

Diabetes, een ziekte met toekomst

Chantal Mathieu

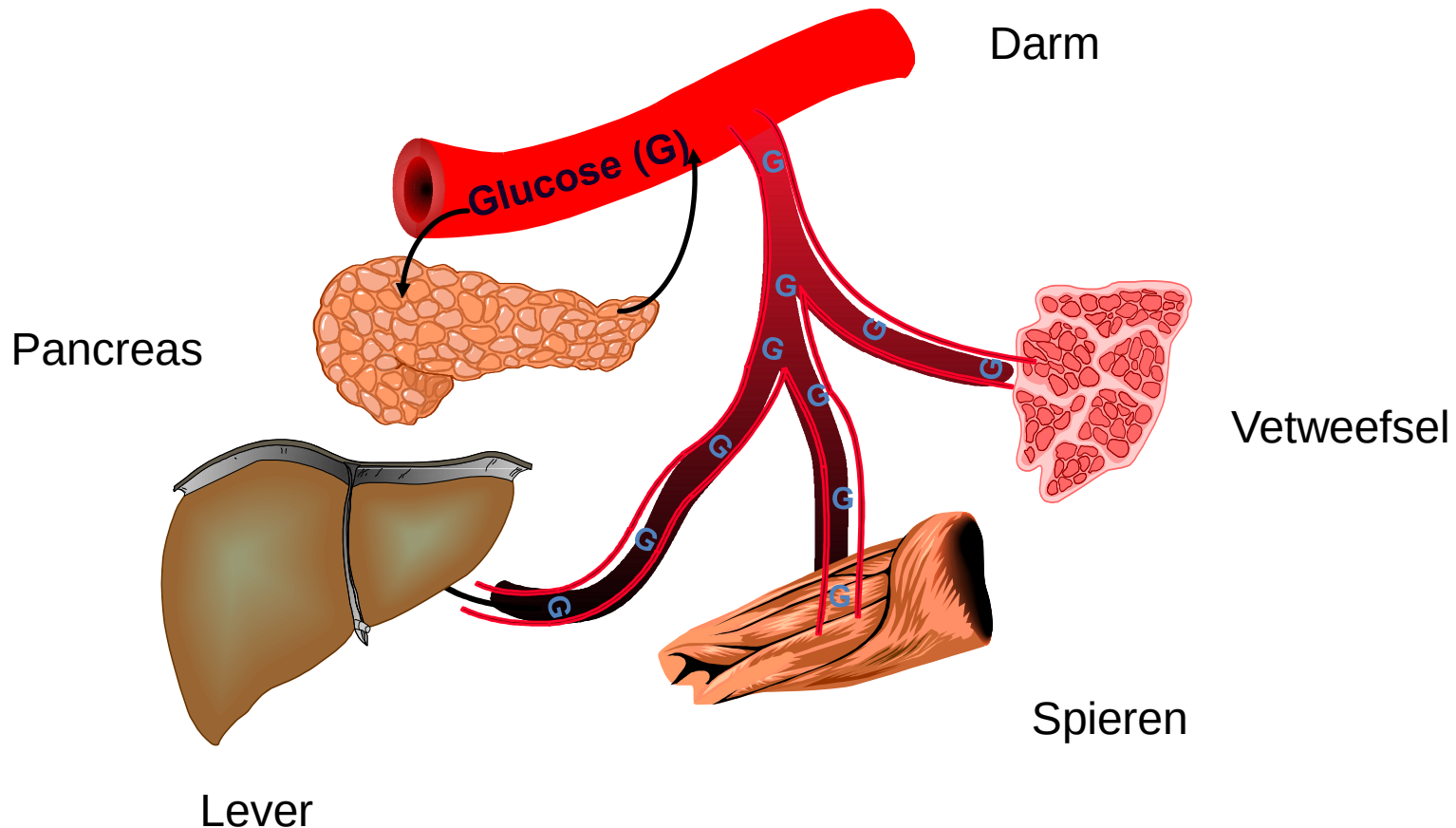
Diensthooft Endocrinologie

KU Leuven

Speaker disclaimer

C. Mathieu is or has been consultant for and KU Leuven has received research support or honoraria from: NovoNordisk, MSD, Eli Lilly, Sanofi, Novartis, AstraZeneca, BMS, Janssen Pharmaceuticals, Pfizer, Medtronic, Roche, Servier

Wat gebeurt er met de glucose die wij opnemen via ons eten?



ADA criteria for diagnosis of diabetes mellitus (2011)

	NORMAL	Diabetes	Impaired glucose tolerance	
Fasting	<100 mg/dl	≥126 mg/dl	≥100 and <126 mg/dl	(IFG)
OGTT (2h after 75g glucose)	<140 mg/dl	≥200 mg/dl	≥140 and <200 mg/dl	(IGT)
Random		≥200 mg/dl		
HbA1c	4-6%	>6.5%		

* In absence of symptoms (polyuria, polydipsia,...) second sample on different day.

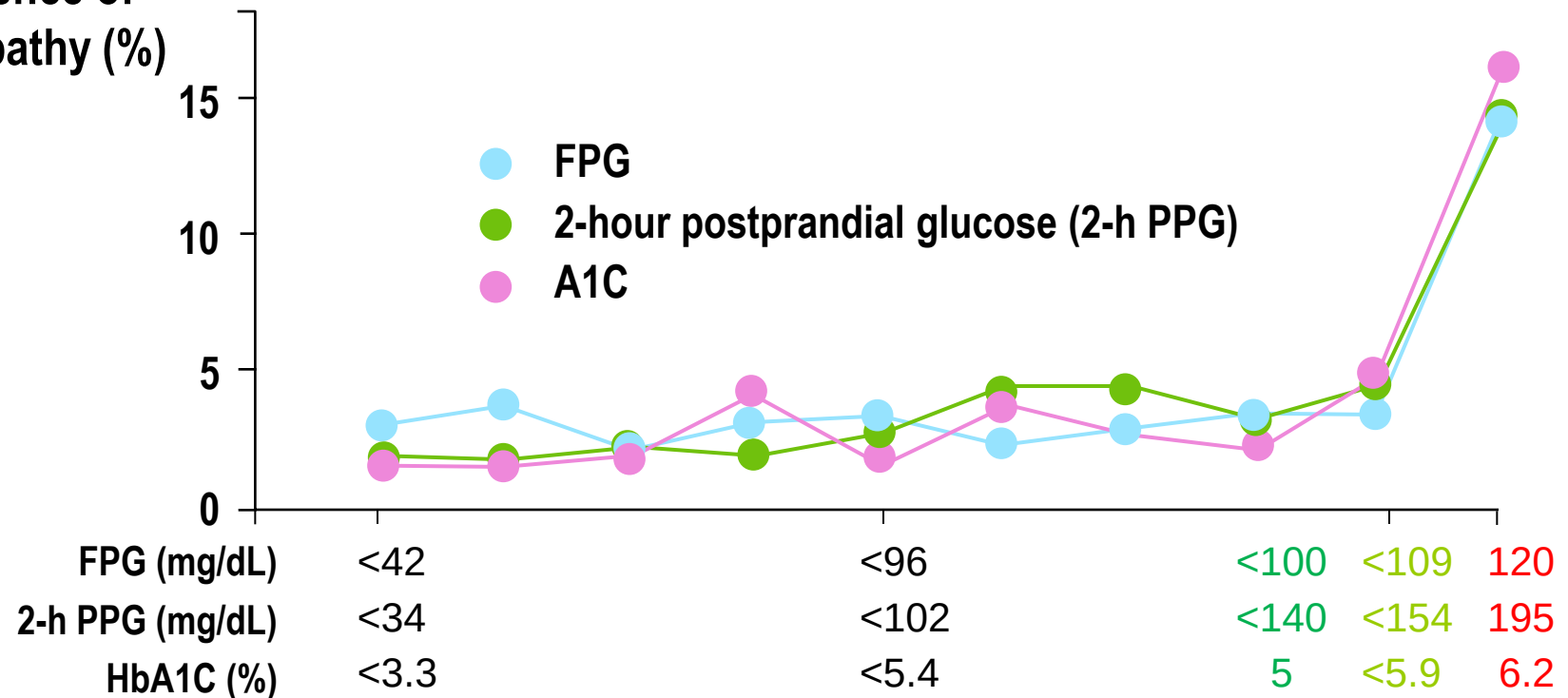
Rationale voor de diagnostische criteria

Glycemische drempels voor retinopathie

Values in Deciles for US Adults Not Known to Have Diabetes

NHANES III

Prevalence of
retinopathy (%)



Waarom is de bloedsuiker controleren zo belangrijk?

Diabetesverwikkelingen

- Acut
- Chronisch

HYPER

Slaperigheid



Moeheid

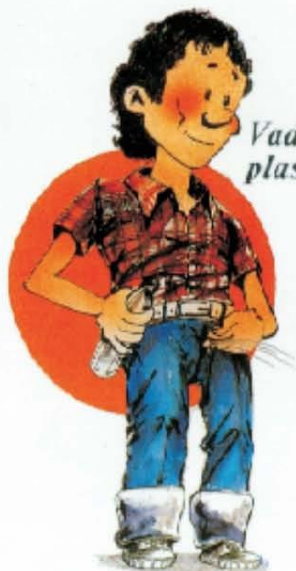
Droge
tong



Dorst



Vaak
plassen



HYPO

Wisselend
humeur



Moeheid



Bleekheid



Slecht
zien



Zweten



Beven

Duizeligheid

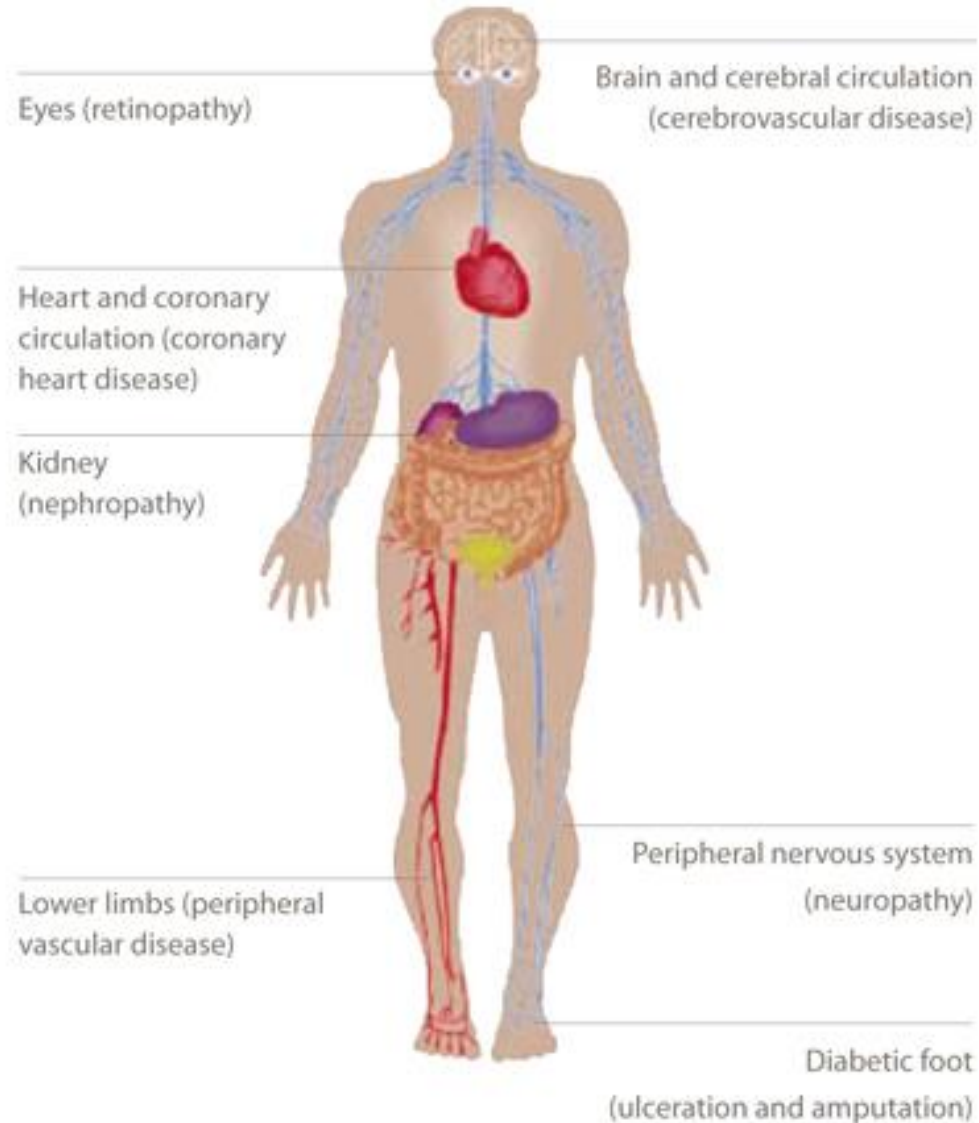


Honger



Hoofd-
pijn

Diabetic complications



Diabetes

Type 1 diabetes

Type 2 diabetes

Zwangerschaps
diabetes

Diabetes na
pancreas operatie

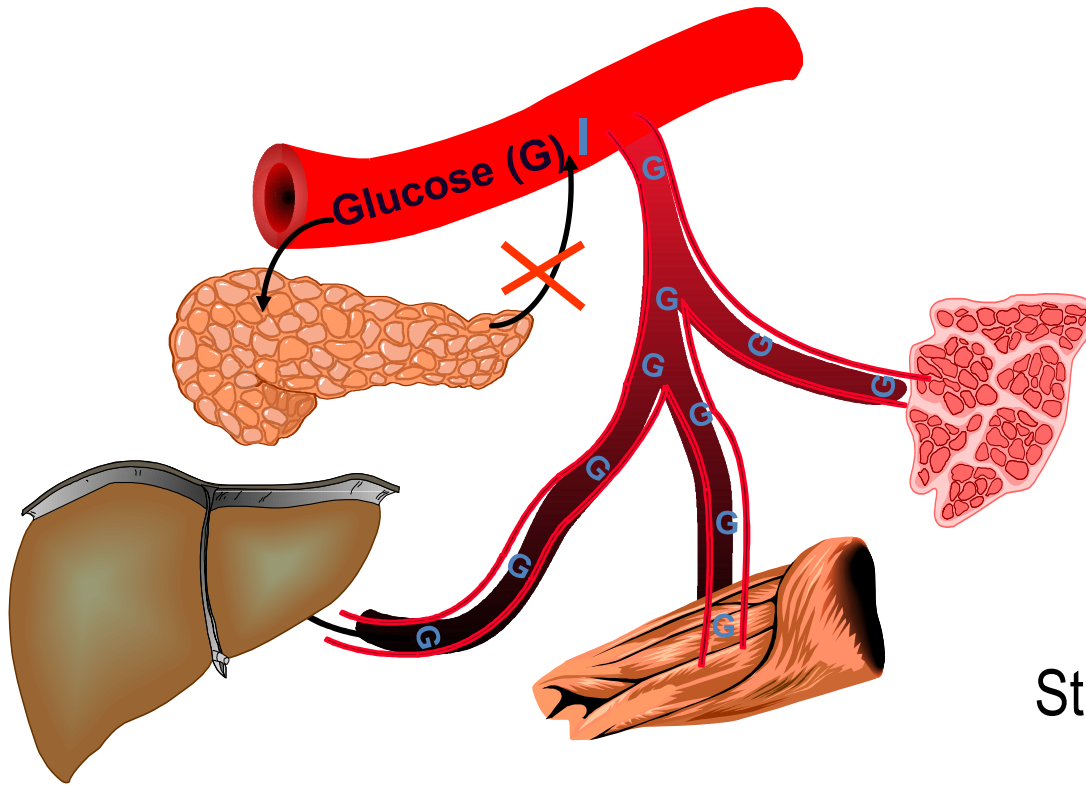
Diabetes door
cortisone

Erfelijke vormen



Type 1 diabetes

Geen insuline productie

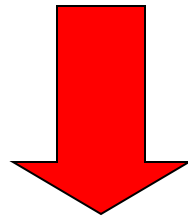


Stijging bloedsuiker

Type 1 diabetes

= Destructie

van de insuline-producerende betacel



Behandeling: Vervangen
van alle functies van de
betacel

Doel van diabetes behandeling

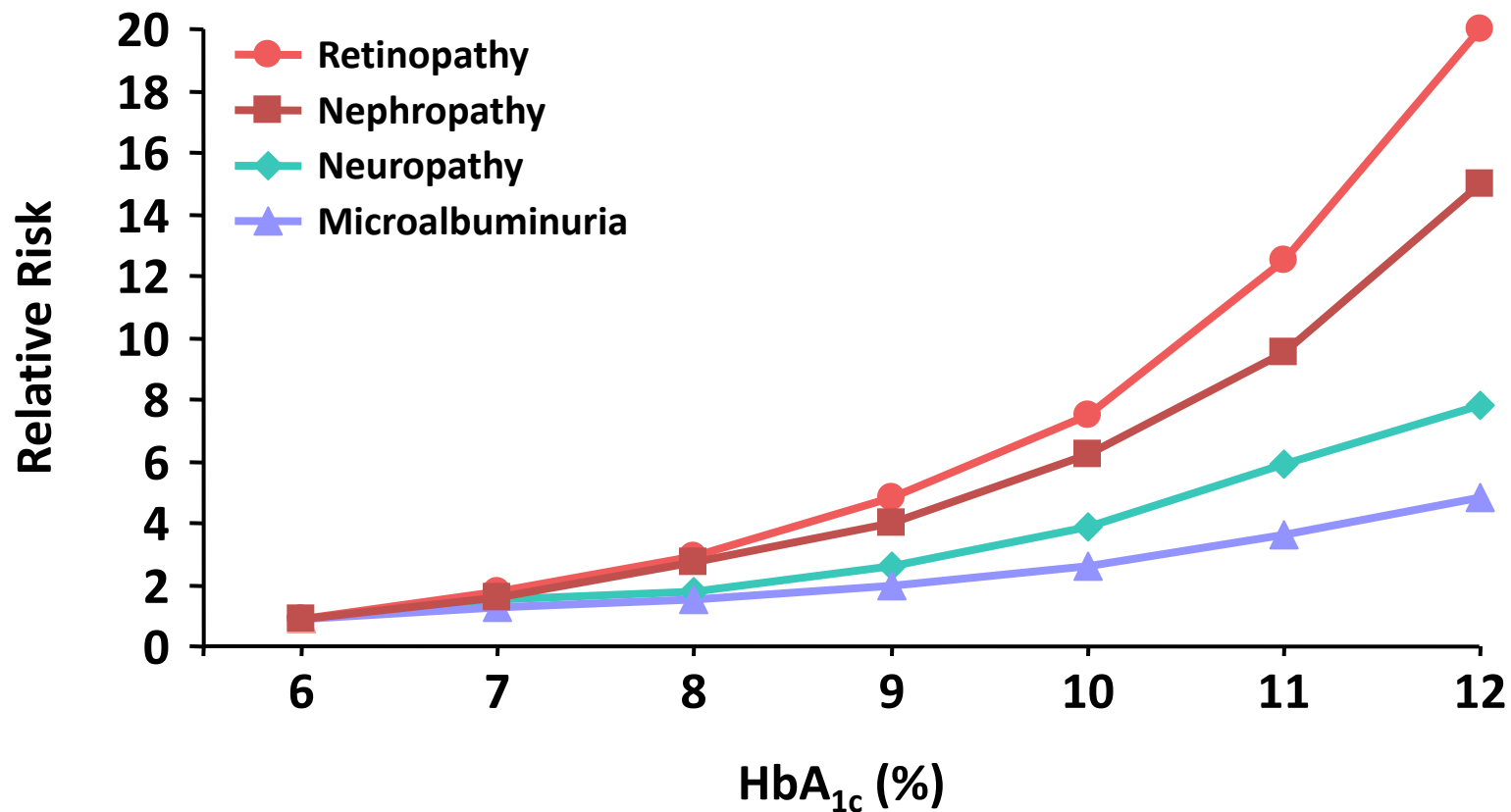
Kwantiteit van leven

en

Kwaliteit van leven

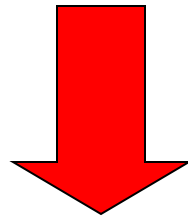
HbA_{1c} and Relative Risk of Progression of Complications in Type 1 Diabetes

Diabetes Control and Complications Trial (DCCT)



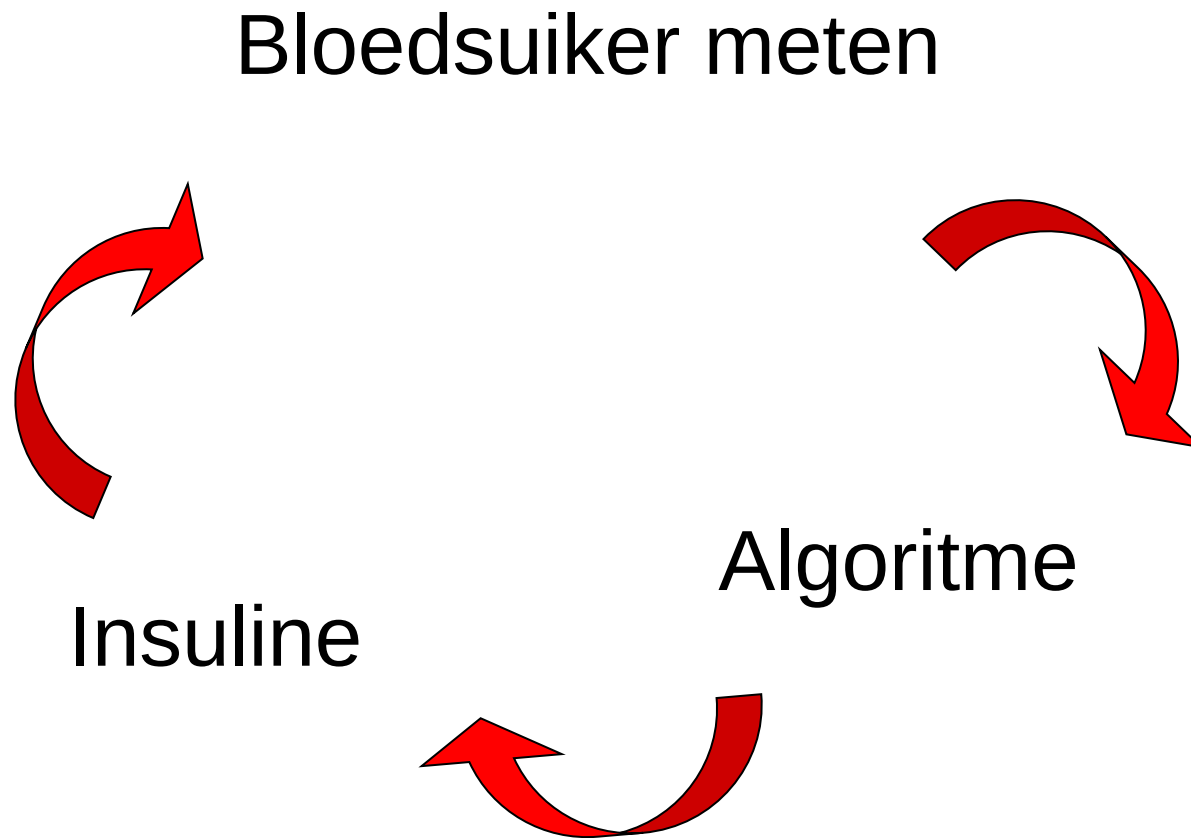
Type 1 diabetes

= Destructie van beta cellen

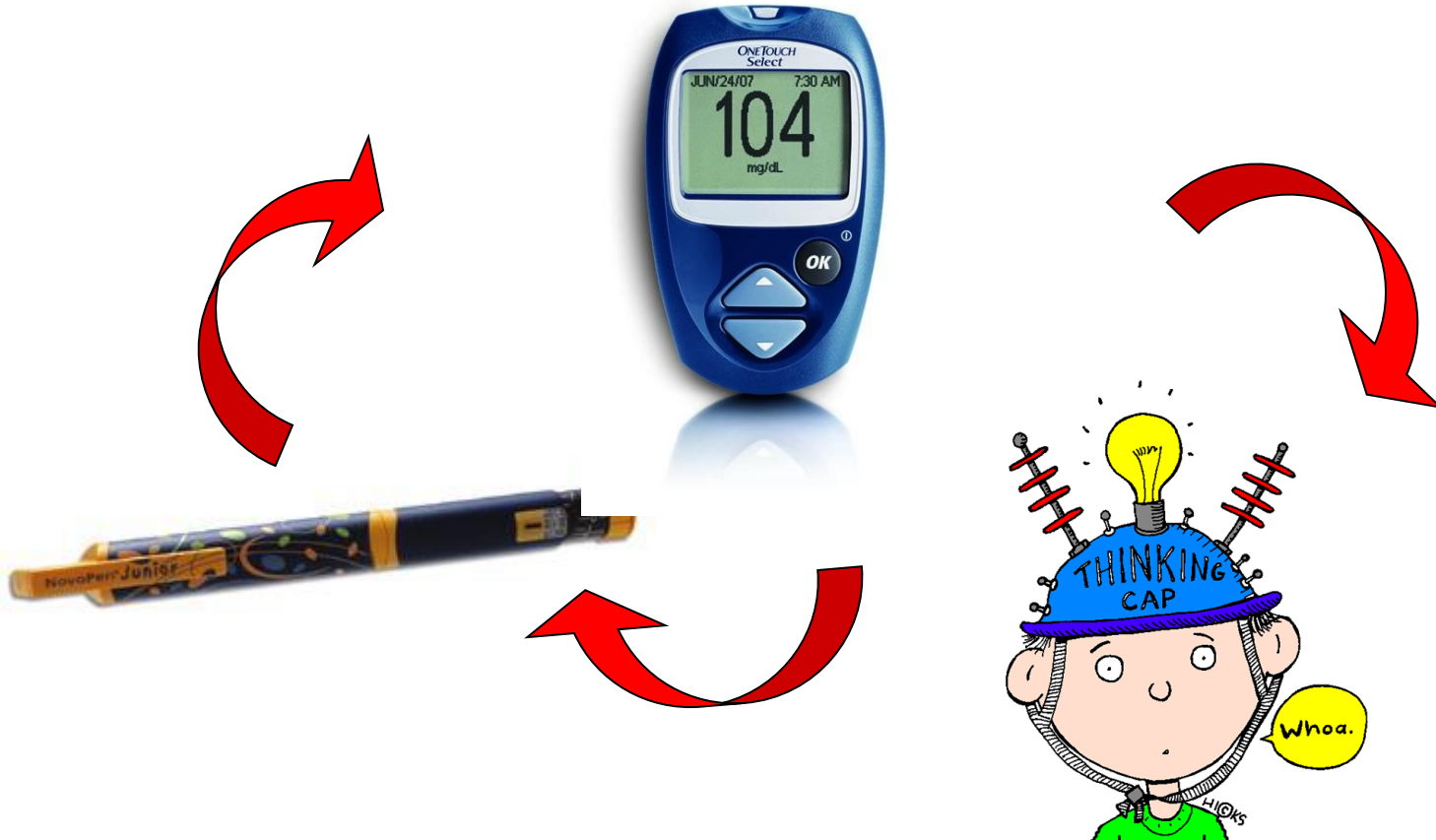


Therapie: Vervangen van
alle beta cel functies

Vervangen van alle beta cel functies



Vervangen van alle beta cel functies



Type 1 diabetes: Middelen

- Insuline
- Educatie en zelf meten van de bloedsuiker
- Dieet
- Lifestyle

Type 1 diabetes: middelen

- Insuline
- Educatie en zelf meten van de bloedsuiker
 - Dieet
 - Lifestyle



Toekomst

- Medicijnen die verwikkelingen tegenhouden

Toekomst

- Medicijnen die verwikkelingen tegenhouden
- Nieuwe insulines:
 - Langer werkend, korter werkend
 - Via de mond
 - Glucose gevoelig

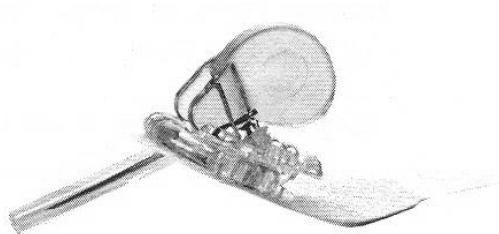
Toekomst

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- Gesloten lus: artificiele pancreas

Artificiële pancreas



Pumps and sensors



Artificiële pancreas



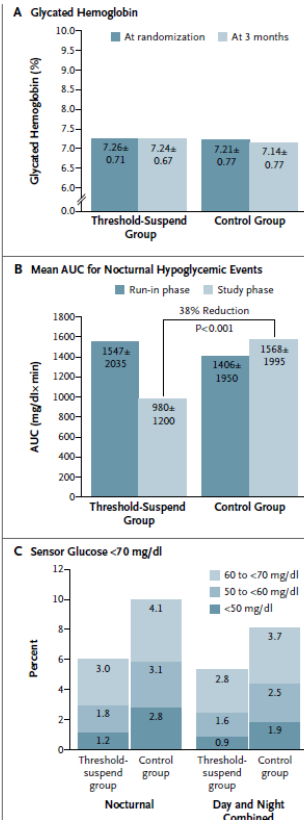
ORIGINAL ARTICLE

Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group*

Figure 2. Primary and key secondary end points.

As shown in Panel A, the mean ($\pm$ SD) changes in glycated hemoglobin concentrations during the study phase (the primary safety end point) were similar in the threshold-suspend and control groups ($0.00\pm 0.44\%$ vs. $-0.04\pm 0.42\%$; difference, 0.05 percentage points; 95% confidence interval [CI], -0.05 to 0.15). As shown in Panel B, the mean area under the curve (AUC) for nocturnal hypoglycemic events during the study phase (the primary efficacy end point) was 37.5% lower in the threshold-suspend group than in the control group ($P<0.001$). As shown in Panel C, the percentage of sensor glucose values that were less than 70 mg per deciliter was lower in the threshold-suspend group than in the control group, whether during nighttime hours (6.0% vs. 10.0%) or during day-time and nighttime hours combined (5.3% vs. 8.1%). The P value was less than 0.001 for each range in the panel. (See Table S2 in the Supplementary Appendix for the percentages of sensor glucose values in all ranges.) To convert values for glucose to millimoles per liter, multiply by 0.05551.



Artificiële pancreas

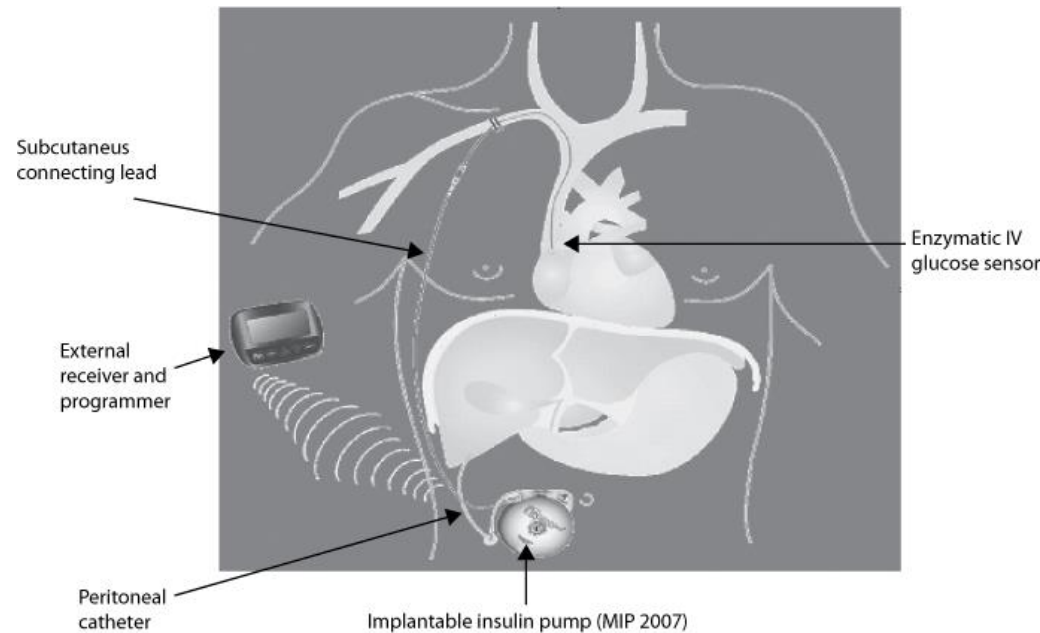
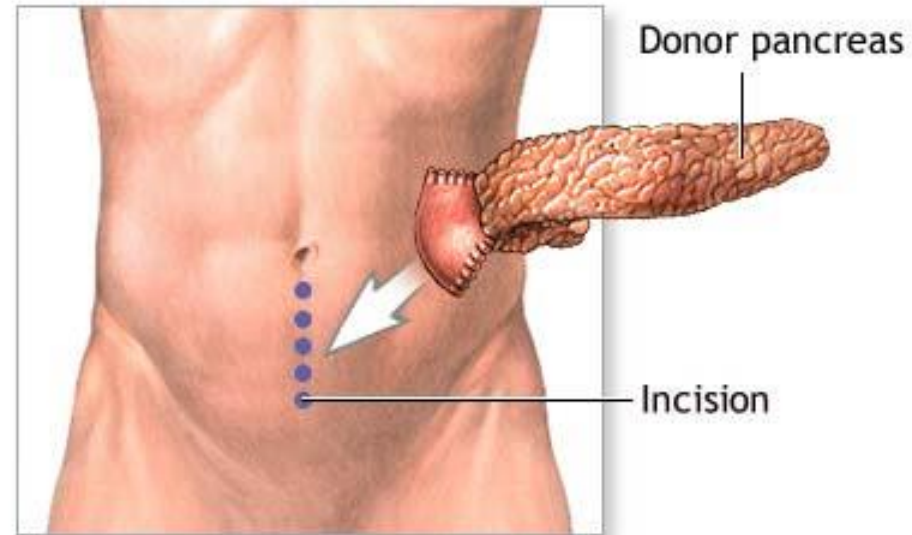
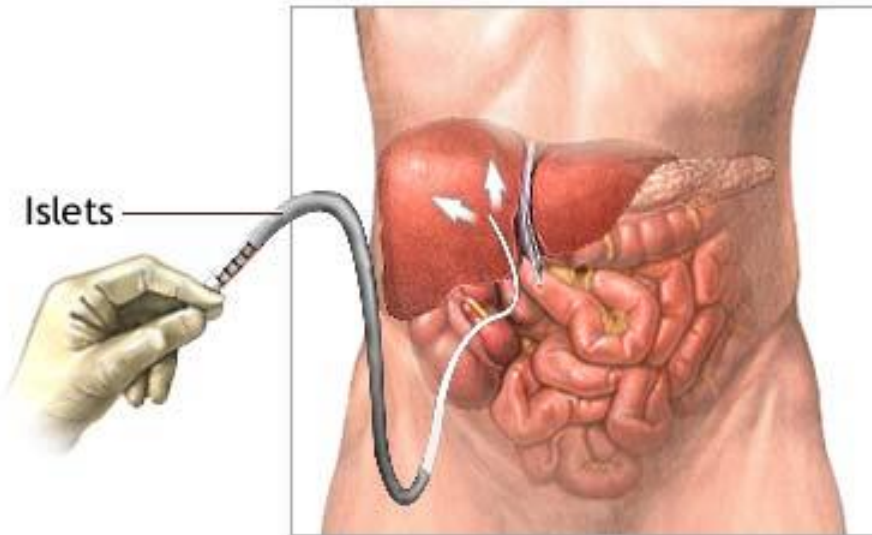


Figure 1. Scheme of human implantation of the Long-Term Sensor System® (LTSS, Medtronic-Minimed), a prototype of implantable artificial beta-cell.

Toekomst

- Medicijnen die verwikkelingen tegenhouden
- Nieuwe insulines:
 - Langer werkend, korter werkend
 - Via de mond
 - Glucose gevoelig
- Gesloten lus: artificiele pancreas
- Transplantatie

Type 1 diabetes



Cure

=

Replacement of pancreatic betacell

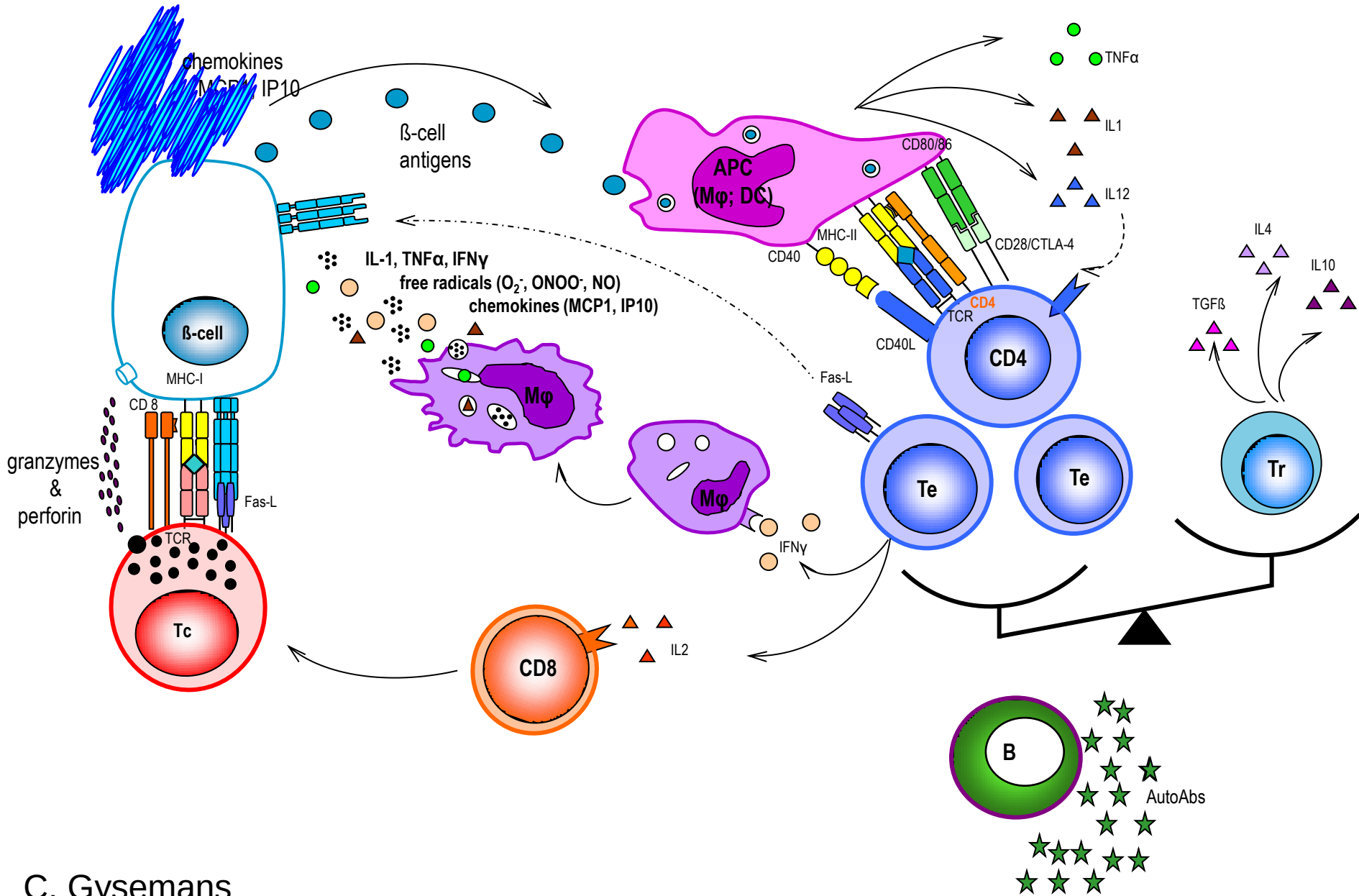
Toekomst

- Medicijnen die verwikkelingen tegenhouden
- Nieuwe insulines:
 - Langer werkend, korter werkend
 - Via de mond
 - Glucose gevoelig
- Gesloten lus: artificiele pancreas
- Transplantatie
- Preventie

Preventie



How are beta-cells destroyed in T1D?



Immune stimulation

Cytokines

Anti-CD4

Thymectomy

Antibodies against cytokines

Bone marrow transplantation

1,25-dihydroxyvitamin D

Irradiation

Anti-CD3

FK506

FTY20

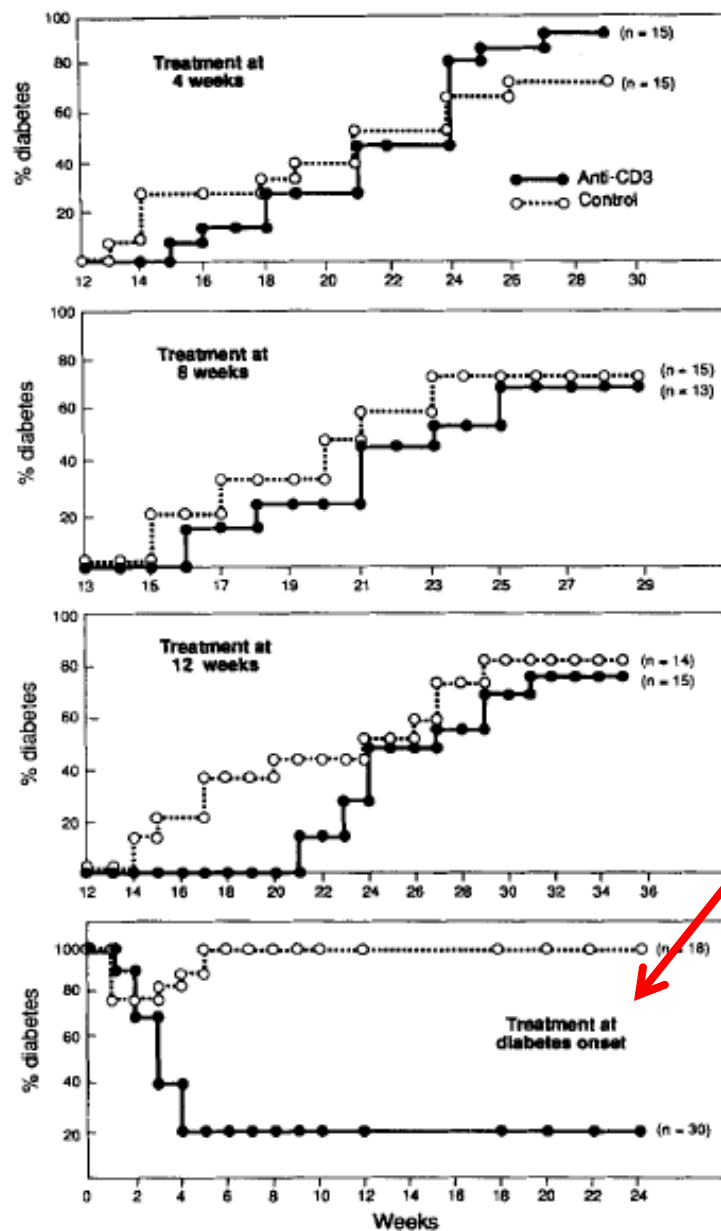
Cyclosporine A

ATG

Anti-CD2

Rapamycin





5-day therapy with 5 $\mu\text{g/day}$ 145-2C11 αCD3 mAb

Antigen-specific
tolerance induction



Global immune
suppression/regulation



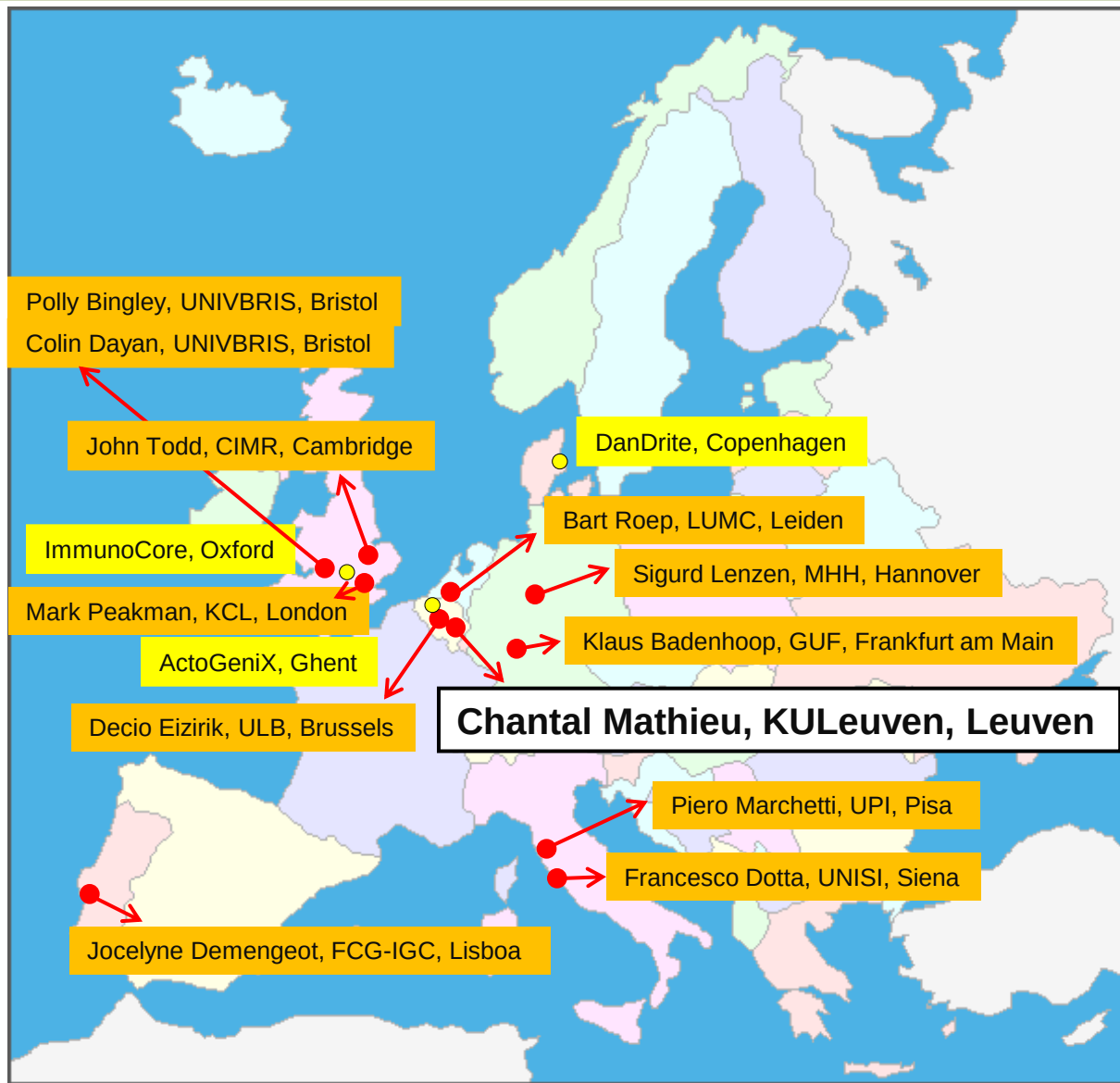
Naimit



NAIMIT

Natural immunomodulators as novel
immunotherapies for
Type 1 diabetes

www.naimit.eu

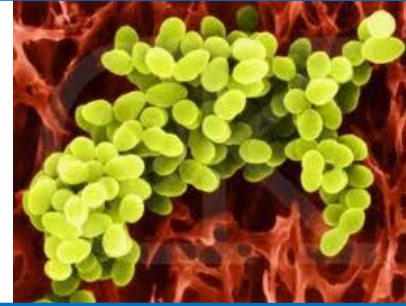


- Academic partners
- SMEs
- Coördinator

Lactococcus lactis : from dairy industry to antigen and therapeutic protein delivery

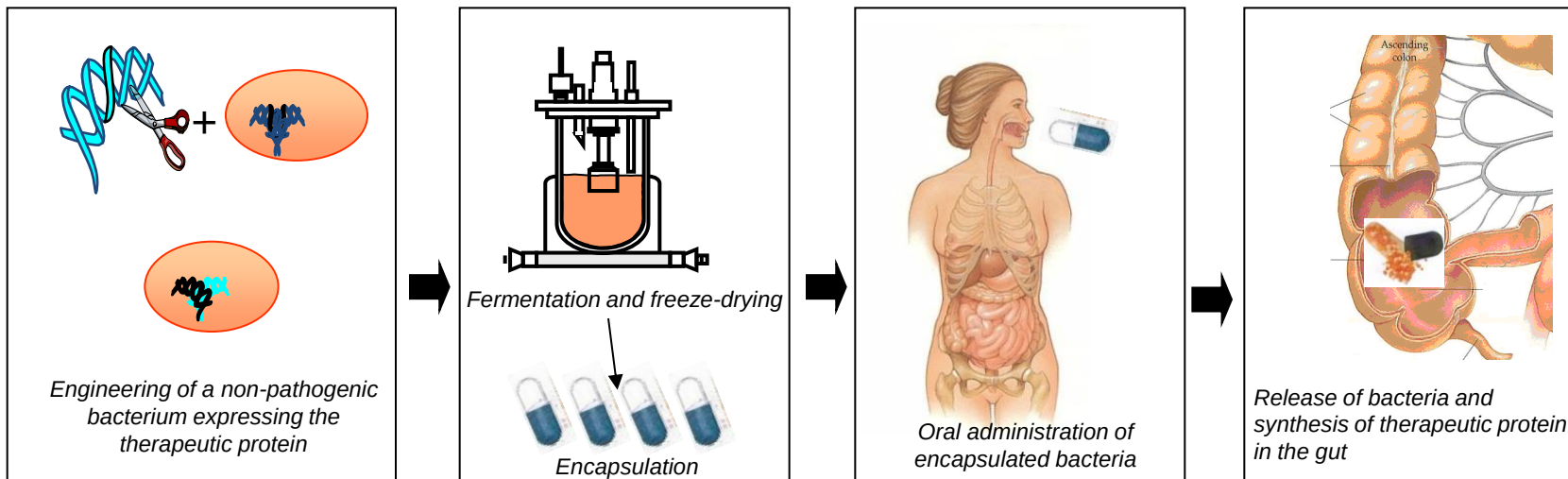
Is a lactic acid bacteria traditionally used in dairy industry in the fermentation of foods. e.g. production of buttermilk and cheese.

It is **non-pathogenic, non-invasive, non-colonizing**, therefore considered as GRAS (generally regarded as safe) organism.

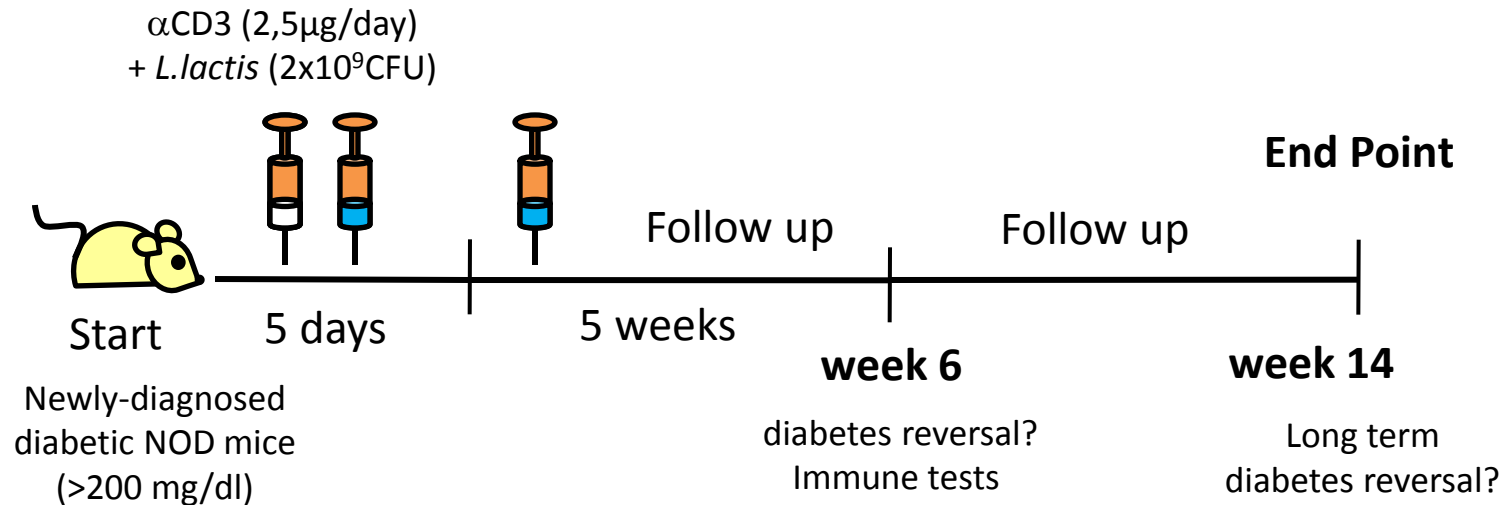


A delivery tool for antigen and therapeutic proteins

- ❖ Genetically engineered to **deliver proteins/peptides** in the gut
- ❖ **Containment system** to prevent survival outside the human body



Experimental design



Groups:

Group 1: α CD3

Group 2: α CD3 + *L.lactis* with empty vector (LL-pT1NX)

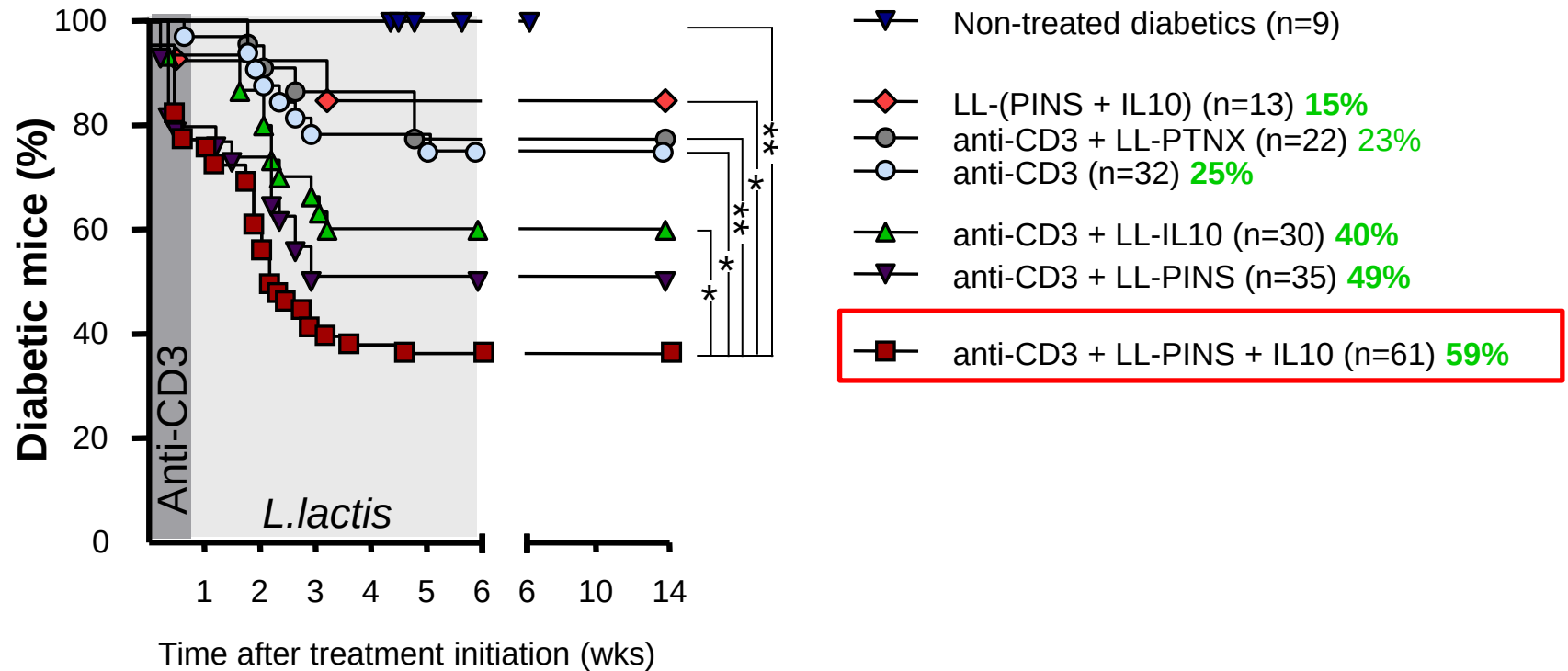
Group 3: α CD3 + *L.lactis* secreting pro-insulin + IL-10 (LL-pins + hIL-10)

Group 4: α CD3 + *L.lactis* secreting pro-insulin (LL-pins)

Group 5: α CD3 + *L.lactis* secreting IL-10 (LL-hIL-10)

Group 6: *L.lactis* secreting pro-insulin + hIL-10

Reversal of diabetes



*,vs. anti-CD3+LL-PINS+IL-10. One symbol represents $0.01 < p < 0.05$; two symbols represent $0.01 < p < 0.001$. Statistical differences were calculated by Mantel-Haenszel logrank test.



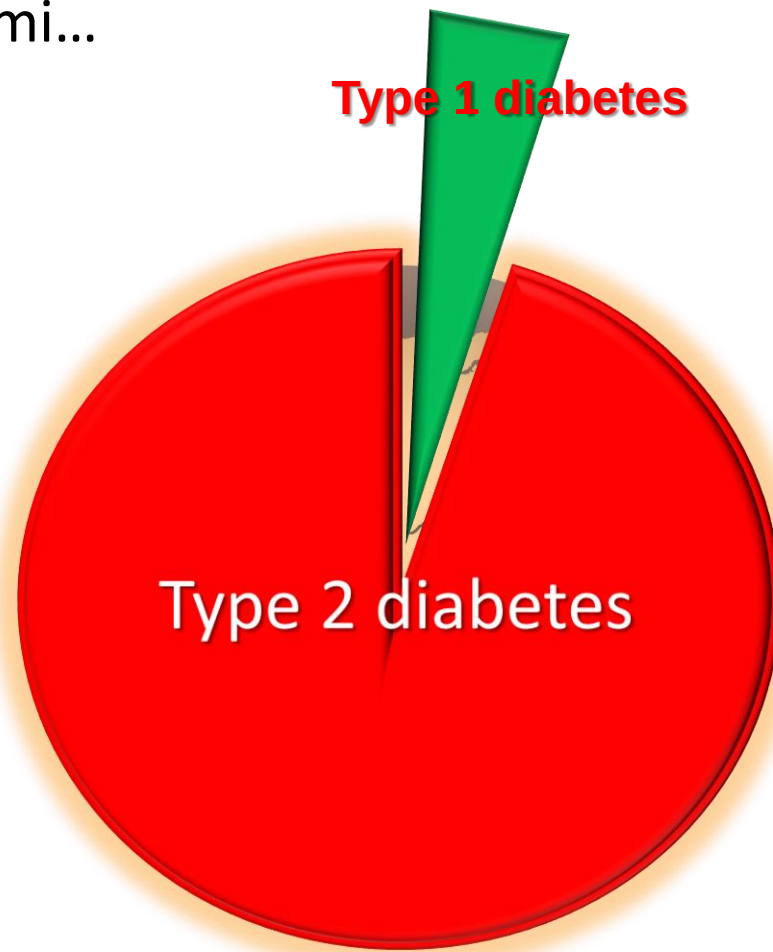
Type 2 Diabetes: the modern day tsunami...
Estimated global prevalence of diabetes



151 million
2000



347 million
2008

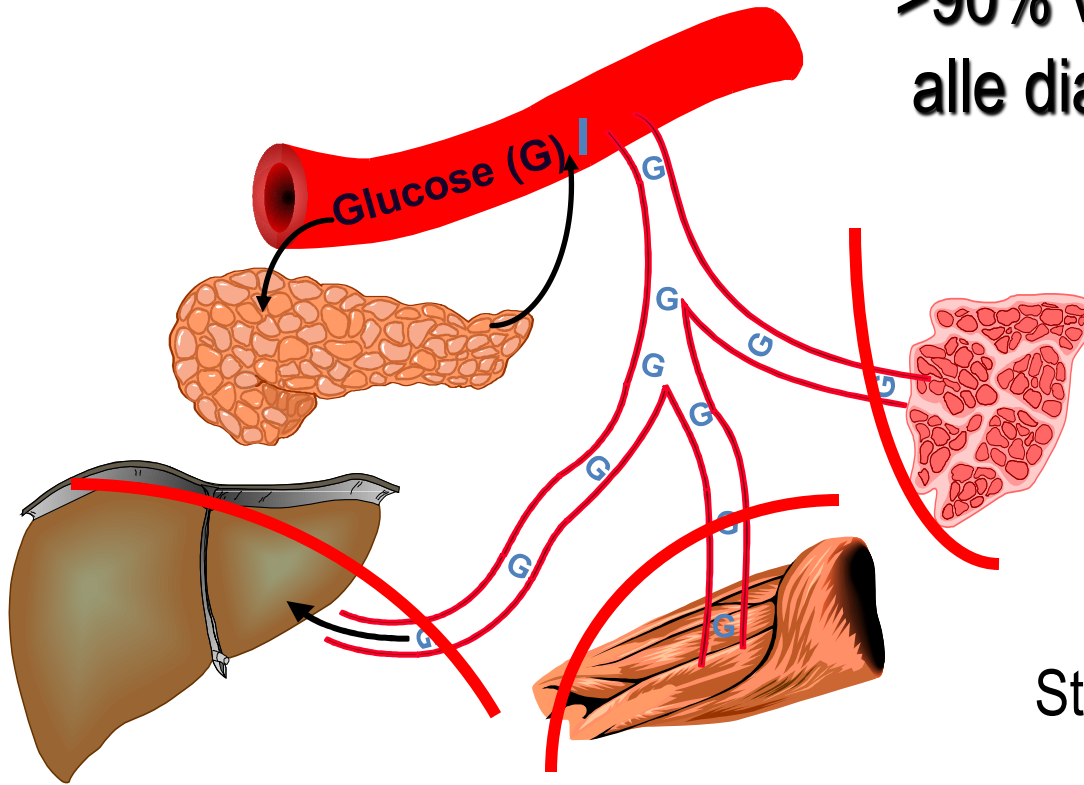


438 million
2030

Type 2 diabetes

Relatief onvoldoende insuline productie

>90% van
alle diabetespatiënten



Hoge weerstandigheid
aan insuline

Stijging glycemie

Type 2 diabetes: Middelen

- Glucose verlagende middelen
- Educatie en zelf meten van de bloedsuiker
- Dieet
- Lifestyle

Type 2 diabetes: Middelen

- Educatie
- Dieet
- Lifestyle
- Multifactoriële benadering
 - Glucose verlagende middelen
 - Zelf meten van de bloedsuiker



FEATURED
BROKERS



OPEN ▾



OPEN ▾



OPEN ▾



OPEN ▾

92 billion dollars

Diabetes is the syndrome of having excess blood sugar due to low levels of insulin or insulin resistance. Approximately 21 million individuals in the U.S. have diabetes, and this number is growing at 10% a year, or over 1.5 million new cases annually.^[1] Age and obesity are both risk factors, and contributes to this number.

While diabetes often cannot be cured, drugmakers and biotech companies make glucose monitors, insulin delivery devices, and drug products to help manage the condition. It is estimated that the total market for diabetes products and related care is worth \$92 billion in the U.S.^[2] Diabetes is especially important to Amylin, Novo Nordisk, Insulet, and DexCom, which focus on this market.

TOP CONTRIBUTORS



SR. DIRECTOR TOP 5%
Dan Pan

subscription fee.

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TRADE FREE FOR 60 DAYS

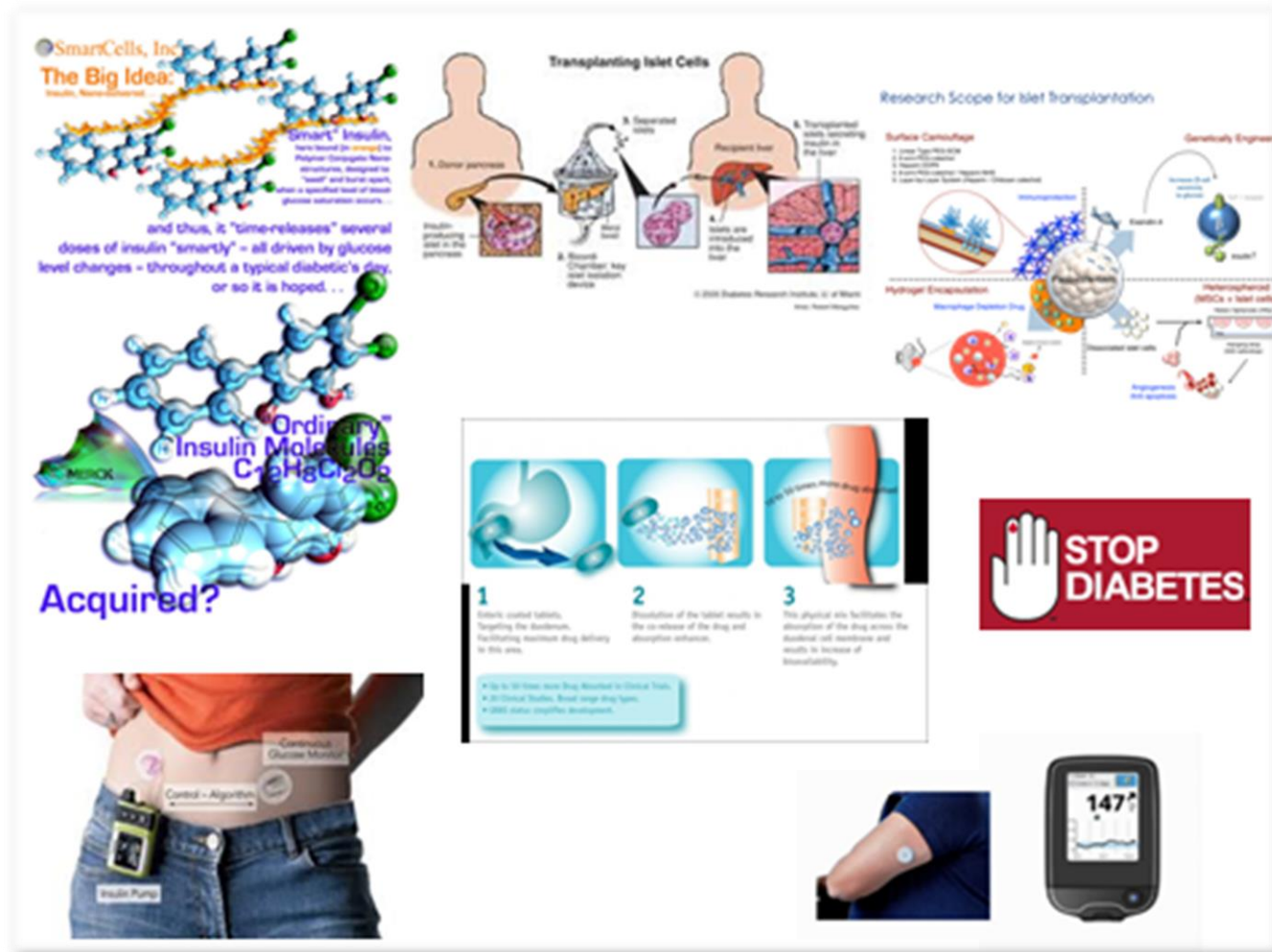
OPEN AN AC

WELCOME TO BETTER

TD Amerit

RECENT NEWS

'We live in interesting times'



Toekomst

- Nieuwe insulines:
 - Langer werkend, korter werkend
 - Via de mond
 - Glucose gevoelig
- Obesitas tegengaan
- Insuline gevoeligheid verbeteren
- Betacellen beschermen/sterker maken
- Incretinesysteem

GLP-1 heeft diverse effecten in het menselijk lichaam

Pancreas

- ↑ Insulin secretion (glucose-dependent)
- ↑ Beta-cell sensitivity
- ↑ Insulin synthesis
- ↓ Glucagon secretion (glucose-dependent)
- ↑ Beta-cell mass*



Brain

- ↓ Energy intake*

Liver

- ↓ Hepatic glucose output

GI tract

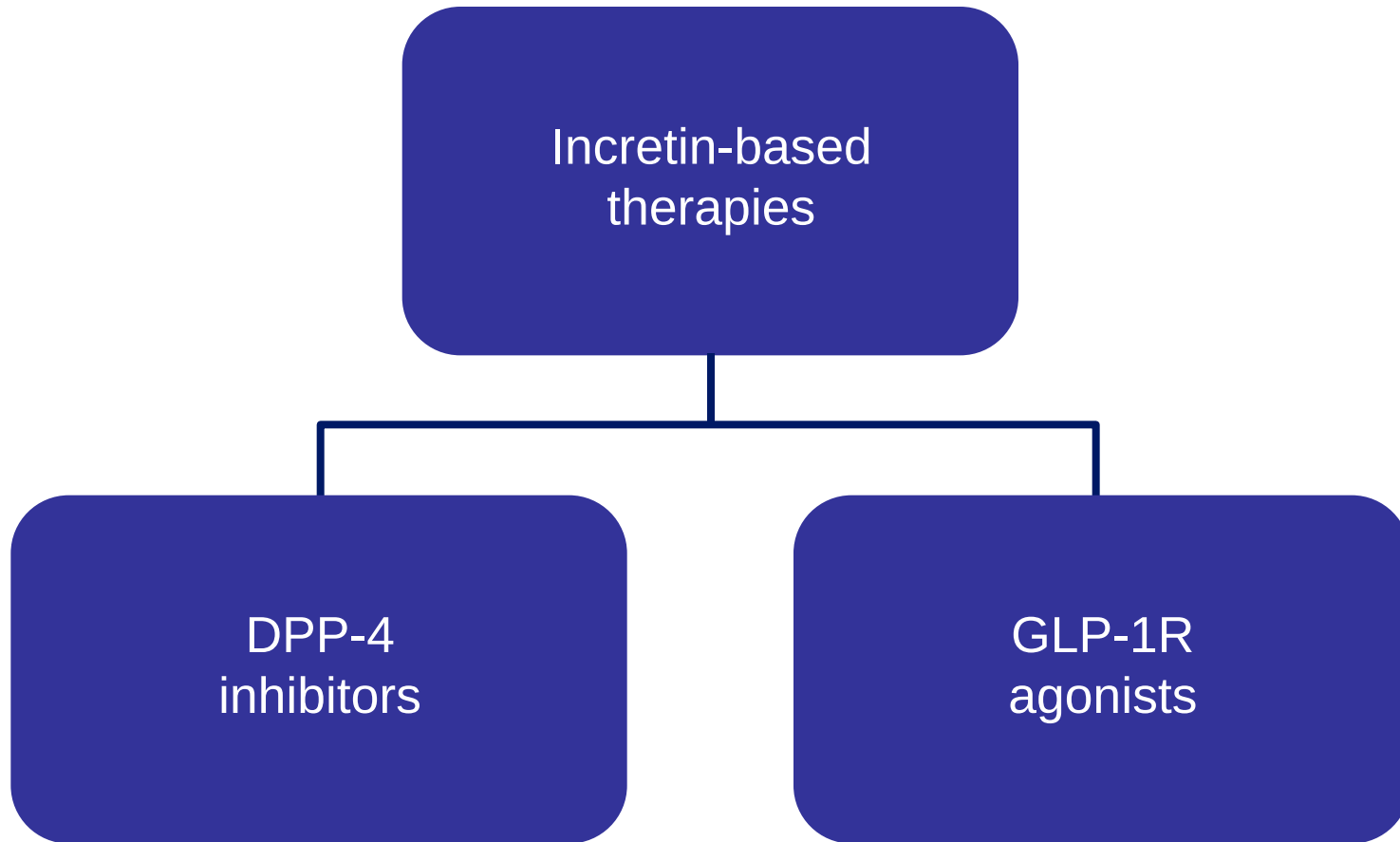
- ↓ Gastric emptying

Heart

- ↑ Cardioprotection
- ↑ Cardiac function

*in animal studies

The family of incretin-based therapies





Plaats van heelkunde???

Diabetes

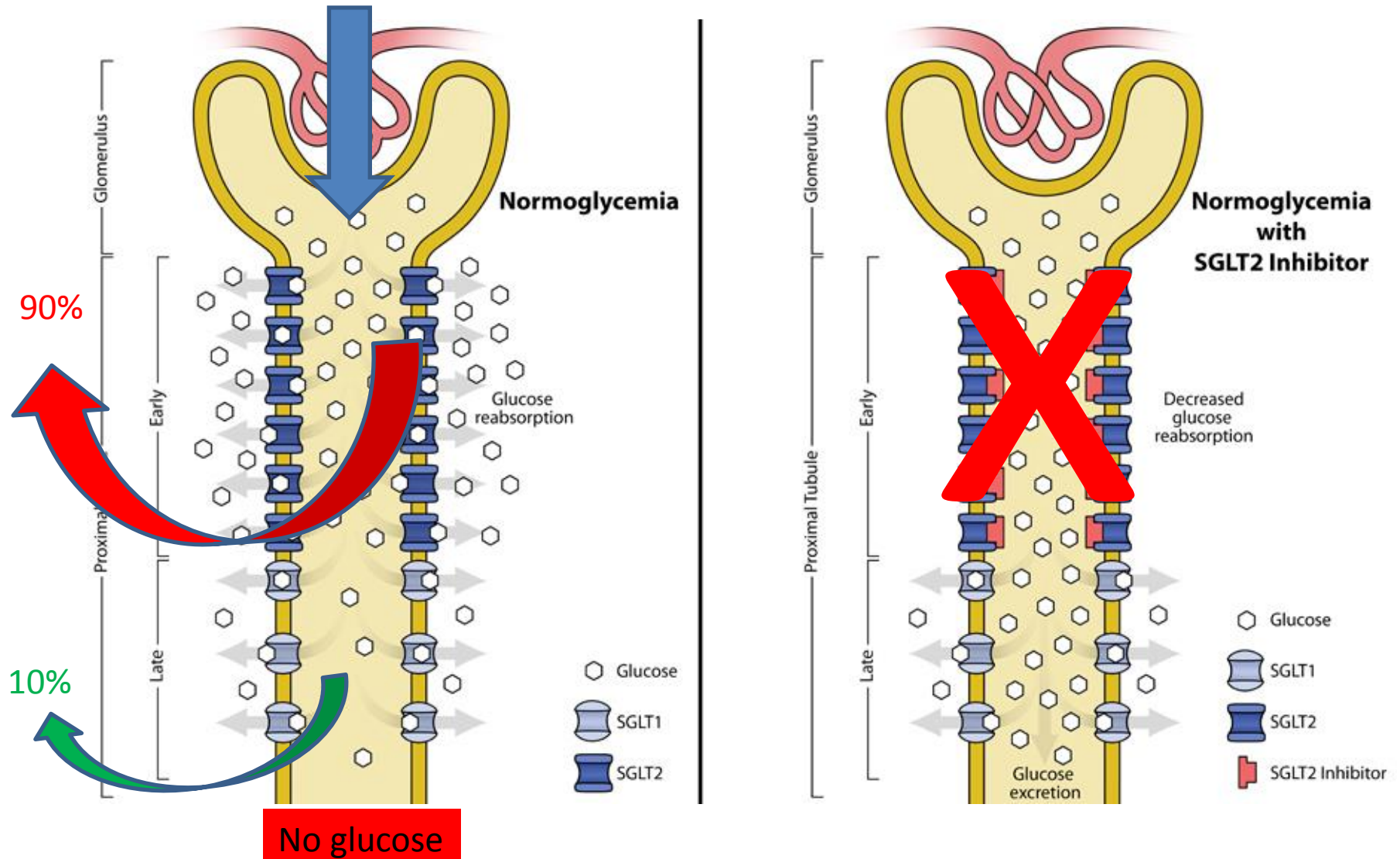


Diabetes



Renal Handling of Glucose

$(180 \text{ L/day}) (900 \text{ mg/L}) = 162 \text{ g/day}$



Diabetes, ziekte met toekomst

- De prevalentie van diabetes neemt toe
- Verwikkelingen van diabetes drijven gezondheidszorg kost
- Genezing/preventie van type 1 diabetes aan de horizon
- Nieuwe middelen maken goede glycemiecontrole in meer mensen mogelijk

