IL-12 Experimental Coexpression Signals and Crystal Variations In Dendritic Cellular Communication

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The Mathematical Learning Space Research Portfolio

1 Abstract

Memory cells can recall neighborhood pathogens with a strong and rapid response in a state of acquired immunity. IL-12 is a signal that sends naive CD4 T cells towards a Th1 phenotype for activation of the immune system to meet antigens on the dendritic cell surface. Cytokines diversity is based dendritic cellular typology. Here an examination of the sequences from an IL-12 coexpression network with experimental evidence is conducted and molecular properties clustered for ontoology enrichment.

2 Introduction

Lymphocytes are about 18-42 percent of circulating white blood cells (leukocytes). T cells (thymus cells) and B cells (bone marrow- or bursa-derived cells) are cellular components of the adaptive immune response where the T cells are involved in cell-mediated immunity and B cells are primarily responsible for humoral immunity (antibodies). The function of T cells and B cells is to recognize antigen presentation specific "non-self" antigens. B cells respond to pathogens with a quanity of antibody production that elminate bacteria and viruses in a friend or foe separation. T helper cells, produce cytokines that lead the immune response and other T cells(cytotoxic) produce toxic granules that contain powerful enzymes that generate death of pathogen-infected cells. Both B and T cells have memory of the pathogen and respond in the same way each time encountered. [1A]

B Cells are the major cells with antibodies in the blood plasma and lymph (humoral immunity). Antibodies (immunoglobulin, Ig), are large Y-shaped proteins used for identification. Mammals have five types of antibody: (1) IgA, (2) IgD, (3) IgE, (4) IgG, and (5) IgM with different biological properties for antigen diversity. [1B]

Antigen and antibody binding has five different protective mechanisms:[1B]

1. Agglutination: Reduces number of infectious units to be dealt with
2. Activation of complement: Cause inflammation and cell lysis
3. Opsonization: Coating antigen with antibody enhances phagocytosis
4. Antibody-dependent cell-mediated cytotoxicity: Antibodies attached to target cell cause destruction by macrophages, eosinophils, and NK cells
5. Neutralization: Blocks adhesion of bacteria and viruses to mucosa

Similar to the T cell, B cells express a unique B cell receptor (BCR) a membrane-bound antibody molecule. All the BCR of any cloned B cell recognizes and binds to only one particular antigen. A critical difference between B cells and T cells is antigen recognition. T cells recognize their cognate antigen in a processed form – as a peptide in the context of an MHC molecule and B cells recognize antigens in their native form. Once a B cell encounters its cognate (specific) antigen and signals from a helper T cell (Th2 type) it differentiates into an effector cell (plasma cell).[1B]

Plasma cells live for 2–3 days and secrete antibodies that bind to antigens and easier targets for phagocytes for activation of the complement cascade. About 10 percent of plasma cells survive to become long-lived antigen-specific memory B cells. Dendritic cells (DCs) are antigen-presenting cells (accessory cells) of the mammalian immune system with their main function to process antigen material and present it on the cell surface to the T cells of the immune system. These messengers are between the innate and the adaptive immune systems. [1B]

Dendritic cells are present in those tissues in contact with the external environment like the skin (Langerhans cell) and in the inner lining of the (1) nose, (2) lungs, (3) stomach and (4) intestines and in the immature state in the blood. Upon activation they migrate to the lymph nodes and interact with T cells and B cells for the adaptive immune response. At certain development stages the branched projections of dendrites is a similar to the tree or large plant. The structures distinct from the dendrites of neurons and immature dendritic cells or veiled cells have large cytoplasmic 'veils' rather than dendrites [1C]

The most common division of dendritic cells is "myeloid" vs. "plasmacytoid dendritic cell" (lymphoid). Toll-like receptors conventional dendritic cell (Myeloid dendritic cell) (cDC or mDC) Most similar to monocytes. mDC are made up of at least two subsets: (1) the more common mDC-1, which is a major stimulator of T cells, (2) the extremely rare mDC-2, a function for infection, Interleukin 12 (IL-12), Interleukin 6 (IL-6), TNF, chemokines TLR 2, TLR 4 Plasmacytoid dendritic cell (pDC) Look like plasma cells, but have certain characteristics similar to myeloid dendritic cells and can produce high amounts of interferon-alpha (interferon-producing cells) TLR 7, TLR 9 [1C]

The markers BDCA-2, BDCA-3, and BDCA-4 can be used to discriminate among the types. Histologic comparison of cell types in a germinal center, including follicular dendritic cells.

1. Centrocytes are small to medium size with angulated, elongated, cleaved, or twisted nuclei.
2. Centroblasts are larger cells containing vesicular nuclei with one to three basophilic nucleoli apposing the nuclear membrane.
3. Follicular dendritic cells have round nuclei, centrally located nucleoli, bland and dispersed chromatin, and flattening of adjacent nuclear membrane. [1C]

Lymphoid and myeloid DCs evolve from lymphoid and myeloid precursors, respectively, and thus are of hematopoietic origin. Follicular dendritic cells (FDC) are mesenchymal and not hematopoietic origin and do not express MHC class II, and in the lymphoid follicles with long "dendritic" processes. [1C]

The dendritic cells are constantly in communication with other cells in the body with direct cell–cell contact based on the interaction of cell-surface proteins like the interaction of the membrane proteins of the B7 family of the dendritic cell with CD28 present on the lymphocyte. However, the cell–cell interaction can also take place at a distance via cytokines. Stimulating dendritic cells in vivo with microbial extracts causes the dendritic cells to rapidly begin producing IL-12. IL-12 is a signal that helps send naive CD4 T cells towards a Th1 phenotype with priming and activation of the immune system. The plasmacytoid DC has the ability to produce huge amounts of type-1 IFNs, which recruit more activated macrophages to allow phagocytosis. [1C]

The pathways

1. hsa04060 Cytokine-cytokine receptor interaction
2. hsa04630 JAK-STAT signaling pathway

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3. hsa04658 Th1 and Th2 cell differentiation
4. hsa04659 Th17 cell differentiation
5. hsa05200 Pathways in cancer
6. hsa05321 Inflammatory bowel disease
7. nt06119 JAK-STAT signaling (viruses)
8. nt06160 Human T-cell leukemia virus 1 (HTLV-1)
9. nt06162 Hepatitis B virus (HBV)
10. nt06164 Kaposi sarcoma-associated herpesvirus (KSHV)
11. nt06165 Epstein-Barr virus (EBV)
12. nt06219 JAK-STAT signaling
13. nt06263 Hepatocellular carcinoma
14. nt06266 Non-small cell lung cancer
15. nt06276 Chronic myeloid leukemia
16. N00053 Cytokine-Jak-STAT signaling pathway

Consider the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway is one of a few pleiotropic cascades to transduce a multitude of signals for development and homeostasis in animals. In mammals, the JAK/STAT pathway is the principal signaling mechanism for cytokines and growth factors with binding of cytokines to their cognate receptor, STATs are activated by JAK tyrosine kinases. Upon activation and dimerization with translocation to the nucleus, modulation of the expression of target genes is done. Activation of STATs, JAKs mediate and recruit other molecules like MAP kinases and PI3 kinase. These molecules process downstream signals via the Ras-Raf-MAP kinase and PI3 kinase pathways and activates additional transcription factors. [401]

In Figure 1 has the Cytokine-Jak-STAT signaling pathway with the relationsip Cytokine $->$ Receptor $->$ JAK $->$ STAT $=>$ PIM1 with KEGG compound ids as (3558, 3562, 3565, 3567, 3569, 3574, 3592, 3593, 3596, 3600, 51561, 2056, 3439, 3458) $->$ (3559, 3560, 3561, 3563, 3566, 1439, 3568, 3570, 3572, 3575, 3594, 3595, 3597, 3601, 149233, 2057, 3454, 3455, 3459, 3460) $->$ (3716, 3717, 3718) $->$ (6772, 6773, 6774, 6775, 6776, 6777 ,6778) $=>$ 5292 [401]

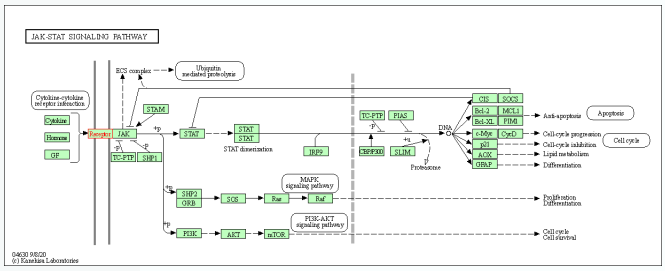

Figure 1: The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway[401]

Genes in this pathway of Figure 1 are provide in Table 1.

ID	Name Description
3558	IL2; interleukin 2
3562	IL3; interleukin 3
3565	IL4; interleukin 4
3567	IL5; interleukin 5
3569	IL6; interleukin 6
3574	IL7; interleukin 7
3592	IL12A; interleukin 12A
3593	IL12B; interleukin 12B
3596	IL13; interleukin 13
3600	IL15; interleukin 15
51561	IL23A; interleukin 23 subunit alpha
2056	EPO; erythropoietin
3439	IFNA1; interferon alpha 1
3458	IFNG; interferon gamma
3559	IL2RA; interleukin 2 receptor subunit alpha
3560	IL2RB; interleukin 2 receptor subunit beta
3561	IL2RG; interleukin 2 receptor subunit gamma
3563	IL3RA; interleukin 3 receptor subunit alpha
3566	IL4R; interleukin 4 receptor
1439	CSF2RB; colony stimulating factor 2 receptor beta common subunit
3568	IL5RA; interleukin 5 receptor subunit alpha
3570	IL6R; interleukin 6 receptor
3572	IL6ST; interleukin 6 signal transducer
3575	IL7R; interleukin 7 receptor
3594	IL12RB1; interleukin 12 receptor subunit beta 1
3595	IL12RB2; interleukin 12 receptor subunit beta 2
3597	IL13RA1; interleukin 13 receptor subunit alpha 1
3601	IL15RA; interleukin 15 receptor subunit alpha
149233	IL23R; interleukin 23 receptor
2057	EPOR; erythropoietin receptor
3454	IFNAR1; interferon alpha and beta receptor subunit 1
3455	IFNAR2; interferon alpha and beta receptor subunit 2
3459	IFNGR1; interferon gamma receptor 1
3460	IFNGR2; interferon gamma receptor 2
3716	JAK1; Janus kinase 1
3717	JAK2; Janus kinase 2
3718	JAK3; Janus kinase 3
6772	STAT1; signal transducer and activator of transcription 1
6773	STAT2; signal transducer and activator of transcription 2
6774	STAT3; signal transducer and activator of transcription 3
6775	STAT4; signal transducer and activator of transcription 4
6776	STAT5A; signal transducer and activator of transcription 5A
6777	STAT5B; signal transducer and activator of transcription 5B
6778	STAT6; signal transducer and activator of transcription 6
5292	PIM1; Pim-1 proto-oncogene, serine/threonine kinase

Table 1A has the activation IDs for 3593 IL12B; interleukin 12B based on Table 1. [401]

1	hsa:116379	hsa:3459	hsa:3587	hsa:5156
2	hsa:1271	hsa:3460	hsa:3588	hsa:5159
3	hsa:1438	hsa:3559	hsa:3590	hsa:53832
4	hsa:1439	hsa:3560	hsa:3594	hsa:53833
5	hsa:1441	hsa:3561	hsa:3595	hsa:5618
6	hsa:149233	hsa:3563	hsa:3597	hsa:58985
7	hsa:163702	hsa:3566	hsa:3598	hsa:64109
8	hsa:1956	hsa:3568	hsa:3601	hsa:9180
9	hsa:2057	hsa:3570	hsa:3953	hsa:9466
10	hsa:2690	hsa:3572	hsa:3977	hsa:116379
11	hsa:3454	hsa:3575	hsa:4352	hsa:1271
12	hsa:3455	hsa:3581	hsa:50615	hsa:1438

Molecular properties are abundant in dimensional reduction for collections of sequences. Examples such as stability, binding potential aliphatic and hydrophobicity along with the charge at different pH is a few of available molecular properties to examine based on the gene ontology ids in Table 2. The net charge of a protein sequence based on the Henderson-Hasselbalch equation based on pH 5, 7 and 9. The aliphatic index is the relative volume occupied by aliphatic side chains (Alanine, Valine, Isoleucine, and Leucine) and is a positive factor for the increase of thermostability of globular proteins. The potential protein interaction index proposed by Boman (2003) based in the amino acid sequence of a protein and provides an overall estimate of the potential of a peptide to bind to membranes or other proteins as receptors. A protein have high binding potential if the index value is higher than 2.48. This index predicts the stability of a protein based on its amino acid composition, a protein whose instability index is smaller than 40 is predicted as stable, a value above 40 predicts that the protein may be unstable. Hydrophobicity is an important stabilization force in protein folding; this force changes depending on the solvent in which the protein is found. [1001]

Table 1 has the molecular properties.

	Protein	Stability Index	Binding Potential	ALiphatic	f.1	CpH5	CpH7	CpH9
1	(RefSeq) interleukin 2	47.7	1.179	108.4	-0.00719	5.507	1.587	-3.212
2	(RefSeq) interleukin 3	58.5	1.369	109.8	-0.14539	6.170	2.647	-0.410
3	(RefSeq) interleukin 4	46.0	1.792	85.5	-0.29542	14.264	8.215	0.648
4	(RefSeq) interleukin 5	44.9	1.186	112.8	-0.01343	6.404	1.888	-1.643
5	(RefSeq) interleukin 6	57.7	1.609	87.5	-0.27075	3.353	-0.644	-5.190
6	(RefSeq) interleukin 7	45.4	1.521	92.5	-0.24011	10.918	5.771	-0.707
7	(RefSeq) interleukin 12A	54.9	1.347	91.8	-0.06640	8.226	1.162	-8.108
8	(RefSeq) interleukin 12B	34.8	1.779	74.2	-0.43902	3.079	-5.887	-17.346
9	(RefSeq) interleukin 13	41.2	0.355	114.2	0.41096	6.844	2.792	-2.685
10	(RefSeq) interleukin 15	53.1	0.980	108.9	0.17037	-0.172	-7.538	-15.299
11	(RefSeq) interleukin 23 subunit alpha	55.6	1.073	96.0	-0.09630	5.274	-2.240	-8.612
12	(RefSeq) erythropoietin	42.4	1.139	106.7	0.02746	6.840	2.560	-2.928
13	(RefSeq) interferon alpha 1	68.5	1.761	90.3	-0.18413	0.431	-4.495	-11.462
14	(RefSeq) interferon gamma	30.3	2.127	75.2	-0.57771	13.718	10.375	6.167
15	(RefSeq) interleukin 2 receptor subunit alpha	52.7	1.940	57.7	-0.54228	5.937	-1.955	-14.338
16	(RefSeq) interleukin 2 receptor subunit beta	58.6	1.336	81.8	-0.27260	-5.403	-19.725	-33.519
17	(RefSeq) interleukin 2 receptor subunit gamma	42.0	1.446	80.0	-0.37317	8.203	-5.180	-17.466
18	(RefSeq) interleukin 3 receptor subunit alpha	44.5	1.611	85.9	-0.20159	16.156	7.254	-6.397
19	(RefSeq) interleukin 4 receptor	61.7	1.337	72.7	-0.33055	-7.103	-32.966	-66.129
20	(RefSeq) colony stimulating factor 2 receptor subunit beta	65.2	1.521	73.4	-0.41806	3.613	-19.960	-40.997
21	(RefSeq) interleukin 5 receptor subunit alpha	43.1	1.177	100.7	-0.05405	2.412	-10.681	-23.473
22	(RefSeq) interleukin 6 receptor	61.4	1.667	74.6	-0.32842	19.629	7.285	-5.704
23	(RefSeq) interleukin 6 cytokine family signal transducer	43.6	1.748	74.0	-0.45654	11.789	-15.971	-38.749
24	(RefSeq) interleukin 7 receptor	50.9	1.458	89.1	-0.21917	1.064	-11.217	-25.050
25	(RefSeq) interleukin 12 receptor subunit beta 1	46.5	1.508	73.9	-0.32674	1.612	-15.578	-38.702
26	(RefSeq) interleukin 12 receptor subunit beta 2	50.3	1.538	85.2	-0.31624	37.107	8.757	-19.205
27	(RefSeq) interleukin 13 receptor subunit alpha 1	47.5	1.583	81.2	-0.39930	5.845	-6.281	-21.585
28	(RefSeq) interleukin 15 receptor subunit alpha	52.1	1.445	74.6	-0.26667	14.581	5.908	-3.277
29	(RefSeq) interleukin 23 receptor	40.2	1.462	86.4	-0.29984	2.402	-15.010	-31.011
30	(RefSeq) erythropoietin receptor	48.0	1.032	89.7	-0.07047	-13.369	-26.936	-39.978
31	(RefSeq) interferon alpha and beta receptor subunit 1	46.2	1.460	87.5	-0.27666	5.294	-8.151	-21.353
32	(RefSeq) interferon alpha and beta receptor subunit 2	57.5	1.539	85.5	-0.27553	-29.436	-45.555	-56.267
33	(RefSeq) interferon gamma receptor 1	48.7	1.470	88.8	-0.23906	-9.536	-25.452	-39.574
34	(RefSeq) interferon gamma receptor 2	52.5	0.932	94.0	0.03056	0.819	-6.745	-14.344
35	(RefSeq) Janus kinase 1	49.8	1.943	80.8	-0.52140	49.391	8.282	-28.870
36	(RefSeq) Janus kinase 2	47.7	1.820	82.7	-0.43295	41.828	3.178	-29.980
37	(RefSeq) Janus kinase 3	52.2	1.443	91.6	-0.14760	42.615	2.983	-32.797
38	(RefSeq) signal transducer and activator of transcription 1	51.0	1.933	87.0	-0.52293	11.609	-10.398	-24.455
39	(RefSeq) signal transducer and activator of transcription 2	55.5	1.735	95.2	-0.42009	3.771	-20.994	-37.606
40	(RefSeq) signal transducer and activator of transcription 3	48.2	1.706	83.5	-0.40338	12.587	-6.255	-22.599
41	(RefSeq) signal transducer and activator of transcription 4	53.5	1.679	89.8	-0.35775	20.120	-4.181	-18.701
42	(RefSeq) signal transducer and activator of transcription 5A	52.8	1.807	88.2	-0.44345	16.515	-7.447	-22.315
43	(RefSeq) signal transducer and activator of transcription 5B	51.4	1.811	85.9	-0.46734	11.584	-11.657	-25.689
44	(RefSeq) signal transducer and activator of transcription 6	54.5	1.368	88.3	-0.26635	14.601	-10.291	-27.059
45	(RefSeq) Pim-1 proto-oncogene, serine/threonine kinase	43.1	1.651	95.9	-0.24665	6.793	-7.046	-15.942

ID	Name	Crystals
1	(RefSeq) interleukin 2	PDB: 1ILM 1ILN 1IRL 1M47 1M48 1M49 1M4A 1M4B 1M4C 1NBP 1PW6 1PY2 1QVN 1Z92 2B5I 2ERJ 3INK 3QAZ 3QB1 4NEJ 4NEM 5LQB 5M5E 5UTZ 6LX3 6LXW 6VWU 6YE3 7DR4
2	(RefSeq) interleukin 3	PDB: 1JLI 5UV8 5UWC 6NMY
3	(RefSeq) interleukin 4	PDB: 1BBN 1BCN 1CYL 1HIJ 1HIK 1HZI 1IAR 1ILL 1ITE 1ITI 1ITL 1ITM 1RCB 2B8U 2B8X 2B8Y 2B8Z 2B90 2B91 2CYK 2D48 2INT 3BPL 3BPN 3QB7 4YDY 5FHX 6OEL
4	(RefSeq) interleukin 5	PDB: 1HUL 3QT2 3VA2
5	(RefSeq) interleukin 6	PDB: 1ALU 1IL6 1N2Q 1P9M 2IL6 4CNI 4J4L 4NI7 4NI9 4O9H 4ZS7 5FUC 7NXZ
6	(RefSeq) interleukin 7	PDB: 1IL7 3DI2 3DI3
7	(RefSeq) interleukin 12A	PDB: 1F45 3HMX
8	(RefSeq) interleukin 12B	PDB: 1F42 1F45 3D85 3D87 3DUH 3HMX 3QWR 4GRW 5MJ3 5MJ4 5MXA 5MZV 5NJD 6UIB 6WDQ
9	(RefSeq) interleukin 13	PDB: 1GA3 1IJZ 1IK0 1J9U 3BPO 3G6D 3ITR 3ITS 3L5W 3L5X 3LB6 4I77 4PS4 5E4E 5L6Y
10	(RefSeq) interleukin 15	PDB: 2XQB 2Z3Q 2Z3R 4GS7
11	(RefSeq) interleukin 23 subunit alpha	PDB: 3D85 3D87 3DUH 3QWR 4GRW 5MJ3 5MJ4 5MXA 5MZV 5NJD 6UIB 6WDQ
12	(RefSeq) erythropoietin	UniProt: P01588 G9JKG7
13	(RefSeq) interferon alpha 1	PDB: 3UX9
14	(RefSeq) interferon gamma	PDB: 1EKU 1FG9 1FYH 1HIG 3BES 6E3K 6E3L
15	(RefSeq) interleukin 2 receptor subunit alpha	PDB: 1ILM 1ILN 1Z92 2B5I 2ERJ 3IU3 3NFP 6VWU 6YIO
16	(RefSeq) interleukin 2 receptor subunit beta	PDB: 1ILM 1ILN 2B5I 2ERJ 3QAZ 4GS7 5M5E 6E8K
17	(RefSeq) interleukin 2 receptor subunit gamma	PDB: 1ILL 1ILM 1ILN 1ITE 2B5I 2ERJ 3BPL 3QAZ 3QB7 4GS7 5M5E 6OEL
18	(RefSeq) interleukin 3 receptor subunit alpha	PDB: 4JZJ 5UV8 5UWC 6NMY
19	(RefSeq) interleukin 4 receptor	PDB: 1IAR 1IRS 1ITE 3BPL 3BPN 3BPO 5E4E 6OEL 6WGL
20	(RefSeq) colony stimulating factor 2 receptor subunit beta	PDB: 1C8P 1EGJ 1GH7 2GYS 2NA8 2NA9 4NKQ 5DWU
21	(RefSeq) interleukin 5 receptor subunit alpha	PDB: 1OBX 1OBZ 3QT2 3VA2 6H41
22	(RefSeq) interleukin 6 receptor	PDB: 1N26 1N2Q 1P9M 2ARW 5FUC 7DC8
23	(RefSeq) interleukin 6 cytokine family signal transducer	PDB: 1BJ8 1BQU 1I1R 1N2Q 1P9M 1PVH 3L5H 3L5I 3L5J
24	(RefSeq) interleukin 7 receptor	PDB: 3DI2 3DI3 3UP1 5J11 6P50 6P67
25	(RefSeq) interleukin 12 receptor subunit beta 1	PDB: 6WDP 6WDQ
26	(RefSeq) interleukin 12 receptor subunit beta 2	
27	(RefSeq) interleukin 13 receptor subunit alpha 1	PDB: 3BPN 3BPO 4HWB 5E4E
28	(RefSeq) interleukin 15 receptor subunit alpha	PDB: 2ERS 2Z3Q 2Z3R 4GS7
29	(RefSeq) interleukin 23 receptor	PDB: 5MZV 6WDQ
30	(RefSeq) erythropoietin receptor	PDB: 1CN4 1EBA 1EBP 1EER 1ERN 2JIX 2MV6 4Y5V 4Y5X 4Y5Y 6E2Q 6MOE 6MOF 6MOH 6MOI 6MOJ 6MOK 6MOL
31	(RefSeq) interferon alpha and beta receptor subunit 1	PDB: 3S98 3SE3 3SE4 4PO6
32	(RefSeq) interferon alpha and beta receptor subunit 2	PDB: 1N6U 1N6V 2HYM 2KZ1 2LAG 3S8W 3S9D 3SE3 3SE4
33	(RefSeq) interferon gamma receptor 1	PDB: 1FG9 1FYH 1JRH 6E3K 6E3L
34	(RefSeq) interferon gamma receptor 2	PDB: 5EH1 6E3K 6E3L
35	(RefSeq) Janus kinase 1	PDB: 3EYG 3EYH 4E4L 4E4N 4E5W 4EHZ 4EI4 4FK6 4GS0 4I5C 4IVB 4IVC 4IVD 4K6Z 4K77 4L00 4L01 5E1E 5HX8 5IXD 5IXI 5KHW 5KHX 5L04 5WO4 6AAH 6BBU 6C7Y 6DBN 6ELR 6GGH 6HZU 6N77 6N78 6N79 6N7A 6N7B 6N7C 6N7D 6RSB 6RSC 6RSD 6RSE 6RSH 6SM8 6SMB 6TPE 6TPF 6W8L
36	(RefSeq) Janus kinase 2	PDB: 2B7A 2W1I 2XA4 3E62 3E63 3E64 3FUP 3IO7 3IOK 3JY9 3KCK 3KRR 3LPB 3Q32 3RVG 3TJC 3TJD 3UGC 3ZMM 4AQC 4BBE 4BBF 4C61 4C62 4D0W 4D0X 4D1S 4E4M 4E6D 4E6Q 4F08 4F09 4FVP 4FVQ 4FVR 4GFM 4GMY 4HGE 4IVA 4JI9 4JIA 4P7E 4YTC 4YTF 4YTH 4YTI 4Z32 4ZIM 5AEP 5CF4 5CF5 5CF6 5CF8 5HEZ 5I4N 5L3A 5TQ3 5TQ4 5TQ5 5TQ6 5TQ7 5TQ8 5USY 5USZ 5UT0 5UT1 5UT2 5UT3 5UT4 5UT5 5UT6 5WEV 5WIJ 5WIK 5WIL 5WIM 5WIN 6AAJ 6BBV 6BRW 6BS0 6BSS 6D2I 6DRW 6E2P 6E2Q 6G3C 6M9H 6OAV 6OBB 6OBF 6OBL 6OCC 6TPD 6VGL 6VN8 6VNB 6VNC 6VNE 6VNF 6VNG 6VNH 6VNI 6VNJ 6VNK 6VNL 6VNM 6VS3 6VSN 6WTN 6WTO 6WTP 6WTQ 6X8E 6XJK
37	(RefSeq) Janus kinase 3	PDB: 1YVJ 3LXK 3LXL 3PJC 3ZC6 3ZEP 4HVD 4HVG 4HVH 4HVI 4I6Q 4QPS 4QT1 4RIO 4V0G 4Z16 5LWM 5LWN 5TOZ 5TTS 5TTU 5TTV 5VO6 5W86 5WFJ 6AAK 6DA4 6DB3 6DB4 6DUD 6GL9 6GLA 6GLB 6HZV 6NY4 7APF 7APG 7C3N
38	(RefSeq) signal transducer and activator of transcription 1	PDB: 1BF5 1YVL 2KA6 3WWT
39	(RefSeq) signal transducer and activator of transcription 2	PDB: 2KA4 6UX2 6WCZ
40	(RefSeq) signal transducer and activator of transcription 3	PDB: 5AX3 5U5S 6NJS 6NUQ 6QHD 6TLC
41	(RefSeq) signal transducer and activator of transcription 4	
42	(RefSeq) signal transducer and activator of transcription 5A	
43	(RefSeq) signal transducer and activator of transcription 5B	PDB: 6MBW 6MBZ
44	(RefSeq) signal transducer and activator of transcription 6	PDB: 1OJ5 4Y5U 4Y5W 5D39 5NWM 5NWX
45	(RefSeq) Pim-1 proto-oncogene, serine/threonine kinase	PDB: 1XQZ 1XR1 1XWS 1YHS 1YI3 1YI4 1YWV 1YXS 1YXT 1YXU 1YXV 1YXX 2BIK 2BIL 2BZH 2BZI 2BZJ 2BZK 2C3I 2J2I 2O3P 2O63 2O64 2O65 2OBJ 2OI4 2XIX 2XIY 2XIZ 2XJ0 2XJ1 2XJ2 3A99 3BGP 3BGQ 3BGZ 3BWF 3C4E 3CXW 3CY2 3CY3 3DCV 3F2A 3JPV 3JXW 3JY0 3JYA 3MA3 3QF9 3R00 3R01 3R02 3R04 3T9I 3UIX 3UMW 3UMX 3VBQ 3VBT 3VBV 3VBW 3VBX 3VBY 3VC4 3WE8 4A7C 4ALU 4ALV 4ALW 4AS0 4BZN 4BZO 4DTK 4ENX 4ENY 4GW8 4I41 4IAA 4JX3 4JX7 4K0Y 4K18 4K1B 4LL5 4LM5 4LMU 4MBI 4MBL 4MTA 4N6Y 4N6Z 4N70 4RBL 4RC2 4RC3 4RC4 4RPV 4TY1 4WRS 4WSY 4WT6 4XH6 4XHK 5C1Q 5DGZ 5DHJ 5DIA 5DWR 5EOL 5IIS 5IPJ 5KCX 5KGD 5KGE 5KGG 5KGI 5KGK 5KZI 5MZL 5N4N 5N4O 5N4R 5N4U 5N4V 5N4X 5N4Y 5N4Z 5N50 5N51 5N52 5N5L 5N5M 5NDT 5O11 5O12 5O13 5TEL 5TEX 5TOE 5TUR 5V80 5V82 5VUA 5VUB 5VUC 6AYD 6BSK 6KZI 6L11 6L12 6L13 6L14 6L15 6L16 6L17 6MT0 6NO8 6NO9 6PCW 6PDI 6PDN 6PDO 6PDP 6QXK 6VRU 6VRV 6YKD

Table 1 has the molecular properties for interleukin 12B.

	Protein	Stability Index	Binding Potential	ALiphatic	f.1	CpH5	CpH7	CpH9
1	1F42	47.7	1.179	108.4	-0.00719	5.507	1.587	-3.212
2	1F45	58.5	1.369	109.8	-0.14539	6.170	2.647	-0.410
3	3D85	46.0	1.792	85.5	-0.29542	14.264	8.215	0.648
4	3D87	44.9	1.186	112.8	-0.01343	6.404	1.888	-1.643
5	3DUH	57.7	1.609	87.5	-0.27075	3.353	-0.644	-5.190
6	3HMX	45.4	1.521	92.5	-0.24011	10.918	5.771	-0.707
7	3QWR	54.9	1.347	91.8	-0.06640	8.226	1.162	-8.108
8	4GRW	34.8	1.779	74.2	-0.43902	3.079	-5.887	-17.346
9	5MJ3	41.2	0.355	114.2	0.41096	6.844	2.792	-2.685
10	5MJ4	53.1	0.980	108.9	0.17037	-0.172	-7.538	-15.299
11	5MXA	55.6	1.073	96.0	-0.09630	5.274	-2.240	-8.612
12	5MZV	42.4	1.139	106.7	0.02746	6.840	2.560	-2.928
13	5NJD	68.5	1.761	90.3	-0.18413	0.431	-4.495	-11.462
14	6UIB	30.3	2.127	75.2	-0.57771	13.718	10.375	6.167
15	6WDQ	52.7	1.940	57.7	-0.54228	5.937	-1.955	-14.338
16	1F42	58.6	1.336	81.8	-0.27260	-5.403	-19.725	-33.519
17	1F45	42.0	1.446	80.0	-0.37317	8.203	-5.180	-17.466
18	3D85	44.5	1.611	85.9	-0.20159	16.156	7.254	-6.397
19	3D87	61.7	1.337	72.7	-0.33055	-7.103	-32.966	-66.129
20	3DUH	65.2	1.521	73.4	-0.41806	3.613	-19.960	-40.997
21	3HMX	43.1	1.177	100.7	-0.05405	2.412	-10.681	-23.473
22	3QWR	61.4	1.667	74.6	-0.32842	19.629	7.285	-5.704
23	4GRW	43.6	1.748	74.0	-0.45654	11.789	-15.971	-38.749
24	5MJ3	50.9	1.458	89.1	-0.21917	1.064	-11.217	-25.050
25	5MJ4	46.5	1.508	73.9	-0.32674	1.612	-15.578	-38.702
26	5MXA	50.3	1.538	85.2	-0.31624	37.107	8.757	-19.205
27	5MZV	47.5	1.583	81.2	-0.39930	5.845	-6.281	-21.585
28	5NJD	52.1	1.445	74.6	-0.26667	14.581	5.908	-3.277
29	6UIB	40.2	1.462	86.4	-0.29984	2.402	-15.010	-31.011
30	6WDQ	48.0	1.032	89.7	-0.07047	-13.369	-26.936	-39.978
31	1F42	46.2	1.460	87.5	-0.27666	5.294	-8.151	-21.353
32	1F45	57.5	1.539	85.5	-0.27553	-29.436	-45.555	-56.267
33	3D85	48.7	1.470	88.8	-0.23906	-9.536	-25.452	-39.574
34	3D87	52.5	0.932	94.0	0.03056	0.819	-6.745	-14.344
35	3DUH	49.8	1.943	80.8	-0.52140	49.391	8.282	-28.870
36	3HMX	47.7	1.820	82.7	-0.43295	41.828	3.178	-29.980
37	3QWR	52.2	1.443	91.6	-0.14760	42.615	2.983	-32.797
38	4GRW	51.0	1.933	87.0	-0.52293	11.609	-10.398	-24.455
39	5MJ3	55.5	1.735	95.2	-0.42009	3.771	-20.994	-37.606
40	5MJ4	48.2	1.706	83.5	-0.40338	12.587	-6.255	-22.599
41	5MXA	53.5	1.679	89.8	-0.35775	20.120	-4.181	-18.701
42	5MZV	52.8	1.807	88.2	-0.44345	16.515	-7.447	-22.315
43	5NJD	51.4	1.811	85.9	-0.46734	11.584	-11.657	-25.689
44	6UIB	54.5	1.368	88.3	-0.26635	14.601	-10.291	-27.059
45	6WDQ	43.1	1.651	95.9	-0.24665	6.793	-7.046	-15.942

Figure 2 has the IL-12 experimental evidence coexpression network based on the Receptor in Figure 1

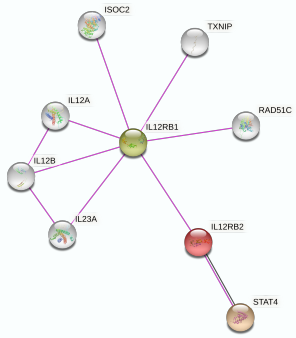

Figure 2: IL-12 experimental evidence coexpression network [?key1] [601]

Table 1 has the descriptions of the molecules in the network of Figure 1.

	Name	Description
1	IL12A	Interleukin-12 subunit alpha; Cytokine that can act as a growth factor for activated T and NK cells, enhance the lytic activity of NK/lymphokine- activated Killer cells, and stimulate the production of IFN-gamma by resting PBMC; Interleukins
2	IL12B	Interleukin-12 subunit beta; Cytokine that can act as a growth factor for activated T and NK cells, enhance the lytic activity of NK/lymphokine- activated killer cells, and stimulate the production of IFN-gamma by resting PBMC; Belongs to the type I cytokine receptor family. Type 3 subfamily
3	IL12RB1	Interleukin-12 receptor subunit beta-1; Functions as an interleukin receptor which binds interleukin-12 with low affinity and is involved in IL12 transduction. Associated with IL12RB2 it forms a functional, high affinity receptor for IL12. Associates also with IL23R to form the interleukin-23 receptor which functions in IL23 signal transduction probably through activation of the Jak-Stat signaling cascade; CD molecules
4	IL12RB2	Interleukin-12 receptor subunit beta-2; Receptor for interleukin-12. This subunit is the signaling component coupling to the JAK2/STAT4 pathway. Promotes the proliferation of T-cells as well as NK cells. Induces the promotion of T-cells towards the Th1 phenotype by strongly enhancing IFN-gamma production; Fibronectin type III domain containing
5	IL23A	Interleukin-23 subunit alpha; Associates with IL12B to form the IL-23 interleukin, a heterodimeric cytokine which functions in innate and adaptive immunity. IL-23 may constitute with IL-17 an acute response to infection in peripheral tissues. IL-23 binds to a heterodimeric receptor complex composed of IL12RB1 and IL23R, activates the Jak- Stat signaling cascade, stimulates memory rather than naive T- cells and promotes production of proinflammatory cytokines. IL-23 induces autoimmune inflammation and thus may be responsible for autoimmune inflammatory diseases.
6	ISOC2	Isochorismatase domain-containing protein 2; Isochorismatase domain containing 2
7	RAD51C	DNA repair protein RAD51 homolog 3; Essential for the homologous recombination (HR) pathway of DNA repair. Involved in the homologous recombination repair (HRR) pathway of double-stranded DNA breaks arising during DNA replication or induced by DNA-damaging agents. Part of the RAD21 paralog protein complexes BCDX2 and CX3 which act at different stages of the BRCA1-BRCA2-dependent HR pathway. Upon DNA damage, BCDX2 seems to act downstream of BRCA2 recruitment and upstream of RAD51 recruitment; CX3 seems to act downstream of RAD51 recruitment.
8	STAT4	Signal transducer and activator of transcription 4; Carries out a dual function: signal transduction and activation of transcription. Involved in IL12 signaling; SH2 domain containing
9	TXNIP	Thioredoxin-interacting protein; May act as an oxidative stress mediator by inhibiting thioredoxin activity or by limiting its bioavailability. Interacts with COPS5 and restores COPS5-induced suppression of CDKN1B stability, blocking the COPS5-mediated translocation of CDKN1B from the nucleus to the cytoplasm. Functions as a transcriptional repressor, possibly by acting as a bridge molecule between transcription factors and corepressor complexes, and over- expression will induce G0/G1 cell cycle arrest. Required for the maturation of natural killer cells.

Table 2 provides values based on each one of these properties.

	Protein	Stability Index	Binding Potential	ALiphatic	f.1	CpH5	CpH7	CpH9
1	IL12A	9.44	0.232	15.8	-0.0114	8.23	1.16	-8.11
2	IL12B	8.17	0.418	17.4	-0.1032	3.08	-5.89	-17.35
3	IL12RB1	29.02	0.940	46.1	-0.2037	1.61	-15.58	-38.70
4	IL12RB2	50.28	1.538	85.2	-0.3162	37.11	8.76	-19.21
5	IL23A	6.85	0.132	11.8	-0.0119	5.27	-2.24	-8.61
6	ISOC2	8.87	0.148	16.1	0.0212	6.69	1.80	-3.89
7	RAD51C	11.99	0.442	27.1	-0.0351	11.34	-1.64	-13.04
8	STAT4	41.03	1.287	68.8	-0.2742	20.12	-4.18	-18.70
9	TXNIP	11.12	0.457	24.4	-0.0681	9.33	1.63	-9.46

In the design of molecular scales for comparision, consider (a) crucianiProperties [3] (b) kideraFactors [4] (c) zScales [5] (d) FASGAI [6] (e) tScales [7] (f) VHSE [8] (g) protFP [9] (h) stScales [10] (i) BLOSUM [11] and (j) MSWHIM [1001]. The Kidera Factors are from multivariate analysis to 188 physical properties of the 20 amino acids with dimensionaltiy reduction techniques. A 10-dimensional vector of orthogonal factors where the first four factors are essentially pure physical properties; the remaining six factors are superpositions of several physical properties are presented in Table 4. [1001]

	Names	HBF	SCS	ESP	H	DBP	PSV	FEP	OAR	PKC	SH
1	IL12A	-27	-35	-11	3	-12	-52	4	-53	16	7
2	IL12B	-5	-38	4	31	-26	-67	-23	-38	-27	16
3	IL12RB1	9	-165	-25	22	-85	-142	21	-132	-66	27
4	IL12RB2	15	-172	21	46	-89	-246	-26	-180	-9	-21
5	IL23A	-9	-34	-13	-7	-11	-37	13	-29	-3	1
6	ISOC2	-22	-43	1	-3	-14	-59	18	-34	2	10
7	RAD51C	-61	-56	9	29	-45	-85	24	-25	9	20
8	STAT4	-94	-74	-2	86	-17	-227	-4	-96	-2	-35
9	TXNIP	0	-60	26	29	-8	-79	-9	-28	-18	14

Table 1: Values multipled by 1000 with 0 decimal places. HBF=Helix/bend preference, SCS=Side-chain size, ESP=Extended structure preference, H=Hydrophobicity, DBP=Double-bend preference,PSV=Partial specific volume, FEP=Flat extended preference, OAR=Occurrence in alpha region, PKC=pK-C, and SH=Surrounding hydrophobicity. [1001]

A cluster analysis was performed based on the Kidera Factors from Table 4 and the cluster dendrogram presented in Figure 6.

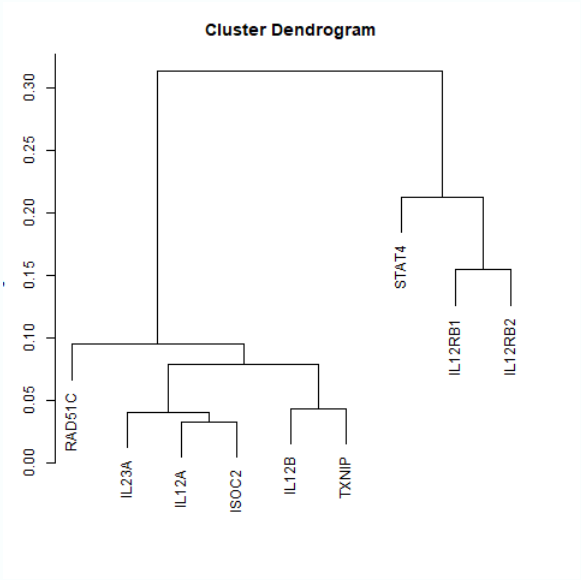

Figure 3: Cluster Analysis of Kidera Factors [1001]

3 Conclusion

Dendritic cells in vivo with microbial extracts created rapid dendritic cells production of IL-12. IL-12 is a signal for CD4 T cells towards a Th1 phenotype. In this brief mathematical biology note, the properties of the 9 molecules in the coexpression network as well as the molecules in the JAK/STAT pathway was presented. The relationship between interleukin and signal transduction was established with respect to the molecular properties with an emphasis on the varied crystals for each of the molecules for further investigation at the atomic and modal values. Kidera factors were also presented and clustered for each of the nine coexpressions for these crystal relationships. Additional studies and separation into categories is needed for feature recognition.

Table 2 has the PMID, Titles and Matching Proteins for the IL-12 Coexpression Network [601]

	PMID	Title	Matching Proteins
1	PMID:22057826	(2012) Association of IFNGR2 gene polymorphisms with pulmonary tuberculosis among the Vietnamese.	IL12B,IL12RB2,STAT4,IL12RB1
2	PMID:32450888	(2020) Interleukin-12 elicits a non-canonical response in B16 melanoma cells to enhance survival.	IL12RB2,STAT4,IL12RB1
3	PMID:31567936	(2019) Associations of IL-12, IL12R polymorphisms and serum IL-12 levels with high-risk human papillomavirus susceptibility in rural women from Luohe, Henan, China.	IL12B,IL12RB2,IL12RB1
4	PMID:30578351	(2018) Human IFN-Gamma immunity to mycobacteria is governed by both IL-12 and IL-23.	IL23A,IL12RB2,STAT4,IL12RB1
5	PMID:26547104	(2016) IL12RB2 Polymorphisms correlate with risk of lung adenocarcinoma.	IL12RB2,STAT4,IL12RB1
6	PMID:25648768	(2015) Jagged-1 signaling suppresses the IL-6 and TGF-Beta treatment-induced Th17 cell differentiation via the reduction of RORGammatIL-17AIL-17FIL-23aIL-12rb1.	IL23A,IL12RB2,STAT4,IL12RB1
7	PMID:26250073	(2015) The immunogenetics of primary biliary cirrhosis: A comprehensive review.	IL23A,IL12RB2,STAT4,IL12RB1
8	PMID:24586521	(2014) The dichotomous pattern of IL-12r and IL-23R expression elucidates the role of IL-12 and IL-23 in inflammation.	IL23A,IL12RB2,STAT4,IL12RB1
9	PMID:25199642	(2014) Identification of IL12RB1 as a novel systemic sclerosis susceptibility locus.	IL12RB2,STAT4,IL12RB1
10	PMID:14707118	(2004) Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris.	IL23A,IL12B,IL12A,IL12RB1
11	PMID:32973967	(2020) SNPs in the interleukin-12 signaling pathway are associated with breast cancer risk in Puerto Rican women.	IL12RB2,STAT4,IL12RB1
12	PMID:31443406	(2019) Immunoregulatory Functions of the IL-12 Family of Cytokines in Antiviral Systems.	IL23A,IL12B,STAT4,IL12RB1
13	PMID:32467824	(2019) Assessing the Role of the Interleukin-12STAT4 Axis in Breast Cancer by a Bioinformatics Approach.	IL12RB2,STAT4,IL12RB1
14	PMID:15778901	(2005) Evaluation of microsatellite markers in association studies: a search for an immune-related susceptibility gene in sarcoidosis.	IL12RB2,STAT4,IL12RB1
15	PMID:24151497	(2013) Association Analysis of IL10, TNF-Alfa, and IL23R-IL12RB2 SNPs with Behcets Disease Risk in Western Algeria.	IL12RB2,STAT4,IL12RB1
16	PMID:24375552	(2014) IL-12Th1 and IL-23Th17 biliary microenvironment in primary biliary cirrhosis: implications for therapy.	IL23A,IL12RB2,IL12RB1
17	PMID:20525402	(2010) Analysis of eight genes modulating interferon gamma and human genetic susceptibility to tuberculosis: a case-control association study.	IL12B,IL12RB2,IL12RB1
18	PMID:26064040	(2015) Powerful Tukeys One Degree-of-Freedom Test for Detecting Gene-Gene and Gene-Environment Interactions.	IL12B,IL12RB2,IL12RB1
19	PMID:23052055	(2013) Production and function of IL-12 in islets and beta cells.	IL23A,IL12RB2,IL12RB1
20	PMID:28804486	(2017) First Association of Interleukin 12 Receptor Beta 1 Deficiency with Sjoegrens Syndrome.	IL12RB2,STAT4,IL12RB1
21	PMID:29017598	(2017) Behcets disease risk association fine-mapped on the IL23R-IL12RB2 intergenic region in Koreans.	IL12RB2,STAT4,IL12RB1
22	PMID:26309811	(2015) In silico model-based inference: an emerging approach for inverse problems in engineering better medicines.	IL12RB2,STAT4,IL12RB1
23	PMID:29123149	(2017) IL-6IL-12 Cytokine Receptor Shuffling of Extra- and Intracellular Domains Reveals Canonical STAT Activation via Synthetic IL-35 and IL-39 Signaling.	IL23A,STAT4,IL12RB1
24	PMID:24610875	(2014) Association study of genes controlling IL-12-dependent IFN-Gamma immunity: STAT4 alleles increase risk of pulmonary tuberculosis in Morocco.	IL12RB2,STAT4,IL12RB1
25	PMID:24648611	(2014) STAT4 gene polymorphisms are associated with susceptibility and ANA status in primary biliary cirrhosis.	IL12RB2,STAT4,IL12RB1
26	PMID:23152861	(2012) IL12RB2 gene is associated with the age of type 1 diabetes onset in Croatian family Trios.	IL12RB2,STAT4,IL12RB1
27	PMID:26242990	(2016) No significant impact of IFN-gamma pathway gene variants on tuberculosis susceptibility in a West African population.	IL12RB2,STAT4,IL12RB1
28	PMID:23291485	(2012) [Analysis of disease-pathway by identifying susceptible genes to primary biliary cirrhosis].	IL12RB2,STAT4,IL12RB1
29	PMID:31516885	(2018) Diagnostic Challenges in the Early Onset of Inflammatory Bowel Disease: A Case Report.	IL23A,IL12RB2,IL12RB1
30	PMID:20531968	(2010) Potential role of ustekinumab in the treatment of chronic plaque psoriasis.	IL23A,STAT4,IL12RB1
31	PMID:26614186	(2015) Potts disease in Moroccan children: clinical features and investigation of the interleukin-12interferon-Gamma pathway.	IL12RB2,STAT4,IL12RB1
32	PMID:31066211	(2019) Hypoxia-induced secretion stimulates breast cancer stem cell regulatory signalling pathways.	IL12RB2,STAT4,IL12RB1
33	PMID:29036979	(2017) [Role of ash2 (absent, small, or homeotic)-like and Jumonji domain-containing protein 3 on histone methylation of interferon-gamma gene and their associations with vascular damage of Kawasaki disease].	IL12RB2,STAT4,IL12RB1
34	PMID:27956825	(2016) Ustekinumab in treatment of Crohns disease: design, development, and potential place in therapy.	IL23A,STAT4,IL12RB1
35	PMID:23559861	(2013) Association of IL-4 gene VNTR variant with deep venous thrombosis in Behcets disease and its effect on ocular involvement.	IL23A,IL12RB2,STAT4
36	PMID:18832727	(2008) Stat4 isoforms differentially regulate inflammation and demyelination in experimental allergic encephalomyelitis.	IL23A,STAT4,IL12RB1
37	PMID:17030948	(2006) IL-23 plays a key role in Helicobacter hepaticus-induced T cell-dependent colitis.	IL23A,STAT4,IL12RB1
38	PMID:27471723	(2015) Current perspective on the role of the interleukin-23interleukin-17 axis in inflammation and disease (chronic arthritis and psoriasis).	IL23A,IL12RB2,IL12RB1
39	PMID:18680750	(2008) The structure of interleukin-23 reveals the molecular basis of p40 subunit sharing with interleukin-12.	IL12B,STAT4,IL12RB1
40	PMID:28003381	(2017) IL-23 Inhibits Melanoma Development by Augmenting DNA Repair and Modulating T Cell Subpopulations.	IL23A,IL12RB2,IL12RB1
41	PMID:26082838	(2015) Enhancing the discovery and development of immunotherapies for cancer using quantitative and systems pharmacology: Interleukin-12 as a case study.	IL12RB2,STAT4,IL12RB1
42	PMID:21052539	(2011) IL-12 and related cytokines: function and regulatory implications in Candida albicans infection.	IL23A,IL12RB2,IL12RB1
43	PMID:20458705	(2010) A novel immunoregulatory function for IL-23: Inhibition of IL-12-dependent IFN-Gamma production.	IL23A,STAT4,IL12RB1
44	PMID:23481504	(2013) CD11c+ alveolar macrophages are a source of IL-23 during lipopolysaccharide-induced acute lung injury.	IL23A,STAT4,IL12RB1
45	PMID:26500048	(2015) Trans-presentation of IL-15 modulates STAT5 activation and Bcl-6 expression in TH1 cells.	IL12RB2,STAT4,IL12RB1
46	PMID:21687641	(2011) Primary biliary cirrhosis: family stories.	IL12RB2,STAT4,IL12RB1
47	PMID:20716621	(2010) Genetic polymorphisms in adaptive immunity genes and childhood acute lymphoblastic leukemia.	IL12RB2,STAT4,IL12RB1
48	PMID:26317679	(2015) Genetics of systemic sclerosis: recent advances.	IL12RB2,STAT4,IL12RB1
49	PMID:27747495	(2015) Ustekinumab in the Treatment of Psoriasis and Psoriatic Arthritis.	IL23A,STAT4,IL12RB1
50	PMID:23864330	(2013) IL-12RBeta1 deficiency: mutation update and description of the IL12RB1 variation database.	IL12RB2,STAT4,IL12RB1
51	PMID:26000122	(2012) Towards systemic sclerosis and away from primary biliary cirrhosis: the case of PTPN22.	IL12RB2,STAT4,IL12RB1
52	PMID:20638243	(2010) Update on the genetics and genomics of PBC.	IL12RB2,STAT4,IL12RB1
53	PMID:24890729	(2014) IL-1Beta promotes the differentiation of polyfunctional human CCR6+CXCR3+ Th117 cells that are specific for pathogenic and commensal microbes.	IL12RB2,STAT4,IL12RB1
54	PMID:27142093	(2016) Sjoegrens syndrome-associated microRNAs in CD14(+) monocytes unveils targeted TGFBeta signaling.	IL12RB2,STAT4,IL12RB1
55	PMID:26440629	(2015) Genetic Variations in Pattern Recognition Receptor Loci Are Associated with Anti-TNF Response in Patients with Rheumatoid Arthritis.	IL12RB2,STAT4,IL12RB1
56	PMID:25552913	(2015) The expression levels of transcription factors T-bet, GATA-3, RORGammat and FOXP3 in peripheral blood lymphocyte (PBL) of patients with liver cancer and their significance.	IL23A,STAT4,IL12RB1
57	PMID:22213332	(2012) Interferon regulatory factor modulation underlies the bystander suppression of malaria antigen-driven IL-12 and IFN-Gamma in filaria-malaria co-infection.	IL23A,IL12RB2,IL12RB1
58	PMID:19119024	(2009) Late developmental plasticity in the T helper 17 lineage.	IL23A,IL12RB2,IL12RB1
59	PMID:30992245	(2019) Circulating growthdifferentiation factor 15 is associated with human CD56bright natural killer cell dysfunction and nosocomial infection in severe systemic inflammation.	IL12RB2,STAT4,IL12RB1
60	PMID:21278737	(2011) Fate mapping of IL-17-producing T cells in inflammatory responses.	IL23A,IL12RB2,IL12RB1
61	PMID:25986483	(2015) A candidate gene study reveals association between a variant of the Peroxisome Proliferator-Activated Receptor Gamma (PPAR-Gamma) gene and systemic sclerosis.	IL12RB2,STAT4,IL12RB1
62	PMID:24490076	(2013) Skewed Helper T-Cell Responses to IL-12 Family Cytokines Produced by Antigen-Presenting Cells and the Genetic Background in Behcets Disease.	IL12RB2,STAT4,IL12RB1
63	PMID:24426833	(2014) Induction of Wnt-inducible signaling protein-1 correlates with invasive breast cancer oncogenesis and reduced type 1 cell-mediated cytotoxic immunity: a retrospective study.	IL12RB2,STAT4,IL12RB1
64	PMID:21093318	(2010) Regulated expression of nuclear receptor RORGammat confers distinct functional fates to NK cell receptor-expressing RORGammat(+) innate lymphocytes.	IL23A,IL12RB2,IL12RB1
65	PMID:21249183	(2011) Proteins encoded in genomic regions associated with immune-mediated disease physically interact and suggest underlying biology.	IL12RB2,STAT4,IL12RB1
66	PMID:18654571	(2008) Genome-wide association studies: a new window into immune-mediated diseases.	IL12B,STAT4,IL12RB1
67	PMID:25798064	(2015) Signal transducer and activator of transcription 4 in liver diseases.	IL12RB2,STAT4,IL12RB1

4 Bibliography

[1A] Wikipedia contributors. "Lymphocyte." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia, 12 Dec. 2021. Web. 3 Jan. 2022.

[1B] Wikipedia contributors. "Adaptive immune system." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia, 12 Nov. 2021. Web. 3 Jan. 2022.

[1C] Wikipedia contributors. "Dendritic cell." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia, 16 Dec. 2021. Web. 3 Jan. 2022.

[2] H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne. (2000) The Protein Data Bank Nucleic Acids Research, 28: 235-242.

[3] Cruciani, G., Baroni, M., Carosati, E., Clementi, M., Valigi, R., and Clementi, S. (2004) Peptide studies by means of principal properties of amino acids derived from MIF descriptors. J. Chemom. 18, 146-155.

[4] Kidera, A., Konishi, Y., Oka, M., Ooi, T., and Scheraga, H. A. (1985). Statistical analysis of the physical properties of the 20 naturally occurring amino acids. Journal of Protein Chemistry, 4(1), 23-55.

[5] Sandberg M, Eriksson L, Jonsson J, Sjostrom M, Wold S: New chemical descriptors relevant for the design of biologically active peptides. A multivariate characterization of 87 amino acids. J Med Chem 1998, 41:2481-2491.

[6] Liang, G., and Li, Z. (2007). Factor analysis scale of generalized amino acid information as the source of a new set of descriptors for elucidating the structure and activity relationships of cationic antimicrobial peptides. Molecular Informatics, 26(6), 754-763.

[7] Tian F, Zhou P, Li Z: T-scale as a novel vector of topological descriptors for amino acids and its application in QSARs of peptides. J Mol Struct. 2007, 830: 106-115. 10.1016/j.molstruc.2006.07.004.

[8] van Westen, G. J., Swier, R. F., Wegner, J. K., IJzerman, A. P., van Vlijmen, H. W., and Bender, A. (2013). Benchmarking of protein descriptor sets in proteochemometric modeling (part 1): comparative study of 13 amino acid descriptor sets. Journal of cheminformatics, 5(1), 41.

[9] Yang, L., Shu, M., Ma, K., Mei, H., Jiang, Y., and Li, Z. (2010). ST-scale as a novel amino acid descriptor and its application in QSAM of peptides and analogues. Amino acids, 38(3), 805-816.

[10] Georgiev, A. G. (2009). Interpretable numerical descriptors of amino acid space. Journal of Computational Biology, 16(5), 703-723.

[11] Zaliani, A., and Gancia, E. (1999). MS-WHIM scores for amino acids: a new 3D-description for peptide QSAR and QSPR studies. Journal of chemical information and computer sciences, 39(3), 525-533.

[400] Kanehisa, Furumichi, M., Tanabe, M., Sato, Y., and Morishima, K.; KEGG: new perspectives on genomes, pathways, diseases and drugs. Nucleic Acids Res. 45, D353-D361 (2017).

[401] Kanehisa, M., Sato, Y., Kawashima, M., Furumichi, M., and Tanabe, M.; KEGG as a reference resource for gene and protein annotation. Nucleic Acids Res. 44, D457-D462 (2016).

[402] Kanehisa, M. and Goto, S.; KEGG: Kyoto Encyclopedia of Genes and Genomes. Nucleic Acids Res. 28, 27-30 (2000).

[403] Petri, V., Jayaraman, P., Tutaj, M., Hayman, G. T., Smith, J. R., De Pons, J., … Jacob, H. J. (2014). The pathway ontology – updates and applications. Journal of Biomedical Semantics, 5, 7. http://doi.org/10.1186/2041-1480-5-7

[601] Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, Simonovic M, Doncheva NT, Morris JH, Bork P, Jensen LJ, von Mering C. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 2019 Jan; 47:D607-613.PubMed

[800] Kim, Sunghwan et al. “PubChem in 2021: new data content and improved web interfaces.” Nucleic Acids Res. vol. 49,D1 (2021): D1388-D1395. doi:10.1093/nar/gkaa971

[1000] R Core Team. “R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.” (2015). URL https://www.R-project.org/.

[1001] Osorio, D., Rondon-Villarreal, P. and Torres, R. Peptides: A package for data mining of antimicrobial peptides. The R Journal. 7(1), 4-14 (2015).

[1002] Grant, B.J. et al. (2006) Bioinformatics 22, 2695–2696.