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 717-783-2548.

1. **Grantee Institution**: Salus University

2. **Reporting Period (start and end date of grant award period):** 01/01/09 – 04/30/10

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Alexander M. Dizhoor, PhD

4. **Grant Contact Person's Telephone Number**: 215-780-1468

5. **Grant ME Number or SAP Number:** SAP# 4100047650

6. **Project Number and Title of Research Project:** 1 - Molecular Mechanisms of Leber's Congenital Amaurosis

7. **Start and End Date of Research Project:** May 1, 2009 – April 30, 2010

8. **Name of Principal Investigator for the Research Project:** Alexander M. Dizhoor, PhD

9. **Research Project Expenses**.

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

   $60,468.56

   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	Position Title	% of Effort on Project	Cost
Savchenko	Research Associate	100%	$38,110

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	Position Title	% of Effort on Project
Dizhoor	PI, Professor	10%

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/NEI; $361,087

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 to be awarded:
Administrative Supplement to Provide Infrastructure Support	■NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)	07.01.2009	$431,465	Funding is under consideration

The funds include electrophysiological equipment required for testing the new genetic model in progress.

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

Yes__X____ No_____

If yes, please describe your plans:

We plan to leverage additional resources to expand instrumental capabilities for electrophysiological study of the transgenic mice generated from this project.

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

The phenotype in human patients described in our recent publication related to this project implies that modifying factors may exist that affect facilitation of the D639Y mutation in humans. We plan to continue with developing the new mouse model and transfer the D639Y transgene in various genetic backgrounds - i.e., mice lacking either isoforms of retinal guanylyl cyclase (RetGC), RetGC1 or RetGC2, or both isoforms altogether, as well as genetic backgrounds lacking isoforms of guanylyl cyclase activating proteins (GCAP) 1 or 2, in order to assess the effect of the possible effects of these proteins as modifying factors in the retinal phenotype related to this mutation.

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.

The new genetic model created during this project adds to the number of transgenic models to be analyzed in-depth using new electrophysiological equipment, for which we intend to secure funds from NIH or private funds in the near future.

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:

We established collaboration with University of Alabama at Birmingham for biochemical analysis of Leber Congenital Amaurosis (LCA)-related mutations and Harvard Medical School for single-cell electrophysiological recordings in the developing genetic mouse model mimicking the LCA-related mutation.

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_____ No___X_____

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

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

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the entire grant award period. 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 (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

The objective of this short pilot exploratory project was to develop the means for the subsequent in-depth long-term study of the mutations in retinal guanylyl cyclase 1(RetGC1) found in patients with Leber Congenital Amaurosis (LCA), an early-childhood onset of blindness. The Specific aims of the project were to produce transgenic mouse model harboring D639Y or R768W substitutions in RetGC1 that were found in patients with LCA amaurosis and were preliminary characterized based on in vitro assay of the mutant RetGC1 activity and binding with its regulatory protein, GCAP1. The second specific aim was to characterize the mouse model created by transgenic expression of the mutant RetGC1. That plan was perhaps overly optimistic given the short term of the proposed pilot study, but we have accomplished all preliminary work and the first set of transgene injections has been accomplished so that we expect the screening for the transgene-positive mice within weeks from the date of this report.

Accomplishments since the beginning of the project on May 1, 2009:

- We have completed biochemical characterization of the D639Y and R768W mutations of RetGC1 in vitro and described it in a peer-review publication demonstrating the lack of activation of the mutant RetGC1 and its failure to bind GCAP1.

- We produced genetic constructs for expression of the modified RetGC1 carrying these mutations in mouse retinas under control of rod opsin promoter (Fig. 1).

- We have started injections of a construct coding for the D639Y RetGC1 mutant in mouse eggs. The injections are to be completed by the end of June 2010. The first litter of the F0 pups from the injections is due July 7, 2010.

- We have also optimized the tail DNA PCR screening test for the presence of the transgene sensitive to ~ 1 copy per genome (Fig. 2).

- We have also established several breeding colonies of mouse lines (produced by the PI group or obtained from other sources) that we will use in breeding of the mutant RetGC1

transgene into various genetic backgrounds once the germ-line transmission of the transgene is confirmed:

- GCE null (mouse line originally produced by Dr. D. Garbers) – this line has no endogenous RetGC1 isozyme expression and it will be used for testing the levels of the D639Y RetGC1 expression when transferred into wild type RetGC1-/- genotype (otherwise it would be impossible to estimate the level of the mutant cyclase expression by immunoblot) and possibly use for breeding heterozygous wild type RetGC1+/- background in order to mimic or approximate normal complement of the total RetGC1 expression levels. This line will also be used to evaluate the effect of relative levels of expression for the wt and the mutant RetGC1.

- Gucy2F-/- (originally developed by Dr. W. Baehr) – this line is lacking the second isozyme of RetGC2 and will be used to test retGC2 as a possible modifying factor for the D639Y-related phenotype.

- Double Gycy2f/GCE knockout.

- Guca1A-/- and Guca1B-/- (both developed in the PI's lab) – these gene knockout lines are lacking guanylyl cyclase activating proteins, GCAP1 or GCAP2, respectively, and they will be used for studying possible modifying effects of the guanylyl cyclase activating proteins on the D639Y phenotype.

In summery, we consider the overall objectives of this pilot project met reasonably well - even though the injection schedule has begun later than we originally planned, and we are yet to start the actual screening among the first generation (F0) mice. We believe we have come to the next step of the project well prepared and look optimistically at the perspectives of the project. After this project was initiated we received a continuation of funding on the PI's NIH grant which included support for the further development of these experiments.

Publication:

Peshenko IV, Olshevskaya EV, Yao S, Ezzeldin HH, Pittler SJ, Dizhoor AM (2010) Activation of retinal guanylyl cyclase RetGC1 by GCAP1: stoichiometry of binding and the effect of new LCA-related mutations. *Biochemistry* 49(4):709-17.

Figures

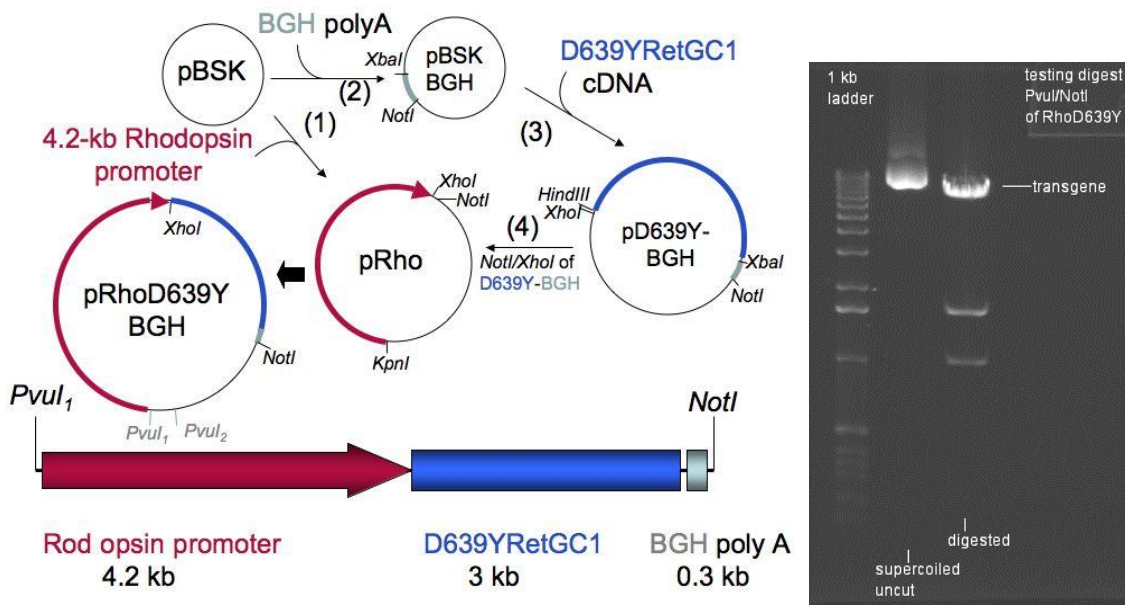

Fig. 1. The transgenic construct was produced through multi-step subcloning of a polyA-signal fragment (BGH), mouse rod opsin promoter region, and RetGC1 cDNA (D639Y) into a modified pBluescript vector, and the final construct was excised using a PvuI/NotI digestion. Agarose gel shows (*left to right*): 1-kb ladder; purified plasmid harboring the pRho-D639YRetGC1-BGH construct; the transgene construct released from the plasmid by the PvuI/NotI endonuclease digestion; the ~8-kb purified fragment was then purified from gel and injected into mouse eggs.

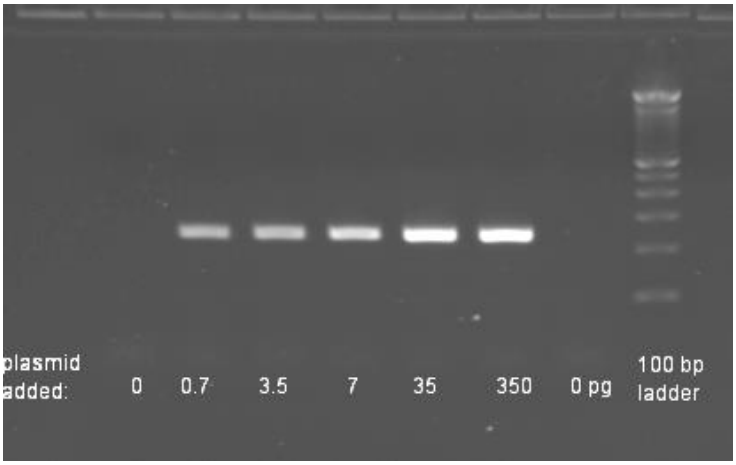

Fig. 2. A "single-copy" gene PCR detection of the transgene in a mouse tail DNA, pg of DNA/2 µg of genomic DNA, 27 cycles.

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
__X___No

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

_____Yes
__X___No

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?

_____Number of hospital and health care professionals involved in the research project

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

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

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

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____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.)

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
_X___ 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, listed in the table, in a PDF version 5.0.5 format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

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. Activation of Retinal Guanylyl Cyclase RetGC1 by GCAP1: Stoichiometry of Binding and the Effect of New LCA-Related Mutations	Igor V. Peshenko, Elena V. Olshevskaya, Suxia Yao, Hany H. Ezzeldin, Steven J. Pittler, Alexander M. Dizhoor	Biochemistry	November 23, 2009	☐Submitted ☐Accepted ☒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:

When we conduct morphological, biochemical and electrophysiological characterization of the mouse model harboring the D639Y guanylyl cyclase mutant, we plan to submit a manuscript describing this model.

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.

None

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.

None

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. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Alexander M. Dizhoor	Professor of Pharmacology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Moscow University, Moscow, Russia (USSR)	B.S.	1977	Biochemistry, Virology
Moscow University, Moscow, Russia (USSR)	PhD	1985	Molecular Biology

A. Research and professional experience:

1977-1979 Junior Researcher, Biological Faculty, Moscow University

1979-1985 Graduate student and pre-doctoral Junior Investigator, Dept. of Virology and A.N.Belozersky Laboratory of Molecular Biology and Bioorganic Chemistry, Moscow University

1985-1990 Investigator and Senior Investigator, Dept. Enzymology, A.N.Belozersky Interdepartmental Laboratory of Molecular Biology and Bioorganic Chemistry, Moscow State University

1989-1990 Visiting scientist at Dept. of Biochemistry, University of Washington (with Dr. K.A.Walsh and Dr. J.B.Hurley)

1990-1992 Leading Investigator, Institute of Physico-Chemical Biology, Moscow, USSR (Russia)

1991 Visiting Scientist, Institute des Pharmacologie Moleculair et Cellulair, CNRS, Sophia Antipolice, Valbonne, France (sabbatical with Dr. M. Chabre)

1991-1997 Associate, Howard Hughes Medical Institute (with Dr. J.B. Hurley), Senior Fellow, Dept. of Biochemistry, then Research Assistant Professor of Biochemistry, University of Washington, Seattle,WA.

1997-2002 Assistant Professor, Associate Professor of Ophthalmology, Pharmacology, Anatomy and Cell Biology, Wayne State University, Detroit, Michigan. Adjunct Professor of Anatomy and Cell Biology, Wayne State University, Detroit, Michigan

2002-present Hafter Chair and Professor of Pharmacology, Pennsylvania College of Optometry (since 2008 – at Salus University), Elkins Park, PA

Professional Service:

NIH Study Sections: BDPE, 2005-2006, ad hoc; 2006- permanent member;
CSR/ ZRG1 CB-G; CSR ZRG1 CB-C(95)S; ZRG1 CB-C (85)S, 2009-2010

B. Selected/representative peer-reviewed publications (out of 62)

Dizhoor, A.M., Chen, Ch.-K., Olshevskaya, E., Sinelnikova, V.V., Philippov, P.P., Hurley, J.B. Role of the acylated amino terminus of recoverin in Ca^{2+}- dependent membrane interaction. Science 259, 829-832 (1993)

Dizhoor, A.M., Lowe, D.G., Olshevskaya, E.V., Laura, R.P., Hurley, J.B. The human photoreceptor membrane guanylyl cyclase, RetGC, is present in outer segments and is regulated by calcium and a soluble activator. Neuron 12, 1345-1352 (1994)

Lowe, D.G., Dizhoor, A.M., Liu, K., Gu, O., Spencer, M., Laura, R., Lu, L., Hurley., J.B. Cloning and expression of a second photoreceptor - specific membrane guanylyl cyclase (RetGC), RetGC-2. Proc. Natl. Acad. Sci. U.S.A.. 92, 5535-5539 (1995)

Dizhoor, A.M., Olshevskaya, E.V., Henzel, W.J., Wong, S., Stults, J.T., Ankoudinova, I., Hurley, J.B. Cloning, sequencing and expression of a 24 kDa Ca^{2+}-binding protein activating photoreceptor guanylyl cyclase. J. Biol. Chem. 270, 25200-25206 (1995)

Dizhoor A.M., Boikov, S.G., Olshevskaya, E.V. Constitutive Activation of Photoreceptor Guanylate Cyclase By Y99C Mutant of GCAP-1: Possible role in causing human autosomal dominant cone degeneration. J. Biol. Chem. 273, 17311–17314 (1998) .

Ames, J.B., Dizhoor, A.M., Ikura, M., Palczewski, K., Stryer, L. Three-dimensional structure of GCAP-2, a calcium sensitive modulator of photoreceptor guanylyl cyclases. J. Biol. Chem. 274, 19329-337 (1999).

Olshevskaya, E.V., Ermilov, A.N., Dizhoor A.M. Dimerization of Guanylyl cyclase- activating protein and a mechanism of photoreceptro guanylyl cyclase activation. J. Biol. Chem. 274, 25583-25587 (1999).

Hurley, J.B. & Dizhoor, A.M. Heterologous expression and assay of photoreceptor guanylyl cyclases and guanylyl cyclase activator proteins. Methods in Enzymology 315, 708-718 (2000) .

Mendez, A., Burns, M.E., Sokal, I., Dizhoor, A.M., Baehr, W., Palczewski, K., Baylor, D.A., Chen, J. Guanylate Cyclase Activating Proteins (GCAPs) set the flash sensitivity of rod photoreceptors. Proc. Natl. Acad. Sci. U.S.A.. 98, 9948-53 (2001).

Peshenko, I.V., Dizhoor, A.M. Guanylyl Cyclase Activating Proteins (GCAPs) Are Ca^{2+}/Mg^{2+}-Sensors: Implications for Photoreceptor Guanylyl Cyclase (RetGC) Regulation in vitro and in vivo. J Biol Chem. 279: 16903-16906 (2004)

Olshevskaya, E.V., Calvert P.D., Woodruff, M.L., Peshenko I.V., Savchenko A.B., Makino C.L., Ho Y-S., Fain G.L., Dizhoor, A.M. The Y99C mutation in guanylyl cyclase activating protein 1 (GCAP1) increases intra-cellular Ca^{2+} and causes photoreceptor degeneration in transgenic mice. Journal of Neuroscience 24, 6078-85 (2004)

Bi, A., Cui, J., Ma, Y.-P., Olshevskaya, E., Pu, M., Dizhoor, A.M., Pan, Z.-H. (2006) Ectopic Expression of a microbial-type rhodopsin restores visual response in mice with photoreceptor degeneration. Neuron 50, 23-33

Peshenko IV, Dizhoor AM. (2007) Activation and inhibition of photoreceptor guanylyl cyclase by guanylyl cyclase activating protein 1 (GCAP-1): the functional role of Mg2+/Ca2+ exchange in EF-hand domains. J. Biol. Chem. 282:21645-52.

Woodruff ML, Olshevskaya EV, Savchenko AB, Peshenko IV, Barrett R, Bush RA, Sieving PA, Fain GL, Dizhoor AM.(2007) Constitutive excitation by Gly90Asp rhodopsin rescues rods from degeneration caused by elevated production of cGMP in the dark. Journal of Neuroscience 27:8805-15.

Woodruff ML, Janisch, KM, Peshenko IV, Tsang, SH, Dizhoor AM, Fain GL. (2007) Modulation of PDE6 turnoff during background illumination in mouse rod photoreceptors. Journal of Neuroscience 28 2064-74

Dizhoor, A.M, Woodruff, M.L, Olshevskaya, E.V, Cilluffo M.C, Carter Cornwall, M., Sieving, P.A, and Fain, G.L. (2008) Night blindness and the mechanism of constitutive signaling of mutant G90D rhodopsin. Journal of Neuroscience 28, 11662-72.

Makino, C.L, Peshenko, I.V., Wen X-H., Elena V. Olshevskaya, E.V., Barrett, R, Dizhoor, A.M. (2008) A Role for GCAP2 in Regulating the Photoresponse: Guanylyl Cyclase Activation and Rod Electrophysiology in GUCA1B Knockout Mice. J. Biol. Chem. 283, 29135-43

Liu X, Pawlyk BS, Adamian M, Olshevskaya EV, Dizhoor AM, Makino CL, Li T. (2009) Increased light exposure alleviates one form of photoreceptor degeneration marked by elevated calcium in the dark. PLos One 4 (12): e8438.

Dizhoor A.M., Olshevskaya E.V., Peshenko I.V. (2010) Mg2+/Ca2+ cation binding cycle of guanylyl cyclase activating proteins (GCAPs): role in regulation of photoreceptor guanylyl cyclase. Molecular and Cellular Biochemistry 334:117–124

Peshenko IV, Olshevskaya EV, Yao S, Ezzeldin HH, Pittler SJ, Dizhoor AM (2010) Activation of retinal guanylyl cyclase RetGC1 by GCAP1: stoichiometry of binding and the effect of new LCA-related mutations. Biochemistry 49(4):709-17.

C. Research Interests: regulation of signaling in retinal photoreceptors, congenital retinal degenerations, calcium-binding proteins, cyclic nucleotides, transgenic animal models.