Washington University in St. Louis
Office of Technology Management

NOVEL KINASE INHIBITOR DRUGS TO TREAT RESPIRATORY DISEASE OR BREAST CANCER

Alevy, Yael, Brett, Thomas, Holtzman, Michael, Patel, Anand, Patel, Dhara, Romero, Arthur
Miller, Qian

T-011991

Disease indications:

- Respiratory diseases - COPD, asthma, bronchitis, cystic fibrosis and other inflammatory airway diseases
- Breast cancer

Drug format: small molecule

Drug class: first in class

Research stage and Preliminary data:

Preclinical development of the lead compound for respiratory disease includes in vitro and in vivo efficacy, selectivity and initial toxicity testing. Preclinical development of the lead compound for breast cancer includes in vitro efficacy and initial toxicity testing.

- Lead optimization and identification – The inventors performed initial studies with compounds based on the patented first generation scaffold. They synthesized second generation compounds and identified one lead compound and two back-up compounds that were more potent (IC50 values in pM range) and had more selective inhibition (custom kinase panel selectively inhibited MAPK13 an MAPK14 targets).
- SAR – The inventors solved the x-ray crystal structure to define the structure activity relationship for these compounds.
- Toxicity studies – The inventors performed studies in human and porcine cell cultures with no evidence of toxicity until mM concentrations.
- ADMET – The inventors demonstrated favorable results from in vitro ADMET assays of microsomal stability and Caco-2 permeability.
- In vivo PK – The inventors performed in vivo PK analysis in rats and mini-pigs with intravenous and oral dosing. The lead compound demonstrated highly favorable Cmax and AUC values in mini-pig with oral dosing at 2 mg/kg, with no observed side effects.
- In vivo efficacy for respiratory disease – The inventors used a pig model to demonstrate effectiveness for blocking inflammatory mucus production without toxicity.
- Pre-IND for respiratory disease – The inventors have begun to construct a pre-IND package for review by the FDA, including a Phase 1 safety study for oral dosing and a Phase 2 proof-of-concept study for inhibition of mucus production in response to nasal allergen challenge or nasal viral infection.
- In vitro efficacy for breast cancer – The inventors demonstrated that nM concentrations of the inhibitors blocked cell growth of breast cancer cell lines (including hormone-negative and HER2

negative lines) without toxicity.

Target: Mitogen-activated protein kinase 13 **(**MAPK13, also known as p38d-MAPK) and MAPK14

Background:

Morbidity and mortality from chronic respiratory diseases such as COPD (chronic obstructive pulmonary disease) and asthma is closely linked to excess mucus production that blocks the airways and prevents normal breathing. In addition, acute respiratory illness from viral infection also activates the pathway to mucus production. However, there are no effective treatments that specifically address the pathogenic overproduction of airway mucus.

Excess mucus is likely due to increased biosynthesis and secretion of the secretory mucins (particularly MUC5AC and MUC5B) that are the major macromolecular constituents of airway mucus. The MAPK13 and MAPK13-14 inhibitors described here target the signaling pathway that leads to excess mucin production in the airway epithelium. Testing the same molecules for breast cancer indications is based on the finding by other researchers that MAPK13 (aka P38 delta MAPK) plays a role in breast cancer progression and lung metastasis.

Keywords: respiratory disease, breast cancer, chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, rhinitis, mucus, kinase inhibitor, MAPK13, p38 delta-MAPK, MAPK14, chronic lung disease

Mode of action:

The inventors defined a signaling pathway from chloride channel calcium activated 1 (CLCA1) to MAPK13 to MUC5AC that is responsible for IL-13 driven mucus production in human airway epithelial cells. Through structural analysis of MAPK13, they designed a set of first generation of small molecular weight compounds that selectively inhibit MAPK13 with high potency. Further validation studies showed that these molecules reduced mucus production by blocking this key checkpoint in the mucus pathway. Therefore, MAPK13 offers a therapeutic approach directly preventing mucus overproduction in inflammatory respiratory disease, offering a treatment to avoid associated morbidity and mortality.

Building on their initial work and early scaffold design, the inventors developed second generation compounds optimized for clinical development. These agents included small molecules that are selective for MAPK13 as well as inhibitors of both MAPK13 and MAPK14. The newer lead compounds are more selective and more potent than the first generations. Furthermore, they have demonstrated efficacy for lowering mucus production in respiratory indications as well as reducing cell growth in breast cancer cell lines.

Competitive edge:

- **Selective inhibition –** demonstrated specificity for MAPK13 and MAPK13-MAPK14 target is likely to minimize side effects from off-target effects
- **Potent -** IC50 values in pM range
- **Unmet medical need –** targets the underlying cellular and molecular mechanism that causes morbidity in a range of respiratory conditions

Patent status

- Anti-mucus drugs and uses therefor (U.S. Patent No. 9187470) – patented 1st generation scaffold, WUSTL Case #T-011991

- U.S. patent application filed on 2nd generation lead compounds, WUSTL Case# T-018607

Publications

- Gerovac, B. J., Yantis, J., Brody, S. L., Keeler, S. P., & Holtzman, M. J. (2018). MAPK13 induction co-locates with MUC5AC to mucin granules. *Am J Respir Crit Care Med*, 197, A1308.
- Alevy, Y. G., Patel, A. C., Romero, A. G., Patel, D. A., Tucker, J., Roswit, W. T., ... & Holtzman, M. J. (2012). IL-13–induced airway mucus production is attenuated by MAPK13 inhibition. *The Journal of clinical investigation*, 122(12), 4555-4568.
- Drugs limiting excess mucus could save lives, *The Source*, Nov. 26, 2102.

Related publication for breast cancer application

- Wada, M., Canals, D., Adada, M., Coant, N., Salama, M. F., Helke, K. L., ... & Hannun, Y. A. (2017). P38 delta MAPK promotes breast cancer progression and lung metastasis by enhancing cell proliferation and cell detachment. *Oncogene*, 36(47), 6649.