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Preventing post-ERCP pancreatitis with a combination of small molecules

Stanford researchers are developing an improved prophylactic against pancreatitis caused by endoscopic retrograde cholangiopancreatography (ERCP), by targeting two key inflammatory pathways. ERCP is a common gastrointestinal procedure that leads to pancreatitis in 3-15% of patients. Post-ERCP pancreatitis can be life-threatening, excruciatingly painful, and costly. Patients and healthcare providers would both benefit from more effective and practical pancreatitis prevention, beyond the current options of indomethacin, stenting, and IV hydration.

The inventors have discovered that calcineurin inhibitors prevent post-ERCP pancreatitis by blocking pressure-induced inflammatory signals. Additionally, a calcineurin inhibitor could be combined with indomethacin to target two distinct inflammatory pathways, achieving higher effectiveness than indomethacin alone. The inventors are formulating this combination for rectal administration to target pancreatic circulation via the portal vein. This method can be smoothly incorporated into ERCP procedures, because rectal indomethacin is the standard-of-care in many facilities.

Stage of Development: Preclinical studies in a mouse model of ERCP showed that calcineurin inhibitors lowered pancreatic inflammation, edema, and tight junction disruption when delivered systemically, intraperitoneally, or via radiocontrast solution.

Applications

- Prophylactic given rectally before any ERCP to prevent pancreatitis

Advantages

- Targets two key inflammatory pathways for greatly increased efficacy over indomethacin alone
- Safer and less time consuming than pancreatic duct stenting and IV hydration
- Minimally invasive rectal delivery directly targets pancreatic circulation
- Easy to implement during ERCP, replacing standard-of-care rectal indomethacin
- Both component drugs are FDA-approved for other indications

Publications

- Orabi et al. Cellular and Molecular Gastroenterology and Hepatology (2017) "Targeted Inhibition of Pancreatic Acinar Cell Calcineurin Is a Novel Strategy to Prevent Post-ERCP Pancreatitis"
- Wen et al. Gastroenterology (2018) "Transient High Pressure in Pancreatic Ducts Promotes Inflammation and Alters Tight Junctions via Calcineurin Signaling in Mice"

Patents

- Published Application: WO2021236222
- Published Application: 20230201171

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