Abl kinase inhibitors promote lung regeneration after pathogen and chemical-induced injury

Duke LICENSING & VENTURES

Value Proposition

Damage to the lung epithelium in response to pathogens is a major health problem worldwide. Parenchymal lung infections disrupt lung epithelial architecture and function by eliciting destruction of airway and alveolar cell populations. Currently there are no approved drugs that directly prevent or repair epithelial cell damage following pathogen-induced lung injury. Therapeutic strategies to protect or promote lung epithelial cell regeneration following injury could profoundly improve patient outcomes when used in combination with antibiotics and supportive care, particularly in the context of infections caused by viruses or resistant bacterial strains. This invention describes a novel treatment strategy for promoting lung repair after injury, a finding that could profoundly reduce mortality after respiratory infections or chemical exposure.

Technology

Duke inventors have reported a novel therapeutic method intended to treat lung epithelium damage. They have discovered a previously unknown role for Abelson (Abl) kinases in the regulation of regeneration in the lung epithelium after pathogen-induced injury. The Abl kinases, Abl1 and Abl2, are a family of non-receptor tyrosine kinases that regulate a wide variety of cellular processes during development and normal homeostasis, but can have deleterious effects on cell survival, proliferation, and cell-cell junction adhesion upon their upregulation following inflammation, tumorigenesis, and oxidative stress. The inventors discovered, using in vitro and in vivo models, that genetic and pharmacological inactivation of Abl kinases mobilizes secretory cells from the distal airway and bronchioalveolar duct junction to promote the expansion of double-positive SCGB1A1+ SPC+ cells leading to enhanced regeneration of the damaged lung alveolar epithelium following bacterial infection induced by live S. aureus and other bacterial and viral pathogens. This technology has been demonstrated with mouse models.

COVID-19 Application

This technology has been demonstrated in mouse models of pathogen-induced lung injury, and has shown that these effects are mediated by a dramatic expansion of progenitor lung epithelial cells that induce lung regeneration after pathogen infection (viral and bacterial). Thus, the ABL kinase inhibitors may have dual

Duke File (IDF)

T-006369

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effects by targeting the virus (including coronavirus) and also promoting regeneration of the host lung epithelium. A 2018 publication from Machamer and colleagues supports the applicability of this technology as an antiviral for coronavirus.

Advantages

- There are currently no FDA-approved treatments for improving respiratory tract injury repair and this invention could be a first in class therapy for such repair
- Abl kinase inhibitors have already been approved for other indications

Publications

- ABL kinase inhibition promotes lung regeneration through expansion of an SCGB1A1+ SPC+ cell population following bacterial pneumonia (PNAS, 2019)
- Coronavirus S protein-induced fusion is blocked prior to hemifusion by Abl kinase inhibitors (Journal of General Virology, 2018)