

### MEMORY T CELLS ELICITED BY MICROORGANISMS CROSS-REACT WITH TUMOR-ASSOCIATED ANTIGENS

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**Background** Individuals are exposed to intracellular pathogens (i.e. viruses and intracellular bacteria) and intestinal microbiota, collectively microorganisms (MOs), which enter the body during the host's lifetime. Altogether, MOs are a natural source of non-self antigens (MoAs) expressed by host's cells in the context of the HLA class I molecules, inducing a wide pool of specific memory CD8<sup>+</sup> T cell clones. Such MoAs may share sequence and structural homology with cellular self-antigens (molecular mimicry), possibly inducing autoimmune reactions leading to autoimmune diseases (ADs). We have recently shown that a molecular mimicry may be found also to self-antigens presented by cancer cells (i.e. tumor-associated antigens, TAAs). Consequently, memory CD8<sup>+</sup> T cell clones specific for the MoAs may turn out to be a natural "anti-cancer vaccination" if a nascent tumor lesion should express TAAs similar or identical to MoAs.

**Methods** In the present study we looked for homology between published TAAs and non-self MoAs. Blast search for sequence homology was combined with extensive bioinformatics analyses. Ex vivo immunological validations have been performed by screening with DNA barcode labeled pMHCs strategy and confirmation by tetramer and dextramer staining procedure.

**Results** Several TAAs and MoAs show sequence and structural similarities as well as comparable patterns of contact with HLA and TCR  $\alpha$  and  $\beta$  chains (figure 1 and 2). The predicted average affinity to HLA molecules of MoAs is very high (<100nM). The structural conformation of MoAs is, in general, highly similar to the corresponding TAA. In some cases, it is identical and contact areas with both HLA and TCR chains are indistinguishable. Moreover, the spatial conformation of TCR-facing residues can be identical in paired TAA and microbiota-derived epitopes, with exactly the same values of planar as well as dihedral angles. Importantly, CD8<sup>+</sup> lymphocytes are able to cross-react against paired TAAs and MoAs supporting the concept that the same T cell can recognise similar peptides.<sup>1,2</sup>

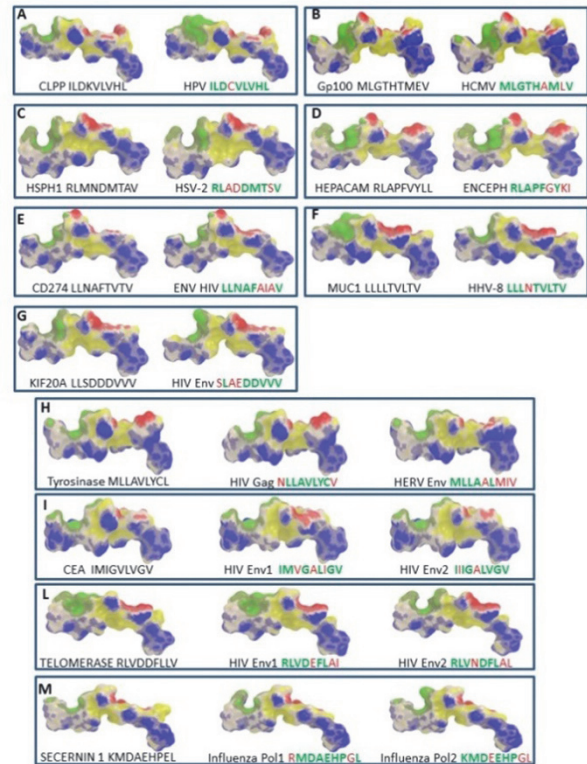
**Conclusions** Here we report for the first time 1) the molecular mimicry between TAAs and MoAs; and 2) cross-reacting CD8<sup>+</sup> T cell responses. Therefore, the T cell memory elicited by MoAs may turn out to be an anti-cancer T cell memory, able to control the growth of cancer developed during the lifetime if the expressed TAA is similar to MoAs. This may ultimately represent a relevant selective advantage for cancer patients and lead to novel preventive

#### REFERENCES

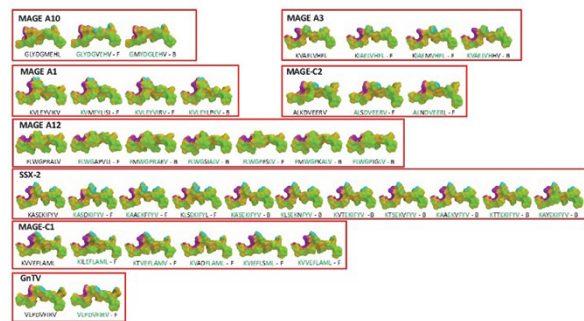
- Ragone C, *et al.* Identification and validation of viral antigens sharing sequence and structural homology with tumor-associated antigens (TAAs). *J Immunother Cancer* 2021;**9**(5):e002694. doi:10.1136/jitc-2021-002694. PMID: 34049932; PMCID: PMC8166618.
- Ragone C, Manolio C, *et al.* Molecular mimicry between tumor-associated antigens and microbiota-derived epitopes. *J Transl Med* 2022;**20**(1):316. doi:10.1186/s12967-022-03512-6. PMID: 35836198; PMCID: PMC9281086.

**Ethics Approval** The study obtained ethics approval by the ethics committee of the National Cancer Institute "Pascale" (Registry Nr. 8 of Oct.2, 2013 and following addendum). All Participants gave informed consent before taking part.

Fig. 2



Abstract 1175 Figure 1 Homology between viral antigens and TAAs



Abstract 1175 Figure 2 Homology between microbiota antigens and TAAs

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