

Small but mighty: How small changes can drive cancer progression

Hien Dang, PhD

J. Wallace Davis and Gail G. Davis Assistant Professor of Surgery

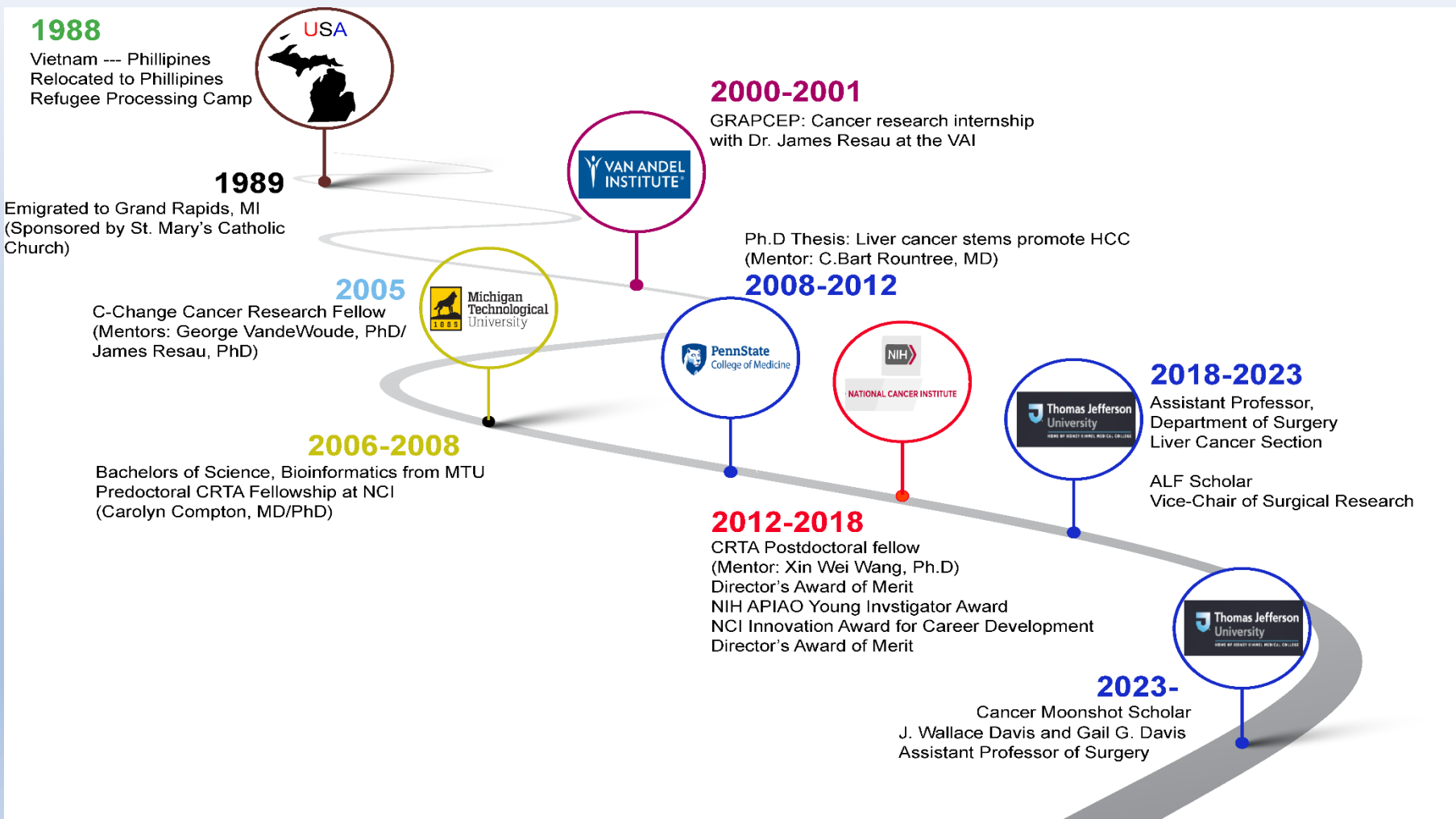
Hien.dang@jefferson.edu

9/18/2024

Outline

- Background of PI
- Background – liver cancer
- Research Project 1:
- Research Project 2:
- Future Research

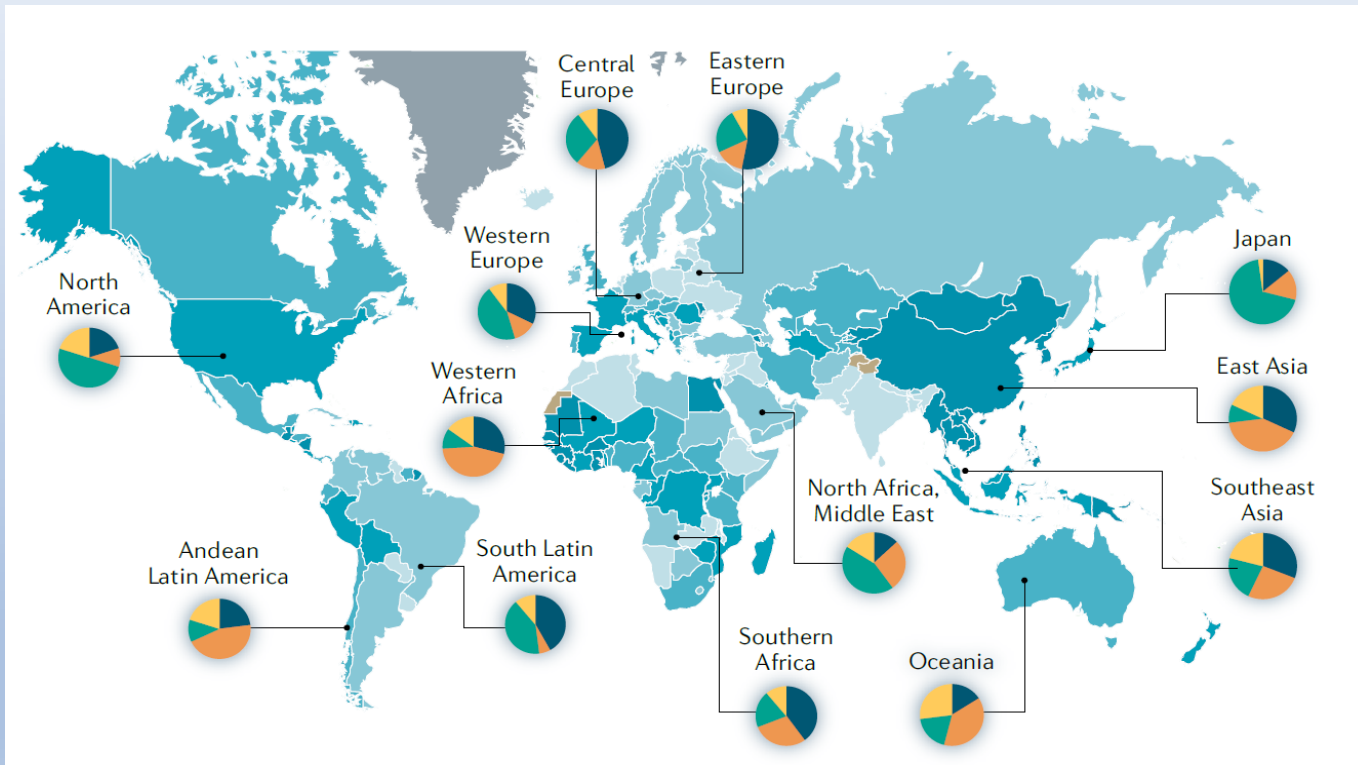
My Research Timeline



Hepatocellular Carcinoma (HCC)



Aflatoxin, alcohol abuse, MASLD/MASH (diabetes, obesity), HBV, HCV, etc.



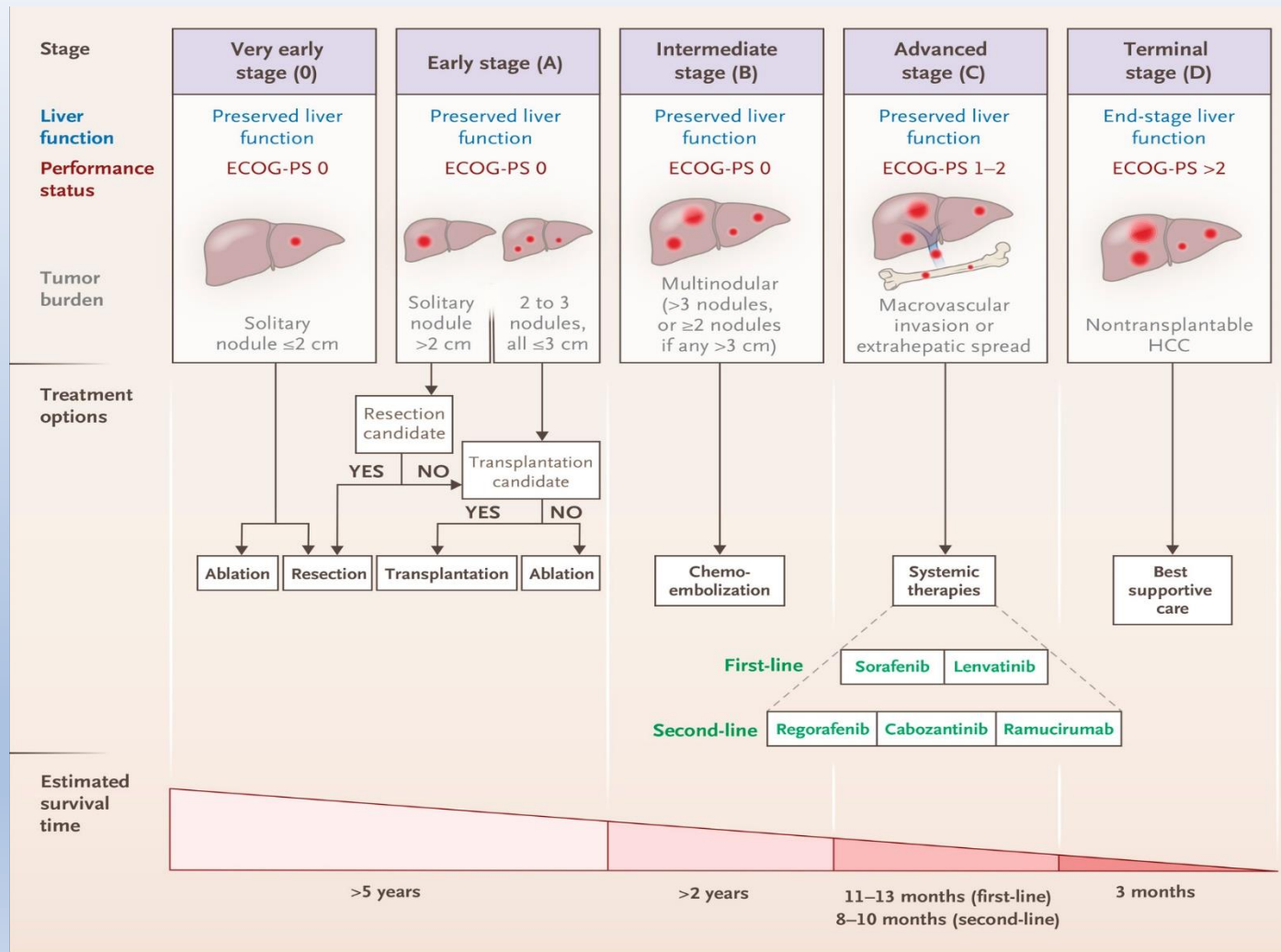
1. *Fatty Liver/Hepatitis*

2. *Fibrosis*

3. *Cirrhosis*
(End Stage liver failure)

**Hepatocellular
Carcinoma**

Diverse etiology: hard to treat tumor type



Etiological Factors

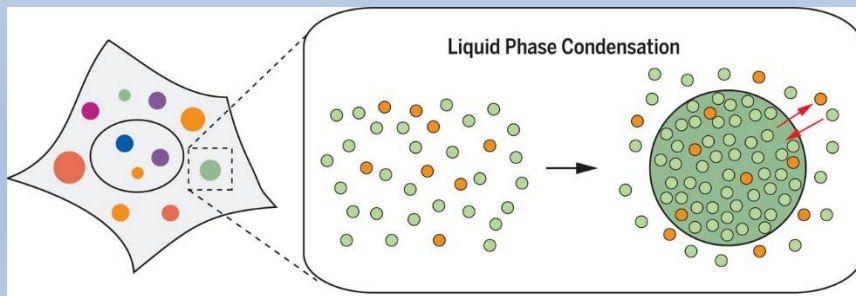
- HBV, HCV, aflatoxin, diet, liver flukes, alcohol

Mechanisms of HCC

- Cancer stem cells
- Driver mutations (TERT, CTNNB1, TP53)
- TGFβ, Wnt/β-catenin signaling, c-Met/HGF signaling
- **NELFE signaling**

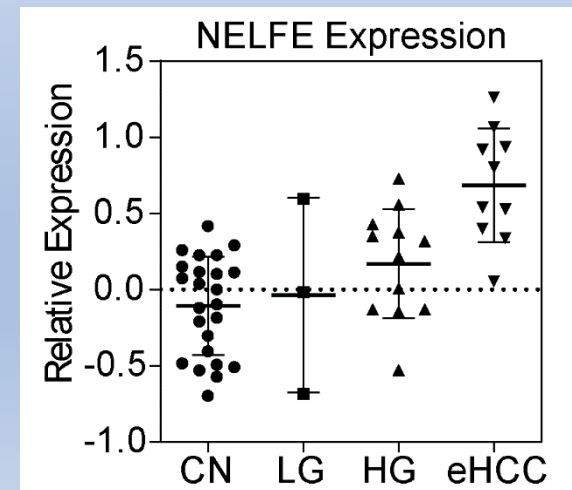
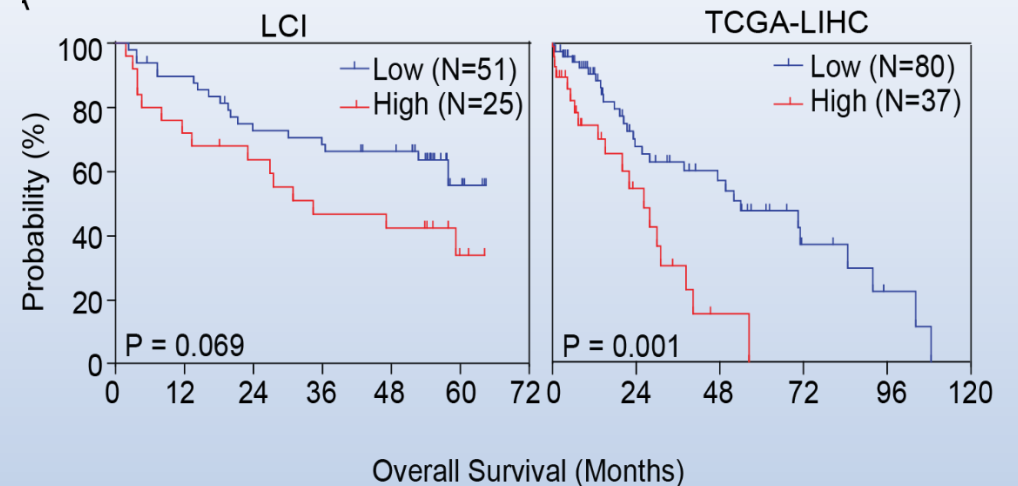
Negative Elongation Factor E (NELFE)

- A part of NELF complex, which regulate transcription (Gilchrist, et al. *Genes Dev.* (2008))
- Undergo liquid-liquid phase separation (LLPS) to suppress transcription (Rawat et al *Mol Cell* (2021))



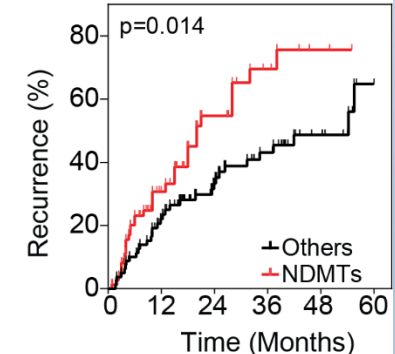
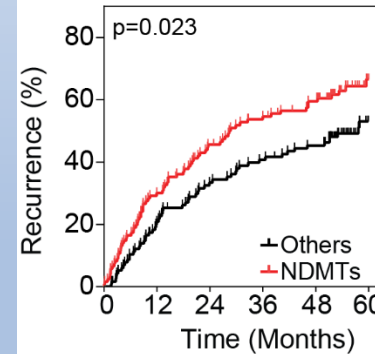
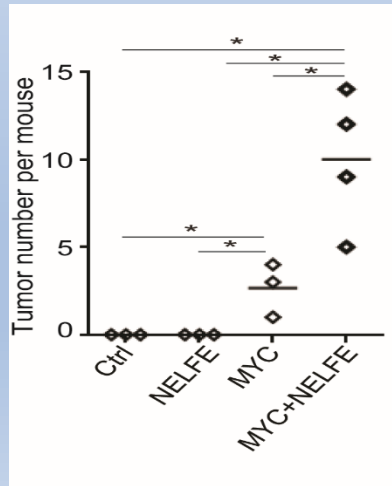
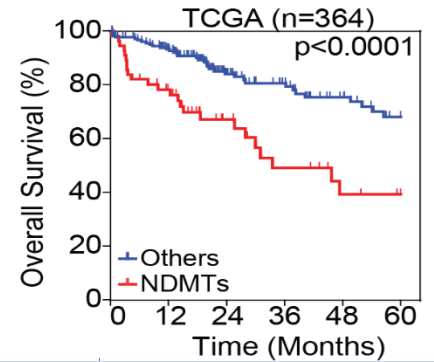
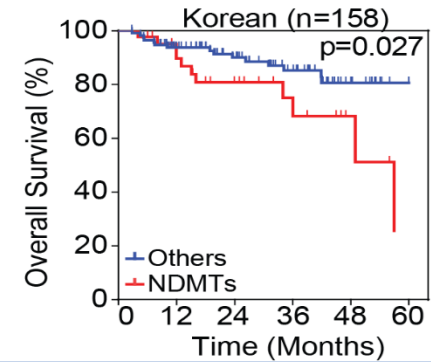
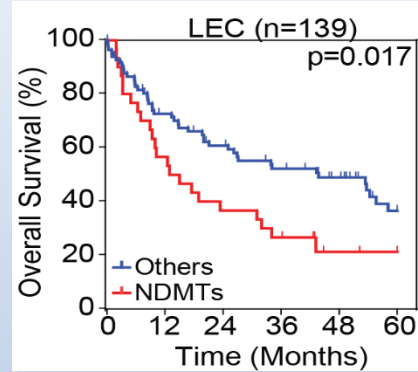
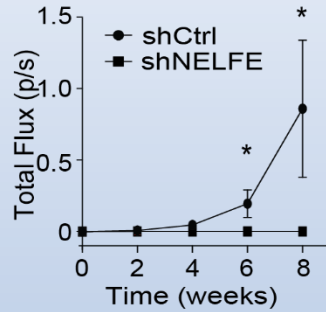
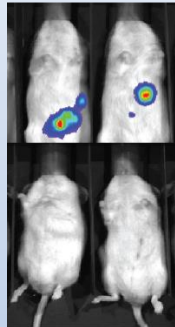
Shin, Y and Brangwynne C. *Science* (2017)

oil droplet in water



Dang et al. *Cancer Cell* (2017)

NELFE activation in HCC is associated with poor outcome

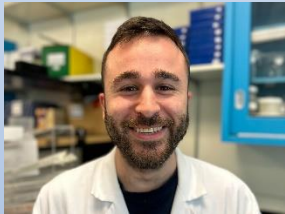


Dang et al. *Cancer Cell* (2017)
 Dang et al. *Scientific Reports* (2019)

NELFE undergoes Liquid-liquid phase separation to modulate the chromatin



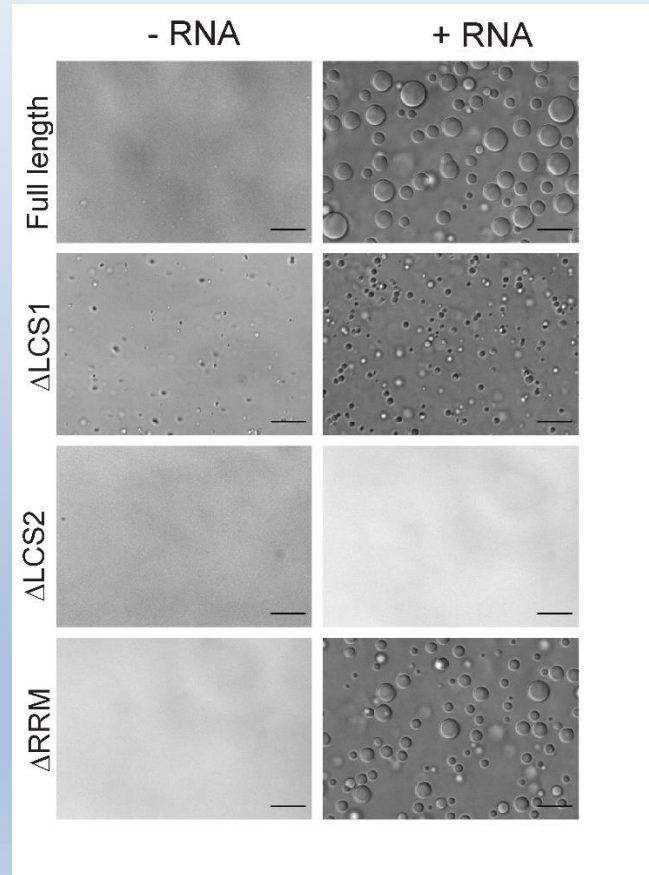
Anna
Barry-Wolbers



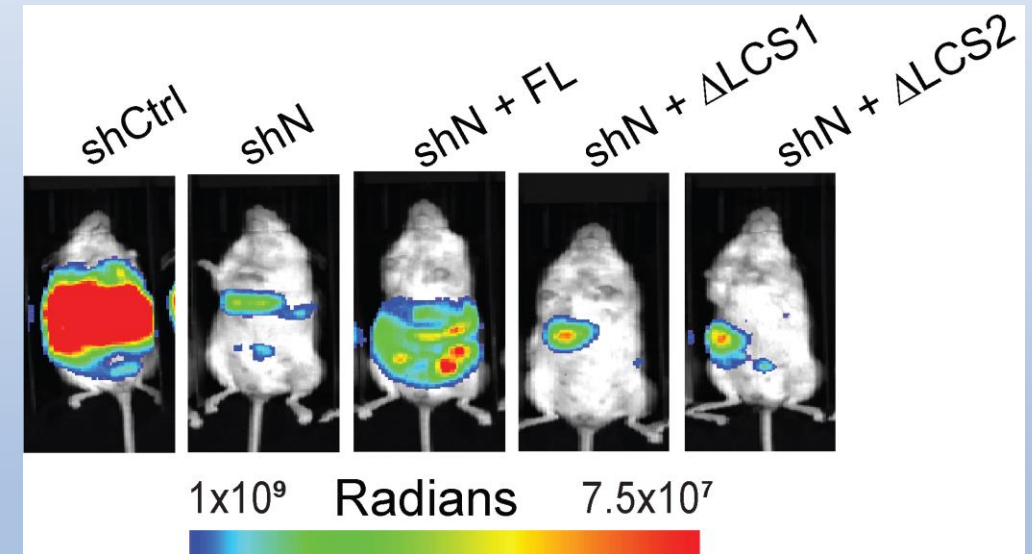
Alvaro Lucci



Kasonde Chewe

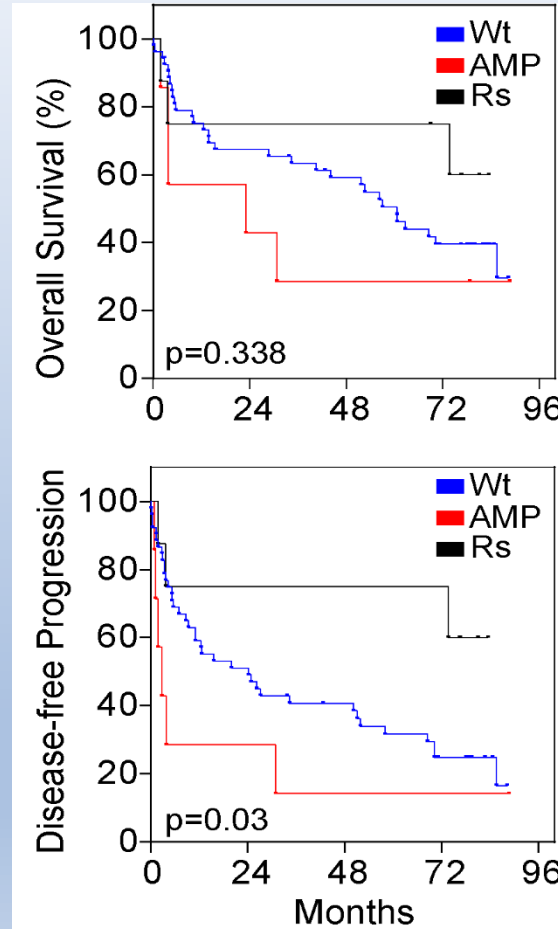
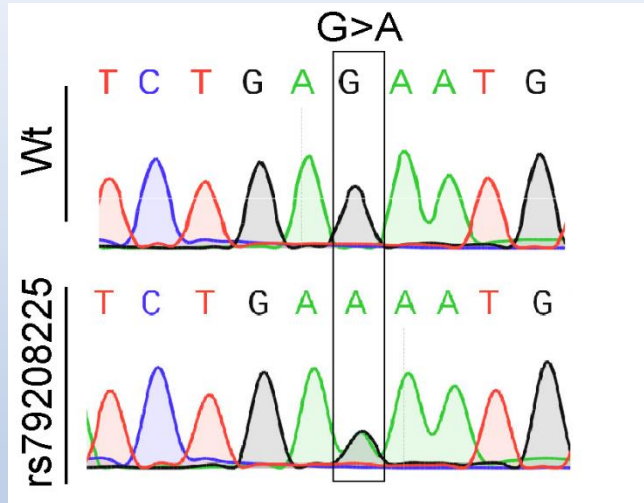


Nicholas Fawzi, PhD, Brown University



Unpublished data

Intronic single nucleotide polymorphism (SNP) in HBV/HCC is associated with better outcome



- rs79208225 SNP <1% in general population, 5% in Southeast Asians
- ~3% HBV HCC patients
- Patients with SNP survive significantly longer (53 v 31 months, $p<0.05$)
- Patients with SNP have significantly longer median time to recurrence (52 vs. 25 months, $p<0.05$)

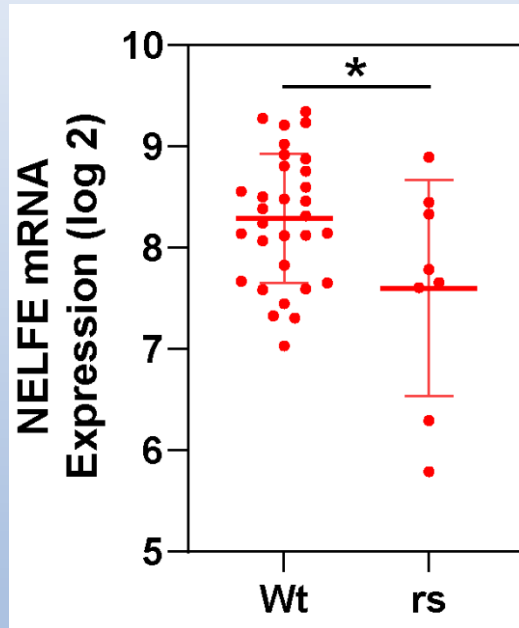
Ryan Lamm Laura Reynolds



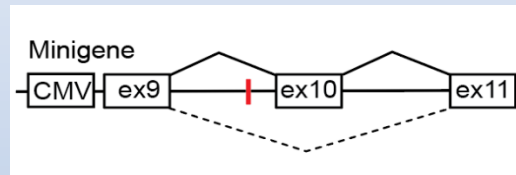
Unpublished data

SNP promotes isoform switching to reduce NELFE Full-length expression

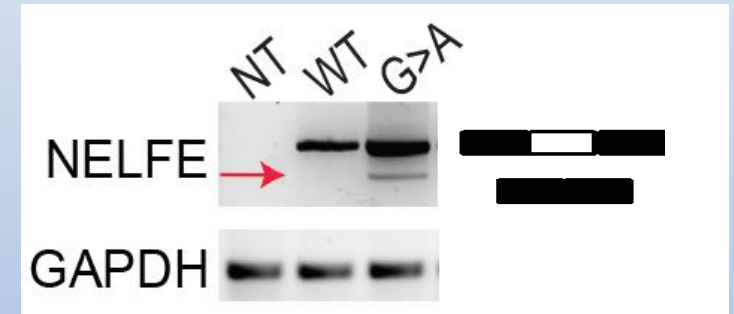
HCC patients



SNP leads to lower NELFE levels



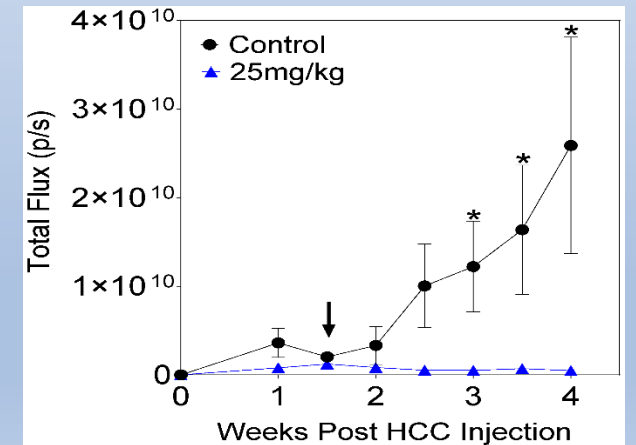
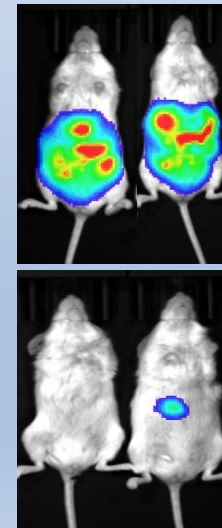
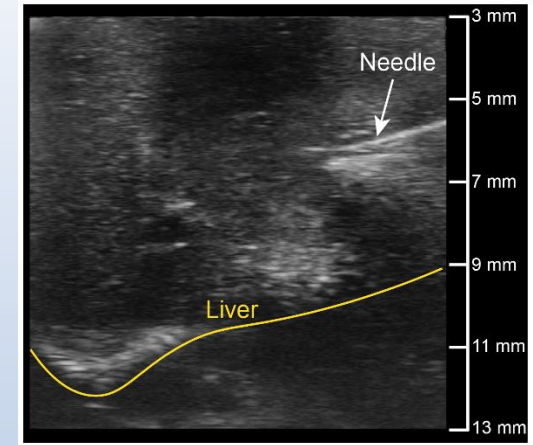
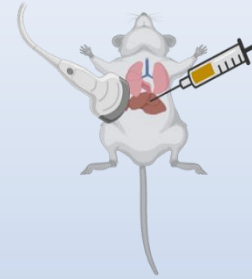
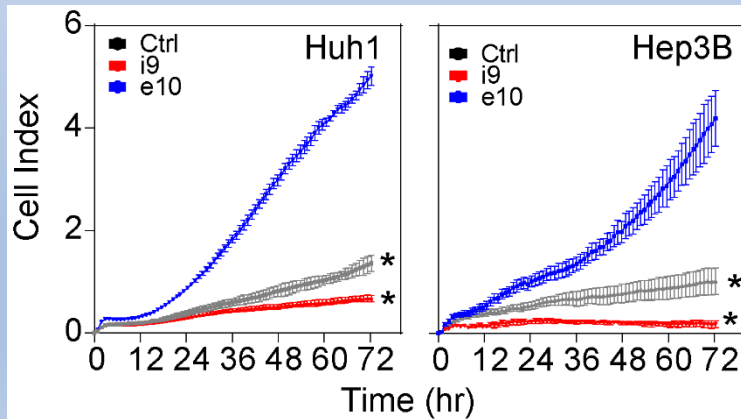
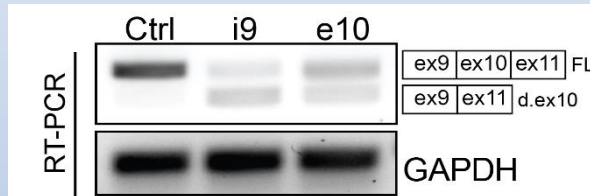
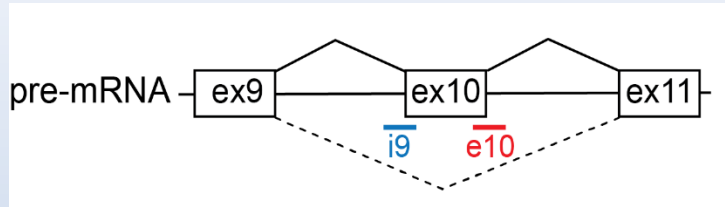
SNP leads to exon 10 exclusion



Hypothesis: The NELFE SNP is “protective” of NELFE HCC subtype

Unpublished data

Can we phenocopy the SNP to decrease tumor burden?

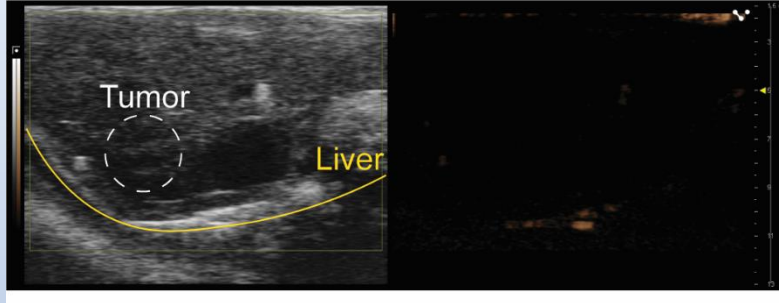


John Eisenbrey, PhD, TJUH

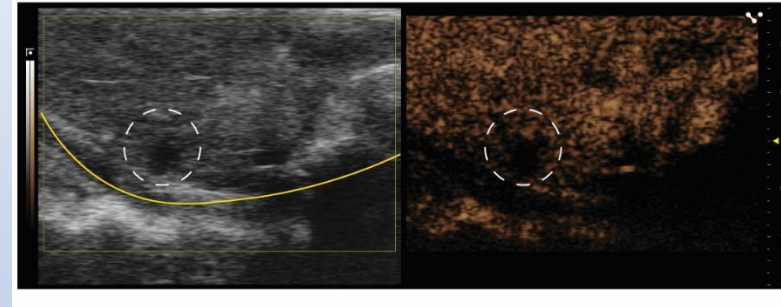
Unpublished data

Gas filled microbubbles for direct tumor targeting

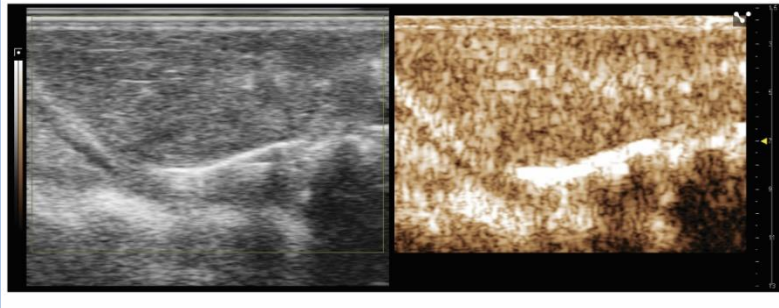
Baseline Pre-Microbubbles



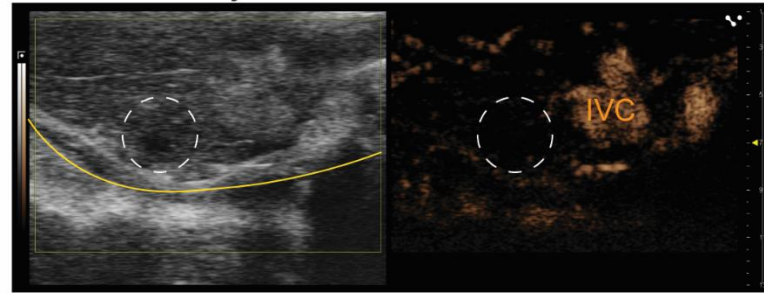
Baseline Microbubbles



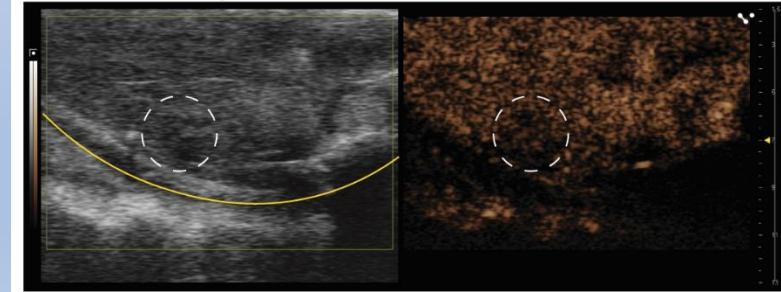
Destructive Pulses



Immediately Post Microbubble Destruction



Reperfusion of Microbubbles



Current and Future

CURRENT

- Ongoing studies to elucidate the mechanism of NELFE LLPS on chromatin
- Ongoing studies to elucidate the mechanism of the SNP in “tumor-suppressive” phenotype
- Pre-clinical studies to determine effect of ASO on various HCC cell models, mouse and human xenografts, organoids, etc.
- Clinical trial to identify prospective HCC patients with the SNP and determine their outcomes
- HCC biospecimen collection

FUTURE

- Can we target the NELFE condensates?
- Identify the composition of the NELFE condensates - RNA/DNA/protein interactions
- Expand the preclinical studies of ASO treatment to pancreatic cancer
- Development of HCC registry to investigate etiologies/mutations/gene signatures associated with response to therapy, etc.
- Can we move our ASO to clinical trials?

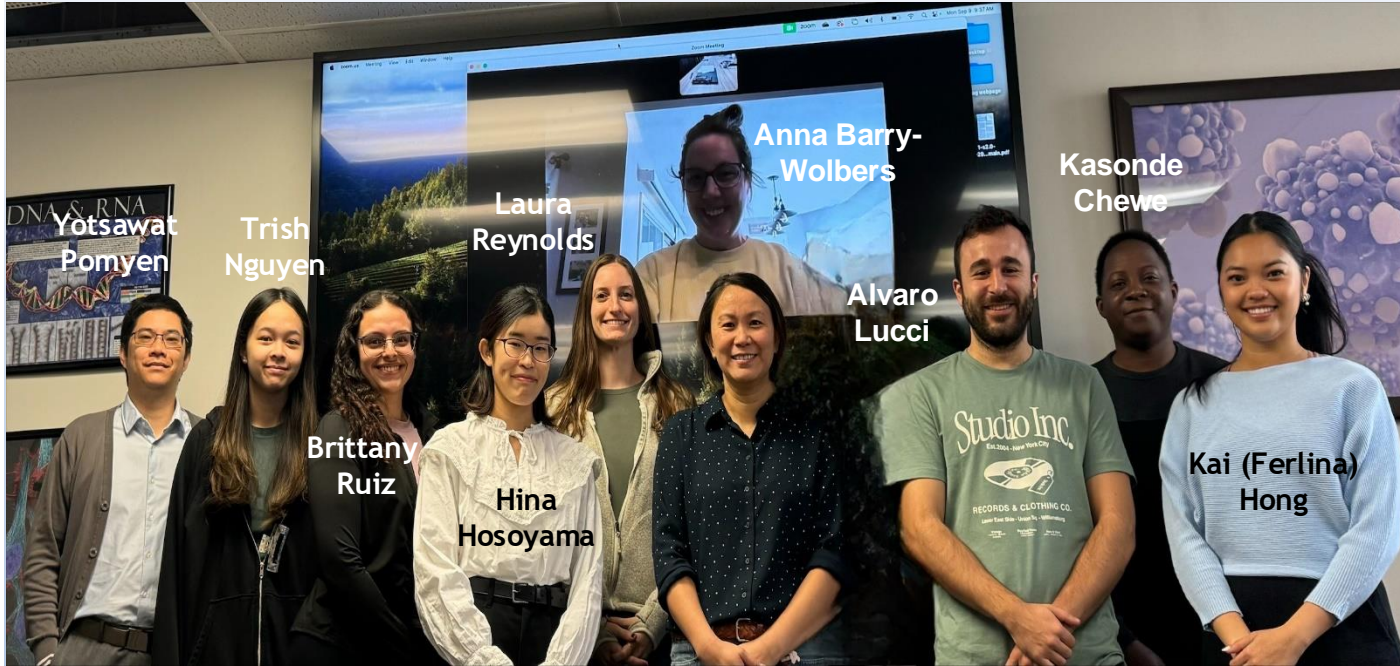


Brittany Ruiz



Kai (Ferlina) Hong

Acknowledgements



Previous lab members:

Ryan Lamm, MD
Kai Zhang, PhD
Adam Wojnar, MS
Meghan Grim, MS

University of Mainz, TRON, Germany

Matthias Gaida, MD
Christoph Eckert, MD

Nippon Medical School, Tokyo, Japan

Masaru Matsumoto, MD, PhD

Thomas Jefferson University

John Eisenbrey, PhD
Corrine Wessner
Ji-Bin Liu, PhD
Scott Keoneman, PhD
Elda Grabocka, PhD

Liver and Pancreatic Multidisciplinary Team

Charles Yeo, MD
Harish Lavu, MD
Daniel Lin, MD
Adam Bodzin, MD
Ashesh Shah, MD
Babar Bashir, MD

Brown University

Nicholas Fawzi, PhD
Victoria Johnson, B.S.

Current Funding

Sidney Kimmel Comprehensive Cancer Center
Biden Cancer Moonshot Scholar (R01)
TC Gives Foundation



JeffersonHealth.org/Cancer