# Dr. John Hiscott

**Immunotherapy of Cancer & Infectious Diseases**
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John Hiscott is the Director of the Pasteur Laboratory, Istituto Pasteur-Fondazione Cenci Bolognetti. The research program of Dr. Hiscott focuses on the early immune response to human pathogenic virus infection, and seeks to develop new immunotherapeutic strategies for the treatment of cancer and infectious diseases. His research has provided contributions to the understanding of the innate immune response to virus infection such as influenza, dengue, hepatitis C, and HIV. Dr. Hiscott is also involved in the development of experimental cancer therapies using oncolytic immunotherapy to specifically target and kill cancer cells. Dr. Hiscott has published more than 250 peer-reviewed research articles and invited reviews, with publications in prestigious international scientific journals, such as *Science, Nature Immunology, Cell Host & Microbe, Cancer Research and Proceedings of the National Academy of Sciences USA*. For his work, Dr. Hiscott has earned numerous awards and distinctions, including the Milstein Award, given by the International Society of Interferon and Cytokine Research for scientific achievement. He was the recipient of Scientist and Senior Investigator awards from the Canadian Institutes of Health Research. He also received the Distinguished Service Award from the Israel Cancer Research Fund, the Beijerinck Visiting Professorship in Virology from Leiden University Medical Center, The Netherlands and is a member of Canada's Who's Who. He is a member of several scientific journal editorial boards, and is Editor-in-Chief of *Cytokine and Growth Factors Review*, a leading immunology review journal.

Prior to joining Istituto Pasteur, Dr. Hiscott was the Director of the Viral Pathogenesis & Therapeutics program at the Vaccine & Gene Therapy Institute of Florida (2010-2015). He is currently Adjunct Professor in the Dept. of Medicine at McGill University, Montreal and previously was Professor of Medicine and Microbiology, as well as Director of the Molecular Oncology Group, Lady Davis Institute for Medical Research, McGill University. Dr. Hiscott received his doctorate degree in Medical Sciences from New York University Medical Center and completed Post-doctoral training at the Roche Institute in New Jersey and at the Institute for Molecular Biology at the University of Zurich.

## Snapshot

- Dr. Hiscott is a world-renowned molecular biologist and virologist; his research has focused on the innate immune response to infectious diseases, cancer and AIDS.

- His research has provided major contributions to models of the host antiviral response to infection and interferon (IFN) gene regulation, involving primary induction of IFN expression through the combined activities of IRF-3 and NF-κB, and secondary amplification of the response via IRF-7 stimulation of the antiviral transcriptional program.

- His laboratory identified the IKK-related kinases – IKKepsilon/TBK-1 - as critical signaling mediators of the innate immune response, thus functionally linking the NF-κB and IRF pathways in the development of the antiviral response

- Research from the Hiscott lab defined the synergism between histone deacetyase inhibitors (Vorinostat) and the oncolytic Vesicular Stomatitis Virus (VSV) in the treatment of human prostate, breast, and colon cancer.

- Editor, Cytokine & Growth Factor Reviews

- Scientific organizer of Cytokines 2008, Montreal Quebec; HTLV2013, Montreal.

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## Major Research Activities

The goals of the research program of Dr. John Hiscott are:
1) to understand the early events involved in the host response to human pathogenic virus infection; and 2) to use our knowledge of virus-host interactions to develop novel anti-cancer oncolytic vaccines.

Three different areas of research are currently being pursued:

1) Molecular interactions and signaling events that regulate the host antiviral immune response to virus infection, mediated through TLR dependent and RIG-I dependent signaling pathways - Interferon gene activation.
2) Development of oncolytic vaccines as cancer therapeutics. Investigation of promising combination therapies to improve the spectra of oncolytic vaccines as cancer therapeutics for solid and hematological malignancies.
3) Pathogenesis and gene expression in human retrovirus infection: analysis of the biochemical and genetic events that determine whether individuals infected with human T cell leukemia virus (HTLV-1) progress to leukemic disease or develop HTLV-1 associated myelopathy (HAM/TSP).

## Important Links

www.vgtifl.org/john-hiscott-phd

http://ladydavis.ca/en/johnhiscott

http://www.milstein-award.org/2003/06/john-hiscott-ph-d-2003/

**Selected Publications** (from ~250 peer-reviewed publications)


1. Olagnier D, Sze A, Bel Hadj S, Chiang C, Ye Z, Lin R, VanGrevenynghe J, **Hiscott J.** HTLV-1 Tax-mediated inhibition of FOXO3a transcriptional activity is critical for viral persistence and transformation. PLoS Pathogens 10: e1004575 doi. 10/1371/journal.ppat 1004575 (2014).

2. Olagnier D, Peri S, Steel C, vanMontfoort N, He Z, Nichols C, Lin R, Balachandran S, **Hiscott J.** Cellular oxidative stress response controls the antiviral and apoptotic programs in dengue virus-infected dendritic cells PLoS Pathogens 10: e1004566 doi. 10/1371/journal.ppat 1004566 (2014).

3. Sgarbanti M, Marsili G, Remoli AL, Stellacci E, Mai A, Rotili D, Perrotti E, Acchioni C, Orsatti R, Iraci N, Ferrari M, Borsetti A, **Hiscott J** and Battistini A. I kappa B kinase I kappa B kinase epsilon targets interferon regulatory factor 1 Mol. Cell. Biol. 34: 1054-1065 (2014).

4. Shulak L, Beljanski V, Chiang C, Dutta S, van Grevenynghe J, Belgnaoui M, Nguyen TL-A, Di Lenardo T, Semmes OJ, Lin R, **Hiscott J.** Histone deacetylase inhibitors potentiate VSV oncolysis in prostate cancer cells by modulating NF-kB dependent autophagy. J. Virol. 88: 2927-2940 (2014).

5. Olagnier D, Scholte FEM, Chiang C, Albulescu IC, Nichols C, He Z, Lin R, Snijder EJ, van Hemert MJ, **Hiscott J**. Inhibition of dengue and chikungunya virus infection by RIG-I-mediated type I IFN-independent stimulation of the innate antiviral response. J. Virol. 88: 4180-4194 (2014). [PMC Journal – In Process]

6. Sze A, Belgnaoui SM, Olagnier D, Lin R, Van Grevenynghe J, **Hiscott J.** Host restriction factor SAMHD1 limits human T cell Leukemia Virus (HTLV-1) infection of monocytes via STING-mediated apoptosis. Cell Host Microbe 14: 422-434 (2013).

7. Goulet ML, Olagnier D, Xu Z, Paz S, Arguello M, Lafferty E, Qureshi S, Sun Q, He Z, Richards S, Smith A, Wilkinson P, Cameron M, Trautmann L, Haddad E, Sekaly RP, Lin R, **Hiscott J.** Broad spectrum Inhibition of virus infectivity using RNA agonists of the RIG-I pathway PLoS Pathogens 9:e1003298 (2013). PMCID: PMC3635991

8. Samuel S, Van Grevenynghe J, Beljanski V, Richards S, He Z, Nichols C, Belgnaoui SM, Steel C, Goulet ML, Shamy A, Brown D, Haddad E, Abesada G, **Hiscott J**. BCL-2 inhibitors sensitize chronic lymphocytic leukemia cells to vesicular stomatitis virus oncolysis by triggering autophagic and apoptotic pathways. Mol. Therapy 21: 1413-1423 (2013).

9. Belgnaoui S, Paz S, Goulet ML, Samuel S, Sun Q, Kikkert M, Iwai K, Dikic I, Lin R, **Hiscott J**. Linear ubiquitination of NEMO negatively regulates the interferon antiviral response through disruption of the MAVS-TRAF3 complex. Cell Host & Microbe 12: 211-222 (2012).

10. Olagnier D, **Hiscott J**. Breaking the barrier: membrane fusion as an innate immune trigger. Nature Immunol. 13:713-715 (2012).

11. Lei Y, Wen H, Yu Y, Taxman D, Zhang L, Widman D, Swanson K, Damania B, Moore C, Giguere P, Siderovski D, **Hiscott J,** Razani B, Ting JP-Y. NLRX1 and TUFM form a mitochondrial complex that regulates type 1 interferon and autophagy. Immunity 36: 933-946 (2012). PMCID: PMC3397828

12. Solis M, Nakhaei P, Jalalirad M, Lacoste J, Douville R, Arguello M, Laughrea M, **Hiscott J.** RIG-I dependent antiviral signaling is inhibited during *de novo* HIV-1 infection by protease-mediated sequestration of RIG-I. J. Virol. 85: 1224-1236 (2011). PMCID: PMC3020501

13. Paz S, Vilasco M, Arguello M, Werden S, Lin R, Meurs E, **Hiscott J**. A functional C-terminal TRAF3-binding site in MAVS participates in positive and negative regulation of the IFN antiviral response. Cell Research 21: 895-910 (2011).

14. Paz S, **Hiscott J**. Curtailing IRF signaling with the E3 ligase RAUL. Immunity 33: 833-835 (2010).

15. Olière S, Hernandez E, Lézin A, Nguyen TL, Arguello M, Wilkinson P, Sekaly R, Césaire R and **Hiscott J**. HTLV-1 evades antiviral immunity via upregulation of SOCS1 PLoS Pathogens, 6: e1001177 (2010). PMCID: PMC2973829

16. Goubau D, Romieu-Mourez R, Solis M, Hernandez E, Mesplede T, Lin R, Leaman D, **Hiscott J.** Transcriptional re-programming of human macrophages reveals distinct apoptotic and anti-tumor functions of IRF-3 and IRF-7. Eur. J. Immunol. 39 : 527-540 (2009).

17. Paz S, Vilasco M, Arguello M, Lacoste J, Nguyen L-A, Shestakova E, Bibeau-Poirier S, Servant M, Lin R, Meurs E, **Hiscott J.** Ubiquitin dependent recruitment of IKKe to the MAVS adapter Mol. Cell. Biol. 29: 3401-3412 (2009).

18. Genin P, Lin R, **Hiscott J**, Civas A. Distinct transcriptional effects of IRF-3 and IRF-7 on human interferon alpha gene expression. Mol. Cell. Biol. 29: 3435-3450 (2009).

19. Nakhaei P, Mesplede T, Sun Q, Solis M, Yang L, Chuang T-H, Ware CF, Lin R, **Hiscott J.** The E3 Ubiquitin ligase TRIAD3A negatively regulates the RIG-I/MAVS signaling pathway by targeting TRAF3 for degradation PLoS Pathogens 5: e1000650 (2009). PMCID: PMC2766052

20. Nguyen L-A, Abdelbary H, Arguello M, Breitbach C, Leveille S, Yasmeen A, Bismar T, Falls T, Werier J**,** Bell JC, **Hiscott J**. Chemical targeting of the innate antiviral response by histone deacetylase inhibitors renders refractory cancers sensitive to viral oncolysis Proc. Natl. Acad. Sci. 105: 14981-14986 (2008). PMCID: PMC2567479

21. Zhao TJ, Yang L, Sun Q, Arguello M**,** Ballard DW, **Hiscott J,** Lin R. The NEMO/IKKγ adapter bridges NF-κB and IRF signaling pathways. Nature Immunology, 8: 592-600 (2007).

22. Romieu-Mourez R, Solis M, Nardin A, Goubau D, Baron-Bodo V, Massie B, Salcedo M, **Hiscott J.** Distinct roles of IRF-3 and IRF-7 in the activation of anti-tumor properties of human macrophages. Cancer Research, 66 : 10576-10585 (2006).

23. tenOever B, Sharma S, Zou W, Sun Q, Grandvaux N, Julkunen I, Akira S, Yeh W, Lin R, **Hiscott J**. Activation of TBK1 and IKKe kinases by VSV infection J. Virol. 78: 10636-10649 (2004). PMCID:PMC516426

24. Stojdl D, Lichty B, tenOever B, Knowles S, Marius R, Reynard J, Ruoso P, Poloquin L, Atkins H, Brown EG, Durbin R, Durbin J, **Hiscott J**, Bell JC. Oncolytic VSV strains with defects in the shutdown of innate immunity are potent systemic anti-cancer agents. Cancer Cell 4: 263-275 (2003).

25. Sharma S, tenOever B, Grandvaux N, Zhou G, Lin R, **Hiscott J**. Triggering the interferon antiviral response through an IKK-related pathway. Science 300: 1148-1151 (2003).