Insulina intel·ligent

XIVè CONGRÉS ACD 2017

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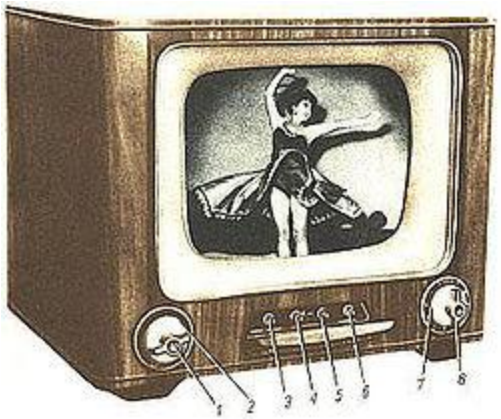
Crean un parche 'inteligente' que suministra insulina a pacientes con diabetes

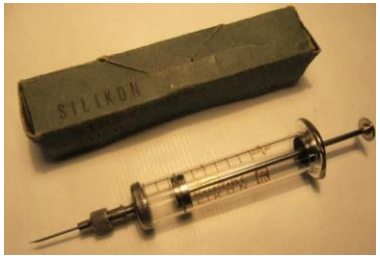
20.01.17 | 17:50h. **EUROPA PRESS | MADRID**

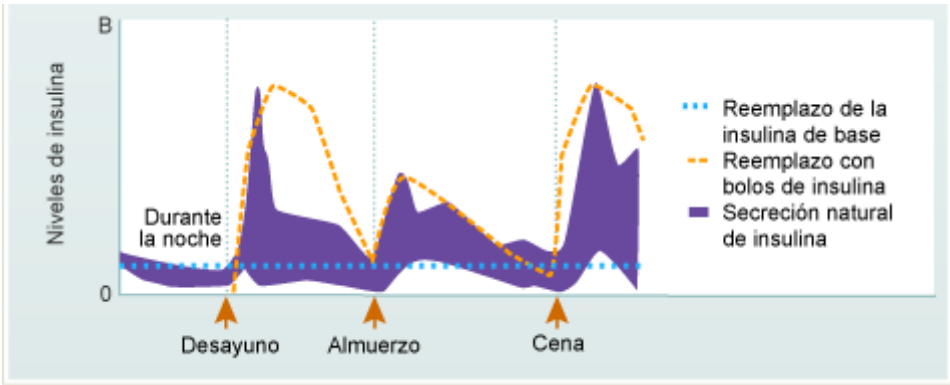
Investigadores de Estados Unidos han creado un parche 'inteligente', probado en ratones, que podría ayudar a suministrar insulina a personas con diabetes tipo 1 y tipo 2 cuando lo necesiten, tal y como publica la revista 'ACS Nano'.

Y es que, las personas con diabetes tipo 1 no producen insulina y los que tienen diabetes tipo 2 no la pueden usar insulina de forma eficaz. En ambos grupos, la glucosa se acumula en la sangre, lo que puede llevar a una serie de problemas de salud, incluyendo enfermedades del corazón, apoplejía, ceguera y amputación de los dedos de los pies, pies o piernas.

HAN PASADO CASI 100 AÑOS







Farmacocinética

Hipoglucemias

Imposibilidad de controlar todas las variables

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 19, Number 1, 2017
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2016.0350

ORIGINAL ARTICLE

Improved Postprandial Glycemic Control with Faster-Acting Insulin Aspart in Patients with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion

Bruce W. Bode, MD, FACE,[1] Joseph A. Johnson, PA-C,[1] Liselotte Hyveled, MSc, Pharm, MMBA,[2] Søren C. Tamer, MSc,[2] and Marek Demissie MD, PhD[2]

Background: Faster aspart is insulin aspart (IAsp) in a new formulation, which in continuous subcutaneous insulin infusion (CSII) in subjects with type 1 diabetes has shown a faster onset and offset of glucose-lowering effect than IAsp.

Methods: This double-blind, randomized, crossover active-controlled trial compared 2-h postprandial plasma glucose (PPG) response, following 2 weeks of CSII with faster aspart or IAsp. Primary endpoint: mean change in PPG 2 h after a standardized meal test ($\Delta PG_{av,0-2h}$). Subjects ($n=43$) had masked continuous glucose monitoring (CGM) throughout.

Results: Faster aspart provided a statistically significantly greater glucose-lowering effect following the meal versus IAsp: $\Delta PG_{av,0-2h}$: 3.03 mmol/L versus 4.02 mmol/L (54.68 mg/dL vs. 72.52 mg/dL); estimated treatment difference (ETD) [95% CI]: −0.99 mmol/L [−1.95; −0.03] (−17.84 mg/dL [−35.21; −0.46]; $P=0.044$). One hour postmeal, PG levels were −1.64 mmol/L (−29.47 mg/dL) lower with faster aspart versus IAsp ($P=0.006$). Interstitial glucose (IG) profiles supported these findings; the largest differences were observed at breakfast: 9.08 versus 9.56 mmol/L (163.57 vs. 172.19 mg/dL; ETD [95% CI]: −0.48 mmol/L [−0.97; 0.01]; −8.62 mg/dL [−17.49; 0.24]; $P=0.057$). Duration of low IG levels (≤3.9 mmol/L [70 mg/dL] per 24 h) was statistically significantly shorter for faster aspart versus IAsp (2.03 h vs. 2.45 h; ETD [95% CI]: −0.42 [−0.72; −0.11]; $P=0.008$). No unexpected safety findings were observed.

Conclusions: CSII delivery of faster aspart had a greater glucose-lowering effect than IAsp after a meal test. CGM results recorded throughout all meals supported this finding, with less time spent with low IG levels.

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 19, Number 3, 2017
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2016.0421

DTT

ORIGINAL ARTICLE

Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes

Satish K. Garg, MD,[1] Stuart A. Weinzimer, MD,[2] William V. Tamborlane, MD,[2] Bruce A. Buckingham, MD,[3] Bruce W. Bode, MD,[4] Timothy S. Bailey, MD,[5] Ronald L. Brazg, MD,[6] Jacob Ilany, MD,[7] Robert H. Slover, MD,[1] Stacey M. Anderson, MD,[8] Richard M. Bergenstal, MD,[9] Benyamin Grosman, PhD,[10] Anirban Roy, PhD,[10] Toni L. Cordero, PhD,[10] John Shin, PhD, MBA,[10] Scott W. Lee, MD,[10] and Francine R. Kaufman, MD[10]

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 19, Number 3, 2017
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2016.0349

DTT

ORIGINAL ARTICLE

"Let the Algorithm Do the Work": Reduction of Hypoglycemia Using Sensor-Augmented Pump Therapy with Predictive Insulin Suspension (SmartGuard) in Pediatric Type 1 Diabetes Patients

Torben Biester, MD,[1] Olga Kordonouri, MD,[1] Martin Holder, MD,[2] Kerstin Remus, RN,[1] Dorothee Kieninger-Baum, MD,[3] Tanja Wadien, RN,[2] and Thomas Danne, MD[1]

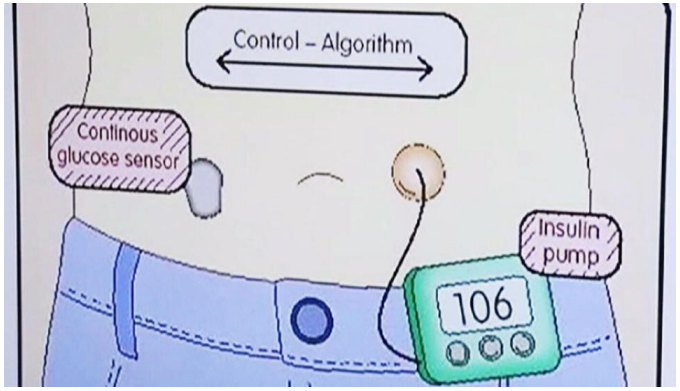
The FDA Approves Medtronic's MiniMed 670G Hybrid Closed Loop System

10/12/16 - NEW NOW NEXT

Autocontrol

Educación

Manejo



El verdadero reto es

Obtener una insulina sensible a la glucosa o con actividad glucosa dependiente

INSULINA INTELIGENTE
GSI/GRS

Journal of Drug Targeting

http://www.tandfonline.com/idrt
ISSN: 1061-186X (print), 1029-2330 (electronic)

J Drug Target, 2015; 23(7–8): 651–655
 DOI: 10.3109/1061186X.2015.1055749

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Smart approaches to glucose-responsive drug delivery

Matthew J. Webber[1,2] and Daniel G. Anderson[1,2,3,4,5]

Endocrinol Nutr. 2016;63(4):143–144

ELSEVIER

Endocrinología y Nutrición

www.elsevier.es/endo

EDITORIAL

Sistemas de liberación de insulina sensibles a la glucosa

CrossMark

Glucose-responsive insulin delivery systems

Mercedes Rigla Cros

¿ En que consisten los GRS?

- Encapsulación
  - Polímeros capaces de sufrir modificaciones estructurales consecuencia de cambios ambientales dando lugar a la liberación de insulina
  - No contienen un sensor ni un efector específico, es el polímero que contiene la insulina el que juega este papel dual
  - Dos componentes en el mismo sistema: glucosensor y sistema de liberación de insulina
- Análogos insulina- proteínas sintéticas de reconocimiento de glucosa

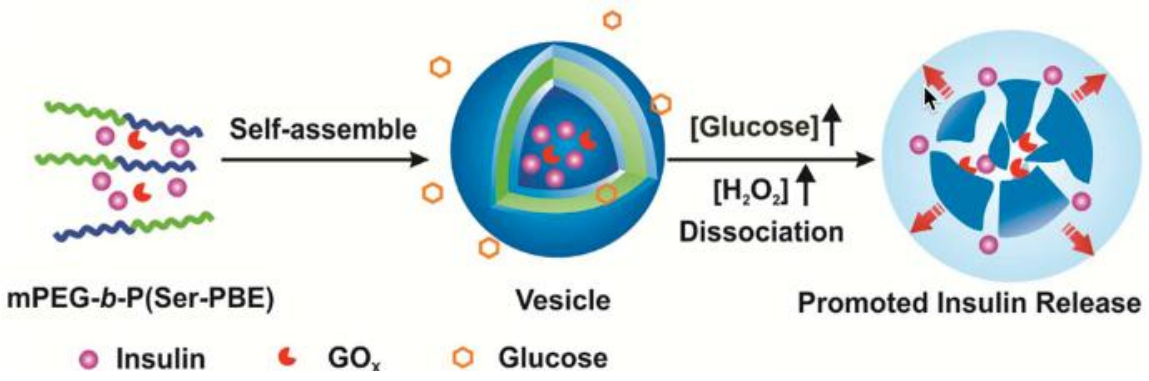
Mecanismos de detección de la glucosa (Glucosensor)

- Naturales (enzimas o proteínas)
  - Enzimas: Glucosa oxidasa
    - El sistema aprovecha cambios producidos tras oxidación de la glucosa : disminución pH, hipoxia, repulsión electrostática, etc
  - Proteínas de unión a la glucosa (lectinas): Concavalina A
    - Cambios viscosidad
    - Unión competitiva a la insulina: liberación de insulina al aumentar concentración glucosa
- Proteínas Sintéticas : acido fenilborónico (PBA)
  - Unión competitiva (encapsulación)
  - Modificación química de las insulinas (análogos)

Webber M.J. J Drug target 2015 ;23
Rigla M (2016). Endocrinol Nutr. 2016(4)
Xiuli Hu, et al. ACS Nano, 2017

Mecanismos de liberación de insulina

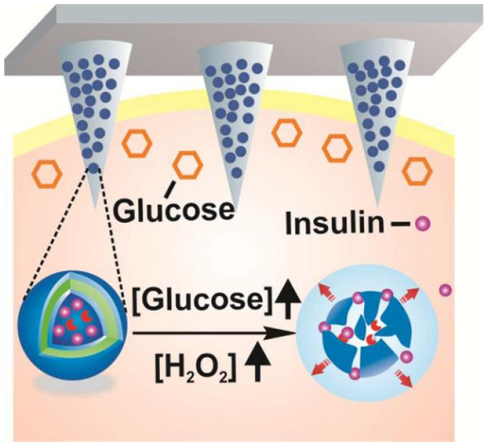
- Cambios transitorios en la porosidad de la membrana
- Exudación del hidrogel
- Contracción del hidrogel
- Disolución de la membrana

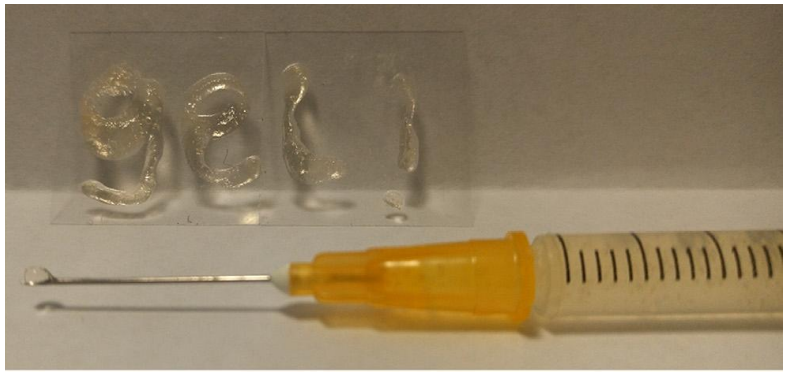


Webber M.J. J Drug target 2015 ;23
Rigla M (2016). Endocrinol Nutr. 2016(4)
Xiuli Hu, et al. ACS Nano, 2017

Materiales/ vías de administración

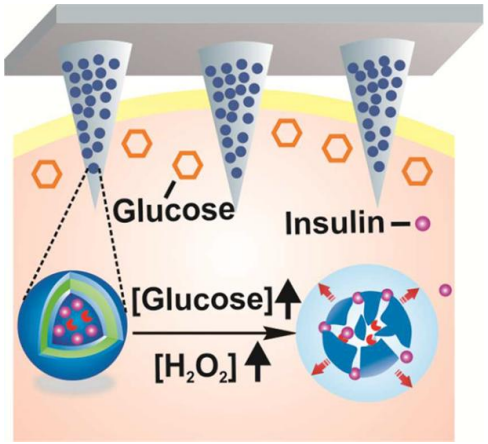
- Dispositivos implantables
- Hidrogel inyectable en tejido subcutáneo
- Parches con microagujas





El sistema ideal

- Alta capacidad de incorporación del fármaco (insulina)
- Capacidad de repuesta rápida, selectiva y repetible/predecible
- Estable
- Excelente biocompatibilidad
- Minima inmunogenicidad
- Facilidad de uso



Webber M.J. J Drug target 2015 ;23
Xiuli Hu, et al. ACS Nano, 2017

¿ Qué tenemos?

A glucose-controlled insulin-delivery system: semisynthetic insulin bound to lectin

M Brownlee, A Cerami

+ See all authors and affiliations

Science
Vol. 206, 07 Dec 1979
DOI: 10.1126/science.505005

Abstract

A stable, biologically active glycosylated insulin derivative that is complementary to the major combining site of concanavalin A has been synthesized. Hormone release is proportional to the quantity of glucose present. Glucose regulation of exogenous insulin delivery could have important applications in the therapy of diabetes mellitus.

Toxicidad

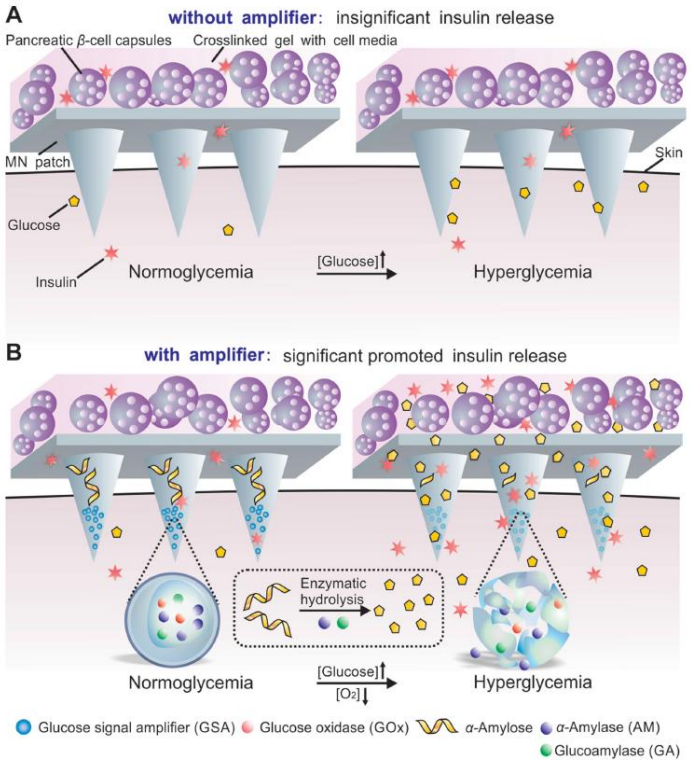
Materials Views
www.MaterialsViews.com

ADVANCED MATERIALS
www.advmat.de

Microneedles Integrated with Pancreatic Cells and Synthetic Glucose-Signal Amplifiers for Smart Insulin Delivery

*Yanqi Ye, Jicheng Yu, Chao Wang, Nhu-Y Nguyen, Glenn M. Walker, John B. Buse, and Zhen Gu**

Respuesta lenta
Rapidez cambio pH in vivo



NANO LETTERS

Letter

pubs.acs.org/NanoLett

Hypoxia and H_2O_2 Dual-Sensitive Vesicles for Enhanced Glucose-Responsive Insulin Delivery

Jicheng Yu,[†,‡] Chenggen Qian,[†,§] Yuqi Zhang,[†,‡] Zheng Cui,[∥] Yong Zhu,[†,∥] Qundong Shen,[§] Frances S. Ligler,[†] John B. Buse,[⊥] and Zhen Gu*[,†,‡,⊥]

[†]Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, Raleigh, North Carolina 27695, United States

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[§]Department of Polymer Science & Engineering and Key Laboratory of High Performance Polymer Materials & Technology of MOE, School of Chemistry & Chemical Engineering, Nanjing University, Nanjing, 210023, China

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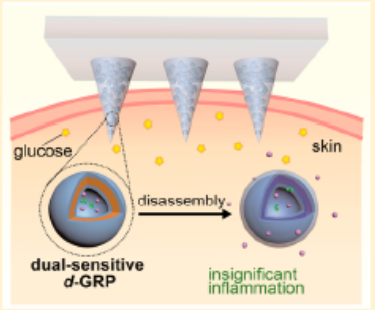
[⊥]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States

Supporting Information

ABSTRACT: A glucose-responsive closed-loop insulin delivery system mimicking pancreas activity without long-term side effect has the potential to improve diabetic patients' health and quality of life. Here, we developed a novel glucose-responsive insulin delivery device using a painless microneedle-array patch containing insulin-loaded vesicles. Formed by self-assembly of hypoxia and H_2O_2 dual-sensitive diblock copolymer, the glucose-responsive polymersome-based vesicles (*d*-GRPs) can disassociate and subsequently release insulin triggered by H_2O_2 and hypoxia generated during glucose oxidation catalyzed by glucose specific enzyme. Moreover, the *d*-GRPs were able to eliminate the excess H_2O_2, which may lead to free radical-induced damage to skin tissue during the long-term usage and reduce the activity of GOx. In vivo experiments indicated that this smart insulin patch could efficiently regulate the blood glucose in the chemically induced type 1 diabetic mice for 10 h.

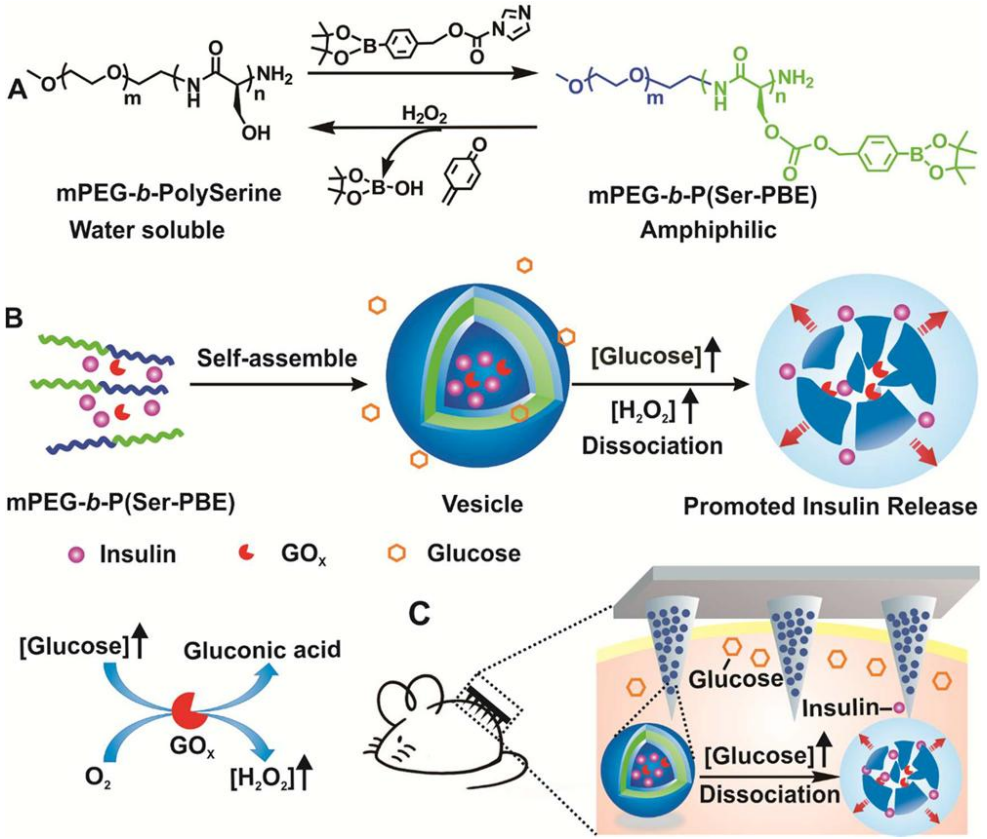


KEYWORDS: *Drug delivery, diabetes, insulin, glucose-responsive, hypoxia-sensitive, H_2O_2-sensitive*

ACSNANO
www.acsnano.org

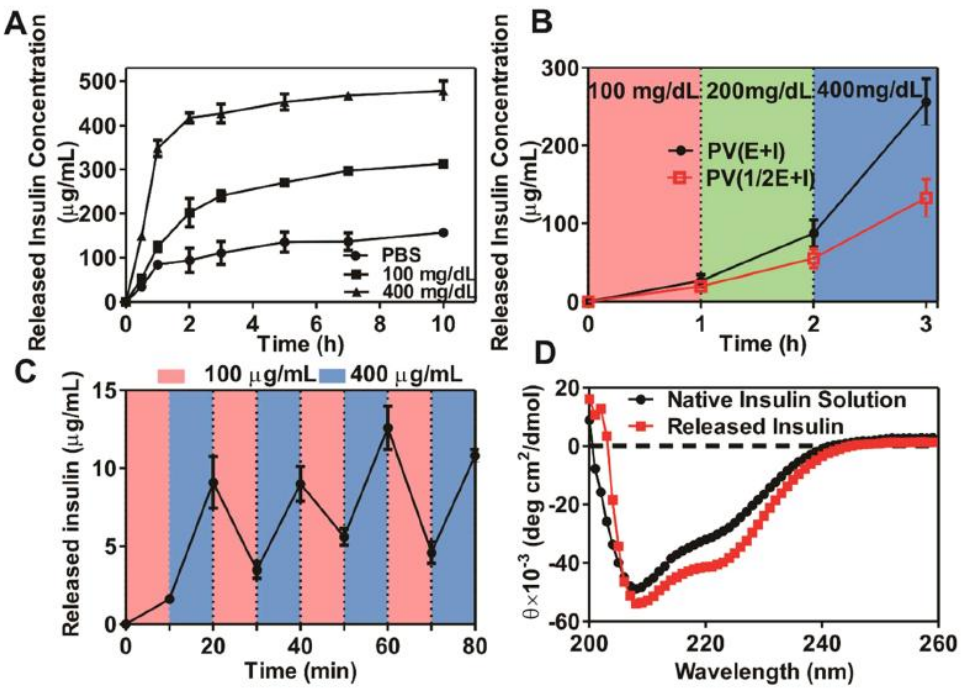
H_2O_2-Responsive Vesicles Integrated with Transcutaneous Patches for Glucose-Mediated Insulin Delivery

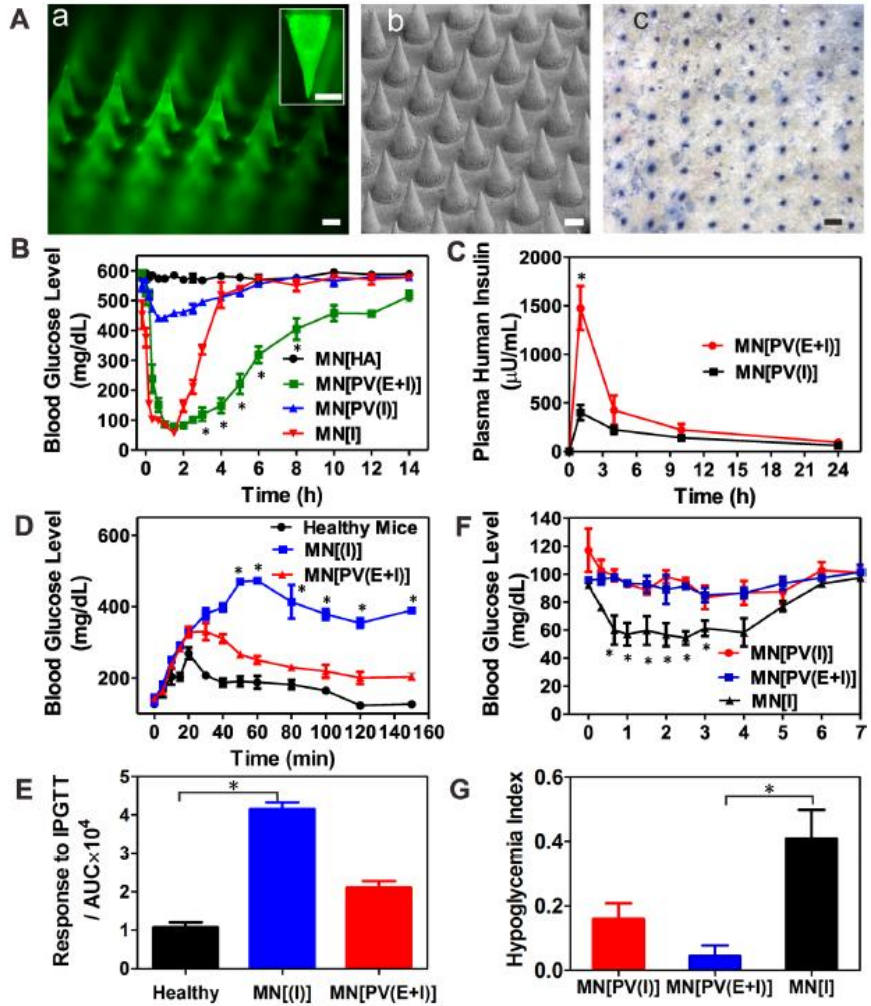
Xiuli Hu,[†,‡] Jicheng Yu,[†] Chenggen Qian,[†] Yue Lu,[†] Anna R. Kahkoska,[§] Zhigang Xie,[‡] Xiabin Jing,[‡] John B. Buse,[§] and Zhen Gu*[,†,§]



In Vitro

In Vivo





ARTICLE IN PRESS

Acta Biomaterialia xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

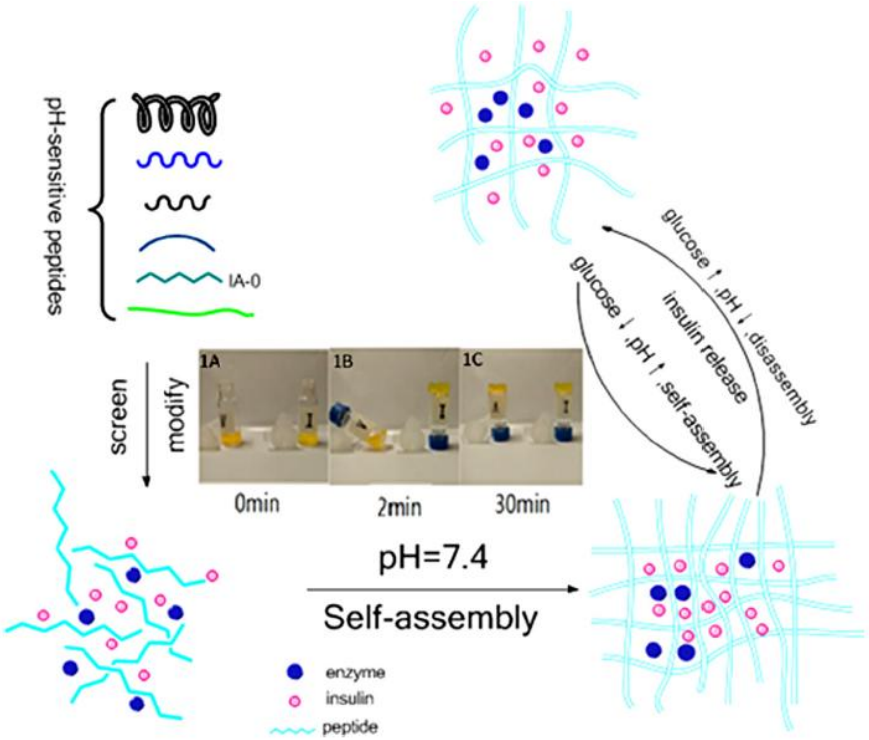
Acta Biomaterialia

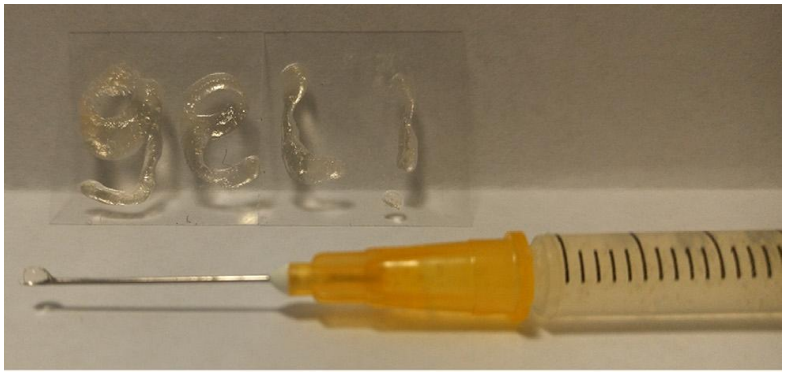
journal homepage: www.elsevier.com/locate/actabiomat

Full length article

pH-sensitive peptide hydrogel for glucose-responsive insulin delivery

Xue Li [a,1], Mian Fu [a,1], Jun Wu [b,e,*,1], Chenyu Zhang [a], Xin Deng [a], Arvind Dhinakar [c], Wenlong Huang [a,d], Hai Qian [a,d,*], Liang Ge [a,*]





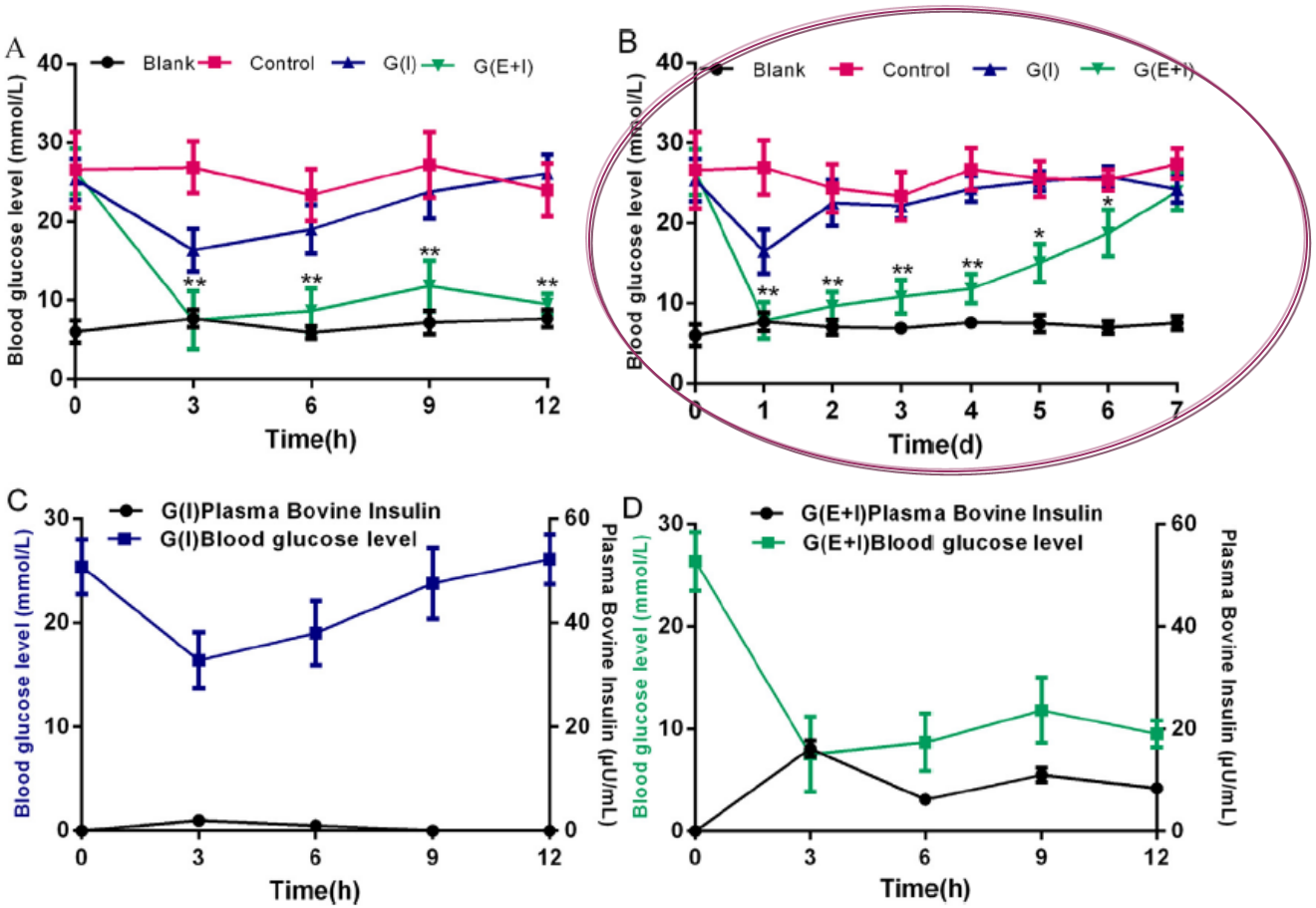


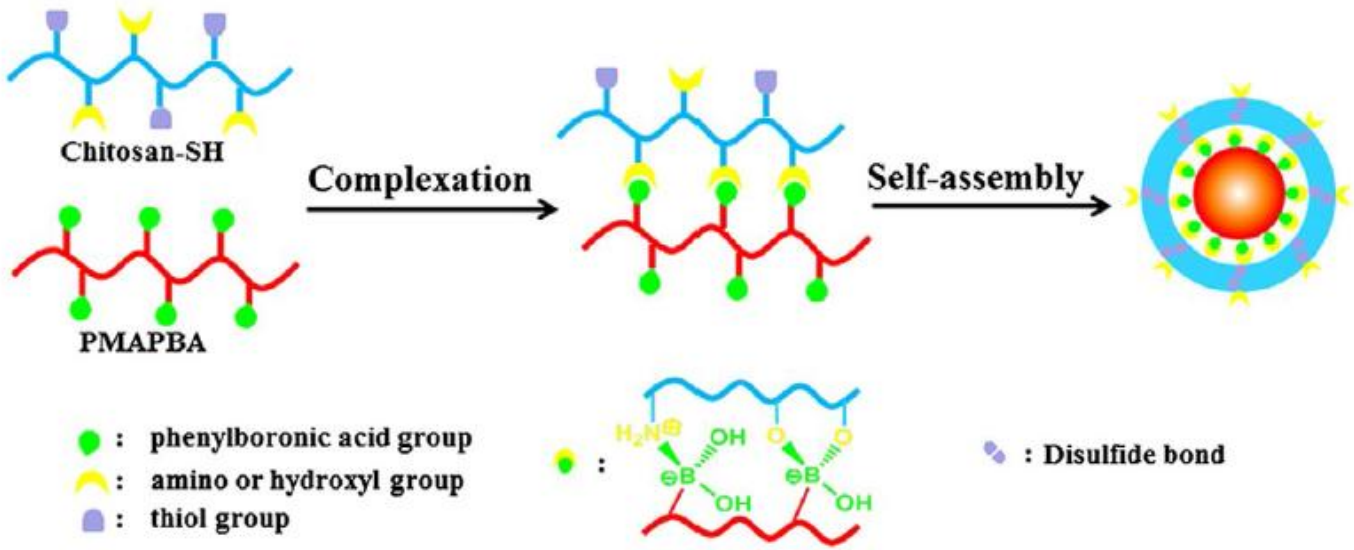
Fig. 7. In *vivo* glucose regulation of drug-loaded hydrogel on STZ-induced diabetic mice. A) The BG levels were continuously monitored in the first 12 h after administration of PBS solution, G (E + I) and G (I) to the STZ-induced diabetic mice. B) The BG level of STZ-induced diabetic mice after treating with PBS solution, (G (E + I)) and (G (I)). C and D) Changes of the BG levels and the plasma insulin concentration of STZ-induced diabetic mice in the first 12 h after treating with: C (G (I)), D (G (E + I)). Data points represent mean ± SD (n = 8). $^{*}p < 0.05$ and $^{**}p < 0.01$ compared to control group.

JOURNAL OF BIOMATERIALS SCIENCE, POLYMER EDITION, 2017
VOL. 28, NO. 1, 93–106
http://dx.doi.org/10.1080/09205063.2016.1246289

Taylor & Francis
Taylor & Francis Group

Development of shell cross-linked nanoparticles based on boronic acid-related reactions for self-regulated insulin delivery

Yanxia Wang[a], Fan Huang[b], Yingjuan Sun[a], Ming Gao[a] and Zhihua Chai[a]



Scheme 1. Proposed formation process of PMAPBA/chitosan-SH nanoparticles.

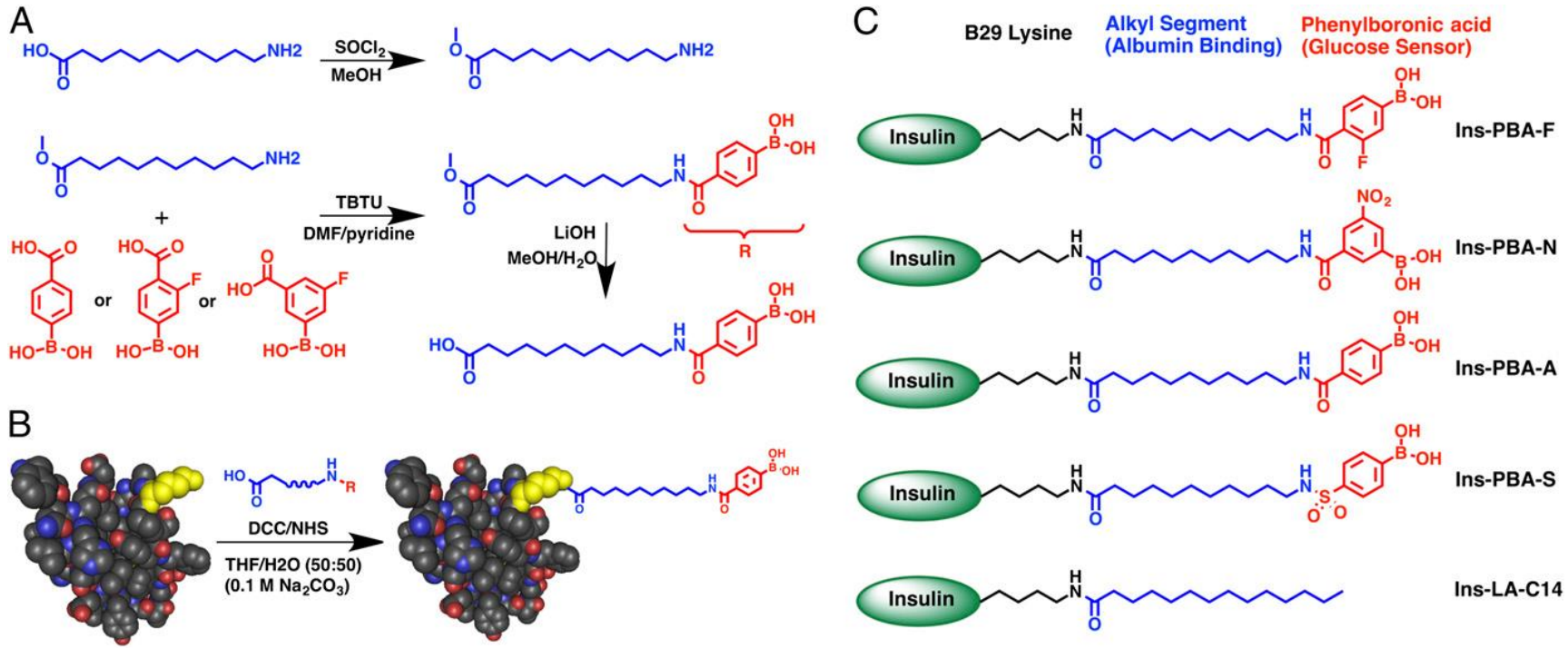
Shell cross-linked nanoparticles were fabricated by the complexation of poly(3-methacrylamido phenylboronic acid) (PMAPBA) and thiolated chitosan (chitosan-SH) via boronic acid-related reactions. The formation of PMAPBA/chitosan-SH nanoparticles was confirmed by transmission electron microscopy, dynamic light scattering, and UV spectroscopy. The nanoparticles had a narrow size distribution with a relatively high positive charge density, and the size and zeta potential of the nanoparticles correlated with the chitosan-SH concentration. Furthermore, owing to the cross-linking of the nanoparticle shell, insulin was encapsulated in the nanoparticles with a loading capacity of up to 18%. The release of insulin from the nanoparticles slowed down because of the presence of disulfide bonds and increased with increasing glucose level in the medium. The structure of the released insulin was not distorted. More importantly, the nanoparticles had good cytocompatibility, as demonstrated by *in vitro* experiments. The simplicity of this strategy along with a high loading capacity, glucose sensitivity, and cytocompatibility of the produced nanoparticles should significantly boost their application in self-regulated insulin delivery.

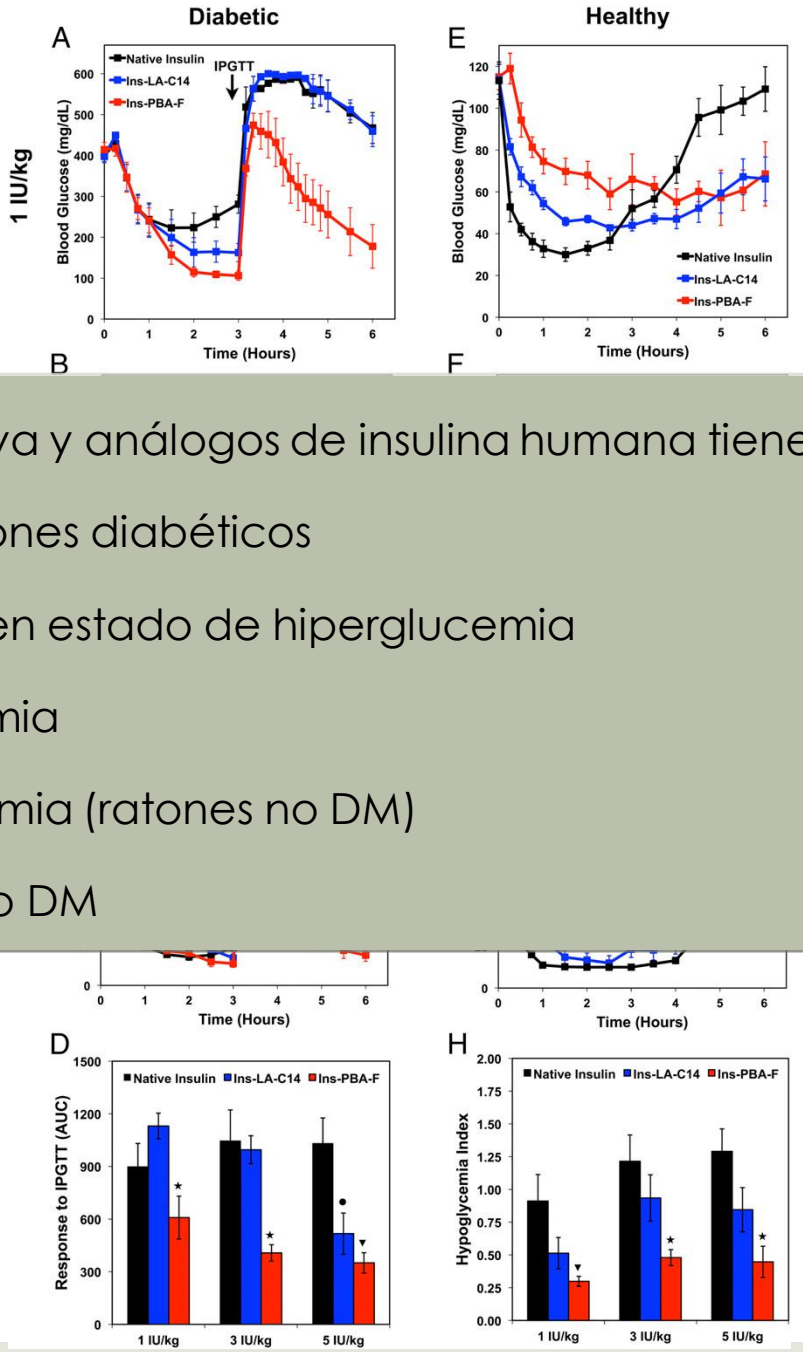
Falta de especificidad y necesidad de pH alcalino

> Current Issue > vol. 112 no. 8 > Danny Hung-Chieh Chou, 2401–2406, doi: 10.1073/pnas.1424684112

Glucose-responsive insulin activity by covalent modification with aliphatic phenylboronic acid conjugates

Danny Hung-Chieh Chou[a,b,c,1,2], Matthew J. Webber[a,c,1], Benjamin C. Tang[a,c,1], Amy B. Lin[a,c], Lavanya S. Thapa[a,c], David Deng[a,c], Jonathan V. Truong[a,c], Abel B. Cortinas[b], Robert Langer[a,b,c,d,e,3], and Daniel G. Anderson[a,b,c,d,e,3]





La insulina Ins-PBA-F comparada con insulina nativa y análogos de insulina humana tiene:

- Una mayor actividad en respuesta al GTT en ratones diabéticos
  - Aumento de la potencia y de la respuesta en estado de hiperglucemia
  - Reducción de la actividad en normoglucemia
- Un índice hipoglucémico menor en normoglucémia (ratones no DM)
- Cinética idéntica a la insulina de un páncreas no DM

Incertidumbres

- ¿Inmunogenicidad?
- ¿Biocompatibilidad?
- ¿ Es fiable la medición de la glucosa?
- ¿Puede un sistema bioartificial replicar el trabajo de la célula beta ?
- ¿ que pasa en caso de cetoacidosis?
- ¿ Realmente puede controlar todas las variables?

Implicaciones

Personas con diabetes

- Desaparecería concepto terapia basal-bolo: autoanálisis, recuento RHC, etc
- Desaparecerían las hipoglucemias
- Desaparecería la variabilidad debida a factores dependientes de la persona: actividad física y ejercicio, ingestas, estrés, etc
- Aumentaría sensación de seguridad: no error de dosis

Impacto en organizaciones / sistemas

- Cambio en los protocolos de insulinización y educación diabetológica
- Desaparición de la monitorización capilar ?
- Sustitución de los actuales sistemas ISCI - MCG?
- Serian los nuevos sistemas de close-loop?
- Acceso universal?

MERCK Be well

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ABOUT US PRODUCTS RESEARCH LICENSING NEWSROOM CAREERS INVESTORS

Licensing

- MRL BD&L Leadership
- Licensing Contacts
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Merck to Acquire SmartCells, Inc.

WHITEHOUSE STATION N.J. and BEVERLY, M.A., Dec. 2, 2010 - Merck & Co., Inc., (NYSE:MRK) and SmartCells, Inc., today announced that they have entered into a definitive agreement under which Merck will acquire SmartCells, a private company developing a glucose responsive insulin formulation for the treatment of diabetes mellitus.

"Maintaining control of blood glucose levels represents a daily challenge for people living with diabetes," said Nancy Thornberry, senior vice president and head, diabetes and obesity franchise, Merck Research Laboratories. "Through the acquisition of SmartCells we have obtained innovative technology that may enable us to develop glucose-responsive insulins. If this investigational technology is ultimately approved for use with patients, it could provide an important new therapy for the treatment of diabetes. This holds the potential to significantly impact the treatment of this disease."

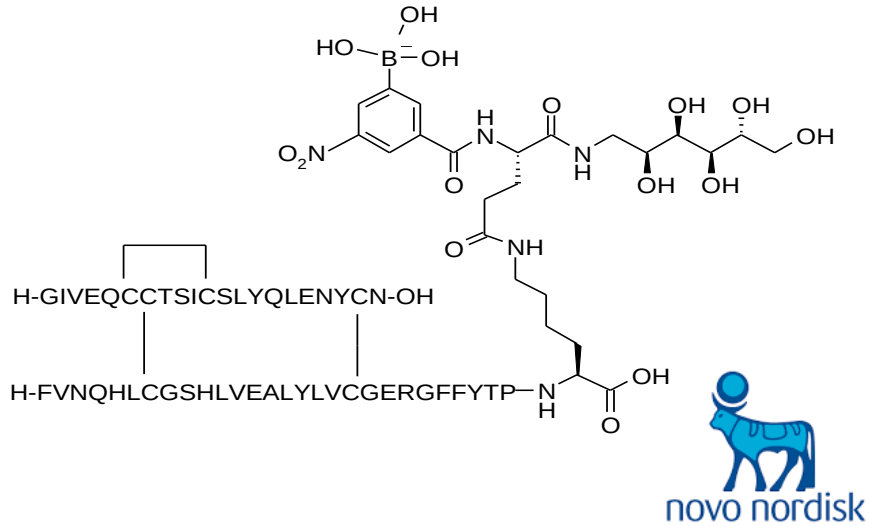
Under the terms of the agreement, Merck will acquire all outstanding stock of SmartCells, Inc. In return SmartCells shareholders will receive an upfront cash payment and be eligible to receive clinical development and regulatory milestones for products resulting from the transaction for potential aggregate payments in excess of $500 million. Sales-based payments for products resulting from the transaction will also be payable. SmartCells' board of directors has unanimously approved the transaction.

"At SmartCells, we have made important progress in rapidly advancing from early concept towards clinical development," said Todd C. Zion, Ph.D., president, co-founder and chief executive officer. "This acquisition positions our novel technology for success in the hands of a leading pharmaceutical company with proven expertise and exceptional resources to deliver breakthrough diabetes products to patients."

SmartCells has developed a technology platform that makes it possible to auto-regulate the release of a therapeutic based on the plasma concentration of a designated molecular indicator. In the case of insulin, the technology employs an approach whereby an insulin therapeutic is available only in the presence of a specific glucose concentration range. If this approach is successful in the clinic, it has the potential to produce insulin analogs that may result in a lower risk of hypoglycemia (low blood sugar) compared with standard insulin analogs and improve control over both fasting and post meal glucose levels.

About SmartCells

SmartCells, Inc. is focused on developing glucose-regulated SmartInsulin products for the treatment of diabetes. The company's core technology was originally developed at The Massachusetts Institute of Technology by its president, co-founder and chief executive officer Dr. Todd Zion. SmartCells has since developed the platform into several clinical candidates with the support of grant awards from the National Institutes of Health and equity investments from members of Boston Harbor Angels, Angel Healthcare Investors, Beacon Angels and Cherrystone Angel Group. For more information, visit www.smartinsulin.com.



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STUDY DETAIL

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A three-part study to evaluate the safety, pharmacokinetics and pharmacodynamics of MK-2640 in healthy participants (Part I) and participants with type 1 diabetes mellitus (Parts II and III) (MK-2640-001)

ClinicalTrials.gov Identifier:	NCT02269735 (view full study on clinicaltrials.gov)
Condition:	Type 1 Diabetes Mellitus
Status:	Completed

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE

For Immediate Release
February 17, 2016

Contact : Becky Bruhn
206-568-1489 or bbruhn@pndri.org

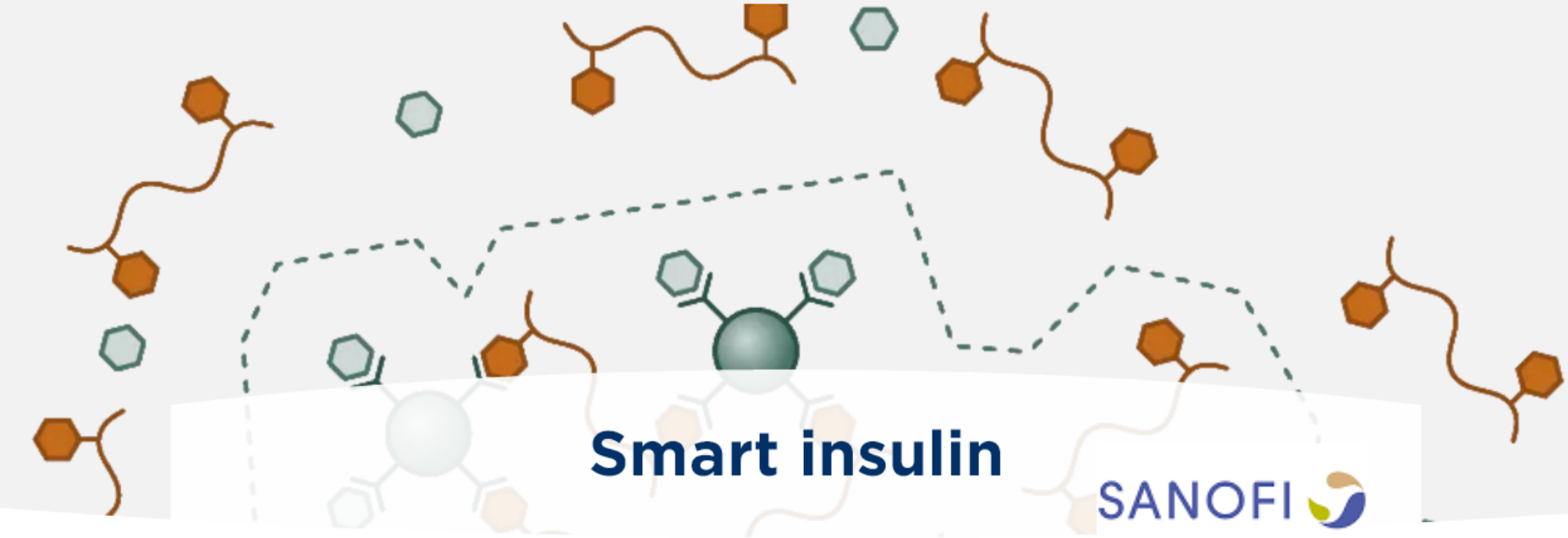
New "Smart Insulin" Technology Acquired by Eli Lilly

Glycostasis, Inc. invention incubated at PNDRI to be further developed by insulin pioneer

Seattle – Glycostasis, Inc., a startup company incubated at the Pacific Northwest Diabetes Research Institute (PNDRI), has been acquired by Eli Lilly and Company.

Dr. John Mulligan, founder and CEO of Glycostasis, has invented a new technology aimed at "smart insulin," which could improve glucose control in people living with diabetes. Lilly, a world leader in the insulin market and a pioneer in insulin research, is acquiring the technology for further development.

The new technology developed by Glycostasis is called "smart insulin" because it aims to regulate blood glucose levels independent of patient input, providing more insulin activity when blood glucose is high, and less when blood glucose is low.

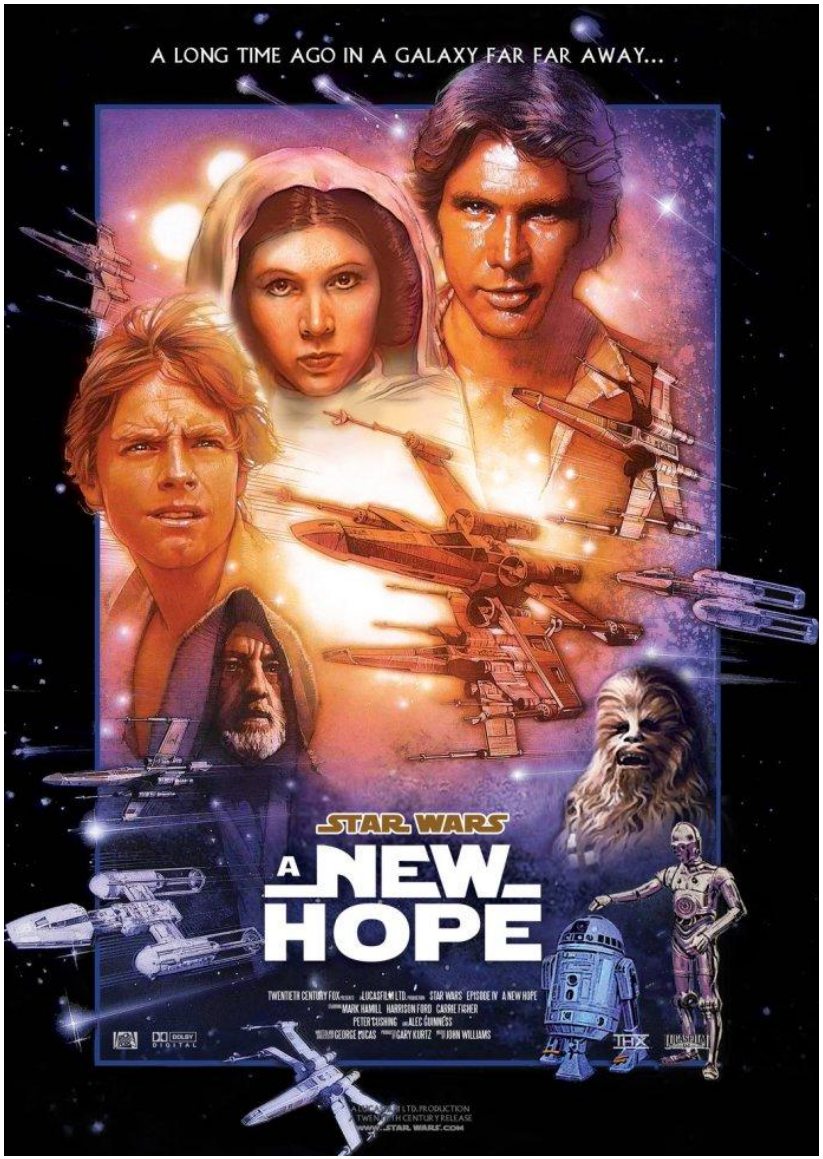


Smart insulin

SANOFI

‘Smart’ insulins or glucose-responsive insulins are being designed to only turn on when they’re needed and off when they’re not. These insulins could make hypos history and help ensure perfect glucose control throughout any given day.

A person with type 1 diabetes would take an injection, or perhaps even a pill, of one of these insulins – enough to cover the needs of a day – and the smart insulin would circulate in the body, inactive, until blood glucose levels start to rise. As glucose levels rise, the insulin would go to work to bring these levels back down



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