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Therapeutic targeting of the functionally elusive TAM receptor family

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Abstract

The TAM receptor family of TYRO3, AXL and MERTK regulates tissue and immune homeostasis. Aberrant TAM receptor signalling has been linked to a range of diseases, including cancer, fibrosis and viral infections. Specifically, the dysregulation of TAM receptors can enhance tumour growth and metastasis due to their involvement in multiple oncogenic pathways. For example, TAM receptors have been implicated in the epithelial–mesenchymal transition, maintaining the stem cell phenotype, immune modulation, proliferation, angiogenesis and resistance to conventional and targeted therapies. Therapeutically, multiple TAM receptor inhibitors are in preclinical and clinical development for cancers and other indications, with those targeting AXL being the most clinically advanced. Although there has been notable clinical advancement in recent years, challenges persist. This Review aims to provide both biological and clinical insights into the current therapeutic landscape of TAM receptor inhibitors, and evaluates their potential for the treatment of cancer and non-malignant diseases.

Introduction

TYRO3, AXL (also known as UFO) and MERTK comprise the TAM receptor tyrosine kinase (RTK) family, which was identified in 1991 (refs. 1–4). Genetic knockout studies demonstrated that the inactivation of individual TAM receptors has little effect on embryonic development, suggesting they are functionally redundant, and developmental defects in mice only occur after the loss of two or more TAM family members[2].

Experimental evidence indicates that the TAM receptors have critical roles in promoting phagocytosis of apoptotic cells, functioning as gatekeepers to prevent hyperreactive immune responses, and regulating vascular integrity and blood vessel permeability[3–6]. In addition, TAM receptors are also referred to as phosphatidylserine virus entry enhancing receptors (PVEERs), due to their ability to interact with phosphatidylserine (PtdSer) present on the viral envelope that facilitates viral entry[7].

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

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In cancer, TAM receptor activation promotes cell proliferation and metastasis[8–11]. Historically, *AXL* cDNA was isolated from primary human myeloid leukaemia cells and, when overexpressed in NIH3T3 cells, induced neoplastic transformation[12,13]. This was followed by the identification of *MERTK* (*c-MER*) from a human B lymphoblastoid cDNA expression library in 1994 (ref. 14). Although *Tyro3* cDNA was isolated from the mouse central nervous system using a similar screening approach, it later showed the ability to promote anchorage-independent growth when transfected into untransformed fibroblasts, a hallmark of oncogenicity[15–17].

Unlike many RTKs, TAM receptors are rarely mutated, and dysregulation of receptor activity is mostly due to gene amplification or activation by their microenvironment, making them ideal therapeutic targets with minimal concerns of developing mutation-driven drug resistance[18]. The majority of TAM receptor inhibitors, including small molecules and biological agents (biologics), have been developed to target or disrupt the AXL signalling pathway. Clinically, AXL inhibitors are in multiple clinical trials for various oncology indications, and MERTK inhibitors are following very similar developmental plans[19]. This Review provides biological and clinical insights into the functional consequences of TAM receptor activation and surveys the current therapeutic landscape of inhibitors that target the TAM receptor family for both cancer and non-cancer indications.

Protein structure of the TAM receptor family

Similarly to many other trans-membrane RTKs, the TAM receptors have an extracellular domain, which consists of two immunoglobulin domains that are essential for ligand binding followed by two fibronectin type III repeats[20]. The intracellular kinase domain is highly conserved between the three receptors, which all feature a KWIAIES sequence that is unique to this family of RTKs[21] (Fig. 1). TAM receptors primarily interact with two ligands, growth arrest-specific protein 6 (GAS6) and vitamin K-dependent protein S1 (PROS1)[22–26] (Box 1). Although structural data for receptor–ligand complexes are not available for TYRO3 and MERTK, the structure of AXL in complex with GAS6 provides insight into the binding configuration between TAM receptors and their ligands[20,27]. An initial 1:1 interaction between the AXL receptor and GAS6 leads to a 2:2 formation of AXL and GAS6, resulting in receptor homodimerization and activation of the intracellular catalytic domain[28]. Autophosphorylation of the TAM receptor catalytic domains promotes binding to the p85 subunit of phosphatidylinositol 3-kinase (PI3K), SRC family members and growth factor receptor-bound protein 2 (GRB2), leading to activation of MEK–ERK signalling[27,29–31].

Ligand-mediated interactions

The GAS6 and PROS1 ligands have sex hormone-binding globulin (SHBG) domains, composed of two LG domains on their carboxy termini, which interact with the extracellular immunoglobulin domains of the TAM receptors and initiate receptor activation. A vitamin K-dependent carboxylation domain (Gla domain) is located in the amino terminus of both GAS6 and PROS1, which is important for binding phospholipids in the cell membrane[27,32]. Another unique feature of the Gla domain is its ability to bind to PtdSer through interaction

with γ-carboxyglutamic acid, a common gateway hijacked by viruses to gain entry into mammalian cells[33–35] (Fig. 2a).

GAS6 is a 75-kDa protein that binds to all three TAM receptors, with strongest binding affinity towards AXL, followed by TYRO3 and weakest affinity for MERTK[36]. Although binding to MERTK is weak, this does not undermine the critical role of GAS6-induced MERTK activation in some tissues[24]. Structural studies revealed two contact points between GAS6 immunoglobulin domains and AXL immunoglobulin domains[20]. The major contact groove or so-called 'high-affinity' interaction occurs between $Ig2^{GAS6}$ and $Ig1^{AXL}$, and the minor contact is between $Ig1^{GAS6}$ and $Ig2^{AXL}$. This distinctive binding conformation facilitates the binding of two GAS6 molecules to homodimeric AXL receptors as seen in the co-complex structure[20]. Although the exact binding conformation between GAS6 and MERTK or TYRO3 requires further clarification, the structural similarities among TAM receptors and their ligands strongly suggest that a similar co-complex structure is likely.

PROS1 is a 73-kDa, vitamin K-dependent protein that bears close structural resemblance to GAS6. Moreover, similar to GAS6, PROS1 forms dimers when binding to TAM receptors[32,37]. The blood PROS1 concentration is significantly higher than that of GAS6 under normal physiological conditions (300 nM versus 0.2 nM)[38–41]. These differences in blood concentration are consistent with PROS1 playing a pivotal role in regulating blood coagulation and having additional functions beyond TAM receptor activation. Biologically, PROS1 acts as a cofactor for protein C to prevent blood coagulation through the inhibition of factor Vα and factor VIIIα. Thus, a deficiency in PROS1 significantly increases the risk of venous thrombosis[42–44]. PROS1 is capable of activating MERTK and TYRO3 but not AXL, leaving GAS6 the predominant, if not only, ligand capable of activating AXL signalling[45].

In addition to GAS6 and PROS1, the proteins TUBBY, TULP1 and GALECTIN 3 have been identified as potential ligands of MERTK that are capable of activating macrophage phagocytosis in retinal epithelium and hepatocytes[46,47]. However, further studies are required to provide more clarity on their roles as activating ligands of TAM receptors.

All three TAM receptors rely on ligand-mediated activation for receptor signalling. Efficient activation of TAM receptors by GAS6 and PROS1 is dependent on vitamin K-dependent γ-carboxylation of the Gla domain[48,49]. Interestingly, inhibition of GAS6 carboxylation or loss of the Gla domain does not prevent GAS6 from binding TAM receptors but inhibits receptor activation[50]. Importantly, PtdSer is found on the surfaces of stressed or apoptotic cells and vesicles such as exosomes. Therefore, all of these membrane surfaces have the potential to interact with GAS6 and PROS1, representing a vital step in TAM receptor activation[50] (Fig. 2a).

Some studies have reported that AXL formed heterodimers with other RTKs in a tissue-dependent manner[51]. In some cases, ligand-independent receptor dimerization and activation have been reported for AXL and, to some extent, TYRO3 (refs. 52,53). Because there is little definitive structural or biochemical evidence to support these observations, additional studies are necessary[54].

Physiological roles of TAM receptors

TAM receptors have important physiological roles in various cellular processes, such as fetal development and adult tissue homeostasis. They function as negative regulators of the immune response and facilitate phagocytic removal of apoptotic cells[4,55]. TAM receptor signalling is equally critical for the preservation of vascular integrity[56]. In addition, aberrant activation of TAM receptors results in abnormalities in the immune, vasculature and male reproductive systems[3,6,57,58].

Immune response functions

TAM receptor expression in the immune system is localized to activated dendritic cells, macrophages, myeloid-derived suppressor cells and natural killer cells, all of which are essential regulators of the innate immune response[56,59]. Mice with genetic ablation of *Tyro3*$^{-/-}$, *Axl*$^{-/-}$ and *Mertk*$^{-/-}$ (TAM TKO) have provided insights into the functional consequences of TAM receptor activation within the immune landscape[56]. For example, receptor crosstalk can occur between TAM receptors and the interferon-α/β receptor (IFNAR)–STAT signalling pathway, which downregulates the inflammatory response through SOCS1 and SOCS3, inhibiting inflammation mediated by Toll-like receptors (TLRs)[60,61]. The role of TAM receptors in natural killer cell maturation and T cell activation has also been reported and is likely to be driven by PROS1 (ref. 54). Activated T cells secrete PROS1 as part of their negative feedback response and animals lacking PROS1 exhibit an exacerbated T cell response upon immunization[62]. Clearly, TAM receptors and their ligands are important players in modulating the magnitude and intensity of the immune response and in maintaining the intricate homeostasis of the innate and adaptive immune pathways.

Phagocytic clearance of apoptotic cells

TAM receptors contribute to phagocytosis and the clearance of cell debris in various cell types (Fig. 2b). Complete loss of all three TAM receptors in mice leads to diminished phagocytic clearance of apoptotic cells and cellular debris by macrophages and dendritic cells, and this failure to maintain tissue homeostasis results in hyperactive and pathogenic inflammatory responses[56]. For example, the elimination of the photoreceptor outer segment in the retina is typically performed by MERTK-expressing phagocytic retinal pigment epithelium. Retinal pigment epithelium cells lacking MERTK fail to remove toxic debris and the resulting hyperactive inflammatory response leads to the death of photoreceptors, retinal degeneration and, ultimately, blindness, as demonstrated in *Mertk*$^{-/-}$ rodent models[63–65]. However, a recent study suggests that TYRO3 function might be concomitantly lost in this model, resulting in exacerbation of the retinal degeneration phenotype[66]. Loss of all three TAM receptors has also been proposed to be responsible for male infertility due to the failure of phagocytic Sertoli cells to clear apoptotic germ cells[3]. Clearly, TAM receptors have a critical role in maintaining appropriate immune homeostasis, and the dysregulation of TAM receptors will result in a plethora of pathogenic inflammatory responses.

Vascular functions

Because GAS6 and PROS1 are essential to the growth and maintenance of endothelial cells and platelets, TAM receptor signalling has been implicated in maintaining blood vessel integrity and permeability, as exemplified by the susceptibility of TAM TKO mice to haemorrhage[56]. In particular, reports have proposed that AXL promotes vessel growth through interaction with VEGFA and signalling through PI3K and AKT (Fig. 2c). For example, loss of AXL leads to the impairment of blood vessel formation both in vitro and in vivo[67,68], whereas inhibition of MERTK or TYRO3 only results in mild effects[69]. However, the role of AXL in blood vessel development needs additional investigation as *Axl*$^{-/-}$ mice appear phenotypically normal without obvious blood vessel dysfunction.

In addition, TAM receptor ligands are known to promote angiogenesis and platelet aggregation[6,70]. *Pros1*$^{-/-}$ mice are embryonically lethal due to substantial vessel leakage and haemorrhage[71,72]. Interestingly, unlike *Pros1*$^{-/-}$ mice, *Gas6*$^{-/-}$ mice appear to be phenotypically normal with adequate platelet counts and clotting factor levels with no reports of spontaneous bleeding or thrombosis[73]. However, when challenged with agonists such as thrombin, *Gas6*$^{-/-}$ mice produced significantly smaller thrombi compared with wild-type controls[74]. These data suggest that pharmacological inhibition of GAS6 could be effective at reducing thrombosis with reduced risk of haemorrhagic complications.

TAM receptor signalling in cancer

Aberrant TAM receptor signalling in cancer growth and progression is well documented[75]. Although not considered conventional oncoproteins, TAM receptors that become aberrantly activated can drive metastasis, facilitate therapeutic resistance and promote cancer cell survival during hypoxia and nutrient deprivation[11,76–78] (Table 1). Activating mutations within the TAM receptor kinase domain are rare, which supports the requirement for ligand-mediated activation.

AXL expression and function

Dysregulated expression of AXL has been reported in cancers of diverse histological origins (Table 1), and GAS6–AXL signalling is associated with various pro-tumorigenic functions[79]. AXL expression is regulated at the transcriptional level in response to external stimuli. For example, under hypoxic conditions, cancer cells stabilize the hypoxia inducible transcription factors 1 and 2 (HIF1 and HIF2), to activate AXL and promote low oxygen adaptation[78]. In contrast, STAT1 regulates *AXL* mRNA downstream of TLR signalling[54,80]. Thus, different stresses can regulate AXL through numerous different transcriptional regulatory elements.

Given that gain-of-function AXL mutations are found in less than 1.5% of AXL-positive cancers, it might be concluded that GAS6 is the primary regulator of AXL activation[79]. However, although elevated GAS6 levels are associated with many AXL-positive cancers, the stoichiometric relationship between GAS6 and AXL is not an exact 1:1 ratio. Such discrepancy is, in part, the result of protease-mediated receptor ectodomain shedding. The extracellular domains of AXL and MERTK can be cleaved by proteases such as ADAM10

and ADAM17, leading to proteolytic shedding of the receptors, which act as soluble receptor traps to regulate free GAS6 and PROS1 levels in blood[81].

AXL facilitates epithelial–mesenchymal transition (EMT), a critical cancer metastasis initiation event that promotes the migratory and invasive capability of tumour cells[79]. Intrinsic AXL signalling positively regulates transcription factors required for EMT, including TWIST, ZEB1, ZEB2 and SLUG, and also promotes the expression of N-cadherin and downregulation of E-cadherin to facilitate EMT[79]. In addition, AXL can facilitate the activation of other key oncogenic pathways, such as those stimulated by MET, SRC and Ras, to promote EMT[78] (Fig. 3).

In response to stress, cancer cells upregulate AXL signalling as a protective measure to ensure survival. In addition, elevated AXL expression is often associated with resistance to therapy in both haematological and solid tumours[82,83]. Specifically, AXL signalling is thought to mediate resistance to the EGFR inhibitor cetuximab and radiation through the activation of AKT and ERK signalling pathways, and decreases tumour cell apoptosis by modulating the activity of c-ABL[84]. Pharmacologic inhibition of AXL restores sensitivity of tumour cells to cytotoxic therapy and significantly reduces the tumour burden in xenograft models of metastatic ovarian cancer[85]. Furthermore, upregulation of AXL signalling is frequently observed in cancers resistant to various tyrosine kinase inhibitors. For example, aberrant AXL expression strongly correlates with erlotinib resistance in non-small-cell lung cancer (NSCLC) and sunitinib resistance in renal cell carcinoma[86]. In both cases, inhibition of AXL genetically or pharmacologically results in re-sensitization to these targeted molecules. Similarly, single-cell profiling identified high AXL levels as a hallmark associated with treatment relapse in BRAF V600E mutant melanoma, indicating that targeting AXL in melanoma might enhance the response to BRAF V600E inhibitors[87]. The success of immune checkpoint therapies has increased interest in targeting the immune system to control tumour growth and metastasis. AXL expression is elevated in patients unresponsive to PD1 immunotherapy, and inhibition of AXL in tumours that are resistant to both immunotherapy and radiation can facilitate the release of tumour antigens, promoting T cell-mediated tumour killing[82]. Taken together, these findings provide a scientific rationale for the addition of AXL inhibitors to immunotherapy or radiation treatment to enhance efficacy.

A subset of cancer cells retain the ability to self-renew and are referred to as cancer stem cells. These cells promote aggressive tumour growth, facilitate metastasis and foster therapeutic resistance[88]. Interestingly, a correlation between AXL expression and cancer stem cell markers, including CD44, ALDH1, ISL1 and CDC2A, has been reported in many cancer types such as cutaneous squamous cell carcinoma, breast cancer and glioblastoma[89–91]. Loss of AXL signalling genetically or through pharmacologic inhibition greatly reduces the ability of cancer cells to form organoids and restores sensitivity to chemotherapy.

A mechanistic link between GAS6–AXL signalling and angiogenesis has recently been established. AXL signalling promotes plasmin production, endothelial cell invasion and angiogenesis in clear cell renal cell carcinoma by positively regulating the plasminogen receptor S100A10. Inhibition of AXL with the small-molecule inhibitor cabozantinib or a

high-affinity soluble AXL (sAXL) Fc fusion decoy receptor reduced blood vessel density and tumour growth in a pazopanib-resistant patient-derived xenograft model of clear cell renal cell carcinoma[92]. This study highlights the role of AXL in regulating angiogenesis through S100A10 signalling in a cancer resistant to a tyrosine kinase inhibitor.

Published data consistently support a role for AXL signalling in positively regulating tumour survival, metastasis and drug resistance, but how AXL governs these multiple functions remains elusive. A likely scenario is that AXL signalling acts to promote cancer cell survival when encountering both intrinsic and external stress stimuli. These stress stimuli could include oxygen or nutrient deprivation, immune cell-mediated attack, cytotoxic chemotherapy or ionizing radiation. Tumour cells elevate AXL expression as part of their survival strategy when encountering an unfavourable growth environment. Therefore, eliminating AXL in cancer cells facilitates enhanced tumour killing and prevents drug resistance[85].

MERTK expression and function

Unlike AXL, which has ubiquitous expression in cancer, elevated MERTK expression is particularly associated with haematological cancers[93–96] (Table 1). MERTK expression in haematological cancers is important for the evasion of innate immune surveillance, thus promoting the growth and proliferation of malignancies such as acute lymphoblastic leukaemia and acute myeloid leukaemia (AML)[97,98]. Aberrant expression of MERTK occurs in 30% of paediatric B cell acute lymphoblastic leukaemias[97]. MERTK expression is upregulated in macrophages during efferocytosis, a process that involves the removal of apoptotic cells through phagocytosis[99]. In glioblastoma, inhibition of MERTK led to a reduction in $CD206^+$ anti-inflammatory M2-like macrophages. Although this effect alone was insufficient to prolong survival, the combination of MERTK inhibition with radiation resulted in a significant reduction in tumour growth, a shift in M2-like to M1-like macrophage polarization and a heightened pro-inflammatory immune response in animal models of glioblastoma[95] (Fig. 3).

Although there are only a few studies reporting high levels of MERTK in solid tumours such as melanoma and prostate cancer, this restricted expression pattern supports its highly controlled regulation in tissues[54]. A role for MERTK in promoting tumour growth has been established in multiple melanoma tumour models. Furthermore, pharmacological inhibition of MERTK can effectively suppress oncogenic signalling in melanoma and reduce tumour growth independently of BRAF status[96]. Although the functional significance of MERTK activity in solid tumours is yet to be fully understood, the inhibition of MERTK has the potential to augment immune responses by amplifying neoantigen production and attracting pro-inflammatory immune cells. Consequently, this implies that MERTK inhibitors could enhance the effectiveness of immune checkpoint therapies and might represent a promising strategy that should be tested in the clinic.

TYRO3 expression and function

Elevated TYRO3 expression has been reported in multiple malignancies such as squamous cell cancer, lung cancer, prostate cancer, thyroid cancer, schwannoma and multiple myeloma

(Table 1), but its functional roles and clinical relevance remain unclear[100–103]. The shared expression pattern of all three TAM receptors in certain cancers implies a degree of functional redundancy. This redundancy is notable because critical oncogenic pathways, such as PI3K–AKT and STAT signalling, can be activated either directly or indirectly through TAM receptor activation. Furthermore, similar biological outcomes, such as the promotion of cancer progression through EMT signalling pathways and the development of therapeutic resistance, have been documented[104,105] (Fig. 3).

TYRO3 demonstrates its distinctive biological activity in the regulation of bone homeostasis. TYRO3 regulates the differentiation and function of osteoclasts, which are responsible for bone resorption in normal bone remodelling. Nevertheless, aberrant TYRO3 signalling can worsen pathological conditions, including osteoporosis and the development of bone metastases[106]. These findings suggest that TYRO3 could be a promising therapeutic target for restoring osteodynamics and to prevent cancer metastasis to bone. Further research is needed to fully elucidate the role of TYRO3 in cancer, as well as to evaluate the potential clinical benefits of TYRO3-targeted therapies.

TAM receptors in non-malignant diseases

Whereas TAM receptors are essential in maintaining the homeostatic balance of the immune, haematopoietic and vascular systems[56], aberrant TAM receptor signalling is often the underlying cause of diseases such as fibrosis, autoimmune disorders and viral infections[56,107,108]. In this section, we will explore the biological consequences of TAM receptor signalling in various non-malignant diseases.

Fibrosis

Tissue fibrosis is characterized by extensive accumulation of extracellular matrix (ECM) and stromal elements in response to chronic inflammation and tissue injury[109]. The TAM receptor family has critical roles during tissue remodelling in fibrotic diseases (Fig. 4). The same GAS6–TAM receptor pathway that transforms epithelial-like cancer cells into mesenchymal cells seems to be adopted by tissues under chronic inflammation to form fibrotic scars[110]. In liver cirrhosis, AXL signalling is activated to induce the transcription of *SLUG*, a critical regulator of EMT[111]. Furthermore, AXL interacts with TGFβ, promoting the deposition of α-smooth muscle actin (α-SMA), collagen and matrix metalloproteinases (MMPs) in a SMAD3-dependent manner[112] (Fig. 4). In a *Gas6*$^{-/-}$ non-alcoholic steatohepatitis model, animals deficient in GAS6 had reduced hepatic inflammation, fibrosis and decreased expression of TGFβ and collagen I[113]. Idiopathic pulmonary fibrosis (IPF) is another potentially deadly fibrotic disease leading to progressive loss of lung function[114]. IPF tissues express elevated levels of TAM receptors and GAS6, and small-molecule inhibitors that target multiple TAM receptor kinases exhibit enhanced anti-fibrotic activity when compared with biologics that specifically target the GAS6 and AXL pathway, suggesting that IPF has co-opted the entire TAM receptor family[115].

Autoimmune disease

The pathology of autoimmune disease is diverse and extremely complex. However, most clinical presentations are associated with abnormal immune complexes and the production

of autoantibodies. Autoimmune diseases promote chronic inflammatory responses, leading to destruction of normal tissue[56]. An important role of TAM receptors in immune regulation is in clearing apoptotic cells, which is primarily driven by MERTK signalling[116]. Loss of MERTK signalling has been described in numerous autoimmune diseases, including systemic lupus erythematosus and multiple sclerosis. For example, Ballantine et al. reported a reduction of intact MERTK receptors on monocytes and macrophages from juvenile patients with systemic lupus erythematosus, consistent with decreased phagocytosis, supporting the essential role of MERTK in apoptotic cell clearance in systemic lupus erythematosus[117]. Myelin is a critical component of the central nervous system, and its disruption is a hallmark of multiple sclerosis[118]. MERTK has an important role in regulating myelin phagocytosis by microglia and macrophages, which are key immune cells involved in multiple sclerosis pathology. MERTK is required for microglial activation and subsequent remyelination[119]. Considering these findings, activation of MERTK emerges as a promising therapeutic avenue in multiple sclerosis, with the potential to alleviate myelin phagocytosis, enhance debris clearance and decrease neuroinflammation[120].

Viral entry

Throughout evolution, viruses have acquired the capability to evade innate immune responses for successful host entry. Among their evasion mechanisms is the ability of virions to encapsulate in a lipid bilayer comprising the host cell's plasma membrane, leading to viral engulfment and release[121]. Viruses that utilize this mode of host cell entry include the Zika, Ebola, Marburg, dengue and West Nile viruses[122–124]. In particular, these enveloped viruses use PVEERs, including AXL, MER and TYRO3, to enter human host cells[125]. It is probable that enveloped viruses exposing PtdSer can form complexes with GAS6 or PROS1 on the Gla domain, thereby enabling them to exploit all three TAM receptors for cellular entry[72]. Because AXL is the most abundant and ubiquitously expressed TAM receptor, it has a higher probability of being used for viral entry. In addition to this mechanism, apoptotic mimicry is another strategy employed by enveloped viruses to gain entry into host cells in an 'immunologically silent' fashion. Viruses expressing PtdSer dock onto host cells expressing TAM receptors, facilitating endocytic engulfment. Upon docking, the virus can also suppress the inflammatory response by facilitating TAM receptor-mediated inhibition of TLR signalling, allowing it to evade immune surveillance[122] (Fig. 2a). Recent Zika and Ebola virus outbreaks have generated significant interest in targeting TAM receptors as a method to inhibit virus uptake by host cells[126,127].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the host cell via binding to angiotensin converting enzyme 2 (ACE2). Bohan et al. reported that the presence of the GAS6–AXL receptor complex can enhance SARS-CoV-2 infection when ACE2 levels are low, even though SARS-CoV-2 does not use AXL receptors for cell entry. Therefore, disruption of the GAS6–AXL–PtdSer complex might be a potential therapeutic approach to lessen the severity of SARS-CoV-2 infection[128].

Translational landscape of TAM receptor inhibition

TAM receptor inhibitors have shown promising results in preclinical and clinical studies for both malignant and non-malignant diseases. Strong evidence has shown that TAM receptor

inhibitors can promote antitumour immune responses, reduce inflammation and improve responses to cancer therapy when combined with standard-of-care treatments. With the growing understanding of TAM receptor signalling and the development of new therapeutic agents, TAM receptor inhibition represents a promising approach for the treatment of a wide range of diseases.

The two major strategies that have been investigated for the inhibition of TAM signalling are inhibiting receptor–ligand interactions and inhibiting kinase activity. The majority of TAM receptor inhibitors are small molecules that block kinase activity, but given the high degree of homology between the kinase domains of TAM receptors, most of these small molecules promiscuously inhibit all three TAM family members as well as other kinase receptors.

Anti-AXL antibodies and sAXL decoy receptors that specifically block the binding between AXL and its ligand GAS6 have been developed and are currently in late-phase clinical trials[36,129]. More recently, an AXL aptamer that inhibits AXL-mediated signalling has also been developed[130]. In addition, two AXL antibody–drug conjugates are currently being tested in the clinic for the treatment of various oncology indications[131,132]. In the section below, we provide a description of TAM inhibitors and their biological properties (Table 2 and Fig. 3).

Small-molecule inhibitors

Most TAM receptor inhibitors are chemically synthesized small molecules designed to interfere with the ATP binding moiety located on the intracellular kinase domain. Multiple small molecules with low nanomolar IC_{50} values against TAM receptors are in preclinical and clinical development.

Clinical development programmes.—Approximately 20 small-molecule inhibitors targeting TAM receptors have been tested in clinical trials, with 15 of them currently undergoing active commercial development (Table 2).

Bemcentinib (BGB324) is a clinical stage AXL inhibitor with an IC_{50} of 14 nM that has 50-fold to 100-fold selectivity for AXL compared with MERTK and TYRO3. The efficacy of bemcentinib was validated in preclinical models of ovarian cancer, glioblastoma, mesothelioma, pancreatic cancer, breast cancer and lung cancer[91,133,134]. In all of these models, bemcentinib was proposed to exhibit its therapeutic efficacy in an AXL-dependent manner[134]. Bemcentinib is now one of the most advanced AXL inhibitors currently in clinical development, with five phase I/II programmes in NSCLC, triple-negative breast cancer (TNBC) and melanoma (NCT03184571, NCT02872259, NCT03184558). In addition to clinical studies in patients with cancer, clinical studies investigating bemcentinib as a treatment for COVID-19 are also ongoing (NCT04890509).

RXDX-106 was developed as a pan-TAM inhibitor and has a slow dissociation rate to improve its potency. RXDX-106 inhibits AXL (IC_{50} = 7 nM), TYRO3 (IC_{50} = 19 nM), MERTK (IC_{50} = 29 nM) and c-MET (IC_{50} = 12 nM). Yokoyama et al. reported that tumour growth inhibition in mice by RXDX-106 was associated with increased tumour-infiltrating lymphocytes, polarization of M1-like intratumoural macrophages and activation of natural

killer cells[135]. Combining RXDX-106 with an anti-PD1 antibody resulted in an enhanced antitumour effect. However, a phase 1 study of RXDX-106 that commenced in March 2018 (NCT03454243) was terminated in 2019 by the sponsor.

MRX-2843 is a MERTK inhibitor (IC_{50} = 1.3 nM) that also inhibits FLT3 with high potency (IC_{50} = 0.64 nM). In comparison with previous generations of the compound, UNC1062 and UNC20205, MRX-2843 showed improved oral bioavailability, enhanced solubility, drug metabolism and pharmacokinetic properties. The in vivo efficacy of MRX-2843 was reported in quizartinib-resistant FLT3-ITD mutant preclinical AML models demonstrating that MRX-2843-treated animals had significantly prolonged overall survival[136]. MRX-2843 was also tested in EGFR inhibitor-resistant NSCLC models and acute lymphoblastic leukaemia, where it exhibited strong anticancer activity and decreased PD1 expression on T cells, leading to immune-mediated therapeutic activity[97,137]. Multiple clinical trials are ongoing to investigate the efficacy of MRX-2843 in relapsed/refractory metastatic solid tumours (NCT03510104), in multiple subtypes of acute leukaemia (NCT04872478, NCT04946890) and in combination with the EGFR inhibitor osimertinib for the treatment of NSCLC (NCT04762199).

Sitravatinib (MGCD516) inhibits all members of the TAM receptor family. Cell-free assays revealed that the IC_{50} for all TAM receptors is below 2 nM. This molecule shows potent antitumour efficacy in preclinical models of renal cell carcinoma, NSCLC, sarcoma and breast cancer[138,139]. However, it is likely that the strong antitumour effect observed is attributable to multi-kinase inhibition beyond the TAM family. Sitravatinib is in late-stage clinical development in more than 30 clinical trials targeting various solid tumour types, including NSCLC and melanoma. It is also being evaluated as part of a combination treatment with anti-PD1 antibodies and chemotherapy (NCT04921358, NCT05461794).

ONO-7475 is a potent inhibitor of AXL (IC_{50} = 0.7 nM) and MERTK (IC_{50} = 1.0 nM). In preclinical models of AXL-expressing, EGFR mutant NSCLC, ONO-7475 treatment sensitized cells to EGFR tyrosine kinase inhibitors, leading to tumour regression and delayed tumour growth. AML cells bearing FLT3 mutations exhibited sensitivity to ONO-7475 treatment, leading to cell death. Furthermore, enhanced efficacy was observed when ONO-7475 was utilized in combination with the BCL-2 inhibitor venetoclax, resulting in a further reduction in the tumour burden[140,141]. However, recruitment was terminated in clinical trials of ONO-7475 for patients with acute leukaemias (NCT03176277).

Multi-kinase Inhibitors that inhibit TAM receptors include crizotinib, sunitinib, bosutinib, gilteritinib, cabozantinib, S49076, SNS314, BMS-777607 and merestinib. These are included in Table 2 and Fig. 3 but not discussed further here. In most cases they lack selectivity for the TAM kinase family and have not demonstrated TAM inhibition as a mechanism of antitumour activity in patients.

Preclinical development programmes.—New small molecules aimed at targeting TAM receptors are in active development and undergoing testing in preclinical settings. Some of these molecules are showcasing novel mechanisms of action.

NPS-1034 is an inhibitor with an IC_{50} of 10.3 nM for AXL and 48 nM for c-MET. This molecule also possesses inhibitory activity at a lower potency against MERTK and several other kinases such as SCF1R, DDR and FLT3. NPS-1034 has anti-proliferative and pro-apoptotic activity in vitro as a single agent. When used in combination with the EGFR inhibitor gefitinib in tumour cell lines, it can overcome drug resistance caused by MET amplification[142].

LDC1267 was developed as a pan-TAM receptor inhibitor and has nanomolar IC_{50} values against all three TAM receptors, with highest inhibitory activity for MERTK at $IC_{50} < 5$ nM. LDC1267 treatment resulted in the enhancement of natural killer cell tumour killing activity in vivo, leading to a significant reduction in murine melanoma metastasis[143].

SGI-7079 is a type II ATP-competitive inhibitor that binds to the hydrophobic pocket of the ‘DFG-out’ conformation of kinases (often associated with an inactive kinase state). SGI-7079 inhibits AXL kinase with an IC_{50} of 58 nM, and partially restored treatment sensitivity to mesenchymal NSCLC cells that were resistant to the EGFR inhibitor erlotinib in an EGFR mutation-independent manner. This molecule also demonstrated potent inhibition of MERTK, TYRO3, FLT1, SYK and PDGFRβ in vitro[144].

The field of TAM receptor-targeted therapies is evolving rapidly, with promising molecules in clinical development and novel mechanisms of action on the horizon. These advancements offer new hope for more effective cancer treatment.

Biologics and novel therapeutic strategies

Biologics have been designed to specifically target and bind TAM receptors, thereby reducing off-target effects and improving therapeutic selectivity compared with small molecules. Biologics have a long half-life, which can lead to sustained and durable inhibition, making them an attractive option for TAM receptor inhibition.

Clinical development programmes.—The landscape of TAM receptor-targeted therapies, including biologics and other novel therapeutic strategies, has witnessed significant advancements in recent years, offering promising avenues in the treatment of various cancer types. Here, we highlight several therapies currently in clinical development.

Batiraxcept (AVB-S6–500) is an engineered ultra-high-affinity sAXL decoy receptor that is distinct from other AXL inhibitors. It was designed to bind and neutralize GAS6 at femtomolar binding affinity. By adopting a directed evolution-based strategy through an unbiased mutation screening approach, sAXL decoy receptor mutants were generated with a 320-fold improvement in binding affinity towards GAS6 compared with the wild-type AXL receptor[36]. Preclinically, batiraxcept displayed significant antitumour activities in preclinical models of ovarian cancer, AML, breast cancer, renal cancer and pancreatic cancer[85]. It also significantly enhances the therapeutic efficacy of cytotoxic chemotherapy, radiation therapy, immune checkpoint blockade (ICB) and anti-angiogenic therapy[92]. In a phase Ib trial, patients dosed with batiraxcept in combination with paclitaxel showed an overall response rate of 34.8% with two complete responses (NCT03639246)[145]. Based on data presented in the phase Ib trial, the US Food and Drug Administration (FDA) granted ‘Fast

Track Designation' to batiraxcept in platinum-resistant recurrent ovarian cancer. However, results from a phase III study, combining batiraxcept with paclitaxel, did not demonstrate a significant improvement in therapeutic outcomes compared with the control treatment. (NCT04729608). Currently, this molecule is being explored in other cancers, including clear cell renal cell carcinoma (NCT04300140), and pancreatic cancer (NCT04983407).

Tilvestamab is a fully humanized AXL blocking antibody that has an affinity of 5–500 pM for the AXL receptor and exhibits little binding to MERTK or TYRO3. Functionally, Tilvestamab blocks GAS6 binding to AXL and exhibits antitumour activity in AML, NSCLC, pancreatic cancer and renal cancer models. Tilvestamab is being tested in a phase I clinical trial in relapsed, platinum-resistant high-grade serous ovarian cancer (NCT04893551).

Enapotamab vedotin (HuMax-AXL-ADC) is an antibody–drug conjugate comprising an anti-AXL antibody conjugated to cytotoxic auristatin E for targeted elimination of AXL-expressing cancer cells. HuMax-AXL-ADC selectively targets cells expressing high levels of AXL to improve the potency of BRAF and MEK inhibitors in melanoma treatment[146]. A phase I/II open-label, dose-escalation trial with an expansion cohort to evaluate the safety and antitumour activity of HuMax-AXL-ADC in patients with solid tumours was completed in 2020 (NCT02988817). Unfortunately, a lack of sufficient clinical efficacy led to the discontinuation of this programme.

Mecbotamab vedotin (CAB-AXL-ADC) is another antibody–drug conjugate targeting AXL-expressing tumour cells. Although there are no research data available in the public domain, a company press release highlighted that this molecule demonstrates conditional activation within the tumour microenvironment, thereby reducing the risk of normal tissue toxicity. Three phase II clinical studies evaluating the safety and efficacy of CAB-AXL-ADC as a monotherapy or in combination with PD1 inhibitors for the treatment of NSCLC, ovarian cancer and other solid tumours are ongoing (NCT04681131, NCT03425279, NCT04918186).

Biologic therapeutics targeting TAM receptors have witnessed significant advancements in recent years. These biologics represent an exciting frontier in oncology research and offer new avenues for improving patient outcomes.

Preclinical development programmes.—YW327.6S2 is an affinity-matured anti-AXL antibody developed using a phage-display platform. This molecule recognizes both human and mouse AXL with a K_D of 1 nM and 545 pM, respectively. YW327.6S2 blocks the ligand–receptor interaction between GAS6 and AXL in a dose-dependent manner and does not cross-react with MERTK or TYRO3. Unfortunately, YW327.6S2 monotherapy did not demonstrate satisfactory efficacy in preclinical in vivo studies and was not pursued as a clinical candidate. It is worth highlighting that the binding of native GAS6 to AXL is very strong (K_D = 32 pM), and the lack of in vivo efficacy observed with YW327.6S2 was likely due to its weaker affinity compared with GAS6 (ref. 147).

AXL aptamer GL21 is a 34-mer, RNA-based aptamer that was generated from a library of single-stranded RNAs using the SELEX platform. In human U87MG glioma cells, GL21 binds to the extracellular binding domain of AXL with a K_D of 12 nM and can disrupt GAS6-mediated AXL activation in vitro. Treatment with GL21 also inhibited tumour growth in a NSCLC lung xenograft model[148]. Due to their small size and high specificity, nucleotide-based aptamers represent a highly versatile class of molecules for clinical use through forming conjugates with drugs such as cytotoxic chemotherapy to deliver target-mediated killing of tumour cells. However, development of GL21 could run into the same problem as YW327.6S2 given its weaker binding affinity towards AXL compared with wild-type GAS6.

Combination therapies

Inhibition of TAM receptor activity can lead to therapeutic resistance, but TAM receptor inhibitors can be combined with cytotoxic therapeutics such as chemotherapy and radiotherapy to overcome treatment resistance[36,149,150]. Importantly, inhibition of individual TAM receptors seems to have minimal toxicity towards normal tissue, with the exception of MERTK inhibition in photoreceptors[56]. For example, a phase I clinical study of the engineered AXL decoy receptor batiraxcept demonstrated a remarkable safety profile in normal healthy volunteers, where biomarker analysis showed complete neutralization of GAS6 (ref. 145). Molecules of this class presented the opportunity to combine TAM receptor inhibitors with standard-of-care treatments without adding further toxicity. Clinically, enhanced antitumour efficacies have been reported with TAM receptor inhibitors used in combination with cytotoxic chemotherapies, immune checkpoint inhibitors or other kinase inhibitors[151–153]. In this section, we will discuss the biological rationale of combining TAM receptor inhibitors with other therapies.

Combinations with RTK inhibitors.—Dysregulated kinase signalling enhances the growth and dissemination of cancer cells, and inhibitors against kinases such as EGFR, BRAF and VEGF have been validated in the clinic to prolong survival of patients with cancer[154,155]. Unfortunately, intrinsic and acquired drug resistance is common for all kinase inhibitors and poses a significant clinical challenge[156]. Both acquired resistance due to crosstalk between kinase receptors and intrinsic, mutation-driven resistance can result in the loss of therapeutic efficacy in patients[157].

TAM receptors share similar downstream effectors with many oncogenic RTKs, and therefore TAM receptor activation can promote drug resistance by signalling to the same downstream effectors when oncogenic RTKs are inhibited[75]. In NSCLC cell lines, elevated AXL expression alone is sufficient to mediate resistance to EGFR inhibition by maintaining the downstream activities of the PI3K–AKT and MEK–ERK signalling pathways[86]. In NSCLC clinical samples derived from patients resistant to EGFR inhibitors, AXL signalling is increased and, potentially, a resistance mechanism.

In addition to compensating for the loss of RTK signalling to critical downstream effectors, AXL can also crosstalk with other RTKs by forming receptor dimers[157]. Dimerization of AXL and EGFR has been reported in head and neck cancer and could be a contributing

factor towards persistent EGFR signalling in the presence of cetuximab[84]. Resistance to PI3K inhibitors can also occur due to AXL–EGFR dimerization, leading to compensatory activation of the PLCγ–PKC–mTOR pathway instead of the PI3K–AKT signalling cascade[51]. In preclinical studies of breast cancer, AXL induces acquired resistance to the HER2 inhibitor lapatinib by promoting dimerization with HER3, bypassing HER2-mediated signalling[158].

Although AXL activity is frequently reported when drug resistance induced by RTK inhibitors occurs, the role of MERTK and TYRO3 in this context remains poorly investigated. Given the overlapping expression of TAM receptors in some cancers, MERTK and TYRO3 are likely to have a role in promoting therapeutic resistance[105,159]. In some tumours, increased MERTK expression compensates for AXL inhibition, and inhibition of MERTK activity can re-sensitize head and neck squamous cell carcinoma, TNBC and NSCLC to AXL inhibition[137,159]. Collectively, these data support the use of TAM inhibitors with other kinase inhibitors to enhance antitumour efficacy and block acquired drug resistance.

Combinations with immune checkpoint blockade.—ICB has achieved impressive clinical success in recent years. However, the patient response varies significantly with a high proportion of non-responders lacking a cytotoxic T cell response[160]. Given that innate immunity has a crucial role in the priming and activation of T cells, research has been focused on the regulation of dendritic cells, antigen-presenting cells, macrophages, myeloid-derived suppressor cells and natural killer cells, which all govern the innate immune response and, interestingly, express high levels of TAM receptors upon ICB treatment[54]. Under physiological conditions, TAM receptor activity is required for preventing hyper-stimulated, uncontrolled inflammatory responses. However, during cancer progression, TAM activation promotes immunosuppression and protects tumour cells from immune surveillance, suggesting that therapeutic blockade of TAM receptor activity in tumours might facilitate immune-mediated tumour killing. Given that AXL and MERTK have highly differentiated but important roles in regulating the immune response, selective inhibition of each receptor can be used to target different components of the innate immune system.

The potential therapeutic benefit of inhibiting AXL signalling in combination with ICB has been reported in preclinical and clinical studies. Aguilera et al. showed that an ICB-resistant subclone of MMTV-PyMT breast cancer possessed higher expression levels of AXL compared with radiation-sensitive and ICB-sensitive cells. Mechanistically, this resistance to ICB therapy can be explained by AXL-expressing tumour cells mediating the downregulation of MHC class I molecules and increasing the numbers of immune-suppressive tumour macrophages. Genetic deletion of AXL in this breast cancer model resulted in significantly enhanced $CD8^+$ T cell infiltration and tumours sensitized to ICB and radiation treatment[82]. Additionally, Tsukita et al. reported a correlation between *AXL*, *PDL1* and *CXCR6* mRNA transcripts in a model of EGFR mutant lung adenocarcinoma. In this model, pharmacologic inhibition of AXL was sufficient to decrease the expression of *PDL1* and *CXCR6* at the transcriptional level[161]. Clinically, the AXL inhibitor bemcentinib is being tested in combination with the immune checkpoint inhibitor pembrolizumab for the treatment of chemotherapy and ICB refractory NSCLC (NCT03184571).

Under physiological conditions, MERTK is essential for maintaining efferocytosis and macrophage polarization. In the tumour microenvironment, elevated MERTK facilitates immune evasion by elevating expression of the tumour-promoting cytokines IL-4, IL-10 and TGFβ[162]. Increased MERTK expression is found on tumour-associated myeloid-derived suppressor cells, suggesting that MERTK signalling favours the recruitment of tumour-promoting immune suppressor cells[163]. However, inhibition of MERTK in patients can potentially have opposing effects due to its non-redundant role in phagocytosis. A soluble MERTK receptor that traps both GAS6 and PROS1 resulted in defective engulfment of apoptotic cells by macrophages and deficient platelet aggregation[164]. Therefore, it will be challenging to identify a MERTK inhibitor that can safely and effectively promote an immune response in tumours.

Combinations with DNA damaging agents.—Cytotoxic agents are often used as front-line therapies for cancer treatment[165,166]. These agents cause cell death in a non-selective manner by inducing lethal amounts of DNA damage that force cancer cells to undergo apoptosis or reproductive cell death. The most common DNA damaging agents that are used in cancer therapy include platinum-based chemotherapies[167], paclitaxel (Taxol)[168], doxorubicin and poly(ADP-ribose) polymerase (PARP) inhibitors[151,169]. Kariolis et al. demonstrated that a sAXL decoy receptor inhibited GAS6-mediated AXL signalling in ovarian cancer cells, leading to increased DNA damage. A combination of this sAXL decoy receptor with doxorubicin resulted in a greater than additive effect in decreasing the tumour burden in vivo compared with either agent alone[85]. Furthermore, Quinn et al. reported that high expression of AXL predicts chemoresistance in patients with ovarian cancer, and treatment of chemoresistant patient-derived xenografts with an AXL inhibitor improved the tumour response to paclitaxel and carboplatin[133]. These studies support the rationale of using AXL inhibitors in tumours that have developed resistance to chemotherapy.

Ionizing radiation is highly effective at treating cancers including head and neck squamous cell carcinoma, breast cancer, lung cancer, prostate cancer and some forms of gliomas[170]. Further enhancement of the therapeutic efficacy of radiotherapy can be achieved when combined with ICB and anti-angiogenic agents. However, despite its clinical success, the failure of radiation therapy to eradicate a tumour can be attributed to both intrinsic and exogenous factors[171]. Elevated expression of AXL is well described in radiation-resistant tumours and inhibitors of AXL are being investigated as radiosensitizers. AXL-induced resistance of tumours to radiotherapy can be achieved through different mechanisms[82]. Specifically, activation of tyrosine 821 on the AXL kinase domain is linked to radiation resistance through c-ABL signalling[84]. AXL signalling has also been implicated as a mechanism of resistance to the combination of EGFR antibody therapy and radiation treatment in head and neck squamous cell carcinoma.

A synergism in tumour cell killing when AXL inhibitors and PARP inhibitors are combined has been reported. PARP inhibitors selectively prevent the addition of branched PAR chains to histones and chromatin-associated proteins to aid in the recruitment of repair proteins for DNA single-strand break repair. Inhibition of PARP in homologous recombination-deficient cancer cells results in synthetic lethality. Interestingly, AXL inhibition has been proposed to induce a ‘transient’ state of homologous recombination deficiency in cancer cells,

sensitizing them to PARP inhibition and providing a scientific rationale for combining AXL and PARP inhibitors[172].

Unfortunately, the importance of MERTK and TYRO3 in the DNA damage and repair response of cells is less well studied. However, as MERTK signalling promotes phagocytic clearance and is required for apoptotic induced immune cell tolerance, MERTK inhibition might increase the therapeutic efficacy of DNA damaging agents by promoting an inflammatory response[173]. As TYRO3 activity is important for the physiological homeostasis of neuronal cells, inhibition of TYRO3 could be beneficial for the treatment of gliomas.

TAM receptor inhibitors for non-malignant indications

Emerging biological evidence supports the expansion of TAM receptor inhibitors for non-oncology indications. GAS6, AXL and MERTK are associated with the pathological development of many fibrotic diseases including non-alcoholic steatohepatitis, alcoholic liver disease, hepatitis C (HCV), IPF and IgA nephropathy[174–177]. The AXL inhibitor bemcentinib has been evaluated in a carbon tetrachloride (CCl_4)-induced mouse liver fibrosis model. In this model, bemcentinib inhibited the activation of hepatic stellate cells, diminished collagen deposition in association with reduced MM9 and reduced α-SMA expression[174]. Similarly, Kariolis et al. showed that inhibition of GAS6–AXL signalling by treatment with a non-clinical version of batiraxcept led to reduced collagen deposition in highly desmoplastic, chemoresistant pancreatic tumours, allowing better tissue penetration and cytotoxic activity of gemcitabine[85]. Therefore, targeting TAM receptor signalling is a potential clinical strategy for treating various types of fibrosis. In addition, the MERTK inhibitor UNC569 (a derivative of MRX-2843) has demonstrated the ability to inhibit the activation of hepatic stellate cells[178].

As discussed earlier, TAM receptor signalling is used by enveloped viruses as a route of entry into mammalian cells. In light of the recent Zika and Ebola virus outbreaks, the clinical use of AXL inhibitors to prevent viral entry through PtdSer-mediated cell internalization has been proposed. Pharmacological inhibition of AXL leads to a reduction in viral titre and viral-induced inflammatory responses in Zika virus-infected human cells[179]. The question remains whether AXL inhibitors possess sufficiently potent antiviral activity to be considered for use in the clinic.

There is some evidence suggesting that TAM receptors serve as a point of entry for SAR-CoV-2 into host cells when ACE2 expression is limited[128], and the AXL inhibitor bemcentinib has been tested in a phase II clinical trial for COVID-19 (NCT04890509). Although the trial reported mixed outcomes, a subset of patients treated with bemcentinib showed symptom improvement with measurable clinical responses. Although this study is intriguing, the use of TAM receptor inhibitors in treatment of COVID-19 will require additional investigation.

Most studies have focused on understanding the pathological outcomes of TAM receptor signalling, and the therapeutic effect of TAM receptor inhibition. However, TAM receptor activation is also necessary as a negative regulator of the inflammatory response, and

its activity is often suppressed in autoimmune diseases. Therefore, development of TAM receptor agonists for autoimmune diseases should be considered[180]. Experimentally, recombinant GAS6 and PROS1 reduce collagen-induced arthritis when administered both systemically and locally[181]. In addition, an AXL activating antibody administered in vivo demonstrated anti-inflammatory effects through the suppression of *IFNβ1* and *IFNα4* at the transcriptional level 2 h post administration[182]. These studies indicate that activating TAM receptors and their ligands is a potential therapeutic strategy for autoimmune diseases.

Summary and outlook

Significant progress has been made in recent years towards understanding the roles of TAM receptors in normal tissue homeostasis and disease states. In particular, the mechanistic consequences of TAM receptor activation in cancer have been the subject of intense study. A large body of literature now supports a critical role for AXL and MERTK in tumour progression and therapy resistance. Compelling preclinical studies have led to the development of therapeutic agents targeting TAM receptors as a family, as well as inhibitors specific to AXL and MERTK. Many of these molecules are demonstrating promising results, with efficacy as a single agent or in combination with other targeted and cytotoxic therapies in preclinical settings, but exactly which tumours will benefit from targeting TAM receptors alone or in combination in the clinic is still under investigation.

More than 20 TAM receptor inhibitors are being clinically developed for treating various malignancies and other diseases (Table 2). Although the majority of these inhibitors are small molecules, biologics in the form of soluble receptor ligand traps, antibodies and antibody–drug conjugates are also being evaluated. Small molecules are cost-effective to synthesize, yet a significant challenge lies in their lack of specificity, which is primarily attributed to structural homology within the catalytic domain of TAM family members. It is important to note that most small molecules are developed to inhibit TAM receptor activities as part of a multi-kinase inhibition approach, and therefore they exhibit potent inhibitory activity against many kinases. Because cancer growth and metastasis are likely to occur due to the dysregulation of many kinases, these types of inhibitors could provide more efficacious antitumour responses than selective agents towards the TAM family alone. However, inhibiting multiple kinases often leads to dose-limiting toxicities. For example, foretinib is a highly potent multi-kinase inhibitor of MET, VEGFR2 and AXL[183], but unfortunately exhibited dose-limiting toxicities during phase II clinical trials that prevented its further clinical development (NCT00920192)[18]. Biologics in the form of antibodies and ligand traps provide a path forward for selectively disrupting TAM receptor–ligand interactions. However, these approaches have their own challenges. In particular, molecules with strong binding affinities are required to successfully disrupt the GAS6–AXL signalling axis due its high native binding affinity in the picomolar range. Additional challenges associated with TAM receptor inhibition are further discussed in Box 2.

Collectively, our understanding of the biology of TAM receptor signalling during physiological and pathological states has led to the development and advancement of TAM receptor inhibitors and, in some cases, activators. In the next 5 years, the clinical success of these molecules will be determined, in the hope that they benefit patients.

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Box 1

GAS6 and PROS1 expression and their roles in regulating receptor activities

Growth arrest-specific protein 6 (GAS6) is expressed in various tissues and cell types, including vascular endothelial cells in the heart, kidney and lungs; platelets; immune cells, such as myeloid cells[184–186]; and in the brain, particularly in astrocytes[187]. GAS6 expression is induced in response to various stimuli, including growth factors, cytokines and oxidative stress. GAS6 has been implicated in the regulation of physiological processes such as coagulation and vascular remodelling, and immune functions such as phagocytosis[188].

Vitamin K-dependent protein S1 (PROS1) expression has been observed in a wide range of tissues and cell types. High PROS1 expression was reported in the neural tissue, liver, kidney, lung and gonads[6]. Cell types that are positive for PROS1 expression include neuronal cells, vascular endothelial cells, platelets, Sertoli cells, retinal pigment epithelium cells and osteoblasts[3,116,189,190]. PROS1 has many overlapping functions with GAS6, including promoting blood coagulation, maintaining vascular function and facilitating phagocytosis[62,72,191]. Dysregulation of PROS1 signalling is associated with the pathogenesis of diseases including thrombosis, inflammation and cancer[188]. Importantly, PROS1 activates MERTK and TYRO3 but not AXL, leaving GAS6 the predominant, if not only, ligand capable of activating AXL signalling[45].

Box 2

Challenges of TAM receptor inhibition

Despite the clinical advances in TAM receptor therapies, several challenges still persist. Although genetic and pharmacological inhibition of individual TAM receptors can suppress tumour growth and improve the antitumour response in the setting of combination therapy, redundancy can occur amongst TAM receptors and generate compensatory signalling. For example, inhibiting AXL leads to MERTK upregulation in some cell types, promoting tumour growth and therapy resistance[159]. Given that TAM family members are functionally redundant, targeting multiple TAM receptors or their ligands, such as growth arrest-specific protein 6 (GAS6), might be more beneficial for certain tumours.

Identifying the precise mechanisms associated with the antitumour effects of TAM inhibitors in the clinic is difficult, given their essential role in fostering the tumour microenvironment. Finding biomarkers that predict the response to TAM inhibition might help overcome these difficulties, enabling patient selection and the monitoring of treatment response and resistance development. Potential biomarkers under investigation include TAM receptor expression in tumour biopsies and circulating soluble AXL and GAS6 levels. Pending positive clinical trial outcomes, biomarkers could become essential for patient selection and improving the clinical utility of TAM inhibitors.

The inhibition of TAM receptors and their ligands GAS6 and vitamin K-dependent protein S1 (PROS1) could have potential undesirable effects in the clinic. For example, Maimon et al. reported that myeloid cell-derived PROS1 has an unexpected function in inhibiting metastasis in lung and breast tumour models[192]. Also, inhibiting TAM receptors and ligands can impair the phagocytosis of apoptotic cells by macrophages and dendritic cells, leading to the accumulation of apoptotic cells. Subsequent autoimmune responses occur, resulting in ocular and central nervous system toxicity and, in some cases, promoting cancer growth[193,194].

A study demonstrated that MERTK activation by PROS1 serves as a co-stimulatory signal for human $CD8^+$ T cells, indicating that MERTK has a pleiotropic function in enhancing both immune activation and immune suppression and presenting challenges in targeting MERTK in cancer[195]. In addition, the inhibition of TAM receptors might have potential undesirable effects on platelet function and coagulation, given that the receptors regulate thrombosis and haemostasis. Inhibiting TAM receptors can also increase PDL1 expression, potentially limiting the therapeutic effects of TAM inhibitors in immune blockade therapy[196]. However, combining TAM inhibitors with PD1 or PDL1 inhibitors could potentially have synergistic antitumour effects and be a promising therapeutic strategy for cancer.

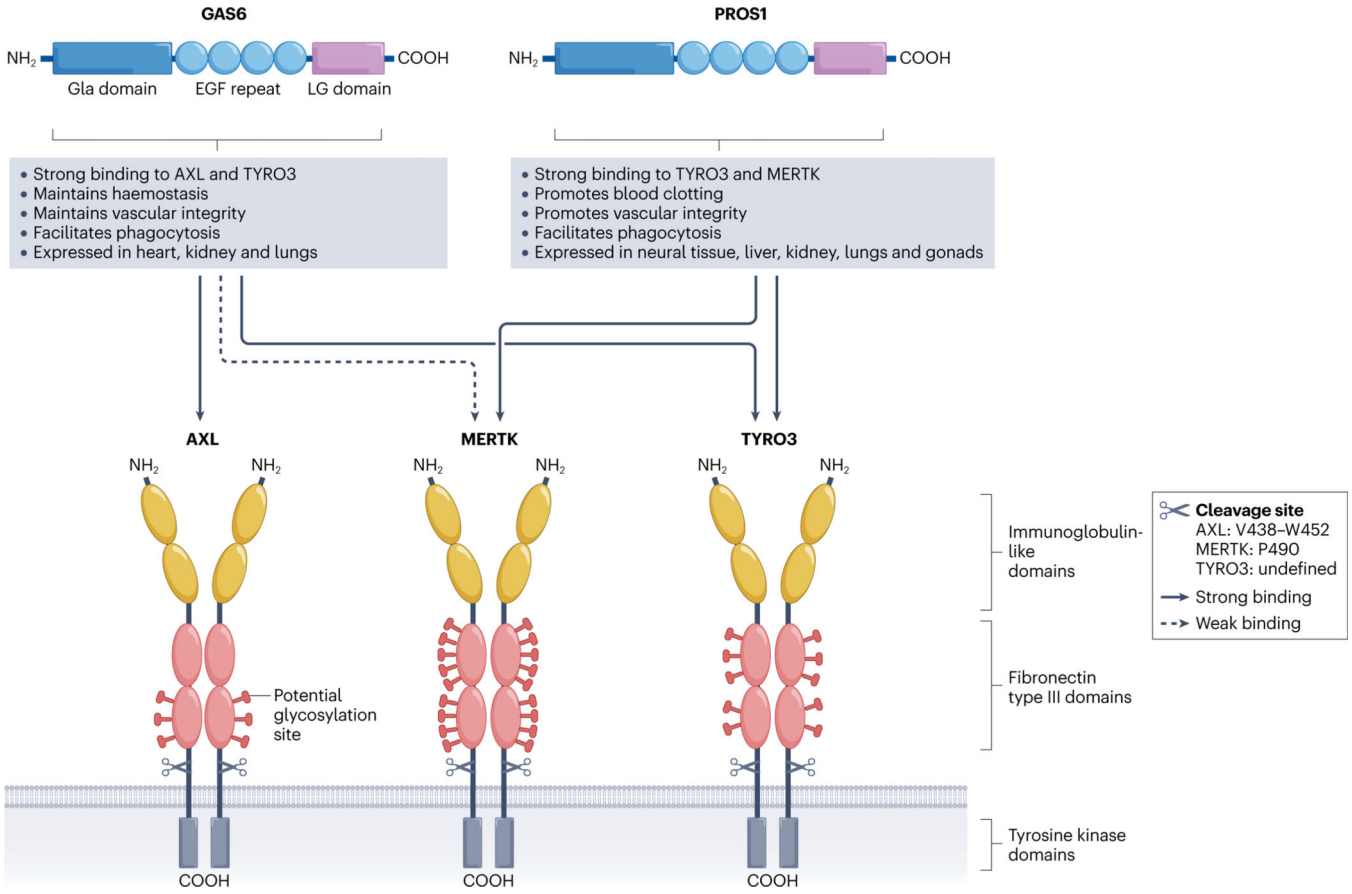

Fig. 1 |. TAM receptors and their interacting ligands.

TAM receptors are activated by growth arrest-specific protein 6 (GAS6) and vitamin K-dependent protein S1 (PROS1). The biological consequences of GAS6 and PROS1 signalling are listed. The three TAM receptors AXL, MERTK and TYRO3 interact with their ligands in the form of a dimer. Ligands also form dimers and bind to the receptor amino-terminal immunoglobulin-like domains, which are connected to two fibronectin type III domains. The intracellular kinase domains of all three TAM family members share close sequence homology and have autophosphorylation sites throughout the domain. Enzyme-induced cleavage can occur in proximity to the cell membrane to release soluble forms of the TAM receptors.

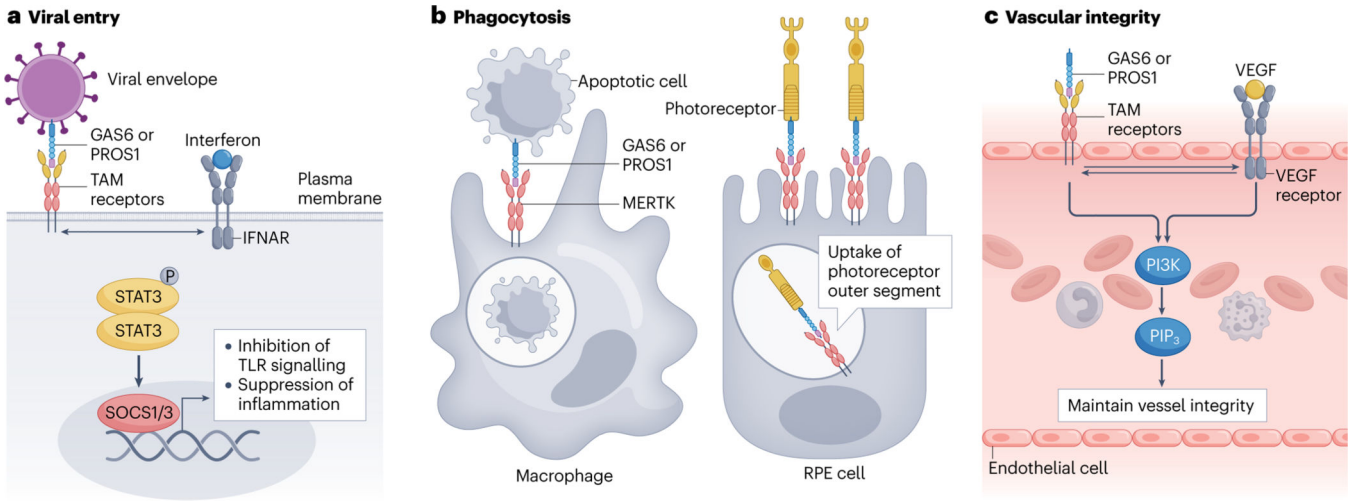

Fig. 2 |. TAM receptor signalling maintains physiological homeostasis.

a, Viral entry into host cells can occur through the binding of growth arrest-specific protein 6 (GAS6) or vitamin K-dependent protein S1 (PROS1), which are expressed on phosphatidylserine-presenting membranes as part of the viral envelope. Upon receptor–ligand binding and activation, TAM receptors suppress the immune response by engaging in crosstalk with the interferon-α/β receptor (IFNAR)–STAT pathway. This pathway leads to SOCS1- and SOCS3-mediated inhibition of Toll-like receptor (TLR) signalling and suppression of inflammatory responses, helping the virus evade immune surveillance. **b**, TAM receptors, particularly MERTK, are required for the phagocytic clearance of apoptotic cells and cellular debris. MERTK is expressed by phagocytes such as macrophages and retinal pigment epithelium (RPE) cells, which recognize and engulf GAS6-expressing and PROS1-expressing apoptotic cells and cellular debris such as photoreceptor outer segments. Phagocytosis restores tissue homeostasis and avoids inflammatory responses and autoimmune disease. **c**, GAS6-mediated and PROS1-mediated TAM receptor activation is essential for blood vessel growth and vascular integrity. Crosstalk between TAM receptors and VEGF receptor signalling facilitates downstream phosphatidylinositol 3-kinase (PI3K)–PIP_3 pathways. Crosstalk between TAM receptors and receptor tyrosine kinase signalling can also occur.

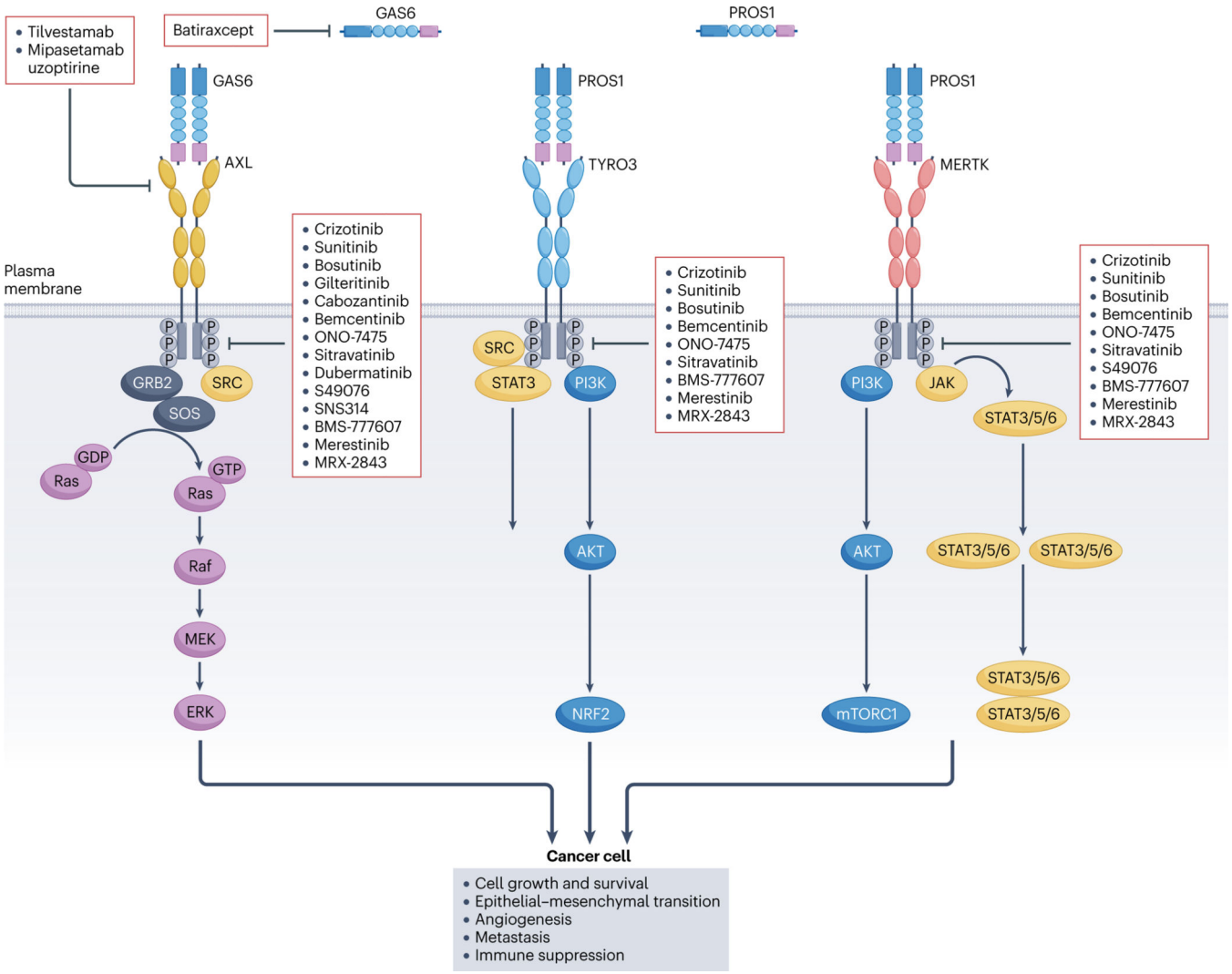

Fig. 3 |. The role of TAM receptor signalling in cancer and the action of specific inhibitors. A subset of the key oncogenic signalling pathways and biological outcomes driven by the TAM receptors AXL, TYRO3 and MERTK in facilitating cancer progression. When activated by growth arrest-specific protein 6 (GAS6) and vitamin K-dependent protein S1 (PROS1), AXL engages the SRC protein, which recruits GRB2 and SOS to facilitate the Ras–Raf–MEK–ERK signalling pathway. TYRO3 signals through the SRC and phosphatidylinositol 3-kinase (PI3K)–AKT pathways, promoting the activation of downstream molecules such as mTORC1 and NRF2. MERTK activation channels into various signalling pathways, notably PI3K–AKT, JAK–STAT3/5/6 and SRC. TAM receptors can recruit and activate overlapping downstream signalling pathways. However, distinct temporal and spatial regulation can produce varied biological outcomes. Upon activation, TAM receptors enhance cancer cell proliferation, tumour cell survival and metastasis. They also stimulate angiogenesis and contribute to immune suppression. Two categories of TAM inhibitors are illustrated. The first includes molecules such as crizotinib, sunitinib and bemcentinib, which directly target the kinase domain of the TAM receptors,

inhibiting kinase activity. The second category, represented by agents such as tilvestamab, mipasetamab uzopritine and batiraxcept, disrupts receptor–ligand binding.

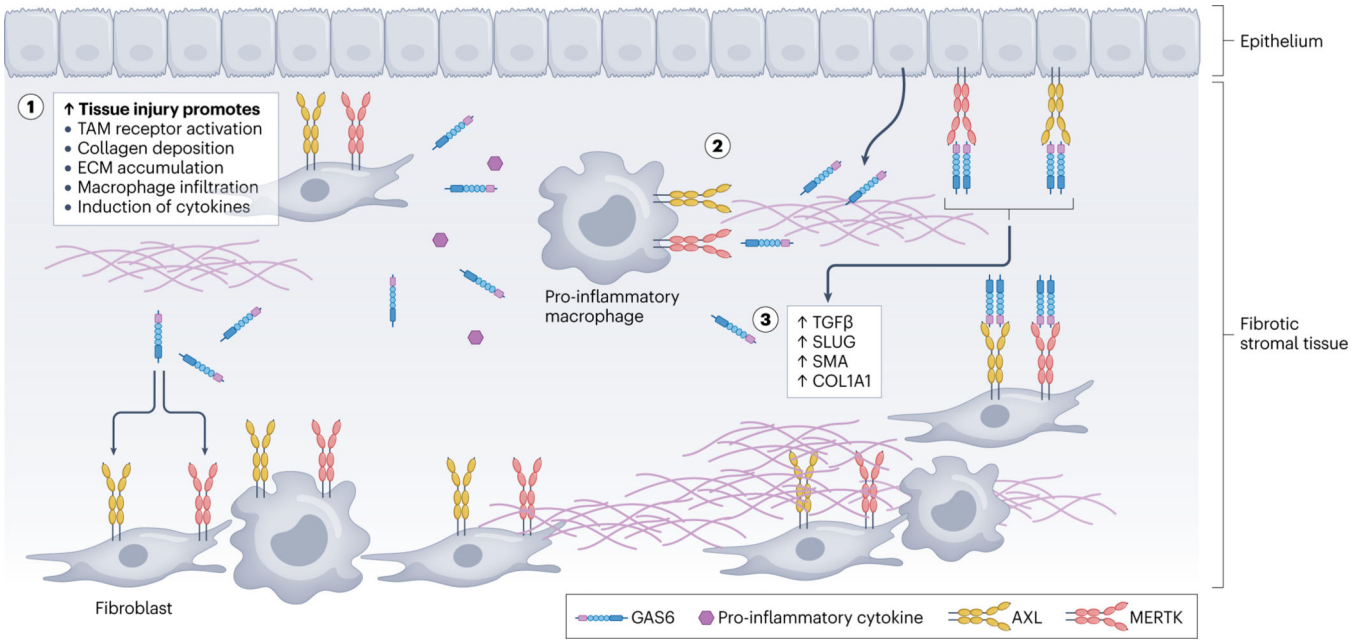

Fig. 4 |. GAS6-mediated TAM receptor signalling promotes fibrosis in response to tissue injury. Chronic inflammation in stromal tissues promotes TAM receptor activity within the tissue microenvironment in different cell types such as epithelial cells, fibroblasts and pro-inflammatory macrophages. This triggers a sequence of biological events leading to tissue fibrosis. Elevated TAM receptor activation boosts the secretion of pro-inflammatory cytokines and promotes macrophage infiltration, leading to epithelial–mesenchymal transition and the deposition of fibrotic matrix (**1**). Stromal cell-derived growth arrest-specific protein 6 (GAS6) is upregulated in response to tissue injury, resulting in TAM receptor activation on cells within the extracellular matrix (ECM). TAM receptor activation facilitates the generation and transformation of myofibroblasts, which further contribute to the deposition of ECM and fibrosis. Additionally, TAM receptor signalling modulates the activity of immune cells, and promotes the release of pro-fibrotic cytokines (**2**). TAM receptors promote TGFβ signalling, a critical mediator of fibrosis. The molecular interplay between TAM receptors and TGFβ signalling results in the upregulation of pro-fibrotic factors, such as SLUG, α-smooth muscle actin (α-SMA) and type I collagen COL1A1(**3**).

Table 1 |

Expression of TAM receptors and ligands and their functional relevance in cancer

Cancer type	AXL	MERTK	TYRO3	GAS6	PROS1
Haematological cancer					
AML	Yes (E, B, F)	Yes (E, F)	Yes (E)	Yes (E, B)	Yes (E)
Chronic myeloid leukaemia	Yes (E, F)			Yes (E)	
B-CLL	Yes (E)				
Acute lymphoblastic leukaemia		Yes (E, F)		Yes (E, F)	
Mantle cell		Yes (E)			
Multiple myeloma	Yes (E)		Yes (E)	Yes (E)	
Solid tumour					
Breast	Yes (E, B, F)	Yes (F)		Yes (E, F)	
Head and neck	Yes (B)				
Colorectal	Yes (E, B, F)			Yes (F)	Yes (E)
Pancreatic	Yes (E, B, F)	Yes (F)		Yes (F)	Yes (E)
Oesophageal	Yes (E, B, F)				
Gastric	Yes (E, B, F)	Yes (B)		Yes (E, F)	
Melanoma	Yes (E, F)	Yes (E, F)	Yes (F)	Yes (F)	
Hepatocellular	Yes (F)				
Squamous cell	Yes (E, F)				
NSCLC	Yes (E, B, F)	Yes (E, F)	Yes (E)	Yes (B)	Yes (E)
Ovarian	Yes (E, B, F)			Yes (E)	
Cervical	Yes (F)				
Endometrial	Yes (E)		Yes (E)	Yes (E)	
Prostate	Yes (E, F)	Yes (E)	Yes (E)	Yes (F)	Yes (E, B, F)
Thyroid	Yes (E, F)		Yes (E, F)	Yes (E, F)	Yes (E)
Bladder	Yes (E, B, F)				
Renal	Yes (E, F)			Yes (E, B, F)	
Mesothelioma	Yes (E, F)				
Oral squamous	Yes (B)				
Glioblastoma	Yes (E, B, F)	Yes (E, F)		Yes (E, B)	Yes (E)
Neuroblastoma	Yes (F)				
Schwannoma	Yes (E, F)	Yes (E)	Yes (E)	Yes (E, F)	
Kaposi’s sarcoma	Yes (E, F)				
Osteosarcoma	Yes (E, B)			Yes (F)	
Rhadomyosarcoma		Yes (E)			

AML, acute myeloid leukaemia; B, validated as a prognostic biomarker; B-CLL, B cell chronic lymphocytic leukaemia; E, elevated expression in tumours; F, positive correlation between expression and functional relevance; GAS6, growth arrest-specific protein 6; NSCLC, non-small-cell lung cancer; PROS1, vitamin K-dependent protein S1.

Table 2 |

Inhibitors of TAM receptors under clinical development

Compound (sponsor)	IC_{50} in vitro (nM)	Clinical stage	Indications	Adverse effects
Crizotinib (Pfizer)	294 (AXL)	Approved	ALK^+ advanced NSCLC, advanced solid or haematological cancers	Abdominal pain, headache, pyrexia
Sunitinib (Pfizer)	5 (AXL)	Approved	Renal cell carcinoma, GIST, pancreatic neuroendocrine tumours	Diarrhoea, fatigue, hypertension
Bosutinib (Pfizer)	560 (AXL)	Approved	Ph^+ chronic myeloid leukaemia, solid tumours, Lewy body dementia	Diarrhoea, rash, liver toxicity
Gilteritinib (Astellas/Kotobuk)	0.73 (AXL)	Approved	Relapsed or refractory FLT3-AML	Neutropenia, anaemia, thrombocytopenia
Cabozantinib (Exelixis/Ipsen)	7 (AXL)	Approved	Advanced renal cancer, hepatocellular cancer, thyroid cancer	Fistulas, intra-abdominal, pelvic abscess
Batiraxcept (Aravive)	NA	Phase III	Platinum-resistant ovarian cancer, renal and pancreatic cancers	NA
Bemcentinib (Bergen Bio)	14 (AXL)	Phase II	TNBC, NSCLC, pancreatic cancer, brain tumour, mesothelioma, COVID-19	NA
Amuvatinib (Astex)	10 (AXL)	Phase II (discontinued)	Small cell lung cancer, metastatic solid tumours	Fatigue, alopecia, diarrhoea
Foretinib (GSK)	11 (AXL)	Phase II (discontinued)	TNBC, $HER2^+$ breast cancer, NSCLC	Fatigue, nausea, hypertension
ONO-7475 (Ono)	2.2 (AXL) 0.4 (MERTK) 1.9 (TYRO3)	Phase I/II	Advanced cancer	NA
Sitravatinib (Mirati)	<1 (AXL) <1 (MERTK) <1 (TYRO3)	Phase I/II	Sarcoma, breast cancer; combination with PD1 inhibitors for solid tumours	NA
Dubermatinib (Sumitomo/Tolero)	27 (AXL)	Phase I	Advanced solid tumours, FLT3-AML	NA
S49076 (Servier)	7 (AXL) 2 (MERTK)	Phase I	Advanced solid tumours	Peripheral oedema, albumin anaemia
SNS314 (Sunesis)	84 (AXL)	Phase I	Advanced solid tumours	NA
BMS-777607 (BMS/Aslan)	1.1 (AXL) 14 (MERTK) 4.3 (TYRO3)	Phase I	Advanced or metastatic solid cancer	Anaemia, nausea, constipation
RXDX-106 (Ignyta)	7 (AXL) 29 (MERTK) 19 (TYRO3)	Phase I (discontinued)	Locally advanced solid tumour	NA
Tilvestamab (Bergen Bio)	NA	Phase I	Ovarian cancer	NA
Mipasetamab uzoptirine (Bergen Bio/ADC)	NA	Phase I	Advanced solid tumour in combination with gemcitabine	NA
Merestinib (Eli Lilly/Dana-Farber)	2 (AXL) 10 (MERTK)	Phase I	Biliary tract carcinoma, NSCLC, refractory AML, mantle cell lymphoma, colorectal cancer	Anaemia, thrombocytopenia, leukopenia, neutropenia, nausea, constipation

Compound (sponsor)	IC_{50} in vitro (nM)	Clinical stage	Indications	Adverse effects
MRX-2843 (Meryx)	1.3 (AXL) 15 (MERTK) 17 (TYRO3)	Phase I	Advanced cancer	NA

ALK^+, anaplastic lymphoma kinase-positive; AML, acute myeloid leukaemia; GIST, gastrointestinal stromal tumour; NA, not available; NSCLC, non-small-cell lung cancer; Ph^+, Philadelphia chromosome-positive; TNBC, triple-negative breast cancer.