Live-Cell Kinetic Assays Reveal That the TGF-b Inhibitor Vactosertib Suppresses T Cell Exhaustion

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Multiple myeloma (MM) is an incurable cancer of malignant plasma cells with a 5-year survival of 54%. Immunotherapy has recently emerged as a highly promising modality to treat MM. CD8+ T-cells are an important part of the immune system, especially for fighting cancer. After fighting cancer cells for extended periods, CD8+ T-cells release cytokines such as TGF-ß1 which reduce T-cell potency in a process called T-cell exhaustion. When T-cells are exhausted, cancer cells proliferate uncontrollably. Vactosertib is known to block TGF-ß1 mediated exhaustion by inhibiting TGF-ß1, but its efficacy at rescuing pre-exhausted T-cells remains unknown. Here, the kinetics of T-cell exhaustion were examined to determine vactosertib's efficacy at suppressing T-cell exhaustion. Healthy human CD8+ T-cells were treated with TGF-ß1 over 3 days and then assayed for Programmed Death 1 (PD1), a cell surface exhaustion marker, using PD1-APC conjugated antibody dye and flow cytometry. To test the efficacy of vactosertib at mediating T-cell exhaustion, its effect at lowering PD1 was measured in healthy CD8+ T-cells and TGF-ß1 stressed CD8+ T-cells after 10 days. Results demonstrated that T-cells do not react to TGF-ß1 between hours 0-24 but are exhausted exponentially between hours 24-72. Healthy T-cells treated with vactosertib expressed less PD1 after 10 days ($p=0.04$). Vactosertib also lowered PD1 in TGF-ß1 stressed T-cells ($p=0.003$). Future tests with therapeutic doses of TGF-ß1 and multiple time points of vactosertib treatment may yield insightful results to determine if vactosertib blocks or reverses T-cell exhaustion and if vactosertib can be utilized clinically.

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