PRECLINICAL TESTING OF NOVEL THERAPEUTIC APPROACHES IN ENDOCRINE TUMOR MODELS

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Endocrine tumors represent a heterogeneous group of neoplasia. Dependent on their cellular origin these tumor cells often retain specific functional properties including hormonal secretion and responsiveness to endocrine regulatory pathways. While some tumors are causing clinical symptoms primarily due to autonomous hormone production others are defined by effects related to their proliferative capacity and ability for metastatic spread. Only a few cell lines are available for endocrine tumors which furthermore do not reflect these heterogeneous functional properties and specific therapeutic response rates of individual tumors. Preclinical tumor models can aid in investigation of a number of aspects including elucidation of functional mechanisms as well as development of therapeutic approaches. Following this approach we have utilized a number of different *in vitro* and *in vivo* models for endocrine tumors. In the proposed presentation some examples including development and testing of novel liposomal agents with targeted properties, preclinical testing of vascular disrupting agents will be highlighted. To facilitate patient individual treatments and thereby to optimize therapeutic efficacy, we are currently aiming at the development and characterization of patient-individual tumor models. To investigate whether morphological and functional characteristics between tumor samples after mouse engraftment in comparison to the original tumor would be comparable, we started examination of implanted material and original patient tumor by histology and immunohistochemistry. First comparisons indicate that the implanted tumors keep the characteristics of the original tumor material in the murine host. These findings need to be further substantiated and additional endpoints such as vascularization and endocrine potential need to be examined. Nevertheless, these tumor models have the potential to evaluate individualized treatment modalities in the future.

The Epidemic of Primary Hyperaldosteronism: Where is the Beef?

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At the onset of this century, the medical literature has been densely seeded by reports that primary hyperaldosteronism is not as rare as previously believed and accounts for ~10% of the cases of hypertension, rather than 0.5-2% as then cited by leading textbooks of the time. Driven by powerful academicians in the hypertension and adrenal field and reinforced by data coming from all over the world, albeit nearly exclusively from referral centers, this new information incited much enthusiasm and was the actual driving force in the formation of the Endocrine Society's sponsored guidelines for the diagnosis and treatment of primary hyperaldosteronism. By the time these guidelines were released, some 2-3 years ago, it became apparent, though not explicitly admitted, that the distinguished members of the guidelines writing committee were somewhat skeptical of the already widespread expectations that a tide of hyperaldosteronism might over flood endocrine practice. Indeed, the claim that one tenth of the hypertensive population harbor primary hyperaldosteronism had little chance of substantiation even at its glorious days. First, hypertension itself is far more common than ever appreciated and its prevalence rises steadily with age at a time in which longevity itself continues to increase. Second, PRA, the basis for the hailed Aldosterone/PRA ratio declines with age, making it difficult to use particularly in the population in which hypertension is now especially prevalent. Third, none of the reports on the epidemic of primary hyperaldosteronism is based on a population study, making the true prevalence of this disease among hypertensive subjects difficult to determine. Fifth, recent reports do not support the initially claimed widespread presence of this disease. Nevertheless, the hyperaldosteronism epidemic legend had a distinct positive impact, as it revived not only the pursuit of this diagnosis under proper clinical circumstances (e.g., young hypertensive subjects, resistant hypertension even with normal K+, adrenal incidentaloma), but invigorated interest in aldosterone and its impact on the cardiovascular system, thus leading to new insights on its role in cardiac, renal and cerebrovascular disease. The revelation of novel interactions between aldosterone and adipose tissue and aldosterone and the brain may well be the most important inadvertent sequels of the short lived epidemic of primary hyperaldosteronism.

PHEOCHROMOCYTOMA: UPDATE

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Pheochromocytoma is a rare and fascinating catecholamine-secreting tumor derived from neural crest cells, which refers to both medullar adrenal tumors and paragangliomas. It was the subject – according to a PubMed search - of 2341 medical articles in the last 5 years. Selected papers with the highest impact on the global perception of the disease were chosen to present the most recent interesting updates.
First, a systematic review of the publications reveals a large variety of non-classical clinical presentations of pheochromocytomas ranging from silent tumors to tako-tsubo syndrome; as well, new publications concerned diagnostic biochemical markers, functional imaging protocols and operative therapeutic approaches of pheochromocytoma. Then, it appears that the field which undoubtedly benefitted the more striking advances is the genetics of pheochromocytomas and paraganglioma: to the known mutations in the REarranged in Transformation (RET) proto-oncogene, in the Von-Hippel Lindau (VHL)-tumor suppressor gene, and in the neurofibromatosis type 1 (NF-1) tumor suppressor gene, new mutations in 5 genes coding the mitochondrial Succinate Dehydrogenase (SDH) Complex (SDHA, SDHB, SDHC, SDHD, SDHAF2) were associated with high predisposition to the disease. All these mutations share a neuronal apoptotic pathway, but in the very last months, an absolutely novel mutation in the gene of a putative transmembrane protein TMEM127 was associated with adrenal pheochromocytoma, opening the way to exploration of totally new pathophysiologic pathway of the disease and to probably other candidate genes. As a result, the proportion of hereditary pheochromocytoma raised from classically admitted 10% to near 32 %. The question of performing a genetic screening in cases of pheochromocytoma is thus critical, and some publications describe relationship between genotype and phenotype (localization of the tumor, catecholamine profile…) which can orientate toward specific gene screening. Finally, new data concerning identification of predictive markers of malignancy as well as new therapeutic possibilities for malignant pheochromocytoma will be reviewed.

CONGENITAL ADRENAL HYPERPLASIA DUE TO STEROID 21-HYDROXYLASE DEFICIENCY
Review of the Endocrine Society Clinical Practice guideline

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Clinical practice guideline for congenital adrenal hyperplasia (CAH) was recently developed by a Task Force which included clinicians experienced in treating CAH. Additional experts were also consulted.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions. The evidence-based guidelines were developed using the Grading of Recommendations, Assessment and Evaluation system to describe the strength of recommendations and the quality of evidence.

Screening and Diagnosis: A universal newborn screening for severe steroid 21-hydroxylase deficiency followed by confirmatory tests is recommended. The diagnosis rests on clinical and hormonal data; genotyping is reserved for equivocal cases and genetic counseling.

Treatment: Glucocorticoid dosage should be minimized to avoid iatrogenic Cushing's syndrome. Mineralocorticoids and, in infants, supplemental sodium are recommended in classic CAH patients. Prenatal treatment of CAH continues to be regarded as experimental. The Task Force recommends against the routine use of experimental therapies to promote growth and delay puberty. Surgical guidelines emphasize early single-stage genital repair for severely virilized girls, performed by experienced surgeons. Bilateral adrenalectomy should be avoided. Clinicians should consider patients' quality of life, consulting mental health professionals as appropriate. At the transition to adulthood, monitoring for potential complications of CAH is recommended. Finally, judicious use of medication during pregnancy and in symptomatic patients with nonclassic CAH is recommended.