BLU-5937: A Selective P2X3 Antagonist With Potent Anti-Tussive Effect and No Taste Alteration

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Targeting P2X3 to Treat Chronic Cough with Potential No Taste Effect

P2X3 homotrimeric receptors are linked to cough hypersensitivity

P2X2/3 heterotrimeric receptors are linked to taste function

Hypothesis:
Selective inhibition of P2X3 homotrimeric receptors would reduce cough without impact on taste perception
P2X2/3 is Linked to Taste Function

• Both P2X2 and P2X3 channels are expressed in taste buds\(^1\)
• Almost all nerve in the fungiform papillae are double stained for P2X2 and P2X3\(^1\)
• Knockout of both P2X2 and P2X3 is required for taste loss in KO mouse\(^2\)

\(^1\)Ishida et al 2009; \(^2\)Finger et al 2005
P2X3 is Linked to Cough Hypersensitivity

Jugular C-fibers (expressing predominantly P2X3) innervating upper airways transmit cough sensitization signals to CNS

Kwong et al 2008: Single-cell RT-PCR analysis of 22 lung specific jugular neurons
BLU-5937: High Selectivity for P2X3 Provides Proof of Concept in Preclinical Models

Overview of Key Preclinical Studies with BLU-5937

- **Cell-based FLIPR assay**: >2000 more selective for hP2X3 vs. hP2X2/3
- **DRG neuron sensitization**: Blocks ATP mediated neuronal sensitization
- **Guinea pig cough model**: Reduces cough at concentration blocking P2X3 but not P2X2/3
- **Rat taste model**: No effect on taste

**BLU-5937**: Potential to reduce cough with no taste effect at targeted therapeutic dose
BLU-5937: Highly Selective for Human P2X3 Receptors

<table>
<thead>
<tr>
<th>BLU-5937</th>
<th>hP2X3 (IC$_{50}$)</th>
<th>hP2X2/3 (IC$_{50}$)</th>
<th>Selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha,\beta$-me ATP 3 µM</td>
<td>11 nM</td>
<td>&gt;30 µM</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>$\alpha,\beta$-me ATP 30 µM</td>
<td>13 nM</td>
<td>&gt;30 µM</td>
<td>&gt;2000</td>
</tr>
</tbody>
</table>

Cloned hP2X3 and hP2X2/3 channels expressed in HEK295 cells; (Ca$^{2+}$ FLIPR)

- Potent antagonist of hP2X3
- Highly selective for hP2X3 vs hP2X2/3
- Not ATP-competitive
- No inhibition of other P2X channels
- Not agonist/antagonist of 159 targets tested
BLU-5937 Blocks ATP-Mediated DRG Neuron Sensitization

1. Inject current
2. Sensitize with ATP
3. BLU-5937
4. Control washout

Using current mode, patch-clamp recording in selected P2X3 expressing DRG neurons from rat
Guinea Pig (CA + Histamine) Cough Model

Total cough average

Histamine (0.6 mM)

Citric acid (CA)  CA + 0.3 mg/kg  CA + 3 mg/kg  CA + 30 mg/kg

Control  BLU-5937  NE0588

Treatments (control, BLU-5937, NEO588) were administered orally 2 hours prior to tussive agent exposure: citric acid (0.1 M, aerosol) and histamine (0.6 mM, aerosol); n=6 / group; *p<0.05 vs (CA + histamine); NEO588 (gefapixant)

BLU-5937 shows similar anti-tussive effect as NE0588, a non-selective gpP2X3 antagonist, at concentration that blocks P2X3 but not P2X2/3
BLU-5937 Reduces ATP Induced Cough Hypersensitivity

Guinea Pig (CA + ATP) Cough Model

**BLU-5937 shows similar anti-tussive effect as NE0588, a non-selective gpP2X3 antagonist, at concentration that blocks P2X3 but not P2X2/3**
BLU-5937 has no Effect on Taste in Rat Model

Rat (Quinine) Taste Model

Mean ± SEM; n= 10/group; * p<0.05 vs control

A weakly selective antagonist for rP2X3, inhibits taste

No taste effect

Treatments (control, BLU-5937, NEO588) were administered ip: animals were water-fasted overnight and presented with one bottle water and quinine (0.3mM) at T$_{max}$; volume of liquid consumed measured for 15 minutes; n=10 / group
BLU-5937: Drug-like Characteristics

- Good oral bioavailability
- Good metabolic stability in human hepatocytes or liver microsomes
  - Dose regimen predicted in man: twice a day (BID)
- Does not cross blood-brain barrier
  - No adverse effect on general behavior / neurological function in rat
- High safety margin in preclinical toxicity studies (rat & dog)
  - Main clinical sign: emesis observed in dogs at high doses (≥ 300 mg/kg/day)

BLU-5937 characteristics and animal proof of concept support moving into clinical studies
BLU-5937: Clinical Plan to Phase 2 Proof-of-Concept

Q3 2018 – Q4 2018
Clinical Phase 1
- Healthy Subjects
  - Tolerability (taste)
  - Dosing for Phase 2

H1 2019 – H1 2020
Clinical Phase 2
- Chronic Cough subjects
  - Efficacy
  - Tolerability (taste)
  - Dosing for Phase 3
BLU-5937: Conclusions

- Potent and highly selective hP2X3 homotrimeric receptor antagonist
- Reduces histamine and ATP-induced cough sensitization in the guinea pig cough model through P2X3 homotrimeric receptor inhibition
- No effect on taste perception at concentration that fully block P2X3 homotrimeric receptors in rat behavioral taste model
- It has excellent drug-like characteristics

BLU-5937 has the potential to inhibit cough hypersensitivity without affecting taste perception in chronic cough