BIOGRAPHICAL SKETCH

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NAME: **ADOLFO GARCIA-OCANA**

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

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
Universidad Autonoma of Madrid, Spain	BSc	06/1987	Biology
Universidad Autonoma of Madrid, Spain	PhD	04/1994	Biochemistry & Molecular Biology
Yale University School of Medicine	Postdoc	12/1998	Metabolism
University of Pittsburgh School of Medicine	Res. Assoc.	04/2001	Diabetes

A. Personal Statement.

I have a longstanding interest in growth factors, hormones, small molecules and intracellular signaling pathways involved in pancreatic beta cell growth, survival and function. My lab showed that hepatocyte growth factor (HGF) increases beta cell proliferation and beta cell mass in vivo and improves islet transplantation by reducing the amount of islets required for successful blood glucose normalization. A thorough search of signaling pathways that could enhance beta cell regeneration uncovered Protein Kinase C ζ (PKC ζ) as a novel key kinase involved in growth factor- and nutrient-mediated beta cell replication. Physiologically, PKC ζ participates in the adaptive β-cell proliferation and expansion induced by mild hyperglycemia (glucose-infusion) and high fat diet feeding. PKC ζ controls the activation of mTOR, the phosphatase PP2A and the transcription factor Myc. In collaboration with Drs. Andrew F Stewart and Robert DeVita, we have recently discovered a new family of human beta cell regeneration drugs based on the alkaloid harmine. Harmine alone or in combination with the clinically-used GLP-1R agonists remarkably enhances human beta cell mass in vivo in mice transplanted with human islets.

I have strong expertise in intracellular signaling, human islet biology, human islet transplantation, mouse models of diabetes, and the generation and phenotypic characterization of genetically-modified mouse models. I currently serve as Core Director of the Human Islet and Adenovirus Core of the Einstein-Sinai Diabetes Research Center. The Core provides key advice, methods, technology and infrastructure to assist investigators in the use of islets for research, which will further our understanding of normal and pathophysiologic islet cell growth and function. Importantly for this proposal, I have expertise in in vivo analysis of beta cell growth, survival and function and the generation and characterization of animal models of diabetes. The following peer-reviewed publications specifically highlight my expertise and qualifications:

a. P. Wang, J.C. Alvarez-Perez, D.P. Felsenfeld, H. Liu, S. Sivendran, A. Bender, R. Sanchez, A. Kumar, D.K. Scott, A. Garcia-Ocaña, A.F. Stewart. A high-throughput chemical screen reveals that harmine-mediated inhibition of DYRK1A increases human pancreatic beta cell replication. ***Nat Medicine***, 21(4):383-8, 2015. PMCID: PMC4690535

b. P. Wang, E. Karakose, H. Liu, E. Swartz, C. Ackeifi, V. Zlatanic, J. Wilson, C. Argmann, D.K. Scott, A. Garcia-Ocaña, and A.F. Stewart. Combined Inhibition of DYRK1A, SMAD and Trithorax Pathways Synergizes to Induce Robust Replication in Adult Human Beta Cells. ***Cell Metab.*** 29:638-652, 2019. PMCID: PMC6402958

c. C. Ackeifi, P. Wang, E. Karakose, J.E. Manning Fox, B.J. González, H. Liu, E. Swartz, K. Kumar, P.E. MacDonald, R. Sanchez, R. DeVita, D. Homann, D. Egli, A. Garcia-Ocaña, D.K. Scott, A.F. Stewart. Dual DYRK1A-GLP1R Modulation Synergistically Increases Human Beta Cell Numbers. ***Sci. Transl. Med.*** Feb 12;12(530). pii: eaaw9996. doi: 10.1126/scitranslmed.aaw9996, 2020. PMCID: PMC7388697

d. C. Rosselot, A. Alvarsson, P. Wang, Y. Li, K. Kumar, R.J. DeVita, A.F. Stewart, S.A. Stanley, A. Garcia-Ocaña. The Harmine and Exendin-4 Combination Markedly Expands Human Beta Cell Mass In Vivo: Quantification and Visualization By iDISCO+ 3D Imaging, ***bioRxiv*** 2020.07.24.220244.

B. Positions and Honors.

1996-1998 Post-doctoral fellow, Dept. of Endocrinology, Yale University School of Medicine.
1998-2001 Research Associate, Dept. of Medicine, Div. of Endocrinology, University of Pittsburgh.
2001-2007 Assistant Professor, Dept. of Medicine, Div. of Endocrinology, and Dept. Cell Biology & Physiology, University of Pittsburgh.
2007-2012 Associate Professor (with tenure), Dept. of Medicine, Div. of Endocrinology, Dept. Cell Biology & Physiology, University of Pittsburgh.
2012- Professor (with tenure), Diabetes, Obesity and Metabolism Institute, Icahn School of Medicine at Mount Sinai, NY.
2015- Core Director, Human Islet & Adenovirus Core at the Einstein-Mount Sinai Diabetes Research Center.

Honors

1991 Young Investigator Award, European Renal Assoc.-European Dialysis and Transplant Assoc.
1996 Post-doctoral fellowship from the North Atlantic Treaty Organization (NATO)
1997 FAES Award on Mineral Metabolic Research from the Spanish Society of Bone & Mineral Res.
2001-2004 Editorial Board of *Endocrinology*
2002-2004 Junior Faculty Award, American Diabetes Association
2003-2019 Ad-hoc grant Reviewer for NIH/NIDDK (SEP, BCBC, SBIR, MCE and CADO), JDRF and ADA
2004 University of Pittsburgh Senior Vice-Chancellor's Research Conference
2012- Editorial Board of *American Journal of Physiology* (Endocrinology and Metabolism)
2014- Editorial Board of *Journal of Biological Chemistry*
2018- Standing Member, Molecular and Cellular Endocrinology (MCE) Study Section, NIH.
2019- Editorial Board of *Diabetes*

C. Contributions to Science

1. Growth factors/hormones and pancreatic β-cell replication, survival and function. My early studies focused on analyzing the impact of hepatocyte growth factor (HGF) on β-cell proliferation and mass in vivo in transgenic mice. We were one of the first research groups to determine that overexpression of a growth factor in β-cells (in this case HGF) was capable of increasing β-cell proliferation and mass in vivo in mice while increasing β-cell function and improving glucose homeostasis at the same time. These observations were the base for future studies in which we demonstrated that systemic HGF administration increases β-cell regeneration in a mouse model of diminished β-cells mass following partial pancreatectomy. We next addressed whether HGF receptor deletion in β-cells had an impact in β-cell growth and function in basal as well as physiologic and pathologic situations. We found that HGF action in β-cells is required for β-cell survival during islet inflammation, for maternal β-cell adaptation during pregnancy, and for β-cell regeneration after partial pancreatectomy. Taken together, these publications document both the importance of HGF for therapeutic approaches in β-cell regeneration and its significance in the response of the β-cell to stress-related environments that could lead to the development of diabetes. My contribution to science also involves collaborating with multiple investigators in this area of research and mentoring of trainees who stayed in my lab over the years developing the ongoing research projects while being trained. In all the mentioned studies, I served as the primary investigator or co-investigator.

a. A. García-Ocaña, K. Takane, M. A. Syed, W.M. Philbrick, R.C. Vasavada, A.F. Stewart. Hepatocyte growth factor overexpression in the islet of transgenic mice increases beta cell proliferation and induces hypoglycemia. ***J. Biol. Chem.*** 275:1226-1232, 2000. PMID:10625667

b. J.C. Alvarez-Perez, S. Ernst, C. Demirci, G.P. Casinelli, J.M.D. Mellado-Gil, R.C. Vasavada, A. Garcia-Ocana. Hepatocyte Growth Factor/c-Met signaling is required for ß-cell regeneration. ***Diabetes*** 63:216-223, 2014. PMCID:PMC3868042

c. N.K. Guthalu, R. Fenutria, I. Pollack, A. Garcia-Ocaña, J. Penninger, R.C. Vasavada. Osteoprotegerin and Denosumab stimulate human beta cell proliferation through inhibition of the Receptor Activator of NF-κB Ligand pathway. ***Cell Metab***, 22:77-85, 2015. PMCID: PMC4597781

d. N. Gómez-Banoy, J.S. Guseh, T. Chen, G. Li, A. Rubio-Navarro, B. Poirier, G. Putzel, C. Rosselot, J. Camporez, V. Bhambhani, S. Hwang, C. Yao, R. Perry, S. Mukherjee, M.G. Larson, D. Levy, G.I. Shulman, A. Garcia-Ocana, M. Hao, B.M. Spiegelman, J.E. Ho, J.C. Lo. Adipsin preserves beta cells in diabetic mice and associates with protection from type 2 diabetes in humans. ***Nat Medicine***, 25:1739–1747, 2019. PMCID: PMC7256970.

2. Pancreatic β-cell adaptation. My lab has always had a deep interest on deciphering the role of hyperglycemia in adaptive β-cell replication and mass expansion. For this purpose, my lab developed a glucose infusion mouse model in which we demonstrated that four days of mild-hyperglycemia was enough to increase cell cycle activation and β-cell replication in these mice. Later on, we also demonstrated that this adaptive mitogenic effect to hyperglycemia was present in human β-cells transplanted in glucose-infused SCID mice. This was the first in vivo demonstration of adaptive human β-cell proliferation to mild changes in blood glucose. However, the intracellular mechanisms regulated by glucose in pancreatic β-cells that lead to this adaptive β-cell proliferation are not fully known. Several collaborative studies with Drs. Scott, Alonso, Mirmira and Danial during the last 5 years have indicated that ChREBP, IRS2, PKC-ζ, mTOR, PP2A, the polyamine pathway, eiF5A hypusination and Myc play an important role in glucose-mediated effects. Publications describing these studies are highlighted below.

a. L. C. Alonso, T. Yokoe, S. Kim, C. P. O'Donnell and A. Garcia-Ocaña. Glucose-infusion in mice: a new model of increased beta cell proliferation. ***Diabetes*** 56:1792-1801, 2007. PMCID: PMC2921922

b. M.R. Metukuri, P. Zhang, L. Alonso, K. Takane, S.C. Strom, R.M. O'Doherty, A.F. Stewart, R. Vasavada, A. Garcia-Ocaña, and D.K. Scott. ChREBP Mediates Glucose-Stimulated Beta Cell Proliferation. ***Diabetes***. 61:2004-2015. 2012. PMCID: PMC3402328

c. J. Lakshmipathi, J.C. Alvarez-Perez, C. Rosselot, G.P. Casinelli, R. Stamateris, F. Rausell-Palamos, C. O'Donnell, R.C. Vasavada, D.K. Scott, L.C. Alonso, A. Garcia-Ocaña. PKC-ζ is essential for pancreatic beta cell replication during insulin resistance by regulating mTOR and cyclin-D2. ***Diabetes*** 65:1283-1296, 2016. PMCID: PMC4839210

d. C. Rosselot, A. Kumar, J. Lakshmipathi, P. Zhang, G. Lu, L.S. Katz, E.V. Prochownik, A.F. Stewart, L. Lambertini, D.K. Scott, A. Garcia-Ocaña. Myc Is Required for Adaptive β-Cell Replication in Young Mice but Is Not Sufficient in One-Year-Old Mice Fed with a High-Fat Diet. ***Diabetes*** 68:1934-1949, 2019. PMCID: PMC6754239

3. Intracellular signaling and regulation of pancreatic β-cell replication and mass. In addition to the contributions described above, I have analyzed signaling pathways that are significant for β-cell replication and expansion with the idea of leveraging this knowledge to enhance β-cell regeneration for diabetes. These studies highlighted a new key kinase involved in β-cell proliferation induced by growth factors and nutrients: the atypical protein kinase C ζ (PKC ζ). Activation of this kinase in β-cells leads to increased β-cell proliferation, mass and insulin expression in vitro and more importantly in vivo in mice. At a translational level, activation of PKC ζ increases β-cell proliferation in adult islets that are refractory to cell replication. Furthermore, we have recently found that activation of PKC ζ is required for compensatory β-cell expansion in hyperglycemia and insulin resistance conditions. Additional mitogenic signaling pathways under study involve Myc, Dyrk1A and NFAT, in collaborative studies with Drs. Scott, DeVita and Stewart. These studies have led to filing a patent on kinase inhibitors that robustly increase human beta cell proliferation. My constant interest for translating the observations from rodents to human cell biology is summarized in a series of reviews in Diabetes that I have co-authored with leaders in the field experts in the regulation of β-cell replication (*Diabetes* 2012, 2014, 2015). In these reviews, we highlight the sparse knowledge on intracellular signaling in human β-cells compared with the vast knowledge in rodent β-cells and the need to expand these studies in human β-cells if we want to have an impact in future diabetes therapies.

a. S. Velazquez-Garcia, S. Valle, T.C. Rosa, K.K. Takane, C. Demirci, J.M. Mellado-Gil, S. Ernst, D. K. Scott, R.C. Vasavada, L.C. Alonso and A. Garcia-Ocaña. Activation of Protein Kinase C Zeta (ζ) in Pancreatic ß-Cells In Vivo Improves Glucose Tolerance and Induces ß-Cell Expansion Via mTOR Activation. ***Diabetes***. 60: 2546–2559, 2011. PMCID: PMC3178296

b. E.M. Levasseur, K. Yamada, A.R. Piñeros Alvarez, W. Wu, F. Syed, K.S. Orr, T.L. Mastracci, A. L. Mosley, Y. Liu, E. Bernal-Mizrachi, L. Alonso, D. Scott, A. Garcia-Ocaña, S.A. Tersey, and R. G. Mirmira. Hypusine Biosynthesis is required for Adaptive β-Cell Proliferation in Response to Obesity. ***Science Signaling***. Dec 3;12(610):eaax0715. doi: 10.1126/scisignal.aax0715, 2019. PMCID: PMC7202401

c. K. Kumar, P. Wang, J. Wilson, V. Zlatanic, C. Berrouet, S. Khamrui, C. Secor, E.A. Swartz, M. Lazarus, R. Sanchez, A.F. Stewart, A. Garcia-Ocaña*, R.J. DeVita*. A novel, in-vivo active, harmine-based β-cell proliferative DYRK1A inhibitor as a potential therapeutic for diabetes. ***J Med Chem***, 63(6):2986-3003, 2020. PMCID: PMC7388697

d. G. Lu, F. Rausell-Palamos, Z. Zhang, R.C Vasavada, Shelley Valle, Matthew Spindler, D. Homann and A. García-Ocana. Dextran Sulfate Ameliorates Type 1 Diabetes, pancreatic beta cell death and autoimmunity. ***Diabetes***. 69(8):1692-1707, 2020. PMCID: PMC7372066

4. Islet transplantation. Beta cell replacement by transplantation of insulin-producing cells is a potential approach to restore glucose homeostasis in diabetes. However, this approach is seriously hampered by the limited survival of the graft. We have published that HGF and its downstream target Akt can improve β-cell survival and decrease the number of insulin-producing cells required for transplantation. Taking advantage of the islet transplant approach we have also recently reported in collaboration with Dr. Nika Danial, the protective effects of phospho-BAD mimetics in mouse and human islets transplanted in immunocompromised mice. These studies highlight several points: the importance of signaling pathway activation for pancreatic β-cell survival; the utility of human islet transplantation in immunocompromised mice as a tool to decipher the effects of physiologic and pharmacologic agents on beta cell proliferation, function and survival; and, the successful collaboration with other researchers.

a. A. Garcia-Ocaña, K.K. Takane, V. Reddy, J.C. Lopez-Talavera, R.C. Vasavada, A.F. Stewart. Adenovirus-mediated hepatocyte growth factor transfer to mouse islets improves pancreatic islet transplant performance and reduces beta cell death. ***J. Biol. Chem.*** 278:343-351, 2003. PMID:12403787

b. P. Rao, J. Roccisana, K. K. Takane, R. Bottino, A. Zhao, M. Trucco and A. García-Ocaña. Gene Transfer of Constitutively Active Akt Markedly Improves Human Islet Transplant Outcomes in Diabetic SCID Mice. ***Diabetes***. 54:1664-1675, 2005. PMID:15919787

c. S. Ljubicic, K. Polak, J.M. Wiwczar, B. Szlyk, Y. Chang, J.C. Alvarez-Perez, G.H. Bird, L.D. Walensky, A. Garcia-Ocaña, N.N. Danial. Phospho-BAD Mimetic Strategies Protect ß-Cells and Restore Functional ß-Cell Mass in Diabetes***. Cell Rep***, 10: 497–504, 2015. PMCID: PMC4991214

d. A. Fu, J.C. Alvarez-Perez, D. Avizonis, T. Kin, G. Bridon, L. Evans, C. Rosselot, G. Bird, J. Shapiro, L.D Walensky, R. Jones, A. Garcia-Ocaña, N.N Danial. Glucose-dependent partitioning of arginine to urea cycle spares ß-cells from inflammation. ***Nat Metab***. 2, 432–446, 2020. PMCID: PMC7568475.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/adolfo.garcia-ocana.1/bibliography/41140401/public/?sort=date&direction=descending

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

Active

1) **"Einstein-Mt. Sinai Diabetes Research Center"**
4/1/20-3/31/25
Principal Investigator: Pessin (Garcia-Ocana, Site PI, Core Director)
Agency: NIH/NIDDK Diabetes Research Centers (P30 DK020541-43)
The Human Islet and Adenovirus Core (HIAC), located at Mount Sinai, has evolved with two broad missions in support of research investigators: 1) to provide key methods, technology and infrastructure to assist

investigators in the use of human islets for research, which will further our understanding of normal and pathophysiologic islet cell function; 2) to generate and make available reagents and tools for studying beta cell regeneration, survival and function, including adenovirus or lentivirus viral vectors for gene delivery of cDNAs and shRNAs of interest to beta cells and other islet cell types.

2) **"Biological and Medicinal Chemistry Approaches to Human Beta Cell Regeneration"** 7/1/20-6/30/24
Principal Investigator: Garcia-Ocana (Stewart, DeVita Co-PIs)
Agency: NIH/NIDDK R01 DK125285-01
The Aims of this application are: 1. Synthesis of TGF-ß inhibitors with chemical linkers to complement our novel DYRK1A inhibitor compounds; 2. Conjugation of Harmine-linker and TGF-ß-inhibitor-linker compounds to two GLP1 receptor agonists and ENTPD3 monoclonal antibodies; and, 3. Specificity and safety of the Harmine-linker and TGF-ß-inhibitor linker conjugates in vivo in human islet engraftment models.

3) **"Myc Physiology in the Pancreatic Beta Cell"**
7/1/20-6/30/24
Principal Investigator: Garcia-Ocana, (Scott, Co-PI)
Agency: NIH/NIDDK R01 DK126450-01
In this application we will the hypothesis that Myc is critical for adaptive β-cell growth and function. Reversing Myc resistance in the T2D-prone or metabolically-stressed aged β-cell can lead to an enhanced adaptive response.

5) **"ChREBP Alpha, Keap1-Nrf2 and Glucose-stimulated Beta Cell Proliferation"**
4/1/17-3/31/22
Principal Investigator: Scott (Garcia-Ocana Co-Investigator)

Agency: NIH/NIDDK R01 DK110156 0.6 calendar months
This proposal will test the hypothesis that ChREBP alpha increases mitochondrial biogenesis, anabolism and glucose-stimulated beta cell proliferation by activating the Keap1-Nrf2 pathway.

6) "**ChREBP Isoforms in Pancreatic Beta Cells"**
4/1/18-3/31/22
Principal Investigator: Scott (Garcia-Ocana Co-Investigator)

Agency: NIH/NIDDK 1R01DK108905
The aims of this project are to determine the effects of increasing or decreasing the abundance of beta cell ChREBPβ on beta cell mass and glucose homeostasis, to determine if exogenous expression of ChREBPα in human islets improves islet transplantation outcomes, and to determine how ChREBPα and ChREBPβ functionally interact to determine the fate of beta cells.

7) "**Type II Kinase Inhibitors to Treat Diabetes"**
4/1/18 - 3/31/23
Principal Investigator: DeVita and Stewart Co-PIs (Garcia-Ocana Co-Investigator)

Agency: NIH/NIDDK 1R01DK116904
This application focuses on the design and synthesis of novel Type II kinase inhibitors to block DYRK1A and drive human beta cell proliferation.

8) **"Evaluating Pancreatic Neuromodulation for Prediabetes and Diabetes"**
1/1/20 - 1/1/23
Principal Investigator: Stanley (García-Ocana Co-Investigator)

Agency: Department of Defense PR191443
This application will test the hypothesis that high fat diet increases islet sympathetic innervation, reduces islet parasympathetic innervation leading to insufficient insulin to maintain normal glucose.

9) **"Dyrk Inhibitors for Human Beta Cell Expansion"**
3/1/15-6/30/25

Principal Investigator: García-Ocana (Stewart, DeVita Co-PIs)
Agency: NIH/NIDDK 1R01DK105015-05.
This application explores the therapeutic potential of Dyrk inhibitors to increase human beta cell replication in vitro and in vivo.

10) **"Neural control of pancreatic endocrine function in obesity and diabetes"**
9/1/20-8/31/25 Principal Investigator: Stanley (García-Ocana Co-Investigator)

Agency: NIH/NIDDK 1R01DK124461-01A1
This application will test the hypothesis that obesity and insulin resistance regulates islet cell function through modulation of islet innervation.

Completed (in the last 3 years)

1) **"Combined Harmalog-TGF beta Inhibitors for Human Beta Cell Expansion"**
9/1/17-8/31/19
Principal Investigator: Garcia-Ocana, (Stewart, co-PI)
Agency: JDRF Research Grant 2-SRA-2017-514-S-B.
This application will explore the combine effect of harmine and TGF beta inhibitors in beta cell proliferation.