BIOGRAPHICAL SKETCH

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NAME: DILWORTH, F. Jeffrey

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Senior Scientist, Ottawa Hospital Research Institute

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Queen's University, Kingston, ON, Canada	B.Sc.(Hons)	04/1992	Biochemistry
Queen's University, Kingston, ON, Canada	Ph.D.	01/1997	Biochemistry
Institut de Génétique et de Biologie Moléculaire et Cellulaire, Strasbourg, France	Postdoctoral	03/2001	Molecular Biology
Fred Hutchinson Cancer Research Center	Postdoctoral	08/2004	Cell Biology

A. Personal Statement

For the past 16 years, my research has focused on understanding the epigenetic mechanisms directing the spatial and temporal control of the muscle-specific gene expression programs. More specifically, we have been working to define the epigenetic factors that control transitions between different satellite cell fates during muscle regeneration. Our group uses both *in vitro* and *in vivo* approaches to address this problem. We have established the first *in vitro* transcription system that allows faithful reproduction of MyoD-dependent transcriptional activation in the test tube. Furthermore, we have developed many important tools to study epigenetic mechanisms of transactivation in cultured cell systems. Using these systems, we have established that the ongoing antagonism between Polycomb and Trithorax group proteins plays a key role in regulating the expansion of muscle progenitor cells to ensure the regeneration of healthy muscle fibers. Furthermore, our work has contributed significantly to the understanding of the transcriptional regulators that target Trithorax group proteins to specific loci to establish muscle-specific gene expression. This work is providing us with important new therapeutic targets that are expected to help modulate satellite cell expansion and/or niche repopulation to ensure more efficient regeneration in muscle wasting diseases and aging.

M.Brand, K. Nakka, J. Zhu and **F.J. Dilworth**. Polycomb/Trithorax Antagonism: Cellular Memory in Stem Cell Fate and Function. *Cell Stem Cell* 4: 518-533, 2019.

H. Faralli, C. Wang, K. Nakka, A. Benyoucef, S. Sebastian, L. Zhuang, A. Chu, C. Palii, C. Liu, B. Camellato, M. Brand, K. Ge, and **F.J. Dilworth**. H3K27-demethylase activity of UTX/KDM6A is essential for skeletal muscle regeneration. *J Clin Invest* 126: 1555-1565, 2016.

K. Singh¶, M. Cassano¶, E. Planet, S.Sebastian, S.M. Jang, G. Sohi, J. Choi, H.D. Youn, **F.J. Dilworth***, and D. Trono*. KAP1 functions as a phosphorylation-inducible activator of MyoD function during skeletal muscle differentiation. *Genes & Dev* 29: 513-525, 2015. (*co-corresponding authors)

S. Sebastian, H. Faralli, Z. Yao, P. Rakopoulos, C. Palii, Y. Cao, K. Singh, Q-C. Liu, A. Chu, A. Aziz, M. Brand, S.J. Tapscott, and **F.J. Dilworth.** Tissue-specific splicing of a ubiquitously expressed transcription factor is essential for muscle differentiation. *Genes & Dev* 27: 1247-1259, 2013.

S. Seenundun, S. Rampalli, Q-C. Liu, A. Aziz, C. Palii, S.H. Hong, A. Blais, M. Brand, K. Ge, **F.J. Dilworth**. UTX-mediated demethylation of H3K27me3 at muscle-specific genes during myogenesis. *EMBO Journal* 29: 1401-1411, 2010.

S. Rampalli, L. Li, E. Mak, K. Ge, M. Brand, S.J. Tapscott, and **F.J. Dilworth**. p38 MAPK signaling pathway regulates recruitment of Ash2L-containing methyltransferase complexes to specific genes during differentiation. *Nature Struct Mol Biol* 14: 1150-1156, 2007.

B. Positions and Honors

Positions and Employment

Ottawa Hospital Research Institute (Ottawa, Canada), Regenerative Medicine Program
- *2010-present* *Senior Scientist*
- *2004-2010* *Scientist*

University of Ottawa (Ottawa, Canada), Department of Cellular and Molecular Medicine
- *2016-present* *Full Professor*
- *2011-2016* *Associate Professor*
- *2004-2011* *Assistant Professor*

University of Ottawa (Ottawa, Canada), Department of Medicine - Division of Neurology
- *2016-present* *Full Professor*
- *2011-2016* *Associate Professor*
- *2004-2011* *Assistant Professor*

University of Ottawa (Ottawa, Canada), Department of Surgery – Division of Orthopaedic Surgery
- *2016-present* *Full Professor*

University of Ottawa (Ottawa, Canada), LIFE Research Institute
- *2019-present* *co-Director, Live Long Section*
- *2017-present* *Steering Committee Member*

University of Ottawa (Ottawa, Canada), Ottawa Institute for Systems Biology
- *2014-present* *Associate Member*

Fred Hutchinson Cancer Research Center (Seattle, WA), Human Biology Division
- *2001-2004* *Associate*

Institut de Génétique et de Biologie Moléculaire et Cellulaire (Strasbourg, France), Transcription
- *1997-2001* *Post-Doctoral Fellow*

Other Experience and Professional Memberships

Professional Activities

2019 - present	LIFE Research Institute, University of Ottawa, co-Director – Live Long Pillar
2016 - present	Canadian Epigenetics, Environment and Health Research Consortium, Executive Committee Member
2016 - present	Ottawa Centre for Epigenetic Research, Director
2014 – 2019	Canadian Neuromuscular Disease Network, Chair – Research Task Force
2010 - present	Ontario Stem Cell Initiative, Member
2005 - present	Stem Cell Network, Member
2004 - present	International Regulome Consortium, Member
2003 - present	Society for Muscle Biology, Member
1994 - present	American Society for Bone and Mineral Research, Member

Review Panel Membership

2019-	Panel co-Chair, Italian Telethon Foundation (Italy)
2019-2020	Special Emphasis Panel Member, National Institutes of Health (USA)
2016-2018	Peer Review Committee, Italian Telethon Foundation (Italy)
2015-	Panel Chair, Congressional Directed Medical Research Program (USA)
2012-2014	Scientific Reviewer, Congressional Directed Medical Research Program (USA)
2008-	Peer Review Committee Member, Canadian Institutes of Health Research (Canada)

Honors

2007-2012	Early Researcher Award, Ontario Ministry of Research and Innovation
2005-2015	Canada Research Chair (Tier II) - Epigenetic Regulation of Transcription, Canadian Institutes of Health Research
2005-2007	New Investigator Grant, Stem Cell Network/ Muscular Dystrophy Canada

2004-2006 Senior Research Fellowship - Phase II, Canadian Institutes of Health Research
2001-2004 Development Grant, Muscular Dystrophy Association, USA
2001-2003 Senior Research Fellowship - Phase I, Canadian Institutes of Health Research
1999 Postdoctoral Fellowship, Medical Research Council of Canada
1998 Postdoctoral Fellowship, Fondation pour la Recherche Médicale
1997-1998 Postdoctoral Fellowship, Natural Science and Engineering Research Council
1995-1996 Ontario Graduate Scholarship
1995 Huntly MacDonald Sinclair Travelling Scholarship, University of California at San Francisco
1994-1995 R.S. MacLaughlin Fellowship, Endowed Research Fellowship - Queen`s University
1994 Leo Foundation 'Young Investigator Award', 9th Workshop on Vitamin D - Orlando, Fla, USA
1993 Merck 'Young Investigator Award', 15th Meeting of the ASBMR - Tampa, Fla USA

C. Contribution to Science

1. Demonstrating that transcription factors play a key role in recruiting the trithorax group epigenetic complexes to muscle genes to regulate gene expression. We have published several papers establishing that transcription factors are responsible for targeting trithorax complexes to specific genomic loci. These findings were highly novel since it showed that mammals use a different mechanism to target trithorax-complexes to genes compared to *Drosophila* where trithorax-complexes are targeted to genomic loci through direct binding of PRE elements within the promoter. Furthermore, our demonstration of the need for specific signaling events (ie p38-mediated phosphorylation of Mef2D) for Ash2L recruitment to muscle genes. This study was novel as it was the first to link a cell signaling pathway with the establishment of histone methylation. These findings suggest that therapeutic modulation of p38 MAPK signaling could be used to control cell fate transitions. Indeed, Merck (Kenilworth, NJ) contacted us to license our Ash2L antibody as a tool to screen their library of p38 MAPK inhibitors for biological function.

H. Faralli, C. Wang, K. Nakka, A. Benyoucef, S. Sebastian, L. Zhuang, A. Chu, C. Palii, C. Liu, B. Camellato, M. Brand, K. Ge, and **F.J. Dilworth**. H3K27-demethylase activity of UTX/KDM6A is essential for skeletal muscle regeneration. *J Clin Invest* 126: 1555-1565, 2016.
K. Singh¶, M. Cassano¶, E. Planet, S.Sebastian, S.M. Jang, G. Sohi, J. Choi, H.D. Youn, **F.J. Dilworth***, and D. Trono*. KAP1 functions as a phosphorylation-inducible activator of MyoD function during skeletal muscle differentiation. *Genes & Dev* 29: 513-525, 2015. (*co-corresponding authors)
S. Seenundun, S. Rampalli, Q-C. Liu, A. Aziz, C. Palii, S.H. Hong, A. Blais, M. Brand, K. Ge, **F.J. Dilworth**. UTX-mediated demethylation of H3K27me3 at muscle-specific genes during myogenesis. *EMBO Journal* 29: 1401-1411, 2010.
S. Rampalli, L. Li, E. Mak, K. Ge, M. Brand, S.J. Tapscott, and **F.J. Dilworth**. p38 MAPK signaling pathway regulates recruitment of Ash2L-containing methyltransferase complexes to specific genes during differentiation. *Nature Struct Mol Biol* 14: 1150-1156, 2007.

2. Demonstrating that a muscle-specific splicing of Mef2D converts the transcription factor from a repressor to an activator in order to precisely control the timing at which muscle functional genes get turned on during differentiation.This work elucidated a novel mechanism used to temporally control gene expression whereby Mef2D is converted from a repressor to an activator by a tissue-specific alternative splicing event that generates an isoform that is resistant to PKA phosphorylation (though the Thr residue targeted by PKA is present in both Mef2D isoforms). This work resolved a paradox in the field by explaining how PKA signaling could be both inhibitory and stimulatory during muscle differentiation. While the phosphorylation of CREB by PKA is required for differentiation, the phosphorylation of Mef2D by PKA prevents expression of late muscle genes to block differentiation. To get around this block in differentiation, we found that muscle cells generate a muscle-specific isoform of Mef2D that evades PKA signaling, allowing Mef2D to activate its target genes in the presence of an otherwise inhibitory PKA signal.

S. Sebastian, H. Faralli, Z. Yao, P. Rakopoulos, C. Palii, Y. Cao, K. Singh, Q-C. Liu, A. Chu, A. Aziz, M. Brand, S.J. Tapscott, and **F.J. Dilworth.** Tissue-specific splicing of a ubiquitously expressed transcription factor is essential for muscle differentiation. *Genes & Dev* 27: 1247-1259, 2013.

3. Identify a role for p38 signaling in controlling myoblast fusion. This work used comparative genomic analysis to identify roles for p38 signaling in processes beyond the activation of myogenin gene expression.

Phenotipically, we observed that p38 signaling was not required for cell migration, but was essential to the fusion of myoblasts. Exploting this phenotype, we used gene expression arrays to identify CD53 as a novel cell surface protein that contributes to muscle cell fusion. In addition, we identified Myogenin gene expression as a key event in cell cycle exit, where its expression acts as a point of no return in the decision for muscle stem cells to undergo terminal differentiation.

Q-C. Liu, X. Zha, H. Faralli, H. Yin, C. Louis-Jeune, E. Perdiguero, E. Pranckeviciene, P. Munoz-Canoves, M. Rudnicki, M. Brand, C. Perez-Iratxeta, and **F.J. Dilworth**. Comparative expression profiling identifies differential roles for Myogenin and p38α MAPK signaling in myogenesis. *J Mol Cell Biol* 4: 386-397, 2012.

4. Establishment of the first *in vitro* transcription systems that reproduced ligand-dependent transcriptional activation by retinoic acid receptor dimers (RAR/RXR) and transcriptional activation by MyoD-E12 heterodimers. Using DNA templates chromatinized *in vitro* and proteins purified from baculovirus infected insect cells, I established a system that would allow transcription from a reporter gene using a promoter that contained binding sites for RAR/RXR. In this system, no gene expression was observed in the absence of retinoic acid, while a dose-dependent increase in expression occurred upon ligand addition. I exploited this system to demonstrate for the first time that chromatin modifying enzymes function sequentially in the process of establishing an active transcription at gene promoters (Mol Cell 6:1049, 2000). To underscore the usefulness of this system, Bristol Myers Squibb (Princeton, NJ) purchased our patent on the system as a tool for screening biologically active analogs of retinoic acid. I have since established an *in vitro* transcription system to study muscle transcription that remains the only tool to reproduce MyoD-dependent gene activation in the test tube (Proc Natl Acad Sci 101:11593, 2004).

F.J. Dilworth*, K. Seaver, A. Fishburn, S. Htet, and S.J. Tapscott*. In vitro transcription system delineates the distinct roles of the coactivators pCAF and p300 during MyoD/E47-dependent transactivation. *Proc Natl Acad Sci USA* 101: 11593-11598, 2004. (*co-corresponding authors)

F.J. Dilworth, C. Fromental-Ramain, K. Yamamoto, and P. Chambon. ATP-driven chromatin remodeling activity and histone acetyltransferases act sequentially during transactivation by RAR/RXR *in vitro*. *Mol Cell* **6**: 1049-1058, 2000.

F.J. Dilworth, C. Fromental-Ramain, E. Remboutsika, A. Benecke, and P. Chambon. Ligand-dependent activation of transcription in vitro by retinoic acid receptor □ /retinoid X receptor □ heterodimers that mimics transactivation by retinoids in vivo. *Proc Natl Acad Sci USA* **96**: 1995-2000, 1999.

5. Demonstrating that the increased biological activity of the vitamin D analogs observed in vitro was due to altered metabolism and protein binding. During my Ph.D. in the Jones laboratory, I performed an in depth study of the different parameters that might explain why the drug MC1288 was 100 times better than 1α,25-dihydroxyvitamin D3 at inducing differentiation *in vitro* but the 2 drugs showed similar efficacy when their calcemic activity were measured *in vivo*. Our studies performed in cultured cells demonstrated that MC1288 was degraded much more slowly than the natural hormone. Furthermore, we found that the drug bound the vitamin D receptor with higher affinity while it bound the vitamin D binding protein with much lower affinity. These observations allowed us to understand the differences between the *in vivo* and *in vitro* results observed with the drug, and provided the chemists with parameters to utilize as they designed the second generation vitamin D analogs. The importance of this work was recognized by the American Society for Bone and Mineral Research through a 'Young Investigator Award', and resulted in a publication in the journal « Biochemical Pharmacology».

F.J. Dilworth, M. Calverley, H. Makin, and G. Jones. Increased biological activity of 20-epi-1,25-dihydroxyvitamin D_3 is due to reduced catabolism and altered protein binding. *Biochem Pharmacol* **47**: 987-993, 1994.

F.J. Dilworth, I. Scott, A. Green, S. Strugnell, Y.-D. Guo, R. Kremer, E. Roberts, H.L.J. Makin, M.J. Calverley, and G. Jones. Different mechanisms of hydroxylation site selection by liver and kidney cytochrome P-450 species (CYP27 and CYP24) involved in vitamin D metabolism. *J Biol Chem* **270**: 16766-16774, 1995.

F.J. Dilworth, G.R. Williams, A-M. Kissmeyer, J. Løgsted-Nielsen, E. Binderup, M.J. Calverley, H.L.J. Makin, and G. Jones. The vitamin D analog KH1060 is rapidly degraded both *in vivo* and *in vitro* via several pathways: Principle metabolites generated retain significant biological activity. *Endocrinology* **138**: 5485-5496, 1997.

D. Research Support

Ongoing Operating

2019-2023 Canadian Institutes of Health Research – CEEHRC Epigenetics Clinical Translation Grants. “Targeting the epigenetic state of refractory and relapsing acute myeloid leukemia”. Duration: 4 years (2/01/2019-1/31/2023). Award $62,500 for the Dilworth Lab. **Role: co-Primary Investigator** (Co-Primary Investigators include Drs. Marjorie Brand, Jean-Francois Couture, F. Jeffrey Dilworth, and William L. Stanford (Lead)).

2018-2023 Canadian Institutes of Health Research – CEEHRC Team Grants Phase II. “Epigenetic changes affecting muscle stem cell function in the aging population”. Duration: 5 years (4/01/2018-3/31/2023). Award $169,550 per year for the Dilworth Lab. **Role: Lead-Primary Investigator** (Co-Primary Investigators include Drs. Paul Beaulé, Marjorie Brand, Sacha Carsen, F. Jeffrey Dilworth, Peter Lapner, Alan Liew (Ottawa Hospital Research Institute) and Guillaume Bourque (McGill University)).

2015-2022 Canadian Institutes of Health Research – Foundation Grant. “Epigenetic regulation of muscle regeneration in health and disease”. Duration: 7 years (7/01/2015-6/30/2022). Award $330,534 per year. **Role: Primary Investigator**

On-going Infrastructure

2015-2020 Canadian Foundation for Innovation/Ontario Research Fund – Innovation Fund 2015 Competition. “Stem Cell Epigenetics and Therapeutics”. Duration: 5 years (07/01/2015-06/30/2020). Award $7,500,000 total. **Role: Co-Investigator.** (Primary Investigator: Dr M.A. Rudnicki; co-investigators include Drs. M. Brand, F.J. Dilworth, L. Megeney, T. Perkins, D. Picketts, W.L. Stanford, D.A. Stewart, B. Thébaud, and J. Wang).