
The 2002 Jeanne Manery Fisher Memorial Lectureship Award

Dr. Mona Nemer

Dr. Mona Nemer is the Director of the Cardiac Growth and Differentiation Laboratory at the Institut des recherches cliniques de Montréal (IRCM) and Professor, Department of Pharmacology, Université de Montréal. A chemist and molecular biologist, Dr. Nemer is recognized for her work in the field of transcriptional regulation of cardiac growth and differentiation. One of the three top scientists working in this field, Dr. Nemer is credited as being the first to isolate transcription factor GATA-4 in cardiac myocyte differentiation and to propose common molecular pathways for cardiac and hematopoietic cell differentiation. Her analysis of cardiac transcription in normal and diseased hearts may lead to a better understanding of, and treatment for, congenital or acquired cardiac disease.

Dr. Nemer received her Ph.D. in 1982, studying the chemistry of nucleotides and nucleosides with Professor Kelvin Ogilvie at McGill University. As a graduate student, Dr. Nemer developed chemistry responsible for automating DNA synthesis. She was also the first to synthesize several modified nucleotides including nucleotide amidites and thiophosphates as replacements for the phosphodiester chain. Such modified oligonucleotides are now used routinely in antisense based mRNA targeting. She completed her postdoctoral research training in molecular biology with Dr. Jacques Drouin at the Institut des recherches cliniques de Montréal (IRCM). During her fellowship, she made important contributions to the mechanisms of action of steroid receptors (glucocorticoid) and was the first to isolate the gene encoding for a novel cardiac hormone called ANF (atrial natriuretic factor). In 1985, Dr. Nemer was appointed to the position of Senior Researcher in the Laboratory of Molecular Genetics at IRCM. In 1991 she was appointed Director of a newly established Research Unit in Cardiac Growth and Differentiation at IRCM.



Early in her career, Dr. Nemer developed an interest in the regulation of the ANF gene. ANF (atrial natriuretic factor), the major secretory product of the heart, is a potent hypotensive peptide hormone. ANF was initially assumed to be an exclusively atrial product, but she showed that this gene was also expressed in ventricles where its presence correlates with cardiac cell growth and ventricular stress. This finding, which was later confirmed by several groups, prompted multicenter clinical studies aimed at correlating plasma ANF levels with the initiation of cardiac stress preceding cardiac dysfunction. These studies confirmed that increased ANF levels constitute an exquisite marker for cardiac dysfunction and subsequently led to the commercialization of diagnostic tests presently in use in Japan, the United States and Europe. In addition to analyzing ANF gene regulation, Dr. Nemer cloned the related BNP gene and used both cardiac natriuretic genes as markers for studying transcriptional regulation in the heart and for isolating the transcription factors that control cardiac cell fate.

Dr. Nemer was the first to tackle the area of cardiac transcription and to establish cellular models and methodologies that allowed analysis of cardiac promoters *in vitro*. This led to identification of novel regulatory pathways including the isolation of several cardiac transcription factors. For example, Dr. Nemer was the first to show the importance of the transcription factor GATA-4 in transcriptional regulation and in cell differentiation in cardiac myocytes. She was the first to clone GATA-4 and to suggest its importance in cardiac development, a suggestion that was proven by others, via generation of knockout animals, to be valid.

Dr. Nemer was also the first to propose a new paradigm for the mechanism underlying cardiac differentiation. Given that the heart is a muscle, paradigms common to both cardiac and skeletal muscle formations had long been sought. Dr. Nemer was the first to note similarities between the mechanisms underlying both the formation of the heart and the generation of different cells in the blood system (the hematopoietic system). She further showed both biochemically, and at the cellular level, that GATA-4 is a key regulator of the heart, both independently and through its interaction with other transcription factors such as the homeodomain factor known as NKX2.5. Dr. Nemer contributed significantly to understanding the role of this factor in the heart by identifying the first target genes of NKX2.5 and natural binding sites, for which she coined the term NKE (the current terminology). GATA-4 and NKX2.5 are the earliest markers of cardiac differentiation and are presently the most studied transcription factors in the field of cardiology. Dr. Nemer has also gone on to identify other collaborators of GATA-4 that modulate cardiac response to various stimuli.

She was the first to identify transcriptional regulatory mechanisms for catecholamine action on cardiac genes. Her group successfully cloned the transcription factor required to mediate α 1-adrenergic stimulation of cardiac genes and several other novel transcription factors that are important regulators of the cardiac genetic program. Her current work focuses on areas of prime importance for cardiac homeostasis, including the nuclear signalling mechanisms of angiotensin

II and endothelin I, as well as the functions of the latter in cardiac development and pathogenesis. In these studies, she combines molecular dissection of transcription complexes with large-scale gene expression profiling and *in vivo* analysis of relevant gene products.

An internationally renowned scientist and a dedicated mentor, Dr. Nemer has contributed significantly to the advancement of biomedical research in Canada. Dr. Nemer is a member of Royal Society of Canada's Academy of Science and holds a Canada Research Chair in Molecular Biology that was granted to her. She was an invited professor at the College de France in 1999 and nominated as vice-chair (2002) and chair (2003) of a Gordon Conference entitled Molecular Mechanism of Hormone Action. Dr. Nemer was a council member of the Medical Research Council of Canada and is presently a member of the Research Policy and Planning Advisory Committee of the Heart and Stroke Foundation of Canada.

Dr. Nemer is regarded as a role model not only by the young female scientists at the IRCM but also by the numerous graduate students, postdoctoral fellows and colleagues that she has supervised or has simply interacted with.