



3. Targeting Intracrine (intra-tumoral) Androgens and Androgen Receptor “Cross Talk” in Prostate Cancer Cell Survival Pathways

STATEMENT OF PROBLEM

The pioneering work of Nobel Prize winner Charles Huggins ushered in the era of endocrine therapy for cancers of the prostate and breast. Therapies targeting the androgen axis remain the most effective treatment for men with advanced prostate cancer. These therapies often dramatically ameliorate clinical symptoms and extend survival. In the US alone, more than 600,000 men are currently under active androgen treatment to reduce circulating androgens or modulate their effects toward prostate cancer cells. Other forms of therapy have limited efficacy against advanced disease.

Although androgen-deprivation is initially quite effective, most men relapse with progressive disease. Substantial research efforts center on understanding this clinical state variously termed ‘androgen independent’, ‘hormone refractory’ and ‘castration resistant’. Progressing cancers nearly all exhibit re-activation of the androgen receptor despite undetectable (or very low) serum androgen levels. This can be inferred from the recurrence of PSA expression detectable in prostate tumors and in the blood. Many studies have put forth AR activation mechanisms. These include promiscuous ligand binding, cross-talk with other growth factor pathways, mutations of the AR and AR amplification. However, the presence of residual androgens in the tumor has not been extensively investigated nor exploited.

Proposed Solution

We need to establish, validate, and target critical pathways that allow prostate cancer cells to survive and proliferate in a castrate host. Long term advances in molecular understanding will enhance our ability to investigate, diagnose and ameliorate human disease with a significant epigenetic component.

Investigators with demonstrated expertise in complementary approaches and differing perspectives will be favored. Teams should collaboratively share knowledge on exploiting the AR signaling axis in the context of therapeutic intent.

We need to determine the ways prostate cancers develops resistance to androgen-deprivation. Castration-resistant prostate cancer accounts for approximately 30,000 deaths per year in the US alone. Although this disease state has been called ‘androgen-independent’, it is clear that many prostate cancers retain sensitivity to further manipulations of hormones and the androgen receptor.

We need to speed up the pace of translational research involving the androgen/AR pathway in prostate cancer, understanding and exploiting the androgen/AR axis for disease stratification and therapeutic intervention. A more detailed understanding of the causes of castration-resistant tumor growth is required. We need to improve cell and tissue-based assays that accurately reflect the *in vivo* status of AR pathway activity (and inhibition) in patients. New drugs and targeting strategies, innovative approaches to assess agent delivery, target inhibition effects, and treatment resistance mechanisms all need to be explored.

The Prostate Cancer Foundation is issuing a request for proposals to support research and infrastructure development designed to target the androgen axis in advanced prostate cancer. Research appropriate for support by this funding opportunity includes but is not limited to:

1. Developing methods for assessing and quantitating components and activities of AR ligand-generating processes (e.g. *de novo* intracrine androgen production, conversion of adrenal androgens, etc) operative in prostate cancers.
2. Developing strategies and creating reagents for inhibiting AR ligand-generating processes (androgen metabolism).
3. Developing strategies and creating reagents for improved inhibition of ligand-AR interactions ('anti-androgens'). Such strategies may target the ligand, the receptor, physical interactions between these components, or may target other regulatory factors (e.g. co-activators) and may exploit the use of pharmacological (drug) or molecular (e.g. antisense, siRNA, other) approaches.
4. Identifying and targeting mechanisms operating to facilitate active cellular androgen transport and/or establishment of intracellular androgen gradients.
5. Identifying and inhibiting target molecules/pathways downstream of ligand/AR interactions that function to execute the AR program for prostate cancer cell survival, proliferation, and/or invasion.
6. Developing molecular signatures reflecting tumor cell activity/dependency on particular androgen/AR metabolic or signaling pathways.
7. Identifying and exploiting tumor resistance (intrinsic or acquired) mechanisms to AR-axis therapeutics.
8. Developing preclinical and clinical systems/approaches designed to rapidly evaluate the effectiveness and determine resistance (intrinsic or acquired) mechanisms of existing and novel therapies.
9. Developing preclinical systems to represent the diversity of prostate cancer AR pathway states existing in human prostate cancers.

10. Developing *ex vivo* imaging (or other) strategies to assess activities of the androgen-AR axis in the context of prostate cancer progression and ‘on-target’ activity of pathway inhibitors.
11. Exploiting combinatorial strategies targeting multiple components of the androgen/AR axis or using chemotherapeutics (and other molecular inhibitors) anticipated to exert synergistic effects with AR-pathways.

Proposals can focus on one or more of these goals. If model systems are employed, proposals should include extensive mechanisms for benchmarking the models against human disease, based on molecular, morphologic, and biologic properties. Teams may focus on a single area, or integrate multiple components into a research strategy. The roles of team members should be clearly articulated and the complementary areas of expertise should be delineated. A clear plan for research collaboration is required.