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Nemours Center for Childhood Cancer Research Team at the Alfred I. duPont Hospital for Children Identifies the Function of a Biomarker Present in Prostate Cancer Cells: New Insight into Therapeutic Benefit for Patients with Advanced Prostate Cancer

Wilmington, Delaware

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Wilmington, DE – The research team at the Nemours Center for Childhood Cancer Research (NCCCR), a newly established division of Nemours Biomedical Research at the Alfred I. duPont Hospital for Children has discovered that the biomarker called prostate specific membrane antigen (PSMA), abundantly present in cancer cells of patients with advanced prostate cancer, has a contributory role in the progression of cancer to an aggressive disease. A biomarker is any biomolecule that is associated with a particular pathological or physiological state of cells and may be used to diagnose and treat a disease or monitor response to therapy.

The discovery, titled "Prostate specific membrane antigen associates with anaphase promoting complex and induces chromosomal instability, " is outlined in the July issue of *Molecular Cancer Therapeutics*, an American Association for Cancer Research journal and provides new insights into therapeutic benefit for patients with advanced prostate cancer.

The research was conducted by Dr. Ayyappan K. Rajasekaran, the Director of NCCCR, and his research team while they were at the University of California, Los Angeles, and at NCCCR. The abundance of PSMA in prostate cancer cells increases as the cancer progresses into a metastatic and hormone-independent advanced disease. Dr. Rajasekaran said, "We strongly suspected that PSMA has a potential role in the progression of prostate cancer into an aggressive disease. But how it participates in disease progression was not clear. Now in this study, we identified that PSMA does have an important causative role in prostate cancer progression."

This study was initiated when the researchers found that PSMA was present at the poles of the dividing cells. These poles are complex structures at the opposite ends of the cells that control the separation of chromosomes equally into daughter cells during cell division. "Presence of PSMA at the poles indicated it might have a role in cell division and chromosome segregation, and we continued our quest to understand this potential function of PSMA," said Dr. Rajasekaran.

Human cells have 46 chromosomes. The chromosomes are vehicles that carry the genetic material DNA from generation to generation. These chromosomes are equally divided into daughter cells during cell division. Cells have several checkpoints to ensure that the chromosomes are equally separated during cell division. Anaphase-promoting complex (APC) is one such checkpoint regulatory protein involved in the proper segregation of chromosomes during cell division. This complex monitors the timing of cell division and provides sufficient time for cells to segregate chromosomes equally into

daughter cells. Often, cancer cells have more than 46 chromosomes, a condition known as aneuploidy, which is a constant feature of aggressive, advanced, and drug-resistant solid tumors, including prostate cancer.

Rajasekaran and his research team found that PSMA-expressing cells spent less time dividing. They found that PSMA interferes with the function of APC and induces aneuploidy in cancer cells. "When PSMA is present, cells hurried to complete their division prior to having all their chromosomes properly segregated," said Dr. Sigrud A. Rajasekaran, the first author of the study and the head of the Cancer Cell Metabolism Laboratory at NCCCR.

PSMA is present in prostate cancer cells but not in normal cells. Therefore, it is an excellent therapeutic target for prostate cancer. There are several ongoing clinical trials for PSMA-based therapeutic interventions. "Since PSMA expression is higher in metastatic compared to benign cancer cells, anti-PSMA-based therapeutic strategies should target metastatic prostate cancer cells, which will benefit patients with advanced prostate cancer," the study states.

Dr. A. Rajasekaran and his team conducted their research on cell lines and are in the process of translating their findings into human clinical trials, which should be available in two to three years.

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About the Nemours Center for Childhood Cancer Research

The Nemours Center for Childhood Cancer Research is a newly established research entity of Nemours Biomedical Research at the Alfred I. duPont hospital for children. The NCCCR is located in a fully renovated laboratory space in 1701 Rockland Road, Wilmington, DE. The goal of the center is to evolve into a leader in research focusing on biomarkers for childhood cancers and cancers that affect families. The NCCCR will closely work together with Helen F. Graham Cancer Center, University of Delaware, Center for Translational Research and the Delaware Biotechnology Institute. The Alfred I. duPont Hospital for Children is a division of Nemours, which operates one of the nation's largest health systems devoted to pediatric patient care, teaching, and research. Set on a 300-acre campus near Wilmington, Delaware, the 200-bed duPont Hospital for Children offers all the specialties of pediatric medicine, surgery, and dentistry. Starting with Alfred I. duPont's bequest over 70 years ago, Nemours has grown into a multi-dimensional organization offering personalized clinical and preventive care focused on children. For more information, please visit Nemours.org.

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About Nemours

Nemours, one of the nation's largest pediatric health systems, is dedicated to achieving higher standards in children's health. Nemours offers an integrated spectrum of clinical treatment coupled with research, advocacy, and educational health and prevention services extending to all families in the communities it serves. Starting with Alfred I. duPont's bequest over seventy years ago, Nemours has grown into a multi-dimensional organization offering personalized clinical and preventive care focused on children.

Nemours owns and operates the Alfred I. duPont Hospital for Children in Wilmington, Delaware and major children's specialty clinics in Delaware (Wilmington), Florida (Jacksonville, Orlando and Pensacola), Pennsylvania (Philadelphia and Bryn Mawr) and New Jersey (Atlantic City and Voorhees). Having recently received preliminary approval from the State of Florida, Nemours will establish a new full-service children's hospital as part of an integrated pediatric health campus in

Orlando. KidsHealth.org, the world's most visited pediatric health care Web site for parents, kids and teens, is a project of Nemours.

Nemours employs over 4,400 individuals, including 430 pediatric physicians, specialists and surgeons who cared for approximately a quarter of a million children in 2007. The organization's goal is to align with parents, physicians, community leaders, children's advocates and elected officials to ensure optimal wellness for every child. Additional information about Nemours can be found at www.nemours.org.

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