Nicotine Dependence Treatment: From Mouse to Man to Medicine

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Our Challenge

• 1 in 5 Americans is tobacco dependent.
• Current FDA-approved medications are successful for only 1 in 3 smokers.
To translate discoveries in neuroscience, pharmacology, genetics and behavioral science to improve treatment for nicotine dependence
Treatment Development for Tobacco Dependence

- Target Identification (Discovery)
- Initial Target Validation (Development)
- Early Human Screening Models
- Pharmacogenetics
- Proof of Mechanism Testing in Rodents and Humans
- Behavioral Pharmacology
- Targeted Therapy Trials
- Cost-Effectiveness Analysis

Transcriptional Profiling
Imaging
Nicotine Addiction is a Chronic, Relapsing Brain Disease

Nicotine-related Brain Reward Pathway
**COMT val^{158}met Polymorphism Predicts Smoking Relapse in Independent Studies**

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Case-Control Study (n=785)</th>
<th>Prospective Clinical Trial (n=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (current v. former smoker)</td>
<td>OR (relapse v. quit) 3.2</td>
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<tr>
<td>3.5</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>P=0.03</td>
<td>P=0.03</td>
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<tr>
<td>2.5</td>
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<td>1.5</td>
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<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>met/met</td>
<td>1.01</td>
<td>met/met</td>
</tr>
<tr>
<td>val/met</td>
<td>1.45</td>
<td>val/met</td>
</tr>
<tr>
<td>val/val</td>
<td>1.8</td>
<td>val/val</td>
</tr>
</tbody>
</table>

Colilla et al., *Pharmacogenetics and Genomics*, 2005
COMT is a Potential Therapeutic Target

- Methylation enzyme involved in the inactivation of dopamine
- Common functional val^{158}met variant (1 in 4 are val/val)
- Val allele is associated with an increase in COMT activity and corresponding decrease in dopamine in frontal cortex
- Carriers of the val allele exhibit deficits in cognitive function

**Hypothesis:** Nicotine deprivation will produce cognitive deficits in smokers with val/val genotypes, an effect that may prompt smoking relapse to reverse deficits.
Imaging-Based Target Validation

Prospective genotyping
met/met: n=11
val/met: n=12
val/val: n=10

Smokers scanned on two occasions (counterbalanced): (1) smoking as usual vs. (2) >14 hrs. abstinent (confirmed with CO)
Fractal N-back (Working Memory Task)

Participant responds to stimuli based on 3 rules:

0 – back     Press the button when you see the target picture

1 – back     Press the button when the picture is the same as the one immediately before

2 – back     Press the button when the picture is the same as the one two before

3 – back     Press the button when the picture is the same as the one three before
Brain Signature of Abstinence Effect on Cognitive Function in COMT val/val group

• Brain activation in smokers with val/val genotypes is reduced in abstinence during performance of difficult cognitive task
• Reduced activation is liked with slower performance in val/val group at higher task difficulty (p=0.03)

Loughead et al, Molecular Psychiatry, 2009
Tolcapone as a “Tool Compound” for Proof of Mechanism Study

- Inhibitor of COMT in central nervous system
- FDA-approved for the treatment of Parkinson’s Disease
- Cognitive enhancing effects
Phase I Safety Study of Tolcapone in Smokers

• Short-term (7-day) treatment with tolcapone 200mg t.i.d. is safe and well tolerated by smokers

• Tolcapone (v. placebo) decreased speed of performance in val/val group, but not the met/met group

• Reversal of dopaminergic deficit in val/val group may reduce abstinence-induced cognitive deficits
Phase II Study of Tolcapone in Smokers

Reversal of abstinence-induced cognitive deficits by tolcapone will provide “proof of mechanism”

PLACEBO/TOLCAPONE®

Day 1 - 9
Medication run up

Day 10 - 13
3.5 days mandatory abstinence (CO confirmed)

Day 14 – 27
WASH-OUT

TOLCAPONE®/PLACEBO

Day 28 - 37
Medication run up

Day 38 - 41
3.5 days mandatory abstinence

fMRI Scan

fMRI Scan
Faster (lower) reaction time on the N-back working memory task predicts 7-day quit success (p=.01; $r^2=.15$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>T</th>
<th>p</th>
<th>Model $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>-0.015</td>
<td>0.104</td>
<td>.92</td>
<td>.01</td>
</tr>
<tr>
<td>Baseline cigs. per day</td>
<td>0.437</td>
<td>3.049</td>
<td>.005</td>
<td>.15</td>
</tr>
<tr>
<td>Baseline 3-Back performance</td>
<td>-0.030</td>
<td>-0.166</td>
<td>.87</td>
<td>.25</td>
</tr>
<tr>
<td>Abstinent 3-Back performance</td>
<td>-0.482</td>
<td>-2.651</td>
<td>.013</td>
<td>.40</td>
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</table>
**Summary: COMT**

**COMT val allele is risk factor for nicotine dependence**

**Cognitive deficits are a core symptom of dependence and predict relapse**

**Smokers with val/val genotype have altered brain function and cognitive deficits in abstinence**

**Proof of mechanism experiments (tolcapone)**

**Convergent behavioral, genetic, and pharmacologic evidence would support COMT as a therapeutic target for tobacco dependence**
Treatment Development for Tobacco Dependence

- Transcriptional Profiling
- Target Identification (Discovery)
- Human Genetics
- Initial Target Validation (Development)
- Proof of Mechanism Testing in Rodents and Humans
- Imaging
- Early Human Screening Models
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- Pharmacogenetics
- Targeted Therapy Trials
Opioid Mechanisms in Nicotine Reward

Nestler
Mouse Model of Nicotine Reward

Pairing Days 2-8

Day 1

Test Day

Work by Julie Blendy
Naloxone on Test Day Blocks Conditioned Rewarding Effects of Nicotine in 129/C57 B16 Mice

* *p<.05

Walters et al, Neuron, 2005
• The human OPRM1 gene includes a common Exon 1 Asn40Asp (A118G) mis-sense single nucleotide polymorphism (SNP).

• G allele associated with reduced mRNA expression and protein levels and is present in 25-30% of persons of European ancestry.

Hypothesis: Smokers with G allele will have a lower liability to relapse in smoking cessation treatment.
Open Label Pharmacogenetic Trial of NRT (TTURC 1, n=600*)

Pre-treatment Assessment & Genotyping

Nicotine nasal spray x 8 wks

95% retention rate

Follow-Up: EOT, 6-months, and 12-months

Transdermal nicotine x 8 wks

*European ancestry only (n=420)
OPRM1 Asn40Asp Variant is Associated with Response to Nicotine Replacement Therapy

Treatment Phase

Follow-up Phase

OR = 1.9, p = .01

Lerman et al., *Pharmacogenomics J*, 2004
What is the Mechanism of Enhanced Therapeutic Response in Smokers with the OPRM1 Asp40 (G) allele?

1. Do carriers of the OPRM1 G allele (loss of function) exhibit reduced nicotine reinforcement?

2. Does naltrexone reduce nicotine reinforcement—particularly in smokers with OPRM1 G allele?

3. Are females more sensitive to opioid system effects on nicotine reward?
Study Population (n=60)

*OPRM1* AA  n=30
*OPRM1* AG/GG  n=30
All European ancestry
smoke >10 cpd
Within Subject Design

**Study Phase 1**

*NTX or PLACEBO*

Day 1: 12.5mg*  
Day 2: 25mg*  
Day 3: 50mg*  
**Day 4**: 50mg*

Observation Period

- CO, medication compliance, side effects assessed in-person daily.

Test Day

Nicotine choice paradigm

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**Study Phase 2**

*NTX or PLACEBO*

Day 1: 12.5mg*  
Day 2: 25mg*  
Day 3: 50mg*  
**Day 4**: 50mg*

Observation Period

- CO, medication compliance, side effects assessed in-person daily.

Test Day

Nicotine choice paradigm

5-7 day Washout
Human Model of Nicotine Reward

- 2 hour deprivation period (to standardize exposure without inducing serious withdrawal symptoms)
- Initial (blinded) exposure to 4 puffs of Quest cigarettes: denic. (.05 mg) vs nic. (.6 mg)
- Assess subjective effects
- Self-administer 4 puffs from either cigarette at 30 minute intervals in 6 trials over a 3-hour period
- Outcome measure is number of nicotine puffs chosen out of 24 = relative reinforcing value of nicotine
Reduced Activity OPRM1 Allele is Associated with Reduced Nicotine Reward

Subjective Ratings (nicotine minus denicotinized cigarette)

OPRM1 Genotype Predicts Nicotine Reinforcement in Females but not in Males

number of nicotine puffs in 24 (across treatments)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA n=30</td>
<td>18</td>
<td>19.65</td>
</tr>
<tr>
<td>GA GG n=30</td>
<td>18</td>
<td>13.58</td>
</tr>
</tbody>
</table>

75% of Puffs from Nicotine

P (genotype by gender interaction) = .036

Estrogen Modulation of MOR Binding

Zubieta et al., J Neuroscience, 2006
Naltrexone Does Not Reduce Nicotine Reward or Interact with OPRM1 Genotype

Number of nicotine puffs in 24 hours

Using Targeted Genetic Mutations in the Mouse to Understand Human OPRM1 SNP (Blendy)
MOPR expression is decreased in A112G knock-in mice

Female G/G mice failed to show a conditioned place preference to morphine-paired environments (10 mg/kg)

Mague, Isiegas, Huang, Liu-Chen, Lerman, Blendy 2009

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MOR Binding as Mechanism for Observed *OPRM1* Association with Nicotine Reward

2x2 Factorial Design: (1) iv nicotine vs. saline (within subject); (2) *OPRM1* genotype (stratified by sex)

N=4 (2 sessions/subject)

VST=ventral striatum; NAC=nucleus accumbens; THAL=thalamus; ACC=anterior cingulate cortex; OCC=occipital cortex (reference region)
Nicotine abstinence-induced rCBF changes by OPRM1 Genotype

Hot color means greater in delta rCBF the AA subgroup. The color bar indicates the range of $t$-values displayed. Spatial location of each slice is indicated by the number in the upper left corner of the slice image and also is labeled by the white lines (for axial slices) and the green lines (for the sagittal slices).

Summary of OPRM1 Work

Preclinical: Blendy Lab

- MOR antagonist blocks nicotine CPP in mice
- Female mice with equivalent of human OPRM1 G show reduced morphine CPP
- MOR expression reduced in mice with G allele

Clinical: Lerman Lab

- Human OPRM1 G allele associated with quit success
- Nicotine reward reduced in female G allele carriers
- Smokers with G allele show less CBF change in nicotine abstinence

Parallel Mouse-Human study: Effects on Nicotine on MOR Binding in Males and Females
Treatment Development for Tobacco Dependence

- Target Identification (Discovery)
  - Transcriptional Profiling
  - Imaging

- Initial Target Validation (Development)
  - Genome-wide Association
  - Proof of Mechanism Testing in Rodents and Humans
  - Behavioral Pharmacology

- Early Human Screening Models

- Pharmacogenetics and Targeted Therapy
  - Cost-Effectiveness Analysis
  - Targeted Therapy Trials
Can we predict who will benefit from different treatments for smoking cessation?
Nicotine Dependent Smokers Alter Smoking to Maintain Nicotine Levels:

- Nicotine intake (i.e. smoking)
- Nicotine removal (i.e. metabolism)

Active

NICOTINE → COTININE

Inactive

CYP2A6

Inactive

CYP2A6

3’Hydroxycotinine
CYP2A6 Gene Mutations Alter Dependence Phenotypes

Genetically slow metabolizers smoke fewer cigs/day and are less dependent

CYP2A6 genotype alters enzyme activity and metabolite ratio

Malaiyandi et al., *Molecular Psychiatry*, 2006
Nicotine Metabolic Profile

NICOTINE
- NICOTINE-1’-N-OXIDE: 4.4%
- NICOTINE GLUCURONIDE: 4.2%

COTININE
- COTININE: 13.0%
- COTININE-N-OXIDE: 2.4%
- COTININE GLUCURONIDE: 12.6%
- TRANS-3’-HYDROXYCOTININE: 33.6%

NORNICOTINE
- NORNICOTINE: 0.4%
- TRANS-3’-HYDROXYCOTININE GLUCURONIDE: 7.4%

CYP2A6
- ~ 80%
Nicotine Metabolite Ratio is a Phenotypic Measure of CYP2A6 Activity

• The ratio of nicotine metabolites: cotinine/3’hydroxycotinine
• A stable measure of nicotine metabolism rate derived from smoking
• Independent of time since last cigarette
• Can be measured in plasma, urine or saliva
• Reflects both genetic and environmental influences on nicotine clearance

Easy to perform in clinical practice
Nicotine Metabolite Ratio Predicts Therapeutic Response to Nicotine Patch

Clinical Pharmacology & Therapeutics, 2006

End of Treatment  
OR=.72 (.57-.91) p=006

6-Month Follow-up

% Quit

1st Qrtl  2nd Qrtl  3rd Qrtl  4th Qrtl  1st Qrtl  2nd Qrtl  3rd Qrtl  4th Qrtl

Slow                                    Fast                                     Slow                                    Fast

3-HC: Cotinine Ratio in Quartiles
Nicotine Metabolite Ratio Predicts Response to Nicotine Patch: Independent Validation (n=568)

Pharmacology, Biochem and Behavior, 2009

% QUIT

OR = 0.54 [95% CI: 0.36–0.82], p = 0.003
Nicotine Metabolite Ratio Predicts Therapeutic Response to Bupropion (n=414)

- Decreased quit rates also observed with placebo
- Increased liability to relapse in fast metabolizers is reversed by bupropion
- Fast metabolizers are candidates for bupropion

OR=4.59 (1.5-13.6), p=.006

% Quit

Patterson et al., *Clinical Pharmacology & Therapeutics*, 2008
Algorithm for Use of Nicotine Metabolite Ratio to Personalize Smoking Cessation Treatment

Plasma, saliva or urine
Nicotine metabolite ratio

Slow Metabolizer
Nicotine Patch
Low cost
Low toxicity

Fast Metabolizer
Bupropion or Varenicline
Higher cost
Greater toxicity
Summary: Nicotine Metabolism

- **CYP2A6 gene linked with dependence phenotypes**
- **Nicotine metabolite ratio is a stable measure of CYP2A6 activity**

Genetically slow metabolizers respond well to transdermal nicotine; fast metabolizers respond well to bupropion.

Targeted therapy based on nicotine metabolite ratio can be cost-effective.

Evidence from prospective targeted therapy trial will support translation to practice.

Test kit in development through industry collaboration.
Summary and Implications

• Genetics and neuroimaging provide powerful new tools for probing the biobehavioral basis of nicotine dependence

• A better understanding of behavior-biology linkages will lead to better treatments and tests to personalize treatment to individual smokers

• Reductions in tobacco use will have a significant public health impact
Acknowledgements

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Rachel Tyndale (U Toronto) Neal Benowitz (UCSF)

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