Rescuing p53 to treat cancer

YALE VENTURES

CCRX

Via alternative splicing and p53 isoforms

Team/Collaborators

LEAD INVENTOR

Christine J. Ko, MD, FOUNDER
Professor of Dermatology and Pathology
>140,000 patient biopsies examined,
>15,000 patient encounters

TEAM

Carolyn Lee, MD PhD
Assistant Professor of Dermatology, Stanford University,
NIH-funded skin cancer research for >1 decade.

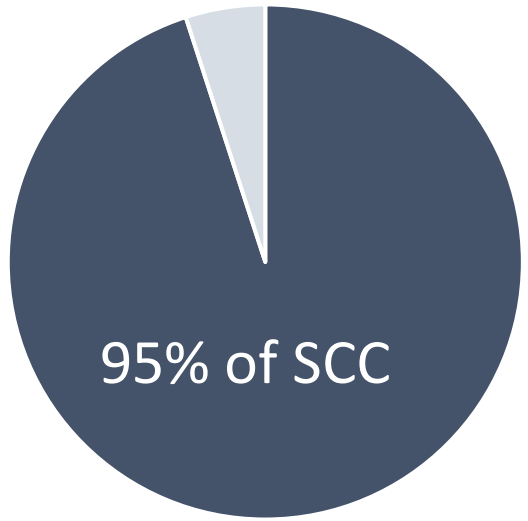
Lalit Golani, PhD
Medicinal Chemist,
Yale Center for Molecular Discovery

Brian Gibbs, PhD
Blavatnik Fellow '25-'26

Skin cancer: The need

1 in 5 Americans with skin cancer by age 70

Squamous cell carcinoma (SCC): 1.9M cases/yr
2nd most common skin cancer

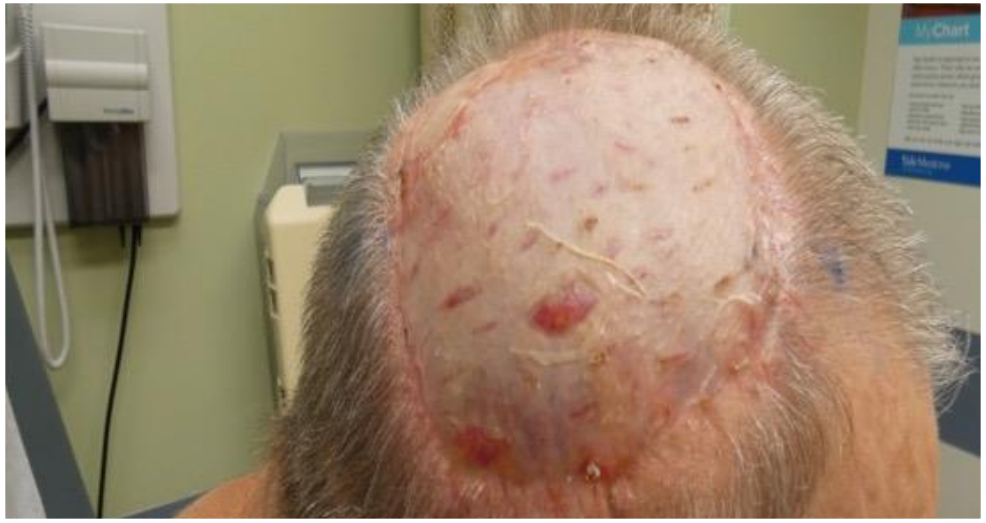


Treatment is lacking for early stage tumors – we will address this

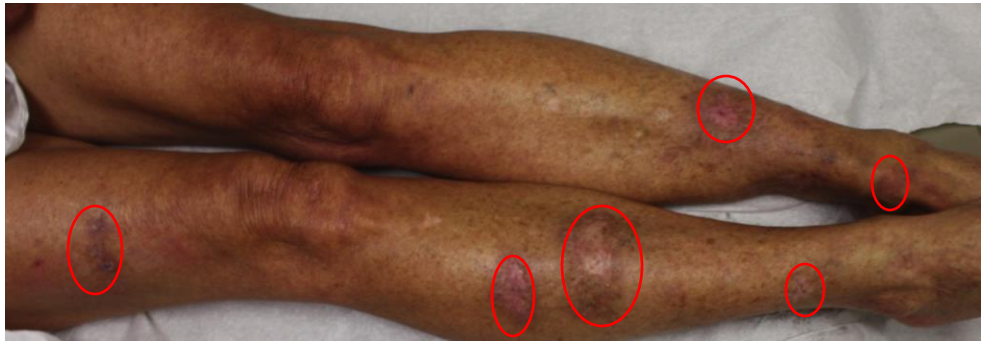
Early stage (< 2 cm)	**No medical treatment**
Late stage	Cytotoxic chemotherapy EGFR inhibitors *(e.g. cetuximab)* PD1 inhibitors *(e.g. cemiplimab, pembrolizumab)*

Yale

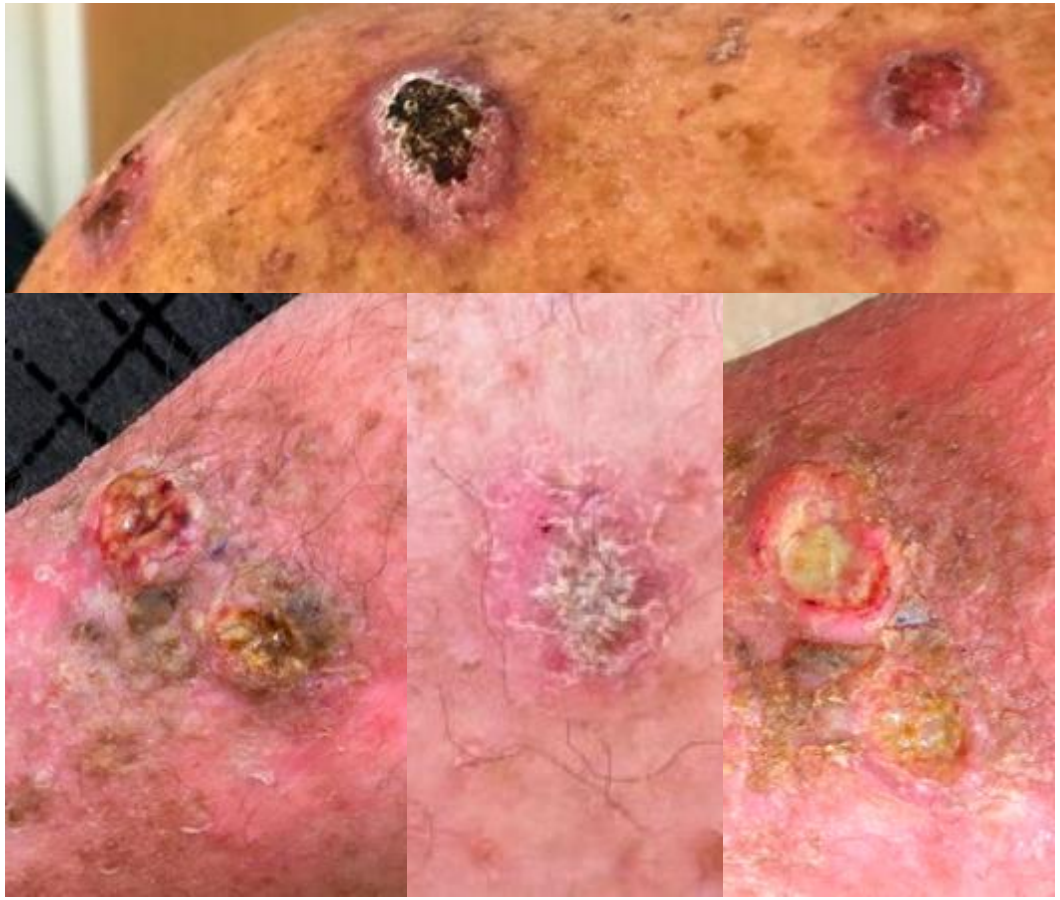
Early stage SCC: Surgery is effective BUT… NOT the SOLUTION!



Even for 1 lesion, scars can be disfiguring

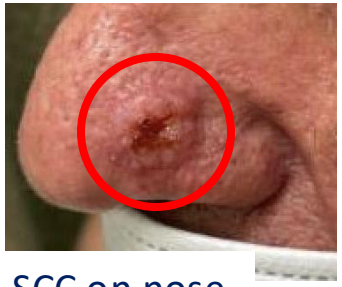


Multiple scars from consecutive surgeries

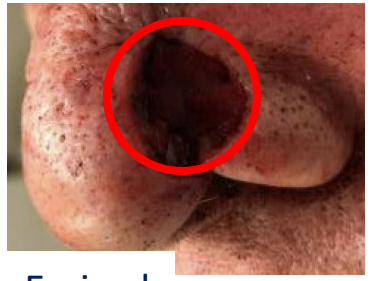


Many lesions, at the same time, in 1 patient; simultaneous surgery not feasible

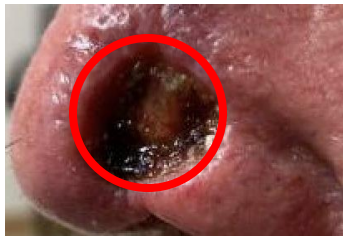
My patients need a better SOLUTION!



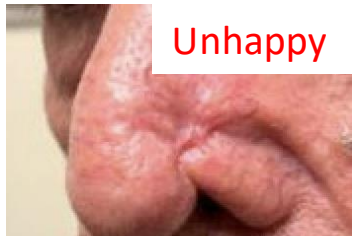
SCC on nose



Excised

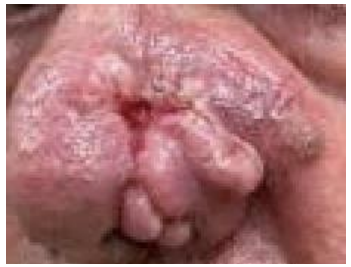


Healing at 2 weeks

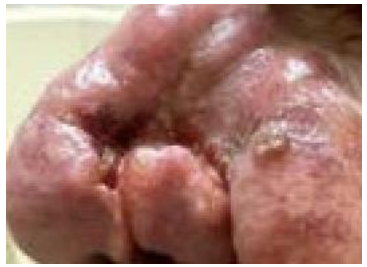


Unhappy

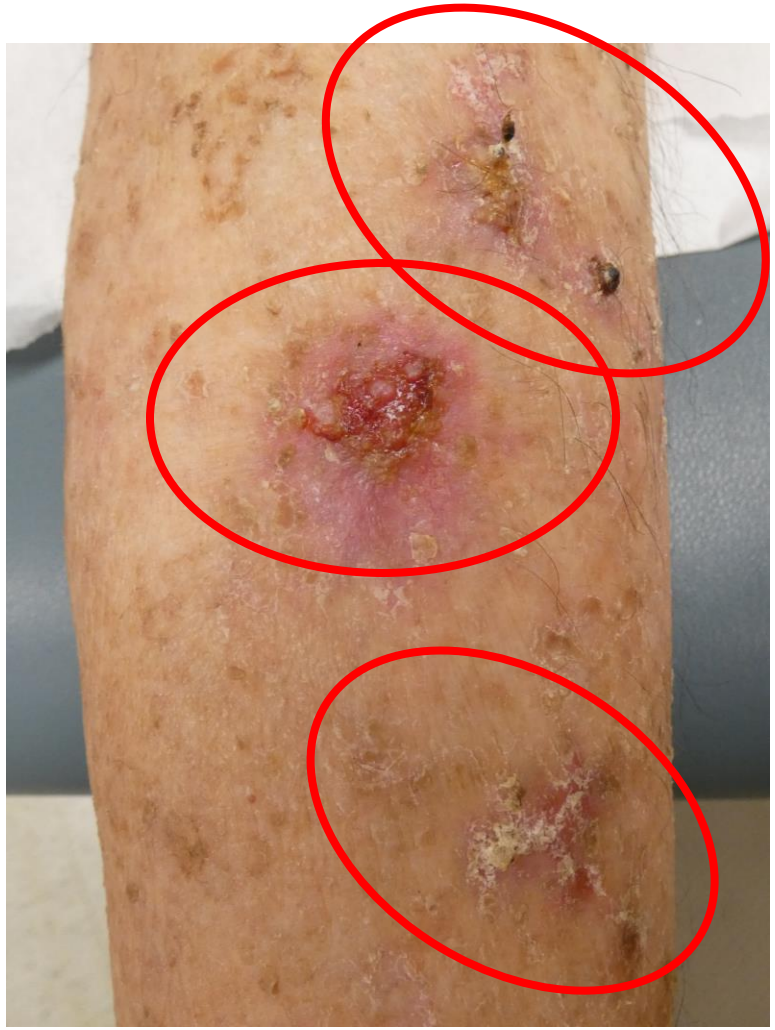
Healing at 2 months

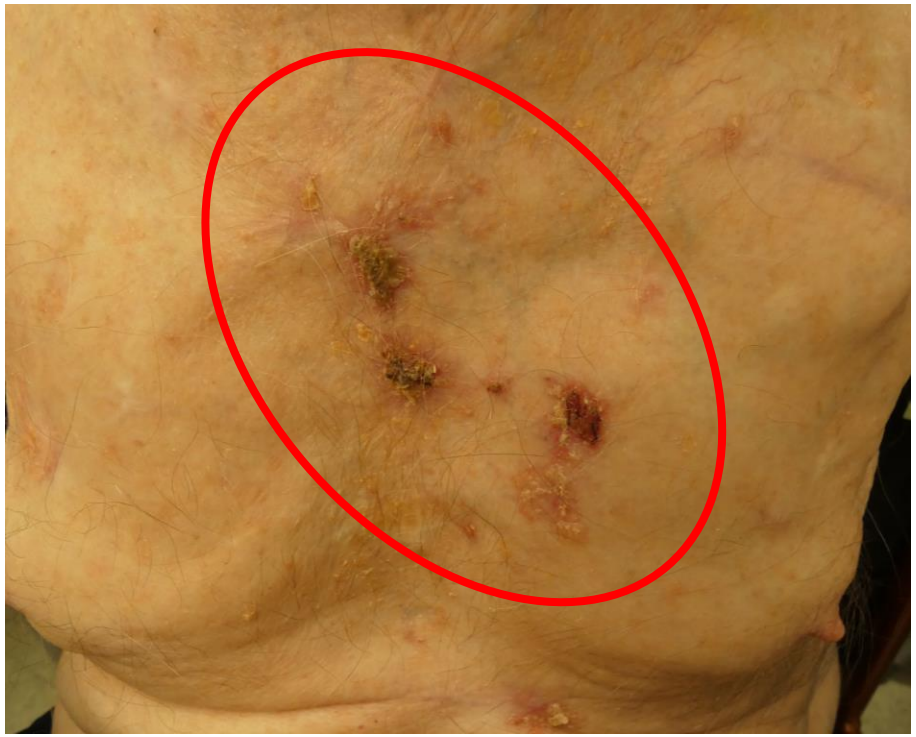


Recurrent at 1 year
Patient refused further surgery



Rapid growth over 2 months





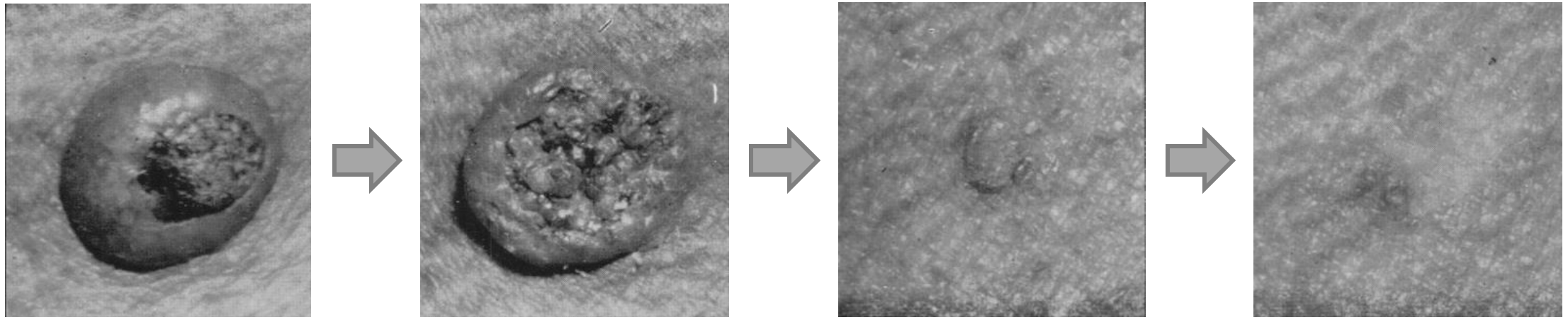
Many lesions, at the same time, in 1 patient:
Surgery leaves large wounds!

Older, thin skin (poor healing)!

Your Body Can Cure SCC

A minority of SCCs can spontaneously regress on their own

1 month: Cancer disappears with minimal scarring



Our research pinpoints **differentiation as the mechanism**

Skin differentiation = dead layer of skin

Source: Fouracres FA et al. Br J Canc 1953;7:58-64, Zito G…Ko CJ, *et al*, *Nat Commun* 2014, Ko CJ, *et al, J Am Acad Dermato*, 2012

Target and Mechanism of Action

Summary of the Biology

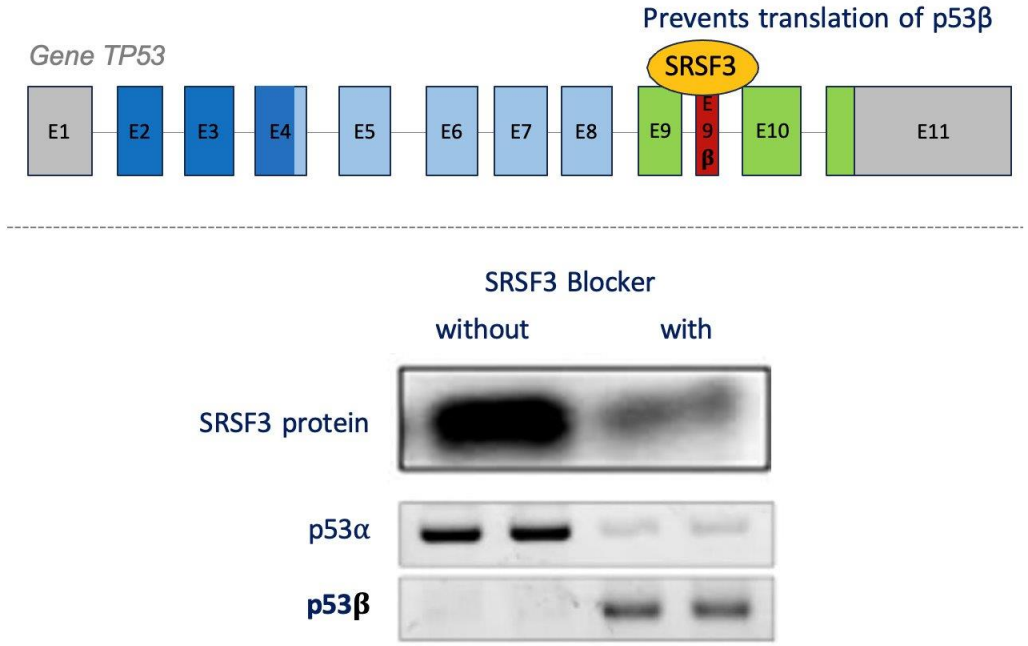
Cancer	Cure *(SRSF3 blocker)*
↑ SRSF3	↓ SRSF3
↓ p53β	↑ p53β

Blocking SRSF3 promotes alternative splicing of p53

KEY PLAYERS
THE HEROINE: p53β
THE VILLAIN: SRSF3
THE KNIGHT: SRSF3 Blocker

Expression of oncogenic **SRSF3 opposes p53β** by preventing translation

SRSF3 Blocker lowers SRSF3 levels and in turn increases p53β



Source: Zhang Y, Cell Death Discov, 2022

Yale

Target and Mechanism of Action

Summary of the Biology

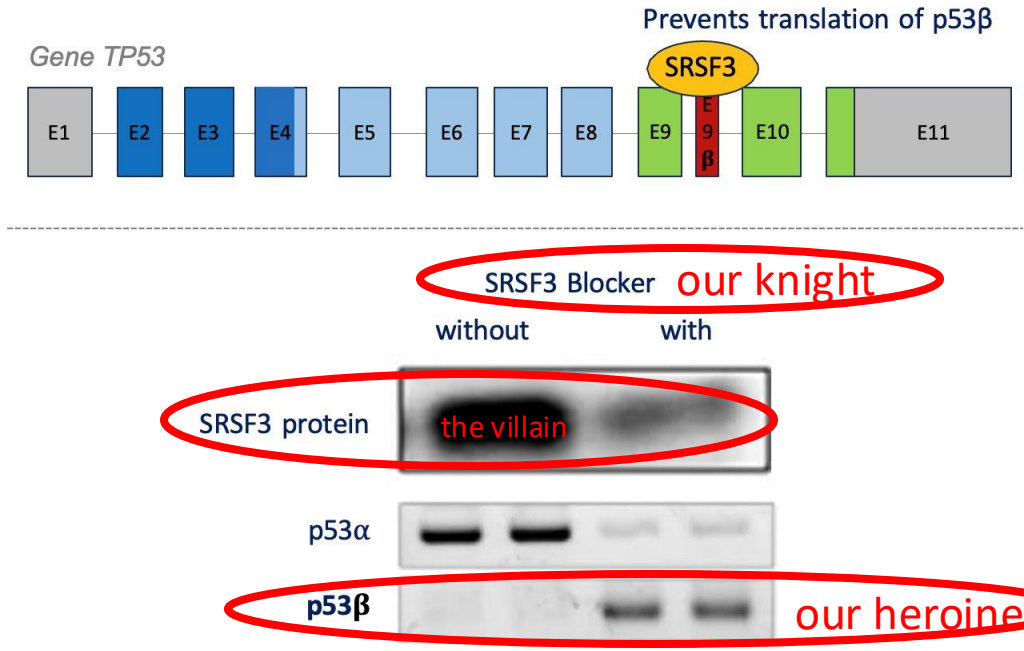
Cancer	Cure *(SRSF3 blocker)*
↑ SRSF3	↓ SRSF3
↓ p53β	↑ p53β

Blocking SRSF3 promotes alternative splicing of p53

KEY PLAYERS
THE HEROINE: p53β
THE VILLAIN: SRSF3
THE KNIGHT: SRSF3 Blocker

Expression of oncogenic **SRSF3 opposes p53β** by preventing translation

SRSF3 Blocker lowers SRSF3 levels and in turn increases p53β



Source: Zhang Y, Cell Death Discov, 2022

Yale

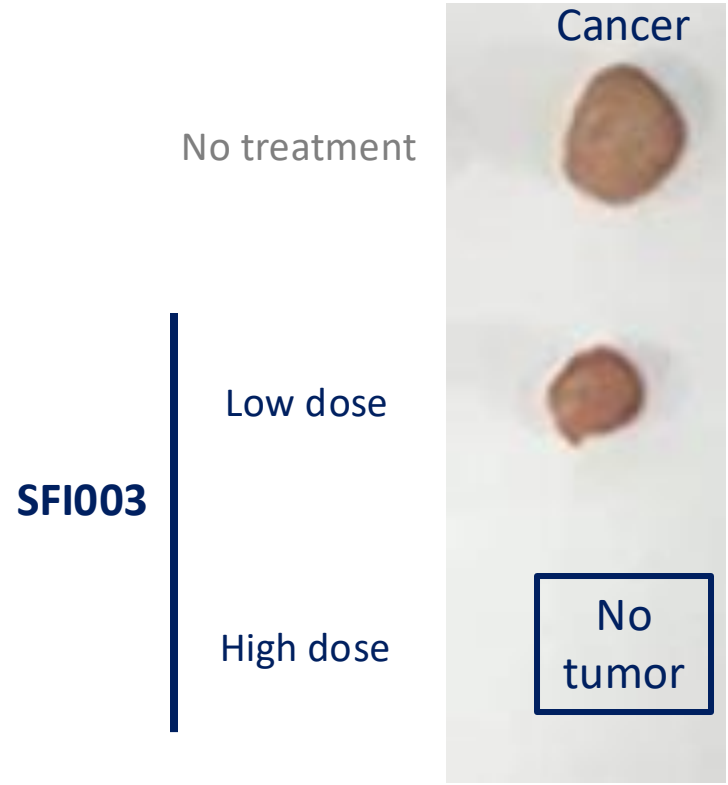
Oral use of tool compound SFI003 leads to tumor regression

KEY PLAYER
THE KNIGHT: SRSF3 Blocker (SFI003)

Oral use of **SRSF3 Blocker (SFI003:** small molecule) in mice:

Complete regression of colon carcinoma grafted to skin in mouse model

With 2 weeks of treatment, **5 of 6 tumors showed complete cancer cure**



Dosage 100-200 mg/kg
Toxicity IC50 ~ 7.5 mM

Proposing a safer and more effective treatment

Yale Ventures IP: (February, 2025)

11 novel SRSF3 inhibitors to look for decreased SRSF3 and increased p53β at nanomolar concentrations

Source: Zhang Y, Cell Death Discov, 2022

Yale

Cutaneous Use of SRSF3 Blocker SFI003

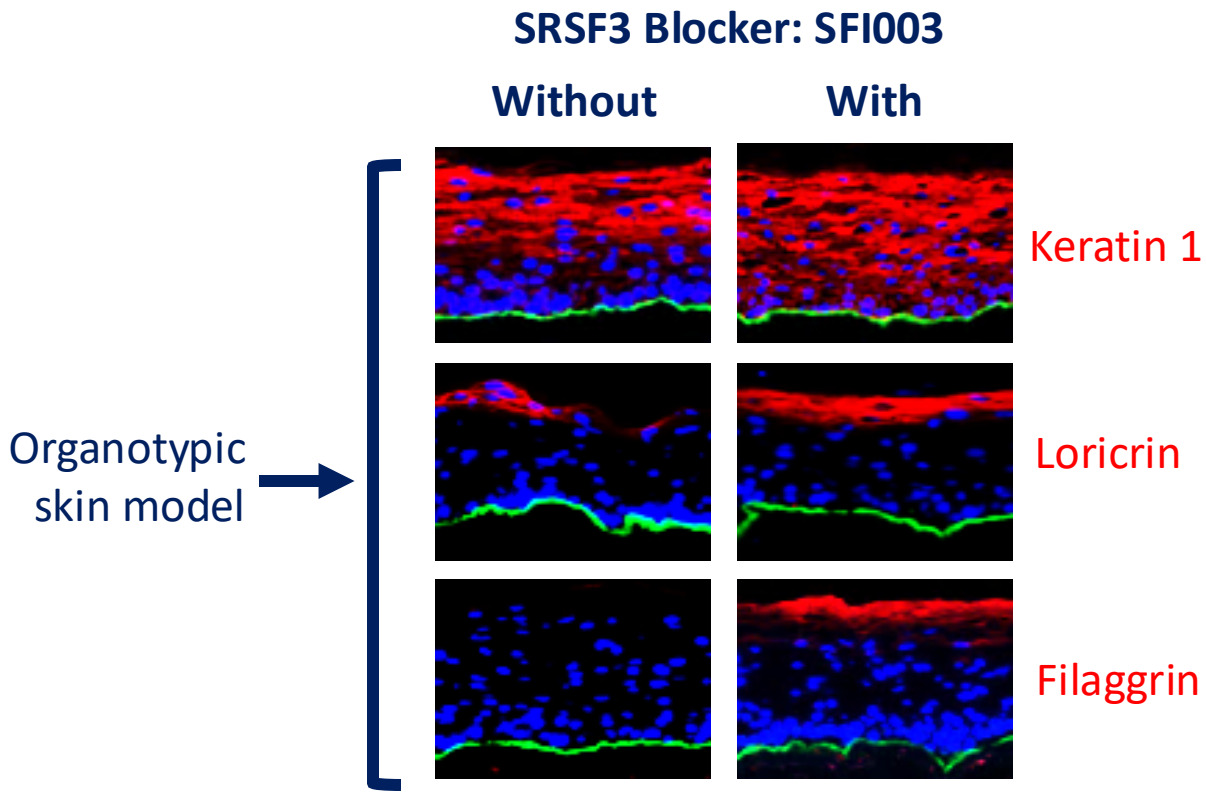
KEY PLAYER
THE KNIGHT: SRSF3 Blocker (SFI003)

Blocking SRSF3 **locally in skin normalizes skin differentiation and promotes cancer regression** in 3 relevant disease models on a molecular level:

1. Cell culture
2. Organotypic model
3. SCC cell lines

Provisional patent filed

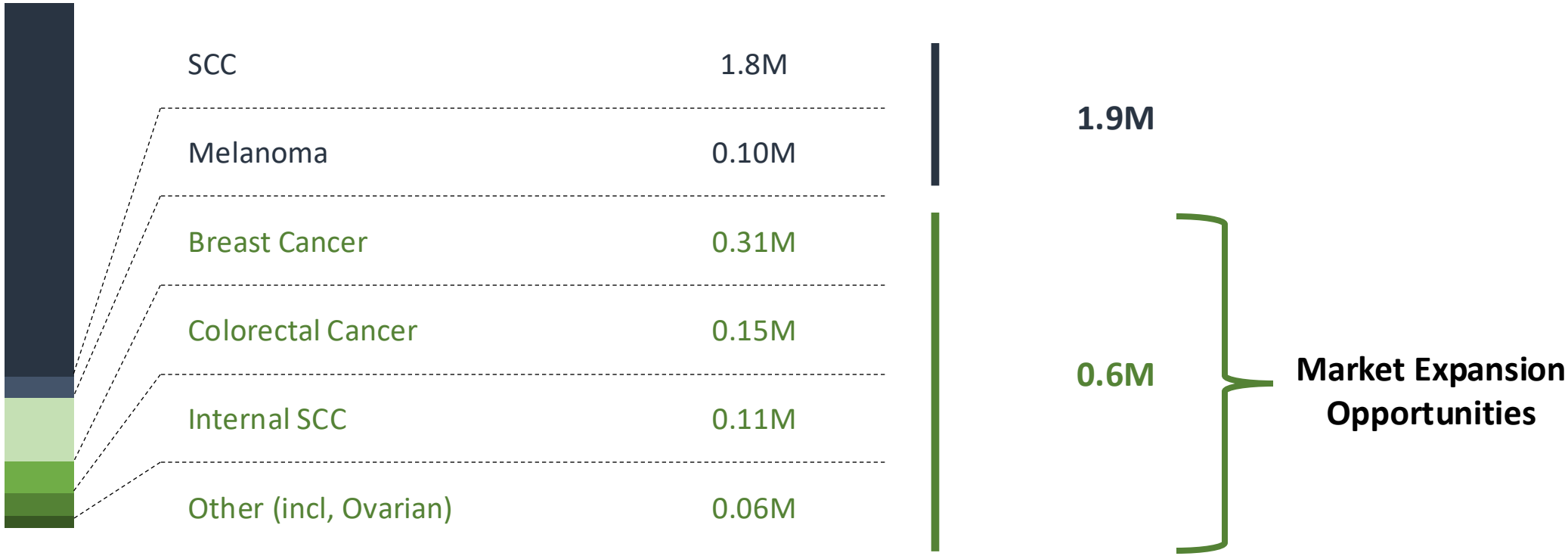
Differentiation proteins (red) are upregulated



Source: Ko and Lee, 2024 submitted

Yale

Market size: Great Commercial Opportunity



Yale

Proposed Use of Funds (Blavatnik Accelerator)

- Synthesized 11 novel SRSF3 inhibitors to look for efficacy at nanomolar concentrations.

Provisional patent filed

- Started *in vitro* testing in colon cancer cell lines to identify a lead compound to advance.

$30k Blavatnik Accelerator Award

- **X-ray crystallography ($15,000)**

Yale crystallography core to co-crystallize SRSF3 and small molecule inhibitors to model best fit.

- **Assay optimization (YCMD: $15,000)**

Demonstrate efficacy of novel compounds.
Dose response comparison with tool compound SFI003.

Blavatnik Development Award

Value inflection point:

Proof of concept for potential lead compound.