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CURE

Constructing a **Eubiosis Reinstatement Therapy** for Asthma

CURE proposes a phage therapy to rebalance the structure of the microbiome in the airways. If proved, this therapy may control the immune dysregulation of asthma and eventually cure it.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 767015

The completion of CURE: the beginning of a new adventure

The concept of eubiosis reinstatement first came into my mind about a decade ago. It was more of a philosophical, or perhaps political, concept implicated in biology: why should we not try to support balance and diversity, as the basis of health, focusing on ecological equilibrium, rather than alluding to war against invading enemies and fostering an obsession with their eradication. CURE gave us a great opportunity to explore several aspects of this concept and, as every successful project, has generated more questions than the ones we could originally think of! We now know that adding a predator in a microbiome system can make the system more stable. We also know that a major challenge with asthma is that it is not conducive to a stable respiratory microbiota composition in time. Immune surveillance at the epithelial barrier is certainly implicated, but the microbial composition per se, remains a key suspect and therefore the CURE hypothesis stands! Unfortunately, we are still at a point where a specific microbial - phage or otherwise - curative treatment for asthma is a vision. It is exciting however that this vision is now clearer, creating the basis for further, deeper, more disruptive studies!

Nikos Papadopoulos, CURE Coordinator

CURE Final Conference

Save the Date!

The CURE consortium cordially invites you to the projects' final conference: "Towards a CURE for Asthma: Accelerating Innovation in Personalised Medicine and Phage Therapies," which takes place on **15 March 2022, 10:00-12:45 and 13:45-15:45 CET.**

The event will be hosted by two Members of the European Parliament, **Tilly Metz (Greens, Luxembourg)** and **Cristian-Silviu Busoi (EPP, Romania)**, both Vice-Chairs of the European Interest Group on Allergy and Asthma.

Supplemental Material

In addition to the live program, the event platform will also feature supplemental materials, both from throughout the project and to compliment some of the sessions. All material will be available with registration one week prior to the event and for a prolonged period following.

The event platform will showcase a special, pre-recorded session with phage researchers from around the globe. We will hear from **Cezmi Akdis, Director of the Swiss Institute of Allergy and Asthma Research (SIAF)**, **Dr Sabrina Green, Director of R&D at TAILOR service Center** (Houston, Texas, USA) and **Dr Maia Gotua, General Director of the GA2LEN Network certified Center of Allergy and Immunology** (Tbilisi, Georgia) who will present best practices and case studies from their pioneering work with bacteriophages.

It will also feature the CURE webinar series, comprised of over 10 presentations made by and for the CURE research teams.

Get access to the live event and the recorded materials in case you can't attend, spaces are limited, register today!

CURE Final Conference – Programme

Welcome and Introduction – 10:00-10:30

MEP Metz will open the day with statements on the importance of research and development in allergy and asthma, innovative medicine and the path forward with the support of the European Union's Research and Innovation Budget. Her address will be complimented by **President of the European Federation of Allergy and Airways Diseases Patients' Association (EFA) Carla Jones.** She brings the patient perspective, highlighting the importance of innovative medicine to patients living with asthma and allergy.

Healthcare Innovation and CURE Project Overview – 10:30-10:45

Focusing in on the project itself, **Barbara Gerratana, Senior Project Adviser at the European Innovation Council**, will help position CURE in the larger context of the European Innovation Council portfolio. **CURE project coordinator and Professor of Allergy and Paediatric Allergy, Nikolaos Papadopoulos** will then delve into the project overview, focusing on outcomes and the project's sustainable impact on innovations in the field of personalised medicine and asthma treatment and care.

Accelerating Innovation in Personalised Asthma Treatment: The Way Ahead and Challenges of Phage Therapies – 11:00-12:00

Following logically, the next session will feature a scientific exploration of personalised asthma treatment and the contributions made by CURE. We will first invite **patient advocate and former EFA President Mikaela Odemyr** to help us define what personalised medicine is, what it can look like and why it is important for patients living with asthma. CURE researchers **Dr Akis Megremis of University of Manchester** and **Dr Vicky Xepapadaki of University of Athens** will then lead the discussion on the importance of innovation to the advancement of personalised medicine, key challenges and opportunities for phage therapy as well as contributions from the CURE project itself.

Keynote Speakers: New Frontiers in Phage Therapy – 12:15-12:45

Following a short break, we will hear from two women who have helped define the world of phage therapy and its path forward. **Dr Nina Chanishvili, Head of R&D at The Eliava Institute of Bacteriophage**, brings over 40 years of experience to her role and will share her journey as a pioneer in the field to detail the history of phage and their recent rise to the spotlight.

Taking us from the present, well into the future, **Professor Martha Clokie of University of Leicester** will tell us of the vast potential of phage therapy. From her diverse experience working with bacteriophages, we will learn how they can be exploited across disciplines, from healthcare to food systems.

The Regulatory and Legal Framework of Phage Therapies at the National and EU Level – 13:45-15:15

The final panel of the day will explore the existing regulatory environment for phages at the EU level, including national case studies from countries that are setting the tone for future phage work. This discussion will be led by**Dr Eric Pelfrene of the European Medicines Agency** and leading phage researchers **Dr Jean-Paul Pirnay of Queen Astrid Military Hospital** in Belgium, and **Dr Andrzej Górski, Phage Therapy Unit Head of Hirszfeld Institute of Immunology and Experimental Therapy** in Poland.

A patient representative will highlight the ethical and practical considerations for patients in the development of new medicines and treatments.

Closing – 15:15-15:45

The day will close with an overview and key takeaways with co-host **MEP Busoi.**

From CURE Vision to Reality:
Implementing Best Practices Across the Globe

Ahead of the final conference, CURE invited Dr Sabrina Green, Director of R&D TAILOR service center and Research Associate at Baylor College of Medicine, to share her insights on best practices in phage therapy. With extensive experience working in the United States and more recent work in Belgian labs, she offers some comparative insights.

Dr. Sabrina Green
Director of Research and Development at TAILOR service center

An American Perspective of Phage Therapy in Europe

Enthusiasm for the implementation of phage therapy has increased over the past few years. This is due to the increase of multidrug resistant bacterial infections and the need for safe, alternative treatments. As is evidenced by the CURE project, phage therapies also show potential to address some underlying mechanisms of noncommunicable diseases, among other applications.

Our phage therapy system in the U.S.

Our group established TAILΦR (Tailored Antibacterials and Innovative Laboratories for Phage (Φ) Research) at Baylor College of Medicine in Houston, Texas, as a not-for-profit service center to source and prepare phages for patients with serious, drug-resistant infections[1] [2]. Since there are no approved phage drugs for infections by the U.S. Food and Drug Administration (FDA), the expanded access pathway is used for individual treatments via approval through an Investigational New Drug (IND) Application[3]. Thus far, TAILΦR and its clinical partners in different institutions across the U.S. have worked together to treat a total of 12 patients using this pathway (paper in preparation). Through this regulatory pathway, treatment for emergency cases can obtain approval within 24 hours, although most IND's can take 30 days to process, up to 2 months in our experience. The time it takes to source and prepare phages safely for individual cases, sometimes months, can be especially difficult for patients in need of phage therapy sooner rather than later.

Is the Belgian Magistral framework the best pathway for phage therapy?

I spent some time in Belgium as a research visitor in the Laboratory of Gene Technology with Prof Rob Lavigne to learn techniques and more about the regulatory system there. Since the Belgian regulatory framework was described in previous CURE publications, I will not go into detail about the specifics. Briefly, in this framework, phages can be delivered in the form of Magistral preparations (compounding pharmacy preparations in the U.S.) to the patient upon prescription by the treating surgeon[4].

[1] Austen L. Terwilliger et al., "Tailored Antibacterials and Innovative Laboratories for Phage (Φ) Research: Personalized Infectious Disease Medicine for the Most Vulnerable at-Risk Patients," PHAGE 1, no. 2 (January 2020): pp. 66-74, https://doi.org/10.1089/phage.2020.0007.

[2] Austen Terwilliger et al., "Phage Therapy Related Microbial Succession Associated with Successful Clinical Outcome for a Recurrent Urinary Tract Infection," *Viruses 13*, no. 10 (December 2021): p. 2049, https://doi.org/10.3390/v13102049.

[3] Gina A. Suh et al., "Considerations for the Use of Phage Therapy in Clinical Practice," *Antimicrobial Agents and Chemotherapy*, 2022, https://doi.org/10.1128/aac.02071-21.

[4] Jean-Paul Pirnay et al., "The Magistral Phage," *Viruses 10*, no. 2 (June 2018): p. 64, https://doi.org/10.3390/v10020064.

The active pharmaceutical ingredient (API), or the phages of magistral formulations are prepared according to a monograph. In this way, physicians can prescribe the personalized phage preparations while pharmacists prepare and dispense these prescriptions with the API or APIs (as different phage APIs can be combined at the pharmacy). These are currently produced by a non-profit Queen Astrid Military Hospital (QAMH), although others can produce the phage as well, and undergo quality checks (QC) by reference laboratories[5]. In practice Sciensano, the Scientific Institute of Public Health is used by QAMH.

I also visited the University Hospital in Leuven, Belgium where their center set up a study protocol called PhageForce. For this protocol, phage therapy is approved as "standard-of-care only in patients for whom no curative treatment alternatives are available"[6]. This group formed a multidisciplinary phage task force that screens patients with difficult-to-treat infections in order to determine their suitability for phage therapy and to set up an optimal treatment protocol. This task force was a requirement by the Federal Agency for Medicines and Health Products (FAGG) to ensure proper documentation and communication. The phages are provided by experts at the Laboratory for Molecular and Cellular Technology at QAMH. In this way, personalized treatments can be delivered to the patients that would benefit the most from this type of therapy. Also, since data from the patient cases (e.g. efficacy, immunological and microbiological data) is collected in a standardized way, the knowledge gained from these cases will further optimize future treatments.

This type of framework and protocol would be ideal for what we are trying to implement in the U.S. For one, we would not have to go through the individual approval process through our regulatory agencies for each individual treatment case. This process can styme treatment when therapy is needed right away for infections in the most vulnerable populations. The Belgian system also allows for tailored phages for individual cases, as opposed to predefined approved cocktails that have gone through costly and time-consuming clinical trials for approval

Our group at Baylor College of Medicine believes that for phage to be effective, they should be tailored for each individual patient case (hence the name of our service center—TAILOR). We develop tailored cocktails against each patient's bacterial isolate. We also take into consideration the antibiotic the patient may be on during treatment because we have found that phage and antibiotics can work synergistically to kill bacteria but can also have antagonistic interactions[7]. Phages can also be tailored to anticipate resistance. A recently published study by Eskenazi et al., has shown that preadapted phages alongside antibiotics during treatment were effective against a Klebsiella pneumonia infection[8]. We recently published a successful E. coli UTI treatment in which we developed a cocktail that contained a phage preadapted to anticipate the resistance mechanisms of the bacteri[a2 9]. This

[5] Gilbert Verbeken and Jean-Paul Pirnay, "European Regulatory Aspects of Phage Therapy: Magistral Phage Preparations," *Current Opinion in Virology* 52 (2022): pp. 24-29, https://doi.org/10.1016/j.coviro.2021.11.005.

[6] Jolien Onsea et al., "Bacteriophage Therapy for Difficult-to-Treat Infections: The Implementation of a Multidisciplinary Phage Task Force (the PHAGEFORCE Study Protocol)," *Viruses 13*, no. 8 (May 2021): p. 1543, https://doi.org/10.3390/v13081543.

[7] Carmen Gu Liu et al., "Phage-Antibiotic Synergy Is Driven by a Unique Combination of Antibacterial Mechanism of Action and Stoichiometry," 2020, https://doi.org/10.1101/2020.02.27.967034.

[8] Anaïs Eskenazi et al., "Combination of Pre-Adapted Bacteriophage Therapy and Antibiotics for Treatment of Fracture-Related Infection Due to Pandrug-Resistant Klebsiella Pneumoniae," *Nature Communications 13*, no. 1 (2022), https://doi.org/10.1038/s41467-021-27656-z.

[9] Keiko C. Salazar et al., "Antiviral Resistance and Phage Counter Adaptation to Antibiotic-Resistant Extraintestinal Pathogenic Escherichia Coli," *MBio 12*, no. 2 (2021), https://doi.org/10.1128/mbio.00211-21.

unique property of phage—its adaptability as opposed to the static drugs we use today can be harnessed to prepare treatments that can work against bacteria that are constantly changing. But we are in need of a system that facilitates this kind of work.

Is this framework possible in the U.S. and other parts of the world?

Since the regulatory aspects of phage therapy is not my expertise it is difficult for me to make an argument as to whether this type of system could be implemented in the United States. However, I can say that the patients that need this treatment the most are the ones that cannot wait these long periods of time for phage therapy. According to a recent Lancet paper, the six leading pathogens responsible for close to 1 million deaths in 2019 were Escherichia coli, followed by Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa[10]. Our group and other groups around the world all have phages that work against these pathogens[11]. At TAILOR we have proven we can successfully prepare and supply phages for 12 patient cases with no adverse effects noted. More phage groups around the U.S. have also developed recently and may supply phages for patient cases as well but will only be able to use the expanded access pathway since this is the only pathway for phage therapy at this time[11]. Hospital-based ethics committees exist already to facilitate decision making in treatment cases. Could these types of committees, similar to PhageForce, decide if phage therapy is applicable for compassionate-use cases in the U.S. or other European countries?

The CURE project has done a great job bringing together experts in the field of phage and phage therapy to tackle asthma. I ask the same community to come together and help us gain public support to build similar regulatory system models that work well, like the one in Belgium, to help patients get the treatment they need now.

Catch Dr Green's presentation in the on-demand library of the CURE final conference

[10] Christopher JL Murray et al., "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis," *The Lancet 399*, no. 10325 (2022): pp. 629-655, https://doi.org/10.1016/s0140-6736(21)02724-0.

[11] McCallin et al., "Current State of Compassionate Phage Therapy," *Viruses 11*, no. 4 (December 2019): p. 343, https://doi.org/10.3390/v11040343.

CURE partners continue to advance in final stages of the project

While many CURE publications are still under final revision, CURE researchers have continued to make an impact throughout the field of allergy and asthma.

Taking stock of biomarkers for allergic diseases

Biomarkers, short for biological markers, are objective measures used to assess "normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention"[12]. Biomarkers can be used to facilitate more accurate and timely diagnosis, treatment and even prevention with the use of modelling techniques. Thus, there has been a concerted effort to identify novel biomarkers in recent years.

CURE researchers from the Swiss Institute of Allergy and Asthma Research (SIAF) contributed to a comprehensive review of available and developing biomarker research used to assess allergic diseases[13].

The review found that, due to the heterogeneity of allergic disease mechanisms and presentations, and in increasing need to validate and standardize novel biomarkers, only a few are currently appropriate for widespread clinical application. There is a particular need to identify biomarkers related to diagnosis and to assist in treatment evaluation and decision-making. They encouraged the continued development of biomarker research to progress personalised treatment for allergic diseases.[13]

Read their full review of existing biomarker research related to allergic diseases.

Monitoring childhood asthma through a pandemic

CURE researchers from the University of Manchester and the University of Athens joined global experts to perform a multinational case-control study evaluating childhood asthma outcomes during the first wave of the COVID-19 pandemic[14].

The study involved 1,054 children with asthma and 505 non-asthmatic children from the Paediatric Asthma in Real Life (PeARL) Initiative. The cohort spans 25 paediatric departments from 15 countries across the world.

[12] Xiao Chloe Wan and Prescott G. Woodruff, "Biomarkers in Severe Asthma," Immunology and Allergy Clinics of North America 36, no. 3 (2016): pp. 547-557, https://doi.org/10.1016/j.iac.2016.03.004.

[13] Ismail Ogulur et al., "Advances and Highlights in Biomarkers of Allergic Diseases," Allergy 76, no. 12 (2021): pp. 3659-3686, https://doi.org/10.1111/all.15089.

Data from the cohort was used to compare acute respiratory and febrile presentations prior to and during the first wave of the pandemic. Interestingly, researchers found that children with asthma had fewer acute respiratory incidents during the pandemic than in the previous year. They also found that asthma control had improved for about one-third of asthmatic children during the same time period. Researchers attributed these changes to "reduced exposure to asthma triggers and increased treatment adherence" likely due to the nature of lockdown measures[14].

Read their full report.

CURE partners advance COVID-19 research

Spanning over four years, the CURE project has endured through the many hardships presented by the COVID-19 pandemic. CURE partners have not only made strides towards project objectives but also contributed to the study of COVID-19, or SARS-CoV-2.

Effects of comorbid allergy and asthma on COVID-19 pathogenesis

CURE researchers from the Swiss Institute of Allergy and Asthma Research (SIAF) contributed to a review of the prevalence and risk of infection, severity and mortality due to COVID-19, for patients with allergy and asthma[15].

Since the beginning of the pandemic, researchers across the globe have been collecting data to help determine protective and risk factors for developing the disease. Studies have determined that allergic disease or atopic status act, by way of their underlying mechanisms, as protective factors against COVID-19 prevalence[16] and severity[17], respectively. However, early studies showed conflicting data about how asthma interacts with the disease. As such, little was also known about the impact of allergic asthma on COVID-19 pathogenesis.

[14] Nikolaos G. Papadopoulos et al., "Childhood Asthma Outcomes during the COVID-19 Pandemic: Findings from the Pearl Multi-National Cohort," *Allergy* 76, no. 6 (2021): pp. 1765-1775, https://doi.org/10.1111/all.14787.

[15] Ya-dong Gao et al., "The Effect of Allergy and Asthma as a Comorbidity on the Susceptibility and Outcomes of COVID-19," *International Immunology*, December 2021, https://doi.org/10.1093/intimm/dxab107.

[16] Susanna C. Larsson and Dipender Gill, "Genetic Predisposition to Allergic Diseases Is Inversely Associated with Risk of Covid-19," *Allergy* 76, no. 6 (December 2021): pp. 1911-1913, https://doi.org/10.1111/all.14728.

[17] Enrico Scala et al., "Atopic Status Protects from Severe Complications of Covid-19," *Allergy* 76, no. 3 (July 2020): pp. 899-902, https://doi.org/10.1111/all.14551.

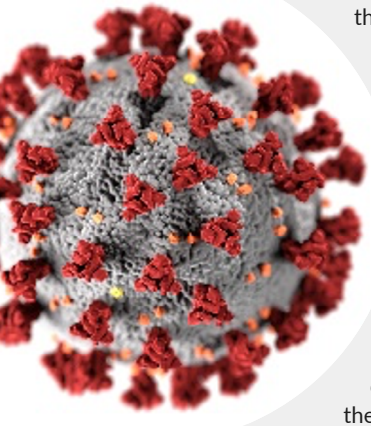
After a comprehensive review of available and developing literature, researchers determined that "allergic asthma is generally associated with lower risk of infection, hospitalization, severe course of disease and mortality due to COVID-19"[12].

Read their full publication for more details.

Pulmonary vascular endothelium changes in asthma may be a protective against COVID-19

Researchers from the Department of Immunology and Allergy at the Medical University of Lodz, Poland recently published an article about the interaction between Human Rhinoviruses (HRVs) and Coronaviruses in the pulmonary vascular endothelium[18].

The pulmonary or lung vascular endothelium is a layer of endothelial cells that line blood vessels and help regulate blood flow through lung tissues[19]. The endothelium plays several important regulatory functions for the health of the lungs[20] and has therefore been referred to as the "orchestra conductor in respiratory diseases"[21].



Researchers found that HRV16, a particular strain of HRV among many, may increase the surface expression of the angiotensin converting enzyme 2 (ACE-2). ACE-2 has already been identified as the receptor for SARS-CoC-2, meaning that it grants it access to host cells and can lead to infection[22]. This interaction suggests that certain types of Rhinoviruses, namely HRV16, may be risk factors for contracting COVID-19.

Interestingly, they also found that Interleukin (IL)-33 may prevent the increase of ACE-2 expression induced by HRV16. IL-33 is a cytokine that is produced by endothelial cells and is thought to alert the immune system to cell damage in the event of infection or other stressors[23] and is associated with the development of asthma[24]. This finding may suggest that IL-33 plays a protective role against SARS-CoV-2 infection and the development of COVID-19 in asthmatic patients.

Read their full publication.

[18] Izabela Gulbas et al., "IL-33 Prevents the Enhancement of AP-N, DPP4, and ACE2 Expression Induced by Rhinovirus HRV16 in the Human Lung Endothelium—Potential Implications for Coronaviral Airway Infections," *Allergy, 2022, https://doi.org/10.1111/all.15251.*

[19] Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. Blood Vessels and Endothelial Cells. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26848/

[20] Fraser R Millar et al., "The Pulmonary Endothelium in Acute Respiratory Distress Syndrome: Insights and Therapeutic Opportunities," *Thorax 71, no. 5 (November 2016): pp. 462-473, https://doi.org/10.1136/thoraxjnl-2015-207461.*

[21] Alice Huertas et al., "Pulmonary Vascular Endothelium: The Orchestra Conductor in Respiratory Diseases," *European Respiratory Journal 51, no. 4 (2018): p. 1700745, https://doi.org/10.1183/13993003.00745-2017.*

[22] Lobelia Samavati and Bruce D. Uhal, "ACE2, Much More than Just a Receptor for SARS-COV-2," *Frontiers in Cellular and Infection Microbiology 10 (May 2020), https://doi.org/10.3389/fcimb.2020.00317.*

Monitoring allergic and anaphylactic responses to COVID-19 vaccines

CURE partners from the Swiss Institute of Allergy and Asthma Research (SIAF) helped to assess reported cases of anaphylaxis in response to the Food and Drug Administration (FDA) -authorised mRNA COVID-19 vaccines[25].

The study involved 22 patients who had a suspected allergic reaction to COVID-19 vaccines administered at a large regional health care network in the United States. Their reported allergic reactions were assessed according to Brighton criteria, and skin prick and basophil activation tests were performed to gauge the role of Immunoglobulin-E (IGE)-mediated allergic disease[26].

The results of the case series suggest that "women and those with a history of allergic reactions appear to have an elevated risk of mRNA vaccine allergy"[24]. The results also indicate that allergic reactions were caused, for most patients, by non-IgE-mediated immune responses to a stabilizing agent in the vaccine known as polyethylene glycol or PGE.
It is important to note that allergic and anaphylactic reactions remain rare across all demographics[24].

Read more about their findings in the full report.

Incongruous antiviral immune response observed with COVID-19

Inflammation is an essential and highly coordinated response that protects us from infection. Interferons (IFNs) play a crucial role in this process; they are "cytokine mediators critically involved in alerting the cellular immune system to viral infection of host cells,... exhibit important antiviral effects ... [and] exert a key influence on the quality of the cellular immune responses"[27]. To have an optimal effect, they must have a coordinated response with other immune functions.

However, CURE researchers from the Biomedical Research Foundation of the Academy of Athens (BRFAA) have found that for COVID-19, patients exhibit an untuned immune response meaning that "interferon (IFN)-mediated antiviral responses [did not] precede pro-inflammatory ones"[28]. Interestingly, patients hospitalised with the flu with similar symptoms, did not exhibit this misfiring suggesting it is a unique disruption caused by COVID-19 that is responsible for disparate rates of hospitalisation, disease severity and mortality.

Read their full study here.

[23] Ben C. Chan et al., "Il33: Roles in Allergic Inflammation and Therapeutic Perspectives," *Frontiers in Immunology 10 (April 2019), https://doi.org/10.3389/fimmu.2019.00364*.
[24] L. C. Sjöberg et al., "Interleukin 33 Exacerbates Antigen Driven Airway Hyperresponsiveness, Inflammation and Remodeling in a Mouse Model of Asthma," *Scientific Reports* 7, no. 1 (2017), https://doi.org/10.1038/s41598-017-03674-0.
[25] Christopher Michael Warren et al., "Assessment of Allergic and Anaphylactic Reactions to Mrna COVID-19 Vaccines with Confirmatory Testing in a US Regional Health System," *JAMA Network Open* 4, no. 9 (2021), https://doi.org/10.1001/jamanetworkopen.2021.25524.
[26] Faisal M Khan et al., "Basophil Activation Test Compared to Skin Prick Test and Fluorescence Enzyme Immunoassay for Aeroallergen-Specific Immunoglobulin-e," *Allergy, Asthma & Clinical Immunology 8*, no. 1 (2012), https://doi.org/10.1186/1710-1492-8-1.
[27] Le Page C, Génin P, Baines MG, Hiscott J. Interferon activation and innate immunity. *Rev Immunogenet*. 2000;2(3):374-86. PMID: 11256746.
[28] Ioanna-Evdokia Galani et al., "Untuned Antiviral Immunity in COVID-19 Revealed by Temporal Type I/III Interferon Patterns and Flu Comparison," *Nature Immunology 22*, no. 1 (April 2020): pp. 32-40, https://doi.org/10.1038/s41590-020-00840-x.

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