Development of AQX-1125, an Allosteric SHIP1 Activator: Pre-Clinical and Early-Stage Clinical Results

Dr. C. Szabo, CSO

Aquinox Pharmaceuticals Inc., Richmond, BC, Canada

Abstract

Pharmacological modulation of the phosphoinositide 3-kinase (PI3K)/Akt pathway is a means to control inflammatory disorders. The SH2-containing inositol-5'-phosphatase 1 (SHIP1) metabolizes PI(3,4,5)P3 to PI(3,4)P2. SHIP1-deficient mice exhibit a marked degree of inflammatory cell recruitment into the lungs. Pharmacological, allosteric activation of SHIP1 has been shown to enhance the degradation of PI(3,4,5)P3 to PI(3,4)P2 and exert anti-inflammatory effects (Ong et al., Blood, 2008). AQX-1125 is a clinical-stage small-molecule allosteric SHIP1 activator that is being developed for inflammatory diseases. The presentation will summarize the *in vitro* effects of AQX-1125, in inhibiting leukocyte chemotaxis, Akt activation, pro-inflammatory mediator production, as well as its anti-inflammatory effects in various rodent models, including ovalbumin-, LPS-, and cigarette smoke-induced airway inflammation. In addition, Phase I clinical safety and pharmacokinetic data will be presented.

Introduction

Targeting SHIP1

- ✓ PI3K pathway is one of the most active areas in Biotech/Pharma
- ✓ PI3K/SHIP1 pathway plays a key role in regulating cell migration and activation
- ✓ SHIP1 is an ideal drug target
- ✓ SHIP1 expression restricted to hematopoietic derived cells - limits off-target toxicity
- ✓ SHIP1 is a novel target distinct from the extensive PI3K investigations
- ✓ Redirects cellular PI3K signalling, rather than preventing it

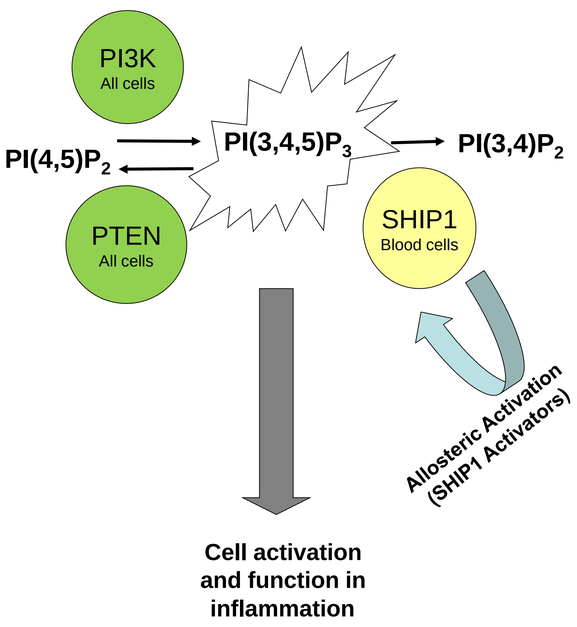


Figure 1. *SHIP1 and PI3K signalling. SHIP1 activators redirect PI3K signalling, PI3K inhibitors block PI3K signalling.*

Background

SHIP enzymes

	hSHIP2	mSHIP1	rSHIP1
hSHIP1	51%	92%	91%
hSHIP1 C2 domain	38%	91%	90%

Figure 2. *SHIP enzyme homology. Reduced homology between SHIP1 and SHIP2 confers selectivity.*

Good homology between human and rodent SHIP1

SHIP1 Activation

Pelorol was the first generation SHIP1 activator isolated. Analogues of Pelorol, AQX-016A and AQX-MN100, were synthesized with greater SHIP1-activating properties[1,2]. These small molecules activate SHIP1 through an allosteric mechanism, via interaction with the C2 domain, and are anti-inflammatory in cellular and murine models.

Contact information

Aquinox Pharmaceuticals Inc.

Suite 430, 5600 Parkwood Way, Richmond, BC, V6V 2M2, Canada

T: 604.629.9223
F: 604.295.4748
aqxpharma.com

Background

SHIP1 Activation

AQX-1125 is a small molecule next generation SHIP1 activator. It has many of the biological effects of the earlier generation SHIP1 activators, but has an improved drug scaffold and superior drug-like properties.

AQX-1125 has completed Phase I safety testing in healthy human volunteers and has progressed into Phase IIa proof-of-concept clinical studies.

Results

AQX-1125 inhibits Akt phosphorylation in SHIP1-proficient MOLT-4, but not in SHIP1-deficient Jurkats

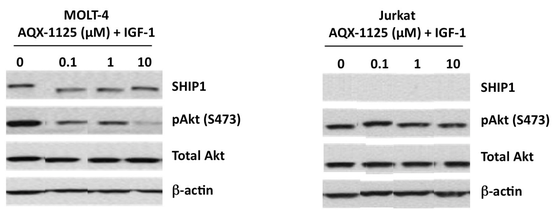
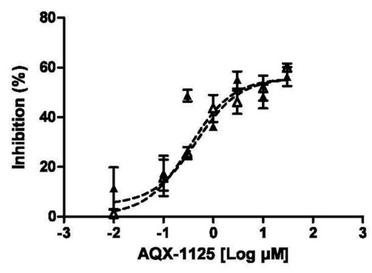


Figure 3. *MOLT-4 and Jurkat cells were treated with AQX-1125 for 30 min, followed by stimulation with IGF-1 for 30 min.*

AQX-1125 inhibits leukocyte chemotaxis

A



B

Cell Type	Chemokine	Chemokine Receptor	Potency of AQX-1125
Monocytes	MCP-1	CCR2	288 nM
B Cells	BCA-1	CXCR5	28 nM
Activated T Cells	IP-10 / I-TAC	CXCR3	70 nM /229 nM
Non-activated T Cells	MIP-1a	CCR1	33 nM
Neutrophils	GRO-a / IL-8	CXCR1/2	30 nM /73 nM

Figure 4 *Human blood monocytes (A) and (B) different leukocyte populations were treated with AQX-1125 for 30 min, followed by induction of chemotaxis with chemokines listed.*

AQX-1125 has diverse *in vivo* utility

Product Profile		Disease	Result
Cystitis, Bladder (Rat)	Cyclophosphamide	Interstitial Cystitis	✓
Fibrosis (Mouse)	Bleomycin	Pulmonary Fibrosis	✓
Airway Inflammation (Rat)	LPS Ovalbumin	Infect./COPD Asthma	✓ ✓
Allergic Rhinitis (Mouse)	Ovalbumin	AR	(✓)
Airway Inflammation (Mouse)	Smoke	COPD	✓
IBD (Rat)	TNBS	IBD	✓
Psoriasis (Mouse)	Imiquimod	Psoriasis	(✓)
Ear Edema (Mouse)	PCA, PMA	Allergic Derm.	✓
Edema (Mouse)	Carrageenan Paw	Inflam. Pain	✓

AQX-1125 inhibits OVA-induced allergic airway inflammation in Brown Norway rats

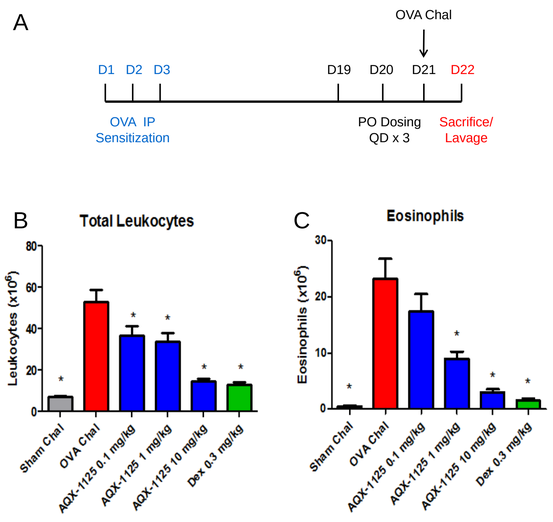


Figure 5*. (A) Male Brown Norway rats were sensitized to OVA, followed by oral AQX-1125 administration and OVA challenge. BAL was performed and resulting data shown expressed as mean±SEM of (B) BAL leukocyte and (C) eosinophil counts, (n=10) *p<0.05 vs OVA.*

Results

AQX-1125 inhibits inflammatory cell accumulation in the BAL of rats after LPS

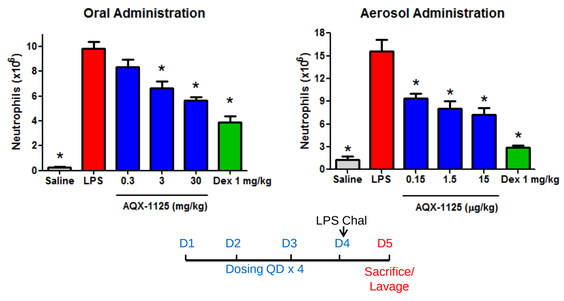


Figure 6. *AQX-1125 reduces neutrophil infiltration in a rat model of lung inflammation induced by intratracheal LPS challenge. Data are expressed as mean±SEM of n=10 determinations.*

AQX-1125 inhibits inflammatory cell accumulation in the BAL of mice after bleomycin

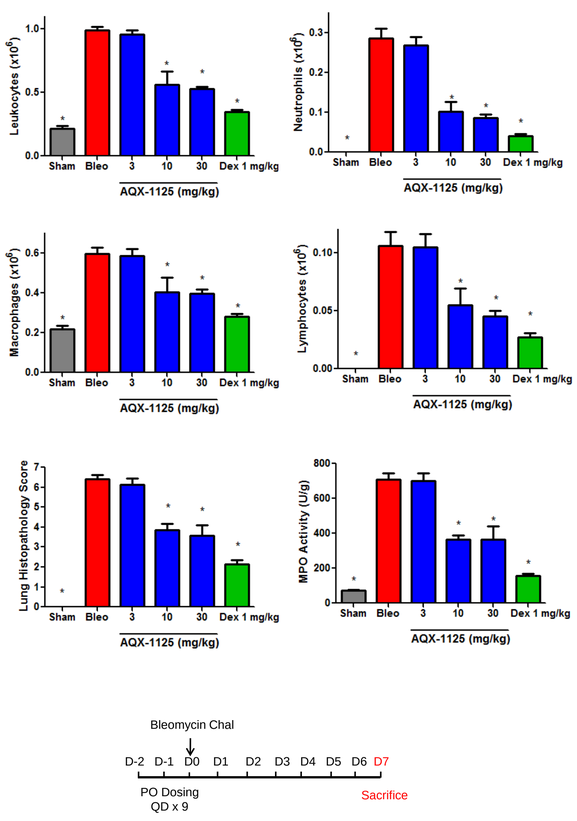
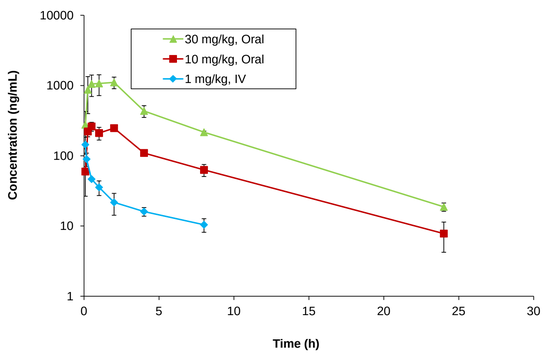


Figure 7. *AQX-1125 reduces leukocyte infiltration. Data are expressed as mean±SEM of n=15 determinations.*

Pharmacokinetics of AQX-1125 in rats



	IV 1 mg/kg	PO 10 mg/kg	PO 30 mg/kg
T_{max} (hr)	0.083	1.00	1.17
C_{max} (μmol/L)	0.45	0.83	3.8
AUC_{inf} /D (h x μmol/L)	0.83	5.5	21.2
$t_{½}$ (hr)	5.6	5.2	4.5
F (%)	N/A	66	85

Figure 8. *Pharmacokinetics of AQX-1125 in male Sprague Dawley rats. AQX-1125 was administered intravenously (IV) or by oral gavage. Plasma concentrations of AQX-1125 were determined at various times. Data are expressed as mean±SD.*

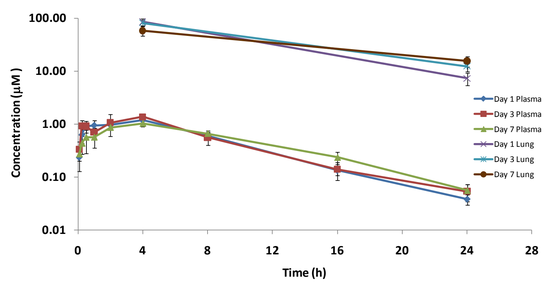
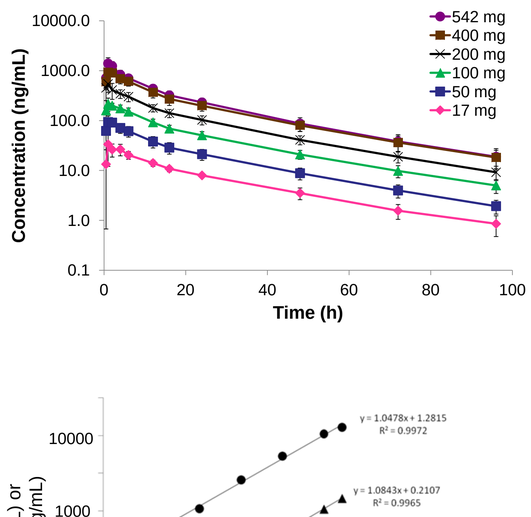


Figure 9. *Pharmacokinetics of AQX-1125 in male Sprague Dawley rats after repeat dosing at 30 mg/kg/day; comparison of plasma and pulmonary concentrations. Please note the significant pulmonary accumulation of the compound at all time points. Data are expressed as mean±SD.*

Results

Pharmacokinetics of AQX-1125 in healthy human volunteers: Dose-proportional exposure; long terminal half-life (22 h)



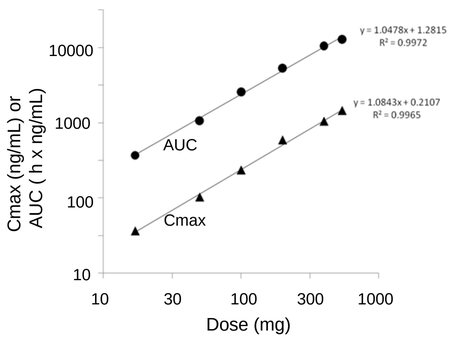


Figure 10. *Pharmacokinetics of AQX-1125 in healthy human volunteers. AQX-1125 was administered orally at the doses shown. Plasma concentrations of AQX-1125 were determined at various times. Data are expressed as mean±SD.*

- AQX-1125 is well tolerated in HHV's (SAD/MAD)
- PK is dose-proportional
- Terminal half-life is ~22h
- No food effects detected on AUC
- Oral bioavailability is high
- PK supports once-a-day dosing

Clinical Direction

- Allergen Challenge (Asthma POC)
  - ➢ Respiratory Clinical Trials Group, London, UK - PIs: Drs. Leaker & O'Connor
  - ➢ Cross-over study (1 active dose + placebo); 22 mild asthmatics, 7 days dosing
  - ➢ Lung function, sputum leukocytes and analyte endpoints
  - ➢ Duration to unblinding ~5-6 months
- LPS Challenge (COPD POC)
  - ➢ Celerion, Belfast, UK - PI: Drs. Smith & Elborn
  - ➢ Two parallel groups, cross-over study (2 active doses + placebo); 40 NH volunteers, 7 days dosing
  - ➢ Sputum leukocytes and analyte endpoints
  - ➢ Duration to unblinding ~5-6 months
- Under Consideration
  - •Pulmonary Fibrosis
  - •Interstitial Cystitis
  - •IBD

Summary

SHIP1 is a novel drug target which controls PI3K-driven cellular migration and activation. SHIP1's restriction to hematopoietic cells and poor homology with SHIP2 reduces the likelihood of off-target, off-tissue toxicity. AQX-1125, a small molecule with PK properties suited to once per day dosing, inhibits the PI3K pathway through activation of SH2-containing inositol-5'-phosphatase 1 (SHIP1), resulting in a reduction of pAkt in T and B lymphocytes. AQX-1125 has significant and diverse *in vivo* utility in inflammatory disease. These data indicate that AQX-1125 has significant clinical potential in inflammatory disorders such as asthma, COPD, pulmonary fibrosis, cystitis, etc. Phase IIa proof-of-concept studies are underway and will be instrumental in determining the potential human clinical therapeutic utility of the compound.

References

1. Helgason *et al*. Targeted disruption of SHIP leads to hemopoietic perturbations, lung pathology, and a shortened life span. Genes & Dev. 1998;12:1610-1620.
2. Ong *et al*. Small molecule agonists of SHIP1 inhibit the phosphoinositide 3-kinase pathway in hematopoietic cells. Blood. 2007;110:1942-1949.