



4. New Predictive Research Models of Prostate Cancer Clinical Biology

Statement of Problem

The Prostate Cancer Foundation invites applications to develop a new generation of Experimental Models of Human Prostate Cancer. PCF will support collaborative efforts with extensive sharing of knowledge and reagents. Teams will design, construct, and characterize model systems mimicking advancing human prostate cancer at the tissue, cellular and molecular levels. The team needs demonstrated expertise in the generation and characterization of genetically engineered autochthonous animal models, xenograft and cell culture systems. Combined research, technological innovation, and extensive collaboration will be required. Applications from both individual investigators and groups of investigators are welcome. PCF hopes to replace the current xenograft and murine models through this funding mechanism.

The goal will be to speed developing, improving and validating effective prevention, detection, and therapeutic intervention strategies for human prostate cancer. New and improved cell and animal models are required to achieve these purposes. It is unclear to what extent existing models emulate the molecular and regulatory changes seen in human disease and reflect the various stages in disease progression. No models are available that emulate the multi-step processes of tumor initiation, progression, and spread. We need to understand the effects of the cancer microenvironment, including the tumor-stroma interactions and the immune system. Current models do not provide adequate guidance for intervention, especially in therapy development. Existing models have evolved with passaging, creating potential problems in lab-to-lab reproducibility.

Proposed Solution

To address these problems, the Prostate Cancer Foundation is issuing Requests for Proposals (RFPs) for support of research and infrastructure development with the goals outlined as follows:

- 1. Assessment and improvement of current models:** profiling existing models and benchmarking them against what is known about the human disease; engineering modifications of these models to improve their utility.
- 2. Development of next generation cell and xenograft models:** developing new cell and xenograft models derived from patient samples that reflect the genetics, progression, and tumor ecology of prostate cancer, and that provide insight into ways to overcome the historic difficulties of generating such models.
- 3. Development of next generation genetically engineered animal models:** developing a new generation of animal models based on current knowledge about

the molecular and cell biology of prostate cancer that mimic the initiation, progression, and spread of prostate cancer, and the role of stroma and immunity.

- 4. Maintenance of access and quality control:** developing mechanisms to ensure that the scientific community has access to and uses the appropriate and accurately characterized models.

RFPs can be responsive to one or more of these goals. All proposals should include extensive mechanisms for “benchmarking” the models against the human disease, based on molecular, morphologic, and biologic properties.

- 1. Assessment and improvement of current models.** Substantial gaps exist in knowledge about the genetics, epigenetics, gene expression, signaling activities, and drug sensitivity of existing models, including cell lines, xenografts, and animal genetic models. Little information is available about ways that the tumor ecology (e.g. stroma, site, immune system) affects these parameters. We seek proposals that will provide new and potentially useful information about the clinical origins, molecular profiles, drug sensitivities, and biological behaviors of existing models and the ways that these are affected by cell or tumor environment (e.g. growth in matrix, mixed cultures, stroma, sites of implantation, etc.) Applications may also include proposals for improving these models, such as modification of genetics or of visualization by imaging. In all cases, determining the relationship of these parameters to the human disease should be included where possible.

- 2. Development of next generation cell and xenograft models.** Only a limited number of prostate cancer xenografts have been generated, and only a very few of these have successfully been established as cell lines. The reasons for this low rate of generating stable cell lines and xenografts despite extensive efforts are unclear, and we seek proposals for new approaches to developing xenografts and cell lines that reflect the various stages of prostate cancer initiation and progression, that recapitulate disease behavior in vivo and/or in vitro, and that shed light on the characteristics of prostate cancer that have been barriers to the generation of a more widely representative portfolio of prostate cancer models derived from patient materials. For example, xenografts derived from clinical bone metastases and xenografts when implanted into mouse tibia or femur result in the characteristic osteoblastic response are highly desired.

- 3. Development of next generation animal models.** Given the vast amount of information gained through genomic, proteomic and epigenetic studies it should be possible to apply this knowledge to develop a new class of animal models that mimic progressive and fatal prostate cancer. The goal is to obtain models that faithfully and reproducibly recapitulate one or more of the molecular and biochemical aspects of prostate biology, such as inflammation, angiogenesis, the role of androgen receptor signaling, marker protein production, seminal vesicle invasion, extracapsular extension, distant site metastasis (especially to the bone) and emergence of the androgen depletion independent disease. It is anticipated that efforts to combine these new models with robust imaging technologies will greatly facilitate the ability to utilize these models. The

PCF encourages proposals that (i) exploit novel techniques to target, regulate and manipulate the expression of genes, siRNAs, and other genetic elements in the various compartments of the prostate gland, its precursors and immediate microenvironment, (ii) establish casual relationships between genetic events, signaling pathways, tumor microenvironment and progressive disease, (iii) guide the selection and validation of therapeutic targets, (iv) elucidate the genetic basis of cancer susceptibility (v) test novel agents for tumor prevention and (vi) help discover pre-malignant molecular and genetic changes that can be exploited for early detection. The models may represent genetically engineered transgenic, knock-in and/or knock-out animals that exploit conditional activation or repression systems as well as xenografts, or cell based systems.

4. Maintenance of access and quality control. To ensure that this work has the maximum benefit in understanding, preventing, and treating prostate cancer, all models and materials developed with this support must be available to the scientific community – both the academic community and the commercial sector. A plan for ensuring the distribution of these materials and an affirmation that such material sharing will occur, must accompany all applications for this support. Royalties and protection of intellectual property are not precluded, but must not be substantial barriers to wide utilization of the models. To maintain quality control, all profiling data for both new and existing models must be posted on a webpage maintained by the Prostate Cancer Foundation, and available to the scientific community. In consultation with the investigators, the PCF will determine key diagnostic characteristics or response criteria for each model that investigators can utilize to verify the identity of the materials they are working with. Future support from PCF will be contingent on investigators demonstrating that they have benchmarked their model