BIOGRAPHICAL SKETCH

NAME: John H. White

POSITION: Professor and Chair, Department of Physiology, McGill University, Montreal, Canada

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Carleton University, Ottawa, On, Canada	B.Sc.	05/1979	Biochemistry
Carleton University, Ottawa, On, Canada	M.Sc.	09/1981	Chemistry
Harvard University, Cambridge, MA Supervisor, C.C. Richardson	Ph.D.	11/1986	Biochemistry
Laboratoire de Génétique Moléculaire des Eucaryotes, Strasbourg, France (Superviser, Pr. Pierre Chambon)	PDF	01/87-02/91	Molecular biology of nuclear receptors

A. Personal Statement. My laboratory has long focused on studying the mechanisms and physiological consequences of regulation of gene transcription by nuclear receptors, in particular the vitamin D receptor (VDR). The lab's work has focused largely on the non-classical physiological actions of vitamin D, whose biologically active form, 1,25-dihydroxyvitamin D (1,25D), controls the ligand-dependent transcriptional regulation functions of the VDR. The laboratory has made major contributions towards understanding the potential role of vitamin D signaling in cancer prevention and in regulation of immune system function. My group has extensive experience in several molecular genetics and genomics techniques. We were the first to employ high-throughput genomics techniques like microarrays to analyze gene regulation by the VDR, which, as detailed below, led to several novel insights into vitamin D biology.

B. Positions and Honors

Academic Experience

Mar. 1991	Assistant Professor,	Dept. of Physiology, McGill University, Montreal.
Jun. 1997	Associate Professor,	Dept. of Physiology, McGill University, Montreal.
Nov. 1997	Associate Professor,	Dept. of Medicine, McGill University, Montreal.
Dec. 1997	Member,	Research Institute of the Royal Victoria Hospital.
Dec. 1998	Member,	Montreal Centre for Experimental Therapeutics in Cancer.
Jan. 2000	Member,	Centre for Advanced Bone and Peridontal Research.
Dec. 2000	Member,	Division of Experimental Medicine.
Jun. 2003	Professor,	Dept. of Physiology, McGill University, Montreal.
Jun. 2003	Professor,	Dept. of Medicine, McGill University, Montreal.
Jun. 2012	Member,	McGill International TB Centre
Jun. 2017	Chair,	Dept. of Physiology, McGill University, Montreal.
Jun. 2022	Chair (reappointed)	Dept. of Physiology, McGill University, Montreal.

Honours, Awards, Recognition

1979	Ontario Graduate Scholarship (Declined)
1979-1984	NSERC Postgraduate Scholarship.
1986	NCIC Postdoctoral Fellowship, (Declined).
1986-1987	NSERC Postdoctoral Fellowship, (held through the end of 1988).

1988	Metzger, White, Chambon (1988) *Nature* highlighted in Scientific American.
1989-1990	Research Fellowship, Centre Nationale de Recherche Scientifique, France.
1990-1991	Research Fellowship, Fondation pour la Recherche Medicale, France.
1992-1996	Fonds de la Recherche en Santé du Québec, Chercheur-boursier "Junior 1"
1996-2000	Fonds de la Recherche en Santé du Québec, Chercheur-boursier "Junior 2".
2000-2004	Fonds de la Recherche en Santé du Québec, Chercheur-boursier "Senior".
2004-2009	Fonds de la Recherche en Santé du Québec, Chercheur-boursier "National".
2007	Article accepted in Scientific American based on Wang et al (2004) *J. Immunol.*
2010	Wang et al (*J. Biol. Chem.*, 2010) chosen 2x by the Faculty of 1000.
2010	An et al. *Mol. Cell. Biol* selected as an editor's choice in *Science Signaling*.
2012	Salehi-Tabar et al (Proc. Acad. Sci. USA) named a top-ten achievement in cancer research in 2012 by the Canadian Cancer Society.
2015	Elected Scientific Chair of the 2017 Vitamin D Workshop, Orlando, Florida.
2017, 2019	Ann Wechsler Award for excellence in U3 undergraduate teaching, Dept. of Physiology.
2017	Promoted to Department of Physiology Chair.
2017	Appointed Joseph Morley Drake Chair of Physiology.
2022	Renewal as Chair of Physiology
2022	Renewal of Joseph Morley Drake Chair
2022	White. J.H. (2022) *Nutrients* 14, 284. Recommended in Faculty Opinions.

C. Contributions to Science (147 peer-reviewed publications, 17,185 citations, H-index: 63)
Google Scholar: https://scholar.google.ca/citations?hl=en&user=bEkT5bMAAAAJ

1. Genomics of vitamin D signaling. We performed the first large-scale gene expression profiling studies of 1,25D signaling. Collectively, these studies identified over 1,000 vitamin D target genes and vastly expanded our knowledge of 1,25D-regulated gene expression. They provided numerous insights into the non-classical actions of 1,25D (those unrelated to calcium homeostasis), in particular its capacity to regulate cell proliferation and differentiation and its role in immune system regulation.

1. Akutsu, N., Lin, R., Bastien, Y., Bestawros, A., Enepekides, D.J., Black, M.J. and **White, J.H.** (2001) Regulation of Gene Expression by 1α,25-dihydroxyvitamin D_3 and its Analog EB1089 under Growth Inhibitory Conditions in Squamous Carcinoma Cells. *Mol. Endocrinol.* **15**, 1127-39. (223 citations).
2. Lin, R., Nagai, Y., Sladek, R., Bastien, Y., Ho, J., Petrecca, K., Sotiropoulou, G., Diamandis, E.P., Hudson, T., and **White J.H.** (2002) Expression profiling in squamous carcinoma cells reveals pleiotropic effects of vitamin D3 signaling on cell proliferation, differentiation and immune system regulation. *Mol. Endocrinol.* **16**, 1243-56. (247 citations)
3. Wang, T.T., Tavera-Mendoza, L., Laperriere, D., Nagai, Y., Burton MacLeod, N., Libby, E., Zhang, R., Bourdeau, V., Konstorum, A., Lallemant, B., Mader, S., **White, J.H.** (2005) Large-scale *in silico* and microarray-based genomic screening of 1,25-dihydroxyvitamin D_3 target genes. *Mol. Endocrinol.* **19**, 2685-95. (739 citations)
4. Verway, M., Bouttier, M., Wang, T.T., Carrier, M., Calderon, M., An, B.-S., Devemy, E., McIntosh, F., Divangahi, M., Behr, M.A. and **White, J.H.** (2013) Vitamin D induces interleukin-1β expression: Paracrine macrophage-epithelial signaling controls *M. tuberculosis* infection. *PLoS Pathogens* **9(6)**: e1003407. doi:10.1371/journal.ppat.1003407. (281 citations).
5. Dimitrov, V., Barbier, C., Ismailova, A., Wang, Y., Dmowski, K., Salehi-Tabar, R., Memari, B., Groulx-Boivin, E. and **White, J.H.** (2021) Vitamin D-regulated gene expression profiles: species-specificity and cell-specific effects on metabolism and immunity. *Endocrinology* **162**, bqaa218. https://doi.org/10.1210/endocr/bqaa218. (60 citations).

2. Anticancer properties of vitamin D. We have been interested in how vitamin D signaling controls cell proliferation in cancer cells. This work has led to discoveries of novel mechanisms of gene regulation by the VDR and how the VDR regulates protein turnover. We found that vitamin D analogues block proliferation of head and neck squamous carcinoma cells (HNSCC) *in vitro* and inhibit squamous tumour growth *in vivo* (1). Our early gene expression profiling studies, described above, were performed in 1,25D-sensitive head and neck squamous carcinoma cells and provided numerous insights into cell-cycle regulation by 1,25D. They were instrumental in leading to the discovery that the 1,25D-bound VDR recruits Sirtuin 1 deacetylase to activate of FoxO protein tumor suppressor proteins and induce cell cycle arrest (2). Subsequently, we found that vitamin D signaling is a master regulator of expression and function of the oncogenic transcription factor cMYC and its antagonist MXD1 (3). 1,25D signaling leads to suppression of cMYC signaling by multiple mechanisms, and subsequent work showed that the 1,25D-bound VDR suppresses cMYC function in part via using the tumor suppressor and E3 ligase FBW7 as a cofactor to drive the proteasomal turnover of cMYC and other cell cycle drivers. (4).

1. Prudencio, J. Akutsu, N., Wong, T., Bastien, Y., Lin, R., Black, M.J., Alaoui-Jamali, M. and **White, J.H.** (2001) Action of low calcemic 1,25-dihydroxyvitamin D3 analog EB1089 in head and neck squamous cell carcinoma. *J. Nat. Cancer Inst.* **93**, 745-53. (97 citations)
2. An, B.-S., Tavera-Mendoza, L.E., Dimitrov, V., Wang, X., Calderon, M., Wang, H.-J., and **White, J.H.** (2010) Stimulation of SIRT1-regulated FoxO protein function by the ligand-bound vitamin D receptor. *Mol. Cell. Biol.* **30**, 4890-4900. *Chosen as an Editor's Choice in Science Signaling [Sci. Signal. (2010) Vol. **3**, Issue 141, p. ec295]*. (154 citations)
3. Salehi-Tabar, R., Nguyen-Yamamoto, L., Tavera-Mendoza, L.E., Quail, T., Dimitrov, V., An, B.-S., Glass, L., Goltzman, D. and **White, J.H.** (2012) The vitamin D receptor as a master regulator of the cMYC/MXD1 network. *Proc. Nat. Acad. Sci. U.S.A.* **109**, 18827-32. *Voted one of the top 10 cancer research stories of 2012 by the Canadian Cancer Society.* (137 citations)
4. Salehi-Tabar, R., Memari, B., Wong, H. Rochel, N. and **White, J.H.** (2019) The E3 ligase FBW7 and the vitamin D receptor are mutual cofactors in protein turnover and transcriptional regulation. *Mol. Cancer Res.* **17**, 709-719. (19 citations).

3. Vitamin D is an inducer of antimicrobial innate immunity. Our early papers revealed a large number of 1,25D target genes whose products are implicated in immune system function (Mol. Endocrinol, 2002, 2005). This led to our discovery of consensus binding sites for the VDR (vitamin D response elements) in the regulatory regions of human genes encoding antimicrobial peptides, DEFB4/HBD2 and CAMP, two of the body's natural antibiotics. We showed that expression of both genes was induced and that treatment of cells with 1,25D led to secretion of anti-bacterial activity (1). This paper opened up the field of study of 1,25D as an inducer of innate immunity in humans. It was highlighted in an article in Scientific American (2; translated into 12 at least languages). We discovered that 1,25D stimulates the NOD2 -> DEFB4 innate immune pathway (3), whose compromised function is associated with increased risk of Crohn's disease (CD). This observation provided a molecular basis for the association between vitamin D deficiency and the pathogenesis of CD, and has been borne out by intervention trials and meta-analyses. We have characterized how 1,25D boosts innate immune responses to *M.tb.* infection, and enhances autocrine/ paracrine innate immune signaling (4). We also found that 1,25D regulates catabolism of branched-chain amino acids (BCAAs), which are used by myeloid cells as metabolic sensors. Their 1,25D-induced catabolism suppresses signaling through metabolic kinase mTOR, enhancing autophagy (5).

1. Wang, T.T., Nestel, F., Bourdeau, V., Nagai, Y., Wang, Q., Wu, J., Tavera-Mendoza, L., Lin, R., Hanrahan, J.W., Mader, S. and **White, J.H.** (2004) Cutting Edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J. Immunol.* **173**, 2909-12. (2,106 citations)
2. Tavera-Mendoza, L. and **White, J.H.** (2007) Cell defenses and the sunshine vitamin. *Scientific American.* November, **297**, 62-72. (172 citations)

3. Wang, T.T, Dabbas, B., Laperriere, D., Bitton, A., Tavera-Mendoza, L.E., Soualhine, H., Dionne, S., Servant, M.J., Bitton, A., Seidman, E., Mader, S., Behr, M. and **White, J.H.** (2010) Direct and indirect induction by 1,25-dihydroxyvitamin D_3 of the NOD2/CARD15-beta defensin 2 innate immune pathway defective in Crohn's disease. *J. Biol. Chem*. **285**, 2227 – 2231. *Recommended 2x by the Faculty of 1000.* (481 citations)
4. Verway, M., Bouttier, M., Wang, T.T., Carrier, M., Calderon, M., An, B.-S., Devemy, E., McIntosh, F., Divangahi, M., Behr, M.A. and **White, J.H.** (2013) Vitamin D induces interleukin-1β expression: Paracrine macrophage-epithelial signaling controls *M. tuberculosis* infection. *PLoS Pathogens* **9(6)**: e1003407. (281 citations)
5. Dimitrov, V., Barbier, C., Ismailova, A., Wang, Y., Dmowski, K., Salehi-Tabar, R., Memari, B., Groulx-Boivin, E. and **White, J.H.** (2021) Vitamin D-regulated gene expression profiles: species-specificity and cell-specific effects on metabolism and immunity. *Endocrinology* **162**, bqaa218. https://doi.org/10.1210/endocr/bqaa218. (60 citations).

4. Vitamin D regulates transcriptional events controlling thymic negative T cell selection and autoimmunity. Recent work has linked vitamin D signaling to molecular events in the thymus that are fundamental for prevention of autoimmunity. The thymus is an organ that is essential for elimination of self-reactive T cells. The lab showed that the critical thymic protein AIRE, whose absence leads to a condition called APECED, characterized by multiple autoimmune conditions, is a cofactor of the vitamin D receptor (1). Intriguingly, loss of vitamin D signaling impairs normal thymic development and AIRE function, and leads to premature thymic aging (2). These findings provide a compelling molecular basis for several clinical studies linking vitamin D deficiency early in life to increased risk of autoimmunity.

1. Artusa, P., Lebel, M.-E., Memari, B., Salehi-Tabar, R., Barbier, C., Karabatsos, S., Ismailova, A., Melichar, H. and **White, J.H.** (2023) Cutting Edge: Aire is a coactivator of the vitamin D receptor. *J. Immunol.* **211**, 175-179. (1 citation)
2. Artusa, P., Nguyen-Yamamoto, L., Barbier, C., Aghazadeh Habash, Y., Ismailova, A., Lebel, M.-E., Salehi-Tabar, R., Ragoussis, I., Goltzman, D., Melichar, H. and **White, J.H.** (2023) Skewed epithelial morphogenesis and premature aging of the thymus in the absence of vitamin D signaling. *Science Adv.* (under revision).

5. Host macrophage innate immune responses to M. tuberculosis infection. We found that signaling through the aryl hydrocarbon receptor (AhR; 1) and the nuclear liver X receptor α (LXRα; 2) is engaged during *M.tb.* infection, and that their agonists reduce mycobacterial viability. The AhR regulates expression of several innate immune cytokines expressed in macrophages (1). LXRα signaling reduces *M.tb.* viability by altering metabolism of cholesterol, a critical *M.tb.* carbon source.

1. Memari, B., Bouttier, B., Dimitrov, V., Behr, M.A., Fritz, J.H., and **White, J.H.** (2015) Engagement of aryl hydrocarbon receptor signaling by *M. tuberculosis*-infected macrophages. *J. Immunol.* **195**, 4479-91. (69 citations)
2. Bouttier, M., Laperriere, D., Memari, B., Verway, M., Mitchell, E., Wang, T.T., Behr, M., Sladek, R., Mader, S. and **White, J.H.** (2016) Alu repeats as transcriptional regulatory platforms in macrophage responses to *M. tuberculosis* infection. *Nucl. Acid. Res.* doi: 10.1093/nar/gkw782. (51 citations).

6. Chemical biology of vitamin D hybrid molecules. An off-shoot of our work on cell cycle regulation by vitamin D signaling led to the development of novel bifunctional hybrid molecules that act as anticancer agents. Hybrids combine fully integrated VDR agonism and histone deacetylase inhibition and are efficacious against a range of cancer models that are resistant to 1,25D monotherapy. 1,25D and histone deacetylase (HDAC) inhibitors synergistically block proliferation of 1,25D-resistant poorly differentiated squamous carcinoma cells. We initially synthesized hybrid molecules that incorporate HDAC inhibitory activity into the secosteroidal backbone of 1,25D (1,2). We then developed a series of

more synthetically accessible non-steroidal hybrid compounds that display enhanced efficacy in vitro (3-5) and *in vivo* in a highly aggressive model of triple-negative breast (5). This work has resulted in 4 patents to date. Current work aims to optimize lead compounds and fully understanding the molecular basis for their anti-tumor and anti-metastatic activities (6).

1. Tavera-Mendoza, L.E., Quach, T., Dabbas, B., Hudon, J., Liao, X., Palijan, A., Gleason, J.L., and **White, J.H.** (2008) Incorporation of histone deacetylase inhibition into the structure of a nuclear receptor agonist. *Proc. Nat. Acad. Sci. U.S.A.* **105**, 8250-55. [Reviewed in Nature Science-Business Exchange: Lou, K.-J. (2008) Engineering Bifunctionality. *Nature SciBX*, **1**(22), pp9,10]. (79 citations)
2. Lamblin, M., Dabbas, B., Spingarn, R., Mendoza-Sanchez, R., Wang, T.T., An, B.-S., Burger, M., Kremer, R., **White, J.H.***, Gleason, J.L.* (2010) Vitamin D receptor agonist/histone deacetylase inhibitor molecular hybrids. *Bioorg. Med. Chem.* **18**, 4119-37. *corresponding authors. (43 citations)
3. Fisher, J., Wang, T.T., Kaldre, D., Rochel, N., Moras, D., **White, J.H.***, Gleason J.L.* (2012) Synthetically accessible non-secosteroidal hybrid molecules combining vitamin D receptor agonism and histone deacetylase inhibition. *Chemistry & Biology* **19**, 963-71. *corresponding authors. (38 citations)
4. Kaldre, D., Wang, T.T., Fischer, J., **White J.H.*** and Gleason J.L.* (2015) Optimization of histone deacetylase inhibitor activity in non-secosteroidal vitamin D receptor agonist hybrids. *Bioorg. Med. Chem.* **23**, 5035-49. *corresponding authors. (13 citations)
5. Bijian, K., Kaldre, D., Wang, T.-T., Bouttier, M, Boucher, A., Alaoui-Jamali, M., **White, J.H.***, Gleason, J.L.* (2018) Efficacy of hybrid vitamin D receptor agonist/histone deacetylase inhibitors in vitamin D-resistant triple-negative 4T1 breast cancer. *J. Ster. Biochem. Mol. Biol.* **177,** 135-139. (12 citations)
6. Barbier, C., Mansour, A., Ismailova, A., Zeitouni, C., Bouttier, M., Scalata, D., Gleason, J. and **White, J.H.** (2022) Molecular mechanisms of bifunctional vitamin D receptor agonist-histone deacetylase inhibitor hybrid molecules in triple-negative breast cancer. *Scientific Reports* **12**, 1-13. (3 citations)

7. Identification and characterization of transcriptional corepressor LCoR. We cloned and characterized nuclear receptor coregulator Ligand-dependent CoRepressor LCoR, and found that it functions by histone deacetylase (HDAC)-dependent and –independent mechanisms (1,2). Unlike corepressors NCoR and SMRT, LCoR binding to receptors is agonist-inducible. We found that LCoR and cofactor HDAC6 are components of polycomb group transcriptional repressor complexes (2). LCoR is also a corepressor of other classes of transcription factors (3,4).

1. Fernandes, I, Bastien, Y., Wai, T., Nygard, K., Lin, R., Cormier, O., Lee, H.S., Eng, F., Bertos, N.R., Pelletier, N., Mader, S., Han V.K.M., Yang, X.J. and **White, J.H.** (2003) Ligand-dependent corepressor LCoR functions by histone deacetylase-dependent and –independent mechanisms. *Molecular Cell*, **11**,139-50. (305 citations)
2. Palijan, A., Fernandes, I., Verway, M., Kourelis, M., Bastien, Y., Tavera-Mendoza, L.E., Sacheli, A., Bourdeau, V., Mader, S., and **White, J.H.** (2009) Ligand-dependent corepressor LCoR is an attenuator of progesterone-regulated gene expression. *J. Biol. Chem.* **284**, 30275-87. (48 citations)
3. Palijan, A., Fernandes, I., Verway, M., Kourelis, M., Bastien, Y., Tang, L., Tavera-Mendoza, L.E., Li, Z., Bertos, N.R., Bourdeau, V., Mader, S., Yang, X.J. and **White, J.H.** (2009) Function of HDAC6 as a cofactor of nuclear receptor corepressor LCoR. *J. Biol. Chem.* **284**, 30264-74. (66 citations)
3. Calderon, M., Verway, M., An, B.-S., DiFeo, A., Bismar, T., Ann, D.K., Martignetti, J.A., Shalom-Barak, T. and **White, J.H.** (2012) Ligand-dependent Corepressor (LCoR) Recruitment by Kruppel-like Factor 6 (KLF6) Regulates Expression of the Cyclin-dependent Kinase Inhibitor CDKN1A Gene. *J. Biol. Chem.* **287**, 8662-74. (50 citations)
4. Calderon, M. Verway, M., Benslama, R.O., Birlea, M., Bouttier, M., Dimitrov, V., Mader, S., and **White, J.H.** (2014) Ligand-dependent corepressor contributes to transcriptional repression by C_2H_2 zinc-finger transcription factor ZBRK1 through association with KRAB-associated protein-1**.** *Nucl. Acids Res.* **42**, 7012-27. (23 citations).