



WPD 
Pharmaceuticals

WPD101 Program RnD Results Presentation



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Overview

The solution's breakthrough is based on GBM-targeted therapy against IL-13RA2 and EphA2 - brain tumor-specific receptors conjugated with bacterial cytotoxins. It is well known that interleukin-13 receptor alpha 2 (IL-13RA2) is a glioblastoma receptor that is abundantly overexpressed in GBMs but absent in normal brain tissue. It is estimated that IL-13RA2 overexpression is reported in >50% of GBM cases. Similarly, EphA2 is a cancer-specific receptor recognized by ephrin A1 cytokine. Its overexpression is also a hallmark of GBM cells. Thus, EphA2 receptors are proposed targets (Wykosky et al., 2005, 2007, Ferluga et al., 2016). Its overexpression is confirmed in the majority of GBM specimens. It is assumed that over 90% of GBM overexpressed at least one of the receptors (Wykosky et al., 2008). Other tumors also express IL-13A2 and EphA2 receptors.

Epidemiology – glioblastoma



Glioblastoma is the most aggressive malignant primary brain tumor. Incidence rate - **3.19 per 100,000 persons** in the United States



15 months - average patient survival rate after glioblastoma diagnosis if cancer is treated

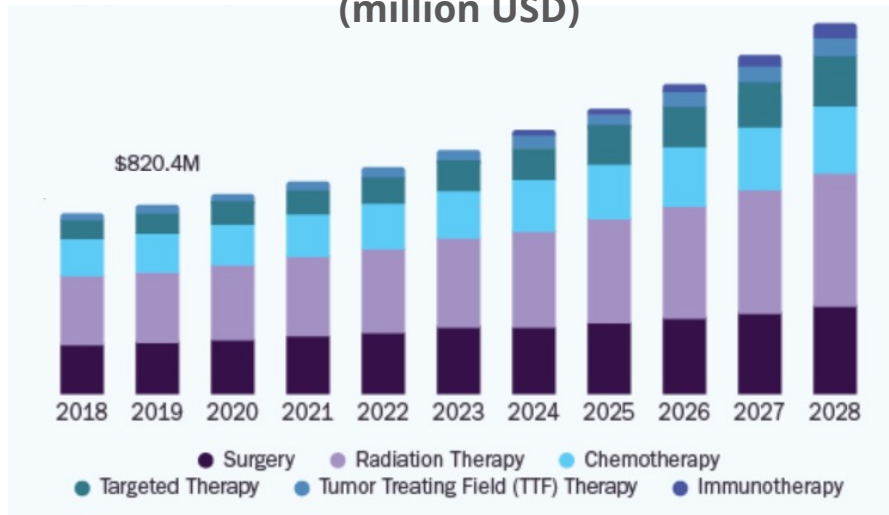
3-4 months – average patient survival rate after diagnosis - no treatment



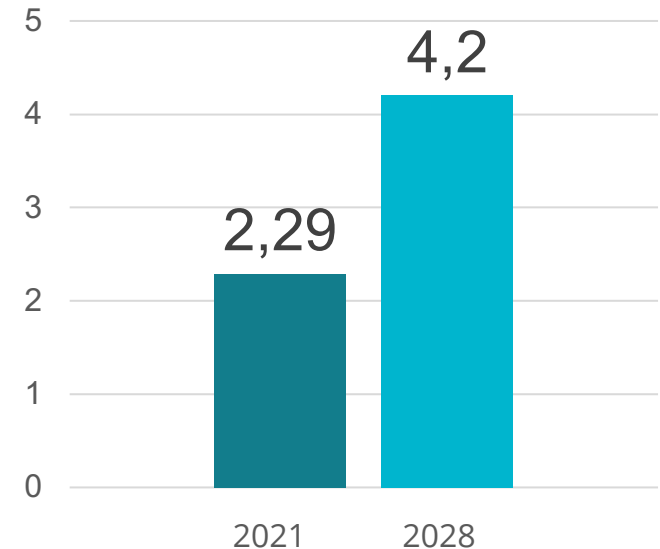
Almost **100% of cases**, recurrence of the disease occurs after about **10 months** after treatment. The patient lives an average of **9 months** after a recurrence.

Glioblastoma market

US GBM treatment market (million USD)



Global GBM treatment market (billion USD)



Almost 100% GBM will recur locally within 2 years after surgical and radiation therapy (60 Gy/30 fractions) with concomitant and adjuvant temozolomide

Current status

WPD101 is currently in the preclinical stage of development. Its consistent anticancer properties are demonstrated and validated in dogs with spontaneous GBM resembling GBM in human patients. The canine model of spontaneous gliomas represents the closest translational model to human diseases and provides a potentially more clinically relevant assessment of potential efficacy in human trials regarding biological and technological aspects of treatment (Figure 3). Canine gliomas and human GBM cells overexpress tumor-associated IL-13RA2 and EphA2 receptors that are not present in normal brain cells. IL-13RA2 and EphA2 are conjointly present in >90% of patients and dogs with GBM. The preliminary preclinical study in mice led to the safe dose determination on the 50 ug/ml (repeated dose study).

Mechanism of action

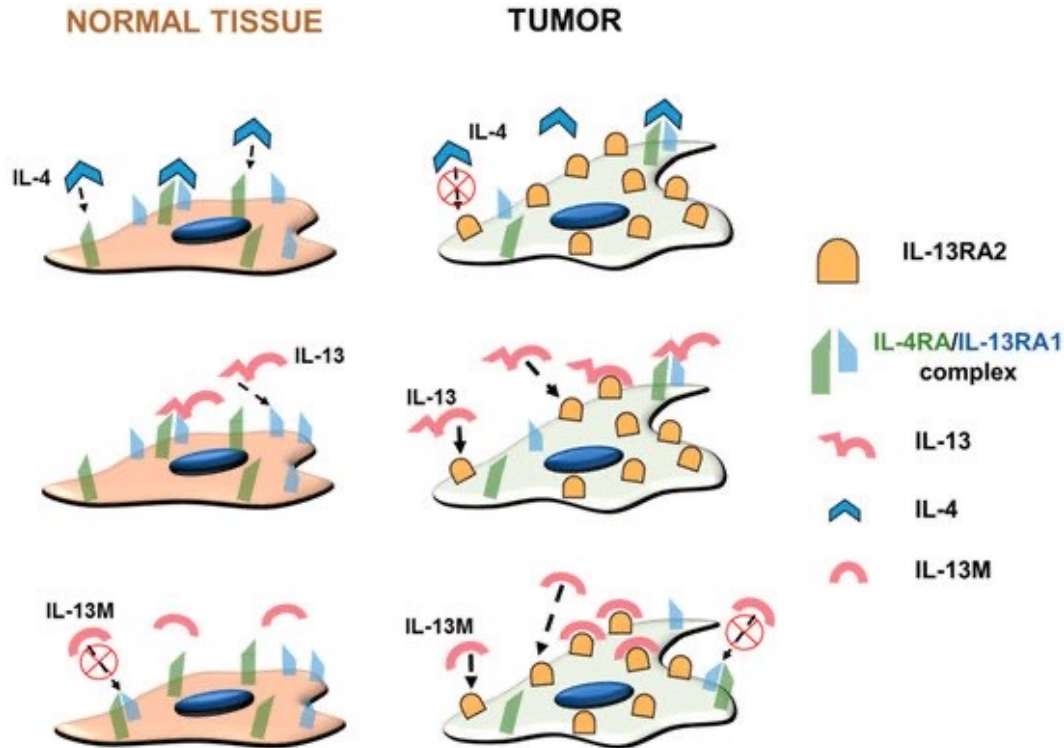


Figure 1. A schematic of the IL-13 receptor system. Normal and tumor cells express IL-4RA/IL-13RA1. IL-4 first binds to IL-4RA, then to the IL-13RA1 in normal cells. On the other hand, IL-13RA2 is expressed by tumor cells. IL-4 binds to IL-4RA/IL-13RA1 but not IL-13RA2. IL-13 binds more readily to IL-13RA2 compared to IL-4/IL-13RA1. By introducing mutations in the IL-13 ligand – IL-13M, the ligands bind primarily to the IL-13RA2.

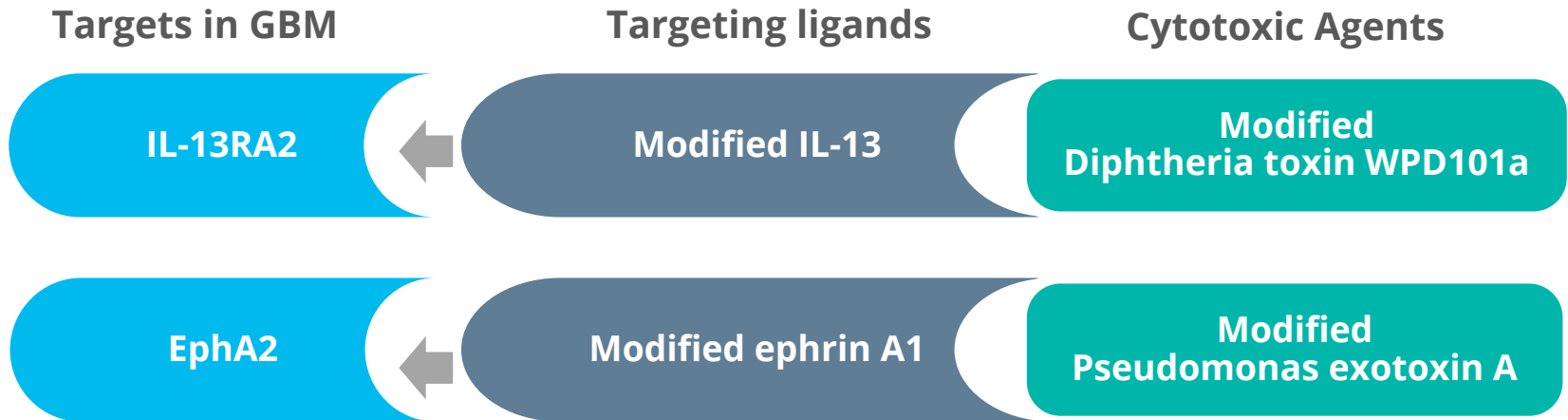
Source: <https://www.mdpi.com/1422-0067/19/11/3326>.

Development strategy

Immunotoxins are fusion proteins comprised of a toxic moiety and a targeting moiety. That allows the concentration of the fusion protein at the plasma membrane of specific cell types.

WPD101 is a unique drug cocktail composed of two immunotoxins targeting IL-13RA2 (WPD101a) and EphA2 (WPD101b) receptors simultaneously. This strategy guarantees specific drug administration to the majority of GBM cells.

Furthermore, to increase tissue distribution, minimize possible side effects, and overcome BBB difficulties, Convection-Enhanced Delivery (CED) of WPD101 directly to the brain tumor will be applied (Debinski and Tatter, 2009).



Mechanism of action

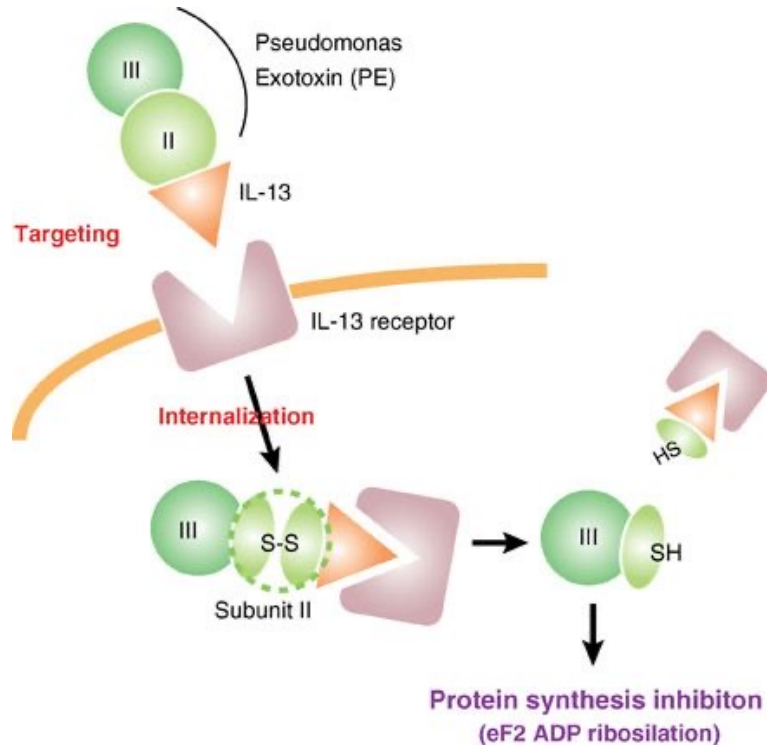


Figure 2. A schematic of the IL-13-based immunotoxins action. IL-13 conjugated to bacteria toxin specifically recognizes and binds to its IL-13RA2 receptor. Receptor-ligand complex is internalized and transported within the cell. Further, bacteria toxin is released and inhibits protein synthesis, leading to intrinsic cell death induction.

Source: https://doi.org/10.1007/978-3-540-4748-1_1476

Gene expression pattern

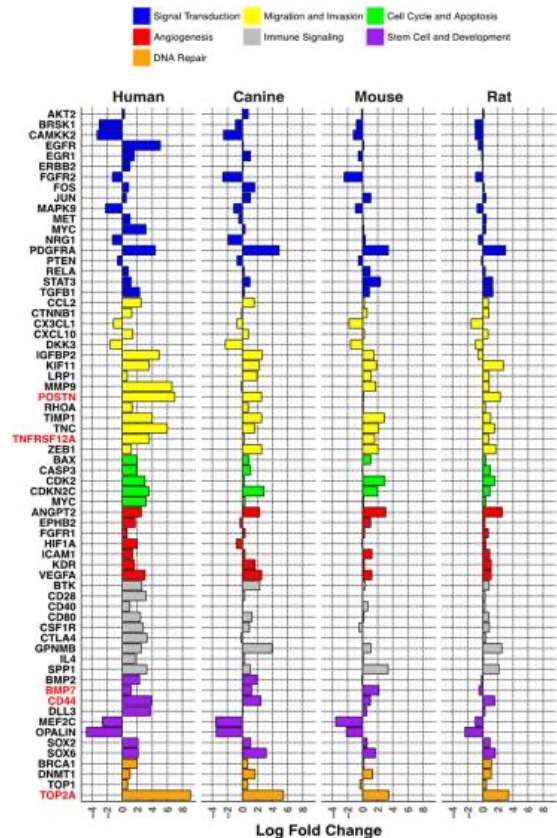


Figure 3. Comparative transcriptional analysis of GBM signature gene expression patterns in human, canine, mouse and rat samples.

Scientific Advice in MHRA

In July 2020, WPD consulted MHRA in Scientific Advice procedure to discuss quality, non-clinical and regulatory aspects of WPD101a for the treatment of glioblastoma multiforme. MHRA accepted WPD drug development plan.



Medicines &
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MHRA

The Phase I clinical trial in dogs with spontaneous malignant gliomas

JOURNAL ARTICLE

Phase I trial of convection-enhanced delivery of IL13RA2 and EPHA2 receptor targeted cytotoxins in dogs with spontaneous intracranial gliomas

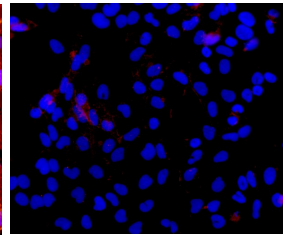
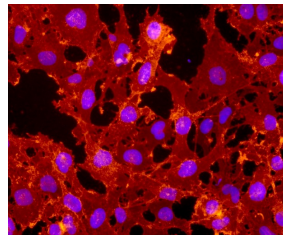
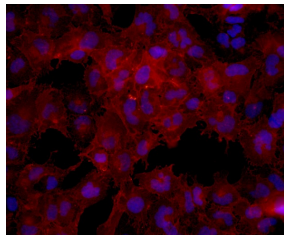
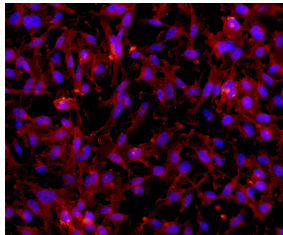
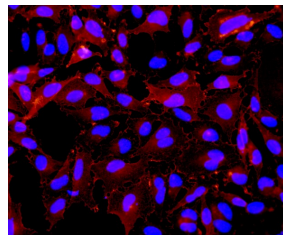
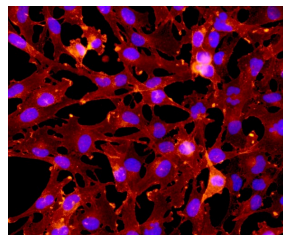
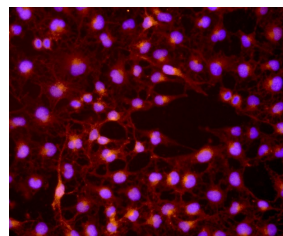
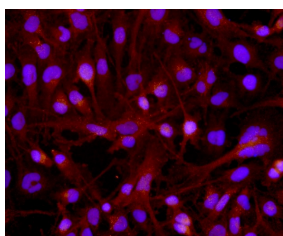
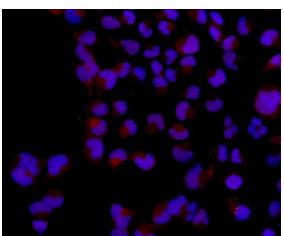
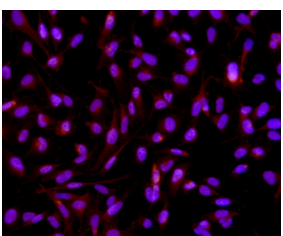
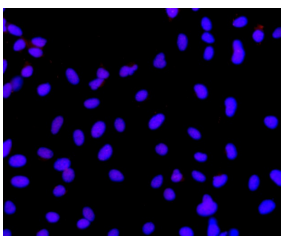
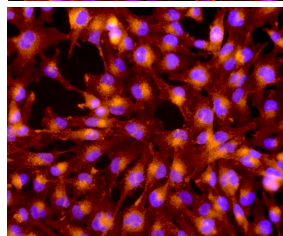
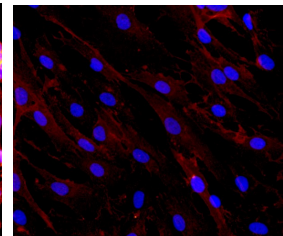
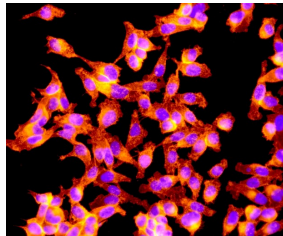
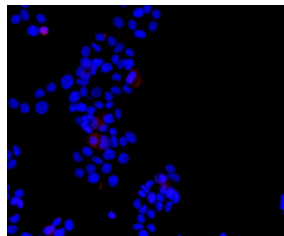
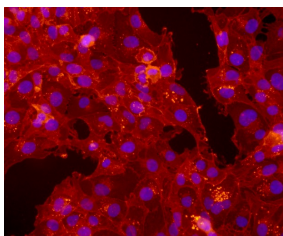
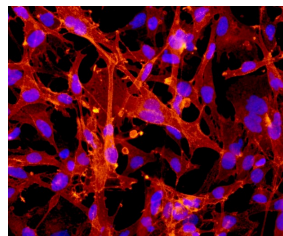
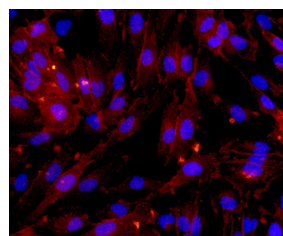
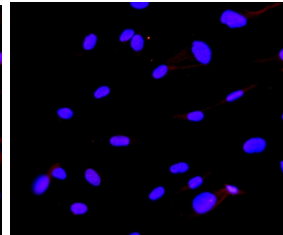
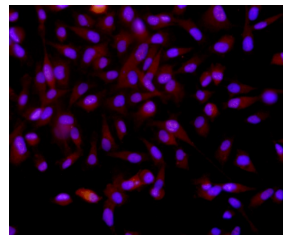
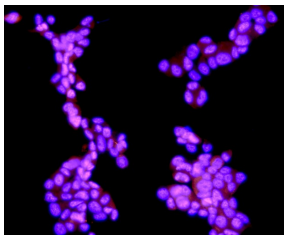
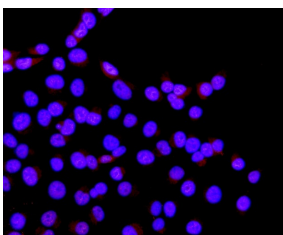
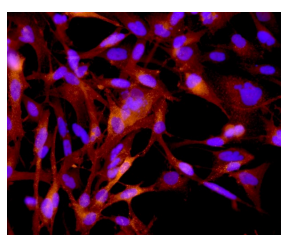
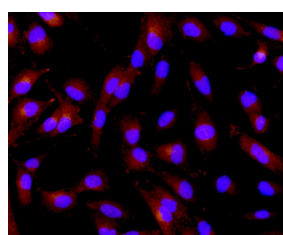
John H Rossmeisl , Denise Herpai, Mindy Quigley, Thomas E Cecere, John L Robertson, Ralph B D'Agostino, Jonathan Hinckley, Stephen B Tatter, Peter J Dickinson, Waldemar Debinski 

Neuro-Oncology, Volume 23, Issue 3, March 2021, Pages 422–434,
<https://doi.org/10.1093/neuonc/noaa196>

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In the published study, 17 dogs diagnosed with glioma and immunohistochemically positive for IL-13RA2 (17/17) or/and EphA2 (11/17) receptors were treated with escalating doses of IL-13- and ephrinA1-based cytotoxins. Cytotoxins were delivered through the Convection Enhanced Delivery (CED) method. CED allowed consistent intratumoral delivery of the cocktail with a median coverage of 70% (range 40-94%) of the tumor. No dose-limiting toxicities were observed. At 42 days of treatment, volumetric tumor reductions were observed in 15/16 dogs, with a median reduction of 42% (range 5-94%). Objective tumor responses were observed in 8/16 (50%) dogs, and the median tumor volume reduction was 79% (range 65-94% of tumor volume regression).

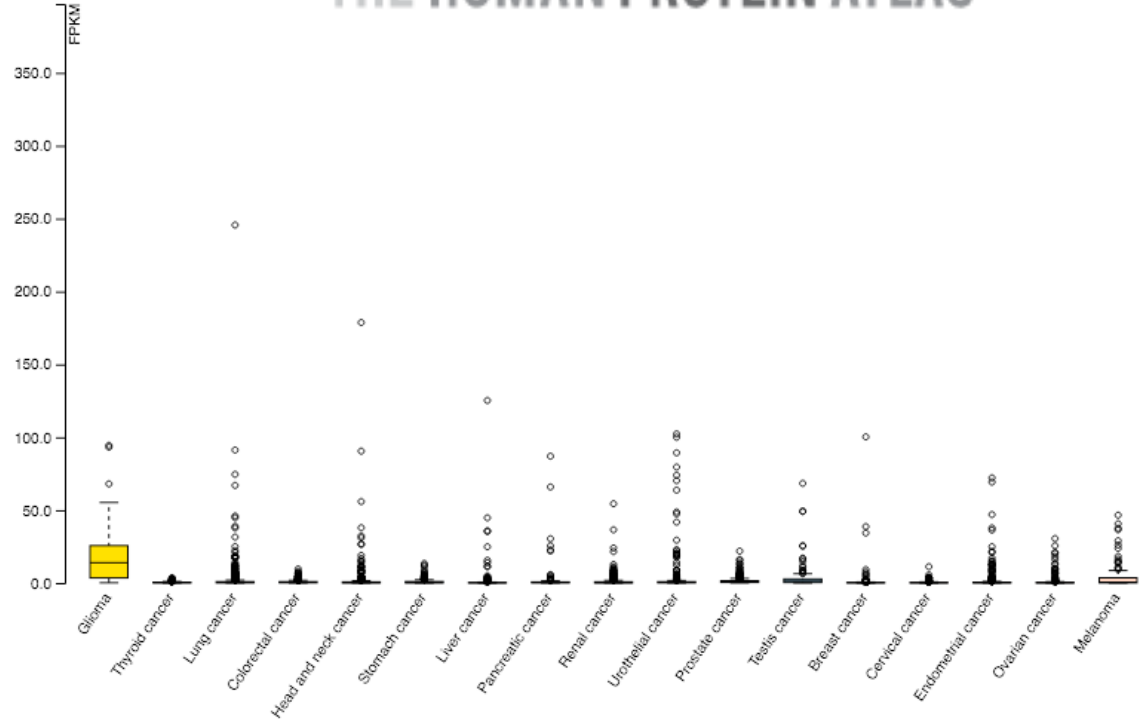
The authors conclude that the CED of IL-13RA2/EphA2 targeting cytotoxins at concentrations ranging from 0.05-1.6 ug/mL was safe and resulted in clinically relevant responses in 50% of dogs with gliomas.

U-251**LN-229****SNB-19****T98G****U-373****H4****EphA2****IL-13RA2****BTCOE 4536****BTCOE 4795****MDA-MB-231****T47D****PC-3****fibroblasts****EphA2****IL-13RA2**

IL-13RA2 expression in tumor tissues

THE HUMAN PROTEIN ATLAS

An elevated level of IL-13RA2 has been reported in various cancer types. However, only in glioma its overexpression is statistically significant.

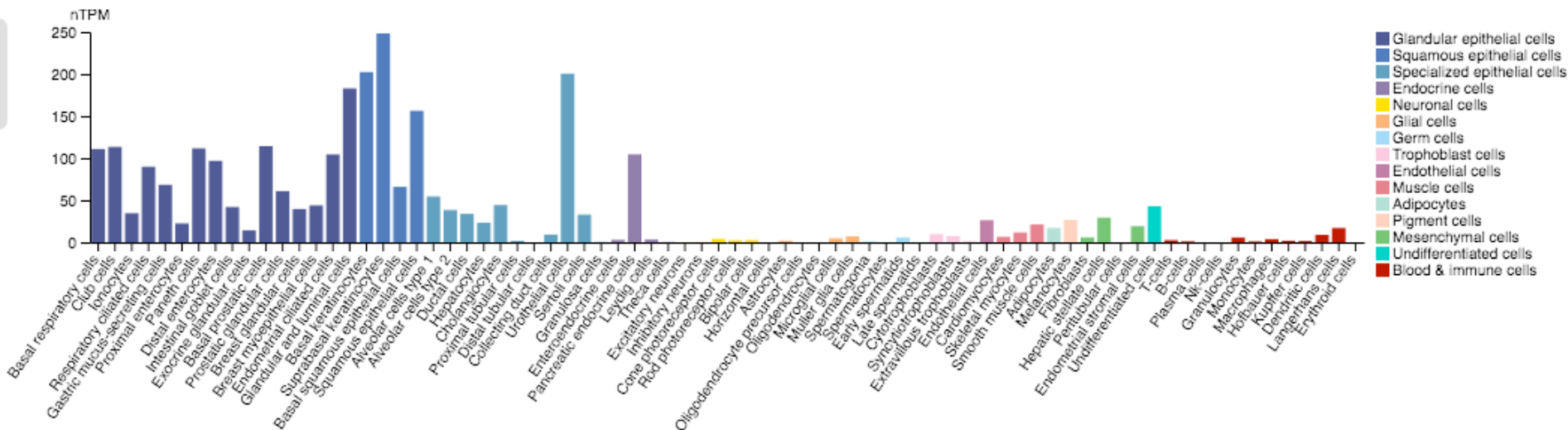


EphA2 expression in normal tissues

Single cell types

RNA single cell type specificity: Cell type enhanced (Suprabasal keratinocytes, Basal keratinocytes, Urothelial cells, Glandular and luminal cells, Squamous epithelial cells)

Group Expression Alphabetical



In normal tissue EphA2 is expressed in keratinocytes, urothelial cells, epithelial cells. Thus, the systemic administration of IL-13RA2-targeting immunotoxins could be limited.

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