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Acute Supra-pharmacologic Weight-based Dexamethasone (AVM0703), 18 mgs/kg Body Weight, Mobilizes Endogenous Bi-specific Natural Killer T-like Cells Independent of Glucocorticoid Receptor Activation

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Background: Glucocorticoids (GC) are a common component of blood cancer regimens, at doses 40 mg or lower due to concerns of pancreatitis and hepatotoxicity (1,2) and neuropsychiatric effects. AVM Biotechnology has developed a high concentration, high volume, preservative-free, patent pending formulation of dexamethasone (Dex) (AVM0703), allowing administration up to 21 mg/kg (1470 mg for 70 kg) in one-hour IV infusion. Prophylactic use of physiologic hydrocortisone reduces the risk of GC neuropsychiatric side-effects (3,4). At supra-pharmacologic doses (>6 mg/kg) AVM0703 mobilizes endogenous bispecific gamma delta invariant TCR+ Natural Killer T-like cells (AVM-NKT) (PCT/US21/19773), via a non-GC receptor, that rapidly home to cancer in tumor models and are directly related to tumor killing. GCs have been reported to induce biological responses independent of GCRs: corticosterone has been shown to bind a G-protein coupled receptor that does not bind either Dex or aldosterone (5,6) and the non-GCR mineralocorticoid receptor has high affinity for prednisone but not Dex.

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Methods: a) Mouse splenocytes or human whole blood were incubated with Dex from 1nM to 1mM. Apoptosis was measured for human whole blood by CBCs and for mouse splenocytes by flow cytometry 4 to 6 hours later. RU486 was used to block expected transmembrane (tm)GCR activity. b) Naïve, tumor bearing and humanized mice were dosed with AVM0703 at human equivalent doses (HED) >18 mg/kg. Depending on the disease state of the mice, novel AVM-NKT were observed in the blood between 3 and 96 hours later, determined by flow cytometry.

Results: a) Apoptosis via the tmGCR was observed at expected concentrations between 10nM and 100uM and was blocked by the GCR antagonist RU486. At concentrations above 250uM, which correspond to in vivo peak blood levels from acute 7mg/kg and greater, no Dex-induced apoptosis was observed. b) Acute supra-pharmacologic AVM0703 induced the appearance of CD3+, CD56+, gdTCR+, invariant TCR+ bi-specific Natural Killer T-like cells, that in a cancer setting also expressed activation markers like CD16 and NKp44. Intriguingly, the AVM-NKT also express B220 in certain settings, and CD3+ B220+ DP has been indicative of IL-2 or IL-12 lymphoma killing (7).

Conclusions: CBC's and clinical chemistries from enrolling clinical trial confirmed the in vitro non-GCR findings.