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DRUG DISCOVERY

Targeting the IL-17 pathway in inflammatory disease

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The discovery of interleukin-17 (IL-17)[1,2] and of T helper 17 (T_H17) cells[3,4] are recent milestones in the field of immunology and inflammation research (see REFS 5,6 for reviews). IL-17 is a pro-inflammatory cytokine that plays a key part in inflammation, autoimmunity and host defence. The first therapeutic antibody that inhibits IL-17 was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of psoriasis in 2015. As understanding of the role of IL-17 in other inflammatory diseases grows, more inhibitors are likely to be approved for additional indications, starting with psoriatic arthritis and ankylosing spondylitis. Several other biologics targeting IL-17A, IL-17F and the IL-17 receptor (IL-17R), as well as biologics that also target tumour necrosis factor (TNF), are being investigated in clinical trials. Biologics that specifically target IL-23, an upstream regulator of the IL-17 pathway, and small molecules that target the transcription factor RORγt to prevent differentiation of precursors into T_H17 cells, are also in clinical trials.

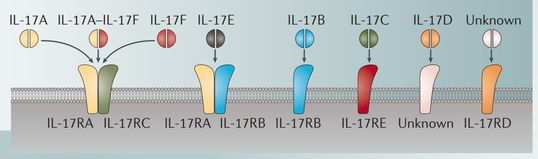
IL-17 and IL-17R signalling

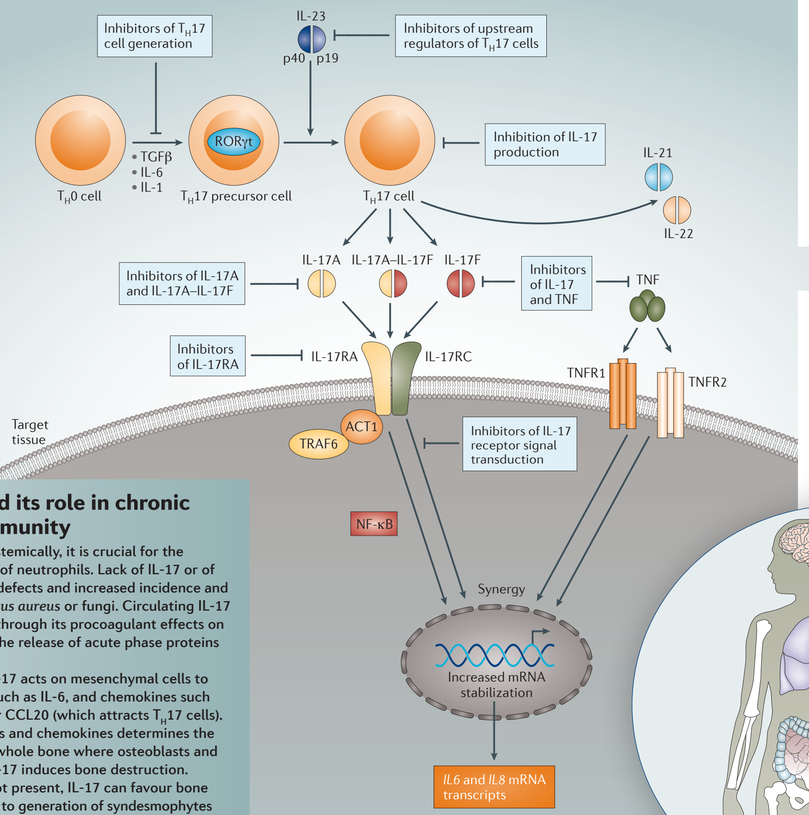
CTLA8, a cytokine produced by T cells, was discovered in 1993 (REF. 1) and subsequently renamed IL-17 (REF. 2) after it was found to stimulate the production of pro-inflammatory cytokines (IL-6 and IL-8) by synoviocytes and other mesenchymal cells.

Five additional genes with homology to the gene encoding IL-17 are now known[7]. The members of the IL-17 family are: IL-17, now referred to as IL-17A; IL-17B, IL-17C and IL-17D, which have not yet been fully studied in inflammation; IL-17E (also known as IL-25), which is a possible regulator of the other members; and IL-17F, which, with a 50% sequence homology, is the closest relative to IL-17A. IL-17A and IL-17F are produced as covalent homodimers and can form IL-17A–IL-17F heterodimers.

The full IL-17 receptor is a multi-chain complex that is composed of IL-17RA and IL-17RC chains for the IL-17A and IL-17F receptor, or of IL-17RA and IL-17RB chains for the IL-17E receptor[8–10].

Binding of IL-17A to IL-17RA leads to the recruitment of the adaptor protein ACT1 (see central figure). ACT1 mediates the ubiquitylation of TRAF6, leading to activation of the NF-κB pathway and increased transcription of the genes encoding IL-6 and IL-8. IL-17 can also activate C/EBPβ and C/EBPδ. The combination of IL-17 ligands and TNF often results in synergistic actions, which can be explained in part by increased mRNA stabilization and overexpression of the TNF type II receptor[6].





IL-17-producing cells

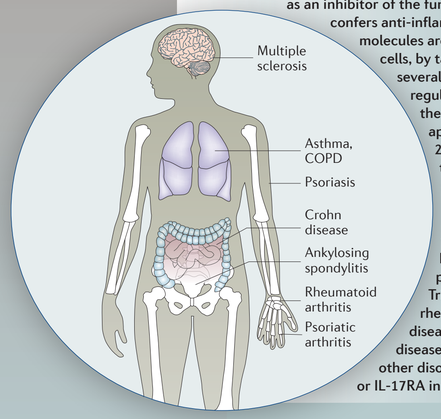
In 2005, T_H17 cells were conclusively shown to be a separate lineage from T_H1 and T_H2 cells in the mouse[3,4]. T_H17 cells express the transcription factor RORγt and produce IL-17A, IL-17F, IL-21 and IL-22 in response to stimulation by TGFβ, IL-1, IL-6 and IL-23. Over the years, more subsets of T cells and other lymphocytes have been identified as sources of IL-17, including $CD8^+$ T cells, γδ T cells, natural killer (NK) cells, NKT cells and group 3 innate lymphoid cells.

Mast cells and neutrophils can engulf IL-17 and represent a local source of stored IL-17. Owing to difficulties in detecting *IL17* mRNA in these cells, it is unclear whether they actually synthesize IL-17. T_H17 cells are characterized by their plasticity: in addition to expressing IL-17, they can express T_H1 cytokines such as interferon-γ, or regulatory T cell cytokines such as IL-10. In the context of inflammation, however, T_H17 cells acquire a plasma cell-like phenotype and express high levels of cytokines.

Inflammatory diseases amenable to IL-17 targeting

Numerous clinical trials of investigational therapeutics that target the IL-17 pathway or T_H17 cells are ongoing (see the table). One approach is the direct targeting of IL-17A with monoclonal antibodies such as secukinumab, a chimeric IL-17A-specific antibody, which in January 2015 was the first approved by the FDA and the EMA for the treatment of psoriasis, or ixekizumab, a humanized IL-17A-specific antibody. Given the shared functions of IL-17A and IL-17F, another option is targeting these molecules with a bispecific antibody, such as bimekizumab. Based on the synergistic interactions of TNF with IL-17A and IL-17F, other options include the use of a single inhibitor with dual specificity, or two separate inhibitors — one that targets IL-17, and another that targets TNF. The IL-17RA chain is the target of the antibody brodalumab, which acts as an inhibitor of the function of IL-17A and IL-17F, but also of IL-25, which confers anti-inflammatory effects. In addition to biologics, numerous small molecules are being developed to inhibit the differentiation of T_H17 cells, by targeting the transcription factor RORγt. Finally, there are several other biologics that have effects on IL-23, an upstream regulator of the T_H17 pathway. Ustekinumab, which targets the p40 subunit that is shared by IL-12 and IL-23, was approved for psoriasis in 2009 and psoriatic arthritis in 2013, and there are several antibodies in development that target the IL-23-specific p19 subunit, with a more specific effect on the IL-17 pathway.

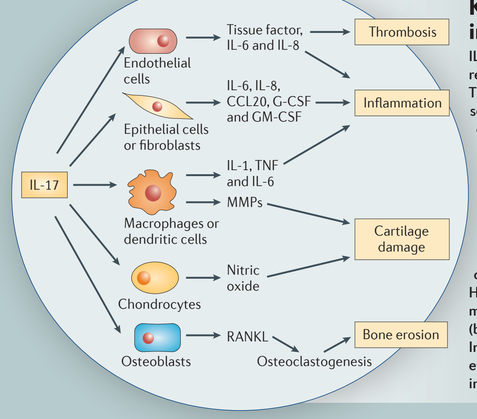
Drugs targeting the IL-17 pathway are now being tested in a growing list of indications. The indications for which these therapeutics are most advanced — that is, have reached or are close to regulatory approval — are psoriasis, psoriatic arthritis and ankylosing spondylitis. Trials are also ongoing or have been completed in rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, hidradenitis suppurativa, multiple sclerosis, Crohn disease, polymyalgia rheumatica, Behçet disease, dry eye, and other disorders. However, trials of antibodies that target IL-17A or IL-17RA in Crohn disease have been unsuccessful.



Key functions of IL-17 and its role in chronic inflammation and autoimmunity

IL-17 has systemic and local effects. Systemically, it is crucial for the recruitment, maturation and activation of neutrophils. Lack of IL-17 or of T_H17 cells is associated with neutrophil defects and increased incidence and severity of infections with *Staphylococcus aureus* or fungi. Circulating IL-17 contributes to systemic inflammation through its procoagulant effects on endothelial cells, and by stimulating the release of acute phase proteins by the liver.

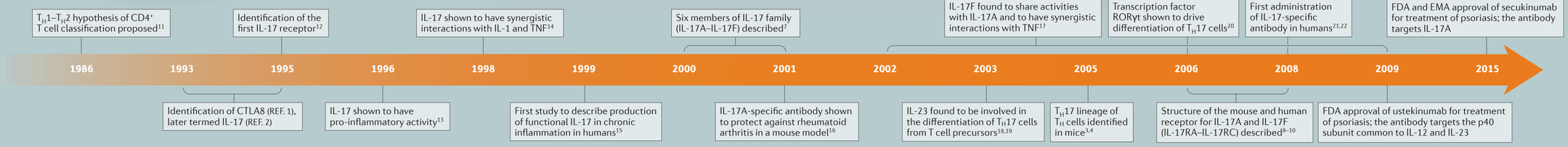
Locally, at sites of inflammation, IL-17 acts on mesenchymal cells to induce the production of cytokines such as IL-6, and chemokines such as IL-8 (which attracts neutrophils) or CCL20 (which attracts T_H17 cells). The combination of induced cytokines and chemokines determines the composition of the local infiltrate. In whole bone where osteoblasts and osteoclasts are in direct interaction, IL-17 induces bone destruction. However, when such interactions are not present, IL-17 can favour bone matrix formation — a process that leads to generation of syndesmophytes (bony growths that fuse the vertebrae) in ankylosing spondylitis.
In the intestine and other mucosal sites, IL-17 seems to have protective effects, as its inhibition was associated with increased disease severity in Crohn disease.



Selected agents targeting IL-17 signalling*

Drug (company)	Indication	Status
IL-17A inhibitors		
Secukinumab (Novartis)	Psoriasis	Approved
	Psoriatic arthritis	Submitted‡
	Ankylosing spondylitis	Submitted‡
	Rheumatoid arthritis	Phase III
	Asthma	Phase II
Ixekizumab (Lilly)	Psoriasis	Submitted‡
	Psoriatic arthritis	Phase III
CNTO 6785 (Janssen)	Rheumatoid arthritis	Phase II
	COPD	Phase II
CJM112 (Novartis)	Hidradenitis suppurativa	Phase II
	Psoriasis	Phase I/II
IL-17A and IL-17F inhibitors		
Bimekizumab (UCB)	Rheumatoid arthritis	Phase II
	Psoriasis	Phase I
	Psoriatic arthritis	Phase I
ALX-0761 (Merck Serono/ Ablynx)	Psoriasis	Phase I
IL-17A and TNF inhibitors		
ABT-122 (AbbVie)	Psoriatic arthritis	Phase II
	Rheumatoid arthritis	Phase II
COVA322 (Janssen/Covagen)	Psoriasis	Phase I/II
	Rheumatoid arthritis	Preclinical
IL-23 p19 inhibitors		
Tildrakizumab (Merck/Sun Pharma)	Psoriasis	Phase III
Guselkumab (Janssen/ MorphoSys)	Psoriasis	Phase III
	Psoriatic arthritis	Phase II
AMG 139 (AstraZeneca/ Amgen)	Crohn disease	Phase II
BI 655066 (Boehringer Ingelheim)	Psoriasis	Phase II
	Crohn disease	Phase II
	Asthma	Phase II
	Ankylosing spondylitis	Phase II
LY3074828 (Lilly)	Psoriasis	Phase I
IL-17RA inhibitors		
Brodalumab (AstraZeneca)	Psoriasis	Phase III
	Psoriatic arthritis	Phase III
RORγt inhibitors		
VTP-43742 (Vitae Pharmaceuticals)	Autoimmune disease	Phase I
	Psoriasis	Preclinical
JTE-151 (Japan Tobacco/Orphagen)	Autoimmune disease, allergy	Phase I
IL-12 p40 and IL-23 p40 inhibitors		
Ustekinumab (Janssen)	Psoriasis	Approved
	Psoriatic arthritis	Approved
	Crohn disease	Phase III
	Ulcerative colitis	Phase III
	SLE	Phase II
	Atopic dermatitis	Phase II
	Ankylosing spondylitis	Phase II

COPD, chronic obstructive pulmonary disease; IL-12 p40, p40 subunit of interleukin-12; IL-17, interleukin-17; IL-17A, interleukin-17A; IL-17F, interleukin-17F; IL-17RA, IL-17 receptor A; IL-23 p19, p19 subunit of interleukin-23; IL-23 p40, p40 subunit of interleukin-23; RORγt, retinoic acid receptor-related orphan receptor-γt; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor. *Product status in July 2015. ‡Licensing application submitted to a major regulatory agency.



References
1. Rouvier, E., Luciani, M. F., Mattei, M. G., Denizot, F. & Golstein, P. *J. Immunol.* **150**, 5445–5456 (1993).
2. Yao, Z. *et al. J. Immunol.* **155**, 5483–5486 (1995).
3. Harrington, L. E. *et al. Nat. Immunol.* **6**, 1123–1132 (2005).
4. Park, H. *et al. Nat. Immunol.* **6**, 1133–1141 (2005).
5. Miossec, P., Korn, T. & Kuchroo, V. K. *N. Engl. J. Med.* **361**, 888–898 (2009).
6. Miossec, P. & Kolls, J. K. *Nat. Rev. Drug Discov.* **11**, 763–776 (2012).
7. Aggarwal, S. & Gurney, A. L. *J. Leukoc. Biol.* **71**, 1–8 (2002).
8. Toy, D. *et al. J. Immunol.* **177**, 36–39 (2006).
9. Kramer, J. M. *et al. J. Immunol.* **176**, 711–715 (2006).
10. Zrioual, S. *et al. J. Immunol.* **180**, 655–663 (2008).
11. Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A. & Coffman, R. L. *J. Immunol.* **136**, 2348–2357 (1986).
12. Yao, Z. *et al. Immunity* **3**, 811–821 (1995).
13. Fossiez, F. *et al. J. Exp. Med.* **183**, 2593–2603 (1996).
14. Chabaud, M., Fossiez, F., Taupin, J. L. & Miossec, P. *J. Immunol.* **161**, 409–414 (1998).
15. Chabaud, M. *et al. Arthritis Rheum.* **42**, 963–970 (1999).
16. Lubberts, E. *et al. J. Immunol.* **167**, 1004–1013 (2001).
17. Zrioual, S. *et al. J. Immunol.* **182**, 3112–3120 (2009).
18. Aggarwal, S., Ghilardi, N., Xie, M. H., de Sauvage, F. J. & Gurney, A. L. *J. Biol. Chem.* **278**, 1910–1914 (2003).
19. Happel, K. I. *et al. J. Immunol.* **170**, 4432–4436 (2003).
20. Ivanov, I. I. *et al. Cell* **126**, 1121–1133 (2006).
21. Hueber, W. *et al. Sci. Transl. Med.* **2**, 52ra72 (2010).
22. Genovese, M. C. *et al. Arthritis Rheum.* **62**, 929–939 (2010).

Abbreviations
ACT1, adaptor protein CIKS; CCL20, CC-chemokine ligand 20; C/EBP, CCAAT/enhancer binding proteins; CTLA8, cytotoxic T-lymphocyte-associated antigen 8; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; RORγt, retinoic acid receptor-related orphan receptor-γt; TGFβ, transforming growth factor-β; TNFR, tumour necrosis factor receptor; TRAF6, tumour necrosis factor receptor-associated factor 6.

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