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Coley remembered – back to the roots. Fevertherapy of cancer in the light of modern immunology.
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ABSTRACT

Background: As a result of the new cancer immunotherapy revolution success stories of terminal cancer patients achieving complete remissions are accumulating. Durable benefit, however, is limited to a minority of patients, while the majority suffered immune-related adverse events (irAEs). irAEs could affect any tissue, their incidence may reach up to 90% of patients and toxicity is dose-dependent. While the combination of two immune checkpoint inhibitors (ICIs) increased efficacy, the incidence of severe adverse events was also increased. Despite a dose-dependent increase in irAEs no improvement in progression-free survival (PFS), overall survival (OS), or disease control rate (DCR) were identified with escalating doses of ICIs. Apparently, the long lasting objective of cancer regression can only be achieved by paying a price: tolerance to healthy self tissues is compromised. Since mild-to-moderate irAEs were demonstrated already at the lowest (0.3 mg/kg) dose with anti-CTLA-4 and anti-PD-1 blockades, respectively, this was interpreted to mean that even very low doses were capable to induce an *auto*-graft versus host disease (auto-GVHD) by the patients' own lymphocytes.

Hypothesis: Combination of a very low-dose anti-CTLA-4 plus anti-PD1 antibody blockade with fever range hyperthermia and conventional interleukin-2 (IL-2) stimulation, a similar anti-cancer effect could be achieved by the patients' own lymphocytes as by adoptive transfer of alloreactive donor lymphocytes but *without* severe GVHD.

Results: The safety and efficacy of the low-dose-combination therapy was demonstrated in 134 out of 148 evaluable stage IV cancer patients with a variety of cancer types. Staging with iRECIST, the overall response (OR) rate was 51 %, while objective response rate (ORR) was 35 %.

Interpretation: Tumors with higher number of tumor neoantigens presented on major histocompatibility complex molecules were more likely to respond to immune checkpoint therapies than were cancers with fewer mutations resulting in longer survival for people who received ICI treatment. The more genetically different a tumour is from normal tissue, the more likely it is that the immune system will recognize and eliminate it as an *allograft* by a graft versus tumor (GVT) response.

Conclusion: One can speculate that with better patient selection and with our low-dose ICI combination treatment protocol could fulfill the promise of Carl H. June, MD, the "father" of CAR T-cell therapy, that the present moment is only "the tip of the iceberg" of effective immunotherapy of cancer. Since our protocol consists only of approved drugs and treatments, our prediction that autoimmune T-cells are powerful therapeutic tools, rather than the "Achilles heel" of cancer immunotherapy, can be confirmed or refuted in prospective controlled clinical trials.