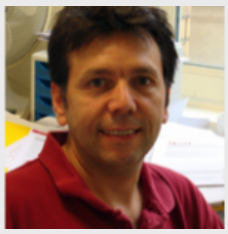

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## The p53 pathway is altered in most, if not all, tumours. In more than half of human cancers, the p53 gene is mutated and, in the other half, the p53 protein is inactivated, often by overexpression of its specific inhibitors MDM2 and MDM4.

A better understanding of the pathways that regulate p53 could lead to development of new and broadly applicable anti-cancer strategies. Our group is using mouse models to gain a better understanding of the regulation of p53.

Much of what we know about the regulation of p53 results from biochemical studies and analyses relying on transfection of expression plasmids into cells in culture. In recent years, studies of several mouse models carrying targeted p53 mutations revealed significant differences between the *in vivo* data and those obtained by earlier *in vitro* approaches. For example, we found that mutation of threonine and proline residues in p53's proline rich domain (PRD), which were thought to be essential for regulation of the protein, did not significantly affect the transactivation or tumor suppressor function of p53 in the mouse – a finding that may explain the sequence variability of the PRD in evolution.

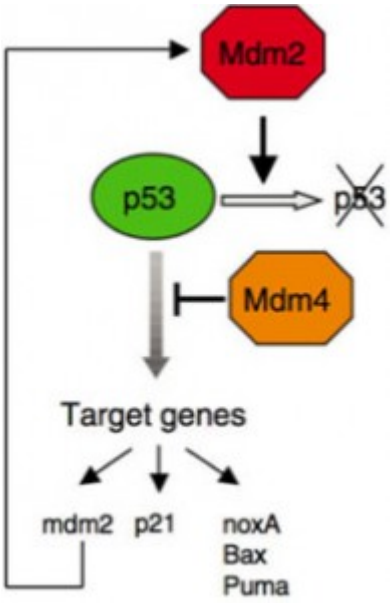


*Figure 1 : A model for co-operative control of p53 by Mdm2 and Mdm4 : Mdm2 promotes the degradation of p53, whereas Mdm4 inhibits the transcriptional activity of p53.*

We also generated the mutant mouse p53ΔP, which expresses a p53 that lacks the proline-rich domain, and has provided tremendous insight into p53 regulation. Studies of this mutant showed that MDM2 and MDM4 have distinct and complementary roles in p53 regulation: MDM2 mainly regulates p53 stability, whereas MDM4 regulates its activity (Fig. 1).

In addition, we have shown that MDM4 is a promising target for anti-cancer strategies, and that the combined use of MDM2 and MDM4 antagonists may reactivate p53 in some cancers. We also recently showed that the capacity of p53 to mediate transcriptional repression is important for strategies against MDM4 to work efficiently in some, but not all tumors. These studies demonstrate just how much information can be gained from studying p53 regulation *in vivo*, as well as the potential of such approaches for developing effective therapies.

Our group is now generating new mutant mice to pursue the analysis of p53 regulation. This approach recently helped us to demonstrate that the Mdm4-S transcript, often overexpressed in human tumors, is a marker, rather than a driver, of cancer progression. Furthermore, we showed that a nonsense mutation leading to the loss of the p53 C-terminal domain leads to increased p53 activity, and this causes bone marrow failure and pulmonary fibrosis. Importantly, the combined observation of aplastic anemia and lung fibrosis is a hallmark of syndromes caused by abnormally short telomeres. This led us to show that p53 is a major regulator of telomere metabolism, via its capacity to downregulate the expression of several key genes, including *Dkc1* (*Dyskerin*) and *Rtel1* (Fig. 2). Indeed,our team has also developped all the necessary tools to identify genes that are directly or indirectly regulated by p53.

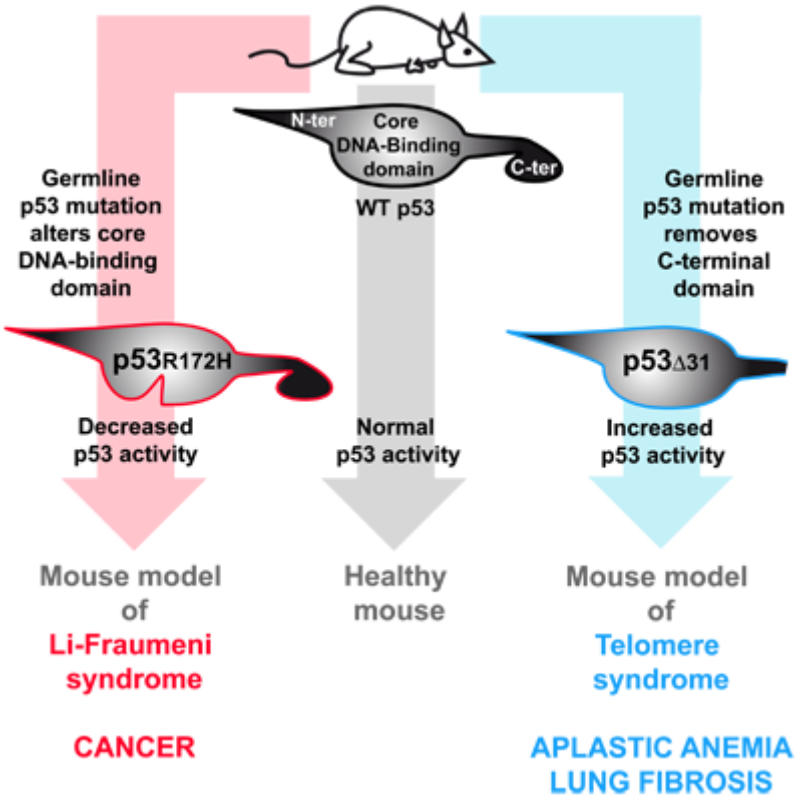


*Figure 2: Schematic diagram showing the different outcomes of a missense mutation affecting the core DNA binding domain of p53, and a nonsense mutation affecting the C-terminus.*

# Key publications

**Year of publication 2020**

Eléonore Toufektchan, Vincent Lejour, Romane Durand, Neelam Giri, Irena Draskovic, Boris Bardot, Pierre Laplante, Sara Jaber, Blanche P Alter, José-Arturo Londono-Vallejo, Sharon A Savage, Franck Toledo (2020 Apr 18)
**Germline mutation of MDM4, a major p53 regulator, in a familial syndrome of defective telomere maintenance.**
*Science advances* : eaay3511 : DOI : 10.1126/sciadv.aay3511

Franck Toledo and Michelle Debatisse (2020 Apr 17)
**Mechanisms generating cancer genome complexity : a look back at the**

**interphase breakage model**
*Science* : Vol. 368, Issue 6488 : eaba0712 : DOI : 10.1126/science.aba0712

**Year of publication 2018**

Eléonore Toufektchan and Franck Toledo (2018 May 6)
**The Guardian of the Genome Revisited: p53 Downregulates Genes Required for Telomere Maintenance, DNA Repair, and Centromere Structure.**
*Cancers (Basel)* : 10(5) : pii: E135

**Year of publication 2017**

Dan Filipescu, Monica Naughtin, Katrina Podsypanina, Vincent Lejour, Laurence Wilson, Zachary A Gurard-Levin, Guillermo A Orsi, Iva Simeonova, Eleonore Toufektchan, Laura D Attardi, Franck Toledo, Geneviève Almouzni (2017 Mar 31)
**Essential role for centromeric factors following p53 loss and oncogenic transformation.**
*Genes & development* : 463-480 : DOI : 10.1101/gad.290924.116

**Year of publication 2016**

Sara Jaber, Eléonore Toufektchan, Vincent Lejour, Boris Bardot, Franck Toledo (2016 Apr 2)
**p53 downregulates the Fanconi anaemia DNA repair pathway.**
*Nature communications* : 11091 : DOI : 10.1038/ncomms11091

**Year of publication 2015**

Bardot B, Bouarich-Bourimi R, Leemput J, Lejour V, Hamon A, Plancke L, Jochemsen AG, Simeonova I, Fang M, Toledo F. (2015 May 28)
**Mice engineered for an obligatory Mdm4 exon skipping express higher levels of the Mdm4-S isoform but exhibit increased p53 activity.**
*Oncogene* : DOI : doi:10.1038/onc.2014.230