AbTx

Embrace the future of ADC technology

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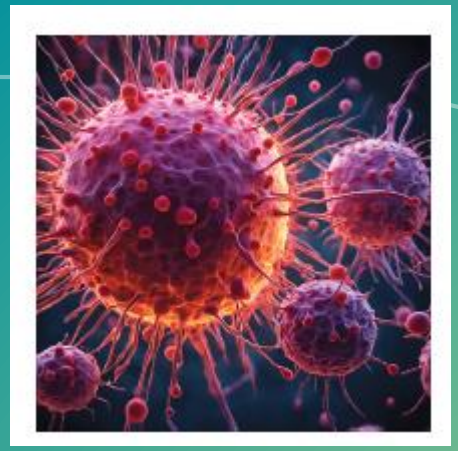

1ères Journées de recherche en Immuno-Oncologie

13 et 14 mars 2025
Agora Hautepierre
CHU Strasbourg

CANCÉROPÔLE Est
Régions Bourgogne-Franche-Comté / Grand Est

Smaller ADC formats based on Therano-Stick ™ technology could make the difference for solid tumors !

Claudine VERMOT-DESROCHES
Cofounder & CSO

DIJON métropole

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Smaller ADC formats based on Therano-Stick ™ technology could make the difference for solid tumors !

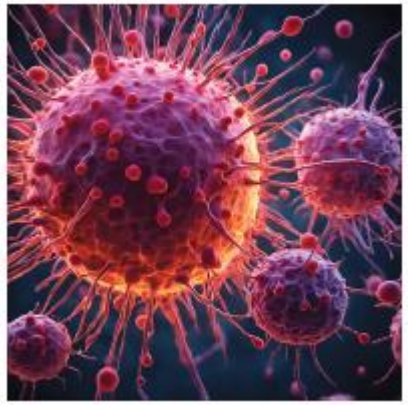
Part 1 : AbTx introduction

Part 2 : ADC, a dynamic field

Part 3 : Pancreatic Cancers is a devastating disease !

Part 4 : ADC investigation for Pancreatic Cancers : a dynamic field

Part 5 : Exploring the unique advantages of FDC to improve ADC therapeutic index



AbTx Creation in 2024

Teams with Complementary Competences
Based on antibody conjugation expertise of Covalab
With an access of a wide range of antibodies

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Meddy El Alaoui, PhD
Chief Executive Officer

- Management of R&D teams
- ADC expert
- 7 publications
- 3 International Awards

Claudine Vermot-Desroches, PhD
Chief Scientific Officer
Outsouced & Part time

- CSO in various biotech companies
- Expert at TheraWings Consulting
- Expertise in Immunotherapies
- 50 publications
- 20 patents / Therapeutic mAbs
- 5 Licensed Therapeutic antibodies

Boris Vuillermoz, PhD
Chief Technolov Officer

- Expertise in mAb design
- 6 publications, 4 patents
- 2 licensed Therapeutic antibodies

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KOLs- Internationally acknowledged experts in the field

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Our vision

AbTx is a preclinical stage biotech company **developing the next generation of oncology treatments**.

Our Strategy

AbTx is a next-gen pure player deploying a **new ADC platform (Therano-Stick ™)** developing **ADC / FDC to improve therapeutic index (efficacy / safety)**

Our solution

Pioneer the development of mAb **enzymatic conjugation** by using its proprietary **Therano-Stick™ platform** with the goal of **transforming the landscape** of targeted therapies.

Mode of actions of ADCs

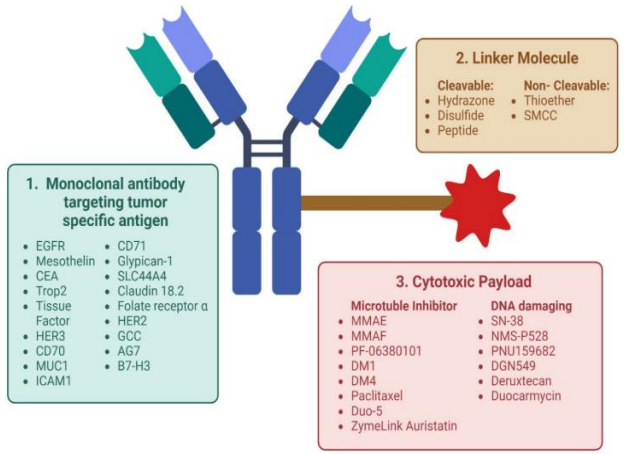


Fig. 1 Structure of ADCs and specific components of ADCs in development for targeting pancreatic cancer
An ADC is composed of three main components: (1) A monoclonal antibody targeting a tumor specific antigen; (2) a linker molecule and (3) a cytotoxic payload that will kill the target cancer cell. Specific antigens, linkers and payloads being developed for the treatment of pancreatic cancer are listed
***ADC**: antibody drug conjugate;**B7-H3**: B7-homolog 3;**CEA**: carcinoembryonic antigen;**EGFR**: epidermal growth factor receptor;**GCC**: Guanylyl Cyclase C;**HER2**: human epidermal growth factor receptor 2;**HER3**: human epidermal growth factor receptor 3;**ICAM-1**: intercellular adhesion molecule 1;**MMAE**: monomethyl auristatin E;**MMAF**: monomethyl auristatin F;**MUC1**: mucin-1;**SMCC**: succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate;**Trop2**: trophoblast antigen 2.*

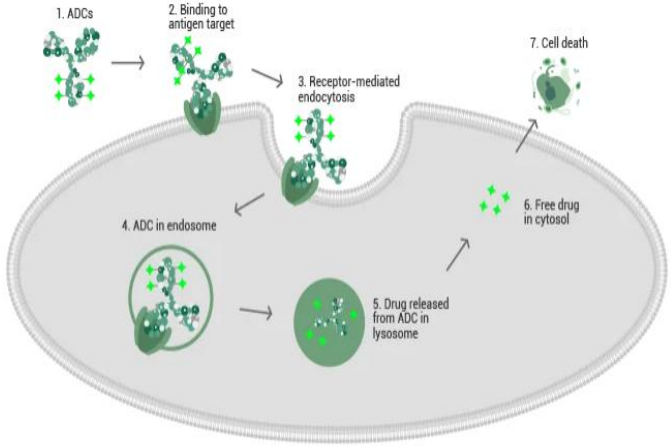


***Figure 1**. General mechanism of action of ADCs. Image Credit: Sino Biological Inc.*

- ADCs consist of an **antibody carrier** (monoclonal, bispecific, or antibody fragment) conjugated to a payload (small drug, enzyme, antibiotic, etc.) via a cleavable or non-cleavable linker.
- These emerging biotherapeutics conjugate **the specificity of immunotherapies** with the potency of chemotherapeutics, allowing **the delivery of extremely toxic drugs to cancer cells with high precision**.
- The chemistry behind the production of ADCs is complex and undergoing active development.
- Target antigens should be highly expressed in tumor tissues, but not expressed in normal tissues.
- Theoretically, by targeting monoclonal antibodies, ADCs can precisely find the lesion and achieve a real **" prescribe the right medicine**

Approved ADCs

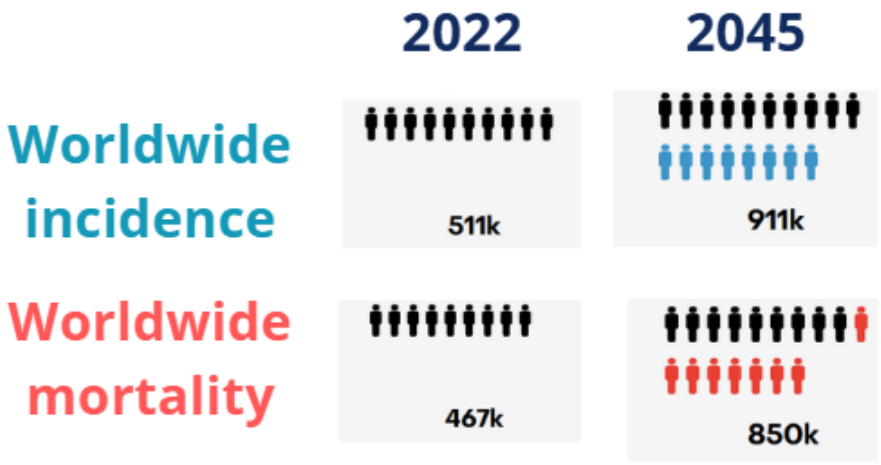
Table 1. Approved ADCs for the Treatment of Solid Tumours and Haematological Malignancies.

ADC Name	Developer	Year of Approval	Indication	Antibody Isotype	Target	Target Description	Payload	Linker Type	Approximate DAR	Payload Mechanism
ADCs with Tubulin Inhibiting Payloads										
Brentuximab vedotin (Adcetris®)	Seagen	2011 (FDA) 2012 (EMA)	HL, Systemic ALCL	IgG1	CD30	Marker of activated lymphocytes	MMAE	Cleavable	4	Tubulin inhibition
Ado-trastuzumab emtansine (Kadcyla®)	Genentech	2012 (FDA) 2013 (EMA)	HER2-positive breast cancer	IgG1	HER2	Growth Factor Receptor	DM-1	Non-cleavable	4	Tubulin inhibition
Polatuzumab vedotin-piiq (Polivy®)	Genentech	2019 (FDA) 2020 (EMA)	DLBCL	IgG1	CD79b	B-cell Receptor component	MMAE	Cleavable	3	Tubulin inhibition
Enfortumab vedotin-ejfv (Padcev®)	Astellas/Seagen	2019 (FDA*) 2022 (EMA)	Urothelial cancer	IgG1	Nectin-4	Adhesion Molecule	MMAE	Cleavable	4	Tubulin inhibition
Belantamab mafodotin-blmf (Blenrep®)	GlaxoSmithKline	2020 (EMA), 2020 (FDA*, To be withdrawn)	MM	IgG1	BCMA	Marker of mature B cells	MMAF	Non-cleavable	4	Tubulin inhibition
Tisotumab vedotin-tftv (Tivdak®)	Genmab/Seagen	2021 (FDA)	Cervical cancer	IgG1	Tissue factor	Blood Clotting Co-factor	MMAE	Cleavable	4	Tubulin inhibition
Mirvetuximab soravtansine-gynx (Elahere®)	ImmunoGen	2022 (FDA*)	Platinum-resistant, FRα-positive epithelial ovarian, fallopian tube, or primary peritoneal cancer	IgG1	FRα	Folic Acid Metabolic Receptor	DM-4	Cleavable	2	Tubulin inhibition
ADCs with DNA-Interactive Payloads										
Gemtuzumab ozogamicin (Mylotarg®)	Pfizer	2000 (Withdrawn) 2017 (FDA) 2018 (EMA)	AML	IgG4	CD33	Myeloid-specific marker	Calicheamicin	Cleavable	2	DNA Cleaving
Inotuzumab ozogamicin (Besponsa®)	Pfizer	2017 (EMA) 2017 (FDA)	ALL	IgG4	CD22	B-cell Receptor component and negative regulator of B-cell receptor signalling	Calicheamicin	Cleavable	6	DNA Cleaving
Trastuzumab deruxtecan-nxki (Enhertu®)	AstraZeneca/Daiichi Sankyo	2019, 2021, 2022 (FDA*) 2021 (EMA)	HER2-positive metastatic breast cancer, HER2-mutated NSCLC, HER2-positive gastric or gastroesophogeal cancer	IgG1	HER2	Growth Factor Receptor	Dxd	Cleavable	8	Topoisomerase inhibition
Sacituzumab govitecan-hziy (Trodelvy®)	Immunomedics/Gilead Sciences	2020 (FDA) 2021 (EMA)	TNBC, HR-Positive, HER2-negative breast cancer, Urothelial Carcinoma	IgG1	TROP-2	Transmembrane Glycoprotein	SN-38	Cleavable	8	Topoisomerase inhibition
Loncastuximab tesirine-lpyl (Zynlonta®)	ADC Therapeutics	2021 (FDA), 2022 (EMA)	DLBCL	IgG1	CD19	B-cell marker and positive regulator of B-cell receptor signalling	PBD Dimer	Cleavable	2	DNA Cross-Linking

ADCs marked with '*' have been granted accelerated approval by the FDA. Blenrep® is to be withdrawn from the US market. Abbreviations: ALCL, Anaplastic Large Cell Lymphoma; ALL, Acute Lymphoblastic Leukaemia; AML, Acute Myeloid Leukaemia; BCMA, B Cell Maturation Antigen; DAR, Drug Antibody Ratio; DLBCL, Diffuse Large B Cell Lymphoma; Dxd, Deruxtecan; DM-1, Maytansinoid DM-1; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FRα, Folate Receptor Alpha; HER2, Human Epidermal Growth Factor Receptor 2; HL, Hodgkin Lymphoma; MM, Multiple Myeloma; MMAE, Monomethyl Auristatin E; MMAF, Monomethyl Auristatin F; NSCLC, Non-Small Cell Lung Cancer; TNBC, PBD, Pyrrolobenzodiazepine; Triple-Negative Breast Cancer; TROP-2, Trophoblast Antigen 2.

Cancers **2023**, *15*, 1845. https://doi.org/10.3390/cancers15061845 https://www.mdpi.com/journal/cancers

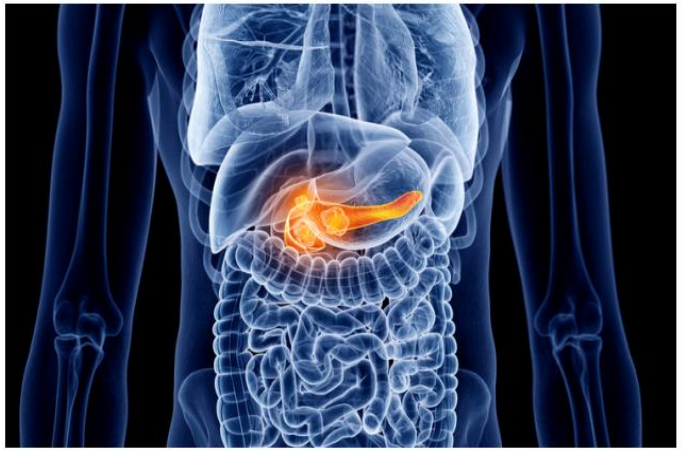
Pancreatic cancer : new therapies are urgently needed !



"Only 10-20% of pancreatic cancer patients are operable and also receive chemotherapy treatment, with only two lines of treatment available. In cases of non-response or resistance, there's nothing left to offer!"

Dr Aurélien Dupré
Digestive Cancer Surgeon
Léon Bérard Center

Why Pancreatic Cancers is so difficult to treat?



- Poor prognosis
- Incidence **in constant increase**
- 2050 : **1st cancer**

- Pancreatic tumors are poorly vascularized, so it is difficult to deliver drugs to the tumor
- Unlike other cancers, Pancreatic tumor cells are encased in a "protective layer" composed of stromal cells and their secreted intercellular matrix
- The dismal outcomes for patients with PDAC reflect an **urgent need to develop more effective treatment approaches**

Pancreatic Cancer chemotherapy treatments…

- To date, the treatment strategies : radiation and chemotherapy.
- Chemotherapy drugs such as the 5-fluorouracil (5-FU), platinum or nitroso-urea, can significantly increase median survival of patients with pancreatic cancer.
- Most patients with PDAC are treated with regimens
  - *such* ***as gemcitabine and nab-paclitaxel, FOLFIRINOX,***
  - or gemcitabine alone, depending on their health status.
- Unfortunately, while these regimens can improve survival, patients with inoperable disease cannot be cured and often rapidly develop treatment resistance and succumb to their cancers in less than 1 year.
- The dismal outcomes for patients with PDAC reflect an urgent need to develop more effective treatment approaches.

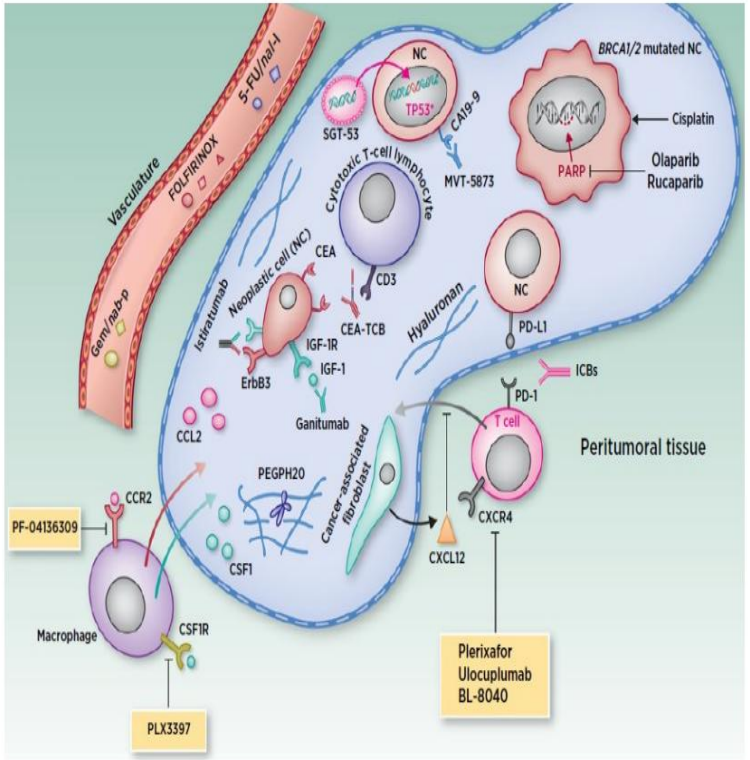


Fig.2 Current and emerging therapies in pancreatic cancers. (Manji, 2017)

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66: 7–30.
2. Jacobetz MA, Chan DS, Neesse A, Bapiro TE, Cook N, Frese KK, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut 2013;62:112–20.
3. Long KB, Tooker G, Tooker E, Luque SL, Lee JW, Pan X, et al. IL6 receptor blockade enhances chemotherapy efficacy in pancreatic ductal adenocarcinoma. Mol Cancer Ther 2017;16:1898–908.

Current Therapeutic Strategies for Pancreatic Cancers : ADC could fill the gap…

REVIEW Open Access

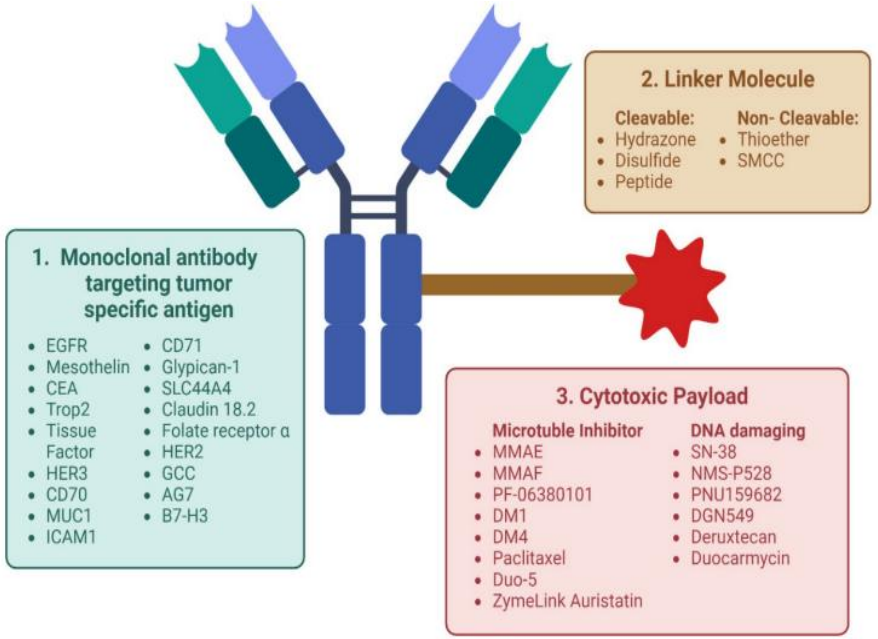
Antibody drug conjugates: hitting the mark in pancreatic cancer?

Nicole L. Wittwer[1,2*], Michael P. Brown[1,2,3], Vasilios Liapis[1,2] and Alexander H. Staudacher[1,2]

Abstract

Pancreatic cancer is one of the most common causes of cancer-related death, and the 5-year survival rate has only improved marginally over the last decade. Late detection of the disease means that in most cases the disease has advanced locally and/or metastasized, and curative surgery is not possible. Chemotherapy is still the first-line treatment however, this has only had a modest impact in improving survival, with associated toxicities. Therefore, there is an urgent need for targeted approaches to better treat pancreatic cancer, while minimizing treatment-induced side-effects. Antibody drug conjugates (ADCs) are one treatment option that could fill this gap. Here, a monoclonal antibody is used to deliver extremely potent drugs directly to the tumor site to improve on-target killing while reducing off-target toxicity. In this paper, we review the current literature for ADC targets that have been examined in vivo for treating pancreatic cancer, summarize current and on-going clinical trials using ADCs to treat pancreatic cancer and discuss potential strategies to improve their therapeutic window.

Keywords Pancreatic cancer, Antibody drug conjugate, Bystander killing



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But also a fine tuning to generate smaller ADC formats could make the difference ..?

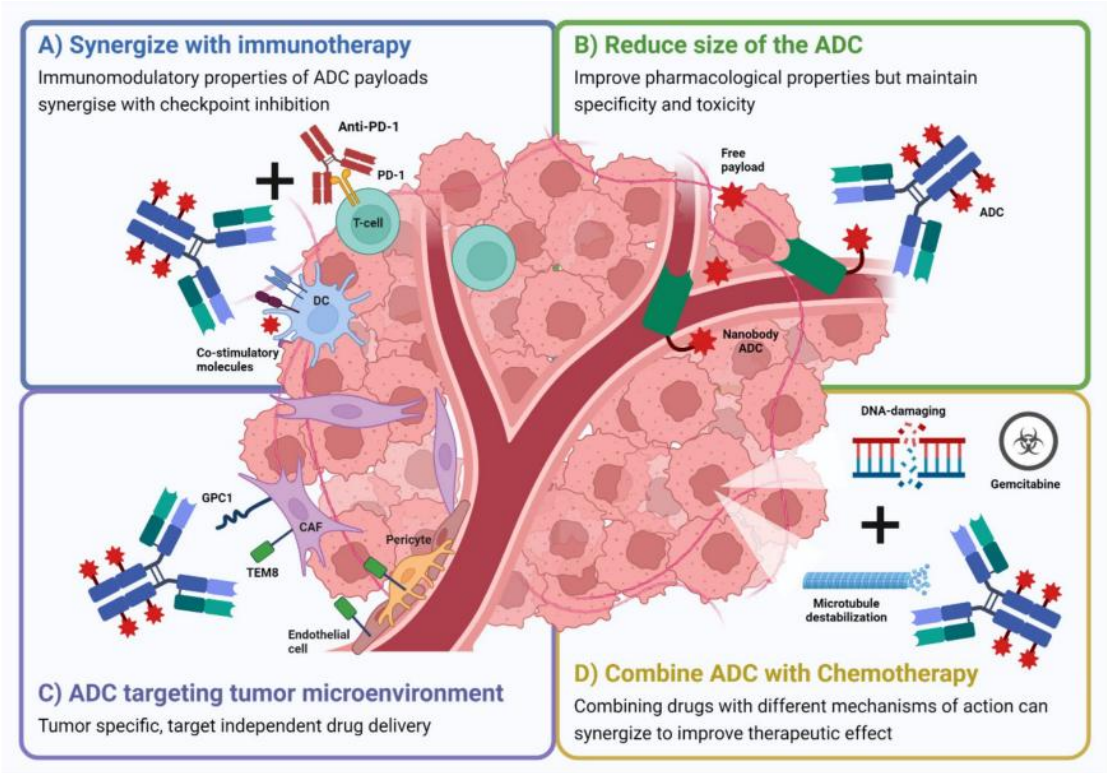
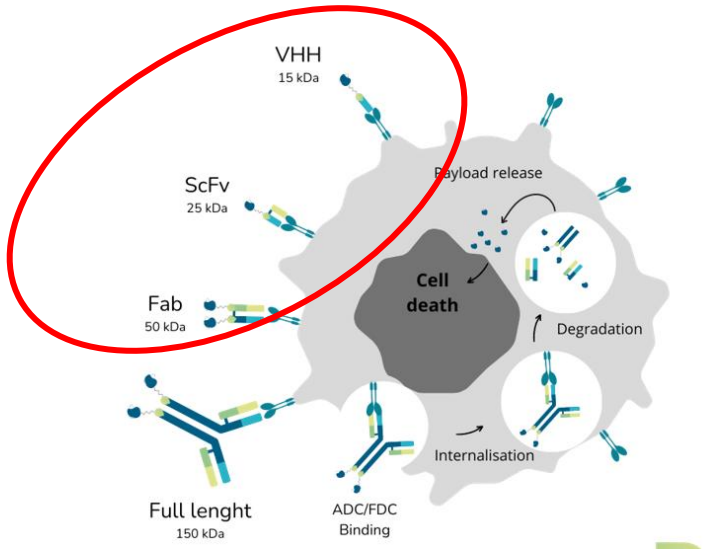


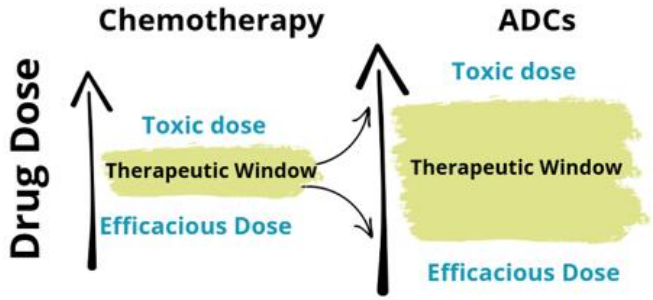
Fig. 2 Strategies to improve ADC efficacy in pancreatic cancer
Schematic representation of different approaches being undertaken to improve efficacy of ADC therapy in pancreatic cancer. **(A)** Synergistic interaction between the ADC and immunotherapy may enhance therapeutic response. ADC payloads are known to exhibit immunomodulation through upregulation of co-stimulatory molecules on dendritic cells, which can synergize with checkpoint inhibition to enhance effector T-cell function. **(B)** Reducing the size of the ADC using nanobody ADCs may help to increase perfusion of the drug into the poorly vascularized and desmoplastic tumor microenvironment (TME) associated with pancreatic cancer. **(C)** Targeting TME associated antigens may bypass the poor internalization associated with tumor antigens but still allow tumor specific delivery of the payload. **(D)** Targeting two different mechanisms of cell death by combining ADCs with chemotherapy such as gemcitabine, may help to overcome resistance and improve efficacy compared to either treatment alone. ***ADC***: *antibody drug conjugate*;***CAF***: *cancer associated fibroblast*;***DC***: *dendritic cell*;***GPC-1***: *glypican-1*;***PD-1***: *programmed cell death protein 1*

- Solid tumors are notoriously hard to eradicate given the **limited penetration of ADC therapies**.
- For this reason, active fields of research continue to explore **new mechanisms of action** including :
  - The use of smaller antibody carriers that have **better tissue diffusion** rates (VHH or monoclonal antibody fragments),
  - The employment of **more efficient cleavable linkers able to release the toxic cargo in the tumor's microenvironment,**
  - As quickly as possible, thus enhancing the bystander effect.

AbTx mission

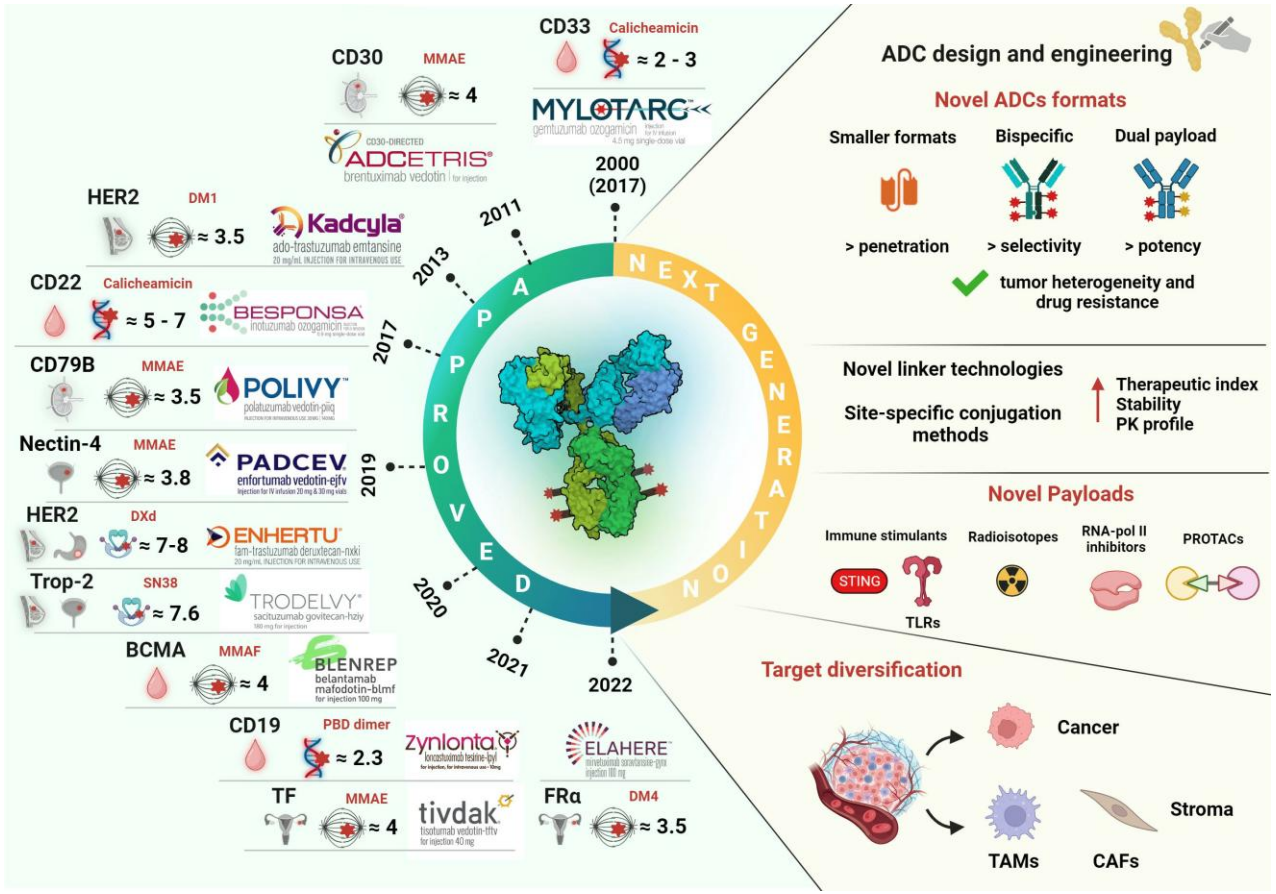
- AbTx mission is **to pioneer the development and advancement of antibody FDC** (Fab, scFv and VHH) by using **Therano-StickTM platform** to transform the landscape of targeted therapies.





TAKE HOME MESSAGE

AbTx is « on the race » for the next generation of ADC



Development of fragment conjugated antibodies based on Therano-Stick™ technology platform to bring the next generation of ADCs to improve treatment of solid

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