CEDARS-SINAI MEDICAL CENTER NEWS

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**HIGHLIGHTS:**
Why some embryos successfully attach to the endometrium and others do not continues to be a mystery because little is known about the molecular mechanisms involved in the human implantation process. Now, researchers at Cedars-Sinai Medical Center have investigated one gene's critical role in this process, thereby bringing them a step closer to finding methods to help the more than 6.1 million women in the United States who suffer from infertility.

# INFERTILITY RESEARCHERS IDENTIFY ONE GENE'S CRITICAL ROLE IN THE HUMAN EMBRYO IMPLANTATION PROCESS

**LOS ANGELES (Monday, Oct. 17, 2005)** − In spite of advances in assisted reproductive technologies, more than 6.1 million women in the United States − roughly 20 percent of all women of reproductive age − suffer from infertility. In order to improve infertility treatments, researchers at Cedars-Sinai Medical Center and the University of California at Los Angeles recently conducted a study of the molecular mechanism involved in the human implantation process, specifically targeting the role of one gene in the success of an embryo to implant itself in the endometrium, the inner lining of the uterus. The study is being presented at the Conjoint Annual Meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society Oct. 15-19, 2005, in Montreal, Quebec, Canada.

"There have been studies done both in the United States and Europe showing statistically that there is a defect in the implantation process in women with endometriosis, a condition affecting many premenopausal women who also suffer from infertility," explains Lee-Chuan Kao, MD, PhD., a reproductive medicine specialist at Cedars-Sinai and co-director of the hospital's Center for Reproductive Medicine. "My interest was to determine exactly the molecular mechanism responsible for implantation failure."

Endometriosis occurs when tissue similar to the lining inside the uterus grows outside the uterus, usually on the surfaces of the ovaries, fallopian tubes and other pelvic structures, making conception more difficult.

Cedars-Sinai is one of less than a half-dozen facilities in the United States trying to dissect the mechanism of human embryo implantation and its link to endometriosis. In this recent study, Kao, working with Margareta Pisarska, MD, co-director of Cedars-Sinai's Center for Reproductive Medicine, and Salma Khan, PhD, also of Cedars-Sinai, focused on one specific endometrial target gene (GlcNAc-6-OST) which has a role in shaping L-selectin ligand, a chemical responsible for the tethering and rolling mechanism described at the human maternal-fetal interface, i.e. a signal that enables the embryo to recognize the lining of the endometrium.

"This gene (GlcNAc-6-OST) gets transcribed and then translated into a protein and this particular protein functions as an enzyme," explains Kao. "It has been shown to be expressed specifically during the window of implantation. My hypothesis is that this particular gene, for a yet-to-be-uncovered reason, is abnormally expressed in women with endometriosis which results in the embryo not being able to find the appropriate place to bind to the endometrium leading to a failure or defect in the implantation process."

The in-vitro study tested whether ovarian hormones, estrogen and progesterone, can regulate the expression of

GlcNAc-6-OST. By treating an endometrial cell line with the ovarian hormones, Kao and his colleagues demonstrated that increasing estrogen during the first part of the menstrual cycle, when ovarian follicles mature to prepare for ovulation, increases the expression of the enzyme. After ovulation, progesterone production further heightens the expression of the enzyme. This up-regulation of the enzyme (when both estrogen and progesterone are present) facilitates the production of L-selectin ligand which enables implantation. When only progesterone was present without estrogen, the gene was suppressed and the endometrium would not be receptive to implantation.

"Our next step," says Kao, "will be to explore other regulatory mechanisms or other chemicals − instead of hormones − that might provide us with a more specific approach to modulate this gene. Additional studies are required before we can apply this information to a clinical situation but I believe we've shown there is definitely a need for more research."

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One of only five hospitals in California whose nurses have been honored with the prestigious Magnet designation, Cedars-Sinai Medical Center is one of the largest nonprofit academic medical centers in the Western United States. For 17 consecutive years, it has been named Los Angeles' most preferred hospital for all health needs in an independent survey of area residents. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthroughs in biomedical research and superlative medical education. It ranks among the top 10 non-university hospitals in the nation for its research activities and was recently fully accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). Additional information is available at www.cedars-sinai.edu.