After his cloning of RARB [1], 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 hospital [4] 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 involved [8-12], 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 response [13-15]. His studies demonstrated that PML/RARA loss allowed the reformation and activation of enigmatic nuclear domains, PML nuclear bodies [16], which initiate senescence in response to stress. PML/RARA disrupts PML bodies [17] and PML NB reformation resulting from PML/RARA degradation is required for therapy response [13-15], reviewed in [18-20]. The conclusions from these murine studies were confirmed by subsequent clinical studies, in particular the dramatic synergy between RA and arsenic for APL eradication [21]. Moreover, his recent identification of the arsenic binding site on PML/RARA [11,12] and the key role of PML in therapy response [15], was corroborated by identification of PML mutations in historical therapy-resistant patients [22,23]. Clinically, his work [21] 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 senescence [26-30], as well as the structural details of ATO binding onto trimers of PML Box2 [12]. 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 neoplasms [31] or NPM1c-driven AMLs treatment with Actinomycin D [32].

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

https://library.cshl.edu/Meetings/Cancer-Genetics/video-pages/de-The.php

References:

1. de The, H., Marchio, A., Tiollais, P., and Dejean, A. (1987). A novel steroid thyroid hormone receptor-related gene inappropriately expressed in human hepatocellular carcinoma. Nature *330*, 667-670. 10.1038/330667a0.
2. de The, H., Marchio, A., Tiollais, P., and Dejean, A. (1989). Differential expression and ligand regulation of the retinoic acid receptor alpha and beta genes. The EMBO journal *8*, 429-433.
3. de Thé, H., Vivanco-Ruiz, M.d.M., Tiollais, P., Stunnenberg, H., and Dejean, A. (1990). Identification of a retinoic acid responsive element in the retinoic acid receptor beta gene. Nature *343*, 177-180.
4. Chomienne, C., Ballerini, P., Balitrand, M., Huang, M., Krawice, I., Castaigne, S., Fenaux, P., Tiollais, P., Dejean, A., Degos, L., and de Thé, H. (1990). The retinoic acid receptor is rearranged in retinoic acid sensitive promyelocytic leukemias. Leukemia *4*, 802-807.
5. de The, H., Chomienne, C., Lanotte, M., Degos, L., and Dejean, A. (1990). The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature *347*, 558-561. 10.1038/347558a0.
6. de Thé, H., Lavau, C., Marchio, A., Chomienne, C., Degos, L., and Dejean, A. (1991). The PML-RAR alpha fusion mRNA generated by the t(15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR. Cell *66*, 675-684.
7. Zhu, J., Gianni, M., Kopf, E., Honore, N., Chelbi-Alix, M., Koken, M., Quignon, F., Rochette-Egly, C., and de The, H. (1999). Retinoic acid induces proteasome-dependent degradation of retinoic acid receptor alpha (RAR alpha) and oncogenic RAR alpha fusion proteins. Proc. Natl. Acad. Sci. USA *96*, 14807-14812.
8. Zhu, J., Koken, M.H.M., Quignon, F., Chelbi-Alix, M.K., Degos, L., Wang, Z.Y., Chen, Z., and de The, H. (1997). Arsenic-induced PML targeting onto nuclear bodies: implications for the treatment of acute promyelocytic leukemia. Proc. Natl. Acad. Sci. USA *94*, 3978-3983.
9. Lallemand-Breitenbach, V., Zhu, J., Puvion, F., Koken, M., Honore, N., Doubeikovsky, A., Duprez, E., Pandolfi, P.P., Puvion, E., Freemont, P., and de The, H. (2001). Role of Promyelocytic Leukemia (PML) Sumolation in Nuclear Body Formation, 11S Proteasome Recruitment, and As(2)O(3)-induced PML or PML/Retinoic Acid Receptor alpha Degradation. J Exp Med *193*, 1361-1372.
10. Lallemand-Breitenbach, V., Jeanne, M., Benhenda, S., Nasr, R., Lei, M., Peres, L., Zhou, J., Zhu, J., Raught, B., and de The, H. (2008). Arsenic degrades PML or PML-RARalpha through a SUMO-triggered RNF4/ubiquitin-mediated pathway. Nat Cell Biol *10*, 547-555. ncb1717 [pii]10.1038/ncb1717.
11. Jeanne, M., Lallemand-Breitenbach, V., Ferhi, O., Koken, M., Le Bras, M., Duffort, S., Peres, L., Berthier, C., Soilihi, H., Raught, B., and de The, H. (2010). PML/RARA oxidation and arsenic binding initiate the antileukemia response of As2O3. Cancer Cell *18*, 88-98. S1535-6108(10)00241-2 [pii]10.1016/j.ccr.2010.06.003.
12. Bercier, P., Wang, Q.Q., Zang, N., Zhang, J., Yang, C., Maimaitiyiming, Y., Abou-Ghali, M., Berthier, C., Wu, C., Niwa-Kawakita, M., et al. (2023). Structural Basis of PML-RARA Oncoprotein Targeting by Arsenic Unravels a Cysteine Rheostat Controlling PML Body Assembly and Function. Cancer Discov *13*, 2548-2565. 10.1158/2159-8290.CD-23-0453.

13. Ablain, J., Leiva, M., Peres, L., Fonsart, J., Anthony, E., and de The, H. (2013). Uncoupling RARA transcriptional activation and degradation clarifies the bases for APL response to therapies. The Journal of experimental medicine *210*, 647-653. 10.1084/jem.20122337.
14. Nasr, R., Guillemin, M.C., Ferhi, O., Soilihi, H., Peres, L., Berthier, C., Rousselot, P., Robledo-Sarmiento, M., Lallemand-Breitenbach, V., Gourmel, B., et al. (2008). Eradication of acute promyelocytic leukemia-initiating cells through PML-RARA degradation. Nat Med *14*, 1333-1342. nm.1891 [pii]10.1038/nm.1891.
15. Ablain, J., Rice, K., Soilihi, H., de Reynies, A., Minucci, S., and de The, H. (2014). Activation of a promyelocytic leukemia-tumor protein 53 axis underlies acute promyelocytic leukemia cure. Nature medicine *20*, 167-174. doi: 10.1038/nm.3441.
16. Daniel, M.-T., Koken, M., Romagné, O., Barbey, S., Bazarbachi, A., Stadler, M., Guillemin, M.-C., Degos, L., Chomienne, C., and de Thé, H. (1993). PML protein expression in hematopoietic and acute promyelocytic leukemia cells. Blood *82*, 1858-1867.
17. Koken, M.H.M., Puvion-Dutilleul, F., Guillemin, M.C., Viron, A., Linares-Cruz, G., Stuurman, N., de Jong, L., Szostecki, C., Calvo, F., Chomienne, C., et al. (1994). The t(15;17) translocation alters a nuclear body in a RA-reversible fashion. EMBO J. *13*, 1073-1083.
18. de The, H. (2018). Differentiation therapy revisited. Nat Rev Cancer *18*, 117-127. 10.1038/nrc.2017.103.
19. de The, H., Pandolfi, P.P., and Chen, Z. (2017). Acute Promyelocytic Leukemia: A Paradigm for Oncoprotein-Targeted Cure. Cancer Cell *32*, 552-560. 10.1016/j.ccell.2017.10.002.
20. Rerolle, D., and de The, H. (2023). The PML hub: An emerging actor of leukemia therapies. J Exp Med *220*. 10.1084/jem.20221213.
21. Lallemand-Breitenbach, V., Guillemin, M.-C., Janin, A., Daniel, M.-T., Degos, L., Kogan, S.C., Bishop, J.M., and de The, H. (1999). Retinoic acid and arsenic synergize to eradicate leukemic cells in a mouse model of acute promyelocytic leukemia. J. Exp. Med. *189*, 1043-1052.
22. Lehmann-Che, J., Bally, C., and de The, H. (2014). therapy resistance in APL. New Engl. J. Med. *371*, 1171-1172.
23. Lehmann-Che, J., Bally, C., Letouze, E., Berthier, C., Yuan, H., Jollivet, F., Ades, L., Cassinat, B., Hirsch, P., Pigneux, A., et al. (2018). Dual origin of relapses in retinoic-acid resistant acute promyelocytic leukemia. Nat Commun *9*, 2047. 10.1038/s41467-018-04384-5.
24. Shen, Z.X., Shi, Z.Z., Fang, J., Gu, B.W., Li, J.M., Zhu, Y.M., Shi, J.Y., Zheng, P.Z., Yan, H., Liu, , and Y. F., e.a. (2004). All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci U S A *101*, 5328-5335.
25. Lo-Coco, F., Avvisati, G., Vignetti, M., Thiede, C., Orlando, S.M., Iacobelli, S., Ferrara, F., Fazi, P., Cicconi, L., Di Bona, E., et al. (2013). Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. The New England journal of medicine *369*, 111-121. 10.1056/NEJMoa1300874.
26. Ivanschitz, L., Takahashi, Y., Jollivet, F., Ayrault, O., Le Bras, M., and de The, H. (2015). PML IV/ARF interaction enhances p53 SUMO-1 conjugation, activation, and senescence. Proc Natl Acad Sci U S A *112*, 14278-14283. 10.1073/pnas.1507540112.

27. Sahin, U., Ferhi, O., Jeanne, M., Benhenda, S., Berthier, C., Jollivet, F., Niwa-Kawakita, M., Faklaris, O., Setterblad, N., de The, H., and Lallemand-Breitenbach, V. (2014). Oxidative stress-induced assembly of PML nuclear bodies controls sumoylation of partner proteins. The Journal of cell biology *204*, 931-945. 10.1083/jcb.201305148.
28. Sahin, U., Ferhi, O., Carnec, X., Zamborlini, A., Peres, L., Jollivet, F., Vitaliano-Prunier, A., de The, H., and Lallemand-Breitenbach, V. (2014). Interferon controls SUMO availability via the Lin28 and let-7 axis to impede virus replication. Nature communications *19*, 4187. doi:10.1038/ncomms5187.
29. Niwa-Kawakita, M., Ferhi, O., Soilihi, H., Le Bras, M., Lallemand-Breitenbach, V., and de The, H. (2017). PML is a ROS sensor activating p53 upon oxidative stress. J Exp Med *214*, 3197-3206. 10.1084/jem.20160301.
30. Tessier, S., Ferhi, O., Geoffroy, M.C., Gonzalez-Prieto, R., Canat, A., Quentin, S., Pla, M., Niwa-Kawakita, M., Bercier, P., Rerolle, D., et al. (2022). Exploration of nuclear body-enhanced sumoylation reveals that PML represses 2-cell features of embryonic stem cells. Nat Commun *13*, 5726. 10.1038/s41467-022-33147-6.
31. Dagher, T., Maslah, N., Edmond, V., Cassinat, B., Vainchenker, W., Giraudier, S., Pasquier, F., Verger, E., Niwa-Kawakita, M., Lallemand-Breitenbach, V., et al. (2021). JAK2V617F myeloproliferative neoplasm eradication by a novel interferon/arsenic therapy involves PML. J Exp Med *218*. 10.1084/jem.20201268.
32. Wu, H.C., Rerolle, D., Berthier, C., Hleihel, R., Sakamoto, T., Quentin, S., Benhenda, S., Morganti, C., Wu, C.C., Conte, L., et al. (2021). Actinomycin D targets NPM1c-primed mitochondria to restore PML- driven senescence in AML therapy. Cancer Discov *11*, 3198-3213. 10.1158/2159-8290.CD-21-0177.