Innovations
UNIVERSITY OF COLORADO
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Improving Cisplatin and Carboplatin Treatment Outcomes via NPEPPS inhibition

Product

Small molecule inhibitor

Indication

Cancers treated with platinum-based drugs

Value Propositions

- Novel biomarker for cisplatin-resistant cancer
- New and more tolerable treatment strategy than conventional chemo alone

Market

- $3.4 billion—Global bladder cancer market (4% CAGR 2021-2028)

Intellectual Property

- Provisional Patent Filed*
- Available for licensing

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Background on CU5509H

Platinum-based chemotherapeutics have a long history with successful applications in testicular, ovarian, bladder, head and neck, and lung cancers. Bladder cancer (BCa) in particular accounts for 430,000 new diagnoses and 170,000 deaths worldwide annually. Cisplatin-based combination chemotherapy, in the form of gemcitabine plus cisplatin (GemCis) or Methotrexate, Vinblastine, Adriamycin, and Cisplatin (MVAC), remains the first-line, standard of care for metastatic BCa. However, these drugs only provide a 5-10% cure rate and come with dose-dependent side effects that limit patient eligibility. Additionally, chemoresistance mechanisms can arise, reducing the efficacy of these drugs. A recently discovered mechanism of response is the import of platinum drugs through volume regulated anion channels (VRACs). One specific mechanism of cisplatin and carboplatin resistance discovered by University of Colorado researchers is through upregulation of puromycin-sensitive aminopeptidase, NPEPPS. NPEPPS binds to VRACs to prevent the import of cisplatin and carboplatin, thus making cells resistant to platinum drugs. This discovery represents the first therapeutically targetable mechanism to control platinum drug import through VRACs. While the focus is on BCa, the mechanism is applicable to any cancer that is treated with platinum-based drugs.

Technical Innovation

Pharmacological inhibition of NPEPPS through an orally deliverable, well-tolerated FDA-approved aminopeptidase inhibitor, Tosedostat, re-sensitizes resistant cells to cisplatin treatment in BCa cell lines and organoids derived from patient tumors that did not respond to cisplatin-based chemotherapy. Thus, this represents a novel treatment regimen where Tosedostat, or another aminopeptidase inhibitors, can be given in combination with platin-based chemotherapy to provide better patient response to chemotherapy and potentially improve patient outcomes and lower the doses necessary for treatment.

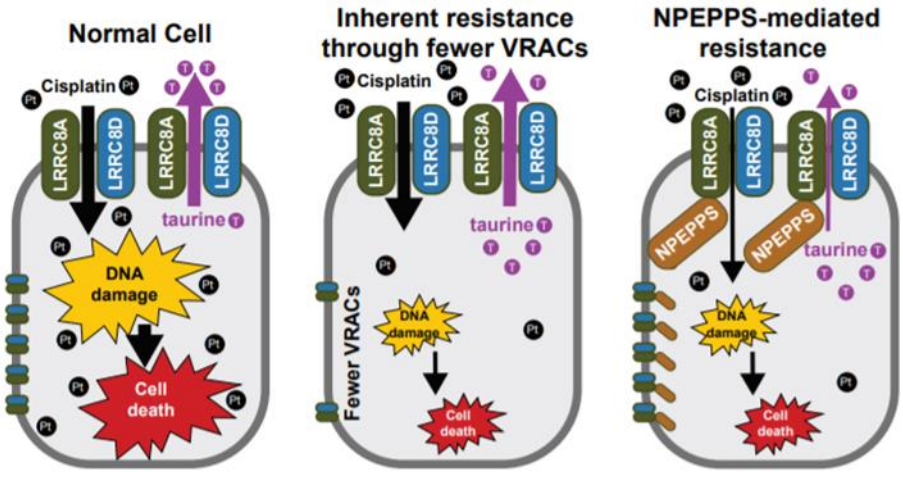

Figure: Model of NPEPPS-mediated cisplatin resistance. Normal functioning cells will import cisplatin through the volume regulated anion channels (VRAC), with LRRC8A and LRRC8D being the primary subunits. A mechanism of cisplatin resistance is to inherently down-regulate VRACs. We propose that NPEPPS interacts with LRRC8A or LRRC8D directly to decrease VRAC activity, which prevents export of taurine and import of cisplatin, hence driving cisplatin resistance.

*Provisional Patent:—"Compositions and methods for improved treatment of platinum-based chemotherapeutic resistant tumors"—Filed February 2021.