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For Immediate Release.

"Pancreatic cancer drug-sensitivity predicted by synergy of PAWI-2 and protein biomarker expression"

Potent inhibitor of pancreatic cancer stem cells that synergizes current standard of care, **PAWI-2** is featured in *Investigational New Drugs.*

San Diego, Calif., September 16, 2020 - Researchers at the Human BioMolecular Research Institute and ChemRegen, Inc., reported that a small molecule potently inhibited pancreatic cancer stem cells and also synergized standard of care drugs. Publishing September 15, 2020, in the journal *Investigational New Drugs*, the team describes how they tested **PAWI-2**, a man-made, drug-like chemical that can be used to inhibit pancreatic cancer stem cells and other cancer. The researchers discovered PAWI-2 acted as a synergist to make heretofore poorly potent drugs that previously did not show much efficacy in humans work much better in *in vitro* studies.

Pancreatic cancer will soon be the second leading cause of cancer-related death for individuals in the United States. Pancreatic cancer is one of the most lethal diagnoses that oncology patients face and is increasing in prevalence. Pancreatic cancer is known to be highly resistant to currently available treatments. Surgical resection with negative margins is the only potentially curative treatment for pancreatic cancer, but only 15%–20% of patients with pancreatic cancer are eligible for resection at initial diagnosis. The remaining pancreatic cancer patients usually have metastatic or locally advanced disease that generally is considered incurable.

Most of the drugs approved by the United States Food and Drug Administration (FDA) for pancreatic cancer including capecitabine, erlotinib, 5-fluorouracil, gemcitabine, irinotecan, nab-paclitaxel, oxaliplatin, etc., are generally chemotherapies. Unfortunately, pancreatic cancer oftentimes becomes resistant to these therapies.

"We need to develop effective new medications for drug resistant pancreatic cancer," said John Cashman, Ph.D., President of Human BioMolecular Research Institute and co-author of the

study. “Using a non-toxic small molecule like **PAWI-2** to stop pancreatic cancer either by itself or in combination with standard of care chemotherapy is very appealing.”

Dynamic medicinal chemistry afforded PAWI-2

A team of medicinal chemists at the Human BioMolecular Research Institute, led by John Cashman, Ph.D., using dynamic medicinal chemistry, developed the compound **PAWI-2**. When added to pancreatic cancer stem cells, **PAWI-2** potently stimulated inhibition of pancreatic cancer stem cell proliferation. When combined with standard of care, PAWI-2 markedly synergized the effect of drugs that previously were observed to be ineffective. This surprising effect was particularly potent against pancreatic cancer stem cells. **PAWI-2** has the ability to rescue the potency of drugs (i.e., erlotinib, trametinib) and inhibit pancreatic cancer stem cell growth. This may have clinical applications.

“At this point, **PAWI-2** appears to have all the properties for a new therapeutic drug candidate for drug resistant pancreatic cancer,” explained Jiongjia Cheng, Ph.D., a researcher in Cashman’s lab and lead author of the paper. “It also makes previously ineffective drugs much more potent in vitro”.

Cashman and Cheng in collaboration with other scientists are now working with San Diego biotech company ChemRegen, Inc. to further develop **PAWI-2** into a therapeutic drug candidate.

How PAWI-2 works

Developing new medications for drug-resistant pancreatic cancer and other cancers is important. Currently, pancreatic cancer is the third most common cause of cancer in the United States but in the near future, it will be the second most common cause of cancer because its incidence is increasing. For pancreatic cancer, the difficult part is: 1) figuring out the cellular signals that direct cancer growth and 2) understanding the basis for resistance to current cancer therapies.

PAWI-2 works as a non-toxic DNA damage pathway inhibitor and activates mitochondrial-controlled p53-dependent apoptotic signaling. Apoptosis is a process that tells the cell when to stop dividing and it influences other cell behaviors, such as proliferation and differentiation. With apoptosis signaling potently turned on, cancer cells are set on a course toward destruction and removal. **PAWI-2** activated apoptosis proteins in mitochondria and chokes cell proliferation, ultimately altering cellular behavior - in this case decreasing pancreatic cancer stem cell growth.

Key molecular regulators of **PAWI-2** could be used to predict synergistic/antagonistic effects between **PAWI-2** and other anti-cancer drugs. Anti-cancer studies showed potency could be quite accurately correlated to phosphorylation of optineurin (OPTN) in PC cells. Synergism/antagonism was also associated with inhibition of pancreatic cancer stem cell marker SOX2 that was observed in these cells. Synergism broadens the potential use of PAWI-2 as an adjunct chemotherapy in patients with pancreatic cancer that have developed resistance to first-line targeted therapies or chemotherapies.

In this report, it was shown that anti-cancer **PAWI-2** is an anti-pancreatic cancer stem cell compound that works against drug-resistant pancreatic cancer stem cells. **PAWI-2** synergized clinically used erlotinib or trametinib in *in vitro* inhibition of drug resistant pancreatic cancer stem cells. **PAWI-2** may afford more efficacious treatment with decreased side effects and also afforded a molecule for both stand alone and combination pancreatic cancer treatment.

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

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The study was authored by Jiongjia Cheng and John Cashman, Human BioMolecular Research Institute. The paper can be found at: (https://doi.org/10.1007/s10637-020-00998-z)

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, cardiovascular disease and cancer. The Institute conducts fundamental studies of central nervous system disorders, heart disease 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.

About ChemRegen Inc.
ChemRegen is a for-profit company doing research directed at identifying small molecules of use for addressing human diseases. The approach is to develop regenerative medicines to work in conjunction with human stem cells to cure major human diseases including heart disease, cancer and other diseases. For more information, visit www.ChemRegen.com.