Press Release

Modifications to a recombinant Mullerian inhibiting substance brings this new biological therapeutic one step closer to clinical testing in ovarian cancer patients

Sept. 17, 2013 — Mullerian inhibiting substance, or MIS, is a reproductive hormone produced in fetal testes, which inhibits the development of female secondary sexual structures in males. Before sexual differentiation, the fetus is bipotential, and the developmental choice of male Wolffian ducts (i.e. prostate, vas deferens) over female Mullerian ducts (i.e. Fallopian tubes, uterus, vagina) in the male is controlled in part by MIS. Because MIS is such a potent inhibitor of the development of Mullerian-derived tissue, it has been proposed as a potential therapeutic of Mullerian-derived tumors such as uterine, Fallopian, cervical, and ovarian cancers.

MIS belongs to the TGF-beta superfamily, a class of proteins involved in many pathologies including cancer. Recombinant TGF-beta proteins have been very difficult to produce because they require dimerization, activating cleavage and disulfide bonding for activity. Because of these peculiarities, MIS can only be feasibly produced in mammalian cells, and not E. coli or yeast, where production yields are much higher, and industrial scaling more straightforward. In mammalian cells, yields and homogeneity of the product can be significant barriers to industrial scaling and ultimate entry into clinical trials. For example, proteolytic degradation was a contributing factor to the failure of topical TGF-B3 in early clinical trials against chemotherapy-induced oral mucositis in patients with lymphomas and solid tumors. Recombinant BMP-2 in a paste form remains the only TGF-B family ligand used in the clinic, and is limited to the specific indication of autologous bone grafting. Progress in the technology of production and purification of TGF-Beta recombinant proteins could help many candidates, including MIS, to achieve their therapeutic potential in the clinic.

A team of researchers from the Massachusetts General Hospital (MGH) and the Massachusetts Eye and Ear Infirmary report that modifications to the protein sequence at the activating cleavage site of MIS to enhance maturation into the active form, and the addition of a leader sequence from albumin, the most highly secreted protein in the blood, results in higher production yield of cleaved active MIS which does not suffer from unwanted proteolytic degradation.
Fetal rat urogenital ridges treated with the new constructs of MIS show Mullerian duct (4+) regression as a measure of bioactivity at lower concentrations and thus increased potency (1μ/ml) (right) when prohormone cleavage is enhanced, compared to wild type (WT) MIS (left) which shows a retained Mullerian Duct (M) (0 regression). The adjacent Wolfian duct (W), shown for comparison, are unaffected (200X).

The report appears in the inaugural edition of the journal Technology, and is entitled "An albumin leader sequence coupled with a cleavage site modification enhances the yield of recombinant c-terminal Mullerian Inhibiting Substance."

"This technology is the culmination of our efforts to scale the production of MIS beyond the lab and into the clinic" says Dr. Donahoe, of MGH, the paper’s senior author. "We show that not only can we produce high levels of this protein, but unexpectedly our modifications increase activating cleavage of MIS while improving the homogeneity of the product, all of which are necessary for translation to the clinic". The enhanced cleavage of MIS resulted in much greater activity when it was tested for its ability to induce Mullerian duct regression ex vivo. These modifications can be incorporated in other technologies such as viral vectors for gene therapy.

"The newly engineered recombinant MIS shows great promise and is a necessary component before clinical application of a biological such as MIS", said Dr. Austen, the Edward D. Churchill Distinguished Professor of Surgery at Harvard Medical School and Massachusetts General Hospital (MGH) Surgeon-in-Chief Emeritus, and Chairman of the MGH Chief’s Council, who was not involved with this study.

Jacques-Pierre Moreau, PhD, CEO of Mulleris Therapeutics, Inc., who is dedicated to developing MIS as a therapeutic, states, "the therapeutic potential of MIS has, so far, been hindered by the scarcity of clinical grade product. The publication of Pepin, et al. represents a major advance in providing a reliable source of this regulatory hormone, thus making clinical development in oncology, endocrinology, and neurology possible".

Family advocates from the McBride Foundation and Commons Development have long provided support to the Pediatric Surgical Research Laboratories, Jack McBride, states, "we feel that our support of Dr. Donahoe’s research over the years is now reaching a state where patients may profit".

The technology surrounding the modification of the MIS peptide is not only applicable to ovarian cancer, but has shown strong promise for other tumor types such as uterine, breast, and cervical cancers. "We choose to go after ovarian cancer, first, since it is the most lethal of these gynecological malignancies, with the fewest treatment options", says Dr. Donahoe. There is also early promise of using MIS gene therapy to treat neurodegenerative diseases using these modified constructs.

Additional co-authors of the Technology paper are David Pepin, Mien van Hoang, Fotini Nicolaou, Kathryn Hendren, Leo Andrew Benedict, Ahmed Al-Moujahed, Amanda Sosulski, Anna Marmalidou, and Demtrios Vavvas.

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