Translational Research in Tobacco Dependence Treatment

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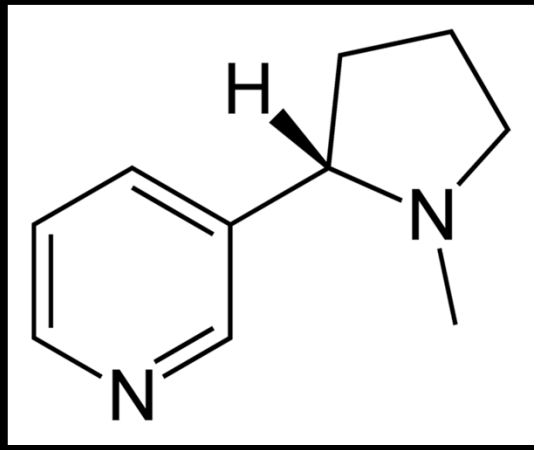
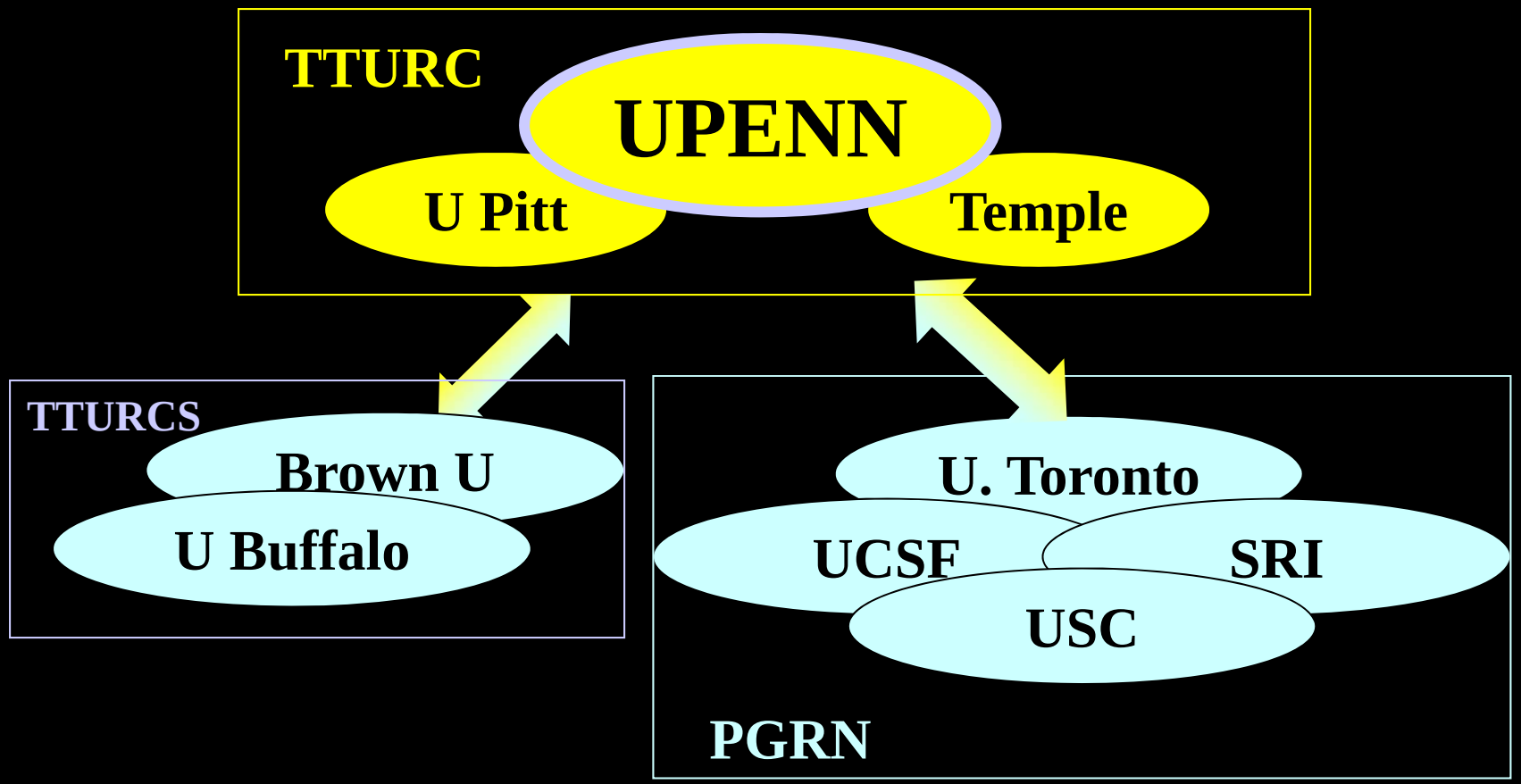
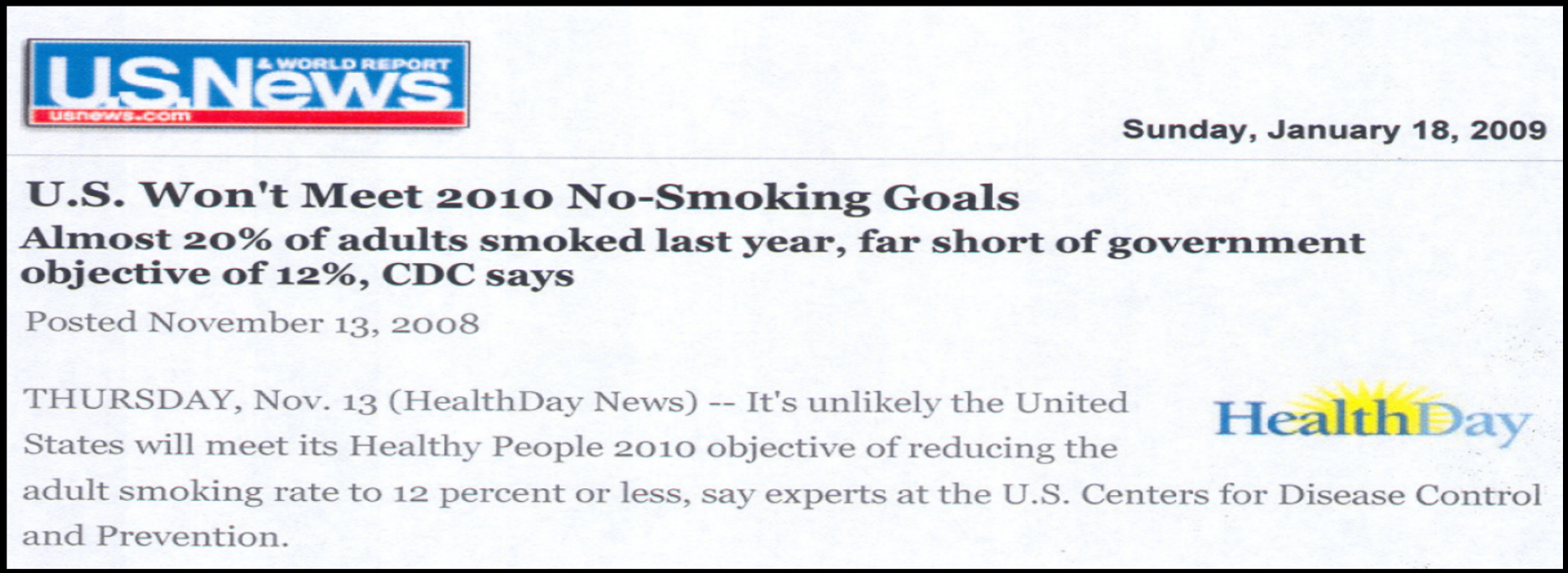


UPENN Transdisciplinary Tobacco Use Research Center (1999-2009)



Our Challenge



U.S. News & World Report
usnews.com

Sunday, January 18, 2009

U.S. Won't Meet 2010 No-Smoking Goals

Almost 20% of adults smoked last year, far short of government objective of 12%, CDC says

Posted November 13, 2008

THURSDAY, Nov. 13 (HealthDay News) -- It's unlikely the United States will meet its Healthy People 2010 objective of reducing the adult smoking rate to 12 percent or less, say experts at the U.S. Centers for Disease Control and Prevention.

HealthDay

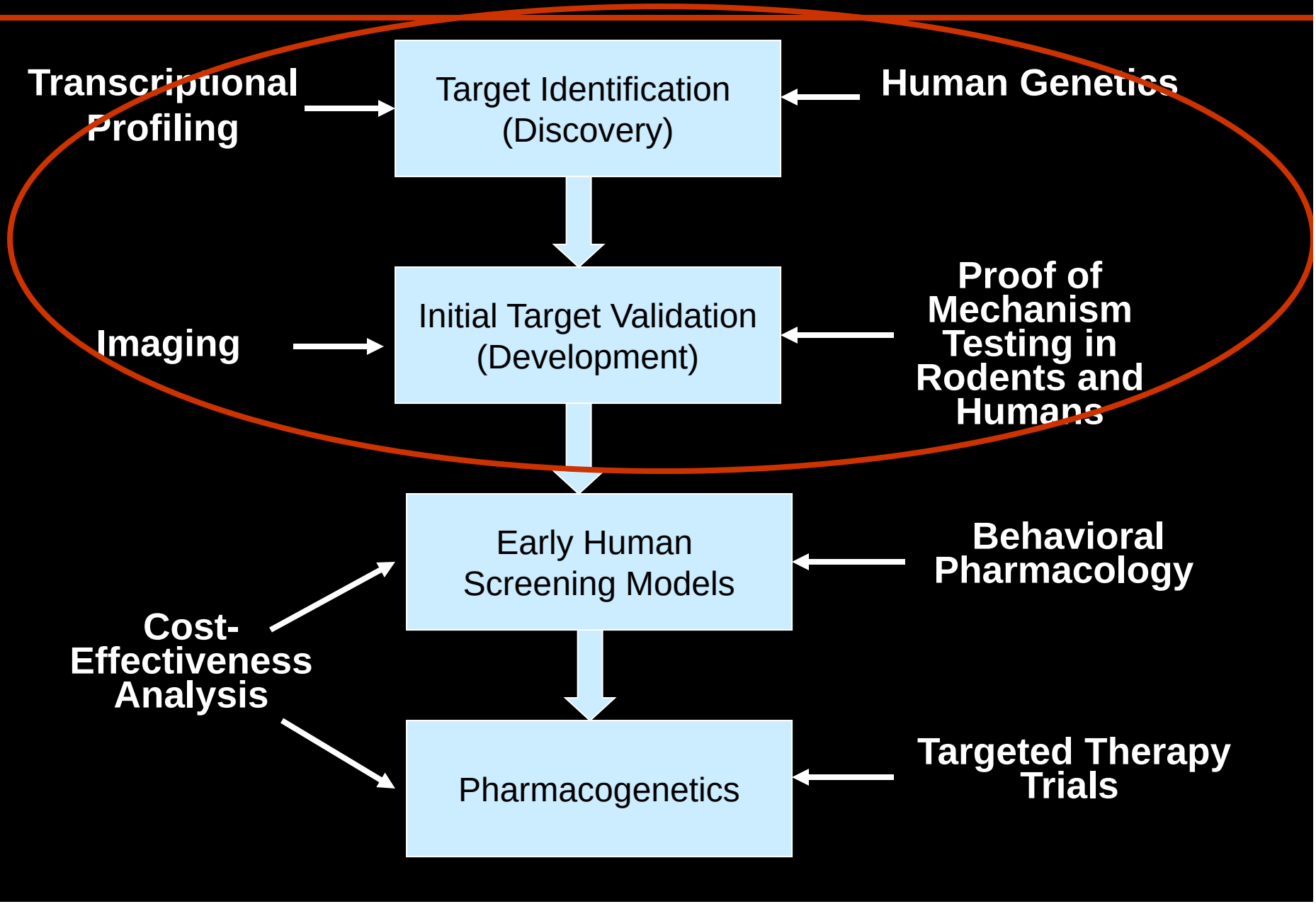
- **1 in 5 Americans is tobacco dependent.**
- **Current FDA-approved medications are successful for only 1 in 3 smokers.**

An Investment in Tobacco Control

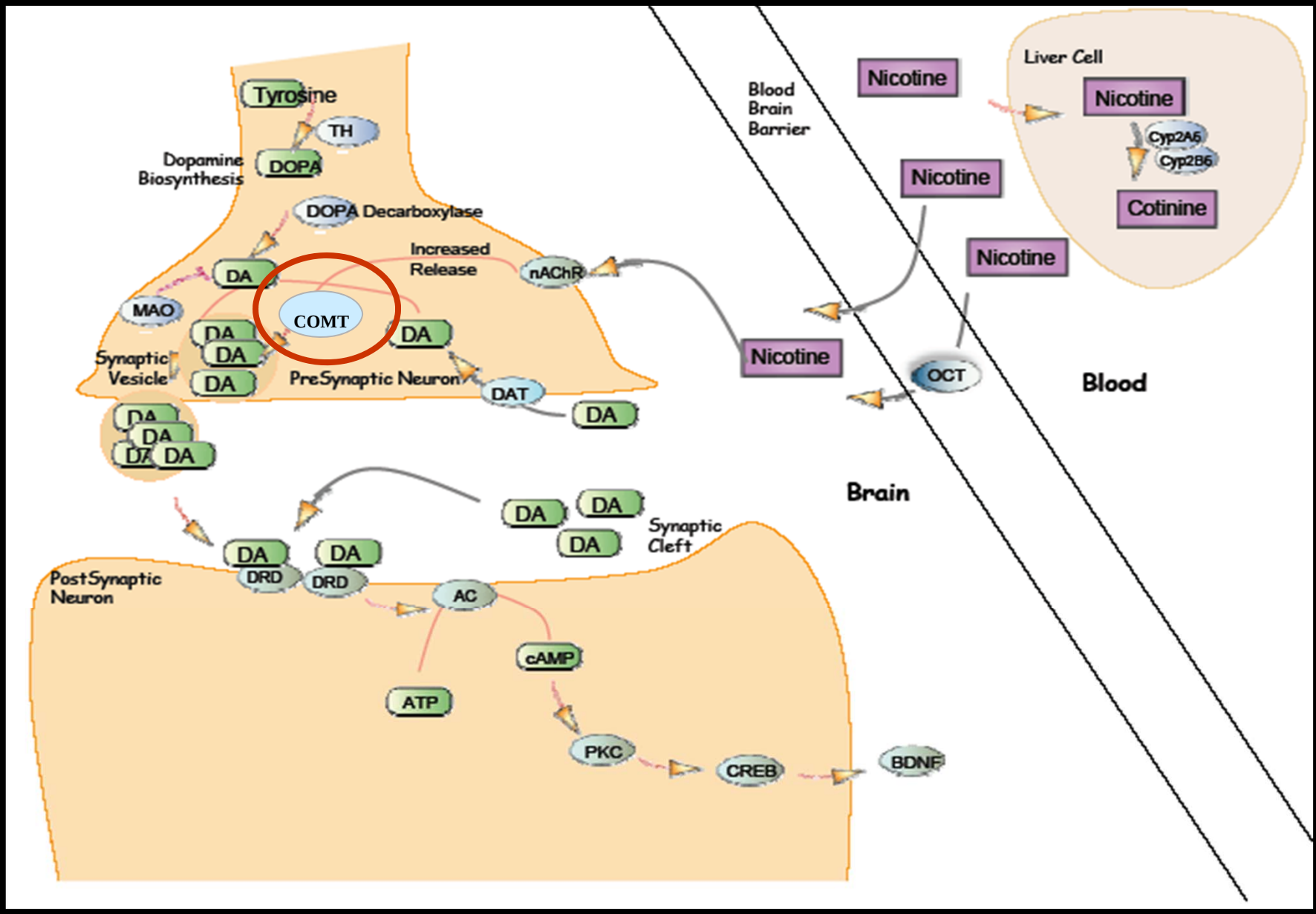
Academic scientists can (and should) contribute to the development of safe and effective medications for nicotine dependence

Lerman et al. Nature Reviews Drug Discovery, 2007

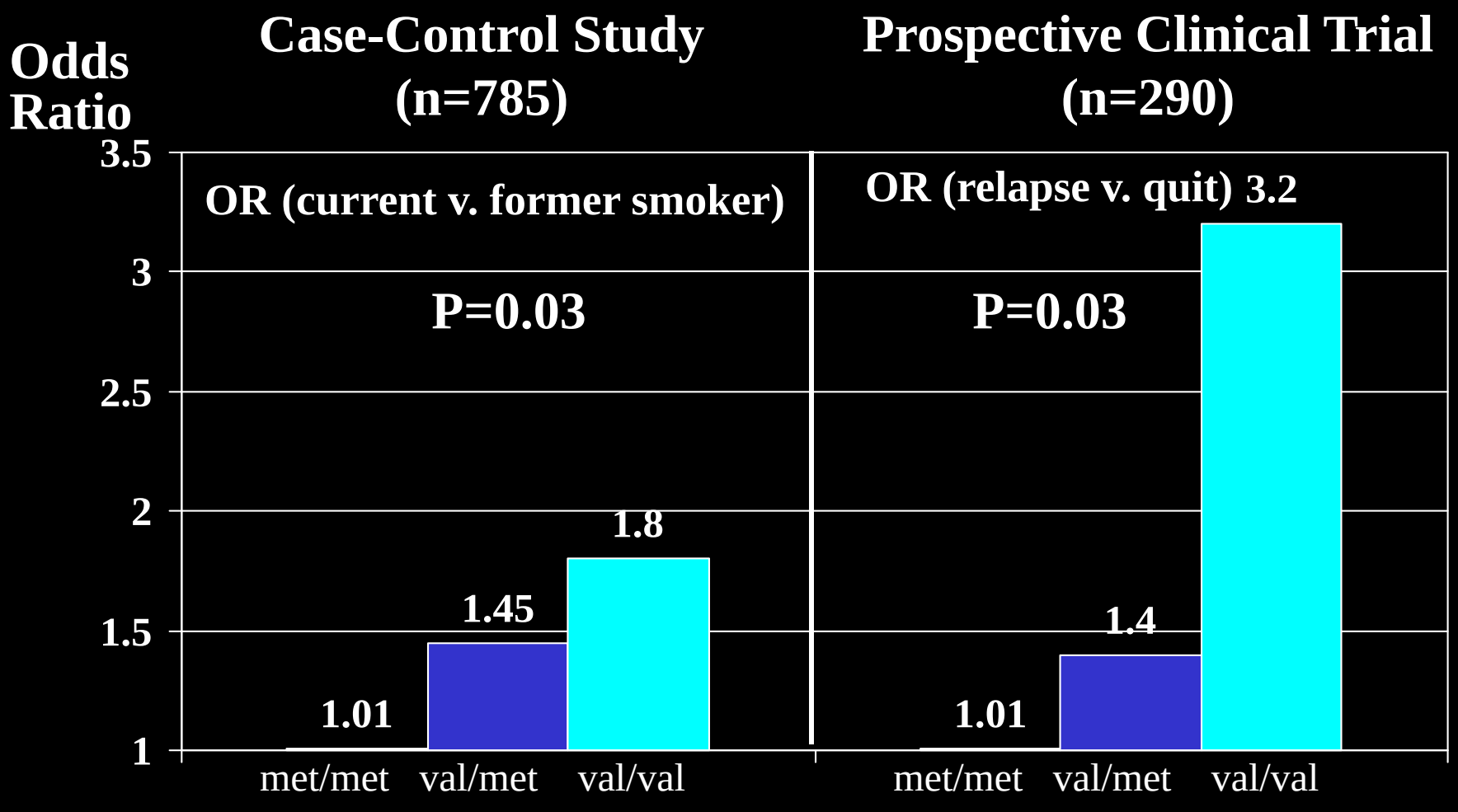
Drug Development for Tobacco Dependence



Nicotine-related Brain Reward Pathway



COMT val^{158}met Polymorphism Predicts Smoking Relapse in Independent Studies



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**

<u>Hypothesis</u>: Nicotine deprivation will produce cognitive deficits in smokers with val/val genotypes, an effect that may prompt smoking relapse to reverse deficits.

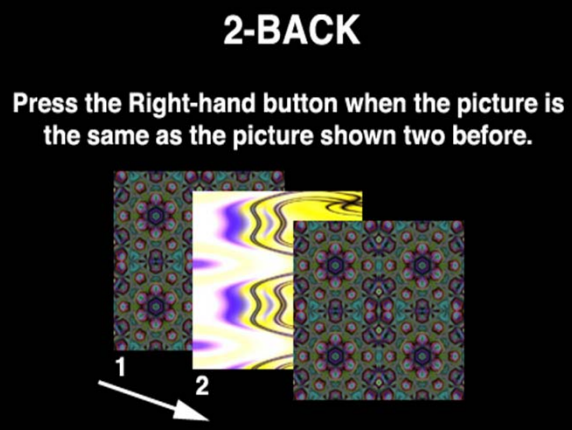
Imaging-Based Target Validation

Prospective genotyping

met/met: n=11

val/met: n=12

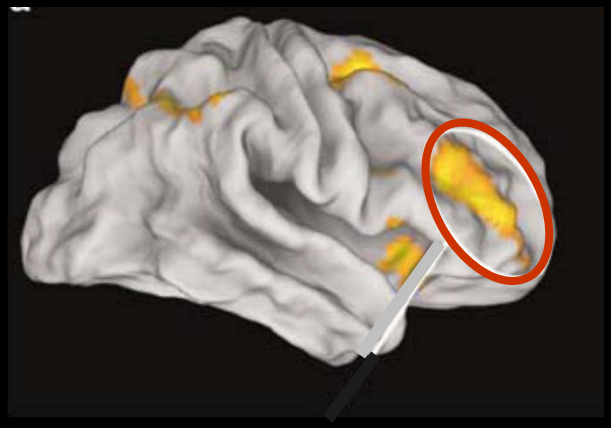
val/val: n=10



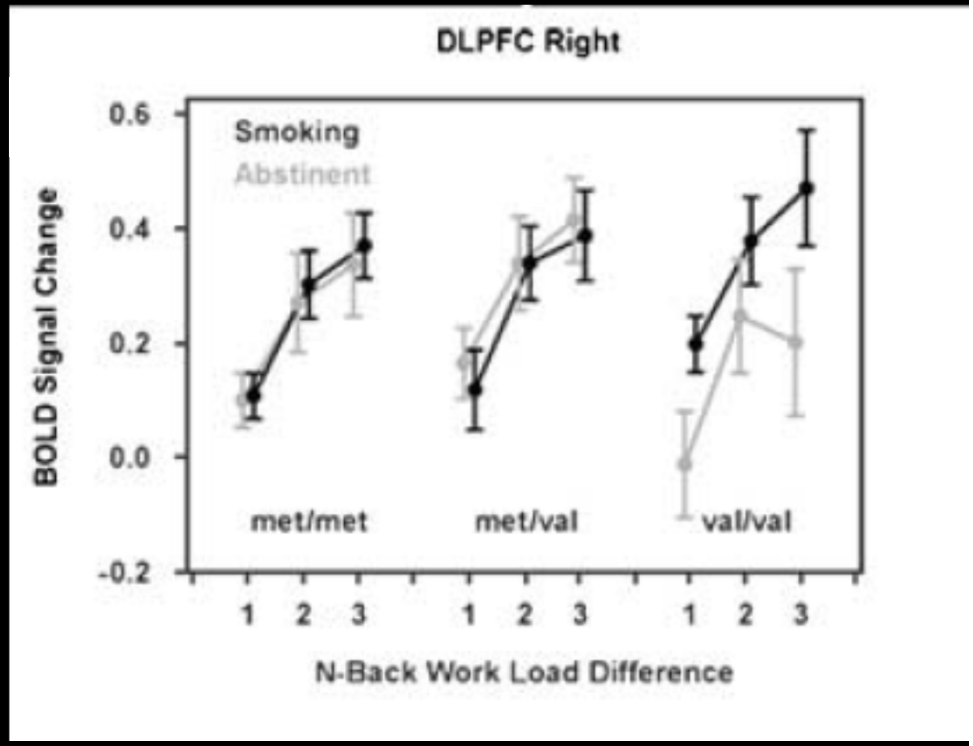
Smokers scanned on two occasions (counterbalanced): (1) smoking as usual vs. (2) >14 hrs. abstinent (confirmed with CO)

Brain Signature of Abstinence Effect on Cognitive Function in *COMT* val/val group

Dorsolateral prefrontal cortex



Genotype x abstinence effect (p=0.0005)



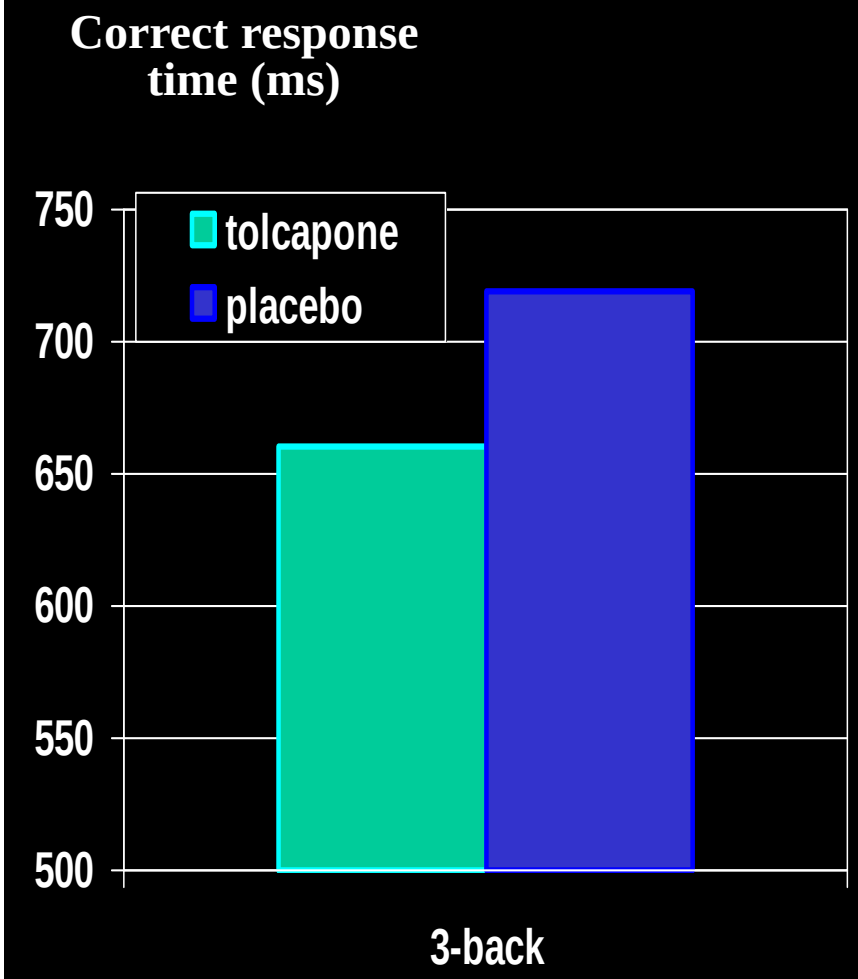
- **Brain activation in smokers with val/val genotypes is reduced in abstinence during performance of difficult cognitive task**
- **Reduced activation is liked with slower performance in val/val group at higher task difficulty (p=0.03)**

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



COMT val/val group

- 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 14 – 27
WASH-OUT

TOLCAPONE®/PLACEBO

Medication run up

Day 1 - 9

Day 10 - 13

3.5 days mandatory abstinence (CO confirmed)

fMRI Scan

Medication run up

Day 28 - 37

Day 38 - 41

3.5 days mandatory abstinence

fMRI Scan

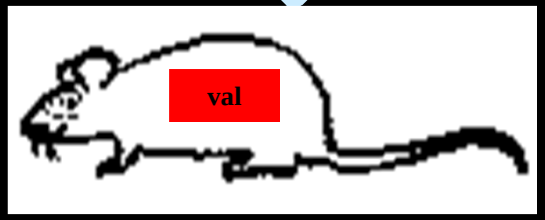
Summary: COMT

COMT val allele is risk factor for nicotine dependence

Cognitive deficits are a core symptom of dependence and predict relapse

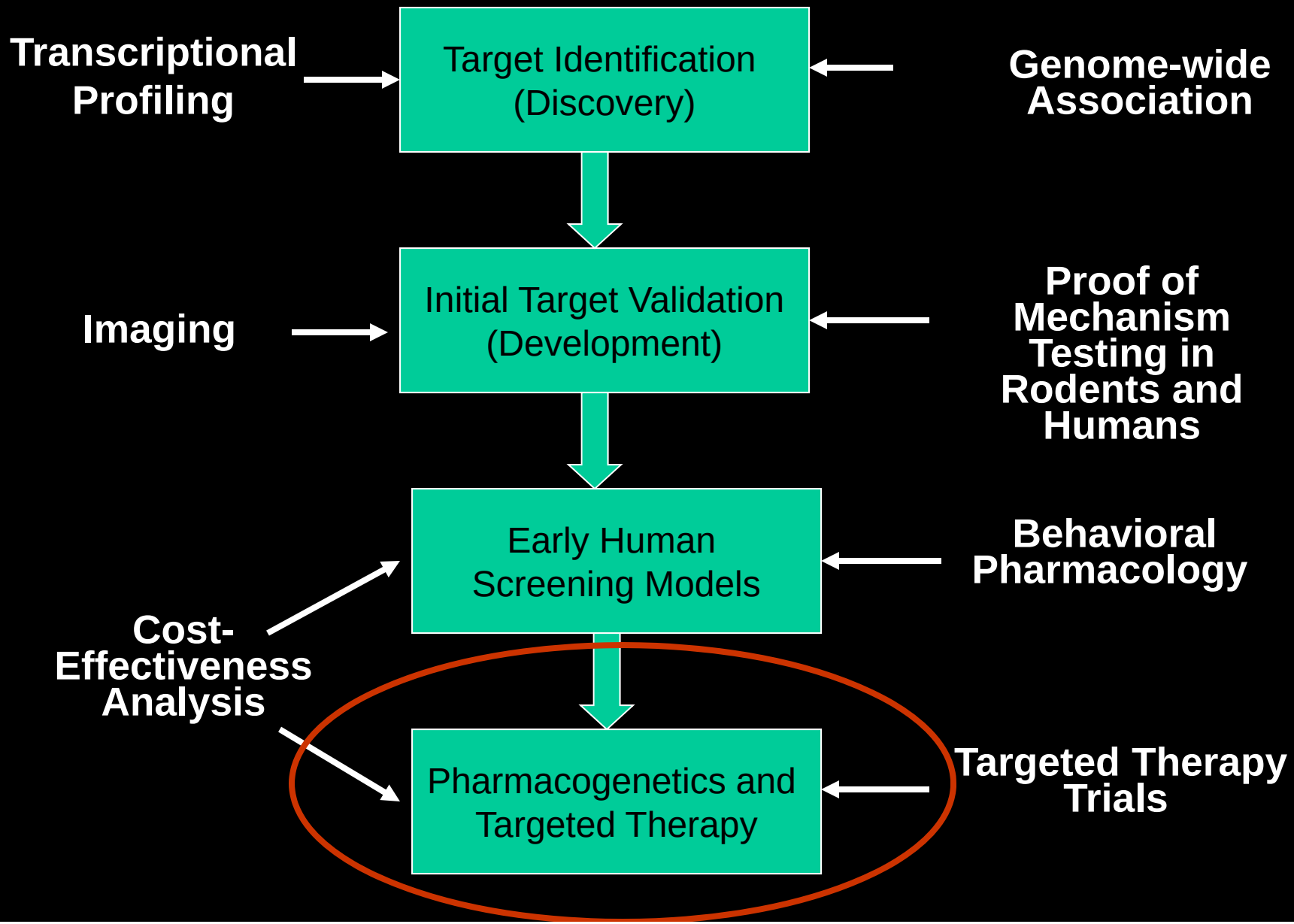
Smokers with val/val genotype have altered brain function and cognitive deficits in abstinence

Proof of mechanism experiments (tolcapone)

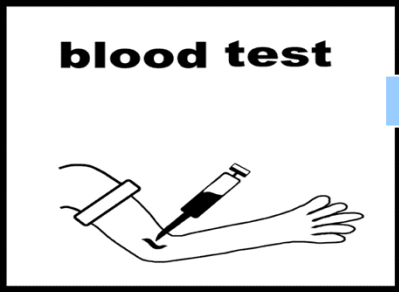


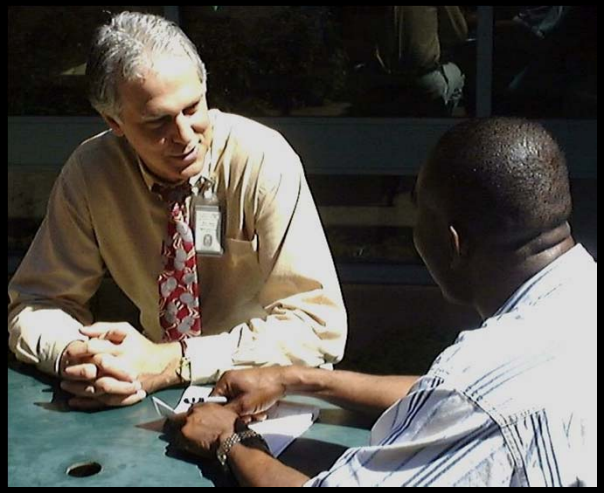
Convergent genetic and pharmacologic evidence would support COMT as a therapeutic target for tobacco dependence

Drug Development for Tobacco Dependence



Targeted Therapy for Tobacco Dependence

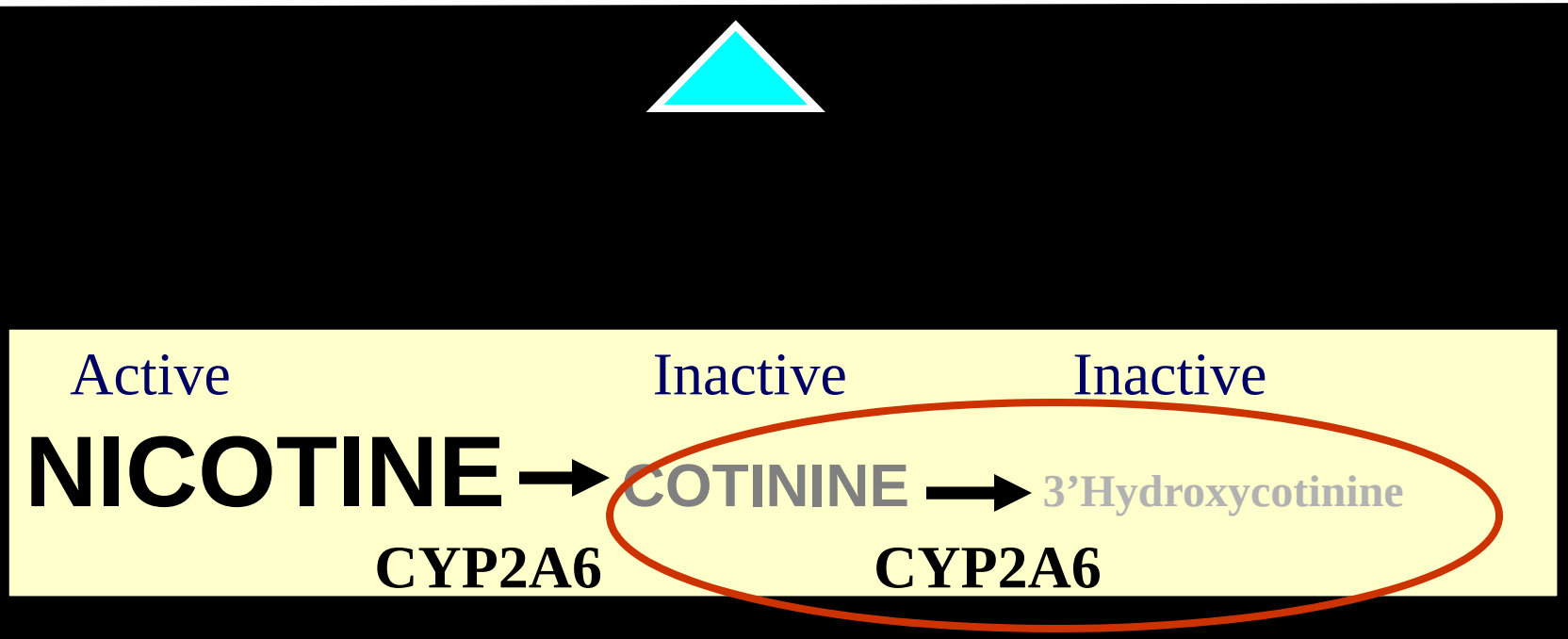




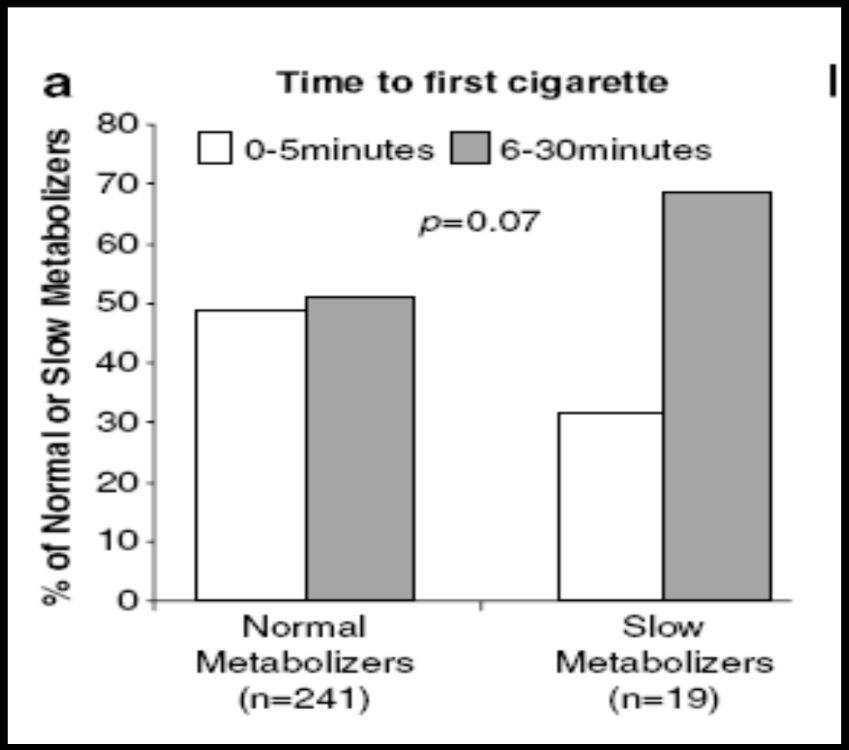
Nicotine Dependent Smokers Alter Smoking to Maintain Nicotine Levels:

Nicotine intake (i.e. smoking)

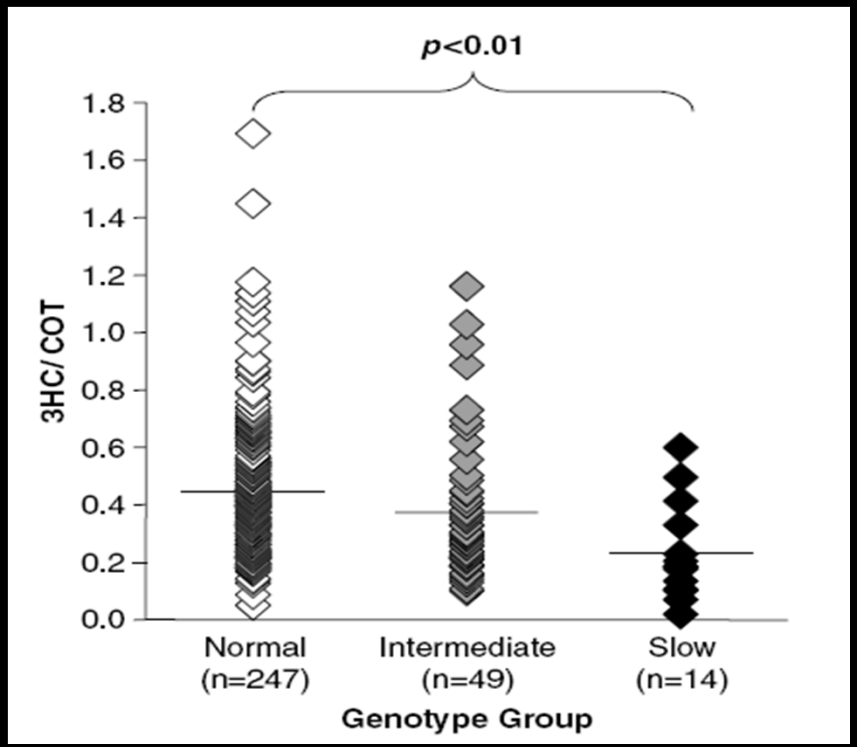
Nicotine removal (i.e. metabolism)



CYP2A6 Gene Mutations Alter Dependence Phenotypes



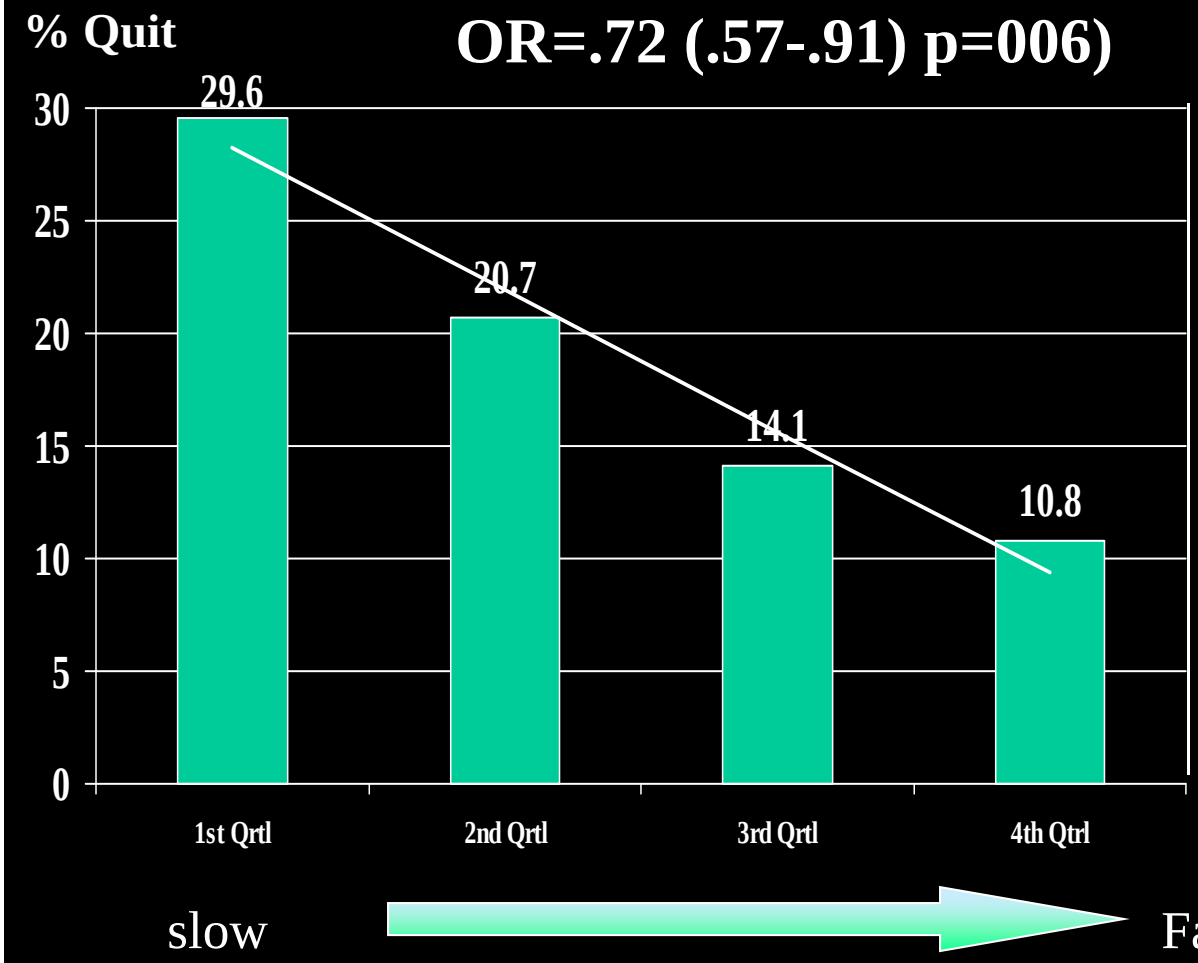
Genetically slow metabolizers smoke fewer cigs/day and are less dependent



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)

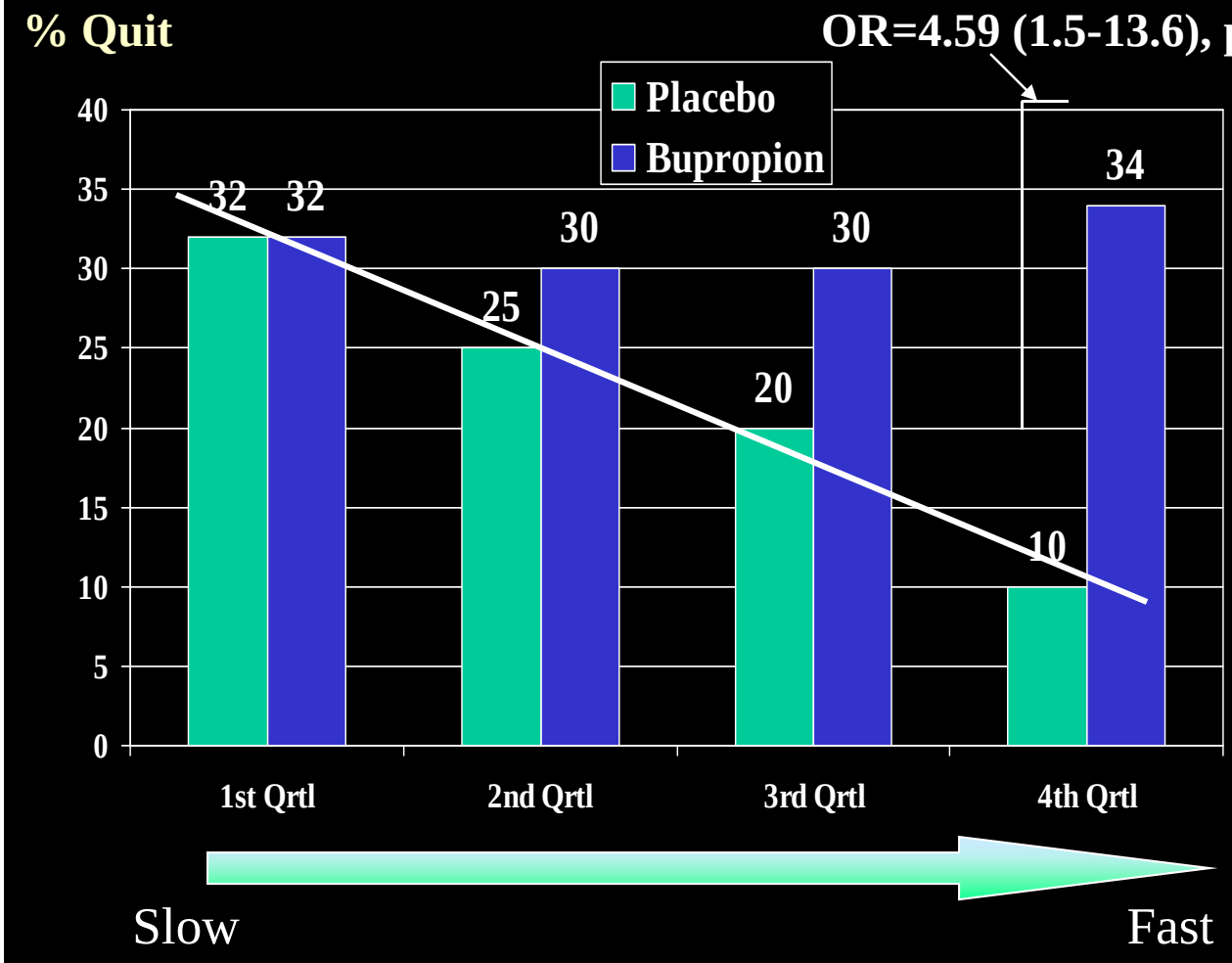


- 30% reduction in quit rates with increasing metabolic rate
- Reduction in plasma nicotine levels from patch
- Findings replicated

Is this specific to nicotine replacement therapy?

Lerman et al., Clinical Pharmacology & Therapeutics, 2006

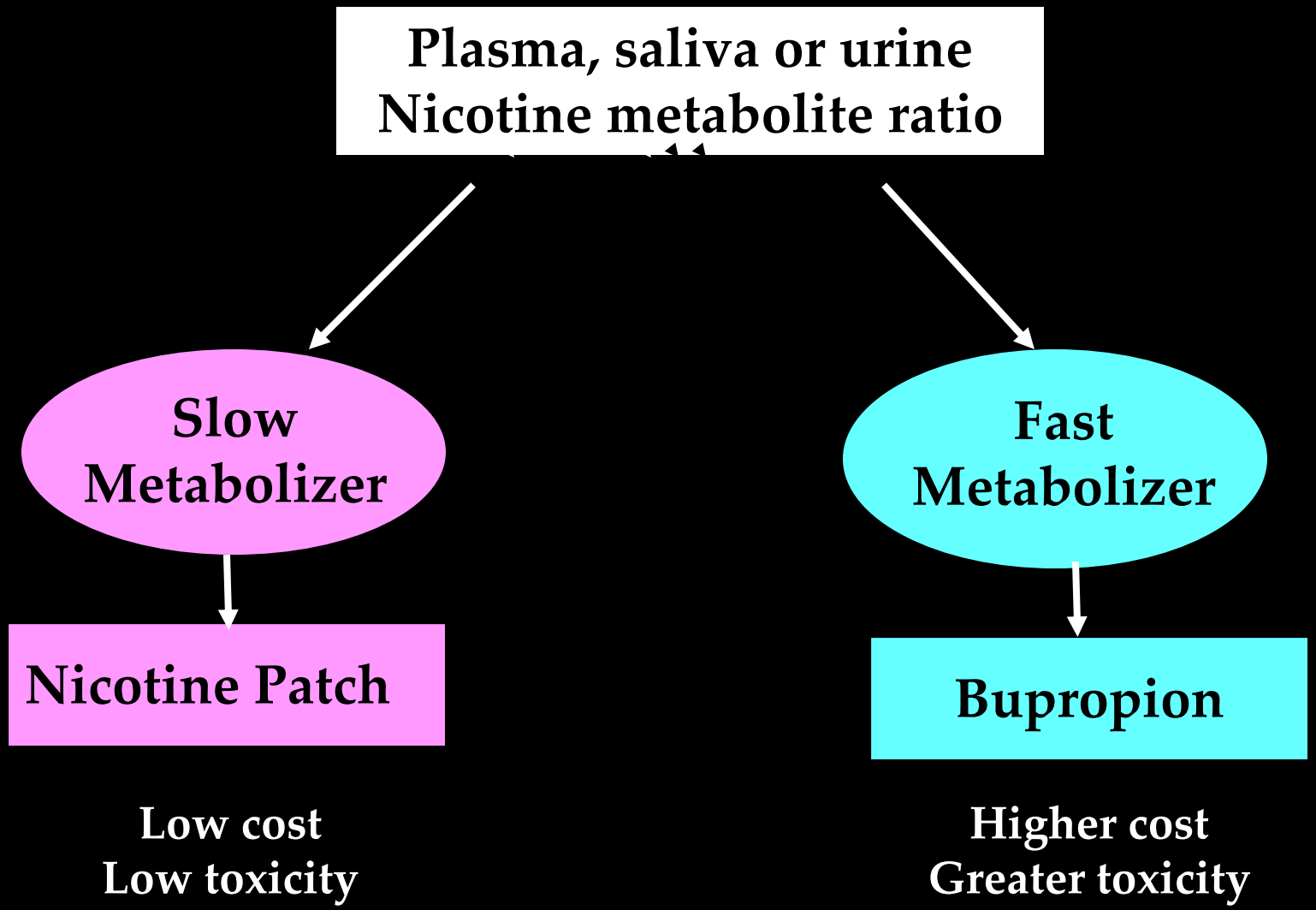
Nicotine Metabolite Ratio Predicts Therapeutic Response to Bupropion (n=414)



- 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



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

Acknowledgements

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