CAPPELLA Report Summary
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Final Report Summary - CAPPELLA (Combating cancer through novel approaches to protein-protein interaction inhibitor libraries)

Inhibition of Protein-protein interaction (PPI) represents an emerging and promising approach for drug discovery and the development of novel cancer therapies. As many PPIs occur within the cell they can only be targeted by small molecule compounds. However, small molecule inhibition of PPIs represents a challenging area in drug design. As PPIs differ structurally from more classical drug targets such as enzymes and receptors, existing compounds have generally delivered disappointing results. This combined with the growing need to discover new therapeutic strategies to combat cancer calls for the development of novel and alternative approaches.

The objective of CAPPELLA is to develop a series of innovative small-ligand tools and libraries that represent new approaches to inhibit PPIs in cancer. The project is a unique opportunity to integrate novel in-silico, chemical, genetic and ADME-based approaches in the design, synthesis and optimisation of libraries and compounds. A key theme is the utilisation of structural motifs found in natural PPI inhibitor compounds. This is coupled with high content testing of the resultant structures on three distinct validated cancer PPI targets namely BRCA2-Rad51, p53-Mdm2 and betacatenin-TCF4, to allow compound rule-sets to be developed and improved.

This project brings together some of Europe’s leading biotech companies (AnalytiCon, IL, Evolva, PharmaMar and BioLigands) and several highly recognised academic institutions (UCPN, UCAMDONC, UT and UNIGE). By combining five distinct, but complementary, chemical design approaches (see illustration below) and testing these in functional assays for the three different targets (all from different partners) in three successive but iterative cycles the project mobilises resources from across Europe.

During the project, the consortium has established and validated state-of-the-art high content functional assays for the three chosen cancer targets to facilitate screening for disruption of PPI’s. These assays include a mammalian 2H assay to detect disruption of p53-Mdm2, in vitro assays allowing identification of beta-catenin-TCF4 inhibitors based on luciferase reporter readout and a biochemical BRCA2-Rad51 interaction assay using an ELISA format.

Screening has been conducted with over 6 000 compounds derived from bio-sources of natural origin and / or marine extracts supplied by the library groups within the consortium. For all three targets, primary screening and additional tests identified numerous putative compound hits, which were prioritised according to structure, activity and amenability to medicinal chemistry development. In addition, structure-based and ligand-based pharmacophore models for virtual screening of the three targets were built and used to screen consortium- and commercial vendor databases providing improved compound hit list to partners.

Results from repeated cycles of screening with purchased or synthesised analogs of compound hits were fed back to compound providers for library optimisation and refinement of pharmacophore models for virtual screening. Potential leads were modified by enzymatic glycosylation in an attempt to optimise their properties. At the end of the project, circa 10...
interesting compound hits have been identified for the 3 targets. Iterative rounds of biological testing, pharmacophore model refinement, and virtual screening resulted in improved compound hits for at least one of the tested PPI targets (beta-catenin:Tcf4).

The biological data for the PPI inhibitory compounds was analysed applying different computer-aided approaches and Structure-activity relationships (SARs) derived from this analysis were used to define several rule-sets for PPI inhibitor compound library design. These rule-sets represent useful starting points for the development of novel drugs against the PPI targets.

The end objective of CAPPELLA, was to identify 5-10 candidate compound families from within the tested libraries that can subsequently be taken forward into pre-clinical testing. The CAPPELLA project thereby ultimately aims to provide novel solutions for improved therapies and better treatment of various types of cancer. Compound classes that specifically disrupt PPI’s could allow for the development of a range of new anti-cancer therapies against a whole series of already validated cancer targets. As the consortium was able to identify 6 new compound families acting on the three targets this end objective was successfully reached.

Dissemination and use

The Small and medium-sized enterprises (SMEs) and industry partners plan to file patent applications to new compositions and new therapeutic uses depending on the innovation. The Research and technological development (RTD) performers will share in any value added through their contribution to the patent rights e.g. through identification of activity using their biological screens.

Dissemination of the scientific results from the project has occurred through publication in scientific journals, poster presentations and contributions at international meetings /conferences. In addition, the CAPPELLA website has been updated at regular intervals with scientific progress for the benefit of the general public.

Publishable results

Results generated during CAPPELLA on UGTs and molecular modelling, by an academic partner (UCPH), have been published in high quality peer reviewed journals (see below). This work provides significant insight into the structure-function relationship of this important group of enzymes.

Title: Catalytic key amino acids and UDP-sugar donor specificity of a plant glucuronosyltransferase, UGT94B1: Molecular modeling substantiated by site-specific mutagenesis and biochemical analyses.
Author(s): Osmani S. A., Bak S., Imberty A., Olsen C., Moller B. L.
Source: Plant Physiology, Volume 148, Issue 3, Pages 1295-1308, Published November 2008

Title: Substrate specificity of plant UDP-dependent glycosyltransferases predicted from crystal structures and homology modeling.
Author(s): Osmani S. A., Bak S., and Moller B. L.
Source: Phytochemistry, Volume 70, Issue 3, Pages 325-347, Published February 2009

Title: Substrate specificities of family 1 UGTs gained by domain swapping.
Author(s): Hansen E. H., Osmani S. A., Kristensen C., Moller B. L. and Hansen J.
Source: Phytochemistry, Volume 70, Issue 4, Pages 473-482, Published March 2009

Title: Effect on glucuronosylation on anthocyanin color stability.
Related information

**Result In Brief**
Targeting protein-protein interactions in cancer

**Documents and Publications**
Final Report - CAPPELLA (Combating cancer through novel approaches to protein-protein interaction inhibitor libraries)

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