Proposal for a Master thesis project (30–60 hp)

Development of an Orbitrap mass spectrometry method for measurement of DNA adducts as biomarker of oxidative damage

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Project description

The genetic units of DNA are prone to site-specific modification by environmental oxidative stress factors such as electrophilic compounds/metabolites and UV radiation. The resulting structurally modified DNA, i.e. DNA adducts, have a potential to increase cancer risk and are used as biomarkers of oxidative damage. The major aim of the project is to develop an Orbitrap mass spectrometry (MS) method to measure potential DNA adducts formed in defined exposure scenarios. The development will be directed to have a sensitive and specific method, and applied in a case-study to correlate measured DNA adducts with oxidative damage, e.g. measurement of: *i*. glycidol induced DNA adducts *in vitro*, and *ii*. 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG, a biomarker for oxidative stress) from UVB radiation in *Daphnia magna* test species.

Depending on the modifying factor and exposure dose, typically only about $1/10^4$ to $1/10^{12}$ DNA bases are modified. Major products from DNA modification generally occur on ring nitrogen positions. DNA adducts can be measured by various methods, such as ^{32}P-post-labelling, LC-ECD, LC-fluorescence and MS techniques (Farmer et al., *Toxicol Appl Pharmacol*, 2005; Balbo et al., *Chem Res Toxicol*, 2014). Amongst them, MS methods give the highest specificity owing to the structural information that can be extracted from the different operating modes. In the project, a method will be developed to analyze the adducts by Orbitrap MS, one of the modern technologies for structural analysis, with resolution of 240,000 at m/z 200 and mass accuracy close to 1 ppm. This high-resolution accurate-mass (HRAM) should make possible to detect and characterize very low levels of adducts generated in complex mixtures/matrix and at the same time get information on adduct structure, i.e. their molecular mass, elementary composition and fragmentation pattern.

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