BIOGRAPHICAL SKETCH

NAME: DAVIDSON Irwin

POSITION TITLE: Research Director CNRS

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Glasgow, Scotland.	BS	07/1980	Molecular Biology
University of Glasgow, Scotland.	PHD	07/1985	Molecular Virology
Laboratoire de Génétique Moléculaire des Eucaryotes	Postdoctoral	09/1988	Regulation of gene expression

A. Personal Statement

I am a Research Director (Principal investigator) at the French Centre National de la Recherche Scientifique (CNRS), and my research is focused on the regulation of gene expression, epigenetics and more recently non-coding RNA. I graduated from the University of Glasgow with a PhD in 1985 and joined the group of Dr Pierre Chambon in Strasbourg as a post-doc to study gene regulation using the SV40 enhancer as a model system. I was recruited as a CNRS staff scientist in 1988, and became an independent group leader in 1992. In 1994 the laboratory moved from the medical faculty building in downtown Strasbourg to the new Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC) in Illkirch. I have been a group leader there until the present day.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

Research assistant. German Cancer Research Center (DKFZ) Heidelberg Germany (Professor Gerhard Sauer).	1980-1981.
Post-graduate student. Medical Research Council Virology Unit Glasgow UK (Professor John H. Subak-Sharpe).	1981-1985.
Post-doctoral fellow. Laboratoire de Génétique Moléculaire des Eucaryotes Strasbourg (Professor Pierre Chambon).	1985-1988.
Staff scientist (CR1 CNRS). Laboratoire de Génétique Moléculaire des Eucaryotes/IGBMC	1988
CNRS staff scientist: Chargé de Recherche 1.	1988-1997
CNRS staff scientist: Directeur de Recherche 2.	1997-2006
CNRS staff scientist: Directeur de Recherche 1	2006-2017
CNRS staff scientist: Directeur de Recherche CE1	2017-

Honors

Grand Prix Alexandre Joannides of the French Academy of Science, 2014.

C. Contributions to Science

For the past 30 years, I have studied the molecular mechanisms regulating gene expression. As a post-doctoral researcher, I characterized cell specific protein binding to the Simian virus 40 enhancer demonstrating its intricate and complex organization including the relationship of the TEAD and AP1 binding sites, that since became a paradigm for the

function of these factors. I purified the TEAD1 protein from Hela cell nuclear extracts and cloned the corresponding gene. The first project I undertook as an independent group leader was a structure-function analyses of this factor to define its DNA binding and transactivation domains. Several years later, we were the first to clone the remaining members of the TEAD family. More than 20 years later we returned to the study of TEAD factors defining their role in muscle differentiation and regeneration.

My group then worked for more than 25 years on the structure and function of the mammalian general transcription factor TFIID, its TATA-binding protein (TBP) subunit as well as male germ cell expressed paralogs of TFIID subunits such as TBP-related factor 2 (TRF2) or TAF7L. We published more than 50 papers on these subjects.

In 2008, the major focus of the group moved from the study of TFIID to investigating regulation of gene expression and epigenetics in melanoma. We studied the role of the TIF1a (TRIM24)-related subfamily of tripartite-motif containing proteins in hepatocellular carcinoma and transcription factors MITF and SOX10 in melanoma. We defined how MITF and SOX10 regulate melanoma cell proliferation, identifying their target genes including long non-coding RNAs (lncRNAs) that are now a major focus of attention, and used mass-spectrometry to identify their potential co-factors. Amongst these co-factors, we studied the chromatin remodeling complexes SWI/SNF, NuRF and NuRD. We defined the role of SWI/SNF in human melanoma cells showing how it is recruited by MITF and/or SOX10 to cis-regulatory elements driving expression of genes involved in melanoma cell proliferation. We defined the role of NuRF in human melanoma cells and in the mouse melanocyte lineage in vivo where we identified its critical role in reactivation of the melanocyte gene expression program in adult melanocyte stem cells during anagen phase. We further defined the critical roles of SWI/SNF and NuRF as MITF and SOX10 co-factors in mouse melanoma in vivo. Through investigating the CHD4 subunit of the NuRD complex melanoma, we defined a novel mechanism by which citrullination regulates glycolysis in a variety of cancer cells and we identified a novel lncRNA LENOX regulating oxidative phosphorylation specifically in melanoma.

We focus our current research on understanding the functions of lncRNAs in melanoma. The highly tumour-specific expression of these lncRNAs makes them attractive therapeutic targets in cancer. Consequently, we turned also to translational research in collaboration with the technology transfer unit SATT to develop anti-sense oligonucleotides (ASO) to target selected lncRNAs as novel therapeutic options in melanoma. Our future research aims to bridge the gap between the molecular and functional characterization of lncRNAs and translational research to assess their potential as therapeutic targets.

Selected citations for the different fields to which I have made a contribution.

The TEAD family: from the SV40 enhancer to myogenic differentiation.

1). **I. Davidson,** C. Fromental, P. Augereau, A. Wildeman, M. Zenke, and P. Chambon. (1986) Cell-type specific protein binding to the enhancer of simian virus 40 in nuclear extracts. **Nature.** *323*, 544-548.

2). **I. Davidson,** J.H. Xiao, R. Rosales, A. Staub, and P. Chambon. (1988) The HeLa cell protein TEF-1 binds specifically and cooperatively to two SV40 enhancer motifs of unrelated sequence. **Cell.** *54*, 931-942.

3) J.H. Xiao, **I. Davidson,** H. Matthes, J. M. Garnier, and P. Chambon. (1991) Cloning, expression, and transcriptional properties of the human enhancer factor TEF-1. **Cell.** *65*, 551-568.

4) J.J. Hwang, P. Chambon, and **I. Davidson.** (1993) Characterisation of the transcription activation function and the DNA binding domain of transcriptional enhancer factor-1. **EMBO. J.** *12,* 2337-2348.

5) P. Jacquemin, J.J. Hwang, J. Martial, P. Dollé, and **I. Davidson.** (1996). A novel family of developmentally regulated transcription factors containing the TEA/ATTS DNA binding domain. **J Biol. Chem.**, *271*, 21775-21785.

6). Benhaddou A, Ye T, Morlon A, Michel I, Jost B, Mengus G, and **Davidson I.** (2012). Transcription factor TEAD4 regulates expression of Myogenin and the unfolded protein response genes during C2C12 cell differentiation. **Cell Death and Differentiation**. Feb;19(2):220-31.

7). Joshi S, Davidson G, Le Gras S, Watanabe S, Braun T, Mengus G and **Davidson I.** (2017). TEAD transcription factors are required for normal primary myoblast differentiation *in vitro* and muscle regeneration *in vivo*. **Plos Genetics**. Feb 8;13(2):e1006600.

Structure and function of TFIID and TAF4.

1). G. Mengus, M. May, L. Carré, P. Chambon, and **I. Davidson.** Human $TAF_{II}135$ potentiates transcriptional stimulation by the AF-2s of the retinoic acid, vitamin D3, and thyroid hormone receptors in mammalian cells. (1997). **Genes Dev.** 11, 1381-1395.

2) C. Birck, O Poch, C. Romier, M. Ruff, G. Mengus, A.C. Lavigne, **I. Davidson**, and D. Moras. (1998) Human $TAF_{II}28$ and $TAF_{II}18$ interact through a histone fold encoded by atypical evolutionary conserved motifs also found in the SPT3 family. **Cell** 94, 239249.

3). Y-G Gangloff, S Werten, C Romier, L Carré, O Poch, D Moras, and **I. Davidson**. (1999) The human TFIID components $TAF_{II}135$-$TAF_{II}20$ and the yeast SAGA components ADA1-$TAF_{II}68$ heterodimerise to form histone-like pairs. **Mol. Cell Biol.** 20, 340-351.

4). Y-G. Gangloff, S. L. Sanders, C. Romier, D. Kirschner, P. A. Weil, L. Tora, and **I. Davidson**. (2001) Histone folds mediate selective heterodimerisation of yeast $TAF_{II}25$ with TFIID components $yTAF_{II}47$ and $yTAF_{II}65$ and with SAGA component ySPT7. **Mol. Cell Biol.** 21, 1841-1853

5). Y-G. Gangloff, C. Romier, S. Thuault, S. Werten, and **I. Davidson** (2001). The histone fold is a key structural motif of transcription factor TFIID. **Trends Biochem Sci,** 26, 250-257

6). Y-G Gangloff, J-C Pointud, S. Thuault, L. Carré, C. Romier, S. Muratoglu, M. Brand, L. Tora, J-L. Couderc, and **I Davidson**. (2001). The TFIID components human $TAF_{II}140$ and *Drosophila* BIP2/$TAF_{II}155$ are novel metazoan homologues of $yTAF_{II}47$ containing a histone fold and a PHD finger. **Mol. Cell. Biol**. **21:**5109-21

7). I. Martianov, G-M. Fimia, A. Dierich, M. Parvinen, P. Sassone-Corsi and **I. Davidson**. (2001). Late arrest of spermiogenesis and germ cell apoptosis in mice lacking the TBP-like TLF/TRF2 gene. **Molecular Cell**. 7, 509-515

8). I. Martianov, S. Brancorsini, A. Gansmuller, M. Parvinen, **I. Davidson** and P. Sassone-Corsi. (2002). Distinct functions of TBP and TLF/TRF2 during spermatogenesis: Requirement of TLF for heterochromatic chromocenter formation in haploid round spermatids. **Development, 129 :** 945-955.

9). I. Martianov, S. Viville, and **I Davidson**. (2002) RNA polymerase II transcription in murine cells lacking the TATA binding protein. **Science**, 298:1036-9

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11). Mengus, G., Fadloun, A., Kobi, D., Thibault, C., Perletti, L., Michel, I., and **I. Davidson**. (2005). TAF4 inactivation in embryonic fibroblasts activates TGFbeta signalling and autocrine growth. **EMBO J.** 24:2753-6

12). Fadloun, A., Kobi, D., Pointud, J-C., Kumar, I., Teletin, M., Bole-Feysot, C., Testoni, B., Mantovani, R., Metzger, D., Mengus, G., and **Davidson, I.** (2007) The TFIID subunit TAF4 regulates keratinocyte proliferation and has cell-autonomous and non-cell-autonomous tumour suppressor activity in mouse epidermis. **Development**. 134(16):2947-58.

13). Alpern, D, Langer, D, Ballester, B, Le Gras, S, Romier, C, Mengus, G, and **Davidson, I.** (2014). TFIID subunit TAF4 directs promoter occupancy of nuclear receptor HNF4A during post-natal hepatocyte differentiation. **ELife**, Sep 10;3. doi: 10.7554/eLife.03613.

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15). Säisä-Borreill S, Davidson G, Kleiber T, Thevenot A, Martin E, Mondot S, Blottière H, Helleux A, Mengus G, Plateroti M, Duluc I, **Davidson I** and Freund JN. (2023). General transcription factor TAF4 antagonizes epigenetic silencing by Polycomb to maintain intestine stem cell functions. **Cell Death and Differentiation** doi: 10.1038/s41418-022-01109-6. Online ahead of print.

TRIM-family proteins and HCC.

1). Herquel B, Ouararhni K, Khetchoumian, K Ignat M, Télétin M, Mark M, Béchade G, Van Dorsselaer A, Sanglier- Cianférani S, Hamiche A, Cammas F, Losson R and **Davidson I**. (2011). Transcription cofactors TRIM24, TRIM28 and TRIM33

associate to form regulatory complexes that suppress murine hepatocellular carcinoma. **Proc Natl Acad Sci U S A. 2011** 108(20):8212-7. Review article by Hatakeyama. (2011). **Nat. Rev. Cancer**, 11 792-804.

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3). Herquel B, Ouararhni K, Martianov I, Le Gras S, Ye T, Keime C, Lerouge T, Jost B, Cammas F, Losson R, and **Davidson, I.** (2013). Trim24 repressed VL30 retrotransposons regulate gene expression by producing noncoding RNA. **Nat. Struc. Mol. Biol.** Mar;20(3):339-46.

Melanoma.

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3). Laurette P, Strub T, Koludrovic D, Keime C, Le Gras S, Seberg H, Van Otterloo E, Imrichova H, Siddaway R, Aerts S, Cornell RA, Mengus G, **Davidson I**. (2015). Transcription factor MITF and remodeller BRG1 define chromatin organisation at regulatory elements in melanoma cells. **Elife**. Mar 24;4. doi: 10.7554/eLife.06857. **Review article**. Beyond MITF: Multiple transcription factors directly regulate the cellular phenotype in melanocytes and melanoma. Seberg et al. Pigment Cell Melanoma Res. 2017 Sep;30(5):454-466.

4). Koludrovic D., Laurette P., Strub T., Keime C., Le Coz M., Coassolo S., Mengus G., Larue L., and **Davidson I.** Chromatin-remodelling complex NURF is essential for differentiation of adult melanocyte stem cells. **PLOS Genet**. 2015 Oct 6;11(10):e1005555. doi: 10.1371/journal.pgen.1005555. **News and Views**: Welsh, SJ and Rizos, H. Melanocyte reprogramming requires chromatin remodelling. **Pigment Cell Mel. Res**. May; 29(3):260-1.

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9). Yao W. German BF, Chraa D, Braud A, Meyer P, Hugel C, Davidson G, Laurette P, Mengus G, Flatter E, Marschall P, Segaud J, Hener P, Lipsker D, **Davidson I**[§] and Li M [§]. Keratinocyte-derived cytokine TSLP promotes growth and metastasis of melanoma by regulating the tumor-associated immune microenvironment. **J. Clin. Invest. Insight**. 2022 Sep 15:e161438. doi: 10.1172/jci.insight.161438. [§] co-corresponding authors.

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