Allergic cross-reactivity made visible:
The solution structure of the major cherry allergen Pru av 1

Philipp Neudecker1, Kristian Schweimer1, Jörg Nerkamp1, Stephan Scheurer2, Stefan Vieths2, Heinrich Sticht1 and Paul Rösch1
1 Lehrstuhl für Struktur und Chemie der Biopolymer, Universität Bayreuth, Bayreuth, Germany
2 Abteilung Allergologie, Paul–Ehrlich–Institut, Langen, Germany
Phone: +49–921–553809; Fax: +49–921–553544; E-mail: philipp.neudecker@uni–bayreuth.de

Birch pollen is often accompanied by hypereosinophilia as a consequence of the allergens’ cross-reactivity in the order as well as food allergens like Api g 1.0101 (Api g 1.0101 from apple (Malus domestica), Pru av 1 from cherry (Prunus avium), Pyr c 1 from pear (Pyrus communis), and Cor a 1.0401 from hazelnut (Corylus avellana)). (Fig. 1).

Introduction
Up to 70 % of birch pollen allergic patients who suffer from clinical syndromes like rhinitis, asthma, and dermatitis also show hypersensitivity to fresh fruit or vegetables. The allergic reactions after ingestion of foodstuff are predominantly characterized by, for example itching and swelling of lips, tongue, and throat, but in rare cases even severe anaphylactic reactions are possible. The symptoms of these type IV allergies are caused by an immune response which is triggered when two receptor-bound immunoglobulin E (IgE) antibodies on the surface of a mast cell or basophil are cross-linked by the same allergen. Pollen–associated food allergies are a consequence of the cross-reaction of pollens–allergen specific IgE antibodies with highly homologous proteins contained in foodstuff. The 17.4 kDa major birch (Betula verrucosa) pollen allergen Bet v 1 is responsible for IgE binding in more than 95 % of birch pollen allergic patients. A series of allergens with high sequence identity to Bet v 1 have been reported, pollen allergens from other trees belonging to the Fagales order as well as food allergens like Api g 1.0101 (Api g 1.0101 from apple (Malus domestica)), Pru av 1 from cherry (Prunus avium), Pyr c 1 from pear (Pyrus communis), and Cor a 1.0401 from hazelnut (Corylus avellana). (Fig. 1).

Methods and Results
In contrast to Bet v 1, the glycine–rich P–loop around Glu45 was recently identified as the binding epitope of a monoclonal murine IgG antibody with high affinity to inhibit binding of serum IgE from allergic patients to Bet v 1. Introduction of four point mutations including E45S indeed reduced the IgE binding capacity by severalfold. In the crystal structure of the complex of Bet v 1 with the IgG Fab fragment the negatively charged side-chain of Glu45 is located in a binding pocket of the antibody with a positively charged amino acid residue from a domain two hydrogen bonds. In addition to E45S, which is found to be solvent–exposed in all 22 accepted structures of Pru av 1 (Fig. 2), 14 of the remaining 15 residues forming the interface between Bet v 1 and the IgG Fab fragment are conserved or substituted conservatively in Pru av 1 (Fig. 1), which strongly suggests this region to be a cross-reactive IgE binding epitope. This is supported by the significantly decreased binding of serum IgE to the Pru av 1 mutants G45P and A75S observed for some patients. It can also provide an explanation why IgE binding to Pru av 1 is only weakly inhibited by preincubation with Api g 1.0101 (Fig. 1), where the P–loop is shorter by a residue and the negatively charged Glu45 is substituted by a positively charged lysine (Fig. 1).

The physiological function of all these allergens is still unknown. They show high sequence similarity to pathogenesis–related proteins, but most of them seem to be expressed constitutively. The striking structural homology with the recently determined crystal structure of the START domain of human MLS64 (Fig. 7) in spite of low sequence identity (Fig. 1) suggests phytoestrogens as putative ligands for Bet v 1 and Pru av 1, which is supported by first NMR spectroscopic data (Fig. 8).

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References