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Designing next-generation drug development in precision medicine

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Breakthrough next-generation sequencing (NGS) systems and computational network methods shape two main strategies in drugs-discovery design. First, based on spatiotemporal genomic clones evolution, novel targetable drugs can be discovered against genome-wide alterations. Primary tumor multiregional NGS analysis before and after neoadjuvant treatment can reveal both intratumor heterogeneity (ITH) and clonal evolution in response to this systemic treatment. Moreover, an innovative noninvasive method of repeated circulating cell-free tumor DNA (ctDNA) followed NGS (ctDNA-NGS) can reveal subclones of plasma levels at different time points. This monitoring of these patients can not only predict therapeutic resistance-based metastatic relapse but also can result in novel drugs development to prevent with high precision metastatic progression. Ultimately, comparison of ITH with ctDNA-NGS in future rationally designed clinical trial opens new horizons of comprehensive intrapatient heterogeneity (IPH) identification that could substantially improve tumor responsiveness and overall survival. Second, in a more distant future, approach understanding of noncoding genome variation and functionality along with exploitation of transcriptional networks, drive the future development of highly effective drugs disrupting deregulated cancer transcriptional biocircuits. Although this ENCODE project–based research direction reflects the pragmatic molecular interaction networks underlying critical biological processes; much more work and time is required for understanding how structural and functional genome changes are underlying therapeutic resistance and relapse. This speech is concentrated on these two main drugs-development strategies. The first one continues to be based on simple, single-gene linear transcription dogma agents. The second innovative highly complex transcriptional networks-based approach aims to the future discovery of drugs disrupting aberrant cancer transcriptional biocircuits.

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An anticancer approach where targeting and immunity physiologically merge

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Current anticancer therapies have two fundamental bases. One is chemical; the killing of cancer cells by the use of small molecular inhibitors that block crucial functional nodes downstream of Ras or downstream of PI3K. The other is immunological; the use of antibodies which block immune checkpoints or the modulation of cytokines involved in cancer immune interactions. Against this therapeutic background, stands the discovery that monomeric beta-galactoside binding protein (βGBP) a molecule recently identified as a cytokine produced by activated CD4+ and CD8+ T cells and by CD8+ memory cells is a specific physiological inhibitor of PI3K and Ras activity, valid intervention points for cancer therapy. Furthermore, βGBP is also a modulator of cytokines involved in oncogenicity, valid intervention targets for cancer immunotherapy. By controlling the PI3K and Ras cascades βGBP activates apoptotic pathways in cancer cells, but not in normal cells, independently of activating oncogenic mutations, absence of tumor suppressor function and drug resistance phenotype. As a therapeutic, βGBP is a strong suppressor of xenograft growth of human tumors carrying Kras mutations and TP53 deficiency in animal models. By inhibiting growth and survival signaling and by raising the expression of cytokines that promote antitumor immunity and abrogating at the same time the expression of cytokines that promote tumor functions βGBP exerts a dual anticancer action not paralleled by other anticancer agents.

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