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 LPA1-6, 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 lysophosphatidylcholine (LPC) to LPA by autotaxin (ATX/Enpp2) (Tokumura et al., 1999; 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 (Eichhartz 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 toward ameliorating several diseases, including cancer, fibrosis, arthritis, hydrocephalus, and traumatic injury.
other LPARs have been validated. LPA₁ and LPA₆ were elucidated through homology searches by comparing amino acid sequences to that of LPA₁ (An et al., 1998; Bandoh et al., 1999). Through efforts aimed at finding ligands for orphan receptors, LPA₂ and LPA₃ were elucidated (Noguchi et al., 2003; Kotersky et al., 2006; Lee et al., 2006). Most recently, LPA₆, a GPCR that is most closely related to LPA₄, 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 Gα subunit to exchange used GDP for GTP. This results in Gα dissociating from Gβ and Gγ, allowing the Gα and Gβγ complexes to signal through downstream effectors. Several Gα subunits have been implicated in LPAR signaling, including Gα₁₂/₁₃, Gα₂₁/₁₁, Gαₛ, and Gαᵢ/O. Downstream effectors include activation of several pathways. The Gα₁₂/₁₃-mediated Rho/ROCK and Rho/SCF pathways have been implicated in cell motility, invasion, and cytoskeletal changes (Sotiropoulos et al., 1999; Kim and Adelstein, 2011; Jeong et al., 2012). The Gα₂₁/₁₁ pathway activates phospholipase C (PLC), which induces IP₃ and subsequently initiates Ca²⁺ 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 Gαₛ pathway leads to adenylyl cyclase (AC) activation and the production of cAMP, preventing cell migration (Jongsma et al., 2011). Activation of Gαᵢ/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-
ion 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, LPA₁, 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)). LPA₂ 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 LPA₁ mechanisms (Contos et al., 2002). LPA₃, 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). LPA₄ influences cell aggregation, cell adhesion, vascular development, and osteogenesis regulation (reviewed in (Mirendil et al., 2004)). Additionally, LPA₅-mediated adhesion appears to counteract LPA₁/LPA₃-stimulated migration processes (Lee et al., 2008). LPA₆ also negatively regulates cell motility and is involved in chemokine release (Jongsma et al., 2011; Lundequist and Boyce, 2011). Although LPA₆ is the most recently discovered LPAR, several genome screening studies have been published linking mutations in LPA₆ to genetic hair loss and autosomal recessive hypotrichosis, or “wooly hair” syndrome (Azeeem et al., 2008; Pasternack et al., 2008; Petukhova et al., 2008). LPA₇ 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; fingeolimod (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 Boyle, 2006)). To this end, several therapeutic advances have been made concerning autoimmune disorders. In fact, an LPA₁₃ 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). LPA₃ 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 Clinical 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 LPA₂ inhibitor AM966 and the LPA₃ antagonist VPC12249 have also shown efficacy in murine IPF studies (Okusa et al., 2003; Swaney et al., 2010). Concurrently, an LPA₂ agonist, oleoyl-methoxy phosphothionate (OMPT), enhanced IPF injury and reduced the therapeutic effects of VPC12249, suggesting that LPA₂ signaling may also be relevant in fibrotic disease. The pan-LPAR antagonist HLZ-56 and LPA₁ 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 LPA₁ antagonists K16425, K16198, 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 signaling, use of the LPA₁ 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, K16425 and BrP-LPA have been shown to decrease the clinical score of murine arthritis (Nikitoriou et al., 2013; Crosa et al., 2014). The development of an LPA₁-induced neonatal model of post-hemorrhagic hydrocephalus was also abrogated utilizing K16425 (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 LPA₃ and LPA₄ 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<sub>n</sub>, S1P<sub>3-5</sub> | ![Image](https://example.com/fty720.png) | FDA approved | Multiple sclerosis              | (Brinkmann et al., 2002; Chun and Hartung, 2010) |
| BMS-986202/AM152 | LPA<sub>n</sub> | See patent WO/2012/162592 A1 for more information | Phase I complete | Idiopathic pulmonary fibrosis   | (BMS, 2011; Bradford, 2012)        |
| BMS-986020     | LPA<sub>n</sub> | See patent WO/2012/162592 A1 for more information | Phase II complete | Idiopathic pulmonary fibrosis   | (BMS, 2014; Bradford, 2012)        |
| VPC 12249      | LPA<sub>n</sub> | ![Image](https://example.com/vpc12249.png) | Preclinical | Idiopathic pulmonary fibrosis   | (Okusa et al., 2003)              |
| AM966          | LPA<sub>n</sub> | ![Image](https://example.com/am966.png) | Preclinical | Idiopathic pulmonary fibrosis   | (Swaney et al., 2010)             |
| Drug         | Target | Structure | Phase   | Indication                                      | Reference                          |
|--------------|--------|-----------|---------|------------------------------------------------|------------------------------------|
| AM095        | LPA₁   |           | Preclinical | Dermal fibrosis, kidney fibrosis                 | (Castelino et al., 2011; Swaney et al., 2011) |
| BMS patent   | LPA₁   | ![Structure](image1) | Preclinical | Spinal injury, neuropathic pain                  | (Nogueira and Vales, 2013)         |
| SAR 100842   | LPA₁, LPA₃ | See patent WO/2013/070879 A1 for more information | Phase II complete | Systemic sclerosis                              | (Bradford, 2012; Sanofi, 2014)    |
| Ki16425      | LPA₁, LPA₃ | ![Structure](image2) | 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   | LPA₁, LPA₃ | R-stereoisomer of Ki16425 | Preclinical | Cancer                                          | (Marshall et al., 2012)           |
| Drug     | Phase | Target  | Indication                                      | Reference                                      |
|----------|-------|---------|------------------------------------------------|------------------------------------------------|
| Ki16198  | Preclinical | LPA₁-₃ | Cancer (Komachi et al., 2012)                   | (Komachi et al., 2012)                        |
| Cmpd. 35 | Preclinical | LPA₂  | Preclinical Cancer (Beck et al., 2008)          | (Beck et al., 2008)                           |
| Anti-LPA | Preclinical | Unavailable | All LPAR signaling                              | (Crack et al., 2014; Goldshmit et al., 2012)  |
| HLZ-56   | Preclinical | ATX, all LPARs | Kidney fibrosis                                | (Niktopoulou et al., 2013; Schiefer et al., 2011; Xu and Prestwich, 2010; Zhang et al., 2009) |
| BrP-LPA  | Preclinical | Unavailable | Cancer, rheumatoid arthritis                     |                                               |
|          |        |         |                                                |                                               |
| Drug          | Target | Structure                                  | Phase  | Indication                       | Reference                                      |
|--------------|--------|--------------------------------------------|--------|----------------------------------|------------------------------------------------|
| ONO-8430506 | ATX    | ![ONO-8430506 Structure](image)            | Preclinical | Cancer                          | (Benesch et al., 2014; Morimoto, 2012)         |
| PF-8380      | ATX    | ![PF-8380 Structure](image)                | Preclinical | Cancer, inflammation             | (Bhave et al., 2013; Gierse et al., 2010; St-Coeur et al., 2013) |
| 4PBPA        | ATX    | ![4PBPA Structure](image)                  | Preclinical | Cancer                          | (Gupte et al., 2011)                            |
| Gintonin     | ATX    | Glycolipoprotein, structure not available   | Preclinical | Cancer                          | (Hwang et al., 2013)                            |
| GWJ-A-23     | ATX    | ![GWJ-A-23 Structure](image)               | Preclinical | Asthma, idiopathic pulmonary fibrosis | (Oikonomou et al., 2012; Park et al., 2013)       |
| S32826       | ATX    | ![S32826 Structure](image)                 | 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\(_{4-6}\), and more recently LPA\(_{7}\) (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 glycolipidprotein complex that results in feedback inhibition of ATX through LPAR signaling (Hwang et al., 2013). These compounds ultimately reduced survival and invasive behaviors of \textit{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 (Giese 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\(_{-}\)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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REFERENCES

An, S., Bleu, T., Hallmark, O. G. and Goetzl, E. J. (1998) Characterization of a novel subtype of human G protein-coupled receptor for lysophosphatidic acid. J. Biol. Chem. 273, 7906-7910.

Azeeem, Z., Jelani, M., Naz, G., Tariq, M., Wasif, N., Kamran-Ul-Hassan Naqvi, S., Ayub, M., Yasinzai, M., Amin-Ud-Din, M., Wali, A., Ali, G., Chishti, M. S. and Ahmad, W. (2008) Novel mutations in G protein-coupled receptor gene (P2RY5) in families with autosomal recessive hypotrichosis (LAH3). Hum. Genet. 123, 515-519.

Bachner, D., Ahrens, M., Betal, N., Schroder, D. and Gross, G. (1999) Developmental expression analysis of murine autotaxin (ATX). Mech. Dev. 84, 121-125.

Bai, C. Q., Yao, Y. W., Liu, C. H., Zhang, H., Xu, X. B., Zeng, J. L., Liang, W. J., Yang, W. and Song, Y. (2014) Diagnostic and prognostic significance of lysophosphatidic acid in malignant pleural effusions. J. Thorac. Dis. 6, 483-490.

Bandoh, K., Aoki, J., Hosono, H., Kobayashi, S., Kobayashi, T., Murakami-Murofushi, K., Tsujimoto, M., Arai, H. and Inoue, K. (1999) Molecular cloning and characterization of a novel human G-protein-coupled receptor, EDG7, for lysophosphatidic acid. J. Biol. Chem. 274, 27776-27785.

Beck, H. P., Kohn, T., Rubenstein, S., Hedberg, C., Schwandner, R., Hasslunger, K., Dai, K., Li, C., Liang, L., Wescbe, H., Frank, B., An, S., Wickrnamasinghe, D., Jaen, J., Medina, J., Hungate, R. and Shen, W. (2008) Discovery of potent LPA\(_{-}\) (EDG4) antagonists as potential anticancer agents. Bioorg. Med. Chem. Lett. 18, 1037-1041.

Benesch, M. G., Tang, X., Maeda, T., Ohhata, A., Zhao, Y. Y., Kok, B. P., Dewald, J., Hitt, M., Curtis, J. M., McMullen, T. P. and Brindley, D. N. (2014) Inhibition of autotaxin delays breast tumor growth and lung metastasis in mice. FASEB J. 28, 2655-2666.

Bhave, S. R., Daday, D. Y., Karvas, R. M., Ferraro, D. J., Kotpatruni, R. P., Jaboan, J. J., Hallahan, A. N., Dewees, T. A., Linkous, A. G., Hallahan, D. E. and Thotala, D. (2013) Autotaxin inhibition with PF-8380 enhances the radiosensitivity of human and murine glioblastoma cell lines. Front. Oncol. 3, 236.
Kanda, H., Newton, R., Klein, R., Morita, Y., Gunn, M. D. and Rosen, S. D. (2008) Autotaxin, an enzyme that produces lysophosphatidic acid, promotes the entry of lymphocytes into secondary lymphoid organs. Nat. Immunol. 9, 415-423.

Kang, Y. C., Kim, K. M., Lee, K. S., Namkoong, S., Lee, S. J., Han, J. A., Jeoung, D., Ha, K. S., Kwon, Y. G. and Kim, Y. M. (2004) Serum bioactive lysophospholipids prevent TRAIL-induced apoptosis via PI3K/Akt-dependent cFLIP expression and Bad phosphorylation. Cell Death Differ. 11, 1287-1298.

Kawaguchi, M., Okabe, T., Okudaira, S., Nishimasu, H., Ishitani, R., Kojima, H., Nureki, O., Aoki, J. and Nagano, T. (2013) Screening and X-ray crystal structure-based optimization of autotaxin (ENPP2) inhibitors, using a newly developed fluorescence probe. ACS Chem. Biol. 8, 1713-1721.

Kim, J. H. and Adelstein, R. S. (2011) LPA(1)-induced migration requires nonmuscle myosin II light chain phosphorylation in breast cancer cells. J. Cell Physiol. 226, 2881-2893.

Komachi, M., Sato, K., Tobo, M., Mogi, C., Yamada, T., Ohta, H., Tomura, H., Kimura, T., Im, D. S., Yanagida, K., Ishii, S., Takeyoshi, I. and Okajima, F. (2012) Orally active lysophosphatidic acid receptor antagonist attenuates pancreatic cancer invasion and metastasis in vivo. Cancer Sci. 103, 1099-1104.

Kotarsky, K., Boketoft, A., Bristulf, J., Nilsson, N. E., Norberg, A., Hansson, C., Olin, C., Sillard, R., Leeb-Lundberg, L. M. and Olde, B. (2006) Lysophosphatidic acid binds to and activates GPR92, a G protein-coupled receptor highly expressed in gastrointestinal lymphocytes. J. Pharmacol. Exp. Ther. 318, 619-628.

Kranenburg, O. and Moolenaar, W. H. (2001) Ras-MAP kinase signal ling by lysophosphatidic acid and other G protein-coupled receptor agonists. Oncogene 20, 1540-1546.

Lafyatis, R. (2014) Transforming growth factor beta-at the centre of systemic sclerosis. Nat. Rev. Rheumatol. 10, 706-719.

Lee, C. W., Rivera, R., Gardell, S., Dubin, A. E. and Chun, J. (2006) GPR92 as a new G12/13- and Gq-coupled lysophosphatidic acid receptor that increases cAMP. J. Biol. Chem. 281, 23589-23597.

Lee, H., Goetzl, E. J. and An, S. (2000) Lysophosphatidic acid and sphingosine 1-phosphate stimulate endothelial cell wound healing. American journal of physiology. Am. J. Physiol. Cell Physiol. 278, C612-618.

Lee, Z., Cheng, C. T., Zhang, H., Subler, M. A., Wu, J., Mukherjee, A., Windle, J. J., Chen, C. K. and Fang, X. (2008) Role of LPA/p2y9/GPR23 in negative regulation of cell motility. Mol. Biol. Cell 19, 5435-5445.

Liao, Y., Mu, G., Zhang, L., Zhou, W., Zhang, J. and Yu, H. (2013) Lysophosphatidic acid stimulates activation of focal adhesion kinase and paxillin and promotes cell motility, via LPA1-3, in human pancreatic cancer. Dig. Dis. Sci. 58, 3524-3533.

Lin, D. A. and Boyce, J. A. (2006) Lysophospholipids as mediators of immunity. Ad. Immunol. 89, 141-167.

Lu, W. Y., Xiong, Z. G., Lei, S., Orser, B. A., Dudek, E., Browning, M. D. and MacDonald, J. F. (1999) G-protein-coupled receptors act via ceramide-generated bioactive lysophosphatidic acid, structurally distant from the Edg family. J. Biol. Chem. 274, 25600-25606.

Noguchi, K., Ishii, S. and Shimizu, T. (2003) Identification of p2y9/GPR23 as a novel G protein-coupled receptor for lysophosphatidic acid, structurally distant from the Edg family. J. Biol. Chem. 278, 1287-1298.

Norman, D. D., Ibezem, A., Scott, W. E., White, S., Parrill, J. A. and Baker, D. L. (2013) Autotaxin inhibition: development and application of computational tools to identify site-selective lead compounds. Bioorg. Med. Chem. 21, 5548-5560.

Oikonomou, N., Mouratis, M. A., Tzouveleakis, A., Kaffe, E., Valavanis, C., Villaras, G., Karameris, A., Prestwich, G. D., Bouros, D. and Aidinis, V. (2012) Pulmonary autotaxin expression contributes to the pathogenesis of pulmonary fibrosis. Am. J. Respir. Cell Mol. Biol. 47, 566-574.

Okusa, M. D., Ye, H., Huang, L., Sigismund, L., Macdonald, T. and Lynch, K. R. (2003) Selective blockade of lysophosphatidic acid LPA receptors reduces murine renal ischemia-reperfusion injury. American journal of physiology. Am. J. Physiol. Renal Physiol. 285, F565-574.

Orosa, B., Garcia, S., Martinez, P., Gonzalez, A., Gomez-Reino, J. J. and Conde, C. (2014) Lysophosphatidic acid receptor inhibition as a new multipronged treatment for rheumatoid arthritis. Am. Rheum. Dis. 73, 298-305.

Park, G. Y., Lee, Y. G., Berdyhev, E., Nyenhus, S., Du, J., Fu, P., Gorshkova, I. A., Li, Y., Chung, S., Karparupu, M., Deng, J., Ranjan, R., Xiao, L., Jaffe, H. A., Corbridge, S. J., Kelly, E. A., Jarjour, N. N., Chun, J., Prestwich, G. D., Kaffe, E., Ninou, I., Aidinis, V., Morris, A. J., Smyth, S. S., Ackerman, S. J., Natarajan, V. and Christian, J. W. (2013) Autotaxin production of lysophosphatidic acid mediates allergic asthmatic inflammation. Am. J. Respir. Crit. Care Med. 188, 928-940.

Pasternack, S. M., von Kugelgen, I., AlAboud, K., Lee, Y.A., Ruschendorf, F., Voss, K., Hillmer, A. M., Molderings, G. J., Franz, T., Ramirez, A., Numberg, N., Nothen, M. M. and Betz, R. C. (2008) G protein-coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth. J. Investig. Dermatol. 1306-1319.

Mirendil, H., Lin, M.-E. and Chun, J. (2013) Lysophospholidic acid receptor: signaling and biochemistry. In Lysophospholidic acid receptors: signaling and biochemistry (J. Chun, T. Hla, S. Spiegel and W. H. Moolenaar, Eds) John Wiley & Sons, Inc., Hoboken, NJ.

Moolenaar, W. H. and van Corven, E. J. (1990) Growth factor-like action of lysophosphatidic acid: mitogenic signalling mediated by G protein. Ciba Found. Symp. 150, 99-106.

Morimoto, T. (2012) Tetrahydropyridine derivative, International Patent: WO/2012/005227 A1. Ono Pharmaceutical Co., Ltd., International. http://www.google.com/patents/WO2012005227A1, Access Date: 2014/09/15.

NCI (2014) A pilot study of a protein profile test in ovarian cancer patients in remission to see if protein changes can predict relapse. https://clinicaltrials.gov/ct2/show/NCT00001938, Access Date: 2014/09/15.

Niktopoulou, I., Kaff, E., Sevastou, I., Siori, I., Samiotaki, M., Madan, D., Prestwich, G. D. and Aidinis, V. (2013) A metabolically-stabilized phosphonate analog of lysophosphatidic acid attenuates collagen-induced arthritis. PloS ONE 8, e70941.

http://dx.doi.org/10.4062/biomolther.2014.109
Savaskan, N. E., Rocha, L., Kotter, M. R., Baer, A., Lubec, G., van Sanofi (2014) Proof of Biological Activity of SAR100842 in Systemic Sclerosis. https://clinicaltrials.gov/ct2/show/NCT01651143, Access Date: 2014/09/15.

Savaskan, N. E., Rocha, L., Kotter, M. R., Baer, A., Lubec, G., van Sanofi (2014) Proof of Biological Activity of SAR100842 in Systemic Sclerosis. https://clinicaltrials.gov/ct2/show/NCT01651143, Access Date: 2014/09/15.

Sano, T., Baker, D., Virag, T., Wada, A., Yatomi, Y., Kobayashi, T., Igarashi, Y. and Tigyi, G. (2002) Multiple mechanisms linked to platelet activation result in lysophosphatidic acid and sphingosine 1-phosphate generation in blood. J. Biol. Chem. 277, 21197-21206.

Sanofi (2014) Proof of Biological Activity of SAR100842 in Systemic Sclerosis. https://clinicaltrials.gov/ct2/show/NCT01651143, Access Date: 2014/09/15.

Sedlakova, I., Vavrova, J., Tosner, J. and Hanousek, L. (2011) Lyso lysophospholipase D, a lysophosphatidic acid-producing enzyme, as autotaxin, a multifunctional phosphodiesterase. J. Biol. Chem. 277, 39436-39442.

Sneddon, A. G., Hsu, X., Kenney, P. A., Merrill, M. M., Babaian, K. N., Zhang, X. Y., Yang, S. F., Lin, X. and Wood, C. G. (2013) Auto-taxin-lysophosphatidic acid signaling axis mediates tumorigenesis and motility by lysophosphatidic acid production. J. Cell Biol. 158, 227-233.

Valet, P., Pages, C., Jeanneton, O., Dauvaid, D., Barbe, P., Record, M., Saulnier-Blache, J. S. and Laffontant, M. (1998) Alpha2-adrenergic receptor-mediated release of lysophosphatidic acid by adipocytes. A paracrine signal for preadipocyte growth. J. Clin. Invest. 101, 1431-1438.

Tanaka, M., Okudaira, S., Kishi, Y., Ohkawa, R., Iseki, S., Ota, M., Noji, S., Yatomi, Y., Aoki, J. and Arai, H. (2006) Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid. J. Biol. Chem. 281, 25822-25830.

Tokumura, A., Fukuoka, K., Akamatsu, Y., Yamada, S., Suzuki, T. and Tsukatani, H. (1978) Identification of vasopressor phospholipid in crude soybean lecithin. Lipids 13, 468-472.

Tokumura, A., Majima, E., Kariya, Y., Tominaga, K., Kogure, K., Yasuda, K. and Fukuzawa, K. (2002) Identification of human plasma lysophosphatidyl D, a lysophosphatidic acid-producing enzyme, as autotaxin, a multifunctional phosphodiesterase. J. Biol. Chem. 277, 39436-39442.

Ueda, H., Matsunaga, H., Olaposi, O. I. and Nagai, J. (2013) Lysophosphatidic acid: chemical signature of neuropathic pain. Biochim. Biophys. Acta 1831, 61-73.

Umezoz-Goto, M., Kishi, Y., Taira, A., Hama, K., Dohmura, N., Takio, K., Yamori, T., Mills, G. B., Inoue, K., Aoki, J. and Arai, H. (2002) Autotaxin has lysophosphatidyl D activity leading to tumor cell growth and motility by lysophosphatidic acid production. J. Cell Biol. 158, 227-233.

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