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Title: Innovative genetic and chemical genetics approaches to understand and treat degenerative diseases.

Abstract:
Drug discovery relies mostly on the prior identification of druggable targets to feed traditional based on target binding or function. However, such targets are difficult to identify for most degenerative and neurological disorders, thereby limiting the full potential of current screening technologies.

During the last decade, we have developed and demonstrated the value of performing HTS with small animal disease models (*C. elegans* and zebrafish) for finding drugs without the prior identification of a target. Going further than pure drug discovery, we have also shown that such a phenotypic screening approach can lead to the rapid identification of druggable targets. This feature is of considerable value, not only for feeding the traditional HTS pipeline with relevant therapeutic targets, but also for basic research by pointing out unsuspected disease mechanisms.

Here, I will present a case study demonstrating the power of such an approach, starting from modelling muscular degeneration in *C. elegans* to pre-clinical trials and target identification. I will further present our current zebrafish chemical genetics platform as well as some of our recent work focusing on motor neuron degeneration and motor neuron diseases. I will also show case in detail some recent transgenic tools we have developed to establish versatile and inducible models of spinal muscular atrophy. In addition/synergy to CRISPR, these tools are opening new avenues to study the genetics of neurodegenerative diseases and to develop versatile models for both basic research and drug discovery.

Short Bio.
Dr Jean Giacomotto started his career in the pharmaceutical industry as an engineer (Sanofi-Aventis, Paris) where he worked at developing *in vitro* and cellular models of degenerative diseases for drug discovery. He then joined the academic (CNRS, Lyon, France) as both engineer and PhD student where he worked at i) adapting drug discovery high throughput screening approach to small animal models such as *C. elegans* and the zebrafish and at ii) recapitulating degenerative genetic diseases in those organisms. He was one of the first to demonstrate the value of these research models for drug discovery and chemical genetics (from project design to translation into clinical trials). In 2011, he joined the Brain and Mind Research Institute (BMRI) in Sydney under the mentoring of Prof Thomas Becker and Prof Max Bennett. At the BMRI, he developed an innovative genetic technology for easing disease modelling and

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drug discovery in zebrafish. He used this technology to recapitulate, for the first time in zebrafish, the different forms of the degenerative motor neuron disorder, Spinal Muscular Atrophy (SMA). In 2015, he joined the Queensland Brain Institute (QBI, Brisbane) where he is still working today at modelling, studying and trying to find treatments against degenerative and neurological disorders. In 2016, Dr Giacomotto received a Lecturer position at the Institute NeuroMyogène (Lyon, France) and has been recently awarded an NHMRC Investigator Fellowship (Emerging Leader). His research is also supported by the NHMRC (project grant), as well as the MNDRIA of Australia, the CureSMA of America, the Rebecca L. Cooper Medical Research foundations and the CIHR (Canadian NIH-equivalent).