MS10-P1 **Crystal structure of the human IgG4 C_H3 dimer reveals the role of Arg409 in Fab-arm exchange.** Anna M Davies,[ab] Theo Rispens,[cd] Tamara H. den Bleker,[cd] James M. McDonnell,[ab] Hannah J. Gould,[ab] Rob C. Aalberse,[cd] Brian J. Sutton[ab]. *[a]King's College London, Randall Division of Cell and Molecular Biophysics, United Kingdom, [b]Medical Research Council & Asthma UK Centre in Allergic Mechanisms of Asthma, United Kingdom, [c]Sanquin Research, The Netherlands, [d]University of Amsterdam, Academic Medical Centre Landsteiner Laboratory, The Netherlands.*
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The four sub-classes of human IgG antibodies all comprise two heavy and light chains, connected by inter-chain disulphide bonds. Unique to IgG4 is the ability to exist as a half molecule, composed of just one heavy and light chain. In a process known as Fab-arm exchange (FAE), IgG4 half molecules are able to combine to form bi-specific antibodies which are functionally monovalent [1]. The ability to undergo FAE depends on the IgG4 core hinge sequence, and the strength of the CH3 dimer interaction, which is in turn determined by the identity of the residue at position 409 located at the dimer interface. In IgG4 residue 409 is arginine, whereas in IgG1, which does not undergoe FAE, the equivalent residue is lysine [2,3]. In the absence of an inter-chain disulphide bond, CH3 dimer dissociation is a rate-limiting step in the FAE mechanism [4]. Knowledge of the FAE mechanism is key to understanding IgG4's biological function, and will also aid in the design of therapeutic monoclonal antibodies. Until recently, only a low resolution crystal structure was available for IgG4 Fc [5]. We now report the crystal structure of the IgG4 CH3 domain dimer at 1.8Å. When compared with Lys409 in high resolution IgG1 crystal structures, Arg409 in IgG4 is found to disrupt a water-mediated hydrogen bond network. A groove at the edge of the CH3 interface also becomes more "open", as the more bulky Arg409 causes a widening of the distance between Ser400 in one domain and Asn390 from the other. The weakening effect exerted by Arg409 on the CH3 interface is doubled due to the two-fold symmetry of the dimer. A structural explanation for the role played by Arg409 in the FAE mechanism is thus provided.

[1] Aalberse, R. C. & Schuurman, J. (2002). *Immunology* 105, 9-19.
[2] van der Neut Kolfschoten, M., Schuurman, J., Losen, M., Bleeker, W. K., Martínez-Martínez, P., Vermeulen, E., den Bleker, T. H., Wiegman, L., Vink, T., Aarden, L. A., De Baets, M. H., van de Winkel, J. G. J., Aalberse, R. C. & Parren, P. W. H. I. (2007) *Science* 317, 1554-1557.
[3] Labrijn, A. F., Rispens, T., Meesters, J., Rose, R. J., den Bleker, T. H., Loverix, S., van den Bremer, E. T. J., Neijssen, J., Vink, T., Lasters, I., Aalberse, R. C., Heck, A. J. R., van de Winkel, J. G. J., Schuurman, J. & Parren, P. W. H. I. (2011). *J. Immunol.* 187, 3238-3246.
[4] Rispens, T., Ooijevaar-de Heer, P., Bende, O. & Aalberse, R. C. (2011). *J. Am. Chem. Soc.* 133, 10302-10311.
[5] Corper, A. L., Sohi, M. K., Bonagura, V. R., Steinitz, M., Jefferis, R., Feinstein, A., Beale, D., Taussig, M. J., Sutton, B. J. (1997) *Nat. Struct. Biol.* 4, 374-381.

Keywords: antibodies; structural biology; X-ray crystallography of immunoglobulins

MS10-P2 **Crystal Structure of Filamentous Aggregates of Human DJ-1** Min-Kyu Kim[a], Young Jun An[a], Chang-Sook Jeong[a], Sangmin Lee[a], Sun-Shin Cha[a,b] *[a]Marine and Extreme Genome Research Center, Korea Ocean Research & Development Institute, Ansan 426-744, Republic of Korea. [b]Department of Marine Biotechnology, University of Science and Technology, Daejeon 305-333, Republic of Korea.*
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Mutations in the *DJ-1* gene have been implicated in the autosomal recessive early onset parkinsonism. DJ-1 is a soluble dimeric protein with critical roles in response to oxidative stress and in neuronal maintenance. However, several lines of evidence suggest the existence of a nonfunctional aggregated form of DJ-1 in the brain of patients with some neurodegenerative diseases. Here, we show that inorganic phosphate, an important anion that exhibits elevated levels in patients with Parkinson disease, transforms DJ-1 into filamentous aggregates. According to the 2.4-Å crystal structure, DJ-1 dimers are linearly stacked through P_i-mediated interactions to form protofilaments, which are then bundled into a filamentous assembly.

Keywords: Parkinson disease, Filamentous DJ-1, inorganic phosphate