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Role of Metabolite Identification in Lead Optimization of Fibrodysplasia Ossificans Progressiva Compounds

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No effective treatments currently exist for fibrodysplasia ossificans progressiva (FOP) patients, and disease progression results in severe restriction of joint function and premature mortality. LDN-193189 has been demonstrated to be efficacious in a mouse FOP disease model. In a previous study, the metabolite identification (MetID) of LDN-193189 provided very valuable information on the major metabolic "soft" spots of this compound, especially on the formation of metabolites that are known to be associated with safety concerns. In this study, we carried out the MetID of backup compounds that were synthesized to overcome LDN-193189 metabolic liabilities. To perform the MetID, the compounds BD1, BD2 and BD3 were incubated in mouse and human microsomes and cytosols, their metabolites were elucidated using LC/UV and mass spectral techniques. To evaluate the formation of potential reactive intermediates, nucleophilic trapping agents, such as glutathione (GSH) and potassium cyanide (KCN) were added to the incubation mixtures fortified with NADPH. LDN-193189 susceptibility on aldehyde oxidase (AO) was addressed by blocking the alfa carbon at the quinoline moiety as in BD2; the MetID confirmed the lack of AO activity for this compound. The aniline formation was avoided by substituting the piperizine moiety for (piperidin-1-yl) ethoxy in BD1, no aniline derivative was observed in its MetID. Finally, we merged the two compounds with isolated successes into BD3, which MetID confirmed that it is not susceptible to AO activity nor forms toxic aniline derivatives. In summary, the present study aimed to highlight the use of MetID in rational drug design and its pivotal role in this project to develop a treatment for the rare FOP disease.

Biography

Elias C Padilha is a PhD Student currently in a Joint Training Program between School of Pharmaceutical Sciences from Sao Paulo, Brazil and The National Center for Advancing Translational Sciences in Maryland, USA. During his training period, he specialized in metabolite identification of novel compounds. With this capability, he offered support for the team in charge of developing a drug candidate to treat the rare disease fibrodysplasia ossificans progressiva. His work has helped to advance the lead optimization which is under development.

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