**INDUCTION OF TRAINED IMMUNITY IN VIVO BY ATTENUATED SALMONELLA LVR01 IN BACTERIA-MEDIATED CANCER THERAPY**
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Research in the field of cancer immunotherapies has grown rapidly in recent decades. Many treatments, such as monoclonal antibodies and CAR-T cells, are available now at the clinic. Despite that, patients partially respond to treatments, and those interventions are expensive. In this context, bacteria to fight cancer are re-emerging, and *Salmonella* is one of the most cost-effective promising effectors.Our group demonstrated the potential of LVR01, an attenuated *Salmonella* Typhimurium constructed by introducing a null deletion into the *aroC* gene, in many preclinical models. LVR01 can accumulate in tumors and suppress tumor growth and metastasis. [1] However, the mechanisms that underlie this antitumoral effect still need to be elucidated. *Salmonella* can eliminate tumoral cells directly, by triggering different types of cell death, or indirectly, by enhancing the antitumor immune response. Particularly, LVR01 induces a proinflammatory tumor micro-environment, and NK cells and macrophages are essential for the antitumor effect. [1,2] Interestingly, cytotoxic CD8 T cells depletion did not affect LVR01 treatment. [1] The critical role of the innate compartment in LVR01-based cancer immunotherapy is evident. Therefore, we hypothesized that LVR01 can be inducing trained immunity (TI), as a mechanims of the antitumor response. Firstly, we evaluated whether LVR01 could induce TI *in vivo* in mice with different genetic backgrounds (BALB/C and C57BL6). For that, we administered LVR01 intraperitoneally (ip) to naive mice, and after seven days, we injected LPS ip and took serum samples at different times. LVR01-treated mice had significantly higher levels of IL-6 and TNF-α. Secondly, we evaluated whether LVR01 could induce TI in two preclinical cancer models (melanoma and non-Hodgkin lymphoma). Naive mice were inoculated with LVR01 ip, and seven days after, tumoral cells were implanted subcutaneously. Mice were followed up daily, tumor size was measured with a calliper, and volume was calculated as (length x width x depth) x π/6. We observed that a single dose of LVR01 before tumor implantation delayed tumor growth and prolonged survival time. This antitumoral effect remained even when tumor cells were implanted 30 days after LVR01 administration (applying the same protocol). The results so far suggest that LVR01 could be inducing TI *in vivo*, which provides short and long-term protection against cancer. Further studies to determine LVR01-induced epigenetic modifications in innate immune cells are mandatory to confirm this hypothesis.

## References

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