First-in-class Phosphorus Dendrimers From Concept to Clinic: Lessons Learned Moving Forward

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Abstract

The development of biocompatible dendrimers as drugs themselves or nanocarriers represents a promising approach for the discovery of new arsenals that can be used to take down unmet medical needs *via* new therapeutic modalities. These developments are possible due to the exceptional physicochemical properties of dendrimers, including their biocompatibility, as well as their therapeutic activity as nanocarriers and drugs themselves. Both the engineered nature of the dendrimer surface and its surface density are crucial and dictate their biological interactions with living systems in terms of biological activity and physicochemical properties. Numerous studies present the use of dendrimers as nano-carriers through encapsulation (drug loading) and electrostatic complexation, which preserves the chemical integrity and pharmacological properties of the drugs, or conjugation, such as with anti-cancer agents for targeted and non-targeted antineoplastic therapy. Despite a large number of preclinical studies, very few dendrimers have crossed the 'valley of death' between preclinical studies and clinical trials. Thus, in the current clinical landscape, only a few numbers of pharmaceutical companies have succeeded in this way. After evaluating the main physicochemical properties related to the respective biological activity of dendrimers in general and phosphorus dendrimers in particular classified as first-in-class or best-in-class, we will examine and analyze, from a cursory glance, the advantages and disadvantages of these two strategies. Since several years, we designed and developed medium generation first-in-class phosphorus dendrimers for instance to take down tumors. In this direction, salient *in vivo* antitumor activities will be presented and discussed. Recently, we moved to original low generation of biocompatible phosphorus dendrimers showing noteworthy *in vitro* and *in vivo* biological activities including antitubercular and antitumoral potencies as well excellent physicochemical properties allowing possible clinical trials. Finally, the concepts of vertical and diagonal translation principles, previously introduced by Keegan Guidolin and Gang Zheng, were also presented and discussed in the potential roadmap of dendrimer development in clinic.