RiboRupt Biotech
Interrupting ribosome biogenesis to cure cancer

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Scientific Founder: Susan J. Baserga, MD PhD

- William H. Fleming MD Professor of Molecular Biophysics & Biochemistry, Genetics and Therapeutic Radiology at Yale
- KOL in the cell biology and biochemistry of the nucleolus and ribosome biogenesis (94+ papers)
- Licensed technology to 2 biotech companies and inventor on 3 patents.
- Elected to the National Academy of Inventors in 2018.

- Team includes: Lisa Ogawa McLean, graduate student, MB&B; Yulia Surovsteva, PhD, Director of Biology, Yale Center for Molecular Discovery; David Lewin, PhD, Sr. Assoc. Dir. Bus. Dev. Yale OCR. david.lewin@yale.edu
Targeting RNA polymerase I (RNAPI) in the nucleolus for cancer therapy

- The nucleolus is both old and re-emerging validated target.

- We have a unique screening platform for nucleolar function developed in my laboratory.

- The screening platform has been validated by genome-wide siRNA, miRNA mimic, lncRNA and FDA-approved drugs screens.
Limited competition targeting RNAPI validates our approach

Senhwa Biosciences Inc. (fka CYLENE Pharmaceuticals)
• CX-5461-small molecule selective inhibitor of RNA polymerase I (for p53 normal cancers)
• Phase I clinical trial for hematologic malignancies (Australia) and breast cancer (Canada)

BMH-21-Johns Hopkins and Bluefields Innovations

A Targeting Modality for Destruction of RNA Polymerase I that Possesses Anticancer Activity

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http://dx.doi.org/10.1016/j.bcr.2013.12.009

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Discovery of novel inhibitors of ribosome biogenesis by innovative high throughput screening strategies.

Scull CE1, Zhang Y1, Tower N2, Barmenasen L2, Padmalayam P, Hackett R1, Zhai L1, Rustwick R2, Schneider DA1.

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Communication

The cytotoxic natural product vioprolide A targets nucleolar protein 14 essential for ribosome biogenesis

Volker Christian Kirsch, Christina Orgel, Simone Braig, Irmela Jeremias ... See all authors

First published: 28 October 2019 | https://doi.org/10.1002/arne.201911158
Robust new screening platform for nucleolar function, including RNAPI

• Proprietary, robust, high throughput phenotypic assay for nucleolar function in human cells.
  • Nucleolar number/function readout.
  • Validated by productive siRNA, miRNA and lncRNA screens.
  • Validated by screen against known cancer therapeutics.
  • Ready for expansion to hit-to-lead program.

siRNA screen published in Cell Reports, 2018

published in Mol. Biol. of the Cell March 2021
Flow chart for high throughput phenotypic screen for anti-RNAPI small molecule discovery

- **Optimize**
  - Fixing & staining conditions
  - incubation times
  - antibody dilution

- **Find controls**
  - Find small molecule controls that give the one nucleolus phenotype
  - seeding density
  - treatment duration

- **Pilot screen**
  - MicroSource Pharmakon 1600 bioactive library:
    - 1600 compounds
  - Tested in Humans bioactive library:
    - 727 compounds
  - Enzo FDA-approved drugs:
    - 640 compounds

- **Screen**
  - Life Chemicals FSP3 synthetic library:
    - 25,246 compounds

Funded by the Breast Cancer Alliance
Lisa Ogawa McLean and the Yale Center for Molecular Discovery
Commercial opportunity for further development of hits from Life Chemicals FSP$^3$ Library screen

Screened 25,246 compounds at 10 μM
- Average Z’ = 0.53
- Average S/B = 3.2

Identified 202 active compounds
- Cut-off = Median + 3 SD
- 137 compounds showed reproducible activity
- Most have anti-RNAPI activity at 10 μM

11 structure clusters were identified using DataWarrior software
- The majority are grouped in a cluster of heterocyclic sulfur-containing compounds

One nucleolus phenotype

funded by the Breast Cancer Alliance  Lisa Ogawa McLean and the Yale Center for Molecular Discovery
Most hits inhibit RNAPI at least as well as BMH-21

190 unique compounds (FDA-approved drugs and Life Chemicals)
n = 3 biological replicates
48 h
Use of Proceeds To Advance Screen Hits To Lead Compounds

Hit validation-dose-response curves, secondary screening assay (5 ethynyl uridine for RNAPI), patent filing once chemotypes have been identified

<table>
<thead>
<tr>
<th>Deliverable</th>
<th>Cost</th>
<th>When</th>
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<tbody>
<tr>
<td>Hit validation</td>
<td>100K</td>
<td>1 year</td>
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<tr>
<td>Find best cancer application</td>
<td>100K</td>
<td>1 year</td>
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<tr>
<td>First-in-class in vivo test</td>
<td>100K</td>
<td>1 year</td>
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Test prioritized hit compounds for efficacy in a broad range of cancer cell lines.

Perform efficacy and toxicity studies in a mouse cancer model.