NATIONAL CANCER INSTITUTE | SBIR DEVELOPMENT CENTER

# THE SPECIFIC AIMS PAGE

**The specific aims page is a critical page in a Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) application.**

The aims page should be treated as a standalone page from which a reviewer can gain a reasonable understanding of the critical components of the project without reading any other parts of the application.

**The first half to two-thirds of the aims page should cover key background information.**

Applicants are allowed only one page for their specific aims. Because three or four primary reviewers are responsible for scoring an application, it is fairly common practice for the primary reviewers to be the only reviewers on the panel to read the application in its entirety. However, for applications that are discussed, the final score will be set after the discussion in the room with 20+ additional peer reviewers.

The NIH Center for Scientific Review receives dozens of applications for each meeting, and other reviewers focus on the Abstract, Significance, and Specific Aims. Therefore, it is critical that the aims page convey why this technology should be funded of the approximately 1,000 applications that are received by the NCI SBIR/STTR program annually.

**The background should clearly convey three things:**

## 01 THE PRODUCT

A clear product description is critical to an SBIR application and is often one of the key differences in distinguishing it from an academic application. Academic applications can often focus on the scientific advancement or knowledge gain, but every part of an SBIR application should focus on the product. Key steps that have been taken toward product commercialization should be highlighted, such as patent filing and discussions with regulatory agencies.

## 02 THE SIGNIFICANCE

The significance of the project should be clear from the aims page without turning to other parts of the application. A problem/proposed solution format often works well to convey significance. If there is an unmet clinical need, it will help the application for this need to be clearly stated.

## 03 THE INNOVATION

How will the product change the current paradigm or practice? How will cancer patients benefit from this product being commercially available? The aims page should convey this information as well as provide some textual highlights of the preliminary data as supporting evidence that the product will perform as proposed.

**The second half to one-third of the aims page should state your specific aims.**

## AIMS & MILESTONES

An often successful format for the aims page is one in which a clear aims statement is made in bold, followed by key assays and models that will be used to achieve the aim, and appropriate milestones. It is critical that each aim have clearly articulated success criteria. Whenever reasonable, the success criteria should be defined by quantitative metric(s). However, for cases in which only qualitative success criteria are appropriate, they should be clearly stated. For fast-track applications, clear go/no-go decision criteria should be stated to justify transitioning from Phase I to Phase II components.

## NEXT STEPS

A statement of next steps is often a nice way to wrap up an aims page. A statement about what will be accomplished during Phase II (for Phase I applications) or after the award ends (for Phase II applications) allows reviewers to judge whether the aims will appropriately set up the project to move on to the next step. A statement of next steps also provides an opportunity to show reviewers that the company is focused on moving the product forward on a path to commercialization and that it will be using SBIR/STTR funding appropriately to help move the product forward.

Overall, the SBIR application must be focused on the product, and each section should focus on how the proposed work will improve or move the product toward commercialization.

**Most important, use the aims page to show how your product, once commercialized, will benefit cancer patients.**

## SPECIFIC AIMS

High-risk types of human papillomaviruses (HPV) are responsible for virtually all cases of human cervical carcinoma, as well as an increasing number of other HPV-associated malignancies, including those of the head and neck, anus and vulva. One growing group of patients particularly affected by HPV includes those with compromised immune systems resulting from HIV infection, other diseases or medical treatments. Perhaps the most noteworthy advance in recent years has been the development of safe and effective vaccines targeted against HPV. However, these vaccines are not beneficial for patients who are already infected, appropriate for use in patients with compromised immune systems, or readily available in all developing countries. Once cancer has developed, current treatment options are relatively limited and focus on physically removing the cancer through surgery. Unfortunately, tumors frequently return, particularly following late-stage diagnosis and/or if the patient is immunocompromised. Chemo- and radio-therapies that rely on the induction of apoptosis in $HPV^+$ tumor cells are relatively ineffective, primarily due to the actions of a virus-encoded oncoprotein, E6, that subverts both intrinsic and extrinsic apoptotic pathways by accelerating the degradation of key molecular players. Therefore, new approaches that can eliminate HPV-containing cells, even in the absence of a functional adaptive immune system, must be developed.

To meet this need, we propose to combine spinacine, a small, naturally occurring molecule whose E6-inhibiting abilities were recently discovered by our laboratory, with existing therapeutic approaches that function by inducing apoptosis. Our laboratory and others have shown that high-risk versions of the HPV E6 oncoprotein induce resistance to both intrinsic and extrinsic apoptosis by mediating the rapid degradation of p53, caspase 8 and FADD [1-6]. The absence of these molecules in turn leads to the protection of infected cells from agents that would otherwise induce programmed cell death. To counter this, we searched for molecules that would inhibit the ability of E6 to bind to its cellular apoptotic partners by screening over 3000 compounds. Spinacine was selected as our lead candidate, because it is able to block the binding of E6 to both caspase 8 and E6AP, thereby sensitizing $HPV^+$ cells to apoptosis triggered by agents such as TRAIL (a ligand that selectively induces apoptosis in cancer cells) and chemotherapeutic drugs such as cisplatin and doxorubicin. As predicted by our model, spinacine restores cellular levels of caspase 8, FADD and p53. Together, these observations support the *scientific premise* of our proposal.

The *long-term goal* of our laboratory is to develop novel, effective therapies for patients suffering from HPV-associated malignancies, and the *overall objective* of this current application is to move our exciting *in vitro* and cellular observations into a mouse xenograft model. In this model, we will 1) Assess the toxicity of spinacine, and 2) Determine the *in vivo* effectiveness of a combinational therapy that pairs spinacine with an agent that induces apoptosis (TRAIL or cisplatin). The *conceptual framework* supporting this proposal states that by targeting the E6/apoptotic protein interactions with small, drug-like molecules such as spinacine, we will be able to increase cellular levels of p53, caspase 8 and FADD. This will sensitize cells to apoptosis, thereby enabling agents that induce apoptosis to eliminate or decrease the growth of $HPV^+$ tumors *in vivo*. All necessary assays, reagents and expertise are available to us, and for these reasons, we are well positioned to immediately undertake the work described in the following specific aims:

> **Specific Aim 1: Determine the toxicity of spinacine in mice.** We will assess the toxicity of spinacine in mice, defining the maximum tolerated dose and identifying the optimum dose with which to carry out experiments designed to test its efficacy.
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> **Specific Aim 2: Evaluate the ability of spinacine to synergize with TRAIL- and/or chemo-based therapies to reduce or eliminate $HPV^+$ tumor growth.** We will assess the ability of spinacine to synergize with hrTRAIL and/or the DNA damaging drug cisplatin to inhibit tumor growth in a xenograft model.

At the conclusion of this work, we will have 1) Determined the toxicity of the E6-inhibiting molecule spinacine in mice, and 2) Evaluated the effectiveness of combining spinacine with TRAIL- and cisplatin-based treatments in an animal model. This work has the potential to save the lives of patients suffering from HPV-associated malignancies.