Focus on…Fel d 1

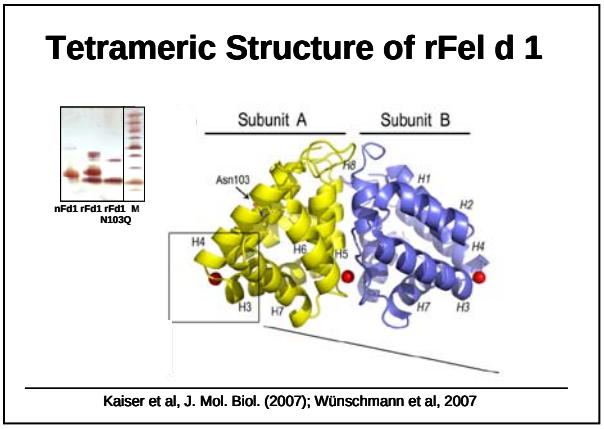

Fig.1*

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 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 prinicipal 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 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 uteroglobulin, 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 T_H2 response.[12] This immune response, characterized by high titer Fel d 1-specific serum IgG and IgG4 in the absence of IgE (IgG^+IgE^{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 T_H2 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 (FcγRI) on antigen-presenting cells.[17] FcγRI-targeted Fel d 1 induced T-cell subsets characteristic of a protective T-cell reponse, including T_H0, regulatory T_H1 and regulatory T_H2, in subjects with allergy. This approach may be useful to improve T-cell based therapies for cat allergy.

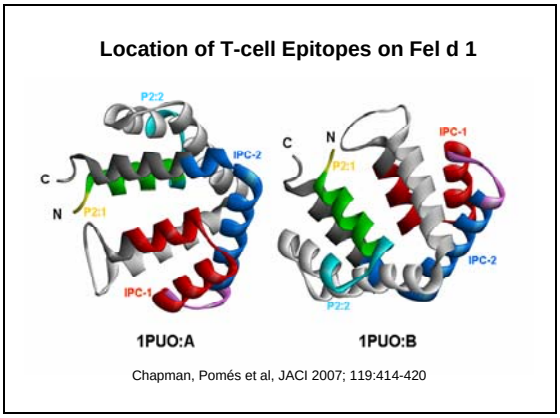

Fig.2*

*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]

References

(1) van Ree R, van Leeuwen WA, Bulder I, Bond J, Aalberse RC. Purified natural and recombinant Fel d 1 and cat albumin in in vitro diagnostics for cat allergy. J Allergy Clin Immunol 1999; 104(6):1223-30.

(2) Ichikawa K, Vailes LD, Pomés A, Chapman MD. Molecular cloning, expression and modelling of cat allergen, cystatin (Fel d 3), a cysteine protease inhibitor. Clin Exp Allergy 2001; 31(8):1279-86.

(3) Ohman JL, Jr., Lowell FC, Bloch KJ. Allergens of mammalian origin. III. Properties of a major feline allergen. J Immunol 1974; 113(6):1668-77.

(4) Mata P, Charpin D, Charpin C, Lucciani P, Vervloet D. Fel d I allergen: skin and or saliva? Ann Allergy 1992; 69(4):321-2.

(5) Morgenstern JP, Griffith IJ, Brauer AW, Rogers BL, Bond JF, Chapman MD et al. Amino acid sequence of Fel dI, the major allergen of the domestic cat: protein sequence analysis and cDNA cloning. Proc Natl Acad Sci U S A 1991; 88(21):9690-4.

(6) Duffort OA, Carreira J, Nitti G, Polo F, Lombardero M. Studies on the biochemical structure of the major cat allergen Felis domesticus I. Mol Immunol 1991; 28(4-5):301-9.

(7) Cain G, Elderfield AJ, Green R, Smillie FI, Chapman MD, Custovic A et al. The effect of dry heat on mite, cat, and dog allergens. Allergy 1998; 53(12):1213-5.

(8) Kristensen AK, Schou C, Roepstorff P. Determination of isoforms, N-linked glycan structure and disulfide bond linkages of the major cat allergen Fel d1 by a mass spectrometric approach. Biol Chem 1997; 378(8):899-908.

(9) Van Milligen FJ, Van SP, Aalberse RC. Structure of the major cat allergen Fel d I in different allergen sources: an immunoblotting analysis with monoclonal antibodies against denatured Fel d I and human IgE. Int Arch Allergy Immunol 1992; 99(1):63-73.

(10) Wünschmann S, Vailes LD, King EM, Aalberse RC, Chapman MD. Expression of a Deglycosylated Recombinant Fel d 1 in *Pichia pastoris*. J Allergy Clin Immunol 2008 2008; 121(2):S214.

(11) Kaiser L, Velickovic TC, Badia-Martinez D, Adedoyin J, Thunberg S, Hallen D et al. Structural Characterization of the Tetrameric form of the Major Cat Allergen Fel d 1. J Mol Biol 2007; 370(4):714-27.

(12) Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 2001; 357(9258):752-6.

(13) Reefer AJ, Carneiro RM, Custis NJ, Platts-Mills TA, Sung SS, Hammer J et al. A role for IL-10-mediated HLA-DR7-restricted T cell-dependent events in development of the modified Th2 response to cat allergen. J Immunol 2004; 172(5):2763-72.

(14) Norman PS, Ohman JL, Jr., Long AA, Creticos PS, Gefter MA, Shaked Z et al. Treatment of cat allergy with T-cell reactive peptides. Am J Respir Crit Care Med 1996; 154(6 Pt 1):1623-8.

(15) Chapman MD, Pomés A, Breiteneder H, Ferreira F. Nomenclature and structural biology of allergens. J Allergy Clin Immunol 2007; 119(2):414-20.

(16) Vailes LD, Sun AW, Ichikawa K, Wu Z, Sulahian TH, Chapman MD et al. High-level expression of immunoreactive recombinant cat allergen (Fel d 1): Targeting to antigen-presenting cells. J Allergy Clin Immunol 2002; 110(5):757-62.

(17) Hulse KE, Reefer AJ, Engelhard VH, Satinover SM, Patrie JT, Chapman MD et al. Targeting Fel d 1 to FcgammaRI induces a novel variation of the T(H)2 response in subjects with cat allergy. J Allergy Clin Immunol 2007.