AACR American Association for Cancer Research®
ANNUAL MEETING 2025 CHICAGO
APRIL 25–30
AACR.ORG/AACR2025
#AACR25

Investigating the Clinical Landscape and Biological Impact of *SF3B1* Hotspot Mutations In Breast Cancer

Riley Bergman

Mentored by Ben Ho Park, MD/PhD
Medical Scientist Training Program and Program in Cancer Biology,
Vanderbilt University School of Medicine,
Nashville, Tennessee, USA

VANDERBILT-INGRAM CANCER CENTER

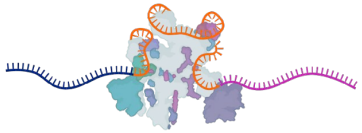
Disclosure Information

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

I have no financial relationships to disclose.

SF3B1 Mutations are Poorly Understood in Breast Cancer

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25



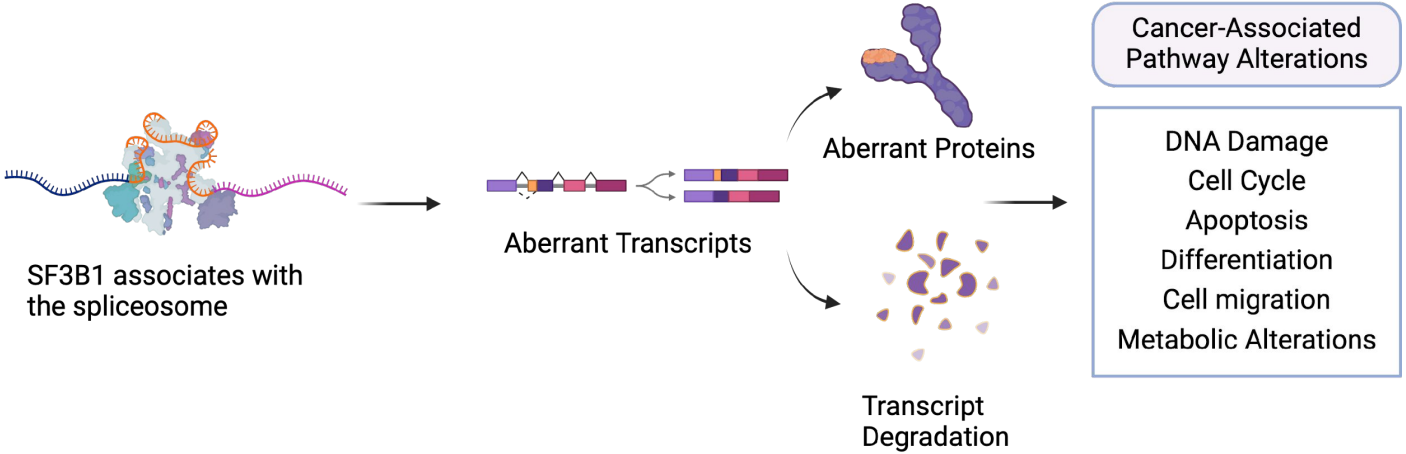
SF3B1 associates with the spliceosome

Current limitations:
Much of what we know is derived from heme malignancies
Widespread changes □ Lack of consensus on the role(s) of SF3B1 in cancer
Relatively low representation in clinical datasets

This study investigates the genetic profile, survival outcomes, and biological impacts of *SF3B1* mutations in breast cancer

SF3B1 Mutations are Poorly Understood in Breast Cancer

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25



Current limitations:

1. Much of what we know is derived from heme malignancies
2. Widespread changes Lack of consensus on the role(s) of SF3B1 in cancer
3. Relatively low representation in clinical datasets

This study investigates the genetic profile, survival outcomes, and biological impacts of *SF3B1* mutations in breast cancer

BioRender

Analysis of *SF3B1* Mutations and Survival in Breast Cancer Patients

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Breast cancer patients with *SF3B1* hotspot mutations (N = 218)

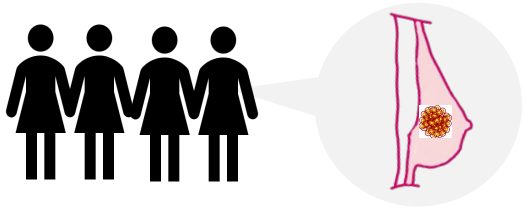
Molecular profiling with Tempus xT assay*

Retrospective review of De-identified patient data

Analysis of *SF3B1* Mutations and Survival in Breast Cancer Patients

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

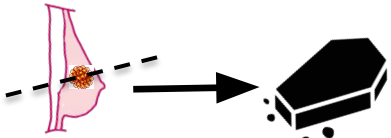
Breast cancer patients with *SF3B1* hotspot mutations (N = 218)



\+

Molecular profiling with Tempus xT assay*

SF3B1 hotspot mutation frequencies were assessed

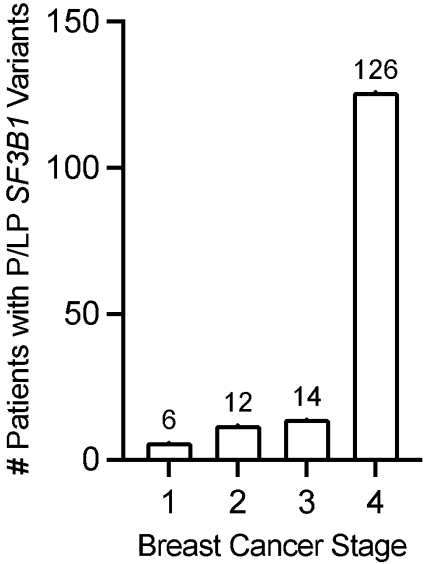


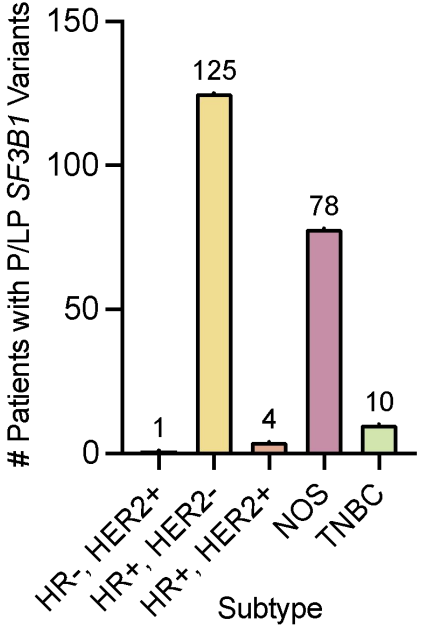
rwOS - Time from biopsy to death

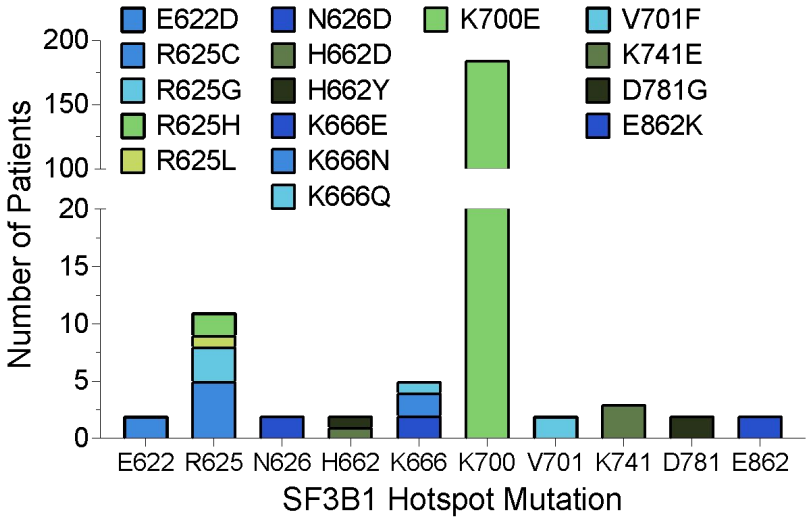
Hazard ratio (HR) was calculated using Cox proportional hazards (CoxPH) model, and p-values were calculated using Wald test

SF3B1 K700E Mutations are Enriched in HR+ HER2- Breast Cancer

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25



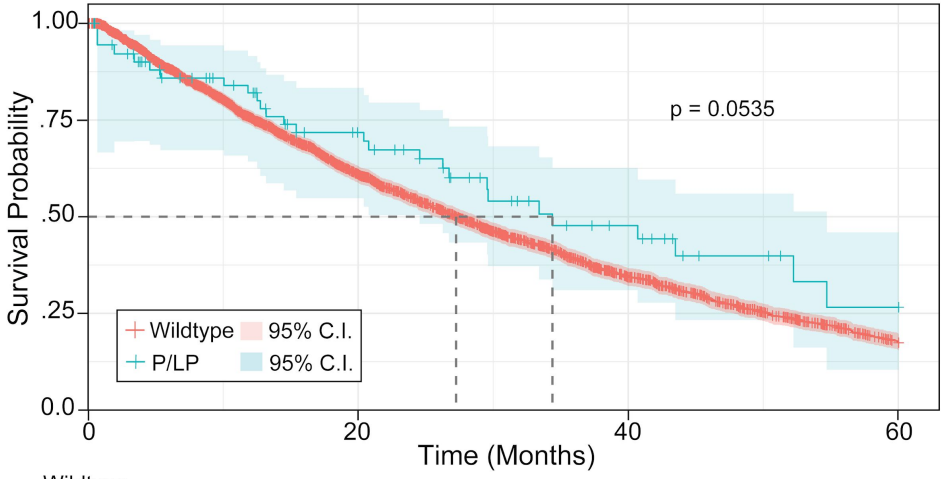




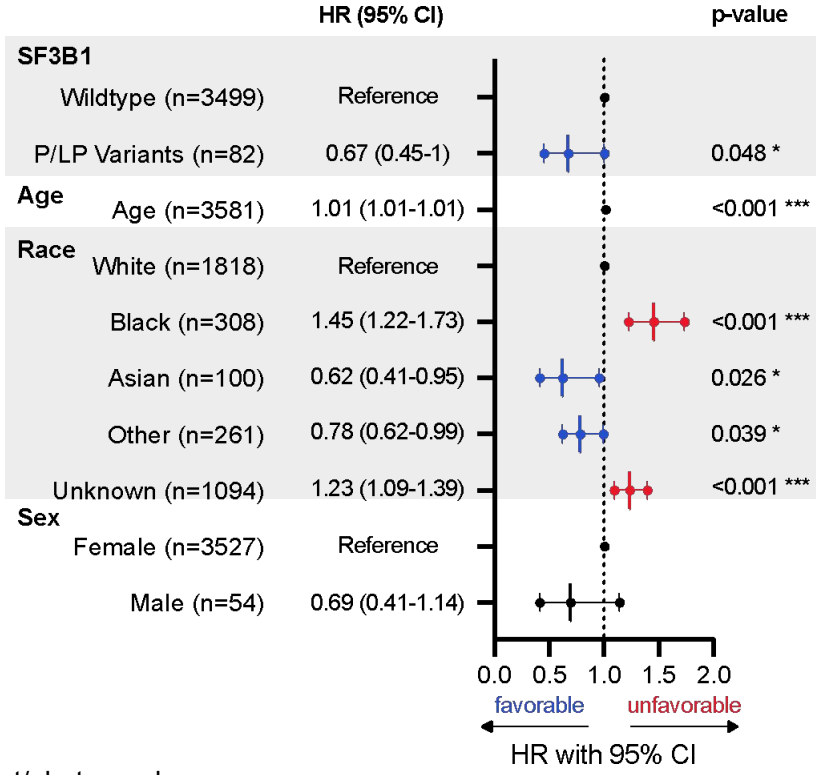
Improved rwOS in Patients with *SF3B1* Mutant HR+, HER2- Breast Cancer

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Overall survival of patients with HR+/HER2- breast cancer

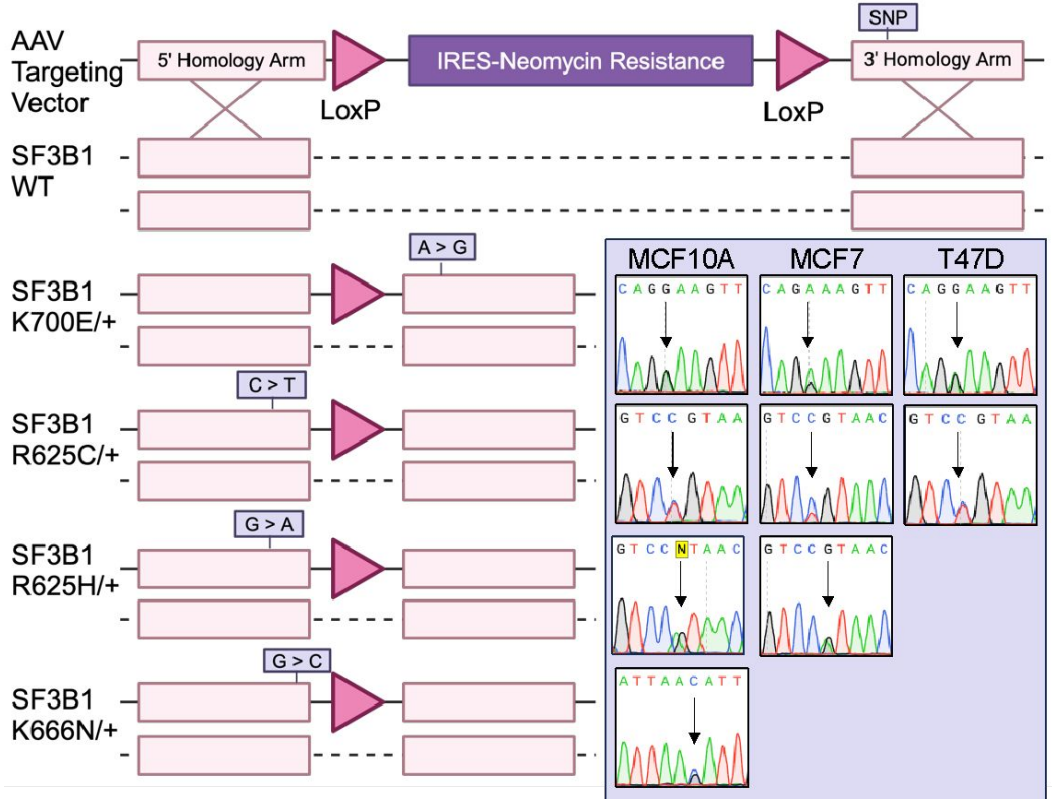


Wildtype				
At Risk	102	1119	459	169
Events	0	766	1198	1390
P/LP				
At Risk	0	32	14	5
Events	0	12	21	25



Generation of an *SF3B1* mutant Isogenic Cell Line Panel

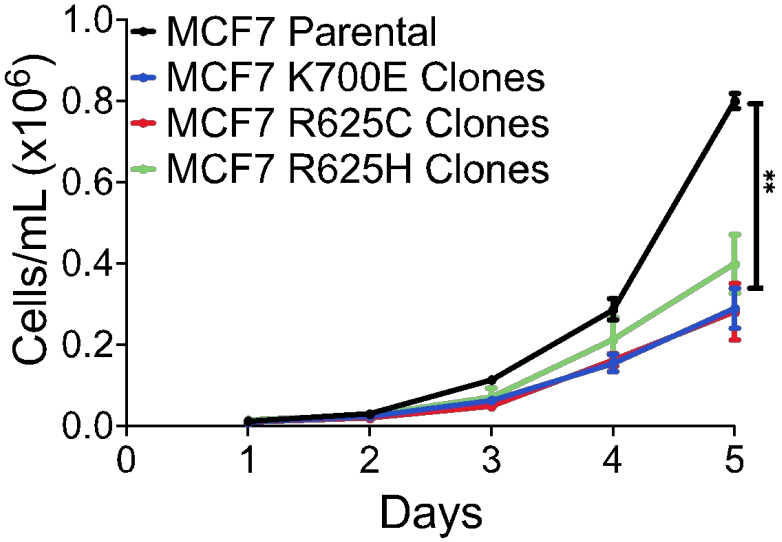
AACR American Association for Cancer Research
ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25



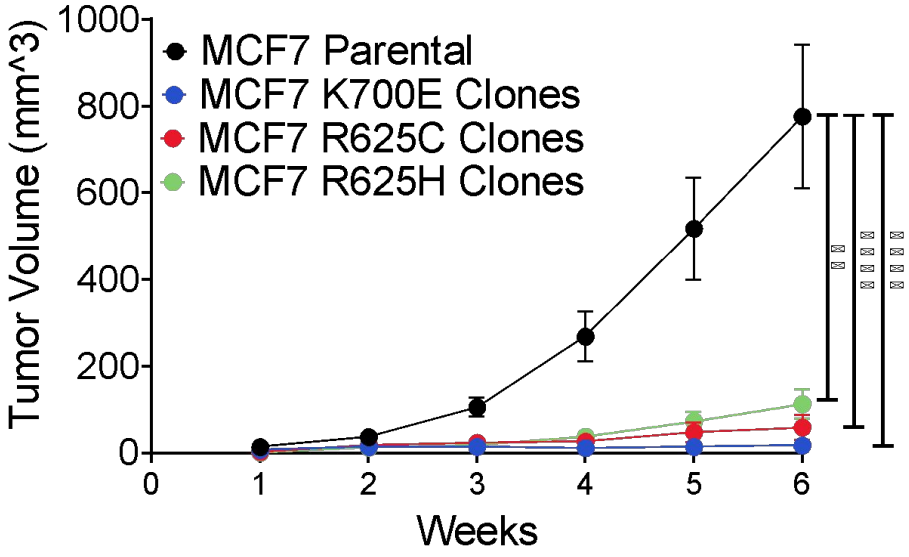
AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

SF3B1 Mutations Lead to Poor Growth

In-vitro growth of MCF7 *SF3B1* mutant clones

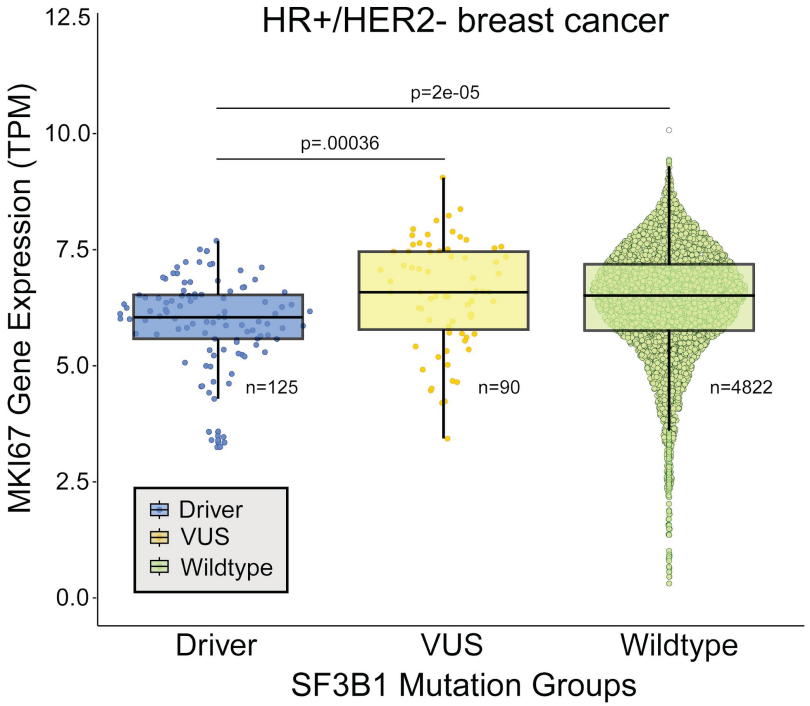


In-vivo growth of MCF7 SF3B1 mutant clones as orthotopic xenografts



SF3B1 Mutations are Associated with Lower Proliferative Indices

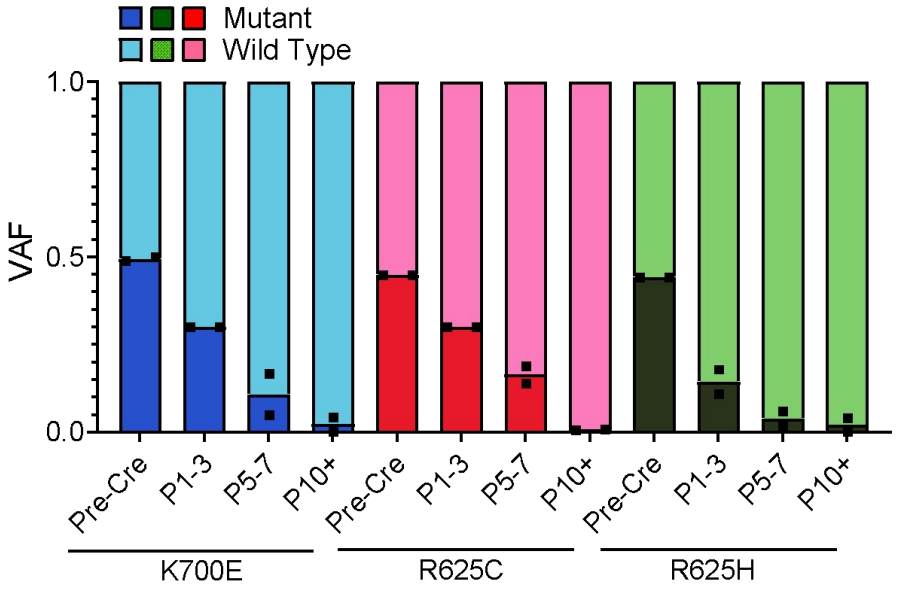
AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25



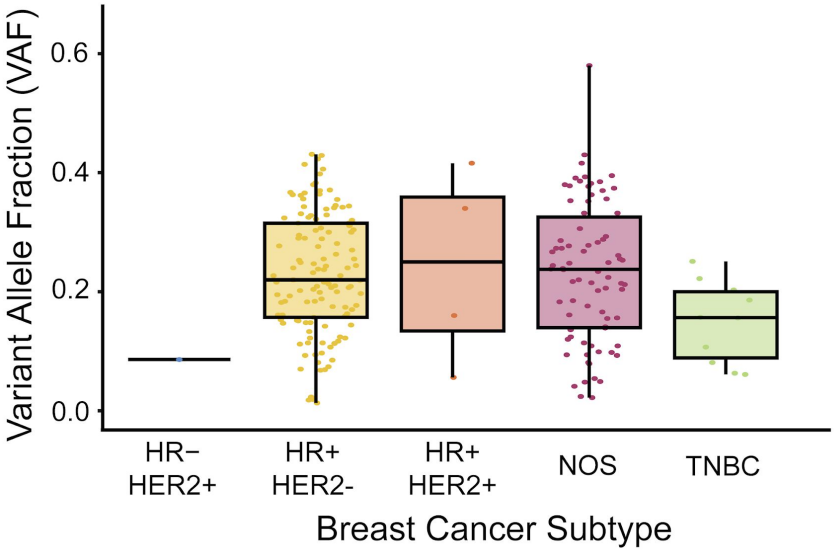
SF3B1 Mutations Undergo Negative Selection *in-vitro* and Variation in Mutant VAF is Observed Clinically

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

VAF in MCF7 *SF3B1* Mutants Across Cell Passages, measured by droplet digital PCR



Variation in VAF for *SF3B1* Driver Mutations in Advanced Breast Cancer



Ongoing efforts to define molecular consequences and therapeutic opportunities

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

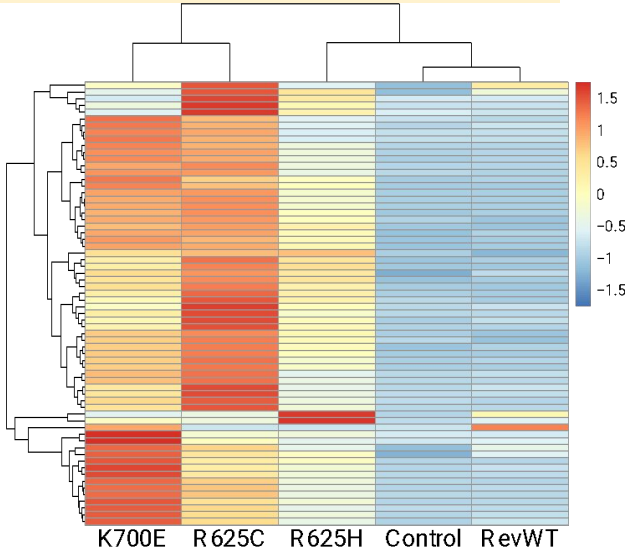
The most comprehensive cell panel & largest clinical cohort of patients with *SF3B1* mutant breast cancer to date shows:

- Improved rwOS in patients with SF3B1 mutations
- Poor cell growth with negative selection

These findings emphasize the attractivity of SF3B1 is a therapeutic target in cancer

Our cell panel provides unique opportunities to:

- Define shared and unique molecular consequences of individual hotspot mutations
- Identify pathway and/or transcript-level therapeutic targets



Acknowledgments

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Vanderbilt Groups

- Park Lab
  - Ben Park, MD PhD
  - Sarah Croessmann, PhD
  - Sarah Reed
  - Bryce Thomas
  - Christin Keeton
  - Lauren Ha
  - Eshani Mehta
  - Ethan Fox
  - Vani Aurora
- Hurley Lab
- Jon Ling, PhD
- Shyr Lab and VANGARD
  - Yu Wang, PhD
  - Shilin Zhao, PhD
  - Qi Liu, PhD

Tempus Collaborators

- Tina M. O'Grady, PhD
- Yingying Yu, MHS
- Stamatina Fragkogianni, PhD
- Amrita A. Iyer, PhD
- All of the patients that make this work possible!

Funding:

- F30CA268325
- T32GM007347
- PEO Scholar Award