



Prostate
Cancer
Foundation

2. Novel Therapeutic Targeting of ETS Gene Fusion and Lethal Prostate Cancer Signal Transduction Pathways

Statement of Problem

We now know that the majority of prostate cancers harbor chromosomal translocations involving ETS transcription factors. This has profoundly impacted the molecular understanding of this cancer. As in many hematological malignancies and sarcomas, translocation of genes in prostate cancer comprise both critical drivers of early tumor biology and potential targets for new antitumor drugs. We need to develop effective therapies to kill or selectively inhibit growth of translocation-containing tumors.

The PCF proposes team-oriented, cross-disciplinary approaches to novel therapeutics to battle ETS translocations in prostate cancer. This RFP will encourage new research teams with complimentary expertise to develop and apply innovative drug targets, therapeutics, or co-targeting opportunities in prostate cancers. These therapies will remove translocations and downstream gene products and pathways.

Proposed Solution

We are soliciting collaborative and multidisciplinary proposals to advance the treatment of prostate cancers defined by ETS translocations. These proposals should focus on three areas:

- (1) **Drug or target discovery in ETS-associated prostate cancer.** To drive the identification of small molecules and biologics that provide tool or lead compounds modulating ETS factor activity, either directly or indirectly. To identify new drug targets elaborated in the setting of oncogenic ETS deregulation.
- (2) **Preclinical or early clinical studies of rational therapeutics directed against ETS-associated prostate cancer.** To apply existing and emerging knowledge of prostate cancer oncogenic mechanisms to test new therapeutics with selective efficacy in ETS translocations, either alone or in combination (“co-targeting”).
- (3) **ETS cancer biology in prostate cancer.** To accelerate understanding of the tumor-promoting mechanisms caused by or associated with ETS translocation.
- (4) **Co-targeting strategies.** We invite investigations of co-targeting strategies related to tumor cell-stromal interactions and subsequent signaling. These paracrine interactions, for example, the case where stromal production of HGF interacts with Met receptor on adjacent tumor cells and leads to proliferation,

invasion and metastasis, are very common and are likely responsible for a portion of observed malignant behavior in prostate cancer. We are interested to know if tumor-stromal signaling co-targeting is necessary to arrest prostate cancer progression.

Key Criteria

- (1) **Innovative and transforming research.** Novel approaches with clear capacity to transform or revolutionize existing treatment avenues relevant to ETS-associated prostate cancer.
- (2) **Collaborative and multidisciplinary emphasis.** Meaningful academic collaborations between three or more investigators/groups with complementary expertise. Collaborations with the biotechnology and pharmaceutical industry are permitted and encouraged. However, no philanthropic funds from the Prostate Cancer Foundation will be awarded to any for-profit entity participating in academic for-profit research collaboration.
- (3) **Scientific merit.** Outstanding and rigorous proposals as determined by peer review.
- (4) **Application to ETS translocations in prostate cancer.** All proposals should address questions with clear relevance to biology and therapeutics of oncogenic ETS deregulation.
- (5) **Potential for rapid progression to clinical testing.** Proposals develop innovative alternative targeting strategies and have milestones with speedy clinical development will be given high priority. In addition, basic science approaches that enhance understanding of ETS tumorigenicity in prostate cancer are encouraged.