

# The fantastic Interleukins

*Role in health and disease*



Juan Carlos Aldave, MD  
Allergy and Clinical Immunology

# **The fantastic Interleukins**

## **Role in health and disease**

Author – Editor: Juan Carlos Aldave

Jr. Domingo Cueto 371, Dpto. 301, Lince

Lima – Perú

Phone: (+51) 948-323-720

[jucapul\\_84@hotmail.com](mailto:jucapul_84@hotmail.com)

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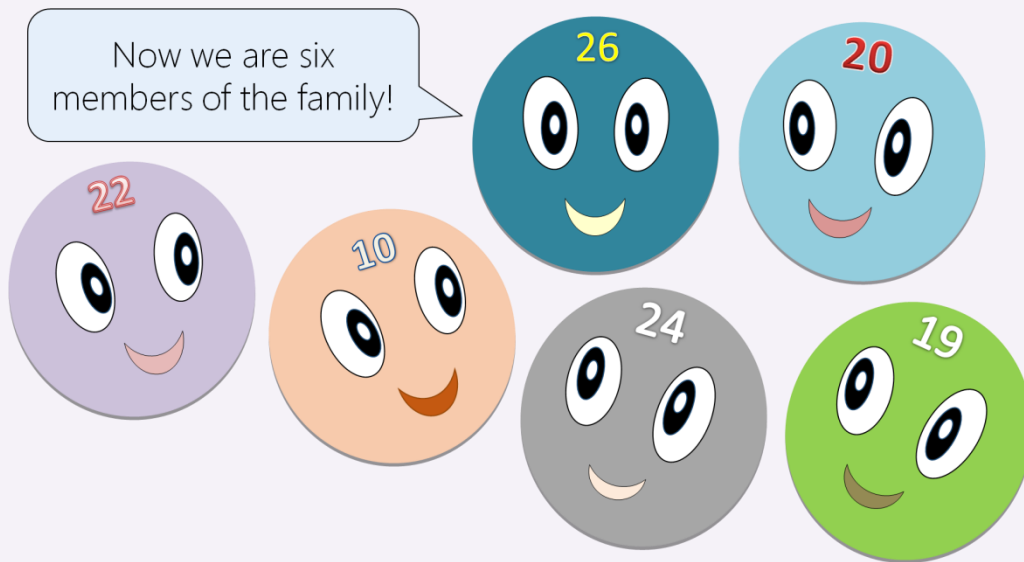
Since we are born, many dangerous microbes and malignant cells threaten our life. Therefore, we need to have powerful cells and molecules capable of defending us. We will call **immune system** to our body defenses, and **immunocytes** to the immune cells that protect us.

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.

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## Shen, the interleukin 26



Shen is part of the IL-10 family and the IL-20 subfamily. Her receptor consists of two chains: IL-10R2 and IL-20R1.

### Where is Shen produced?

Cells that produce IL-26 include T lymphocytes, especially TH17 cells, and NK lymphocytes.

Shen has several antimicrobial actions:

- Promotes the secretion of proinflammatory cytokines IL-1 $\beta$ , IL-8 and TNF- $\alpha$ . Do not forget that IL-8 attracts neutrophils.
- Destroys extracellular bacteria through membrane pores.
- Participates in the recognition of microbial DNA.
- Promotes antiviral defense by stimulating interferon production.



### Are there people who cannot produce IL-26?

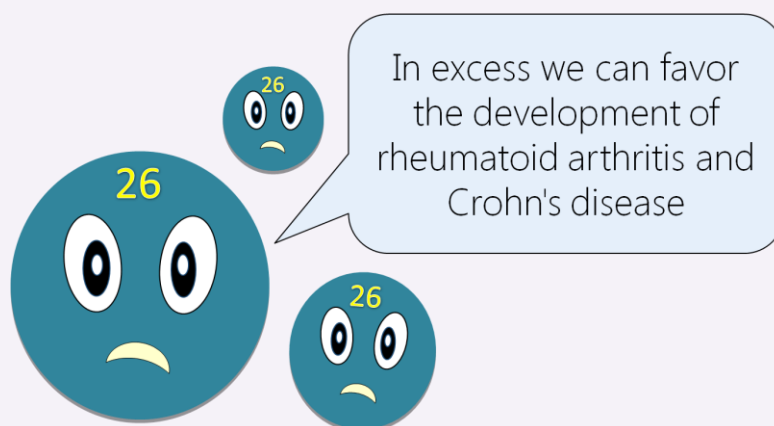
Children with genetic defects in IL-10 receptor (IL-10R1 or IL-10R2) develop severe early-onset inflammatory diseases (inflammatory bowel disease with perianal fistulas, folliculitis, arthritis) secondary to impaired IL-10 signaling.

IL-26 could be useful to prevent osteoclast-induced bone lysis.

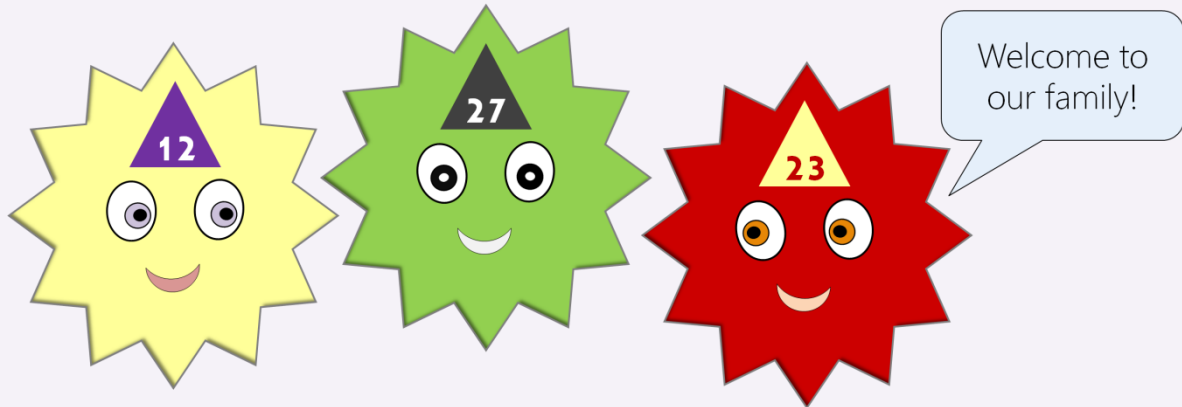
### Are there people who fabricate IL-26 in excess?

TH17-derived interleukin 26 can promote the development of Crohn's disease, rheumatoid arthritis and multiple sclerosis. Therapies targeting TH17 immunity are useful in patients with these autoimmune diseases.

Shen might be useful as a biomarker for neutrophilic diseases such as non-TH2-mediated asthma.



# Luna, the interleukin 27



Luna, nuestra hermosa interleucina 27, es parte de la familia de la IL-12. Tiene 2 subunidades: p28 (¡esta subunidad es la IL-30!) y EBI-3. Su receptor consta de 2 cadenas: gp130 (también forma parte de los receptores de IL-6, IL-11 e IL-35) e IL-27R $\alpha$ .

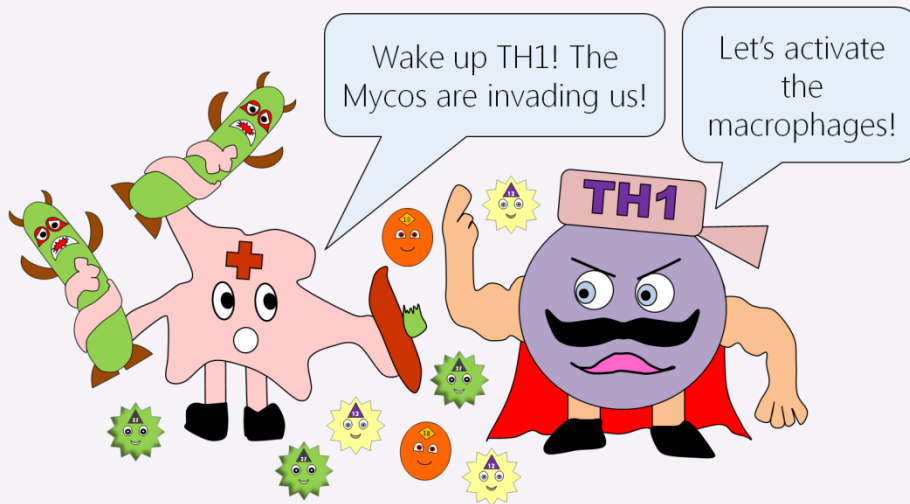
## Where is Luna produced?

Luna, que puede ser fabricada por células dendríticas activadas, macrófagos y células epiteliales, tiene efectos complejos sobre el sistema inmunitario. Sus acciones inflamatorias son:

- Promueve la diferenciación de nuestros linfocitos CD4 TH1 mediante la inducción del factor de transcripción T-bet, para así combatir microbios intracelulares y células tumorales malignas.
- Favorece la activación de nuestros linfocitos NK.

Luna también tiene efectos antiinflamatorios:

- Inhibe la inmunidad TH17 actuando a través de STAT1.
- Induce la síntesis de IL-10 para activar linfocitos T reguladores.



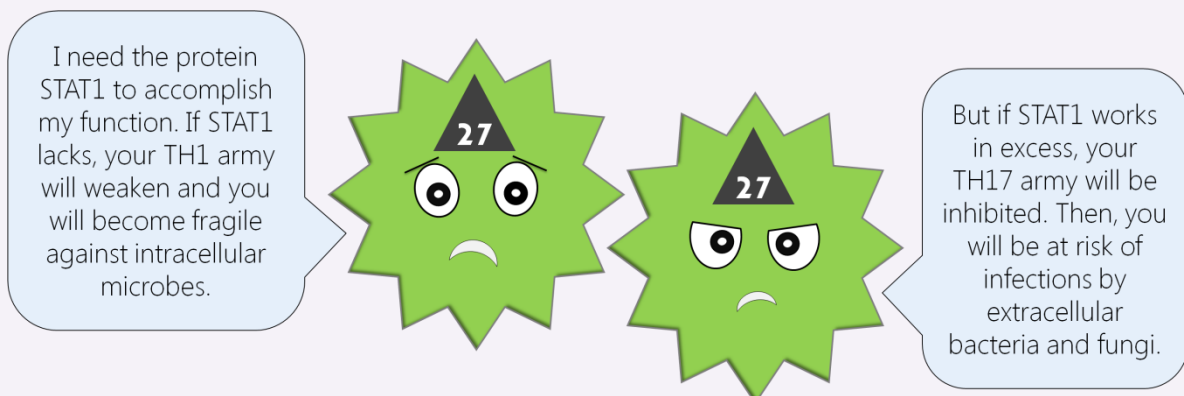
### Are there people who cannot produce IL-27?

Patients with absent or reduced STAT1 function have impaired signaling of several TH1 cytokines (e.g. interferon- $\gamma$ , IL-27, interferons  $\alpha$  and  $\beta$ ), becoming susceptible to infections by intracellular microorganisms such as mycobacteria and viruses.

### Are there people who fabricate IL-27 in excess?

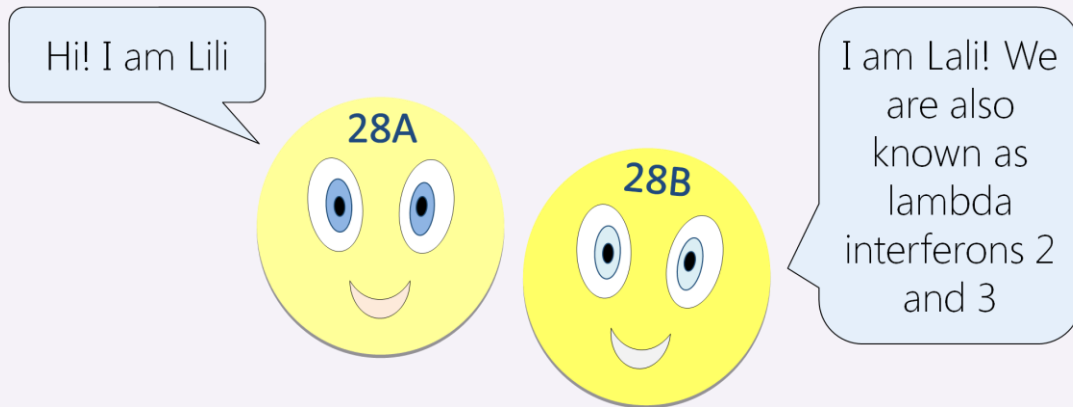
Patients with STAT1 gain-of-function mutations are characterized by an excessive activity of interferons and IL-27, which results in:

- Susceptibility to infections by extracellular fungi and bacteria, as a consequence of a weak TH17 army.
- Autoimmune phenomena such as lupus-like syndrome.





# Lili and Lali, the interleukins 28



Lili is our interleukin 28A, also known as interferon-lambda 2 (IFN- $\lambda$ 2). Her sister Lali is our IL-28B (IFN- $\lambda$ 3). Both belong to the IL-10 family, together with interleukins 10, 19, 20, 22, 24, 26 and 29.

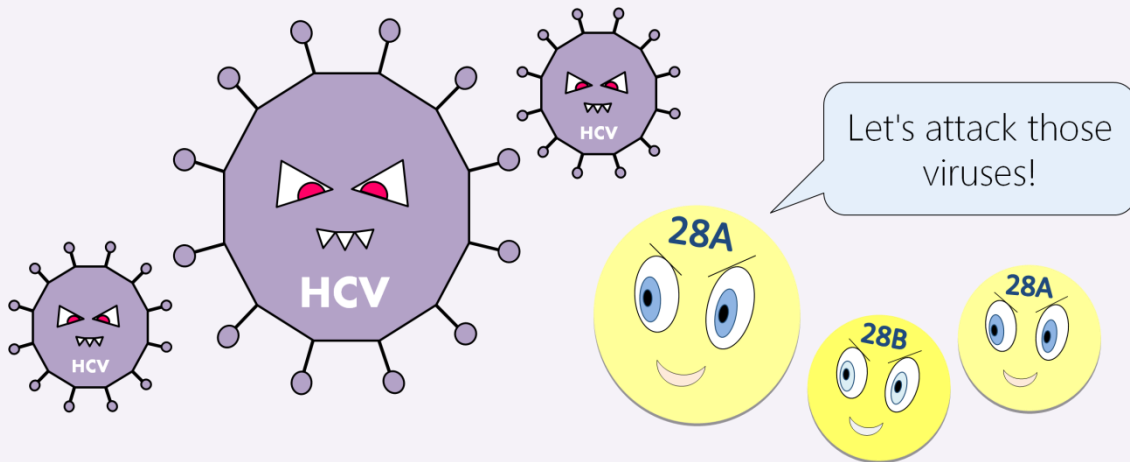
Both sisters exert their actions, essentially antiviral, through a receptor formed by the chains IL-28R1 and IL-10R2.

## Where are they produced?

Lili and Lali are synthesized by various cells, mainly dendritic cells, in response to viral attacks, in order to enhance our TH1 immune army. Both cytokines are capable of inhibiting the replication of hepatitis B and C viruses, as well as stimulating the destruction of cancer cells.

On the other hand, Lili and Lali may contribute to the development of tolerogenic dendritic cells, capable of inducing T regulatory lymphocytes.

Both cytokines have inhibitory activity over the TH2 immune army.



### Are there people who cannot produce IL-28?

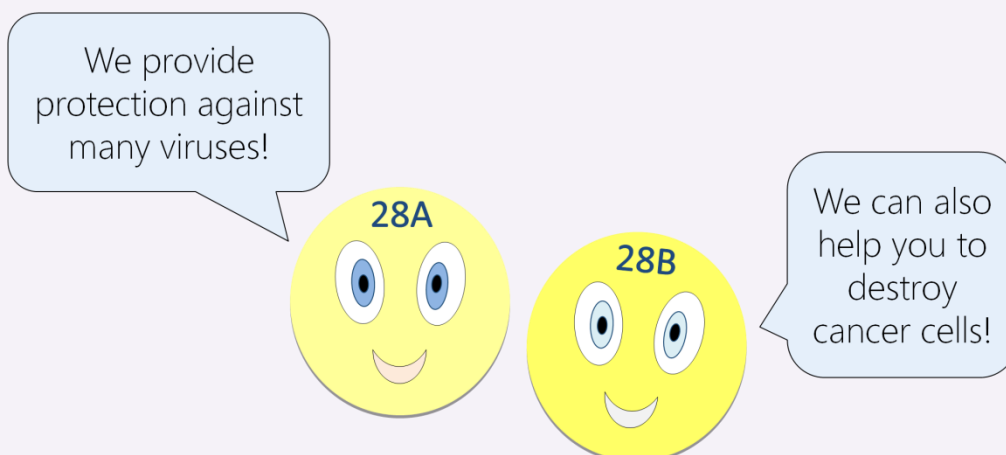
Genetic immunodeficiencies caused by absence of IL-28 have not been described.

Certain polymorphisms in the IL-28B gene predict clinical response to hepatitis C treatment with ribavirin plus interferon  $\alpha$ .

After reviewing their actions, we deduce that Lili and Lali have therapeutic potential against viral infections, malignant tumors and allergic diseases.

### Are there people who fabricate IL-28 in excess?

Unnecessary production of IL-28A or IL-28B may favor the development of autoimmune diseases such as Sjögren's syndrome.



# Areli, the interleukin 29



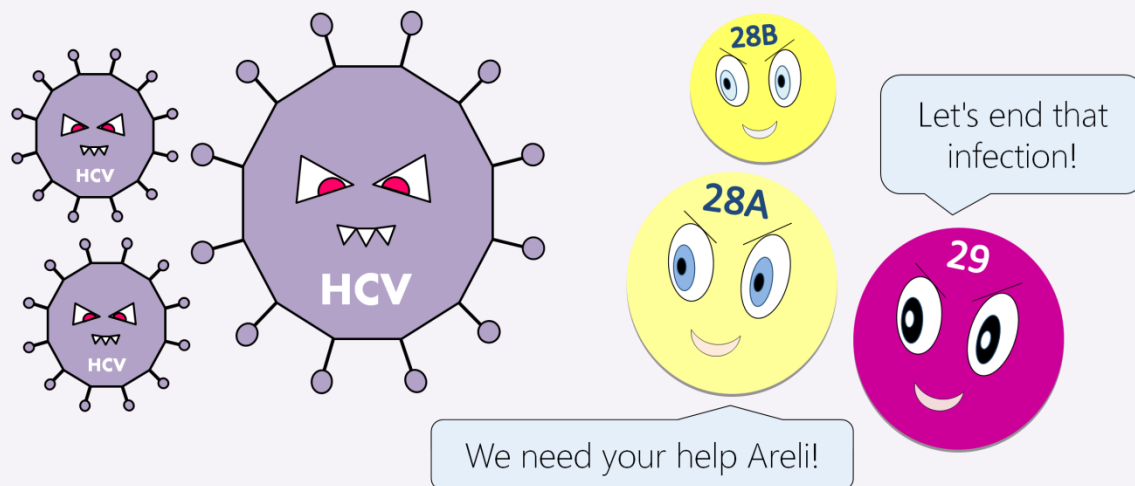
Areli, our beautiful interleukin-29, also called IFN- $\lambda$ 1, completes the family of interferons type III (lambda interferons) together with Lili and Lali (interleukins 28A and 28B). All of them fulfill their functions through a receptor formed by the chains IL-28R1 and IL-10R2.

Areli is also part of the IL-10 family, together with interleukins 10, 19, 20, 22, 24, 26 and 28.

## Where is Areli produced?

Areli is produced by several cells, mainly dendritic cells, in response to viral attack, aiming to boost our TH1 defense army. Like her sisters Lili and Lali, Areli has antiviral and antitumor effects.

Other important actions of Areli are: contribution to the development of tolerogenic dendritic cells, and inhibition of the TH2 immune army.



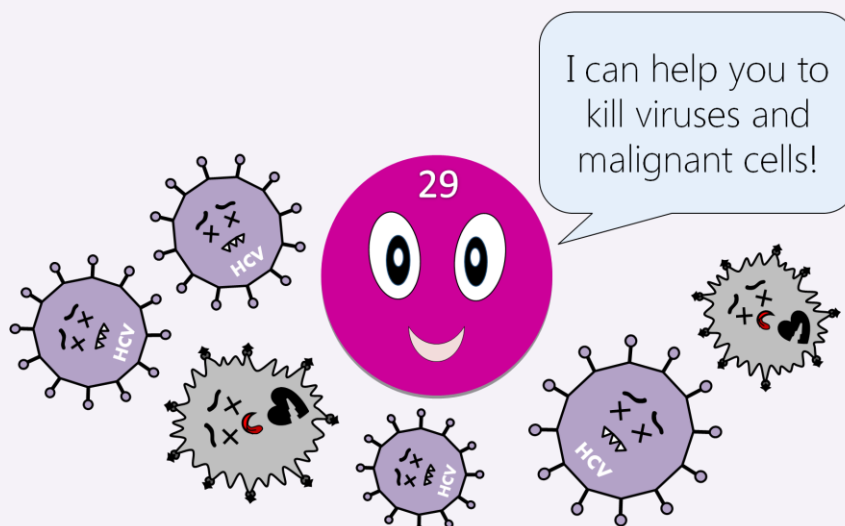
### Are there people who cannot produce IL-29?

To date, no patients with clinically relevant defects in the IL-29 gene have been reported.

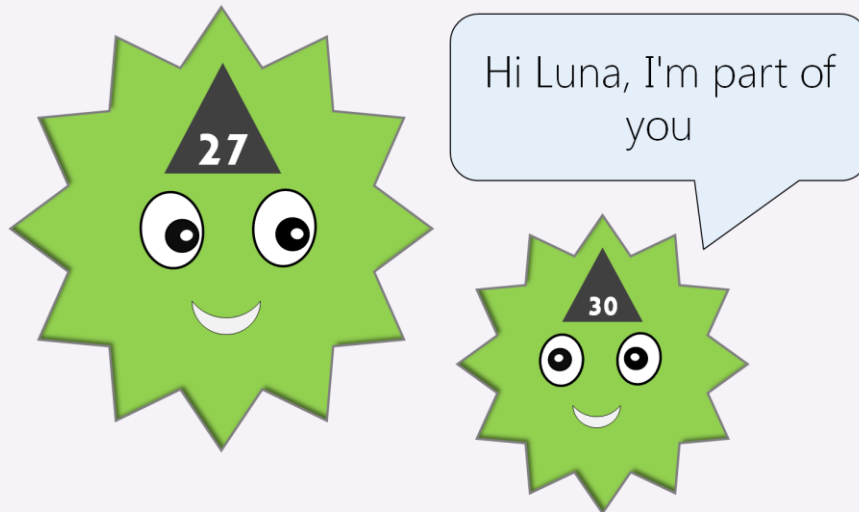
Pegylated Interferon Lambda-1a has inhibitory activity against hepatitis C virus. Other potential applications of this drug are cancer and severe allergies.

### Are there people who fabricate IL-29 in excess?

Local excess of IL-29 synthesis may favor the development of autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis.



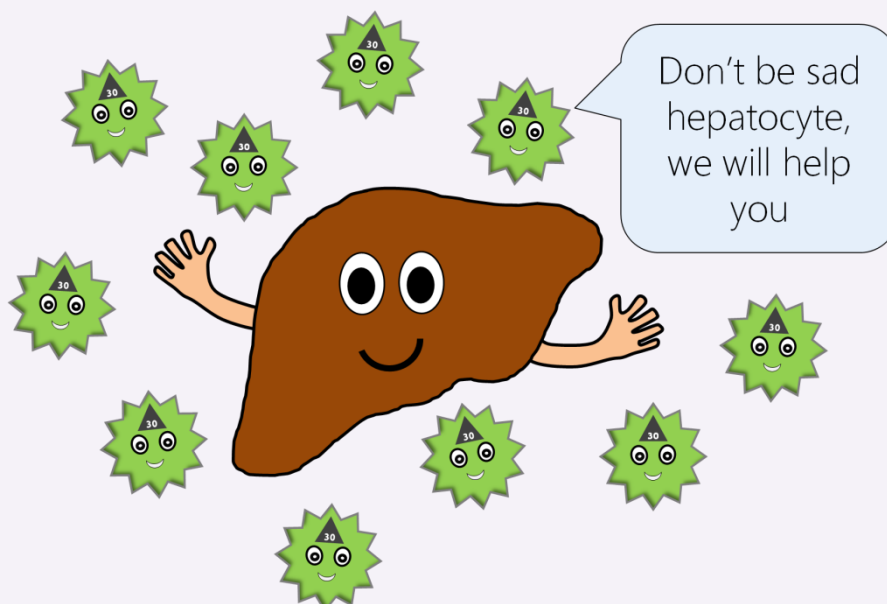
# Fanny, the interleukin 30



Fanny, our interleukin 30, is the p28 subunit of Luna, our interleukin 27.

## Where is Fanny produced?

IL-30 is a potent anti-inflammatory cytokine. Its best known role is the prevention and treatment of liver damage caused by inflammatory phenomena.



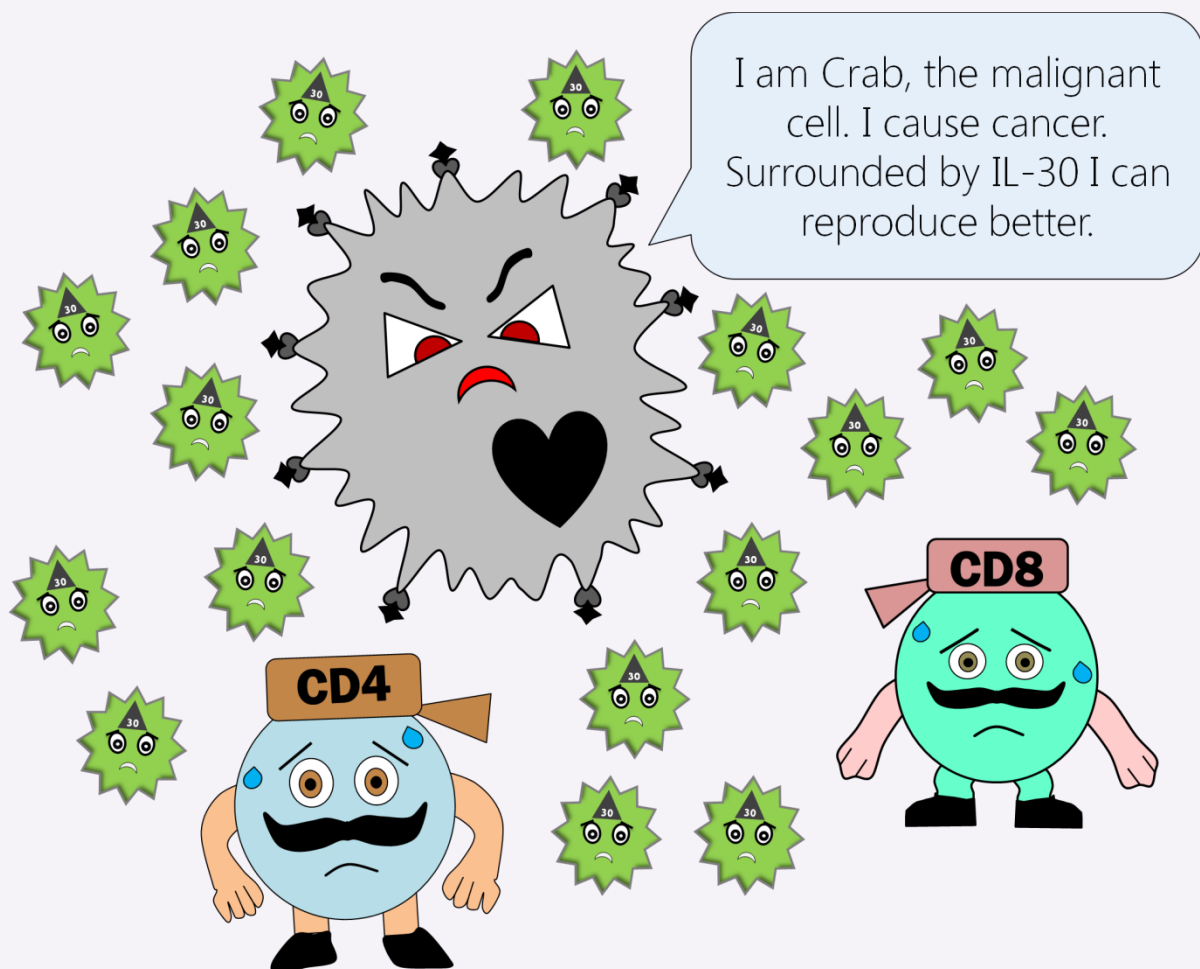
## Are there people who cannot produce IL-30?

Primary immunodeficiencies due to lack of interleukin 30 have not been described.

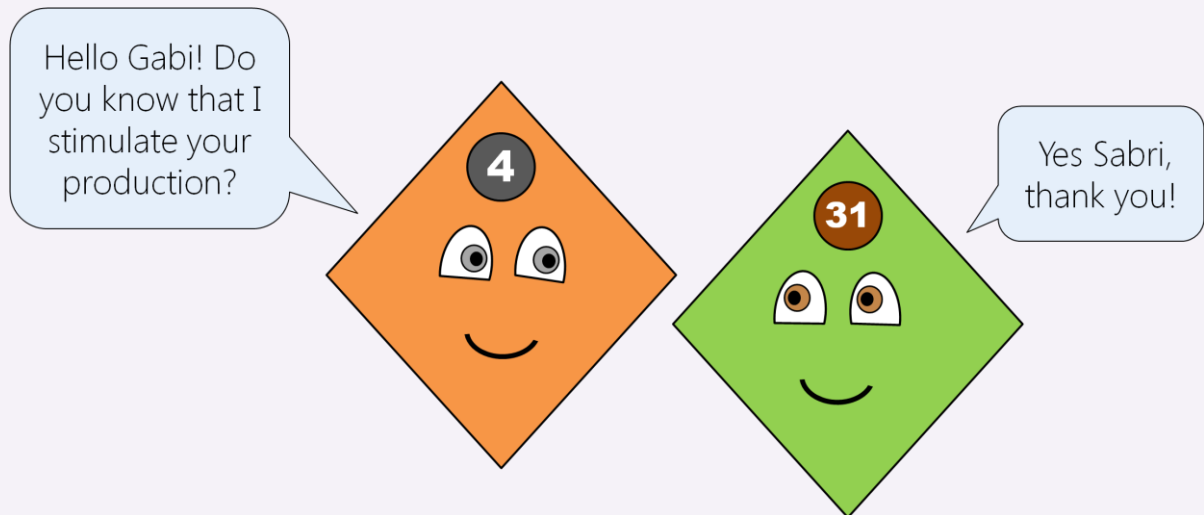
The anti-inflammatory effect of IL-30 can be harnessed for the management of patients with sepsis.

## Are there people who fabricate IL-30 in excess?

Local overload of interleukin 30 could inhibit the attack of our immune system to malignant cells, becoming a risk factor for the appearance of cancer.



# Rachel, the interleukin 31



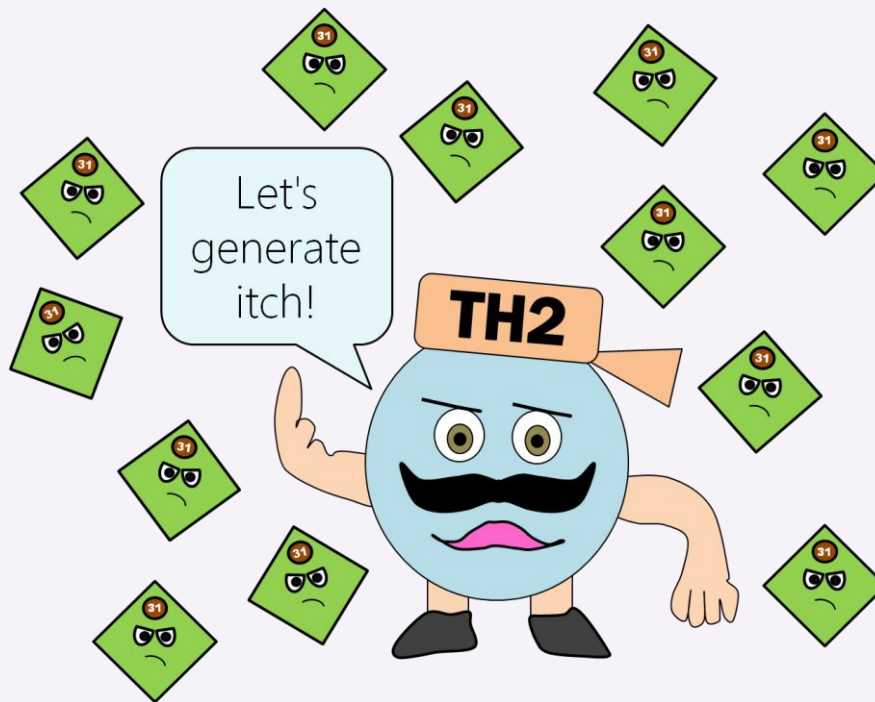
Our interleukin 31 is a TH2 inflammatory cytokine whose most prominent role is generation of pruritus. Its receptor is made up of two subunits: IL-31RA and OSMR $\beta$  (oncostatin M receptor  $\beta$ ).

## Where is Rachel produced?

Rachel is synthesized by activated T lymphocytes, both CD4 and CD8, especially by TH2 commanders. Her production is stimulated by the action of IL-4. Other cells capable of making IL-31 are monocytes, macrophages, dendritic cells, mast cells, keratinocytes and fibroblasts.

Rachel has several actions that increase TH2 inflammation:

- Activates the sensation of pruritus by acting on receptors in the peripheral sensory nerve cells.
- Induces the production of inflammatory chemokines by eosinophils and epithelial cells including keratinocytes.



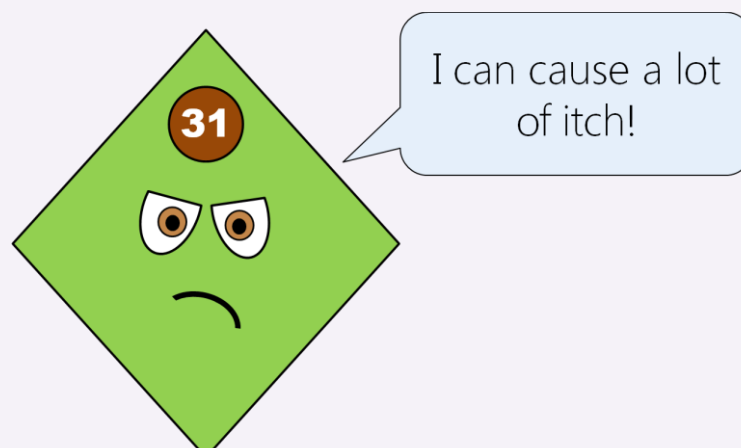
### Are there people who cannot produce IL-31?

Immunodeficiencies due to IL-31 absence have not been reported.

### Are there people who fabricate IL-31 in excess?

IL-31 favors the development and progression of inflammatory diseases with pruritus (e.g. atopic and non-atopic dermatitis, contact dermatitis, prurigo, chronic urticaria, mastocytosis).

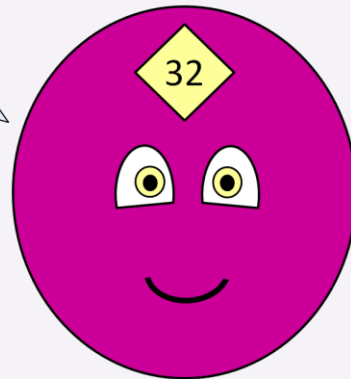
In patients affected by these pathologies, IL-31 is a potential marker of severity, as well as a therapeutic target.





# Gabi, the interleukin 32

Hi! I am Gaby, the interleukin 32, an expert in generating inflammation.



Now we will meet Gaby, our powerful interleukin 32. Its action is essentially proinflammatory. To date, its receptors have not been defined.

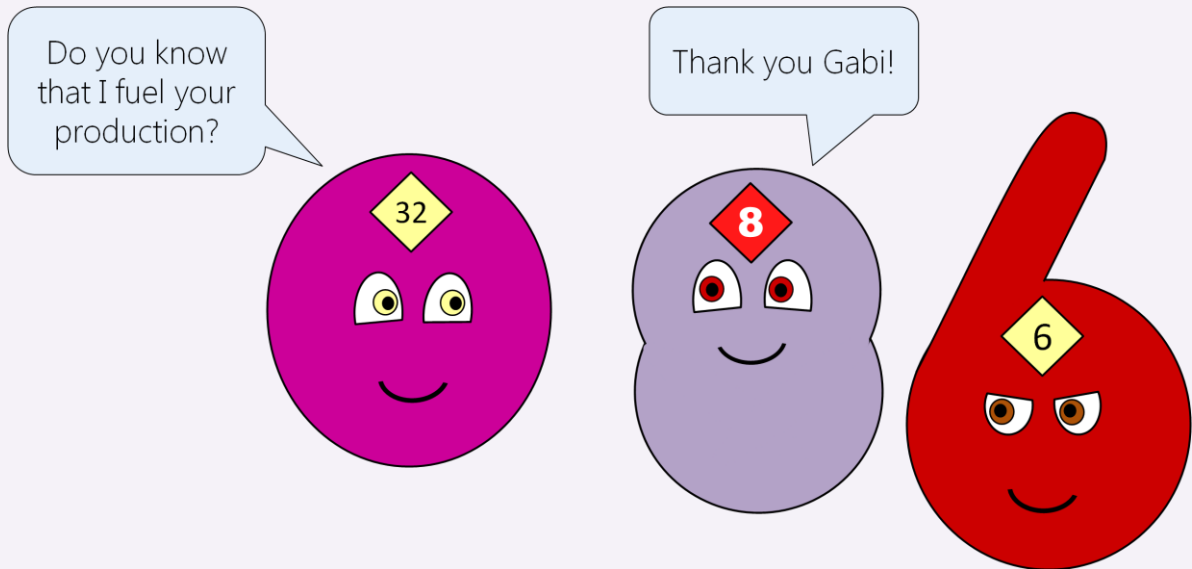
## Where is Gaby produced?

Several cells are able to synthesize IL-32, including monocytes, macrophages, NK lymphocytes, T lymphocytes and epithelial cells.

Gabi induces the production of other inflammatory cytokines such as interleukin 6, interleukin 8 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). It also promotes apoptosis of epithelial cells and osteoclast differentiation.

## Are there people who cannot produce IL-32?

Immunodeficiencies because of IL-32 absence have not been described yet.

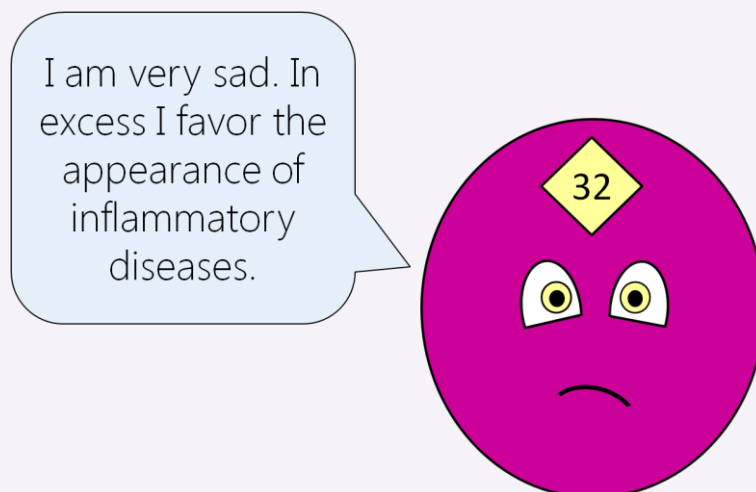


### Are there people who fabricate IL-32 in excess?

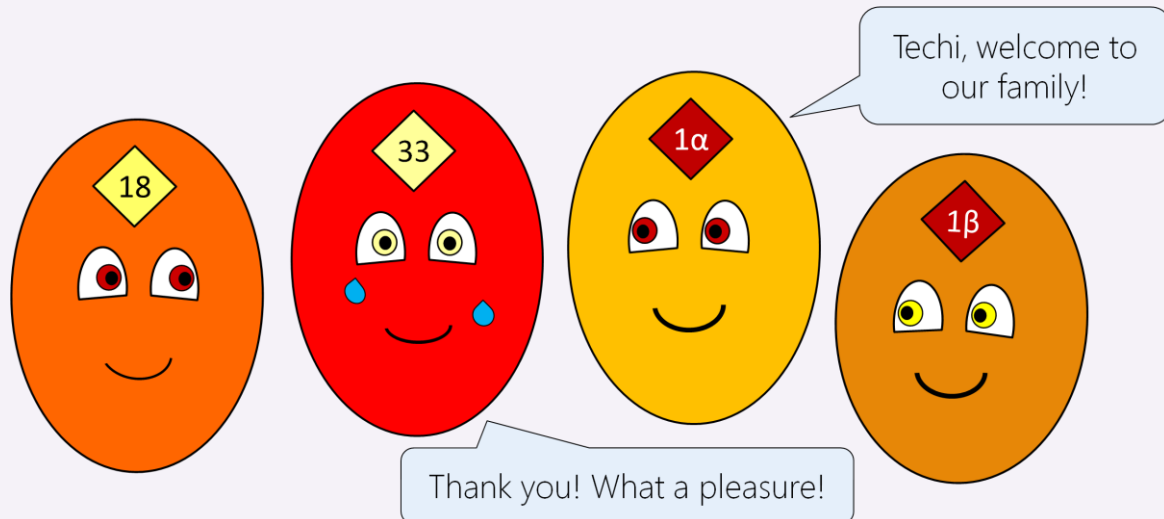
Excessive activity of interleukin 32 in healthy tissues may lead to the development of chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, chronic rhinosinusitis, atopic dermatitis and cancer.

In these diseases, IL-32 can serve as a biomarker of severity and as a therapeutic target.

To date, anti-IL-32 monoclonal antibodies have not been developed.



# Techi, the interleukin 33



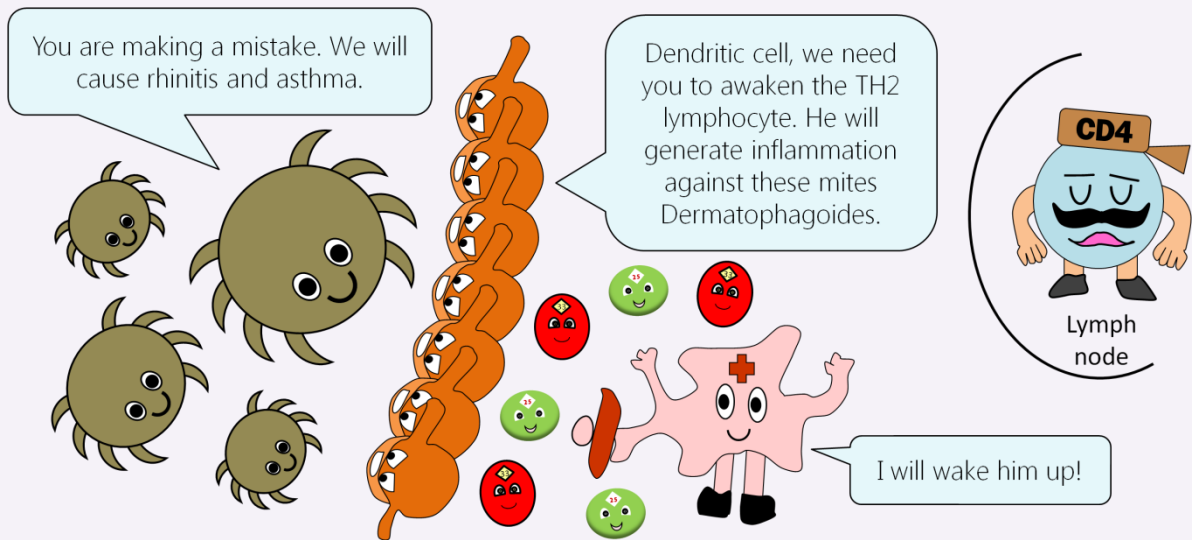
IL-33 is a member of IL-1 family, along with other six inflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ ) and four anti-inflammatory interleukins (IL-1Ra, IL-36Ra, IL-37, IL-38).

Techi stimulates TH2 immunity through the receptor ST2, which also has regulatory function in its soluble form.

## Where is Techi produced?

Techi is produced by epithelial cells (e.g. keratinocytes) and stromal cells (e.g. fibroblasts) in response to cell damage. She is also released from necrotic cells to promote inflammation, thus fulfilling her role of 'alarmin'.

Techi has multiple inflammatory actions. She induces maturation of proinflammatory dendritic cells, stimulates type 2 innate lymphoid cells, and promotes activation of basophils, eosinophils and mast cells.



### Are there people who cannot produce IL-33?

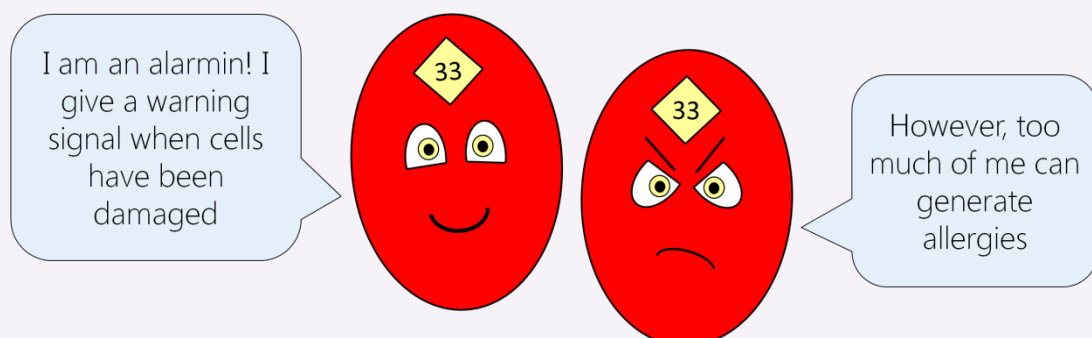
There are no reports of immunodeficiencies caused by IL-33 absence.

### Are there people who fabricate IL-33 in excess?

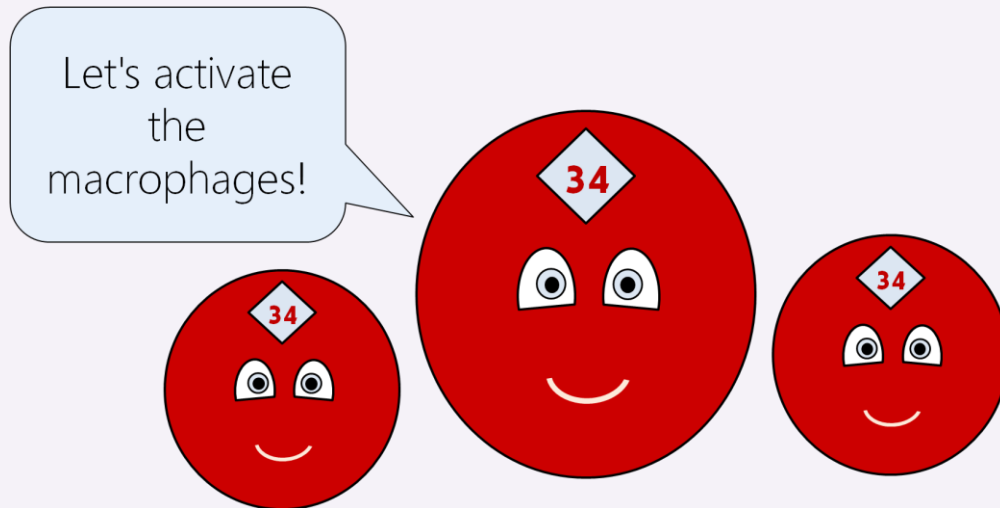
Excessive production of IL-33, conditioned by genetic variants and environmental factors (e.g. viruses, cigarette smoke, environmental pollutants), favors the development of inflammatory diseases such as bronchial asthma and atopic dermatitis.

Certain viral infections activate bronchial epithelial cells to produce the TH2-inducing cytokines IL-33, IL-25 and TSLP (thymic stromal lymphopoietin).

IL-33 can damage the skin barrier by reducing filaggrin expression.



# Gina, the interleukin 34



We will now study Gina, our interleukin 34. This proinflammatory cytokine acts through the receptor named CSF1R ('colony-stimulating factor 1 receptor'). CSF1R also mediates CSF1 signaling.

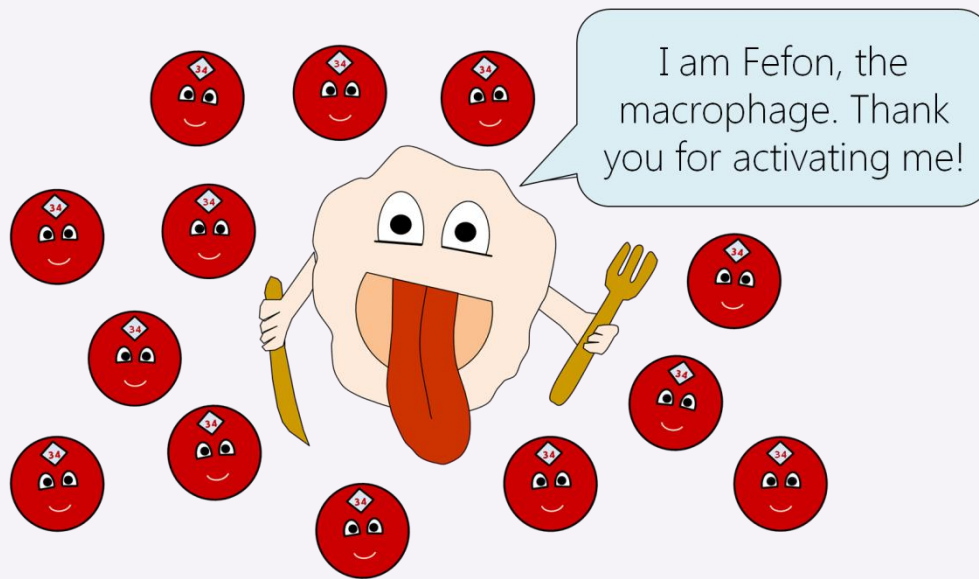
## Where is Gina produced?

Gina is manufactured in the spleen, liver, heart, brain, kidneys, thymus, ovaries, testes, prostate, skin and intestines.

She induces the differentiation, proliferation and survival of monocytes/macrophages, microglia, osteoclasts and Langerhans cells, thereby promoting inflammatory response.

## Are there people who cannot produce IL-34?

Patients with primary immunodeficiencies caused by lack of IL-34 have not been reported yet.



### Are there people who fabricate IL-34 in excess?

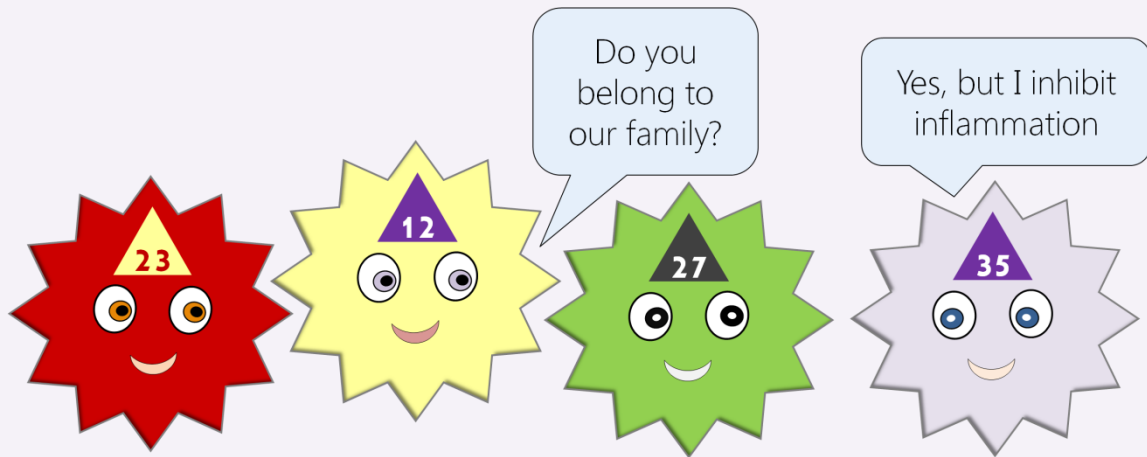
IL-34 overload may favor the development of inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, pigmented villonodular synovitis).

Cabiralizumab is an anti-CSF1R monoclonal antibody that blocks the action of IL-34 and CSF1. It has therapeutic potential for patients affected by monocyte-induced inflammatory diseases.

In addition, the combination of Cabiralizumab and Nivolumab (anti-PD-1 monoclonal antibody) is being evaluated for the treatment of neoplasms. The basis of this therapy is to inhibit the development of pro-tumor macrophages.



# Carla, the interleukin 35



Carla is a member of the IL-12 family, along with interleukins 12, 23 and 27. However, unlike her sisters, Carla has anti-inflammatory actions.

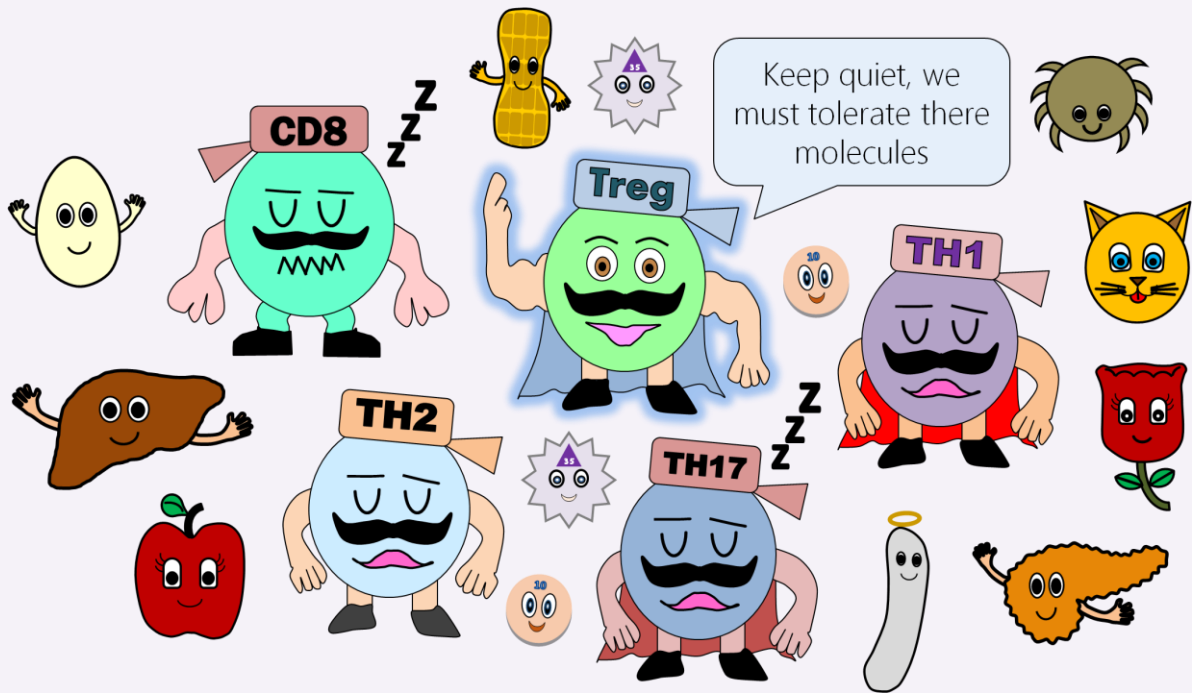
Carla has 2 subunits: p35 (it is also part of Bolli, our interleukin 12) and EBI3 (it also makes up Luna, our interleukin 27).

IL-35 receptors are formed by the combination of the IL-12R $\beta$ 2 and gp130 chains (IL-12R $\beta$ 2/gp130, IL-12R $\beta$ 2/IL-12R $\beta$ 2 and gp130/gp130). Remind that IL-12R $\beta$ 2 is also part of the IL-12 receptor and that gp130 also builds the receptors of interleukins 6, 11 and 27.

## Where is Carla produced?

Carla is synthesized by T regulatory lymphocytes, monocytes, endothelial and epithelial cells. Her major actions are:

- Inhibition of inflammatory effector T lymphocytes.
- Activation of T and B regulatory lymphocytes.



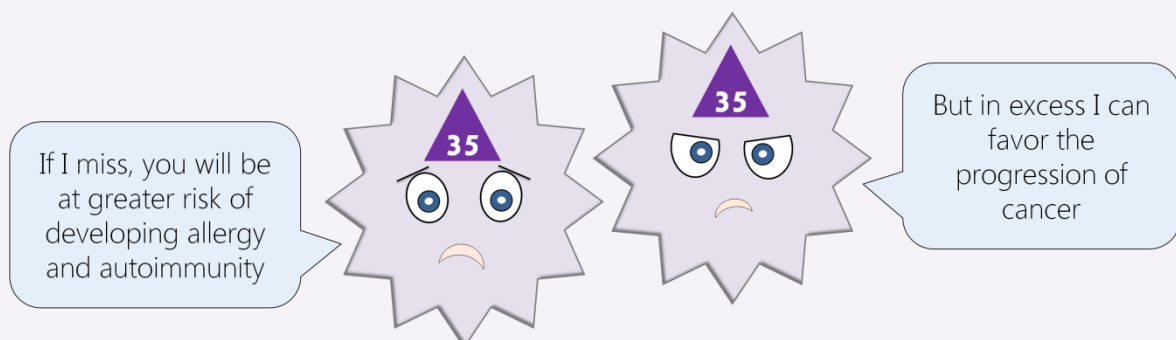
### Are there people who cannot produce IL-35?

Children lacking T regulatory lymphocytes have early-onset autoimmunity. For example, patients with Foxp3 deficiency develop IPEX syndrome (immune dysregulation, autoimmune polyendocrinopathy, enteropathy, X-linked).

Local deficit of IL-35 can facilitate the development of autoimmune and allergic diseases. Recombinant IL-35 could play a therapeutic role in these diseases.

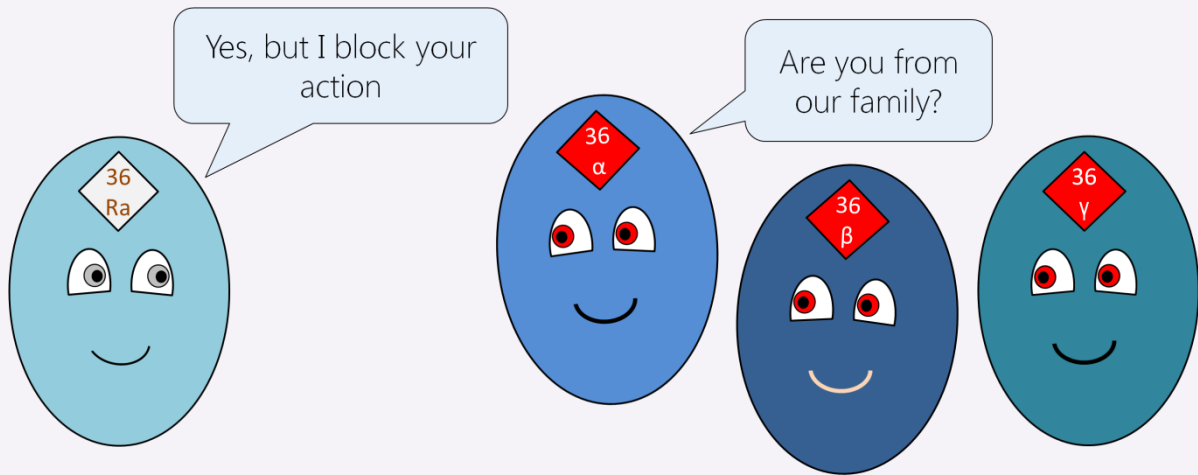
### Are there people who fabricate IL-35 in excess?

Local excess of IL-35 may favor the progression of cancer.





# Adela, IL-36 $\alpha$ , and her family



There are four subtypes of interleukin 36: three have inflammatory activity (IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ ) and one is the natural antagonist (IL-36Ra or IL-36 receptor antagonist). All of them belong to the interleukin-1 family.

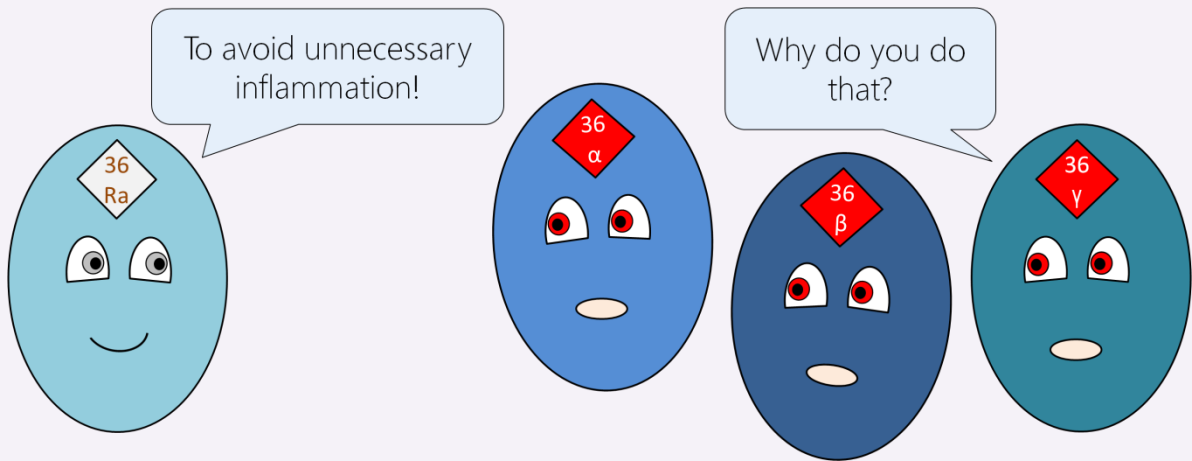
IL-36 receptor consists of 2 subunits: IL-36R and IL-1RAP (Interleukin-1 receptor accessory protein).

## Where are they produced?

Adela and her sisters are synthesized by epithelial and endothelial cells, especially in the skin, as well as by macrophages.

Our cytokines IL-36 $\alpha$ , IL-36 $\beta$  and IL-36 $\gamma$  are proinflammatory; they induce innate immune response following tissue damage. In addition, they favor proliferation of T lymphocytes and differentiation towards TH1/TH17 lymphocytes.

In contrast, IL-36Ra has anti-inflammatory activity by antagonizing the action of IL-36 $\alpha$ , IL-36 $\beta$  and IL-36 $\gamma$ .



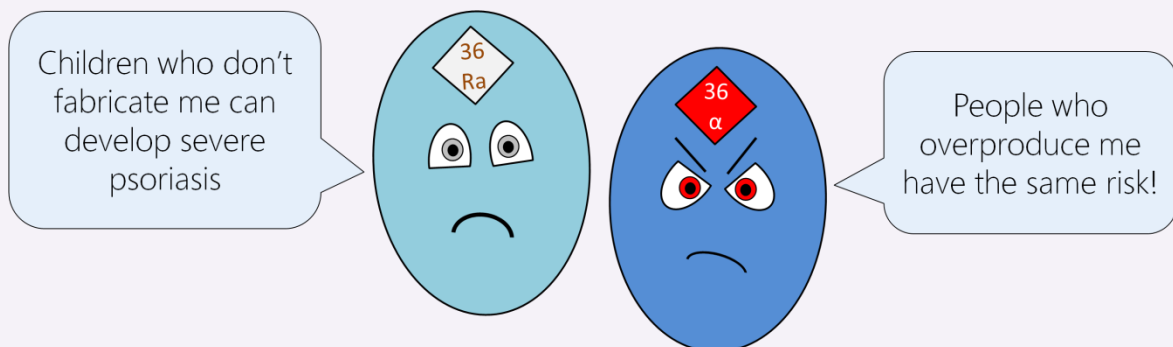
### Are there people who cannot produce IL-36?

There are people who cannot make IL-36Ra. The resulting disease is called DITRA (Deficiency of the Interleukin 36 Receptor Antagonist), characterized by early-onset generalized pustular psoriasis (fever, pustular rash, leukocytosis, elevation of acute phase reactants).

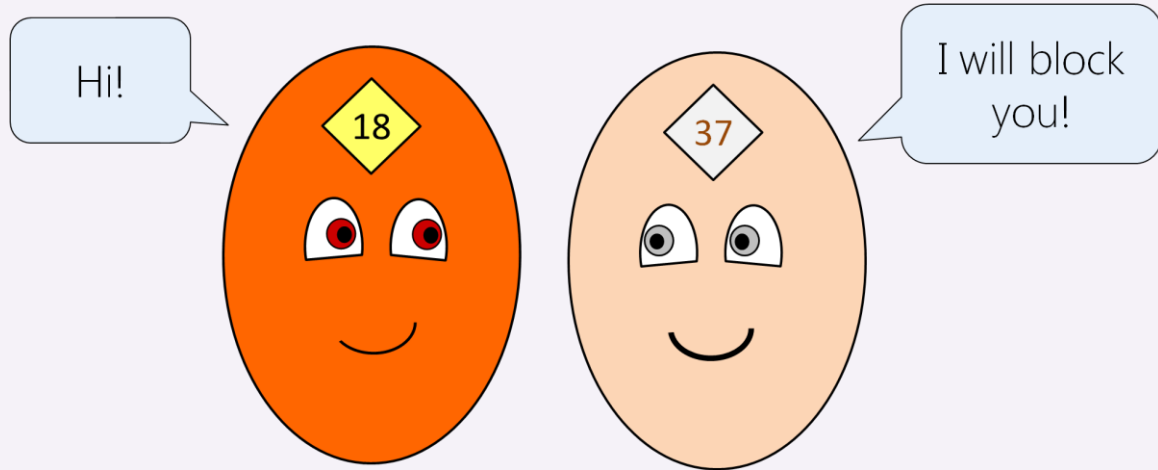
### Are there people who fabricate IL-36 in excess?

Excessive synthesis of IL-36 $\alpha$ , IL-36 $\beta$  or IL-36 $\gamma$  favors the development of severe forms of psoriasis.

Affected patients may benefit from biological therapies that neutralize these cytokines or their receptor (e.g. ANB019, an anti-IL-36R monoclonal antibody, still under investigation).



# Ethel, the interleukin 37



IL-37 is an anti-inflammatory cytokine that antagonizes IL-18. Remind that both molecules belong to the interleukin-1 family, together with other pro-inflammatory (IL-1 $\alpha$ , IL-1 $\beta$ , IL-33, IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ ) and anti-inflammatory cytokines (IL-1Ra, IL-36Ra, IL-38).

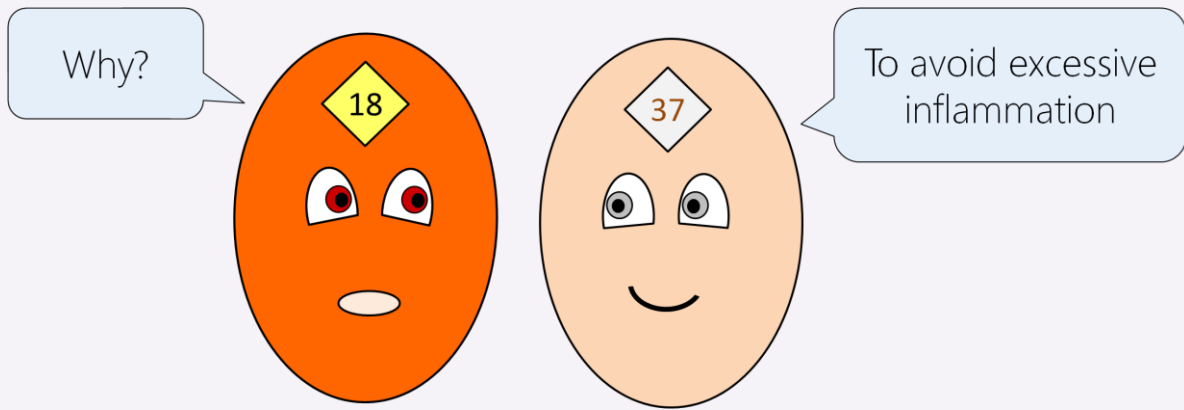
Ethel exerts her functions through the molecules IL-18R $\alpha$  and the inhibitory component IL-1R8 (IL-1 receptor family member 8).

## Where is Ethel produced?

Interleukin 37 is synthesized by monocytes. In addition, various tumor cells are capable of producing this cytokine, perhaps to escape from the attack of the immune system.

Ethel has anti-inflammatory actions, which include:

- Antagonism of IL-18.
- Inhibition of dendritic cells.



### Are there people who cannot produce IL-37?

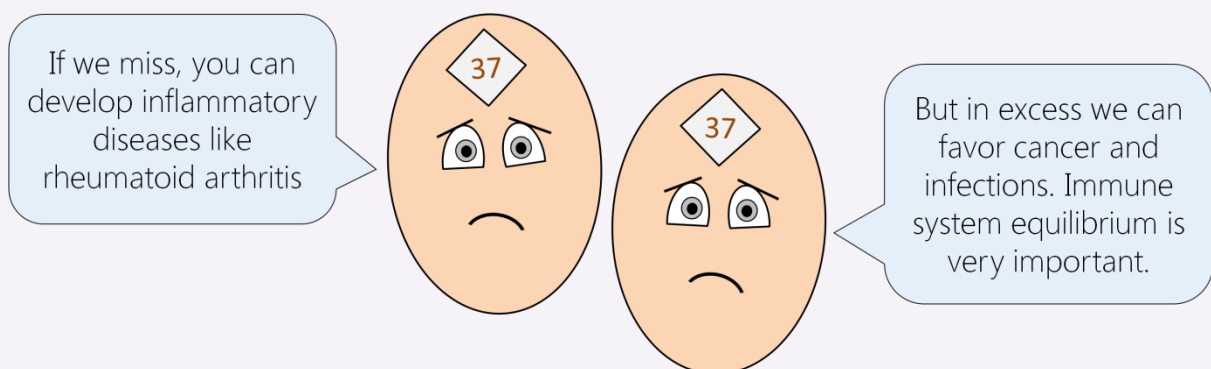
Local decrease of IL-37 could favor the onset or progression of inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis and systemic lupus erythematosus.

Patients affected by these diseases could benefit from the use of recombinant human IL-37.

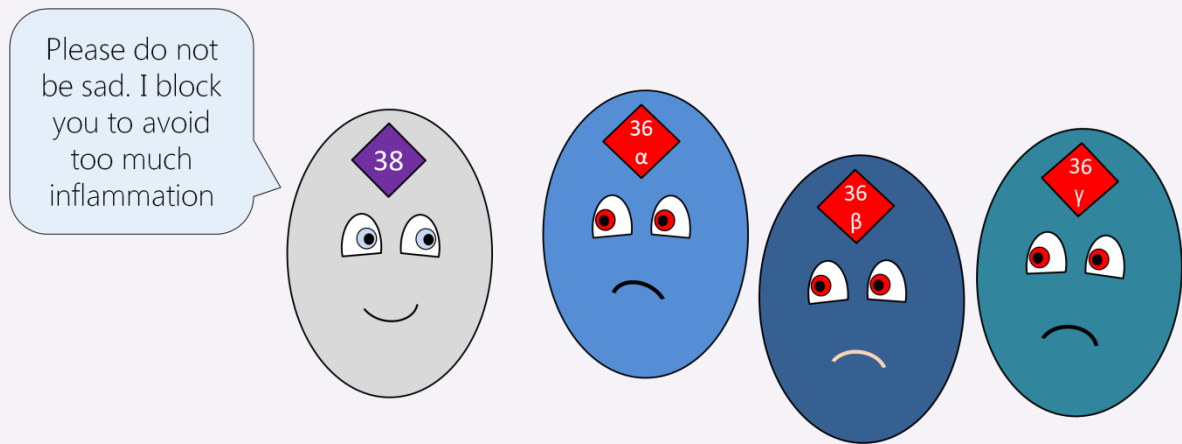
### Are there people who fabricate IL-37 in excess?

Local excess of IL-37 may be a risk factor for the development of infections (e.g. tuberculosis) or cancer (e.g. squamous cell carcinoma). A pro-angiogenic role of IL-37 in proliferative retinopathy has been described.

However, it has also been reported that IL-37 might have antitumor effect by inhibiting angiogenesis.



# Gladys, the interleukin 38



Let's welcome Gladys, our interleukin 38! Like her sister Ethel, Gladys is an anti-inflammatory cytokine. Interleukin-38 is the last of the 11 members of the interleukin-1 family (IL-1 $\alpha$ , IL-1 $\beta$ , IL-1Ra, IL-18, IL-33, IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ , IL-36R $\alpha$ , IL-37 and IL-38).

IL-38 exerts her actions through IL-36R and, to a lesser extent, through IL-1R1 (interleukin-1 receptor type 1).

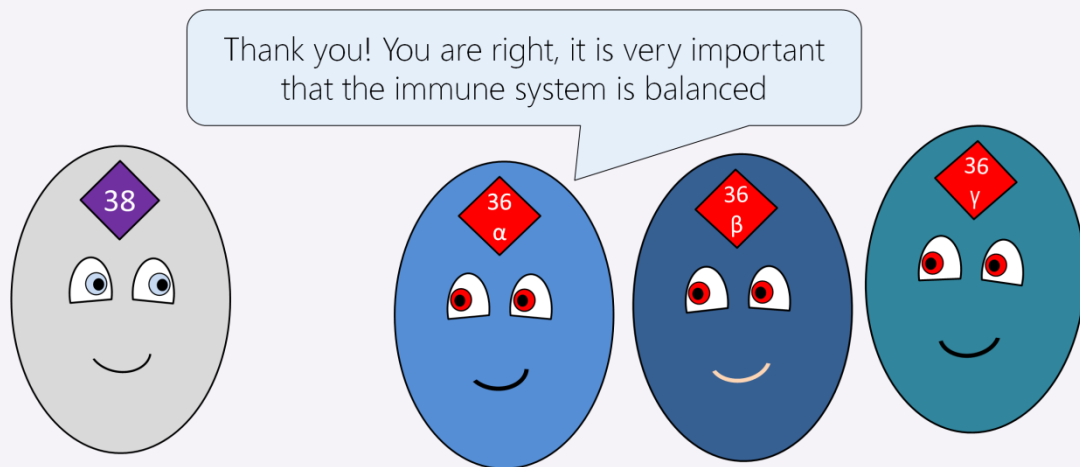
## Where is Gladys produced?

Gladys can be synthesized in several tissues such as the skin, spleen, placenta, thymus, tonsils and salivary glands.

Gladys, whose structure is similar to the molecules IL-1Ra and IL-36Ra, has the following anti-inflammatory actions:

- Antagonizes the inflammatory action of IL-36.
- Inhibits the activation of TH17 immunity, including the production of IL-17, IL-22 and IL-8.

- Es liberada por células apoptóticas para limitar la respuesta inflamatoria de los macrófagos.



### Are there people who cannot produce IL-38?

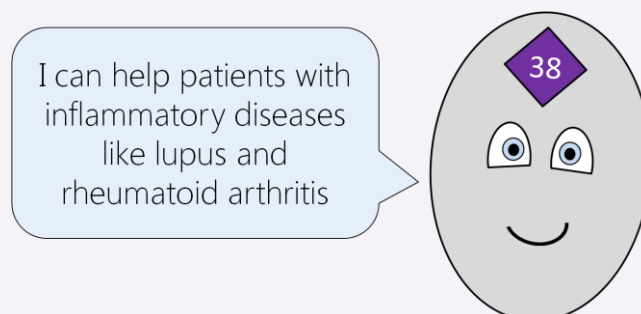
Genetic polymorphisms that reduce the synthesis or activity of IL-38 may favor the development of inflammatory diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus).

Recombinant IL-38 has a potential therapeutic role in these diseases.

### Are there people who fabricate IL-38 in excess?

Given its immunosuppressive effect, local excess of IL-38 could favor the development of infections and cancer.

Elevated levels of IL-38 have been reported to predict a better response to telbivudine in patients with chronic hepatitis B.



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



## Contributors:

- Juan Félix Aldave Pita, MD
- Bertha Alicia Becerra Sánchez
- Ana Ponce de León Camahualí

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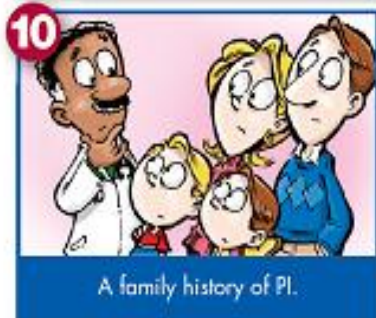
- Jeffrey Modell Foundation
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*"For God so loved the world that he gave his one and only Son, that whoever believes in him shall not perish but have eternal life". John 3:16*



# 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.**



"These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. ©2013 Jeffrey Modell Foundation"

[www.INFO4PI.org](http://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)

- Book 1: The Immunocytes
- Book 2: The TH17 army against Candida
- Book 3: The TH1 army against Mycobacteria
- Book 4: The TH2 army against worms
- Book 5: The battle against Pneumococcus
- Book 6: Los Inmunocitos contra el cáncer
- Book 7: T regs: controlling the immune army
- Book 8: When the Immunocytes get sick...
- Book 9: When the Immunocytes go crazy...
- Book 10: The Immunocytes and transplantation
- Book 11: The armor of the Immunocyte Felix
- Book 12: The fantastic Interleukins

#### Contact the Author:

Jirón Domingo Cueto 371, Of. 301, Lince, LIMA 14

Lima, Perú

Phones: +51 948-323-720

+51 988-689-472

[jucapul\\_84@hotmail.com](mailto:jucapul_84@hotmail.com)

[funny.immunology@gmail.com](mailto:funny.immunology@gmail.com)

[www.alergomed.org/immunocytes](http://www.alergomed.org/immunocytes)