

The continuing effect of the discovery of IgE by Kimishige Ishizaka



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Sadly, Kimi Ishizaka died on July 6, 2018. I would like to take the opportunity to consider his role in the discovery of IgE and the effect of that discovery. All of us owe an enormous debt to those who established the relevance of IgE and the importance of its receptor on basophils and mast cells. In my own case, I owe a special debt for the pleasure and extraordinary education derived from working with him at Hopkins between September 1971 and October 1974.

The initial evidence about the presence of specific allergenic factors in serum (Reagins) dates back to the seminal studies of Prausnitz and Küstner in the 1920s.¹ Kimi realized early on that the only way to identify reagins was to take advantage of the Prausnitz-Küstner (P-K) test, and he focused on purifying this activity in allergic sera. Initial studies published in 1964 suggested that P-K activity was present in the fraction of serum containing monomeric IgA.² However, Kimi was not convinced about IgA, and he settled down to investigate (1) whether purified IgA antibodies against blood group A had P-K activity, (2) whether IgA antibodies could be separated from P-K activity by size or electrophoretic activity, and (3) whether the “purified” P-K activity could be fully absorbed with anti-IgG, anti-IgM, and anti-IgA. Those studies succeeded in producing a rabbit antibody to the P-K activity.² The results led directly to proof that the reagins in serum that carried P-K activity were not IgG, IgA, IgM, or IgD, and in 1966, he named the new isotype gamma E.³

Although the scientific effect of the discovery came from the proof that IgE was a separate isotype, the clinical effect came largely from the ability to measure IgE antibody levels. In this the Swedish group of Hans Bennich and Gunnar Johansson played an important role.⁴ Gunnar had identified a myeloma protein, initially referred to as ND, which was not IgG, IgM, IgA, or IgD. The plasma from that patient contained approximately 20 mg of ND protein, and therefore it was relatively easy to purify. However, like all myeloma proteins, its specificity was not known, and progress was slow. In 1966, Bennich and Johansson contacted Dennis Stanworth in the United Kingdom for help in defining ND.

There was an elegant connection between the work with the myeloma ND and earlier work on the structure of immunoglobulin molecules. Rodney Porter started working in London in the 1950s, and at that time, John Humphrey provided hyperimmune

rabbit serum and advised on the use of papain to digest the IgG molecule. It was this digestion that led to the terms Fab and Fc.⁵ A few years later, Stanworth was telling John Humphrey about the problems with establishing what type of immunoglobulin ND protein was, and Humphrey suggested trying to block P-K activity with ND in the skin. This they published in 1967, and in the next year, they published that it was the Fc fragment of ND that could block P-K activity.⁴ Given that Ishizaka had already collaborated with the Swedish group to show that the antibody against ND bound to the same protein as his antibody against P-K activity (ie, gamma E), the information that it was the Fc fragment of ND that blocked P-K activity effectively sealed the question. An unbiased view of the history (ie, by the current author) would say that the successful convergence of the work of the 2 groups accelerated acceptance of the new isotype and also led to rapid progress on both sides of the Atlantic (Fig 1). The Swedish group had already developed antibodies against the Fc fragment of ND, and together with Dr Wide, they published the first article about the RAST in 1967.⁴ The combined work of the 2 groups paved the way for registration of the new isotype at the World Health Organization in 1968, which involved Ishizaka, Bennich, Johansson, and Stanworth.^{2,4}

CONTRIBUTIONS OF IgE MEASUREMENT TO UNDERSTANDING ALLERGIC DISEASE

The effect of the assays for IgE antibodies on the study of allergic disease is difficult to exaggerate. This is particularly true for the investigation of new or apparently new syndromes and also for the investigation of cohort studies. Sera can be stored frozen for many years so that the assays can be done together on a large cohort. In addition, it is possible to go back and carry out new assays on sera from a cohort that was enrolled several years earlier. The IgE assays can be fully quantitative over the range 0.1 to greater than 100 IU/mL. The importance of this quantitation is that it makes it possible to consider specific IgE as a percentage of total IgE and also the relationship between IgE antibodies and antibodies of other isotypes, particularly IgG₁ and IgG₄.

IgE antibody titers and the relevance of specific IgE to asthma

The importance of dust mites to asthma became clear in Europe, Japan, Australia, and New Zealand over the same few years that IgE was established (ie, 1966-1972). A wide range of data showed not only that some allergens are more strongly associated with asthma than others but that the titers of IgE antibodies to perennial allergens are very strongly associated with asthma. More recently, Soto-Quiros et al⁶ demonstrated not only that dust mite was the dominant allergen related to asthma, but also that high-titer IgE to dust mite was a very strong predictor of the relationship between rhinovirus infection and asthma.

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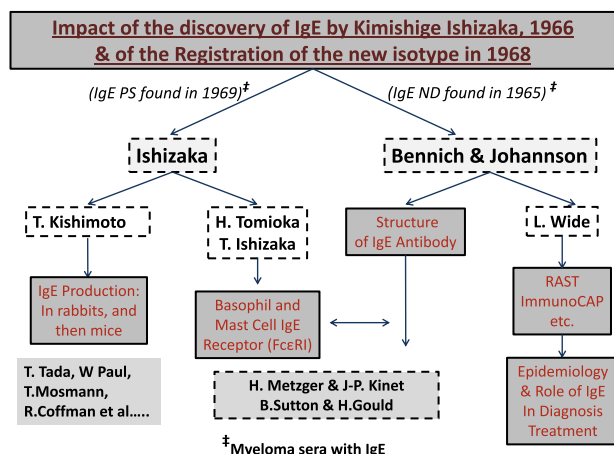


FIG 1. The effect of Dr Ishizaka's discovery and naming of IgE in 1966 led in 1967 to confirmation that the ND myeloma protein was IgE. Subsequently, work by the Ishizaka group established that the same receptor for IgE was present on mast cells and basophils and also pointed to the beginnings of the cellular immunology of IgE production. By contrast, the work of Bennich and Johansson led to widespread acceptance of IgE and IgE antibody assays in the investigation of allergic disease.

IgE antibodies to component proteins in an allergen extract

In his early work on P-K activity, Ishizaka was using purified Antigen E (now Amb a 1), a gift from Dr T. P. King at the Rockefeller Institute in New York. He also knew that purified allergens could be radiolabeled more effectively than crude allergen extracts.^{2,3} Since the RAST was introduced, many changes have been made to the solid phase and to the labeling of anti-IgE, but the principle remains the same. However, it remains true that using allergen extract can easily underestimate the importance of specific proteins or glycoproteins. The main examples of the importance of components have come from food allergy and include the following:

1. It is not uncommon that children raised in an area with birch trees have a strongly positive IgE assay result for peanut, which is entirely explained by IgE to Ara h 8 and is not related to anaphylaxis.
2. Cat-pork syndrome reflects cross-reactivity between cat serum albumin (Fel d 2) and pork serum albumin (Sus s 1). Fel d 2 is a minor component of cat extract, and consequently, the cat assay can both underestimate the quantity of specific IgE to Fel d 2 and wrongly suggest the relevance of cat allergen as an inhalant.⁷
3. A further example of the significance of a minor component comes from the importance of IgE to the wheat component Tri a 19 in patients with wheat-dependent exercise-induced anaphylaxis.⁸
4. The oligosaccharide galactose- α -1,3-galactose has emerged as a regional cause of 2 novel forms of anaphylaxis. The first of these was the reaction to cetuximab in patients with cancer, and the second was delayed anaphylaxis to red meat. Without the ability to design IgE assays for components, studies on this antigen, which is a hapten present on both glycoproteins and glycolipids, would have been very difficult.⁹

T cells in relation to IgE production and the increase in type 2 immunity

Kimi started studies on IgE production with Kishimoto in the early 1970s (ie, before CD markers or cytokines).² Tomio Tada, who had also worked with Dr Ishizaka, began thinking about different types of helper cells as early as 1978; indeed, it was he who coined the terms T_H1 and T_H2 .² By 1980, Bill Paul had started work on IL-4, which was ultimately recognized as the primary switch factor for IgE production. The functional distinction of T_H1 and T_H2 came with Mosmann and Coffman in 1986 and related primarily to T-cell function. However, in many ways it was the discovery of IgE that drove the science of defining what is now type 2 immunity.¹⁰

CONCLUSION

Those of us who knew Dr Ishizaka well will miss him, and as with other significant figures in our lives, we will regret the questions we did not ask and the answers that no one else can provide. His work has had an enormous effect on our field and has played a central role in raising the scientific reputation of all aspects of our specialty. Starting with the definition of IgE as a separate isotype of immunoglobulin in 1966, he went on to collaborate with the Swedish team so that the assays for IgE and IgE antibodies became recognized worldwide. In addition, his own group played a major role in studies on Fc ϵ RI, establishing its presence on both mast cells and basophils.² In addition, he and Terri established that the IgE receptors on basophils needed to be cross-linked to release histamine.

Over the last 50 years, the field of immediate hypersensitivity, previously known as Gell and Coombs type I but now more often referred to as type 2, has expanded in multiple ways. IgE has played a central role that has focused the evidence about isotype switching, the relevance of T cells and T cell-derived cytokines, the purification of allergens, and the relevance of these antibodies to many different allergic syndromes.

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