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Editorial

Targeted Inhibitors for Steroid Transforming Enzymes

Enormous advances have taken place in elucidating the mechanistic enzymology and structural biology of key-enzymes involved in steroid hormone biosynthesis and metabolism. Concurrently, efforts have intensified to develop inhibitors of many of these key-enzymes with the goal of developing therapeutic agents that may be efficacious for the treatment of a host of steroid hormone dependent diseases. These diseases include breast, prostate and endometrial cancer as well as diseases in which dysregulation of steroid hormone signaling contributes to metabolic syndrome and obesity. The advances in enzymology and inhibitor development are now merging so that rational drug design is now possible. It is with this backdrop that the editors of this special issue invited leaders in the field to contribute to this special issue on "Targeted Inhibitors for Steroid Transforming Enzymes". Simultaneously, a call for full-length papers was made by the journal so that these could be included in this special issue. This effort led to the eleven-invited reviews and five full length papers that make up this issue.

The special issue commences with a review by Akhtar and colleagues on the mechanism of action of aromatase and how this can be applied to other P450 enzymes e.g. 17-hydroxylase-17,20-lyase (CYP17), both of which catalyze hydroxylation as well as acyl-carbon bond cleavage reactions. This is then followed by articles from the Brodie and Njar groups on aromatase inhibitors to treat hormone dependent breast cancer and CYP17 inhibitors to treat castrate resistant prostate cancer, respectively. Each of these approaches has led to clinically useful drugs e.g. exemestane and abiraterone acetate that will improve the lives of thousands if not millions of patients. Steroid 5α-reductase inhibitors, finasteride and dutatseride, which are used for the treatment of benign prostatic hyperplasia and prostate cancer are then reviewed by the Tindall group. Collectively all these drugs inhibit the local formation of estrogens and androgens in target tissues e.g. breast and prostate and by so doing deprive steroid receptors of their ligands. With the recognition that local production of steroid hormones is important in malignancy, another approach is to prevent release of estrone from stores of estrone sulfate or block the release of dehydroepiandrosterone (DHEA) from DHEA-sulfate with sulfatase inhibitors, and this concept is reviewed by Geisler and colleagues. The concept that hydroxysteroid dehydrogenases (HSDs) are involved in the pre-receptor regulation of steroid hormone action in steroid target tissues by converting potent hormones into their cognate inactive metabolites, and can be targeted for drug development is then reviewed in six-articles by Penning, Thomas, Marchais-Oberwinkler, Poirier, Byrns and El-Kabbani.

The full-length papers that follow deal with topics such as aromatase inhibiton and bone mineral density, inhibitors of aldosterone synthase, inhibition of 11β-HSD isoforms by natural products and endocrine disrupting perfluoroalkylated analogs, and pharmacophore virtual screening to attain HSD inhibitors with specificity.

The special editors of this series hope that the articles will help scientists with the current status of the topic, provide an appreciation of the unanswered questions, and what the next steps may be.

"A prepared mind leads to discovery"

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