

Focus on...Fel d 1

The domestic cat (*Felis domesticus*) is a common household pet and a significant source of indoor allergens. IgE mediated sensitization to allergens from *F. domesticus* affects approximately 10% of the western world. Symptoms range from

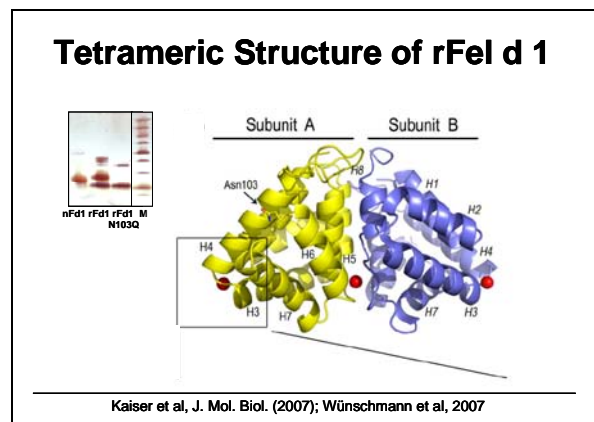
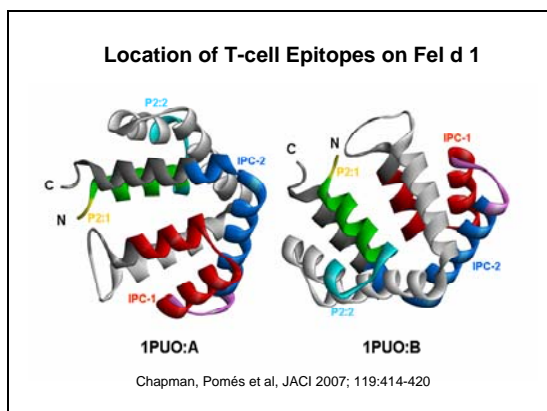


Fig.1* mild rhinitis and conjunctivitis to life-threatening asthmatic responses. Fel d 1 is the most potent allergen in cat dander^(1;2), eliciting IgE responses in 95% of patients with allergy to cat.^(1;3) The most important sources of the allergen are the sebaceous, salivary and perianal glands, while the skin and the fur represent the principal reservoirs.⁽⁴⁾ Fel d 1 is a thermostable 35kDa tetrameric glycoprotein formed by two non-covalently linked heterodimers (Fig.1).⁽⁵⁻⁷⁾ The heterodimers are composed of a 70 residue light chain and a glycosylated heavy chain of 92 amino acids, referred to as chain 1 and chain 2, respectively. Within each heterodimer, chains are linked through disulfide bridges.⁽⁸⁾ It has been reported that natural epithelia extracts and house dust extracts can contain complete tetramers (35kDa), separate heterodimers (17kDa), and separate chains 1 and 2.⁽⁹⁾ Expression of recombinant Fel d 1 in *Pichia pastoris* results in hyperglycosylated and non-glycosylated heterodimers and tetramers, while dis-

*Fig.1: Structure of the Fel d 1 tetramer with N-glycosylation site at Asn103.⁽¹¹⁾ Inset: Silver-stained SDS Page of natural (nFd1), recombinant (rFd1) and de-glycosylated recombinant Fel d 1 (rFd1-N103Q).⁽¹⁰⁾

ruption of the N-glycosylation motif (N103) in rFel d 1 removes the hyperglycosylated forms (Fig.1, inset). This improved rFel d 1 behaves as the structural and antigenic equivalent of natural Fel d 1.⁽¹⁰⁾ The recent resolution



of the crystal structure of Fel d 1 suggests Fig.2*

that Ca^{2+} plays a key role in the formation of the tetramer. While the physiological role of Fel d 1 remains unclear, the structure is strikingly similar to uteroglobin, a steroid-inducible molecule with potent anti-inflammatory and immunomodulatory properties.⁽¹¹⁾ A unique feature of Fel d 1 is its ability to induce a form of tolerance described as a modified $\text{T}_\text{H}2$ response.⁽¹²⁾ This immune response, characterized by high titer Fel d 1-specific serum IgG and IgG4 in the absence of IgE ($\text{IgG}^+\text{IgE}^{\text{neg}}$) is not associated with allergic symptoms or asthma. Fel d 1 T-cell epitopes have been identified on both chains (Fig.2) and IL-10-producing CD4^+ T cells were recognized as key elements of the modified $\text{T}_\text{H}2$ response.⁽¹³⁻¹⁵⁾ In a recent study of Hulse et al induction of this specific T-cell subset was approached by targeting Fel d 1 to the high-affinity IgG receptor ($\text{Fc}\gamma\text{RI}$) on antigen-presenting cells.⁽¹⁷⁾ $\text{Fc}\gamma\text{RI}$ -targeted Fel d 1 induced T-cell subsets characteristic of a protective T-cell response, including $\text{T}_\text{H}0$, regulatory $\text{T}_\text{H}1$ and regulatory $\text{T}_\text{H}2$, in subjects with allergy. This approach may be useful to improve T-cell based therapies for cat allergy.

*Fig.2: T cell epitopes in Chain 2 (white) (P2:1 in yellow , P2:2 in turquoise blue and overlapping residues in green) and in Chain 1 (grey) of Fel d 1 (IPC-1 in red and IPC-2 in blue).^(13,14)

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