

## Title: Differential Impact of TIM-3 Ligands on NK Cell Function

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- A. TIM-3 is co-expressed with CD44 and marks cells with heightened effector potential.
- B. Among the four putative TIM-3 ligands, galectin-9 most consistently suppresses NK cell-mediated cytotoxicity through interactions with TIM-3 and CD44, respectively, while simultaneously promoting IFN-γ release via TIM-3.
- C. In HNSCC patients, an elevated intratumoral TIM-3<sup>+</sup> NK cell gene signature is associated with worse outcomes in those with HPV-driven disease, potentially due to higher galectin-9 levels in HPV<sup>+</sup> compared to HPV<sup>-</sup> patients.