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Tumorigenesis is a multistep process in which chromosomal instability plays an important role.

## We have shown that telomere instability due to excessive shortening is the main driving force of chromosome aberrations during the early stages of cell transformation. Our work has shown that this chromosome instability is associated with genome-wide changes in the chromatin landscape, which are directly correlated with transcriptome changes mainly affecting the non coding genome, including microRNAs.

We have discovered that the **deregulation of microRNAs following chromosome instability** is responsible for the acquisition of tumor related phenotypes and the induction of a metastable state of cell differentiation in which epithelial cells respond to a senescence microenvironment by engaging in transitions deemed to be important for different steps in the **metastatic progression of carcinomas**. During this process, transformed epithelial cells acquire stem cell characteristics with renewal capacity, become cell-autonomous tumour initiating cells and are endowed of mesenchymal differentiation potential. Our laboratory is interested in exploring the molecular mechanisms that drive the production of **cancer stem cells** and specifically in dissecting the microRNA/transcription factor circuitry that connects such differentiation metastability to tumour aggressiveness. Identifying key actors in this circuitry will open the possibilities for drug development.

Our laboratory is also interested in understanding the molecular bases of **telomerase-independent telomere maintenance mechanisms** (ALT). Indeed, a non-negligible proportion of cancer cells use recombination instead of telomerase to maintain telomere length. On the other hand, there is increasing evidence that anti-telomerase therapies may favor the

emergence of ALT mechanisms, thus allowing the tumor cell to escape. We have shown that recombination between telomeres occur in specialized PML bodies specifically found in ALT cells. We are currently studying the mechanisms by which telomeres are recruited to these structures and how recombination reactions, which are normally suppressed at telomeres, are allowed in the ALT context. Understanding how ALT mechanisms work will open a new path in anti-tumour strategies.

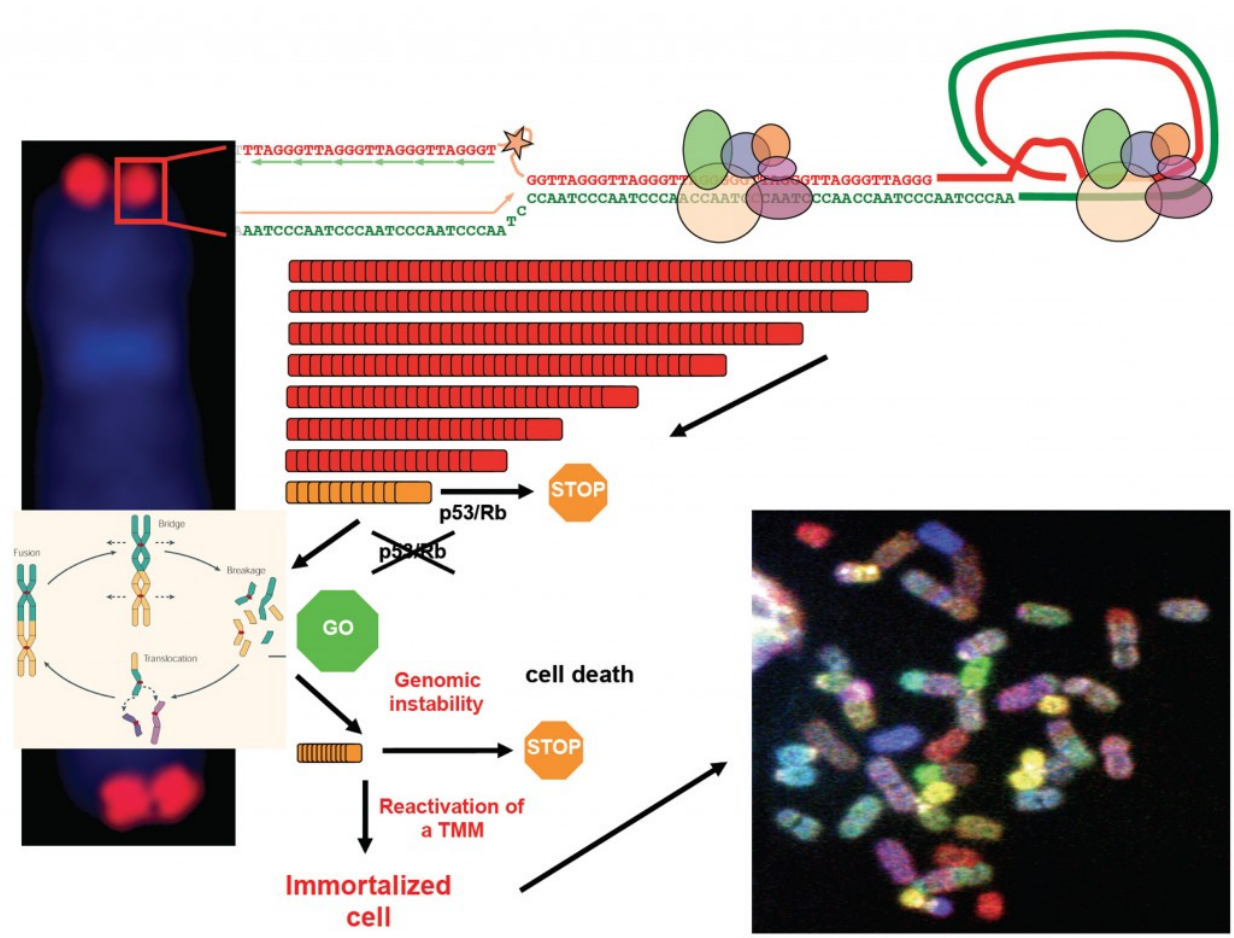


*Figure 1: Telomeres protect chromosome ends. Telomere length, which is important for function, decreases with cell divisions until telomeres become dysfunctional, triggering cell growth arrest. In the presence of a disabled p53 pathway, telomeres further shorten causing chromosome ends to fuse and to initiate cycles of breakage-fusion-bridge, thus causing genome instability (CIN) and cell death, unless a telomere maintenance mechanism (TMM) is reactivated. The immortalized CIN+ cell presents an epithelial-to-mesenchymal transition and bears genome-wide microRNA deregulation. In the presence of a senescent microenvironment, the CIN+ cell becomes tumorigenic and acquires stem cell features. We study the molecular bases of this process.*

Finally, we are interested in understanding the role of RTEL1, a helicase whose gene is found associated with severe forms of Hoyeraal-Hreidarsson syndrome. Although the protein has been involved in telomere and genome instability in the mouse, we have found that it plays an

important role in non-coding RNA trafficking and RNP biogenesis in human cells. One major aim of our work is to define the contribution of RNA-related defects to the disease manifestations.

# Key publications

### Year of publication 2019

Emilia Puig Lombardi, Allyson Holmes, Daniela Verga, Marie-Paule Teulade-Fichou, Alain Nicolas, Arturo Londoño-Vallejo (2019 Jul 9)
**Thermodynamically stable and genetically unstable G-quadruplexes are depleted in genomes across species.**
*Nucleic acids research* : 47 : 6098-6113 : DOI : 10.1093/nar/gkz463

Pinskaya M., Saci Z., Gallopin M., Nguyen N.H., Gabriel M., Firlej V., Descrimes M., de la Taille A., Londo~no-Vallejo A., Allory Y., Gautheret D., Morillon A. (2019 Jan 1)
**Blind exploration of the unreferenced transcriptome reveals novel RNAs for prostate cancer diagnosis**
*bioRxiv* : DOI : 10.1101/644104

### Year of publication 2018

Porreca RM, Glousker G, Awad A, Matilla Fernandez MI, Gibaud A, Naucke C, Cohen SB, Bryan TM, Tzfati Y, Draskovic I, Londoño-Vallejo A (2018 Mar 7)
**Human RTEL1 stabilizes long G-overhangs allowing telomerase-dependent over-extension**
*Nucleic Acids Research* : DOI : 10.1093/nar/gky173

### Year of publication 2015

Michael Schertzer, Karina Jouravleva, Mylene Perderiset, Florent Dingli, Damarys Loew, Tangui Le Guen, Barbara Bardoni, Jean-Pierre de Villartay, Patrick Revy, Arturo Londoño-Vallejo (2015 Jan 27)
**Human regulator of telomere elongation helicase 1 (RTEL1) is required for the nuclear and cytoplasmic trafficking of pre-U2 RNA.**
*Nucleic acids research* : 1834-47 : DOI : 10.1093/nar/gku1402

### Year of publication 2014

Stéphane Terry, Ihsan Y El-Sayed, Damien Destouches, Pascale Maillé, Nathalie Nicolaiew, Guillaume Ploussard, Fannie Semprez, Cynthia Pimpie, Himisha Beltran, Arturo Londono-Vallejo,

Yves Allory, Alexandre de la Taille, David S Salomon, Francis Vacherot (2014 Aug 15)
**CRIPTO overexpression promotes mesenchymal differentiation in prostate carcinoma cells through parallel regulation of AKT and FGFR activities.**
*Oncotarget* : 11994-2008

Maya Jeitany, Jose Ramon Pineda, Qingyuan Liu, Rosa Maria Porreca, Françoise Hoffschir, Chantal Desmaze, David C Silvestre, Patrick Mailliet, Marie-Pierre Junier, Arturo Londoño-Vallejo, Evelyne Ségal-Bendirdjian, Hervé Chneiweiss, François D Boussin (2014 Apr 30)
**A preclinical mouse model of glioma with an alternative mechanism of telomere maintenance (ALT).**
*International journal of cancer* : 1546-58 : DOI : 10.1002/ijc.29171