Development of dendritic cell vaccine drugs based on the effcient cell expansion technology against intractable malignancies.

Target disease: Pancreatic cancer

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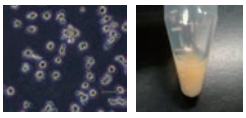
Synopsis

Cancer vaccines are now drawing attention as a 4th alternative for treating intractable advanced cancers resistant to standard therapies (surgery, radiotherapy and chemotherapy). The mainly used dosage forms of such vaccines are cancer antigen peptides and cancer antigen-pulsed dendritic cells (DCs). Despite the clinical evaluation of such cancer vaccines pursued globally, very few technologies have so far shown clear clinical efectiveness. DCs can induce Th cell polarization in vitro with certainty, and are believed to induce antitumor immunity with greater certainty than the peptides alone. An example of a pharmaceutical product with DCs as the main component is the proprietary cell drug Provenge (Dendreon Corp., USA), which is meant for treating hormone therapy-resistant advanced prostate cancer and has received manufacturing and marketing approval in USA in 2010. However, this drug can prolong the patient's life only for 3-4 months and it also contains numerous miscellaneous cells. Therefore, there is need for cell drugs with better purity and higher quality.In Japan DC vaccines are provided to patients only by some facilities as advanced medical treatment or treatment at the patient's own expense. The quality of such vaccines varies from one medical institution to another and also from patient to patient. Besides this, it is still impossible to undertake proper clinical evaluation, particularly a clinical trial of a pharmaceutical product, as no GMP-compliant manufacturing process for cell drugs of specifc quality has been established.The technology of "mass expansion of DCs from peripheral blood mononuclear cells" developed by us for which a patent has been applied for will be used in this R&D project. We aim to establish GMP compliant production technology in collaboration with tella Inc., which has experience of using DC vaccines with a recognized level of clinical efectiveness in more than 7,000 cases, to manufacture a pharmaceutical product of uniform quality while maintaining specifcations at par with the DC vaccines produced through this company's current SOP, and to start a clinical trial one year later after collecting CMC data needed for the trial.

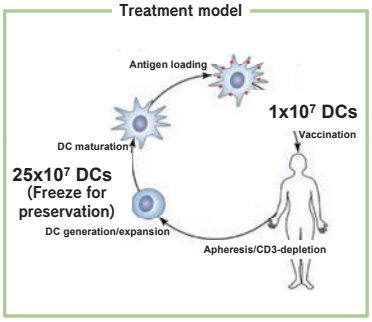
The procedure of DC-based immunotherapy; patients with advanced cancers would be treated with highly amplified and good qualified dendritic cells that are produced in compliance with GMP.



Expanded Dendritic cells
Development code: TLP1-001

Core technologies Patent applied for

1. CD3-depletion
2. Floating cultivation
3. Optimized cytokines
4. Optimized antigens



Quality standards applied to DC vaccines

Microbiological Controls	Negative for Bacterial and Fungal Contamination
Purity	>80% As determined by flow cytometry, light scatter or staining with non-DC lineage markers.
Morphology	Immature: loosely adherent, floating, roundish cells with some extensions
	Mature: loosely attached, veiled and clustered cells
Phenotype	Monocyte-derived: Immature: CD14$^{-/\sim}$CD83^{-}CD80$^{-/\sim}$CD86^{0}MHC class^{I} MHC class II^{+}CCR5^{+} Mature: CD83^{+}CD80^{+}CD86^{+}MHC class I^{+}MHC class II^{+} CCR7^{+}
	CD34^{+} cell-derived: Interstitial: CD14^{-} CD1a^{-} CD83^{+} CD80^{+} CD86^{+} MHC class^{I} MHC class II^{+} Langerhans cells: CD14^{+}CD1a^{+}CD83^{+}CD80^{+}CD86^{+}MHC class I^{+}MHC class II^{+}
Viability	>70% as determined by Trypan blue exclusion
Stability of DC phenotype	Determined after one and two days of subsequent culture in medium either without or with cytokines
	'Without test': DCs must remain viable and maintain their characteristic morphology and phenotype over two days in medium without cytokines (characteristic of fully mature and stable DCs)
Induction of immune response	Mixed lymphocyte reaction: T-cell proliferation at DC/PBMC (peripheral blood mononuclear cell) ratio of 1:20 in at least one donor.
	Recognition of loaded antigen by T cells, as determined by cytotoxicity assay or cytokine production (especially important when antigen is loaded before freezing)
Antigen-loaded state	Only possible when DCs are loaded with well-defined antigens, such as peptides, proteins or RNA
	Antigen-specific stimulation assay: tests ability of antigen-loaded DCs to stimulate antigen-specific T cells (from T-cell lines or reporter cell lines transfected with T-cell receptor and reporter constructs)

The table is adapted from reference number [62].

Recent developments in patented DC-based immunotherapy for various malignancies
Harada Y., et al. *Recent Patents on Regenerative Medicine* 2011.

Manufacturing in nearly full compliance with the recommended SOP as specified in Recommendations from the ISBTc-SITC/FDA/NCI Workshop on Immunotherapy Biomarkers (Butterfield LH, et al. Clin Cancer Res; 17:3064-3076, 2011)

Intellectual property information : Patent pending

Related keywords : Dendritic cells, Cancer vaccine, Pancreatic cancer