

Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is “None”, please specify “None” as your response. “Not applicable” is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-231-2825.

1. **Grantee Institution:** University of Pittsburgh- of the Commonwealth System of Higher Education
2. **Reporting Period (start and end date of grant award period):** 1/1/2011 - 12/31/2014
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Margaret C. McDonald, PhD
4. **Grant Contact Person’s Telephone Number:** 412-383-7474
5. **Grant SAP Number:** 4100054875
6. **Project Number and Title of Research Project:** 06 – Glioma Vaccine Clinical Trials
7. **Start and End Date of Research Project:** 1/1/2011 – 12/31/2012
8. **Name of Principal Investigator for the Research Project:** Hideho Okada, MD, PhD
9. **Research Project Expenses.**

9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

\$ 220,893.88

9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Dorko	Clinical Research Coordinator	75% January 2011 - August 2012; 50% September 2012 - December 2012; 25% January 2013	\$96,819.59
Hill	Data Manager	75% January 2011 – December 2012; 50% January 2013	\$70,867.04
Johnson	Clinical Research Coordinator	30% January 2011 – December 2012	\$53,207.25

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Okada	Principal Investigator	10%
Davis	Research Manager	10%
Vargas	Clinical Research Coordinator	20%
Hahn	Regulatory Coordinator	20%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes X No _____

If yes, please indicate the source and amount of other funds:

NIH/NCI R21CA133859 (Okada, PI): A Bi-Institutional Pilot Study of Vaccinations for Patients with Low Grade Glioma \$500,000 total costs

Voices against Brain Cancer \$100,000 total costs

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes X No _____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert “not funded” in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds awarded:
R21 CA177787-01: Phase I Vaccine Study Using Brain Tumor Initiating Cells in WHO Grade II Gliomas	X NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _)	October 2013	\$375,000 (direct costs)	\$320,000 (direct costs)

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes _____ No X

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

Future plans include development of follow-up Phase II studies.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes _____ No X _____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. Recruitment of Out-of-State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes _____ No X _____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes X _____ No _____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

These funds were used to support clinical coordinators and a data manager, which had a direct and positive impact by enhancing clinical trial infrastructure at our institution.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes X No _____

If yes, please describe the collaborations:

These trials fostered collaborations with Wake Forest University and the University of Minnesota. Specifically, researchers at Wake Forest University participated in the design of trial UPCI 07-057 and enrolled one patient to the study. Researchers at the University of Minnesota contributed to the 11-136 study through the supply of GBM6 vaccine material.

16(B) Did the research project result in commercial development of any research products?

Yes _____ No X _____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes X _____ No _____

If yes, please describe involvement with community groups that resulted from the research project:

An annual fundraising event series ([Denise's People](#)) was initiated and led by family members of patients who participated in the UCPI 08-135 study.

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under

item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (β) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Project Overview:

We will examine trials of novel tumor peptide-based vaccines, including safety and efficacy studies of: vaccinations with glioma-associated antigen (GAA) peptides emulsified in vaccine adjuvant Montanide ISA-51 and in combination with polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose (poly-ICLC) in patients with either newly diagnosed low-grade glioma (LGG) with high risk factors for recurrence (UPCI 07-057) or in patients with recurrent LGG (UPCI 08-135). In June 2012, we received approval to expand this project to include a newly opened vaccine trial, UPCI 11-136, which targets the same patient populations and uses the same treatment regimens, but with fewer eligibility restrictions, allowing for a broader patient base while maintaining the same expected outcomes and specific aims. The vaccine approaches described in this project offer immunotherapeutic potential to reduce the risk of tumor recurrence, which may translate into improved patient survival.

UPCI 07-057:

Objectives: Primary objectives are determination of both immunological activity and safety of the regimen. To assess induction of GAA-specific T-cell response, we will determine the response rate and magnitude of immune response in post-vaccine peripheral blood mononuclear cells (PBMC) against the GAA peptides in response to this form of vaccine, using interferon (IFN)- γ -enzyme-linked immuno-spot (ELISPOT) and tetramer assays. For safety, the incidence and severity of adverse events (AE) associated with the vaccine regime will be assessed, with an early stopping rule based on the frequency of regimen limiting toxicity (RLT). Other exploratory

objectives include: (1) clinical response, (2) radiological response, (3) two-year progression-free survival (PFS), and (4) evaluation of tumor tissues for biological correlates.

Methods: Eligible patients are human leukocyte antigen (HLA)-A2+ patients (age ≥ 18 years old) with histologically diagnosed supratentorial World Health Organization (WHO) grade II astrocytoma or oligoastrocytoma with “high-risk” factors, defined as: (1) age ≥ 40 with any extent of resection, (2) age 18-39 with incomplete resection (post-op MRI showing >1 cm residual disease, based on the maximum dimension of residual T2 or fluid-attenuated inversion-recovery [FLAIR] abnormality from the edge of the surgical cavity either laterally, antero-posteriorly, or supero-inferiorly), or (3) tumor size ≥ 4 cm (any age).

Eligible patients are stratified based on whether they have undergone prior radiation therapy. Cohort 1 includes patients who have undergone surgery or biopsy alone (no postoperative radiation or chemotherapy) and have a baseline MRI scan (within four weeks of the first vaccine) that shows stable disease or regression (no progression from the initial surgery/biopsy). Cohort 2 includes patients who received surgery or biopsy and radiation therapy (RT), which was completed ≥ 6 months prior to enrollment and have a stable MRI scan (no progression after RT). Prior chemotherapy excludes patients from both cohorts. The sample size was originally nine patients per cohort; however, the sample size for Cohort 1 has been expanded to a maximum of 18 because of the high accrual rate in this cohort.

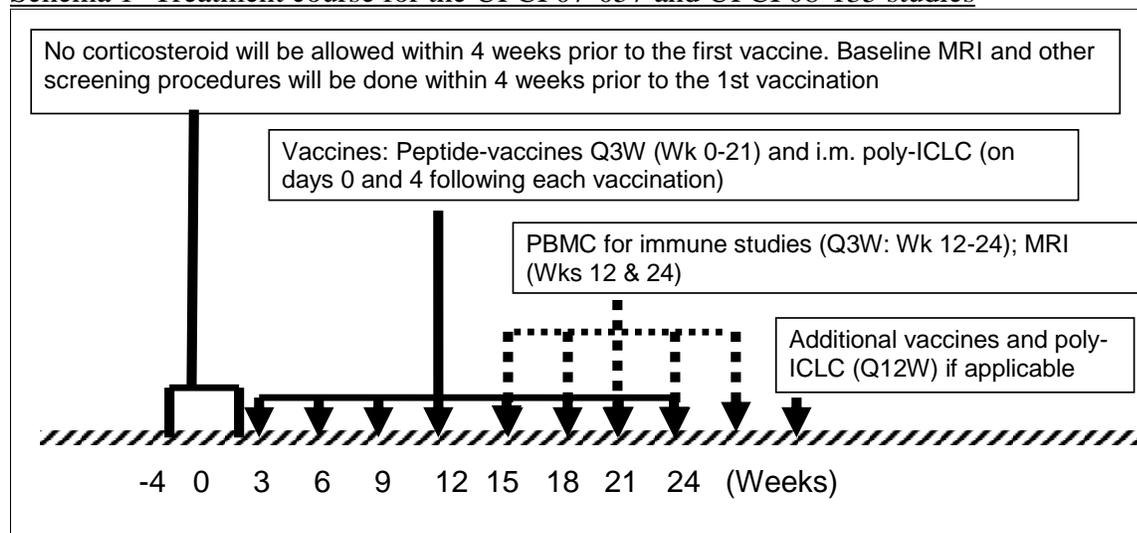
All participants must have discontinued dexamethasone (or similar corticosteroid medications) at least four weeks before administration of the first vaccine. Participants are treated with subcutaneous (s.c.) injections of GAA/TT-vaccines on an outpatient basis on Weeks 0, 3, 6, 9, 12, 15, 18, and 21; poly-ICLC is administered (20 mg/kg i.m.) on the day of, and on Day 4 after, each vaccine. (See Table 1 and Schema 1 for the list of antigens and the treatment schedule, respectively.) Participants are evaluated for any possible AE, RLT, and clinical response by clinic visits and MRI. PBMC samples are drawn at pre-vaccine and post-vaccine time points to evaluate immune responses.

Table 1. List of antigen peptides used in UPCI 07-057 and UPCI 08-135 studies

Antigen Peptide	Presented By:	Prevalence in HG / GIIA
IL-13R α 2 _{345-353:1A9V}	HLA-A2	$>80\%$ / low
EphA2 ₈₈₃₋₈₉₁	HLA-A2	75-80% / 50%
Survivin _{96-104:M2}	HLA-A2	All astrocytoma (GII-IV)
WT1 _{126-134:Y1}	HLA-A2	All astrocytoma (GII-IV)
Tetanus Toxoid (Tet _{A830})	Pan-DR	(heterologous antigen)

HG; high grade (grade III-IV) glioma, GIIA; grade II astrocytoma

Schema 1- Treatment course for the UPCI 07-057 and UPCI 08-135 studies



Results: A total of 12 patients were enrolled in Cohort 1. The regimen was well-tolerated, although most patients experienced mild and transient (Common Terminology Criteria for Adverse Events [CTCAE]) Grade 1 or 2 flu-like symptoms, including low-grade fever, chills, myalgia, headache, and fatigue. Ten of the 12 patients in Cohort 1 completed the initial course of eight vaccines. Of the two patients who did not complete the eight vaccines, one was taken off due to rapid tumor progression; the other one was taken off due to the occurrence of Grade 3 fever following the seventh vaccine, which is a dose-limiting toxicity (DLT). This is the only patient who demonstrated DLT; the symptom subsided with the use of over-the-counter non-steroidal anti-inflammatory drug by the next day. Among the 10 patients who completed the initial eight vaccines, two have completed the total 24 months of the entire protocol-defined vaccine course (initial eight vaccines and six booster vaccines), and still remain progression-free (at 40 and 42 months since the original diagnosis). Eight have been taken off due to radiologic (one) or symptomatic (one) progression. Median progression-free survival period is 21 months since diagnosis (range 10-42 months).

In Cohort 2 (patients with prior radiotherapy), only one patient was enrolled. This patient completed the total 24 months of the vaccines (initial eight vaccines and six booster vaccines), and remains progression-free at 63 months since the original diagnosis. Immune response data from this trial and UPCI 08-135 are presented below.

We have closed enrollment in this study; and a new study, UPCI 11-136, which targets the same patient populations without the eligibility restriction for HLA-A2⁺ patients, has been open since November 2012. Updates for this trial are also summarized below.

UPCI 08-135:

Objectives: This is a pilot vaccine study in adults with recurrent WHO grade II glioma. The overall objective of this study is to collect immunological and safety data that will be used to decide whether a larger study of clinical efficacy is warranted in these patients. All patients on the study will be followed for a minimum of two years so that the actual two-year overall

survival (OS), and six-month and two-year progression-free survival (PFS) rates can be determined in an exploratory manner. The detailed methods for evaluation of the primary and exploratory endpoints are the same as in the UPCI 07-057 study.

Methods: Eligible patients are HLA-A2+ patients (age ≥ 18 years old) with histologically diagnosed supratentorial WHO grade II glioma with recurrence. Patients have to be off steroids for 4 weeks before initiation of vaccines and have a lymphocyte count of 400/ μL or more. The sample size for this study is nine patients. Participants are treated with s.c. injections of GAA/TT-vaccines on an outpatient basis on Weeks 0, 3, 6, 9, 12, 15, 18, and 21; poly-ICLC is administered (20 mg/kg i.m.) on the day of and on Day 4 after each vaccine. Please see Table 1 and Schema 1 for the list of antigens and the treatment schedule, respectively. Participants are evaluated for any possible AE, RLT, and clinical response by clinic visits and MRI. PBMC samples are drawn at pre-vaccine and post-vaccine time points to evaluate immune responses.

Results: A total of 10 patients were enrolled. Of those, nine completed the initial eight vaccines despite the fact that all patients had recurrent LGG at the time of study entry. However, eight of those nine have recurred to date. One patient remains progression-free at 37 months since the first vaccine. One patient was removed from the study after four vaccines due to rapid tumor progression. The median progression-free survival period is 12 months (since the first vaccine). The toxicity profile was very similar to that of UPCI 07-057. There were no RLTs. Immune response data from this trial and UPCI 07-057 are presented below.

We have closed enrollment in this study. A new study, UPCI 11-136, which targets the same patient populations (but without the eligibility restriction for HLA-A2⁺ patients), has been open since November 2012. Updates for this trial are summarized below.

Immune response data from UPCI 07-057 and 08-135 studies: All but two patients (one in UPCI 07-057 and one in UPCI 08-135), who had disease progression before the first post-vaccine PBMC sampling on Week 15, had PBMCs available for immunological analysis. In 10 of 11, one of one, and five of nine evaluable patients in Cohort 1 of UPCI 07-057, Cohort 2 of UPCI 07-057, and UPCI 08-135 (“Cohort 3”), respectively, vaccination-induced immune reactivity to at least one of the vaccine-targeted GAAs was observed by IFN- γ ELISPOT assays (Table 2). Positive IFN- γ responses against at least three of the four GAA epitopes were observed in nine of 11, and three of nine cases in UPCI 07-057 Cohort 1 and UPCI 08-135, respectively. Nine of 10 in UPCI 07-057 Cohort 1 but only one of nine in UPCI 08-135 responded to the Tet peptide.

Table 2. Patient demographics and clinical and immunological responses

Cohort	ID	Gender	Age	Tumor Type	Tumor Size	Previous Tx	# of Vac	IFN- γ ELISPOT					PFS	Dx to 1 st V	OS
								IL13R α 2	EphA2	WT1	Sur	Tet			
07-057 Cohort 1	1	M	42	OA	774	None	3	NA	NA	NA	NA	NA	3	7	14
	2	F	29	A	1,960	None	12	40	54	39	2	NA	17	6	57
	3	M	47	A	4,085	None	10	82	322	419	350	186	14	3	25
	4	F	34	A	3,361	None	8	288	359	262	196	0	10	2	>50
	5	M	31	A	121	None	7	180	119	271	49	474	>47	11	>58
	6	M	57	A	5,780	None	11	145	236	144	112	77	17	2	>48
	7	M	35	A	1,972	None	9	0	533	377	69	90	14	4	33
	8	M	49	A	241	None	12	20	5	4	7	267	19	10	>48
	9	F	38	A	496	None	14	189	118	120	132	461	>42	4	>46
	10	M	51	OA	1,136	None	14	41	342	700	125	151	>37	10	>47
	11	M	39	OA	1,836	None	12	304	193	285	116	69	19	5	43
	12	F	30	OA	2,520	None	8	51	514	253	81	56	11	2	>29
Cohort 2	1	F	26	A	1,782	RT	14	21	128.5	40	5	NA	>45	22	>67
08-135 (Cohort 3)	1	F	49	A	5,344	None	10	6	0	8	3	0	11	26	>88
	2	F	44	A	1,512	RT	3	NA	NA	NA	NA	NA	2	44	57
	3	M	36	OA	1,236	BCNU & TMZ	10	82	210	47	450	337	12	66	96
	4	F	28	OA	3,522	None	11	38	30	19	21	31	13	65	>110
	5	M	35	OA	1,154	TMZ	8	6	32	18	14	23	6	36	74
	6	F	49	OA	442	None	8	97	707	109	50	41	6	52	>96
	7	F	38	O	1,591	None	10	24	14	43	354	31	12	17	>60
	8	M	26	O	1591	None	8	0	27	9	0	5	>41	11	>52
	9	F	39	O	4,489	None	11	13	97	203	134	0	16	57	>93
	10	M	49	OA	226	TMZ & RAD001	14	10	230	9	0	28	29	132	>164

Abbreviations: M, male; F, female; OA, oligoastrocytoma; A, astrocytoma; O, oligodendroglioma; Tx, therapy; RT, radiation therapy; BCNU, bis-chloroethylnitrosourea; TMZ, temozolomide; RAD001, Everolimus; Vac, vaccine; Sur, survivin; Tet, Tetanus; “Dx to 1st v”, periods from diagnosis to the first vaccine. PFS (since the first vaccine), periods from diagnosis to the first vaccine and OS (overall survival since diagnosis) are described in months. NA, samples not available due to early progression or assay failure. For analyses of IFN- γ ELISPOT assays, only the data from Weeks 0, 15, 18, 21, and 24 were used. The Week 0 spot numbers were subtracted from spot numbers for the four post-vaccine assays, and if the results were <0, they were set to 0. For each patient, the mean of these four corrected spot numbers/1x 10⁵ cells was computed and shown, after eliminating missing data; this procedure was carried out for each of the four antigens. Positive responses are highlighted with yellow. Age (years) at the time of study entry. Tumor size (mm²) is based on two-dimensional, perpendicular measurement of T2-FLAIR abnormal signal at the baseline. Previous Tx are prior nonsurgical treatments.

When magnitude of IFN- γ ELISPOT response was compared against each of the four GAAs between UPCI 07-057 Cohort 1 and UPCI 08-135 (Table 3), UPCI 07-057 Cohort 1 patients demonstrated a significantly higher magnitude of IFN- γ response than UPCI 08-135 patients for IL-13R α 2 (p=0.030), WT1 (p=0.0098), and Tetanus (p=0.021) epitopes as well as for all four GAA epitopes combined (p=0.031). The EphA2 epitope also demonstrated the same trend but without statistical significance (p=0.095). Interleukin (IL)-5 ELISPOT assays were performed to assess type-2 adaptive immune responses against the vaccine-targeted GAAs in six (Patients 2-7), one, and six (Patients 1, 3, 4, 6-8) in UPCI 07-057 Cohort 1, UPCI -7-057 Cohort 2, and UPCI 08-135 (“Cohort 3”), respectively (Table 3). In corresponding cases, IFN- γ responses were significantly higher than IL-5 responses in each of IL13R α 2, EphA2, and WT1 epitopes (p=0.0020, 0.0059, 0.014). The Survivin (p=0.067), but not the Tetanus (p=0.32) epitope, showed a similar trend.

Table 3 Summary of statistical analyses

Comparison		P-Value	Groups	Median	IQR	Method
IFN- γ ELISPOT in Cohorts 1 and 3	IL-13R α 2	0.030	Cohort 1	81.5	40.2,185	Wilcoxon Test (median values are spots/10e5 cells)
			Cohort 3	13.3	6.00, 37, 5	
	EphA2	0.095	Cohort 1	236	119, 350	
			Cohort 3	32.0	27.3, 210	
	WT1	0.0098	Cohort 1	262	132, 331	
			Cohort 3	18.5	8.67, 47.0	
	Survivin	0.45	Cohort 1	112	59.2, 128	
			Cohort 3	20.5	3.00, 134	
	All 4 GAAs	0.031	Cohort 1	224	147, 260	
			Cohort 3	20.5	3.00, 134	
	Tetanus	0.021	Cohort 1	139	21.0, 318	
			Cohort 3	27.0	19.0, 41.4	
IFN- γ and IL-5 ELISPOT (All Cohorts Combined)	IL-13R α 2	0.0020	IFN- γ	81.5	30.8, 120	
			IL-5	1.50	0.00, 13.0	
	EphA2	0.0059	IFN- γ	210	41.5, 341	
			IL-5	3.33	1.25, 5.75	
	WT1	0.014	IFN- γ	109	40.9, 266	
			IL-5	23.0	8.67, 67.6	
	Survivin	0.067	IFN- γ	69.0	34.9, 273	
			IL-5	23.0	2.75, 43.5	
	Tetanus	0.32	IFN- γ	36.8	11.8, 110	
			IL-5	68.8	23.2, 276	
	Comparison		P-Value	CV for Cox or rho for Spearman		Method
	PFS and IFN- γ ELISPOT	Cohort 1	0.95	0.0000662		Cox Proportional Hazards Model; Likelihood Ratio Test
Cohort 3		0.095	0.00261			
PFS for Cohorts 1 and 3		0.26	0.612			
Baseline Tumor Size and PFS		0.24	0.00018			
Age and IFN- γ ELISPOT		0.46	0.17		Spearman Test	
Baseline Tumor Size and Overall IFN- γ ELISPOT Response		0.21	0.20			

For analyses of IFN- γ ELISPOT assays, only the data from Weeks 0, 15, 18, 21, and 24 were used. The Week 0 spot numbers were subtracted from spot numbers for the four post-vaccine assays, and if the results were <0, they were set to 0. For each patient, the mean of these four corrected spot numbers was computed, after eliminating missing data; this procedure was carried out for each of the four antigens. To assess the association of tumor size and PFS with ELISPOT response, the means for the four antigens were summed to give a single number for each patient. N/R = not relevant. Boldface type = P values <0.05. CV = coefficient of variation. Rho is the same as r-value. IQR = interquartile range.

Results from trials 07-057 and 08-135 were recently published in *Clinical Cancer Research* (Okada et al. [Induction of robust type-1 CD8+ T-cell responses in WHO grade II low-grade glioma patients receiving peptide-based vaccines in combination with poly-ICLC. Clinical Cancer Research 2014 Nov 25. \[Epub ahead of print\]](#)).

UPCI 11-136:

Objectives: Although the regimen examined in the prior two studies was shown to be safe and induce robust GAA-specific T-cell responses, less than half the population is positive for HLA-A2, so using these peptides may not be feasible. We, therefore, implemented a Phase I study to assess a vaccination regime consisting of intradermal (i.d.) injections of lysate derived from cultured brain tumor-initiating cells (BTICs) and concurrent topical application of an immunoadjuvant (imiquimod) in adults with WHO grade II LGGs. Our objective is to collect immunological and safety data to determine whether a larger study of clinical efficacy is warranted. We hypothesize that this form of vaccine will safely induce potent anti-glioma immune response, which may eventually translate to prevention of progression and malignant transformation of their LGGs.

Methods: There are three cohorts of patients (n=9/cohort). Eligibility criteria for Cohorts 1 and 2 are essentially identical to those for corresponding cohorts in UPCI 07-057, except that patients are not required to be positive for HLA-A2. Eligibility criteria for Cohort 3 are similar to those for UPCI 08-135 but allow patients who are stable after chemotherapy and do not require HLA-A2+ status. Vaccines will be administered on an outpatient basis on Weeks 0, 3, 9, 15, and 21. Each patient will receive 1 mg protein (1 vial = 0.5 mL total volume) divided into two syringes (0.5 mg protein/each) to be given by i.d. injection at two separate sub-inguinal sites. Imiquimod cream, 5%, is supplied in single-use packets. Each packet of Imiquimod (12.5 mg) will be divided between the two vaccination sites at each administration session. Imiquimod will be applied just prior to vaccination and reapplied in an identical manner at the vaccination sites 24 hours later. All patients will have available medications for potential anaphylaxis (diphenhydramine, hydrocortisone, and epinephrine).

Results: This study was implemented in November 2012, and 14 patients were enrolled through October 2014 (four, one, and nine patients in Cohorts 1, 2 and 3, respectively). In Cohort 1, all patients completed the scheduled five vaccinations, and two of them are still receiving booster vaccines; the other two patients have progressed. The only patient in Cohort 2 completed the scheduled five vaccines but recently (September 2014) progressed. All nine patients in Cohort 3 completed the initial five vaccines; to date, six of them are still receiving booster vaccines. The other three patients have progressed. None of these patients demonstrated vaccine-related RLT. Once immune-response analyses are completed, we plan to submit results for publication.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be “No.”

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

Yes
 No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

Yes (UPCI 07-057 and 08-135 have been completed)

No (UPCI 11-136 is still ongoing)

If “Yes” to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both “No.”)

18(C) How many hospital and health care professionals were involved in the research project?

One hospital and more than 20 health care professionals, including physicians, nurses, and regulatory specialists

18(D) How many subjects were included in the study compared to targeted goals?

54 Number of subjects originally targeted to be included in the study

37 Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:

24 Males

13 Females

 Unknown

Ethnicity:

1 Latinos or Hispanics

36 Not Latinos or Hispanics

 Unknown

Race:

 American Indian or Alaska Native

 Asian

 Blacks or African American

 Native Hawaiian or Other Pacific Islander

37 White

 Other, specify: _____

 Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

Allegheny County

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?

Yes
 No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?

Yes
 No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

- Project 01 – Smith – Three cases of isolated
- Project 01 – Smith – Investigation of NEB1 deletions
- Project 03 – Zhang – Molecular profiling of aromatase
- Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes X No _____

If yes, please describe your plans:

Upon completion of UPCI 11-136, we plan to publish results in a peer-reviewed journal.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project.

Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

While no direct impact has been made (at this point) on the incidence of disease, death from disease, or stage of disease at time of diagnosis, the results from these vaccine studies indicate safety and robust inductions of GAA-specific CD8+ T-cell responses, supporting further development of these immunotherapeutic approaches to cancer treatment.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment.

Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

Safety and immunological activities of the peptide vaccine have been shown through UPCI 07-057 and 08-135 studies. Preliminary data from the UPCI 11-136 study also show safety of

the GBM6-based vaccine.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes _____ No X

If “Yes” to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is “No.”)

- a. Title of Invention:
- b. Name of Inventor(s):
- c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):
- d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes _____ No _____

If yes, indicate date patent was filed:

- e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes _____ No _____

If yes, indicate number of patent, title and date issued:

Patent number:

Title of patent:

Date issued:

- f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes _____ No _____

If yes, how many licenses were granted? _____

- g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes _____ No _____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes _____ No X _____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

NAME Okada, Hideho	POSITION TITLE Kathleen M. Plant Distinguished Professor in Neurological Surgery		
eRA COMMONS USER NAME okadah			
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Nagoya University School of Medicine-Japan	MD	1991	Medicine
Nagoya University School of Medicine-Japan	PhD	1996	Medicine
Handa Municipal Hospital-Japan	Internship	1991-1992	
	Residency		
Nagoya University Hospital, Dept. Neurosurgery	Residency	1992-1996	Neurosurgery

A. Personal Statement

I am a creative physician-scientist who has developed therapeutic modalities in the laboratory, translated them into clinical protocols, and used my expertise as both scientist and clinician to assess the clinical data from ongoing trials. My work has consistently focused on immunotherapeutic strategies aimed at a daunting challenge in oncology – malignant brain tumors. I conducted one of the first immune gene therapy trials in patients with malignant glioma. My success in navigating the detailed regulatory processes that such trials require demonstrates my attention to detail and breadth of knowledge from basic science to clinical care. My lab work was the first to identify and fully characterize cytotoxic T-lymphocyte (CTL) epitopes for gliomas. My seminal discovery of CTL epitopes in glioma-associated antigens and the work on the mechanisms underlying the adjuvant effects of poly-ICLC enabled me to launch novel glioma vaccine trials in combination with poly-ICLC as an adjuvant. The first of these – a phase I study – has yielded evidence for the safety of the vaccine and its ability to evoke potent immunological responses as well as clinical activities in some patients. These efforts have also been supported by my mechanistic studies delineating the role of an integrin receptor very late activation antigen (VLA)-4 and chemokine CXCL10 in efficient trafficking of T-cells to brain tumor sites. I have held four Investigational New Drug approvals for my own vaccine trials.

From 2004 through 2014, I served as a Co-Leader of the Brain Tumor Program at the University of Pittsburgh Cancer Institute and worked to expand the program by developing strong interdisciplinary and translational research activities among program members. In 2014, I joined the Brain Tumor Research Center of Neurological Surgery at the University of California, San Francisco (UCSF) to pursue robust inter-disciplinary research on brain tumor immunology and immunotherapy. In 2010, I was selected to be a member of the American Society for Clinical Investigation, which is an honor society of physician-scientists, those who translate findings in the laboratory to the advancement of clinical practice.

B. Positions and Honors

Professional Positions

1996-1997	Visiting Research Associate, Department of Neurosurgery, University of Pittsburgh School of Medicine (UPSOM)
1997-1998	Visiting Research Instructor, Department of Neurosurgery, UPSOM
1998-2001	Research Assistant Professor, Department of Neurosurgery, UPSOM
2001-2006	Tenure Track Assistant Professor, Department of Neurosurgery and Surgery, UPSOM
2004-2014	Co-Program Leader, Brain Tumor Program, University of Pittsburgh Cancer Institute
2007-2008	Tenure Track Associate Professor, Department of Neurosurgery and Surgery, UPSOM
2009-2012	Tenured Associate Professor, Department of Neurosurgery, Surgery and Immunology

2012-2014 Professor, Department of Neurosurgery, Surgery and Immunology UPSOM
2014-present Kathleen M. Plant Distinguished Professor in Neurological Surgery at UCSF

Certification and Licensure

1991 Medical License for Japan
2003 Japanese Board of Neurological Surgery
2004 Medical Physician and Surgeon, issued by Pennsylvania Department of State

Awards and Honors (selected)

1996 Uehara Memorial Foundation Postdoctoral Scholarship
1998 First Place Award for Scientific Excellence and Potential, 10th Annual UPCI Scientific Retreat
2001 Doris Duke Charitable Foundation's Clinical Scientist Development Award
2003 James S. McDonnell Foundation 21st Century Science Initiative Research Award: Brain Cancer Research
2007 Excellence in Translational Medicine Award 2006-07 from Journal of Translational Medicine
2009 Appointed Council in the Clinical Immunology Society
2010 Selected to be a member of the American Society for Clinical Investigation (ASCI)
2010 Team Science Recognition Award by Society for Immunotherapy of Cancer
2009, 2011 and 2013 Faculty Honoree in the Annual Convocation of University of Pittsburgh

Study Sections and Advisory Committees - Extramural Grant Reviewer:

2006-present Italian Association for Cancer Research Regular Reviewer
2007 DOD Breast Cancer Research Program Immunological Sciences - Reviewer
2007-8 DOD Prostate Cancer Research Program Synergistic Idea Development Award #2
Ad Hoc Reviewer
2008 NIH/NINDS P50 proposal *Ad Hoc* Reviewer
2009 Cancer Immunology and Immunotherapy (CII) – *Ad Hoc* Reviewer
2009 NIH: Cancer Immunology and Immunotherapy (CII) – *Ad Hoc* Reviewer3
2010 NIH: Special Emphasis Panel/Scientific Review Group 2010/05 ZRG1 OTC K (05)
M meeting – *Ad Hoc* Reviewer
2010 NIH/NCI: Cancer Immunology and Immunotherapy (CII) – *Ad Hoc* Reviewer
2011-present NIH Clinical Oncology (CONC) Chartered Member

C. Selected Publications (from a total of more than 100 peer reviewed publications)

1. Okada H, Kalinski P, Ueda R, et al. Induction of CD8+ T-cell responses against novel glioma-associated antigen peptides and clinical activity by vaccinations with α -type-1-polarized dendritic cells and poly-ICLC in patients with recurrent malignant glioma. *J Clin Oncol.* 29(3):330-6 (2011).
2. Fujita M, Kohanbash G, Fellows-Mayle W, et al. COX-2 blockade suppresses gliomagenesis by inhibiting myeloid-derived suppressor cells. *Cancer Res.* 71(7):2664-74 (2011).
3. Yeung JT, Hamilton RL, Okada H, et al. Increased expression of tumor-associated antigens in pediatric and adult ependymomas: implication for vaccine therapy. *J Neurooncol.* 111(2):103-11 (2013).
4. Yeung JT, Hamilton RL, Ohnishi K, et al. LOH in the HLA class I region at 6p21 is associated with shorter survival in newly diagnosed adult glioblastoma. *Clin Cancer Res.* 19(7):1816-26 (2013).
5. Liu Y, Kosaka A, Ikeura M, et al. Premetastatic soil and prevention of breast cancer brain metastasis. *Neuro-Oncol.* 15(7):891-903 (2013).
6. Kohanbash G, McKaveney K, Sakaki M, et al. GM-CSF promotes the immunosuppressive activity of glioma-infiltrating myeloid cells through interleukin-4 receptor- α . *Cancer Research* 73(21):6413-23 (2013).
7. Pollack IF, Jakacki RI, Butterfield LH, et al. Antigen-specific immune responses and clinical outcome following vaccination with glioma-associated antigen peptides and poly-ICLC in children with newly-diagnosed malignant brainstem and non-brainstem gliomas. *J. Clin Oncol.* 32(19):2050-8 (2014).