

After his cloning of RARB¹, identification of its self-regulation and identification of the first retinoic acid response element^{2,3}, during his MD/PhD training with A. Dejean, in P. Tiollais' laboratory, in the Pasteur Institute, Hugues de Thé has made a series of striking contributions to our current understanding of acute promyelocytic leukemia (APL) and the therapeutic effects of retinoic acid (RA) and arsenic trioxide (ATO). These now culminate in an elegant model to mechanistically explain the dramatic clinical efficacy of a combination of these drugs, which he promoted and has become the gold standard to cure APL patients.

These two drugs, RA and ATO, were empirically shown by Chinese clinicians to have clinical efficacy in APL, allowing him to discover APL-associated RARA alterations in St. Louis hospital⁴ and then, in collaboration with A. Dejean, to molecularly clone the PML/RARA driver of APL^{5,6}. He later showed that both RA and arsenic initiate PML/RARA protein degradation^{7,8} and proposed that the later could explain their therapeutic efficacy. His group extensively characterized the biochemical pathways involved⁸⁻¹², incidentally identifying a novel molecular pathway of protein degradation initiated by poly-sumoylation. Using mouse models, he was then able to shift away from the historical paradigm of transcription-driven APL differentiation to establish the novel degradation-based model for therapy response¹³⁻¹⁵. His studies demonstrated that PML/RARA loss allowed the reformation and activation of enigmatic nuclear domains, PML nuclear bodies¹⁶, which initiate senescence in response to stress. PML/RARA disrupts PML bodies¹⁷ and PML NB reformation resulting from PML/RARA degradation is required for therapy response¹³⁻¹⁵, reviewed in¹⁸⁻²⁰. The conclusions from these murine studies were confirmed by subsequent clinical studies, in particular the dramatic synergy between RA and arsenic for APL eradication²¹. Moreover, his recent identification of the arsenic binding site on PML/RARA^{11,12} and the key role of PML in therapy response¹⁵, was corroborated by identification of PML mutations in historical therapy-resistant patients^{22,23}. Clinically, his work²¹ was instrumental in initiating the first trials with the frontline RA/arsenic association, which ultimately cured virtually all APL patients, without any chemotherapy^{24,25} and are now used worldwide. Beyond this spectacular clinical success, this is one of the only malignancies where the mechanisms of therapy response are understood in some mechanistic details.

Overall, H de Thé's team has discovered the actual biochemical and cellular activities of RA and arsenic as targeted APL therapies, demonstrated the feasibility of drug-induced oncoprotein degradation and crafted the bases for the current clinical standard that allows definitive APL cures. His current research includes basic studies on the mechanisms of PML nuclear body biogenesis, sumoylation, redox controls and senescence²⁶⁻³⁰, as well as the structural details of ATO binding onto trimers of PML Box2¹². The key role of PML in APL response suggested that PML nuclear bodies may exert therapeutic benefit in other leukemias, as in interferon response of JAK2-mutant myeloproliferative neoplasms³¹ or NPM1c-driven AMLs treatment with Actinomycin D³².

A historical overview of the APL story was recently presented at a Cold Spring Harbor Laboratory Meeting: Cancer Genetics: History & Consequences:

https://drive.google.com/file/d/1AsiYOiE8CKl_s_nxPWHYlksV1Gtdxwq7/view

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