Crossing the Rubicon: NIDA/Industry Partnerships

Phil Skolnick, Ph.D., D.Sc. (hon.)
Director, DPMCCDA
Teva has entered the addiction field with a Phase 2 study of TV-1380 for cocaine addiction. This candidate is an albumated (to increase the t½) form of butyrylcholinesterase, an enzyme which metabolizes cocaine.
NIDA/Industry (esp. Big Pharma) Collaboration Is A Relatively Recent Phenomenon

Why now?

- Retreat from psychiatric drug development – most potential candidates to treat SUDs are repurposed from psychiatry portfolios (few bespoke SUD programs).
Companies Are Paring Back Internal Neuroscience R&D

April 2009 Sanofi overhauls its pipeline, ending development of more than a dozen drugs and vaccines, including an antidepressant. The following year, the company cuts hundreds of sales jobs, citing its reduced activities in central nervous system (CNS) research.

January 2010 GlaxoSmithKline ends neuroscience drug R&D in Harlow, England, and abandons some areas of neuroscience research, including depression and pain.

July 2010 A year after its acquisition of Schering-Plough, Merck & Co. closes a neuroscience research lab in the U.K. and consolidates activities at two sites in the U.S.

December 2011 Novartis announces the closure of its neuroscience R&D site in Basel, Switzerland, and the formation of a smaller group in Cambridge, Mass., to study the genetics of certain CNS disorders.

February 2012 AstraZeneca announces it will lay off some 2,200 scientists, mostly in neuroscience R&D. The firm is closing a research lab in Montreal and ending R&D in Södertälje, Sweden.
An Increased Level Of Interest In Collaboration Is A Relatively Recent Phenomenon

Why now?

• Retreat from psychiatric drug development – most potential candidates to treat SUDs are from a psychiatry portfolio (few bespoke SUD programs).

• SUDs now represent a “rescue” indication for these molecules.

• Data demonstrating the market potential of medications to treat SUDs.
Why Has The Pharma/Biotech Sector Remained (Largely) Indifferent To SUDs?

- *Perceived small market size (ROI)*
- Regulatory hurdle: current focus on abstinence (as opposed to reduced use)
- A fractured advocacy message (meds vs no meds and views in between)
- Corporate image and liability issues
- Uncertainty about reimbursement
U.S. Suboxone® Sales Reached $1.49 Billion in 2012—More Than Viagra® or Adderall®

Source: Drugs.com, citing use of the IMS Health “Multinational Integrated Data Analysis System” (MIDAS)
### 2011 U.S. Estimates of Current (past month) Drug Use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use During Past Month</th>
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<tbody>
<tr>
<td>Marijuana</td>
<td>18.1 Million</td>
</tr>
<tr>
<td>Rx Pain Relievers (nonmedical use)</td>
<td>4.5 Million</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.4 Million</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>439,000</td>
</tr>
<tr>
<td>Heroin</td>
<td>281,000</td>
</tr>
</tbody>
</table>

Source: U.S. Substance Abuse and Mental Health Services Administration  
“2011 National Survey on Drug Use & Health” ~ 67,500 randomly selected individuals
Rough Estimate of U.S. Market for a First-in-Class Cocaine Addiction Treatment

1.4 M regular users

If 20% seek treatment each year, then market = 280,000/year

If average treatment duration is 6 months & the medication costs $700/mo, then sales >$1 BB per year
TITLE OF CRADA: Evaluation of Teva’s Proprietary Compound, TV-1380, for the Treatment of Cocaine Dependence.

PHS [IC] Component: National Institute on Drug Abuse (NIDA)
IC Extramural Investigator/Officer: Dr. Shwe M. Gyaw

Collaborator: Teva Pharmaceutical Industries, Ltd.
Collaborator Principal Investigator: Dr. Yossi Gilgun-Sherki

TERM OF CRADA: Three (3) years from the Effective Date.

ABSTRACT OF THE RESEARCH PLAN

The National Institute on Drug Abuse (NIDA) and Teva Pharmaceutical Industries, Ltd. have entered into an Extramural Clinical Cooperative Research and Development Agreement (CRADA) to conduct a Phase II clinical trial of the safety and efficacy of Teva’s proprietary compound, TV-1380, in the treatment of cocaine dependence. TV-1380 contains an enzyme that metabolizes cocaine and has been shown to decrease concentrations of cocaine in plasma, heart, and brain.
Pathways of cocaine metabolism

(-)-Cocaine

Butyrylcholinesterase

N-demethylase

Liver carboxylesterase

(-)-Norcocaine

5%

Butyrylcholinesterase

(-)-Ecggonine methyl ester

~45%

Benzoic acid

(-)-Benzoyldeconine

~45%

Methanol

(+)-Norecgonine methyl ester

~5%

Benzoic acid

(+)Norcocaine

(-)-Cocaine
Cocaine as BChE substrate

Cocaine docked into human butyrylcholinesterase
A Cocaine Hydrolase Engineered from Human Butyrylcholinesterase Selectively Blocks Cocaine Toxicity and Reinstatement of Drug Seeking in Rats

Stephen Brimijoin*,1, Yang Gao1, Justin J Anker2, Luke A Gliddon2, David LaFleur3, R Shah3, Qinghai Zhao3, M Singh3 and Marilyn E Carroll2

1Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN, USA; 2Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA; 3Drug Development, CoGenesys Inc., Rockville, MD, USA

Successive rational mutations of human butyrylcholinesterase (BChE) followed by fusion to human serum albumin have yielded an efficient hydrolase that offers realistic options for therapy of cocaine overdose and abuse. This albumin-BChE prevented seizures in rats given a normally lethal cocaine injection (100 mg/kg, i.p.), lowered brain cocaine levels even when administered after the drug, and provided rescue after convulsions commenced. Moreover, it selectively blocked cocaine-induced reinstatement of drug seeking in rats that had previously self-administered cocaine. The enzyme treatment was well tolerated and may be worth exploring for clinical application in humans.

Neuropsychopharmacology advance online publication, 16 January 2008; doi:10.1038/sj.npp.1301666

**Keywords:** cocaine overdose rescue; addiction relapse; protein-based therapeutics for cocaine abuse; albumin fusion proteins; operant conditioning; drug self-administration rodent model
BChE - cocaine hydrolase

Successive Mutation Generations

- wild type BChE
- A199S/F227A/S287G/A328W/Y332A
- F227A/S287G/A328W/Y332A
- A199S/S287G/A328W/Y332G
- A328W/Y332A
- A199S/S287G/A328W/Y332G

cocaine $k_{cat}$


Brimijoin, et al., Neuropsychopharmacol. 2008
TV-1380 Eliminates cocaine by hydrolysis in rats

Rats were given TV-1380 (3 mg/kg) or saline, through the tail vein. Ten minutes later they received 30 µCi 3H-cocaine (3.5mg/kg), also through the tail vein. Tissues were collected at 10 min (6 rats).

Brimijoin et al., 2008
Effects of An Engineered Esterase In A Rat Relapse Model

Cocaine 1\textsuperscript{st} time
acquisition

Cocaine stop
maintenance
extinction

Cocaine 2\textsuperscript{nd} time
reinstatement

Lever Pressing

Elapsed time (weeks)
TV-1380 Eliminates Responding Following Re-exposure to Cocaine

From: Dr. Merav Bassan, TEVA
Modification of pharmacokinetic and abuse-related effects of cocaine by human-derived cocaine hydrolase in monkeys

Charles W. Schindler¹, Zuzana Justinova¹,², David Lafleur³, Doug Woods⁴, Viktor Roschke³, Hussein Hallak⁵, Liora Sklar-Tavron⁵, Godfrey H. Redhi¹, Sevil Yasar⁶, Jack Bergman⁷ & Steven R. Goldberg¹

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, DHHS/NIH/NIDA Intramural Research Program, Baltimore, MD, USA¹, Department of Psychiatry, University of Maryland School of Medicine, MPRC, Baltimore, MD, USA², Zyngenia, Inc., Gaithersburg, MD, USA³, 709 Market Street East, Gaithersburg, MD, USA³, Teva Innovative Ventures, Teva Pharmaceutical Industries Ltd., Israel⁵, Division of Geriatric Medicine and Gerontology, Johns Hopkins University, School of Medicine, Baltimore, MD, USA⁶ and Harvard Medical School-McLean Hospital, Belmont, MA, USA⁷
Serum TV-1380 Concentrations over Time

Opinions or conclusions expressed by Dr. Skolnick in connection with this presentation, a final draft of which has not been reviewed by Teva Pharmaceutical Industries Ltd. do not necessarily reflect the views of the company.
Time course of plasma cocaine concentration (40 mg/kg, i.v.)

Opinions or conclusions expressed by Dr. Skolnick in connection with this presentation, a final draft of which has not been reviewed by Teva Pharmaceutical Industries Ltd. do not necessarily reflect the views of the company.

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Efficacy and Safety of TV-1380 as Treatment for Facilitation of Abstinence in Cocaine-Dependent Subjects

This study is currently recruiting participants.
Verified June 2013 by Teva Pharmaceutical Industries

Sponsor:
Teva Pharmaceutical Industries

Information provided by (Responsible Party):
Teva Pharmaceutical Industries

ClinicalTrials.gov Identifier:
NCT01887366
First received: June 24, 2013
Last updated: June 28, 2013
Last verified: June 2013

The primary objective of this study is to assess the efficacy and safety of TV-1380 [Recombinant human serum albumin (HSA) mutated butyrylcholinesterase (AlbuBChE)] in facilitating abstinence in cocaine-dependent subjects.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine Addiction</td>
<td>Drug: TV-1380 150 mg</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Drug: TV-1380 300 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug: Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A 12-week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Once-Weekly Intra-Muscular Injections of TV-1380 (150 mg/Week or 300 mg/Week) as Treatment for Facilitation of Abstinence in Cocaine-Dependent Subjects
NIDA and AstraZeneca partner to develop potential addiction medication

Announcement

May 10, 2013

NIDA and AstraZeneca, a global research-based biopharmaceutical company, have joined efforts to explore a novel medication to treat drug addiction. The scientific partnership will explore a specific molecule that modulates the activity of glutamate – an excitatory neurotransmitter. Preclinical studies with this class of molecule indicate that it could be effective for treating a range of mental disorders, including abuse of substances ranging from tobacco to cocaine.
News & Analysis

An Audience with...

Menelas Pangalos

AstraZeneca, along with many of its big pharma peers, has struggled to deliver new drugs in recent years. In the hopes of turning the company around, its Chief Executive Officer Pascal Soriot recently shuffled the scientific management and promoted Menelas Pangalos to head up the discovery and early-stage development of small molecules. Pangalos has been with AstraZeneca since 2010 and has previously worked at Pfizer as head of neuroscience research and development (R&D), as well as at Wyeth and GlaxoSmithKline. Part of AstraZeneca's salvation may be in prioritizing projects better. We are also becoming less afraid to take and the right risks. The reduction in size has made us better, not worse.

about their business. The neuroscience group for example, are raising funding for some of

done a deal with Regulus Therapeutics in the microRNA space, another innovative, risky therapeutic approach that has potential.

Psychiatry: Neurodevelopmental disorders have taken on higher priority, including autism. Addiction has been added to their priority list, as are ‘behavioral symptoms of dementia.’ AZ is deliberately eschewing the search for symptomatic treatments and we should be willing to take some smart risks. The sponsor has been taken off us a bit less risk averse and more excited about stuff at the cutting edge. This is a very early stage.

The US National Institute on Drug Abuse.
Biotie puts cocaine dependence drug into Phase II

WORLD NEWS | MAY 13, 2013

KEVIN GROGAN

Following in the footsteps of Selincro, its recently-launched drug to cut alcoholic urges, Biotie Therapies Corp has started a mid-stage study of nepicastat for cocaine dependence.

The Finnish drugmaker noted that an 11-week Phase II study, with funding from the US National Institute on Drug Abuse, is expected to enroll about 180 treatment-seeking cocaine-dependent subjects. The study will be conducted at 12 US clinics specialising in the treatment of drug dependence and is expected to take two years to complete.
The Selective Dopamine β-Hydroxylase Inhibitor Nepicastat Attenuates Multiple Aspects of Cocaine-Seeking Behavior

Jason P Schroeder\textsuperscript{1}, S Alisha Epps\textsuperscript{1}, Taylor W Grice\textsuperscript{1} and David Weinshenker\textsuperscript{1,2}

\textsuperscript{1}Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA

Although norepinephrine (NE) does not typically modulate cocaine self-administration under traditional schedules of reinforcement, it is required for different inducers of the reinstatement of cocaine-seeking behavior via activation of multiple adrenergic receptor subtypes. We predicted that blockade of NE synthesis would attenuate all known modalities of reinstatement and showed previously that the selective dopamine β-hydroxylase inhibitor, nepicastat, had no effect on either maintenance of operant cocaine self-administration maintained on a fixed-ratio 1 schedule or reinstatement of food seeking but did abolish cocaine-primed reinstatement. In the present series of studies, we first evaluated the dose-dependent effect of nepicastat (5, 50, or 100 mg/kg) on novelty-induced locomotor activity and found that it blunted exploration only at the highest dose. Next, we assessed the ability of nepicastat (50 mg/kg) to reduce breakpoint responding for cocaine on a progressive ratio schedule and reinstatement induced by drug-associated cues and stress. We found that nepicastat significantly lowered the breakpoint for cocaine, but not for regular chow or sucrose, and attenuated cue-, footshock-, and yohimbine-induced reinstatement. Combined, these results indicate that nepicastat can reduce the reinforcing properties of cocaine under a stringent schedule and can attenuate relapse-like behavior produced by cocaine, formerly cocaine-paired cues, and physiological and pharmacological stressors. Thus, nepicastat is one of those rare compounds that can reduce reinforced cocaine seeking as well as all three reinstatement modalities, while sparing exploratory behavior and natural reward seeking, making it a promising pharmacotherapy for cocaine addiction.

Neuropsychopharmacology advance online publication, 23 January 2013; doi:10.1038/npp.2012.267

Keywords: dopamine β-hydroxylase; norepinephrine; dopamine; cocaine; reinstatement; nepicastat
NIDA and Lightlake Therapeutics partner to expand access to medication to treat opioid overdose

Announcement

August 21, 2013

NIDA and Lightlake Therapeutics Inc., a biopharmaceutical company developing novel treatments for addictions and conducting clinical trials with intranasal naloxone for the treatment of binge eating disorder, have entered into a partnership to apply this technology towards the treatment of opioid overdose. Clinical trials are expected to begin fall 2013.

Naloxone is an injectable medicine that can rapidly reverse the overdose of prescription and illicit opioids. An intranasal delivery system for naloxone could widely expand its availability and use in preventing opioid overdose deaths, a public health problem of epidemic proportion in the U.S.

For more on the role of naloxone in preventing opioid overdose deaths, see: www.fda.gov/downloads/Drugs/NewsEvents/UCM318909.pdf (PDF, 29KB).

To learn more about NIDA’s medications development program, go to: www.drugabuse.gov/about-nida/organization/divisions/division-
U.S. WorldMeds begins new drug trial

U.S. WorldMeds LLC has begun enrolling patients in a Phase III clinical trial that will complete the development program for lofexidine hydrochloride, known as Lofexidine. The trial gauges the drug’s effectiveness in the treatment of withdrawal symptoms associated with opiate detoxification, a news release from the company said.

The trial was made possible by a three-year, $15 million grant to the Louisville-based pharmaceutical company by the Bethesda, Md.-based National Institute on Drug Abuse.

Lofexidine is approved in the United Kingdom as BritLofex and has been used in the successful detoxification of more than 200,000 opiate addicts, the news release said. U.S.
Savant HWP Announces NIDA Funding for Pre-clinical Development of 18-MC as Potential Treatment for Addiction, Obesity

- Targeting the Brain's Central Reward Pathway Offers Therapeutic Approach to Many Forms of Addiction, Overeating and Other Compulsive Behavior

SAN CARLOS, Calif., Jan. 3, 2013 /PRNewswire/ -- Savant HWP, Inc. today announced the receipt of a three-year grant to support the development of 18-MC (18-methoxycoronaridine) as a potential orally active treatment for drug addiction, obesity and other forms of compulsive behavior. The grant, Award Number U01DA034986 given by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH), provides a total of $6,486,657 to support IND-enabling studies and GMP Scale-Up of 18-MC for use in clinical trials. Savant expects to begin human clinical safety studies of 18-MC in Brazil in early 2013, where the drug will also be studied as a potential treatment for leishmaniasis, and to begin U.S. clinical development in addiction in 2014.