Harnessing p53beta as a medical treatment for skin cancer

YALE VENTURES

CCRX

Developing the first topical medical treatment for squamous cell carcinoma of the skin

Team/Collaborators

LEAD INVENTOR

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

TEAM and CONSULTANTS

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

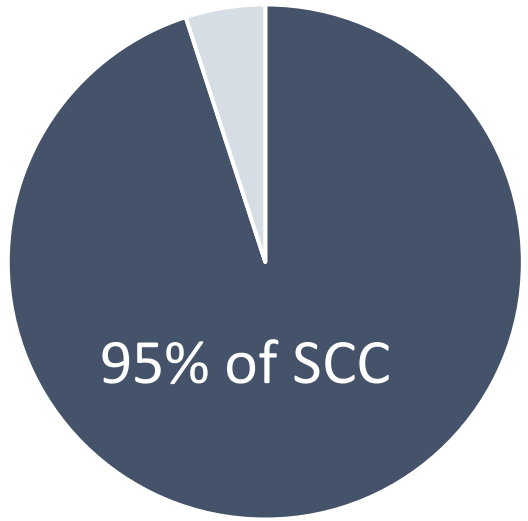
Lalit Golani, PhD
Medicinal Chemist,
Yale Center for Molecular Discovery

Ho-Joon Lee, PhD
Research Scientist,
Yale University, Department of Genetics

Skin cancer: The need

1 in 5 Americans with skin cancer by age 70

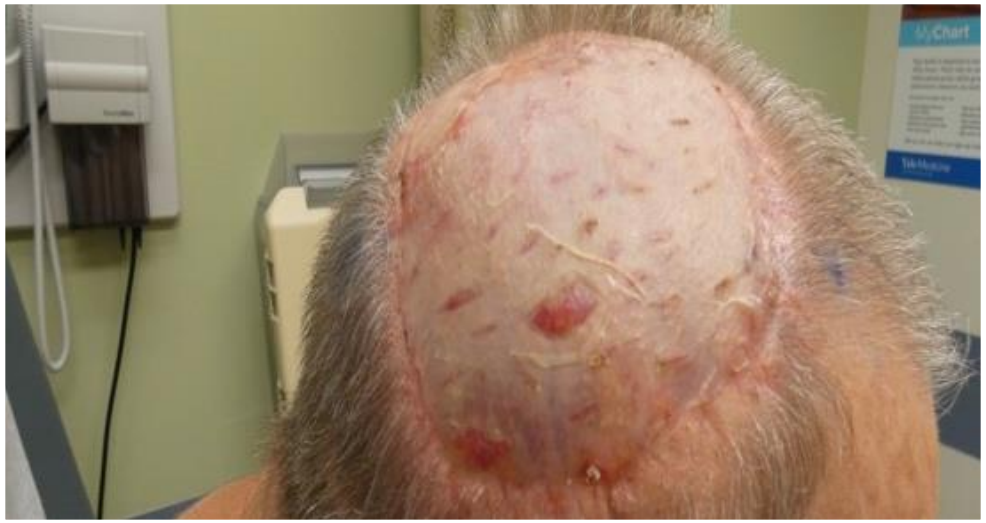
Squamous cell carcinoma (SCC): 1.8M cases/yr
2nd most common skin cancer



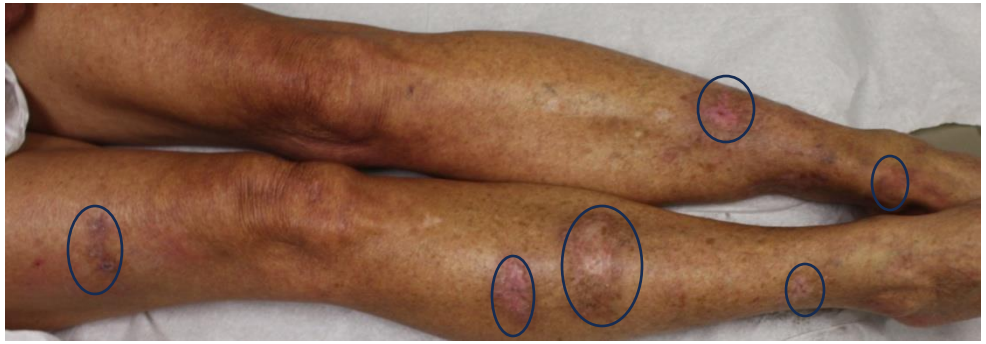
Treatment is lacking for early stage tumors – we will address this

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

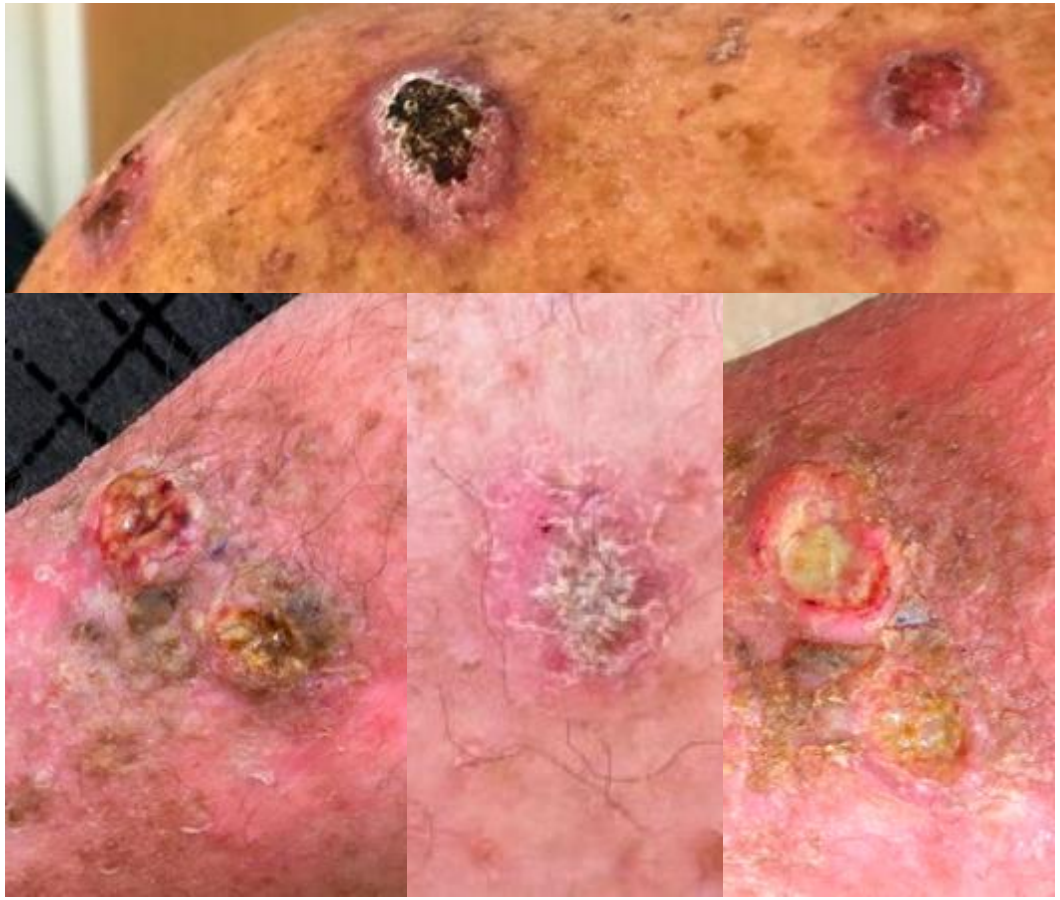
Early stage SCC: Surgery is effective BUT…



Even for 1 lesion, scars can be disfiguring



Multiple scars from consecutive surgeries

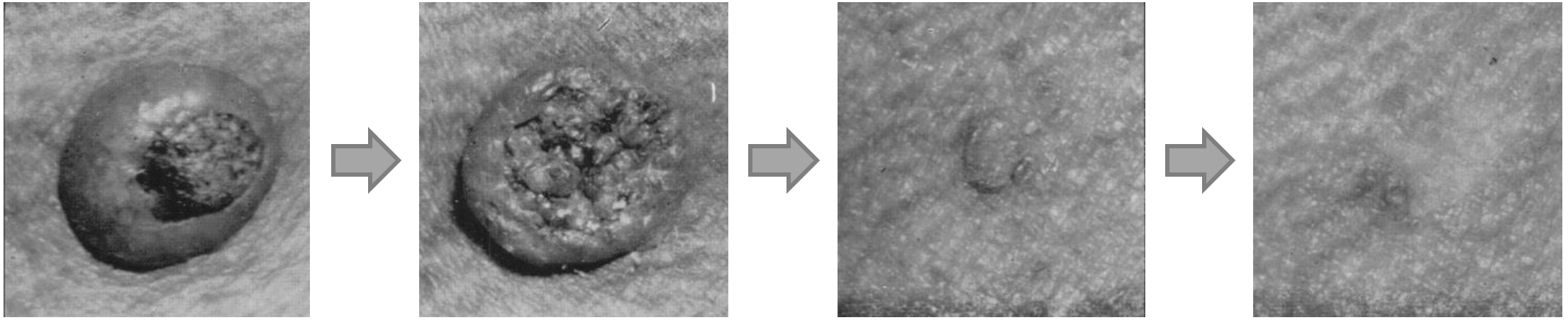


Many lesions, at the same time, in 1 patient; simultaneous surgery not feasible

Your body can cure SCC

A minority of SCCs can spontaneously regress on their own

1 month: Cancer disappears with minimal scarring

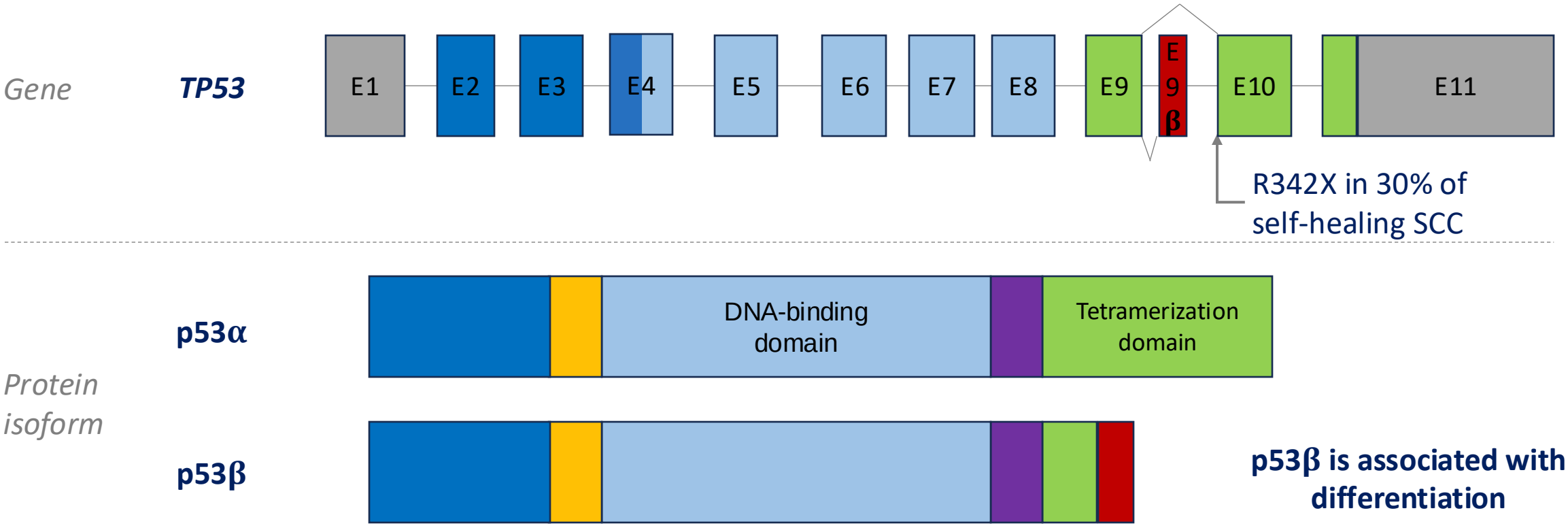


Our research pinpoints **differentiation as the mechanism**

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

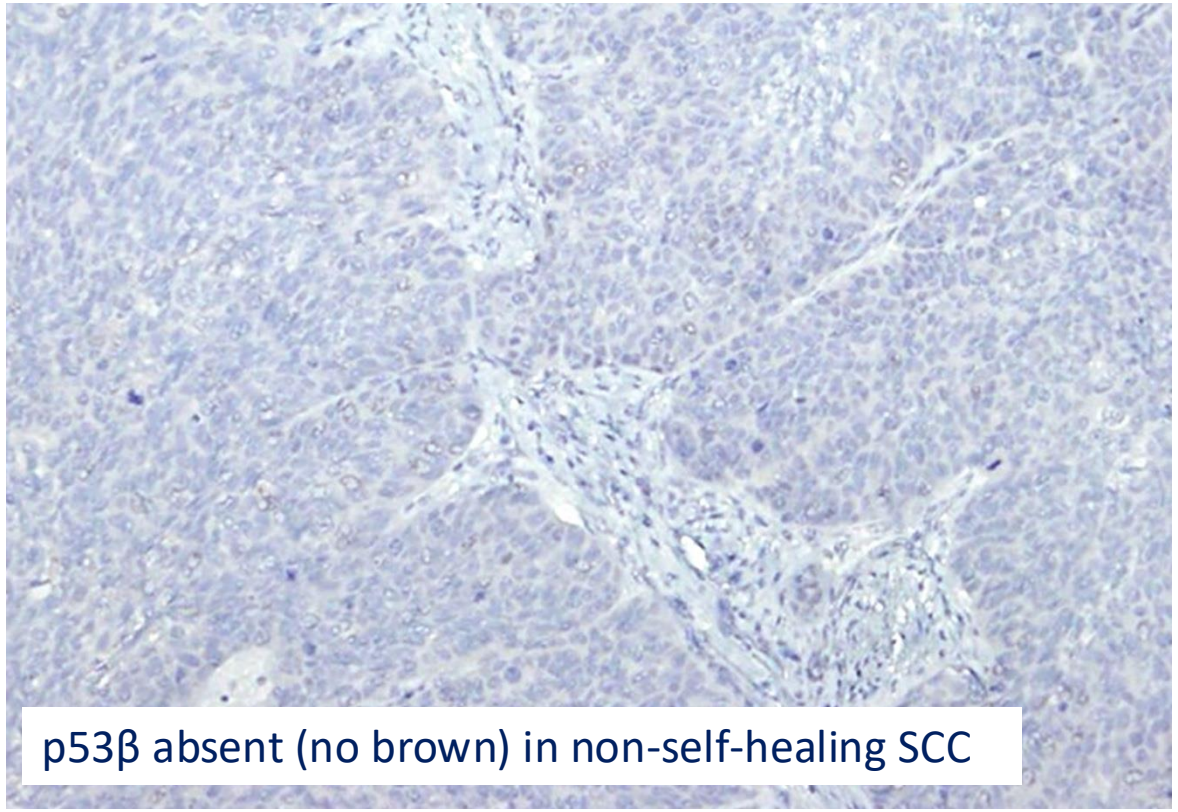
Differentiation cures SCC via the p53 pathway



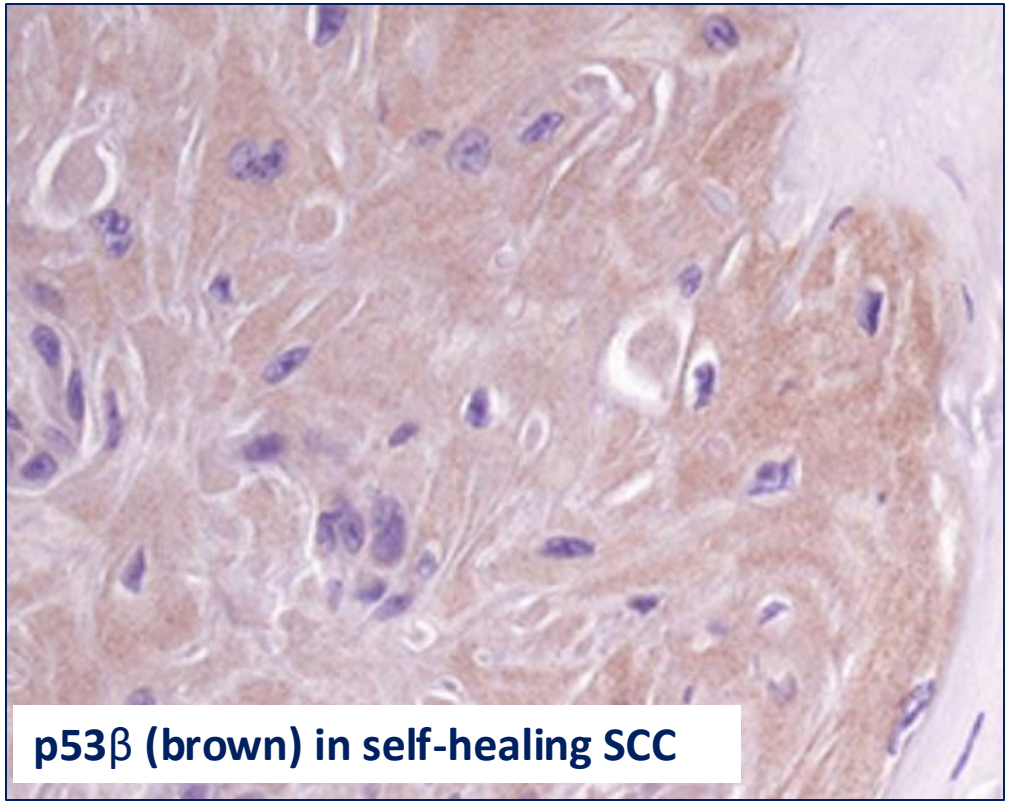
Source: Lim YH…Ko CJ, J Invest Dermatol 2016; Ko CJ, et al, J Am Acad Dermatol 2017

Differentiation cures SCC via the p53 pathway

KEY PLAYER
THE HEROINE: p53β



p53β absent (no brown) in non-self-healing SCC



p53β (brown) in self-healing SCC

Source: Ko CJ *et al*, J Clin Pathol 2018

Can we use this p53β signal to induce differentiation and cure cancer?

Skin differentiation = Cancer regression and cure

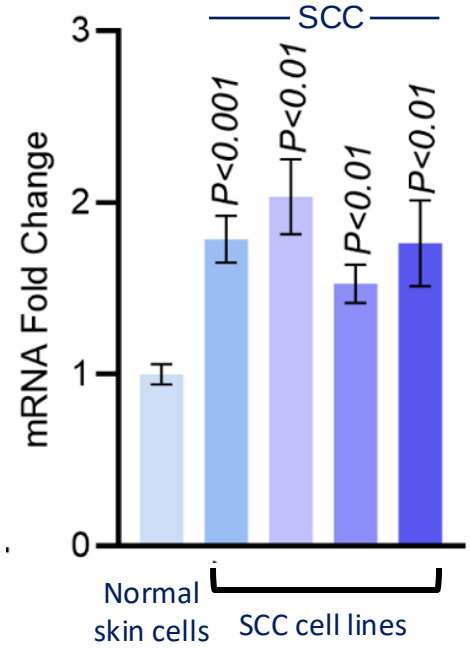
SRSF3 levels as a surrogate of p53β levels

(SRSF3 opposes p53β)

KEY PLAYER

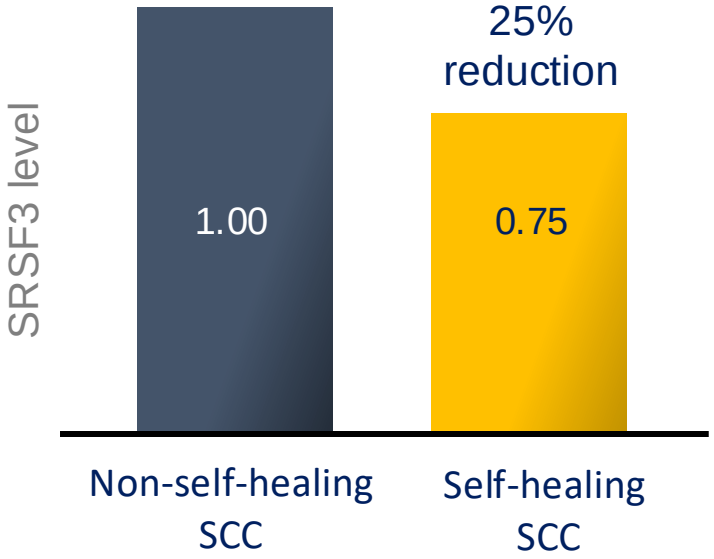
THE VILLAIN: SRSF3

Higher SRSF3 in SCC cell lines



Less SRSF3 in self-healing SCC patient samples

p-value < 0.01



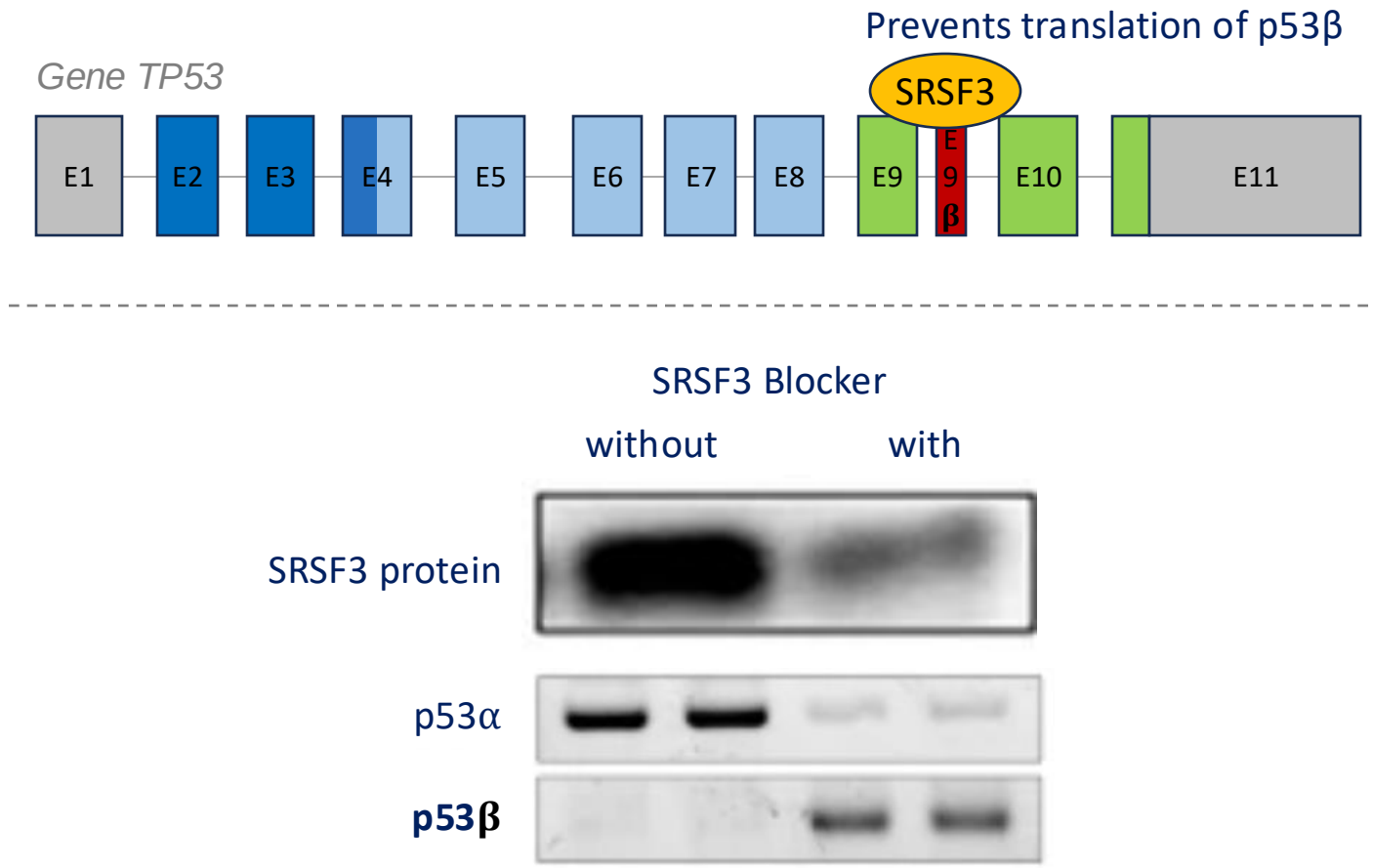
Source: Ko and Lee, 2024 submitted

Blocking SRSF3 promotes alternative splicing of p53β

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

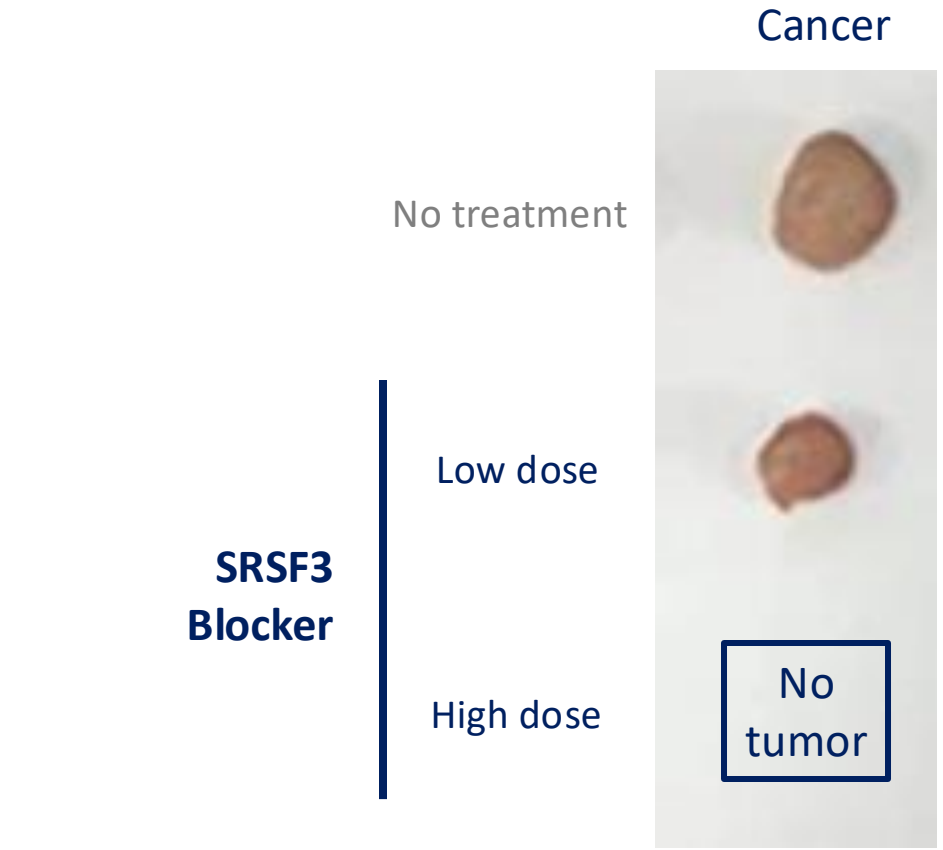
Oral use of SRSF3 leads to tumor regression

KEY PLAYER
THE KNIGHT: SRSF3 Blocker

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

Complete regression of carcinoma in mouse model

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



Source: Zhang Y, Cell Death Discov, 2022

A novel topical SRSF3 Blocker is needed for SCC

Summary of the biology…

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

Our strategy to address an unmet need…

SRSF3 Blocker oral use:
good safety profile in mice but not optimized for topical use

Even safer: Topical/non-systemic SRSF3 blocker for SCC

Novel: non-oral use of SRSF3 Blocker

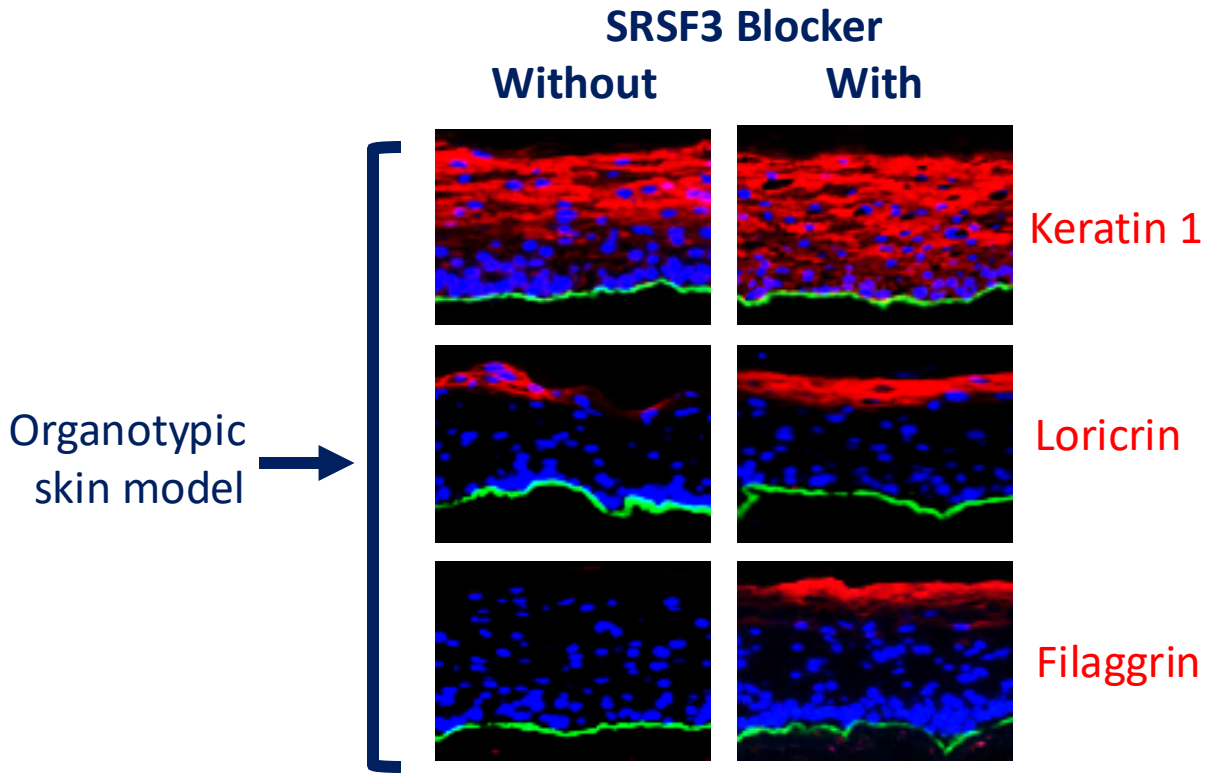
KEY PLAYER
THE KNIGHT: SRSF3 Blocker

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

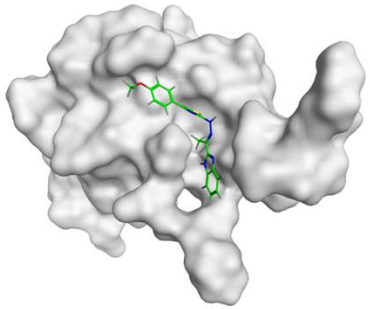
Differentiation proteins (red) are upregulated

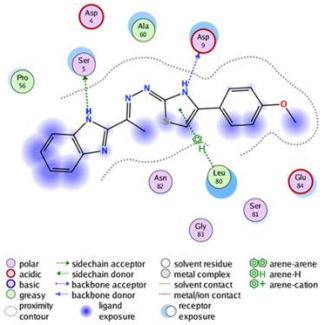


Source: Ko and Lee, 2024 submitted

SRSF3 Blocker to novel compounds

SRSF3 Blocker: Base compound





Molecular weight 363
Log P 4.59
Low affinity

11 confidential compounds
for composition of matter

In the last month, with YCMD medicinal chemistry, we designed novel compounds

Source: Ko and YCMD, 2024, confidential data

Blavatnik funds for two parallel aims

H1 2025 | H2 2025 | H1 2026

Aim 1
$100k

Preclinical confirmation of 11 (+ from Aim 2) novel compounds

Demonstrate efficacy of novel compounds for SCC

Validate *in vitro* and *in vivo models* of skin cancer at nanomolar concentrations **with topical/localized use** → **Dose response** comparison with known SRSF3 Blocker

Aim 2
$200k

Improve & expand on known SRSF3 Blocker (Dr. Golani, Dr. Ho-Joon Lee)

Optimize hits, expand existing patent protection for families of SRSF3 blockers

Co-crystallize SRSF3 Blocker and SRSF3 → **In silico screen** for small molecules → **HTS screen** as needed; initial med chem optimization

Value inflection point: Optimized lead compound for localized use in skin (topical, percutaneous, intralesional)