

A Focus on IL-17 Targeting Treatments in Psoriasis

Joseph Fabre, Jérôme Giustiniani, Frank Antonicelli, Yacine Merrouche, Martine Bagot, Armand Bensussan

Joseph Fabre, Jérôme Giustiniani, Yacine Merrouche, Institut Jean Godinot, Unicancer, F- 51726 Reims, France

Joseph Fabre, Jérôme Giustiniani, Frank Antonicelli, Yacine Merrouche, University Reims-Champagne-Ardenne, DERM-I-C, EA7319, 51 rue Cognacq-Jay, F-51095 ReimsCedex, France

Martine Bagot, Armand Bensussan, Institut National de la Santé et de la Recherche Médicale (INSERM) U976, Hôpital Saint Louis, 75010 Paris, France

Martine Bagot, Armand Bensussan, University Paris Diderot, Sorbonne Paris Cité, Laboratoire Immunologie Dermatologie & Oncologie, UMR-S 976, F-75475, Paris, France

Armand Bensussan, OREGABIOTECH, 15 chemin du Saquin F-69130 Ecully, France

Correspondence to: Pr Armand Bensussan, Research Director, Director, Laboratory INSERM UMR-S 976, Université Paris Diderot, Sorbonne Paris Cité, Hôpital Saint-Louis, Equerre Bazin, 1, avenue Claude Vellefaux, 75475 PARIS CEDEX 10, France.

Email: armand.bensussan@inserm.fr

Telephone: +33-149813513

Received: April 7, 2016

Revised: May 2, 2016

Accepted: May 5, 2016

Published online: June 27, 2016

ABSTRACT

Psoriasis is a frequent and chronic disease of the skin and less often of the joint that associates erythema, keratinizing troubles and inflammatory phenomenon. Usually benign, it can severely impact quality of life in patients suffering from severe forms. Appearing in 2005, biotherapies like Tumor Necrosis Factor alpha inhibitors have permitted outstanding clinical response and brought patients the hope of durable disease remission. Nevertheless, treatments efficacy tends to decrease over time leading to symptoms relapse in many patients, for which new treatment targets have been needed. Recent advances in molecular biology, and genetics, have allowed the characterization of a distinct subtype of T helper lymphocyte found as infiltrates surrounding the capillaries in the dermis and the epidermis in psoriasis-presenting patients. These Th17 helpers cells express and secrete a

pro-inflammatory cytokine called interleukin 17, which play a key-role in inflammation and psoriasis pathophysiology. Therefore, molecules interfering with this pathway have been studied intensively. The purpose of this review is to report the results of such strategy.

Key words: Psoriasis; Inflammation; Interleukin 17; Interleukin 17-inhibitors

© 2016 The Authors. Published by ACT Publishing Group Ltd.

Fabre J, Giustiniani J, Antonicelli F, Merrouche Y, Bagot M, Bensussan A. A Focus on IL-17 Targeting Treatments in Psoriasis. *Journal of Dermatological Research* 2016; 1(2): 22-26 Available from: URL: <http://www.ghrnet.org/index.php/jdr/article/view/1677>

INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects mostly the skin and sometimes the joints with a high frequency of 2 to 3% of the population^[1]. The most common clinical presentation comprises erythema, squamous plaques and pruritus. These symptoms are caused by keratinocytes proliferation, deregulation, inflammation and blood vessels dilatation.

Psoriasis is usually non-life threatening but often associated with an altered quality of life. The severity of the disease depends on its extension, resistance to therapies or unusual clinical presentations (erythrodermia, pustulosis, and associated psoriatic rheumatism)^[2].

Clinical signs usually appear after exposure to environmental factors, like stress, traumatism, infections, or medications^[3]. Beside progress in its understanding, the causes of the disease still need to be discovered. Heredity has an important role as demonstrated in several population studies, and the incidence of psoriasis is greater among first and second-degree relatives of patients^[4]. This genetic predisposal is complex, mainly based on variants of a chromosomal locus called psoriasis susceptibility 1 (PSORS1)^[5].

Some authors have hypothesized that the main cause is autoimmunity, provoked by the development of self-reactive T lymphocytes against unidentified epidermal antigens, while others are in favor of an autoimmune origin caused by the production of

pro-inflammatory cytokines like Tumor Necrosing Factor alpha (TNF α), interleukin 23 (IL-23) and interleukin 17 (IL-17).

Inflammation mechanisms in psoriasis are being better and better understood, and depend on interactions between epithelial cells, dendritic cells and T lymphocytes, it is creating a self-entertaining loop responsible for the chronicity of the damages. The technical advances in molecular biology and genetics have found a particular subset of T helper lymphocytes called Th17 and its secreted cytokine IL-17 both to be frequently infiltrated in the surroundings of psoriatic patients' blood vessels and to be of importance in psoriasis pathophysiology. IL-17 has six isoforms, from IL-17A to IL-17F, whose biological activity is mediated via the IL-17 receptor (IL-17R) leading to the activation of cell signaling^[6,7]. Several studies have already reported significant clinical results of IL-17 pathway targeting. We discuss here the rationale of such a strategy.

HISTOLOGIC DESCRIPTION OF PSORIATIC LESIONS

Psoriasis usually affects scalp, sacral region and extensor surfaces of extremities and involvement of flexural and intertriginous areas (inverse psoriasis) are less often. Approximately 5% of patients will develop one of the five arthritis forms: peripheral type, peripheral symmetric, polyarthritis, asymmetrical joint type, spondyloarthropathy and mutilating peripheral type.

Classical forms associate at diverse degrees, hyperkeratosis, parakeratosis, acanthosis, hypogranulation, hypervascularization, superficial dermal lymphocytic infiltrate, and Munro-Sabouraudmicroabcess.

In early stage, we observe blood vessels dilatation and elongation in the papillary derma, associated with edema and lymphocytic infiltrate called perivascular cuffing. In the lumen of the vessels, which are dilated and serpentine, neutrophils and lymphocytes can be found directing towards the epidermis. Rare extravasated erythrocytes are also observed. At this stage, the epidermis is still considered normal^[8].

Then, the epidermis thickens and begins to lose its layer of granular cells. Dunes of parakeratosis form as a consequence of shortened cellular turnover time. Keratinocyte proliferation and maturation becomes too rapid and results in incomplete differentiation. Intracellular abnormalities are visible such as intact nuclei, extracellular lipid release when it should cement the adhesion of corneocytes.

Because of this loss of adherence, characteristic scales of psoriasis desquamate. Early sign of Munro microabcess appear under the form of scattered neutrophils amongst mounds of parakeratosis.

Later evolution leads to the condensation of the stratum spinosum (acanthosis) and to epidermal psoriasiform hyperplasia consisting in regular elongation of the rete ridges and thinning of suprapapillary plates. The mitotic activity is important, and parakeratosis progresses until a complete loss of granular layer. Neutrophils and other inflammatory cells transmigrate through the epidermis towards parakeratotic scale realizing collections in the cornea, which define the Munro microabscesses^[9].

The same process takes place in the stratum spinosum and defines "spongiform pustule of Kogoj". To note, when subcorneal abscesses predominate the disease is named Pustular psoriasis. The inflammatory infiltrate in the derma becomes heavier, recruiting T lymphocytes, a few Langerhans cells and some neutrophils. Beyond the basal lamina the presence of CD11c macrophages is

detected. Beside neutrophils, numerous lymphocytes intertwine with keratinocytes in the epidermis and bear CD8⁺ markers. In the derma, lymphocytes are rather a mixture of CD4⁺ and CD8⁺ with a predominance of the earlier^[10,11].

CHARACTERISTICS OF IL-17

There have been evidences of the role of T cells in psoriasis since the observation of critical responses of patients treated with immunosuppressors like cyclosporine, alefacept and abatacept^[12-14]. Also, there is a high expression of Th17-secreted cytokines, IL-17 and IL-22, in psoriasis patients' skin lesions, joints, and serum^[15]. The main sources of IL-17 production are Th17, but mast cells, cytotoxic CD8⁺ T cells, natural killer cells, neutrophils, and macrophages also produce it.

IL-17 is a cytokine that helps host to defend himself against bacteria and fungus^[16]. French research teams played a key role in its discovery. IL-17 was initially discovered and named CTLA8 by Rouvier and collaborators in 1993^[17]. A few years later, Yao et al proposed the term IL-17 after cloning its sequence from a human cDNA library^[18]. Fossiez et al in 1996, observed that synoviocytes from patients presenting rheumatoid arthritis released IL-17 that stimulated epithelial, endothelial and fibroblastic cells to secrete pro-inflammatory actors such as IL-6, IL-8, granulocyte-colony-stimulating factor and prostaglandin E2. They also showed IL-17 could modulate the proliferation and the maturation of neutrophils^[19]. To date, six members of the IL-17 family have been identified and sequenced: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. The primary Th17 cell effector cytokine is IL-17A, and is constituted as a homodimeric, disulfide-linked glycoprotein containing 155 amino acids and has a molecular weight of 35Kd. There is a varying homology between IL-17A and the other family members ranging from 55% with IL-17F to 17% with IL-17E. IL-17A and F exist as both homodimers and IL-17A/F heterodimers^[20]. They share close activities, yet the IL-17A seems more efficient at activating gene expression than IL-17F and IL-17A/F^[21]. Oppositely IL-17E (IL-25), which displays the lowest homology with IL-17A, acts as a regulator of IL-17 functions probably via receptor competition, and participates in the Th2 cell responses against parasites and allergy^[22].

THE TH17 AXIS AND THE RECEPTOR FOR IL17

The IL-17 receptor family comprises 5 subunits named IL-17RA to IL-17RE. Their sequences are different beside the facts that many of their genes are clustered on chromosome 3. They each present a single, 499-866 amino acids long, transmembrane domain. The extracellular fibronectin-like and SEFIR domains are conserved between all subunits^[23]. Interaction between IL-17A and its receptor IL-17RA happens with a high affinity and drives signaling via a complex constituted of the association of the two subunits IL-17RA and IL-17RC. At a lesser degree, IL-17RA also binds IL-17F, and IL-17A/IL-17F and seems to be critical for their transduction^[24]. A recent study suggests that IL-17RA might also be a part of the IL-25 receptor complex since *Il17ra*^{-/-} mice are refractory to the effects of IL-25. IL-17RA is used by multiple cytokines indicating that it could be analogous to common cytokine receptor subunits such as gp130 in the IL-6 family^[25]. Downstream, the transcription factor nuclear factor- κ B (NF κ B) is then activated and favours pro-inflammatory gene expression^[26]. Despite the fact that IL-17RA is ubiquitous, this subunit has been found to have a tissue-dependent expression. Although macrophages and DCs are also responsive to IL17, IL-

IL-17RA is particularly found with high levels in haematopoietic tissue^[27,28], which can be surprising because the greatest activity of IL-17A has been observed in epithelial, endothelial, and fibroblast cells^[28]. In lymphocytes, only a small number of IL-17A-induced genes have been identified and they are different from those induced in other cell types^[29]. An example of a dynamic regulation of IL-17RA has been reported in CD8⁺ cells, where its synthesis is upregulated by IL-15 and IL-21, whereas stimuli inducing the phosphoinositide 3-kinase (PI3K) pathway limit its expression. Unlike many cytokine receptors, high levels of IL-17RA are required to effectively transduce signal, whose intensity correlates to the density of IL-17RA at the surface of the cells^[30]. A decrease of IL-17RA is also observed in response to IL-17 binding due to an internalization of the complex IL-17RA/IL-17A. The consequence is a rapid drop of IL-17A concentration in the milieu^[31].

The composition of IL-17RA complexes is still debated. Most authors say individual subunits are expressed at the surface membrane as monomers. The fixation of the ligand causes subunit oligomerization and the juxtaposition of kinases or adaptors related to the receptor^[32]. Other studies showed that receptors could exist as pre-associated, multi-subunit complexes such as TLRs, TNF receptors (TNFRs) and erythropoietin receptor (EPOR)^[33]. Fluorescence Resonance Energy Transfer (FRET) studies showed that among IL-17R subunits, IL-17RA can form ligand-independent complexes^[34]. Conversely, some data of immunoprecipitation are in favor of a ligand-dependent binding of the complex IL-17RA/IL-17RC^[35]. Further information is given by native gel analysis where two IL-17RA subunits assemble with one IL-17RC subunit. Like the EPOR, IL-17RA ligand binding provokes important conformational changes in the subunits relative positions, which allow intracytoplasmic signaling partners like JAKs to interact with appropriate targets as shows FRET analysis. The explanation may be that IL-17RA dimers submit dissociation and rearrange with IL-17RC to form heterodimers. The other possibility could be the recruitment of IL-17RC by IL-17RA to create a trimer or a larger complex along cytoplasmic signaling molecules such as ACT1^[23].

TREATING PSORIASIS

The main score to quantitatively evaluate psoriasis severity is the Psoriasis Area Severity Index (PASI) first introduced by Frederickson and Peterson in 1978. The calculation of this index takes into account for each body region the percentage area affected and the intensity of redness, thickness and scaling from 0 (none) to 4 (severe)^[36]. Modern treatments of psoriasis have greatly improved the quality of life of patients, and the targeting of the IL-17 pathway seems to keep its promises. Two major approaches have been developed so far, one aiming at directly interfering with the ligand IL-17A, and the other one focusing on the receptor preventing the IL-17 transduction signal thereof. In recent trials, the success of the treatments has been measured by indicating the proportion of people achieving a "PASI 75, 90 or 100" which indicates the value of the reduction of the PASI score from the start to the endpoint of the trial.

DIRECT TARGETING OF IL-17

Langley *et al.* were the firsts to report 2 phase 3 trials about the activity of Secukinumab (SK), a monoclonal IgG1k antibody used to target IL-17A in moderate to severe psoriasis^[37]. The ERASURE (Efficacy of Response and Safety of Two Fixed SK Regimens in Psoriasis) trial randomized 738 patients between SK

and placebo. The posology was 300 or 150 mg to be administered once weekly for 5 weeks, then every 4 weeks. PASI 75 and PASI 90 were reached at week 12 by 81.6% and 59.2% of the 300 mg and 71.6% and 39.1% of the 150 mg cohort versus 4.5% and 1.2% in the placebo group, respectively. The second study, FIXTURE (Full Year Investigative Examination of SK vs Etanercept Using Two Fixed Secukinumab Regimens in Psoriasis) examined 1306 patients treated with the two same modalities of SK or etanercept at a dose of 50 mg twice weekly for 12 weeks then once weekly. There, at 12 weeks, PASI 75 and 90 were achieved by 77.1%/54.2% with 300 mg, 67.0%/41.9% with 150 mg of SK, and 44.0%/20.7% with 50 mg of etanercept, respectively. Of note, tolerance was remarkable and no difference between secondary effects rate was observed between groups. Infections were similar across all treatment arms and mild to moderate candidiasis occurred in less than 5% in the SK arms, and almost 1% of patients taking etanercept. Rare grade 3 neutropenia were seen amongst patients undergoing SK therapy and none for those taking etanercept. FUTURE 1, a phase 3 randomized study included 606 patients suffering from psoriasis and psoriasis arthritis. Higher dose of SK were tested, 10 mg/kg every 2 weeks during 4 weeks and then 150 mg or 75 mg every weeks from week 8 versus placebo. To note, a third of the patients had received anti-TNF treatments before the inclusion, and half of them had concomitant methotrexate administration during the trial. The ACR 20, 50 and 70 at 24 weeks were respectively obtained by 50.0, 34.7 and 18.8% of the participants having a 150 mg dose, versus 50.5, 30.7 and 16.8% for those having the 75 mg dose and only 17.3, 7.4 and 2.0% for patients receiving the placebo. Skin disease measures were statistically in favor of the treatment arms. FUTURE 2 reported similar good results on 397 patients randomized between different secukinumab doses and placebo. Both studies described few serious adverse events and no opportunistic infections^[38].

The latest bioterapy, Ixekizumab is promising. The phase 2 study by Leonardi^[38] credits it for excellent results at a maximal dose of 150 mg. PASI 75 rates were superior to 80% and PASI 100 was reached in almost 40% of patients with an observed efficiency starting from the first week.

Professor Griffiths *et al.* recently published the results of two randomized, prospective, double blind multicenter phase 3 studies UNCOVER-2 and UNCOVER-3^[39]. The study included respectively 1224 and 1346 patients to be treated with Ixekizumab, etanercept and placebo for chronic plaque psoriasis. PASI 75 was obtained in 4 weeks by 80.0 to 87.4% of the patients in the experimental arm depending on the periodicity of the injections. The pooled adverse events were around 2% and no death happened.

TARGETING THE IL-17R

As mentioned previously, different subunits assemble around IL-17RA to form the receptor complex, explaining why blocking it with antibodies has been foreseen for therapy.

Papp *et al.*^[40] reported encouraging results of a 16 weeks phase 2 studies with brodalumab, a fully human mAb targeting IL-17RA. One hundred ninety eight patients receiving 4 doses schemes were evaluated: 70, 140, 210 and 280 mg subcutaneously. The mean improvements in the PASI scores were 45.0%, 85.9%, 86.3% and 76.0% respectively for the experimental arms versus 16.0% in the placebo group ($p < 0.001$). Besides, the clinical response was rapid, as early as 2 weeks, and measures of the quality of life were improved significantly by brodalumab treatments. The same author confirmed these good results in an extension study at the doses of

Table 1 Results of IL-17 pathway targeting.

	Secukinumab ^[37]	Ixekizumab ^[39]	Brodalumab ^[42]
Highest PASI 75 reported at 12 weeks (%)	81.6	89.7	83.3
Highest PASI 90 reported at 12 weeks (%)	59.2	70.7	70.3
Highest PASI 100 reported at 12 weeks (%)	28.6	40.5	41.9
Highest Grade \geq 3 adverse events rate reported at 12 weeks (%)	1.2	2	23

Comparison of the highest results reported by recent trials evaluating the efficacy of IL-17 pathway targeting therapies based on the Psoriasis Area Severity Index (PASI). PASI 75/90/100 indicates the value of the treatment response and the percentage of patients reaching it. References are indicated between brackets.

210 and 140 mg every two weeks. PASI 75, PASI 90 and PASI 100 responses rates were 86%, 70% and 51%, respectively. Tolerance appeared satisfactory since the most frequently encountered adverse events were nasopharyngitis (26.5%), upper respiratory tract infections (19.9%), arthralgia (16.0%) and back pain (11.0%), while 13.3% patients developed grade 3 or more toxicity^[41]. The following randomized phase 3 double blind multicentre placebo controlled trial^[42] confirmed brodalumab efficacy. The two most efficient doses (140 and 210 mg) were compared. Of the 661 patients included, at week 12 PASI 75 was obtained in 60% of 140 mg-group, 83.0% of 210 mg-group and 3.0% placebo group. Static physician global assessment was achieved by 54% (140 mg) and 76% (210 mg) vs 1% (placebo) for an acceptable safety profile (23% of adverse of events of grade \geq 3).

CONCLUSION AND FORESIGHT

Undoubtedly, the last decade has seen tremendous improvements in the management of psoriasis. The advances in immunology have identified novel targets and the IL-17 pathway was proved to be efficient with acceptable toxicity in randomized phase 3 trials (Table 1). Nevertheless, long-term surveillance is required to potentially detect serious late side effects such as cancers^[43]. Future studies will have to investigate the global strategy, what molecule to use and when, and also to test associations to know whether interfering at different key-steps and on different actors of the inflammatory sequence of psoriasis can prove their usefulness.

ACKNOWLEDGEMENTS

This review article has been written in the loving memory of Doctor Jean-François Fabre, a conscientious dermatologist who always was attentional to his patients, and his family.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

REFERENCES

- Burden-Teh E, Thomas KS, Ratib S, Grindlay D, Adaji E, Murphy R. The Epidemiology of Childhood Psoriasis: A Scoping Review. *British Journal of Dermatology*. 2016.
- Bonnet MC, Bagot M, Bensussan A. Anticorps monoclonaux ciblant l'IL-17A ou son récepteur dans le psoriasis: Une nouvelle approche thérapeutique ? *médecine/sciences* 2012; 28(12): 1035–7.
- Van den Berg WB, McInnes IB. Th17 cells and IL-17 A—Focus on immunopathogenesis and immunotherapeutics. *Seminars in Arthritis and Rheumatism*. 2013 Oct; 43(2): 158–70.
- Lønnberg AS, Skov L, Skytthe A, Kyvik KO, Pedersen OB, Thomsen SF. Heritability of psoriasis in a large twin sample. *British Journal of Dermatology*. 2013 Aug; 169(2): 412–6.
- Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, Ding J, Li Y, Tejasvi T, Gudjonsson JE, Kang HM, Allen MH, McManus R, Novelli G, Samuelsson L, Schalkwijk J, Stähle M, Burden AD, Smith CH, Cork MJ, Estivill X, Bowcock AM, Krueger GG, Weger W, Worthington J, Tazi-Ahmini R, Nestle FO, Hayday A, Hoffmann P, Winkelmann J, Wijmenga C, Langford C, Edkins S, Andrews R, Blackburn H, Strange A, Band G, Pearson RD, Vukcevic D, Spencer CC, Deloukas P, Mrowietz U, Schreiber S, Weidinger S, Koks S, Kingo K, Esko T, Metspalu A, Lim HW, Voorhees JJ, Weichenthal M, Wichmann HE, Chandran V, Rosen CF, Rahman P, Gladman DD, Griffiths CE, Reis A, Kere J; Collaborative Association Study of Psoriasis (CASP); Genetic Analysis of Psoriasis Consortium; Psoriasis Association Genetics Extension; Wellcome Trust Case Control Consortium 2, Nair RP, Franke A, Barker JN, Abecasis GR, Elder JT, Trembath RC. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nature Genetics*. 2012 Nov 11; 44(12): 1341–8.
- Reynolds JM, Angkasekwinai P, Dong C. IL-17 family member cytokines: Regulation and function in innate immunity. *Cytokine & Growth Factor Reviews*. 2010 Dec; 21(6): 413–23.
- Isailovic N, Daigo K, Mantovani A, Selmi C. Interleukin-17 and innate immunity in infections and chronic inflammation. *Journal of Autoimmunity*. 2015 Jun; 60: 1–11.
- Conrad C, Lapointe A-K. Le psoriasis au centre de l'attention. *Revue Médicale Suisse*. 2011; (289): 747.
- Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009 Jul 30; 361(5): 496–509.
- Barr RJ, Young EM. Psoriasiform and related papulosquamous disorders. *J Cutan Pathol*. 1985 Oct; 12(5): 412–25.
- Krueger JG. Psoriasis pathophysiology: current concepts of pathogenesis. *Annals of the Rheumatic Diseases*. 2005 Mar 1; 64(suppl_2): ii30–6.
- Kraan MC, van Kuijk AWR, Dinant HJ, Goedkoop AY, Smeets TJM, de Rie MA, Dijkmans BA, Vaishnav AK, Bos JD, Tak PP. Alefacept treatment in psoriatic arthritis: Reduction of the effector T cell population in peripheral blood and synovial tissue is associated with improvement of clinical signs of arthritis. *Arthritis & Rheumatism*. 2002 Oct; 46(10): 2776–84.
- Colombo MD, Cassano N, Bellia G, Vena GA. Cyclosporine Regimens in Plaque Psoriasis: An Overview with Special Emphasis on Dose, Duration, and Old and New Treatment Approaches. *The Scientific World Journal*. 2013; 2013: 1–11.
- Mease PJ. Psoriatic arthritis: Treatment update. *Bulletin of the NYU hospital for joint diseases*. 2011; 69(3): 243.
- Nogralas KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I, Khatcherian A, Gonzalez J, Pierson KC, White TR, Pensabene C, Coats I, Novitskaya I, Lowes MA, Krueger JG. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *British Journal of Dermatology*. 2008 Aug.
- Cypowij S, Picard C, Maródi L, Casanova J-L, Puel A. Immunity to infection in IL-17-deficient mice and humans: HIGHLIGHTS. *European Journal of Immunology*. 2012 Sep; 42(9): 2246–54.
- Rouvier E, Luciani MF, Mattei MG, Denizot F, Golstein P. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. *J Immunol*. 1993; 150(12): 5445–56.
- Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, Armitage RJ. Human IL-17: a novel cytokine derived from T

- cells. *J Immunol.* 1995; **155**(12): 5483-6.
- 19 Fossiez F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, Pin JJ, Garrone P, Garcia E, Saeland S, Blanchard D, Gail- lard C, Das Mahapatra B, Rouvier E, Golstein P, Banchereau J, Lebecque S. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *The Journal of experimental medicine.* 1996; **183**(6): 2593–603.
 - 20 Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diag- nosis and pharmacologic treatment of psoriatic arthritis in patients with psoria- sis. *Drugs* 2014; **74**: 423-41.
 - 21 Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nature Reviews Immunology.* 2009 Aug; **9**(8): 556-67.
 - 22 Kleinschek MA, Owyang AM, Joyce-Shaikh B, Langrish CL, Chen Y, Gorman DM, Blumenschein WM, McClanahan T, Brombacher F, Hurst SD, Kastelein RA, Cua DJ. IL-25 regulates Th17 function in autoimmune inflammation. *The Journal of Experimental Medicine.* 2007 Jan 22; **204**(1): 161-70.
 - 23 Gaffen S. IL-17 receptor composition. *Nature Reviews Immunol- ogy.* 2015 Nov 23; **16**(1): 4-4.
 - 24 Hymowitz SG, Filvaroff EH, Yin J, Lee J, Cai L, Risser P, Maruoka M, Mao W, Foster J, Kelley RF, Pan G, Gurney AL, de Vos AM, Starovasnik MA. IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding. *The EMBO journal.* 2001; **20**(19): 5332-41.
 - 25 Rickel EA, Siegel LA, Yoon B-RP, Rottman JB, Kugler DG, Swart DA, Anders PM, Tocker JE, Comeau MR, Budelsky AL. Identifi- cation of Functional Roles for Both IL-17RB and IL-17RA in Mediating IL-25-Induced Activities. *The Journal of Immunology.* 2008 Sep 15; **181**(6): 4299-310.
 - 26 Toy D, Kugler D, Wolfson M, Bos TV, Gurgel J, Derry J, Tocker J, Peschon J. Cutting Edge: Interleukin 17 Signals through a Hetero- meric Receptor Complex. *The Journal of Immunology.* 2006 Jul 1; **177**(1): 36-9.
 - 27 Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, Armitage RJ. Human IL-17: a novel cytokine derived from T cells. *The Journal of Immunology.* 1995; **155**(12): 5483-6.
 - 28 Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, Fujikado N, Tanahashi Y, Akitsu A, Kotaki H, Sudo K, Nakae S, Sasakawa C, Iwakura Y. Differential Roles of Interleukin-17A and -17F in Host Defense against Mucoepithelial Bacterial Infection and Allergic Responses. *Immunity.* 2009 Jan; **30**(1): 108-19.
 - 29 Onishi RM, Gaffen SL. Interleukin-17 and its target genes: mech- anisms of interleukin-17 function in disease. *Immunology.* 2010; **129**(3): 311-21.
 - 30 Kirkham BW, Kavanaugh A, Reich K. Interleukin-17A: a unique pathway in immune-mediated diseases: psoriasis, psoriatic arthritis and rheumatoid arthritis. *Immunology.* 2014; **141**(2): 133-42.
 - 31 Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. *J Am Acad Dermatol.* 2014; **71**(1): 141-50.
 - 32 Mease PJ. Inhibition of interleukin-17, interleukin-23 and the TH17 cell pathway in the treatment of psoriatic arthritis and psoriasis. *Curr Opin Rheumatol.* 2015; **27**(2): 127-33.
 - 33 Gu C, Wu L, Li X. IL-17 family: cytokines, receptors and signal- ing. *Cytokine.* 2013; **64**: 477-485.
 - 34 Beringer A, Noack M, Miossec P. IL-17 in Chronic Inflammation: From Discovery to Targeting. *Trends Mol Med.* 2016; **22**(3): 230-41.
 - 35 Jinna S, Strober B. Anti-interleukin-17 treatment of psoriasis. *J Dermatolog Treat.* 2016: 1-5
 - 36 Fredrikson T, Pettersson U. Severe Psoriasis-Oral Therapy with a New Retinoid. *Dermatologica.* 1978; **157**: 238-44.
 - 37 Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E, Tsai TF, Wasel N, Tying S, Salko T, Hampele I, Notter M, Karpov A, Helou S, Papavassilis C; ERASURE Study Group; FIXTURE Study Group. Secukinumab in Plaque Psoriasis — Results of Two Phase 3 Trials. *New England Journal of Medicine.* 2014 Jul 24; **371**(4): 326-38.
 - 38 Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson- Heredia E, Braun D, Banerjee S. Anti–interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *New England Journal of Medicine.* 2012; **366**(13): 1190-9.
 - 39 Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *The Lancet.* 2015; **386**(9993): 541-51.
 - 40 Papp KA, Leonardi C, Menter A, Ortonne J-P, Krueger JG, Kri- corian G, Aras G, Li J, Russell CB, Thompson EH, Baumgartner S. Brodalumab, an anti–interleukin-17–receptor antibody for psoriasis. *New England Journal of Medicine.* 2012; **366**(13): 1181-9.
 - 41 Papp K, Leonardi C, Menter A, Thompson EH, Milmont CE, Kri- corian G, Nirula A, Klekotka P. Safety and efficacy of brodalumab for psoriasis after 120 weeks of treatment. *Journal of the American Academy of Dermatology.* 2014 Dec; **71**(6): 1183-90.e3.
 - 42 Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, Toth D, Langley RG, Cather J, Gottlieb AB, Thaçi D, Krueger JG, Rus- sell CB, Milmont CE, Li J, Klekotka PA, Kricorian G, Nirula A. A prospective phase 3, randomised, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *British Journal of Dermatology.* 2016 Feb.
 - 43 Patel S, Patel T, Kerdel FA. The risk of malignancy or progres- sion of existing malignancy in patients with psoriasis treated with biologics: case report and review of the literature. *International Journal of Dermatology.* 2015 Dec.