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Toxicology and Pharmacokinetics of Novel Anti-Tumor Guanosine Phosphate Analogues - an In Silico Approach

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Abstract
Drug candidates must prove both effectiveness and safety. A series of novel guanosine phosphate analogues for the treatment of non-melanoma skin cancer (NMSC) was recently identified by molecular modeling[1]. Efficacy in vitro has been proved in monolayer cultures of malignantly transformed human cells[2] and in organotypic NMSC models.

In this study we assess drug safety in silico by predicting key parameters such as acute and chronic toxicity, absorption and distribution[3,4]. We compared the entire series of novel guanosine phosphate analogues, especially the most promising drug candidates OxBu and OxHex, to a series of reference compounds: adefovir, tenofovir, aphidicolin, 5-fluoruracil, ingenol mebutate and δ aminolevulinic acid. Adefovir and tenofovir are close in structure to the test compounds, aphidicolin addresses the identical target. In NMSC therapy 5-fluoruracil is the gold standard, ingenol mebutate is the latest innovation and δ aminolevulinic acid is widely used.

Acute and chronic toxicity. OxBu and particularly OxHex are less hepatotoxic in man than 5-fluoruracil. Nephrotoxicity will probably occur and can be expected according to the effects of adefovir, tenofovir and high doses of aciclovir. OxBu, OxHex are predicted less toxic in the rat than adefovir, tenofovir and ingenol mebutate. LD50, LC50 and chronic LOAEL values predicted for OxBu and OxHex are close to each other but higher than for therapeutically used reference compounds.

Absorption and distribution. Human skin permeability is predicted to be equal for OxBu and 5-fluoruracil and higher for OxHex following the application of aqueous solutions. Applied orally, human intestinal absorption is low. Blood brain barrier permeation of OxBu and OxHex is predicted to be lower than of 5-fluoruracil or of ingenol mebutate in mice.

In conclusion, the application of in silico technologies may contribute to effective and safe drugs by reducing animal experiments in pre-clinical drug assessment. Although prediction power of in silico methods depends on the investigated parameter, novel guanosine phosphate analogues are predicted to have a desirable benefit-to-risk-ratio.

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