Nuclear Medicine and Biology 43 (2016) 215–225

Contents lists available at ScienceDirect

Nuclear Medicine and Biology

journal homepage: www.elsevier.com/locate/nucmedbio

The inextricable axis of targeted diagnostic imaging and therapy: An immunological natural history approach

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ARTICLE INFO

Article history:
Received 10 September 2015
Received in revised form 13 November 2015
Accepted 16 November 2015
Available online xxxx

Keywords:
Tilmanocept
Macrophage
CD206
Imaging
Immunodiagnostic
Immunotherapy

SUMMARY

In considering the challenges of approaches to clinical imaging, we are faced with choices that sometimes are impacted by rather dogmatic notions about what is a better or worse technology to achieve the most useful diagnostic image for the patient. For example, is PET or SPECT most useful in imaging any particular disease dissemination? The dictatorial approach would be to choose PET, all other matters being equal. But is such a totalitarian attitude toward imaging selection still valid? In the face of new receptor targeted SPECT agents one must consider the remarkable specificity and sensitivity of these agents. ^{99m}Tc-Tilmanocept is one of the newest of these agents, now approved for guiding sentinel node biopsy (SLNB) in several solid tumors. Tilmanocept has a K_d of 3×10^{-11} M, and it specificity for the CD206 receptor is unlike any other agent to date. This coupled with a number of facts, that specific disease-associated macrophages express this receptor (100 to 150 thousand receptors), that the receptor has multiple binding sites for tilmanocept (>2 sites per receptor) and that these receptors are recycled every 15 min to bind more tilmanocept (acting as intracellular "drug compilers" of tilmanocept into non-degraded vesicles), gives serious pause as to how we select our approaches to diagnostic imaging. Clinically, the size of SLNs varies greatly, some, anatomically, below the machine resolution of SPECT. Yet, with tilmanocept targeting, the SLNs are highly visible with macrophages stably accruing adequate ^{99m}Tc-tilmanocept counting statistics, as high target-to-background ratios can compensate for spatial resolution blurring. Importantly, it may be targeted imaging agents per se, again such as tilmanocept, which may significantly shrink any perceived chasm between the imaging technologies and anchor the diagnostic considerations in the targeting and specificity of the agent rather than any lingering dogma about the hardware as the basis for imaging approaches. Beyond the elements of imaging applications of these agents is their evolution to therapeutic agents as well, and even in the neo-logical realm of *theranostics*. Characteristics of agents such as tilmanocept that exploit the natural history of diseases with remarkably high specificity are the expectations for the future of patient- and disease-centered diagnosis and therapy.

1. Diagnosis and imaging: setting up the therapeutic continuum

In the preceding 25 years there has evolved a confluence of tumor biology ideology, nuclear medicine and surgical oncology that has led to the development of the theory of the "sentinel node" [1–5]. Data accrued over the intervening years have provided a confirmation of the sentinel node theory as it relates to the incorporation of sentinel lymph node detection/biopsy in breast cancer and melanoma patient outcome in surgical practice [6–14]. Sentinel node theory holds that there is a predictable anatomical relationship between the immediate tumor environment and the proximate lymphatic system such that assessment of this nexus can provide a reliable appraisal of the nodal disease stage and reduce or eliminate the need for expanded surgery as this relates to lymphadenectomy, and be equally predictive of nodal status with similar outcomes with regard to any such expatiated surgery [15–24]. The initial sentinel lymph node biopsy (SLNB) forays relied on the application of dyes injected into or around the tumor

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http://dx.doi.org/10.1016/j.nucmedbio.2015.11.007

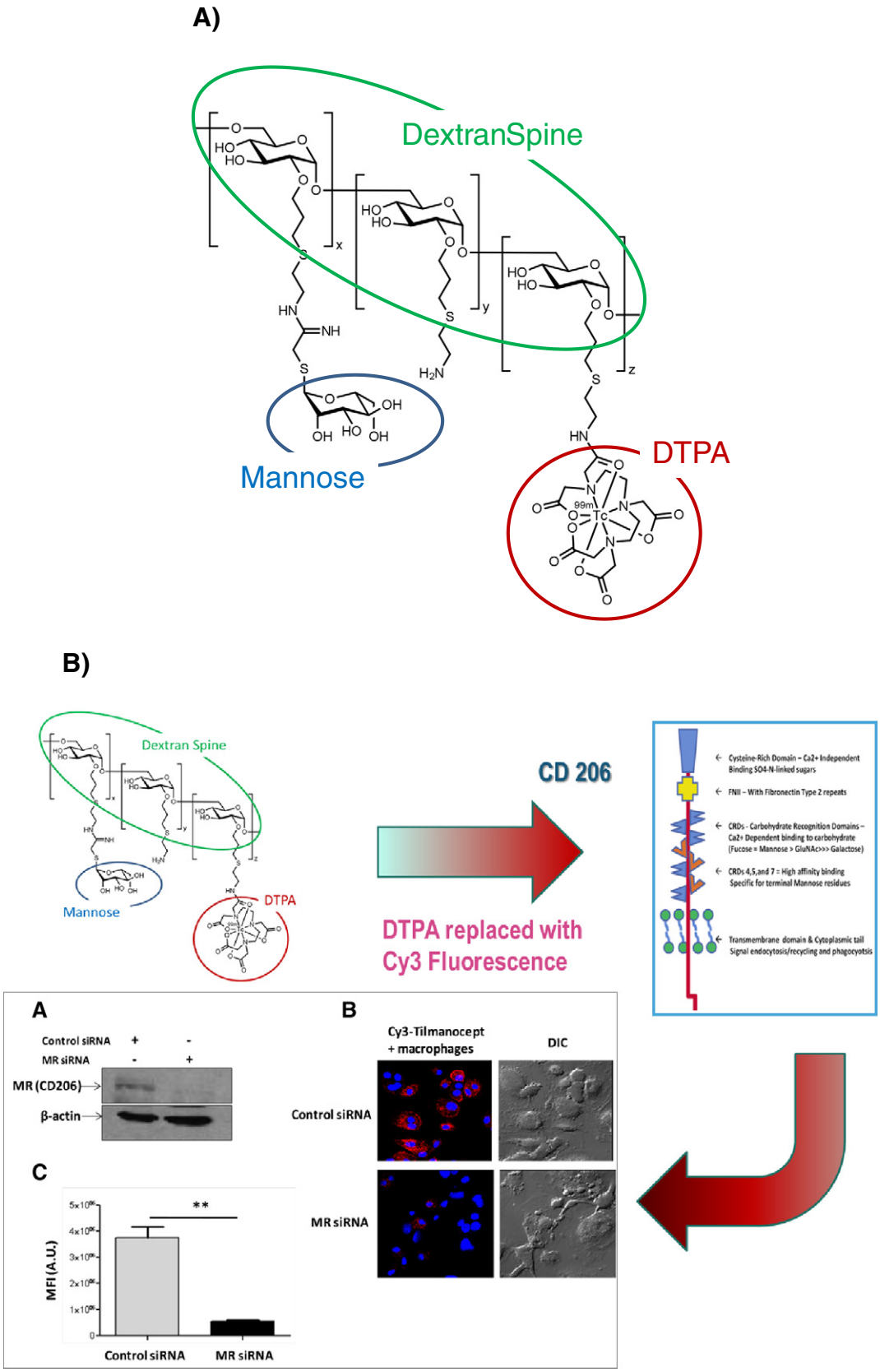

Fig. 1. A. ^{99m}Tc-tilmanocept (Lymphoseek®; Navidea). B. Tilmanocept specifically binds to CD206.

area, with visual tracing of these dyes, or "chasing" the drainage of the dyes into the lymphatic ducts and nodes. The flow and adsorption of the dyes into proximal nodes (and in many cases distal nodes) were implicative of a node's anatomic or biological linkage to the tumor bed and increased potential for the residence of tumor cells whose derivation was from the primary tumor [25–31]. This procedure of SLNB was