

Bugs as drugs, on the way to becoming a reality

There is ever increasing evidence to suggest that in cancer, exposure to micro-organisms, whether as part of the host microbiome or as environmental bacteria, may be a contributing factor both in disease progression as well as in its resolution. Microbial preparations have been used with success as stand-alone cancer treatment, as example the vast anecdotal evidence in the late 19th century on the therapeutic benefit to patients with sarcoma of Coley's toxin, a suspension of *Streptococcus pyogenes* and *Serratia marcescens*. More recently live attenuated *Mycobacterium bovis Bacille Calmette Guerin* (BCG) has received market approval for treatment of non-muscle invasive bladder cancer. Indeed, BCG can be considered the first successful immunotherapy against a human tumour.

Immunotherapy offers a very promising treatment for cancer, each approach targeting different pathways aimed at slowing cancer cell proliferation, limiting metastatic spread, and restoring immune function to re-establish elimination and equilibrium phases in this disease. Agents under clinical investigations include Checkpoint Inhibitors and cytokines as well as oncolytic viruses and non-specific immune modulators. The latter act by modulating the immune system in a general way to ensure the development of immune responses aimed at recognizing and attacking cancer cells. The more common non-specific immune modulators used are Toll-like receptors (TLR) like Imiquimod. However, the use of microbes which are "sensed" by the immune system through a diverse and varied range of pattern recognition receptors not limited to TLRs alone, and which are expressed by many different immune cells could provide a more proficient approach able to induce wide-ranging immune responses by both the innate and adaptive immune system. A number of microbes are being investigated or are under clinical evaluation as alternatives to BCG including non-pathogenic, heat-killed, or extracts thereof, of mycobacteria such as *M. obuense*, *M. phlei*, *M. smegmatis* or *M. vaccae*. Reported studies thus far have pointed to limited toxicity and some remarkable therapeutic effects.

This talk will reflect on recent mycobacteria-based preparations, their clinical use and future potential in cancer.