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Promising Pharmacological Directions in the World of Lysophosphatidic Acid Signaling

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Abstract

Lysophosphatidic acid (LPA) is a signaling lipid that binds to six known lysophosphatidic acid receptors (LPARs), named LPA_1-LPA_6. These receptors initiate signaling cascades relevant to development, maintenance, and healing processes throughout the body. The diversity and specificity of LPA signaling, especially in relation to cancer and autoimmune disorders, makes LPA receptor modulation an attractive target for drug development. Several LPAR-specific analogues and small molecules have been synthesized and are efficacious in attenuating pathology in disease models. To date, at least three compounds have passed phase I and phase II clinical trials for idiopathic pulmonary fibrosis and systemic sclerosis. This review focuses on the promising therapeutic directions emerging in LPA signaling toward ameliorating several diseases, including cancer, fibrosis, arthritis, hydrocephalus, and traumatic injury.

Key Words: Lysophosphatidic acid receptor, Pharmacology, Autotaxin, Cancer, Autoimmune disease, Fibrosis

INTRODUCTION

Lysophosphatidic acid (LPA) is a bioactive lipid that is concentrated in serum and is essential for a variety of cellular and developmental processes (reviewed in (Choi *et al*., 2010)). While LPA does play a structural role in cell membranes, extracellular LPA is a highly selective and specific activator of a class of G protein-coupled receptors (GPCRs) called LPA receptors (LPARs) (reviewed in (Yung *et al*., 2014)). There are currently six recognized LPARs, named LPA_{1-6} , with clear homologs between human (*LPAR1-6*) and mouse (*Lpar1-6*) genes (reviewed in (Chun *et al*., 2010)). All six receptors are expressed throughout the body during development and adulthood in unique spatiotemporal patterns. These receptors are involved in a variety of necessary functions, including cell survival, proliferation, migration, differentiation, vascular regulation, and cytokine release (reviewed in (Yung *et al*., 2014)).

LPA can be produced in several ways through the activity of intracellular or extracellular enzymes. The two most prominent pathways involve the conversion of lysophosphatidyl choline (LPC) to LPA by autotaxin (ATX/*Enpp2*) (Tokumura *et al*., 2002; Umezu-Goto *et al*., 2002) and conversion of phosphatidic acid to LPA by phospholipase A1 or A2 (PLA1/PLA2) (Fourcade *et al*., 1995; Sonoda *et al*., 2002). Intriguingly, ATX is highly expressed in blood, brain, kidney, the lymphatic system, and tissue surrounding injury (Bachner *et al*., 1999; Savaskan *et al*., 2007; Kanda *et al*., 2008), suggesting important LPA-mediated mechanisms in these areas. Additionally, LPA is secreted by activated platelets and mature adipocytes (Eichholtz *et al*., 1993; Valet *et al*., 1998; Sano *et al*., 2002). Because of its important roles throughout the body, aberrant LPA signaling has also been implicated in several diseases. This review focuses on the agents that have been developed to modulate LPA signaling and tested in disease models.

LYSOPHOSPHATIDIC ACID RECEPTOR SIGNALING

Interest in LPA as a signaling molecule dates back to the late 1970s when effects on intracellular calcium release, platelet aggregation, and blood pressure were reported (Tokumura *et al*., 1978; Gerrard *et al*., 1979). While the involvement of G proteins was postulated (Moolenaar and van Corven, 1990), the mechanism of LPA signaling was not elucidated until 1996 when the first LPA receptor was cloned (Hecht *et al*., 1996). Since the discovery of LPA_1 (originally Vzg-1 or Edg-2), five

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other LPARs have been validated. LPA_2 and LPA_3 were elucidated through homology searches by comparing amino acid sequences to that of LPA_1 (An *et al*., 1998; Bandoh *et al*., 1999). Through efforts aimed at finding ligands for orphan receptors, LPA_4 and LPA_5 were discovered (Noguchi *et al*., 2003; Kotarsky *et al*., 2006; Lee *et al*., 2006). Most recently, LPA_6, a GPCR that is most closely related to LPA_4, was added to the ranks of LPA receptors (Pasternack *et al*., 2008; Yanagida *et al*., 2009).

LPAR signaling occurs through a variety of intracellular cascades (reviewed in (Mirendil *et al*., 2013)) (Fig. 1). The binding of LPA or an LPA analog to its 7-transmembrane GPCR allows the G_α subunit to exchange used GDP for GTP. This results in G_α dissociating from G_β and G_γ, allowing the G_α and $G_{\beta\gamma}$ complexes to signal through downstream effectors. Several G_α subunits have been implicated in LPAR signaling, including $G_{\alpha12/13}$, $G_{\alpha q/11}$, $G_{\alpha s}$, and $G_{\alpha i/O}$. Downstream effectors include activation of several pathways. The $G_{\alpha12/13}$-mediated Rho/ROCK and Rho/SRF pathways have been implicated in cell motility, invasion, and cytoskeletal changes (Sotiropoulos *et al*., 1999; Kim and Adelstein, 2011; Jeong *et al*., 2012). The $G_{\alpha q/11}$ pathway activates phospholipase C (PLC), which induces IP3, and subsequently initiates Ca^{2+} and diacyl glycerol signaling (Sando and Chertihin, 1996). This cascade can result in vasodilation and a variety of transcriptional changes, including protein kinase C-induced cell growth, immune recruitment, and changes in learning and memory (Lu *et al*., 1999; Seewald *et al*., 1999; Cummings *et al*., 2004; Ruisanchez *et al*., 2014). Induction of the $G_{\alpha s}$ pathway leads to adenylyl cyclase (AC) activation and the production of cAMP, preventing cell migration (Jongsma *et al*., 2011). Activation of $G_{\alpha i/O}$ is the most versatile, as downstream effectors include PLC, Ras/MAPK-induced morphological changes (Kranenburg and Moolenaar, 2001), PI3K/Rac-mediated migration (Jimenez *et al*., 2000), modula-

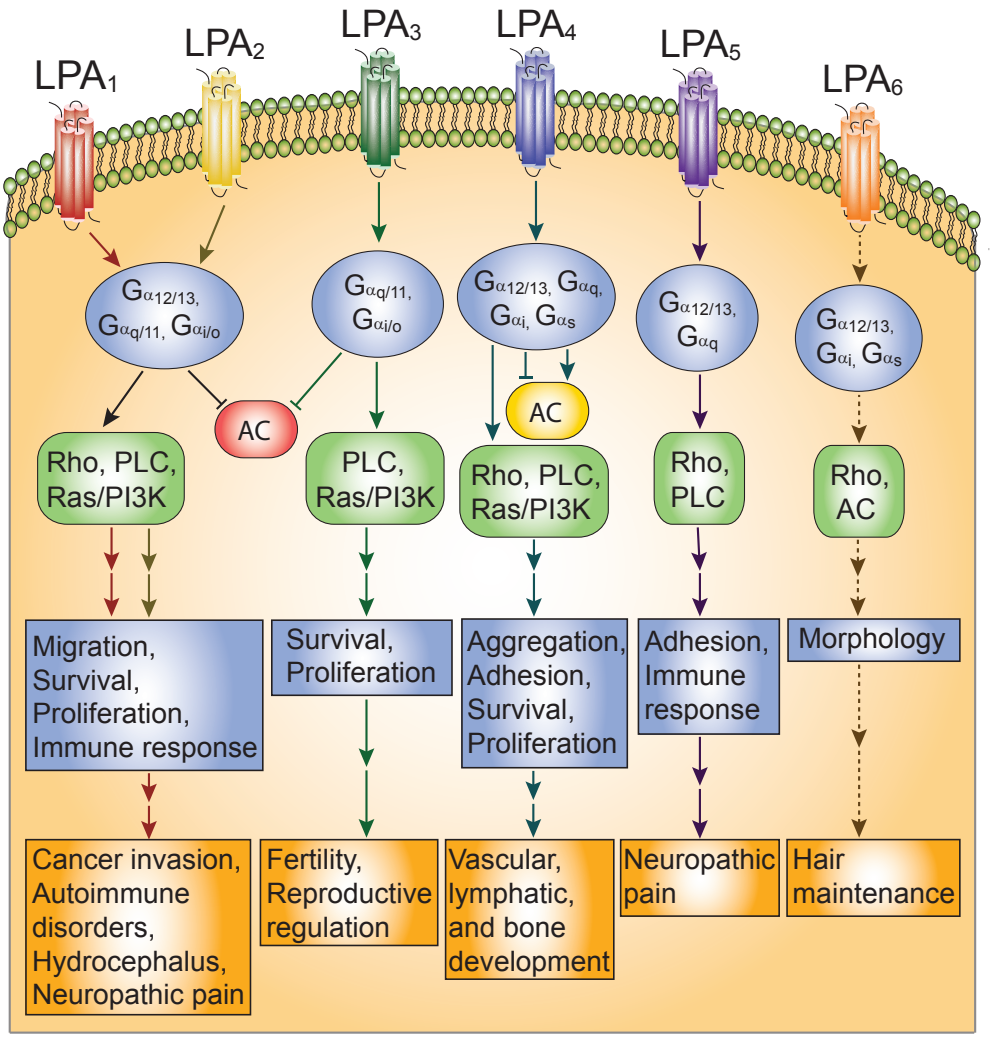


Fig. 1. LPAR signaling and functional outcomes. LPAR signaling details are highlighted for each receptor, based on canonical GPCR pathways that have been validated. Dashed lines indicate preliminary data that require further confirmation. Activated downstream effectors are shown in green, inhibited effectors in red, and effectors that are differentially activated or inhibited in yellow. The cellular effects of activating each LPAR are listed beneath the G_α cascades, followed by ultimate phenotypical outcomes as highlighted in this review. Antagonism or functional knockout of each LPAR has been proven to inhibit these disorder phenotypes.

tion of PI3K/Akt survival mechanisms (Kang *et al*., 2004; Ye *et al*., 2002), and inhibition of AC.

Each LPAR has multiple important regulatory functions throughout the body (reviewed in (Yung *et al*., 2014)). Many of these have been elucidated through the use of knockout animals, pharmacological LPAR agonists or antagonists, and gene association studies. The first discovered LPAR, LPA_1, appears to be responsible for several developmental, physiological, and pathological processes. These include cell survival, proliferation, adhesion, migration, immune function, and myelination (reviewed in (Fukushima *et al*., 2001)). LPA_2 signaling has also been implicated in cell survival, migration, immune function, and myelination (reviewed in (Ishii *et al*., 2004)), often appearing to contribute to complementary LPA_1 mechanisms (Contos *et al*., 2002). LPA_3, while expressed in many different tissues, is most heavily characterized as being involved in reproduction; it mediates fertility, embryo spacing, and embryo implantation (Ye *et al*., 2005). LPA_4 influences cell aggregation, cell adhesion, vascular development, and osteogenesis regulation (reviewed in (Mirendil *et al*., 2013)). Additionally, LPA_4-mediated adhesion appears to counteract LPA_1/LPA_2-stimulated migration processes (Lee *et al*., 2008). LPA_5 also negatively regulates cell motility and is involved in chemokine release (Jongsma *et al*., 2011; Lundequist and Boyce, 2011). Although LPA_6 is the most recently discovered LPAR, several genome screening studies have been published linking mutations in LPA_6 to genetic hair loss and autosomal recessive hypotrichosis, or "wooly hair" syndrome (Azeem *et al*., 2008; Pasternack *et al*., 2008; Petukhova *et al*., 2008). LPA_6 is also under investigation for further functionality. The effects of LPAR signaling are outlined in Figure 1.

PHARMACOLOGICAL ADVANCES MODULATING LPA SIGNALING

As LPAR signaling has been strongly implicated in many disease states, great interest has been expressed in developing specific LPAR inhibitors. Currently, no LPA or LPAR-targeting drugs have been FDA approved, though several are in development or undergoing clinical trials (Yung *et al*., 2014) (Table 1). Furthermore, the ability to develop safe and efficacious drugs targeting lysophospholipid signaling has already been proven; fingolimod (FTY720), an analog of sphingosine 1-phosphate (S1P) and inhibitor of S1P receptors, has been FDA-approved for the treatment of multiple sclerosis (Brinkmann *et al*., 2002; Chun and Hartung, 2010; Calabresi *et al*., 2014).

LPA signaling has long been implicated in immune reactions (reviewed in (Lin and Boyce, 2006)). To this end, several therapeutic advances have been made concerning autoimmune disorders. In fact, an $LPA_{1/3}$ inhibitor, SAR100842, has completed phase II clinical trials to protect against systemic sclerosis (Sanofi, 2014), an autoimmune disorder characterized by accumulated collagen in connective tissue, leading to scarring of the skin and vasculature (Lafyatis, 2014). LPA_1 inhibitors are also of great interest in fibrosis, with BMS-986202 (previously AM152) having successfully completed phase I and BMS-986020 beginning phase II clinical trials for idiopathic pulmonary fibrosis (IPF) (2011, Amira Pharmaceuticals Announces Completion of Phase 1 Clnical Study for AM152, a Novel LPA1 Receptor Antagonist. In PR Newswire, PRNewswire.com. http://www.prnewswire.com/news-releases/amira-pharmaceuticals-announces-completion-of-phase-1-clinical-study-for-am152-a-novel-lpa1-receptor-antagonist-121087874.html, Access Date: 2014/09/15; BMS, 2011, 2014). The LPA_1 inhibitor AM966 and the $LPA_{1/3}$ antagonist VPC12249 have also shown efficacy in murine IPF studies (Okusa *et al*., 2003; Swaney *et al*., 2010). Concurrently, an LPA_3 agonist, oleoyl-methoxy phosphothionate (OMPT), enhanced IPF injury and reduced the therapeutic effects of VPC12249, suggesting that LPA_3 signaling may also be relevant in fibrotic disease. The pan-LPAR antagonist HLZ-56 and LPA_1 inhibitor AM095 attenuated kidney and dermal fibrosis in mouse models by preventing Smad2 phosphorylation, which reduced TGFβ signaling and subsequent CTGF release (Castelino *et al*., 2011; Swaney *et al*., 2011; Geng *et al*., 2012), a mechanism that may be central to LPAR inhibitor effectiveness in other fibrotic disorders.

Much of the enthusiasm for LPAR therapies is directed at cancer, as LPAR signaling has been shown in numerous studies to promote motility and invasion of several cancer types, including breast, ovarian, colon, and brain tumors (Mills *et al*., 2002; Hama *et al*., 2004; Hoelzinger *et al*., 2008; Hayashi *et al*., 2012). *In vitro* studies utilizing the pan LPAR/ATX antagonist α-bromomethylene phosphonate LPA (BrP-LPA) and $LPA_{1/3}$ antagonists Ki16425, Ki16198, and Debio 0719 have been shown to decrease tumor aggressiveness and increase radiosensitivity through varied mechanisms, including inhibited Rho/ROCK and MEK/ERK signaling, prevention of FAK/paxillin localization to focal adhesions, and reduced matrix metalloproteinase accumulation (Hama *et al*., 2004; Zhang *et al*., 2009; Komachi *et al*., 2012; Marshall *et al*., 2012; Schleicher *et al*., 2011; Liao *et al*., 2013; Su *et al*., 2013). While many studies focus on the migratory effects of LPA_1 signaling, use of the LPA_2 inhibitor "compound 35" attenuated Erk phosphorylation and reduced proliferation of colorectal cancer cells (Beck *et al*., 2008). LPA itself has been proposed as a screening molecule for ovarian cancer, as increased levels of LPA have been repeatedly observed in the blood of patients with malignant ovarian tumors and may have prognostic value in lung cancer patients as well (Sedlakova *et al*., 2011; Bai *et al*., 2014; NCI, 2014). Although no LPAR-targeting cancer drugs have reached clinical trial stages thus far, pharmaceutical inquiry is progressing rapidly and the initiation of cancer-focused clinical trials is projected to follow.

In addition to cancer and fibrosis, LPAR inhibitors have been utilized as potential therapeutics in other areas of study. For instance, Ki16425 and BrP-LPA have been shown to decrease the clinical score of murine arthritis (Nikitopoulou *et al*., 2013; Orosa *et al*., 2014). The development of an LPA-induced neonatal model of post-hemorrhagic hydrocephalus was also abrogated utilizing Ki16425 (Yung *et al*., 2011). While LPA signaling is reported to be involved in wound-healing processes (Lee *et al*., 2000), it may exacerbate severe trauma. In fact, anti-LPA antibodies that diminish LPAR binding and activation have shown some efficacy in modulating murine brain lesion severity and recovery (Goldshmit *et al*., 2012; Crack *et al*., 2014), although the actual mechanism of these immunological agents remains to be determined. Additionally, Bristol-Myers Squibb has patented LPAR inhibitors for spinal cord injury and neuropathic pain indications (Nogueira and Vales, 2013), since there is a substantial body of evidence implicating LPA_1 and LPA_5 signaling in the initiation and maintenance

Table 1. Summary of compounds that target LPA signaling. The name, target, structure and development stage for each LPA signaling antagonist discussed in the article are outlined, along with their therapeutic indications

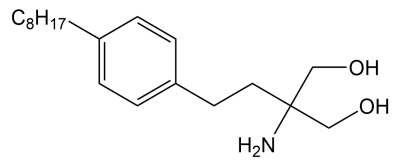
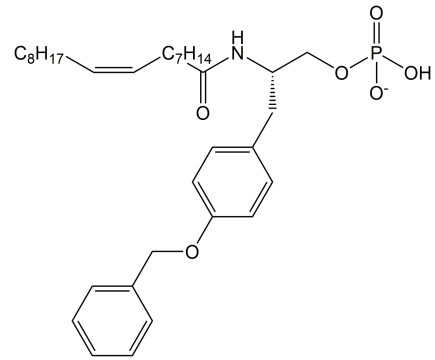
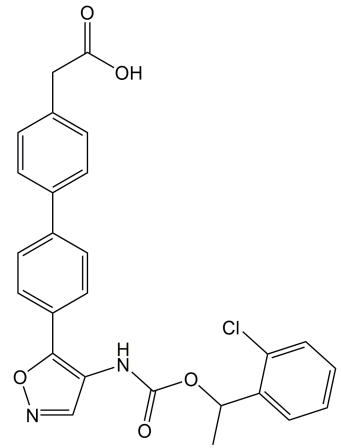
Drug	Target	Structure	Phase	Indication	Reference
FTY720	$S1P_1$, $S1P_{3-5}$		FDA approved	Multiple sclerosis	(Brinkmann *et al*., 2002; Chun and Hartung, 2010)
BMS-986202/AM152	LPA_1	See patent WO/2012/162592 A1 for more information	Phase I complete	Idiopathic pulmonary fibrosis	(BMS, 2011; Bradford, 2012)
BMS-986020	LPA_1	See patent WO/2012/162592 A1 for more information	Phase II complete	Idiopathic pulmonary fibrosis	(BMS, 2014; Bradford, 2012)
VPC 12249	LPA_1		Preclinical	Idiopathic pulmonary fibrosis	(Okusa *et al*., 2003)
AM966	LPA_1		Preclinical	Idiopathic pulmonary fibrosis	(Swaney *et al*., 2010)

Table 1. Continued

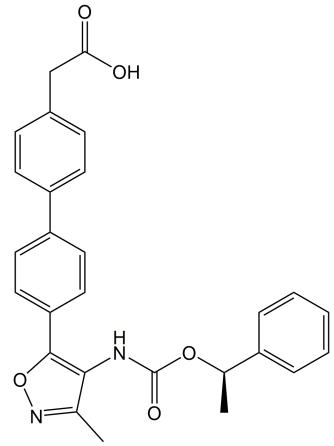
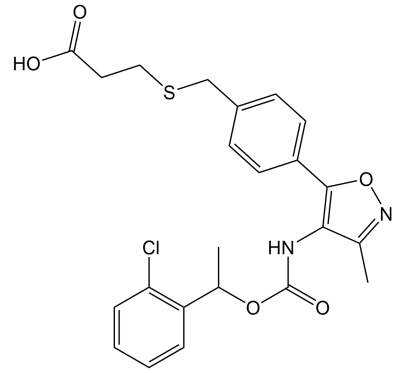
Drug	Target	Structure	Phase	Indication	Reference
AM095	LPA_1		Preclinical	Dermal fibrosis, kidney fibrosis	(Castelino *et al*., 2011; Swaney *et al*., 2011)
BMS patent	LPA_1	See patent WO/2013/070879 A1 for more information	Preclinical	Spinal injury, neuropathic pain	(Nogueira and Vales, 2013)
SAR 100842	LPA_1, LPA_3	See patent WO/2012/162592 A1 for more information	Phase II complete	Systemic sclerosis	(Bradford, 2012; Sanofi, 2014)
Ki16425	LPA_1, LPA_3		Preclinical	Cancer, rheumatoid arthritis, hydrocephalus	(Hama *et al*., 2004; Liao *et al*., 2013; Orosa *et al*., 2014; Su *et al*., 2013; Yung *et al*., 2011)
Debio 0719	LPA_1, LPA_3	R-stereoisomer of Ki16425	Preclinical	Cancer	(Marshall *et al*., 2012)

Table 1. Continued

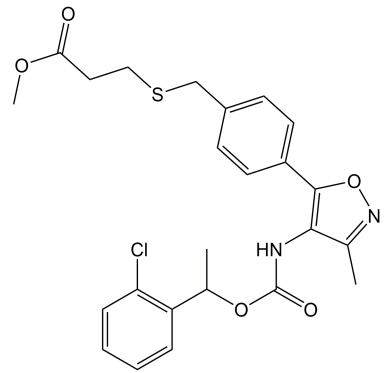
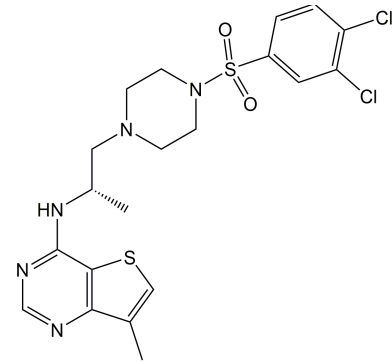
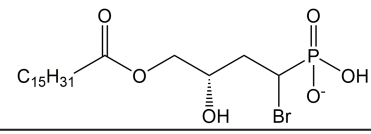
Drug	Target	Structure	Phase	Indication	Reference
Ki16198	LPA_{1-3}		Preclinical	Cancer	(Komachi *et al*., 2012)
Cmpd. 35	LPA_2		Preclinical	Cancer	(Beck *et al*., 2008)
Anti-LPA	All LPAR signaling	Antibody	Preclinical	Traumatic brain injury	(Crack *et al*., 2014; Goldshmit *et al*., 2012)
HLZ-56	All LPARs	Unavailable	Preclinical	Kidney fibrosis	(Geng *et al*., 2012)
BrP-LPA	ATX, all LPARs		Preclinical	Cancer, rheumatoid arthritis	(Nikitopoulou *et al*., 2013; Schleicher *et al*., 2011; Xu and Prestwich, 2010; Zhang *et al*., 2009)

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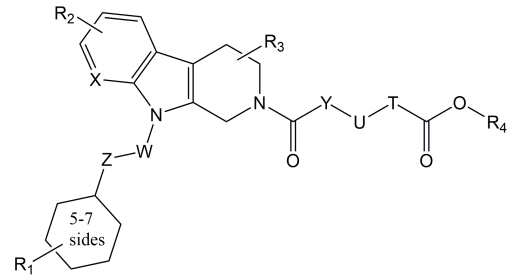
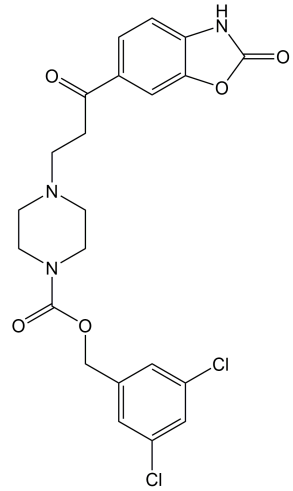
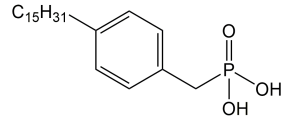
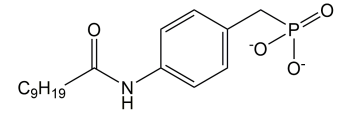
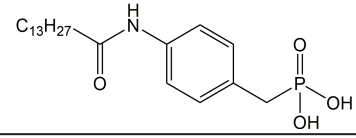
Table 1. Continued

Drug	Target	Structure	Phase	Indication	Reference
ONO-8430506	ATX	 Backbone only, see patent WO/2012/005227 A1	Preclinical	Cancer	(Benesch *et al.*, 2014; Morimoto, 2012)
PF-8380	ATX		Preclinical	Cancer, inflammation	(Bhave *et al.*, 2013; Gierse *et al.*, 2010; St-Coeur *et al.*, 2013)
4PBPA	ATX		Preclinical	Cancer	(Gupte *et al.*, 2011)
Gintonin	ATX	Glycolipoprotein, structure not available	Preclinical	Cancer	(Hwang *et al.*, 2013)
GWJ-A-23	ATX		Preclinical	Asthma, idiopathic pulmonary fibrosis	(Oikonomou *et al.*, 2012; Park *et al.*, 2013)
S32826	ATX		Preclinical	Glaucoma	(Iyer *et al.*, 2012)

of neuropathic pain (reviewed in (Ueda *et al*., 2013)).

The most common output for screening drug efficacy against an LPAR is determining the status of Ca^{2+} influx within the tested cell types. Generally, LPAR agonists will increase intracellular Ca^{2+} mobilization while LPAR antagonists will inhibit Ca^{2+} release. Using this method, several studies have been published on the synthesis and relative efficacy of potential therapeutics against LPA_{1-3}, LPA_{1-5}, and more recently LPA_{1-6} (reviewed in (Im, 2010)). While this article only discusses pharmacological modulators with functional, disease-related readouts, a more comprehensive list of LPAR agonists and antagonists can be found in a previous review (Yung *et al*., 2014).

COMPOUNDS TARGETING ATX INHIBITION

In addition to direct pharmacological modulation of LPARs, several research groups have targeted the upstream enzyme ATX for discovery of potential therapeutics (Table 1). ATX inhibitors prevent the enzymatic conversion of LPC to LPA. As ATX expression can account for at least half of plasma LPA levels (Tanaka *et al*., 2006; van Meeteren *et al*., 2006), these drugs ultimately attenuate LPA signaling. Although this pathway lies upstream of LPAR signaling, targeting ATX allows for structure-based drug design (Fells *et al*., 2013; Kawaguchi *et al*., 2013; Norman *et al*., 2013), a process that is limited in LPAR drug discovery because of the lack of receptor crystal structures; work in progress should rectify this deficiency.

In particular, oncology researchers are interested in developing these agents. Several ATX inhibitors have been synthesized and tested in tumor migration, metastasis, survival, and radiosensitivity studies. These inhibitors include the small molecules ONO-8430506 (Benesch *et al*., 2014) and PF-8380 (Bhave *et al*., 2013; St-Coeur *et al*., 2013), lipid analogs 4PBPA (Gupte *et al*., 2011) and pan-ATX/LPAR antagonist BrP-LPA (Xu and Prestwich, 2010; Schleicher *et al*., 2011), and gintonin - a plant-derived LPA/ginseng glycolipoprotein complex that results in feedback inhibition of ATX through LPAR signaling (Hwang *et al*., 2013). These compounds ultimately reduced survival and invasive behaviors of *in vitro* cancer cells and tumor xenografts. As ATX and LPARs are often upregulated in cancer (reviewed in (Gotoh *et al*., 2012)), the success of these compounds in research may spur therapeutic development.

ATX antagonism is also being investigated as a solution to inflammatory disease. PF-8380 has been shown to drastically reduce plasma LPA concentrations during inflammation (Gierse *et al*., 2010), suggesting that targeting ATX may be useful to reduce chronic inflammation. As mentioned above, BrP-LPA has been utilized to ameliorate arthritis in mice (Nikitopoulou *et al*., 2013). Furthermore, GWJ-A-23 showed efficacy in attenuating allergen-induced asthmatic attacks and bleomycin-induced IPF (Oikonomou *et al*., 2012; Park *et al*., 2013). The effects of reduced LPA signaling stretch even further, as the potent ATX inhibitor S32826 has been utilized to decrease intraocular pressure in a rabbit model of glaucoma (Iyer *et al*., 2012).

CONCLUSION

Over the past four decades, interest in the signaling lipid LPA has grown from understanding its synthesis to encompassing several key processes in development and disease. To this end, several compounds have been fine-tuned by researchers and pharmaceutical companies to inhibit LPARs and ATX in order to mitigate the destructive pathologies related to cancer, autoimmune diseases, and other afflictions. The LPA_1-targeting inhibitors SAR100842, BMS-986202, and BMS-986020 have passed phase I or phase II clinical trials with the potential of advancing toward FDA approval. The increasing availability of chemical tool compounds will enhance our understanding of LPAR signaling mechanisms in disease towards the development of new disease-modifying therapeutics.

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CONFLICT OF INTEREST

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