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Editorial

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If at first you don't succeed……..try, try again…..
–Thomas H Palmer

Improved cancer vaccines through gene transfer

The development of cancer immunotherapies has been pursued for a long time, advanced by increasing knowledge of cancer biology, the immune system and the adaptation of new technologies.[1] The dream of therapeutic cancer antisera was eventually realized by the confluence of improvements brought by the discoveries of tumor cell surface receptors, monoclonal antibodies and recombinant DNA technology that led to the generation of humanized monoclonal antibodies that are now approved therapies for lymphoma, breast and colon cancers.[2–5] The tenacity of tumor immunologists should be acknowledged and played no small part in this achievement that required over a century of experimentation and refinement!!

The parallel effort to develop effective vaccines for cancer therapy and prevention will likely follow a similar path of incremental knowledge and technology breakthroughs. Currently, among the leading cancer vaccines in late stage clinical trials are dendritic cell (DC) and allogeneic whole tumor cell vaccines.[6–8] This special issue of *Cancer Gene Therapy* is focused on improvements to these types of cancer vaccines utilizing gene transfer technology.

Several papers in this issue describe the use of vectors to genetically modify DC vaccines to improve their efficacy. Trakatelli et al employed carnarypox vectors encoding MAGE-1 and MAGE-3 minigenes to modify DC from melanoma patients. The genetically modified DC demonstrated improved antitumor immune responses compared to more conventionally prepared DC loaded with the corresponding MAGE peptides. A similar approach is reported by Medin et al for prostate cancer therapy utilizing retroviral vectors to modify DC to express prostate-specific membrane antigen (PSMA), prostate-specific antigen (PSA) and the immunomodulatory molecule CD25. To increase the scope of presented antigens, including those that are patient specific, Kyte et al describe methods and characterization of DC transfected with autologous tumor mRNA. The article by Wargo et al regarding melanoma antigen-engineered DC provides data and perspectives regarding the important role of natural killer cells in generating effective DC vaccines.

The remaining articles in this focus issue describe gene transfer approaches to improve whole tumor cell vaccines. Pandha et al have demonstrated the superiority of whole tumor cell vaccines killed *ex vivo* by expression of the herpes simplex thymidine kinase "suicide" gene and exposure to the prodrug ganciclovir. The authors hypothesize that this approach is more conducive to tumor antigen crosspriming following intradermal vaccination. In a related study, Djeha et al report similar beneficial effects in a breast cancer animal model of *ex vivo* "suicide" gene/prodrug therapy employing the combination of nitroreductase/CB 1954 that was further enhanced by concomitant expression of the immunomodulatory molecule HSP70. Deriy et al describe the genetic modification of whole tumor cells to permit their opsonization and DC targeting by endogenous naturally occurring antibodies. In this clever approach, whole tumor cells are transduced with the alpha 1,3 galactosyltransferase gene to induce expression of alpha-gal epitopes that are recognized by naturally occurring alpha gal antibodies that comprise approximately 1% of circulating immunoglobulins. These approaches may complement genetically modified tumor cell vaccines currently in later stage clinical trials for prostate and lung cancers that have been engineered respectively to express GM-CSF and to suppress transforming growth factor-beta.[9,10]

These approaches reflect the power and promise of gene transfer technology to contribute to the improvement of vaccines for cancer therapy. A future review article to be published in this journal will describe the importance of applying these advances to the field of cancer prevention.[11] Further improvements in cancer vaccines through gene transfer technologies are certain and will likely become an integral component of future vaccines that are destined to advance cancer treatment and prevention.

Robert E Sobol, Kevin J Scanlon
E-mail: rsobol@magnum-rx.com

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