A new oral drug for asthma treatment
The leadership team is expert in asthma/lung physiology, medicinal chemistry, drug development, & clinical medicine

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The program has received generous funding:
A novel asthma strategy: target GABA$_A$ receptors in the lung

Innovation:
- New molecular entities
- Small molecule (positive modulators)
- Oral delivery
- First line therapy
- No steroids
- Better compliance
Pending patents claiming novel drug compositions and uses

Columbia/UWM Research Foundation patents on novel asthma treatment

PCT [8/2017 submission]
Inventors: Arnold, Alexander E.; Stafford, Douglas C.; Cook, James M.; Emala, Charles W.
Title: Novel GABA(A) receptor modulators and methods to control airway hyperresponsiveness and inflammation in asthma.
Claims: 35 claims pending on novel drug compositions and methods of use

PCT/US2013/060859 Filed: Sept. 20, 2013
Inventors: Stafford, Douglas C.; Cook, James M.; Arnold, Alexander E.; Emala, Charles W.; Gallos, George, and; Stephen, Michael Rajesh.
Title: Novel GABAA agonists and methods of using to control airway hyper-responsiveness and inflammation in asthma.
Claims: 13 claims pending on novel drug compositions and methods of use
A compelling opportunity for improved asthma treatment

The Opportunity

- Chronic disease economics with large global prevalence
- Current first-line drugs have safety/efficacy liabilities
- Current inhaler medications have compliance liabilities
- Differentiated product – new drug composition, no inhaler
- Developing for first-line asthma indication
- Patents pending on compositions and therapeutic uses
The innovation

- Fundamentally novel asthma drug target identified
- Target has been safely drugged for other indications
- No use of steroids or $\beta_2$-adrenergic agonists
- Drug design is a small molecule for oral dosing
- Development team is recognized as experts in target/compound class
- Several well-characterized leads
- Leads have good animal safety, pharmacokinetics, and lung exposure
- Efficacy has been demonstrated in established animal disease models
- Compound class has low cost of manufacturing

A ground-breaking approach in targeting and compound design

The innovation
Asthma is a growing healthcare challenge

- 25 million Americans (~8% of population; 2015 data)
- Most common chronic disease in children
- Over 2 million emergency room visits
- More than $56 billion US disease burden

Content source: National Center for Environmental Health
Lung inflammation and airway smooth muscle hyperresponsiveness are hallmarks of asthma

Asthma features targeted by treatment:

- Inflammation (excess mucus)
  - corticosteroids
  - leukotriene receptor antagonists
- Airway smooth muscle constriction
  - $\beta_2$-adrenergic agonists
Objectives of asthma treatment:

- Reduce impairment
  (frequency and intensity of symptoms)
- Reduce risk
  (likelihood of future asthma attacks, progressive decline, and medication side effects)
But, asthma is not well controlled

According to the "Real-World Evaluation of Asthma Control and Treatment" (REACT) study, more than half (55 percent) of Americans with moderate-to-severe asthma self reported they do not have their asthma symptoms under control despite the fact that most had health insurance and regular doctor visits.
Limitations of current asthma therapies

- Disease resistance (ICS)
- Imprecise use/poor compliance (inhalers)
- Growth delay, osteoporosis, cataract formation, adrenal suppression, infection, dysphonia, cough, throat irritation (ICS, oral CS)
- Poor efficacy (LTRA)
- Toxicity of lipox5 inhibitors (Zileuton)
- Plasma monitoring (theophylline)
- “Black Box” warning (LABAs)

Biologics
- Can be very effective
- High cost (> $30,000/yr)
- Not first-line therapy

54.9% of adult and 78.3% of pediatric patients are non-adherent to medication therapy

From FDA’s LABA black box warning

. . . Based on the available information, FDA concludes there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma.
Innovation in asthma therapy: modulate GABA$_A$ receptor function in the lung

GABA$_A$ receptors are present on lung cell types responsible for asthma pathophysiology

- Airway smooth muscle
- Immune/inflammatory cells

GABA$_A$ receptors are established drug targets

- Chloride ion channel
- Well characterized CNS activity
- Positive modulators work at allosteric sites and increase channel efficacy
- Receptor is readily druggable; approved small molecule drugs in wide-spread clinical use
GABA\textsubscript{A} receptors on airway smooth muscle have restricted subunit expression

RT-PCR analysis of airway smooth muscle RNA shows GABA\textsubscript{A} receptors restricted to α4 and α5 containing subtypes

Lane
1 = MW standards
2 = Buffer control
3 = Cultured human ASM
4 = Freshly dissected human ASM
5 = Human brain

Mouse spleen cells (mixed immune cell population) express GABA$_A$ receptor subunits (western blot). Positive control is mouse brain.
Targeting GABA$_A$ receptors in the lung

Key points to consider:

- $\alpha$4 and $\alpha$5 GABA$_A$ receptors are expressed in both airway smooth muscle and immune/inflammatory cells.

- UWM researchers have >30 years experience designing GABA$_A$ receptor ligands with $\alpha$-subtype selectivity.

- Novel GABA$_A$ receptor ligands are derivatives of benzodiazepines; possessing desirable selective receptor efficacy, good oral availability, good PK, and general safety.

- These compounds are readily manufacturable at large scale and low cost.

- Asthma compounds retain target selectivity and therapeutic efficacy, but restrict CNS exposure (to preclude any CNS effects).

Representative data on various $\alpha$4 and $\alpha$5 GABA$_A$ selective receptor ligands are shown in the following slides.
Positive allosteric modulators target discrete GABA_A receptors

XHE-III-74 has GABA_A-R selectivity to α4 subtype

Patch clamp of α_xβ_yγ_x expressing oocytes showing selectivity to α4–subunit containing GABA_A receptors

Optimization of substituted imidazobenzodiazepines as novel asthma treatments.


Notes:
• Prior to animal testing, compounds must be non-toxic and metabolically stable in vitro.
• Because GABA$_A$ receptor modulators have well-known CNS suppressive activity; to be suitable for asthma, compounds must be devoid of $\alpha1$ efficacy and CNS exposure.
• The rotarod is an established assay for assessing any motor impairment due to CNS exposure.

Compound 1 does not cause CNS motor impairment

Rotarod studies in mice showing no motor impairment (latency) up at 100 mg/Kg po (contrast diazepam control at 5 mg/kg ip).
Selective GABA<sub>A</sub> compounds relax airway smooth muscle

\[ \alpha_4 \text{ (compound 1) and } \alpha_5 \text{ (compound 2) selective GABA}_A \text{ receptor ligands relax guinea pig tracheal smooth muscle (A) and human tracheal smooth muscle (B) in vitro.} \]

Muscle strips were precontracted with substance P or acetylcholine.
Mechanism of action: GABA<sub>A</sub> receptor modulation of lymphocyte Ca<sup>2+</sup> signaling

Human Jurkat T-cells were stimulated with PMA/PHA (phorbol myristate acetate/phytohemagglutinin). Change in [Ca<sup>2+</sup>] was measured with a cell-permeable fluorescence probe Fluo-4.
Selective GABA<sub>A</sub> compounds are orally available with good PK, and minimal brain exposure.
Selective GABA\textsubscript{A} compounds relax airway smooth muscle in asthmatic mice

Mice are sensitized and challenged with ovalbumin (Ova S/C), leading to lung inflammation and airway hyperresponsiveness that models human asthma. Efficacy of compounds (sRAW) in conscious mice following airway challenge with methacholine is measured using a non-invasive airway monitoring device (Buxco). CTL = control (no treatment); ALB = albuterol; 1 = compound 1; 2 = compound 2.
Selective GABA$_A$ compounds reduce lung inflammatory cells in asthmatic mice

As described previously, mice are sensitized and challenged with ovalbumin (Ova S/C) leading to lung inflammation and airway hyperresponsiveness that models human asthma. Efficacy of compounds is measured by flow cytometric analysis of specific cell types from bronchoalveolar lavage fluid (BALF). CCR3$^+$, GR1$^+$, CD4$^+$ and CD11b$^+$ cell populations are quantified. Dex = dexamethasone; 1 = compound 1; 2 = compound 2; control = unsensitized mice; *, p≤0.05; **, p≤0.01; ***, p≤0.001.
As described previously, mice are sensitized and challenged with ovalbumin (Ova S/C) leading to lung inflammation and airway hyperresponsiveness that models human asthma. Efficacy of compound is measured by flow cytometric analysis of specific cytokines in lung homogenate. IL-4, IL-17a and TNFα are down-regulated. *, p≤0.05; **, p≤0.01; ***, p≤0.001.
Summary of studies

Key scientific takeaways:

• A restricted set of GABA\textsubscript{A} receptors are found on target tissues, allowing for ligands (drugs) with narrowly tailored effects.

• Novel ligands with \(\alpha_4\) and \(\alpha_5\) selectivity have good drug-like properties and pharmacodynamic performance in relevant \textit{in vitro} and \textit{in vivo} models.

• Compounds have good oral availability, good PK, and no observable toxicities.

• Compounds lack brain exposure and are devoid of CNS adverse effects.

• Targeting lung GABA\textsubscript{A} receptors is a compelling drug strategy to safely reduce key asthma features of airway smooth muscle hyperreactivity and lung inflammation.

• Clinical leads identified
Selected publications:


Moving the program forward

Research Proof Of Concept
- Target validation
- Initial compounds
- Lead optimization
- Oral PK/ADME/tox
- Efficacy in PD models

IND
- Lead optimization
- Lead lock
- GLP/IND-enabling pkg.
- Formulation
- CM&C
- API/DP manufacturing
- Clinical plan

Clinical Proof Of Concept
- Phase I
- Phase IIa

- 2 Patent pending (US/EU/CA/JP)
- NIH R01 grants (UWM, Columbia)
- UWM-RF grant
- Numerous publications
- Partnering discussions
- Additional patents
- Translational grants
- Expanded immunoRx indications
A new oral drug for asthma treatment

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