Curriculum Vitae

Personal information

Luc Baeyens

Work experience

01/2021 - present	Federal Agency for Medicine and Health Products, Belgium	GMP inspector	Medicine, Biotechnology, Pharmacy
03/2020 - 09/2021	Brantsandpatents, Ghent, Belgium	Patent Scientist	Medicine, Biotechnology, Pharmacy
05/2017 - 02/2020	Free University Brussels, Belgium	Principal Investigator, Associate Professor	Medicine
06/2015 - 04/2017	University of California, San Francisco, USA	Associate Specialist, Assistant Professor	Medicine
11/2012 - 05/2015	University of California, San Francisco, USA	Postdoctoral Scholar	Medicine
01/2010 - 12/2010	Hubrecht Institute, Utrecht, The Netherlands	Postdoctoral Scholar	Medicine
02/2009 - 10/2012	Free University Brussels, Belgium	Postdoctoral Scholar	Medicine
07/2004 - 12/2008	Free University Brussels, Belgium	PhD student	Medicine

Education and training

EDUCATION

09/1999 - 07/2001	Free University Brussels	B.A.	Cum Laude, Biology	
09/2001 - 07/2004	Free University Brussels	M.S.	Cum Maxima Laude,	Biology
08/2004 - 06/2008	Free University Brussels	Ph.D.	Medical Sciences	

LICENSES, CERTIFICATION

01/2006 - 12/2006	FELASA Laboratory Animal Science Accreditation, Brussels

Additional information

Publications

PEER REVIEWED PUBLICATIONS

1. Baeyens L, De Breuck S, Lardon J, Mfopou JK, Rooman I, Bouwens L. In vitro generation of insulinproducing beta cells from adult exocrine pancreatic cells. Diabetologia 2005;48:4957. (IF: 5.822)
2. Baeyens L, De Breuck S, Lardon J, Mfopou JK, Rooman I, Bouwens L. In vitro generation of insulin-producing beta cells from adult exocrine pancreatic cells. Diabetologia. 2005 Jan; 48(1):49-57. PMID: 15616797
3. De Breuck S, Baeyens L, Bouwens L. Expression and function of leukaemia inhibitory factor and its receptor in normal and regenerating rat pancreas. Diabetologia 2006;49:108116. (IP: 5.822)
4. De Breuck S, Baeyens L, Bouwens L. Expression and function of leukaemia inhibitory factor and its receptor in normal and regenerating rat pancreas. Diabetologia. 2006 Jan; 49(1):108-16. PMID: 16369772
5. Rooman I, De Medts N, Baeyens L, Lardon J, De Breuck S, Heimberg H, Bouwens L. Expression of the Notch signaling pathway and effect on exocrine cell proliferation in adult rat pancreas. Am J Pathol 2006;169:12061214. (IF: 5.487)
6. Baeyens L, Bonné S, German MS, Ravassard P, Heimberg H, Bouwens L. Ngn3 expression during postnatal in vitro beta cell neogenesis induced by the JAK/STAT pathway. Cell Death Differ. 2006 Nov; 13(11):1892-9. PMID: 16514419
7. Baeyens L, Bonne S, German MS, Ravassard P, Heimberg H, Bouwens L. Ngn-3 expression during postnatal in vitro beta cell neogenesis induced by the JAK/STAT pathway. Cell Death Differ 2006;13:18921899. (IF: 8.254)
8. Rooman I, De Medts N, Baeyens L, Lardon J, De Breuck S, Heimberg H, Bouwens L. Expression of the Notch signaling pathway and effect on exocrine cell proliferation in adult rat pancreas. Am J Pathol. 2006 Oct; 169(4):1206-14. PMID: 17003479
9. Baeyens L, Bouwens L. Can beta cells be derived from exocrine pancreas? Diabetes Obes Metab 2008;10 Suppl 4:170178. (IF: 3.441)
10. Baeyens L, Bouwens L. Can beta-cells be derived from exocrine pancreas? Diabetes Obes Metab. 2008 Nov; 10 Suppl 4:170-8. PMID: 18834444
11. Baeyens L, Bonne S, Bos T, Rooman I, Peleman C, Lahoutte T, German MS, Heimberg H, Bouwens L. Notch signaling as gatekeeper of rat acinartobeta cell conversion in vitro. Gastroenterology 2009; 136(5): 175060. (IF: 12.716)
12. Tassenoy A, De Mey J, Stadnik T, De Ridder F, Peeters E, Van Schuerbeek P, Wylock P, Van Eeckhout GP, Verdonck K, Lamote J, Baeyens L, Lievens P. Histological findings compared with magnetic resonance and ultrasonographic imaging in irreversible postmastectomy lymphedema: a case study. Lymphat Res Biol. 2009; 7(3):145-51. PMID: 19778202
13. Baeyens L, Bouwens L. Cellular plasticity of the rodent pancreas. Biol. Chem. 2009; 390(10): 9951001. (IF: 3.035)
14. Baeyens L, Bonné S, Bos T, Rooman I, Peleman C, Lahoutte T, German M, Heimberg H, Bouwens L. Notch signaling as gatekeeper of rat acinar-to-beta-cell conversion in vitro. Gastroenterology. 2009 May; 136(5):1750-60.e13. PMID: 19208356
15. Baeyens L, Bouwens L. Cellular plasticity of the pancreas. Biol Chem. 2009 Oct; 390(10):995-1001. PMID: 19642874
16. Willekens I, Buls N, Lahoutte T, Baeyens L, Vanhove C, Caveliers V, Deklerck R, Bossuyt A, de Mey J. Evaluation of the radiation dose in microCT with optimization of the scan protocol. Contrast Media Mol Imaging. 2010 Jul;5(4):2017. (IF: 3.392)
17. Willekens I, Buls N, Lahoutte T, Baeyens L, Vanhove C, Caveliers V, Deklerck R, Bossuyt A, de Mey J. Evaluation of the radiation dose in micro-CT with optimization of the scan protocol. Contrast Media Mol Imaging. 2010 Jul-Aug; 5(4):201-7. PMID: 20665903
18. Mfopou J.K.*, Baeyens L.*, and Bouwens, L. Hedgehog signals inhibit postnatal beta cell neogenesis from adult rat exocrine pancreas in vitro. Diabetologia 2012 Apr;55(4):102434. (*Equal contribution of J.Mfopou and L.Baeyens). (IF: 6.973)
19. Mfopou JK, Baeyens L, Bouwens L. Hedgehog signals inhibit postnatal beta cell neogenesis from adult rat exocrine pancreas in vitro. Diabetologia. 2012 Apr; 55(4):1024-34. PMID: 22237687
20. Jakob B Hansen; Morten Fog Tonnesen, Ph.D.; Andreas N Madsen; Peter H Hagedorn; Josefine Friberg; Lars G Grunnet; Scott Heller; Anja Ø Nielsen; Joachim Størling; Luc Baeyens; Leeat AnkerKitai; Klaus Qvortrup; Luc Bouwens; Shimon Efrat; Mogens Aalund; Nancy C Andrews; Nils Billestrup; Allan E Karlsen; Birgitte Holst; Flemming Pociot; Thomas MandrupPoulsen. Divalent metal transporter 1 regulates ironmediated ROS and cell fate in response to cytokines. Cell Metab. 2012 Oct 3;16(4):44961. (IF: 13.668).
21. Hansen JB, Tonnesen MF, Madsen AN, Hagedorn PH, Friberg J, Grunnet LG, Heller RS, Nielsen AØ, Størling J, Baeyens L, Anker-Kitai L, Qvortrup K, Bouwens L, Efrat S, Aalund M, Andrews NC, Billestrup N, Karlsen AE, Holst B, Pociot F, Mandrup-Poulsen T. Divalent metal transporter 1 regulates iron-mediated ROS and pancreatic ß cell fate in response to cytokines. Cell Metab. 2012 Oct 3; 16(4):449-61. PMID: 23000401
22. Houbracken I, Baeyens L, Ravassard P, Heimberg H, Bouwens L. Gene delivery to pancreatic exocrine cells in vivo and in vitro. BMC Biotechnol. 2012 Oct 22;12:74. (IF: 6.531)
23. Houbracken I, Baeyens L, Ravassard P, Heimberg H, Bouwens L. Gene delivery to pancreatic exocrine cells in vivo and in vitro. BMC Biotechnol. 2012; 12:74. PMID: 23088534
24. Van de Casteele M*, Leuckx G*, Baeyens L, Cai Y, Yuchi Y, Coppens V, De Groef S, Eriksson M, Svensson C, Ahlgren U, AhnfeltRønne J, Madsen OD, Waisman A, Dor Y, Jensen JN, Heimberg H. Neurogenin 3+ cells contribute to betacell neogenesis and proliferation in injured adult mouse pancreas. Cell Death Dis. 2013 Mar 7;4. (*Equal contribution). (IF: 6.044)
25. Van de Casteele M, Leuckx G, Baeyens L, Cai Y, Yuchi Y, Coppens V, De Groef S, Eriksson M, Svensson C, Ahlgren U, Ahnfelt-Rønne J, Madsen OD, Waisman A, Dor Y, Jensen JN, Heimberg H. Neurogenin 3+ cells contribute to ß-cell neogenesis and proliferation in injured adult mouse pancreas. Cell Death Dis. 2013; 4:e523. PMID: 23470530
26. D'Hoker J*, De Leu N*, Heremans I, Baeyens L, Minami K, Cai Y, Lavens A, Chintinne M, Stangé G, Magenheim J, Swisa A, Martens G, Pipeleers D, Van de Casteele M, Seino S, Keshet E, Dor Y and Heimberg H. Conditional hypovascularisation and hypoxia in islets does not influence adult beta cell mass and function. Diabetes 2013 Dec;62(12) 416573: (*Equal contribution). (IF: 7.895).
27. D'Hoker J, De Leu N, Heremans Y, Baeyens L, Minami K, Ying C, Lavens A, Chintinne M, Stangé G, Magenheim J, Swisa A, Martens G, Pipeleers D, van de Casteele M, Seino S, Keshet E, Dor Y, Heimberg H. Conditional hypovascularization and hypoxia in islets do not overtly influence adult ß-cell mass or function. Diabetes. 2013 Dec; 62(12):4165-73. PMID: 23974922
28. Baeyens L, Lemper M, Leuckx G, De Groef S, Bonfanti P, Stangé G, Shemer R, Nord C, Scheel DW, Pan FC, Ahlgren U, Gu G, Stoffers DA, Dor,Y Ferrer J, Gradwohl G, Wright CVE, Van de Casteele M, German MS, Bouwens L* and Heimberg H*. Transient cytokine treatment induces acinar cell reprogramming and generates functional beta cell mass in diabetic mice. Nat. Biotechnol. 2014 Jan;32(1):7683 (IF: 39.08). **Retraction Note 2020**
29. Baeyens L, Lemper M, Leuckx G, De Groef S, Bonfanti P, Stangé G, Shemer R, Nord C, Scheel DW, Pan FC, Ahlgren U, Gu G, Stoffers DA, Dor Y, Ferrer J, Gradwohl G, Wright CV, Van de Casteele M, German MS, Bouwens L, Heimberg H. Transient cytokine treatment induces acinar cell reprogramming and regenerates functional beta cell mass in diabetic mice. Nat Biotechnol. 2014 Jan; 32(1):76-83. PMID: 24240391
30. Cai Y1, Yuchi Y, De Groef S, Coppens V, Leuckx G, Baeyens L, Van de Casteele M, Heimberg H. IL6-dependent proliferation of alpha cells in mice with partial pancreatic duct ligation. Diabetologia. 2014 Jul;57(7):14207. (IF: 6.88)
31. Cai Y, Yuchi Y, De Groef S, Coppens V, Leuckx G, Baeyens L, Van de Casteele M, Heimberg H. IL-6-

dependent proliferation of alpha cells in mice with partial pancreatic-duct ligation. Diabetologia. 2014 Jul; 57(7):1420-7. PMID: 24759958
32. Goethals LR, Bos TJ, Baeyens L, De Geeter F, Devoogdt N, Lahoutte T. Camelid reporter gene imaging: a generic method for in vivo cell tracking. EJNMMI Res. 2014 Jun 26;4:32. (IF: 4.32)
33. Goethals LR, Bos TJ, Baeyens L, De Geeter F, Devoogdt N, Lahoutte T. Camelid reporter gene imaging: a generic method for in vivo cell tracking. EJNMMI Res. 2014; 4:32. PMID: 25024930
34. Van de Casteele M, Leuckx G, Cai Y, Yuchi Y, Coppens V, De Groef S, Van Gassen N, Baeyens L, Heremans Y, Wright CV, Heimberg H. Partial duct ligation: βcell proliferation and beyond. Diabetes. 2014 Aug;63(8):256777. (IF: 8.474).
35. Van de Casteele M, Leuckx G, Cai Y, Yuchi Y, Coppens V, De Groef S, Van Gassen N, Baeyens L, Heremans Y, Wright CV, Heimberg H. Partial duct ligation: ß-cell proliferation and beyond. Diabetes. 2014 Aug; 63(8):2567-77. PMID: 25060885
36. Lemper M, Leuckx G, Heremans Y, German MS, Heimberg H, Bouwens L, Baeyens L. Reprogramming of human pancreatic exocrine cells to βlike cells. Cell Death Differ. 2014 Dec 5. doi: 10.1038/cdd.2014.193. [Epub ahead of print] (IF: 8.385)
37. Lemper M, Leuckx G, Heremans Y, German MS, Heimberg H, Bouwens L, Baeyens L. Reprogramming of human pancreatic exocrine cells to ß-like cells. Cell Death Differ. 2015 Jul; 22(7):1117-30. PMID: 25476775
38. De Groef S, Leuckx G, Van Gassen N, Staels W, Cai Y, Yuchi Y, Coppens V, De Leu N, Heremans Y, Baeyens L, Van de Casteele M, Heimberg H. Surgical Injury to the Mouse Pancreas through Ligation of the Pancreatic Duct as a Model for Endocrine and Exocrine Reprogramming and Proliferation. J Vis Exp. 2015; (102):e52765. PMID: 26273954
39. De Groef S, Staels W, Van Gassen N, Lemper M, Yuchi Y, Sojoodi M, Bussche L, Heremans Y, Leuckx G, De Leu N, Van de Casteele M, Baeyens L, Heimberg H. Sources of beta cells inside the pancreas. Diabetologia. 2016 Sep; 59(9):1834-7. PMID: 27053238
40. Lemper M, De Groef S, Stangé G, Baeyens L, Heimberg H. A combination of cytokines EGF and CNTF protects the functional beta cell mass in mice with short-term hyperglycaemia. Diabetologia. 2016 Sep; 59(9):1948-58. PMID: 27318836
41. De Groef S, Renmans D, Cai Y, Leuckx G, Roels S, Staels W, Gradwohl G, Baeyens L, Heremans Y, Martens GA, De Leu N, Sojoodi M, Van de Casteele M, Heimberg H. STAT3 modulates ß-cell cycling in injured mouse pancreas and protects against DNA damage. Cell Death Dis. 2016; 7(6):e2272. PMID: 27336716
42. Staels W, De Groef S, Bussche L, Leuckx G, Van de Casteele M, De Leu N, Baeyens L, Heremans Y, Heimberg H. Making ß(-like)-cells from exocrine pancreas. Diabetes Obes Metab. 2016 Sep; 18 Suppl 1:144-51. PMID: 27615144
43. Baeyens L, Hindi S, Sorenson RL, German MS. ß-Cell adaptation in pregnancy. Diabetes Obes Metab. 2016 Sep; 18 Suppl 1:63-70. PMID: 27615133
44. Pappalardo Z, Gambhir Chopra D, Hennings TG, Richards H, Choe J, Yang K, Baeyens L, Ang K, Chen S, Arkin M, German MS, McManus MT, Ku GM. A Whole-Genome RNA Interference Screen Reveals a Role for Spry2 in Insulin Transcription and the Unfolded Protein Response. Diabetes. 2017 Jun;66(6):1703-1712. doi: 10.2337/db16-0962. Epub 2017 Feb 28.
45. Coppens V, Leuckx G, Heremans Y, Staels W, Verdonck Y, Baeyens L, De Leu N, Heimberg H.Semi-automated digital measurement as the method of choice for beta cell mass analysis. PLoS One. 2018 Feb 6;13(2):e0191249. doi: 10.1371/journal.pone.0191249.
46. Tang SC, Baeyens L, Shen CN, Peng SJ, Chien HJ, Scheel DW, Chamberlain CE, German MS.Human pancreatic neuro-insular network in health and fatty infiltration.Diabetologia. 2018 Jan;61(1):168-181. doi: 10.1007/s00125-017-4409-x.
47. Luc Baeyens, Marie Lemper, Willem Staels, Sofie De Groef, Nico De Leu, Yves Heremans, Michael S German and Harry Heimberg. 2017. (Re)generating human beta cells: status, pitfalls and perspectives. Physiol Rev. 2018 Jul 1;98(3):1143-1167. doi: 10.1152/physrev.00034.2016.
48. Staels W, Verdonck Y, Heremans Y, Leuckx G, De Groef S, Heirman C, de Koning E, Gysemans C, Thielemans K, Baeyens L, Heimberg H, De Leu N. Vegf-A mRNA transfection as a novel approach to improve mouse and human islet graft revascularisation. Diabetologia. 2018 Aug;61(8):1804-1810. doi: 10.1007/s00125-018-4646-7.
49. Pinho AV, Van Bulck M, Chantrill L, Arshi M, Sklyarova T, Herrmann D, Vennin C, Gallego-Ortega D, Mawson A, Giry-Laterriere M, Magenau A, Leuckx G, Baeyens L, Gill AJ, Phillips P, Timpson P, Biankin AV, Wu J, Rooman I. ROBO2 is a stroma suppressor gene in the pancreas and acts via TGF-β signalling. Nat Commun. 2018 Nov 30;9(1):5083. doi: 10.1038/s41467-018-07497-z.

BOOKS AND CHAPTERS

1. **Baeyens L**, Rooman I and Bouwens L. Stem Cell Therapy for Diabetes. Book chapter. Humana Press 2010. ISBN 9781607613664.

Projects

HONORS AND AWARDS

2004	PhD Fellowship of the Institute for the Promotion of Innovation through Science and Technology in Flanders (IWT Vlaanderen).
2009	Fund for Scientific Research Flanders (FWO) postdoctoral fellowship
2011	EFSD/JDRF/Roche Young Investigator Award in Innovative Therapy for Type 1 Diabetes
2012	Fund for Scientific Research Flanders (FWO) postdoctoral fellowship
2013	Best Oral Presentation prize, 5th Islet Society Meeting, Vancouver, Canada
2014	JDRF Advanced Postdoctoral Grant

2016	Nominee Helmholtz-Nature Medicine Young Investigator Award
2016	ERC Starter Grant – H2020
2017	FWO Odysseus Grant
2019	JDRF Project Concept Grant

KEYWORDS/AREAS OF INTEREST

IP protection, Patent Law, Medicine, Biotechnology, Regenerative Therapy, Exosome Therapy, Pregnancy, Diabetes, cell biology, organoid culture, pancreas, beta cells, insulin, metabolism, regeneration, transcription factors, acinar cells, cytokines, physiology/development.

RESEARCH AND CREATIVE ACTIVITIES SUMMARY

I currently work as Patent Scientist at Brantsandpatents where I handle mainly files in Life Sciences. I prepare patent applications, advise on patentability and freedom to operate, and assist in Opposition Cases.

During the course of my scientific career, I have established a new model for in vitro transdifferentiation of rat acinar cells to beta-like cells with functional properties. I also developed an innovative study demonstrating in vivo reprogramming of adult murine acinar cells to functional beta cells using a pharmacological treatment, both published in leading journals. I worked on a novel method to trigger human beta cell replication, as well as on the establishment of a humanized mouse model to study human pancreas development and regeneration. I possess expert capabilities in cell culture techniques, histological and molecular biology, human developmental biology, cloning and viral vector design, next generation sequencing and rodent surgery.

-Baeyens L, Bonne S, Bos T, Rooman I, Peleman C, Lahoutte T, German MS, Heimberg H, Bouwens L. Notch signaling as gatekeeper of rat acinar-to-beta cell conversion in vitro. Gastroenterology 2009; 136(5): 1750-60. (IF: 12.716)

Highlighted in: Tack J, Carethers J. This month in Gastroenterology. Gastroenterology 2009 MAY:136(5):1467-1470

Highlighted in: De la O JP, Murtaugh LC. Notch signaling: Where Pancreatic Cancer and Differentiation meet. Gastroenterology 2009 MAY:136(5):1499-1502

-Baeyens L, Bonne S, German MS, Ravassard P, Heimberg H, Bouwens L. Ngn3 expression during postnatal in vitro beta cell neogenesis induced by the JAK/STAT pathway. Cell Death Differ 2006;13:1892-1899. (IF: 8.254)

-Baeyens L, De Breuck S, Lardon J, Mfopou JK, Rooman I, Bouwens L. In vitro generation of insulin-producing beta cells from adult exocrine pancreatic cells. Diabetologia 2005;48:49-57. (IF: 5.822)

These publications show my ability ability to design and validate a novel model for rat acinar cell differentiation towards functional beta-like cells in vitro. I was the first to report that rat acinar cells do not only possess the potential of forming duct- or hepatocyte-like cells in vitro, but also insulin-producing beta cells. This collective work has served as a basis for future studies on acinar cell plasticity in vitro and in vivo.

-Baeyens L, Lemper M, Leuckx G, De Groef S, Bonfanti P, Stangé G, Shemer R, Nord C, Scheel DW, Pan FC, Ahlgren U, Gu G, Stoffers DA, Dor,Y Ferrer J, Gradwohl G, Wright CVE, Van de Casteele M, German MS, Bouwens L* and Heimberg H*. Transient cytokine treatment induces acinar cell reprogramming and generates functional beta cell mass in diabetic mice. Nat. Biotechnol. 2014 Jan;32(1):76-83 (IF: 39.08).

Highlighted in: Worchel HN, Magnuson MA. Cytokine-driven beta cell production in vivo. Nat. Biotechnol. 2014 Jan:32(1):63-64.

F1000 recommendation.

This ground-breaking publication caused a paradigm shift in the field of beta cell regeneration and received numerous media attention. I was the first to develop in vivo model for cytokine-mediated beta cell regeneration and highlighted the potential of terminally differentiated mouse acinar cells to respond to pro-endocrine signals and reprogram to functional beta-like cells. 2020 Retraction Note: inconsistencies in data reproduction.

-Lemper M, Leuckx G, Heremans Y, German MS, Heimberg H, Bouwens L, Baeyens L. Reprogramming of human pancreatic exocrine cells to β-like cells. Cell Death Differ. 2014 Dec 5. doi: 10.1038/cdd.2014.193. [Epub ahead of print] (IF: 8.385)

This publication is the first report on the potential of human acinar cells to reprogram to functional beta-like cells in vitro. This proof-of-concept study demonstrated that upon introduction of activated MAPK and STAT3 human acinar cells differentiate towards a beta-like phenotype through of Neurogenin-3 positive intermediate. These cells are functionally immature in vitro but acquire functionality following engraftment in immune-compromised mice. I was senior author on this study and developed and supervised this work.

Memberships

MEMBERSHIPS

2003 - 2020	European Association for the Study of Diabetes (EASD)
2009 - 2015	Beta Cell Biology Consortium (BCBC)
2013 - 2020	American Diabetes Association (ADA)

SERVICE TO PROFESSIONAL PUBLICATIONS

2008 - 2020	Ad hoc referee for Journal of Pathology (2 papers in last 5 years), BMC Biology (2 papers in last 5 years), PlosOne (1 paper in last 5 years), Diabetologia (2 papers in last 5 years) and Molecular and Cellular Endocrinology (1 paper in last 5 years)

Other Relevant Information

Recently we discovered that, in contrast to rodents, human beta-cell proliferation and function dramatically responds to human placental exosomes in a species and cell-type specific fashion. **Our long-term goal** is to understand how these exosomes function and apply that knowledge to the development of practical beta-cell regeneration/replacement therapies for people with diabetes. **Our immediate goal** as outlined in this application, is to develop tools, reagents and methods for studying exosome-beta-cell interactions and to use them to test hypotheses regarding exosome function. This information will be applied to the development of improved therapies for people with diabetes.

Specific Aim 1: Develop improved tools and resources for studying human placental exosome/beta-cell interactions. To accelerate human placenta-exosome-islet studies, we will develop improved tools that overcome current experimental limitations. Currently we require concurrently harvested fresh human placentas and human islets. Therefore, we propose to develop other sources of human placental exosomes, including frozen exosomes, term placentas, and exosomes from human serum. In addition, we propose to develop data resources from exosome-treated human islets: comparative proteomic data by mass spectroscopy, protein translation data from sequencing of ribosome-associated RNA, and single-cell RNA sequencing. These data resources will be useful for developing new hypotheses and interpreting studies regarding the mechanisms of exosome regulation of the beta-cell.

Specific Aim 2: Determine if feedback regulates placental exosomes. Most endocrine axis are tightly regulated by negative feedback, and there is no reason to expect that the placenta-beta-cell axis is an exception. We will test whether glucose, insulin or other related signals regulate the production, contents or function of human placental exosomes.

Specific Aim 3: Determine how exosomal contents regulate human beta cells. In addition to the protein contents, exosomes carry RNA, including miRNA, mRNA, lncRNA, and others. Based on published studies and our own unpublished data, we already have some knowledge of the miRNA contents of human placental exosomes. We will supplement this with RNA-seq performed on exosome RNA for longer RNAs (especially mRNA and lncRNA). Based on these data, we will begin by testing two families of miRNAs that are expressed abundantly in human placental exosomes and show marked placental specificity. We will test both the necessity and sufficiency of each cluster of miRNAs in exosome regulation of beta-cell proliferation and function by several different methods.

Specific Aim 4: Determine how human placental exosomes regulate components of the hPL-serotonin-beta-cell pathway. First, we will explore how the placental exosomes impact the serotonin pathway, asking first how they regulate the expression of the genes in the serotonin pathway, and the proteins as well. We can start these studies with our preliminary studies but will also use the knowledge we gain from Aim 3 regarding the active RNA and proteins in the exosomes to test specific mRNA and protein targeting. We will also investigate how exosomes impact the expression and signaling of the prolactin and growth hormone signaling pathways components in human beta-cells, since it has been suggested that these pathways are normally blocked in beta-cells [5].

Once complete, this information will accelerate efforts to understand how human placental exosomes regulate human beta cells and to apply exosomes to the generation of new beta cells for people with diabetes.