In about 1901 Ehrlich suggested that the immune system could attack foreign things but not it's own host (attacking self = horror autoxicus).

In about 1901 Ehrlich suggested that the immune system could attack foreign things but not it's own host (attacking host = horror autoxicus)

Ehrlich, who was so right about so many properties of the immune system, was wrong in this case. For example, in 1904 Donath and Landsteiner showed that the death of red blood cells in some patients when they were cold was caused by autoantibodies specific for erythrocytes (Donath J LK. Uber paroxysismal Hamoglobinurie. Munchener Medizinische Wochenschrift. 1904. 51:1590-3.)

So strong was Ehrlich's reputation that it took more than 50 years for the existence of many autoimmune diseases to be accepted. Nowadays more than 100 such illnesses have been given names.

Here are a few of the known autoimmune diseases

Disease	% in USA population	Ratio females vs males	HLA linkage
Alopecia	0.21	2.9	DRB1*1104, DQB1*0301/0303
Ankylosing sarcoidosis	1.3	0.26	B27
Crohn's disease	0.69	1.5	DRB1*0405
Type 1 diabetes	0.3	0.97	DQ2 DQ8
Graves disease	0.63	3.5	DR3
Multiple sclerosis	0.24	3.8	DRB1*1501
Polymyalgia rheumatica	0.24	1.8	DR4??
Psoriasis	3.15	1.5	C*06:02
Scleroderma	0.16	1.8	DRB1 DQB1 DPB1
Rheumatoid arthritis	0.56	4	DRB1 0401, 0404, 0405 0408 0101 0102 1001 1401
Sjogren's syndrome	0.29	8.1	DRB1
Systemic lupus erythematosis	0.07	6	DRB1*03:01

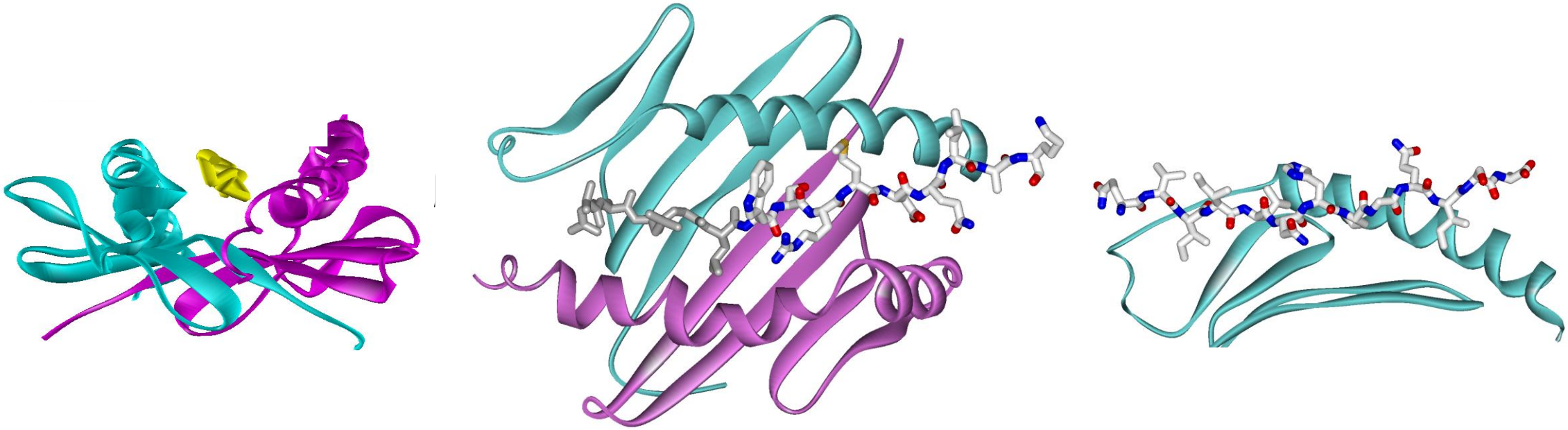
What's HLA?

It is the most polymorphic locus in the human genome.

It codes for 8 different proteins the genes for all of these are strongly polymorphic.

Its products affect immune responses including propensity for autoimmune disease.

Structure of an MHC II protein bound to a peptide

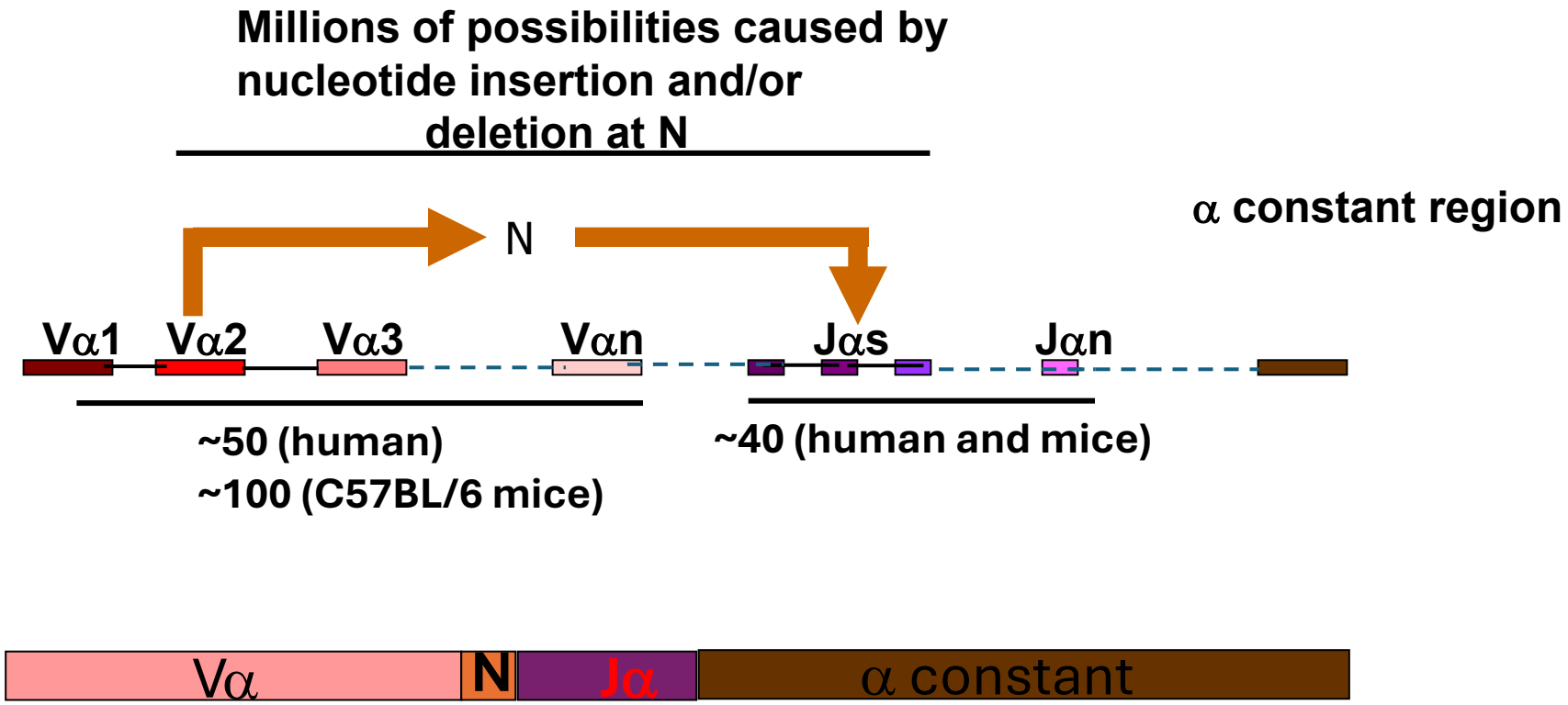


Peptides engaged to MHC II are usually 9 amino acids long although they can be extended beyond the MHC II groove.
MHC II + peptide usually stimulates CD4 T cells

Dai et al. Immunity 2008

Random rearrangement of TCR α and β genes

TCRα



So for mouse αβ T cells the following combinations are possible:

Alpha chain

50 V regions x 50 J regions x unknown number of N region sequences (eg 2 variable amino acids = 20 x 20) = ~ 1 million different TCR alpha sequences

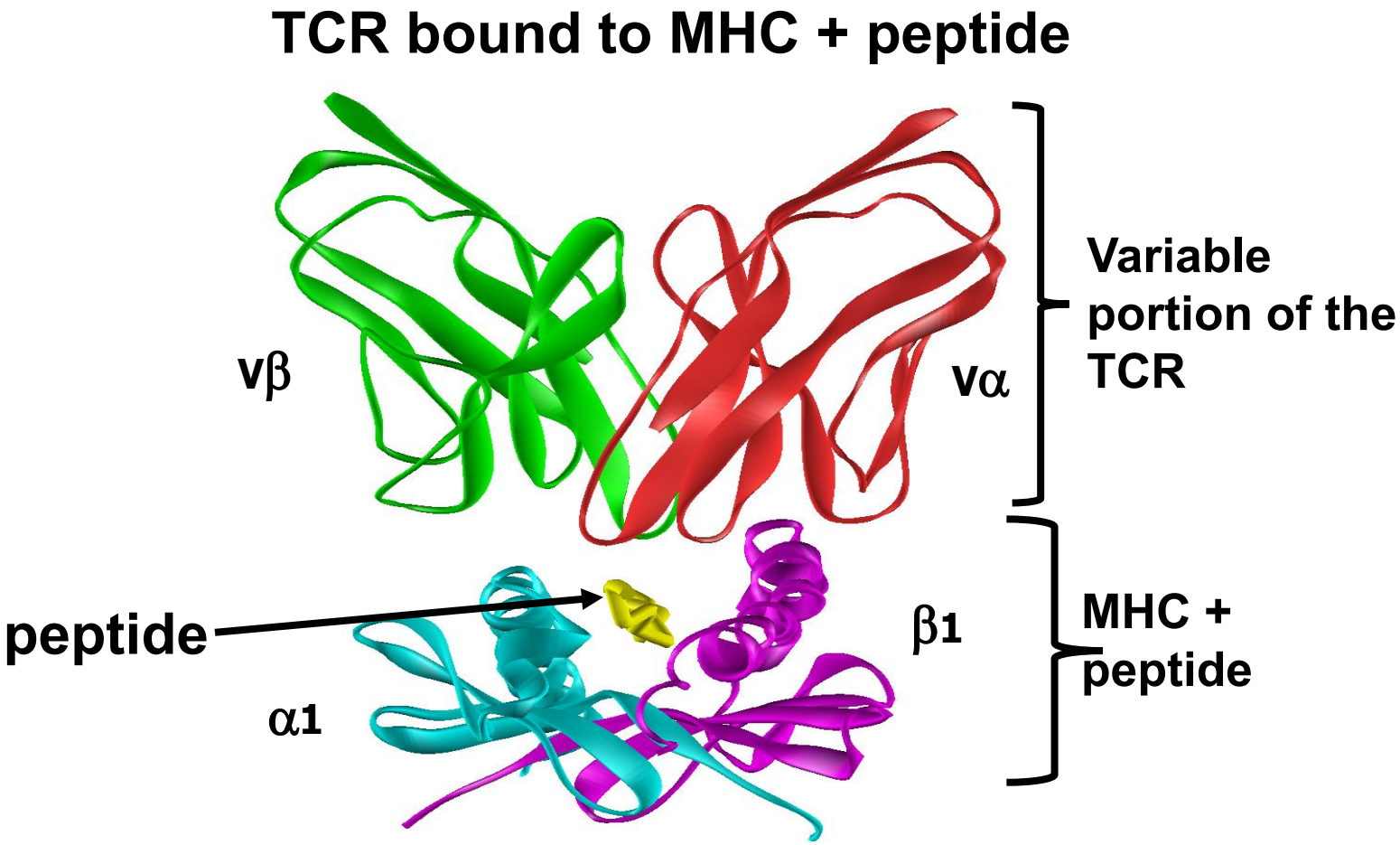
Beta chain

50 V regions x 6 D regions x 12 J regions x ~400 N regions (2 variable amino acids= 20 x 20 x 2 D regions) = ~ 1.4 x 106 different TCR beta sequences

Total number of combinations = 10^6 x 1.4 x 10^6 = ~ 10^{12}

Inevitably some of these 10^{12} will bind host MHC + host peptide

The TCRs on αβ T cells usually react with host MHC proteins bound to peptides



Dai et al. Immunity 2008

p

Ways of removing/inactivating self reactive T cells:

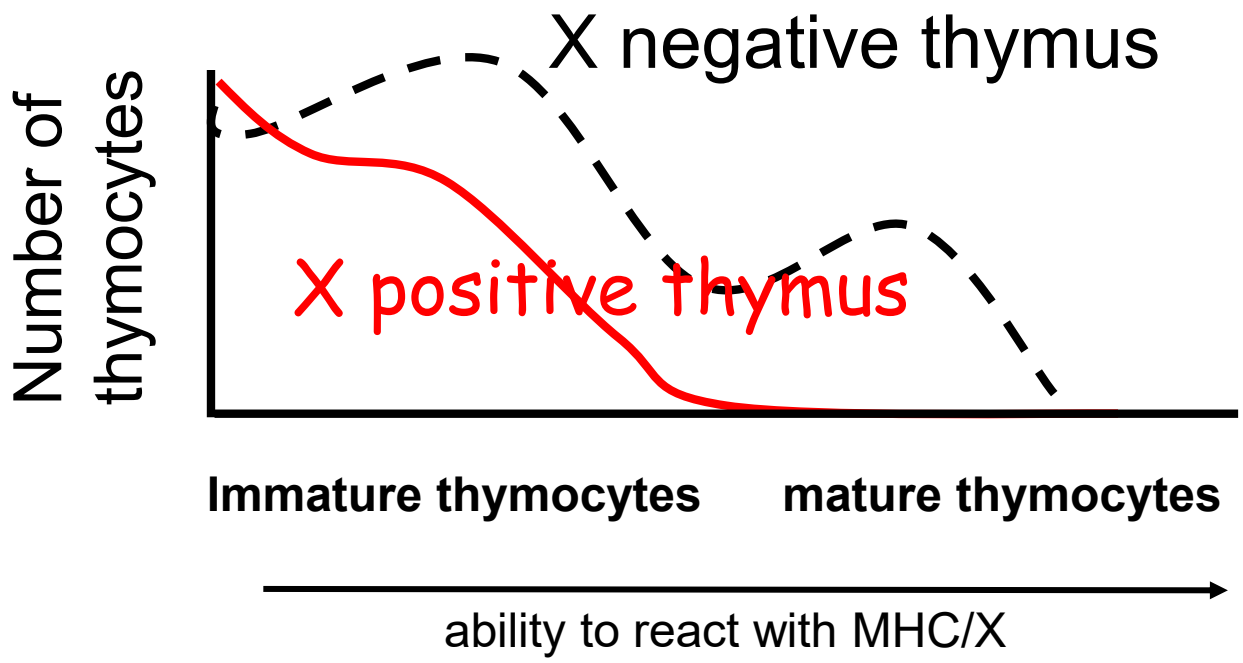
1. Immature T cells (thymocytes) arrange their T cell receptor (TCR) alpha and beta chain genes in the thymus and express the products as TCRs on their surfaces.

Do the thymocytes that express TCRs that can bind MHC + host peptides in the thymus die?

Ways of removing/inactivating self reactive T cells:

1. Do the thymocytes that express TCRs that can bind MHC + host peptides die? Yes they do.

Most of the thymocytes that react with MHC + host peptide die



Kappler Roehm and Marrack Cell 1987

Several other ways of removing/inactivating self reactive T cells:

2. **Mature T cells that are repeatedly exposed to their targets (eg MHC bound to self peptides} are inactivated.**

This phenomenon is most often studied using T cells reacting to chronic infections or tumor cells.

Several other ways of removing/inactivating self reactive T cells:

3. Mature T cells are quietened down by Regulatory T Cells that, by various means, inhibit active T cells.
Production of regulatory T cells depends on the transcription factor FoxP3.
Individuals who can't synthesize FoxP3 (IPEX patients) suffer from many autoimmune diseases.

Table 3 Initial presenting features

Feature	No of patients	References
Diarrhoea	19	14, 18, 25, 27–29, 31, 32, 35, 40, 41, this report
T1DM	14	14, 22, 23, 25, 26, 29, 31, 32, 35, 37, this report
Eczema or atopic dermatitis	9	14, 18, 22, 24, 29–31, 38
Poor feeding, ileus	3	22, 29
Anaemia or thrombocytopenia	3	22, 24, 33
Hypothyroidism	2	22, 33
Lymphadenopathy	2	29, 30
Respiratory distress	1	23
Bruising	1	22

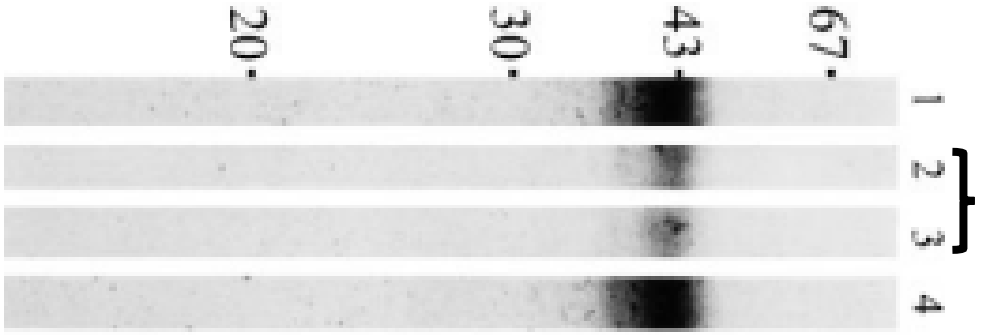
Wilden et al
J Med Genet 2002
Patients were infants

Other phenomena to consider

T cells may respond to peptides that are altered in the periphery such that they do not precisely match peptides present in the thymus

For example, antibodies against citrullinated peptides/proteins are found in Rheumatoid Arthritis patients.

Obtain sera from RA patients.
Test whether antibodies in the sera bind citrullinated filaggrin
in the absence of added peptide (lane 1)
in the presence of non citrinullated filaggrin (lane 4)
or in the presence of citrinullated filaggrin peptides (Lanes 2 and 3)



Since B cells (the source of antibodies) need T cell help to make antibodies, this suggests that some of the T cells in these patients react with possibly citruliinated filaggrin peptides bound to MHC

Schellekens et al J.Clin. Invest 1998

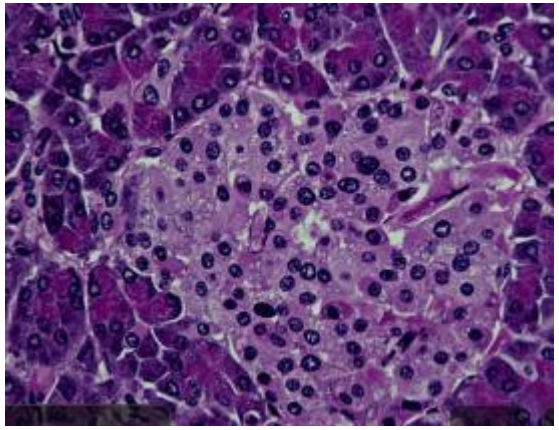
What about Type 1 Diabetes?

Mice seem to be a pretty good model for T1D because the H2 (mouse MHC) allele known to drive T1D in mice (IAg7, NOD mice) is very similar to the T1D linked MHC alleles, DQ2 and DQ8, in humans.

The antigens involved are similar. Insulin etc

A peptide from insulin beta chain, 9-23, induces T1D in young NOD mice.

Diabetogenic CD4 T cells from diabetic mice had been isolated and cloned (Haskins et al Diabetes 1988)



Islets of Langerhans
Containing alpha, beta, delta,epsilon and PP cells

T cells from pancreatic islets in diabetes-suffering mice have been isolated and cloned.

Previous studies indicated peptides containing the sequence WX(R/K)M(D/E) might be involved in stimulating T cells from diabetic mice (Judkowski , JI 2001 Toshida Int Immunol 2002)

Mass spectrometry and sequence comparisons showed that this sequence is similar to that of part of chromogranin A, a protein that is cut into many fragments in pancreatic islets.

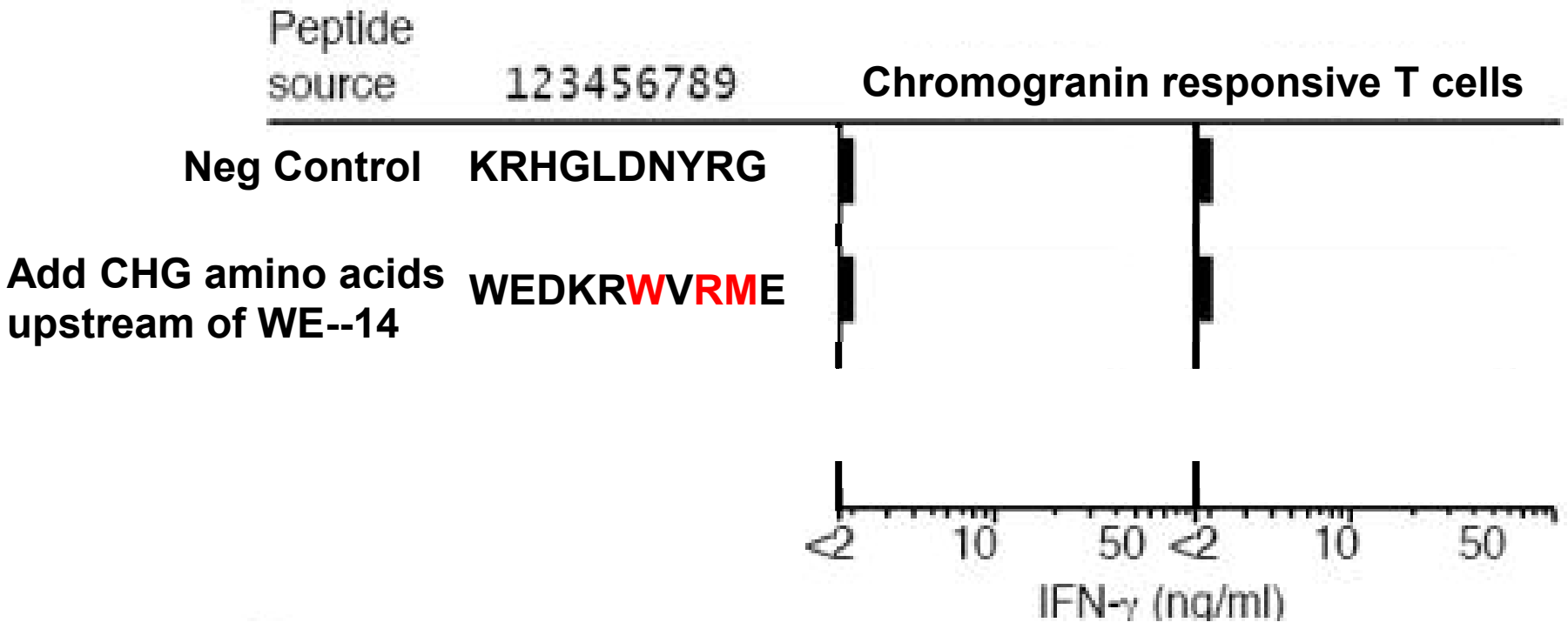
A peptide of ChromograninA, WE-14, looks as though it might be a candidate

Sequence of WE-14 WSRMDQLAKELTAE.

But this sequence doesn't stimulate diabetes inducing T cells very well.

What about the Chromogranin sequences upstream of WE-14?

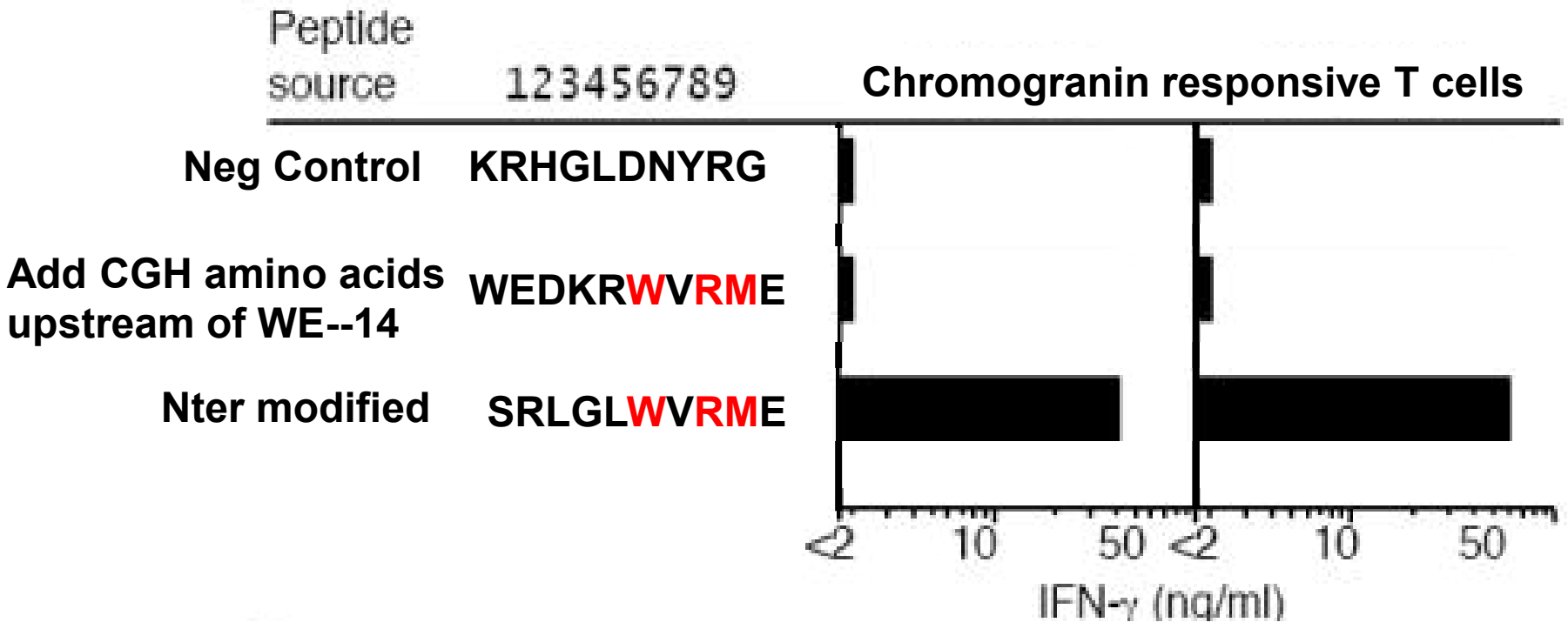
But a peptide expressing the expected 9 amino acid fragment (WEDKRWSRMD) of Chromogranin (CHG) doesn't stimulate the isolated diabetogenic T cells.



Stadinski, Delong et al. Nat Immunol 2010

But a peptide expressing the expected 9 amino acid fragment (WEDKRWSRMD) of Chromogranin (CHG) doesn't stimulate the isolated diabetogenic T cells.

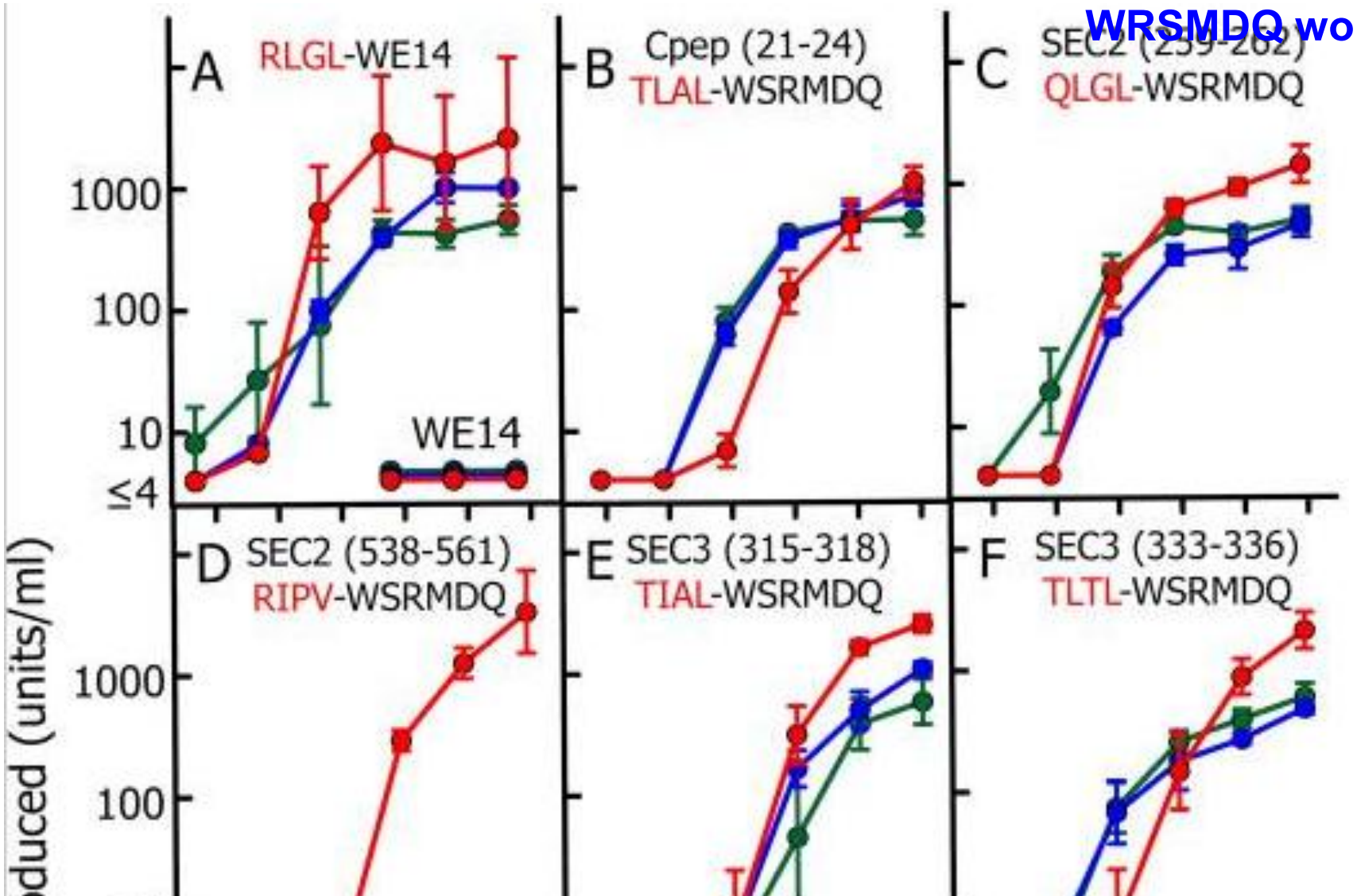
Whereas a peptide in which the Nter 5 amino acids of the chromogranin sequence are changed "randomly" (SRLGLWVRME) DOES stimulate the T cells



Stadinski, Delong et al. Nat Immunol 2010

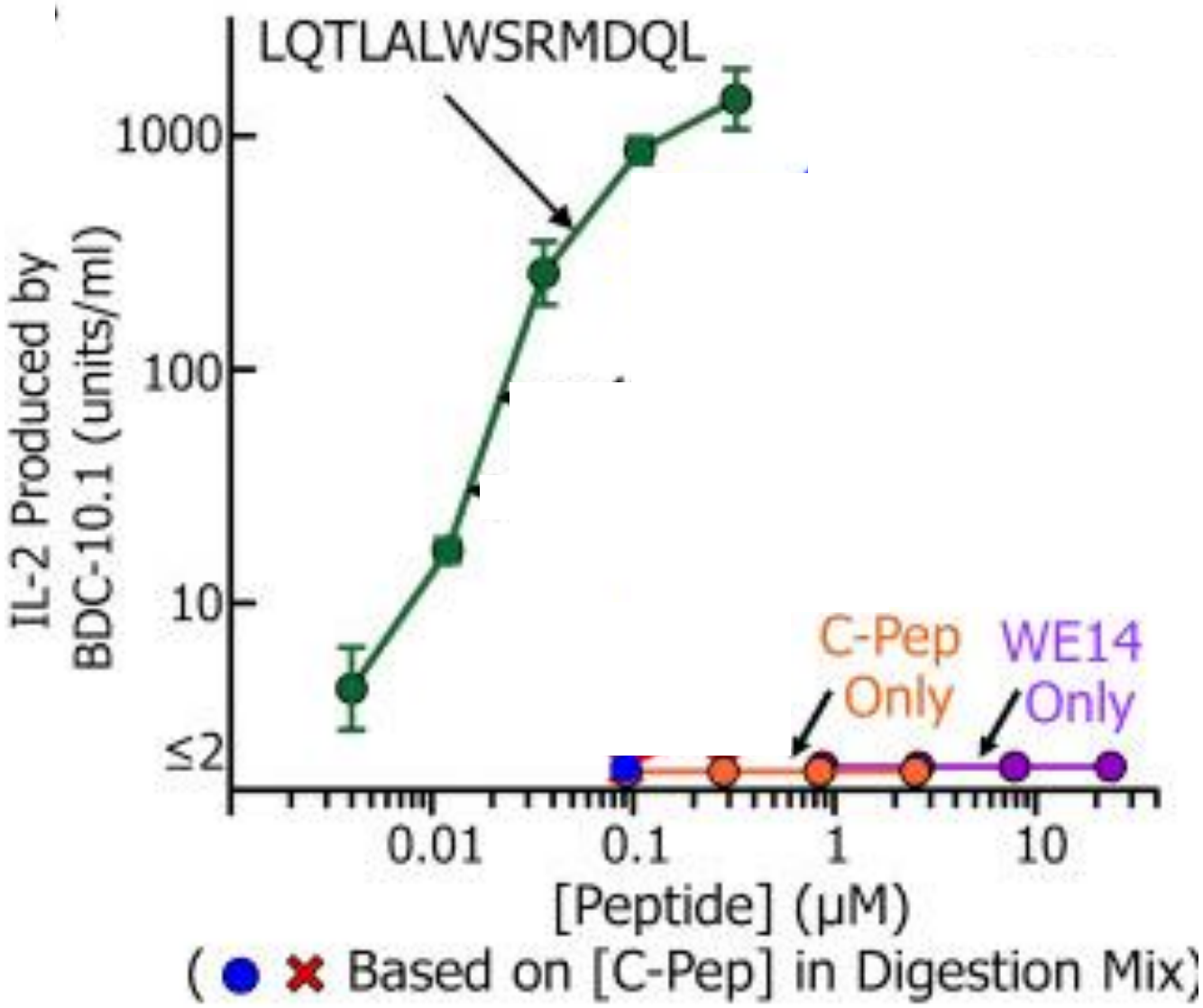
Three different responding T cells

Covalent addition of some peptides from proteins in pancreatic beta cells to WE14 or the assumed peptide WRSMDQ work magnificently

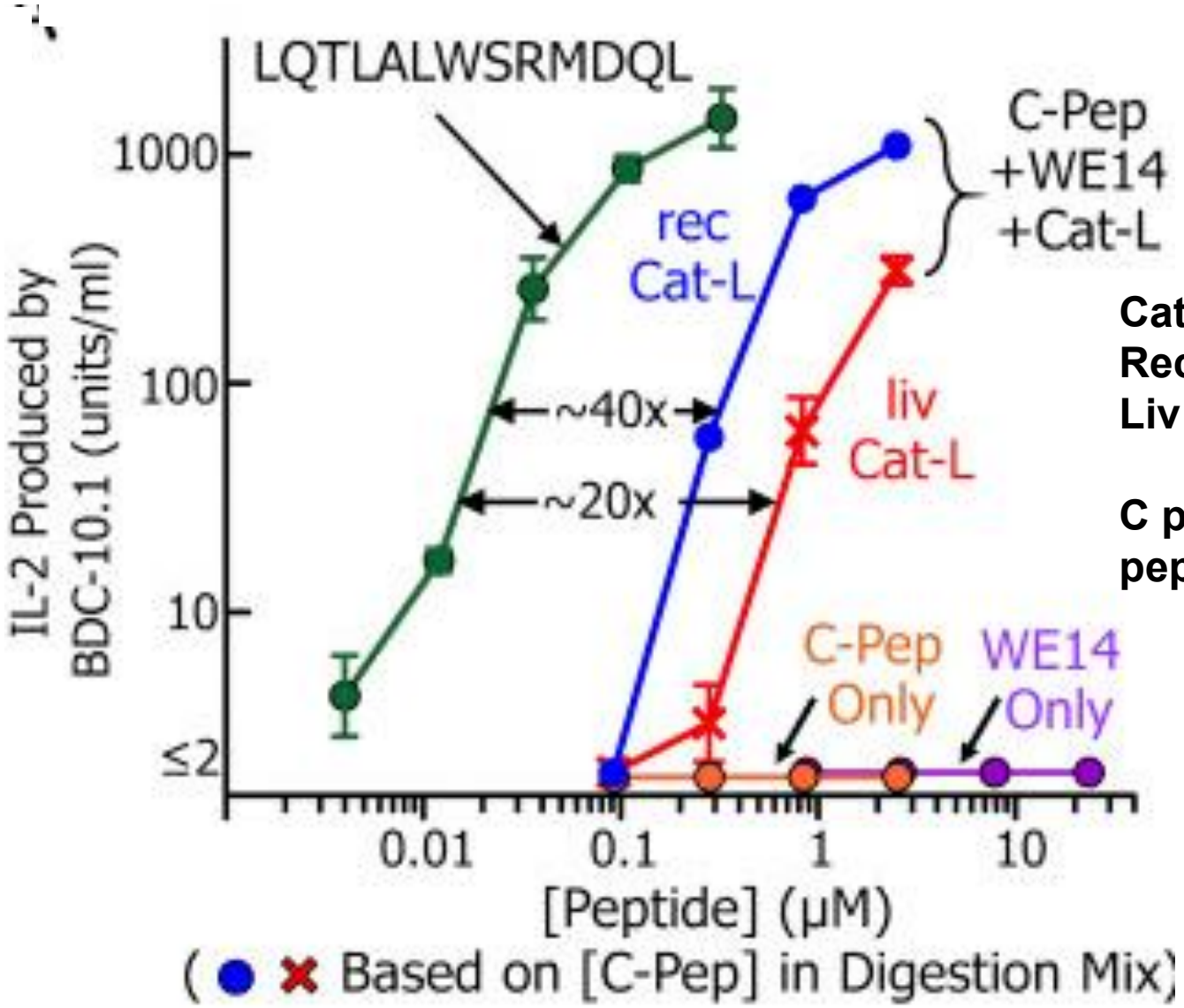


Reed et al J Exp Med 2021

What's going on???


LQTLALWSRMDQL
1000
100
10
≤2
IL-2 Produced by BDC-10.1 (units/ml)
C-Pep Only
WE14 Only
0.01
0.1
1
10
[Peptide] (μM)
(● ✖ Based on [C-Pep] in Digestion Mix)

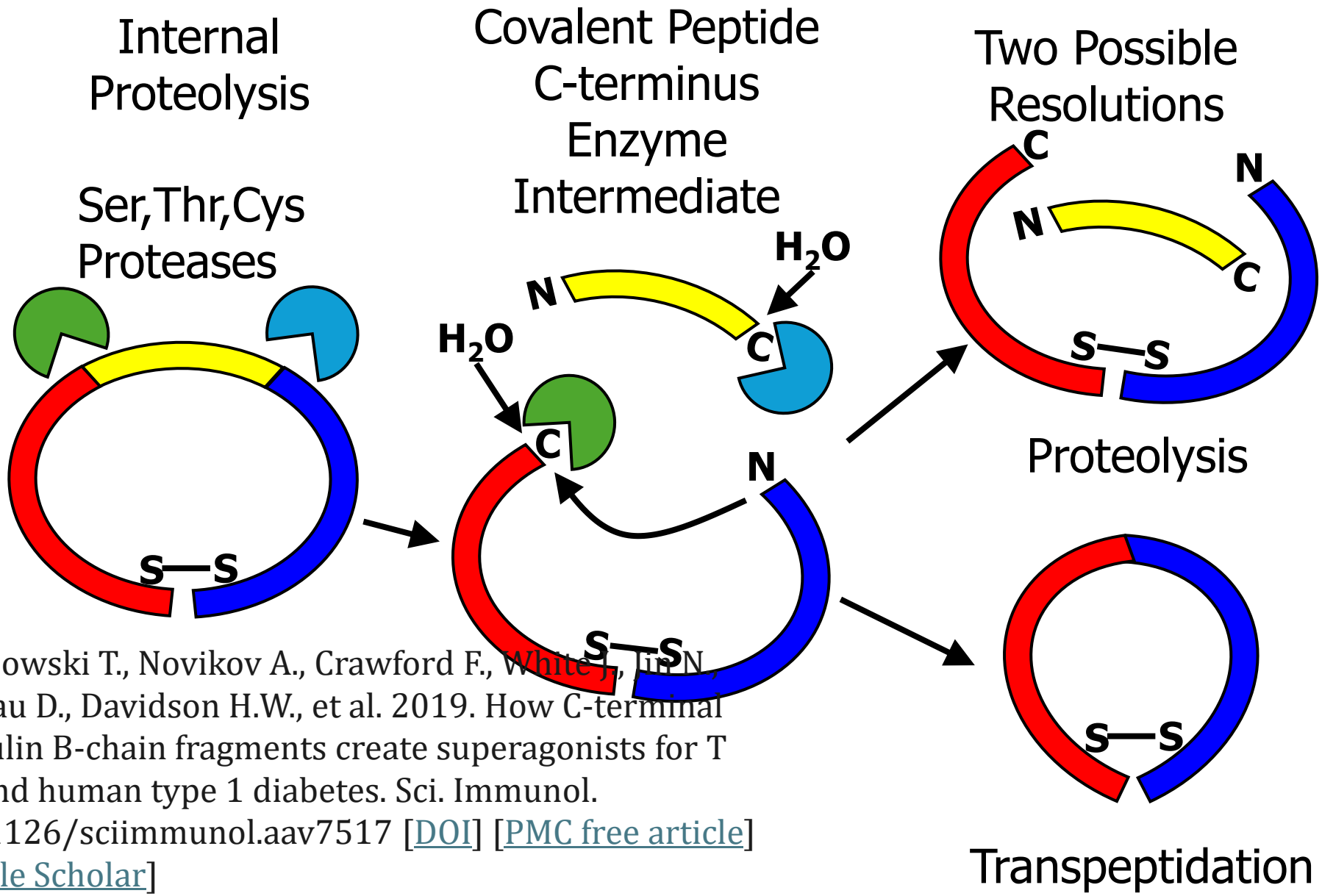
The stimulatory peptides are made by transpeptidation in this case of insulin C-peptide and the WE14 fragment



Cat-L= Cathepsin L
Rec = recombinant Cathepsin L
Liv = liver Cathepsin L

C peptide = fragment of a linking peptide of insulin

How Does Transpeptidation Work?



1.Wang, Y., Sosinowski T., Novikov A., Crawford F., White J., Jin N., Liu Z., Zou J., Neau D., Davidson H.W., et al. 2019. How C-terminal additions to insulin B-chain fragments create superagonists for T cells in mouse and human type 1 diabetes. Sci. Immunol. 4:eaav7517 10.1126/sciimmunol.aav7517 [DOI] [PMC free article] [PubMed] [Google Scholar]

WE14

WSRMDQLAKELTAE

Mouse insulin C peptide

EVEDPQVAQLQLELGGGPGAGDLQTLALEVAQQ

WE14

WSRMDQLAKELTAE

Mouse insulin C peptide

EVEDPQVAQLQLELGGGPGAGDLQTLALEVAQQ

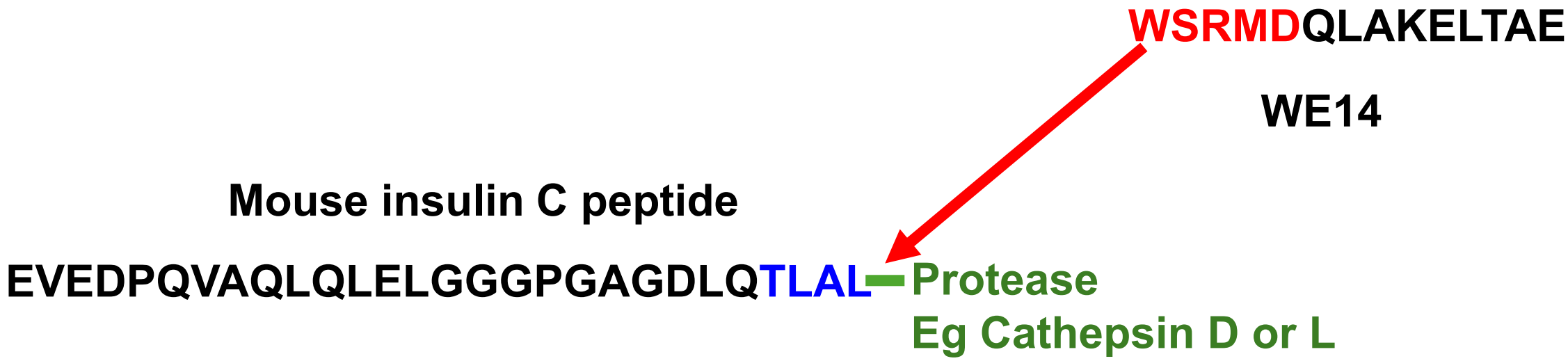
Protease
Eg Cathepsin D or L

WSRMDQLAKELTAE

WE14

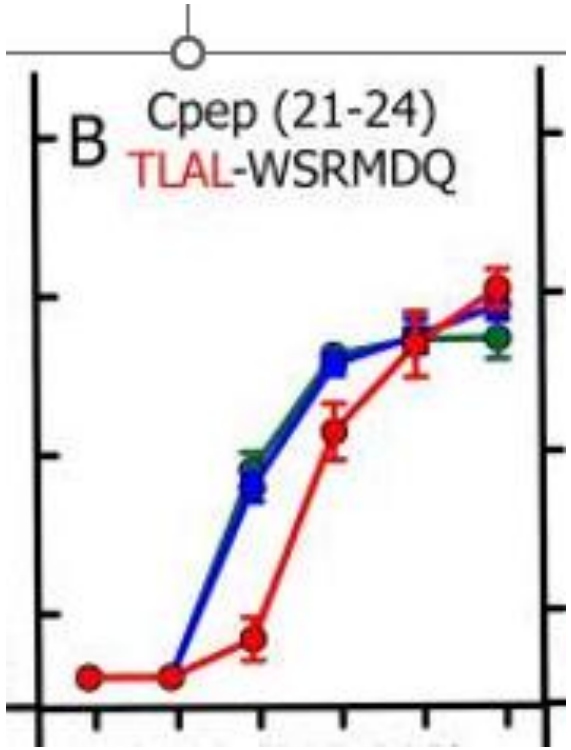
Mouse insulin C peptide

EVEDPQVAQLQLELGGGPGAGDLQTLAL — Protease
Eg Cathepsin D or L


WSRMDQLAKELTAE
WE14
Mouse insulin C peptide
EVEDPQVAQLQLELGGGPGAGDLQTLAL
Protease
Eg Cathepsin D or L

Part of insulin C peptide covalently linked to WE14

EVEDPQVAQLQLELGGGPGAGDLQTLALWSRMDQLAKELTAE



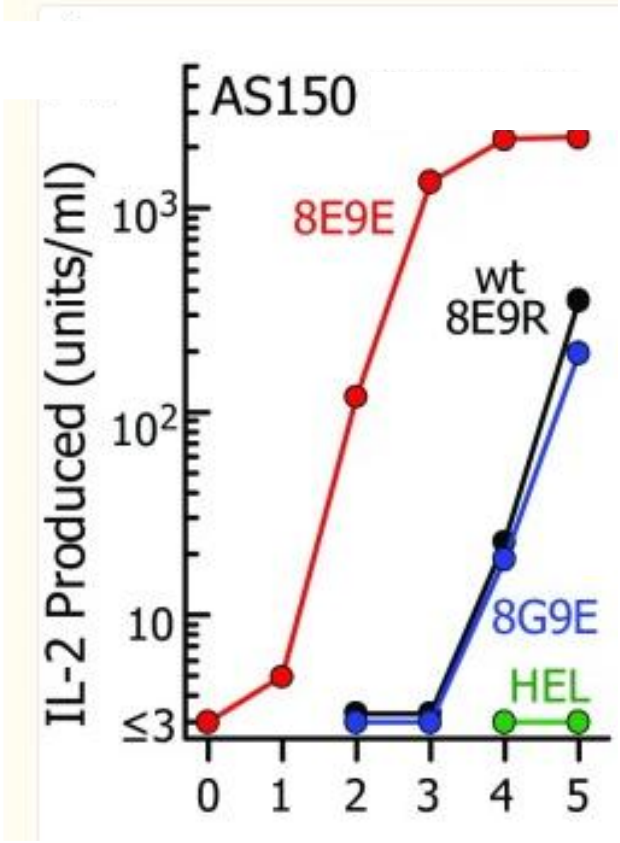
Transpeptidation occurs in a cell compartment with low levels of water and high levels of proteins/peptides which include protease(s).
These properties would apply to the insulin granules in pancreatic beta cells.

It is favoured if the two peptides to be joined are from the same protein.

A similar phenomenon is involved in stimulation of T cells by insulin peptides

Mouse IAg7, human DQ2 and Human DQ8
All have an arginine positioned to interact with amino acid 9 (an arginine) of the insulin peptide

123456789
HLVEALYLVCGERG



Michels et al Diabetes 2017
Wang et al PNAS 2018
Wiles et al. Proteome Res. 2019
Baker et al. Diabetes. 2019
Wang et al Sci. Immunol 2019
Wiles et al. Front Immunol. 2021

To think about:

Clinically, autoimmune diseases are usually treated globally with immunosuppressants such as…..

Corticosteroids

Calcineurin inhibitors, like tacrolimus (Envarsus XR® or Protopic®) and cyclosporine

Inosine monophosphate dehydrogenase (IMDH) inhibitors, like mycophenolate mofetil

Janus kinase inhibitors, like (Xeljanz®). These drugs reduce inflammation by limiting the activity of certain enzymes (Janus kinases). They're a type of immunomodulator.

Mechanistic target of rapamycin (mTOR) inhibitors, such as sirolimus (Rapamune®). mTOR inhibitors keep cells from growing and multiplying.

Antibodies against cytokines or their receptors

Removal of B cells by anti-CD20 or CAR T cells

And, for type 1 diabetes, Insulin

Work on transpeptidation done by colleagues and others

Chromogranin A is a T cell antigen in human type 1 diabetes.
Gottlieb PA et al. Autoimmun. 2014 May;50:38-41.

Identification of Hybrid Insulin Peptides (HIPs) in Mouse and Human Islets by Mass Spectrometry.
Wiles TA et al. Proteome Res. 2019 Mar 1;18(3):814-825.

Jason Groegler

CD4 T Cells Reactive to Hybrid Insulin Peptides Are Indicators of Disease Activity in the NOD Mouse.
Baker RL et al. Diabetes. 2018 Sep;67(9):1836-1846.

Characterization of Human CD4 T Cells Specific for a C-Peptide/C-Peptide Hybrid Insulin Peptide.
Wiles TA, et al. Front Immunol. 2021 May 25;12:668680.

Hybrid Insulin Peptides Are Autoantigens in Type 1 Diabetes.
Baker RL et al. Diabetes. 2019 Sep;68(9):1830-1840.

Tolerogenic Delivery of a Hybrid Insulin Peptide Markedly Prolongs Islet Graft Survival in the NOD Mouse.
Jamison B. et al. Diabetes. 2022 Mar 1;71(3):483-496.

Novel T-Cell Reactivities to Hybrid Insulin Peptides in Islet Autoantibody-Positive At-Risk Individuals.
Hohenstein AC et al. Diabetes. 2025 Jun 1;74(6):933-942.

Antigen-specific immunotherapy with a $CD4^+$ T cell neoepitope restrains $CD8^+$ T cell differentiation in murine pancreatic islet grafts.
DiLisio JE et al. Nat Commun. 2026 Mar 24. doi: 10.1038/s41467-026-70878-2.

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