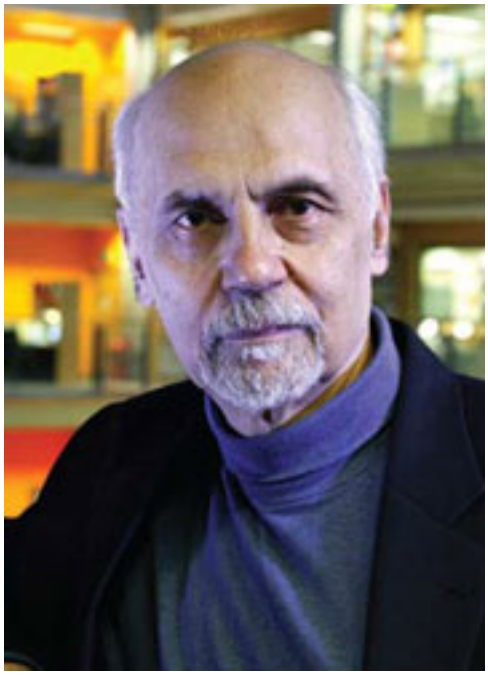
Prof. Fotis C. Kafatos
Professor of Immunogenetics, Imperial College, London; Founding President of the European Research Council



Most important awards, prizes and academies

Awards: G.J. Mendel Honorary Gold Medal for Merit in the Biological Sciences, Academy of Sciences of the Czech Republic (1995); Honorary Professor, University of Heidelberg, Germany (2000); Honorary Medal for Distinction in Biology, Academy of Athens (2000); Taxiarchis of Phoenix Medal, awarded by the President of the Hellenic Republic (2003); Medal of Honour, City of Heraklion, Crete (2004); Bundesverdienstkreuz 1. Klasse, awarded by the President of the Federal Republic of Germany (2004). *Academies*: European Molecular Biology Organisation (1977); American Academy of Arts and Sciences (1980); National Academy of Sciences, USA (1982); Academia Europaea (1991); Churchill College, University of Cambridge (1993); Académie des sciences, France (2002); Pontifical Academy of Sciences (2003); Royal Society, London (2003).

Summary of scientific research

My group is studying the interactions between Plasmodium parasites and the mosquito, *Anopheles gambiae*. Molecular genetic studies on this socially important organism, a vector responsible for more than two million deaths from malaria each year in Africa, capitalise on

recent developments in genome analysis, transgenesis and the comparative study of innate immunity. We aim to trace the immune responses of the mosquito to the parasite, through highly collaborative research, involving close interactions with laboratories in Europe, the USA and Africa (see references). Genomic characterisation of *Anopheles* is an important aspect of our studies. Our pilot EST project identified for the first time a wealth of new *A. gambiae* genes. We have constructed detailed genetic and physical maps of *A. gambiae*, localizing genes that are involved in refractoriness to the parasite. The genetic markers are also facilitating the analysis of mosquito population biology and refractoriness in Africa. Sequencing of a 528 kb chromosomes DNA region encompassing one of these genes has permitted a first genomic comparison between *A. gambiae* and *D. melanogaster*. Furthermore, we actively promoted, participated in and helped lead an international collaboration for the whole genome sequencing of *A. gambiae*, which was achieved in 2002 and was recognised as a landmark in malaria research. Previously, we generated hemocyte-like cell lines which help in analysing mosquito immunity by DNA microarrays and other techniques. Insects and vertebrates share ancient, potent defence mechanisms of innate immunity (distinct from the antibody and T-cell receptor-based adaptive immunity of vertebrates). Our major aim is to dissect these mechanisms in the mosquito, and focus on those pertaining to parasite intrusion. To this effect, we have constructed *A. gambiae* cDNA microarrays and used them to analyse global expression profiles of cells and whole mosquitoes in response to microbial challenge, sterile or septic injury and malaria infection. These studies identified novel immune elicitor-specific gene clusters potentially implicated in biochemical and physiological responses to infections. Responses to the parasite extensively overlap with responses to bacterial challenge but not to injury. Furthermore, parasites co-cultured with mosquito cell lines elicit robust responses suggesting specific recognition of the parasite by the mosquito immune surveillance system. Comparison of response profiles of malaria susceptible and refractory mosquitoes has indicated significant differences in immune competence and redox state. Some of the differentially expressed genes are likely to be implicated in the mechanism of parasite killing in the refractory mosquitoes. Among the molecules transcriptionally up-regulated by bacterial and parasite infections, we have identified a new family of thioester-containing proteins (aTEPs), resembling the complement factors that until recently were considered a hallmark of vertebrates. Using dsRNA knockdown in cell lines, we demonstrated that TEPI is required for promotion of early phagocytosis, indicating conservation of an ancient complement-like function. We are now extending our analysis to other members of the family. Cell biological studies use advanced light microscopy techniques in conjunction with specific antibodies. The aTEP system is of particular interest, as Plasmodium needs to evade two complement systems - in the mammalian host and in the insect vector. We have recently shown that TEP1 is responsible for killing Plasmodiumin a refractory strain of *A. gambiae*. Transformation techniques provide a crucial tool for genetic and genomic studies. We have participated in developing two genetic transformation methods based on the Minos transposable element in the *A. gambiae* cell lines and in the germ line of *A. stephensi* (an important urban vector of malaria in the Indian subcontinent). Refinements underway include development of inducible systems for conditional gene expression and vectors for in vivo RNAi knock-down of genes. With these techniques we can analyse in vivo functions of

candidate genes (selected by genetics, cell biology, biochemistry, microarray profiling and bioinformatics) that may be involved in vital physiological pathways of the mosquito, or in mosquito/parasite interactions. Ultimate benefits may be the identification of targets for new environmentally friendly insecticides or targets to block parasite transmission. Future research will continue to address the genetic, genomic, molecular, and cellular mechanisms that permit the malaria parasite to develop within the mosquito.

Main publications

Articles: Zheng, L., Collins, F.H., Kumar, V. and Kafatos, F.C., A detailed genetic map for the X chromosome of the malaria vector, *Anopheles gambiae*, *Science*, 261, pp. 605-608 (1993); Zwiebel, L.J., Saccone, A.Z., Besansky, N.J., Favia, G., Collins, F.H., Louis, C. and Kafatos, F.C., The White Gene of *Ceratitis Capitata*: A Phenotypic Marker for Germline Transformation, *Science*, 270, pp. 2005-2008 (1995); Hoffmann, J.A., Kafatos, F.C., *et al.*, Phylogenetic Perspectives in Innate Immunity, *Science*, 284, pp. 1313-1318 (1999); Catteruccia, F., Nolan, T., Loukeris, T.G., Blass, C., Savakis, C., Kafatos, F.C. and Crisanti, A., Stable germline transformation of the malaria mosquito *Anopheles stephensi*,*Nature*, 405, pp. 959-962 (2000); Han, Y.S., Thompson, J., Kafatos, F.C. and Barillas-Mury, C., Molecular interactions between *Anopheles stephensi* midgut cells and *Plasmodium berghei*: The Time Bomb Theory of ookinete invasion of mosquitoes, EMBO J., 19 (22), pp. 6030-6040 (2000); Levashina, E., Moita, L., Blandin, S., Vriend, G., Lagueux, M. and Kafatos, F.C., Conserved Role of a Complement-like Protein in Phagocytosis Revealed by dsRNA Knockout in Cultured Cells of the Mosquito, *Anopheles gambiae*, *Cell*, 104, pp. 709-718 (2001); Osta, M.A., Christophides, G.K. and Kafatos, F.C., Effects of Mosquito Genes on Plasmodium Development, *Science*, 303, pp. 2030-2032 (2004); Blandin, S., Shiao, S.-H., Moita, L.F., Waters, A.P., Kafatos, F.C. and Levashina, E.A., Complement-like protein TEP1 is a determinant of vectorial capacity in the malaria vector *Anopheles gambiae*, *Cell*, 116, pp. 661-670 (2004); Kafatos, F.C., Eisner, T., Unification in the century of biology,*Science* 2004 Feb 27; 303(5662) 1257; Abraham, E.G., Pinto, S.B., Ghosh, A., Vanlandingham, D.L., Budd, A., Higgs, S., Kafatos, F.C., *et al.*, An immune-responsive serpin, SRPN6, mediates mosquito defense against malaria parasites, *Proc. Natl. Acad. Sci. USA* 2005 Nov 8; 102(45) 16327-32; Volz, J., Osta, M.A., Kafatos, F.C., and Muller, H.M., The roles of two clip domain serine proteases in innate immune responses of the malaria vector Anopheles gambiae, *J. Biol. Chem*. 2005 Dec 2; 280(48) 40161-8; Michel, K., Budd, A., Pinto, S., Gibson, T.J., and Kafatos, F.C., *Anopheles gambiae* SRPN2 facilitates midgut invasion by the malaria parasite *Plasmodium berghei*, *EMBO Rep*. 2005 Sep; 6(9) 891-7; Meister, S., Kanzok, S.M., Zheng, X.L., Luna, C., Li, T.R., Hoa, N.T., Clayton, J.R., White, K.P., Kafatos, F.C., *et al.*, Immune signaling pathways regulating bacterial and malaria parasite infection of the mosquito *Anopheles gambiae*, *Proc. Natl. Acad. Sci. USA*2005 Aug 9; 102(32) 11420-5; Vlachou, D. and Kafatos, F.C., The complex interplay between mosquito positive and negative regulators of Plasmodium development, *Curr. Opin. Microbiol.* 2005 Aug; 8(4) 415-21; Belyakin, S.N., Christophides, G.K., Alekseyenko, A.A., Kriventseva, E.V., Belyaeva, E.S., Nanayev, R.A., Makunin, I.V., Kafatos, F.C., and Zhimulev, I.F.,

Genomic analysis of Drosophila chromosome underreplication reveals a link between replication control and transcriptional territories, *Proc. Natl. Acad. Sci. USA* 2005 Jun 7; 102(23) 8269-74; Kriventseva, E.V., Koutsos, A.C., Blass, C., Kafatos, F.C., et al, AnoEST: toward *A. gambiae* functional genomics, *Genome Res.* 2005 Jun; 15(6) 893-9; Michel, K. and Kafatos, F.C., Mosquito immunity against Plasmodium, *Insect Biochem. Mol. Biol.* 2005 Jul; 35(7) 677-89; Danielli, A., Barillas-Mury, C., Kumar, S., Kafatos, F.C., and Loukeris T.G., Overexpression and altered nucleocytoplasmic distribution of *Anopheles*ovalbumin-like SRPN10 serpins in Plasmodium-infected midgut cells, *Cell Microbiol.* 2005 Feb; 7(2) 181-90; Hall, N., Karras, M., Raine, J.D., Carlton, J.M., Kooij, T.W., Berriman, M., Florens, L., Janssen, C.S., Pain, A., Christophides, G.K., James, K., Rutherford, K., Harris, B., Harris, D., Churcher, C., Quail, M.A., Ormond, D., Doggett, J., Trueman, H.E., Mendoza, J., Bidwell, S.L., Rajandream, M.A., Carucci, D.J., Yates, J.R. 3rd, Kafatos, F.C., *et al.*, A comprehensive survey of the Plasmodium life cycle by genomic, transcriptomic, and proteomic analyses, *Science* 2005 Jan 7; 307(5706) 82-6; Volz, J., Muller, H.M., Zdanowicz, A., Kafatos, F.C., and Osta, M.A., A genetic module regulates the melanization response of *Anopheles* to Plasmodium, *Cell Microbiol*. 2006 Sep; 8(9) 1392-405; Vlachou, D., Schlegelmilch, T., Runn, E., Mendes, A., and Kafatos, F.C., The developmental migration of Plasmodium in mosquitoes, *Curr. Opin. Genet. Dev.* 2006 Aug; 16(4) 384-91; Lycett, G.J., McLaughlin, L.A., Ranson, H., Hemingway, J., Kafatos, F.C., *et al.*, *Anopheles gambiae* P450 reductase is highly expressed in oenocytes and in vivo knockdown increases permethrin susceptibility, *Insect Mol. Biol.* 2006 Jun; 15(3) 321-7; Moita, L.F., Vriend, G., Mahairaki, V., Louis, C., and Kafatos, F.C., Integrins of *Anopheles gambiae* and a putative role of a new beta integrin, BINT2, in phagocytosis of *E. coli*, *Insect Biochem. Mol. Biol.* 2006 Apr; 36(4) 282-90.