

Antigen presenting cell (APC)-targeted hCG β vaccine for cancer therapy

M. Morse¹, R. Chapman², T. Clay¹, T. Osada¹, A. Hobeika¹, J. Green³, T. Davis³, T. Keler³

¹Duke University Medical Center, Durham, NC, ²Henry Ford Health Systems, Detroit, MI, ³Celldex Therapeutics, Inc., Phillipsburg, NJ.

Abstract

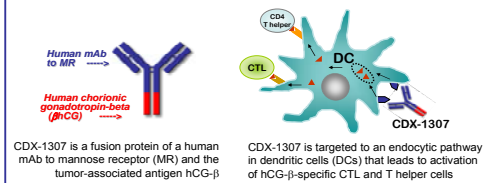
Background: CDX-1307 is a novel vaccine approach designed to target antigens directly into the endocytic compartments of dendritic cells (DCs) and other professional APCs. The β subunit of human chorionic gonadotropin (hCG β) is selectively over-expressed by a number of epithelial tumors and has been reported to correlate with stage of disease and prognosis. We have coupled this tumor-associated antigen to a human monoclonal antibody (B11) that targets mannose receptors on human dendritic cells and macrophages, and have demonstrated the efficacy of this approach in preclinical models using hCG β -expressing tumors and cell lines.

Methods: In this phase I, dose-escalating study, sequential cohorts of 6 patients with relapsed epithelial tumors receive 4 biweekly intradermal injections of CDX-1307 at either 0.3, 1.0 or 2.5 mg, or 2.5 mg concurrent with GM-CSF. Objectives: safety and tolerability; DLT, humoral and cellular immune response, and clinical activity.

Results: Enrollment in the first three cohorts (n=18) is complete with no DLTs. Common potential treatment-related toxicities were injection site reaction (n=5) and fatigue/malaise (n=4), and were generally mild to moderate in severity. One transient Grade 3 generalized allergic reaction in the 1.0 mg cohort was suspected possibly related to either a nut allergy or CDX-1307. One mixed response was seen, with variable effects on circulating hCG β . CDX-1307 localized to dermal macrophages and DCs in post-treatment biopsies.

Conclusions: Administration of CDX-1307 is well tolerated and results in antigen localization in APCs of the skin. Immune response and tumor impact are under evaluation. Further development includes systemic delivery that may provide antigen targeting to a broad APC population, and combination with immunostimulants to generate optimal immune responses.

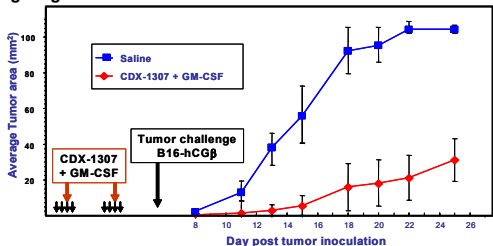
CDX-1307 – mechanism of action



Advantages of APC-Targeting

- Efficacy**
- > Strong binding and specific delivery to DCs in vivo
 - > Robust immune responses
- Manufacturing**
- > Uses standard mAb production & purification
 - > Well-characterized product
 - > Not patient specific
 - > Low clinical dose requirements

Targeting to Dendritic Cells in vivo Generates Anti-Tumor Immunity



Rationale for targeting hCG β in cancer immunotherapy

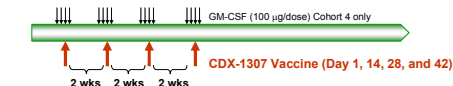
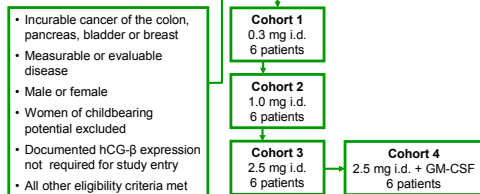
- > hCG β is overexpressed by common cancers and not found in most normal tissues
- > Elevated hCG β expression is associated with a poor outcome in several cancers
- > Humoral response to hCG β is associated with improved survival in colorectal patients (Moultan HM et al., *Clin. Can. Res.* 8: 2044, 2002)
- > hCG β is structurally similar to TGF β and in vitro studies suggest that it may help prevent apoptosis in bladder cancer cells

Frequency and significance of hCG β expression by selected epithelial cancers

Tissue of origin	hCG β (in serum or urine)	hCG β (tissue IHC)	Prognostic value (number of studies)
Bladder	60% (n = 461)	35% (n = 104)	Yes (2)
Breast	19% (n = 72)	57% (n = 131)	No (1)
Colorectal	17% (n = 436)	41% (n = 732)	Yes (4)
Pancreas	48% (n = 196)	56% (n = 107)	Yes (3)

Adapted from R.K. Iles / *Molecular and Cellular Endocrinology* 260-262 (2007) 264-270 265

Clinical Study Schema



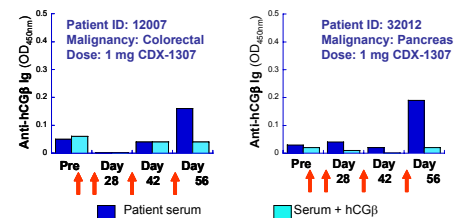
Patient Characteristics

	0.3 mg n=6	1.0 mg n=6	2.5 mg n=6	2.5 mg + GM-CSF n=3
Median age (years)	64	56	60	63
Male (N [%])	4 (67%)	3 (50%)	6 (100%)	2 (67%)
Primary cancer (N [%])				
Pancreatic	3 (50%)	1 (17%)	2 (33%)	0 (0%)
Colorectal	1 (17%)	5 (83%)	4 (66%)	2 (66%)
Other	2 (33%)	0 (0%)	0 (0%)	1 (33%)
Number of previous anticancer regimens (mean [range])	2.5 (2-4)	4.0 (2-6)	3.5 (2-5)	4.3 (3-6)
Years from diagnosis to study entry (mean)	2.9	2.8	3.9	4.6

Anti-hCG β Immune Responses

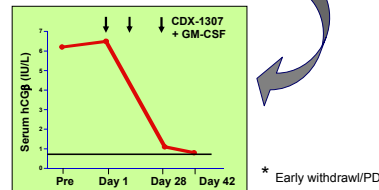
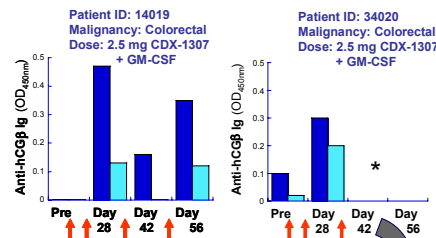
Cohorts 1-3 (CDX-1307 alone):

- > Most patients did not demonstrate significant anti-hCG β immune responses
- > 2 patients developed anti-hCG β responses after 4 doses



Cohort 4 (CDX-1307 + GM-CSF):

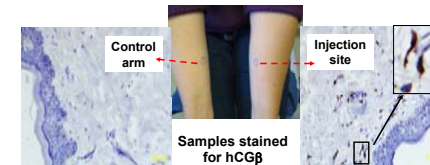
- > 2 of 3 patients developed significant anti-hCG β immune responses after 2 doses
- > In one patient the immune responses was coincidental with a drop in serum hCG β



Cellular immune responses to hCG β (ongoing)

Analysis of cryopreserved PBMC from pre and post timepoints with ELISPOT, CFC, and proliferation assays using hCG β overlapping peptide pool.

Targeted delivery in vivo



Skin punch-biopsies taken from injection site and opposite limb 48 hours after CDX-1307 injection (1 mg, i.d.)

Adverse events potentially related to treatment

Body System / Event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Fatigue	3 (16.7%)		1 (5.6%) ¹
Injection site reaction (erythema, irritation, pain)	8 (44.4%)		
Hypersensitivity			1 (5.6%) ¹
Blood alkaline phosphatase increased			1 (5.6%) ¹

Data presented for first three cohorts. Table excludes Grade 1 events occurring in a single patient.
¹ Events occurred in the same patient.

Clinical Findings

- > >60% of patients exhibited elevated levels of serum hCG β .
- > One patient (pancreatic cancer) had a mixed response (26% reduction in lesions), other patients have progressed.
- > One patient with a humoral immune response experienced an acute reduction in circulating hCG β .

Summary

- ✓ Administration of CDX-1307 is well tolerated.
- ✓ Intradermal administration of CDX-1307 results in hCG β localization in antigen-presenting cells of the skin.
- ✓ Initial data suggest that the addition of GM-CSF markedly enhances immune responses to hCG β (completion of the fourth cohort is pending).
- ✓ IV administration that may provide antigen targeting to a broad APC population is currently in a phase I clinical trial.