



History of Metformin: Diabetes Therapy with Ancient Roots

Galega officinalis

Used in ancient Egypt, to relieve diabetes-like symptoms

1922 Werner and Bell

1957 1st clinic trial France

1958 Sterne

1972 CAN

1995 USA

>48,000,000 prescriptions USA

2010

CN1C=NC2=C1C(=O)N(C)C2

The New England
Journal of Medicine

Copyright © 2002 by the Massachusetts Medical Society

VOLUME 346 FEBRUARY 7, 2002 NUMBER 6

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2012 VOL. 366 NO. 24

A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes

TODAY Study Group[†]

THE LANCET • Vol 352 • September 12, 1998

ARTICLES

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)

The New England Journal of Medicine

EFFECTS OF METFORMIN ON SPONTANEOUS AND CLOMIPHENE-INDUCED OVULATION IN THE POLYCYSTIC OVARY SYNDROME

JOHN E. NESTLER, M.D., DANIELA J. JAKUBOWICZ, M.D., WILLIAM S. EVANS, M.D., AND RENATO PASQUALI, M.D.

Metformin in HIV

Metformin in the Treatment of HIV Lipodystrophy Syndrome

A Randomized Controlled Trial

Colleen Hadigan, MD; Colleen Corcoran, NP; Nesli Basgoz, MD; Benjamin Davis, MD; Paul Sax, MD; Steven Grinspoon, MD

JAMA. 2000;284(4):472-477. doi:10.1001/jama.284.4.472

The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials

Siddharth H Sheth and Robin J Larson

BMC Infectious Diseases 2010 10:183

<https://doi.org/10.1186/1471-2334-10-183> | © Sheth and Larson; licensee BioMed Central Ltd. 2010

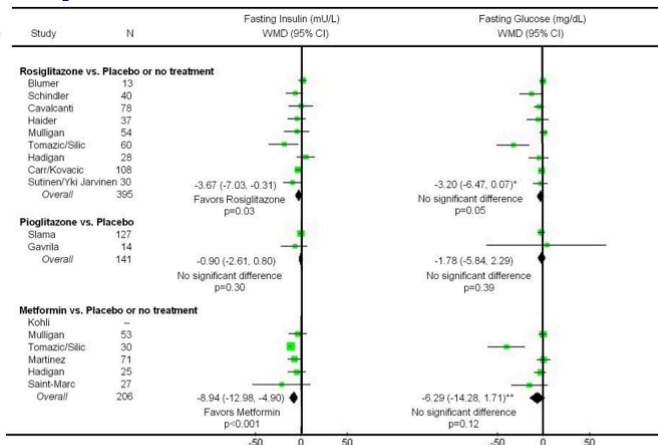
Received: 23 June 2009 | Accepted: 23 June 2010 | Published: 23 June 2010

Metformin in HIV

The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials

Siddharth H Sheth and Robin J Larson

BMC Infectious Diseases 2010 10:183



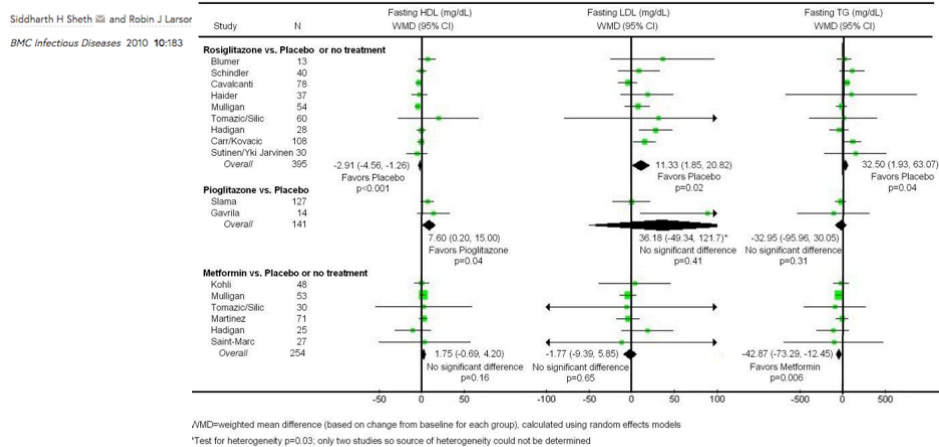
WMD=weighted mean difference (based on change from baseline for each group), calculated using random effects models

*Test for heterogeneity p=0.02, excluding Tomazic:WMD -1.48 (-3.37, 0.41), test for heterogeneity p=0.51, test for overall effect p=0.13

**Test for heterogeneity p=0.002, excluding Tomazic:WMD -1.01 (-4.33, 2.31), test for heterogeneity p=0.47, test for overall effect p=0.55

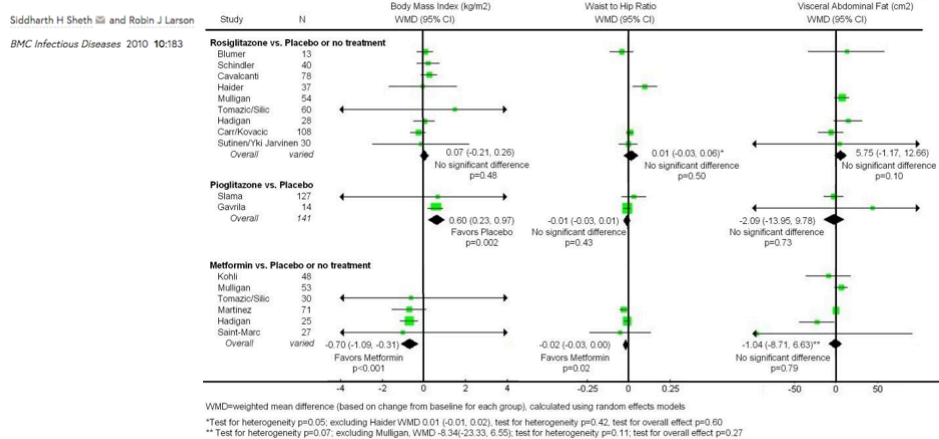
Metformin in HIV

The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials



Metformin in HIV

The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials



Metformin: Anti-Cancer Activity

RESEARCH POINTERS

BMJ VOLUME 330 4 JUNE 2005

Metformin and reduced risk of cancer in diabetic patients

Josie M M Evans, Louise A Donnelly, Alistair M Emslie-Smith, Dario R Alessi, Andrew D Morris

Metformin, widely given to patients with type 2 diabetes, works by targeting the enzyme AMPK (AMP activated protein kinase), which induces muscles to take up glucose from the blood. A recent breakthrough has found the upstream regulator of AMPK to be a protein kinase known as LKB1.^{1,2} LKB1 is a well recognised tumour suppressor. Activation of AMPK by metformin and exercise requires LKB1, and this would also explain why exercise is beneficial in the primary and secondary prevention of certain cancers.³ We hypothesise that metformin use in patients with type 2 diabetes may reduce the risk of cancer.

What this paper suggests

Metformin may reduce the risk of cancer in patients with type 2 diabetes

What research is needed now

A more rigorous cohort study, before experimental work is initiated

Metformin: Anti-Cancer Activity

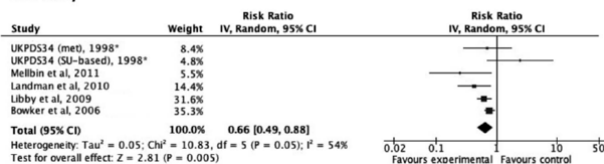
OPEN ACCESS Freely available online

PLoS one

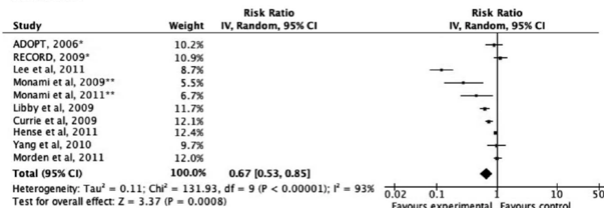
Cancer Risk in Diabetic Patients Treated with Metformin: A Systematic Review and Meta-analysis

Hiroshi Noto^{1,2*}, Atsushi Goto^{1,2}, Tetsuro Tsujimoto^{1,2}, Mitsuhiko Noda^{1,2}

Mortality



Incidence



Metformin: Anti-Aging

OPEN ACCESS Freely available online

PLoS one

Metformin Induces a Dietary Restriction–Like State and the Oxidative Stress Response to Extend *C. elegans* Healthspan via AMPK, LKB1, and SKN-1

Brian Onken, Monica Driscoll*



ARTICLE

Received 2 Nov 2012 | Accepted 26 Jun 2013 | Published 30 Jul 2013

DOI: 10.1371/journal.pone.0198888

Metformin improves healthspan and lifespan in mice

Alejandro Martín-Montalvo^{1*}, Evi M. Mercken^{1*}, Sarah J. Mitchell^{2,3}, Hector H. Palacios¹, Patricia L. Mote⁴, Morten Scheibye-Knudsen⁵, Ana P. Gomes⁶, Theresa M. Ward⁷, Robin K. Minor¹, Marie-Josée Blouin¹, Matthias Schwaiblmair⁸, Michael Pollak⁹, Yongqiang Zhang⁹, Yixiang Yu¹⁰, Kevin G. Becker⁹, Vilhelm A. Bohr¹¹, Donald K. Ingram¹², David A. Sinclair¹³, Norman S. Wolf¹⁴, Stephen R. Spindler¹⁵, Michel Bernier¹⁶ & Rafael de Cabo¹



Metformin Retards Aging in *C. elegans* by Altering Microbial Folate and Methionine Metabolism

Filipe Cabreiro,¹ Catherine Au,^{1,4} Kit-Yi Leung,^{1,4} Nuria Vergara-Irigaray,¹ Helena M. Cochemé,¹ Tahereh Noori,¹ David Weinkove,² Eugene Schuster,¹ Nicholas D.E. Greene,³ and David Gems^{1*}

Metformin Mechanism Diabetes and Cancer

The Journal of
Diabetes
and
Tissue

LETTER

doi:10.1038/nature11808

Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP

Russell A. Miller¹, Qingwei Chu¹, Jianxin Xie², Marc Foretz^{3,4,5}, Benoît Viollet^{3,4,5} & Morris J. Birnbaum¹

Glucose production rate for the brain depress hepatic glucose hyperglycaemia of type 2 diabetes mellitus. Biguanides effective in biguanides, which in

LETTER

doi:10.1038/nature13270

Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase

The Peutz-Jeghers syndrome (PTC) phosphatase (P) adult mice

Anita K. Madhuj^{1,2,3}, Derek M. Efron^{1,2,3}, Yasmeen Bahimi¹, Xian-Man Zhang¹, Demetrios T. Braddock⁴, Ronald A. Albright⁴, Brett J. Prigaro⁵, John L. Wood⁶, Sanjay Biswas⁷, Michael H. Malinski^{8,9}, Michael J. Toner¹⁰, Isaac Dukes-Panayiotou¹¹, Hui-Young Lee¹, Gary W. Cline¹, Varman T

LETTERS

nature
medicine

LETTERS

Metformin is considered to be one of the most for treating type 2 diabetes because it specifically omegogenesis without increasing insulin secretion or posing a risk of hypoglycaemia^{1,2}. For agent has been prescribed to patients with type eye the underlying mechanism by which metfo

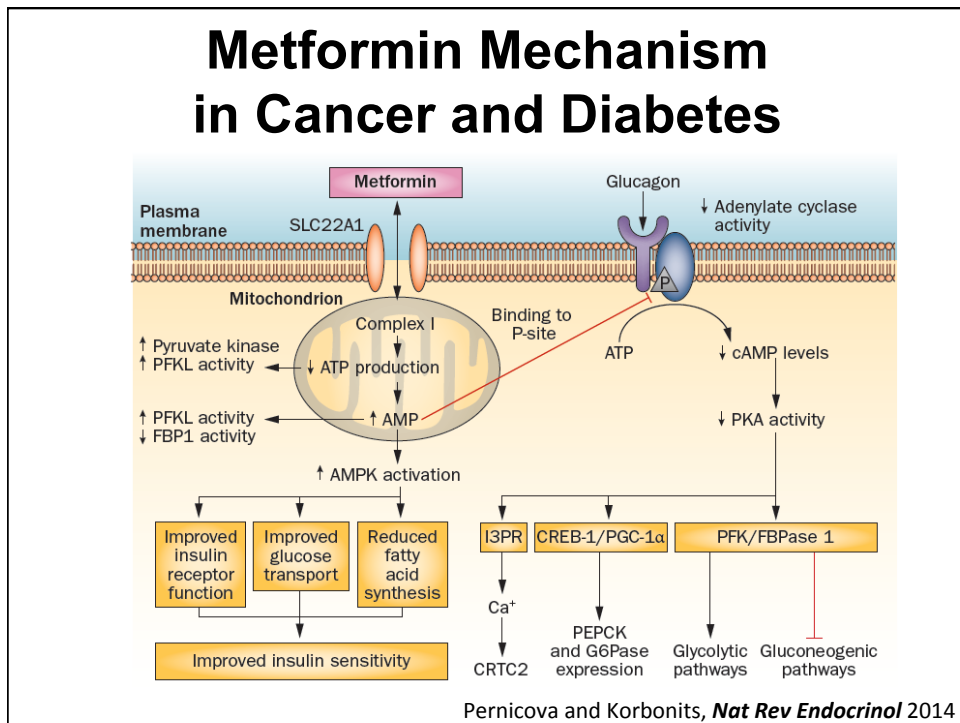
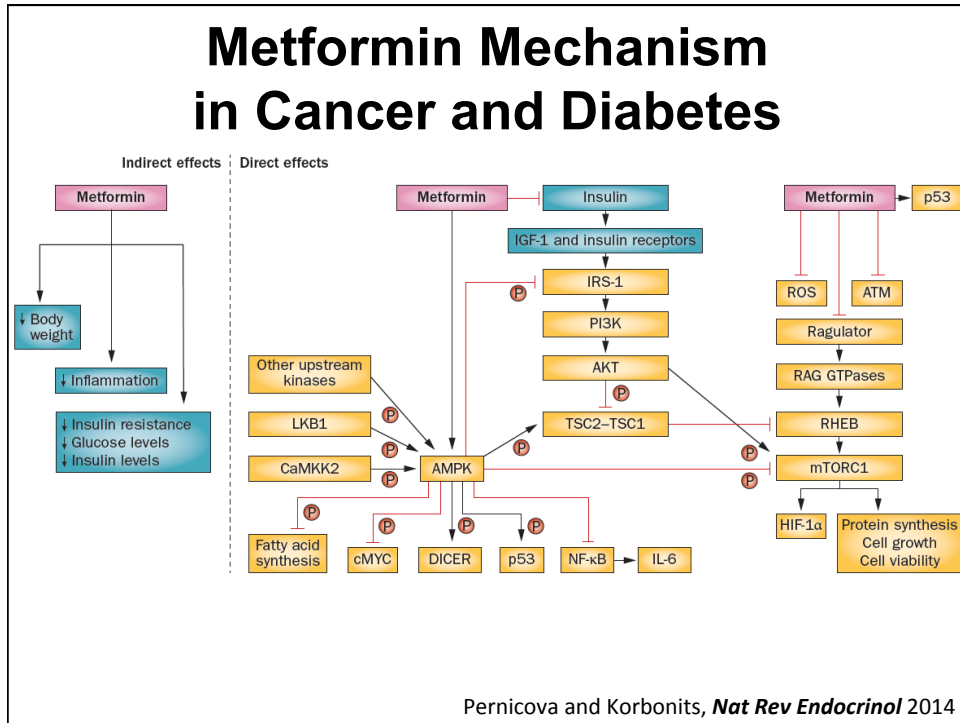
Morgan D Fullerton^{1,2,9}
Zhi-Ping Chen¹, Hayley
D Graham-Hardie⁶, S I
Bruce E Kemp^{3,5} & Greg

Metformin activates a duodenal Ampk-dependent pathway to lower hepatic glucose production in rats

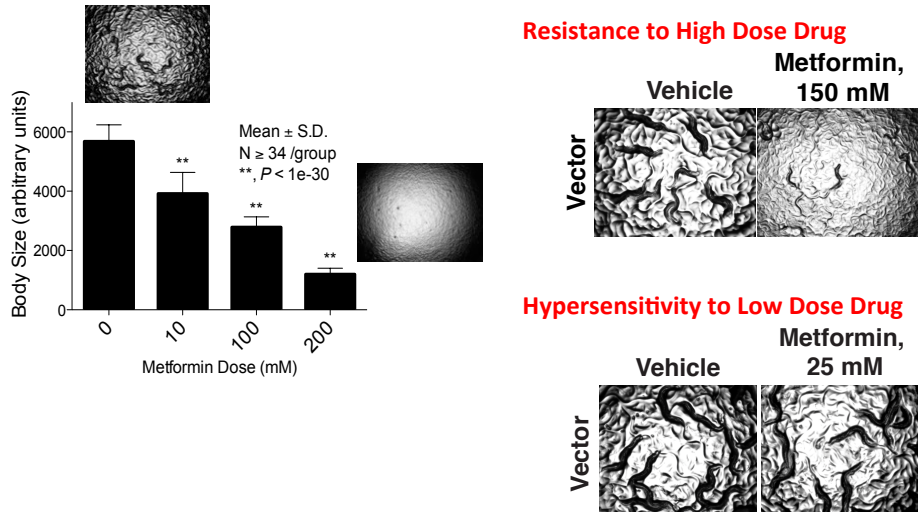
Frank A Duca¹, Clémence D Côté^{1,2}, Brittany A Rasmussen^{1,2}, Melika Zadeh-Tahmasebi^{1,2}, Guy A Rutter⁴, Beatrice M Filippi¹ & Tony K T Lam^{1,3,5}

Metformin is a first-line therapeutic option for the treatment of type 2 diabetes, even though its underlying mechanisms of action are relatively unclear^{1–6}. Metformin lowers blood glucose levels by inhibiting hepatic glucose production (HGP), an effect originally postulated to be due to a

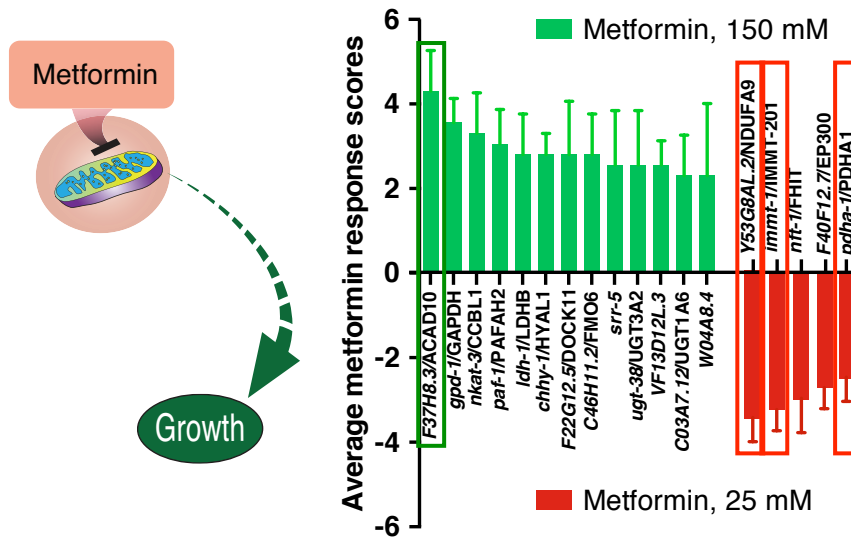
liver kinase B1 (LKB1)-dependent phosphorylation of AMPK^{3,14}. Validation of this mechanism includes data showing that chemical inhibition of AMPK negates the ability of metformin to inhibit HGP in hepatocytes⁷, and hepatic knockout of SIRT1 (encoding LKB1) abolishes the ability of chronic metformin to activate hepatic Ampk



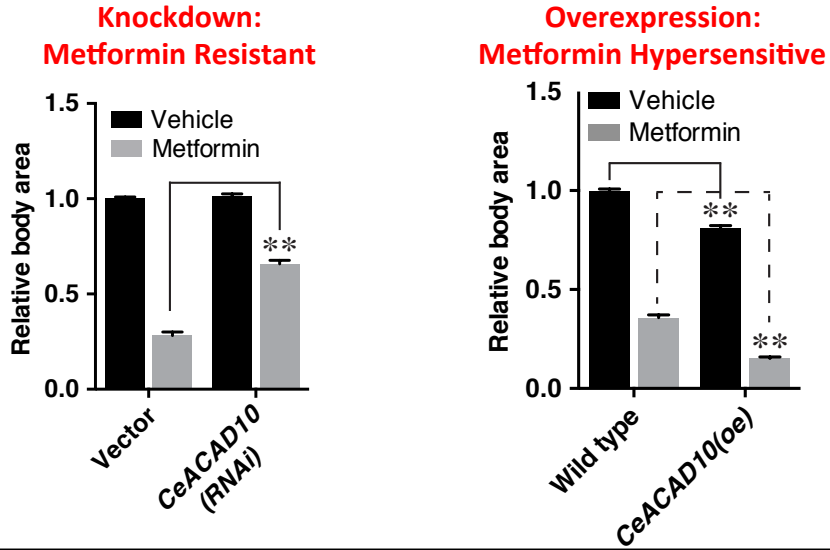
Metformin Effects on *C. elegans* Growth



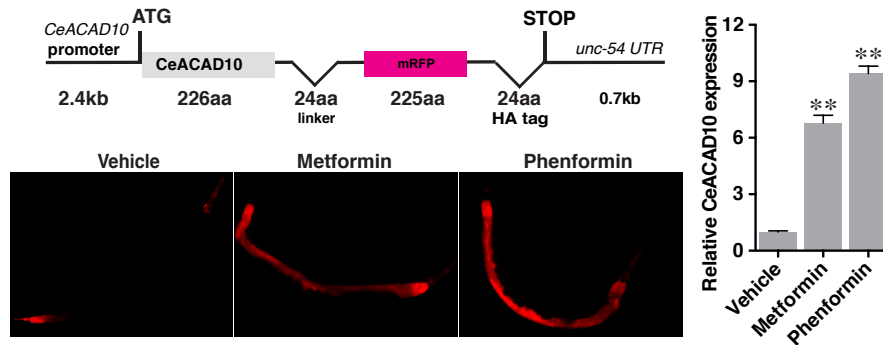
Search for Metformin Response Genes: 1000 Metabolic Gene RNAi



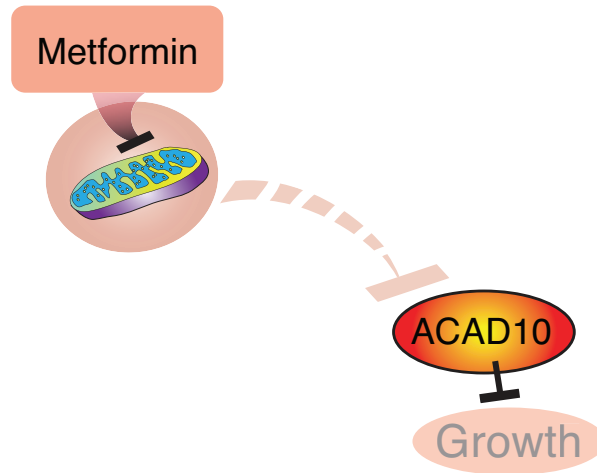
CeACAD10 Mediates Metformin Response



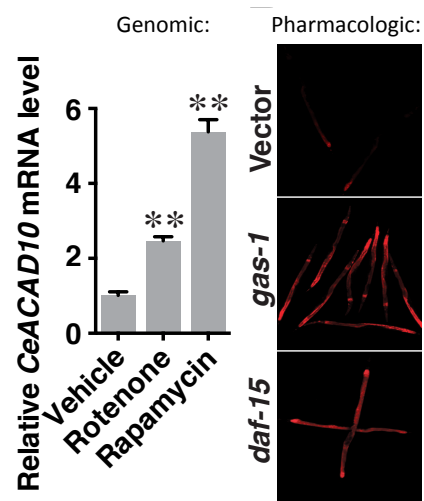
Biguanides Increase CeACAD10 Expression



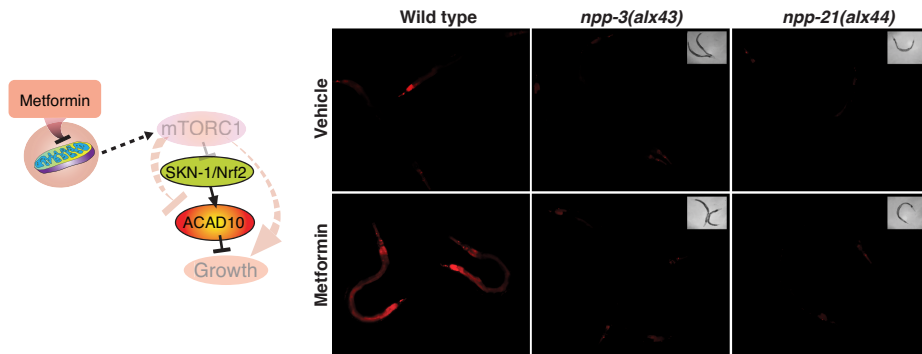
Biguanides Increase CeACAD10 Expression to Inhibit Growth



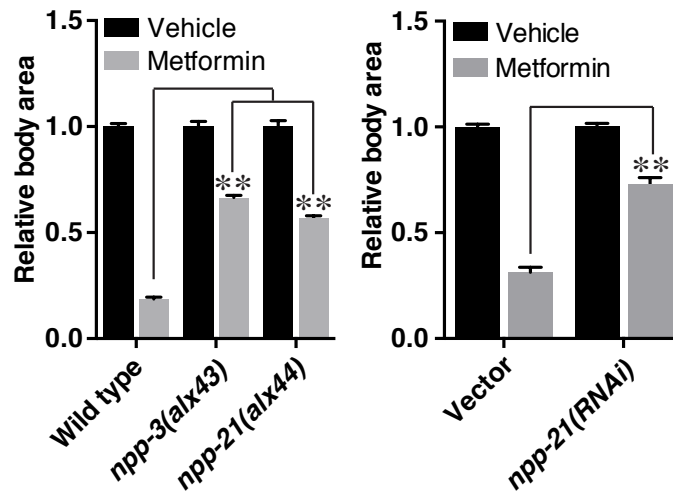
Mitochondria and TOR Complex 1 Are in the Metformin-CeACAD10 Pathway



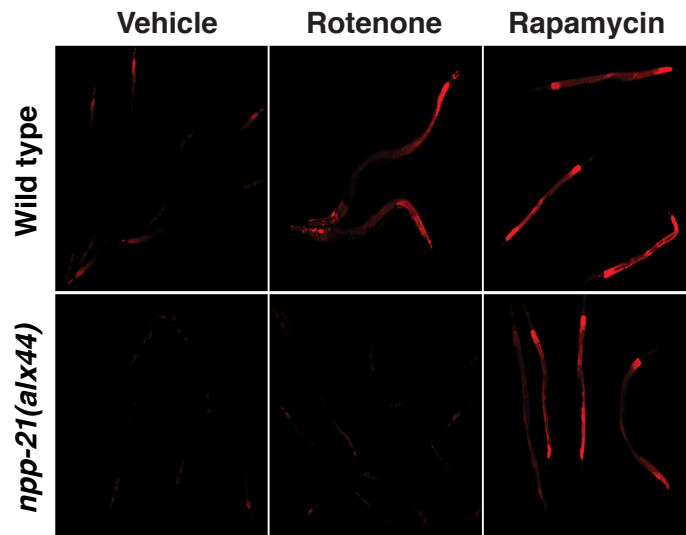
Metformin-Mitochondria Connect to TORC1-ACAD10 Through the NPC



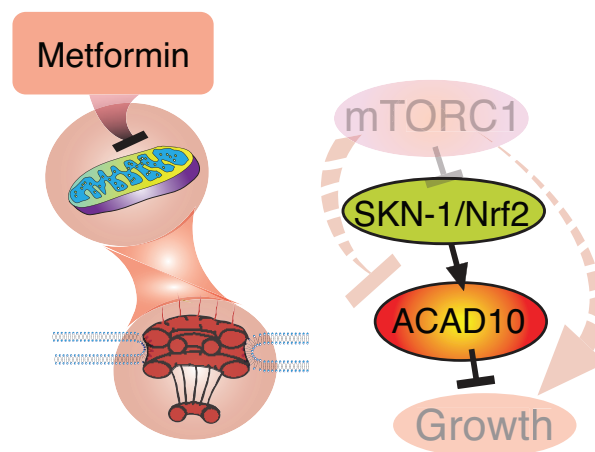
NPC Mutations Prevent Metformin Effects on *C. elegans* Growth



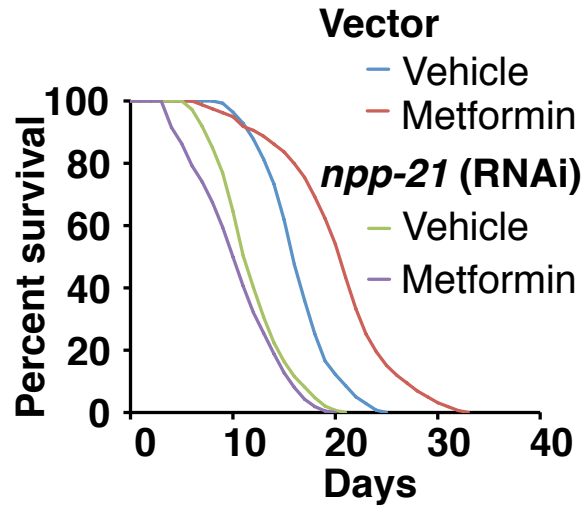
The NPC Sits Between Mitochondria and TORC1



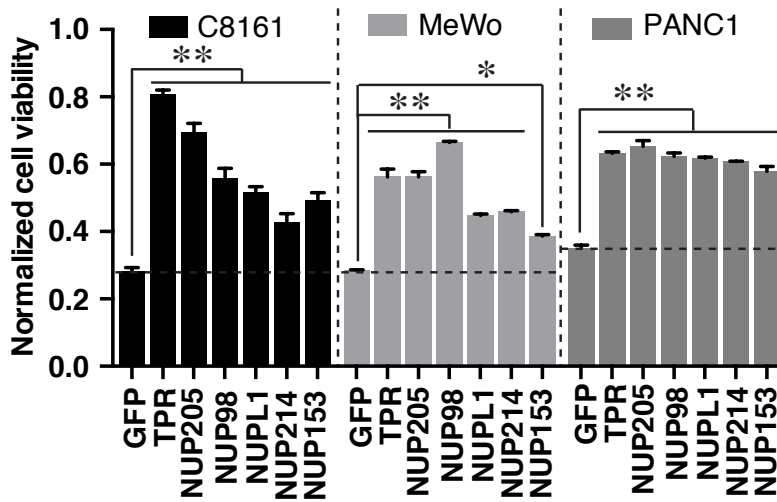
The NPC Sits Between Mitochondria and TORC1

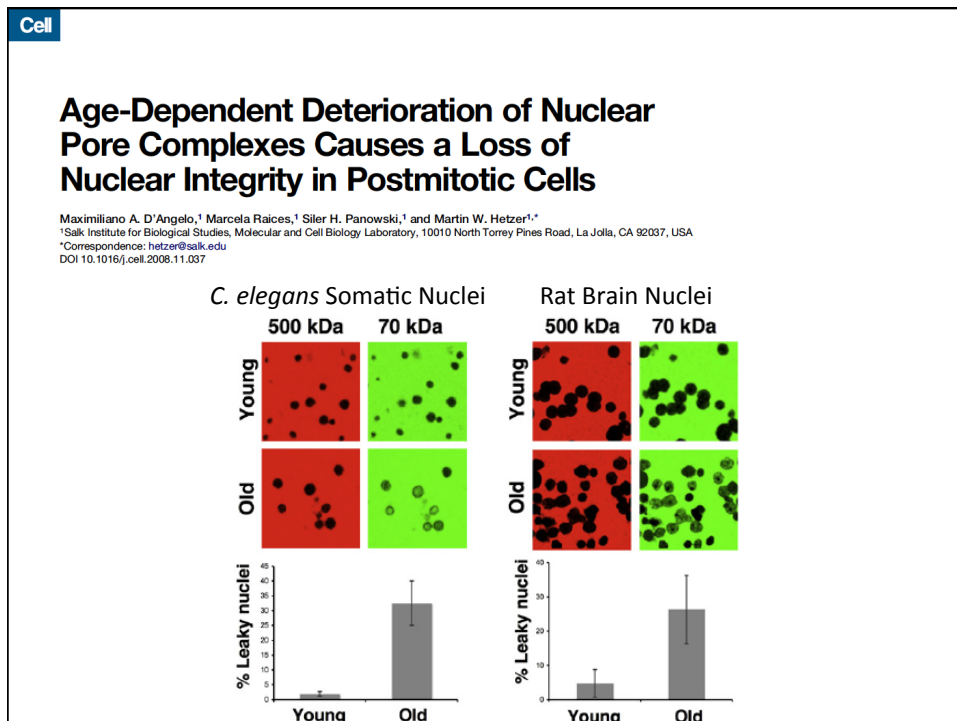
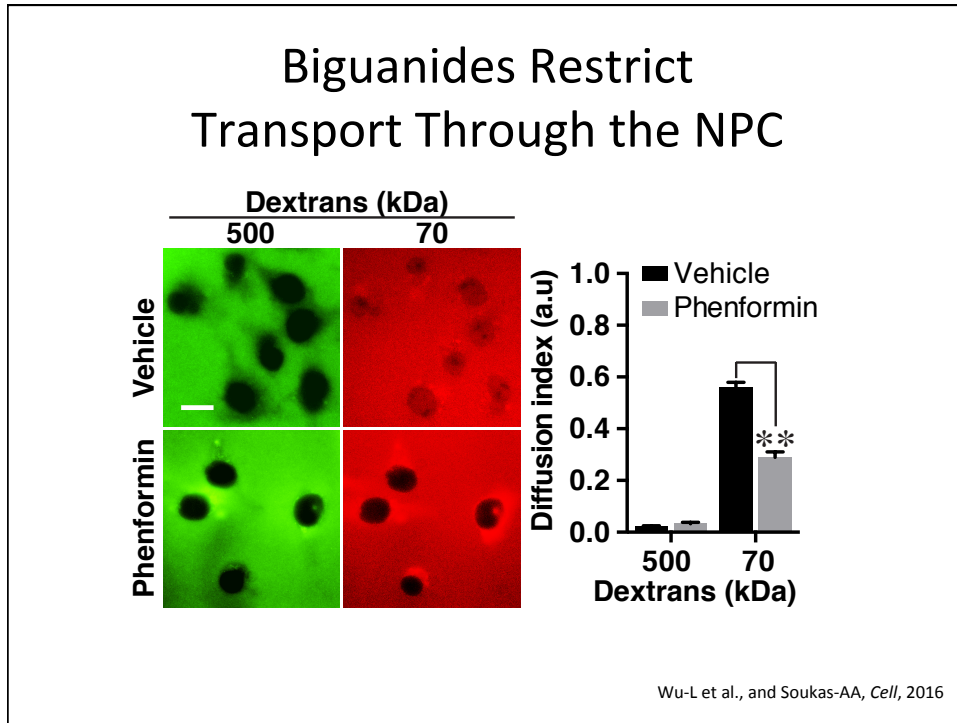


ACAD10 and NPC Necessary for Metformin to Extend Lifespan

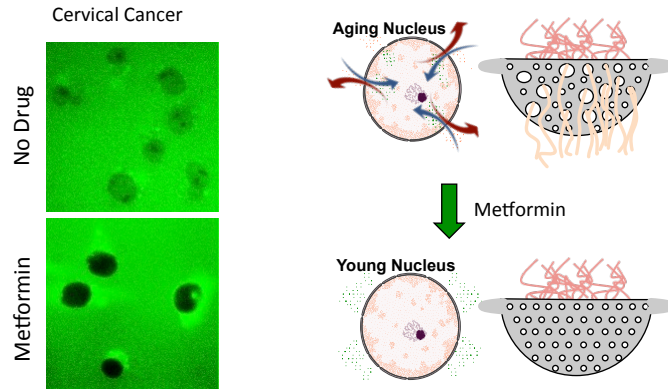


NPC Necessary for Phenformin to Block Cancer Cell Growth



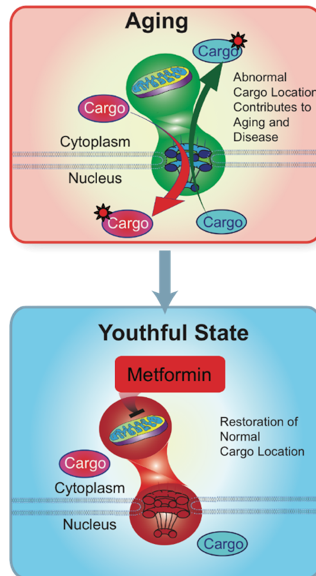


Metformin Reverses Nuclear Leakiness in Aging and Disease



Wu-L et al., and Soukas-AA, *Cell*, 2016

Metformin Ancient Signaling Relay



Wu-L et al., and Soukas-AA, *Cell*, 2016

Metformin in HIV: Future Directions

- Does metformin prevent aging associated pathology in HIV infection?
- Does metformin restore adipocyte reserve?
- What pathways mediate the health promoting effects of metformin downstream of its primary targets?

Acknowledgements



Lianfeng Wu

Lab Members

Ben Zhou
Lucydalila Cedillo
Patrick Griffin
Sainan Li
Daniel Baker
Michael Kacergis
Christopher Webster
Reece Akana
Elizabeth Pino
Denzil Douglas
Minsheng Yuan
Mariama Runcie
Samuel Doernberg
Andrea Escobar
Jonathan You
Alison Yan

Collaborators

MGH
Bin Zheng
Robert Gerszten
Jose Florez
Michael Talkowski

Harvard

Chad Cowan
Steve Gygi
Joao Paulo

MIT

Christopher Carr

Mentors

MGH

Gary Ruvkun
Joe Avruch
Hank Kronenberg
Anne Klibanski
Mason Freeman
Vamsi Mootha
David Altshuler

Rockefeller

Jeffrey Friedman

Funding

NIH/NIA
NIH/NIDDK
Broad Institute
MGH Howard M. Goodman Fellowship
Ellison Medical Foundation
AFAR
Glenn Foundation
Charles H. Hood Foundation
BADERC
NORC-H

