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Development of anticancer prohibitin ligands to treat cancers, cardiac and immunological disorders

Flavaglines are a family of anticancer natural products that relieve the resistance to cancer chemotherapies and display a strong cytotoxicity that is specific to cancer cells. We identified the first synthetic flavaglines that inhibit cell proliferation and viability (IC50≈1nM) at lower doses than did the parent natural compounds. A ligand for affinity chromatography was synthesized based on our SAR information, and used for the identification of prohibitins-1 and -2 as the molecular targets. Prohibitin-1 (PHB1) and its homolog prohibitin-2 (PHB2) are pleiotropic proteins that act as a hub for many signaling pathways. We demonstrated that the binding of flavaglines to PHBs prevents the interaction between PHBs and C-RAF and, thereby, inhibits C-RAF activation and subsequently C-RAF-MEK-ERK signaling, which is critical to the survival and proliferation of cancer cells. With our collaborators, we found that another PHB ligand, fluorizoline, also block C-RAF activation. Despite decades of research effort, clinically effective medicines targeting C-RAF and KRAS remain elusive. Our recent results open a novel avenue to inhibit both C-RAF and KRAS signaling with PHB ligands. We also demonstrated that these compounds protect the heart from the adverse effects of cancer chemotherapies involving anthracyclines. We showed that this cardio protection is mediated by the activation of the mitochondrial PHB-STAT3 complex. In addition to these lines of research, we also developed a totally new family of PHB ligands that modulate the immune function. The structure-activity relationships of these new drugs and their detailed mechanism of action will also be presented.

Biography

Laurent Desaubry is a CNRS Research Director in the University of Strasbourg in France (http://desaubry.u-strasbg.fr/) and adjunct professor at Tianjin University of Science and Technology (TUST) in China. In 1992, he received a PhD degree in medicinal chemistry from Strasbourg University. Next, he worked as a Postdoctoral fellow at SUNY at Stony Brook, USA. He made another Postdoctoral internship in Prof Pierre Chambon's laboratory before to get a CNRS Research Senior Scientist at the University of Strasbourg-CNRS. He was promoted CNRS Research Director (corresponds to full professor) in 2014 and became also a Professor at TUST in 2015.

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