## BIOGRAPHICAL SKETCH

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NAME: Ralph A. DeFronzo, MD

eRA COMMONS USER NAME (credential, e.g., agency login): DEFRONZO

POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Yale University | BS | 1964 | Biology/Biochem |
| Dartmouth Medical School | BMS | 1967 | Medicine |
| Boston College Graduate School | MS | 1969 | Biochemistry |
| Harvard Medical School | MD | 1969 | Medicine |
| Johns Hopkins Hospital | | 1969-71 | Intern/Resident |

**A. Personal Statement:** I have spent over 40 years examining the pathogenesis of type 2 diabetes mellitus (T2DM) and developing innovative approaches to this common metabolic disease which is associated with significant morbidity and mortality. I developed the euglycemic insulin and hyperglycemic clamp techniques (AJP, 1979) which, to this day, remain the gold standard for measuring insulin resistance and insulin secretion, respectively, and adapted these techniques to study glucose metabolism in small animals including mice and rats. Our group was the first to combine radioisotopes with the insulin clamp in man to separate the individual contributions of muscle and liver to whole body insulin resistance. We also were the first group to combine limb catheterization, indirect calorimetry, vastus lateralis muscle biopsy, and magnetic resonance imaging to quantitate the intramyocellular pathways responsible for impaired insulin action in T2DM, and all of these techniques have been adapted to study small animals. Our group also was the first to demonstrate that the insulin signaling pathway was markedly impaired in T2DM and obese individuals and that the site of the defect resided at the level of insulin receptor substrate (IRS)-1 (JCI, 2000). My work also has demonstrated the pivotal role of lipotoxicity (increased muscle long chain fatty acyl CoAs) in the development of both muscle and hepatic insulin resistance and the reversal of lipotoxicity by the thiazolidinedione class of drugs. I have published extensively on the link between hypertension/dyslipidemia/endothelial dysfunction/lipotoxicity and the insulin resistance (metabolic syndrome). This work has been consecutively funded by the NIH for 42 years (1975-2017) and by the VA since I moved to San Antonio in 1989. For this work, I have received the lifetime scientific achievement awards from the American Diabetes Association (Banting Award, 2008) and the European Association for the Study of Diabetes (Claude Bernard Award, 2008) and am the recipient of the 2017 Harold Hamm International Prize for Biomedical Research in Diabetes. I directed the multicenter metformin trials that resulted in the approval of this medication by the FDA (NEJM, 1995) and was the principal investigator of the recently completed ACT NOW study which demonstrated an 72% decrease in the conversion rate of IGT to T2DM with pioglitazone (NEJM, 2011). I also am responsible for the construction of the Texas Diabetes Institute (2000), which cares for approximately 10,000 diabetic patients annually. At the national level, I have served on virtually every committee of the American Diabetes Association, including director and co-director of the ADA annual scientific meeting. In summary, I have a longstanding, well-documented track record of scientific achievement and clinical service to the diabetic community. My work has been innovative, creative, ground-breaking and, most importantly, reproduced by investigators throughout the world. With my background in diabetic nephropathy and work with the SGLT2 inhibitor class of drugs, I can be a valuable asset for your NIH O'Brien Kidney Center Application.

**B. Positions and Honors**

1965-1967 Dartmouth Medical School, Hanover, NH
1967-1969 Harvard Medical School, Boston, MA
1969-1971 Resident, Johns Hopkins Hospital
1971-1973 Endocrine Fellow/Clinical Associate, Baltimore City Hospital & Gerontology Res Ctr, NIMHCD
1973-1975 Renal Fellow, Hospital of University of Pennsylvania
1975-1988 Assistant/Associate Professor of Medicine, Yale University School of Medicine
1985-1988 Director, Diabetes Clinic, West Haven VA Hospital, West Haven, CT
1988-present Professor of Medicine, Chief of Diabetes Division, Univ of Texas Health Science Center and South Texas Veterans Health Care System, Audie L. Murphy Division, San Antonio
1988-present Director, Diabetes Research Unit, CRC, UTHSCSA
1996-present Deputy Director, Texas Diabetes Institute

**Professional Honors**

1975-present Member, Am Fed Clin Res, Am Diabetes Assoc, Am Soc Nephrol, International Soc Nephrol
1975/1976 Board Certification in Internal Medicine and Nephrology
1980-present Member, American Society of Clinical Investigation
1983-1988 Editor, Diabetes/Metabolism Reviews
1984-1986 Chairman, Professional Education Committee, American Diabetes Association
1986-1999 National Diabetes Advisory Board
1987 Lilly Award, American Diabetes Association
1988 Banting Lecture, Canadian Diabetes Association
1988-1998 Editor, Diabetes Reviews, American Diabetes Association
1990-1996 Associate Editor, American Journal of Physiology (Endocrinology and Metabolism)
1990-1992 President, Texas Affiliate, American Diabetes Association
1989-1991 Chairman, National Research Policy Committee, American Diabetes Association
1991, 1995 Editor, International Textbook of Diabetes, John Wiley (1993, 1997, 2003, 2011, 2015)
1991-1994 Board of Directors, American Diabetes Association
1991-1994 Chairman, Scientific and Medical Oversight Committee, ADA
1993–1998 Member, Editorial Board, Diabetologia
1998,2000 Director, ADA Workshop on Molecular Biology of Diabetes Mellitus
2001 Albert Renold Award, American Diabetes Association
2003 Novartis Award, Outstanding Clinical Investigator, North America
2004-2013 Ralph A. DeFronzo Postdoctoral Fellowship, Mexican Society of Endocrinology & Nutrition
2007 Johns Hopkins Society of Scholars
2007 Distinguished Leader in Insulin Resistance Award, 5th World Congress on Insulin Resistance,
2008 Claude Bernard Award for Lifetime Scientific Achievement, EASD, Rome, Italy
2008 Italian Diabetes Mentor Prize, Italian Diabetes Society, Rome, Italy 2008
2008 Banting Award for Lifetime Scientific Achievement, ADA, San Francisco, June 2008
2009 Philip Bondy Lecture, Yale University School of Medicine, New Haven, CT
2010 Australian Diabetes-Endocrine Honorary Lecture, Sydney, Australia
2012 CODHy: Outstanding Clinical Investigator Award, Barcelona, Spain
2014 American College of Nutrition: Outstanding Scientific Achievement Award, San Antonio, TX
2015 Samuel Eichold Memorial Award for Contributions in Diabetes, ACP, Boston, April 2015
2015 George Cahill Memorial Lecture, University of Montreal, Montreal, Canada, February 2015
2015 Priscilla White Memorial Lecture, Joslin Clinic & Brigham Hospital, Boston, MA, April 2015
2016 ACE Distinction in Endocrinology Award, Annual ACE/AACE Meeting

**C. Contributions to Science (from > 800 publications in peer reviewed journals)**

**1. Elucidation of the pathogenesis of type 2 diabetes mellitus (T2DM): defining the role of insulin resistance at the whole body, organ, cellular, and biochemical/molecular levels.**

Using the euglycemic insulin clamp technique in combination with radioisotopes, indirect calorimetry, leg and hepatic vein catheterization, magnetic resonance spectroscopy, and muscle biopsy, we conclusively demonstrated, for the first time, that: (i) both muscle and liver of T2DM patients are severely resistant to insulin; (2) excess hepatic glucose production via the gluconeogenic pathway was the primary disturbance responsible for fasting hyperglycemia; (3) muscle insulin resistance and impaired hepatic glucose uptake were the primary factors responsible for postprandial hyperglycemia; (4) defects in muscle insulin signal transduction, glucose

transport, and glucose phosphorylation resulted in major defects in insulin-stimulated glycogen synthesis and glucose oxidation; (5) glucose-mediated glucose uptake was severely impaired in T2DM patients; (6) mitochondrial dysfunction was associated to insulin resistance in T2DM.

The euglycemic insulin clamp was developed in my laboratory and we were the first to use radioisotopes in humans to demonstrate that fasting hyperglycemia resulted from excessive HGP. The triple tracer/forearm catheterization technique and hexokinase activity/mRNA/protein assays were developed in our lab and we were the first to demonstrate *in vivo* in human muscle the severe defects in glucose transport and phosphorylation. We also were the first to demonstrate that the insulin signaling pathway (IRS-1/PI-3 kinase/Akt) was severely impaired in T2DM.

DeFronzo RA, et al, AJP 237:E214-E223, 1979; DeFronzo RA, et al, JCI 76:149-155, 1985; Pendergrass M, et al, AJP 292:E92-100, 2007; Cusi K, et al, JCI 105:311-320, 2000; Pendergrass M, et al, Diabetes 47:387-394, 1998; Ferrannini E, et al, Metabolism 37:79-85, 1988; DeFronzo RA. Diabetes 58:773-95, 2009.

**2. Elucidation of the pathogenesis of T2DM: defining the role of impaired beta cell function.**

Our group was amongst the first to define the contributions of impaired beta cell function (insulin secretion) and insulin resistance in the natural history of T2DM. From the San Antonio Metabolism (SAM) and VAGES Studies, we defined, using the hyperglycemic clamp, OGTT, and euglycemic insulin clamp: (i) the need to distinguish between insulin secretion (plasma C-peptide response) and beta cell function ($\Delta$C-peptide/$\Delta$glucose $\div$ insulin resistance) in evaluating the health of the beta cell; (ii) the marked reduction ($\geq$50%) in beta cell function in individuals in the upper tertile of NGT and even more marked reduction ($\geq$80%) in individuals with IGT; (iii) the inverted U-shaped curve (Starling's Curve of the Pancreas) relating insulin secretion to the FPG. Our work was the first to demonstrate that the insulin secretion/insulin resistance (disposition) index worked well when utilizing the plasma insulin response (sum of insulin secretion plus insulin clearance) but broke down when using insulin secretion (i.e. C-peptide response). Our lab was the first to define the very distinct pathogenic mechanisms responsible for IFG (impaired first phase insulin secretion and hepatic insulin resistance) versus IGT (impaired second phase insulin secretion and muscle insulin resistance). Our lab also was the first to conclusively demonstrate the role of both lipotoxicity and glucotoxicity in the demise in beta cell function in patients with T2DM.

All of the techniques and analyses used in these studies were developed in my laboratory and the study designs/patient populations were part of grants funded by the NIH, VA Health Care System, and ADA.

DeFronzo RA. Diabetes 37:667-687, 1988; Gulli G, et al, Diabetes 41:1575-1586, 1992; Abdul-Ghani M, et al, Diabetes 55:1430-1435, 2006; Ferrannini E, et al, JCEM 90:493-500, 2005; Abdul-Ghani M, et al, Diabetes Care 29:1130-1139, 2006; Kashyap S, et al, Diabetes 52:2461-2474, 2003; DeFronzo RA, et al, JCEM 99:3774-81, 2014

**3. Role of Lipotoxicity in the Development of Insulin Resistance and Beta Cell Failure in T2DM**

Using the insulin clamp technique, we were the first to demonstrate that a physiologic increase in the plasma free fatty acid (FFA) concentration for as little as 2-4 hours in NGT subjects caused severe insulin resistance in muscle due to defects in both glucose oxidation and glycogen synthesis. We were the first to demonstrate that a physiologic increase in plasma FFA in NGT subjects markedly impaired insulin signaling (IRS-1, PI-3 kinase, Akt) by causing serine phosphorylation of IRS-1. We further demonstrated, using MRS, that intramyocellular lipid content was increased in obese NGT and obese T2DM subjects and was closely related to the severity of insulin resistance. We also demonstrated in muscle biopsies from obese NGT and T2DM subjects an increase in long chain FACoAs, DAG, and ceramides and that the increase in these lipotoxic molecules was closely associated with the severity of insulin resistance. Reduction of plasma and intramyocellular lipid content with acipimox (inhibits lipolysis) and with pioglitazone both improved muscle insulin sensitivity in association with a reduction in intramyocellular lipid content and muscle long chain FACoA levels. We also demonstrated that a physiologic increase in plasma FFA concentration markedly inhibited mitochondrial ATP synthesis, oxidation, and inner membrane potential in NGT subjects and stimulated basal HGP (gluconeogenesis) and impaired the suppression of HGP production by insulin. We were the first to demonstrate that chronic physiologic elevation (48 hours) in plasma FFA markedly impaired insulin secretion in NGT genetically predisposed individuals (offspring of two diabetic parents).

All of these studies were designed by me, were carried out with techniques developed in my lab, and were based upon my seminal observations that a sustained physiologic increase in plasma FFA concentration caused severe muscle insulin resistance and impaired insulin secretion.

Thiebaud D, et al, Metabolism 21:1128-1136, 1982; Belfort R, et al, Diabetes 54:1640-1648, 2005; Bajaj M, et al, Diabetes 54:3148-3153, 2005; Bajaj M, et al, JCEM 95:1916-1923, 2010; Gastaldelli A, et al, JCEM 89:3914-3921, 2004; Gastaldelli A, et al, J Clin Endocrinol Metab 91:806-812, 2006; Kashyap S, et al AJP 287:E537-E546, 2004; DeFronzo RA et al, Diabetologia 53:1270-87, 2010.

**4. Role of Glucotoxicity in the Development of Insulin Resistance and Beta Cell Failure in T2DM**

In vitro studies provided evidence that elevated medium glucose levels caused insulin resistance in cultured myocytes and adipocytes. Our studies were the first to provide *in vivo* evidence for the role of glucotoxicity in causing insulin resistance in muscle and impairing beta cell function. Using the partially pancreatectomized diabetic rat, we showed that inhibition of renal glucose reabsorption with phlorizin (has no direct effects on insulin sensitivity or insulin secretion) completely normalized glucose tolerance, insulin sensitivity, and insulin secretion. Further, we demonstrated that the improvement in insulin resistance was the result of enhanced GLUT-4 translocation. We have reproduced all of these findings in T2DM patients using a highly specific SGLT2 inhibitor. Many additional findings have emanated from these studies: (i) reduction in plasma glucose conc with the SGLT2 inhibitor was offset by ~50% by a stimulation of EGP; (ii) stimulation of EGP was associated with an increase glucagon and inhibition of insulin secretion; (iii) glucosuric effect of the SGLT2 inhibitor was offset by a marked increase (~40-50%) in glucose reabsorption by the SGLT1 transporter; (iv) the renal mechanism via which the SGLT2 inhibitor induced glucosuria was related to a decrease in plasma glucose threshold (<40 mg/dl) at which glucose spills into the urine.

The concept of treating T2DM with an inhibitor of renal glucose transport was generated from my micropuncture experience as a renal fellow and all of the techniques and study designs used in the rat and human studies to validate the glucotoxicity hypothesis were developed by me.

Rossetti L, et al, JCI 79:1510-1515, 1987; Rossetti L, et al, JCI 80:1037-1044, 1987; Kahn B, et al, JCI 87:561-570, 1991; Merovci A, et al, JCI 124:509-14, 2014; Merovci A, et al, JCEM 100:1927-32, 2015; DeFronzo RA, et al, Diabetes Care 36:3169-3176, 2013; Abdul-Ghani MA, et al, Diabetes 62:3324-8, 2013.

**5. Treatment of T2DM: A Pathophysiologic Approach**

I have been actively involved in the development of new techniques and approaches for the treatment of T2DM for over 40 years. I personally designed and supervised all of the studies that resulted in approval of metformin by the FDA and elucidating its mechanism of action. I was intimately involved with studies which defined the potent effect of thiazolidinediones to improve beta cell function and enhance insulin sensitivity in liver and muscle. In muscle we were the first to show that thiazolidinediones markedly enhanced insulin signal transduction (IRS-1, PI-3 kinase, Akt) and reduced the content of toxic lipid metabolites by increasing PGC-1 and mitochondrial genes involved in lipid oxidation. We also were the first to demonstrate that pioglitazone reduced liver fat content and improved NASH. We also were the first to show that thiazolidinediones had a potent effect to increase and preserve beta cell function and markedly reduced (by 72%) the conversion of IGT to T2DM (ACT NOW study). We also were the first to completely define the mechanism of action of GLP-1 receptor agonists (exenatide) on oral glucose tolerance in T2DM subjects (50% reduction in glucose absorption and 50% suppression of HGP; the reduction in HGP was explained by a decrease in glucagon [50%] and increase in insulin [50%] secretion). We also demonstrated that the major mechanism of action of DPP4 inhibitors resulted from inhibition of glucagon secretion leading to suppression of HGP. I also was responsible for the development of the SGLT2 inhibitor class of drugs for the treatment of T2DM (see #4 above). Most recently, we demonstrated the marked superiority of a pathophysiologic triple therapy approach to the treatment of T2DM (GLP-1 RA to improve beta cell function; pioglitazone to improve insulin resistance and beta cell function; metformin to suppress HGP) compared to the stepwise approach advocated by most national/international diabetes organizations (start with metformin, then add a sulfonylurea, then add insulin) with respect to reduction in HbA1c, weight gain, incidence of hypoglycemia, improvement in beta cell function, and improvement in insulin resistance.

Reasner CA, et al, Contemp Int Med 6:30-40, 1994; Abdul-Ghani MA, et al, Diabetes Obes Metab 17:268-275, 2015; Cervera A, et al, AJP 294:E846-E852, 2008; Balas B, et al, JCEM 92:1249-1255, 2007; Coletta DK, et al, Diabetologia 52:723-32, 2009; Bajaj M, et al, JCEM 95:1916-1923, 2010; Miyazaki Y, et al, Diabetes 52:1943-1950, 2003 DeFronzo RA, et al, NEJM 364:1104-15, 2011; Gastaldelli A, et al, AJP 292:E871-883, 2007; Belfort R, et al, NEJM 355:2297-2307, 2006; Merovci A, et al, JCI 124:509-14, 2014.

All of the above studies were designed and carried out by me using techniques developed in my laboratory.

**List of Published Work in My Bibliography:**
**https://www.ncbi.nlm.nih.gov/pubmed/?term=defronzo (descending order)**

**D. Additional Information: Research Support and/or Scholastic Performance**

**1. NIH (RO1DK24092) – Preservation of Beta Cell Function in Prediabetes: IGT and IFG**

Role: Principal Investigator Dates: 10/82 to 6/22

Aim: To examine the effect of various pharmacologic interventions on beta cell function, insulin sensitivity, and glucose tolerance status in individuals with isolated impaired glucose tolerance and impaired fasting glucose.

**2. ADA Fellowship - ADA Mentor Minority-Based Postdoctoral Fellowship Program**

Role: Principal Investigator Dates: 07/02 to 12/17

Aim: This project provides stipend support to minority postdoc fellows to receive training in diabetes research.

**3. NIH - S-GRD-1516-MW33/U01DK098246** GRADE Study Dates: 01/01/13 - 06/30/18

Title: Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study

Role: Co-Investigator (PI: John M. Lachin, MD)

Aim: Comparison of the relative attributes, including the durability of the glycemia-lowering effects, adverse effects, effects on CVD risk factors and quality-of-life, tolerability and cost-effectiveness, of five commonly used anti-diabetic medications with different glucose lowering mechanisms, when used in combination with metformin in metformin-treated and drug-naive patients with recent-onset type 2 diabetes (n=6500). This grant has no overlap with the current NIH grant.

**4. NIH - 1R01DK103841-01A1** Dates: 09/01/15-08/31/18

Role: Principal Investigator

Durability of Early Combination Therapy Versus Conventional Therapy in New Onset T2DM

This grant compares a therapeutic approach for T2DM based upon pathophysiology versus the standard ADA stepwise approach with metformin followed by a sulfonylurea and then insulin. This grant has no scientific or budgetary overlap with the current NIH grant.

**5. NIH - 1R01 DK107680-01A1** Dates: 07/01/16-06/30/21

Role: Principal Investigator

SGLT2 Inhibition and Stimulation of Endogenous Glucose Production

In the present grant we will define the organ (liver and/or kidney) responsible for the increase in EGP and the mechanism(s) (stimulation of glucagon secretion, inhibition of insulin secretion, activation of the renal nerves) responsible for the rise in EGP. We also will examine whether a GLP-1 receptor agonist, by inhibiting glucagon/increasing insulin secretion, can block the rise in EGP following SGLT2 inhibition.

OVERLAP: None

**6. NIH - U01 DK085524** Dates: 09/01/15-04/30/20

Role: Sub-Award PI

Discovery of Functional Variants in Type 2 Diabetes Genes in Mexican Americans

This proposal aims to build on and expand the research activities of the T2D-GENES consortium. A better understanding of the genetic contribution to diabetes development will provide novel approaches for the characterization, treatment and potential prevention of this costly disease.

OVERLAP: None