AGX101- A novel TM4SF1-directed ADC for the treatment of solid tumors

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Abstract

Angiex is developing a TM4SF1-directed ADC, AGX101, which is entering Phase 1 trials. TM4SF1 is a novel ADC antigen that is highly expressed in tumor cells and tumor associated vascular endothelium. TM4SF1 is differentiated from other ADC targets by its internalization via microtubules to the nucleus. AGX101 has been shown to be potent both *in vitro* and *in vivo*, with an EC50 between 10-100 pM against various cell lines, and complete tumor regressions in multiple human tumor xenograft models in mice. AGX101 is the first in Angiex's pipeline of Nuclear Delivery Antibody-Drug Conjugates™, and proof of concept for Angiex's Nuclear Delivery Platform™.

Background

TM4SF1 (Transmembrane-4 L-six family member-1), a small membrane with tetraspanin topology, is a solid tumor antigen that is characterized by its (a) high expression in tumor cells originated from solid tumors[1,3] and tumor endothelium but low expression in normal endothelium[1,2,4], and (b) internalization to the nucleus via microtubules[6]. This unusual expression pattern and unique internalization pathway enable TM4SF1 to be leveraged as an ADC target with a dual mechanism of action[1-5].

TM4SF1 enables two hallmarks that render cancer lethal, inducing angiogenesis[2,4] and activating invasion and metastasis[3]. The induction of angiogenesis enables unlimited growth potential to the tumor. Invasion and metastasis play a critical role in turning cancers from benign to malignant. Furthermore, high TM4SF1 expression correlates with early mortality across the majority of solid tumors.

AGX101 is a novel TM4SF1-directed antibody-drug conjugate (ADC) engineered to have a drug-to-antibody ratio (DAR) of 2 via site specific conjugation of a tubulin inhibitor payload. AGX101 is highly potent in vitro and effectively regresses tumors in vivo. AGX101 is now entering the clinic and is expected to dose its first patient in Q4 2022.

TM4SF1 is highly expressed in most solid tumors

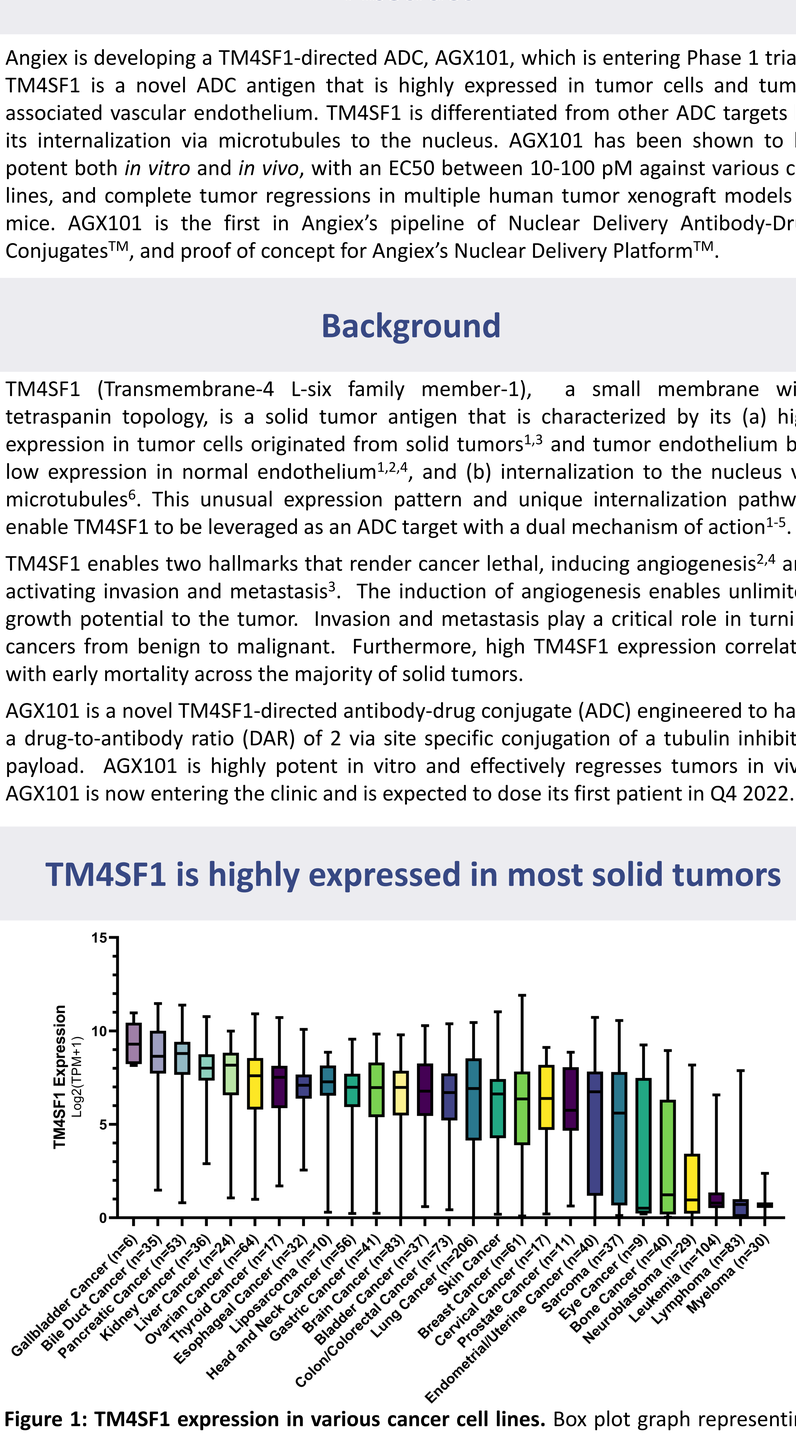

Figure 1: TM4SF1 expression in various cancer cell lines. Box plot graph representing single cell TM4SF1 RNA-seq expression from the Cancer Cell Line Encyclopedia among various cancer cell lines and grouped into cancer types. Data adopted from DepMap Public 22Q2 primary files[7].

Angiex ADCs interacts tumor cells and tumor vascular endothelium with minimal binding to normal tissue

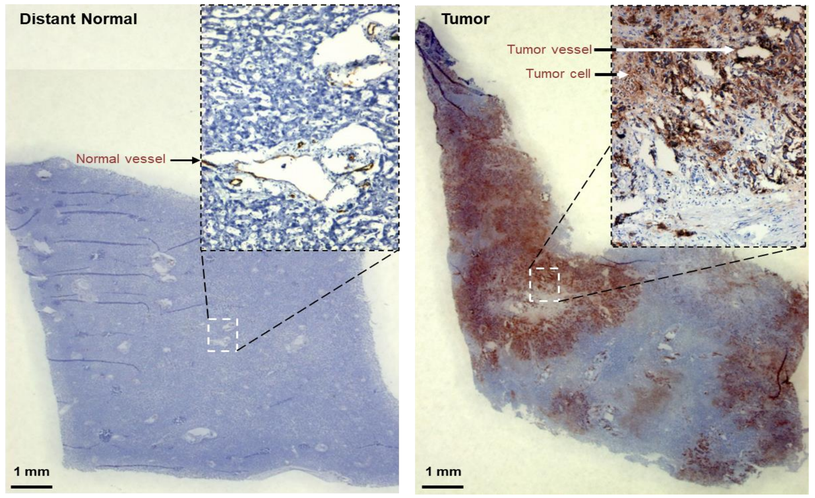

Figure 2: TM4SF1 is highly expressed in both tumor cells and tumor vascular endothelial cells. Distant normal and tumorous liver tissue sections were stained for TM4SF1 using Angiex antibodies. IHC showed very strong TM4SF1 staining on tumor cells and tumor vascular endothelial cells, but minimal TM4SF1 staining in distant normal tissue.

Angiex ADCs follow a novel internalization pathway from cell membrane to nucleus

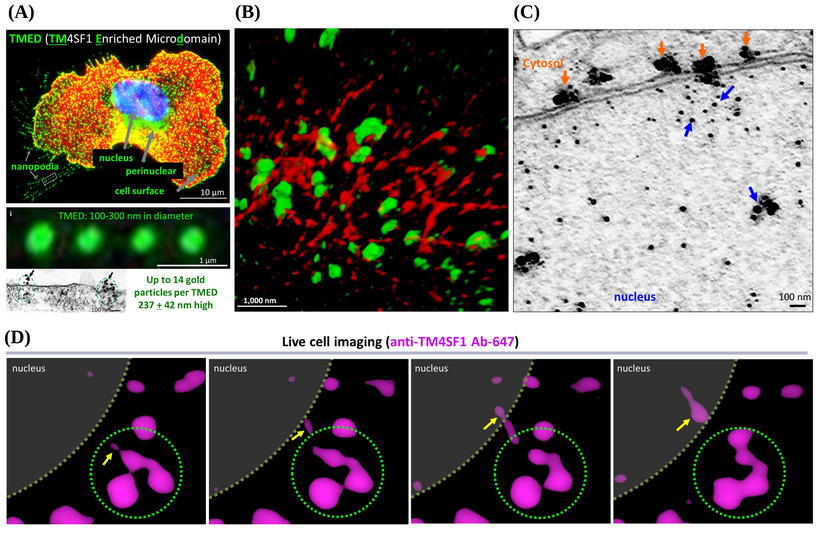

Figure 3: Nuclear trafficking of TM4SF1-enriched microdomains (TMED). Representative images in HUVEC reveal that TM4SF1 forms cell surface microdomains TMED **(A),** internalizes along microtubules **(B),** and enters the nucleus **(C)**. Sequential images acquired via live cell imaging demonstrate TMED entering the nucleus **(D)**.

AGX101, Angiex's lead drug, is highly potent *in vitro* against both endothelial cells and tumor cells

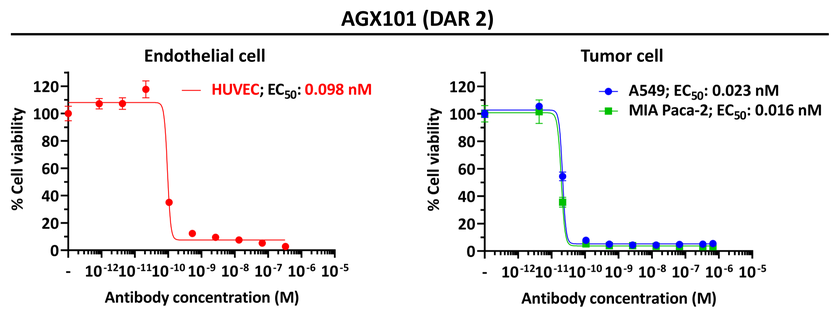

Figure 4: *In vitro* potency of AGX101. AGX101 showed picomolar potency in both endothelial cells (HUVEC) and tumor cells (A549 lung and Mia PaCa-2 pancreatic).

AGX101 is highly effective *in vivo*

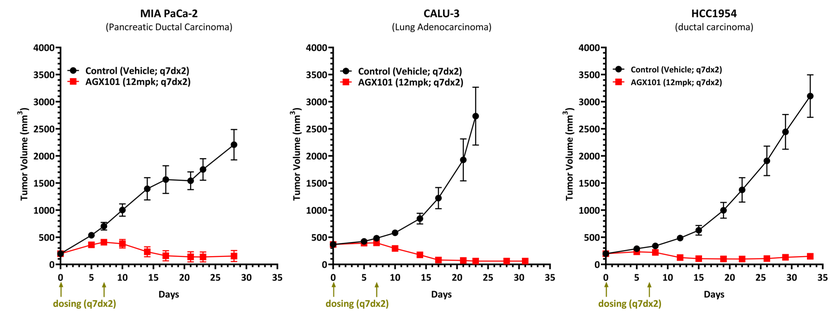

Figure 5: *In vivo* efficacy of AGX101 against human tumor xenografts. Mice bearing either MIA PaCa-2, CALU-3, or HCC1954 tumors were treated with either vehicle control or AGX101 at 12 mg/kg q7dx2. Systemic injection of AGX101 induced effective tumor regressions in all 3 human xenograft models. The tumor regression study was conducted by CrownBio.

Conclusion

A Phase 1 Dose Escalation/Safety Study of AGX101 is opening and recruiting an "All Comers" solid tumor patient pool. The primary objectives are to determine the maximum tolerated dose (MTD), to characterize dose-limiting toxicities (DLTs), and to determine a recommended Phase 2 dose (RP2D). Additional objectives include an evaluation and characterization of PK, assessment of disease response and evaluation of predictive markers for success. In addition to providing insight on further development of AGX101, this trial will serve as proof of concept for the Nuclear Delivery Platform™.

References:

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