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For Immediate Release.

Drug candidate PAWI-2 fights drug-resistant pancreatic cancer stem cell tumors.

San Diego, Calif., May 27, 2024 – A collaborative team at the Human BioMolecular Research Institute **(**HBRI) utilized a grant award from The Conrad Prebys Foundation to continue to develop a drug candidate that potently inhibits drug resistant human pancreatic cancer stem cell proliferation and inhibits metastasis and relapse via a novel mechanism.

Worldwide, pancreatic cancer is a major health problem and almost 0.5 million people were diagnosed with pancreatic cancer in 2020. In the United States, more than 64,000 adults will be diagnosed with pancreatic cancer in 2023. Pancreatic cancer is highly resistant to currently available treatments. Current standard of care chemotherapies causes serious side effects. Most pancreatic cancer patients are resistant to clinical therapies. Combination therapy has showed superior efficacy over single-agent treatment. However, most therapy has failed to show a significant improvement in overall survival due to treatment-related toxicity. Developing efficacious clinically useful pancreatic cancer therapies remains a challenge. We showed the efficacy of an innovative pathway modulator, **p**53-**A**ctivator **W**nt **I**nhibitor-**2** (PAWI-2) against tumors arising from human pancreatic cancer stem cells (i.e., hPCSCs, FGβ_3 cells). PAWI-2 is a potent inhibitor of tumor growth. We showed PAWI-2 potently inhibited growth of tumors from hPCSCs in orthopic xenograft models of both male and female mice. PAWI-2 worked in a non-toxic manner to inhibit tumors. Compared to vehicle-treated animals, PAWI-2 modulated molecular regulators of tumors. Anti-cancer results showed PAWI-2 *in vivo* efficacy was correlated to *in vitro* potency to inhibit FGβ_3 cells. PAWI-2 represents a safe, new approach to combat pancreatic cancer.

Small molecules like PAWI-2 are important in exploration of intracellular pathways involved in normal and pathological processes. Molecular pathway signaling plays a central role in tissue maintenance and cancer. This report showed a that PAWI-2 was efficacious to block proliferation of pancreatic cancer stem cell-derived tumors *in vivo*. The paper was featured in the journal *New Investigational Drugs.*

The work is important because drug-resistant pancreatic cancer is one of the most lethal diagnoses that an oncology patient faces and is increasing in prevalence. Pancreatic cancer soon will be the second leading cause of cancer-related death in the United States. Pancreatic cancer mortality is increasing because many therapeutics are ineffective or prone to drug resistance, and surgical intervention only addresses a small percentage of patients. As a result, new medications for drug-resistant pancreatic cancer and other cancers are urgently needed.

Medicinal chemists and stem cell biologists at the Human BioMolecular Research Institute (HBRI), in San Diego, CA, have reported on a compound that revealed a molecular cascade linking signaling through Wnt and p53 to the regulation of TCF/LEF transcriptional activation. This may have importance for tissue morphogenesis and anti-cancer drug discovery efforts.

Writing on May 26, 2024, in the journal *New Investigational Drugs*, the study used small molecule PAWI-2 to inhibit pancreatic cancer tumor proliferation *in vivo*. PAWI-2 showed a mechanism involving mitotic assembly stress to modulate Wnt signaling.

"*The finding that mitotic stress or DNA damage regulates Wnt responsiveness is important because it explains why stressed cells cannot regenerate and heal tissue damage*" explains co-author Emily Cashman. "*By blocking the ability to respond to Wnt signaling, cellular stress prevents cells from migrating, replicating and differentiating. This impacts cancer cell proliferation*."

The report describes *in vivo* efficacy of PAWI-2 against pancreatic cancer stem cell tumors. An initial "hit" compound was identified in a high throughput screen of ~76,000 drug-like compounds designed to regulate the ability of Wnt/β-catenin to induce target genes. PAWI-2 was developed based on an extensive structure-activity relationship study for inhibition of Wnt3a in HEK293T cells. After numerous rounds of medicinal chemical refinement, PAWI-2 was developed. PAWI-2 is more potent than the original "hit" compound and has many advantages in terms of improved pharmaceutical properties. In other published studies, PAWI-2 has been shown to potently inhibit colon, prostate, and breast cancer *in vitro* and *in vivo*.

"*PAWI-2 may lead to treatment applications in a whole host of cancers that may prove efficacious in clinical trials*"… explains co-author Dr. John Cashman. "*As anti-cancer PAWI-2 drug development progresses, we expect PAWI-2 to be less toxic than current therapeutics for pancreatic cancer, and patients will benefit from improved safety, less side effects and possibly with significant cost-savings."*

How the compound works

Chemists and biologists at HBRI are among the first group to design, synthesize and apply small molecule PAWI-2 to afford a pharmacologically active compounds efficacious against pancreatic cancer stem cell tumor proliferation *in vivo*. PAWI-2 blocks Wnt signaling and simultaneously activates p53. PAWI-2 interacts at diverse cell process points from DNA replication to cell motility and cytoarchitecture that play key roles in development, tissue

homeostasis, and disease including cancer. Revealing links between PAWI-2 functional activity, Wnt inhibition and p53 induction might be fundamentally important in cancer prevention.

Publication

"Effect of PAWI-2 on pancreatic cancer stem cell tumors." Cashman JR, Cashman EA. *Investigational New Drugs,* 2024:10.1007 [PMID: 38789849 DOI: 10.1007/s10637-024-01447-x]

Media contacts: To arrange on-site, phone, or Skype interviews with the researchers involved in this study, please contact John Cashman at HBRI (858) 458-9305 or JCashman@hbri.org.

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"We need to develop effective new medications for drug resistant pancreatic cancer," said John Cashman, Ph.D., President of the Human BioMolecular Research Institute. "Using a non-toxic small molecule drug candidate to kill pancreatic cancer stem cells either by itself or in combination with standard of care chemotherapy is very appealing."

About Human BioMolecular Research Institute
The Human BioMolecular Research Institute is a non-profit research institute conducting basic research focused on unlocking biological and chemical principles related to diseases of the human brain and cancer. The Institute conducts fundamental studies of central nervous system disorders and cancer including stem cell approaches and translates findings into new drug development to address human illness. In addition, the Institute promotes scientific learning through community service and public access by disseminating information and sharing research with collaborators, colleagues and the public. For more information, visit us at www.HBRI.org.

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