Modern management of childhood diabetes mellitus

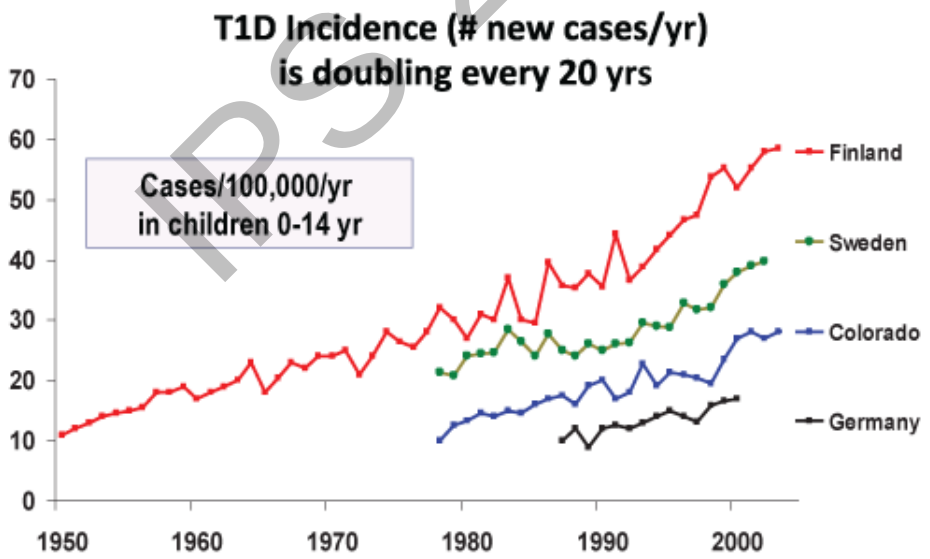
Professor Philippe LYSY, MD PhD
Pediatric endocrinology and diabetology
Institut de Recherche Expérimentale et Clinique
Université Catholique de Louvain

Type 1 diabetes (T1D) in numbers

≈ **30 million** cases worldwide

15% of T1D patients are **children**, prevalence ≈ 0.5%

In the USA, represents **$14.9 billion** annual costs



Ph. Lysy

Ann NY Acad Sci. 2008; 1150:1-13

Diagnosis of T1D

1. randomly: ≥ 200 mg/dL **+** symptoms
   (! Glycemia during ketoacidosis may be < 200 mg/dL)

   Type 1

2. fasting: ≥ 126 mg/dL

   Type 1 + others

2. 2h OGTT: ≥ 200 mg/dL
3. HbA1C: ≥ 6.5%

   Type 2 + Monogenic

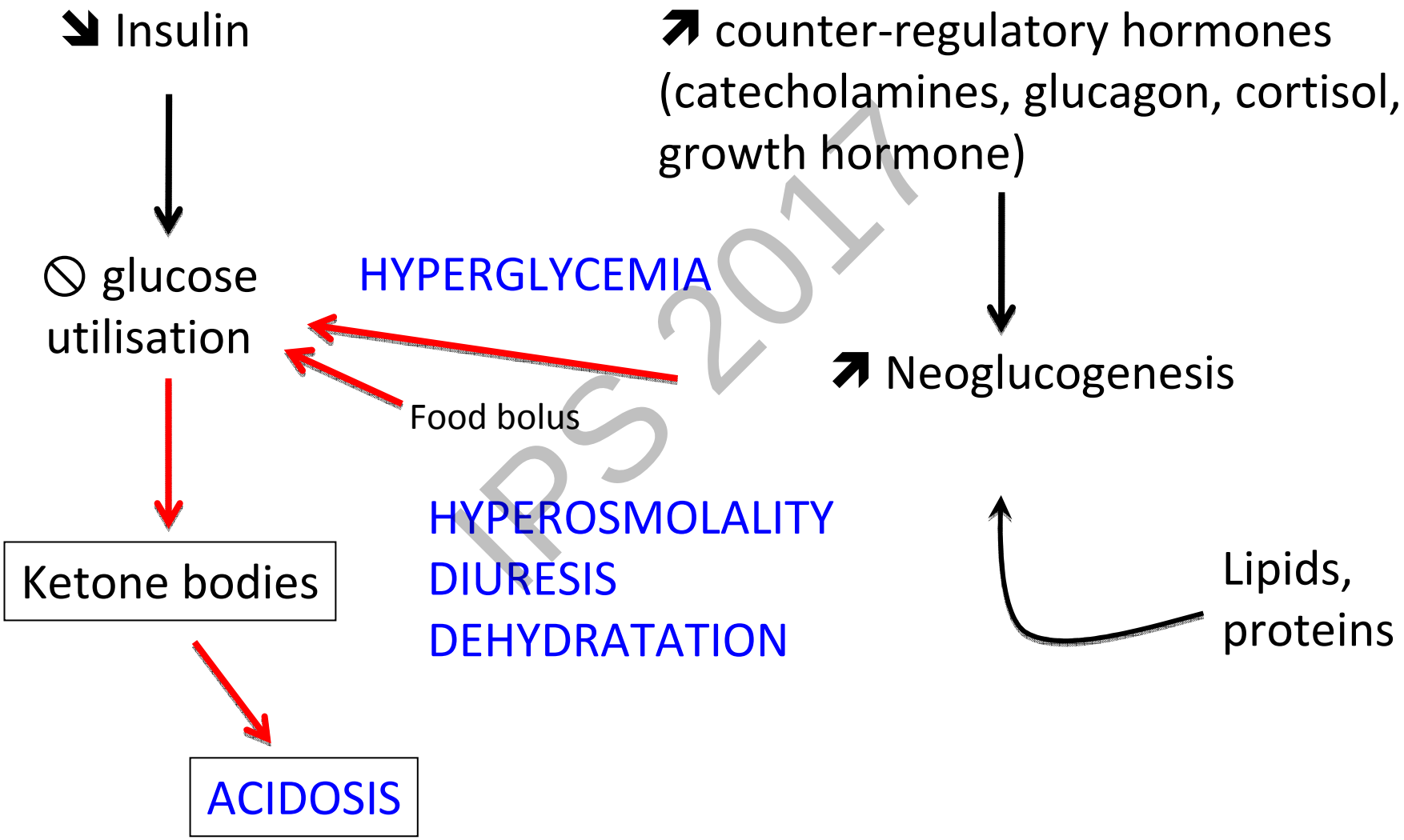
Auto-antibodies

Islet cell autoantibodies (ICA):

- Glutamic acid decarboxylase (**GAD65**).
- Insulinoma-associated antigen-2 (**IA2**, also ICA 512 or tyrosine phosphatase)
- Insulin autoantibodies (**IAA**)
- Zinc transporter (**ZnT8**)

= markers ± « pathogens » ?

Acute presentation = diabetic ketoacidosis



Diabetic ketoacidosis: diagnosis

- Hyperglycemia (≥ 200 mg/dL)
- pH <7.3 and/or bicarbonate < 15 mmol/L

Stages:

Mild = pH vein <7.30, bicarbonate <15 mM
Moderare = pH vein <7.2, bicarbonate <10 mM
Severe = pH vein <7.1, bicarbonate <5 mM

→ Intraveinous insulin therapy

Types of insulin

Current insulins = human biosynthetic

ANALOGUES = structurally modified

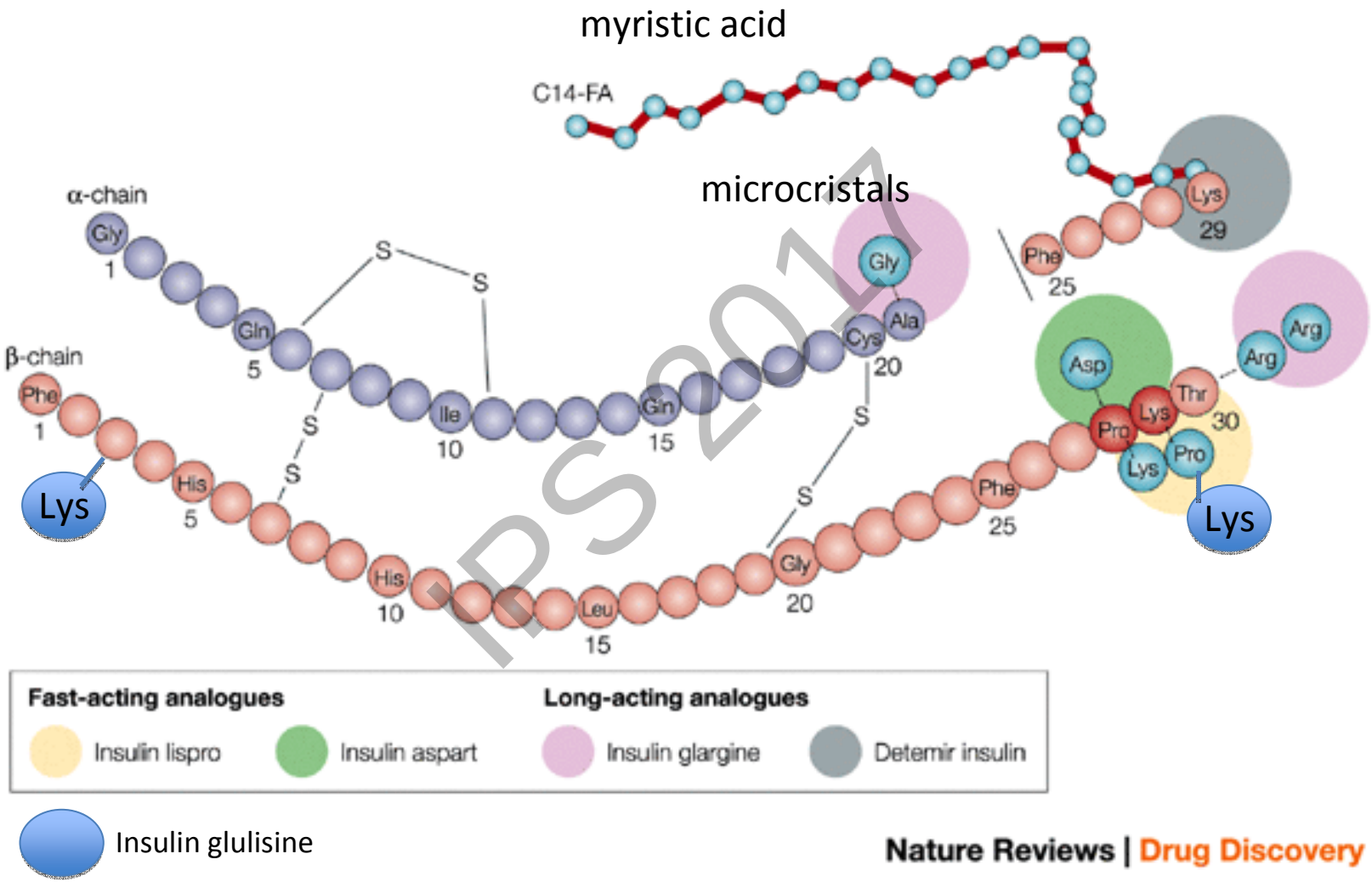
Before: porcine/bovine -> immunogenic

2 groups of insulin:

Rapids

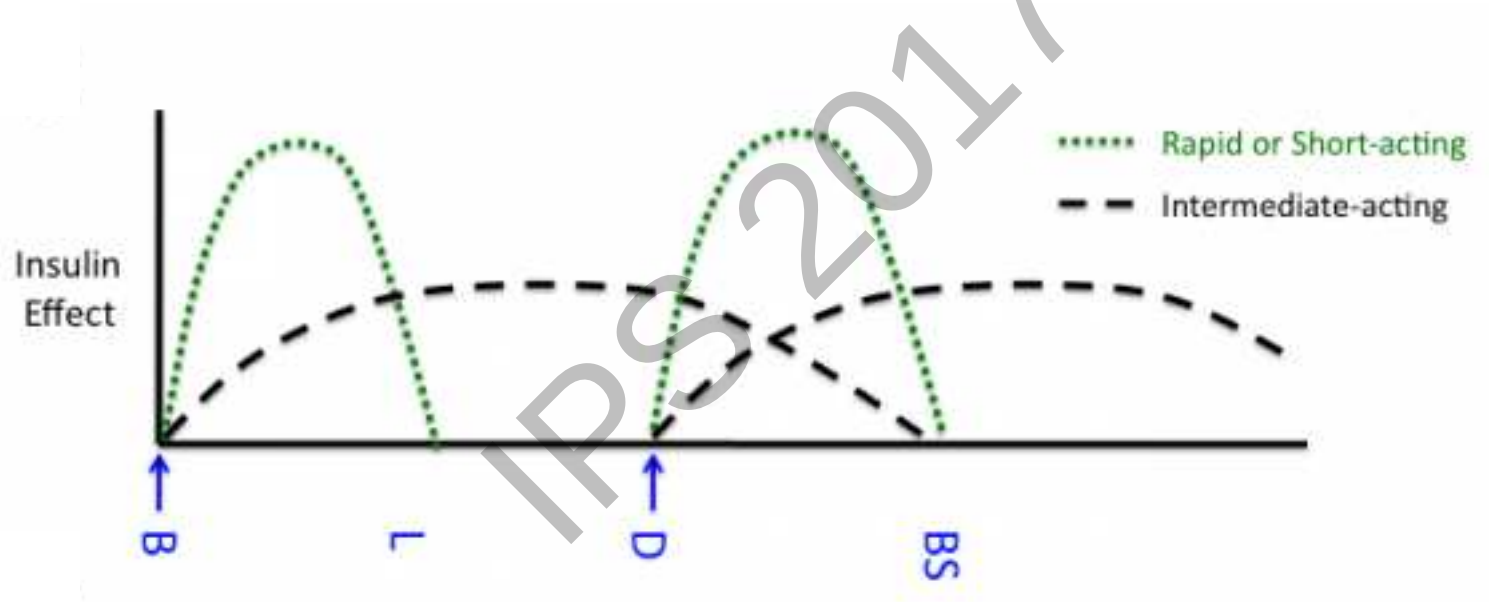
Long-acting

Structure of analogues



Insulin treatment:
1) subcutaneous injections

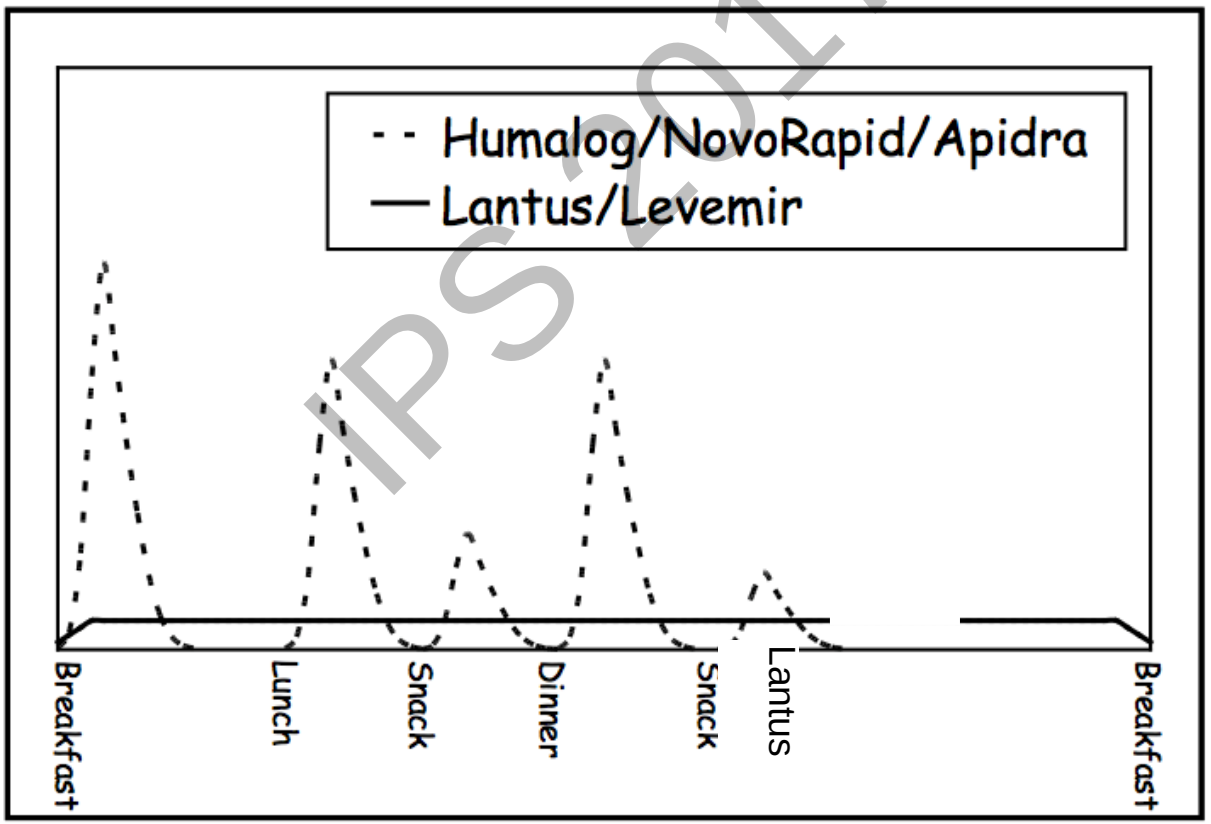
- Schemes
  - 2 injections



  - Indications: young children

Insulin treatment:
1) subcutaneous injections

- Schemes
  - 5 injections (basal bolus / ‘multiple daily injections’)



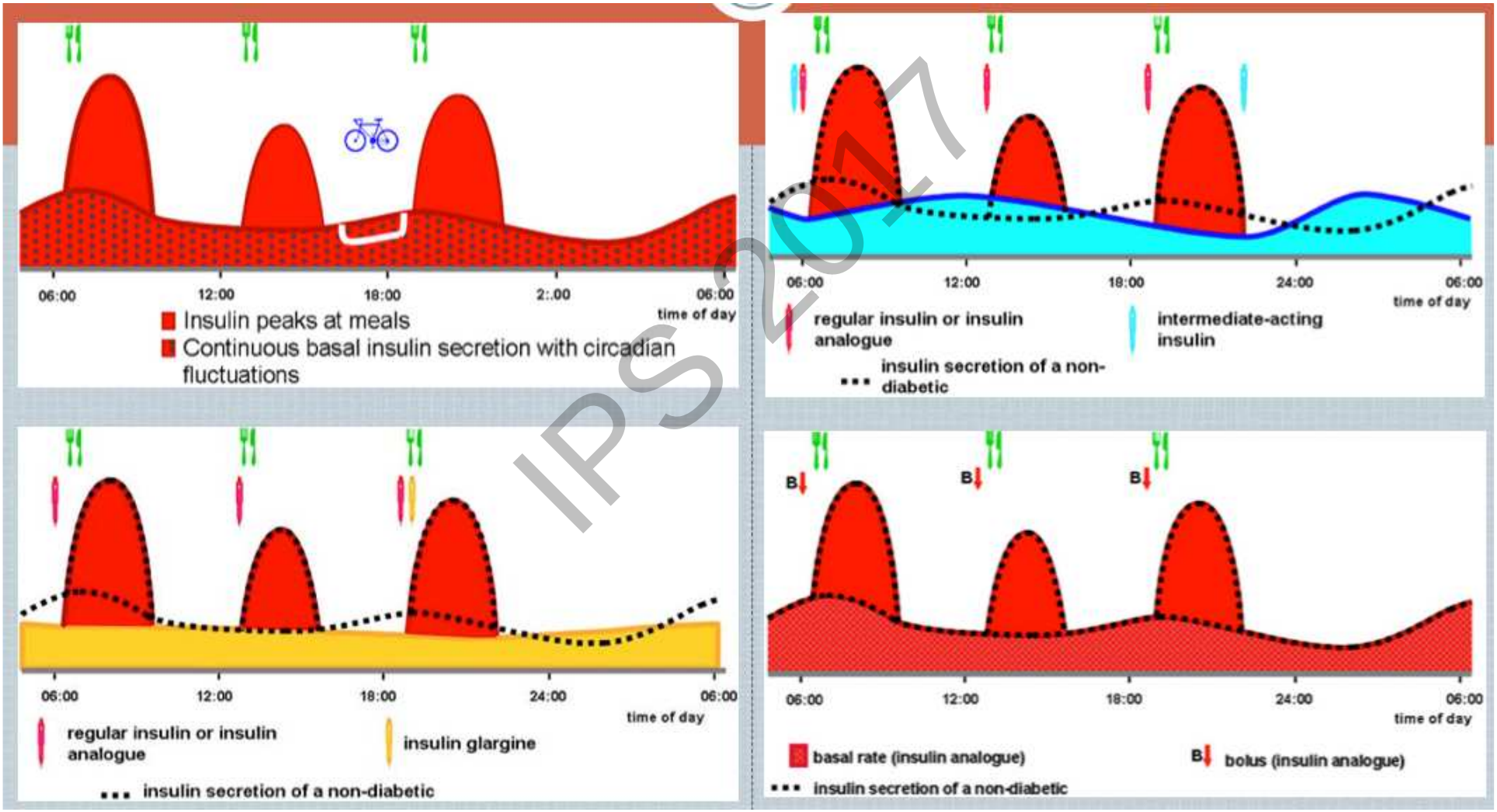
Insulin treatment:
2) continuous insulin subcutaneous infusion (insulin pump therapy)

Medtronic 640g

Accu-Check Insight (Roche)

Omnipod
(Insulet Corporation)

Insulin treatment:
2) continuous insulin subcutaneous infusion (insulin pump therapy): reproduce physiology



Insulin pump therapy: efficacy?

Diabetologia. 2008 Jun;51(6):941-51. doi: 10.1007/s00125-008-0974-3. Epub 2008 Mar 20.

Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis.

Jeitler K[1], Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, Siebenhofer A.

Exp Clin Endocrinol Di

Benefits of cor

Levy-Shraga Y[1], Ler

Diabetes Care. 2013 J

Insulin regime **Youth study.**

Pihoker C[1], Badaru Klingensmith GJ; SEARCH for Diabet

Diabetologia. 2013 Nov

Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study.

Johnson SR[1], Cooper MN, Jones TW, Davis EA.

Pediatr Diabetes. 2014 Feb 4. doi: 10.1111/pedi.12121. [Epub ahead of print]

Insulin pump use in young children in the T1D Exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy.

Blackman SM[1], Raghinaru D, Adi S, Simmons JH, Ebner-Lyon L, Chase HP, Tamborlane WV, Schatz DA, Block JM, Litton JC, Raman V, Foster NC, Kollman CR, Dubose SN, Miller KM, Beck RW, Dimeglio LA.

Nat Rev Endocrinol. 2013 Nov;9(11):629-30. doi: 10.1038/nrendo.2013.190. Epub 2013 Oct 1.

Diabetes: Insulin pumps in children with T1DM--we told you so.

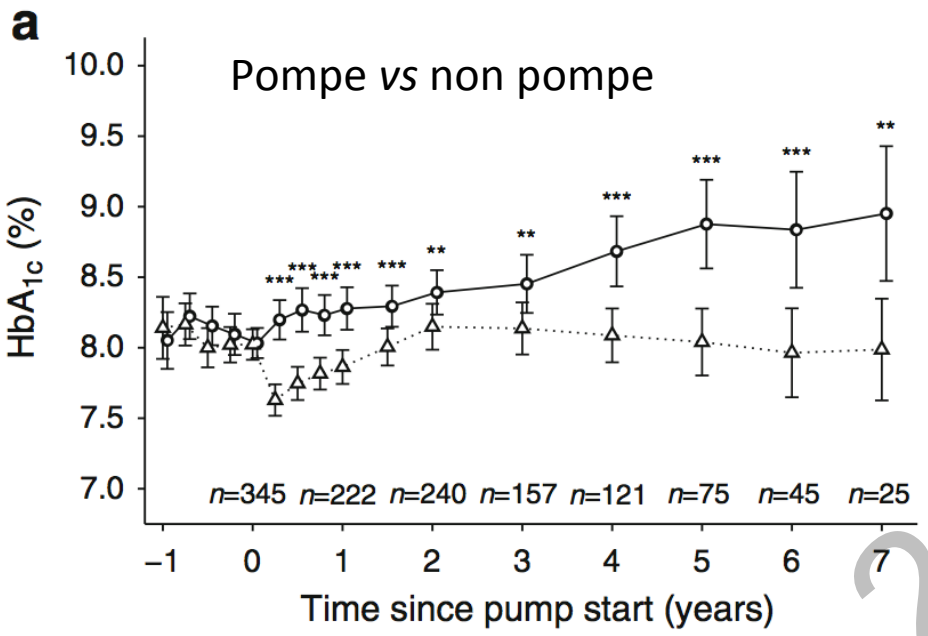
Tamborlane WV[1], Sherr JL.

Author information

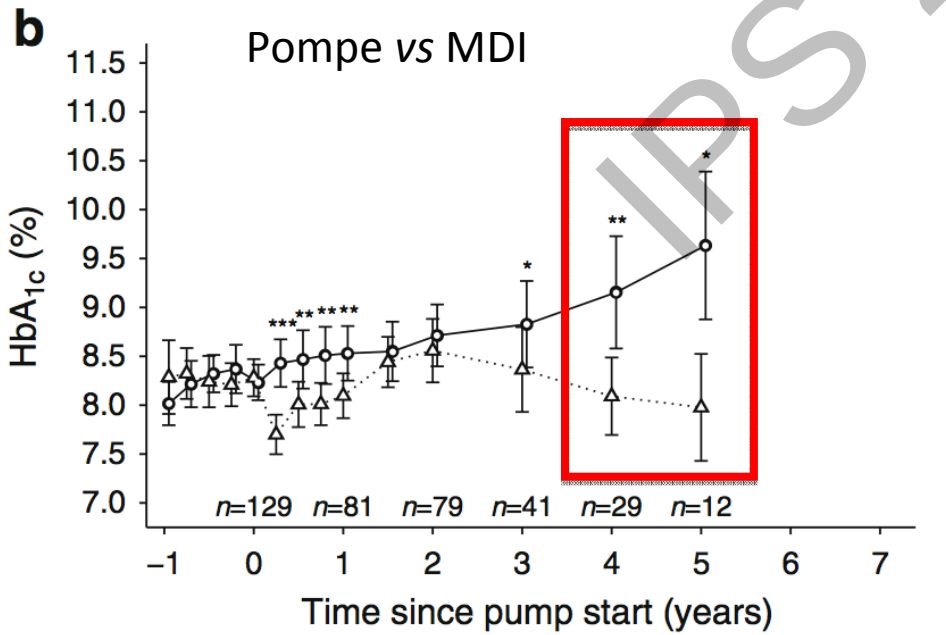
Comment on

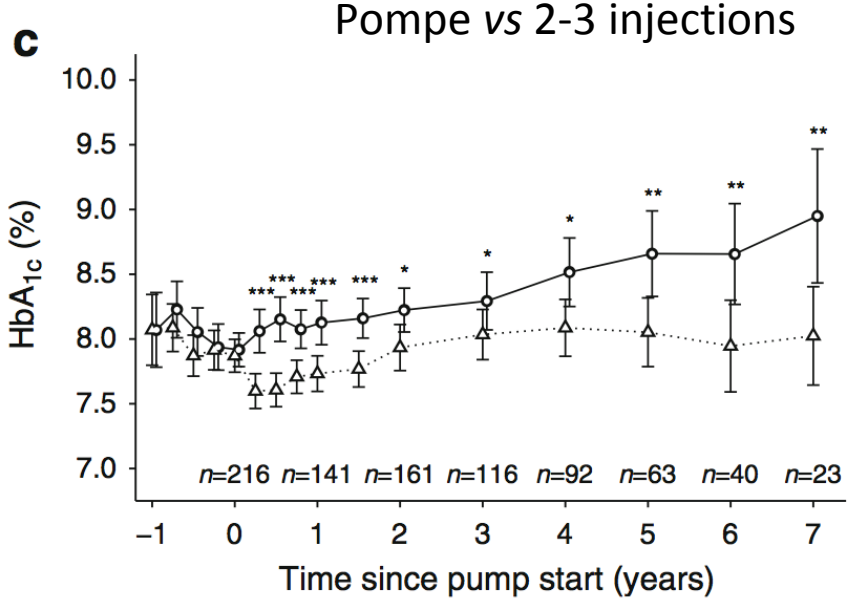
Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed i 2013]

Johnson *Diabetologia* 2013



Demographics	Pump cohort	Matched non-pump cohort	*p* value
n	355	355	
Age at diagnosis (years)	7.3 (3.5)	7.4 (3.5)	0.859
Age at pump start (years)	11.5 (3.7)	11.5 (3.7)[b]	0.952
Diabetes duration at pump start (years)	4.1 (3.0)	4.1 (3.0)[b]	0.891
Length of follow-up (years)	3.5 (2.5)	3.6 (2.5)	0.229
Sex			0.016*
Girls (*n*)	200	169	
Boys (*n*)	155	186	
HbA_{1c} (%)	8.0 (1.0)	8.0 (1.0)	0.566
HbA_{1c} (mmol/mol)	63.9 (10.9)	63.9 (10.9)	
Severe hypoglycaemia rate[a]	14.7	6.8	0.001**
DKA hospitalisation rate[a]	2.0	1.1	0.366
BMI *z* score	0.69 (0.79)	0.78 (0.83)	0.113

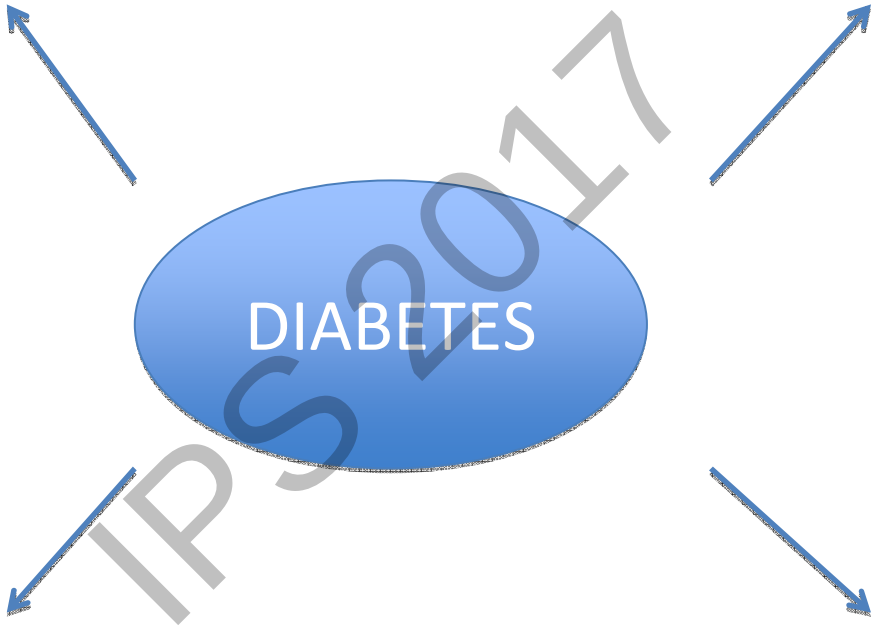




Ways to explore ?

Prevent disease onset
= primary prevention

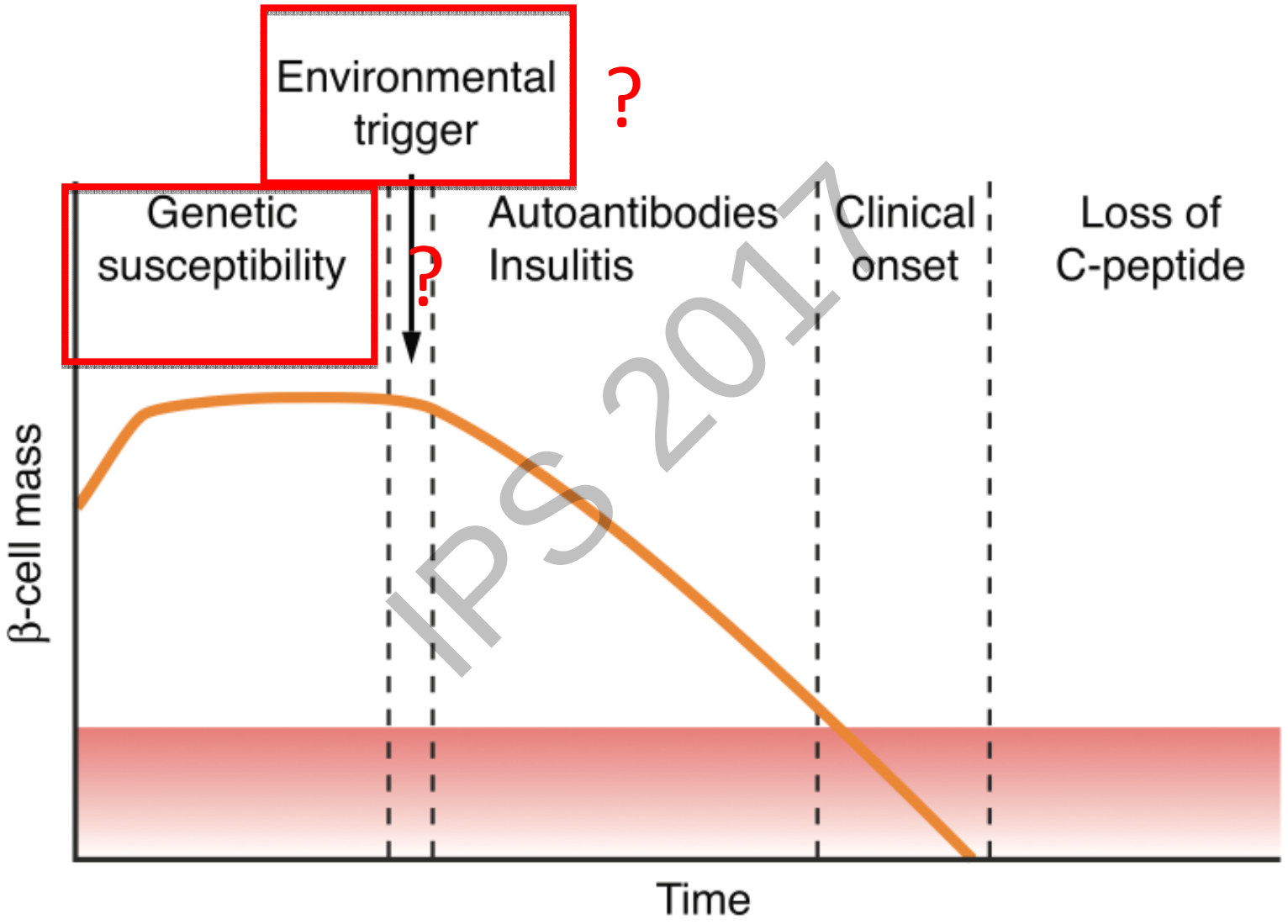
Improve care



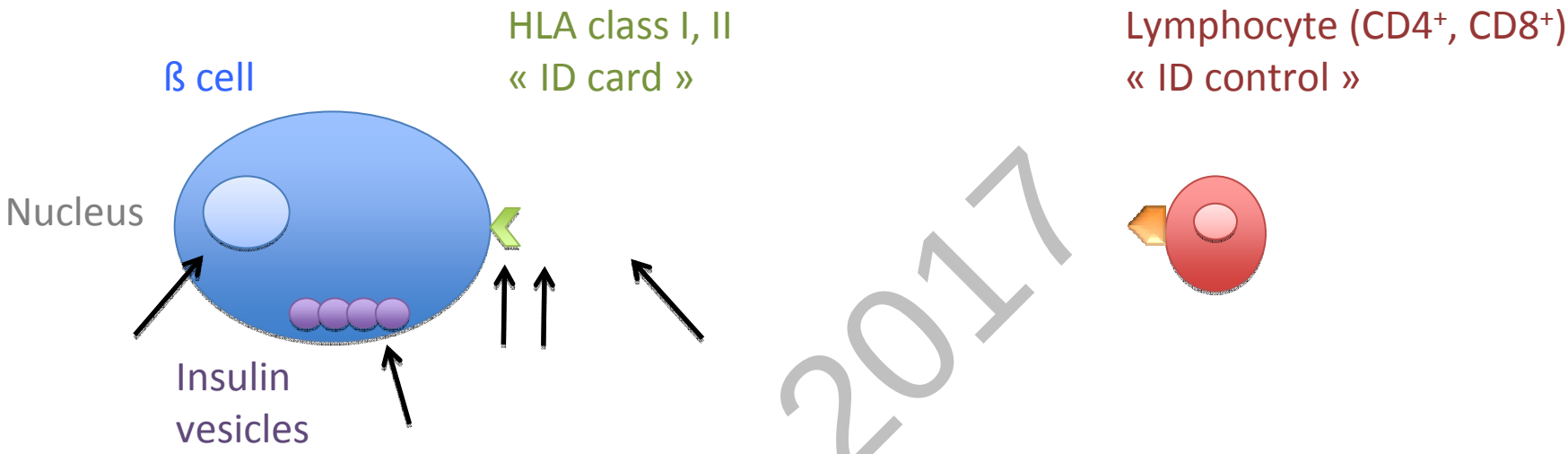
Improve treatment efficacy

Find a cure

Clues for primary prevention ?



Genetic susceptibility = ?

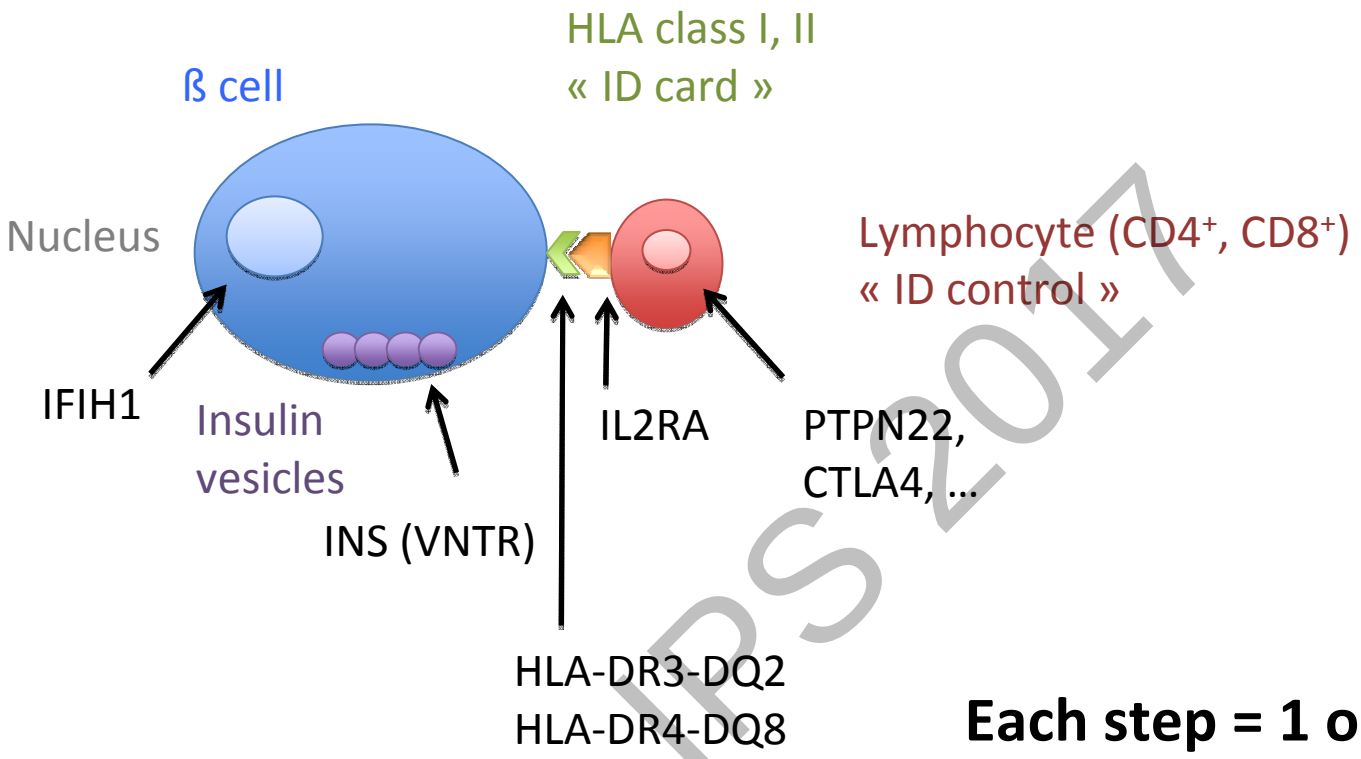


If control is ok, lymphocytes pass by…

If « accentuation » ou « attenuation » in one key step…

destruction of the ß cells

Genetic susceptibility = ?

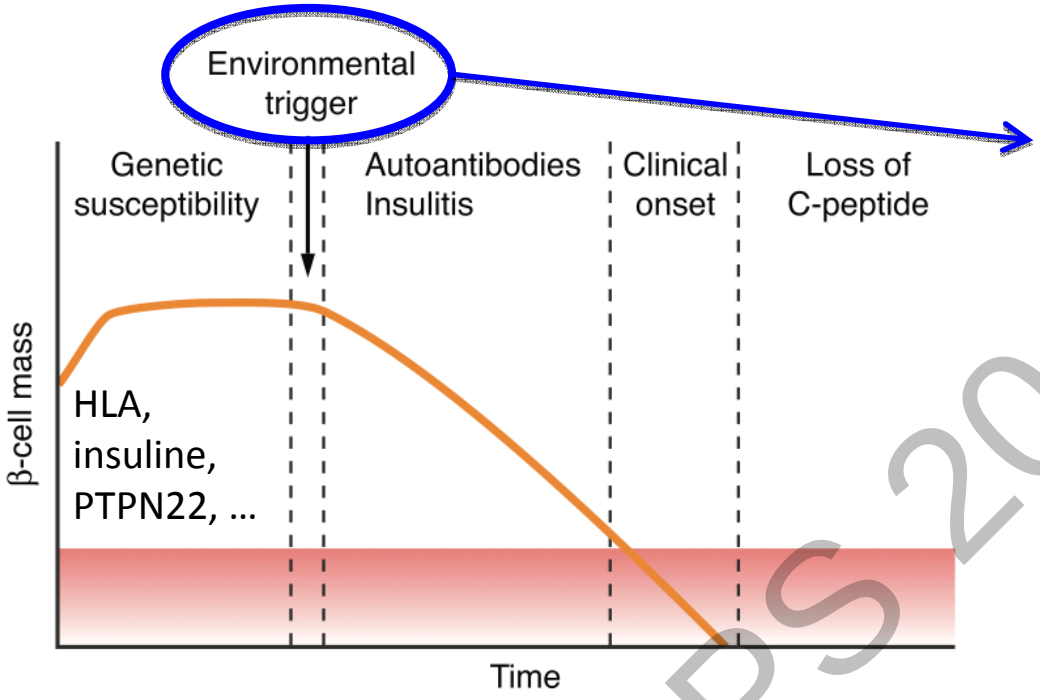


Each step = 1 or several genes

polymorphisms
epigenetic modifications
(mutations)

Ph. Lysy

Type 1 diabetes: the origins



Diet ?

Cow's milk proteins ?

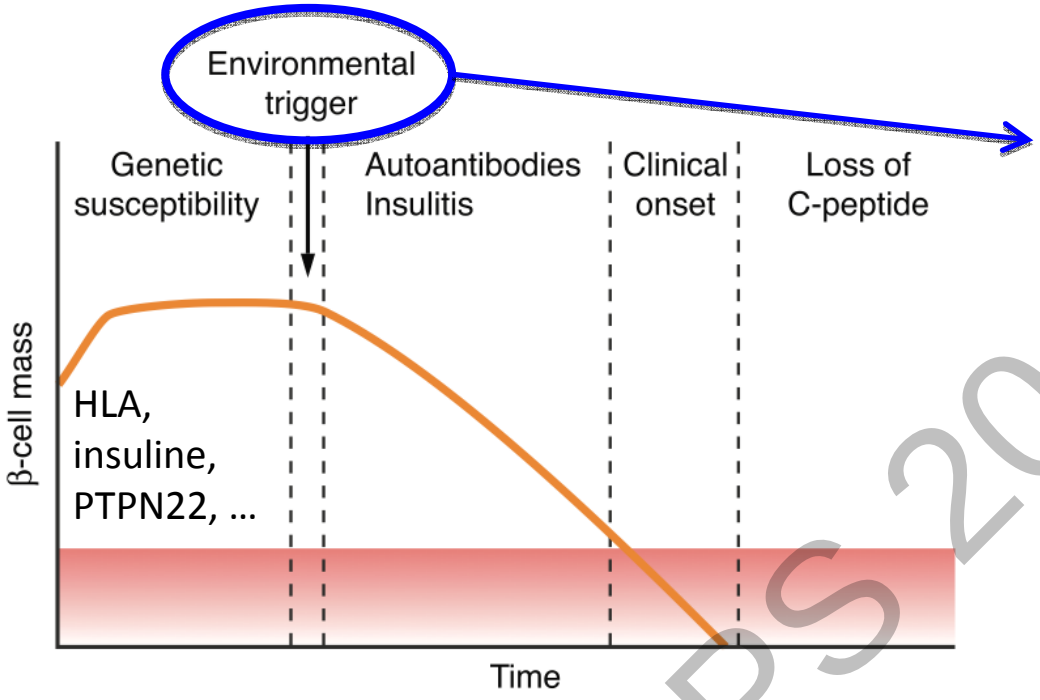
✖ TRIGR study, JAMA 2014
n=2159, 78 centers, 2002-> 2013

Gluten ?

↘ T1D incidence in NOD mice (Hansen 2014)
↗ Tregs in pancreas

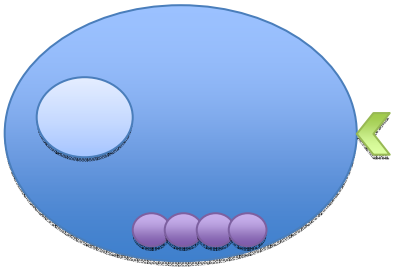
Ph. Lysy

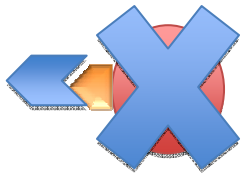
Type 1 diabetes: the origins



-> CURRENTLY NO DIET RECOMMANDATION

Primary prevention = block immunity ?



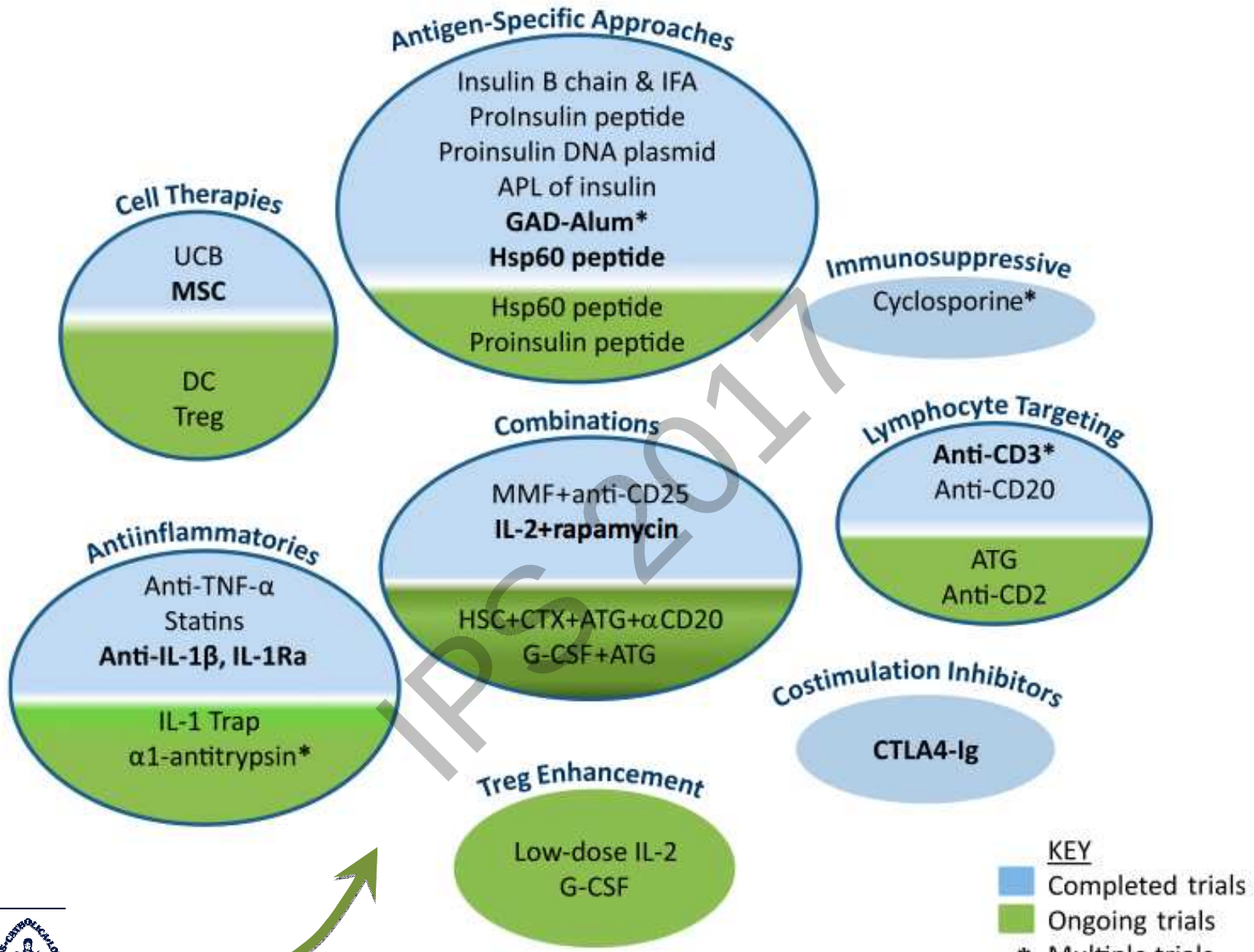


1. Target lymphocytes ? — infections, side effects, no anti-diabetic effect
   ex: cyclosporin

2. « Desensitize » lymphocytes ? — no anti-diabetic effect
   ex: insulin, GAD65, Diap277

3. Block « receptors »? — no anti-diabetic effect
   ex: anti-CD3, anti-CD20

-> CURRENTLY NO EFFICACIOUS STRATEGY



UCL Université catholique de Louvain

TARGET ß CELLS

Staeva Diabetes 2013

Improve diabetes care

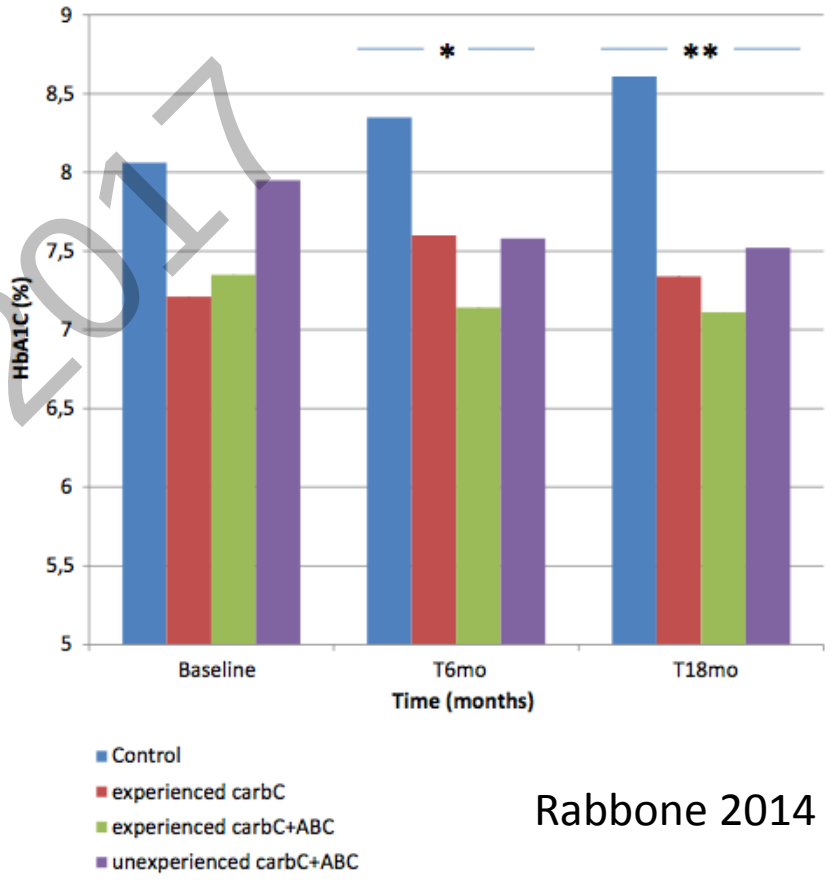
Constraint #1 = daily glucose check (≥5x/day)…

Glycemia reflects health status = indispensable

What are the novelties in glucose monitoring ?

Improve diabetes care:
1. make glucose monitoring more ‘useful’

Insulin bolus calculators:



Rabbone 2014


9:37
GLUCI-CHEK
Roche
Chercher un aliment / plat
Hyperglycémie
Hypoglycémie
Autre
Sport
Stress
Collation


9:40
Recherche
Salade de pâtes
100 g
150 g
200 g
--- g
20 g. de glucides
Échelle lipidique
Index glycémique
Ajouter à mon repas
Ma note
Énergie 183 kj
Protéines 12 g
Glucides 20 g
Sucres 4 g


9:48
Journal mensuel
juin 2013
0 Hyper
1 Hypo
Synthèse
lundi 3 juin 2013
21:00 Sport 2
22:37 Hypoglycémie
mardi 4 juin 2013
19:40 Soirée arrosée 3
mercredi 5 juin 2013
10:00 Sport 1
11:12 Collation 1

Improve diabetes care:
2. make glucose monitoring more ‘fun’

Graphique de tendances

Représentation visuelle des mesures de glycémie dans le temps d'après les fiches de résultats de tests.

Carnet de suivi glycémique

Affichage des mesures de glycémie d'après les fiches de résultats de tests.

Statistiques

Affichage des moyennes des mesures de glycémie, des écarts-types et du nombre total de tests d'après les fiches de résultats de tests.

Alertes

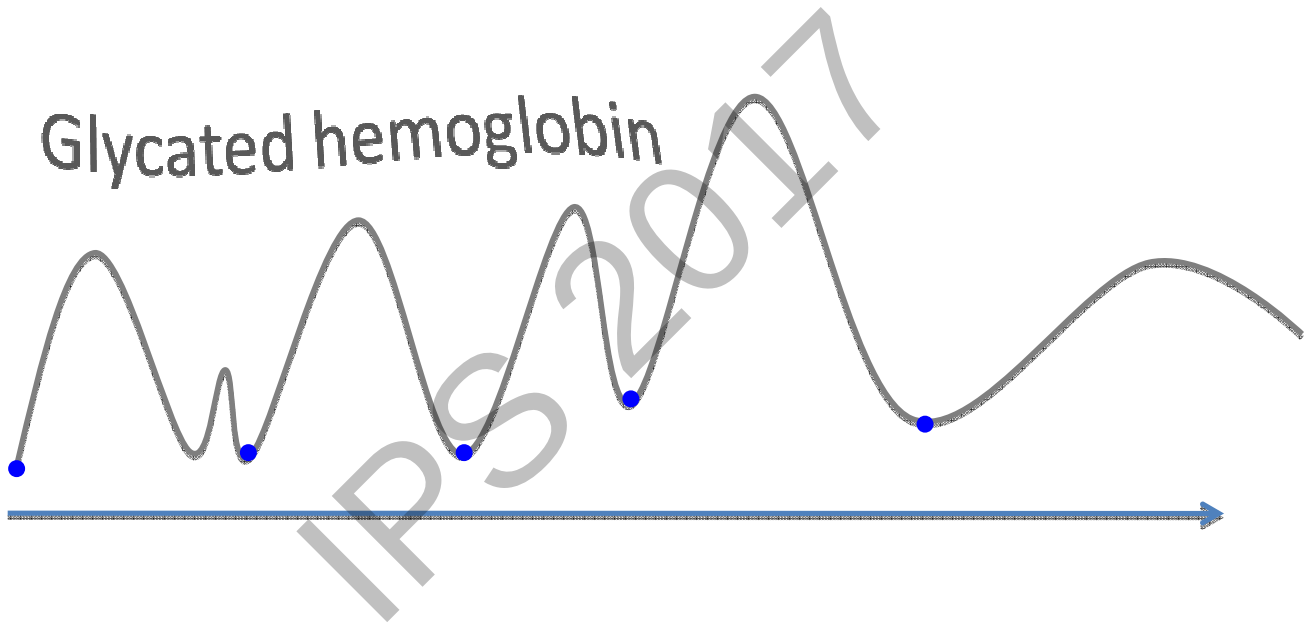
Les mesures de glycémie s'affichent dans des fiches de résultats de tests qui sont colorées en fonction des limites d'hypoglycémie et d'hyperglycémie préalablement définies par le médecin.

Résultat Jaune = supérieur à la limite d'hyperglycémie

Résultat Rose = inférieur à la limite d'hypoglycémie

Résultat Bleu = objectif glycémique atteint

Improve diabetes care:
3. make glucose monitoring more ‘real’



Real-time monitoring = continuous glucose monitoring (CGM)

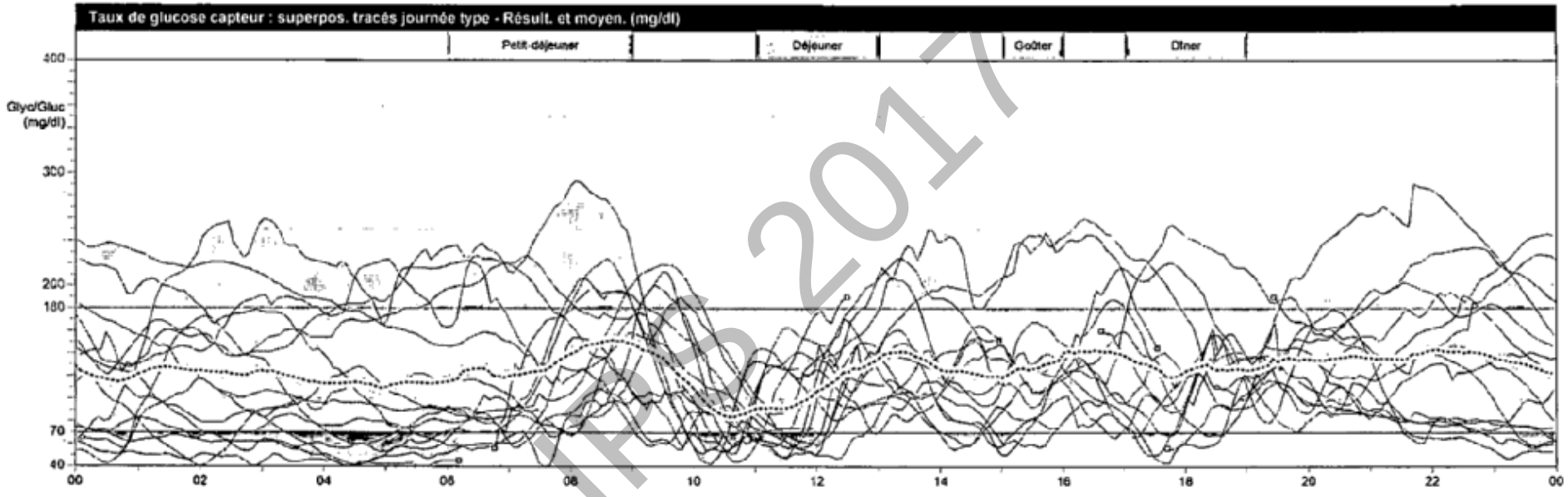
Several systems

Freestyle Libre (Abbott)

iPro – Minilink (Medtronic)

Dexcom G4 Platinum

Continuous glucose monitoring (CGM)



Improve treatment efficacy

WHY ?

Germany/Austria, HbA1c <7.5%: **56%**

US, HbA1c <7.5%: **22%**

Diabetologia 2014

HOW ?

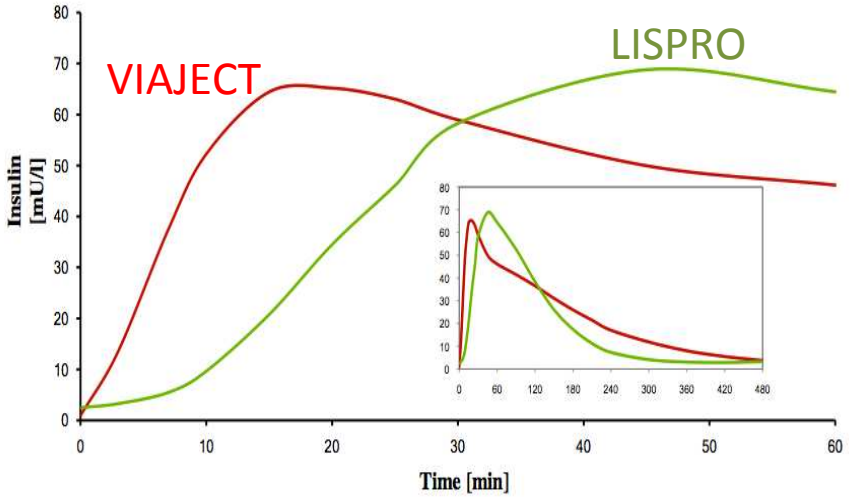
New insulins

New insulin pumps

Artificial pancreas

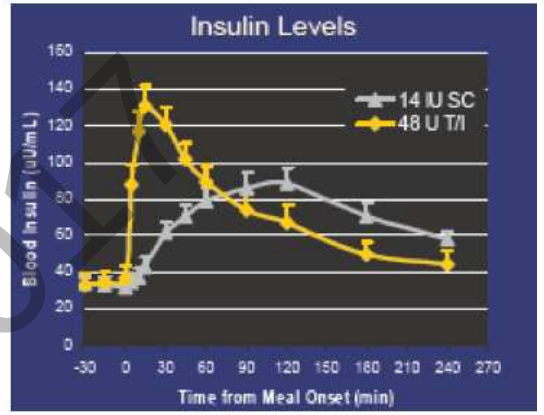
NEW INSULINS

ULTRAFAST



- ↓ post-prandial hyperglycemia
- ↓ hypoglycemia

INHALED



Afrezza®

Non inferiority for T2D

Less concerns for lung function

ULTRALONG

Degludec

Category	Trials	Change in HbA_{1c} (%-points): IDeg–IGlar		
		n (total)	Estimate	95% CI
$T1DM_{B/B}$	3583	IDeg 637	0.06	−0.04; 0.15
	3770	IGlar 321		
$T2DM_{insulin\text{-}naïve}$	3579	IDeg 1,290	0.08	−0.01; 0.16
	3586	IGlar 632		
	3672			

Non inferior to glargine

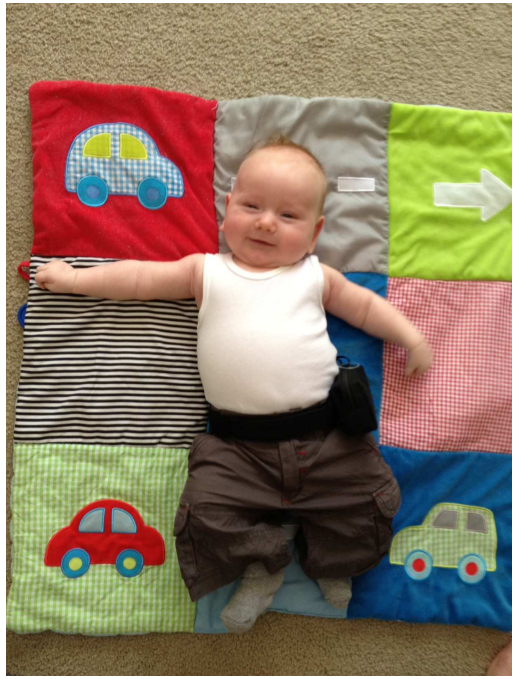
Less nocturnal hypoglycemia

New methods of insulin administration ?

Current insulin pumps are efficacious

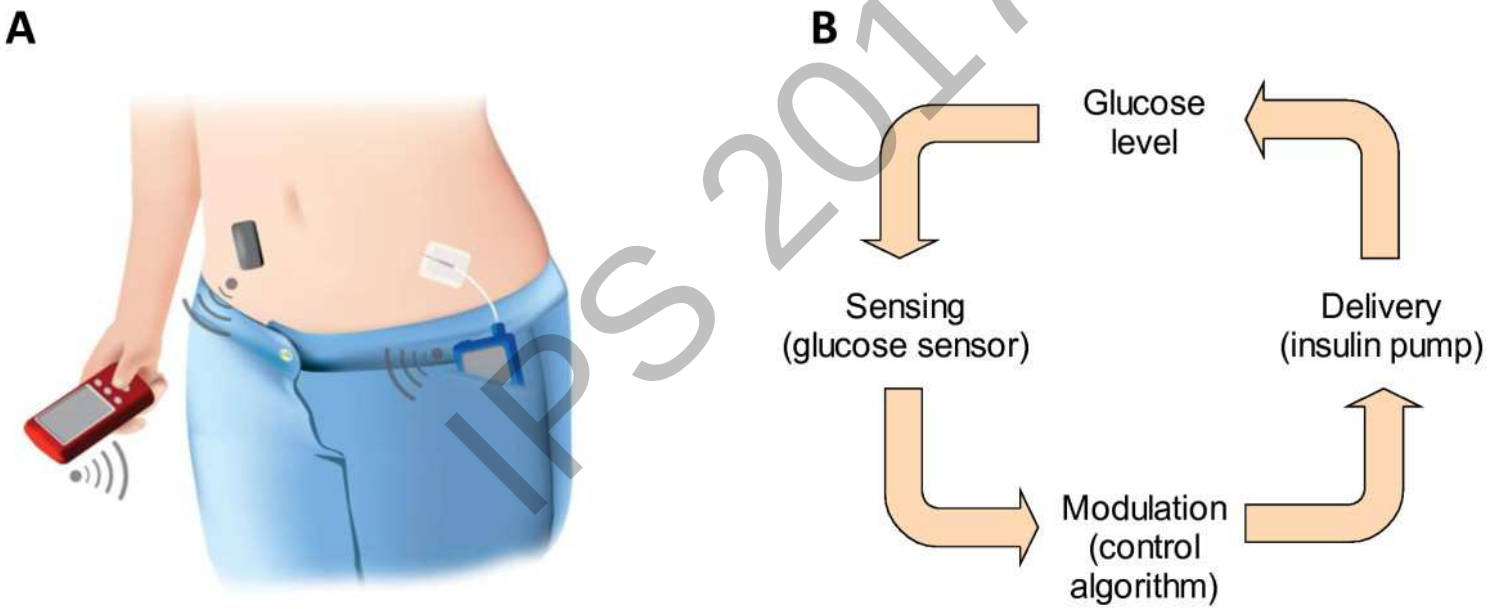
BUT need for a tier to administer boluses

Represents a problem for young children



Objective = artificial pancreas

= closed-loop system



Goals: better glycemic control + lower hypoglycemia

Wearable system

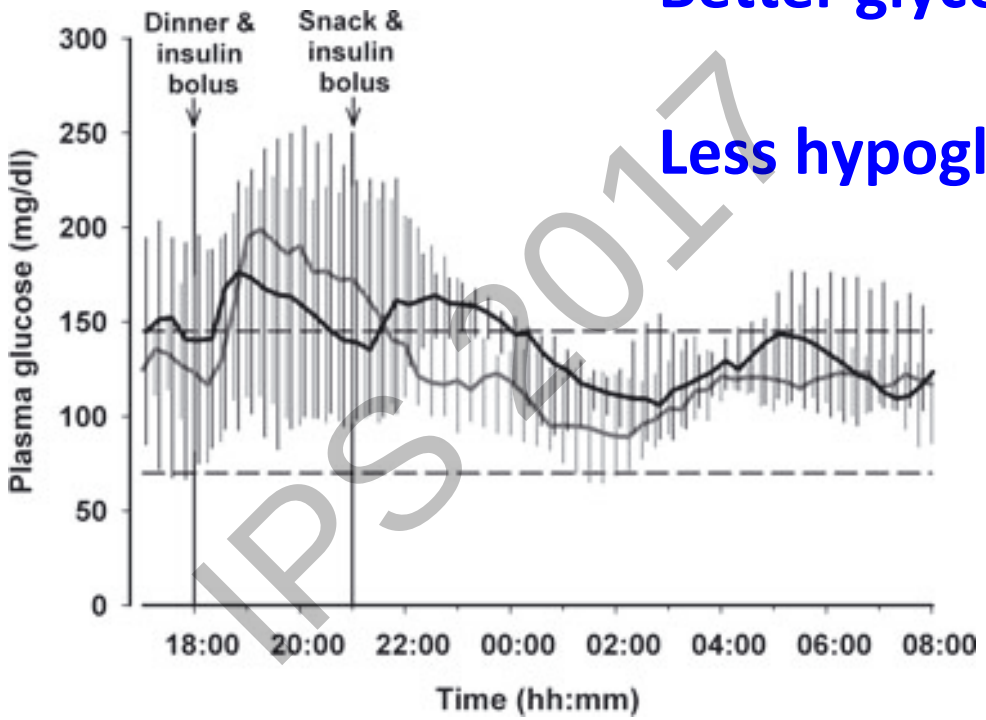
Hovorka
Cambridge, UK

« Off-the-shelf »

Artificial pancreas: results

Better glycemic means

Less hypoglycemias



Recent study: 8 patients, mean age 14.3 years (Diabetes Care 2012)

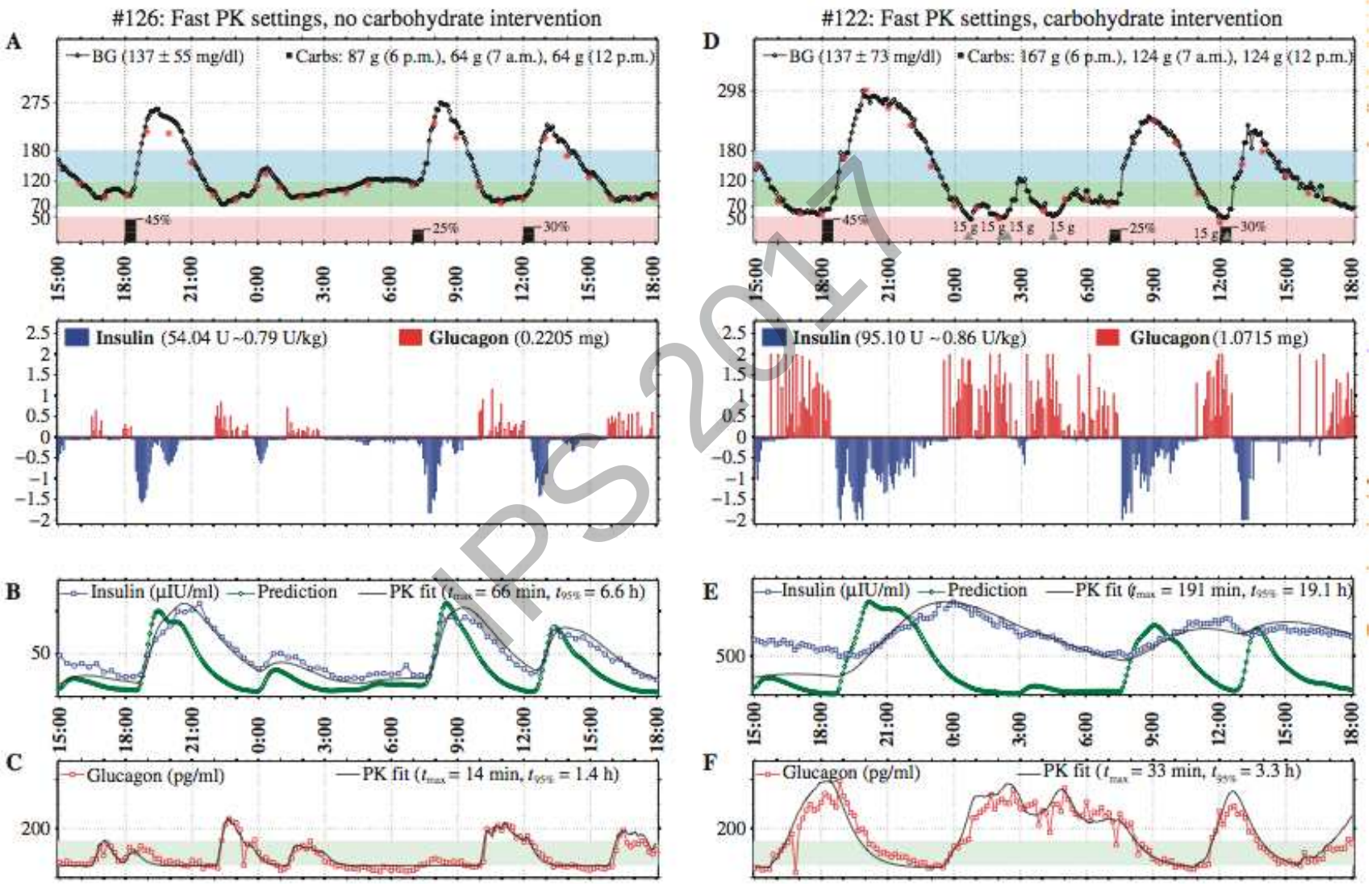
Development of bihormonal system

E. Damiano
Boston University

S. Russell
MGH, Boston

Bihormonal = insulin + glucagon

Bihormonal ‘closed-loop’: results



Science Translational Medicine 2010

http://sites.bu.edu/bionicpancreas/aboutus/

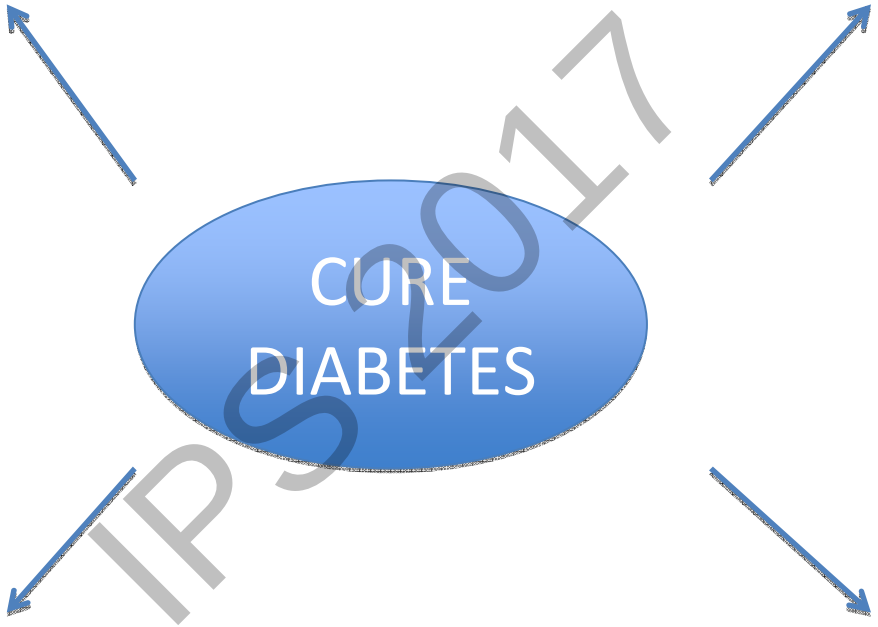
- ↓ Glycemic mean
- ↓ hypoglycemia in real situation (NEJM 2014)

File to FDA in 2017

Find a cure

Pancreas transplantation

Islet transplantation

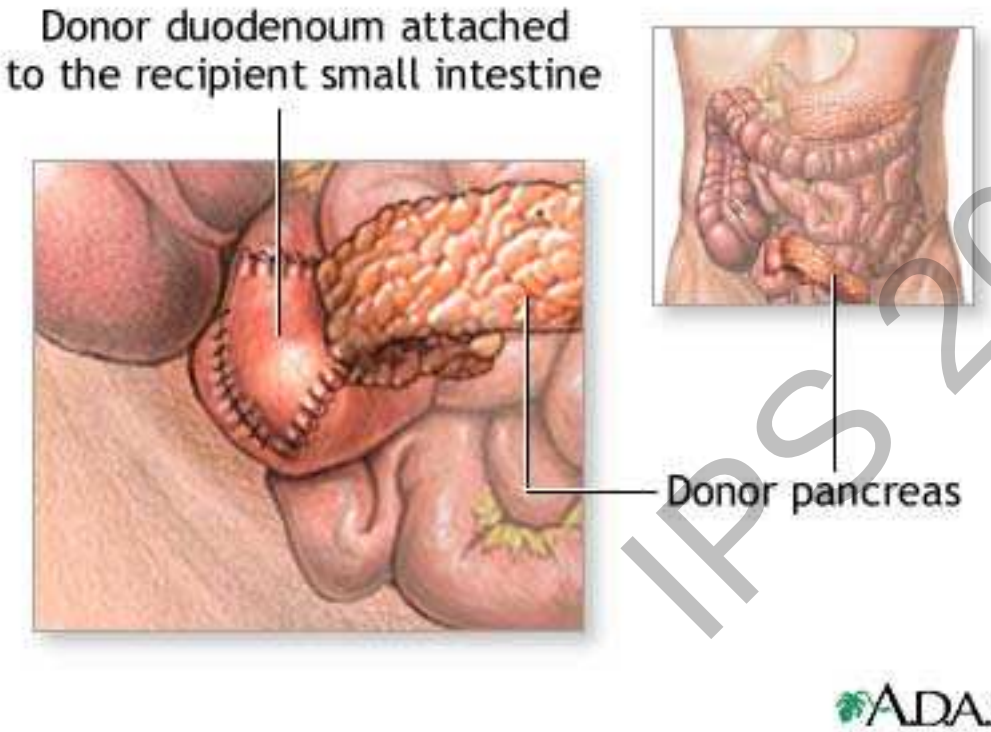


Proliferation of endogenous ß cells

Stem cell transplantation

Cliniques universitaires SAINT-LUC UCL BRUXELLES
Un hôpital pour la Vie

Pancreas transplantation



- Not always curative !

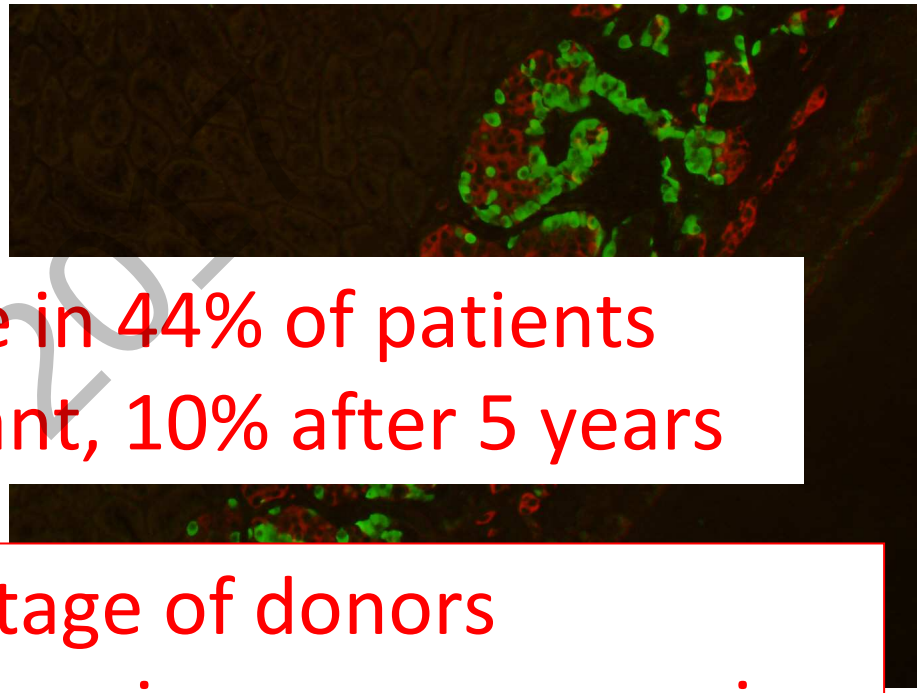
- Insulin independance in 30% after 5 years and in 10% after 10 years post-transplant

- Mortality : up to 10% after 10 years

- Shortage of donors !

-> not in the pediatric setting

Transplantation of islets of Langerhans



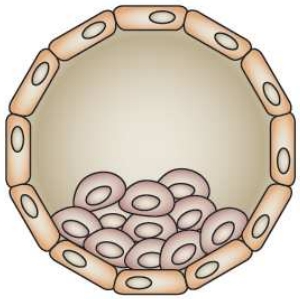
Insulin independance in 44% of patients
3 years after transplant, 10% after 5 years

Shortage of donors
Lifetime immunosuppression

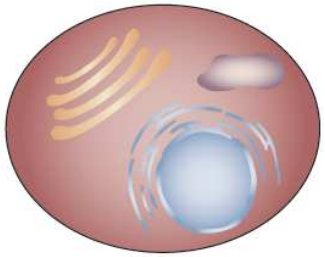
1×10^6 islets per pancreas

Need of ≈ 500,000 islets to cure diabetes in humans

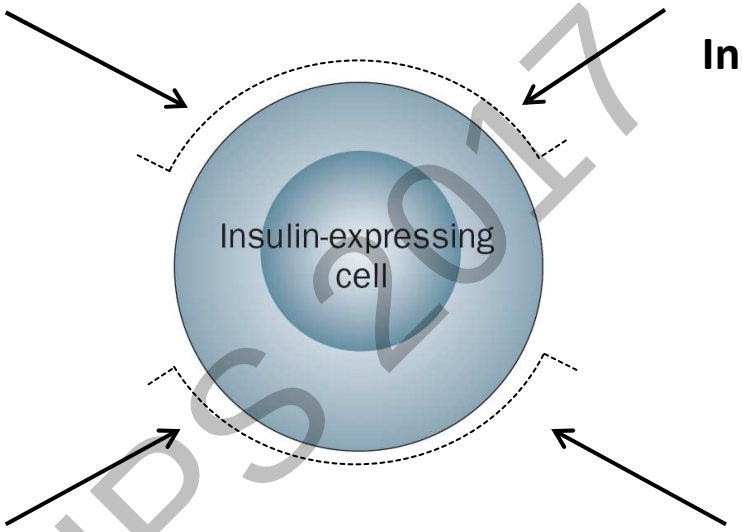
Alternative sources of transplantable β cells



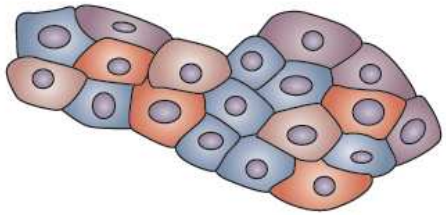
Embryonic stem cells



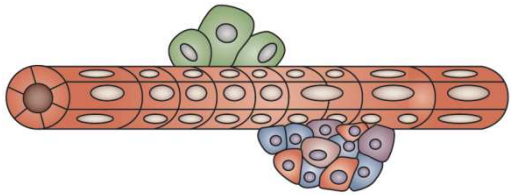
Induced pluripotent stem cells



β-cell replication

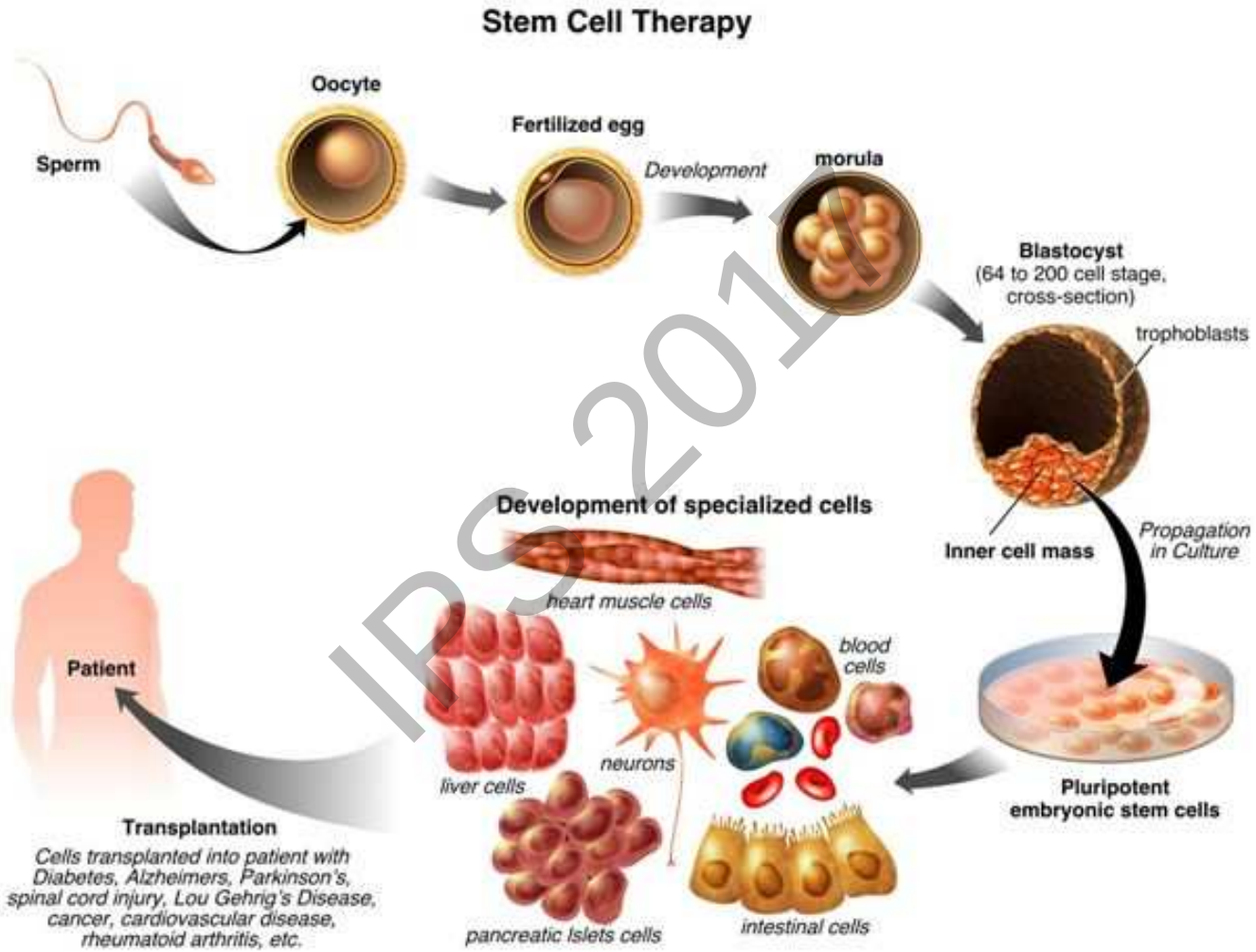


Pancreas progenitors: Pancreatic ducts

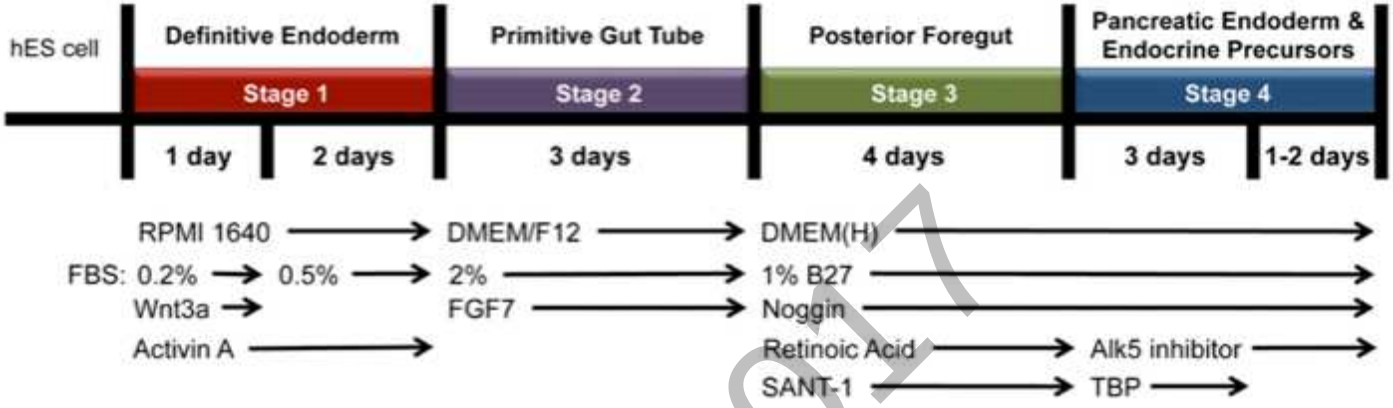


Adapted from Aguayo-Mazzucato & Bonner-Weir *Nat. Rev. Endocrinol.* 2010

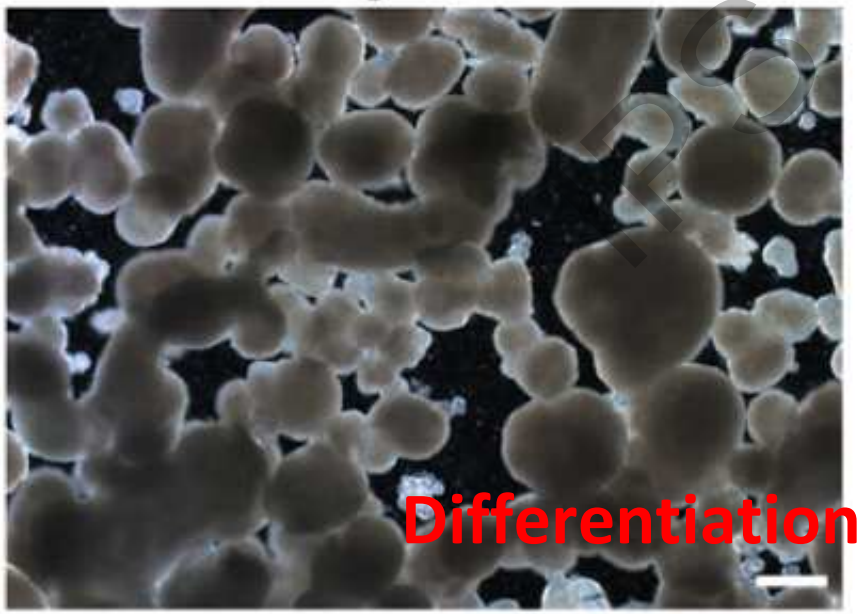
Embryonic stem cells



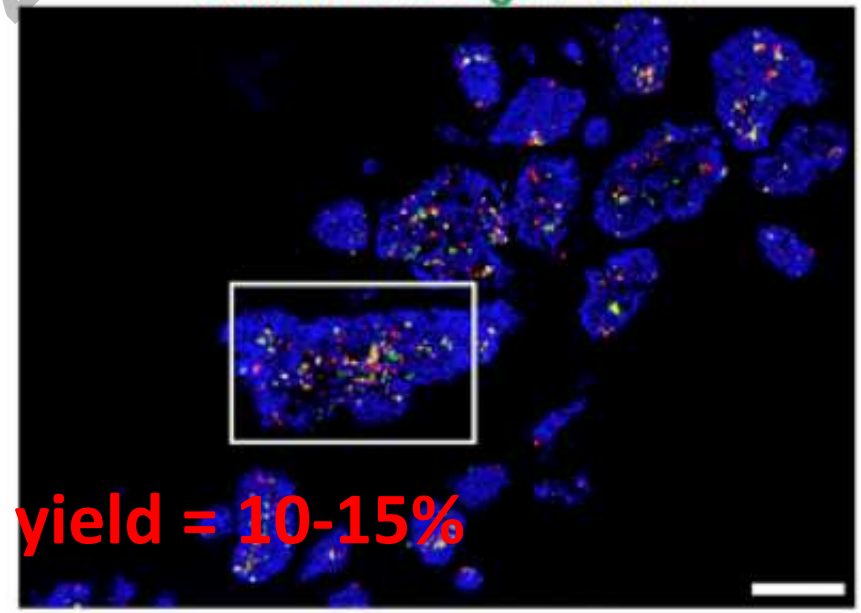
Embryonic stem cells



Brightfield



Insulin Glucagon DAPI

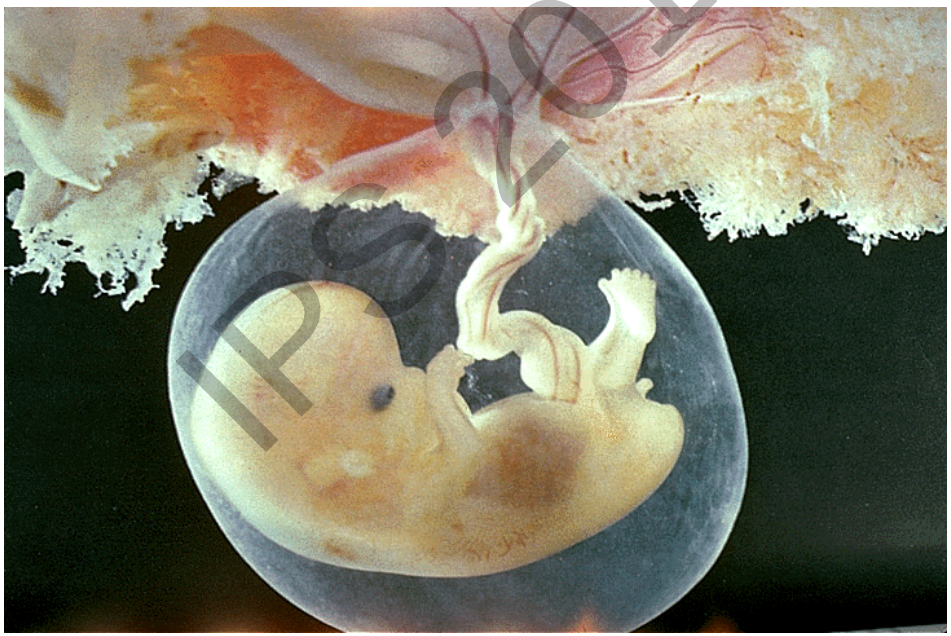


Differentiation yield = 10-15%

Embryonic stem cells

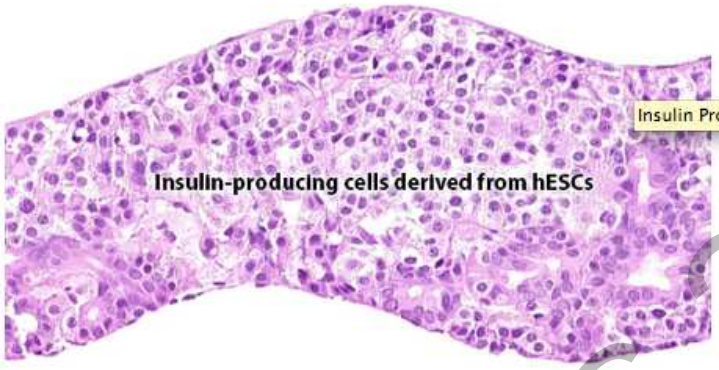
Difficulties:

- ethically sensitive sampling of embryos
- tumor formation *in vivo*

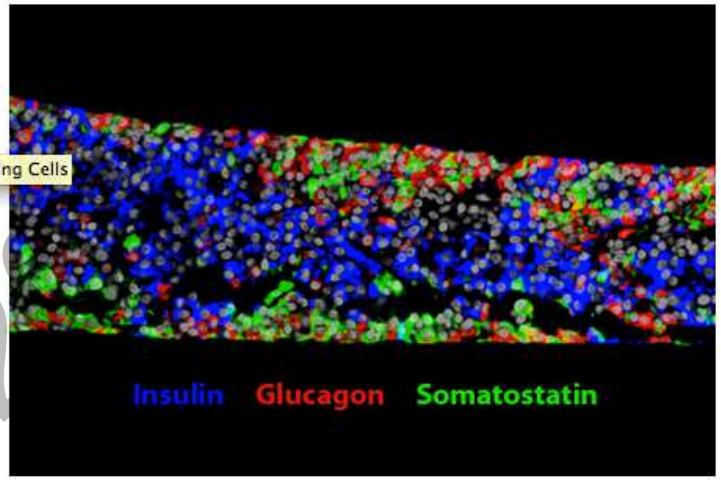


VIACYTE

To date, over a thousand VC-01 pre-clinical study implants have matured into insulin-producing grafts. The VC-01 therapy has consistently been capable of controlling blood glucose in mice at a human set point. The main efforts of the company are focused on the completion of pre-clinical safety studies with a goal of beginning human trials within two years.



After 16 weeks, PEC-01 cells have developed into islet-like structures.



The mature cells in the VC-01 combination product produce insulin, glucagon and somatostatin.