SHORT COMMUNICATIONS

ComGenex, Inc., Budapest, Hungary and ComGenex International, Inc., South San Francisco, CA, USA

Retrometabolism design concepts and realization for combinatorial libraries

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Design concepts for combinatorial libraries which consider pharmacokinetics and metabolism (ADME) fate of the library members desides conventional diversity [1] have a growing importance when lead search goes *in vivo*.

In a continuing effort of developing library designs with ADME admissible properties, the concept of the "Total Coverage" diversity is introduced [1], including compound sets with high diversity in the classical sense [2] plus information on the first level retrometabolites and metabolites of the library members [3].

The presentation is accounting on the realization of this concept. The "Mediverse" set of compounds is a library of 10,000 heterocyclic organic compounds, selected by a multilevel diversity calculation from a synthesized library of more than 100,000, then completed with structural formula of the first level metabolites and some of the retrometabolites of the library members which are themselves members of the same Mediverse library (crypto-retrometabolites, cryptolites). While the metabolites are serving for a preliminary estimation of the expected metabolic fate of a member hit, cryptolites offer a way to diminish the otherwise high hit fallout during the ADME test phase. In the "Lead Rescue" approach, associated with the Mediverse libraries, cryptolites of the hits proven to be ineffective under *in vivo* conditions are offered "off-the-shelf" for testing, shortening thus significantly the feedback from *in vivo* ADME testing to focussed library design.

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Biopharmaceutical studies on drug/conjugated metabolite interactions: application of organic sulfonic compounds as biodistribution promoters

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A series of our biopharmaceutical investigations [1–3] focused on the actions of conjugated drug metabolites on the pharmacokinetics of the parent drug using acetaminophen (APAP) and its conjugated metabolite acetaminophen *O*-sulfate (APAPS), revealed that: (1) APAPS competitively displaced the serum protein binding of APAP; (2) APAPS increased the total body clearance (CL_{total}) of APAP; and (3) APAPS increased the tissue distribution of APAP into various organs. A recent comparative study [4] on the actions of stereoisomers of APAPS on the pharmacokinetics of APAP clarified that (4) the same tendencies in biopharmaceutical interaction to APAP could be observed in one of the stereoisomers, *o*-acetylaminophenol *O*-sulfate, which is not the metabolite of APAP but an externally administered sulfonic compound. These results led to a new strategy, the pharmaceutical modification of biodistribution characteristics of drugs by the concomitant administration of organic sulfonic compounds without pharmacological activity.

In this study, a sulfonic acid derivative of glutathione (GSH), glutathionesulfonic acid sodium salt (GSO_3Na), was synthesized as a model organic sulfonic compound which was designed to be a new biodistribution promoter. Under the constant infusion of GSO_3Na, the distribution volume (Vd_{ss}) of thiopental sodium (TPS), a model drug, decreased significantly, whereas the CL_{total} was not changed in rats. Tissue-to-plasma concentration ratio (Kp) of TPS increased approximately 2-times in the liver under the constant infusion of GSO_3Na. However, under the constant infusion of GSH, those changes in pharmacokinetic parameters of TPS were insignificant. In the case of APAPS and its stereoisomers, competitive displacement of protein binding of APAP by concomitantly administered biodistribution promoters was a simple account for the modification of pharmacokinetic parameters of APAP [3, 4]. However, in the case of GSO_3Na, the changes in biodistribution of TPS could not fully explained by the displacement of protein binding. Other mechanisms, such as effects on regulation of carrier-mediated transport systems by a concomitantly administered organic sulfonic compound in biodistribution process of a drug, might be involved in the latter case.

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