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BIOGRAPHICAL SKETCH

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NAME: Fredric Austin Gorin

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

POSITION TITLE: Professor and Chairperson of Neurology (MED), Professor in Molecular Biosciences (VET)

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 California, Davis	B.S.	06/1973	Biochemistry
Washington U. Med. School, St. Louis, Missouri	MD-PhD	06/1979	Physiology/Biophysics
Jewish Hospital of St. Louis, Washington U. Med. School, St. Louis, Missouri	Internship	06/1980	Internal Medicine
UC San Francisco, San Francisco, California	Residency	06/1983	Neurology

NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.

A. **Personal Statement** I am chairperson of the Department of Neurology, School of Medicine and professor in the Department of Molecular Biosciences, Veterinary School at UC Davis. I oversee 42 basic and clinical faculty and 200+ employees in Neurology. In the Molecular Biosciences department, I have had the opportunity, as a member of the PTX graduate group executive committee, to co-write the newly NIH-fundeded "Pharmacology Training Program: From Bench to Bedside". My graduate training in small molecule drug design generated a predictive pharmacophore for enkephalin opioid peptides bound to the mu opioid receptor that has been experimentally validated. After many years of molecular and cell biological research at UCSF and UCD, I returned to small molecule drug design 15 years ago using the FDA-approved diuretic, amiloride, as a parent molecule to investigate pH-volume regulation in brain astrocytes and in human glioblastomas. In the course of these studies my group identified that modifying amiloride with 5' benzyglycine (**UCD38B,** US pat #2012/0108494 A) changed the molecule's drug profile such that UCD38B selectively kills proliferating and non-proliferating normoxic and hypoxic glioma cells utilizing intracellular mechanisms that differ from fundamentally from those of amiloride. UCD38B kills glioblastomas, but not astrocytes, via a programmed necrotic cell death mechanism by initiating 'mis-trafficking' of an endosomal subset containing urokinase protein cargo to perinuclear mitochondria. Collaborating with Sphaera Drug has lead to the synthesis and identification of 6 non-toxic small molecules that possess single micromolar potencies and utilize the same intracellular mechanisms as UCD38B. Our current lead small molecule, **cmpd 357**, crosses the blood brain barrier, is non-toxic in rodents. In collaboration with J. Sarkania's glioma group, we determined that UCD38B and cmpd 357 preferentially kill hypoxically reprogrammed patient-derived glioma 'stem-like' cells that co-express stem cell biomarkers and increased levels of the intracellular drug target, uPA and PAI-1. This project will investigate the pharmacology and the cellular mechanisms of 3-amino-5- arylamino-6-chloro-N-(diaminomethylene) pyrazine-2-carboxamides.

B. Positions and Employment

1983 Adjunct Assistant Professor, Department of Biochemistry & Biophysics, University of California, San Francisco, San Francisco, California

1984 Adjunct Assistant Professor, Department of Neurology, University of California, San

Francisco, California
1985 Assistant Professor, Department of Neurology, University of California, Davis
1991 Associate Professor, Department of Neurology, University of California, Davis
1997- Professor, Department of Neurology, University of California, Davis
2008-10 Director of Outpatient Neurology, University of California, Davis
2010-11 Vice-Chair and Hospital Chief of Neurology, University of California, Davis
2010- Professor, Department of Molecular Biosciences, Veterinary School, UC Davis
2011- Hospital Chairperson, Department of Neurology, University of California, Davis
2011- Medical Staff Executive Committee
2012- Departmental Chairperson, Department of Neurology, University of California, Davis
2012- UC Davis Council of Chairs

Other Experience and Professional Memberships
1985 Credentialed in Neurology, American Board of Psychiatry and Neurology
1996- American Physiological Society (member)
1996- The American Neurological Association (fellow)
2004- Society for Neuro-Oncology (member)
2008 American Association for Cancer Research
2010- American Chemical Society (member)
2013- American Society for Pharmacology and Experimental Therapeutics
2003- Journal of Integrative Neuroscience (editorial board)
2013- Cancer Research (reviewer)
2014- J Pharm Exp Ther and Molec Pharm (reviewer)
2013- Journal of Neurological Disorders (editorial board),
2014- Journal of Neurology and Neurological Disorders (editorial board)

Honors/Awards:
Phi Beta Kappa (1972),
Phi Kappa Phi (1972),
UC Davis Graduation with Highest Honors (1973),
Research fellowship, U. So. Calif., Dept. Pharmacology, (l972),
Medical Scientist Training Program (MD-PhD,1993-9, GM-020l6, NIH), Washington University Medical School, St. Louis
Highest Rated American Heart Association Research Proposal in California (1988),

Patents: US Patent No. 6,096,520 "Brain Glycogen Phosphorylase Cancer Antigen " (Ludwig Institute for Cancer Research, Brussels, ref: LUD 5445.1 and US patent # 6,096,520) V. Brichard, A. van Pel, T. Boon-Falleur, F. Gorin., U.S. Patent Application (US 2006/0160746) “Amino acid and peptide conjugates of amiloride and methods of use thereof” F. Gorin, M. Nantz. (US2006/0160746,WO 2005/073247). “Inhibitors of Intracellular Urokinase Plasminogen Activator and Methods of Use Thereof”. F. Gorin, M. Nantz (US2012/0108494 A, WO2009020877)

C. Contributions to Science

***Proposed and Experimental Validation of Enkephalin Pharmacophore Bound to Mu Opioid Receptor*:**
I utilized early computer-based conformational analysis, energy calculation models, and computer graphics system to align enkephalin peptides with the crystallographic structures of opiate alkaloids. By combining these methodologies, I identified a potential pharmacophore recognized by the mu opioid receptor (**a,b**). The proposed pharmacophore successfully predicted the binding and biological activities of conformationally constrained peptides that I subsequently synthesized and biologically evaluated in the Marshall lab at Wash U and those of our commercial partner, Burroughs-Welcome (**c,d**).

a) Gorin, F.A. and Marshall, G.R. (1977) Proposal for the Biologically Active Conformations of Opiates and Enkephalin. Proc. Natl. Acad. Sci. USA 74: 5l79-5l83.
b) Gorin, F.A., Balasubramanian, T.M., Barry, C.D. and Marshall, G.R. (1978) Elucidation of the Receptor-Bound Conformation of the Enkephalins. J. Supramolec. Structure 9: 27-39 (1978).

c) Marshall, G.R., Gorin, F.A., and Moore, M.L..(1978) Peptide Conformation and Biological Activity. In: Annual Reports in Medicinal Chemistry, Vol. 13, F.H. Clarke, ed., Academic Press, New York, pp. 227-238.
d) Gorin, F.A., Balasubramanian, T.M., Cicero, T.J., Schweitzer, J. and Marshall, G.R. (1979) Novel Analogues of Enkephalin: Identification of Functional Groups Required for Biological Activity. J. Medicinal Chem. 23: 1113-1122.

Chromosomal Mapping of First Human Muscle Disorder (McArdle'sDisease) and identification of intracellular mechanisms mediating neutrally-regulated, coordinated expression of glycolytic genes in skeletal muscle*.* After completing my internship and Neurology residency, I joined the Fletterick lab in UCSF Biochemistry that crystallographically determined the tertiary structure of rabbit muscle glycogen phosphorylase. I cloned exonic portions of the human gene encoding myophosphorylase and with Yuet-Wai Kan's group chromosomally mapped the first human muscle disorder (McArdle's Disease) resulting from genetic mutations of myophosphorylase (**a**). Subsequent studies in my lab identified that high frequency neural activity in fast-twitch glycolytic skeletal muscle coordinately regulates expression of myophosphorylase and other glycolytic genes by altering their transcript stability via calcium transients released from the sarcoplasmic reticulum (**b,d**). We identified a consensus region in the 3' non-translated portion of the transcript that mediates this calcium signaling. Translationally, we identified that regenerated fast-twitch muscle associated with neural reinnervation expresses a metabolic defect in glycogenolysis that becomes metabolically symptomatic with high intensity exercise (**c**) and which is observed in patients that sustained traumatic injuries.

a) Lebo RV, Gorin F, Fletterick RJ, Kao FT, Cheung MC, Bruce BD, Kan YW.High-resolution chromosome sorting and DNA spot-blot analysis assign McArdle's syndrome to chromosome 11. Science. 1984 6;225(4657):57-9. PubMed PMID: 6587566
b) Matthews, C. Froman, B., Carlsen, R., Gorin F. (1998). Nerve-dependent factors regulating transcript levels of glycogen phosphorylase in skeletal muscle. Cellular and Molec. Neurobiology 18(3):319-338.
c) Gorin F.A., Herrick, K, Froman, B., Palmer W. Tait, R., Carlsen, R. (1996). Botulinum-induced muscle paralysis alters metabolic gene expression and fatigue recovery. Am. J. Physiol. 270 (Reg Integ Comp 39:)R238-R245.
d) Vali, S., Pessah, I., Carlsen, R.C., and Gorin, F. (2000) Sarcoplasmic Calcium Mediates Activity-dependent Regulation of Glycogen Phosphorylase Gene Expression in Contractile Skeletal Muscle Cells. J. Cell. Physiol.185:184-199.

Cellular Mechanisms Controlling Abnormal Intracellular pH and the Resultant Cessation of Perinecrotic Glioma Cell Proliferation. 31-P spectroscopy had surprisingly identified that high grade glial cancers were normacidic or alkalotic. My lab and the Cala lab at UCD identified abnormal post-translational regulation of the Na+/H+ Exchanger in human glioblastoma cell lines (**a**). Subsequently, my lab determined that the extracellular acidosis of pHext 6.0 surrounding perinecrotic tumor regions (**b**) arrested glioma cell cycle progression by altered intracellular localization of cyclin D1 (**c)**. In these acidotic environments multiple human high grade glioma cell lines were shown as a consequence of overactive NHE1 to contain excess intracellular calcium that was stored in the endoplasmic reticulum and mitochondria (**d**).

a) McLean, L., Roscoe, J. Cala, P.M., Gorin, F.A. (2000) Gliomas display altered pH regulation by NHE1 compared with nontransformed Astrocytes. Am J. Physiol.278:C676-C688,
b) Gorin F, Harley W, Schnier J, Lyeth B, Jue T (2004) Perinecrotic glioma proliferation and metabolic profile within an intracerebral tumor xenograft.Acta Neuropathol (Berl).107(3):235-44.
c) Schnier JB, Nishi K, Harley WR, Gorin FA. An acidic environment changes cyclin D1 localization and alters colony forming ability in gliomas. J Neurooncol. 2008 89(1):19-26. PubMed PMID: 18404250.
d) Harley W, Floyd C, Dunn T, Zhang XD, Chen TY, Hegde M, Palandoken H, Nantz MH, Leon L, Carraway KL 3rd, Lyeth B, Gorin FA. Dual inhibition of sodium-mediated proton and calcium efflux triggers non-apoptotic cell death in malignant gliomas. Brain Res. 2010 Dec 2;1363:159-69. doi: 10.1016/j.brainres.2010.09.059. Epub 2010 Oct 13. PubMed PMID: 20869350;

Identification of Class of Small Molecules that Selectively Kill Proliferating and Non-Proliferating Hypoxically Transformed Glioma Cells by Inducing Endocytotic 'Mis-trafficking'*.* 5' modification of amiloride produced cell permeant and impermeant small molecules that kill gliomas by targeting intracellular urokinase (uPA) bound to the endogeneous serpin PAI-1 (a,c). The anti-glioma cytotoxicity of these small molecules requires that they are {i} cell permeant, {ii} act intracellularly, {iii} initiate mis-trafficking of a subset of

endosomes containing urokinase protein cargo (c) and {iv} selectively kill glioma cells by a novel programmed form of necrosis (b)

a) Massey, AP, Harley, WR, NagaRekha Pasupuleti, Gorin, FA, Nantz MH 2-Amidino Analogs of Glycine-Amiloride Conjugates: Inhibitors of Urokinase-type Plasminogen Activator. Bioorg Med Chem Lett. 2012 Apr 1;22(7):2635-9. Epub 2012 Jan 4. PubMed PMID: 22366654; PubMed Central PMCID: PMC3329872.
b) Pasupuleti N, Leon L, Carraway KL 3rd, Gorin F. 5'-Benzylglycinyl-Amiloride Kills Proliferating and Nonproliferating Malignant Glioma Cells through Caspase-Independent Necroptosis Mediated by Apoptosis-Inducing Factor. J Pharmacol Exp Ther. 2013 Mar;344(3):600-15. doi: 10.1124/jpet.112.200519. Epub 2012 Dec 14. PubMed PMID: 23241369
c) Pasupuleti N, Grodzki AC, Gorin F. Mis-trafficking of endosomal urokinase proteins triggers drug-induced glioma nonapoptotic cell death. Mol Pharmacol. 2015 Apr;87(4):683-96. PubMed PMID: 25634671; PubMed Central PMCID: PMC4366798.
Gorin FA, Pasupuleti N, Mahajan D, Dugar S. Killing Glioma 'Stem-like' Cells via Drug-Induced Relocation of Endosomal Urokinase Proteins. Anticancer Agents Med Chem. 2016 Jun 28. [Epub ahead of print] PubMed PMID: 27357540
d) Gorin FA, Pasupuleti N, Mahajan D, Dugar S. Killing Glioma 'Stem-like' Cells via Drug-Induced Relocation of Endosomal Urokinase Proteins. Anticancer Agents Med Chem. 2016 Jun 28. [Epub ahead of print] PubMed PMID: 27357540.

Complete List of Publications in MyBibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/1lcnHt-E3ut/bibliography/42289426/public/?sort=date&direction=ascending

D. Research Support (Ongoing and past 3 years)

UC Davis Research Investments in the Sciences and Engineering (RISE) Program Role: co-PI	**Center for Content Rich Evaluation of Therapeutic Efficacy (cCRETE).** Develop cell microsystems where micro-patterned co-cultures of cancer and noncancer cells are juxtaposed with arrays of sensor elements that monitor downstream readouts of cell-drug interactions. Co-PI will focus on assays of invasive potential and inflammatory markers that will be assessed by measuring cell secreted proteases in vitro and in vivo. Gorin group will also use vivo imaging of orthotopic glioblastoma xenografts that assess therapeutic efficacy and will validate the new assays with in vivo assays of cell invasion and inflammation.	6/1/12-7/31/15
1R21CA178578-01A1 Role: co-PI	**Fluorescent Lifetime Technique for detection of Radiation Necrosis vs Glioma.** FLT previously shown to distinguish between GBM and normal brain tissue intraoperatively. Now used to distinguish between radiation necrosis and GBM. Gorin lab will utilize ICH biomarkers to characterize inflammatory alterations of early, mid, and late stages of radiation necrosis in rodent model.	9/1/14-8/31/16
NIH R01NS060880 Role: PI	**Novel Glioma uPA Inhibitor Design Guided by Intracellular Signaling Pathways** As PI designed and directed pre-clinical drug discovery program that determined drug mechanism by which 5' derivatives of amiloride were cytotoxic to glioblastoma cell lines	9/1/109 - 10/1/12
Komen Foundation Role: co-PI	**Induction of apoptosis of highly invasive breast cancer cells by novel small molecule inhibitors of intracellular urokinase plasminogen activator.** Identified that UCD38B vs amiloride was cytotoxic to a wide range of breast cancer cell lines	9/1/11 - 9/1/14
NIH T32 GM099608	**Pharmacology Training Program: From Bench to Bedside.** On executive committee that planned and I co-	6/1/12 -

Role: co-PI	wrote proposal to train UCD graduate students in pre-clinical drug discovery	7/3/17
NIH T32MH082174 Role: Trainer	**Training Program in Basic Neuroscience** Trainer of UC Davis Neuroscience graduate students	10/03/ 07