



# **Interleukin 17E (IL-17E)**

## **PRODUCT PROFILE**

**Non-Confidential**

### **LORUS THERAPEUTICS, INC.**

2 Meridian Road  
Toronto, Ontario, M9W 4Z7  
CANADA

Tel: (416) 798-1200

Fax: (416) 798-2200

Web: [www.lorusthera.com](http://www.lorusthera.com)

## Product Overview

IL-17E (IL-25) is a recently identified proinflammatory cytokine that induces a Th2-type immune response, including the expansion of eosinophils through the production of IL-5. Lorus has discovered that recombinant human IL-17E has potent anticancer properties against a range of solid tumors in vivo, including human melanoma, pancreatic, colon, lung, ovarian and breast tumor models. Furthermore, in comparison with the efficacies of standard chemotherapeutic drugs administered concurrently, the anti-tumor activity of IL-17E was equal or superior to bevacizumab, irinotecan, gemcitabine, erlotinib, docetaxel, cisplatin and paclitaxel. These studies suggest that recombinant IL-17E has strong potential as a cancer immunotherapy.

## Preclinical evaluation of IL-17E

IL-17E is currently in preclinical development. Lorus has completed anti-tumor efficacy studies on IL-17E in mouse models of human tumors, and has done preliminary evaluation of toxicity with doses that exceed efficacious doses. As well, initial studies have been done on the anti-tumor mechanism of action of IL-17E in vivo, as described below.

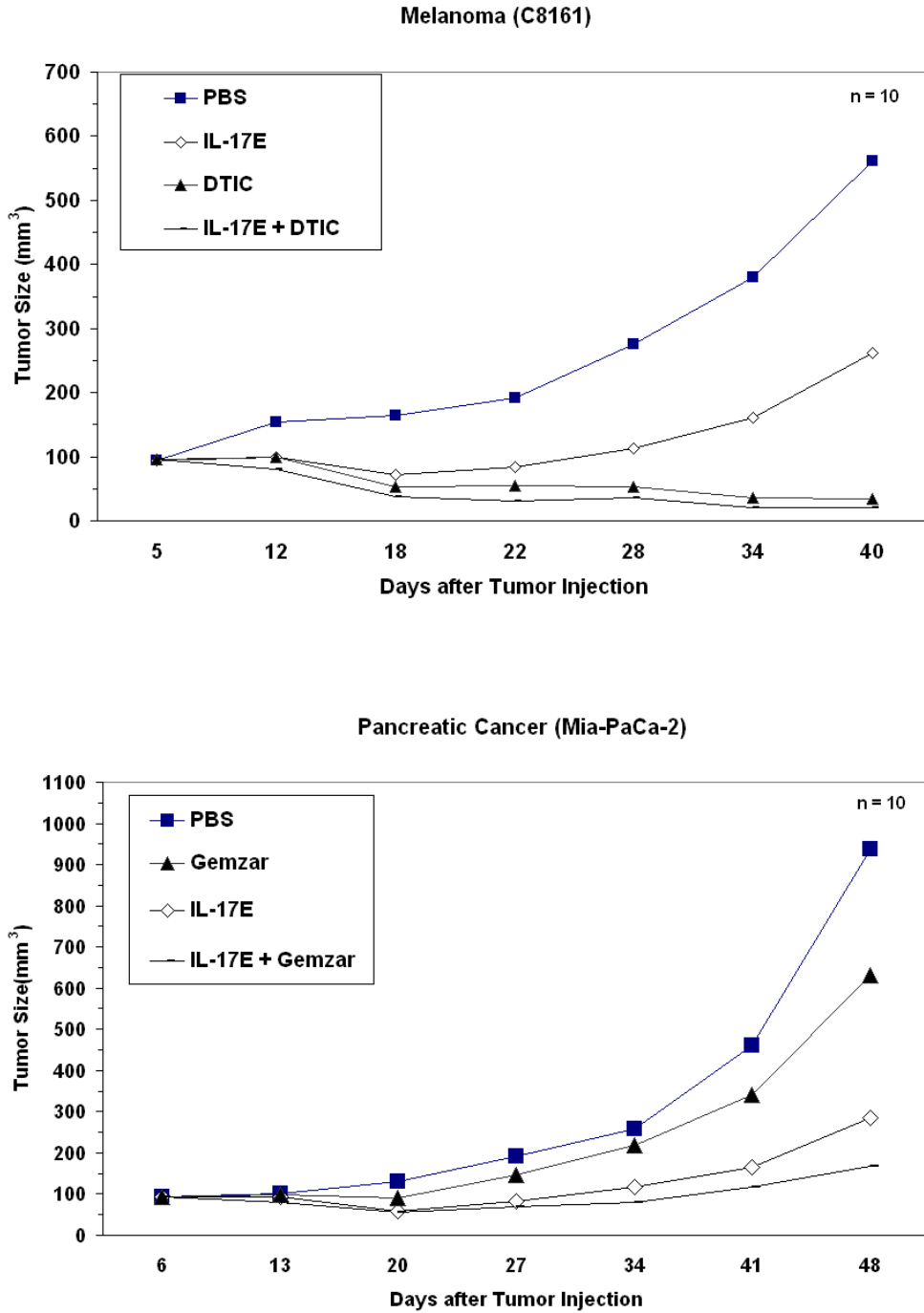
*Efficacy.* Lorus has completed efficacy studies in several solid tumor models in vivo with IL-17E, both as a monotherapy and in combination with chemotherapeutic agents. IL-17E shows exceptional in vivo anti-tumor activity in a variety of mouse models of human solid tumors, including lung cancer, breast cancer, malignant melanoma, colon cancer, and pancreatic cancer (1). Figure 1 illustrates the potent anti-tumor activity of IL-17E alone or in combination studies in mice harboring human malignant melanoma and pancreatic cancer xenografts. As shown below, IL-17E treatment induced regression in these tumor models.

*Toxicity.* No significant toxicity (lethality or decreased body weight) has been observed with IL-17E, in conjunction with efficacy studies in nude mice (1, 2). Formal IND-enabling, dose-escalation studies are planned to fully examine IL-17E-related toxicities.

*Mechanism of Action.* Two distinct anti-cancer mechanisms have been described for IL-17E:

1. Immune modulation. IL-17E stimulates the production of the cytokine IL-5, leading to activation and tumor infiltration of eosinophils that have direct and indirect anti-tumor activities. Tumor-bearing mice treated with IL-17E showed a significant increase in serum levels of IL-5, as well as increased numbers of eosinophils in peripheral blood, spleen and tumors, as compared to tumor-bearing control mice. IL-17E-treated mice also show a significant increase in the number of splenic B-cells in vivo and activation of B cell signaling pathways (1).
2. Direct cytotoxic activity. IL-17E has direct cytotoxic activity against cancer cells that express the IL-17E receptor. Recent studies have demonstrated that IL-17E is significantly more active against breast cancer cells that express IL-17E receptor compared to normal breast cells lines expressing low levels of this receptor. Cytotoxic activity of IL-17E is mediated through induction of apoptosis through receptor-mediated caspase activation (2).

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**Figure 1.** Antitumor activity of human IL-17E against malignant melanoma and pancreatic cancer xenografts, alone and in combination with cancer therapeutics. Plots show sizes of tumor sizes (mm<sup>3</sup>) in CD-1 mouse models over the course of the study. For each study, hIL-17E was administered by intravenous (i.v.) injection at 0.04 mg/kg every two days. Dacarbazine (DTIC) was given at 80mg/kg/mouse, 1X per week, by intraperitoneal injection. Gemcitabine was given at 100 mg/kg, 1X per week, by i.v. injection. For combination studies, each agent was administered

at the same dose level used for single-agent experiments. Control groups were given 100 ul PBS by i.v. injection every two days. All treatments were administered for the duration of the study.

### **IL-17E Clinical Development Path**

Lorus Therapeutics is planning to advance IL-17E through a preclinical IND-enabling program to support Phase I cancer trials. The Phase I clinical trial aims to establish safety, recommended phase II dose (RP2D) and demonstrate proof of biological activity. Whilst the detail of the design will be dependent on the pre-clinical data Lorus envisages a two stage approach with: 1. an initial dose finding study in a classical phase I patient population to identify RP2D and 2. a subsequent expansion cohort to further characterize safety and tolerability of the chosen dose and demonstrate proof of biological activity through matched pre- and post-treatment assessment of serum, peripheral blood mononuclear cells (PBMC) ± tumor biopsies. Lorus has completed efficacy studies in several solid tumor models in vivo with IL-17E, both as a monotherapy and in combination with chemotherapeutic agents. IL-17E shows in vivo anti-tumor activity in a variety of mouse models of human solid tumors, including lung cancer, breast cancer, colon cancer, ovarian cancer with regression shown in malignant melanoma and pancreatic cancer. Pancreatic cancer and malignant melanoma have been chosen as lead cancer indications for initial testing of IL-17E in clinical studies. The choice of these cancer types is based primarily on strong anti-tumor efficacy of IL-17E in preclinical studies.

### **Cancer indications proposed for IL-17E clinical studies**

#### **1. Advanced pancreatic cancer**

Pancreatic cancer is the fourth most common cause of cancer death in the US, with 37,390 Americans expected to succumb to the disease in 2012. (3). An estimated 43,920 new cases of pancreatic cancer will be diagnosed in the US this year. It is a difficult-to-treat tumor type with an overall five-year survival rate of 6%, the lowest for any cancer (3). Few drugs are approved for the treatment of pancreatic cancer. The current gold standard for first-line therapy, gemcitabine, provides a median overall survival of 5.7 months. Another drug, erlotinib, was approved based on a survival benefit of two weeks and a one-year survival increase from 19% to 24% when combined with gemcitabine. An older chemotherapy drug, 5-FU, has become redundant due to its side effect profile. Pancreatic cancer clearly has a high unmet need for new, efficacious and safer therapies.

#### **2. Malignant melanoma**

Melanoma is the fifth most common cancer in the US (3), with an estimated 76,250 new cases expected to be diagnosed in 2012. Approximately 9,180 Americans will die from malignant melanoma this year. Chemotherapeutic agents such as dacarbazine and dacarbazine-combinations have unfavorable side effect profiles. Cytokine-based therapies such as interferon-alpha 2b and interleukin-2/aldesleukin produce durable though modest responses in a small percentage of patients, again with significant toxicities. The combination of high-dose IL-2 and dacarbazine produces higher response rates but does not show superior overall survival compared to chemotherapy alone and is associated with significant toxicity (4). Two recent approvals for late-stage melanoma, ipilimumab and vemurafenib, represent a more targeted approach but an urgent need remains for safer and more effective therapies for malignant melanoma of all stages.

#### **3. Other solid tumors**

IL-17E has also shown potent anticancer properties against a range of other solid tumors, including colon, non-small cell lung, ovarian and breast tumor models with very low toxicity.

- US 2012 statistics:

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- Non-small cell lung cancer: Incidence: 192,200 / mortality : 136,300
- Colon cancer: Incidence: 103,170 / mortality : 51,690
- Ovarian cancer: Incidence: 22,280 / mortality : 15,500
- Breast cancer: Incidence: 229,060 / mortality: 39,920

### **IL-17E administration and biomarker strategy for IL-17E in a clinical setting**

In clinical studies, IL-17E would be administered by intravenous or subcutaneous injection every other day for the duration of treatment, based on dosing in preclinical efficacy studies. A relevant biomarker for clinical studies is serum IL-5, since this cytokine is part of the IL-17E anticancer mechanism of action and is induced in a dose-response manner in a melanoma tumor model following treatment with IL-17E (1).

### **Competitive Environment**

Cytokines, and interleukins especially, are actively being developed as cancer therapies. These include a variety of non-targeted cytokines that stimulate the immune system (e.g. IL-7, IL-12, IL-18), as well as modified versions of approved cytokine drugs. IL-17E has potential advantages compared to other cytokines currently in development for cancer therapy. For example, cytokines that show anti-tumor activity often need to be further optimized to reduce toxicity or enhance efficacy (5, 6). By contrast, IL-17E has an acceptable therapeutic index and should be suitable as a systemic therapy without the need for further optimization or modification. In addition, the contemplated clinical use for many anticancer cytokines is not clear, and many anticancer cytokines are envisioned either as adjuvants for cancer vaccines or as T-cell growth factors for adoptive T-cell regimens, rather than being used on their own as cancer therapies (7). IL-17E has a clear development path as a cancer therapeutic for treatment of many solid tumor types, based on its potent preclinical efficacy and anti-cancer mechanism of action.

### **Intellectual Property**

IL-17E is protected by patent applications that are pending in Canada, Europe and the US (based on International Application No. PCT/CA06/00311; Filed March 8, 2006). Patent claims cover IL-17E as a pharmaceutical composition to treat cancer, and the use of IL-17E to treat cancer indications, alone and in combination with chemotherapies and immunotherapeutic drugs.

Lorus licensed the global IP rights to IL-17E from Genentech in May 2012.

### **Key Concepts for IL-17E clinical development**

Based on our analysis and data, Lorus is confident that IL-17E has potential as a novel therapeutic for solid tumors, and is well positioned for success in advanced pancreatic cancer and malignant melanoma in particular. Several key factors support the development and future commercialization of IL-17E in these cancers:

- Strong preclinical antitumor data with no apparent toxicity at efficacious doses
- Equal or superior antitumor activity compared to approved cancer therapies
- Novel mechanism of action
- Minimal competition in this class of drugs, especially in advanced pancreatic cancer
- Biomarker strategy based on measurement of serum IL-5
- Long patent life
- Significant potential for use in combination therapies
- Strong market potential

**References**

1. Benatar T, et al. (2010). *Cancer Immunol Immunother* 59:805-17
2. Furuta S, et al. (2011). *Sci Transl Med.* 13:78ra31.
3. *Cancer Facts & Figures 2012.* American Cancer Society.
4. Bhatia S, et al. (2009). *Oncology (Williston Park).* 23(6):488-96.
5. Margolin K. (2008). *Expert Opin Biol Ther.* 8:1495-505.
6. Shaker MA, et al. (2009). *J Pharm Sci.* 98:2268-98.
7. Cheever MA. (2008). *Immunol Rev.* 222:357-68.