INVION

Targeting inflammation

INV102 (nadolol)

A new approach to the treatment of chronic airway disease

Treating the airway: background and rationale

- Existing drugs do an excellent job in opening constricted airways:
  bronchodilators include β-adrenergic and anti-muscarinic drug classes

- Existing drugs do an excellent job in decreasing inflammatory cells in the airway:
  inhaled corticosteroid (ICS) and anti-IL5 monoclonal antibody drug classes

- Fixed combinations of beta agonists and ICS are the mainstay treatment of airway disease:
  e.g. Symbicort® and ADVAIR®

- **However: these drugs have had NO positive impact on death due to chronic airway disease; death is due to increased abnormal mucus and inflammation**

Nadolol franchise: market size, relevance and interconnectedness

Chronic Obstructive Pulmonary Disease (COPD) is an umbrella term used to describe chronic lung diseases that cause limitations in lung airflow.

$47.1 billion by 2017

The global market for respiratory drugs is estimated to be **$47.1 billion by 2017**.

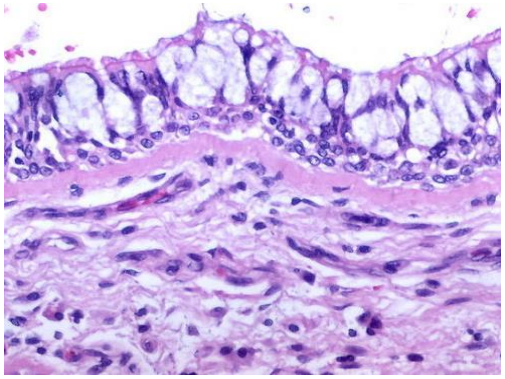
Nadolol is targeted to be used in conjunction with existing therapies to make them safer and more effective representing a niche in an existing large and growing market.

$3.8 billion by 2017

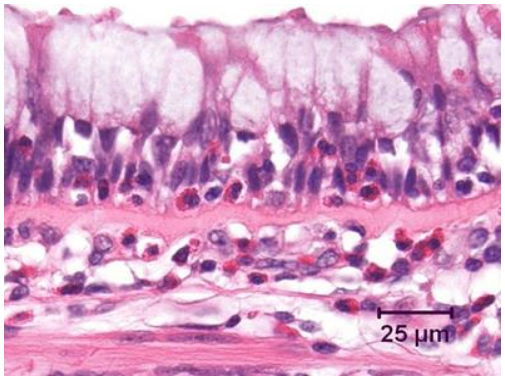
The smoking cessation drug market is predicted to be **$3.8 billion by 2016.**

Nicotine-focussed therapies comprise the bulk of the existing market, but they do not address lung healing. **Nadolol** represents an opportunity to add-on and expand an existing market.

The “vicious cycle” of chronic inflammatory airway disease



Normal Histology



Mucous metaplasia found in COPD, asthma and CF

Inflammation from:
- cigarette smoke
- chronic infection (C.F.)
- allergen, O_3 (asthma)

Increased IL-8 and beta-arrestin pathway activity

Increased goblet cell production/ loss of ciliated epithelial cells

↓ mucin clearance
↑ abnormal mucins
↑ total mucus

Increased recruitment of inflammatory cells (PMN/EOS)

Increased damage from inflammatory cells / infection

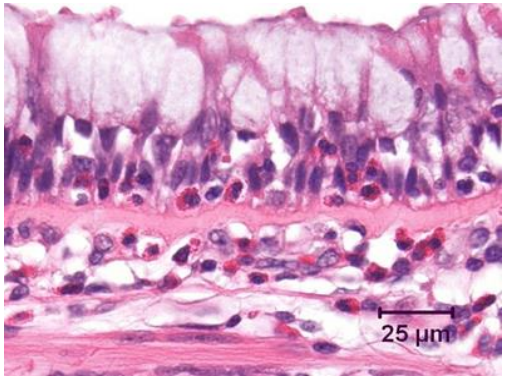
Changes in basal cell populations

INVION
Targeting inflammation

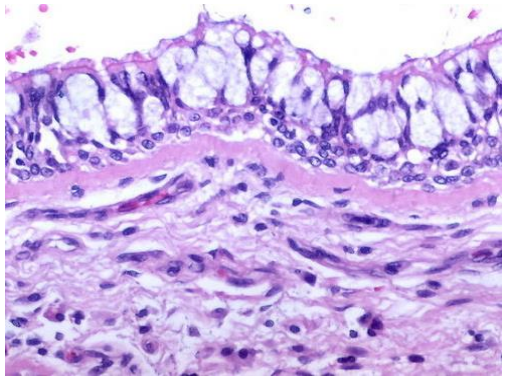
Nadolol has unique properties that could treat airway disease

- In cell experiments, INV102 (nadolol):
  - Blocks the β-arrestin pathway on airway epithelial cell β2 receptors (Lefkowitz)
- In animal experiments, nadolol:
  - Blocks (prevents) or reduces (treats) the increase in goblet cells caused by inflammation
  - Blocks the β-arrestin pathway in airway β2 receptors
  - Reduces markers of airway inflammation (IL-5) and abnormal mucus production (MUC5AC)
- In human studies, orally administered nadolol
  - Decreases biomarkers of inflammation (IL-8) and β-arrestin pathway activation (ERK2)
  - Decreases airway hyper-responsiveness, a hallmark of asthma
  - Can be safely administered by titration to minimize risk of cardiovascular side effects

Nadolol could reverse the “vicious cycle” of airway inflammation



Mucous metaplasia found in COPD, asthma and CF



Normal Histology

Nadolol

Shown in clinical trial

DECREASED IL-8 and beta-arrestin pathway activity

DECREASED goblet cell production/ loss of ciliated epithelial cells

↑ mucin clearance
↓ abnormal mucins
↓ total mucus

DECREASED recruitment of inflammatory cells (PMN/EOS)

DECREASED damage from inflammatory cells / infection

Restoration of ciliated epithelial cells

INVION
Targeting inflammation

Oral nadolol program: progress and active clinical trials and results

Clinical benefits

- ✓ the only drug targeted to address the unmet medical need of mucous metaplasia in the airway
- ✓ targeted as an add-on to existing therapies to make them safer and more effective by reducing mucous production
- ✓ targeted to assist lung healing and aid smoking cessation in patients trying to quit

Development strategy

- ✓ proof of concept
- ✓ identify speed to market commercial strategy (smoking cessation)
- ✓ identify wider use and IP opportunity (inhaled nadolol)
- ✓ phase II trials in mild asthma and smoking cessation
- > safety and biomarker data from phase II trials underpins inhaled drug program
- > endpoint in smoking cessation trial leads to EOPIII / Phase III

Development program

- ✓ pharmacology is based on biased ligand and inverse agonist activity at beta receptor in airway
- ✓ chemistry and manufacturing, including titration dose development
- ✓ toxicology and metabolism profile
- ✓ IND status
- ✓ 2 x proof of concept studies in patients with mild asthma (Hanania)
- ✓ phase II in mild asthma (NIH sponsored, ongoing) & Phase II in smoking cessations (reports Q3 2015)
- ✓ interim data shows clinical relevant changes in biomarkers of inflammation
- > Final data to characterize airway epithelial response through biochemical markers; design next oral and inhaled studies; and create new intellectual property based on correlations of safety and efficacy with biochemical marker profiles.

Oral nadolol: 155 patients phase II smoking cessation study reporting Q315.

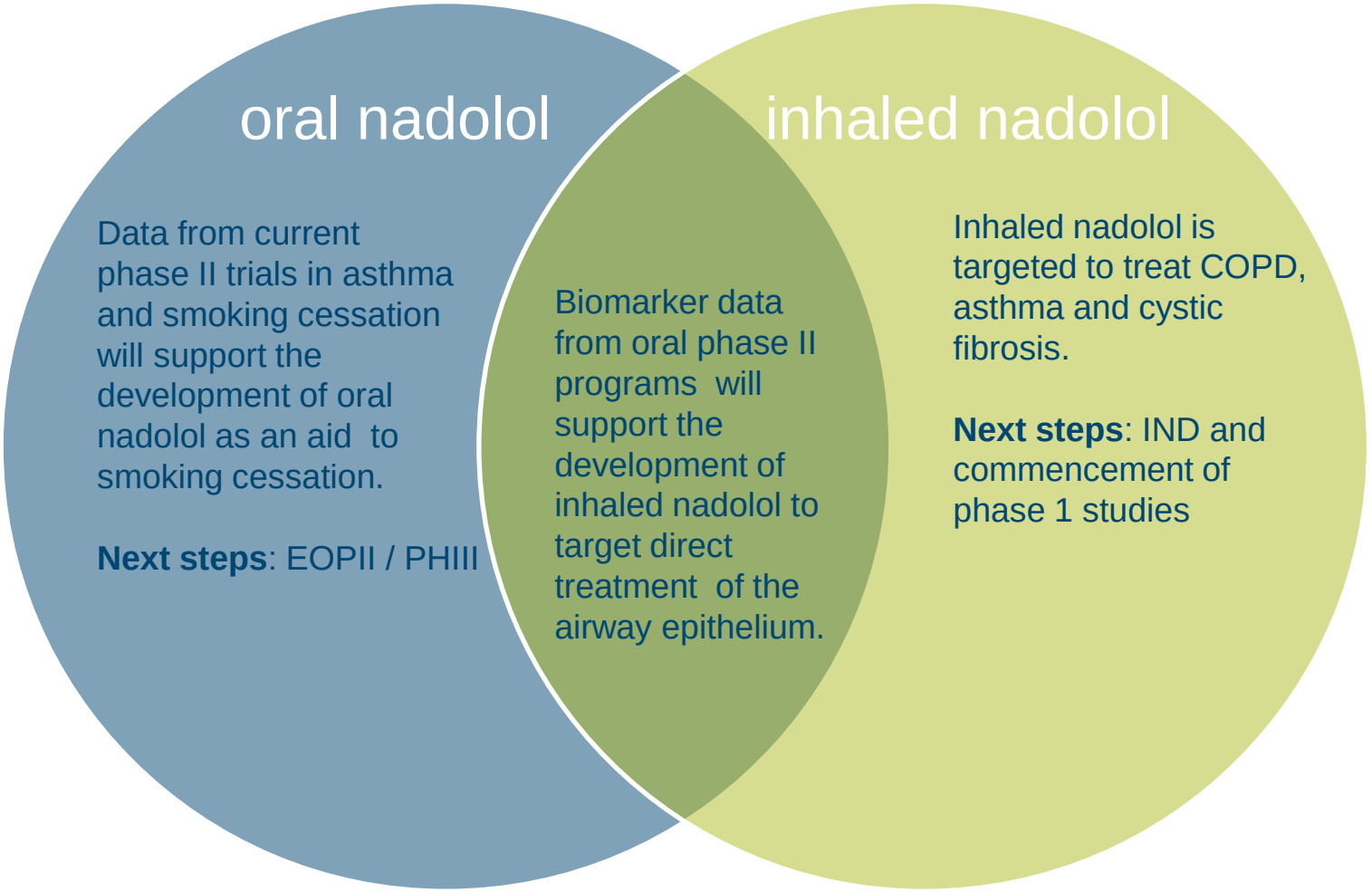
Leveraging the data: upcoming analysis and reporting

Third quarter planned analyses and reporting		Fourth Quarter
Biomarkers	**Smoking cessation**	**Combined data**

> Report on effects of nadolol vs placebo on key biomarkers
  > IL-8 (neutrophil attraction)
  > ERK2 (beta arrestin pathway)
  > MUC 5AC (abnormal mucus)
> Secondary analysis of responders and biomarker changes - identifying markers that are/are not useful in longer term studies
	> Report on smoking cessation rates in nadolol treatment versus placebo
	> Secondary analyis is on reduction versus cessation rates
	> Dose responses and responders as a function of dose, titration and history
		> Correlation of smoking cessation/ reduction data with baseline biomarkers
		> Correlation of smoking cessation/ reduction data with biomarker changes
		> New IP prosecution

INVION
Targeting inflammation

Nadolol franchise: progressively de-risked



INVION
Targeting inflammation

Inhaled nadolol program: progress and clinical development strategy

Clinical benefits

- ✓ once daily dosing directly to the site of injury at 1/100 of the oral dose to mitigate systemic side effects
- ✓ targeted for long term use in COPD, severe asthma and cystic fibrosis as an add-on to existing therapies to make them safer and more effective by reducing mucous production an enabling lung healing
- > Medium-term development: combination therapies
  - > inhaled nadolol + LABA + ICS (Asthma)
  - > inhaled nadolol + LAMA + ICS (COPD)
  - > inhaled nadolol + antibiotics (CF)

Status of collaboration with 3M Drug Delivery systems for proprietary formulation and device using 3M's pressurised metered dose inhalation (pMDI) technology

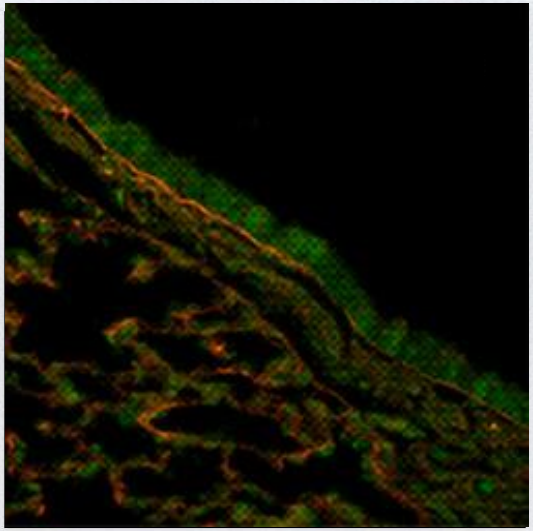
- ✓ Formulation and device selected
- ✓ Toxicology supplies manufactured
- ✓ Clinical supplies manufactured
- ✓ Toxicology supplies provided to CRL (Montreal QUE); toxicology studies have commenced

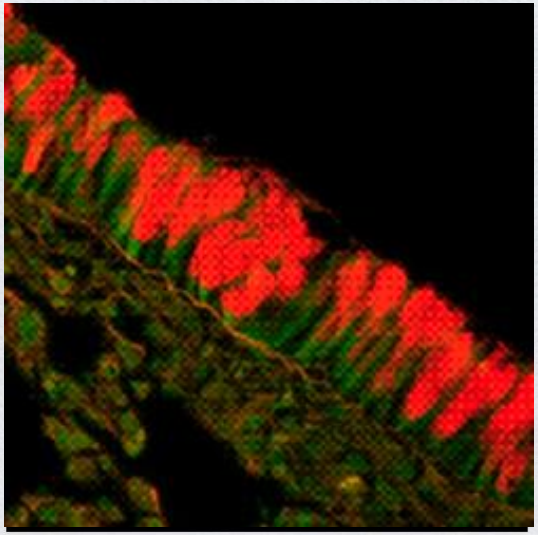
Development program

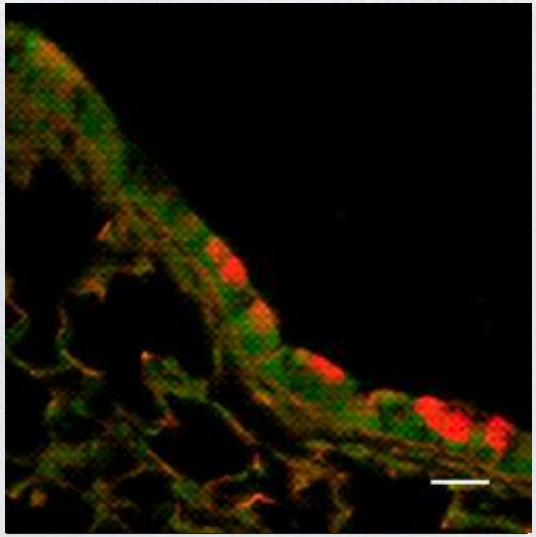
- ✓ Pre-IND status with FDA
- ✓ Commencement of toxicology studies
- > IND submission (2016)
- > Phase I and Phase II clinical studies in asthma, COPD and cystic fibrosis (2016-7)

INVION

Targeting inflammation







Nguyen LP., et.al., 2011. Complementary anti-inflammatory effects of a β-blocker and a corticosteroid in an asthma model. Arch Pharmacol. 2011: Oct 2; Nguyen, LP, et al. (2008). Am J Respir Cell Mol Biol 38:256-262