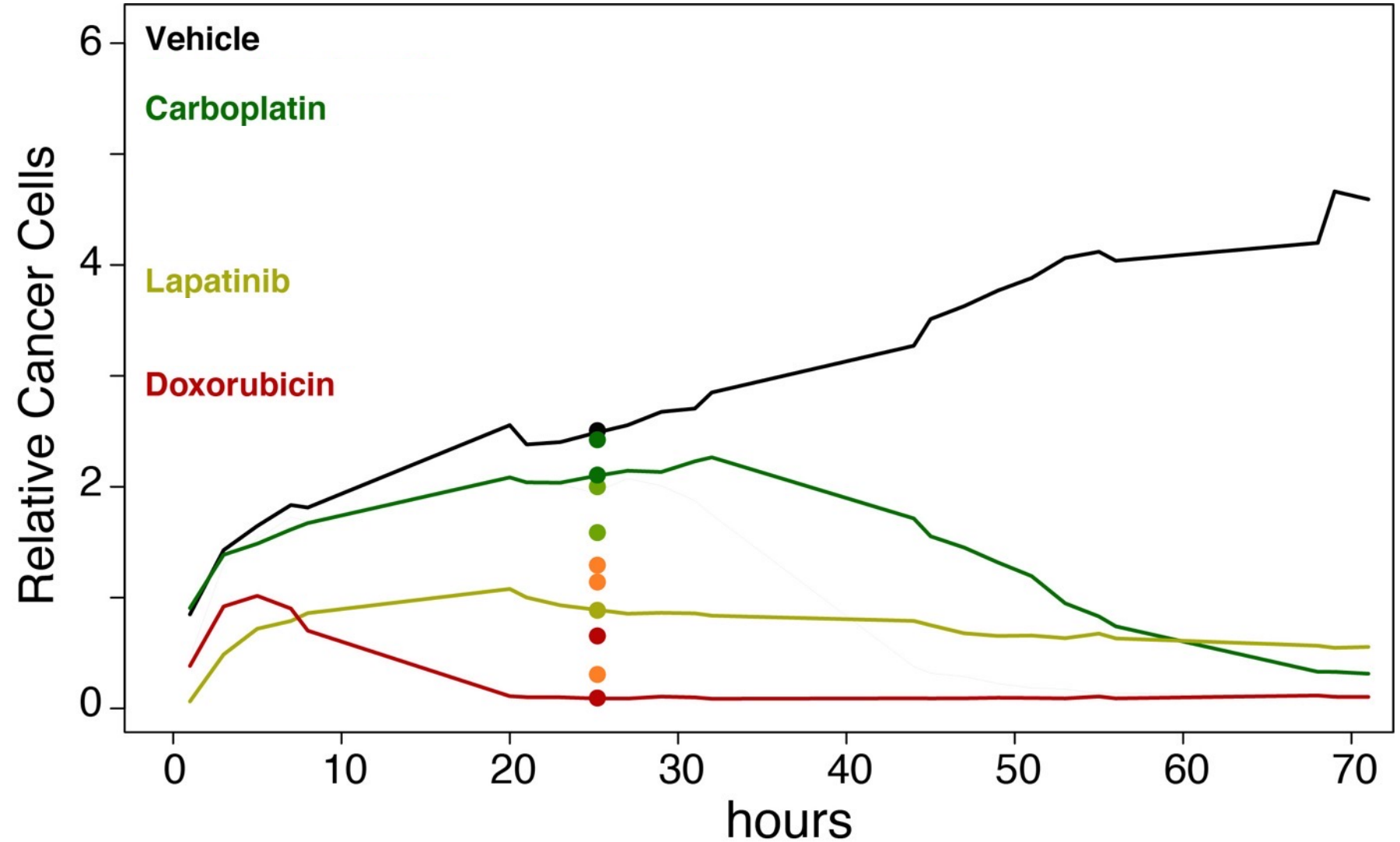
UGA-screening Platform: *time-course on top chemotherapies*

UGA Screen Platform



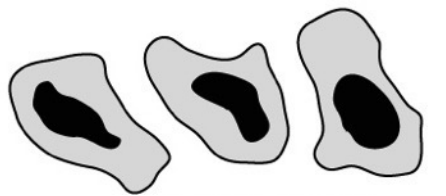
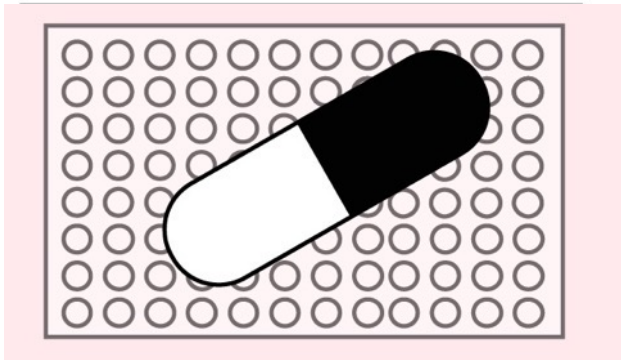
NALM6

(leukemia cell-line)



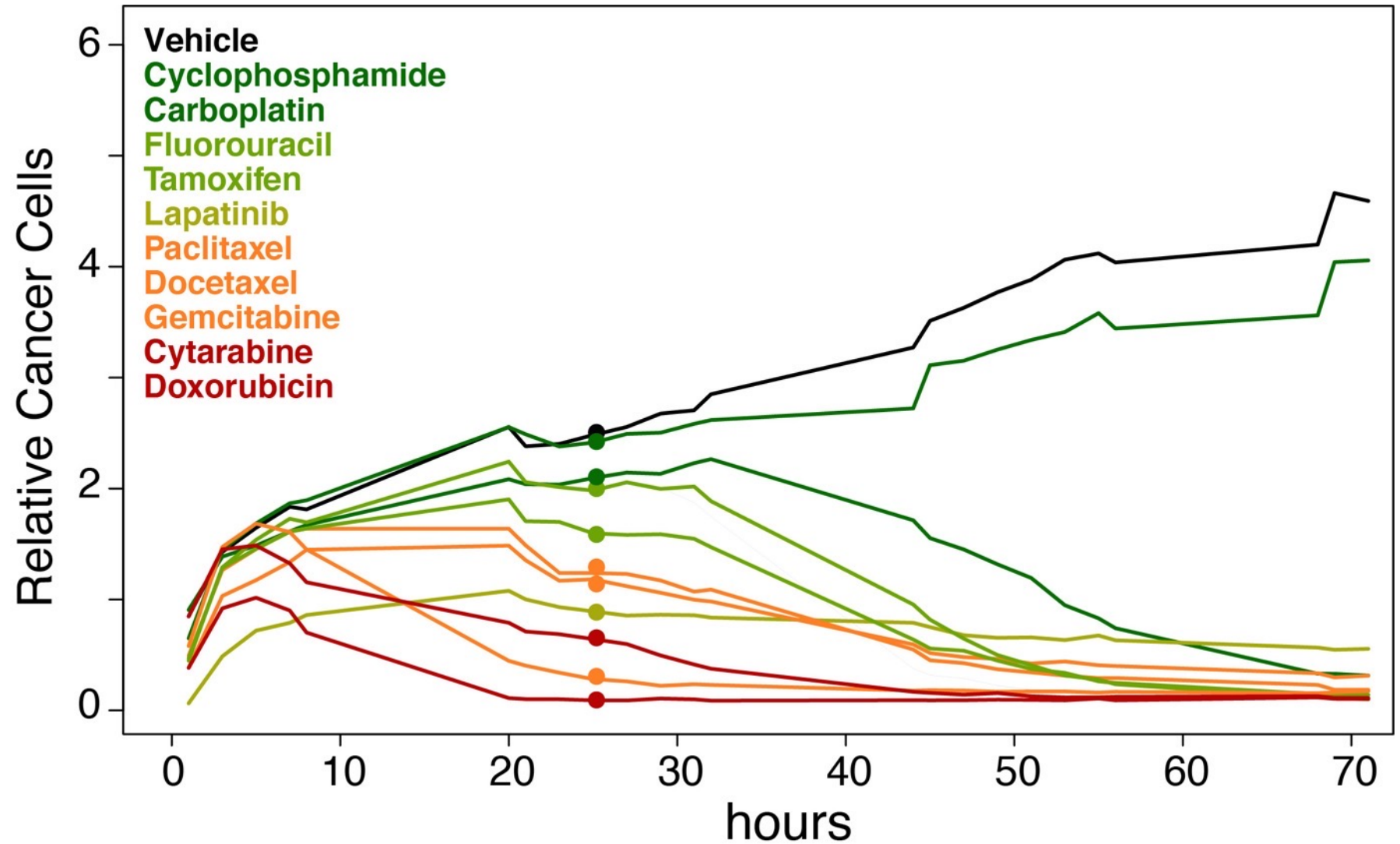
UGA-screening Platform: *time-course on top chemotherapies*

UGA Screen Platform



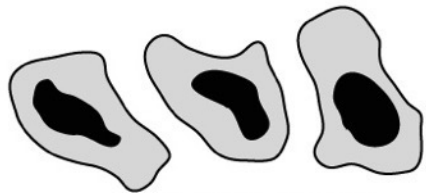
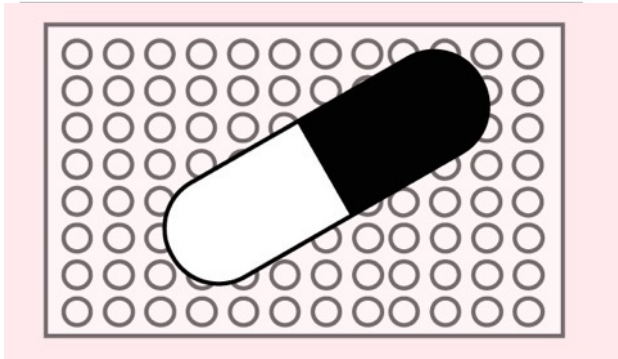
NALM6

(leukemia cell-line)



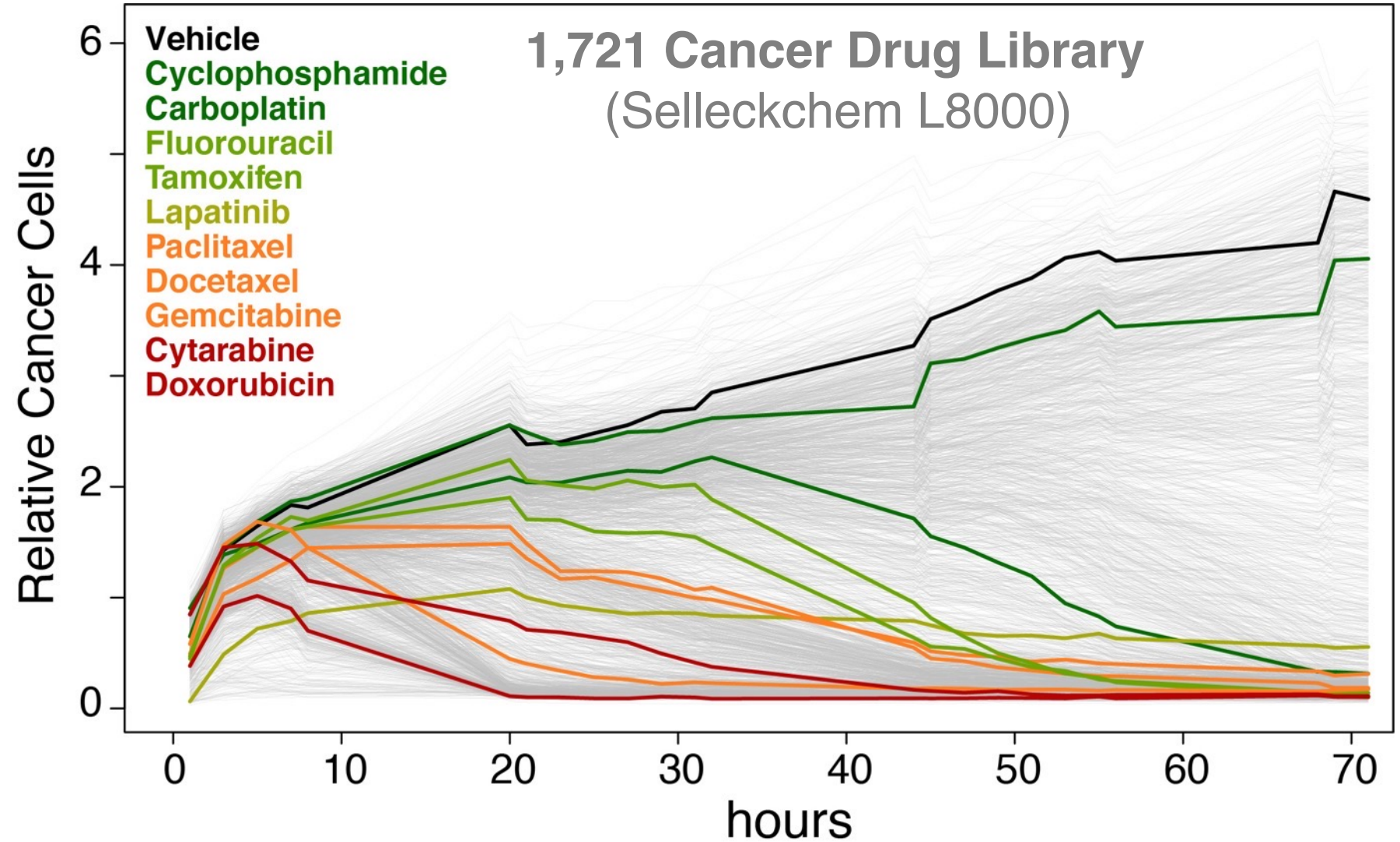
UGA-screening Platform: *time-course on top chemotherapies*

UGA Screen Platform



NALM6

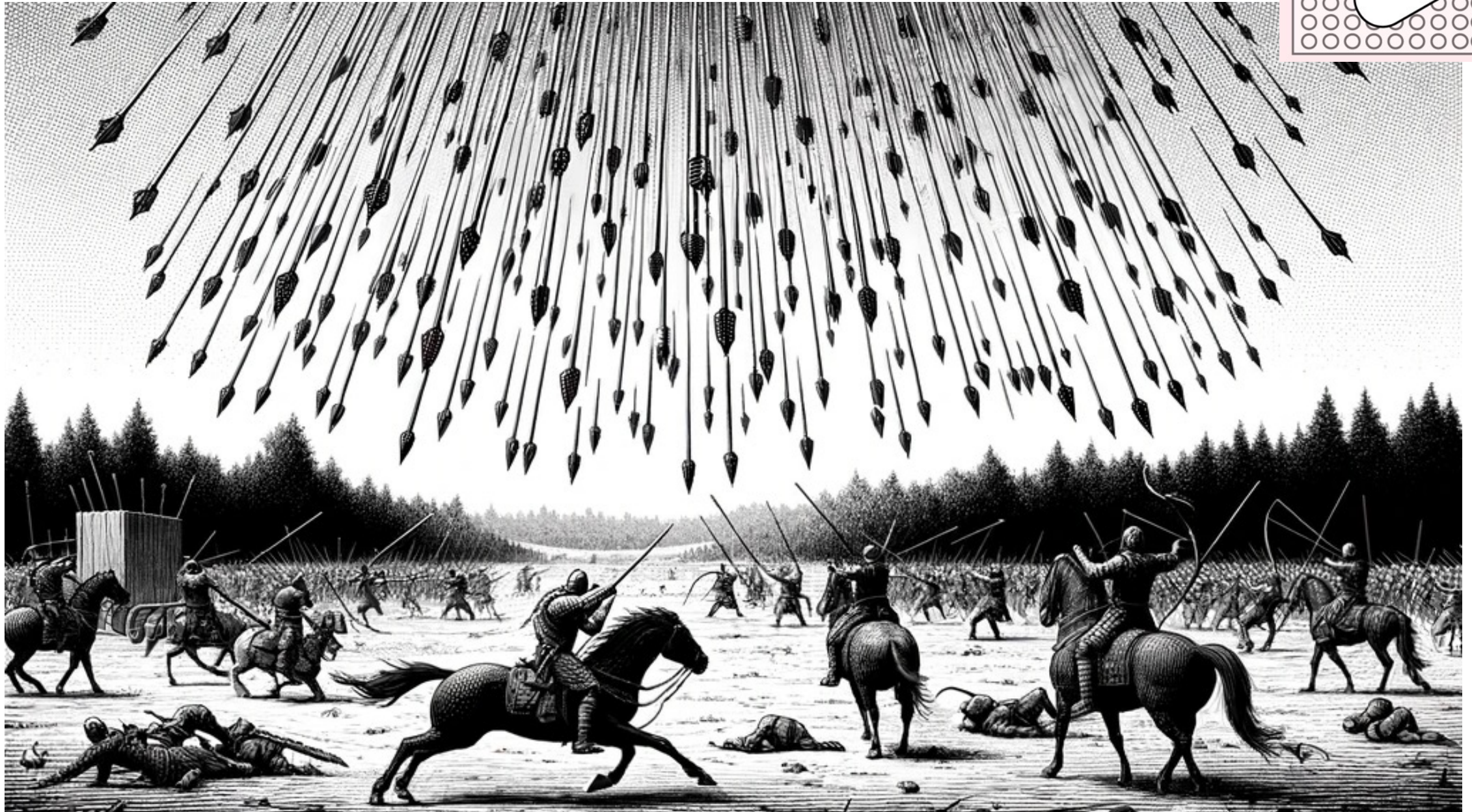
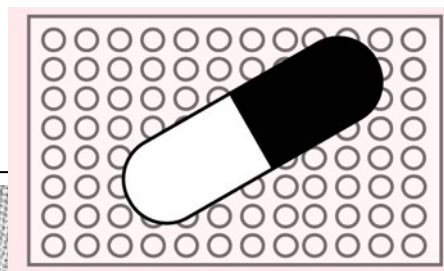
(leukemia cell-line)



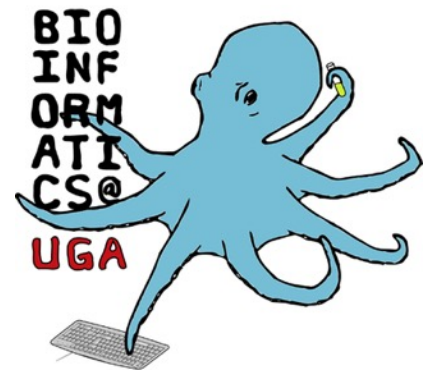
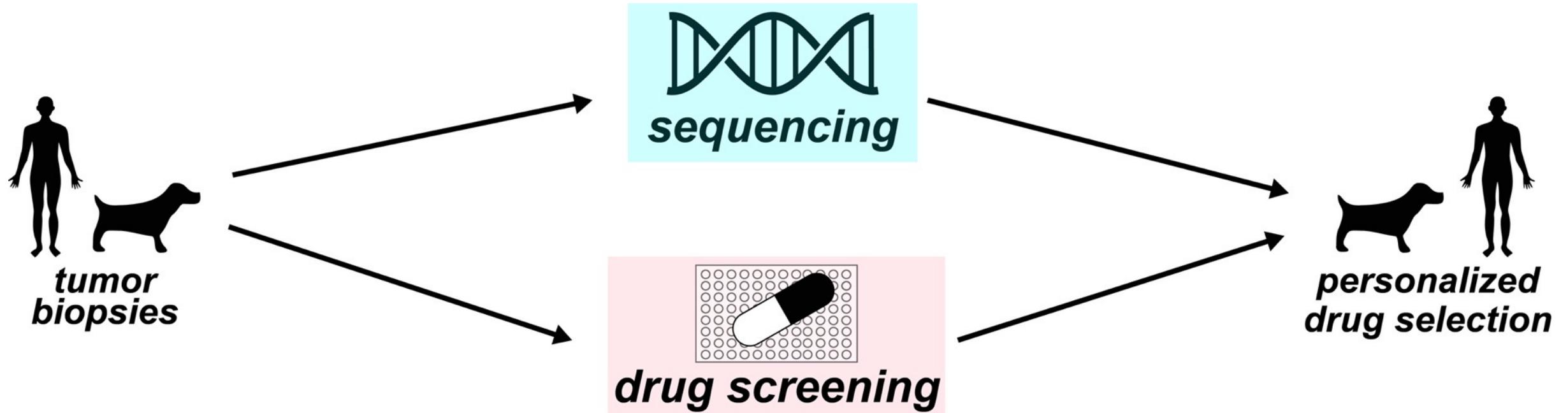
Clinical Work: characterize the battlefield of patients



Lab work: drugs efficacy under clinical conditions



Douglass Lab: #1 genomic diagnostics #2 drug-screening

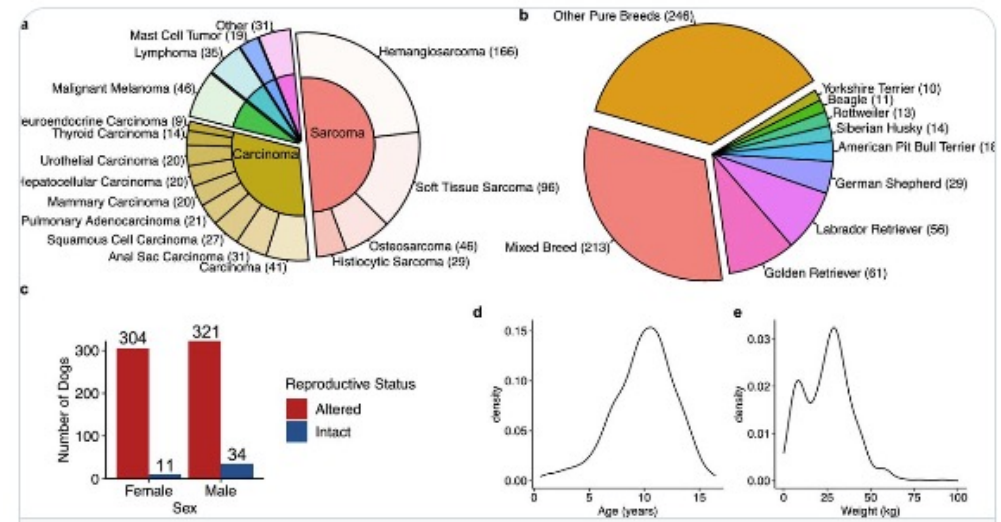
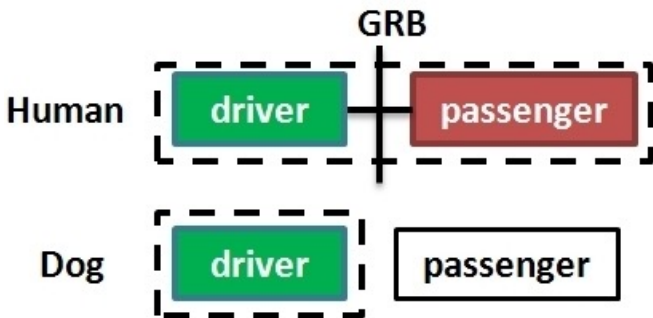


Zhao Lab, Biochemistry & Molecular biology, Institute of Bioinformatics szhao@uga.edu

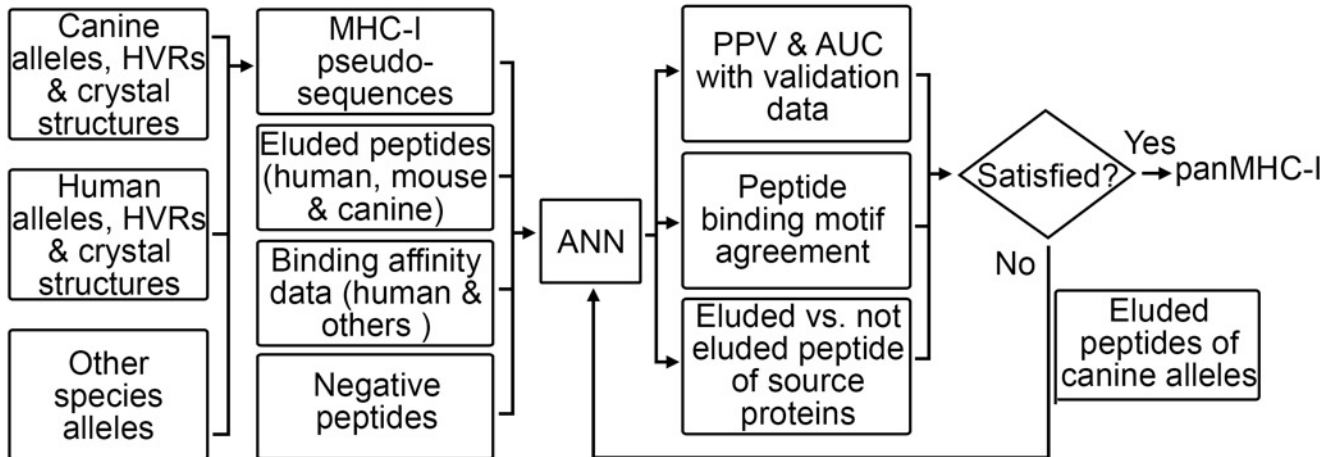
- **Project 1:** Man's best friend for cancer driver-passenger discrimination
- **Project 2:** Cancer immunotherapy & cancer vaccine development



Using #GenomicSequencing approaches in a study supported by @theNCI Oncology Models Forum, researchers @universityofga & @FidoCure revealed #genetic similarities between tumors in pet dogs and human cancers @SciReports nature.com/articles/s4159....



- <https://www.axios.com/newsletters/axios-vitals-f22c0566-6834-4f6c-815a-4f42ba034cb5.html>
- <https://www.fiercebiotech.com/research/new-research-mans-best-friend-opens-door-accelerating-cancer-drug-development-humans>
- <https://www.genomeweb.com/scan/canine-human-cancers-share-oncogene-mutations-study-finds>
- <https://www.salon.com/2023/07/12/cancer-in-dogs-and-humans-share-more-genetic-similarities-than-previously-thought-study/>
- <https://www.independent.co.uk/news/health/dogs-cancer-tumours-humans-research-b2372456.html>
- <https://www.telegraph.co.uk/news/2023/07/09/dogs-could-help-cure-cancer-genes-harvard-study/>

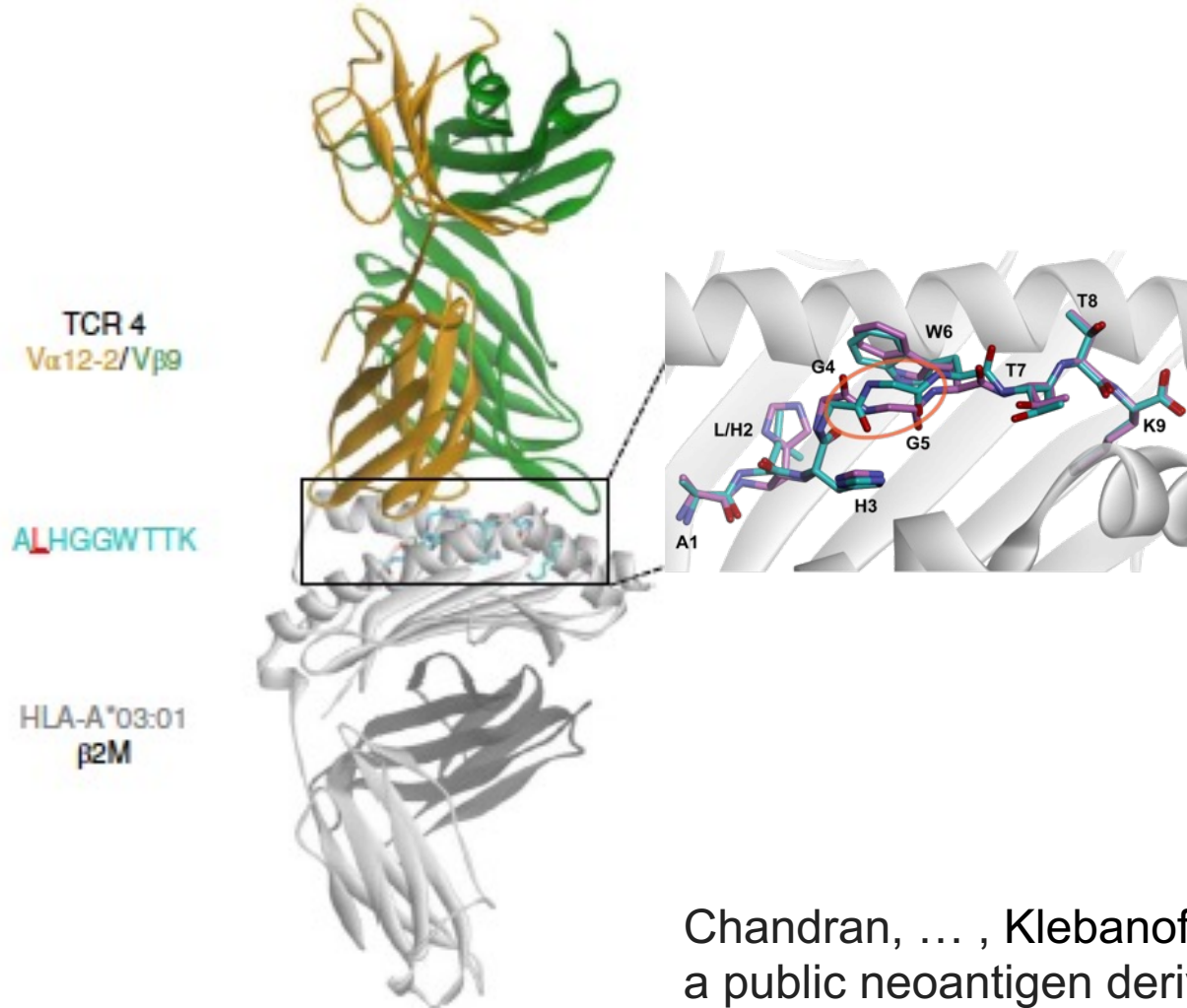


Funding



Preventive cancer vaccine with public neoantigens: immunogenic mutant peptides from hotspot mutations

PIK3CA H1047L



Challenges:

- >1,000 hotspot mutations
- >36,000 human MHC alleles
- <30 public neoantigens reported
- Clinical trial: 10-20 years

Chandran, ... , Klebanoff. 2022 Immunogenicity and therapeutic targeting of a public neoantigen derived from mutated *PIK3CA*. *Nat Med* **28**, 946–957

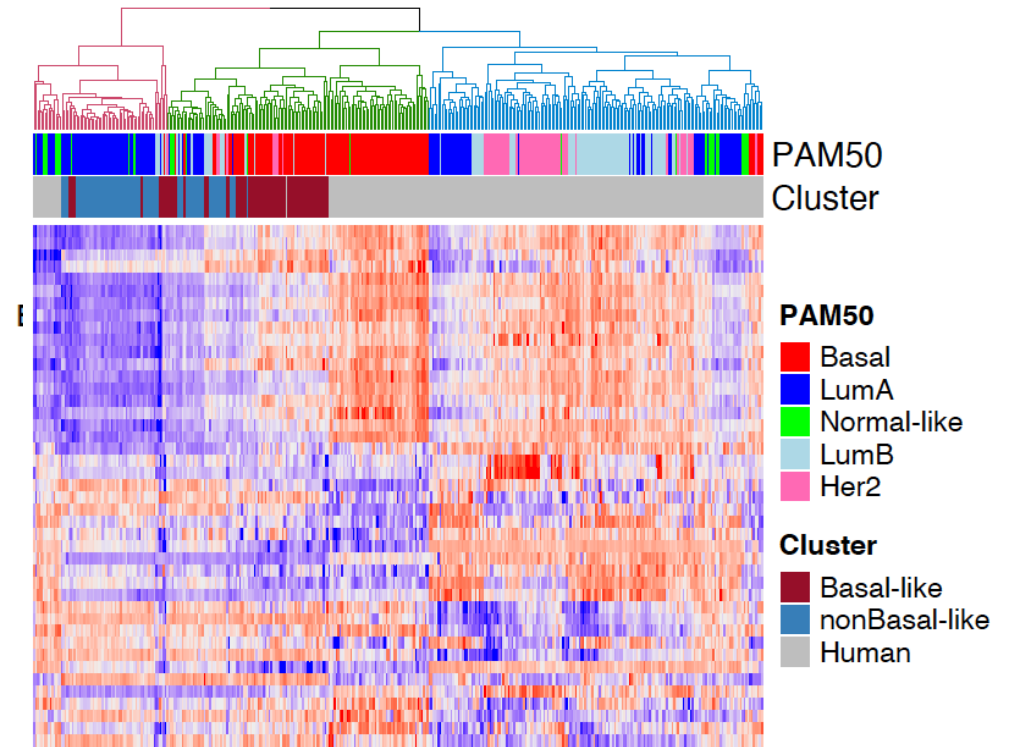
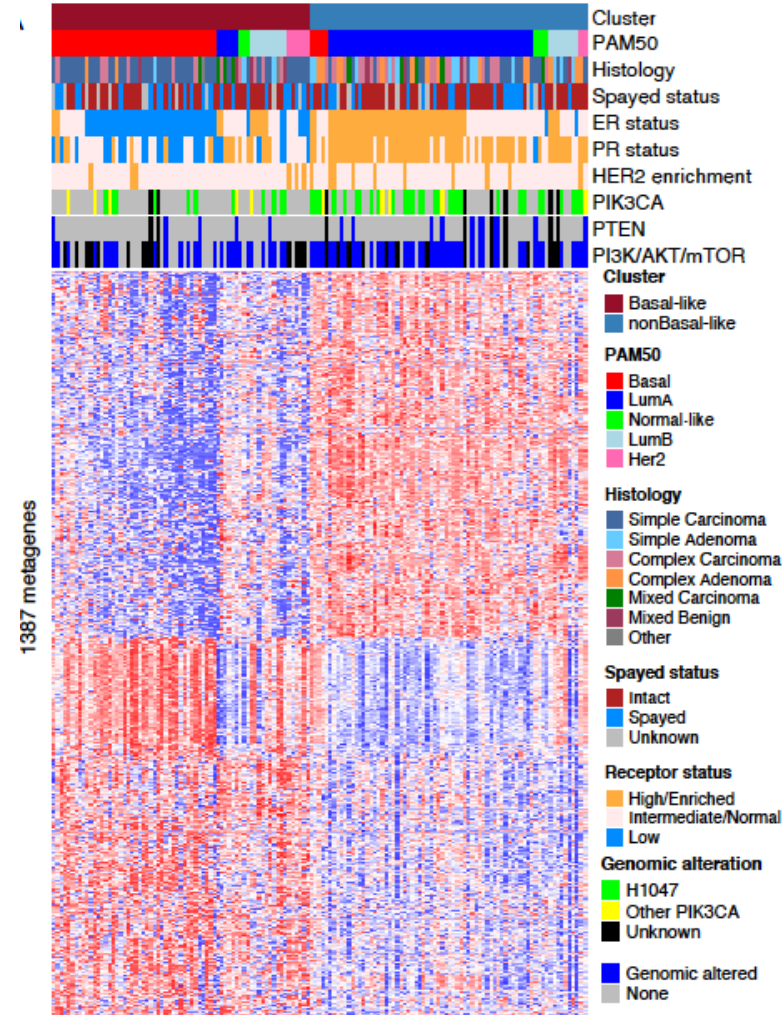
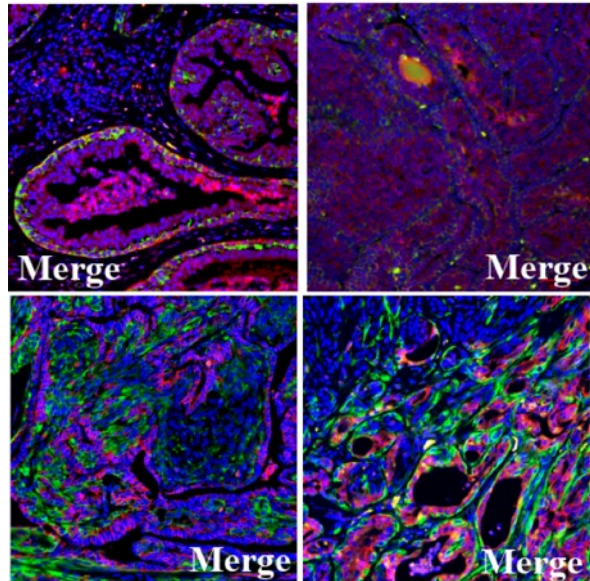
Why dog?

- Short life span: shorter trial
 - ~5 years for dogs vs. 10-20 years for humans
- >300 pure breeds
 - MHC alleles restricted in a breed
 - Breed-predisposition to specific cancer types – increased hotspot mutations
- Fewer hotspot mutations
 - hotspot mutations shared with humans – more likely to be drivers
- Molecularly resemble human cancer types/subtypes

CNN report on cancer vaccine development with dogs

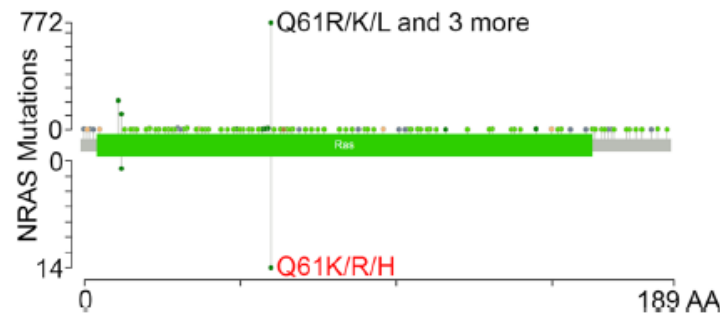
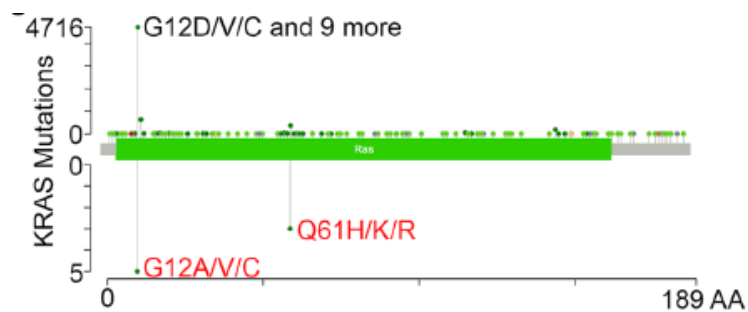
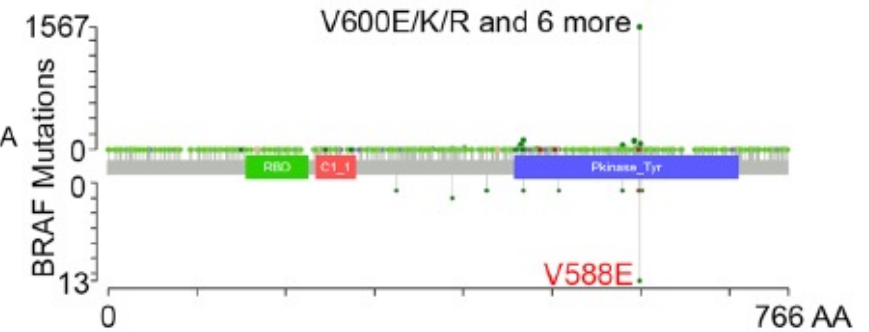
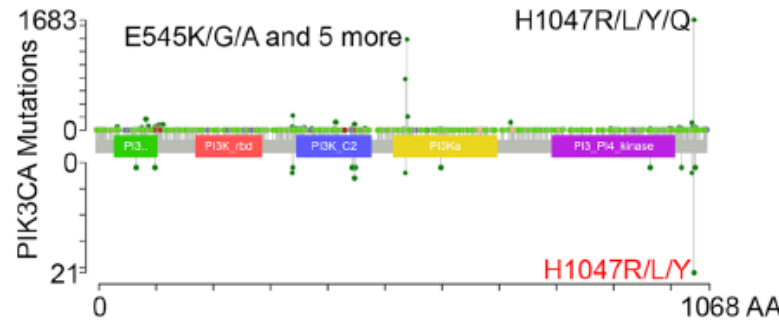
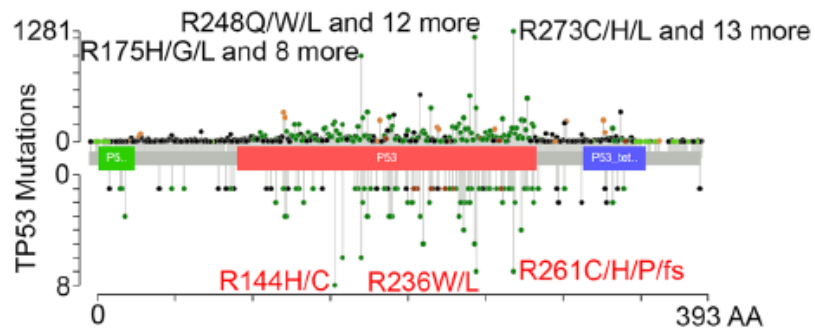
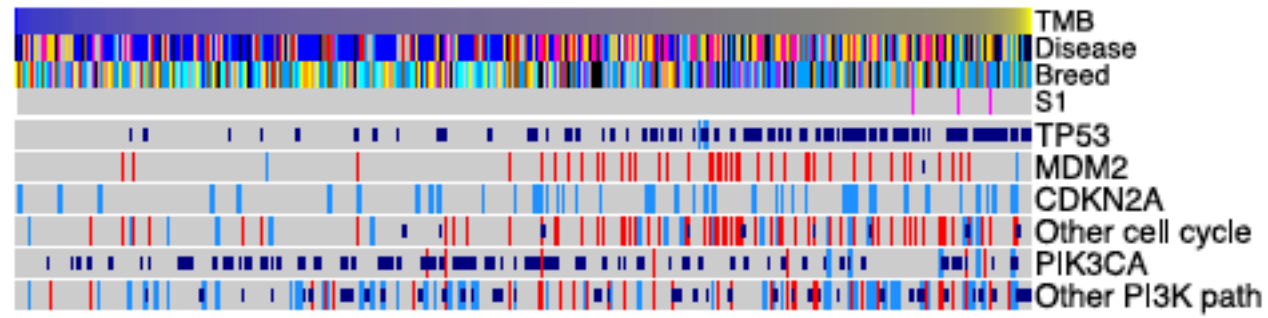
<https://www.cnn.com/2019/06/21/health/cancer-vaccine-dog-trial/index.html>

A canine mammary cancer subtype matches human basal-like/triple negative breast cancer



- Tang et al. Genome Research 2011
- Tang et al. Oncogene 2014
- Liu et al. Cancer Research 2014
- Liu et al. PLOS Genetics 2015
- Wang et al. Cancers 2018
- Wang et al. Oncotarget 2018
- Alsaihati et al. Nature Communications 2021
- Rodrigues et al. Scientific Reports 2023
- Watson et al. Breast Cancer Research 2023

1,400 canine case sequencing: well-known hotspot mutations shared between dog & human cancers



Alsaihati et al. Nature Communications 2021
Rodrigues et al. Scientific Reports 2023

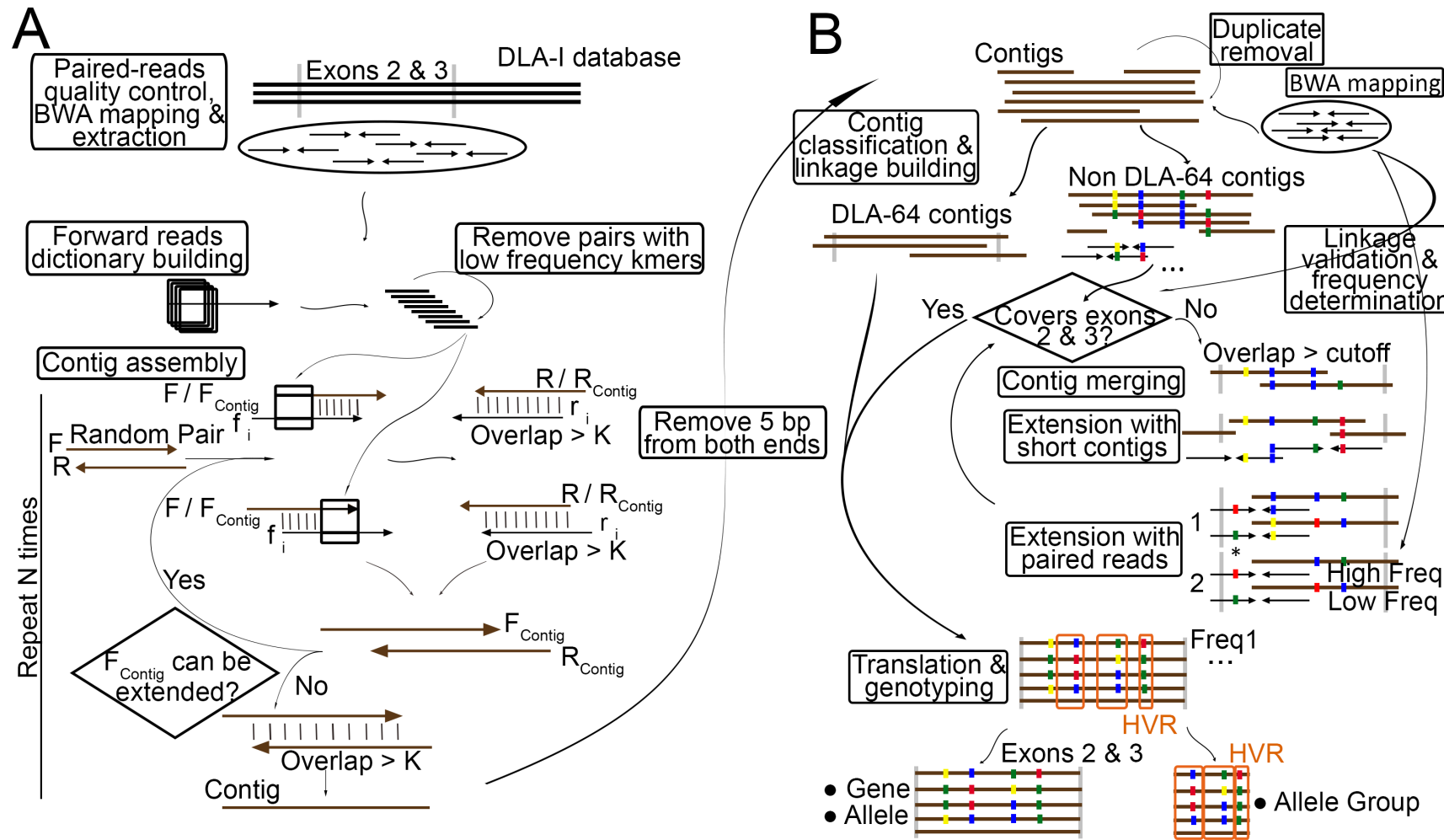
Key resources lacking for dog

Dog & human resource published						
	Human MHC-I			Canine MHC-I		
Genes	HLA-A	HLA-B	HLA-C	DLA-88	DLA-12	DLA-64
Alleles	8012	9573	7995	150	28	9
pMHC Crystal Structures	>313	>196	>10	3	0	0
Peptide binding data	>1,236,500 of ~222 alleles			4,000 of 3 alleles		
Antigen prediction Tools	>44			0		
TCRs	>300 millions			<100		

Build software, experimental systems & data for dog

- Mutation discovery pipeline
- TCR repertoire sequencing protocols and software tools
- MHC-I/II genotyping
- Peptide/MHC-I/II prediction
- Clinical trials

MHC-I genotyping: A Kmer-based paired-end read (KPR) *de novo* assembler and genotyper



software for human genotyping not working for dog: >25,000 human vs 185 dog alleles

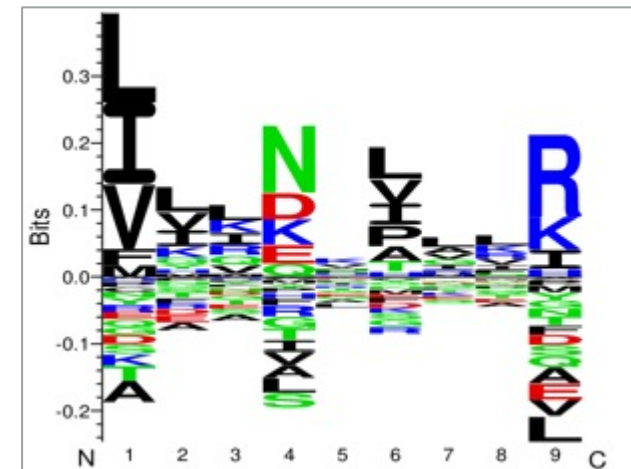
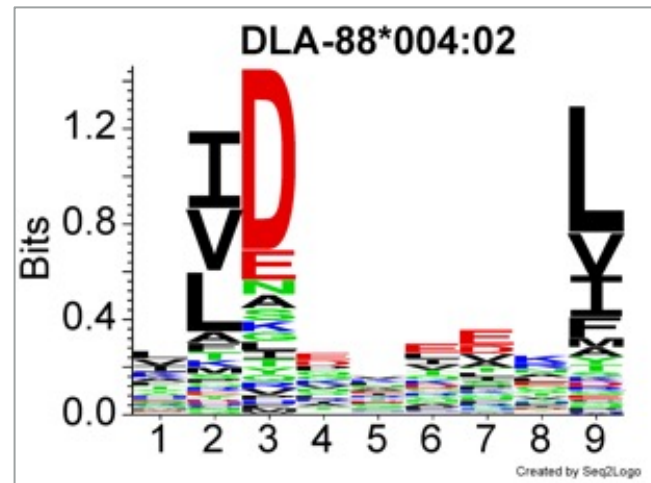
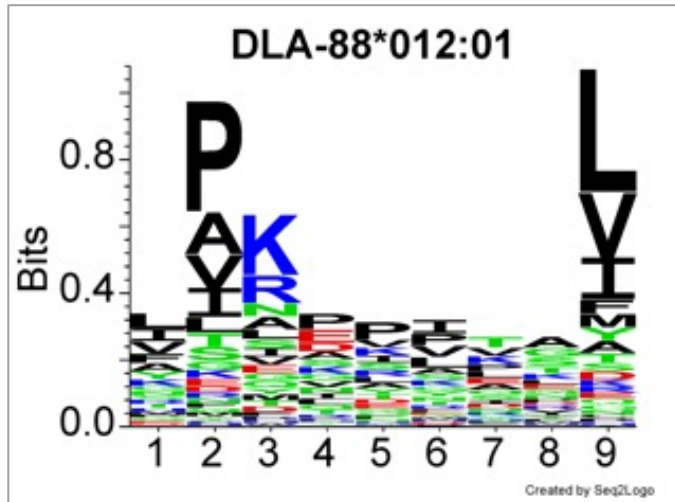
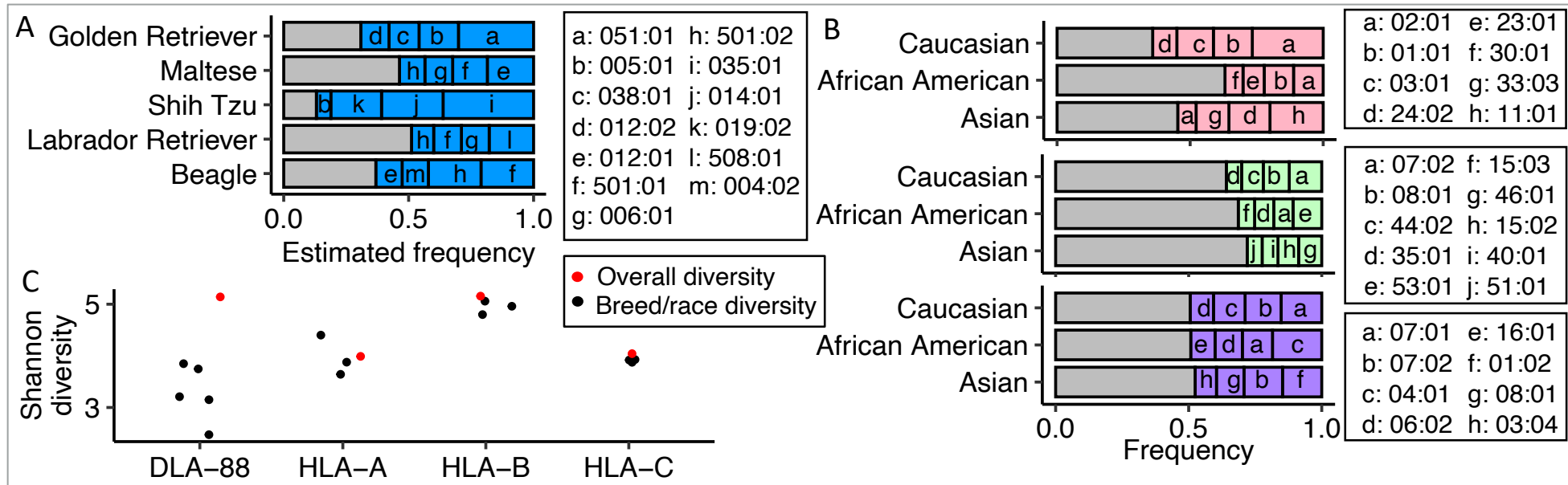
Feng et al. iScencie 2023

<https://github.com/ZhaoS-Lab/KPR.git>

Public canine RNA-seq data

Group	Sample No.	Samples Passed-QC	Dog No.	Dogs Passed-QC	Dogs breed-validated	
Abnormal blood	86	71	62	23	3	
Normal blood	44	39	39	26	5	
Abnormal lymphoid	38	37	24	23	0	
Normal lymphoid	25	25	15	15	1	
T-cell lymphoma	15	14	15	14	10	
Tumors with infiltrating T-cells	B-cell lymphoma	66	66	66	66	35
	Mammary tumor	161	159	161	158	110
	Osteosarcoma	89	89	89	89	48
	Oral melanoma	76	75	76	75	33
	Hemangiosarcoma	74	73	74	73	41
	Glioma	39	35	39	35	12
	Bladder carcinoma	26	26	26	26	0
	Prostate carcinoma	11	11	11	11	0
	Oral squamous cell carcinoma	10	0	10	0	0
	Melanoma	2	2	2	2	0
Non-cancer diseases	129	123	114	106	0	
Normal tissues	320	308	174	167	13	
Matched normal tissues	100	90	24	24	4	
Unclassified	50	50	41	41	11	
Total	1,361	1,293	1,063	976	326	

Prevalent alleles, immunopeptidome



OUHSC
Dr. William H. Hildebrand
Dr. Hooman Yari

FidoCure
Dr. Lucas Rodrigues

Dr. Kun-Lin Ho
Dr. Josh Watson
Dr. Yuan Feng
Dr. Burair A. Alsaihati
Dr. Tianfang Wang
Dr. Deli Liu
Dr. Jie Tang
Dr. Wenjua Zhang
Dr. Jingxuan Chen
Ms. Huan Xiong
Dr. Xinfu Zhang
Other past members



NCI R01 CA252713, R01 CA182093, 1U01CA272268
American Kennel Club
Morris Animal Foundation
Nan Stuart, The Hadley and Marion Stuart Foundation
Portuguese Water Dog Foundation
Newfoundland Club of America Charitable Trust
English Cocker Spaniel Club of America –Health & Rescue Organization
English Cocker Spaniel Club of Northern California
Dog breeders and owners

UGA
Dr. Corey Saba
Dr. Dong An
Dr. Biao He
Dr. Tianming Liu

Emory
Dr. Yong Wan
Dr. Yuming Zhu

Tufts
Dr. Cheryl London
Dr. Heather L Gardner

UMass
Dr. Jillian Richmond