



IgE  
turns **50**

Celebrating the  
**50-year anniversary**  
of the discovery  
of Immunoglobulin E.

**ThermoFisher**  
SCIENTIFIC





*Achievement, good  
standing and prest**IgE**—  
since 1967.*



To celebrate the 50th anniversary of IgE's discovery, let's honor the history.

**The discovery that revealed  
the secret of allergies.**

PREST**IgE** Since 1967

**ThermoFisher**  
S C I E N T I F I C



## Prologue

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### The allergy concept emerges

At the end of the 19th century, immune phenomena were considered as relatively stable mechanisms that protected against infectious diseases; little was yet known about the immune system's ability to change in terms of reactivity.

In 1906, a young Austrian pediatrician – Clemens von Pirquet – suggested that the first contact with an antigen can change the immune system to induce tolerance or hypersensitive reactions upon the second follow-up contact. He called this idea 'Allergy'.

At about the same time, Charles Richet – a French physiologist studying the pathological effects of marine animal toxins in dogs – was the first to describe severe reactions due to hypersensitivity. To cut costs, he had been forced to re-inject toxins into those dogs that had survived a first dose. To his great surprise, he observed that this second exposure caused systemic shock and rapid death in several animals. Relating his findings to the immune system and its change in reactivity, he called these phenomena 'Anaphylaxis' or 'counter-protection'.

In 1921, Prausnitz and Kustner were able to show that allergic symptoms could be transferred from one individual to another using blood serum. This suggested that hypersensitivity was associated with a factor in the blood capable of mediating allergic reaction – a 'reaginic' activity of some sort.

But it would take more than 40 years for scientists to finally identify the new class of immunoglobulin associated with these phenomena: IgE. A discovery that would mark the start of an unprecedented transfer of scientific research into clinical application – and result in thousands of publications and vastly improved quality of life for millions: The history of IgE.



## 1967

### IgE sees the light of day

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In 1965, a Swedish farmer visits his doctor with a persisting back problem. He is diagnosed with a rare form of blood cancer; myeloma. But something very unexpected is detected in his blood. A discovery destined to change the world of allergy diagnostics.

Professor Gunnar Johansson, at the time a PhD student at Uppsala University Hospital, noticed what could be a new class of immunoglobulin in the farmer's blood sample. He named his discovery IgND after the patient's initials.

Two years, Johansson and colleague Hans Bennich were able to show that allergic symptoms could be transferred between individuals using blood serum containing IgND, thereby repeating the classical Prausnitz and Küstner (PK) test from 1921.

At the same time, Professor Kimishige Ishizaka's group in Denver, Colorado, were investigating a substance they called E-globulin, which seemed to possess similar characteristics to IgND. But despite several efforts, they failed to isolate it. Nevertheless, after having exchanged data, the two teams could confirm that they had indeed found the same substance.

Johansson and Bennich became the first to purify and analyze the new immunoglobulin. The two teams jointly declared the discovery of Immunoglobulin E or, quite simply, IgE.

Gunnar Johansson and Hans Bennich became the first to purify and analyze the new immunoglobulin.



## 1960s

### Uppsala: a leading center for biochemistry

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By the mid-60s, the hunt for IgE had boiled down to a race between two independent teams: Ishizaka's team in Denver and Johansson's team in Uppsala.

Both teams were searching for very low concentrations of 'something' in the blood capable of mediating allergic reaction. A search that would require the very best isolation technologies available. And in this, the setting would prove decisive.

Uppsala in the 1960s was already an exciting place for a biochemist, and an excellent setting for Johansson and Bennich's research. As a leading center for biochemistry, full of confidence from its rich history of scientific prosperity, the city of Uppsala was home to the best methods for purifying and analyzing proteins available at that time – as well as the innovative thinkers behind them.

Led by professors and Nobel Laureates The Svedberg and Arne Tiselius, research teams at Uppsala University had invented cutting-edge technologies such as ultra-centrifugation and electrophoresis for separating and analyzing proteins. Furthermore, their colleague and oncologist Jan G. Waldenström had already discovered IgM, and Tiselius – himself already the first to isolate IgG – was at the time working closely with the Uppsala-based Pharmacia company to develop dextran products such as Sephadex for purifying biomolecules.

It was in this context that Johansson and Bennich sought the explanation for the 'reaginic' activity first proposed in 1921 by attempting to isolate the new mysterious class of antibody they suspected was behind it. That they succeeded in being the first to isolate IgE is in no small measure due to the unique attributes of their hometown.



## 1967

### The first IgE blood test

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In 1966, a 33-year-old MD and serial inventor named Leif Wide heard about the ongoing struggles of two competing research teams in Uppsala and Denver: to purify and identify a new type of immunoglobulin that could mediate allergic symptoms.

Together with Johansson and Bennich, Wide set out to develop a test sensitive enough to measure the very low levels of IgE present in blood. Within a year, they had succeeded and were able to establish that patients with allergic symptoms often had elevated levels of IgE in their blood. For the first time, a blood-based test for investigating allergy was available, thus minimizing the need to expose patients to allergens in diagnostic practice.

Moreover, by binding the reagent to a solid-phase, the test could be directly performed on a simple blood sample, thereby avoiding a tedious separation step. The three co-workers named their test RIST.

Excited about the usefulness of RIST in clinical practice, Wide, together with researchers Rolf Axén and Jerker Porath, started collaboration with Pharmacia to develop an improved test based on the company's product Sephadex. To further improve test quality, Wide also experimented with layering the Sephadex solid-phase surface, thereby inventing the sandwich technology commonly known as sandwich-ELISA. The new test was called RAST (RadioAllergoSorbent Test). Capable of detecting very low levels of IgE antibodies directly in the blood of atopic individuals, it was perfect for routine clinical practice.

Together, the RIST and RAST tests lay the foundation for Pharmacia's world-leading position in allergy diagnostics.

## 1972

**Phadebas IgE** becomes the first commercially available total IgE test.

## 1974

**Phadebas RAST** was launched. For the first time, measuring IgE antibodies was a reality.



## 1980s

# Understanding allergic symptoms and IgE

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Most people are aware that allergic symptoms are caused by the release of powerful signal substances such as histamine that can cause everything from mild reactions such as a runny nose or skin rash to severe symptoms such as asthma, eczema and even systemic shock. But it wasn't until the 1980s that scientists understood how these symptoms came about – or the central part that IgE antibodies played in the process.

In principle, allergic reactions are misguided inflammatory reactions triggered by normally harmless substances from our day-to-day environment – allergens. An allergen is typically a protein found in for example plant pollens, animal dander and foods such as peanut, egg and milk.

In allergic individuals, one or more of these allergens may be recognized as potentially dangerous. On first exposure, their immune system starts to produce antibodies that can bind to that antigen to protect the individual in the future. In atopic allergy (the most common type of allergy), the antibody formed is IgE.

1980's research into exactly how IgE binds to other compounds, based on a deeper insight into IgE-receptors, opened the door to a better understanding of the origin of allergic symptoms.

It was discovered that an allergic individual's 'memory' of having first been exposed to an allergen is stored as IgE antibodies attached side-by-side on a special type of white blood cell. These blood cells, known as mast cells, contain the powerful signal substances that on their release create the inflammatory response we call allergy. On second exposure, sensitized individuals may suffer a reaction if the allergen cross-links adjacent IgE antibodies, triggering the release of the inflammatory chemicals inside the mast cell.

This is why measuring levels of IgE antibodies in blood is a good way of determining the risk of allergic reaction, and why IgE-testing is still a leader in allergy diagnostics.





## 1986

# Phadiatop<sup>®</sup>, the first test to detect atopic disease

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The first Phadiatop test was designed to support clinicians in diagnosing respiratory allergy by screening a mixture of common inhalant allergens. Later Phadiatop Infant was developed – optimized for young children – that in addition included some food allergens relevant for this age group.

A few years earlier, a group of senior scientists at Pharmacia had set out to develop a ‘yes-or-no’ test for the most common types of respiratory atopic allergy. A test that would take into account cross-reactivity and the interplay of sensitization to multiple allergens, and that would be applicable to populations all over the world.

The result was a unique and well-balanced combination – a carefully composed mixture of the most common types of allergens – that could help to rule in or out atopic allergy with a sensitivity and specificity as high as 95%.

In the late 80s, Phadiatop was made available as a RAST test and in 1992 it was moved over to the ImmunoCAP<sup>®</sup> technology. Offering reliable results of very high clinical relevance – an able single atopy screening test – it proved popular with clinicians and laboratories alike.

The first “screening” test for atopic allergy become available under the name Phadiatop<sup>®</sup> after the term “atopy.”

“Atopy” is a concept used to describe patients with sensitization to common allergens and thus prone to develop atopic allergies such as rhinitis and asthma.



**1987**

## PhARF, the most prestigious prize in allergy

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### **Annual award**

to encourage progress in allergy research, especially contributions from outstanding young researchers.

Twenty years after the discovery of the immunoglobulin E, Pharmacia founded the most distinguished award in allergy: The Pharmacia Allergy Research Forum Award – or simply PhARF.

Its objective was to encourage progress in allergy research, especially contributions from outstanding young researchers. Since then, some 30 scientists have received both funding and recognition and many have gone on to become leading experts in their field. Today, PhARF is a collaboration between Uppsala University and Thermo Fisher Scientific.

In 2017, PhARF celebrates its 30th anniversary, exactly 50 years after Johansson's and Ishizaka's groups' independent discovery of the last human immunoglobulin: IgE.



**1989**

## Pharmacia CAP System launched

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In 1989, Pharmacia launched Pharmacia CAP System® by introducing a new solid-phase called ImmunoCAP®. This new technology fixated allergens that could bind IgE antibodies in patient blood samples onto a porous 3D solid-phase with a very large inner surface. Because so much more allergen could be bound compared to the previously used paper discs, sensitivity was greatly improved.

But just as importantly, Pharmacia CAP System also provided a way to perform quantitative measurements of IgE with much greater precision and reproducibility. Suddenly, test results were comparable between laboratories – and over time, a universal method for measuring IgE was born.

For researchers, this meant better tools for statistical risk assessment and an improved understanding of the clinical relevance of IgE antibody levels.

For clinicians, it provided a reliable blood-based test that minimized the need to expose patients to allergens, as well as a richer theoretical background on which to base avoidance advice, treatment strategy and statistical risk.

### **Pharmacia CAP System®**

provided a way to perform quantitative measurements of IgE with much greater precision.



## 1990s

### Quality Club – Setting the standard in quality assurance

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With the introduction of the Pharmacia CAP System® in 1989, it became possible to perform quantitative measurements of IgE antibodies with great reproducibility. The superior testing performance of ImmunoCAP® Specific IgE, made it possible to compare test results between laboratories and over time. It was the birth of a standardized assay; a universal method today considered the gold standard for IgE antibody measurement.

To ensure equivalent, reliable and accurate test results globally, an external assessment program monitoring laboratory performance was established: Quality Club.

Since its forming in the early 1990's, Quality Club has been supporting laboratories all over the world through a system of monthly reports that permit laboratories to evaluate their testing procedures to maintain high accuracy and reliability.

Today, Quality Club is the world's largest allergy proficiency testing community, with a membership of over 900 laboratories in over 50 countries – that, together, are setting the standard in allergy diagnostics.



## 1995

### Premiere for automated allergy testing

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UniCAP® 100 integrated automated sample handling, measuring instrumentation and data evaluation software, enabling laboratories around the world to perform about 50 IgE tests in just one single run with the possibility of two runs during a working day (100 tests). Tests were run in small plastic capsules – ImmunoCAP® – that could easily be kept in carriers, each containing up to 16 tests of the same allergen.

UniCAP 100 greatly increased the testing efficiency of laboratories all over the world, earning Pharmacia a well-deserved reputation as a reliable and preferred supplier.

Over the years, UniCAP grew in both capacity and flexibility, supporting everyone from the smallest laboratories to the biggest allergy testing facilities.

In 2010, the systems changed their name to Phadia Laboratory Systems with Phadia® 2500 and Phadia® 5000 as the latest additions to the product family.

#### **UniCAP® 100**

was introduced, the world's first automated laboratory system for allergy testing.



## 1999

# The dawn of Component Resolved Diagnostics

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IgE tests for specific protein components in natural sources became available in clinical practice in 1999. In addition to pointing out the offending allergen source, it was now possible to also identify the actual protein component – or components – that give rise to the allergic symptoms.

Because they helped address central clinical and immunological questions, these new tools quickly gained in importance. In addition to measuring the amount of IgE present in a blood sample, it was just as important to understand the characteristics of the protein to which an individual was sensitized: more stable proteins could often be linked to a higher risk for severe reactions; the immune system could react similarly to proteins of different sources, thereby giving rise to cross-reactivity; and immunotherapy could be made more effective by knowing the exact protein a patient was sensitized to.

Component Resolved Diagnostics was improved by the discovery of recombinant allergens that could be produced with consistent quality and without genetic or biological variation. In 1995, the first components were made available for research use, starting with birch components Bet v 1 and Bet v 2 and Timothy grass pollen components Phl p 1, Phl p 2 and Phl p 5. And in 1999, Pharmacia launched a panel of allergen components for clinical use, coining the phrase 'Component Resolved Diagnostics' (CRD).

Over the years, the number of allergen components offered by Thermo Fisher Scientific (previously Pharmacia/Phadia), increased to over a hundred to form the broadest platform on the market.



**2005**

## ImmunoCAP® Rapid – the first IgE point-of-care test

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In 2005, the first point-of-care test for allergen-specific IgE was introduced: ImmunoCAP® Rapid. For the first time, physicians in primary care were able to evaluate patients with suspected allergic symptoms – directly in their own office – based on a single drop of blood. Tests were provided for different symptom profiles and age groups, to include 8-10 of the most common associated allergen sources.

ImmunoCAP Rapid made it possible for clinicians to quickly confirm or refute their suspicions – is it allergy – or not? – then discuss treatment and further actions with the patient. All at the same visit.

Currently, ImmunoCAP Rapid is available in parts of Europe and Japan.



**2009**

## Multiplex IgE array – a new member of the ImmunoCAP® family

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### **ImmunoCAP® ISAC**

offers simultaneous testing of IgE antibodies to multiple allergen components from a single drop of blood.

ImmunoCAP® ISAC premiered simultaneous testing for sensitization of over 100 different allergen components from more than 50 different sources from a single drop of blood.

Based on many years of cutting-edge research and experience in molecular allergology, this new-thinking test combined the broadest allergen component platform on the market with innovative biochip technology.

ImmunoCAP ISAC quickly became a popular testing strategy for complex patient cases where, because of polysensitization, symptoms may be unclear.

Now the test is gaining in popularity in clinical practice where it saves both time and costs, in for example cases of unexpected anaphylaxis or for reducing the need for long elimination diets, especially in polysensitized children with severe eczema. And all with one single test.





## 2010-2017

# Continuous improvements

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Recent years have seen the continuous improvements in all product areas.

ImmunoCAP® Allergen Components provides an ever increasing number of both recombinant and native allergen components, and is by far the widest, most complete, allergen spectrum for molecular allergy diagnostics on the market.

ImmunoCAP ISAC – now offering 112 allergen components in one run – is rapidly gaining use in everyday clinical practice.

Phadia Laboratory Systems provide a growing family of effective automation systems, ranging from smaller flexible instruments to larger systems with great capacity.

And software improvements are frequently released, for more effective and easier instrument operation with Phadia Prime, as well as for software-assisted interpretation of results with ImmunoCAP ISAC Xplain.

Finally yet importantly, increasing and stricter quality and regulatory *in vitro* diagnostics (IVD) requirements will hopefully lead to a better standardized and regulated IVD market for allergy testing.



## The Future

# Thermo Fisher Scientific, ImmunoDiagnostics

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For more than 40 years, we have been a global leader in allergy *in vitro* diagnostics. And we will continue to lead this market, driving positive change, until we have created a world where all allergic patients are diagnosed in time for appropriate treatment.

Our mission is to improve the management of allergic disorders by providing healthcare professionals with superior diagnostic tools and clinical expertise. To this end we are continuously enhancing and refining all of our product platforms, ceaselessly looking for new ways to support our customers; as your trusted partner today and in the future.

Together, we will continue to create history. IgE history.



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1800 ABACUS (AUS) 0800 222 170 (NZ) | [info@abacusdx.com](mailto:info@abacusdx.com) | [www.abacusdx.com](http://www.abacusdx.com)

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