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Prostate cancer
Important steps and considerations in the design of therapeutic vaccines

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Vaccine-based immunotherapy can increase the overall survival of patients with advanced prostate cancer. However, the efficacy of vaccine-elicited anticancer immune responses is heavily influenced by the physical, nutritional, and psychological status of the patient. Given their importance, these parameters should be carefully considered for the design of future clinical trials testing this immunotherapeutic paradigm in prostate cancer patients.

We have recently demonstrated the ability of a prostatic acid phosphatase (PAP)-derived 15-mer peptide (PAP-114) to reduce the growth of established TRAMP C1 tumors in a preclinical murine model.[1] Although these results are encouraging and illustrate the potential of vaccine-based immunotherapy, they were obtained using relatively young animals (maximum 12 w of age, which equates to 10–20 y in humans). Thus, our findings might not represent the responsiveness/effectiveness of anti-cancer vaccines in old mice or in prostate patients, the average age of whom is 65 y.

Overall, both the innate and adaptive immune systems are attenuated during senescence, and this is manifested, in part at least, by a general decline in the diversity of the T cell repertoire, a reduction in the number of naïve T cells and a proportional increase in the prevalence of memory T cells. Senescence is associated by a limited proliferative potential and a chronic low-grade systemic inflammation.[2] It is therefore important that the development of vaccines and their translation into the clinic take into consideration the influence of age and other factors on their efficacy. In this setting, the nutritional, physical, and psychological status of patients are indeed critical for improving their "immunological fitness."

Although preclinical models do not entirely reflect the clinical situation and have other limitations, they do have merits. We propose that long peptides not only induce stronger, antigen-specific immune responses, thereby potentially limiting the induction of regulatory T (Treg) cells, but that they also are cheaper and easier to manufacture to a clinical grade than whole protein-based vaccines. The path towards the development of peptide-based vaccines involves the identification of relevant immunogenic regions in tumor-associated antigens, followed by studies in wild-type or humanized (expressing human MHC molecules) mice (**Fig. 1**). The relative efficacy of different vaccine formulations, including purified peptides, peptides linked to delivery systems or peptide-coding cDNA (administered with or without adjuvants), is also an important parameter to assess, as is the influence of the concomitant administration of immunomodulatory agents on the development of effective anti-cancer immune responses. An example of the latter is a monoclonal antibody against CD274 (best known as PD-L1), which influences the presence and immunosuppressive activity of Treg cells (so-called "immune checkpoint blockade"). The widespread adoption of anti-cancer vaccines into clinical practice requires the development of optimized formulations and approaches that are capable of[1] breaking immunological tolerance;[2] overcoming local and systemic tumor-driven immunosuppression;[3] operate in spite of age-related immune dysfunctions; and[4] targeting metastatic disease. These issues can be investigated (and potentially addressed) using induced, engineered and spontaneous heterotopic and orthotopic mouse tumor models (**Fig. 1**).

Although orthotopic models might be considered less relevant than genetically modified models, they do allow for the assessment of vaccine efficacy and the influence of age-related immune dysfunction in old mice. Recently, Bouchlaka et al., found that macrophages from old mice and elderly people produce higher levels of tumor necrosis factor α (TNFα) and interleukin (IL)-6 than macrophages derived from young mice and humans.[3] Age therefore dictates the ability of some cells to produce pro-inflammatory cytokines, a phenomenon that has been referred to as "inflammaging"[4]. It has also been demonstrated that the attenuated response to vaccines in old mice/patients

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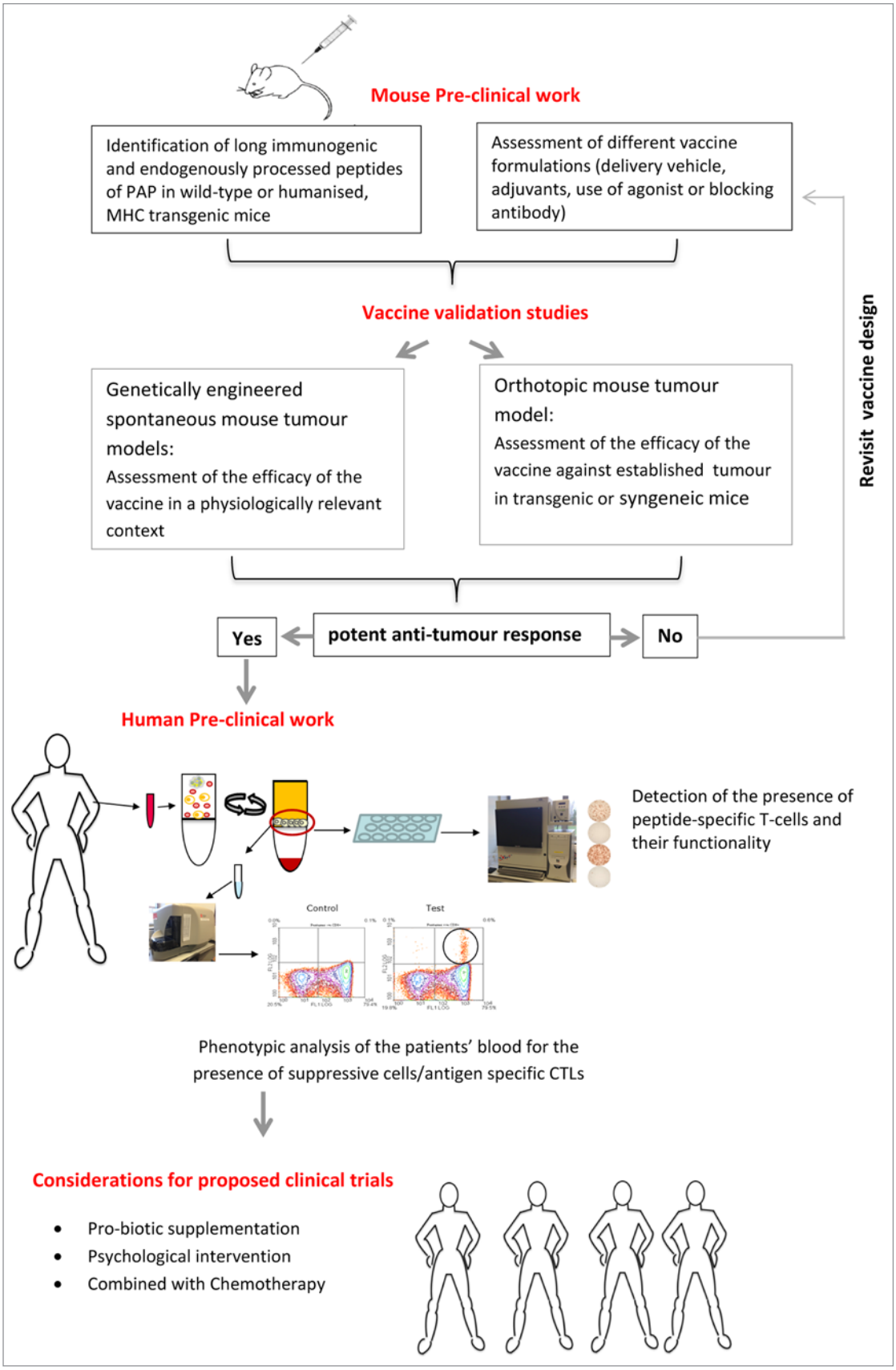

Figure 1. Important steps to be taken from the formulation of an anticancer vaccine to the implementation of clinical trials. The development of a prostate acid phosphatase (PAP)-targeting vaccine for the treatment of prostate carcinoma patients is employed as an example. CTL, cytotoxic T lymphocyte.

can be partially restored by the inclusion of additional co-stimulatory signals. Thus, it is essential to demonstrate the efficacy of vaccines destined to old cancer patients in preclinical models that are based on appropriately aged animals.

An essential and substantive proportion of immune responses is generated at the mucosae of the gastrointestinal system, and this is driven (or at least modulated) by gut microflora.[5] The gut microflora can indeed influence various immunological functions, including the establishment of anti-inflammatory responses.[6] Although people over 60 typically exhibit a marked reduction in the intestinal bacteria that are known to fortify gastrointestinal health, this defect can be resolved, at least partially, using probiotics that are specifically fermented by the beneficial microbiota in the gut (e.g., galactooligosaccharides). The importance of the gut microflora for the development of anti-cancer immunity has recently been illustrated by reports that the temporary disappearance of the microbiota upon antibiotic treatment reduces the anti-neoplastic efficacy of chemotherapy alone or chemotherapy combined with immunotherapy.[7] An inappropriate diet, the lack of specific digestive enzymes and other factors including the general physical and psychological health also influence immunological functions in humans.

The ability of stress to accelerate the effects of aging on immunity[8] and influence the efficacy of vaccination should also be considered in the design, translation, and clinical implementation of therapeutic vaccines.[9] Each patient is unique with respect to their neoplasm, gut microbiota, and general immunological status. Moreover, the mental attitude of individual patients toward their disease and their experience of living with cancer vary to a significant degree, and recent research has demonstrated that psychological and/or behavioral factors can influence tumor incidence and/or progression.[10] Similarly, an increasing number of studies has highlighted the health benefits that are associated with positive emotions. However, to date, no clinical trial has attempted to restore/improve the patient's intestinal microbiota while providing psychological interventions that are aimed at minimizing patient-to-patient differences and maximizing the efficacy of vaccination prior to, or throughout immunotherapy.

In summary, immunity is influenced by dietary factors which influence the gut flora, the general state of health, and the psychological capacity of an individual to cope with stress. Although not all of these parameters can be studied and manipulated in a clinical trial, the restoration/improvement of the gut microbiome and the improvement of the psychological status of the patient would be relatively easy and cost-effective to evaluate.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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