Supplementary information S1 | Main clinical and biological findings from high- to low-dose IL-2 clinical trials

Year	Trial	Disease(s)	N patients	Daily Il-2 dose, MIU (adjusted dose#, MIU)	IL2 administration schedule	**Total IL2 (MIU)** (time, days)	Main biological findings	Main clinical findings	Refs.
Historical high-dose IL-2 selected clinical trials in cancer									
1983	Clearance rates and systemic effects of IL-2-containing preparations	Melanoma	2	Injections of partially purified supernatant s of PHA stimulated lymphocytes			Serum half-life of 22'	Severe side effects	1
1985-1993	Treatment of Melanoma or RCC using high-dose bolus IL-2	Melanoma and Renal Cell Carcinoma	283	0.72/kg (50)	2 cycles of 15 IV injections administered every 8 hours; another 2 cycles for responders	Up to **3000**		High Toxicity; complete response in 7% of RCC and 7% of melanoma patients	2
1991-2003	Randomized study of high-dose and low-dose IL-2 in patients with RCC	Renal Cell Carcinoma	306	0.072/kg or 0.72/kg (5 and 50)	3 injections per day IV, until MTD or 15 injections	**133** and **602**		Toxicity markedly reduced at lower doses; Higher and more durable responses at higher doses	3
Low-dose IL-2 in autoimmune diseases									
2007-2010	Evaluation of clinical efficacy and immunologic responses after IL-2 therapy in HCV-related vasculitis patients	Hepatitis C Virus induced Vasculitis	10	1.5 then 3	Four 5-day courses	**52.5** (60)	Increase of $CD4^+$Tregs (x3) and $CD8^+$ Tregs (x8) Increase of NK and cd56 bright NKs; Decrease of B cells.	Grade 1 & 2 AEs; no vasculitis or HCV-replication flares; improvement of the vasculitis in 8/10 patients.	4
2011-2012	Dose-effect relationship of low-dose IL-2 in type 1 diabetes	T1D	24	0.3, 1, 3	One 5 day-course	**1.5, 5, 15** (5)	Dose-dependent increase of $CD4^+$ Tregs and $CD8^+$ Tregs; Dose dependent decrease of B cells; No effects on NK or Teffs. Imprinting of a dose-dependent regulatory-tuned milieu.	Good tolerance; Grade 1 and 2 AEs; more days with AEs in the placebo group than in any other group.	5,6
2013-	Dose Finding Study of IL-2 at Ultra-low Dose in Children With Recently Diagnosed Type 1 Diabetes	T1D	24	0.25, 0.5, 1	One 5 day-course, followed by 1 injection every 2 weeks	**7.5, 15, 30** (365)	Double blind, in progress.	Good long-term tolerance on the first 18 patients treated for at least 6 months.	1
2012-2013	Effects of Low-Dose Recombinant IL-2 to Promote Treg in Alopecia Areata	Alopecia Aerata	5	1.5 then 3	Four 5-day courses	**52.5** (60)	Increase of Tregs and decrease of $CD8^+$ Teffs in scalp biopsies during and after IL-2 treatment.	Regrowth of body or scalp hair in all 5 patients, of scalp hair in 4.	7
2013-	Induction of Regulatory T Cells by Low Dose IL-2 in Autoimmune and Inflammatory Diseases	Moderate forms of: Rheumatoid arthritis, Ankylosing spondylitis, SLE, Psoriasis, Behcet's Disease, Wegener's granulomatosis, Takayasu's disease, Crohn's Disease, Ulcerative colitis, Autoimmune hepatitis and Sclerosing cholangitis	132	1	One 5 day-course, followed by 1 injection every 2 weeks	**17.5** (182)	Increase in $CD4^+$ Tregs in all 35 patients treated so far (x2); No significant increase in Teffs, NKs or eosinophil; decrease of anti-DNA antibodies levels in SLE.	Clinical improvements in SLE and other diseases	2
2014	Low-dose IL-2-therapy in one SLE patient refractory to standard therapies	Severe SLE	1	1.5 then 3	Four 5-day courses	**52.5** (60)	Treg increase; decreased of anti-dsDNA antibody levels.	Well tolerated; Major clinical improvement	8

2014	Low-dose Interleukine-2 in active systemic lupus erythematosus.	SLE	40	1	3 courses of daily injections every other day for 2 Weeks	21 (90)	Treg increase (x2); decreased of anti-dsDNA antibody levels.	Well tolerated; Major clinical improvement in 36/40 patients who showed both clinical and serological remission.	‡
Low-dose IL-2 in allo-immune diseases									
2007-2011	Ultra-Low Dose IL-2 for Refractory Chronic Graft Versus Host Disease	cGVHD	23	0.3, 1, 3/m^2 (0.54 to 5.4)	Daily administration for 8 weeks, (4 weeks hiatus, follow up administration for responders)	**32 to 320** (56 to 365)	CD4 Treg increase (x8); NK cell increase (x2) Asymptomatic peripheral-blood eosinophilia	Grade-3 and -4 AEs; 12 partial response; Tapering of corticosteroids by 60% in responders	9,10
2007-2014	Ultra Low-Dose IL-2 for GVHD Prophylaxis	Prevention of GVHD	16	0.1 and 0.2/m^2 (0.18 to 0.36)	3 times per week for 6 to 12 weeks	**3.3 to 13** (42 to 84)	Expansion of Tregs (x2); No expansion of $CD8^+$ memory Teffs or NK cells	No grade-3 and -4 GVHD; Less infections than in control group	11
Low-dose IL-2 in healthy volunteers									
2012-2014	Ultra-low Dose IL-2 in Healthy Volunteers	Healthy Volunteers	21	0.05, 0.1, 0.2/m^2 (0.09 to 0.36)	One 5 day-course	**0.45 to 1.8** (5)	Expansion of $Helios^+$ and $Helios^-$ Tregs; Dose dependent increase of CD56 bright NKs; Increase in serum IP10; No increase in IL2, IFNg, IL10, IL115, IL17	Well tolerated All grade-1 AEs, except for 1 grade-2 injection site reaction	12
Low-dose IL-2 in non-human primates									
2012-2013	Low-dose IL-2 in non-human primates	Healthy macaques	7	0.1, 0.6, 1/m^2 (0.18 to 1.8)	Daily for 28 days	**5.04 to 50,4** (28)	No effects at .1 and .6 MIU; At 1 MIU, Expansion of $CD4^+$ Tregs (x15), $CD8^+$ (x10), CD4 Teff (x5); No expansion of $CD8^+$ memory T cells or NKs cells	No adverse events	13

[#] Adjusted doses correspond to an adult of 70 kg/1.8 m^2

[*] NCT01862120; DK data

[†] NCT01988506; DK data

[‡] Di Yu and Zhanguo Li, Personal communication

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