Introduction

• Natural Products (NPs) are one of the main sources for cancer drug discovery. In the past 30 years, the percentage of NP or NP-inspired new chemical entities (NCEs) has risen to 74%, in the antitumor arena [1].

• Fundación MEDINA owns one of the largest and most diverse microbial NP libraries in the world (>190,000 strains, >200,000 extracts) [2,3], which has been successfully used to identify bioactive compounds in different High-throughput Screening (HTS) campaigns.

• Pancreatic cancer (PC) shows a high fatality rate [4], and has no cure. Thus, the identification of efficient chemotherapeutic agents is crucial.

• In this study, we have identified and isolated 6 new benzophenone derivatives, onychocholones A-F from the fungus Onychocha sp with antitumoral activity in pancreatic Cancer Stem Cells (CSC) in vitro and in vivo.

Compound identification and isolation

Microbial NP HTS
(93,600 crude extracts)

Cytotoxicity
(BxPC3, MiaPaCa-2, PANC-1)
517 actives

Confirmation
Dose-response curves
Avoid known compounds

Bio-guided Extract Fractionation
Compound Isolation

Hit selection

6 Onychocholones

Onychocolone A

Mechanism of Action

Onychocolone A decreases MEK2 and ERK1/2 in pancreatic cells specifically

In vitro

Effect on Cancer Stem Cells (CSC)

In vivo

Conclusions

- Onychocholone A showed a cytotoxic effect on pancreatic CSCs mediated by the inhibition of the MEK onco-signaling pathway.
- The in vivo efficacy of Onychocholone A was demonstrated by the reduction of tumor growth in a heterotopic pancreatic xenograft mouse model generated by CSC, and the data support that Onychocholone A is a promising new small molecule for hit-to-lead phase for the development of a new treatment of pancreatic cancer.

References