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"Anticorpi neutralizzanti ad ampio spettro e un nuovo meccanismo di diversificazione"

We have developed cell culture-based high-throughput methods to interrogate with high efficiency human memory B cell and plasma cell repertoires and to isolate antibodies selected on the basis of their neutralizing potency and breadth. Relevant examples are antibodies that neutralize all influenza A viruses[1] or even four paramyxoviruses[2]. By targeting conserved structures, these broadly neutralizing antibodies are less prone to select escape mutants and are therefore promising candidates for prophylaxis and therapy of infections, as well as tools for vaccine design [3]. The value of such a target-agnostic approach to vaccine design is illustrated by our discovery of extremely potent antibodies that neutralize human cytomegalovirus, which led to the identification of their viral ligand [4], a pentameric complex that was finally produced and tested as an effective vaccine [5]. By reconstructing the genealogy trees of specific B cell clones, we investigate the role of somatic mutations in affinity maturation and in generation of antibody variants with broader or different specificity. We found that affinity maturation is achieved rapidly, often through a single mutation, but numerous redundant mutations accumulate, leading to extensive intraclonal diversification that may broaden reactivity against homologous viruses [6]. In some cases however, somatic mutations appear to be able to generate autoantibodies, as found in patients with pemphigus and autoimmune pulmonary alveolar proteinosis [7,8]. Recently, while searching for antibodies that broadly bind to malaria variant antigens, we

discovered a new mechanism of antibody diversification, which relies on the interchromosomal transposition of genomic DNA sequences into rearranging immunoglobulin genes, followed by somatic mutations [9]. In my presentation I will briefly review our work on the role of somatic mutations in affinity maturation and intraclonal diversification and discuss, in more details, the recent findings on the antibodies against malaria variant antigens generated by interchromosomal DNA transposition, their properties and the nature of the target antigens.

(1) Corti et al. *Science* 333, 850 (2011); (2) Corti, et al., *Nature* 501, 439 (2013); (3) Corti & Lanzavecchia *Annu Rev Immunol* . 31, 705 (2013); (4) Macagno et al., *J Virol* 84, 1005 (2010); (5) Kabanova et al. *PNAS* 111, 17965 (2014); (6) Pappas et al., *Nature* 516, 418 (2014); (7) Di Zenzo et al., *J Clin Invest* 122, 3781 (2012); (8) Piccoli et al. *Nat Commun.* 6:7375. (2015); (9) Tan et al, *submitted*