

## New molecule holds promise in potential therapies for cancer and rare diseases

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Graphical abstract. Credit: *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.110641

Researchers at the University of California, Irvine and the Italian Institute of Technology have developed a new molecule, ALY101, that shows promising anti-cancer activity against a wide range of tumor cell types and in mouse models of a common type of melanoma. The findings, "Structure-based Design of CDC42 Effector Interaction Inhibitors for the Treatment of Cancer," are now published in *Cell Reports*.

The collaboration between Marco De Vivo, Ph.D., director of the Molecular Modeling and Drug Discovery Laboratory at IIT, and the laboratory of Anand Ganesan, Ph.D., MD, professor of dermatology at UCI, integrated computational chemistry approaches and wet biology assay systems at both institutions, resulting in a unique approach to developing drugs that acts to block protein-protein interactions that underpin basic cellular processes including tumor initiation, growth, metastasis and blood vessel formation. These interactions are part of the cellular machinery that can become dysregulated in diseases such as cancer and neurofibromatosis.

Their work focused initially on blocking the interaction of members of the CDC42 family of GTPases with a key kinase, PAK1, which is amplified in breast, colon and other cancers and active in the pathology of rare diseases such as neurofibromatosis and Ewing sarcoma.

"We identified a previously unknown PAK1 binding pocket present only in CDC42, and we used this pocket at the interface between both proteins to disrupt the interaction that would normally lead to PAK1 activation. By blocking this interaction, we can inhibit the excessive



PAK1 activity that drives cellular changes that lead to cancer and other diseases," said De Vivo. "We used computer simulations of both proteins to design compounds able to bind to that pocket and modeled blockade of the interaction between both proteins using a range of simulated compounds that we 'screened' for *in silico* and then synthesized the most promising ones for further experimental tests."

Specifically, the lead compound discovered in the collaboration, ALY101, works by blocking the interaction, which normally converts PAK1 from an inactive to an active state. Other researchers have demonstrated that suppressing or inhibiting PAK1 activity in <u>tumor cells</u> sensitizes them to a broad range of different anticancer agents, enhancing their antitumor activity.

This rational approach for structure-based <u>drug design</u> has been fully integrated with wet biology assay workflows in the Ganesan lab at UCI.

"This compound and the effects of the drug on the tumor and its microenvironment has potential applications both as monotherapy or in combination regimens to reduce dose limiting toxicities of existing agents, or as a treatment for tumors that have developed resistance to other agents" Ganesan said. "In a broader context, these studies provide a roadmap for the rational structure-based design of drugs targeting GTPase family member proteins, known to be an important, but difficultto-target to treat cancer."

These results also have led to the launch of a start-up, Alyra Therapeutics, dedicated to expanding the platform developed by De Vivo and Ganesan and further development of ALY101 and other compounds as new potential treatments for cancer, neurofibromatosis and other diseases where small GTPases and their signaling interactions play a role in disease pathology.



Alyra's lead program, ALY101, was developed from this work and acts to restore normal cell signaling processes that may become dysregulated in patients with certain cancers and rare diseases such as neurofibromatosis type 2.

"We are extremely pleased to see the publication of Dr. De Vivo and Ganesan's work outlining the activity of ALY101," said Mark Benedyk, Ph.D., Alyra President and CEO. "The integrated approach pursued by both labs has efficiently generated multiple compounds that block the CDC42/PAK1 interaction, validating our platform and similar projects are underway to address other small GTPase proteins outside of the CDC42 family. The significance of their discovery with regards to the potential treatment of <u>cancer</u> and neurofibromatosis type 2 cannot be underestimated."

**More information:** Sohail Jahid et al, Structure-based design of CDC42 effector interaction inhibitors for the treatment of cancer, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.110641. www.cell.com/cell-reports/full ... 2211-1247(22)00393-X

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