PL08 Marine derived anticancer compounds, a journey from the seaside to clinical trials

J. Jimeno, G. Faircloth, J.A. López-Martín and I. Manzanares
PharmaMar R&D, Madrid, Spain & Boston, Massachusetts, USA.

Nature has been an instrumental tool in the acquisition of new therapeutics. Terrestrial derived natural drugs are essential components in the anticancer armamentarium both in the palliative and in the curative setting; the complexity and the policlonal nature of the cancer cell anticipate the need to design rationally based combinations including cytotoxics and "targeted/selective" entities. The sea covers more than 70% of the surface of our planet and represents 95% of the biosphere; evolutionary speaking marine based organisms have had to deal with the survival challenge during more than 600 million years anticipating a highly functional enzymatic capability to produce complex chemical entities. A demonstrative example of the therapeutic potential of the marine ecosystem stands in the discovery, development and regulatory approval 25 years ago of citarabine, a synthetic derivative of a family of nucleotides analogs identified in the Caribbean sponge *Cryptothethya*; ARA-C is an essential component in the curative treatment of acute myeloid leukemia. In line with the relevance of biodiversity our expedition programs have and are covering most of the seas of the planet such program has resulted in a continuous growing library that currently includes more than 28.000 taxonomically classified organisms and more than 100 chemical entities discovered. Our criteria to select compounds for clinical development includes: new chemical entity, innovative mechanism of action, positive therapeutic index in experimental models and feasibiliy for supply. **Ecteinascidin-743** (ET-743), an alkaloid discovered in the Caribbean tunicate *Ecteinascidia turbinata*, is in advanced phase II trials, the available data demonstrates that the compound is feasible in adult and pediatric patients and evidence of antitumor activity in patients with advanced solid tumors resistant to conventional therapy has been generated. **Aplidine** is a new cyclopdepsipeptide discovered in the Mediterranean tunicate *Aplidium albicans*; the phase I program has just been completed with data supporting a positive therapeutic index in adult patients with advanced pretreated solid tumors and lymphoma. Phase II studies are underway. Both compounds share innovative mode of actions including DNA binding/interaction with nuclear transcription factors and targeting of the VEGF pathway for ET-743 and Aplidine respectively. **Kahalalide F (KF)** a peptide based entity is completing the phase I program in patients with advanced prostate cancer with evidence of feasibility in such critical setting; KF appears to target lysosomes and mechanistic work proposes that the erb-2 pathway might be one of the putative targets for this compound. ES-285 is a new chemical entity suggested to interact with Rho related pathways. **ES-285** displays *in vivo* activity against hepatoma and prostatic cancer xenografts and a phase I program is under implementation. In a seven years journey in the planet of clinical development we have learned the need to make strong-interdisciplinary focus in pharmacological development (supply, formulation, analytical methods) as well as in the identification of xenotoxicities, a potential limiting factor for clinical development. Our program has generated the availability of innovative preclinical models to better characterize the therapeutic index of a given candidate thus maximizing the feasibility in the clinical scenario. To implement these actions a continuous collaboration including marine biologists, medicinal chemists, preclinical scientists-toxicologists, pharmacologists and medical oncologists is essential.

References: 1. Delaloge et al. (2001) J Clin Oncol 19(5):1248-55. **2.** Depenbrock et al. (1998) British J Cancer 78(6), 739-744. **3.** Erba et al. (2001) Eur J Cancer 37: 97-105. **4.** Gould (2001) The book of life: history of the evolution of life on Earth. New York: WW Norton & Co. Inc. **5** Jin et al. (2000) Proc Natl Acad Sci USA; 97: 6775-9.

Dr. José Jimeno
Dr. Jimeno graduated as an MD Cum Laude at the University of Zaragoza (Spain) in 1981. He did his fellowship in Medical Oncology at the National Cancer Institute in Bari, Italy. Furthermore, he joined the pharmaceutical industry and has had relevant positions in the R&D area at Farmitalia Carlo Erba (Milan, Italy) and at US Bioscience (Watford, UK): He has published over 50 papers in the field of cancer research, holds the European Certification of Medical Oncology (Copenhagen, 1990) and is an active member of the ESMO, AACR and ASCO. Dr. Jimeno joined PharmaMar in late 1994.