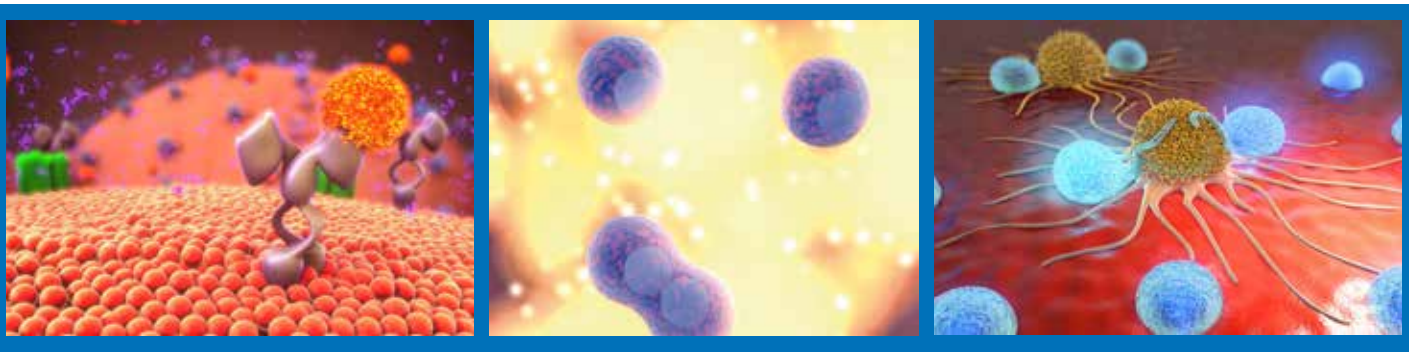
Micro-immunotherapy
International Medical Experience



Chronic inflammation and **micro-immunotherapy**

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Inflammatory response

Inflammation is a physiological immune system response that is triggered when potentially harmful agents are detected and/or when tissue integrity is endangered. It is an essential, beneficial process, as it allows to remove damaged cells, irritant factors or pathogens, and promotes injured tissue repair and/or recovery of its function[1].

By its characteristics, inflammation must be a self-limited response, with a rapid return to homeostasis. Long-term activation of this process increases the risk of chronic inflammation, thus damaging tissue integrity and inducing immunosuppression[2]. Unresolved chronic inflammation is a common factor in the initiation and progression of almost all neurodegenerative, autoimmune, aging-associated diseases and/or cancer[3–7].

Characteristics of chronic inflammation

Chronic inflammation mainly results from persistence in the body of "stress-factors", such as infectious and toxic agents, damaged cells, or molecules produced as a result of abnormalities in the cells' regulatory mechanisms. These factors can cause an overproduction of pro-inflammatory cytokines and chemokines, reactive oxygen and nitrogen species (ROS, RNS) and other tissue-infiltrating lymphocyte induced-molecules, amongst others. Sustained overproduction of these inflammatory mediators and the damage caused to the surrounding cells would contribute to the amplification of the acute inflammatory process, leading to chronicity[4].

Cytokines involved in chronic inflammation may be divided into two groups: those mediating humoral responses, such as interleukin 4 (IL-4), IL-5, IL-6, IL-7 and IL-13; and those mediating cellular responses, such as IL-1, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, interferons, tumour growth factor beta (TGF-β) and tumour necrosis factor alpha (TNF-α)[8]. However, several of them can contribute simultaneously to both processes and many show dual actions, either stimulating or blocking a same process, depending on their target cell, its location and its microenvironment.

Role of inflammation in chronic diseases

Chronic diseases are long-term, slowly progressive disorders. They include multiple conditions, such as cardiovascular diseases, cancer, chronic respiratory diseases, diabetes, neurological and psychiatric disorders, sensory disorders, degenerative motor system diseases, gastrointestinal diseases, oral diseases, genitourinary disorders, congenital malformations, and skin diseases[9]. According to the "Center for Disease Control and Prevention" (CDC), chronic diseases cause about 6 out of 10 deaths per year around the world, and their treatment accounts for 86% of USA total healthcare costs[3].

Multiple studies report a strong association between inflammation and chronic diseases mostly reflected by the presence of common biochemical markers[5,10,11]. These include most remarkably, pro-inflammatory cytokines and chemokines (such as TNF-α or interleukins 1, 6 and 8), ROS and RNS, angiogenic factors such as vascular endothelial growth factor (VEGF), prostaglandins such as prostaglandin E2 (PGE2), inflammatory enzymes such as cyclooxygenase 2 (COX-2), matrix metalloproteases (MMPs), adhesion molecules and other factors such as C-Reactive Protein (CRP)[3].
It must be noted that the expression of most of these molecules is mediated by two main signalling pathways, chiefly regulated by NF-κB (nuclear factor κB) and STAT3 (signal transducer and activator of transcription 3) transcription factors. These pathways are also involved in cell proliferation and survival events. In fact, multiple studies demonstrate the key role of NF-κB in the activation and mediation of chronic inflammatory responses and its link with several disorders, including cardiovascular, diabetes, cancer and osteoporosis[12–16].

Examples of chronic diseases where high levels of pro-inflammatory molecules have been detected are:

- Autoimmune diseases, such as rheumatoid arthritis or multiple sclerosis.[17–19]
- Cancer[10,20]
- Cardiovascular diseases [10,21]
- Neurological and ageing-related disorders, such as Alzheimer's or Parkinson's [4,5,22,23]
- Metabolic diseases, such as obesity, metabolic syndromes, or diabetes.[10,20,24,25]
- Inflammatory bowel diseases[26]

Objectives of micro-immunotherapy

- Restore the balance of the main signalling pathways involved in the development and persistence of inflammatory conditions.
- Limit the development of chronic inflammation from acute episodes.
- Promote resolution of inflammation and tissue recovery.

Objectives of the formula INFLAM

The objective of the active ingredients used in the micro-immunotherapy formula INFLAM in inflammatory events and, particularly, in chronic pathological processes, is described below.

1- Composition

Formula INFLAM*

Interleukin 1 (IL-1)	17 CH
Interleukin 1 Ra (IL-1 Ra)	3 CH
Interleukin 2 (IL-2)	9 CH
Interleukin 4 (IL-4)	7 CH
Interleukin 6 (IL-6)	9 CH
Interleukin 8 (IL-8)	9 CH
Interleukin 10 (IL-10)	4 CH
Interleukin 13 (IL-13)	9 CH
Ciliary Neuro Trophic Factor (CNTF)	17 CH
Leukemia Inhibitory Factor (LIF)	17 CH
Oncostatin M (OSM)	9 CH
Platelet Derived Growth Factor (PDGF)	5 CH
Prostaglandin E2 (PGE2)	200 K
Rantes	17 CH
Transforming Growth Factor beta (TGF-β)	5 CH
Tumor Necrosis Factor alpha (TNF-α)	17 CH
Specific Nucleic Acid SNA® – INFLAMa-01	18 CH
Specific Nucleic Acid SNA® – INFLAMb-01	18 CH

**The active substances used in the Formula INFLAM are aimed at upregulating, downregulating or maintaining the biological activity of the substances involved in the development of chronic inflammation.*

2- Sequential mechanism of the formula INFLAM

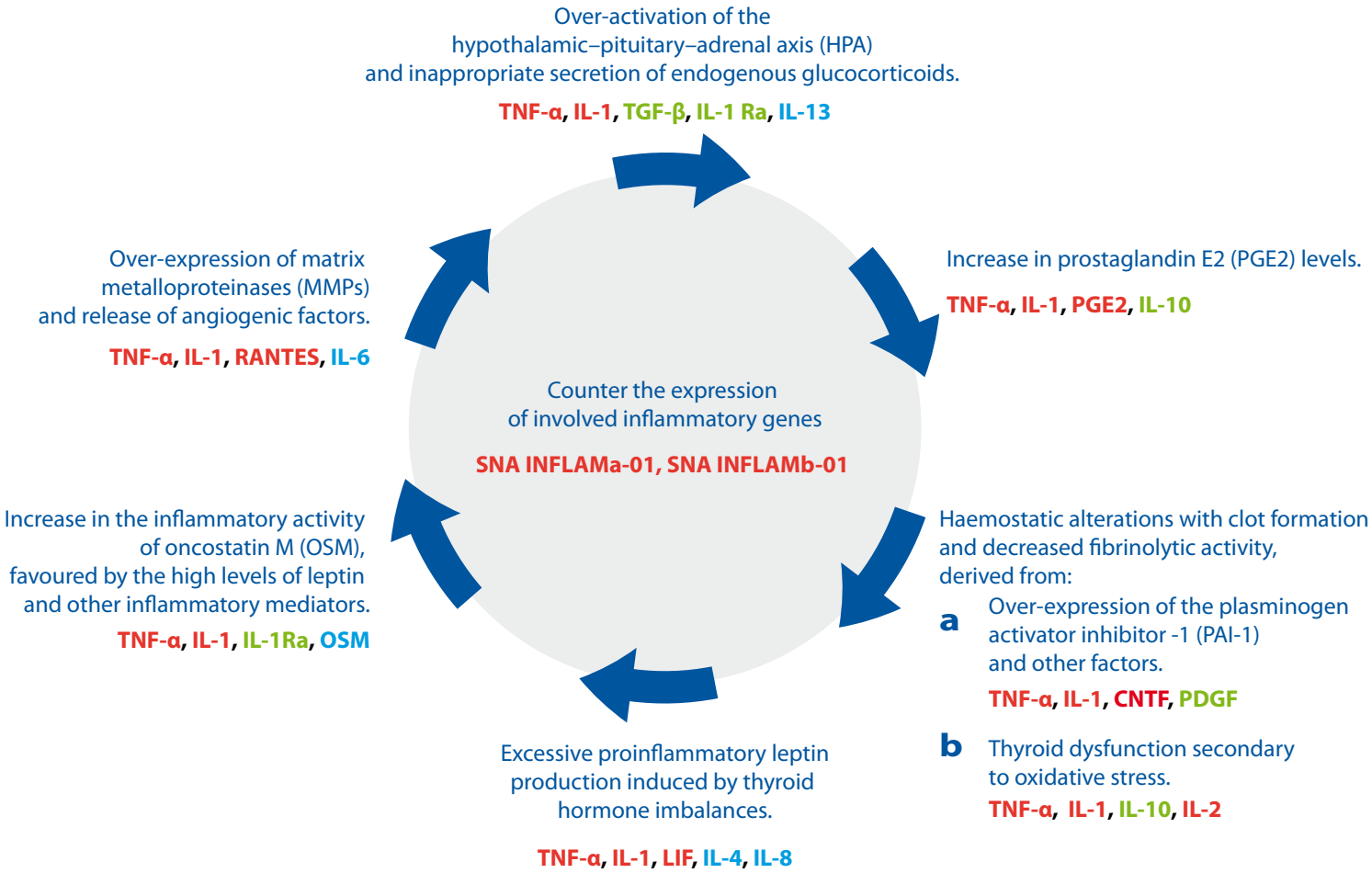

Figure 1. *Sequential schematic representation of the micro-immunotherapy formula INFLAM in pathological inflammation and its objectives at different levels.*

The composition of the formula INFLAM has been established according to the following sequential mechanism:

1. Hypothalamic–pituitary–adrenal axis (HPA) and endogenous glucocorticoids

Glucocorticoids are steroid hormones that play a key role in the maintenance of body homeostasis. They regulate a high number of physiological processes, including the intermediate metabolism, the immune function, skeletal growth, cardiovascular function, reproduction and cognition[27–29]. They are produced and released by the adrenal cortex, tightly controlled by the hypothalamic–pituitary–adrenal axis (HPA), and their synthesis depends on the activity of two 11beta-hydroxysteroid dehydrogenases (11β-HSD)[30].

11β-HSD1 is in charge of transforming cortisone into active cortisol and catalyses intracellular regeneration of glucocorticoids, mainly in the liver, adipose tissue and brain. 11β-HSD2 is the enzyme that inactivates glucocorticoids, both cortisol and corticosterone, and is mainly located in the kidneys, placenta and colon[30–33].

The activity of the HPA axis and the production of glucocorticoids are usually increased in inflammatory processes[30,34–37]. In fact, during persistent pathological inflammation, glucocorticoids play a key role in physiological responses aimed at the resolution of the inflammation, at both systemic and tissue-specific levels. They antagonise the action of inflammatory cytokines, such as TNF-α or IL-1, and suppress critical inflammatory signalling pathways, including those mediated by NF-kB[38].

It has been described that a higher susceptibility to the inflammatory disease and to autoimmunity could be related to disorders in the HPA axis activity and to an inadequate systemic production of endogenous cortisol. In chronic inflammatory diseases, the evidence even highlights resistance to glucocorticoids[39–41]. These imbalances could be related to the expression patterns of the enzyme 11β-HSD1, involved in the transformation of cortisone into cortisol, and to abnormalities in glucocorticoid receptor (GR) signalling[35–37,39,42,43]. In fact, studies show that both IL-1α and IL-1β can block translocation of GR[44] and that TNF-α has an inhibitory effect on their function[45]. On the contrary, anti-inflammatory cytokines, such as TGF-β, can modulate the activation of the HPA axis, antagonising the secretion of factors involved in cortisol release[46].

Furthermore, it has been seen that high concentrations of pro-inflammatory cytokines can increase the expression of 11β-HSD1[47], and there are evidences that their deficit or inhibition worsen acute inflammation events. However, there is no consensus among researchers regarding chronic inflammation. Current studies show both beneficial effects, as in metabolic inflammation (e.g.: atherosclerosis, obesity, diabetes)[32], and deleterious effects, as in inflammatory bowel disease or rheumatoid arthritis. In these, inhibition of 11β-HSD1 could worsen fibrosis and angiogenesis, events that are associated with progression of chronic tissue-damage[32,33,48].

Objectives of micro-immunotherapy:

TNF-α **IL-1** **TGF-β** **IL-1Ra** **IL-13**	To modulate the HPA axis overactivation, variations in 11β-HSD1/HSD2 expression, as well as resistance to glucocorticoids and disorders in GR receptors signaling. To this end, the Formula INFLAM aims to restrain pro-inflammatory cytokines-mediated abnormalities in glucocorticoid signaling as well as to stimulate the action of its antagonists: IL-1Ra and TGF-β, cytokines that can counteract the secretion of cortisol releasing factors. INFLAM seeks also to modulate IL-13 effects, given its capacity to upregulate 11β-HSD2 expression without favouring glucocorticoid imbalances, which could result from an excess of this cytokine[49,50].

2. Prostaglandin E2 production

Prostaglandin E2 (PGE2) is a lipid mediator produced from arachidonic acid (AA) by means of the action of cyclooxygenase[51]. It is essential in many biological functions, such as regulation of immune responses, blood pressure, gastrointestinal integrity, and fertility[52]. In fact, the synthesis or deregulated degradation of PGE2 has been associated with a wide range of pathological conditions[53].

Among its functions, it has an important pro-inflammatory effect. PGE2 is synthesized in the inflamed tissue and contributes to the classical signs of inflammation: redness, swelling and pain[54]. It also regulates cytokine production in dendritic cells and enhances differentiation of T cells[55]. PGE2 also acts in synergy with inflammatory mediators, such as TNF-α, to promote NF-κB-dependent gene transcription and expression[56], a pathway on which COX-2 expression also depends[57,58].

On the other hand, PGE2 can exert its inflammatory action by means of the inhibition of anti-inflammatory events. With this regard, PGE2 blocks the production of IL-10, a cytokine that inhibits NF-κB activity in monocytes, macrophages and T cells[59], by interfering with its production by CD4 T cells[60].

Finally, it must be noted that potent pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) can induce glucocorticoid release, stimulating directly or indirectly the production of prostaglandin E2[61–64], which has been also linked to the activation of the HPA axis[65,66].

Objectives of micro-immunotherapy:

PGE2 **TNF-α** **IL-1** **IL-10**	To balance the synthesis and limit the action of prostaglandin E2, as well as other involved inflammatory mediators, by acting on its main precursor, COX-2. Additionally, it is sought to stimulate important inhibitors of the main pro-inflammatory pathways, such as IL-10, as it interferes with NF-κB expression in monocytes, macrophages and T cells.

3. Thrombotic disorders, plasminogen activator inhibitor 1 (PAI-1) activity, fibrinolysis and other coagulation disorders

In healthy individuals, the natural anticoagulant mechanisms limit the thrombotic response. However, in inflammation these pathways are depressed by pro-inflammatory mediators. Among other haemostatic disorders favouring pro-coagulant activity, inflammation increases the levels of plasminogen activator inhibitor (PAI-1)[67,68]. PAI-1 inhibits the enzymes tPA and uPA, serine proteases that transform plasminogen into plasmin[69–72]. This in turn degrades components of the extracellular matrix, such as proteoglycans, fibronectin, and laminin, facilitating leukocyte migration in repair events and activation of matrix metalloproteases (MMPs)[70]. PAI-1-mediated inhibition causes a reduction of fibrinolytic activity[72,73]. In fact, an increased activity of PAI-1 has been related to chronic inflammation events, metabolic syndrome, insulin resistance, infiltration of macrophages, etc. and a higher risk of developing cardiovascular disease due to thrombotic disorders and formation of clots[74].

Furthermore, the different inflammatory mediators can increase both platelet count and their ability to respond to thrombin[73,75]. Platelets are involved in many thrombotic disorders for their ability to aggregate and form clots in response to activation[76], taking part in the origin of autoimmune and inflammatory diseases. A variety of platelet markers have been detected in systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, spondyloarthropathies, vasculitis, and several autoimmune and inflammatory disorders. In most of these, platelets circulate in an activated state and tend to form immune complexes with other inflammatory cells[77].

Objectives of micro-immunotherapy:

TNF-α IL-1 CNTF PDGF	To downregulate PAI-1 levels through reducing the influence of inflammatory mediators, such as TNF-α and IL-1. Furthermore, it is intended to readjust haemostatic balance modulating on the one hand thrombopoiesis and anticoagulant activity by means of using, amongst others, regulatory factors of this process, such as CNTF (Ciliary Neurotrophic Factor), and on the other, stimulating thrombomodulin expression thus preventing transformation of fibrinogen into fibrin by means of the use of PDGF (Platelet-Derived Growth Factor).

4. Imbalance in thyroid hormone levels

Thyroid hormones act as pleiotropic regulators of cell growth, differentiation and proliferation events. They are involved in multiple metabolic processes, such as regulating oxygen consumption in almost all tissues and protecting them against oxidative stress. 5-triiodothyronine (T3) is generated in peripheral tissues[78,79] mainly from thyroxine (T4), by the action of iodothyronine deiodinases. In fact, enzymes such as type 1, 2, and 3 (D1, D2, and D3) deiodinases involve a potent mechanism of activation (D1 and D2) or inactivation (D3) of thyroid hormones[79,80].

It must be noted that thyroid hormones are involved in the regulation of multiple fundamental genes, including plasma proteins, oncogenes, inflammatory genes and components of the coagulation system[81]. It has been seen that thyroid dysfunction affects the haemostatic function, so patients with these disorders usually show abnormalities in the coagulation system[82–84]. Patients with hypothyroidism, even moderate or subclinical, are usually at a high risk of cardiovascular diseases, with increased coagulability and reduced fibrolytic activity[85–87].

Chronic inflammatory and autoimmune states very commonly involve changes in the metabolism of thyroid hormones associated with the presence of oxidative stress[88–90]. These thyroid dysfunctions include mainly the non-thyroidal illness syndrome (NTIS)[88], hypothyroidism characterised by a downregulation of conversion of T4 into T3 through the inhibition of deiodinase-1, the hormone-activating enzyme.

Oxidative stress also contributes to the inhibition of D2 and stimulation of D3 activity[91,92]. It must be noted that both hyperthyroidism and hypothyroidism cause oxidative stress by different mechanisms, contributing to the vicious circle of thyroid aggression[88].

In line with this, in several studies the appearance of thyroid dysfunctions, including autoimmunity events, has been re-

lated to inflammatory cytokine-mediated signalling. For instance, it has been seen that TNF-α can reduce T3 and TSH (Thyroid Stimulating Hormone) levels in serum[93] and that IL-1 inhibits the D1 enzyme[94,95]. It has been also described that IL-2 can inhibit thyroid function, while the anti-inflammatory cytokine IL-10 can protect against autoimmune thyroiditis[96] and inhibit the production of IL-17 by TCD4+ lymphocytes. This synthesis of IL-17 is critical in the pathogenesis of autoimmune and inflammatory diseases, including the thyroid ones[97].

Objectives of micro-immunotherapy:

TNF-α IL-1 IL-10 IL-2	To readjust hormonal balance, regulating the expression of pro-inflammatory genes involved in thyroid dysfunction such as TNF-α and IL-1, cytokines that enhance oxidative stress and reduce T3 and TSH levels. The Formula INFLAM uses also IL-10 with the aim of reducing lymphocyte infiltration, relieving disease progression. Furthermore, INFLAM is oriented to modulate IL-2, for its capacity to promote regulatory T cell activity, but without inhibiting TSH-stimulated thyroid function.

5. *High levels of pro-inflammatory leptin*

Multiple studies implicate leptin, the hormone produced mainly by adipocytes and related to appetite control, in the pathogenesis of chronic inflammation[98]. In fact, despite being commonly correlated with systemic inflammation states during obesity, it is also known to enhance the development of cardiovascular disorders, type 2 diabetes, autoimmunity, inflammatory bowel disease, and cancer[99,100].

Several studies suggest that leptin levels are significantly higher in patients with subclinical hypothyroidism[101,102], thus establishing a link between the blood levels of thyroid hormones with the metabolism of leptin[103].

Leptin stimulates the activation of innate immune cells, including dendritic cells, monocytes, macrophages, neutrophils or natural killer cells[98,104–106]. Additionally this hormone upregulates the expression of the leukocyte antigen HLA-DR and stimulates the production of inflammatory cytokines such as IL-6 or TNF-α in monocytes[107], cytokines that are involved in inflammatory hyperleptinemia[108]. Leptin also stimulates the chemotaxis of neutrophils and the release of reactive oxygen species[109]. It also promotes the activation of T cells and the Th1-type response, increasing the production of interferon gamma (IFN-γ) and IL-2, and suppressing the production of Th2-type cytokines, such as IL-4[110].

Objectives of micro-immunotherapy:

TNF-α IL-1 IL-4 IL-8	To limit leptin expression, by inhibiting the action of inflammatory cytokines such as the leukaemia inhibitory factor (LIF), responsible for increasing leptin levels111. Furthermore, it is sought to modulate the influence of other mediators, such as IL-4, a cytokine with anti-inflammatory effects mediated by the suppression of the production of IL-1 or TNF- α[112,113] and IL-8, a pro-inflammatory factor promoting angiogenesis and cancer progression, when it is excessively expressed.

6. *Oncostatin M mediated signalling*

Oncostatin M (OSM) is a member of the IL-6 cytokine family. Its expression is regulated by different mediators, including leptin[114] and prostaglandin E2[115]. Oncostatin M is secreted by different cell types, including lymphocytes, macrophages and neutrophils, though it can also be produced by tumour cells[116–118]. It acts as a chemotactic agent during inflammatory responses[119,120] and activates signalling cascades involved in the regulation of local and systemic responses, such as those mediated by STAT3, MAPK (mitogen-activated protein kinases) and NF-κB[121,122]. It has been shown that OSM can favour pathological conditions associated to chronic inflammation, such as osteoarthritis, Alzheimer's disease, inflammatory disorders of the skin, cardiovascular diseases and atherosclerosis, among others[123].

On the other hand, different studies suggest that depending on the cellular microenvironment, OSM could mediate both pro- and anti-inflammatory effects[120,124]. In this regard,

it must be mentioned that OSM is able to both inhibit the action of inflammatory cytokines such as TNF-α, GM-CSF (granulocyte-macrophage colony stimulating factor) and IL-8 in fibroblasts[125], and to enhance the adipose tissue polarisation of M1 pro-inflammatory macrophages towards an M2 anti-inflammatory phenotype[126].

Objectives of micro-immunotherapy:

TNF-α IL-1 IL-1Ra Oncostatin M	To limit the action of pro-inflammatory cytokines activated by OSM such as IL-1 and TNF-α, while also simulating their antagonists, like IL-1Ra. Likewise, INFLAM seeks to modulate the anti-inflammatory effects of OSM.

7. Degradation of the extracellular matrix mediated by metalloproteinases

The matrix metalloproteinases (MMPs) are endopeptidases that participate in degradation and remodelling of the extracellular matrix (ECM) through hydrolysis of its components. In chronically inflamed tissues, the ECM fragments released as a result of MMP action enhance immune cell activation, perpetuating the inflammatory response[127,128] and favouring the induction of proangiogenic factors commonly found in chronic and degenerative diseases[129–131].

It has been shown that inflammatory cytokines such as IL-1, TNF-α or RANTES induce the secretion of different MMPs[132–135], while antiinflammatory mediators such as IL-10 can inhibit their expression or stimulate their inhibitors[136]. Other proinflammatory cytokines such as IL-6 and OSM can also stimulate the expression of MMP inhibitors[137,138].

Objectives of micro-immunotherapy:

TNF-α IL-1 RANTES IL-6	To favour the regulated expression of MMPs, controlling the pathological effects of their imbalances, such as excessive ECM degradation. Likewise, the Formula INFLAM seeks to reduce the effects of pro-inflammatory and pro-angiogenic cytokines such as RANTES, and modulate the effect of cytokines such as IL-6, through its positive action at MMP inhibitors level.

8. Specific nucleic acids

SNA INFLAM Ma1 SNA INFLAM Ma2	In the Formula INFLAM, various specific oligonucleotides are used with the aim of counteracting sequences of genes of inflammatory nature.

Conclusion

The Formula INFLAM acts at different levels in order to exert an effect upon different mechanisms involved in chronic inflammation. INFLAM seeks to help the immune system to resolve inflammatory phenomena and prevent them from persisting. Furthermore, its sequential composition can act in synergy with other treatments in the context of a global therapeutic strategy.

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