

Human BioMolecular



Research Institute

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For Immediate Release

PAWI-2 overcomes tumor stemness and drug resistance via cell cycle arrest in integrin β_3 -KRAS-dependent pancreatic cancer stem cells

Small molecule PAWI-2 potently ameliorates drug-resistant human pancreatic cancer stem cells, featured in *Scientific Reports* (a *Nature* research publication).

San Diego, California., June 8, 2020 – Researchers at the Human BioMolecular Research Institute and ChemRegen, Inc., have reported on a small molecule p53 Activator Wnt Inhibitor-2 (PAWI-2) that potently inhibits human pancreatic cancer stem cells. Writing June 8, 2020 in the journal *Scientific Reports*, the team describes how they tested PAWI-2, a synthetic, drug-like compound that can be used to decrease human pancreatic cancer.

“Pancreatic cancer remains a major health problem in the United States and soon will be the second most common cause of mortality due to cancer. A majority of pancreatic cancer patients are often resistant to clinical therapies. Thus, it remains a challenge to develop an efficacious clinically useful pancreatic cancer therapy” said Jiongjia Cheng, Ph.D., lead author of the study. “Using a non-toxic small molecule to decrease pancreatic cancer is very attractive.”

Medicinal chemistry leads to safe anti-cancer drug

In earlier studies, the research team reported on the small molecule that was useful against prostate, breast, colon and pancreatic cancer that might one day become a drug therapy to treat other cancers. Now, Drs. Jiongjia Cheng and John Cashman at ChemRegen and the Human BioMolecular Research Institute, respectively, showed a molecule called PAWI-2 is useful to kill human pancreatic cancer stem cells. When added to human pancreatic cancer stem cells, PAWI-2 potently ameliorated drug-resistant human pancreatic cancer stem cells. When PAWI-2 was added to pancreatic

cancer stem cells with erlotinib (a standard of care therapy) PAWI-2 enhanced inhibition by erlotinib on cell viability and self-renewal capacity, compared to erlotinib alone. Analysis showed a dose-dependent inhibition of cell viability for PAWI-2 alone or a PAWI-2-erlotinib combination. PAWI-2 synergized erlotinib's effects on pancreatic cancer stem cells. PAWI-2 made erlotinib much more effective. The findings showed PAWI-2 is a new approach to reverse tumor stemness that can re-sensitize human pancreatic cancer stem cells to drug inhibition.

“In the future, this molecule could be used alone or with other chemotherapy albeit at lower doses, as a new therapeutic drug to combat pancreatic cancer. This may lead to much less toxicity to the patient,” explained Jiongjia Cheng, Ph.D., a researcher in Cashman’s lab and lead author of the paper.

Cheng is working with San Diego non-profit Human BioMolecular Research Institute, to further develop PAWI-2 into a therapeutic drug.

How PAWI-2 works

Development of new medications for pancreatic cancer and other cancers is important. Pancreatic cancer is the third most common cause of cancer death. Despite its prevalence, therapeutic options for pancreatic cancer are limited to surgery and/or combination chemotherapy and radiotherapy. Due to drug resistance and drug-induced side effects, first-line chemotherapies have made minimal impact on pancreatic cancer treatment.

Cancer stem cells are hallmarks of cancer and inherently resistant to medical therapy. Cancer stem cells become enriched in humans following chemo- or radiotherapy. This implicates cancer stem cells as key contributors to tumor dormancy, metastasis, and relapse. These functional features of cancer stem cells make them different from bulk tumor cells and enable cancer stem cells to initiate and maintain tumor development from tumor cells present in a malignant tumor.

For pancreatic cancer, like other cancers, the challenging part is figuring out the cellular pathways that direct cancer growth and how these pathways can be interrupted and halted. A non-toxic chemical that inhibits key cancer-promoting pathways is a very promising strategy.

Given the important role of human pancreatic cancer stem cells in pancreatic cancer, a novel treatment strategy that targets pancreatic cancer stem cells or their extrinsic and intrinsic molecular pathway regulators could be of significant clinical utility to treat pancreatic cancer. PAWI-2 kills drug-resistant human pancreatic cancer stem cells and synergizes erlotinib by targeting a molecular pathway named optineurin and causes optineurin-dependent cancer cell cycle arrest. Development of PAWI-2 as an anti-PC drug candidate addresses an unmet clinical need. PAWI-2 may also improve standard of care for patients because it synergizes eradication of human pancreatic cancer stem cells.

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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 co-authored by Jiongjia Cheng, Human BioMolecular Research Institute and ChemRegen Inc.; and John Cashman, Human BioMolecular Research Institute.

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 stem cells to cure major human diseases including heart disease, cancer and other diseases. For more information, visit www.ChemRegen.com.