



Preface

Emerging Nanomedical Solutions for Angiogenesis Regulation



This special issue on *Angiogenesis Regulation* in *Advanced Drug Delivery Reviews* is dedicated to the 10 year memorial of **Judah Folkman**, who founded the field of angiogenesis research [1]. Angiogenesis is the physiological process by which new blood vessels form from pre-existing vessels [2]; a process that occurs during embryonic development, growth, and wound healing. However, pathological angiogenesis is also a fundamental process involved in more than 80 diseases including the malignant transformation of tumors, tumor growth, and metastasis [3,4]. The field of angiogenesis began in the early 1970s when Judah Folkman proposed that tumor growth would be halted if the tumor were deprived of a blood supply. Fifty years later, Folkman's controversial idea is now widely accepted and angiogenesis inhibitors hold great promise for the treatment of cancer and other angiogenesis-dependent diseases. This special issue gives the ADDR readers an up-to-date comprehensive view on the different aspects of therapeutic and imaging toward diseases with angiogenic etiologies. The following articles in this issue also present the development of new macromolecules- and nanoparticle-based systems to overcome many challenges in identifying and treating angiogenesis-related diseases and their potential applications.

Since the approval of bevacizumab as anti-angiogenic therapy in 2004 by the FDA, an array of angiogenesis inhibitors have been developed and approved. However, results were disappointing with regard to their therapeutic efficacy. RNA interference approaches offer the possibility of rational design with high specificity, lacking in many current drug treatments for various diseases including cancer. Gene therapy has become a promising strategy for the treatment of such a disordered state through the introduction of exogenous nucleic acids that express or silence the target agents, thereby engineering neovascularization in both directions. **Satchi-Fainaro and her coworkers** summarize the advances in the last decade in the field of angiogenesis-targeted RNA interference approaches, with special emphasis on oncology applications, including experimental evidence and clinical trials data on angiogenesis regulation by RNA interference. **Green** follows up on this theme showing key factors targeted for therapeutic angiogenesis and anti-angiogenesis gene therapy, non-viral nanoparticle-mediated approaches to gene delivery, and recent gene therapy applications in pre-clinical and clinical trials for cancer and other diseases such as ischemia, tissue regeneration, and wet age-related macular degeneration.

The evaluation and modulation of the enhanced permeability and retention (EPR) effect in each tumor or metastasis is currently a major issue still limiting the impact and activity of nanomedicines. **Kiessling and Lammers** describe the different methods used for the alteration of angiogenic vessels to improve drug delivery to tumors. Their review

also sheds light on pharmacological (permeabilisation, normalisation, disruption, and promotion) and physical (hyperthermia, radiotherapy, sonoporation, and phototherapy) strategies to enhance EPR-mediated drug targeting to tumors. The article by **Aime and colleagues** focuses on contrast-enhanced MRI as a versatile tool for functional and molecular characterization of pathological angiogenesis. Aime and coworkers highlight the benefits of nano-sized systems that can be tailored and decorated with targeting and therapeutic moieties, which can amplify the MRI response. **Blinder, Urban and colleagues** present to the readers of ADDR the latest and most novel imaging approaches used to study different aspects of brain vasculature and vascular dynamics alongside neuronal dynamics; focusing mainly on two-photon microscopy and functional ultrasound.

There is a strong focus in the nanomedicine field at present on looking beyond the extravasation-dependent ("passive") tumor targeting of the EPR effect for nanomedicine delivery and efficacy. In addition to the evaluation of EPR-mediated drug delivery, this ADDR special issue proceeds with the topic of targeted delivery of drugs to tumors, which represents a significant advancement in cancer diagnosis and therapy [5]. The next two articles of this issue focus on the enhancement of drug delivery and therapeutic outcome due to molecules expressed on cell surface, such as integrins, which are cell-adhesion molecules involved in angiogenesis signaling pathways and are overexpressed in diverse angiogenic processes. **Vicent and coworkers** cover recent and relevant examples of different integrin-assisted nano-systems including polymeric nano-constructs, liposomes, and inorganic nanoparticles applied in drug or gene therapy as well as imaging and theranostics (*therapy* and *diagnostics*). Their review critically addresses the overall benefits of integrin-targeting, with a special focus on arginine-glycine-aspartic (RGD)-containing peptides that bind to specific integrins. Further, the review by **David** describes the most studied peptide ligands aimed at targeting cells in the tumor microenvironment, discusses major obstacles and principles in the design of ligands for drug targeting and provides an overview of homing peptides in ligand-targeted nanomedicines that are currently in development for cancer therapy and diagnosis.

In the late 19th century, William B. Coley noticed that injection of streptococcal organisms to sarcomas, led to shrinking of the tumors [6]. This observation has opened the path to research the effects of the immune system on cancer cells and their microenvironment. It is now clear that virtually every neoplastic lesion contains immune cells and that the tumor-associated inflammatory response enhances tumorigenesis and cancer progression [7]. New nano-sized therapies that can simultaneously control cancer progression and inflammation within the

tumor microenvironment will yield greater therapeutic efficacy. **Mulder et al.** bring to the readers of ADDR a comprehensive overview on a family of devastating diseases with different phenotypic consequences, such as atherosclerosis, rheumatoid arthritis, inflammatory bowel disease and cancer that are driven and progress by inflammation and angiogenesis. **Jain et al.** summarizes the challenges in the treatment of primary and metastatic brain tumors using anti-angiogenic therapies alone or in combination with radio-, chemo- and immuno- therapies. This review article also discusses the emerging strategies to improve the treatment outcome using both pharmacological and physical approaches and their limitations.

The uniqueness of this special issue of ADDR on Angiogenesis Regulation is that it integrates the very latest innovative and translational nanoparticle design strategies to further improve the treatment efficacy and to modulate diverse and complex pathologies that are angiogenesis-related. Starting with oligonucleotide-, EPR- and ligand-mediated delivery systems to tumors, and proceeding with the imaging characterization of pathological angiogenesis. Finally, ending with the topic of inflammation within the tumor microenvironment which plays a major role in tumor progression and response, and gains great focus in the academic, industrial and clinical research and development community.

We would like to thank all contributors who made this issue on Emerging Nanomedical Solutions for Angiogenesis Regulation possible. We sincerely hope that it will allow drug delivery researchers to become inspired by the diverse aspects of the complex puzzle of tumor cells and their microenvironment relationship and how the design of macromolecules and nanotherapeutic systems can address the challenges they bring and introduce a new way of thinking. **We believe that this "out of the box" approach is based on the sound foundation and the**

inspirational legacy that Judah Folkman has left behind for the well-being of society.

References

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