Translational Research in Tobacco Dependence Treatment

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• 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 medications for nicotine dependence

Drug Development for Tobacco Dependence

Transcriptional Profiling → Target Identification (Discovery) → Initial Target Validation (Development) → Early Human Screening Models → Pharmacogenetics

Imaging → Proof of Mechanism Testing in Rodents and Humans → Behavioral Pharmacology

Human Genetics

Cost-Effectiveness Analysis

Targeted Therapy Trials
Nicotine-related Brain Reward Pathway

- Tyrosine
- Dopamine Biosynthesis
- DOPA Decarboxylase
- DOPA
- TH
- Increased Release
- nAChR
- DA
- Pre-Synaptic Neuron
- MAO
- Synaptic Vesicle
- COMT
- DA
- Post-Synaptic Neuron
- DA
- DRD
- DRD
- AC
- cAMP
- PKC
- CREB
- BDNF
- ATP
- Blood Brain Barrier
- Nicotine
- Liver Cell
- Cyp2A6
- Cyp2B6
- Cotinine
- OCT
- Blood
- DA
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**COMT val^{158}met Polymorphism Predicts Smoking Relapse in Independent Studies**

Colilla et al., *Pharmacogenetics and Genomics*, 2005

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Case-Control Study (n=785)</th>
<th>Prospective Clinical Trial (n=290)</th>
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<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>
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<tr>
<td>3</td>
<td>P=0.03</td>
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<tr>
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<td>met/met, val/met, val/val</td>
<td>met/met, val/met, val/val</td>
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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

- Dorsolateral prefrontal cortex

Genotype x abstinence effect (p=0.0005)

- 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 at high task difficulty
- No effect of tolcapone in met/met group
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
Convergent genetic and pharmacologic evidence would support COMT as a therapeutic target for tobacco dependence.

**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)
Drug Development for Tobacco Dependence

- Transcriptional Profiling
- Target Identification (Discovery)
- Initial Target Validation (Development)
- Early Human Screening Models
- Pharmacogenetics and Targeted Therapy
- Genome-wide Association
- Proof of Mechanism Testing in Rodents and Humans
- Behavioral Pharmacology
- Cost-Effectiveness Analysis
- Targeted Therapy Trials
Targeted Therapy for Tobacco Dependence

blood test

- Blood test
- DNA structure
- Nicotine Transdermal System
- Zyban 150mg Tablets
- Consultation between two individuals
Nicotine Dependent Smokers Alter Smoking to Maintain Nicotine Levels:

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

**Nicotine metabolism**
- NICOTINE → COTININE (CYP2A6)
- COTININE → 3’Hydroxycotinine (CYP2A6)

**CYP2A6**
- Active
- Inactive
- Inactive
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)

- 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)

% Quit

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<thead>
<tr>
<th>1st Qrtl</th>
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<th>3rd Qrtl</th>
<th>4th Qrtl</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>32</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Bupropion</td>
<td>32</td>
<td>30</td>
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OR=4.59 (1.5-13.6), p=.006

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

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
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
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