BIOGRAPHICAL SKETCH

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NAME: Chunhai “Charlie” Hao

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

POSITION TITLE: Professor of Pathology and Laboratory Medicine

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 DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Jilin Medical College, Jilin City, China | M.D | 12/1982 | Medicine |
| Norman Bethune University of Medical Sciences | M.Sc. | 12/1985 | Pathology |
| Changchun, China |  |  |  |
| University of Saskatchewan, Saskatoon, Canada | Ph.D. | 04/1991 | Anatomy & Cell Biology |
| University of Western Ontario, London, Canada | FRCPC | 06/1997 | Neuropathology |

**A. Personal Statement**

As a MD/PhD, I have been practicing neuropathology and conducting laboratory research since 1997 after the completion of clinical residency training. My career goal is to develop new and effective therapeutics for clinical treatment of patients. To this end, I have been focusing my bench research on ubiquitination and sumoylation for development of pathway-targeted new drugs. Recently, my team has developed cell-based screen platform of targeted protein degradation for the discovery of small molecule degraders that can induce ubiquitination and degradation of pathogenic proteins. Using this platform, we have discovered hit and lead compounds as the first small molecule degraders of small ubiquitin-like modifier-1 (SUMO1) for anticancer drug development. Using the innovative technologies such as CRIPSR-CAS9 genome-wide screen and compound-pull down proteomics, we have identified the ubiquitin ligase complex CAPRIN1-CUL1-FBXO42 that mediates the compounds-induced ubiquitination and degradation of SUMO1 protein. In addition, we have discovered the small molecule degraders of amyloid precursor protein (APP), which is currently under development as antiaging drugs for treatment of Alzheimer’s disease (AD). The ultimate goal is to develop these small molecule degraders as the first-in-class anticancer and antiaging drugs for clinical treatment of patients diagnosed with these diseases.

1. Bellail AC, Jin H, Lo HY, Jung SH, Hamdouchi C, Kim D, Higgins RK, Blanck M, le Sage C, Cross B, Li J, Mosley AL, Wijeratne AB, Jing W, Ghosh M, Zhao YQ, Hauck PM, Hamandochi C, Shekhar A, Hao C. SUMO1 small-molecule degraders induce the protein ubiquitination and degradation through CAPRIN1-CUL1-FBXO42 ubiquitin ligase for cancer therapy. *Science Translational Medicine* (pending review).
2. Bellail AC, Olson JJ, Hao C. SUMO1 modification stabilizes CDK6 protein and drives the cell cycle and glioblastoma progression. *Nature Communications* 2014 June 23; 5:4234. PMID: 24953629. PMCID: PMC4090607
3. Bellail AC, Olson J, Yang X, Chen Z, Hao C. A20 ubiquitin ligase-mediated polyubiquitination of RIP1 inhibits caspase-8 cleavage and TRAIL-induced apoptosis in glioblastoma. *Cancer Discovery* 2012 Feb; 2(2):140-155. Epub 2012 Jan 24. PMID: 22585859. PMCID: PMC3354650

**B. Positions and Honors**

Positions and Employment

1997 – 2002 Assistant Professor of Pathology, University of Alberta, Edmonton, Alberta, Canada

1997 – 2004 Neuropathology Attending, University of Alberta Hospital, Alberta Children Hospital

2002 – 2004 Associate Professor of Pathology, University of Alberta, Edmonton, Alberta, Canada

2004 – 2013 Associate Professor of Pathology, Emory University, Atlanta, GA

2004 – 2013 Neuropathology Attending, Emory Healthcare, Atlanta, GA

2013 – 2014 Associate Professor of Pathology, McGill University, Montreal, Quebec, Canada

2013 – 2014 Neuropathology Attending, Montreal Neurological Institute and Hospital, McGill

2014 – 2017 Senior Staff Physician, Chief of Neuropathology, Henry Ford Health System, Detroit, MI

2018 – Bicentennial Chair, Professor, Pathology & Laboratory Medicine and Neurological surgery

 Indiana University School of Medicine

2018 – Neuropathology attending, Indiana University Health

Other Experiences and Professional Memberships

1997 – Fellow of Royal College of Physicians & Surgeons of Canada, Division of Medicine (FRCPC)

1997 – Licentiate of the Medical Council of Canada

1997 – Specialist Certificate in Neuropathology, Royal College of Physicians & Surgeons of Canada

1997 – Canadian Association of Neuropathologists (CANP)

2000 – American Association of Neuropathologists (AANP)

2001 – American Association of Cancer Research (AACR)

2002 – Society for Neuro-Oncology (SNO)

2003 – American Association for the Advancement of Science

2003 – 2015 Licentiate of the State of Georgia, USA

2014 – Licentiate of the State of Michigan, USA

2017 – Licentiate of the State of Indiana, USA

2017 – Licentiate of the State of Maryland, USA

2005 – 2006 Ad hoc reviewer, Cancer Progression and Therapeutics of CIHR, Canada

2005 – 2005 Ad hoc reviewer, National Natural Science Foundation, USA

2009 – 2011 Ad hoc reviewer, NIH/NCI Cancer Molecular Pathobiology Study Section (CAMP)

2009 – 2009 Ad hoc reviewer, American Association for the advancement of Science (AAAS), USA

2016 – Ad hoc reviewer, NIH/NCI Development Therapeutics Study Section (DT)

2020 – Ad hoc reviewer, NIH/NCI the special panel SEP-5: NCI Clinical and Translational Grants

Honours

2000 – 2004 Clinical Investigator of Alberta Heritage Foundation for Medical Research, Canada

2005 – 2010 Georgia Cancer Coalition Distinguished Scholar, Georgia, USA

2018 – Bicentennial Chair, Indiana University School of Medicine

**C. Contributions to Science**

**1. My first contribution was the discovery that TRAIL is nontoxic for clinical trials.** Soon after I became a faculty, I participated clinical trials of cancer immunotherapy and started my bench research of the cancer apoptosis pathway of tumor necrosis factor-related apoptosis ligand (TRAIL). In 2000, tagged recombinant human forms of TRAIL (rhTRAIL) were generated for clinical trials but found toxic to human astrocytes and hepatocytes. Clinical trials were stalled in “steering anti-cancer drugs away from the TRAIL” (*Nat Med* 6; 2000:502). In contrast, however, we found that the native form of non-tagged rhTRAIL (amino acids 114-281) was nontoxic to human astrocytes and hepatocytes. To test this *in vivo*, we treated our chimeric mice carrying human hepatocytes and demonstrated that non-tagged rhTRAIL is non-toxic to human chimeric liver and other tissues in mice. Our observation was eported at the 2004 AACR annual meeting by organizers. Phase I trials were launched with this TRAIL and showed that it is was safe and well tolerated in patients.

a. Hao C, Beguinot F, Condorelli G, Trencia A, Van Meir EG, Yong VW, Parney IF, Roa WH, Petruk KC. Induction and intracellular regulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) mediated apotosis in human malignant glioma cells. Cancer Res. 2001;61(3):1162-70. Epub 2001/02/28. PubMed PMID: 11221847.

b. Mercer DF, Schiller DE, Elliott JF, Douglas DN, Hao C, Rinfret A, Addison WR, Fischer KP, Churchill TA, Lakey JR, Tyrrell DL, Kneteman NM. Hepatitis C virus replication in mice with chimeric human livers. Nat Med. 2001;7(8):927-33. Epub 2001/08/02. doi: 10.1038/90968. PubMed PMID: 11479625.

c. Hao C, Parney IF, Roa WH, Turner J, Petruk KC, Ramsay DA. Cytokine and cytokine receptor mRNA expression in human glioblastomas: evidence of Th1, Th2 and Th3 cytokine dysregulation. Acta Neuropathol. 2002;103(2):171-8. Epub 2002/01/26. doi: 10.1007/s004010100448. PubMed PMID: 11810184.

d. Hao C, Song JH, Hsi B, Lewis J, Song DK, Petruk KC, Tyrrell DL, Kneteman NM. TRAIL inhibits tumor growth but is nontoxic to human hepatocytes in chimeric mice. Cancer Res. 2004;64(23):8502-6. Epub 2004/12/03. doi: 10.1158/0008-5472.CAN-04-2599. PubMed PMID: 15574753.

**2. My 2nd contribution came from the delineation of TRAIL pathways in normal human neural cells.** To examine the therapeutic potentials of TRAIL in treating human brain tumors, we established the cultures of human astrocytes and neurons, examined TRAIL’s pathway in the cells and found that the normal neural cells are resistant to TRAIL because of the lack of the cell surface expression of TRAIL death receptor. These finding suggest the safety of TRAIL in treatment of human brain cancers

a. Song JH, Bellail A, Tse MC, Yong VW, Hao C. Human astrocytes are resistant to Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis. J Neurosci. 2006;26(12):3299-308. Epub 2006/03/24. doi: 10.1523/JNEUROSCI.5572-05.2006. PubMed PMID: 16554480.

b. Wang CX, Song JH, Song DK, Yong VW, Shuaib A, Hao C. Cyclin-dependent kinase-5 prevents neuronal apoptosis through ERK-mediated upregulation of Bcl-2. Cell Death Differ. 2006;13(7):1203-12. Epub 2005/11/08. doi: 10.1038/sj.cdd.4401804. PubMed PMID: 16273078.

**3. The 3rd contribution was the finding of the mechanism of TRAIL resistance in cancers.** To examine the therapeutic potentials of TRAIL in treating of cancers, we examined a large panel of human cancers-derived cell lines and xenografts. While TRAIL treatment triggers apoptosis in a few cell lines, the vast majority of the cell lines are resistant to the treatment. In sensitive cells, TRAIL binds on the cell surface death receptor DR5 and induces the assembly of a death-inducing signaling complex (DISC) where caspase-8 is cleaved and initiates intracellular apoptotic process. In resistant cells, however, intracellular regulatory proteins c-FLIP, PED/PEA-15 and RIP are recruited to the DISC and inhibit caspase-8 cleavage. Our findings predict the human cancer resistance to TRAIL treatment as evident late on in clinical trials.

1. Xiao C, Yang BF, Asadi N, Beguinot F, Hao C. Tumor necrosis factor-related apoptosis-inducing ligand-induced death-inducing signaling complex and its modulation by c-FLIP and PED/PEA-15 in glioma cells. J Biol Chem. 2002;277(28):25020-5. Epub 2002/04/27. doi: 10.1074/jbc.M202946200. PubMed PMID: 11976344.
2. Song JH, Song DK, Herlyn M, Petruk KC, Hao C. Cisplatin down-regulation of cellular Fas-associated death domain-like interleukin-1beta-converting enzyme-like inhibitory proteins to restore tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in human melanoma cells. Clin Cancer Res. 2003;9(11):4255-66. Epub 2003/10/02. PubMed PMID: 14519653.
3. Song JH, Song DK, Pyrzynska B, Petruk KC, Van Meir EG, Hao C. TRAIL triggers apoptosis in human malignant glioma cells through extrinsic and intrinsic pathways. Brain Pathol. 2003;13(4):539-53. Epub 2003/12/06. PubMed PMID: 14655759.
4. Song JH, Tse MC, Bellail A, Phuphanich S, Khuri F, Kneteman NM, Hao C. Lipid rafts and nonrafts mediate tumor necrosis factor related apoptosis-inducing ligand induced apoptotic and nonapoptotic signals in non small cell lung carcinoma cells. Cancer Res. 2007;67(14):6946-55. Epub 2007/07/20. doi: 10.1158/0008-5472.CAN-06-3896. PubMed PMID: 17638906.

**4. The 4th contribution was the discovery of that ubiquitination controls TRAIL resistance in cancer stem cells.** Since 2002, cancer stem cells or tumor-initiating cells have been identified in the tumorigenesis, progression and drug resistance. To test TRAIL effects on the stem cells, we revealed that the ubiquitin enzyme A20 controls TRAIL resistance through the ubiquitination of RIP and inhibition of caspase-8 cleavage in the cancer stem cells-enriched neurospheres generated from glioblastoma tissues. Inhibition of A20 eliminates the self-renewal and tumorigenesis of neurospheres in mouse xenografts; thus the data identify A20-mediated ubiquitination as the cancer therapeutic target. The manuscript was published in *Cancer Discovery*, a new high impact journal of the AACR with its press release.

1. Qi L, Bellail AC, Rossi MR, Zhang Z, Pang H, Hunter S, Cohen C, Moreno CS, Olson JJ, Li S, Hao C. Heterogeneity of primary glioblastoma cells in the expression of caspase-8 and the response to TRAIL-induced apoptosis. Apoptosis. 2011;16(11):1150-64. Epub 2011/08/31. doi: 10.1007/s10495-011-0645-6. PubMed PMID: 21877214; PMCID: PMC3257579.
2. Bellail AC, Olson J, Yang X, Chen Z, Hao C. A20 ubiquitin ligase-mediated polyubiquitination of RIP1 inhibits caspase-8 cleavage and TRAIL-induced apoptosis in glioblastoma. *Cancer Discovery* 2012 Feb; 2(2):140-155. Epub 2012 Jan 24. PMID: 22585859. PMCID: PMC3354650

c. AACR press release*: http://www.aacr.org/home/public--media/aacr-press-releases.aspx?d=2680*

**5. The most recent contribution was the discovery of small molecule degraders of SUMO1 protein as new anticancer drugs.** In examining how ubiquitin-mediated TRAIL resistance, we identified another ubiquitin-like protein termed SUMO1 (small ubiquitin-like modifier-1) in the DISC. SUMO1 knockdown abolishes TRAIL resistance in the stem cells. While the data suggest that targeting of SUMO1 may provide an combination treatment with TRAIL, we found it was very hard for us to do so back then due to our limited experience in the field. Therefore, we decided to focus limited resources on SUMO1 pathways in glioblastoma. After several years of working through three institutes, we demonstrated that SUMO1 conjugation pathway that drives the cell cycle and glioblastoma progression through the conjugation of the cyclin-dependent kinase-6 (CDK6). Using glioblastoma cell-based drug screening, we identified the SUMO1 inhibition compound (SMIC1) from NCI pharmacological compounds. The data presented here in preliminary studies show for the first time that SMIC1 treatment blocks SUMO1-CDK6 conjugation, arrests cell cycle and inhibits glioblastoma growth. The objective of this proposal is to develop SMIC1 as a new anticancer drug for the treatment of glioblastoma.

a. Bellail AC, Olson JJ, Hao C. SUMO1 modification stabilizes CDK6 protein and drives the cell cycle and glioblastoma progression. *Nature Communications* 2014;5:4234. Epub 2014/06/24. doi: 10.1038/ncomms 5234. PubMed PMID: 24953629; PMCID: PMC4090607.

b. The article was recommended in F1000Prime on July16th 2014: [http://f1000.com/prime/718463136](https://owa.hfhs.org/owa/redir.aspx?C=p1PMNDh-9ESNyrgpwautDs427PR8btIIA1_UzyMfku1wNgViSmgfGPRE-bXHbzmbyjW09nLlC_g.&URL=http%3a%2f%2ff1000.com%2fprime%2f718463136)

c. Article was highlighted by the Canadian Association for Neuroscience on July 17th 2014: [http://can-acn.org/scientists-find-important-piece-in-the-brain-tumour-puzzle](https://owa.hfhs.org/owa/redir.aspx?C=p1PMNDh-9ESNyrgpwautDs427PR8btIIA1_UzyMfku1wNgViSmgfGPRE-bXHbzmbyjW09nLlC_g.&URL=http%3a%2f%2fcan-acn.org%2fscientists-find-important-piece-in-the-brain-tumour-puzzle)

d. The US provisional patent #62/669640 under the title “Compositions and Methods for treated cancers”, filed on the 11th of May, 2018 and the Patent Cooperation Treaty (PCT) filed in the 11th of May, 2019, pending the approval by US Patents office( the Inventors: Dr. Anita Bellail and Dr. Chunhai Hao).

**Complete List of Published Work in My Bibliography:**

[**http://www.ncbi.nlm.nih.gov/sites/myncbi/1fujc6qV\_lcQk/bibliography/47924561/public/?sort=date&direction=ascending**](https://owa.hfhs.org/owa/redir.aspx?C=p1PMNDh-9ESNyrgpwautDs427PR8btIIA1_UzyMfku1wNgViSmgfGPRE-bXHbzmbyjW09nLlC_g.&URL=http%3a%2f%2fwww.ncbi.nlm.nih.gov%2fsites%2fmyncbi%2f1fujc6qV_lcQk%2fbibliography%2f47924561%2fpublic%2f%3fsort%3ddate%26direction%3dascending)

**D. Additional Information: Research Support and/or Scholastic Performance**

**Pending Research Support**

NIH/NCI, RR44CA265547 2021

Role: PI (multi-PIs: Bellail, Hamdouchi)

Title: Development of SUMO1 small molecule degraders as the first in class anticancer drugs for metastatic colorectal cancer.

**Ongoing Research Support**

NIH/NCI, R01 CA203893 2016.12.15 – 2021.11.30

Role: PI

Title: SUMO1 inhibition compound as a new anticancer drug for glioblastoma therapy

The goal is to develop SMIC1 as a new anticancer drug for glioblastoma therapy through examination of the bioactivity and mechanisms of drug action and therapeutic efficacy in treatment of the cancer xenografts.

NIH/NCI, P30CA082709-20 (PI: Loehrer, PI) 1999.09.22-2024.08.31

Role: Co-Investigator

Title: Indiana University Melvin and Bren Simon Cancer Support Grant.

Goal: This strategic plan, which has its underpinnings with education and impact to our catchment area, is composed of four pillars that are foundational to the IUSCC. These pillars include: 1) Biology to Bedside Research; 2); Precision Medicine; 3) Prevention, Early Detection and Population Health: Local-Global Approaches; and 4) Health Care Disparities, Survivorship, and Symptom Science.

IUSM Physician Scientist Initiative (Start-up fund) 2018.01.13 – 2022. 01.12

Role: PI

The Physician Scientist Initiative provides start-up package in the recruitment of Dr. Hao to build up his research program at Indiana University School of Medicine.

**Research Support Completed during the last Three Years**

Source: NIH/NCI, 1R43CA224461-01A1 2018.06.30 – 2019.12.30

Role: PI: Bellail A, Co-PI: Hao C

Title: Development of Small Molecule SUMO1 Inhibitors for Treatment of Glioblastoma

The goal of this grant is to identify the chemical leads with improved potency and drug-like features through chemical modification of he hit compound

Source: Elsa U. Pardee Foundation, 2016.10.01 – 2017.09.30

Role: PI: Bellail A, Co-PI: Hao C

Title: Development of potent SUMO1 as a new anticancer drug for cancer treatment