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Hyku: tapping new targets by taking chemoproteomics beyond cysteine

In co-leading Hyku's $56M seed round, RA Capital added to its portfolio of chemoproteomics companies

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Chemoproteomics company Hyku is expanding the druggable proteome with a library of small molecules targeting histidine, tyrosine and lysine residues, and a cell-based screening method that enables the company to quickly determine to which proteins they bind.

Hyku Biosciences Inc. was incubated by RA Ventures, and announced a $56 million seed round last month co-led by RA Capital, Droia Ventures and Novartis Venture Fund.

Milind Deshpande, a venture partner at RA and acting CEO of Hyku, told BioCentury that the last 10-15 years have brought a "renaissance" in small molecule drug development fueled by covalent chemistry. By forming a covalent bond with a target protein, such drugs aren't limited to the standard approach of targeting active sites on enzymes. However, covalent binders have mostly been limited to targeting cysteines within proteins, an amino acid that accounts for only 2% of residues in the human proteome.

"Our quest was to understand if we can selectively target other nucleophilic amino acids such as histidine, tyrosine and lysine," he said. "These amino acids are functionally and structurally a lot richer, they are involved in different biological processes as compared to cysteine, and we can uncover a different part of the proteome if we can target them."

Adding those three amino acids, he said, promised to increase the proportion of the proteome that could be targeted to 14%.

To achieve this, RA Ventures turned to chemistry published by University of Texas at Austin's Ku-Lung (Ken) Hsu, now one of Hyku's scientific co-founders.

In a paper published in 2020, Hsu described a series of sulfonyl triazoles and a sulfur-triazole exchange reaction by which the compounds compounds bound tyrosine residues on proteins. The authors also reported the ability to tweak the reactivity of the triazoles by changing their substituents, and the use of the triazoles to disrupt protein function by specifically bonding with non-catalytic tyrosine and phosphotyrosine in lysates and live cells.

Deshpande said Hyku worked with Hsu to better understand how the electrophilicity of a pharmacophore could be matched with the nucleophilicity of a target amino acid, with the goal of expanding the chemistry beyond sulfur triazoles to target histidine and lysine in addition to tyrosine.

"By adjusting the substituents on the pharmacophores that we use, we can dial up their reactivity or electrophilicity," he said. "These pharmacophores then will react with amino acids that are not so nucleophilic. Where we have enhanced nucleophilicity or reactivity of the amino acids within the microenvironment of the protein, we have chemistries where we can dial down the reactivity or the electrophilicity of these pharmacophores."

Hyku used these structure-activity relationships to build a compound library of small molecules capable of selectively targeting histidine, tyrosine and lysine residues.

The company is now mapping the druggable proteome by incubating the library members with cells and using mass spectroscopy and data analytics to identify which of their constituent proteins are covalently modified.

"We can screen our entire collection of 4,000 compounds in a cell-based experiment in about a week," said Deshpande. "The output that we get is a list of proteins within the cell that are covalently modified. We also know exactly which amino acid is covalently modified. It's a really nice map of the druggable space."

With a map drawn, Deshpande said Hyku uses crystallographic data or AlphaFold to understand where the amino acids targeted by the company's small molecules are located within the three-dimensional structures of the proteins. "If we find there is a deep binding site," said Deshpande, "that is an attractive proposition."

Binding pockets that are amenable to further optimization are an "excellent starting point for medicinal chemistry," he added.

Hyku has profiled the stability of its small molecules in plasma and human liver microsomes, and built quantum mechanical models to help balance their stability in biological fluids with the need for reactivity in the protein microenvironment.

Deshpande said the company is initially focusing on cancer and that it is mapping the druggable proteome of cancer cell lines including ovarian and lung cancers. The company has two lead programs: one for non-small cell lung cancer and one for an undisclosed indication.

RA's Laura Tadvalkar acknowledged the Inflation Reduction Act's bias against small molecules has affected Hyku's target selection.

"The Hyku team worked with our TechAtlas team to identify targets and specific indications where they could innovate while mitigating the worst impacts of the IRAs penalties," she said. "It's a different strategy than a company like Hyku might have taken five years ago, before the IRA. But we still see the opportunity and value in what Hyku is doing in this more focused way."

Several other companies are also developing chemoproteomic platforms, including Belharra Therapeutics Inc., which was co-founded by one of the field's pioneers, Scripps Research's Benjamin Cravatt, who was also behind one of the field's first start-ups, Vividion Therapeutics Inc., which Bayer AG (Xetra:BAYN) acquired for $1.5 billion.

While Vividion was founded to exploit covalent reactions with cysteine residues in proteins, and more recent start-up Matchpoint Therapeutics Inc. is largely following suit, Belharra is using a light-based approach to probe protein interactions that it thinks will work independently of any specific amino acid.

Frontier Medicines Corp., another RA portfolio company, has at least one cysteine-targeting program but has not disclosed the amino acid targets of all its preclinical programs. Frontier is using covalent ligands in cell line screens to identify transient binding sites on hard-to-drug proteins, including sites that are only exposed in disease-specific contexts. The company triangulates the chemoproteomics data with sequencing and structural information to predict which binding sites would make functionally relevant targets.

RA participated Frontier's series A and B rounds, but did not incubate the company as it did in the case of Hyku. Tadvalkar said Frontier introduced RA to the promise of covalent chemistry.

"Covalent chemistry is an evolving and rapidly growing space," she said. "RA will often make multiple bets in spaces that we're really excited about. In this case, it was really a complementary technology that allows Hyku to go after different types of targets and indications."

Tadvalkar noted that Hyku's other investors complement each other. Droia Ventures and Novartis Venture Fund co-led the company's seed round, along with participation from The Mark Foundation for Cancer Research, KB Investment and Eisai Innovation.

"We have a strategic investor in the Novartis Venture Fund," she said. "Droia is a largely oncology focused fund that we've worked with on several deals; they bring a lot of depth of knowledge and relationships" in the cancer space. The Mark Foundation for Cancer Research is a venture philanthropy group that funded some of Hsu's early scientific work and bring "relationships with KOLs in various areas of oncology," while KB is "international" and Eisai another strategic fund, she added.

Deshpande said the $56 million raise would be sufficient to advance a drug candidate to the clinic. A timeline for starting human testing has not yet been disclosed.

COMPANY PROFILE

Hyku Biosciences Inc.
Lexington, Mass.
Technology: Small molecule-based chemoproteomics platform
Origin of technology: University of Texas at Austin, University of Virginia
Disease focus: Cancer
Clinical status: Preclinical
Founded: 2021 by Milind Deshpande and Ku-Lung Hsu
Academic collaborators: University of Texas at Austin
Corporate partners: None
Number of employees: 14
Funds raised: $56 million
Investors: Droia Ventures, Eisai Innovation, KB Investment, Novartis Venture Fund, RA Capital Management, The Mark Foundation for Cancer Research
CEO: Milind Deshpande
Patents: None issued