“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
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

UGA-Cancer Center, April 9, 2024
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

Predicting and prioritizing oncogenic mutations requires structural and biological context
Systems and data-driven approaches to investigate oncoproteins
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

**Hypothesis**: Exon 20 insertion mutations impact catalytic activity by altering kinase conformational regulation
Several insertion mutations activate EGFR in a ligand-independent manner.
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

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)
Q1: #Kinases with mutation in the gatekeeper position?

Q2: #Ligands interacting with gatekeeper residue?

ProKinO is open-source and widely used

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.

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.

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

19/SEP/2021 – 14/JUL/2022

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https://prokino.uga.edu/
Acknowledgements

Kannan ESBG 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 Eyers (U. Liverpool)
PDBe-KB team (EBI)
IDG Consortium (NIH, UNC Chapel Hill)

Funding

NIH Common fund
Douglass Lab: #1 genomic diagnostics #2 drug-screening

tumor biopsies -> sequencing

drug screening -> personalized drug selection
FFPE tissue: lung cancer

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

![Graph showing relative cancer cells over time for different drugs]

- Vehicle
- Cyclophosphamide
- Carboplatin
- Fluorouracil
- Tamoxifen
- Paclitaxel
- Docetaxel
- Lapatinib
- Cytarabine
- Gemcitabine
- Doxorubicin

*Lancet Oncol, 2021, 22, 1367*
ULA-screening Platform: time-course on top chemotherapies

NALM6 (leukemia cell-line)
UGA-screening Platform: time-course on top chemotherapies

Assay Drug Dev Tech, 2015, 13, 456
UGA-screening Platform: time-course on top chemotherapies

UGA Screen Platform

NALM6 (leukemia cell-line)

1,721 Cancer Drug Library (Selleckchem L8000)

Relative Cancer Cells

Vehicle
Cyclophosphamide
Carboplatin
Fluorouracil
Tamoxifen
Lapatinib
Paclitaxel
Docetaxel
Gemcitabine
Cytarabine
Doxorubicin

hours

0 10 20 30 40 50 60 70
Clinical Work: characterize the battlefield of patients
Lab work: drugs efficacy under clinical conditions
Douglass Lab: #1 genomic diagnostics #2 drug-screening

- Sequencing
- Tumor biopsies
- Drug screening
- Personalized drug selection
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

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**Graphic:**
- **GRB**
- **Human:** Driver, Passenger
- **Dog:** Driver, Passenger

---

### Canine alleles, HVRs & crystal structures
- MHC-I pseudo-sequences
- Eluded peptides (human, mouse & canine)
- Binding affinity data (human & others)
- Negative peptides

### Human alleles, HVRs & crystal structures
- Eluded peptides (human, mouse & canine)
- Binding affinity data (human & others)
- Negative peptides

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**Flowchart:**
- **ANN**
- **PPV & AUC with validation data**
- **Peptide binding motif agreement**
- **Eluded vs. not eluded peptide of source proteins**

---

**Legend:**
- Yes: panMHC-I
- No: Satisfied

---

**References:**
- [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.independent.co.uk/news/health/dogs-cancer-tumours-humans-research-b2372456.html](https://www.independent.co.uk/news/health/dogs-cancer-tumours-humans-research-b2372456.html)
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
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. 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

<table>
<thead>
<tr>
<th>Dog &amp; human resource published</th>
<th>Human MHC-I</th>
<th>Canine MHC-I</th>
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<tr>
<td><strong>Genes</strong></td>
<td>HLA-A</td>
<td>HLA-B</td>
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<tr>
<td>Alleles</td>
<td>8012</td>
<td>9573</td>
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<td>pMHC Crystal Structures</td>
<td>&gt;313</td>
<td>&gt;196</td>
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<tr>
<td>Peptide binding data</td>
<td>&gt;1,236,500 of ~222 alleles</td>
<td>4,000 of 3 alleles</td>
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<tr>
<td>Antigen prediction Tools</td>
<td>&gt;44</td>
<td></td>
</tr>
<tr>
<td>TCRs</td>
<td>&gt;300 millions</td>
<td>&lt;100</td>
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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. iScience 2023
https://github.com/ZhaoS-Lab/KPR.git.
## Public canine RNA-seq data

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample No.</th>
<th>Samples Passed-QC</th>
<th>Dog No.</th>
<th>Dogs Passed-QC</th>
<th>Dogs breed-validateed</th>
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<td>114</td>
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<td>1,293</td>
<td>1,063</td>
<td>976</td>
<td>326</td>
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Prevalent alleles, immunopeptidome

A. Golden Retriever
MALTESE
Shih Tzu
Labrador Retriever
Beagle

Shannon diversity

A: 051:01  h: 501:02
B: 005:01  i: 035:01
c: 038:01  j: 014:01
d: 012:02  k: 019:02
e: 012:01  l: 508:01
f: 501:01  m: 004:02
g: 006:01

B. Caucasian
African American
Asian

Overall diversity
Breed/race diversity

C. DLA-88*012:01

Bits

Created by SeqLog

D. DLA-88*004:02

Bits

Created by SeqLog
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