Prof. Thierry Boon-Falleur
Professor

Most important awards, prizes and academies

Awards: Prix Rik et Nel Wouters pour la recherche sur le cancer (1986); Prix De Vooght d'Immunologie (1986); Cancer Research Institute, Award for Research in Immunology (1987); Dr Joseph Steiner Cancer prize (1990); Prix Francqui (1990); Prix Louis Jeantet (1994); Rabbi Shai Shacknai Memorial Prize in Immunology and Cancer Research (1994); Prix Sandoz d'Immunologie (1995); Prix Léopold Griffuel (1999). *Academies*: Belgian Immunological Society; Société Belge de Biologie Cellulaire; Membre Titulaire, Académie Royale de Médecine de Belgique (1994); Associate Member, Académie Royale des Sciences, des Lettres et des Beaux-Arts de Belgique (1996). Scientific Committees: Fonds National de la Recherche Scientifique; Caisse Générale d'Epargne et de Retraite; Committee of Cancer Experts of the European Community (1985-1993); Scientific Council of the Institut Curie, Paris; Fédération belge contre le Cancer. *Editorial Boards*: *The European Journal of Immunology*; *Immunity*; *Cancer Cell*; *International Journal of Cancer*.

Summary of scientific research

Cancer immunotherapy is based on the notion that it is possible to artificially improve the immune response to tumor antigens to make it reach its full potential. Unlike responses directed against viral antigens, anti-tumoral responses may not have been perfected throughout evolution, because

escaping cancer probably conferred little or no selective advantage. Our interest in tumor immunology started with a fortuitous observation made with a mouse tumor which was strictly non-immunogenic. Mice from which this tumor was removed by surgery did not show any protection against a challenge with the same tumor cells. We observed that by treating the tumor cells in vitro with a mutagen we obtained tumor cell mutants that were rejected in the mice by a T lymphocyte mediated process. Remarkably the mice that had rejected these "tum-" mutants showed a degree of protection against a challenge with the original non-immunogenic tumor cells. This led to two conclusions. First, all mouse tumors bear tumor-specific antigens recognized by T cells even though many of them are non-immunogenic. Second, it is possible to create conditions that favor the T lymphocyte responses against the tumor antigens. On the basis of these findings we launched an effort to identify the antigens recognized on mouse tumors by T cells. A first step was to obtain in vitro cytolytic T lymphocytes (CTL) that specifically lysed the tumor cells. Antigenic transfectants could be detected on the basis of their ability to stimulate the proliferation of the relevant CTL clone and the genes coding for the antigens could be retrieved from these transfectants by using appropriate cosmid technology. Later the genes coding for these antigens were identified. Our results demonstrated that there are two major genetic processes that produce tumor-specific antigens. The first is the acquisition of mutations by the cancer cell, which generate peptides because of an amino-acid change. Mutated peptides either become capable of binding to major histocompatibility complex molecules or contain a new epitope. The second is the expression by the tumor of a gene which is not expressed in the normal cells of the adult. Around 1985 we began to examine whether the results obtained in mice could be extended to man. We focused our efforts on melanoma. Stimulation of T lymphocytes with autologous melanoma cells produced cytolytic T cells that appeared to lyse the tumor cells specifically. This led to the identification of the first gene coding for a human tumor-specific antigen recognized by T cells. This previously unknown gene was named MAGE and it was soon found to be expressed in many tumors and not in normal cells with the exception of male germline cells. Antigens encoded by cancer-germline genes ought to be very suitable as therapeutic vaccines for cancer-patients as they are strictly tumor-specific and present on a large proportion of tumors. Gene mutation was also found to be a major source of human tumor-specific antigens. Finally, we observed that CTL of melanoma patients can respond to antigens encoded by melanocytic differentiation genes, such as tyrosinase and Melan-A. Our first clinical trial involved the vaccination of metastatic melanoma patients with an antigenic peptide which is encoded by MAGE-3and presented by HLA-A1. Seven patients out of 26 showed evidence of tumor regression. No toxicity was observed. Similar results were observed after vaccination with the MAGE-3 protein or with an ALVAC recombinant virus coding for MAGE sequences. We have therefore developed highly sensitive approaches for the detection of CTL responses combined with an analysis of the T cell receptor diversity of the responding CTL. These approaches are beginning to show a correlation between CTL responses and tumor regressions. We will use these approaches to try to understand why only a minority of cancer patients respond to therapeutic vaccination.

Main publications

Van Pel, A., Boon, T., Protection against a non-immunogenic mouse leukemia by an immunogenic variant obtained by mutagenesis, *Proc. Natl. Acad. Sci. USA*, 79, pp. 4718-4722 (1982); De Plaen, E., Lurquin, C., Van Pel, A., Mariamé, B., Szikora, J-P., Wölfel, T., Sibille, C., Chomez, P. and Boon, T., Immunogenic (tum-) variants of mouse tumor P815: Cloning of the gene of tum- antigen P91A and identification of the tum- mutation, *Proc. Natl. Acad. Sci. USA*, 85, pp. 2274-2278 (1988); Lurquin, C., Van Pel, A., Mariamé, B., De Plaen, E., Szikora, J-P., Janssens, C., Reddehase, M.J., Lejeune, J. and Boon, T., Structure of the gene coding for tum- transplantation antigen P91A. A peptide encoded by the mutated exon is recognized with Ld by cytolytic T cells, *Cell*, 58, pp. 293-303 (1989); van der Bruggen, P., Traversari, C., Chomez, P., Lurquin, C., De Plaen, E., Van den Eynde, B., Knuth, A. and Boon, T., A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma, *Science*, 254, pp. 1643-1647 (1991); Traversari, C., van der Bruggen, P., Luescher, I., Lurquin, C., Chomez, P., Van Pel, A., De Plaen, E., Amar-Costesec, A. and Boon, T., A nonapeptide encoded by human gene MAGE-1 is recognized on HLA-A1 by cytolytic T lymphocytes directed against tumor antigen MZ2-E, *Journal of Experimental Medicine*, 176, pp. 1453-1457 (1992); Gaugler, B., Van den Eynde, B., van der Bruggen, P., Romero, P., Gaforio, J.J., De Plaen, E., Lethé, B., Brasseur, F. and Boon, T., Human gene MAGE-3 codes for an antigen recognized on a melanoma by autologous cytolytic T lymphocytes, *Journal of Experimental Medicine*, 179, pp. 921-930 (1994); Coulie, P., Lehmann, F., Lethé, B., Herman, J., Lurquin, C., Andrawiss, M. and Boon, T., A mutated intron sequence codes for an antigenic peptide recognized by cytolytic T lymphocytes on a human melanoma, *Proceedings of the National Academy of Sciences USA*, 92, pp. 7976-7980 (1995); Mandruzzato, S., Brasseur, F., Andry, G., Boon, T. and van der Bruggen, P., A CASP-8 mutation recognized by cytolytic T lymphocytes on a human head and neck carcinoma, *Journal of Experimental Medicine*, 186, pp. 785-793 (1997); Ikeda, H., Lethé, B., Lehmann, F., Van Baren, N., Baurain, J.-F., De Smet, C., Chambost, H., Vitale, M., Moretta, A., Boon, T. and Coulie, P.G., Characterization of an antigen that is recognized on a melanoma showing partial HLA loss by CTL expressing an NK inhibitory receptor, *Immunity*, 6, pp. 199-208 (1997); Marchand, M., Van Baren, N., Weynants, P., Brichard, V., Dréno, B., Tessier, M-H., Rankin, E., Parmiani, G., Arienti, F., Humblet, Y., Bourland, A., Vanwijck, R., Liénard, D., Beauduin, M., Dietrich, P-Y., Russo, V., Kerger, J., Masucci, G., Jäger, E., De Greve, J., Atzpodien, J., Brasseur, F., Coulie, P.G., van der Bruggen, P., and Boon, T., Tumor regressions observed in patients with metastatic melanoma treated with an antigenic peptide encoded by gene MAGE-3 and presented by HLA-A1, *International Journal of Cancer*, 80, pp. 219-230 (1999); Morel, S., Lévy, F., Burlet-Schiltz, O., Brasseur, F., Probst-Kepper, M., Peitrequin, A-L., Monsarrat, B., Van Velthoven, R., Cerottini, J-C., Boon, T., Gairin, J.E. and Van den Eynde, B., Processing of some antigens by the standard proteasome but not by the immunoproteasome results in poor presentation by dendritic cells, *Immunity*, 12, pp. 107-117 (2000); Coulie, P.G., Karanikas, V., Colau, D., Lurquin, C., Landry, C., Marchand, M., Dorval, T., Brichard, V., and Boon, T., A monoclonal cytolytic T-lymphocyte response observed in a melanoma patient vaccinated with a tumor-specific antigenic peptide encoded by gene MAGE-3,*Proceedings of the National Academy of Sciences USA*, 98,

pp. 10290-10295 (2001).