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**Q1 Your work combines frontline paediatric care with genetic immunology research. How does this dual perspective shape the questions you choose to investigate in primary immunodeficiency (PID)?**

My journey has been a long one. I am a paediatric immunologist and principal investigator of a PID research laboratory, and this combination has allowed me to forge a unique path that integrates clinical expertise with pioneering research. Today, we increasingly refer to PID as inborn errors of immunity, which better reflects the underlying genetic basis of these disorders.

My interest began in the early 2000s, when I was treating patients with pulmonary disease and became increasingly involved in caring for patients with severe infectious diseases. Many of these patients were later found to have inborn errors of immunity. I then completed a fellowship in Hôpital Necker, Paris, France, where I gained a lot of experience treating patients with immune disorders, followed by a PhD focusing on chronic infectious and inflammatory diseases. In 2017, I secured a university position and established an independent PID research laboratory.

This combination of clinical care and research has been particularly exciting because it allows me to focus on translational research: what we often describe as 'from bedside to bench and back again'. In clinical practice, I encountered many patients in whom we could not identify the underlying molecular defect and, as a result, could not offer optimal treatment. Conducting research alongside clinical care enables us to address this gap.

Another key motivation for combining research with clinical work is the rapid expansion of knowledge in this field. Advances in next-generation sequencing, including whole-exome and whole-genome sequencing, have led to the identification of more than 500 genetic defects associated with inborn errors of immunity. When I began my career, only around 100 genes had been described. Today, new disease-causing genes are reported almost weekly, making it increasingly difficult for clinicians alone to stay fully informed about diagnosis and treatment. This was a major reason for establishing and leading a dedicated PID research laboratory.

In our laboratory, we work very closely with clinical colleagues. I am a paediatrician and primarily see children, but I also coordinate the Center for Primary Immunodeficiency Ghent (CPIG),

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in Belgium. Together with adult immunologists, geneticists, specialists from other disciplines, and researchers involved in these disorders, we discuss patients on a weekly basis. When we cannot identify an underlying molecular defect through standard diagnostics, we perform additional functional assays in my research laboratory to pinpoint which immune pathways are affected.

When we identify a novel genetic variant, a major challenge is determining whether it is truly disease causing or merely coincidental. Proving causality is the reason this translational research laboratory was established. To give an idea of the timeline, during the past year we identified three novel genes associated with inborn errors of immunity. From the initial diagnosis to establishing a clear genotype–phenotype correlation, this process takes, on average, more than 3 years, even with high-throughput assays and close collaboration with partners at Ghent University; the Flemish Institute for Biotechnology, Ghent, Belgium; and international colleagues.

We also frequently encounter novel variants of uncertain significance. We call these Class 3 variants. Using detailed pathway analyses in our laboratory, we can determine whether these variants are pathogenic. We always start from the patient, design extensive functional experiments, and aim to prove causality. Once causality is established, we can move to the next crucial step: targeted treatment.

Inborn errors of immunity are clinically very heterogeneous. While many patients present with recurrent or invasive infections, others have predominantly non-infectious manifestations, such as immune dysregulation, autoimmunity, autoinflammation, or an increased risk of malignancy. I often say that these disorders are 'more than meets the eye'. Because treatment depends entirely on the underlying molecular defect, identifying that defect is essential. Some patients require regular Ig infusions, others need haematopoietic stem cell transplantation, and for some, gene therapy is an option. Understanding the precise mechanism is therefore critical for appropriate management.

**Q2 The CPIG now cares for over 2,000 patients. What have been the most significant challenges in building such a large, specialised centre, and how have these shaped patient outcomes?**

In the early 2000s, we were following approximately 200 patients. The growth to over 2,000 patients reflects a major expansion, driven by close collaboration across disciplines. Establishing a truly multidisciplinary team was the greatest challenge.

Although I am an immunologist and pulmonologist, patients with inborn errors of immunity are also seen by dermatologists, rheumatologists, gastroenterologists, and many other specialists. Building a multidisciplinary team that included both paediatric and adult care was essential. Over the past 20 years, we have also seen a shift in patient demographics. Initially, around 80% of our patients were children, whereas today the cohort is approximately evenly split between paediatric and adult patients.

There are several reasons for this shift. Earlier diagnosis and improved targeted treatments have significantly improved survival, allowing many children to reach adulthood. In addition, increased awareness, driven by our multidisciplinary approach, has led to more diagnoses in adults. Although these are genetic disorders, symptoms do not always present in childhood; many patients first develop symptoms in their 30s or 40s.

I am very proud of our multidisciplinary team. Since 2015, the CPIG has been recognised as an international Jeffrey Modell Foundation Diagnostic and Research Center, reflecting excellence in both clinical care and research. In 2019, we also became a European Reference Network (ERN) centre for PID.

We have weekly multidisciplinary meetings involving clinicians, diagnostic laboratories, and research teams. This close integration is highly synergistic, improving diagnosis, enabling targeted treatment, and ultimately enhancing patient outcomes.

**What are the main reasons for these genetic diseases not manifesting until adulthood?**

In the majority of adult patients, we identify germline mutations. One explanation is that disease manifestation depends on exposure to specific micro-organisms. During the COVID-19 pandemic, I was involved in an international consortium that showed that persons with previously uneventful medical histories could develop severe or fatal COVID-19 due to monogenic defects affecting Type I interferon pathways.

In other words, the timing of the first clinical manifestation may depend on when a person encounters a pathogen for which they have an impaired immune response. Other factors include epigenetic influences and modifying genes. Even within the same family, individuals carrying the same mutation can show very different phenotypes, a phenomenon known as incomplete penetrance. Monoallelic expression in specific cell types may also contribute to this variability.

**Q3 Your team has identified novel disease-causing mutations, including *GTF3A* and *RC3H1*. What do these discoveries tell us about the mechanisms underlying immune dysregulation?**

Regarding *GTF3A*, our team, in close collaboration with Michaela Gack's laboratory at the Cleveland Clinic Institute in Florida, USA, described the first human patients with biallelic *GTF3A* mutations. These patients presented with herpes simplex encephalitis. *GTF3A* encodes transcription Factor IIIA, which is essential for the transcription of 5S ribosomal RNA.

Although ribosomal RNA and pseudogenes, previously considered as 'junk DNA', have traditionally received less attention, we found that patients with *GTF3A* mutations had reduced transcription of a 5S ribosomal RNA pseudogene 141 (RNA5SP141) causing impaired innate immune response upon viral infections. Experimental studies showed that this pseudogene, rather than the virus itself, triggers innate immune signalling and Type I interferon responses during herpes simplex virus infection. This provides a novel insight into human antiviral immunity and demonstrates an unexpected role for ribosomal RNA and pseudogenes in innate immune defence. We have since identified additional patients and are exploring broader phenotypes, including potential roles in adaptive immunity.

With respect to *RC3H1* (roquin-1), we were the first to describe biallelic mutations in humans associated with severe hyperinflammatory syndromes. While this pathway had been studied in mice, it had not previously been linked to human disease.

Subsequent identification of patients carrying monoallelic mutations, who presented with comparatively milder autoimmune phenotypes, suggests a gene dosage effect: biallelic mutations drive severe hyperinflammation, while a single mutantv allele is sufficient to predispose to autoimmune disease. Additional studies in our laboratory are ongoing to formally test this hypothesis. Studying rare disorders in this way also provides valuable insights into more common autoimmune and rheumatological diseases.

**Do you see more monoallelic or biallelic mutations in inborn errors of immunity?**

It is very heterogeneous. In inborn errors of immunity, we see biallelic, monoallelic, and X-linked mutations. Initially, these disorders were considered strictly Mendelian, but we now recognise that incomplete penetrance and variable expressivity are common. Notably, our work on *RC3H1*, and that of others on several genes previously described as autosomal recessive defects, shows that monoallelic variants can cause disease, challenging the traditional view that those individuals are asymptomatic carriers.

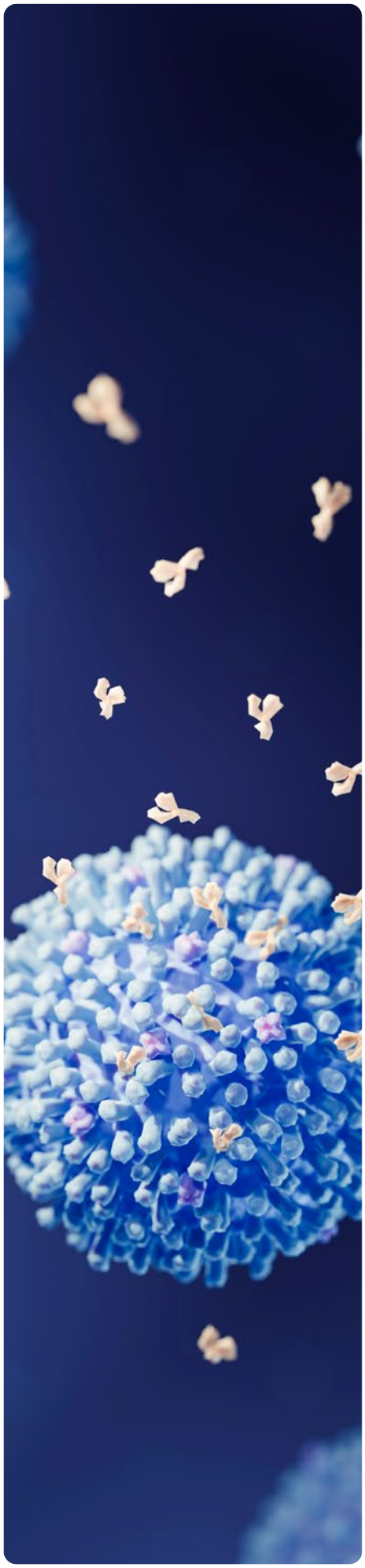
## Q4 How have advances in genetic and molecular diagnostics changed the way clinicians approach children with severe or unexplained infections?

In the past, when a child presented with a single invasive infection, such as invasive pneumococcal disease, clinicians might have considered this 'bad luck'. As a paediatric immunologist, I never accept this explanation. Many children of the same age are exposed to *Streptococcus pneumoniae*, yet only a small number develop severe disease. This strongly suggests an underlying inborn error of immunity.

Diagnosing an inborn error of immunity is a very long process. I often refer to it as a diagnostic odyssey. As mentioned earlier, even once a novel variant is identified, proving its causality takes an average of 3 years, and often closer to 3–5 years. By the time a patient reaches my clinic, they have usually already been seen by four or five other physicians over many years.

Worldwide, the average diagnostic delay for patients with inborn errors of immunity is 8–10 years, which is extremely long. During this period, patients suffer from recurrent or severe infections, irreversible organ damage, and significant psychological burden. Advances in genetic and molecular diagnostics are therefore crucial, not only for diagnosis, but also for guiding targeted treatment decisions and improving patient outcomes. Every child or adult who presents with invasive or recurrent infections should be screened for an inborn error of immunity. First, this helps prevent further invasive infections such as pneumococcal meningitis, which can lead to irreversible complications or death. Second, it allows for targeted treatment, as each of the 500 identified genetic defects has its own specific therapeutic approach.

Third, identifying the underlying genetic defect is essential for the family. It enables appropriate genetic counselling, assessment of siblings, and early identification of affected relatives. Our ultimate goal is to diagnose these children before they present with severe infections. While it is not feasible to screen for all



500 genetic defects, improved genetic diagnostics allow us to adapt management strategies. For example, if a patient carries a monogenic defect associated with increased risk of autoimmunity or malignancy, we will adjust follow-up and surveillance accordingly. Without a molecular diagnosis, clinicians must wait for symptoms to appear. Knowing the genetic defect allows us to anticipate complications and manage patients proactively rather than reactively.

**Are there screening guidelines for at-risk children?**

There are guidelines, including the widely used '10 warning signs' for inborn errors of immunity in children and adults. These are mainly aimed at general physicians, as most patients are first seen in primary care. The guideline states that, if a patient presents with two or more of these warning signs, the patient should be referred to an immunologist.

However, these warning signs do not capture all presentations. For example, current guidelines suggest that more than one invasive infection should raise suspicion, but even a single invasive infection should prompt evaluation, in my view. A cornerstone of medical teaching said: "When you hear hoofbeats, think horses, not zebras," meaning common diagnoses should come first. But inborn errors of immunity demand the opposite instinct: consider rare diagnoses when the presentation does not fit common partners.

**Q5 Translating genetic discoveries into tangible clinical benefit remains a major challenge in rare immune disorders. What strategies have proven most effective in moving your laboratory findings into routine care?**

Collaboration is key. In rare immune diseases, we may be studying only a single patient, making international collaboration essential. Translational research in rare diseases relies on sharing data, samples, and expertise across centres, both nationally and internationally, as well as sharing results through publications and presentations at international meetings, such as the European Society for Immunodeficiencies (ESID) and others. This culture of collaboration is one of the greatest strengths within this field.

The COVID-19 pandemic provides a powerful example. During this time, all borders between centres effectively disappeared. Laboratories and clinicians worked together globally, sharing data and samples in real time. This unprecedented collaboration, led by Jean-Laurent Casanova and Helen Su through the COVID Human Genetic Effort, allowed researchers to demonstrate within 6 months that a significant proportion of patients with severe COVID-19 had monogenic defects affecting Type I interferon immunity.

This same collaborative approach underpins our work. When we identify a novel mutation, we present it at meetings and discuss it with colleagues. Often, other centres recognise similar patients, and we form international cohorts. Conversely, if I encounter a patient with a mutation outside my laboratory's focus, I send samples to colleagues with the appropriate expertise. This continuous exchange between clinicians and research centres is essential for translating discoveries into clinical practice.

**"Future progress will depend on expanding our understanding of defects in non-coding regions, RNA genes, and somatic mutations"**

## Q6 Looking ahead, which emerging areas will most transform diagnosis and management of inborn errors of immunity?

Despite major advances in next-generation sequencing, we still fail to identify a molecular defect in approximately 60% of patients with suspected inborn errors of immunity. This shows that we are not yet at the end of the diagnostic journey and that we are now confronted with important limitations.

Future progress will depend on expanding our understanding of defects in non-coding regions, RNA genes, and somatic mutations. Over recent years, we have increasingly identified patients with somatic mutations causing inborn errors of immunity. These are known as phenocopies, which represent one of the most challenging and fascinating areas in the field.

Phenocopies include not only somatic mutations but also autoantibodies against cytokines that are essential for immune responses. COVID-19 again played a key role in highlighting the importance of autoantibodies against cytokines, particularly Type I interferons. Since then, many other infectious diseases have been linked to similar mechanisms. Expanding knowledge in this area will be critical for future diagnostics and treatment.

I want to end on a message of hope. More than 500 genetic defects have now been described, with over 200 identified in recent years alone. This rapidly expanding knowledge allows us to move towards increasingly personalised medicine. Not only can we better treat infectious susceptibility, but we can also offer targeted therapies for patients with immune dysregulation.

In the past, patients often received broad immunosuppressive treatment with significant side effects. Today, identifying the precise molecular defect allows for more targeted therapy, such as through repurposing of drugs used in common rheumatological and autoimmune disorders.

Gene therapy, while currently available for only a few inborn errors of immunity, represents a rapidly advancing and promising frontier in the field. Overall, the diagnostic and therapeutic landscape for patients with inborn errors of immunity is evolving very rapidly.