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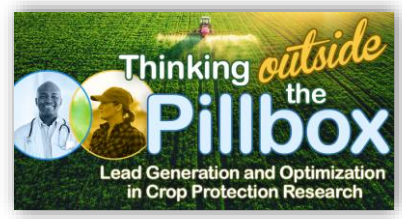
How has ACS Webinars® benefited you?

ACS Chemistry for Life®

"As a retired research chemist who was active in crop protection, this ACS Webinar was a valuable update on the state of the art."



Fan of the Week

Gary D. Grantham, Ph.D.
Grantham Consulting,
ACS member for 50 years strong!

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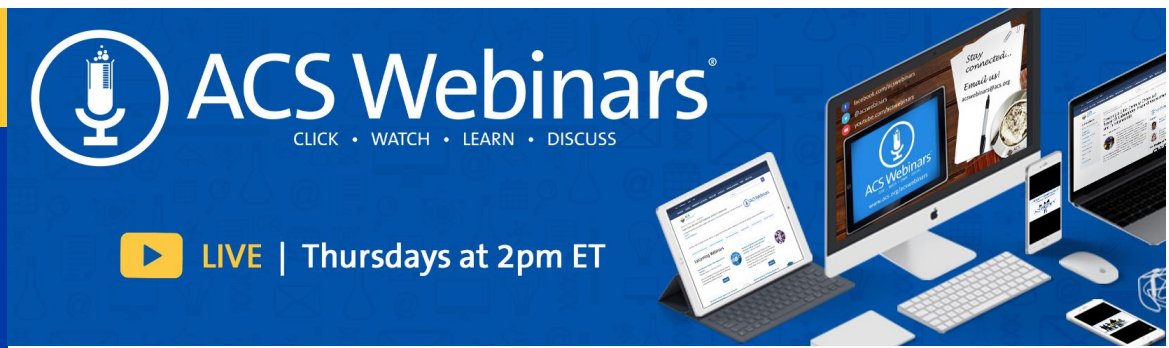

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2018 Winners: AstraZeneca, DuPont, Pfizer, SeattleGenetics

www.acs.org/heroes

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9

Upcoming ACS Webinar!

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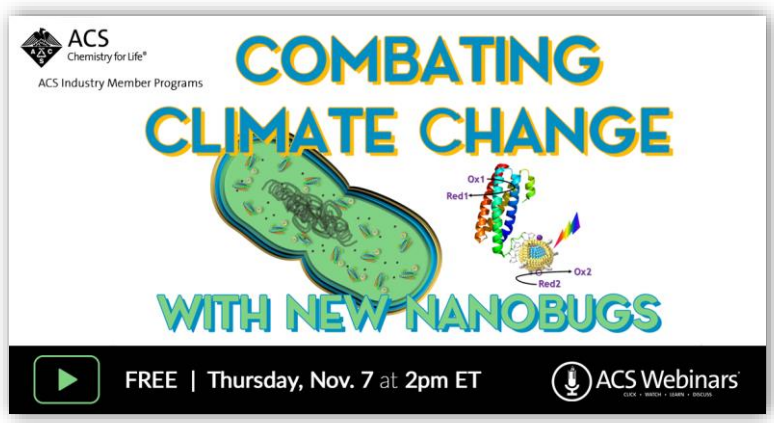
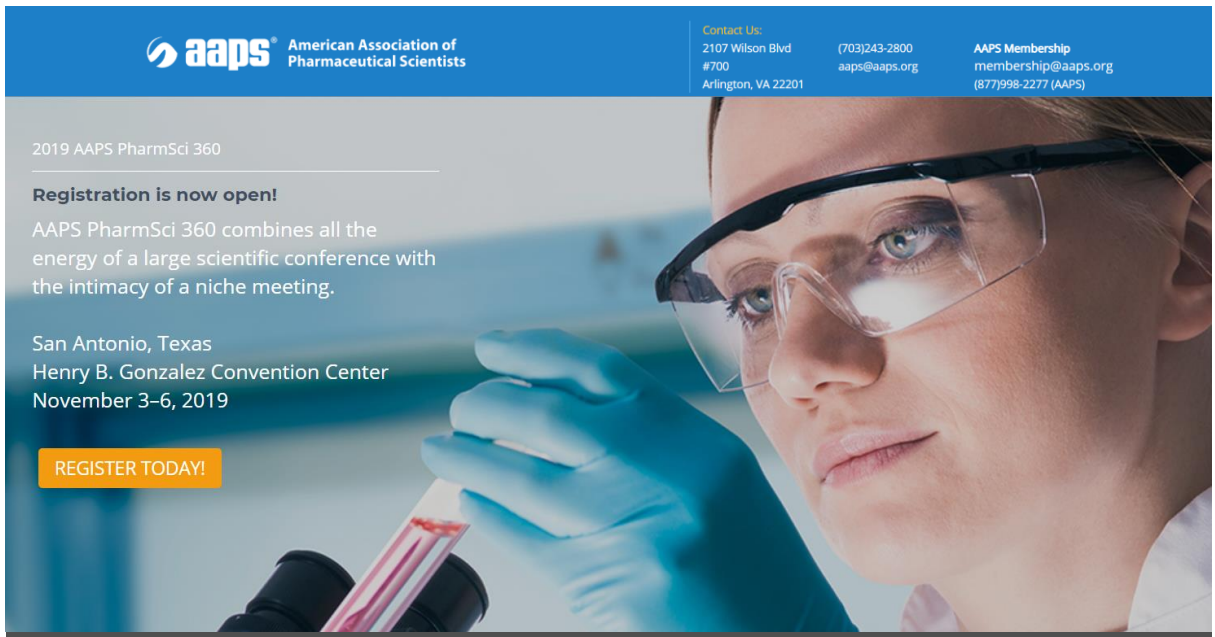


https://www.acs.org/content/acs/en/acs-webinars/technology-innovation/nanobugs.html

10



11

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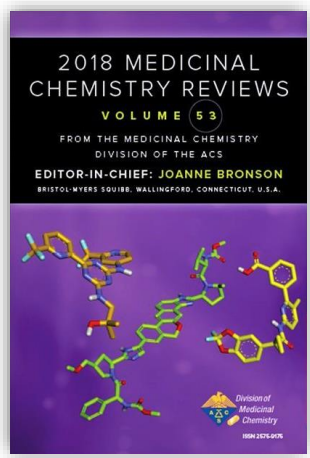

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12

Celebrating 5 years & 50 Drug Discovery Webinars!

http://bit.ly/acsDrugDiscoveryArchive

ACS Chemistry for Life®

2014

Drug Discovery Series #1 - Current Drug Discovery and Development Process
(DDS #1) Watch this overview of the drug discovery and development process to learn the stages and challenges in every step.

Primer in Drug Target Classes
(DDS #2) Listen in on a discussion on the big four druggable families and the difference between small molecule and biotherapeutic targets.

Key Concepts in Identifying Drug Leads
(DDS #3) Discover how drug-likeness is a decisioning concept, explore the Rule of Five, and show how lessons from the past may guide the present.

Lead Optimization - Building Efficacy & Safety
(DDS #4) Learn strategies on how to effectively optimize small molecule hits and rapidly assess your findings.

Tips for Filing IND and Starting your Clinical Trials
(DDS #5) What do you need to know when filing for Investigational New Drug submissions to the United States Food and Drug Administration?

The Role of Chemistry in Clinical Trials: The Big Expense & Lessons Learned
(DDS #6) Learn how the properties of the candidate impact decisions in the discovery process.

Pharmacoeconomics and IP Strategies in Drug Development
(DDS #7) Review the basic principles of Pharmacoeconomics in drug development strategies as well as its role in determining health insurance coverage of drug products.

Future of Drug Discovery - Challenges, Risks and Rewards
(DDS #8) Explore how new risks and challenges will be dealt with in the future and the key skill sets required of future medicinal chemists.

2015

Designing Better Drug Candidates
(January) Learn various factors that can be used to improve candidate quality from Dr. Paul Leeson.

Strategies to Improve Solubility of Drug Candidates
(February) Learn a number of different strategies for improving drug solubility through structural modification.

Fragment-Based Drug Design Strategies
(March) Finding the right drug target is becoming increasingly difficult. Learn how focusing on the smaller picture can have big results.

Screening Strategies
(April) Learn the pros and cons of different screening strategies.

Avoiding PAINS (pan-assay interference compounds)
(May) Jonathan Baell shares some tips on how to avoid the dead ends of drug discovery.

Accessing CNS Positron Emission Tomography (PET) Ligand Discovery
(June) Jon Lai Zhang as he lays out a set of preferred parameters for which has yielded successful PET ligands and reduced resources and timelines.

X-ray Crystallography in Drug Discovery
(July) Jon Mason and Mike Congreve describe what protein-ligand X-ray data can do for you.

Choices and Trends in Solid Dosage Form Selection
(August) Discover the pros and cons of the different solid dose forms and what to consider when selecting.

Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies
(September) Gain an understanding of acceptable drug delivery approaches to support preclinical dose escalation.

Pharmacokinetic Considerations in Drug Design and Development
Learn about key pharmacokinetic concepts including clearance, volume of distribution, half-life and protein binding.

Prodrugs in Drug Discovery
(November) John Higgins shares the utility of prodrugs, their general properties and pharmaceutics for optimal performance.

2016

I - Time: The Fourth Dimension in Drug Discovery
The Importance of Drug-Target Kinetics in Drug Design
Robert Copeland - Epizyme, Inc
Dan Evanson - Carmot Therapeutics
Long-Acting Injectable Medications: Strategies and Mechanistic Considerations
Jules Remahan - Alkermes
Annette Bak - Merck
Modified Release Formulations for Solubility Starved Compounds
Mengkee Hu - Merck
John Morrison - BMS
The Medicinal Chemist of Tomorrow (Special Topic)
Joe Barrish - Achillon
Ravi Nargund - Merck
Molly Schmid - Tech Coast Angels
II - Beyond Traditional Small Molecules
Design of Deliverable Macrocycles
Scott Lokey - UC Santa Cruz
Nicholas Meanwell - BMS
Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates
L. Nathan Tumey - Pfizer
Peter Senter - Seattle Genetics
Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides
Punit Seth - Ionis
Richard Olson - BMS
Crystallography as a Drug Design and Delivery Tool (Special Topic)
Robert Wendsor - Crystal Pharmatech
Vincent Stoll - Abbvie
Andrew Bruhnsill - Merck
III - Pharmacology Revisited
Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites?
Deepak Dalvie - Pfizer
Frederick Peter Guengerich - Vanderbilt University
Rational Design of Small Molecules Targeting RNA
Matt Disney - Scripps Rl Florida
Amanda Garner - University of Michigan
Cell Penetrating Peptides to Improve Cellular Drug Uptake
Dehua Pei - The Ohio State University
Scott Hart - Bristol-Myers Squibb

2017

I - Fighting Cancer
Fighting Cancer: Targeting CNS Malignancy with Kinase Inhibitors
Timothy P. Heffron - Genentech
Mark Wittman - Bristol-Myers Squibb
Fighting Cancer: Epigenetic targets for Oncology
Stuart Conway - Oxford
Sharan Bagal - AstraZeneca
Fighting Cancer: Allostery and Targeting Cancer Cell Metabolism
Stefan Gross - Agios
Scott Edmundson - AstraZeneca
Special Broadcast
Cystic Fibrosis: Discovery of CFTR Modulators
Peter Grootenhuis - Vertex
Nick Meanwell - Bristol-Myers Squibb
II - Anti-Infectives
Anti-Infectives: Rational Approaches to the Design and Optimization
Jason Sello - Brown University
Courtney Aldrich - University of Minnesota
Tuberculosis: An Introduction for Medicinal Chemists
Carl Nathan - Weill Cornell Medicine
Christopher Boyce - Merck
Viral Hepatitis: The Search for a Cure
Mike Sofia - Arbutus Biopharma
Stephen Mason - CaroGen Corporation
Special Broadcast
Spinal Muscular Atrophy
Kevin Hodgetts - Harvard Medical School
Alyson Weidmann - ACS Publications
III - Immunology
Psoriasis: Treatment and Novel Approaches
Frank Narjes - AstraZeneca
John Morrison - Bristol-Myers Squibb
Lupus: Treatment and Novel Approaches
Laurence Menard - Bristol-Myers Squibb
Mary Struthers - Bristol-Myers Squibb

2018

Jan 25 — A New Strategy in Drug Discovery: Protac-Induced Protein Degradation
Ian Churcher - Benevolentbio
Aaron Balog - Bristol-Myers Squibb

Feb 22 — Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry
Annette Bak - AstraZeneca
Donna Huryn - University of Pittsburgh
Erika Arvajo - Bristol-Myers Squibb
Nunzilam Zaveri - Astraea Therapeutics

Mar 29 — A Nanomedicine Overview for mRNA Delivery: Innovative Methods Using Lipid Nanoparticles
Marianna Yanez Arteta - AstraZeneca
Dennis Luerig - Genentech

Apr 26 — Nanomaterials for Fighting Antibiotic-Resistant Bacteria
Vincent Rotello - University of Massachusetts at Amherst
Christopher England - American Chemical Society

May 31 — Advanced Nano-Delivery Systems: Facilitating Tumor Delivery and Mitigating Resistance
Mansoor Amiji - Northeastern University
Venkat Krishnamurthy - AstraZeneca

Jun 28 — Pitfalls and Promise of Central Nervous System Drug Discovery
Valentin Gribkoff - Yale University
Nicholas Meanwell - Bristol-Myers Squibb

Jul 26 — How to Optimize Central Nervous System Therapeutics: Med Chem Strategies, Tactics, and Workflows
Craig Lindsley - Vanderbilt Center for Neuroscience Drug Discovery
Amy Newman - Intramural Research Program, NIH

Sept 20 — A Novel Strategy for the Treatment of Chronic Pain: Antagonising PAR2 with a Monoclonal Antibody
Pete Thornton - AstraZeneca
Nunzilam Zaveri - Astraea Therapeutics

Oct 18 — How to Predict Human CNS PK/PD: Preclinical Experiments and Advanced Mathematical Modelling
Elizabeth de Lange - Leiden Academic Center for Drug Research
Alexander Tropsha - University of North Carolina

Nov 29 — Human Exosomes: An Ideal Vehicle for Delivery of Therapeutic RNAs to Cells and Organs
Hadi Valadi - University of Gothenburg
Alexander Kapustin - AstraZeneca

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2019 Drug Design and Delivery Symposium

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Jan 31 — **How to Succeed in Drug Discovery: Insight from Medicinal Chemists** (1.5 hrs.)
John Lowe III - JL3 Pharm
Mark Murcko - Relay Therapeutics
Ann Weber - Kallyope
William Greenlee - MedChem Discovery Consulting

Feb 28 — **Cosolvent Molecular Dynamics: Mapping Protein Surfaces to Discover Allosteric Sites**
Heather Carlson - University of Michigan
Rommie Amaro - UC San Diego

Mar 28 — **Women at the Interface of Computational Chemistry and Drug Discovery** (1.5 hrs)
Zoe Cournia - Biomedical Research Foundation and *JCIM*
Kate Holloway - Gfree Bio
Yvonne C. Martin - Previously of Abbott Laboratories
Shana Posy - Bristol-Myers Squibb

Apr 18 — **Effective Exploration of Chemical Space in Hit-Finding**
Hanneke Jansen - Novartis Institutes for BioMedical Research
Zoe Cournia - Biomedical Research Foundation and *JCIM*

May 30 — **Widening the Therapeutic Window: Kinetic Selectivity and Target Vulnerability**
Peter Tonge - Stony Brook University and *ACS Infectious Diseases*
Stewart Fisher - C4 Therapeutics

Jun 27 — **Precision Control of CRISPR-Cas9**
Amit Choudhary - Broad Institute of Harvard and MIT
Venkat Krishnamurthy - AstraZeneca

Aug 8 — **Transformation of Recombinant Cells to FDA Approved Products: Clinical Development to Marketplace** (New Date)
Rodney Ho - University of Washington
Venkat Krishnamurthy - AstraZeneca

Aug 22 — **The Evolving Outsourcing Landscape in Pharma R&D: Pros and Cons of Different Models**
Bart DeCorte - MercachemSyncom
Allen Reitz - Fox Chase Chemical Diversity Center

Sep 19 — **Thinking Outside the Pillbox: Lead Generation and Optimization in Crop Protection Research**
Fides Benfatti - Syngenta

Oct 24 — **Treating Diabetes: Designing the Once-Weekly and Oral GLP-1 Semaglutide**
Jesper Lau - Novo Nordisk A/S

Nov 28 — **Prodrugs**
Jarkko Rautio - University of Eastern Finland

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AstraZeneca
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Nicholas Meanwell
Bristol-Myers Squibb
ACS MEDI


Janice Silverman
American Chemical Society


John Morrison
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15

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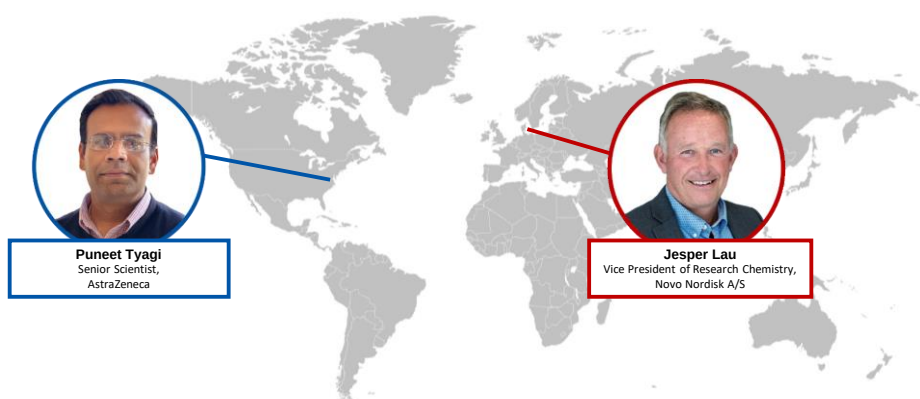
Treating Diabetes: Designing the Once-Weekly and Oral GLP-1 Semaglutide



Puneet Tyagi
Senior Scientist,
AstraZeneca

Jesper Lau
Vice President of Research Chemistry,
Novo Nordisk A/S

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16

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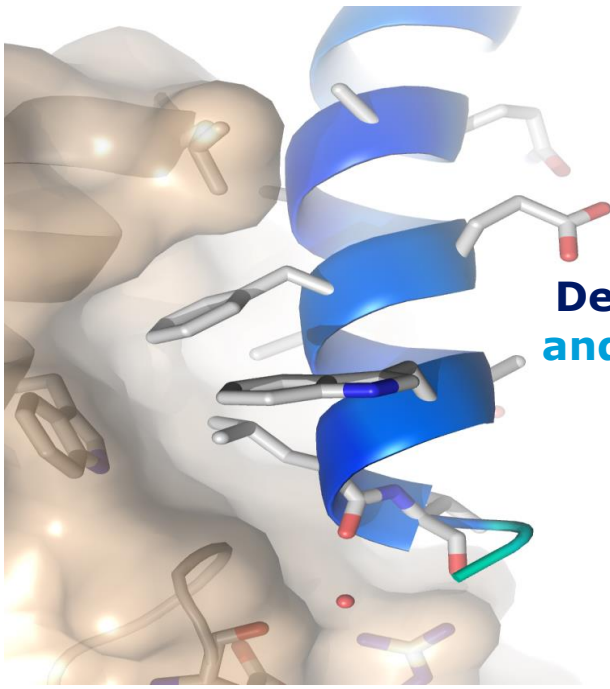


Designing the Once-Weekly and Oral GLP-1 Semaglutide

Jesper Lau
Vice President
Novo Nordisk

18

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

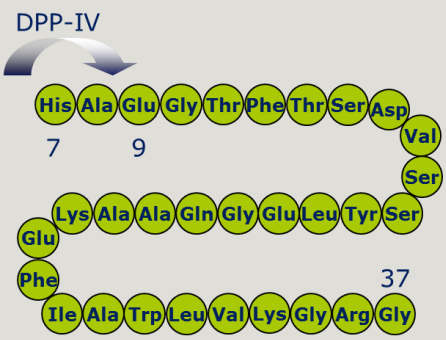
What is Glucagon-like-peptide-1?

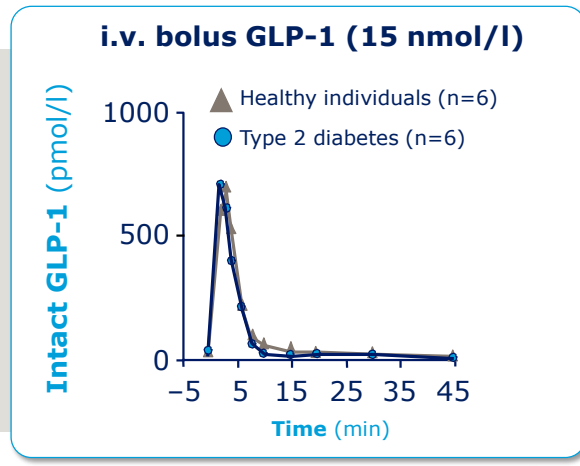
- A long acting artificial synthetic peptide
- A 32 amino acid natural peptide hormone
- A peptide released from the L-cells
- A peptide that increases appetite

** If your answer differs greatly from the choices above tell us in the chat!*

Native GLP-1 has limited clinical value because of its short half-life

19





Enzymatic cleavage
High clearance (4–9 l/min)

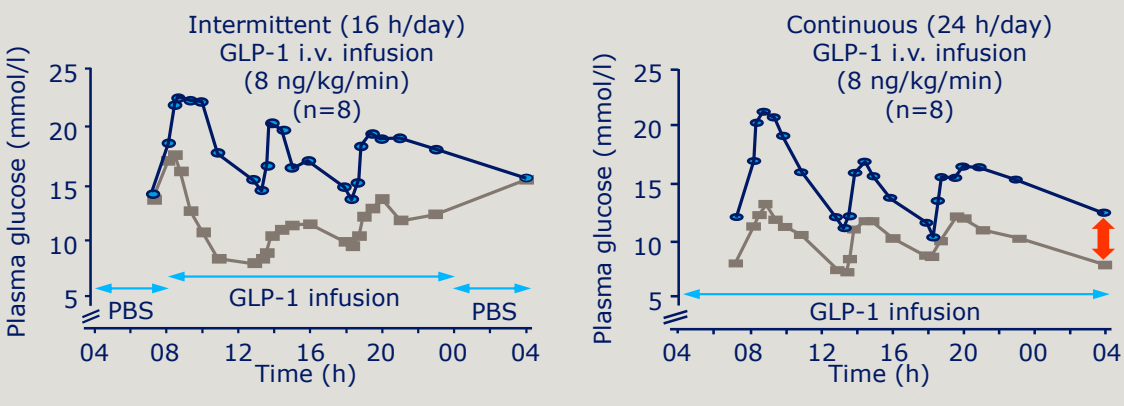
t½ = 1.5–2.1 minutes
(i.v. bolus 2.5–25.0 nmol/l)

life-changing careers

PK data adapted from Vilsbøll et al. J Clin Endocrinol Metab 2003;88:220–224

Native GLP-1 must be administered continuously to realise full therapeutic potential k

20



Blood glucose profiles: Day 0 Day 7

life-changing careers

Adapted from Larsen et al, Diabetes Care 2001;24:1416–1421.

PBS, phosphate-buffered saline.

Discovery of the Insulinotropic Effect of GLP-1

Bayliss and Starling proposed that intestinal mucosa contained a hormone which stimulated the exocrine secretion of the pancreas

Early clinical potential

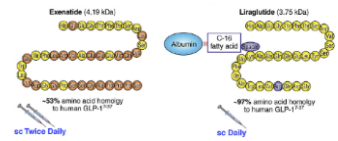
Kreymann, Williams, Ghatei and Bloom, Lancet 1987;1300-1303

Nathan, Schreiber, Fogel, Mojsov and Habener, Diabetes Care 1992;15(2):270-276

Nauck, Kleine, Ørskov, Holst, Willms and Creutzfeldt, Diabetologia 1993;36:741-744

First two GLP-1 RA approvals

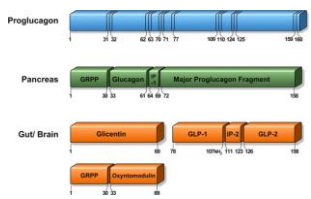
2005 and 2009



1902 **1983** **1987** **1989** Biological & clinical recognition **2005** Technical evolution **2017**

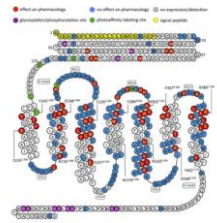
Human proglucagon gene was cloned

Bell, Nature 1983;302:716-718

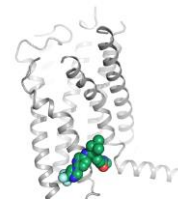


GLP-1 receptor cloned

Thorens, PNAS 992;89:8641-45



GPCR class B structures



life-changing careers

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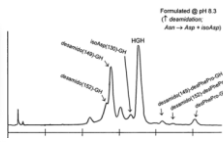
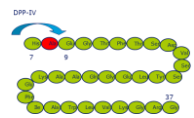
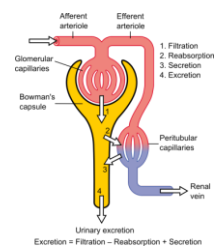
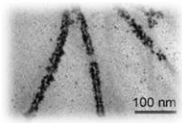
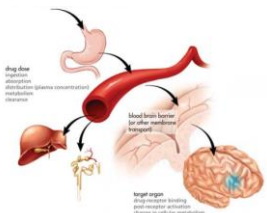
Key puzzle for successful GLP-1 engineering

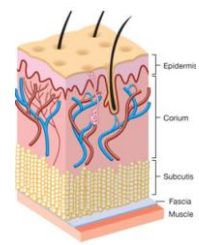












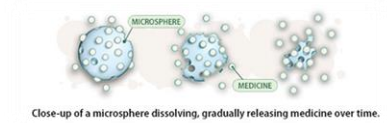
life-changing careers

novo nordisk

Once weekly GLP-1:
Parallel explorations of protraction enablers

Several strategies have been explored by industry:

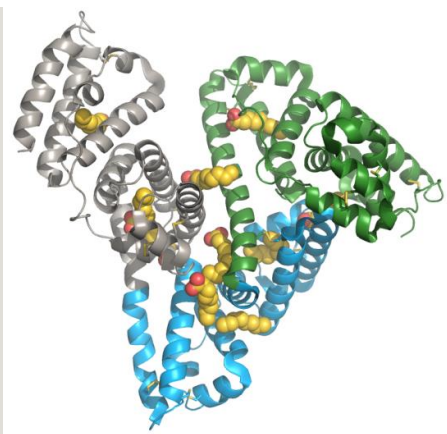
- **Sustained release:**
  - Bydureon (BMS/AstraZeneca), Taspoglutide (Roche/Ipsen)
- **Fusion proteins:**
  - Albiglutide (GSK)
  - Dulaglutide (GLP-1 Fc, LY2189265,Lilly)
  - GLP-1 transferrin (PF-4856883, Pfizer)
- **Pegylation:**
  - GLP-1 PEG (Lilly)
- **Reversible albumin binding**
  - Semaglutide (Novo Nordisk)



Close-up of a microsphere dissolving, gradually releasing medicine over time.

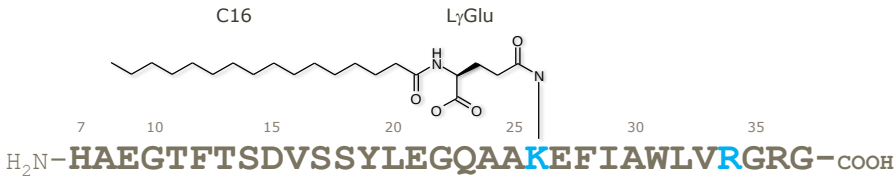
Human serum albumin

- Is a large (>60kDa) natural human protein
- Circulates in the blood in high concentrations (~40mg/ml)
- Has a long plasma T½ (3 weeks)
- Binds fatty acids reversibly (transport and solubility)



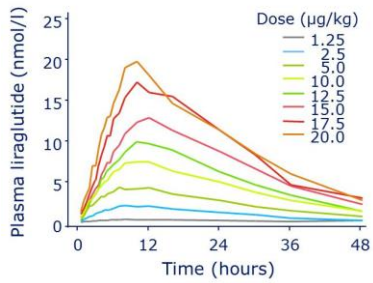
Liraglutide obtains a once-daily profile by reversible binding to albumin

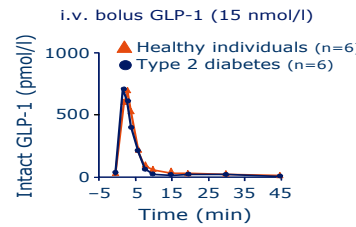
25



PK parameters

- T_{max}: 9–12 h
- $T_{½}$: 11–15 h
- Bioavailability: 55%





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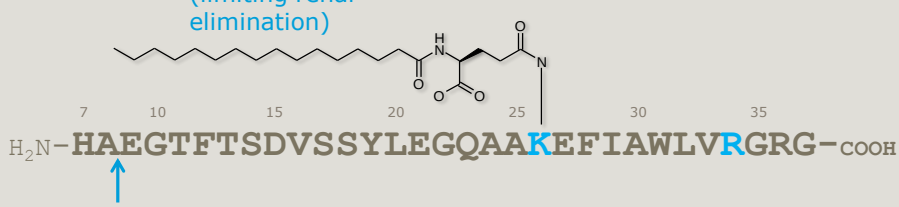
Adapted from Elbrønd et al. Diabetes Care 2002;25:1398–1404. n=72 (n=8 for each dose)

Four key hurdles to engineering a superior once - weekly GLP-1

26

1. **Albumin binding** (limiting renal elimination)
2. **Access to the right target tissues**



3. **DPP-IV stability**
4. **Maintain high receptor affinity**

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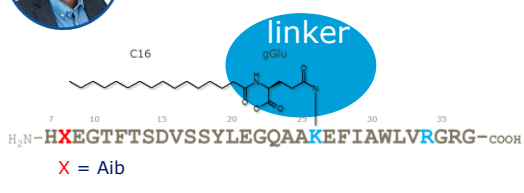
Lau, J. *et al* J. Med. Chem; 2015, *58*, 7370-7380

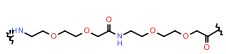
27

Linker exploration of GLP-1

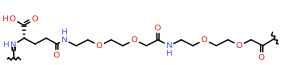


gGlu:

2xOEG:



gGlu-2xOEG:



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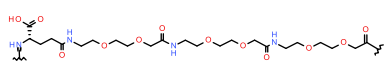

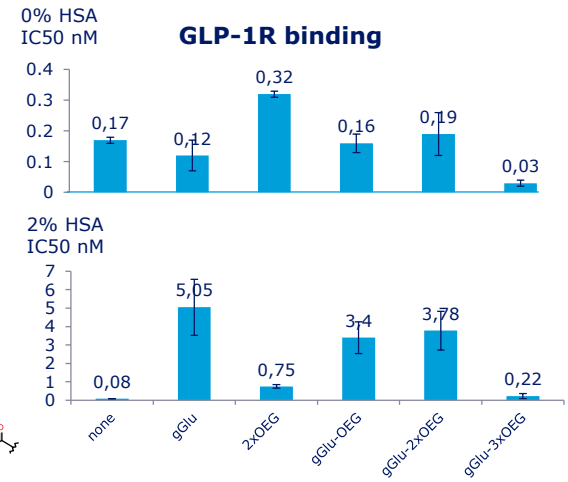

RATIO 2%/0 % HSA	0,5	42	2,3	21	20	8,0

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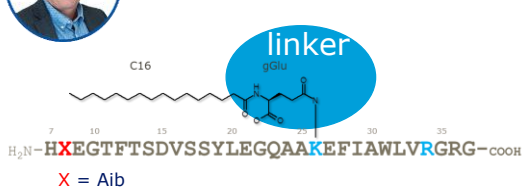
Lau, J. *et al* J. Med. Chem; 2015, *58*, 7370-7380

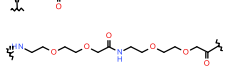
28

Linker exploration of GLP-1

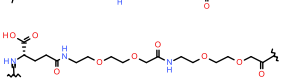


gGlu:

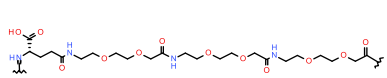
2xOEG:

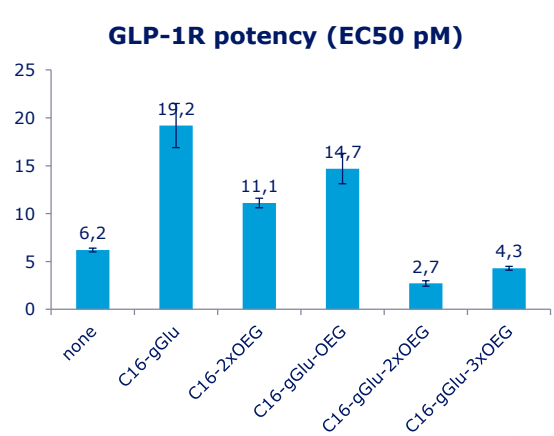


gGlu-2xOEG:



gGlu-3xOEG:





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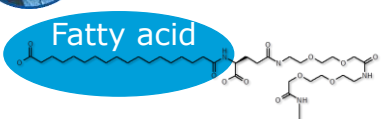
Lau, J. *et al* J. Med. Chem; 2015, *58*, 7370-7380

Prolonging the half-life from once-daily to once-weekly by fatty acid exploration

29

Fatty acid



H_2N-HXEGTFTSDVSSYLEGQAAKEFIAWLVRGRG-COOH

X = Aib

C16 acid

C12 diacid

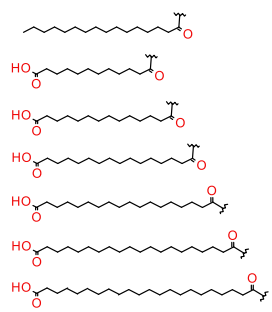
C14 diacid

C16 diacid

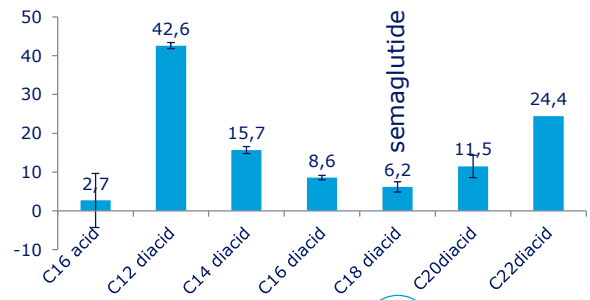
C18 diacid

C20 diacid

C22 diacid



GLP-1R potency (EC50 pM)



	C16 acid	C12 diacid	C14 diacid	C16 diacid	C18 diacid	C20diacid	C22diacid
Relative Albumin binding	20	0,9	3,3	22	940	85	116

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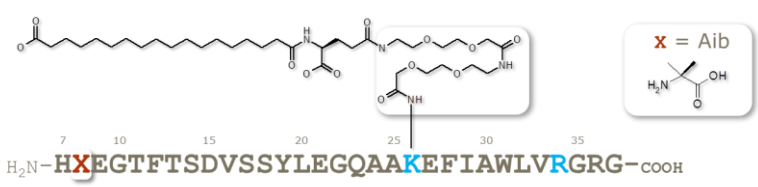
Lau, J. *et al* J. Med. Chem; 2015, *58*, 7370-7380

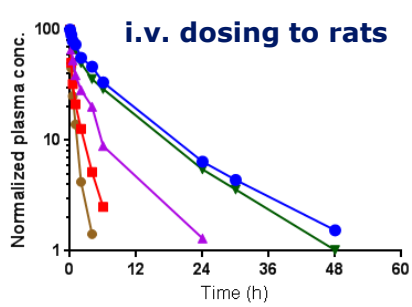
30

Systemic half-life increases

- with increasing length of di-acid



i.v. dosing to rats



C20 diacid
C18 diacid
C16 diacid
C14 diacid
C12 diacid

Semaglutide

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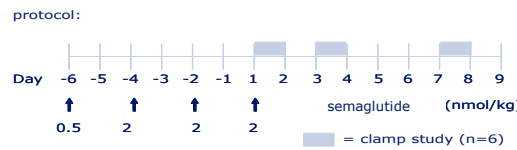
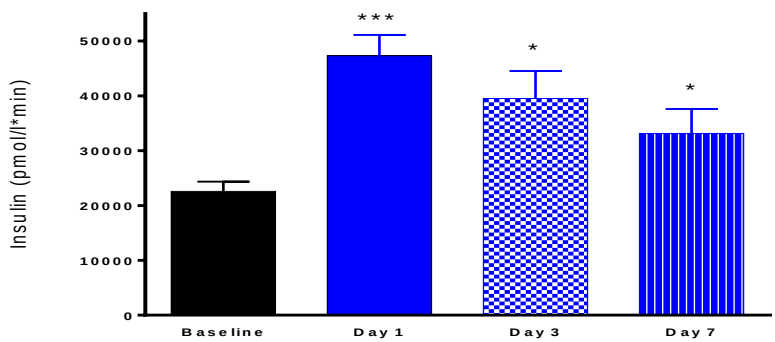
Lau, J. *et al* J. Med. Chem; 2015, *58*, 7370-7380

7 Days duration of action of semaglutide

- in mini pigs, hyperglycaemic clamp

31





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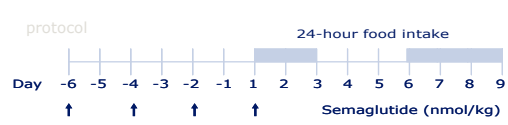
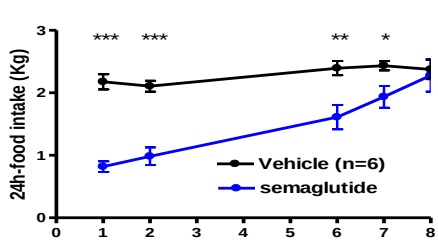
Efficacy and duration of action of semaglutide

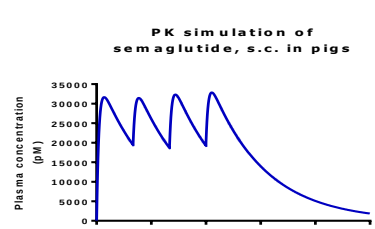
- in LYD pigs

32

- **Effect on appetite in LYD pigs:**
  - Dose dependent effect on appetite
  - 7 days duration of action







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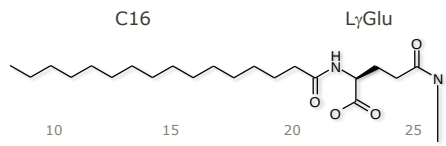
unpublished

33

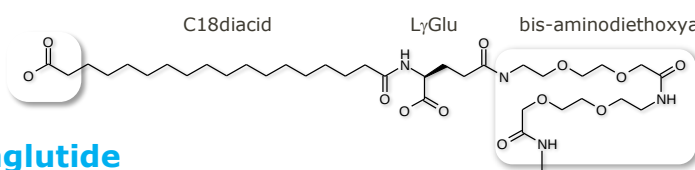
GLP-1 Once-daily vs Once-Weekly
- Minor Structural differences

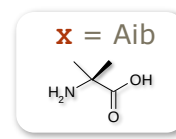
Liraglutide



H_2N–HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG–COOH

Semaglutide





H_2N–HXEGTFTSDVSSYLEGQAAKEFIAWLVRGRG–COOH

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Semaglutide was selected as once weekly lead
- based on animal data

	Liraglutide	Semaglutide
Mini pig s.c. availability	**66%**	**94%**
MRT minipig (s.c. dosing)	**23hrs**	**64hrs**
In vivo potency (db/db mice)	**6.9 nmol/kg**	**0.3 nmol/kg**
T½ humans (s.c. dosing)	**13hrs**	**?**
Expected Human dose	**<2mg/day**	**<2mg/week**

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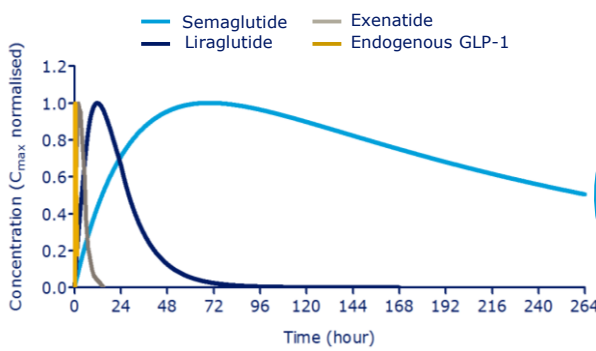
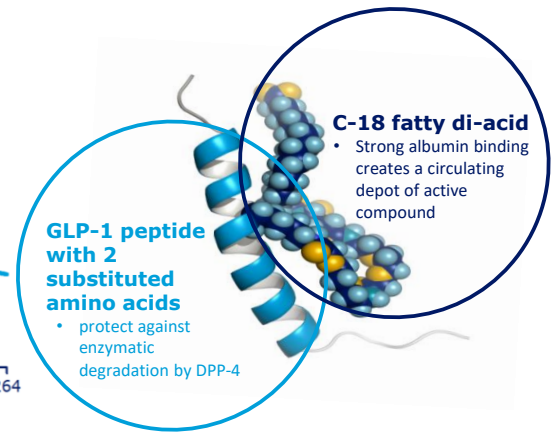
Semaglutide has an optimal pharmacokinetic profile for once weekly dosing…

35





Simulation of pharmacokinetic profile

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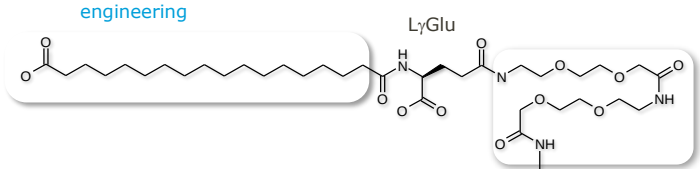
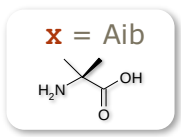
Semaglutide is the result of a few smart modifications to the human GLP-1 molecule

36

Fatty acid optimisation for strong albumin binding. NN protein chemical engineering

OEG linker for peptide flexibility and optimised binding to receptor





Aib is an unnatural amino acid for preventing peptidase degradation

Peptide chain based on liraglutide discovery (human GLP-1): NN protein chemical engineering and alanine scan

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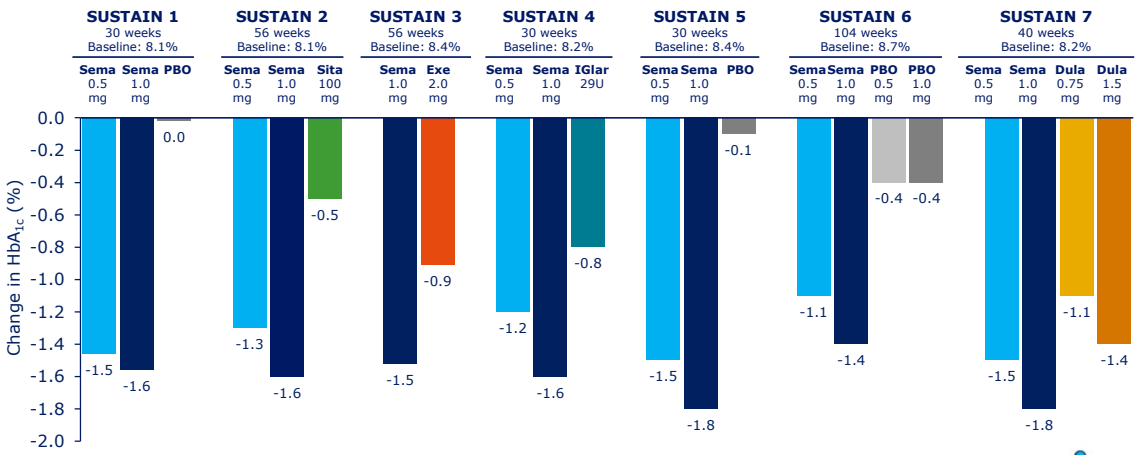
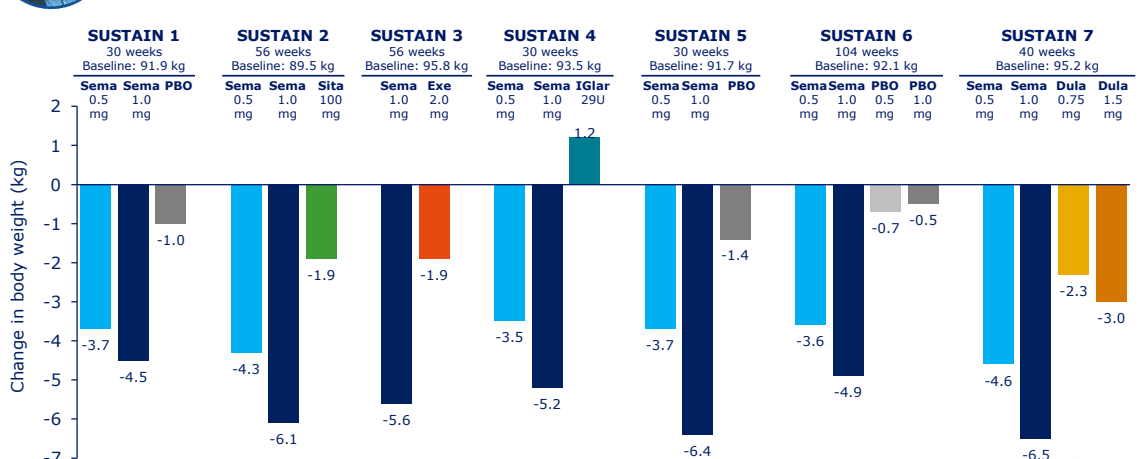
Once-weekly semaglutide provides unprecedented glucose regulation…



Dula: Dulaglutide (Trulicity®); Exe: exenatide (Bydureon®); IGlar: insulin glargine (Lantus®); PBO: placebo; Sita: sitagliptin

… and unprecedented weight loss

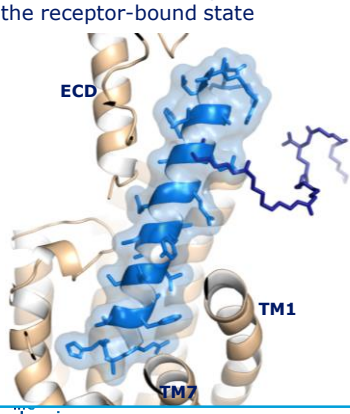


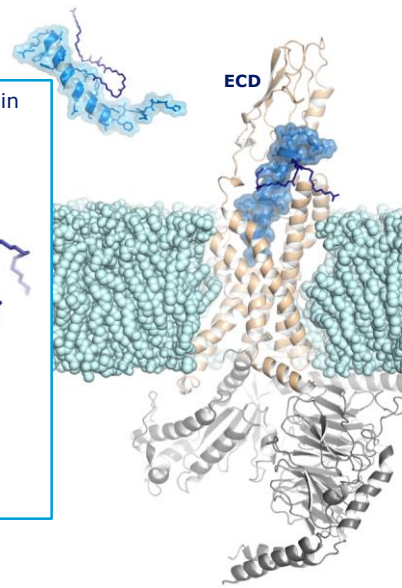
Dula: Dulaglutide (Trulicity®); Exe: exenatide (Bydureon®); IGlar: insulin glargine (Lantus®); PBO: placebo; Sita: sitagliptin

…and a highly selective binding to the human GLP-1 receptor

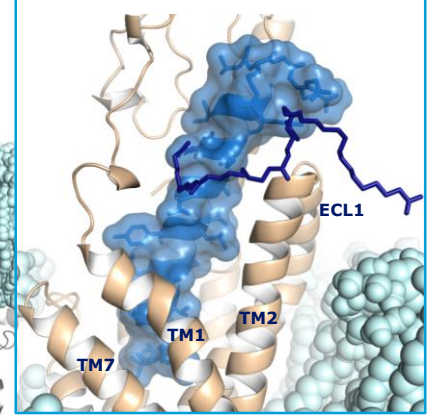
39

GLP-1 almost entirely α-helical in the receptor-bound state





Binding site defined primarily by ECD, ECL1, TM1, TM2 and TM7

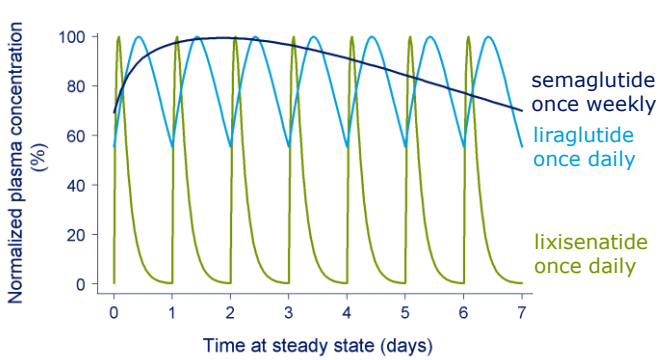


Why is semaglutide different?

Continuous plasma exposure with little fluctuation and higher concentration in specific area of the appetite centre

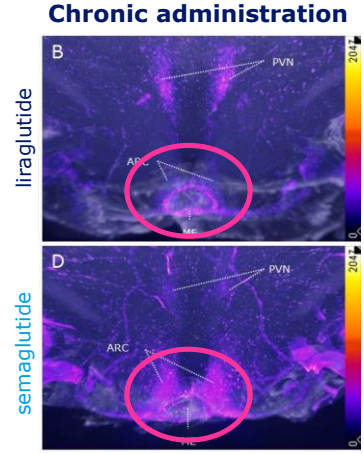
40

Simulated pharmacokinetic profiles



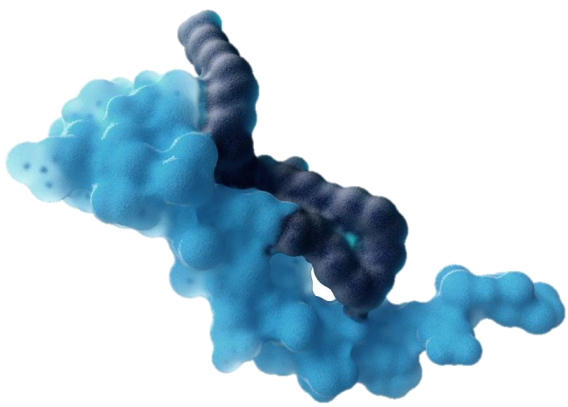
PK modelling
Sources: Watson E, et al., *J. Clin. Pharm* 2010; 50: 886–894 (liraglutide), meta-analysis ClinPharm trials (semaglutide – data on file) and Frank T (2013) *J Pharm Drug Deliv Res.* 2013; 2:1 (lixisenatide)

Chronic administration



Semaglutide - a convenient once-weekly GLP-1 with superior blood glucose regulation

41



Semaglutide

- is an analogue of human GLP-1
- has a once weekly profile through binding to albumin
- has a high potency and long duration of action in animals which translate to an excellent profile in humans
- holds great opportunity for oral administration

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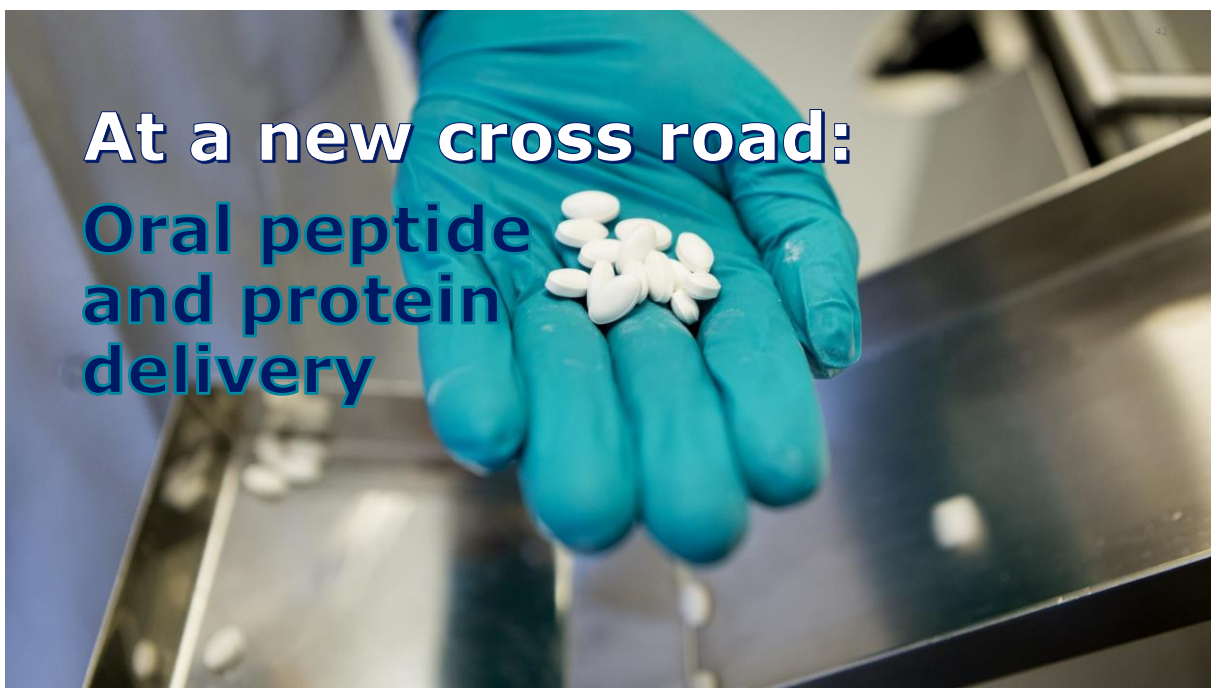


43

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which statement is wrong? Oral GLP-1 peptide delivery is a challenge due to:

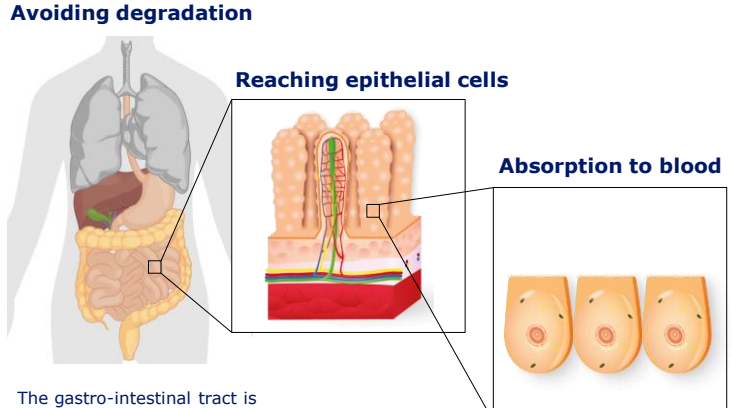
- Enzymatic degradation in the intestinal tract
- The intestinal uptake due to the size of the peptide
- The clinical trials are very difficult
- An absorption enhancer may be required

** If your answer differs greatly from the choices above tell us in the chat!*

44

There are many barriers to oral protein delivery

Avoiding degradation

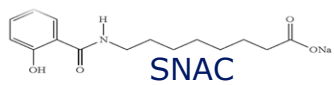


The gastro-intestinal tract is designed to degrade proteins by enzymes and low pH

Proteins are lipophobic: no passive transport through the intestinal wall

Oral delivery platforms

Eligen®



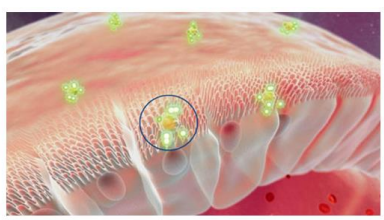
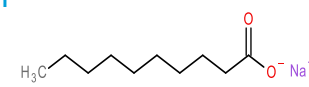
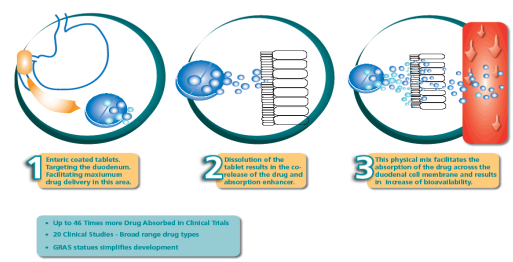


Fig. 1: Eligen Technology in action. As depicted inside the blue circle, delivery agents (small white dots) chaperone a therapeutic molecule (the green entity) entering into the outer membrane of an epithelial gastrointestinal cell. The gastrointestinal tract is on the top and the blood stream is on the bottom right

GIPET®





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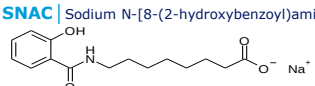
Understanding the absorption of oral semaglutide/SNAC tablets

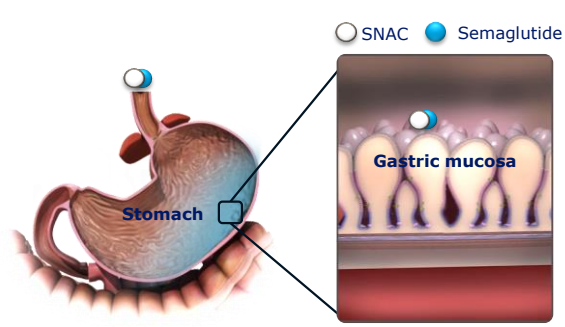
SNAC | Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate



SNAC is an enhancer that facilitates absorption

The available data for semaglutide co-formulated with SNAC support that absorption takes place in the stomach in a localised buffered environment

The effect is strictly time- and size-dependent and occurs primarily via trans-cellular route



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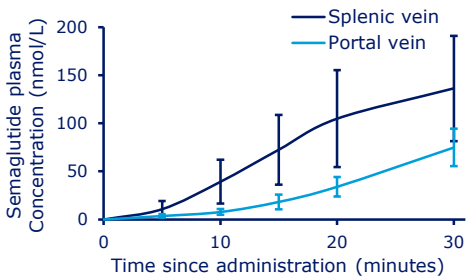
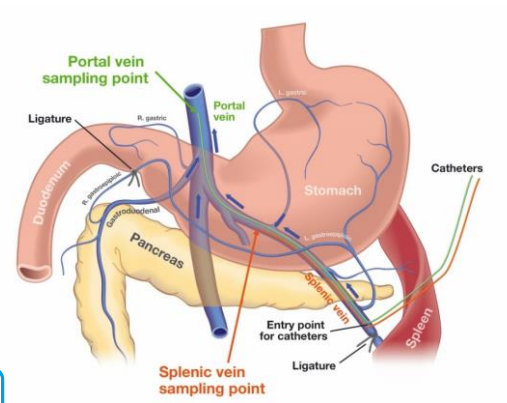
Stomach is the predominant site of absorption

Highest concentration of semaglutide observed in vena linealis in dogs

Plasma concentration of semaglutide after 10 mg oral dose in dogs



Semaglutide levels were higher in the splenic vein over the first 30 min after dosing ($AUC_{0\text{-}30min}$ splenic/portal: 1.9)



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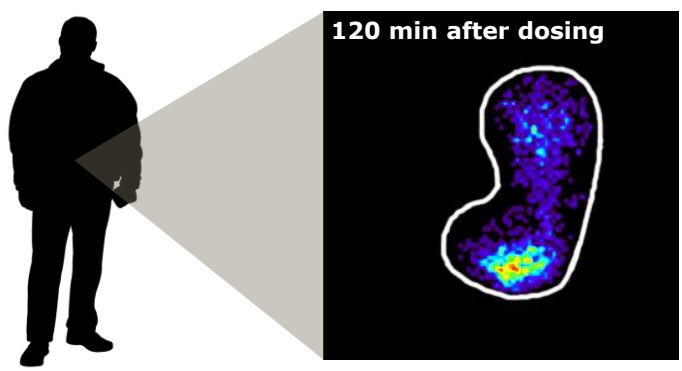
Complete tablet erosion of oral semaglutide occurs in the stomach

Scintigraphic imaging of an indium-111 labelled tablet



- Mean time to complete tablet erosion was 85 minutes (95% CI: [62;118])

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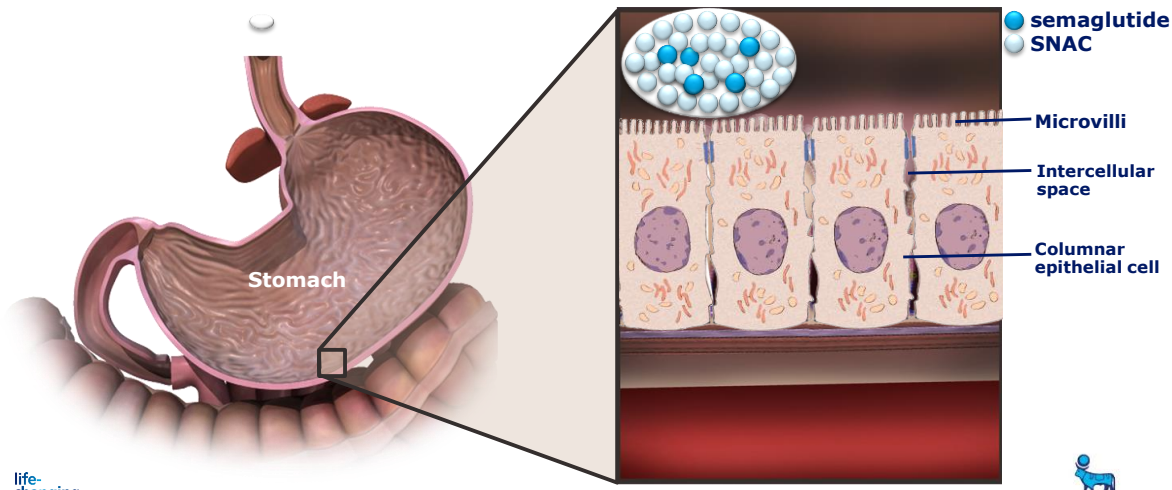
SNAC carrier facilitates semaglutide absorption



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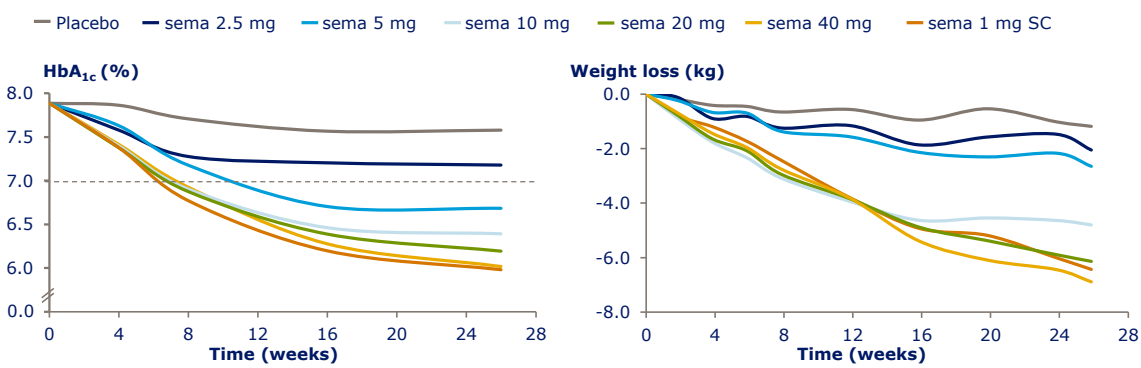
SNAC: Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate

50

Oral semaglutide dose dependently reduced HbA_{1c} and body weight in phase 2 trial

HbA_{1c} reduction from a mean baseline of 7.9%

Weight loss from a mean base line of 92 kg



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Data on graph are estimated mean +/- standard error of the mean
SC: subcutaneous; Sema: semaglutide
Main inclusion criteria: Type 2 diabetes; 7.0% ≤ HbA_{1c} ≤ 9.5%; Treatment with diet and exercise +/-metformin
Source: Trial NN9924-3790

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Conclusion

51

Semaglutide:

- Is a once weekly GLP-1 analog that binds to albumin
- Is an analog of human GLP-1
- Was selected as once weekly candidate based on long duration of action in pigs
- Once weekly profile was confirmed in humans
- Has now shown great opportunity for both once weekly dosing and oral treatment

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Thanks to the Semaglutide Team

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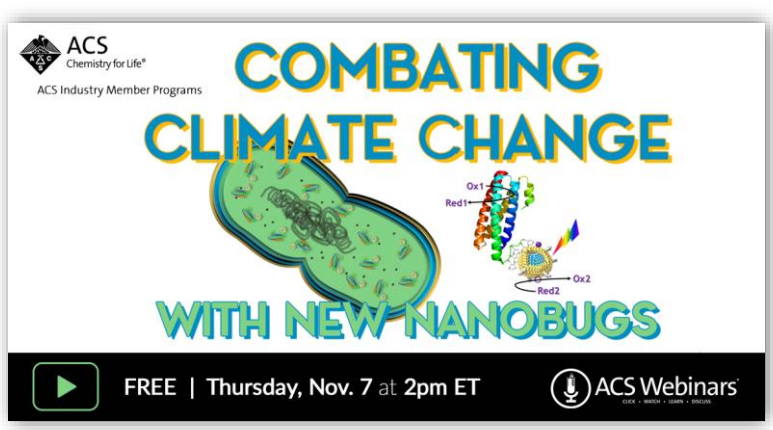

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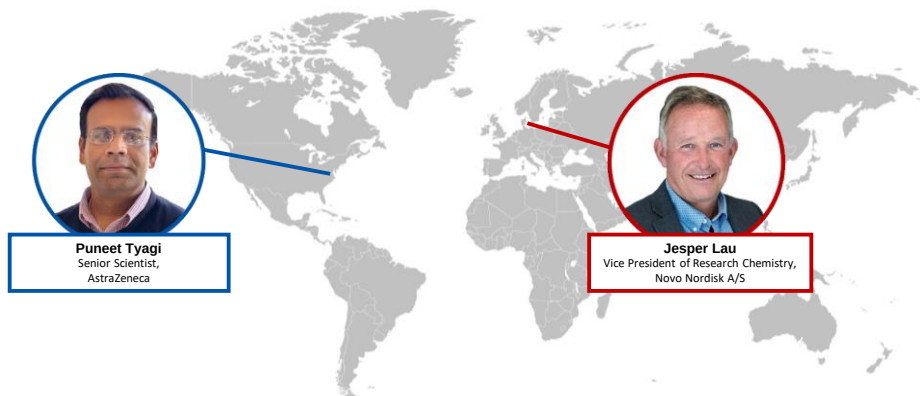

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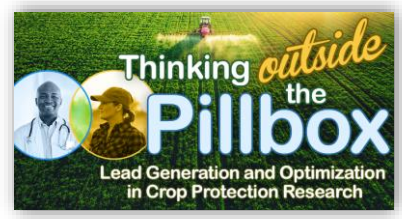

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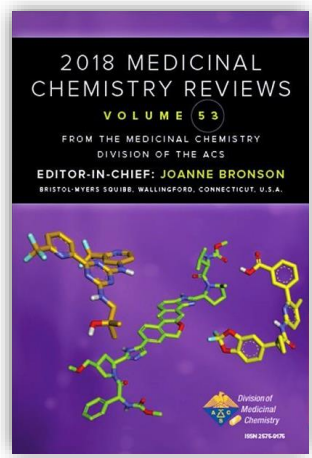

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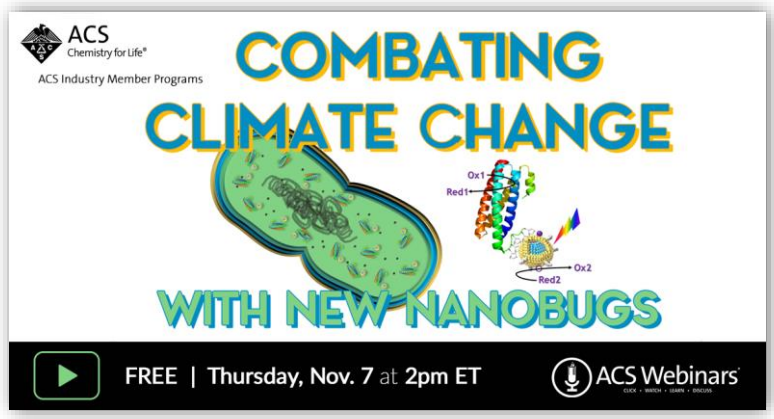

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