Mitochondrial Pyruvate Carrier Complex: From the Control of Cellular Metabolism to the Promise of New NASH Drugs

Jerry Colca, Ph.D.

Cirius Therapeutics

The Trail to Today's Talk

1980
Upjohn/Takeda

1985
Selection of pioglitazone

1995
The PPARγ target

1999
Market Approval for Rosiglitazone and Pioglitazone

1997-2000
Troglitazone selective hepatoxicity

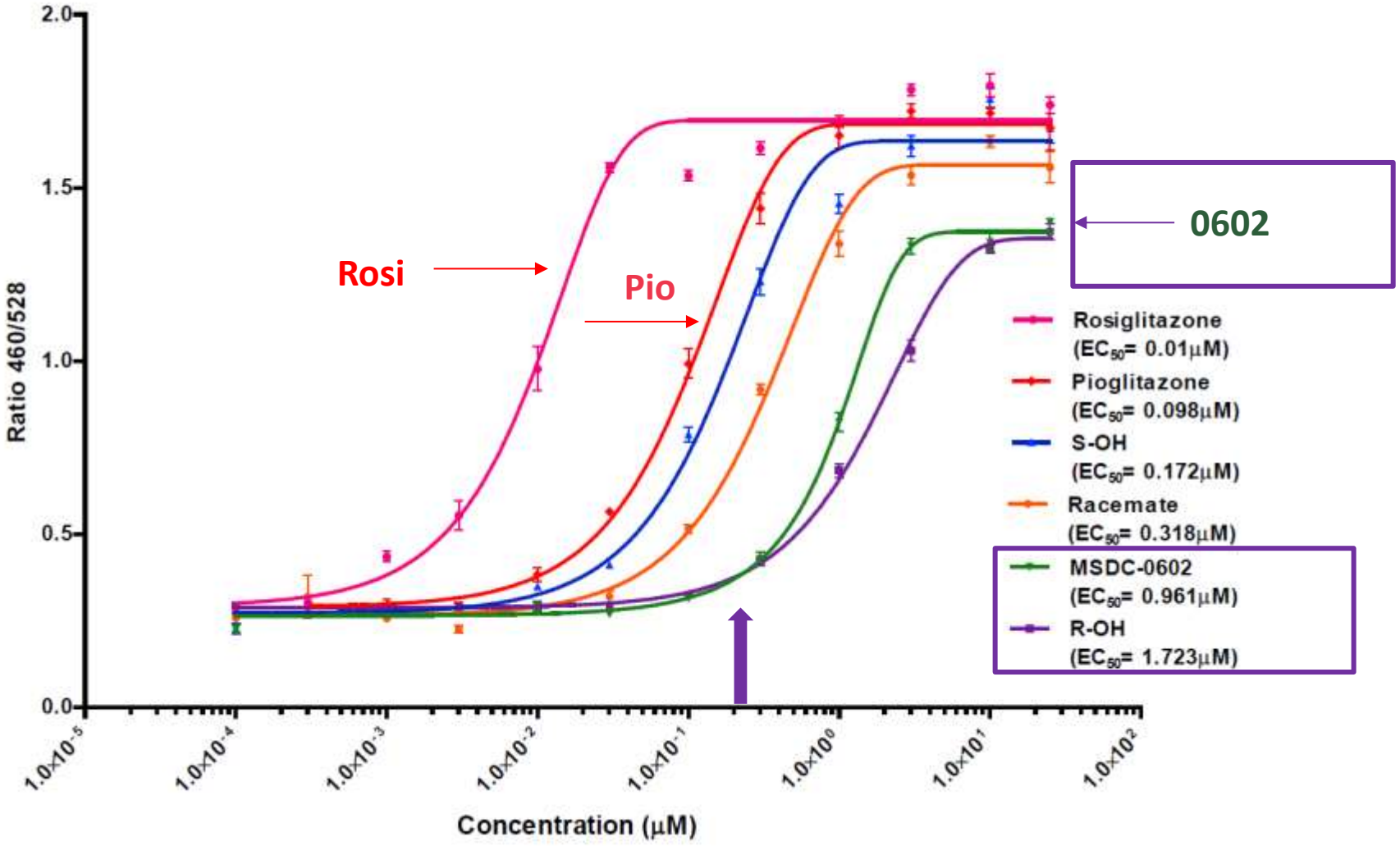
2007-
Rosiglitazone CV questions

2006-2009
Medicinal Chemistry effort to remove direct PPARγ interaction while maintain mitochondrial target

2013
Identification of the Mitochondrial Pyruvate Carrier as the mitochondrial target

Mitochondrial Pyruvate Carrier Complex: From the Control of Cellular Metabolism to the Promise of New NASH Drugs

Pharmacology *versus* Direct Activation of PPARγ



At clinical Cmax, the mitochondrial target is fully engaged with little direct PPARγ activation

Pioglitazone *versus* Rosiglitazone in NASH

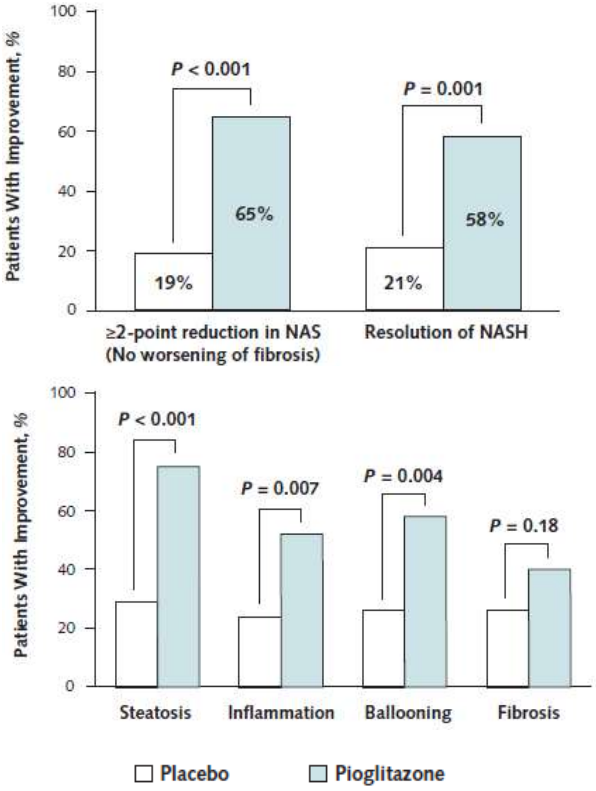
Annals of Internal Medicine ORIGINAL RESEARCH

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized, Controlled Trial

Kenneth Cusi, MD; Beverly Orsak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fermin Tio, MD; Jean Hardies, PhD; Celia Darland, RD; Nicolas Musi, MD; Amy Webb, MD; and Paola Portillo-Sanchez, MD

*n=101, diabetes or pre-diabetes patients w/ biopsy-confirmed NASH, 18-month primary**



JAMA Internal Medicine | Original Investigation

Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis

A Meta-analysis

Giovanni Musso, MD; Maurizio Cassader, PhD; Elena Paschetta, MD; Roberto Gambino, PhD

RESULTS This study analyzed 8 RCTs (5 evaluating pioglitazone use and 3 evaluating rosiglitazone maleate use) enrolling 516 patients with biopsy-proven NASH for a duration of 6 to 24 months. Among all studies combined, thiazolidinedione therapy was associated with improved advanced fibrosis (OR, 3.15; 95% CI, 1.25-7.93; $P = .01$; $I^2 = 0\%$), fibrosis of any

CONCLUSIONS AND RELEVANCE Pioglitazone use improves advanced fibrosis in NASH, even in patients without diabetes. Whether this finding translates to improvement in risk for clinical outcomes requires further study.

JAMA Intern Med. doi:10.1001/jamainternmed.2016.9607
Published online February 27, 2017.

"It is unclear why pioglitazone use (and not rosiglitazone use) accounted for all of the benefits observed with thiazolidinedione therapy in our analysis….."

At the exposures in the clinical studies, rosiglitazone has a much greater effect on PPARγ than on the mitochondrial target

Further optimization for the mitochondrial target could lead to improved efficacy in NASH

MSDC-0602K- a PPARγ sparing modulator of the mitochondrial target

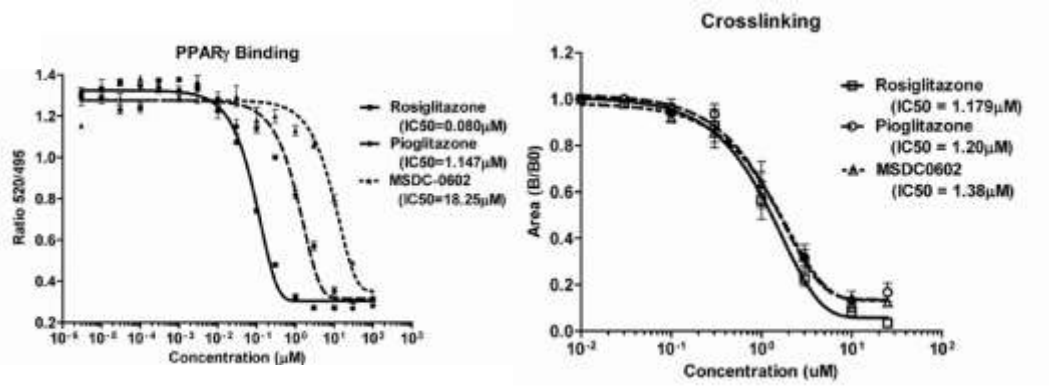
Insulin Resistance and Metabolic Derangements in Obese Mice Are Ameliorated by a Novel Peroxisome Proliferator-activated Receptor γ-sparing Thiazolidinedione*

Received for publication, March 19, 2012, and in revised form, May 22, 2012 Published, JBC Papers in Press, May 23, 2012, DOI 10.1074/jbc.M112.363960

Zhouji Chen‡, Patrick A. Vigueira‡§1, Kari T. Chambers‡2, Angela M. Hall‡, Mayurranjan S. Mitra‡, Nathan Qi¶, William G. McDonald‖, Jerry R. Colca‖, Rolf F. Kletzien‖, and Brian N. Finck‡§3

From the ‡Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110, the §Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan 48109, and ¶Metabolic Solutions Development Company, Kalamazoo, Michigan 49007

Background: Thiazolidinediones may have insulin-sensitizing effects independent of the nuclear receptor PPARγ.
Results: A novel PPARγ-sparing thiazolidinedione ameliorated insulin resistance and inflammation in obese mice.
Conclusion: The insulin-sensitizing effects of thiazolidinediones are separable from the ability to bind PPARγ.
Significance: Identification of other molecular targets of thiazolidinediones may generate new therapeutics for treatment of insulin resistance and diabetes.



"The insulin-sensitizing effects…are separable from…PPARγ"

Reduced PPAR binding

Simi

ORIGINAL ARTICLE JBMR®

An Insulin-Sensitizing Thiazolidinedione, Which Minimally Activates PPARγ, Does Not Cause Bone Loss

Tomohiro Fukunaga,[1] Wei Zou,[1] Nidhi Rohatgi,[1] Jerry R Colca,[2] and Steven L Teitelbaum[1,3]
[1]Department of Pathology and Immunology, Washington University in St. Louis School of Medicine, St. Louis, MO, USA
[2]Metabolic Solutions Development Company, Kalamazoo, MI, USA
[3]Department of Medicine, Division of Bone and Mineral Diseases, Washington University in St. Louis School of Medicine, St. Louis, MO, USA

Journal of Bone and Mineral Research, Vol. 30, No. 3, March 2015, pp 481–488
DOI: 10.1002/jbmr.2364

Clinical Proof-of-Concept Study With MSDC-0160 a Prototype mTOT-Modulating Insulin Sensitizer

JR Colca[1], JT VanderLugt[1], WJ Adams[1], A Shashlo[1], WG McDonald[1], J Liang[2], R Zhou[2] and DG Orloff[2]

VOLUME 93 NUMBER 4 | APRIL 2013 | www.nature.com/cpt

"Thus, mTOT modulators may have glucose-lowering effects similar to those of pioglitazone but without adverse effects associated with PPARγ agonists."

Insulin sensitizers in 2013: new insights for the development of novel therapeutic agents to treat metabolic diseases

Jerry R Colca†, Steven P Tanis, William G McDonald & Rolf F Kletzien
†*Metabolic Solutions Development Company, Kalamazoo, United States*

Insulin-sensitizing thiazolidinediones (TZDs) correct a root cause of type 2 diabetes and potentially other diseases of metabolic dysfunction, including

A Study to Evaluate the Safety, Tolerability & Efficacy of MSDC 0602K in Patients With NASH (EMMINENCE)

The Mitochondrial Target is the Pyruvate Carrier (MPC)

Identification of a Mitochondrial Target of Thiazolidinedione Insulin Sensitizers (mTOT)—Relationship to Newly Identified Mitochondrial Pyruvate Carrier Proteins 125I-labeled photoprobe → mitochondrial protein

Jerry R. Colca[1]*, William G. McDonald[1], Gregory S. Cavey[2], Serena L. Cole[1], Danielle D. Holewa[1], Angela S. Brightwell-Conrad[1], Cindy L. Wolfe[1], Jean S. Wheeler[1], Kristin R. Coulter[1], Peter M. Kilkuskie[1], Elena Gracheva[3], Yulia Korshunova[3], Michelle Trusgnich[3], Robert Karr[3], Sandra E. Wiley[4], Ajit S. Divakaruni[4], Anne N. Murphy[4], Patrick A. Vigueira[5], Brian N. Finck[5], Rolf F. Kletzien[1]

PLOS ONE | www.plosone.org May 2013 | Volume 8 | Issue 5 | e61551

Loss of Mitochondrial Pyruvate Carrier 2 in the Liver Leads to Defects in Gluconeogenesis and Compensation via Pyruvate-Alanine Cycling

Kyle S. McCommis,[1,4] Zhouji Chen,[1,4,5] Xiaorong Fu,[2] William G. McDonald,[3] Jerry R. Colca,[3] Rolf F. Kletzien,[3] Shawn C. Burgess,[2] and Brian N. Finck[1,*]

Cell Metabolism 22, 1–13, October 6, 2015 ©2015 Elsevier Inc. 13

KO of either mpc1 or mpc2 is protective of a high fat diet

A Mitochondrial Pyruvate Carrier Required for Pyruvate Uptake in Yeast, *Drosophila*, and Humans

Daniel K. Bricker *et al.*

Science **337**, 96 (2012);
DOI: 10.1126/science.1218099

Rutter, Utah

Identification and Functional Expression of the Mitochondrial Pyruvate Carrier

Sébastien Herzig *et al.*

Science **337**, 93 (2012);
DOI: 10.1126/science.1218530

Martinou, Geneva

The mitochondrial pyruvate carrier mediates high fat diet-induced increases in hepatic TCA cycle capacity

Adam J. Rauckhorst[1,11], Lawrence R. Gray[1,11], Ryan D. Sheldon[1], Xiaorong Fu[7,8], Alvin D. Pewa[1], Charlotte R. Feddersen[2], Adam J. Dupuy[2], Katherine N. Gibson-Corley[3], James E. Cox[9,10], Shawn C. Burgess[7,8], Eric B. Taylor[1,4,5,6,*]

MOLECULAR METABOLISM 6 (2017) 1468–1479

Thiazolidinediones are acute, specific inhibitors of the mitochondrial pyruvate carrier

Ajit S. Divakaruni[a], Sandra E. Wiley[a], George W. Rogers[b], Alexander Y. Andreyev[a], Susanna Petrosyan[a], Mattias Loviscach[c], Estelle A. Wall[a], Nagendra Yadava[d], Alejandro P. Heuck[e], David A. Ferrick[b], Robert R. Henry[c,f], William G. McDonald[g], Jerry R. Colca[g], Melvin I. Simon[a,1], Theodore P. Ciaraldi[c,f], and Anne N. Murphy[a,1]

Departments of [a]Pharmacology and [b]Medicine, University of California at San Diego, La Jolla, CA 92093; [c]Seahorse Bioscience, North Billerica, MA 01862; [d]Veterans Affairs San Diego Healthcare System, La Jolla, CA 92161; [e]Pioneer Valley Life Sciences Institute, Springfield, MA 01107; [f]Department of Biochemistry and Molecular Biology, University of Massachusetts, Amherst, MA 01003; and [g]Metabolic Solutions Development Co., Kalamazoo, MI 49007

Contributed by Melvin I. Simon, February 21, 2013 (sent for review January 28, 2013)

Targeting the Mitochondrial Pyruvate Carrier Attenuates Fibrosis in a Mouse Model of Nonalcoholic Steatohepatitis

Kyle S. McCommis,[1] Wesley T. Hodges,[1] Elizabeth M. Brunt,[2] Ilke Nalbantoglu,[2] William G. McDonald,[1] Christopher Holley,[1] Hideji Fujiwara,[1] Jean E. Schaffer,[3] Jerry R. Colca,[3] and Brian N. Finck[1]

HEPATOLOGY, VOL. 65, NO. 5, 2017

MSDC-0602 effects on fibrosis require hepatocyte MPC

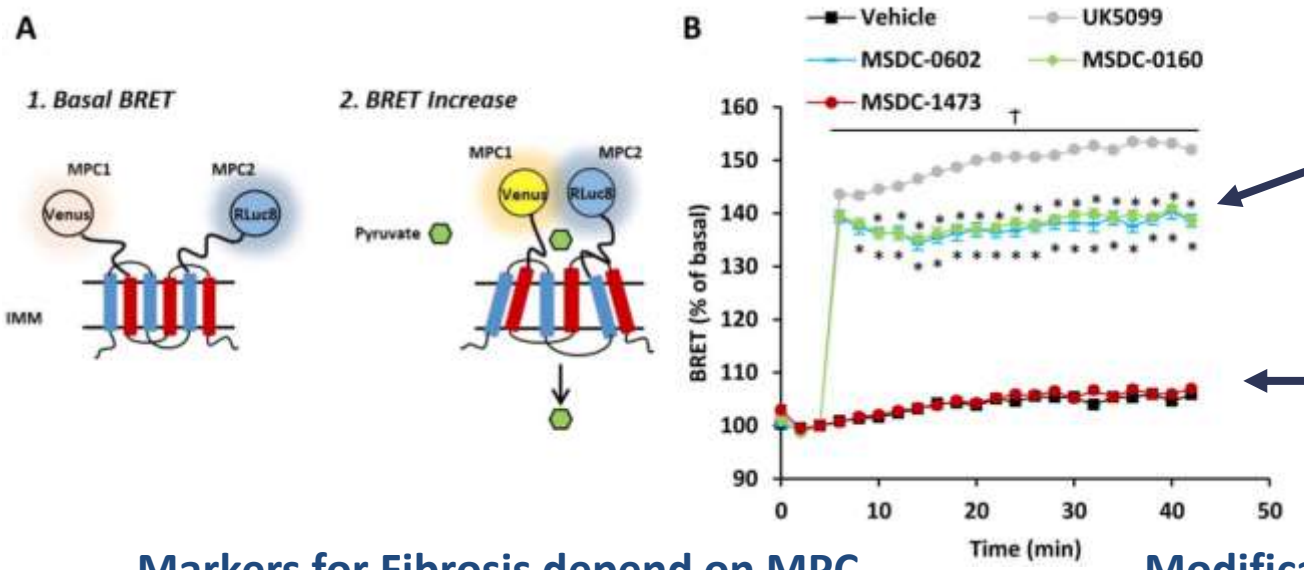
Mitochondrial target of thiazolidinediones

J. R. Colca, W. G. McDonald & R. F. Kletzie
Metabolic Solutions Development Company, Kalamazoo, MI, USA

Diabetes, Obesity and Metabolism 2014.

Targeting the Mitochondrial Pyruvate Carrier Attenuates Fibrosis

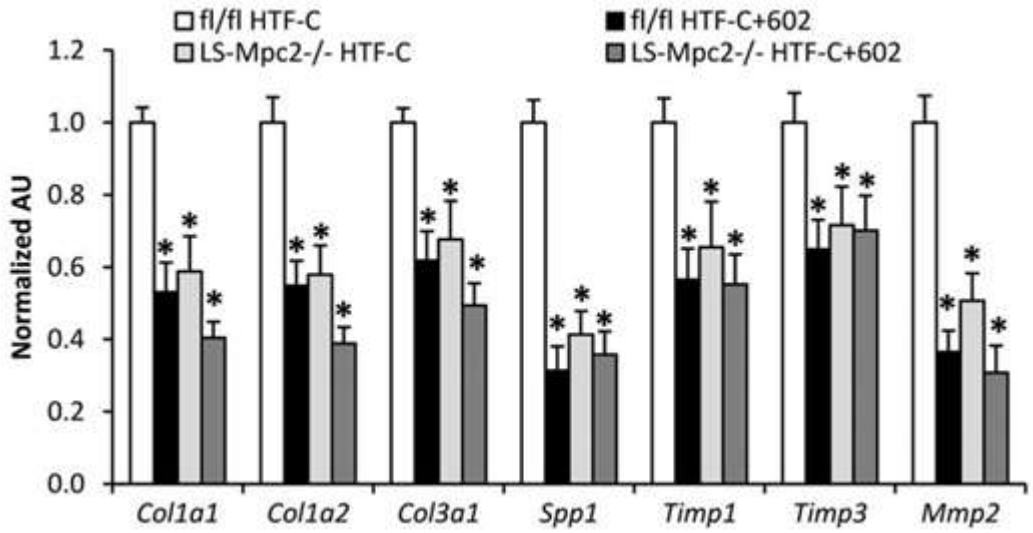
HEPATOLOGY
AASLD
HEPATOLOGY, VOL. 65, NO. 5, 2017



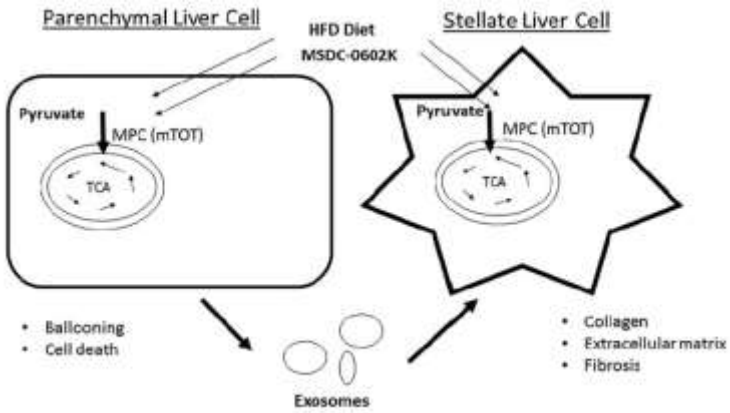
Active compounds directly interact

Inactive compounds do not

Markers for Fibrosis depend on MPC

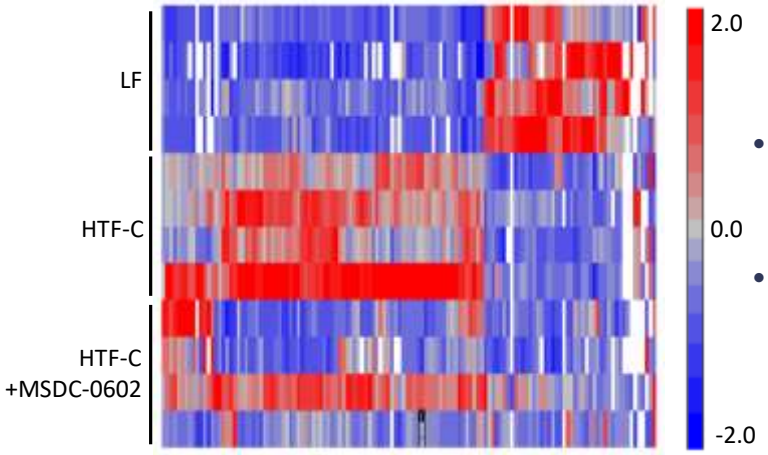


Modification of pyruvate usage protects against HFD injury

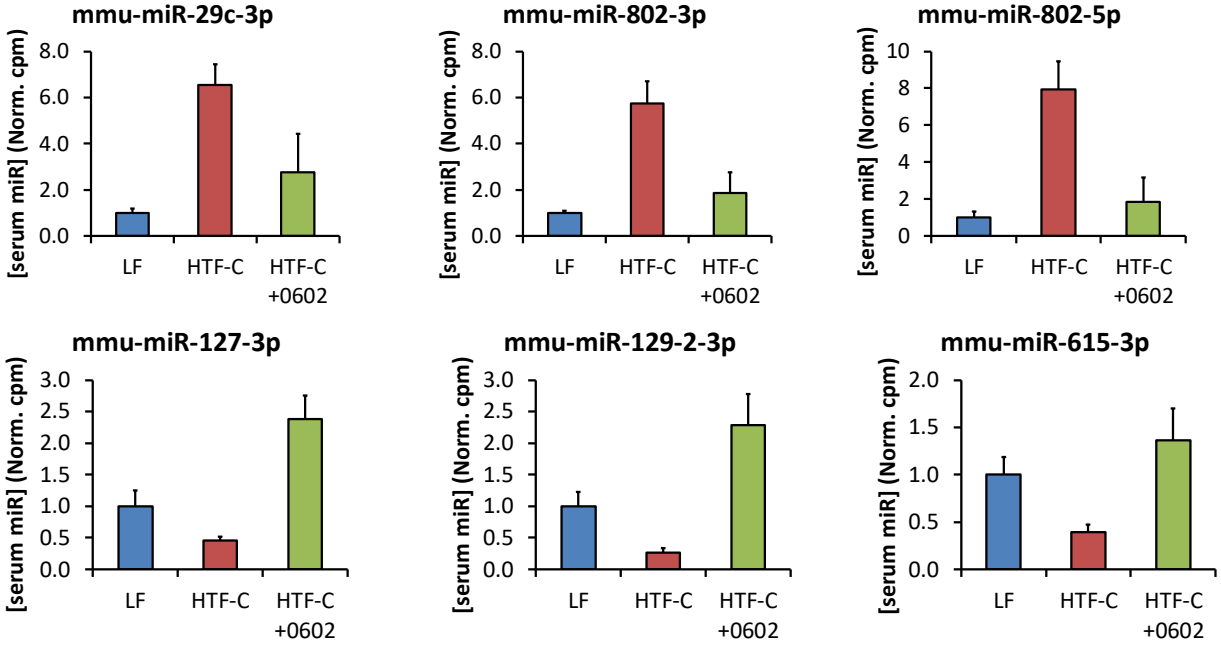


miRNA modifications by HTF-C/MSDC-0602K

McCommis et al, Presented at AASLD 2017



- C57Bl/6 mice were provide a low fat (LF) or a high transfat/fructose/cholesterol diet (HTF-C) with or without MSDC-0602K (30 mg/kg/day).
- The HTF-C diet produced reciprocal changes in large numbers of miRNAs. Most changes were reversed with 0602K treatment as shown by the heat map. Some examples are shown below.

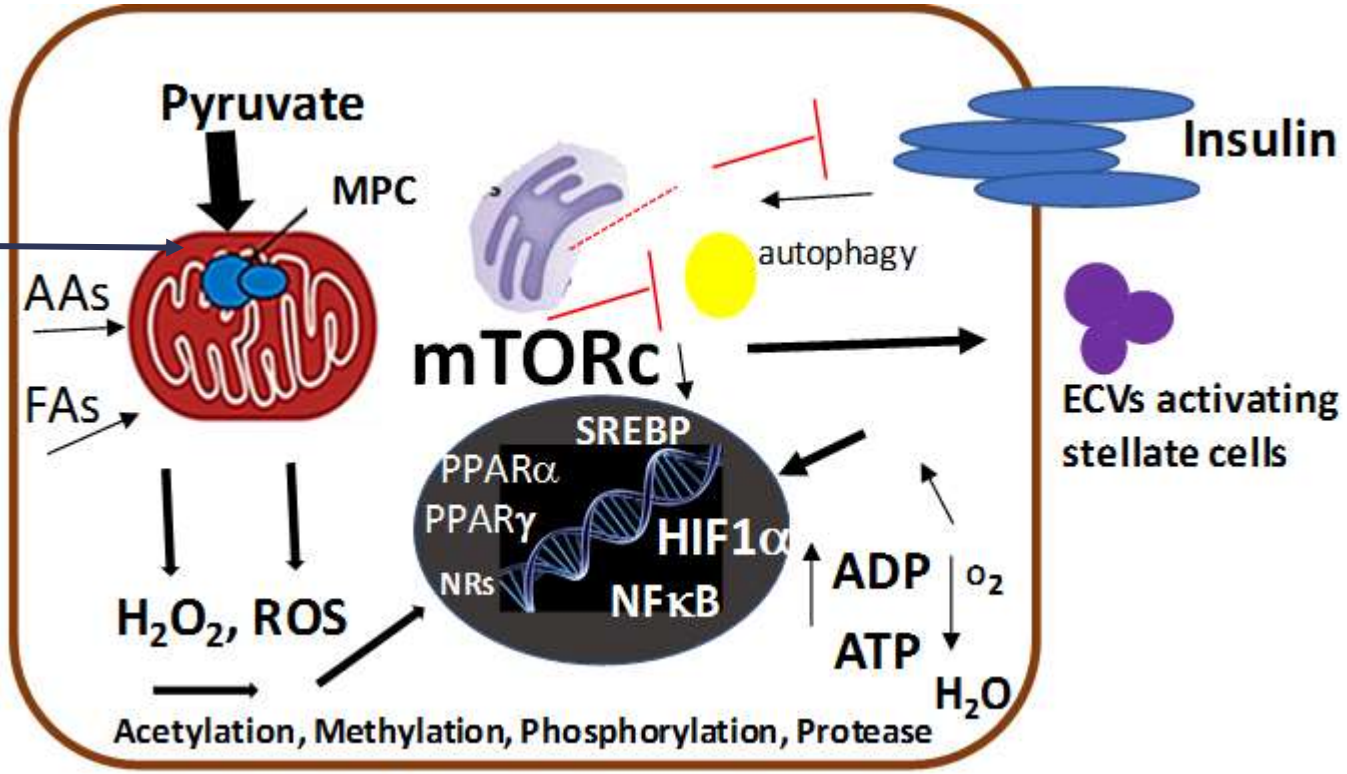


At least part of the changes in signals derived from hepatocytes to drive fibrosis are likely miRNAs

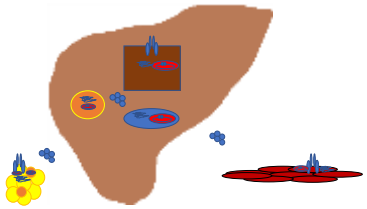
How does overnutrition cause liver damage?/ How does modulating pyruvate usage work?

The Pyruvate Carrier (MPC) is a major connection in the sensing and response to overnutrition

Liver specific KO or addition of 0602K is protective



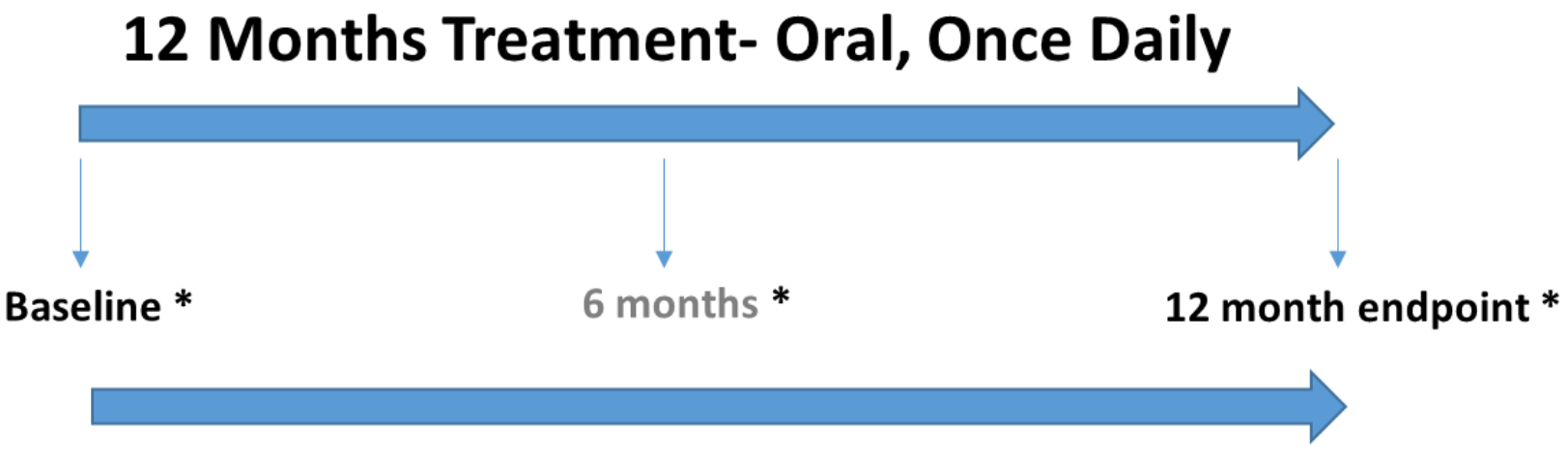
- Effects on hepatic parenchymal cells
- Other hepatic cells
- Extrahepatic pharmacology (adipose, muscle, macrophages, etc)



The ongoing clinical trial- NCT02784444

The EMMINENCE Trial

Effects of an **M**PC **M**odulator in **N**ASH: **E**valuation of a **N**ew **C**hemical **E**ntity (MSDC-0602K)



Placebo
62.5 mg
125 mg
250 mg

N=85/group

***Secondary biomarkers will explore whether histological improvement might be predicted from non-invasive measurements**

***The primary endpoint of EMMINENCE trial is reduction of NASH pathology as measured by liver biopsy.**

Conclusions

- Study of the antidiabetic drug pioglitazone led to the identification of the mitochondrial pyruvate complex (MPC) as a drug target.
- The MPC plays a role in sensing and directing the effects of overnutrition on liver pathology.
- MSDC-0602K, a selective modulator of the MPC, is currently being evaluated in a 52 week Phase 2b clinical trial in biopsy-confirmed NASH.
- Ongoing studies will elucidate the interconnected aspects (Cross Talk) of this pharmacology. Non-invasive measurements might be predictive of histological improvements.
- This mode of metabolic action may be useful as a stand-alone treatment for NASH and/or in combination with other treatment modalities.