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Investigation into the mechanism of action of B cell antagonists through a targeted metabolomics approach

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B cells are known to play a critical role in many disease settings such as multiple sclerosis, transplant rejection and immune mediated diseases. A phenotypic screen was undertaken to identify inhibitors of proliferation of primary human B cells. This screen yielded multiple chemical series; however, in each case, the mechanism of action/molecular efficacy target was unknown. For one key series emerging from this effort, preliminary physical data indicated that deoxycytidine kinase (dCK) interacted with this scaffold, and could be the efficacy target. The application of our targeted metabolic analysis methodology, however, showed a spectrum of changes inconsistent with dCK inhibition. This provided critical evidence that dCK was not the molecular target of the chemical series, and allowed re-focusing of target identification efforts beyond dCK.

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