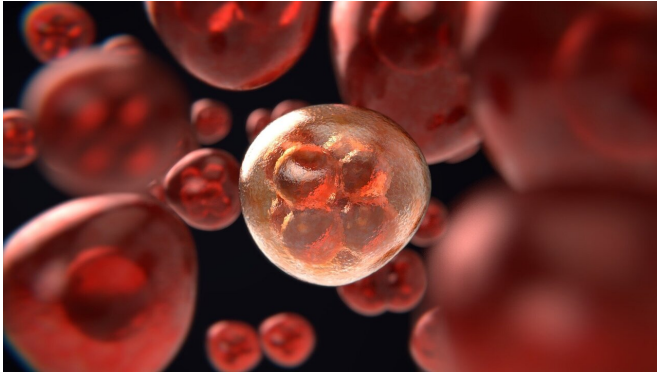


# Scientists identify new target for wide array of cancers

12 August 2020, by Brian Wallheimer



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Many types of human cancers exhibit changes in kinase and phosphatase balances. Drugs that inhibit kinase activity have shown success in the clinic as cancer therapeutics, but the phosphatases still remain a largely underexploited target class due primarily to the lack of understanding of how they cause diseases.

Purdue University's Zhong-Yin Zhang's team has discovered a novel "phosphatase cascade" that plays a critical role in pancreas, liver, kidney, lung, breast, prostate, brain and other types of cancers. Their findings, published today in the *Proceedings of the National Academy of Sciences*, show that a "pro-oncogenic" phosphatase PRL2 exerts its effect by down-regulating PTEN, a tumor-suppressive phosphatase frequently lost in [human cancers](#).

"This suggests that PRL2 could be a cancer drug target," said Zhang, Distinguished Professor of Medicinal Chemistry, the Robert C. and Charlotte P. Anderson Chair in Pharmacology and director of the Purdue Institute for Drug Discovery. "Rather than targeting kinases in the PI3K-AKT pathway, which has seen limited efficacy due to both on-

and off-target side effects, we may be able to inhibit the PRL2 [phosphatase](#) and restore levels of PTEN to suppress tumor formation. That's exciting and could impact many forms of cancer."

Kinases attach [phosphate groups](#) to proteins while phosphatases remove them, and both have the potential to change proteins in ways that turn cells cancerous. Zhang's team showed that PRL2 removes a phosphate from tyrosine 336 in PTEN. When that happens, PTEN is ubiquitinated, or essentially marked for degradation, lowering its levels and ability to fight cancer progression.

The scientists discovered that high PRL2 expression is correlated with low PTEN level and reduced overall patient survival in several human malignancies. When PRL2 was deleted from a cancer-prone, PTEN-deficient mouse model, PTEN levels returned to normal and cancer progression ceased.

"This sheds light on how PRL2 causes [cancer](#) and validates it as a target for PTEN-restoration therapy," said Zhang, who is a member of the Purdue Center for Cancer Research. "It also shows the potential for looking not only to kinases as a way to inhibit tumorigenesis, but also to phosphatases."

Zhang's lab earlier identified a promising method for PRL2 inhibition. PRL2 functions as a trimer, and the molecule Cmdp-43 has been shown to disrupt the ability of PRL2 to come together. Zhang is continuing development of the drug.

**More information:** Qinglin Li et al. Mechanism of PRL2 phosphatase-mediated PTEN degradation and tumorigenesis, *Proceedings of the National Academy of Sciences* (2020). [DOI: 10.1073/pnas.2002964117](#)

Provided by Purdue University

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