SUPPLEMENTARY INFORMATION

Supplemental Table 1 (with references): Past, ongoing, and near future trials in Type 1 diabetes

Indication	Mechanisms	Examples	Target	Reference
Prediabetes	Antigen specific immune modulation	Parental insulin	Beta cell protective/Tolerance to insulin	[1]
		Oral insulin	Tolerance to insulin	[2]
		Alum GAD65	Tolerance to GAD65	[3]
		Intranasal Insulin	Mucosal Antigen Specific Tolerance	[4,5]
		Cow's mild avoidance	Prevention of cellular activation by molecular mimic	[6]
	Beta cell protective (reduce free radicals)	Nicotinamide	Beta cells	[7]
		Omega-3-fatty acids	Beta cell protective	[8]
	Toleragenic	Vitamin D	Dendritic cells	[9]
Prediabetes with glucose impairment*	Induction of regulatory mechanisms	Teplizumab/ Otelixizumab	CD3/T cells (non-depleting)	[10]
	B cell depletion	Rituximab	CD20/B cells (depleting)	[11]
New onset diabetes	Induction of regulatory cells/mechanisms	Teplizumab/ Otelixizumab	CD3	[12,13]
	Cell depletion	Thymoglobulin	T lymphocytes	[14,15]
		Rituximab	CD20	[16]
		Anti-CD5 immunoconjugate	CD5 (B cells)	[17]
		Alefacept	CD2: (depleting for memory T cells and NK cells)	[18]
	Anti-Cytokine	Ustekinumab	IL-12	[19]
		Canikinumab	IL-1	[20]
		Anakinra (IL-1RA)	IL-1 receptor	[21]
		Daclizumab /(Zenapax) Basiliximab (Simulect)	IL-2receptor	[22]
		"Power mix"	IL-1, IL-15	[23]
	Anti-inflammatory	Etanercept (soluble TNFR2)	TNF	[24]
		Lisofylline	Beta cells	[25]
		Alpha-1 anti-trypsin (Aralast NP)		[26]
	Costimulation blockade	CTLA4Ig (Abatacept)	B7.1 and B7.2	[27]
		Alefacept	LFA-3/CD2	[28]
	Targeted immune modulation	Gleevec	Tyrosine Kinase	[29]
	Broad immune suppression	Azathioprine, prednisone	T and B cell activation and proliferation	[30]
		Mycophenolate Mofetil with Daclizumab	Lymphocyte proliferation and IL-2rec	[31]

		Cyclosporine Tacrolimus	Calcineurin	[32,33]
		Interleukin-2 (IL-2) with Rapamycin	Downregulate T effector while sparing T regulatory function	[34]
	Antigen specific immune modulation	GAD65alum	Tolerance to GAD65	[3]
		HSP60 (DiaPep277)	Immune modulatory	[35]
		Proinsulin DNA	Antigen-specific tolerance vaccination	[36]
	Cellular therapy	Granulocyte-Colony Stimulating Factor	Enhance T regulatory cell numbers	[37]
		Adult human mesenchymal stem cells	Impart immune regulation	[38]
		Insulin-treated EDCI fixed cells	Tolerance induction	[39]
		CD34+ cells	Stem cell immune modulation	[37]
		Expanded T regulatory cells	Augment regulatory T cell numbers	[40]
		Autologous dendritic cell therapy (with and without beta cell peptides)	Tolerogenic vaccine	[41]
		Umbilical cord blood infusion	Enhance T regulatory cell numbers	[42]
Diabetes recurrence following islet transplantation	Broad immune suppression	Tacrolimus, Rapamycin, Daclizumab	"Edmonton Protocol": Calcineurin, mTOR, IL-2rec	[43,44]
		Campath-1H	CD52: T-cell depleting mAb	[45]
		Alefacept	CD2	[28]
		Teplizumab	CD3	[46,47]
	Anti-inflammatory	Lisofylline		[48]
	Antigen processing	Deoxyspergualin	Monocytes	[49]

*** Relatives of patients with T1D who are positive for multiple autoantibodies or who have indeterminant glucose tolerance have a > 70% risk of diabetes over a 7 year observation period[50]. They are considered similar to patients with T1D without manifest hyperglycemia.**

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Supplemental Table 2. Ongoing trials for Type 1 diabetes

Study Title	Agent	Phase	Patient population	Clinicaltrials.gov
Biologics				
AbATE	Teplizumab (anti-CD3 mAb)	2	New onset T1DM	NCT00129259
DEFEND-1	Otelixizumab (anti-CD3 mAb)	3	New onset T1DM	NCT00678886
Protégé	Teplizumab	3	New onset T1DM	NCT00385697
Protégé Encore	Teplizumab	3	New onset T1DM	NCT00920582
Anti-CD3 Prevention Trial	Teplizumab	2	Prevention for at risk relatives	NCT01030861
START	Thymoglobulin	2	New onset T1DM	NCT00515099
Effects of Recombinant Human Glutamic Acid Decarboxylase	GAD65-alum	2	New onset T1DM	NCT00529399
A Phase III Study to Investigate the Impact of Diamyd in Patients Newly Diagnosed With	GAD65-alum	3	New onset T1DM	NCT00723411

Type 1 Diabetes (EU)				
Novel Therapy Combining Regenerative Stimuli Immunomodulation to Preserve Beta Cell Function in New Onset Type 1 Diabetes	Lansoprazole Sitagliptin GAD65	2	New onset T1DM	NCT00837759
Subcutaneous Administration of Otelixizumab to T1DM Patients	Otelixizumab	1	T1DM	NCT00946257
Delay	Teplizumab	2	Recent onset T1DM (4-12 mos)	NCT00378508
Anti-Interleukin-1 in Diabetes Action (AIDA)	IL-1 receptor antagonist (Anakinra)	3	New onset T1DM	NCT00711503
Cells				
Cord Blood Infusion for Type 1 Diabetes Mellitus (T1DM)	Cord blood	1	T1DM	NCT00989547
Autologous Dendritic Cell Therapy for Type 1 Diabetes Suppression: A Safety Study	Dendritic cells	1	T1DM	NCT00445913
Cord Blood Plus Vitamin D and Omega 3s in T1D	Umbilical cord blood Vitamin D Omega 3 fatty acits	2	T1DM	NCT00873925
Umbilical Cord Blood Infusion to Treat Type 1 Diabetes	Umbilical cord blood	1		NCT00305344
Small molecules				
Intranasal Insulin for Prevention of Type 1 Diabetes	Intranasal insulin	2	Prevention for at risk relatives	NCT00223613
Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus	Oral insulin	3	Prevention for at risk	NCT00419562
Trial of Intranasal Insulin in Children and Young Adults at Risk of Type 1 Diabetes	Intranasal insulin	2	Prevention for at risk	NCT00336674
Tolerability, Safety, and	INGAP	1	T1DM	NCT00995540

Efficacy Study of INGAP Peptide to Treat Type 1 Diabetes Mellitus in Adults	peptide			
Other				
Effect of Metabolic Control at Onset of Diabetes on Progression of Type 1 Diabetes	Intensive glucose control	3	New onset T1DM	NCT00505206
Phase 1 Study of BHT-3021 in Subjects With Type 1 Diabetes Mellitus	Proinsulin DNA vaccine	1	T1DM	NCT00453375