Challenges in Neuroscience Discovery and Development

What has Changed and Where are We Headed?

Darryle D Schoepp, Ph.D.
Vice President and Therapeutic Area Head, Neuroscience
Summary of Talk

• Historically how successful have we been in Neuroscience Therapeutics?
• What has led to / defined past success?
• What is different now?
• What does future success look like?
• What we now need to do?
• Recent example: Belsomra (Suvorexant) “Trifecta of Target Validation”
Global burden of neurologic and psychiatric disorders

- The **disability-adjusted life year (DALY)** is a measure of overall disease burden.
- Each DALY represents 1 year lost due to ill-health, disability or early death.
- WHO estimates that in the United States between 2000 and 2012, disorders of the nervous system accounted for 7 of the 20 highest causes of DALYs.

1 WHO global health estimates 2014
http://www.who.int/healthinfo/global_burden_disease/en/
2008 Neuroscience Overview

- **Psychiatry**
  - Largest value accounting for ~ 48% of all CNS sales
  - Significant unmet need especially in schizophrenia and depression / bipolar where opportunity still exists for novel drugs

- **Neurology**
  - Growing sector of CNS need as aging population drives prevalence in neurodegenerative disorders

What can we say about these classes of drugs?

*Source: Merck Commercial data and input; IMS 2008; CNS Market Outlook to 2012, Business Insights; Datamonitor CNS Market Overview April 2008*
# Neuroscience Therapeutic Mechanisms in 2010

<table>
<thead>
<tr>
<th>Neurotransmitter Class</th>
<th>System / Function</th>
<th>Drugs Approved</th>
<th># of Top 60 Drugs</th>
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<td>- GABA</td>
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<td>6 / 60</td>
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Source: Verispan, VONA, Drugs.com
• Imipramine was first tried against psychotic disorders such as schizophrenia, but proved insufficient.

• At the first international congress of neuro-pharmacology in Rome, September 1958 Dr Freyhan from the University of Pennsylvania discussed as one of the first clinicians the effects of imipramine in a group of 46 patients, most of them diagnosed as "depressive psychosis".

• The patients were selected for this study based on symptoms such as depressive apathy, kinetic retardation and feelings of hopelessness and despair.

• In 30% of all patients, he reported optimal results, and in around 20%, failure.
Antidepressant New Drug Approvals – Iteration of Serendipity

Year of FDA Approval

- 1980: nomifensine
- 1985: trazodone
- 1990: bupropion
- 1995: buspirone
- 2000: fluoxetine
- 2005: sertraline

Color codes:
- SSRI
- SNRI
- NRI and/or DRI
- 5-HT₂ antagonist
- 5-HT₁A agonist

OUS approvals:
- reboxetine......1997
- tianeptine......1988
- zimelidine......1974
Drug Sales for Major Therapeutic Areas – 2005-2020
Top 200 Drugs

Source: EvaluatePharma
Neuroscience Drugs Patent Cliff - Top Contributing Drugs

Yearly top CNS drug sales

Sales in $MM

Source: EvaluatePharma
Historically how successful have we been in Neuroscience Therapeutics?

What has led to / defined past success?

- What is different now?
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- What we now need to do?

- Recent example: Belsomra (Suvorexant) “Trifecta of Target Validation”
Each year, CDER approves hundreds of new medications, most of which are variations of previously existing products. These new products contribute to quality of care, greater access to medication, more consumer choice, and a competitive marketplace that enhances affordability and public health.

However, products in a small subset of these new approvals, which we refer to as novel new drugs, are among the more truly innovative products that often help advance clinical care to another level.

At the end of each calendar year, CDER summarizes these new products.
41 novel new drug approvals in CY 2014 is more than the average number approved annually during the past decade.

From 2005 through 2013, CDER has averaged 25 novel new drug approvals per year.
Class of 2014: 41 Novel New Drug US Approvals

Innovation in Neuroscience is “Still” Rare

- Only ONE Neuroscience compound on first-in-class list
- Two on entire list of 41 but one was a PET diagnostic (Neuraceq / 18F-florbetaben)
Novel New Drug US Approvals by Year
Innovation in Neuroscience is “Still” Rare

How many Neuroscience compounds on first-in-class lists?
### Neurotransmitter Class

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**L-DOPA: First Rationally Designed CNS Drug?**

1910: Dopamine synthesized
1913: L-DOPA isolated from Fava beans
1938: L-Dopa Decarboxylase Discovered
1957: Brain dopamine is involved in motor function
1959: Dopamine enriched in striatal / motor brain regions
1960: Severe dopamine depletion in Parkinson’s brain
1961: L-DOPA clinical trial for dopamine replacement
1967: High dose chronic L-DOPA therapy introduced
1969: L-DOPA plus DOPA decarboxylase inhibitor therapies introduced
Using Human Biology to Shape Therapeutic Approaches and Select the Best Drug Targets

What’s in our toolbox?

- Genetics
- Pathophysiology
- Pharmacology

Understanding of human disease

New ideas for drug targets

1. Modify/prevent disease
   - Target Pathophysiology
     - Alpha Synuclein
     - Lewy body

2. Restore function
   - Subthalamic Nucleus Neuronal Firing Rate Increases with Parkinson’s Disease Progression
   - STN activity: Naive Rat
   - STN activity: 6-OHDA Lesioned Rat
Using Human Biology to Shape Therapeutic Approaches and Select the Best Drug Targets

**What’s in our toolbox?**

- **Genetics**
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**Understanding of human disease**

1. **Modify/prevent disease**
   - Example: target pathophysiology
     - Amyloid
     - BACE INHIBITION – MK8931

2. **Restore function**
   - Example: Restoring acetylcholine signaling
     - Normal Brain
     - Alzheimer’s Brain

- Cholinergic Neurons
  - Vehicle
  - Compound
  - Receptor PAMs
    - Nicotinic Muscarinic
Class of 2014: Many New Drugs for Orphan Diseases

About 41% of the novel new drugs approved in 2014 (17 of 41) were approved to treat rare or “orphan” diseases that affect 200,000 or fewer Americans. This is significant because patients with rare diseases often have few or no drugs available to treat their conditions.

What does this mean for the Neuroscience area?
Neuroscience Diseases– What to Chose?

Major Diseases

- Alzheimer’s Disease
- Parkinson’s Disease
- Pain / Migraine
- Schizophrenia
- Depression
- Insomnia

Consider:
- Supporting science
- Ability to translate
- Address medical needs
- Major markets

“Rare” / Orphan Diseases

- Well defined patient populations
- Broader applications may also be possible
- Means to interrogate a novel mechanism

- Tauopathies (e.g. FTLD / PSP)
- Lewy Body Dementia
- ALS
- Gauchers Disease
- Narcolepsy
- Others.....

Consider:
- Very strong supporting science
- Increased POS
- Benefit versus risk more favorable
- Very high medical need
- Faster path to POC / Registration
**Panel: Diseases with tau inclusions**

- Alzheimer’s disease
- Amyotrophic lateral sclerosis and parkinsonism-dementia complex
- Argyrophilic grain disease
- Chronic traumatic encephalopathy
- Corticobasal degeneration
- Diffuse neurofibrillary tangles with calcification
- Down’s syndrome
- Familial British dementia
- Familial Danish dementia
- Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations)
- Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations)
- Gerstmann-Sträussler-Scheinker disease
- Guadeloupean parkinsonism
- Myotonic dystrophy
- Neurodegeneration with brain iron accumulation
- Niemann-Pick disease, type C
- Non-Guamanian motor neuron disease with neurofibrillary tangles
- Pick’s disease
- Postencephalitic parkinsonism
- Prion protein cerebral amyloid angiopathy
- Progressive subcortical gliosis
- Progressive supranuclear palsy
- SLC9A6-related mental retardation
- Subacute sclerosing panencephalitis
- Tangle-only dementia
- White matter tauopathy with globular glial inclusions

**Alzheimer’s Disease**

**Progressive supranuclear palsy**
OGA Inhibitors Increase Tau O-GlcNAcylation and Reduce Formation of Toxic Tau Species

- In adult brain, tau is O-GlcNAcylated at several sites
- OGA inhibitors increase tau O-GlcNAcylation

Pathological tau aggregates Modified in various ways:
  - Hyperphosphorylated (P)
  - Acetylation (A)
  - Nitrated (N)
  - Ubiquitinated (U)

- OGA inhibitors block formation of pathological tau
Preclinical data demonstrated that MK-8719 dose dependently elevated brain O-GlcNAcylation and reduced pathological tau in the brains of Tg4510 mice.

* p<0.05, **p<0.01 ***p<0.001
Contrasting Clinical Approaches for “Anti-Tau” POC

- **Merck’s First-in-Class BACE inhibitor (MK-8931)** – Initiated 2012
  - ~2,000 patients with Mild to Moderate Alzheimer’s Disease
    - Primary Endpoint: Change from Baseline in AD Cognitive and Functional measures
    - 78 weeks of treatment with estimated study completion date in 2017
  - ~1,500 patients with Prodromal Alzheimer’s Disease
    - Collaborations with GE Healthcare (PET-flutemetamol) and Luminex (CSF tau/Aβ) collaborations for patient selection
    - Primary Endpoint: CDR-Sum of boxes
    - 104 weeks of treatment with estimated study completion in 2018

Clinical POC Trial in Progressive Supranuclear Palsy (PSP)

*Image of a graph showing the change in PSPRS over weeks.*

*Image citation: Lancet Neurol 2014*

*Published Online May 27, 2014*

*http://dx.doi.org/10.1016/S1474-4422(14)00088-2*
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Recent success example: Belsomra (Suvorexant) “Trifecta of Target Validation”
Introducing
A DIFFERENT APPROACH TO TREATING INSOMNIA

Belsomra® (suvorexant)
5, 10, 15, 20 mg tablets

FDA APPROVED*
Belsomra: genetics, pathophysiology and pharmacology

Discovery of Orexin (hypocretin) peptides - 1998
Orexin 2 receptor identified as cause of canine narcolepsy - 1999
Loss of Orexin neurons in Narcolepsy patients - 2000
Orexin Antagonist Discovery Programs - 2005

Suvorexant PhIII - 2008
Suvorexant Approval - 2009
First Human Dose - 2014
Narcoleptic Dogs

Loss of Orexin neurons in Narcolepsy patients
Orexin peptide KO mice show sleep phenotype
Narcolepsy Patient
Normal

Narcolepsy Patient
Normal
Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial

Lancet Neurol 2014; 13: 461–71

David Michelson, Ellen Snyder, Erin Paradis, Mary Chengan-Liu, Duane B Snively, Jill Hutzelmann, James K Walsh, Andrew D Krystal, Ruth M Benca, Martin Cohn, Christopher Lines, Thomas Roth, W Joseph Herring

Sleep Onset Effects
Subjective Time To Sleep Onset (sTSO)

Suvorexant vs. Placebo at Month 12 p-value (nominal) <0.01

Time (months)

Adjusted Mean Change from Baseline sTSO with 95% CI (minutes)

Suvorexant: n=492 (Month 1)
Placebo:  n=245 (Month 1)

Sleep Maintenance Effects
Subjective Total Sleep Time (sTST)

Suvorexant vs. Placebo at Month 12 p-value (nominal) <0.001

Time (months)

Adjusted Mean Change from Baseline sTST with 95% CI (minutes)

Suvorexant: n=492 (Month 1)
Placebo: n=245 (Month 1)
Introducing
A DIFFERENT APPROACH TO TREATING INSOMNIA

Sleep architecture (Gotter et al., 2014 BMC Neurosci; Winrow et al. 2012 Neuropharm.)
qEEG by sleep stage analysis (Fox et al., 2013 Neuropsychopharm.; Ma et al., 2014 Sleep)
Locomotor performance (Ramirez et al., 2013 Front Neurosci.)
Alcohol interaction (Ramirez et al., 2013 Front Neurosci.)
Effects on cognition (Uslaner et al., 2013 Science Transl. Med; Winrow & Renger 2014 BJP)
Salience gating and arousability (Tannenbaum et al., 2014 Front Behav Neurosci)

Belsomra® (suvorexant)
5, 10, 15, 20 mg tablets

MSD
Be well
Using Human Biology to Shape Therapeutic Approaches: Orexin Future Areas

**Target**

**Orexin Hyper-activity**

Orexinergic System Dysregulation, Sleep Impairment, and Cognitive Decline in Alzheimer Disease

“The orexinergic system seems to be dysregulated in AD, and its output and function appear to be overexpressed along the progression of the neurodegenerative process.”

“...we hypothesize that, .....orexin receptor antagonists will be used as potential drugs targeting ....the management of sleep disturbances in AD patients

Liguori et al., 2015 *JAMA Neurol.* 2014

**Target**

**Orexin Hypo-Activity**

Agonist Replacement Therapy Narcolepsy

Mieda, et al, 2004
Conclusions: Opportunities in Neuroscience Therapeutics

- **YES…** Neuroscience disorders are complex and there is much we do not yet know….

- **BUT……** The need for therapies to treat nervous system disorders are now even greater and ….

- **TODAY…..** Understanding of human biology / pathophysiology of the nervous system is advancing rapidly and …. 

- **LOOKING AHEAD….** promising new approaches, drug targets and biomarkers for disease will continue to advance so that …. 

- **NEW THERAPIES WILL COME….** from new approaches linked to our increasing understanding of human disease biology
Merck Neuroscience Pipeline Approach to Increase POS and Patient Value

- High quality molecules and positioning to test important disease hypotheses
- Development approaches that provide the greatest opportunities of demonstrating meaningful clinical advantages

Industry Leading First-in-Class Development Candidates and Products

- Alzheimer’s disease
- Parkinson’s disease
- Pain
- Cognition
- Schizophrenia
- O-GlcNAcase inhibitor neurodegeneration
- Alzheimer’s disease modification
- BRIDION™ (sugammadex) neuromuscular blockade reversal agent
- BELSOMRA™ (suvorexant) dual orexin receptor antagonist

Discovery Registration
Thank You!

Merck Orexin Team – MK4305 Suvorexant – Many, many contributors
Special Thanks……………………Well Done!!!!!!

John Renger
Paul Coleman
Chris Winrow
Tony Gotter
Pam Tannenbaum
Jason Uslaner
Richard Hargreaves
Joe Herring
David Michelson
Carol Sable
Eric Luthi

Merck OGA Team /Alectos – MK8719

Merck BACE Team – MK8931

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