Chapter 1

General introduction and thesis overview
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As many experts have already begun to assert, combination therapies may be “the key to most cancer treatments”\(^1\). This view is becoming increasingly accepted amongst experts in the field of cancer research as both our knowledge of disease progression and our understanding of the limitations of current therapeutic strategies increase. Robert Weinberg has eloquently described the current situation and the changing views in the field as the following excerpt from the textbook of the Biology of Cancer, 2007 shows\(^2\):

> “Traditionally, new drugs have been evaluated as single agents during preclinical development and phase I trials. This practice contrasts with the growing belief of cancer researchers that most monotherapies are unlikely to yield curative treatments and that, with rare exceptions, truly successful clinical outcomes will depend on the use of a combination of anti-cancer drugs.”

In this vein, the work described in the following chapters was performed in order to investigate the potential of increasing the efficacy of vascular-targeted cancer therapies through various combination strategies. In these chapters, new combination strategies and optimized drug combinations are assessed based on screening for increased efficacies in various in vitro and in vivo preclinical models.

The potential of angiogenesis inhibition as a form of cancer therapy was first recognized by Judah Folkman in 1971. He theorized that tumor growth was angiogenesis dependent and that targeting tumor neovascularization could provide a new form of cancer therapy\(^3\). This revelation led to the initial hope in the early 90’s that anti-angiogenic compounds would represent a unique approach to cancer therapy, as it was believed that targeting angiogenesis through non-malignant, and therefore genetically stable endothelial cells, would allow for the avoidance of drug resistance\(^4\). These initial hopes, however, were not sustained, as clinical experience quickly revealed that resistance to anti-angiogenic cancer treatment strategies was possible, and in many cases inevitable, and effective clinical therapies with angiogenesis inhibitors alone have been nearly non-existent\(^5\). Notwithstanding, the dependence of tumor growth on angiogenesis has been widely accepted and has been included as one of the malignant hallmarks of cancer\(^6\). Regardless of its possible limitations, targeting tumor angiogenesis has become a viable treatment strategy. Various anti-bodies targeted to angiogenic growth factors and receptor tyrosine kinase inhibitors targeting angiogenic growth factor receptors have been developed and are routinely implemented in the clinical treatment of cancer today\(^7\)-\(^9\).

It has been established that when used as single drug therapies, many of these agents have a limited capacity to enhance progression free and overall patient survival benefits, mainly due to
disease and/or patient heterogeneity, toxicity and the development of drug resistance. As angiogenesis is an intricately regulated process controlled by a system of highly robust and redundant cell signaling pathways, targeting multiple and possibly distinct signaling pathways may allow for more effective inhibition, as well as the possibility of identifying synergistic drug combinations through the lateral inhibition of multiple targets in non-overlapping pathways. The development of optimized drug combinations therefore represents an avenue by which effective tumor growth inhibition could be achieved via anti-angiogenic mechanisms. Drug combinations may also allow for a reduced probability of developing drug resistance as well as the potential to minimize side effects as a result of enhanced selectivity due to multi-target interactions.

The chapters of this thesis are divided into two parts. Part I focuses on the use of anti-angiogenic strategies in the treatment of cancer and the optimization of multi-drug combinations of such targeted agents. Part I will be introduced by a review (Chapter 2) which addresses the use of antiangiogenics in cancer therapy and methods to increase its clinical efficacy through its combination with different treatment modalities. This is followed by a research article (Chapter 3) which describes the in vitro and in vivo characterization of an experimental anti-angiogenic compound and demonstrates the capacity of angiogenesis inhibitors to reduce tumor growth in vivo. Chapter 4 will provide a brief introduction to the motivation for developing optimized multi-drug combinations for the treatment of cancer and introduce the optimization techniques used in the following research chapters. Additional background on the use of response surface modeling to control or predict the behavior of complex biological systems is provided in Chapter 5. Finally, Chapters 6 and 7 will describe two separate in vitro drug optimization studies.

Part II is focused on the use of angiostatic agents in combination with light based-therapies for the treatment of cancer and non-cancerous neovascularization based diseases. This will mainly include the combination of angiogenesis inhibitors with photodynamic therapy (PDT). PDT can elicit anti-cancer effects through the selective closure of blood vessel. This frequently leads to hypoxia in the treated tumor tissue and to the subsequent induction of angiogenesis, which represents a large limiting factor in the efficacy of this treatment for cancer. Therefore, the combination of anti-angiogenics with PDT carries the potential to enhance efficacy by inhibiting this PDT-induced angiogenic tissue response. Anti-angiogenic can also be applied as a pre-treatment to induce a vascular normalization effect in tumor vasculature. This phenomenon can help to enhance the delivery of cytotoxic drugs, as well as increase tumor oxygenation, which can enhance the efficacy of oxygen-dependent therapies such as PDT. Part II of this thesis will be introduced based on a review chapter (Chapter 8), describing the use of angiogenesis inhibitors
in combination with PDT. This is followed by three research chapters (Chapters 9-11) investigating different combination therapy strategies involving angiogenesis inhibitors and light therapy in preclinical tumor models.

References