“Novel targets in multiple myeloma and other disorders”

Background and Description of Invention. Multiple Myeloma (MM) is the second most frequent hematological cancer after non-Hodgkin’s lymphoma and is characterized by the accumulation of neoplastic plasma cells in the bone marrow. Despite recent advances in therapies and improved patient outcomes, MM remains an incurable cancer, hence novel therapies are urgently needed. Herein, the inventors propose a new synthetic-lethal strategy to treat MM and other hematological cancers, including lymphoma and leukemia, by selectively targeting cancer cells presenting with endogenous DNA damage and low YAP1 levels. Specifically, the invention illustrates an approach in which the genetic inhibition of serine-threonine kinase 4 (STRK4) reactivates the Hippo mediator YAP1, which, by interacting with ABL1, triggers apoptosis in hematologic malignancies with intrinsic DNA damage, independently of the mutational status of p53.

Patent information. The international patent application was published as WO2014068542. Patent applications pending in Europe and US. A further international patent application, from the same inventors, relating to STK4 inhibitors for the treatment of hematological malignancies was filed and published as WO2016161145. Patent applications pending in Europe and US. The patented technology is available for licensing worldwide.

Stage of Development. DNA damage elicits genomic instability in cancer cells. While epithelial cancer cells presenting DNA damage inactivate tumor suppressor p53 to prevent the ensuing apoptosis, in hematological cancers the relevance of ongoing DNA damage and the mechanism undertaken by hematopoietic cells to survive genomic instability are largely unknown. The inventors identified a p53-independent network in MM and other hematopoietic disorders centered on the nuclear relocalization of the pro-apoptotic ABL1 kinase as a result of widespread DNA damage (Cottini F. et al., Rescue of Hippo coactivator YAP1 triggers DNA damage-induced apoptosis in hematological cancers. Nat Med. 2014). In response to DNA damage, nuclear ABL1 triggers cell death through its interaction with the Hippo pathway coactivator YAP1, which in turn stabilizes p73 and coactivates p73 proapoptotic target genes. Nonetheless MM, lymphoma and leukemia cells are able to survive by genetically inactivating or by exploiting the low expression levels of YAP1. Gain-of-function studies show that increased YAP1 levels in hematological cancer cells promote apoptosis by increasing the stability of the tumor suppressor p73 and its downstream targets, suggesting that re-expression of YAP1 might trigger nuclear ABL1-induced apoptosis. YAP1 is under the control of a serine-threonine kinase, STK4. Importantly, the inventors demonstrated that functional or pharmacological inhibition of STK4 restores YAP1 levels and induces a robust apoptosis in vitro and in vivo, thereby harnessing the ongoing DNA damage present in MM and other hematological cancer cells as a potential Achille’s heel (Cottini et al., Awakening the Hippo co-activator YAP1, a mercurial cancer gene, in hematologic cancers. Mol Cell Oncol. 2014).
We seek a potential commercial partner with a strong focus on kinase inhibitors in order to develop new therapeutic agents for the treatment of multiple myeloma and other hematological cancers.

**Potential Applications and Competitive Advantages.** Novel therapies targeting STK4 represent a promising novel strategy to improve patient outcome in MM and other hematological disorders. Among the advantages of such approaches are (i) the druggability of the proposed target, and (ii) the possibility to target MM patients regardless of their mutational status of p53.

For further information on this project please contact:

**Business Contact**
Paola Vella  
Head, Office of Biotechnology Transfer  
San Raffaele Hospital and Scientific Institute  
Tel: +39 02 2643 4281  
Fax: + 39 02 2643 8138  
E-mail: vella.paola@hsr.it

**Scientific Contact**
Dr. Giovanni Tonon  
Functional Genomics of Cancer Unit  
San Raffaele Hospital and Scientific Institute  
Tel: +39 02 2643 5624  
Fax: + 39 02 2643 5602  
E-mail: tonon.giovanni@hsr.it