14-3-3Stabs Report Summary

Project ID: 286418
Funded under: FP7-PEOPLE
Country: Netherlands

Final Report Summary - 14-3-3STABS (Small molecule stabilizers of 14-3-3 Protein-Protein Interactions as novel drugs in cancer and neurodegenerative diseases)

The objective of this IAPP is the development and characterization of small molecule stabilizers of protein-protein interactions as a novel class of biological tool compounds and potential therapeutic drugs for the treatment of cancer as well as neurodegenerative diseases (Alzheimer’s -, Parkinson’s Disease), respectively. As biological targets we work on 14-3-3 proteins, an important class of adapter proteins that regulate a multitude of enzymes and proteins involved in the development of cancer and neurodegenerative diseases.

The proposed project is based on the new approach to develop small molecules that bind selectively to the interaction surface of specific disease-related protein complexes thereby stabilizing their interaction which might lead to a beneficial therapeutic effect. This approach is complementary to today’s strategy of developing inhibitors that target the active site of single enzymes and opens new possibilities to address “undruggable targets”. In fact, small molecule stabilizers of protein-protein-interactions have the potential to deliver a target-specific, target-oriented and more efficient modulation of the protein function than “classical” inhibitors.

Since the beginning of the project we have developed a number of screening assays to identify small-molecule stabilizers of 14-3-3 protein-protein interactions and have screened the 180,000-compound library of the LDC with the HTRF technology. For each of the 14-3-3 protein complex targets we could identify promising hit molecules that were subsequently tested in orthogonal assays including FP, SPR, ITC and cellular reporter gene assays. Medicinal chemistry optimization programs have been started on validated hit molecules and a reasonable SAR could be established. In contrast to our hopes, the medicinal chemistry optimization was much more difficult and not as steep as wished for. This, however, could be expected from such a difficult target and is in line with experiences in industry as well as in academia when addressing PPIs for drug discovery or chemical biology purposes.

In conclusion we are currently in the development of a number of promising lead candidates for the development of therapeutic small-molecule stabilizers of 14-3-3 PPIs. We are confident that by this we can contribute to much improved solutions in high medical demand areas like cancer and neurodegeneration. One important outcome of this IAPP is the establishment of a number of drug development projects with major pharmaceutical companies.

Related information

| Result In Brief | Novel disease targets |

Reported by

TECHNISCHE UNIVERSITEIT EINDHOVEN
Netherlands

Subjects