

Dissecting the mode of action of targeted leukemia therapies

Hugues de Thé^{1,2,3}

¹ Oncologie Cellulaire et Moléculaire, PSL University, INSERM UMR 1050, CNRS UMR 7241, Paris, France. ² INSERM UMR 944, CNRS UMR 7212, Université de Paris, IRSL, Hôpital St. Louis, Paris, France. ³ Department of Hematology, Hôpital Saint Louis (Assistance publique Hôpitaux de Paris) and Paris University, Paris, France.

Our understanding of cancer has tremendously progressed in the past 30 years. The successive discovery of oncogenes, tumor suppressor genes, our understanding of signaling pathways, epigenetic regulations, immune interactions and the technological power of multi-omics have profoundly changed our vision of these devastating diseases. We are now faced with new challenges: the diversity of tumors, which emerge as a myriad of orphan diseases, and the integration of multiple layers of information (notably functional genomics) into prediction of tumor behavior and therapeutic sensitivity to conventional or innovative agents.

Our own empirical approach has been to leverage a simple, highly medically relevant, but rarely explored parameter: unexpected but unambiguous therapy response in patients. Exploration of the biological bases of therapy response in different models of cancer has led to some unexpected findings. Perhaps because we started from patient response, many of the therapeutic models derived from these studies ultimately proved highly relevant to patient care.

In the field of leukemia, we will present the dissection of the basis for acute promyelocytic leukemia response to retinoic acid and arsenic. These converge onto mysterious nuclear domains, PML bodies, that enforce stress-induced senescence. Unexpectedly, the same pathway is implicated in MPN response to interferon, suggesting that it may represent a shared effector pathway of different anticancer therapies. These studies reconstructing therapy response have also unraveled novel important biological pathways (nuclear domains, proteolysis, stress response). Overall, tumors and tumor responses are a powerful source of inspiration for basic biology and academia-driven translational studies.