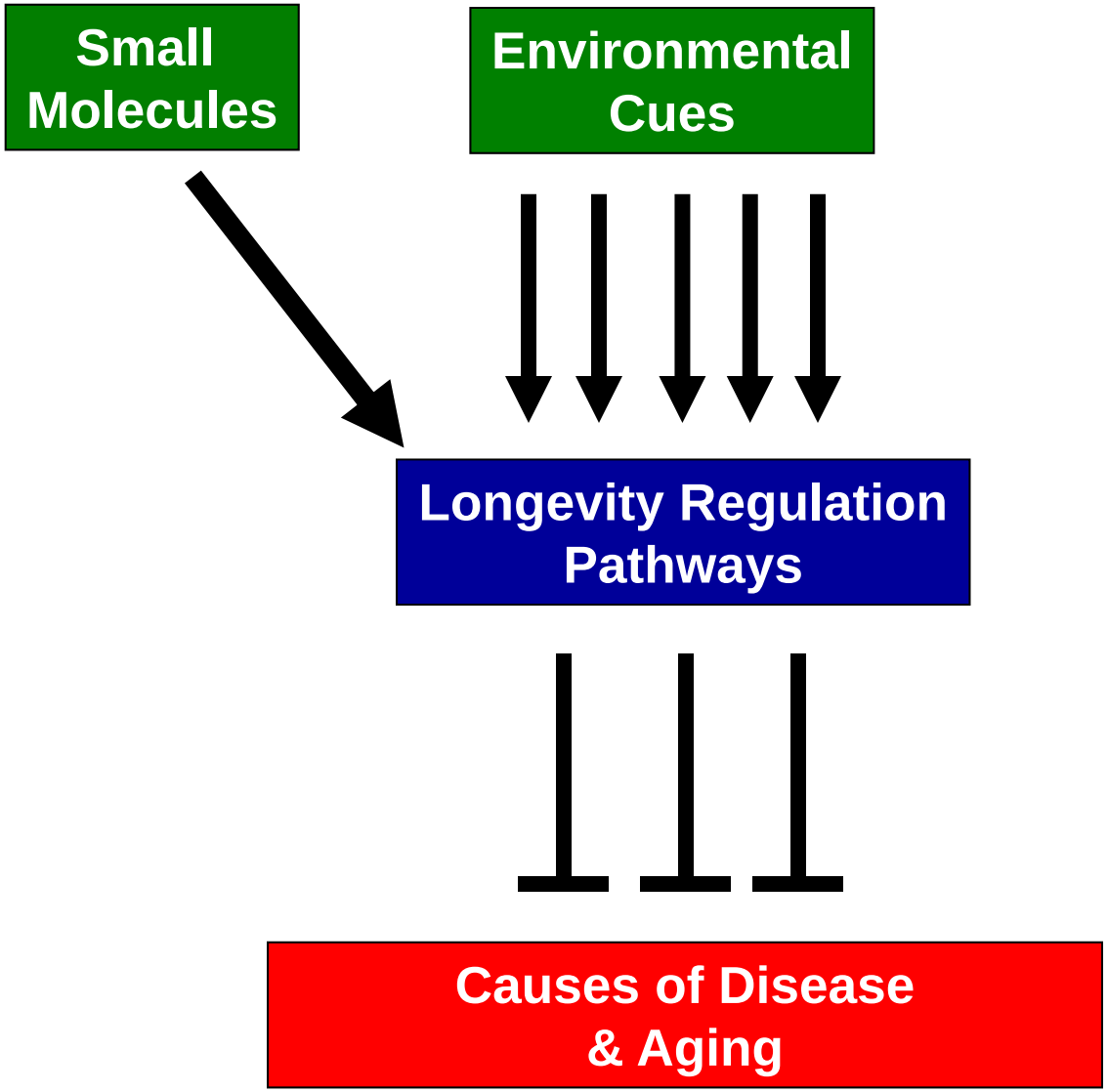
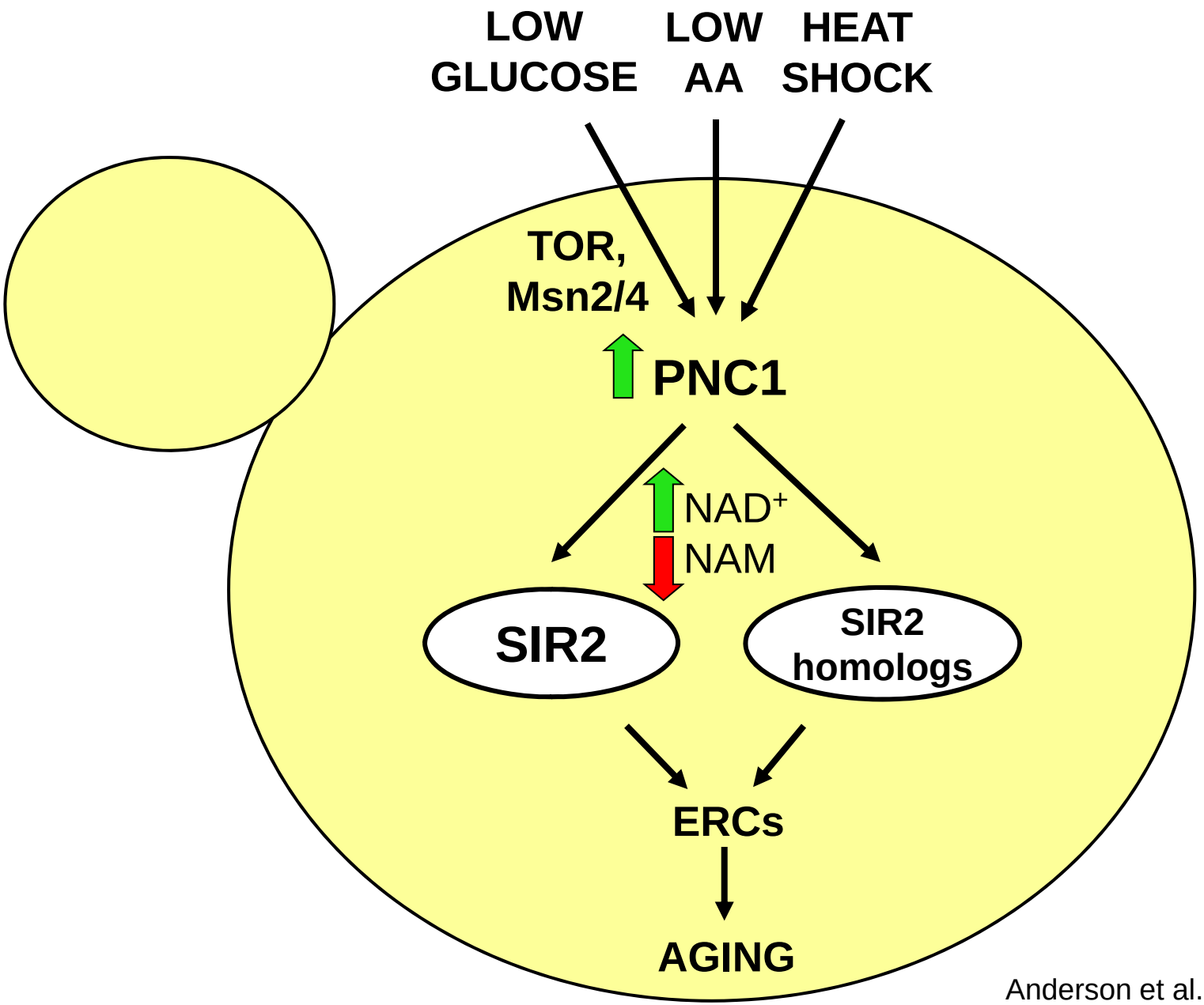
David Sinclair, Ph.D.

Departments of Pathology and Genetics

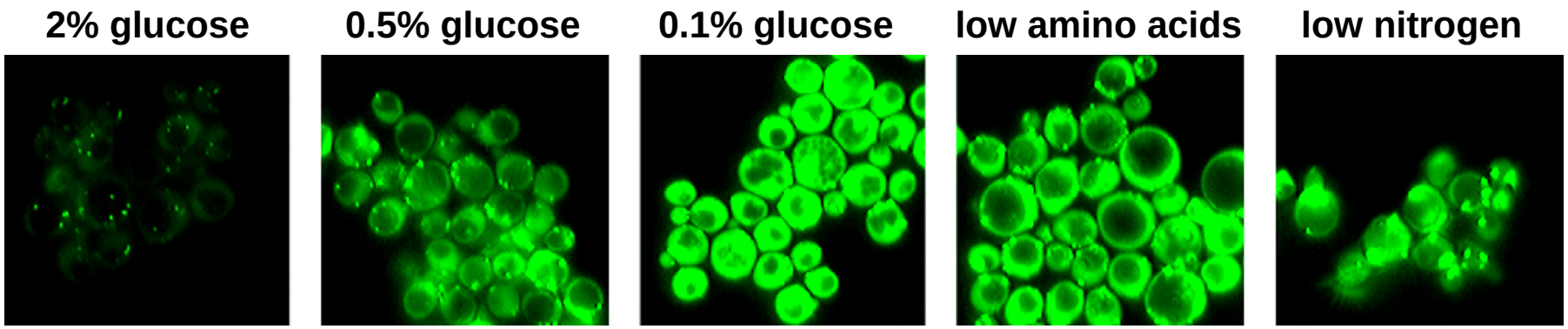
Harvard Medical School
Boston

Disclosure statement: DAS is a consultant to Sirtris and Genocea.


Small Molecules
Environmental Cues
Longevity Regulation Pathways
Causes of Disease & Aging

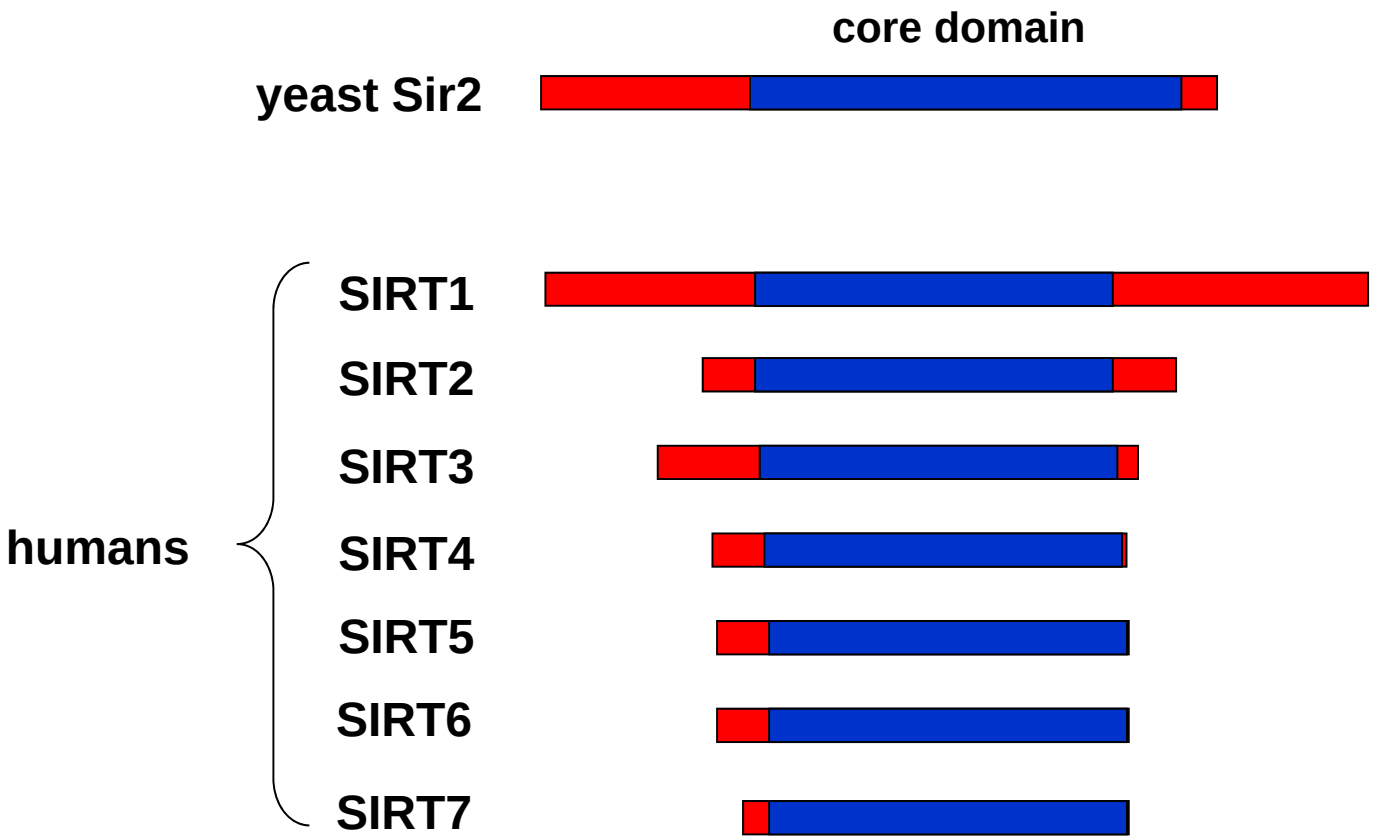


Anderson et al., *Nature* (2004)
Lamming et al., Science (2005)
~~Medvedik et al., *PLoS Biol.* (2007)~~



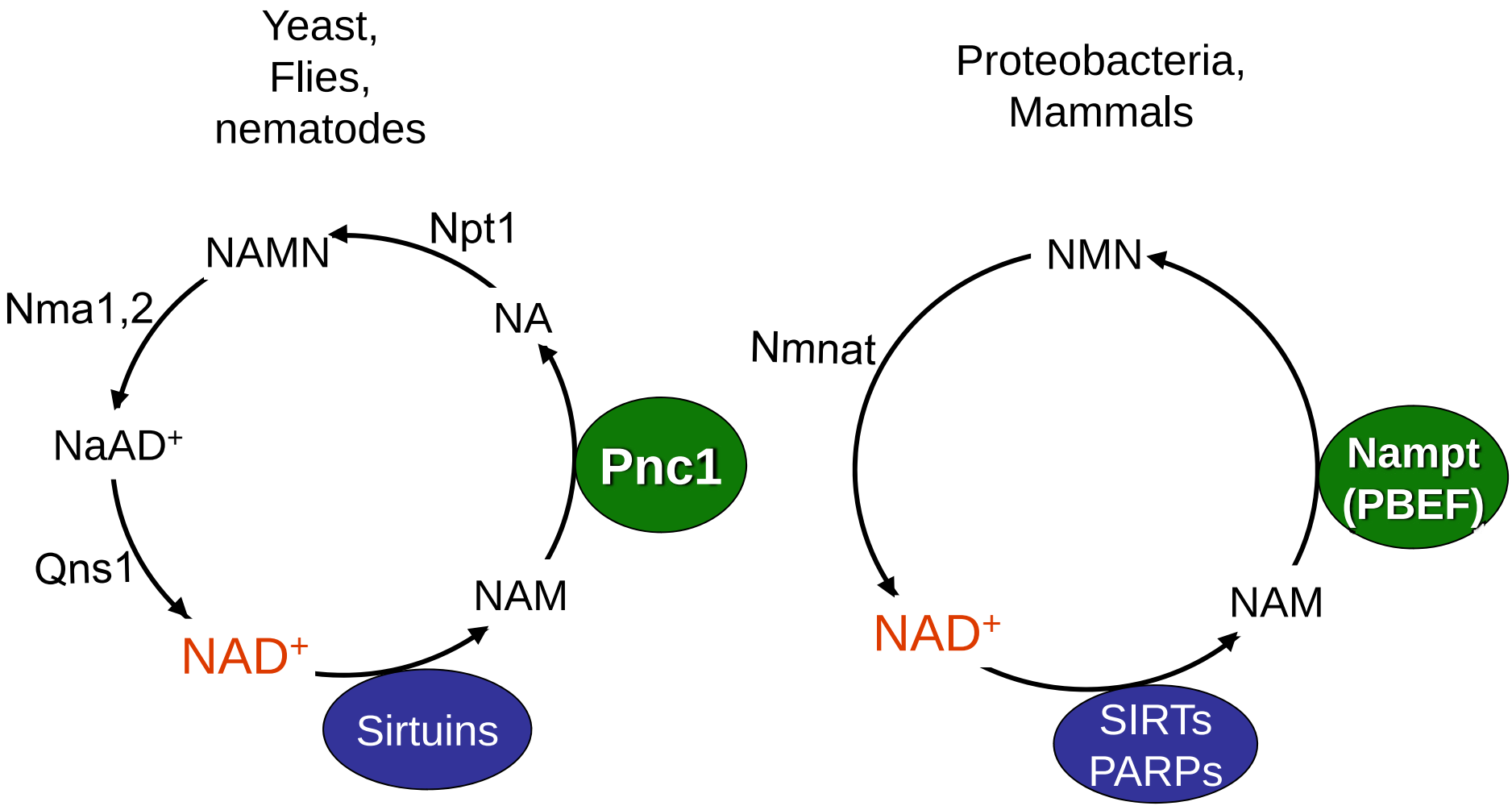
Anderson et al., *Nature* (2003)

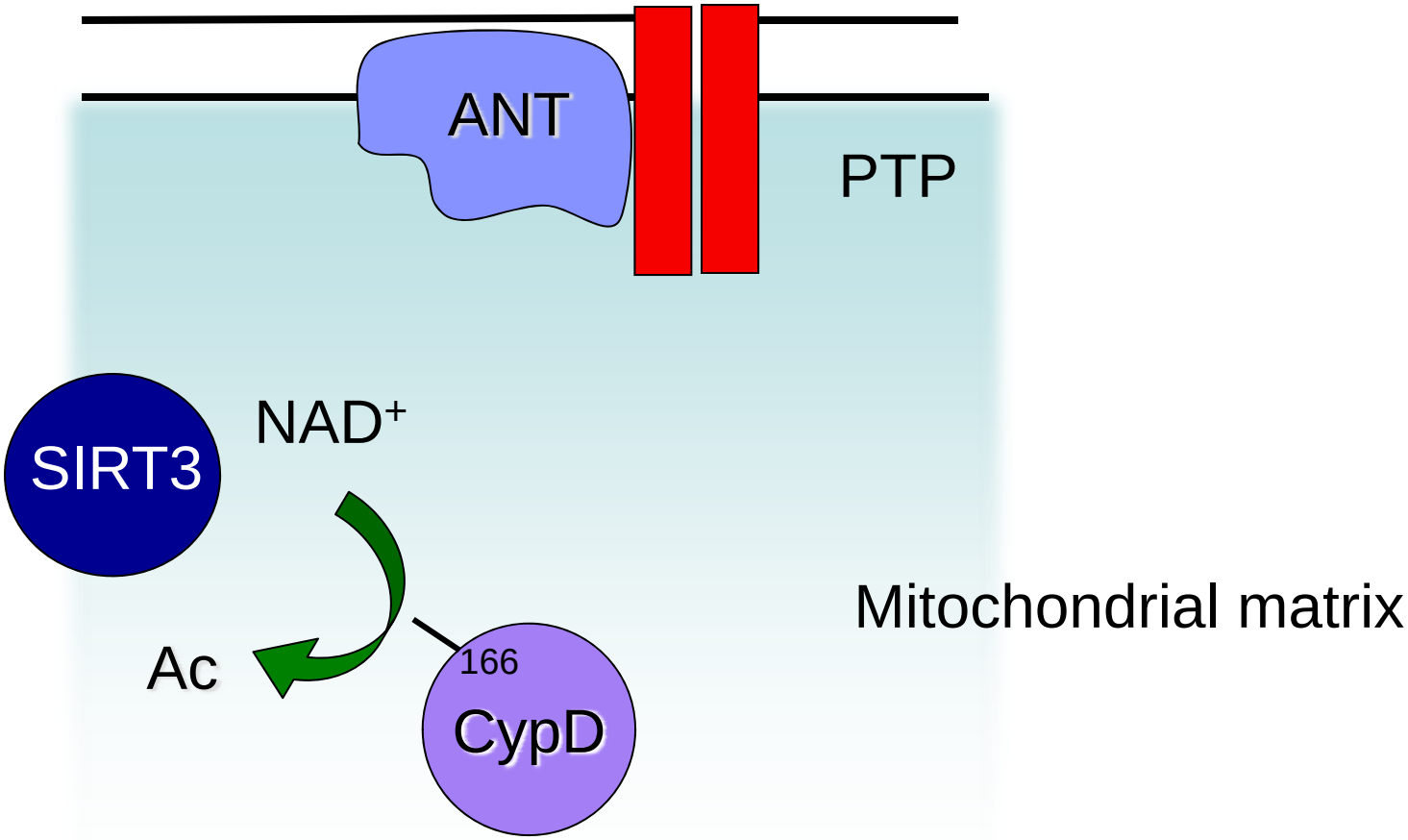
Humans possess 7 NAD$^+$-dependent deacetylases a.k.a. “sirtuins”

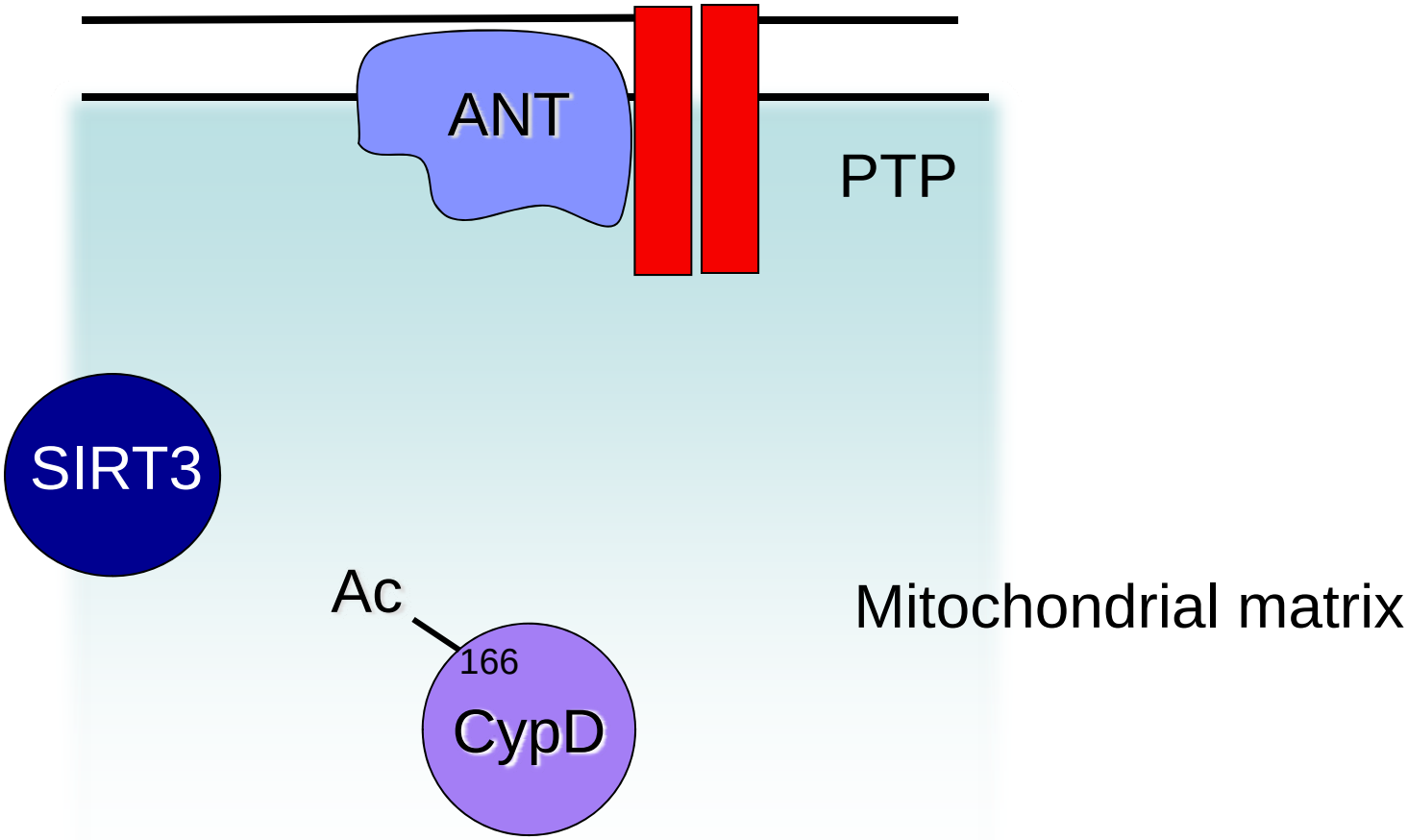


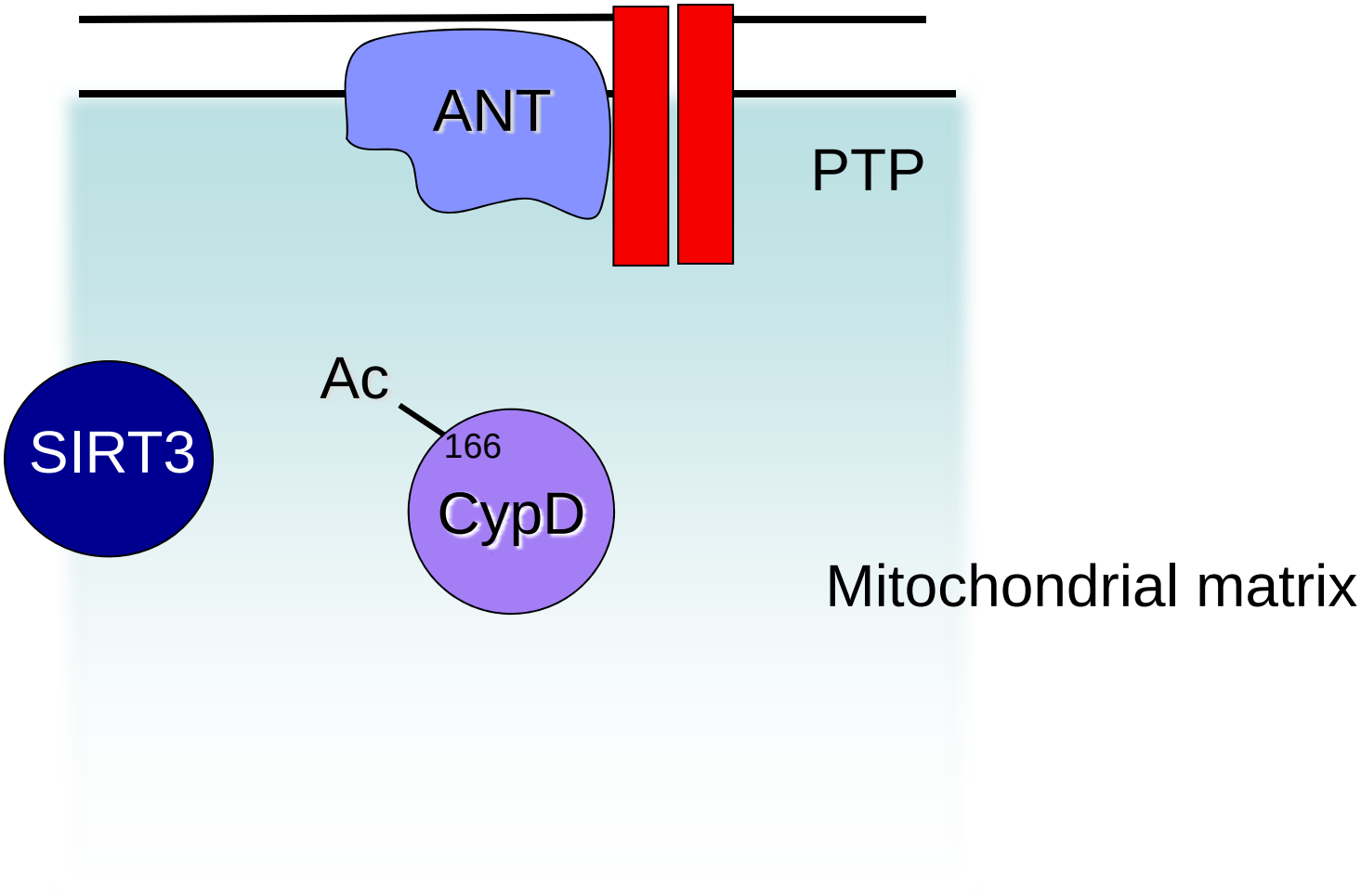
Save the date: Sirtuin session tomorrow 5 PM

The NAD^+ salvage pathway

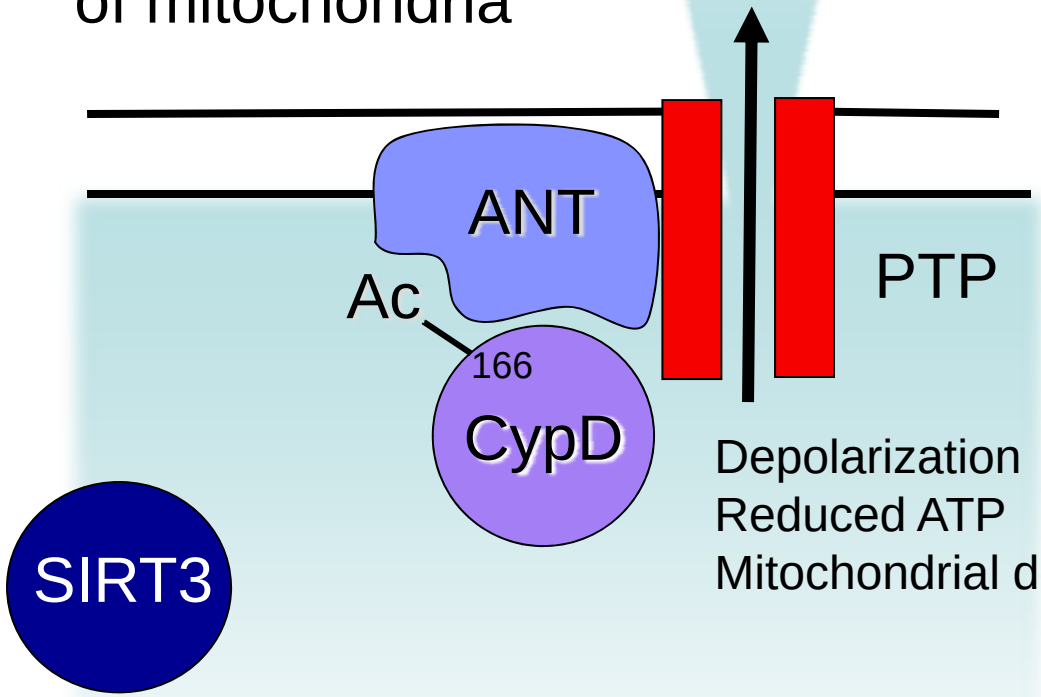



ANT
PTP
SIRT3
NAD+
Ac
166
CypD
Mitochondrial matrix


ANT
PTP
SIRT3
Ac
166
CypD
Mitochondrial matrix


ANT
PTP
Ac
166
CypD
SIRT3
Mitochondrial matrix

Leakage of solutes out of mitochondria

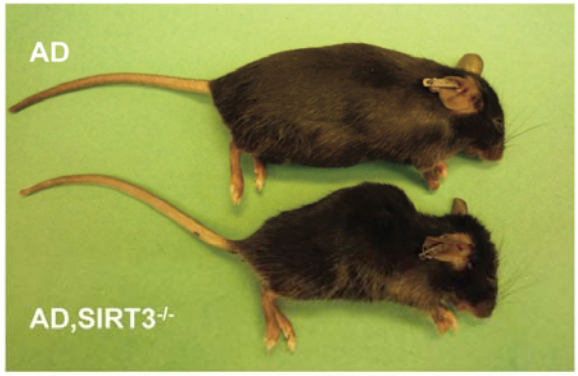


Depolarization
Reduced ATP
Mitochondrial destruction

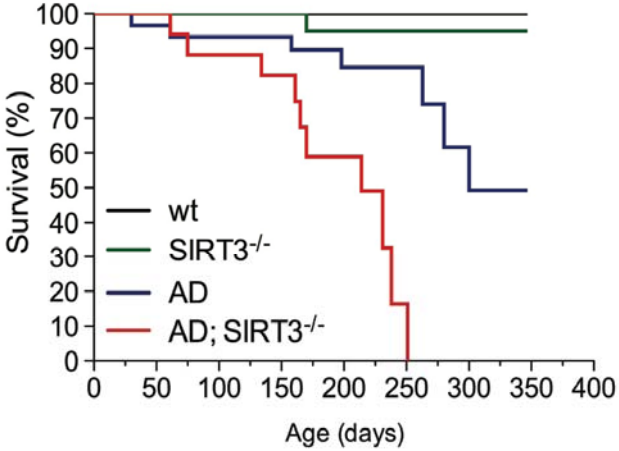
Neurodegeneration, Cardiac hypertrophy

Mitochondrial matrix

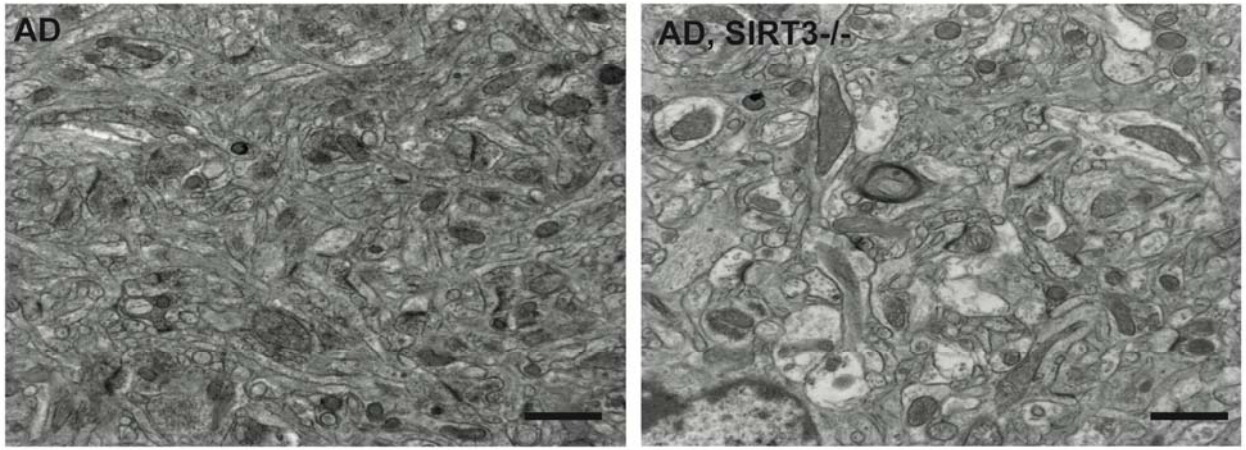
c


AD
AD,SIRT3-/-

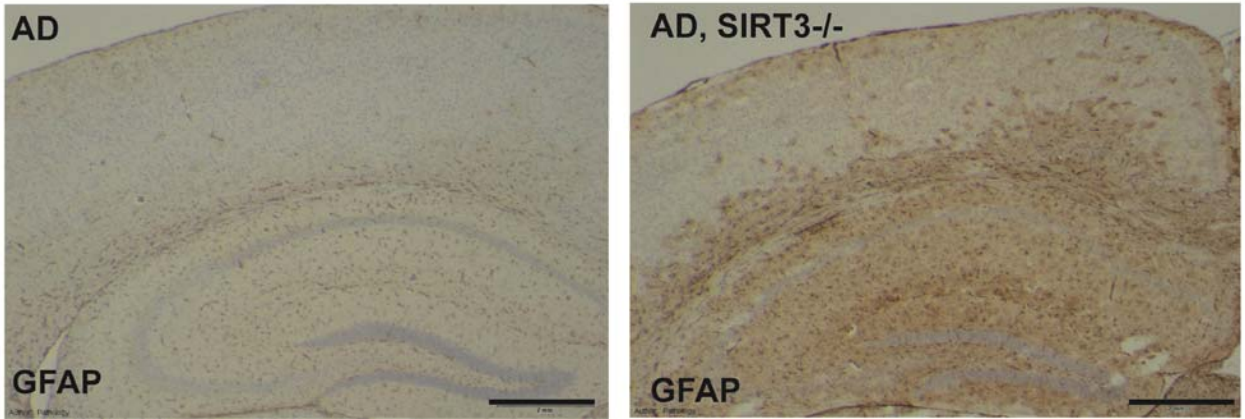
d

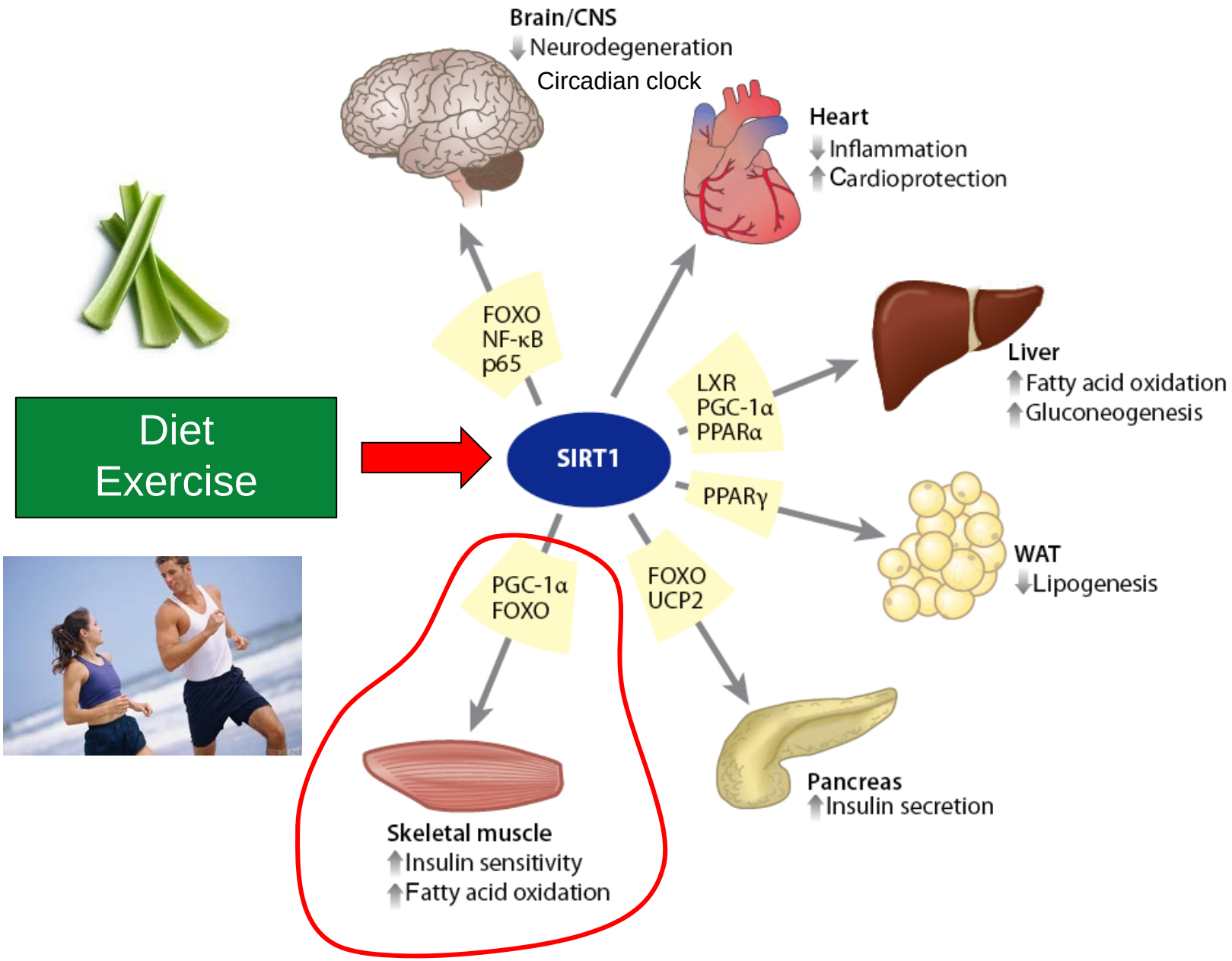

Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
Age (days)
wt
SIRT3-/-
AD
AD; SIRT3-/-

e


AD
AD, SIRT3-/-

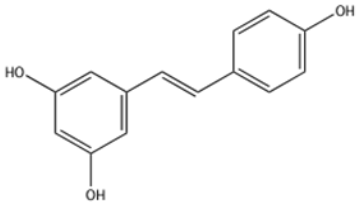
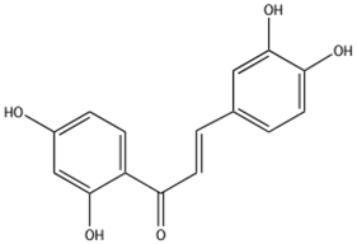
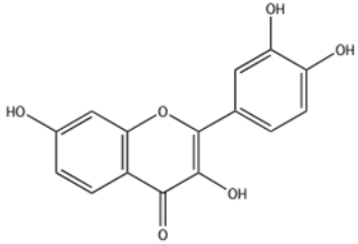
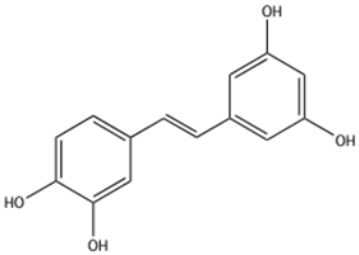
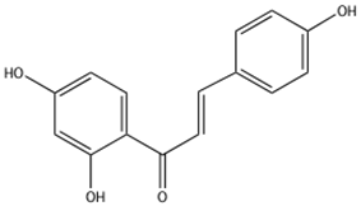
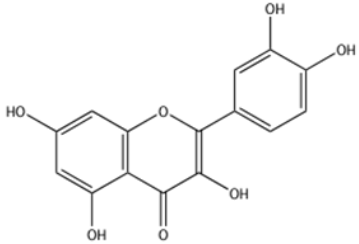
f


AD
GFAP
AD, SIRT3-/-
GFAP



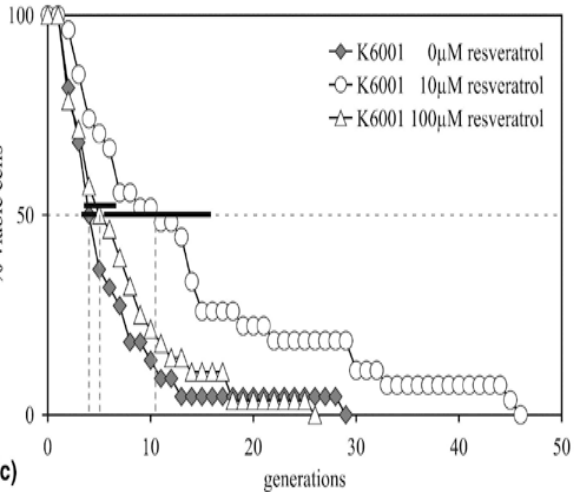
Haigis and Sinclair, *Annual Reviews*, 2010

Representatives from three classes of plant-derived STACs

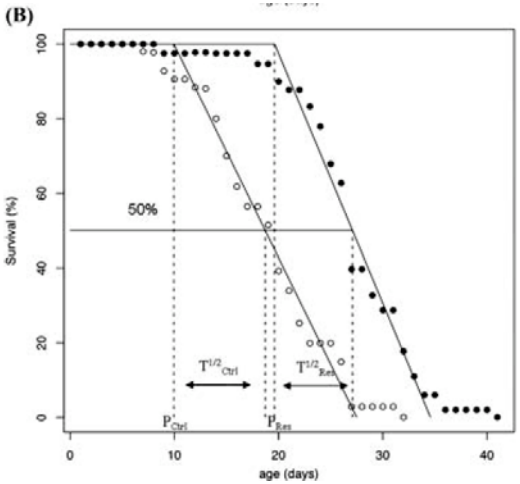
Stilbenes	Chalcones	Flavones
Resveratrol (13.0x) 	**Butein (8.5x)** 	**Fisetin (6.6x)** 
Piceatannol (9.0x) 	**Isoliquiritigenin (7.6x)** 	**Quercetin (4.6x)** 

Howitz et al., *Nature*, Aug (2003)

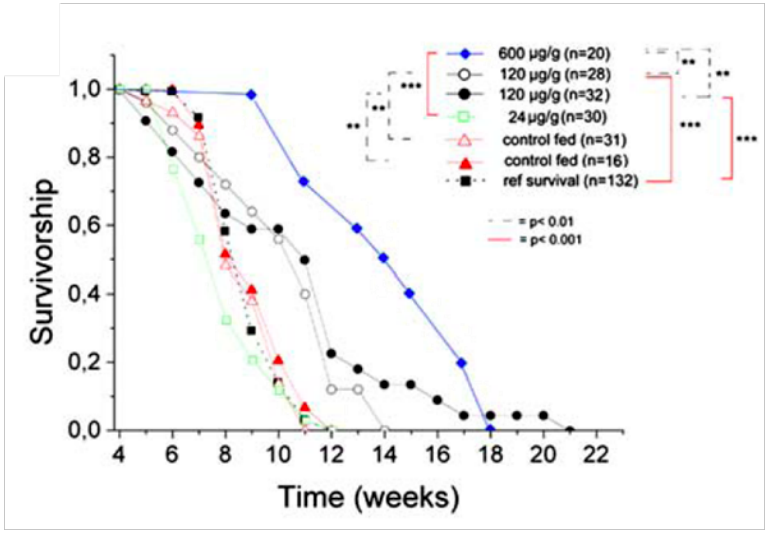
Jarolim *et al.*, 2004



Gruber *et al.*, 2007



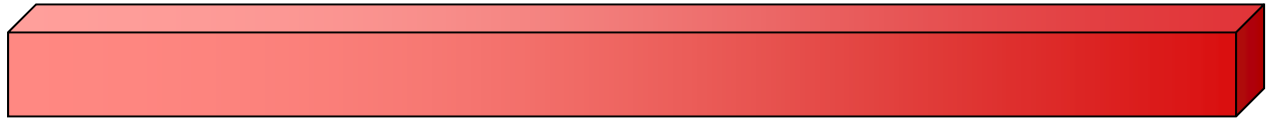
Valenzano *et al*., 2006



Calorie Restriction (EOD)

Lean Diet (SD)

High Calorie Diet (HC)



Activator

Activator

Rafa deCabo

Standard diet

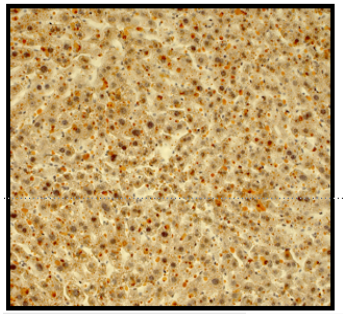
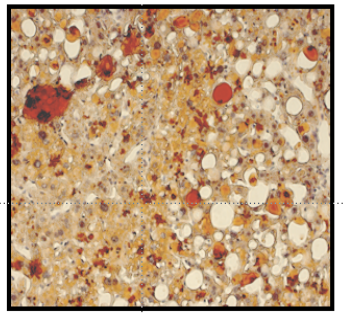
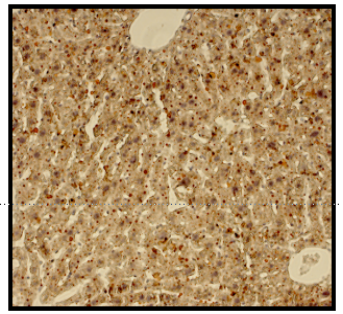
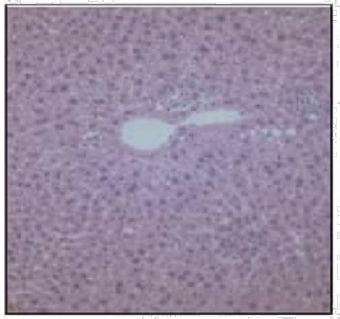
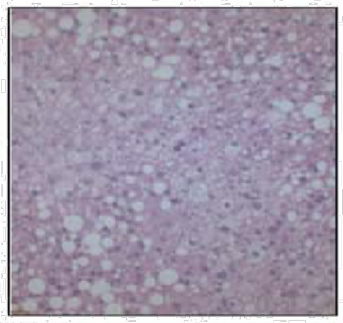
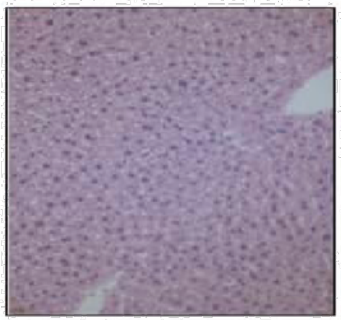
High calorie diet

High calorie diet + resveratrol

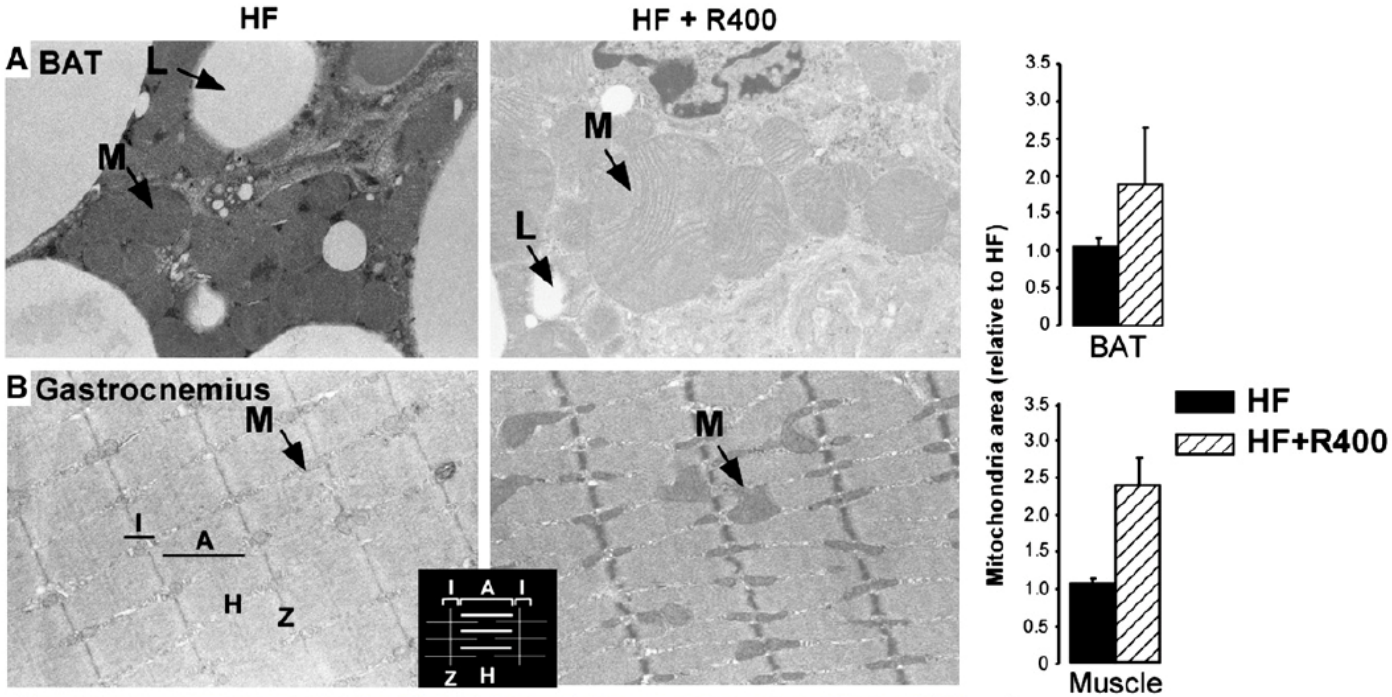
15 month old mice

**photo by Doug Hansen

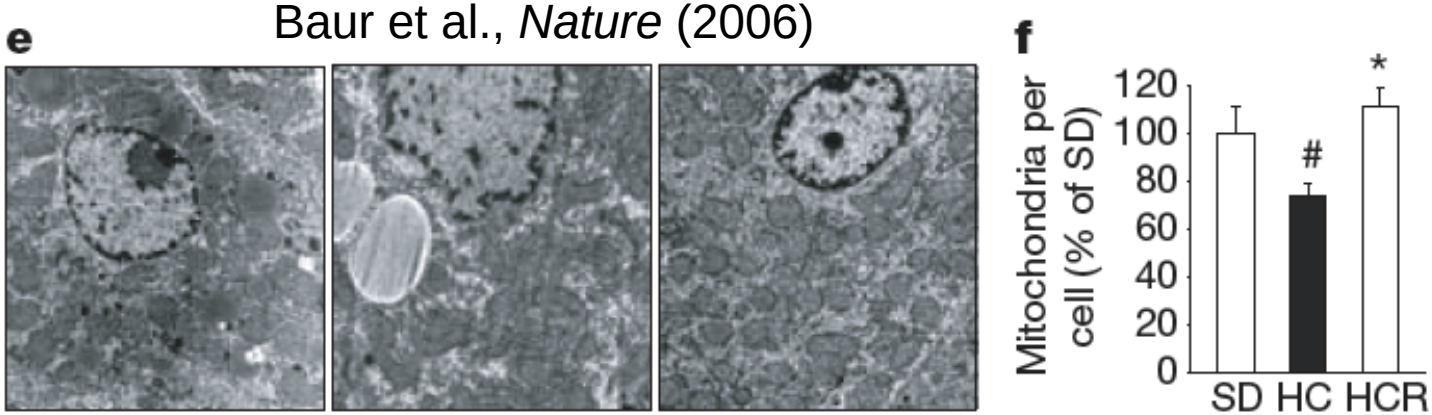
LIVER

	Standard diet (SD)	High calorie (HC)	High calorie + resv (HCR)
Fixed whole liver			
Oil Red O fat stain			
H&E			

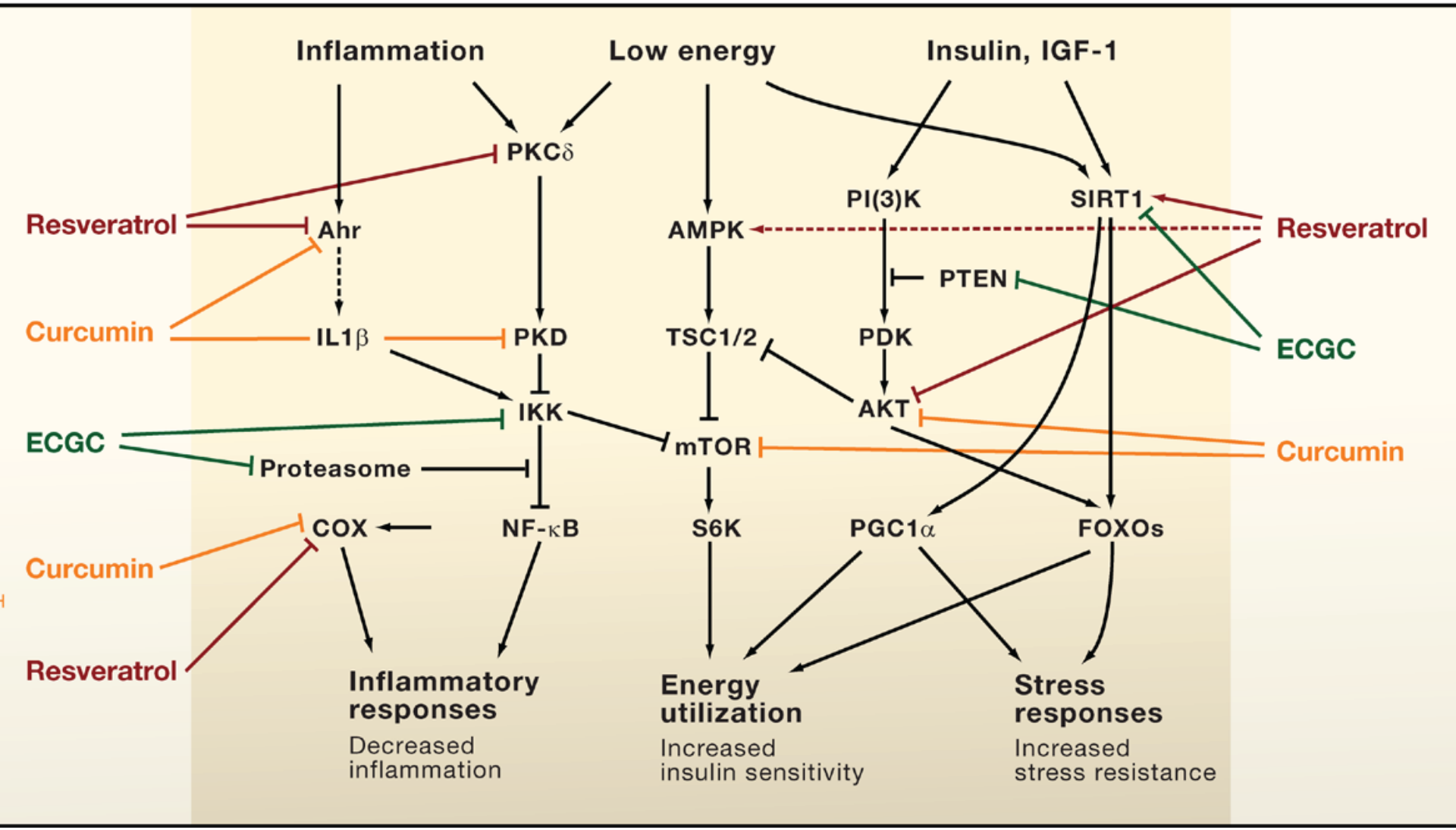
Lagouge et al., *Cell* (2006)



Baur et al., *Nature* (2006)

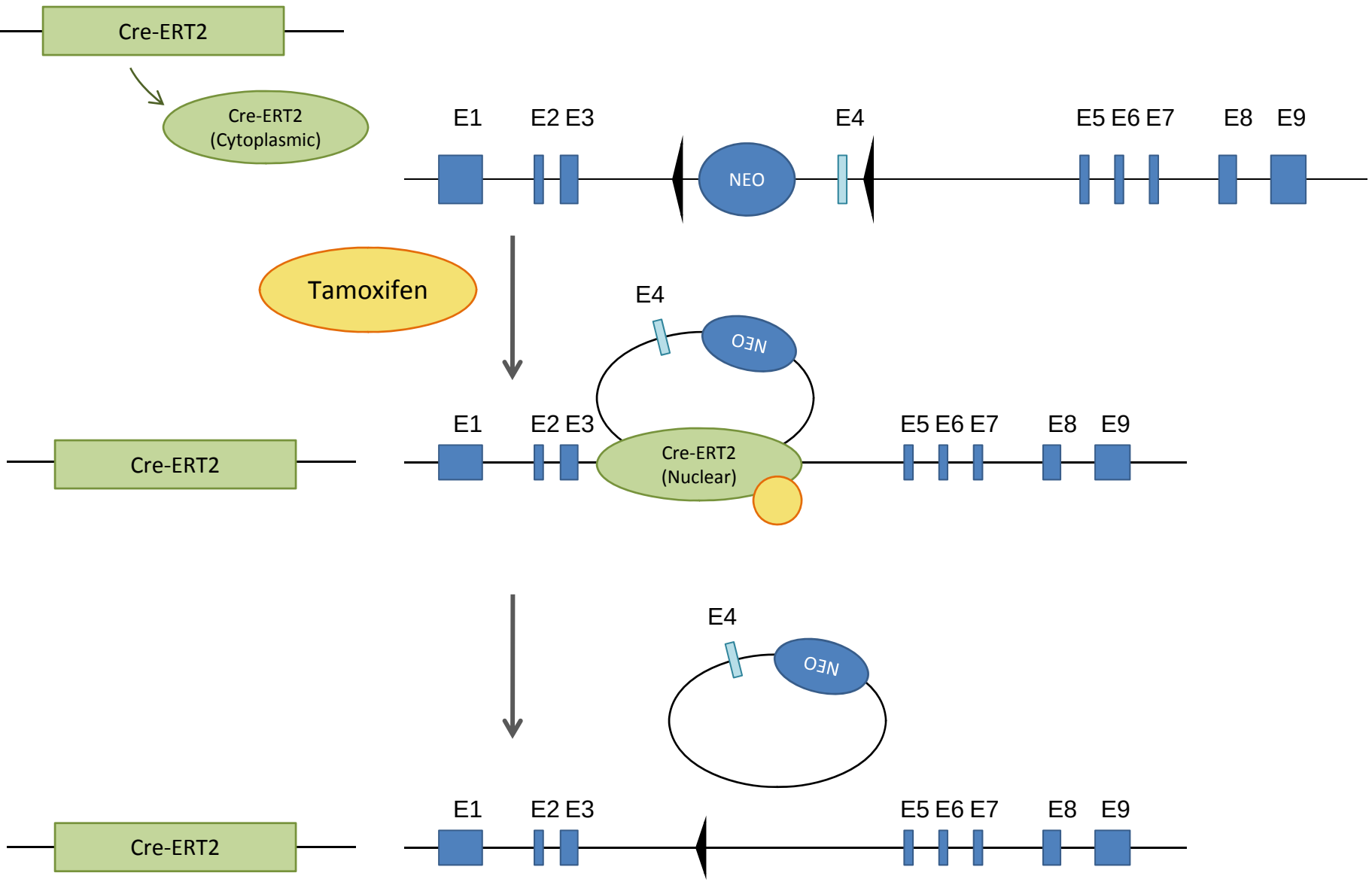


Last mouse
Resveratrol fed every other day
36 months of age

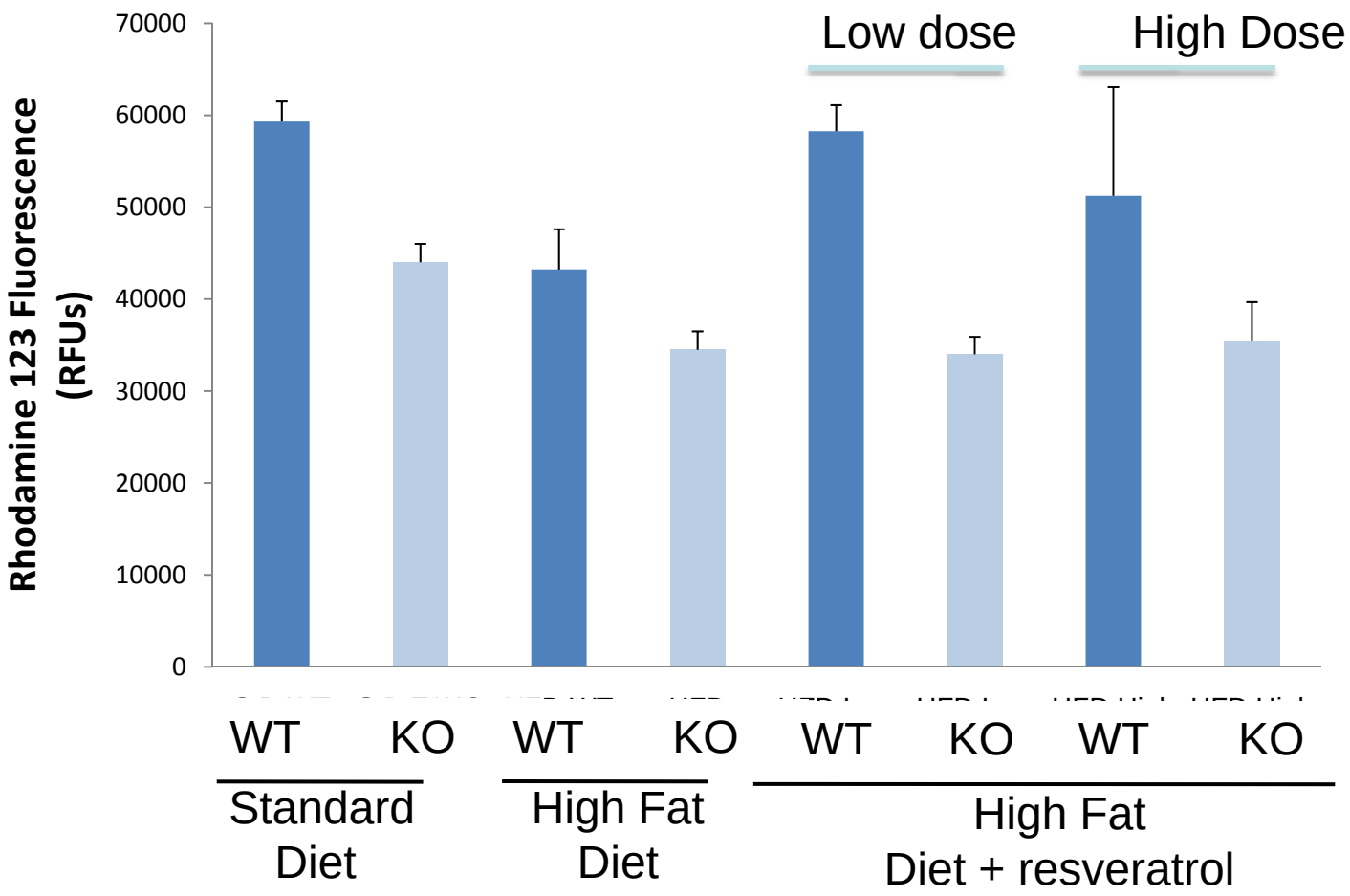


Howitz and Sinclair, Cell (2008)

Generation of inducible SIRT1-knockout mice

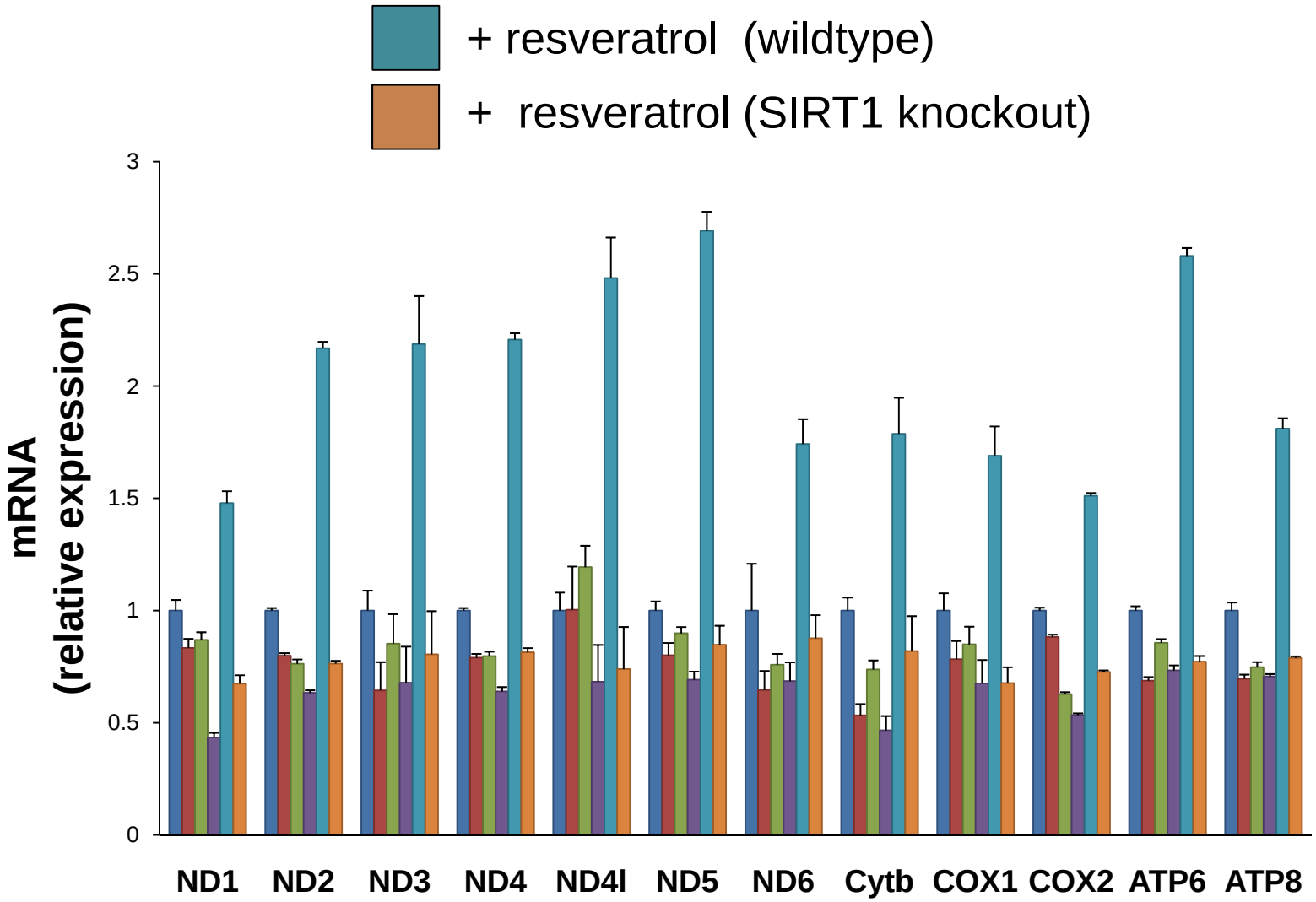


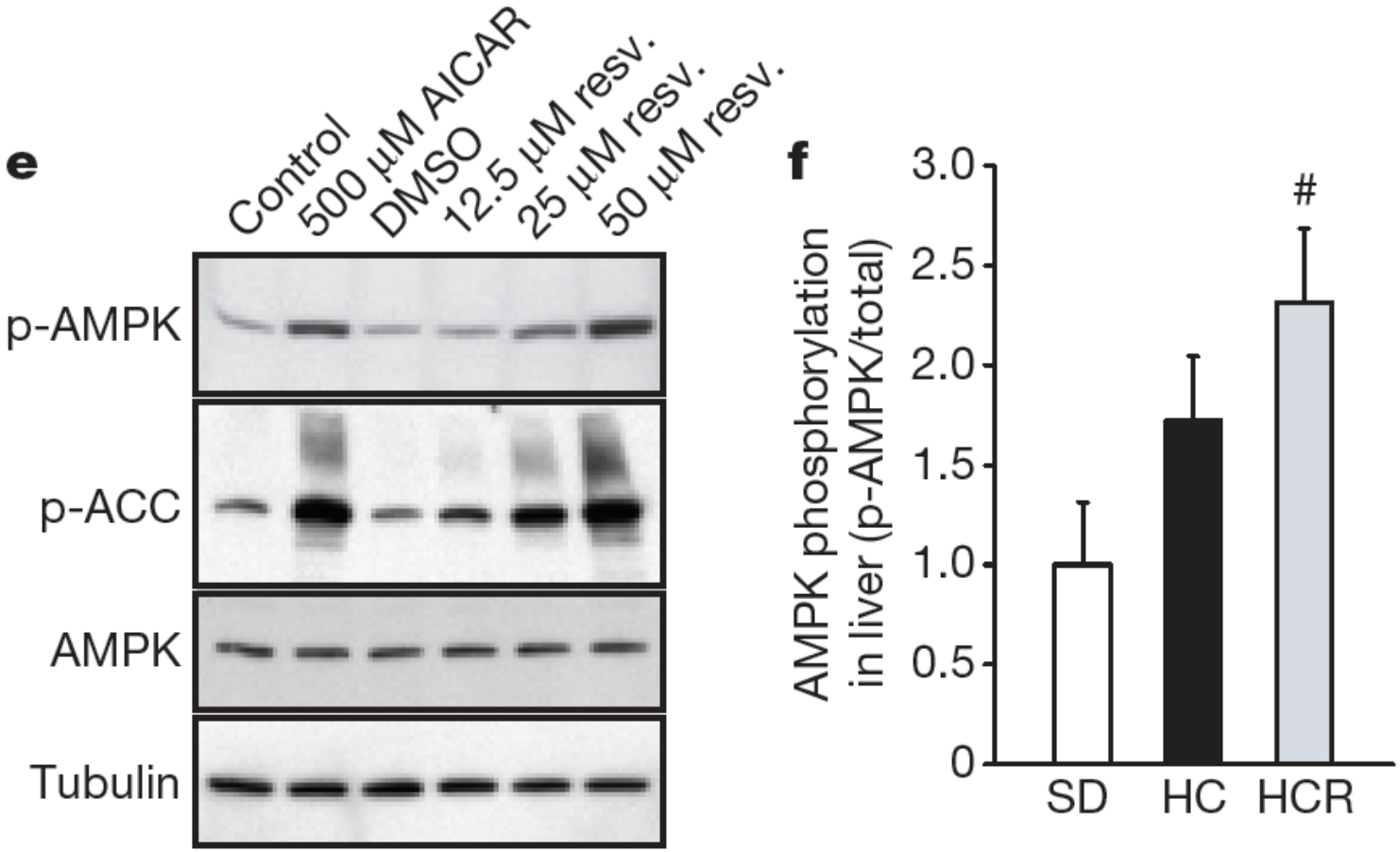
Mitochondrial membrane potential



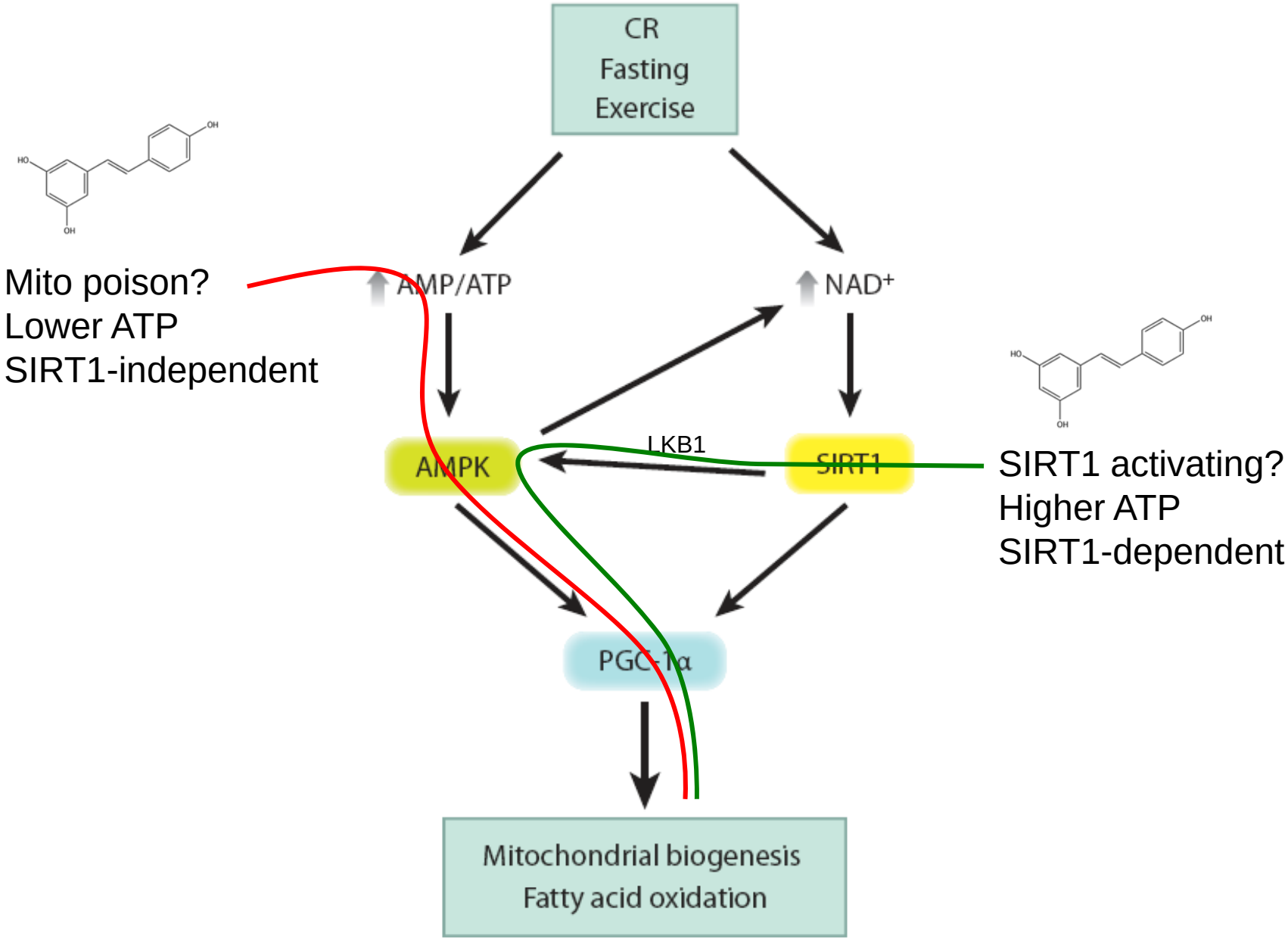
Low dose = 100 mg/kg/d
High dose = 400 mg/kg/d

Mitochondrially-encoded ETC genes



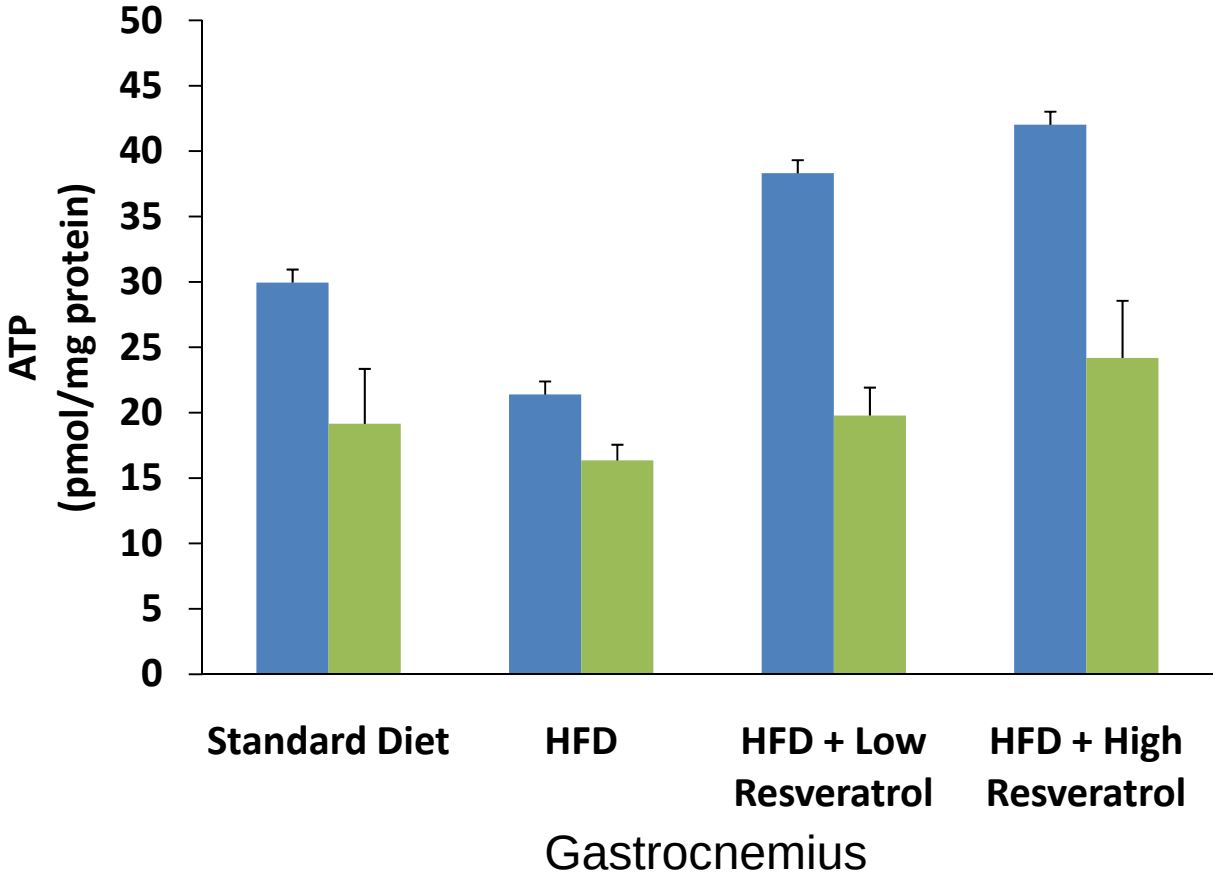


Baur et al., *Nature* (2006)

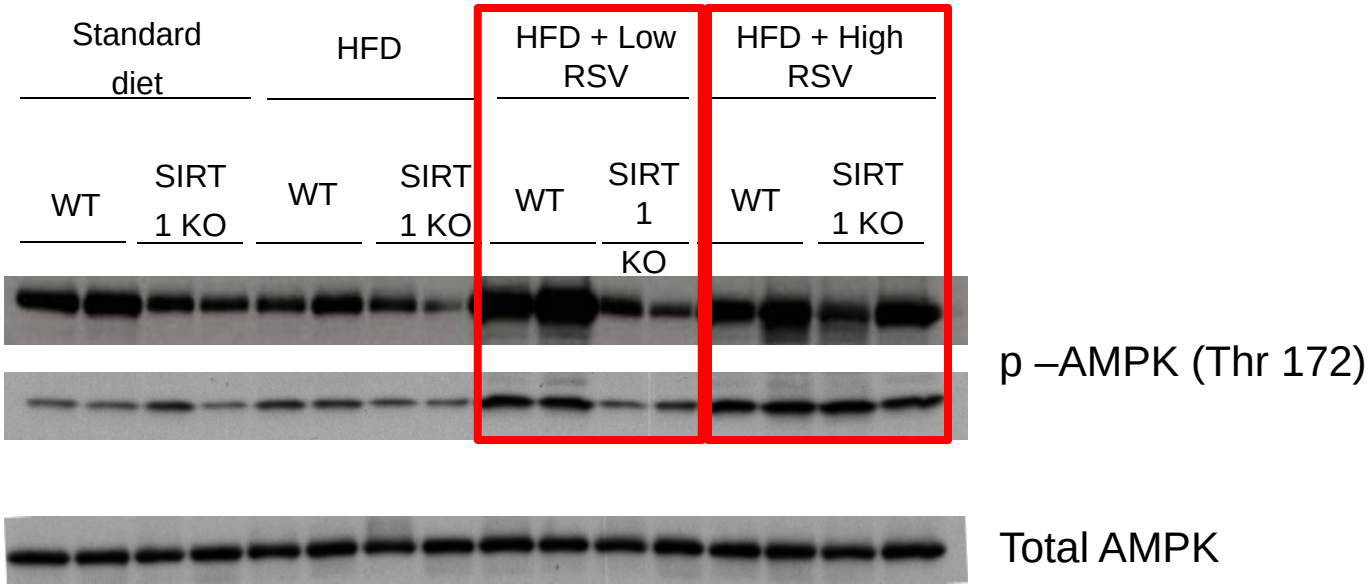


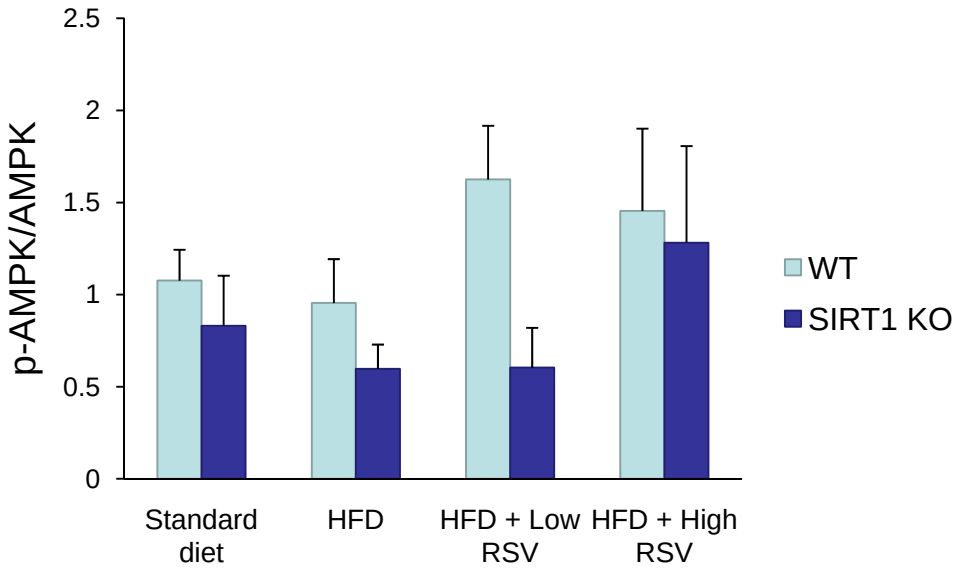
Haigis and Sinclair, Annu Rev Pathol., 2010

Resveratrol increases ATP in a SIRT1-dependent manner *in vivo*



Is AMPK activation SIRT1-dependent?





Discovery and Development of SIRT1 activators (STACs)

2003-4

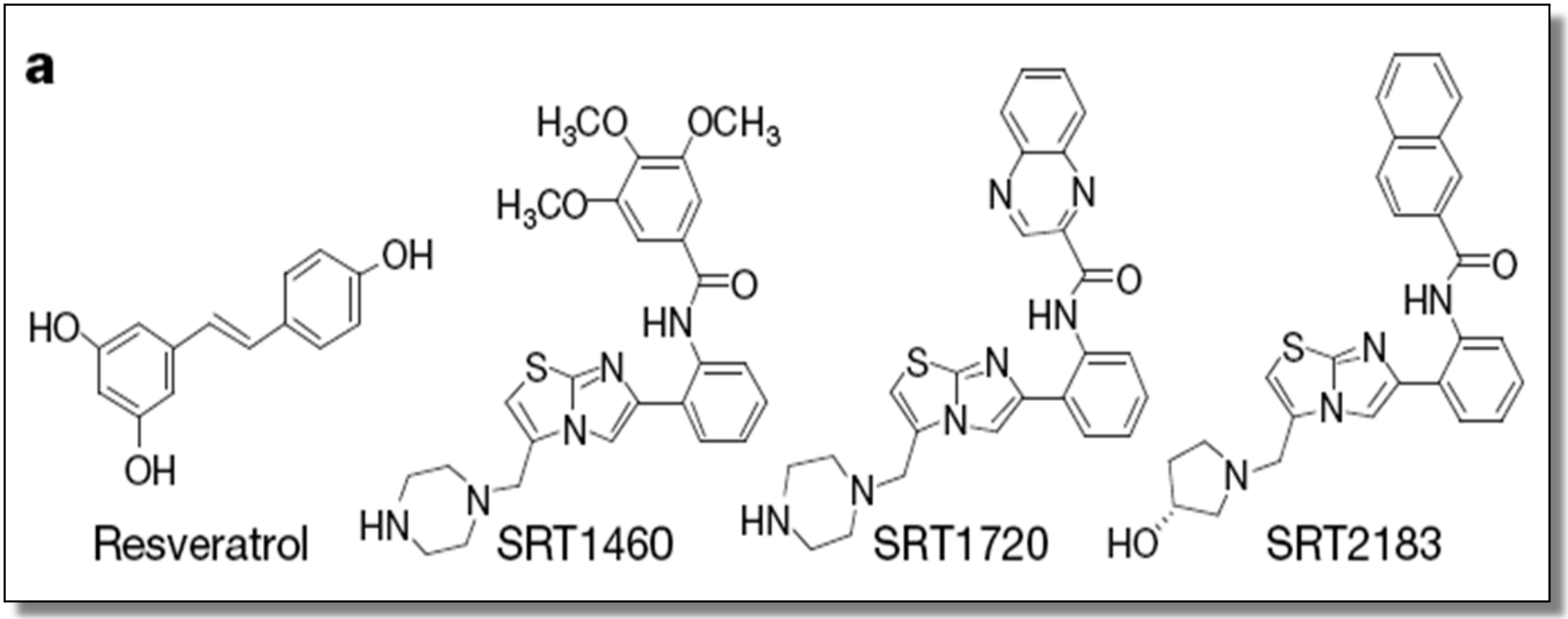
1st screen of ~18,000 molecules: found 18
(best in class - resveratrol)

2005-9

Screened 1,000,000 molecules: 6 novel chemical scaffolds
Synthesis of 4000+ STACs
Potency increase 10,000-fold
Efficacy in rodent models of type II diabetes and neuroD

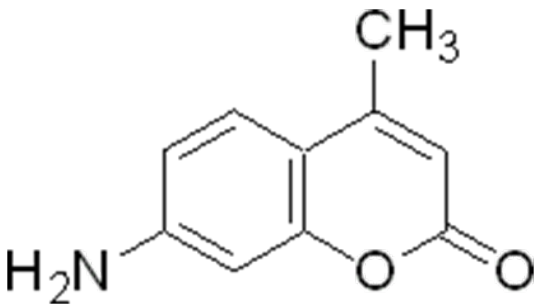
2010-11

Human safety and efficacy studies with synthetic STACs
Human data to be publicly released June, 2011 (ADA meeting)

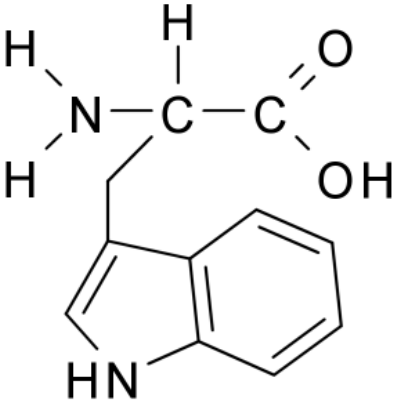


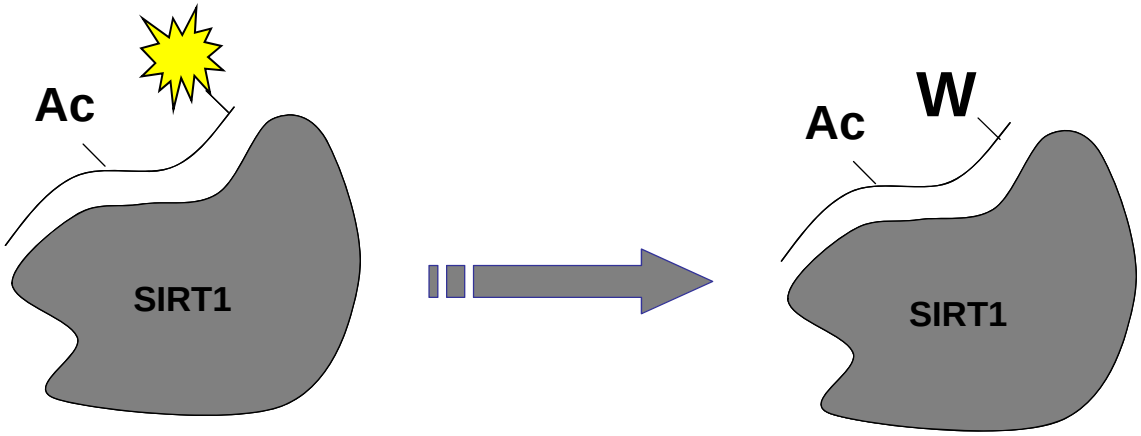
Milne et al., Nature (2007)

Amino methyl coumarin (AMC)

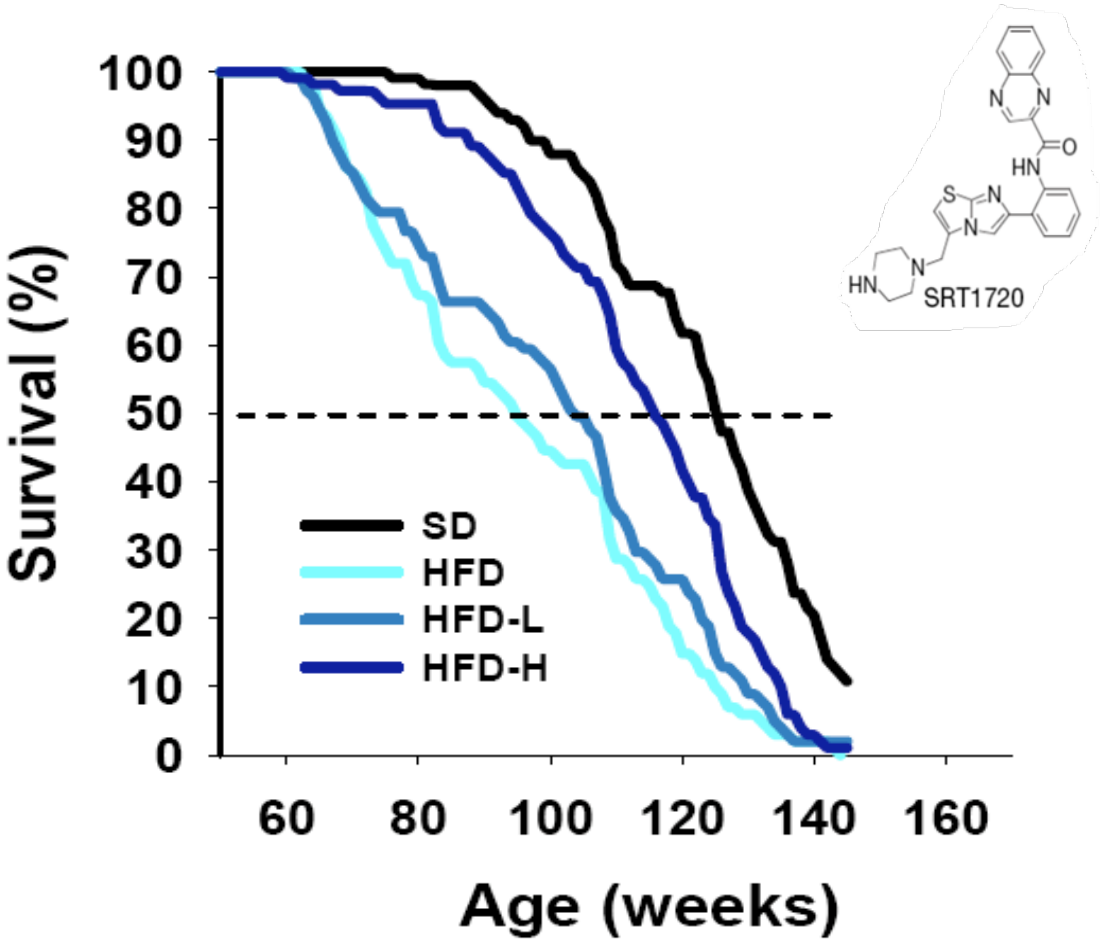


Tryptophan (W)



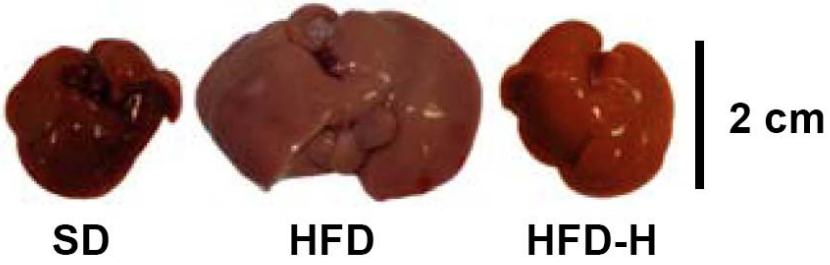


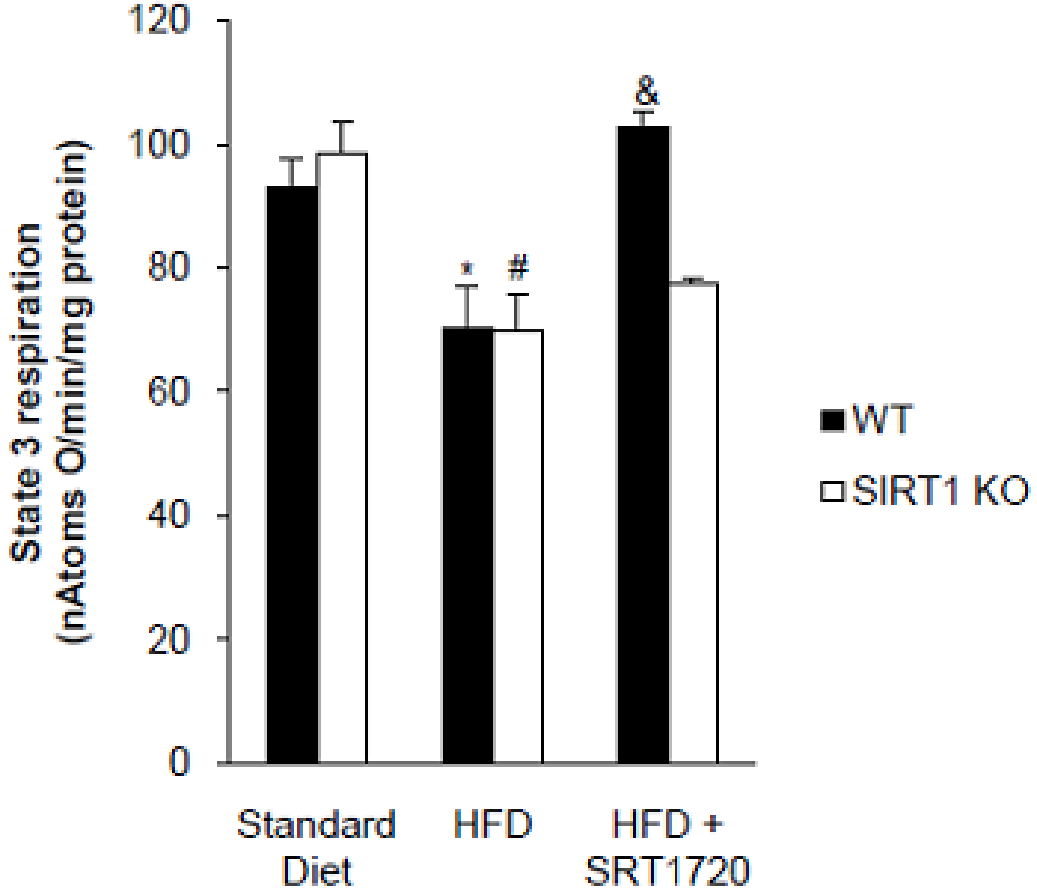
Dai *et al.*, JBC (2010)



SRT1720

Supported by an NIH/NIA-Sirtris
CRADA to Rafa deCabo





Joseph Baur, Rafa deCabo, Robin Minor

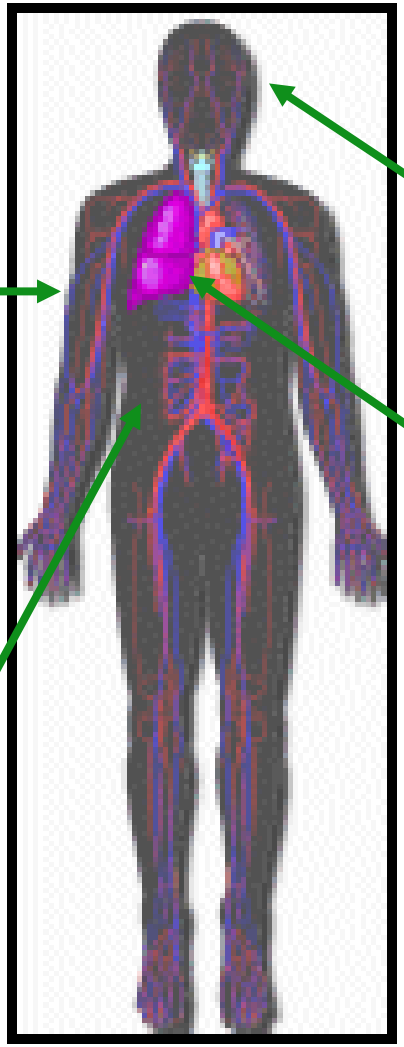
SRT2104 and SRT2979

Muscle Disorders

Sarcopenia
Disuse Atrophy

Metabolic Disease

Type 2 Diabetes
Others



Ophthalmic Diseases

AMD
Dry eye

Respiratory

COPD

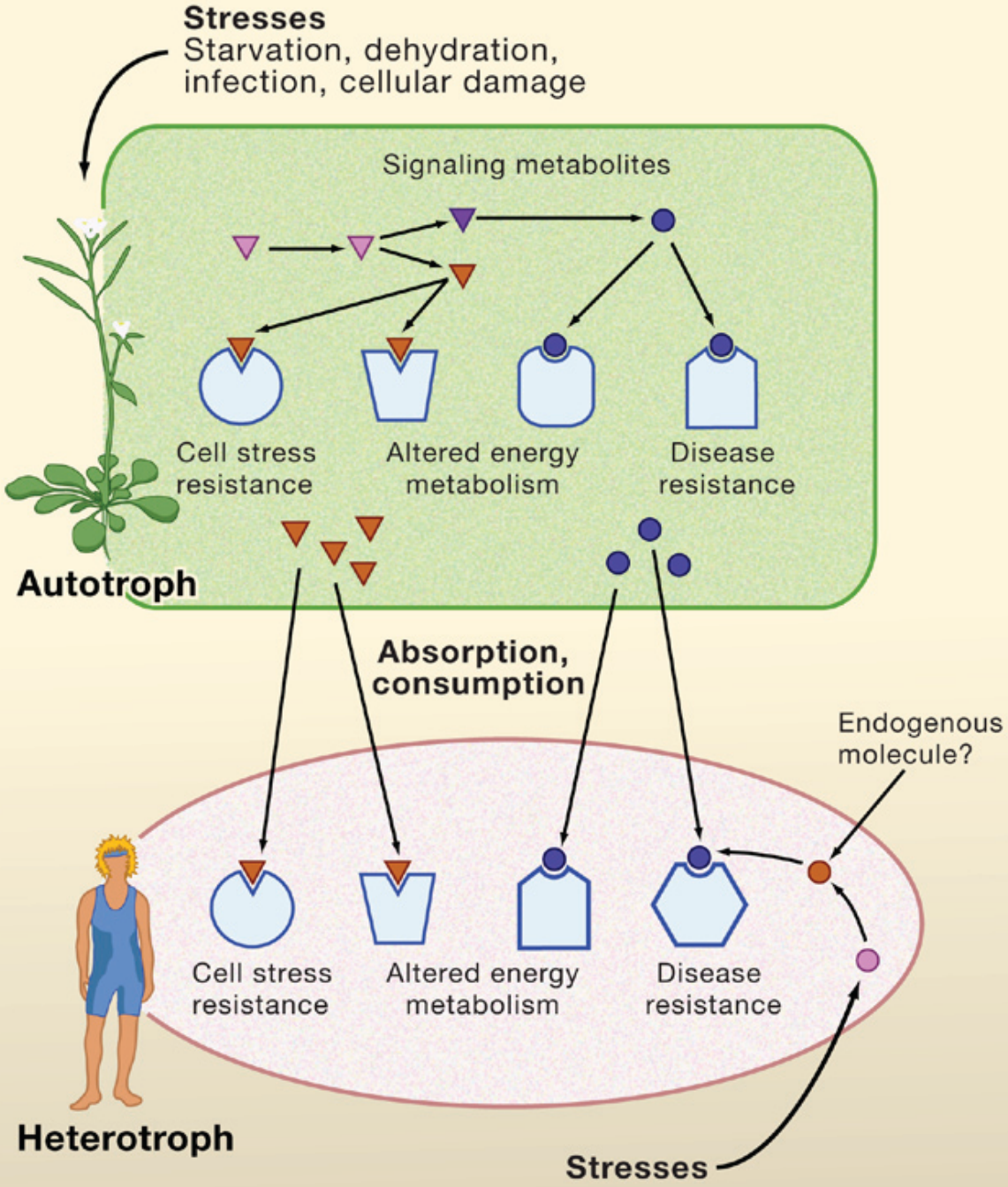
Others

Inflammatory Bowel
Sepsis

Table 1

Disease	Drug	ClinicalTrials.gov Identifier	Status	Start date to completion date	Sponsor/Collaborators	Phase	Observations
Healthy adults	Resveratrol	NCT00721877	Completed	Aug 2008	University of Arizona/ Natl. Cancer Institute	I	Effect of resveratrol on CYP enzymes, phase II metabolism. Safety assessment of resveratrol
	SRT2104	NCT00920660	Completed	Apr 2009 to Jun 2009	GlaxoSmithKline	I	Effects on several biomarkers
		NCT00933062	Completed	Mar 2009 to May 2009	GlaxoSmithKline	I	
		NCT00933530	Completed	May 2008 to Nov 2008	GlaxoSmithKline	I	Dose-escalation clinical study
		NCT00937872	Completed	Nov 2008 to Dec 2008	GlaxoSmithKline	I	
		NCT00938275	Completed	Jan 2009 to Mar 2009	GlaxoSmithKline	I	Effect of food and gender o pharmacokinetics
		NCT00964340	Recruiting	Oct 2009 to Jan 2010	GlaxoSmithKline	I	Evaluation of exercise tolerance
	SRT2379	NCT01018628	Recruiting	Dec 2009 to Jul 2010	GlaxoSmithKline	I	Dose-escalation clinical study
Alzheimer's disease	Resveratrol	NCT00678431	Recruiting	Jan 2008 to Jun 2011	Dept. Veterans Affairs/ Alzheimer's Association	III	Coadministered with glucose and malate as a dietary supplement
		NCT00743743	Not yet open	Sept 2008 to Dec 2010	Medical College of Wisconsin	III	
Cancer (solid tumor)	Resveratrol	NCT00098969	Completed	Sept 2004	University of Michigan/ Natl. Cancer Institute	I	Fast elimination of resveratrol and its metabolites (1)
Cognitive function and cerebral blood flow	Resveratrol	NCT01010009	Completed	Jun 2008 to Mar 2009	Northumbria University	–	Resveratrol as a dietary supplement
Colon cancer	Resveratrol	NCT00256334	Recruiting	Jul 2005 to Dec 2009	University of California	I-II	Testing for Wnt signaling
		NCT00433576	Completed	Dec 2006	University of Michigan/ Natl. Cancer Institute	I	
		NCT00578396	Ongoing	Jan 2008 to Jun 2010	University of California/ Gateway for Cancer Research	I	Dietary supplement, grape-derived
	SRT501	NCT00920803	Completed	Aug 2008 to Nov 2009	GlaxoSmithKline	I	
Diabetes mellitus, type 2	Resveratrol	NCT01038089	Not yet open	Jan 2010 to Dec 2010	Boston University	–	Dietary supplement
	SRT2104	NCT00937326	Recruiting	Jul 2009 to Mar 2010	GlaxoSmithKline	II	
		NCT01018017	Not yet open	Feb 2010 to Oct 2010	GlaxoSmithKline	II	
		NCT01031108	Not yet open	Feb 2010 to Jan 2010	GlaxoSmithKline	I	
Metabolic syndrome	Resveratrol	NCT00654667	Recruiting	May 2007	University of California	II	
Multiple myeloma	SRT501	NCT00920556	Recruiting	Mar 2009 to Dec 2010	GlaxoSmithKline	II	Alone or in combination with bortezomib
Obesity	Resveratrol	NCT00998504	Recruiting	Oct 2009 to Jul 2010	Maastricht University/DSM Nutritional Products, Ltd	–	Dietary supplement. Effects on fat oxidation
Obesity, metabolic syndrome, diabetes, aging	Resveratrol	NCT00823381	Recruiting	Jan 2009 to Jan 2010	Washington University/DSM Nutritional Products, Inc.	–	Dietary supplement. Effects on skeletal muscle gene expression
Sepsis	SRT2104	NCT01014117	Recruiting	Dec 2009 to Jun 2010	GlaxoSmithKline	I	
Skeletal muscle atrophy	SRT2104	NCT01039909	Not yet open	Jan 2010 to Sept 2010	GlaxoSmithKline	I	

A. Camins et al., Biochimica et Biophysica Acta (2010)



Adversity
↓
Xenohormetic molecule synthesis
↓
Intracellular target proteins
↓
Increased survival
↓
Inter-species transfer
↓
Modulation of target proteins
↓
Increased health and survival due to xenohormesis

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