

**MIDD0301:
A first-in-class drug for asthma**

The scientific team is expert in asthma/lung physiology, medicinal chemistry, drug development, & clinical medicine

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Assoc. Professor
James Cook, PhD
Distinguished Professor
Douglas Stafford, PhD, MS
Director, Milwaukee Inst. for Drug Discovery
Chemistry & Biochemistry
University of Wisconsin-Milwaukee



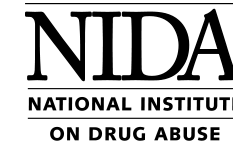
Charles Emala, MD, MS
Henrik H. Bendixen Professor of Anesthesiology
Vice Chair for Research
Columbia University College of Physicians & Surgeons



Mitchell Grayson, MD
Director, Division of Allergy and Immunology
Professor of Pediatrics, Nationwide Children's
Hospital and The Ohio State University



The program has received generous funding:



National Heart, Lung,
and Blood Institute

Richard and Ethel
Herzfeld Foundation



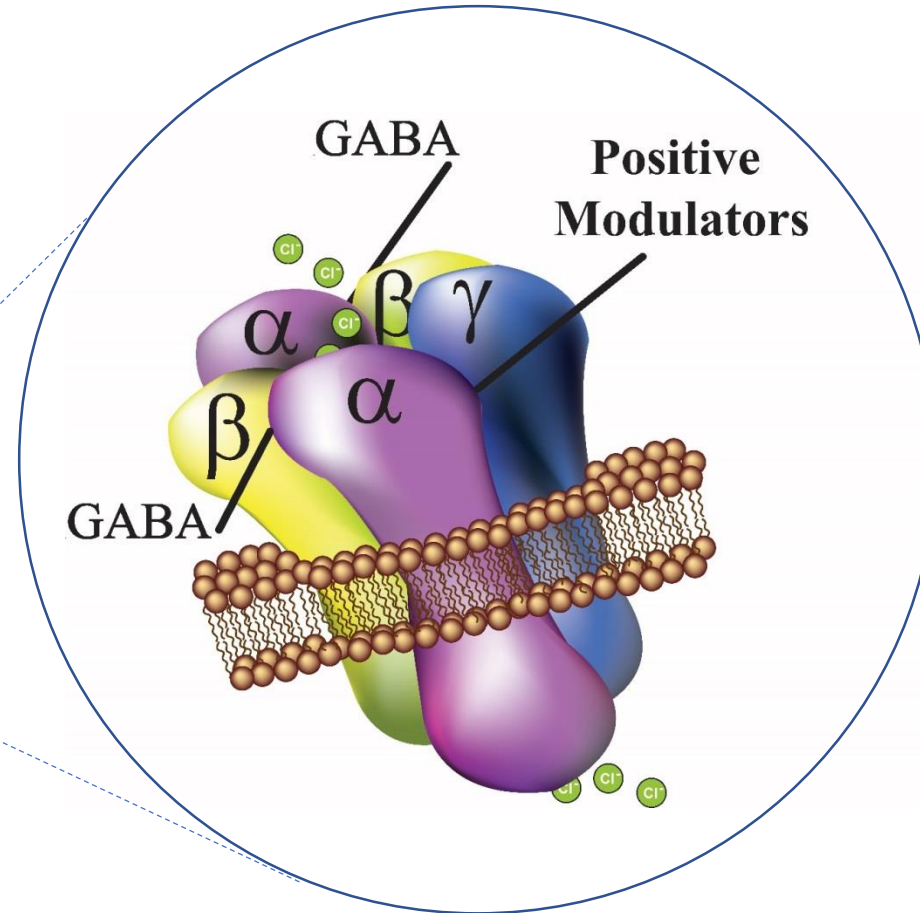
The Lynde and Harry
BRADLEY
FOUNDATION



New product design features:

- **New molecular entities**
- **Small molecule (positive modulators)**
- **Oral delivery**
- **First line therapy**
- **No steroids**
- **Better compliance**

**A novel asthma strategy:
target GABA_A receptors
in the lung**



GABA_A receptor

Pending patents claiming novel drug compositions and uses

Columbia/UWM Research Foundation patents on novel asthma treatment

PCT/US2017/047185, Filed Aug. 16, 2017

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

US Patent No. 9,879,020, Filed: Sept. 1, 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: 10 claims on novel drug compositions and methods of use

A compelling need for improved asthma treatment

The Opportunity

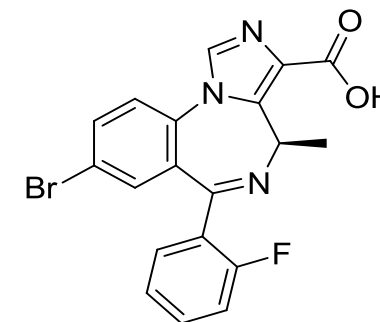
- Chronic disease economics with large global prevalence
- Current first-line drugs have safety/efficacy liabilities
- Current inhaler medications have compliance liabilities
- Differentiated product – new drug composition, no inhaler
- Developing for first-line asthma indication
- Patents pending on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



A ground-breaking approach in targeting and compound design

The Innovation

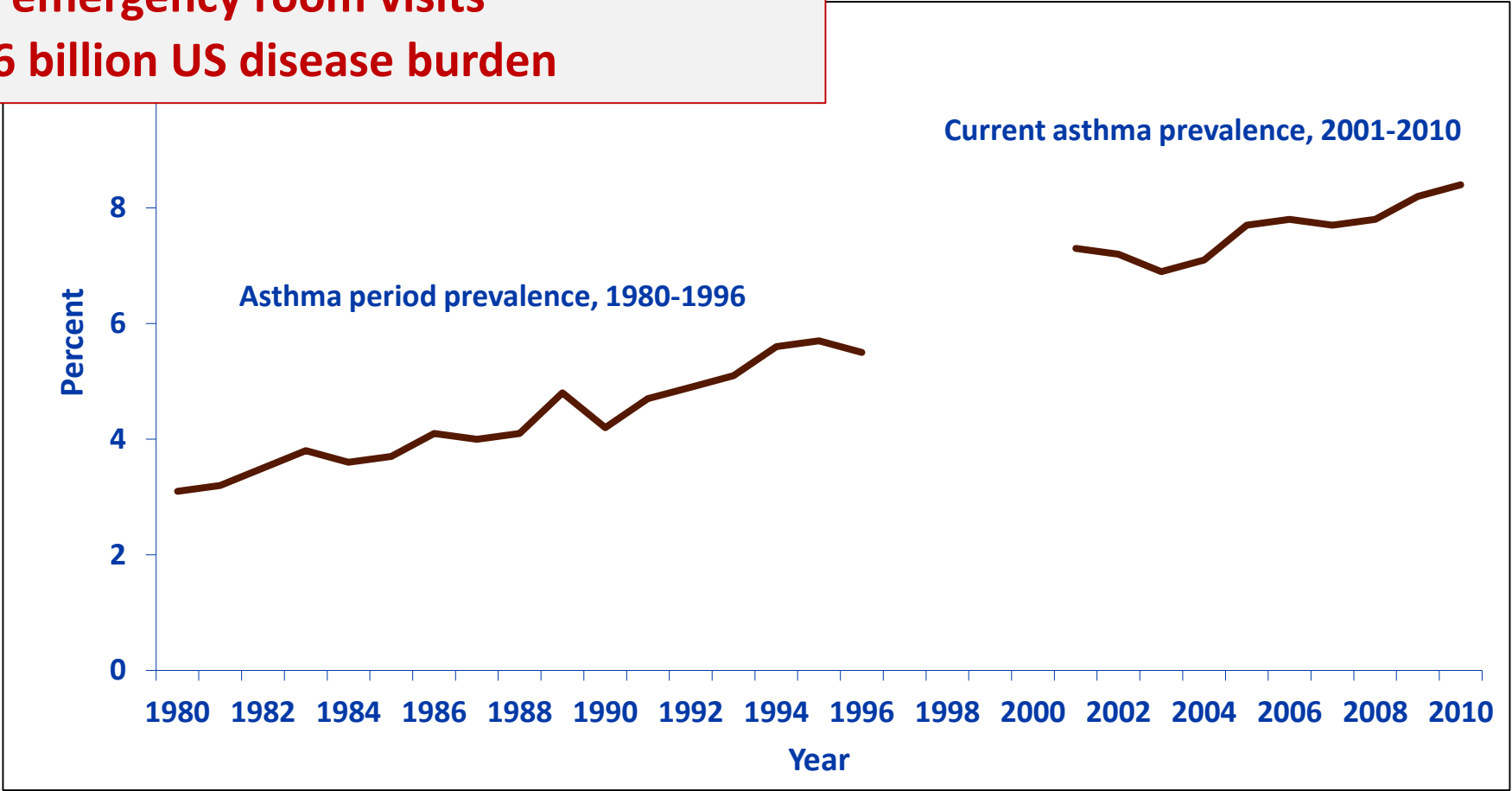
- Fundamentally novel asthma drug target identified
- Target has been safely drugged for other indications
- No use of steroids or β_2 -adrenergic agonists
- Drug design is a small molecule for oral dosing
- Development team is recognized as experts in target/compound class
- Identification of a first-in-class lead – MIDD0301
- Lead has good animal safety, pharmacokinetics, and lung exposure
- Efficacy has been demonstrated in established animal disease model
- Compound class has low cost of manufacturing



MIDD0301

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

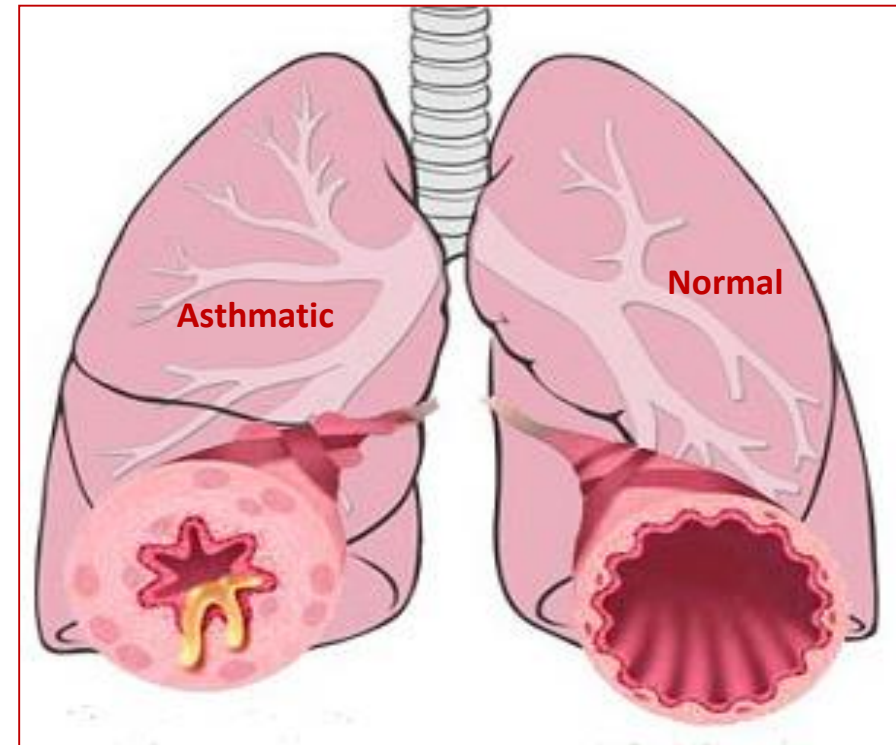
Asthma treatment targets key disease features:

Inflammation (excess mucus)

- corticosteroids
- leukotriene receptor antagonists

Airway smooth muscle constriction

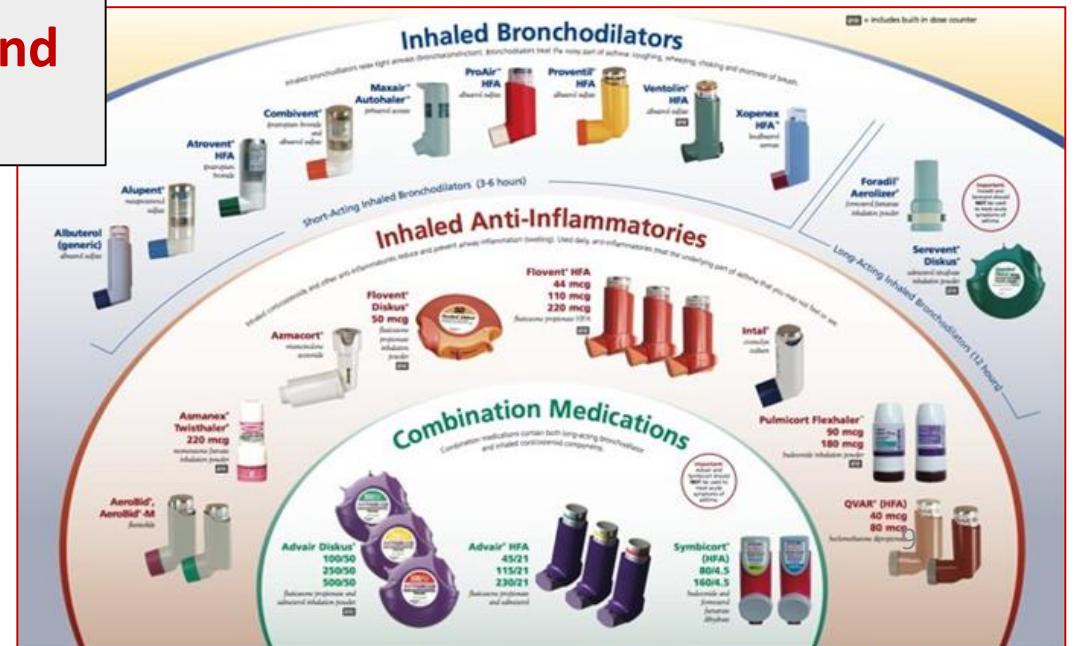
- β_2 -adrenergic agonists



Numerous inhaler medications are used for first-line treatment

Objectives of asthma treatment:

- Reduce impairment (frequency and intensity of symptoms)
- Reduce risk (likelihood of future 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.

Current asthma drugs have significant liabilities

- 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)

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



Biologics

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

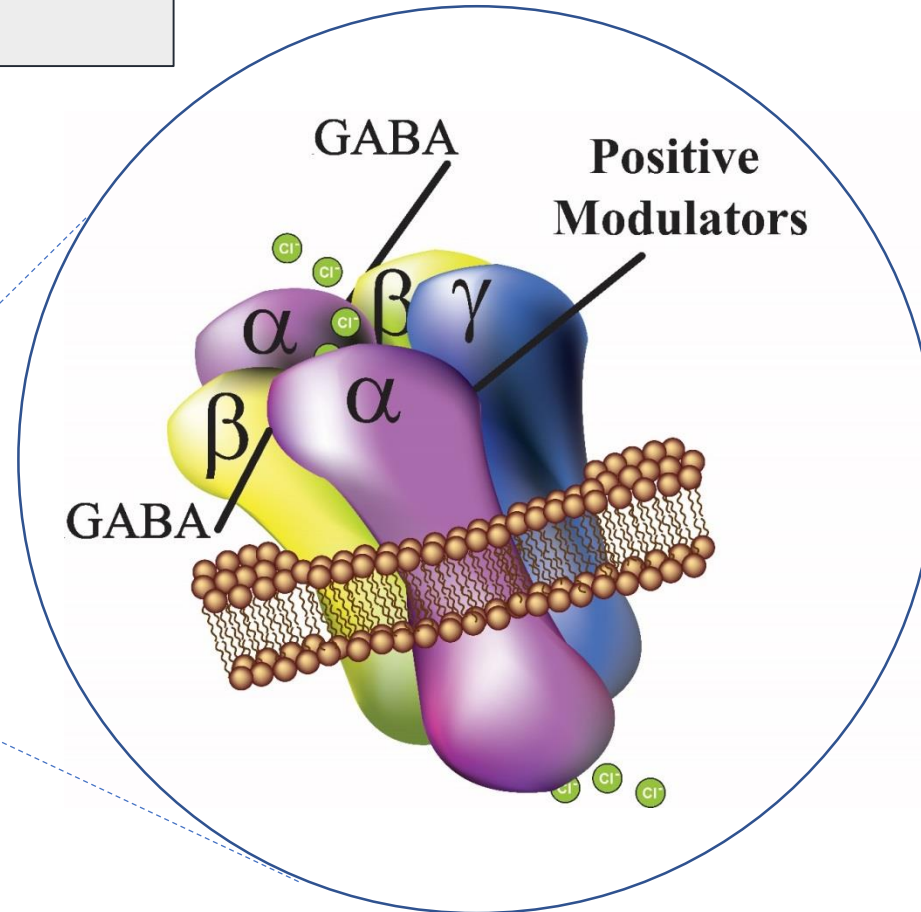
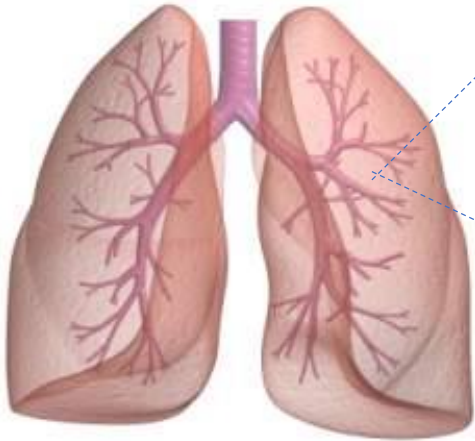
From FDA's LABA black box warning

... 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

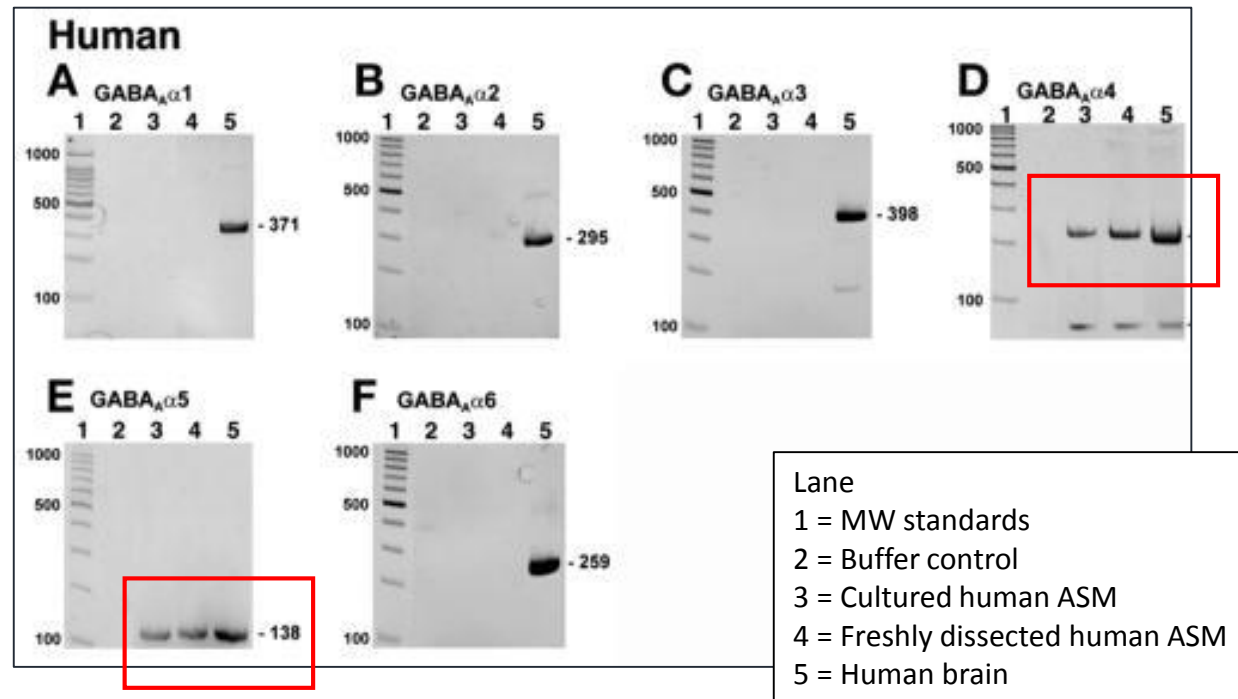


GABA_A receptors are established drug targets

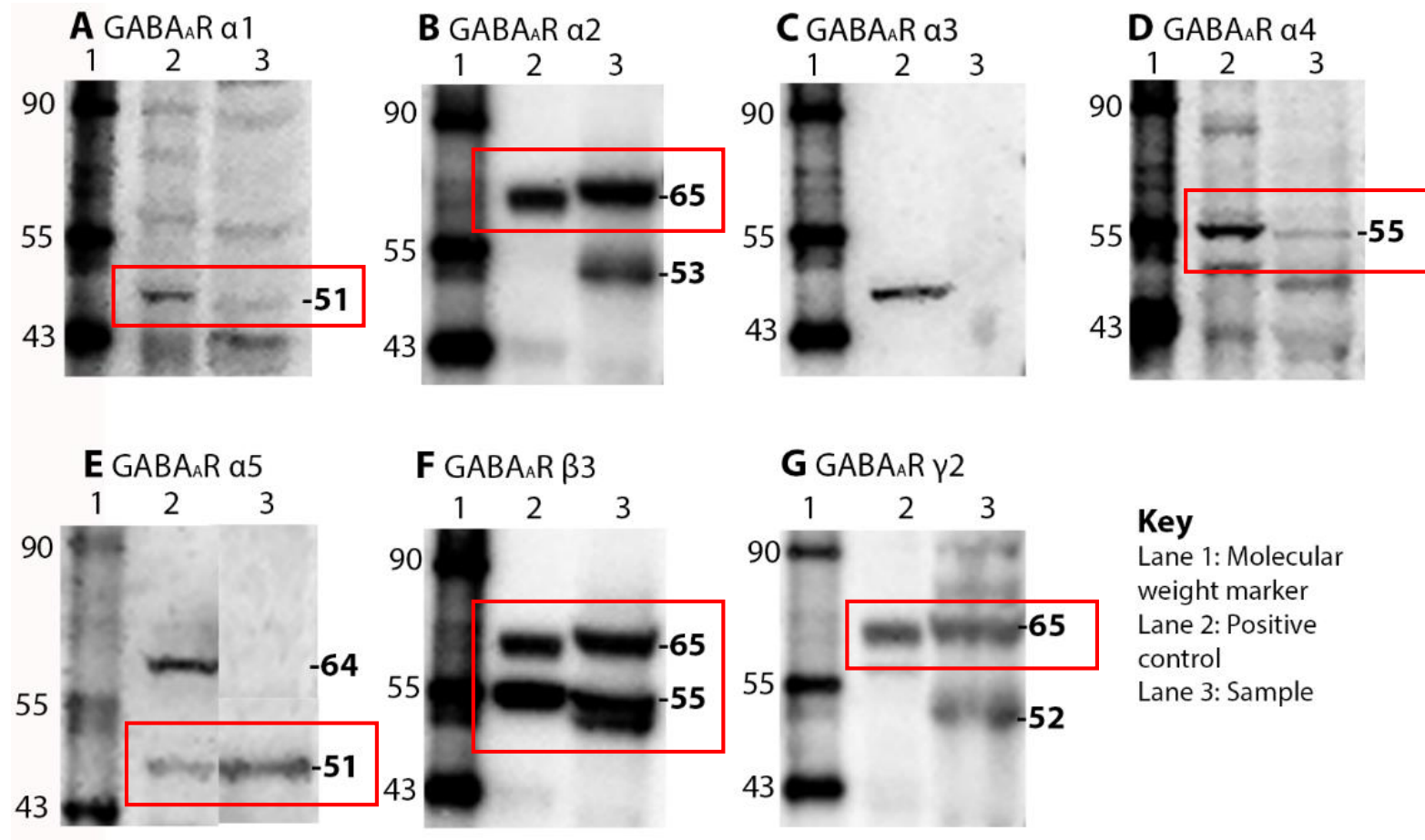
- Chloride channel
- Well characterized CNS activity
- Positive modulators work at allosteric sites and increase channel efficacy
- Receptor is readily druggable; approved small molecule drugs in wide-spread clinical use

GABA_A receptors on airway smooth muscle have restricted subunit expression

RT-PCR analysis of airway smooth muscle RNA shows GABA_A receptors restricted to $\alpha 4$ and $\alpha 5$ containing subtypes



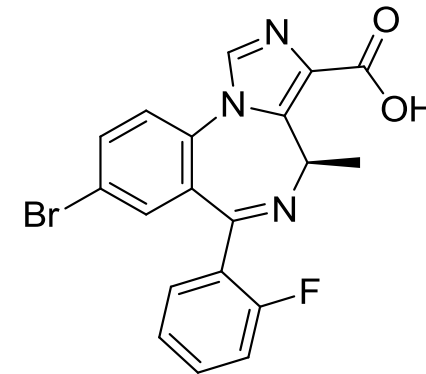
GABA_A receptor subunits are also expressed on immune cells



Mouse spleen cells (mixed immune cell population) express GABA_A receptor subunits (western blot). Positive control is mouse brain.

Foundation of a new asthma drug discovery strategy: Target GABA_A receptors in the lung

- Overlapping subsets of GABA_A receptors are expressed in both airway smooth muscle and immune/inflammatory cells.
- The underlying mechanism of GABA_A ion channel allosteric modulation is well-understood.
- GABA_A receptors are well-known drug targets (for CNS conditions).
- UWM is a global leader in the design of GABA_A receptor ligands with α -subtype selectivity and drug properties (PD and PK).

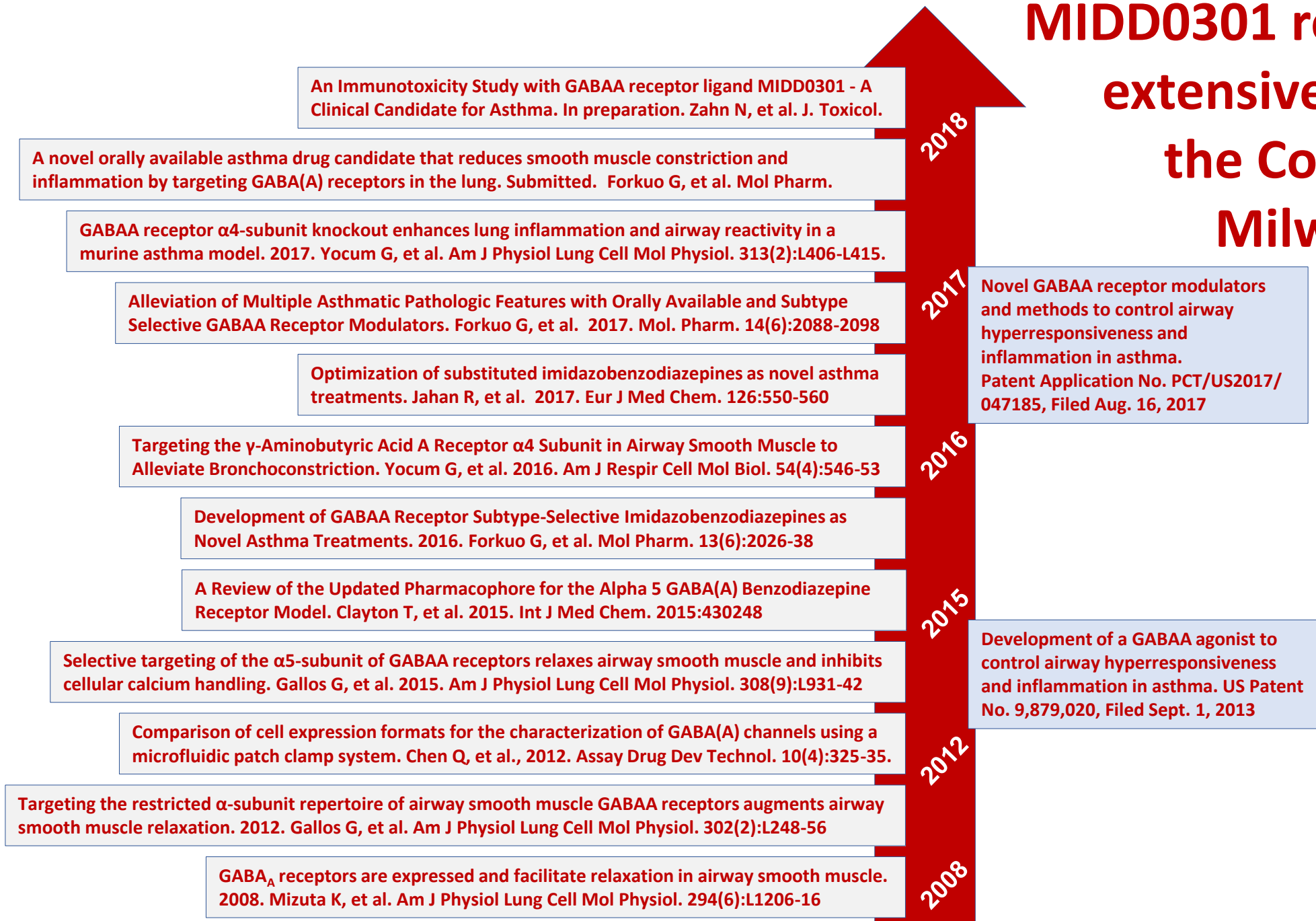


MIDD0301

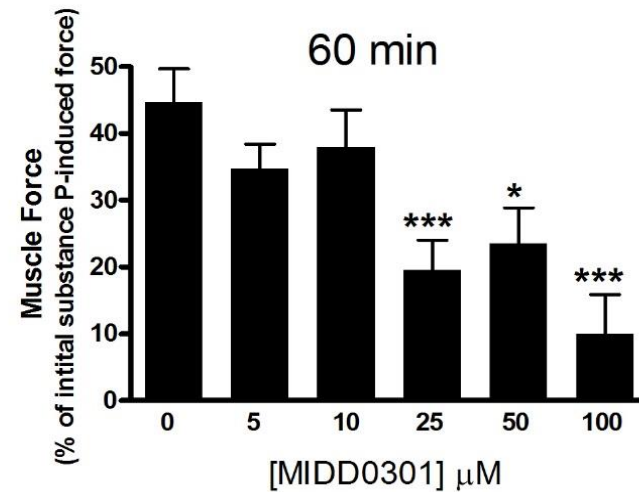
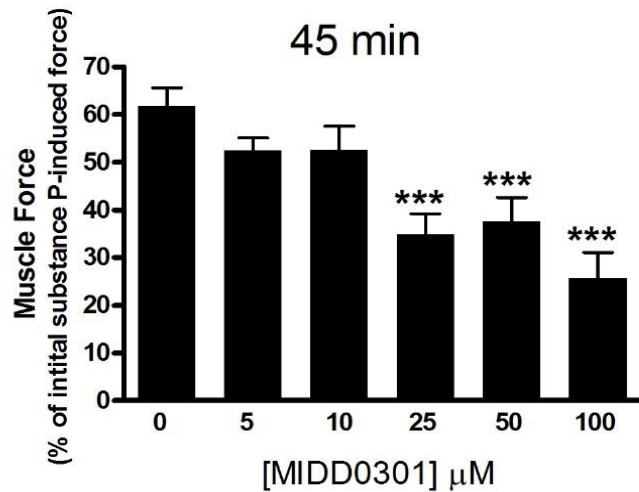
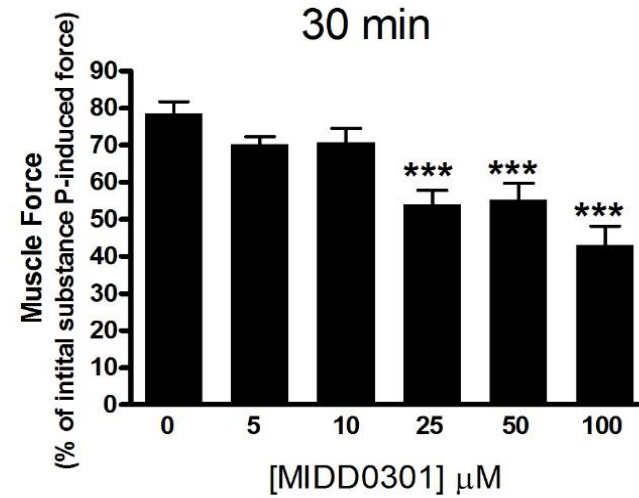
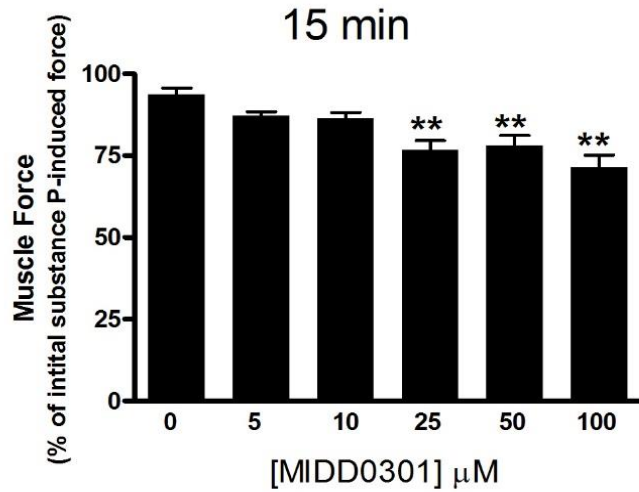
Objective: Design and optimize GABA_A receptor ligands with oral availability, safety, and therapeutic efficacy in asthma models.

Result: From dozens of novel compounds synthesized and tested, MIDD0301 was identified as a clinical lead for FIH evaluation.

MIDD0301 resulted from extensive research by the Columbia/UW-Milwaukee team

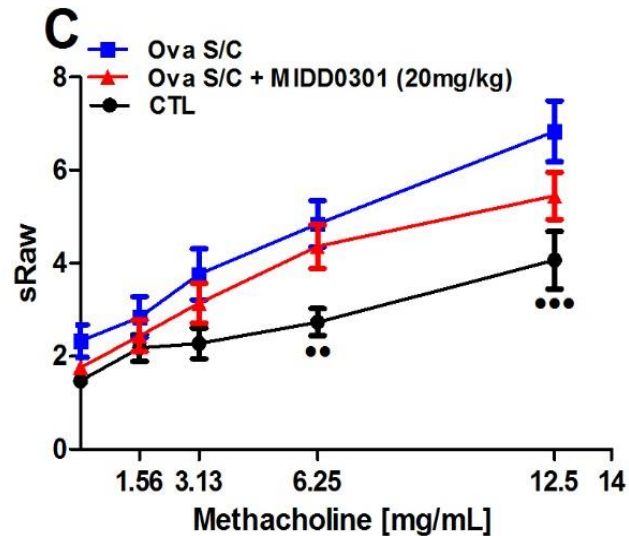
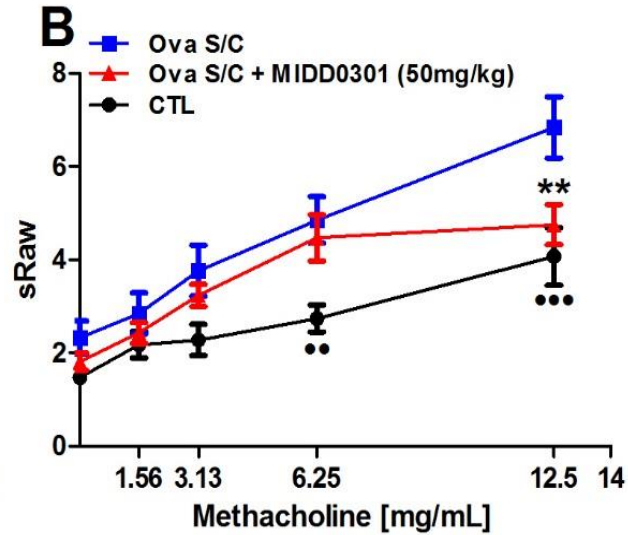
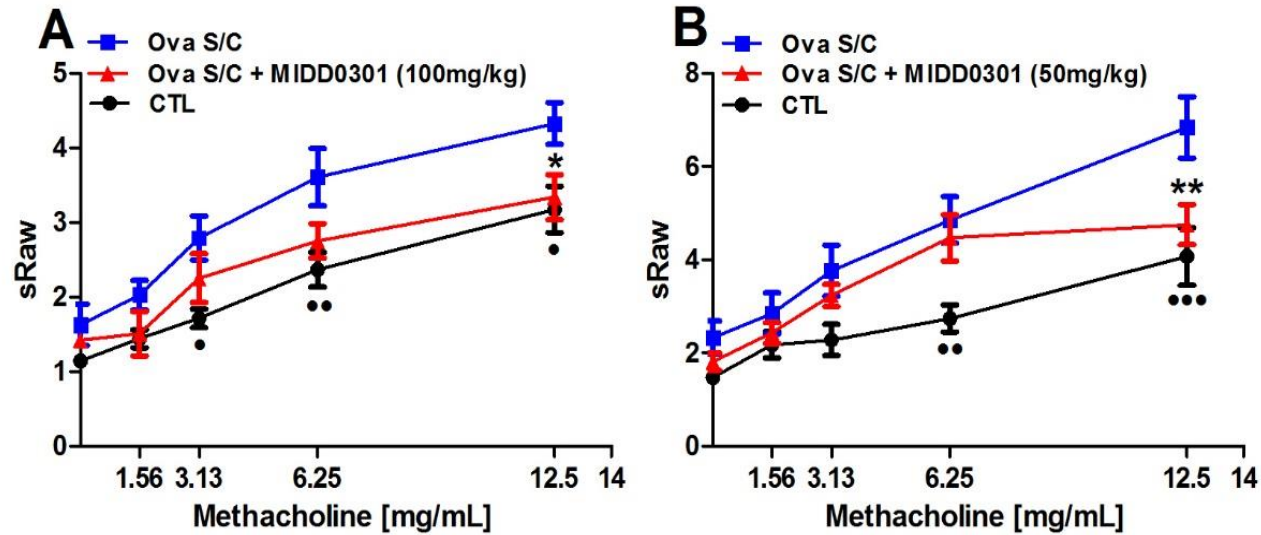


MIDD0301 relaxes pre-contracted airway smooth muscle



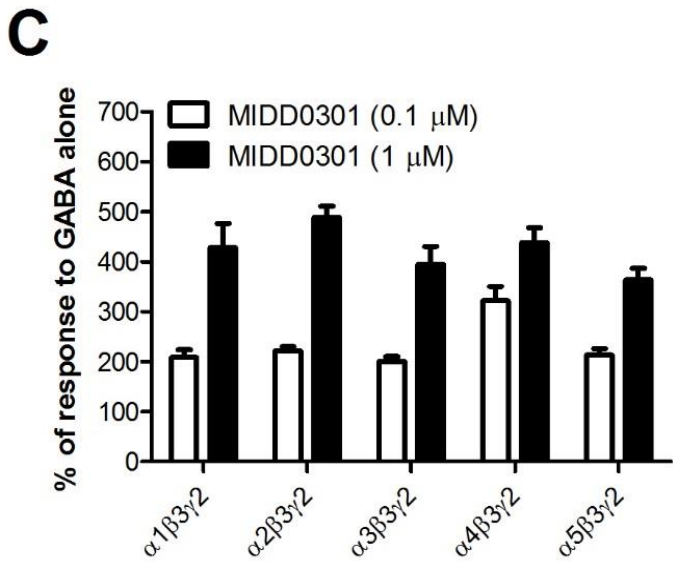
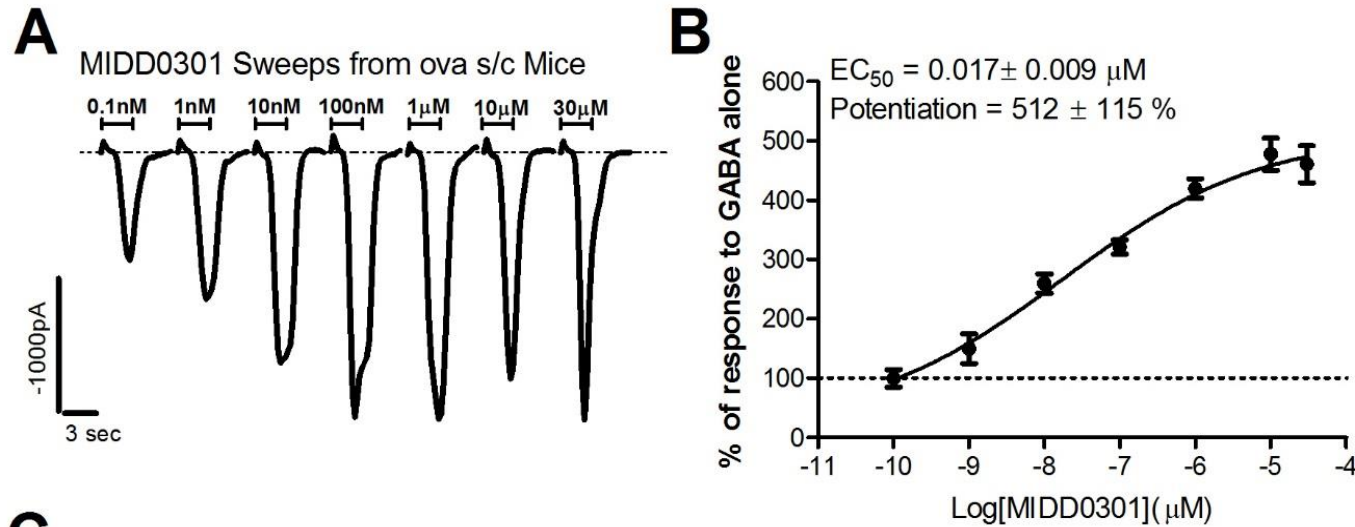
Muscle force in guinea pig airway smooth muscle contracted with 1 μM substance P. MIDD0301 induced a significant relaxation of substance P-contracted guinea pig tracheal rings compared to vehicle control (0.1% DMSO). Muscle force is expressed as a percent of the initial muscle remaining at various time points. (*) $p < 0.05$; (**) $p < 0.01$; and (***) $p < 0.001$, compared to vehicle control.

Oral MIDD0301 reduces airway hyperresponsiveness (sRaw) in asthmatic mice



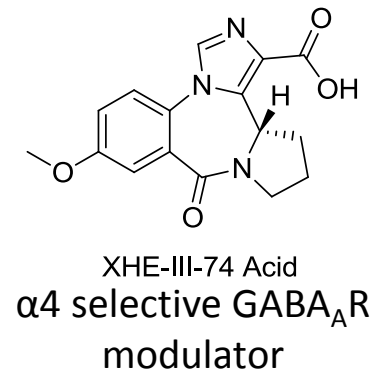
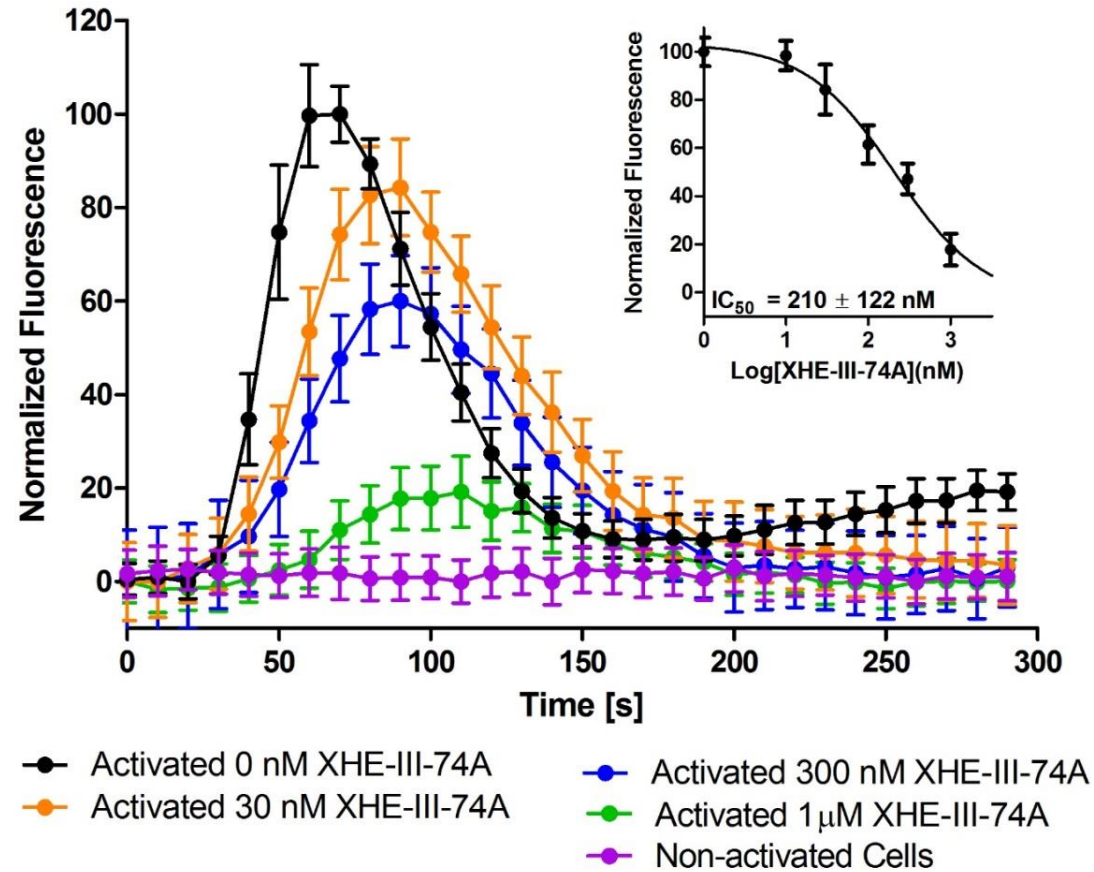
Specific airway resistance (sRaw) was measured in spontaneously breathing asthmatic (Ova S/C) mice at increasing nebulized dosages of methacholine. Ova S/C mice were given vehicle or (A) 100 mg/kg, (B) 50 mg/kg, (C) 20 mg/kg of MIDD0301 orally b.i.d. for 5 days. (*) $p < 0.05$ and (**) $p < 0.01$ significance for the MIDD0301 group and (●) $p < 0.05$, (●●) $p < 0.01$, and (●●●) $p < 0.001$ significance between control mice compared to ova s/c mice.

MIDD0301 targets CD4⁺T lymphocyte GABA_AR and modulates membrane current



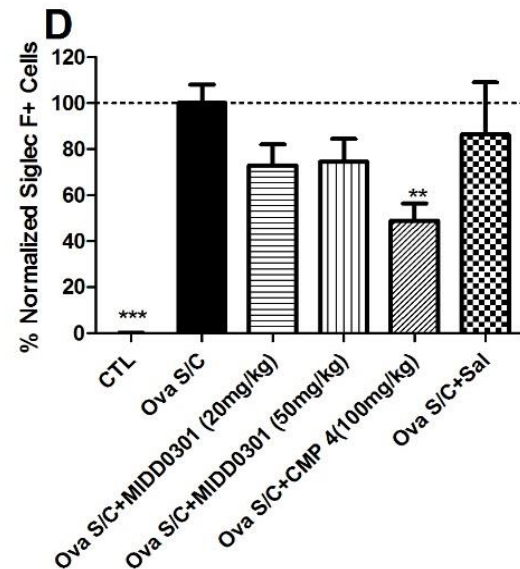
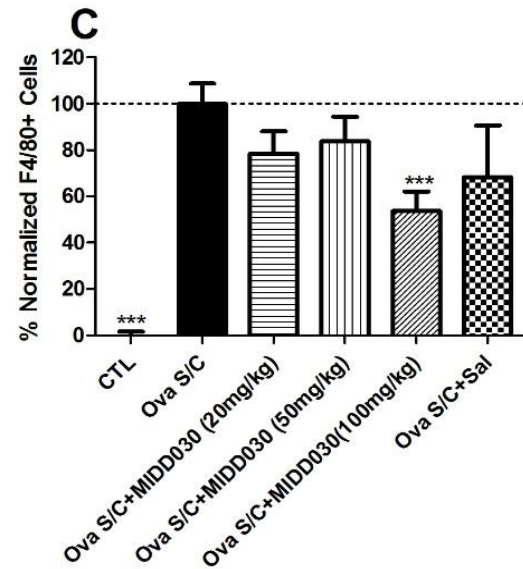
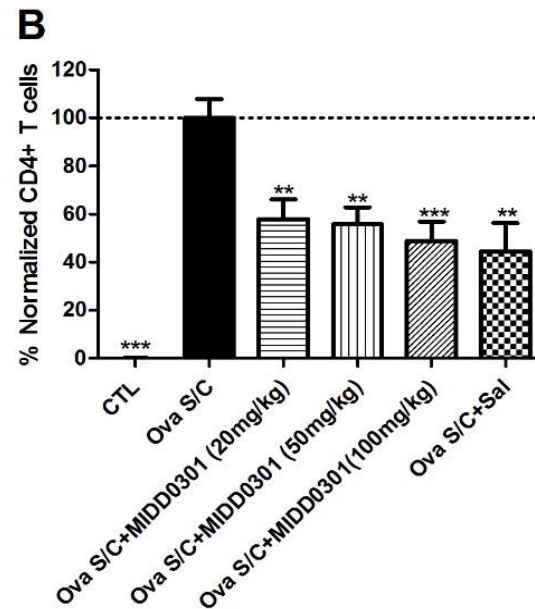
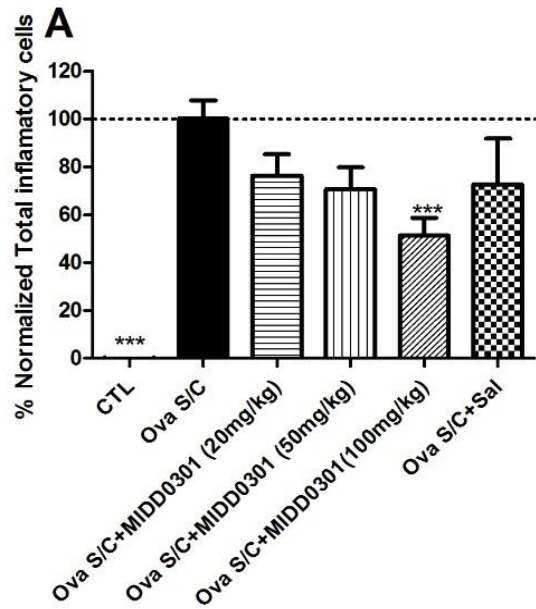
Induced electrophysiological responses by MIDD0301. A) Patch clamp current responses of CD4⁺ T lymphocytes isolated from ova s/c mice in the presence of 600 nM GABA and increasing concentrations of MIDD0301. B) Normalized current responses of isolated CD4⁺ T lymphocytes (ova s/c mice) in the presence of 600 nM GABA (100 %) and increasing concentrations of MIDD0301 for eight independent measurements. C) Average enhancement of current evoked to GABA by 0.1 μM or 1 μM of MIDD0301 using transiently transfected cells with α GABA_AR subunits, as indicated, along with β3 and γ2 subunits measured by patch clamp.

Mechanism of action: lymphocyte GABA_A receptor mediated modulation of Ca²⁺ signaling



Human Jurkat T-cells were stimulated with PMA/PHA (phorbol myristate acetate/phytohemagglutinin). Change in [Ca²⁺] was measured with a cell-permeable fluorescence probe Fluo-4.

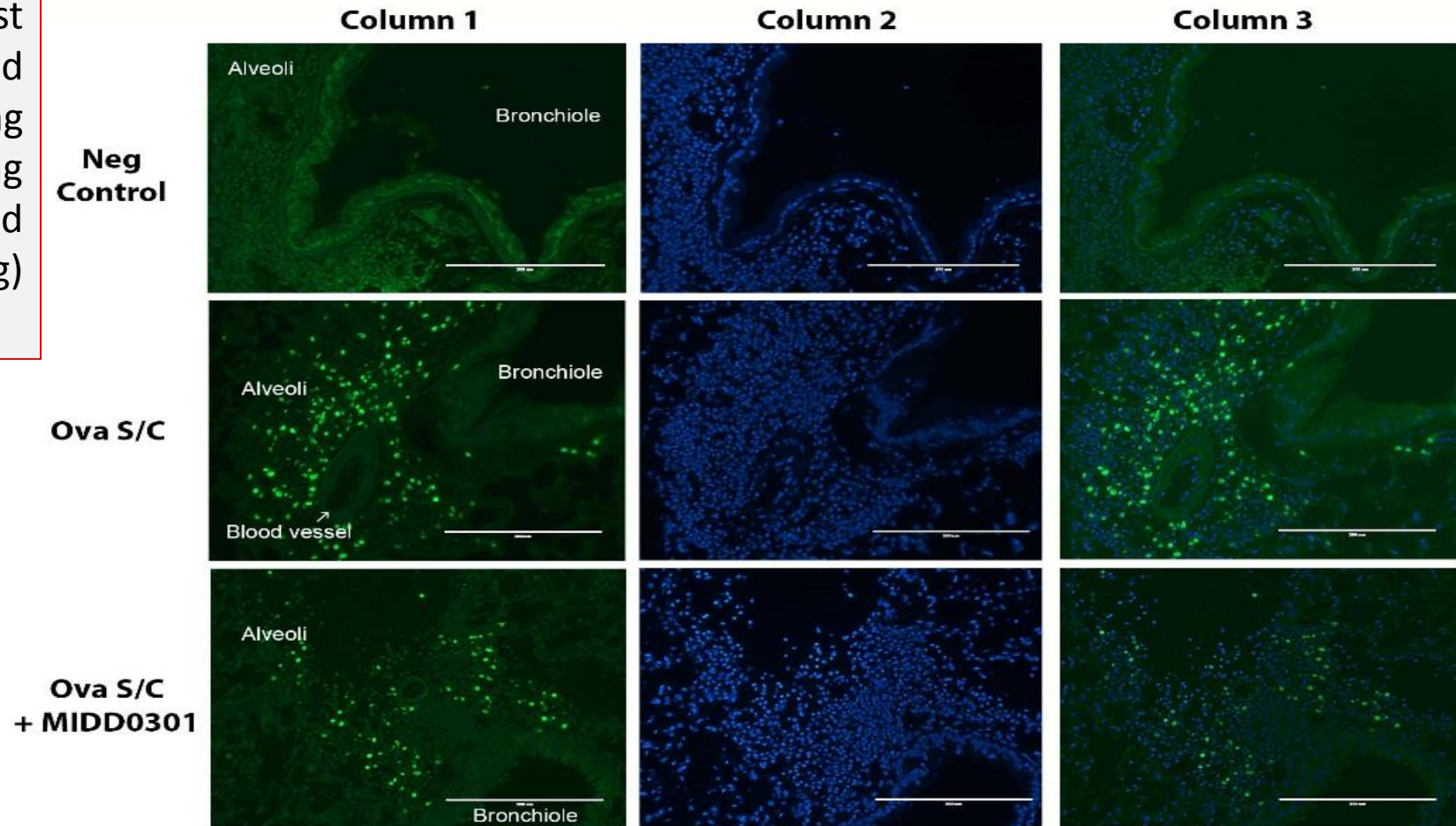
Oral MIDD0301 reduces inflammatory cell numbers in bronchoalveolar fluid from asthmatic mice



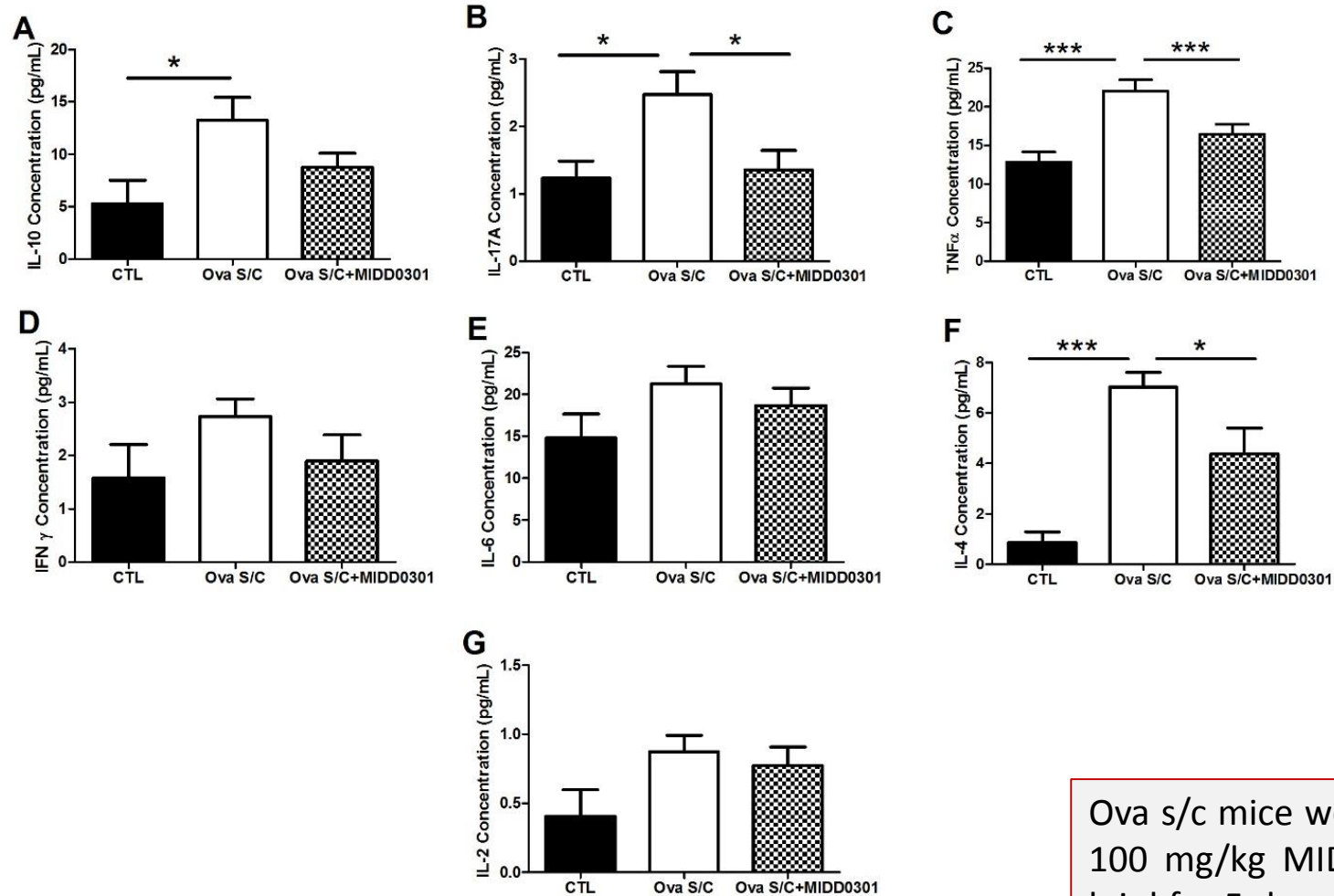
Ova s/c mice were administered vehicle, MIDD0301 (20, 50 or 100 mg/kg), or salmeterol (1 mg/kg) via oral gavage b.i.d. for 5 days. BALF was harvested from each animal and used for (A) quantification of total inflammatory cells using anti-CD45 APC antibody and flow cytometry. (B) CD4⁺ T cell, (C) F4/80⁺ cell, and (D) Siglec F⁺ cell populations as quantified by flow cytometry. Significance indicated as *, **, and *** for p < 0.05, p < 0.01, and p < 0.001 compared to vehicle treated ova s/c mice.

Oral MIDD0301 reduces inflammatory cell proliferation in asthmatic lung

Lung from mice injected i.p. with EdU and visualized with a fluorescent azide to visualize cells that underwent the S phase during a four-hour period (column 1). Slides were counterstained with Hoechst 33342 (column 2) and superimposed images in column 3. Row 1 presents lung images of control mice. Row 2 depicts lung images of vehicle-treated ova s/c mice and row 3 images of MIDD0301 (100 mg/kg) treated ova s/c mice.

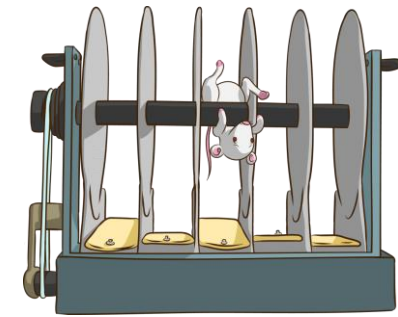
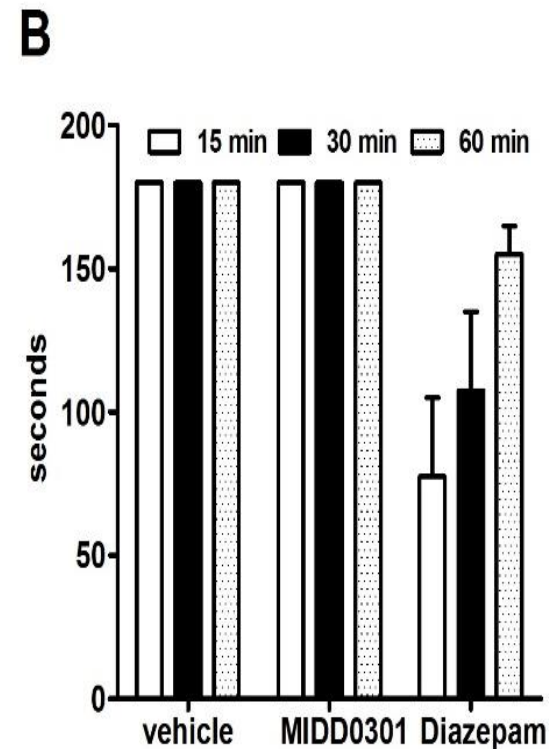
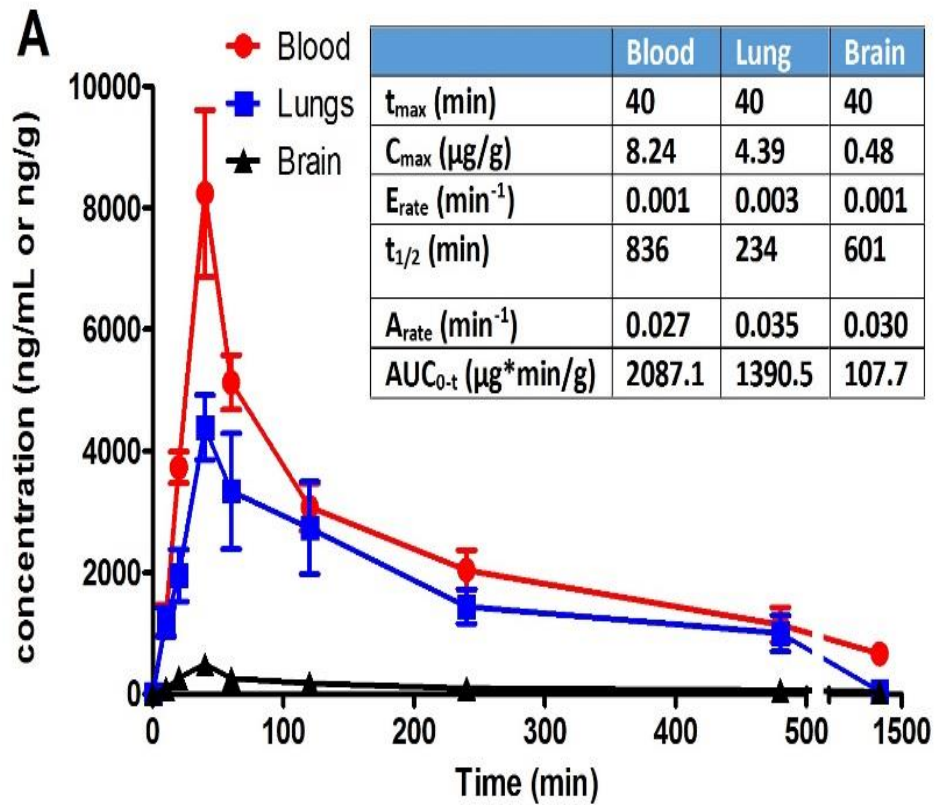


Oral MIDD0301 reduces inflammatory cytokines in lung homogenates from asthmatic mice



Ova s/c mice were administered vehicle or 100 mg/kg MIDD0301 by via oral gavage b.i.d for 5 days. Significance *, **, and *** indicate $p < 0.05$, $p < 0.01$, and $p < 0.001$ compared to vehicle treated ova s/c mice.

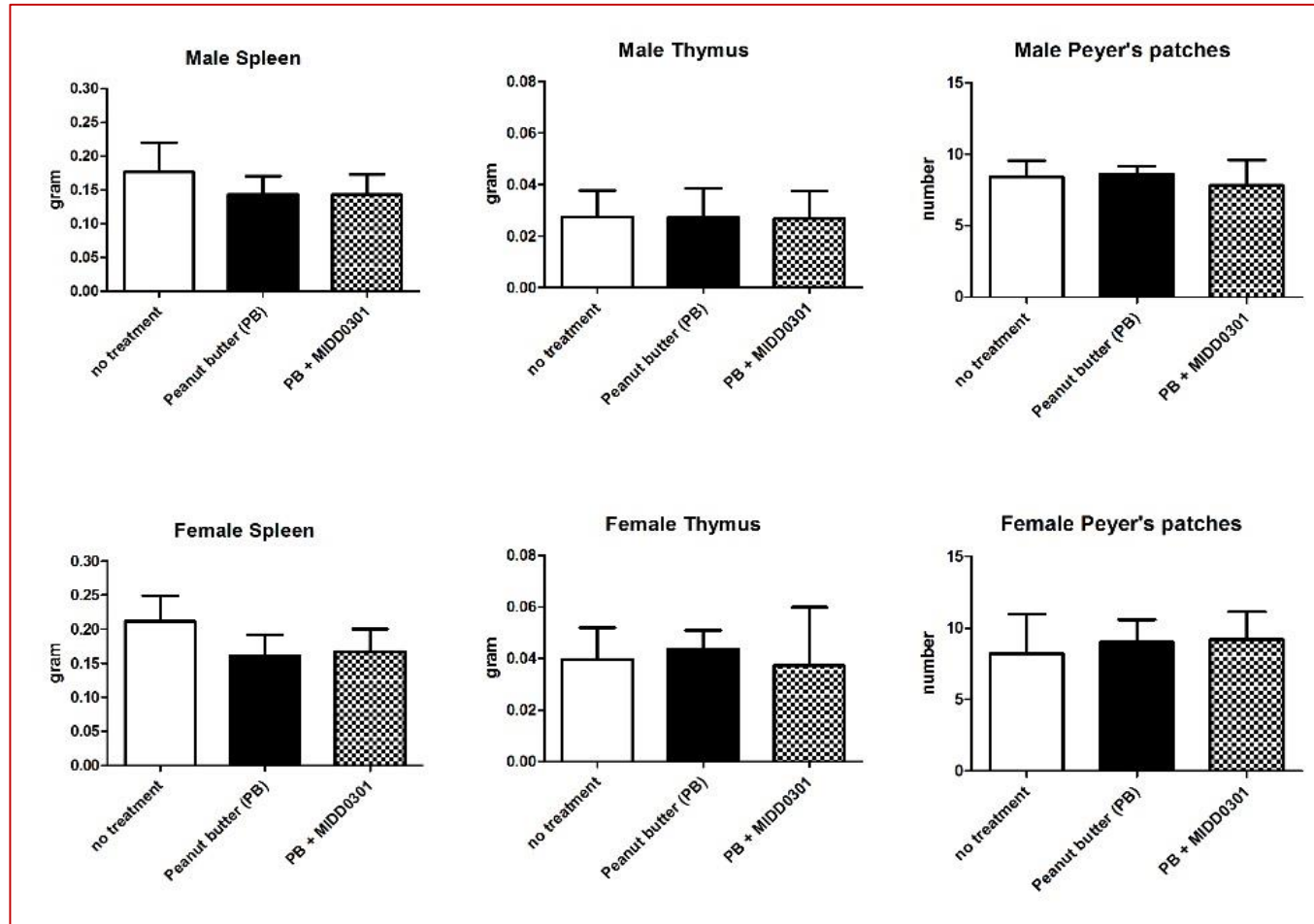
MIDD0301 has extended plasma and lung half-life without brain exposure or motor impairment



Rotarod

PK profile of MIDD0301 in mouse blood, lungs, and brain. A) Time-dependent systemic distribution of MIDD0301 (25 mg/kg via oral gavage). B) Sensorimotor rotarod coordination study in mice treated orally with 100 mg/kg MIDD0301, compared to 5 mg/kg i.p. diazepam.

MIDD0301 does not alter systemic immune organs



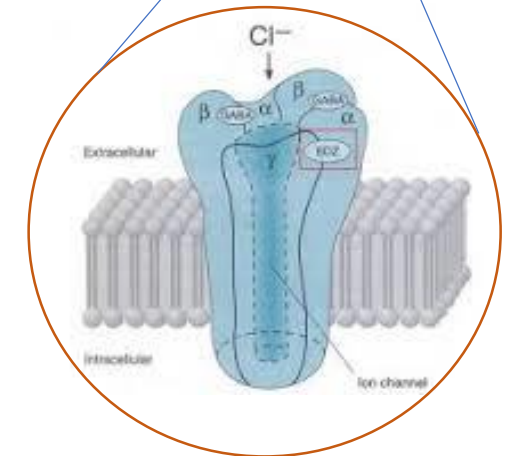
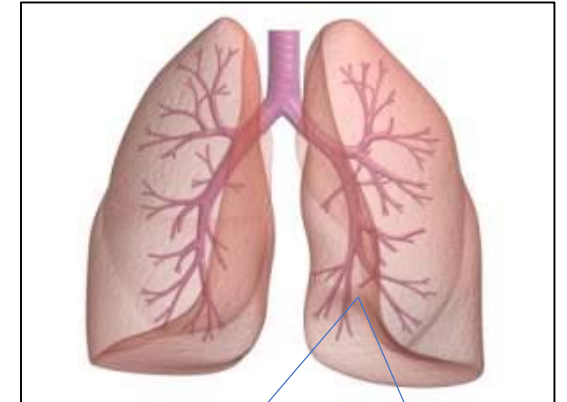
Swiss Webster mice were administered peanut butter (PB) or (PB) + 100 mg/kg MIDD0301 b.i.d. for 28 days. organs were harvested and weighted or Peyer's patches counted.

Not shown: no changes in serum proteins or blood cell numbers were observed nor histological changes in spleen or thymus.

Summary of studies

Key scientific takeaways:

- GABA_A receptors (well-known, druggable) have been discovered on lung airway smooth muscle and immune cells that can be targeted together with small molecule modulators.
- Lead compound MIDD0301 relaxes airway smooth muscle and reduces inflammatory markers (cellular and cytokine) when administered orally in an accepted asthma disease model.
- MIDD0301 has good oral availability, good PK (enabling QD or BID dosing), and no observable toxic metabolites or related toxicities.
- MIDD0301 lacks brain exposure and is devoid of CNS adverse effects.
- MIDD0301 is based on a well-known chemical backbone used in currently approved drugs; supporting human safety and tolerability.
- API is stable and readily scalable at low cost; solid oral formulation will use existing methods.





PANTHERICS

Incorporated

Pantherics Incorporated was formed to advance asthma drug development

- **Wisconsin corporation founded in 2017**
- **Executive management team experienced in new business formation, biomedical product development, and finance**
- **Scientific team includes key academic collaborators who developed the asthma drug program**
- **Seek exclusive licenses to enabling GABA_AR ligand patents**
- **Seek funding to advance lead compound to clinical POC**

The Pantherics team

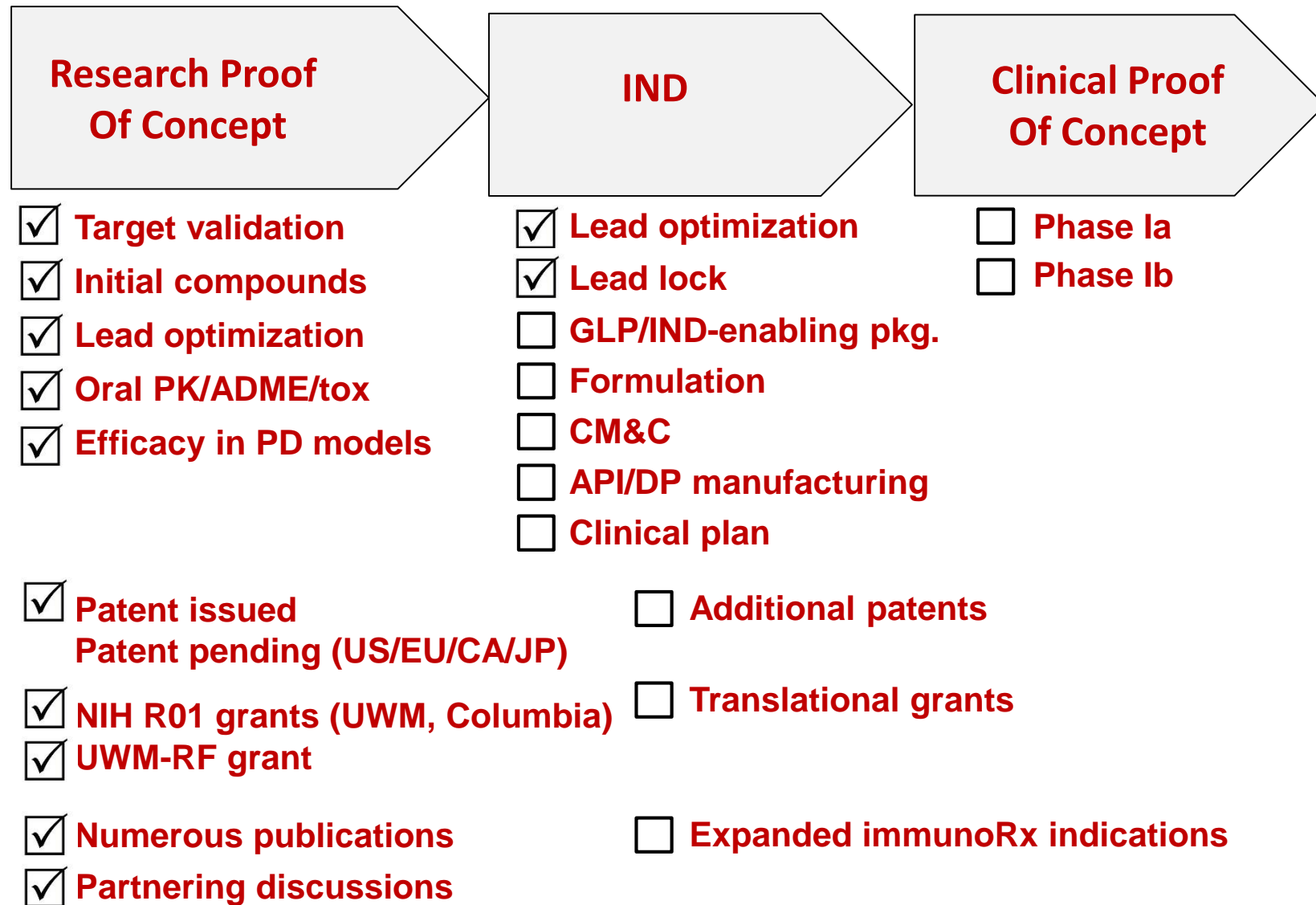
Executive management

Douglas Stafford CEO	30 years leadership in business formation, operations, IP, product development, and strategic partnerships. Director of the Milwaukee Institute for Drug Discovery at UW-Milwaukee. Previously, Exec. VP, GenExel-Sein, Inc. (South Korea); COO and later CEO of Ophidian Pharmaceuticals, Inc.; and, Director, Manufacturing and Product Development, Baxter Healthcare Corporation (various divisions). PhD immunology Tufts University Medical School; MS management, Lesley College.
Alexander Arnold CSO	Assoc. Prof. of Chemistry at UW-Milwaukee and expert in chemical biology, with focus on drug discovery and development (cancer, CNS, asthma programs); more than 60 scientific publications and expert in GABAA receptor targeting, compound synthesis, pharmacodynamic models, pharmacokinetics, and drug safety. PhD, Organic Chemistry, Univ. of Groningen (under Nobel Laureate Bernard Feringa) and post-doctoral positions at UC San Francisco and St. Jude Children's Research Hospital.
Loren Peterson CFO	40 years experience in industrial and VC financial management. Previously, Managing Director and CFO of Venture Investors (largest WI VC firm); CEO of ZyStor Therapeutics; CEO of Sheffield Pharmaceuticals; CFO of Bock Pharmacal; and, Partner at Coopers & Lybrand. BS in Business Administration at Univ. Nebraska-Lincoln, Certified Public Accountant.

Scientific/Medical Advisors

James Cook	Distinguished Professor, Chemistry, UW-Milwaukee with more than 30 years' experience in organic and medicinal chemistry and leading expert in GABA _A R drug targeting; more than 450 scientific publications and 50 patents. PhD, University of Michigan, Post-Doctoral Univ. of British Columbia.
Charles Emala	Henrik H Bendixen Endowed Professor of Anesthesiology and Vice-Chair for Research, Columbia Univ. College of Physicians and Surgeons. Previously Assoc. Professor of Anesthesiology, Johns Hopkins. Over 120 research publications and international expert in lung physiology. MD, Univ. of MD, and residency and fellowship (anesthesiology and critical care), Johns Hopkins.
Mitchell Grayson	Chief, Allergy and Immunology, Nationwide Children's Hospital for and Ohio State University Dept. of Pediatrics. BoD American Academy of Allergy, Asthma, and Immunology. Previously Professor, Pediatrics, Allergy and Immunology, Children's Hospital of MCW. MD, Univ. of Chicago and fellowships in internal medicine (Univ. Penn) and allergy and immunology (Johns Hopkins).

Moving the program forward



MIDD0301:

A first-in-class drug for asthma



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