hERGscreen *project*

"hERG related risk assessment of botanicals"

PIRSES-GA-2011-295174

Project Summary Final Report

of hERGscreen project

April 2016

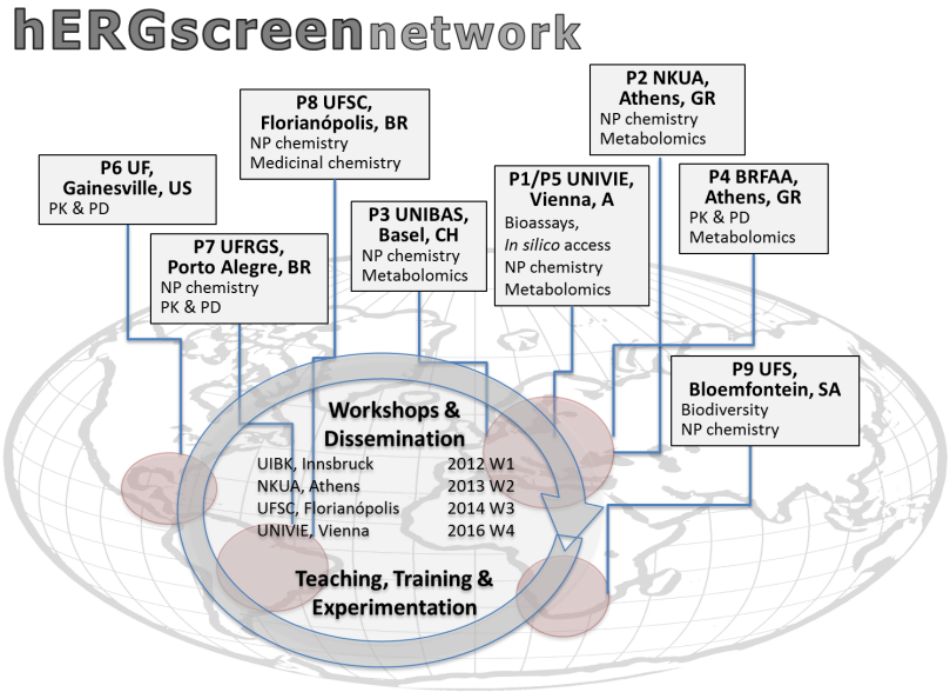
SEVENTH FRAMEWORK PROGRAMME

Project Summary

hERGscreen *project*

Publishable Project Summary

The main goal of this project was the establishment of a network between European, South American, North American and South African educational and research entities. This attempt was based on an innovative scientific project aiming towards the identification of hERG (human Ether-à-go-go Related Gene) channel blockers in commonly consumed botanicals and supplements. Blocking these ion channels may result in ventricular tachyarrhythmia and an increased incidence of sudden death. Thus, the hERG channel is considered as an important anti-target. Several drugs have been removed from the market for this reason, and compounds have been blocked from proceeding further into phases of clinical development. As botanicals (comprising dietary supplements, spices, herbal medicinal products) continue to increase in popularity there is an urgent need to critically assess the potential cardiotoxic risks of these products.



Within the project 415 different plant species originating from South America, South Africa, the Alpine and the Mediterranean area were selected by the involved partners for further investigation based on their usage for consumption for human health purposes or as nutritional supplements. In addition, since direct structural information of the hERG channel is

Project Summary

hERGscreen *project*

still lacking, computational models (3D pharmacophore models) were developed, validated and used to virtually identify potentially hERG interacting constituents by screening natural product databases. Overall 918 extracts were prepared from the 415 selected botanicals and screened *in vitro* for their hERG blocking properties on *Xenopus laevis* oocytes using a voltage clamp technique.

Within this *in vitro* screening 23 extracts derived from 18 different plant species revealed significant hERG inhibiting activity and were further investigated by means of extract profiling and micro-fractionation, followed by *in vitro* activity screening. From the nine most promising plant extract ~60 constituents could be isolated. They were also tested *in vitro* and 13 of them were found to potently block the hERG channel in a concentration dependent manner. For these most active ones the hERG blocking activities were also established in mammalian cells.

As example, one of these compounds is voacangine originating from the root bark extract of *Voacanga africana.* It is used in West and Central African folk medicine and currently becoming increasingly popular as legal high in Europe. For this natural compound and the plant extract itself, a full pharmacokinetic (PK) study was performed including the establishment of a population pharmacokinetic model. This allowed to characterize the PK parameters and to distinguish differences in the biological parameters, between pure voacangine and the "parent extract".

The overall results obtained within the hERGscreen project have helped to elaborate and evaluate hERG channel related safety aspects aiming towards the risk assessment of frequently consumed botanicals.

All the research performed within this project was done in the course of numerous researcher exchanges as well as during master and PhD theses. A large number of short term and extended secondments of scientific staff was accomplished (74 months in total), and used to train early researchers in new techniques, exchange knowledge by giving numerous lectures and spreading scientific expertise in a continuous exchange. The organization of several workshops assured the proper dissemination of the produced knowledge throughout all the scientific community but also the public. Core scientific knowledge was produced and exchanged continuously during secondments, project meetings, conferences and workshops. Partnerships and tight collaborative networks have been created and lay the base for future cooperation.

Project Summary

hERGscreen *project*

The hERGscreen project was of high relevance for public health worldwide, since it aimed to critically assess the potential cardiotoxic risks of plant derived products and, thus, to improve consumer and patient safety by identifying safety liabilities of botanicals. Moreover, we were able to create a unique consortium, trained many graduate and undergraduate students, gained a lot of new experiences, exchanged plenty of expertise, and established a great platform for future collaborations.

The hERGscreen Team January 2013, September 2014 and January 2016 (left to right)

For further information visit the hERGscreen website, available under: http://hergscreen.univie.ac.at/home/.