Metabolic Syndrome, Diabetes & NAFLD Symposium --- 3rd Global NASH Congress

London, UK 10-11, February 2020

A **new oral insulin sensitizing agent-**

an approach to treating the overlapping pathology of NASH and diabetes

Jerry R. Colca, Ph.D

CSO, Cirius Therapeutics

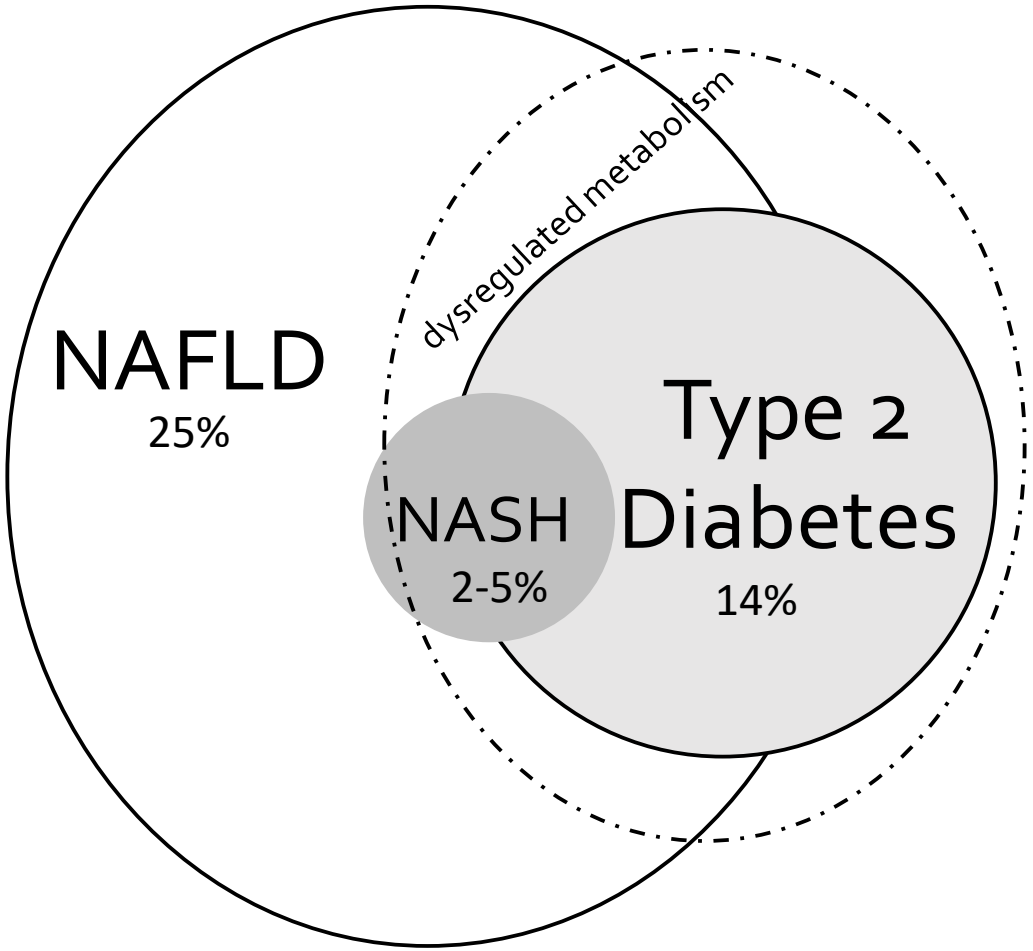
Pharmacology Meets Pathophysiology

CIRIUS therapeutics

Overview

- The overlap/relationship of fatty liver (NAFLD/NASH) and Diabetes Common pathology- Insulin Resistance
- The concept of insulin resistance in human disease (Reaven 1980's)
- The first generation Insulin Sensitizers- emergence of pioglitazone (1985) **Pleotropic pharmacology, Unknown mechanism of action, PPARγ hypothesis**
- Medicinal Chemistry approaches- **mitochondrial** vs nuclear receptor targets
- The surprising discovery of the mitochondrial target as the pyruvate carrier (MPC) and a next-generation of oral insulin sensitizer
- Clinical development of MSDC-0602K as a next-generation insulin sensitizer

Diseases of Metabolic Dysfunction



NAFLD ⇌ **NASH**

- Impaired wound repair
- progressive oxidative damage

Prediabetes (or IGT) ⇌ **Diabetes (T2D)**

- β-cell function
- Counter-regulatory functions

Postprandial insulin secretion is compromised
In T2D, but ***fasting insulin is elevated***

Complex genetics and epigenetics play a role

But the common pathology is Insulin Resistance

Insulin Resistance in Human Disease

"…Based on these considerations the possibility is raised that resistance to insulin-stimulated glucose uptake and hyperinsulinemia are involved in the etiology and clinical course of three related diseases-NIDDM, hypertension, and CAD." Gerald M. Reaven, 1988 Banting Lecture, Diabetes 37:1595-607, 1988

"Of course, I don't believe in the insulin resistance syndrome, except for the fact that the effects of pioglitazone prove that it is so"- private conversation with Stephen R. Bloom circa 1988

A Pleiotropic Effect of "Insulin Sensitizers"

DIABETES CARE, VOLUME 15, NUMBER 8, AUGUST 1992

1992

New Oral Thiazolidinedione Antidiabetic Agents Act as Insulin Sensitizers

CECILIA A. HOFMANN, PHD
JERRY R. COLCA, PHD

Of the 12 million people in the U.S. afflicted with NIDDM (1), nearly

ity of insulin to suppress hepatic glucose production becomes impaired (7), and

NEW AGENTS: THIAZOLIDINEDIONES — Thiazolidinediones represent a new structural class of antidiabetic compounds that were discovered empirically by observing their hypoglycemic effects in animal models of NIDDM (10; Fig. 2). Included in this class are the agents ciglitazone, pioglitazone, englitazone, and CS-045. The latter three agents are now undergoing active testing, and a recent report demonstrated efficacy for treating NIDDM patients (11). Analogues of this class lower plasma glucose levels, as well

Addressing the Insulin Resistance Syndrome

A Role for the Thiazolidinediones

P. Zimmet*

The global epidemic of type 2 diabetes and cardiovascular disease (CVD) is mirrored by increasing prevalence of the Insulin Resistance Syndrome (IRS) or Metabolic Syndrome. Accumulating data indicate that insulin resistance is the common denominator underlying this cluster of related CVD risk factors. Therapeutic interventions that address insulin resistance and other components of the IRS may be of benefit in reducing the significant health and socioeconomic burden presented by diabetes and CVD. Evidence is discussed that the thiazolidinediones, which improve glycemic control by directly targeting insulin resistance, have the additional benefit of improving many of the CVD risk factors in the IRS, and thus have the potential to reduce CVD in patients with type 2 diabetes. (Trends in Cardiovasc Med 2002;

(J. Endocrinol. Invest. 27: 982-991, 2004)

An overview of the beneficial cardiovascular effects of thiazolidinediones

Fadi A El-Atat,
John Nicasio,
Luther T Clark &
Samy I McFarlane†
†Author for correspondence
State University of New York,
450 Clarkson Avenue,
Box 50 Brooklyn, NY, USA
Tel: +1 718 270 3711
Fax: +1 718 270 6358
smcfarlane@downstate.edu

Cardiovascular disease is a major cause of morbidity and mortality in people with
and those with the metabolic syndrome. With the rising prevalence of these disor
is now reaching epidemic proportions around the globe, cardiovascular disease is
expected to rise substantially. Although lifestyle and dietary interventions are the
approaches in the management of diabetes and the metabolic syndrome, pharma
is almost always necessary to achieve optimal control of glycemia, elevated blood
microalbuminuria, dyslipidemia and other associated cardiovascular disease risk fa
Therapeutic agents that have beneficial cardiovascular effects are attractive choic
treating these high-risk patients. Thiazolidinediones have recently gained momen

Annals of Internal Medicine EDITORIAL

Pioglitazone: An Addition to Our Toolbox for Patients With Diabetes and Nonalcoholic Steatohepatitis?

This article was published at www.annals.org on 21 June 2016.

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

doi: 10.1111/1753-0407.12399

2016

Journal of Diabetes •• (2016) ••–••

COMMENTARY

The IRIS (Insulin Resistance Intervention after Stroke) trial: A new perspective on pioglitazone

Highlights
- The TZD, pioglitazone, reduced stroke and MI by 24% in 3876 insulin resistant patients with a history of recent stroke or TIA.
- The progression to diabetes was also reduced by 52% in this group of patients - many of whom had pre-diabetes.
- Pioglitazone is the sole glucose-lowering drug demonstrated to reduce atherosclerotic events.

REVIEW ARTICLE

Thiazolidinediones

A Pharmacological Overview

David R. Owens
University Hospital of Wales and Llandough Hospital NHS Trust, Penarth, UK

DRUG THERAPY

Thiazolidinediones

Hannele Yki-Järvinen, M.D., F.R.C.P.

The Roles of Insulin Resistance, Hyperinsulinemia, and Thiazolidinediones in Cardiovascular Disease

Gabriel I. Uwaifo, MD, Robert E. Ratner, MD

Although it is difficult to distinguish between the relative effects of insulin resistance and hyperinsulinemia, insulin resistance is clearly associated with significantly increased cardiovascular and cerebrovascular risk. This effect is consistent across the spectrum of worsening glycemic control, from the onset of impaired glucose tolerance to the development of clinical diabetes. It is more difficult to discriminate between the roles of elevated circulating insulin and proinsulin levels; the association between insulin levels and cardiovascular risk is weak. The thiazolidinediones (TZDs) significantly improve insulin sensitivity and exert numerous effects on the vascular bed, including improved endothelial function, decreased vascular inflammation, decreased plasma free fatty acid levels, improved dyslipidemic profiles,

The metabolic syndrome described by Reaven and other researchers[1–7] provided a pathophysiologic framework for investigating the increased cardiovascular risk and subsequent development of clinical events related to atherosclerosis. Although the original components of the metabolic syndrome included obesity, hypertension, dyslipidemia, impaired glucose tolerance and diabetes mellitus, it has been presumed that insulin resistance is the central pathogenic basis for the syndrome, with hyperinsulinemia frequently used as its marker.[2,8–16]

The thiazolidinediones (TZDs) are ligands of the peroxisome proliferator-activated receptor-γ (PPAR-γ). These agents significantly improve peripheral insulin

REVIEW ARTICLE

Pleiotropic effects of thiazolidinediones: Taking a look beyond antidiabetic activity

S. Giannini[1], M. Serio[1], and A. Galli[2]
[1]Endocrinology Unit; [2]Gastroenterology Unit, Department of Clinical Pathophysiology, University of Florence, Italy

ABSTRACT. Thiazolidinediones (TZD) [Troglitazone (TRO), Pioglitazone (PGZ), Rosiglitazone, (RGZ)] are a novel class of antidiabetic drugs for patients with Type-2 diabetes mellitus (T2DM) able to decrease blood glucose, working through a reduction

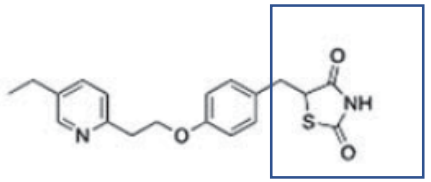
cells, the PPARγ activation by TZD determines modulatory effects on growth factor release, production of cytokine, cell proliferation and migration, extracellular matrix remodeling and control on cell cycle progression and differentiation. In

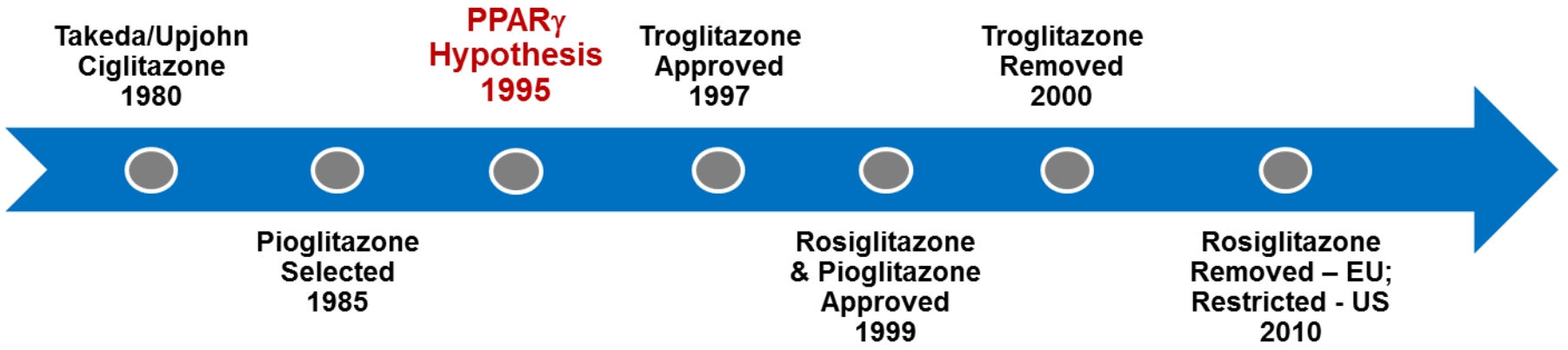
- The mechanism of action of these compounds was not clear
- They were discovered empirically with no concept of mechanism
- More than "insulin sensitizers" they are metabolic modulators

The history of the TZDs

Empirical discovery

- Lowered glucose and lipids
- But also lowered insulin
- "insulin sensitizers" Preserved the pancreas
- Mechanism of Action unknown





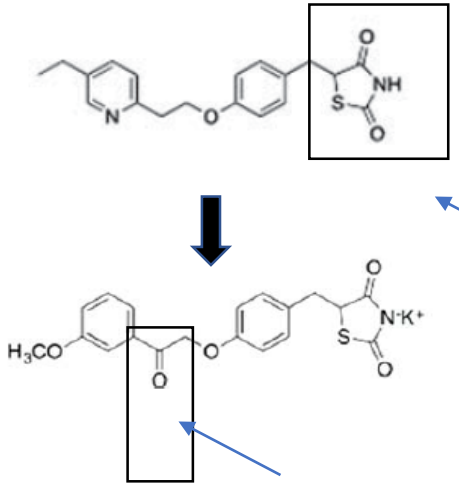
Unlike rosiglitazone, pioglitazone has shown significant CV benefit

- PROActive
- IRIS

- **2012**- Identification of mitochondrial target of TZDs as the mitochondrial pyruvate carrier
- MSDC- PPAR-sparing, MPC-modulating TZDs in development

Approaches to improvement on pioglitazone

Selectively eliminate binding to PPARγ while maintaining pharmacology (keep the TZD ring make improvements)



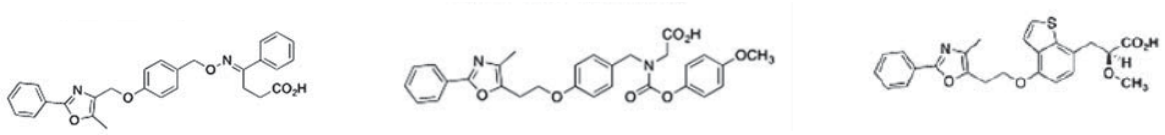
TZD ring

Removes PPAR binding, but keeps the MPC

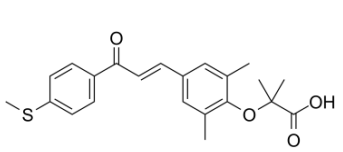
Non PPARs

Removal of TZD and start over
This led to combined agonists of various PPAR transcription factors (γ, α, and then by further design, δ)

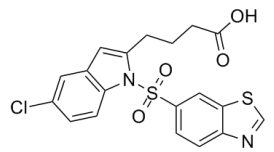
Glitizars, e.g. TAK-559, Muraglitigar,Farglitizar,Aliglitazar, etc



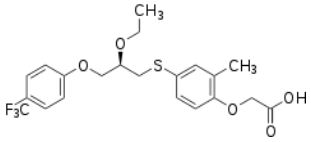
Selected combinations (e.g., Genfit, Inventiva, Cymabay)



Elafibranor α,δ agonist



Lanifibranor α,δ,γ agonist



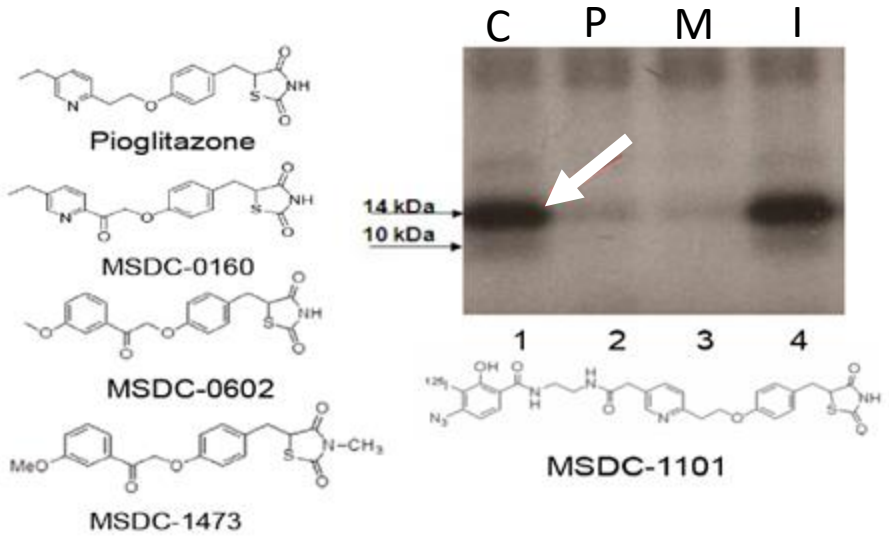
Seladelpar δ agonist

The PPARs

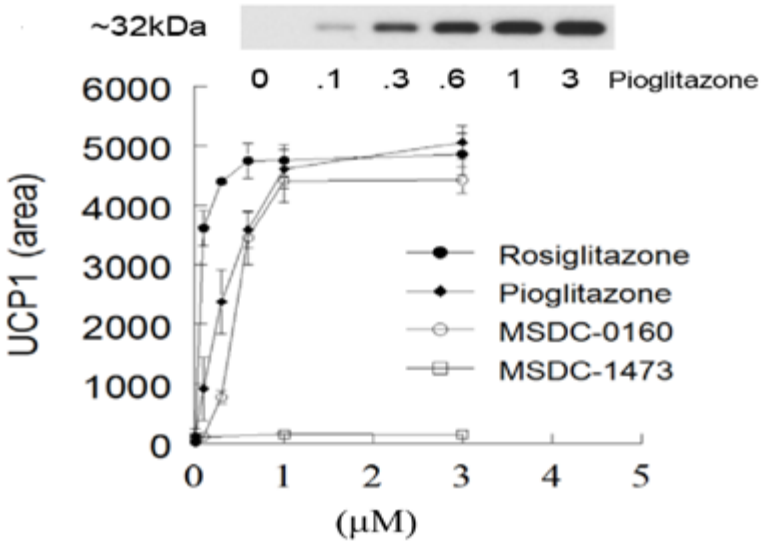
- Colca, J.R. and Kletzien, R.F. (2006). What has prevented the expansion of the insulin sensitizers? Exp. Opin. Invest. Drugs 15:205-210
- Colca J.R., Tanis S.P., McDonald W.G., and Kletzien R.F. (2013) Insulin sensitizers in 2013: new insights for the development of novel therapeutic agents to treat metabolic diseases. Exp. Opin. Invest. Drugs 23: 1-7.
- Tanis SP (2018) PPARγ-sparing thiazolidinediones as insulin sensitizers. Design, synthesis and selection of compounds for clinical development. Bioorg Med Chem. 2018 26(22):5870-5884.

Brief Summary of Road to the MPC

Competition of crosslinking of TZD probe

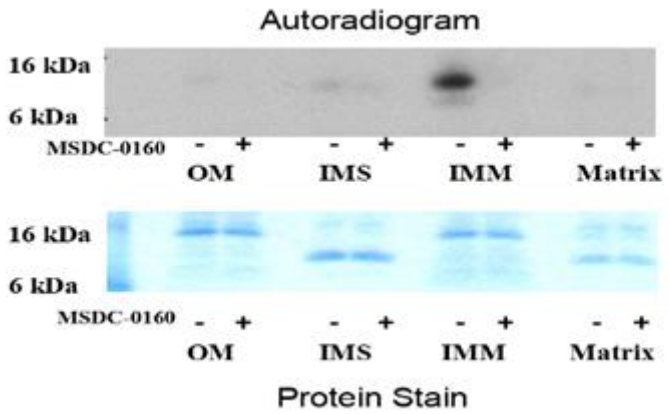


Differentiation of Brown Adipose Tissue

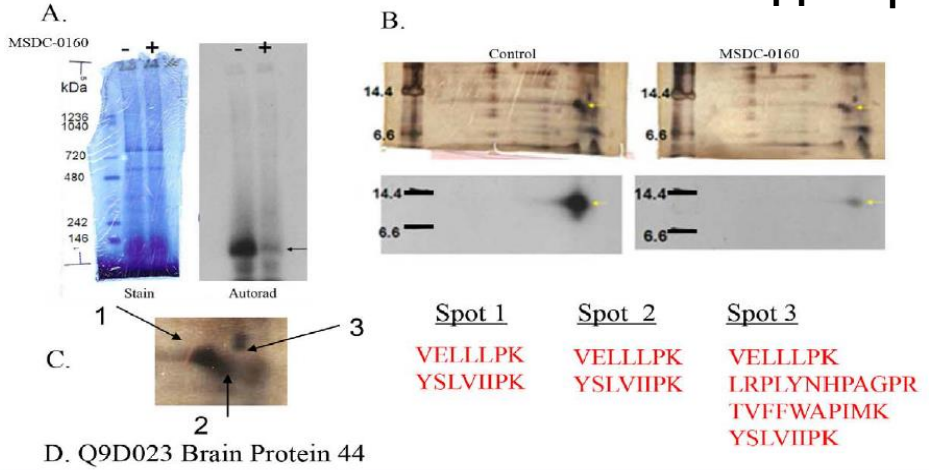


- Selective crosslinking to protein in mitochondrial membranes
- Not competed by inactive analogs

Located in the inner mitochondrial membrane



Purified and identified at the BRP44- mpc2



D. Q9D023 Brain Protein 44

maaagarglratyhrlmdkvelllpkklrplynhpagprtvffwapimkwglvcagladmarpaeklstaqstvlmatgfiws ryslviipknwslfavnffvgsagasqlfriwrynqelkskgiq

Brief Summary of Road to the MPC

Science AAAS

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

Science AAAS

Identification and Functional Expression of the Mitochondrial Pyruvate Carrier
Sébastien Herzig *et al.*
Science **337**, 93 (2012);
DOI: 10.1126/science.1218530

Two independent groups identify BRP44 as a component of the long-sought after mitochondrial pyruvate carrier

PNAS

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 [f]Medicine, University of California at San Diego, La Jolla, CA 92093; [b]Seahorse Bioscience, North Billerica, MA 01862; [c]Veterans Affairs San Diego Healthcare System, La Jolla, CA 92161; [d]Pioneer Valley Life Sciences Institute, Springfield, MA 01107; [e]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)

All active TZDs, including pioglitazone and rosiglitazone show the entry of pyruvate

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

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,[3] Christopher Holley,[1] Hideji Fujiwara,[1] Jean E. Schaffer,[1] Jerry R. Colca,[3] and Brian N. Finck[1]

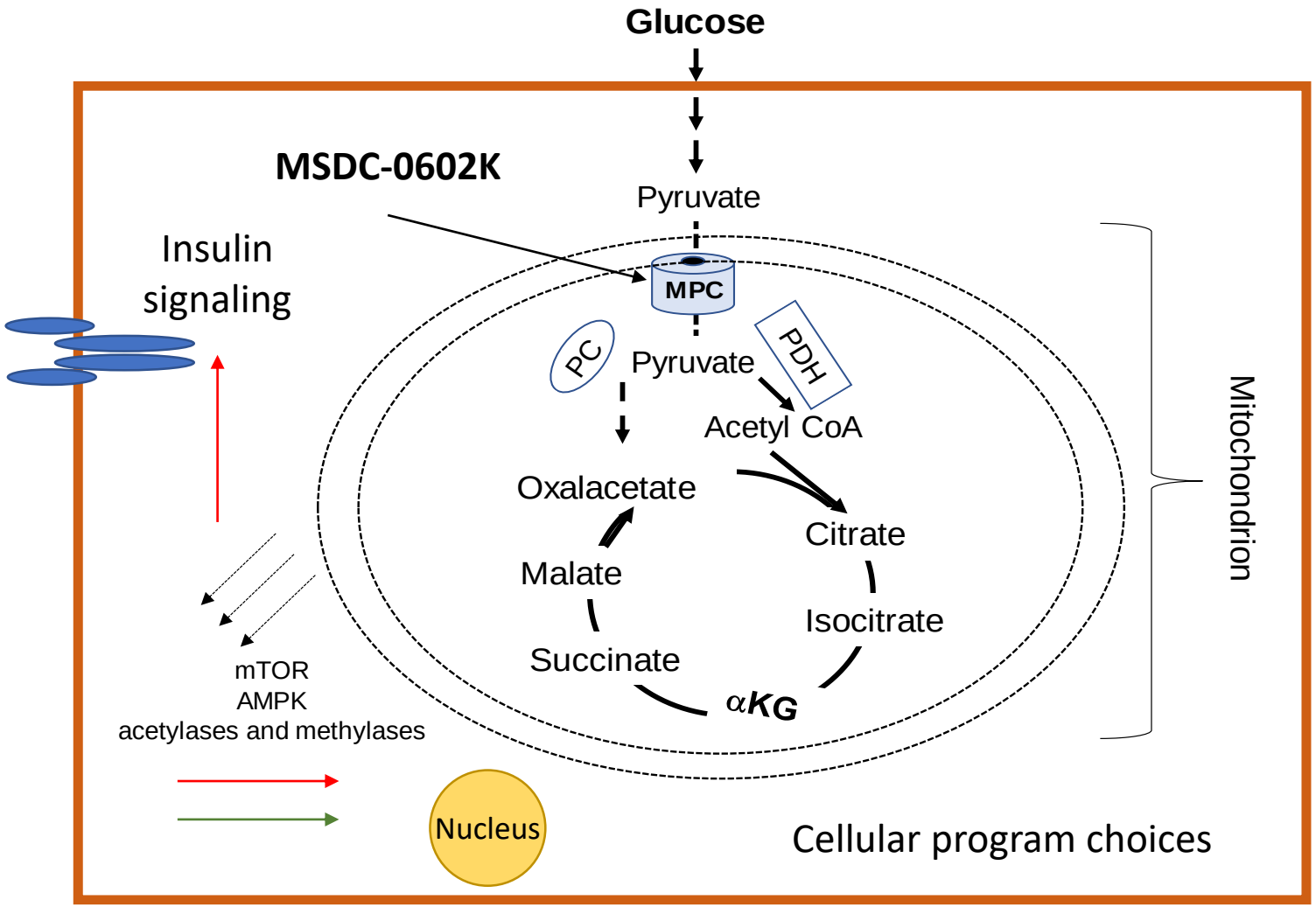
MOLECULAR METABOLISM

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,*]

Liver-specific KO of MPC components protects against fatty liver

Mechanism of Action



- Excess nutrients drive a program of increased storage and insulin resistance (MPC is the gate-keeper)
- Pyruvate carboxylase (PC) and pyruvate dehydrogenase complexes (PDH) act on mitochondrial pyruvate maintaining carbon flow in the TCA (citric acid cycle)
- Downstream pathways includes nutrient sensors and transcriptional networks

- **Slowing pyruvate entry rebalances metabolic signals, reversing these signals**

MOA- Undoing the over nutrition signal

Development Pathway
Followed our experience with pioglitazone

- Cellular assays with BAT differentiation and mitochondrial effects
- Mouse models with direct comparison to pioglitazone

Over 100 analogs examined for similarity to pioglitazone, except for selection against PPARγ binding

→ MSDC-0602 → MSDC-0602K

↓

- Preclinical development followed pioglitazone pathway
- Phase 1b and 2a clinical trials direct comparison to 45 mg pioglitazone to established exposures needed for similar activity on glucose metabolism/insulin

↓

Phase 2b conducted for 1 year at 3 exposures based on Phase 2a study in T2D

Phase 2b dose-ranging study

Research Article
NAFLD and alcohol-related liver diseases

JOURNAL
OF HEPATOLOGY

Insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled phase IIb study

Stephen A. Harrison[1,*], Naim Alkhouri[2], Beth A. Davison[3], Arun Sanyal[4], Christopher Edwards[3], Jerry R. Colca[5], Bo Hyun Lee[5], Rohit Loomba[6], Kenneth Cusi[7], Orville Kolterman[8], Gad Cotter[3], Howard C. Dittrich[5]

[1]*Hepatology, Radcliffe Department of Medicine, University of Oxford, UK;* [2]*Texas Liver Institute, San Antonio, TX, USA;* [3]*Momentum Research, Inc., Durham, NC, USA;* [4]*Virginia Commonwealth University School of Medicine, Richmond, VR, USA;* [5]*Cirius Therapeutics, Inc., San Diego, CA, USA;* [6]*NAFLD Research Center, University of California at San Diego, La Jolla, CA, USA;* [7]*University of Florida, Gainesville, FL, USA;* [8]*Pendulum Therapeutics, San Francisco, CA, USA*

Table 1. Baseline characteristics and concomitant medications at study entry of patients randomized in the EMMINENCE study.*

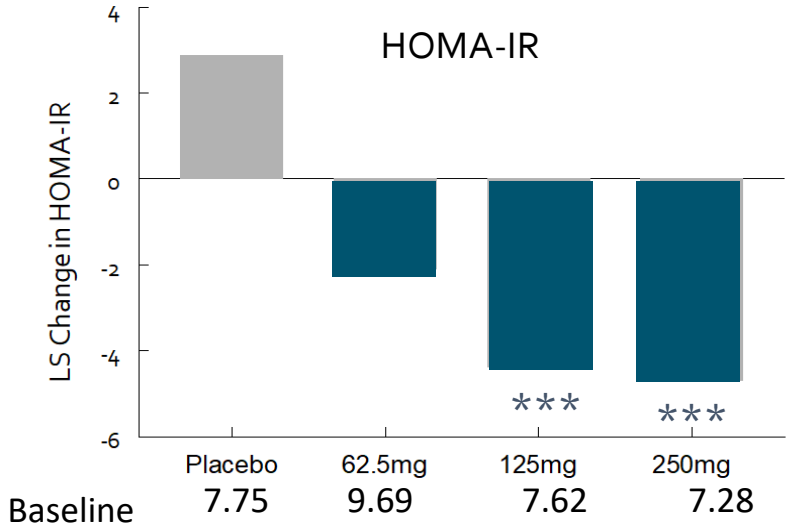
Disease	Placebo (n = 94)	MSDC-0602K 62.5 mg (n = 99)	MSDC-0602K 125 mg (n = 98)	MSDC-0602K 250 mg (n = 101)	Total (N = 392)
Age, years (mean [SD])	54.6 [11.21]	56.9 [10.28]	56.0 [10.89]	56.8 [10.42]	56.1 [10.70]
Sex (M:F)	43:51	43:56	35:63	43:58	164:228
Race (Black or African American:White)	5:85	3:93	3:91	3:91	14:360
Ethnicity (Hispanic or Latino:not Hispanic or Latino)	25:69	32:67	29:69	33:68	119:273
Weight, kg (mean [SD])	102.08 [21.527]	98.93 [20.185]	99.95 [19.175]	98 [18.871]	99.7 [19.922]
BMI, kg/m^2 (mean [SD])	35.03 [5.574]	34.68 [5.177]	35.93 [6.121]	35.03 [6.118]	35.16 [5.761]

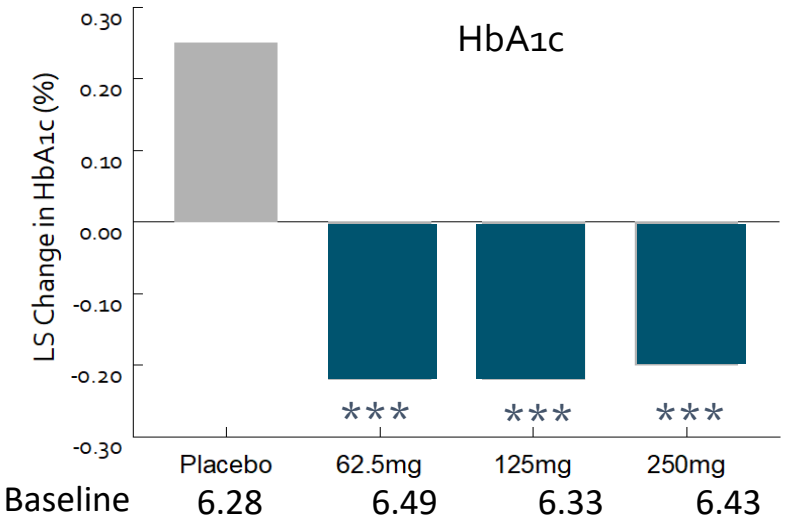
- 3 doses were chosen to backed the exposures that are achieved in clinical trials with 45 mg pioglitazone.
- Given once daily for 1 year
- Approximately half of the subjects in each group also had T2D

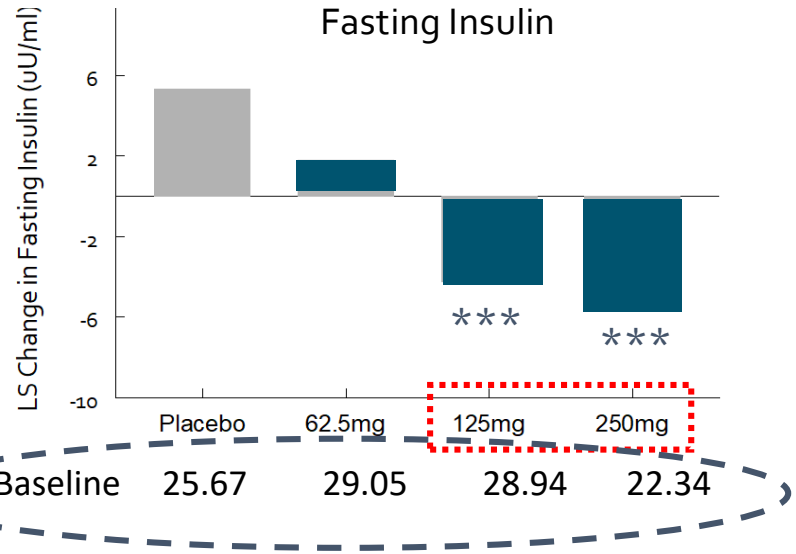
- As predicted from preclinical and Phase 2a studies, full insulin sensitizing pharmacology was obtained at the middle dose.
- No dose limiting issues and no edema was seen at highest dose, which produced twice the exposures of drug and active metabolite

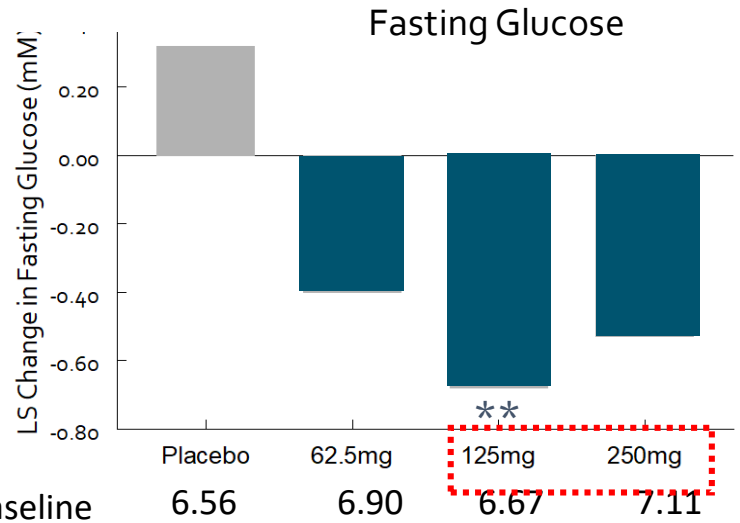
Glycemic Parameters LS Change from Baseline

(12 month endpoint)







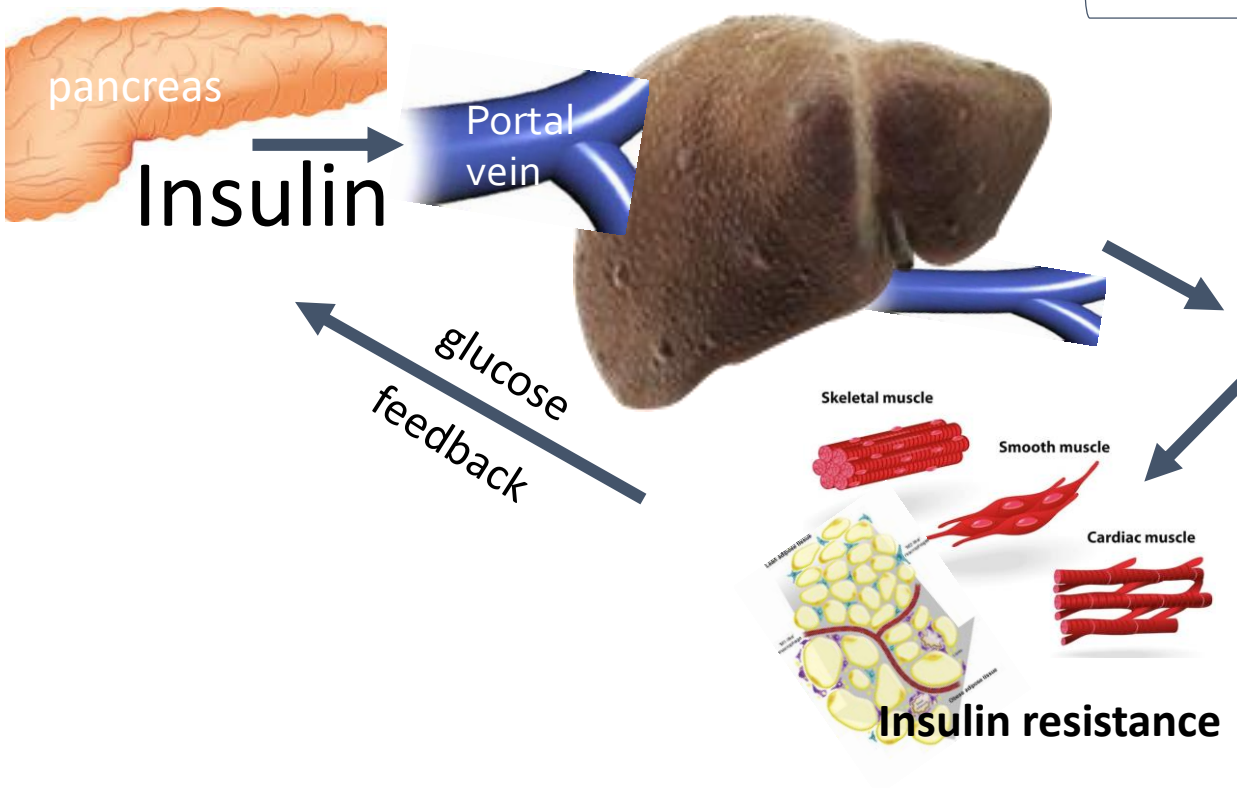


Normal fasting insulins are <10 µU/ml

Full pharmacology is achieved at the 125 and 250 mg doses

In the 4-7 µM range, consistent with the with the MPC hypothesis

Insulin Resistance and decreased hepatic clearance contribute to hyperinsulinemia



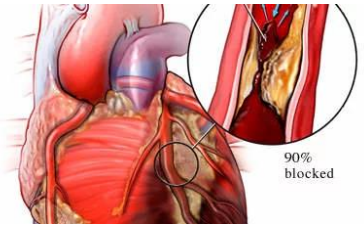
Overnutrition stimulus

Hyperinsulinemia

- Secreted
- Reduced clearance

[Insulin and other related variants- inflammation, lipoproteins, etc]

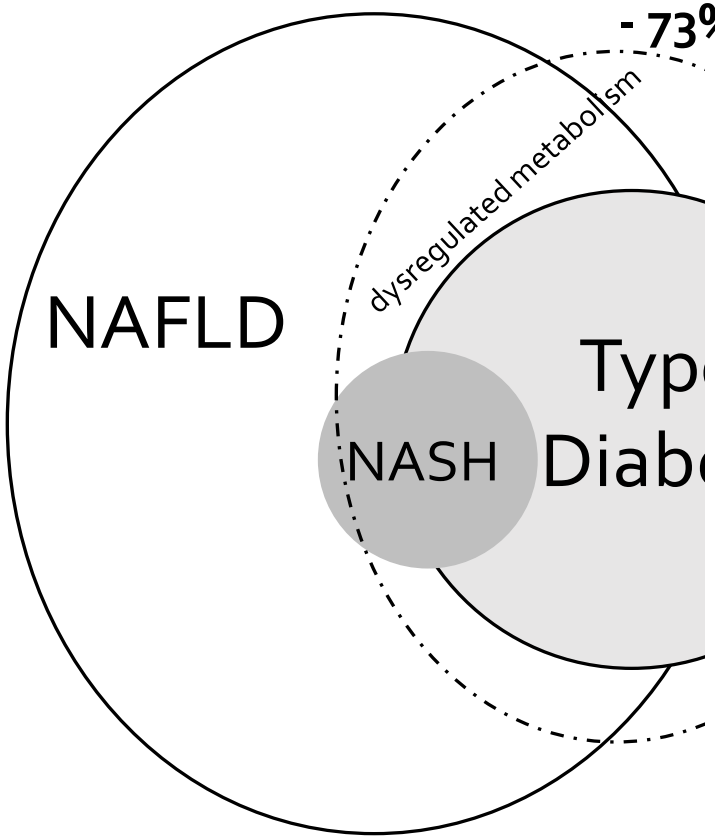
Macrovascular disease

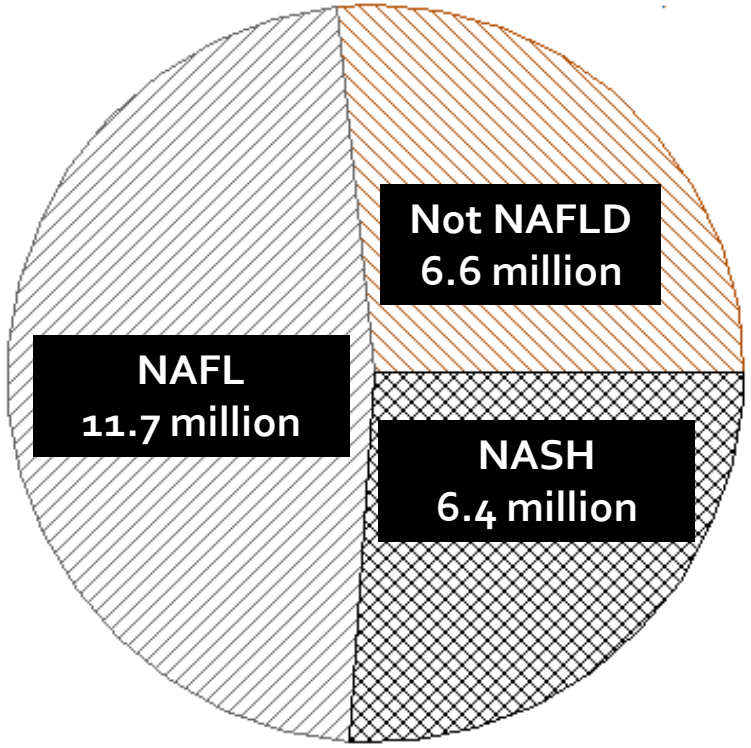


- Increase in peripheral insulin is progressive with liver damage
- Pancreas compensates by increasing insulin secretion
- Failure to completely compensate, loss of beta cell function, results in rising glucose and eventually T2D

Diseases of Metabolic Dysfunction

US T2D Prevalence is 24.7 million (9.9%)
- 73% of T2D patients have fatty liver*





	NAFLD (NASH + NAFL)	NASH
Total	18.1 million	6.4 million
CV Deaths	**1,368,955**	**883,469**
Liver Deaths	812,230	794,638
Liver Transplants	64,878	64,013

*2017 estimate, Younossi *et al*, *Diabetes Care* 2020;43:283-289

- CV risk elevated across the spectrum of fatty liver disease
- Highest risk subjects can be identified by dysregulation of glucose metabolism, elevated fasting insulin, and markers of liver injury

Conclusions

- There is a need for an insulin sensitizer to treat the insulin resistance and hyperinsulinemia seen in NAFLD/NASH and Type 2 diabetes
- It has proven difficult to improve upon the first generation insulin sensitizer pioglitazone. The mitochondrial target, important for overcoming the effects of overnutrition had been overlooked.
- Location and identification of the mitochondrial target as the MPC has made possible the development of a new class of insulin sensitizers that avoid direct activation of nuclear receptors and dosing to full effect.
- MSDC-0602K phase 2b trial confirmed that it can be dosed to full insulin sensitizing pharmacology without dose limiting side effects.
- Reduction of insulin resistance and hyperinsulinemia may be useful to lower cardiovascular complications of these overlapping pathologies