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.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100050904

6. **Project Number and Title of Research Project:** 54. Therapeutic Targeting of Malarial Placental Cytoadherence

7. **Start and End Date of Research Project:** 3/12/2012 - 12/31/2013

8. **Name of Principal Investigator for the Research Project:** Channe D. Gowda, 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:

   $ 107,100

   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
Lengel, Kathleen	Lab Researcher	100	$14,515
Griffin, Kathleen	Senior Research Support Technician	33	$25,926
Bewley, Maria	Associate Professor	10	$11,481
Hanner, Verna	Lab attendant	5	$558

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
Gowda, Channe	PI, Professor	5
Flanagan, John	Professor	5

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_____ No____X_____

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

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_____ No_____X_____

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:
None	☐NIH ☐ Other federal (specify:____) ☐ Nonfederal source (specify:_)		$	$

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 are planning to submit a grant application this year to NIH.

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

The proteins that we expressed and purified in this study allow us to analyze the chondroitin 4-sulfate- binding site in VAR2CSA. We are continuing studies to express full length VAR2CSA and purify a sufficient amount of protein to study its structure and chondroitin 4-sulfate-binding site. Thus, the data obtained from this study and those anticipated in the near future serve as important preliminary data for grant applications to NIH to study the structure of VAR2CSA and to determine its chondroitin 4-sulfate-binding site. We also plan to identify small molecule inhibitors that prevent the sequestration of malaria parasite-infected red blood cells in the placenta, which contributes to pregnancy-associated malaria. The anticipated results of these studies will be useful in developing therapeutics and/or a vaccine for malaria.

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.

This funding allowed us to forge a strong collaboration between the PI's and Dr. John

Flanagan's lab. The expertise of the latter lab in structural Biology is crucial for the submission of the planned grant application to NIH.

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_____ No_____X_____

If yes, please describe the collaborations:

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 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 (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

The malaria parasite protein, VAR2CSA, is a member of the *Plasmodium falciparum* erythrocyte binding protein-1 family that is expressed on the surface of parasite-infected red blood cells (IRBCs). It mediates the placental sequestration through binding to placenta-specific chondroitin 4-sulfate (C4S) chains of low sulfated chondroitin sulfate proteoglycan (CSPG) receptor. Thus, the key host-IRBC interaction in PM is between the parasite protein VAR2CSA and the host receptor C4S. The high affinity binding of VAR2CSA to C4S involves a dodecasaccharide (12-mer) motif containing 2 sulfate groups. VAR2CSA is a single span transmembrane protein with a large functional ectodomain, consisting of six adhesive domains called Duffy-binding like (DBL) domains. How VAR2CSA interacts with placental C4S is not known.

Specific Aims: (1) To express the full-length ectodomain and the N-terminal half of VAR2CSA in a mammalian expression system. (2) To localize the C4S-binding site in VAR2CSA and identify the VAR2CSA peptide motifs that interact with C4S. Our overall approach here is to obtain codon-optimized parasite *var2csa* DNA, clone and transiently express the entire ectodomain and the N-terminal portion encompassing DBL1x-DBL-3x into HEK293 cells as secretory molecules, and purify and characterize the recombinant proteins. Using the purified recombinant VAR2CSA proteins, we will localize the region in VAR2CSA involved in specific binding of C4S by electron cryomicroscopy using N-terminal and C-terminal tag-specific antibodies and gold particles conjugated C4S probes. We will also identify the VAR2CSA peptide motifs that interact with C4S using photoreactive C4S probes and mass spectrometry. These studies will demonstrate the feasibility of obtaining meaningful structures of the large VAR2CSA-C4S complex that can be used to guide inhibitor-optimization.

Progress Made

VAR2CSA is a very large (~350 kDa) malaria parasite (*Plasmodium falciparum*) protein expressed on the surface of infected erythrocytes and mediates the adherence of the infected cells

in human placenta, contributing to pregnancy associated malaria. One of the major goals of the grant was to express and purify the functional, extracellular portion (~300 kDa) of VAR2CSA (DBL1x-DBL6ε; 7713 bp; 2571 aa) and its N-terminal portion (DBL1x-3x, ~178 kDa; 4620 bp; 1540 aa and DBL1x-4ε, ~228 kDa; 5694 bp; 1898 aa) and C-terminal portion (DBL4ε-6ε, ~138 kDa; 3228 bp; 1076 aa). Malaria genes are highly AT rich and as such do not express in other systems. Therefore, the *var2csa* gene was optimized for a mammalian expression system, and cloned into a pCC1 vector. Also, malaria proteins lack protein glycosylation and therefore, 13 Asn residues of the potential *N*-linked glycosylation sites of *var2csa* were mutated to Ala. The DBL1x-3x and DBL4ε-6ε portions of VAR2CSA were subcloned in-frame into the pSecTag2/Hygro (Invitrogen) vector for expression in the HEK293F cell line (Invitrogen). The vector contains the hygromycin resistance gene for cell selection. Proteins expressed using this vector possess the murine Ig κ-chain leader sequence (for protein secretion) at their N-terminus and c-myc epitope (Western blots) and His_6-tag (purification tag) at their C-terminus. This work was customized by GenScript.

We standardized the Invitrogen FreeStyle 293F Protein Expression System for the expression of DBL1x-3x and DBL4ε-6 by transient transfection of HEK293F cells. This system involves tranfection of HEK-293F cells with the expression plasmids in 293fectin reagent and opti-MEM medium (Invitrogen) and growing of transfected cells in suspension culture using serum-free FreeStyle 293F Expression Medium in a CO_2 incubator with an orbital shaker. Initially, we tested the expression of proteins using the Invitrogen control plasmid, pSecTag2/Hygro/PSA, expressing prostate-specific antigen and VAR2CSA DBL1x-3x by harvesting protein media and concentrating proteins by TCA precipitation. Protein expression was examined by SDS-PAGE and Western blotting analyses of the transfected culture media over a period of eight days. The results showed that both PSA control and DBL1x-3x were expressed and the highest levels of proteins were seen at 4 days post-transfection (Figures 1 and 2). We also expressed the C-terminal half (DBL4ε-6ε) of VAR2CSA (Figure 3) using procedure described above for DBL1x-3x.

Next, we scaled up the expression of DBL1x-3x and DBL4ε-6ε in HEK293F cells for protein production and standardized purification procedures, which involve an initial Ni-affinity chromatography followed by cation-exchange chromatography and size-exclusion chromatography. We found that DBL1x-3x protein expressed at moderate levels (1-2 mg/L), whereas DBL4ε-6ε protein highly expressed (7-8 mg/L). Using these procedures, we have been able to purify ~16 mg of DBL4ε-6ε (Figure 4). In efforts to determine the crystal structure of DBL4ε-6ε, we performed crystallization trials at various conditions using 6 mg protein/ml solution. The protein appears to crystallize in 100 mM TAPS buffer, pH 9.0, containing 100 mM potassium thiocyanate and PEG 400 (40% v/v) (Figure 5). Based on these results, we are currently optimizing crystallization conditions and planning to scale up the screen to obtain crystals suitable for structural studies. Additionally, we are planning to assess the C4S-binding ability of DBL4ε-6ε. We have also purified DBL1x-3x (Figure 6) expressed in HEK293F, but noticed that this protein has a tendency to aggregate. We are currently trying to resolve this problem and trying to analyze its C4S-binding property using the protein that is purified.

The cloning of full length VAR2CSA (DBL1x-6ε; ~300 kDa) and the N-terminal portion comprising DBL1x-4ε (~228 kDa) to the pSecTag2/Hygro vector for protein expression in

HEK293F cells was found to be more challenging than we anticipated. GenScript, the company that we originally employed for this work, found that subcloning of the full length *var2csa* gene into the expression vector in a single step was not possible because of complications due to DNA recombination. Subsequently, we contracted to another company, NorClone, for subcloning both DBL1x-6ε and DBL1x-4ε genes into the expression plasmid using a different cloning strategy. This company was also unable to generate the cloned plasmids. Currently, we are planning to subclone the full length VAR2CSA and DBL1x-4ε by using a two-stage cloning strategy and we anticipate that this method will work and that we will be able express VAR2CSA and DBL1x-4ε and purify these proteins to undertake further studies.

The goals of Specific Aim 2 could not be accomplished within the grant award period because: (1) subcloning of full length VAR2CSA into the protein expression plasmid has been a major challenge. (2) Setting up of the protein expression system and developing the gene cloning strategies took considerable period of time. (3) Given these, the duration of the grant award period was sufficient. However, we are continuing to pursue different strategies to express the full length protein and planning to accomplish the stated goals. We feel that the progress that we made during the grant award period is substantial and the results will allow us to analyze the chondroitin 4-sulfate-binding characteristics of DBL1x-3x, the functional region of VAR2CSA. These data will be useful for the submission of the planned grant application to NIH.

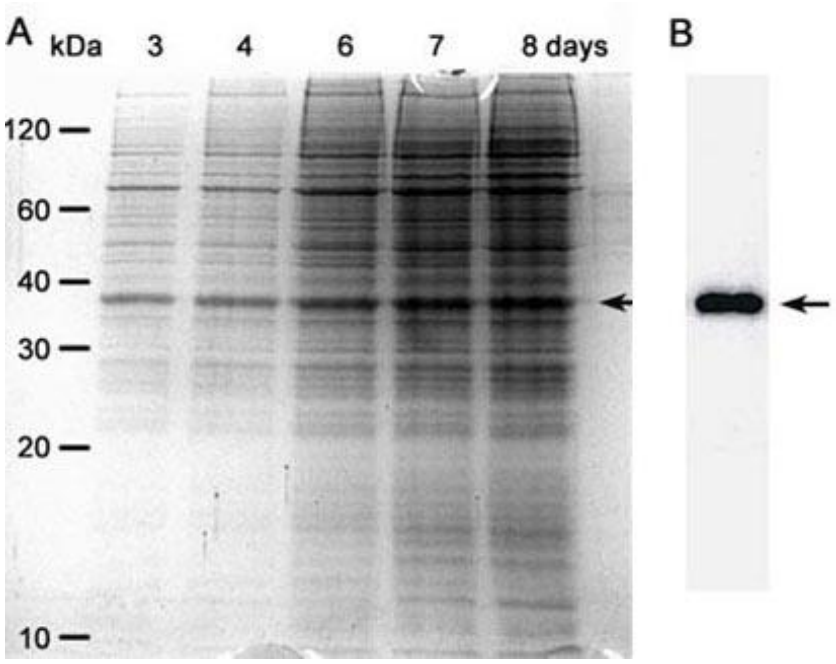

Figure 1. (**A**) SAS-PAGE analysis of culture supernatants of cells expressing PSA (MW ~33kDa) at the indicated time points by using 15% SDS gel. (**B**) Western blotting analysis of culture supernatant of cells expressing PSA by using anti-myc antibody and chemiluminescence detection. Arrow in the right margin shows the PSA protein band. The positions and molecular mass (kDa) of standard proteins electrophoresed on the same gel are shown in the left margin.

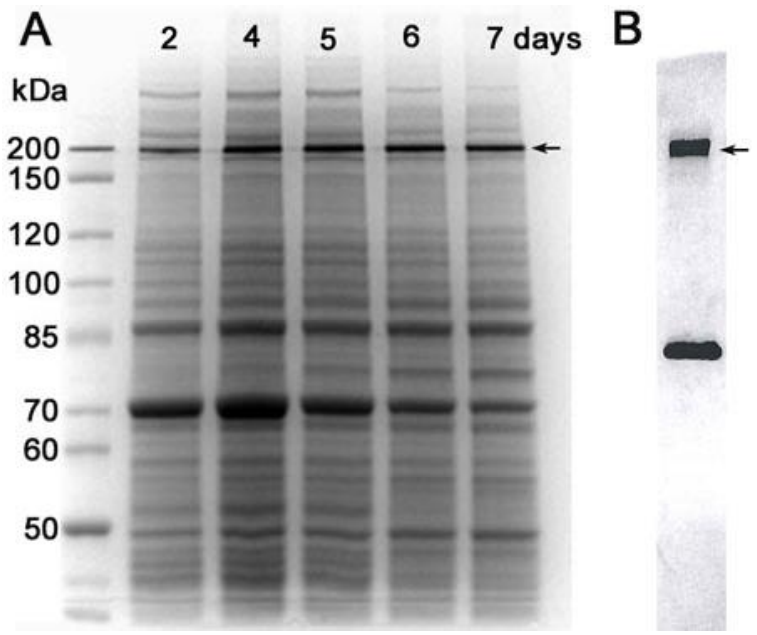

Figure 2. (**A**) SAS-PAGE analysis of culture supernatants of cells expressing DBL1x-3x (at the indicated time points using 7.5% BioRad TGX gel. (**B**) Western blotting (PVDF membranes) analysis of culture supernatant of cells expressing DBL1x-3x using an anti-myc antibody and chemiluminescence detection. Arrow in the right margin shows the DBL1x-3x protein band; the lower band in panel B due to nonspecific staining of a HEK cell protein. The positions and molecular mass (kDa) of standard proteins electrophoresed on the same gel are shown in the left margin.

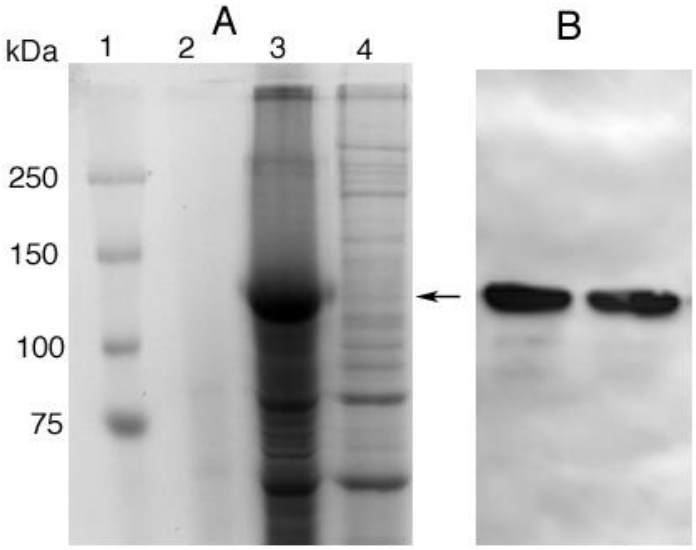

Figure 3. (**A**) SDS-PAGE analysis of HEK293F cells expressing DBL4ε-6ε. Lane 1, Molecular mass (kDa) marker proteins; lane 2, Culture supernatant of untransfected cells; lane 3, Culture supernatant of cells transfected with DBL4ε-6ε expression plasmids; lane 4, whole lysate of cells

transfected with DBL4ε-6ε expression plasmids. (**B**) Western blotting (PVDF membranes) analysis of culture supernatant of cells expressing DBL4ε-6ε by using anti-His tag antibody and chemiluminescence detection. Arrow shows the DBL4ε-6ε protein band. The positions and molecular mass (kDa) of standard proteins electrophoresed on the same gel are shown in the left margin.

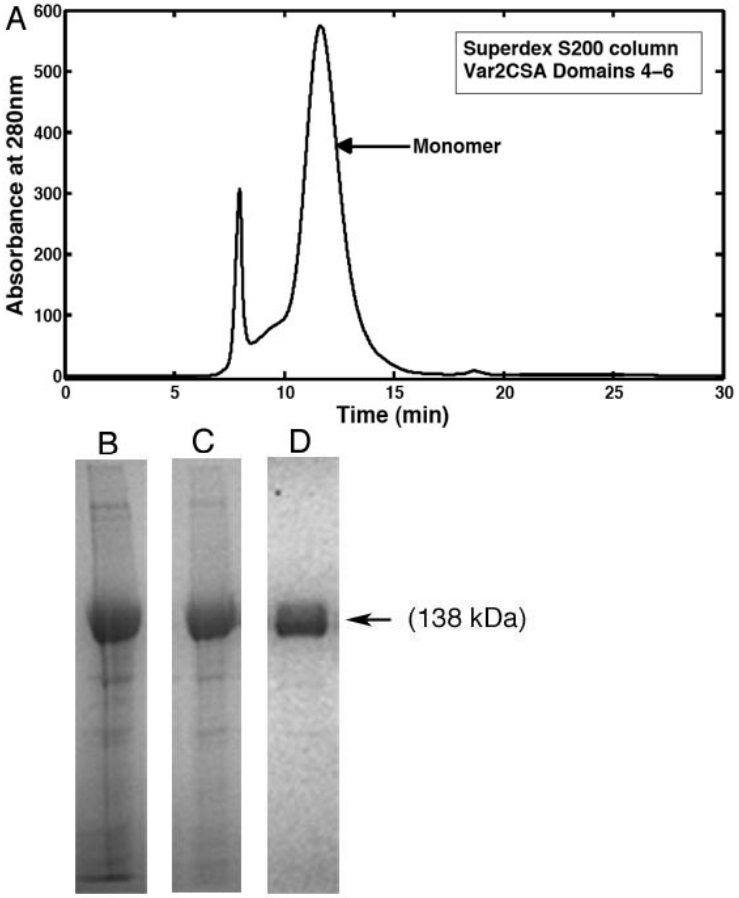

Figure 4. Purification of VAR2CSA DBL4ε-6ε protein. (A), Elution pattern of DBL4ε-6ε protein on size-exclusion column; (B-D), SDS-PAGE analysis of DBL4ε-6ε purified by column chromatography. (B), DBL4ε-6ε bound to Ni-affinity column; (C) DBL4ε-6ε bound to cation-exchange column; (D), DBL4ε-6ε purified by size-exclusion chromatography (panel A).

Figure 5. DBL4ε-6ε crystallization screen. Image shown is 24 h after initial set up. Needle-shaped crystals are observable, growing from a nucleation center in the bottom middle of the figure and extending diagonally. Fifteen hundred and thirty six individual conditions were screened, encompassing pH 2-11 units and low and high ionic strengths. Crystals were clearly observable in 100 mM potassium thiocyanate, 40 % PEG 400 and 100 mM TAPS at pH 9.0 after the first 24 h and remained at the fourth time point of 2 weeks. These crystallization trials were performed under oil using very small sample sizes. We are beginning experiments to screen around these conditions and scale up the screen to volumes where we can extract the crystals and collect data on them to assess their diffraction limit.

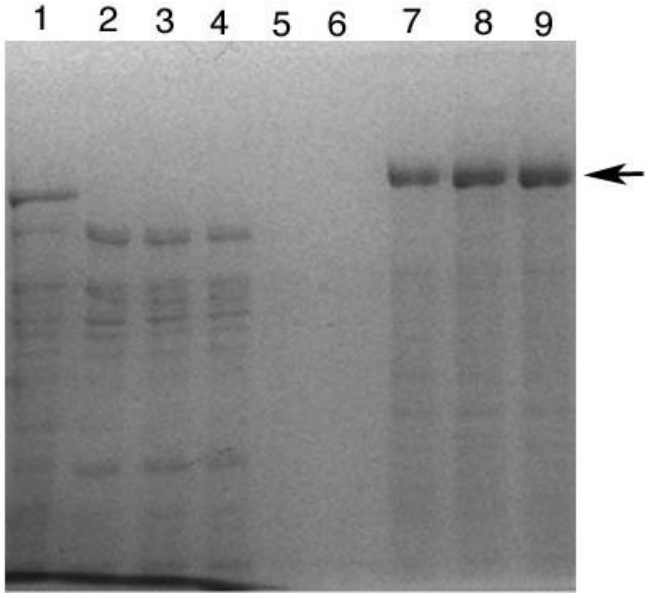

Figure 6. Purification of VAR2CSA DBL1x-3x protein. The DBL1x-3x protein bound to Ni-affinity column was chromatographed on cation-exchange column and the bound protein was eluted with 100-1.0 M NaCl gradient. The fractions were analyzed by SDS-PAGE. Lane 1, Culture supernatant of HEK293F cells expressing DBL1x-3x; lanes 2-4, column flow through fractions; lanes 5and 6, column wash; lanes 7-9, fractions containing bound DBL1x-3x eluted with NaCl gradient. Arrow shows the DBL1x-3x protein band (~178 kDa).

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

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:
_____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 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				☐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:

We will submit one or more manuscripts for publication.

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.

BIOGRAPHICAL SKETCH

NAME Gowda, Channe D	POSITION TITLE Professor of Biochemistry and Molecular Biology
eRA COMMONS USER NAME: cgowda	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Mysore, Mysore, India	BS	1971	Physics, Chem., Math
University of Mysore, Mysore, India	MS	1973	Organic Chemistry
University of Mysore, Mysore, India	PhD	1978	Organic Chemistry

A. Personal Statement

For the past several years, my research interest has been to study malaria parasite-host interactions in the context of malaria pathophysiology and immunology. Specifically, we have been studying: (i) adherence of parasite-infected red blood cells (IRBCs) in the placenta, and (ii) parasite-host interactions that initiate cell signaling and regulate innate immune responses. In both projects, our work has been very productive and represents important original contributions to the malaria field. The current proposal is based on the knowledge that we gained in previous studies on how the malaria parasite, *Plasmodium falciparum*, sequesters in the placenta contributing to placental malaria (PM). Our previous accomplishments include the identification, localization and structural characterization of placental chondroitin sulfate proteoglycan (CSPG) receptor that interact with VAR2CSA, the *P. falciparum* erythrocyte membrane protein 1 that mediates the adherence of IRBCs to the placenta. We have also elucidated the chondroitin 4-sulfae (C4S) structural motif that interacts with IRBCs and determined various functional groups of this C4S motif that are involved in IRBC binding. Further, we have developed methods for purification of the placental CSPG and C4S oligosaccharides of defined size and sulfate contents. These studies have significantly contributed to the understanding of placental malaria cytoadherence and substantially impacted the field. In this grant application we propose to: (i) define the precise structure of C4S motif that is involved in IRBC binding, (ii) identify small molecule inhibitors that block the interaction of VAR2CSA/IRBC with C4S, and (iii) gain insight into domain organization in VAR2CSA and C4S-binding site by using NMR, X-ray crystallography and other biophysical techniques and use this information to validate inhibition of VAR2CSA-C4S interactions by small molecule inhibitors. To achieve these goals, we collaborate with investigators who have expertise and proven track records of accomplishments. In addition to malaria research, I am a recognized expert in glycobiology and have a proven record of accomplishment in studying the structures and functions of glycoproteins and proteoglycans. These expertise and those of the proposed collaborators put us at the competitive edge to productively accomplish the goals of the proposed studies.

B. Positions and Honors

Positions and Employment

1975-1986 Lecturer, Department of Chemistry, University of Mysore, Mysore, India.

1980-1981 Alexander von Humboldt Foundation Fellow, Institute of Biochemistry, Univ. of Kiel, Germany.

1983-1985	Postdoc. Scholar, Dept. Biological Chemistry, Hershey Med Center, Hershey, PA.
1986-1989	Instructor, Dept. of Pharmacology, New York University Medical Center, NY.
1989-1994	Assistant Professor, Department of Biochemistry and Molecular Biology, Georgetown University Medical Center, Washington, DC.
1994-2000	Associate Professor, Department of Biochemistry and Molecular Biology, Georgetown University Medical Center, Washington, DC.
2001-present	Professor, Department of Biological Chemistry and Molecular Biology, Penn State University College of Medicine, Hershey, PA.

Other Experience and Professional Memberships

Society Membership

1987-present	Society for Glycobiology, USA.
1995-present	American Society for Biochemistry and Molecular Biology.
1995-present	American Chemical Society.
1999-present	American Association for the Advancement of Science.
2000-present	American Society of Tropical Medicine and Hygiene.
2003-present	American Society of Microbiology.
2004-present	American Society for Investigative Pathology.
2011-present	American Association of Immunologists.

Study Sections and Grant Review Panels

1996	Ad-hoc Member, Cell Biology Study Section, US Army Breast Cancer Program.
2000	Ad-hoc Member, Comparative Medicine Study Section, NIH.
2000	Ad-hoc Member, Targeted Drug Discovery for Cancer Study Section, NCI, NIH.
2001	Ad-hoc Member, Biochemistry Study Section, NIGM, NIH.
2002-	Grant Review, The Wellcome Trust, London, UK - three times during this period.
2005	Member, GCRC Site Visit to Univ. of Rochester, Rochester, NY, NCRR, NIH.
2005	Ad-hoc Member, Pathogenic Eukaryotes (PTHE) Study Section, NIAID, NIH.
2005-present	Member, Promotion and Tenure Committee, Department of Biological Chemistry, Penn State University College of Medicine, Hershey, PA, Hershey.
2006	Member, Study Section, Special Panel for Innate Immunity to Parasites, NIH.
2006 and 09	Grant Reviewer, Swiss National Science Foundation, Switzerland.
2007	Member, Special Panel for Infectious, Reproductive, Asthma & Pulmonary Diseases Study Section, NIH.
2008	Member, Study Section on Special Emphasis Panel for Development of Novel Interventions and Tools for the Control of Malaria, Neglected Tropical Diseases and their Vectors.
2009	Grant Reviewer, Maryland Industry and University Joint Research Program, MD.
2010	Grant Reviewer, The Netherlands Org. for Health Research and Development
2011-present	Member, Scientific-Advisory groups, International Center of Excellence in Malaria Research, Thailand.

Journal's Editorial Board member

2003-2008 & 2011-present	*Journal of Biological Chemistry*, American society for Biochemistry and Molecular Biology.
2006-present	*Current Chemical Biology*, Bentham Publishers.
2008-present	*Open Glycosciences*, Bentham Publishers.
2009-present	*Pathology and Laboratory Medicine International*, Dove Med. Press.

2009-present	*Hematology Research and Reviews*, Dove Medical Press.
2009-present	Molecular Biology International, SAGE-Hindawi Publishers.
2010-present	*Infection and Immunity*, American Society for Microbiology.

Awards

1974	Gold medalist and cash award by the University of Mysore, India, for First Rank in MS.
1980-1981	The Alexander von Humboldt Foundation Fellowship, Germany
1993	Shannon Grant Award from NIH.
1998-2000	Burroughs Wellcome Fund award for New Initiatives in Malaria Research.
2006-08	Outstanding Mentor Award for serving in American Society Microbiology. Mentoring Program.
2007 and 08	Star Award Recognition for Teaching by PSU Hershey Medical Students.