Immunotherapy for Type 1 Diabetes

Colin M Dayan

Cardiff University, University of Bristol,

UK T1D Immunotherapy Consortium

Disclosures

- I have lectured for or been involved as an advisor to the following companies:
- Novonordisk, Sanofi-genzyme, Janssen, Servier, Lilly, Astrazeneca, Provention Bio, UCB, MSD.
- I hold a patent jointly with Midatech plc.

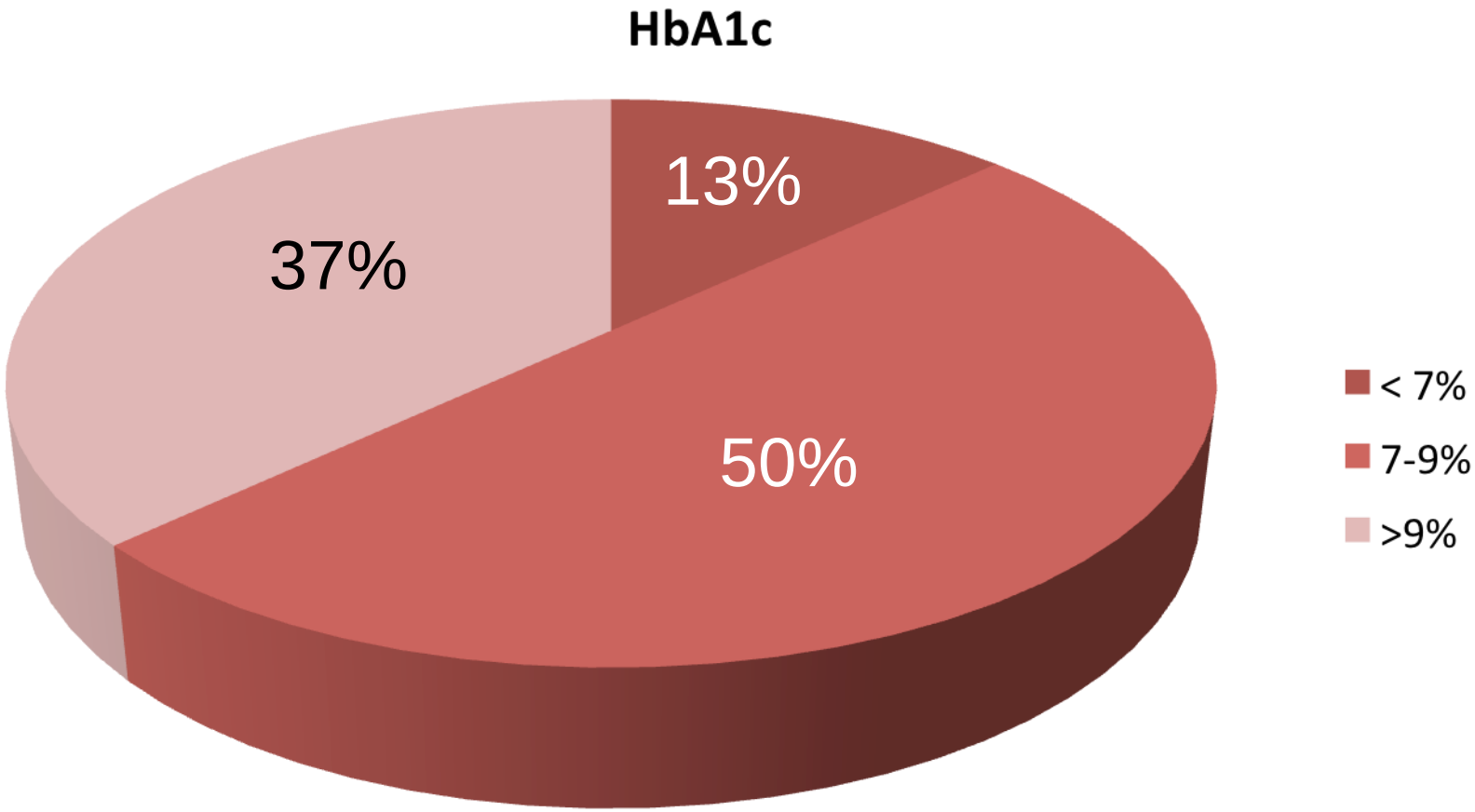
- “The transformation and subsequent eradication of type 1 diabetes is possible – it just requires sufficient ambition and focus”

Sufficient ambition …and focus

Type 1 diabetes

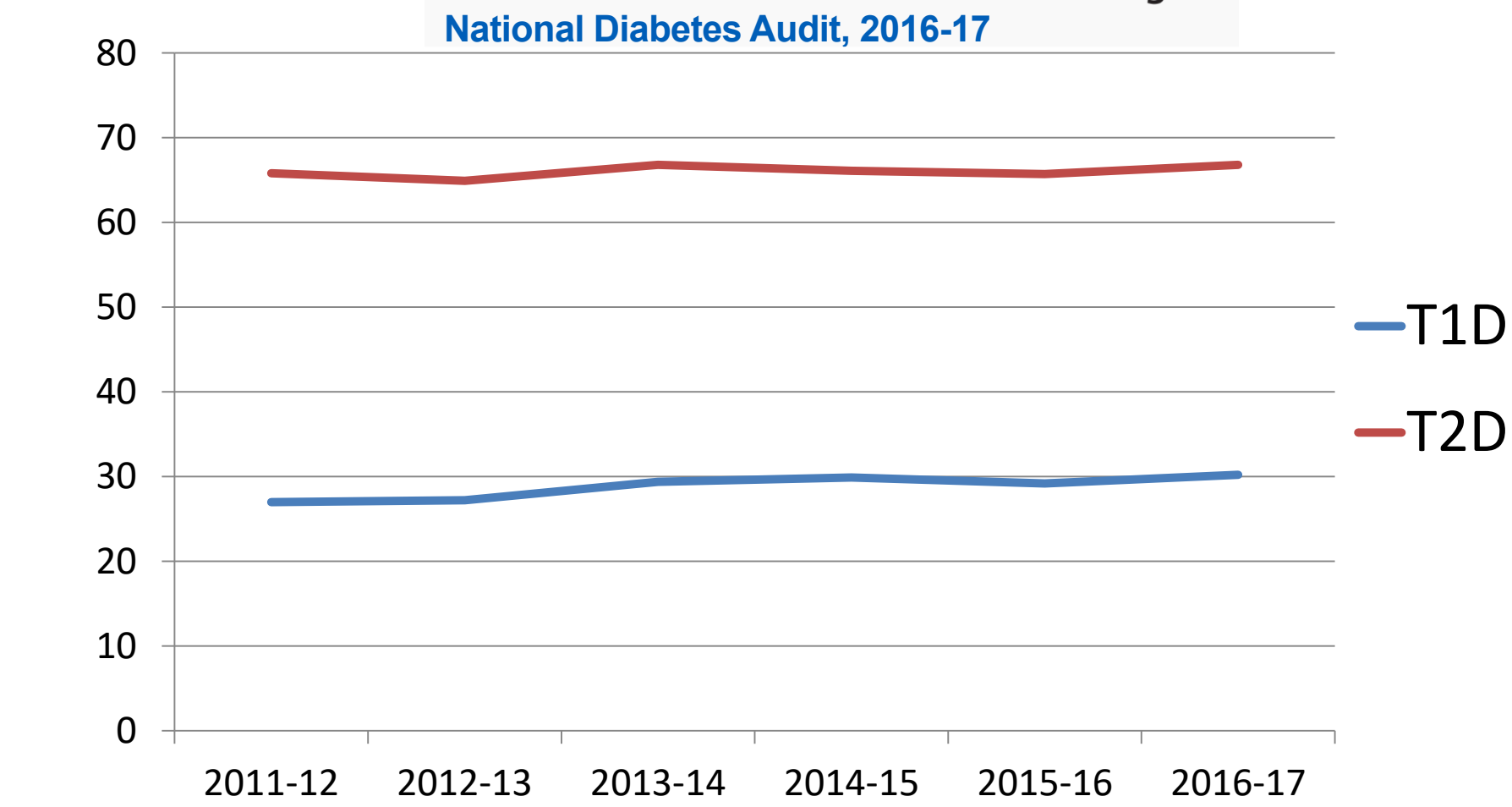
- ….. The unmet need….
- …we have to want to do this enough…

HbA1c levels in T1D in Scotland 2008 (n= 21,719)

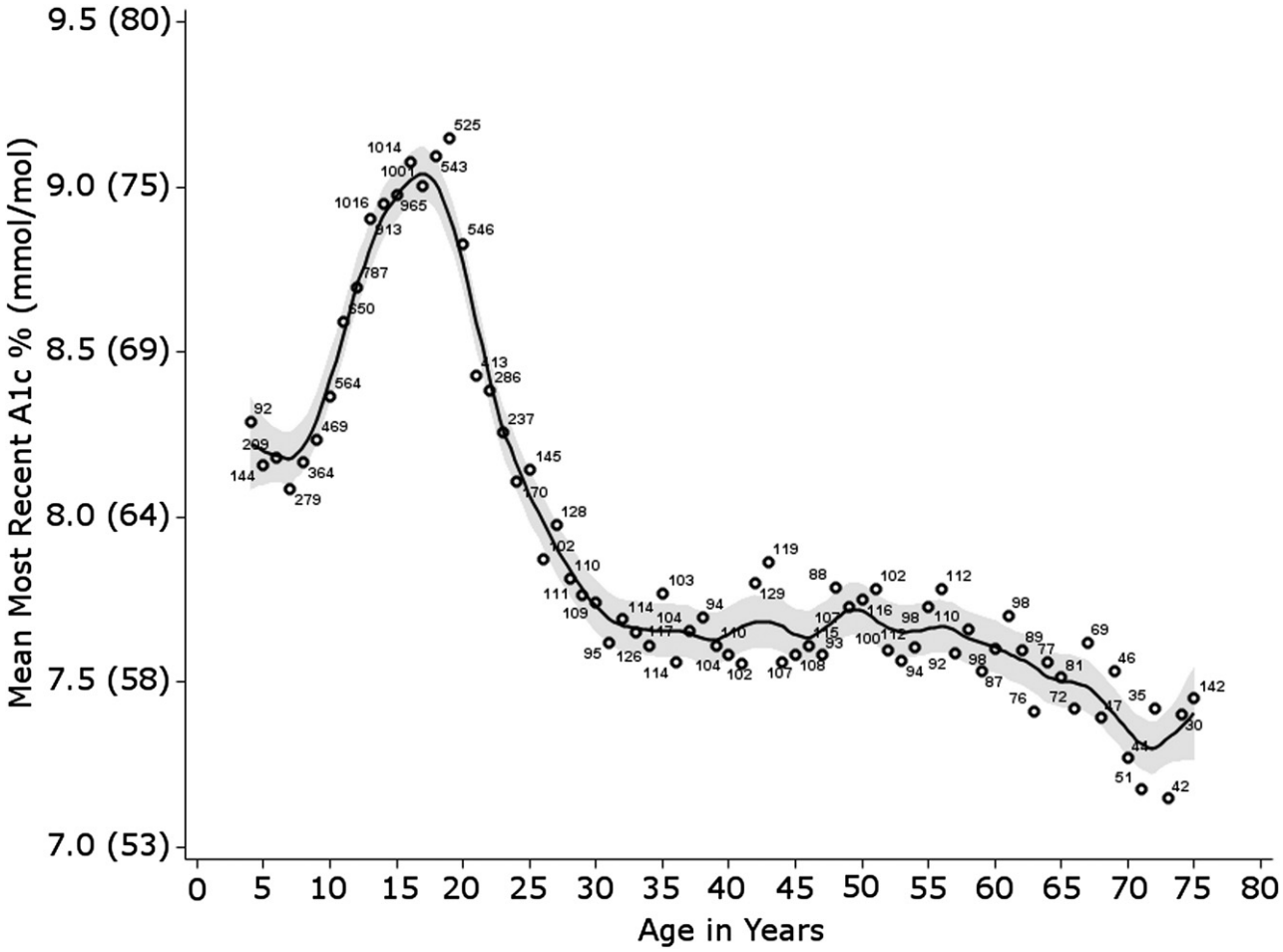


(*Livingstone et al 2012*)

UK NDA – HbA1c < 7.5%



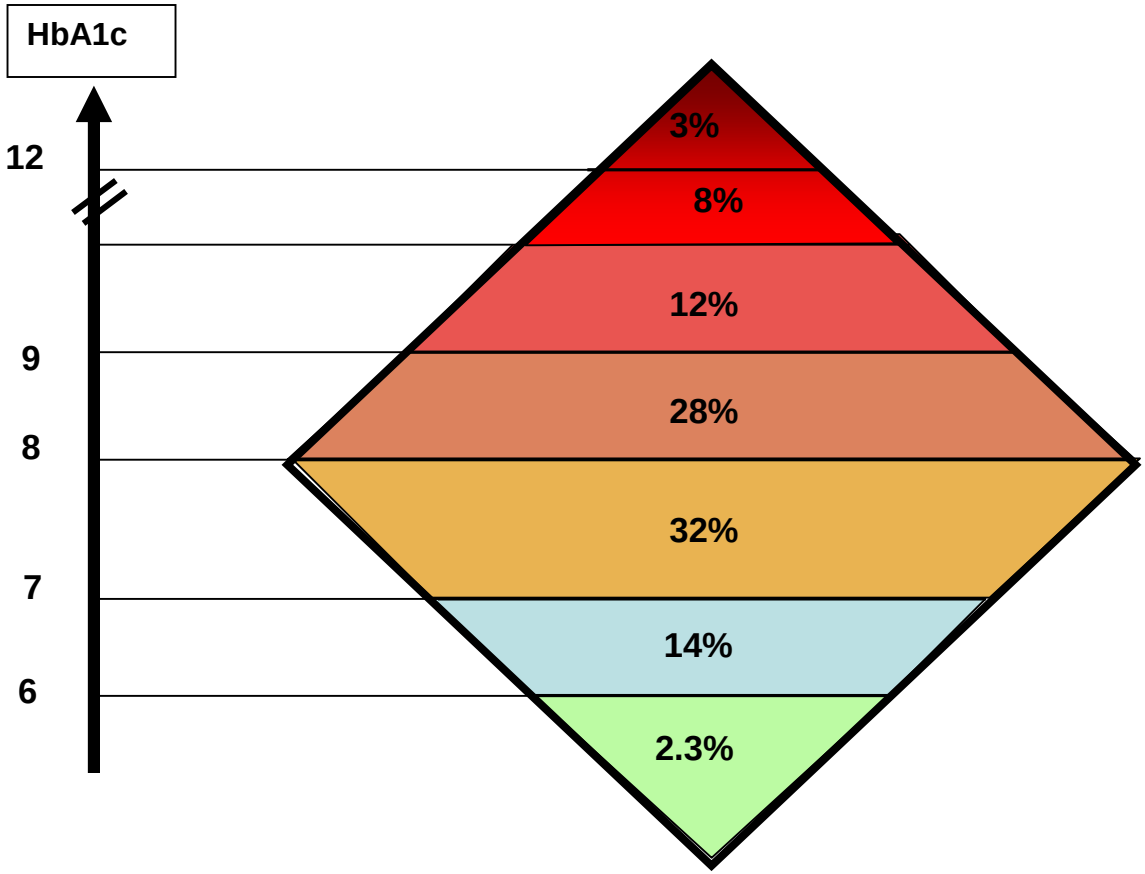
T1D Exchange data 2014 (USA)



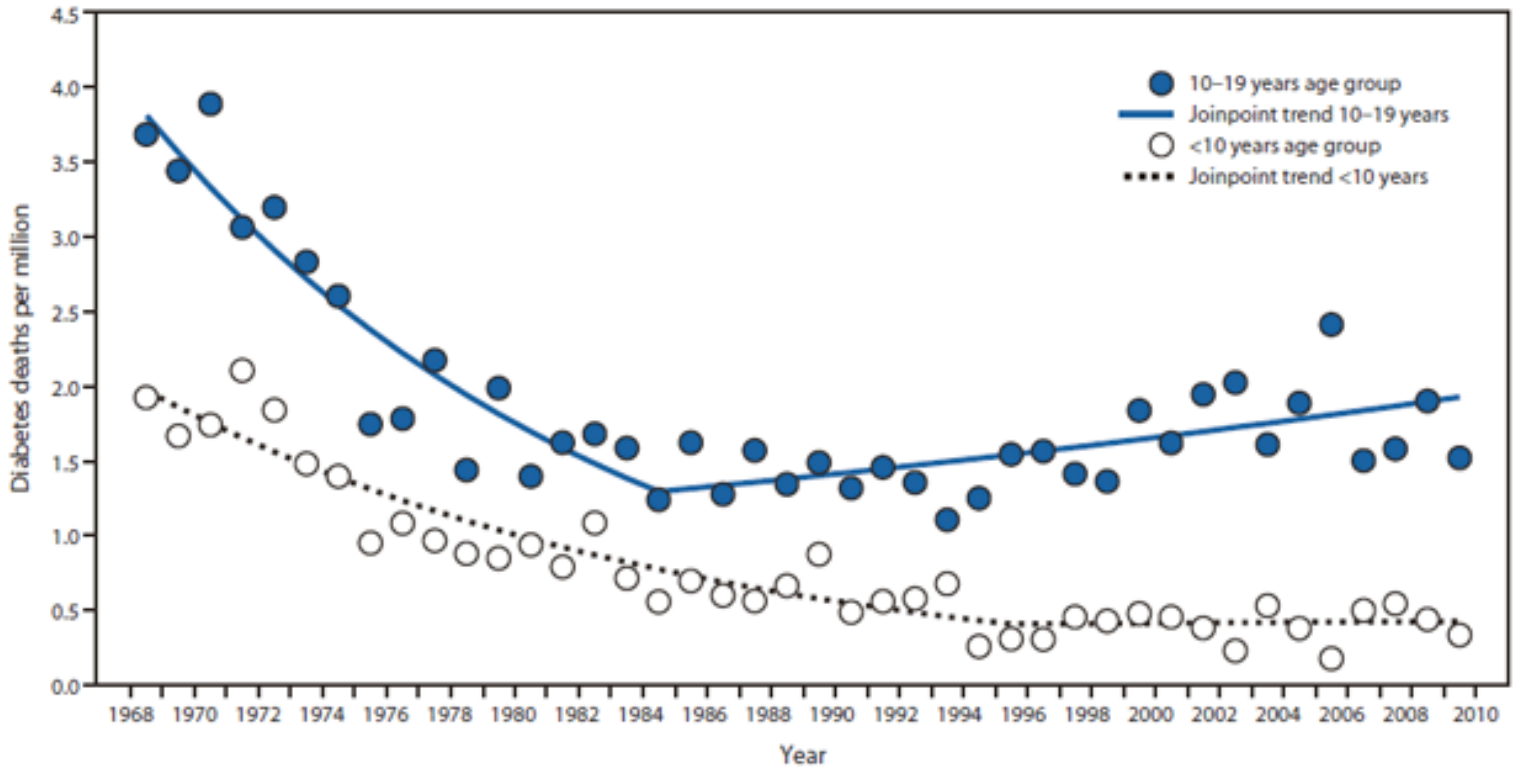
Miller et al 2015

Achieving ideal glycaemic control with insulin is almost impossible

(n=1000 from diabetes clinic)



Diabetes Death Rates Among Youths Aged ≤19 Years — United States, 1968–2009



Center for Disease Control and Prevention, 2012

Excess mortality in young people with T1D is due to DKA and hypoglycaemia

Excess all-cause mortality before age 30 in childhood onset type 1 diabetes: data from the Brecon Group Cohort in Wales

Diana R Wasag,[1] John W Gregory,[2] Colin Dayan,[3] John N Harvey,[1] on behalf of the Brecon Group

What this study adds?

- A near threefold excess mortality persists with no clear evidence of change over time in this age group (before age 30) when compared with other surveys.
- Before age 30, the excess mortality is not due to nephropathy and microvascular complications.
- Ketoacidosis remains the leading cause of death in these patients. Hypoglycaemia also contributes to mortality.

N= 3642

Arch Dis Child. 2018 Jan;103(1):44-48

The unmet need….

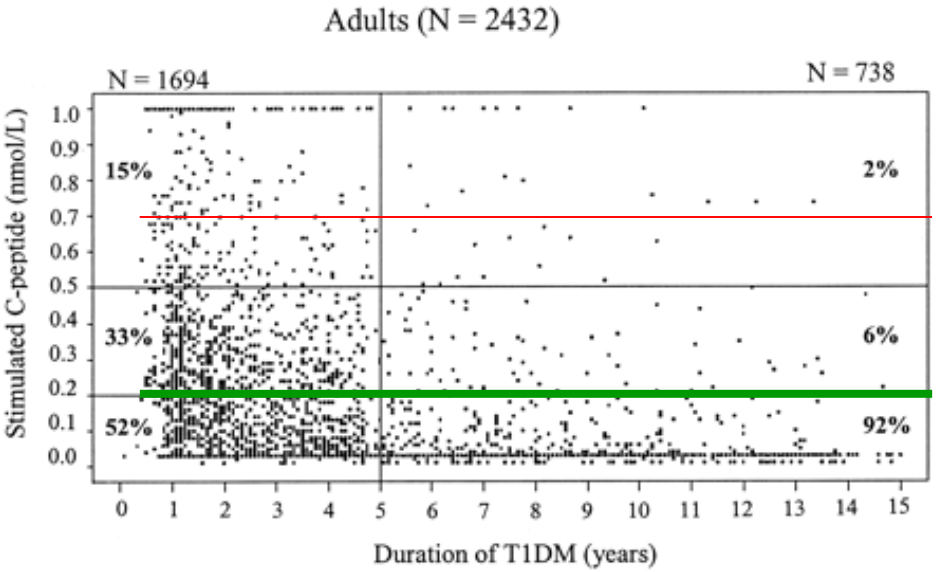

10:00
AM
120
mg/dL
0.5 U
Act. Insulin

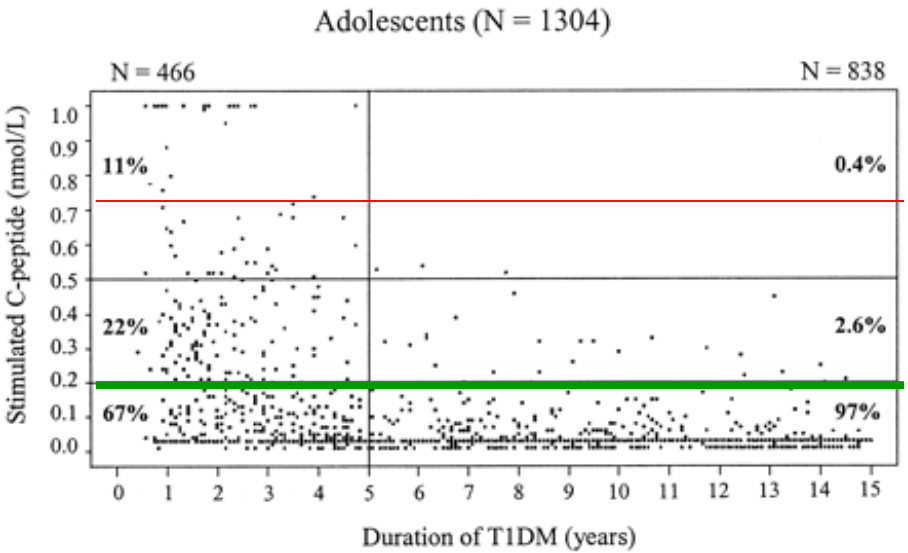
Type 1 diabetes

- …… the benefits of c-peptide (beta cell) preservation

Loss of beta cell function after Dx

Palmer et al 2004





Adults

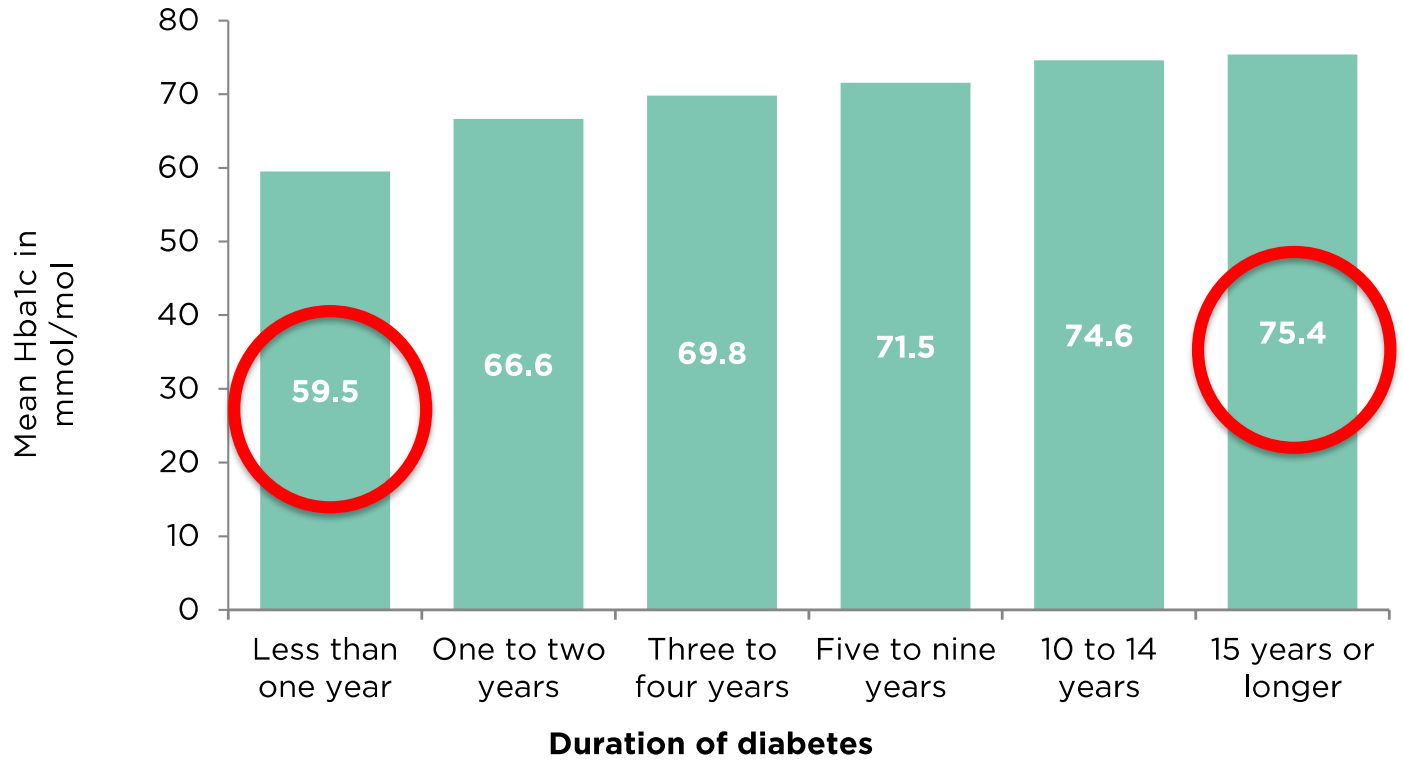
5th pc normal

"Clinically Significant"

Adolescents

UK NPDA

Figure 11: Mean HbA1c for children and young people with Type 1 diabetes by duration of diabetes for England and Wales, 2015/16



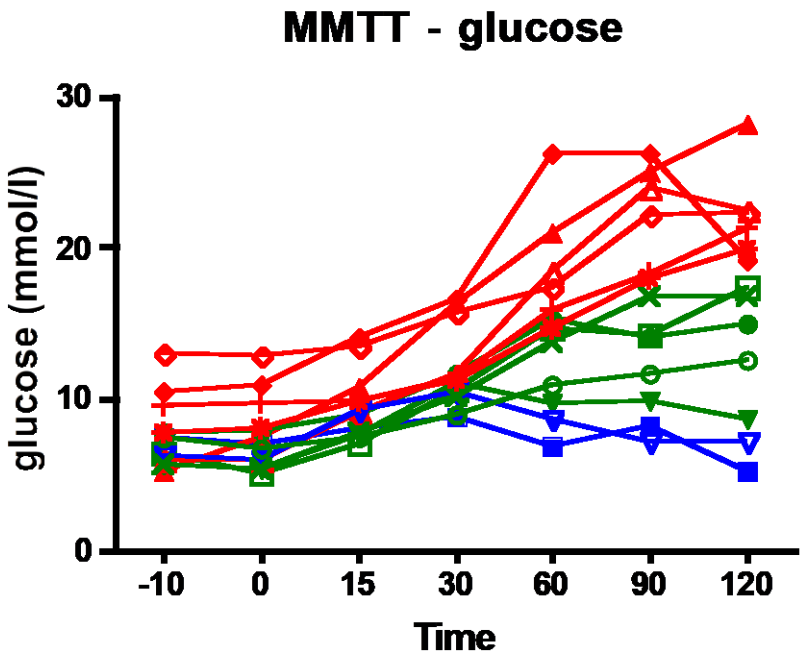
HbA1c: 58mmol/mol =7.5%; 75mmol/mol=9.0%

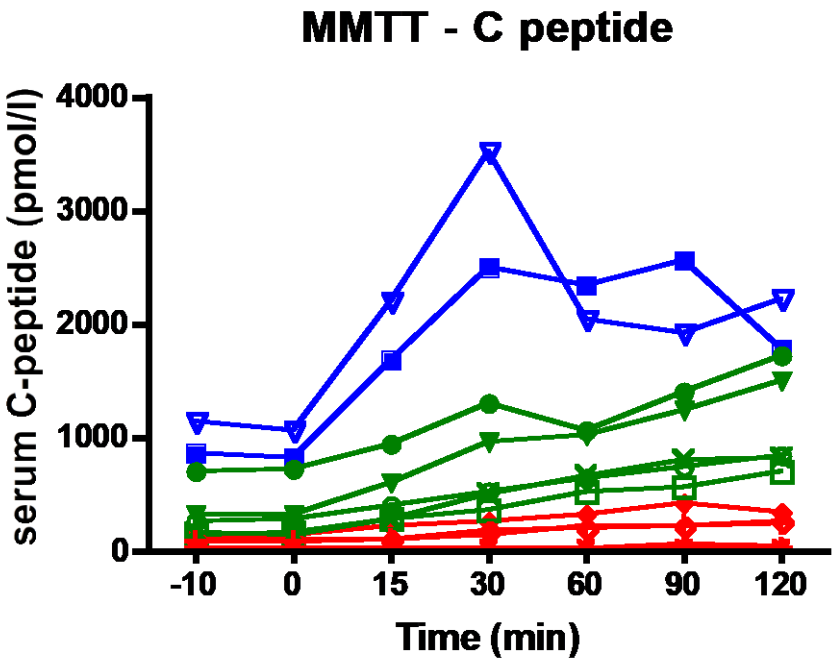
Effects of preserved insulin (c-peptide) – data from children

C-peptide	HbA1c	% < 7.5	Insulin (U/kg/d)
< 0.04	8.49	18.4	1.07
0.04-0.2	8.10	32.3	1.08
> 0.2	7.47	51.9	0.93

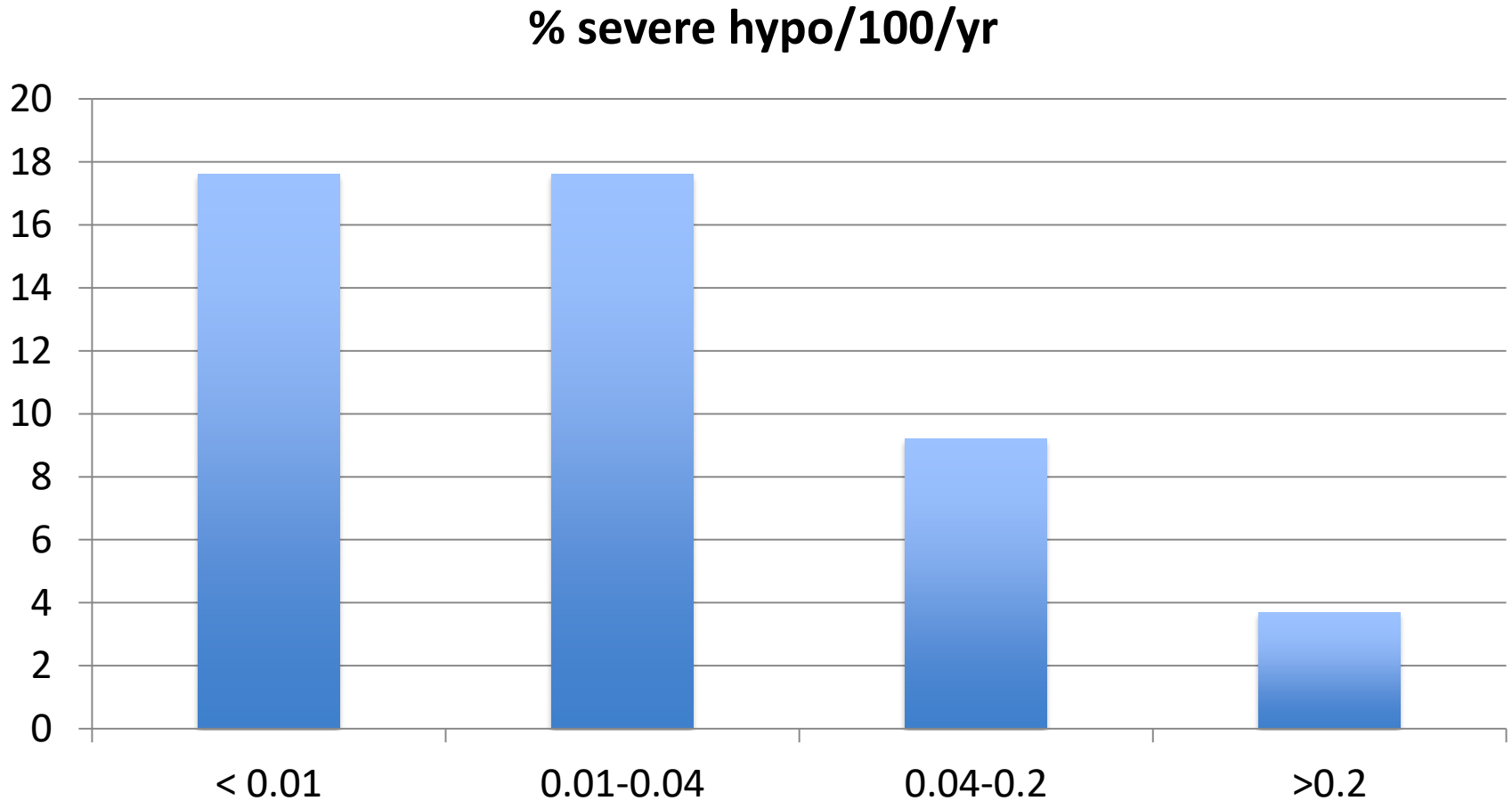
Sorensen et al 2013

Mixed Meal Tolerance Test



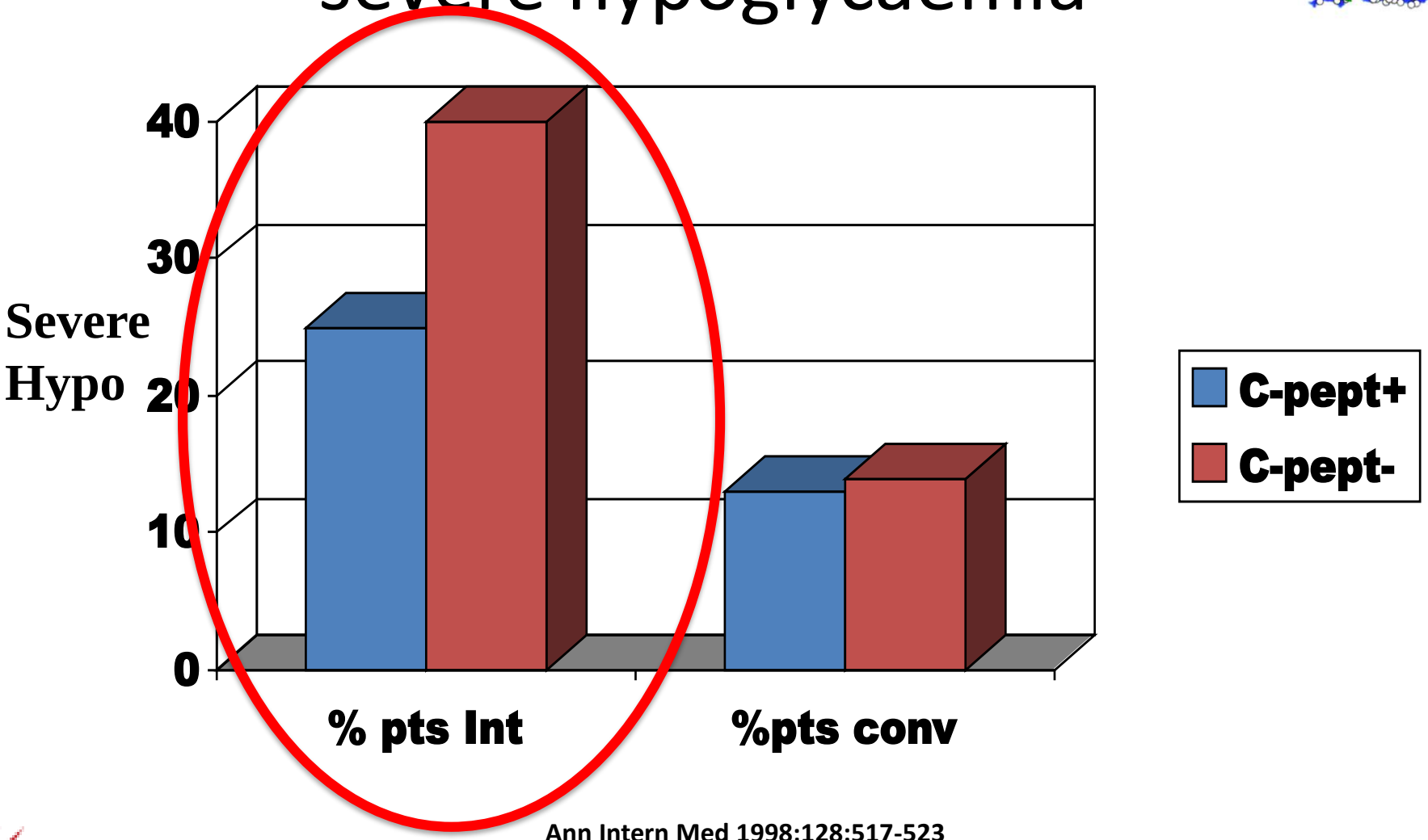


Risk of severe hypoglycaemia in Danish children



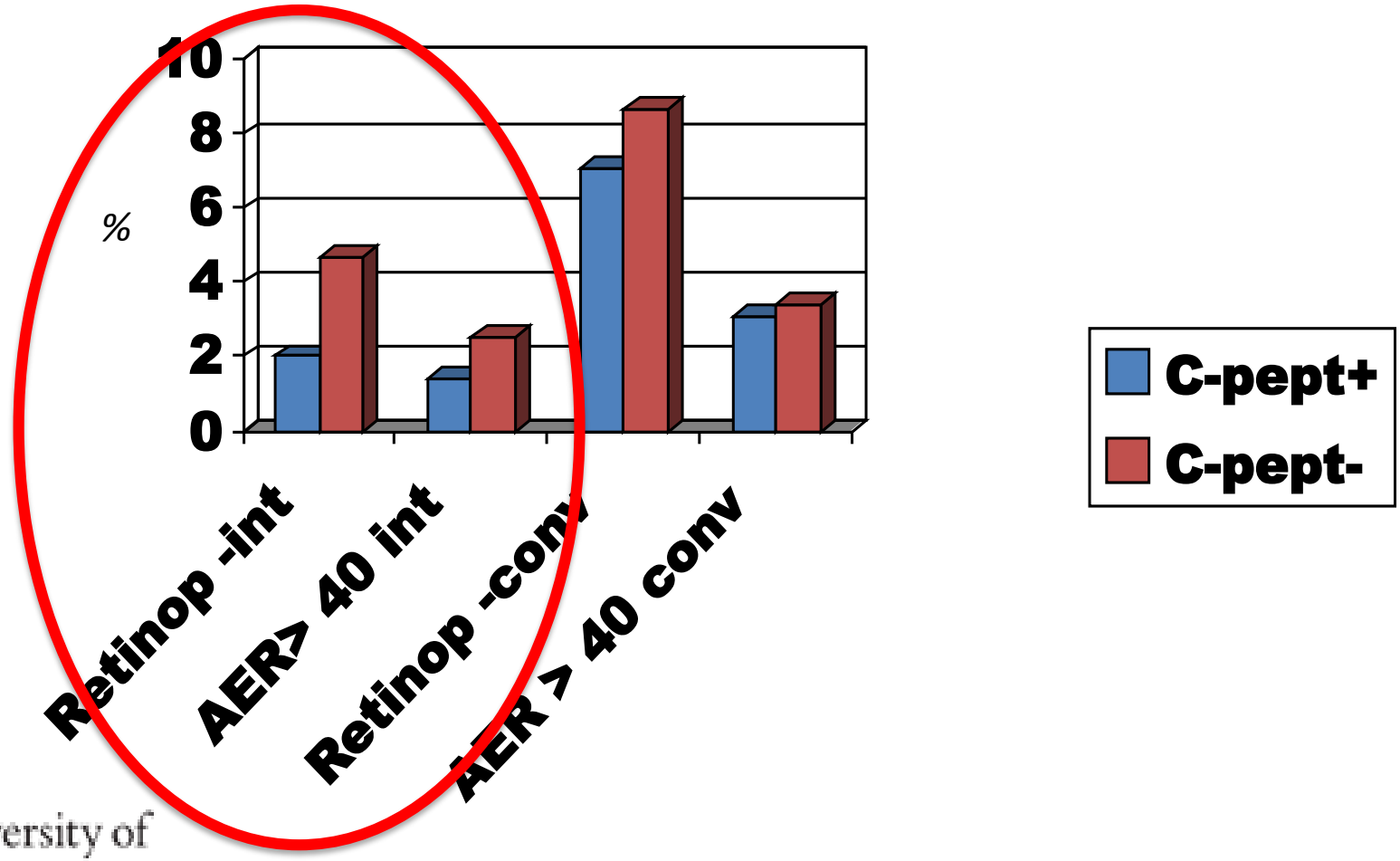
Sorensen et al 2013

Residual insulin reduces the risk of severe hypoglycaemia



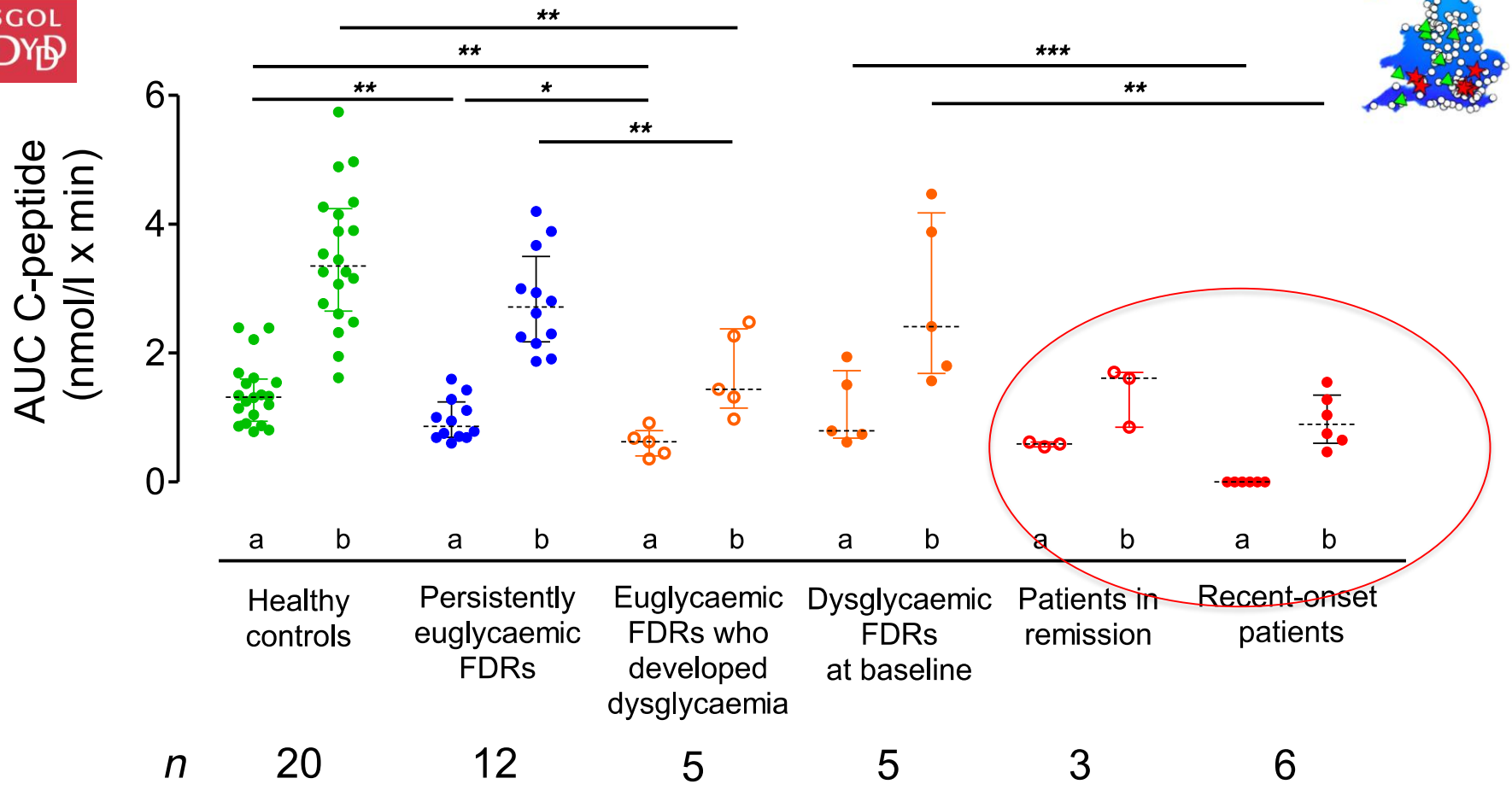
Ann Intern Med 1998;128:517-523

Long term outcomes in DDCT study vs c-pept at entry



Why do people like Libre?

- Because of the arrows….making life more predictable

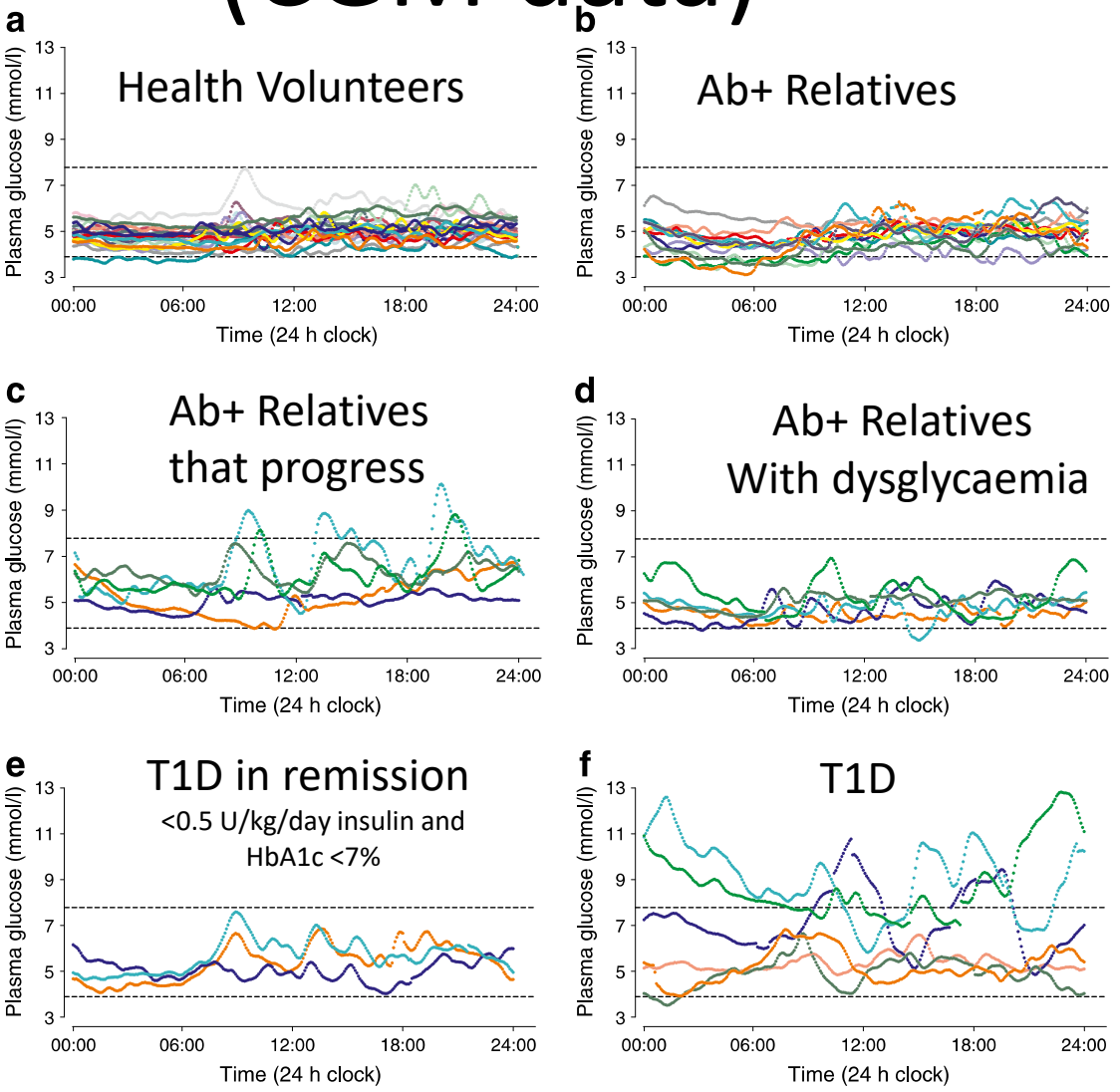


ESM Figure 1 - Baseline first-phase C-peptide release (a) and second-phase C-peptide release (b) during hyperglycaemic clamp for the various groups of participants. Data are dot plots with indication of median values and interquartile range.

*p<0.05, **p<0.01, ***p<0.001

Keymeulen et al 2015

Glycemic Variability (CGM data)



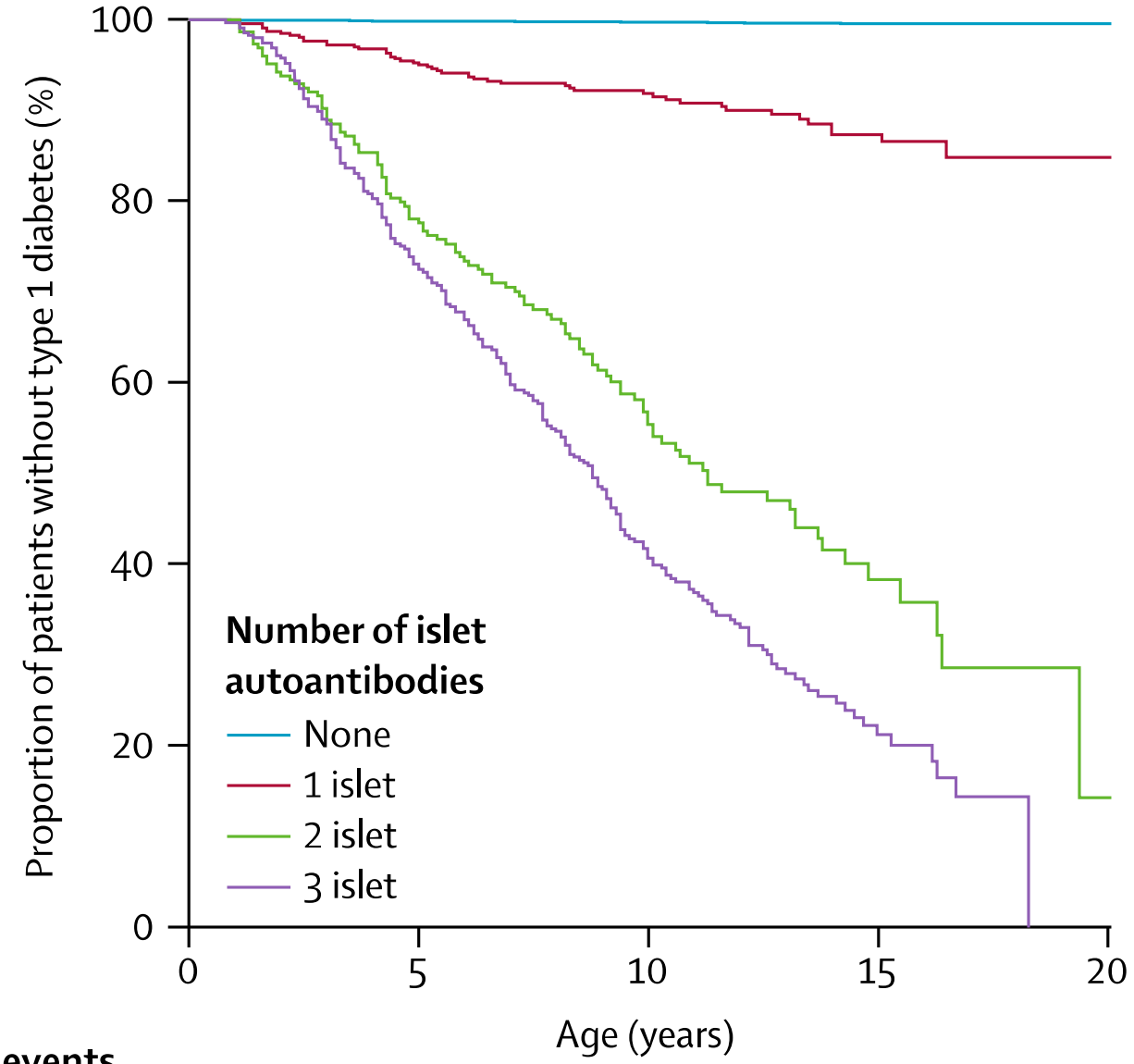
Keymeulen et al 2015

Goal

- *"The best beta cells are your own beta cells"*
- *Preserving as much endogenous beta cell function as possible for as long as possible has the potential to improve short and long term outcomes markedly in T1D*
  - *Glucose variability*
  - *Hypoglycaemia*
  - *Ketoacidosis*
  - *Achievable HbA1c*
  - *Reduced complications – "legacy effect"*

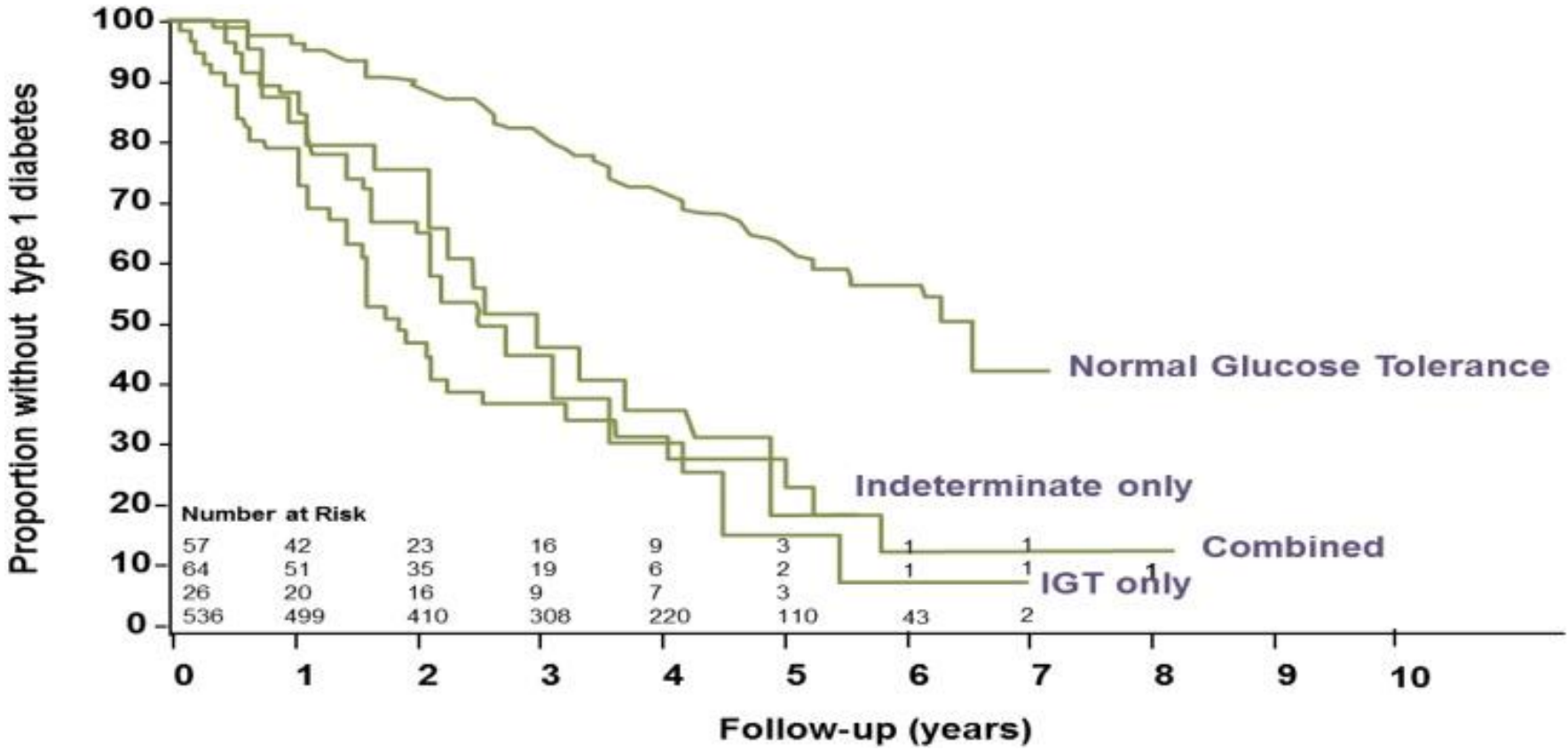
- *Preserving as much endogenous beta cell functions as possible for as long as possible has the potential to improve outcomes markedly in T1D….especially for those least engaged with their therapy*

Autoantibodies are present many years before people are diagnosed with type 1 diabetes

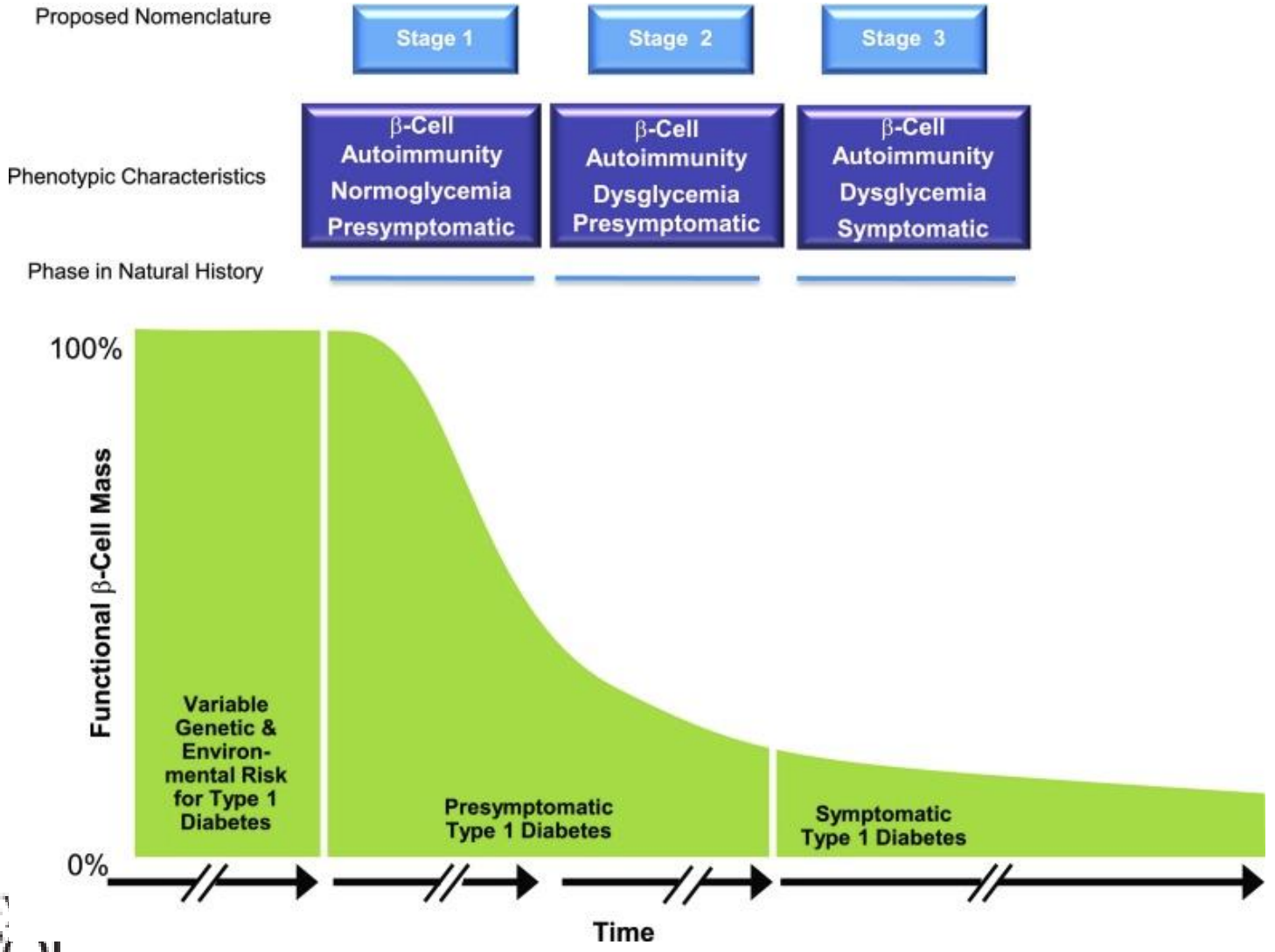


Number of events

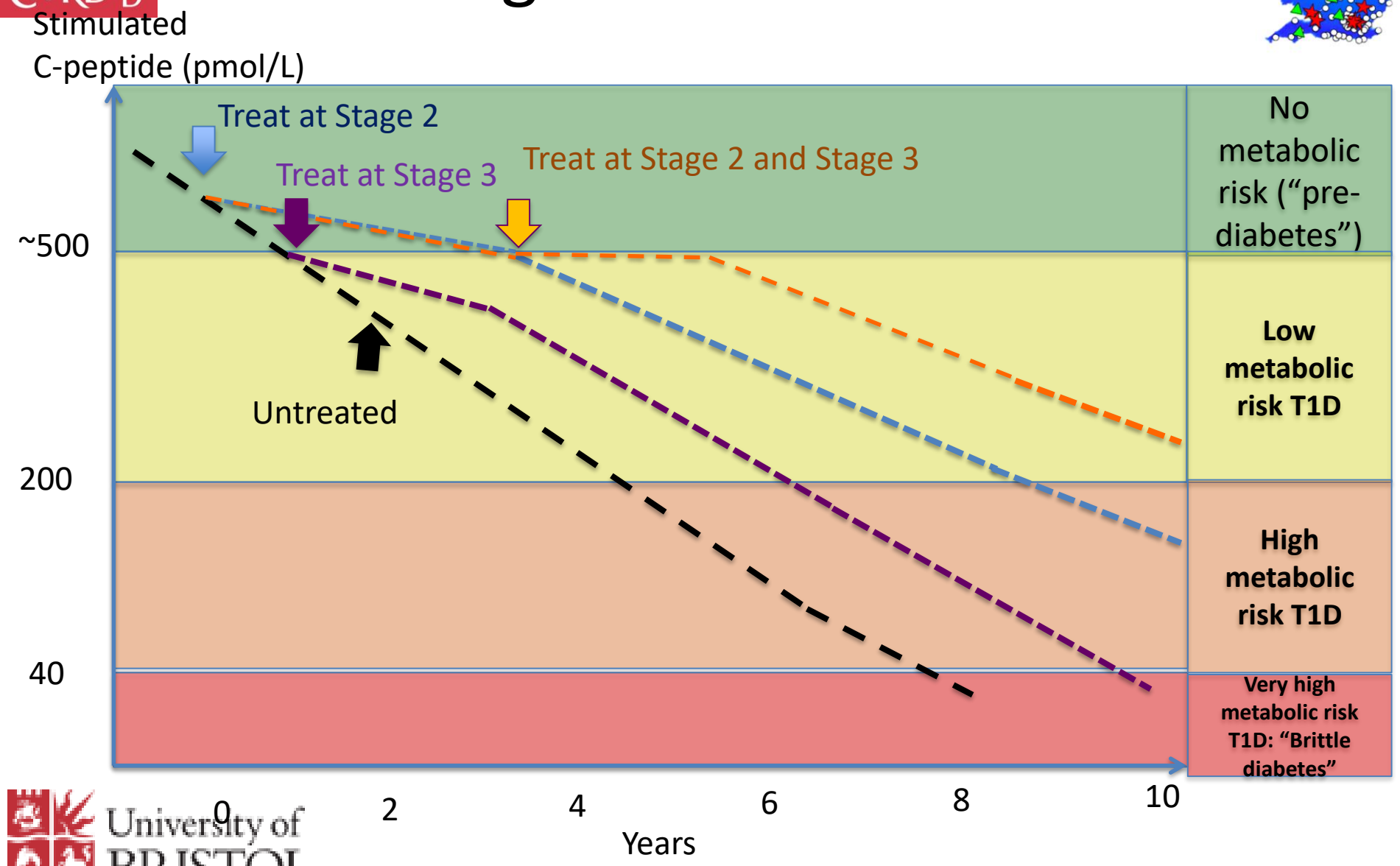
Progression from dysglycaemia



Staging of type 1 diabetes



Maintaining low metabolic risk T1D



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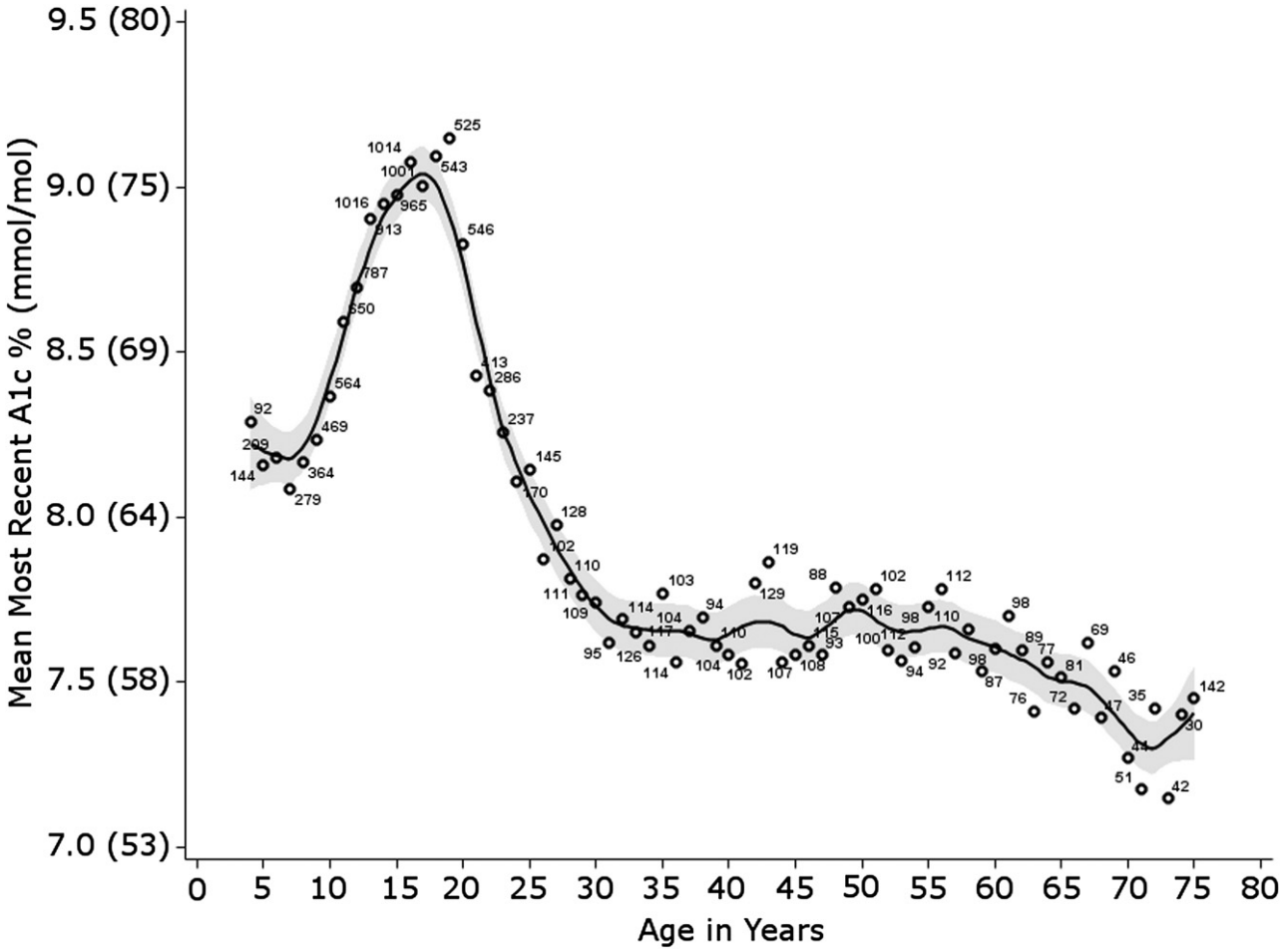

Miller et al 2015

Low risk immunotherapy

Immunointervention: Optimising benefit vs risk

Different types of immunotherapy

Treatment	Example	Risk of side-effects
General Immunosuppression	Drugs use for organ transplants	High

Different types of immunotherapy

Treatment	Example	Risk of side-effects
General Immunosuppression	Drugs use for organ transplants	High
Selective immunosuppression	Newer drugs used for example in arthritis, skin diseases	Low

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Boosting immune regulation	“vaccines”, protective cells, drugs to boost protective cells	Very low

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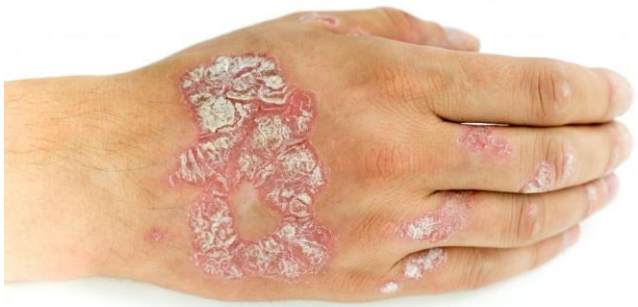
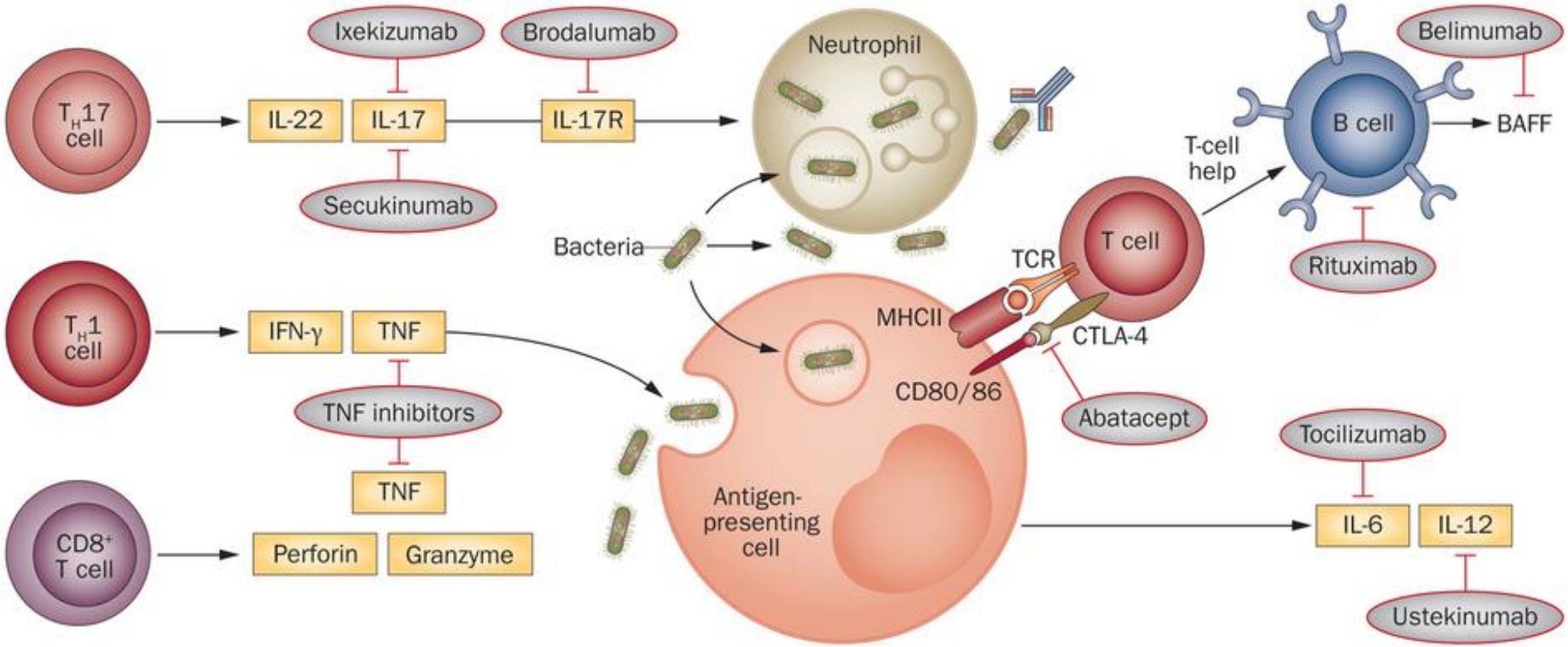
Immunobiologics licensed for psoriasis

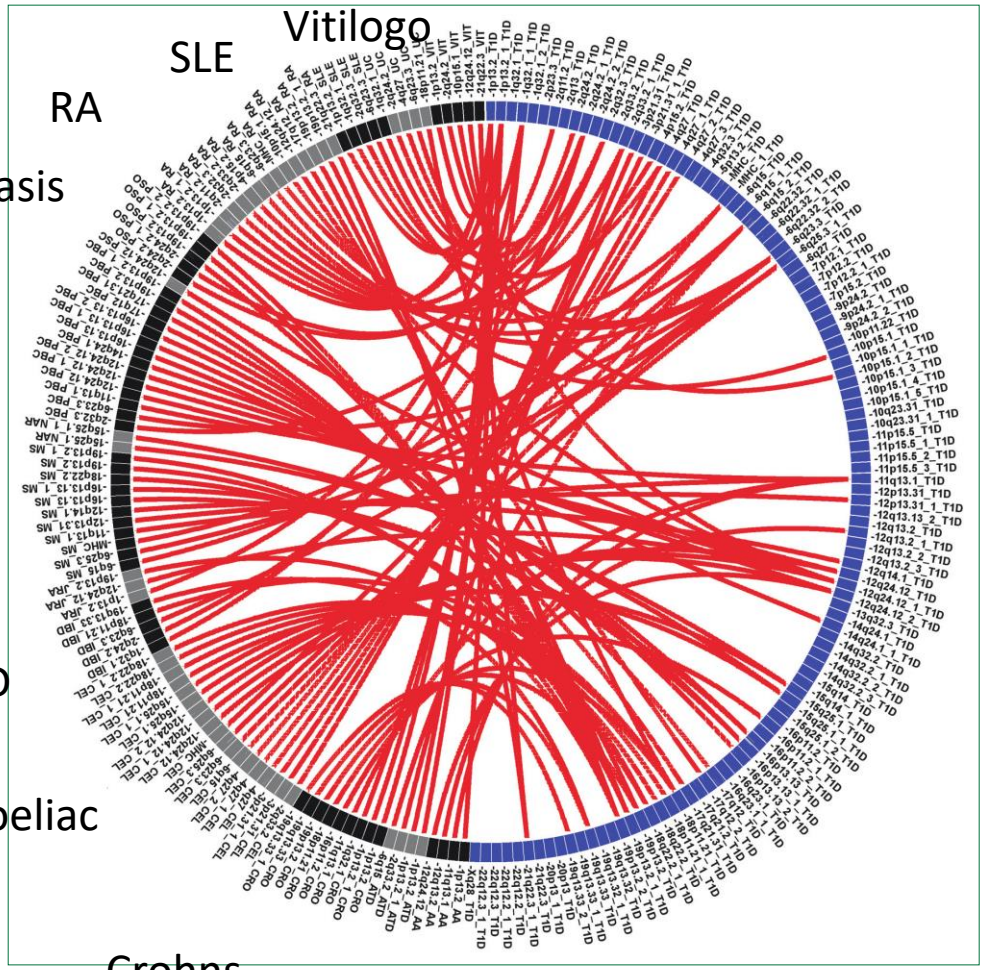
- Anti-TNF
  - Infliximab
  - Etanercept
  - Adilimumab
- Anti-IL-12/IL-23
  - Ustekinumab
- Anti-IL-17
  - Ixekizumab
  - Secukinumab
  - Brodalumab
- Anti-IL-23
  - Guselkumab



The immune system



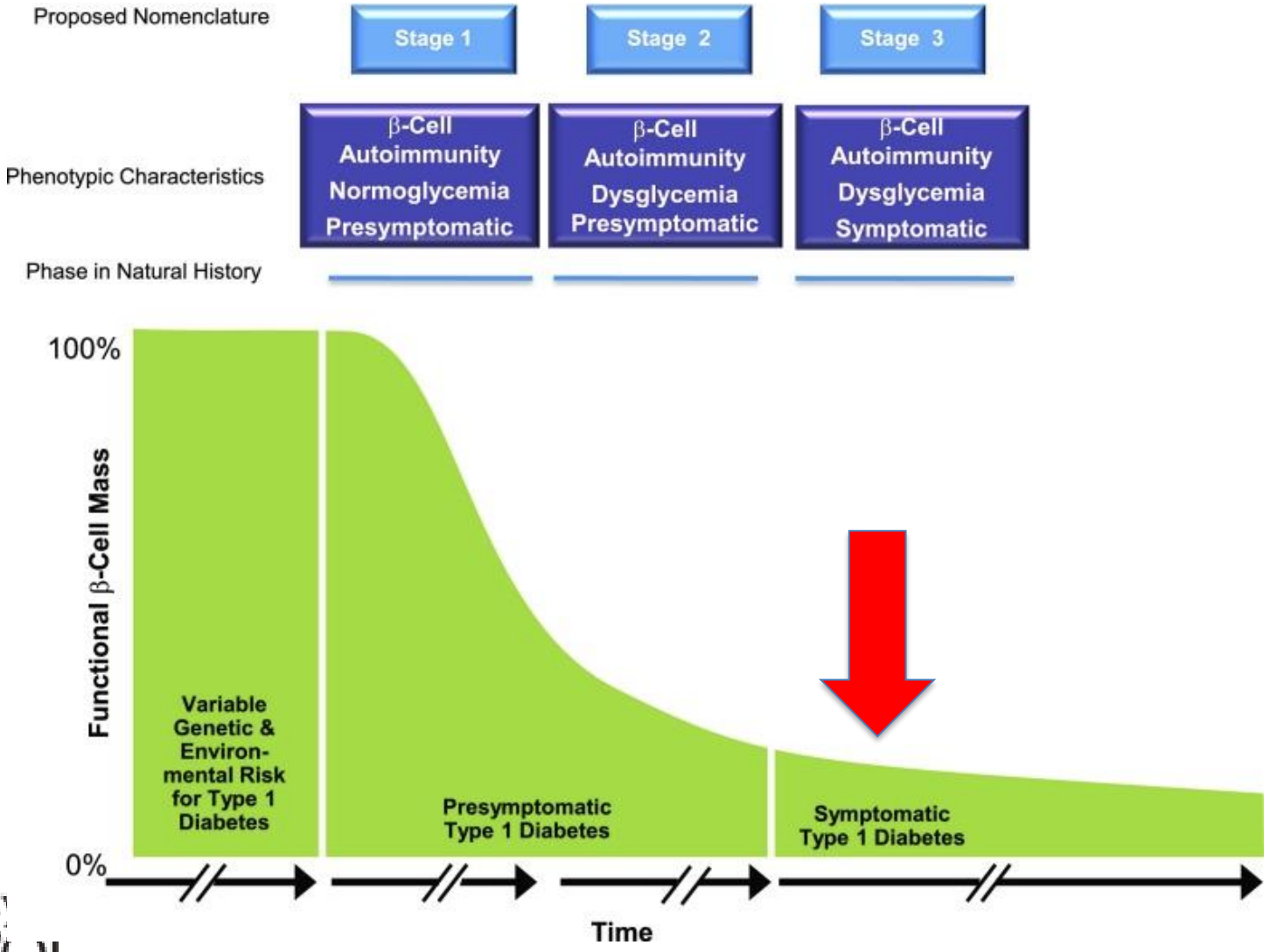
Genetic overlap with other autoimmune diseases (around 50%)



Pociot and Lernmark 2016

Figure 5: **Circos plot of the sharing between type 1 diabetes loci with other immune-mediated diseases**
Data are retrieved from the ImmunoBase website. Associated loci for each disease are listed around the circumference according to chromosomal order. About half of the type 1 diabetes peak SNPs show association with another disease. All type 1 diabetes peak SNPs are shown in the blue part of the circle, and red lines identify pleiotropic risk SNPs. SNP=single nucleotide polymorphism. AA=alopecia areata. ATD=autoimmune thyroid disease. CEL=coeliac disease. CRO=Crohn's disease. IBD=inflammatory bowel disease. JRA=juvenile rheumatoid arthritis. MS=multiple sclerosis. NAR=narcolepsy. PBC=primary biliary cirrhosis. PSC=primary sclerosing cholangitis. PSO=psoriasis. RA=rheumatoid arthritis. SLE=systemic lupus erythematosus. T1D=type 1 diabetes. UC=ulcerative colitis. VIT=vitiligo.

Immunotherapy of type 1 diabetes



Immunotherapies with clinical trial evidence of beta cell preservaton

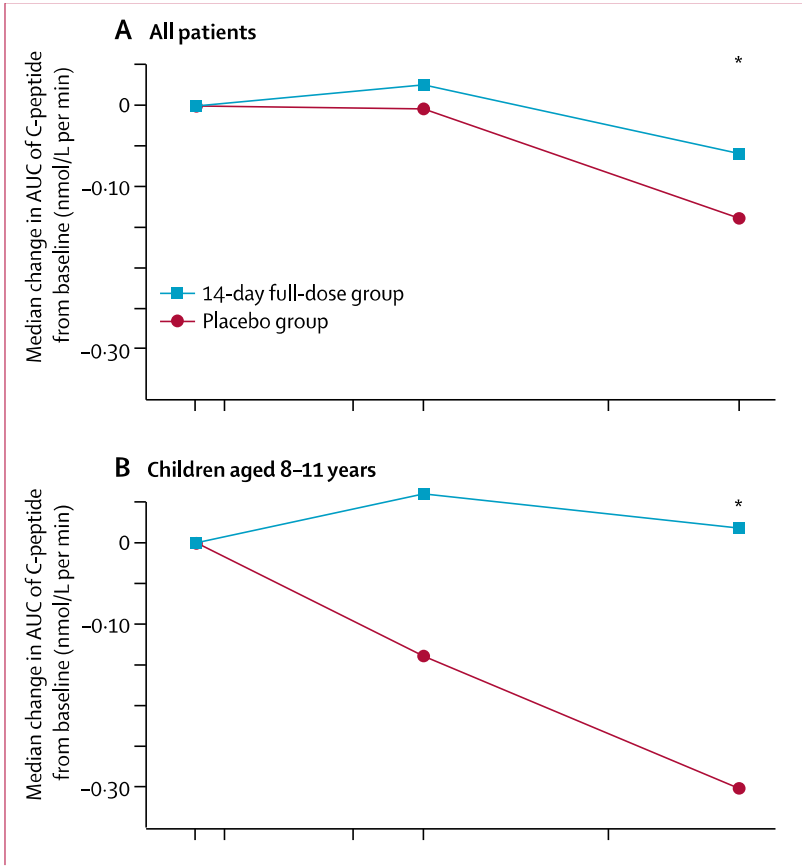
- Anti-CD3
- Anti-CD2
- Anti-CD20
- ATG
- CTLA-4Ig
- (anti-TNF)

Most durable effects from T cell depletion and repopulation

- Anti-CD3
- ATG
- Alefacept

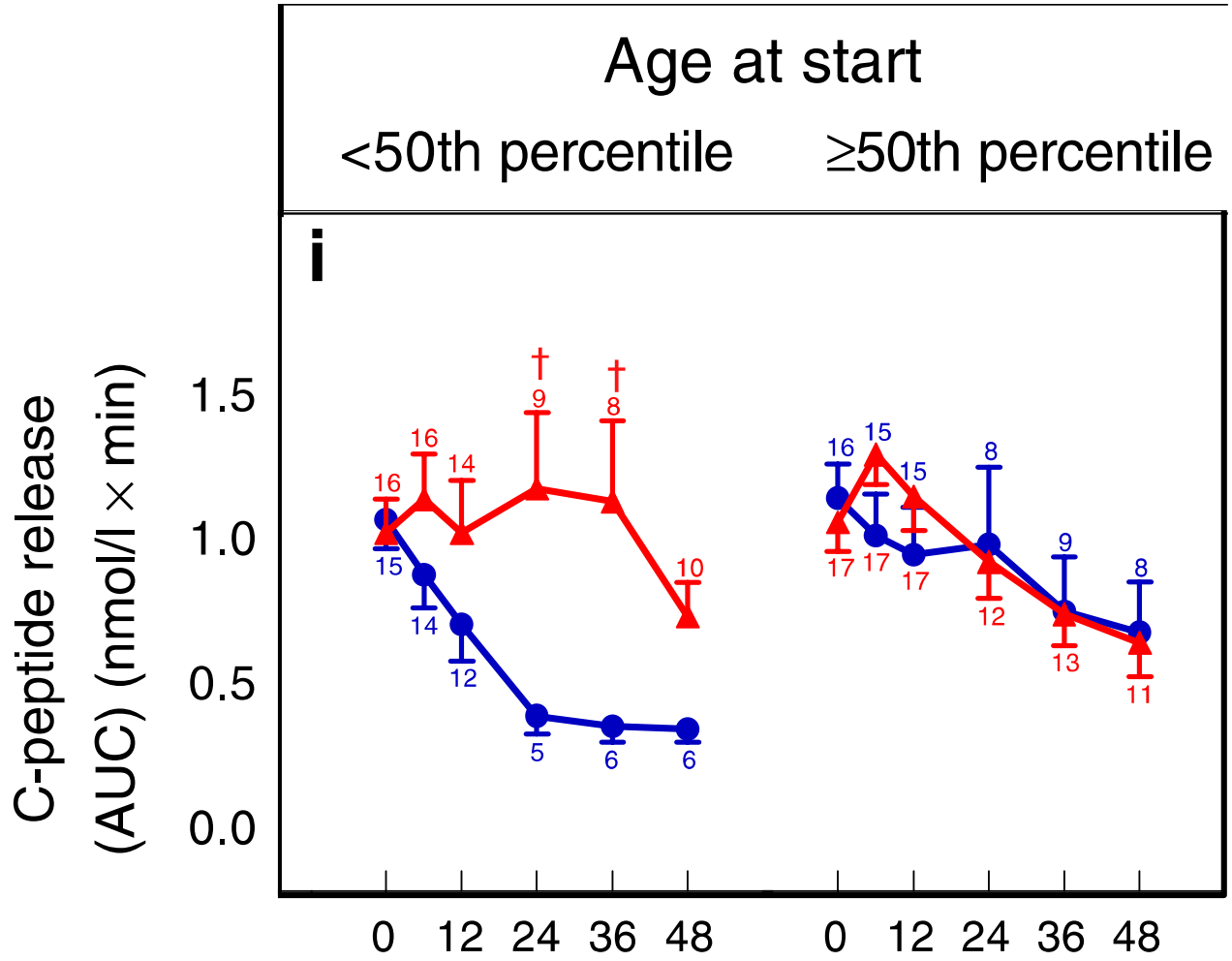
Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial

*Nicole Sherry, William Hagopian, Johnny Ludvigsson, Sunil M Jain, Jack Wahlen, Robert J Ferry Jr, Bruce Bode, Stephen Aronoff, Christopher Holland, David Carlin, Karen L King, Ronald L Wilder, Stanley Pillemer, Ezio Bonvini, Syd Johnson, Kathryn E Stein, Scott Koenig, Kevan C Herold, Anastasia G Daifotis, for the Protégé Trial Investigators**



4 year outcomes with anti-CD3

(Belgian Diabetes Registry Otelixizumab study)



Keymeulen et al 2010

Teplizumab (Anti-CD3) AEs

Immune system disorders	18 (9%)	3 (3%)	9 (9%)	3 (3%)
Cytokine release syndrome †	12 (6%) *	2 (2%)	8 (8%) *	0
Infections and infestations	94 (45%)	53 (52%)	55 (52%)	54 (55%)
Upper respiratory tract infection	26 (12%)	19 (19%)	21 (20%)	15 (15%)
Nasopharyngitis	21 (10%)	9 (9%)	13 (12%)	11 (11%)
Acute mononucleosis-like syndrome †	15 (7%)	4 (4%)	5 (5%)	8 (8%)
Total serious adverse events	19 (9%)	11 (11%)	12 (11%)	9 (9%)

Protégé study, n= 516

Sherry et al 2011

ATG -AEs

Table 2—Adverse events

Adverse effect category	ATG and GCSF		ATG only		Placebo	
	Events	Patients	Events	Patients	Events	Patients
All immune system disorders	33	21 (75.0)	38	23 (79.3)	0	0 (0)
Serum sickness only	20	20 (71.4)	21	21 (72.4)	0	0 (0)
Cytokine release syndrome only	11	10 (35.7)	17	14 (48.3)	0	0 (0)
CD4 lymphocyte decrease or other*	42	21 (75.0)	43	22 (75.9)	4	3 (9.7)
General disorders and administration**	16	7 (25.0)	18	8 (27.6)	1	1 (3.2)
Infections and infestations	14	9 (32.1)	9	7 (24.1)	16	9 (29.0)
Surgical and medical procedures	1	1 (3.6)	0	0 (0)	1	1 (3.2)
Psychiatric disorders	7	2 (7.1)	1	1 (3.4)	0	0 (0)
Injury, poisoning, and procedural complications	4	1 (3.6)	2	2 (6.9)	5	5 (16.1)
Nervous system disorders	4	4 (14.3)	11	4 (13.8)	5	2 (6.5)
Metabolism and nutrition disorders	7	4 (14.3)	4	2 (6.9)	4	4 (12.9)
Vascular disorders	0	0 (0)	2	2 (6.9)	1	1 (3.2)
Neoplasms: benign, malignant, and unspecified	0	0 (0)	1	1 (3.4)	1	1 (3.2)
Respiratory, thoracic, and mediastinal	2	2 (7.1)	3	2 (6.9)	1	1 (3.2)
Blood and lymphatic system disorder	1	1 (3.6)	1	1 (3.4)	2	2 (6.5)
Cardiac disorders	1	1 (3.6)	0	0 (0)	0	0 (0)
Ear and labyrinth disorders	1	1 (3.6)	0	0 (0)	0	0 (0)
Total	161	28 (100)	152	29 (100)	67	31 (100)

Data are *n* or *n* (%). *75% of the events were decreased lymphocytes. Others listed were decreased neutrophils, decreased white blood cells, increased alanine aminotransferase, increased alkaline phosphatase, and increased bilirubin. **Mostly fever and flu-like symptoms.

Haller et al 2018

Abatacept AEs

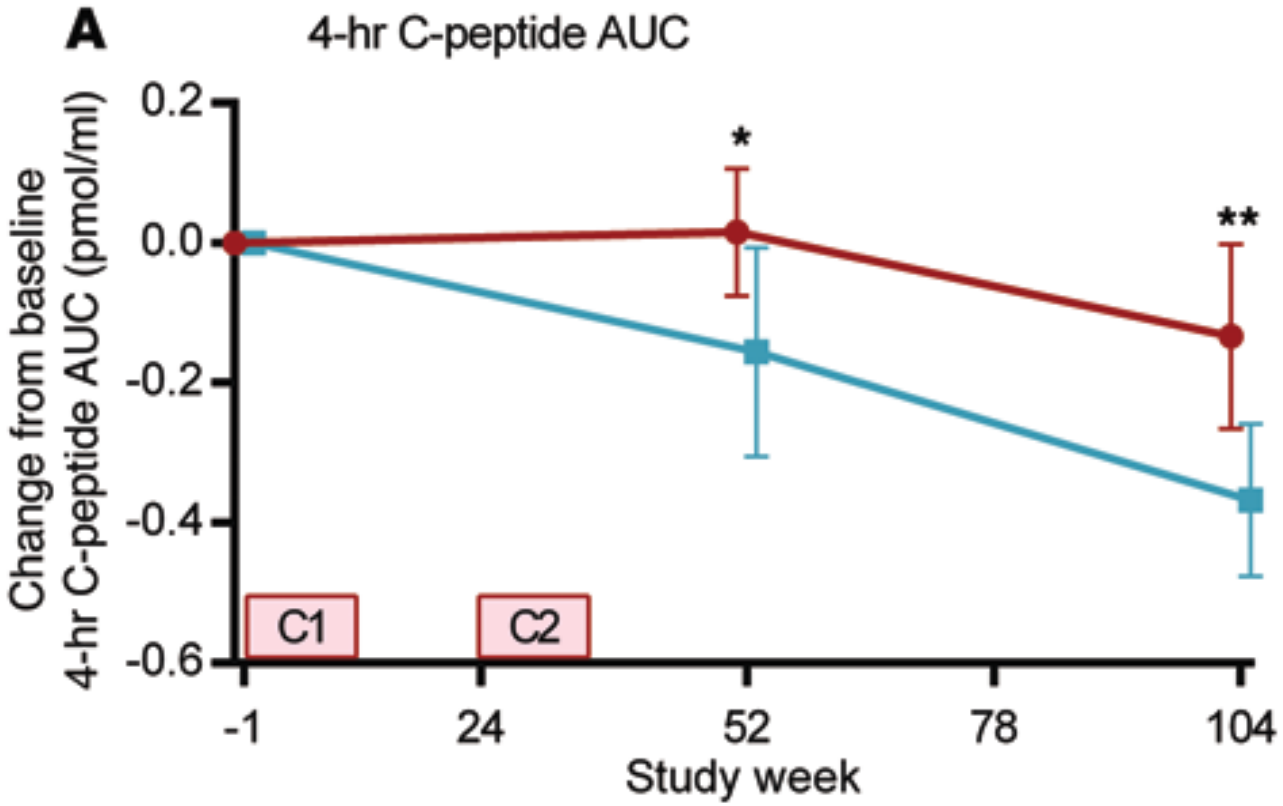
Grade	Treatment Group	
	Abatacept	Placebo
	No. of subjects (%*)	No. of subjects (%*)
0	14 (18.2)	8 (22.9)
1	1 (1.3)	1 (2.9)
2	44 (57.1)	17 (48.6)
3	12 (15.6)	7 (20.0)
4	5 (6.5)	2 (5.7)
5**	1 (1.3)	0 (0.0)
Total	77	35

Infection	63	32 (41.6)	31	15 (42.9)

Alefacept (anti-CD2)

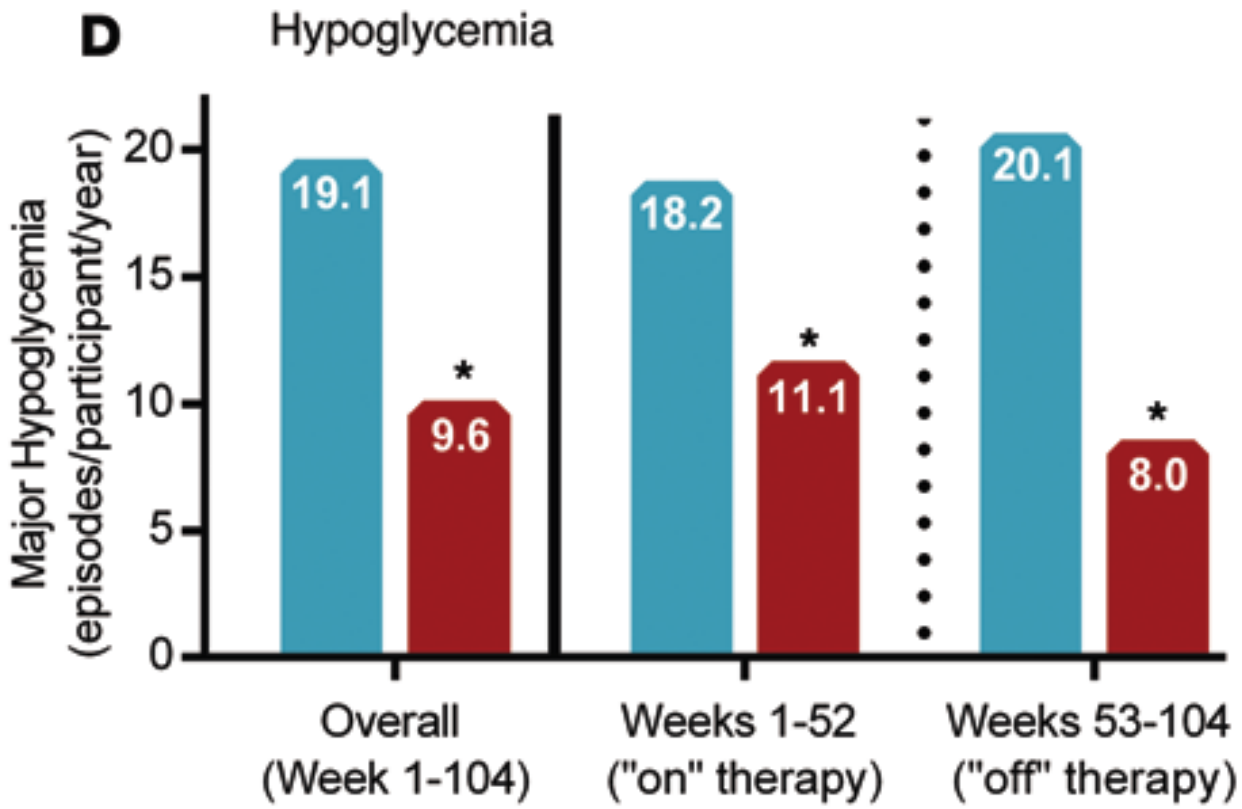
- Licensed for use in psoriasis
- Weekly intramuscular injection for 12 weeks (2 courses)
- No local reactions or increased risk of infections noted
- Improved insulin levels for 2 years
- …drug no longer available (manufacturer ceased production)

Alefacept treatment



Rigby et al 2015

Alefacept – Reduced hypoglycaemia



Rigby et al 2015

USTEKID: ustekinumab in adolescents with new-onset T1D

Funder: UK NIHR Efficacy and Mechanism Evaluation Programme

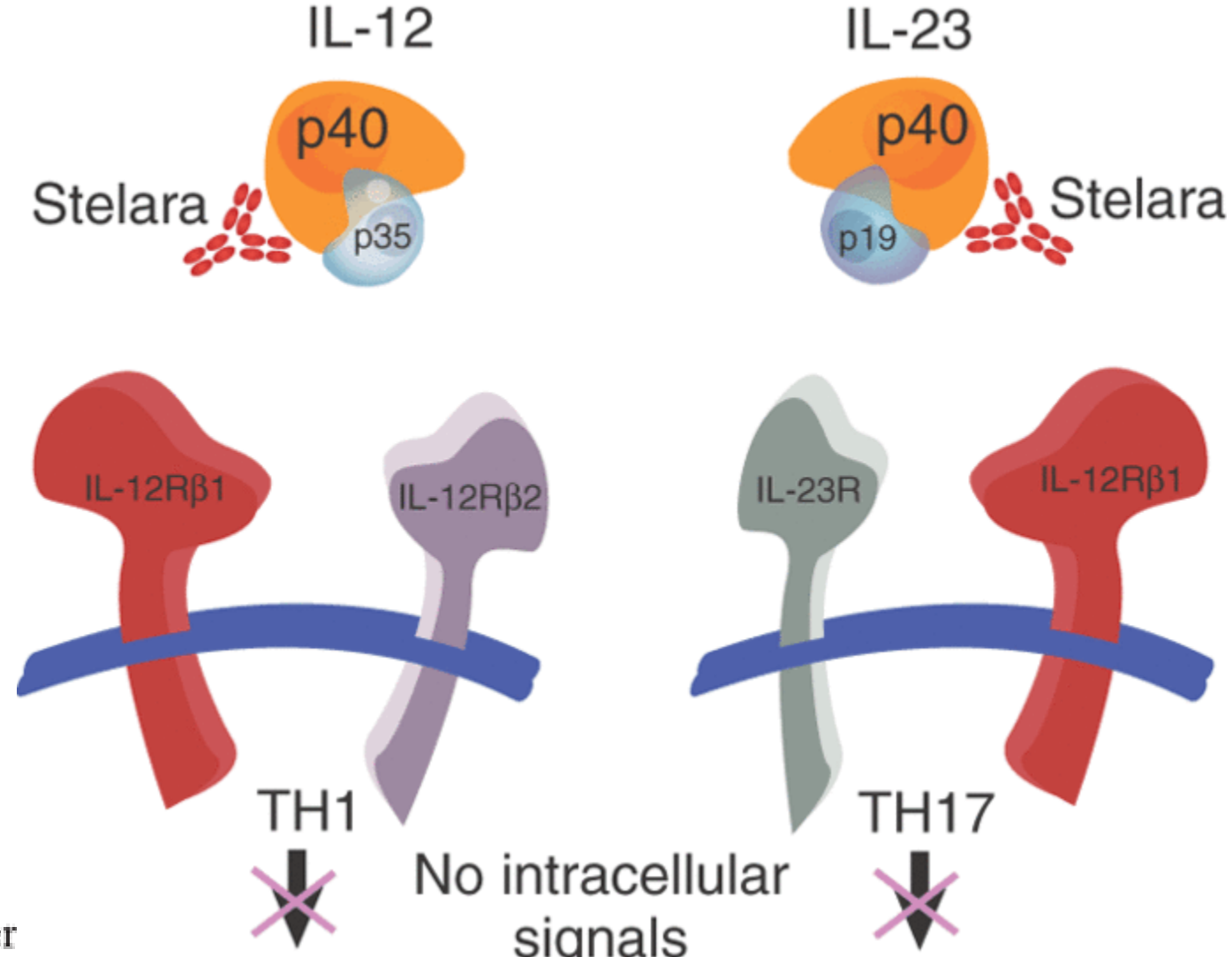
Ustekinumab – a licensed s.c. therapy for psoriasis in 12-18yr olds

www.journalslibrary.nihr.ac.uk

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people:...

Stelara® (ustekinumab)

Mechanism of action: inhibits generation of Th1 and Th17 T cells



Reported SEs with Ustekinumab

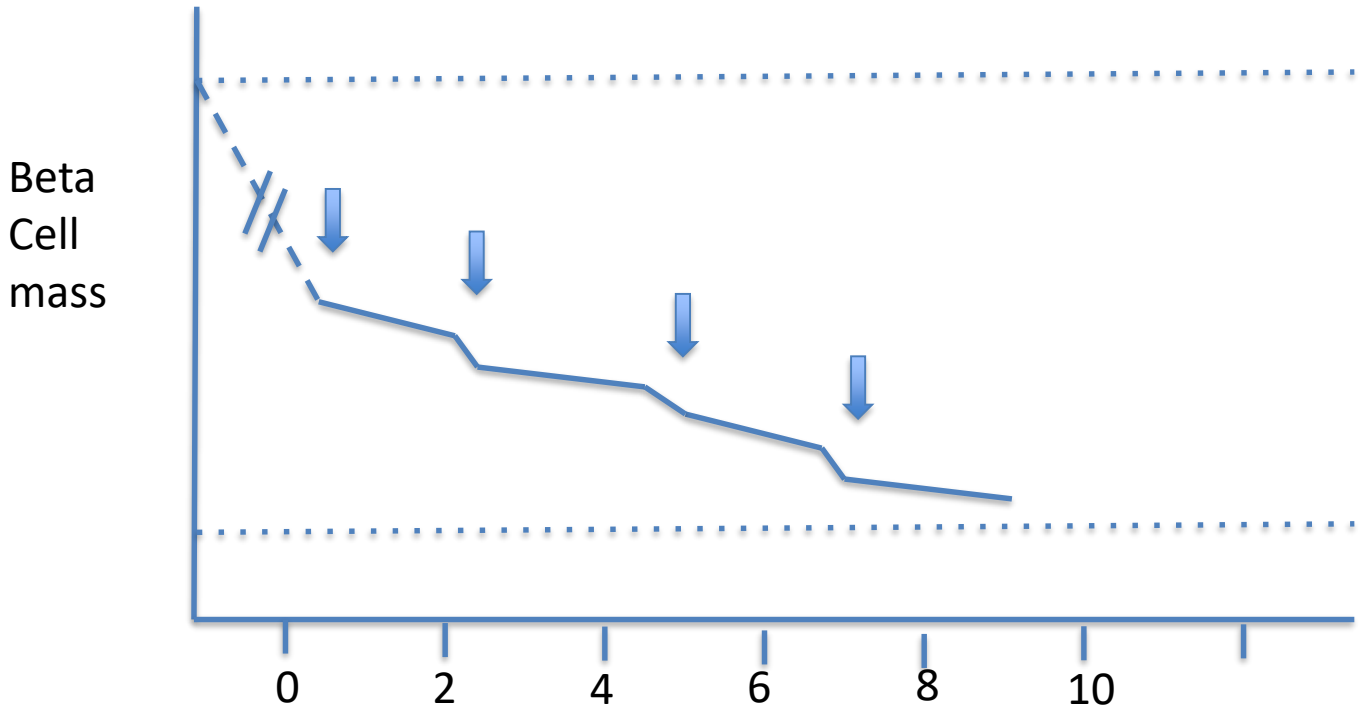
Table 1. Adverse reactions reported by ≥1% of subjects through Week 12 in Ps STUDY 1 and Ps STUDY 2

		STELARA®	
	Placebo	45 mg	90 mg
Subjects treated	665	664	666
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

Some New Onset T1D studies due to report in 2019

- Anti-IL-21
- Anti-TNF
- Anti – IL-6R
- [Also Trialnet Anti-CD3 prevention study)

Sequential preservation



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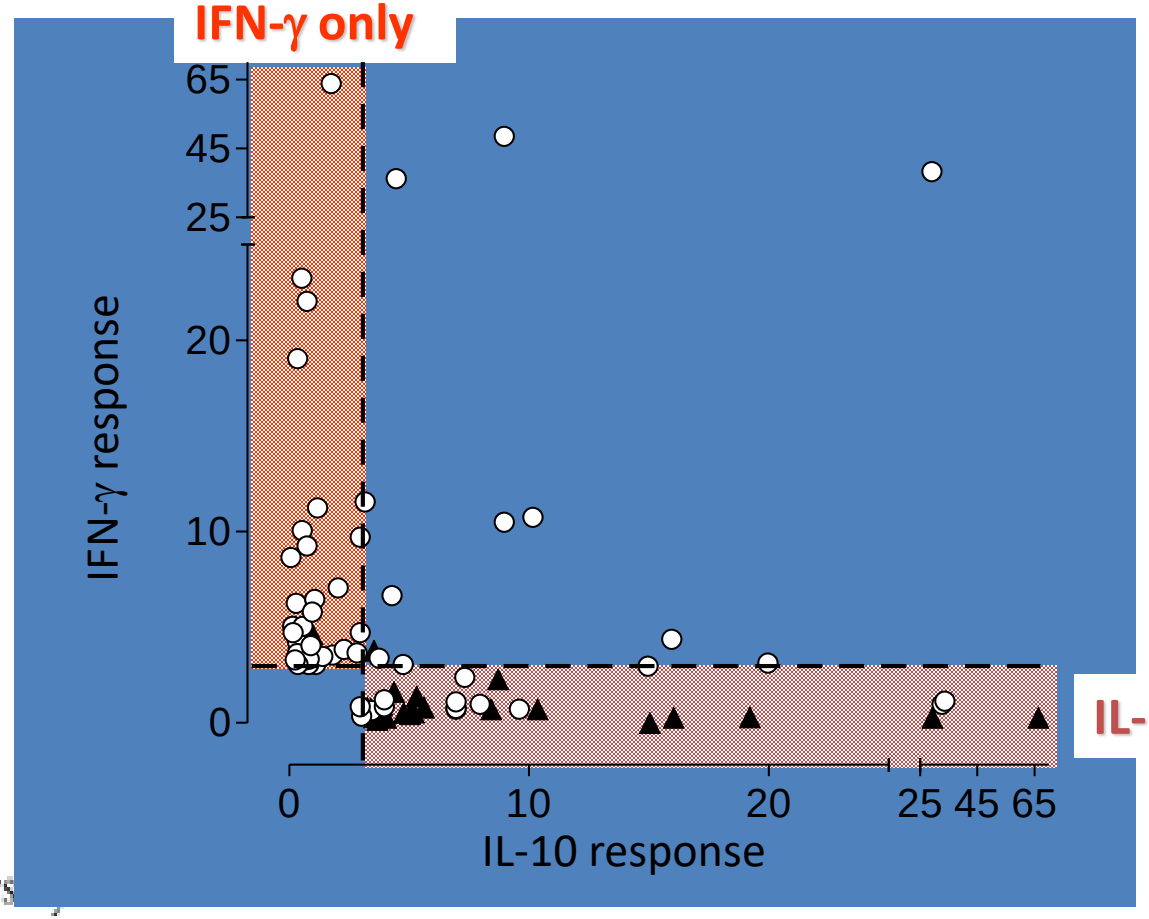
Boosting immune regulation	“vaccines”, protective cells, drugs to boost protective cells	Very low

Polarization of autoreactive T cell responses in T1DM



Arif et al 2004

MP

Antigen Specific Immunotherapy
An “unvaccine”

- Give self-antigen
- In non-immunogenic form
- In absence of inflammation
- To boost regulatory T cells
- Reduce effector T cells

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

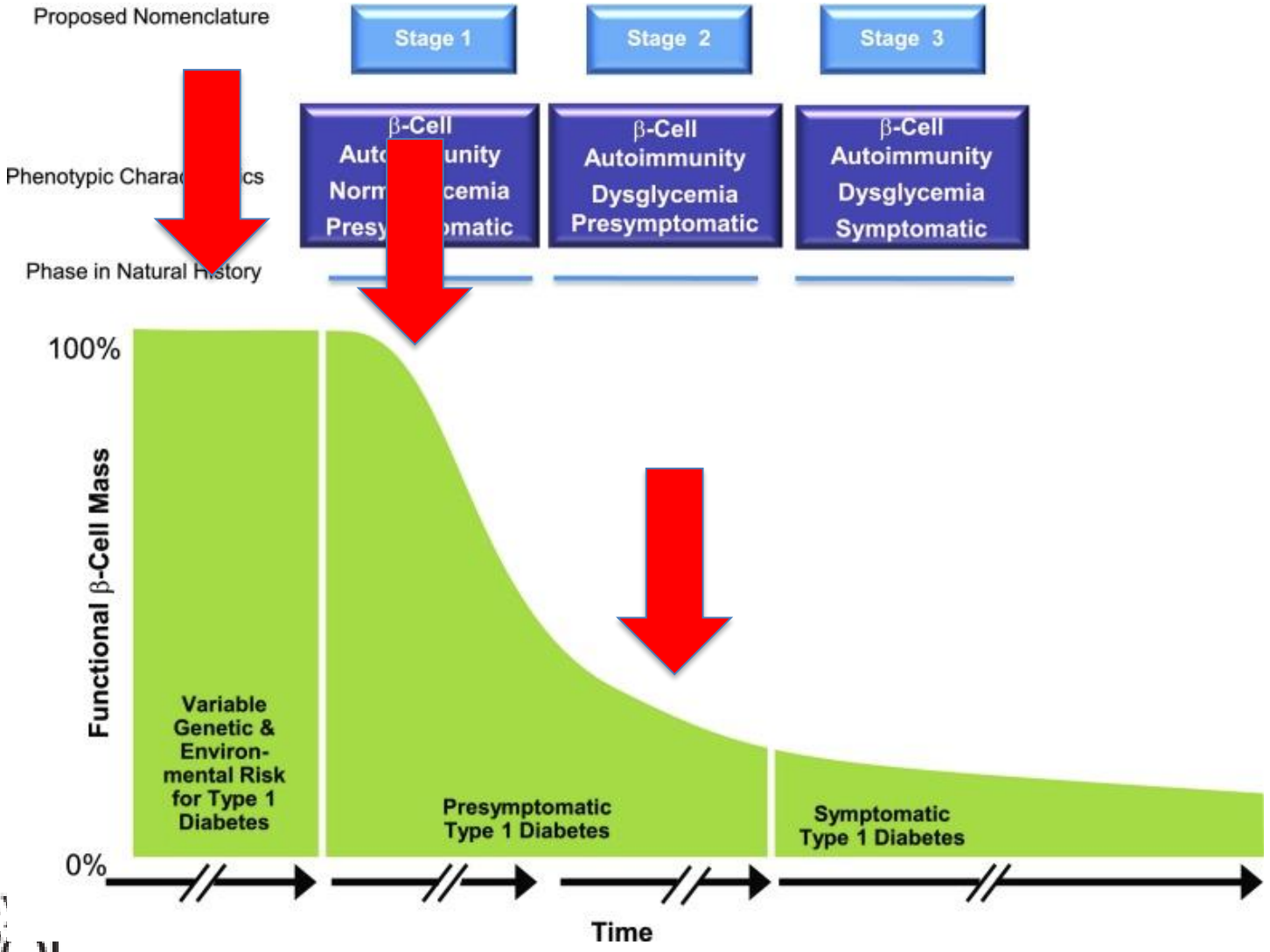
AUTOIMMUNITY

Metabolic and immune effects of immunotherapy with proinsulin peptide in human new-onset type 1 diabetes

Mohammad Alhadj Ali,[1]* Yuk-Fun Liu,[2,3]* Sefina Arif,[2] Danijela Tatovic,[1] Hina Shariff,[2] Vivienne B. Gibson,[2] Norkhairin Yusuf,[2] Roman Baptista,[2,4] Martin Eichmann,[2] Nedyalko Petrov,[4] Susanne Heck,[4] Jennie H. M. Yang,[2] Timothy I. M. Tree,[2] Irma Pujol-Autonell,[2] Lorraine Yeo,[2] Lucas R. Baumard,[2] Rachel Stenson,[1] Alex Howell,[1] Alison Clark,[1] Zoe Boult,[5] Jake Powrie,[3] Laura Adams,[3] Florence S. Wong,[1] Stephen Luzio,[6] Gareth Dunseath,[6] Kate Green,[7] Alison O'Keefe,[7] Graham Bayly,[7] Natasha Thorogood,[7] Robert Andrews,[7] Nicola Leech,[8] Frank Joseph,[9] Sunil Nair,[9] Susan Seal,[9] HoYee Cheung,[9] Craig Beam,[10] Robert Hills,[11] Mark Peakman,[2,4,12†‡] Colin M. Dayan[1‡]

Peptide therapy given up to 12 times was safe with no hypersensitivity or exacerbation of disease

Immunotherapy of type 1 diabetes



Risk of diabetes

GPPAD

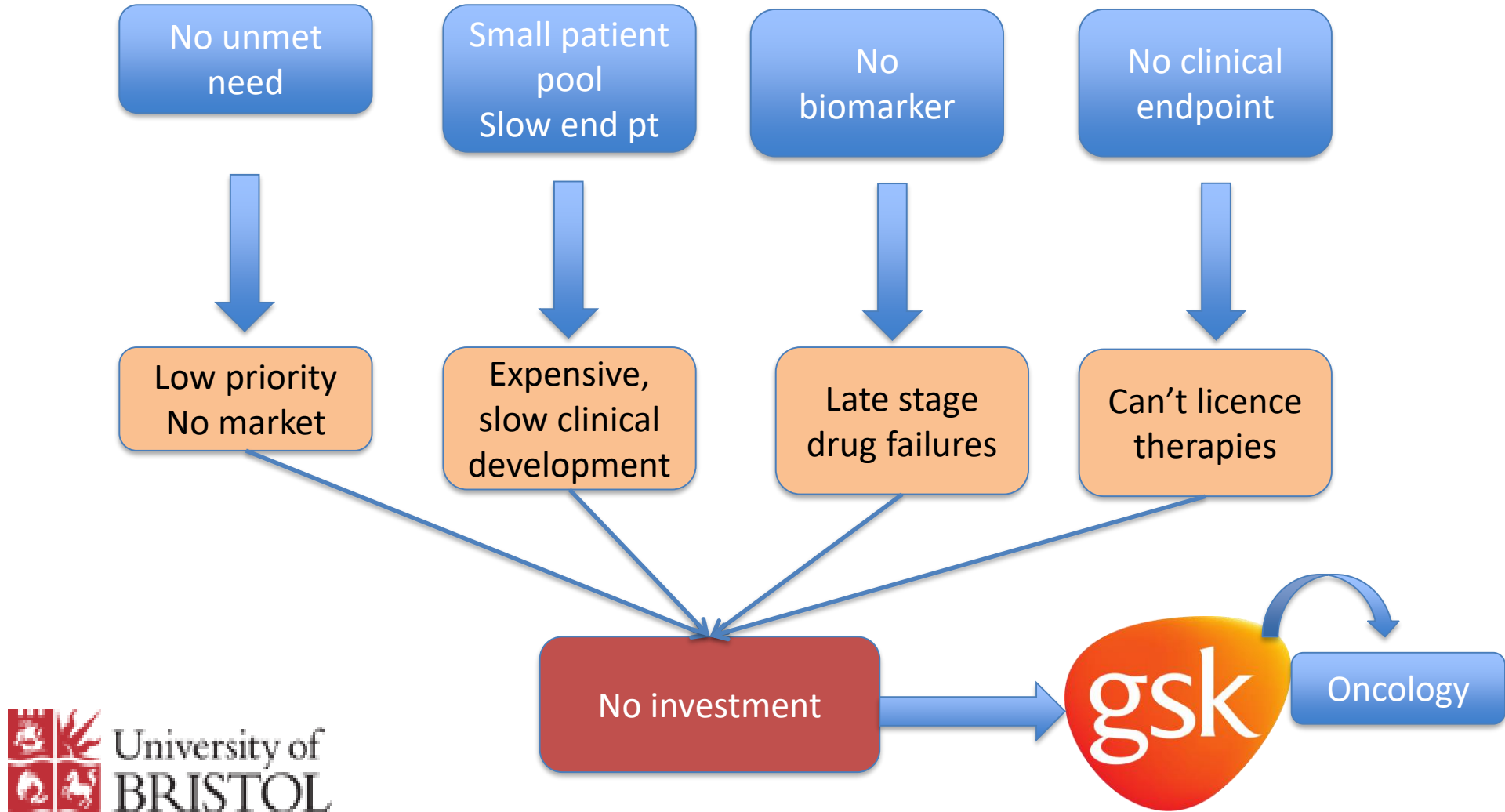
GLOBAL PLATFORM FOR THE PREVENTION OF AUTOIMMUNE DIABETES

A WORLD WITHOUT 1

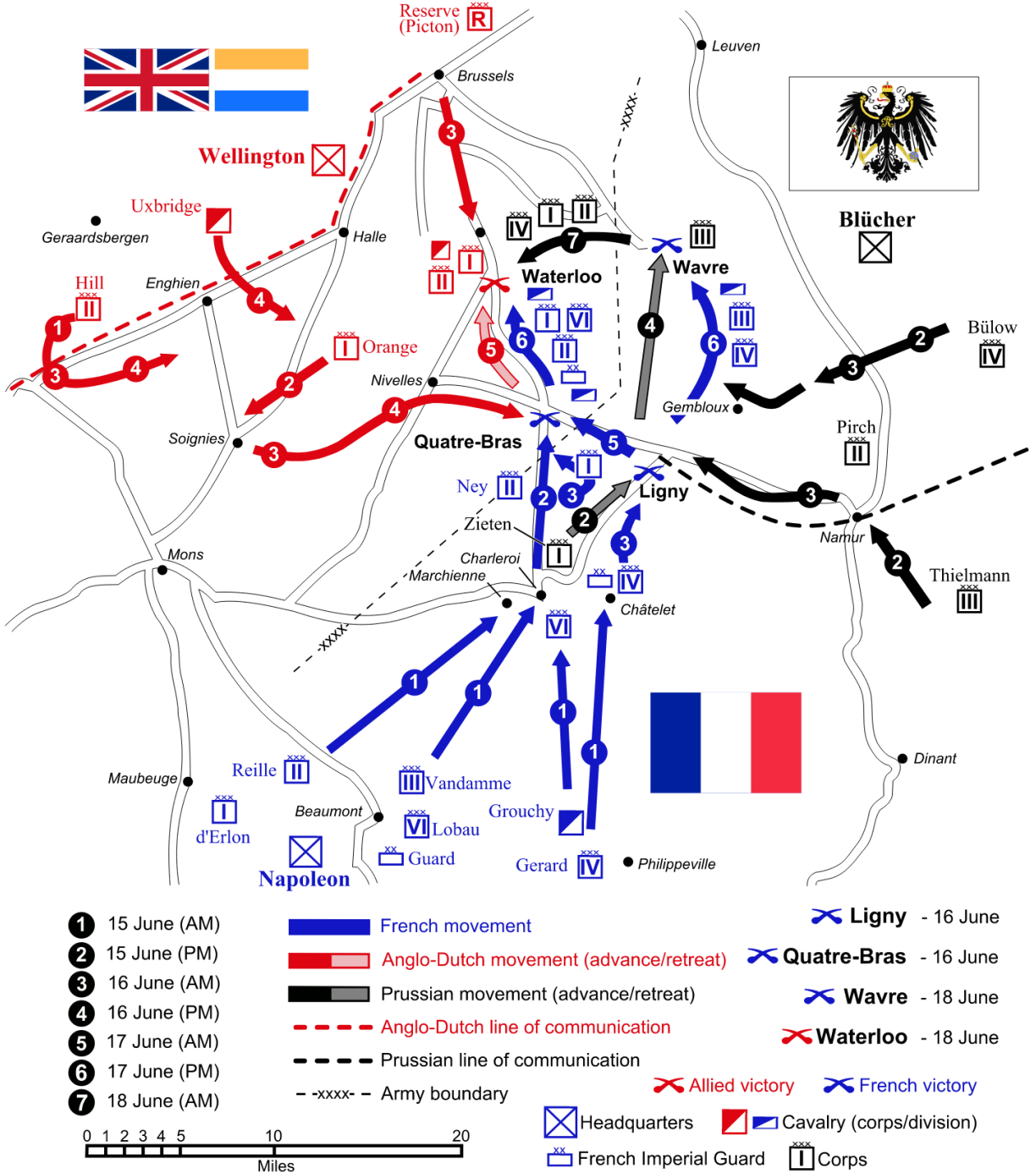
Why is there no licensed therapy for T1D?

1. **The "Curse" of insulin**
   - Unmet need is not perceived
2. **Need to treat soon after diagnosis**
   - < 5% of people can take part in trials and "protected"
3. **Trial end point (MMTT) "difficult"**
   - Slow (12 months)
   - Unsuitable for children
4. **No surrogate biomarkers or imaging technique**
   - Can't screen drugs rapidly against target
   - Can't dose optimise
5. **No defined clinical endpoint**
   - No regulatory approval path
6. **Only a "cure" will do…and it should be low risk!**
   - No other autoimmune disease is cured

A commercial disaster area



Unravelling the knot


Reserve (Picton)
Brussels
Leuven
Wellington
Uxbridge
Geraardsbergen
Halle
Hill
Enghien
Orange
Nivelles
Soignies
Quatre-Bras
Waterloo
Wavre
Blücher
Bülow
Gembloux
Pirch
Ligny
Ney
Zieten
Charleroi
Marchienne
Châtelet
Namur
Thielmann
Mons
Maubeuge
Reille
d'Erlon
Beaumont
Napoleon
Vandamme
Lobau
Guard
Grouchy
Gerard
Philippeville
Dinant
1 15 June (AM)
2 15 June (PM)
3 16 June (AM)
4 16 June (PM)
5 17 June (AM)
6 17 June (PM)
7 18 June (AM)
French movement
Anglo-Dutch movement (advance/retreat)
Prussian movement (advance/retreat)
Anglo-Dutch line of communication
Prussian line of communication
-xxxx- Army boundary
0 1 2 3 4 5 10 20
Miles
Ligny - 16 June
Quatre-Bras - 16 June
Wavre - 18 June
Waterloo - 18 June
Allied victory
French victory
Headquarters
Cavalry (corps/division)
French Imperial Guard
Corps

Advanced composite endpoints

Table 1	Beta score	Beta-2	Beta-3	Beta-4	Beta-5
Daily insulin/kg	X	X	X	X	X
HbA1c	X	X	X	(X)	(X)
Fasting glucose	X	X			
90 min stimulated c-peptide	X				
Fasting c-peptide		X	X	X	X
CGM – time in range			X	X	X
CGM -hypoglycaemia				X	X
Fingerstick post-prandial c-peptide					X

Aim to collect evidence for beta 5:

- Lower burden for children
- More rapid end point

Stop making patients feel guilty

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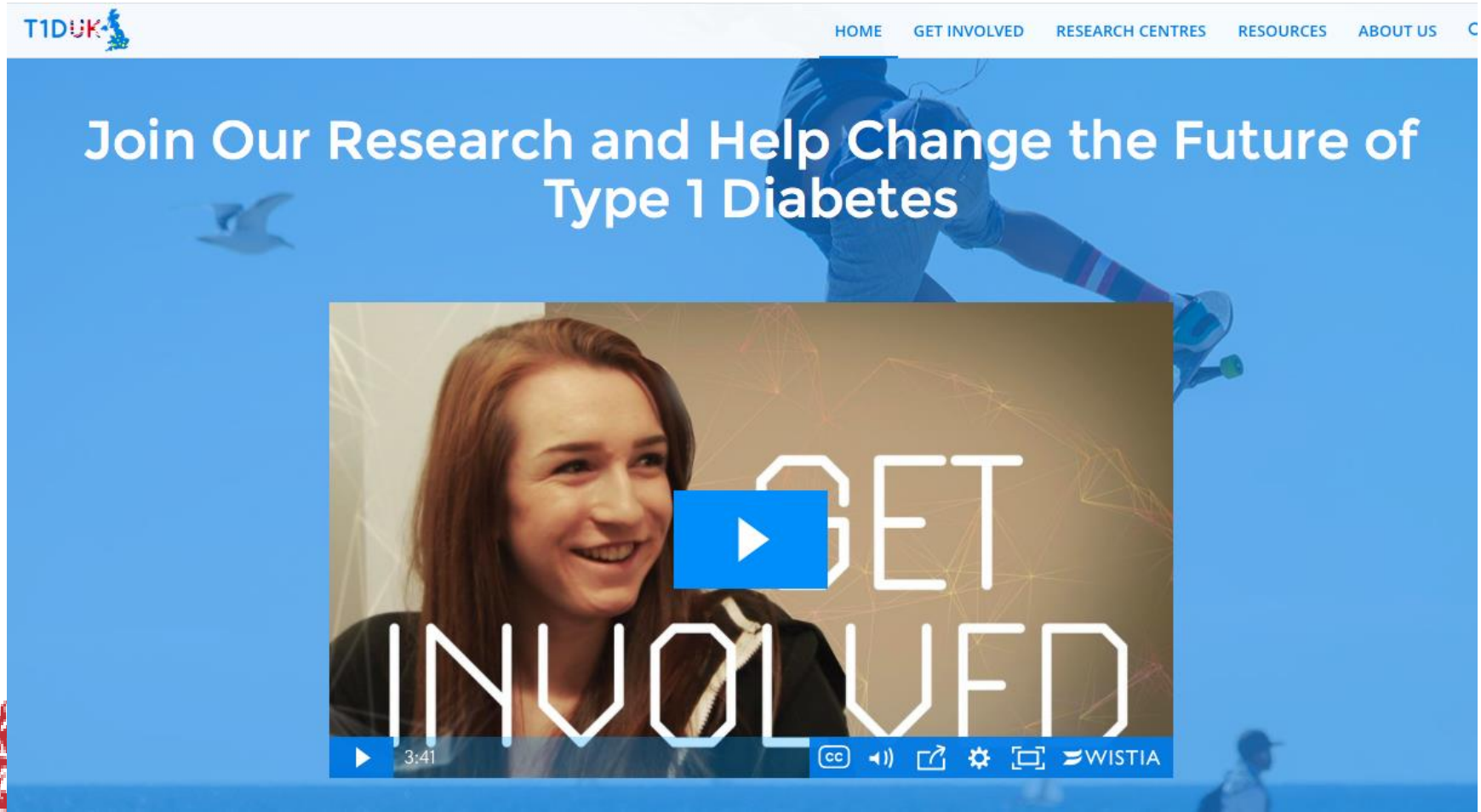
PRIFYSGOL CAERDYDD

T1D UK

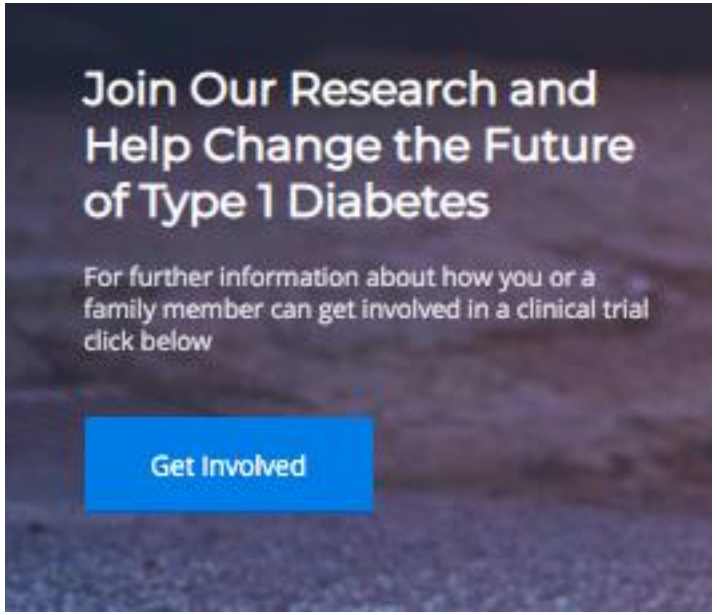
IMMUNOTHERAPY

University of BRISTOL

www.type1diabetesresearch.org.uk



T1D UK Consortium



Conclusions

- Significant unmet need of glycaemic control in T1D
- Benefits of even short term preservation of small amounts of c-peptide preservation
  - Short term: Less hypoglycaemia, more time in range less DKA
  - Medium term – death rates, DKA rates, pregnancy outcomes, educational outcomes
  - Long term: reduced long-term complications
- Low risk immunotherapy is here today – let's get it over the line
- Antigen specific immunotherapy and disease prevention will be here tomorrow

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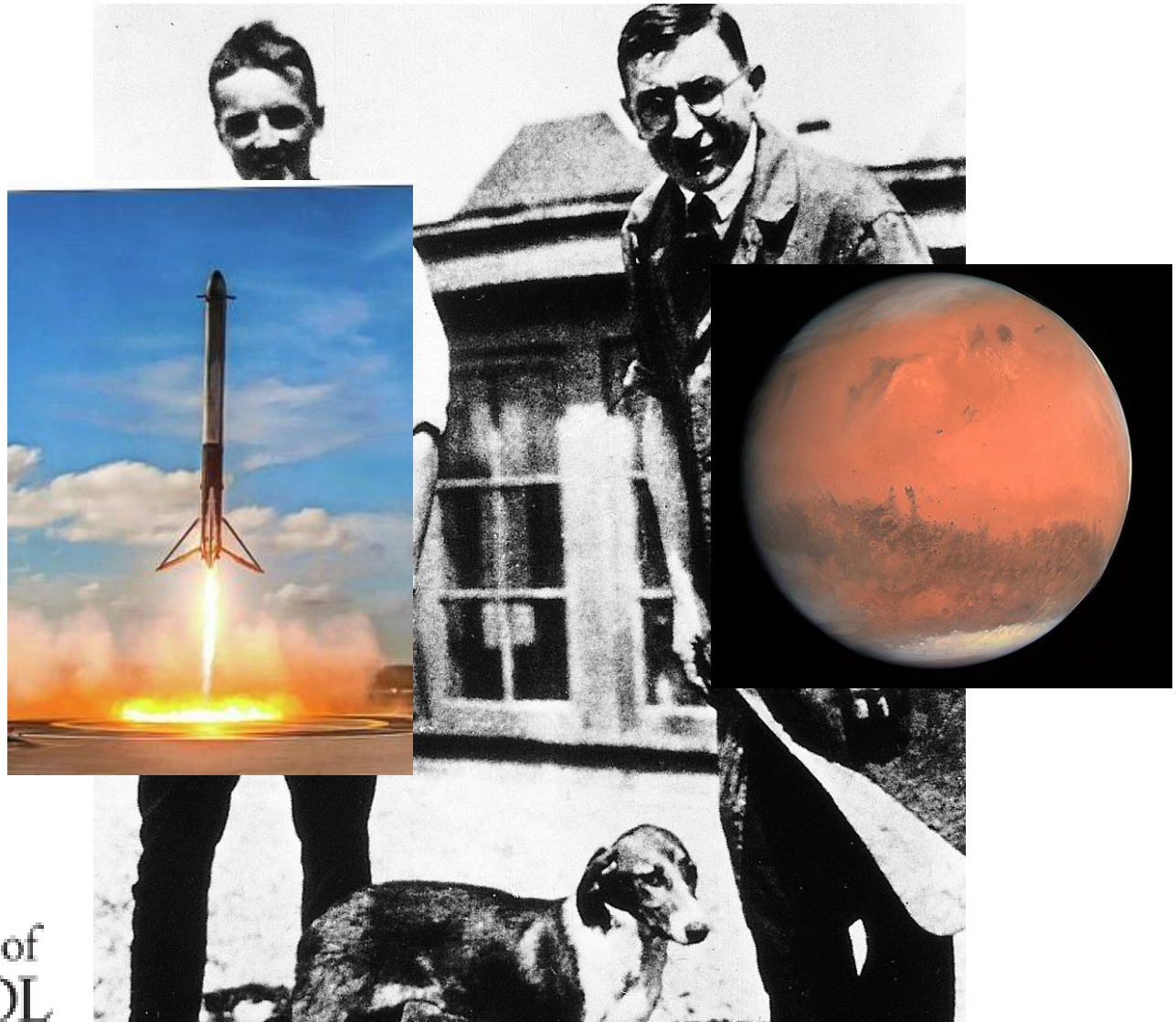
Eradication of Type 1 diabetes 2041



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Vision post-2021

2021 2025 2031 2035 2041

Antigen specific immotherapy

Diabetes Prevention begins

Many companies marketing other low-risk immunotherapies

First beta cell preserving therapy licensed

Beta cell preservation becomes priority at diagnosis:
"As much as possible for as long as possible"

40% of adults and 20% of children > 200pmol for 5yrs

- T1D incidence falls
- Low c-peptide T1D is rare

Diagnose T1D Earlier (more c-peptide)

Beta cell regenerative therapies

Beta cell restoration in longstanding patients