



Weill Cornell Medicine

Small Molecule Inhibitors of CRL4 Ubiquitin Ligase for Cancer Treatment

Lead Inventor:

Pengbo Zhou, Ph.D.

Professor of Pathology and Laboratory Medicine,
Weill Cornell Medical College

Business Development Contact:

Jamie Brisbois

Manager, Business Development and Licensing

(646) 962-7049

jamie.brisbois@cornell.edu

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Background & Unmet Need

- Cullin 4 (CUL4) is a molecular scaffold of the CUL4-RING ubiquitin ligase (CRL4), which controls the stability and cellular levels of proteins via the ubiquitin-proteasome pathway
- CUL4 proteins play a significant role in nucleotide excision repair after UV irradiation, as well as the cell cycle, cell signaling, and histone methylation
- CUL4A is amplified or expressed at abnormally high levels in multiple cancers, including breast cancer, squamous cell carcinoma, hepatocellular carcinomas, and lung cancer
- Moreover, CUL4A and 4B overexpression is implicated in tumor progression, metastasis, and a poorer survival rate for patients with lung, colorectal, cervical, esophageal, and breast cancers
- **Unmet Need:** Novel inhibitors of CUL4 proteins for treatment of CUL4-expressing cancers

Technology Overview

- **The Technology:** Specific inhibitors of CUL4 for treatment of CUL4-expressing cancers
- **The Discovery:** CUL4 inhibitors were identified through a robust high-throughput screening and assay workflow of ~240K compounds
- Lead compounds were subsequently optimized via several rounds of SAR to produce the current lead compounds PA-201 and PA-1
- Compounds are currently in the hit-to-lead stage, with additional medicinal chemistry to improve potency ongoing
- **PoC Data:** PA-1 demonstrates tumor killing ability *in vitro* and in *in vivo* xenograft models of MDA-MB-468 breast cancer cells, a CUL4-high cell line
- shRNA CUL4 inhibition sensitizes tumors to the topoisomerase 1 inhibitor topotecan (P=9.1E-3), suggesting that CUL4 inhibitors may be combined with chemotherapy

Inventors:

Pengbo Zhou
Liang Ma
David Warren
Lei Shi
Chenyi Yang

Patents:

US Patent [8,513,181](#)
US Patent [10,617,683](#)
US Patent [9,295,376](#)
[US Application](#)
[EP Application](#)

Publications:

[Wang et al. Am J Pathol.](#) 2021.
[Jia et al. J Biol Chem.](#) 2017.
[Hannah et al. Gene.](#) 2015.
[Liu et al. Mol Cell.](#) 2009.

Biz Dev Contact:

Jamie Brisbois
646-962-7049
jamie_brisbois@cornell.edu

Cornell Reference:

D-4233, D-5220, D-5925,
D-8297

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Technology Applications

- Precision cancer therapy for patients with CUL4-high tumors, such as CUL4-high colorectal, breast, lung, and ovarian cancer

Technology Advantages

- CUL4 is overexpressed and linked to tumor progression and metastasis in multiple tumor types, providing for multi-indication development
- CUL4 is a readily measurable biomarker, enabling precision medicine strategies

Supporting Data / Figures

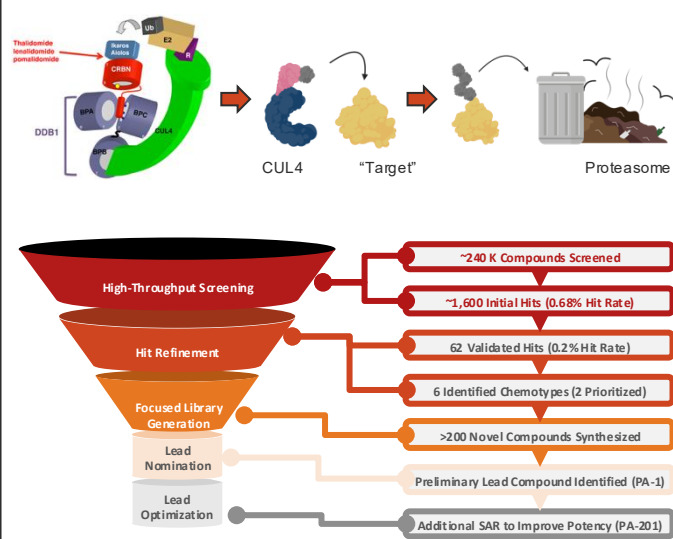


Figure 1: Top: Graphical abstract of CUL4 ubiquitin ligase system
Bottom: Overview of high throughput screening assay and workflow to derive lead CUL4 inhibitor compounds.

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US Patent [10.106.853](#)

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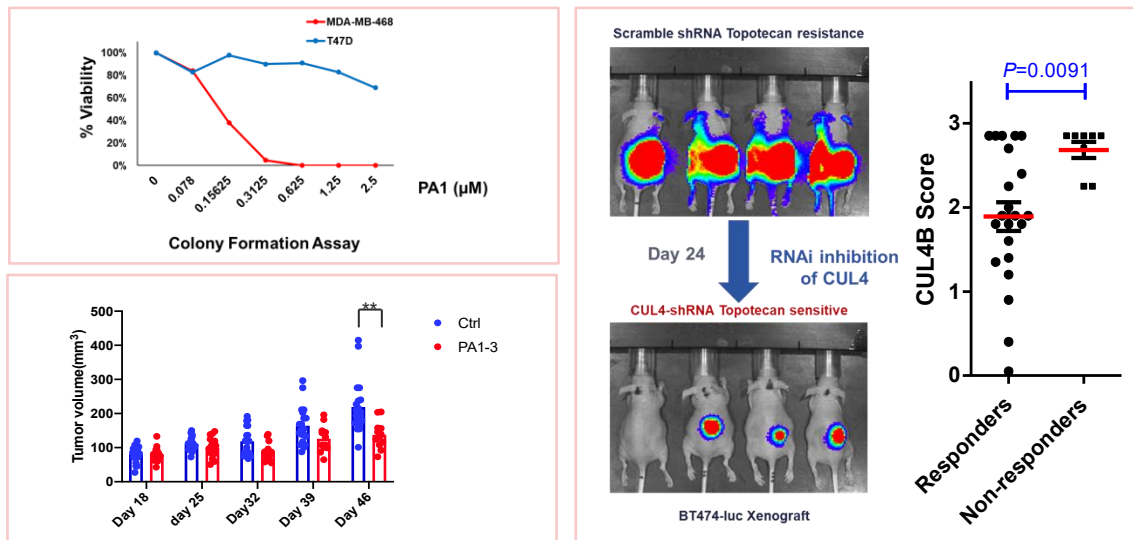


Figure 2: Top Left: CUL4 inhibitors inhibit cell viability in CUL4-high MDA-MB-468 breast cancer cells, but not in CUL4-low T47D breast cancer cells **Bottom Left:** CUL4 inhibitors slow tumor growth in an MDA-MB-468 xenograft mouse model. PA1-3 is a derivative of PA-1. Mice were dosed at 50 mg/kg 3 times per week starting on day 18 **Right:** RNAi inhibition of CUL4 in the BT474 breast cancer xenograft model sensitizes tumors to topotecan chemotherapy.

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