A clinical overview of immunologic diseases

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Why Immunology?

All disease is immunology*!

*if you ignore some metabolic diseases.

- You'd be dead without it
  Medical science would be nowhere without it
  It's so complicated no one can really claim to understand it all
- Common ways of thinking between immunologists and statisticians

What makes an immunologist?

General science

BSc. biomedical sciences

General immunology

MSc. Immunology

Specialise in Immunology
(or at least a tiny bit of it!)

PhD. Immunology
of HIV and NK cells

Clinical trial laboratory scientist

Research supported by SSAT

R&D SYSTEMS a bio-techne brand

Periodic Table of Human Cytokine and Chemokine Families

Key (Additional Information in Notes Section): Molecule Number (1*) — Structure (see Table 2) — Native MW (kDa) Mature Form Unless Noted in Parentheses (17–18) — ORF % AA Sequence Identity (Human to Mouse, unless indicated) (60) — Abbreviated Name (IL-1α) — Full Name (Interleukin-1 alpha) — Alternate Name (IL-1F1) — Receptors (IL-1 RI; IL-1 RAcP; IL-1 RII)

Note: Information shown in gray is still inconclusive in the literature.

Table 1. Families

I	β-Trefoil SF/IL-1 Family	VI	4 Helix Bundle SF/gp130 Users	XI	Tumor Necrosis Factor SF
II	4 Helix Bundle SF/Rγc Family	VII	4 Helix Bundle SF/Non-gp130 Users	XII	C Chemokine Family
III	4 Helix Bundle SF/IFN-λ Family	VIII	4 Helix Bundle SF/Rβc Family	XIII	CX3C Chemokine Family
IV	4 Helix Bundle SF/IFN α/β Family	IX	4 Helix Bundle SF/IL-10 Family	XIV	CC Chemokine Family
V	4 Helix Bundle SF/RTK Users	X	Cysteine-Knot SF/IL-17 Family	XV	CXC Chemokine Family

Note: There is no association between families and color.

Table 2. Structure Key

Monomer	Heterodimer
Homodimer	Heterotrimer
Homotrimer	Secreted
Homotetramer	Intracellular
Homooligomer	Solubilized
Single Pass (Type I) Transmembrane	
Single Pass (Type 2) Transmembrane	

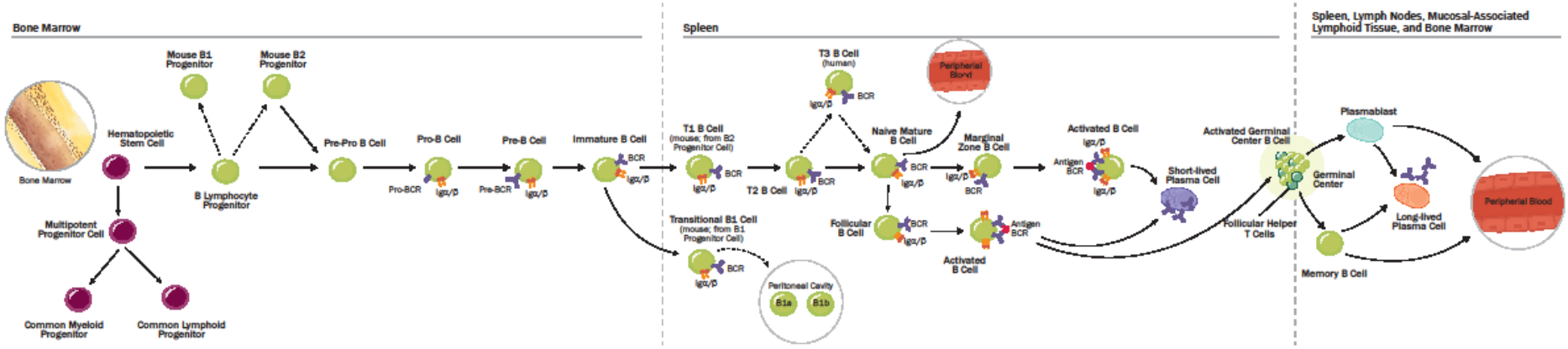
No.	Family	MW (kDa)	ORF % AA Identity	Abbreviated Name	Full Name	Alternate Name	Receptors
1*	I	17–18	60	IL-1α	Interleukin-1 alpha	IL-1F1	IL-1 RI; IL-1 RAcP; IL-1 RII
2*	XV	10–11	53	CXCL7	Chemokine (C-X-C motif) ligand 7	NAP-2; LDGF; MDGF; SCYB7; PPBP	CXCR1; CXCR2
3*	I	17–18	78	IL-1β	Interleukin-1 beta	IL-1F2	IL-1 RI; IL-1 RAcP; IL-1 RII
4*	I/II	25–27(Pro); 15–18(M)	(–)	IL-37	Interleukin-37	IL-1F7; IL-1H4	IL-18 Rα; IL-18BP; SIGIRR
5*	XI/XII/XIII	17–20(sol); 30–36(TM)	80	TNFSF13	Tumor Necrosis Factor Superfamily 13	APRIL; CD256; TALL-2	TACI; BCMA
6	XIV	8–9	35	CCL1	Chemokine (C-C motif) ligand 1	I-309; SCYA1; TCA3(mouse)	CCR8
7*	XIV	8–9	51	CCL8	Chemokine (C-C motif) ligand 8	MCP-2; SCYA8; HC14	CCR1; CCR2b; CCR3; CCR5
8*	XIV	8–12	75	CCL19	Chemokine (C-C motif) ligand 19	MIP-3β; EBI1-L/ELC; Exodus-3; SCYA19	CCR7; CCX-CKR; CCRL1; CCRL2
9*	XIV/XV	10–11	57	CCL27	Chemokine (C-C motif) ligand 27	CTACK; Eskine; ALP; SCYA27	CCR10
10*	XV	8–9	70(Porcine IL-8)	CXCL8	Chemokine (C-X-C motif) ligand 8	IL-8; GCP-1; NAP-1; MDNCF	CXCR1; CXCR2
11*	I	22–24	77	IL-1ra	Interleukin-1 Receptor Antagonist	IL-1F3; IL-1RN; IRAP	IL-1 RI; IL-1 RII
12	I/II	17–18	82	IL-38	Interleukin-38	IL-1F10; IL-1HY2; FIL1θ	IL-1 Rrp2
13*	XI/XII/XIII	26–27(sol); 29–32(TM)	76	TNFSF14	Tumor Necrosis Factor Superfamily 14	LIGHT; HVEM Ligand	HVEM; LT-βR; DcR3
14*	XIV	8–13	58	CCL2	Chemokine (C-C motif) ligand 2	MCP-1; SCYA2; MCAF; JE (mouse)	CCR1; CCR2b; CCR3; DARC; CCBP2
15*	XIV	13	58	CCL11	Chemokine (C-C motif) ligand 11	Eotaxin; SCYA11	CCR3; CCR5; CXCR3; DARC; D6
16*	XIV	8–9	67	CCL20	Chemokine (C-C motif) ligand 20	MIP-3α; LARC; Exodus-1; SCYA20	CCR6
17	XIV/XV	8–9	64	CCL28	Chemokine (C-C motif) ligand 28	MEC; SCYA28	CCR3; CCR10
18*	XV	13–14	68	CXCL9	Chemokine (C-X-C motif) ligand 9	MIG; SCYB9	CXCR3; CXCR3b; CCR3
19*	I	17–18	66	IL-18	Interleukin-18	IL-1F4; IFN-γ Inducing Factor; IL-1γ	IL-18 Rα; IL-18 Rβ/AcPL
20*	I/II	15–19	56	IL-2	Interleukin-2	TCGF	IL-2 Rα; IL-2 Rβ; Common gamma chain (γc); HSPGs
21*	II/III	22–23	37	TSLP	Thymic Stromal Lymphopoietin		TSLP R; IL-7 Rα
22*	IV/V	17–22	57–63	IFN-α	Interferon-alpha		IFN-α/β R1; IFN-α/β R2
23*	V/VI	38–45	79(ECD)	SCF	Stem Cell Factor	c-kit Ligand; KL	CD117/c-kit
24*	VI	22–25	82	CNTF	Ciliary Neurotrophic Factor		apoE; CNTF Rα; gp130; LIF Rα; IL-6 Rα
25*	VII	17–26	66	GH	Growth Hormone		Growth Hormone R; Prolactin R
26	VII/VIII	15–16	85	Leptin		OB	Leptin R; Siglec-6
27*	IX	18–19	73	IL-10	Interleukin-10		IL-10 Rα; IL-10 Rβ
28*	X	20–22; 15(non-CHO)	61	IL-17A	Interleukin-17A	IL-17; CTLA-8	IL-17 RA; IL-17 RC; IL-17 RD/Sef
29*	XI	19–25	75	TNFSF1	Tumor Necrosis Factor Superfamily 1	TNF-β; LT-α; Lymphotoxin; TNF-B	TNF RI; TNF RII; HVEM; LT-β R; TAJ
30	XI	29–33	56	TNFSF7	Tumor Necrosis Factor Superfamily 7	CD27 Ligand; CD70	CD27
31*	XI/XII/XIII	25–28(sol); 32–37(TM)	66	TNFSF15	Tumor Necrosis Factor Superfamily 15	VEGI; TL1A	DR3; DcR3
32*	XIV	7–8	71	CCL3	Chemokine (C-C motif) ligand 3	MIP-1α; LD78α; SCYA3	CCR1; CCR4; CCR5; CCBP2
33*	XIV	8–9	67(Canine CCL13)	CCL13	Chemokine (C-C motif) ligand 13	MCP-4; CKβ10; NCC-1; SCYA13	CCR2b; CCR3; CCR5; CXCR3; DARC
34*	XIV	20–22	70	CCL21	Chemokine (C-C motif) ligand 21	6Ckine; Exodus-2; SLC; SCYA21	CCR7; CCRL1; CXCR3 (mouse)
35*	XIV/XV	6–7	64(Mouse KC) 67(Rat CINC-1)	CXCL1	Chemokine (C-X-C motif) ligand 1	Gro-α; MGSA; SCYB1	CXCR2; DARC
36*	XV	10–14	70	CXCL10	Chemokine (C-X-C motif) ligand 10	IP-10; SCYB10	CXCR3; CXCR3b; CCR3
37*	I	18–20	52	IL-33	Interleukin-33	IL-1F11; NF-HEV; C9orf26	ST2; IL-1 RAcP
38*	I/II	15–19	40	IL-4	Interleukin-4	BSF-1	IL-4 Rα; Common gamma chain (γc); IL-13 Rα1
39*	II/III	13–14	60	IL-13	Interleukin-13		IL-13 Rα1; IL-13 Rα2; IL-4 Rα
40	IV/V	23–25	67	IFN-β	Interferon-beta	Fibroblast-IFN	IFN-α/β R1; IFN-α/β R2
41*	V/VI	34–36	71	FLT-3 Ligand	Fms-like Tyrosine Kinase 3 Ligand		FLT-3
42	VI	22–23	79	CT-1	Cardiotrophin-1	CTF-1	LIF Rα; gp130
43*	VII	23–25	60	PRL	Prolactin		Prolactin R
44*	VII/VIII	24–33	29	IL-31	Interleukin-31		IL-31 RA; OSM Rβ
45*	IX	25–32	69	IL-19	Interleukin-19	ZMDA-1; NG.1	IL-20 Rα; IL-20 Rβ
46	X	18–24	90	IL-17B	Interleukin-17B	IL-20; ZCYTO7	IL-17 RB
47*	XI	16–18(sol); 26–27(TM)	77	TNFSF2	Tumor Necrosis Factor Superfamily 2	TNF-α; Cachectin; TNF-A	TNF RI; TNF RII
48	XI	32–42	70	TNFSF8	Tumor Necrosis Factor Superfamily 8	CD30 Ligand; CD153	CD30
49*	XI/XII/XIII	14–15(sol); 20–22(TM)	53	TNFSF18	Tumor Necrosis Factor Superfamily 18	GITR Ligand; TL6; AITR Ligand	GITR
50*	XIV	7–8	95(Human CCL3)	CCL3L1	Chemokine (C-C motif) ligand 3L1	LD78β; SCYA3L1	CCR1; CCR3; CCR5
51*	XIV	8–10	61(Porcine CCL14)	CCL14	Chemokine (C-C motif) ligand 14	HCC-1; SCYA14	CCR1; CCR3; CCR5
52*	XIV	7–8	64	CCL22	Chemokine (C-C motif) ligand 22	MDC; STCP-1; SCYA22	CCR4; DARC; CCBP2
53	XIV/XV	7–9	66(Mouse MIP-2) 60(Rat CINC-3)	CXCL2	Chemokine (C-X-C motif) ligand 2	MIP-2α; Gro-β; SCYB2	CXCR2; DARC
54*	XV	8–9	66	CXCL11	Chemokine (C-X-C motif) ligand 11	ITAC; IP-9; H174; SCYB11	CXCR7; CXCR3; CXCR3alt; CXCR3b; CCR3; CCR5; DARC
55*	I	16–18	54	IL-36α	Interleukin-36 alpha	IL-1F6; IL-36E	IL-1 Rrp2; IL-1 RAcP
56*	I/II	16–17	63	IL-7	Interleukin-7		IL-7 Rα; Common gamma chain (γc)
57*	II/III	19–21	68	IL-28A	Interleukin-28A	IFN-λ2; ZCYTO20	IL-28 Rα; IL-10 Rβ
58*	IV/V	24–25	(–)	IFN-Ω	Interferon-omega	IFN-α-II1	IFN-α/β R1; IFN-α/β R2
59*	V/VI	36–39	68	IL-34	Interleukin-34	C16orf77	M-CSF R; PTP-ζ
60*	VI	21–22	87*	Neuropoietin		CT-2; CTF-2	CNTF Rα; gp130
61	VII	22–24	24	CSH1	Chorionic Somatomammotropin Hormone 1	Placental Lactogen-1	Prolactin R
62*	VII/VIII	35–37	58	IL-12/IL-35 p35	Interleukin-12/Interleukin-35 p35	CLMF35; NKSF; IL-12 A/α	IL-12 Rβ1; IL-12 Rβ2
63*	IX	17–18	77	IL-20	Interleukin-20	ZCYTO10	IL-20 Rα; IL-20 Rβ; IL-22 Rα1
64*	X	20*	79	IL-17C	Interleukin-17C	CX2	IL-17 RA; IL-17 RE
65*	XI	31–34	76	TNFSF3	Tumor Necrosis Factor Superfamily 3	LT-β; TNF-C	LT-β R
66*	XI	27–30	30	TNFSF9	Tumor Necrosis Factor Superfamily 9	4-1BB Ligand; CD137 Ligand	CD137/4-1BB; TLR4; TNF RI
67*	XI/XII/XIII	18–23(sol); 33–38(TM)	60	TNFSF20	Tumor Necrosis Factor Superfamily 20	BAFF; TALL-1; BLyS	BAFF-R; BCMA; TACI
68*	XIV	7–8	77	CCL4	Chemokine (C-C motif) ligand 4	MIP-1β; LAG-1; SCYA4; ACT-2	CCR1; CCR2b; CCR5; CCBP2
69*	XIV	8–10	38(Mouse CCL9)	CCL15	Chemokine (C-C motif) ligand 15	MIP-1δ; MIP-5; HCC-2; SCYA15	CCR1; CCR3; DARC
70*	XIV	11–13	(–)	CCL23	Chemokine (C-C motif) ligand 23	MPIF-1; CKβ8; MIP-3; SCYA23	CCR3; FPRL-1; FPR-2
71	XIV/XV	6–7	58(Mouse DCIP-1) 56(Rat CINC-2)	CXCL3	Chemokine (C-X-C motif) ligand 3	MIP-2β; Gro-γ; SCYB3	CXCR2; DARC
72*	XV	8–14	97(SDF-1β)	CXCL12	Chemokine (C-X-C motif) ligand 12	SDF-1; PBSF	CXCR4; CXCR7
73*	I	20–24	38	IL-36β	Interleukin-36 beta	IL-1F8; IL-1H2	IL-1 Rrp2; IL-1 RAcP
74*	I/II	20–30	57	IL-9	Interleukin-9	TCGF p40	IL-9 R; Common gamma chain (γc)
75	II/III	19–21	65	IL-28B	Interleukin-28B	IFN-λ3; IL-28C; ZCYTO22	IL-28 Rα; IL-10 Rβ
76*	IV/V	20*	55	IFN-ε	Interferon-epsilon		IFN-α/β R1; IFN-α/β R2
77*	V/VI	32–45	78	LIF	Leukemia Inhibitory Factor	HILDA; D Factor	gp130; LIF Rα; IGF-II R
78*	VI	23–30	47	IL-6	Interleukin-6	BSF-2; IFN-β2	IL-6 Rα; gp130
79	VII	22–24	25	CSH2	Chorionic Somatomammotropin Hormone 2	Placental Lactogen-2	Prolactin R
80*	VII/VIII	15–25	29	IL-3	Interleukin-3	MCGF; Multi-CSF	IL-3 Rα; Common beta chain (βc)
81*	IX	23–29	81	IL-22	Interleukin-22	IL-TIF; ZCYTO18	IL-22 Rα1; IL-10 Rβ
82*	X	25*	86	IL-17D	Interleukin-17D		Unknown Receptor
83*	XI	29–30(sol); 32–34(TM)	42	TNFSF4	Tumor Necrosis Factor Superfamily 4	OX40 Ligand; TXGP1; CD252	OX40/CD134
84*	XI	30–34	61	TNFSF10	Tumor Necrosis Factor Superfamily 10	TRAIL; APO-2 Ligand	TRAIL R1–4; Osteoprotegerin
85*	XI/XII/XIII	12–19	60	XCL1	Chemokine (C motif) ligand 1	Lymphotactin; SCM-1α; Lymphotaxin; SCYC1; ATAC	XCR1
86*	XIV	7–8	97(Human CCL4)	CCL4L1	Chemokine (C-C motif) ligand 4L1		CCR1; CCR2b; CCR3; CCR5
87*	XIV	8–11	61*	CCL16	Chemokine (C-C motif) ligand 16	LEC; HCC-4; SCYA16	H4; CCR1; CCR2; CCR5; CCR8
88	XIV	10–11	60	CCL24	Chemokine (C-C motif) ligand 24	Eotaxin-2; MPIF-2; SCYA24	CCR3
89*	XIV/XV	6–8	73	CXCL4	Chemokine (C-X-C motif) ligand 4	PF-4; Oncostatin-A; SCYB4	CXCR3b
90*	XV	9–10	43	CXCL13	Chemokine (C-X-C motif) ligand 13	BCA-1; BLC; SCYB13; Angie	CXCR5
91*	I	18–20	48	IL-36γ	Interleukin-36 gamma	IL-1F9; IL-1H1; IL-1E	IL-1 Rrp2; IL-1 RAcP
92*	I/II	15–18	73	IL-15	Interleukin-15		IL-15 Rα; IL-2 Rβ; Common gamma chain (γc)
93*	II/III	17–34	(–)	IL-29	Interleukin-29	IFN-λ1; ZCYTO21	IL-28 Rα; IL-10 Rβ
94*	IV/V	25–26	35	IFN-κ	Interferon-kappa		IFN-α/β R1; IFN-α/β R2
95*	V/VI	32–33	47	OSM	Oncostatin M		LIF Rα; gp130; OSM Rβ
96*	VI	20–23	88	IL-11	Interleukin-11	AGIF	gp130; IL-11 Rα
97*	VII	19–21	75	IL-23 p19	Interleukin-23 p19	IL-23α; p19	IL-23 R; IL-12 Rβ1
98*	VII/VIII	20–21	71	IL-5	Interleukin-5	EDF	IL-5 Rα; Common beta chain (βc)
99*	IX	26–38	70	IL-24	Interleukin-24	MDA-7	IL-20 Rα; IL-20 Rβ; IL-22 Rα1
100	X	18–24	80	IL-17E	Interleukin-17E	IL-25	IL-17 RA; IL-17 RB
101*	XI	16–20(sol); 33–40(TM)	77	TNFSF5	Tumor Necrosis Factor Superfamily 5	CD40 Ligand; TRAP; CD154	CD40
102*	XI	40(sol); 54–56(TM)	85	TNFSF11	Tumor Necrosis Factor Superfamily 11	RANK Ligand/TRANCE; OPG Ligand; ODF	RANK; Osteoprotegerin
103*	XI/XII/XIII	12–19*	98(XCL1)	XCL2	Chemokine (C motif) ligand 1	SCM-1β; SCYC2	XCR1
104*	XIV	7–9	82	CCL5	Chemokine (C-C motif) ligand 5	RANTES; SIS5; SCYA5	GPR75; CCR1; CCR3; CCR5; DARC; CCBP2
105	XIV	8	65	CCL17	Chemokine (C-C motif) ligand 17	TARC; SCYA17	CCR4; DARC; CCBP2
106*	XIV	13–17	40	CCL25	Chemokine (C-C motif) ligand 25	TECK; SCYA25; CKβ15	CCR9; ACKR4; CCRL1
107*	XIV/XV	7–8	96(CXCL4)	CXCL4v1	Chemokine (C-X-C motif) ligand 4v1	PF-4v1; SCYB4v1	CXCR3b
108	XV	9–10	97	CXCL14	Chemokine (C-X-C motif) ligand 14	BRAK; MIP-2γ; SCYB14	CXCR4; Unknown Receptor
109	I	17–18	90	IL-36Ra	Interleukin-36 Receptor Antagonist	IL-1F5; IL-1HY1; IL-1L1	IL-1 Rrp2
110*	I/II	15–17	58	IL-21	Interleukin-21	Za11	IL-21 R; Common gamma chain (γc)
111*	II/III	20–22	73	IFN-λ4	Interferon-lambda 4		IL-28 Rα; IL-10 Rβ
112*	IV/V	35–45; 150–220	70	M-CSF	Macrophage Colony-Stimulating Factor	CSF-1	M-CSF R
113*	V/VI	22–24	96	CLC	Cardiotrophin-like Cytokine	CLCF1; BSF-3; NNT-1	CNTF Rα; CLF1; gp130; LIF Rα
114*	VI	28–30	72	IL-27 p28	Interleukin-27 p28	IL-30; IL-27α; p28	IL-27 Rα/WSX-1; gp130; IL-6 Rα
115*	VII	19–21	74	G-CSF	Granulocyte Colony-Stimulating Factor	C17orf33; CSF-3	G-CSF R
116	VII/VIII	16–32	53	GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor	CSF-2	GM-CSF Rα; Common beta chain (βc)
117*	IX	19–21	(–)	IL-26	Interleukin-26	AK155	IL-20 Rα; IL-10 Rβ
118*	X	20–24	56	IL-17F	Interleukin-17F	ML-1	IL-17 RA; IL-17 RC
119*	XI	23–26(sol); 39–40(TM)	77	TNFSF6	Tumor Necrosis Factor Superfamily 6	Fas Ligand; CD178	DcR3; Fas/CD95
120*	XI	15–18(sol); 32–35(TM)	89	TNFSF12	Tumor Necrosis Factor Superfamily 12	TWEAK; APO-3 Ligand; DRG3L	TWEAK R
121	XI/XII/XIII	85–95(sol); 95–100(TM)	60(ECD)	CX_3CL1	Chemokine (C-X3-C motif) ligand	Fractalkine; Neurotactin; SCYD1	CX_3CR1
122	XIV	8–9	61	CCL7	Chemokine (C-C motif) ligand 7	MCP-3; SCYA7; NC-28	CCR1; CCR2b; CCR3; CCR5; DARC
123*	XIV	8–9	(–)	CCL18	Chemokine (C-C motif) ligand 18	PARC; DC-CK1; MIP-4; SCYA18	CCR3; DARC; PITPNM3/NIR1; GAG
124	XIV	8–10	49	CCL26	Chemokine (C-C motif) ligand 26	IMAC; Eotaxin-3; MIP-4α; SCYA26	CCR1; CCR3; CCR5; CX_3CR1
125*	XIV/XV	7–11	55*	CXCL5	Chemokine (C-X-C motif) ligand 5	ENA-78; SCYB5	CXCR2; DARC
126*	XV	31–35(sol); 48–58(TM)	40(ECD); 50(Chemokine)	CXCL16	Chemokine (C-X-C motif) ligand 16	SR-PSOX; SCYB16	CXCR6; OxLDL
127*	XIV/XV	6–8	67(Guinea pig GCP-2)	CXCL6	Chemokine (C-X-C motif) ligand 6	GCP-2; SCYB6	CXCR1; CXCR2
128*	XV	10–12(Pro); 7–8(M)	71	CXCL17	Chemokine (C-X-C motif) ligand 17	VCC-1; DMC	CXCR8/GPR35
129*		45–47	95	IL-14	Interleukin-14	α-Taxilin	Unknown Receptor
130*		20–22	86	IL-16	Interleukin-16	LCF	CD4
131*		15–31	(–)	IL-32	Interleukin-32	TAIF; NK4	PR3; PKCε; PKCδ; STAT3; Paxillin

* Notes

1. IL-1α: IL-1α is synthesized as a 31–34 kDa glycosylated, phosphorylated and myristoylated proform that shows bioactivity, both intracellularly and extracellularly. Proteolysis generates a soluble C-terminal form that is 159 amino acids in length.
2. CXCL7: In this poster, CXCL7 is equivalent to NAP-2. LDGF, PBP, βTG and NAP-2 are all cleavage products of a 14–18 kDa, 128 amino acid (aa) precursor generally referred to as LDGF. LDGF is not secreted but processed internally. The largest isoform is PBP at 12 kDa (aa 35–128), followed by CTAP-III (aa 44–124) and βTG (aa 48–128) at 11–12 kDa. NAP-2 (aa 55/56/59–128, or 59–124) is the smallest at 10–11 kDa. NAP-2 heterodimerizes with CXCL12.
3. IL-1β: The 31 kDa proform is proteolytically cleaved to generate a secreted, 153 amino acid (aa) mature form. The % aa sequence identity refers to the mature form.
4. IL-37: IL-37 contains a cleavable, 45 amino acid (aa) N-terminal propeptide. There are multiple isoform variants. Isoform "b" is the standard form (aa 46–218) that is both secreted and reported to undergo translocation into the nucleus. It apparently possesses anti-inflammatory properties. Other isoforms show amino acid substitutions or deletions within the first 62 aa. There does not appear to be a rodent ortholog to human IL-37.
5. TNFSF13: APRIL is a transmembrane protein that undergoes cleavage in the Golgi to generate soluble APRIL. There are at least four alternative splice forms of APRIL.
7. CCL8: CCL8 heterodimerizes with CCL2 and CCL11 and appears to inhibit CCL7 activity.
8. CCL19: CCL19 heterodimerizes with CCL22.
9. CCL27: In rodent, a 42 amino acid (aa) substitution for aa 1–24 generates a non-secreted, nuclear target isoform.
10. CXCL8: Although definitive IL-8 contains amino acids (aa) 23–99, the most prominent isoform is N-truncated IL-8 (aa 28–99). There is one isoform variant that contains an 11 aa substitution for aa 92–99. IL-8 as a monomer is highly active on CXCR1 while homodimeric IL-8 is highly active on CXCR2. CXCL8 heterodimerizes with CXCL4.
11. IL-1ra: There are at least four splice variants; one contains a signal sequence for extracellular secretion, while three others lack a signal sequence and are retained intracellularly.
13. TNFSF14: Proteolysis generates a soluble circulating isoform. A Glu214Lys transition results in increased bioactivity due to a reduction of LIGHT binding to DcR3.
14. CCL2: CCL2 heterodimerizes with CCL8, CCL11, CCL13, CCL5, and CXCL4. There is one potential splice form that shows a Met substitution for amino acids 65–99. Homooligomerization may be necessary for full bioactivity.
15. CCL11: CCL11 is O-glycosylated and heterodimerizes with CCL2 and CCL8.
16. CCL20: CCL20 undergoes cleavage to generate 13, 52, and 55 amino acid isoforms that lack activity. CCL20 has antimicrobial activity.
18. CXCL9: CXCL9 heterodimerizes with CXCL12.
19. IL-18: IL-18 undergoes non-signal sequence mediated secretion. It contains a 36 amino acid (aa), 6–7 kDa N-terminal prosequence that is cleaved to generate a mature molecule. There is at least one splice form that shows an absence of aa 27–30. This isoform is a 24 kDa proteolysis-resistant cytokine that may homodimerize.
20. IL-2: Mouse IL-2 has strain-specific variants that contain multiple Gln residues. Although considered to be a circulating monomer, in mouse, IL-2 is also reported to dimerize and exert a cytotoxic function.
21. TSLP: TSLP has at least two isoforms; one represents the standard long form of 131 amino acids (aa), while the other utilizes an alternate start site, generating an antimicrobial short form that is 9 kDa and 62 aa long (aa 97–159).
22. IFN-α: IFN-α is actually the product of 13 IFN-α genes located on Chr9p21 in human. The mature products are either 165 or 166 amino acids (aa) in length, and share approximately 80% aa sequence identity with each other. Only two IFN-α products are glycosylated.
23. SCF: Human SCF is a type I transmembrane protein that undergoes proteolysis to generate a 31 kDa, 165 amino acid soluble form. Alternative splicing gives rise to a typically cell-associated 32 kDa isoform.
24. CNTF: CNTF can signal through both an IL-6R:gp130:LIFR complex and a CNTFRα:gp130:LIFR complex.
25. GH: There are two genes for GH; one in pituitary and one in placenta. The mature placental and pituitary products share 93% amino acid sequence identity. GH has multiple isoforms that range from 17 kDa to ≈ 90 kDa, the larger forms being intracellular in nature.
27. IL-10: IL-10 is expressed by a novel subset of CD27+ B cells termed B10 cells. Notably, human IL-10 is active on mouse cells while mouse IL-10 is inactive on human cells.
28. IL-17A: IL-17(A) is secreted as both a glycosylated and nonglycosylated protein. It heterodimerizes with IL-17F.
29. TNFSF1: Secreted LT-α is known to be part of a trimeric complex, either as part of a homotrimer, or a heterotrimer with LT-β in either a 1:2 or 2:1 stoichiometry. The heterotrimer is membrane-bound due to the transmembrane nature of LT-β.
31. TNFSF15: TL1A is expressed by multiple cell types and exhibits unique characteristics. It is found on both dendritic cells and T cells, but cleaved only on the dendritic cell surface, and it binds to two receptors DR3 and DcR3 where DR3 ligation promotes T cell expansion, and DcR3 ligation opposes T cell expansion.
32. CCL3: CCL3 heterodimerizes with CCL4. It may also be cleaved at the N-terminus.
33. CCL13: There are two isoforms that show a five and seven amino acid truncation at the amino terminus, resulting in altered bioactivity. CCL13/MCP-4 heterodimerizes with CCL2, CCL8, and CCL21. There is no rodent counterpart to human CCL13.
34. CCL21: CCL21 heterodimerizes with BCA-1.
35. CXCL1: CXCL1 heterodimer formation is postulated to occur with CXCL4, CXCL7, and CXCL8.
36. CXCL10: CXCL10 heterodimerizes with CCL22.
37. IL-33: IL-33 has two fundamental forms: a 30–31 kDa, 270 amino acid (aa) proprotein that contains an NLS (aa 1–65), and a series of proteolytically-processed mature forms that are secreted (aa 95–109–270). One splice variant shows a deletion of aa 72–113 and is constitutively active.
38. IL-4: IL-4 has one splice variant (IL-4δ2) that shows an absence of amino acids 46–61. This isoform is secreted by neither Th1 nor Th2 T cell subsets, but is associated with the onset of asthma.
39. IL-13: IL-13 is nonglycosylated.
41. FLT-3L: FLT-3 Ligand is synthesized as an integral membrane protein that may undergo proteolysis to yield a 29–30 kDa soluble form.
43. PRL: PRL undergoes cleavage, generating 15–22 kDa fragments. The molecule is variably glycosylated and undergoes phosphorylation.
44. IL-31: IL-31 appears to play a major role in itch sensation by binding to keratinocytes and inducing the release of β endorphin, which subsequently binds to μ-opioid receptors on cutaneous nerve endings.
45. IL-19: There are two extended isoform variants relative to standard IL-19; one contains a 38 amino acid (aa) extension, while a second contains an 86 aa substitution for aa 127–177.
47. TNFSF2: Membrane-bound TNF-α is proteolytically cleaved to generate soluble, trimeric 55 kDa TNF-α.
49. TNFSF18: GITR Ligand in human is unusual in that it exists in a monomer-dimer-trimer equilibrium in solution. Mouse GITR Ligand is different in that it is principally a dimer in solution. Neither human or mouse GITR Ligand are active on the other's cells.
50. CCL3L1: The CCL3L1 gene represents a duplication of CCL3 and may exist as two or more copies in any one individual. CD26 cleavage of CCL3L1 generates an isoform that has a very high affinity for CCR1 and CCR5. Two additional CCL3L genes also exist (CCL3L2 and CCL3L3), with CCL3L3 encoding a chemokine identical in amino acid (aa) sequence to CCL3L1, and CCL3L2 encoding a shortened molecule that may not act as a chemokine. CCL3L1 and CCL3 share 95% aa sequence identity.
51. CCL14: CCL14 circulates at 1–80 nM in plasma. There are two isoforms; one is the standard, short form that is 93 amino acids (aa) in length, and a second is a 108 aa long form. Truncation by eight aa at the N-terminus may generate a circulating monomer. There is no rodent counterpart to human CCL14.
52. CCL22: CCL22 shows strong broad-spectrum antimicrobial activity. N-terminal processing eliminated bioactivity. CCL22 heterodimerizes with CXCL10, CCL19, and CCL7.
54. CXCL11: CXCL11 undergoes both N- and C-terminal processing. N-terminal processing reduces bioactivity while C-terminal truncation abolishes HSPG binding.
55. IL-36α: This molecule is a short, five amino acid N-terminal prosegment.
56. IL-7: IL-7 has two short isoform variants, one that shows a deletion of amino acids (aa) 77–120 (which was used to calculate the accompanying aa sequence identity), and another that utilizes an alternate start site at Met52 that is accompanied by a deletion of aa 77–138.
57. IL-28A: Although the IFN-λs can be secreted by a wide variety of cells following viral infection, the target cells for the IFN-λs appear to be epithelium and hepatocytes.
58. IFN-Ω: There is no direct rodent counterpart to human IFN-Ω.
59. IL-34: IL-34 and M-CSF share the same receptor (M-CSF R/c-fms). Although both drive monocytes into an immunoregulatory macrophage phenotype (IL-10hi IL-12lo), IL-34-induced macrophages are high in CCL24/Eotaxin-2 and low in CCL2/MCP-1 production, while M-CSF promotes the opposite pattern.
60. Neuropoietin: Although the gene for Neuropoietin in human is degenerate, it is functional in chimpanzee whose amino acid (aa) sequence was used for the aa sequence identity calculation.
62. IL-12/IL-35 p35: IL-12/IL-35 p35 heterodimerizes with p40 to generate IL-12, and with EBI3 to generate IL-35. IL-12 p35 is glycosylated and this modification is required for secretion.
63. IL-20: IL-20 does not appear to be glycosylated, and there is at least one isoform variant that shows a deletion of amino acids 127–151.
64. IL-17C: IL-17C is unusual in that it is secreted by, and acts on, epithelium. The molecular weight listed is the predicted value.
65. TNFSF3: LT-β forms a heterotrimeric complex with LT-α, contributing either one or two subunits to the complex. LT-β is transmembrane and thus the heterotrimeric complex does not circulate. Mouse LT-β is 66 amino acids longer than human LT-β due to the unusual transformation of an intron into an exon in the mouse gene.
66. TNFSF9: Relative to other TNFSF members, 4-1BB Ligand possesses a unique extended, three-blade propeller-shaped trimeric structure. This may generate reverse signaling accompanied by a very close approximation of ligand and receptor-expressing cells.
67. TNFSF20: BAFF is a monocyte/macrophage product that has regulatory effects on B cells. BAFF has three isoform variants; there is a full-length form that undergoes cleavage to generate a soluble form, a transmembrane-bound short form that heterodimerizes with the full-length form, and an even shorter isoform that may act intracellularly.
68. CCL4: CCL4 heterodimerizes with CCL3, and these two molecules share 67% amino acid (aa) sequence identity. CCL4 may also be represented by two genes, LAG-1 and Act-2 that differ only by a Gly-to-Ser transition at position 70 in their aa sequence.
69. CCL15: N-terminal cleavage between Asn45-Ser46 results in enhanced activity on CCR1. The stated amino acid sequence identity of 38% is based on a human CCL15 mouse CCL9 alignment.
70. CCL23: An alternate splice form shows an 18 amino acid substitution for Arg46. There is no known rodent ortholog.
72. CXCL12: CXCL12 has seven isoforms, six of which are named (SDF-1α, β, γ, δ, ε, φ). The SDF-1α ORF is 89 amino acids (aa) in length, while the other splice variant ORFs range from 90–140 aa. All six named isoforms share the same initial 88 amino acids while the seventh "unnamed" variant shows a 65 aa substitution for aa 29–93 of SDF-1β. CXCL12 heterodimerizes with CCL14, CXCL7, and CXCL9.
73. IL-36β: IL-36β contains a four amino acid (aa) N-terminal prosegment, and exhibits one isoform variant that contains a 70 aa substitution for aa 88–164.
74. IL-9: IL-9 appears to be the product of at least three distinct T cell subsets: Th2, Th17 and Th9. It is noted for its ability to promote mast cell function and activate megakaryocyte progenitor cells.
76. IFN-ε: The molecule weight listed refers to IFN-ε in bacteria.
77. LIF: LIF has at least two isoforms; one is secreted and exhibits both phosphorylation and mannose-rich glycosylation, while the other is a 17 kDa and is retained intracellularly.
78. IL-6: IL-6 is both phosphorylated and sulfated, and shows O- and N-linked glycosylation. The level of glycosylation is correlated with the [illegible]
80. IL-3: In contrast to human IL-3, mouse IL-3 can potentially use two βc-like chains, an AIC2B chain (or βc) and a unique AIC2A chain that actually binds IL-3.
81. IL-22: IL-22 receptors are found on epithelial cells, not immune cells. IL-22 is also reported to exist in a membrane-associated state.
82. IL-17D: The molecular weight listed refers to IL-17D in E. coli.
83. TNFSF4: OX40 Ligand is an essential mediator of proper APC T cell stimulation. Soluble OX40 Ligand circulates at 100 ng/mL. One isoform variant potentially codes for a soluble molecule.
84. TNFSF10: In human, there are three reported short isoform variants of 8 kDa, 11 kDa and 11 kDa. Splicing does not appear to occur in mouse.
85. XCL1: XCL1 is an NK cell/CD8+ T cell product that chemoattracts neutrophils. It exists as both a monomer and homodimer, with the monomer serving as a ligand for XCR1 and the dimer as a "ligand" for HSPG. XCL1 contains O-linked glycosylation, a modification that almost doubles its molecular weight on SDS-PAGE.
86. CCL4L1: CCL4L1 is one of two CCL4-associated paralogs (similar structure; different function) genes, the other being CCL4L2. The number of CCL4L1 genes/individual varies, and at least one splice form has been identified. CCL4L2 is five amino acids (aa) longer than CCL4L1 and has at least seven splice variants. CCL4 and CCL4L1 share 97% aa sequence identity.
87. CCL16: CCL16 does not appear in mouse due to mutations in its LEC gene. CCL16 undergoes proteolysis at both the N- and C-termini, generating short forms of 70, 78, and 93 amino acids (aa). CCL16 has been reported to bind to the H4 histamine receptor (Kd = 17 nM). The cited aa sequence identity uses the rodent aa sequence.
89. CXCL4: CXCL4 heterodimerizes with CXCL8, CCL5, CXCL1, CCL2, and CXCL12, and it apparently binds to FGF-2 and VEGF-A.
90. CXCL13: CXCL13 forms a heterodimer with CCL21 and CCL19. It also acts as a chemoattractant for B cells but not PMNs, T cells, or monocytes.
91. IL-36γ: IL-36γ contains a potential 17 amino acid (aa) N-terminal propeptide. One splice variant contains an Ile substitution for aa 19–64.
92. IL-15: IL-15 apparently circulates as a non-disulfide-linked heterodimer with proteolytically-cleaved IL-15Rα. It also has a 13–14 kDa alternative splice variant that contains a 10 amino acid (aa) substitution for aa 1–37. This form is either retained intracellularly or secreted as a complex with IL-15Rα.
93. IL-29: The mouse IL-29 gene appears to be nonfunctional.
94. IFN-κ: IFN-κ seems to have a restricted expression pattern, being limited to keratinocytes, dendritic cells, and monocytes. It is poorly secreted, preferentially acting on the cell surface or intracellularly.
95. OSM: OSM is secreted as either a 196 amino acid (aa) mature molecule of 32 kDa, or one of two 34–36 kDa proprecursors that exhibit reduced bioactivity. Human and rat OSM activate two receptor complexes, one comprised of gp130:LIF R and another generated by gp130:OSM R. Mouse OSM, by contrast, only acts through the gp130:OSM R complex.
96. IL-11: IL-11 is not glycosylated, a condition that regulates overall IL-11 bioactivity.
97. IL-23 p19: IL-23 p19 heterodimerizes with p40 to generate IL-23. Like IL-12 p35, p19 requires an association with p40 for efficient secretion. The p35:p40 (IL-12) cytokine acts on naive T cells, while p19:p40 (IL-23) acts on memory T cells.
98. IL-5: Notably, IL-5 is both N- and O-glycosylated. While N-linked carbohydrate stabilizes the molecule, O-linked carbohydrate reduces bioactivity.
99. IL-24: IL-24 has at least six alternative splice forms; all are shorter than the standard form, and all lack the same amino acid (aa) sequence (aa 102–184). IL-24 is glycosylated, a modification that is essential for bioactivity.
101. TNFSF5: CD40 Ligand is both membrane-bound and soluble, with the soluble form generated by proteolysis of CD40 Ligand embedded in intracellular vesicle membranes.
102. TNFSF11: RANK Ligand has three isoforms; one is full-length at 317 amino acids (aa) and undergoes cleavage to generate a 40 kDa soluble form; a second isoform is missing aa 1–73 and is by definition soluble; the third form is missing aa 1–47 and thus is transmembrane but without a cytoplasmic domain.
103. XCL2: XCL2 is likely the result of a duplication of the XCL1 gene. Relative to XCL1, it binds HSPG with very high affinity and has a markedly different expression pattern. Both mouse and rat lack this gene duplication. The molecular weight listed is based on XCL1.
104. CCL5: CCL5 contains O-linked glycosylation and undergoes N-terminal processing. One potential isoform variant has been reported that contains a 91 amino acid (aa) substitution for aa 64–91. Heterodimers with CXCL4 and CCL2 have been reported, and CCL5 homooligomers are likely to form in the presence of HSPG.
106. CCL25: Two alternative splice forms exist; one shows an absence of Ala109 while a second contains a 20 amino acid (aa) substitution for aa 65–150, a change that creates an antagonist to the full-length form.
107. CXCL4v1: CXCL4v1 is the result of a gene duplication of CXCL4, and it exhibits 30x greater antiangiogenic activity that CXCL4.
110. IL-21: IL-21 has one 15 kDa isoform variant that contains an 11 amino acid (aa) substitution for aa 140–155 and appears to be retained (in part) on the cell surface.
111. IFN-λ4: The majority of individuals appear to have an inactivated IFN-λ4 gene. This inactivation seems to allow for the successful clearance of hepatitis C virus.
112. M-CSF: The M-CSF gene contains an alternative ORF that encodes a 25 amino acid (aa) peptide. Notably, this is actually recognized by CD8+ T cells which typically only recognize peptides of 9–11 aa length. There are three M-CSF isoforms, all are transmembrane with mature lengths of 522, 406, and 224 aa, respectively. Proteolytic cleavage of the two longest isoforms generates soluble M-CSF; the smallest isoform is always membrane-bound.
113. CLC: CLC is only secreted when noncovalently complexed to either CNTF Rα or CLF1/CRLF1, two soluble receptor-like molecules. This requirement for heterodimerization is a characteristic shared with the cytokines IL-23 p19, IL-27 p28, and IL-12 p35.
114. IL-27 p28: IL-27 p28 either noncovalently heterodimerizes with EBI3 to form (secreted) IL-27, or forms a heterodimer with CLF1/CRLF1 that acts through the IL-6R:gp130 receptor complex. In mouse, IL-27 p28 is secreted as a monomer that apparently signals through the IL-6R:gp130 complex.
115. G-CSF: There are two alternative splice forms of G-CSF relative to the standard form; one shows a deletion of amino acids (aa) 66–68, while another shows a deletion of aa 69–104.
117. IL-26: There is no mouse ortholog for human IL-26.
118. IL-17F: IL-17F heterodimerizes with IL-17A, generating a 36–40 kDa product with reduced bioactivity.
119. TNFSF6: Fas Ligand is expressed as either a transmembrane protein or soluble polypeptide. In mouse, an alternative splice form creates soluble Fas Ligand; in human, soluble Fas Ligand formation only occurs following proteolysis. This generates both a soluble form and an intracellular fragment that serves as a transcriptional repressor. One human isoform variant generates a truncated transmembrane molecule.
120. TNFSF12: Due to the hybridization of TWEAK and APRIL transcripts, a mRNA containing TWEAK cytoplasmic and transmembrane domains, plus the APRIL extracellular domain is known to exist. This creates a 48 kDa hybrid molecule. TWEAK may also heterotrimerize with VGSD.
123. CCL18: CCL18 was formed by the fusion of two MIP-1α-like genes. It is known to circulate at levels between 30–1000 ng/mL, and shows strong antimicrobial activity. No true rodent counterpart to CCL18 is known.
125. CXCL5: Increased bioactivity may result from proteolysis at the N-terminus, while deamination/citrullination of an N-terminal Arg results in decreased bioactivity. The percent identity shown excludes the mouse CXCL5/LIX C-terminal extension.
126. CXCL16: CXCL16 exists in both a transmembrane and soluble form. Both forms bind to CXCR6 and act as either an adhesion molecule or chemoattractant.
127. CXCL6: CXCL6 is expressed by both macrophages and epithelium. It is chemotactic for neutrophils and bactericidal against both Gram positive and Gram negative bacteria.
128. CXCL17: CXCL17 is a mucosally-derived chemokine that attracts macrophages and exhibits antimicrobial activity against E. coli. CXCL17 may contain a prodomain encompassing amino acids 22–63 that is cleaved to generate mature CXCL17.
129. IL-14: IL-14, now known as α-Taxilin, was originally thought to be a unique high molecular weight interleukin involved in B cell growth (HMW-BCGF). Subsequent studies have redefined "IL-14", and it is now considered to be an isoform variant of α-Taxilin that includes amino acids 136–546. This α-Taxilin isoform is secreted by follicular dendritic cells and activated T cells, is found in the circulation, and possibly promotes B cell Ig isotype switching.
130. IL-16: Lymphocyte chemoattractant factor (LCF), previously known as IL-16, is derived from a large precursor protein that undergoes Caspase-3 cleavage to generate a bioactive, 121 amino acid LCF C-terminal fragment. Expressed by both CD4+ and CD8+ T cells, the actual precursor to LCF is itself a splice variant of an even larger precursor protein.
131. IL-32: The molecule termed IL-32 is a highly complex protein that appears to be primate-specific. There are at least nine alternative splice forms, the longest being called IL-32γ at 234 amino acids in length. Most "IL-32" isoforms are expressed intracellularly where they bind to multiple transcriptional regulators and other IL-32 isoforms. IL-32γ may exist as a transmembrane molecule that undergoes cleavage by PR3, releasing a 22–23 kDa bioactive soluble molecule.

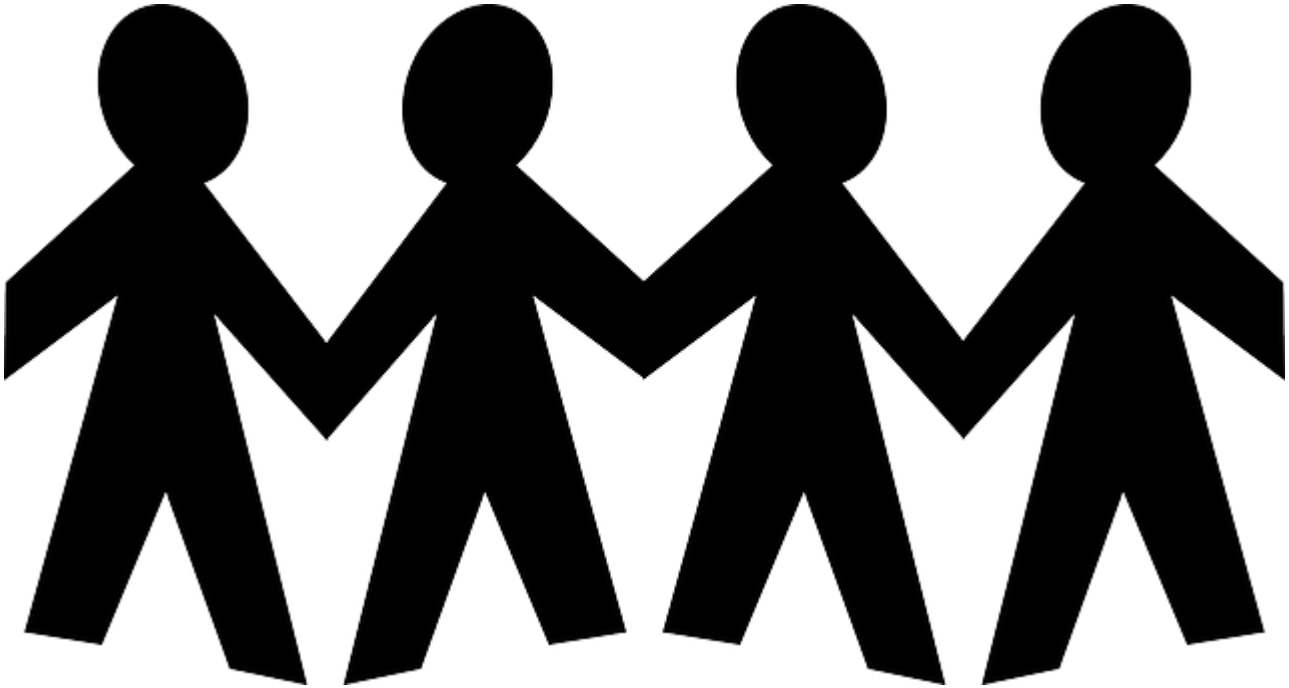
R&D SYSTEMS a biotechne brand

B Cell Development

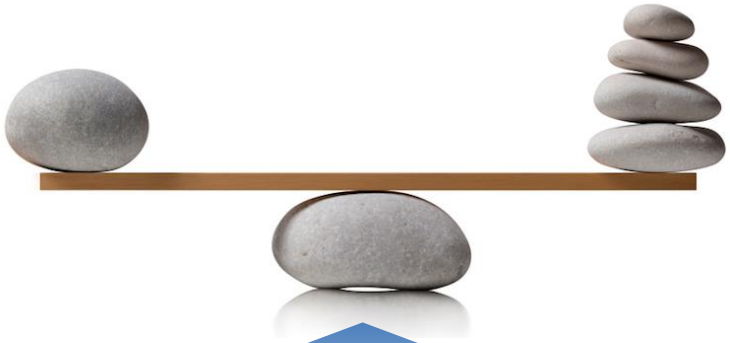


Stages of Development	Common Lymphoid Progenitor	B Lymphocyte Progenitor	Mouse B1 Progenitor	Mouse B2 Progenitor	Pre-Pro B Cell	Pro-B Cell	Pre-B Cell	Immature B Cell	B1a Cell (from mouse B1 progenitor cell)	B1b Cell (from mouse B1 progenitor cell)	Transitional B Cell	Mouse T1 B Cell (from mouse B2 progenitor cell)	Mouse T2 B Cell (from mouse B2 progenitor cell)	Marginal Zone B Cell	Follicular B Cell	Activated Germinal Center B Cell	Memory B Cell	Plasmablast	Plasma Cell
Human Markers																			
Positive markers	CD10/Neprilysin CD34 Pax5	CD10/Neprilysin CD34 Pax5			CD10/Neprilysin CD34 CD38 Pax5	CD10/Neprilysin CD19 CD20/MS4A1 CD24 CD34 CD38 C1q R1/CD93 IL-3 R IL-7 Rα Pax5	CD10/Neprilysin CD19 CD20/MS4A1 CD24 CD38 C1q R1/CD93 IL-3 R IL-4 Rα IL-7 Rα Pax5	CD10/Neprilysin CD19 CD20/MS4A1 CD21 CD24 CD38 CD40 C1q R1/CD93 IL-4 Rα			CD5 CD19 CD20/MS4A1 CD21 CD23/FcεRII CD24 CD38 C1q R1/CD93 TACI			CD1c CD19 CD20/MS4A1 CD21 CD27 FCRL3/FcRH3 TACI	CD19 CD20/MS4A1 CD21 CD22/Siglec-2 CD23/FcεRII CXCR5 MHC class II TACI	CD19 CD20/MS4A1 CD27 CD38 CD40 CD83 MHC class II TACI	CD19 CD20/MS4A1 CD21 CD27$^{int/+}$ TACI	BCMA CD27^{hi} CD38 C1q R1/CD93	BCMA BLIMP1 CD27^{hi} CD38^{hi} Syndecan-1/CD138 CXCR4
Negative markers					CD117/c-kit^{low}	CD117/c-kit^{low}	CD117/c-kit CD34	CD117/c-kit CD27 IL-7 Rα			CD10/Neprilysin^{low} CD27				CD10/Neprilysin CD24^{low} CD27 CD38^{low}		C1q R1/CD93	CD19^{low} Syndecan-1/CD138$^{-/low}$	CD19^{low} CD20/MS4A1$^{-/low}$ MHC class II^{low}
Mouse Markers																			
Positive markers	IL-7 Rα Flt-3/Flk-2	Ly6D IL-7 Rα Flt-3/Flk-2	CD19 C1q R1/CD93	B220/CD45 R	B220/CD45 R CD43 C1q R1/CD93 CXCR4 Flt-3/Flk-2 IL-7 Rα	B220/CD45 R CD19 CD24 CD43 IL-7 Rα	B220/CD45 R CD19 CD24 IL-7 Rα	B220/CD45 R CD19 CD24 C1q R1/CD93 IgM	CD1d^{int} CD5 CD19^{low} CD43	CD1d^{int} CD19^{low} CD43		B220/CD45 R CD19 CD24 C1q R1/CD93 IgM	B220/CD45 R CD19 CD24 C1q R1/CD93 IgM IgD	B220/CD45 R CD1d CD19^{int} CD21^{hi} IgM^{hi}	B220/CD45 R CD1d^{int} CD19^{int} CD23/FcεRII CXCR5 IgD^{lo}	B220/CD45 R CD19 CD40 MHC class II	B220/CD45 R CD19 CD21 CD27$^{int/+}$ CD40 MHC class II	CD19 CD27^{hi} CD38 Syndecan-1/CD138	BLIMP1 CD27^{hi} CXCR4^{lo} Syndecan-1/CD138
Negative markers	Lin (CD3, CD4, CD8, Gr-1/Ly-6G, Integrin αM/CD11b, TER-119) CD117/c-kit Sca-1/Ly6 Ly6D	Lin (CD3, CD4, CD8, Gr-1/Ly-6G, Integrin αM/CD11b, TER-119) CD117/c-kit Sca-1/Ly6	Lin (CD3, CD4, CD8, Gr-1/Ly-6G, Integrin αM/CD11b, TER-119) B220/CD45 R^{low}	Lin (CD3, CD4, CD8, Gr-1/Ly-6G, Integrin αM/CD11b, TER-119) CD19 C1q R1/CD93	Lin (CD3, Gr-1/Ly-6G, Integrin αM/CD11b, TER-119) CD19 CD24^{low} CD117/c-kit IgM	Lin (CD3, Gr-1/Ly-6G, Integrin αM/CD11b, TER-119) CD117/c-kit^{low} IgM	Lin (CD3, Gr-1/Ly-6G, Integrin αM/CD11b, TER-119) CD43 IgM	CD23/FcεRII CD43 IgD	CD23/FcεRII	CD5 CD23/FcεRII		CD43 IgD^{low}	CD43	CD23/FcεRII CD43 C1q R1/CD93 IgD^{low}	CD21^{low} CD43 IgM^{low}			B220/CD45 R^{low}	B220/CD45 R^{low} CD19 CD38^{low} MHC class II$^{-/low}$

A brief demonstration of the ‘human’ immune system



A healthy immune response is balanced



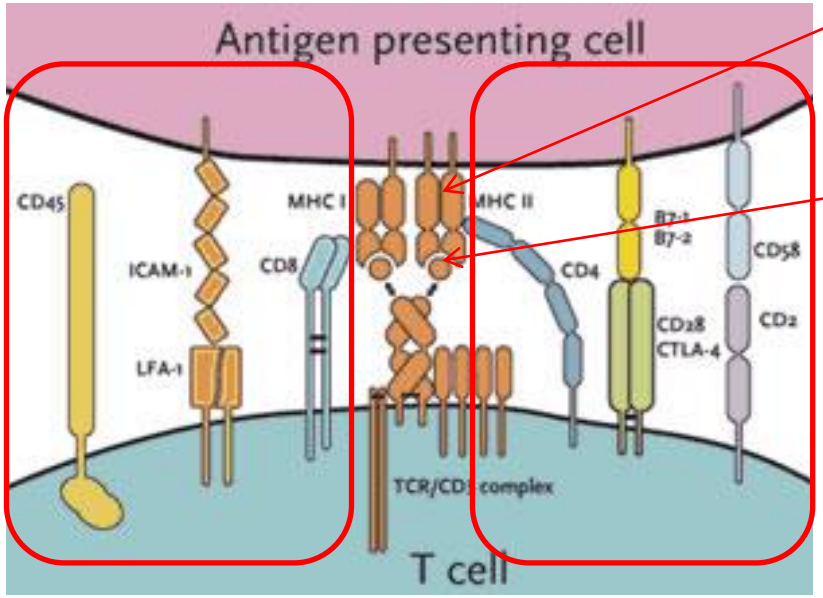
Imbalance can lead to localised or systemic dysfunction.
Loss of response, excessive response, response to the wrong thing

Activation & inhibition

- Immune system is governed by inhibitory and activatory signals
- Co-stimulation required for activation and fine tuning of immune response

Shows antigen to T cells
Can be 'professional APC'
e.g. Macrophage, dendritic cell, B cell
Or not, e.g. any other cell

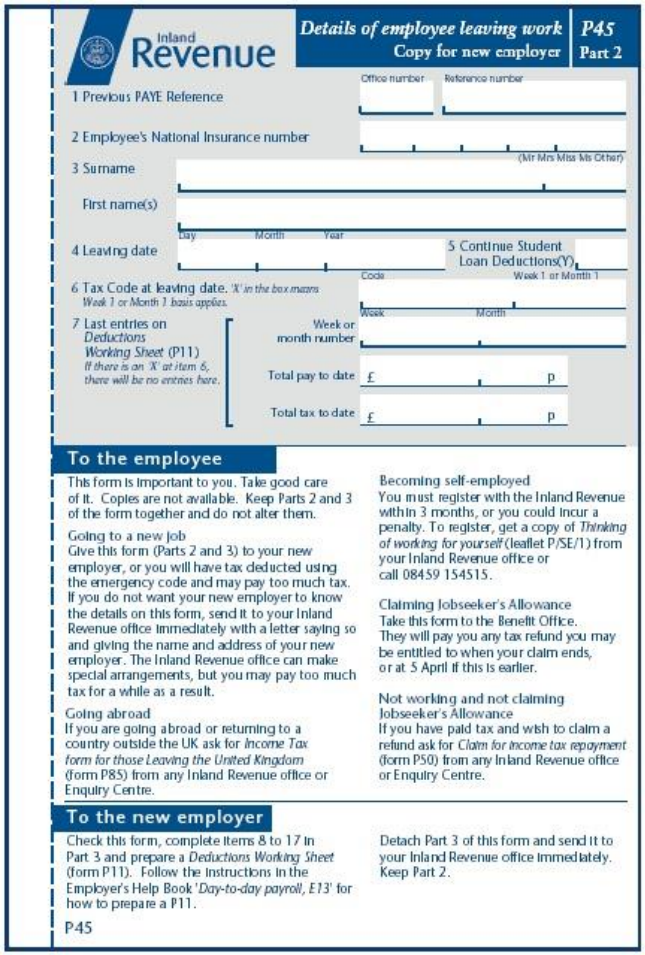
T cell recognises and reacts to antigen.
Responses tuned by costimulatory molecules



MHC I/II present host or foreign antigen
self vs. non self
Antigen

Result can be tolerance (self usually), release of cytokines, killing of APC, activation of APC – apoptosis, cytokine release, etc.

Redundancy



Inland Revenue

Details of employee leaving work | **P45 Part 2**
Copy for new employer

Office number | Reference number

1 Previous PAYE Reference

2 Employee's National Insurance number

(Mr Mrs Miss Ms Other)

3 Surname

First name(s)

4 Leaving date — Day Month Year

5 Continue Student Loan Deductions(Y)

6 Tax Code at leaving date. *'X' in the box means Week 1 or Month 1 basis applies.* — Code | Week 1 or Month 1

7 Last entries on *Deductions Working Sheet* (P11) *If there is an 'X' at item 6, there will be no entries here.* — Week or month number | Total pay to date £ p | Total tax to date £ p

To the employee

This form is important to you. Take good care of it. Copies are not available. Keep Parts 2 and 3 of the form together and do not alter them.

Going to a new job
Give this form (Parts 2 and 3) to your new employer, or you will have tax deducted using the emergency code and may pay too much tax. If you do not want your new employer to know the details on this form, send it to your Inland Revenue office immediately with a letter saying so and giving the name and address of your new employer. The Inland Revenue office can make special arrangements, but you may pay too much tax for a while as a result.

Going abroad
If you are going abroad or returning to a country outside the UK ask for *Income Tax form for those Leaving the United Kingdom* (form P85) from any Inland Revenue office or Enquiry Centre.

Becoming self-employed
You must register with the Inland Revenue within 3 months, or you could incur a penalty. To register, get a copy of *Thinking of working for yourself* (leaflet P/SE/1) from your Inland Revenue office or call 08459 154515.

Claiming Jobseeker's Allowance
Take this form to the Benefit Office. They will pay you any tax refund you may be entitled to when your claim ends, or at 5 April if this is earlier.

Not working and not claiming Jobseeker's Allowance
If you have paid tax and wish to claim a refund ask for *Claim for income tax repayment* (form P50) from any Inland Revenue office or Enquiry Centre.

To the new employer

Check this form, complete items 8 to 17 in Part 3 and prepare a *Deductions Working Sheet* (form P11). Follow the instructions in the Employer's Help Book '*Day-to-day payroll, E13*' for how to prepare a P11.

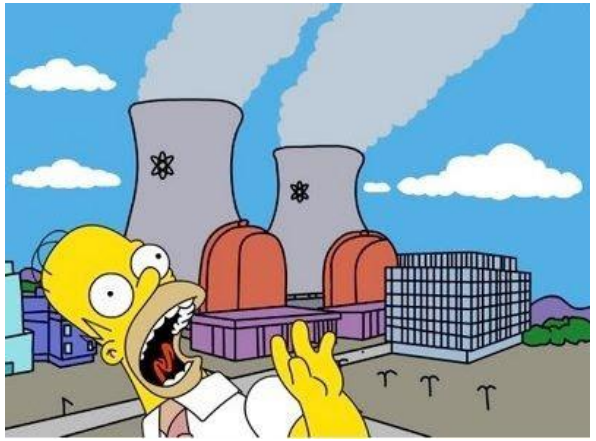
Detach Part 3 of this form and send it to your Inland Revenue office immediately. Keep Part 2.

P45

Large number of redundant pathways in the immune system

Backup systems for backup systems

in case things fail



Infections

- The reason the immune system exists!
- Most infections are dealt with without you knowing – innate immune system
  - Macrophages, monocytes, basophils, eosinophils, neutrophils, natural killer cells…
  - Complement, various serum proteins e.g. major basic protein, opsins
  - Very effective!
    especially in crocodiles

If the innate immune system doesn't kill it…

- The adaptive immune system joins in
  - T cells – cellular immune response.
    T helper cells ($CD4^+$) – modulate other cells
    Cytotoxic T cells ($CD8^+$) – kill other cells
  - B cells – humoral immune response
    Generate antibodies – IgG, IgM, IgD, IgE, IgA
    Present antigen and help modulate other cells
- Allows immune memory
  Swift response to pathogen rechallenge

Pathogens are crafty too

- Keep changing
  - Influenza
    Antigenic drift (subtle changes between seasons)
    Antigenic switch (big changes – new to immune system)
- Hide or remain dormant
  - Mycobacteria hide in macrophages and downregulate MHC so they can't be seen
  - hide in immune privileged site e.g. toxoplasmosis, JC virus, prions?
- Target immune system
  - HIV targets $CD4^+$ T cells – overstimulates immune system to the point of exhaustion leading to immunocompromise (AIDS)

Cancer

- Immunosenescence
  The aging immune system is less able to perform surveillance
- Increased risk of infections
- Mutant host cells not identified and controlled
- Tumour cells hide by upregulating inhibitory markers and/or downregulating activatory markers
  Quick to adapt and escape control

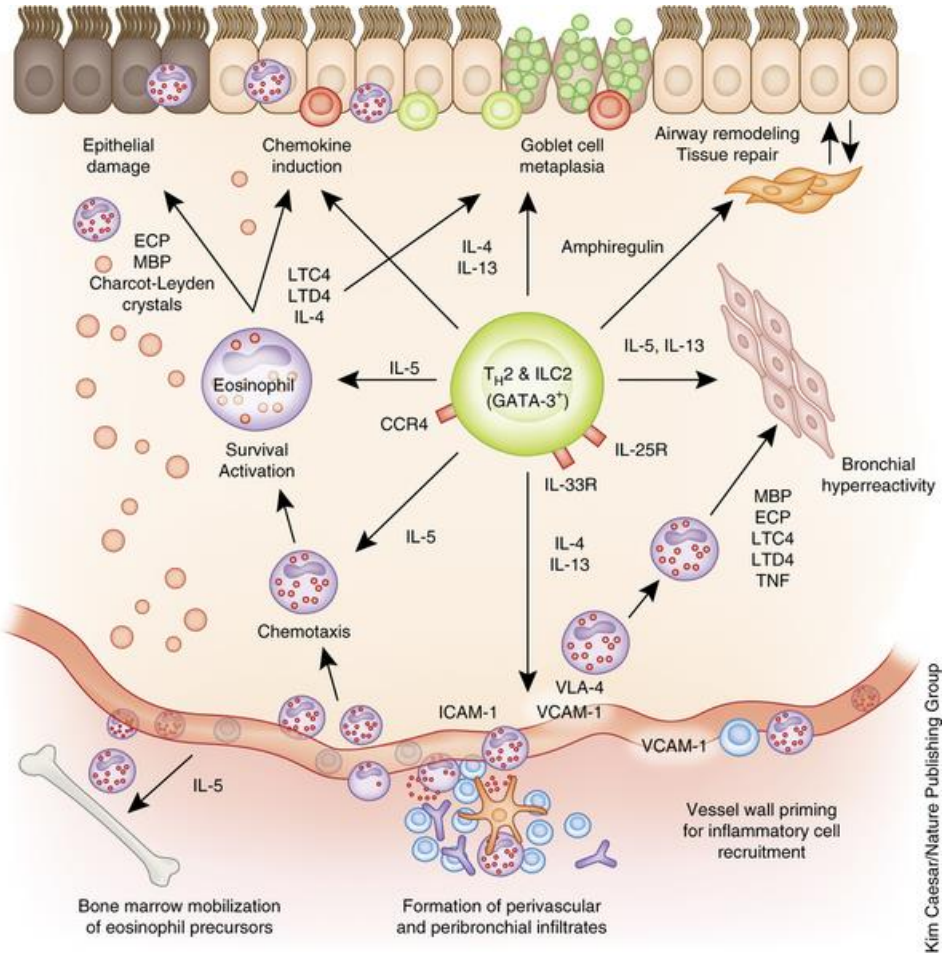
Autoimmunity

- **Hygiene hypothesis**
  The immune system needs to direct it's response towards pathogens. Without pathogens, it will find another target to attack.

- Lower incidence of autoimmune conditions in children exposed to animals e.g. city vs. country life

Asthma

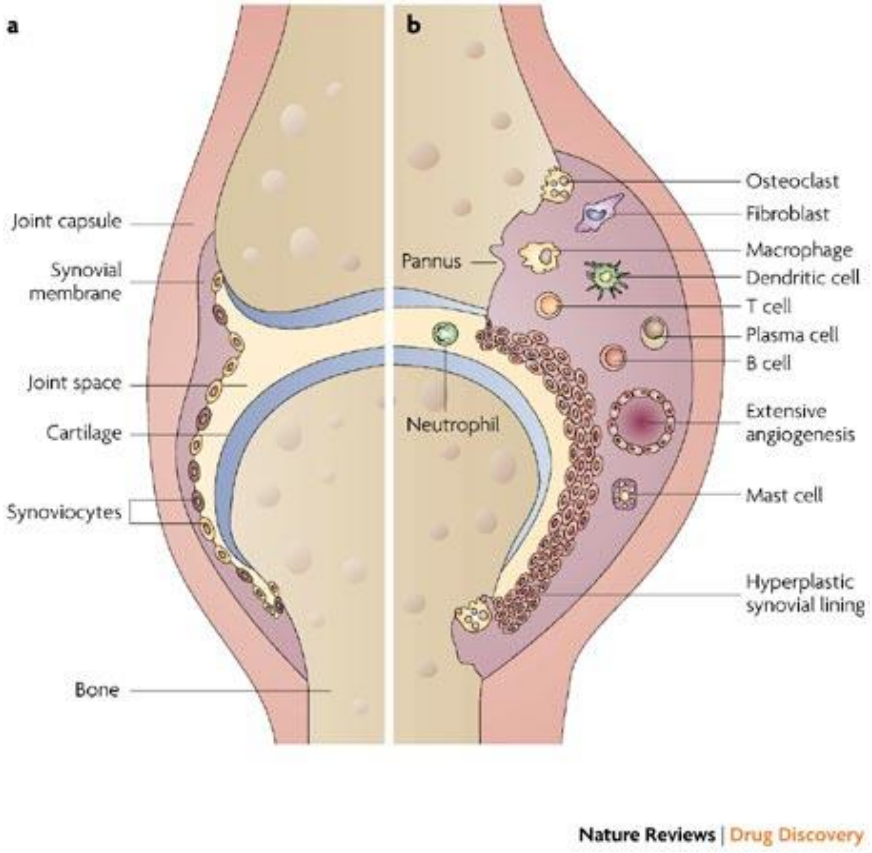
- Inflammatory disease causing airway constriction in response to a variety of triggers
- Prevalence globally 1-18%
  UK approx. 5%
  Increasing since 1960s
- Treated with: LABA, steroids (inhaled & systemic)
  Leukotriene inhibitors (montelukast), anti-IgE
  Research into antibodies to: IL-13, IL-5, IL-4



Nature Immunology Volume: 16, Pages:45–56 2015)
DOI:doi:10.1038/ni.3049

Rheumatoid arthritis

- Most common autoimmune condition approx. 0.5-1% prevalence, ~3:1 women:men
- Synovitis with pannus formation in articular cartilage leading to joint erosion and destruction. Systemic symptoms.
- Treated with steroids, DMARDs – MTX, leflunomide (General immunosuppression)
  targeted therapies with antibodies to:
  TNFα, IL6, IL-1, CLTA-4, CD20 (B cells)



Strand *et al*. *Nature Reviews Drug Discovery* **6**, 75–92 (January 2007) | doi:10.1038/nrd2196

Systemic lupus erythematosus

- Severe systemic autoimmune disease affecting all organs
- 9:1 female:male, prevalance ~0.1%, higher in Black vs white, diagnosis usually in teenagers
- Wide range of autoantibodies produced:
  Anti-nuclear, anti-dsDNA, anti-phospholipid, etc.
- Life threatening due to involvement of kidneys, lungs, heart and brain
- Treated with immunosuppressive agents and steroids
  Biologic treatment with anti-Blys/BAFF (B cell signalling)
- Challenging to develop therapies due to multi-system involvement and endpoints

Immune dysfunction

Immunology also covers:

Allergy & hypersensitivity
4 types covering anaphylaxis to metal allergy

Transplant rejection

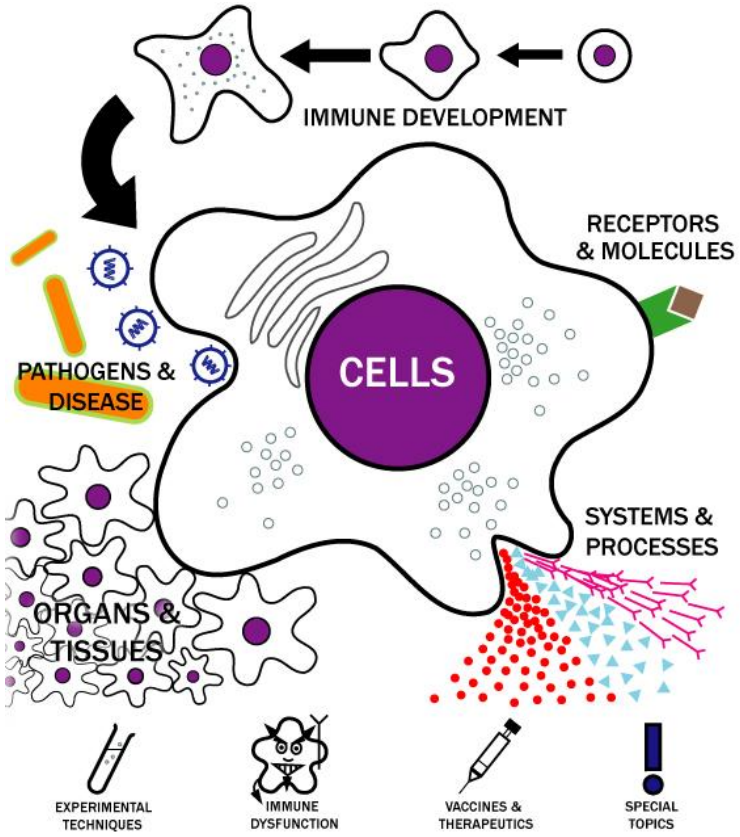
Vaccine development

And many more diseases

Most with multiple redundant pathways open to multiple treatment strategies

British Society for immunology 60
CELEBRATING THE FIRST 60 YEARS

http://bitesized.immunology.org/



The future…

- Responses to Infectious disease will remain a vital area of research
- Use of immunomodulation:
  to target cancer and infectious disease
  to hone and refine response to immunisations
- To understand and reduce immunosenescence in older age
- Lots more difficult questions and challenges…