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Navigating the complexities of pancreatic ductal adenocarcinoma: A review on therapeutic models and RAS inhibitors☆

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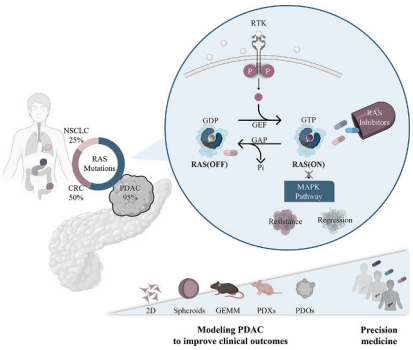
GRAPHICAL ABSTRACT



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ABSTRACT

Pancreatic cancer is one of the most lethal types of cancer, known for a poor prognosis. Currently, the standard of care for unresectable tumors consists of combinations of cytotoxic chemotherapy. Thus far, targeted therapies against specific oncogenic pathways have not been approved for clinical use. Most cases of pancreatic cancer are sporadic/non-hereditary Pancreatic Ductal Adenocarcinomas (PDACs) and are caused by activating mutations in the *KRAS* oncogene. For the past four decades, KRAS was considered "undruggable". However, numerous multi-selective and mutant-specific RAS inhibitors are now under active development. In this review, we present experimental models of PDAC that facilitate studies of response to therapy and drug resistance. We also discuss recent evidence on targeted therapeutic strategies under preclinical and clinical evaluation, with emphasis on the KRAS signaling.

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1. Introduction

Pancreatic cancer has had a rising incidence rate over the last decade and is currently the third leading cause of cancer-related deaths worldwide, with the lowest 5-year survival. The survival rate has seen little improvement, from less than 5 % in the 90́s up to 13 % in 2020[1]. This bad prognosis is attributed to late diagnosis and lack of therapeutic options. Indeed, our understanding of PDAC biology remains incomplete and is principally responsible for the little progress in the clinical field over the past 20 years[2]. At present, the most effective treatment is surgical resection with adjuvant therapy, which only applies to 20 % of patients, with a recurrence rate as high as 85 %[3]. So far, postoperative treatment with FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) and mFOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan and oxaliplatin) has been demonstrated to provide the longest median Overall Survival (OS) (54 months) in patients with resectable disease[4]. Unfortunately, most patients cannot benefit from surgery, as at the time of diagnosis, they display locally advanced or metastatic disease.

For unresectable tumors, the standard of care consists of combinations of highly cytotoxic agents such as nab-paclitaxel plus gemcitabine or FOLFIRINOX, as well as PARP inhibitors. However, these treatments only provide modest improvements in OS in the range of weeks to months[5–7]. Gemcitabine, a synthetic pyrimidine nucleoside analog with a cytotoxic effect, was approved in 1997 after demonstrating an improvement in OS compared to 5-fluorouracil (5-FU)[8]. Later, the combination of gemcitabine with Nanoparticle albumin-bound paclitaxel (Nab-paclitaxel) was approved, although it only resulted in a small improvement in OS[6]. Similarly, no difference was observed in OS with the use of PARP inhibitors, approved for patients with germline mutations in *BRCA1* and *BRCA2*[9].

Overall, little progress has been made in the last decades in first-line treatment, which still relies on cytotoxic chemotherapy[10]. Therefore, there is undoubtedly an urgent need to develop novel therapies that block specific oncogenic pathways with reduced toxicity. Currently, numerous ongoing clinical trials are investigating the efficacy of inhibitors against somatic mutations[10,11]. However, thus far, few targeted therapeutic approaches have been approved for clinical use with limited success[11].

Most cases of pancreatic cancer are sporadic/non-hereditary Pancreatic Ductal Adenocarcinomas (PDACs) and are caused by the accumulation of somatic mutations in oncogenes and tumor suppressor genes. Specifically, KRAS is the most frequently mutated oncogene in 95 % of all pancreatic tumors, with activating mutations mainly at codon 12. Additionally, tumor suppressor genes are usually inactivated later in tumorigenesis and are present in 50–80 % of PDACs, including *TP53*, *CDKN2A* and *SMAD4*[12–15]. Other less commonly mutated genes found in ~ 10 % of tumors include *TGFBR1*, *TGFBR2*, *GLI3*, *ARID1A, GNAS* and *MLL3*[16].

Apart from point mutations, other types of genomic changes, such as copy number alterations, chromosomal rearrangements and structural variants are also detected mostly in advanced and metastatic pancreatic tumors[13,17]. This comes in agreement with the low difference in driver genes and low genetic heterogeneity observed between primary tumors and metastases[18]. However, despite the limited genetic heterogeneity, PDAC belongs to one of the most heterogeneous tumors with diverse signaling, which makes it highly chemoresistant[19].

In this review, we present a brief overview of experimental models of PDAC and evaluate their complementarity to study response to therapy and drug resistance. Furthermore, we focus on recent evidence on targeted therapeutic strategies currently in preclinical and clinical trials against the KRAS signaling network.

2. Modelling pancreatic ductal adenocarcinoma

PDAC research demands models that accurately reflect the complexity of the disease. Latest advances in PDAC therapy suggest that patients should be selected for precision treatments based on the genetic, molecular and cellular characteristics of the tumor. Here, we briefly explore key models including cell lines, spheroids, organoids and mouse models as well as their contribution to precision therapy.

2.1. Two-Dimensional (2D) cell lines

Two-dimensional (2D) cell lines grow from murine or human cells on monolayer plastic surfaces. Monolayer cells are known for their rapid growth and expansibility, thus being the most common tool used in high-throughput drug screenings. They are also easily genetically manipulated, facilitating studies of PDAC biology and the identification of genes to target PDAC. PDAC cell lines genetically engineered with CRISPR/Cas9 systems have been used to investigate mechanisms of drug resistance, revealing that the ABCG2 efflux pump contributes to chemoresistance[20,21]. However, the rate of success for establishing PDAC 2D cell lines from human tumor samples is low and this model fails to replicate the intratumoral heterogeneity and the tumor microenvironment (TME) that characterize PDAC. Additionally, 2D cell lines lack extracellular matrix (ECM), nutrient and oxygen gradients, as well as cell–cell interactions, essential features of tumor evolution. Finally, 2D cells are under selective pressure from culture conditions and they undergo genetic shifts and clone selectivity[20,22,23] (Table 1).

2.2. Spheroids

To address the limitations of 2D cell lines, more complex three-dimensional (3D) models have been developed. Even as single-type 3D cultures, spheroids display increased expression of ECM proteins and alter metabolism, thus better mimicking PDAC tumors. [20,24]. Because of their 3D structure, spheroids are composed of a hypoxic core and outer cells exposed to the environment, generating an oxygen and nutrient gradient similar to a solid tumor. Additionally, heterospheroids contain more than one cell type, such as cancer stem cell-like (CSCs) cells and stromal cells. Therefore, they provide insights about cell interactions and drug response and resistance. A recent study showed that spheroids generated from primary murine cell lines may contain CSC populations, associated with increased tumorigenicity and resistance to chemotherapy[25–27]. Indeed, heterospheroids often demonstrate resistance to PD-1/PDL-1 inhibition, both alone and in combination with gemcitabine[20,28,29]. Generally, the presence of stromal cells or other distinct cell populations make spheroids a good model to study response in pharmacological assays [25,30–32]. Therefore, the sensitivity obtained in in vitro assays with spheroids correlates well with in vivo sensitivity[25,30,33]. Interestingly, the complexity of these cultures can be advanced by including other cell types, such as endothelial cells, to reproduce the vascularity of the tumor are under development[25,34]. Despite their advantages, spheroids are very often generated from 2D cell lines, which limits their heterogeneity and distances them from the clinical reality. Unlike 2D cells, this 3D model has a more limited lifetime, which makes it unsuitable for large, reproducible assays (Table 1).

2.3. Patient-Derived organoids (PDO)

Organoid cultures have emerged as a valuable tool for pancreatic cancer research, as they present key advantages in modeling PDAC. More specifically, Patient-Derived Organoids (PDOs) are three-dimensional (3D) in vitro models that better resemble the structural and cellular characteristics of the original tumor (Fig. 1). They are cultured in matrixes that contain ECM-mimicking proteins in culture media supplemented with nutrients and growth factors. This enables the study of different stages of the disease from resectable to metastatic tumors, providing insights into tumor biology and evolution[35–37]. Several related platforms have been developed. An outstanding example includes organoid profiling by single-cell RNA sequencing that investigated how tumor cell states influence the response to therapy[38,39].

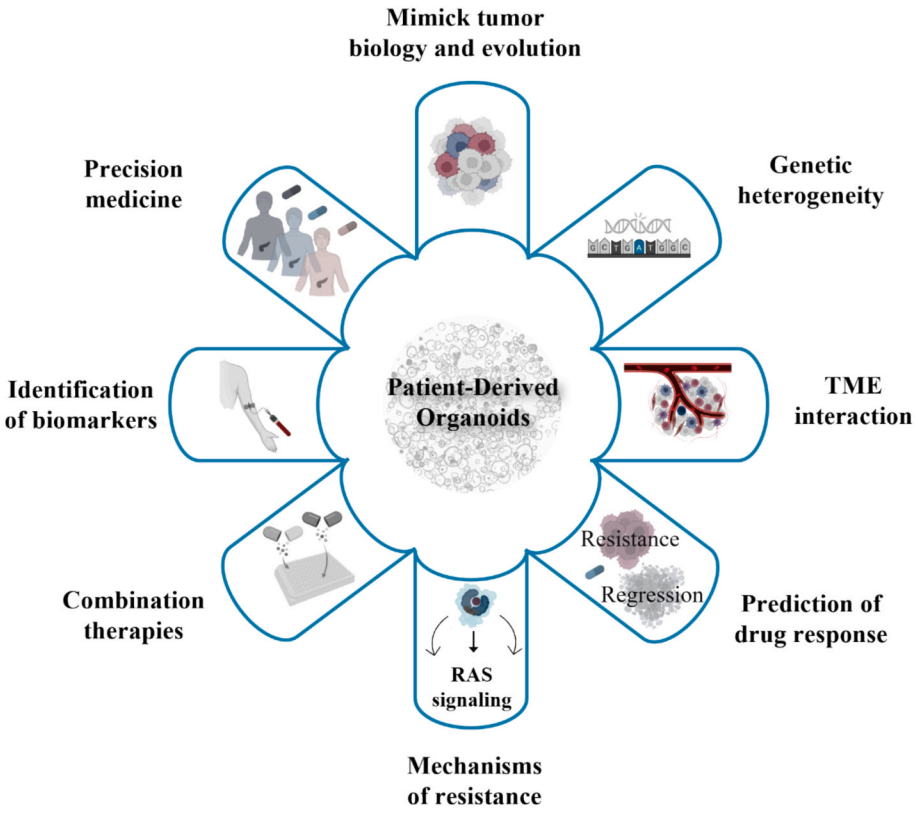

Fig. 1. Schematic representation of applications and advantages of Patient-Derived Organoids.

Another remarkable advance includes the optimization of organoid isolation to generate cultures derived from intraductal papillary mucinous neoplasms (IPMNs). Thus, creating a biobank of PDOs that can be used to study the evolution of these lesions to cancer. It is also worth mentioning that genomic and histological characterization of these samples allowed the identification of IPMN subtypes and their evolution into malignant cells[40,41]. Unlike less complex in vitro models that undergo genetic changes over time, PDOs maintain the genetic background and changes of the original tumors, being more representative of the original tumor [42] (Table 1).

Although with some limitations, organoid cultures can incorporate non-tumoral cells, such as immune cells and fibroblasts[37]. This allows the study of interactions with the tumor microenvironment (TME) and the effect of multiple drug treatments like chemo-, radio- or immunotherapy on PDAC human tumors[43,44]. The relevance of including other cell types in organoid cultures was reinforced when it was observed that the presence of cancer-associated fibroblasts (CAFs) impacts the response of tumor cells to chemotherapy, making them more resistant[38,39,45]. Importantly, it was demonstrated that the presence of TME compartments in organoid cultures alters their transcriptional profile[39].

PDOs are also useful for high-throughput drug screenings of various agents and combinations, accelerating the identification of effective treatments (Fig. 1). As the only culture model that mimics the genetic background of PDAC, it better reflects the diverse response to different therapies, within and across patients[46,47]. Therefore, organoids are often used in personalized pharmacological studies for precision medicine[47,48]. Studies with PDOs revealed their sensitivity to therapeutic compounds that were not previously identified. Unlike 2D cell lines, PDOs can be established from both tumoral and normal tissues, enabling the identification of compounds that selectively target cancerous tissue while being non-toxic to healthy tissue, increasing their value in precision medicine (Fig. 1).

Given the highly resistant nature of PDAC, organoids are also a robust tool for accurate pharmacotyping [37,46]. Recent studies successfully predicted patient clinical response to neoadjuvant chemotherapy using organoids as a preclinical tool[49]. Moreover, studies with PDOs have also revealed novel synergistic drug combinations both in cytotoxic and targeted therapy[49,50]. As a patient-specific model, PDOs can also be used for the discovery of biomarkers to stratify patients and predict response to therapy[51] (Fig. 1). Interestingly, protein markers of extracellular vesicles present in organoid culture media were also present in the plasma of PDAC patients, distinguishing them from patients with benign gastrointestinal lesions.

PDOs can also be used to predict clinical outcomes. Unfortunately, to prove the clinical value of PDOs, only retrospective studies can be performed. Due to the limited survival rate of PDAC patients, such studies often lack sufficient sample size and patient follow-up [38]. However, ongoing trials aim to assess guided-therapy using organoids in second-regimen chemotherapy, palliative care, multi-omic profiling and pharmacotyping (NCT04931394, NCT04931381, NCT05842187, NCT04469556). Recent research has already identified prediction models that can anticipate response in chemotherapy-naïve patients with an efficacy of 91,1% for first-line treatment and 80 % for second-line treatment[52]. Equally importantly, the prospective Harnessing Organoids for Personalized Therapy (HOPE) trial showed a correlation between sensitivity to drug profiles of PDOs and patient outcome[53]. Undoubtedly, all preclinical models have limitations, yet PDOs seem to be a scalable approach that enhances preclinical therapy and could guide precision medicine of PDAC[54].

2.4. *Mouse models – Genetically engineered mouse models (GEMMs)*

Mouse models provide controllable systems to study cancer complexities in a physiological context. Genetically engineered mouse strains faithfully reproduce the natural history of pancreatic human tumors, enabling a better understanding of PDAC biology[55]. Genetic systems of GEMM models include Cre or Flp recombinases, which are

Table 1
Summary of PDAC Models.

Model	Characteristics	Advantages	Disadvantages	Pre-clinical relevance
2D cell lines	2D monolayer cells Adhesion on plastic surface	− Cost-effective −High-throughput screenings −Easy genetic manipulation	−Limited cell heterogeneity −Selection through multiple passaging −Lack of cell–cell interactions −Lack of TME −Poor predictive value	−Drug discovery −Mechanisms of drug resistance
Spheroids	3D multicellular aggregates	−Cell-cell interaction −Oxygen and nutrient gradients −Multiple cell types −Physiological relevance	−Commonly established from 2D cell lines (low heterogeneity) −Short lifespan −Culture variability	−Spatial organization of cell types −Characterization of immune population −TME cells in drug resistance
Organoids	3D self-organizing structures commonly derived from patient tissue	−Retain main tumor characteristics −Generated at any stage of PDAC −High heterogeneity −Long-term amplification −Personalized medicine applications	−Includes stromal components −Transcriptome selectivity −Variable culture conditions −High-cost	−Single-organoid characterization −Patient-specific drug sensitivities −Correlation with patient response −Drug resistance mechanisms
PDX	Patient-derived tumor tissue grown in mice	−Retain main tumor characteristics −At early development, maintains tumor TME −In vivo studies can be performed	−Time-consuming process −Immunological limitations −TME of mouse origin −High-cost	−Pharmacotyping platforms −In vivo/ in vitro correlation −Translational applications −Clinical proof of concept

conditionally expressed under the control of different promoters (Table 2). This allows spatio-temporal elimination or the expression of different modified alleles. The most frequent promoters used in GEMMs in pancreatic research are *Pdx1* or *Ptf1a/P48*, expressed at early stages of embryonic development [56]. The Cre recombinase is often found fused to the ERT2 sequences, which permits further timing control due to Cre activation upon exposure of the mice to tamoxifen [57,58]. Another model for the Cre recombinase is under the control of a Tet-off system and the Elastase promoter [*Elastase-tTA* and *Tet-O*-Cre]. This allows its expression in the embryonic stages by the absence of doxycycline. Alternatively, in adult mice, crosses are set up in the presence of doxycycline and Cre recombinase is expressed upon removal of doxycycline [59].

Due to its high frequency in PDAC, *KRAS* mutations are considered

Table 2
Summary of reported *Kras-driven* GEMM models.

Driver mutation	Other modifications	Promoters	Tumor initiation	PanIN	PDAC	Met.	Ref
$Kras^{+/LSLG12D}$	—	*Pdx1*-Cre *Ptf1a*-Cre	Prenatal	Yes	Yes	Yes	[56]
$Kras^{+/LSLG12D}$	$Ink4a/Arf^{lox/lox}$	*Pdx1*-Cre	Prenatal	Yes	Yes	Yes	[60]
$Kras^{+/LSLG12D}$	$Tp53^{+/R172H}$	*Pdx1*-Cre	Prenatal	Yes	Yes	Yes	[62]
$Kras^{+/LSLG12D}$	TGF-β $IIR^{lox/lox}$	*Pdx1*-Cre	Prenatal	Yes	Yes	Yes	[90]
$Kras^{+/LSLG12D}$	$Ink4a/Arf^{-/-}$ $Tp53^{lox/lox}$ $Tp53^{lox/lox}$; $Ink4a/Arf^{-/-}$ $Smad4^{lox/lox}$	*Pdx1*-Cre	Prenatal	Yes	Yes	Yes	[61]
$Kras^{+/LSLG12D}$	—	*Nestin*-Cre	Prenatal	Yes	No	No	[64]
$Kras^{+/LSLG12Vgeo}$	$Tp53^{-/-}$ Cerulein	*Elastase-tTa* *Tet-O*-Cre	Prenatal Postnatal	Yes Yes	Yes Yes	No Yes	[59]
$Kras^{+/LSLG12D}$	—	*Elastase*-CreER	Postnatal	Yes	NA	No	[58]
$Kras^{+/LSLG12D}$	—	*Elast.*-CreERT2 *Mist1*-Cre*ERT2*	Postnatal	Yes	No	No	[57]
$Kras^{+/G12D}$	*β-catenin*	*Ptf1a*-Cre		No	Yes	NA	[93]
$Kras^{+/LSLG12D}$	*MUC1*	*Ptf1a*-Cre	Postnatal	Yes	Yes	Yes	[97]
$Kras^{+/LSLG12D}$	$Tp53^{+/lox}$ $Smo^{lox/lox}$	*Ptf1a*-Cre	Postnatal	Yes	Yes	NA	[98]
$Kras^{+/LSLG12D}$	$Brca2^{Tr/Δ11}$ $Tp53^{+/R270H}$ $Brca2^{+/Tr}$ $Tp53^{+/R270H}$ $Brca2^{Tr/Δ11}$	*Pdx1*-Cre	Prenatal	Yes	Yes	NA Yes	[63]
$Kras^{+/LSLG12D}$	$Lkb1^{lox/lox}$	*Pdx1*-Cre	Prenatal	Yes	Yes	NA	[66]
$Kras^{+/LSLG12D}$	*Notch 1*$^{lox/lox}$	*Pdx1*-Cre	Prenatal	Yes	No	No	[91]
$Kras^{+/G12D}$	$Pten^{lox/lox}$	*Pdx1*-Cre	Prenatal	Yes	Yes	Yes	[65]
$Kras^{+/LSLG12D}$	*Notch 2*$^{lox/lox}$	*Ptf1a*-Cre	Prenatal	No	Yes	No	[92]
$Kras^{+/LSLG12D}$	$Rosa26^{+/LSL-lacZ}$ $Rac1^{lox/lox}$ $Tp53^{+/LSLR172H}$	*Ptf1a*-Cre	Postnatal	Yes	Yes	NA	[94]
$Kras^{+/LSLG12Vgeo}$	$Tp53^{lox/lox}$	*Elastase-tTa* *Tet-O*-Cre	Postnatal	Yes	Yes	Yes	[69]
Ink4a/Arf							
$Kras^{+/G12D}$	$Rb^{lox/lox}$	*Pdx1*-Cre	Postnatal	Yes	Yes	Yes	[64]
$Kras^{+/G12D}$	$Ikk^{lox/lox}$	*Ptf1a*-Cre	Postnatal	Yes	No	Yes	[95]
$Kras^{+/LSLG12D}$	$Usp9x^{+/lox}$	*Pdx1*-Cre	Prenatal	Yes	Yes	NA	[96]

the earliest alteration to drive pancreatic carcinogenesis. The first GEMM model that demonstrated the ability of *Kras* to initiate PDAC progression came with the development of a conditional *Kras*^{G12D} knock-in allele. This mouse strain allowed the expression of an endogenous mutant *Kras* oncogene in pancreatic cells during the early embryonic stage, resulting in the generation of Pancreatic Intraepithelial Neoplastic (PanIN) lesions that eventually progress to PDAC, histologically indistinguishable from those present in patients[56]. A few years later, several studies demonstrated that additional inactivation of the common tumor suppressors *p16Ink4a/p19Arf*, *Tp53*, *Lkb1, Brca1/2, Rb, Pten* and *Smad4* accelerates progression of PanINs to invasive PDAC with complete penetrance[60–67] (Table 2). Similarly, GEMMs expressing the *Kras* G12V variant specifically in pancreatic acinar cells resulted in PanIN and rarely in PDAC lesions[59]. Further studies with this mouse strain validated that loss of the tumor suppressors *p16Ink4a/p19Arf* or *Tp53 resulted in* PDAC development in all the mice [59,68](Table 2).

Interestingly, mutant *Kras* expression in adult mouse acini fails to induce pancreatic lesions even in the presence of inactivated *Tp53* or *p16Ink4a/p19Arf* [37,44]. Yet, these models do develop PanIN lesions and PDAC in the context of chronic pancreatitis, induced by the exposure to cerulein (a cholecystokinin analog)[59,68]. Indeed, chronic pancreatitis speeds disease progression and is essential for tumor development when the expression of the *Kras* oncogene in acinar cells starts in adulthood[59]. Embryonic acinar cells are more tolerant and permissive to transformation than adult acinar cells, which acquire a less differentiated phenotype[69]. The resistance of adult acinar cells to this transformation can be explained by their different transcriptional profile [70]. Embryos show a higher percentage of multipotent progenitors compared to the adult tissue. When these cells undergo activation of the *Kras* oncogene, they are more likely to transform into PanIN and PDAC [71]. In the adult pancreas, these multipotent progenitors are only present in 1 % of the cells, suggesting less capacity for transformation [72]. Nevertheless, some recent studies have now described the presence of different acinar compartments, including an acinar population, characterized by the expression of Trefoil factor 2 (Tff2), that is resistant to *Kras* oncogenic transformation[73]. Indeed, *Kras*^{G12D}-targeted Tff2^{+} cells are resistant to PDAC initiation. However, in the context of pancreatitis, these cells expand and acquire a cancer stem/progenitor cell-like state[73]. Other studies also confirmed the importance of KRAS levels in acinar transformation. Interestingly, the KRAS levels reduce before birth, resulting in only 25 % of adult acinar cells with detectable KRAS levels. Hence, adult cells have low sensitivity to *Kras* oncogenes, due to their low levels of expression[74,75]. Therefore, the presence of inflammation is essential to activate metaplastic conversion. This hypothesis has been further confirmed by studies that link levels of *Kras* activity to acinar transformation[74]. High RAS activity is necessary for its transformation, leading to acinar cell senescence that generates inflammation and fibrosis, resembling the histological features of chronic pancreatitis[76,77].

Importantly, it has recently been described that acinar cells expressing the *Kras* oncogenes must first override cell competition signals through the EphA2 receptor to remain in the tissue and drive early disease[78,79]. Similarly, transforming growth factor (TGF)-β-activated kinase 1 (TAK1), a kinase that regulates cell survival and inflammatory pathways, has also been described to prevent the elimination of transdifferentiated cells through receptor-interacting protein kinase 1 (RIPK1)-mediated apoptosis and necroptosis, thereby enabling the development of PDAC[80].

These observations prove GEMMs as a powerful tool to model human pathologies such as chronic pancreatitis, which is so far the best-established risk factor and has long been linked to the development of pancreatic cancer in adult patients[81,82]. It has previously been described that normal acinar cells present in human pancreatic tissue that express oncogenic *Kras* are not necessarily transformed. This suggests that such adult acinar cells are resistant to the expression of the *Kras* oncogene[83–85]. This has also been demonstrated in human tissue, where the presence of inflammatory stimuli is necessary for the activation of *Kras* and further metaplastic conversion[77]. These results lead to claiming that oncogenic *Kras* activated by upstream effectors, has retarded kinetics in recovering its inactive state. Thus, leading to an overactive molecule that, together with different inflammatory stimuli, leads to the development of new lesions[77].

We and others have demonstrated that the ablation of either *Egfr* [86,87] or *Raf1*[88], a downstream effector of *Kras* signaling, has a direct effect on the development of PDAC tumorigenesis. Our studies have shown that concomitant elimination of both *Egfr* and *Raf1*, significantly prevents the development of *Kras/Tp53*-driven PDAC tumors[88]. It was also shown that *Ras*-mutant adult cells activate *Wnt5a* and cell dormancy state, to avoid cell expulsion and survive before undergoing malignant transformation/expansion[79]. In this context, the GEMM models described above allow us to directly eliminate specific target genes in already established tumors[88,89].

Many of these models add, in addition to mutations in *Kras*, other changes in different genes altered in PanINs and PDACs and serve as an excellent tool to validate pharmacological approaches (Table 2). Some recapitulate mutations in the transforming growth factor beta receptors RI and RII (TGFBR1, TGFBR2) that have been identified in a smaller percentage as modifications and favor the transition of lesions classified as PanINs to PDAC tumors[90]. In addition to these mutations, different signaling pathways can modify lesion progression, such as the Notch pathway. *Notch*, which is composed of two paralogues, *Notch 1* and *2*, is known to be upregulated in pancreatic tumors. Along with *Kras* activation, loss of *Notch 1* accelerates tumor progression, while the loss of *Notch 2* slows it down[91,92]. Another example is the activation of proteins such as beta-Catenin, which can also promote pancreatic tumor formation. When beta-Catenin protein is stabilized in the presence of activated oncogenic *Kras*, PanIN formation is blocked[93].

Other modifications studied with the use of GEMMs are mutations in *Rac1* or *Ikk2*, which were found to be necessary for early metaplastic changes and associated neoplasia in pancreatic cancer development [94,95]. In contrast, there are other genes, such as *Usp9x,* whose deletion, along with *Kras* activation, accelerates tumor progression, validating its function as a tumor suppressor[96]. Other studies with GEMM models reveal the role of membrane proteins in the development of pancreatic injury. In particular, the membrane glycoprotein *Muc1* has been shown to increase tumor progression in the presence of oncogenic forms of *Kras*[97], but deletion of others, such as the transmembrane protein Smoothened (Smo), does not affect and is not required for PDAC formation[98].

Overall, studies with GEMMs demonstrate that mouse tumors initiated by the same endogenous mutations as their human counterparts have remarkable histological similarities to human lesions, from PanINs to PDAC[99] (Table 2). Yet, GEMMs also allow the study of the metastatic nature of PDAC. More specifically, it has been demonstrated that the widely used GEMM strains *Kras*^{G12D}; *Tp53*^{R172H} and *Kras*^{G12D}; *p16Ink4a/p19Arf*^{KO} develop highly metastatic PDACs to various distal sites[60]. Furthermore, recent studies have also validated the function of *Zdhhc2*, *Nemo*, *Sema3D* and *Loxl2* in the highly metastatic *Kras*^{G12D}, *Tp53* ^{R172H} strain [100–103]. These murine PDACs also display increased genomic instability, reflecting the complexity of human locally advanced and metastatic pancreatic tumors[62]. Similarly, mouse models developed in our lab that harbor the *Kras* mutation G12V, such as *Kras*^{G12V}; *Tp53*^{KO} and *Kras*^{G12V}; *p16Ink4a/p19Arf* ^{KO,} also display liver metastasis[59,68]. Additionally, *Smad4*^{KO}, together with G12D-mutant *Kras,* also results in metastasis. Undoubtedly, such models serve as a powerful tool to assess the invasion properties of tumor cells. Taking it a step further, they also reveal the function of specific genes in the metastatic process. However, as PDACs often develop very fast in GEMM models and mice need to be sacrificed at humane endpoint, this limits the duration of studies. Therefore, surgically removing the primary tumors could be used to assess the metastatic rate in the long term. Other preclinical models to study hepatic metastasis or peritoneal

dissemination include implantation methods. These surgical procedures usually refer to intrasplenic inoculation of cells, as well as hemi-splenic and portal-vein injections[104].

2.5. Patient-Derived xenografts (PDXs)

Although GEMMs are a powerful model to study PDAC, implantation models are widely used in preclinical studies, due to their time- and cost-effectiveness[105]. Patient-derived xenografts (PDXs) are generated by subcutaneous or orthotopic implantation of human tumor samples into immunocompromised mice. These models faithfully reproduce the tumor histopathology, including vascularity, lymphatic drainage and necrotic tissue[25,106]. Orthotopic implantation is often used for site-specific therapy, as it mimics histologically the pancreatic microenvironment[107] and may present metastatic potential. However, tumor growth needs to be monitored by peritoneal ultrasound[108]. For this reason, although subcutaneous models fail to recapitulate the location of the original lesion, they are usually preferred as the tumors are easier to measure[104]. PDXs preserve the original tumor heterogeneity and characteristics of the TME. Therefore, it is a long-established model of drug response and toxicity evaluation [25,109,110]. However, in vivo passaging leads to replacement of the original TME with the murine TME components of the host[25,111–114].

Overall, PDX models are widely used, as they allow for in vivo studies of human tumor samples that retain the genetic characteristics of the original tumors[105]. Yet, after several passages, the tumors may undergo genetic alterations, often in copy number variations [115,116]. Other disadvantages of PDX models also include the low presence of immune cells in the host immunocompromised animals, which affects tumor evolution and drug response[25,117,118]. Additionally, accessibility to samples of patients with advanced disease is often limited, despite efforts to generate PDXs from fine-needle aspiration (FNA), circulating tumor cells (CTCs) and metastatic tissue[25,119]. Therefore, the restricted sample size and time-consuming procedures to obtain fresh patient-derived tissue make these models unfeasible to treat with large panels of drugs and combinations[38,120].

Another preclinical approach that combines the advantages of both models includes patient-derived xenograft organoids (PDXOs). PDOXs allow the amplification of human samples for wider application, while maintaining the original characteristics of the patients tumor. New studies demonstrated that both PDXOs and PDXs have similar responses to different therapies, confirming that the characteristics are shared between models[38,121,122]. However, tumor amplification and organoid establishment are considerably time-consuming, thus limiting the applicability of this model.

In summary, PDAC models are constantly evolving, while presenting advantages and disadvantages, and should be used complementarily in translational studies (Table 1).

3. KRAS oncogenes and signaling

3.1. KRAS structure and isoforms

RAS proteins are small guanosine triphosphatases (GTPases) that fluctuate between their inactive GDP-loaded state to the active GTP-loaded state. RAS is mostly found in its active form bound to GTP, due to its strong affinity for the increased presence of GTP intracellularly [123]. Indeed, oncogenic mutants of RAS have amino acid exchanges that generate long-term active RAS molecules[124]. Mechanistically, conversion between the two forms of RAS is mediated by GTPase-activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs), respectively (Fig. 2). GAPs such as NF1 provide an important catalytic group for GTP hydrolysis, while GEFs such as SOS1/2 induce the release of GDP and add GTP[125]. Structurally, the RAS protein has two different regions, the N-terminal and the C-terminal. The N-terminal in the cytoplasmic region is known as the catalytic or G domain and has

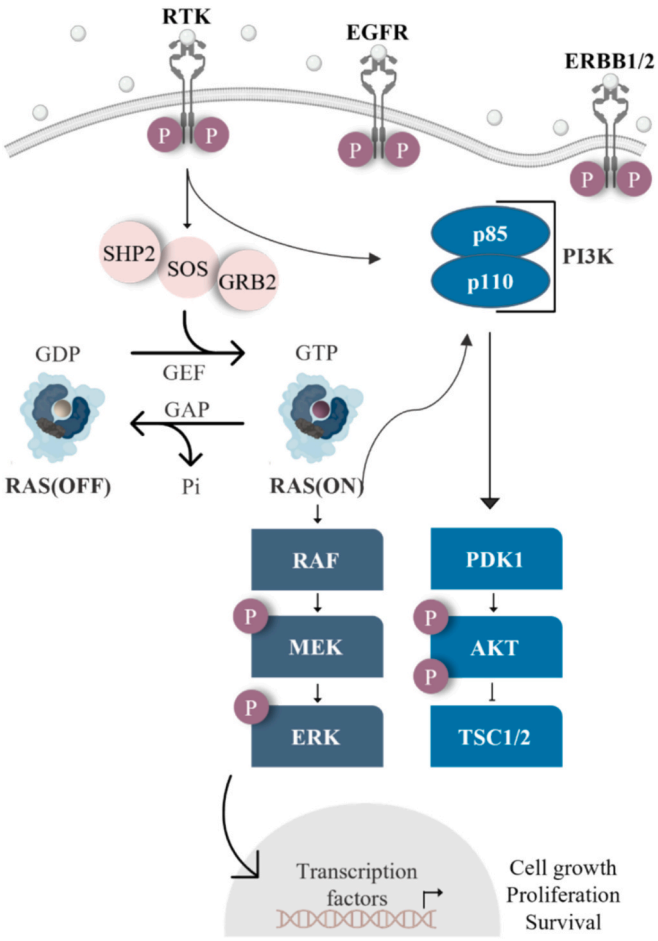

Fig. 2. Schematic representation of RAS activation and downstream signaling cascades.

two lobes. The effector lobe contains catalytic machinery as well as the I/II switch regions. The other lobe is a phosphate loop that undergoes conformational changes as it shifts from the inactive to the active state [125,126].

RAS genes encode the three paralogues HRAS, NRAS and KRAS, including the two spliced isoforms KRAS4A and KRAS4B[127]. Each *Ras* paralogue has a distinct organ-specific role, explaining the different tissue-specific tumorigenic mutations [128–130]. It is worth mentioning that various studies have validated the important role of *Kras* in embryonic development. In detail, mice lacking *Kras* die embryonically between E12.5 and 15.5, due to severe damage in the ventricular myocardium with abnormalities in cardiomyocyte proliferation and thinner ventricular walls. They also demonstrate anemia, liver defects and an increase in apoptotic rate in motor neurons of the spinal cord [130,131]. On the contrary, other studies have shown that *Nras* and *Hras* expression is not required for embryonic development, with normal development of mice [131]. However, it was also shown that mice lacking expression of the two paralogues have lower weaning rates due to postnatal respiratory failure[132]. Last, ablation of *Hras* and *Nras* in GEMMs during embryogenesis results in no overexpression of *Kras,* confirming that expression of *Kras* is sufficient to maintain embryonic viability[133].

Mechanistically, when *Kras* genes were replaced by *Hras* genes that were controlled by the regulatory regions of *Kras*, mice developed normally and grew to adulthood. The only observed adverse effect was dilated cardiomyopathy and high blood pressure, hypothesized to be an effect of the lack of *Kras* during development[134]. This study showed that the importance of *Kras* is mainly due to its unique expression

pattern, rather than its biological functions[134]. Importantly, germline expression of non-oncogenic activated forms of KRAS results in Noonan syndrome, a developmental disorder characterized by multiple alterations, including facial dysmorphic characteristics, congenital heart disease, skeletal and neurocognitive abnormalities[135,136]. While selective ablation of the KRAS4A isoform does not result in any obvious phenotype, expression of KRAS4A in the absence of KRAS4B prevents postnatal development[137,138]. In adult tissue, KRAS4A is more dynamically regulated, with a slightly increased ratio, and high expression is detected in cancer cells[139,140]. In detail, *KRAS* mutations account for 95 % of PDAC, 50 % of colorectal adenocarcinomas and 25 % of lung adenocarcinomas[141]. Mutations in *KRAS* primarily affect codons 12, 13 or 61, leading to constitutively active GTP-RAS molecules that do not respond to GAP-catalyzed intrinsic hydrolysis [124]. The most common *KRAS* activating mutations in PDAC are detected in codon 12 and include G12D (44 %), G12V (30 %), G12R (20 %) and G12C (1 %)[142]. Interestingly, each isoform exhibits distinct sensitivities to GAP/GEF modulations and controls specific transcriptional networks in different cellular settings[143,144].

There is little consensus on the potential implications of the wild-type forms of RAS proteins. In mice, the loss of wild-type *Hras* alleles during the early stages of cancer, combined with a *Kras* mutation, promotes early tumor formation. When combined with mutations in tumor suppressor genes, such as *Tp53*, this leads to the development of more aggressive tumors in mice, highlighting the importance of wild-type allele expression in modulating the early stages of PDAC[145]. Regarding *Nras*, studies have shown that this paralogue can exhibit different mechanisms in various types of cancer. For instance, the loss of wild-type *Nras* promotes oncogenesis in lung *Kras*-driven tumors but inhibits cancer progression in skin Hras-driven cancers[145]. The distinct effects of wild-type *N* and *Hras* remain unclear and appear to be context-dependent. Some studies have indicated that the loss of wild-type *Ras* alleles in cell lines derived from late-stage pancreatic ductal adenocarcinoma (PDAC) inhibits tumor growth[145]. However, other research involving human cohorts revealed the opposite: patients with higher levels of wild-type *Nras* had higher overall survival rates[146]. Considering all of this, further trials are necessary to analyze the possible implications of these two paralogues in PDAC.

3.2. KRAS signaling

RAS signaling plays a critical role in malignant transformation and tumor growth. Upon activation, the oncogenic isoforms initiate intracellular signaling that regulates survival, differentiation and proliferation[147]. Among the downstream signaling cascades, the mitogen-activated kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3K) pathway are best characterized, as they are highly dysregulated in many types of cancers[148]. In detail, RAS is activated by different cellular receptors including receptor tyrosine kinases (RTKs), G-protein coupled receptors (GPCRs) and integrin family members (Fig. 2). Commonly, RTKs induce activation of the RAS/MAPK pathway after their dimerization upon ligand binding. Subsequent autophosphorylation of their intracellular domain recruits the growth factor receptor-bound protein (GRB2) by interacting with its SH2 domain, which binds to the phosphotyrosine residues of the active receptor. GRB2 also attaches its SH2 domain to other adaptor proteins, such as the non-receptor protein tyrosine phosphatase (SHP2), resulting in the recruitment of GEFs. Alternatively, GRB2 binds with its SH3 domain to SOS1/2, the major RAS GEF, to allow for RAS activation[149] (Fig. 2). In turn, activated RAS-GTP interacts through the N-terminal RAS-binding domain (RBD) with the three downstream RAF (Rapidly Accelerated Fibrosarcoma) proteins A-RAF, B-RAF and C-RAF (encoded by *Raf1*). Through this interaction, the RAF kinase domains phosphorylate two serine residues of the catalytic domain of MEK, thereby activating the downstream kinases MEK1/2. MEK further catalyzes the phosphorylation and activation of the kinases ERK1/2 after transient formation of heterodimers [150] (Fig. 2). These Serine/Threonine kinases phosphorylate more than 150 substrates in different subcellular locations. In the cytosol, ERK phosphorylates and regulates metabolic enzymes and structural proteins, while in the nucleus, it promotes the transcription of a wide variety of factors, most of them implicated in cell proliferation and survival [151]. Another equally important RAS effector is the PI3K signaling cascade which has a key role in promoting cell survival[141]. PI3K is recruited to activate RTKs by its regulatory p85 subunit. Once active, the catalytic p110 subunit generates the second messenger phosphatidyl inositol 3,4,5-triphosphate (PIP3), which recruits the protein kinase B (AKT) to the membrane[143]. Activated AKT mediates several mechanisms of cell growth and survival (Fig. 2).

Moreover, KRAS interacts with a wider network of effectors through non-canonical pathways. These effectors include the Ras-related protein (RAL)-GEF, T-cell lymphoma invasion and metastasis 1/Ras-related C3 botulinum toxin substrate 1 (TIAM1/RAC1), phospholipase C epsilon (PLCε) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) pathways, which promote cytoskeletal remodeling, metabolic reprogramming, and cell survival[152–154]. KRAS signaling through RAL-GEFs (RALGDS, RGL1/2) activates RAL-GTPases (RALA/B). RALA has been reported to play a role in tumor initiation, while RALB activates the TANK-binding kinase 1/I-kappa-B kinase epsilon (TBK1/IKKε) complex, sustaining cytokine signaling and Janus kinase/signal transducer and activator of transcription (JAK/STAT) activation [153,155]. Both GTPases drive micropinocytosis, vesicle trafficking, and invasive capacity[153,155]. RAS can recruit the GEF TIAM1 to activate the GTPase RAC1, which mediates cytoskeletal reorganization through changes in actin dynamics, enhancing cell migration and metastasis [156]. The PLCε contains a specific RAS-binding domain and, when active, hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to generate two important second messengers: inositol trisphosphate (IP3) and diacylglycerol (DAG) which control the efflux of calcium and the activation of protein kinase C (PKC) contributing promoting proliferation and inflammation[157]. Finally, NF-KB is also activated through RALB via the RALB-Exocyst Complex Component 2 (EXOC2)-TBK1 complex, promoting anti-apoptotic gene expression and improving survival under stress conditions[155].

4. KRAS inhibitors

4.1. Multi-selective RAS inhibitors

During the last decades, KRAS was considered undruggable until the discovery of the allosteric targeting of G12C in the inactive GDP-bound state[158]. Since then, numerous inhibitors have been developed with promising results. Recently, multi-selective RAS-ON inhibitors that target the GTP-bound active state, such as RMC-7977, have recently appeared. This inhibitor forms a tri-complex with cyclophilin A (CYPA) and RAS and has high affinity for wild-type (WT) and mutant KRAS, HRAS and NRAS [159]. This molecule demonstrated wide and potent antitumor activity in preclinical models of PDAC, colorectal cancer (CRC) and non-small cell lung cancer (NSCLC)[159] (Table 3). RMC-7977 prevents cell proliferation and survival by inhibiting downstream RAF-MEK-ERK and PI3K-AKT signaling in PDAC cell lines and organoids and induces apoptosis by activating cleaved PARP and CASP3 in tumor cell lines [159,160]. Moreover, treatment with RMC-7977 resulted in extended survival of various allograft and xenograft models of PDAC, as well as the KPC GEMM (*Kras*$^{LSL.G12D/+}$;*Trp53*$^{LSL.R172H/+}$;*Pdx1*-Cre) [160]. Yet, relapsed tumors revealed that *Myc* copy number gain enables tumor cells to escape RAS-GTP inhibition, while resistance can also occur with gains in other genes, such as Jun and PI3K family members [160]. Remarkably, the anti-tumoral effect of RMC-7977 is also mediated by increased T cell proliferation and infiltration. Thus, the combination with anti-PD1, CD40 agonists and dual checkpoint inhibitors resulted in durable tumor regression [161].

Another covalent RAS-ON inhibitor, Daraxonrasib (RMC-6236), is

Table 3
RAS inhibitors in preclinical studies.

Inhibitor	Provider	Type of cancer	Preclinical models	Ref.
RMC-7977	Revolution Medicines	CRC/ NSCLC/ PDAC	Cell lines, organoids, allograft, xenograft, GEMMs	[159–161]
ADT-007/ ADT-1004	ADT Pharma, Nerd Bio	CRC/PDAC	Cell lines, organoids, allograft, xenograft	[166–170]
BI-2865	Boehringer Ingelheim	CRC/PDAC	Cell lines, xenografts	[175–179]
BI-2493	Boehringer Ingelheim	CRC/PDAC	Cell lines, xenografts	[175,176]
BI-2852	Boehringer Ingelheim	CRC/GC/ NSCLC/ OC/PDAC	Cell lines, spheroids, organoids	[163–166]
BAY-293 (SOS1-RAS)	Bayer AG	PDAC	Cell lines, spheroids, organoids	[182–184]
BI-3406 (SOS1-KRAS)	Boehringer Ingelheim	CRC/ NSCLC/ PDAC	Cell lines, xenografts	[183,185,186]

CRC = colorectal cancer, PDAC = pancreatic ductal adenocarcinoma, NSCLC = non-small cell lung cancer, GC = gastric cancer, OC = ovarian cancer, GEMMs = genetic engineered mouse models.

structurally similar to RMC-7977. Daraxonrasib has demonstrated efficient RAS inhibition in preclinical in vitro and in vivo cancer models, significantly preventing cell proliferation and tumor growth[162]. Moreover, Daraxonrasib results in improved response to immunotherapy with anti-PD1 and anti-CTLA4[162,163]. It is worth mentioning that optimization of RMC-7977 to Daraxonrasib demonstrated how preclinical tools validated the potential of targeting RAS(ON) variants, thus paving the way for an optimized compound with benefits for patients [162,164]. Currently, the Phase I/Ib clinical trial NCT05379985 evaluates the efficacy and safety of treatment with a 300 mg dosing of Daraxonrasib 300 mg. Early promising results have demonstrated an ORR of 36 % in KRASG12X patients and 27 % in patients with other RAS mutations in PDAC patients[165] (Table 4). However, recent results found, that patients treated with Daraxonrasib in monotherapy can develop resistance through MYC and PI3K gains, as well as through alterations in RAF and upregulation of RTKs[166]. Further, there were found amplifications in the KRAS oncogene[166]. Altogether, these findings suggest that patients might benefit from the combination of Daraxonrasib with other RAS inhibitors to make the RAS protein completely unavailable to effectors, by which the tumor cells can develop mechanisms of resistance[166]. Daraxonrasib is now being widely used in combination with G12C (NCT06128551) and G12D inhibitors and/or chemotherapy (NCT06162221, NCT06445062, NCT06625320, NCT06881784) (Table 4).

ADT-007 is also a panRAS inhibitor, targeting the three paralogs of RAS and the WT and mutant alleles of KRAS (Table 3). This compound stands out due to its selective mechanism in effectively blocking nucleotide-free RAS, thus preventing GTP loading and disrupting the binding of RAF and PI3K [167,168]. Through this mechanism, ADT-007 inhibits all RAS isoforms that are pathologically activated, either by mutations in RAS itself or by upstream RTK mutations, while leaving healthy cells unharmed. However, ADT-007 does not respond to downstream mutations or activations. This was demonstrated in vitro assays in which ADT-007 inhibited the growth of KRAS-WT and KRAS-mutant (G12C, G12D, G12R, G12V and G13Q) cancer cells, but did not affect the growth of BRAF-mutant and normal cells[168,169]. When tested in CRC PDOs, the compound reduced tumor burden, highlighting its potential for clinical use[160]. Moreover, it led to tumor regression in both immunocompetent and xenograft mouse models of CRC and PDAC [167,168]. ADT-007 also demonstrated the ability to modulate TME by increasing T-cell activation and adjusting the myeloid cell population [168]. Currently, an optimized prodrug, ADT-1004, is under preclinical evaluation, showing similar promising results and potential for translation to clinical trials[170,171].

BI-2852 binds to the switch I/II pocket of RAS proteins, inhibiting both RAS-ON and RAS-OFF states[172–174] (Table 3). It has a higher

Table 4
PanRAS and PanKRAS inhibitors under clinical studies.

Inhibitor	Clinical trial	Combination	Tumor type	Phase	Preclinical models	Ref.
Daraxonrasib Revolution Medicines	NCT05379985		CRC/NSCLC/ PDAC	I-IB	Cell lines, xenografts	[162–165]
	NCT06128551	RMC-6291	CRC/NSCLC/ PDAC	IB		
	NCT06162221	RMC-6291 Pembrolizumab Chemotherapy	NSCLC/Lung Cancer Solid Tumors	IB-II		
	NCT06445062	Bevacizumab, 5-FU/ Cetuximab, mFOLF./ Gemc., Nab-paclitaxel/ Bevacizumab, 5-FU, Zoldonrasib/ Cetuximab Zoldonrasib, mFOLF./ Zoldonrasib, Gemc., Nab-paclitaxel	Metastatic CRC/ Metastatic PDAC	I-II		
	NCT06625320	Gemcitabine/Irinotecan/ Nab-paclitaxel/5-FU/ Leucovorin/Oxaliplatin	Metastatic PDAC	III		
	NCT06881784	Docetaxel	Metastatic NSCLC	III		
	NCT06922591	TNG462	NSCLC/PDAC	I-II		
BI-3706674 Boehringer Ingelheim	NCT06056024	–	EAC/GAC/ GEJAC	I	Cell lines, xenografts	[180,181]
BI-1701963 Boehringer Ingelheim	NCT04111458	Trametinib	KRAS Mutated Solid Tumor	I	Cell lines, xenografts	[185–187]
	NCT04185883	Sotorasib	KRAS G12C Mutated	IB		
	NCT04627142	Irinotecan	Metastatic CRC	I		
	NCT04835714	BI-3011441	KRAS Mutated Solid Tumors	I		
	NCT04973163	BI-182391	KRAS Mutated Solid Tumors	I		
	NCT04975256	MRTX849	KRAS G12C Mutated	I-IB		
	NCT06620848	Adebremilab	CCA	II		
	NCT06773130	Nimotuzumab	Metastatic PDAC	I-II		

5-FU = 5-fluorouracil, Gemc. = Gemcitabine, mFOLF. = mFOLFIRINOX, CRC = colorectal cancer, NSCLC = non-small cell lung cancer, PDAC = pancreatic ductal adenocarcinoma, EAC = oesophageal adenocarcinomas, GAC = gastric adenocarcinoma, GEJAC = gastroesophageal junction adenocarcinoma.

affinity for KRAS but can interact with all RAS isoforms due to the conserved nature of the pocket[173,174]. BI-2852 demonstrated the ability to inhibit cell proliferation in diverse cancer models, including cell lines, spheroids and organoids, specifically in PDAC. However, some variations in the response of PDOs to the inhibitors were observed, indicating that the compound efficacy relies in other tumor characteristics in addition to RAS. Additionally, feedback regulation of the RAS pathway indicated a reduction in BI-2852 activity, suggesting that resistance may occur through this mechanism[175]. These new inhibitors, which can block all forms of RAS, may offer patients greater benefits. Although mutations in *Nras* or *Hras* are not predominant in PDAC, the correlation between the presence of wild-type forms of these paralogues and the compensatory effects in PDAC remains unclear [145].

Beyond panRAS inhibitors, panKRAS inhibitors are under preclinical and clinical studies. BI-2865 and its structural analog BI-2493 bind non-covalently to the KRAS inactive state at distinct sites, inhibiting KRAS WT and the mutant variants G12C, G12D, G12V and Q61X[176,177] (Table 3). Both compounds reduced proliferation in cell lines. Moreover, BI-2493 demonstrated increased efficacy in cells with amplified KRAS WT, as well as disruption of downstream pathways. BI-2493 also significantly suppressed tumor growth in xenografts[176]. Interestingly, BI-2865 reversed multidrug resistance (MDR) by competitively binding to P-glycoprotein (P-gp), a transmembrane transport protein that controls drug efflux [178,179]. Thus, the combination of BI-2865 and paclitaxel significantly decreased tumor growth in P-gp overexpressing xenograft models[180]. Together, these findings supported the development of BI-3706674 for clinical use. BI-3706674 is a non-covalent KRAS-OFF inhibitor that blocks the interaction of the GDP-bound state of KRAS with SOS, with high affinity for KRAS WT and the KRAS mutant alleles G12A, G12D, G12V, G13D and Q61H[181]. Through this mechanism, the compound produces strong anti-proliferative activity in the RAS-MEK-ERK pathway, which is demonstrated by the inhibition of ERK1/2 phosphorylation and down-regulation of DUSP6[181,182]. This multi-KRAS inhibitor leads to increased efficacy in KRASG12V-mutant tumor cell lines and xenografts, along with amplifications of the KRAS WT allele (copy number $>$ 10), frequent in the GDP-bound inactive state. These data support further clinical testing (NCT06056024) in gastroesophageal cancers with these genomic alterations[181,182] (Table 4). BI-3706674 leads to the development of resistance through activation of RTKs. Indeed, BI-3706674 has demonstrated synergy with the EGFR monoclonal antibody Cetuximab in xenograft models[182]. Further studies using ex vivo organoids help identify other resistant mechanisms and future drug combinations [182].

Another approach to (indirectly) inhibit KRAS is to target GEFs that facilitate the GDP to GTP exchange. The BAY-293 and BI-3406 compounds target the SOS1 catalytic domain responsible for the protein–-protein interaction (PPI) with KRAS[183,184]. Both compounds demonstrated inhibition of downstream effectors of the KRAS cascade in G12C and G12D models[183,184] (Table 3). Specific studies of BAY-293 in 2D and 3D NSCLC showed that SOS1 inhibition also reduces MYC expression even when its levels are high[185]. BI-3406 proved to reduce tumor growth in a wider panel of KRAS mutations, also including G12V and G13D PDX models[186]. The activity of this inhibitor was also characterized by a modulation of the TME by reducing the presence of CAFs and macrophages in the tumor[187]. Furthermore, BAY-293 and BI-3406 enhanced the activity of MEK inhibitors[184,187]. Based on these promising results, the inhibitor BI-1701963 was developed for clinical use. This SOS1 inhibitor is now under clinical testing (NCT04111458), including combinations with G12C inhibitors (NCT04185883, NCT04975256, NCT04973163), MEK inhibitors (NCT04111458, NCT04835714) or chemotherapeutic agents (NCT04627142) (Table 4) [186,188].

4.2. Mutant-specific RAS inhibitors

4.2.1. KRAS G12D inhibitors

Structure-based drug design recently defined MRTX1133 as the first noncovalent selective G12D inhibitor[189]. MRTX1133 has a high-affinity interaction with GDP-loaded KRAS and has been widely used in preclinical studies. Both its anti-tumoral effect and its ability to inhibit KRAS activity were first validated in xenograft models of PDAC, CRC and NSCLC[189]. In vitro assays with PDAC cell lines and organoids demonstrated that MRTX1133 exhibits dose-dependent inhibition of KRAS-driven signaling and viability[189]. The same study also provided a combination of viability screening and identified synergistic effects with ERBB-family and PI3K inhibitors in PDAC and CRC cells[189]. Similarly, the dual inhibition of $KRAS^{G12D}$ after the combination of MRTX1133 with the panERBB inhibitor Afatinib resulted in enhanced tumor regression and extended survival of orthotopic PDAC mouse models. Further studies using orthotopic and autochthonous KPC GEMMs demonstrated that its efficacy is associated with reprogramming fibroblasts and immune cells of the TME[190,191]. Both studies revealed an increase in tumor-infiltrating T cells and validated their contribution to the antitumoral effect of MRTX1133 and thus, synergy with immune checkpoint blockade against PDAC[190,191]. Currently, MRTX1133 is under first-in-human clinical investigation (NCT05737706) to evaluate safety and efficacy properties (Table 5).

Distinctly, another G12D-selective inhibitor, HRS-4642, is a non-covalent inhibitor that binds to both the active and inactive form of KRAS with higher affinity than MRTX1133, preventing its binding to SOS1 and RAF1[192]. Preclinical studies demonstrated a significant reduction of tumor size in CRC and PDAC allograft and xenograft models at low doses[192]. Interestingly, genome-wide CRISPR-Cas9 screening in HRS-4642 resistant PDAC cells revealed sensitization targets related to KRAS signaling and proteasome activity. Thus, the combination with the proteasome inhibitor Carfilzomib resulted in enhanced tumor regression and increased immune cell infiltration[192]. The clinical properties of HRS-4642 are currently being evaluated in a first-in-human trial (NCT05533463) in patients with $KRAS^{G12D}$ solid tumors [193] (Table 5).

Zoldonrasib (RMC-9805) is a RAS-ON inhibitor that selectively forms a tri-complex with KRASG12D and cyclophilin A and has demonstrated tumor regression in PDAC PDXs and cell-derived xenografts (CDXs). Importantly, enhanced synergy was observed upon its combination with other RAS-ON, SHP2 and mTOR inhibitors, resulting in improved tumor response[194]. Zoldonrasib also synergized with anti-PD1 inhibitors through cytokine modulation in the TME[194]. Early results of the clinical trial NCT06040541 indicated that Zoldonrasib had an ORR of 30 %, without any severe toxicity. Currently, multiple combination treatments are being included in the study (Table 5).

4.2.2. KRAS G12C inhibitors

Although KRASG12C-mutated tumors are not common among pancreatic cancer, they are more present in other cancer types like NSCLC and CRC in frequencies of 12 % and 3 %, respectively[123]. During the last decade, multiple G12C-selective inhibitors have been developed, yet just two are approved for clinical use. Sotorasib (AMG510) is a small molecule that irreversibly inhibits KRAS by covalently binding to the switch II pocket only present in its inactive GDP-bound state. It was approved in 2021 by the FDA, after phase I/II clinical trial CodeBreaK100 (NCT03600883) resulted in promising efficacy and safety in patients with locally advanced or metastatic NSCLC [195,196]. This first trial also included 38 patients with PDAC who harbor a G12C mutation, previously treated with chemotherapy. In detail, Sotorasib induced response rates of 42 % and 21 % in NSCLC and PDAC patients, respectively, and a median overall survival of 12.5 and 6.9 months, respectively, with tolerable side effects [195,197]. Currently, Sotorasib is under clinical evaluation in combination with other treatments in $KRAS^{G12C}$ mutant advanced solid tumors,

Table 5
Selective KRAS G12D and G12C inhibitors approved or under clinical studies.

Inhibitor	Clinical trial	Combination	Tumor type	Phase	ORR %	Preclinical models	Ref.
KRAS G12D							
HRS-4642 Jiangsu Heng Rui Medicine	NCT05533463	–	BC/ CC/ CCA/ EC/ OC/ PDAC	I	39/50/22/ 57,5/45/4	Cell lines, organoids, allograft, xenograft	[183,184]
	NCT06385678	Adebrelimab/ SHR-9839/ Cetuximab/ Pemetred Disodium, Cisplatin, Carboplatin	Metastatic Solid Tumors	IB-II	NR		
	NCT06427239	Adebremilab	PDAC	I-II	NR		
	NCT06620848	Adebremilab	CCA	II	NR		
	NCT06773130	Nimotuzumab	Metastatic PDAC	I-II	NR		
MRXT1133 Mirati Therapeutics	NCT05737706	–	CRC/NSCLC/ PDAC	I-II	NR	Cell lines, organoids, xenograft, GEMMs	[180–182]
Zoldonrasib Revolution Medicines	NCT06040541	Daraxonrasib	CRC/NSCLC/ PDAC	I-IB	NR/NR/ 30	Cell lines, xenografts	[185]
KRAS G12C							
Sotorasib Amgen	NCT03600883	Docetaxel	NSCLC	FDA	36	Cell lines, xenograft	[186–188]
Adagrasib Mirati Therapeutics	NCT03785249	Docetaxel Cetuximab	NSCLC	FDA	43		[189–192]
Divarasib Genentech	NCT04449874	Cetuximab Erlotinib	CRC/NSCLC/ PDAC	I	29,1/53,4/ 42,8		[196,197]
Olomorasib Eli Lilly and Company	NCT04956640	Pembrolizumab	CRC/NSCLC/ PDAC	I	9/60/42		[123,198]
Glecirasib Jacobio Pharmaceuticals	NCT05002270	–	CRC/PDAC	I-II	33,3/42		[199,200]

CRC = colorectal cancer, NSCLC = non-small cell lung cancer, PDAC = pancreatic ductal adenocarcinoma, EAC = oesophageal adenocarcinomas, BC = bladder cancer, CC = cervix cancer, CCA = cholangiocarcinoma, EC = endometrium cancer, OC = ovarian cancer, FDA = FDA-approved, NR = not reported, GEMMs = genetic engineered mouse models.

CodeBreaK 101 (NCT04185883). Moreover, phase III trial CodeBreaK 200 (NCT04303780) is also testing the benefit of Sotorasib in NSCLC against the commonly used docetaxel.

Adagrasib (MRTX849), an FDA-approved KRAS-OFF G12C-selective inhibitor, showed efficacy in studies with G12C-mutated cell lines and xenograft models [198]. The phase I/II clinical trial KRYSTAL-1 (NCT03785249) demonstrated a favorable safety profile of Adagrasib in CRC, PDAC and NSCLC tumors harboring KRAS G12C mutations. Adagrasib also demonstrated good pharmacokinetic properties with a longer half-life than Sotorasib in previously treated patients with KRAS G12C-mutated NSCLC[199]. Treatment with Adagrasib resulted in a 33.3 % response rate with a progression-free survival of 6.6 months in pretreated patients with PDAC[200]. The KRISTAL-1 trial also demonstrated a response rate of 34 % in CRC after combination with cetuximab (EGFR inhibitor), leading to FDA approval in patients with advanced or metastatic CRC previously treated with chemotherapy[201]. Currently, phase III trial KRISTAL-12 (NCT04685135) evaluates the efficacy of Adagrasib versus docetaxel in previously treated patients with NSCLC [190].

Other recently developed G12C-selective inhibitors include Divarasib, Olomorasib and Glecirasib, with promising preclinical results in cell lines and xenograft models[202203204]. Divarasib is a covalent inhibitor that binds to the cysteine residue and blocks KRAS into its inactive state with higher potency and selectivity than Sototrasib and Adagrasib. Clinically, it has demonstrated improved response in patients with advanced or metastatic solid tumors[205]. The reported response rate was 53.4 % in NSCLC and approximately 29.1 % in CRC with median progression-free survival of 13.7 and 6.9, respectively[196]. Its efficacy is currently being evaluated in combination with cetuximab and erlotinib (anti-EGFR), with improved anti-tumoral activity in patients with prior anti-G12C treatments (NCT04449874)[206] (Table 5).

Olomorasib is another second-generation inhibitor that binds to KRAS in its inactive state. It is currently in phase I-II trials (NCT04956640) in NSCLC, CRC and PDAC[207] (Table 5). Early results demonstrated ORR of almost 60 % in patients with naïve NSCLC tumours, 9 % in patients with CRC, and 42 % in patients with PDAC[123] (Table 5). Olomorasib is also being tested in combination with other drugs such as pembolizumab (anti PD-1) (NCT06119581) as first-line treatment in NSCLC[207].

Glecirasib is an orally administered covalent KRAS G12C inhibitor currently in Phase I-II evaluation for PDAC (NCT05002270) and NSCLC (NCT05009329) (Table 5). Preliminary results for NSCLC reveal ORR of 47.9 % and a good safety profile [208]. Thus, new clinical trials are moving to combinations with JAB-3312 (anti-SHP2) versus immune and chemotherapy (NCT06416410). Glecirasib also achieved a promising and well-tolerated ORR of 46.4 % in patients with PDAC [209].

5. Future perspectives

Several large-scale genomic studies of pancreatic cancer have reported mutations involved in at least 12 signaling pathways and frequent chromosomal rearrangements[210–212]. This complex heterogeneity in signaling is partially responsible for the limited success of most clinical trials carried out during the last two decades[11]. Thus far, significant progress has been made to identify molecular subtypes according to the transcriptomic profiles of PDACs[213]. In the concept of PDAC classification, it was recently described in GEMM and PDX models that tumors resistant to KRAS inhibition shift from classical to mesenchymal subtype and serve as a reservoir for disease relapse[123]. This highlights the necessity for prognostic signatures to predict response to therapy and the development of resistance in advanced tumors. Indeed, it is worth acknowledging recently developed transcriptomic signatures for personalized adjuvant chemotherapy[214,215].

Currently, cytotoxic chemotherapy is the standard treatment, with OS ranging from weeks to months, with increased toxicities[216]. Undoubtedly, there is an urgent need to develop novel targeted therapies that block specific oncogenic pathways with reduced toxicity. Although recently developed RAS inhibitors have demonstrated significant antitumor activity in preclinical models, they have resulted in the appearance of drug resistance in early clinical trials[160,217,218]. Hence, more efficient therapeutic combinations are needed against KRAS-driven cancers. Our laboratory presented a novel approach based on double targeting of KRAS signaling by inhibition of *Egfr* and *Raf1*, inducing a complete regression of 50 % of the analyzed PDAC[88].

Other preclinical studies also reported therapeutic activity after inhibition of other components of the KRAS signaling network, including SHP2, MEK and ERK downstream kinases[219]. However, clinical assessment of these compounds as monotherapy led to limited response, while suggesting the possible potential of future synergistic combinations. Indeed, it was recently highlighted that more combination therapies are needed to maximize clinical benefit[220,221]. Also contributing to the need for combination therapies are the non-canonical RAS effectors, their activation can promote cancer cells to evade RAS-targeting therapies, contributing to intrinsic and acquired resistance[218,222].

Yet, further studies are still needed targeting the extended KRAS signaling network in different nodes[211]. This requires better molecular characterization of PDACs at different stages, with the use of various and complementary preclinical models, as well as advanced technological approaches[223,224].

Despite recent significant advances in the field, many challenges remain to achieve rational KRAS-targeted therapies against PDAC. Preclinically, the complementarity of the different models facilitates the study of the characteristics of pancreatic cancer. On one hand, GEMM models recapitulate very well the human disease, including the nature of the complex TME. However, they can be time-consuming and more expensive than other implantation models. Importantly, they are a valuable tool to assess vivo toxicities before moving to the clinical setting. Yet, animal experimentation often fails to predict human toxicity in pharmaceutical development. On the other hand, patient-derived models such as PDO and PDX reflect the genomic heterogeneity of human tumors, there is limited information on mutation-specific responses to strategies against KRAS or the KRAS signaling network.

Clinically, even though RAS inhibitors have shown promise in preclinical models, none have been approved for PDAC patients so far. Ongoing trials have given a significant response in patients, yet intrinsic and acquired resistance mechanisms limit the durability of KRAS inhibitors. Moreover, the clinical setting in pancreatic cancer is often restricted due to patient-enrolling barriers and lack of patient stratification. Unfortunately, PDAC patients are often present at advanced stages, with poor performance status, thus making them ineligible for trials. Another challenge is the short survival time, which limits opportunities for longitudinal studies or multiple lines of therapy. Last, many clinical trials do not stratify patients by specific RAS or other mutations (TP53, SMAD4, CDKN2A), contributing to heterogeneous responses and preventing the identification of subgroups that may benefit from specific therapies[209,210].

In summary, overcoming the limitations of preclinical models and clinical trial designs is essential for advancing KRAS-targeted therapy in PDAC. To our consideration, current challenges should be addressed by global efforts of all parties, including clinicians, patients, investigators, industry and related agencies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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