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Genetic and mechanism-based therapeutic approaches to treat human autoimmune diseases

Professor John Todd FRS PhD

Director, JDRF/WT Diabetes & Inflammation Laboratory

NIHR Cambridge Biomedical Research Centre (renewed for 5 years at $180,000,000)

Cambridge Institute for Medical Research

University of Cambridge

Addenbrooke's Hospital

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Acknowledgements

JDRF/WT Diabetes & Inflammation Laboratory (DIL)

JDRF Diabetes—Genes, Autoimmunity and Prevention (D-GAP)

David Clayton & Linda Wicker, co-PIs

Sarah Nutland & team: NIHR BRC Cambridge BioResource

Helen Stevens & team: samples; Matt Woodburn; Sample IT

Neil Walker & team: data

Olly Burren & team: informatics – T1DBase

Jason Cooper, Jo Howson, Vincent Plagnol, Chris Wallace: stats

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Jennie Yang, Kate Downes, Marcin Pekalski, Xaq Castro, Calli Dendrou, Laura Esposito, Lucy Davison, Sarah Howlett, Jan Clark, Dan Rainbow

T1DGC and WTCCC

Juvenile Diabetes Research Foundation & Wellcome Trust; NIDDK; NIHR Cambridge Biomedical Research Centre

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CIMR Cambridge Institute for Medical Research

wellcome trust

Istituto di Neurogenetica
e Neurofarmacologia, Cagliari
Responsabile Scientifico
Progetto Progenia
Dott.ssa Manuela Uda

National Institute of Health
National Institute on Aging,
Baltimora, USA
Responsabile Scientifico
Progetto Progenia
Dott. David Schlessinger

Con il Patrocinio di:

Provincia dell'Ogliastra
Comune di Lanusei
Comune di Arzana
Comune di Ilbono
Comune di Elini

In collaborazione e con il supporto di:

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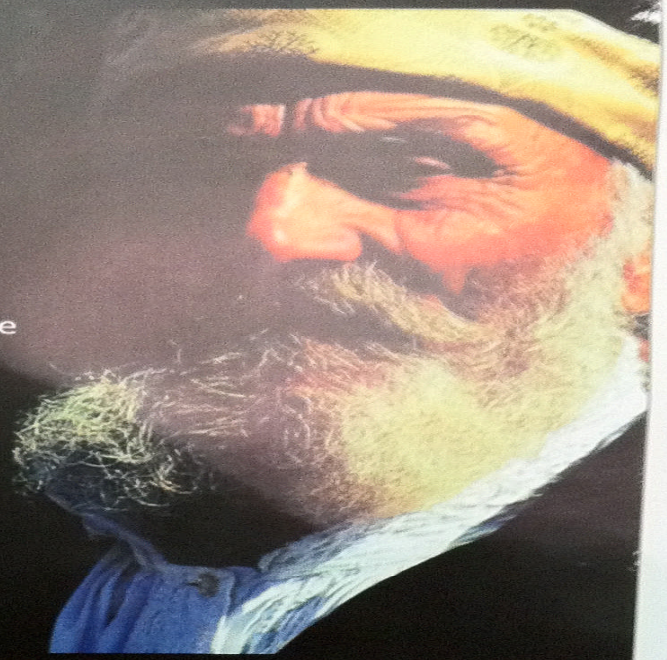

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genetico:
una ricchezza
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Risultati e Prospettive

16 Maggio 2009, ore 9.30
Lanusei, Aula Magna
Liceo Scientifico Statale
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www.progenia.sardegna.it

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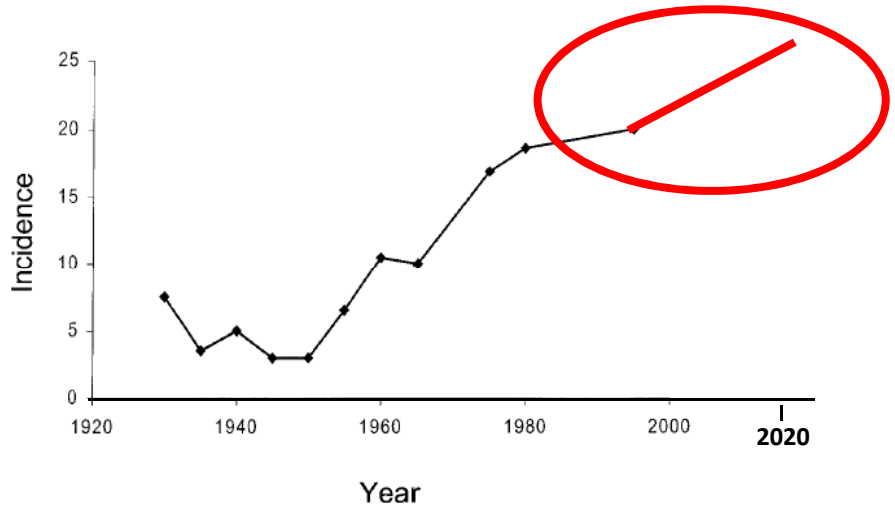
T1D to double in under 5's by 2020



cases/100,000/year

Patterson CC et al. *Lancet* 373:2027-33 (2009)

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Genetic and mechanism-based therapeutic approaches to treat human autoimmune diseases

- Natural history of type 1 diabetes
- Pathology of type 1 diabetes
- Genetics of susceptibility
- IL-2 pathway and Tregs
- IL-2: treatment and prevention of type 1 diabetes

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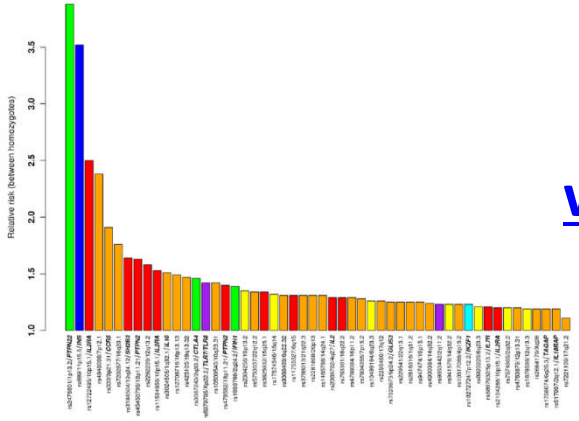
Over 50 regions of the human genome control diagnosis of type 1 diabetes



www.t1dbase.org

Genes to biology & mechanism

Four major predisposing pathways (so far):

(1) Cytokine production and signalling

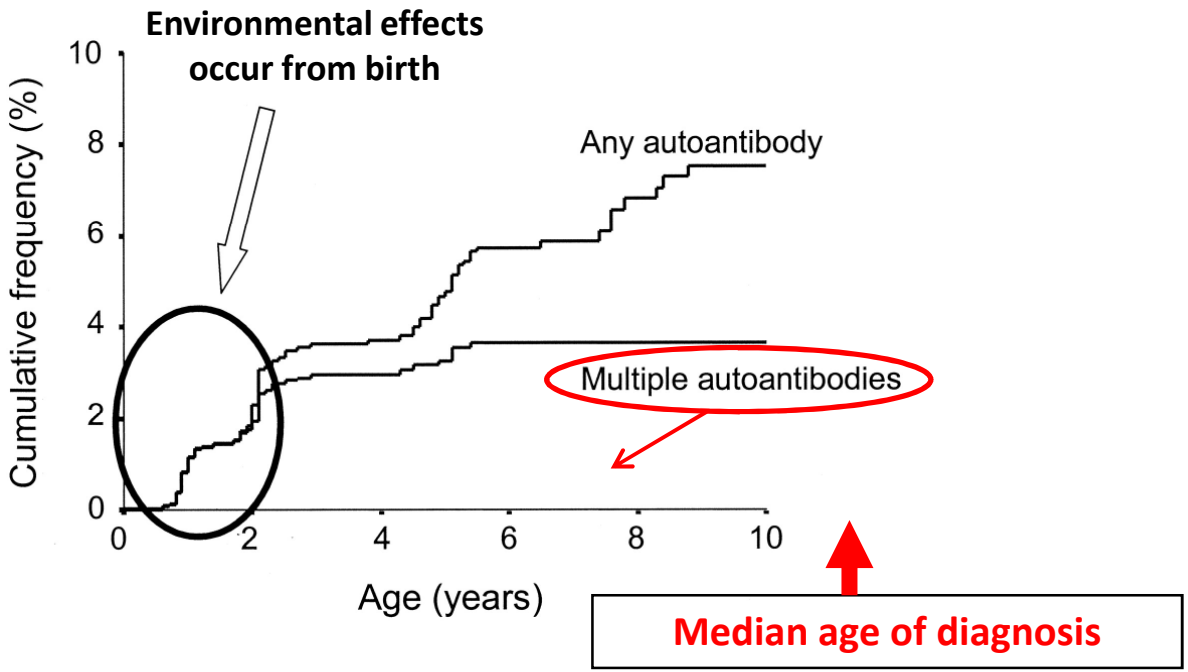
(2) Decreased T cell signalling and activation

(3) Increased type 1 interferon production and anti-viral responses

(4) Antigen presentation and T cell repertoire formation

No evidence of gene polymorphisms specific for beta cell function!!

Type 1 diabetes-predictive autoantibodies: defective tolerance is a very early event



Autoantibody production is dependent on autoreactive T cells specific for islet antigens

Natural history of type 1 diabetes. Siljander, HT et al Diabetes 58, 2835-42, 2009

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Screening in order to find the pre-diabetics that are optimal subjects for new treatments

- Population-based autoantibody screening
  - HLA risk taken into account
- Family history-based screening
  - Children of T1D parents
  - Siblings of diabetic patients
  - Cambridge, London, Bristol & Cardiff: D-GAP

KING'S College LONDON

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Diabetes - Genes, Autoimmunity and Prevention

Cambridge BioResource

JDRF Juvenile Diabetes Research Foundation

dedicated to finding a cure

NHS National Institute for Health Research

University of BRISTOL

Cambridge University Hospitals NHS Foundation Trust

Unaffected Siblings: Geographical placement

Approved Sites

Cambridge

Bury St Edmunds

Ipswich

Northampton

Oxford

Colchester

Brighton

Huntingdon

Year 3

Watford

Peterborough

Great Yarmouth

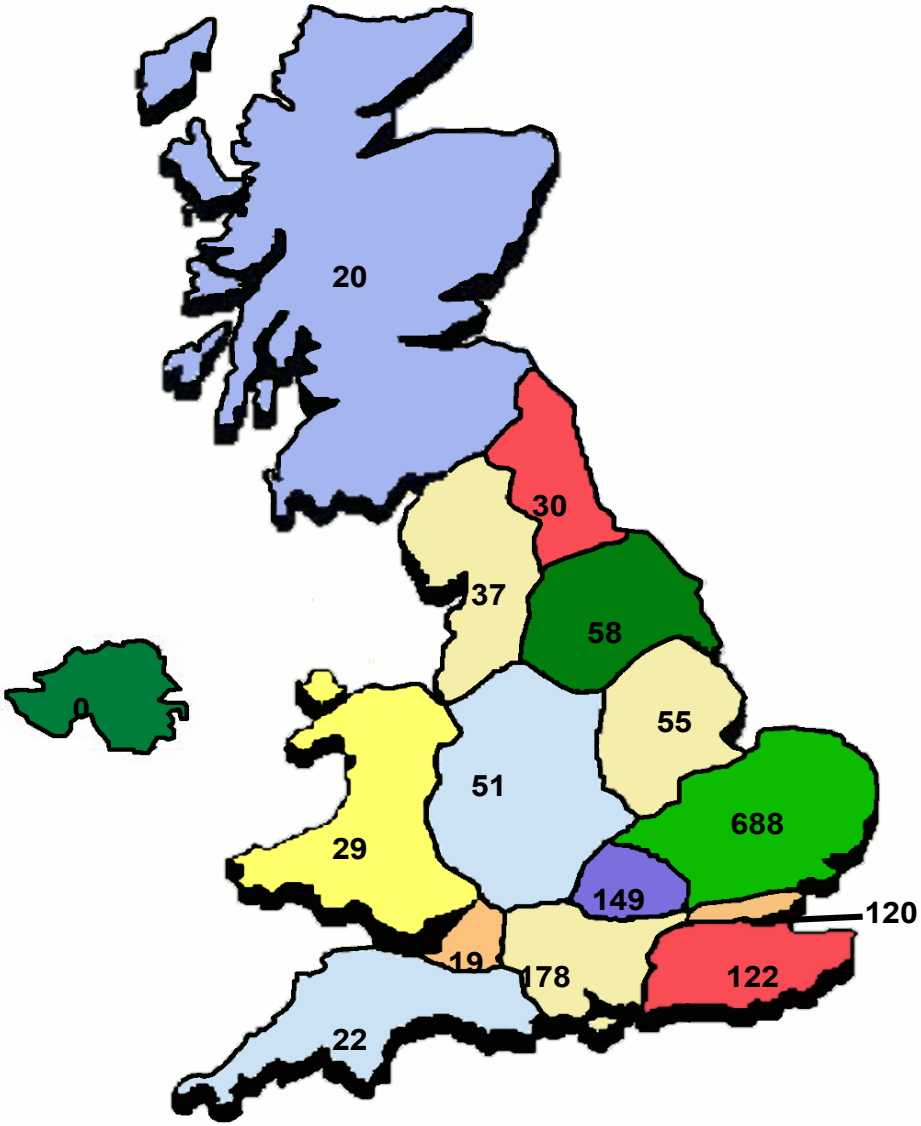
Portsmouth

Waiting Approval

Basildon
Southend
Chelmsford
Stoke on Trent
Reading

Closed Sites

Stevenage/Welwyn
Luton & Dunstable



Unknown/Other 22

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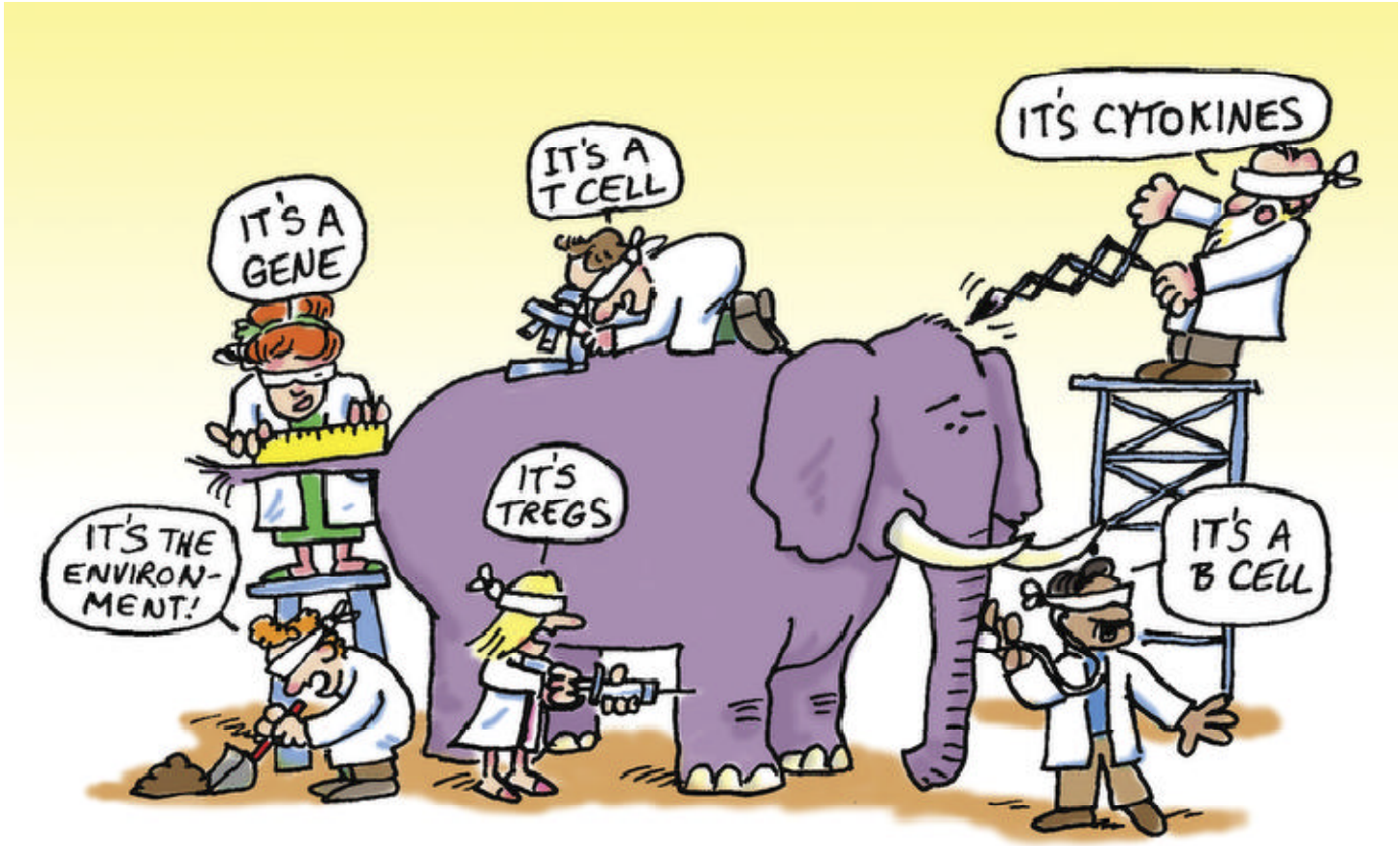
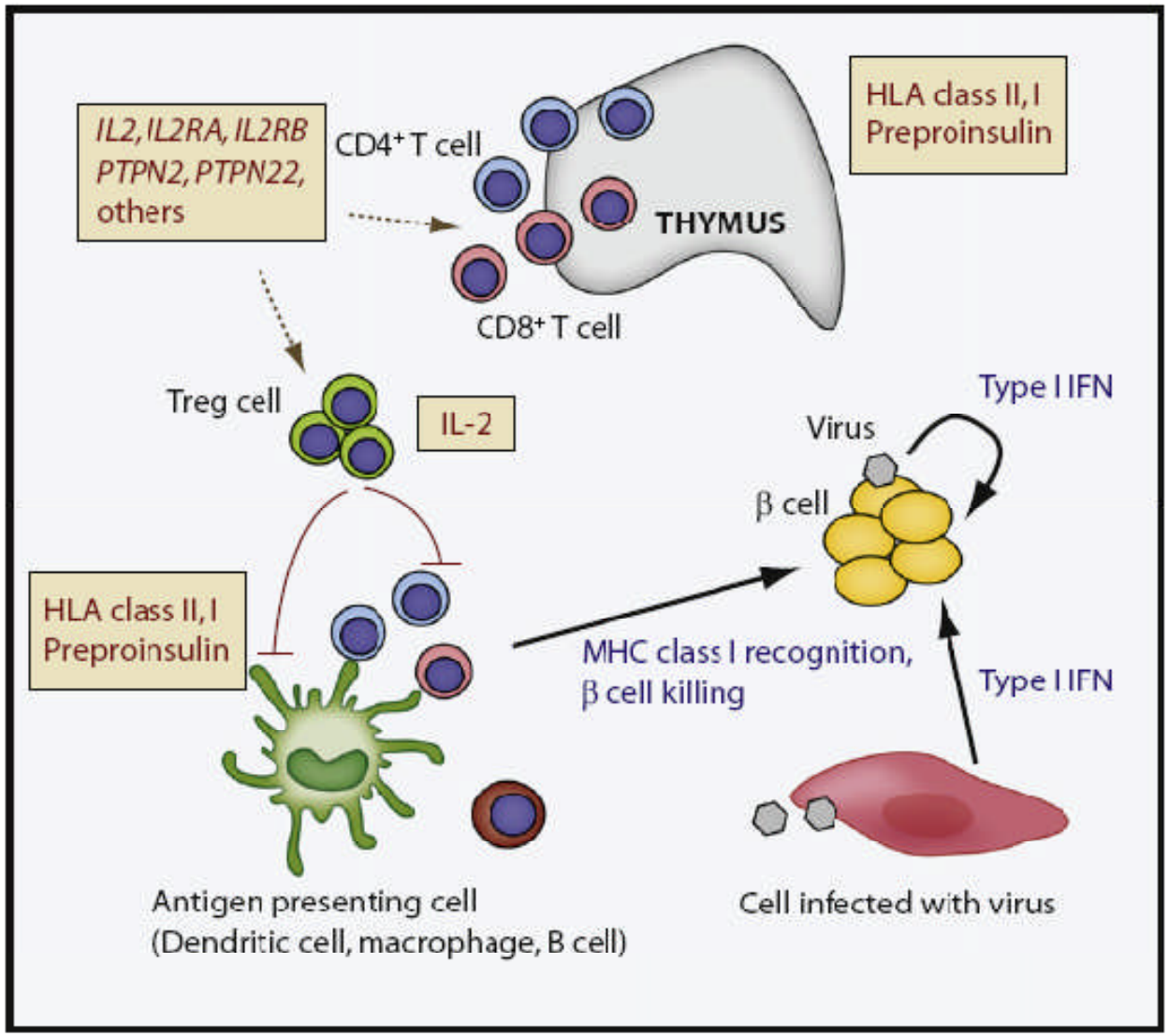
What causes Type 1 diabetes?
A pathologist's view point

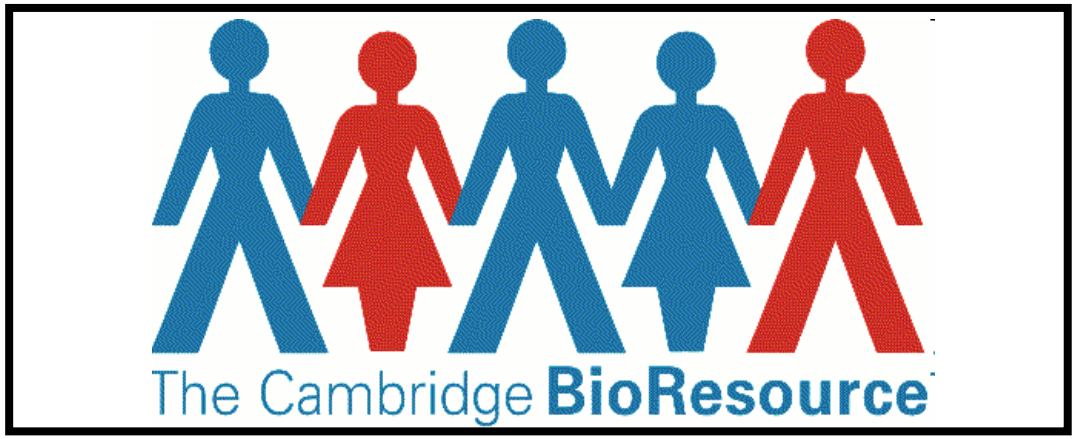


www.ScienceTranslationalMedicine.org 10 August 2011


IL2, IL2RA, IL2RB
PTPN2, PTPN22,
others
CD4+ T cell
THYMUS
HLA class II, I
Preproinsulin
CD8+ T cell
Treg cell
IL-2
Type I IFN
Virus
β cell
HLA class II, I
Preproinsulin
MHC class I recognition,
β cell killing
Type I IFN
Antigen presenting cell
(Dendritic cell, macrophage, B cell)
Cell infected with virus

Genes to biology

The Cambridge BioResource: a resource of >9,000 local volunteers including T1D, SLE, RA, and MS patients willing to be invited to a wide range of medical research studies, SELECTED by genotype & RECALLABLE



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NHS
National Institute for Health Research
Cambridge Biomedical Research Centre

MRC Medical Research Council

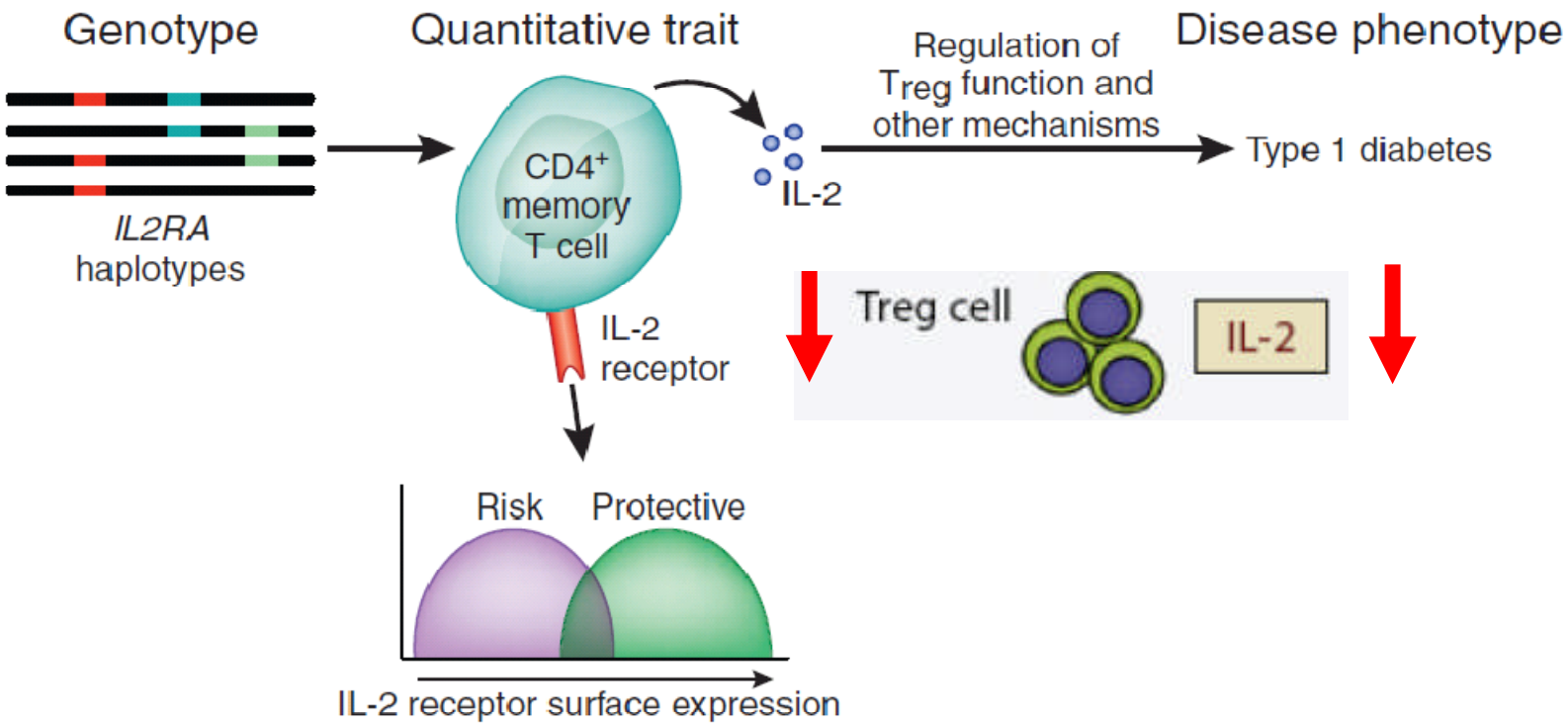
NHS
Blood and Transplant

CIMR Cambridge Institute for Medical Research

wellcome trust

JDRF Juvenile Diabetes Research Foundation International
dedicated to finding a cure

The interleukin-2 pathway is a major aetiological pathway in -human- type 1 diabetes



Dendrou, Plagnol, Nutland, Todd, Wicker, et al. *Nature Genetics* 41:1011-1015 (2009)

Gregersen. News & Views. *Nature Genetics* 41:1011-1015 (2009)

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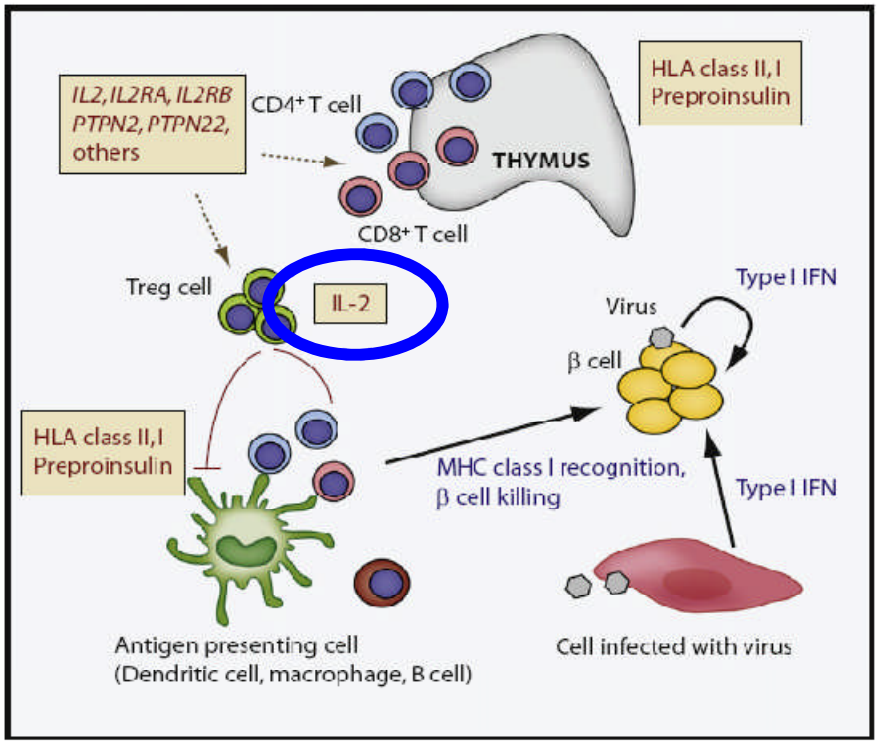

+ IL-2

Health

Less IL-2 and IL-2 signalling

Autoreactive T cells and APCs: T1D

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary

Search

Study 53 of 85 for search of: low dose interleukin 2

Previous Study Return to Search Results Next Study

Full Text View | Tabular View | No Study Results Posted | Related Studies

Dose-effect Relationship of Low-dose IL-2 in Type 1 Diabetes (DF-IL2)

This study is currently recruiting participants.

Verified on May 2011 by Assistance Publique - Hôpitaux de Paris

Primary Outcome Measures:

- Kinetic parameters of Treg proportions variation within CD4+ T cells in peripheral blood
  - [Time Frame: from Day+0 to Day+60]
  - [Designated as safety issue: No]

Secondary Outcome Measures:

- Improvement of residual secretion of insulin assessed by the AUC of peptide C during a standardized test meal in IL-2 vs placebo treated patients
  - [Time Frame: at Day+0 and Day+60]
  - [Designated as safety issue: No]
- Doses 3, 1 and 0.33 million units s.c. for 5 days

Future: David Klatzmann, Paris, applying for European funding (4 Oct, LOI) for a Phase 2 trial of low dose proleukin in 200 newly-diagnosed T1D: Linda Wicker and John Todd to participate and recruit to the trial and analyse samples

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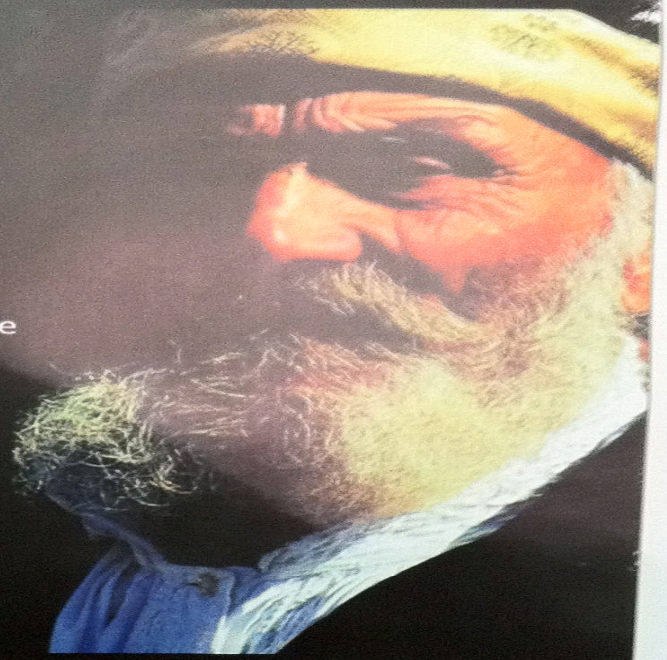

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