DISTRIBUTION AND METABOLISM OF NATURAL AND SYNTHETIC XENOBIOTICS: FROM THE COMPREHENTION OF REACTIONAL PROCESS TO TISSUE IMAGING GENERATION

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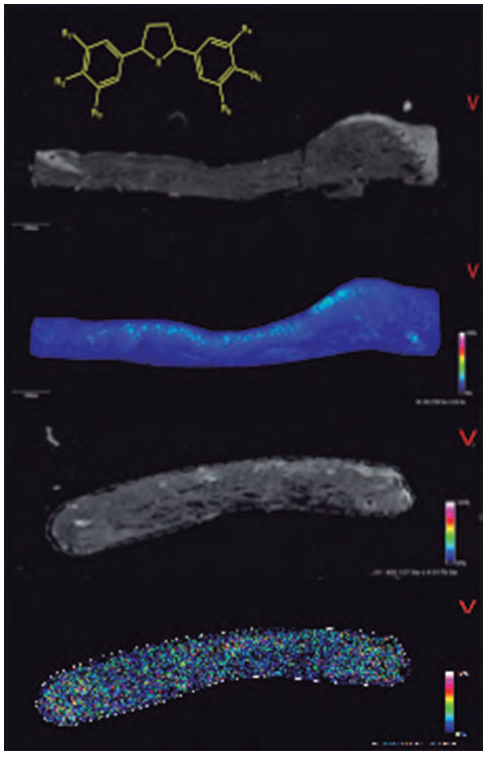

Figure 1. MALDI-MS/MS, image reconstructed from the protonated ions of a new anti-leshimaniosis agent (patent under analysis). Optical image (obtained by scanner), used to create the MALDI-MS/MS image illustrated in details of pig skin anatomy.

Several actions for the development of bioactive natural products have been taken at national and state level, in majority ones that led to the identification of substances with therapeutic potential, but also compounds with ecological relevance. A prerequisite for clinical and compound stability studies is the chemical characterization of active targets and also the elucidation of possible metabolites. In this context, the project aims the establishment of a working flow that envisions supporting pre-clinical studies or for understand ecological interactions. Since the platform model still is somewhat uncommon the team size may oscillate during project execution, having involved in this first two fifteen members. The possibility of a variable group size occurs in function of the demand and opportunity of identifying a potentially active compound as well as having it in sufficient quantity for studies, which finally is the limiting factor for different works. Furthermore, the groups exhibit diverse characteristics concerning their publication potential and speed of obtaining results, which makes the global analysis a little different.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

The selected active natural products were submitted to biomimetic studies, in which the organometallic catalyst was introduced instead of the more common metalloporphyrins, achieving for biomimetic reactions very high yields. In two cases, the yields of catabolized active compounds exceeded 90%, which is extremely significant. In more than 10 cases, the main products obtained by biomimetic reactions were the same as observed in the microsomal metabolism. This enabled the perspective of producing phase one metabolites for further pharmacokinetic analysis. The fragmentation studies in gas phase allowed the definition of three complete pathways from three classes of natural products. Additional collaborative work open the possibility to introduce strategies for the identification of plant secondary metabolites on the GNPS platform. The inicital pharmacokinetic study has clarified the elimination mechanism and half life time of the several alkaloids, and terpenoids. Initial results has shown the viability of the proposal and has generated the expectation of better understanding the absorption, distribution and metabolization mechanism for selected natural products. The MALDI-imaging development allowed us to verify in details the distribution of specific compounds and its metabolites in several organs. The same methodology was also applied to understand ecological function of Natural Products.

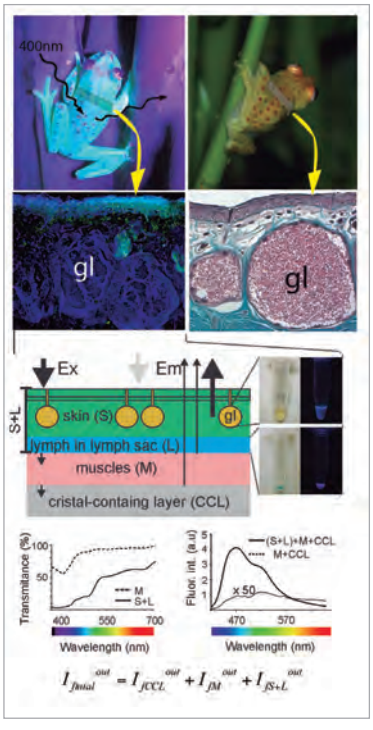

Figure 2. Fluorescence in Hypsiboas punctatus. ***Top****. Adult males under UV-blue light (left), and under white light (right).* ***Middle****. Transverse sections of dorsal skin. Confocal images of fresh dorsal skin samples using a 405 nm laser line (left), and stained histological section (right). Fluorescence emission is observed from epidermis, dermis and glands (gl).* ***Bottom****. Schematic representation of the skin and subcutaneous structures. Incident excitation light and fluorescence emission from each tissue layer are attenuated by the structures above and depend on the transmittance of each layer. Fluorescence from subcutaneous structures is almost completely filtered by skin with lymph. The total observed fluorescence take into account the contribution of each tissue of the frog. We considered that the photon flux reaching CCL may be estimated as the incident photon flux (I0) attenuated by the absorption of S+L and M.*

MAIN PUBLICATIONS

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