Project Review

"Metabolism of steroids via humanized livers in mice"

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Anabolic steroids are widely misused in sports. Because anabolic steroids are extensively metabolised in the human body, methods for the detection of these steroids need to focus on metabolites rather than on the parent drug. The liver is the principal organ where anabolic steroids are metabolised.

Recently, several anabolic steroids have appeared on the market either as so-called prohormones, available as “nutritional” supplement, or underground as designer steroid (e.g. THG). Regular anabolic steroids –like all other drugs- from pharmaceutical companies undergo a vast amount of toxicological tests before they are administered to test subjects in the final phase before their release on the market. This is not the case for these new steroids. Hence, essential toxicological data is missing and administration of these steroids to human subjects for the identification of marker metabolites for their detection is medically and ethically questionable.

This study will evaluate an animal model in which mice harbouring a functional human liver will be used for investigation of the metabolism of steroids. In contrast to, in-vitro models using single cells or cell cultures, this animal uses a functional human liver and resembles administration studies better than any other model available so far.

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Results and Conclusions

The aim of this project was to investigate whether the uPA$^{+/+}$-SCID mice transplanted with human hepatocytes can be used as an alternative for the human excretion studies and in vitro hepatocytes cultures. This small animal model would be used to investigate drug metabolism and to find urinary markers that allow for the detection of steroid abuse.

The metabolic profile of the chimeric mouse model was first validated with 3 selected steroids. The results of the administration studies with androst-4-ene-3,17-dione (AD), methandienone (MTD) and 19-norandrost-4-ene-3,17-dione (19-norAD) to the chimeric mice showed a good correlation with the previously described metabolism in humans. Moreover the major metabolites described in humans were all confirmed in the chimeric mice. To further illustrate the applicability of the chimeric mice, new marker metabolites for 17α-methyltestosterone (17α-MT) and stanozolol were found and implemented in the routine doping control screening since they are longer detectable (e.g. 4,16-dihydroxystanozolol).

All these results including the analytical data were presented at conferences (6 presentations/posters) and/or via 7 scientific publications.

The model combines the ethical advantages of in vitro studies with the reality of in vivo studies. In the future this promising mouse model will be used to further encourage the fight against doping by evaluating some prohormones and food supplements based on the urinary results of the chimeric mice.