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Reply-To: Cancer Cell Editorial Office <cancer@cell.com>
To: Xu Guo <20011009gx@gmail.com>

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Thank you,
Cancer Cell

MIF-CD74 signaling drives immune modulation in medulloblastoma
Benjamin Draper; Zhen You; Dean Thompson; Xu Guo; Alaide Morcavallo; Alberto Delaidelli; Bethany Remeniuk; Bei Hopkins; Natalie Monteiro; Darren Locke; Miao Liu; Jacob Torrejon Diaz; Chantelle E Bowers; Kevin Greenslade; Barbara Martins da Costa; Karen Barker; Colin Kwok; Olumide Ogunbiyi; Anya Fletcher; Stacey Richardson; Carlos custodia; Rafael Roque; Regan Barfoot; Rebecca M Hill; Olivier Saulnier; Thomas S Jacques; Michael D Taylor; Claudia Faria; Olivier Ayrault; Poul H Sorenson; John Anderson; Louis Chesler; Steve Clifford; L Frank Huang; Laura K Donovan

Relapsed medulloblastoma remains a significant therapeutic challenge as it is near universally fatal. Our initial gene expression studies revealed that core immune signatures from the diagnostic tumor are largely preserved at recurrence. However, spatial phenotypic analyses indicated a shift in immune composition towards a highly immunosuppressive profile in relapsed Group3 and Group4 medulloblastomas. We developed an algorithm to identify the key ligand-receptor interactions between medulloblastoma tumor cells and the immune microenvironment using single-cell RNA sequencing data. The most significant pairing identified was MIF-CD74 which we validated empirically through disrupting this interaction in a novel MYCN-driven model of relapsed medulloblastoma. We demonstrate that CD74-targeting modulates the immune microenvironment and mitigates tumor growth, validating the use of our algorithm to identify significant tumor-immune interactions. These findings establish diagnostic and relapsed medulloblastoma as profoundly immune-compromised malignancies and validate the MIF-CD74 pathway as a promising therapeutic target.