Cunha C, Giovannini G, Pierini A, Bell AS, Sorci G, Riuzzi F, Donato R, Rodrigues F, Velardi A, Aversa F, Romani L and Carvalho A. (2011). Genetically-determined hyperfunction of the S100B/RAGE axis is a risk factor for aspergillosis in stem cell transplant recipients. *PLoS One. 6*:e27962.

Invasive aspergillosis (IA) is a major threat to the successful outcome of hematopoietic stem cell transplantation (HSCT), although individual risk varies considerably. Recent evidence has established a pivotal role for a danger sensing mechanism implicating the S100B/receptor for advanced glycation end products (RAGE) axis in antifungal immunity. The association of selected genetic variants in the S100B/RAGE axis with susceptibility to IA was investigated in 223 consecutive patients undergoing HSCT. Furthermore, studies addressing the functional consequences of these variants were performed.
Susceptibility to IA was significantly associated with two distinct polymorphisms in RAGE (-374T/A) and S100B (+427C/T) genes, the relative contribution of each depended on their presence in both transplantation counterparts [patient SNPRAGE, adjusted hazard ratio (HR), 1.97; P = 0.042 and donor SNPRAGE, HR, 2.03; P = 0.047] or in donors (SNPS100B, HR, 3.15; P = 7.8e-4) only, respectively. Functional assays demonstrated a gain-of-function phenotype of both variants, as shown by the enhanced expression of inflammatory cytokines in RAGE polymorphic cells and increased S100B secretion in vitro and in vivo in the presence of the S100B polymorphism. These findings point to a relevant role of the danger sensing signaling in human antifungal immunity and highlight a possible contribution of a genetically-determined hyperfunction of the S100B/RAGE axis to susceptibility to IA in the HSCT setting.