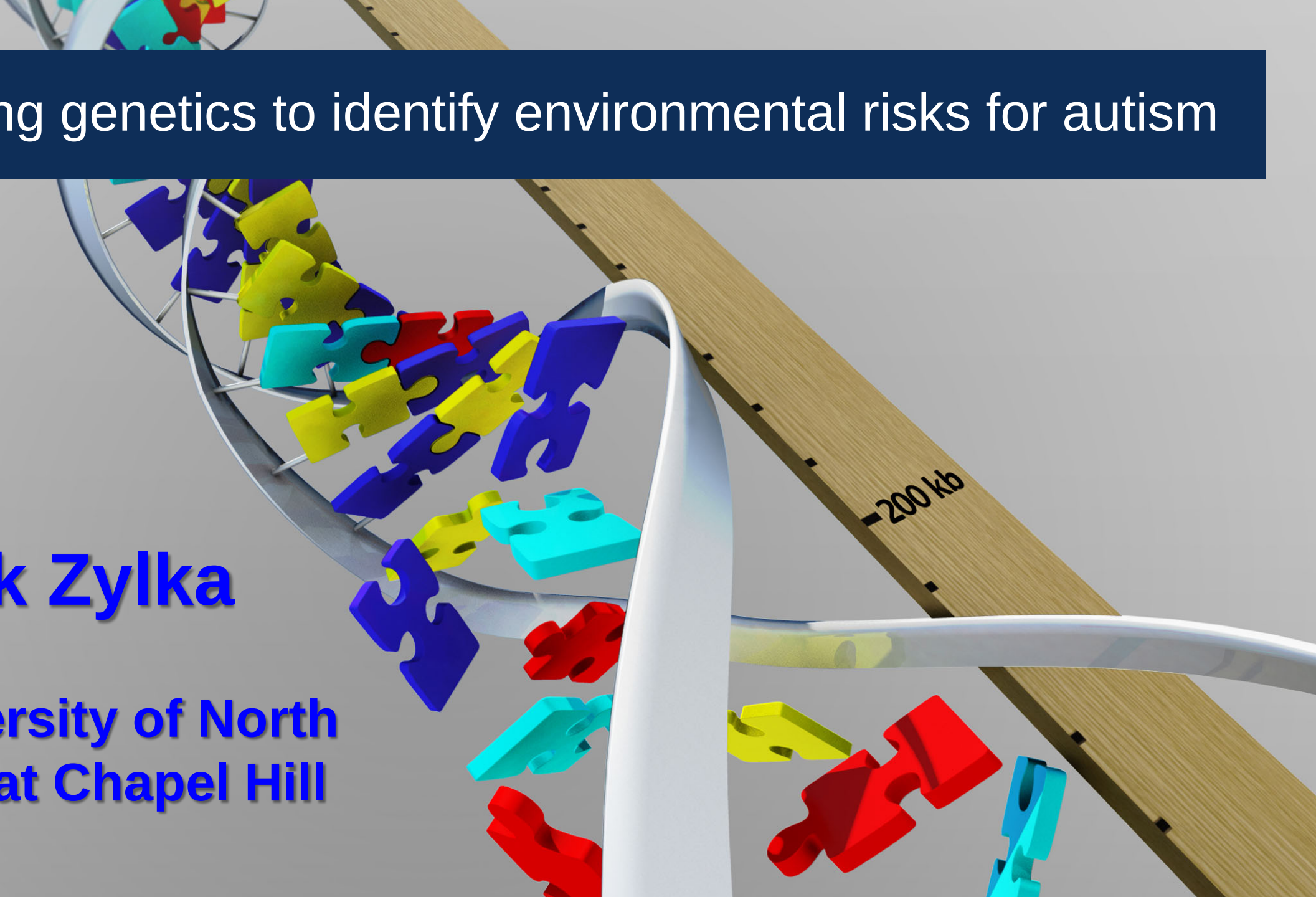


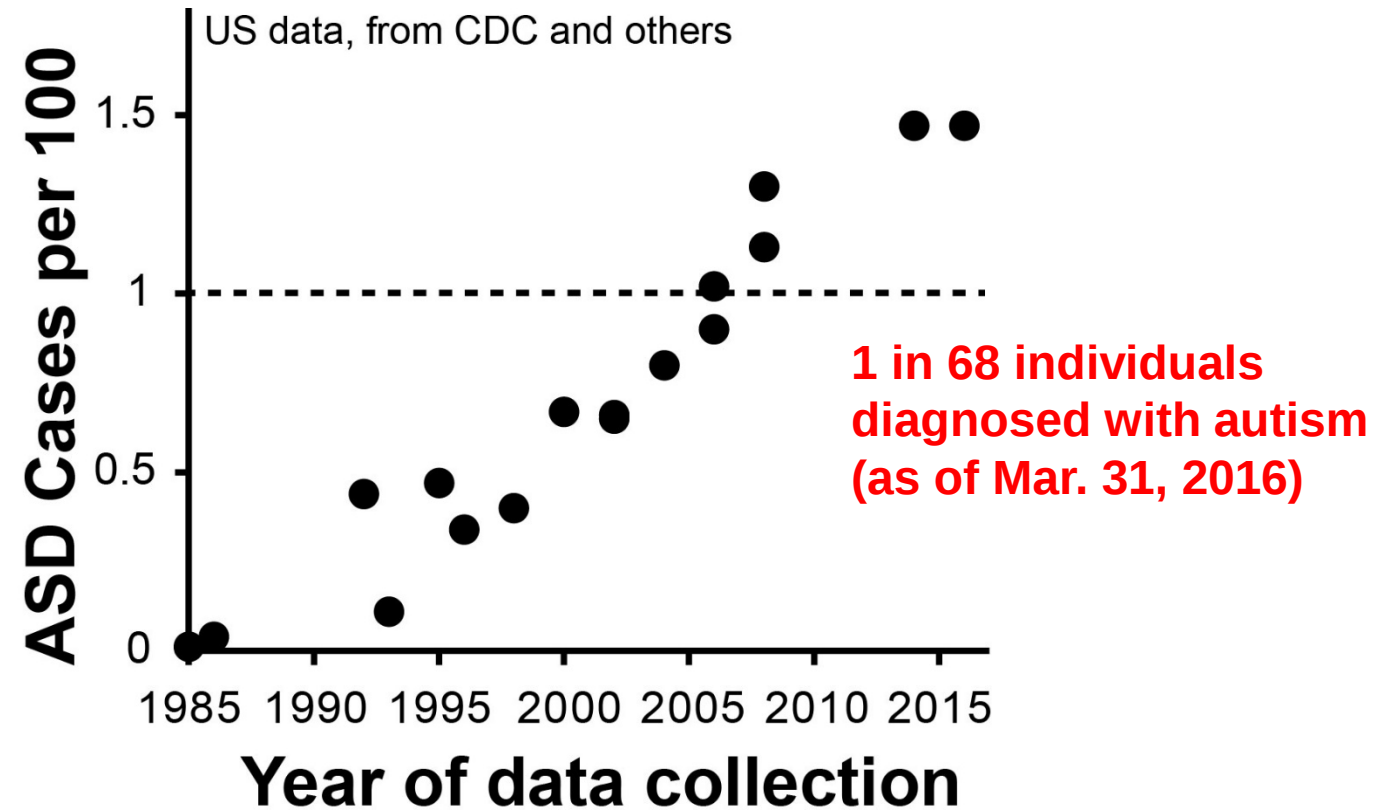
Exploiting genetics to identify environmental risks for autism

Mark Zylka

**The University of North
Carolina at Chapel Hill**

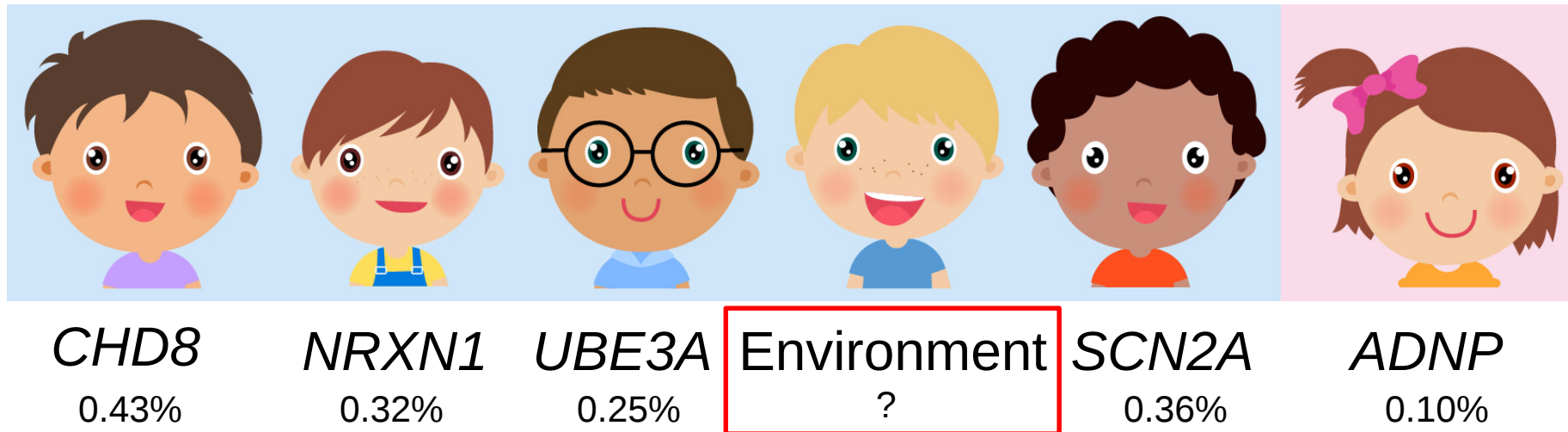


Autism is a major health problem



Strong sex bias: Boys are 4.5x more likely to be identified with autism than girls

Hundreds of *de novo* gene mutations are linked to autism risk



- Our inability to identify environmental threats to the brain early—before they cause disease—represents a major biomedical challenge.
- Unlike *de novo* gene mutations, which cannot be avoided, chemical exposures can often be minimized or eliminated, particularly during critical periods of brain development.

Reducing prevalence of an avoidable form of autism



CHD8

0.43%

NRXN1

0.32%

UBE3A

0.25%



SCN2A

0.36%

ADNP

0.10%

- Prospective approach: Identify environmental-use chemicals that target the same molecular pathways that are affected by *de novo* autism-linked mutations.
- Using high-throughput screening and transcriptomics approaches

Pathways implicated in autism

1. WNT/ β -catenin pathway - (Valproic acid)
2. Synaptic Function – hyper / hypoexcitability (Pyrethroids)
3. Neuroinflammation – (Strobilurin fungicides)

WNT/ β -catenin pathway

Enrichment of factors regulating canonical Wnt signaling among autism risk genes

Alan Packer, Simons Foundation

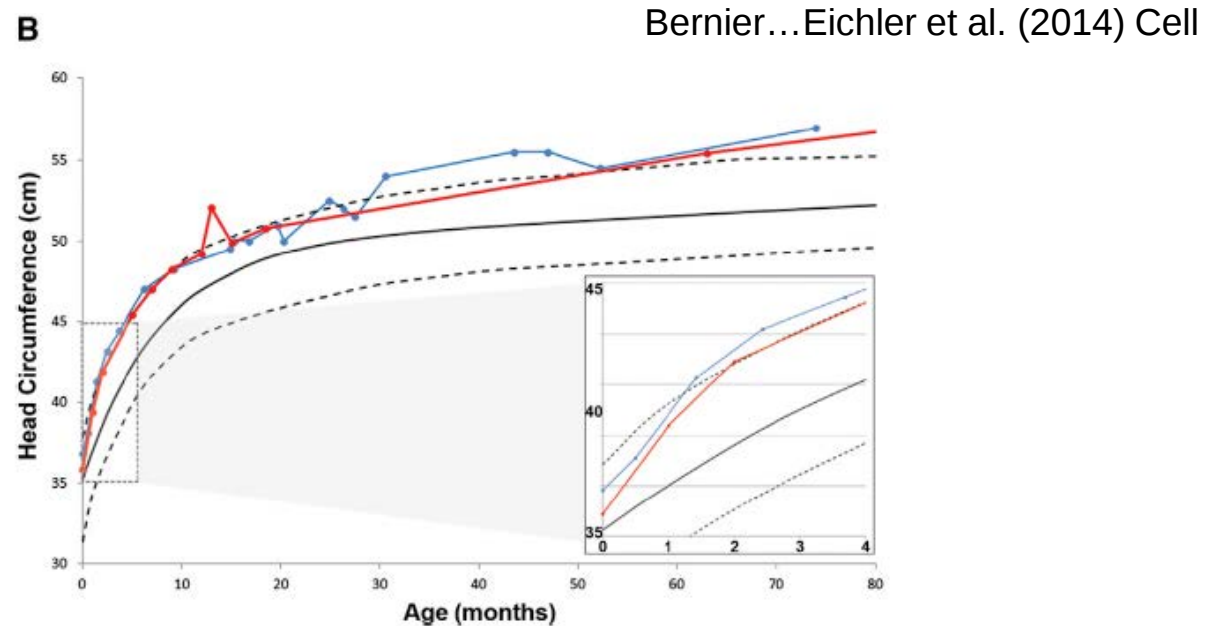
Molecular Psychiatry advance online publication, 13 December 2016; doi:10.1038/mp.2016.228

CHD8

A



B



Cortical overgrowth is a common phenotype in many individuals with autism

WNT/ β -catenin pathway

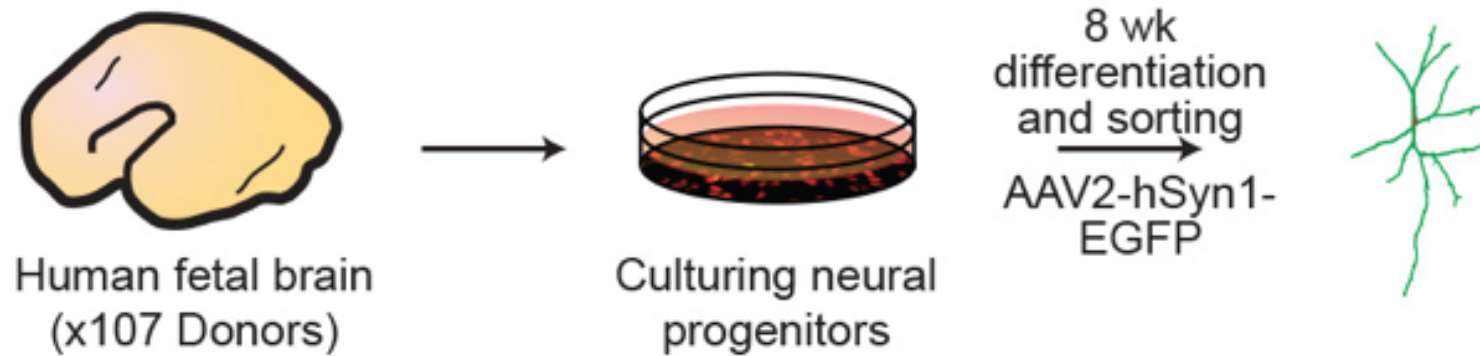
Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism

Christensen et al. (2013) JAMA

Identify additional chemicals that act like valproic acid
(Wnt reporter screens, transcriptomics with Wnt target genes).

Incorporate human genetic diversity into neurotoxicity tests

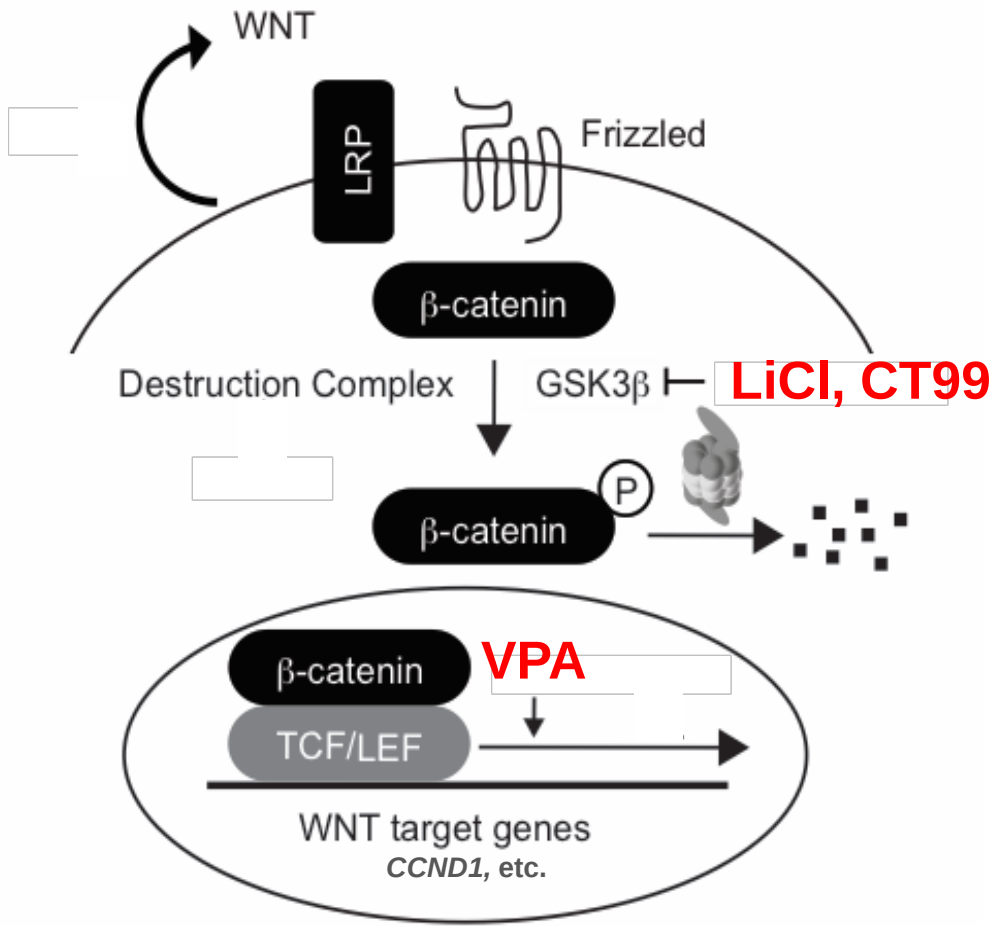
Human genetic diversity panel - neural progenitor cells



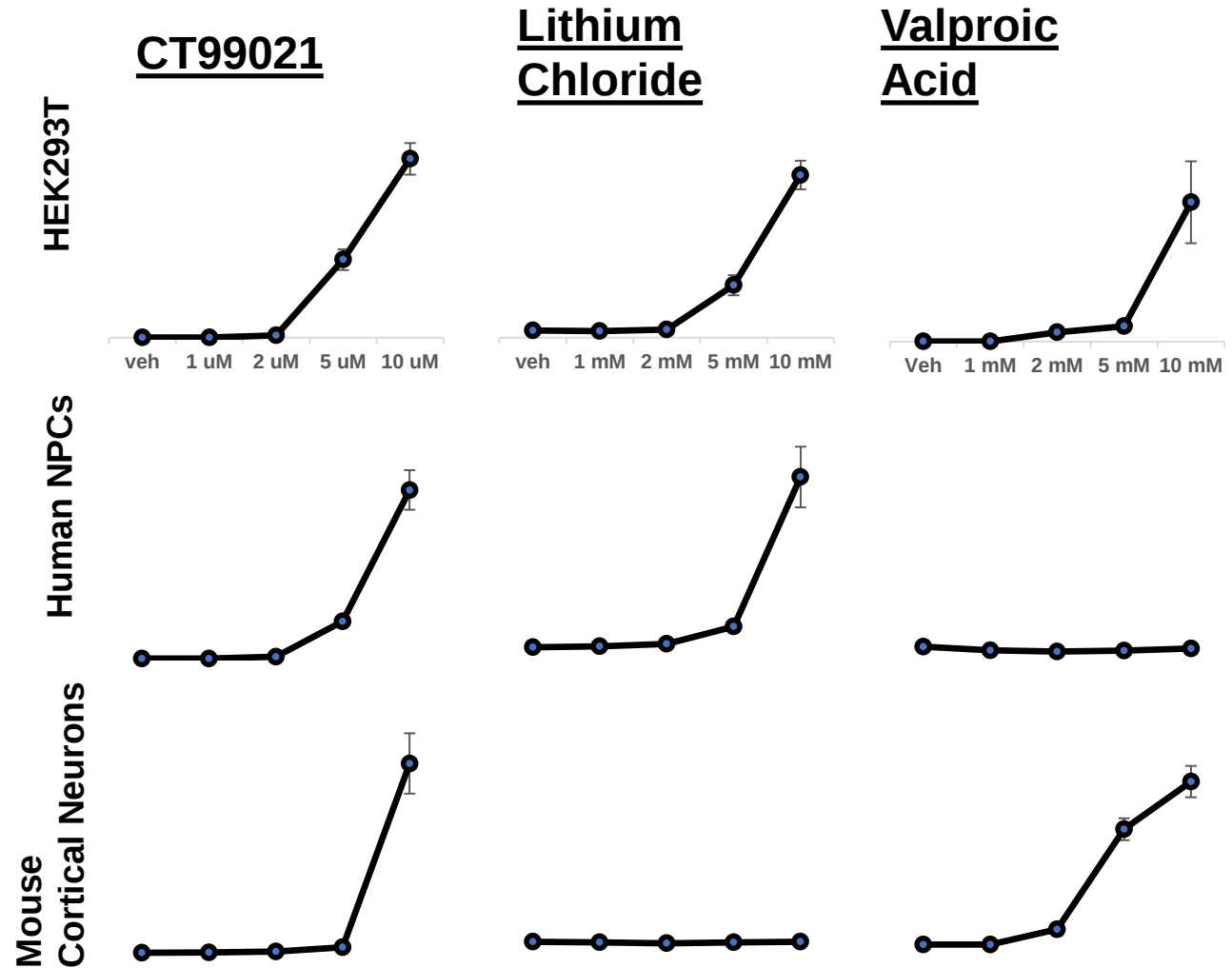
Jason Stein
Assistant Professor, Dept. Genetics
UNC Neuroscience Center



Chemical Modulation of Wnt Signaling



Wnt Sensitive Luciferase Reporter



Pathways implicated in autism

1. WNT/ β -catenin pathway - (Valproic acid)
2. Synaptic Function – hyper / hypoexcitability (Pyrethroids)
3. Neuroinflammation – (Strobilurin fungicides)

Pyrethroid exposure linked to increased autism risk

Class II Pyrethroids increase autism risk following prenatal (3rd trimester) exposure

Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study

Janie F. Shelton,¹ Estella M. Geraghty,² Daniel J. Tancredi,^{3,4} Lora D. Delwiche,¹ Rebecca J. Schmidt,¹ Beate Ritz,^{5,6,7} Robin L. Hansen,^{3,8} and Irva Hertz-Picciotto^{1,8}
(2014) Environmental Health Perspectives

Prenatal exposure to pyrethroid pesticides and childhood behavior and executive functioning

Melissa A. Furlong^{a,*}, Dana Boyd Barr^b, Mary S. Wolff^c, Stephanie M. Engel^d

^a Department of Community, Environment, and Policy, Mel and Enid Zuckerman College of Public Health, University of Arizona, United States

^b Department of Environmental Health, Rollins School of Public Health, Emory University, United States

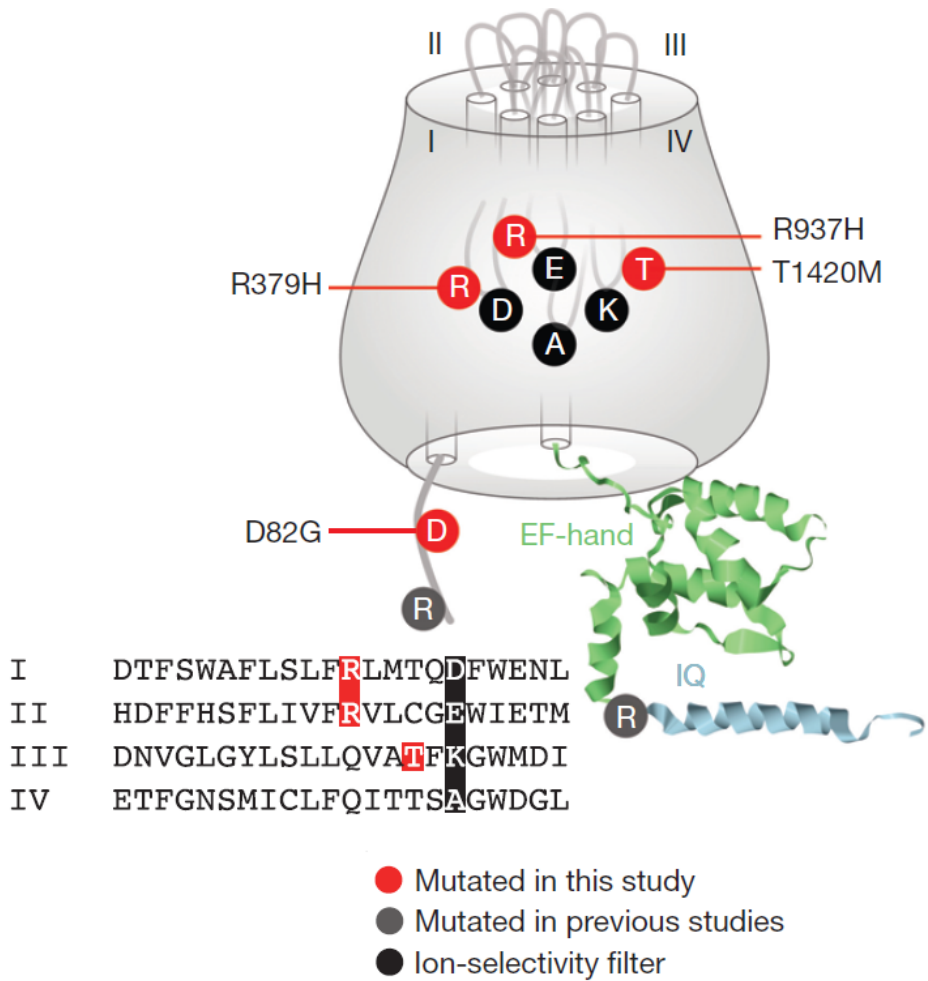
^c Department of Environmental Medicine and Public Health, Mount Sinai School of Medicine, United States

^d Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, United States

(2017) Neurotoxicology

Pyrethroids target a voltage gated sodium channel linked to ASD

SCN2A / Nav 1.2 (152 kb)



Autism-linked mutations dampen or eliminate channel function.

Ben-Shalom...Bender et al (2017) *Biol. Psychiatry*

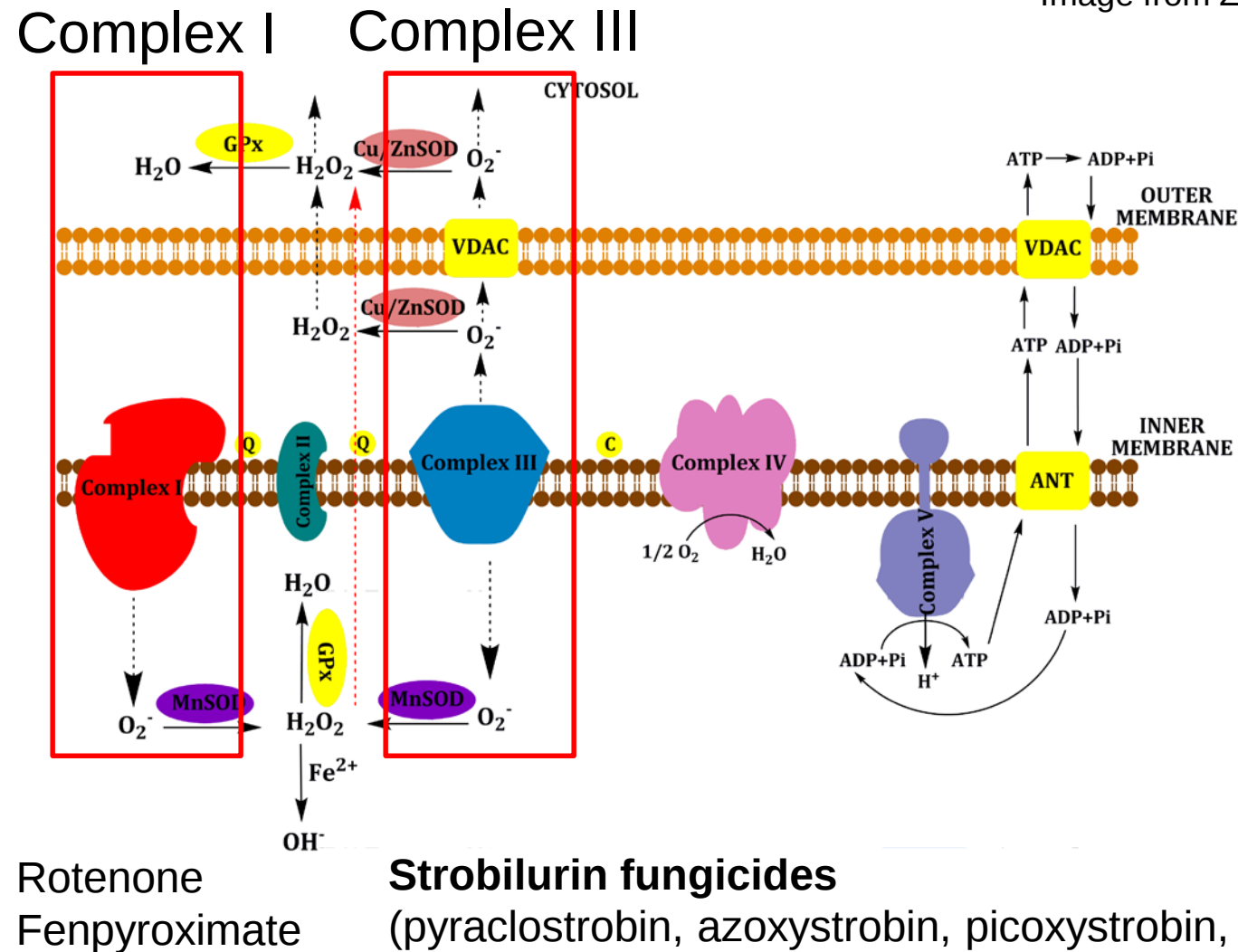
De Rubeis et al. (2014) *Nature*

Pathways implicated in autism

1. WNT/ β -catenin pathway - (Valproic acid)
2. Synaptic Function – hyper / hypoexcitability (Pyrethroids)
3. Neuroinflammation – (Strobilurin fungicides)

Strobilurin fungicides inhibit mitochondrial complex III

Image from Zapico, Aging and Disease. 2013

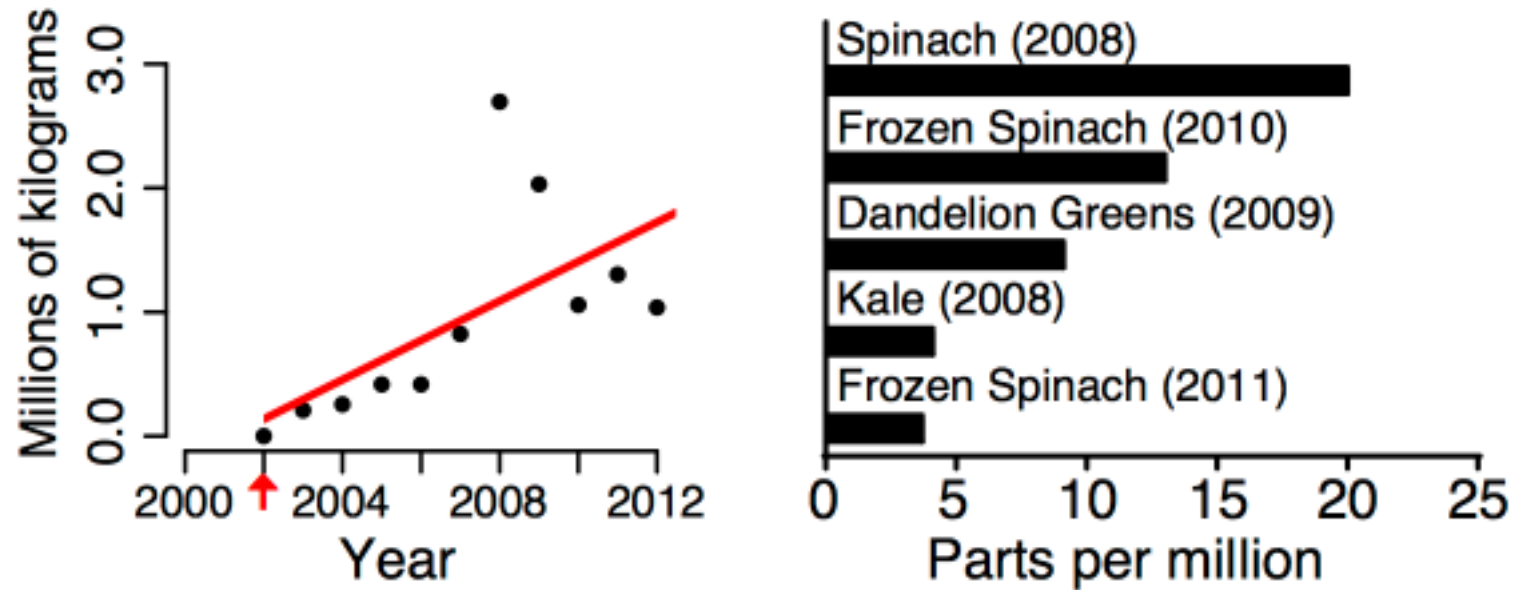


Are strobilurin fungicides on foods?



Are strobilurin fungicides on foods? Yes.

Pyraclostrobin



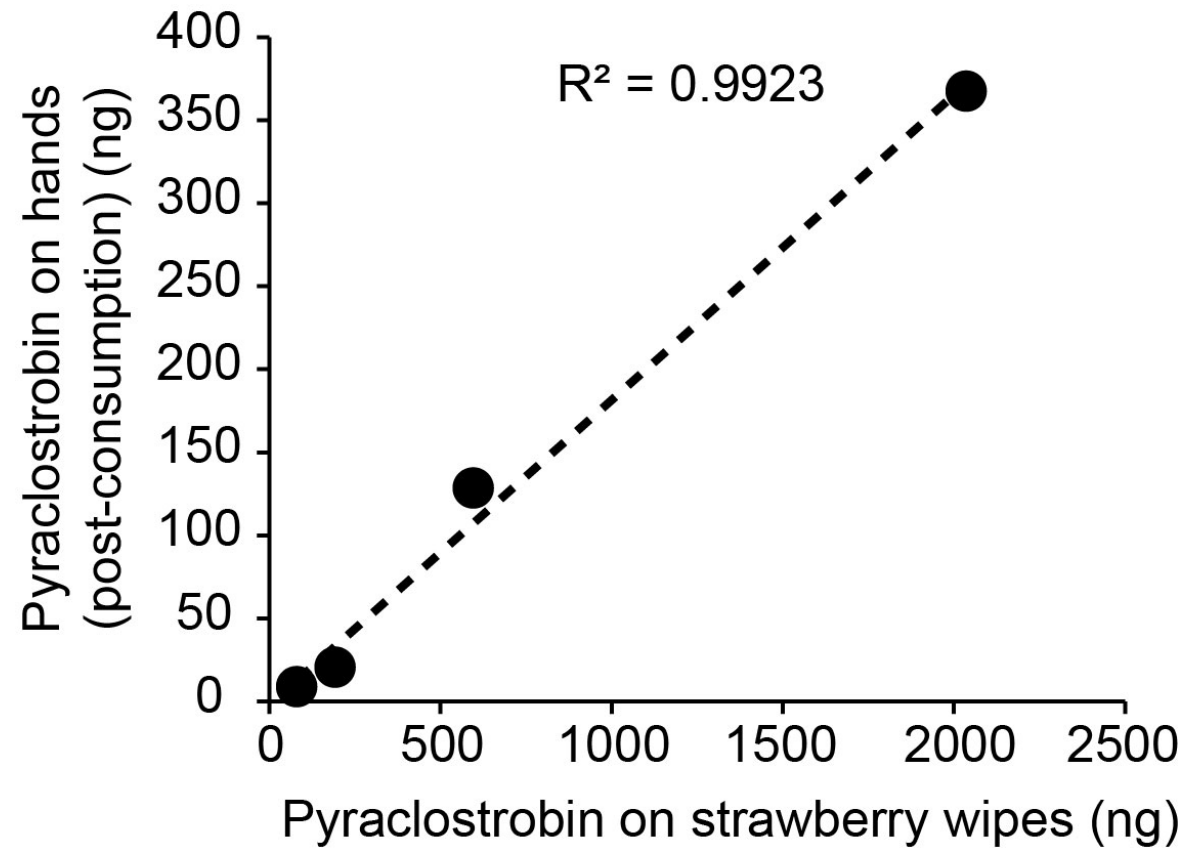
Strawberry study



Heather Stapleton, Duke



And Kate Hoffman



(12) **United States Patent**
Cornish et al.

(10) **Patent No.:** **US 8,138,196 B2**
(45) **Date of Patent:** **Mar. 20, 2012**

(54) **ANTIFUNGAL WALLBOARDS AND BUILDING MATERIALS AND METHODS FOR THE PRODUCTION THEREOF**

(75) Inventors: **Alexander Cornish**, Basel (CH); **Anja Greiner**, Weinheim (DE); **John R. James**, Greensboro, NC (US); **Gertrude Knauf-Beiter**, Stein (CH); **Johann Steiner**, Basel (CH)

(73) Assignee: **Syngenta Crop Protection, Inc.**, Greensboro, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 958 days.

(21) Appl. No.: **11/917,167**

(22) PCT Filed: **Jun. 13, 2006**

(86) PCT No.: **PCT/GB2006/002167**

§ 371 (c)(1),
(2), (4) Date: **Jun. 5, 2008**

(87) PCT Pub. No.: **WO2006/134347**

PCT Pub. Date: **Dec. 21, 2006**

(65) **Prior Publication Data**

US 2008/0280929 A1 Nov. 13, 2008

Related U.S. Application Data

(60) Provisional application No. 60/690,403, filed on Jun. 14, 2005.

(51) **Int. Cl.**
A01N 43/54 (2006.01)
E04C 2/26 (2006.01)

(52) **U.S. Cl.** **514/269; 52/309.3**

(58) **Field of Classification Search** None
See application file for complete search history.

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Primary Examiner — Shanon A Foley

(74) *Attorney, Agent, or Firm* — William A. Teoli, Jr.

(57) **ABSTRACT**

The present invention relates to, inter alia, methods for the treatment of wallboards and the treated wallboards. In particular, the invention relates to the treatment of wallboards with a fungicidally effective amount of a strobilurin or strobilurin-type fungicide. In a particular embodiment the fungicide is azoxystrobin. The invention also provides for the treatment of wallboards and building materials with combinations of fungicides present in synergistic amounts.

6 Claims, No Drawings

Wallboards containing azoxystrobin are marketed for use throughout homes

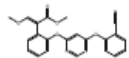
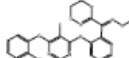
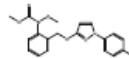
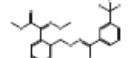




Strobilurin fungicides in house dust: is wallboard a source?

Ellen M. Cooper¹ · Rosie Rushing² · Kate Hoffman¹ · Allison L. Phillips¹ · Stephanie C. Hammel¹ · Mark J. Zylka³ · Heather M. Stapleton¹

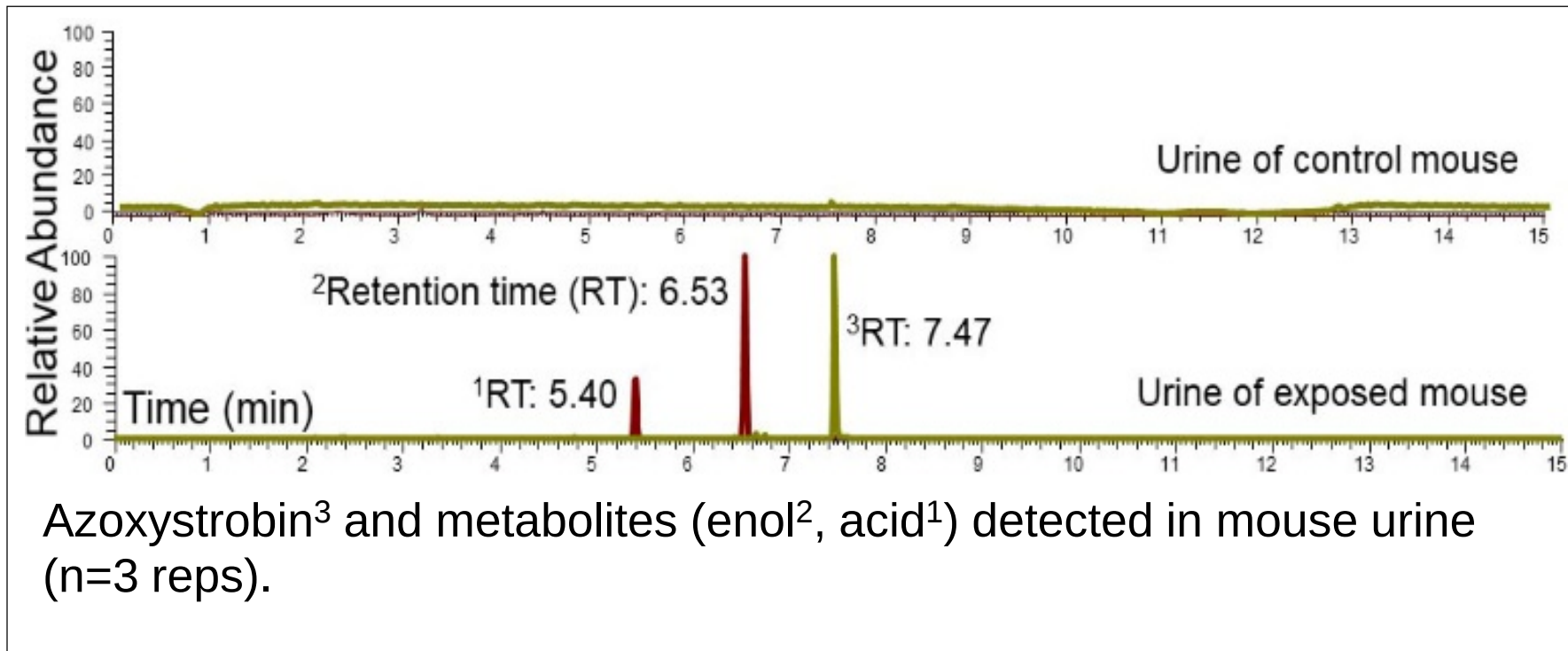
Table 2 Detection frequency and summary statistics for strobilurins in house dust

				
	Azoxystrobin	Fluoxastrobin	Pyraclostrobin	Trifloxystrobin
Detection <i>n</i> = 188	175 (93%)	138 (73%)	69 (36%)	71 (38%)
MDL^a	0.366 ± 0.726	0.103 ± 0.208	0.590 ± 1.14	0.046 ± 0.091
Summary				
Minimum	<MDL	<MDL	<MDL	<MDL
Median	2.39	0.113	<MDL	<MDL
Maximum	10,587	40.7	35.6	2.61
Geomean	3.35	0.318	0.513	0.051

^aMDL values were calculated individually for each sample based on the mass of dust analyzed and averaged across samples for this table



Detecting azoxystrobin metabolites in urine



Pilot experiment (40 mg/kg Azoxystrobin, *p.o.*), mass spec by Kun Lu (UNC)

Acknowledgments

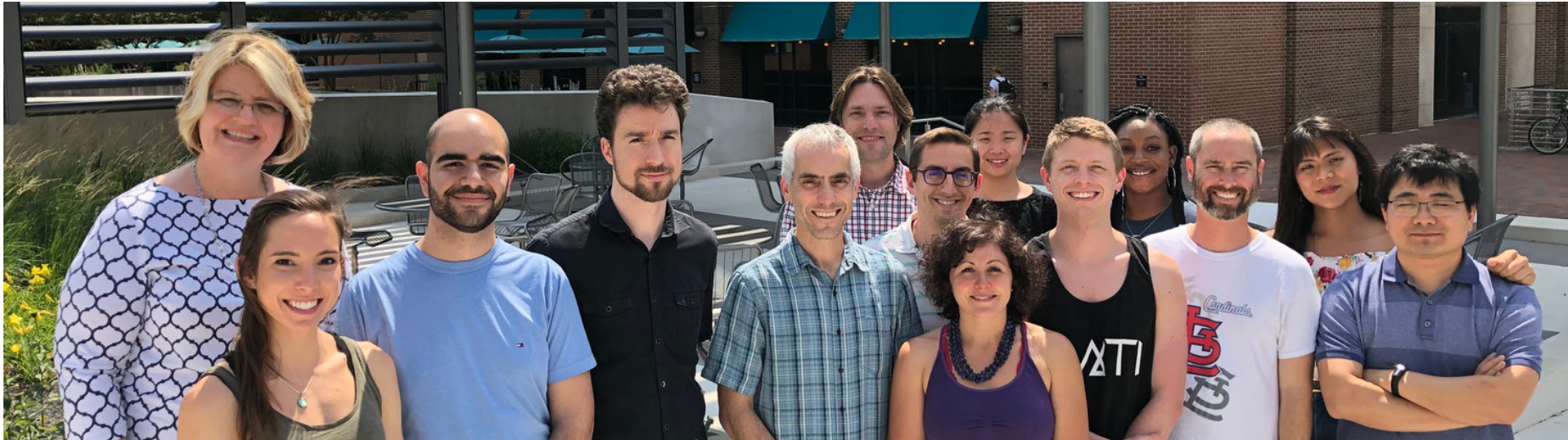
Justin
Wolter

Jeremy
Simon

Helen
Mao

Amber
Scott

Harper
Fauni



Bonnie Taylor-
Blake

Jessica
Jimenez

Baris
Oztemiz

Travis
Ptacek

Giulia
Fragola

Jesse
Niehaus

Eric
McCoy

Lei Xing

 @MarkZylka

Brandon Pearson
Alex Tuttle
Justin Wolter, Jason Stein
Kun Lu
(not shown)

Duke:
Heather Stapleton
Kate Hoffman

Support

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