BIOGRAPHICAL SKETCH

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NAME: **NORTHCOTT, Paul Andrew**

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

POSITION TITLE: **Assistant Member**

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/YY	FIELD OF STUDY
Palm Beach Atlantic University, FL, USA	B.Sc.	04/2000	Biology
McMaster University, ON, Canada	M.Sc.	11/2004	Medical Genetics
University of Toronto, ON, Canada	Ph.D.	11/2010	Cancer Genetics
The Hospital for Sick Children, ON, Canada	Postdoctoral	02/2012	Cancer Genomics
German Cancer Research Center, B-W, DE	Postdoctoral	02/2015	Cancer Genomics

A. Personal Statement

My research is focused on improving our understanding of the genes and pathways driving the pathogenesis of medulloblastoma, the most common type of malignant pediatric brain tumor. We are using next-generation sequencing (NGS) combined with a variety of integrative computational approaches to discover genomic, epigenomic, and transcriptomic alterations across large cohorts of human medulloblastomas with the aim of delineating the full landscape of germline and somatic *drivers* responsible for medulloblastoma initiation, maintenance, progression, relapse, and metastasis. Novel candidate genes identified through these efforts are being functionally validated improve understanding of medulloblastoma pathogenesis and to generate improved preclinical models that faithfully recapitulate the underlying molecular and biological heterogeneity of the disease.

B. Positions and Honors

Positions and Employment

2000-03 Teaching Assistant – Biochemistry I & II, McMaster University, Hamilton, ON
2004-05 Research Technologist, Pathology & Molecular Medicine, Juravinski Cancer Centre, Hamilton, ON
2005-06 Research Technologist II, Developmental & Stem Cell Biology, The Hospital for Sick Children, Toronto, ON
2010-12 Postdoctoral Fellow, Developmental & Stem Cell Biology, The Hospital for Sick Children, Toronto, ON
2012-15 Senior Researcher and Subgroup Leader, Division of Pediatric Neurooncology (B062), German Cancer Research Center (DKFZ), Heidelberg, Germany
2015-present Assistant Member, Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, TN, USA

Other Experience and Professional Memberships

2006-present Member, American Association for Cancer Research (AACR)
2007-present Member, Society for Neuro-Oncology (SNO)
2016-present Member, Children's Oncology Group (COG)
2016-present Scientific Advisory Board Member, The Brain Tumor Charity

Honors

1996-99	Provost's Scholarship (PBA)
1997-99	Mary Sisler Pre-Medical Scholarship (PBA)
1997-98	Provost's List (PBA)
1998-99	President's List (PBA)
1999-2000	President's Scholarship (PBA)
2000	Graduate Entrance Scholarship (McMaster University)
2000-03	Graduate Scholarship (McMaster University)
2006	University of Toronto Fellowship (U of T)
2008	AACR-Aflac Scholar-in-Training Award (AACR)
2008	McMurrich Research Award (U of T)
2008	Dr. Rajalakshmi S. Dittakavi and Dr. Prema M. Rao Graduate Award (U of T)
2009	University of Toronto Fellowship (U of T)
2009	AACR-Bristol-Myers Squibb Oncology Scholar-in-Training Award (AACR)
2009	Hoshino Award, World Federation of Neuro-Oncology (WFNO) Quadrennial Meeting
2009	CIHR National Poster Competition – Gold Award
2010	AACR-Bristol-Myers Squibb Oncology Scholar-in-Training Award (AACR)
2010	Young Investigator Award, Basic Science, Canadian Neuro-Oncology (CNO) Meeting
2011	Keystone Symposia Future of Science Fund Scholarship
2011	Stuart Alan Hoffman Memorial Prize (U of T)
2012	Roman Herzog PostDoctoral Fellowship (Hertie Foundation)
2013	Lap-Chee Tsui Publication Award for 2012 (CIHR Institute of Genetics)
2014	DKFZ Alumni Award (German Cancer Research Center, DKFZ)
2014	Pediatric Basic Science Award (Society for Neuro-Oncology Annual Meeting)
2015	2015 V Foundation V Scholar Award
2016	Inaugural AACR NextGen Grant for Transformative Cancer Research
2016	Pew-Stewart Scholar for Cancer Research
2016	Sontag Foundation Distinguished Scientist Award

C. Contributions to Science

1. Medulloblastoma comprises four distinct diseases

As a PhD student in the laboratory of Dr. Michael Taylor at the Hospital for Sick Children in Toronto Canada, my thesis focused on the genomic analysis of medulloblastoma, the most common malignant childhood brain tumor. Using a combination of state-of-the-art high-resolution DNA copy-number and gene expression array platforms, we analyzed unprecedented cohorts of primary patient samples in order to discover the molecular mechanisms underlying medulloblastoma development. In addition to identifying previously undisclosed recurrent copy-number alterations and implicating new *driver* genes, these efforts helped to reveal the extent of molecular heterogeneity among medulloblastomas, identifying four highly disparate molecular subgroups of the disease – WNT, SHH, Group 3, and Group 4. This work was the first to demonstrate a clear correlation between molecular subgroup affiliation and patient outcome, having significant implications from both biological and clinical perspectives. These findings precipitated the subsequent consensus recognition that the disease consists of four distinct molecular subgroups, changing the way medulloblastoma is studied in the laboratory and how it is treated in the clinical setting around the world.

a. **Northcott PA**, Korshunov A, Witt H, Hielscher T, Eberhart CG, Mack S, Bouffet E, Clifford SC, Hawkins CE, French P, Rutka JT, Pfister S, Taylor MD. Medulloblastoma comprises four distinct molecular variants. Journal of Clinical oncology: official journal of the American Society of Clinical Oncology. 2011;29(11):1408-14.

b. Taylor MD, **Northcott PA**, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM. Molecular subgroups of medulloblastoma: the current consensus. Acta neuropathologica. 2012;123(4):465-72. PMCID: PMC3306779.

c. **Northcott PA**, Korshunov A, Pfister SM, Taylor MD. The clinical implications of medulloblastoma subgroups. Nature reviews Neurology. 2012;8(6):340-51.

d. Shih DJ, **Northcott PA**, Remke M, Korshunov A, Ramaswamy V, Kool M, Luu B, Yao Y, Wang X, Dubuc AM, Garzia L, Peacock J, Mack SC, Wu X, Rolider A, Morrissy AS, Cavalli FM, Jones DT, Zitterbart K, Faria CC, Schuller U, Kren L, Kumabe T, Tominaga T, Shin Ra Y, Garami M, Hauser P, Chan JA, Robinson S, Bognar L, Klekner A, Saad AG, Liau LM, Albrecht S, Fontebasso A, Cinalli G, De Antonellis P, Zollo M, Cooper MK, Thompson RC, Bailey S, Lindsey JC, Di Rocco C, Massimi L, Michiels EM, Scherer SW, Phillips JJ, Gupta N, Fan X, Muraszko KM, Vibhakar R, Eberhart CG, Fouladi M, Lach B, Jung S, Wechsler-Reya RJ, Fevre-Montange M, Jouvet A, Jabado N, Pollack IF, Weiss WA, Lee JY, Cho BK, Kim SK, Wang KC, Leonard JR, Rubin JB, de Torres C, Lavarino C, Mora J, Cho YJ, Tabori U, Olson JM, Gajjar A, Packer RJ, Rutkowski S, Pomeroy SL, French PJ, Kloosterhof NK, Kros JM, Van Meir EG, Clifford SC, Bourdeaut F, Delattre O, Doz FF, Hawkins CE, Malkin D, Grajkowska WA, Perek-Polnik M, Bouffet E, Rutka JT, Pfister SM, Taylor MD. Cytogenetic prognostication within medulloblastoma subgroups. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2014;32(9):886-96. PMCID: PMC3948094.

2. Structural variants as oncogenic drivers of medulloblastoma subgroups

During the pre-NGS era, structural variants present in cancer genomes were best-studied using array-based DNA copy-number platforms. As a PhD student, I utilized SNP oligonucleotide arrays to investigate the spectrum of copy-number alterations across unprecedented cohorts of primary medulloblastoma specimens. This strategy implicated somatic defects in the chromatin machinery, including gene amplifications and deletions affecting histone methyltransferases, demethylases, and other chromatin-associated genes, as an emerging mechanism important in medulloblastoma development. Furthermore, novel candidate oncogenes were identified as targets of recurrent activation, including a microRNA cluster known as *miR-17/92*, which I confirmed to be recurrently amplified and up-regulated in the SHH subgroup. After receiving my PhD, I continued as a postdoc in the Taylor lab during which time I co-founded the Medulloblastoma Advanced Genomics International Consortium (MAGIC) – a global initiative consisting of >45 participating institutions through which we amassed >1,200 samples suitable for molecular profiling. This allowed me to comprehensively investigate the genomic landscape across medulloblastoma subgroups and identify previously unreported *driver* genes. Among these were the first recurrent fusion gene reported in medulloblastoma – *PVT1-MYC* – that was present exclusively in *MYC*-amplified Group 3, and recurrent tandem duplication of *SNCAIP*, a Parkinson's Disease gene altered by a stereotypical structural variant in Group 4. Collectively, my efforts focused on full characterization of the medulloblastoma genomic landscape identified novel mechanisms and new candidate *drivers* important in medulloblastoma development, prompting current efforts focused on functional validation and evaluation of novel molecularly targeted therapeutic targets based on these findings.

a. **Northcott PA**, Nakahara Y, Wu X, Feuk L, Ellison DW, Croul S, Mack S, Kongkham PN, Peacock J, Dubuc A, Ra YS, Zilberberg K, McLeod J, Scherer SW, Sunil Rao J, Eberhart CG, Grajkowska W, Gillespie Y, Lach B, Grundy R, Pollack IF, Hamilton RL, Van Meter T, Carlotti CG, Boop F, Bigner D, Gilbertson RJ, Rutka JT, Taylor MD. Multiple recurrent genetic events converge on control of histone lysine methylation in medulloblastoma. Nature genetics. 2009;41(4):465-72. PMCID: PMC4454371.

b. **Northcott PA**, Fernandez LA, Hagan JP, Ellison DW, Grajkowska W, Gillespie Y, Grundy R, Van Meter T, Rutka JT, Croce CM, Kenney AM, Taylor MD. The miR-17/92 polycistron is up-regulated in sonic hedgehog-driven medulloblastomas and induced by N-myc in sonic hedgehog-treated cerebellar neural precursors. Cancer research. 2009;69(8):3249-55. PMCID: PMC2836891.

c. **Northcott PA**, Shih DJ, Peacock J, Garzia L, Morrissy AS, Zichner T, Stutz AM, Korshunov A, Reimand J, Schumacher SE, Beroukhim R, Ellison DW, Marshall CR, Lionel AC, Mack S, Dubuc A, Yao Y, Ramaswamy V, Luu B, Rolider A, Cavalli FM, Wang X, Remke M, Wu X, Chiu RY, Chu A, Chuah E, Corbett RD, Hoad GR, Jackman SD, Li Y, Lo A, Mungall KL, Nip KM, Qian JQ, Raymond AG, Thiessen NT, Varhol RJ, Birol I, Moore RA, Mungall AJ, Holt R, Kawauchi D, Roussel MF, Kool M, Jones DT, Witt H, Fernandez LA, Kenney AM, Wechsler-Reya RJ, Dirks P, Aviv T, Grajkowska WA, Perek-Polnik M, Haberler CC, Delattre O, Reynaud SS, Doz FF, Pernet-Fattet SS, Cho BK, Kim SK, Wang KC, Scheurlen W, Eberhart CG, Fevre-Montange M, Jouvet A, Pollack IF, Fan X, Muraszko KM, Gillespie GY, Di Rocco C, Massimi L, Michiels EM, Kloosterhof NK, French PJ, Kros JM, Olson JM, Ellenbogen RG, Zitterbart K, Kren L, Thompson RC, Cooper MK, Lach B, McLendon RE, Bigner DD, Fontebasso A, Albrecht S, Jabado N, Lindsey JC, Bailey S, Gupta N, Weiss WA, Bognar L, Klekner A, Van Meter TE, Kumabe T, Tominaga T, Elbabaa SK, Leonard JR, Rubin JB, Liau LM, Van Meir EG,

Fouladi M, Nakamura H, Cinalli G, Garami M, Hauser P, Saad AG, Iolascon A, Jung S, Carlotti CG, Vibhakar R, Ra YS, Robinson S, Zollo M, Faria CC, Chan JA, Levy ML, Sorensen PH, Meyerson M, Pomeroy SL, Cho YJ, Bader GD, Tabori U, Hawkins CE, Bouffet E, Scherer SW, Rutka JT, Malkin D, Clifford SC, Jones SJ, Korbel JO, Pfister SM, Marra MA, Taylor MD. Subgroup-specific structural variation across 1,000 medulloblastoma genomes. Nature. 2012;488(7409):49-56. PMCID: PMC3683624.

3. Super-enhancers drive medulloblastoma oncogenes and reveal subgroup-specific cellular origins
As a postdoc and subgroup leader working at the German Cancer Research Center (DKFZ) under the leadership of Dr. Stefan Pfister and focused on application of integrative approaches to link different levels of NGS data, I identified two novel medulloblastoma oncogenes – *GFI1* and *GFI1B* – as the most predominant *drivers* of the often poor prognosis Group 3 and Group 4 subgroups. These genes were determined to be activated by a mechanism we termed 'enhancer hijacking', whereby a series of often disparate structural variants (i.e. duplications, deletions, inversions, and translocations) were found to relocate highly active enhancers and super-enhancers proximal to *GFI1* and *GFI1B* loci, leading to their respective activation. Although previously observed in hematopoietic malignancies, this finding was the first report of its kind in human brain tumors, implicating 'enhancer hijacking' as a newly identified mechanism of oncogene activation in solid tumors such as medulloblastoma. My recent efforts aimed at describing the enhancer landscape of medulloblastoma comprehensively annotated active regulatory elements across subgroups in an unprecedented cohort of primary samples, making this study the first of it's depth and magnitude for any single cancer entity. This study disclosed ~20,000 previously unreported enhancers and demonstrated clear utility associated with conducting epigenome studies in primary patient material as opposed to long-term cell lines grown in culture. Moreover, these analyses disclosed clinically relevant, subgroup-specific oncogenic pathways and identified master transcription factors responsible for subgroup identity, implicating cellular origins. These cutting edge, integrative genome-epigenome studies have revealed important oncogenic and developmental insights into medulloblastoma pathogenesis, providing a framework for similar studies in other cancer entities and implicating novel avenues for therapeutic intervention, especially in Group 3 and Group 4 subgroups of the disease.

a. **Northcott PA**, Lee C, Zichner T, Stutz AM, Erkek S, Kawauchi D, Shih DJ, Hovestadt V, Zapatka M, Sturm D, Jones DT, Kool M, Remke M, Cavalli FM, Zuyderduyn S, Bader GD, VandenBerg S, Esparza LA, Ryzhova M, Wang W, Wittmann A, Stark S, Sieber L, Seker-Cin H, Linke L, Kratochwil F, Jager N, Buchhalter I, Imbusch CD, Zipprich G, Raeder B, Schmidt S, Diessl N, Wolf S, Wiemann S, Brors B, Lawerenz C, Eils J, Warnatz HJ, Risch T, Yaspo ML, Weber UD, Bartholomae CC, von Kalle C, Turanyi E, Hauser P, Sanden E, Darabi A, Siesjo P, Sterba J, Zitterbart K, Sumerauer D, van Sluis P, Versteeg R, Volckmann R, Koster J, Schuhmann MU, Ebinger M, Grimes HL, Robinson GW, Gajjar A, Mynarek M, von Hoff K, Rutkowski S, Pietsch T, Scheurlen W, Felsberg J, Reifenberger G, Kulozik AE, von Deimling A, Witt O, Eils R, Gilbertson RJ, Korshunov A, Taylor MD, Lichter P, Korbel JO, Wechsler-Reya RJ, Pfister SM. Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. Nature. 2014;511(7510):428-34. PMCID: PMC4201514.

b. Lin CY, Erkek S, Tong Y, Yin L, Federation AJ, Zapatka M, Haldipur P, Kawauchi D, Risch T, Warnatz HJ, Worst BC, Ju B, Orr BA, Zeid R, Polaski DR, Segura-Wang M, Waszak SM, Jones DT, Kool M, Hovestadt V, Buchhalter I, Sieber L, Johann P, Chavez L, Gröschel S, Ryzhova M, Korshunov A, Chen W, Chizhikov VV, Millen KJ, Amstislavskiy V, Lehrach H, Yaspo ML, Eils R, Lichter P, Korbel JO, Pfister SM, Bradner JE, **Northcott PA**. Active medulloblastoma enhancers reveal subgroup specific cellular origins. Nature. 2016 Jan 27. doi:10.1038/nature16546. [Epub ahead of print] PubMed PMID: 26814967.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Bc6cxlSOdl/collections/49363748/public/

D. Research Support

Ongoing Research Support

5 P30CA021765-36	Roberts (PI)	04/01/1997-02/29/2019
Cancer Center Support Grant (NCI) - Developmental Funds (Northcott)		07/01/2015-06/30/2017

Title: Functional Characterization of Recurrently Mutated Neuronal Transcription Factors in Medulloblastoma
Role: PI

The V Foundation V Scholar Award — Northcott (PI) — 11/01/2015-11/01/2017
Title: Functional Characterization of Hotspot *KBTBD4* Mutations in High-Risk Medulloblastoma
Role: PI

AACR NextGen Grant for Transformative Cancer Research — Northcott (PI) — 07/01/2016-06/30/2019
Title: Integrative Functional Genomics of Recurrent Childhood Medulloblastoma
Role: PI

Pew-Stewart Scholar for Cancer Research — Northcott (PI) — 08/01/2016-07/31/2020
Title: Molecular Dissection of Intratumoral Heterogeneity Driving Medulloblastoma Relapse
Role: PI

The Sontag Foundation Distinguished Scientist Award — Northcott (PI) — 10/01/2016-09/30/2020
Title: Molecular and Functional Dissection of Group 4 Medulloblastoma Origins
Role: PI

Completed Research Support

Roman Herzog Postdoctoral Fellow (Hertie Foundation) — Northcott (PI) — 03/01/2012-02/28/2014
Title: Integrative Genomics of Medulloblastoma
Role: Postdoctoral Fellow

Restracomp Fellowship (Hospital for Sick Children) — Northcott (PI) — 09/01/2010-08/31/2012
Title: High-Resolution Copy-Number Analysis of Medulloblastoma Subgroups
Role: Postdoctoral Fellow