BIOGRAPHICAL SKETCH

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NAME: Maguire, Casey A.

POSITION TITLE: Assistant Professor of Neurology

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

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 Maine, Orono, ME	BSc.	05/2000	Microbiology
University of Rochester School of Medicine and Dentistry, Rochester, NY	Ph.D.	05/2006	Microbiology and Immunology
The Massachusetts General Hospital, Boston, MA Harvard Medical School, Boston, MA	Postdoctoral fellow	08/2010	Gene Therapy/Molecular Imaging/Brain Tumors

A. Personal Statement

I am an assistant professor at Harvard Medical School with my research laboratory at the Massachusetts General Hospital (MGH). Since beginning graduate school in 2000, my research efforts have been focused on developing engineered viruses to treat human disease. I have extensive training with virus vector development, genetic engineering, gene delivery to the CNS and other organs in preclinical animal models, and *in vivo* bioluminescence imaging. The main focus of my laboratory is to develop gene delivery systems both as effective research tools as well as future therapeutics to treat CNS disease, including brain tumors. Currently with collaborator David Corey, we are making strides in the preclinical development of gene therapies for hereditary deafness. My long term goal is to develop vectors that overcome barriers to gene delivery systems, such as the immune response, which would allow their use in a worldwide patient population.

1. Maguire CA, Balaj L, Sivaraman S, Crommentuijn M, Ericsson M, Mincheva-Nilsson L, Baranov V, Gianni D, Tannous BA, Sena-Esteves M, Breakefield XO, Skog J. (2012). Microvesicle-associated AAV vector as a novel gene delivery system. Molecular Therapy 20(5):960-71. PMCID: PMC3345986

2. Zappulli V, Friis KP, Fitzpatrick Z, Maguire CA, Breakefield XO. (2016). Extracellular vesicles and intercellular communication within the nervous system. Journal of Clinical Investigation. 126 (4):1198-1207.

3. György B, Sage C, Indzhykulian AA, Scheffer DI, Brisson AR, Tan S, Wu X, Volak A, Mu D, Tamvakologos PI, Li Y, Fitzpatrick Z, Ericsson M, Breakefield XO, Corey DP, Maguire CA. (2017). Rescue of Hearing by Gene Delivery to Inner-Ear Hair Cells Using Exosome-Associated AAV. Molecular Therapy. Molecular Therapy. 2017 Feb 1;25(2):379-391. Cover Image.

4. Wassmer SJ, Carvalho LS, György B, Vandenberghe LH, Maguire CA. (2017). Exosome-associated AAV2 vector mediates robust gene delivery into the murine retina upon intravitreal injection. Scientific Reports. Mar 31;7:45329

B. Positions and Honors

Positions and Employment

2000-2006 Graduate Student, University of Rochester School of Medicine and Dentistry, Rochester, NY

2006-2009	Postdoctoral fellow, Neurology Department, MGH and Neuroscience Program, HMS, Boston, MA
2009	Investigator, Novartis Vaccines and Diagnostics, Cambridge, MA
2009-2010	Postdoctoral fellow, Neurology Department, MGH and Neuroscience Program, HMS, Boston, MA
2009-	Advisor to MGH Virus Vector Core, AAV production
2010-2012	Consultant for Exosome Diagnostics, Inc. New York, NY
2010-2012	Instructor in Neurology, MGH/HMS
2010-	Assistant in Neuroscience, MGH, Department of Neurology
2013-	Assistant Professor of Neurology, HMS
2015-	Consultant for Gerson Lehrman Group
2016-	Consultant for Guidepoint

Other Experience and Professional Memberships and Activities

2002-	Member, American Society of Gene and Cell Therapy
2011	Member, Academy of Molecular Imaging
2011-	Member, International Society for Extracellular Vesicles

Honors

2008	First Place, Third Annual Massachusetts General Hospital Research Fellows Poster Celebration
2010	Travel Award, American Society of Gene and Cell Therapy, 13th Annual Meeting
2016	Partners Healthcare Innovation Discovery Award

C. Contribution to Science

1. Development of an enhanced gene delivery system based on extracellular vesicles and a virus vector. Our laboratory was the first to show that a gene therapy vector, adeno-associated virus (AAV) vector, could associate with extracellular vesicles (EVs), and be used to overcome limitations of conventional AAV vectors, including low transduction efficiency and antibody neutralization. In 2012 we were awarded an R21 to develop this technology for GBM treatment. We are currently collaborating with several labs to evaluate this vector system (called exo-AAV) in several preclinical models of human disease including deafness, Alzheimer's Disease, glioblastoma, and muscular dystrophy. The goal is to develop exo-AAV into a clinical product. I served as the primary or co-investigator in all of these studies and I am the primary inventor of the technology.

a. Maguire CA, Balaj L, Sivaraman S, Crommentuijn M, Ericsson M, Mincheva-Nilsson L, Baranov V, Gianni D, Tannous BA, Sena-Esteves M, Breakefield XO, Skog J. (2012). Microvesicle-associated AAV vector as a novel gene delivery system. Molecular Therapy 20(5):960-71. PMCID: PMC3345986.

b. György B, Fitzpatrick F, Crommentuijn MHW, Mu D, Maguire CA. (2014). Naturally enveloped AAV vectors for shielding neutralizing antibodies and robust gene delivery *in vivo.* Biomaterials. 35(26):7598-609. PMCID: PMC4104587

c. Hudry E, Martin C, Gandhi S, György B, Scheffer DI, Mu D, Merkel SF, Mingozzi F, Fitzpatrick Z, Dimant H, Masek M, Ragan T, Tan S, Brisson AR, Ramirez SH, Hyman BT, Maguire CA. (2016) Exosome-associated AAV vector as a robust and convenient neuroscience tool. Gene Therapy.23(4):380-92.

d. György B, Sage C, Indzhykulian AA, Scheffer DI, Brisson AR, Tan S, Wu X, Volak A, Mu D, Tamvakologos PI, Li Y, Fitzpatrick Z, Ericsson M, Breakefield XO, Corey DP, Maguire CA. (2017). Rescue of Hearing by Gene Delivery to Inner-Ear Hair Cells Using Exosome-Associated AAV. Molecular Therapy. Jan 9. pii: S1525-0016(16)45434-1. doi: 10.1016/j.ymthe.2016.12.010.Cover Image.

2. Novel gene therapy approaches for brain tumors. Glioblastoma multiforme (GBM) is a deadly primary brain tumor with no known cure. As a postdoctoral fellow at the MGH working with gene therapy experts Xandra Breakefield and Miguel Sena-Esteves, I made a seminal contribution to *in vivo* gene delivery for anti-

glioma therapy. I helped develop and characterize the concept of a “zone of resistance” to cancer, a novel method of gene delivery to treat brain tumors by genetically modifying normal cells in their vicinity. In this strategy, the viral vector delivers a gene for a secreted anti-tumor protein and is directed to the normal brain instead of tumor cells. This resulted in the most robust anti-tumor effect obtained with an AAV vector in a preclinical glioma model at that time. The second project sought to design novel AAV vectors which possessed desirable properties for GBM cell transduction. I created a library of mutant AAV capsids using the method of DNA shuffling and in a proof-of-concept study, performed an *in vitro* selection for viral vectors which efficiently infected glioma cells. I successfully selected a vector which efficiently delivered transgenes to a variety of glioma cell lines, including primary glioma cells. This study selected a useful vector for transgene delivery in GBM research. I was the first author and primary driver of the experimental design and performance of this work. My lab continues to focus on gene therapy development for treatment of GBM with past funding from the American Brain Tumor Association.

a. Maguire CA, Meijer DH, LeRoy SG, Tierney LA, Broekman MLD, Costa FF, Breakefield XO, Stemmer-Rachamimov A, Sena-Esteves M. (2008). Preventing growth of brain tumors by creating a zone of resistance. Molecular Therapy 16(10):1695-702. PMCID: PMC2863297

b. Maguire CA, Gianni D, Meijer DH, Shaket LA, Hiroaki W, Rabkin SD, Gao G, Sena-Esteves M. (2010). Directed evolution of adeno-associated virus for glioma cell transduction. Journal of Neuro-Oncology. 96(3):337-47. PMCID: PMC2892971

c. Crommentuijn MHW, Maguire CA, Niers JM, Vandertop WP, Badr CE, Wurdinger T, Tannous BA. (2016). Intracranial AAV-sTRAIL combined with lanatoside C prolongs survival in an orthotopic xenograft mouse model of invasive glioblastoma. Molecular Oncology. 10(4):625-34. Cover Image.

d. Crommentuijn MHW, Kantar R, Noske DP, Vandertop WP, Badr CE, Wurdinger T, Maguire CA, Tannous BA. (2016). Systemically administered AAV9-sTRAIL combats invasive glioblastoma in a patient-derived orthotopic xenograft model. Molecular Therapy-Oncolytics. 22;3:16017.

3. Elucidating a cellular entry mechanism of extracellular vesicles (EVs) as well as novel EV purification methods for biomarker discovery. EVs are carriers of genetic information, miRNA, mRNA, and proteins from their cells of origin. This makes EVs a highly valuable source of biomarker information which can be harvested noninvasively from biofluids vs invasive biopsy procedures. While characterizing the exo-AAV gene delivery system mentioned above in contribution 1, we discovered that the glycosaminoglycan, heparin, blocked EV uptake into recipient cells. We showed that heparin blocked entry of EVs derived from both normal and tumor cells, with tumor cell EVs being more sensitive to lower concentrations of heparin. I made the initial discovery and was the lead investigator in this study. Subsequently, another group confirmed our results showing that heparin blocked EV uptake as well as showed that EV uptake was dependent on the presence of heparan sulfate proteoglycans (HSPG) on the cell surface. Our work helped identify a major mechanism of EV entry into cells, thus furthering our understanding of EV biology. Furthermore, it identified a method to purify EVs for biomarker discovery and we have developed a heparin affinity technology for EV isolation. Finally, our finding that tumor cell EVs are more sensitive to heparin entry blockade, may aid in the development of anti-tumor therapeutics by blocking transfer of tumorigenic EVs into recipient cells.

a. Atai NA, Balaj L, van Veen H, Breakefield XO, Jarzyna PA, Van Noorden CJF, Skog J, Maguire CA. (2013). Heparin blocks transfer of extracellular vesicles between donor and recipient cells. Journal of Neuro-Oncology. 115(3):343-51. PMCID: PMC3856724

b. Balaj L, Atai NA, Chen W, Mu D, Tannous BA, Breakefield XO, Skog J, Maguire CA. (2015). Heparin affinity purification of extracellular vesicles. Scientific Reports 5:10266, PMCID: PMC4437317

4. Characterization and development of virus vectors for CNS gene delivery applications. Efficient *in vivo* gene delivery to the CNS with virus vectors is challenging due to many obstacles including the blood-brain barrier, off-target organ uptake, and immune responses to the vector. I have been directly involved in several research projects involving the utilization of virus vectors for CNS gene transfer. We have made significant contributions to the field of both gene delivery and gene therapy, including preclinical development of gene

therapy for CNS disorders, characterization of AAV vectors interaction with endothelium, and discovery of gender-specific gene delivery enhancement in murine models of human disease.

a. Maguire CA*, Crommentuijn MHW*, Mu D, Hudry E, Serrano-Pozo A, Hyman BT, Tanous BA. (2013). Mouse gender influences brain transduction by intravascularly-administered AAV9. Molecular Therapy. Aug;21(8):1470-1. *Co-first authors.

b. Gong Y, Mu D, Prabhakar S, Moser A, Musolino P, Ren JQ, Breakefield XO, Maguire CA, Eichler F. (2015). Adeno-associated virus serotype 9-mediated gene therapy for X-linked Adrenoleukodystrophy (X-ALD). Molecular Therapy. 23(5):824-34.

c. Dashkoff J, Lerner EP, Truong N, Klickstein JA, Fan Z, Mu D, Maguire CA, Hyman BT, Hudry H. (2016) Tailored transgene expression to specific cell types in the central nervous system after peripheral injection with AAV9. Molecular Therapy-Methods and Clinical Development. Dec 7;3:16081.

d. Merkel SF, Andrews AM, Lutton EM, Mu D, Hudry E, Hyman BT, Maguire CA*, Ramirez SH*. (2017) Trafficking of AAV vectors across a model of the blood-brain barrier; a comparative study of transcytosis and transduction using primary human brain endothelial cells. Journal of Neurochemistry. Jan;140(2):216-230. doi: 10.1111/jnc.13861.*Co-corresponding authors.

5. Establishment of a multi-reporter system for *in vivo* preclinical imaging. *In vivo* bioluminescence imaging using luciferases which catalyze substrate-dependent light emission, has revolutionized molecular biology as it allows non-invasive sequential imaging of reporter gene expression. The advantage of using bioluminescent imaging compared to endpoint analysis is that it provides real-time, non-invasive measurement of *in situ* biological events, thereby giving a more complete "picture" of the kinetics of an entire process. As a postdoctoral fellow in the laboratory of imaging expert Dr. Bakhos Tannous, I was the driver in the development of a triple luciferase reporter system in which three different aspects of anti-glioblastoma (GBM) therapy was measured. In our proof-of-concept model we monitored transgene delivery by a viral vector using one luciferase (north American firefly luciferase, Fluc), tumor growth using a second luciferase (Vargula hilgendorfii luciferase, Vluc), and NFκB transcription factor activation (Gaussia princeps luciferase, Gluc) in response to an anti-tumor protein, soluble tumor necrosis factor related apoptosis-inducing ligand (sTRAIL), encoded by the viral vector. The different reporters were monitored by sequential imaging after administering the appropriate substrate for each luciferase. This work was important as it should be a useful tool for basic biological research where multiple biological processes can be monitored noninvasively. Additionally, using the DNA shuffling techniques, we generated a mutant Gaussia luciferase (Gluc) library using DNA shuffling and we isolated several Gluc variants with properties desirable for high-throughput screening applications. One of these clones was awarded a US patent.

a. Maguire CA, Deliolanis NC, Pike L, Niers J, Tjon-Kon-Fat L, Sena-Esteves M, Tannous BA. (2009). Gaussia luciferase variant for high-throughput applications. Analytical Chemistry. 15;81(16):7102-6. PMCID: PMC2846205

b. Degeling MH*, Maguire CA*, Bovenberg MS, Tannous BA. (2012). Sensitive assay for mycoplasma detection in mammalian cell culture. Analytical Chemistry. 1;84(9):4227-32.*: Co-First Authors PMCID: PMC3341502

c. Maguire CA, Bovenberg SM, Crommentuijn MHW, Niers JM, Kerami M, Teng J, Sena-Esteves M, Badr CE, Tannous BA. (2013). Triple bioluminescence imaging for in vivo monitoring of cellular processes. Molecular Therapy- Nucleic Acids. 2:e99. doi: 10.1038/mtna.2013.25. PMCID: PMC3696905

d. Maguire CA. (2014). Bioluminescence-based monitoring of virus vector-mediated gene transfer in mice. In: Badr, Christian E., ed. *Bioluminescent Imaging, methods and protocols.* Methods Mol Biol.1098:197-209.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/casey.maguire.1/bibliography/43968887/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

Cure Alzheimer's Fund Maguire (PI) 11/20/15-11/19/17
Extracellular vesicle-based targeting of CD33-mediated pathology for Alzheimer's Disease therapy.
The goal of this proposal is to use genetically modified exosomes to target and inactivate CD33 receptor activity allowing microglial degradation of Aβ.
Role: PI

1R21-NS088013-01A1 Brenner (PI) 07/01/15-06/30/17
Translation of AAV P0 ICE Schwannoma Gene Therapy to Clinical Trials
The goal of this application is to determine the toxicity and efficacy parameters of our vector necessary for submission of a FDA Pre-IND package, and establish whether AAV immunity alters the efficacy and/or toxicity of AAV-P0-ICE for optimization of clinical trial design
Role: Investigator

UPenn Orphan Disease Center Grant; Eichler (PI) 01/01/17-12/31/17
Biodistribution of Intrathecal AAV9-mediated Gene Therapy in AMN .
The main goal of this project is to develop preclinical data for a future human gene therapy trial to treat Adrenomyeloneuropathy (AMN).
Role: Co-investigator

Completed Research Support

UPenn Orphan Disease Center Grant; Eichler (PI) 01/01/16-12/31/16
Adeno-associated virus serotype 9-mediated gene therapy for Adrenomyeloneuropathy (AMN)
The main goal of this project is to develop preclinical data for a future human gene therapy trial to treat AMN.
Role: Co-investigator

UPenn Orphan Disease Center Grant; Maguire (Co-I) 12/01/14-11/31/15
Adeno-associated virus serotype 9-mediated gene therapy for Adrenomyeloneuropathy (AMN)
The main goal of this project is to develop preclinical data for a future human gene therapy trial to treat AMN.
Role: Co-investigator

American Brain Tumor Association Discovery Grant; Maguire (PI) 07/01/14-06/30/15
IL-13Ralpha2-targeted Multi-AAV Vector Delivery System for GBM Tumoricidal Therapy
The goal of this proposal is to target GBM tumors with our vexosome technology and kill invasive tumor cells with vector-encoded anti-tumor proteins.
Role:PI

R21 NS081374-01 Maguire (PI) 09/01/12-08/31/14
A hybrid microvesicle/virus vector for targeted gene transfer to the brain
The goal of this study is to develop a novel hybrid gene delivery system which can cross the blood-brain barrier for treatment of brain tumors.
Role: PI