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# Lipids: Metabolism, Nutrition & Health

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### Targeting the phospholipase A<sub>2</sub>-autotaxin axis: A challenge to develop novel agents for the treatment of inflammatory and autoimmune diseases

Phospholipases A<sub>2</sub> (PLA<sub>2</sub>) are enzymes that hydrolyze the sn-2 ester bond of the membrane phospholipids releasing free fatty acids and lysophospholipids. Arachidonic acid can be converted into a variety of eicosanoids by various enzymes, while lysophosphatidylcholine into lysophosphatidic acid (LPA) by a secreted enzyme that exhibits lysophospholipase D activity known as autotaxin (ATX). Both enzymes are involved in the production of inflammatory mediators and thus, constitute attractive targets for the development of novel agents for the treatment of inflammatory diseases. In addition, increased ATX expression and LPA production have been detected in a variety of cancers, which renders this enzyme a target for cancer treatment. A variety of small molecule PLA<sub>2</sub> inhibitors have been developed and some of them reached clinical trials. In the case of ATX, several inhibitors have been reported, however only limited studies using animal models are known. In our labs, we have developed several classes of novel PLA<sub>2</sub> inhibitors including 2-oxoamides and thiazolyl ketones targeting GIVA cPLA<sub>2</sub>, and fluoro ketones targeting GVIA iPLA<sub>2</sub>. We have recently shown that administration of fluoro ketone FKGK18 to non-obese diabetic mice significantly reduced diabetes incidence in association with improved glucose homeostasis and  $\beta$ -cell preservation. In this presentation, we will discuss our most recent potent PLA<sub>2</sub> and ATX inhibitors. We will present two novel classes of highly potent inhibitors: 2-oxoesters for GIVA cPLA<sub>2</sub> and beta-lactones for GVIA iPLA<sub>2</sub>. Such inhibitors were found to suppress the release of PGE<sub>2</sub> in renal mesangial cells. A lipidomic approach to monitor the effect of inhibitors will be discussed.

### Biography

George Kokotos is the Chairman of the Department of Chemistry at the University of Athens, Greece. He has studied Chemistry at the University of Athens where he also obtained his PhD. He then conducted Post-doctoral work in the Department of Pharmaceutical and Biological Chemistry at the University of London. He was the Visiting Professor in the Department of Chemistry and Biochemistry at the University of California, San Diego. He has authored over 140 publications in peer-reviewed journals and edited two books on Bioactive Lipids and Lipases. He is also a co-inventor of more than 12 patents.

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