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Cytosolic phospholipase A₂, a powerful regulator of inflammation and a potent candidate for therapeutic intervention in chronic disease

Eicosanoids, the oxygenated metabolites of arachidonic acid (AA) comprise a large family of bioactive lipids that have diverse roles in regulating homeostatic processes, in modulating inflammation and immune responses. Phospholipase A₂s (PLA₂s) are a group of enzymes that hydrolyze the sn-2 position of membrane phospholipids to release (typically unsaturated) fatty acids, including AA, and lysophospholipids. Three major classes of PLA₂s exist in the mammalian system, including low molecular weight extracellular or secretory, sPLA₂; high molecular weight calcium-independent, iPLA₂; and the group IVA calcium-dependent cytosolic PLA₂, cPLA₂α. The latter has received the most attention because it is widely expressed in nearly all mammalian cells and due to its active participation in cell metabolism. cPLA₂α is identified as the rate-limiting provider of proinflammatory mediators, including AA, and is thus an attractive target for the development of novel anti-inflammatory agents. It is found that cPLA₂α plays a major role in the chronic inflammation characterizing both psoriasis and rheumatoid arthritis. Novel inhibitors showing high potency and selectivity targeting cPLA₂α are developed. These represent different chemistries, thus enabling various regimes for formulation, administration and tissue accumulation. Results will be presented to demonstrate mode of action for potent cPLA₂α inhibitors in relevant cellular model systems for psoriasis and rheumatoid arthritis, efficacy in animal models of disease and Proof of concept for treatment of human disease.

Biography

Berit Johansen is Professor of Biotechnology at Norwegian University of Science and Technology (NTNU), Norway; and CSO of Avexxin AS. She has a PhD in Molecular Genetics from NTNU. She has spent several periods as a Visiting Scientist at many international universities and companies, including: UCLA, Biogen Inc., University of Groningen, University of Uppsala and UCSD. Her scientific interests encompass unraveling cellular communication processes involving lipid signaling, with special emphasis on phospholipase A₂ (PLA₂) enzymes, including drug development targeting cPLA₂ α. She has received the Young Scientist Award from European Federation of Biotechnology in the year 2003.

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