

A Phase I Trial of FAP-Exd (AVA6103), a Fibroblast Activation Protein (FAP)-enabled pre|CISION® Peptide-drug Conjugate Delivering Sustained Tumor Microenvironment (TME) Release of Exatecan in Patients with FAP-positive Solid Tumors

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Introduction and Rationale

- AVA6103 is a pre|CISION® peptide drug conjugate (PDC) comprising a peptide linked to the TOPI inhibitor **exatecan**, and **cleaved specifically by fibroblast activation protein-α (FAP)**, which is overexpressed by cancer associated **fibroblasts (CAFs)** in the TME of many solid tumors
- FAP is selectively expressed by CAFs within tumors, with limited normal tissue expression. Therefore, **exatecan is released in the tumor microenvironment (TME), improving the therapeutic window and maximizing efficacy** whilst **reducing adverse effects** compared to treatment with exatecan alone

pre|CISION® PDCs offer key advantages over conventional ADC approaches:

- Optimized Dosing of Exatecan**
The maximum tolerated dose of FAP-Exd is significantly higher than conventional exatecan allowing greater tumor concentration
- FAP-Exd is inert without FAP**
FAP-Exd is completely inert unless FAP+ CAFs are present to cleave the peptide and release exatecan
- Sustained tumor release**
High tumor levels of both PDC and released exatecan persist over five days, whereas conventional exatecan rapidly clears from circulation and the tumor within hours

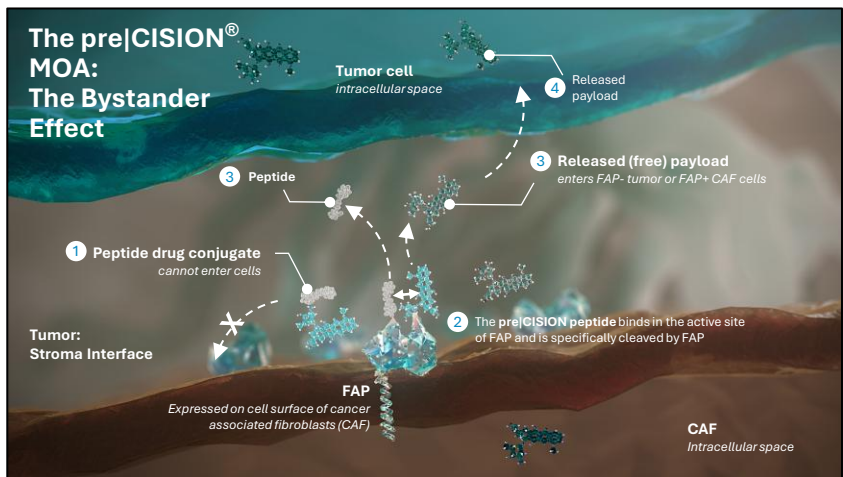


FIGURE 1. Mechanism of action of pre|CISION® FAP-Exd

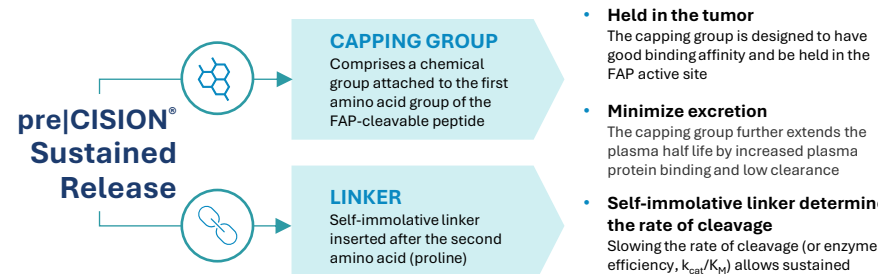
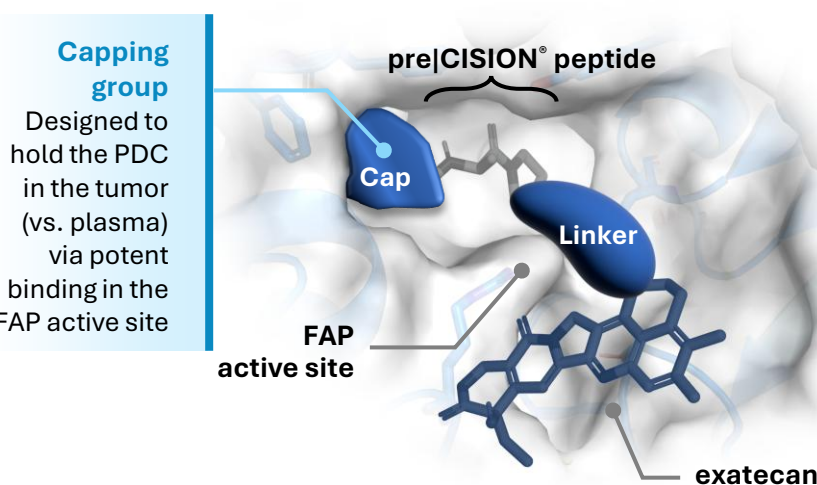


FIGURE 2. The sustained release mechanism of pre|CISION® FAP-Exd

AVA6103 (FAP-Exd): Generation 2 of the pre|CISION® Platform

- AVA6103 uses pre|CISION® technology to **extend the half-life** of released exatecan in tumor across the entire cell cycle
- Increases tumor exatecan** exposure by tuning release kinetics via modified **capping group and linker** (alter the k_{cat}/K_M of the conjugate)
- Slower exatecan release plus extended conjugate plasma PK gives **sustained release mechanism**, lower plasma exatecan and **reduced systemic exposure**

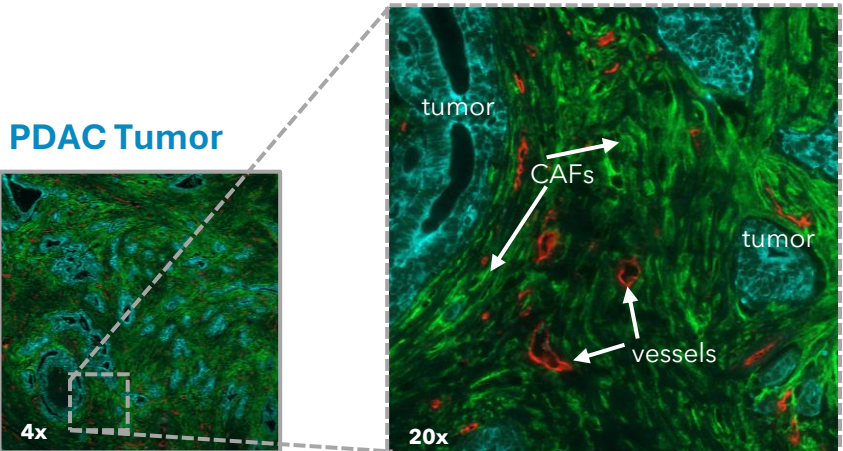
Figure 3: Schematic showing AVA6103 docked into the FAP active site, containing a capping group, D-Ala-Pro pre|CISION® dipeptide unit, self-immolative linker and exatecan. After cleavage of the pre|CISION® dipeptide by FAP, the linker undergoes self-immolation and free exatecan is released. AVA6103 docked into the FAP active site



Pancreatic Cancer Tumor Architecture and FAP Expression Makes for a Strong Indication for AVA6103

- FAP is highly expressed by CAFs throughout the Pancreatic TME; mIF staining shows FAP+ CAFs in **close proximity to both blood vessels and cancer cells** – ideal architecture for payload delivery, cleavage and bystander uptake
- PDAC is therefore a **strong clinical indication for AVA6103**: abundant stromal FAP drives tumor-selective exatecan release, maximizing tumor exposure while limiting systemic toxicity

FIGURE 4. The bystander effect of the pre|CISION® platform warhead delivery. The close proximity of blood vessels (●) FAP+ CAFs (●) cancer cells (●) allows pre|CISION® compounds to be readily delivered, cleaved, and taken up by neighboring cancer cells



Pancreatic Cancer Shows the Highest Prevalence of FAP Expression Across Gastrointestinal Tumors

- DAB staining demonstrates high **FAP protein** levels in PDAC tissue
- FAP mRNA and protein are **strongly correlated across solid tumors** (Spearman's $\rho=0.7091$, $p=0.0182$), validating mRNA data as a predictor of stromal FAP protein levels
- PDAC sits at the top of this relationship, with **high, confirmed FAP mRNA and protein levels in the tumor**

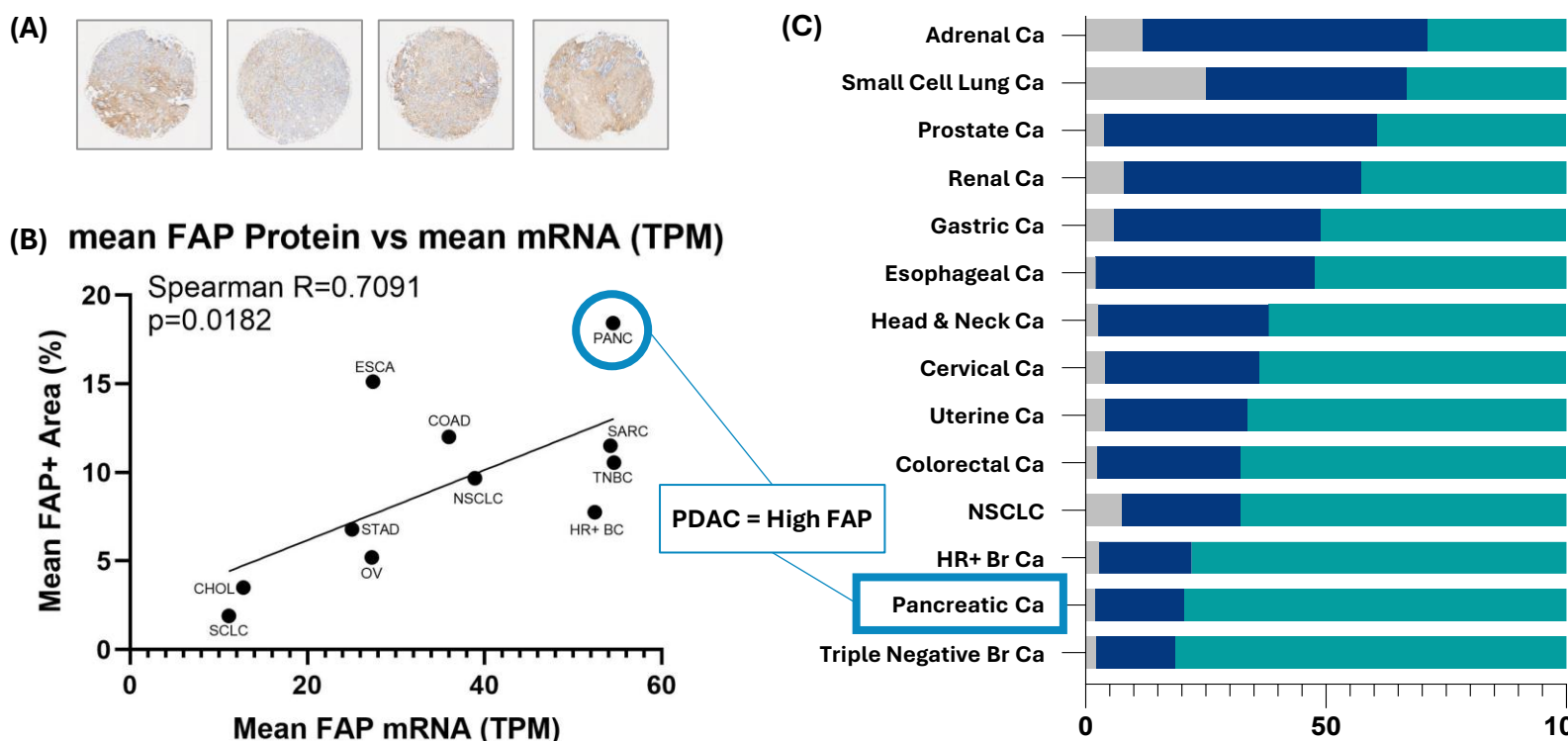
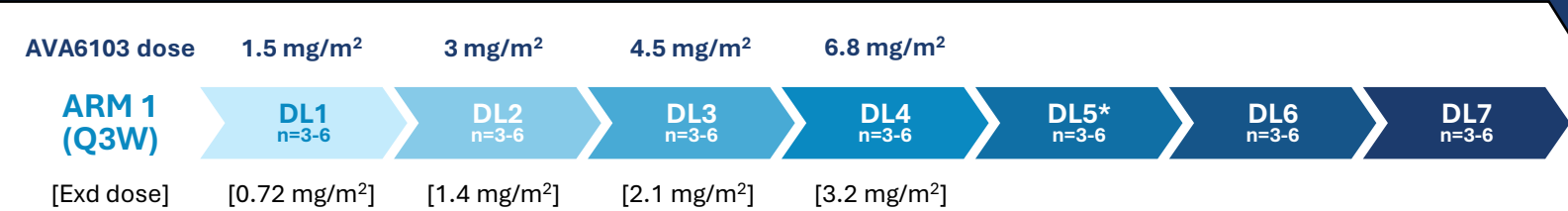


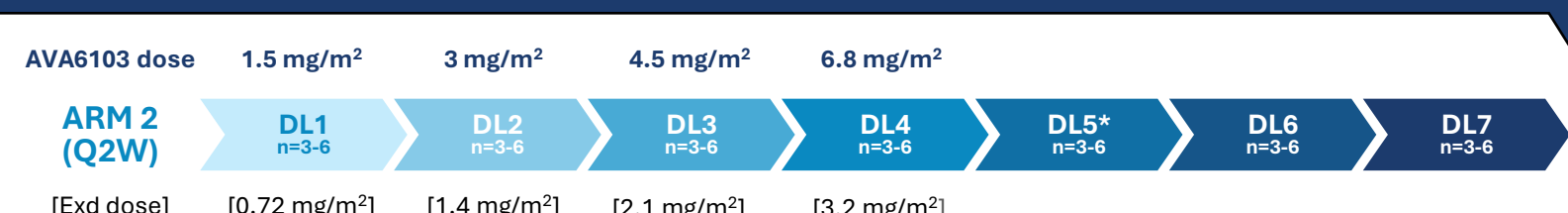
Figure 5. (A) Representative FAP IHC in PDAC tissue. (B) mean FAP Protein vs mean mRNA (TPM). (C) Tempus AI LENS analysis: PDAC among the tumor types with highest FAP prevalence, supporting AVA6103 evaluation in this setting. Pancreatic Cancer N = 9351.

FOCUS-01 AVA6103 (FAP-Exd): Phase I Trial Design and Patient Population

Phase 1A Dose Escalation (Parallel Arms)



12-week Topo I Dose Intensity 2.9 mg/m² 5.6 mg/m² 8.4 mg/m² 12.8 mg/m² Planned dose levels (actuals determined by observed safety and BOIN) Enhertu starting dose 0.76 mg/m² Dxd approved dose 5.16 mg/m² Dxd *DL5 anticipated same payload level as approved dose of Enhertu



12-week Topo I Dose Intensity 4.3 mg/m² 8.4 mg/m² 12.6 mg/m² 19.2 mg/m² Planned dose levels (actuals determined by observed safety and BOIN) *DL5 anticipated same payload level as approved dose of Enhertu

PANCREATIC CANCER PATIENT POPULATION

Pancreatic cancer and AVA6103

- Pancreatic cancer patients are enrolled in the Q2W arm to match standard of care therapies
- Tumor FAP levels will be assessed in PDAC patients to explore the relationship between stromal FAP expression and clinical response to AVA6103

Biomarker-guided development

- Pancreatic cancer's uniformly high FAP positivity means nearly all patients are candidates for AVA6103, avoiding the enrichment problem that limits many targeted therapies in PDAC

Topoisomerase I inhibitor mechanism validated

- Topo I inhibition is clinically validated in PDAC (FOLFIRINOX, NALIRIFOX); AVA6103 releases exatecan selectively in FAP-rich stroma, raising tumor exposure while limiting systemic toxicity

Unmet need remains despite recent advances

- Despite recent advances in RAS inhibitor therapies, many patients ultimately progress, leaving pancreatic cancer an indication of high unmet need in which alternative, mechanistically distinct treatment options are required

OBJECTIVES

Primary objectives

- Safety and tolerability of AVA6103 at the Q3W and Q2W dosing intervals
- Determination of the MTD and/or recommended Phase 2 dose (RP2D) for expansion at each dosing interval

Secondary objectives

- To characterize the PK of AVA6103, its leaving group AVA10344 and exatecan in plasma as monotherapy, after single and multiple dosing
- Initial antitumor activity by RECIST v1.1 including ORR, DOR, BOR, DCR, PFS and OS

Exploratory objectives

- FAP protein expression and enzymatic activity in tumor and plasma
- Intratumoral concentrations of AVA6103, AVA10334 and exatecan

KEY INCLUSION/EXCLUSION CRITERIA

Population

- Adult male or female with ECOG PS 0–1 and life expectancy ≥ 3 months
- Histologically or cytologically confirmed locally advanced (unresectable) and/or metastatic FAP-positive tumors: cervical/vulvar, SCLC, gastric/GEJ, pancreatic, HR+ breast, CRC
- Progressed on, ineligible for, or declining all standard-of-care or FDA-approved therapy

Organ function

- Adequate hematologic, renal, and liver function
- QTCF ≥ 470 ms

Disease and medical history

- No active CNS metastases

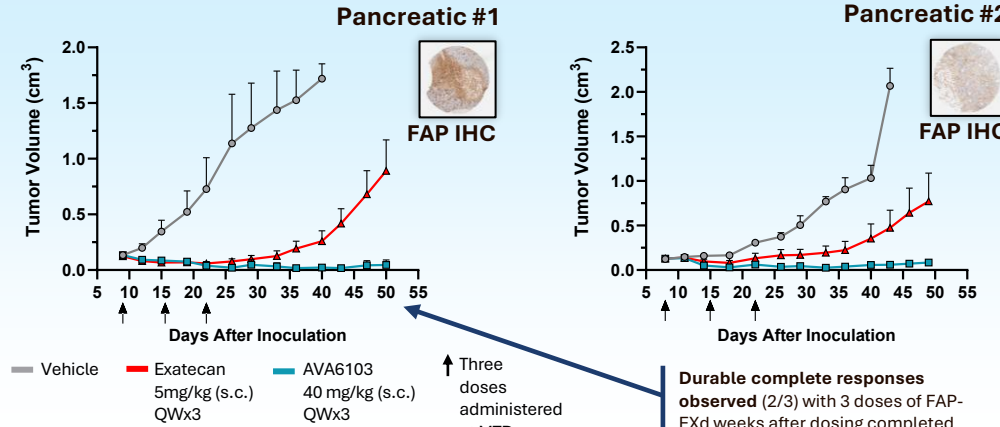
- Active HIV, HBV or HCV infection, or severe infection requiring IV antibiotics within 21 days

Other requirements

- Negative pregnancy test; highly effective contraception through 6 months after last dose

Multiple Durable Complete Responses Continue Weeks After Dosing in Mouse PDX Models of Pancreatic Cancer

FAP-Exd (AVA6103) Treatment Results in Complete Responses in High and Mid-FAP Models



- AVA6103 demonstrated **superior efficacy** to exatecan in **2 pancreatic PDX models** with greater TGI and sustained tumor regressions even after treatment cessation
- Pancreatic #1 – 2/3** mice exhibited **complete responses**
- Pancreatic #2 – 3/3** mice exhibited **partial responses**

FAP-Exd (AVA6103) Results in Deep Tumor Responses

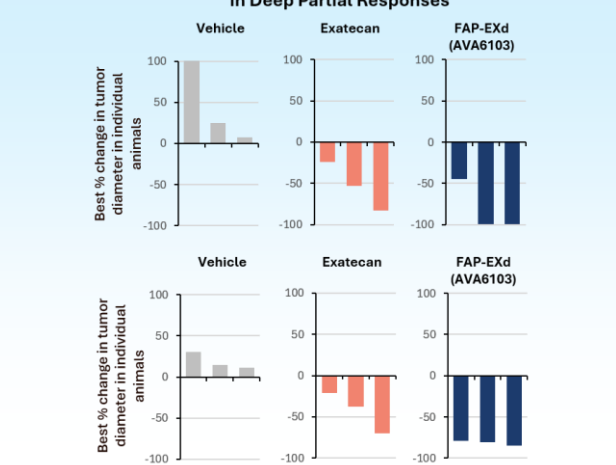


FIGURE 6. Mean tumor volume (±SEM) over time in two Pancreatic cancer PDX models following SC treatment with AVA6103 (40 mg/kg), exatecan (5 mg/kg), or a vehicle control (n=3 or 4 per group). Terminal tumor volumes continued until termination of the last animal in the group. Inset shows IHC staining for FAP in previously archived cores of this PDX model. (Rink et al., 2026)

Molecular Characteristics of Pancreatic Cancer Support AVA6103 Clinical Development

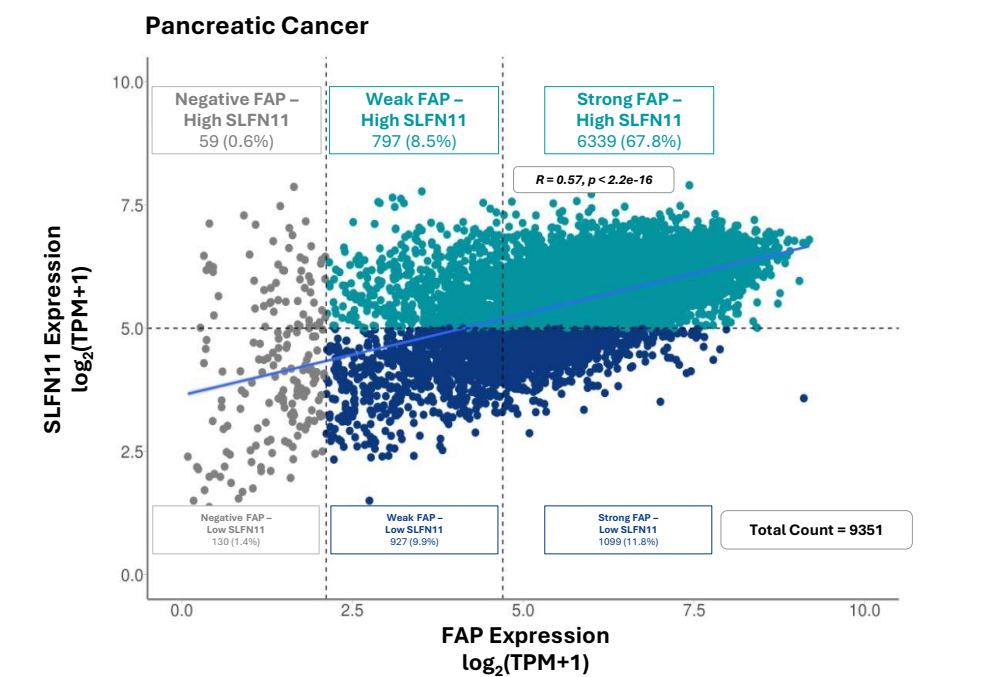


FIGURE 7. Correlation between FAP and SLFN11 mRNA expression (log₂(TPM+1)) across pancreatic cancer samples from the Tempus LENS dataset. Each point represents an individual tumor. Colors denote expression-defined subgroups: teal indicates FAP+ / SLFN11^{High} patient population. SLFN11-High was defined as expression above the pan-cancer median (log₂(TPM+1) and FAP+ cut-points to define FAP+ were the same across the entire database and were set based on known/published positive rates for IHC in 3 diseases: gastric, triple negative breast cancer and SCLC (Mona et al., 2022; Chen et al., 2022).

- SLFN11 has been shown to **confer sensitivity to DNA-damage inducing agents such as TOPI inhibitors** (Zhang et al., 2021)
- To evaluate the translational relevance of **SLFN11 in the context of FAP-targeted delivery**, RNA expression data were extracted from the **Tempus LENS database** across multiple solid tumor types
- FAP+ / SLFN11^{High} (teal)** expression identifies patient populations with an **enhanced likelihood of responding to AVA6103** and other pre|CISION® enabled DNA damage agents, **improving the probability of clinical benefit**
- Additionally, **FAP or SLFN11 expression does not significantly change** between pre- and post- TOPI treated samples, supporting the use of **pre|CISION® medicines as second- or third-line therapy** in pretreated patients
- A total of **six indications** were selected in which to conduct a **first-in-human (FIH), Phase 1** open-label, multicenter **dose escalation study investigating AVA6103**, which began treating patients in **March 2026**

CONCLUSIONS

- Pancreatic cancer is among the most desmoplastic solid tumors**, with a dense stroma of activated fibroblasts and remodeled ECM that restricts conventional drug penetration and contributes to poor outcomes
- FAP is expressed in 98% of pancreatic tumors** – the highest proportion of any GI cancer – and mIF staining shows FAP+ CAFs in close proximity to both blood vessels and cancer cells, the architecture required for payload delivery, cleavage and bystander uptake
- FAP protein expression correlates closely with FAP mRNA** across solid tumor types ($p=0.7091$, $p=0.0182$), confirming that the stromal FAP target is abundant and measurable in pancreatic cancer
- AVA6103 turns the stroma into a cytotoxic payload reservoir**: the pre|CISION® peptide is cleaved only by membrane-bound FAP, releasing exatecan within the tumor to maximize intratumoral exposure while limiting systemic toxicity – a mechanism supported by the established clinical activity of topoisomerase I inhibition in PDAC
- AVA6103 is being evaluated in the FOCUS-01 Phase 1 trial** across six FAP-positive indications, with parallel Q2W and Q3W dose escalation arms using a BOIN design and a planned Phase 1b pancreatic expansion cohort at the RP2D, including paired biopsies to confirm tumor exposure

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