Use of sarcodes for immune factors/cytokines in the treatment of autoimmunity

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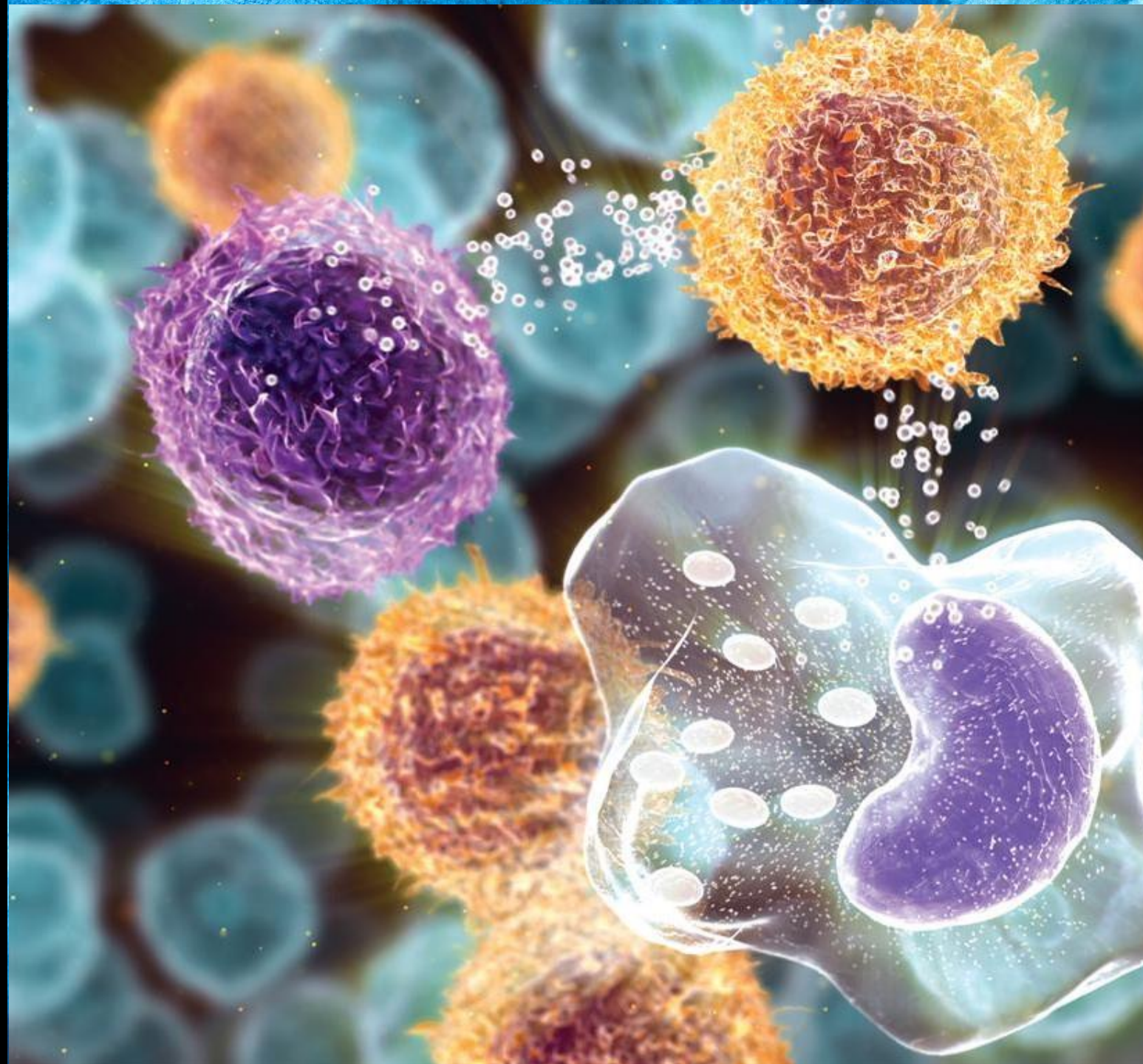
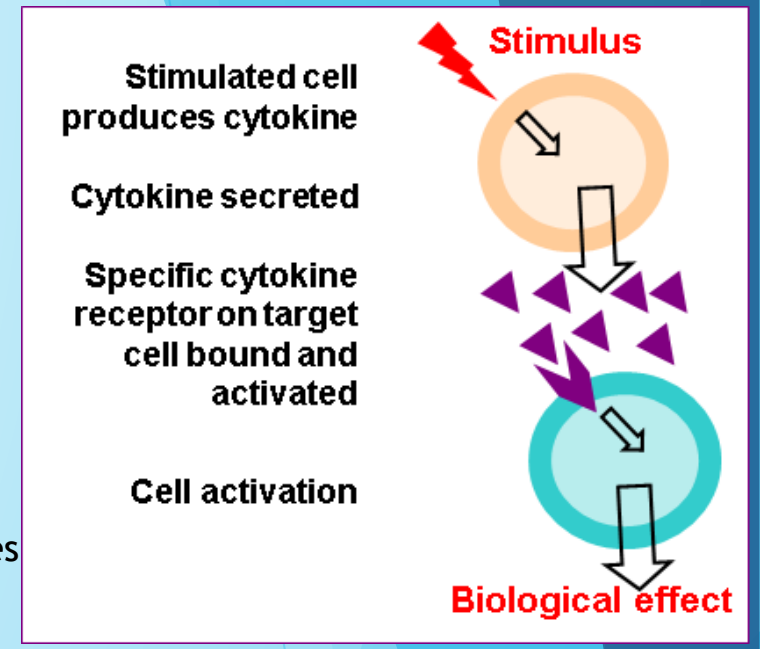


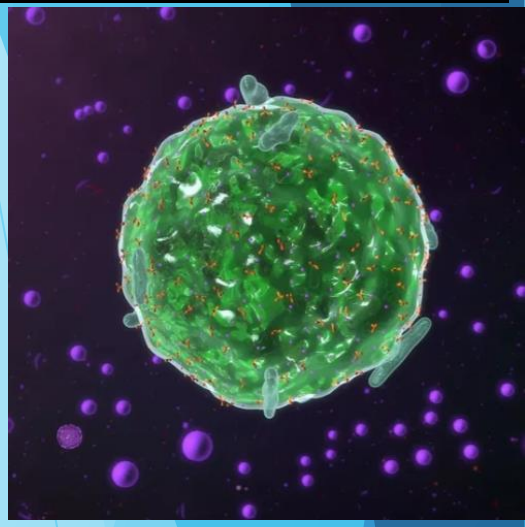
What are cytokines?



Source: British Society for Immunology

- Cytokines are signalling molecules that have key role in determining Th-T helper cell differentiation. They bind to specific receptors on cells, activating downstream signaling pathways that regulate gene transcription.
- T-helper cells (TH1 and TH2) activate immune response to infection or disease.
- Th1 cells activate cellular immune response: IL-2 and Interferon Gamma (IFN-γ), powerful cytokines that help to activate macrophages and other immune cells to fight cancer and infection.
- Th2 cells activate the antibody-mediated immune response, recruiting B cells to produce antibodies to neutralize or destroy pathogens by producing other cytokines (e.g. IL-4, IL-5, IL-6, IL-10 and IL-13)
- TH17 cells represent another subset with roles in immune responses and disease pathogenesis.
- Imbalances in Th cell subsets can lead to various diseases
- Pharmaceutical therapies targeted at these imbalances are a growing area of R&D.
- Cytokines have a large distribution of sources for their production; most cell nuclei are capable of producing interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α), particularly endothelial cells, epithelial cells, and resident macrophages.
- An immune response is defined by the amounts of cytokines produced by the responding T cells and Antigen producing cells.

Homeopathic Research on use of cytokines for autoimmunity: IL-10



LDCs: low dose cytokines

SKA: Sequential Kinesthetic Application

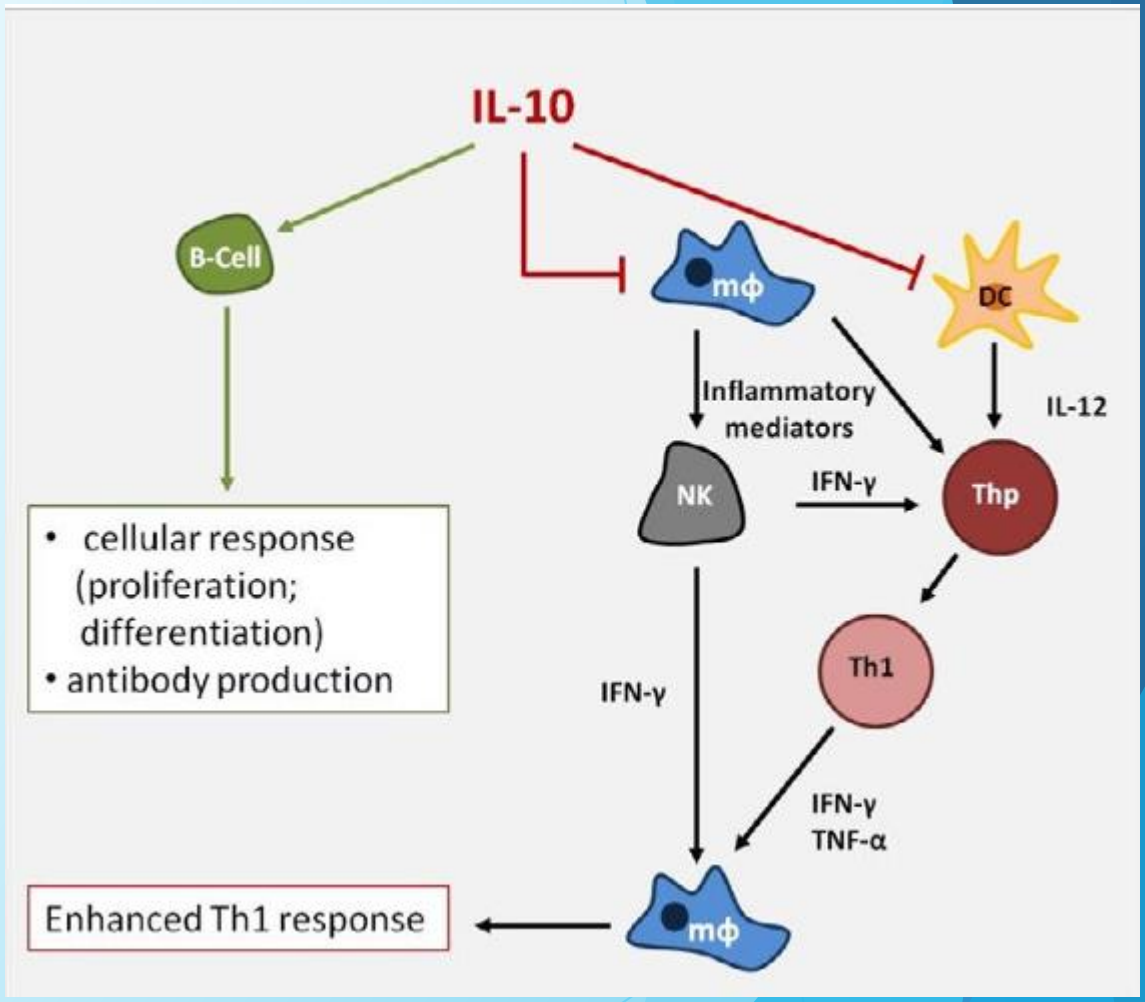
LDM: Low Dose Medicine, "an innovative medical paradigm born from the fusion of the most recent knowledge in the fields of molecular biology, Psycho-Neuro-Endocrine-Immunology (PNEI) and nanoconcentrations research"

https://www.oatext.com/Twenty-five-years-of-studies-and-trials-for-the-therapeutic-application-of-IL-10-immunomodulating-properties-From-high-doses-administration-to-low-dose-medicine-new-paradigm.php?fbclid=IwY2xjawIhxQoBHd10x0DLedJnSZtRfVKF4OzRmalShaC3_l2F2qfsehCK1bUwPGEZnPAqRQ

Interleukin-10 (IL-10)

Benefits of IL-10

- Prompts an anti-inflammatory response starting 72 hours after inflammatory event.
- Key to balancing immune response after inflammatory events. e.g in myocardial infarction, animal studies show it reduces severity of proinflammatory responses and contributes to improved left ventricular function afterwards.
- Prevents hyper-activation of immune response
- Checks inflammation to regain homeostasis
- Stimulates the production of acute phase proteins in the liver
- Inhibitory markers of inflammation such as IL-1; IL-6; TNF-α; GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor) and IFN-γ
- Activates B-cell response
- No compensatory pathways exists; IL-10-receptor interaction loss of function results in signaling failure



IL-10 is able to modulate the immune reactivity activating the cellular response via B-Cells and inhibiting the IFN-γ- mediated Th1 response.

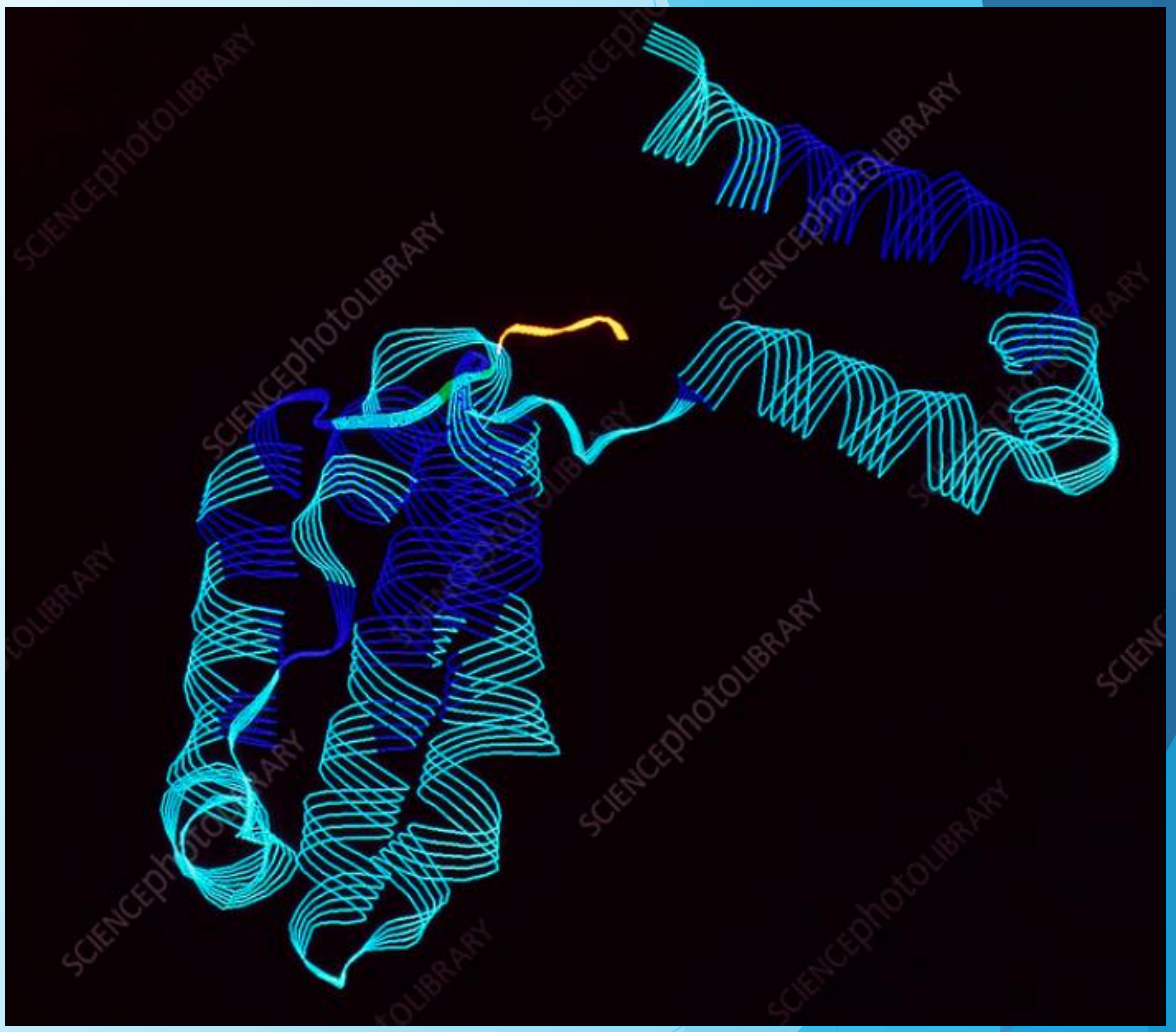
Interleukin-10 (IL-10)

Lack of IL-10

- hypersensitivity reactions
- diseases such as rheumatoid arthritis, psoriasis and other autoimmune Th1-dependent diseases or inflammatory forms such as colitis and Crohn's disease

IL-10 overexpression

- Induces T h2-driven allergic response: food allergy, asthma, eosinophilic esophagitis and atopic dermatitis
- increased production of IL-4 and IL-5 cytokines and IgE antibodies.
- Pivotal in development, progression and recurrence of melanoma, carcinoma and lymphoma
- Leads to inability to clear pathogens, eg HIV, HBV, HCV, EBV and HPV, enabling chronicity



IL-10 Source: Science Photo Library

Interleukin-10 (IL-10)

Low Dose IL-10 Cytokine Studies

1.Gariboldi S, Palazzo M, Zanobbio L, Dusio GF, Mauro V, et al (2009) Low dose oral administration of cytokines for treatment of allergic asthma. *Pulm Pharmacol Ther* 22: 497-510.

2.D'Amico L, Ruffini E, Ferracini R, Roato I (2012) Low Dose of IL-12 stimulates T Cell response in cultures of PBMCs derived from Non Small Cell Lung Cancer Patients. *J Cancer Ther* 3: 337-342.

3.Cardani D, Dusio GF, Luchini P, Sciarabba M, Solimene U, et al (2013) Oral Administration of Interleukin-10 and Anti-IL-1 Antibody Ameliorates Experimental Intestinal Inflammation. *Gastroenterol Res* 6: 124-133.

4.Radice E, Miranda V, Bellone G (2014) Low-doses of sequential-kinetic-activated interferon-gamma enhance the ex vivo cytotoxicity of peripheral blood natural killer cells from patients with early-stage colorectal cancer. A preliminary study Intern. *Immunopharm* 19: 66-73.

5.Roberti ML, Ricottini L, Capponi A, Sclauzero E, Vicenti P, et al. (2014) Immunomodulating treatment with low dose Interleukin-4, Interleukin-10 and Interleukin-11 in psoriasis vulgaris. *J Biol Regul Homeost Agents* 28: 133-9.

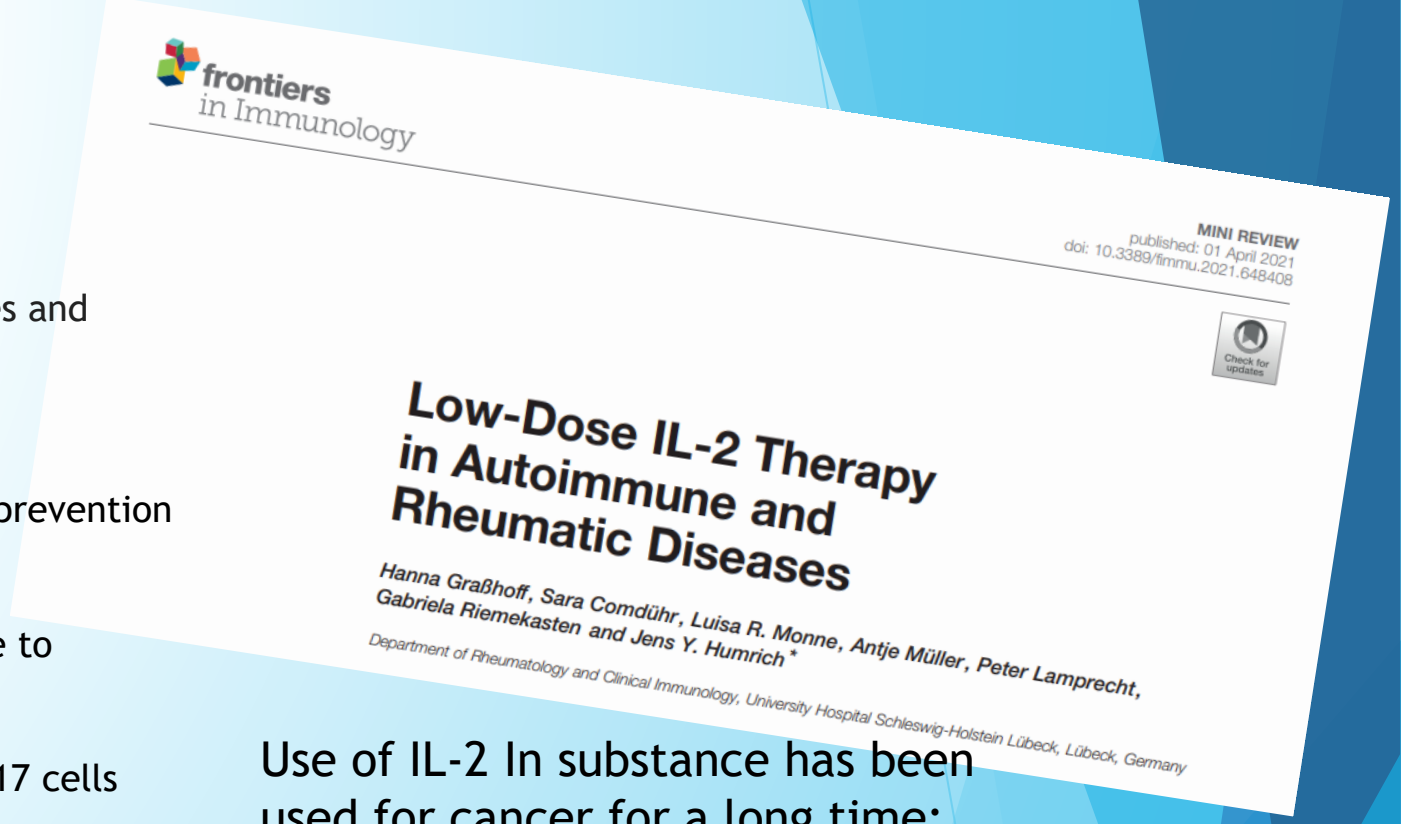
Abstract:

Interleukin-10 is the prototype of the anti-inflammatory cytokines. Its inhibitory action is exerted primarily towards the most typical markers of inflammation, such as IL-1; IL-6; TNF-α; GM-CSF and IFN-γ. The immunomodulatory action of IL-10 has meant that it was immediately regarded as a potential therapeutic tool for diseases in both acute and chronic inflammatory basis as well as in autoimmune diseases with inflammatory component. Recombinant human IL-10 has been tested in healthy volunteers, patients with Crohn's disease, rheumatoid arthritis, psoriasis, hepatitis C, HIV. The results obtained showed a positive immunomodulatory capacity of IL-10, but also underlined significant critical points, in particular the dose-dependent side effects. These pitfalls can be avoided by the use of low-dose IL-10 prepared according to the Sequential Kinetic Activation (SKA) method.

Interleukin-2 (IL-2)

Interleukin-2 (IL-2) signals influence

- lymphocyte subsets during differentiation, immune responses and homeostasis.
- Key in production of Tregs --t-cell regulators.
- Tregs are essential to immunological self-tolerance and the prevention and control of autoimmune diseases
- inhibits germinal center formation (lymphoid tissue response to antigens with antibodies) and autoantibody generation
- constrains the differentiation of naïve helper T cells into Th17 cells (lead to immune dysfunction, e.g. PANS/PANDAs and more)



Use of IL-2 In substance has been used for cancer for a long time:

- severe toxicity
- severe side effects

https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2021.648408/full?fbclid=IwY2xjawIhqDkBHRxMapcVw2t4hdjIaJZJFCDLWMDeik5A_7jkI8tnJy52xfsVLdCGRTxDEQ#B65

TABLE 1 | Summary of results from clinical studies with low-dose IL-2 therapy in autoimmune and rheumatic diseases.

Condition	Trial phase/study aims	Groups	IL-2 administration	Biological responses	Clinical responses	Safety data	Ref.
HCV-induced vasculitis	Single-centre, uncontrolled, phase I/IIa clinical trial: safety, biological efficacy, clinical outcomes	IL-2: n=10	s.c. injections of 1.5 MIU/d for 5 d, followed by three 5-d courses of 3 MIU/d at weeks 3, 6, and 9 (9 weeks)	%T_{reg} ($CD4^+CD25^{hi}CD127^{lo}FOXP3^+$) ↑, % $CD8^+$ ($CD8^+CD25^+FOXP3^+$) T_{reg} ↑, ratio T_{reg}/T_{con} ↑, T_{reg} supp. =, NK cells/µl ↑, $CD56^{bright}$ NK cells/µl ↑, $CD19^+$ B cells/µl ↓, CD19+IgD +CD27+ B cells/µl ↓, transcriptome: T_{reg} and NK cell function related ↑, inflammatory and oxidative stress mediators ↓	improvement in vasculitis in 8 of 10 patients, decrease in cryoglobulins in 7 of 10 patients, complement C4 ↑, modest decrease in HCV viral load	SAE: Ø; TR-AE: injection-site reaction, asthenia, influenza-like symptoms, myalgia, dental abscess	(47)
Insulin-dependent type 1 diabetes mellitus	Single-centre, uncontrolled phase I clinical trial: safety, biological efficacy	IL-2: n=9	s.c. injections of 4.5 MIU/d 3x/week for 4 weeks; loading dose of rapamycin 2 mg/d, followed by dose adjustments to maintain blood levels of 5-10 ng/ml for 3 months	T_{reg}/µl ($CD3^+CD4^+FOXP3^+$) ↑, % T_{reg} ($CD4^+CD25^+CD127^{lo}$) ↑, FOXP3 gene demethylation ↑, %IFNg+ among T_{reg} ($CD4^+FOXP3^+$) =, IL-2 responsiveness in T_{reg} ($CD4^+CD25^+$) measured by STAT5 phosphorylation ↑, % $CD45RO^-$ and $CD45RO^+$ among $CD4^+$ and $CD8^+$ T cells =, % $CXCR3^+$, $CRTH2^+$, $IFNg^+$ and $IL\text{-}17^+$ among $CD4^+CD45RO^+$ =, $CD56^+$ NK cells/µl ↑, % $CD56^{bright}$ NK cells ↑, eosinophils/µl ↑, lymphocytes/µl =, monocytes/µl =, $CD4^+/CD8^+$ ratio =, sIL-2R↑ (correlation with increase in % T_{reg}, NK cells, eosinophils)	transient β-cell dysfunction, peak C-peptide levels from MMTT ↓, stable HbA_{1c} was achieved with increasing doses of insulin	SAE: Ø; TR-AE: injection-site reaction, fatigue, malaise, abdominal pain	(51)
	Single-centre, randomized, placebo-controlled, double-blind, dose-finding, phase I/II clinical trial: safety, biological efficacy, clinical outcomes	n=24, randomized to placebo, or 0.33, 1 or 3 MIU/d IL-2 (1:1:1:1)	s.c. injections of 0·33 MIU, 1 MIU, or 3 MIU/d for 5 consecutive days (1 cycle)	T_{reg}/µl and % T_{reg} ($CD4^+CD25^{hi}CD127^{lo}$ $FOXP3^+$) ↑ (dd), iEmax and iAUC in %T_{reg} ↑ (dd), iEmax % NK cells and % T_{eff} =, % $CD19^+$ B cells ↓, $CD19^+$ B cells/µl ↓ (dd), iEmin for change in % $CD19^+$ B cells ↓, eosinophils ↑	no significant differences between groups in daily insulin dose, fasting glycaemia, fasting plasma C-peptide and iAUC during an MMTT, HbA_{1c}	SAE: Ø; TR-AE: injection-site reaction (dd), influenza-like symptoms (dd), nausea (dd), allergic rhinitis, diarrhea, fatigue, ophthalmic migraine	(52)
	Single-centre, randomized, placebo-controlled, double-blind, dose-finding, phase I/II clinical trial (ref. 52): biological efficacy, immunophenotyping	see ref. 52	see ref. 52	T_{reg}/µl and % T_{reg} ($CD4^+CD25^{hi}CD127^{lo}FOXP3^+$) ↑ (dd), T_{reg}/T_{eff} ratio ↑, duration of T_{reg} increase (dd), % $CD8^+CD25^+Foxp3^+$ T_{reg} ↑ (dd), % $CD25^{hi}CD127^{lo}CD45RA^-$ T_{reg} of $CD4^+$ ↑ (dd), CD25 (MFI), GITR, CTLA-4 and basal pSTAT5 in T_{reg} ↑ (dd), IL-2 responsiveness in T_{reg} ($CD4^+FOXP3^+$) measured by STAT5 phosphorylation =, counts lymphocytes, $CD4^+$, $CD8^+$ T cells, NK cells during cycle ↓ after cycle ↑ (dd), % $CD4^+$, $CD8^+$ T cells =, % $CD19^+$ B-cells and $CD19^+$ B cells/µl ↓ (dd), % NK cells ↑ (dd), % $CD56^{bright}$ among NK cells ↑ (dd), plasma levels of IL-2, sIL-2R, IL-5, IL-10, IL-17, TNF-a, TGF-b1, CCL22, CXCL10 ↑ (dd), transcriptome: B cell related ↓, cell cycle and transcription ↑, chemokine and NK cell related ↑ (dd), FOXP3 target genes ↑ (dd), suppression of T_{eff} cell responses (IFNg) against beta-cell antigens (dd); placebo group: no relevant changes	see ref. 52	no detection of anti-IL-2-antibodies; see also ref. 52	(53)
	Single centre, uncontrolled, adaptive dose-finding phase, I/II clinical trial: safety, biological efficacy, acute cellular	Learning phase: n=10; adaptive phase: n=30	learning phase: s.c. injections of one single dose per patient either of 0.004 (n=2), 0.16 (n=2), 0.60 (n=2), 1.00 (n=2), or 1.50 (n=2)	T_{reg}/µl and % T_{reg} ($CD3^+CD4^+CD25^{hi}CD127^{lo}$) ↑ (dd) peak by d2/3 (d1 ↓); IL-2 doses to induce 10%/20% increases in T_{reg}: 0.101 MIU/m^2 and 0.497 MIU/m^2, IL-2 plasma levels ↑ (peak at 90 min, dd), MFI CD25, pSTAT5, CTLA-4, FOXP3, CXCR3, CCR6, % $Ki67^+$ of $CD45RA^-$ memory T_{reg} ↑ (dd, peaks between 90 min. and d2), CD122 MFI in memory T_{reg} ↓ (dd,	Mean glucose ↓, HbA_{1c} ↓, basal insulin dose ↓, non-fasting C-peptide =	SAE: Ø TR-AE: injection-site reaction, common cold, nasal congestion, CRP ↑ (dd, peak by d1)	(54)

TABLE 1 | Continued

Condition	Trial phase/study aims	Groups	IL-2 administration	Biological responses	Clinical responses	Safety data	Ref.
			single dose per patient. based on dose-finding results of interim analyses to achieve T_{reg} increases of 10% and 20% from baseline	µl ↓, $CD8^+$ T cells/µl, $CD19^+$ B cells/µl, NK cells/µl ↓ (dd, recovering to baseline by d4); eosinophils/µl ↓ at 90 min, followed by increase with peak by d1 (dd), % $CD56^{bright}$ NK cells ↑ (at 90 min ↓), MFI pSTAT5, %Ki67 of $CD56^{bright}$ NK cells ↑			
	Multicentre, randomized, double blind, placebo-controlled, dose-finding phase I/II clinical trial in children: safety, biological efficacy, clinical efficacy	n=24, randomized to placebo or 0.125, 0.250, 0.500 MIU/m^2 IL-2 (7:5:6:6)	s.c. injections of placebo or IL-2 at doses of 0.125, 0.25 or 0.5 MIU/m^2 daily for five days and then fortnightly for 1 year	% T_{reg} ($CD4^+CD25^{hi}CD127^{lo}FOXP3^+$) ↑ (dd), T_{reg}/T_{eff} ratio ↑, maintenance of T_{reg} response with 2 highest doses, $CD25^+$ T_{eff} =, B cells =, NK cells =, sIL-2RA and VEGFR2 levels predicted T_{reg} response after the 5-day course; eosinophils ↑; placebo group: no relevant changes	no significant change between IL-2 and control group in C-peptide iAUC in MMTT, HbA_{1c}, fasting blood glucose, fasting C-peptide level, insulin requirements. In patients with T_{reg} increase > 60% from baseline (d5): improved maintenance of induced C-peptide production at 1 year	SAE: Ø; TR-AE: injection-site reactions	(55)
Systemic lupus erythematosus	Pilot study / compassionate use in refractory SLE: safety, biological efficacy, clinical outcomes	IL-2 + SOC: n=1	four cycles with daily s.c. injections between 1.5 and 3.0 MIU/d for 5 d; separated by resting periods of 9-16 d (9 weeks)	T_{reg}/µl and % T_{reg} during cycles ($CD3^+CD4^+Foxp3^+CD127^{lo}CD25^{hi}$) ↑	decrease in SLEDAI from 14 to 4 after 1st cycle, no development of new organ manifestations/disease flares during treatment, reduction of daily GC dose, decrease in anti-dsDNA-Abs, normalization of CK	SAE: Ø; TR-AE: injection-site reaction, increased day and night sweats, transient fever	(56)
	Single-centre, uncontrolled phase I/IIa clinical trial: biological efficacy of short-term treatment (immuno-phenotyping data of first 5-day cycle from first 5 patients of PRO-IMMUN trial)	IL-2 + SOC: n=5	s.c. injections of 1.5 MIU/d for 5d (1 cycle)	T_{reg}/µl and % T_{reg} ($CD3^+CD4^+Foxp3^+CD127^{lo}$) ↑; % $CD25^{hi}$ of T_{reg} ↑; MFI CD25 in T_{reg} ↑; % $Ki67^+$ of T_{reg} ↑, % $CD39^+$ of T_{reg} ↑, % $Helios^+$ of T_{reg} =, Treg/Tcon proliferation ratio ↑ in 4/5 patients, $CD3^+CD4^+$ T_{con}/µl =, CD25 MFI in $CD3^+CD4^+$ T_{con} =; % $CD25^{hi}$ of $CD3^+CD4^+$ T_{con} ↑; % $Ki67^+$ of $CD3^+CD4^+$ T_{con} (=↑), % $Ki67^+$ of $CD8^+$ T cells, NKT cells, NK cells, $CD56^{bright}$ NK cells ↑; counts and % $CD8^+$ cells, NK T cells, NK cells =; % $CD56^{bright}$ of NK cells ↑	not evaluated	not evaluated	(25)
	Single-centre, uncontrolled phase I/IIa clinical trial: biological efficacy (immuno-phenotyping data from 23 patients), clinical outcomes	IL-2 + SOC: n=38	three cycles of s.c. injections of 1 MIU every other day for 2 weeks followed by a 2-week break in treatment (10 weeks)	% T_{reg} ($CD3^+CD4^+CD25^{hi}CD127^{lo}$) ↑, T_{reg} supp. ↑, % T_{FH} of total CD4+ ($CD4^+CXCR5^+PD\text{-}1^+CCR7^-$) ↓, % T_H17-like of total CD4+ ($CCR6^+CXCR3^-CCR4^+CCR7^-$) ↓, ($T_{FH}$ + T_H17) cells/T_{reg} cells ↓, % $CD3^+CD4^-CD8^-\alpha\beta$ T cells ↓, % T_H1-like ($CXCR3^+CCR6^-CCR4^-CCR7^-$) =, % T_H2-like ($CXCR3^-CCR6^-CCR4^+CCR7^-$) =, eosinophils ↑	SRI-4 response rates: 31.6%/ 71.1%/ 89.5% at week 2/4/12; GC dose ↓; improvement/resolution in rash, alopecia, arthritis, fever, serositis; resolution of leukopenia/ thrombopenia in 94.7/100% of patients, complement C3 and C4 ↑; anti-dsDNA-Abs ↓, proteinuria ↓	SAE: Ø; TR-AE: injection-site reaction, influenza-like symptoms, very low frequency of total AEs (7 AEs in 38 pat.), total IgG ↓	(57)
	Single-centre, uncontrolled, dose-adaption phase I/IIa clinical trial in refractory SLE (PRO-IMMUN): safety, tolerability, biological efficacy, dose-dependency of	IL-2 + SOC: n=12	four cycles with s.c. injections between 0.75 and 3.0 MIU/d for 5 d separated by resting periods of 9-16 d (9 weeks)	T_{reg} /µl and % T_{reg} ($CD3^+CD4^+FOXP3^+CD127^{lo}$) ↑ (dd),% $CD25^{hi}$ of T_{reg} ↑ (dd), % $CD25^{hi}$ T_{reg} of $CD3^+CD4^+$ ↑, (dd) $CD25^{hi}$ T_{reg}/µl ↑ (dd), MFI CD25 in T_{reg} ↑ (dd), % $Ki67^+$ of T_{reg} ↑ (dd), ratio counts T_{reg}/T_{con} ↑, ratio $Ki67^+$ $T_{reg}/Ki67^+$ T_{con} ↑; corr. increase % $CD25^{hi}$ T_{reg} with increase % $Ki67^+$ T_{reg}, % $CD39^+$ of T_{reg} ↑, % $Helios^+$ of T_{reg} =, % $CD137^+$ of T_{reg} ↑; T_{reg} supp. and FOXP3 demethylation =, higher % of $CD25^{hi}$ and $CD137^+$ T_{reg} in responders after 4 cycles, corr. increase % $CD25^{hi}$ T_{reg} with decrease in SLEDAI, % $CD45RO^-CCR7^+$ of T_{reg} ↓ (during	Decrease in SLEDAI score/clinical response in 83%/67% of patients at day 62 (significant decrease already after 2nd cycle), improvement / resolution in arthritis, myositis, rash, alopecia; no severe disease flare; PGA ↓; frequency of BILAG severity categories A and B ↓; complement	SAE: Ø (5 unrelated SAE in FU-phase); TR-AE (dd): injection-site reactions, fever and chills, influenza-like symptoms, headache, dizziness, arthralgia, myalgia; transient increases in	(58)

(Continued)

TABLE 1 | Continued

Condition	Trial phase/study aims	Groups	IL-2 administration	Biological responses	Clinical responses	Safety data	Ref.
	biological responses, clinical outcomes			cycles), % $CD45RO^+CCR7^{+/-}$ of T_{reg} =, % $CXCR5^+$ of T_{reg} (TfR) ↓, sIL-2R ↑ (dd), corr. increase sIL-2R and GC dose with increase % $CD25^{hi}$ T_{reg} and increase % $Ki67^+$ T_{reg}; T_{corr}/µl ($CD3^+CD4^+FOXP3^-$) =, % $CD25^{hi}$ in T_{con} = (at highest dose ↑), MFI CD25 in T_{con} =, % $Ki67^+$ of T_{con} ↑ (dd), % $CD45RO^{+/-}CCR7^{+/-}$ T_{con} subsets =, % $CD3^+CD4^-CD8^-$ T cells =, % T_{FH} of T_{con} ($CXCR5^+$ and $CD45RO^+CCR7^-$ $CXCR5^+PD\text{-}1^+$) ↓, % T_H17-like of T_{con} ($CD45RO^+CCR7^-$ $CCR6^+CXCR3^-CCR4^+$) =; $CD19^+$ B cells/µl ↓, counts and % $CD19^+$ IgD^+CD27^+ B cells ↓, counts $CD19^+$ IgD^-CD27^+ and $CD19^+$ IgD^-CD27^- ↓, counts and % of $CD19^+$ $CD20^-CD27^{hi}HLA\text{-}DR^{+/-}$ =; counts $CD8^+$ cells, NK T cells, NK cells =, % $Ki67^+$ of $CD8^+$ T cells, NK T cells, NK cells ↑ (dd), eosinophils ↑	C3 ↑ (during cycles); anti-dsDNA-Abs =	CRP (dd), D-dimers and other acute-phase proteins without clinical relevance during cycles (complete normalization in resting phases); ECG, abdominal ultrasound, echocardiography, lung function =	
	Single-centre, open-label, controlled phase I/II clinical trial in lupus nephritis: safety, biological efficacy, clinical outcomes	IL-2 + SOC: n=18, SOC: n=12	3 cycles of s.c. injections of 1 MIU every other day for 2 weeks followed by a 2-week break in treatment (10 weeks)	% T_{reg} ($CD3^+CD4^+CD25^{hi}CD127^{lo}$) ↑, stronger increase of % T_{reg} in patients who achieved remission; sIL-2R (sCD25) =; control group: no relevant changes	Higher remission rate in IL-2 group compared to SOC at week 10: 55.6% vs 16.7%, p=0.068; improved renal outcomes in IL-2 group at week 10 compared to baseline: 24-h UPE ↓, hematuria↓, albumin (s) ↑, leukocyturia =, urea nitrogen (s) =, creatinine (s) =, eGFR =	SAE: Ø; TR-AE: injection-site reaction, fever, influenza-like symptoms, nausea, and diarrhea	(59)
	Single-centre, uncontrolled phase I/II clinical trial in refractory SLE: biological efficacy, clinical outcomes	IL-2 + rapamycin: n=50	s.c. injection of 100 WIU 3-5d/months combined with rapamycin (0.5 mg, once every other day, oral) for 24 weeks	T_{reg}/µl ($CD4^+CD25^+FOXP3^+$) ↑ at week 12 and 24, T_H17 cells/µl ($CD4^+$ $IL17^+$) =, ratio T_H17/T_{reg} ↓ at week 24	Decrease in SLEDAI score after 6 (p=0.002), 12 (p<0.0001), 24 weeks (p<0.0001) compared to baseline; prednisone dose ↓; DMARD dose =	SAE: Ø; TR-AE: not evaluated	(60)
	Single-centre, randomized, double-blind, placebo-controlled phase II clinical trial: safety, clinical efficacy	IL-2 + SOC: n=30 placebo +SOC: n=30	3 cycles of s.c. injections of 1 MIU every other day for 2 weeks followed by a 2-week break in treatment (10 weeks)	IL-2 group: %T_{reg} ($CD3^+CD4^+CD25^{hi}CD127^{lo}$) ↑; % NK cells ↑, % $CD56^{bright}$ of NK cells ↑, % $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells =; placebo group: no relevant changes	SRI-4 response rates: 55.17%/65.52% in IL-2-group vs 30.00%/36.67% in placebo group at week 12 (p=0.052) and week 24 (p=0.027); primary endpoint at week 12 not met;no sign. difference between IL-2 and placebo group in change of SLEDAI, BILAG, PGA, and prednisone dose; higher improvement rate for rash and arthritis in IL-2 group, complete remission in pat. with lupus nephritis in 53.85% in IL-2 group vs 8.33% at week 12 (p=0.013) and 16.67% at week 24 (p=0.036) in placebo group; 24-h UPE ↓, (s) albumin ↑, complement C3/C4 ↑	SAE: Ø; TR-AE: injection-site reaction, influenza-like symptoms, fever; lower incidence of infections in IL-2 group than in placebo group	(61)

(Continued)

TABLE 1 | Continued

Condition	Trial phase/study aims	Groups	IL-2 administration	Biological responses	Clinical responses	Safety data	Ref.
					(ns), anti-dsDNA-abs ↓ in IL-2 group compared to baseline		
	Randomized, double-blind, placebo-controlled, multiple ascending dose phase Ib clinical trial: safety, biological efficacy	NKTR-358 3.0 µg/kg (n=9), 6.0 µg/kg (n=9), 12.0 µg/kg (n=9), 24.0 µg/kg (n=9); placebo: n=12	s.c. injections of NKTR-358 at 3.0 µg/kg, 6.0 µg/kg, 12.0 µg/kg, 24.0 µg/kg once every 2 weeks, 3 times in total (4 weeks)	T_{reg}/µl and % T_{reg} ($CD4^+FOXP3^+CD25^{hi}$) ↑ (dd), % $Ki67^+$ of T_{reg} ↑ (dd), FOXP3 demethylation ↑, expression of CD25, Helios, CTLA-4 in T_{reg} ↑ (dd), $CD56^+$ NK cells ↑ (dd), $CD56^{bright}$ NK subset ↑ (dd), $CD4^+$ and $CD8^+$ T cells =; placebo group: no relevant changes	Reduction of CLASI-A score ≥ 4 points compared to baseline at day 43 in 7/18 patients; SLEDAI =; joint scores =	SAE: Ø; TR-AE: injection-site reaction, influenza-like symptoms, eosinophilia; no detection of anti-IL-2-antibodies	(62)
Alopecia areata	Single-centre uncontrolled phase I clinical trial in refractory disease: biological efficacy, clinical outcomes	IL-2: n=5	s.c. injections of 1.5 MIU/d for 5 d, followed by three 5-d courses of 3 MIU/d at weeks 3, 6, and 9 (9 weeks)	T_{reg}/µl ($CD3^+CD4^+FOXP3^+CD127^{lo}CD25^+$) ↑ (ns); skin biopsies: T_{reg} ↑ in 4/5 patients, $CD8^+$ T cells ↓, persistent T_{reg} increase 2 months after end of treatment	Regrowth of scalp hair in 4/5 patients, continuation of improvement up to 6 months; median SALT scores 2/6 months after end of treatment: 76/69 (Baseline: 82); DLQI ↓	SAE: Ø; TR-AE: asthenia, arthralgia, urticaria, injection-site reaction	(63)
Autoimmune hepatitis	Pilot study / compassionate use in refractory disease: biological efficacy, clinical outcomes	IL-2: n=2	6 monthly cycles of s.c. injections of 1 MIU for 5d (6 month)	% T_{reg} ($CD4^+FOXP3^+CD25^+$) ↑, % $CD45RA^+FOXP3^{lo}$ and $CD45RA^-FOXP3^{hi}$ ↑, % $Ki67^+$ of T_{reg} ↑, MFI CD25 and FOXP3 ↑, sIL-2R ↑; % $CD4^+$ T_{con} and NK cells ↓	Normalization of liver enzymes and serum levels of IgG in 1 patient	Not evaluated	(64)
RA, AS, SLE, psoriasis, Behçet's disease, GPA, Takayasu's disease, CD, UC, AIH, sclerosing cholangitis	Multicentre, uncontrolled phase I/IIa clinical basket trial in 11 autoimmune diseases (TRANSREG): safety, biological efficacy, disease selection	RA (n=4), AS (n=10), SLE (n=6), psoriasis (n=5), Behçet's disease (n=2), GPA (n=1), Takayasu's disease (n=1), CD (n=7), UC (n=4), AIH (n=2), sclerosing cholangitis (n=4) (in total 46 patients)	induction phase: s.c. injections of 1 MIU/d for 5 d; maintenance phase: fortnightly injections of 1 MIU/d for 6 months	T_{reg}/µl and % T_{reg} ($CD4^+FOXP3^+CD127^{lo}CD25^{hi}$) ↑ (peak at d8), AUC %$T_{reg}$ ↑, T_{con} ($FOXP3^-$ $CD4^+$ and $CD8^+$ cells) =, activated T_{eff} ($CD4^+CD25^{lo/+}FOXP3^-$) =, T_{reg}/T_{eff} ratio ↑, T_{reg}/activated $CD4^+$ T_{con}↑, counts and % $CD3^+$, $CD4^+$ T cells, NK cells = (↑ at d8), counts and % $CD8^+$ T cells, $CD19^+$ B cells = (% ↓ at d8), =, % $CD56^{bright}$ of NK cells ↑, eosinophils ↑ (transient), plasma levels of $T_H1/T_H2/T_H17/T_{reg}$ cytokines =, similar biological efficacy (T_{reg} expansion) across all 11 diseases, no differences due to different background therapies; transcriptome: FOXP3, IL-2R, CTLA-4 genes and related pathways ↑, T_{reg} signature genes ↑	Significant improvement in CGI; improvement in disease-specific scores (AS, UC, SLE, psoriasis); % of patients with fatigue and arthralgia ↓; improvement in EuroQL-5D-5L-score (ns),	SAE: Ø (7 unrelated SAE); TR-AE: injection-site reaction, seasonal upper and lower respiratory tract infections, no detection of anti-IL-2-antibodies	(65)
Primary Sjögren's syndrome	Single-centre, open-label, controlled phase I/II clinical trial: biological efficacy of short-term treatment	IL-2 + SOC: n=99, SOC: n=91	s.c. injections of 0.5 MIU/d for 5d (1 cycle)	T_{reg}/µl ($CD4^+CD25^+FOXP3^+$) ↑, T_H17 cells/µl ↑, T_H17/T_{reg} ratio ↓; control group: no relevant changes	no difference in disease activity between IL-2 and control group; glucocorticoid and DMARDs usage ↓ (long-term)	SAE: Ø; TR-AE: injection-site reactions, influenza-like symptoms,	(66)

(Continued)

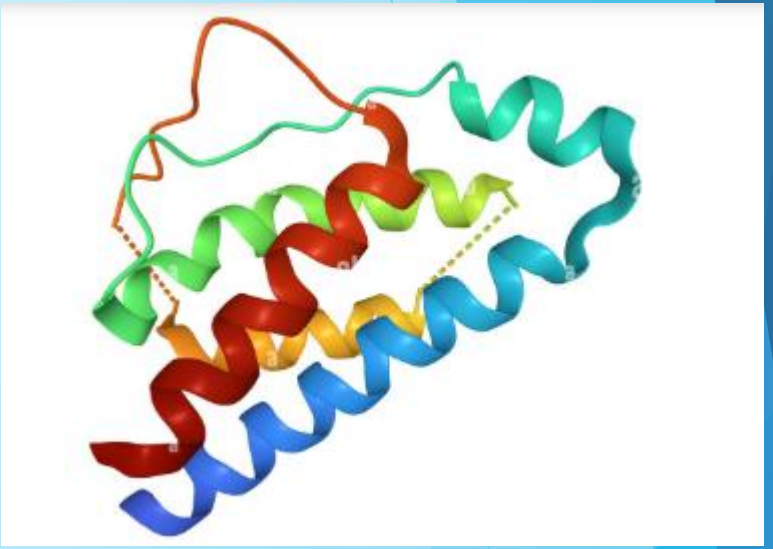
TABLE 1 | Continued

Condition	Trial phase/study aims	Groups	IL-2 administration	Biological responses	Clinical responses	Safety data	Ref.
Polymyositis/ Dermatomyositis	Single-centre, open-label, controlled phase I/II clinical trial: biological efficacy of short-term treatment	IL-2 + SOC: n=31, SOC: n=116	s.c. injections of 0.5 MIU/d for 5d (1 cycle)	T_{reg}/µl ↑, counts T cells, B cells, $CD4^+$ T cells, $CD8^+$ T cells ↑, T_H1 ↑, T_H2 ↑, T_H17 ↑, NK cells =; (gating strategy / definition of subsets not provided); control group: no relevant changes	VAS, ESR, CK, CK-MB, LDH, HBDH ↓ in IL-2 and control group compared to baseline, VAS ↓ in IL-2 group compared to control group (short-term)	not evaluated	(67)
Psoriatic arthritis	Single-centre, uncontrolled phase I/II clinical trial: safety, biological efficacy, clinical outcomes of short-term treatment	IL-2 + SOC: n=22	s.c. injections of 0.5 MIU/d for 5 d (1 cycle)	T_{reg}/µl and % ↑, T_H17/µl ↑, ratio T_H17/T_{reg} = , T_H1/µl =, T_H2/µl =, ratio T_H1/T_H2 =; % T_H17 cells ↑, % T_H1 =, % T_H2 = ; (gating strategy / definition of subsets not provided)	TJC, SJC, VAS, ESR, DAS28-ESR, PGA, DLQI, HAQ ↓ in IL-2 group compared to baseline (short-term)	SAE: Ø; TR-AE: injection-site reaction	(68)
Amyotrophic lateral sclerosis	Single centre, parallel three-arm, randomized, double-blind, placebo-controlled phase IIa clinical trial: safety, biological efficacy, clinical outcomes	IL-2 + riluzole: 1 MIU (n=12), 2 MIU (n=12),; placebo + riluzole: n=12	3 cycles with s.c. injections of 1 or 2 MIU/d or placebo for 5 d every 4 weeks (9 weeks)	T_{reg}/µl and % T_{reg} ($CD4^+FOXP3^+CD127^-CD25^{hi}$) ↑ (dd), T_{reg} supp. ↑, % NK cells ↑, % $CD8^+$ T cells ↑, % $CD4^+T_{con}$ ↑, % monocytes ↓, MFI CD25 in T_{reg} ↑, MFI CD25 in $CD4^+$ T_{con} ↑, eosinophils ↑, plasma levels of CCL2 ↓ (dd), CCL17 and CCL18↑ (dd),; placebo group: no relevant changes	No significant differences in disease progression among the three groups regarding ALSFRS-R score, decline in vital capacity and plasma NFL-MSD levels	SAE: Ø; TR-AE: injection-site reaction (dd), influenza-like symptoms(dd), nausea/vomiting, urinary retention	(69)

Abs, antibodies; AIH, autoimmune hepatitis; ALSFRS-R score, Amyotrophic lateral sclerosis Functional Rating Scale - Revised; AS, ankylosing spondylitis; AUC, area under the curve; BILAG, British Isles Lupus Assessment Group; CD, Crohn's disease; CGI, Clinical Global Impression Scale; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity; CK, Creatine kinase; d, days; Corr., correlation; DAS, disease activity score; dd, dose-dependent effect; DLQI index, Dermatology Life Quality Index; DMARD, disease-modifying anti-rheumatic drug; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; GC, glucocorticosteroids; GPA, granulomatosis with polyangiitis; HBDH, α-hydroxybutyrate dehydrogenase; HC, healthy controls; HCQ, hydroxychloroquine; HCV, hepatitis C virus; HAQ, Health Assessment Questionnaire; iAUC, incremental area under the curve; iEmax, incremental maximum effect; iEmin, maximum decrease below baseline; LDH, lactate dehydrogenase; MFI, mean fluorescence intensity; MIU, million International Units; MMTT, mixed meal tolerance test; NFL, neurofilament light chain; NK cells, natural killer cells; NKT cells, natural killer T cells; ns, not significant; PGA, Physician's Global Assessment; RA, rheumatoid arthritis; s, serum; SAE, serious adverse event; SALT, severity of alopecia tool; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index ; sIL-2R, soluble interleukin-2 receptor; SJC, swollen joint count; SLE, systemic lupus erythematosus; SRI-4, SLE Responder Index-4; SOC, standard-of-care treatment; T_{eff}, effector T cells; TJC, tender joint count; TR-AE, treatment-related adverse event; T_{reg}, regulatory T cells; T_{reg} supp., in vitro suppressive function of T_{reg}; UC, ulcerative colitis; VAS, visual analogue scale; VEGFR2, vascular endothelial growth factor receptor 2; 24-h UPE, 24 hour urine protein excretion.

Interleukin-2 (Il-2)

SUMMARY AND PERSPECTIVE: Data from several pilot studies and clinical trials, including first randomized trials, broadly and reproducibly prove that low-dose IL-2 therapy is very safe and capable to selectively expand a functionally competent Treg population independent of the underlying disease. In addition, these trials provided preliminary evidence for the clinical efficacy of low-dose IL-2- therapy in a large variety of inflammatory and autoimmune diseases. Low-dose IL-2 therapy therefore can be considered a novel targeted treatment option with a potentially broad applicability in various autoimmune, inflammatory and rheumatic diseases….The identification of molecular, cellular and epigenetic key events in response to low-dose IL-2 therapy at a common and disease-specific level, and of biomarkers which can predict the biological and clinical responsiveness to low-dose IL-2 therapy by advanced immunophenotyping technologies will allow to select appropriate diseases or patient subgroups and to stratify patients according to their individual immune signatures in the future…



IL-2, Source: Alamy

IL-2, Interleukin-2

Cytokine and Growth Factor Reviews 67 (2022) 80–88

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journal homepage: www.elsevier.com/locate/cytogfr

Emerging mechanisms and applications of low-dose IL-2 therapy in autoimmunity

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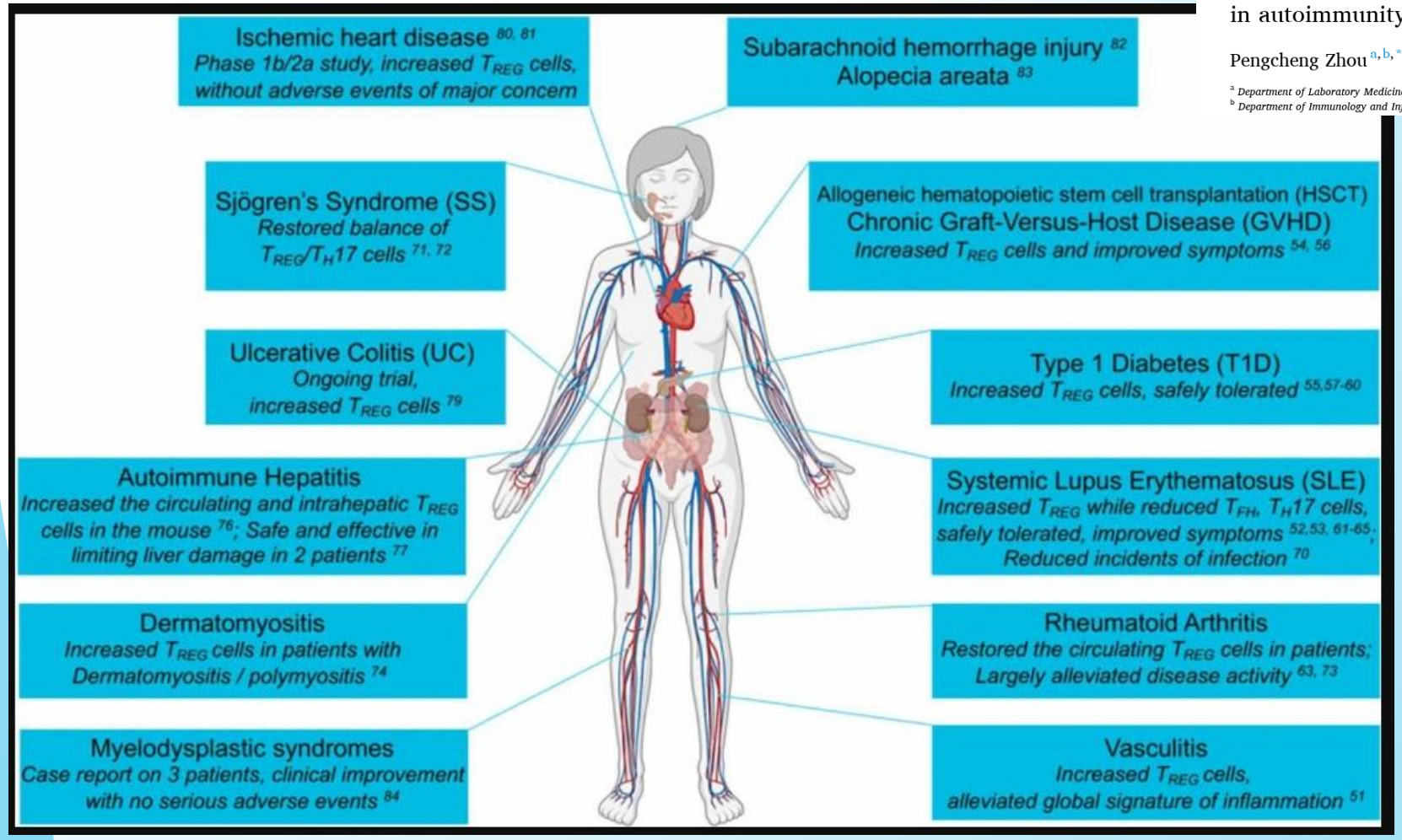


https://www.sciencedirect.com/science/article/pii/S1359610122000478?fbclid=IwY2xjawIhvagBHZZDJFSuRhvCetP55pPPjjyAaRIm7OQ8oOaq6hQnK5OhloM4RTcBdgQX3w

BIOLOGICS

IL-2 treatment can be dangerous. Here's how drug firms are trying to fix it

c&en CHEMICAL & ENGINEERING NEWS

By addressing problems with interleukin-2's toxicity and half-life, drug companies hope to build a safer, more targeted immunotherapy for cancer or autoimmune diseases

by *Megha Satyanarayana*

April 4, 2021 | A version of this story appeared in **Volume 99, Issue 12**

THE BIG DEAL AROUND IL-2

Biotechnology firms based on interleukin-2 (IL-2) are launching, striking deals, and getting acquired.

LAUNCHES

Company		Initial funding	Technology	Date announced
Anaveon		$37 million	Antibody-coupled IL-2	February 2019
Asher Biotherapeutics		55 million	Antibody-coupled IL-2	March 2021
Bright Peak Therapeutics		35 million	Engineered IL-2	July 2020
Synthekine		82 million	Engineered IL-2	September 2020
Werewolf Therapeutics		56 million	Engineered IL-2	November 2019
Xilio Therapeutics		30 million	Protein-coupled IL-2	September 2018 (as Akrevia Therapeutics)

DEVELOPMENT DEALS

Funder	Partner	Up-front funding	Technology	Date announced
Bristol Myers Squibb	Nektar Therapeutics	$1 billion	Pegylated IL-2	February 2018
Eli Lilly and Company	Nektar Therapeutics	150 million	Pegylated IL-2	July 2017

ACQUISITIONS

Acquirer	Target	Price	Technology	Date announced
Merck & Co.	Pandion Therapeutics	$1.85 billion	Antibody-coupled IL-2	February 2021
Sanofi	Synthorx	2.5 billion	Engineered IL-2	December 2019

Sources: Companies. **Note:** This list is not exhaustive.

https://cen.acs.org/pharmaceuticals/biologics/safer-IL2-cancer-immunotherapy-autoimmunity/99/i12

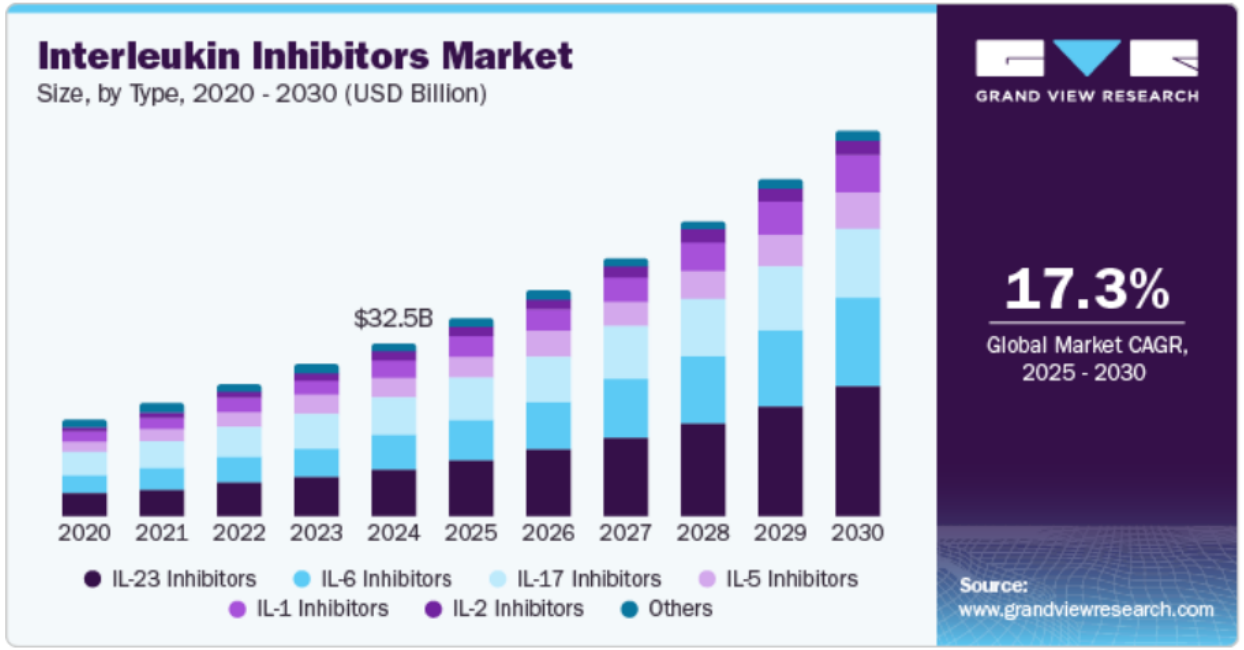
Interleukin Inhibitors Market Size, Share & Trends Analysis Report By Type, By Route Of Administration (SC, IV), By Application (RA, Psoriasis, IBD, Asthma), By End-use, By Region, And Segment Forecasts, 2025 - 2030

Report ID: GVR-3-68038-172-6 | Number of Report Pages: 100 | Format: PDF, Horizon Databook

Historical Range: 2018 - 2023 | Forecast Period: 2025 - 2030 | Industry: Healthcare

Interleukin Inhibitors Market Size & Trends

The global interleukin inhibitors market size was estimated at USD 32.5 billion in 2024 and is projected to grow at a CAGR of 17.3% from 2025 to 2030. Rheumatoid arthritis (RA), psoriasis, and inflammatory bowel disease (IBD) are increasingly prevalent, driving the demand for effective treatment options. The rising incidence of these disorders significantly underscores the urgent need for IL inhibitors, which serve as a crucial catalyst for market expansion and the development of targeted therapeutic solutions.



Some well-known interleukin inhibitors

Anakinra (Kineret)

Rilonacept (Arcalyst)

Tocilizumab (Actemra)

Sarilumab (Kevzara)

Ustekinumab (Stelara)

Risankizumab (Skyrizi)

Secukinumab (Cosentyx)

Brodalumab (Siliq

Ixekizumab (Taltz)

Canakinumab (Ilaris)

Guselkumab (Tremfya)

https://www.grandviewresearch.com/industry-analysis/interleukin-inhibitors-market

My approach to use of cytokines in autoimmune cases

- Research pattern of Th1/Th1 immune dysregulation based on the diagnosis (es). Keep in mind in homeopathic doses we are promoting BALANCE. (Not a question of high or low as in allopathic medicine)

- If possible, muscles test for cytokine imbalances.

- Make sure constitutional remedy is resonating well first
- Anticipate in advance:

  =remedies for acute illness, including Narayani War to all

  =flare remedy(ies) where indicated
- If the client is on suppressive medications:

  -some healing essential before weaning
- -tautopathics at 12c while they continue
- Withdrawal after reason for the drug is improved with homeopathy

  - tautopathics in ascending potencies as they quit

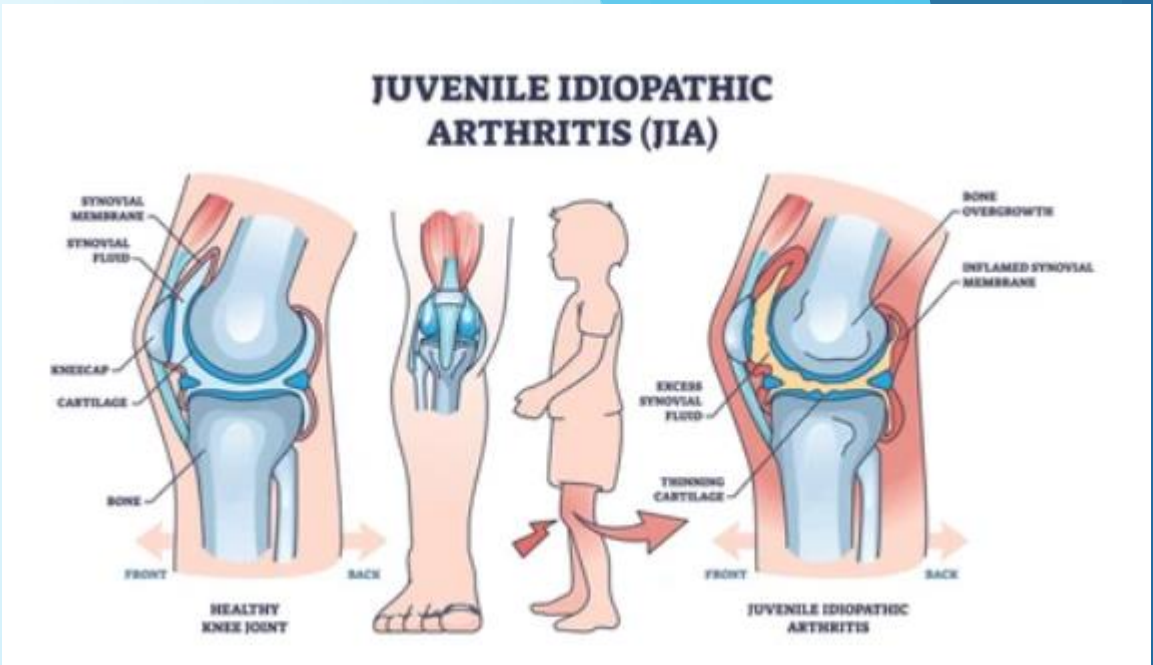
  -other help for withdrawal:

  -Nux vomica

  -acute remedies based on anticipated withdrawal issues
- Start homeopathic cytokines a few days after confiirming constitutional is resonating well, usually in LM3 potency.
- Use water dosing with succussion before each dose (generally 5 times)
- Use 5-cup method (or more cups) with ultrasensitive clients

Case 1: Jonathan, 24 years old in Jan. 2023

- Diagnosed with Juvenile Rheumatoid Arthritis at age 10
  - All affected joints >right side.
  - Knees are worst, swell daily-- up to 5 times their size at least every two weeks, cannot squat or fully bend knees since 10, constant pain, limps, stiffness
  - Fingers get red and swell, wrists are painful.
  - Recently ankles and elbows have begun to swell and hurt.
  - <Motion and heat
  - Pain varies from aching to stabbing
  - Synovial fluid sample from right knee: nucleated cell count 2450 (ref range <than 150) --indicative of severe inflammatory condition.



- Excessive hair loss in last year. Father also has diffuse hair loss.
- Hx of eczema since a toddler (not currently, as long as avoids dietary triggers)
- Auto accident caused TBI in 2017: craniectomy, cranioplasty, shunt was used. L side paralysis but now he can move ok. Lost left peripheral vision; cannot drive.
- Tendency to constipation, flatulence
- Gluten, dairy, corn <eczema and joint pain (avoids them)
- Desires icy cold drinks and anything coffee flavored, especially coffee ice cream and iced coffee

On no allopathic meds although in daily pain. Takes curcumin and anti-inflammatory herbs.

Case 1: Jonathan, 24 years old. JIRA

“I am a musician. Music was the one thing that I had that made me special and talented. Am really good at it. When I woke up from the accident and my left side was paralyzed I thought, ‘OMG I can’t play music anymore?’ Who am I if I am not a musician? What do I do now as a person? Where do I put all that stuff that I am as a person. I don’t have that outlet any more. That was something that affected me more on a spiritual level. I lost my ability to put myself in that place, to put the lava lamp on and play music alone in my room.

I would look as if my dream would be to earn money writing and performing music, but I know how the music industry works. That is the dream, so part of me knows that if I got there, I would hate it. Playing, writing and performing music waken the world to what art can still do to people. That, to me, is magic. When you think about Led Zeppelin and a song that still moves you 50 years later, that is magical to me. These are the kinds of things that drive me as a person and inspire me, that I hold value in. I focus more on emotion. How I make people feel is most important. I am hurt most knowing I hurt someone. You can tell I love to talk, I love to communicate.

My Dad is the one who was a musician. It is because of him I played music. That originally got me enthused about music.”

Case 1: Jonathan, 24 years old, JIRA

- Very loquacious.
- Parents divorced when he was 5, very close to mom
- Low self esteem, lack of confidence (repeats this phrase over and over). Never felt like he was worth anything.
- Depressed and often suicidal from his earliest memories. “No point in living.”
- Bullied throughout middle school “I was a skinny nerd who could not stand up for himself”
- Bullying stopped but had few friend in high school.
- Hospitalized once for suicidal ideation at 18, feels thankful he survived the experience of dealing with others at the hospital
- Plays guitar and drums, mostly in his room by himself. Creating things, music, art speak to his soul.
- Always trying to get Dad’s respect and acknowledgement, but Dad is critical, always negative. He can never please him.
- Now on disability for TBI. (horrible car accident, in a coma for days)
- Girlfriend broke up with him after his accident, and his few friends stopped visiting. Felt abandoned.
- Big fear is to be totally alone in the world once parents die.
- Etiology: what preceded start of JRA?
    - He practiced drums at Guitar Center. People would tell him he was good.
    - People told his Dad they saw him and thought he was good. Someone told him his Dad said, “He has no idea what he is doing.”

Case 1: Jonathan, 24 years old, JIRA

Constitutional prescription: Lycopodium

lM3 daily, 1M weekly

For acute pain as needed: Narayani Rheumatism & arthritis mix 200c

4 weeks later: Arnica 50m followed by Nat Sulph 50M one hour later

(to clear residual damage from TBI)

Clinical Immunology and Immunopathology
Volume 86, Issue 2, February 1998, Pages 192-198

Regular Article

A Mixed Th1/Th2 Cell Cytokine Response Predominates in Systemic Onset Juvenile Rheumatoid Arthritis: Immunoregulatory IL-10 Function ☆

Syed Raziuddin, Sultan Bahabri, Abdullah Al-Dalaan, A.K. Siraj, Sultan Al-Sedairy

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Abstract

The immune response identified by the induction of Th1/Th2 cells plays a critical role in the pathogenesis of various inflammatory and immune disorders. We have determined that in children with systemic onset juvenile rheumatoid arthritis (JRA), peripheral blood mononuclear cells (PBMC) constitutively and after stimulation with various antigens*in vitro*induce a higher secretion of interleukin-4 (IL-4) and IL-10 with a characteristic deficiency of IL-2 and interferon-γ (IFN-γ). This cytokine pattern is a representative of a mixed Th1/Th2 cell response in JRA. The CD3/CD28 costimulatory molecule was found to be a potent inducer of IL-4 and IL-10 secretion. PBMC-derived augmented IL-10 secretion was inhibited by exogenous Th1 cell type recombinant cytokines (IL-2, IL-12, and IFN-γ). Although IL-10 inhibits PBMC-induced proinflammatory IL-1α and tumor necrosis factor-α secretion, it had no major effect on IL-6 production. The finding of a distinctly enhanced mixed Th1/Th2 cell response cytokine (IL-4 and IL-10) pattern in JRA provides a framework for developing strategies for immunologic intervention in this rheumatic disorder in children.

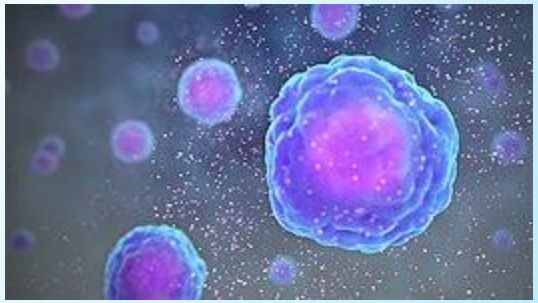
https://www.sciencedirect.com/science/article/abs/pii/S0090122997944573#:~:text=The%20finding%20of%20a%20distinctly%20enhanced%20mixed,intervention%20in%20this%20rheumatic%20disorder%20in%20children.

Case 1: Jonathan, 24 years old, JIRA

Three days after starting Lycopodium, started:

Cytokines: IL-10, IL 4, IL-2, IL-6, Interferon gamma, TFG beta, melanocyte stimulating hormone, thymus gland, red bone marrow

LM3 nightly

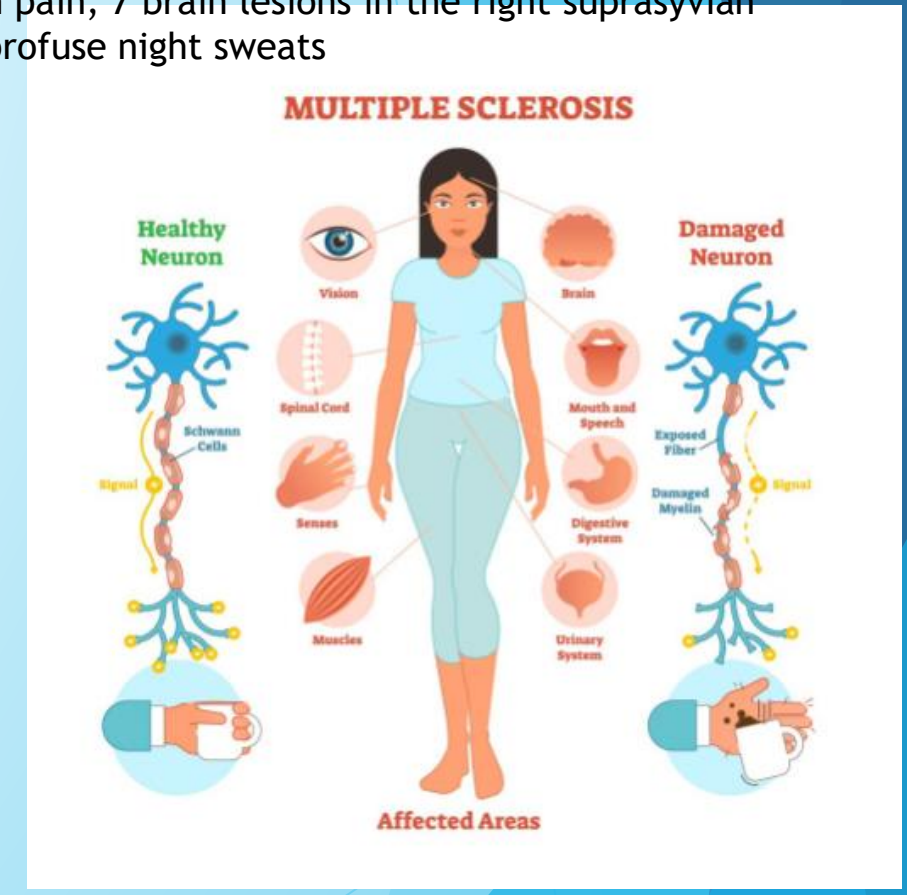


Case 1: Jonathan, 24 years old

- 2 days after starting Lyco, greater hair loss but feeling more confident and knee pain is less
- 2 weeks later: Squatting and fully bending knees for the first time in 14 years
- 4 weeks later: Started a full-time job; happy with it, proud of himself
- 6 weeks later: Losing less hair, no more pain, starting to date again, job going well.

Case 2: Annie, 61 years old in 2019, Multiple Sclerosis

- Obesity (gastric bypass in 2000, 2nd revision with tummy tuck in 2007, 3rd revision in 2009).
- Diagnosis: Multiple Sclerosis in 2007, Left side weakness and numbness alternating with pain, 7 brain lesions in the right suprasyvian region of the brain consistent with demyelinating disease as of April 2019. Chilly with profuse night sweats
- 2009 bleeding ulcer, removed surgically
- 2010 hospitalized with MS
- Left C4-5 facet hypertrophy (vertebral joint enlargement in neck), left paracentral /c5-6 disc protrusion
- Right sided sciatica, chronic low back pain
- Right rotator cuff tendinosis with partial tear
- Gastro-esophageal reflux, daily burning pain after meals in stomach and esophagus
- Recurrent migraines
- Recurrent Herpes 1 infections
- Paranasal sinus disease (polypoid mucosal thickening in bilateral frontal, ethmoid, sphenoid and maxillary sinuses.)
- Chronic fatigue
- Fibromyalgia—burning, shooting pains throughout her body.
- Insomnia due to anxiety



Taking oxycodone, trazodone, escitalopram oxalate, valium, phenobarbital, lexapro, rosuvastatin, carafate, natalizumab, alprazolam, monthly b 12 injections, dexlansopazole, gabapentin

Case 2: Annie, 61 years old in 2019, Multiple Sclerosis

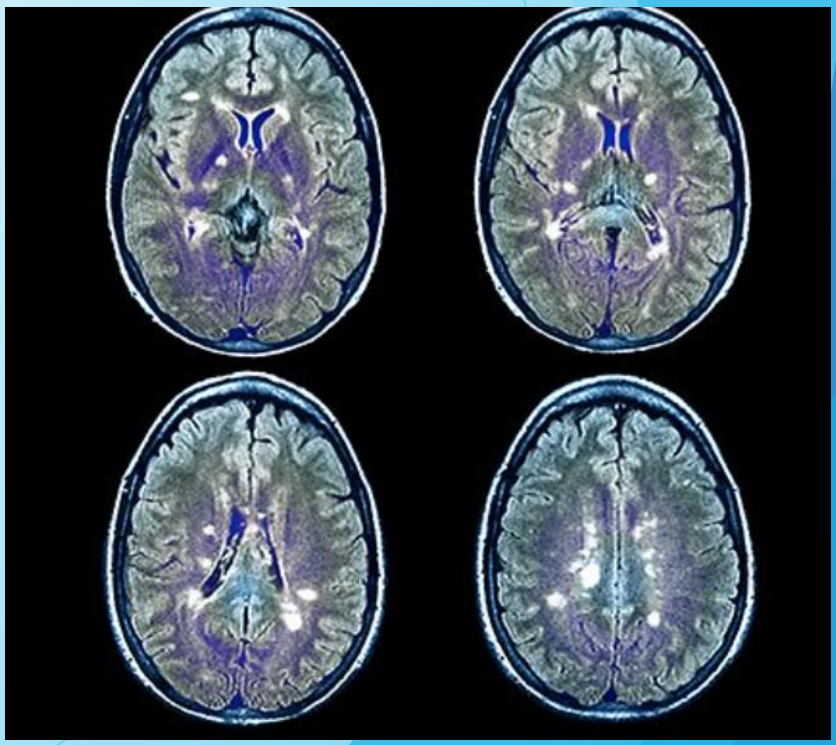
Initial intake

- Primary concern: extreme pain under sternum, no negative findings on EKG.
  Diagnosed with anxiety with palpitations, <resting/lying/sitting
- 2 weeks ago threw back out, sciatica still there but getting better
- Pain at the base of neck is extreme burning
- Left side weakness, burning pain in all joints, <damp and cold
- Fastidious about cleaning, order
- Anxiety, life is painful and a daily struggle
  Whole childhood she was teased and belittled about her weight.
  Teen pregnancy with black boyfriend—ostracism.
- Both adult children struggle with opiate addiction
- 2 Grandchildren by son's ex who live in her house with ex's new husband.
  (Ex has passed.) They are demanding and often not respectful.
- Suffered many loses in last year
  - first husband passed
  - daughter-in-law passed
  - best friend passed

Case 2: Annie, 61 years old in 2019, Multiple Sclerosis

- Constitutional: arsenicum album. Starting at 30c and moving up to 10m over course of 3 years
- Also did
  - Acute, as needed, remedies for reflux, vaginitis, fibromyalgia, joint pain, sciatica, bronchitis, cold/sinus infection, COVID, herpes
  - Acute remedies for post surgical healing with rotator cuff surgery.
  - Nutrient absorption sarcodes for severe iron deficiency anemia and other deficiencies
  - Ascending nosode treatment for herpes 1 virus
  - Pain and anxiety improved enough that she weaned off all meds listed with the help of tautopathics, acutes and nux v.

but brain lesions still present on MRI in July of 2022.



Case 2: Annie, 61 years old in 2019, Multiple Sclerosis

IFN-γ and IL-6, -12 and -4 levels were higher in RR-MS patients compared to controls (P=0.0009, 0.0114, 0.0297 and 0.0004, respectively). IL-1 levels were higher in controls compared with RR-MS patients. IL-4 levels were higher in RR-MS patients with mild disability compared to those with moderate and severe disability (P=0.0375). TNF-α and IL-10 levels were higher in RR-MS patients with inactive disease compared with those with active disease. IL-17 levels showed a trend towards being higher in RR-MS patients with inactive disease compared to those with active disease (P=0.0631). Low TNF-α and high IFN-γ levels were independently associated with RR-MS (P=0.0078 and 0.0056, respectively) and also with the activity of the disease (P=0.0348 and 0.0133, respectively). Results indicated that RR-MS patients, even in the remission clinical phase, exhibit a complex system of inflammatory and anti-inflammatory cytokines that may interact to modulate the progression and activity of the disease.

Cytokine profile in relapsing-remitting multiple sclerosis patients and the association between progression and activity of the disease

Authors: Ana Paula Kallaur, Sayonara Rangel Oliveira, Andréa Name Colado Simão, Elaine Regina Delicato de Almeida, Helena Kaminami Morimoto, Josiane Lopes, Wildea Lice de Carvalho Jennings Pereira, Renato Marques Andrade, Larissa Muliterno Pelegrino, Sueli Donizete Borelli, Damácio Ramon Kaimen-Maciel, ✉ Edna Maria Vissoci Reiche

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Case 2: Annie, 61 years old in 2019, Multiple Sclerosis

January 2023 she starts Cytokines LM3:

IL-6, IL-12, Il-4, IL-1, TNF-a, IL-10, IFN-y, red bone marrow, thymus gland (IL-17 added much later)

- Annual MRI in July 2023 shows all brain lesions are gone.
- no longer has numbness and weakness on the left side. Joint pain is very minimal or gone.
- Brief return flare of MS in April 2023 when son died of a fentanyl overdose. Treated with ignatia and Narayani grief remedy.
- Annual MRI in July 2024 still shows no brain lesions
- MS in remission and she is doing yoga again and enjoying life and maintaining a healthy weight. She became a Buddhist in a formal ceremony two weeks ago.

Case 3, Dylan, 10 years old in June 2020

- PANDAS/PANS and Autism Spectrum
  - High DNAse B strep antibodies 354 (ref range 0-170)
  - High antibodies to gliaden (gluten peptides) 146 (ref range 0-19),
  - Mold IGG: aspergillus fumigate 72.6 (0-1.9), penicillin chrysog 61.6 (0-1.9)
  - very high measles and mumps titers (had measles rash after MMR at age 4)
  - elevated IgG4, high titers for West Nile virus, chlamydia pneumonae, bartonella, lyme disease, HHV6
  - Elevated VEGF 372 (ref rage 62-79)
  - IGG subclass 4 163.6 (ref range 4-136)
  - Low lipase, low ferritin, elevated prolactin 23.7 (4-15.2) (stress) ,
  - Sleep apnea with adeno-tonsillar hypertrophy
  - Mast cell activation disorder
  - Ehlers Danlos connective tissue disorder
  - Tics, restrictive eating, anxiety
  - Gag reflex easily triggered (father also has this)
  - Extreme fear of vomiting

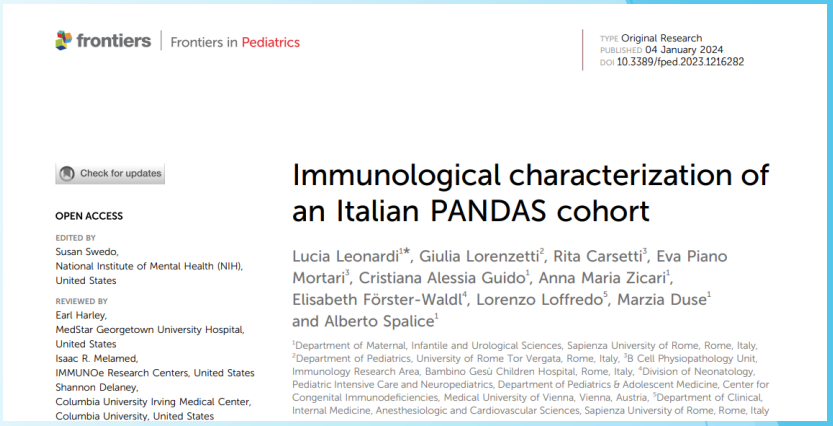
Case 3, Dylan, 10 years old in June 2020

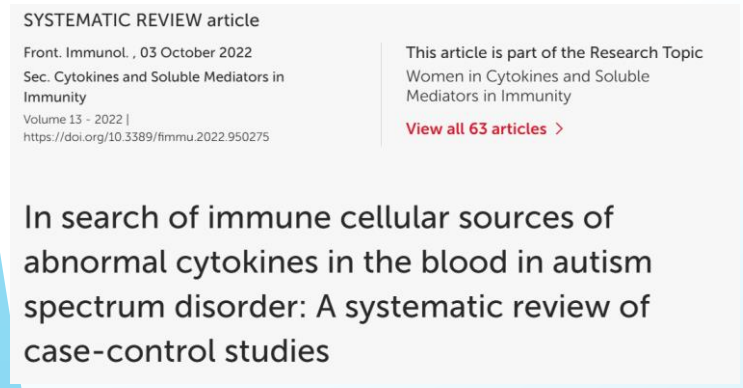
- Fears narrow spaces
- Fear of vomiting, will not eat in school just in case, feels lump sensation in throat when anxious, fear causes choking sensation and gagging which can lead to vomiting, extreme fear of dentist
- Fear of embarrassing himself
- Fear of death and death of his parents
- Sleeps on abdomen, perspires a lot during sleep, talks in his sleep
- OCD –but hides it, has to count and even up.
- Sensitive to tags and clothing
- Anticipatory anxiety, <any presentation, performance, test
- Anxious with physical restlessness in crowded places, >ice cold drinks, >cold application to forehead
- No appetite first thing in the morning. Mom has him eat a small amount in the car on way to school.
- Eye blinking tic
- Obstructed sensation in left ear, sound sensitivity in both ears
- Very attached to mother
- Timid

Case 3, Dylan, 10 years old in June 2020

- Contitutional remedies: Rhus tox 30c, Medor 1m weekly June – Nov 2020–improvements in socialization, eating, anxiety, sleep
    - Bryonia Nov. 2020-January 2021 overcame anorexia/extreme anxiety with move to new school
    - Cuprum Feb 2021-Dec 2022, great improvement confidence and fears, lump sensation gone
    - Dysprosium carb Dec 2022 on– doing well in school and social life. Fears and anxiety diminished
- Flare remdies:
    - Scutellaria –nervous fear, anxiety, insomnia, difficulty with focus, loss of appetite, nausea
    - China (period of paranoia that others were looking at him and thinking negatively of him)
    - Lac H (after spoke of shooting himself before his birthday arrived)
    - Sanicula (sudden onset extreme depression with nervous irritability, anxiety and enuresis)
- Treated for strep, sinus infections, assorted colds and illness with Narayani war, gave aconitum and rescue remedy in potency to take in panic attacks.
- Also given lymphatic drainage remedies for adenoid/tonsil enlargement.
- Nutrient absorption sarcodes for B12, folate, B6, iron, b-complex, C, methionine, leucine
- Treated with sarcodes for digestive enzymes to increase his enzyme prodution of DPPIV, lipase, pancreatinum, pepsinum secretin.
- Treated with okoubaka 30c and gluten 6c to desensitize to gluten
- Treated with Hist/DAO 15x to increase DAO production/histamine degradation capacity

a trend toward higher TNFalpha and IL-17 levels, and lower C3 levels, was detected in the PANDAS patients compared to the control group. Maternal autoimmune diseases were described in 53.3% of PANDAS patients and neuropsychiatric symptoms other than OCD and tics were detected in 76.9% patients. ASO titer did not differ significantly between the two groups. A possible correlation between enduring inflammation (elevated serum TNF-α and IL-17) and the persistence of neuropsychiatric symptoms in PANDAS patients beyond infectious episodes needs to be addressed. Further studies with larger cohorts would be pivotal to better define the role of TNF-α and IL-17 in PANDAS pathophysiology





We found that compared with controls, in subjects with autism, cytokines IL-6, IL-17, TNF-α, and IL-1β increased in the plasma and serum. We also identified monocytes, neutrophils, and CD4+ T cells as potential sources of these elevated cytokines in autism. Cytokines IFN-γ, TGF-β, RANTES, and IL-8 were increased in the plasma/serum of subjects with autism, and IFN-γ was likely produced by CD4+ T cells and natural killer (NK) cells, although conflicting evidence is present for IFN-γ and TGF-β. Other cytokines—IL-13, IL-10, IL-5, and IL-4—were found to be unaltered in the plasma/serum and post-stimulated blood immune cells in autistic individuals as compared with controls. The frequencies of T cells, monocytes, B cells, and NK cells were unchanged in subjects with autism as opposed to controls, suggesting that abnormal cytokines were unlikely due to altered cell numbers but might be due to altered functioning of these cells in autism. Our results support existing studies of abnormal cytokines in autism and provide comprehensive evidence of potential cellular sources of these altered cytokines in the context of autism.

https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.950275/full

Case 3, Dylan, 10 years old in June 2020

- Began cytokines in LM3 in March 2023:

  TNF alpha, IL-6, IL-1b, IFN-y, IL-8, TGF-B, IL-10, IL-2, VEGF, immunoglobulin, thymus gland, red bone marrow

  As of July 2023, he no longer feels anxious. No more panic attacks or tics. His was an awards presenter at a large theater and enjoyed it!
- December 18, 2023: exposure/reaction to solvent, did tautopathic solvent detox
- Treated easy gag reflex with sarcodes of glossopharyngeal nerve, vagus nerve, cranial nerve 5 and 9, medulla oblogata and mastic gum starting December 2023.
- Ascending potencies of strep tilsch starting in Jan 2024
- He stopped having any gag attacks as of August 2024.
- No longer has PANS/PANDAS flares.
- He is a freshman at a private high school that had an admissions process . He has no supports and thriving.
- ASD??

Homeopathic Cytokines for Treatment of Long COVID

- Biomarkers for long COVID:
  - high levels of interferon gamma
  - anti-bodies to interferon-gamma (and other cytokines in many)
- May be why EBV, CMV, Herpes viruses are activated with covid and Vax
- Lowering of IFN-y correlates to resolution of symptoms

› Sci Adv. 2024 Feb 23;10(8):eadi9379. doi: 10.1126/sciadv.adi9379. Epub 2024 Feb 21.

Spontaneous, persistent, T cell–dependent IFN-γ release in patients who progress to Long Covid

Benjamin A Krishna [1 2], Eleanor Y Lim [1 2 3], Marina Metaxaki [1], Sarah Jackson [1 2 3], Lenette Mactavous [3]; NIHR BioResource [4]; Paul A Lyons [1 2], Rainer Doffinger [5], John R Bradley [2 4 6 7], Kenneth G C Smith [1 2], John Sinclair [2], Nicholas J Matheson [1 2 3 8], Paul J Lehner [1 2 3], Nyaradzai Sithole [1 2 3], Mark R Wills [1 2]

Affiliations + expand

PMID: 38381822 PMCID: PMC10881041 DOI: 10.1126/sciadv.adi9379

Lingering IFN-γ May Be Responsible for Long COVID Symptoms

High levels of IFN-γ persisted in some long COVID patients for up to 31 months, making it a reliable biomarker

UNIVERSITY OF CAMBRIDGE
Published: Feb 21, 2024 | 3 min read

frontiers | Frontiers in Immunology

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Check for updates

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Autoantibodies in COVID-19: implications for disease severity and clinical outcomes

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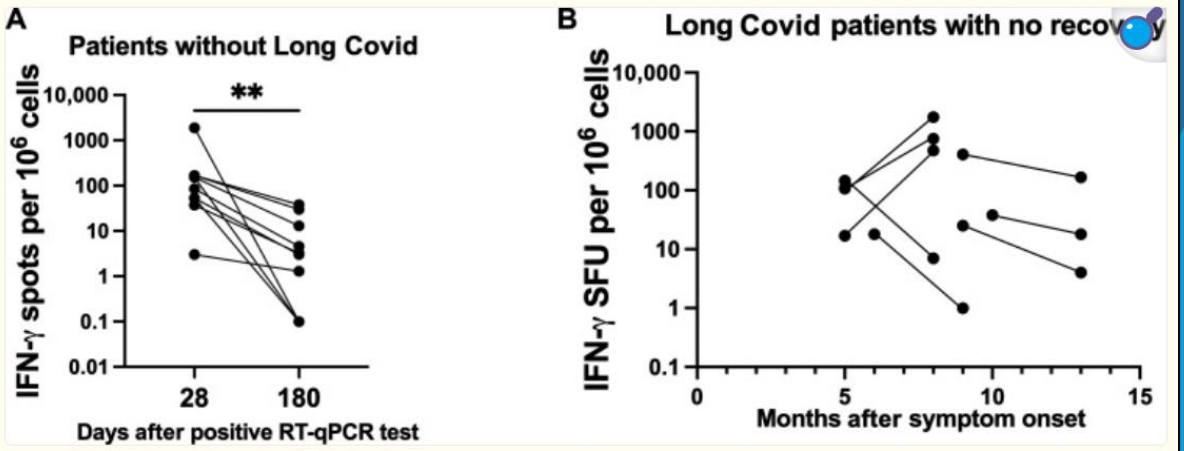
Fig. 2. Spontaneous IFN-γ production resolves in individuals with symptom resolution.



https://pmc.ncbi.nlm.nih.gov/articles/PMC10881041/

https://www.cam.ac.uk/research/news/long-covid-linked-to-persistently-high-levels-of-inflammatory-protein-a-potential-biomarker-and#:~:text=A%20University%20of%20Cambridge%2Dled,the%20event%20of%20a%20future

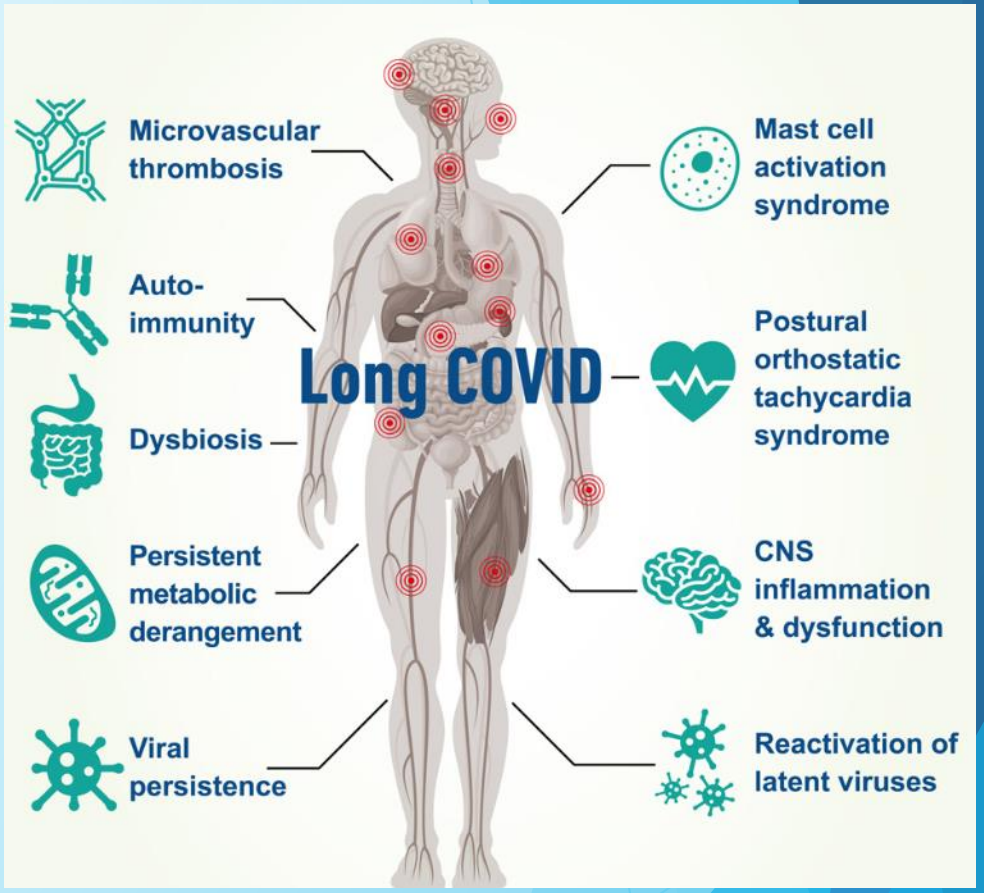
https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1509289/full

Homeopathic Cytokines for Treatment of Long COVID

- IFN-y LM3 daily
- Antibodies to IFN-y LM3 daily (sold under the name Anaferon from Materia Medica Pharmacy in Russia)

My experience

- Everyone who muscle tests for antibodies to interferon gamma also test for spike protein.
- Give spike protein in ascending potencies (with Vaccine if indicated)
- If possible, test for other autoantibodies and imbalanced cytokines.
- ANA is also fairly common and can be added to the mix in LM3



1.Biological mechanisms underpinning the development of long COVID
2.Perumal, Rubeshan et al.
3.iScience, Volume 26, Issue 6, 106935

Sources of potentized cytokines (low dose cytokines)

- GUNA based in Italy –if you are in Europe (not U.S. for IL-2)

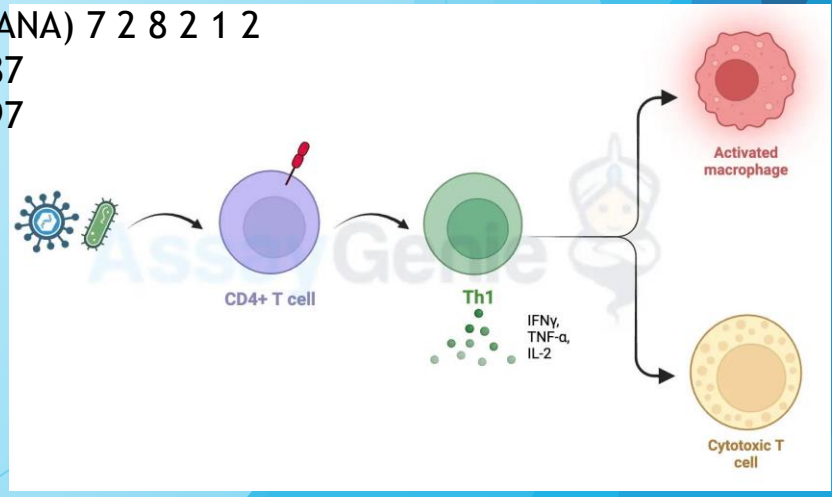
- https://www.ergopathics.com/ Canada for electromagnetic signature vials
  - LWP Cytokine And Immune 1 Test Kit –40 vials of cytokines and immune factors $105 Canadian
  - Cytokines / Interleukin—30 vials of cytokines $95 Canadian

- Amazon sells Anaferon (Ab to IFN-y from Russia), and it is sold OTC in other countries (e.g. Mexico)

- Patented products, e.g. 2LARTH® (IL-1ß, TNF-α, and IL-2) https://www.labolife.com/micro-immunotherapy/ see: https://pmc.ncbi.nlm.nih.gov/articles/PMC8268272/ (their own published study)

- Use a radionics machine (These rates work on a base 10 machine such as Sulis or Bionetix.)

INTERFERON 5 9 6 3 3 8	INTERLEUKINE 9 4 7 4 6 8 2
INTERFERON ALPHA 4 4 6 4 7 6 4	INTERLEUKINE 10 4 6 7 8 9 7
INTERFERON BETA 3 35 6 7 7 4	INTERLEUKINE 11 3 4 7 1 6 3
INTERFERON GAMMA 6 8 1 3 9	INTERLEUKINE 12 3 5 8 6 9 4
INTERLEUKINE 3 6 6 7 2 6 9	ANTI NUCLEAR ANTI BODIES(ANA) 7 2 8 2 1 2
INTERLEUKINE 4 3 7 1 5 7 5	RED BONE MARROW 586787
INTERLEUKINE 5 4 4 6 5 8 9	THYMUS GLAND 847697
INTERLEUKINE 6 4 4 5 6 9 1	
INTERLEUKINE 7 3 3 6 5 8 7	
INTERLEUKINE 8 3 6 8 2 8 9	



Source: Assay Genie

- *Thank you for your attention and interest!*

HOMEOPATHY ROCKS!

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Addendum:

Lymphatic drainage mix: gallium aparine 30c, yellow 30c, clay 30c, koch's lymph 30c and lymph 30c

Many children with ASD, ADD, ADHD, PANS/PANDAS have significant glymphatic congestion, to the point that you can see hardened, swollen lymph lines down the back of the neck or swollen nodes behind the ears and on the neck. This congestion contributes to inability to detoxify form the brain. This remedy can be used in conjunction with a castor oil complex with heat and gentle massage –in a downward motion only—along the lymph lines. I usually give in LM3 or LM4 or 30c depending on the sensitivity of the person.

Glymphatic drainage mix: glial cells, deep cervical lymph gland, jugular trunk righ, jugular trunk left, gallium aparine, thoracic duct, corticotrophin releasing factor, lymph, pituitary, yellow, sycamore seed, astrocytes, methylene blue, microglia, hedera helix