

Department for Medical Technologies & Regenerative Medicine

AG Schenke-Layland

Beta Cell Replacement

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Beta Cell Replacement

- 1) Diabetes Mellitus
- 2) Artificial Pancreas
- 3) Islet Transplantation
- 4) Bioartificial Pancreas

Diabetes Mellitus

Introduction

Diabetes Mellitus

> 500 M people worldwide (aged 20-79), about 10% of the world population

Increased to >750 M by 2045 (46%)

Undiagnosed Diabetes mellitus

World Bank income classification	Proportion undiagnosed (%)	Number of people with undiagnosed diabetes (million)
High-income countries	28.8	29.9
Middle-income countries	48.4	200.4
Low-income countries	50.5	9.5

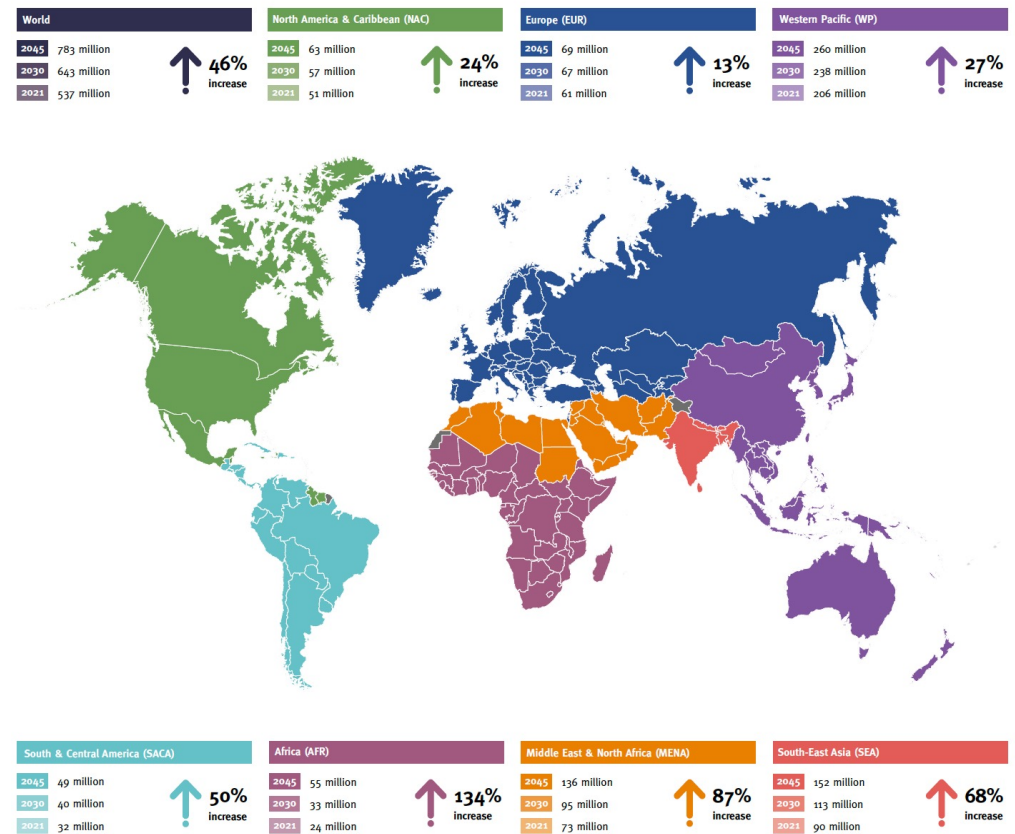
Limited access to education and healthcare

mild to no symptoms in T2DM

Up to 50% are undiagnosed

90% live in low and middle income countries

Map 1 Number of people with diabetes worldwide and per IDF Region in 2021–2045 (20–79 years)

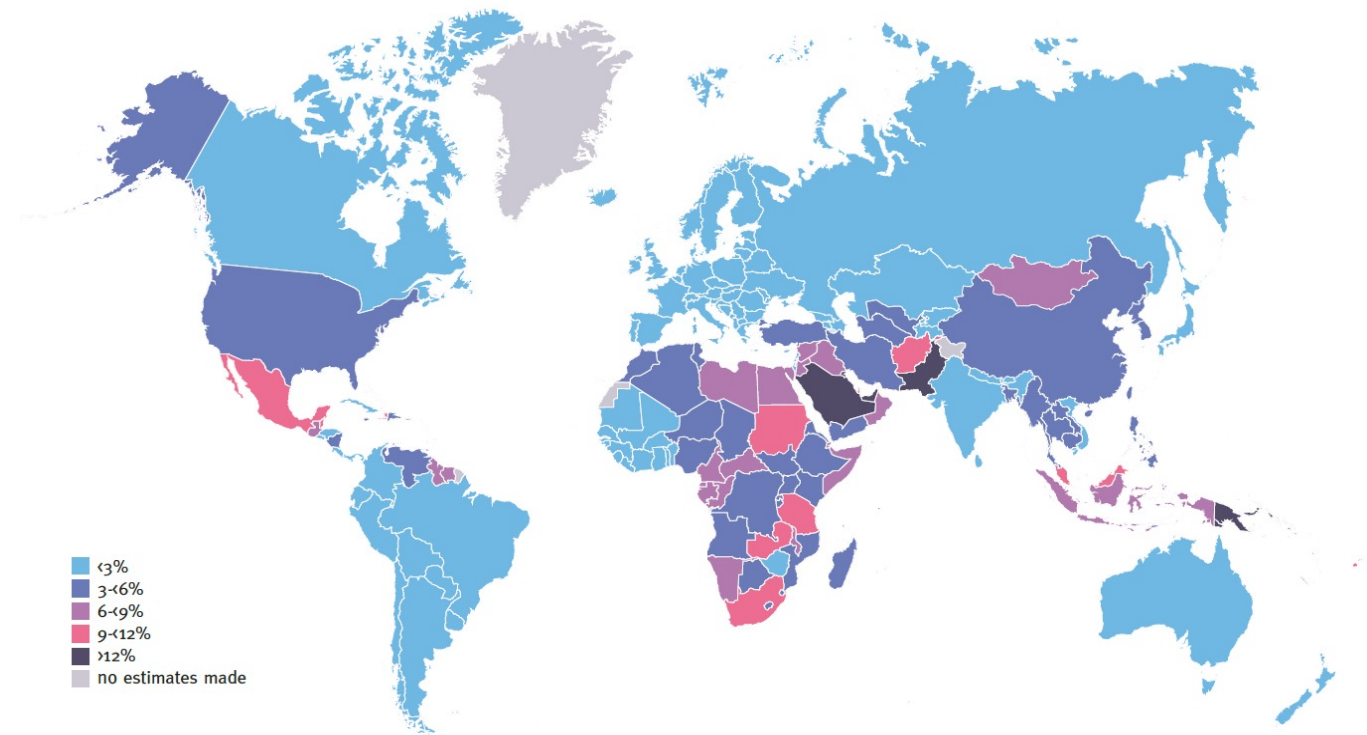


Introduction

Mortality

Approx. 7M died in 2021 due to diabetes and its complications

Proportion of total deaths related to diabetes among people under 60



Introduction

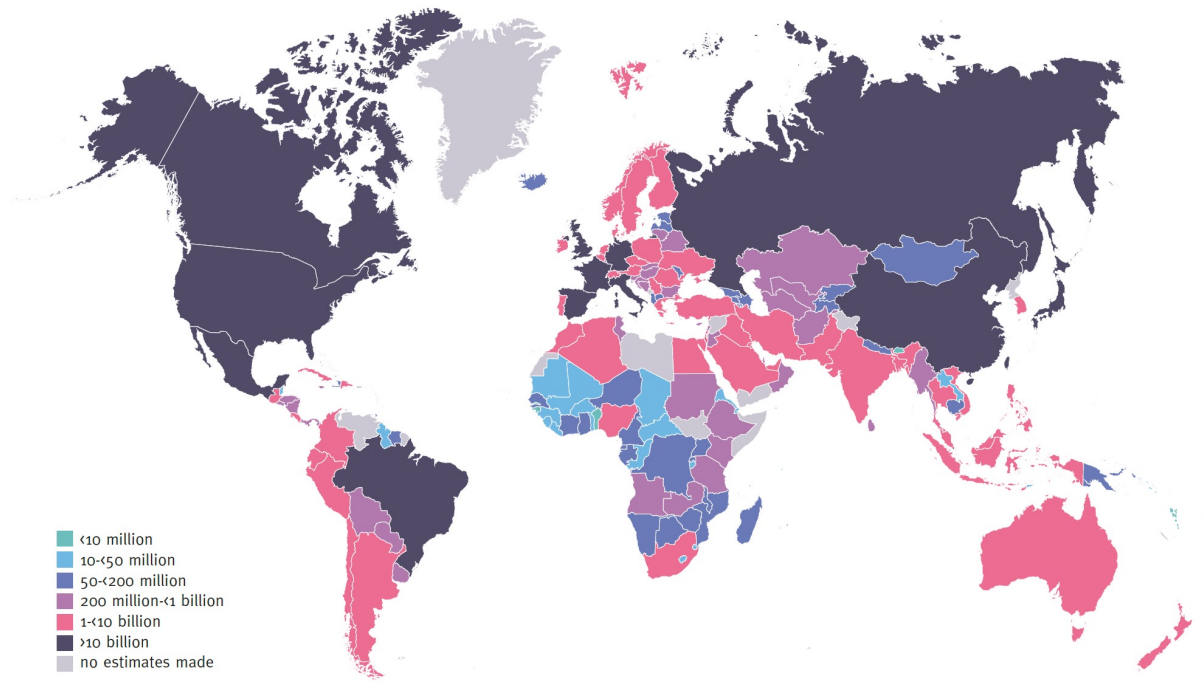
Gloabal Impact

Expenses in 2021 **\$966B**

Expenses by 2045 **\$1,050B**

Expenses for Insulin **\$34.8B**

Total diabetes-related health expenditure (USD) for adults (20–79 years) with diabetes, 2021



Rank	Country or territory	Diabetes-related health expenditure (USD) per person with diabetes (20–79 years)
1	Switzerland	12,828
2	United States of America	11,779
3	Norway	11,166
4	Iceland	8,401
5	Luxembourg	8,193
6	Denmark	7,844
7	Ireland	7,843
8	Sweden	7,675
9	Germany	6,661
10	Austria	6,575

Pathogenesis

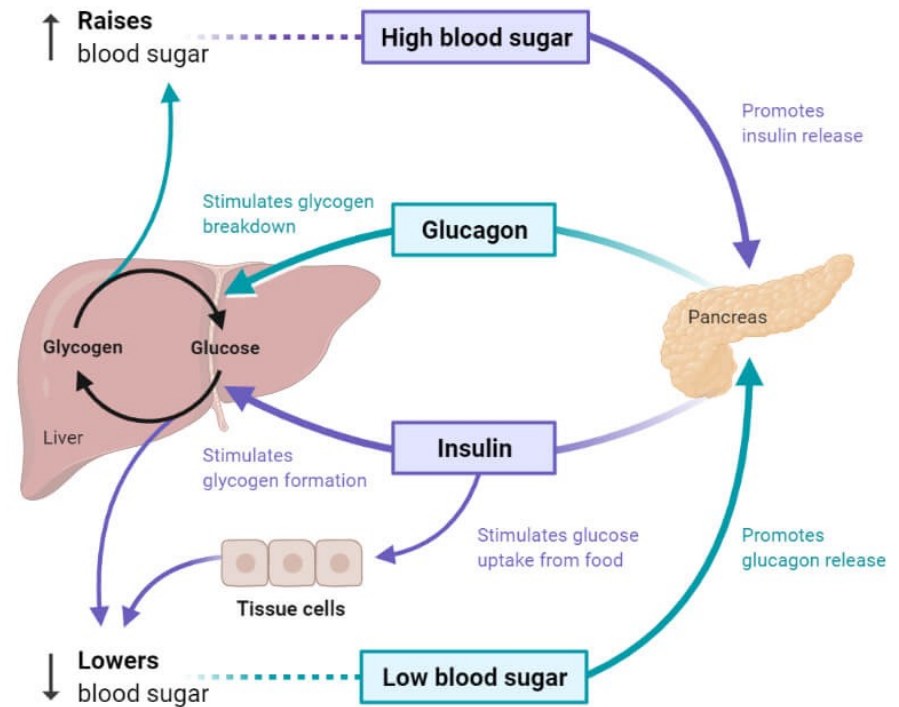
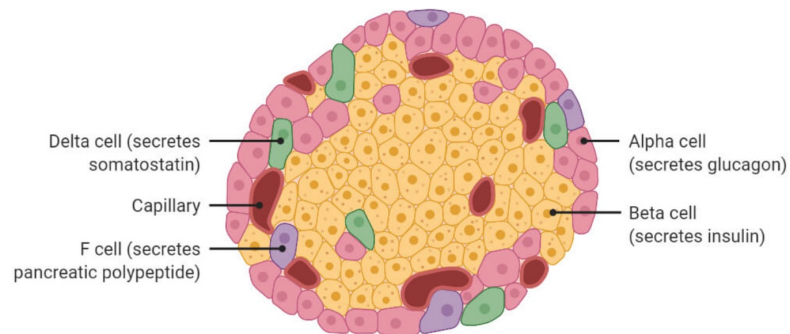
Pancreas and pancreatic hormones

Exocrine - digestive enzymes

Endocrine - Langerhans Islets

Insulin (lowers blood nutrient levels)

Glucagon (promotes glucose synthesis/release)



Pathogenesis

Diabetes mellitus

Chronic condition with a misfunctional insulin secretion or consumption

Type-1 Diabetes mellitus (T1DM)

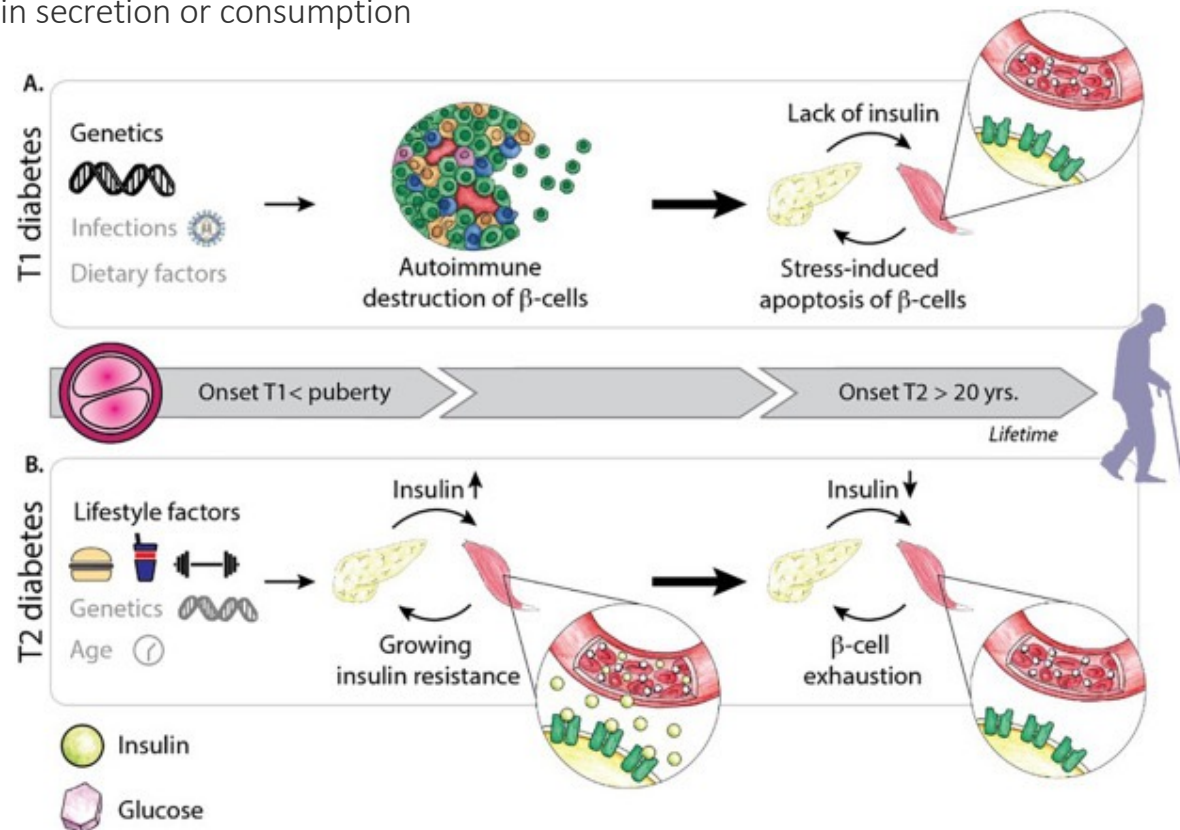
Juvenile

Insulin-dependent

Type-2 Diabetes mellitus (T2DM)

Age-related

Gestational Diabetes (GDM)



Diagnosis

Symptoms

thirst, hyperurination, weight loss, fatigue,
hunger, blurred vision

Clinical parameters for hyperglycemia

Short term

Blood glucose concentration

Long term

HbA1c – glycosylated hemoglobin
8-12 weeks

Test	Diabetes Should be diagnosed if ONE OR MORE of the following criteria are met	Impaired Glucose Tolerance (IGT) Should be diagnosed if BOTH of the following criteria are met	Impaired Fasting Glucose (IFG) Should be diagnosed if THE FIRST OR BOTH of the following are met
 Fasting plasma glucose	≥ 7.0 mmol/L (126 mg/dL)	< 7.0 mmol/L (126 mg/dL)	$6.1 - 6.9$ mmol/L (110 - 125 mg/dL)
	or	and	and if measured
 Two-hour plasma glucose after 75g oral glucose load (oral glucose tolerance test (OGTT))	≥ 11.1 mmol/L (200 mg/dL)	≥ 7.8 and < 11.1 mmol/L (140-200 mg/dL)	< 7.8 mmol/L (140 mg/dL)
	or		
 HbA1c	≥ 48 mmol/mol (equivalent to 6.5%)		
	or		
 Random plasma glucose in the presence of symptoms of hyperglycaemia	≥ 11.1 mmol/L (200 mg/dL)		

Complications

Hypoglycemia

BGL < 3.9 mmol/L (70 mg/dl)

Symptoms:

trembling, anxiety, hunger, lack of concentration

>> loss of consciousness, seizure, coma

Hypoglycaemic episodes often occur overnight
(90-140 non-severe, 1-2 severe events)

Hyperglycemia

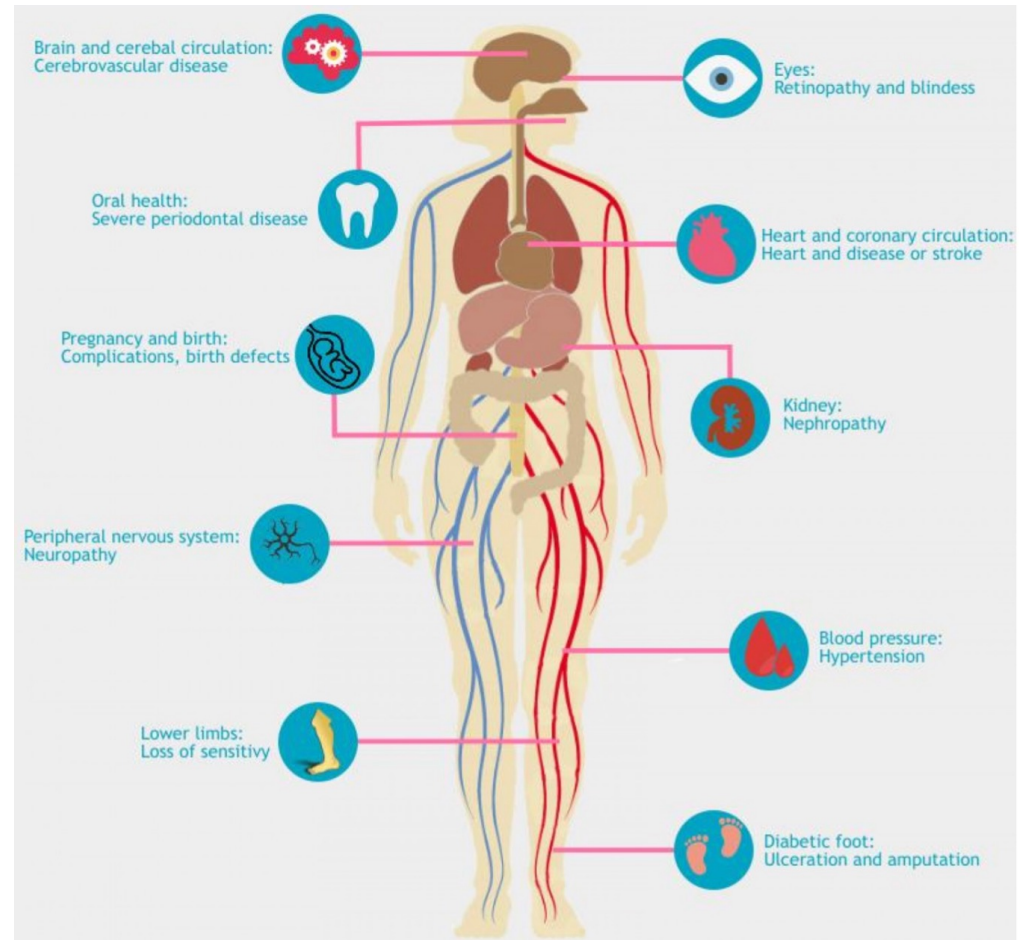
Acute complication: Diabetic ketoacidosis (DKA)

lipolysis & liver ketogenesis

>> hypotension and shock

leading cause of mortality in T1DM

Longterm effects on various organs



Treatment

Goals

- Avoid hypoglycemic and hyperglycemic event
- Stable blood glucose levels (3.9 – 10 mmol/L)
- Reduce HbA1c

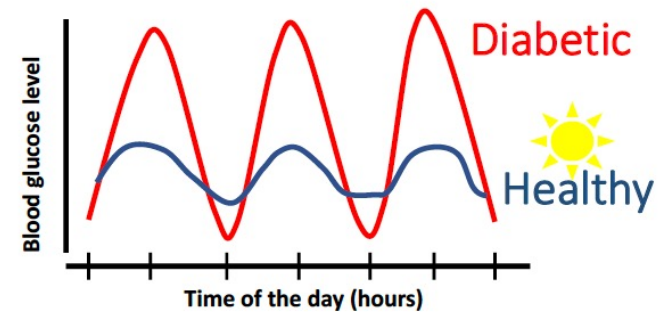
Guidelines

- T1DM: insulin-dependent
- T2DM: lifestyle >> oral medication >> insulin

Self-monitoring of blood glucose

- finger pricking up to several times a day
- amperometric, colorimetric or fluorescence based detection of fresh capillary blood glucose levels
- Consumables: test strips and needles

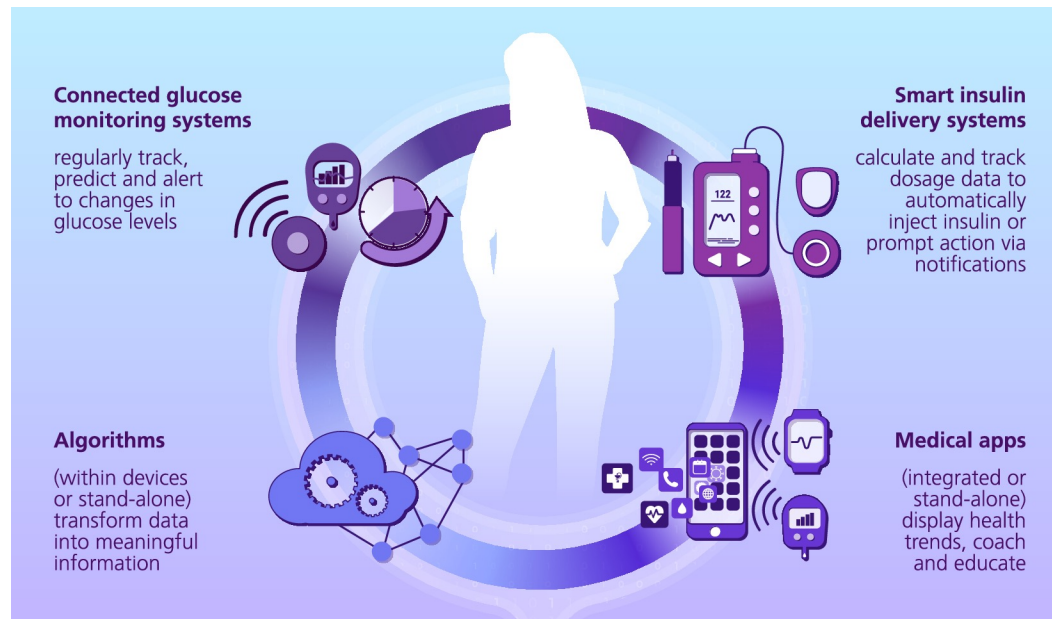
Seminar: Minimally Invasive and Implantable Sensors for Continuous Glucose Monitoring (CGM)



Optimizing diabetes care by smart implantable devices

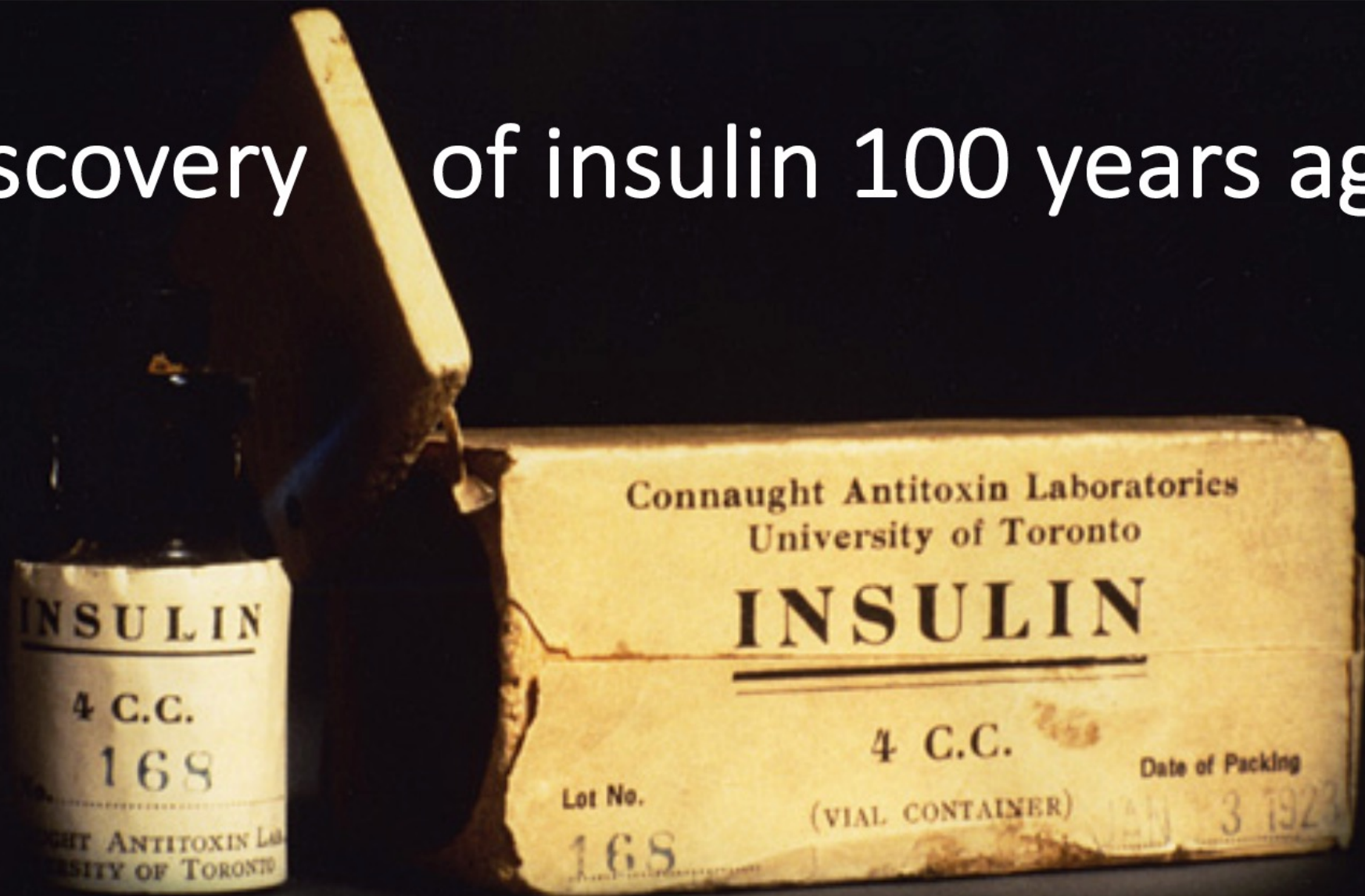
Smart Glucose Monitoring

Smart Insulin Delivery



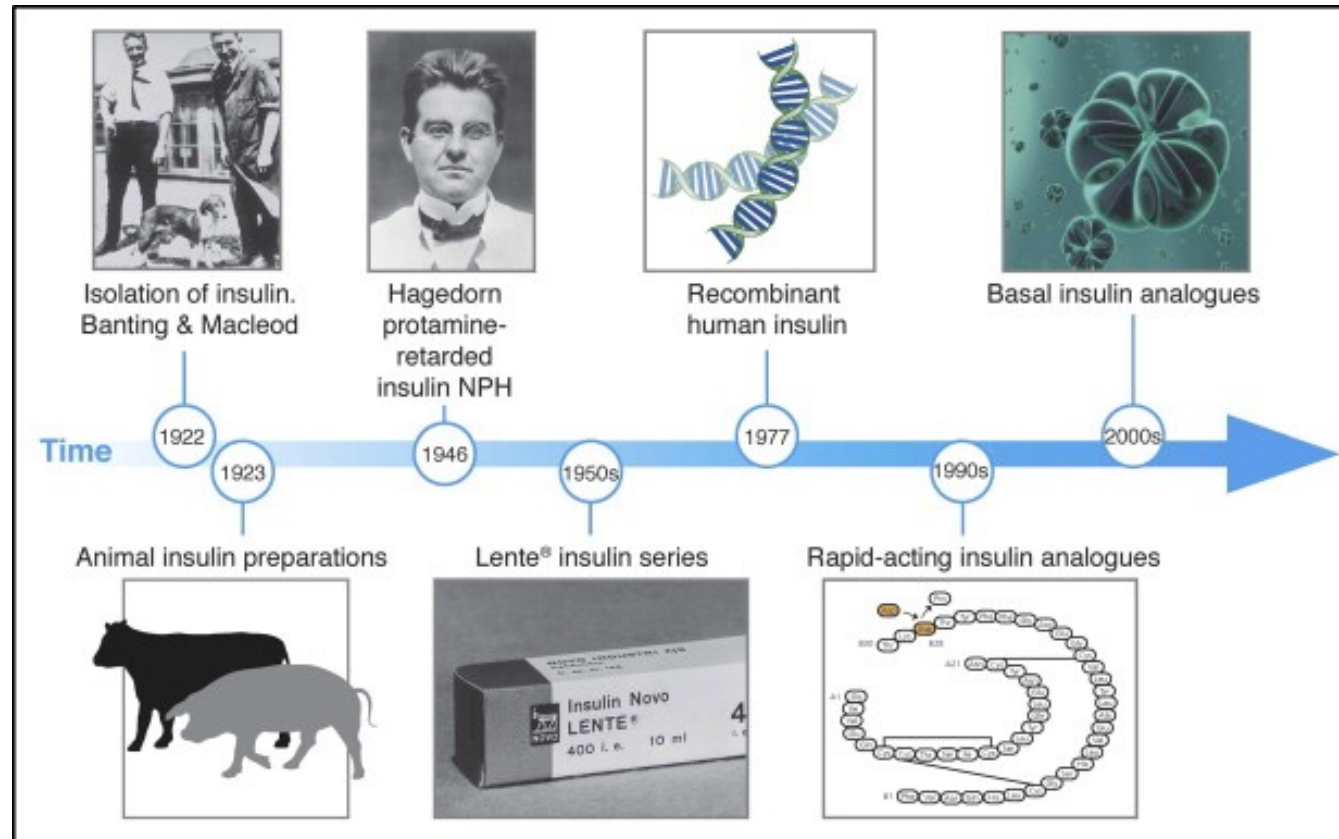
Artificial Pancreas

Discovery of insulin 100 years ago



Insulin

Development



Insulin

Insulin types

Insulin and long-term and fast-acting analogues
Designed to allow basal and bolus injection

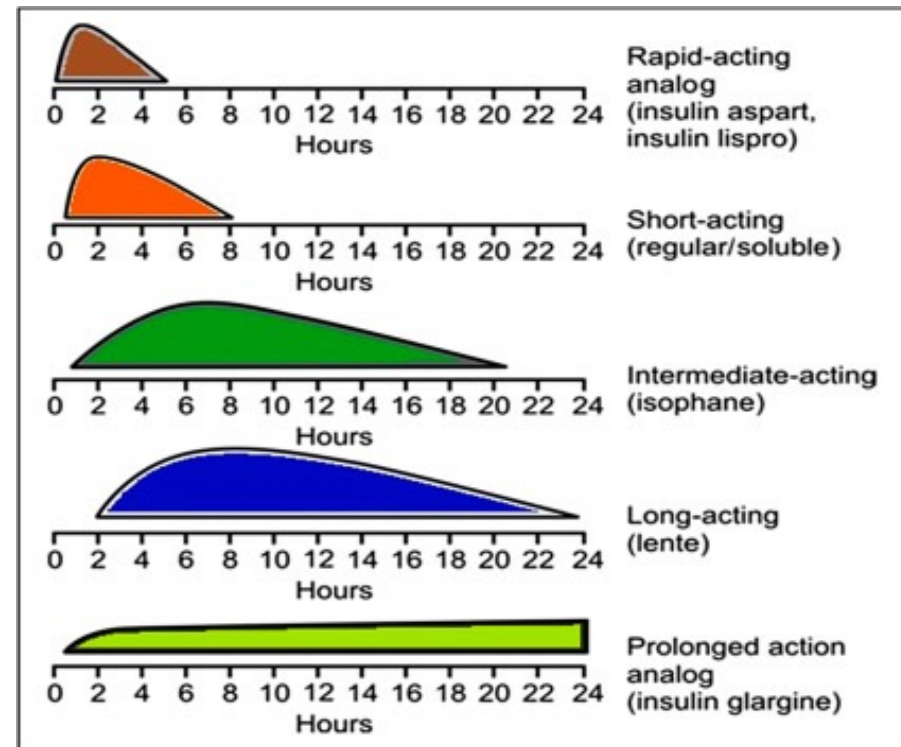
Basal (40-50%):
constant injections to maintain a certain insulin level,
especially overnight

Bolus (50-60%):
Individual supplementation according to food intake,
exercise...

Patients have to calculate and administer insulin
according to:

- insulin to carbohydrate ration
- high glucose levels

>> highly individual and dependent on day-time, hormone
levels, exercise



Insulin Pumps

Insulin Pumps

- Computerized insulin reservoir
- Subcutaneous insulin delivery
- Steady flow of basal insulin, button of device to add bolus insulin dosage
- Tube and cannula inserted (3-7 days)

Advantages

- fewer needle sticks
- better coverage over night/morning
- Dosing for snacks, exercise is faster, easier and more accurate

Disadvantages

- programm the pump every day
- exchange tubing every few days
- carry device with you
- control your blood glucose levels to assess performance



Closed Loop Systems

(Hybrid) Closed-Loop

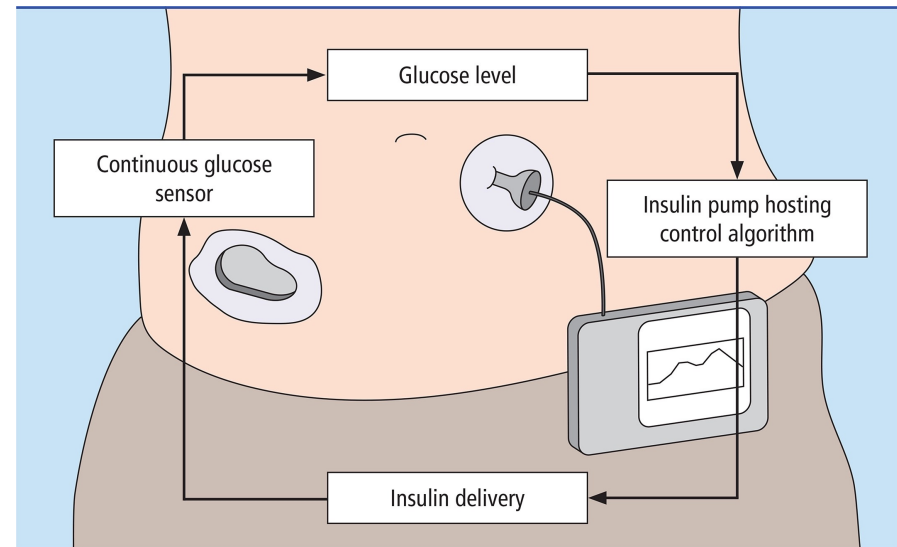
Sensor augmented pump therapy

From decision support towards decision making

Hybrid:

manual calculation/administration of insulin for carbohydrate intake

e.g. Medtronic MiniMed, t:slim X2, Dana RS, CamAPS



Real Closed Loop Systems

Combination with fast reacting insulins to allow automated response to food intake

Bi-hormonal systems including glucagon

Algorithms to predict the food induced glucose changes

Variable thresholds for desired glucose levels e.g. for long drives or exercise

e.g. iLet, implantable artificial pancreas

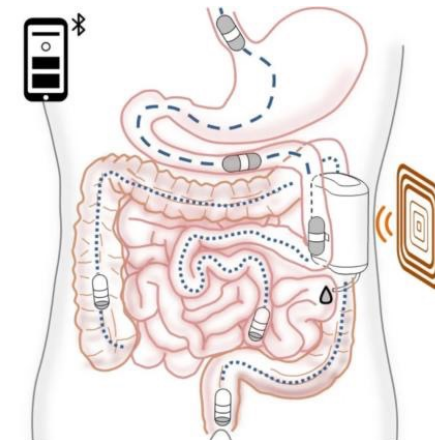
Implantable Systems

Implantable Insulin Pumps

Implantation into the abdominal cavity
Faster glucose/insulin kinetics



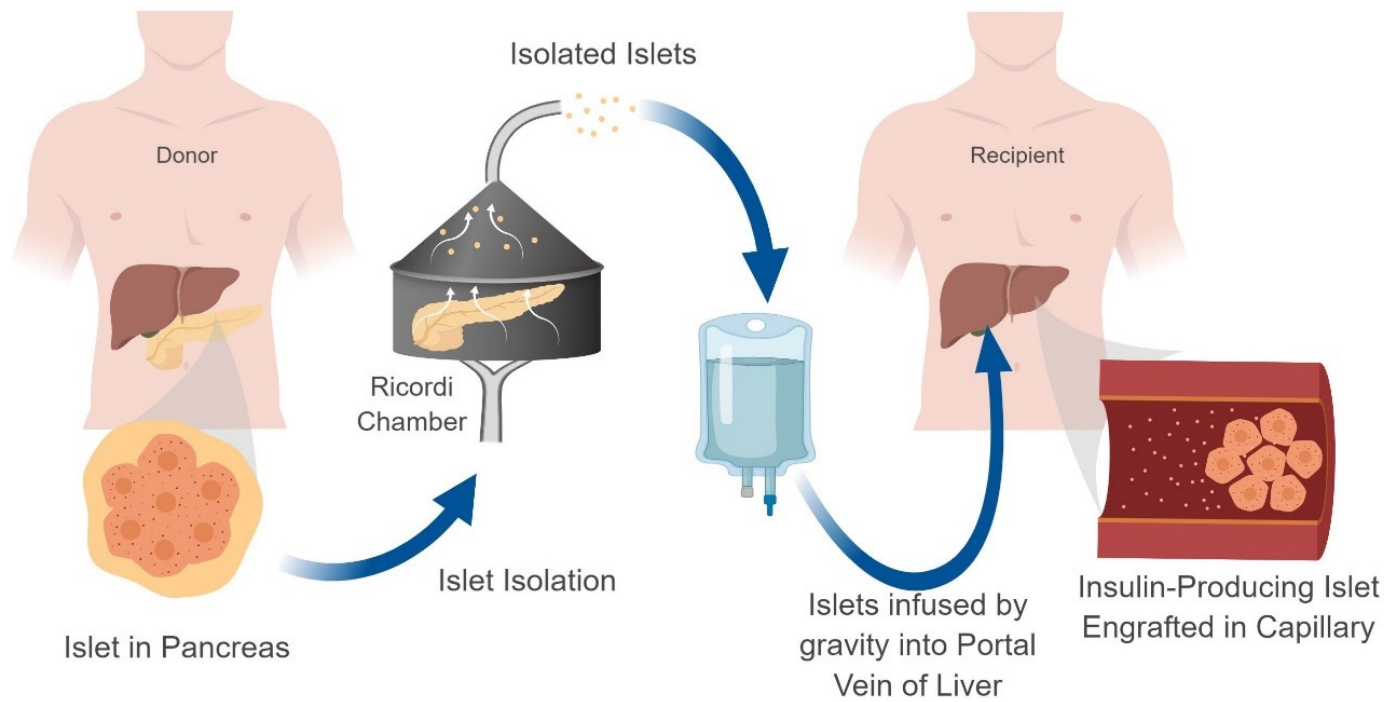
physiologicdevices.com



Islet Transplantation

Islet Transplantation

Edmonton Protocol

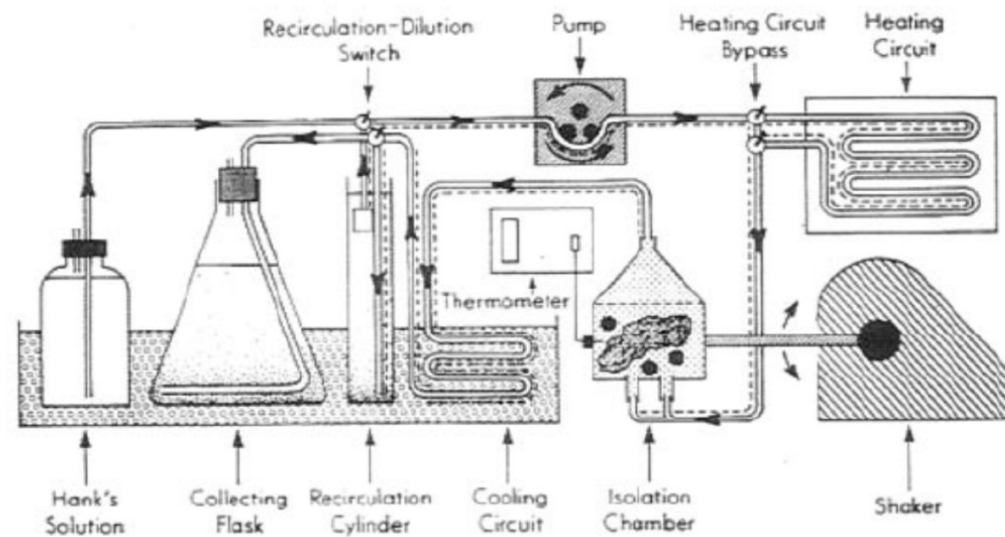


Islet Transplantation

Reprinted from DIABETES, VOL. 37, NO. 4, APRIL 1988
Copyright 1988 by THE JOURNAL OF THE AMERICAN DIABETES ASSOCIATION.

Automated Method for Isolation of Human Pancreatic Islets

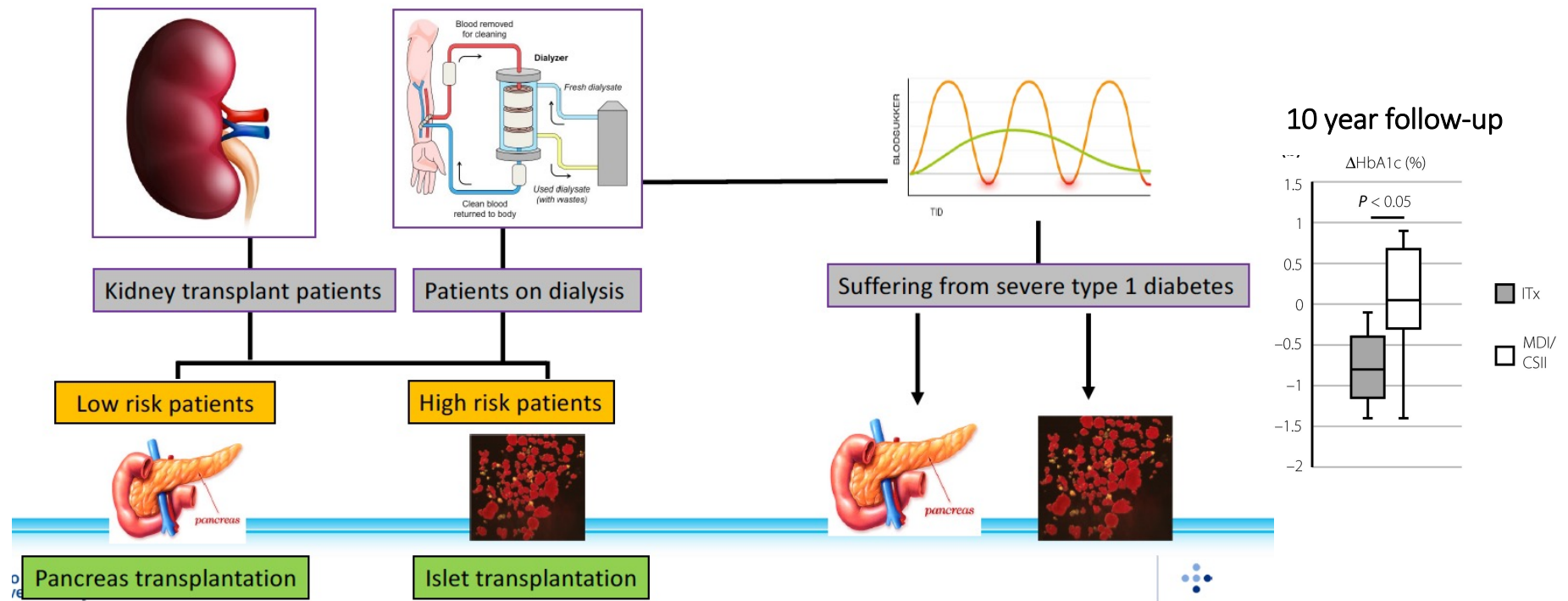
CAMILLO RICORDI, PAUL E. LACY, EDWARD H. FINKE, BARBARA J. OLACK,
AND DAVID W. SCHARP



cen processor

Islet Transplantation

Who is offered a beta cell replacement today?



Islet Transplantation

Allogenic islet transplantation

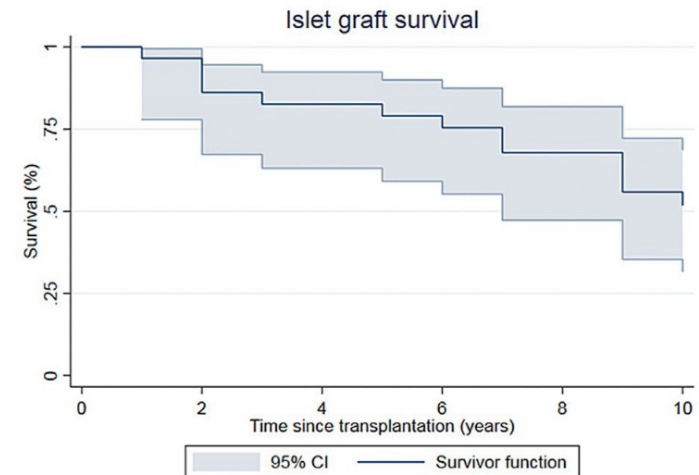
- Fourth line treatment option
- Poor long-term graft survival due to alloimmune or autoimmune effects
 - Graft rejection in 20% within the first year
 - Insulin independence in 5% of the patients after 10 years

- Costs vs insulin injection decrease after 10 years
- Lifelong therapy with immunosuppressants
- Accessible to <0.5% of T1DM; donor organ scarcity

Need for alternative cell sources & delivery systems

- Xenogeneic
- Stem cell derived
- Immunoprotectant Implants

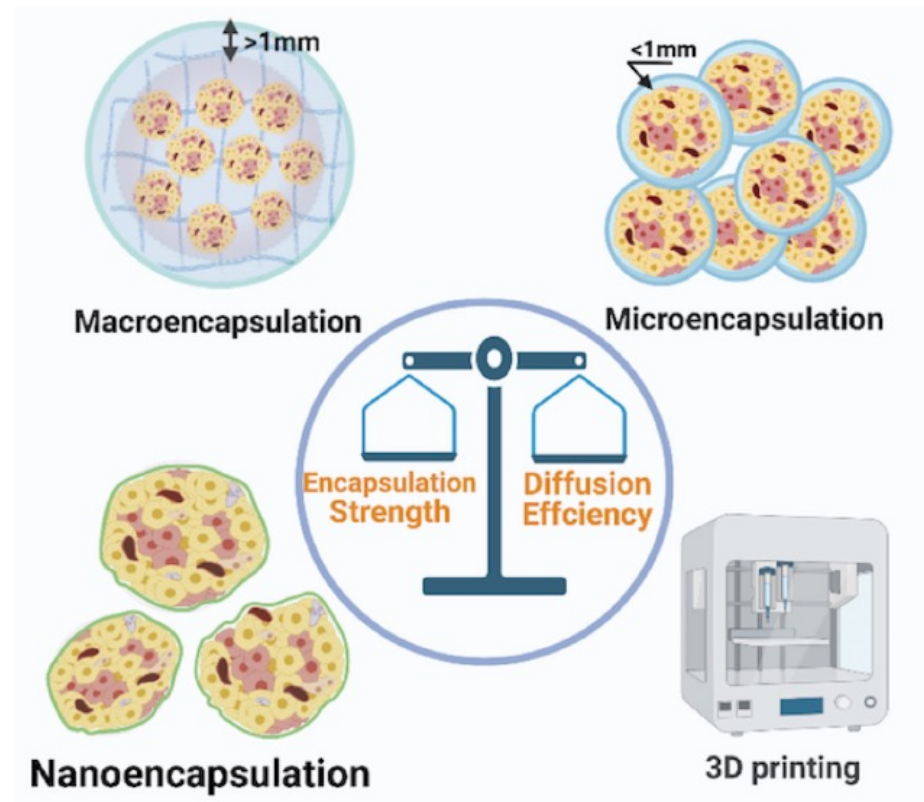
Seminar: Stem cells for beta cell replacement



Bioartificial Pancreas

Cell-based Implants

Endogenous and immunogenic protection of transplanted cells



Microencapsulation

Microencapsulation

Ensure biocompatibility & avoid fibrotic overgrowth

Spherical shape & high surface-to-volume ratio resembles native islets & diffusion properties

Selective permeability

Enlarged diameter reduces foreign body response – vs non encapsulated islets

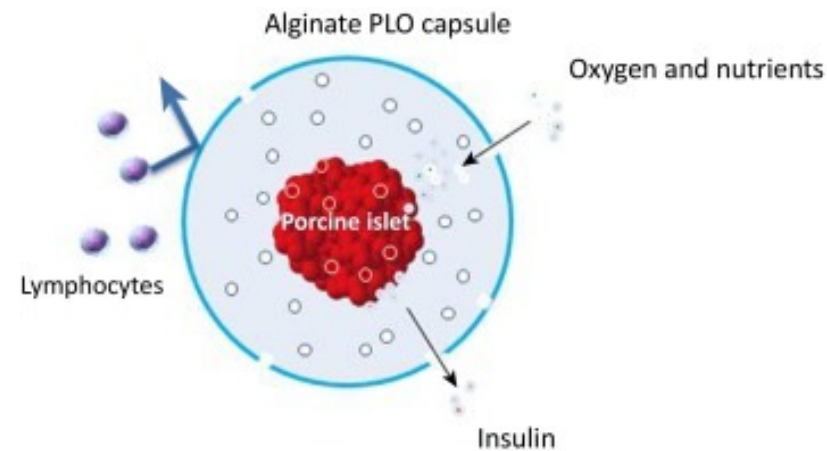
Alginate: biocompatible, stable and perfusable



Legoy et al, Sci Rep, 2020

μ ED in Phase I/II clinical trials

e.g. DIABECCELL

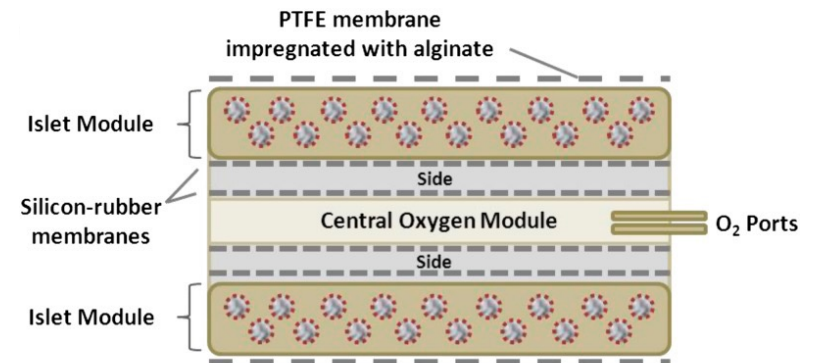


Trends in Biotechnology

Macroencapsulation

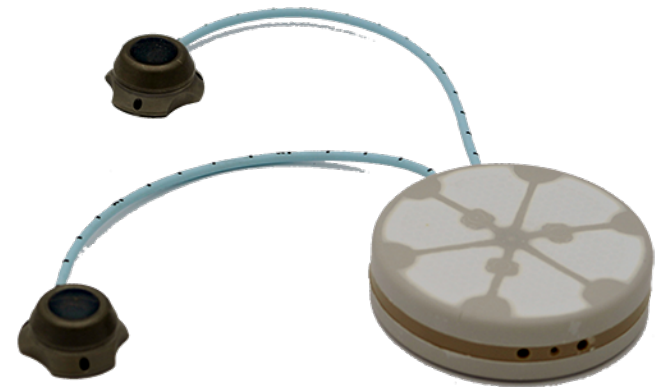
Challenges

- Diffusion/transport
- Cell loading capacity
- Implant geometry, thickness
- Biocompatibility
- vascularization
- >> loss in viability and function



MED in Phase I/II clinical trials

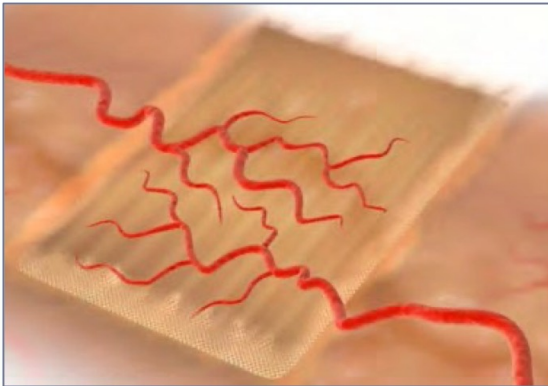
e.g. β Air, CellPouch, ENCAPTRA, MAILPAN



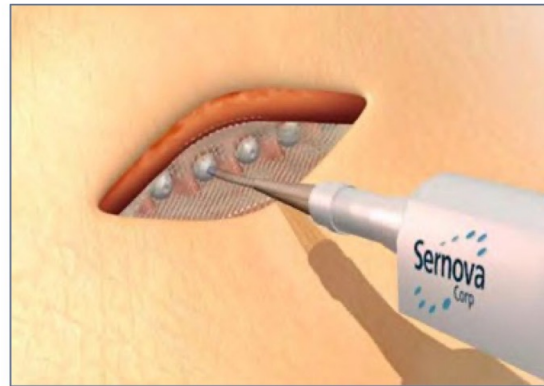
Beta-O2.com

Macroencapsulation

CellPouch™



Proprietary Cell Pouch is placed deep under the skin, allowing for vascularization & creating a natural environment for long-term function of therapeutic cells



Therapeutic cells are transplanted directly into the vascularized tissue chambers of the proprietary Cell Pouch



Therapeutic cells are responsive to endogenous regulation and release missing proteins or hormones into the bloodstream to correct biological dysfunction

Macroencapsulation

CellPouch™

BEFORE ISLET TRANSPLANT (baseline)

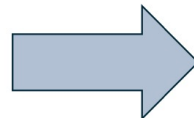
83 kg – Bodyweight

6.5 – Hemoglobin A1C

14U – Daily use of Insulin

15-16U short acting insulin

4 severe hypoglycemic
events per week



Post ISLET TRANSPLANT*

*Marginal Islet Dose

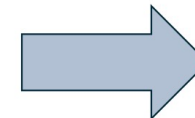
71 kg – Bodyweight

5.6 – Hemoglobin A1C

8U – Daily use of Insulin

14-15U short acting insulin

0 severe hypoglycemic
events per week



Post TOP-UP INFUSION** (32 months after baseline)

**Marginal Islet Dose intraportal top up

71 kg – Bodyweight

5.0 – Hemoglobin A1C

0U – Daily use of Insulin

0U – short acting insulin

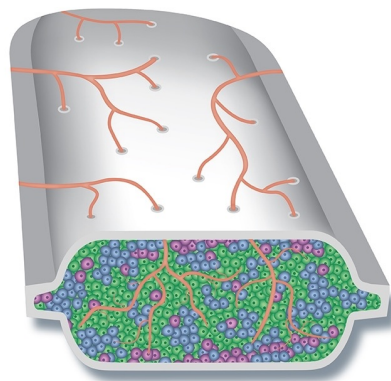
0 severe hypoglycemic
events per week

Macroencapsulation

Viacyte™

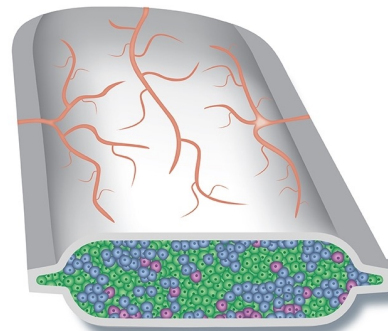
PEC-Direct

Clinical Stage



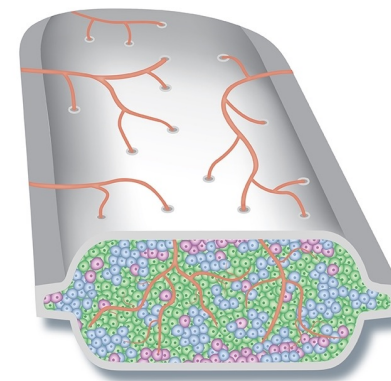
PEC-Encap

Clinical Stage



PEC-QT

Discovery Stage



Alpha cell / glucagon

Beta cell / insulin

Delta cell / somatostatin

Summary

Biological or artificial insulin delivery systems

Main goal: maintain blood glucose levels in a tight range

Automated insulin delivery – basal and bolus

Reduction of patient self-management, better compliance & quality of life

Decision making by smart systems

Challenges

Bench-to-bedside translation

Efficacy & Safety

Regulatory aspects & Standardization

Time-consuming & costly

Timetable

	Monday	Wednesday	Thursday
KW19	Cardiovascular Tissue Engineering Beta cell Replacement	Seminar: 4D Bioprinting Seminar: Implantable cardiac sensors	Lab Work Group A AG Schenke-Layland Silcherstraße 7/1
KW20	No Lecture	Seminar: CGM JC: Intro	Lab Work Urology
KW21	Advanced Imaging & Microscopy	Seminar: Stem-cells for T1DM JC: Tang et al.	Public holiday
KW24	Lecture (Prof. Loskill)	Seminar (Loskill)	Lab Work Group B AG Schenke-Layland Silcherstraße 7/1

Lab Work: Characterization of materials for Islet transplantation

Thank you for your attention!

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