

Natural products from marine fungi for the treatment of cancer

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Characterisation of candidate structures to the stage of *in vivo* proof of concept

The development of clinically relevant lead structures requires efforts beyond screening: An interdisciplinary approach is necessary to characterise hit candidates to the stage of *in vivo* proof of concept ready to enter further drug development in order to valorise the results of the project. This includes the development of robust, sustainable processes for the production of these compounds.

Therefore, the Kiel Centre for Marine Natural Products (KiWiZ) initiated and coordinates an EU FP7 research project, MARINE FUNGI, focussing on the development of anti-cancer drugs from marine fungi (fig. 1). MARINE FUNGI covers two approaches to gain effective producer strains, which will be led to the stage of *in vivo* proof of concept building the basis for clinical trials (fig. 1, 2).

Fig. 1 MARINE FUNGI is aimed to develop a process concept providing the technological basis for a sustainable use of marine microbial products in oncology.

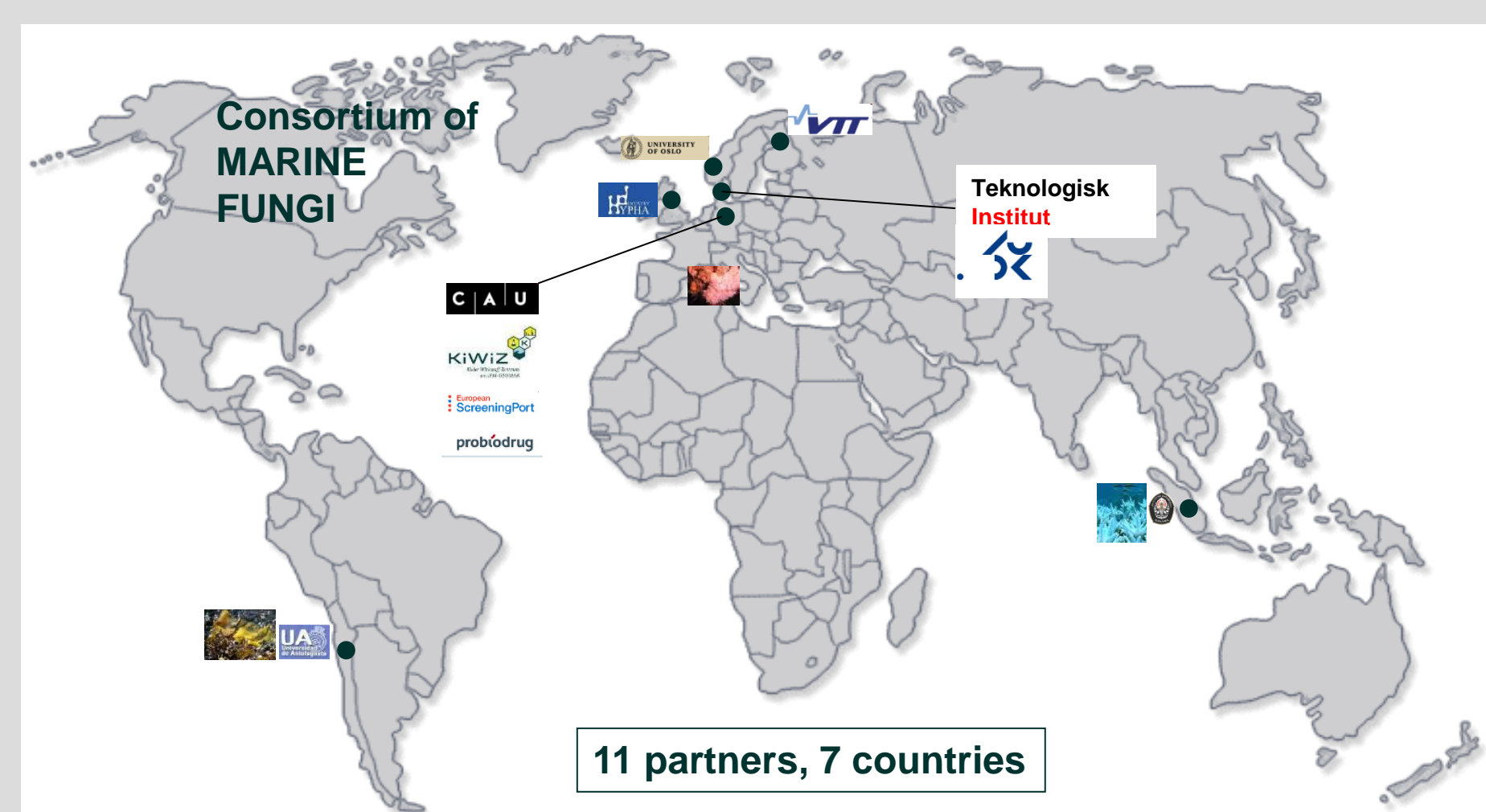
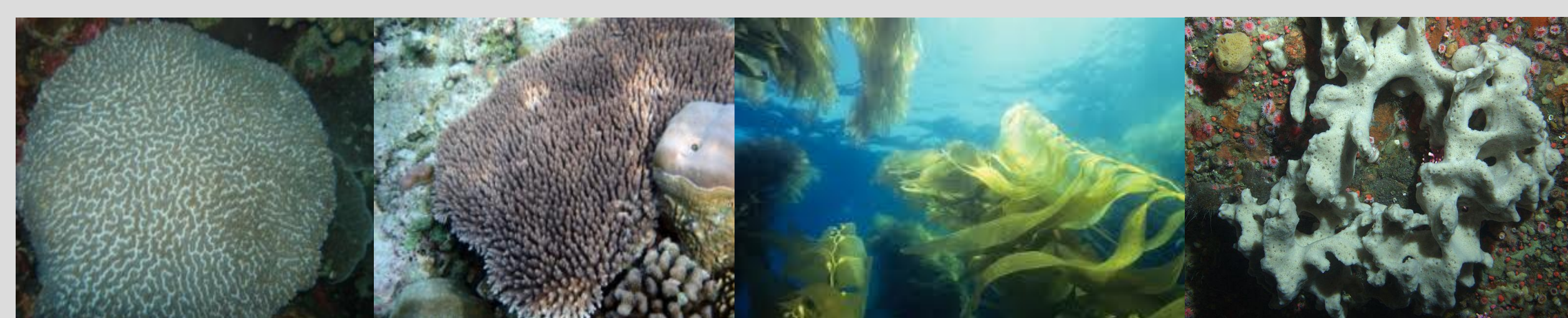
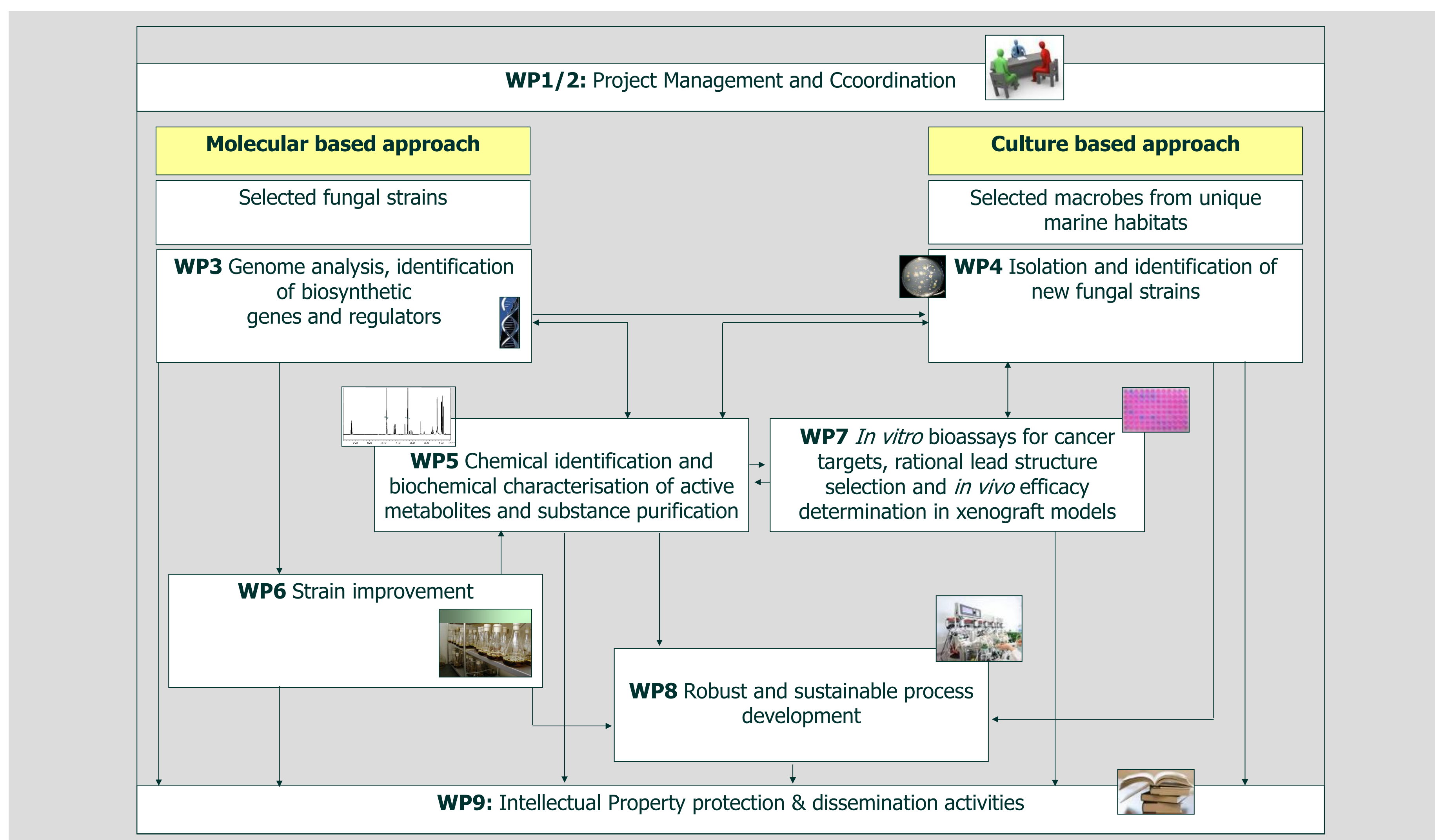


Fig. 2 MARINE FUNGI formed a new strongly interacting research network comprising the scientific and technological actors, including 3 SMEs and 2 ICPC partners. Corals, algae and sponges are the sources for new fungal metabolites. More than 500 isolates are screened for their secondary metabolites until the end of 2012.

Marine fungi as a good source for new natural products

Though marine fungi are a potent group of secondary metabolite producers, they are not well characterised and underutilised in terms of biotechnological application. Here, we demonstrate the sustainable exploitation of marine natural resources providing appropriate culture conditions for the group of marine fungi, thus enabling efficient production of marine natural products in the laboratory and also in large scale cultures, avoiding harm to the natural environment. In the focus are new anti-cancer compounds.

Two approaches are used to gain effective producer strains (fig. 1):
a) Candidate strains originating from our unique strain collection of marine fungi are characterised and optimised using molecular methods. The genomes of these strains are sequenced during the project (fig. 3).

b) New fungi are isolated from unique habitats, i.e. tropical coral reefs, endemic macroalgae and sponges from the Mediterranean. Culture conditions for these new isolates are optimised for the production of new anti-cancer metabolites.

Current status of MARINE FUNGI

- Three fungal genomes are sequenced. The search for biosynthetic and regulatory genes is ongoing.
- More than 500 new fungal isolates were gained, taxonomic affiliation is done by molecular and microscopic methods.
- New strains are cryoconserved and established as the projects strain collection.
- Nearly 2500 extracts were screened in the preliminary panel.
- 50 compounds were screened in the full panel leading to a selection of 6 compounds ready for liability testing.
- A process concept for these compounds is build comprising fermentation in stirred tank reactors and subsequent purification.
- *S. brevicaulis* is optimised by mutagenesis experiments, a library of UV mutants was established.
- 8 PhD students are involved in MARINE FUNGI.
- A website was set up, a weekly blog informs about news.

For further information visit: www.marinefungi.eu

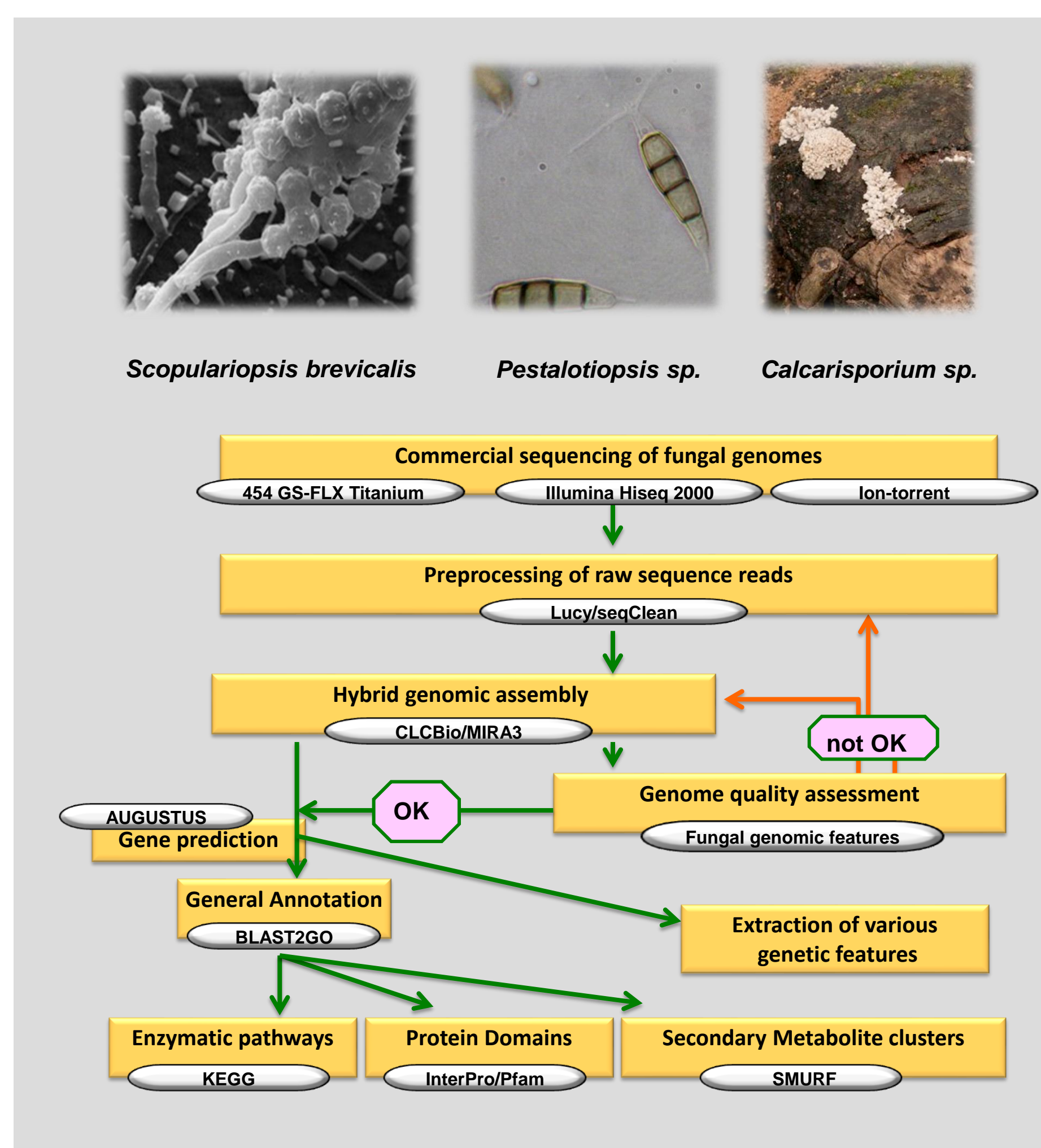


Fig. 3 Three fungal strains were chosen for genome sequencing. The genomes will help to identify biosynthesis genes and give insights into regulatory features.

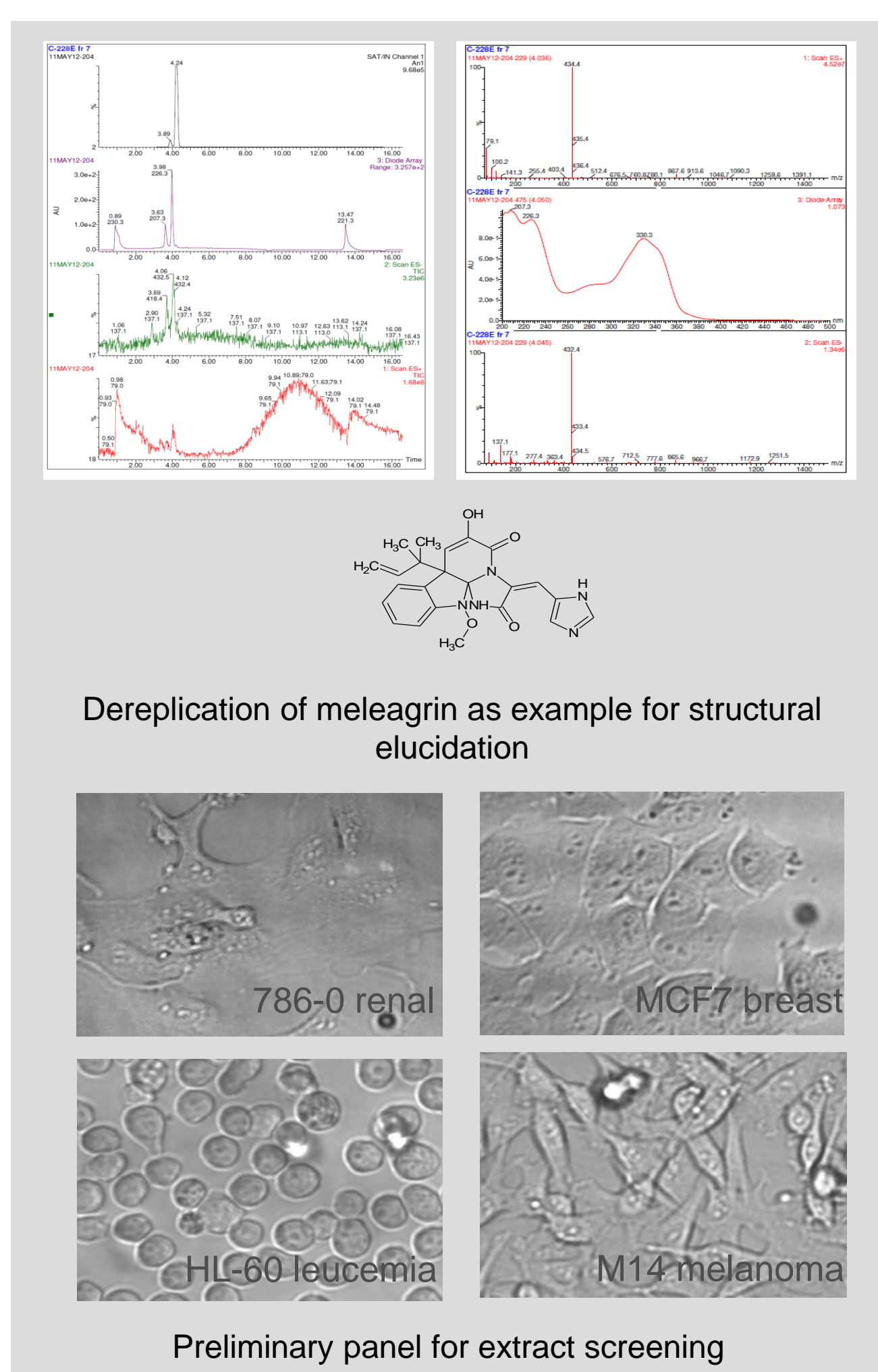


Fig. 4 All extracts and pure compounds originating from the initial screening and subsequent purification are screened against various panels of cancer cell lines.