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Developing Clinical Evaluation Guidance For Therapeutic Cancer Vaccines

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HEALTH CANADA

History of Immunotherapy

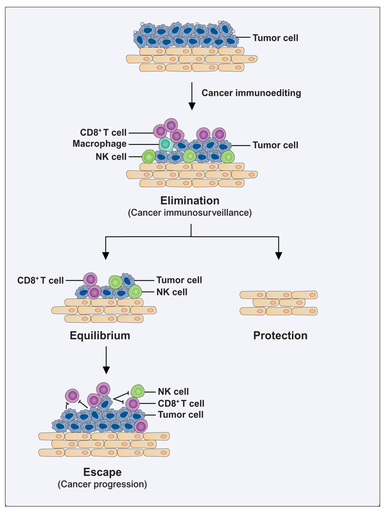
- **Cancer is a multifactorial disease with complex interplays that include immunological mechanisms.**
- **The premise of immunotherapy for the treatment of cancer is not new.**
- **William Coley, (1862-1936) an orthopedic surgeon, is considered the "Father of Immunotherapy" for his investigations and treatment of patients with Coley's toxin, which began in 1891.**
- **The toxin was used to induce cancer regression, initially for the treatment of unresectable sarcoma.**
- **It consisted of a combination of heat inactivated *Streptococcus pyogenes* and *Serratia macrescens* (now called mixed bacterial vaccine).**
- **This treatment had varying results due to different treatment schedules, routes of administration, non-standardized formulation and production; the use fell out of favour by the 1940s.**
- **However, this research demonstrated that inducing infections (erysipelas) in humans would stimulate or enhance the immune system to attack the malignant tumour and in some cases lead to tumour regression.**

Cancer Immunoediting

Cancer immunoediting is a term that describes the role of the immune system in cancer control. It consists of three phases:

- **elimination by immune effector cells of nascent transformed cells**
- **tumour variants become resistant to the immune effectors during equilibrium**
- **tumour growth continues and eventually is able to escape the effects of the immune system causing malignancy.**

Figure 1: Schematic Representation of Cancer Immunoediting.



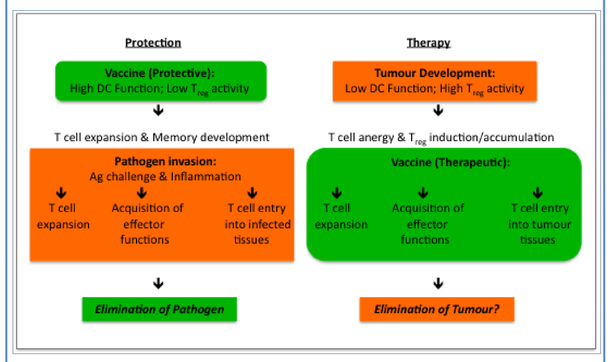
Evading Immune Destruction, biooncology.com

Protective vs Therapeutic Vaccines

The goal of cancer vaccines differs from that of protective vaccines:

- **protective vaccines aim to induce a memory response by the activation of pathogen-specific T cells and antibody production**
- **TCVs stimulate the immune system to produce cancer-specific T cells as well as overcome tumour induced immune suppression.**

Figure 2: Differing effects on the human immune system with the administration of protective versus therapeutic vaccines.



Seminars in Immunology 2010; 22(3): 174.

Vaccine Adjuvants

Adjuvants are added to vaccines for a variety of reasons, including:

- **to reduce the amount of antigen required to elicit an immune response**
- **in the case of cancer vaccines, they act to stimulate the immune system to respond to a weak antigen**
- **safety of vaccine adjuvants must also be taken into consideration in the assessment of TCVs.**

Table 1: Categories of Vaccine Adjuvants

Mineral salts	Aluminum hydroxide Aluminum phosphate Calcium phosphate
Immunostimulatory adjuvants	Cytokines (e.g., IL-2, IL-12, GM-CSF) Saponins (e.g., QS21) MDP derivatives CpG oligos LPS MPL polyphosphazenes
Lipid particles	Emulsions (e.g., Freund's, SAF, MF59) Liposomes Virosomes Iscoms Cochleates
Microparticulate adjuvants	PLG microparticles Poloxamer particles Virus-like particles
Muscosal adjuvants	Heat-labile enterotoxin Cholera toxin Mutant toxins (e.g., LTK63 and LTR72) Microparticles Polymerized liposomes

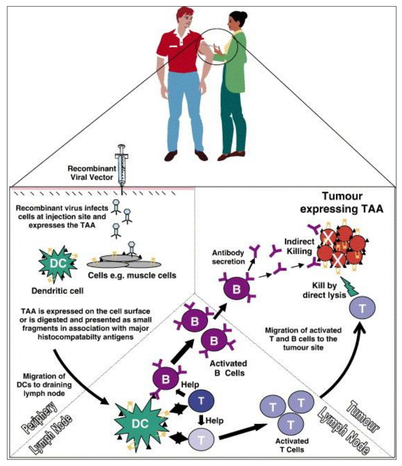
Nature Biotechnology 1999; 17(11): 1076.

Therapeutic Cancer Vaccine Platforms

Therapeutic cancer vaccines may be autologous or allogeneic and may take a variety of forms, including:

- **peptide/small epitope vaccines**
- **DNA vaccines**
- **dendritic cell vaccines**
- **whole cell vaccines**
- **recombinant viral/bacterial vaccines.**

*Figure 3: Mechanism of Action of an **Allogeneic** Therapeutic Cancer Vaccine.*



Advances in Drug Development Reviews 58(8): 933.

Future Directions

- **consider what immunotherapies may require a new regulatory framework**
- **acquire sufficient knowledge to allow the application of science in a consistent and rational manner for development and decision-making**
- **refine the scope and type of quality standards that would result in consistent and reliable products**
- **define the scope and type of pre-clinical and clinical trials, including the most suitable statistical methodologies.**

Table 2: Recent Phase II/III Clinical Trials of TCVs.

Vaccine platform	Example	Cancer Type
Peptides/Protein		
Peptides	gp100 (modified), MUC-1 (Stimuvax), HER2/neu	Melanoma, lung
Protein	MAGE-A3, NY-ESO	Melanoma
Antibody	Anti-idiotype	Lymphoma
Glycoproteins	sTn-KLH	Melanoma
Recombinant vectors		
Poxvirus	rV, rF-PSA-TRICOM	Prostate
S. cerevisiae	yeast-ras	Pancreatic
Listeria	Listeria-mesothelin	Pancreatic
Tumor Cells		
Autologous	adeno-CD40L, colon (BCG)	CLL, colon, melanoma
Allogeneic	GVAX (+GM-CSF)	Pancreatic
Dendritic cell/autologous tumor cell fusions		Myeloma
Dendritic cells/APCs		
APC–protein	Sipuleucel-T (PAP-GM-CSF)	Prostate
Dendritic cell–peptide	Glioma peptides	Glioma, melanoma
Dendritic cells–vector infected	rV, rF-CEA-MUC1-TRICOM	Colorectal

Journal of the National Cancer Institute 2012; 104(8): 600.

ABSTRACT / RESUMEN

III-03CAN - DEVELOPING CLINICAL EVALUATION GUIDANCE FOR THERAPEUTIC CANCER VACCINES

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Introduction: Therapeutic cancer vaccines (TCVs) are designed to target and destroy malignant tumours present in the body, with minimal effects on other tissues. TCVs stimulate the immune system to attack and kill tumour cells that the host immune system may not recognize and/or boost the host's immune response to the tumour.

Objectives: In order to prepare our employees to smoothly integrate the submission and reviews of TCVs, the creation of a clinical review guidance on TCVs is proposed.

Methodology: Analysis and consolidation of the available scientific literature and guidance documents from other regulatory agencies worldwide was performed.

Results: There are many unique considerations to be examined in the regulation of TCVs. These include potentially longer response times to vaccine treatment compared to traditional chemotherapy; choice of the appropriate surrogate endpoints; and optimization of the timing of administration of other standard cancer therapy during TCV trials. The safety of the vaccine platform, vaccine adjuvants, and immune effects of the vaccine also need to be considered.

Conclusions: BGTD has the opportunity demonstrate clinical and regulatory leadership by providing guidance and training sessions to educate our reviewers on TCVs, and to ensure that TCVs are an efficacious and safe part of cancer treatment.

III-03CAN - DESARROLLO DE ORIENTACIÓN PARA LA EVALUACIÓN CLÍNICA DEL CÁNCER DE VACUNAS TERAPÉUTICAS

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Introducción: Las vacunas terapéuticas para el cáncer (VTCs) constituyen una terapia prometedora diseñada para atacar y destruir tumores malignos en el cuerpo, con efectos mínimos sobre otros tejidos, en contraste con la quimioterapia tradicional.

Objetivos: Con el fin de preparar a nuestros empleados para integrar sin problemas la presentación y avaluación de las VTCs, se propone la creación de una guía clínica.

Metodología: Se realizó un exámen consolidado de la literatura científica disponible y de las guías de otros organismos reguladores.

Resultados: Hay muchas consideraciones particulares que deben de examinarse en la regulación de las VTCs. Estas consideraciones comprenden, entres otras un tiempo más prolongado de respuesta al tratamiento comparado con la quimioterapia tradicional, la elección de los criterios indirectos de valoración apropiados, y el calendario de administración con otros medicamentos durante los estudios clínicos. La categoría de vacunas, adyuvantes y efectos de imunidad de estas vacunas deben de considerarse.

Conclusiones: La Direccion de productos biologicos (BGTD) tiene la oportunidad de demostrar liderazgo clínico y regulatorio, proporcionando sesiones de orientación y formación para educar a nuestros evaluadores en el campo de las VTCs, y para asegurar que las VTCs son eficaces y seguras en tanto que son parte de los regímenes de tratamiento del cáncer.

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