

## **Mycobacterial immunotherapy for prostate cancer: where can we go from here?**

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The effects of mycobacteria in prostate cancer have not been fully elucidated. Former studies indicated that mycobacterial immunotherapy conferred a survival benefit in patients with advanced prostate cancer and recent evidence supports the safety and efficacy of new mycobacterial agents in many malignancies; thus, modern, carefully designed, randomized controlled trials of mycobacterial immunotherapy for prostate cancer could be warranted.

**Pullquotes:**

“mycobacteria are safe, well-tolerated and could initiate effective anti-tumour responses”

Impressive advances in the field of prostate cancer immunotherapy have been made in the past decade. For example, Sipuleucel-T was approved by the FDA in April 2010 for use in patients with metastatic castration-resistant prostate cancer. However, the clinical results remain modest: overall survival is prolonged by only a few months and no benefit is seen in progression-free survival, whereas checkpoint inhibition suffers from similar limitations<sup>1</sup>. As such, the success of immunotherapies in the context of genitourinary malignancies remains confined to the use of BCG against non-muscle-invasive bladder carcinomas. Even so, our understanding of molecular immunology has increased substantially in recent years, and new ways of expanding the role of immunotherapy are constantly being considered.

It is well understood that the development of prostate cancer immunotherapies is inherently complex. Finding the optimal scheme for administration and using well-validated biomarkers or volumetric criteria of response are considerable challenges in clinical trial design. Also, prostatic malignancies have biological characteristics widely considered as unfavorable, such as a low immune cell density or mutational burden. However, high infiltrating immune cell density or mutational burdens do not necessarily correlate with clinical benefit<sup>2</sup>. Also, the introduction of PSA screening has resulted in a large diagnostic migration towards low-risk tumours that need to be addressed but not overtreated. Interestingly, patients with low disease burden are less likely to have tumour-induced immune dysfunction and could, therefore, be better suited for immunotherapies that generate early anti-tumour responses. Ideally, such therapies should be safe to administer in patients with low-stage prostate cancer, dampen cancer-induced immunosuppression, recruit appropriate populations of effector cells in the tumour microenvironment, induce measurable effects in tissues or biological fluids and be easily combined with existing treatments without increasing toxicity risk.

Some evidence suggests that mycobacterial preparations could fulfill one or more of these

criteria: work on animal and cell line models has previously shown that mycobacterial extracts inhibit the proliferation of transformed cells and restore T<sub>H</sub>1 immunity, while recently discovered mycobacterial strains, such as *M. vaccae* and *M. obuense*, are able to stimulate  $\gamma\delta$  T-cells, a critical component of anti-tumour immunity<sup>3</sup>. Whether these results can be translated in prostate cancer patients is currently unknown, but there are some lessons to be learned from the administration of mycobacteria against various malignancies. For example, SRL172 (heat-killed *M. vaccae*) has been administered to patients with metastatic renal cell carcinoma (RCC) after nephrectomy<sup>4</sup>. No statistically significant differences in survival were seen between the SRL172 and the biological therapy (IL-2 or TNF $\alpha$ ) arm, but the survival of patients receiving chemotherapy was worse than that of patients who received other treatments ( $p < 0.001$ ), suggesting that SRL172 is at least as effective as traditional disease modifiers. Another group randomized 419 patients with stage III-IV non-small cell lung cancer to SRL172 plus chemotherapy versus chemotherapy alone. No difference in overall survival was initially found, but re-analysis of the study data (based on the observation that only 53% of patients in the combination arm received more than two SRL172 injections) indicated that patients with non-squamous lung adenocarcinoma adhering to the full dosing schedule lived on average 357 days (95% CI: 293-421) versus only 222 days (95% CI: 180-263) in the chemotherapy group<sup>5</sup>. To date, only a few formal trials have investigated the effects of intradermal IMM-101 (heat-killed *M. obuense*) immunotherapy; the largest was a phase II study (NCT01303172) assessing the safety and efficacy of IMM-101 combined with gemcitabine in 110 patients with locally advanced or metastatic pancreatic adenocarcinoma<sup>6</sup>. Overall survival for the intention-to-treat population was 6.7 months for IMM-10 plus gemcitabine versus 5.6 months for gemcitabine alone (HR 0.68; 95% CI: 0.44–1.04,  $p = 0.074$ ). Differences in overall survival between the two arms were also observed in the metastatic disease subgroup (OS: 7.0 versus 4.4 months; HR 0.54, 95% CI: 0.33–0.87,

p=0.01), whereas injection site reactions were mild to moderate.

With regards to prostate cancer, most studies on mycobacterial immunotherapies were performed before the study of molecular biology or monoclonal antibody technology and are, therefore, difficult to interpret. However, in a 1973 trial that aimed to determine the effect of BCG on survival and immunological parameters in patients with prostate cancer of all stages, interim reports showed a favourable safety profile of intradermal administration. Overall survival differences between the intervention and control arms reached statistical significance (OS for all stages: 37.5 vs 21 months, p=0.02), whereas stage-specific survival differences were larger in lower stage disease <sup>7</sup>. Although initially all patients were treated, stratification and randomization was consistent after 1976 and the results indicated that intradermal BCG is effective, safe and able to stimulate the immune system. Similar but sparse results were replicated by other, smaller studies in the 70s and 80s. More recently, in a 1998 phase I/II trial, SRL172 was administered in 10 patients with hormone-resistant, advanced prostate cancer <sup>8</sup>. The injection only caused mild redness and swelling (5-8 mm) at the administration site in most patients and fever in one, but no other major systemic reactions were recorded. PSA reduction was seen in 5 men, two of whom received SRL172 as their only treatment. The results also indicated that men with advanced prostate cancer have a T<sub>H</sub>2 cytokine profile within their peripheral blood mononuclear cells, which predominantly secrete IL-4. Interestingly, SRL172 vaccination was associated with IL-2 production in three out of 10 men, a cytokine considered as a critical component of cell-mediated immunity.

Collectively, these results indicate that mycobacteria are safe, well-tolerated and could shift immune responses from T<sub>H</sub>2 (predominantly humoral and associated with cancer progression) to T<sub>H</sub>1 (predominantly cell-mediated and associated with anti-tumour responses). Improvements in trial design could enable the study of mycobacterial strains that are well-tolerated when delivered systemically (such

as *M. vaccae* and *M. obuense*) and could, therefore, be administered early in the treatment pathway, before prostate cancer-induced or treatment-related immune dysfunction is established. Experimental evidence supports the notion that early disease modulation could be effective; for example, the therapeutic vaccination of TRAMP mice against specific prostate tumour antigens is more effective in mice with prostatic intraepithelial neoplasia compared to those with already established cancers <sup>9</sup>. Monitoring tumour responses in early stages is challenging, but recent advances in imaging could enable the longitudinal monitoring of low-risk tumours and facilitate repeated sampling of a particular disease focus. Other interventions have been previously tested in this manner <sup>10</sup> and it could be possible to extend these methodologies in immunotherapy trials. Whether such trials would have any practical value remains to be seen, but in an era in which effective prostate cancer treatments are highly desirable, having a fresh, critical look into concepts previously dismissed as, apparently, ineffective could be a way forward.

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