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Hugues de Thé

Cellular and Molecular Oncology (2014-)

BIOGRAPHY

Hugues de Thé received a dual formation in medicine and basic sciences and has been at the forefront of translational leukaemia research. In Necker hospital, he got an advanced training in physiopathology and the biological bases of therapeutics. During his PhD in Pierre Tiollais's laboratory at the Pasteur institute, he learnt molecular biology and applied it to cancer biology. Since, his research was aimed at linking molecular cell biology to therapeutic responses in cancer. His studies on acute promyelocytic leukemia and the targeting of PML/RARA by retinoic acid and arsenic have led to the cure of this once intractable disease and made it a paradigm for targeted therapies.

The retinoic acid receptors

Insertion of the hepatitis B virus in a liver cancer had occurred in an unknown gene with homology to nuclear receptors. This allowed the molecular cloning of one of the retinoic acid receptors, RARB (Nature, 1988). The latter is auto-regulated by its ligand, allowing him to identify the first response element for these receptors (Nature, 1990). These studies, realized with A. Dejean, not only contributed to understanding the molecular basis of some liver cancers, but also yielded critical tools to analyse this novel signalling pathway that plays a key role in tissue homeostasis or embryonal development.

The discovery of PML/RARA

Among the multiple effects of retinoic acid, one of the most surprising is its ability to induce terminal differentiation of acute promyelocytic leukemia cells (APL) in vivo. Clinically, this yields complete, although generally transient, remissions. This malignancy is molecularly characterized by a specific chromosomal translocation whose breakpoint was mapped to the vicinity of another retinoic acid receptor, RARA. In collaboration with L. Degos (St. Louis Hospital) and A. Dejean, he first demonstrated that the RARA gene is rearranged in all APLs tested (Leukemia, 1990), then molecularly cloned the translocation breakpoint and identified the PML/RARA fusion transcript (Nature 1990, Cell 1991). Subsequent work demonstrated that PML/RARA is the primary and often sole molecular driver of this condition. Since retinoic acid is clinically efficient only in APL and directly binds PML/RARA, this constituted one of the first examples of oncogene-targeted therapies.

From transcriptional activation to proteolysis

PML/RARA is a transcriptional repressor silencing expression of hematopoietic differentiation genes. PML/RARA binding to retinoic acid turns it into a transcriptional activator, explaining induction of cellular differentiation. APL became a model of differentiation therapy through therapy-induced transcriptional reactivation, a concept that fuelled significant work in many other conditions.
The discovery, by Chinese groups, of the therapeutic effects of arsenic trioxide radically changed the perspective. Indeed, arsenic also induces differentiation in patients, but does not activate PML/RARA-regulated transcription. Moreover, remissions are often long-lasting and cures were observed with single agent arsenic. Together with Z. Chen (RuiJin Hospital, Shanghai), he could show that the two active drugs both initiate degradation of the PML/RARA protein and proposed a key role of oncoprotein catabolism in therapy response (PNAS 1997, 1999).

Arsenic targets PML

Arsenic directly targets PML and PML/RARA, demonstrating that arsenic is also a targeted therapy. His team explored in detail PML degradation by arsenic, demonstrating that catabolism is linked to changes in subcellular localization and post-translational modifications (PNAS, 1997). V. Lallemand-Breitenbach demonstrated that PML SUMO-conjugation initiates PML proteolysis (JEM, 2001), as it allows recruitment of the RNF4 ubiquitin ligase (Nat Cell Biol, 2008), after direct fixation of arsenic onto PML (Science, Cancer Cell 2010). This biochemical cascade is accompanied by profound modifications of PML distribution within the nucleus. PML nucleates specific domains, PML nuclear bodies, linked to senescence and inflammation. PML/RARA disorganizes these domains, a feature that promotes transformation. Therapy-induced PML/RARA degradation restores PML nuclear bodies (Blood, 1993, EMBO J 1994, PNAS 1997). In non-leukemic cells, arsenic also sharply enhances PML nuclear body formation prior to its degradation and thus became an invaluable tool to decipher the basis for their assembly and explore their functions, as detailed below.

Towards an integrated model for therapy response

The respective roles PML/RARA degradation and transcriptional reactivation in therapy response remained controversial. Analysis of APL mouse models allowed the distinction between leukemic blast differentiation and loss of self-renewal, two features that are linked, but not identical for leukemic cells (Nat Rev Cancer, 2010, 2018). Transcriptional activation (or de-repression) yields differentiation, while PML/RARA degradation drives loss of self-renewal (Nat Med 2008, JEM 2013, Nat Med 2014). Reformation of PML nuclear bodies triggers growth arrest and senescence, at least in part through activation of P53. This model, highlighting the key role of normal PML in APL cure explains the potency of arsenic treatment, since this drug targets both PML/RARA (for degradation) and PML (for NB formation prior to PML degradation). Mutations of the arsenic-binding site of PML/RARA, but also PML, in therapy-resistant patients have strongly supported the role of PML in APL therapy (NEJM 2014, Cancer Cell 2017). The key role of PML/RARA degradation in therapy response explained the dramatic synergy of the two drugs in animal models, where their combination is always curative, while none of them alone is (JEM 1999). This observation laid the ground for clinical studies which have now conclusively demonstrated that virtually all patients can be cured, without any chemotherapy (PNAS 2004, reviewed in Cancer Cell 2017).

From PML nuclear body organization to their physiological roles

Driven by the key role of PML nuclear bodies in APL cure, the team has invested significant efforts to unravel their biogenesis and functions. PML drives formation of these membrane-less organelles, forming their external shell and recruiting multiple partner proteins whose only similarities is to undergo SUMO-conjugation and contain a SUMO-interacting motif (SIM). Our studies have demonstrated that PML oxidation drives NB biogenesis. The latter is followed by PML sumoylation, partner recruitment and partner sumoylation through recruitment of UBC9 (Cancer Cell, 2010, JCB, 2014, Nat Com 2022). PML nuclear bodies could be stress-induced catalytic chambers for sumoylation. Recently, we identified a solvent-exposed cysteine in the B2 box of PML that is directly targeted by arsenic in the context of a PML trimer, formally demonstrating that arsenic is a PML-targeted therapy. This residue is normaly involved in the sensing of reactive oxygen species, a function highjacked by arsenic in APL therapy. The team also demonstrated that PML plays a key physiological role in oxidative stress response, notably through enhancement of P53 activation (JEM, 2017).

A recent review of APL work and our contribution delivered at the CSHL meeting "Cancer Genetics: history and consequences", is accessible online

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

Towards other models ?

In studies supported by an ERC advanced grant (2018, PML-THERAPY), the team is interested in the involvement of PML in other leukemia/treatment pairs, as well as the physiological functions of PML. In that line, we are re-exploring the bases for response to conventional chemotherapy, both in mice models and in patients. Finally, with ERC support (2025, RARA-AMLs) we are revisiting the effects of retinoids in non-APL myeloid leukemias.

CV

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Career

- Professor, Collège de France, Cellular and Molecular Oncology Chair, 2014-
- Physician, Paris Hospitals, 1995-
- Professor of Biochemistry, Paris Diderot University, 1995-2014.
- Department director, CNRS, INSERM, Paris Diderot University, 1995-2018.
- Director of Research (Associate professor) INSERM, 1993-1995
- Assistant Professor, INSERM, 1991-1993
- MD/PhD program, post-doc INSERM, P. Tiollais, 1988-1991
- Residency, Paris hospitals (medical research) P. Tiollais, Pasteur Institute, 1984-1988
- Medical School, Lyon, Paris, 1978-1984

Diplomas

- Ph.D., Pierre et Marie Curie University, 1990
- M.D., Paris Descartes University, 1989
- Master in Biochemistry, Pierre et Marie Curie University, 1983

Honours

- Prix Yvelines (Ligue contre le Cancer), 1992
- Prix R. Mandé (French Academy of Medicine) 1996
- Prix Rosen (Fondation pour la recherche Médicale) 1999
- Prix Mergier-Bourdeix (French Academy of Sciences) 2004
- EMBO member (2004)
- Griffuel Award, ARC (2010)
- Prix Claude Bernard, Ville de Paris (2010)
- French Legion of honour (2010)
- Senior grant European Research Council (ERC) 2011
- Member, the French Academy of Science (2011)
- Foreign cooperation award, the People's Republic of China (2011)
- Carreras Award, European Society of Hematology (2014)
- Ernest Beutler Award, American Society of Hematology (2016)
- Sjöberg Award, the Swedish royal academy of sciences (2018)
- Senior grant European Research Council (ERC) 2018
- Senior grant European Research Council (ERC) 2025

Committees

- Adviser to the director of INSERM (1997-2001)
- President of the scientific advisory board ARC (2003-2005)
- President of the scientific advisory board, the Bettencourt Schueller Foundation (2014-)

BIBLIOGRAPHY

Major publications (1987-2025)

1. de The, H., A. Marchio, P. Tiollais, and A. Dejean, A novel steroid thyroid hormone receptor-related gene inappropriately expressed in human hepatocellular carcinoma. **Nature**, 1987. 330(6149): p. 667-70.

2. Brand, N., M. Petkovich, A. Krust, P. Chambon, H. de The, A. Marchio, P. Tiollais, and A. Dejean, Identification of a second human retinoic acid receptor. **Nature,** 1988. 332(6167): p. 850-3.

3. de The, H., A. Marchio, P. Tiollais, and A. Dejean, Differential expression and ligand regulation of the retinoic acid receptor alpha and beta genes. **The EMBO journal**, 1989. 8(2): p. 429-33.

4. Chomienne, C., P. Ballerini, M. Balitrand, M. Huang, I. Krawice, S. Castaigne, P. Fenaux, P. Tiollais, A. Dejean, L. Degos, and H. de Thé, The retinoic acid receptor is rearranged in retinoic acid sensitive promyelocytic leukemias. **Leukemia,** 1990. 4: p. 802-807.

5. de The, H., C. Chomienne, M. Lanotte, L. Degos, and A. Dejean, The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. **Nature,** 1990. 347(6293): p. 558-61.

6. de Thé, H., M.d.M. Vivanco-Ruiz, P. Tiollais, H. Stunnenberg, and A. Dejean, Identification of a retinoic acid responsive element in the retinoic acid receptor beta gene. **Nature,** 1990. 343: p. 177-180.

7. de Thé, H., C. Lavau, A. Marchio, C. Chomienne, L. Degos, and A. Dejean, The PML-RAR alpha fusion mRNA generated by the t(15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR. **Cell**, 1991. 66(4): p. 675-84.

8. Daniel, M.-T., M. Koken, O. Romagné, S. Barbey, A. Bazarbachi, M. Stadler, M.-C. Guillemin, L. Degos, C. Chomienne, and H. de Thé, PML protein expression in hematopoietic and acute promyelocytic leukemia cells. **Blood,** 1993. 82: p. 1858-1867.

9. Warrell, R., H. de Thé, Z. Wang, and L. Degos, Acute promyelocytic leukemia. **New Engl. J. Med.,** 1993. 329: p. 177-189.

10. Koken, M.H.M., F. Puvion-Dutilleul, M.C. Guillemin, A. Viron, G. Linares-Cruz, N. Stuurman, L. de Jong, C. Szostecki, F. Calvo, C. Chomienne, L. Degos, E. Puvion, and H. de Thé, The t(15;17) translocation alters a nuclear body in a RA-reversible fashion. **EMBO J.,** 1994. 13: p. 1073-1083.

11. Stadler, M., M.K. Chelbi-Alix, M.H.M. Koken, L. Venturini, C. Lee, A. Saïb, F. Quignon, L. Pelicano, M.-C. Guillemin, C. Schindler, and H. de Thé, Transcriptional induction of the PML growth suppressor gene by interferons is mediated through an ISRE and a GAS element. **Oncogene,** 1995. 11: p. 2565-2573.

12. André, C., M.-C. Guillemin, J. Zhu, M.H.M. Koken, F. Quignon, L. Hervé, M.K. Chelbi-Alix, D. Dhumeaux, Z.Y. Wang, L. Degos, Z. Chen, and H. de Thé, The PML and PML/RAR-alpha domains. From autoimmunity to molecular oncology and from retinoic acid to arsenic. **Exp. Cell Res**., 1996. 229: p. 253-260.

13. Chen, G.Q., X.G. Shi, W. Tang, S.M. Xiong, J. Zhu, X. Cai, Z.G. Han, J.H. Ni, G.Y. Shi, P.M. Jia, M.M. Liu, K.L. He, C. Niu, J. Ma, P. Zhang, T.D. Zhang, P. Paul, T. Naoe, K. Kitamura,

W. Miller, S. Waxman, Z.Y. Wang, H. de The, S.J. Chen, and Z. Chen, Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): I. As2O3 exerts dose-dependent dual effects on APL cells. **Blood,** 1997. 89(9): p. 3345-53.

14. Quignon, F., Z. Chen, and H. de Thé, Retinoic acid and arsenic: towards oncogene targeted treatments of acute promyelocytic leukaemia. **Biochim. Biophys. Acta**, 1997. 1333: p. M53-M61.

15. Zhu, J., M.H.M. Koken, F. Quignon, M.K. Chelbi-Alix, L. Degos, Z.Y. Wang, Z. Chen, and H. de The, Arsenic-induced PML targeting onto nuclear bodies: implications for the treatment of acute promyelocytic leukemia. **Proc. Natl. Acad. Sci. USA**, 1997. 94: p. 3978-3983.

16. Quignon, F., F. de Bels, M. Koken, J. Feunteun, J.-C. Ameisen, and H. de Thé, PML induces a caspase-independent cell death process. **Nature Genet.,** 1998. 20: p. 259-265.

17. Koken, M.H.M., M.-T. Daniel, M. Gianni, A. Zelent, J. Licht, A. Buzyn, P. Minard, L. Degos, B. Varet, and H. de The, Retinoic acid, but not arsenic trioxide, degrades the PLZF/RARalpha fusion protein, without inducing terminal differentiation or apoptosis, in a RA-therapy resistant tt(11;17) (q23;q21) APL patient**. Oncogene**, 1999. 18: p. 1113-1118.

18. Lallemand-Breitenbach, V., M.-C. Guillemin, A. Janin, M.-T. Daniel, L. Degos, S.C. Kogan, J.M. Bishop, and H. de The, Retinoic acid and arsenic synergize to eradicate leukemic cells in a mouse model of acute promyelocytic leukemia. **J. Exp. Med**., 1999. 189: p. 1043-1052.

19. Venturini, L., J. You, M. Stadler, R. Galien, V. Lallemand, M.H.M. Koken, M.G. Mattei, A. Ganser, P. Chambon, R. Losson, and H. de The, TIF1gamma, a novel member of the transcriptional intermediary factor 1 family. **Oncogene,** 1999. 18: p. 1209-1217.

20. Zhu, J., M. Gianni, E. Kopf, N. Honore, M. Chelbi-Alix, M. Koken, F. Quignon, C. Rochette-Egly, and H. de The, Retinoic acid induces proteasome-dependent degradation of retinoic acid receptor alpha (RAR alpha) and oncogenic RAR alpha fusion proteins. **Proc. Natl. Acad. Sci. USA,** 1999. 96: p. 14807-14812.

21. Lallemand-Breitenbach, V., J. Zhu, F. Puvion, M. Koken, N. Honore, A. Doubeikovsky, E. Duprez, P.P. Pandolfi, E. Puvion, P. Freemont, and H. de The, 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**, 2001. 193(12): p. 1361-72.

22. Bertheau, P., F. Plassa, M. Espie, E. Turpin, A. de Roquancourt, M. Marty, F. Lerebours, Y. Beuzard, A. Janin, and H. de The, Effect of mutated TP53 on response of advanced breast cancers to high- dose chemotherapy. **Lancet,** 2002. 360(9336): p. 852-4.

23. Guillemin, M.C., E. Raffoux, D. Vitoux, S. Kogan, H. Soilihi, V. Lallemand-Breitenbach, J. Zhu, A. Janin, M.T. Daniel, B. Gourmel, L. Degos, H. Dombret, M. Lanotte, and H. De The, In Vivo Activation of cAMP Signaling Induces Growth Arrest and Differentiation in Acute Promyelocytic Leukemia. **J Exp Med,** 2002. 196(10): p. 1373-1380.

24. Zhu, J., Z. Chen, V. Lallemand-Breitenbach, and H. de Thé, How acute promyelocytic leukemia revived arsenic. **Nature Reviews on Cancer**, 2002. 2: p. 705-713.

25. Kamashev, D.E., D. Vitoux, and H. De Thé, PML/RARA-RXR oligomers mediate retinoid- and rexinoid- /cAMP in APL cell differentiation. **J. Exp. Med.,** 2004. 199: p. 1-13.

26. Lallemand-Breitenbach, V., J. Zhu, S. Kogan, Z. Chen, and H. de The, Opinion: how patients have benefited from mouse models of acute promyelocytic leukaemia. **Nat Rev Cancer**, 2005. 5(10): p. 821-7.

27. Zhu, J., J. Zhou, L. Peres, F. Riaucoux, N. Honore, S. Kogan, and H. de The, A sumoylation site in PML/RARA is essential for leukemic transformation**. Cancer Cell**, 2005. 7(2): p. 143-53.

28. Condemine, W., Y. Takahashi, J. Zhu, F. Puvion-Dutilleul, S. Guegan, A. Janin, and H. de The, Characterization of endogenous human promyelocytic leukemia isoforms. **Cancer Res**, 2006. 66(12): p. 6192-8.

29. Bertheau, P., E. Turpin, D.S. Rickman, M. Espie, A. de Reynies, J.P. Feugeas, L.F. Plassa, H. Soliman, M. Varna, A. de Roquancourt, J. Lehmann-Che, Y. Beuzard, M. Marty, J.L. Misset, A. Janin, and H. de The, Exquisite sensitivity of TP53 mutant and basal breast cancers to a dose-dense epirubicin-cyclophosphamide regimen. **PLoS medicine**, 2007. 4(3): p. e90.

30. Condemine, W., Y. Takahashi, M. Le Bras, and H. de The, A nucleolar targeting signal in PML-I addresses PML to nucleolar caps in stressed or senescent cells. **J. Cell Sci**., 2007. • 120.

31. Medyouf, H., H. Alcalde, C. Berthier, M.C. Guillemin, N.R. dos Santos, A. Janin, D. Decaudin, H. de The, and J. Ghysdael, Targeting calcineurin activation as a therapeutic strategy for T-cell acute lymphoblastic leukemia. **Nature medicine**, 2007. 13(6): p. 736-41.

32. Zhu, J., R. Nasr, L. Peres, F. Riaucoux-Lormiere, N. Honore, C. Berthier, D. Kamashev, J. Zhou, D. Vitoux, C. Lavau, and H.s. de The, RXR is an essential component of the oncogenic PML/RARA complex in vivo. **Cancer Cell,** 2007. 12(1): p. 23-35.

33. Lallemand-Breitenbach, V., M. Jeanne, S. Benhenda, R. Nasr, M. Lei, L. Peres, J. Zhou, J. Zhu, B. Raught, and H. de The, Arsenic degrades PML or PML-RARalpha through a SUMO-triggered RNF4/ubiquitin-mediated pathway. **Nat Cell Biol**, 2008. 10(5): p. 547-55.

34. Nasr, R., M.C. Guillemin, O. Ferhi, H. Soilihi, L. Peres, C. Berthier, P. Rousselot, M. Robledo-Sarmiento, V. Lallemand-Breitenbach, B. Gourmel, D. Vitoux, P.P. Pandolfi, C. Rochette-Egly, J. Zhu, and H. de The, Eradication of acute promyelocytic leukemia-initiating cells through PML-RARA degradation. **Nat Med**, 2008. 14(12): p. 1333-42.

35. de The, H. and Z. Chen, Acute promyelocytic leukaemia: novel insights into the mechanisms of cure. **Nat Rev Cancer**, 2010. 10(11): p. 775-83.

36. El Hajj, H., M. El-Sabban, H. Hasegawa, G. Zaatari, J. Ablain, S.T. Saab, A. Janin, R. Mahfouz, R. Nasr, Y. Kfoury, C. Nicot, O. Hermine, W. Hall, H. de The, and A. Bazarbachi, Therapy-induced selective loss of leukemia-initiating activity in murine adult T cell leukemia. **J Exp Med**, 2010. 207(13): p. 2785-92.

37. Jeanne, M., V. Lallemand-Breitenbach, O. Ferhi, M. Koken, M. Le Bras, S. Duffort, L. Peres, C. Berthier, H. Soilihi, B. Raught, and H. de The, PML/RARA oxidation and arsenic binding initiate the antileukemia response of As2O3. **Cancer Cell,** 2010. 18(1): p. 88-98.

38. Lallemand-Breitenbach, V. and H. de The, PML nuclear bodies. **Cold Spring Harb Perspect Biol.,** 2010. 2: p. a000661.

39. Zhang, X.W., X.J. Yan, Z.R. Zhou, F.F. Yang, Z.Y. Wu, H.B. Sun, W.X. Liang, A.X. Song, V. Lallemand-Breitenbach, M. Jeanne, Q.Y. Zhang, H.Y. Yang, Q.H. Huang, G.B. Zhou, J.H. Tong, Y. Zhang, J.H. Wu, H.Y. Hu, H. de The, S.J. Chen, and Z. Chen, Arsenic trioxide controls the fate of the PML-RARalpha oncoprotein by directly binding PML. **Science,** 2010. 328(5975): p. 240-3.

40. Ablain, J. and H. de The, Revisiting the differentiation paradigm in acute promyelocytic leukemia. **Blood,** 2011. 117(22): p. 5795-802.

41. Ablain, J., R. Nasr, A. Bazarbachi, and H. de The, Oncoprotein proteolysis, an unexpected Achille's Heel of cancer cells?. **Cancer Discovery**, 2011. 1: p. 117-127.

42. Chen, S.J., G.B. Zhou, X.W. Zhang, J.H. Mao, H. de The, and Z. Chen, From an old remedy to a magic bullet: molecular mechanisms underlying the therapeutic effects of arsenic in fighting leukemia. **Blood,** 2011. 117(24): p. 6425-37.

43. de The, H., M. Le Bras, and V. Lallemand-Breitenbach, The cell biology of disease: Acute promyelocytic leukemia, arsenic, and PML bodies. **The Journal of cell biology**, 2012. 198(1): p. 11-21.

44. Lallemand-Breitenbach, V. and H. de The, Hematopoietic cells burn fat to prevent exhaustion. **Cell stem cell,** 2012. 11('): p. 447-449.

45. Lallemand-Breitenbach, V., J. Zhu, Z. Chen, and H. de The, Mechanisms of APL cure through PML/RARA degradation by As2O3. **Trends in Molecular Medicine**, 2012. 18: p. 36-42.

46. Ablain, J., M. Leiva, L. Peres, J. Fonsart, E. Anthony, and H. de The, Uncoupling RARA transcriptional activation and degradation clarifies the bases for APL response to therapies. The **Journal of experimental medicine**, 2013. 210(4): p. 647-53.

47. Ablain, J., K. Rice, H. Soilihi, A. de Reynies, S. Minucci, and H. de The, Activation of a promyelocytic leukemia-tumor protein 53 axis underlies acute promyelocytic leukemia cure. **Nature medicine,** 2014. 20: p. 167-74.

48. Lehmann-Che, J., C. Bally, and H. de The, therapy resistance in APL. **New Engl. J. Med**., 2014. 371: p. 1171-1172.

49. Sahin, U., O. Ferhi, X. Carnec, A. Zamborlini, L. Peres, F. Jollivet, A. Vitaliano-Prunier, H. de The, and V. Lallemand-Breitenbach, Interferon controls SUMO availability via the Lin28 and let-7 axis to impede virus replication. **Nature communications**, 2014. 19: p. 4187.

50. Sahin, U., O. Ferhi, M. Jeanne, S. Benhenda, C. Berthier, F. Jollivet, M. Niwa-Kawakita, O. Faklaris, N. Setterblad, H. de The, and V. Lallemand-Breitenbach, Oxidative stress-induced assembly of PML nuclear bodies controls sumoylation of partner proteins. **The Journal of cell biology**, 2014. 204(6): p. 931-45.

51. Vitaliano-Prunier, A., J. Halftermeyer, J. Ablain, A. de Reynies, L. Peres, M. Le Bras, D. Metzger, and H. de The, Clearance of PML/RARA-bound promoters suffice to initiate APL differentiation. **Blood,** 2014. 124(25): p. 3772-80.

52. Ablain, J., B. Poirot, C. Esnault, J. Lehmann-Che, and H. de The, p53 as an Effector or Inhibitor of Therapy Response. **Cold Spring Harb Perspect Med**, 2015. 6(1): p. a026260.

53. El Hajj, H., Z. Dassouki, C. Berthier, E. Raffoux, L. Ades, O. Legrand, R. Hleihel, U. Sahin, N. Tawil, A. Salameh, K. Zibara, N. Darwiche, M. Mohty, H. Dombret, P. Fenaux, H. de The, and A. Bazarbachi, Retinoic acid and arsenic trioxide trigger degradation of mutated NPM1, resulting in apoptosis of AML cells. **Blood,** 2015. 125(22): p. 3447-54.

54. Ivanschitz, L., Y. Takahashi, F. Jollivet, O. Ayrault, M. Le Bras, and H. de The, PML IV/ARF interaction enhances p53 SUMO-1 conjugation, activation, and senescence. **Proc Natl Acad Sci U S A,** 2015. 112(46): p. 14278-83.

55. Ferhi, O., L. Peres, S. Tessier, H. de The, and V. Lallemand-Breitenbach, Comment on "SUMO deconjugation is required for arsenic-triggered ubiquitylation of PML". **Sci Signal,** 2016. 9(440): p. tc1.

56. de The, H., P.P. Pandolfi, and Z. Chen, Acute Promyelocytic Leukemia: A Paradigm for Oncoprotein-Targeted Cure. **Cancer Cell**, 2017. 32(5): p. 552-560.

57. Niwa-Kawakita, M., O. Ferhi, H. Soilihi, M. Le Bras, V. Lallemand-Breitenbach, and H. de The, PML is a ROS sensor activating p53 upon oxidative stress. **J Exp Med**, 2017. 214(11): p. 3197-3206.

58. de The, H., Differentiation therapy revisited. **Nat Rev Cancer**, 2018. 18(2): p. 117-127.

59. Lallemand-Breitenbach, V. and H. de The, PML nuclear bodies: from architecture to function. **Curr Opin Cell Biol**, 2018. 52: p. 154-161.

60. Lehmann-Che, J., C. Bally, E. Letouze, C. Berthier, H. Yuan, F. Jollivet, L. Ades, B. Cassinat, P. Hirsch, A. Pigneux, M.J. Mozziconacci, S. Kogan, P. Fenaux, and H. de The, Dual origin of relapses in retinoic-acid resistant acute promyelocytic leukemia. **Nat Commun**, 2018. 9(1): p. 2047.

61. Wang, P., S. Benhenda, H. Wu, V. Lallemand-Breitenbach, T. Zhen, F. Jollivet, L. Peres, Y. Li, S.J. Chen, Z. Chen, H. de The, and G. Meng, RING tetramerization is required for nuclear body biogenesis and PML sumoylation. **Nat Commun**, 2018. 9(1): p. 1277.

62. Esnault, C., R. Rahme, K.L. Rice, C. Berthier, C. Gaillard, S. Quentin, A.L. Maubert, S. Kogan, and H. de The, FLT3-ITD impedes retinoic acid, but not arsenic, responses in murine acute promyelocytic leukemias. **Blood**, 2019. 133(13): p. 1495-1506.

63. Dagher, T., N. Maslah, V. Edmond, B. Cassinat, W. Vainchenker, S. Giraudier, F. Pasquier, E. Verger, M. Niwa-Kawakita, V. Lallemand-Breitenbach, I. Plo, J.J. Kiladjian, J.L. Villeval, and H. de The, JAK2V617F myeloproliferative neoplasm eradication by a novel interferon/arsenic therapy involves PML. **J Exp Med**, 2021. 218(2).

64. Geoffroy, M.C., c. Esnault, and H. de The, Retinoids in haematology, a timely revival? . **Blood,** 2021. 137(18): p. 2429-2437.

65. Wu, H.C., D. Rerolle, C. Berthier, R. Hleihel, T. Sakamoto, S. Quentin, S. Benhenda, C. Morganti, C.C. Wu, L. Conte, S. Rimsky, M. Sebert, E. Clappier, S. Souquere, S. Gachet, J. Soulier, S. Durand, J.J. Trowbridge, P. Benit, P. Rustin, H. El Hajj, E. Raffoux, L. Ades, R. Itzykson, H. Dombret, P. Fenaux, O. Espeli, G. Kroemer, L. Brunetti, T.W. Mak, V. Lallemand-Breitenbach, A. Bazarbachi, B. Falini, M.F. Martelli, and H. de The, Actinomycin D targets NPM1c-primed mitochondria to restore PML- driven senescence in AML therapy. **Cancer Discov**, 2021. 11(12): p. 3198-3213.

66. Tessier, S., O. Ferhi, M.C. Geoffroy, R. Gonzalez-Prieto, A. Canat, S. Quentin, M. Pla, M. Niwa-Kawakita, P. Bercier, D. Rerolle, M. Tirard, P. Therizols, E. Fabre, A.C.O. Vertegaal, H. de The, and V. Lallemand-Breitenbach, Exploration of nuclear body-enhanced sumoylation reveals that PML represses 2-cell features of embryonic stem cells. **Nat Commun**, 2022. 13(1): p. 5726.

67. Bercier, P., Q.Q. Wang, N. Zang, J. Zhang, C. Yang, Y. Maimaitiyiming, M. Abou-Ghali, C. Berthier, C. Wu, M. Niwa-Kawakita, T. Dirami, M.C. Geoffroy, O. Ferhi, S. Quentin, S. Benhenda, Y. Ogra, Z. Gueroui, C. Zhou, H. Naranmandura, H. de The, and V. Lallemand-Breitenbach, Structural basis of PML/RARA oncoprotein targeting by arsenic unravels a cysteine rheostat controlling PML body assembly and function. **Cancer Discov**, 2023. 3(12):2548-2565.

68. Rerolle, D. and H. de The, The PML hub: An emerging actor of leukemia therapies. **J Exp Med,** 2023. 220(8).

69. Rérolle D, Wu HC, de Thé H. Acute Promyelocytic Leukemia, Retinoic Acid, and Arsenic: A Tale of Dualities. **Cold Spring Harb Perspect Med.** 2024. 14(9):a041582.

70. Letai, A and de Thé, H Conventional chemotherapy: millions of cures, unresolved therapeutic index. **Nat Rev Cancer** 2025. (3):209-218