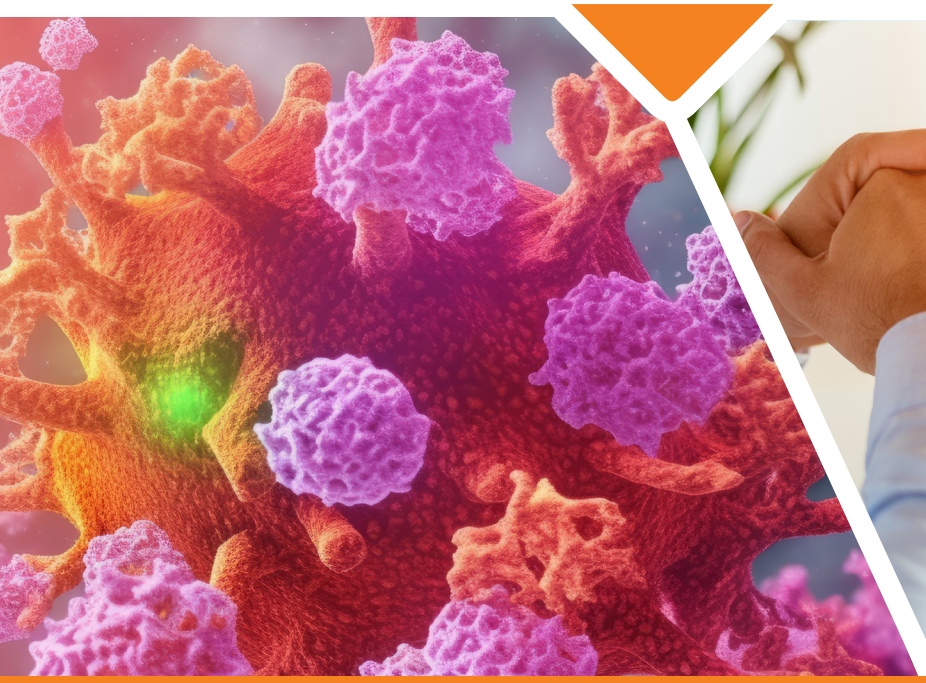
Micro-immunotherapy
International Medical Experience

# Micro-immunotherapy & Epstein-Barr Virus Infections



## Comprehensive guide to effectively managing EBV with micro-immunotherapy

# Prescribing **micro-immunotherapy** for EBV-related diseases

Essentially 2 formulas can be prescribed in micro-immunotherapy practice to treat EBV-related conditions: **the formula EBV** and the **formula XFS.** Both exert immunoregulatory objectives and are prescribed depending on the extent of immune dysfunction observed in the patient.

## APPLICATION* OF THE FORMULAS EBV & XFS

*According to the clinical experience of doctors of the International Associations of Micro-immunotherapy

### Normoreactive or hyporeactive lymphocyte typing

FORMULA **EBV**

- Acute status → **1-2** per day → Until symptoms disappear
- Maintenance therapy → **1** per day → For at least 6 months

### Hyperreactive lymphocyte typing

FORMULA **XFS**

- Acute status → **1** per day → Until sumptoms disappear
  - → Then switch to maintenance therapy with the **formula EBV**

- Main components of micro-immunotherapy formulas: low doses & ultra-low doses of cytokines, nucleic acids, SNAs.

Dive into the immunoregulatory objectives of the formulas EBV and XFS on page 12.

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## WHAT PRACTITIONERS SAY ABOUT MICRO-IMMUNOTHERAPY FOR EBV INFECTIONS

**Testimonial**

"In the clinical practice of my specialty, I often check for the reactivation of the Epstein-Barr virus in chronic conditions with unclear aetiology, in viral infections that do not respond well to established treatments, and in conditions such as lichen planus, psoriasis, alopecia areata, or medication-induced exanthems.

In this context, micro-immunotherapy is part of the diagnostic and therapeutic toolkit I use in my daily clinical practice. It gently regulates the immune system and is thus crucial for achieving a long-standing recovery".

**Dr Cristina Zemba**, dermatologist (Barcelona, Spain)

## Introduction

The Epstein-Barr virus (EBV) or herpesvirus 4 is a DNA virus belonging to the Gammaherpesvirinae subfamily[1]. It is among the most common of human viruses, being present in over 90% of the world population.

The virus is generally transmitted orally through saliva during childhood or adolescence. In developing countries, primary infection occurs during the first years of life and is asymptomatic. In developed countries, there is a tendency for delayed primary infection in adolescents and young adults, manifesting clinically as infectious mononucleosis[2].

After primary infection, like other herpes viruses, EBV remains latent in the organism (in B lymphocytes). It may then reactivate periodically in situations of immunodeficiency caused by factors such as chronic stress, malnutrition, other infections or intake of certain medications.

EBV should be a key target in diagnostic and therapeutic strategies as it is a driving factor in the onset and progression of chronic disease[3,4], contributing both to compromising the immune system and impairing its performance in the long run.

On both the diagnostic and the therapeutic level, micro-immunotherapy provides a valuable approach to understanding the context-dependent role of an EBV burden in each particular patient case and effectively managing the infection by supporting the antiviral defence through its fine-tuned immunoregulatory action.

In order to provide health professionals with a general framework to better understand and manage EBV-related conditions, this brochure includes a description of the immune response to EBV as well as the micro-immunotherapy approach to sustainably treating EBV infections and associated diseases

## The known and the unknown: A deep dive into EBV-associated diseases

EBV might be suspected in infectious mononucleosis and cancers:

### Diseases typically associated with EBV[3-6]

- Infectious mononucleosis
- Burkitt's lymphoma
- Hodgkin's lymphoma
- Nasopharyngeal cancer
- Stomach cancer
- Lymphoma after stem cell transplant

But as well in other chronic and autoimmune diseases:

### Common pathologies in clinical practice with association to EBV,[7-17]

- Rheumatoid arthritis
- Sjögren's syndrome
- Autoimmune thyroiditis
- Systemic lupus erythematosus
- Long COVID
- Multiple sclerosis
- Chronic fatigue syndrome
- Depression

## EBV Infection / Reactivation : A Brief Overview

Overall, after entering host cells, EBV initiates a dual life-cycle comprising lifelong, nonproductive latency in B cells and productive lytic replication.

### Primary infection

The Epstein-Barr virus enters the host infecting epithelial cells of the oropharyngeal mucosa through the upper respiratory tract, transmitted via saliva. From there, it targets naive B cells using its glycoprotein gp350 to bind to B cell receptor CD21+, followed by the binding of three other viral proteins (gp85, gp25, and gp42) to the human leukocyte antigen class II (HLA II). This interaction allows the viral genome to enter B cells, where it persists as an episome in the cell nucleus.

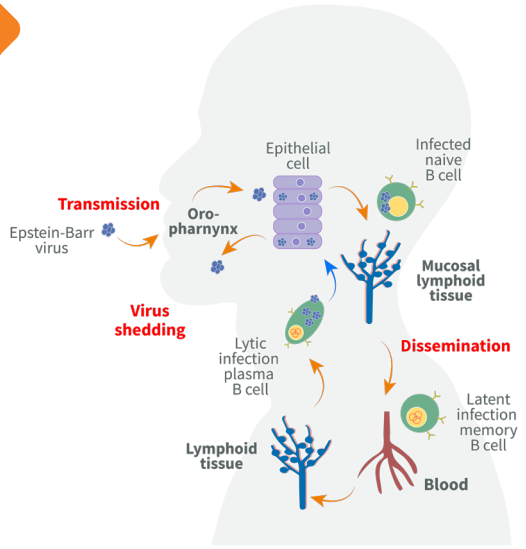



*Fig. 1: Epstein-Barr virus infection cycle*

These infected B cells mature into memory B cells and circulate through the bloodstream, maintaining a lifelong latent infection[18-21] (see Fig. 1).

Clinical symptoms of primary EBV infection, such as fever, sore throat, and lymphadenopathy, are generally attributable to the virus's lytic phase and the associated immune response, including the action of cytotoxic CD8+ T cells.

### Reactivation

However, despite the robust initial immune response, EBV has developed sophisticated mechanisms to evade immune detection and establish latency in memory B cells. For instance, the virus downregulates the expression of immunogenic viral proteins and modulates the host cell's antigen presentation pathways to avoid recognition by cytotoxic T cells. Periodic reactivation of the virus can occur, particularly under conditions of immunosuppression or stress. This reactivation can lead to the release of new virions (lytic phase), subsequent infection of new cells, and the potential triggering of an immune response that can range from subclinical to symptomatic[21].



## Role of the Immune System in EBV Infections

The immune system plays a vital role in controlling Epstein-Barr virus (EBV) infections and managing their associated pathogenesis. Upon initial infection, the innate immune response, mainly involving Natural Killer (NK) cells and dendritic cells, acts to limit viral replication initiating inflammatory mechanisms whilst activating adaptive immunity and antibody production.

The adaptive immune response, particularly cytotoxic CD8+ T cells, is crucial for recognising and destroying EBV-infected cells. CD8+ T cells detect infected B cells through viral antigens presented by HLA class I molecules, while CD4+ T helper cells support this process by producing cytokines such as interferon-gamma (IFN-γ), which enhances the antiviral response. After primary infection, EBV is predominantly kept in check by memory T cells[22].

Known factors that compromise the immune system and thereby favour EBV reactivation include chronic stress, immunodeficiency, inflammatory processes, coinfections (e.g. COVID-19, HPV, VZV,

CMV), oxidative stress, mitochondrial dysfunction and intake of certain medication (e.g. corticosteroids, immunosuppressants)[21].

**Practical tip**

It is crucial to consider the bidirectional relationship between inflammation and EBV reactivation. EBV reactivation triggers an inflammatory response, and excessive inflammation due to various factors can, in turn, lead to virus reactivation. Therefore, considering and addressing concomitant causes of inflammation whilst implementing antiviral strategies can help break the cycle of inflammation and reactivation, leading to more effective and lasting results in managing EBV-related conditions.

Given the complexity of EBV's life cycle and its role in the onset and progression of chronic diseases, effective management strategies are essential. Allopathic therapeutic possibilities are still limited, based specifically on symptomatic relief, and directed almost exclusively at treating the acute infection. Immunoregulatory therapies, such as micro-immunotherapy, can significantly impact the management of EBV infections and associated diseases by modulating the immune response to restore or maintain balance and control viral activity.

## Guidelines for the Management of EBV Infections in Daily Clinical Practice

### 1. When Should an EBV Infection / Reactivation Be Suspected?

- Symptoms of infectious mononucleosis may include fatigue, malaise, headache, fever, sore throat, nausea, swollen lymph nodes and splenomegaly[3].
- On the other hand, the appearance of unexplained fatigue or exhaustion, episodes of fever of unknown aetiology, rhinitis or chronic sinusitis, as well as joint pain or night sweats may be signs of Epstein-Barr virus reactivation[23]. However, these signs are nonspecific and require a differential diagnosis.
- An underlying EBV reactivation is also frequently observed in certain autoimmune diseases (e.g. multiple sclerosis), lymphomas, chronic fatigue syndrome, cases of recurrent infections, or even in patients under stressful conditions. In fact, stress can lead to a suppression of cellular immunity, which in turn favours the reactivation of latent infections[10,23].

## 2. Serological Diagnosis of EBV

Serology measures immune reactivity based on antibody patterns. Due to its cost-effectiveness and expression of results, it is the most widely utilised method in current clinical practice.

### 2.1. Important Considerations on the Use of Serology

- It is important to **use the same laboratory for repeated tests** on the same patient. Different laboratories may employ varying techniques (e.g., immunofluorescence, chemiluminescence, enzyme-immunoassay) and kits, which can affect the results.

- Serology is a good starting point but **not an optimal tool for monitoring disease progression or objectively assessing treatment efficacy.** Antibodies may increase after treatment, as the humoral response is linked to the cellular response, and variations in the latter can affect serology. **Assessment of the patient's clinical condition and the status of cellular immunity (through lymphocyte typing) should at all times guide diagnostic conclusions.**

Additional tests may be necessary to confirm the diagnosis or monitor the response to treatment. Inflammation, in particular, should be considered, as it can influence serological results.

### 2.2. Interpretation of EBV Serology

Unlike other viruses, the serological diagnosis of EBV requires examining three types of antibodies: antibodies to VCA (viral capsid antigen), EA (early antigen) and antibodies to the Epstein-Barr nuclear antigen (EBNA).

This diagnostic test is based on the detection of antibodies that target virus antigens (IgM and IgG):

- During primary infection, IgM antibodies against viral capsid antigen (VCA) appear first, followed by IgG which gradually increase and remain positive throughout life, while IgM antibodies disappear again after two or three months.

- Immediately after, early antigen (EA) IgG antibodies appear.

- IgG antibodies to Epstein-Barr nuclear antigen (EBNA) appear weeks or months later and remain positive throughout life: latent phase.

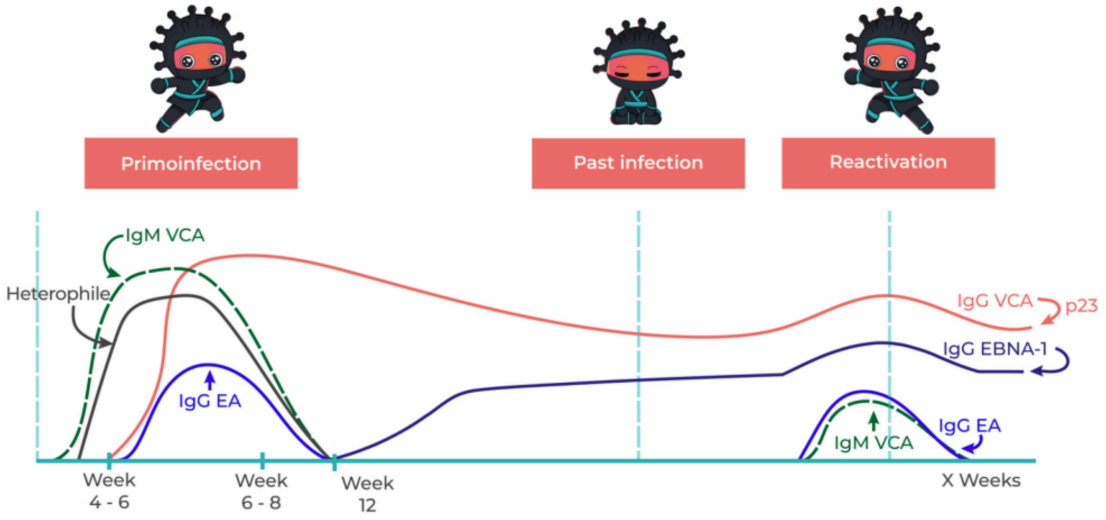



*Fig. 2. Antibody kinetics in EBV infection / reactivation (Source: ©DetectEBV)*

A guide for interpreting the serology results based on antibody kinetics in EBV infection is presented below.

| **Markers / Possible interpretations** | **IgM VCA** capsid | **IgG VCA** capsid | **IgG EBNA** nuclear | **IgG EA** early antigen |
|---|---|---|---|---|
| **No previous infection** | - | - | - | - |
| **Primary infection / Chronic infection** | + | +/- | - | +/- |
| **Persistent primary infection** | +/- | ++ | - | - |
| **Past infection** | - | + | + | - |
| **Reactivation** | +/- | + | + | +/- |

*Fig. 3. Differential diagnosis of EBV infections (Source: ©DetectEBV)*

In general lines, one can retain the following:

- A high level of anti-VCA IgG and negative anti-EBNA IgG suggests a recent primary infection. Nonetheless, it might also be a sign of a persistent primo-infection (chronic mononucleosis). In this case, it is recommended to test for IgM antibodies to EBV-associated antigens.

- Concurrent positive levels of anti-VCA, anti-EBNA and anti-EA IgG levels may be a sign of viral reactivation.

- In the presence of elevated levels of anti-VCA IgG and anti-EBNA IgG, a reactivation of the virus may be suspected, although it might also suggest an old infection since, in some cases, these antibodies remain elevated even in the absence of active infection.

## The Micro-immunotherapy Approach to EBV Infections

Micro-immunotherapy (low-dose immunotherapy) is a therapeutic approach based on the natural functioning of the immune system that aims to restore optimal immune function through sequential administration of low doses of immune mediators (mainly cytokines). By mimicking the body's natural immune response, micro-immunotherapy seeks not only to **bolster the body's capacity to manage pathogens** but also to **restore a balanced and effective immune response** over time.

### What is micro-immunotherapy?

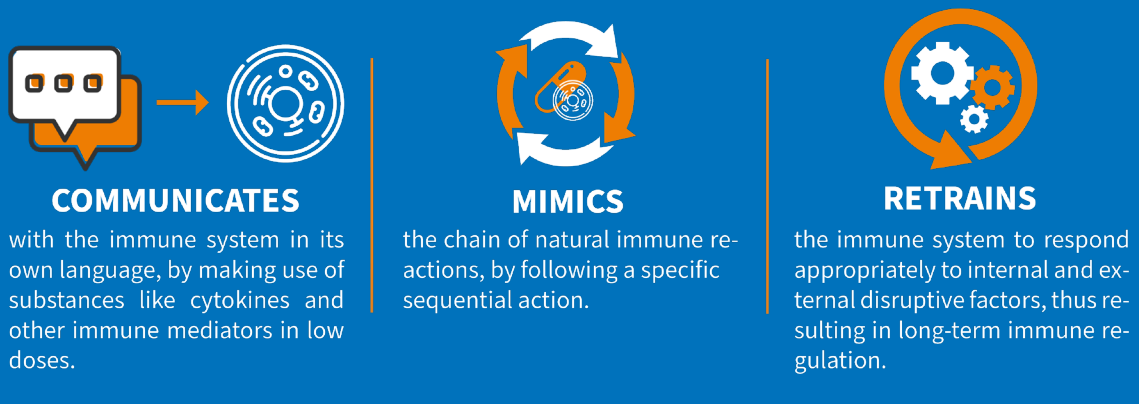
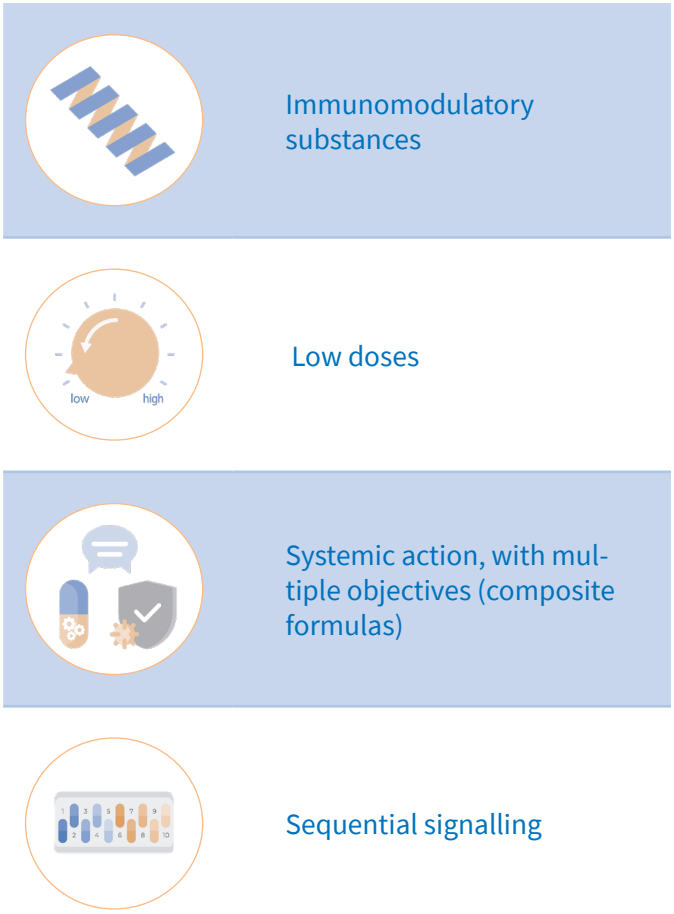



*Fig.4: Mechanism of action of micro-immunotherapy formulas*

EBV is notorious for its dual life cycle, comprising latency and lytic replication phases. The virus switching from latency to active replication is involved in the onset and progression of a variety of chronic diseases. Despite its widespread nature, there is currently no allopathic treatment **specifically targeting EBV infections.** The persistent challenge posed by EBV in the medical field underscores the need for innovative treatment methods.

Micro-immunotherapy's **multicomponent, fine-tuned action** is uniquely positioned to address the complexities associated with EBV-related conditions. It aims not only to **limit viral replication**, but to **optimise the body's natural defences against EBV**, favouring **immune surveillance** and contributing to **driving EBV back to latency.** It thereby helps **alleviate symptoms** associated with the infection, such as **fatigue**, and **prevent disorders associated with reactivation**, such as immunodeficiency or recurrent infections.



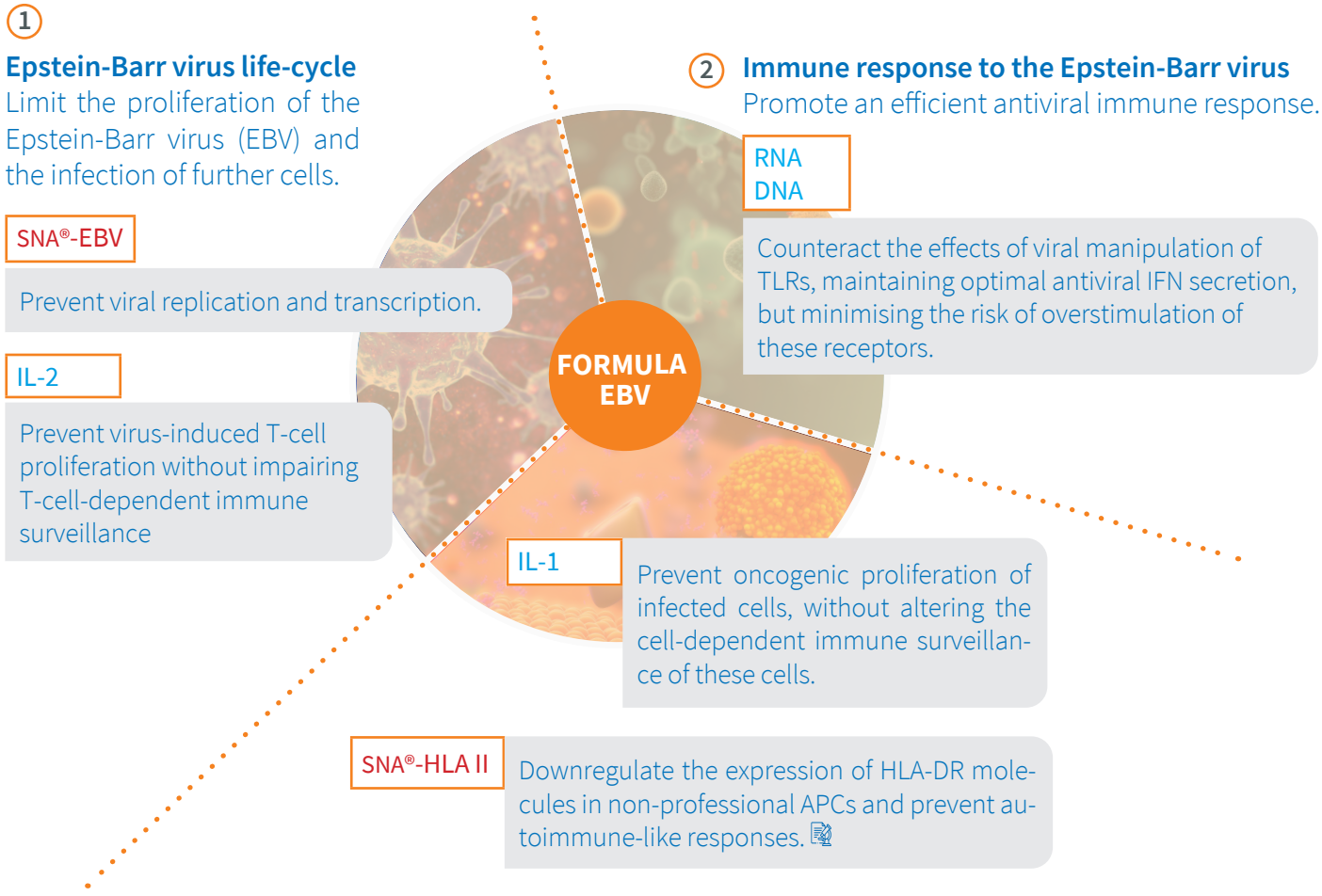

Micro-immunotherapy can be used across all age groups. It is well-tolerated given the low dosages and easy to take sublingually. There are no reported interactions with other medications, like antiviral medication, antipyretics, analgesics, or corticosteroids. This highlights its compatibility and safety as part of a broader therapeutic regimen.


*Fig.5: Benefits of micro-immunotherapy*

Essentially 2 formulas are used in micro-immunotherapy to manage EBV infections depending on whether the patient's immune system is in a hyporeactive (**formula EBV**) or hyperreactive state (**formula XFS**) (See page 2 for dosages)

## **Formula EBV:** Immunoregulatory Objectives

The micro-immunotherapy formula EBV is the formula of choice to treat an EBV burden in case of a hyporeactive immune status. Its immunoregulatory objectives are the following:



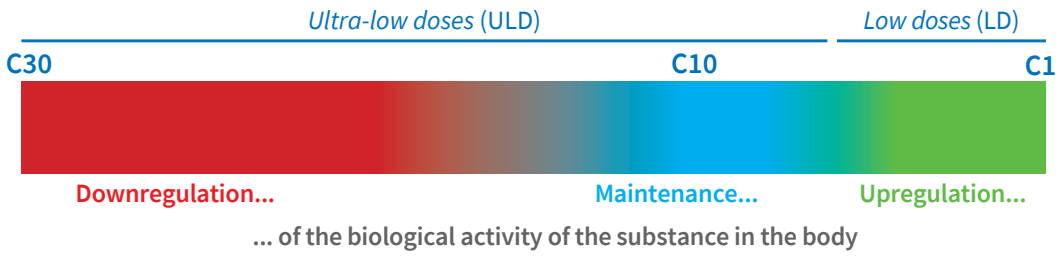




*Fig.6: Composition and immunoregulatory objectives of the formula EBV*

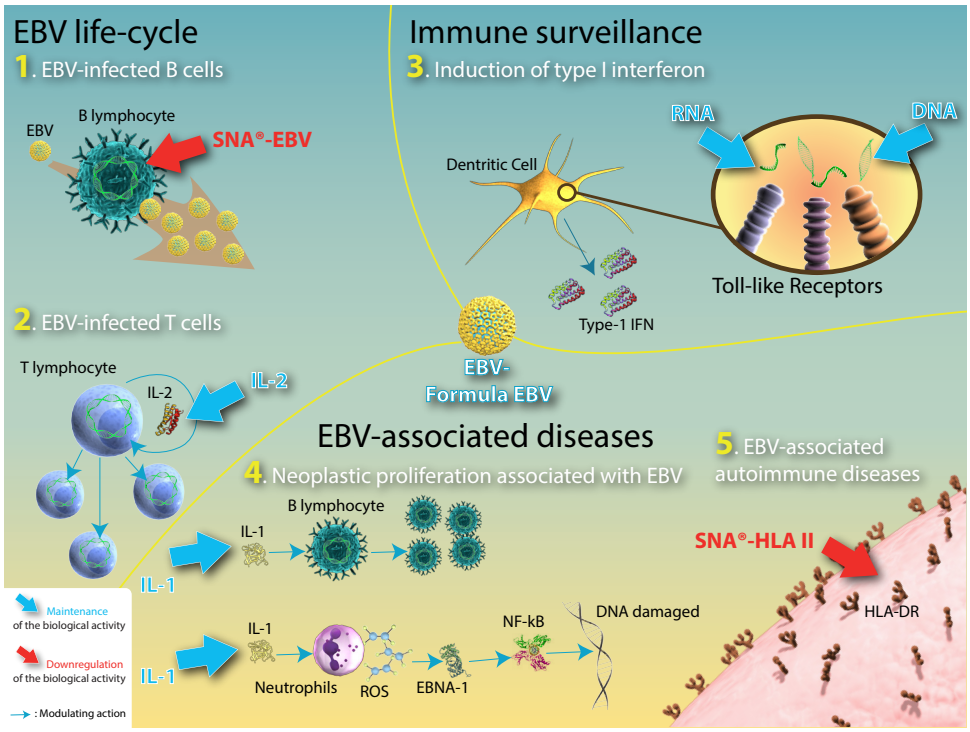
## Study:

HLA-II is one of the main entry receptors for EBV into its target cells and plays an important role in the induction of immune cell anergy. A 2024 study examined the potential of micro-immunotherapy as a therapeutic option for immune support during EBV reactivation by studying the effect of the 2LEBV® medicine in various in vitro immune models of uninfected cells. In this context, a reduction of histocompatibility antigen class II expression (HLA-DR and HLA-DP) was observed in endothelial cells stimulated with IFN-γ and in M1 macrophages treated with LPS, respectively. This suggests an immunomodulatory effect of micro-immunotherapy in the antiviral response[28].

**Understanding the Mode of Action of a Micro-Immunotherapy Formulation: Pre Clinical Evidence from the Study of 2LEBV® Active Ingredients**

https://www.mdpi.com/2075-1729/14/1/102

## Mechanism of action:




**Link to comprehensive breakdown of the model of the mechanism of action**

## Formula XFS

Hyperreactive immune statuses are associated with increased secretion of proinflammatory cytokines, depletion in cytotoxic function of CD8+ T cells and greater oxidative and nitrosative stress. These factors are involved in the onset and development of chronic fatigue syndrome. By addressing these factors, the formula XFS contributes to the normalisation of immune function.

**Note:**

As an immunomodulatory treatment, micro-immunotherapy can also be useful in situations of chronic stress that favour viral reactivation:

- **Formula MISEN:** Acts on different physiopathological mechanisms associated with chronic stress and ageing. The recommended dosage is 1 capsule/day for 3-6 months.

Other possible synergies between micro-immunotherapy formulas depending on the patient case include:

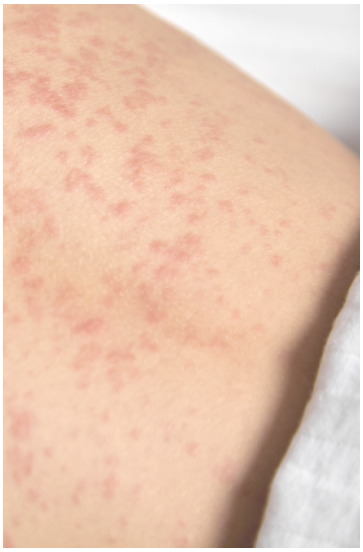
- **Formula MIREG + EBV:** In case of chronic infection with an underlying metabolic imbalance.
- **Formula EID + EBV:** In case of severe cellular immunodeficiency.

## Case Reports

### Dr Cristina Zemba (Spain)

#### CASE 1

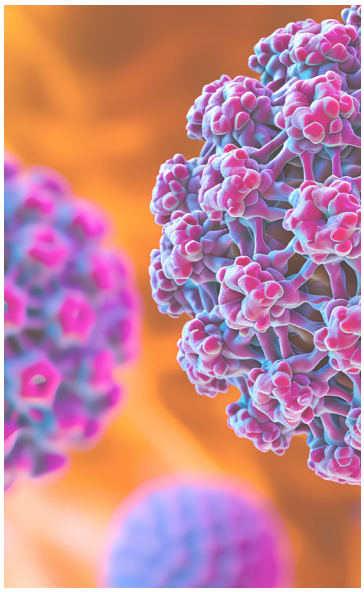
A 32-year-old male patient presented with a pruritic rash, widespread on the trunk and limbs, evolving over 4 months, and diagnosed by biopsy as pityriasis lichenoides. Six months earlier, he had contracted COVID-19 with high fever and headaches. He had a history of mononucleosis at the age of 15. In this context, it was suspected that the SARS-CoV-2 infection may have induced a reactivation of the Epstein-Barr virus. Indeed, serology results were compatible with viral reactivation. Treatment with the formula EBV was initiated, resulting in the clearance of lesions after 4 months.



## CASE 2

A 38-year-old female patient presented with abundant vulvogenital condylomas. Cytology results were negative. Treatment was initiated with the micro-immunotherapy formula PAPI and monthly cryotherapy for the lesions. Since there was no improvement after 6 months and the lesions persisted, Epstein-Barr virus reactivation was suspected due to the patient's chronic stress. Serology results were compatible with viral reactivation. The formula EBV was added to the formula PAPI, and within 1 month, the condylomas began to regress, disappearing after 2 months of combined treatment.

## CASE 3



A 45-year-old male patient suffered from recurrent genital herpes for 2 years, experiencing flare-ups once or twice a month. He was prescribed suppressive treatment with antivirals for 6 months. Despite the treatment, he continued to have bimonthly outbreaks. When the antivirals were discontinued, biweekly flare-ups resumed. He then attended my consultation and was prescribed the formula HERP. He took it for 4 months and, although the outbreaks were less intense, they still recurred every month and a half. At this point, lymphocyte typing and EBV serology were performed. The serology was compatible with a clinical picture of "chronic mononucleosis". Therefore, the formula EBV was added to the formula HERP. From that moment on, the outbreaks ceased.

### Practical tip

EBV reactivation is frequently associated with coinfections (e.g. HPV, VZV, HSV-1, HSV-2), whereby in case of blockages in the treatment of these infections it is recommended to check for an EBV reactivation diagnostically and treat it with micro-immunotherapy in case of a positive result.

## Dr Renate Schied (Austria)

# CHRONIC FATIGUE SYNDROME

## Patient case

A 31-year-old female patient visits my practice for the first time in 2017. She presents with extreme fatigue, stating she does not feel “fit at all for her age”. She reports a high susceptibility to infections, particularly pharyngitis, and frequent medical leave from work. Her medical history is notable for extensive antibiotic use.

In her teenage years, the patient experienced frequent episodes of pneumonia. At age 16, she commenced oral contraceptive therapy for acne management. She discontinued the oral contraceptive at age 19 but resumed its use after a few months. At age 23, she discontinued the contraceptive again, resulting in a 7-month period of amenorrhea.

The patient also reports cognitive difficulties, including poor memory and concentration.

## Diagnostics

› **Lymphocyte typing** shows selective non-adaptation with hyperreactivity. The picture of a ‘podium’ is formed by the T4, T8 and T4/T8 columns, indicating impaired defence in the extracellular range. In addition, the picture of a ‘cathedral’ is formed by columns T8c, T8s and T8c/T8s, which is indicative of a viral burden that might be blocking immune performance in the extracellular range. The picture of a ‘cathedral’ nonetheless indicates that the immune system has a good response capacity, where the prognosis is favourable.

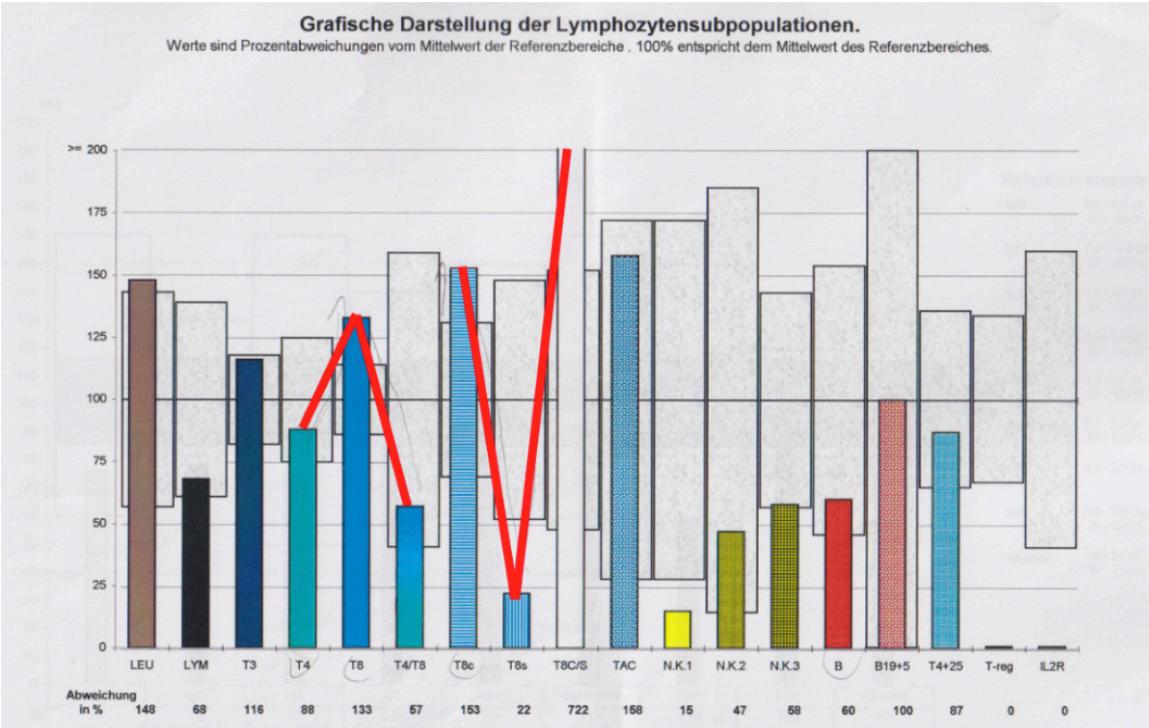
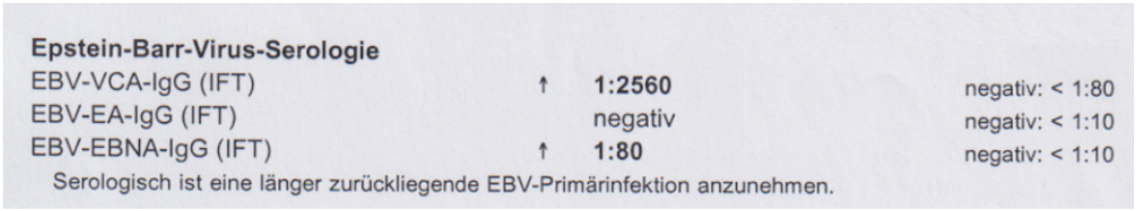



*Fig. 7: Lymphocyte typing (2017)*

› **Protein profile:** No relevant findings

› **EBV serology:** Sharply elevated levels of anti-VCA IgG and anti-EBNA IgG are indicative of EBV reactivation, which is further confirmed by the clinical presentation of the patient and lymphocyte typing.



| Epstein-Barr-Virus-Serologie | | | |
|---|---|---|---|
| EBV-VCA-IgG (IFT) | ↑ | 1:2560 | negativ: < 1:80 |
| EBV-EA-IgG (IFT) | | negativ | negativ: < 1:10 |
| EBV-EBNA-IgG (IFT) | ↑ | 1:80 | negativ: < 1:10 |

Serologisch ist eine länger zurückliegende EBV-Primärinfektion anzunehmen.

*Fig. 8: EBV serology (2017)*

› **Micronutrient analysis:** reveals selenium and vitamin D3 deficiencies.

## Treatment

› Micro-immunotherapy **formula XFS** (1 capsule/day for 1 month)

› Then switch to micro-immunotherapy **formula EBV** (1 capsule/day for 5 months)

› Selenium and D3 supplementation

› Symbiosis control

› Bioidentical hormones as progesterone low

› Vitamin C infusion

### Practical tip

Micro-immunotherapy can be combined synergistically with other treatment approaches such as micronutrient medicine or microbiological therapy.

## Follow-up

Over the course of treatment, the patient's infections have improved and hormone levels have returned to the normal range. However, fatigue has not improved. The patient does not come back to my practice until three years later, reporting that her fatigue did not improve and that she saw a specialist in chronic fatigue syndrome (CFS) who prescribed her with Cipralex. She has now resumed working, her infections have improved but her fatigue remains unchanged.

## Follow-up diagnostics

**Lymphocyte typing** shows selective non-adaptation with hyporeactivity (low T8 cells and B cells). The picture of a 'cathedral' is observed in the columns T4, T8 and T4/T8 ratio (T4 cells have increased) and in columns T8c, T8s and T8c/T8s ratio, indicating greater immune flexibility. In addition, the increase in NK cells indicates improved cytotoxic capacity.

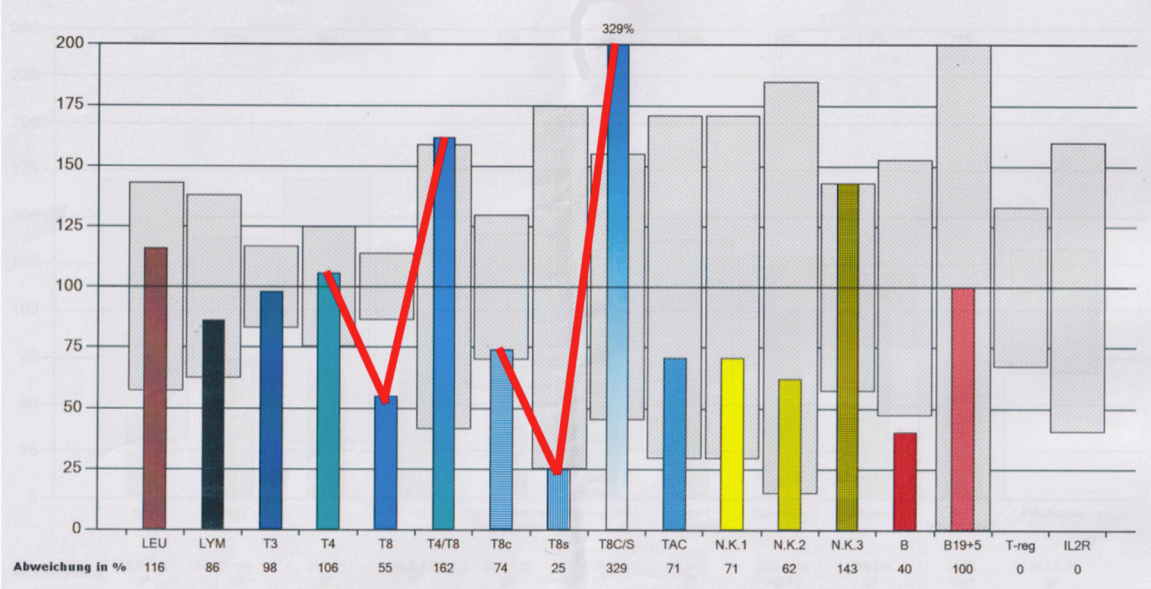



*Fig. 9 : Lymphocyte typing (2021)*

**Protein profile:** No relevant findings

**EBV serology:** Anti-VCA IgG have decreased by half. However, anti-EBV EBNA IgG remain unchanged, indicating persistent reactivation.

**Epstein-Barr-Virus-Serologie**

| | | |
|---|---|---|
| EBV-VCA-IgG (IFT) | **1:1280** | negativ: < 1:80 |
| EBV-EA-IgG (IFT) | negativ | negativ: < 1:10 |
| EBV-EBNA-IgG (IFT) | **1:80** | negativ: < 1:10 |

Serologisch ist eine länger zurückliegende EBV-Primärinfektion anzunehmen.

*Fig. 10: EBV serology (2021)*

**Micronutrient analysis:** Selenium and vitamin D3 deficiencies remain unchanged.

## Treatment

Micro-immunotherapy **formula EBV** (1 capsule/day) in 10-day alternation with the **formula MISEN** (1 capsule/day) for 6 more months.

Me2vie therapy

Citric acid cycle infusions

- Vitamin D3 supplementation (10000 IE / day)
- Selenium supplementation

### Follow-up

After this additional half year of therapy, her fatigue has significantly improved, and she has even started exercising again. As she lives far away and is currently satisfied with her condition, no further follow-up lab tests have been performed.

### What To Retain From This Clinical Case

This case is illustrative of a treatment strategy adapted to an initial picture of immune hyperreactivity associated with EBV reactivation. Immune regulation with the **formula XFS** was aimed at inducing an antiviral effect whilst keeping the inflammatory response under control. Thus, the blockage underlying recurrent infections was addressed, which resulted in greater immune flexibility and symptomatic relief. Nevertheless, after a long period of allopathic treatment, EBV reactivation persisted as confirmed not only by serology (lower anti-VCA but still elevated anti-EBNA) but also the ongoing CFS symptoms. Due to this prolonged interruption in treatment with the micro-immunotherapy approach, it was necessary to adapt, resume and extend the treatment accordingly, with the patient's fatigue improving significantly over the subsequent 6 months of treatment.

## Conclusion

The clinical importance of the Epstein-Barr virus infection lies in the fact that after primary infection it remains latent in the body and may undergo periodic reactivation. This virus has been linked to a multitude of clinical conditions, from mild clinical symptoms to severe and/or chronic diseases. Reactivations occur in the context of immune suppression, which may be due to different factors like immunosuppressive drugs, stress, co-infections or severe diseases such as cancer.

Based on its fine-tuned immunoregulatory action, micro-immunotherapy can be a great ally in maintaining or restoring appropriate immune function in the context of EBV infections and associated diseases.

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