THE UNIVERSITY OF TOKYO

COINS Seminar #6

Current paradigm of therapeutic cancer nanomedicine and its prospective: A gap between preclinical and clinical Outcomes

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Venue: Room #56, Engineering building #5, The University of Tokyo

—Abstract—

The current paradigm of cancer nanomedicines relies heavily on long circulation time, enhanced permeability and retention (EPR) effect, and cell specific interactions.

EPR effect is the single most cited term in literature from the past decades covering cancer nanomedicine for therapy and diagnosis. It has been supported by high accumulation in the tumor of intravenously introduced nanoparticles. However, the degree of accumulation widely fluctuates in animal tumor models and clinical tumors. Although EPR effect may exist, its nature is not fully understood and there is no practical way to predict its extent, especially in clinical settings, for any given solid tumor. This presentation discusses the heterogeneity and potential uncertainty of the EPR effect.

The concept of a “Magic Bullet” implicitly presumed that soluble or nanosized drug carriers possessed a homing function to the targeted disease sites, solid tumors, because of their design for specific cancer cell interaction. This paradigm continues till now and intensive researches have been being conducted for the last three decades in this paradigm which has seemingly been proven in in vitro tests and small animal cancer models by xenografting human tumors or genetically engineering. However, the approach has not yet proven its efficacy in clinical settings. It is known that the accumulation of the drug carriers at a target tumor, which is limited to a small fraction of total dose, is governed by various physiological and physicochemical factors, such as vascular permeability and interstitial pressure, rather than specific secondary interactions.

Moreover, cancer cells and malignant tumors are not fully understood, and new discoveries continue to decipher new aspects of tumor origination, physiology, and cell biology. A tumor is not merely a large, isolated mass of identical cancer cells. Genetic instability contributes to the ability of cancer cells to survive, proliferate, and disseminate, but this same instability also leads to tumor cell heterogeneity and diversified epigenetic regulation. In addition, tumors are now gaining recognition as a sort of organized tissue/organ with stromal cells ostensibly recruited from the host body. Accordingly the current paradigm of EPR effect and targeted drug delivery which was developed based on an overly simplified tumor models may require modification or a shift to reflect at least current understanding of tumor physiology and cancer biology, particular

ly tumor heterogeneity. In addition due to the poor predictive power of current preclinical models for clinical outcome, we may need to review how closely current in vitro and in vivo models do resemble clinical tumors.

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