# GLAX Health Announces the Discovery of Androgen Receptor Inhibitors for Prostate Cancer Therapy.  Dr. Rakesh Srivastava

*Discovery of Novel Androgen Receptor inhibitors by Dr. Rakesh Srivastava and colleagues*


Dr. Rakesh Srivastava

DOVER, DELAWARE, UNITED STATES, October 11, 2022 /EINPresswire.com/ -- GLAX Health Announces the Discovery of Androgen Receptor Inhibitors for Prostate Cancer Therapy.  Dr. Rakesh Srivastava

GLAX Health is a biotech company engaged in the development of novel drugs for the treatment of cancer and other human diseases (http://glaxhealth.com).  Dr. Rakesh K. Srivastava (President and CEO of GLAX Health) and his colleagues discovered new drugs that inhibit AR transcription and prostate cancer cell growth.

Significance of Androgen Signaling Pathway for Prostate Cancer and other human diseases?

An androgen-dependent condition, disease, or disorder is a medical condition that is dependent on the presence of androgenic activity in the body.  Androgens help with bone density, muscle development, puberty, red blood cell production, sexual desire, and function. High androgen levels may cause acne, amenorrhea, abnormal menstruation, excessive hair growth or hair loss, high blood pressure and high cholesterol, infertility, obesity, and cancer.  High levels of androgens in a female can cause acne, irregular period, difficulty becoming pregnant, changes in female body shape, decrease in breast size, increase in body hair in a male pattern, lack of menstrual periods and oily skin. High androgen levels lead to symptoms such as body hair growth, acne, irregular periods and weight gain.  Hyperandrogenism can cause several diseases such as polycystic ovary syndrome, adrenal hyperplasia, cushing's disease, cancer, male pattern baldness in women, hypertension, and vascular disease. The inhibition of androgen / androgen receptor signaling can be used for the treatment and preventiojn of diseases such as cancer, insulin resistance, dyslipidemia, hypertension, and vascular diseases.

Androgen receptors (AR) are expressed in many cancers such as prostate cancer, breast cancer, kidney cancer, astrocytoma, basal cell carcinoma, bladder cancer, cervical cancer, colon cancer, desmoid tumors, esophageal carcinoma, gastric cancer, brain cancer, head and neck cancer, juvenile nasopharynx fibroma, melanoma, basal cell carcinoma, meningioma, lung cancer, ovarian cancer, cervical cancer, connective tissue tumors, pancreatic cancer, testicular cancer, thyroid cancer, rectal cancer, renal cancer, salivary gland cancer, sarcoma, uterine cancer, and mesothelioma (Endocr Relat Cancer. 2016; 23: T179-T197). AR is a steroid receptor transcriptional factor for testosterone and dihydrotestosterone consisting of four main domains, the N-terminal domain, DNA-binding domain, hinge region, and ligand-binding domain (LBD). Testosterone and dihydrotestosterone (DHT) bind to the LBD, followed by the conformational change of AR (Nat Commun. 2021; 12: 2705). After ligand binding in the cytoplasm, AR translocates into the nucleolus, forms a dimer, and binds to the androgen-response element of the promoter and the enhancer of targeted genes through the zinc-finger of the DBD. The NTD includes the transcriptional regulatory region, activation function-1 (AF1), and the LBD includes activation function-2 (AF-2). Upon DNA binding, the AR dimer forms a complex with coactivator and coregulatory proteins at the AF-1 and AF-2 regions. AR regulates the gene expressions with diverse functions located downstream of the androgen-response element. In prostate cancer, the actions of AR are the synthesis of PSA, regulation of lipid metabolism, promotion of growth, and several other functions. (Cold Spring Harb Perspect Med. 2017; 7: a030452).

Among U.S. men, prostate cancer is the second leading cause of cancer-related death (Henley et al Cancer 2020; 126:2225-49; World J Mens Health 2019; 37: 288–295). The prevalence of TMPRSS2-ERG was 30% to 50% in patients with localized prostate cancer (World J Mens Health. 2019; 37: 288–295). Stromal AR plays a transcription of TMPRSS2 gene was regulated by AR (World J Mens Health. 2019; 37: 288–295). Loss of stromal AR also suppressed the development of prostatic intraepithelial neoplasia by modulating pro-inflammatory cytokines/chemokines in a mouse model of prostate cancer (World J Mens Health. 2019; 37: 288–295). AR plays pivotal roles in various cancers, including metastatic castration-resistant prostate cancer (CRPC) (Cancers. 2021;13: 5417). Androgen deprivation therapy can suppress hormone-naïve prostate cancer, but prostate cancer changes AR and adapts to survive under castration levels of androgen. These mechanisms include AR point mutations, AR overexpression, changes in androgen biosynthesis, constitutively active AR splice variants without ligand binding, and changes in androgen cofactors. AR was found to be active in CRPC, therefore is a novel target for the treatment of CRPC. Point mutations in the AR gene were found in 15% to 30% of CRPC patients (World J Mens Health. 2019; 37: 288–295). These point mutations can activate AR by losing the specificity of the agonist (Cancers. 2021;13: 5417). Progesterone, estrogen, flutamide, bicalutamide, and enzalutamide can activate AR with the T878A point mutation (World J Mens Health. 2019; 37: 288–295; Case Reports Eur Urol. 1997; 31: 216-9). AR gene amplification was found in 30% to 50% of CRPC patients, resulting in the overexpression of AR (Cancer Res. 1997; 57: 314-9). Prostate cancer cells with AR amplification can survive under androgen deprivation therapy, progressing to CRPC (Cancers. 2021;13: 5417).

Dr. Srivastava Rakesh says aberrant AR activation in cells initiates oncogenic transformation, leading to prostate cancer development. AR inhibitors can be used to eliminate not only cancer cells but also cancer stem cells. Targeted therapies are being used in cancer patients due to better survival and fewer side effects when compared to traditional chemotherapy. Dr. Srivastava believes AR inhibitors can also be combined with other chemotherapy and irradiation to get a maximum therapeutic response. Activation of the AR pathway can induce immunosuppression and immunotherapy resistance. Therefore, inhibition of the AR pathway by these novel drugs may be beneficial for the treatment of various cancers. They not only inhibit the growth of cancer cells but also enhance the effectiveness of immunotherapy. Dr. Srivastava says future plans are underway, in collaboration with global partners, to further validate and perform clinical trials in near future.

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