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Targeting Receptor Tyrosine Kinases using Monoclonal Antibodies: The Most Specific Tools for Targeted-Based Cancer Therapy

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Running title: Monoclonal antibodies and RTKs targeted therapy

Abstract:

Receptor tyrosine kinases (RTKs) family is comprised of different cell surface glycoproteins. These enzymes participate and regulate vital processes such as cell proliferation, polarity, differentiation, cell to cell interactions, signaling, and cell survival. Dysregulation of RTKs contributes to the development of different types of tumors. RTKs deregulation in cancer has been reported for more than 30 RTKs. Due to critical roles of these molecules in cancer, the specific targeting of RTKs in malignancies is a promising approach. Targeted cellular and molecular therapies have been known as a new type of therapeutics, preventing tumor cell proliferation and invasion by interrupting with molecules necessary for tumor growth and survival. Specific targeting of RTKs using monoclonal antibodies (mAbs) in malignancies as well as in autoimmune disorders is of great interest. The growing number of mAbs approved by the authorities implies on the increasing attentions and applications of these therapeutic tools. Due to the high specificity, mAbs are the most promising substances that target RTKs expressed on the tumor cell surface. In this communication, we review the recent progresses in development of mAbs targeting oncogenic RTKs for cancer treatment.

Keywords: Cancer, monoclonal antibody, receptor tyrosine kinase, targeted therapy

INTRODUCTION

Current chemotherapy and radiotherapy modalities and the combinational regimens have improved the life quality of cancer patients. In spite of considerable progresses in the management and treatment of cancer patients; however, their applications have severe side effects on normal cells. Therefore, developing more specific drugs is important to overwhelm the current shortcomings of these modalities. In this context, targeted-based cancer therapy (targeted therapy) agents have significantly progressed and several drugs have got the approval of authorities for application in cancer therapy.

The purpose of targeted cancer therapy is destroying tumor cells by targeting antigens expressed by the cells. Among several targets, receptor tyrosine kinases (RTKs) have distinct properties that make them suitable targets for therapy. RTKs have special biological features and structure for signal transduction [1]. RTKs with oncogenic property have no or minimum activity in normal cells, however their deregulations are seen in cancerous cells. RTK-like orphan receptor 1 (Ror1) is an example that is expressed at a noteworthy level during embryogenesis in neuronal and other fetal tissues [2]. It is also overexpressed on the surfaces of different tumor cells, including chronic lymphocytic leukemia (CLL) [3-5], acute myelogenous leukemia (AML), acute lymphoid leukemia (ALL), mantle cell lymphoma (MCL) [6], hairy cell leukemia (HCL) [6], melanomas [7, 8], and lung cancer [9].

The RTKs roles have been extensively investigated in progression and metastasis of cancer [10, 11]. Aberrant RTKs expression and activation are linked to cancer development, transformation and metastasis [12-14]. Currently, different RTKs are under intensive research for targeting tumor cells [15].

Monoclonal antibodies (mAbs) are the most specific and ideal tools for targeting cell-surface antigens expressed by tumor cells. Due to the high specificity of mAbs, they have fewer side effects compare to other agents such as cytotoxic drugs and small molecule inhibitors (SMIs). Furthermore, mAbs have different mechanism of action to destroy the targeted cells. Some antibodies disrupt the kinase signaling through inhibiting ligands and receptor internalization as well as preventing homo/hetero-dimerization of RTKs, which might result in direct apoptosis. Other mechanisms include effector cells activation [(antibody-dependent cell-mediated cytotoxicity (ADCC)], complement activation [complement dependent cytotoxicity (CDC)] and direct necrosis of malignant cells [4, 16-18].

Currently, several anti-RTK mAbs have shown proper therapeutic effects and thus were approved for cancer therapy. The most famous approved mAbs for targeting RTKs are specific to human epidermal growth factor receptor (EGFR), HER2 (ErbB2) and VEGFRs (Table **1**). In this paper: 1) the structure and function of selected RTKs appropriate for mAb therapy, 2) current mAbs applied for cancer therapy, and 3) promising mAbs targeting oncogenic RTKs in preclinical or clinical settings have been described.

Table **1.** Oncogenic RTKs for mAb targeted cancer therapy.

RTK	**Chromosome location**	**Mechanism of overexpression**	**Malignancies (examples)**	**Development phase**	
				Preclinical	**Clinical trials**
ALK	2p23	Translocation	NSCLC, colorectal carcinoma, breast, oesophageal and renal cell cancers	+	+
AXL	19q13.1	overexpression	AML, CML, NSCLC, lung, colon, breast, esophageal, thyroid and pancreatic cancers, gastrointestinal stromal tumors, astrocytoma-glioblastoma	+	-
CCK4	6p21.1	Mutation	Squamous cell carcinoma, small cell lung, breast, colon and gastric cancers, AML	+	-
DDR1	6p21.33	Mutation, overexpression	NSCLC, breast and ovarian cancers, hepatocellular carcinoma, AML	+	-
DDR2	1q23.3	Mutation	Head and neck squamous cell carcinoma, breast and lung cancers, NSCLC, CML	+	-
EGFR1	7p11.2	Mutation, overexpression	Breast cancer, hepatocellular and head and neck squamous cell carcinomas	+	+
EGFR2	17q12	Mutation, overexpression	Breast cancer, gastric adenocarcinomas	+	+
EGFR3	12q13.2	Mutation, overexpression	Breast cancer	+	-
EGFR4	2q34	Mutation, overexpression	Breast cancer, melanoma	+	-
EPHA1	7q35	Mutation, overexpression	NSCLC, prostate cancer, esophageal squamous cell carcinoma	+	-
EPHA2	1p36.13	Mutation, overexpression	Hepatocellular and colorectal carcinomas, breast cancer, osteosarcoma	+	-
EPHA3	3p11.1	Mutation, overexpression	Glioblastoma, lung cancer, melanoma, ALL, T-cell leukemia, Hodgkins lymphoma	+	-
EPHA4	2q36.1	Mutation	NSCLC, gastric cancer	+	-
EPHA5	4q13.1	Mutation	Breast cancer, hepatocellular carcinoma, ALL	+	-
EPHA6	3q11.2	Mutation	Renal cell carcinoma	+	-
EPHA7	6q16.1	Mutation, overexpression	Hepatocellular carcinoma	-	-
EPHA8	1p36.12	Mutation, overexpression	Colorectal carcinoma, liver tumors	-	-
EPHA10	1p34.3	Mutation, overexpression	Breast cancer, CLL		
EPHB1	3q22.2	Mutation, overexpression	NSCLC, cervical and ovarian cancers	+	-
EPHB2	1p36.12	-	Cervical and breast cancers, melanomas, hepatocellular carcinoma	+	-
EPHB3	3q27.1	-	NSCLC, breast cancer, colorectal carcinoma	+	-
EPHB4	7q22.1	Mutation, overexpression	Breast, melanoma and glioma cancers	+	+
EPHB6	7q33-q35	Mutation, overexpression	CLL, NSCLC, breast cancer		

FGFR1	8p12	Mutation	Lung and breast cancers	+	+
FGFR2	10q26.13	Mutation, overexpression	Lung, breast, thyroid, prostate cancer, cholangiocarcinoma, astrocytoma	+	+
FGFR3	4p16.3	Mutation	Bladder cancer, lung and head carcinomas	+	+
IGF1R	15q26.3	Mutation, overexpression	CLL, breast and pancreatic cancers, hepatocellular and oral squamous cell carcinomas	+	+
IGF2R	6q25.3	Mutations, overexpression	Hepatocellular, squamous cell and colorectal carcinomas, breast, pancreatic and prostate cancers, NSCLC	+	+
FLT3	13q12.2	Mutation, overexpression	AML, acute promyelocytic leukemia	+	+
INSR	19p13.2	Mutation, overexpression	Colorectal carcinoma, prostate cancer	+	+
INSRR	1q23.1	Mutation, overexpression	Neuroblastomas	+	+
KIT	4q12	Mutation	AML, melanoma, ovarian carcinoma, gastrointestinal stromal tumors	+	+
LTK	15q15.1	Mutation	Gastric cancer, lymphomas and leukemias	+	+
MER	2q13	Mutation	Glioblastoma, hepatocellular carcinoma, astrocytoma	+	+
MET	7q31.2	Mutation, overexpression	Hepatocellular carcinoma, CLL, breast, pancreatic and lung cancers, gastric adenocarcinoma	+	+
MUSK	9q31.3	Mutation, overexpression	Ovarian cancer	-	-
NTRK1	1q21-22	Translocation, mutation, overexpression	Thyroid and breast cancers, lung adenocarcinoma, colorectal and oral squamous cell carcinomas	+	+
NTRK2	9q22.1	Translocation	Neuroblastoma, astrocytoma, oral squamous cell carcinoma	+	+
NTRK3	15q25.3	Translocation	Neuroblastoma, breast cancer	+	+
PDGFRA	4q12	Mutation	Lung adenocarcinoma, gastrointestinal stromal tumors	+	+
PDGFRB	5q32	Mutation	Gastrointestinal stromal tumors, glioblastoma	+	+
RET	10q11.2	Mutation	NSCLC, medullary thyroid carcinoma	+	+
RON	3p21.31	Mutation, overexpression	Pancreatic and breast cancers, NSCLC, laryngeal and head and neck squamous cell carcinomas	+	+
ROR1	1p31.3	Overexpression	CLL, ALL, AML, MCL, HCL, melanoma, prostate, lung, breast, pancreatic, colon, ovarian, and uterus cancers	+	+
ROR2	9q22.31	Mutation	Melanoma, medulloblastoma, leiomyosarcoma, gastrointestinal stromal tumor, hepatocellular, renal cell and head and neck carcinomas, osteosarcoma, prostate, testicular, colon cancers	+	-
ROS1	6q22	Deletion, inversion, translocation	NSCLC, cholangiocarcinoma, ovarian and gastric cancers, colorectal carcinoma	+	-
RYK	3q22.2	Translocation, mutation	CML, ovarian cancer	+	-
TEK	9p21.2	Mutation	Bladder cancer, glioblastoma, AML	+	-
TIE	1p34.2	Mutation	Glioblastoma	+	-
TYRO3	15q15.1	Mutation	Melanoma, colon, thyroid, and breast cancers	+	-
VEGFR1	13q12.3	Mutation, overexpression	Ovarian cancer, NSCLC, colorectal carcinoma	+	+
VEGFR2	4q12	Mutation, overexpression	Renal cell and hepatocellular carcinomas	+	+
VEGFR3	5q35.3	Mutation, overexpression	Ovarian and gastric cancers, bladder carcinoma	+	+

ALK: anaplastic lymphoma kinase, ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, CLL: chronic lymphocytic leukemia, CML: chronic myeloid leukemia, DDR: discoidin domain receptor, EGFR: epidermal growth factor receptor, EPH: ephrin receptors, FGFR: fibroblast growth factor receptor, IGFR: insulin growth factor receptor, INSR: insulin receptor, LTK: leukocyte tyrosine kinase, MCL: mantle cell lymphoma, HCL: hairy cell leukemia, MuSK: muscle-specific kinase, NSCLC: non-small cells lung carcinoma, NTRK: neurotrophic tyrosine kinase, PDGFR: platelet-derived growth factor receptor, ROR: receptor tyrosine kinase-like orphan receptor, RYK: receptor related to tyrosine kinases, VEGFR: vascular endothelial growth factor receptor [19].

RECEPTOR TYROSINE KINASES (RTKs)

The large family of RTKs consists of cell surface receptors discovered more than 25 years ago [20] which are divided into 20 sub-families with 58 members [21]. These receptors are involved in crucial processes, for instance in cell proliferation, differentiation, cell-cell interaction, migration, signaling, metabolism and survival [22]. RTKs structure consists of 3 distinct regions, including extracellular, transmembrane and cytoplasmic domains [23]. The extracellular part of RTKs contains the ligand binding site that interacts with the surface, soluble and extracellular matrix proteins [24]. This part is also involved in the RTKs dimerization that is critical for the activation of tyrosine kinase (TK) in the cytoplasmic portion of the RTKs [14, 19, 25]. The extracellular regions of RTKs have a combination of several globular domains, including immunoglobulin (Ig)-like, cysteine-rich, fibronectin type III-like, EGF-like, and Sema domains [23]. The cytoplasmic part consists of a lipophilic transmembrane helix and is followed by different regions such as the TK domain and carboxy-terminal region. Several serine and tyrosine residues at the cytoplasmic region are phosphorylated following ligand binding to extracellular part. Indeed, these serine and tyrosine residues serve as docking sites for proteins having Src homology (SH) 2 domain to regulate RTKs catalytic function [14, 19, 26]. Among different regions of RTKs, the TK domain shows the highest conservation level [27]. Adenosine triphosphate (ATP) binding site mutations might change the activity of receptor and consequently inactivate the biological function of the receptor that might change the RTK to pseudo-RTK without or with low enzymatic activity [26, 28]. The carboxy-terminal tail of RTKs is the most distal and non-catalytic part. This region has the highest degree of heterogeneity in length and sequence, even among members of the same RTK subclass. The carboxy-terminal tail contains tyrosine residues that are phosphorylated by intracellular kinases. Some reports have shown the crucial role of C-terminal part in modulating kinase activity that provides proper conformation for TK domain [26].

Aberrant activation of RTKs owing to receptor overexpression, gene amplification, impaired downregulation, chromosomal translocation, and mutations contribute to cancer development and progression [19, 29, 30]. RTKs dysregulation have been reported for more than 30 RTKs (Table **1**) [13]. These changes in the structure of RTKs make these receptors become potent oncoproteins, leading to the neoplastic alteration [13, 30].

In the following sections, different RTKs that are proper for mAb targeting have been described.

RTKs: PROPER TARGETS FOR CANCER THERAPY

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

EGFR (ErbB-1/HER1), HER2/neu (ErbB-2), HER3 (ErbB-3), and HER4 (ErbB-4) are EGFR (ErbB) family members that play important roles in the normal cell functions regulation. Overexpression and mutation are involved in EGFR abnormal activation that is related to several tumors development. Therefore, specific inhibition of EGFR is one of the key targets for cancer treatment. In this context various mAbs have been approved for targeting solid tumors that overexpress the members of this family. Due to the overexpression of EGFR family members, mAbs targeting these RTKs are appropriate drugs for the treatment of several malignancies (Table 2) [31, 32].

Cetuximab (Erbitux) is a chimeric anti-EGFR mAb approved on February 12, 2014 for metastatic colorectal carcinoma (mCRC) patients refractory to irinotecan-based chemotherapy. Cetuximab was the first mAb approved to treat this type of cancer and is indicated in combination therapy with irinotecan, a chemotherapy drug approved for colorectal cancer treatment, or alone if irinotecan is intolerable for patients [33]. Cetuximab is prescribed as second- or third-line of therapy in mCRC [33] and the head and neck squamous cell carcinoma [32]. Moreover, on July 6, 2012, the FDA approved cetuximab in combination with chemotherapy drugs (irinotecan, 5-fluorouracil, and leucovorin) for application as first-line treatment of EGFR-expressing mCRC patients having wild-type *K-ras* (mutation-negative) (http://www.fda.gov). Cetuximab inhibited the binding of activating ligand to EGFR and also prevented receptor dimerization, leading to disruption of the signal transduction cascade [34].

Table **2.** Current therapeutic monoclonal antibodies for targeted-based cancer cell therapies.

Name	Trade name	Target	Antibody format	Malignancy	Stage for treatment		
					Preclinical	Clinical trial	Approved for treatment
AVE1642	ND	IGF1R	Humanized IgG1	NSCLC, multiple myeloma, Ewing's sarcoma	+	I	NY
Bevacizumab	Avastin	VEGF	Humanized IgG1	Glioblastoma, NSCLC, metastatic colon and kidney cancer	+	I-IV	+
Cetuximab	Erbitux	EGFR	Chimeric IgG1	Head and neck squamous cell carcinoma, MCC	+	I-IV	+
Cirmtuzumab (UC-961)	ND	ROR1	Humanized IgG1	CLL	+	I	+

Cixutumumab (IMC-A12)	ND	IGF1R	Fully human IgG1	Thymic carcinoma, soft tissue sarcomas, osteosarcoma, breast cancer, Ewing's sarcoma	+	I-II	NY
Dalotuzumab (MK-0646,)	ND	IGF1R	Humanized IgG1	Advanced colorectal carcinoma, NSCLC	+	I-II	NY
Figitumumab (CP-751871)	ND	IGF1R	Fully human IgG1	Adrenocortical carcinoma, NSCLC, multiple myeloma	+	I	NY
Ganitumab	ND	IGF1R	Fully human IgG1	Metastatic solid tumors	+	I-II	NY
Narnatumab (IMC-RON8)	ND	RON	Humanized IgG1	Advanced solid tumors	+	I	NY
Onartuzumab (MetMAb)	ND	MET	Humanized IgG1	Advanced NSCLC	+	II	NY
Panitumumab	Vectibix	EGFR	Fully human IgG1	Metastatic colon cancer	+	I-IV	+
Pertuzumab	Perjeta	HER2	Humanized IgG1	Metastatic breast cancer	+	I-IV	+
PF-03446962	ND	ALK1	Humanized IgG2	HCC, Advanced malignant pleural Mesothelioma, relapsed or refractory urethelial cancer	+	NY	NY
RG1507	ND	IGF1R	Fully human IgG1	Metastatic NSCLC	+	I-II	NY
Robatumumab (SCH717454)	ND	IGF1R	Humanized IgG1	Advanced colorectal carcinoma, NSCLC	+	I-II	NY
Trastuzumab	Herceptin (Herclon)	HER2	Humanized IgG1	Breast cancer, gastric adenocarcinoma, gastroesophageal junction adenocarcinoma	+	I-IV	+
Trastuzumab emtansine	Kadcyla	HER2	Humanized IgG1	Advanced breast cancer	+	I-IV	+

CLL: chronic lymphocytic leukemia, EGFR: epidermal growth factor receptor, HCC: hepatocellular carcinoma, HER: human epidermal growth factor receptor, IGFR: insulin growth factor receptor, MCC: metastatic colorectal carcinoma, ND: not defined, NSCLC: non-small cells lung carcinoma, NY: not yet, ROR: receptor tyrosine kinase-like orphan receptor, VEGFR: vascular endothelial growth factor receptor

Panitumumab (Vectibix) is a fully human mAb specific for EGFR used as second- or third-line of the treatment for mCRC patients akin to cetuximab [33, 35]. This mAb was approved on September 27, 2006, for EGFR-expressing mCRC cases with cancer progression or following chemotherapy regimens containing fluoropyrimidine, oxaliplatin, and irinotecan (http://www.fda.gov/). Panitumumab in combination with chemotherapy might also be useful for NSCLC patients treatment [36]. The mechanism of action is similar to cetuximab, but it does not promote ADCC [37]. Panitumumab in combination with folinic acid, fluorouracil, oxaliplatin has also been approved as first-line therapy in mCRC patients [38].

The ErbB-2/HER2, another EGFR family member, has intensively been investigated as an important RTK which is overexpressed and/or hyperactivated in various malignancies. The extracellular region of the receptor is divided into four domains. No ligand has been recognized for HER2. HER2 overexpression can transform cells in a ligand-independent manner which

makes it unusual member in ErbB family [39]. The HER2 importance in targeted therapy is highlighted by several molecular and pathological outcomes. HER2 amplification is related to the processes of tumorigenesis and pathologic features such as tumor size, invasion, and metastatic spread. HER2 has higher expression and activity in metastatic tumors than in non-aggressive tumors [40]. HER2 overexpression is found in 10-34% of invasive breast cancers with a poor prognosis [41]. Furthermore, overexpression of HER2 has been detected in several tumors such as lung, ovary, salivary gland, prostate, colon, and pancreatic cancers [40] as well as in hematologic malignancies such as ALL and AML [42].

Trastuzumab (Herceptin) was the first anti-HER2 mAb approved for application in $HER2^+$ breast cancer patients [43]. Trastuzumab is a humanized IgG1 mAb and has shown a 35% response rate in metastatic breast cancer (MBC) patients who received no earlier chemotherapy [44]. A phase III clinical trial on MBC patients with HER2 amplification has showed that trastuzumab with chemotherapy combinational regimen was associated with a few months delay in disease progression (median, 7.4 vs. 4.6 months), a higher rate of objective response (50% vs. 32%) and survival (median, 25.1 vs. 20.3 months) [45]. Trastuzumab was approved on September 25, 1998 by the FDA for MBC patients with HER2 protein overexpression and who have received chemotherapy drugs for metastatic disease treatment (http://www.fda.gov/). In January 2010, the European Medicines Agency (EMA) approved trastuzumab in combination with chemotherapy for the treatment of metastatic stomach adenocarcinoma or gastroesophageal junction with HER2 overexpression [46]. Trastuzumab acts via inhibition of receptor homo/hetero-dimerization, internalization and endocytic destruction [47, 48]. Although trastuzumab is well-accepted as the standard drug in the breast cancer therapy, up to 40% of MBC patients do not respond to trastuzumab and in those who respond, the median progression time is less than one year [49, 50]. Moreover, acquired trastuzumab resistance is a serious concern ending in disease progression [50, 51]. In general, these limitations call for design of new and superior mAbs for MBC therapy.

Pertuzumab (Perjeta) is a newly approved anti-HER2 mAb that prevents ligand-dependent HER2:HER3 dimerization and reduces intracellular signaling pathways [52]. Pertuzumab received approval for the treatment of $HER2^+$ MBC patients in June 8, 2012. The combination of pertuzumab, trastuzumab and docetaxel has been found to have an overall survival benefit in $HER2^+$ MBC patients used in the first-line setting [53]. Recently, the FDA approved the combination of trastuzumab, pertuzumab, and docetaxel as first-line treatment for MBC patients

(http://www.fda.gov/). At present, pertuzumab in combination with trastuzumab and platinum-fluoropyrimidine is under study in a phase II clinical trial as a first-line therapy in gastric cancer [54].

Fourth HER2-targeted agent, trastuzumab emtansine (T-DM1, Kadcyla) was approved on February 22, 2013, as a single agent for $HER2^+$ MBC patients, who have received trastuzumab and/or a taxane [55].

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

VEGF-A (usually referred to VEGF), VEGF-B, VEGF-C, VEGF-D, and placental growth factor are members of VEGF family that are expressed by various solid tumors [56]. Members of this family induce angiogenesis through binding to VEGFR1-3 expressed on the vascular endothelium. Angiogenesis is defined as a controlled process accountable for new blood vessels formation and is correlated to advanced-stage disease as well as clinically aggressive tumor subtypes [56]. Angiogenesis regulation is achieved by a variety of endogenous activators and inhibitors during the normal physiological processes such as the menstrual cycle and wound healing [57]. VEGF is predominate stimulator of angiogenesis during physiological condition such as embryogenesis, skeletal growth and reproductive functions as well as pathological angiogenesis associated with solid tumors [56]. Inhibition of angiogenesis prevents tumor expansion, survival and metastasis. In this perspective, blocking tumor cells angiogenesis is the main focus of several drug discoveries for solid tumors.

Bevacizumab (Avastin), an angiogenesis inhibitor, is an anti-VEGF humanized mAb that prevents binding of VEGF to VEGFRs and was approved for the treatment of MBC [58], mCRC [59] and NSCLC [60] patients in combination with cytotoxic chemotherapy [37, 61]. Bevacizumab is also used in combination with IFN-α in metastatic renal cell carcinoma therapy [62, 63]. Combination of bevacizumab and chemotherapy drugs has improved the survival of patients with mCRC and NSCLC compared to chemotherapy alone [64, 65]. Bevacizumab increased overall survival of mCRC patients 4.7 and 2.1 months following first-line and second-line therapies, respectively as described in a phase III clinical trial [66]. The increasing use of bevacizumab has resulted in the appearance of bevacizumab-resistant tumor cells as a result of

the upregulation of other angiogenic factors [67]. These findings proposed requisite for targeting cancer cells via multi-targets to inhibit compensatory mechanisms in tumor escape.

INSULIN GROWTH FACTOR RECEPTOR (IGFR)

The insulin-like growth factor 1 receptor (IGF1R) is a member of RTK family ubiquitously expressed in most human cells with the exception of hepatocytes and mature B lymphocytes [68]. The IGF1R is activated by its ligands insulin-like growth factor (IGF)-1 and -2 and plays important roles in cell proliferation control in mammalian cells *in vitro* and *in vivo*, regulation of lipids, proteins, and carbohydrates metabolism and the maintenance of glucose homeostasis [69, 70]. IGF-1 has a critical function in hypertrophy of skeletal muscle and other target tissues mainly through IGF1R. Mice lacking IGF1R die in late stage of development showing the strong growth-promoting effect of this RTK [69].

The IGF1R is dysregulated in several cancers such as lung, prostate and breast cancers [71]. The anti-apoptotic effects of IGF1R raised tolerance to SMIs and cytotoxic drugs. In breast cancer, IGF1R expression induced tumor cell resistance to EGFR inhibitors like erlotinib. It is described that crosstalk between EGFR and IGF1R and the common signaling pathway are the main reason for tumor cell resistance [72]. Importantly, in prostate cancer IGFIR signaling is crucial for cell survival and growth when cancer cells progress to androgen independence [73].

Currently, several anti-IGF1R mAbs are under study for application in solid tumors treatment. Ganitumab (AMG 479) is one of the successful mAbs for targeting $IGF1R^{+}$ tumors. The safety, maximum-tolerated dose (MTD), pharmacokinetics, and evidence of anti-tumor activity have been studied in several trials [74]. Fatigue, fever, thrombocytopenia, chills, rash, and anorexia were the most common adverse effects. A maximum dose of 20 mg/kg was shown to be safe and anti-tumor effects were promising [74]. A phase II study evaluated the ganitumab monotherapy safety and efficacy in metastatic Ewing family or desmoplastic small round cell tumors. Of 35 subjects examined for response, partial response and disease stability were observed at 5% and 48% of patients, respectively [75]. In metastatic pancreatic cancer, the ganitumab efficacy and safety were evaluated in a phase II clinical trial. Ganitumab was well-tolerated and improved 6-month overall survival rate in 57% of patients [76].

Cixutumumab (IMC-A12) is a fully human IgG1 mAb specific to the IGF1R with potential anti-tumor effects. This mAb prevented the binding of the IGF-1 to IGF1R and inhibited the activation of phosphoinositol 3-kinase (PI3K)/Akt signaling pathway and reduced the survival of cancer cell followed by induction of apoptosis [77]. The effects were tested in several cancers, including thymic, head and neck and hepatocellular carcinomas, soft tissue sarcomas, osteosarcoma, breast, prostate, islet cell, and pancreatic cancers (Table **2**) [77].

RG1507 is another fully human IgG1 mAb specific for IGF1R which was assessed in a phase I trial in children with relapsed or refractory solid tumors. Although, dose-limiting toxicities were not observed, no objective responses were seen [78]. Dalotuzumab (MK-0646) [79], figitumumab (CP-751871) [80], robatumumab (SCH717454) [81], and AVE1642 [82] are other anti-IGF1R mAbs that have been evaluated in several malignancies in preclinical stages with promising results.

Axl RECEPTOR TYROSINE KINASE

Axl is a member of the TAM (Tyro3, Axl and Mer) family [83]. The TAM members are distinguished by having a conserved sequence in the TK domain and adhesion molecule-like domains in the extracellular part [83]. Almost the entire ectodomain of TAM members comprise of Ig-like and fibronectin type III domains. These structures are vital in cell to cell contacts and are similar to the structure of neural cell adhesion molecule which consists of five Ig domains and two fibronectin type III domains [83]. TAM members are involved in the clearance of apoptotic cells. Protein S and growth arrest-specific factor 6 (GAS6), bind to the apoptotic cells surface and directly bind to TAM members expressed on phagocytes and finally engulf and clear apoptotic cells [84]. Axl is overexpressed in several cancers, including Burkitt's lymphoma [85], CLL [86], hepatocellular carcinoma [87], multiple myeloma [88], breast [89], and pancreatic cancers [90] and is correlated with cancer poor prognosis [91]. Axl is involved in proliferation and invasion of tumor cells, mainly in pancreatic carcinoma [90].

Currently, anti-Axl mAbs are under investigation in preclinical stages. Two anti-Axl mAbs (D9 and E8), have been shown to hamper Axl activity and stopped pancreatic cancer cells proliferation and migration. These mAbs inhibited Axl phosphorylation and Akt pathway

downstream with no effect on GAS6 binding, reduced the expression of Axl due to internalization in pancreatic cells. Anti-Axl mAbs therapy in xenografted mice declined subcutaneous and orthotopic pancreatic tumor xenografts growth [92].

DISCOIDIN RECEPTOR (DDR)

Discoidin receptors (DDR1 and DDR2) are two closely related RTKs that contain a discoidin homology domain in their extracellular regions [93, 94]. The DDRs were firstly identified by homology cloning based on their catalytic kinase domains, and then different types of collagen were recognized as DDR functional ligands [93, 95].

Human DDR1 coding gene is located to chromosome 6 between the HLA-E and HLA-C genes [96]. Structurally, DDR1 has a discoidin homology domain which contains the collagen binding site, a discoidin-like domain which involves in collagen-induced receptor activation. DDR1 transmembrane domain mediates collagen-independent receptor dimerization and a large intracellular part with phosphorylated tyrosines that may serve as docking sites for DDR binding proteins and a TK domain [97].

DDRs play roles in the regulation of critical cellular processes like cell differentiation, proliferation, migration and survival [98]. They control remodeling of extracellular matrixes by modulating the expression and activation of matrix metalloproteinase (MMP) [98]. Indeed DDRs are exclusively located on the cells to be sensors for extracellular matrix and also to be a regulator of a wide range of cell functions as mentioned above [97].

The DDR1 transcript is expressed in several normal tissues, restricted to epithelial cells with the highest level in lung, brain, spleen, kidney, and placenta [98-100]. Mutations and altered expression of DDRs are observed in many cancer types implies that they might be involved in the development and progression of cancers [97]. DDR1 upregulation has been reported in several types of cancers for instance in NSCLC [101], primary and MBC [99], brain tumors [102], ovarian [103, 104], and prostate cancers [105]. It is worthy to consider that findings related to the DDR1 expression encounters conflicting results in breast cancer [106]. DDR1 can be inhibited by imatinib, ponatinib and DDR1-IN-1 (selective type II inhibitor) inhibitors may have application in malignancies such as lung cancer [107-109]. However, currently no specific therapeutic mAb to this molecule has been developed [110].

EPHA and EPHB

Eph family receptor interacting proteins (Eph receptors) represent the largest family of RTKs [111]. Eph receptors are segregated into the two subclasses A (EphA1–A8, EphA10) and B (EphB1–B4, EphB6) according to their extracellular sequence homology, binding affinity and structure [112, 113]. The Eph ligands, ephrins, are divided into ephrin A (GPI anchored proteins) and ephrin B (transmembrane proteins) groups, based on their structure and sequence similarities [112, 114]. Cell to cell interactions are necessary in Eph activation through ephrin ligands binding because all Eph receptors and their ligands are membrane-bound proteins [111]. Eph and ephrins interactions lead to a bidirectional signaling in both the receptor and the ligand bearing cell [115].

Eph receptors are involved in a broad range of biological functions, including angiogenesis, cell attachment and cell segregation [116]. For instance, the Eph receptors have significant roles in the neuronal and vascular networks establishment during embryonic development and regulation of excitatory synapses function [117]. Eph receptors play functions in a variety of aspects of the tumor formation, including tumorigenesis, proliferation and metastasis [113, 118-120].

Regarding the expression profile, the Eph receptors/ephrins family has wide expression in adult tissues with organ-site-specific patterns. For instance EphA6, EphA8 and EphB1 transcripts have unique pattern in normal brain and testis [121]. The Eph receptors protein expression is downregulated in normal adult tissues [122, 123]. Eph and ephrin proteins are expressed at lower levels in adult comparing with embryonic tissues. This low-level expression may play a function in architecture of the kidney, the vasculature and the adult gut [124, 125]. On the contrary, Eph receptors and ephrins are relatively expressed at high level in the adult's brain [124, 126].

Eph receptors and ephrins are differentially expressed in a variety of human cancers [111]. For instance, EphA2 overexpression has been reported in breast, colorectal, prostate, lung, hepatocellular, and gastric and brain tumors [124, 125, 127]. Moreover, Eph receptors expression has been found in several leukemias such as AML [128].

Base on Eph receptors characteristics, there is a focus on Eph targeted cancer therapy. A fully human mAb (1C1) targeting EphA2 has been generated by Jackson et al [129]. 1C1 selectively bond to EphA2 and stimulated tyrosine phosphorylation, internalization and degradation of the

EphA2 receptor. Considering this internalize, an antibody-drug conjugate (ADC) has been prepared as a vehicle for delivery of cytotoxic drug to the cancer cells. EphA2 ADC selectively targeted and inhibited the growth of endometrial and ovarian malignant cells expressing EphA2 *in vitro* and *in vivo* [129-131]. After success in preclinical studies, this anti-EphA2 immunoconjugate has been studied in clinical trial phase I. Clinical trial data showed that the immunoconjugate did not have safety profile and the trial was terminated due to treatment-related bleeding and coagulation events [132]. Although findings were disappointing; however, targeting other Eph family members by mAbs is still ongoing. In this context, recently anti-EphA10 mAb has been introduced that significantly inhibited breast cancer cells proliferation and proposed EphA10 as a promising target for breast cancer therapy [123].

Met oncogene

c-Met, also named Met is a proto-oncogene that encodes hepatocyte growth factor receptor (HGFR). The coding gene is located on chromosome 7q31. Met is the hepatocyte growth factor (HGF) high affinity receptor which is structurally composed of α and β chains disulfide-linked heterodimer with 45 and 145 kDa mass, respectively. The α chain and the N-terminal of the β chain form the extracellular region of Met [133]. Met is a master regulator RTK of cell survival, growth, differentiation, mobility, and cell division and have an essential role in normal development [134]. During embryogenesis, HGF and Met expression are vital for cell growth, development of hepatocytes, placental trophoblasts, and myoblasts [135, 136]. After birth, activation of the HGF-Met pathway appears to be involved in hepatic, renal, and other organ regeneration after injury, epithelial-mesenchymal transition (EMT) and wound healing [137].

Met and HGF interaction results in autophosphorylation of several key tyrosine residues, which recruit different downstream molecules, including phosphorylation of tyrosine residues 1234 and 1235 in the kinase domain that is crucial for kinases activation [137]. Activated Met phosphorylates and binds to growth factor receptor-bound protein 2 (Grb2) and Grb2-associated binding protein 1 (Gab1), acting as a scaffold protein and stimulating Met interactions with molecules involved in the PI3K/Akt, the signal transducer and activator of transcription factor (Stat), the mitogen-activated protein kinase (MAPK) and the NF-κB pathways [137].

Altered Met levels, and activity have been noted in several cancers, such as renal, colon, melanoma, and breast cancers [137]. Met is dysregulated in tumors by gene amplification,

translocation, mutation, and overexpression of Met and HGF proteins. Met dysregulation is correlated with an increased tendency for metastatic disease and poor overall survival. Blocking Met or HGF leads to cell growth inhibition and apoptosis induction and tumor cells necrosis. Therefore, targeting HGF and Met is an area of active research [138]. Several mAbs targeting Met have been developed with promising results in cancer therapy.

Onartuzumab (MetMAb) is an affinity-matured and humanized monovalent mAb that binds to the Sema domain of Met. It has been demonstrated that onartuzumab blocked HGF binding and prevented Met phosphorylation and signaling. Biochemical data and crystallography of onartuzumab antigen-binding site has shown that it binds to extracellular domain of Met. Therefore, onartuzumab specifically blocks binding of HGF α-chain to Met [139]. These finding propose that α-chain dimerization on Met leads to Met signaling activation [139]. In a KP4 pancreatic tumor cell mouse xenograft model onartuzumab suppressed tumor cell growth, decreased the Met phosphorylation and increased the mice survival [140]. Observing the effectiveness of onartuzumab in the animal model led to start clinical trials.

A dose-escalation phase I clinical trial checked the effects of onartuzumab and its combination with bevacizumab in 43 advanced solid tumors patients [140]. Onartuzumab half-life was 11 days, and no adverse effects were observed in combination with bevacizumab. Mild adverse reactions were hypo albuminuria, fatigue and peripheral edema [140]. In a phase II study, onartuzumab and erlotinib combination was evaluated in advanced NSCLC patients after initial therapy [141]. Patients randomly received 15 mg/kg onartuzumab every three weeks in combination with 150 mg erlotinib daily. Combination of onartuzumab with erlotinib showed a considerable improvement in progression free survival (1.5 to 2.9 months) and median overall survival from 3.8 to 12.6 months [141]. Interestingly, onartuzumab has been shown to be effective in EGFR-driven tumors acquire resistance to erlotinib [142]. In another phase II clinical trial, onartuzumab in combination with erlotinib was used in advanced and previously treated NSCLC patients [142]. This combination improved progression free survival and overall survival of patients with Met-overexpressed tumors [142]. Currently, a phase III clinical trial is testing the onartuzumab and erlotinib combination in NSCLC (http://clinicaltrials.gov).

In a recent study, p21-activated kinase 1 (PAK1) which is a central protein in pancreatic adenocarcinoma cells survival and downstream signaling pathways has been shown to be responsible for resistance to anti-Met mAbs and SMIs (such as onartuzumab and crizotinib,

respectively). In human, PAK1 expression has been shown to be highly associated with Met expression and is linked to tumor metastasis [143]. PAK1 inhibition blocked signaling to cytoskeletal effectors and tumor cell motility driven by HGF/Met. Combination of anti-Met mAbs with PAK1 inhibitors has been shown to overcome resistance mediated by PAK1. Inhibition of PAK1 attenuated *in vivo* tumor growth and metastasis in a model of pancreatic adenocarcinoma [143].

CE-355621 mAb is another anti-Met mAb that inhibited ligand-dependent activation of Met in A549 cell line. This mAb antagonized Met function by inhibiting the receptor activation and downregulating of downstream signaling pathways. In multiple xenograft tumor models, significant inhibition of Met activity and consequently tumor growth has been demonstrated. For instance, CE-355621 has been shown to inhibit up to 98% of U87MG glioblastoma cell and GTL-16 gastric cancer cells growth in xenograft models [144].

RECEPTEUR D'ORIGINE NANTAIS (Ron)

The Ron (macrophage-stimulating protein receptor, MST1R) RTK belongs to Met family kinase. Ron stimulates proliferation, survival, cell migration, and invasion in the presence of ligand [145]. Ron also plays a role in the innate immunity by regulating macrophages migration and phagocytic activity [145]. It is expressed on epithelial cells and macrophages and controls the inflammatory response to various insults. All functional responses mediated by Ron and Met are initiated by their respective ligand [145]. Ron is produced as a single premature 180 kDa chain and then is cleaved into a 160 kDa β-chain and a 40 kDa α-chain. The α-chain is bound to the extracellular region of the β-chain by a disulfide bridge [146]. The Sema domain on the N-terminal of the Ron binds to HGF and macrophage stimulating protein (MSP) as ligands [147]. Subsequently, ligand binding induces Ron autophosphorylation that generates docking sites for downstream signaling molecules. Activated Ron interacts with the PI3K subunit PIK3R1, phospholipase C (PLC) γ1 or the adapter Gab1. Then, these downstream effector molecules recruit and activate the Ras/Erk, PI3K/Akt axis or PLCγ/PKC signaling pathways [147]. Ron signaling promotes epithelial cell proliferation, migration and survival at the wound site which stimulates wound healing process [147].

Ron expression profile in malignancies showed that it is overexpressed in several cancers, including pancreatic cancer cells and pancreatic cancer stem cells [148, 149], rectal cancer [150], and DLBCL [151]. Lack of both Met and Ron expression was shown to be associated with inferior overall survival in DLBCL patients [151]. Moreover, abnormal overexpression of Ron induced the generation of oncogenic variants such as Ron160 and Ron165. Currently, seven Ron oncogene variants have been recognized which are produced by alternative splicing or protein truncation [152-154]. Ron160 is expressed in primary invasive ductal, lobular and lymph node-involved breast cancer cells [154]. This variant is mostly observed in invasive ductal and lymph node-involved cases. Blocking of Ron160 signaling by PHA665752 inhibitor blocked Du4475 cell anchorage-independent growth and prompted apoptotic cell death. In addition, PHA665752 inhibitor prevented 3T3-Ron160 and Du4475 cell-mediated tumor cell growth implanted in mouse mammary fat pad [154].

Ron has been considered as a RTK for mAb targeting. In this milieu, anti-Ron mAbs inhibited 60% of subcutaneous and orthotopic tumor growth in nude mice model [155]. Likewise, anti-Ron antibody has also been demonstrated to be suitable for delivery of chemotherapeutics agents to the cancer cells. Anti-Ron mAb Zt/c9 doxorubicin immunoliposomes (Zt/c9-Dox-IL) has been shown to direct the toxin into the pancreatic CSCs ($CD24^{+}CD44^{+}ESA^{+}$). Zt/c9-Dox-IL binding to Ron expressed on CSCs rapidly stimulated Ron internalization that led to doxorubicin uptake and subsequently reduced the viability of CSCs [149].

The inhibitory effects of anti-Ron mAbs have been examined in colon cancer. Zt/g4 mAb downregulated Ron expression in SW620 colon cancer cell line both in concentration and time dependent manner. Antibody-induced receptor internalization is the mechanism of Ron downregulation. Ron downregulation led to intracellular signaling inhibition by decreasing Erk1/2 and Akt phosphorylation. Moreover, Zt/g4 mAb changed SW620 cell morphology and affected its colony formation and increased its sensitivity in response to gemcitabine-induced cytotoxicity.

Anti-Ron mAb Zt/f2 targets an epitope located in a 49 amino acid residues of the β-chain extracellular domain of Ron [156]. This sequence is vital in Ron maturation and activation regulation. In mice models, Ron targeting by anti-Ron mAb Zt/f2 inhibited tumor growth of oncogenic Ron160 expressing NIH-3T3 cells. Moreover, this mAb attenuated cell-mediated tumor growth of colon cancer HT-29 in athymic nude mice [156].

In addition to solid tumors, Ron overexpression has been demonstrated in Burkitt's lymphoma (BL) cell lines and human lymphoma samples [157]. Anti-Ron mAb Zt/f2 also downregulated cell proliferation and colony formation and induced tumor cell apoptosis and cell cycle arrest in Raji BL cells [157].

IMC-Ron8, the first anti-Ron mAb entered into the clinical trial, downregulated the expression of Ron in pancreatic cancer cells and inhibited MSP-induced Ron activation, survivin expression and Akt and Erk activation. The co-treatment of pancreatic cells with panobinostat (PS) and anti-Ron mAb decreased Ron expression and Akt activation, and increased cleavage of PARP compared to both treatments alone [148].

Overall, reported data shows that anti-Ron mAbs reduced Ron expression, impaired signaling events and enhanced sensitivity towards cytotoxic drugs in cancer cells [158].

TROPOMYOSIN-RELATED KINASE (TrkA/NTrk1)

The first member of tropomyosin-related kinase (Trk) family was primarily discovered as a new oncogene in colon carcinoma at 1986 [159]. TrkA/Ntrk1 is a normal cellular counterpart of the oncogenic Trk and is highly expressed in the developing nervous system [160]. TrkB/NTrk2 and TrkC/NTrk3 are other members of Trk family with highly sequence homology to TrkA [160]. TrkA is a functional and high-affinity nerve growth factor (NGF) receptor that mediates some of the signal transduction processes induced by this neurotrophic growth factor [161].

Trk receptors were introduced as important prognostic factors in neuroblastoma, in a way that TrkA and TrkB are correlated with favorable and unfavorable disease, respectively [162, 163]. Truncated forms of Trk receptors have been identified lacking the kinase domain. For example alternative TrkA splice variant has only functional extracellular domains and is expressed in human neuroblastoma [164]. This oncogenic NGF-unresponsive isoform antagonizes NGF/TrkA signaling that is accountable for arresting of neuroblastoma cell growth. During tumor progression, the truncated form provides a mechanism for switching anti-oncogenic signals of NGF/TrkA/Ras/MAPK to tumor-promoting signals of truncated-TrkA/IP3K/Akt/NF-κB [164].

Due to the importance of TrkA-NGF pathway in anti-oncogenic signals, targeting of TrkA with mAbs specific for docking site of TrkA would be an appropriate strategy to inhibit neuroblastoma progression and growth.

Tanezumab, a humanized NGF blocking mAb, has recently shown hopeful results in clinical trials for osteoarthritic pain because NGF/TrkA signaling is important for normal and pathological feeling of pain [165]. However, TrkA could not pass the criteria as an appropriate target for cancer therapy by mAbs. Moreover, there are reports that proposed TrkA for cancer targeting by other modalities like SMIs [166-169].

RECEPTOR TYROSINE KINASE-LIKE ORPHAN RECEPTOR 1 (Ror1)

Ror family, consists of Ror1 and Ror2, is another member of the RTK families that is evolutionarily conserved [170]. Ror1 consists of three domains, immunoglobulin (Ig)-like, cysteine rich (CRD) and kringle (KNG), in the extracellular part [171]. Of the three extracellular regions, CRD region has been described to have the antigen binding site [172, 173]. The cytoplasmic part contains a TK domain with protein kinase activity, and further downstream serine, threonine- and proline-rich motifs. Ror1 is located on chromosome 1p31.3 and consists of 937 amino acids with an estimated molecular weight of 97-105 kDa. Human and mice Ror1 also have 97% amino acid identity [174, 175]. Ror1 and Ror2 have important roles in embryonic skeletal and cardiac as well as nervous system development in mouse [2, 176]. In this regard, Ror1 and Ror2 adjust hippocampal neurons neurite growth and branching pattern that are important in brain development [177]. In adults, Ror1 has been indicated to be expressed at mRNA level in several tissues, including colon, adipocytes, kidney, liver, lung, Ovary, lymph nodes, prostate, and testis [178]. However, Ror1 protein has not been detected in adult normal tissues [178].

Interestingly, Ror1 overexpression has been found in several malignancies, including CLL [179], ALL [180], AML [6, 181], HCL [6], MCL [6], melanoma [7], breast, pancreatic, lung [182], and ovarian cancers [14]. Recently it is shown that Ror1 can contribute in CLL leukemogenesis by interacting with T-cell leukemia 1 (TCL1) and causing elevated Akt activation and leukemia cell proliferation [183].

Overexpression of Ror1 on cancer cells and lacking expression in normal tissues introduced Ror1 as an appropriate target for cancer therapy. During the recent years that Ror1 has been recognized as an important tumor antigen, a few mAbs have been produced for therapeutic approaches [4, 178, 184]. Up to date, only an anti-Ror1 mAb, cirmtuzumab (humanized) (UC-961) has passed the preclinical stages. This mAb has been developed from the D10 anti-Ror1 mAb. This mAb showed a high specificity and affinity (KD=4nM) for Ror1. Intravenous injection of cirmtuzumab followed by infusion of human $Ror1^{+}CD5^{+}B220^{low}$ murine leukemia cells from Ror1xTCL1 transgenic mice, as well as of human $Ror1^{+}$ CLL cells into the peritoneal cavity of Rag-2-/-/γc-/- immunedeficient mice, induced clearance of leukemic cells in the spleen and peritoneal cavity. Cirmtuzumab had not only a direct killing effect on tumor cells but was also internalized by malignant B cells. An ADC using this mAb showed promising results with enhanced cytotoxic activity against Ror1 expressing cells. Cirmtuzumab-ADC cleared Ror1 expressing CLL cells *in vivo* in xenografted mice and *in vitro* using adenocarcinoma cell lines of the breast and pancreas [185].

Overall, among 30 known oncogenic RTKs, several have not been well-studied for targeted therapy or several obstacles are in front of researchers to target them by mAbs. Proper and suitable RTKs for mAb targeting such as Musk, Mer, Eph receptors, NTrk, Ror2, Ros, Ryk, Tek, Tie, and Tyro3 are overexpressed in several tumors. A few mAb against these RTKs are in early stages of preclinical studies. More studies are necessary to investigate these RTKs for targeted therapies.

CONCLUSION

Oncogenic RTKs are one of the appropriate classes of surface molecules for mAb targeted therapy. However, in spite of large efforts in targeting RTKs by specific mAbs, the evidences show the unsuccessfulness of this field and only a few antibodies have been entered clinical trials or have been approved by FDA for clinical application. Several obstacles, including differential post-translational modification of RTKs within a tumor population in different cancers as well as within different individual patients, paradigm of CSCs and the lack of enough information about their characteristics are in front of researchers. A better understanding of molecular, genetic and epigenetic factors involved in the pathogenesis of cancer, especially in a patient-based manner might be a suitable way to cure cancer in each patient. Tumor heterogeneity and the presence of several types of cancer cells within a special tumor suggest that the future of cancer targeted therapy may apply to target a particular cellular or molecular pathway within a specific cell type (cell-based therapy). On the other hand, current evidences show a better response in combinational therapy that targets different critical and pivotal molecules involved in cancer growth and progression. Overall, cancer therapy by mAbs may need to define new critical and vital targets on cancer cells and new approaches are warranted, and current methods might be necessary to be revised.

Competing interest

The authors have no relevant affiliation or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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