Small-molecule NADPH oxidase 2 (NOX2) inhibitors for reducing oxidative stress and inflammation
Background

The NADPH oxidase 2 (NOX2) multi-subunit complex is one of the most abundant and central sources of reactive oxygen species (ROS) and causes oxidative stress and inflammation in relation to many diseases. Inhibition of NOX2 is a direct way of attenuating oxidative stress and has great potential as a therapeutic strategy – for example against rheumatoid arthritis, acute lung inflammation, fibrosis, some cancer forms, neurodegenerative diseases like multiple sclerosis, and stroke. Despite the fact that NOX2 is an attractive drug target, academic and industrial groups have mostly failed in developing specific, reliable, and bioavailable NOX2 inhibitors.

The invention

We used fragment-based drug discovery to design and synthesize high-affinity, specific, and cell-active small-molecule NOX2 inhibitors. Unlike other compounds, ours bind the cytosolic p47phox subunit of NOX2 instead of the transmembrane subunit and thereby block the interaction with p22phox. This prevents assembling and activation of NOX2, in a selective manner, leading to reduced levels of superoxide (figure) and related inflammation and tissue damage.

Key selling points

- NOX2 inhibitors offer opportunities against a wide range of unmet medical needs
- Our NOX2 inhibitors are novel and drug-like
- The mechanism-of-action is clear and specific towards the NOX2 subunit p47phox
- Direct target-binding to p47phox, affinities, and p47phox-p22phox inhibition have been demonstrated by several biophysical methods
- Compounds are active in various cells - macrophages, microglia, and dendritic cells
- Strong, interdisciplinary team with expertise in biotech, medicinal chemistry, and NOX2 disease-biology

Development status

Further optimization and characterization of our compounds are ongoing with the aim of providing highly potent and bioavailable lead candidates for pre-clinical drug development against rheumatoid arthritis, acute lung inflammation, and multiple sclerosis. Current focus is on medicinal chemistry using biostructural data (figure), DMPK assessment, and cell-based assays, followed by testing in an arthritis model.

Intellectual property rights

A priority patent application No. 1921533.4 was filed on 29th November 2019 and extended as PCT patent application no. PCT/EP2020/083895: both patent applications filed in the name of the University of Copenhagen.