Nicotine Dependence Medication Development and Pharmacogenetics

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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.
An Investment in Tobacco Control

Academic scientists can (and should) contribute to the development of safe and effective treatments for nicotine dependence

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
- Cost-Effectiveness Analysis
- Imaging
- Human Genetics
- Proof of Mechanism Testing in Rodents and Humans
- Behavioral Pharmacology
- Targeted Therapy Trials
Nicotine Addiction is a Chronic, Relapsing Brain Disease

**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>
</tr>
<tr>
<td>3.5</td>
<td>P=0.03</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>2.5</td>
<td>1.45</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.01</td>
<td></td>
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</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)
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).

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®

Medication run up
Day 1 - 9

Day 14 – 27 WASH-OUT

3.5 days mandatory abstinence (CO confirmed)

fMRI Scan

TOLCAPONE®/PLACEBO

Medication run up
Day 28 - 37

Day 38 - 41

3.5 days mandatory abstinence

fMRI Scan
Faster (lower) reaction time on the N-back working memory task following a quit attempt 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>
</tr>
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</table>
Convergent behavioral, genetic, and pharmacologic evidence would support COMT as a therapeutic target for tobacco dependence.

**Summary: COMT**

*COMT* val allele is a 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

- Target Identification (Discovery)
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- Pharmacogenetics
- Cost-Effectiveness Analysis
- Imaging
- Transcriptional Profiling
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Opioid Mechanisms in Nicotine Reward

[Diagram showing neural pathways involving nicotine, alcohol, opioids, GABA, DA, glutamate inputs, and NAc and VTA regions.]

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

• 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
- Transdermal nicotine x 8 wks

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

95% retention rate

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

\[ OR = 1.9, \ p = .01 \]

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

Observation Period

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

**Test Day**

Nicotine choice paradigm

5-7 day Washout

**Study Phase 2**

*NTX or PLACEBO

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

Observation Period

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

**Test Day**

Nicotine choice paradigm
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)

75% of Puffs from Nicotine

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

P (genotype by gender interaction) = .036

Estrogen May Affect MOR Binding

Zubieta et al., Am J Psych, 1999
Naltrexone Does Not Reduce Nicotine Reward or Interact with OPRM1 Genotype

Using Targeted Genetic Mutations in the Mouse to Understand Human OPRM1 SNP (Blendy)

Mague et al., *PNAS*, in press
Examine MOR Binding as Mechanism for Observed *OPRM1* Association with Nicotine Reward

Hypotheses:

1. Reduced baseline MOR binding availability associated with G allele

2. Nicotine increases MOR binding in AA but not G* group

Exploratory analysis of estradiol levels and MOR binding by *OPRM1*

2x2 Factorial Design: (1) nicotine vs. denic cig (within subject); (2) *OPRM1* genotype
Target Identification
(Discovery)

Initial Target Validation
(Development)

Early Human Screening Models

Pharmacogenetics and
Targeted Therapy

Transcriptional Profiling

Imaging

Genome-wide Association

Proof of Mechanism Testing in Rodents and Humans

Behavioral Pharmacology

Cost-Effectiveness Analysis

Targeted Therapy Trials

Treatment Development for Tobacco Dependence
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  Inactive  Inactive
NICOTINE $\rightarrow$ COTININE $\rightarrow$ 3’Hydroxycotinine
CYP2A6  CYP2A6
**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 Metabolite Ratio Predicts Therapeutic Response to Nicotine Patch (n=480)

% Quit

OR=.72 (0.57-.91) p=006

- 30% reduction in quit rates with increasing metabolic rate
- Reduction in plasma nicotine levels from patch
- Findings replicated

Is this specific to nicotine replacement therapy?

Lerman et al., Clinical Pharmacology & Therapeutics, 2006
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

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
    - Higher cost
    - Greater toxicity

Low cost
Low toxicity

Higher cost
Greater toxicity
### Is This Cost-Effective?

<table>
<thead>
<tr>
<th>Cost/ life-year saved-incremental cost-effectiveness ratio:</th>
</tr>
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<tbody>
<tr>
<td>Nicotine metabolite ratio testing: $1,000</td>
</tr>
<tr>
<td>Annual mammography: $16,000</td>
</tr>
<tr>
<td>Hypertension treatment: $50,000</td>
</tr>
<tr>
<td>Living in a smoke-free environment: priceless</td>
</tr>
</tbody>
</table>
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 is 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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