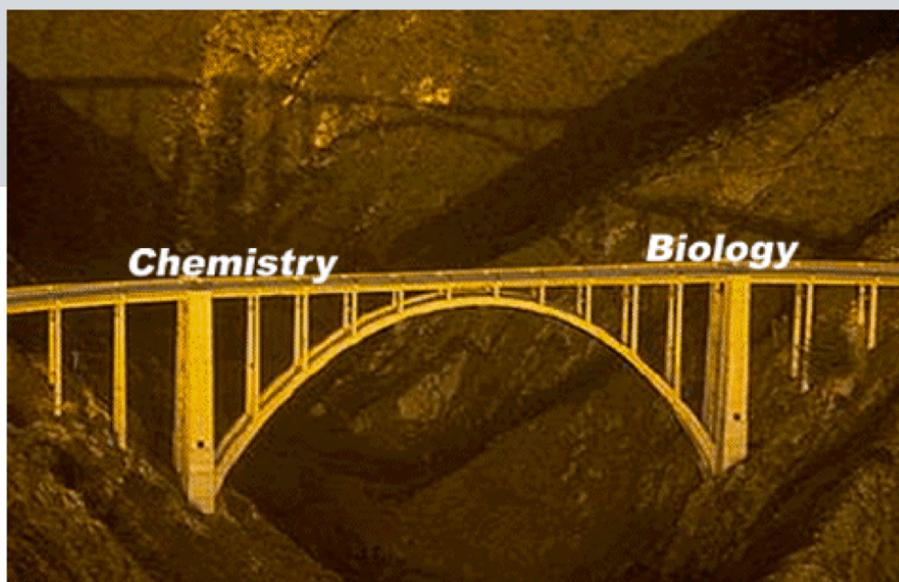


# Chemical Genetics

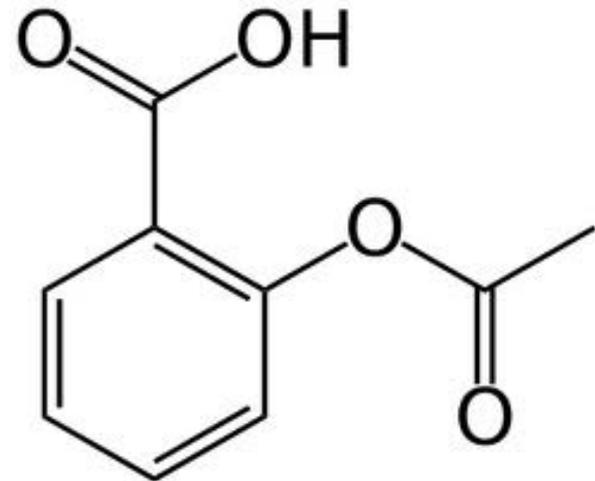


Victoria Van Vreede  
& Erin Tapper

# What is chemical genetics?

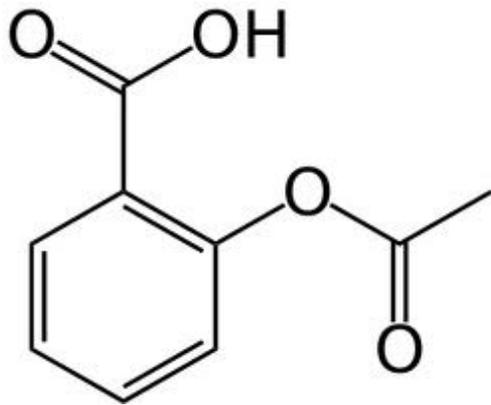


# Why is it important?

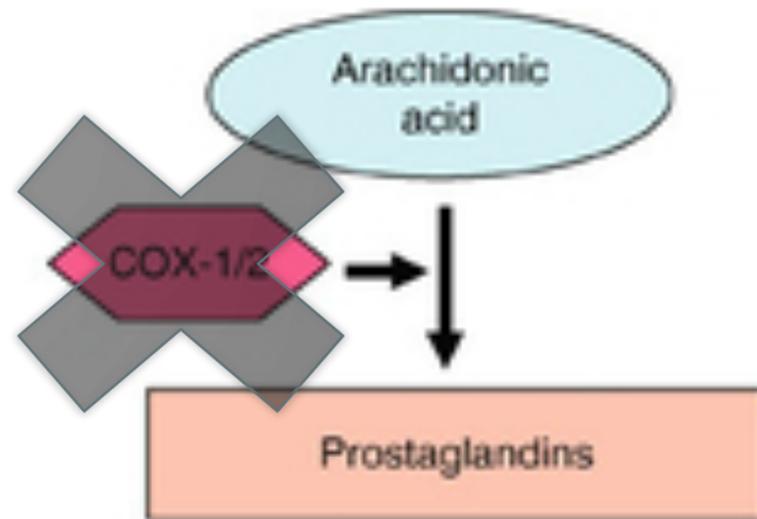


**Aspirin**

# Why is it important?

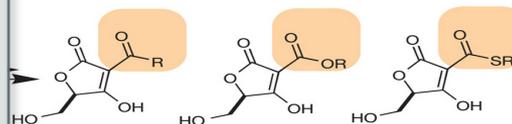


**Aspirin**

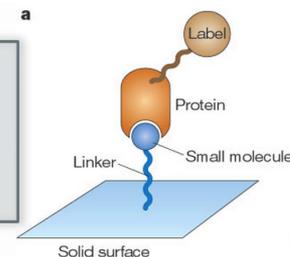


# How does Chemical Genetics work?

Create chemical libraries



Test chemicals with assays

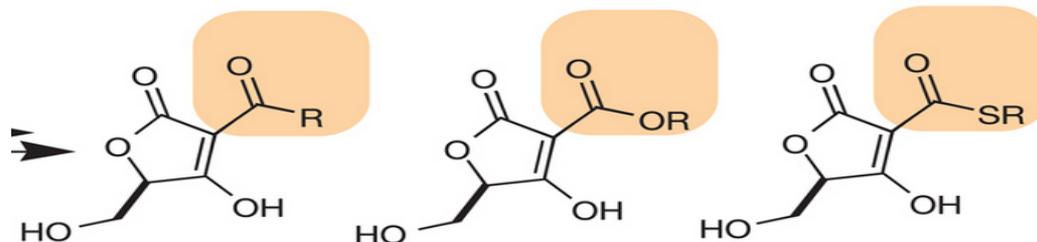


Use the Results

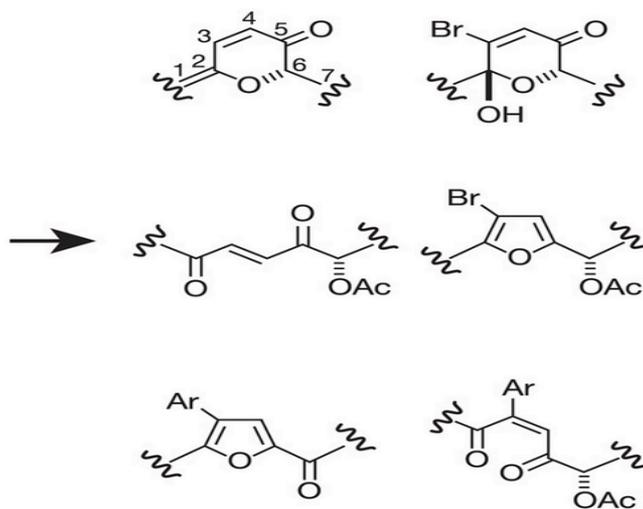


# How do we create libraries?

Focused  
Library



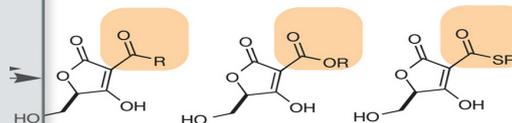
Diversity  
Oriented  
Library



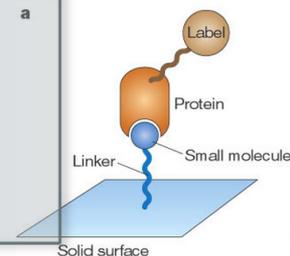
**Restrictions**

# How does Chemical Genetics work?

Create chemical libraries



Test chemicals with assays



Use the Results



# Chemical Assay Screens

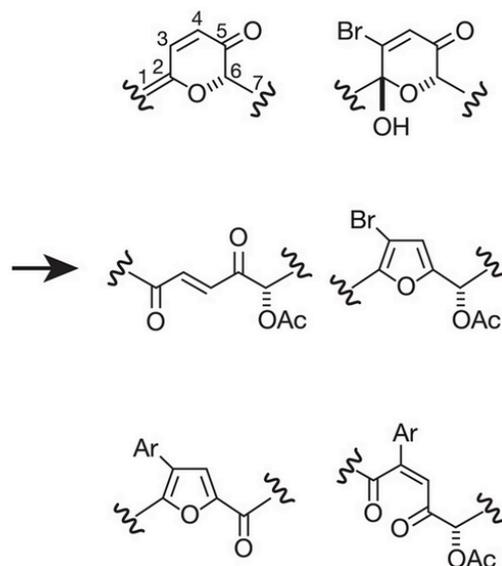
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1. Virtual screening

2. Protein-binding assays

3. Phenotypic outcomes

# Virtual screening



 AutoDock

# Screening Experiments

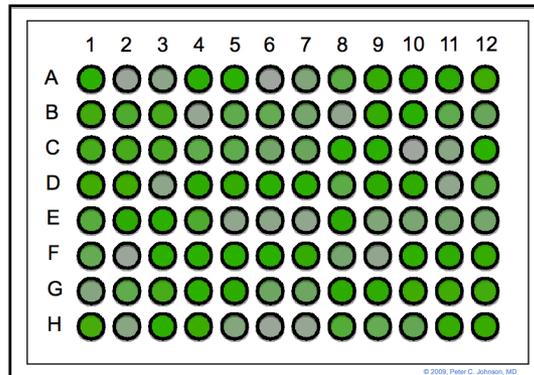
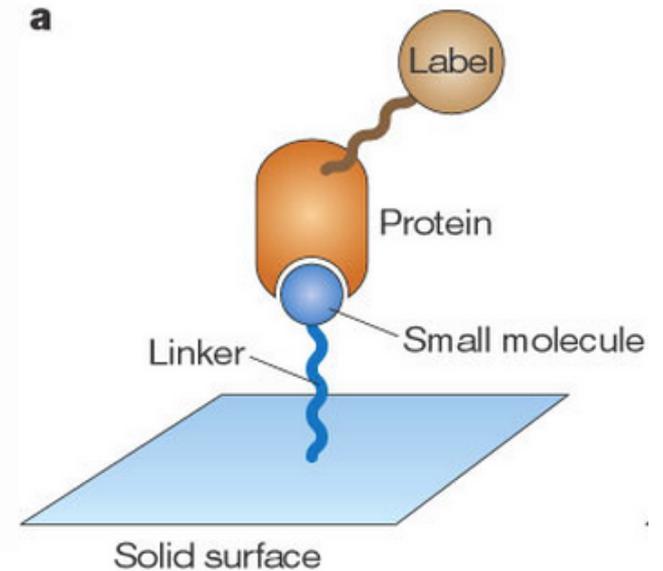
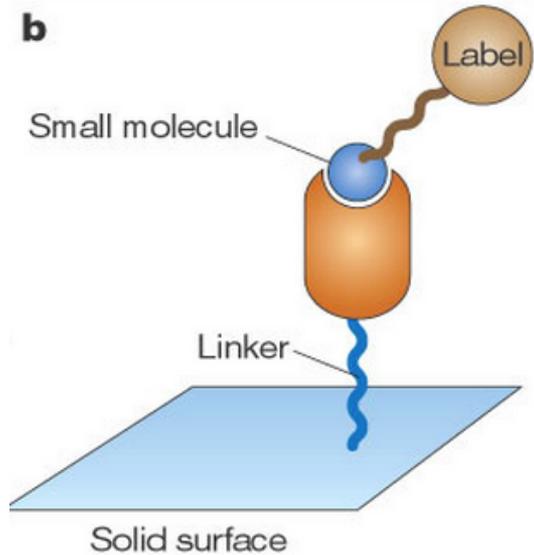
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1. Virtual screening

**2. Protein-binding assays**

3. Phenotypic outcomes

# Protein Binding Assays



# Screening Experiments

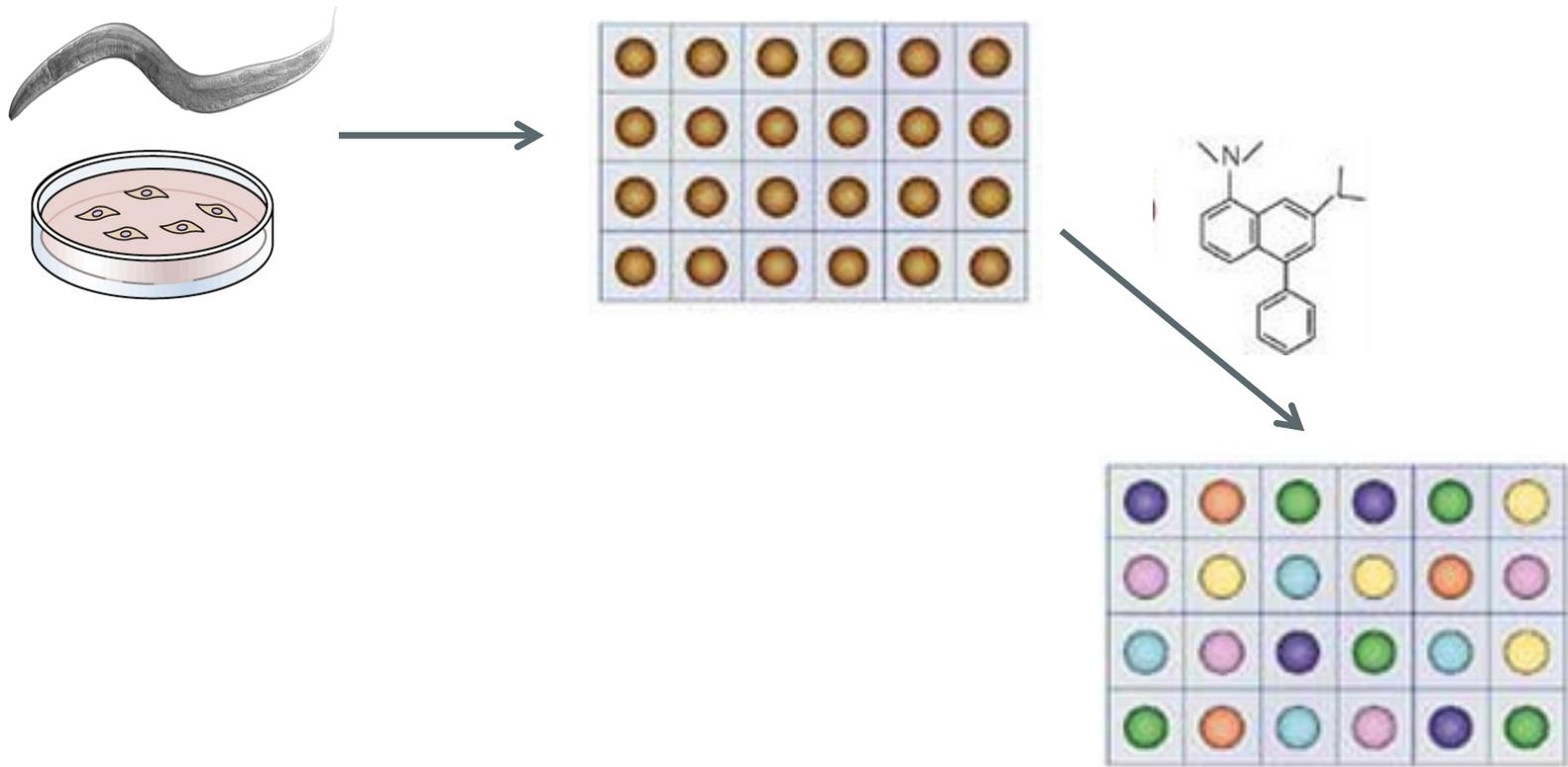
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1. Virtual screening

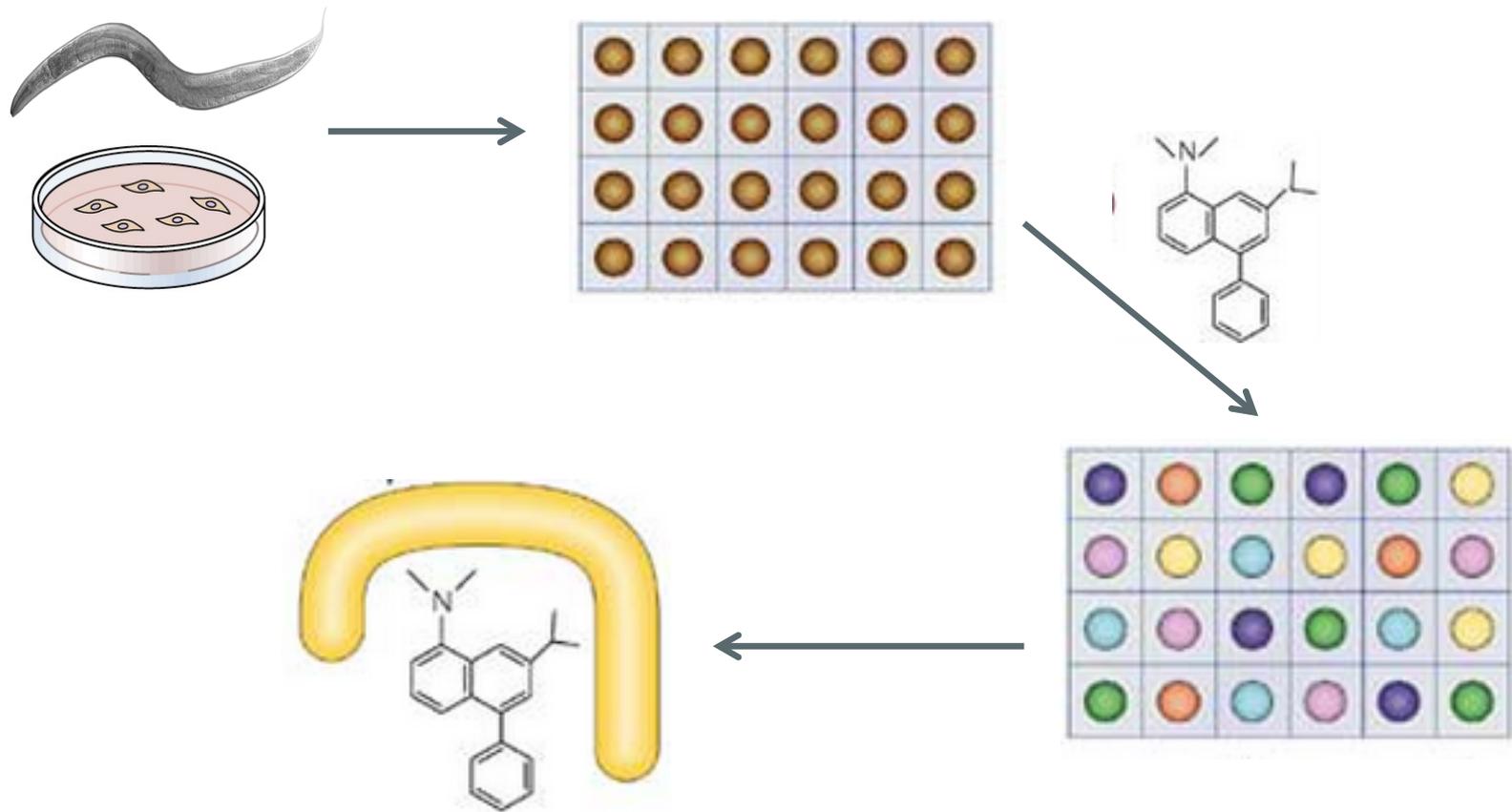
2. Protein-binding assays

**3. Phenotypic outcomes**

# Phenotypic Outcomes

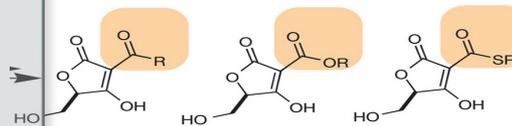


# Phenotypic Outcomes

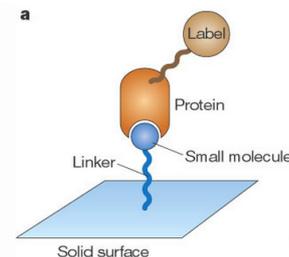


# How does Chemical Genetics work?

Create chemical libraries



Test chemicals with assays



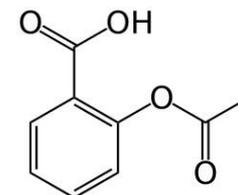
Use the Results



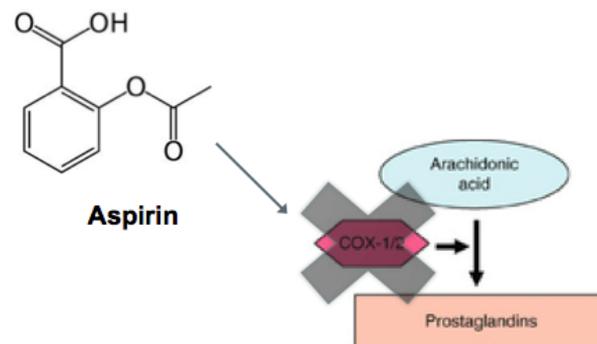
# Using Chemical Genetics



New Drug Leads

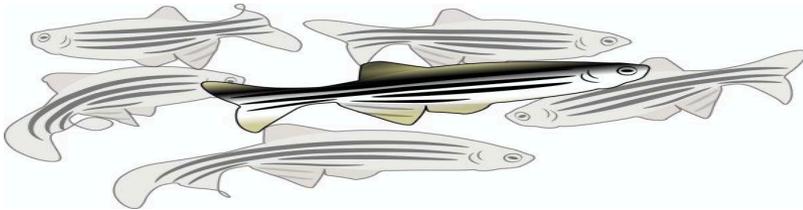


Understanding cellular pathways



# Using Chemical Genetics

Dr. Leonard Zon, M.D.  
Boston Children's Hospital



Stem cell transplants – PGE2

1<sup>st</sup> to pass Stage I of human clinical trials -Prohema

Compound Summary for: CID 16760703



## Valproic Acid

**Also known as:** Sodium valproate, Valproate sodium, Sodium 2-propylpentanoate, Valproic acid sodium salt, Epilim, 1069-66-5, Valproic acid sodium, DEPACON, Eureka

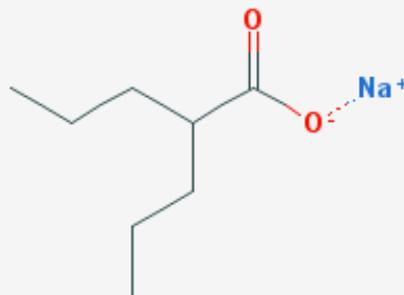
**Molecular Formula:**  $C_8H_{15}NaO_2$  **Molecular Weight:** 166.193269 **InChIKey:** AEQFSUDEHCCHBT-UHFFFAOYSA-M

A fatty acid with anticonvulsant properties used in the treatment of epilepsy. The mechanisms of its therapeutic actions are not well understood. It may act by increasing GAMMA-AMINOBUTYRIC ACID levels in the brain or by altering the properties of voltage dependent sodium channels. *From: MeSH*

### Table of Contents [Show subcontent titles](#)

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Pharmacology for a drug or inhibitor



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[advanced assay search](#)

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[by name or id](#)  
[advanced search](#)

**valproic acid**

ChemBankID: 471

[\[help\]](#)

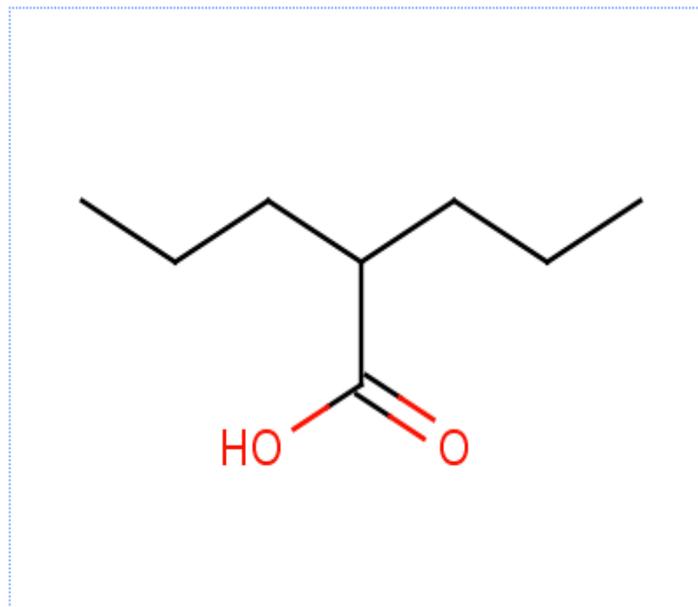
Molecular Weight: 144.21143

Rotatable Bonds: 5

HBond Acceptors: 2

HBond Donors: 1

LogP by GhoseCrippen: 2.749

[\[view all descriptors\]](#)[\[find similar molecules\]](#)[\[export as SDF\]](#)**Biochemical Interactions**

acts as an inhibitor of protein [Glycogen synthase kinase-3](#)  
acts as an inhibitor of proteins with deacetylase activity [12197307](#)

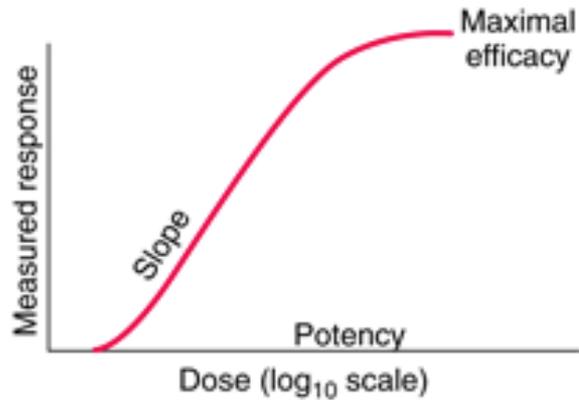
Not my protein

**Therapeutic Indications**

Seizures  
Bipolar Disorder  
Epilepsy  
Migraine

# Advantages and Disadvantages

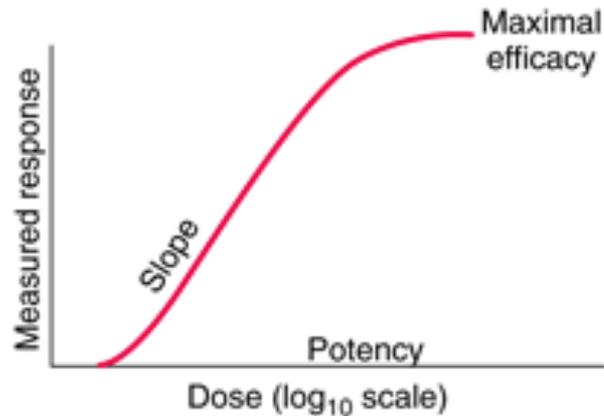
## Reversible



Can affect only 1 domain

# Advantages and Disadvantages

Reversible

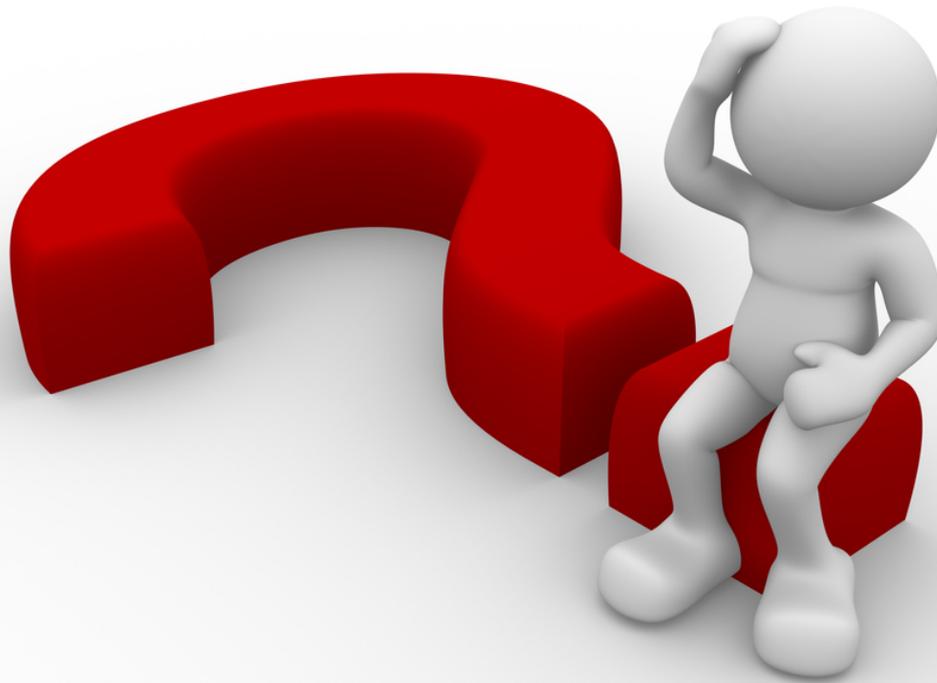


Specificity

Timely Process

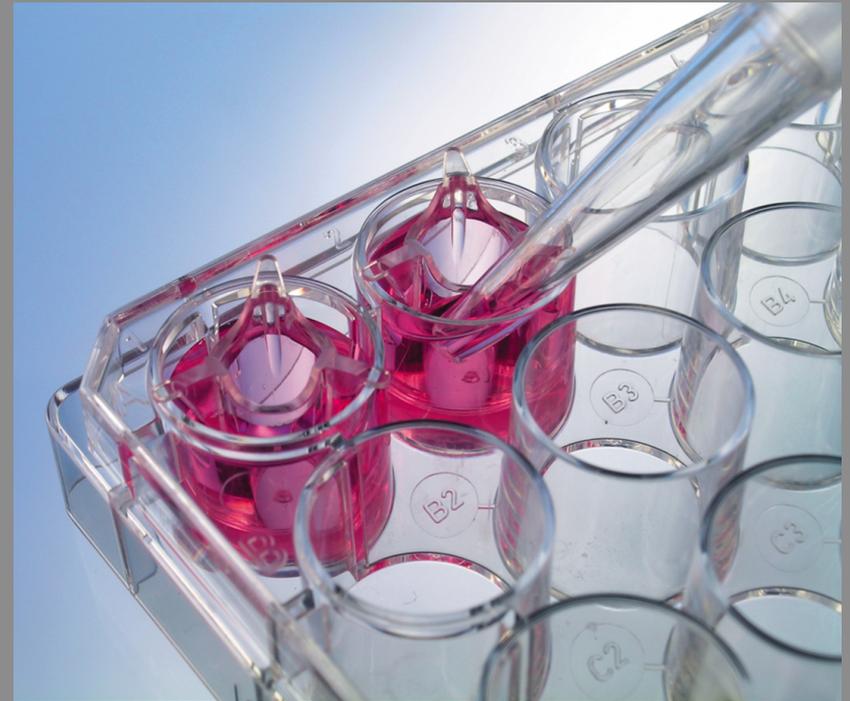
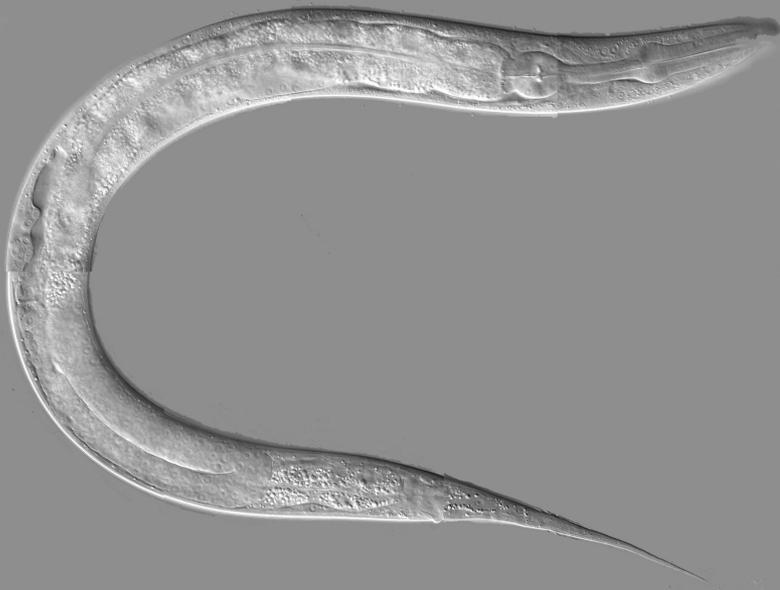
Can affect only 1  
function

# Questions?



# A whole-organism screen identifies new regulators of fat storage

George A Lemieux, Zena Werb, Kaveh Ashrafi, *et al*



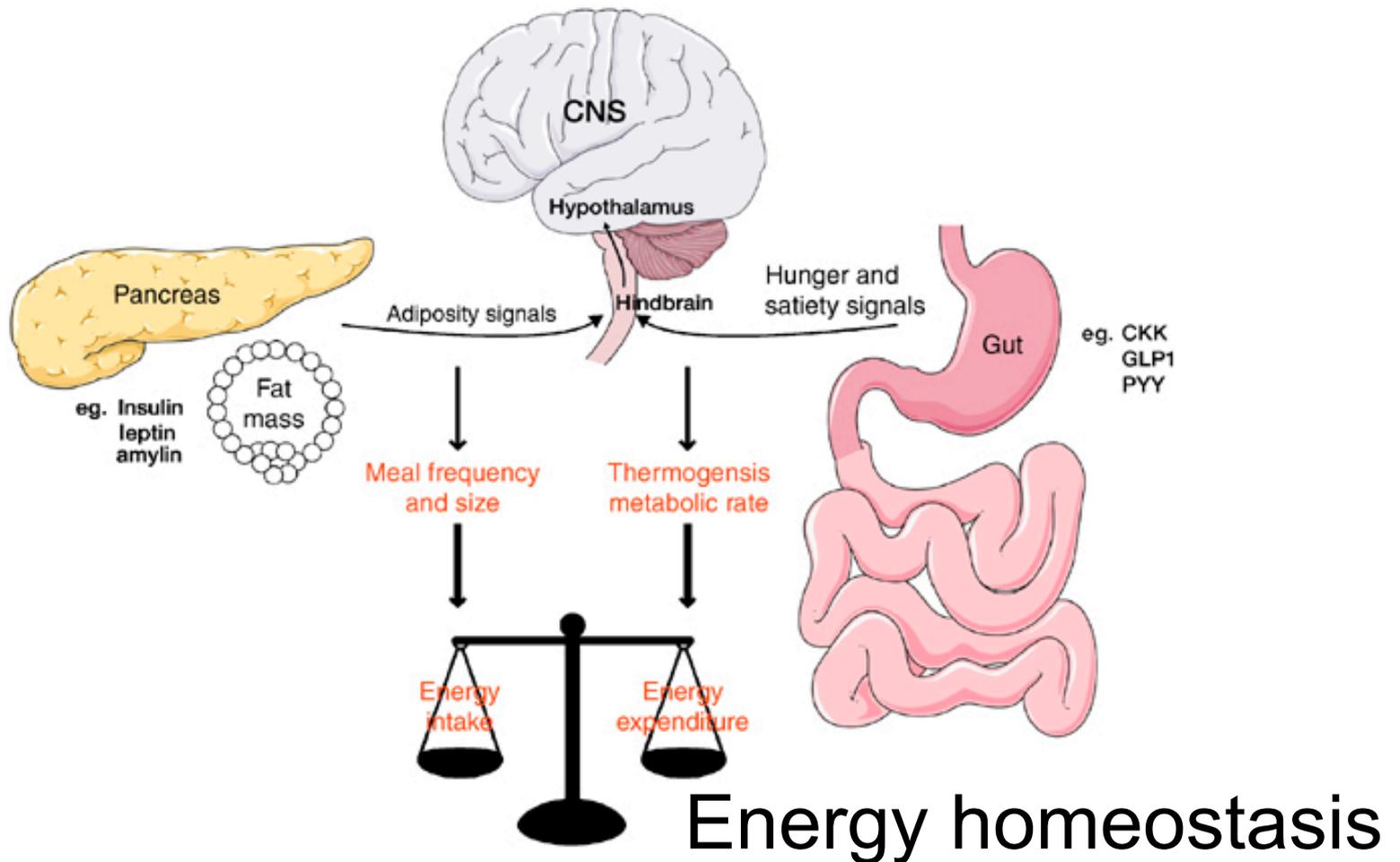
# Focus of paper

1. Identify small molecules that are effective within the intact animal
2. Reveal relationships between pathways that influence energy homeostasis

# Diabetes, obesity, and cancer are societal problems



# Energy metabolism plays a role

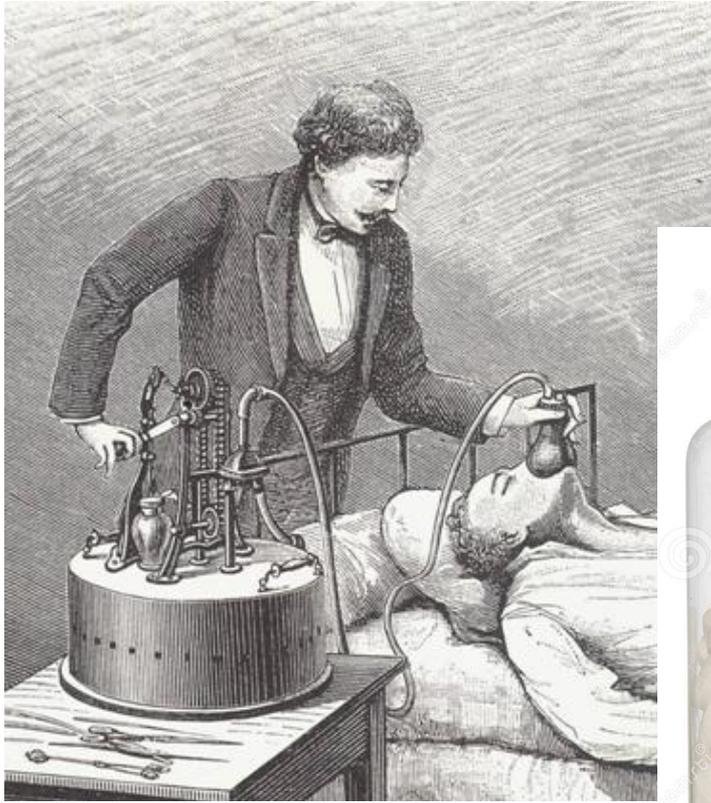


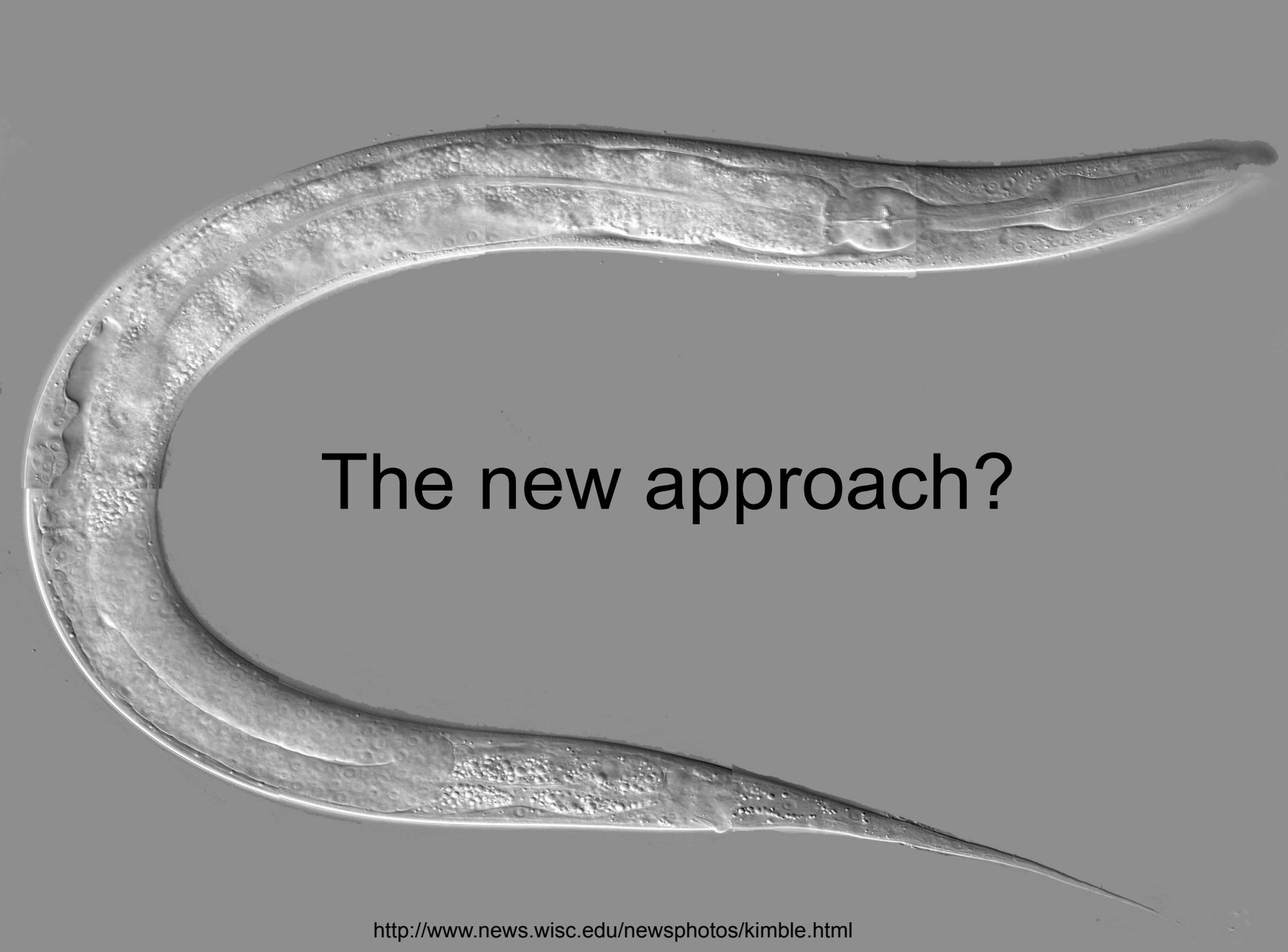
# How can we treat these diseases?

## Pharmacological agents



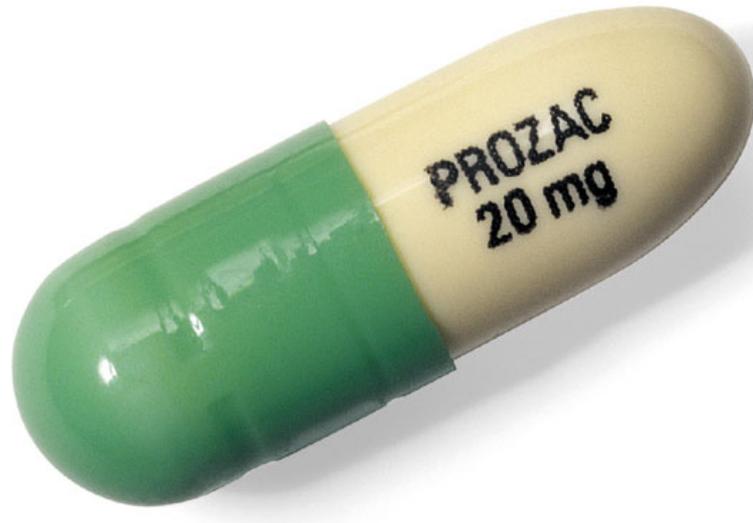
# How do we identify these drugs?





The new approach?

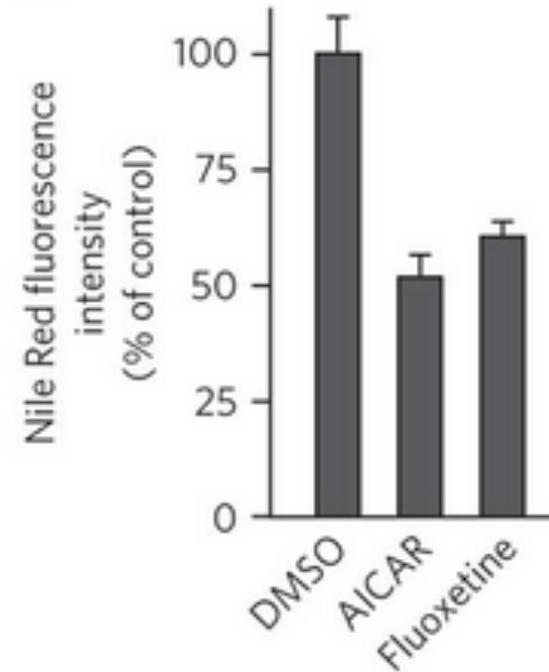
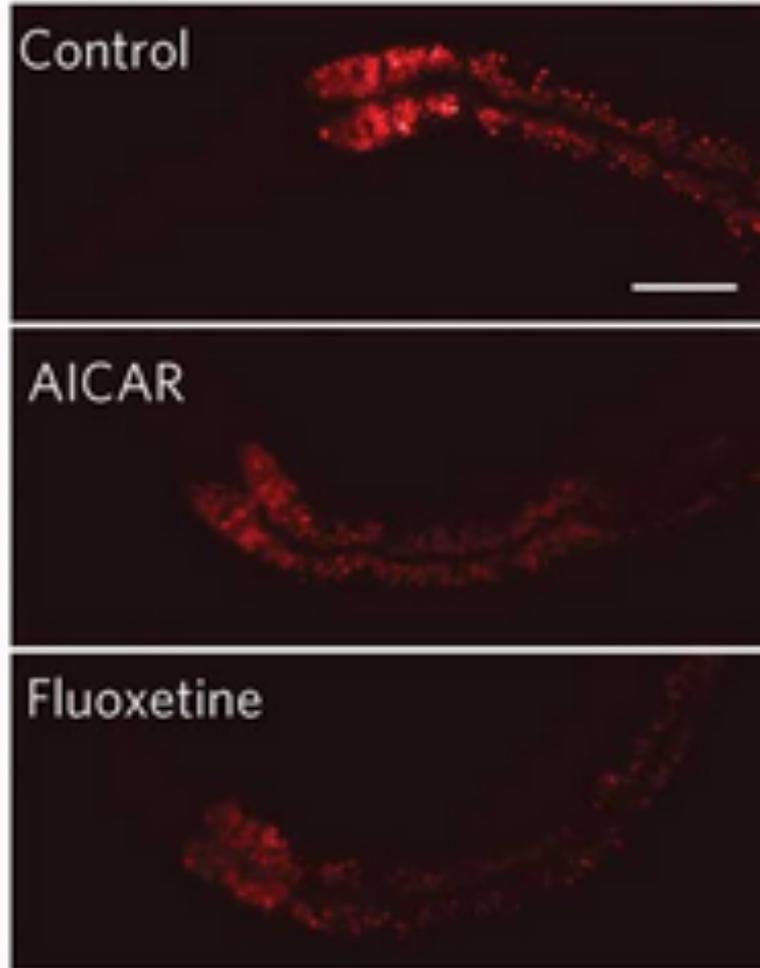
# How to validate Nile Red staining?



Known modifiers of lipid metabolism

# Screen for modulators of lipid metabolism

Nile Red



# Focus of paper

1. Identify small molecules that are effective within the intact animal
2. Reveal relationships between pathways that influence energy homeostasis

# Screening of uncharacterized small molecules



3,200 compounds in diversity library

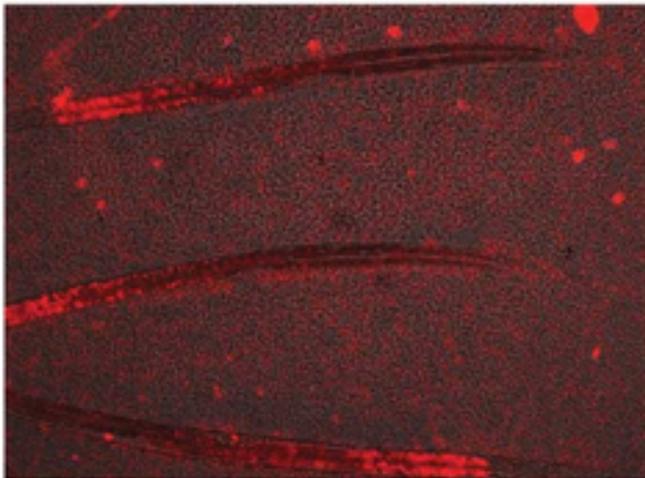
**c**

Synchronized L1  
nematodes

Food, Nile Red,  
compound library

48 hr, 20 °C

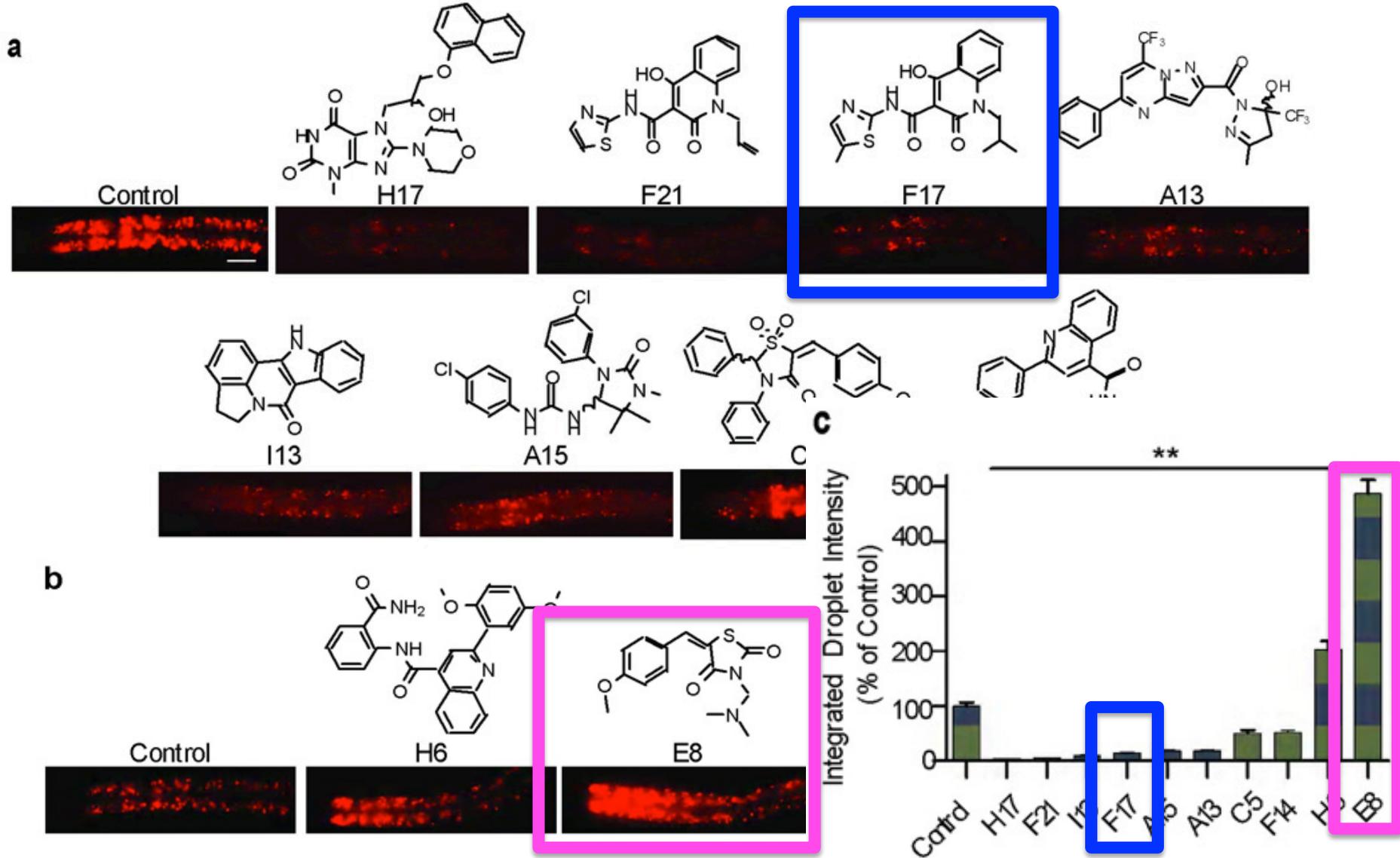
Young adults



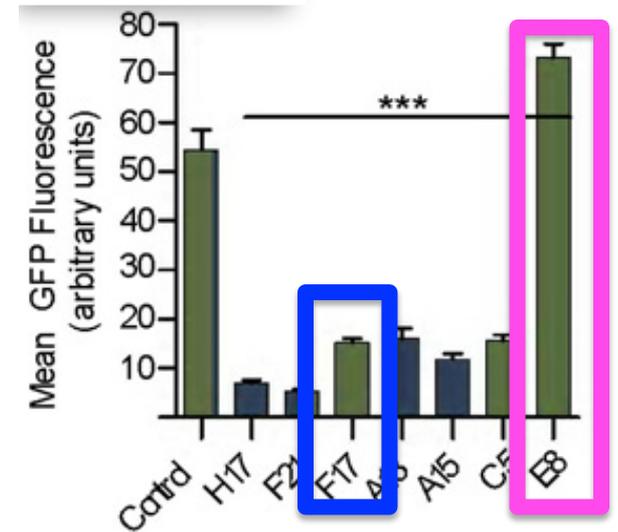
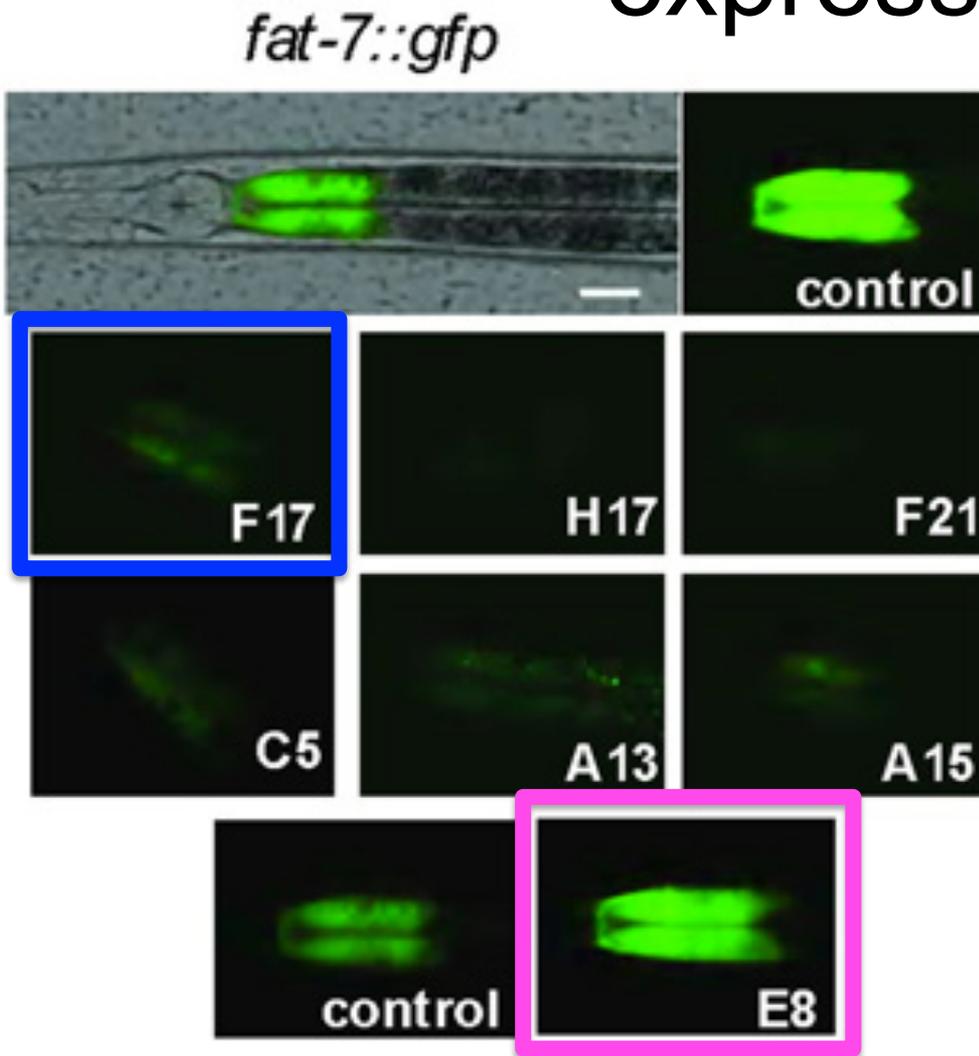
Acquire brightfield &  
red-fluorescence  
images

Compare Nile Red fluorescence and developmental stage relative to control-treated animals.

# Drugs effect Red Nile intensity

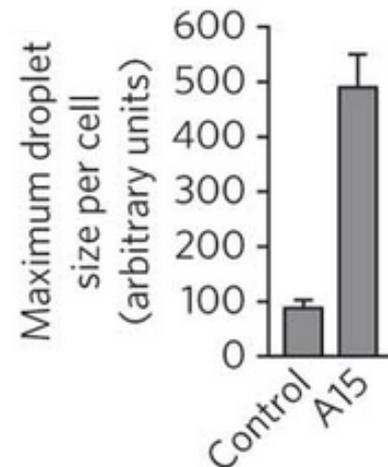
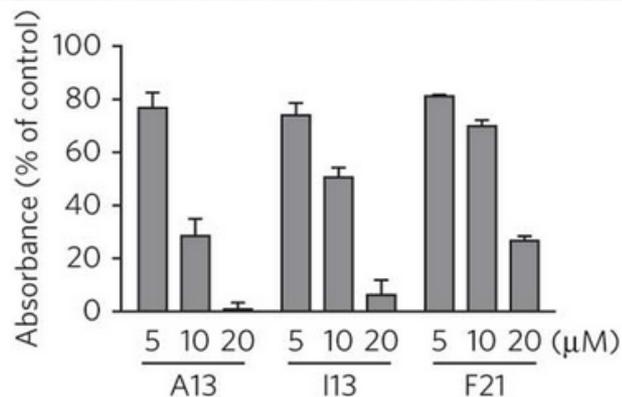
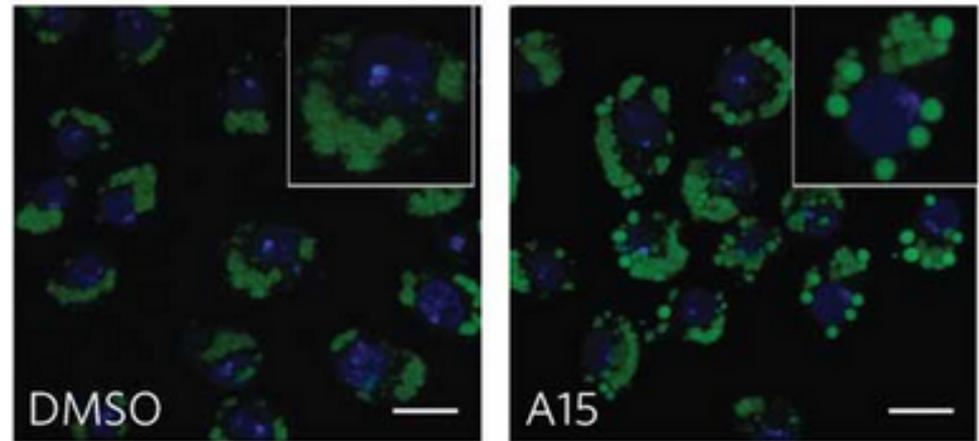
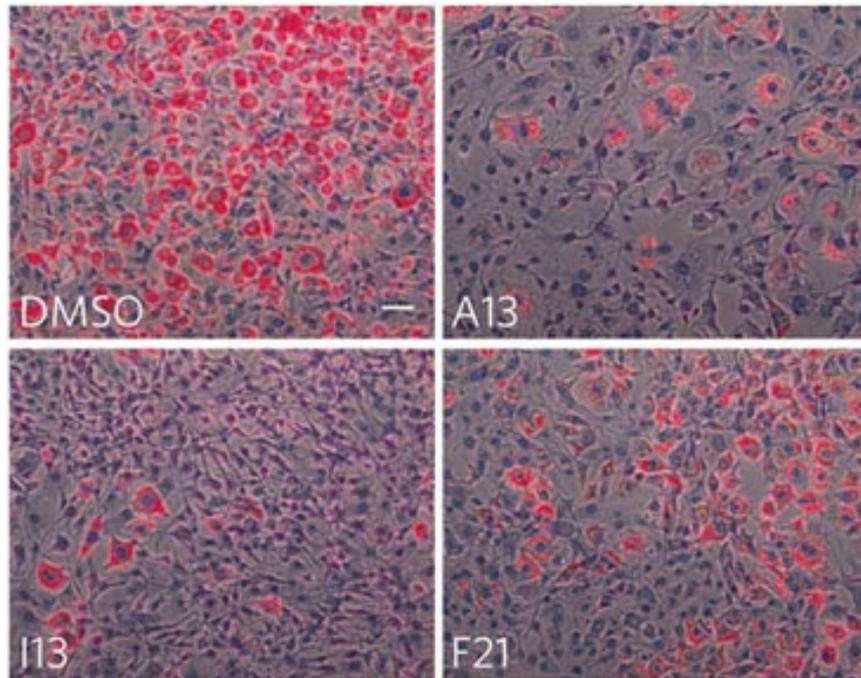


# Parallel induced change in GFP expression



Proof of principle

# Drugs also effect Nile Red intensity in mammalian and insect cells

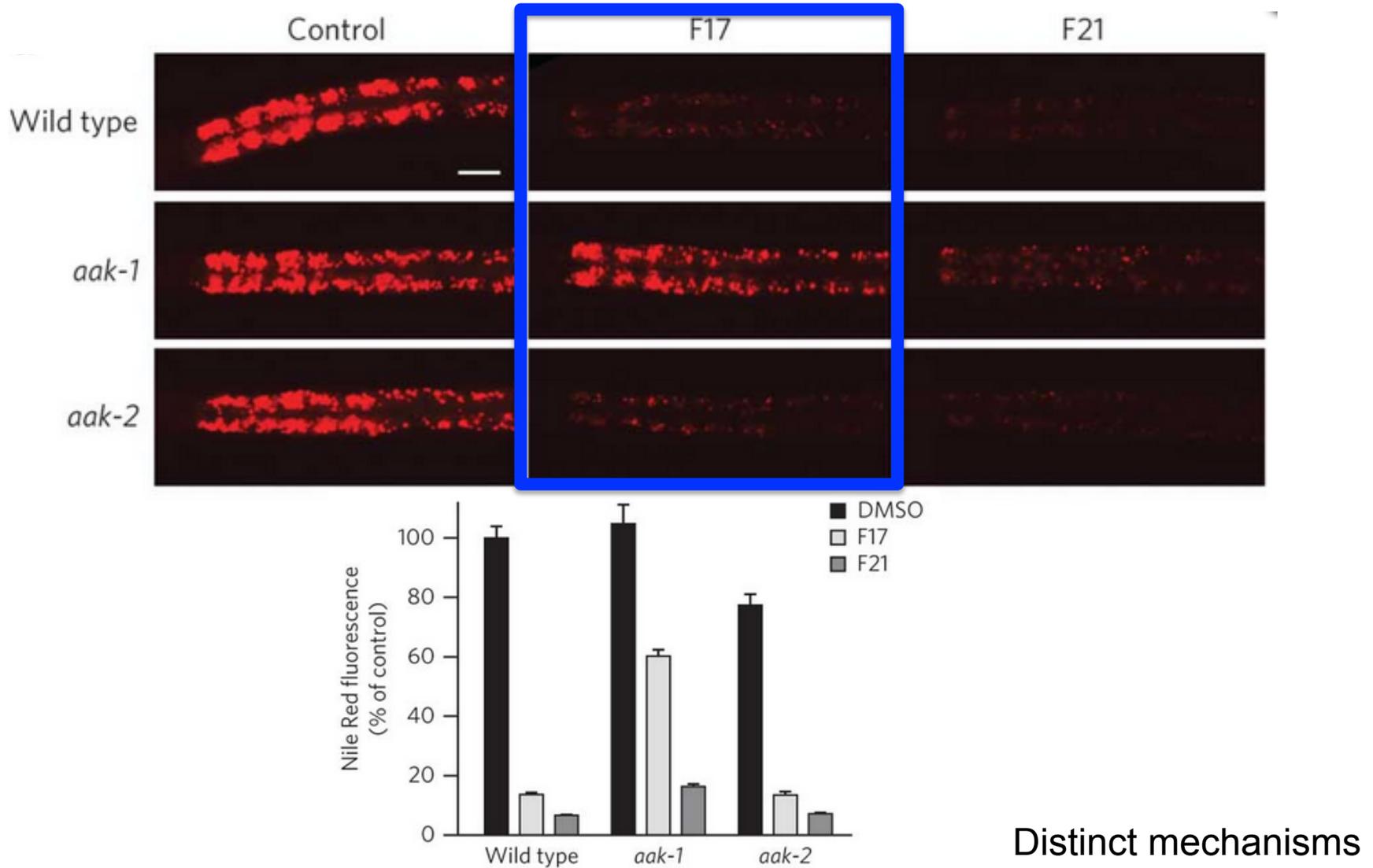


# Goals

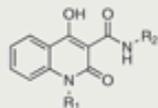
1. Identify small molecules that are effective within the intact animal
2. Reveal relationships between pathways that influence energy homeostasis



# Resistance of *aak-1* mutants to F17 effects



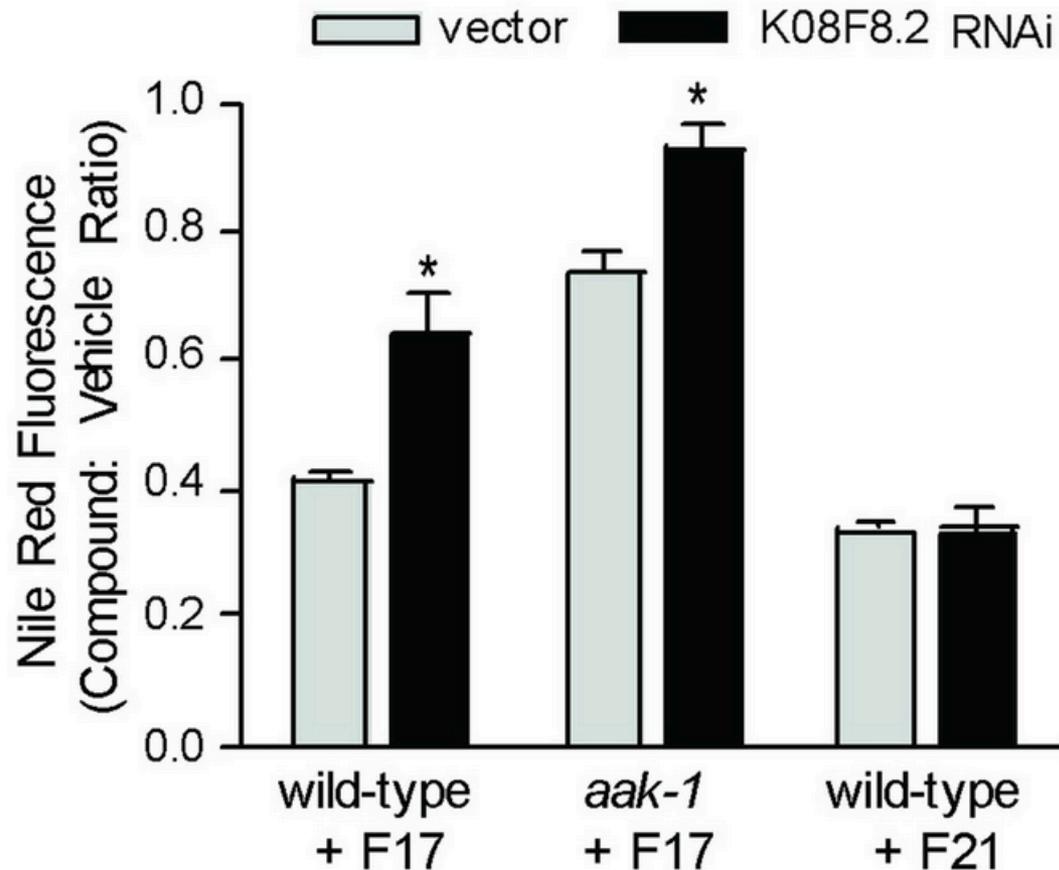
# Nile Red intensity dependent on structure



Compound	$R_1$	$R_2$	Nile Red (% of control) <sup>a</sup>	aak-1 suppressed?
F17			14	Yes
F17-1564	Methyl		28	Yes
F17-4059			40	Yes
F17-8860			16	Yes
F21			7	No
F17-5735			1	Yes
F17-8949			22	No
F17-3115			100	nd <sup>b</sup>
F17-9110			100	nd
F17-8895			100	nd
F17-4816			100	nd
F17-4038			100	nd
F17-0796			237	nd

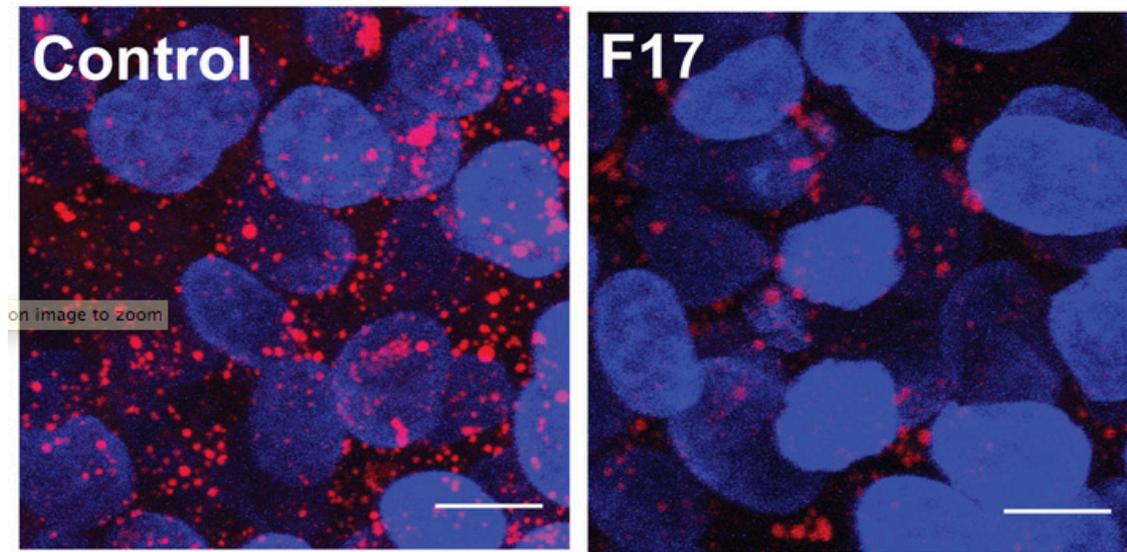
<sup>a</sup>Integrated intensity of wild-type *C. elegans* treated with compound expressed as a percentage of DMSO-treated control. <sup>b</sup>nd, not determined.

# F17 leads to increased Nile red intensity in *aak-1* RNAi worms

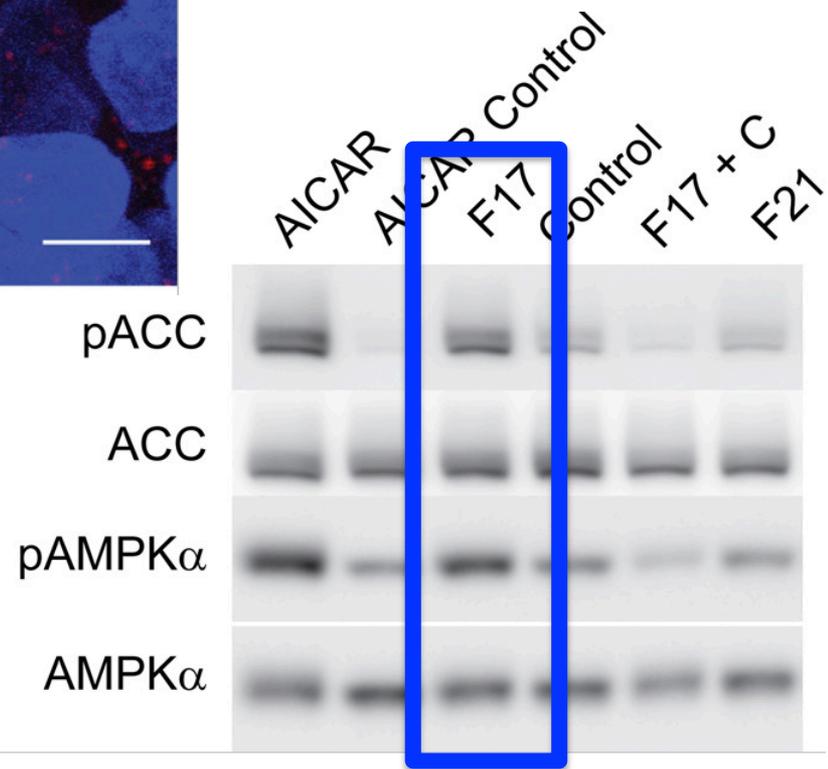


K08F8.2 and AAK-1 mediate F17 phenotype

# F17 activation of AMPK pathway



Human liver cells



# Why is this important?





# Genetic analysis of pathway using RNAi animals

RNAi depletion of SREBP *C. elegans*



Nile Red with E8 or H6  
(increased Nile Red previously)



RNAi animals not susceptible to Nile Red-increasing

RNAi yielding deficiencies in fat metabolism



Nile Red with Nile Red-reducing compounds



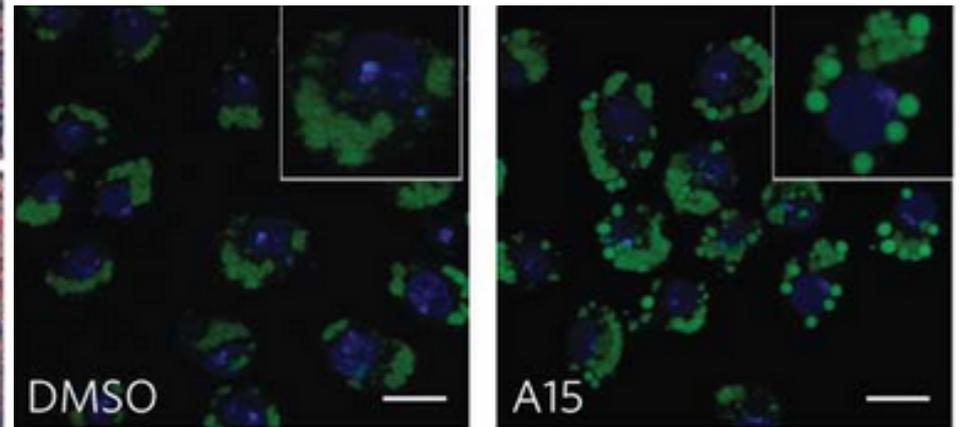
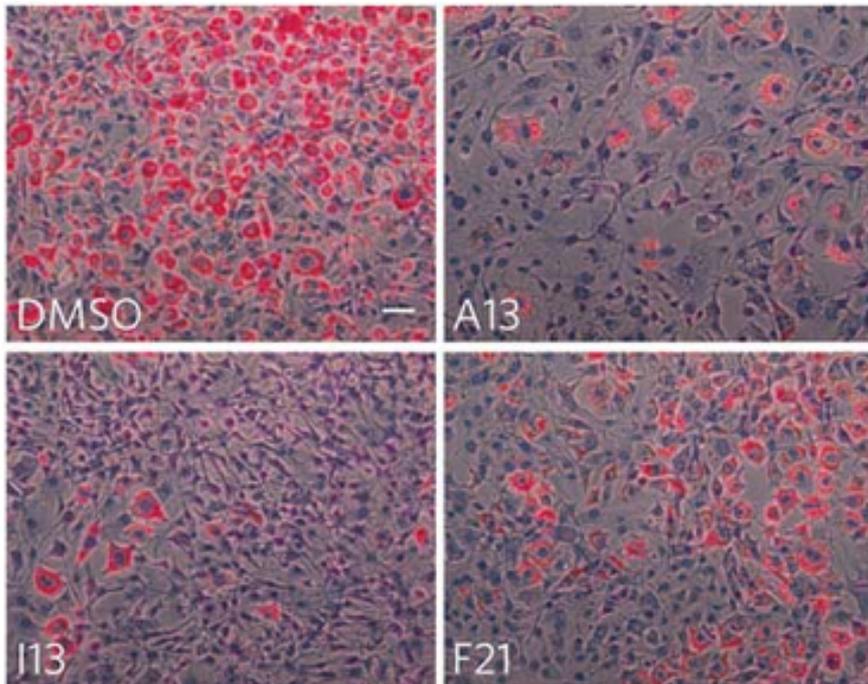
All animals susceptible to fat reduction

Exception=mutant animals with *aak-1* deletion



# Directed approaches to identify drugs

## Nile Red



Drugs change Nile Red