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The challenges facing block copolymer micelles for cancer therapy: *In vivo* barriers and clinical translation☆

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ABSTRACT

The application of block copolymer micelles (BCMs) in oncology has benefitted from advances in polymer chemistry, drug formulation and delivery as well as *in vitro* and *in vivo* biological models. While great strides have been made in each of these individual areas, there remains some disappointment overall, citing, in particular, the absence of more BCM formulations in clinical evaluation and practice. In this review, we aim to provide an overview of the challenges presented by *in vivo* systems to the effective design and development of BCMs. In particular, the barriers posed by systemic administration and tumor properties are examined. The impact of critical features, such as the size, stability and functionalization of BCMs is discussed, while key pre-clinical endpoints and models are critiqued. Given clinical considerations, we present this work as a means to stimulate a renewed focus on the unique chemical versatility bestowed by BCMs and a measured grasp of representative *in vitro* and *in vivo* models.

Contents

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1. Introduction

The medical application of micelle-based nanotechnology dates back to the pioneering work of Speiser at the ETH in Zurich with the development of drug delivery systems for controlled release. In 1976, he explored the use of solidified micelles, termed 'nanoparts', and put forth that "the partition of drugs in such nanoparts seemed to be promising as a new parenteral drug delivery system for long-term therapy" [1,2]. The principles of this seminal publication indeed led to the first drug delivery application of block copolymer micelles (BCMs) by Ringsdorf [3]. Decades later, impactful contributions by Kataoka, Kabanov and others have resulted in BCM formulations that have now reached late-stage clinical development [4–6].

BCMs are nano-sized aggregates of amphiphilic copolymers with a size range of about 10 to 100 nm (Fig. 1). They consist of a hydrophobic core that serves as loading space for hydrophobic drugs and an outer shell, or corona, comprised of hydrophilic material that provides a protective interface between the micelle core and external medium. In aqueous media, at copolymer concentrations at or above the critical micelle concentration (CMC), self-assembly results in micelles possessing greater thermodynamic and kinetic stability than that achieved using small-molecule surfactants [7,8]. Indeed, the copolymers can be tailored to result in stable micelles that are optimized for tumor-selective delivery of therapeutic agents [9–11]. By formulating small-molecule chemotherapeutics in BCMs, their solubility can be enhanced while their pharmacokinetic, as well as biodistribution profiles, can be favorably altered. Such modulation of the *in vivo* distribution of small-molecule agents enables a reduction in often dose-limiting normal tissue toxicities and can yield significant improvements in their therapeutic index [12,13]. Therefore, BCMs provide a functional platform for the design of nano-sized drug delivery systems (NDDSs) to overcome the challenges faced by conventional chemotherapeutics. The chemical diversity of monomers that form the copolymer building blocks offers synthetic versatility enabling customization at the molecular level, and control of the physico-chemical properties of the BCMs (*i.e.* size, morphology, stability, and surface properties) [14]. The ease of chemical modification of the copolymers also allows for optimization of drug loading (*via* physical encapsulation or conjugation) and release, as well as surface functionalization with radionuclides and/or targeting moieties (Fig. 1) [15–17]. Initially regarded as "pharmaceutical curiosities" [2], BCMs presently have the potential to offer three key advantages over conventional formulation strategies: (1) increased solubility of the encapsulated drug [18], (2) high adaptability of the physico-chemical properties of the BCM system [11,19], and (3) improved biodistribution of drug and thereby reduced systemic toxicity [20].

However, despite intense research activity on NDDSs such as BCMs, and subsequently, an extensive number of publications generated on this topic over the past several decades (Fig. 2), clinical translation has proven challenging. In particular, the achievement of significant improvements in efficacy, characterized by concomitant reductions in tumor burden, disease recurrence and metastatic progression, remains an elusive goal [21–25]. Today, NDDS-based cancer therapy finds itself at a crossroads, challenging the unique promise and ultimate clinical relevance of nanomedicines [22,23,26]. Of note, its disputed state brings into question the future of BCMs, nearly four decades following their emergence as a drug delivery platform. In particular, it has become increasingly evident that the realization of substantial clinical benefits requires clear elucidation of the biological complexity of the drug delivery process and its use as a driving force to guide the development of future nanomedicines. The major challenge remains overcoming the physiological and biophysical barriers imposed by the host, tumor and host–tumor interactions, while integrating due recognition of the vast extent of inter-patient and intra-tumoral heterogeneity [7,27]. BCMs, in particular, stand out among the advanced NDDSs owing to their potential versatility. Yet, their viability as a successful drug delivery platform relies on the design and implementation of novel approaches that exploit and/or overcome pathophysiological mechanisms.

This review aims to provide a discussion of the attributes and shortcomings of BCM-mediated cancer therapy, particularly within the context of biological barriers and, ultimately clinical translation. The design of new and more effective cancer therapy strategies calls for a comprehensive understanding of the underlying pathological mechanisms hindering and/or helping the targeted delivery of BCMs to tumors, the factors driving the success of NDDSs, as well as an awareness of the significant discrepancies observed between pre-clinical and clinical outcomes. First, we aim to provide a review of the key *in vivo* barriers impeding the effective delivery of chemotherapeutics *via*

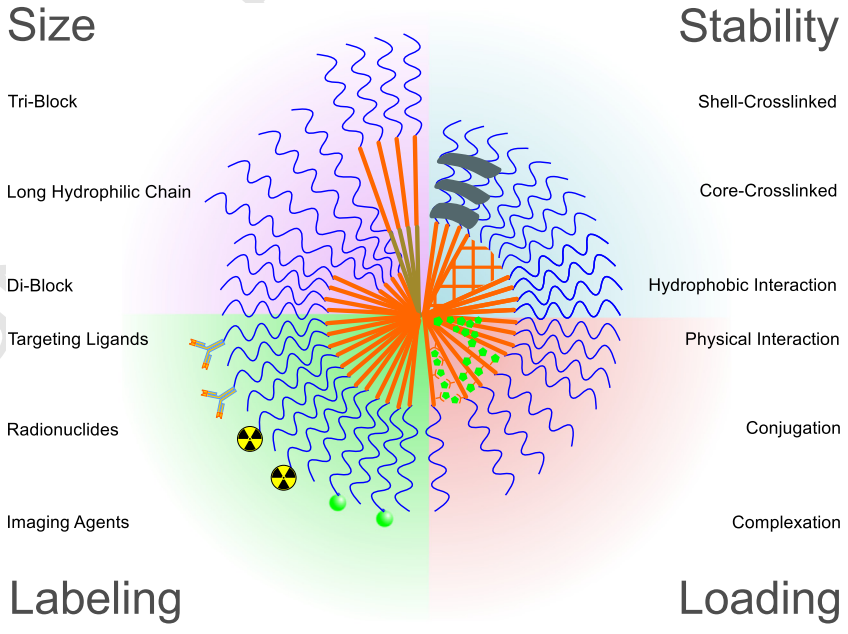

Fig. 1. Versatility of BCM chemistry. BCMs provide a flexible platform for the design of NDDSs given the synthetic versatility that enables customization at the molecular level. Among a wide range of factors which influence key physico-chemical properties and *in vivo* performance, we illustrate select parameters which have been varied as a means to control size, stability, loading and labeling of BCMs.

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