# ImmunoTools *special* Award 2014

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## Involvement of A to I RNA editing on myeloid leukemia and myeloid cell commitment and differentiation.

Post-transcriptional modification events, such as RNA editing, are emerging as new players in several human diseases, including tumours. The type of RNA editing that is most prevalent in human, converts adenosine residues into inosine (A-to-I editing) in double-stranded RNA (dsRNA) through the action of ADAR enzymes ('adenosine deaminase acting on RNA'). Inosine essentially mimics guanosine, and hence ADARs introduce virtual A->G point mutations that modify both RNA primary sequence (such as codons, splicing sites and miRNA seed sequences) and structures (for example pre-miRNAs) with substantial effects on the RNAs and edited protein they produce (1). Three ADAR members (ADAR1, ADAR2 and ADAR3) are known to exist in mammals, but only ADAR1 and ADAR2 display enzymatic activity. Genetic ablation of Adar1 or Adar2 in mice is lethal, indicating that physiological “correction” of encoded RNAs by these enzymes is essential for normal development (2,3). Given the biological relevance of RNA editing, it is not surprising that many works have revealed the RNA editing machinery is dysregulated in different cancers (4). However, only recently it has been shown a mechanistic connection between a specific editing on RNA target genes and brain cancer (5). Despite these recent studies, little is known on the involvement of both the ADAR enzymes in the growth arrest and/or differentiation of hematopoietic cells. Of note, it has been shown that ADAR1 is essential for hemapopoietic stem cells (HSCs) self-renewal be required for normal hematopoiesis and for promoting malignant progenitor reprogramming in chronic myeloid leukemia (6).

My PhD thesis will focus on the investigation RNA editing landscape in hematopoietic cells as well as myeloid-derived cancer cells. To this aim, leukemic cells isolated from pediatric and adult patients suffering of myeloid leukemia will be analyzed both for ADARs expression at transcriptional and protein levels as well as for editing activities on known editable substrates. As controls monocytes and dendritic cells, which are isolated from peripheral blood of healthy individuals, will be used. At the same time, I will analyze the association between ADARs expression and activity in human leukemia cell lines, treated with different reagents (TPA, ATRA, 1,25-dihydroxyvitamin D3, IFN-gamma, M-CSF, GM-CSF, IL-4).

In this project, the expression of surface markers, such as CD11b, CD14, CD11c, CD14, CD16, CD1a, CD80, CD86, HLA-ABC, HLA-DR and CD56 and other proteins

which are regulated during activation/differentiation will be tested. Known editable target genes will also be used to verify the activity of the endogenous enzymes. A comprehensive characterization of the RNA editing in monocytes, macrophages and dendritic cells as well as myeloid cancer cells, could help enormously our knowledge of both immune system and cancer. If specific editing and/or ADARs will be identified as a key component of monocyte differentiation and/or human myeloid leukemia, it could provide an essential impact on future clinical implications in leukemia.

**References**

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