BIOGRAPHICAL SKETCH

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NAME: Keith L. Black, M.D.

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

POSITION TITLE: Chairman and Professor, Department of Neurosurgery; Director, Maxine Dunitz Neurosurgical 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
University of Michigan, Ann Arbor, MI	BS with distinction	1978	Biomedical Science
University of Michigan, Ann Arbor, MI	MD with distinction	1981	Medicine
University of Michigan, Ann Arbor, MI		1981-1982	General Surgery Internship
University of Michigan, Ann Arbor, MI		1982-1987	Neurosurgery Residency

A. Personal Statement

I am the Chairman of the Department of Neurosurgery and Director of the Maxine Dunitz Neurosurgical Institute at Cedars-Sinai Medical Center (CSMC). My research work includes development of a vaccine to enhance the body's immune response to brain tumors, biology of blood-brain barrier and biochemical modulation of the blood-brain barrier (BBB), targeted drug delivery, cancer stem cells, microwave tumor ablation, nanotechnology for drug delivery, optical-guided surgery for brain tumors, and Alzheimer's retinal imaging. My research on drug delivery through the BBB was consistently funded by the NIH for over 20 years and was awarded the NINDS-NIH Jacob Javitz Award in 2000.

B. Positions and Honors

Position and Employment

1988-1997	Head, Neurosurgical Oncology, Div. of Neurosurgery, UCLA Medical Center, Los Angeles, CA
1991-1997	Associate Chief-Research Affairs, Div. of Neurosurgery, UCLA Medical Center, Los Angeles, CA
1992-1997	Ruth & Raymond Stotter Chair, Dept. of Surgery, UCLA Medical Center, Los Angeles, CA
1994-1997	Professor of Surgery, Division of Neurosurgery, UCLA Medical Center, Los Angeles, CA
1995-1997	Professor of Neurology, UCLA Medical Center, Los Angeles, CA
1997-Present	Ruth & Lawrence Harvey Chair in Neuroscience, Cedars-Sinai Medical Center, Los Angeles, CA
1997-2006	Director, Division of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA
1997-Present	Director, Maxine Dunitz Neurosurgical Institute, Department of Surgery, Los Angeles, CA
1998-2000	Chairman, Department of Neurological Surgery, University of California, Irvine, CA
1998-2003	Professor, Department of Neurological Surgery, University of California, Irvine, CA
2006-Present	Chairman, Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA
2008-Present	Professor, Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA

Other Experience and Professional Memberships:

1982- Present	Congress of Neurological Surgeons
1991- Present	American Association of Neurological Surgeons
1993 – Present	Neurosurgical Society of America
1993-1994	Neurology Study Section A
1994-1999	Board of Scientific Counselors, NINDS, NIH
1994-1999	Search Committee, Scientific Director, NINDS, NIH
1995 - Present	American Academy of Neurological Surgery
1995, 2002, 2009	American Board of Neurological Surgery Guest Examiner
1997	Testimony before United States Senate, National Cancer Act
1998- Present	Gene Therapy and Molecular Biology, Editorial Board
2000	Brain Tumor Progress Review Group, NCI & NINDS

2000-2004	National Advisory Neurological Disorders & Stroke Council of NIH
2001 – Present	Neurosurgery Quarterly, Editorial Board
2002 – Present	Society for Neuro-oncology
2003 – Present	American Association for Cancer Research
2003 - Present	Frontiers in Bioscience, Editorial Board
2004 – 2006	Independent Citizens Oversight Committee (ICOC) California Institute for Regenerative Medicine created under Proposition 71 Committee Member
2007 – Present	Society of Neurological Surgeons
2010, 2011, 2014	NIH Director's Pioneer Award Panel Interviewer
2011	Public Library of Science (PLoS), Editorial Board

Honors

1975	Westinghouse Science Award
1979	American College Scholarship Award for Academic Excellence
1980	National Medical Fellowship Franklin C. McLean Award for Outstanding Medical Scholarship
1981	National Medical Fellowship Kaiser Award for Outstanding Medical Scholarship
1985	American College of Surgeons – Shering Scholar
1990	Richard F. and Eleanor W. Dwyer Award for Excellence in Cancer Research
1994-Present	Best Doctors in America
1995	Charles R. Drew University of Medicine and Science Medal of Honor
1997	Cover Time Magazine: Heroes of Medicine
1999	American Academy of Achievement Golden Plate Award
1999	National Medical Fellowships Distinguished Service Award
2000	Cover Newsweek Japan: Key Players in the 21st Century
2000	Esquire Magazine: The 21 Most Important People of the 21st Century
2001	National Academy of Science Special Recognition
2000	NINDS-NIH Jacobs Javitz Award
2001-Present	America's Top Doctors
2002	The 1000 Most Creative Individuals in the USA
2002	Essence Magazine: The 40 Most Inspiring African Americans
2003	Candle Award in Science and Technology: Morehouse Technology
2006	Trumpet Award in Medicine (Sponsored by Turner Broadcasting)
2010	Black Entertainment (BET) Award in Public Service
2011	National Urban League (NUL) Whitney M. Young, Jr. Living Legend Award
2012	Hope of Los Angeles Award
2018	Cedars-Sinai Pioneer in Medicine Award

C. Contribution to Science

1. Biology of blood-brain barrier (BBB) and biochemical modulation of the blood-brain tumor barrier (BTB)

The blood-brain barrier limits the ability of chemotherapeutic drugs to reach tumors within the brain. We discovered that bradykinin, a naturally occurring peptide, allows delivery of therapeutic chemicals to the tumor without affecting healthy brain tissue. Based on these findings, we developed and patented RMP-7, a synthetic version of bradykinin. We continued our efforts to fine-tune selective opening and modulation of the BBB for more effective delivery of chemotherapeutic drugs and were able to show increased response to chemotherapy in patients with metastatic brain tumors from lung cancer from nine percent to 41 percent. We identified that nitric oxide-generating compounds, phosphodiesterase 5 (PDE5) inhibitors, and potassium channel activators, have an advantage over bradykinin since the inhibitors help deliver small drugs and high molecular weight therapeutics such as monoclonal antibody and nano-molecules into the brain. These findings suggest that PDE5 in metastatic brain tumors serve as an effective target for pharmacological modulation of BTB permeability to enhance selective delivery of chemotherapeutic drugs to metastatic brain tumors. I served as primary investigator in these studies.

a. Black KL, Cloughesy T, Huang SC, Gobin YP, Zhou Y, Grous J, Nelson G, Farahani K, Hoh CK, Phelps M.Intracarotid infusion of RMP-7, a bradykinin analog, and transport of gallium-68 ethylenediamine tetraacetic acid into human gliomas. J Neurosurg. 1997 Apr;86(4):603-9. PubMed PMID: 9120622.

b. Ningaraj NS, Rao M, Hashizume K, Asotra K, Black KL. Regulation of blood-brain tumor barrier permeability by calcium-activated potassium channels. J Pharmacol Exp Ther. 2002 Jun;301(3):838-51. PubMed PMID: 12023511.

c. Ningaraj NS, Rao M, Black KL: ATP-Sensitive Potassium Channel-Mediated Blood Brain Tumor Barrier Permeability Increase in a Rat Brain Tumor Model. Cancer Res. 63(24):8889-911,2003.

d. Black KL, Yin D, Konda BM, Wang X, Hu J, Ko MK, Bayan JA, Sacapano MR, Espinoza AJ, Ong JM, Irvin D, Shu Y.Different effects of KCa and KATP agonists on brain tumor permeability between syngeneic and allogeneic rat

models. Brain Res. 2008 Aug 28; 1227:198-206. doi: 10.1016/j.brainres.2008.06.046. Epub 2008 Jun 21. PubMed PMID: 18602898; PubMed Central PMCID: PMC2605468

2. Tumor Immunology and Cancer Vaccines

For the past decade and a half, we made significant headway in the development of an effective vaccine for brain cancer. We developed a dendritic cell vaccine that enhances the body's immune response against brain cancer. We identified antigens expressed in glioma and glioblastoma multiforme (GBM) cells that were used as targets for vaccine therapy and discovered that high numbers of recently generated CD8+ T lymphocytes (tumor-killing immune cells) determines more favorable response to immune therapy vaccine. We also found that the combination of our vaccine and chemotherapy significantly slowed tumor progression and extended survival of patients with GBM. The two-year survival of patients treated with the combination of vaccine and chemotherapy was 42%, compared to 8% for patients not treated with the vaccine. In a Phase 1 of clinical trial of ICT 107, a vaccine for newly diagnosed GBM patients that targets cancer stems, 69% of patients had an increased survival rate of 32 months. By comparison, typical survival rates range from 12 to 15 months after diagnosis. I am co-Investigator in these studies.

a. Yu JS, Wheeler CJ, Zeltzer PM, Ying H, Finger DN, Lee PK, Yong WH, Incardona F, Thompson RC, Riedinger MS, Zhang W, Prins RM, Black KL. Vaccination of malignant glioma patients with peptide-pulsed dendritic cells elicits systemic cytotoxicity and intracranial T-cell infiltration. Cancer Res. 2001 Feb 1;61(3):842-7. PubMed PMID: 11221866.
b. Wheeler CJ, Das A, Liu G, Yu JS, Black KL. Clinical responsiveness of glioblastoma multiforme to chemotherapy after vaccination. Clin Cancer Res. 2004 Aug 15;10(16):5316-26. PubMed PMID: 15328167.
c. Phuphanich S, Wheeler CJ, Rudnick JD, Mazer M, Wang H, Nuño MA, Richardson JE, Fan X, Ji J, Chu RM, Bender JG, Hawkins ES, Patil CG, Black KL, Yu JS. Phase I trial of a multi-epitope-pulsed dendritic cell vaccine for patients with newly diagnosed glioblastoma. Cancer Immunol Immunother. 2013 Jan;62(1):125-35. doi: 10.1007/s00262-012-1319-0. Epub 2012 Jul 31. PMCID: PMC3541928.
d. Jouanneau E, Black KL, Veiga L, Goverdhana S, Zhai Y, Zhang X., Panwar A, Mardiros A, Wang HQ, Gragg A, Zandian M, Irvin D, Wheeler CJ. Intrinsically de-sialylated CD103+ CD8 T cells mediate beneficial anti-glioma immune responses. Cancer Immunol Immunother. 2014 Sep;63(9):911-24. doi: 10.1007/s00262-014-1559-2. Epub 2014 Jun 4.

3. Brain Cancer Biomarkers

Brain cancer is one of the most difficult to treat and the patients' survival remains 15.8 months on average. Using genomic and proteomic technologies we discovered specific human glial tumor markers which were further used for translational research. One of the novel markers, the structural tumor vessel wall protein laminin-411, is currently in clinical trial as a prognostic and diagnostic marker for human glial tumor progression. The other tumor marker is the most often overexpressed in GBMs, epithelial growth factor receptor and its mutated form EFGR/EGFRvIII. I am co-Investigator in these studies.

a. Ljubimova JY, Lakhter AJ, Loksh A, Yong WH, Riedinger MS, Miner JH, Sorokin ML, Ljubimov AV, Black KL 2001. Overexpression of α4 chain-containing laminins in human glial tumors identified by gene microarray analysis. Cancer Res 61:5601-5610. PMID: 11454714.
b. Ljubimova JY, Fujita M, Khazenzon NM, Das A, Pikul B, Sekiguchi K, Sasaki T, Black KL, 2004. Laminin-8 association with glial tumor grade, recurrence and patient survival. Cancer 101:604-612. PMID: 15274074.
c. Brennan CW, Verhaak RG, McKenna A, Black KL, Chin L., 2013. TCGA Research Network. The somatic genomic landscape of glioblastoma. Cell. 155:462-477. PMCID: PMC3910500
d. Ceccarelli M, Barthel FP, Malta TM, Sabedot TS, Salama SR, Murray BA, Morozova O, Newton Y, Radenbaugh A, Pagnotta SM, Anjum S, Wang J, Manyam G, Zoppoli P, Ling S, Rao AA, Grifford M, Cherniack AD, Zhang H, Poisson L, Carlotti CG Jr, Tirapelli DP, Rao A, Mikkelsen T, Lau CC, Yung WK, Rabadan R, Huse J, Brat DJ, Lehman NL, Barnholtz-Sloan JS, Zheng S, Hess K, Rao G, Meyerson M, Beroukhim R, Cooper L, Akbani R, Wrensch M, Haussler D, Aldape KD, Laird PW, Gutmann DH; TCGA Research Network, Noushmehr H, Iavarone A, Black KL, Verhaak RG, et al. Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma. Cell. 2016 Jan 28;164(3):550-63. doi: 10.1016/j.cell.2015.12.028. PMCID: PMC4754110.
e. Edwards L, Li A, Berel D, Madany M, Kim N, Liu M, Hymowitz M, Uy B, Jung R, Xu M, Black KL, Rentsendorj A, Fan X, Zhang W, Yu JS. ZEB1 regulates glioma stemness through LIF repression. Scientific Reports. 2017 Feb 28; 7:69. doi:10.1038/s41598-017-00106-x

4. Nanotechnology

We developed a novel efficient drug delivery system for cancer treatment based on nanotechnology. Our nano-platform for drug delivery is a natural-derived nano-biopolymer that is non-toxic, non-immunogenic, and biodegradable. Several drug

versions based on naturally occurring nano-platform were synthesized for experimental treatment of animals with implanted human brain and breast tumors. The drug based on this universal nano-platform is called Polycefin. Polycefin allows attaching several anti-tumor agents at the same time for synergistic effect to stop tumor growth, formation of new blood vessels in the tumor and reduce tumor spread and is proven to bypass the BBB. I am co-Investigator in these studies.

a. Lee BS, Fujita M, Khazenzon NM, Wawrowsky KA, Wachsmann-Hogiu S, Farkas DL, Black KL, Ljubimova JY, Holler E. Polycefin, a new prototype of a multifunctional nanoconjugate based on poly(beta-L-malic acid) for drug delivery. Bioconjug Chem. 2006 Mar-Apr;17(2):317-26. PMCID: PMC3487710.
b. Ding H, Inoue S, Ljubimov AV, Patil R, Portilla-Arias J, Hu J, Konda B, Wawrowsky KA, Fujita M, Karabalin N, Sasaki T, Black KL, Holler E, Ljubimova JY. Inhibition of brain tumor growth by intravenous poly (β-L-malic acid) nanobioconjugate with pH-dependent drug release [corrected]. Proc Natl Acad Sci U S A. 2010 Oct 19;107(42):18143-8. doi: 10.1073/pnas.1003919107. Epub 2010 Oct 4. Erratum in: Proc Natl Acad Sci U S A. 2010 Nov 9;107(45):19603. PMCID: PMC2964197.
c. Ljubimova JY, Ding H, Portilla-Arias J, Patil R, Gangalum PR, Chesnokova A, Inoue S, Rekechenetskiy A, Nassoura T, Black KL, Holler E. Polymalic acid-based nano biopolymers for targeting of multiple tumor markers: an opportunity for personalized medicine? J Vis Exp. 2014 Jun 13;(88). doi: 10.3791/50668. PMCID: PMC4118553.
d. Chou S, Gangalum PR, Patil P, Cavenee WK, Furnari F, Galstyan A, DingH, Chesnokova A, Mashouf A, Fox I, Black KL, Holler E, Ljubimov AV, Ljubimova. JY. Simultaneous blockade of CK2 and EGFR pathways by tumor-targeted nanobioconjugates significantly improves therapeutic efficacy against glioblastoma multiforme. J Control Release. 244 (2016) 14-23. doi: 10.1016/j.jconrel.2016.11.001. PMCID: PMC5308909.

5. Imaging Technologies for Brain Tumor

We developed an imaging technology that can accurately discriminate between tumor and normal tissue. Surgeons in the operating room are able to shine a laser light during surgery to diagnose tumors instantaneously and discern the borders of tumors with greater precision. This technology measures the light re-emitted by molecules when stimulated by light. I am co-Investigator in these studies.

a. Butte PV, Fang Q, Jo JA, Yong WH, Pikul BK, Black KL, Marcu L. Intraoperative delineation of primary brain tumors using time-resolved fluorescence spectroscopy. J Biomed Opt. 2010 Mar-Apr;15(2):027008. doi: 10.1117/1.3374049. PMCID: PMC4171753.
b. Butte PV, Mamelak A, Parrish-Novak J, Drazin D, Shweikeh F, Gangalum PR, Chesnokova A, Ljubimova JY, Black KL. Near-infrared imaging of brain tumors using the Tumor Paint BLZ-100 to achieve near-complete resection of brain tumors. Neurosurg Focus. 2014 Feb;36(2):E1. doi: 10.3171/2013.11.FOCUS13497. PubMed PMID: 24484247.
c. Patil, R, Ljubimov AV, Gangalum PR, Ding H, Portilla-Arias J, Wagner S, Inoue S, Konda B, Rekechenetskiy A, Chesnokova A, Markman JL, Ljubimov VA, Li D, Prasad RS, Black KL, Holler E, Ljubimova JY. 2015. MRI virtual biopsy and treatment of brain metastatic tumors with targeted nanobioconjugates: nanoclinic in the brain. ACS Nano 9:5594-5608. PMCID: PMC4768903.
d. Kittle D, Vasefi F, Patil CG, Mamelak AN, Black KL, Butte PV. Real time optical Biopsy: Time-resolved Fluorescence Spectroscopy instrumentation and validation. Scientific Reports. 2016 Dec 8;6:38190. doi: 10.1038/srep38190. PMCID: PMC5144092.

6. Alzheimer's Disease

Alzheimer's disease is one of the leading causes of death in the United States, is incurable and prevalent in the aging population. The likelihood of Alzheimer's disease diagnosis happens at the late stage often when there are symptoms of irreversible memory loss. We have developed technology to look at the build-up of beta amyloid plaques in the brain thru the eyes, as a way of early diagnosis of Alzheimer's disease. This technology utilizes Curcumin, an active ingredient in turmeric that binds to beta amyloid plaques and gives off a natural fluorescence. We are also studying both an immune-based drug that reverses Alzheimer's in animal models and a targeted immunotherapy approach that appears critical in prevention of the disease. I am co-Investigator in these studies.

a. Koronyo-Hamaoui M, Koronyo Y, Ljubimov AV, Miller CA, Ko MK, Black KL, Schwartz M, Farkas DL.Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. Neuroimage. 2011 Jan;54 Suppl 1:S204-17. doi: 10.1016/j.neuroimage.2010.06.020. Epub 2010 Jun 13. PMCID: PMC2991559.
b. Koronyo Y, Salumbides BC, Sheyn J, Pelissier L, Li S, Ljubimov V, Moyseyev M, Daley D, Fuchs DT, Pham M, Black KL, Rentsendorj A, Koronyo-Hamaoui M. Therapeutic effects of glatiramer acetate and grafted CD115+ monocytes in a mouse model of Alzheimer's disease. Brain. 2015 Jun 6. pii: awv150. [Epub ahead of print] PMCID: PMC4840949.

c. Koronyo Y, Biggs D, Barron E, Boyer DS, Pearlman JA, Au WJ, Kile SJ, Blanco A, Fuchs DT, Ashfaq A, Frautschy S, Cole GM, Miller CA, Hinton DR, Verdooner SR, Black KL, Koronyo-Hamaoui, M. Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease. JCI Insight. 2017 Aug 17;2(16). pii: 93621. doi: 10.1172/jci.insight.93621. [Epub ahead of print]. PubMed PMID: 28814675.

d. Rentsendorj A, Sheyn J, Fuchs DT, Daley D, Salumbides BC, Schubloom H, Hart NJ, Li S, Hayden EY, Teplow DB, Black KL, Koronyo Y, Koronyo-Hamaoui M. A Novel Role for Osteopontin in Macrophage-Mediated Amyloid-β Clearance in Alzheimer's Models. Brain, Behavior, and Immun. 2017 Aug 30. pii: S0889-1591(17)30409-9. doi: 10.1016/j.bbi.2017.08.019. [Epub ahead of print]. PubMed PMID: 28860067.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1NY69n4iOGQAq/bibliograpahy/48094821/public/?sort=date&direction=descending

Ongoing Research Support

1. R01 CA188743 Ljubimova (PI) 04/15/2015 – 03/31/2020
NIH/NCI
Differential Nano MRI imaging for brain tumor metastases diagnosis and treatment monitoring.
We propose to develop diagnostic and treatment (thera nostic) nanoconjugates capable of passing BTB and effective targeting and inhibition of metastatic tumor growth.
Role: Co-Investigator

2. R01 CA206220-01 Ljubimova (PI) 04/01/2016 – 03/31/2021
NIH/NCI
Nanoconjugate delivery of proliferation and checkpoint inhibitors to treat glial tumors
We will introduce new generation of nanobioconjugates that pass-through BBB, activate general and local brain tumor immune systems and specifically block GBM molecular markers, significantly prolonging survival of tumor-bearing animals.
Role: Co-Investigator

3. 1R01CA209921-01 Holler (PI) 06/13/2016 – 05/31/2020
NIH/NCI
Glial tumor image-guided surgery and treatment
This grant is focused on developing new imaging and drug delivery technologies to specifically image cancer cells during surgical resection, while providing means to focally treat residual tumor deposits interspaced in normal brain.
Role: Co-Investigator

4. 1R01CA230858-01 Ljubimova (PI), Ding (PI) 12/03/2018 – 11/30/2023
NIH/NCI
Nano immunoconjugates to treat primary and metastatic HER2 positive breast cancer
We propose to develop novel nano-immunodrug strategies to provide a multipronged attack against breast cancer cells through their direct killing and through the orchestration of a potent general and local, broad-spectrum, and long-lasting immune response to select the most efficacious treatment regimen.
Role: Co-Investigator

Completed Research Support (selected from more than 50 awarded grants)

1. U01 CA151815 Ljubimova (PI) 09/20/2010 – 07/31/2016
NIH/NCI
Nanoconjugate based on polymalic acid for brain tumor treatment.
The aim of this grant is to prepare the leading drug to treat brain tumors. The drug delivery nanoconjugate should be characterized by using rodent and non-human primates to be delivered through blood brain barrier and blood tumor barrier, to be non-toxic, non-immunogenic.
Role: Co-Investigator

2. BTAP-011 Black (PI) 03/01/2017 - 12/31/2018 (BTAP011)
BTAP-013 Black (PI) 06/01/2017 – 12/31/2018 (BTAP013)
BLTAP Foundation
Role of particle-induced inflammation on progression of brain tumors (BTAP011) and neurodegenerative brain diseases (BTAP013)
To determine inflammatory molecular changes in the brain potentially leading to the development of brain tumors and neurodegenerative diseases after exposure of mice to air pollution using state-of-the-art quantitative transcriptome sequencing by RNAseq method and proteomics analysis to identify changes in the brain.
Role: Principal Investigator