

Islet Regeneration for Insulin Independence

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Opportunity Overview

Even though new therapies are available to treat type 2 patients and numerous insulin preparations are available to treat both type 1 and 2 diabetes, none address the underlying cause of diabetes: too few beta cells.

Dr. Claresa Levetan and Perle Biosciences, Inc. are exploring the sale or license of five U.S. patents covering Islet Neogenesis Therapy, a combination therapy that increases pancreatic beta cells and protects them through a generalized immune tolerance agent, such as cyclosporine.

Islet Neogenesis Therapy utilizes the efficacy of shorter bioactive Reg peptides to transform progenitor cells within the pancreas into new islets that generate new beta cells which produce insulin. More than 70 publications have now demonstrated the role of the regenerating (REG gene) and Reg (protein) family, and the efficacy of shorter bioactive Reg peptides to transform progenitor cells within the pancreas into new islets.

By combining an immune tolerance agent with shorter bioactive Reg peptides, the potential now exists to address the underlying cause of diabetes, which neither insulin nor any current diabetes therapies on the market address. Within the U.S., the number of people diagnosed with diabetes is projected to increase to nearly 42 million by 2030. Projected diabetes-related medical costs are likewise expected to increase to \$472.0 billion by 2030.

Dr. Levetan's U.S. patents were issued from 2014 to 2016. They will expire from 2032 to 2034.

Potential indications for Islet Neogenesis Therapy include: type 1 and type 2 diabetes, Pre-Diabetes, Latent Autoimmune Diabetes of Adulthood, and diseases of insulin deficiency, beta cell deficiency, insulin resistance and impaired glucose metabolism.

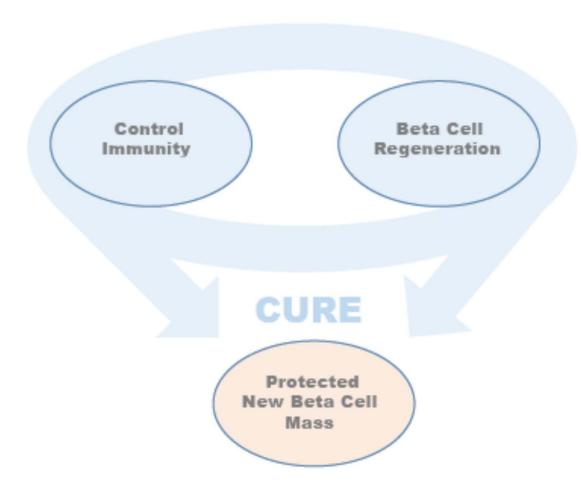
In recent years, the FDA has approved the majority of Biologic License Applications, and annual revenues of U.S. biotechnology firms have increased substantially.

Dr. Levetan is a practicing physician, researcher, and inventor. She is the recipient of the prestigious Roche Diagnosed award for innovative diabetes research. Dr. Levetan founded Perle Biosciences in 2013.

Dr. Levetan's patents represent a significant business opportunity for the buyers or licensees to commercialize new Islet Neogenesis Therapies.



Islet Neogenesis Therapy



In humans, protection from autoimmune attack alone will not allow beta cells to automatically regenerate. Humans need a regenerator agent to stimulate progenitor cells into new islets.

Beta cells must be housed within functional islets. And islets require the blood rich environment of the pancreas to survive.

Dr. Levetan's inventions identify regeneration agents which specifically target the pancreatic receptors and generates new islets within the pancreas without the need for transplants.



Islet Neogenesis Therapy

Islet Neogenesis Therapy Overview — The Human Genome Project has enabled researchers to discover that the same genes initiating the formation of new islets in fetal development also emerge when the pancreas is injured as a means of protection. More than 70 publications have now demonstrated the role of the regenerating (REG gene) and Reg (protein) family, and the efficacy of shorter bioactive Reg peptides to transform progenitor cells within the pancreas into new islets.

Human Phase 2B trials have successfully been conducted in both type 1 and type 2 diabetes patients resulting in significant lowering of hemoglobin A1C among type 2 patients and significant rises in stimulated C-peptide, a marker of endogenous insulin production, even among type 1 patients with type 1 for 20 years. Reg peptides provide a completely unique and innovative approach, and have the potential for insulin independence among type 1 and 2 patients.

Specificity – The Reg proteins are a family of C-type lectin proteins that are expressed by the pancreas. A Reg knockout mouse model has demonstrated the important role of Reg genes in glucose homeostasis with diminished [(3)H] thymidine incorporation in isolated islets from Reg knockout mice, and hyperplastic islets were induced by the injection of gold thioglucose with the average islet size in Reg knockout mice being significantly smaller than that of control Reg(+/+) mice.

The ability to translate this exciting genomic science into therapeutics has been shown by the discovery and efficacy of the shorter bioactive peptide regions of the Reg gene proteins. These shorter Reg gene peptides (Islet Neogenesis Associated Protein/INGAP, Human proslet Peptide/HIP, Peptides Healing Islets of Langerhans/PHIL) have been shown as potential therapeutic agents in type 1 and type 2 diabetes.



Technology Insights – Summary of the Patents

Patent No.	Title	Issuance	Expiration
8,808,689	Insulin independence among patients with diabetes utilizing a PPI combination with an immune tolerance agent	Aug. 2014	Oct. 2032
8,911,776	Generation of new pancreatic beta cells	Dec. 2014	Oct. 2032
8,911,776	Generation of new pancreatic beta cells	Sept. 2015	Jan. 2033
9,321,812	Insulin independence among patients with diabetes utilizing an optimized hamster Reg3 gamma peptide	Apr. 2016	Aug. 2034
9,511,110	Generation of new pancreatic beta cells	Dec. 2016	Jun. 2033



Technology Insights – U.S. Patent 8,808,689

(12) United States Patent Levetan

(54) INSULIN INDEPENDENCE AMONG PATIENTS WITH DIABETES UTILIZING A PPI IN COMBINATION WITH AN IMMUNE TOLERANCE AGENT

- (71) Applicant: Claresa Levetun, Bryn Mawr, PA (US)
- (72) Inventor: Claresa Levetan, Bryn Mawr, PA (US)
- (73) Assignor: Perle Bioscience, Inc., Atlanta, GA (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- (21) Appl. No.: 13/768,472
- (22) Filed: Feb. 15, 2013

Related U.S. Application Data

- (63) Continuation-in-part of application No. 13/662,209, filed on Oct. 26, 2012, and a continuation-in-part of application No. 13/662,232, filed on Oct. 26, 2012, and a continuation-in-part of application No. 13/662,245, filed on Oct. 26, 2012, and a continuation-in-part of application No. 13/662,253, filed on Oct. 26, 2012.
- (60) Provisional application No. 61/749,197, filed on Jan. 4, 2013, provisional application No. 61/706,225, filed on Sep. 27, 2012.
- (51) Int. Cl. A01N 63/00 (2006.01) C12N 5/00 (2006.01) A61K 35/407 (2006.01)

(10) Patent No.:

US 8,808,689 B1 Aug. 19, 2014

(45) Date of Patent:

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(57) ABSTRACT

To date, no immune tolerance agent or combination of immune tolerance agents has been able to sustain insulinindependence among type 1 diabetes patients. This patent provides methods and pharmaceutical compositions for providing insulin independence among newly diagnosed and existing type 1 diabetes. Methods include utilization of PPIs, which increase gastrin resulting in the transformation of human ductal tissue into insulin-secreting new beta cells, used in combination with an immune tolerance agent to protect the new insulin-producing beta cells generated by the PPI from immune destruction. Compositions and methods are provided for beta cell generation therapy comprising at least one member from a group of PPIs with formulations selected from immune tolerance agents, when used in combination result in insulin-independence among new and existing type 1 patients whom currently require insulin to sustain life. Compositions and methods are provided for insulin-independence among type 2 patients using PPIs when combined with therapeutic agents utilized for the treatment of type 2 diabetes.

14 Claims, 11 Drawing Sheets

Insulin independence among patients with diabetes utilizing a PPI combination with an immune tolerance agent

Issued August 19, 2014 and assigned to Perle Biosciences, Inc. Application filed February 15, 2013 with priority to October 26, 2012. Expires in October 2032.

- Novel therapies, pharmaceutical compositions and methods for treating conditions that are associated with or are a risk factor for impaired glucose homeostasis utilizing a proton pump inhibitor (PPI) along or in combination with an immune tolerance agent.
- Humans have a relatively low rate of beta cell turnover and immune tolerance alone in man does not provide regeneration of new beta cells to maintain insulin independence.
- This invention provides methods for the treatment of diabetes wherein new islets can be formed from human ductal progenitors in the presence of a regeneration agent such as PPIs, which increase gastrin, resulting in the formulation of new islets containing new pools of beta cells.
- 14 claims, 1 independent.



Technology Insights – U.S. Patent 8,911,776

(12) United States Patent Levetan

(54) GENERATION OF NEW PANCREATIC BETA CELLS

(71) Applicant: Claresa Levetan, Bryn Mawr, PA (US)

(72) Inventor: Claresa Levetan, Bryn Mawr, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 13/662,209

(22) Filed: Oct. 26, 2012

(65) Prior Publication Data

US 2014/0120154 A1 May 1, 2014

(51) Int. Cl. (2010.01) C12N 5/071 (2006.01) A61K 39/00 (2006.01) A61K 35/39 (2006.01)

(58) Field of Classification Search

None

See application file for complete search history.

(10) Patent No.: (45) Date of Patent:

US 8,911,776 B2 Dec. 16, 2014

References Cited U.S. PATENT DOCUMENTS

Uniprot. D6W5J8 Human.*

* cited by examiner

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(74) Attorney, Agent, or Firm — James A. Italia; Italia IP

(57) ABSTRACT

The present invention relates to novel therapies for treatment of new and existing type 1 and type 2 diabetes, PreDiabetes, Latent Autoimmune Diabetes of Adulthood, and diseases of insulin deficiency, beta cell deficiency, insulin resistance and impaired glucose metabolism. In particular, the present invention identifies common peptides within the human Reg1a, Reg1b, Reg3a and Reg4, as signaling peptides for beta cell generation acting through the human Reg Receptor on the surface of human pancreatic extra-islet tissue. This invention identifies a specific binding region of the Reg Receptor from which peptidomimetics and stimulating antibodies have been developed for the generation of new beta cells which may be administered directly to patients with said conditions including type 1 diabetes, type 2 diabetes, PreDiabetes and other conditions of beta cell deficiency, and provides specific methodology for protecting new beta cells generated for usage in type 1 diabetes and Latent Autoimmune Diabetes of Adulthood. This invention also provides for ex-vivo generation and delivery of beta cells utilizing the inventions described

13 Claims, 22 Drawing Sheets

Generation of new pancreatic beta cells

Issued December 16, 2014. Application filed October 26, 2012. Expires in October 2032.

- Novel therapies derived from bioactive regions of the human Reg1a, Reg1b, Reg3a and Reg4 gene proteins for the generation of new pancreatic beta cells for treatment of new and existing type 1 and 2 diabetes.
- The invention identifies unique bioactive peptide sequences within the human Reg 1a, Reg1b, Reg3a and Reg4 proteins that bind directly to a human pancreatic receptor on extra-islet exocrine tissue inclusive of ducts, acinar cells and progenitor cells contained within these cells, resulting in new beta cell formation.
- This invention identifies a specific binding region of the Reg Receptor from which peptidomimetics and stimulating antibodies have been developed for the generation of new beta cells.
- This invention also provides for ex-vivo generation and delivery of beta cells utilizing.
- 13 claims, 1 independent.



Technology Insights – U.S. Patent 9,133,440

US 9,133,440 B2

(12) United States Patent

(45) Date of Patent: Sep. 15, 2015

(10) Patent No.:

(54) GENERATION OF NEW PANCREATIC BETA

(71) Applicant: Claresa Levetan, Bryn Mowr, PA (US) (72) Inventor: Claresa Levetan, Bryn Mawr, PA (US)

Subject to any disclaimer, the term of this potent is extended or adjusted under 35 U.S.C. 154(b) by 81 days.

(21) Appl. No.: 13/662,253

Oct. 26, 2012

Prior Publication Data US 2014/0120064 A1 May 1, 2014

(51) Int. Cl. C12N 5/071 CWK 14/435

A61K 35/39 (2015.01)(52) U.S. CL

CI2N 5/0676 (2013.01); A6IK 35/39 (2013.01); C07K 14/07 (2013.01); C07K 144G5 (2013.01); C72N 250L/998 (2013.01)

(58) Field of Classification Search

See application file for complete search history.

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(74) Attorney, Agent, or First - James A. Italia; Italia IP

ABSTRACT

The present invention relates to novel therapies for treatment of new and existing type 1 and type 2 diabetes, PreDiabetes, Latent Autoimmune Diabetes of Adulthood, and diseases of insulin deficiency, beta cell deficiency, insulin resistance and impaired glucose metabolism. In particular, the present invention identifies common pentides within the human Reg In, Reg Ib, Reg In and Reg I, as signaling peptides for beta cell generation acting through the human Reg Receptor on the surface of human pancreatic extra-islet tissue. This invention identifies a specific binding region of the Reg Receptor from which poptidomimetics and stimulating antibodies have been developed for the generation of new beta cells which may be administered directly to patients with sold conditions including type 1 diabetes, type 2 diabetes, PreDiabetes and other conditions of beta cell deficiency, and provides specific methodology for protecting new beta cells generated for usage in type I diabetes and Latent Autoimmune Diabetes of Adulthood. This invention also provides for ex-vivo generation and delivery of beta cells utilizing the inventions described within

10 Claims, 22 Drawing Sheets

Generation of new pancreatic beta cells

Issued September 15, 2015. Application filed October 26, 2012. Expires in January 2033.

- Novel therapies derived from bioactive regions of the human Reg1a, Reg1b, Reg3a and Reg4 gene proteins for the generation of new pancreatic beta cells for treatment of new and existing type 1 and 2 diabetes.
- The invention identifies unique bioactive peptide sequences within the human Reg 1a, Reg1b, Reg3a and Reg4 proteins that bind directly to a human pancreatic receptor on extra-islet exocrine tissue inclusive of ducts, acinar cells and progenitor cells contained within these cells, resulting in new beta cell formation.
- The 7-9 amino acid peptide sequences described in this invention are highly homologous and found within the Reg1a, Reg1b, Reg3a and Reg 4 proteins and bind to the Reg Receptor.
- This invention also provides for ex-vivo generation and delivery of beta cells utilizing.
- 10 claims, 2 independent.



Technology Insights – U.S. Patent 9,321,812

(12) United States Patent Levetan

- INSULIN INDEPENDENCE AMONG PATIENTS WITH DIABETES UTILIZING AN OPTIMIZED HAMSTER REG3 GAMMA
- (71) Applicant: Claresa Levetan, Bryn Mowr, PA (US)
- (72) Inventor: Claresa Levetan, Bryn Mowr, PA (US)
- (73) Assignee: Perle Bioscience, Charleston, SC (US)
- Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-

- (21) Appl. No.: 14/453,414
- (22) Filed: Aug. 6, 2014
- Prior Publication Data

US 2016/0039875 A1 Feb. 11, 2016

(51)	Int. Cl.	
	A61K 32/00	(2006.01)
	C87K 7/08	(2006.01)
	A61K 38/10	(2006.01)
	A61K 38/13	(2006.01)
	A61K 47/48	(2006.01)
	A61K 45/06	(2006.01)

(52) U.S. CL

CPC . C07K 708 (2013.01); A61K 38/10 (2013.01); A61K 38/13 (2013.01); A61K 45/06 (2013.01); A61K 47/40(215 (2013-01))

Field of Classification Search None

See application file for complete search history.

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(45) Date of Patent:

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Primary Eurosiner - Marcela M Cordero Garcia (74) Attorney, Agent, or Firm - James A. Italia; Italia IP

ABSTRACT

Embodiments of the present invention provide for novel therapies, pharmaceutical compositions and methods for insulin independence utilizing a new optimized hamster Reg3 gamma peptide, which is new to the art and has not previously been considered for development in the 30 year history since its discovery. Methods, pharmaceutical compositions and therapies novel to the prior art are utilized in this invention to render patients with recent onset and existing type 1 diabetes insulin independent by an optimized homster Reg3 gamma poptide and an immune tolerance agent for type I patients to become insulin independent and used alone without on immune tolerance agent for type 2 diabetes. While not wishing to be bound by theory, optimized Reg3 gamma poptides increases beta cell generation by its demonstrated properties shown within of transforming ductal pencreatic cells into new

16 Claims, No Drawings

Insulin independence among patients with diabetes utilizing an optimized hamster Reg3 gamma peptide

Issued April 26, 2016 and assigned to Perle Biosciences. Application filed August 6, 2014. Expires in August 2034.

- Novel therapies, pharmaceutical compositions and methods for insulin independence utilizing a new optimized hamster Reg3 gamma peptide.
- Methods, pharmaceutical compositions, and therapies novel to the prior art are utilized in this invention to render patients with recent onset and existing type 1 diabetes inulin independent by an optimized hamster Reg3 gamma peptide and an immune tolerance agent for type 1 patients to become insulin independent and used alone without an immune tolerance agent for type 2 diabetes.
- The optimized hamster Reg3 gamma peptides increases beta cell generation by its demonstrated properties of transforming ductal pancreatic cells into new islets.
- 16 claims, 2 independent.



Technology Insights – U.S. Patent 9,511,110

(12) United States Patent

(54) GENERATION OF NEW PANCREATIC BETA

(71) Applicant: Claresa Levetan, Bryn Mawr, PA (US)

(72) Inventor: Claresa Levetan, Bryn Mawr, PA (US)

Assignee: Perle Bioscience, Inc., Atlanta, GA (US)

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 238 days.

(21) Appl. No.: 13/662,245

Oct. 26, 2012 (22) Filed:

Prior Publication Data US 2014/0120097 A1 May 1, 2014

(51) Int. CL A61K 38/08 (2006.01)C07K 16/28 (2006.01)

(52) U.S. CL A61K 38/08 (2013.01); C07K 16/2839 (2013.01); C07K 2317/34 (2013.01); C07K 2317/75 (2013.01)

(58) Field of Classification Search See application file for complete search history.

References Cited

U.S. PATENT DOCUMENTS

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(10) Patent No.:

US 9.511.110 B2 (45) Date of Patent: Dec. 6, 2016

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Primary Examiner - Gerald R Ewoldt (74) Attorney, Agent, or Firm - James A. Italia; Italia IP

ABSTRACT

The present invention relates to novel therapies for treatment of new and existing type 1 and type 2 diabetes, PreDiabetes, Latent Autoimmune Diabetes of Adulthood, and diseases of insulin deficiency, beta cell deficiency, insulin resistance and impaired glucose metabolism. In particular, the present invention identifies common peptides within the human Reg1a, Reg1b, Reg3a and Reg4, as signaling peptides for beta cell generation acting through the human Reg Receptor on the surface of human pancreatic extra-islet tissue. This invention identifies a specific binding region of the Reg Receptor from which peptidomimetics and stimulating antibodies have been developed for the generation of new beta cells which may be administered directly to patients with said conditions including type 1 diabetes, type 2 diabetes, PreDiabetes and other conditions of beta cell deficiency, and provides specific methodology for protecting new beta cells generated for usage in type 1 diabetes and Latent Autoimmune Diabetes of Adulthood. This invention also provides for ex-vivo generation and delivery of beta cells utilizing the inventions described within.

15 Claims, 22 Drawing Sheets

Generation of new pancreatic beta cells

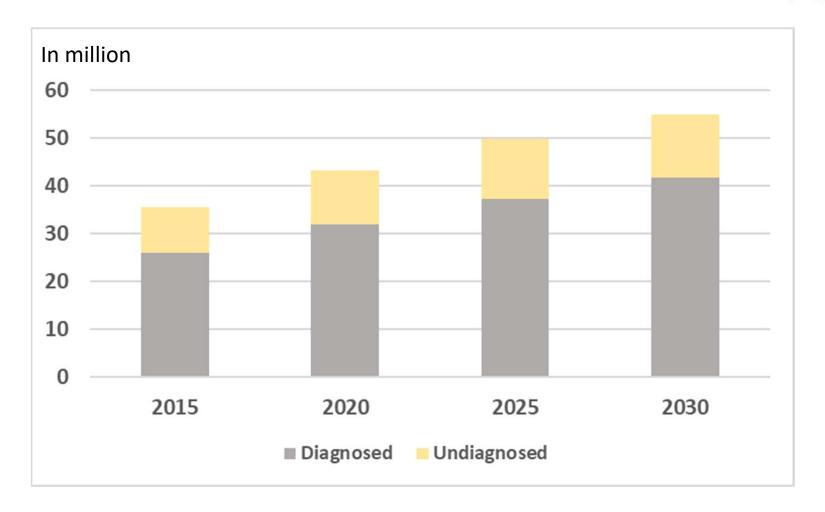
Issued December 6, 2016, and assigned to Perle Biosciences, Inc. Application filed October 26, 2012. Expires in June 2033.

- Novel therapies derived from bioactive regions of the human Reg1a, Reg1b, Reg3a and Reg4 gene proteins for the generation of new pancreatic beta cells for treatment of new and existing type 1 and 2 diabetes.
- The 7-9 amino acid peptide sequences described in this invention are highly homologous and found within the Reg1a, Reg1b, Reg3a and Reg 4 proteins and bind to the Reg Receptor.
- This invention also describes a specific 20-amino acid binding region within the Reg receptor that is contained within its 919 amino acid Reg receptor, which is where the Reg peptides bind.
- This invention also includes the generation of stimulating antibodies from the 20-amino acid binding site within the 919-amino acid Reg receptor, for usage in the generation of new beta cells.
- This invention also provides for ex-vivo generation and delivery of beta cells utilizing.
- 15 claims, 1 independent.



Projected Cases of Diabetes in the U.S.

The number of people in the U.S. with diabetes is projected to be 54.9 million by 2030.

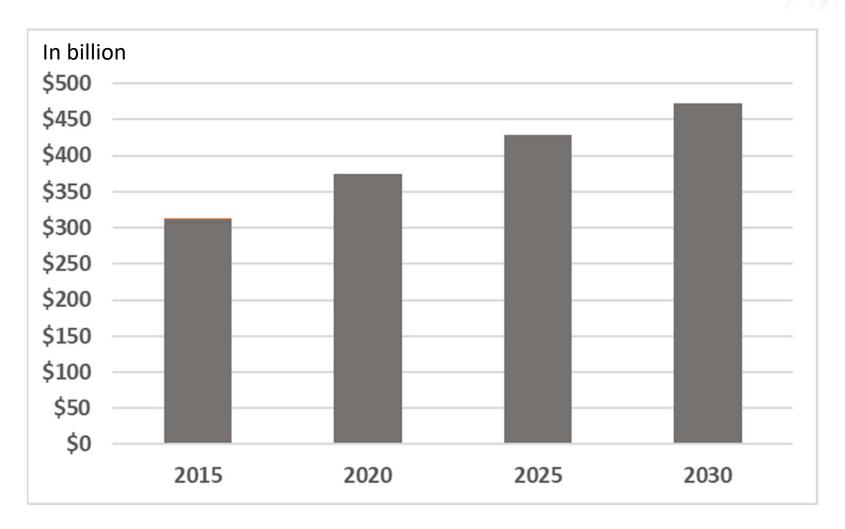


Source: Diabetes 2030: Insights from Yesterday, Today, and Future Trends – Population Health Management, February 1, 2017.



Projected Annual Diabetes-Related Medical Costs

Annual U.S. medical costs of treating diabetes is projected to grow to \$472 billion by 2030.



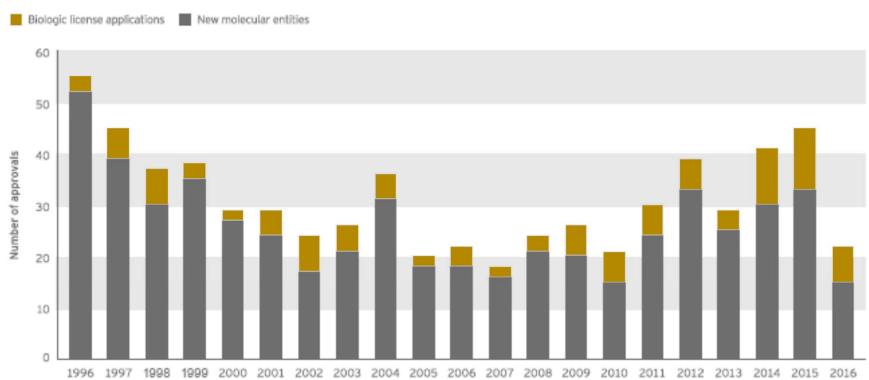
Source: Diabetes 2030: Insights from Yesterday, Today, and Future Trends – Population Health Management, February 1, 2017.



Annual U.S. FDA Biologic Approvals

The U.S. FDA has continued to approve a majority of Biologic License Applications.





US product approvals are based only on approvals by FDA's Center for Drug Evaluation and Research (CDER).

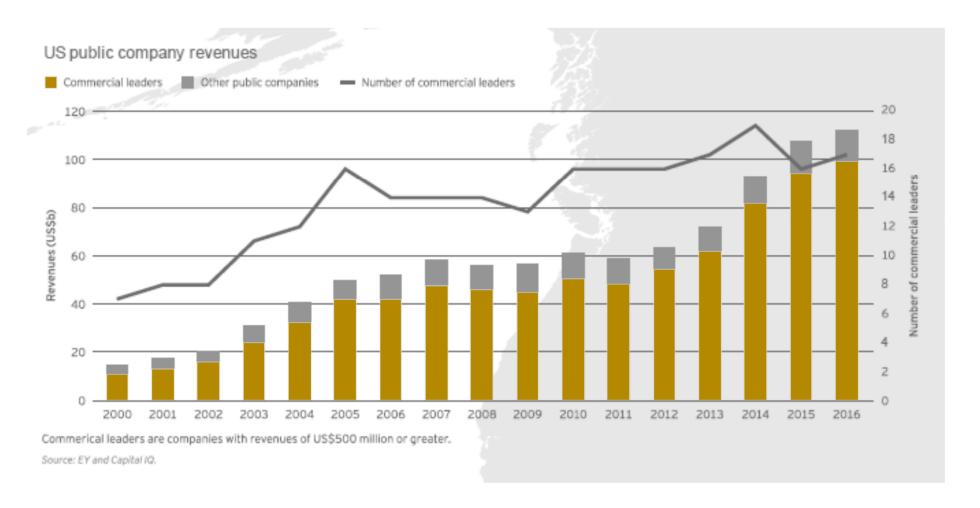
Source: EY and FDA.

Source: Biotechnology Report 2017 – Beyond borders – Stay the course, Ernst & Young, P. 6.



Annual Revenues of U.S. Biotech Firms

Annual revenues of U.S. biotechnology firms continue to grow.



Source: Biotechnology Report 2017 – Beyond borders – Stay the course, Ernst & Young, P. 38.



Dr. Claresa Levetan

- Founder and Chief Scientific Officer of Perle Bioscience, Inc.
- Emory University School of Medicine Graduate; Mount Sinai Medical Center, N.Y. Resident/Fellow
- Currently Thomas Jefferson University Hospital (Philadelphia, Pa.) affiliate
- Received the American College of Endocrinology's Highest Distinction in Clinical Endocrinology Award presented to the endocrinologist recognized as having achieved distinction in clinical endocrinology
- Former professor and Chief of Endocrinology and Diabetes at Drexel University College of Medicine
- Former Co-founder and Chief Scientific and Medical Officer and lead scientist of CureDM, Inc. CureDM's intellectual property portfolio was licensed to Sanofi-Aventis.
- Served as associate editor of the journals, Clinical Diabetes and Diabetes Forecast
- Recipient of the prestigious Roche Diagnosed award for innovative diabetes research
- Invited visiting scholar at Harvard University's Joslin Diabetes Center
- Investigator on the National Institute of Health's Diabetes Prevention Program and Woman's Health Initiative. Served on the steering committee of the NIH and CDC's National Diabetes Education Program.
- Co-chair of the American College of Endocrinology's Diabetes Outpatient and Inpatient consensus Conferences

