Yale Engage Cancer: Novel Cancer Therapeutics & Delivery Systems

Thursday, November 5\textsuperscript{th}, 2020
11:00a.m – 12:30p.m
Scientist, scholars, and physicians . . .

- Engaged in research
- Engaged in policy
- Engaged in innovation
- Engaged in the clinic
Welcome

- Charles Fuchs, M.D, MPH, Richard Sackler and Jonathan Sackler Professor of Medicine (Medical Oncology) and Professor of Chronic Disease Epidemiology; Director, Yale Cancer Center and Physician-in-Chief, Smilow Cancer Hospital
- Tim Shannon, M.D, General Partner, Canaan

Presentations

- Ranjit Bindra, M.D, Ph.D., Professor of Therapeutic Radiology, Yale School of Medicine; Co-Director, Yale Brain Tumor Center
- Sidi Chen, Ph.D., Assistant Professor, Yale School of Medicine
- Craig Crews, Ph.D., John C. Malone Professor of Molecular, Cellular, and Developmental Biology and Professor of Chemistry, of Pharmacology, and of Management, Yale School of Medicine; Executive Director, Yale Center for Molecular Discovery
- Faye Rogers, Ph.D., Associate Professor of Therapeutic Radiology, Yale School of Medicine
- Josh Bilenker, M.D, Chief Executive Officer, Loxo Oncology at Lilly

Discussion & Questions
Ranjit Bindra, M.D., Ph.D.
Professor of Therapeutic Radiology, Yale School of Medicine;
Co-Director, Yale Brain Tumor Center
1. **Disruptive, cutting-edge science**…

**NATURAL PRODUCTS**

**Science**

Structure elucidation of colibactin and its DNA cross-links

Menghao Xue, Cheng Su, Kian E. Lim, Alan K. Hoody, Kevin M. Wernimont, Zhizhou Wang, Madeline C. Frieschinger, Eithne F. Shine, Wentei Wang, Selkh R. Hassan, James M. Crompton

**LETTER**

MicroRNA silencing for cancer therapy targeted to the tumour microenvironment

Christopher T. Song, Youhand Mei, Jonathan T. Caruso, Fanchen Li, Elizabeth J. Palan, Christian G. Caruso, and C. Patrick Brown

**IL-18BP is a secreted immune checkpoint and barrier to IL-18 immunotherapy**

Nature

2. **Pivotal studies, excellence in clinical research**…

**ORIGIN ARTICLE**

Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): overall survival and updated results of a randomised, double-blind, phase 3 trial


3. **Rapid translation into biotech/pharma**…

**ARVINAS**

**Next Cure**

**KLEO PHARMACEUTICALS**

**EVOLVE IMMUNE THERAPEUTICS**

**CYBEREXA**

**simcha THERAPEUTICS**

**Yale**

Improving the health, welfare and prosperity of the global community.

$873 million

48 venture-backed companies

1367 active patents

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Yale Venture Capital

Yale Venture Capital
My Background

Basic Science World
- PI of an NIH-funded DNA repair lab
- Oncology synthetic lethal drug screens

Clinical World
- Adult/Pediatric Brain Tumor RadOnc
- Run phase I/II oncology clinical trials

Biotech World
- Active biotech entrepreneur
- Cybrexa: IND→Phase I in 1Q21
Exploiting Oncometabolite-induced BRCAAness

**Basic Science Discovery**

- Oxaloacetate → αK(s)G-dependent dioxygenases (KDM4A/B) → S-2HG → DSB → Homologous Recombination → PARPi Sensitivity (BRCAAness)

**Clinical Trial Translation**

- Clinical Trials Testing PARPi’s for HR-defecting IDH1/2m cancers
  - OLAPCO, olaparib, solid tumors (NCT02576444; Eder)
  - ETCTN 10129, olaparib, solid/CNS tumors (NCT03212274; LoRusso, Bindra)
  - PNOC017, BGB290+TMZ, peds IDH1/2m glioma (NCT03749187; Marks, Bindra)
  - ABTC1801, BGB290+TMZ, adult IDH1/2m glioma (NCT03914742; Bindra, Schiff)
  - ETCTN 10264, olaparib, IDH1/2m AML, (NCT03953898; Prebet)

**Introductory Text**

A collaborative effort across multiple Yale labs...

...and trialists

- Ranjit Bindra
- Peter Glazer
- Murat Gunel
- S. Halene
- Pat LoRusso
- Paul Eder
- T. Prebet

*Multiple outside collaborators not shown...*
Targeting NAD Metabolism Defects in Cancer

NAMPT inhibitors

Promising drugs in need of biomarkers

Clinical Trials
Sidi Chen, Ph.D.
Assistant Professor, Yale School of Medicine
Research vision to advance cancer immunotherapy

Program 1: Novel checkpoints

Program 2: Next-gen CARs

Program 3: MAEGI

Dong et al. 2019 Cell

Ye et al. 2019 Nat Biotechnol

Dai et al. 2019 Nat Methods

Wang et al. 2019 Nat Immunol
MAEGI is a new class of cancer immunotherapy

Multiplexed Activation of Endogenous Genes as Immunotherapy

- Robust response
- Priming and activation of T cells
- Increased frequencies of TAA-specific T cells
- Enhanced recognition and killing of cancer cells by T cells

- Low expression of tumor-associated antigens (TAA)
- CRISPRa boosts the presentation and immune recognition of TAA
- Induction of systemic adaptive immunity against TAA

Wang et al. 2019 *Nat Immuno*
MAEGI works in animal models, poised for translation

In vivo efficacy in animal models of:
- Breast cancer
- Melanoma
- Pancreatic cancer
Craig Crews, Ph.D.
John C. Malone Professor of Molecular, Cellular, and Developmental Biology and Professor of Chemistry, of Pharmacology, and of Management, Yale School of Medicine; Executive Director, Yale Center for Molecular Discovery
Crews Lab: Applied Chemical Biology

Carfilzomib/Kyprolis™

PROTEOLIX
ONYX PHARMACEUTICALS
AMGEN
Crews Lab: Applied Chemical Biology

PROTAC

Target Protein

Target is degraded by the proteasome.

ARVINAS
Libraries
• >10,000 bioactive compounds and >250,000 diverse synthetic drug-like molecules
• Human siRNA collection targeting >18,000 genes

Equipment
• Liquid handlers
• Platereaders
• High-content microscope
• FLIPR

Yale Center for Molecular Discovery
Founded 2003
Craig Crews, Executive Director

“Industry-trained scientists, doing industry-style research in an-industry like setting…”

“meeting the innovative and individual needs of Yale projects.”

We Need:
Real world direction from industrial partners
1) Unmet Needs?
2) New Indications?

YCMD: Yale’s Biomedical Translational Hub
Faye Rogers, Ph.D.
Associate Professor of Therapeutic Radiology, Yale School of Medicine
Targeted Therapeutics for Gene Amplified Cancers

Gene amplification is a critical factor driving major oncogenic processes:
- Cell Proliferation
- Decreased Apoptosis
- Angiogenesis
- Migration and Invasion

Current Treatment Strategy: Target the Overexpressed Protein Product

Advantage: hijacking the cell’s own machinery reduces normal tissue toxicity and off-target effects
A Broadly Applicable Novel Drug Platform

Multiple cancer types can be targeted with our approach

- 461 amplified genes
- 14 cancer subtypes

519, 971 unique triplex targeting sequences throughout the human genome

- Brain
  - EGFR
  - MYC
  - PDGFR
  - MET
  - KIT

- Lung
  - EGFR
  - MYC
  - ERBB2
  - ZNF703
  - PRDM14
  - BIRC5

- Breast
  - ERBB2
  - PIK3CA
  - MYC
  - GRB7
  - ERCC5

- Melanoma
  - BRAF

- Ovarian
  - ERBB2
  - KRAS

- Colorectal
  - BRAF
  - KRAS
  - ERBB2

Directly convert the amplified oncogene to DNA damage

- Triplex Formation
- Replication Stress
- DNA Damage Response
- p53 Independent Pathway
- Apoptosis

DNA Damage Response

- ATM
- CHEK1
- CHEK2
- S139 P
- Y142 P
- H2AX
- XPD

Apoptosis

- p53 Independent Pathway
- Chk1 P
- Chk2 P
- ATM P

Additional Cancer Types

- Brain
- Lung
- Breast
- Melanoma
- Ovarian
- Colorectal
- Gastric
Josh Bilenker, M.D
Chief Executive Officer, Loxo Oncology at Lilly
Discussion
ATTEND

Defining Mechanisms and Biomarkers of Sensitivity &
Resistance to Anti-Cancer Treatments
Date: Wednesday, December 9th, 2020
Time: 1:00p.m-2:30p.m EST

CONNECT

Please direct general questions, opportunities, and, information to:

Kathy Lynch
University Director,
Corporate Strategy & Engagement
Kathleen.lynch@yale.edu

Or:

Yale Cancer Center
https://www.yalecancercenter.org/

Yale Office of Cooperative Research
https://ocr.yale.edu/
Thank you for participating!