The fantastic Interleukins

Role in health and disease

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Allergy and Clinical Immunology

Chapters 13 - 25

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Role in health and disease

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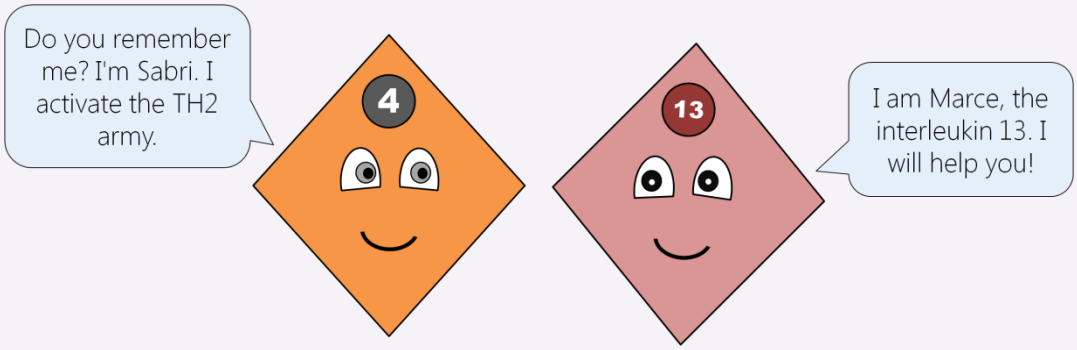
Since we are born, many dangerous microbes and malignant cells threaten our life. Therefore, we need to have powerful cells and molecules capable of defending us. We will call immune system to our body defenses, and immunocytes to the immune cells that protect us.

Our immunocytes are very strong to attack threatening organisms and cells. However, they tolerate certain molecules such as self proteins, good microbes, food and harmless substances.

Immunocytes communicate between them and with other cells through proteins called interleukins. In this book we will learn in a very simple and didactic way about our 38 interleukins and their role in health and disease.

Marce, the interleukin 13



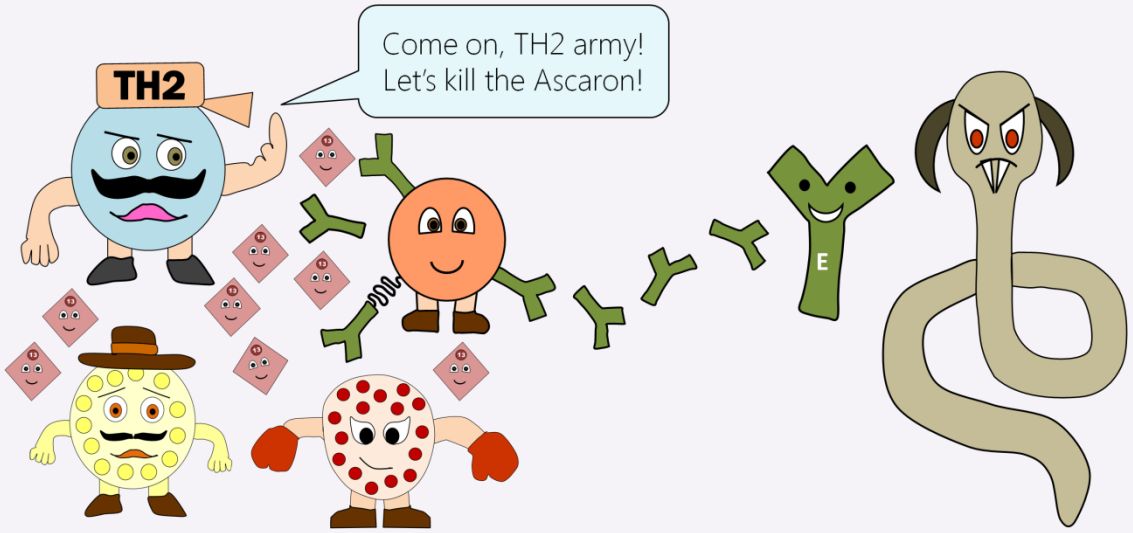
IL-13 exerts similar actions to IL-4; both cytokines induce the TH2 immune response against helminths. An important difference between them is that IL-13, unlike IL-4, does not have a receptor on T lymphocytes; therefore, IL-13 cannot directly promote the differentiation of CD4 TH2 lymphocytes.

The major receptor of IL-13 is formed by the IL-4Rα chain (it is also part of the IL-4 receptor) and the IL-13Rα1 chain.

Where is Marce produced?

Marce is synthesized by TH2 lymphocytes, type 2 innate lymphoid cells, basophils, mast cells and eosinophils. Marce amplifies the TH2 immune response through the following actions:

- Induces synthesis of IgE by B lymphocytes.
- Activates mast cells and eosinophils.
- Increases mucus production by epithelial cells.
- Stimulates smooth muscle contraction.
- Promotes tissue remodeling.



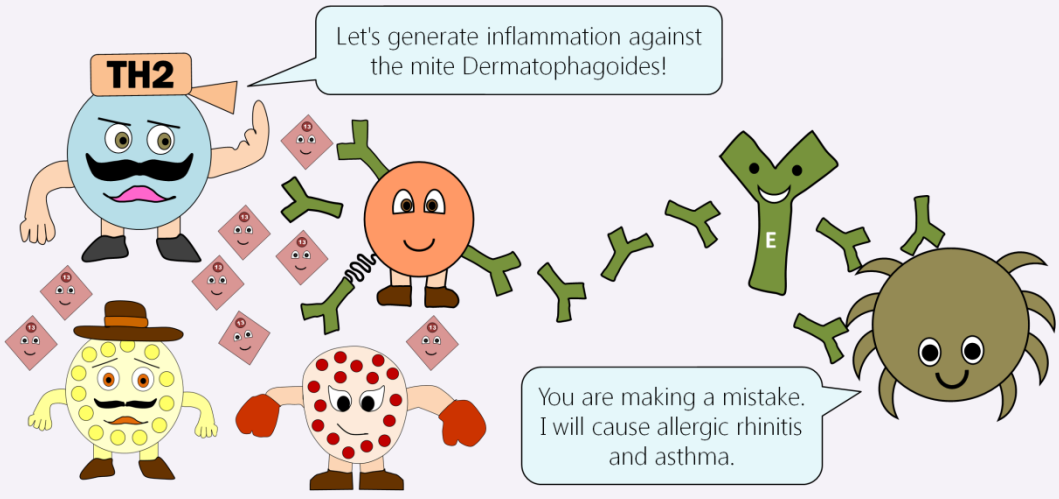
Are there people who cannot produce IL-13?

Immunodeficiencies due to lack of IL-13 have not been described.

Are there people who fabricate IL-13 in excess?

Yes, an excess of IL-13 favors the development of TH2 allergic diseases (e.g. asthma, allergic rhinitis). Certain polymorphisms in the IL-13 gene generate susceptibility to these allergies.

Anti-IL-13 monoclonal antibodies (e.g. Lebrikizumab and Tralokinumab) could be useful to treat TH2 allergies. These drugs are especially useful in patients with high levels of serum periostin (biomarker of IL-13 activity).



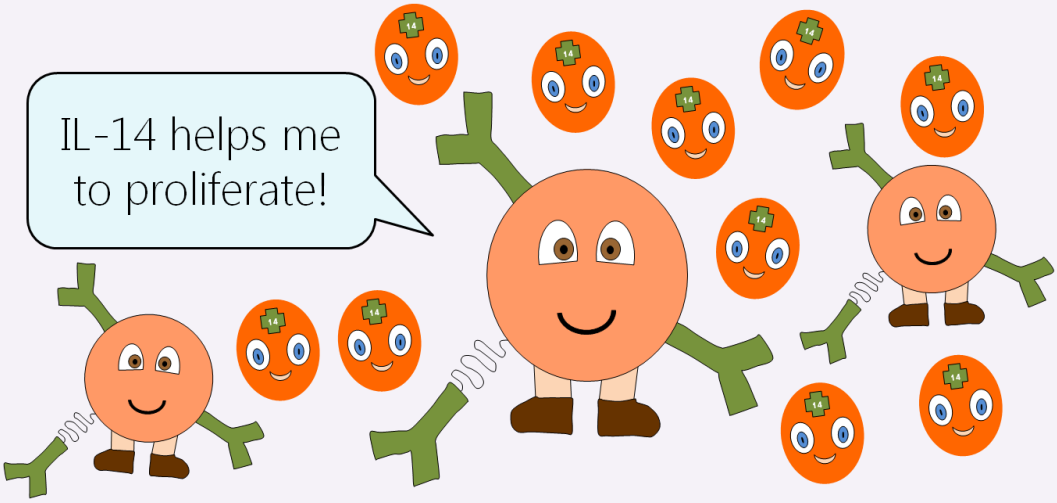
Iris, the interleukin 14

Interleukin 14 is also known as alpha-taxilin or high molecular weight B-cell growth factor (HMW-BCGF). Its receptor is expressed primarily in activated B lymphocytes.

Where is Iris produced?

The main sources of IL-14 are T lymphocytes and some tumor clones of T and B cells.

The main function of Iris is to induce the proliferation of activated B lymphocytes.



Are there people who cannot produce IL-14?

To date, no human immunodeficiencies have been reported due to the absence of IL-14

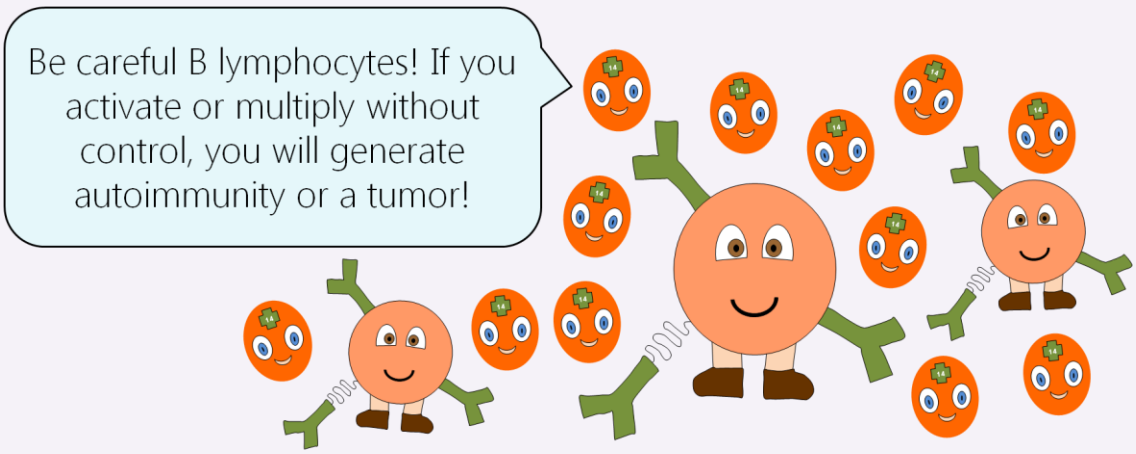
Are there people who fabricate IL-14 in excess?

IL-14 favors the proliferation of B lymphocytes, which could be useful to fight against infections.

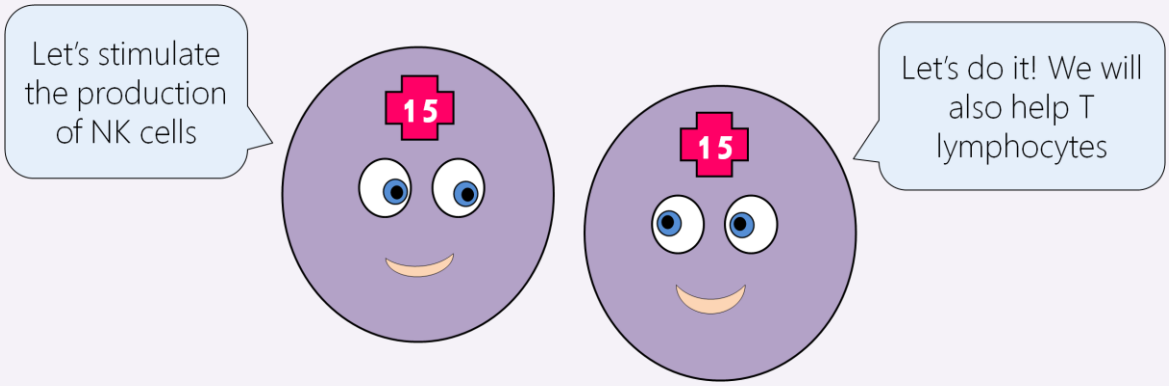
However, the activity of IL-14 becomes dangerous if activated B lymphocytes are:

- Malignant, capable of inducing B cell neoplasms (e.g. B lymphomas).
- Self-reactive, capable of generating autoimmune diseases by autoantibody production (e.g. systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, etc.).

Could IL-14 be a therapeutic target in patients with B-cell neoplasms or autoimmunity? We do not know yet, but it is an interesting hypothesis that could be investigated.



Vicki, the interleukin 15



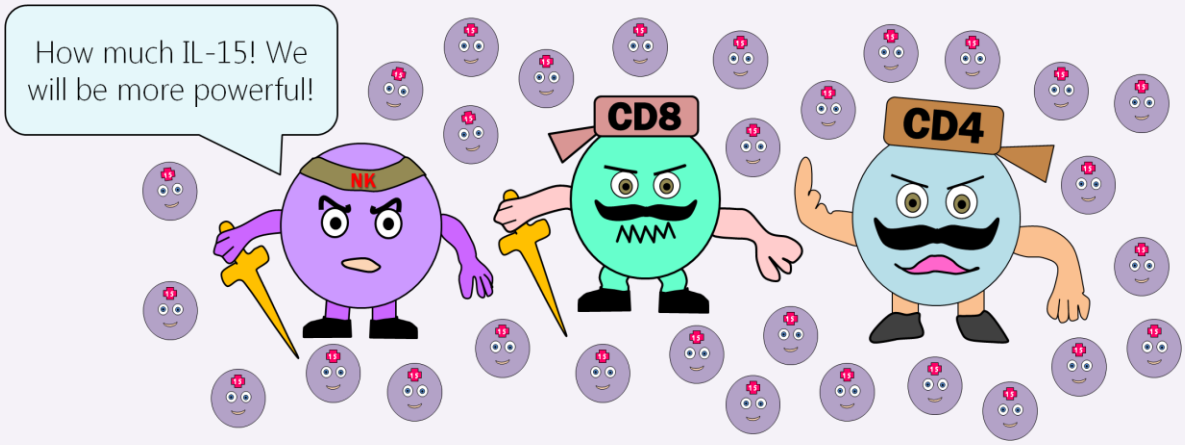
IL-15 exerts similar actions to IL-2 (they are structurally similar), although with greater influence in the production of NK lymphocytes.

The receptor of Vicki, our IL-15, consists of 3 subunits: IL-15Rα, IL-2Rβ and the common gamma chain (γc). Do not forget that γc is also part of the receptors of interleukins 2, 4, 7, 9 and 21.

Where is Vicki produced?

Many cells are capable of making IL-15, including monocytes/macrophages, dendritic cells, activated T CD4 lymphocytes, keratinocytes, skeletal muscle cells, fibroblasts, epithelial cells, bone marrow stromal cells and nerve cells.

The major role of IL-15 is to induce the production and activation of NK lymphocytes. It also activates T lymphocytes and innate lymphoid cells. Furthermore, it promotes the survival of neutrophils and eosinophils.



Are there people who cannot produce IL-15?

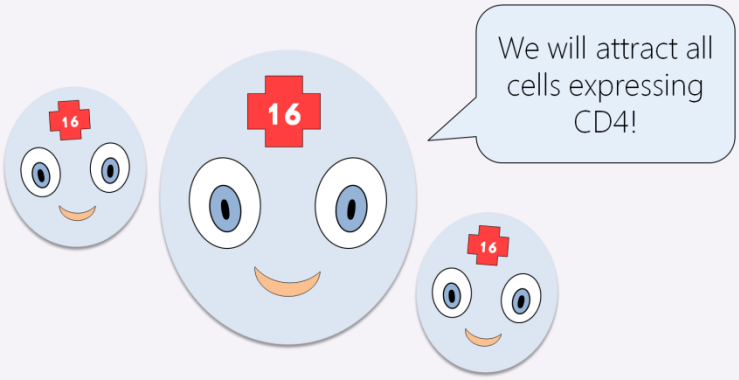
Children lacking γc have severe X-linked combined immunodeficiency. They cannot produce T or NK lymphocytes because signaling of interleukins 2, 7 and 15 is abolished.

Human recombinant IL-15 may help patients with neoplasms and immunodeficiencies by potentiating T and NK lymphocytes.

Are there people who fabricate IL-15 in excess?

Excessive activity of IL-15 may favor the development of autoimmune diseases (e.g. type 1 diabetes, systemic lupus erythematosus, sarcoidosis, pemphigus, rheumatoid arthritis, celiac disease, psoriasis, etc.). In patients with these diseases the use of anti-IL-15 monoclonal antibodies might be useful.

Jess, the interleukin 16



Jess is a cytokine with chemotactic activity. Its receptor is the CD4 protein, so, Jess attracts cells expressing this molecule (e.g. T CD4 lymphocytes, monocytes/macrophages, dendritic cells, mast cells, eosinophils).

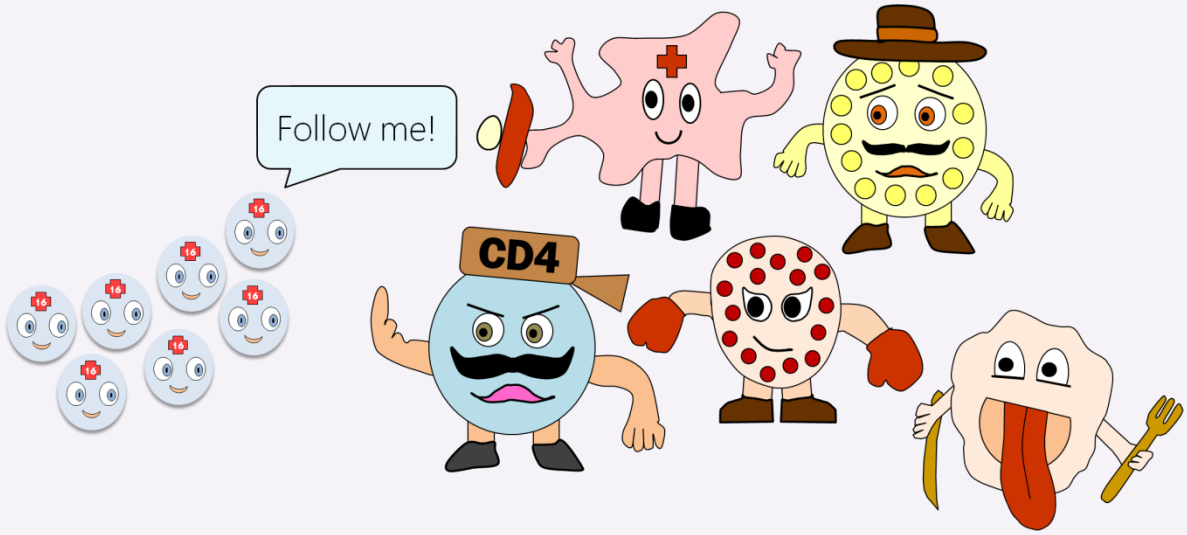
Jess was also called 'lymphocyte chemoattractant factor'.

Where is Jess produced?

Cells that produce IL-16 include T lymphocytes, eosinophils, mast cells, monocytes, dendritic cells, epithelial cells and fibroblasts. Jess is synthesized when caspase 3 cleaves the precursor pro-IL-16.

In addition to its chemotactic ability, Jess modulates the action of T lymphocytes:

- Promotes TH1 immunity by activating secretion of TNF-α, IL-1β and IL-15.
- Reduces TH2 inflammation by inhibiting the synthesis of IL-4 and IL-5.



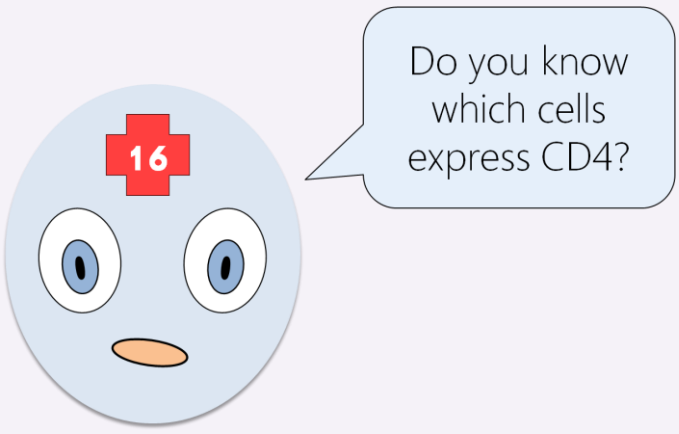
Are there people who cannot produce IL-16?

Immunodeficiencies caused by genetic defects of IL-16 have not been described yet.

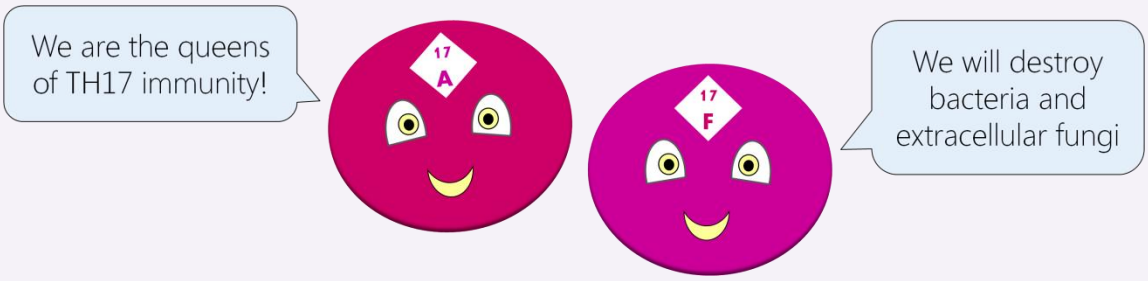
¿Hay personas que fabrican IL-16 en exceso o inapropiadamente?

Polymorphisms in the IL-16 gene that increase the activity of this cytokine may favor the development of inflammatory diseases (e.g. rheumatoid arthritis, endometriosis, reperfusion injury, multiple sclerosis, chronic hepatitis B, transplant rejection, cancer).

IL-16 serum levels could be a biomarker of activity in these diseases. Moreover, affected patients could benefit from the use of anti-IL-16 antibodies.



Anne, the IL-17A, and her sisters



The interleukin 17 family has 6 members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also named IL-25) and IL-17F.

Anne is our powerful IL-17A. She acts through IL-17RA receptor to protect us from the attack of extracellular fungi and bacteria (e.g. *Candida albicans*, *Staphylococcus aureus*). The same functions are fulfilled by her sister Ana, our IL-17F, through its receptor formed by the subunits IL-17RA and IL-17RC.

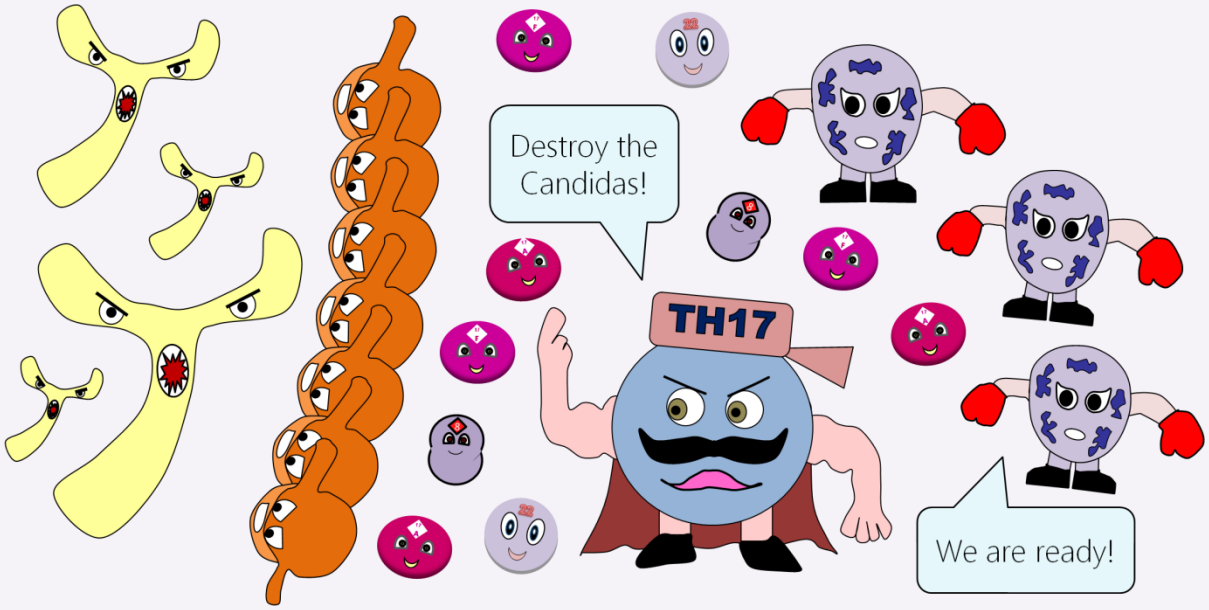
Where are they produced?

Anne and Ana are mainly produced by TH17 lymphocytes and type 3 innate lymphoid cells. Both have proinflammatory actions:

- Activation of epithelial cells to synthesize antimicrobial peptides and chemokines.
- Recruitment and activation of neutrophils.

Are there people who cannot produce IL-17A or IL-17F?

Patients with pathogenic mutations in the IL-17F, IL-17RA or IL-17RC genes are susceptible to infections by extracellular fungi and bacteria, especially *Candida albicans*.

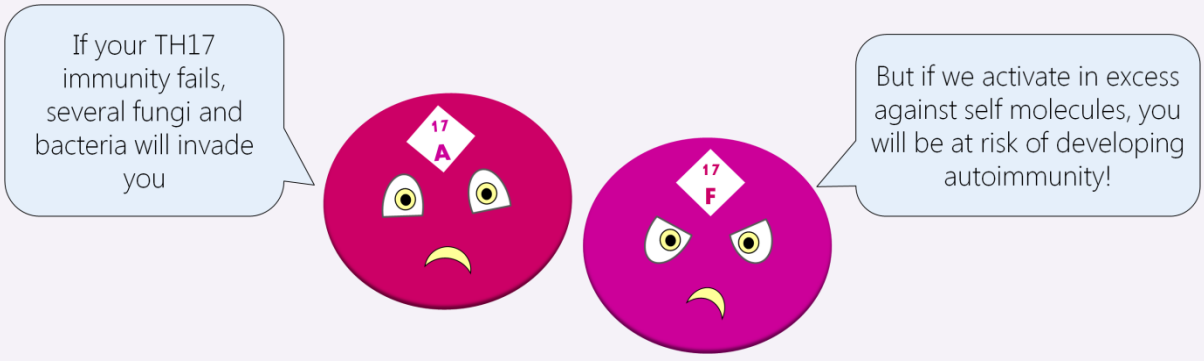


The same problem affects patients with genetic defects that impede the development of TH17 lymphocytes (e.g. CARD9, STAT3 or ACT1 deficiencies, STAT1 hyperfunction).

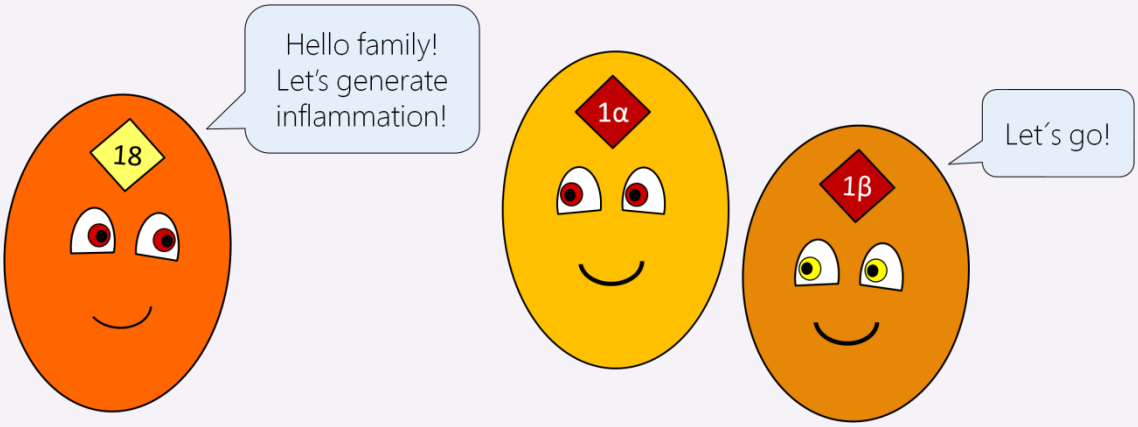
Are there people who fabricate IL-17A or IL-17F in excess?

Several autoimmune diseases (e.g. rheumatoid arthritis, psoriasis, neutrophilic asthma) occur due to a pathologic activity of our TH17 army with excessive production of IL-17A and IL-17F. Affected patients may improve with drugs targeting these cytokines, such as:

- Secukinumab and Ixekizumab (anti-IL-17A antibodies).
- Bimekizumab (dual inhibitor of IL-17A and IL-17F) or Brodalumab (anti-IL-17RA monoclonal antibody).



Pia, the interleukin 18



IL-18 belongs to the IL-1 superfamily. It is also called 'interferon-gamma inducing factor'. Its biological activity can be neutralized by IL-18bp (IL-18 binding protein).

Where is Pia produced?

Pia can be synthesized by macrophages, dendritic cells, epithelial cells, chondrocytes and osteoblasts.

The inflammatory action of Pia includes the activation of TH1 and NK cells. Pia induces interferon-γ synthesis and cellular cytotoxicity.

Are there people who cannot produce IL-18?

Human primary immunodeficiencies due to IL-18 gene mutations have not been described yet.

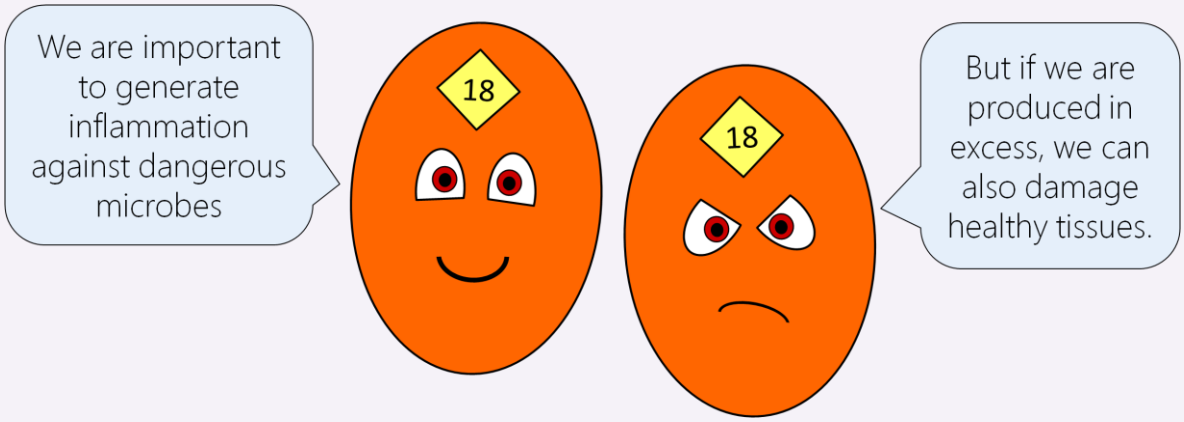
Recombinant human IL-18 could be useful to treat patients with cancer or chronic infections, because of its immune stimulatory activity.

Are there people who fabricate IL-18 in excess?

Yes. Excessive IL-18 production may favor the development of autoimmune and inflammatory diseases (e.g. rheumatoid arthritis, psoriasis, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, Alzheimer's disease, macrophage activation syndrome, hemophagocytosis, autoinflammatory disorders).

In patients with these diseases, IL-18 can be a therapeutic target. For example:

- Tadekinig alfa (human recombinant IL-18bp) is a compound that targets and neutralizes IL-18. Its usefulness has been investigated for the treatment of rheumatoid arthritis, psoriasis and adult-onset Still's disease.



Vane, the interleukin 19

In comparison to other cytokines, there is modest research on IL-19 physiology. Nevertheless, we will review about it.

IL-19 belongs to the interleukin 10 family, along with other cytokines (IL-10, IL-20, IL-22, IL-24, IL-26, IL-28 and IL-29).

However, unlike IL-10 which essentially has regulatory activity, IL-19 can induce the activation of our TH2 army and the proliferation of keratinocytes through its receptor formed by the IL-20R1 and IL-20R2 subunits.

Where is Vane produced?

Vane is produced by various cells, including monocytes, keratinocytes, endothelial cells, epithelial cells and B lymphocytes.

Vane can favor the synthesis of interleukins 4, 5, 10 and 13 from T lymphocytes, thus favoring TH2 immunity. She is also capable of inducing expression of keratinocyte growth factor (KGF).

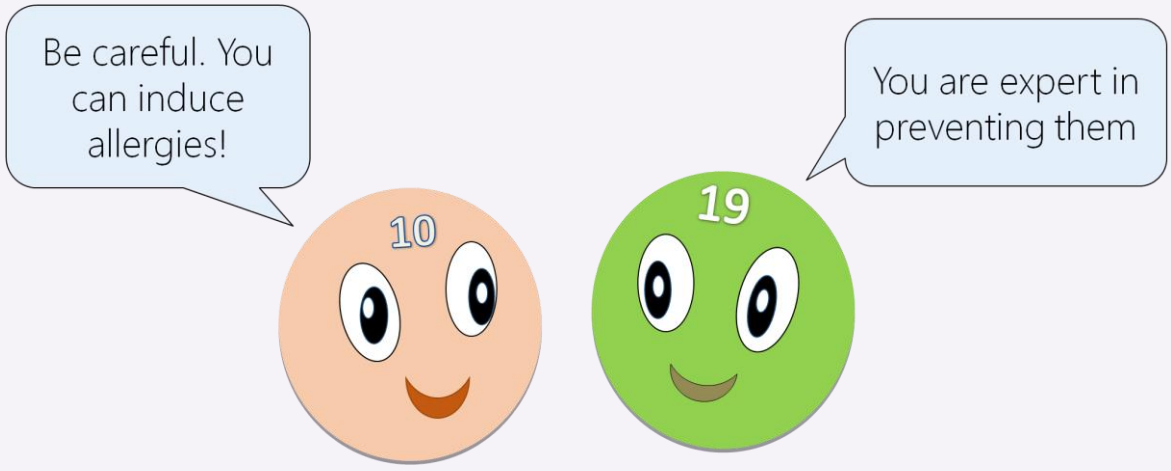
Are there people who cannot produce IL-19?

To the best of our knowledge, there are no reports of people with primary immunodeficiency due to lack of IL-19 synthesis.

Are there people who fabricate IL-19 in excess?

Increased levels of IL-19 have been reported in patients with bronchial asthma. Excessive production of IL-19 could favor the development of TH2 allergic diseases such as asthma or atopic dermatitis.

Moreover, Vane could favor the onset of psoriasis by inducing keratinocyte growth factor (KGF).



Kate, the interleukin 20

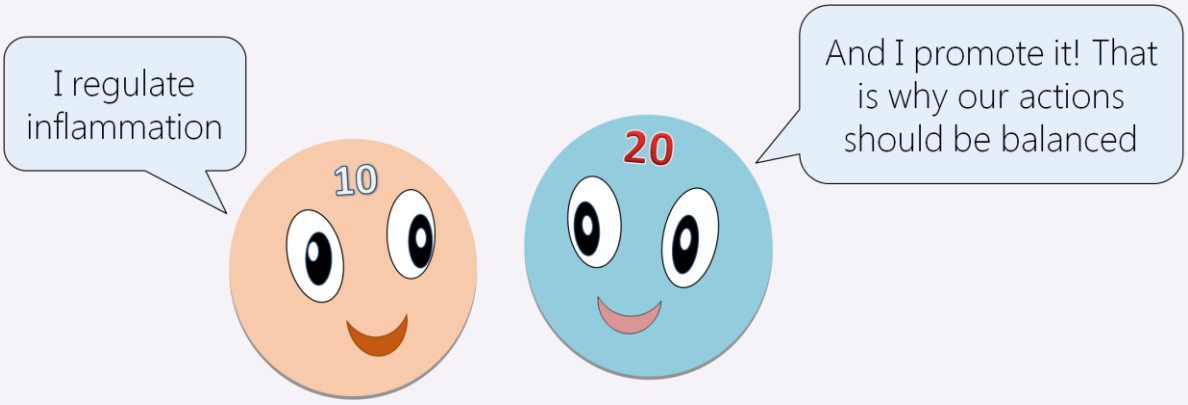
Kate is a member of the interleukin IL-10 family, which includes interleukins 19, 20, 22, 24, 26, 28 and 29. Kate is also recognized as the leader of the interleukin 20 subfamily, together with interleukins 19, 22, 24 and 26, because they share subunits in their respective receptors.

Kate acts through 2 types of receptors: one consists of the IL-20R1 and IL-20R2 subunits; the other is formed by the IL-22R1 and IL-20R2 chains.

Where is Kate produced?

Kate can be synthesized by monocytes, keratinocytes, epithelial cells, dendritic cells and endothelial cells.

Unlike IL-10, Kate is essentially proinflammatory. Her major activity is to induce the proliferation and differentiation of epithelial cells during inflammatory processes, especially in the skin. She can also favor the expansion of multipotent hematopoietic progenitor cells.



Are there people who cannot produce IL-20?

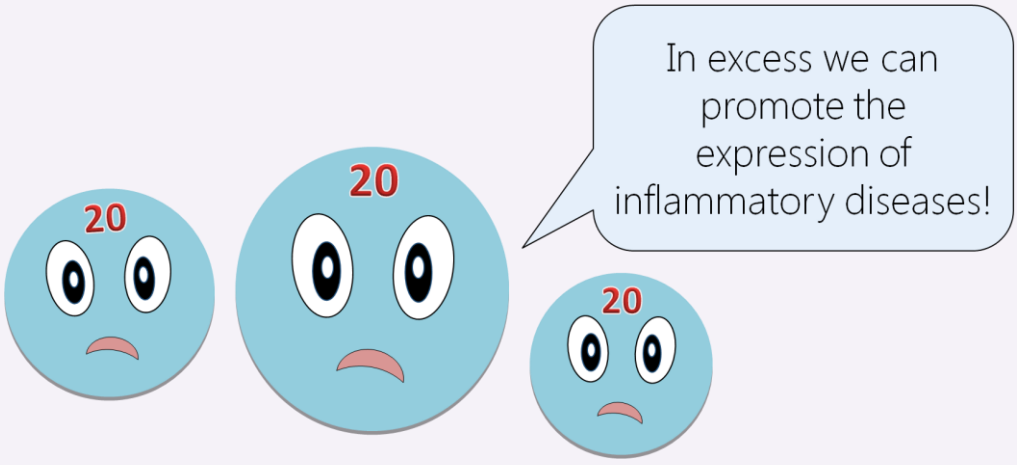
To date, no individuals with inherited errors of IL-20 production have been reported.

Are there people who fabricate IL-20 in excess?

Similar to interleukin 19, IL-20 may have an inductive role in the pathogenesis of psoriasis.

In addition, an excess of IL-20 activity has been reported in other inflammatory diseases (asthma, rheumatoid arthritis, systemic lupus erythematosus, obesity, atherosclerosis, ulcerative colitis, osteoporosis, multiple myeloma).

For this reason, IL-20 can represent a biomarker of disease activity and a therapeutic target in affected patients.

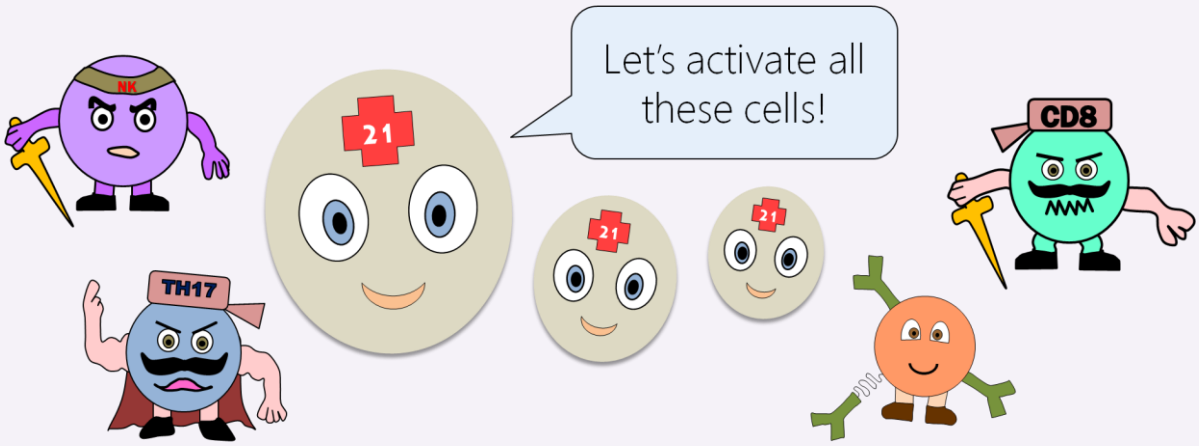


Lisa, the interleukin 21

Lisa exerts her immune-stimulating actions through the IL-21R receptor, which is made up of the IL-21Rα subunit and the common gamma chain (γc). Remember that γc is also part of the receptors of interleukins 2, 4, 7, 9 and 15.

Where is Lisa produced?

The main source of IL-21 are T lymphocytes, mainly follicular helper T cells, which potentiate B lymphocytes in the follicles of secondary lymphatic organs such as lymph nodes and spleen. Other sources of IL-21 are TH2, TH9, TH17 and NKT lymphocytes.



Lisa is able to stimulate:

- Proliferation, specialization and maturation of B lymphocytes.
- Cytotoxic activity of CD8 and NKT lymphocytes.
- Activation of TH17 lymphocytes.

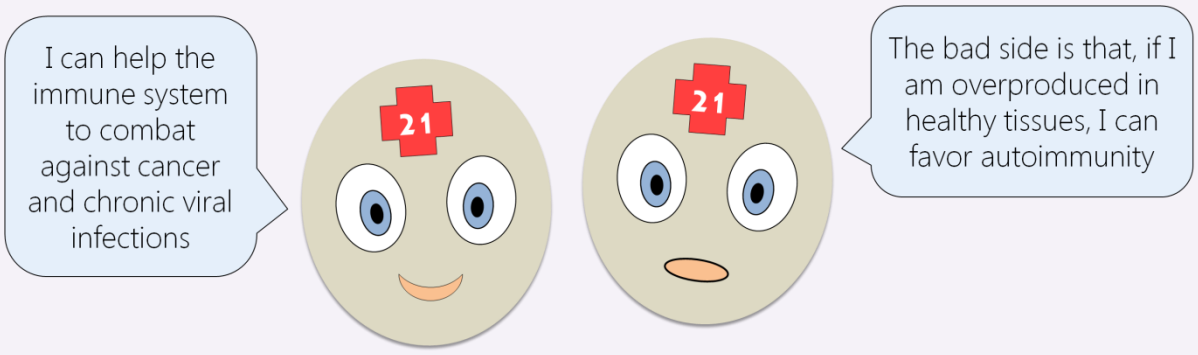
Are there people who cannot produce IL-21?

X-linked severe combined immunodeficiency (X-SCID) occurs due to pathogenic mutations in the γc gene. Patients with X-SCID are fragile against all types of microbes because the signaling of interleukins 2, 4, 7, 9, 15 and 21 is impaired.

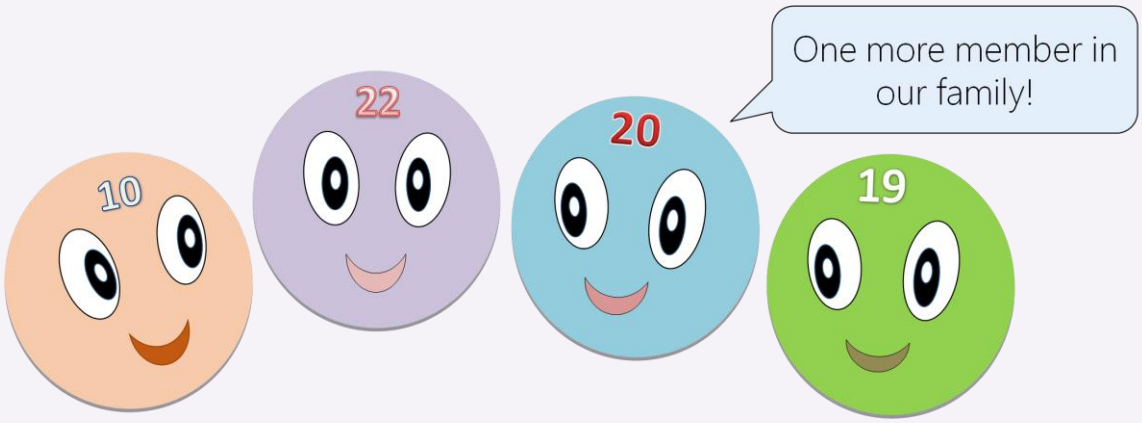
Recombinant human IL-21 (Denenicokin) is a potential therapy against neoplasms and chronic viral infections by potentiating CD8 and NKT lymphocytes.

Are there people who fabricate IL-21 in excess?

Overproduction of IL-21 after recognition of self molecules favors the development of autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, psoriasis, type 1 diabetes). Anti-IL-21 monoclonal antibodies may have a therapeutic role in these diseases.



Sami, the interleukin 22



Our wonderful Sami belongs to the family of IL-10 and the subfamily of IL-20. Its receptor is made up of the IL-22R1 and IL-10R2 chains.

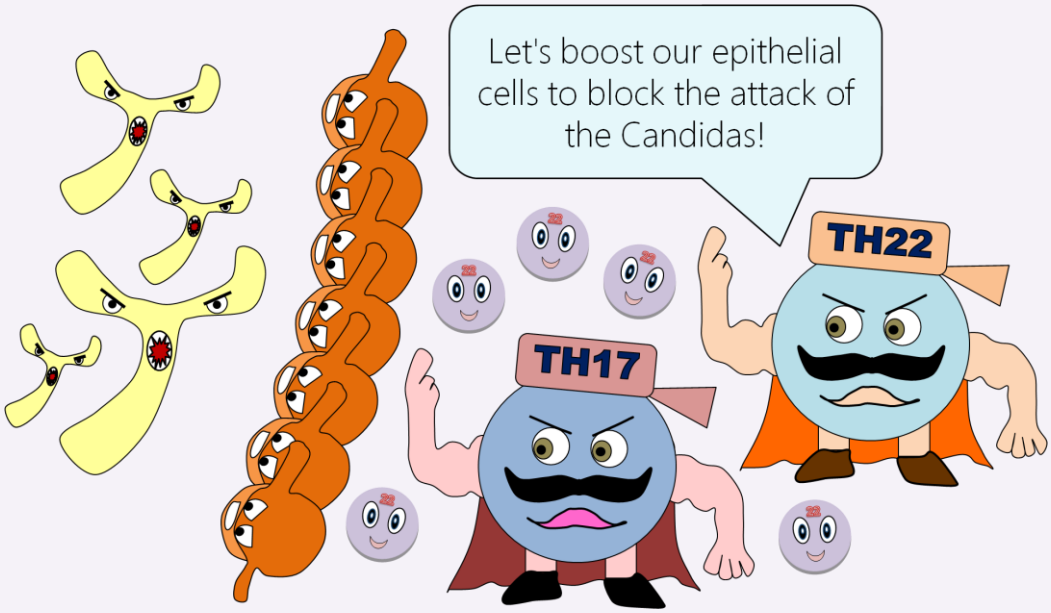
A differential feature of Sami among cytokines is that she is produced by immune cells but acts on non-hematopoietic stromal cells.

Where is Sami produced?

Sami can be synthesized by several types of cells: TH22 lymphocytes, TH17 lymphocytes, type 3 innate lymphoid cells, lymphoid tissue inducer cells, mast cells and NK lymphocytes.

The main target cells of IL-22 are keratinocytes and epithelial cells of the kidney, gut, liver, pancreas and lung.

Sami promotes innate defense against pathogenic microbes, synthesis of antimicrobial peptides (e.g. defensins), cell proliferation and tissue repair.



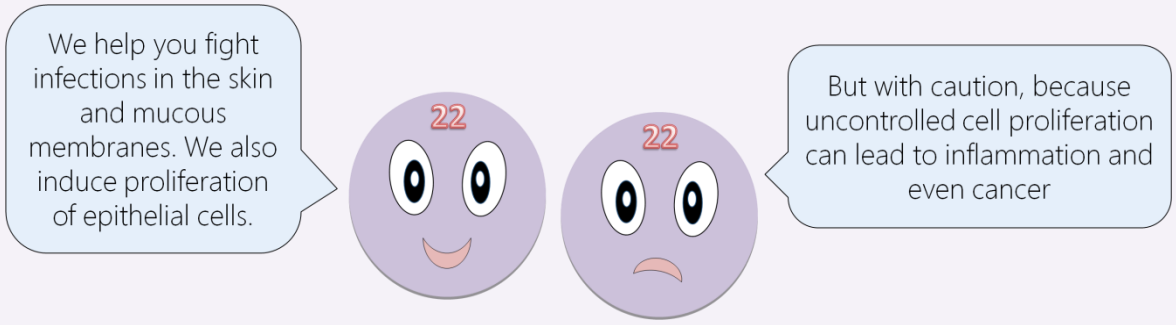
Are there people who cannot produce IL-22?

Patients with genetic defects affecting TH17 immunity (e.g. STAT1 hyperfunction, CARD9 deficiency) are less able to produce IL-22. As a consequence, innate defense in skin and mucosas is weakened, thereby increasing the risk of fungal and bacterial infections.

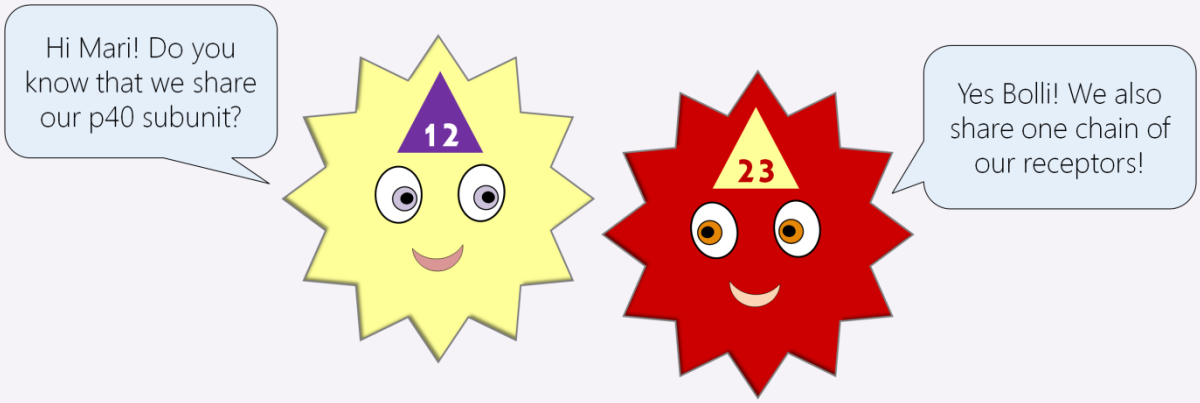
Are there people who fabricate IL-22 in excess?

Patients with psoriasis and atopic dermatitis have increased IL-22 levels in the skin. By inducing proliferation of epithelial cells, excess IL-22 can promote the appearance of epithelial neoplasms and inflammatory diseases such as rheumatoid arthritis.

Fezakinumab (anti-IL-22) could not reach commercialization.



Mari, the interleukin 23



Mari has 2 subunits: IL-23p19 and IL-12p40. Remind that IL-12p40 is also part of Bolli, our interleukin 12.

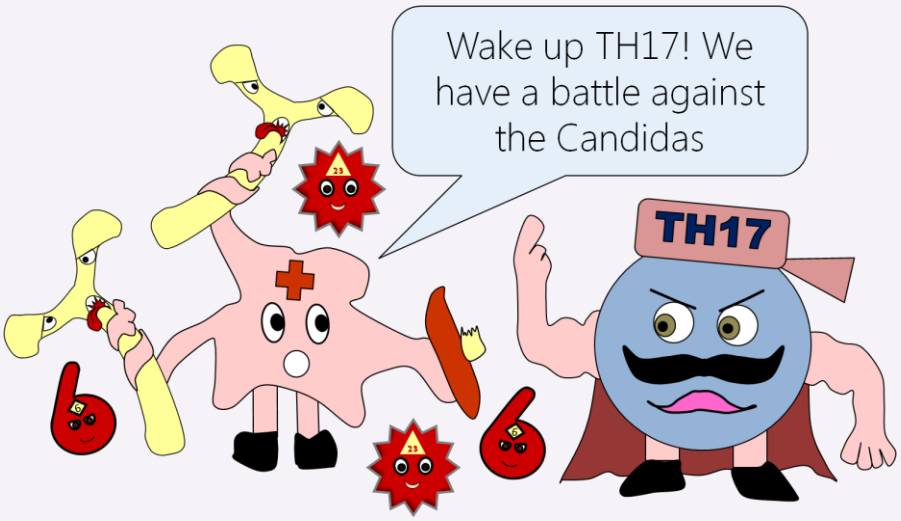
The receptor of IL-23 is composed of 2 chains: IL-12Rβ1 (it also makes up the IL-12 receptor) and IL-23R.

Where is Mari produced?

Mari is mainly produced by dendritic cells and macrophages in response to the attack of extracellular bacteria and fungi (e.g. *Candida albicans, Staphylococcus aureus*). Mari is an essential component in the fight against these microbes by inducing the differentiation of our TH17 lymphocytes.

Are there people who cannot produce IL-23?

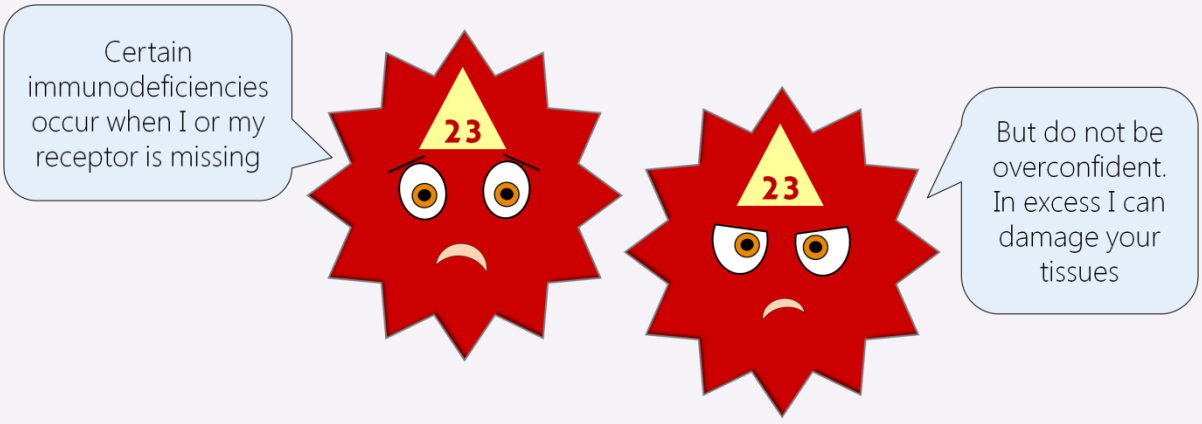
Individuals with genetic deficiencies of the IL-12p40 subunit or the IL-12Rβ1 chain have impaired signaling of interleukins 12 and 23, becoming susceptible to infections by several microbes, both intracellular (e.g. mycobacteria, *Salmonella spp*, *Histoplasma capsulatum*) and extracellular (e.g. *Candida albicans*).



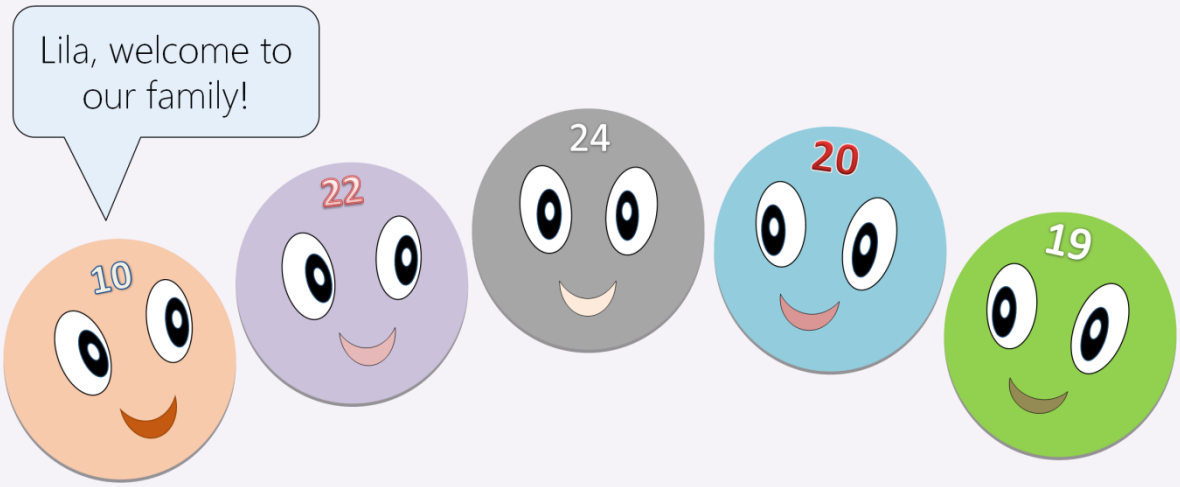
Are there people who fabricate IL-23 in excess?

Excessive production of IL-23 against self molecules promotes the appearance of inflammatory diseases, such as psoriasis, Crohn's disease, spondyloarthropathies and lupus. Affected patients may benefit from IL-23 inhibition. For example:

- The monoclonal antibodies Guselkumab and Tildrakizumab are directed against the subunit IL-23p19, thus inhibiting the activity of the TH17 immune army.
- The biological drug Ustekinumab neutralizes the IL-12p40 subunit of interleukins 12 and 23. In consequence, it exerts an inhibitory effect on both TH1 and TH17 armies.



Lila, the interleukin 24



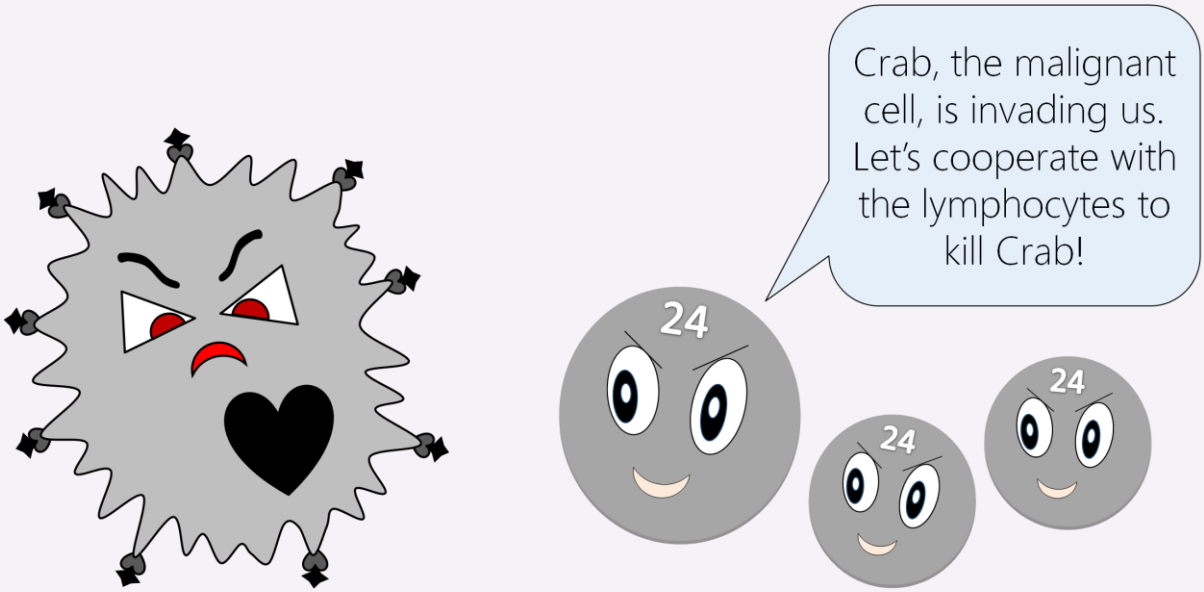
Lila, also called MDA-7 (melanoma differentiation associated gene-7), belongs to the IL-10 family and the IL-20 subfamily. It performs its functions through 2 receptors: IL-20R1/IL-20R2 and IL-22R1/IL-20R2.

Lila loves to inhibit the growth of malignant cancer cells.

Where is Lila produced?

Lila can be synthesized by hematopoietic cells (e.g. monocytes, T lymphocytes, B cells) and non-hematopoietic cells (e.g. melanocytes, keratinocytes). She has diverse biological functions related to cell proliferation, differentiation and apoptosis. However, its most recognized ability is to block the proliferation of tumor cells.

Recent research has shown that IL-24 might have inhibitory activity against influenza virus.



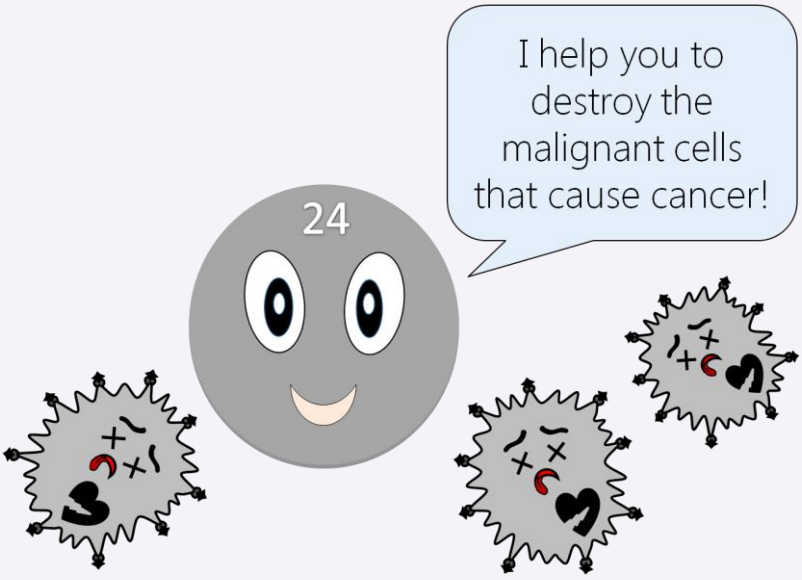
Are there people who cannot produce IL-24?

Primary immunodeficiencies due to mutations in the IL-24 gene have not been reported.

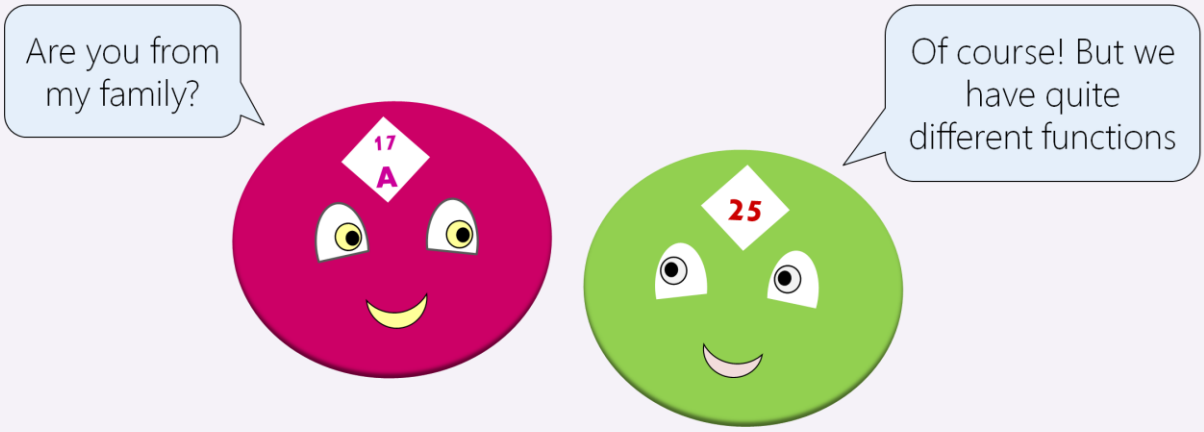
Therapy with recombinant IL-24 has the potential to inhibit the growth of malignant cells in patients with cancer.

Are there people who fabricate IL-24 in excess?

Excessive synthesis of IL-24 could favor the onset of inflammatory diseases such as psoriasis.



Flor, the interleukin 25



Flor, also known as IL-17E, is a member of the interleukin 17 family. However, unlike her sisters IL-17A and IL-17F, Flor is a cytokine that activates our TH2 army. Her receptor has 2 chains: IL-17RA and IL-17RB.

Where is Flor produced?

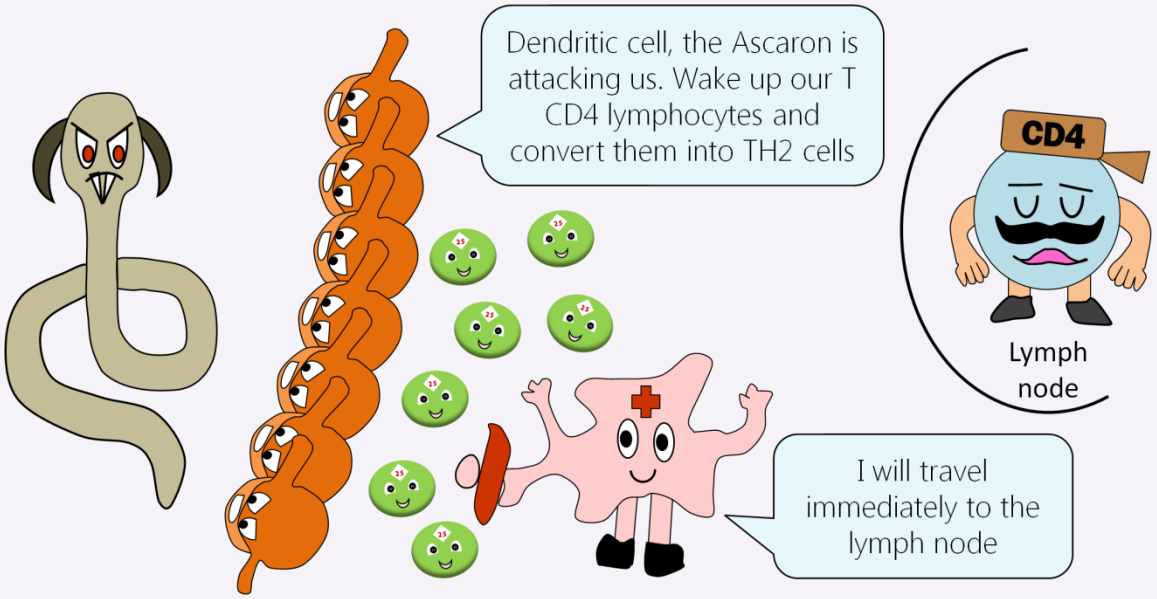
Flor is made by epithelial cells and several cells of the TH2 army (TH2 lymphocytes, eosinophils, mast cells and basophils).

Flor activates our TH2 army in the battle against helminths, by promoting synthesis of IgE and interleukins 4, 5, 9 and 13.

It is very interesting to note that, like IL-24, Flor has the ability to destroy malignant cells that cause cancer.

Are there people who cannot produce IL-25?

IL-25-deficient mice are less able to expel the helminth *Nippostrongylus brasiliensis*.

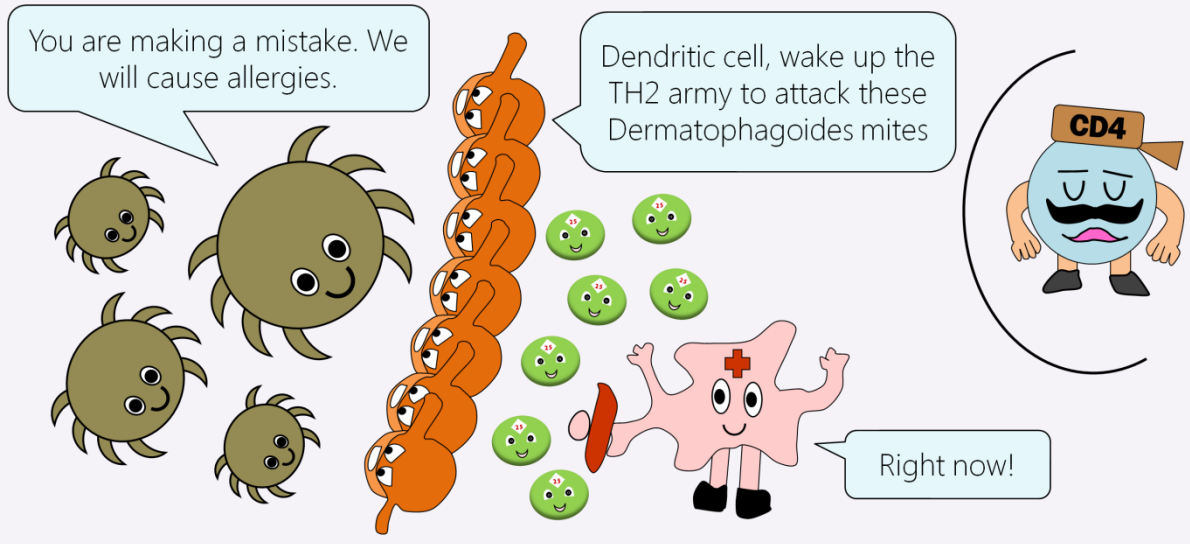


Patients with genetic mutations in *IL17RA* are susceptible to extracellular fungal and bacterial infections, because of impaired signaling of IL-17A and IL-17F.

IL-25 is a potential treatment for cancer.

Are there people who fabricate IL-25 in excess?

Excessive production of IL-25 after exposure to beneficial or harmless molecules (e.g. *Dermatophagoides* mites) induces the development of TH2 allergies (e.g. asthma, allergic rhinitis). Affected patients may benefit from anti-IL-25 biological therapies.



In this book we have learned about the role of interleukins in the normal function of our immune system and in distinct immunological diseases (immunodeficiencies, autoimmunity, allergies, autoinflammation and cancer).

Do not miss our next educational books, where we will continue learning on the fantastic world of Immunology.

Juan Carlos Aldave, MD

Allergy and Clinical Immunology

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Sponsors:

- Jeffrey Modell Foundation
- Luke Society International

"For God so loved the world that he gave his one and only Son, that whoever believes in him shall not perish but have eternal life". **John 3:16**

10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. **If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.**

1. 
Four or more new ear infections within one year.

2. 

Two or more serious sinus infections within one year.

3. 
Two or more months on antibiotics with little effect.

4. 
Two or more pneumonias within one year.

5. 

Failure of an infant to gain weight or grow normally.

6. 
Recurrent, deep skin or organ abscesses.

7. 
Persistent thrush in mouth or fungal infection on skin.

8. 
Need for intravenous antibiotics to clear infections.

9. 

Two or more deep-seated infections including septicemia.

10. 
A family history of PI.

"These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested.

www.INFO4PI.org

Juan Carlos Aldave, MD

Allergy and Clinical Immunology

"Proper functioning of our immune system is essential for life. The purpose of this book series is to introduce everyone into the fantastic world of Immunology".

Book series: Funny Immunology to Save Lives

(Editions in English and Spanish)

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Book 10:	The Immunocytes and transplantation
Book 11:	The armor of the Immunocyte Felix
Book 12:	The fantastic Interleukins

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