Et si on se projetait? Perspectives futures dans la prise en charge du diabète

Chantal Mathieu MD PhD

Endocrinologie, UZ Leuven

Leuven, Belgium

Conflits d’intérêt

Advisory boards: Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Imcyse, Insulet, Zealand Pharma, Avotres, Mannkind, Sandoz and Vertex.

Speaker’s Bureau: Novo Nordisk, Sanofi, Eli Lilly and Company, Boehringer Ingelheim, Astra Zeneca and Novartis

Research support: Imcyse and ActoBio Therapeutics

Programme

- Future d’ insuline, technologie…
- Future de la prévention/interventions

The challenge of insulin therapy

Dose of insulin:
(G)estimation based on bloodglucose level to start with, on planned meal, on planned exercise….

Injecting under the skin:
not in portal vein

Variability of insulin preparations

Injecting under the skin:
once injected, insulin action will happen

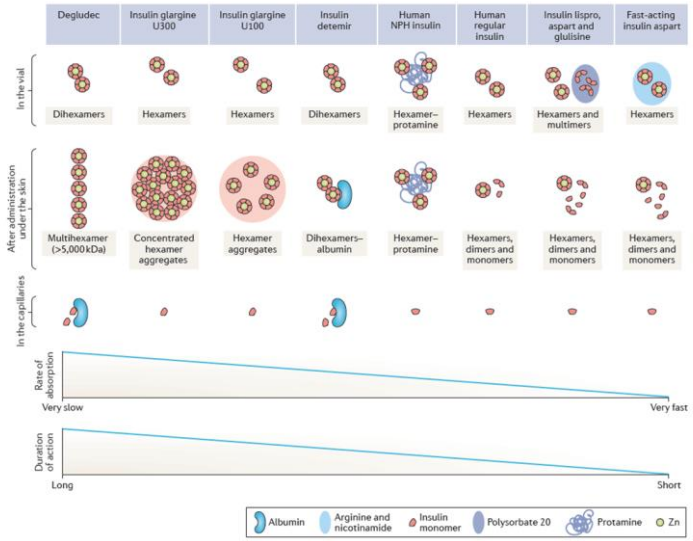
The challenge of insulin therapy: Now

Insulin analogues

Smart pens

Apps assisting in education

Implantable pumps



The challenge of insulin therapy: Now

Insulin analogues

Smart pens

Apps assisting in education

Hybrid Closed Loop systems

Implantable pumps

The challenge of insulin therapy: Now

Complication protection

The challenge of insulin therapy: 5 years

Smaller sensors, more durable

Easier pump systems, durable catheters

The challenge of insulin therapy: 5 years

Smaller sensors, more durable

Easier pump systems, durable catheters

HCL in patchpump

Bi-hormonal pump

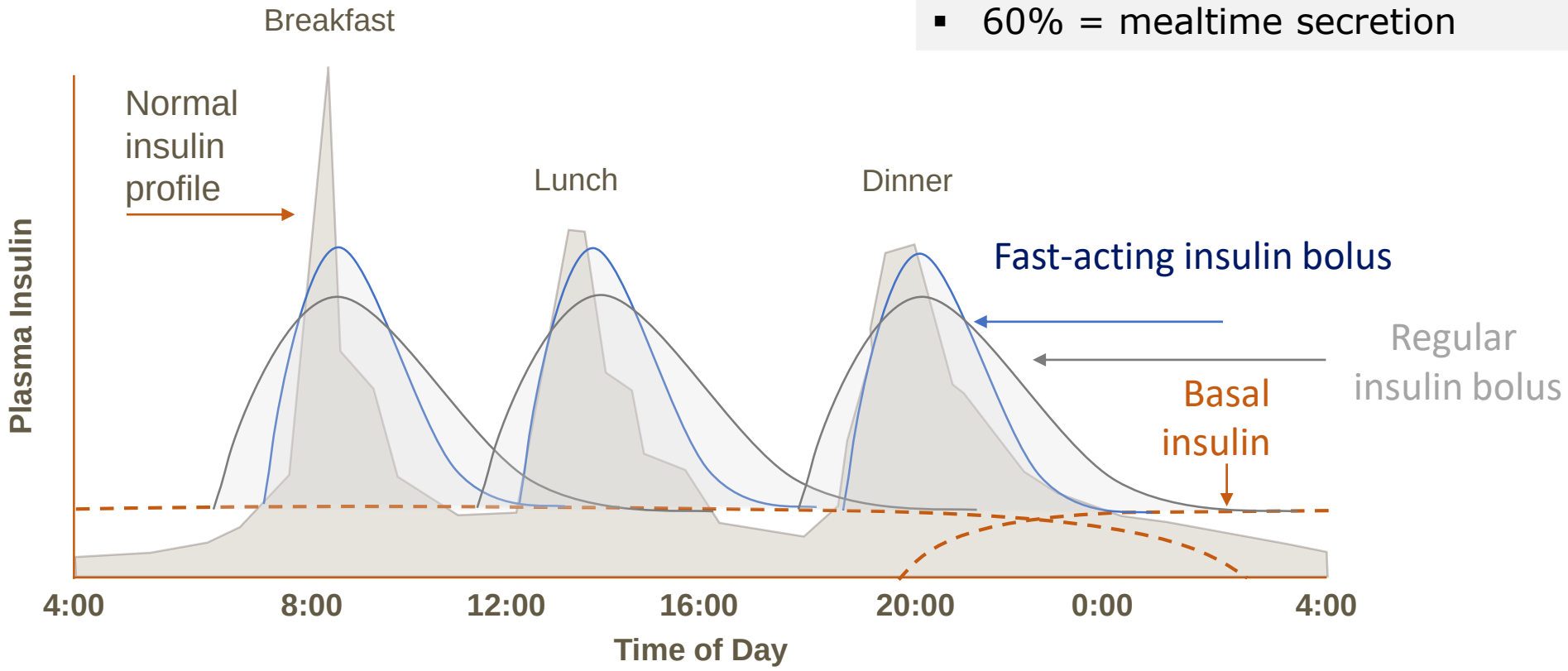
More performant algorithms
Meal simplification- estimation

Multi-metabolite sensors

Novel insulin preparations

Physiologic insulin replacement

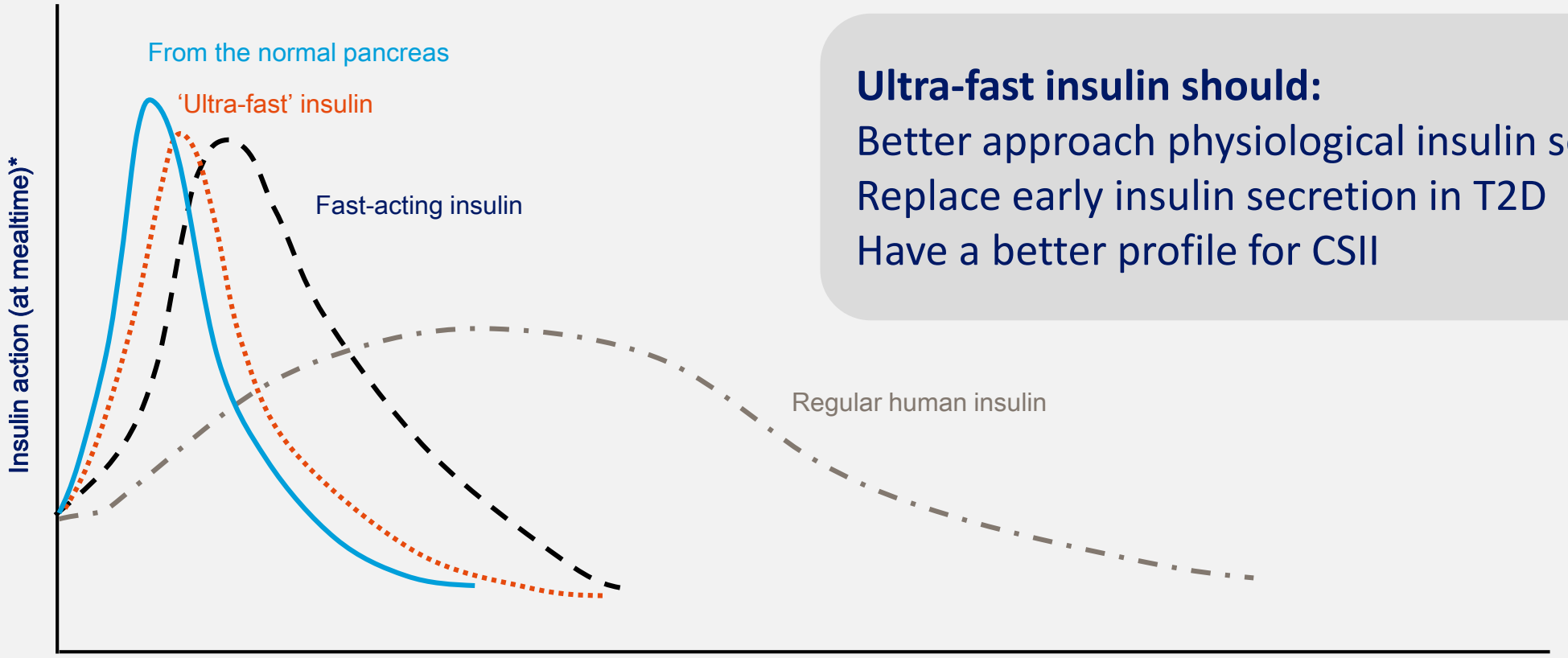
Physiological insulin secretion: 0.6 IU / kg / day
- 40% = basal secretion
- 60% = mealtime secretion



Mealtime bolus insulin is designed to prevent the predicted postprandial increase in glucose, therefore maintaining tight glycaemic control.

Adapted from Magaji V, Johnston JM. *Clin Diabetes.* 2011;29(1):3-9.

Ultra-fast insulin: approaching a physiological insulin profile even further



Ultra-fast insulin should:

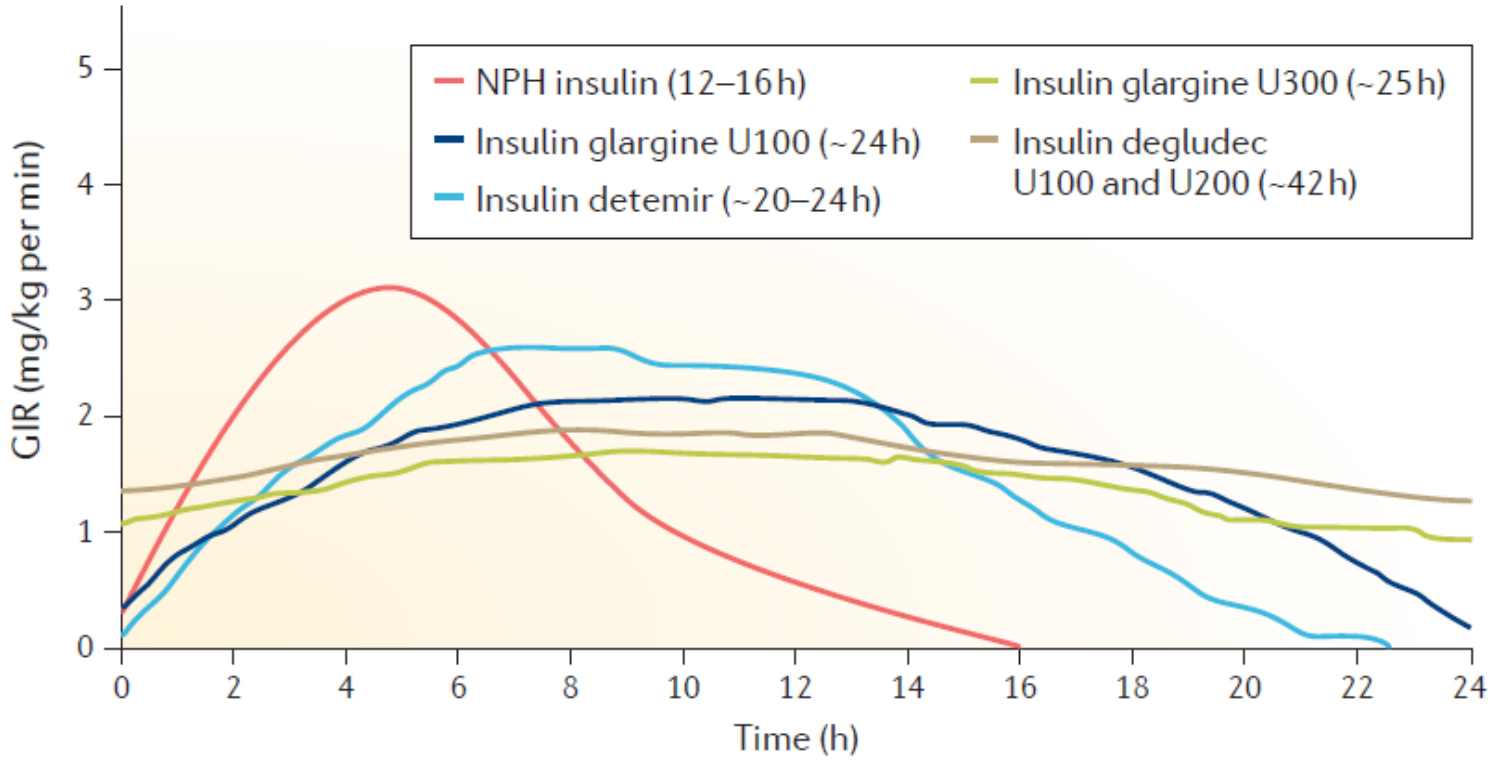
Better approach physiological insulin secretion in T1D

Replace early insulin secretion in T2D

Have a better profile for CSII

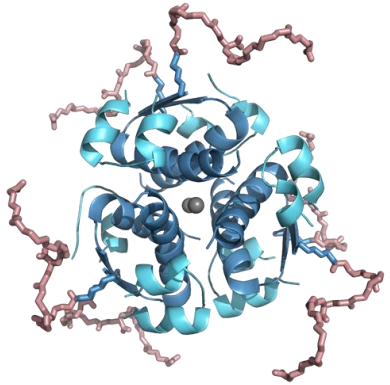
*Adapted from Home. *Diabetes Obes Metab* 2015;17:1011–20

Basal insulins



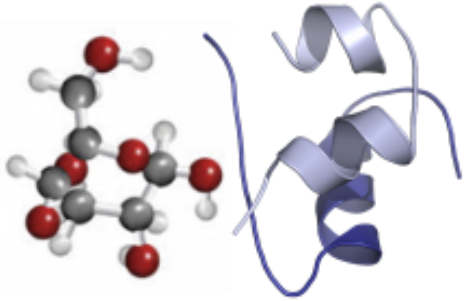
Mathieu C. et al *Nat Rev Endocrinol* 2017

A glimpse into the future of insulin treatment



Once-weekly insulin

Oral insulin



Glucose-sensitive insulin

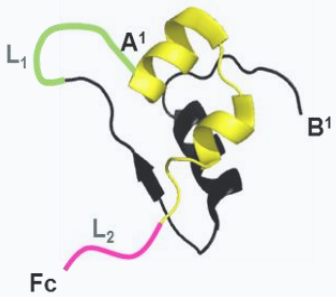
Convenience	Simplicity	Improved safety

Technology/devices will evolve in parallel and complement the advances in therapeutic options

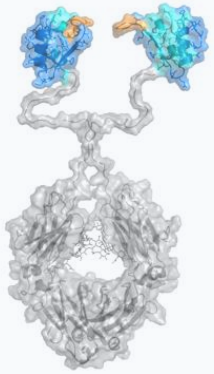
Once-weekly insulins

Fc fusion

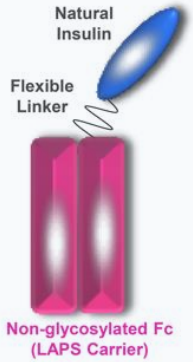
AstraZeneca



Eli Lilly:
Basal Insulin-Fc
(BIF)

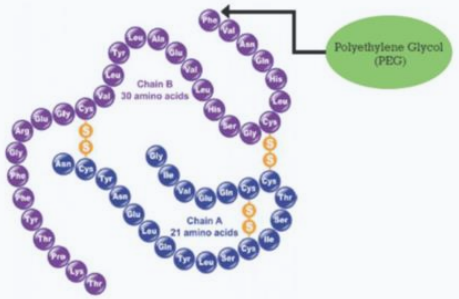


Hanmi:
HM12460A



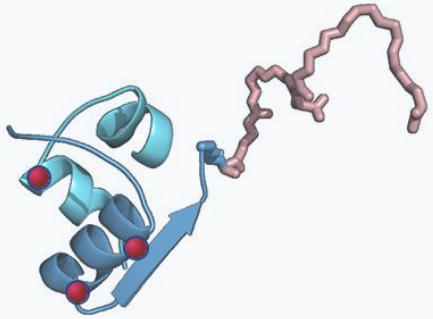
PEGylated

Antria/Rezolute:
AB101



Acylated

Novo Nordisk:
insulin icodec

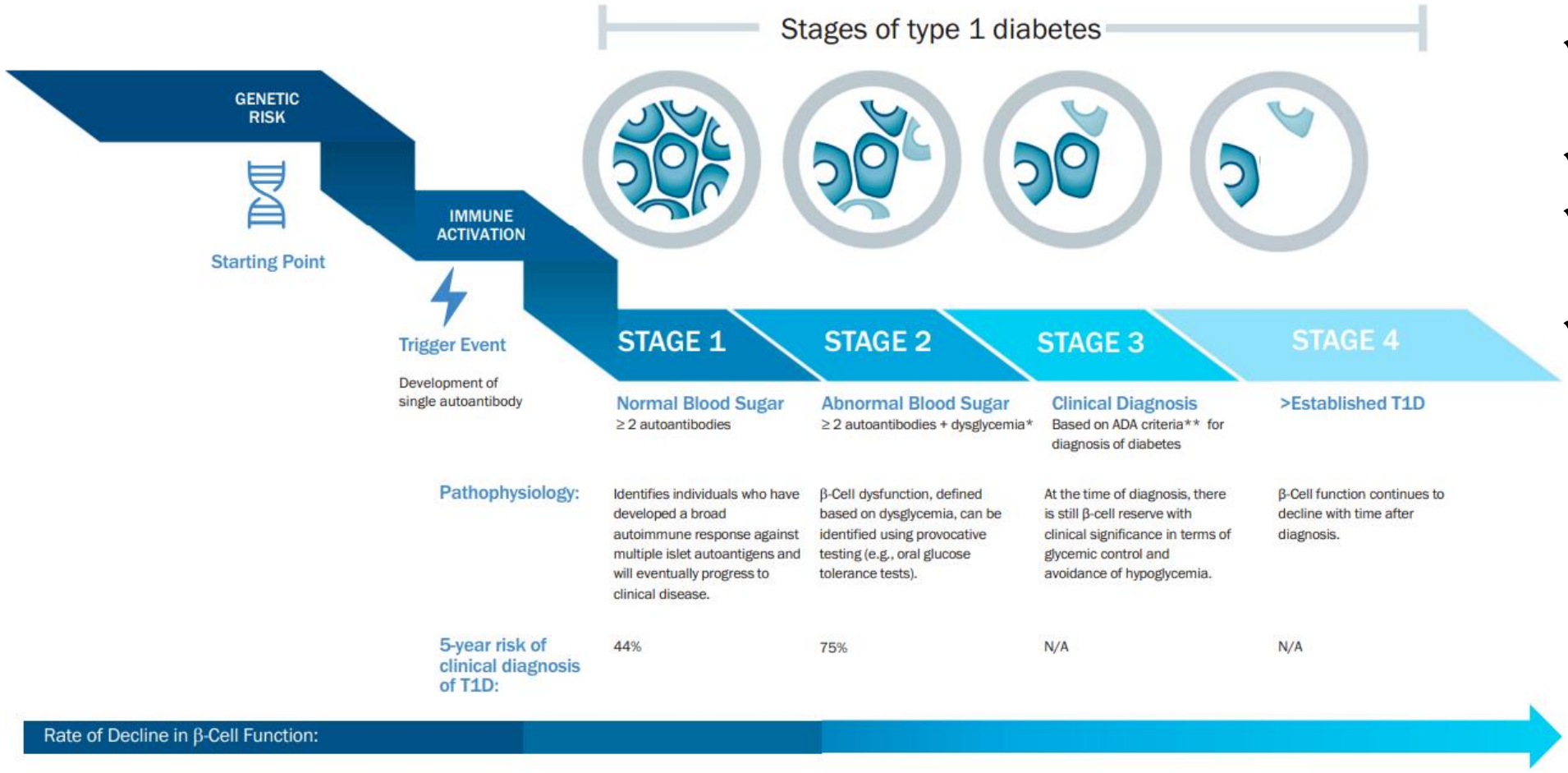


**Fc, antibody fragment crystallizable domain; PEG, polyethylene glycol.*

DeVries, J Novel pharmacological strategies to develop weekly insulin. Rosenstock, J (Chair), Weekly basal insulin- the wave of the future. Symposium at the 80th scientific sessions by the American Diabetes Association. https://virtual.lww.com/ADA2020Sessions/Pages/virtual-meeting.aspx. 2020.

Mais… si l’on pouvait prévenir ou arrêter le diabète de type 1….?

T1D: NOUVELLE DÉFINITION



- ✓ ~5% des personnes diabétiques
- ✓ Déficit en insuline
- ✓ Besoin d'insulinothérapie
- ✓ Enfants, adoléscents et adultes

Sims E. et al Diabetes Care 2022; *Adapted from www.TrialNet.org*

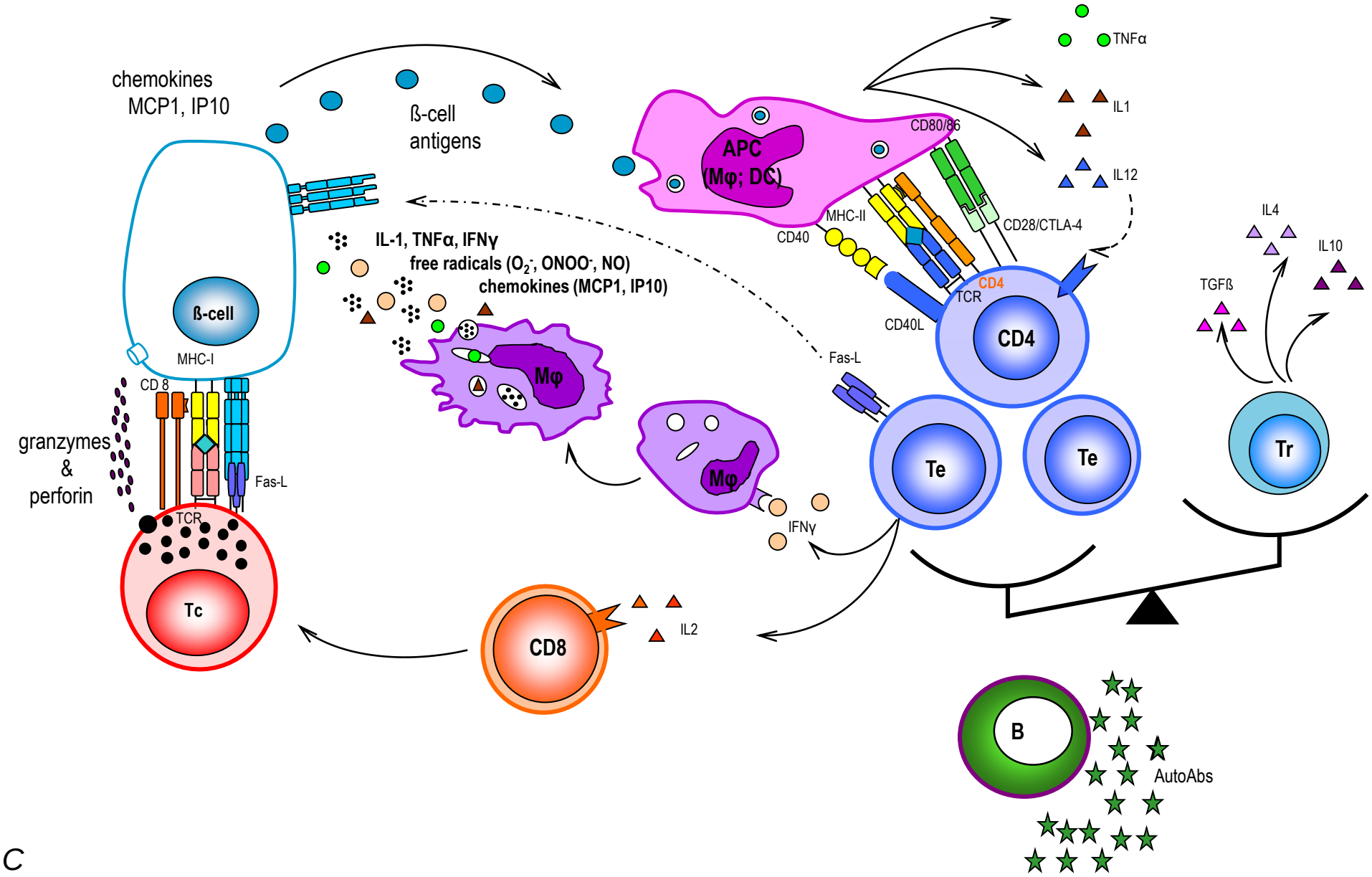
Pourquoi n’a t’on pas encore arrêté cette maladie?

- Phase préclinique prolongée
- Jeunes et enfants
- Modèle animal
- Tissu cible (cellule bèta): accès difficile, visualisation
- Marqueurs dans le sang

Arrêter T1D: Qu’avons-nous appris?

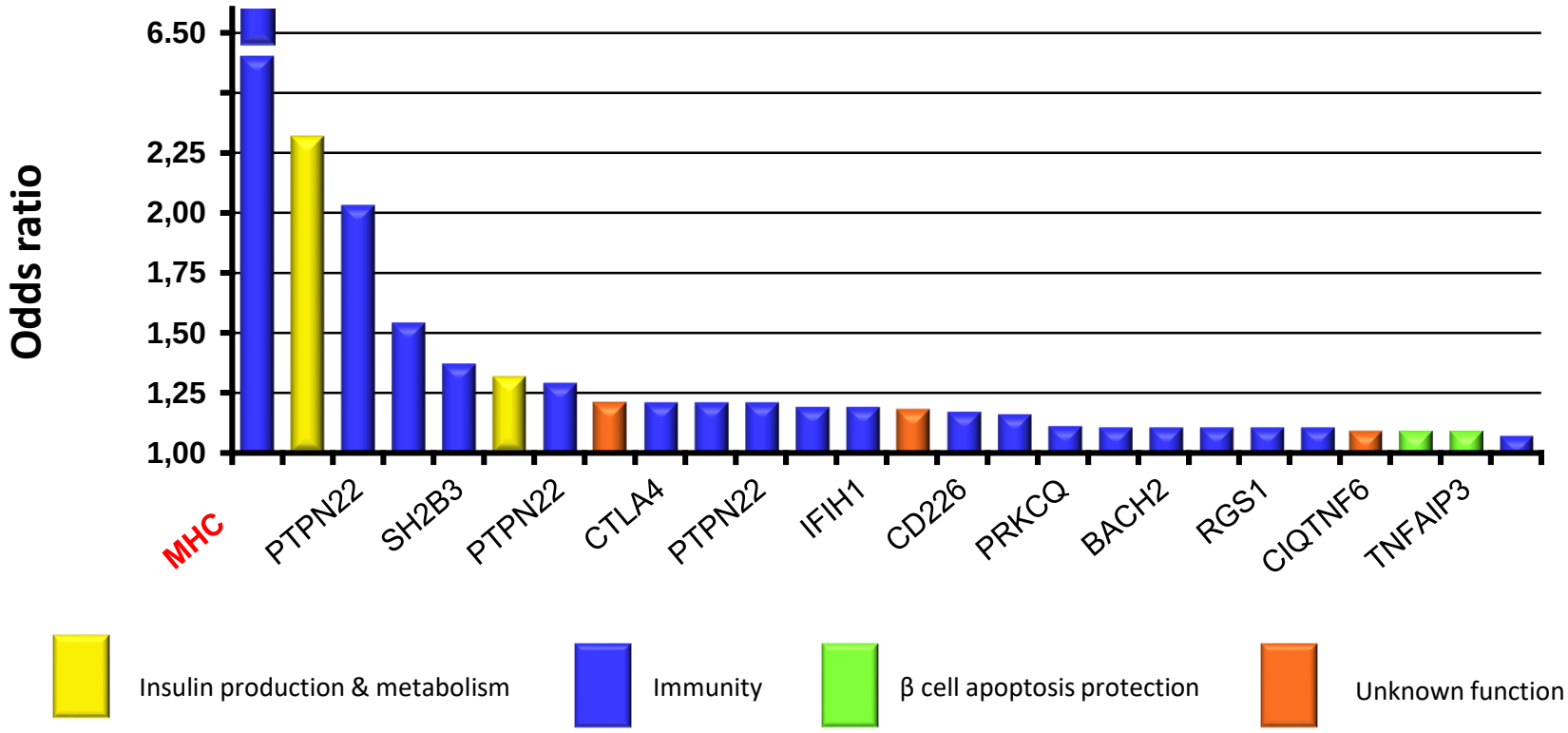
- Le système immunitaire joue un rôle central

Comment les cellules bèta sont-elles détruites en T1D?



Gysemans C

Prédisposition génétique



HLA, human leukocyte antigen.

Concannon P, et al. N Engl J Med 2009;360:1646–54.

INCIDENCE de T1D

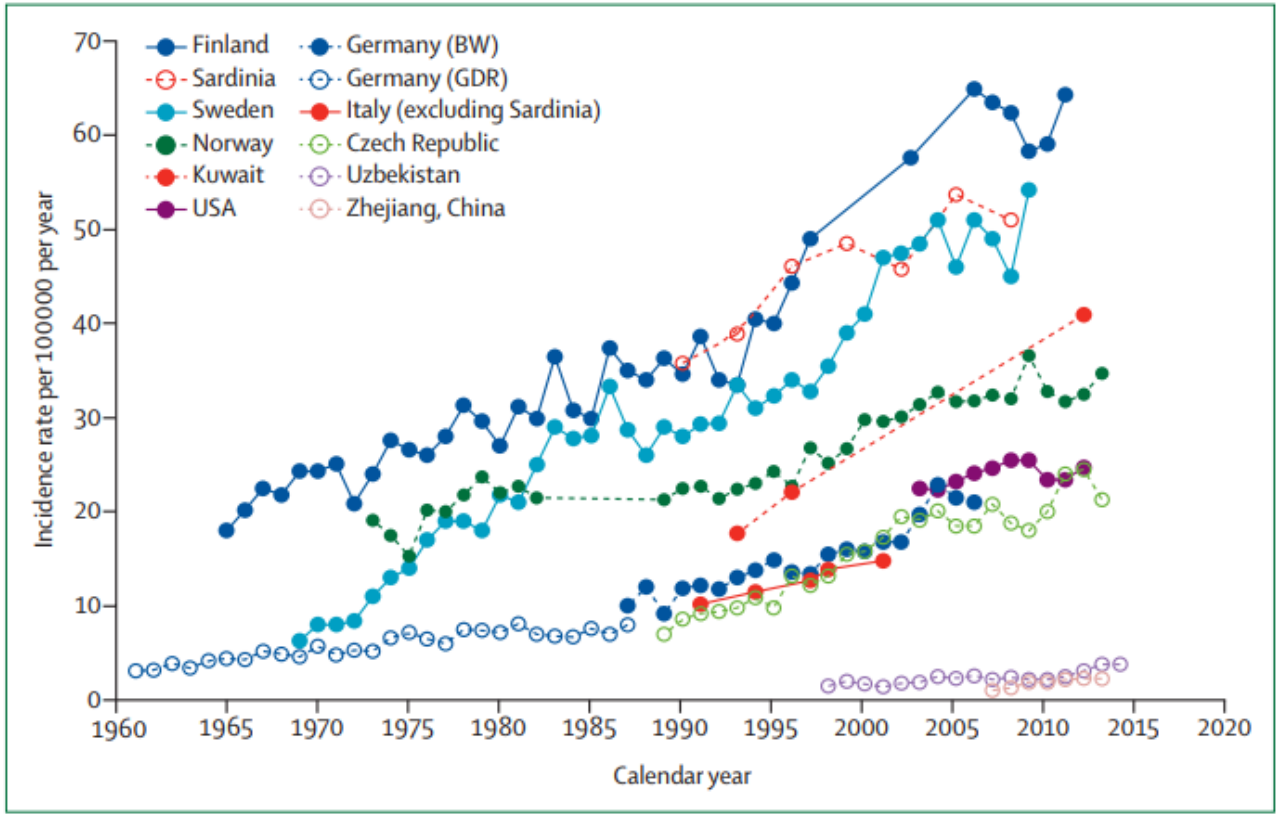


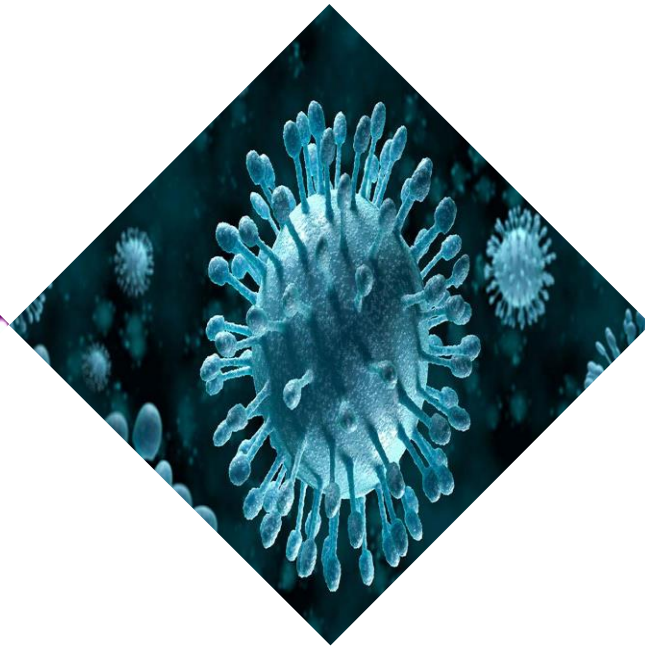
Figure 1: **Time trends in incidence of type 1 diabetes**
Published data taken from references listed in the appendix pp 1,5–6. GDR=German Democratic Republic (former Eastern Germany). BW=Baden-Württemberg.

Norris JM et al. Lancet Diabetes Endocrinol 2020

Déclancheurs

Toxins

Virus

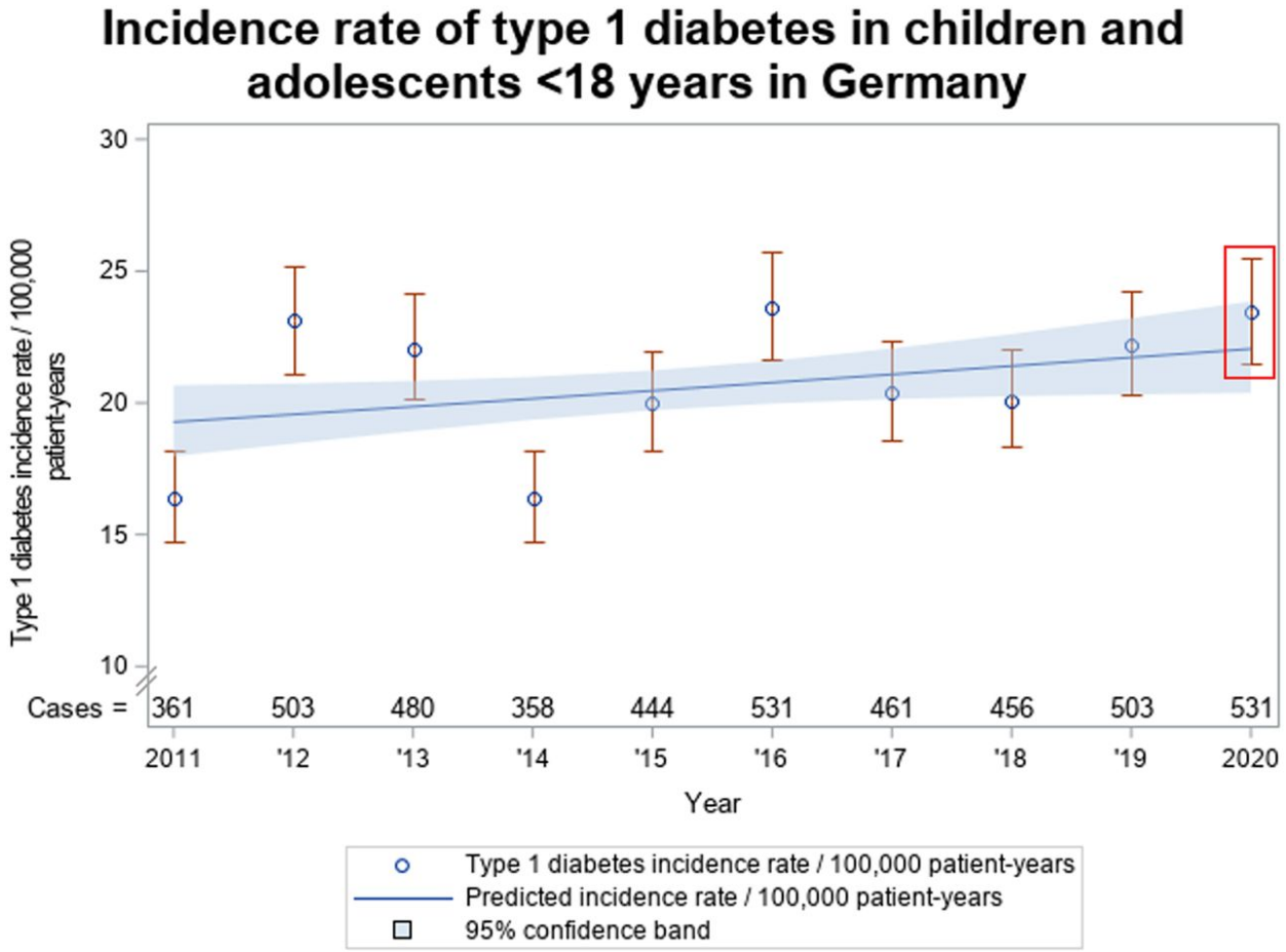


Diet

Microbiome

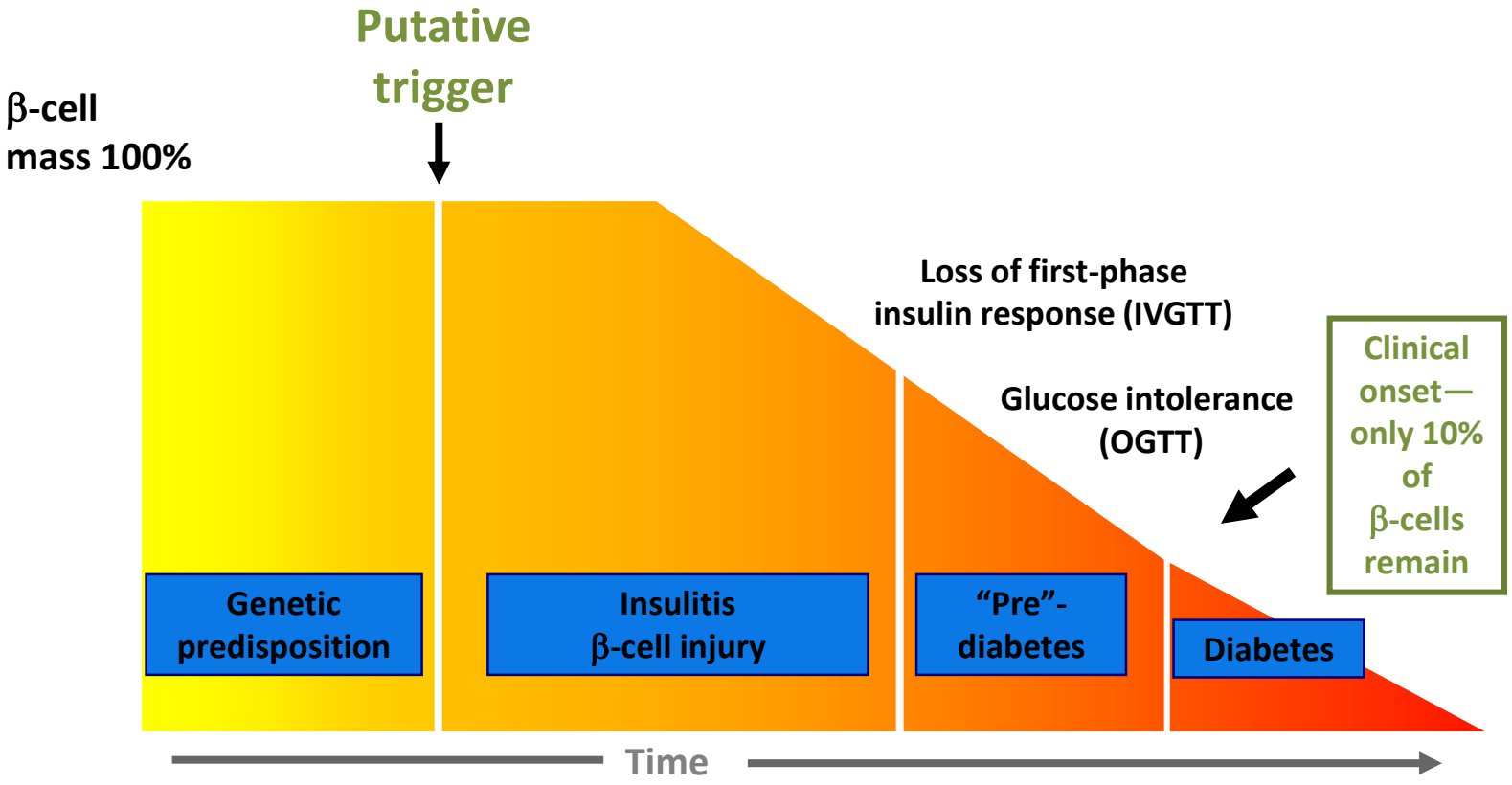
Rewers M et al. Curr Diab Rep 2013

INCIDENCE de T1D… COVID



Tittel SR et al. Diabetes Care 2020

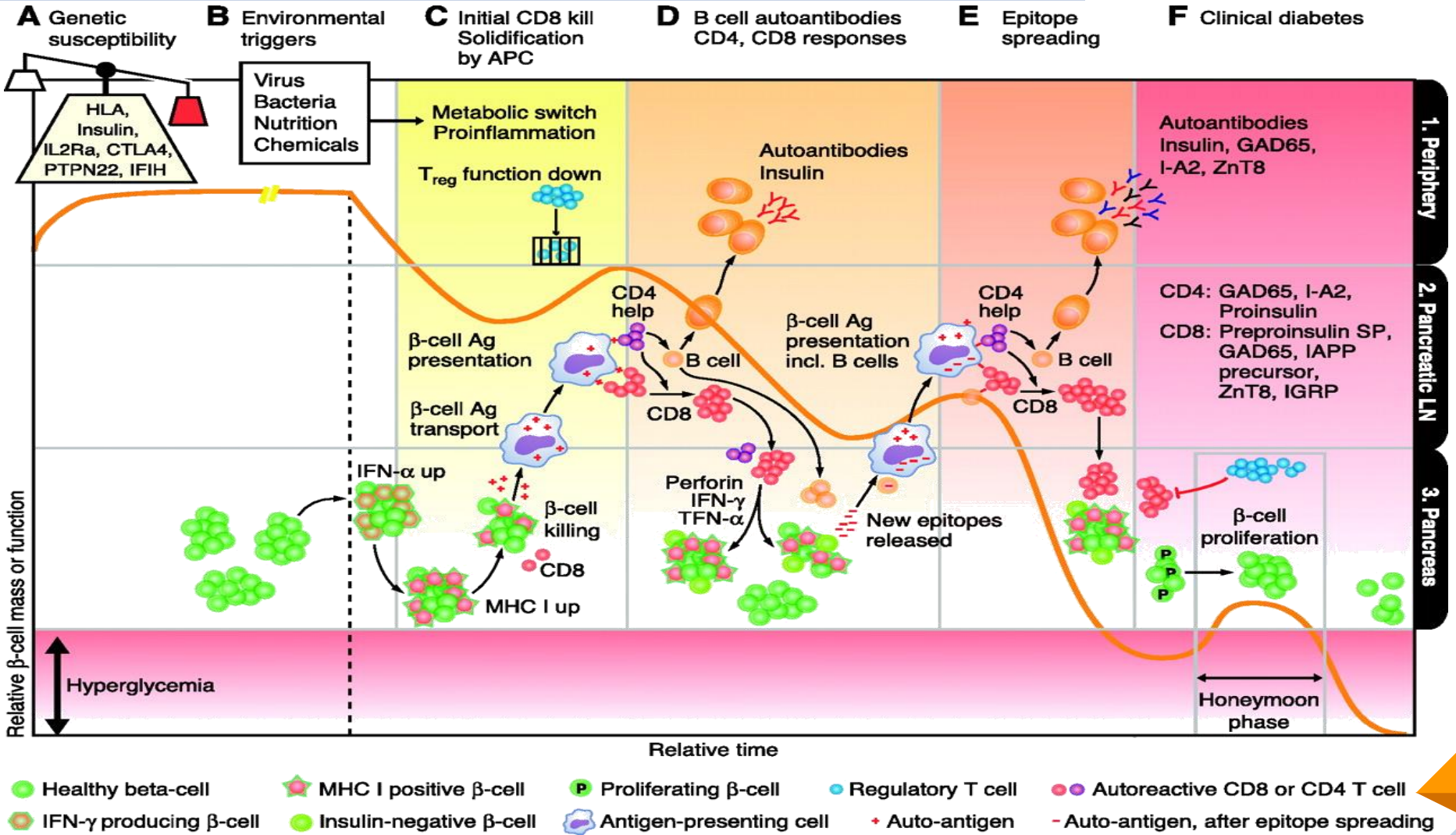
Histoire naturelle de T1D



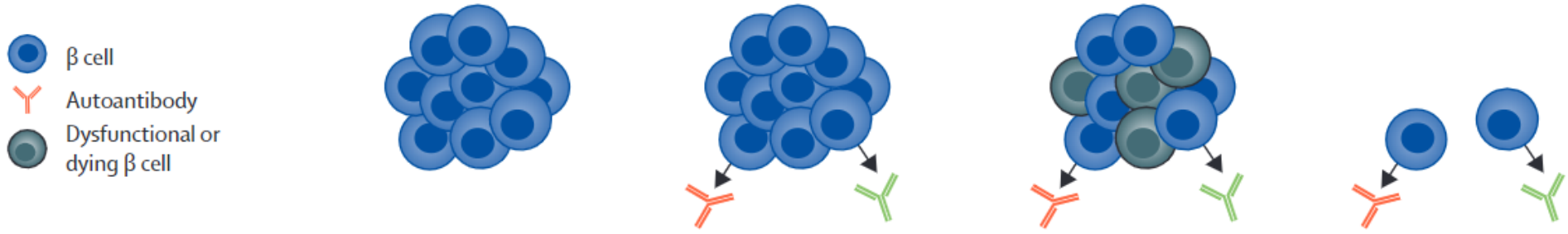
GAD65, glutamic acid decarboxylase; ICA, islet cell antibodies; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

Eisenbarth GS. N Engl J Med 1986;314:1360–8.

Histoire naturelle de T1D



Arrêter T1D: Qu'avons-nous appris?



	Stage 0	Stage 1	Stage 2	Stage 3
Defining characteristics	• 0–1 positive autoantibodies • No dysglycaemia • Clinically asymptomatic	• ≥2 positive autoantibodies • No dysglycaemia • Clinically asymptomatic	• 2 positive autoantibodies • Dysglycaemia • Clinically asymptomatic	• 2 positive autoantibodies • Hyperglycaemia • Clinically symptomatic
β-cell mass	100%	100%	100% (decrease starting 6 months before stage 3)	10–20%
Prevention trial category	Primary prevention	Secondary prevention	Secondary prevention	Tertiary prevention
Past prevention trial examples	• TRIGR (cow milk protein) • FINDIA (bovine insulin) • BABYDIET (gluten)	• DENIS (nicotinamide) • ENDIT (nicotinamide) • Belgian trial (parenteral insulin) • DPT-1 (oral insulin) • DIPP (intranasal insulin) • TrialNet study (oral insulin) • DIAPREV-IT (GAD-alum)	• DPT-1 (parenteral insulin) • DIAPREV-IT (GAD-alum) • TrialNet teplizumab (anti-CD3 monoclonal antibody)	• Haller et al (2019)[20] • Rigby et al (2015)[21] • Herold et al (2002)[22] • Keymeulen et al (2005)[23] • Orban et al (2011)[24] • Pescovitz et al (2009)[25]

Dayan CM et al Lancet 2021

Arrêter T1D: Qu’avons-nous appris?

- Le système immunitaire joue un rôle central
- Immunomodulation de longue durée prévient le diabète dans la souris NOD (et arête la progression dans l’homme….)

Immunomodulation dans la souris NOD

Anti-CD3

Immune stimulation

Cytokines

FK506

Anti-CD4

FTY20

Thymectomy

Cyclosporine A

Antibodies against cytokines

mATG

Bone marrow transplantation

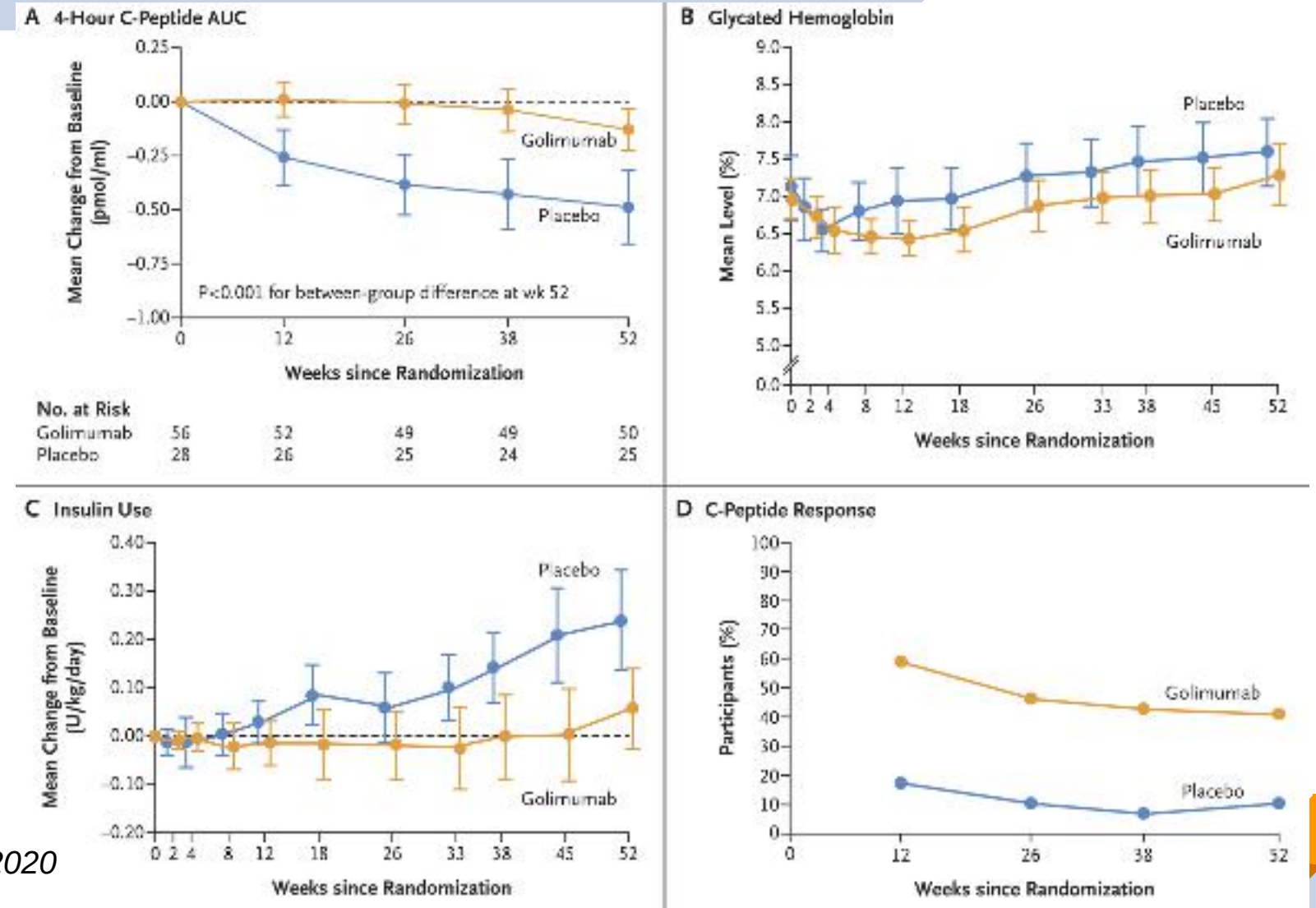
Anti-CD2

1,25-dihydroxyvitamin D

Irradiation

Rapamycin

Immunomodulation de longue durée: GOLIMUMAB



T. Quattrin et al NEJM 2020

Arrêter T1D: Qu’avons-nous appris?

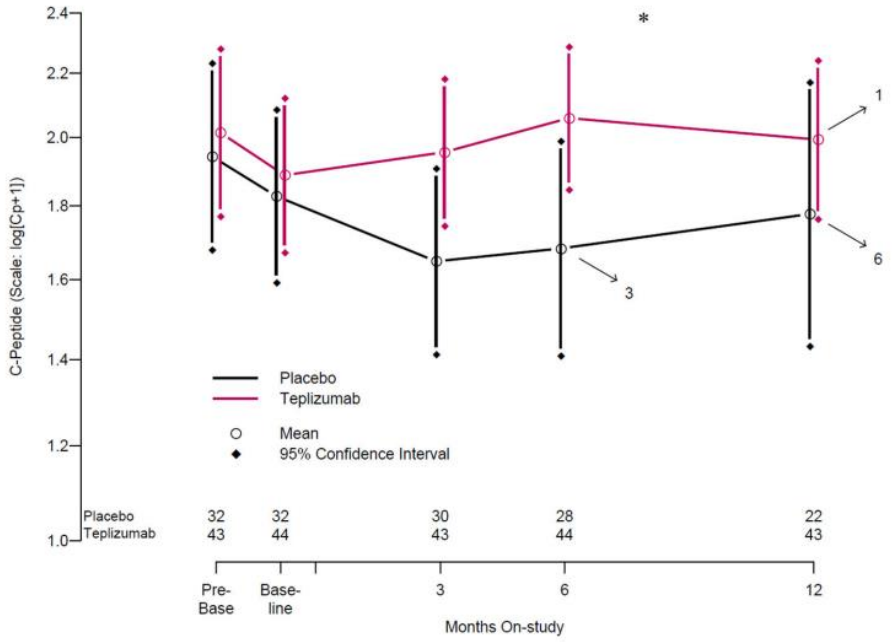
- Le système immunitaire joue un rôle central
- Immunomodulation à court terme prévient le diabète dans la souris NOD et de façon temoraire dans l’homme

ETUDES HUMAINES D'IMMUNOMODULATION

Cyclosporin	Transient effect
Teplizumab Anti-CD3	Transient effect
Otelixizumab Anti-CD3	Transient effect (dose-dependent)
Etanercept (anti-TNFα)	?? Effect
Golimumab (anti-TNFα)	?? Effect
Mycophenylate+Anti-CD25	No effect
Rituximab Anti-CD20	Transient effect
Abatacept CTLA4-Ig	Transient effect
Canakinumab Anti-IL1-β	No effect
Anakinra IL-1RA	No effect
High dose ATG	No effect
Low dose ATG (+G-CSF)	Transient effect
Rapamycin/IL-2 therapy	Worsening effect
Glivec	?? Effect

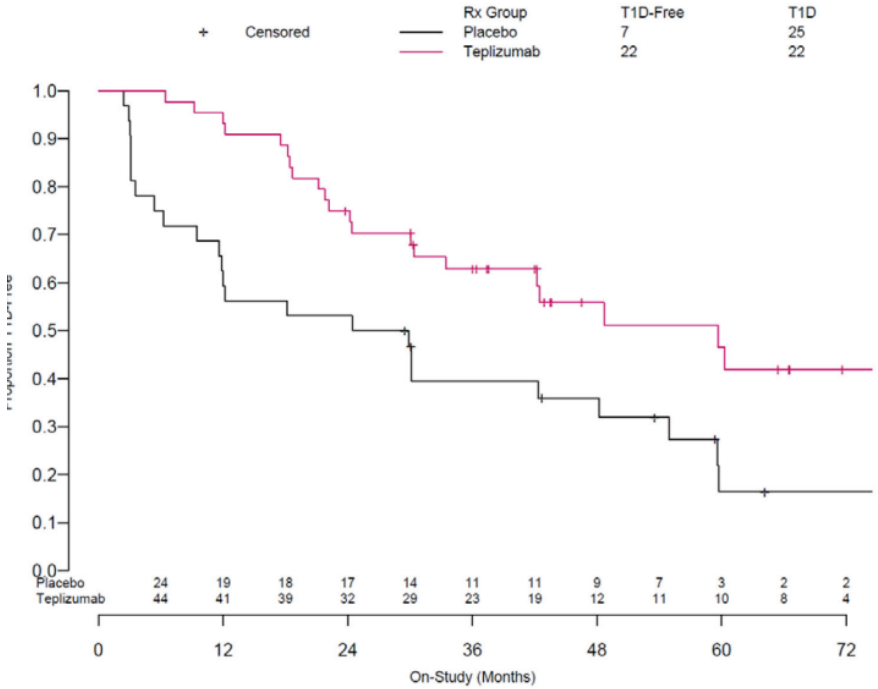
Arrêter T1D: Qu'avons-nous appris?

Teplizumab (anti-CD3 mAb) prolonge la survie des cellules bèta chez les gens à haut risque de T1D (Stage 2)



Préservation de C-peptide

Délais de 3 ans *



*32.5 mo delay (27.1 vs 59.6mo)

Sims E. et al Sci Transl Med 2021

Arrêter T1D: Qu'avons-nous appris?

Table 2. Adverse Events during Active Follow-up.*

Adverse Event Category	Teplizumab		Placebo	
	Events (N=112)	Participants (N=44)	Events (N=23)	Participants (N=32)
	no.	*no. (%)*	*no.*	*no. (%)*
Blood or bone marrow†	45	33 (75)	2	2 (6)
Dermatologic or skin†	17	16 (36)	1	1 (3)
Pain	11	5 (11)	5	3 (9)
Infection	8	5 (11)	5	3 (9)
Gastrointestinal	5	4 (9)	3	3 (9)
Metabolic or laboratory	7	4 (9)	2	2 (6)
Pulmonary or upper respiratory	6	4 (9)	0	0
Constitutional symptoms	3	2 (5)	0	0
Allergy or immunologic	2	2 (5)	0	0
Cardiac, general	1	1 (2)	1	1 (3)
Endocrine	0	0	2	2 (6)
Vascular	1	1 (2)	1	1 (3)
Neurologic	1	1 (2)	0	0
Ocular or visual	1	1 (2)	0	0
Musculoskeletal or soft tissue	2	1 (2)	0	0
Hepatobiliary or pancreatic	0	0	1	1 (3)
Syndrome	1	1 (2)	0	0
Hemorrhage or bleeding	1	1 (2)	0	0

* Events listed were attributed as possibly, probably, or definitely related to the trial agent by the trial-site investigator.
† The frequency of this type of event differed significantly between the two groups (P<0.001).

Herold K. et al NEJM 2019

Arrêter T1D: Qu’avons-nous appris?

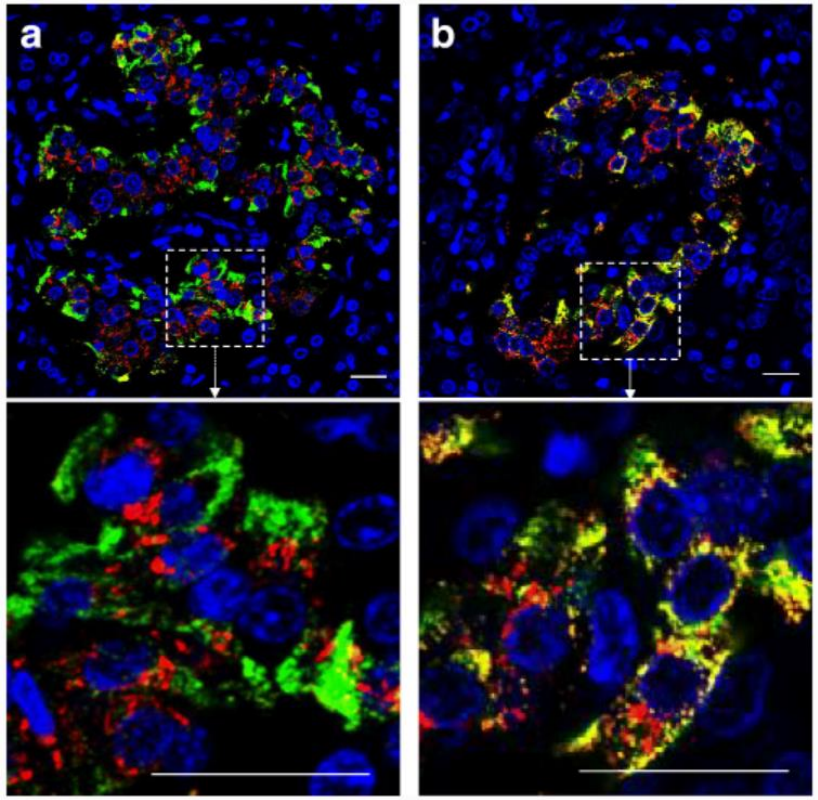
- Le système immunitaire joue un rôle central
- Immunomodulation prévient le diabète dans la souris NOD et de façon temoraire dans l’homme
- T1D est une maladie hétérogène

T1D est une maladie hétérogène

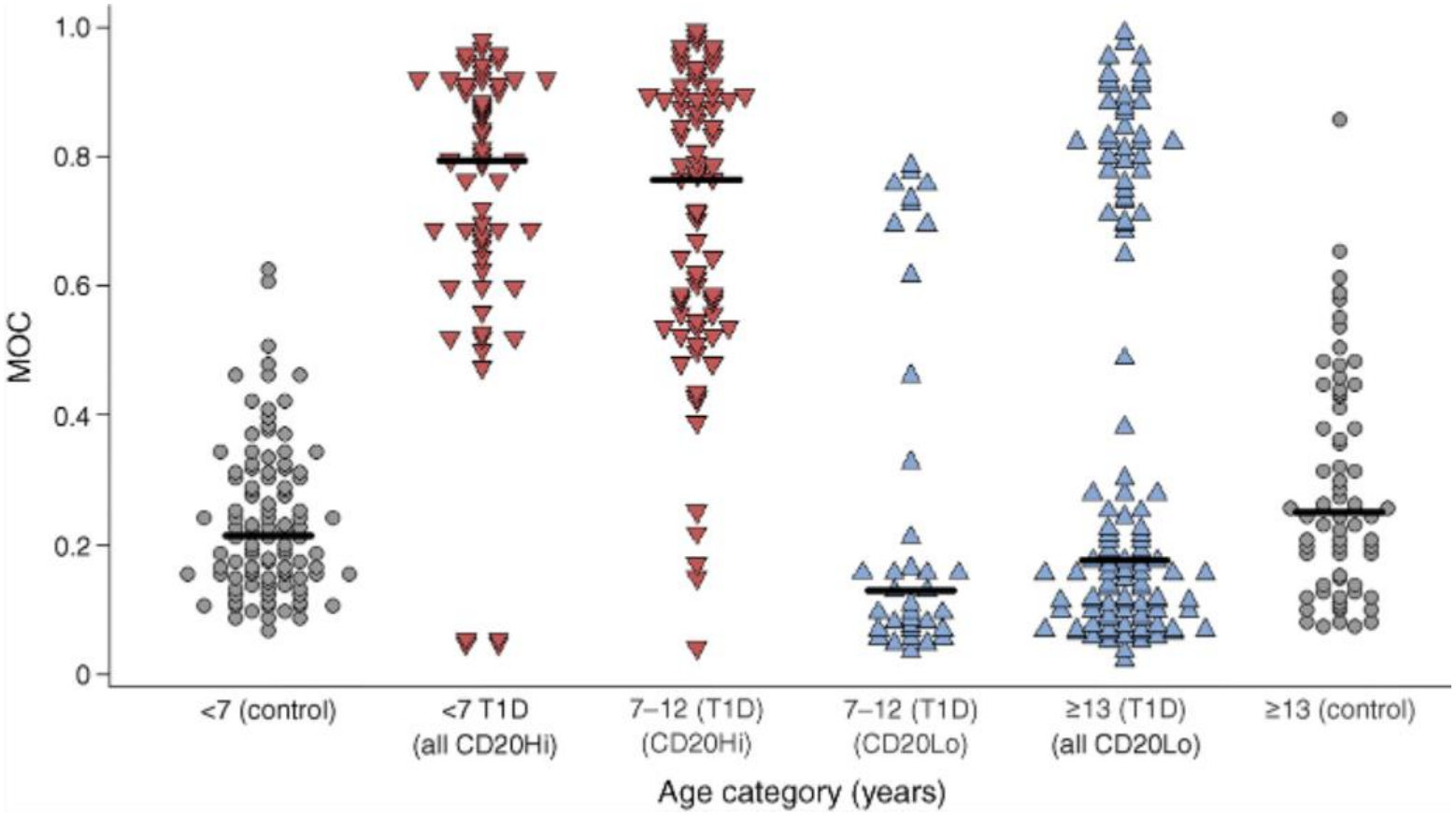
Just type 1	Type 1, Celiac disease, Graves RA, alopecia
Onset 6 months	Onset 75years
IAA	IAA, GAD, IA2, ZnT8
HbA1c 10%	HbA1c 6.5%
Cpeptide unmeasurable	Lifelong Cpeptide left
Complications	

Diagnosis
Clinical behaviour

Quality of insulitis differs by age: role of B lymphocytes



Fluorescence micrographs showing (a) Islet in which proinsulin and insulin are segregated. Enlarged region (dotted square in upper panel) is shown in the lower panel. (b) Islet with aberrant proinsulin processing. Enlarged region (dotted square in upper) is shown in lower panel. Green, insulin; red, proinsulin; yellow, co-localisation of the antigens. Scale bar, 20 μm



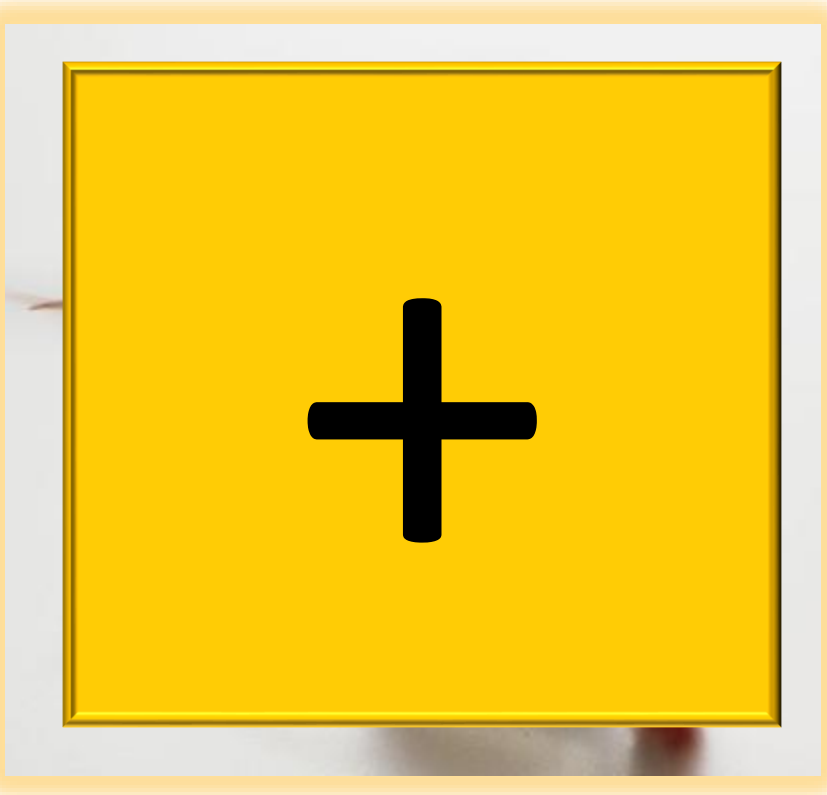
Dot plot showing distribution of the MOC (a measure of proinsulin–insulin co-localisation) in individual islets from pancreas samples obtained within 2 years of diagnosis of type 1 diabetes for individuals with disease onset at <7 years, 7–12 years and ≥13 years. Individuals in each age group were separated into CD20Hi (red) and CD20Lo (blue) subgroups, respectively. Data from control individuals without diabetes are presented as grey circles for those aged <7 years (far left) or ≥13 years (far right). Black horizontal bars represent median values for each group

Leete P et al. Diabetologia 2020

Arrêter T1D: Qu’avons-nous appris?

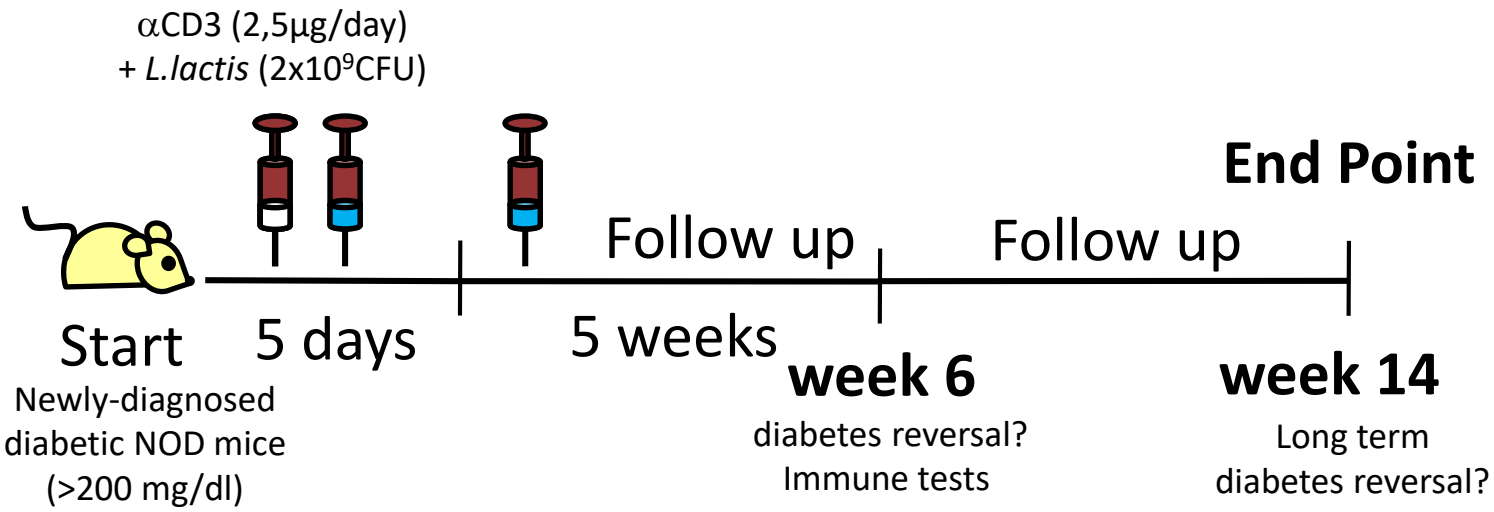
- Le système immunitaire joue un rôle central
- Immunomodulation prévient le diabète dans la souris NOD et de façon temoraire dans l’homme
- T1D est une maladie hétérogène
- Combinaisons de thérapies

Induction de tolérance



Immunomodulation

Experimental design

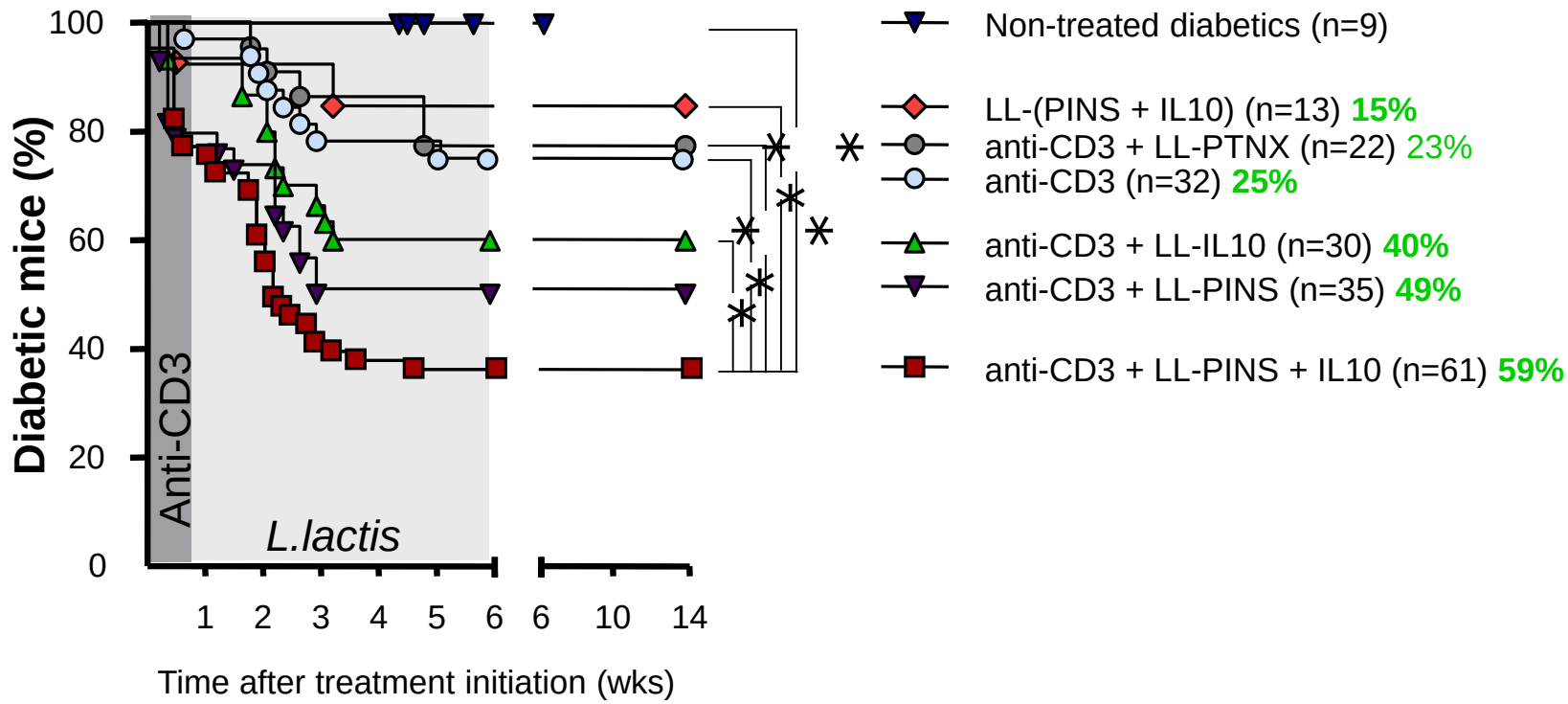


Groups:

Group 1: αCD3
Group 2: αCD3 + *L.lactis* with empty vector (LL-pT1NX)
Group 3: αCD3 + *L.lactis* secreting pro-insulin + IL-10 (LL-pins + hIL-10)
Group 4: αCD3 + *L.lactis* secreting pro-insulin (LL-pins)
Group 5: αCD3 + *L.lactis* secreting IL-10 (LL-hIL-10)
Group 6: *L.lactis* secreting pro-insulin + hIL-10

Takiishi et al JCI 2012, 122(5): 1717-25

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.

Takiishi et al. JCI 2012, 122(5): 1717-25

Precigen ActoBio Announces Positive Topline Results from Phase 1b Study of AG019 ActoBiotics™, A Novel Therapy Designed to Address the Underlying Cause of Type 1 Diabetes

- Primary endpoint met assessing safety and tolerability in the Phase 1b monotherapy portion of the study -

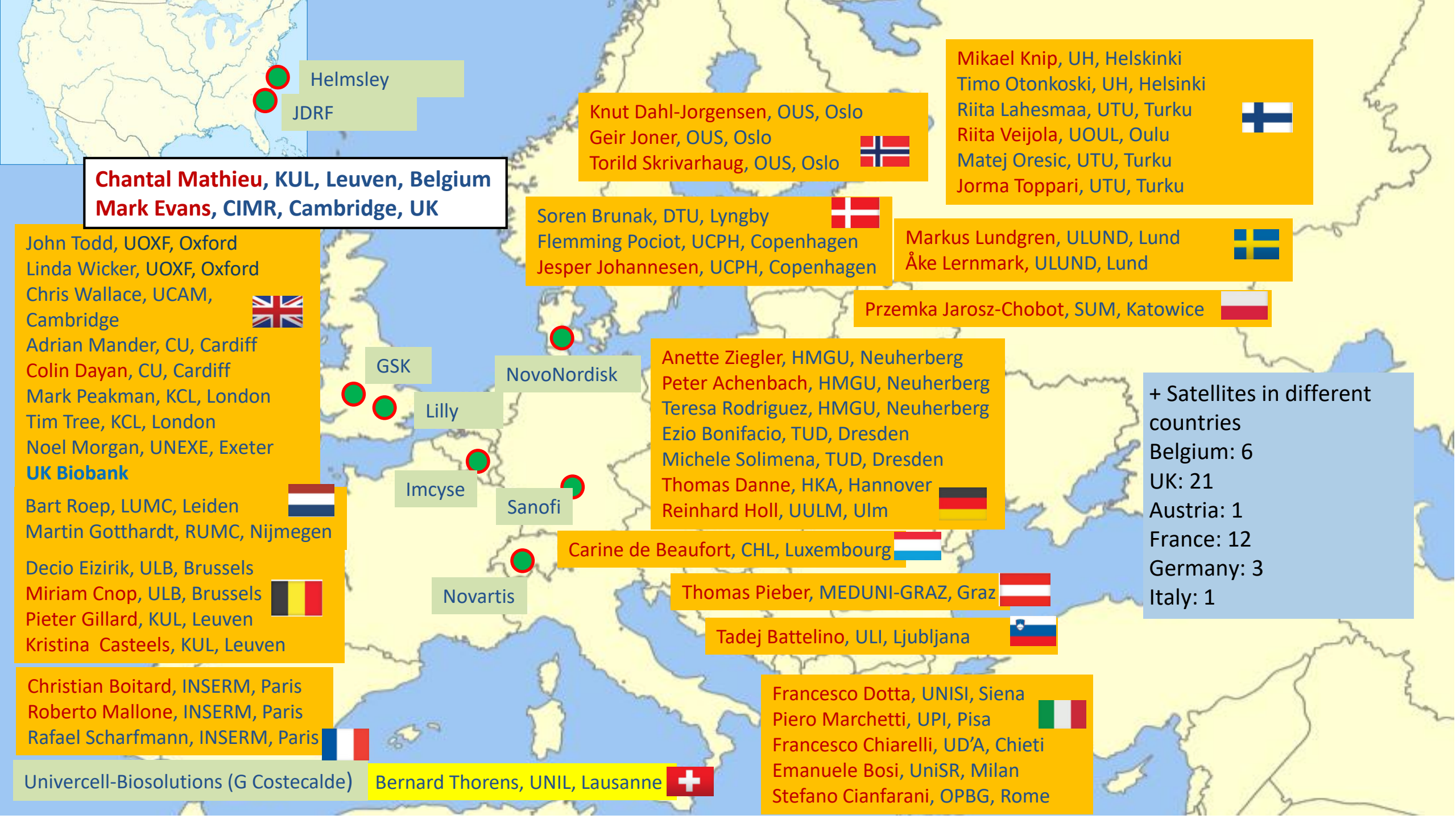
- Preliminary results demonstrate an encouraging trend in C-peptide levels, a biomarker for T1D disease progression -

- Preliminary data shows an increase in the frequency of islet-specific Tregs, a potential mechanistic indicator of therapeutic activity -

PRECIGEN ACTOBIO

August 10th 2020

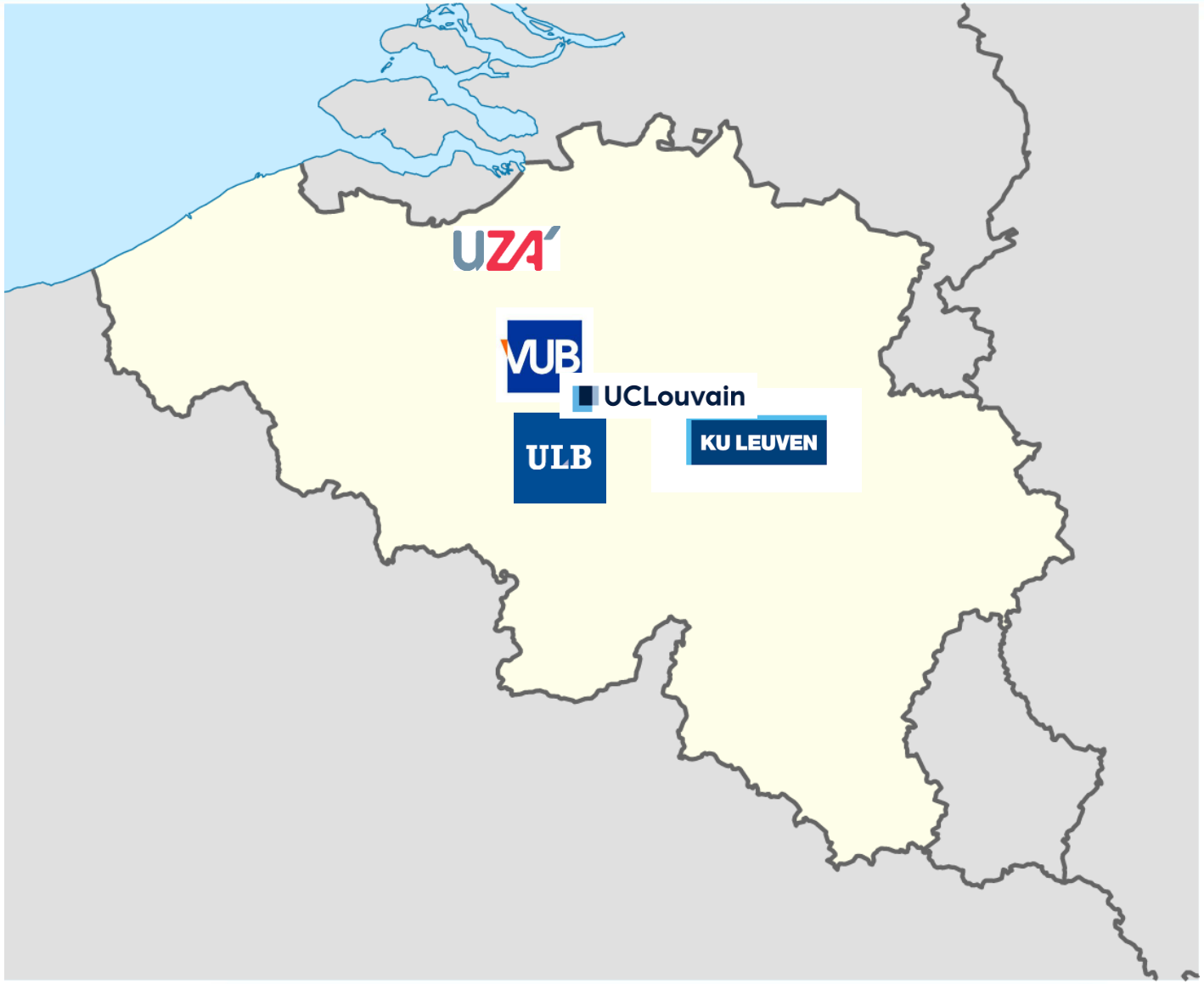
www.innodia.eu


Helmsley
JDRF
Chantal Mathieu, KUL, Leuven, Belgium
Mark Evans, CIMR, Cambridge, UK
John Todd, UOXF, Oxford
Linda Wicker, UOXF, Oxford
Chris Wallace, UCAM, Cambridge
Adrian Mander, CU, Cardiff
Colin Dayan, CU, Cardiff
Mark Peakman, KCL, London
Tim Tree, KCL, London
Noel Morgan, UNEXE, Exeter
UK Biobank
Bart Roep, LUMC, Leiden
Martin Gotthardt, RUMC, Nijmegen
Decio Eizirik, ULB, Brussels
Miriam Cnop, ULB, Brussels
Pieter Gillard, KUL, Leuven
Kristina Casteels, KUL, Leuven
Christian Boitard, INSERM, Paris
Roberto Mallone, INSERM, Paris
Rafael Scharfmann, INSERM, Paris
Univercell-Biosolutions (G Costecalde)
Bernard Thorens, UNIL, Lausanne
Knut Dahl-Jorgensen, OUS, Oslo
Geir Joner, OUS, Oslo
Torild Skrivarhaug, OUS, Oslo
Mikael Knip, UH, Helskinki
Timo Otonkoski, UH, Helsinki
Riita Lahesmaa, UTU, Turku
Riita Veijola, UOUL, Oulu
Matej Oresic, UTU, Turku
Jorma Toppari, UTU, Turku
Soren Brunak, DTU, Lyngby
Flemming Pociot, UCPH, Copenhagen
Jesper Johannesen, UCPH, Copenhagen
Markus Lundgren, ULUND, Lund
Åke Lernmark, ULUND, Lund
Przemka Jarosz-Chobot, SUM, Katowice
GSK
NovoNordisk
Lilly
Imcyse
Sanofi
Novartis
Anette Ziegler, HMGU, Neuherberg
Peter Achenbach, HMGU, Neuherberg
Teresa Rodriguez, HMGU, Neuherberg
Ezio Bonifacio, TUD, Dresden
Michele Solimena, TUD, Dresden
Thomas Danne, HKA, Hannover
Reinhard Holl, UULM, Ulm
Carine de Beaufort, CHL, Luxembourg
Thomas Pieber, MEDUNI-GRAZ, Graz
Tadej Battelino, ULI, Ljubljana
Francesco Dotta, UNISI, Siena
Piero Marchetti, UPI, Pisa
Francesco Chiarelli, UD'A, Chieti
Emanuele Bosi, UniSR, Milan
Stefano Cianfarani, OPBG, Rome
+ Satellites in different countries
Belgium: 6
UK: 21
Austria: 1
France: 12
Germany: 3
Italy: 1

Etudes INNODIA

	MELD-ATG A CLINICAL TRIAL BY INNODIA	Impact	Ver-A-TID A CLINICAL TRIAL BY INNODIA	CFZ533 ISCALIMAB IN COLLABORATION WITH INNODIA
Age groups (years)	**5 – 25**	**18 – 45**	**18 – 45**	**6 – 21**
Number of participants	**N=114**	**N=84**	**N=120**	**N=102**
Design	Randomised to different parallel arm of amount of trial medication (total 32 placebo) (ATG)	Randomised to different cohorts based on treatment arm and age (Immotope)	Randomised 2:1 (Verapamil SR: placebo)	Randomised 2:1 (CFZ533: placebo) (fully-human anti-CD40 monoclonal antibody non-depleting for B lymphocytes)
Treatment	**Infusion** 2 consecutive days	**Injections** 6 times fortnightly (2nd step has booster dose at 24 weeks)	**Tablets** Once daily for 1 year (titrated 120mg to 360mg)	**IV / SC** 1st dose IV, then home SC injections for 1 year
Visits	1, 2, 4 weeks 3, 6, 12 months	4, 24 and 48 weeks	4 and 6 weeks 3, 6, 9, 12 months	Monthly for 1st year, then twice per year
Duration	~12 months	~12 months	12 months	12 mo treatment ~16 - 36 mo total

Etudes INNODIA en Belgique



www.innodia.eu

Arrêter T1D: Qu’avons-nous appris?

- Le système immunitaire joue un rôle central
- Immunomodulation prévient le diabète dans la souris NOD et de façon temoraire dans l’homme
- T1D est une maladie hétérogène
- Combinaisons de therapies
- Prédiction et prévention

Ou sont les gens à haut risque…..?

www.bdronline.be

Visiteur ⁞⁞ Professionnels FR NL EN

Registre Belge du Diabète

BDR



- Accueil
- Buts
- Qui sommes-nous
- Patients diabétiques
- Apparentés
- Résultats
- Prélèvements apparentés
- Faire un don

Le Registre Belge du Diabète asbl

Le **Registre Belge du Diabète** ou **BDR** fut créé en 1989 dans le but de collecter des données chez des patients développant un diabète avant l'âge de 40 ans, ou chez des personnes présentant un tel risque. A cette fin, un réseau national de médecins et de leurs collaborateurs a été developpé.

Nouvelles

- Actions en faveur du BDR
- Actualité
- BDR dans la presse
- Communiqués de presse

De cette manière, le BDR peut réaliser les objectifs suivants pour cette tranche d'âge:

- déterminer et suivre **l'ampleur** du problème du diabète chez les enfants, les adolescents, et les jeunes adultes
- rendre possible un **diagnostic précoce** de la maladie, si possible à un stade préclinique
- identifier les **causes** sous-jacentes de la maladie et les facteurs influençant sa progression
- identifier des personnes à **haut risque** de diabète, et de ses complications
- composer, recruter, et suivre des goupes de participants dans le cadre **d'études cliniques, visant à prévenir ou guérir la maladie**
- **élaborer et distribuer l'information** sur les nouveaux développements

La production d'insuline sensible au glucose par des implants dérivés de cellules souches chez des patients diabétiques de type 1.

Pour les résultats récent cliquez ici.

Built by: Webtool-Design

Plan du site ⁞⁞ Contactez-nous ⁞⁞ Les mentions légales

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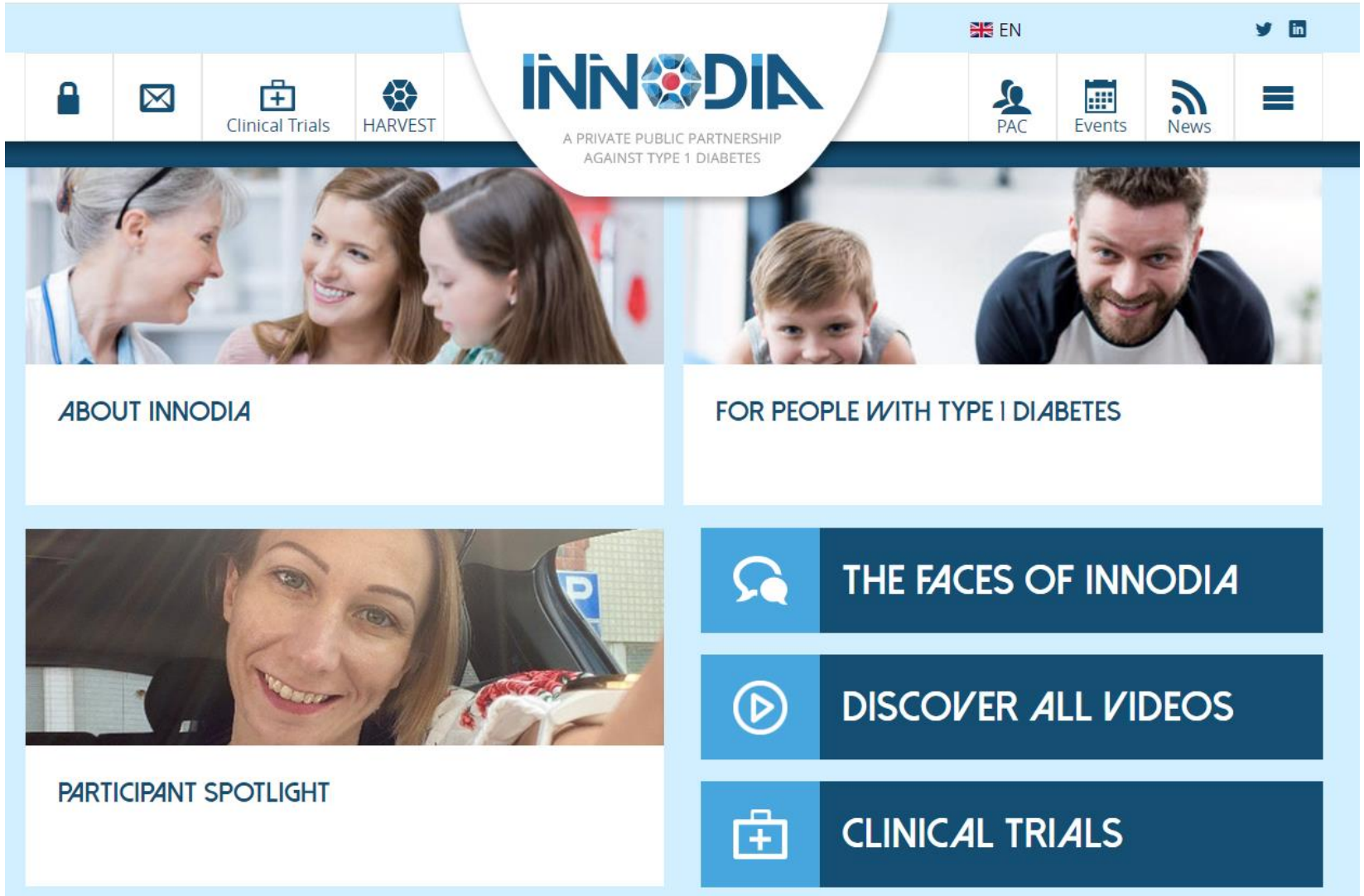

Conclusion

- Future d’ insuline, technologie…
- Future de la prévention/interventions