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Plasma metabolomic signature of novel signal transduction inhibitors: From preclinical identification to clinical validation

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Early clinical studies of novel agents evaluate both pharmacokinetic and pharmacodynamic profiles. In preclinical oncology studies, the biomarker of interest can be measured in tumor material but in clinical development, not all tumors are accessible and patients cannot be regularly biopsied. Therefore, identification of circulating biomarkers is extremely useful in assisting clinical development of novel oncology products. We have been using non-targeted followed by targeted LCMS to evaluate if plasma metabolomics can be used to monitor the effect of novel signal transduction inhibitors. We show that significant differences in the plasma metabolome of genetically engineered PTEN+/- mice when comparing with littermate controls and in mice bearing PTEN-/- human tumor xenografts compared with non-tumor bearing animals. This signature can be reversed by a PI3K inhibitor. The plasma metabolomic signature of nude mice bearing a B-RAF of K-RAS mutant tumor xenograft is different to that observed in PTEN-/- animals and can be reversed using a MEK inhibitor in mice bearing human tumour xenograft. The metabolic signatures include amino acids, carnitine derivatives and lipids some of which are affected by time of day and food intake. Therefore, the effect of food and sampling time need to be incorporated in the analysis. Despite these variations, the preclinical signatures identified following a PI3K or MEK inhibitor can be observed in patients following treatment with a pan class I PI3K inhibitor and a MEK inhibitor. These data suggest that plasma metabolomic is a valid strategy to monitor the pharmacodynamic development of novel anticancer agents.

Biography

Florence I. Raynaud completed her Ph.D. at the University of Strasbourg, France where she carried out her first post-doctoral position. She is currently leader of the drug metabolism and pharmacokinetics team at the Institute of Cancer Research where she is involved in the preclinical and clinical development of novel anticancer agents. She has been involved in the preclinical development of 20 novel agents that have reached clinical trials. These include abiraterone which has been registered for advanced prostate cancer. She is the author of over 100 publications and is on the editorial board of Clinical Cancer Pharmacology.

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