Incretins mimetics – end of diabesity ?

Outline

- diabesity : type II diabetes-obesity world wide pandemia
- diet and exercise – first line prevention
- current therapies - standard of care
- future therapies-Incretins gut peptides
- GPCR/GLP1R small chemical moieties: MedChem challenge

EPFL
Sciences de la Vie -SV

Prof Roger G. Clerc

Each of You Knows a Relative, a Friend, a Neighbor Who Suffers-Suffered from a Disease

Illness is the night-side of life, a more onerous citizenship.

Everyone who is born holds a dual citizenship, in the kingdom of the well and in the kingdom of the sick.

Although we all prefer to use only the good passport, sooner or later each of us is obliged, at least for a spell, to identify ourselves as citizen of the other place.

Susan Sontag

Susan Sontag, USA 1933-2004

Roger G. Clerc : a biosketch between academia and industry

Studies / Master

UNIVERSITÉ DE GENÈVE

Medicine
Molecular Biology

ETH

PhD

Molecular Biology
Cell Biology
Virology

FMI
Friedrich Miescher Institute for Biomedical Research

Professor

Writing high impact
Publications epigenetics
teach doctoral classes

Writing paper gene regulation
Designing & interpreting
Experiments
Giving Talks

Postdoc

Cancer Center
Mamalian genetic

MIT

UNI BASEL

Roche

Designing projects
Develop NME‘s
Writing patents, reports
Metabolic diseases

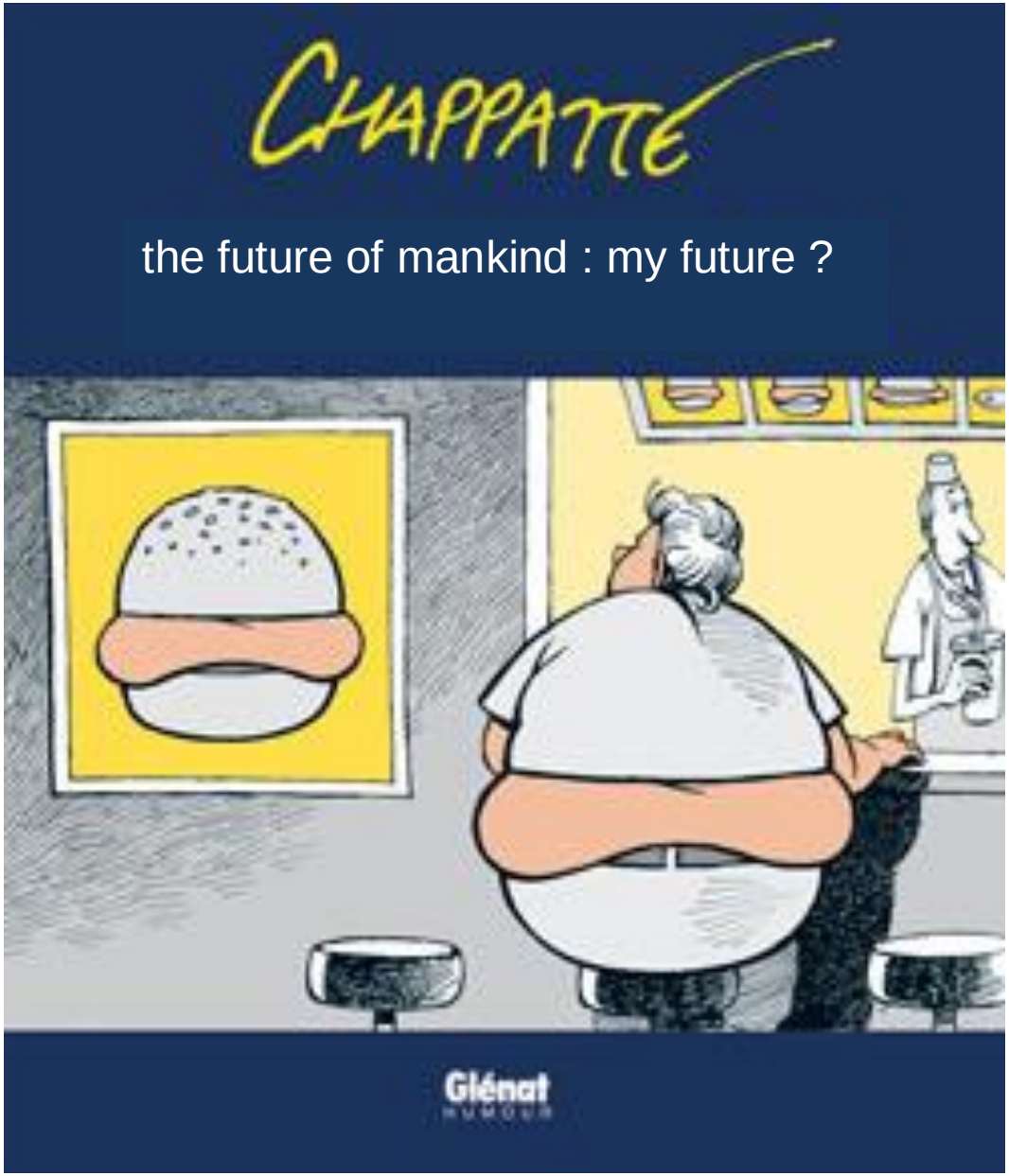
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Principal scientist, research area leader

Disclaimer Prof Roger G Clerc

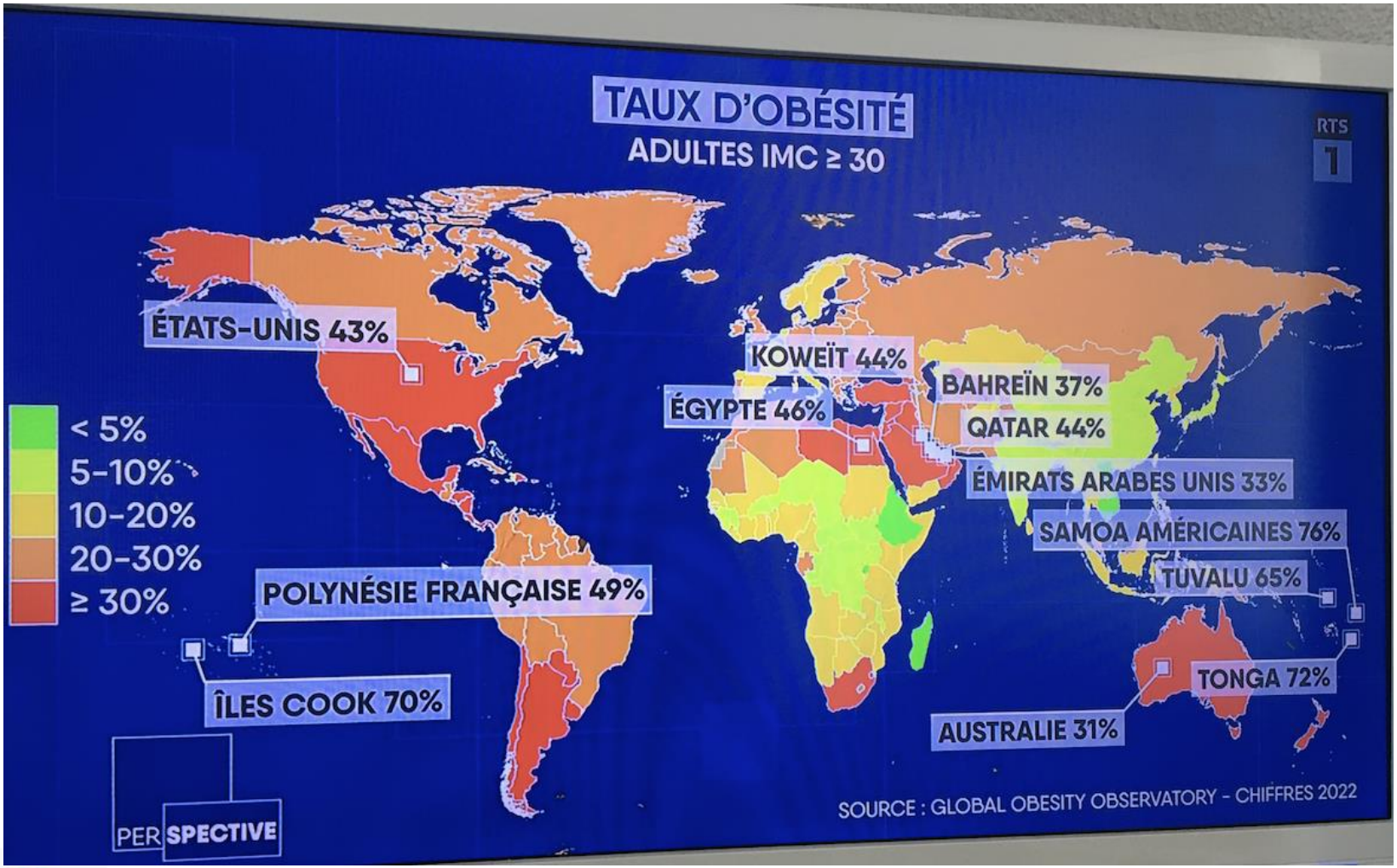
- **Introductory overview of the drug discovery process, not dedicated to any specific particular drug discovery process, branding or trade mark.**
- **No commercial interest with former employers (see Professor emeritus see LinkedIn page)**
- **The course may touch issues eg. in metabolic diseases and comorbities in CVD; based on past experience, the audience may be confronted/offended by eg. self assessing diabesity/waist hip ratio/cancer risk assessment/gender dysphoria/grossophobia (non exclusive listing)**
- **These topics/workshops are not exclusive part of the requirements for the fullfillment of the course credits; attendants are welcome not to participate and leave the auditorium as appropriate.**

The advent of incretins like GLP1 GIP co-agonists : the end of a worldwide metabolic diseases pandemia ?



Patrick Chappatte

Obesity and type II diabetes - metabolic syndrome global pandemia



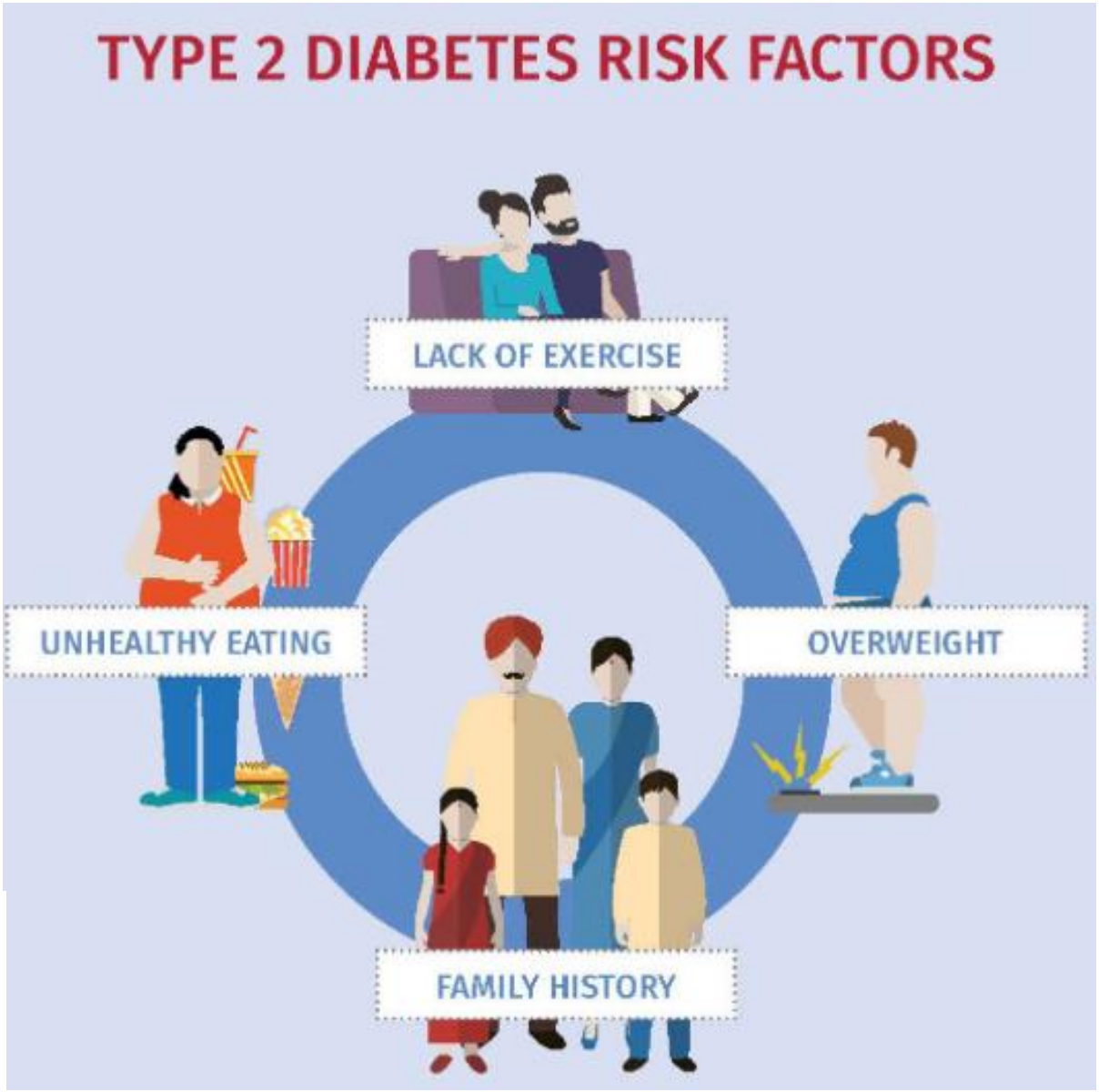
Major medical need – a global metabolic syndrome pandemia prevalence according to WHO 2022

Metabolic diabesity syndrome : a public health challenge

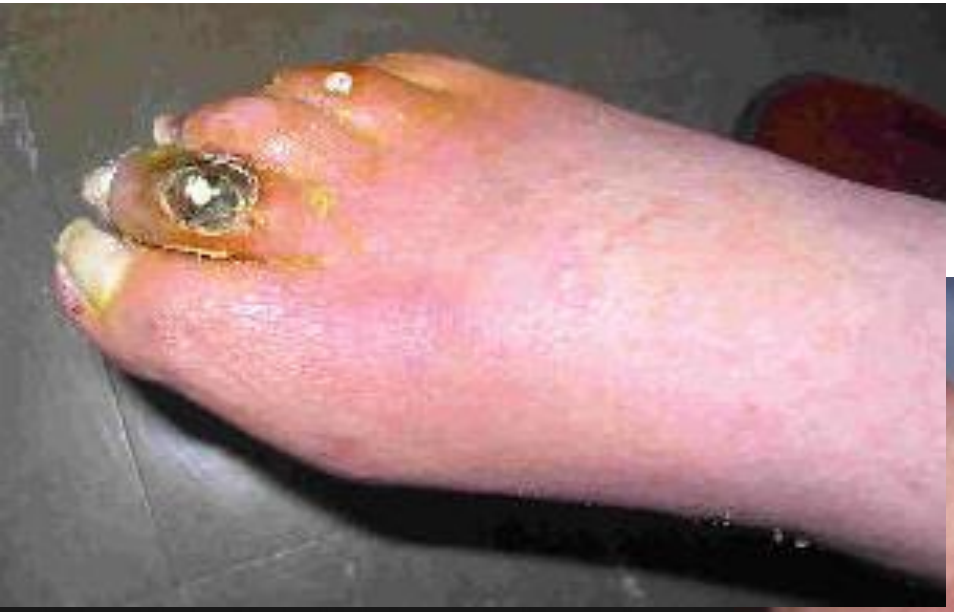
#	Country	Income group	% obesity
19	United States	High income	42.74
20	Saudi Arabia	High income	42.45
21	Palau	High income	42.08
22	Puerto Rico	High income	42.05
23	Iraq	Upper-middle income	41.41
24	Jordan	Lower-middle income	39.93
25	Chile	High income	39.67
26	Barbados	High income	38.90
27	Palestine	Lower-middle income	38.52
28	Libya	Upper-middle income	37.91
29	Bahrain	High income	37.25
30	Panama	High income	37.06
31	Mexico	Upper-middle income	36.86
74	Poland	High income	28.28
75	Peru	Upper-middle income	28.12
76	Tunisia	Lower-middle income	27.71
77	United Kingdom	High income	27.63
78	Greenland	High income	27.58
79	Guatemala	Upper-middle income	27.57
80	Slovakia	High income	27.57
81	Azerbaijan	Upper-middle income	27.33
82	Czechia	High income	26.85
83	Kyrgyzstan	Lower-middle income	26.83
84	Canada	High income	26.73
85	Lithuania	High income	26.02
152	Tanzania	Lower-middle income	12.95
153	Kenya	Lower-middle income	12.87
154	Nigeria	Lower-middle income	12.84
155	Bhutan	Lower-middle income	12.68
156	Switzerland	High income	12.47

...er-middle ...me	15.44
... income	15.33
...h income	14.98
... income	14.93
...er-middle ...me	14.21
... income	14.06
...h income	13.97
...h income	13.55
...er-middle ...me	13.28

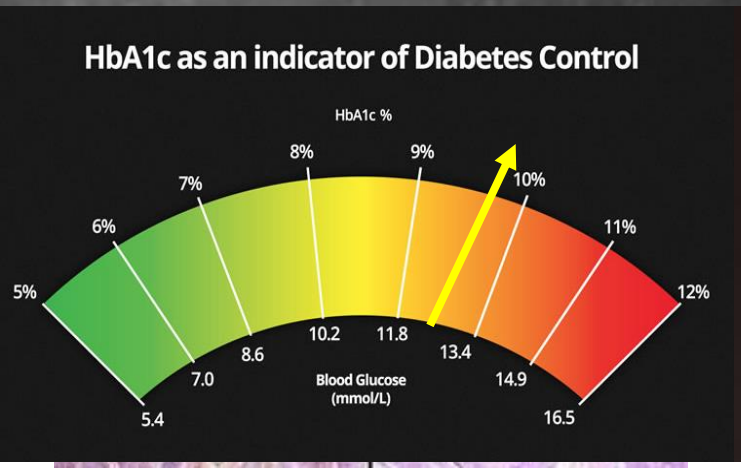
Metabolic syndrome : a public health challenge

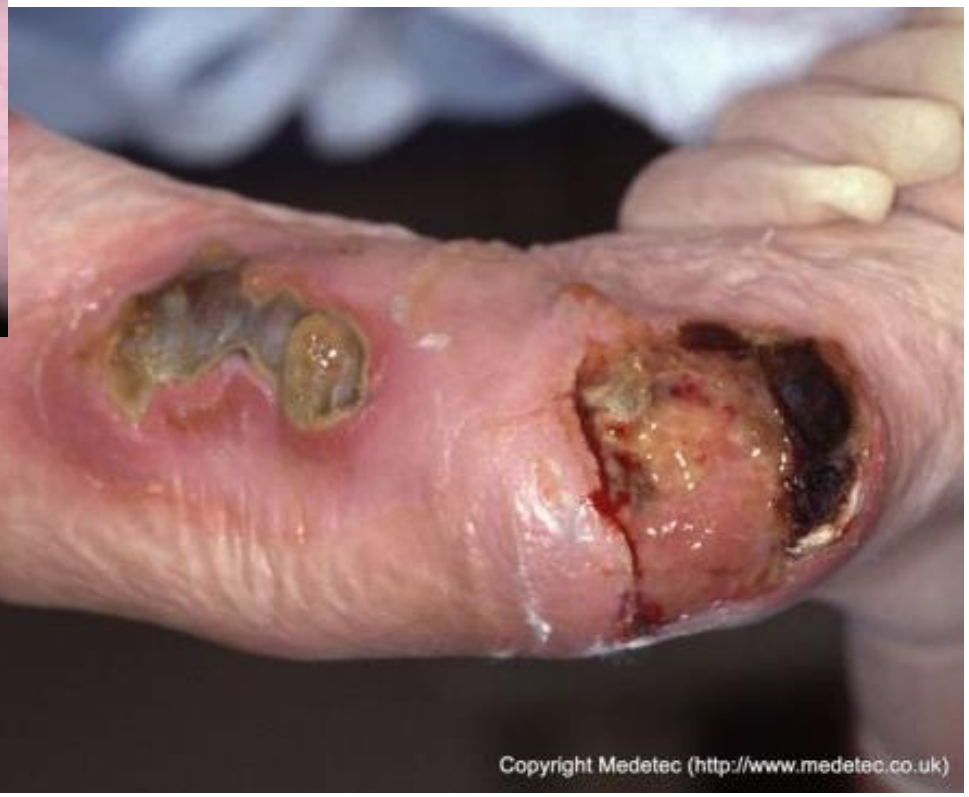


Advanced type II diabetes : peripheral ischaemia-necrosis
Insulin resistance as a consequence of obesity



MEDICAL NEED : IMPROVE TYPE II DIABETES **USING A MEDICINAL CHEMISTRY DESIGN**



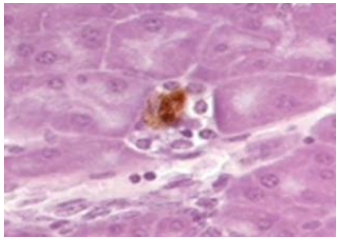


MACRO- AND MICROVASCULARIZATION IMPAIREMENTS

Progression to type II diabetes : pancreatic beta cells exhaustion

pathophysiology of an insidious disease

Stage I II III IV



Obese
Peripheral insulin resistance

Pre-diabetic/obese
Impaired glucose tolerance

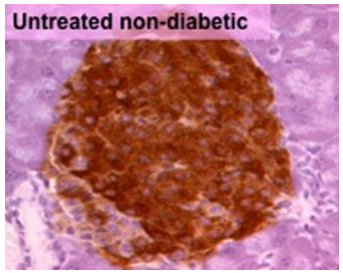
β-cell failure and insulin resistance

diet

Early diabetes

Late diabetes
hyperglycaemia

Prevention
- insulin sensitization
- organoprotection ?
- decrease vascular risk?



Intervention
- Normalize glucose
- Preserve β-cell insulin?
- decrease vascular risk?

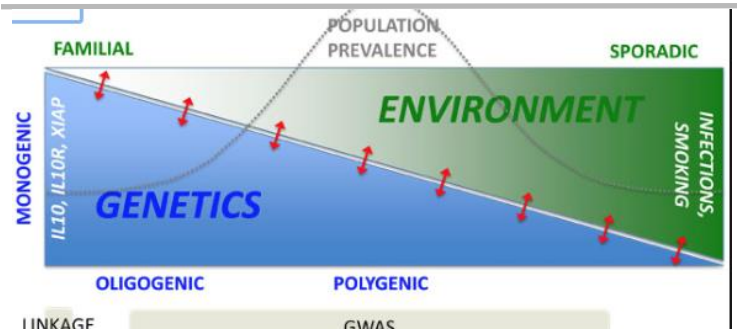
Vascular complications

insulin

← Environment + "obesigenes" →

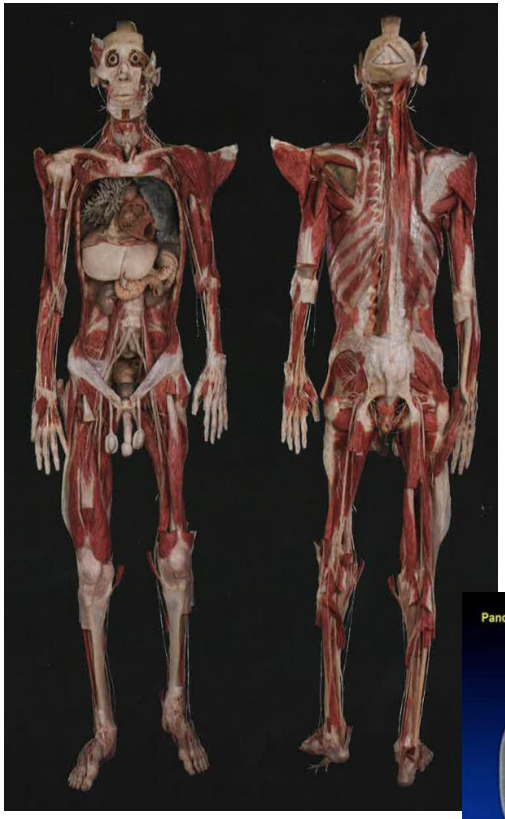
← "+diabetogenes" →

Physiopathology of metabolic syndrome : when patients become insulin resistant

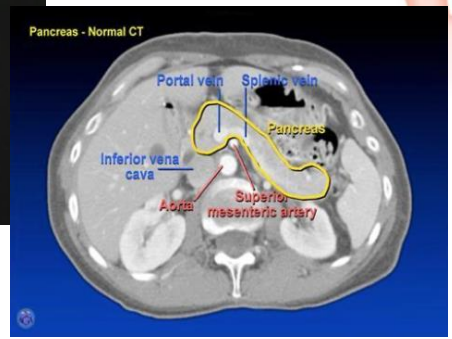


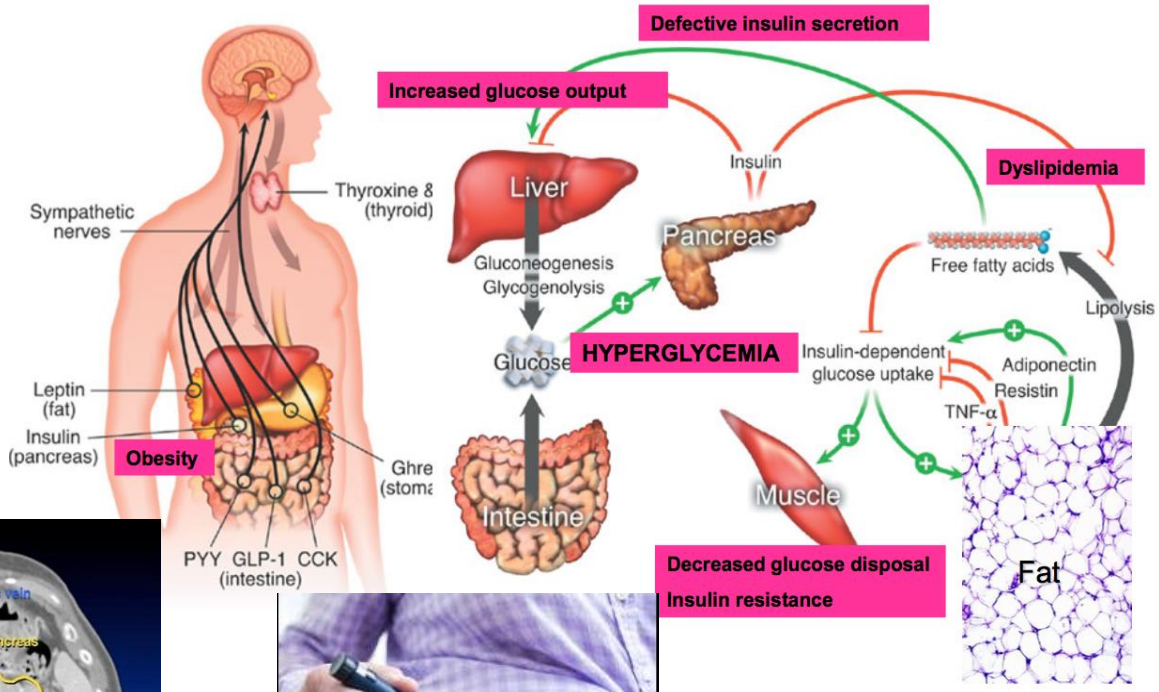
Metabolic Sydrome and Tissue-Tissue Cross Talk

MEDICAL CHALLENGE : COMPLEX TRAITS DISEASE : GENETICS AND ENVIRONEMENT PLAY A COMBINED ROLE



Gubener Plastinate GmbH
Guben Germany





Type I diabetes develops as an auto immune disease

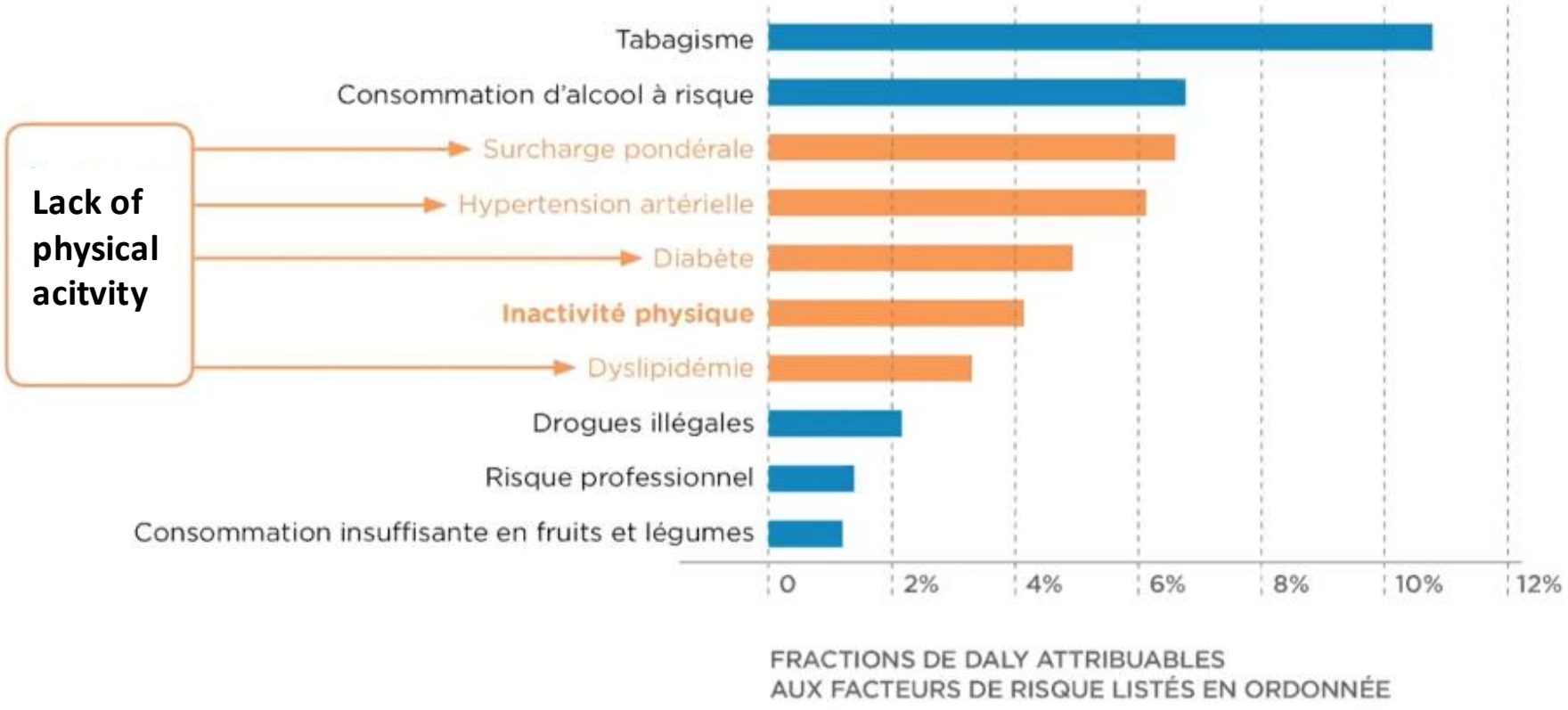
(prevalence 5-10% of all diabetic patients)

Cases of type 1 diabetes, which is caused by the body's own immune system attacking pancreatic cells, rose in young people during the COVID pandemic Credit: BSIP/Universal Images Group via Getty

Nature News July 21. 2023

Type II diabetes and metabolic syndrome pandemia : best preventive medicine : exercise every day !

FIGURE 3
CLASSEMENT DES PRINCIPAUX FACTEURS DE RISQUES RESPONSABLES
DES ANNÉES DE VIE PERDUES DANS LES PAYS DÉVELOPPÉS, 2004 (ADAPTÉ DE WHO 2009)



Risk factors involved in life expectancy reduction in developed countries (loss of lived years)

(adapted from WHO 2009 from Prof V Gremaux CHUV UNIL)

GLOBAL HEALTH METRICS | VOLUME 396, ISSUE 10258, P1223-1249, OCTOBER 17, 2020

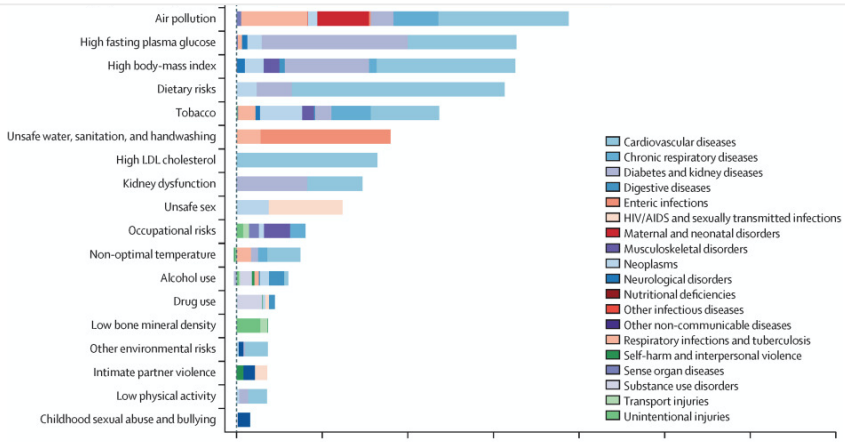
Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019

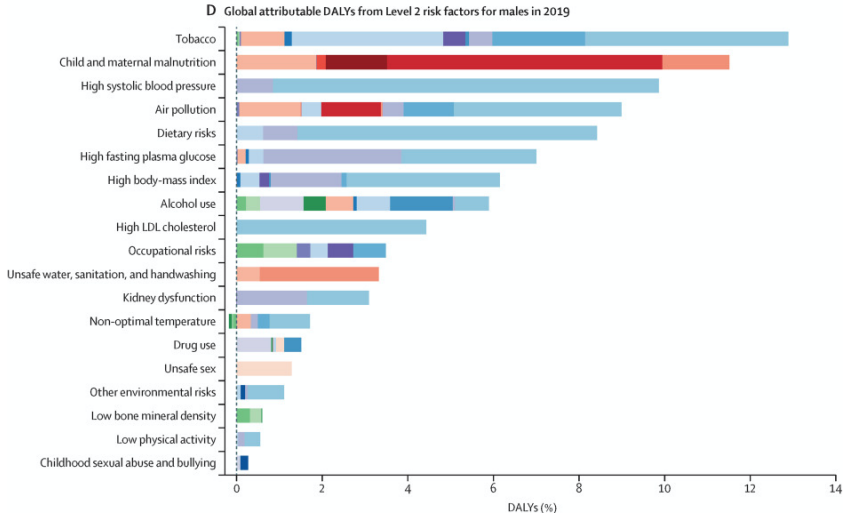
GBD 2019 Risk Factors Collaborators [†] • Show footnotes

Open Access • Published: October 17, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)30752-2 •

THE LANCET

Global burden of 87 risk factors in 204 countries and territorie...

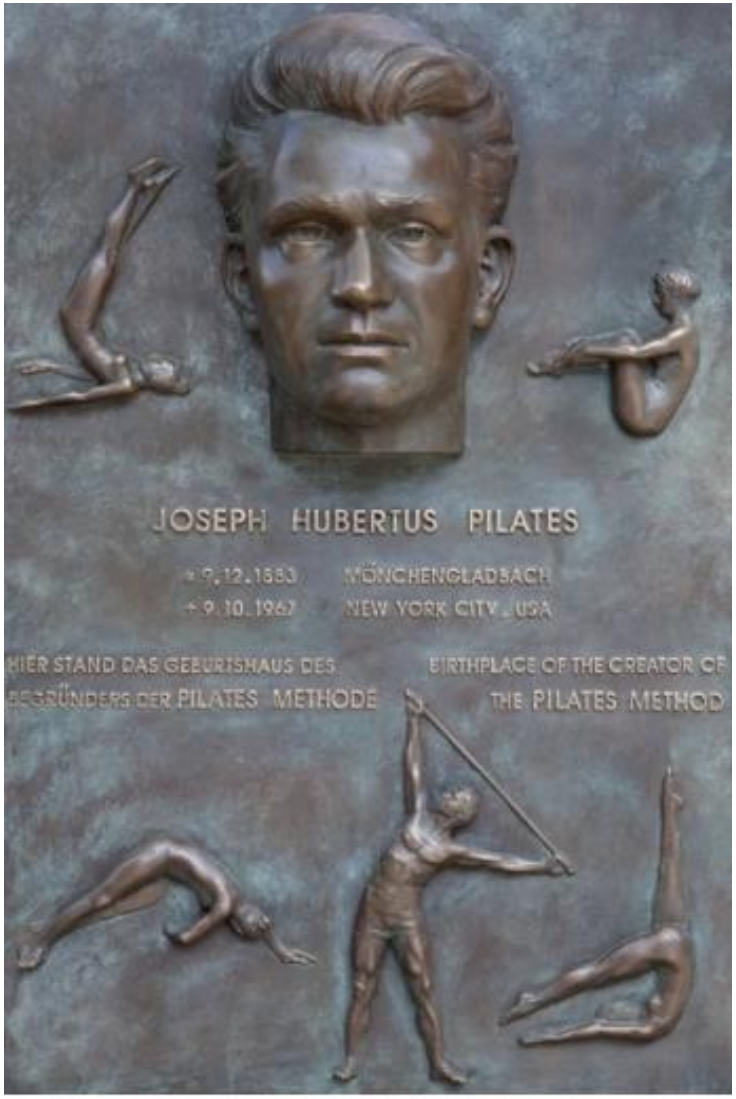




BENEFITS OF PHYSICAL ACTIVITY : THE SEDENTARITY DISEASES

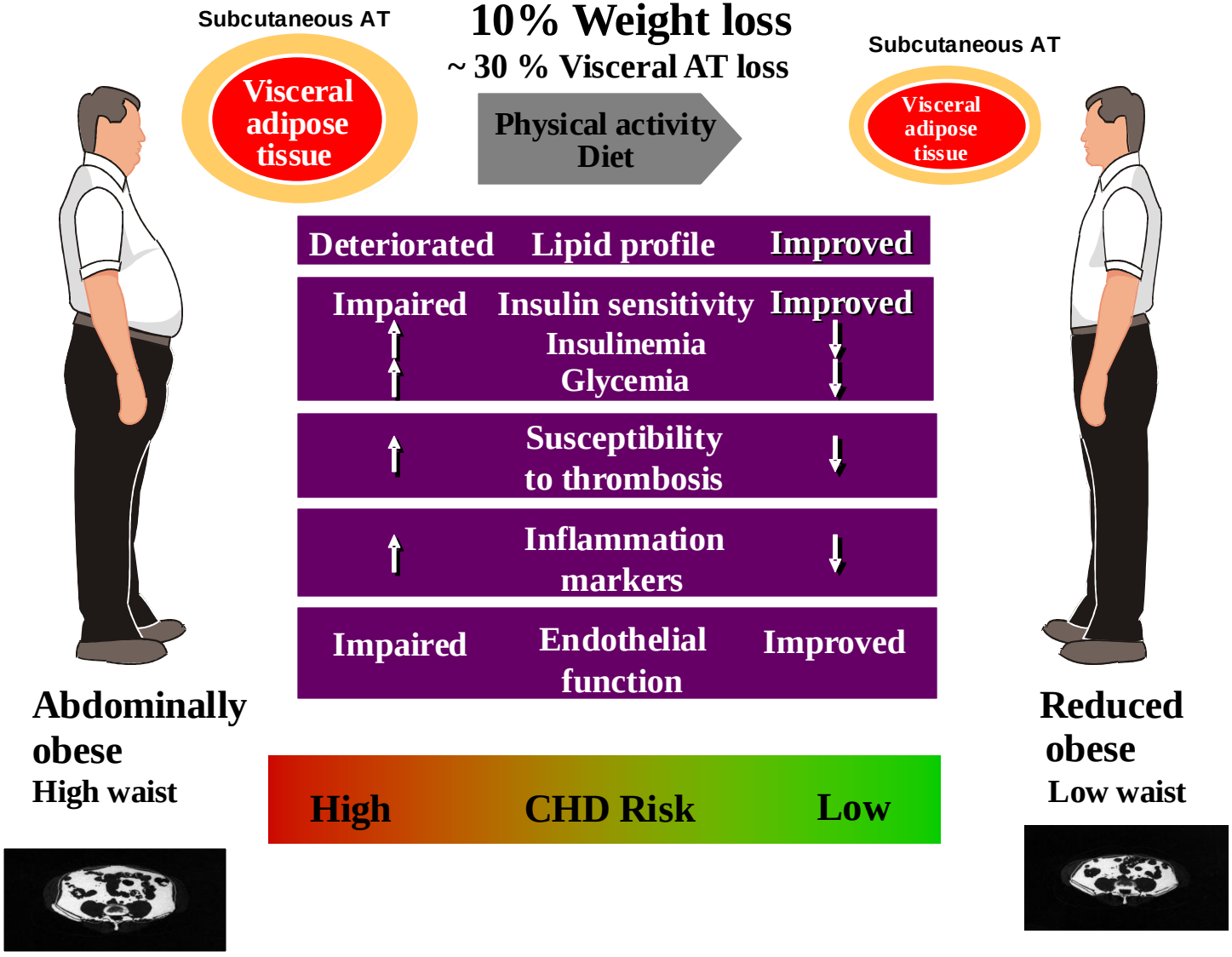
	ADULTES, TOUS ÂGES
MORTALITÉ, TOUTE CAUSE	Diminution du risque
SANTÉ CARDIOMÉTABOLIQUE	Diminution du risque de maladie cardiovasculaire et de mortalité cardiovasculaire Diminution du risque d'hypertension Diminution du risque de diabète de type 2
CANCER	Diminution du risque de cancer de la vessie, du sein, du colon, de l'endomètre, de l'œsophage, du rein, de l'estomac et du poumon
SANTÉ MENTALE	Réduction du risque de démence Amélioration des fonctions cognitives Amélioration de la qualité de vie Amélioration du sommeil Réduction du risque de dépression
STATUT PONDÉRAL	Effet supplémentaire sur la perte de poids lorsque l'activité physique est combinée avec une restriction alimentaire modérée Perte de poids et prévention de la reprise de poids lorsqu'une quantité suffisante d'activité physique d'intensité modérée à élevée est atteinte.
	PERSONNES ÂGÉES
CHUTES	Réduction du risque de chute Réduction du risque de blessure liée à une chute
CAPACITÉ PHYSIQUE	Amélioration de la capacité physique chez la personne âgée avec et sans fragilités.
	FEMMES ENCEINTES OU EN POST-PARTUM
DURANT LA GROSSESSE	Réduction du risque d'une prise de poids excessive Réduction du risque de diabète gestationnel Aucun risque pour le fœtus lié à une activité physique d'intensité modérée
DURANT LA PÉRIODE DU POST-PARTUM	Réduction du risque de dépression post-partum

Metabolic syndrome pandemia :
best preventive medicine : exercise every day !



JH. Pilates (1883-1967), a precursor of exercising deep muscles and fascia

Clinical Endpoint of metabolic syndrome : first line therapy : exercise and diet !



Adapted from Després et al. BMJ (2010) 322:716-720

University sport activities :
my contribution : bike tour
800 km 5 days

Mit dem Rad auf Eucor-Tour

Jedes Jahr radeln Eucor-Studierende die fünf Unistädte am Oberrhein ab

FOTOS: TEAM TOUR EUCOR

erie Schaub

ruhe, Straßburg, Mulhouse, el, Freiburg. Fünf Eucor-Unis, pen, fünf Tage auf dem Sattel, ecke von 600 bis 800 Kilome- lieber in die Pedale tritt, als Bänken im Hörsaal zu sitzen, Eucor-Unis mit dem Fahrrad n. Jeden Frühling organisieren nde an dem Karlsruher Institut nologie (KIT) die „Tour Eucor", dtour, bei der jede Eucor-Uni ufziel ist. „Die Initial-Idee für Tour Eucor 1998 war relativ erklärt Paul Knipper aus dem ationsteam. Damit der Eucor- nicht nur auf dem Papier steht,

endet nach wie vor zwar in Karlsruhe, aber teilnehmen können alle Mitarbeiterinnen und Mitarbeiter, Studierende und Alumni der fünf oberrheinischen Universitäten.

„Keine Hobbybastler"

Die Pioniere gründeten einen Verein, der mittlerweile zu einem professionellen Organisationsteam herangewachsen ist. Neben Streckenführerinnen und Streckenführern stellt das Team zehn Begleiterinnen und Begleiter zusammen, die mit den Tourmobilen die Radsportlerinnen und Radsportler verpflegen und sich um den Gepäcktransport kümmern. Diese logistische Höchstleistung begeistert so manchen Teilnehmenden. „Das sind keine Hobbybastler, die kommen mit dem Mercedeslaster auf die Minute genau an. Es ist beeindruckend, wie die das organisieren", so Roger Clerc. Der Professor für Biomedizin und Molekularbiologie an der Universität Basel fährt selbst seit drei Jahren mit und befürchtet, der einzige Dozent zu sein, der sich für die Eucor-Strecke auf den Sattel schwingt. Denn die Lehrenden machen sich auf den circa 700 Kilometern rar. „Viele haben Bedenken, weil sie dieselben Studenten ja bei den Prüfungen wiedertreffen könnten", sagt Clerc, der als

Damit jeder auf seine Kosten kommt, gibt es unterschiedliche Routen, die nach Schwierigkeitsgraden eingeteilt sind. In der Kategorie „blau" fahren gemütliche Stadtradfahrer immer den direktesten Weg zwischen den Etappen. Steigungen werden vermieden, heißt es auf der Homepage. Die „Hellroten" haben eine ähnliche Strecke zu bewältigen, nehmen aber kleine Steigungen für einen schönen Ausblick in Kauf. Gruppe „mittelrot" hat etwas mehr Geschwindigkeit und Berge auf der Strecke. „Dunkelrot" setzt noch eins drauf, aber die Profis und Rennradler befinden sich meist in den schwarzen Gruppen. „Hellschwarz" eignet sich für Radsportler - die „Dunkelschwarzen" suchen die ultimative Herausforderung, nehmen jeden Berg mit und legen die längste Strecke zurück.

Einzige Bedingung für die Teilnehmer: Das Rad muss fahrtüchtig sein und jeder sollte einen Ersatzschlauch

im Gepäck haben. Denn Pannen passieren immer wieder. Manchmal aber auch, weil die Räder nicht ausreichend auf solche Strecken vorbereitet wurden. Da wetzen sich schnell Bremsen ab oder alte Schläuche platzen. Deshalb sollte jeder Teilnehmer seinen Drahtesel vor der Tour nochmal gründlich unter die Lupe nehmen, raten die Radprofis vom Team.

Eucor an der frischen Luft erleben

Und dann kann's losgehen. Ob sportliche Herausforderung, Gruppenerlebnis oder Rheinidylle, den persönlichen Anspruch kann sich jeder Teilnehmer selbst aussuchen. Das Ziel für Michael Winz, Student in Freiburg, war es, fünf Tage auf dem Fahrrad zu sitzen und für die „Vaude Transschwarzwald" zu trainieren, ein Etappenrennen für Freizeitsportlerinnen und Freizeitsportler und Profis. Auch er findet die Radtour „eine tolle Sache". Die gemeinsamen Erlebnisse auf der Strecke und das Abendprogramm in den Eucor-Städten schweißen zusammen. Auch wenn die Kontakte nicht immer von Dauer sind, haben sich während der Tour schon interessante Bekanntschaften ergeben. Roger Clerc profitiert gerne von seinen jüngeren Weggefährten, um mit ihnen

Beyond BMI: omental fat distribution vs skin fat and waist-hip ratio as compagnion diagnostics

INA FASSBENDER/AFP VIA GETTY

Players in an 'overweight football league' warm up before a match in Germany. To join, members must have a BMI of at least 31.

BEYOND BMI: HOW TO REDEFINE OBESITY

The main diagnostic test for obesity accounts for only height and weight, leaving out a slew of factors that influence health. **By McKenzie Prillaman**

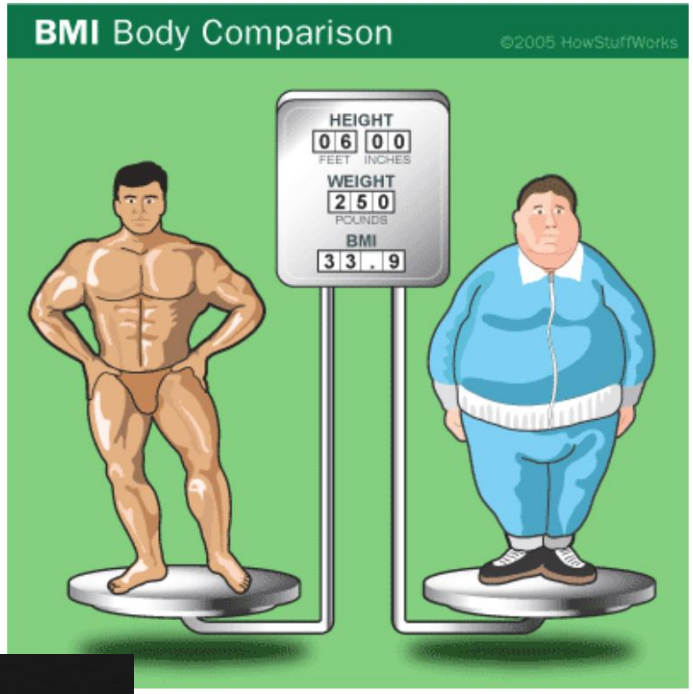
disease. In June, the American Medical Association (AMA) called for more weight-related metrics to be used in conjunction with BMI owing to its imperfections and questionable history.

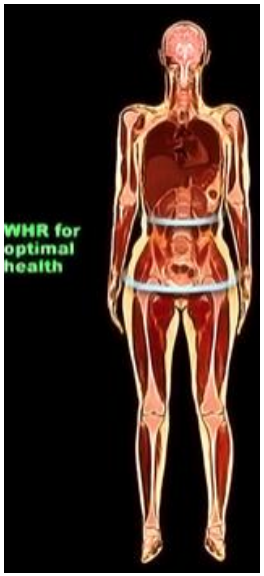
But, with global rates of obesity having tripled over the past 50 years, and a wave of cutting-edge weight-loss drugs now hitting the market, a high BMI still reigns as the main criterion for obesity treatment. Specialists worry that the surging demand for the drugs will exacerbate reliance on BMI as a solo diagnostic tool.

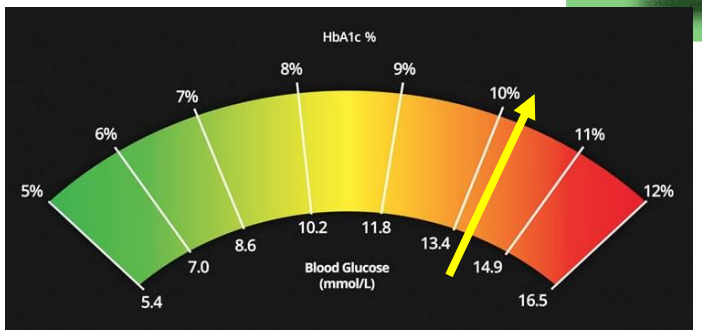
"When we look at just height and weight, we don't know anything about the health status of the individual," Stanford says.

Metabolic syndrome pandemia and the short cuts: not only BMI (body mass index) and WHR (waist hip ratio) : viceral fat vs sub cut fat content are mainly relevant

$$BMI = \frac{weight}{(height)^2}$$



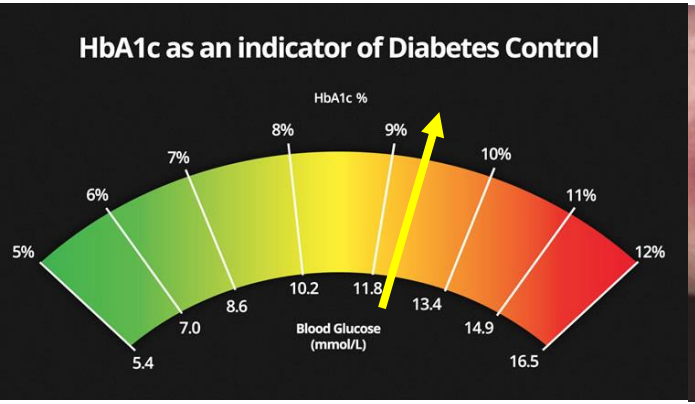


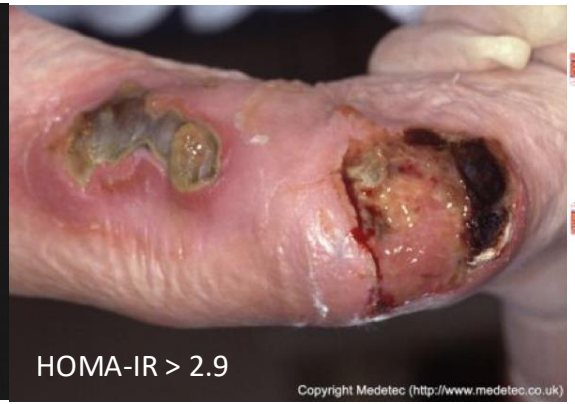


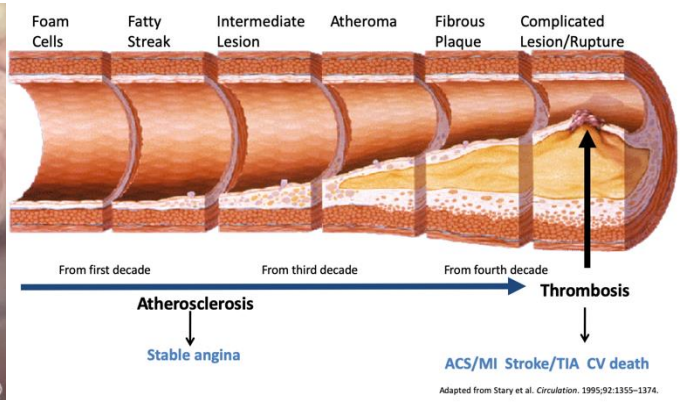
My therapeutic target : metabolic syndrome, diabetes, atherosclerosis obesity

A medicinal chemistry approach to treatment of type II diabetes and obesity

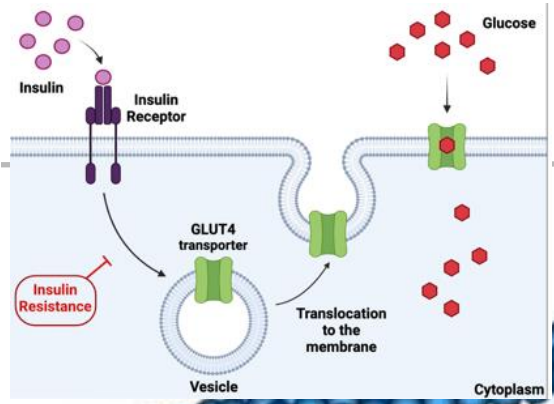
Roger G Clerc EPFL EDOC EDBB EDMS EDCB



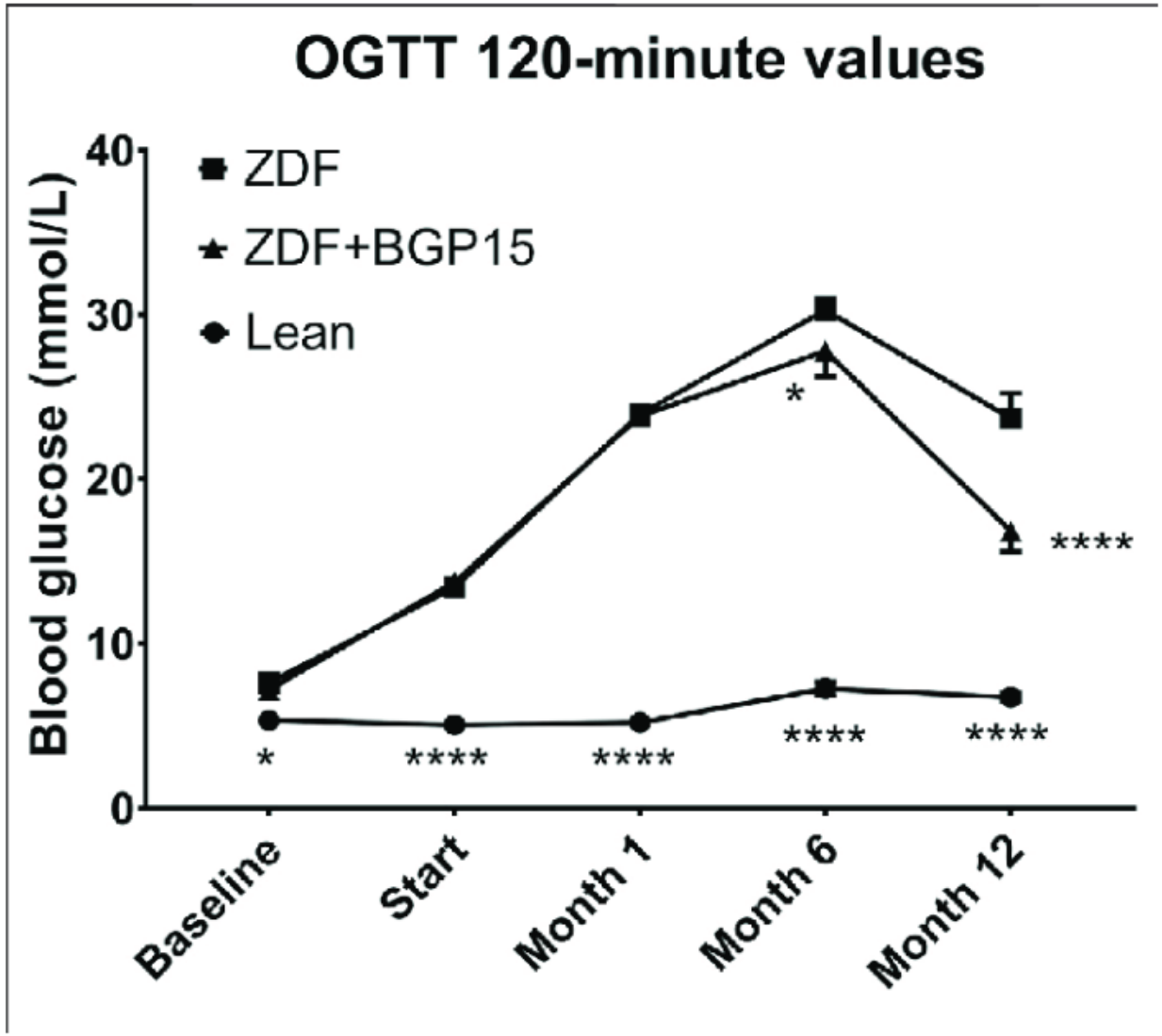




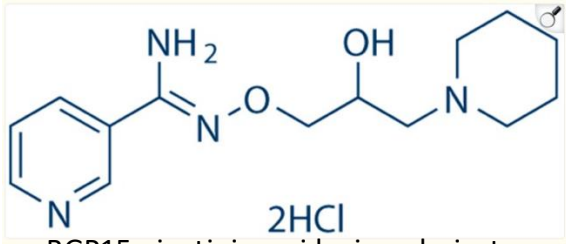
The underlying molecular mechanism 0f PPAR agonists in insulin resistance



Type II diabetes develops as a consequence of the metabolic syndrome : oral glucose tolerance as a measure of the metabolisation of CBH



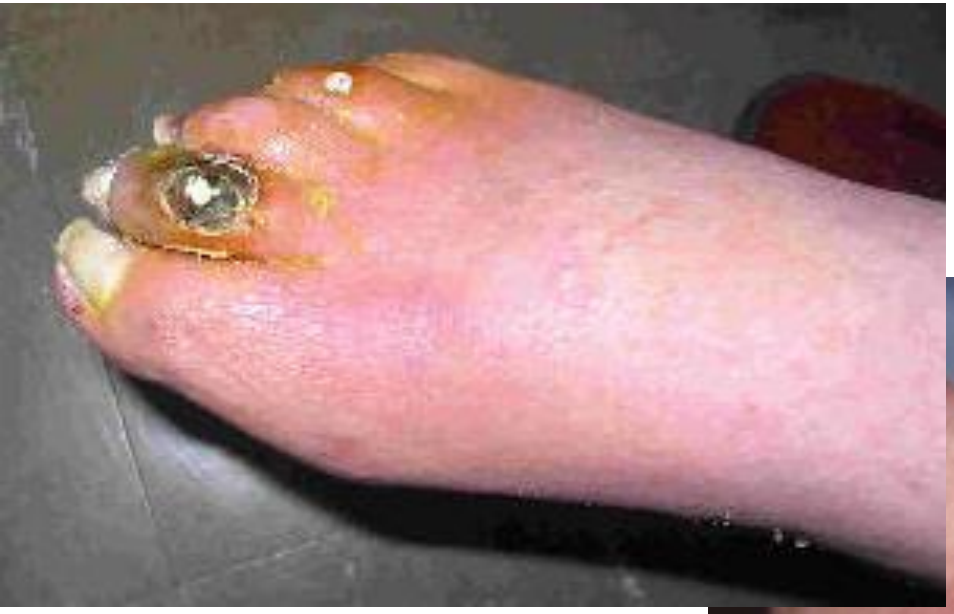
BGP15 insulin sensitizer



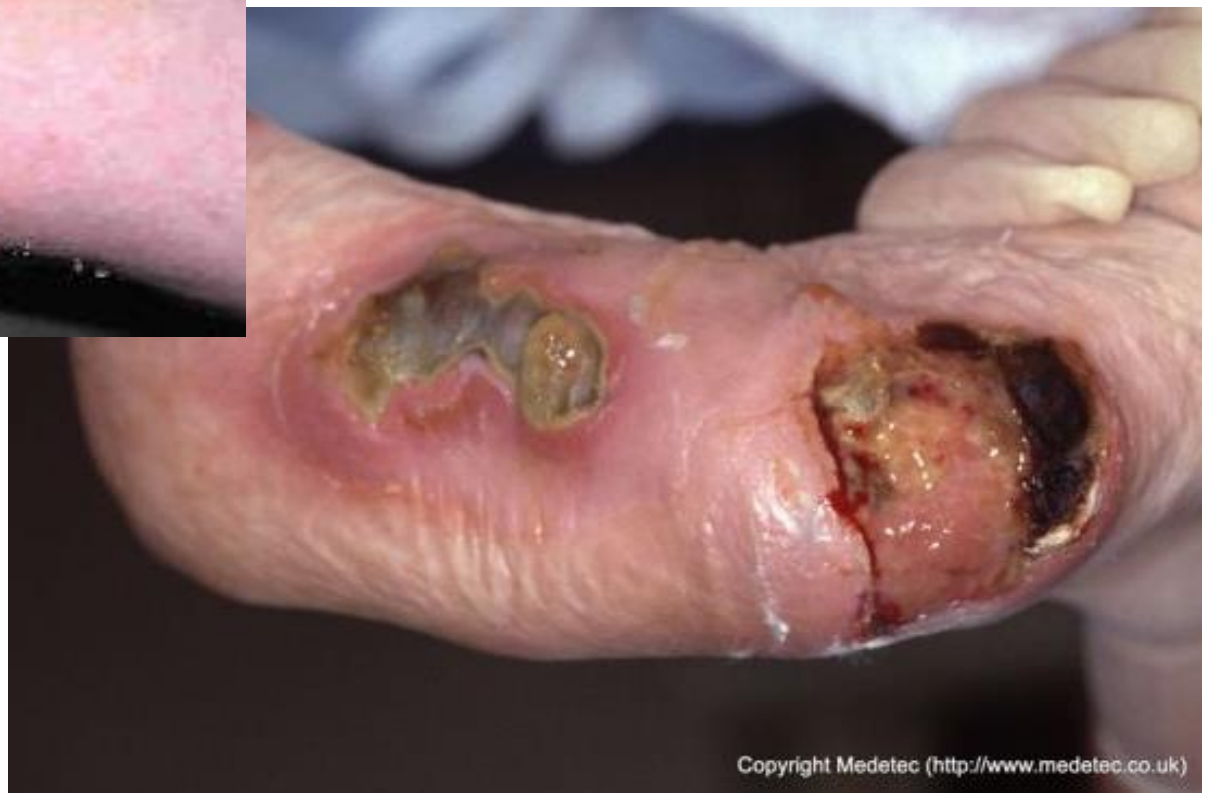
BGP15 nicotinic amidoxime derivate

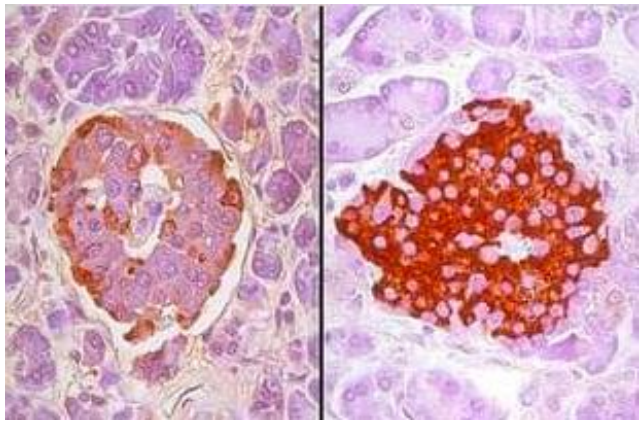
| Oral glucose tolerance test (OGTT) 120-min values during the study. Data are presented as group means. For a

Advanced type II diabetes : peripheral ischaemia-necrosis



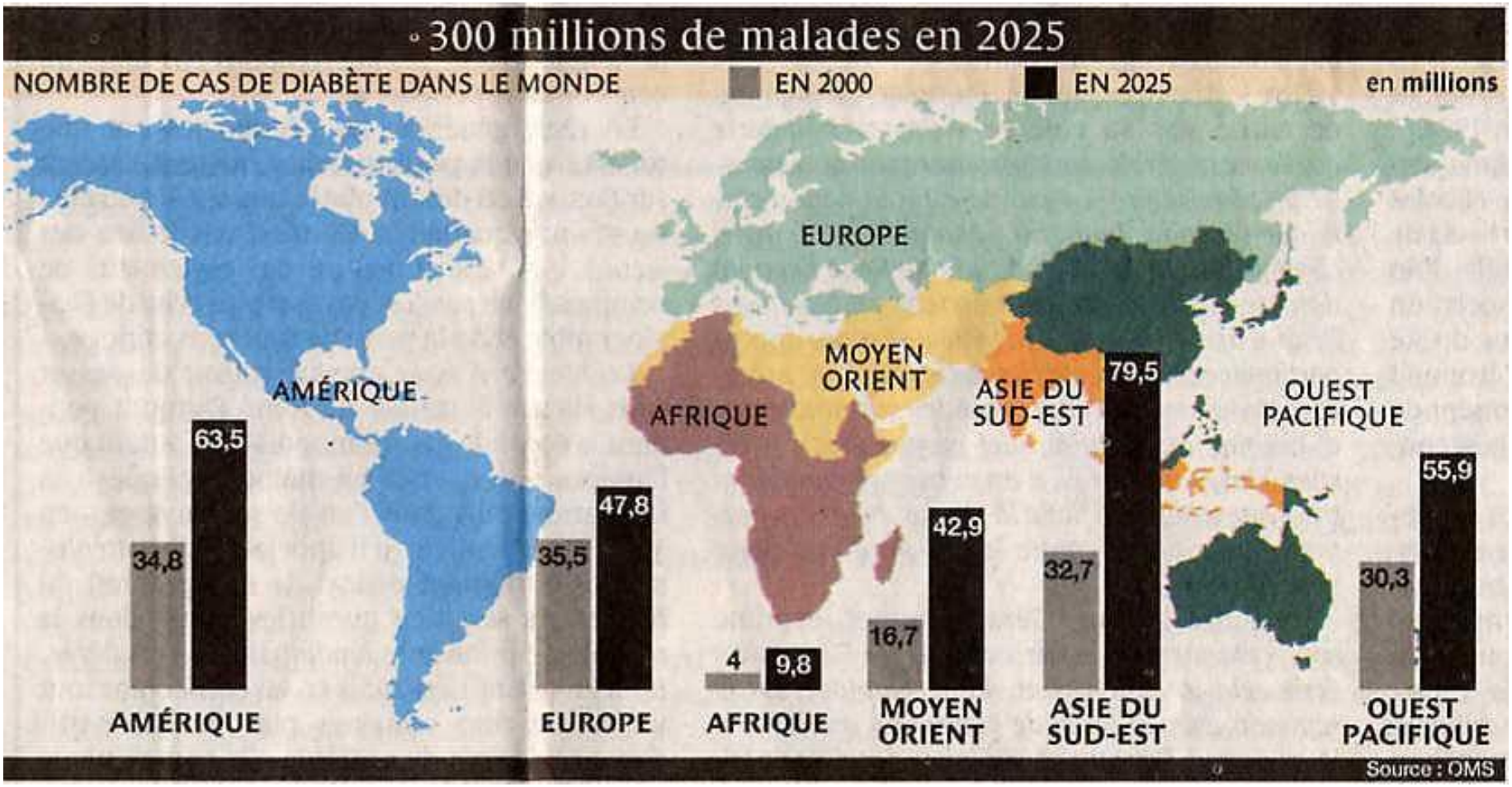
MEDICAL NEED : IMPROVE TYPE II DIABETES **USING A MEDICINAL CHEMISTRY DESIGN**





MACRO- AND MICROVASCULARIZATION IMPAIREMENTS

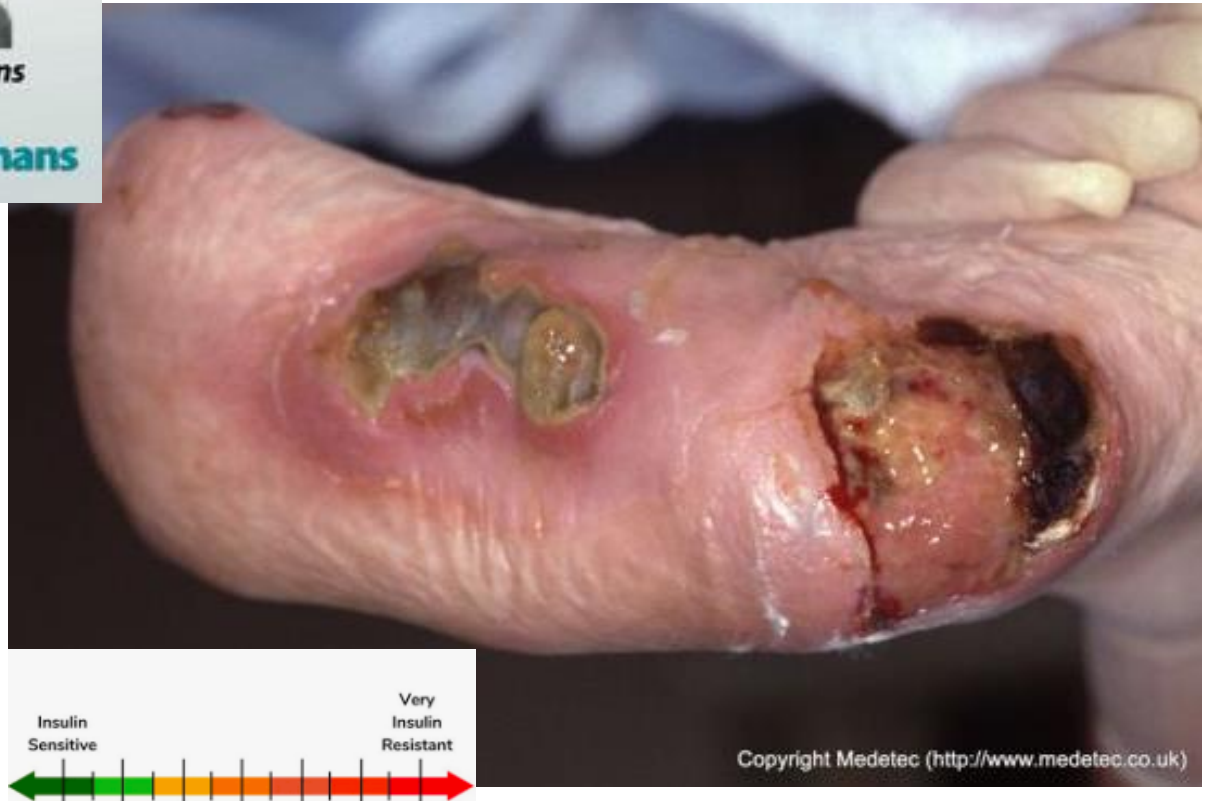
Type II diabetes and metabolic syndrome global pandemia _ 2025 : WHO



Le Monde

Advanced type II diabetes : peripheral ischaemia-necrosis

MEDICAL NEED : IMPROVE INSULIN SENSITIVITY **USING A MEDICINAL CHEMISTRY DESIGN**



INAUGURAL-DISSERTATION.

ZUR

ERLANGUNG DER DOCTORWÜRDE

IN DER

MEDICIN UND CHIRURGIE

VORGELEGT DER

MEDICINISCHEN FACULTÄT

DER FRIEDRICH-WILHELMS-UNIVERSITÄT

ZU BERLIN

UND ÖFFENTLICH ZU VERTHEIDIGEN

am 18. Februar 1869

VON

Paul Langerhans

aus Berlin.

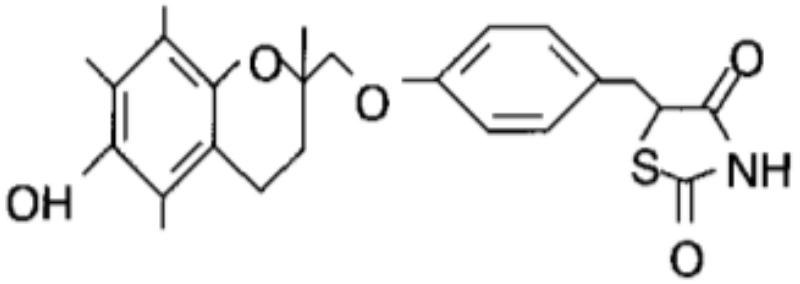
OPPONENTEN:

O. Locillet de Mars, Dd. med.
O. Soltmann, Dd. med.
Paul Ruge, Stud. med.

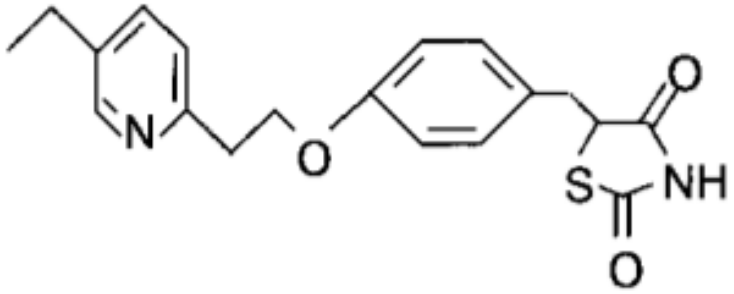
BERLIN.

Type II diabetes develops as a consequence of the metabolic syndrome key drivers PPARγs (thiazolidinedione) medicines

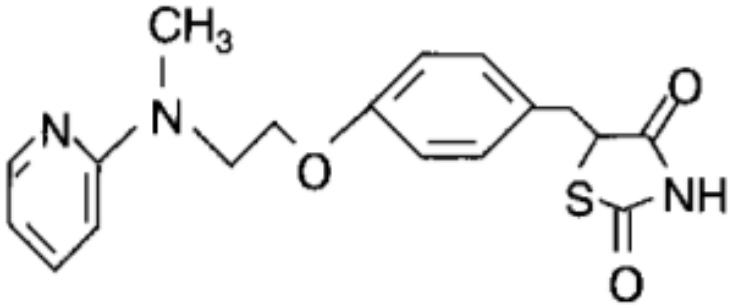
Diabetes/obesity itself is an emergent lasting pandemia
not like eg. COVID-19 which turned an evasive pandemia :



Troglitazone

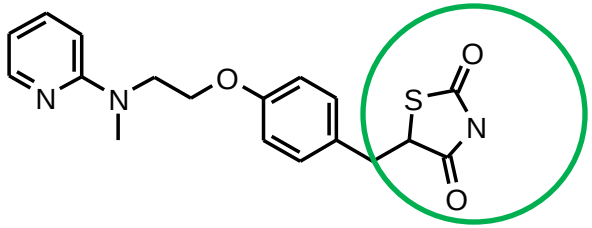


Pioglitazone



Rosiglitazone

PPARγ medicinal chemistry: : «me too», patent bashing, time to market



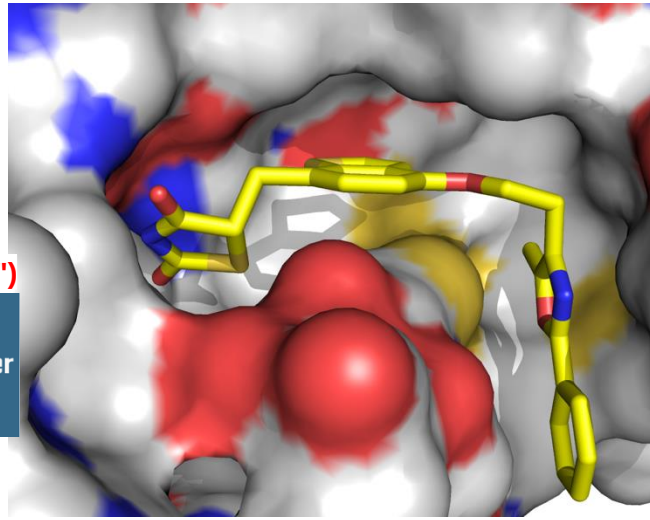
thiazolidinedione controversial head piece in PPARγ

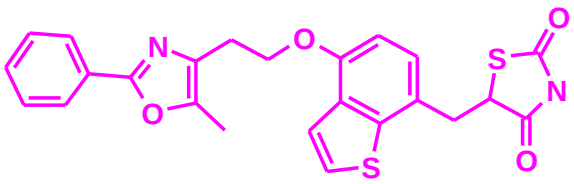
Rosiglitazone (Prototypical PPARgamma Agonist)

GSK

GSK-Tail (Phenyloxazole)

Benzothiophene Spacer (Boehringer "Invention")



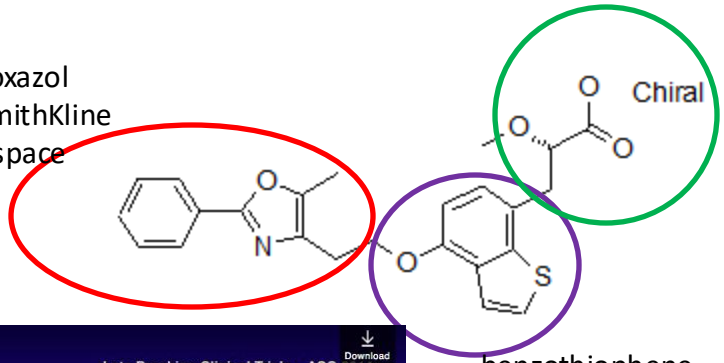


Edaglitazar

Boehringer Inc

Replacement of thiazolidinedione controversial head piece in PPARγ

Phenyloxazol GlaxoSmithKline patent space

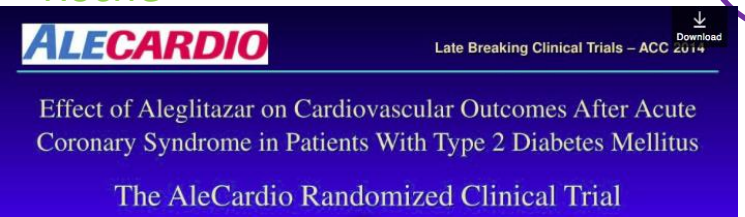


Aleglitazar

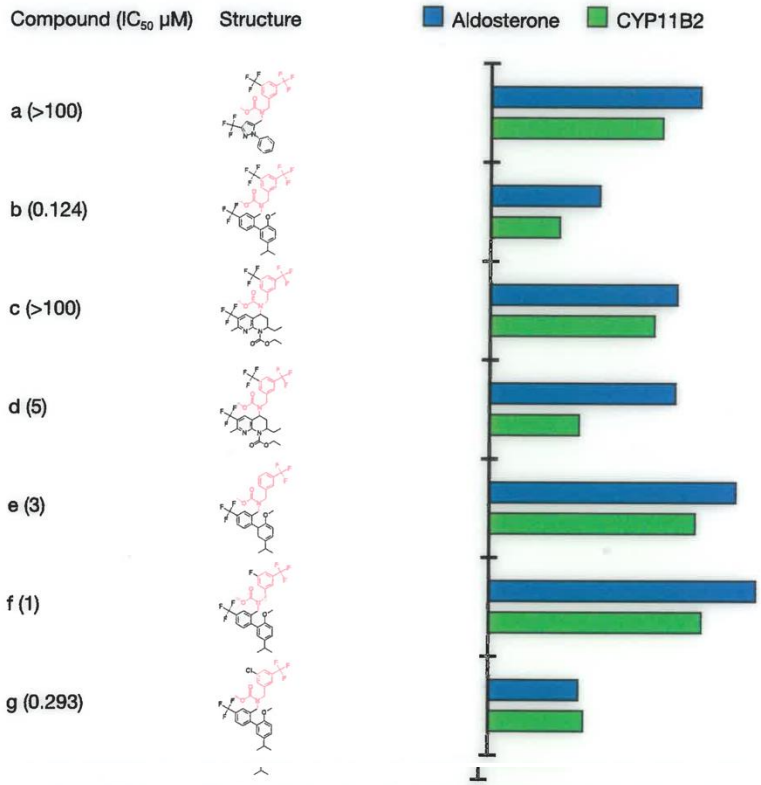
Roche

benzothiophene Boehringer Manheim patent space

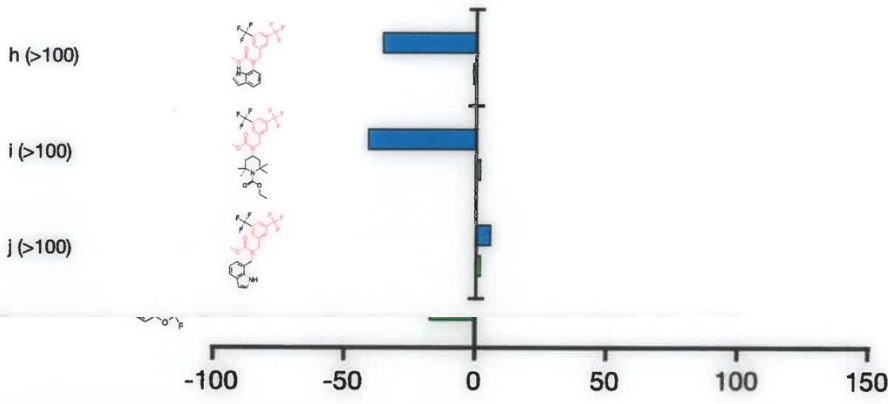
***In vitro* Activity**	IC_{50} α/γ/δ [nM]	35 / 66 / 21
	EC_{50} α/γ/δ [nM]	53 / 32 / 44



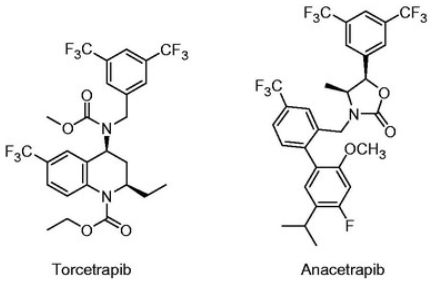
1a. Compounds with methyl-(3-trifluoromethyl-benzyl)-carbamic acid methyl ester motif of torcetrapib (IN RED COLOUR) attached to a suitable THQ-replacement



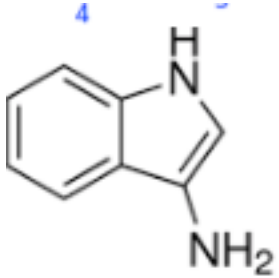
1b. Compounds with methyl-(3-trifluoromethyl-benzyl)-carbamic acid methyl ester motif of torcetrapib (IN RED COLOUR) but no suitable THQ-replacement



IC_{60} of CETP activity determined using a scintillation proximity assay.
nd, not determined (benzoic acid derivative).

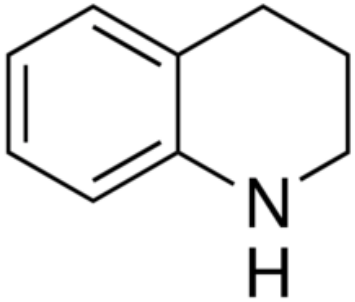


An example of assay read out and medicinal chemistry MDO



Indole

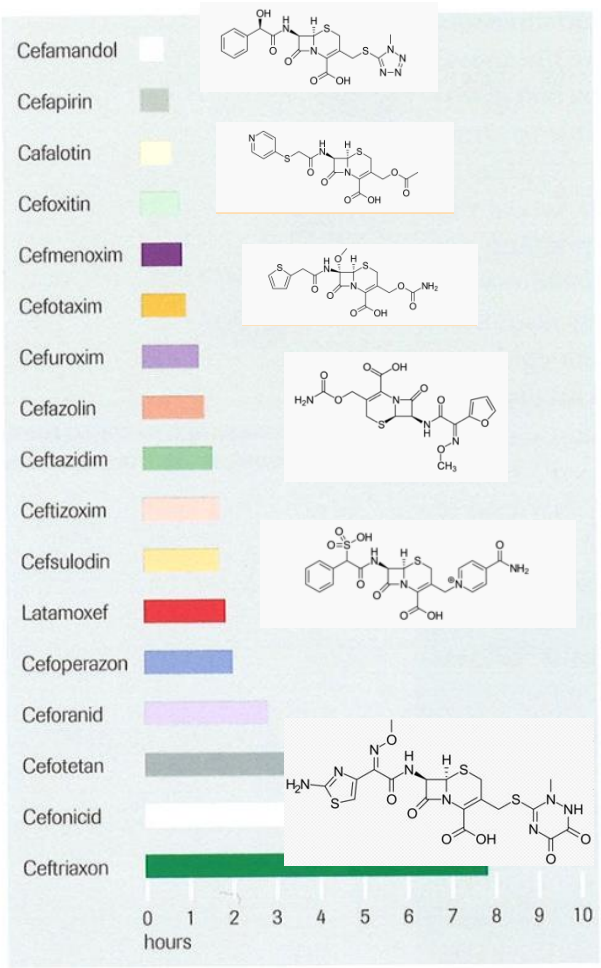
Composé organi

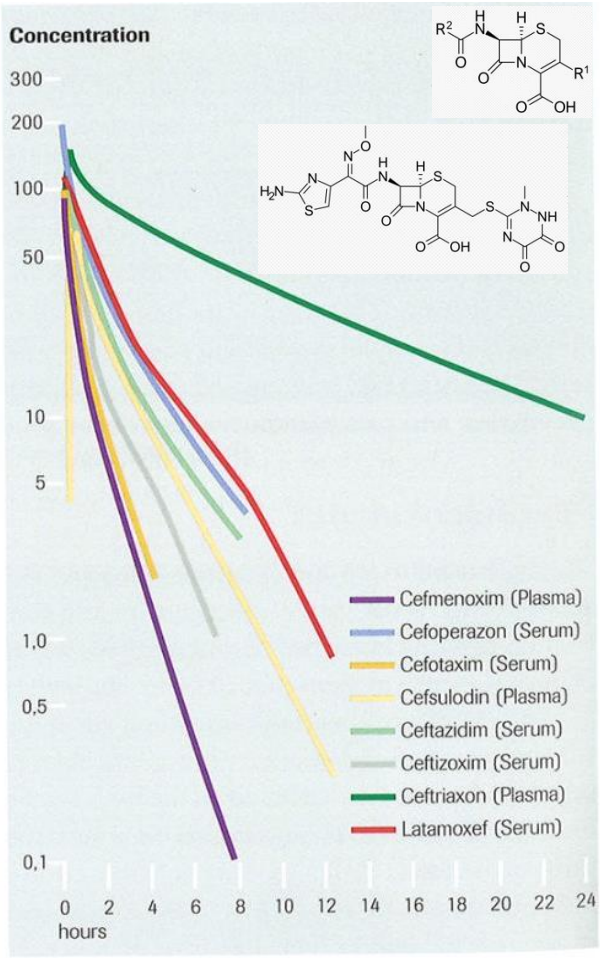


T15504 ALDRICH
1,2,3,4-Tetrahydroquinoline
98%
Synonym: THQ

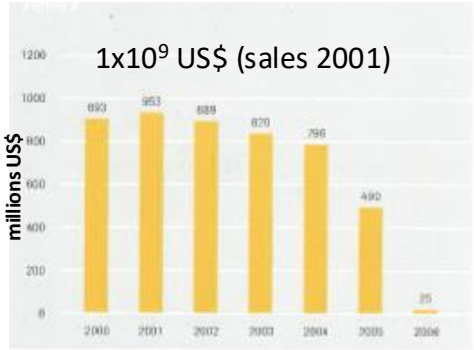
Clerc RG. and Niesor EJ. (2012) American Heart Association Washington DC

World most prescribed cephalosporin: unique PK “once a day” ceftriaxone “blockbuster”





Yearly sales of Roche Rocephin from 2000 to 2006



Rocephin patent expires 2005

PPARγ has been called a «thrifty allele»

« A DAY WITHOUT UNI SPORT IS NOT A SUCCESSFUL DAY ! «

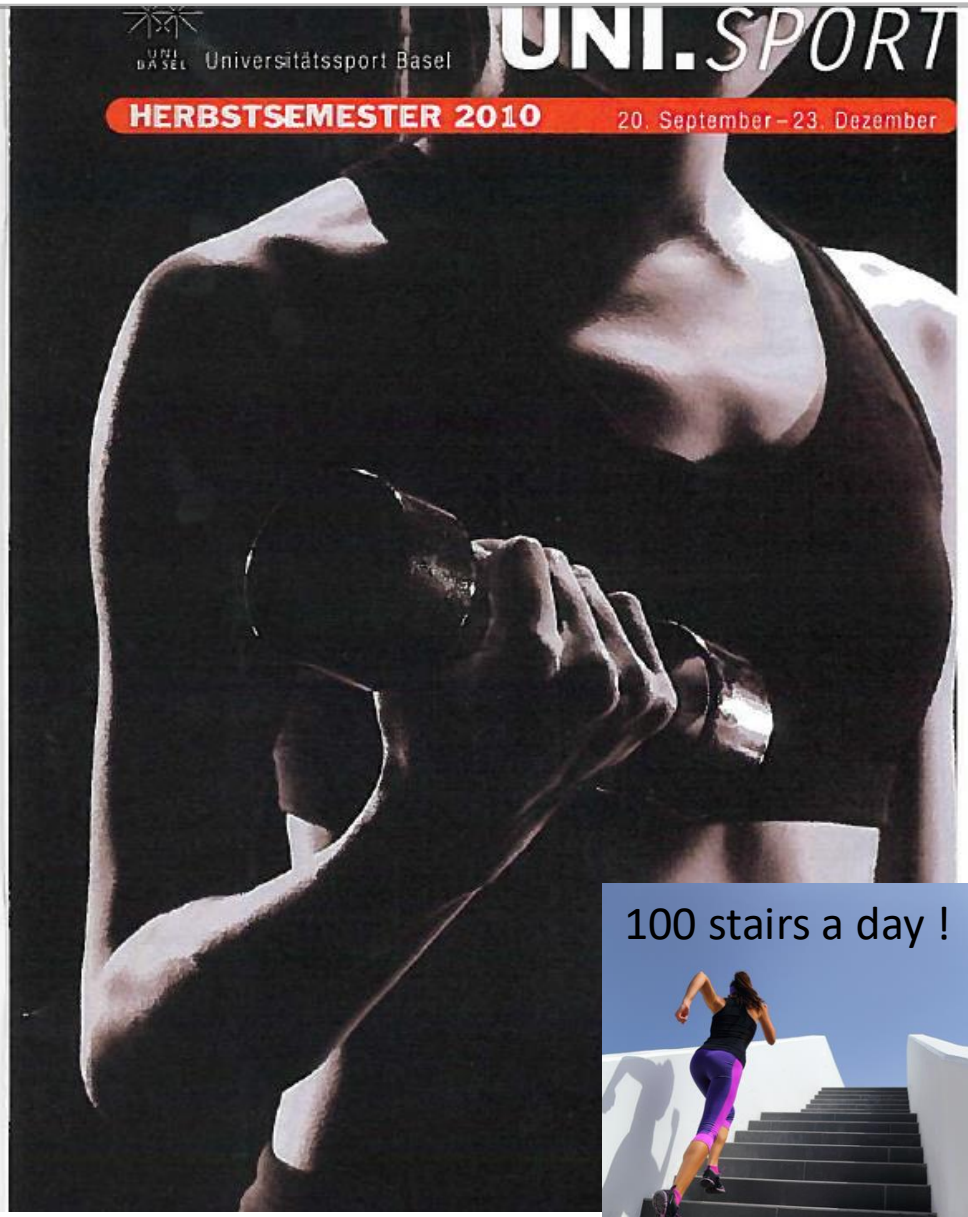
«Sparsame Gene»: Trainiere jeden Tag beim Unisport!

Das Universitätsstudium und insbesondere seine Prüfungen innerhalb bestimmter Fristen sind stressig. Wir sind so mit einem Lebensstil konfrontiert, welcher uns - nicht nur an der Universität - immer mehr geistige Leistungen in immer kurzfristigeren Zeithorizonten abverlangt, wobei wir uns oft nicht mehr ausreichend körperlich aktiv bewegen. Zu dieser Bewegungsarmut gesellt sich oft eine ungesunde Ernährung. Viele Menschen sind daher übergewichtig und entwickeln metabolisches Syndrom mit u.a. erhöhtem Blutzucker, Bluthochdruck und erhöhten Blutfettwerten.

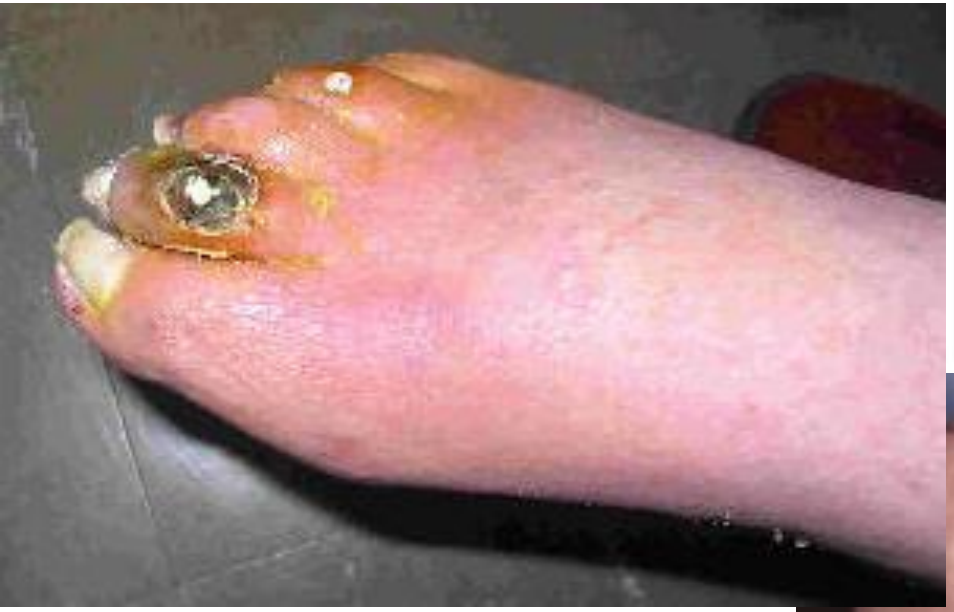
Unser Genom hat sich in Millionen von Jahren entwickelt, in denen Nahrungsmangel herrschte. Der Mensch der Urzeit war ein hoch beweglicher Jäger, der nur selten etwas zum Essen fand. Sein Körper passte sich evolutiv daran an, diese rare kostbare Energie in seinen Geweben dank der "sparsamen Gene" zu speichern. An den erst seit wenigen Jahrzehnten herrschenden „plötzlichen" Überschuss an sehr kalorienreicher Nahrung und die mangelnde körperliche Bewegung heutzutage, konnte sich unser Genom noch nicht anpassen. Um das empfindliche Gleichgewicht unserer körperlichen und geistigen Gesundheit zu erhalten, ist es deshalb notwendig, regelmässig sportliche Aktivitäten, die Spass machen, zu betreiben. Auch eine intelligente Ernährung, mit wenig Zucker und gesättigten Fetten, dafür aber reich an Ballaststoffen und Eiweiss, und ein nur moderater Alkoholkonsum, sind notwendig, um unsere "sparsamen Gene" so zu trainieren, dass wir kein metabolisches Syndrom entwickeln. Deswegen gibt es Unisport: um die Balance zwischen Körper und Gehirn während dem Studium beizubehalten

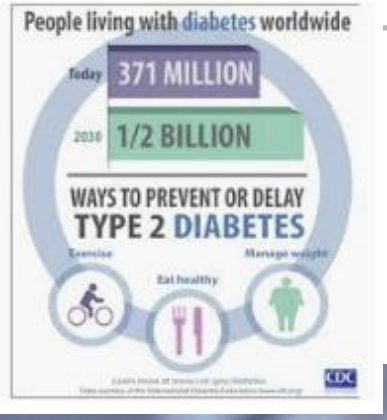
Buchen Sie daher jeden Tag einen Sport-Termin im Kalender und geniessen Sie das aussergewöhnliche Sportangebot der Universität! Über 80 verschiedene Sportarten werden im neuen Unisport-Programm angeboten. Beteiligen Sie sich aktiv am Unisport. „A day without sport is not a successful day!"

Prof. Dr. Roger G. Clerc
Dozent Universität Basel
und Teilnehmer am Universitätssport

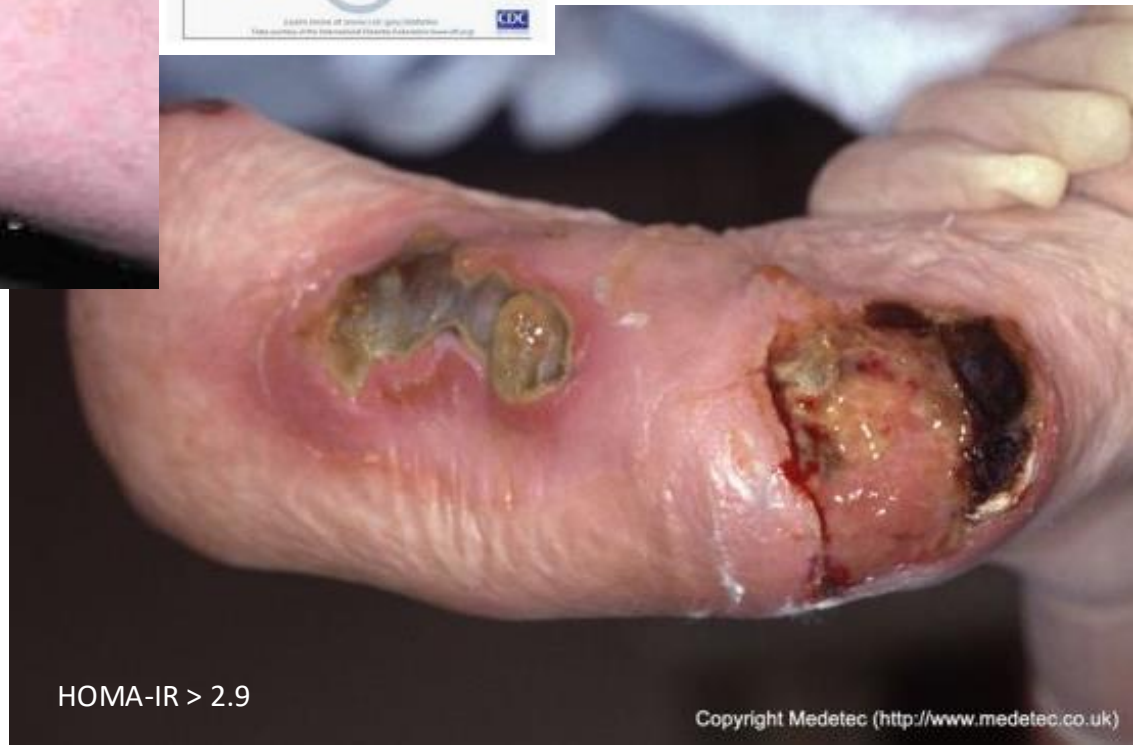


Advanced type II diabetes : recurrent clinical cases





DIABETIC LIMB SALVAGE CONFERENCE



A CLINICAL CASE (switzerland)

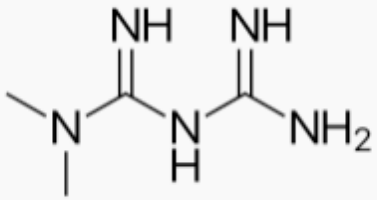
- 45 y old chronic T2D patient
- HbA1c >7% BMI >30 WHR >1
- HOMA-IR >2.9
- ER - lower limb septic amputation
- MRSA (Staph aureus) +++
- Last resort antibiotics failed
- Fatal septicemia -sepsis

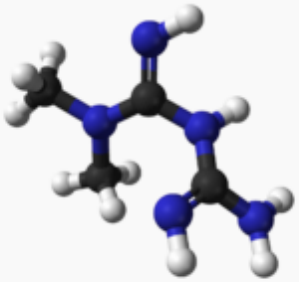
Metabolic syndrome – when patients become insulin resistant
MACRO- AND MICROVASCULARIZATION IMPAIREMENTS

Biguanides – a classical in mgmt of Type II diabetes

(repurposed as antiageing medicine ?)

Metformine



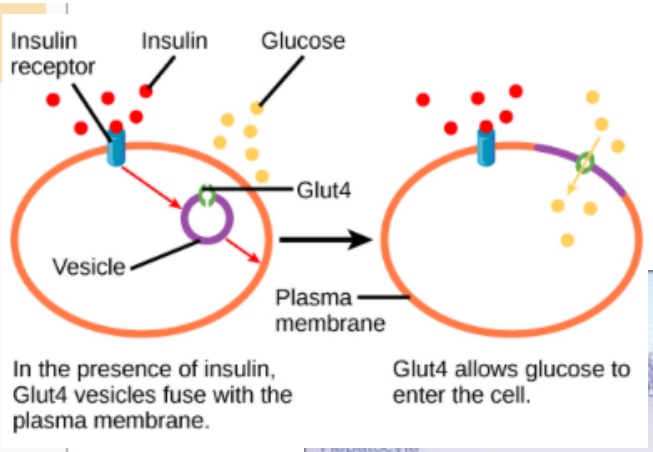


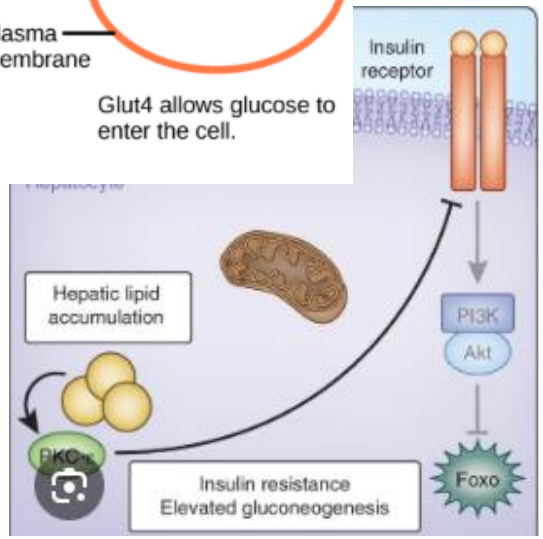
Identification

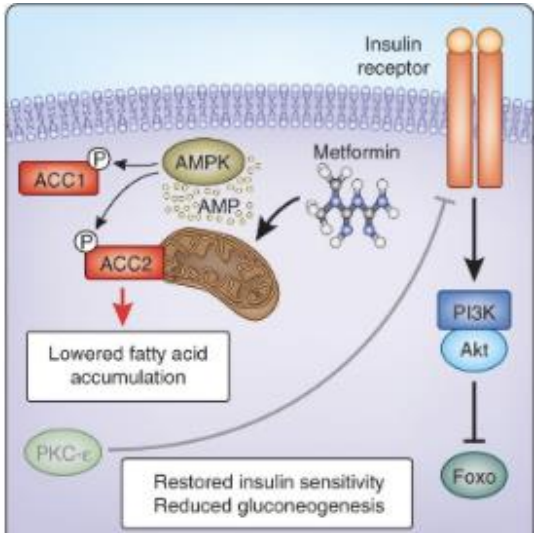
N° CAS	657-24-9 1115-70-4 (HCl)
N° ECHA	100.010.472
N° CE	211-517-8
Code ATC	A10BA02
DrugBank	APRD01099
PubChem	4091
SMILES	[afficher]
InChI	[afficher]

Propriétés chimiques

Formule	$C_4H_{11}N_5$ [Isomères]







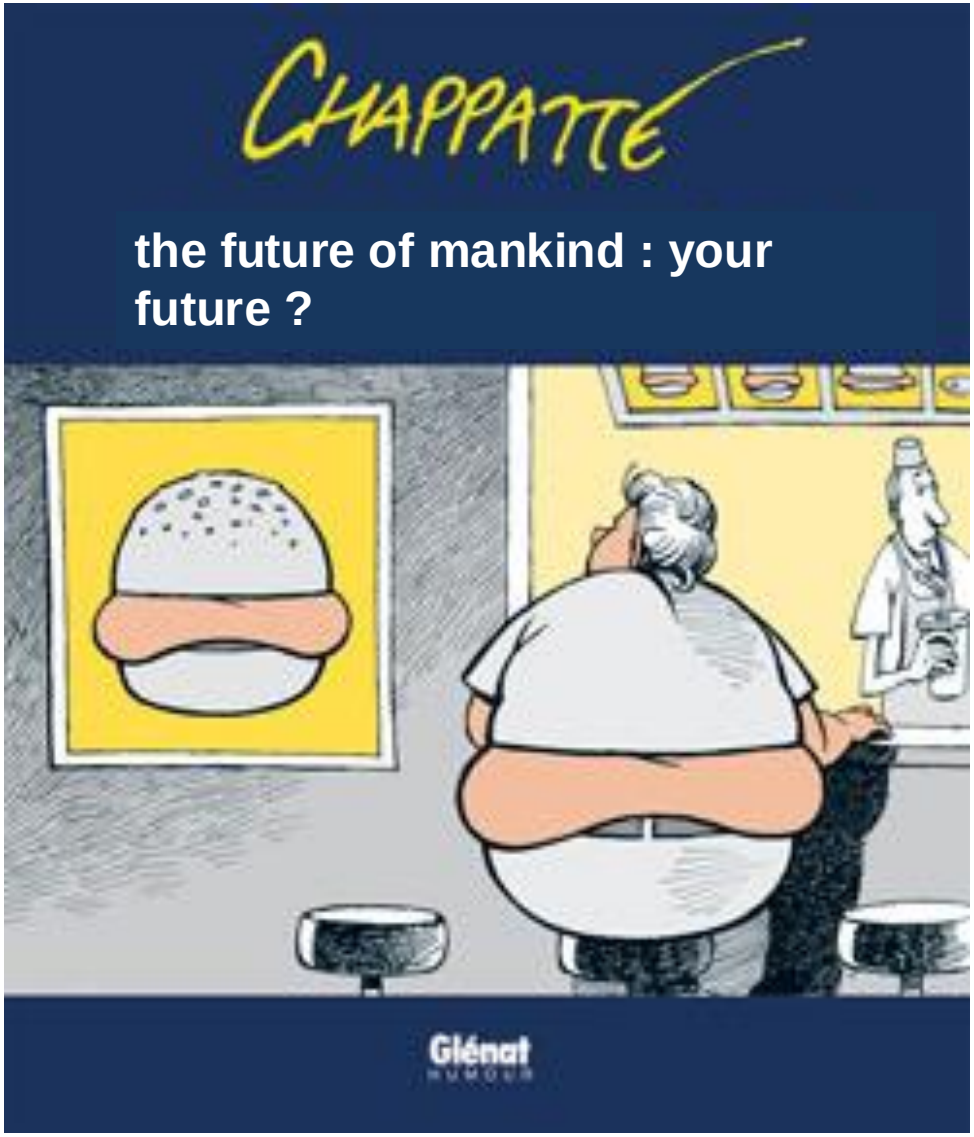
An »old » normoglycemic medicine in primary clinical intention of T2D management

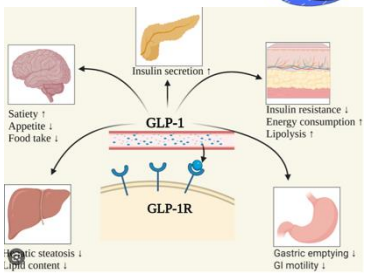
NB : the exact underlying molecular mechanism still not well understood

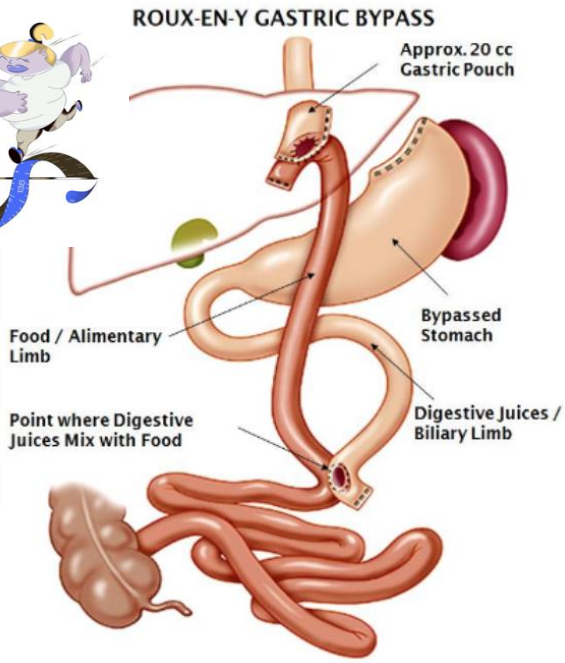
reduces neoglycogenolysis, increases insulin »sensitization » muscle/adipocytes insulin signaling activated

(adverse effects of metformin: lactic acidosis, hypoglycemia)

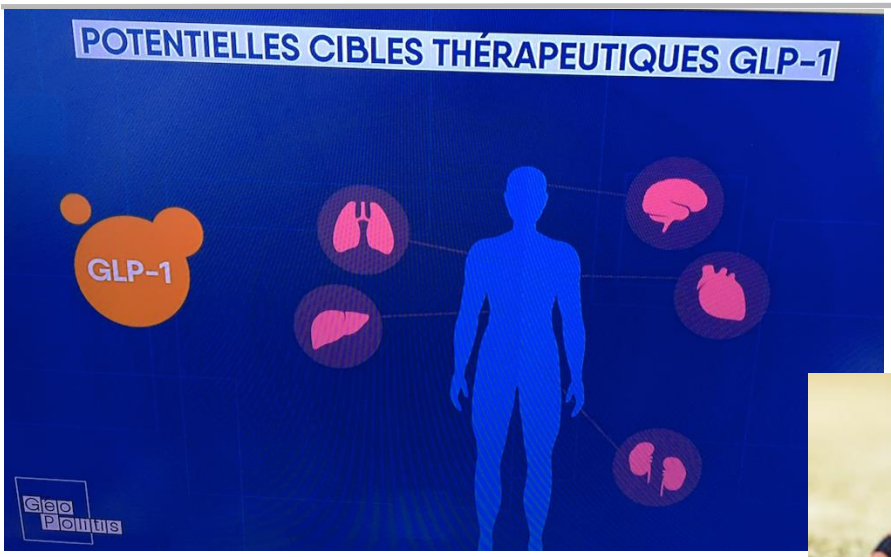
Type II diabetes and metabolic syndrome pandemia : a cartoonist view of a threat - towards the end of IR/obesity ?







INCRETINS : from a salamander venom to ML-guided SMC medicine : 35 years to making a medicine available to ALL patients in need !



771-P

Efficacy of CT-996, an Oral Small Molecule GLP-1 Receptor Agonist, in Human GLP-1 Receptor Knock-in Mice and Obese Cynomolgus Monkeys

Jian Luo[1], Ruben Rodriguez[1], Anne Hergarden[1], Ted Tracy[1], Davina Lam[1], Sumanta Garai[1], Daniel Marshall[1], Stig Hansen[2], Manu Chakravarthy[1]

[1]Carmot Therapeutics, a member of the Roche group; [2]Kimia Therapeutics.

The advent of the glucagon peptide superfamily – 1980-1990s

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 265, No. 33, Issue of November 25, pp. 20259–20262, 1990
Printed in U.S.A.

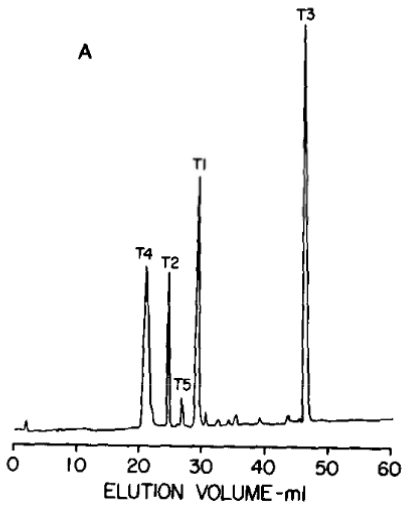
Purification and Structure of Exendin-3, a New Pancreatic Secretagogue Isolated from *Heloderma horridum* Venom*

(Received for publication, April 10, 1990)

John Eng‡§¶, P. C. Andrews‖, Wayne A. Kleinman‡, Latika Singh, and Jean-Pierre Raufman****

*From the ‡Solomon A. Berson Research Laboratory, Veterans Affairs Medical Center, Bronx, New York 10468, the §Department of Medicine, Mount Sinai School of Medicine, New York, New York 10029, the ‖Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, Michigan 48109, and the **Department of Medicine, State University of New York-Health Science Center, Brooklyn, New York 11203*

An amino-terminal histidyl structure (His[1]) is characteristic of most peptides in the glucagon superfamily. minal sequencing was used to screen for new His[1] peptides that might be members of the glucagon superfamily. Gila



% HOMOLOGY		5 10 15 20 25 30 35 40 45
100	EXENDIN-3	H S D G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S #
32	HELOSPECTIN	H S D A T F T A E Y S K L L A K L A L Q K Y L E S I L G S S T S P R P P S S
26	HELODERMIN	H S D A I F T E E Y S K L L A K L A L Q K Y L A S I L G S R T S P P P #
41	SECRETIN	H S D G T F T S E L S R L R D S A R L Q R L L Q G L V #
48	GLUCAGON	H S Q G T F T S D Y S K Y L D S R R A Q D F V Q W L M N T
50	GLP-1	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R #
29	GLP-2	H A D G S F S D E M N T I L D N L A A R D F I N W L I Q T K I T D R
37	PHI	H A D G V F T S D F S R L L G Q L S A K K Y L E S L I #
29	VIP	H S D A V F T D N Y T R L R K Q M A V K K Y L N S I L N #
26	GIP	Y A E G T F I S D Y S I A M D K I R Q Q D F V N W L L A Q K G K K S D W K H N I T Q
13	GRF	Y A D A I F T N S Y R K V L G Q L S A R K L L Q D I M S R Q Q G E S N Q E R G A R A R L #
24	PACAP38	H S D G I F T D S Y S R Y R K Q M A V K K Y L A A V L G K R Y K Q R V K N K #

Papers : the advent of the glucagon peptide superfamily - 1990s

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 265, No. 33, Issue of November 25, pp. 20259-20262, 1990
Printed in U.S.A.

Purification and Structure of Exendin-3, a New Pancreatic Secretagogue Isolated from *Heloderma horridum* Venom*

(Received for publication, April 10, 1990)

John Eng‡§¶, P. C. Andrews‖, Wayne A. Kleinman‡, Latika Singh, and Jean-Pierre Raufman****

*From the ‡Solomon A. Berson Research Laboratory, Veterans Affairs Medical Center, Bronx, New York 10468, the §Department of Medicine, Mount Sinai School of Medicine, New York, New York 10029, the ‖Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, Michigan 48109, and the **Department of Medicine, State University of New York-Health Science Center, Brooklyn, New York 11203*

An amino-terminal histidyl structure (His[1]) is characteristic of most peptides in the glucagon superfamily. An assay for His[1] peptides performed by amino-terminal amino acid sequencing was used to screen venom from the Gila monster lizard, *Heloderma horridum*. Two His[1] peptides were identified: helospectin and a new His[1] peptide that has been named exendin-3 to indicate that it is the third peptide to be found in an exocrine secretion of *Heloderma* lizards which has endocrine activity, the first two being helospectin (exendin-1) and helodermin (exendin-2). In the lot of *H. horridum* venom tested, exendin-3 was 5–10-fold more abundant in molar concentration than helospectin. The structure of exendin-3 was analyzed by amino acid sequencing and mass spectrometry. Exendin-3 is a 39-amino acid peptide with a mass of 4200. It contains a carboxyl-terminal amide and has a strong homology with secretin at its amino-terminal 12 amino acids. The complete structure of exendin-3 is His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-amide. It is 32 and 26% homologous with helospectin and helodermin, respectively. It has greatest homology with glucagon (48%) and human glucagon-like peptide-1 (50%). Exendin-3 (3 μM) stimulated increases in cellular cAMP and amylase release from dispersed guinea pig pancreatic acini.

The glucagon superfamily consists of a diverse group of biologically active peptides that are structurally related by having an amino-terminal histidine residue (His[1]) and a phenylalanine residue at position 6 (Phe[6]) (1) or one of several variant structures such as Tyr[1]-Phe[6] (2, 3), His[1]-Tyr[6] (4), or His[1]-Leu[6] (5). An assay for His[1] can potentially be used to identify peptides belonging to this family. Although special chemical methods have been reported for the detection of His[1] peptides (6, 7), a more general method of assaying for His[1] is amino-terminal amino acid sequencing. This assay was used recently to monitor the purification of glucagon from chinchilla pancreas (8). To test the hypothesis that His[1] is a chemical marker for biologically active peptides, amino-terminal sequencing was used to screen for new His[1] peptides that might be members of the glucagon superfamily. Gila monster venom was chosen for screening because venoms from *Heloderma suspectum* and *Heloderma horridum* had been shown previously to contain two biologically active His[1]-Phe[6] peptides, helospectin (9) and helodermin (10). When *H. horridum* venom was examined with the His[1] assay, a previously unrecognized His[1]-Phe[6] peptide was detected. In this study, we report the purification and structural characterization of this new peptide. It is named exendin-3 to identify it as the third peptide found in an exocrine secretion of *Heloderma* lizards which has endocrine activity. Like the earlier exendins, it is a pancreatic secretagogue.

MATERIALS AND METHODS

H. horridum venom (lot 74F-0240), diphenylcarbamyl chloride-treated trypsin, carboxypeptidase Y, and carboxypeptidase P were purchased from Sigma. Endoproteinase Glu-C (V8 protease) was purchased from Boehringer Mannheim.

His[1] Assay and Amino Acid Sequencing—Amino-terminal amino acid analysis was performed by a single cycle of Edman degradation using an automated gas-phase protein sequenator in combination with an on-line PTH[1]-derivative analyzer (Applied Biosystems). The molarity of the analyzer's weak solvent was adjusted to position PTH-His to elute between PTH-Ala and PTH-dehydroSer. Purified peptides and peptide fragments were sequenced with the gas-phase sequenator.

Isolation of His[1] Peptides from Heloderma Venom—Venom (25 mg) was dissolved in water to a concentration of 10 mg/ml and passed through a C_{18} Sep-Pak cartridge (Waters Associates, Milford, MA). The C_{18} cartridge was washed with 5 ml of water and eluted with 2 ml of 0.1% trifluoroacetic acid, 60% acetonitrile. Peptides in the eluate were separated by HPLC on an 8-mm × 10-cm MB C_{18} Radial-Pak column (Waters Associates). The column was eluted with a linear gradient from 20 to 60% acetonitrile in 0.13% heptafluorobutyric acid at a flow rate of 2 ml/min. One-minute fractions were collected. Aliquots from each fraction were assayed for His[1] content.

Enzyme Cleavages—Purified exendin-3 (10 nmol) was dried and digested separately with 0.2 μg of trypsin or 2 μg of V8 protease in 0.1 ml of 0.1 M ammonium bicarbonate overnight at room temperature. Peptide fragments were purified by HPLC on a Nova C_{18} Radial-Pak column (Waters Associates). The elutions were performed with a linear gradient from 0 to 40% acetonitrile in 0.1% trifluoroacetic acid at a flow rate of 1 ml/min.

Exendin-3 (1 nmol) was incubated with carboxypeptidase Y or carboxypeptidase P (1 μg each) in 0.05 ml of 0.05 M sodium acetate, pH 5.5, at room temperature for timed intervals up to 6 h. Aliquots from the mixtures were analyzed for release of free amino acids.

Amino Acid Analysis—Peptides were dried and hydrolyzed with gas-phase 6 M HCl at 150 °C for 60 min. Amino acids were analyzed with an automated amino acid derivatizer (Applied Biosystems) connected to an on-line phenylthiocarbamyl-derivative analyzer.

* This work was supported in part by the Department of Veterans Affairs. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¶ To whom correspondence should be sent: Solomon A. Berson Research Laboratory, Veterans Affairs Medical Center, Bronx, New York 10468. Tel.: 212-584-9000 (ext. 1710).

[1] The abbreviations used are: PTH, phenylthiohydantoin; HPLC, high pressure liquid chromatography; FAB-MS, fast atom bombardment-mass spectrometry; VIP, vasoactive intestinal peptide.

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 267, No. 11, Issue of April 15, pp. 7402-7405, 1992
Printed in U.S.A.

Isolation and Characterization of Exendin-4, an Exendin-3 Analogue, from *Heloderma suspectum* Venom

FURTHER EVIDENCE FOR AN EXENDIN RECEPTOR ON DISPERSED ACINI FROM GUINEA PIG PANCREAS*

(Received for publication, August 12, 1991)

John Eng‡§¶, Wayne A. Kleinman‡, Latika Singh‖, Gurcharn Singh‖, and Jean-Pierre Raufman‖

From the ‡Solomon A. Berson Research Laboratory, Veterans Affairs Medical Center, Bronx, New York 10468, the §Department of Medicine, Mount Sinai School of Medicine, New York, New York 10029, and the ‖Department of Medicine, Division of Digestive Diseases, State University of New York-Health Science Center, Brooklyn, New York 11203-2098

The recent identification in *Heloderma horridum* venom of exendin-3, a new member of the glucagon superfamily that acts as a pancreatic secretagogue, prompted a search for a similar peptide in *Heloderma suspectum* venom. An amino acid sequencing assay for peptides containing an amino-terminal histidine residue (His[1]) was used to isolate a 39-amino acid peptide, exendin-4, from *H. suspectum* venom. Exendin-4 differs from exendin-3 by two amino acid substitutions, Gly[2]-Glu[5] in place of Ser[2]-Asp[5], but is otherwise identical. The structural differences make exendin-4 distinct from exendin-3 in its bioactivity. In dispersed acini from guinea pig pancreas, natural and synthetic exendin-4 stimulate a monophasic increase in cAMP beginning at 100 pM that plateaus at 10 nM. The exendin-4-induced increase in cAMP is inhibited progressively by increasing concentrations of the exendin receptor antagonist, exendin-(9–39) amide. Unlike exendin-3, exendin-4 does not stimulate a second rise in acinar cAMP at concentrations >100 nM, does not stimulate amylase release, and does not inhibit the binding of radiolabeled vasoactive intestinal peptide to acini. This indicates that in dispersed pancreatic acini, exendin-4 interacts only with the recently described exendin receptor.

An assay for His[1] peptides was recently used to identify the presence of helospectin and a new, previously unrecognized His[1]-Phe[6] peptide in *Heloderma horridum* venom (1). This new peptide, designated exendin-3, is a pancreatic secretagogue. At concentrations greater than 100 nM, exendin-3 interacts with VIP[1] receptors on guinea pig pancreatic acini to stimulate an increase in cellular cAMP and amylase release (2). At lower concentrations (0.1–10 nM), however, exendin-3 interacts with a putative exendin receptor that causes an increase in acinar cAMP but not amylase release. This conclusion is based on the observation that increasing concentrations of a specific antagonist, exendin-3-(9–39) amide, progressively inhibit exendin-3-induced increases in cAMP (2). Because venom from a closely related lizard, *Heloderma suspectum*, has been shown to contain helodermin (3), a peptide closely related in structure to helospectin (4), a search was undertaken for a His[1] peptide in *H. suspectum* venom that might be analogous to exendin-3. We report the isolation from *H. suspectum* venom of such an analogue that has been named exendin-4. Exendin-4, unlike exendin-3, is not a pancreatic secretagogue. Instead, it interacts exclusively with the newly described exendin receptor (2) to increase pancreatic acinar cAMP.

MATERIALS AND METHODS

H. suspectum venom (lots HS198Z and HS208Z) was purchased from Miami Serpentarium Laboratories (Salt Lake City, UT). Diphenylcarbamyl chloride-treated trypsin was purchased from Sigma. Endoproteinase Asp-N was purchased from Boehringer Mannheim.

His[1] Assay and Amino Acid Sequencing—Amino-terminal amino acid analysis was performed by a single cycle of Edman degradation using an automated gas phase protein sequenator in combination with an on-line PTH-amino acid analyzer (Applied Biosystems, Foster City, CA). PTH-His was positioned to elute between PTH-Ala and PTH-dehydro-Ser. Purified peptides and peptide fragments were sequenced with the gas phase sequenator.

Isolation of His[1] Peptides from Heloderma Venom—Venom (25 mg) was dissolved in distilled water (10 mg/ml) and passed through a C_{18} Sep-Pak cartridge (Waters Associates, Milford, MA). The C_{18} cartridge was washed with 5 ml of water and eluted with 2 ml of 0.1% trifluoroacetic acid, 60% acetonitrile. Peptides in the eluate were separated by HPLC on an 8 mm × 10-cm μBondapak C_{18} Radial-Pak column (Waters Associates). The column was eluted with a linear gradient (20–60%) of acetonitrile in 0.13% heptafluorobutyric acid at a flow rate of 1 ml/min. One-minute fractions were collected, and aliquots were assayed for His[1] content.

Enzyme Cleavages—Purified exendin-4 (5–20 nmol) was digested with 0.2 μg of trypsin or with 0.2 μg of endoproteinase Asp-N. The peptide fragment exendin-(9–39) amide was prepared as described previously (2). Although this fragment was previously referred to as exendin-3-(9–39) amide (2), the name has been shortened to exendin-(9–39) amide to indicate that the carboxyl-terminal 31 amino acids of exendin-3 and exendin-4 are identical. Peptide fragments were purified by HPLC on a Nova C_{18} Radial-Pak column (Waters Associates).

Amino Acid Analysis—Peptides were dried and hydrolyzed with gas phase 6 M HCl at 150 °C for 60 min. Amino acids were analyzed with an automated amino acid derivatizer (Applied Biosystems) connected to an on-line phenylthiocarbamyl-derivative amino acid analyzer.

Mass Spectrometry—The mass of the COOH-terminal fragment generated by trypsin digestion of exendin-4 was determined by fast atom bombardment-mass spectrometry. Mass accuracy of greater than ±0.1 unit was achieved by peak matching to appropriate cesium chloride cluster ions. Fast atom bombardment-mass spectrometry was performed by the Laboratory for Macromolecular Analysis at the

* This paper was supported in part by the Department of Veterans Affairs. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

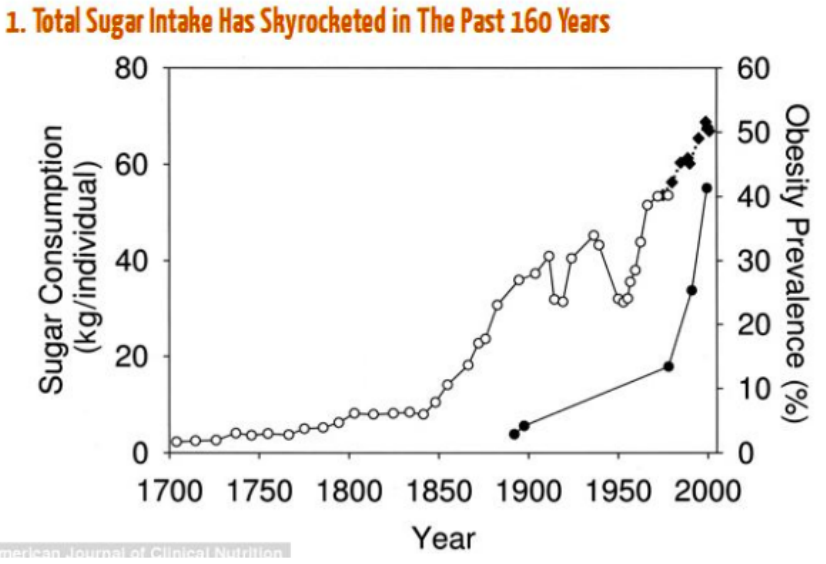
¶ To whom reprint requests and correspondence should be addressed: Solomon A. Berson Research Laboratory, Veterans Affairs Medical Center, Bronx, NY 10468. Tel.: 212-584-9000 (ext. 6069).

[1] The abbreviations used are: VIP, vasoactive intestinal peptide; PTH, phenylthiohydantoin; HPLC, high performance liquid chromatography.

Peptide drugs – pharmaceutical sciences inspired by natural products

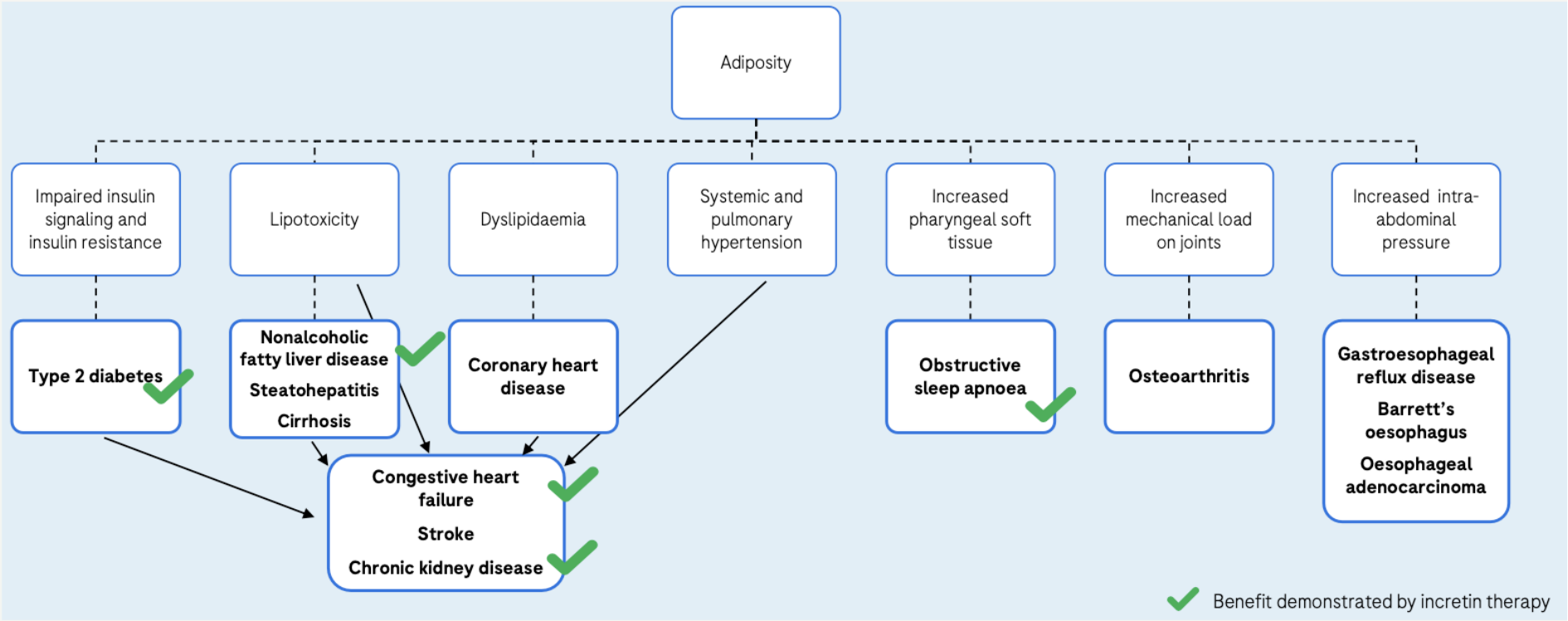
- Gila monster: a species of venomous lizard; Mexico
- Eats only 4 times a year
- When fasting, it shuts down the pancreas, stopping insulin
- When its time to eat, it restarts pancreas with exendin-4 in its saliva -

  a GLP-1R agonist



Exenatide (Byetta. Lilly) is a synthetic version of exendin-4

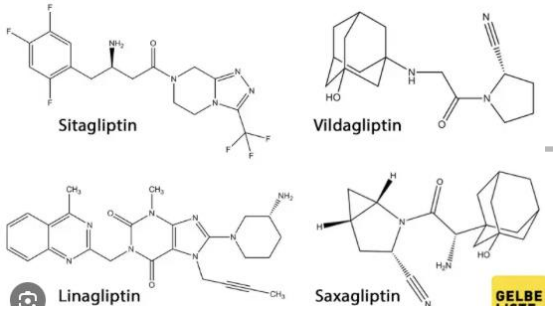
Obesity is associated with multiple complications
BMI>30 carry hazard ratio for overall mortality elevated more than 40%

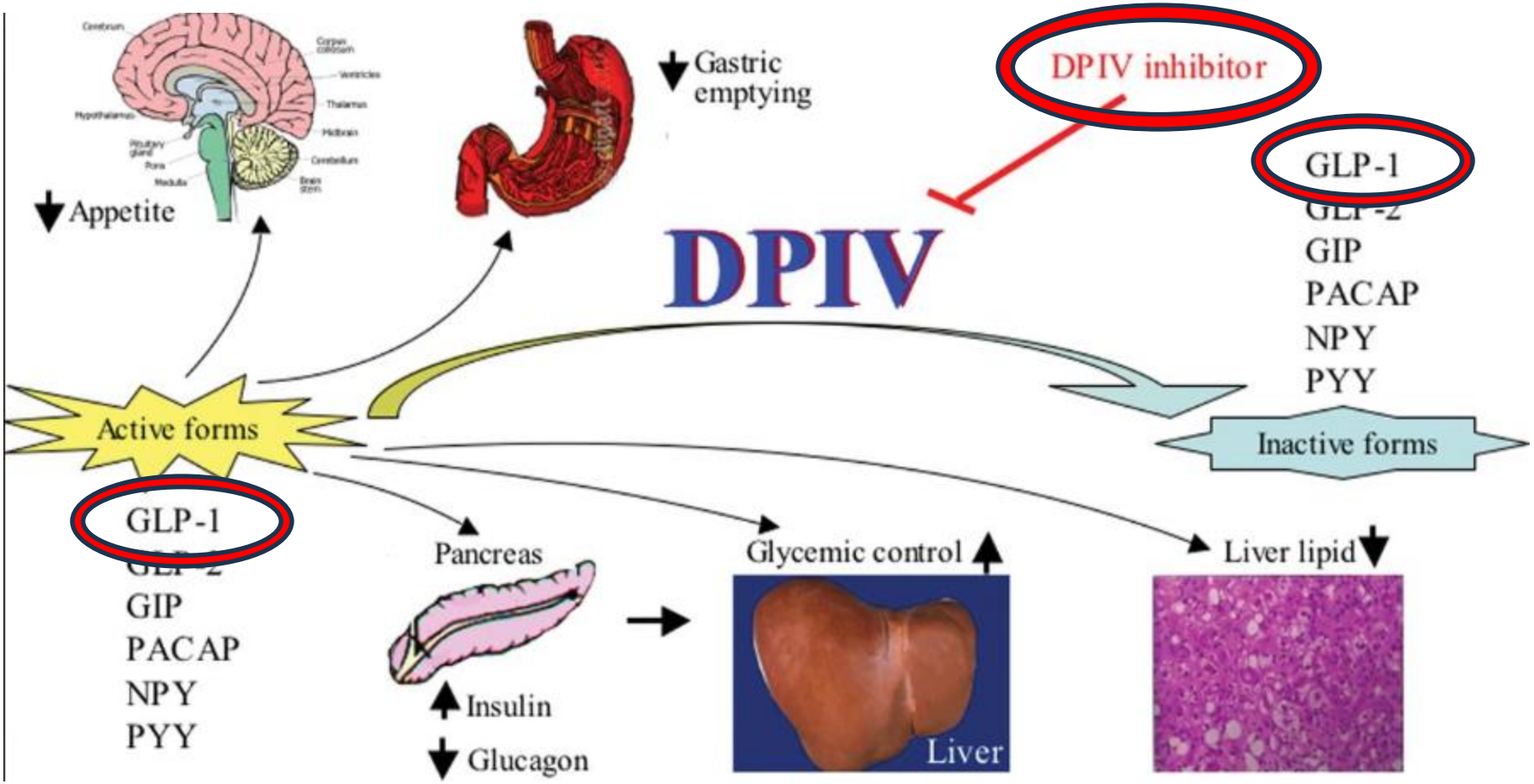


A critical threshold of weight loss is needed for disease modification (≥10% body weight loss)[2]

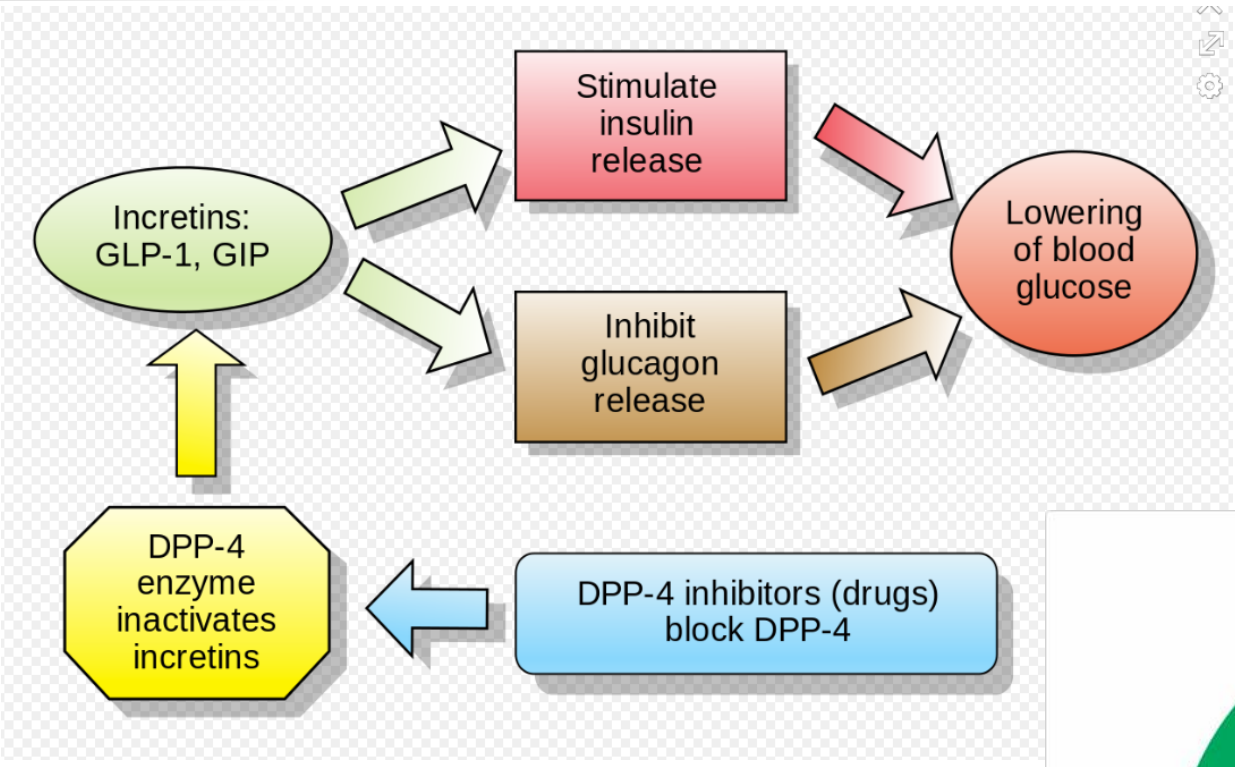
1. Müller et al. Anti-obesity drug discovery: advances and challenges. Nat Rev Drug Discov 21,2. Ryan et al, Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. Curr Obes Rep. 2017, Obesity Reviews, Volume: 22, Issue: 1, First published: 07 September 2020, DOI: (10.1111/obr.13112)

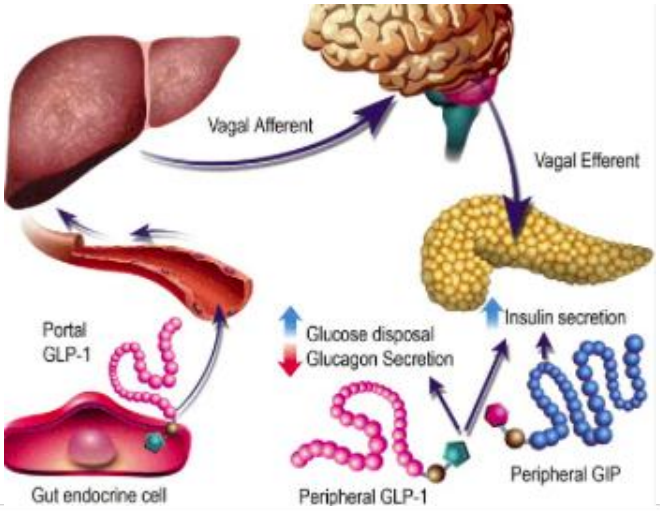
Peptide drugs – incretins – GLP1 in diabetes – vs DPP4 inhibitors - gliptins

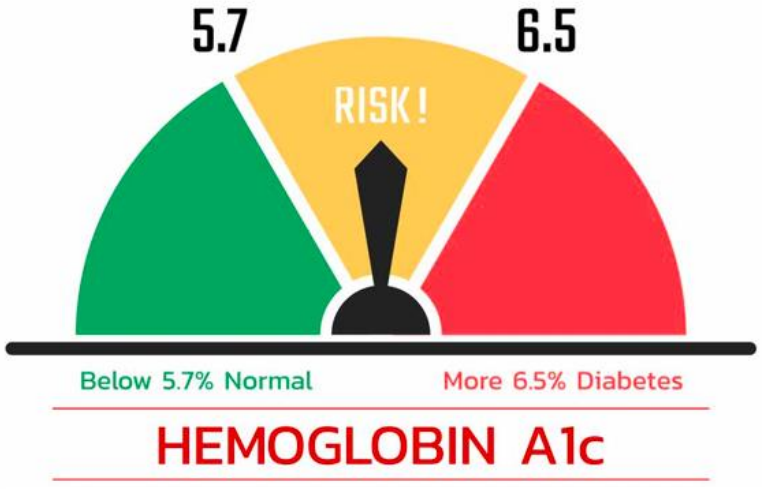




Peptide drugs – GLP1r incretins
lowering blood glucose, gastric emptying and body weight control







average glycemic level over 4-6 w !

GLP1 GIP1 receptor agonists (incretins) from gut cells have entered the clinics in the last decade in the management of diabetes type II and as a ”surprise” during late phase clinical trials in the obesity (BMI>30) first approved peptides drawback: short half life, hence recurrent injections (invalidating patient care)

Peptide drugs – GLP1 receptor and incretins

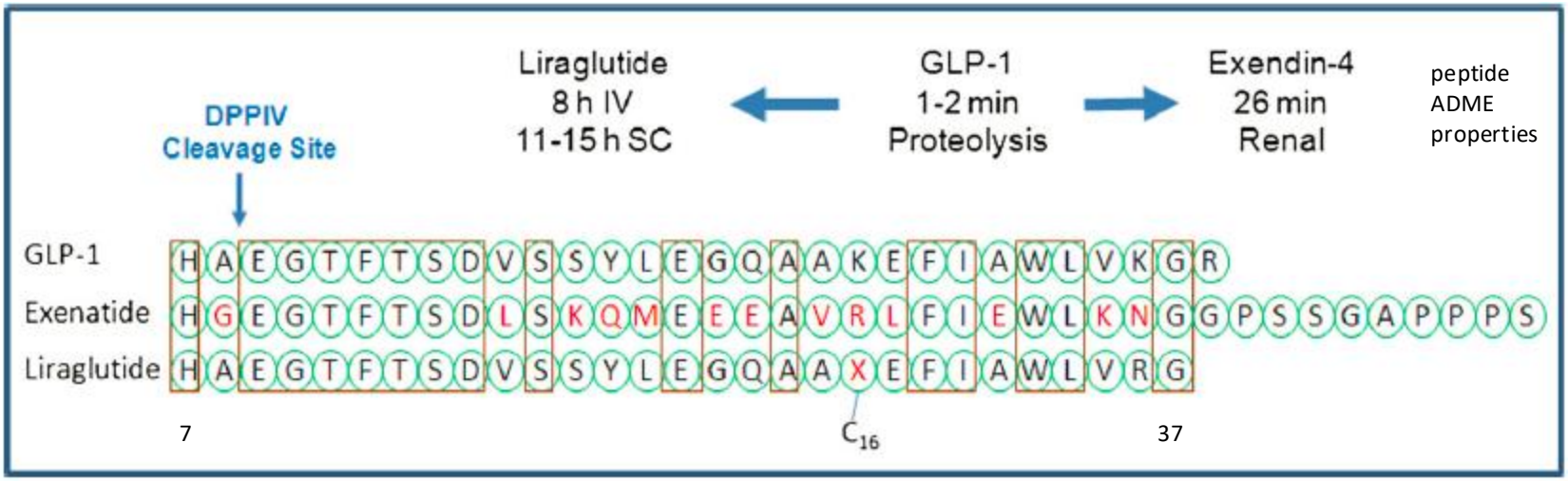


Fig. 2. Strategies to enhance peptide stability: GLP-1 peptide has a half-life of 1–2 min.

- **GLP1 receptor agonists (incretins) from gut L cells-ileum/colon- have entered the clinics in the treatment of diabetes type II, drawback: short half life**
- **Exendin-4 (synthetic Exenatide) has improved PK PD properties (lower clearance) allowing once a week dosing as compared to GLP1 (rapidly cleaved by peptidase DDPIV)**
- **Major challenges with the development of peptide drugs are stability and cost of goods (now about 2% of drug market)**

GLP1 peptides in drug research and development

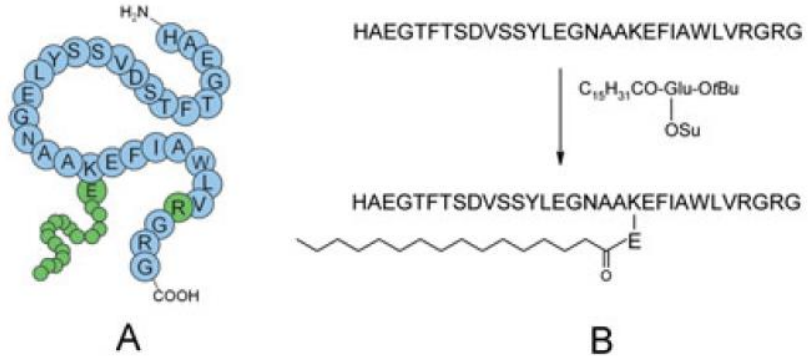
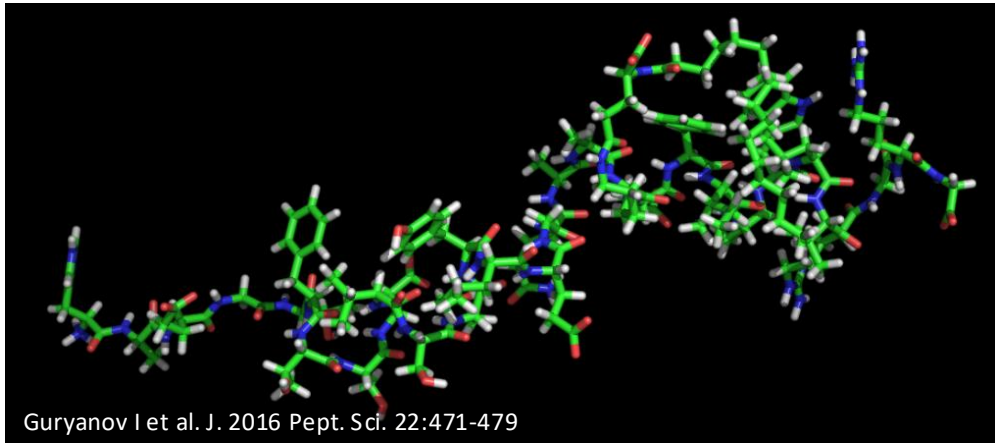
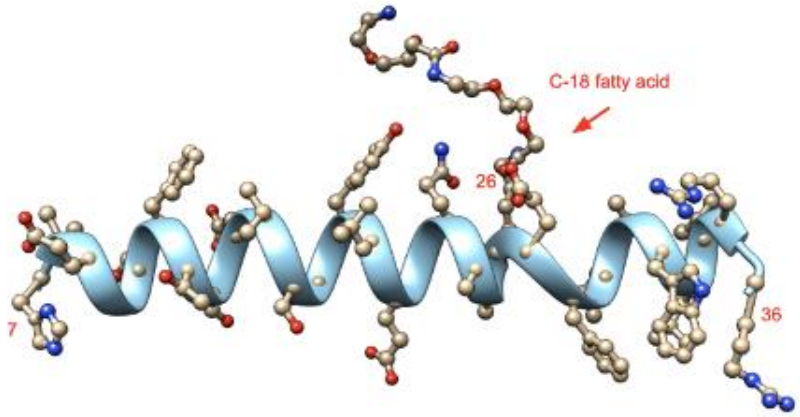


Figure 1. (A) The amino acid sequence of liraglutide. The changes with respect to glucagon-like peptide-1 (7-37) are shown in green; (B) A scheme of preparation of liraglutide by chemical modification of a recombinant peptide precursor (OSu, 1-oxysuccinimidoyl).



- Example **LIRAGLUTIDE** GLP1 (7-37) receptor agonist linked to 16C fatty acid residues (lipopeptide binds to albumin (not covalently) to stabilize the peptide)
- Example **DULAGLUTIDE** GLP1 receptor agonist linked to Fc fragment of antibody human IgG4
- Both medication for Type II diabetes, with improved administration (stabilized GLP1 peptide (compliance !) Liraglutide which mimics the action of glucagon-like peptide is also clinically approved as an obesity treatment.

INCRETINS : a salamander saliva poison peptide is turning a game changer in the management of metabolic diseases – TIID/pandemia



1. 2D and 3D structures of Semaglutide. a. The amino acid sequence of Semaglutide (PubChem) is numbered from 7 to 37. The sequen

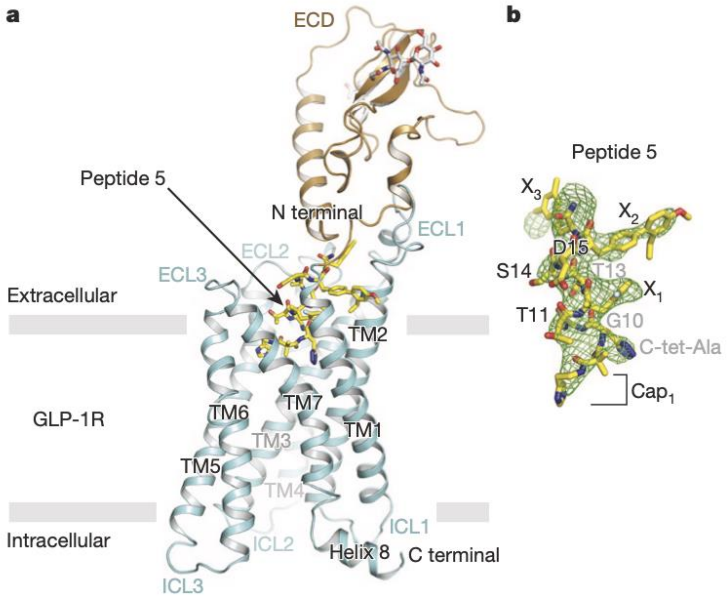


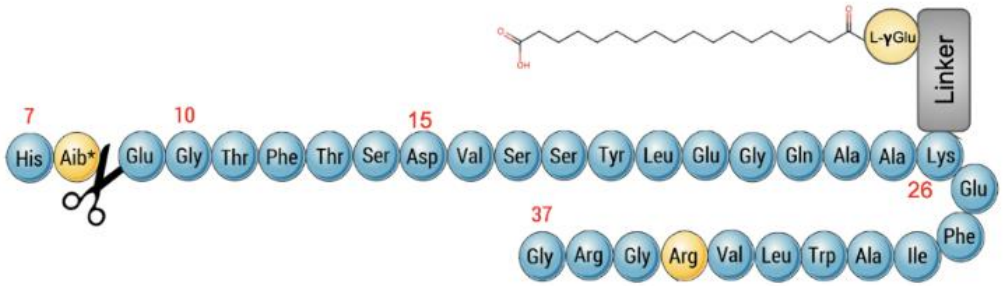
Figure 1 | The overall structure of GLP-1R in complex with peptide 5.

Semaglutide ; synthetic peptide with improved PK PD

C18 fatty acid chain linked to Lys26 increses albumin binding hence improved PK

IUPAC Name	Semaglutide is a synthetic peptide (see the amino acid sequence below)
3D Structure of Semaglutide	Chain P in PDB ID 7ki0

a



*Aib = α-aminoisobutyric acid

b

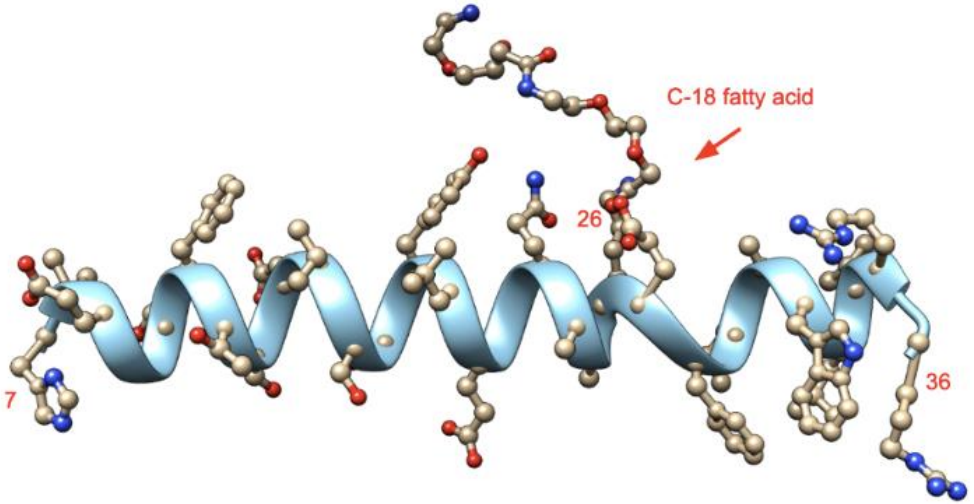
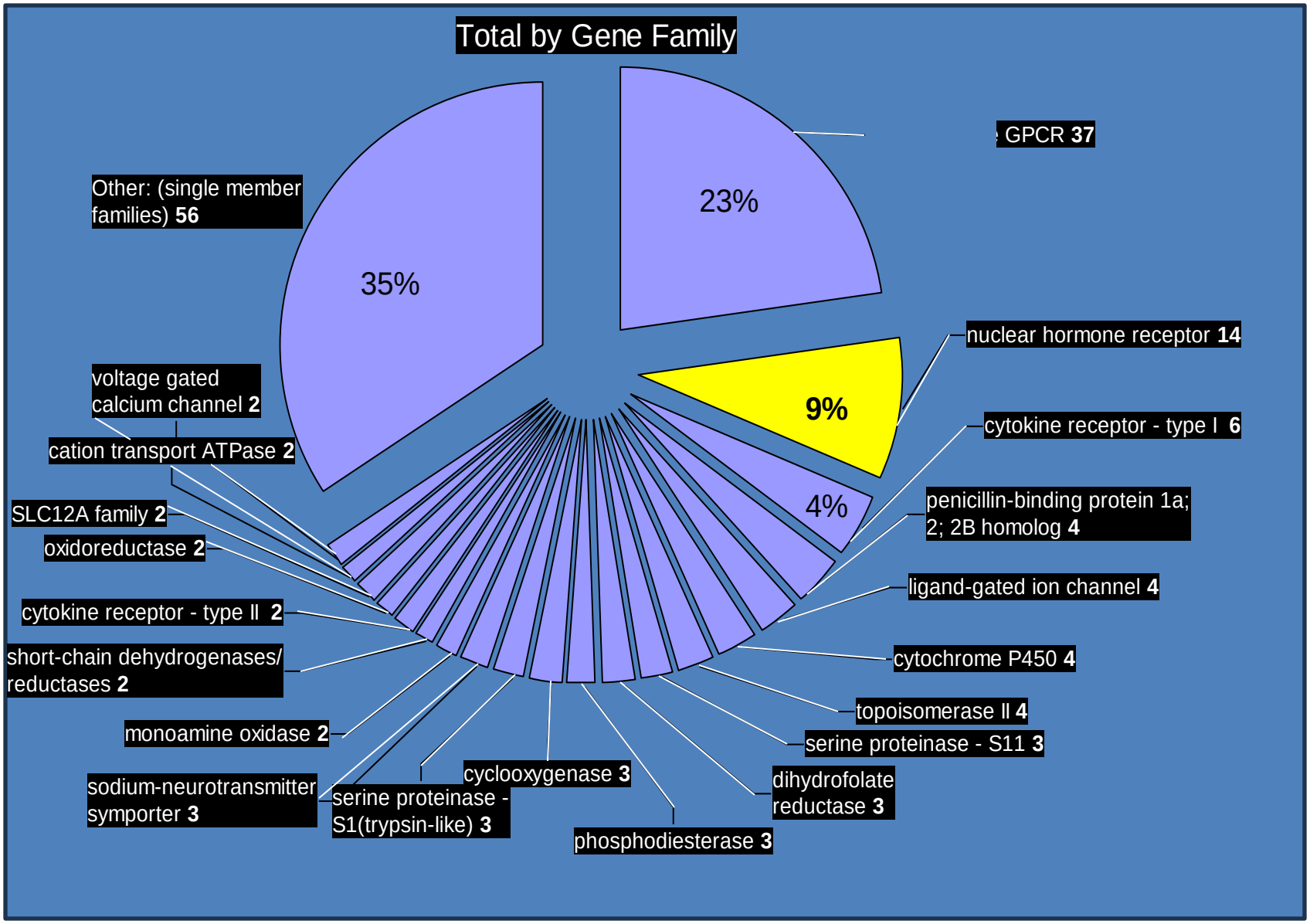


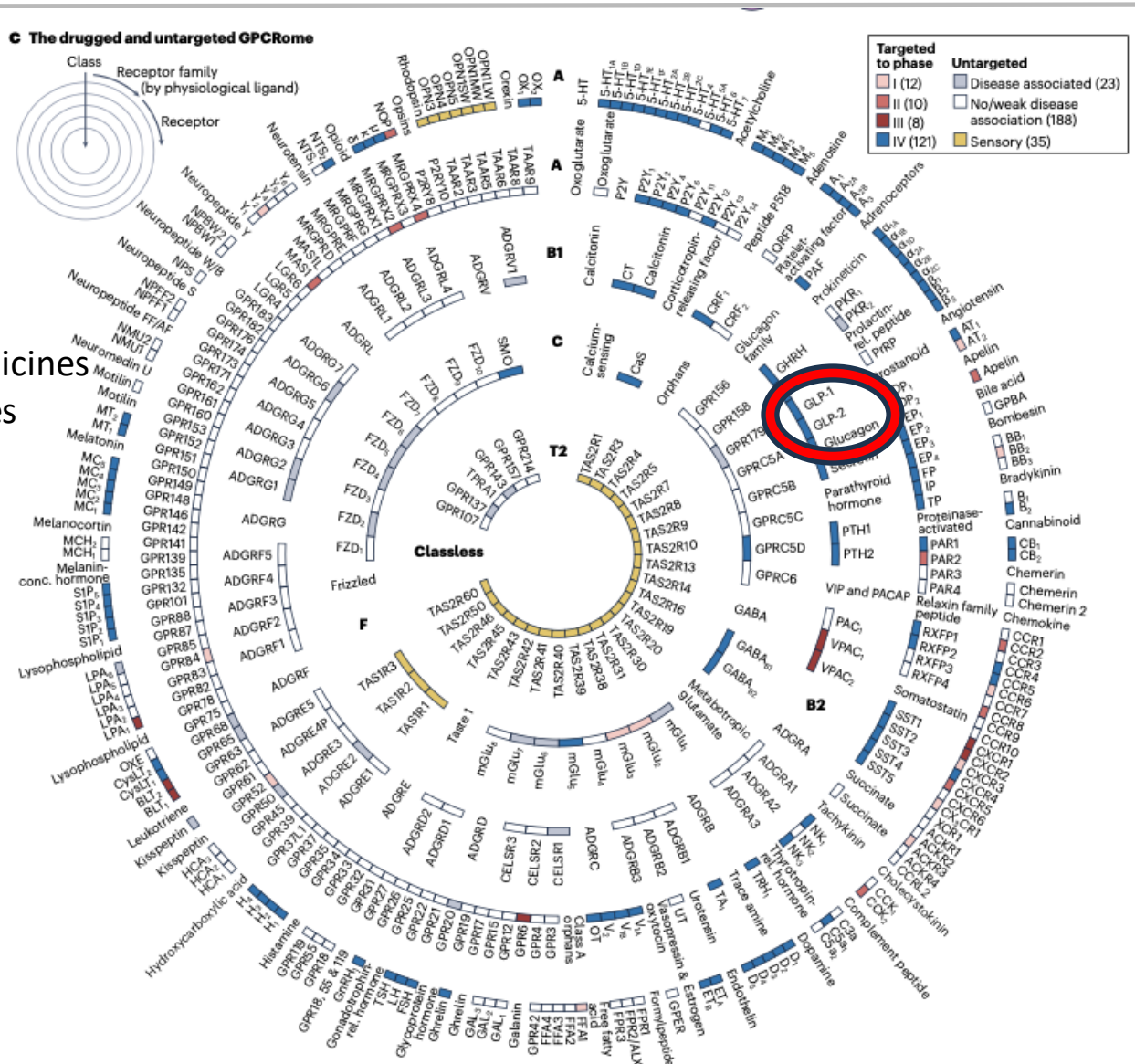
Figure 1. 2D and 3D structures of Semaglutide. a. The amino acid sequence of Semaglutide (PubChem) is numbered from 7 to 37. The sequence schematic shown is based on information presented in Knudsen and Lau, 2019. Amino acid modifications are highlighted in yellow and the DPP4 cleave site is indicated with the scissors. b. 3D structure of Semaglutide (PDB ID 7ki0, Zhang et al., 2021). Note: The C-18 fatty acyl chain shown here

GPCRs are the most precedented drug target family



36% (n=516) of all approved medicines act on GPCRs : the largest drug target family by 2024

- 800 GPCRs (current estimate)
- 121 drugged GPCRs (2024)
- 516 GPCRs based approved medicines
- ie. 36% of all approved medicines



Sanchez Lorente J et al Nature Reviews drug discovery 2025
https://doi.org/10.1038/s41573-025-01139-y

Tirzepatide – Zepbound® : dual co-agonist GLP1 and GIP

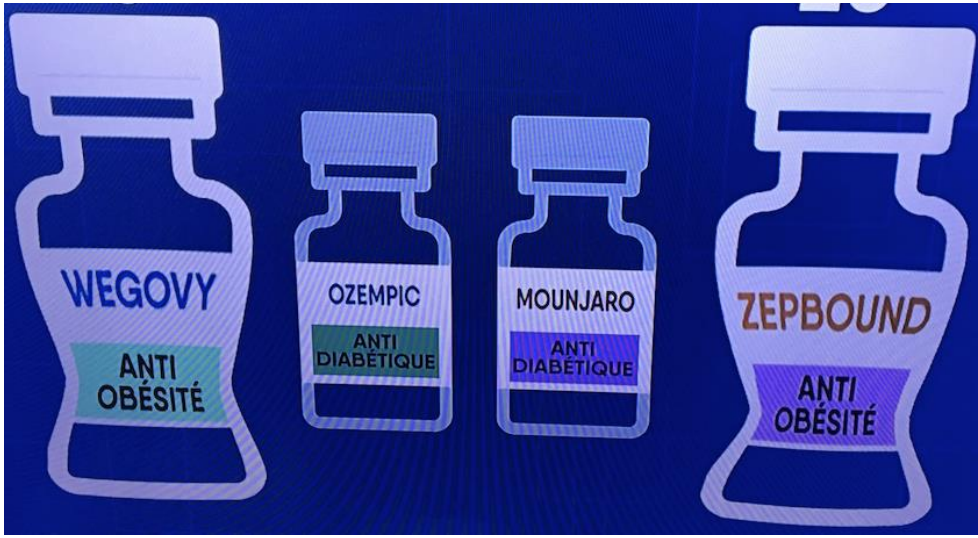
À propos des extraits optimisés • Commentaires

Tirzépatide

Médicament

Le tirzépatide est une molécule identifiée pour son potentiel dans le traitement du diabète de type 2. Il a la propriété d'être activateur du récepteur du GLP1, de même que du récepteur du peptide insulinotrope dépendant du glucose. Il s'administre par voie sous-cutanée de manière hebdomadaire. Wikipédia ›

tirzepatide

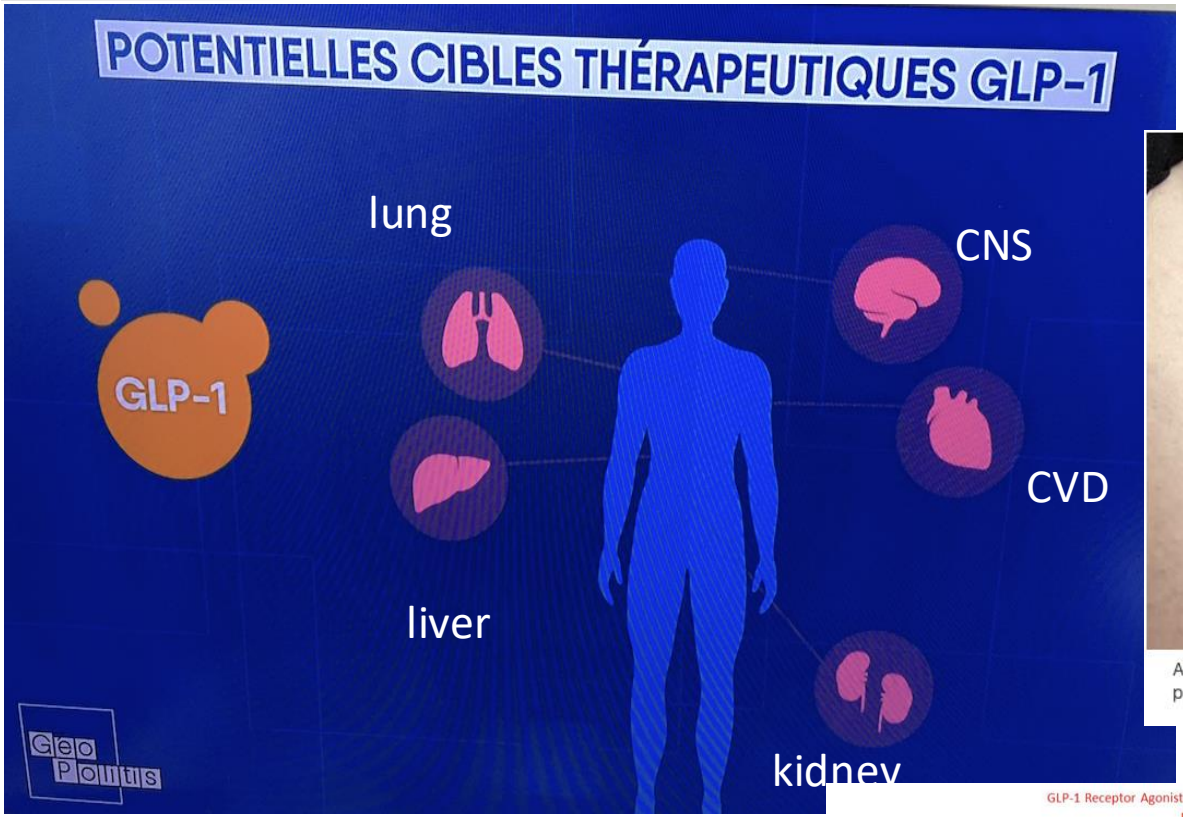


semaglutide

different formulations/galenics hence different pathologies eg Moujaro 25% BW loss in 20 weeks as Ozempic 17,5% BW loss in 15 weeks

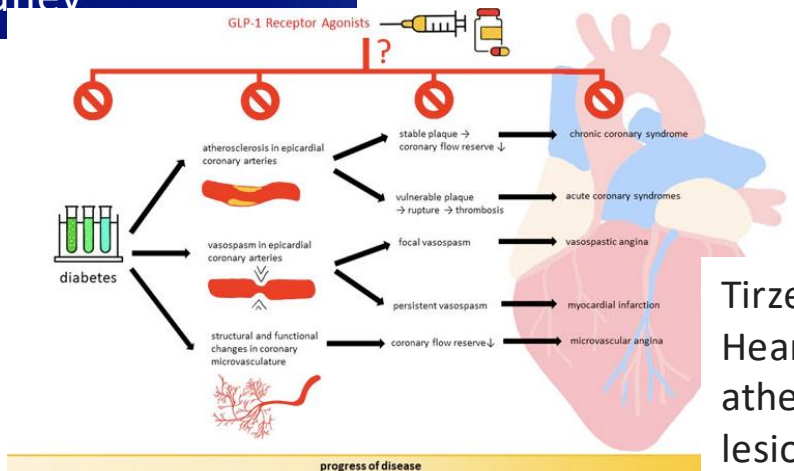
GLP1 agonists : tomorrow wonder medicine ?

but definitely eye-opening



An ongoing trial is testing the effects of Zepbound (tirzepatide) on heart disease in people with obesity and diabetes. (Shelby Knowles/Bloomberg via Getty)

protective effects of incretin signaling in ER and mitochondrial stress for neuronal degeneration, management, further investigate the incretin-derived effects observed in PD an AZ patients.



Tirzepatide
Heart diseases
atherosclerosclerotic lesions

Les Suisses champions des injections amincissantes

Wegovy, Saxenda et autres produits ce perte de poids séduisent en Suisse.

par
Pauline Rumpf

Physicians-overall population should be working against the **grossophobia** (or fatphobia) a discrimination against overweight people

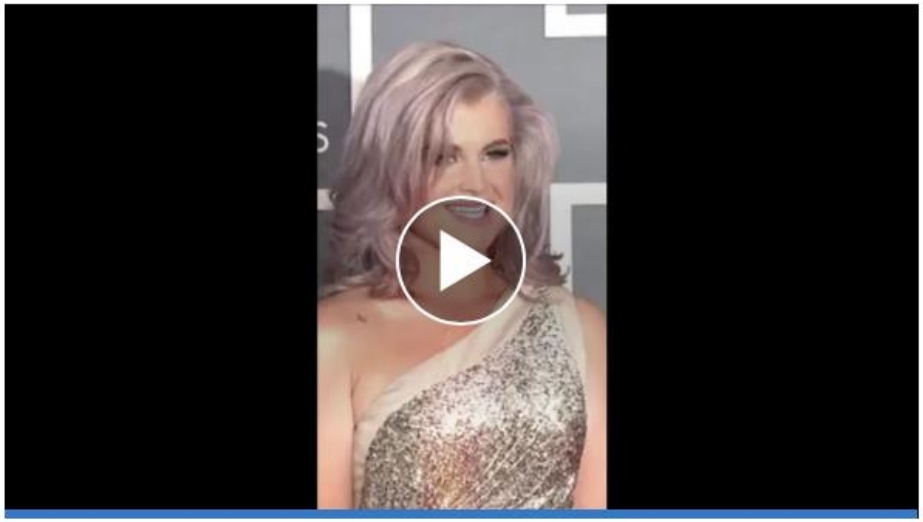
« TIK TOK syndrome »

diabetes patients struggle to find Ozempic/Wegovy (GLP1/2 agonist) as it soars in popularity in cosmetic weight loss management

Popstars effect on biologicals production – incretins shortage

Kelly Osbourne says Ozempic use is 'amazing' after mom Sharon's negative side effects

JAY STAHL USA TODAY



Show Caption

Kelly Osbourne is making headlines again for her controversial comments.

This time, the TV personality and daughter of Sharon and Ozzy Osbourne defended her use of Ozempic, a drug that is intended to treat those with Type 2 diabetes. On the Dolly Parton Pet Gala red carpet, Osbourne opened up about her opinions on Ozempic in an interview with E! News.

- **Redirect/misuse of incretins have geopardized drug makers production lines of life threating medicines : T2D patients in danger !**
- **Incretins are designed for patients suffering from metabolic diseases such as diabetes and not for popstars and social media influencers promulgating pharmacological solutions in weight loss by convenience (instead of promoting diet and exercise !)**
- **Pharma/Biotech production shortage !!**

GLP1 agonist tomorrow : incretin mimetics oral SMW cpds work in progress !

771-P

Efficacy of CT-996, an Oral Small Molecule GLP-1 Receptor Agonist, in Human GLP-1 Receptor Knock-in Mice and Obese Cynomolgus Monkeys

Jian Luo[1], Ruben Rodriguez[1], Anne Hergarden[1], Ted Tracy[1], Davina Lam[1], Sumanta Garai[1], Daniel Marshall[1], Stig Hansen[2], Manu Chakravarthy[1]

[1]Carmot Therapeutics, a member of the Roche group; [2]Kimia Therapeutics.

Purpose

In the present studies we characterize CT-996, a potent, oral, small molecule, signal-biased GLP-1 receptor agonist, and evaluate its effect on glucose response, weight loss, and food intake in pre-clinical models.

Conclusions

- CT-996 is a small molecule GLP-1RA that exhibits biased cAMP signaling and reduced receptor internalization.
- Daily oral dosing of CT-996 enhanced glucose homeostasis and reduced weight and fat mass after 4-week treatment in obese cynomolgus monkeys.
- All doses of CT-996 were well-tolerated in cynomolgus monkey studies.
- These observations corroborate the continued development of CT-996 as a next-generation GLP-1RA. CT-996 is currently being evaluated in a Phase 1 clinical trial.

Acknowledgements

- Contribution to discovery: Sean Zhou, Ray Fucini, Xiaohui Du, and David Lloyd
- Presentation support: Damian Bialonczyk

Disclosures

- All authors are current or former employees of Carmot Therapeutics, a member of the Roche group.

Presented at the ADA 84th Scientific Sessions in Orlando, FL. June 21–24, 2024

Introduction

- Injectable GLP-1 receptor agonists (GLP-1RA) have demonstrated significant efficacy in glycemic control and weight management.
- While semaglutide is available in an oral peptide formulation, it requires specific timing and administration conditions.
- The increasing use of injectable incretin therapies underscores the urgent need for simpler, cost-effective solutions.
- Here, we describe CT-996, a potent, oral small molecule GLP-1RA, and present preclinical efficacy studies to support its development for daily oral use in humans.

Methods

In Vitro Characterization

- cAMP accumulation was measured in HEK293 cells expressing either human or cynomolgus monkey GLP-1R 30 minutes after stimulation. Maximal β-arrestin recruitment after stimulation was measured in HEK293 cells expressing human GLP-1R-LgBit and SmBiT-human-β-arrestin-2. Internalization was measured in HEK293 cells expressing HiBiT-tagged human GLP-1R 60 minutes after stimulation.
- Insulin secretion was measured in EndoC-bH5® cells, a human pancreatic β-cell line, 40 minutes after stimulation in the presence of 11 mM glucose. Curves depict non-linear regression analysis of data normalized to vehicle and a high dose of GLP-1. Insulin data is also normalized to total protein content. Data are mean ± SD of 2-3 replicates per concentration.

Mixed Meal Tolerance Test (MMTT) in Humanized GLP-1R Knock-in Mice

- Male humanized GLP-1R knock-in (hGLP-1R KI; Taconic) mice, aged 8-14 weeks, were fasted overnight. Vehicle and CT-996 were administered orally 30 minutes before the MMTT (Ensure, 10 ml/kg).

Glucose Stimulated Insulin Secretion (GSIS) in Obese Monkeys

- Male obese cynomolgus monkeys, > 8 years old (KBI), were fasted overnight.
- Vehicle and CT-996 were administered orally 2-3 hours prior to intravenous glucose tolerance test (IVGTT; 0.5 g/kg).

28-Day Daily Dose Study in Obese Monkeys

- Twenty-four (24) male cynomolgus monkeys, each weighing > 8 kg with BMI > 40 were included. Some of the animals had plasma glucose above 6 mmol/L.
- CT-996 was administered once daily.
- MMTT (Ensure, 5 ml/kg) was administered on Day 1, 3 hours post dose.
- Chow intake was recorded at each meal, and body weight was assessed weekly.
- Body composition was measured using dual-energy X-ray absorptiometry (DEXA) at baseline and Day 29.

Results

CT-996 is a potent and cAMP-biased GLP-1R agonist

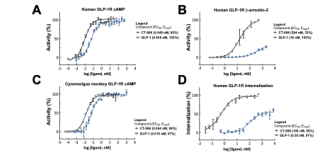


Figure 1. Dose response curves for human GLP-1R cAMP accumulation (A), Human GLP-1R β-arrestin recruitment (B), Cynomolgus monkey GLP-1R cAMP accumulation (C), and human GLP-1R internalization (D) in response to endogenous ligand GLP-1 (black circles) or CT-996 (blue circles).

CT-996 dose-dependently enhanced GSIS in human β-cells

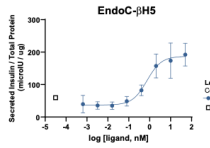


Figure 2. Dose response curves of insulin secretion after stimulation with CT-996 in the presence of 11 mM glucose. Abbreviations: nM is nanomolar, ug is microgram, and microIU is microinternational unit.

CT-996 improved glucose following MMTT in hGLP-1R KI mice

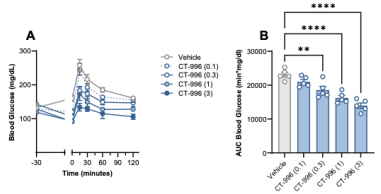


Figure 3. Mean (± SE) (A) glucose response to an MMTT and (B) the area under the glucose curves in hGLP-1R KI mice 30 minutes after vehicle and CT-996 administration. Statistical differences were evaluated using a one-way ANOVA followed by Bonferroni post hoc test. ** p < 0.01, **** p < 0.0001.

CT-996 dose-dependently enhanced GSIS in obese monkeys

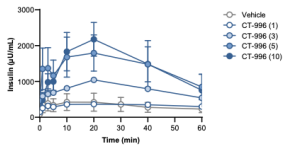


Figure 4. Effects of oral CT-996 on GSIS during IVGTT in obese cynomolgus monkeys. Plasma insulin concentrations are represented as mean (± SE) following intravenous glucose challenge (2-3 hours after vehicle and CT-996 administration).

CT-996 improved postprandial glucose following MMTT in obese monkeys

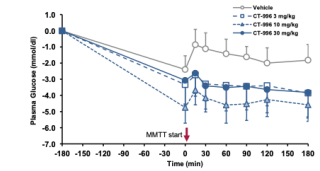


Figure 5. Effects of oral CT-996 on postprandial glucose in obese cynomolgus monkeys. Plasma glucose change is represented as mean (± SE) from baseline. N = 6/group. MMTT was administered on Day 1, 3 hours post CT-996 administration.

CT-996 progressively lowered body weight in obese monkeys

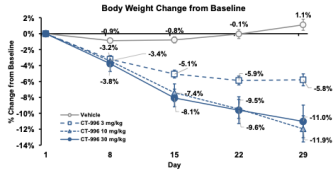


Figure 6. Effects of CT-996 on body weight in obese cynomolgus monkeys following once-daily oral administration. Weekly body weight percent change is represented as mean (± SE) from baseline. N = 6/group.

CT-996 preferentially reduced fat mass in obese monkeys

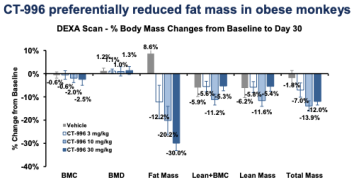


Figure 7. Effects of daily oral CT-996 on body composition in obese cynomolgus monkeys. Percent change from baseline [Mean (± SE)]. N = 6/group. Abbreviations: BMC is bone mineral content and BMD is bone mineral density.

CT-996 drastically suppressed chow intake in obese monkeys

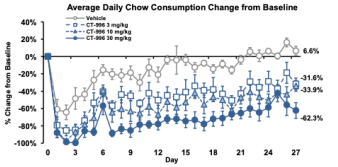
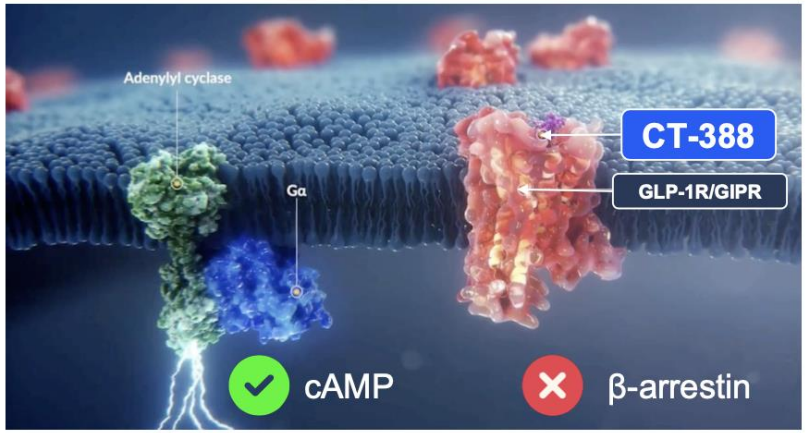


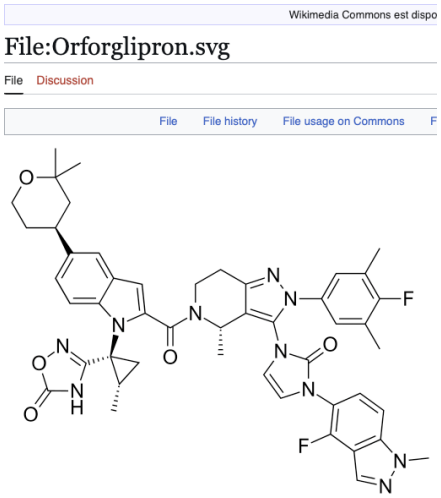
Figure 8. Effects of daily oral CT-996 on chow intake in obese cynomolgus monkeys. Daily chow consumption percent change is represented as mean (± SE) from baseline. N = 6/group.

Papers : GLP1 agonist tomorrow : SMW cpds – work in progress :

developing nonpeptidic small-molecule drugs targeting GLP-1R remains a challenge

- **Obesity**
  - Heterogenous, chronic, relapsing disease affecting millions worldwide[1,2]
  - Additional treatment options are needed
- **CT-388**
  - *Dual GLP-1/GIP receptor agonist* being developed for obesity, type 2 diabetes (T2D), and other weight-related comorbidities[3]
  - *Potent with minimal-to-no β-arrestin recruitment on both receptors*, which leads to reduced receptor internalization and potentially prolonged pharmacological activity[3]





The NEW ENGLAND JOURNAL of MEDICINE

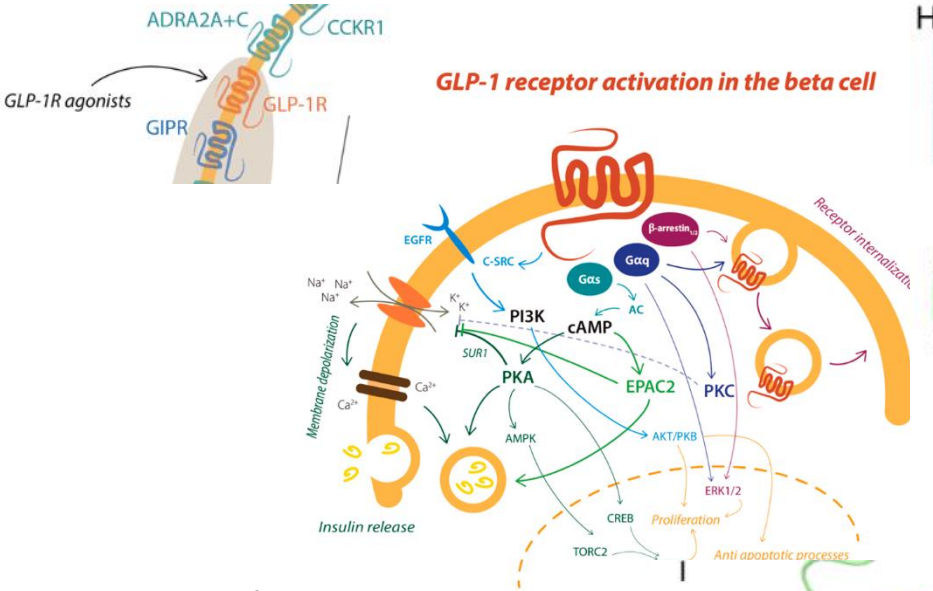
ESTABLISHED IN 1812 SEPTEMBER 7, 2023 VOL. 389 NO. 10

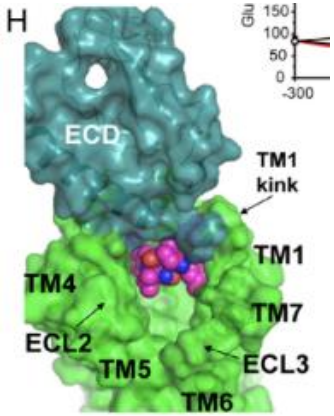
Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

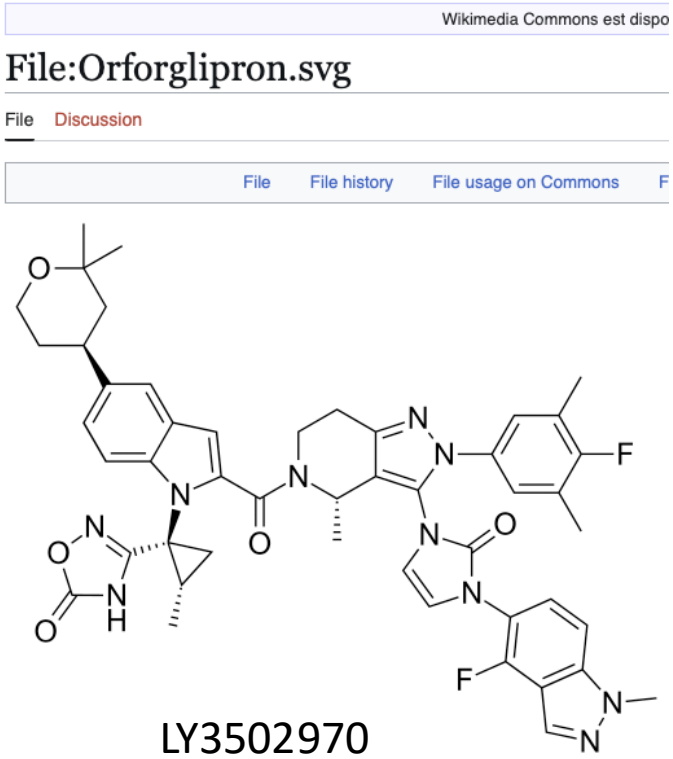
Sean Wharton, M.D., Thomas Blevins, M.D., Lisa Connery, M.D., Julio Rosenstock, M.D., Sohini Raha, Ph.D., Rong Liu, Ph.D., Xiaosu Ma, Ph.D., Kieren J. Mather, M.D., Axel Haupt, M.D., Deborah Robins, M.S., Edward Pratt, M.D., Christof Kazda, M.D., and Manige Konig, M.D., Ph.D., for the GZGI Investigators*

ABSTRACT

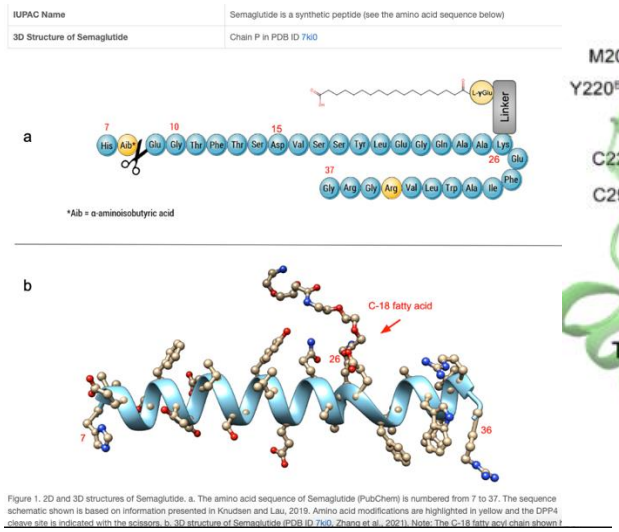
GLP1R_incretins : from biologicals to small Mr compound

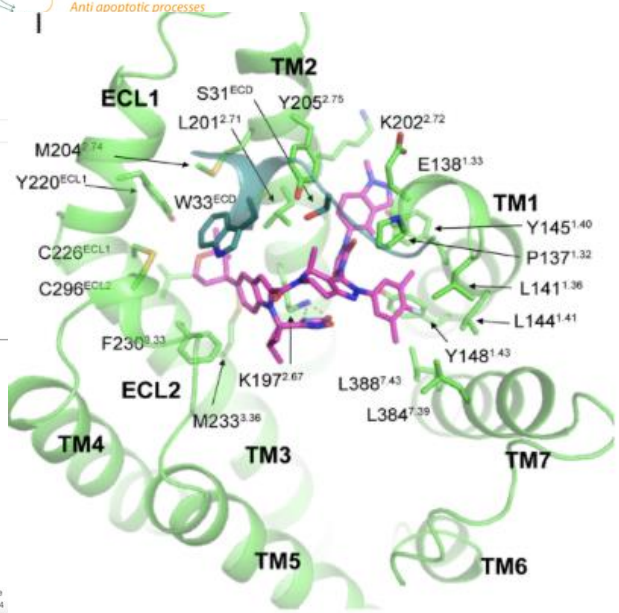






MW 4,2 kDa

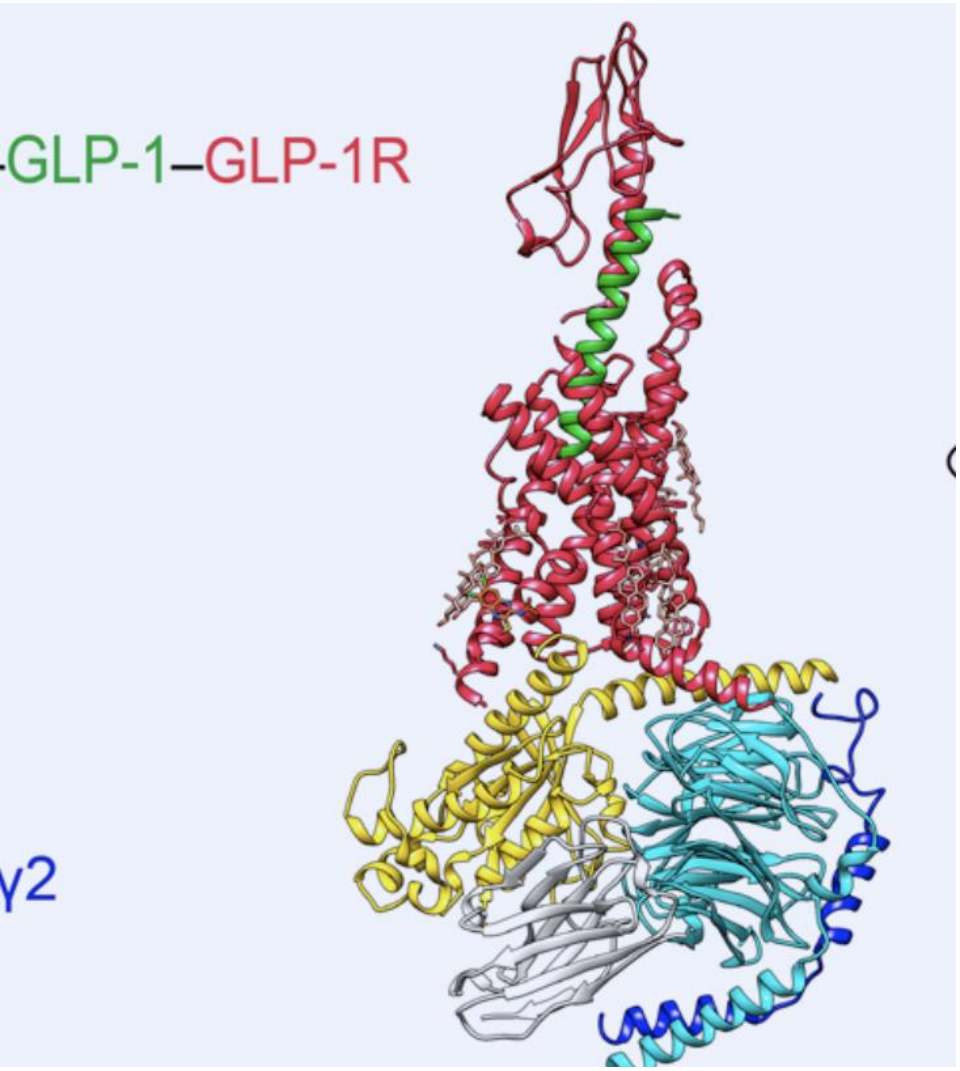


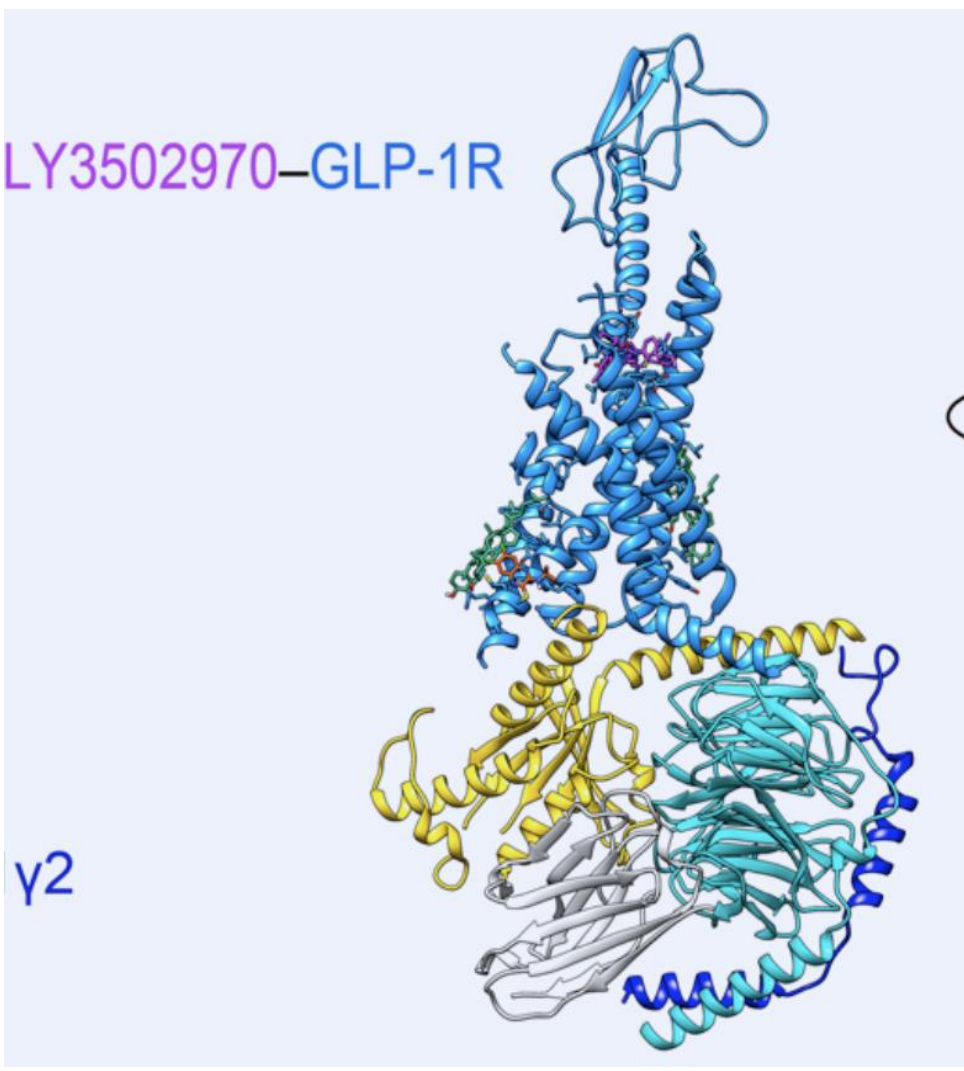


LY3502970
MW 882 Da

A high-resolution structure of LY3502970 in complex with active-state GLP-1R revealed a unique binding pocket in the upper helical bundle where the compound is bound by the extracellular domain (ECD), extracellular loop 2, and transmembrane helices 1, 2, 3, and 7.

Cryo EM : GLP-1 peptide vs Orforglipron (LY3502970)





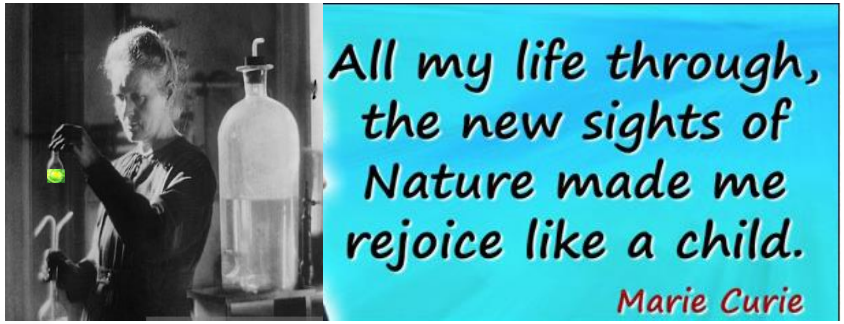
Are these incretin «biologicals» days soon over ?

(current overall costs : CHF 500.-/mois exclusion criteria BMI 30)

An ongoing trial is testing the effects of Zepbound (tirzepatide) on heart disease in people with obesity and diabetes. (Shelby Knowles/Bloomberg via Getty)

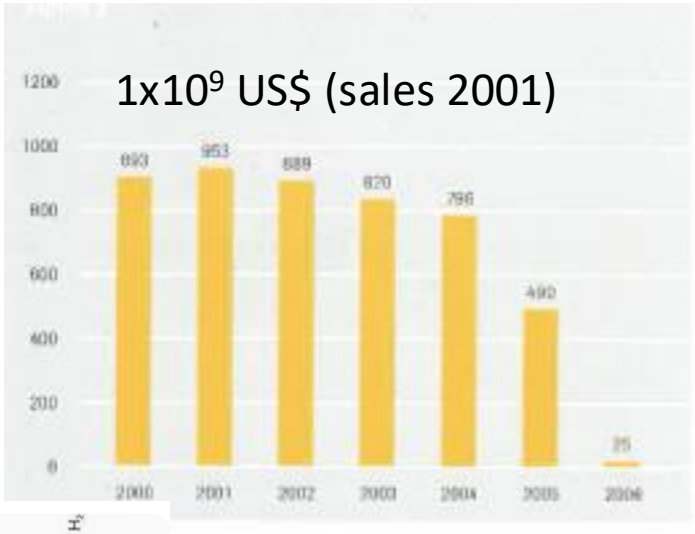
THANK YOU.....

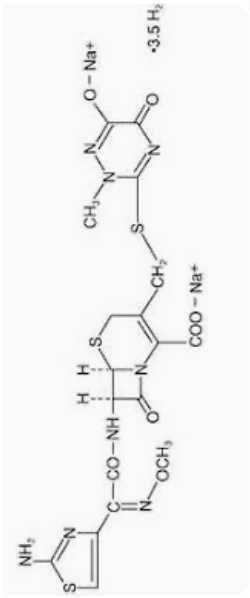
DO YOU HAVE ANY QUESTIONS ?



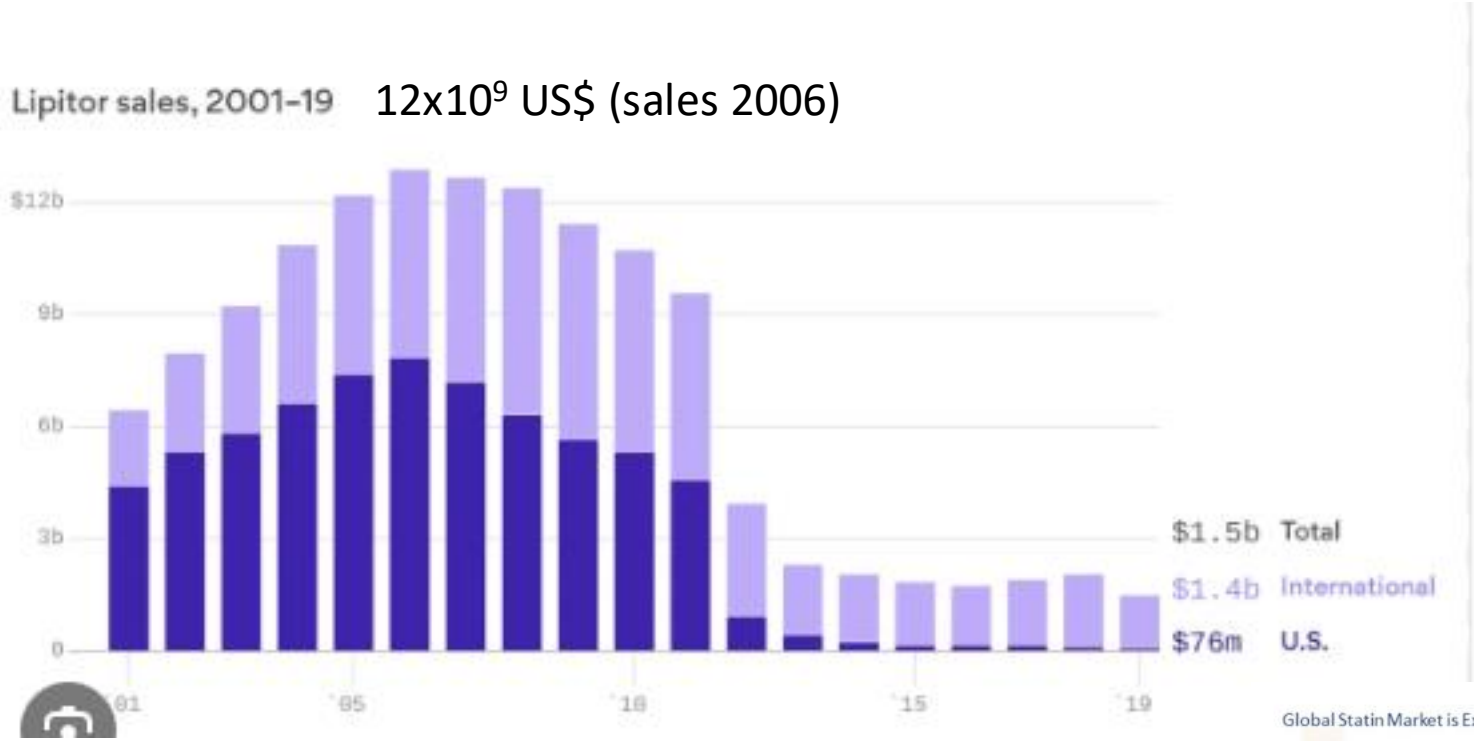
Overall sales of «blockbusters» : medicines reaching yearly ≥ 1 billion US$ revenue
BU slide

Yearly sales of Roche Rocephin from 2000 to 2006

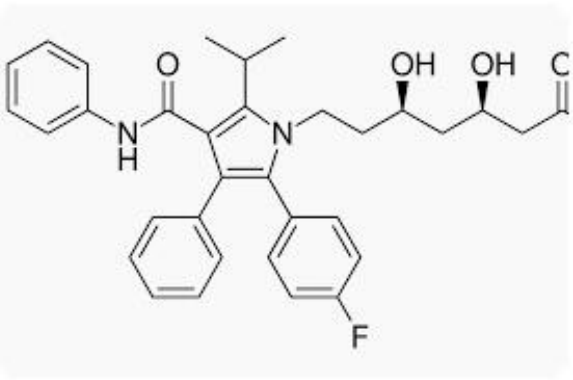


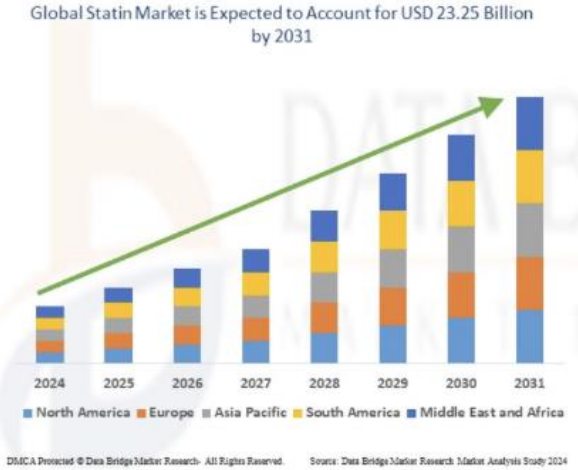


Overall sales of «blockbusters» : medicines reaching yearly ≥ 1 billion US$ revenue
BU slide



12x10^9 US$ (sales 2006)





N E W L A Y O U T

1,000,000,000 *CHF investment*

7,000,874 *hours of work*

6,587 *experiments*

423 *researchers*

1 *medicine*

Health Hackathon
4 & 11.12.2025

With Prof Susan M Gasser
and Prof Olivier Michielin

THE MAKING OF AN INNOVATIVE MEDICINE

Introductory workshops on translational biomedical research and drug discovery and development

BIO-698 resumes Thursday September 11. 2025
4:15 PM @ AAC

EPFL

Sciences de la Vie -SV

Prof Roger G. Clerc