EP2 Receptor Antagonists for the Treatment of Neurological Diseases

From the laboratory of:
Raymond J. Dingledine (Pharmacology)

Cale Lennon
Director, Licensing
OTT Breakfast Club
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Neurodegenerative Diseases

10 Million in U.S. Affected

- Parkinson's (1M)
- Alzheimer's (5M)
- Amyotrophic Lateral Sclerosis (ALS) (30K)
- Stroke (1M)
- Epilepsy (3M)

• Inflammatory response - both friend and foe
• Dominant player: COX-2 pathway
Challenges With COX-2 Inhibition

- PGH2
- Gastric acid/mucous
- Inflammation/Pain
- GI Smooth Muscles
- Bronchodilator/contractor
- Intraocular pressure
- Platelet aggregation

**COX-2**

- Prostaglandins
- Thrombosis (Stroke, Heart Attack)

**VIOXX**

*Arthritis pain alleviated... even if it kills you.*

**BEXTRA**

Linked to increased risk of heart attack
Target for Brain Anti-inflammatory: EP2 Receptor

Therapeutic Candidate Profile:
EP2 receptor-specific antagonist that crosses the blood brain barrier
Compound Development

Cell based assay: inhibition of PGE$_2$-induced cAMP accumulation in EP2 neural cells

262,371 compounds screened

656 primary hits

Secondary screens for selectivity: 13 compounds

SAR to improve PK profile

Lead compound: TG6-10-1
EP2 receptor antagonist
EP2 Receptor Antagonist Reduces Mortality and Neurodegeneration After Status Epilepticus
First-in-class therapeutic for treatment of inflammation-associated injury in the CNS

1\textsuperscript{st} Generation: U.S. and international patents pending

2\textsuperscript{nd} Generation: provisional patent filed 4/14

POC in other neurodegenerative disease models

Identify preclinical candidate and backup (selectivity, solubility, PK, off-target activity)