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The regenerative therapy of type 1 diabetes mellitus

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Girne, Northern Cyprus
53rd Turkish National Diabetes Congress

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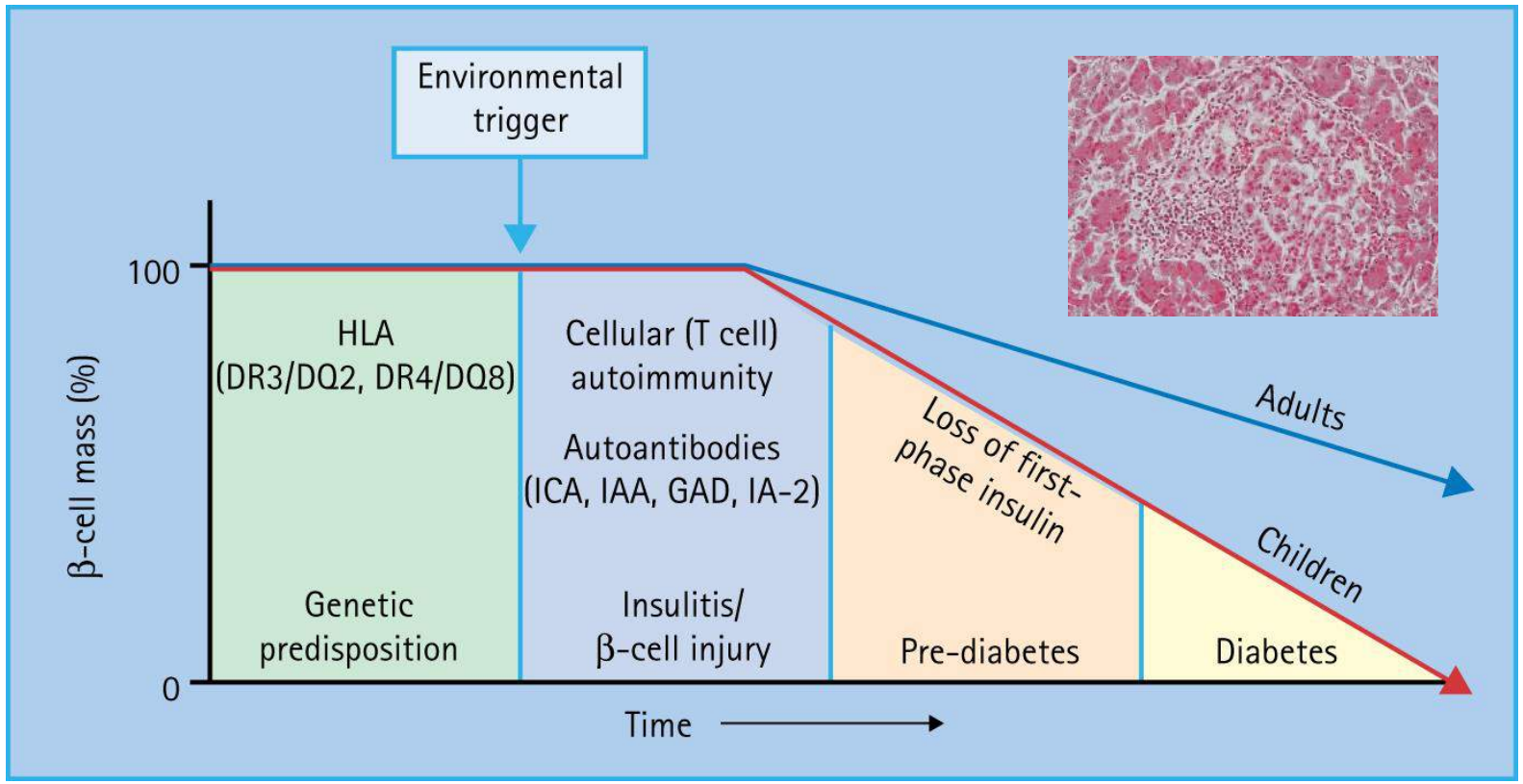
Natural history of type 1 diabetes

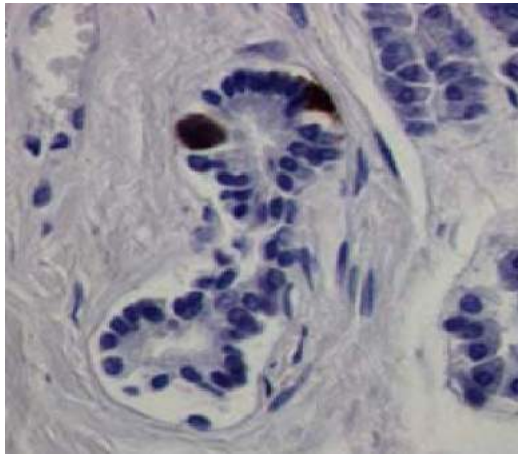


<u>Diagnosis of type 1 diabetes</u>

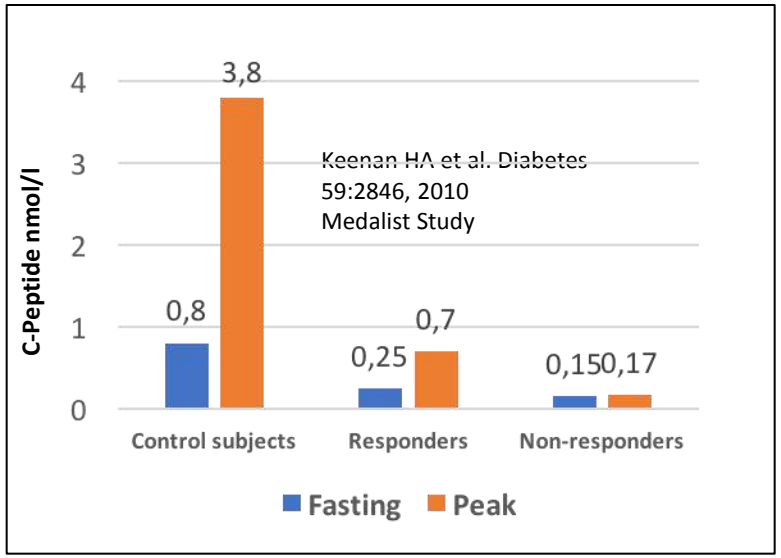
- Beta cell auto-antibodies GAD, insulin, IA2, Zinc transporter
- Loss of FPIR (prediabetes)
- C-peptide basal or stimulated after diabetes diagnosis
- Initial insulin treatment

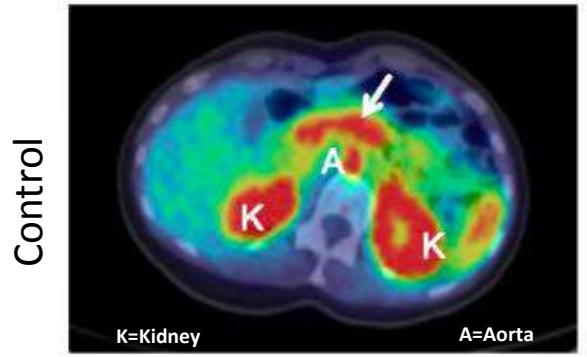
Evidence for Pancreatic regeneration in T1DM

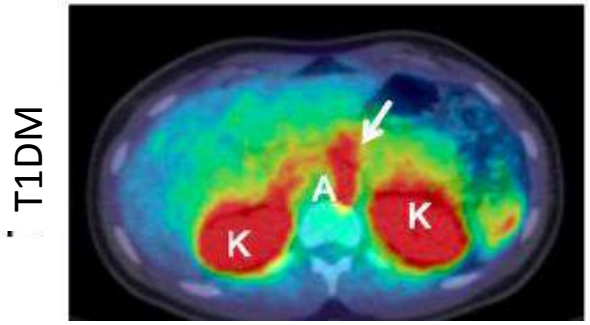
- Persistent fasting C-peptide > 0.03 nmol/l in 67.4% of type 1 diabetic (T1DM) patients
- >0.2 nmol/l fasting C-peptide responsive to mixed meal tolerance test (MMTT)
- Insulin positive cells in exocrine and ductular pancreas in T1DM brain-dead donors
- 40% of normal [^{11}C] 5-hydroxytryptophan retention in position emission tomography



Meier, J.J., Diabetologia 48: 2221, 2010







Eriksson O et al. Diabetes, 63:3428, 2014

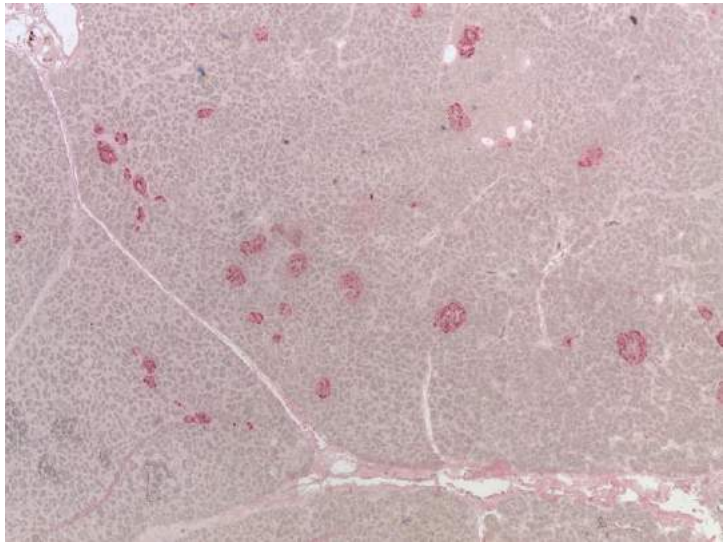
Evaluation of beta cell reserve

- **Applied Research** - Positron emission tomography – hydroxytrytophan, vesicular monoamine transporter type 2
- **Basic Research** - Immunohistochemistry of pancreas, morphometry
- **Clinical** – C-peptide level (nmol/l), insulin daily dose, risk assessment for loss of beta cell reserve

Inclusion criteria for current intervention trials

- C-peptide > 0.2 nmol/l
- 1 autoantibody in significant titre
- Intensive insulin therapy (not conventional, not insulin pump) with self measurement of blood glucose, initial insulin therapy (no temporary administration of OAD)

Adult nesidioblastosis



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Endogeneous Insulin Reserve by Stimulation Tests

C-peptide Stimulation Tests

- Mixed meal tolerance test (MMTT) 6 kcal/kg
- Glucagon stimulation test (GST) Glucagon 1 mg i.v.

Type 1 diabetes family risk screening

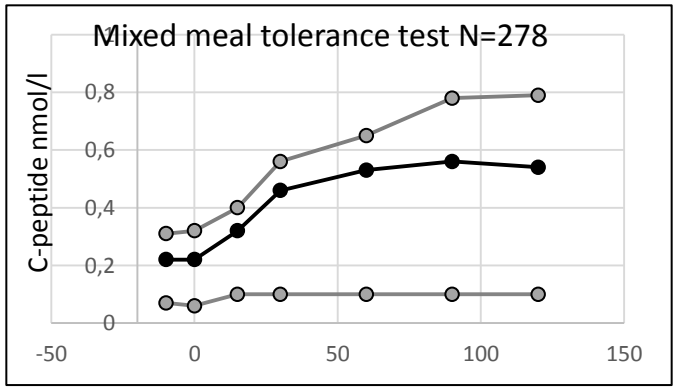
- Intravenous glucose tolerance test 5g/kg (maximum 35 g) First phase insulin release (FPIR) 1+3 min
- Oral glucose tolerance test OGTT) 75 g

C-peptide

Basal 0.17 nmol/l
Peak Stimulated with MMTT 0.40 nmol/l
Peak Stimulated with Glucagon 0.30 nmol/l
90 min MMTT 0.36 nmol/l, all (mean nmol/l) 0.31
6 min GST 0.27 nmol/l
Present cutoff's for inclusion criteria of intervention studies
Stimulated > 0.2 nmol/l

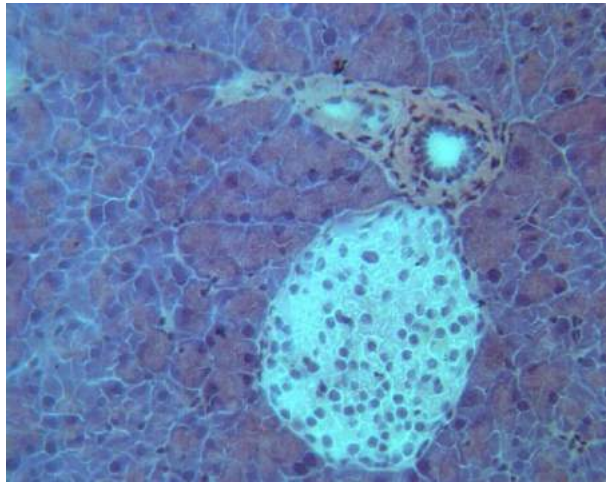
Cutoff for > 45% 5 y risk of type 1 diabetes

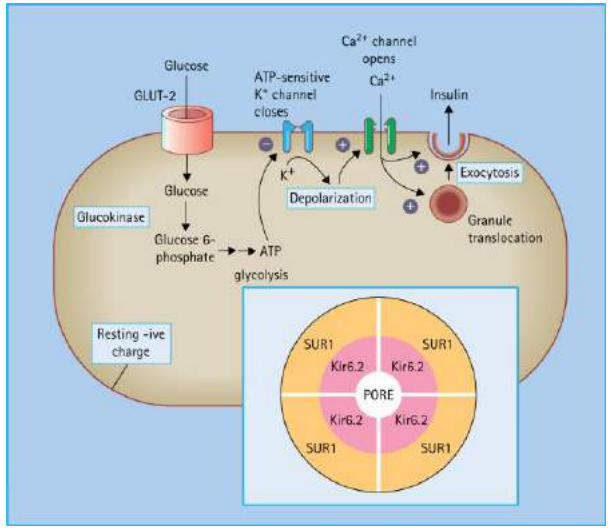
FPIR 1+3 min > 60 µU/ml insulin older than 8 yrs of age
OGTT > 114 mg/dl 2 h 75 g (IGT > 140 mg/dl !!)



Greenbaum C, Diabetes Care 31:1966, 2008
Diabetes Prevention Trial Study Group-1, NEJM 346:1685, 2002

Technological approaches to regeneration or replacement





- **Therapy aiming at Replacement of beta cells**
  - Pancreas and islet transplantation
  - Stem cell based approaches
    - **Direct reprogramming** Mesenchymal stem cells (MSC) in clinical trials
    - Generation of beta-cell like cells from iPS cells generated from somatic cells – **indirect reprogramming**
- **Therapy aiming at Regeneration of beta cells**
  - Intensive insulin therapy to foster honeymoon period (functional regeneration)
  - Immunintervention as a means to support pancreatic islet regeneration
  - Transdifferentiation from non-stem cells

Pancreas and islet transplantation

PANCREAS

In Germany 100-120 per year, 250 patients on waiting list,

Eurotransplant region 192 patients transplanted (2015), but 961 brain-dead organ donors
www.eurotransplant.org

Simultaneous Pancreas-Kidney transplantation beneficial in patients with kidney failure, but not pancreas transplantation alone

PANCREATIC ISLET

Pro

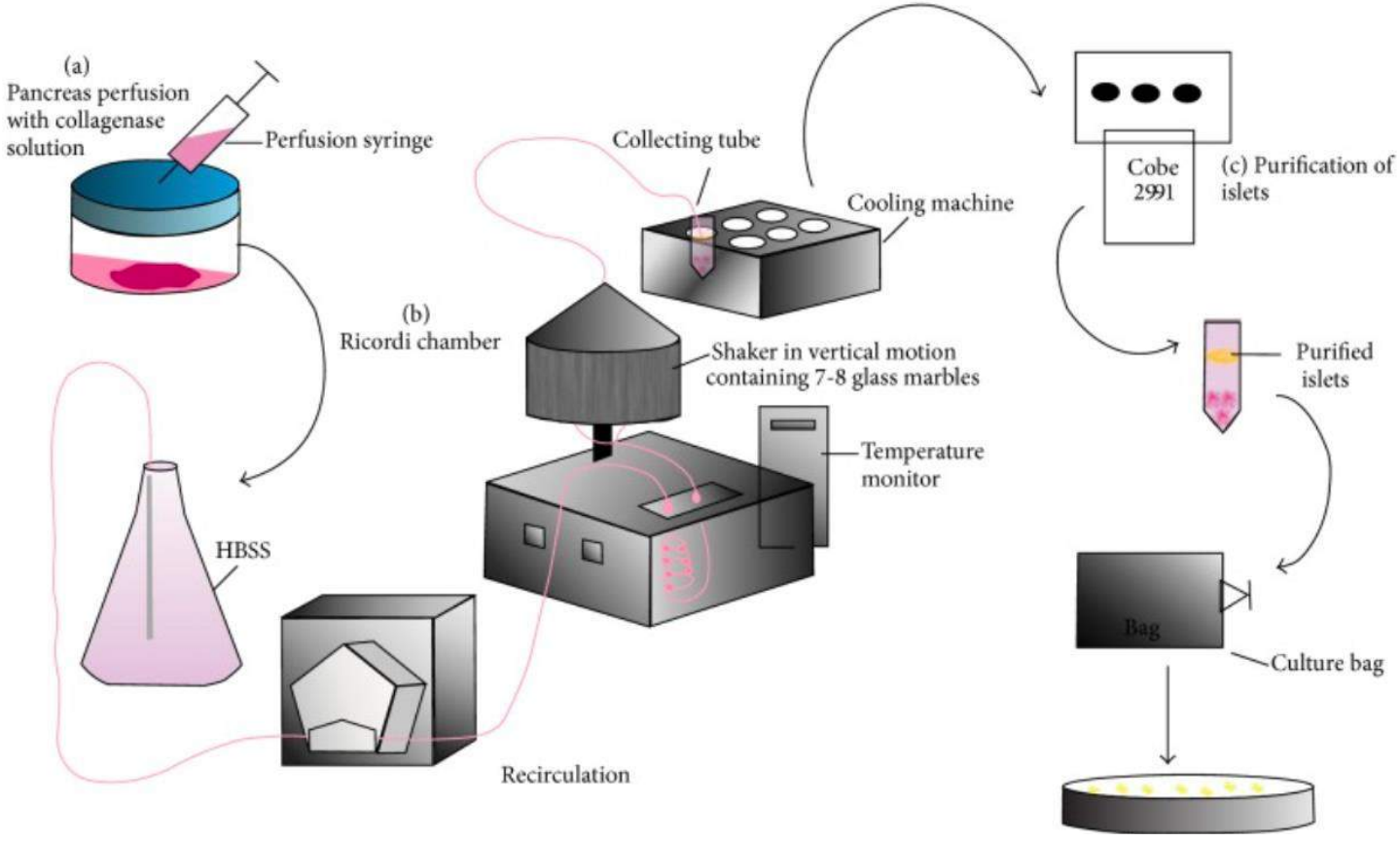
90% of subjects permanently without severe hypoglycemia
70% of subjects 2 years of improved glycemia
40% achieve 2 years of insulin independence

Contra

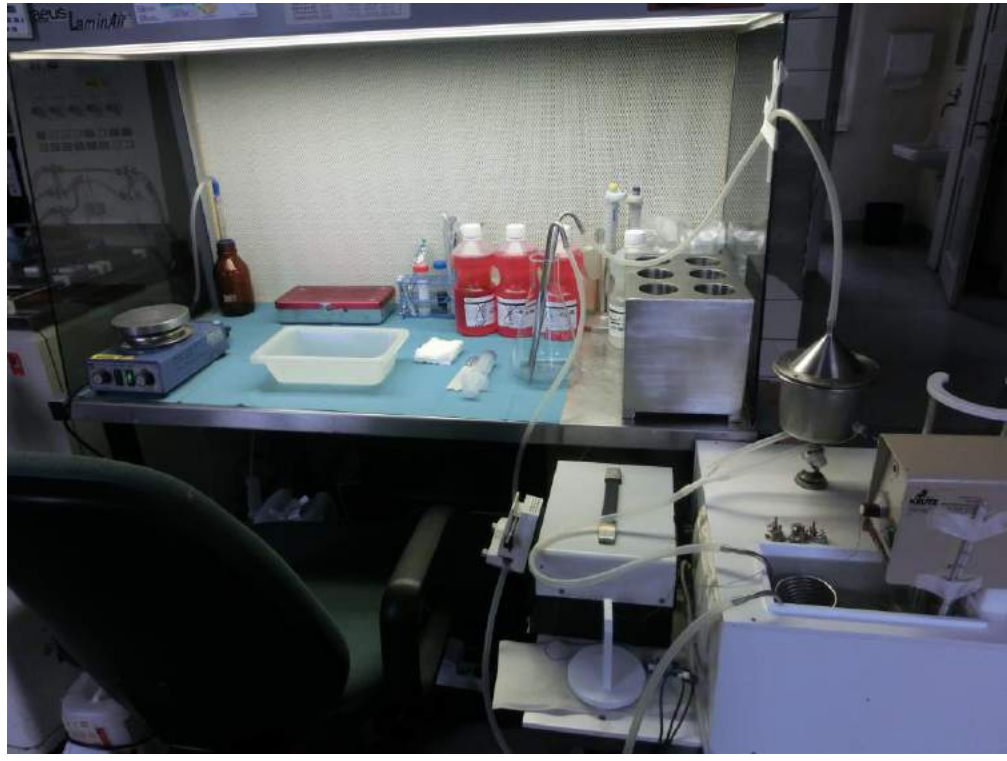
Only 50% of donor pancreases allocated, the rest with insufficient quality for islet isolation
2 or more donors required, many islets die shortly after Tx
Islet allograft supply limits applicability to 1000 patients/year in Eurotransplant region
Allograft function decreases with time
Immunosuppression-related complications: decline of renal function
Infections, malignancy risk
No clear survival benefit
Alternative medical treatments rapidly improving (insulin pump, hybrid closed loop system, CGM)

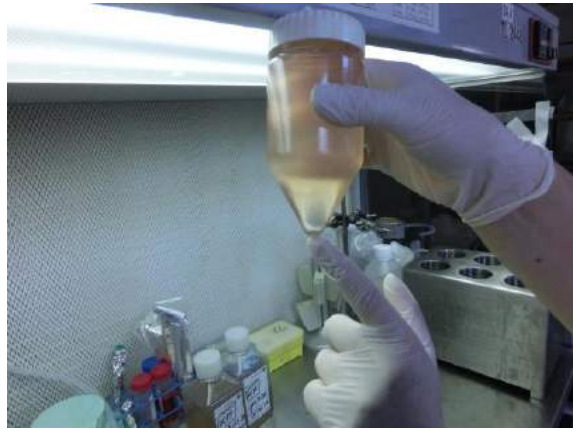
Harlan DM. Diabetes Care 2016 39:1072-4.

Pancreatic islet isolation –



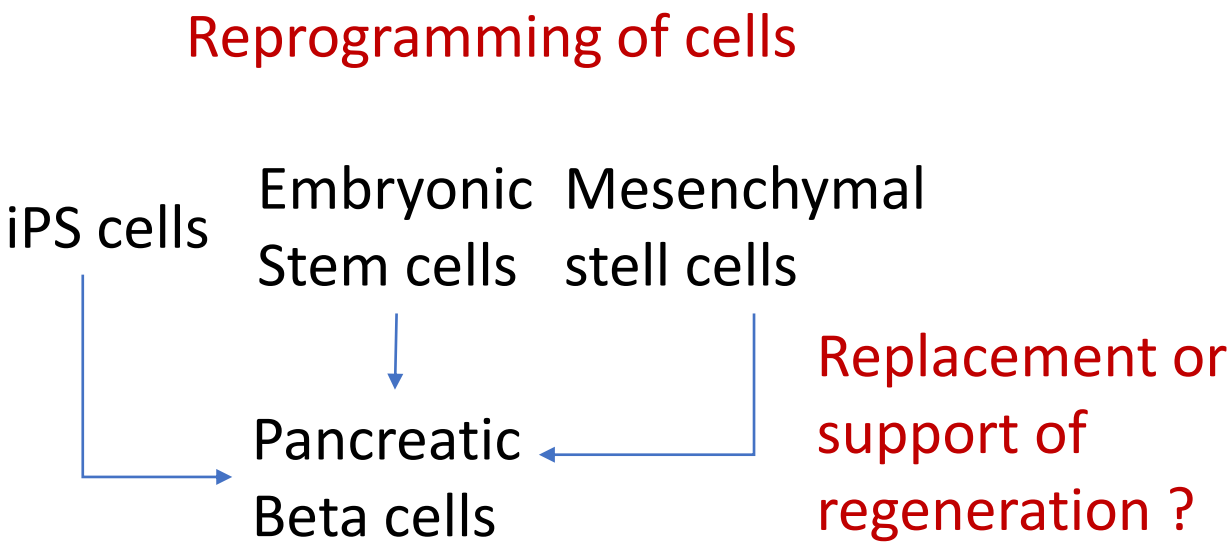
Purified islets culture





- In vitro expansion of human pancreatic beta cells leads to dedifferentiation of beta-cells

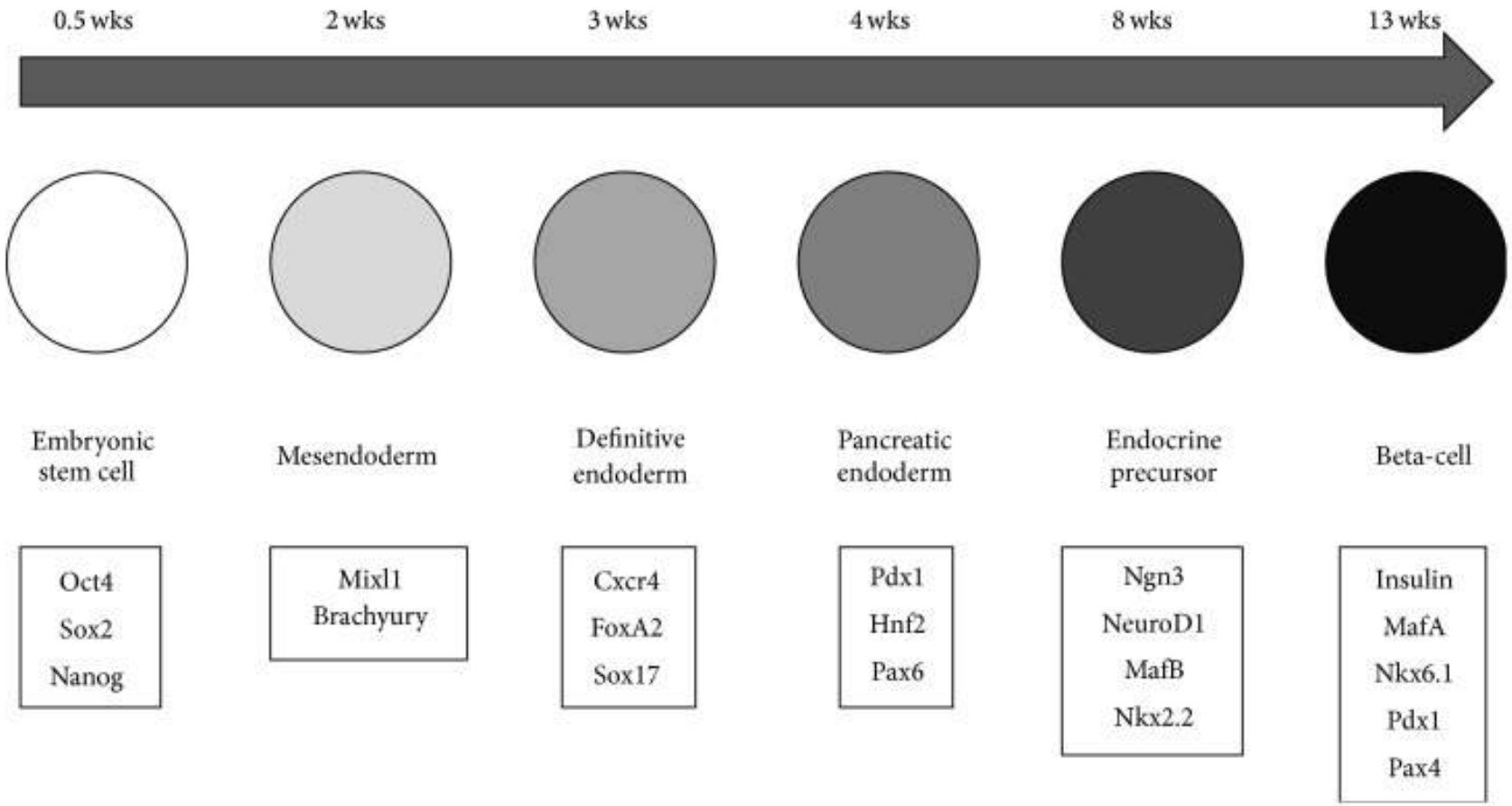
Stem cell based Approaches



- Mesenchymal stem cells (MSC) – 5 clinical trials
- 3[#] favour regeneration without initial culture to induce/support insulin secretion
- 2[##] favour reprogramming/replacement as they claim to have attained insulin secreting cells prior to implantation
- Embryonic stem cells (ESC) and Induced pluripotent stem cells (iPS) – human beta-cell like cells, but no clinical trial available to this end

[#] Cai J et al. Diabetes Care 39:149, 2016. Carlsson PO et al. Diabetes 64:587, 2015. Hu J et al. Endocrine J 60:347, 2013
[##] Thakkar UG et al. Cytotherapy 17:940, 2015. Dave SD et al. Clin Exp Med 15:41, 2015

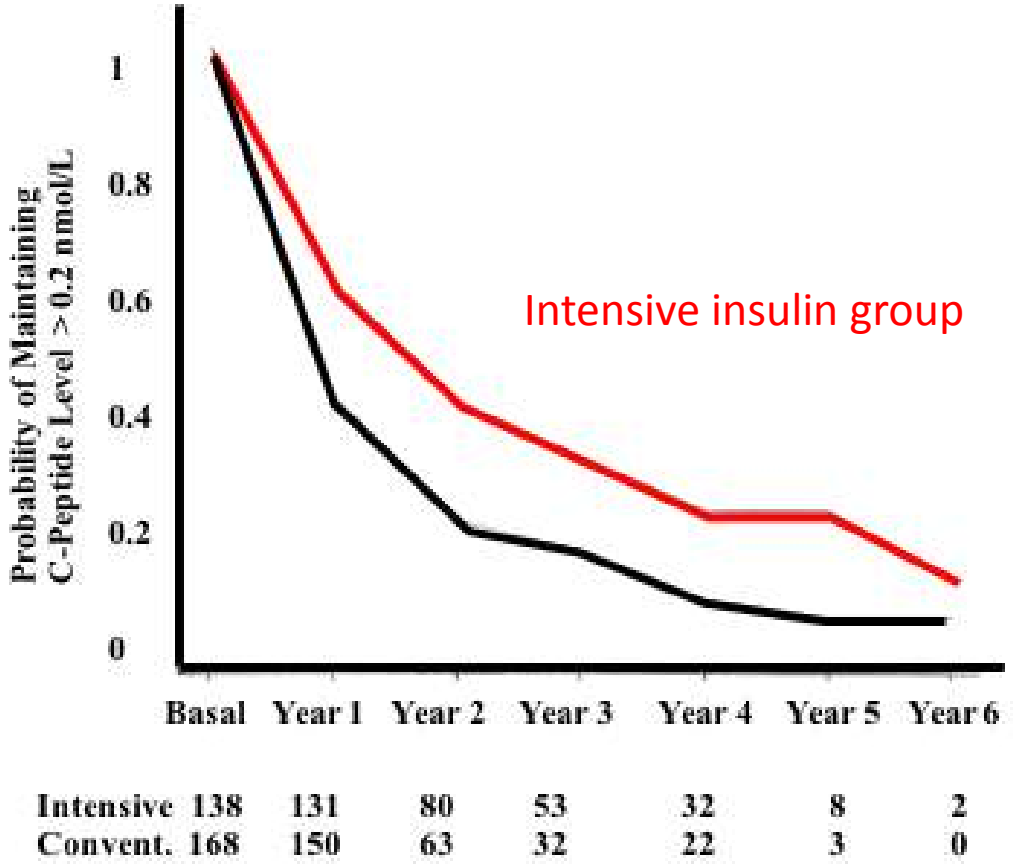
Generating beta cells from stem cells



Rekittke NE et al. Stem Cells Int. 2016:3764681

Intensive insulin therapy – near normal glucose control

- Intensive insulin therapy slows down stimulated C-Peptide decrease
- 30% higher C-Peptide compared to conventional insulin therapy
- Glp-1 agonist exenatide reported to protect transplanted beta cell mass in 50% of studies



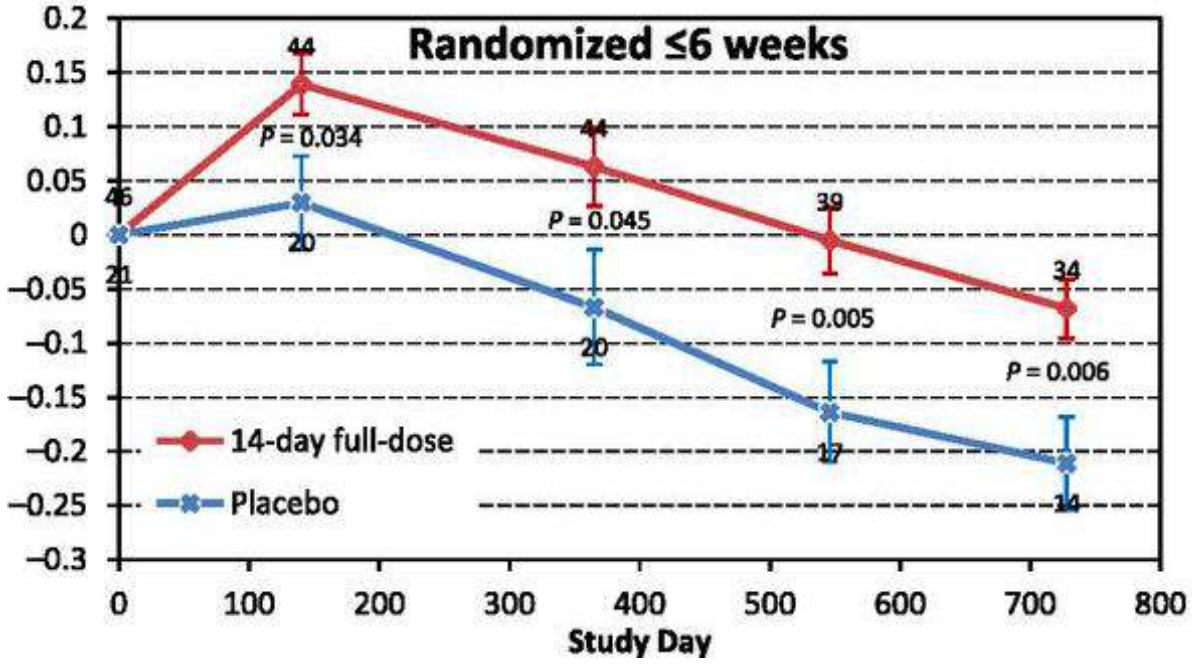
DCCT, Ann. Intern. Med. 128:517-23, 1998
Linn T et al. BMC Endocr Disord 3:5, 2003

Immunintervention

Ongoing trials in
Adult newly diagnosed patients

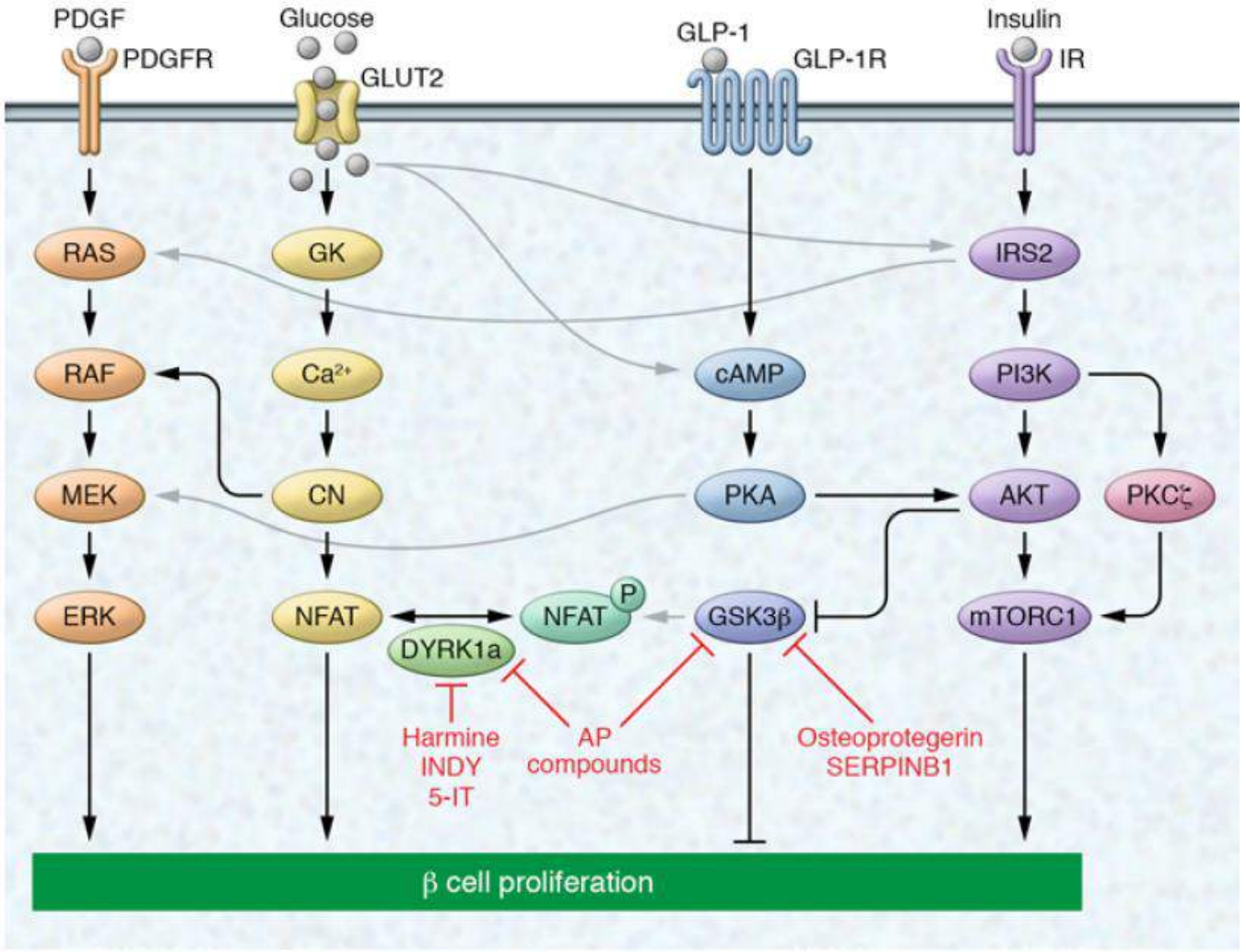
- Il-8 antagonist ladarixin (small molecule), Dompe, Italy.NCT02814838
- Vaccination with proinsulin-related peptide with CSSC redox motif (Imcyse; belgium)

Teplizumab (anti-CD 3 antibody) Protege Trial



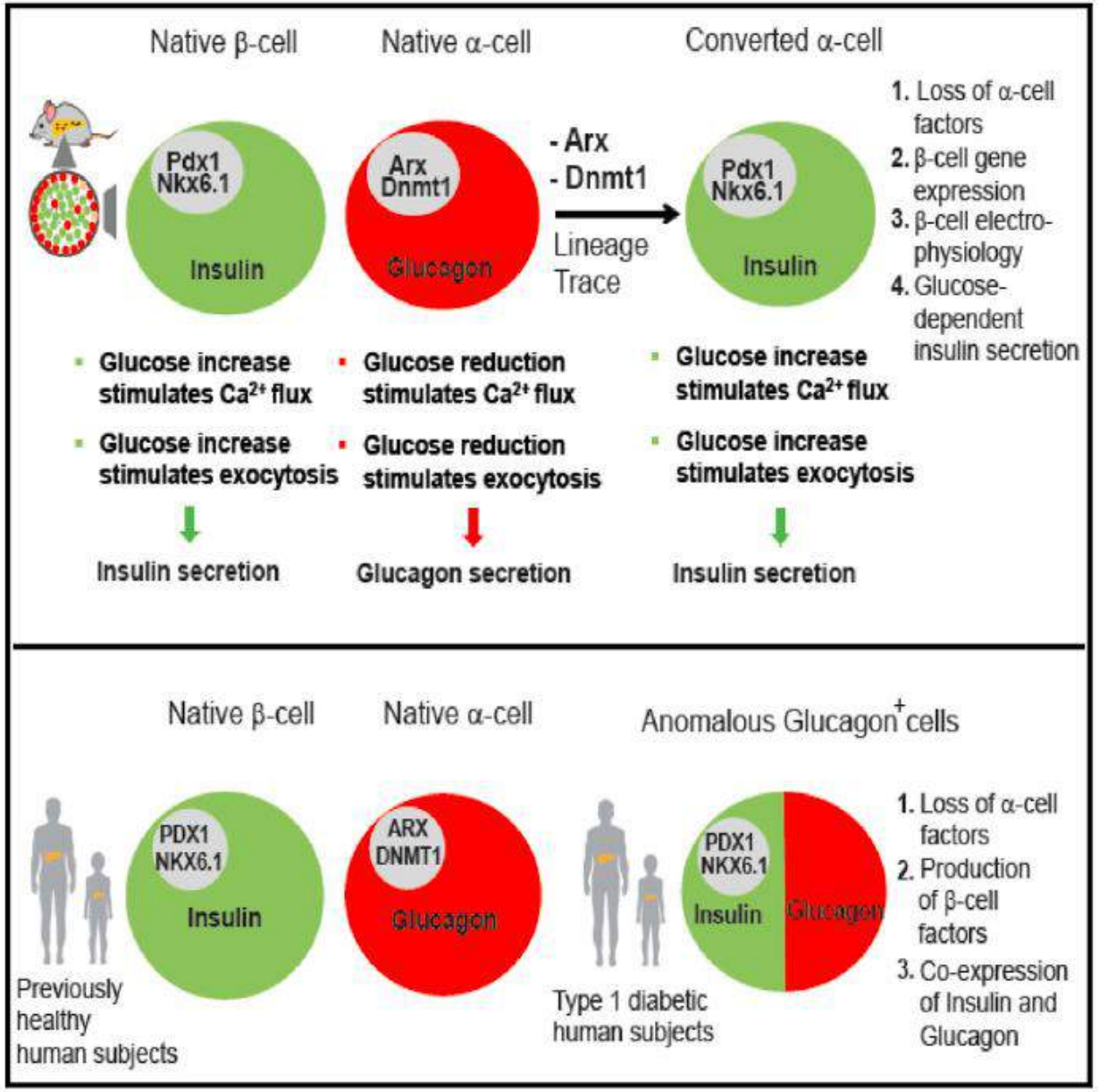
Hagopian W et al. Diabetes 2013;62:3901-3908

Screening in human pancreatic beta cells

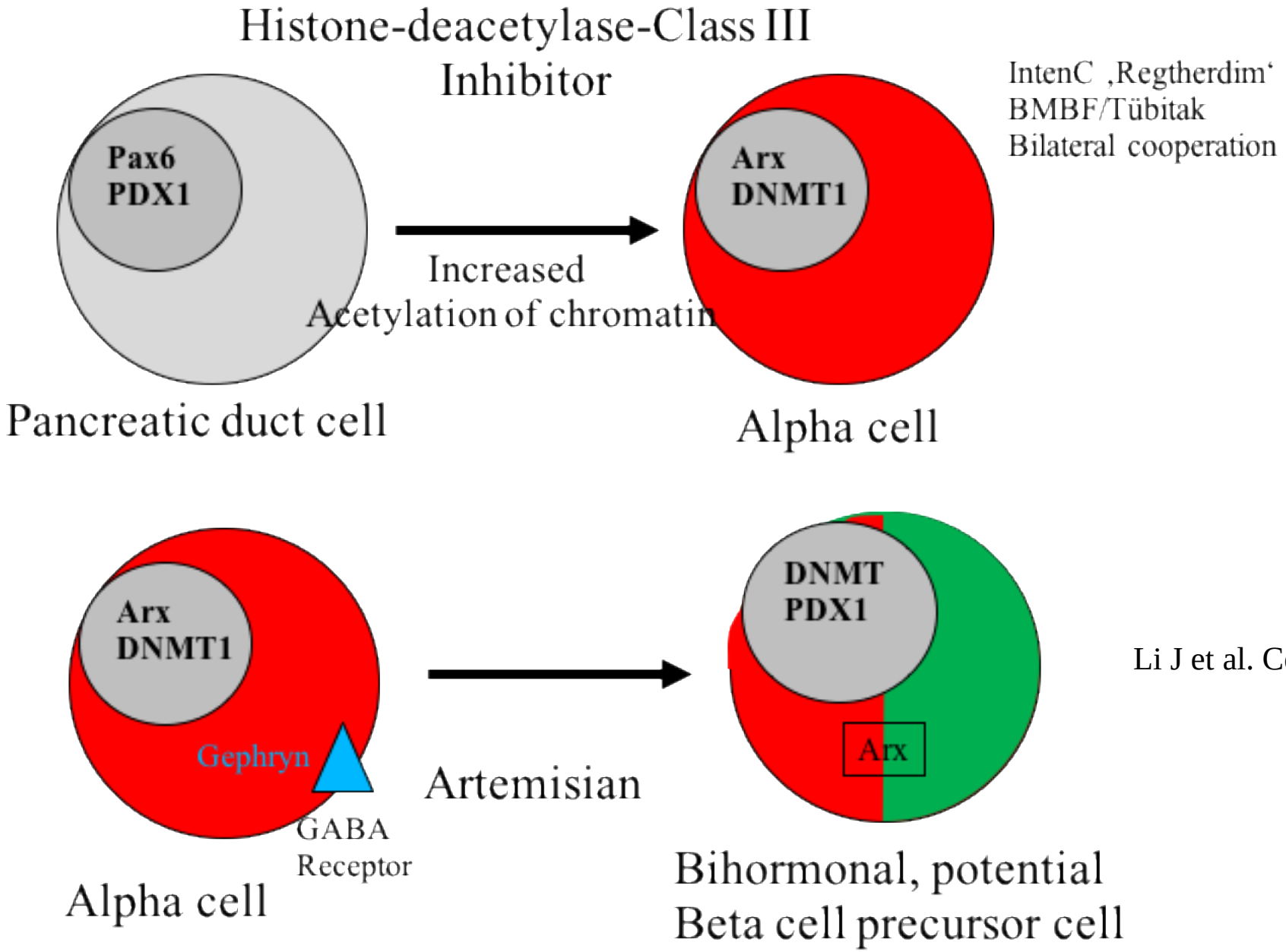


Benthuysen JR et al
J Clin Invest
126:3651-3660, 2016

Adult pancreatic alpha cells into beta cells



Chakravarty H et al. Cell Metab 25:622, 2017



Li J et al. Cell 168:86-100, 2017

Thanks for your attention

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