



Preclinical Research Supporting a p53-Therapeutics, Inc. Strategy to Overcome Cisplatin Resistance in Head and Neck Cancer

[Providence, Rhode Island, October 14, 2026] – p53-Therapeutics, Inc., a biotechnology company developing a new class of small-molecule cancer therapeutics, today shared a publication of new preclinical research from the El-Deiry Lab at Brown University describing a potential combination strategy to overcome chemotherapy resistance in *TP53*-mutated head and neck squamous cell carcinoma (HNSCC). The study, a preprint by Tian *et al.* available on *bioRxiv*, examines how activating the integrated stress response (ISR) may make cisplatin-resistant cancer cells more vulnerable to apoptosis.

Cisplatin is a standard chemotherapy for patients with HNSCC, but resistance frequently limits its benefit. *TP53* mutations occur in an estimated 65–86% of HNSCC cases, making this a clinically important area for new therapeutic approaches.

In the study, the authors report that the small molecule PG3 and cisplatin acted synergistically in *TP53*-deficient HNSCC cells, reducing cell viability and inducing apoptosis. The researchers identified signaling through the HRI–ATF4–NOXA pathway as central to this effect.

The work uncovered a possible mechanism of treatment adaptation: cisplatin and the PG3-plus-cisplatin combination were associated with reduced ATF4 levels, potentially through degradation mediated by β -TrCP. When the team inhibited β -TrCP1, CK1 δ , or CK2, they blocked ATF4 degradation and increased apoptosis.

““This research reflects our commitment to advancing the scientific understanding of mechanisms relevant to treatment resistance” said Founder and Chairman of p53-Therapeutics, **Wafik S. El-Deiry, M.D., Ph.D., FACP**. “By pairing an ISR inducer with cisplatin and an ATF4-stabilizing strategy, we see an opportunity to address chemoresistance in a biologically defined subset of head and neck cancers.”

The authors propose that triple combinations—an ISR inducer, a DNA-damaging drug such as cisplatin, and an inhibitor of β -TrCP, CK1 δ , or CK2—could produce stronger and more durable anti-tumor effects and help overcome chemoresistance in HNSCC.

The research is a preprint and has not yet been peer reviewed. The findings are preclinical and do not establish safety or efficacy in humans.

Key findings

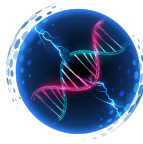
- PG3 and cisplatin synergized to inhibit viability and induce apoptosis in *TP53*-deficient HNSCC cells.
- The effect was regulated through the HRI–ATF4–NOXA pathway.
- Cisplatin activated HRI and contributed to ISR induction through degradation of CReP by the E3 ligase β -TrCP.
- Inhibiting β -TrCP1, CK1 δ , or CK2 prevented ATF4 degradation and enhanced apoptosis.
- The results support further development of triple-treatment strategies for chemoresistant HNSCC.

Read the preprint:

“Integrated stress response activation in combination PG3 and cisplatin-treated *TP53*-mutated head and neck squamous carcinoma cells induces potent apoptotic response,” available at:

<https://www.biorxiv.org/content/10.64898/2026.09.22.752907v1>

<https://p53-therapeutics.com/>



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About p53-Therapeutics, Inc.:

The company's two lead programs, small molecules targeting cancers characterized by *TP53* mutations, are currently being evaluated in Investigational New Drug (IND)-enabling studies. p53-Therapeutics was awarded funding through the Rhode Island New Business Attraction Program to support IND-enabling studies and to facilitate its move to the Rhode Island. The award, provided through the Rhode Island Life Science Hub (RILSH), offers financial support for life sciences companies establishing a presence in Rhode Island. RILSH was established by Rhode Island Governor Daniel McKee and Speaker of the House of Representatives Joseph Shekarchi, in 2023 with a \$45 million investment in the life sciences, and a mandate to create business development opportunities for companies, and develop much-needed wet lab incubator spaces. p53-Therapeutics is a **foundational tenant at Ocean State Labs, powered by Portal Innovations**. The company has laboratory space and office space for its workforce and looks forward to becoming part of the vibrant life sciences ecosystem in Rhode Island. The company is collaborating with Provid Pharmaceuticals for large scale drug synthesis as well as numerous analogs of lead compounds in the p53-Therapeutics pipeline.



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p53-Therapeutics, Inc. is developing a new class of small molecule cancer therapeutics to effectively bypass mutations in the p53 tumor suppressor gene to treat patients with cancer. *TP53* mutations occur frequently across tumor types. *TP53* is mutated in most human cancers and at an even higher frequency among difficult to treat cancers and in patients that fail first-line therapies. Particularly high mutation rates occur in head and neck, ovarian, colorectal, lung and brain cancer, among others. P53-Therapeutics uses a novel approach with candidate drugs that biochemically and functionally replace this most important cancer suppressor to address therapy resistance in the clinic. The Company is developing molecules to target a broad range of p53-mutated cancers based on compelling pre-clinical safety, efficacy and biomarker data with line of sight to IND filing and strong IP position.