insulinoma (IN) and 3 with non-insulinoma (non-IN), underwent ICPS. Blood samples were collected for measurement of plasma glucose (PG), PCP, and PI using a Roche Cobas 8000 module e602 which does not measure insulin aspart at before and every 10-20 minutes during intravenous infusion of insulin aspart at the rate of 0.05-0.075 unit/kg/hr. The test was terminated if the patients had a PG level of <40 mg/dL. There was no difference in baseline biochemical data between two groups. At the end of the test, IN had significantly higher PCP level (range: 0.60-10.20 *vs.* 0.31-0.48 ng/mL and median: 4.67 *vs.* 0.47 ng/mL; $p = 0.017$), lower percentage of PCP suppression (range: 2.10-53.10% *vs.* 63.08-91.24% and mean: 24.78 ± 19.4% *vs.* 73.17 ± 15.7%; $p = 0.005$), higher PI level (range: 1.13-113.70 *vs.* 0.22-0.73 μIU/mL and median: 21.29 *vs.* 0.49 μIU/mL; $p = 0.017$) and lower percentage of PI suppression (range: -14.63-81.32% *vs.* 88.14-96.10% and mean: 28.45 ± 36.2% *vs.* 93.31 ± 4.5%; $p = 0.003$) than did the non-IN. No overlapping of these parameters was observed between IN and non-IN. Using the same cut-off levels as the supervised 72-hour fast test, the insulin criterion (≥3 μIU/mL) in ICPS had a sensitivity of 86% and a specificity of 100% and the C-peptide criterion (≥0.6 ng/mL) in ICPS had a sensitivity of 100% and a specificity of 100%. There was a high correlation of 89% between using PCP and PI responses. In conclusion, ICPS using an RA is effective in the diagnosis of insulinoma.

Neuroendocrinology and Pituitary

RESEARCH ADVANCES IN PITUITARY TUMORS

TBR-760, a Chimeric Somatostatin-Dopamine Compound, Arrests Aggressive Non-Functioning Pituitary Adenoma Growth In Vivo

Heather A. Halem, PhD[1], Ute Hochgeschwender, PhD[2], Arunthi Thiagalingam, PHD[3], Michael D. Culler, PHD[1].

[1]Tiburio Therapeutics, Cambridge, MA, USA, [2]Central Michigan University, Mt. Pleasant, MI, USA, [3]Ipsen Bioscience, Cambridge, MA, USA.

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TBR-760 is a chimeric dopamine (DA)-somatostatin (SST) compound with potent agonist activity at both DA type 2 (D2R; EC_{50} 0.064nM) and SST type 2 (SSTR2; EC_{50} 1.2nM) receptors. Prior studies have demonstrated that the chimeric DA-SST compounds are more potent and effective than either individual or combinations of individual DA and/or SST analogs in inhibiting secretion from pituitary adenomas. Non-functioning pituitary adenomas (NFPA) express high levels of D2R as well as lower levels of SSTRs, including the type 2 receptor (1), and thus have an appropriate receptor profile to respond to TBR-760. The present study examines the ability of TBR-760 to inhibit tumor growth in a mouse model of aggressive NFPA. Heterozygous and null mutant mice lacking one or both copies, respectively, of the pro-opiomelanocortin (POMC) gene (POMC-KO mice) (2) spontaneously develop aggressive, non-secreting pituitary adenomas (3). The POMC-KO mouse tumors have been shown to express D2R and SSTR2 at a similar level as human NFPAs (4). In addition, merging of microarray data (Affymetrix, U133 plus_2.0 and Mouse Genome 430 2.0 arrays), reveals 154 common gene signatures between human NFPAs and the POMC-KO mouse tumors. In an initial study, heterozygous POMC-KO mice with an established pituitary tumor of approx. $10mm^3$ (mean volume 8.9±0.3), as determined by MRI, were treated with a range of TBR-760 doses (0.125 to 12.5mg/kg, sc, QD) for 60 days. During that time, tumors in vehicle-treated mice increased in size by 890±0.7%, whereas all doses of TBR-760 tested resulted in a nearly complete inhibition of tumor growth from treatment initiation. We then compared the effect of the TBR-760 chimera with that of its individual SST agonist (SSTA) and DA agonist (DAA) components on tumor growth in the POMC-KO mice. As in the earlier study, TBR-760 treatment (1mg/kg, sc, QD), initiated when the mice had an established tumor of approx. $10mm^3$, completely arrested tumor growth during the 8 weeks of treatment (final mean tumor volume of $8.5±1.3mm^3$ vs. $54.61±10.6mm^3$ in vehicle-treated mice). Treatment with equimolar or 10x-higher doses of the individual SSTA or DAA, either alone or in combination, had no significant effect on tumor growth, except in the lower dose DAA group where a modest suppression of tumor growth was observed. These data demonstrate that only the dual DA-SST chimeric compound, TBR-760, completely arrested tumor growth in the POMC-KO mouse model of NFPA. Further, despite the highly aggressive nature of the POMC-KO tumors, significant tumor shrinkage was observed in 20% of the mice treated with TBR-760. These results support the development of TBR-760 as a medical therapy to prevent or arrest the growth of NFPAs and, potentially, to induce NFPA shrinkage. References: (1) Florio et al., 2008 Endocr Relat Cancer; 15: 583-596. (2) Yaswen et al., 1999 Nat Med; 9:1066-70 (3) Karpac J et al., 2006 Cell Mol Biol; 52: 47-52.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

Interactions Between Macrophages and Cancer Stem-Like Cells Promote Mammary Tumor Angiogenesis Under Obesity

Lauren Hillers-Ziemer, B.S.[1], Rachel McMahon, DVM[2], Margaret Hieptas, B.S.[2], Gretchen Paderta, B.S.[3], Jessica McCready, PhD[4], Jennelle LeBeau, B.S.[4], Lisa Arendt, DVM,PHD[5].

[1]Graduate Program in Cellular and Molecular Biology, University of Wisconsin Madison, Madison, WI, USA, [2]School of Veterinary Medicine, University of Wisconsin Madison, Madison, WI, USA, [3]University of Wisconsin Madison, Madison, WI, USA, [4]Assumption College, Worcester, MA, USA, [5]School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI, USA.

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Obesity is a growing health concern worldwide and increases the incidence of multiple types of cancer, including breast cancer. Obese breast cancer patients often develop more aggressive tumors than lean patients and have increased risk for metastasis, tumor recurrence and mortality. Here, we sought to address how obesity alters the biology of breast cancer to promote aggressive tumors. To induce obesity, we fed mice either a control diet (CD) or high fat diet (HFD) for 16 weeks, then transplanted Met-1 tumor cells into mammary fat pads and monitored tumor growth. At end stage, tumors from HFD-fed mice were significantly