Nov-002, a cellular redox modulator, enhances the antitumor effect of adoptively transferred T cells in a murine melanoma model

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ABSTRACT

Oxidative signaling involving the glutathione system of redox control has been implicated in the regulation of T cell function. NOV-002, a glutathione disulfide mimetic, added to standard chemotherapy increased anti-tumor activity and survival in advanced non-small cell lung cancer patients compared to chemotherapy alone. Similarly, NOV-002 treatment significantly increased circulating T cell levels in these patients. Here, we investigated whether the addition of NOV-002 to our previously established murine adoptive therapy (AT) regimen could enhance the antitumor activity of the transferred T cells. Adoptive transfer of syngeneic Pmel+ CD8+ T cells activated in the presence of IL-12 (PmelIL12) into lymphopenic hosts is effective in repressing previously established B16 tumors. Daily administration of NOV-002 (25 mg/kg, i.p.) for 7 days following AT in C57BL/6 mice resulted in a significant delay in tumor progression when compared to mice subjected to AT alone, consistent with a marked enhancement of Pmel+ anti-tumor immune activity. This enhanced antitumor effect was accompanied by a significantly longer median overall survival in mice treated with AT + NOV-002 compared to those treated with AT + saline (45 vs 28 days; 95% CI 34-56 days vs 23-32 days, respectively, p<0.001). We then investigated whether NOV-002 creates a more favorable micro-environment for expansion of transferred Pmel cells in a lymphopenic host. To this end, non-tumor bearing mice were treated with cyclophosphamide (CTX, 200mg/kg) to induce lymphopenia or saline, and 7 days later 5x10^5 Pmel cells were adoptively transferred into all mice. In addition, mice were treated with either NOV-002 (25 mg/kg, i.p.) or saline daily for 7 days following AT. All mice were vaccinated with gp100 (the melanoma tumor antigen towards which the Pmel T cells are specifically reactive) 24 hours after AT to elicit in vivo activation and proliferation of transferred Pmel cells. On day 3 after vaccination, peripheral blood was collected, and analyzed by flow cytometry for the presence of donor Pmel cells (= Ly5.1+ cells) which represents T cell priming in response to vaccination. A significantly lower frequency of donor Pmel cells were seen in the animals treated with CTX relative to saline controls (9% vs. 20%; p<0.01). The addition of NOV-002 to CTX treatment, however, resulted in significantly higher frequencies of activated Pmel cells than CTX alone (18% vs. 9%; p<0.03), and which were comparable to levels seen in saline controls. Taken together, these results indicate that NOV-002 enhances the effect of AT thereby generating a significantly greater anti-tumor T cell response, decreasing tumor growth and increasing survival. Moreover, NOV-002 enhances the expansion of CD8+ T cells in a lymphopenic host. These findings are consistent with the hypothesis that enhanced immune responses may contribute to the clinical profile of NOV-002 in oncology trials.

Conclusions

• NOV-002 potentiates the anti-tumor effect of adoptively transferred pmelIL12 T cells in a melanoma model, resulting in significant delays in tumor growth and increased survival relative to adoptive transfer alone.
• NOV-002 administration in a non-tumor bearing lymphopenic host resulted in significantly increased numbers of circulating adoptively transferred Pmel cells.
• Further studies are needed to determine precise mechanisms by which NOV-002 enhances expansion of adoptively transferred Pmel cells in a lymphopenic host in response to vaccination, and enhances their anti-tumor activity.
• Those results extend earlier in vivo and in vitro findings (see references below), suggesting that NOV-002 possesses immunomodulatory activity that is of potential relevance to its clinical efficacy profile.

References


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References

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