



PEMED 2018

Personalized and Precision Medicine
International Conference

June 25-27, 2018 | Paris

Polypharmacology of Anti-Cancer Antibodies

Prof. Yosef Yarden

Weizmann Institute of Science, Israel

Both biological and pathological networks acquire robustness due to their modular structures. Hence, effective pharmacological interception of oncogenic networks requires polypharmacology, namely the use of pharmaceutical agents acting on multiple targets or disease pathways. Along with the ability of drug combinations to block acquired resistance to targeted cancer therapies, polypharmacology often translates to enhanced toxicity or adverse effects. Kinase inhibitors that simultaneously blocks several protein kinases exemplify the potential of polypharmacology. Thus, sorafenib, a drug approved for treatment renal cell cancer and hepatocellular carcinoma, inhibits two receptors, VEGFR and PDGF-receptors, as well as three members of the Raf family of cytoplasmic kinases.

In general, monoclonal antibodies (mAbs) elicit milder side effects, hence their use in combinations holds promise. However, due to the mono-specific nature of mAbs, their use in polypharmacology requires either applications of antibody mixtures or the use of genetic engineering (to design bi- or tri-specific antibodies). Remarkably, the immune system makes extensive use of polyclonal, rather than monoclonal antibodies. My lecture will describe pioneering, relatively effective and safe mixtures of mAbs, both approved and experimental. Lessons learned with treated breast cancer, melanoma and lung cancer will be discussed in an effort to define the principles governing effective utilization of antibody polypharmacology in oncology.

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