

## Moshe Szyf, Bio

Szyf's research has focused on understanding the basic principles of the DNA methylation machinery for the last three decades. He received his Ph. D from the Hebrew University working with Aharon Razin on basic mechanisms of DNA methylation. Szyf then went on to a postdoctoral fellowship in Genetics at Harvard Medical School and was appointed to an assistant professor at McGill University in Pharmacology and Therapeutics in 1989. Szyf is currently a James McGill and Glaxo SmithKline-CIHR professor of Pharmacology at McGill University. In 1994 following a decade of studies of the DNA methyltransferase gene and its regulation Szyf has proposed that DNA methyltransferase is a prime anticancer target (*Trends Pharmacol. Sci.* **15**, 233 (1994) and has filed a number of broad patents based on these ideas. The laboratory of Szyf developed antisense and direct inhibitors of DNA methyltransferase in collaboration with Hybridon Inc. in Worcester Ma. and has demonstrated their efficacy as anticancer agents in preclinical models (*Proc. Natl. Acad. Sci. USA* **94**, 684-689 (1997). This has led to the foundation of the first pharma in the world dedicated to epigenetic drugs MethylGene in Montreal. Szyf's vision that DNA methylation machinery is a therapeutic targets is now a decade later accepted by all and several large Pharma are developing drugs targeting the DNA methylation machinery. The laboratory of Szyf has demonstrated that DNA methylation is a reversible biological signal (*Nature* **397**, 579-583 (1999; *Proc. Natl. Acad. Sci. USA* **96**, 6107-6112 (1999). This paved the way to realizing that DNA methylation could be modulated after birth and responsive to external environmental signals. In collaboration with Dr. Michael Meaney, Szyf's lab discovered an epigenetic mechanism by which maternal behavior results in a stable alteration of the glucocorticoid receptor gene by DNA methylation in the hippocampus of the offspring (Weaver et al. *Nature Neuroscience* **7**, 847 (2004). New data from his lab shows that a similar process is associated with human suicide McGowan et al. *PLoS ONE* **3**, e2085 (2008) and that marks of childhood adversity are found in adult human brains McGowan *Nat Neurosci* **12**, 342 (2009). This data provides a paradigm on how "nurture" alters "nature". This last discovery was selected by Quebec Science as one of the most important 10 discoveries of the year 2009. Szyf's work has led to a paradigm shift in our understanding of the relationship between the environment and the genome and introduced the idea that the social environment could talk to the genome and sculpt the genome. An additional novel concept introduced by Szyf is that the epigenome serves as a mechanism of an adaptive response of the genome to signals in early life. These signals trigger a systemic response in the epigenome that programs the genome to adapt to the anticipated life long environment. The idea of a response rather than a stochastic change in epigenetic markings is diametrically different from the random-chance appearance of single nucleotide polymorphisms. The current application goal is to unravel this fundamental environmental response on an identical genetic background. The lab of Dr Szyf has developed some of the most advanced methods for computing whole-genome DNA methylation arrays, which are at the basis of this application.

Szyf has led several international collaboration and cross-disciplinary teams. Szyf is currently the founding co-director of the Sackler institute for epigenetics and psychobiology and is a fellow of the Canadian Institute for Advanced Research Experience-based Brain and Biological Development program, a high power interdisciplinary group. Szyf has funded international collaborations with China and Israel and is a co applicant on NIH grants with Dr Gao in North Carolina working on epigenomics of behavioral disorders and Dr Bennet in Chicago working on mapping the epigenome of the religious orders study. Dr Szyf is a PI on grants from the National Cancer Institute of Canada, the Canadian Institute of Health Research and NICHD. He has been a past recipient of a Human Science Frontiers program award. Szyf has published more than 140 papers in peer reviewed journals, almost all on epigenetics. His papers are frequently cited well above the impact of the journal. From example his paper in *Nature Neuroscience* on epigenetic programming by maternal care has been the most cited paper in *Nature Neuroscience*. Szyf is an inventor on dozens of issued and patents in the application process, all the patents relate to "epigenetics" based therapeutics.