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:** The Institute for Cancer Research

2. **Reporting Period (start and end date of grant award period):** 1/1/2012 – 6/30/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Maria Minko Gill

4. **Grant Contact Person's Telephone Number:** 215-728-2659

5. **Grant SAP Number:** 4100057660

6. **Project Number and Title of Research Project:** 05-Role of Lin28B in the Enhanced Cancer Susceptibility Caused by Inactivation of Rpl22

7. **Start and End Date of Research Project:** 1/1/2012 – 6/30/2013

8. **Name of Principal Investigator for the Research Project:** David L. Wiest, Ph.D.

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:

   $ 374,333

   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
Wiest, David	PI	5% years 1-2	$11,386.78
Rao, Shuyun	Postdoctoral/Research Associate	100% years 1-2	$75,858.82

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
None		

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____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:
Role of ER stress responses in pathogenesis and treatment of T-ALL	☐NIH ☐ Other federal (specify:_____) ☒ Nonfederal source (specify: LLS)	March 2013	$600,000	$600,000
R01 - Regulation of Hematopoiesis by Ribosomal Protein Paralogs	☒ NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	March 2014	$2,212,853	Pending/ Fundable score
R56 - Regulation of Hematopoiesis by Ribosomal Protein Paralogs	☒NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	June 2013	$446,250	$446,250

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?

Based on the funding that we have now obtained from the LLS and the NIH, we intend on determining how endoplasmic reticulum stress pathways contribute to the development of T-ALL and whether those pathways serve as targets for therapeutic intervention in cases where the Rpl22 locus is deleted.

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___X_____ No_____

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

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				1
Unknown				
Total				**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				1
Unknown				
Total				**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				1
Other				
Unknown				
Total				**1**

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

Yes____X_____ No_____

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

Shuyun Rao, Ph.D. was recruited from the University of Miami to work on this project.

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 CURE funds enabled me to expand the range of research conducted my laboratory. We previously focused on understanding the basic mechanisms underlying T lymphocyte development; however, the CURE funds enabled us to evaluate the clinical implications of our findings.

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.

Aim 1 To understand how Rpl22 mutations induce Lin28.
We have shown that Rpl22 inactivation increases cellular predisposition to transformation by inducing the expression of stem cell gene *Lin28b*. *Lin28b*, in turn, is thought to promote transformation by impairing the processing of Let7 microRNAs, thereby de-repressing their targets, c-Myc and Ras (Figure 1). We further showed that Rpl22 loss induced Lin28B expression in an NFκB-dependent manner (Figure 2). However, we had not yet determined how inactivation of *Rpl22* resulted in increased NFκB activity. We have now identified two ways through which Rpl22 inactivation may contribute to activation of NFκB. They are: 1) the paralog of Rpl22, Rpl22-Like1 (Rpl22L1); and 2) endoplasmic reticulum (ER) stress pathways.

Because we recently reported that Rpl22 and Rpl22L1 antagonistically control the emergence of hematopoietic stem cells (*Zhang et al., 2013)*, we thought that Rpl22L1 function might also be involved in the predisposition to transformation observed in *Rpl22* mutant cells. To address this possibility, we asked whether Like1 expression was affected by the loss of Rpl22. Indeed, when Rpl22 expression was knocked down using shRNA constructs in mouse embryonic fibroblasts (MEF), both Rpl22L1 and Lin28B protein levels were increased (Figure 3A). This was also true in human T-acute lymphoblastic leukemia cells (T-ALL; Figure 3B). Thus, Lin28B induction correlated with the increased expression of Rpl22L1 that results from Rpl22 knockdown. To assess whether the induction of Lin28B that is observed upon Rpl22 knockdown was dependent upon Rpl22L1, we employed primary MEF cells from *Rpl22+/+*, *Rpl22+/-*, and *Rpl22-/-* mice (Figure 4A). We observed that both Lin28B and Rpl22L1 protein levels were elevated in *Rpl22+/-*, and *Rpl22-/-* MEF. Moreover, the knockdown of Rpl22L1 in these cells reversed the increase in Lin28B expression, returning to baseline. This was also true in *RPL22* mutant T-ALL (Molt16). Molt16 expresses higher levels of both Rpl22L1 and Lin28B than Jurkat cells in which

the *RPL22* gene is intact (Figure 4B). Together, these data demonstrate that Rpl22L1 is required for the induction of Lin28B in *Rpl22* mutant cells. Nevertheless, it remains unclear whether Rpl22L1 is regulating Lin28B through a direct mechanism, or alternatively is regulating Lin28B indirectly by regulating NFκB activity.

The other pathway through which *Rpl22* inactivation might regulate NFκB activity is ER stress responses. ER stress pathways are attractive candidates because: 1) Rpl22 has been linked to the PERK/ATF4 ER stress pathway in lower organisms (Figure 5A); and 2) the PERK/ATF4 ER stress pathway has been shown to activate NFκB (Figure 5A). We propose the following model whereby *Rpl22* inactivation perturbs stress responses and induces NFκB. During abrupt and intense surges in protein synthesis, phosphorylation of EIF2α serves to transiently dampen protein synthesis by stress granule mediated repression until the ER stress response can increase production of cellular chaperones and achieve balance with the rate of new protein synthesis. Because a recent report by the Hannon lab suggested that Rpl22 is involved in stress granule function, we propose that Rpl22-deficiency impairs the cell's ability to repress translation in response to ER stress, which exacerbates the stress response and leads to NFκB induction. We think this occurs selectively during certain developmental transitions where cells undergo abrupt changes from relative quiescence to metabolically intensive processes requiring large increases in protein synthesis. These would include erythroid development, and the pre-TCR induced transition during αβ T cell development, from which T-ALL are thought to arise. Indeed, we found by immunoblotting analysis of *Rpl22-/-* thymocytes that they exhibit hyperactivation of the PERK-eIF2α ER stress pathway, in that the phosphorylation of both PERK and EIF2a are elevated in Rpl22-/- thymocytes (Figure 5B). Likewise, stimulation of a thymic lymphoma through the pre-TCR, which initiates the developmental transition regulated by Rpl22, induces eIF2α phosphorylation and this is exacerbated by the concomitant delivery of a suboptimal dose of the ER stressor, tunicamycin (Figure 5C). Importantly, the exacerbated level of eIF2α phosphorylation can be achieved by shRNA-mediated knockdown of Rpl22 alone (Figure 5C). Collectively, these data suggest that Rpl22 loss/inactivation results in hyperactivation of ER stress responses, which have been implicated in activation of NFκB signaling, raising the possibility that they link Rpl22 inactivation with Lin28B induction (Figure 6A). Indeed, the accumulation of unfolded proteins in the ER activates PERK signaling, which has been shown to activate NFκB (Figure 6A). To directly test whether the induction of ER stress responses were responsible for activation of NFκB upon Rpl22 loss, we attenuated ER stress signaling using shRNA knockdown of PERK. Interestingly, knockdown of PERK in Rpl22-/- MEF reduced both the phosphorylation of NFκB p65 and the expression of Lin28B, upon which the increased transformation potential of Rpl22-/- MEF depends (Figure 6B). This was also true in Rpl22-/- thymic lymphomas (Figure 6B), indicating the activation of ER stress pathways by Rpl22 loss may predispose to transformation in multiple tissues.

A second goal of Aim1 was to determine if Rpl22 was unique in its ability to regulate Lin28B expression as a mechanism for predisposing to transformation. To investigate whether the link between *Rpl22* inactivation and Lin28B induction was unique to Rpl22 or was perhaps observed upon loss of other ribosomal proteins (RP), we assessed the level of Lin28B expression in MEF in which Rpl24 and Rpl11 had been knocked down using shRNA. Nevertheless, despite effective knockdown of Rpl24 and Rpl11, Lin28B mRNA levels were unchanged (Figure 7). These data

indicate that the Lin28B induction that accompanies inactivation of *Rpl22* is not a general cellular response to loss of RP.

Aim 2. To investigate the basis by which Lin28B promotes transformation in acute assays.
While Lin28b negatively regulates the processing of Let-7 micro-RNAs (MiR), Let-7 independent functions of Lin28B have also recently been uncovered. In order to gain insight into how Lin28B induction might be promoting transformation in *Rpl22* mutant cells, we investigated whether expression of Let-7 family miRs was altered. In accordance with the increased expression of Lin28B, MEF lines in which Rpl22 was knocked down also exhibited reduced expression of several Let-7 miR family members (Figure 8). The reduction in Let-7 miR expression, in turn, was accompanied by increased expression of oncogene targets Myc and Ras, which they negatively regulate (Figure 8). These findings indicate that changes in Let-7 miRs and their targets accompany Rpl22 knockdown, raising the possibility that Rpl22 loss/inactivation promotes transformation in a Let-7 dependent manner.

Aim 3. To generate in vivo models where we can assess the role of Lin28B in development of T lineage malignancies.
No progress was made on Aim 3. However, we were able to leverage theses CURE funds to obtain additional funding to support this research. These studies are now being pursued under a different funding mechanism from the Leukemia and Lymphoma Society.

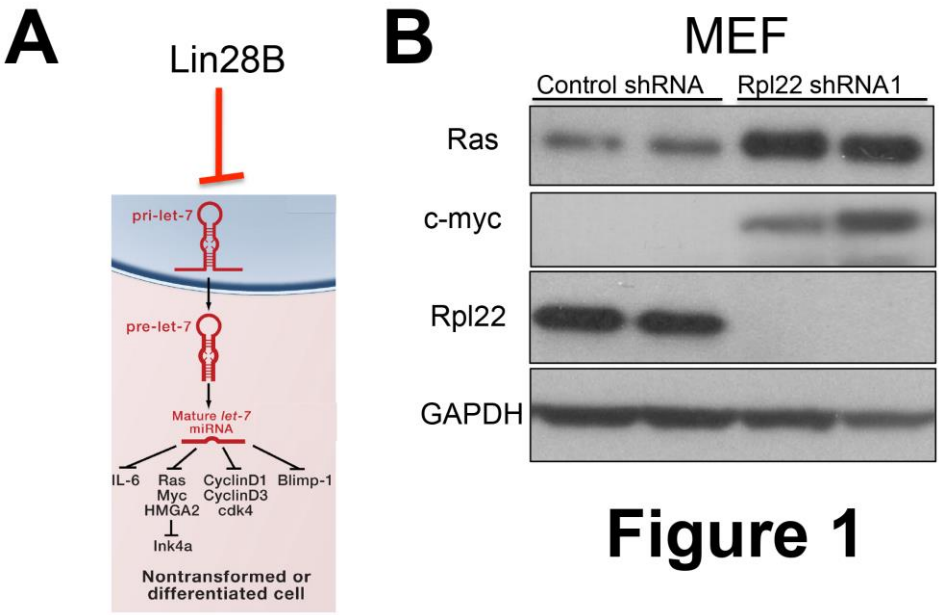
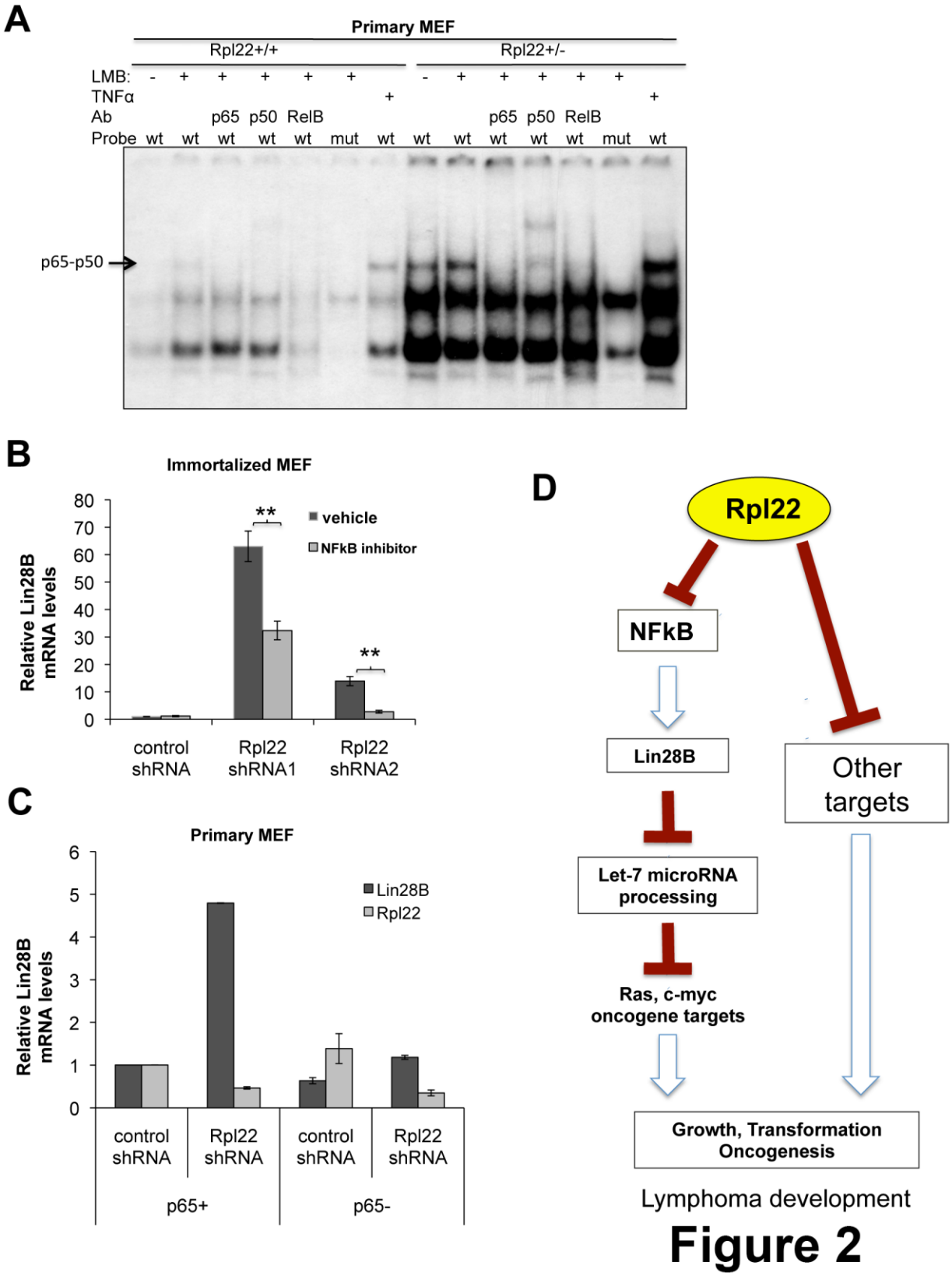


Figure 1


A
Primary MEF
Rpl22+/+
Rpl22+/-
LMB: - + + + + + - + + + + +
TNFα + +
Ab p65 p50 RelB p65 p50 RelB
Probe wt wt wt wt wt mut wt wt wt wt wt wt mut wt
p65-p50
B
Immortalized MEF
Relative Lin28B mRNA levels
vehicle
NFkB inhibitor
**
**
control shRNA
Rpl22 shRNA1
Rpl22 shRNA2
C
Primary MEF
Relative Lin28B mRNA levels
Lin28B
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Rpl22 shRNA
control shRNA
Rpl22 shRNA
p65+
p65-
D
Rpl22
NFkB
Lin28B
Let-7 microRNA processing
Ras, c-myc oncogene targets
Other targets
Growth, Transformation Oncogenesis
Lymphoma development

Figure 2

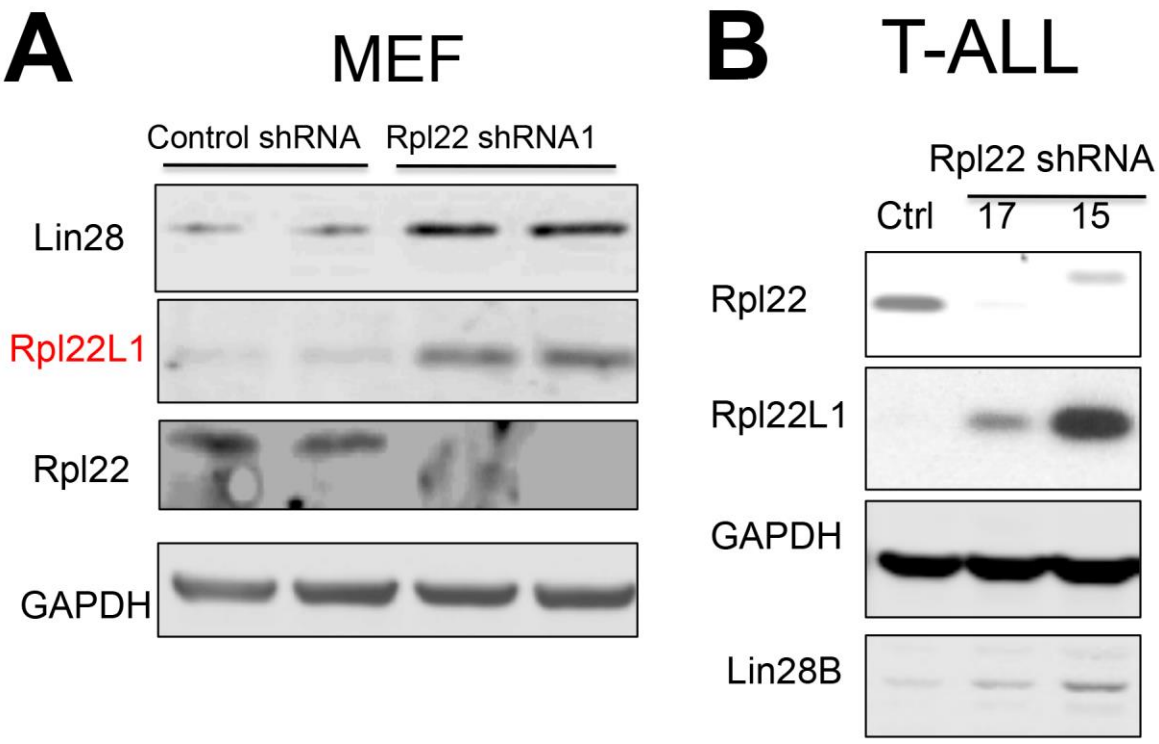

Figure 3

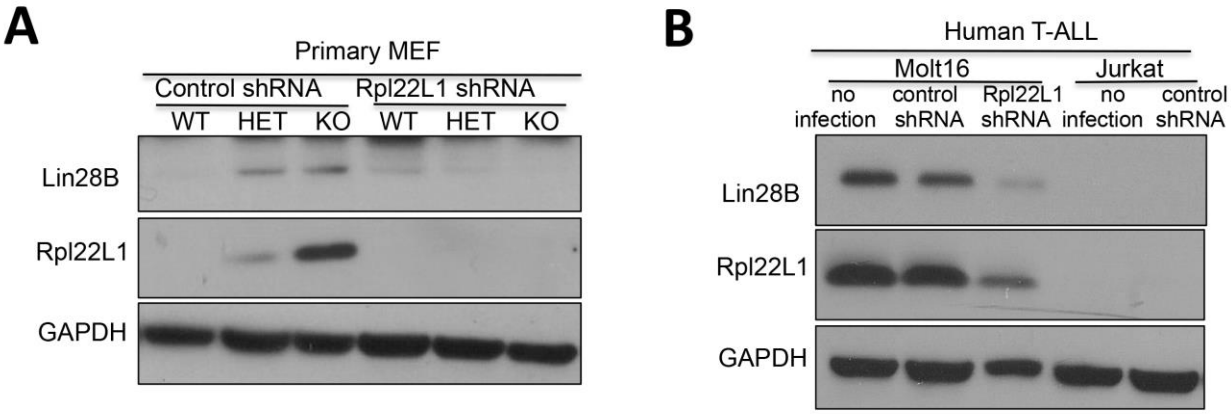

Figure 4

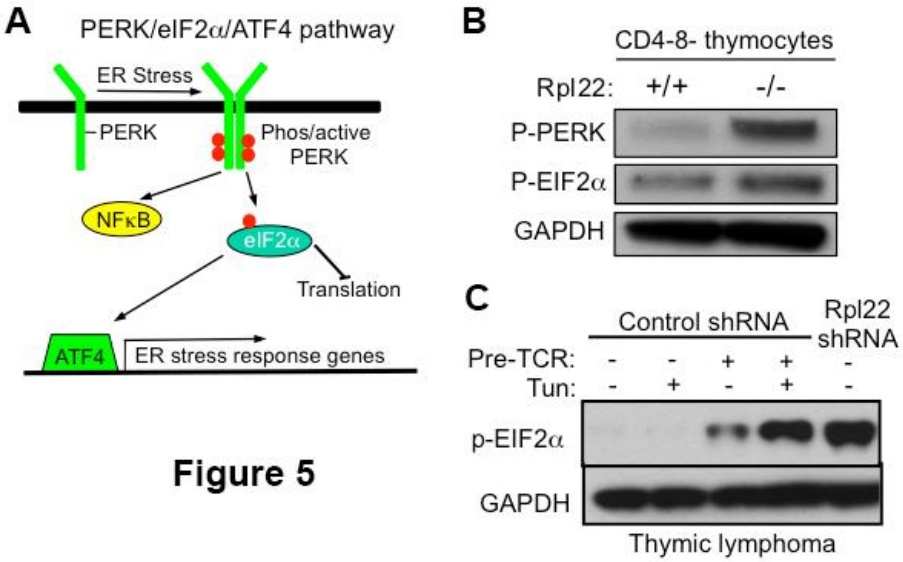

Figure 5

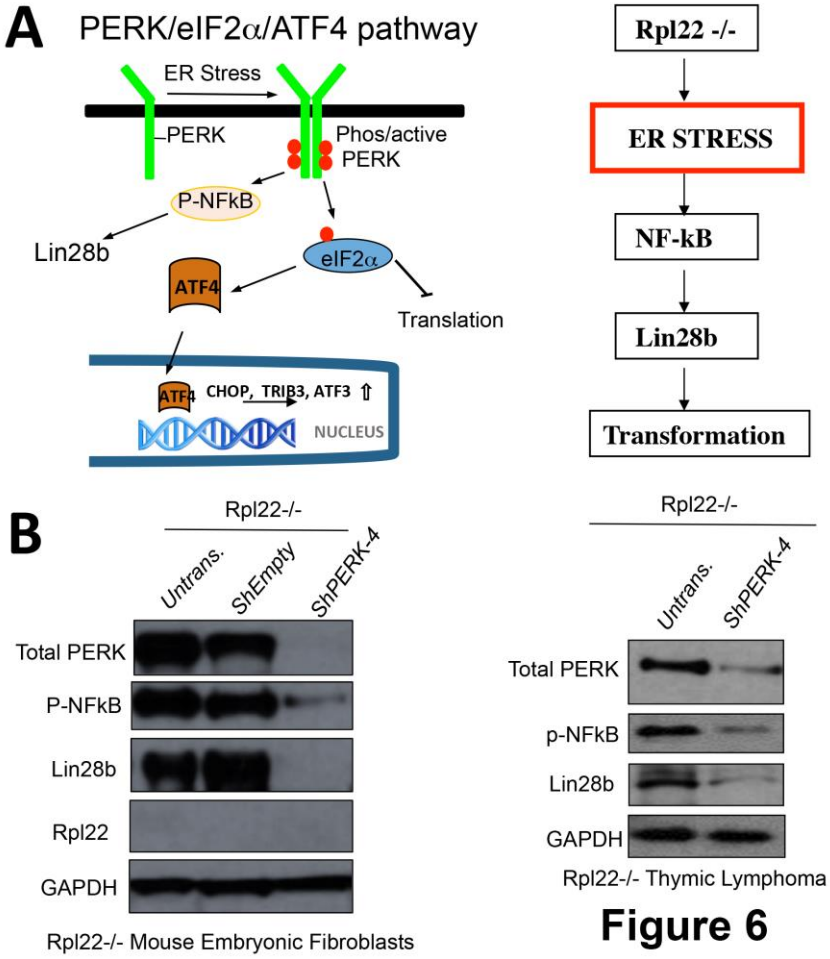

Figure 6

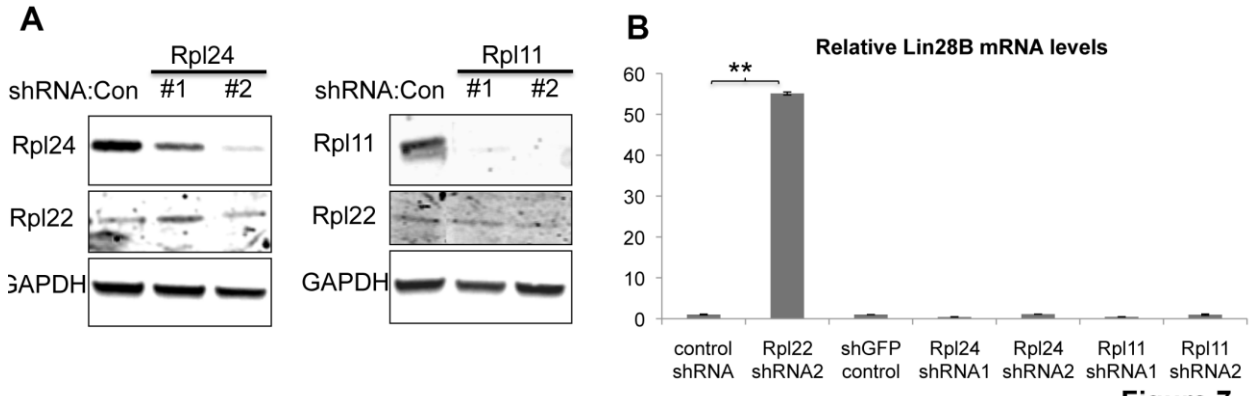

Figure 7

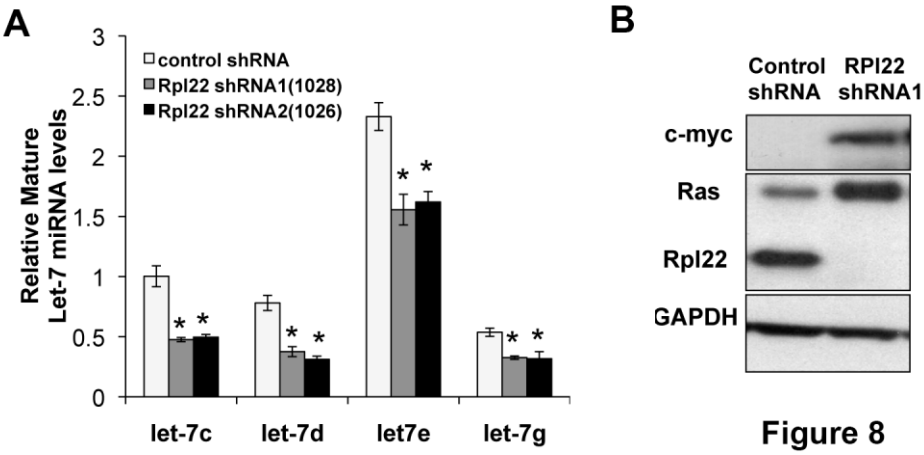

Figure 8

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. Inactivation of ribosomal protein L22 promotes transformation by induction of the stemness factor, Lin28B	Shuyun Rao, Sang-Yun Lee, Alejandro Guitierrez, Jacqueline Perrigoue, Roshan J. Thapa, Zhigang Tu, John R. Jeffers, Michele Rhodes, Stephen Anderson, Tamas Oravecz, Stephen P. Hunger, Roman A. Timakhov, Rugang Zhang, Siddharth Balachandran, Gerard P. Zambetti, Joseph R. Testa, A. Thomas Look, David L. Wiest	Blood Journal	March 2012	☐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 have two manuscripts in preparation. The first is by Shuyun Rao, et al. and details the basis by which Rpl22 regulates its paralog Rpl22-Like1 and how it functions as an oncogene. The second is by Nehal Solanki-Patel and described the role of ER stress pathways in the increased predisposition to transformation exhibited by Rpl22 mutant cells.

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.

We have identified ER stress signaling pathways as novel targets for therapeutic intervention in T-ALL and possibly other cancers where Rpl22 has been inactivated.

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____X_____ No_____

If yes, please describe your plans:

Our intention is to file on the role of Rpl22 mutations as a prognostic indicator in T-ALL. We are considering developing and commercializing a diagnostic test based on this information.

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

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Wiest, David L., Ph.D.	Professor Deputy Chief Scientific Officer
eRA COMMONS USER NAME DWIEST	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Pennsylvania State University, University	B.S.	05/84	Microbiology
Duke University, Durham, NC	Ph.D.	02/91	Immunology

A. PERSONAL STATEMENT

I have been working in the area of T cell development for nearly 20 years and have made a number of seminal contributions on our understanding of the molecular basis by which T cell receptor signals control cell fate in the thymus. Accordingly, my laboratory has extensive experience in the analysis of immune cell development and function. One molecular effector of particular interest in the regulation of immune cell development and function is the ribosomal protein Rpl22. We have demonstrated that Rpl22 is specifically required for the development of αβ lineage T cells (Anderson et al., 2007). More recently, we have demonstrated that Rpl22 serves as a tumor suppressor in the context of thymic lymphoma and T acute lymphoblastic leukemia (Rao et al., 2012) and have determined that Rpl22 plays an important role in regulating stress responses (including ER stress).

B. POSITIONS

Graduate Training, Laboratory of Dr. Yair Argon, Duke University, Durham, NC 1984-1991
Department of Microbiology and Immunology

Postdoctoral Fellow, Laboratory of Dr. Alfred Singer, Experimental Immunology 1991-1995
Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD
Faculty, FAES Graduate Immunology Course

Associate Member, Division of Basic Science, Institute of Cancer Research, 1995-2001
Fox Chase Cancer Center, Philadelphia, PA

Member, Division of Basic Science, Institute for Cancer Research, 2001-2008
Fox Chase Cancer Center, Philadelphia, PA

Adjunct Associate Professor of Microbiology and Immunology, 2004-present
Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA

Professor, Division of Basic Sciences, Institute for Cancer Research, 2008-present
Fox Chase Cancer Center, Philadelphia, PA

Leader, Blood Cell Development and Cancer Keystone Initiative, 2008-present
Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA

Co-Leader, Immune Cell Development and Host Defense Program , 2009-present
Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA

Deputy Chief Scientific Officer, Institute for Cancer Research, 2010-present
Fox Chase Cancer Center, Philadelphia, PA

HONORS

Arthur M. Conant Award for Excellence in Research, Duke University, Durham, NC 1990

Awarded Postdoctoral Fellowships from Damon Runyon-Walter Winchell Cancer Fund, 1991
American Cancer Society. Accepted Support From Cancer Research Institute

Member, NIH Cellular and Molecular Immunology-B Study Section	2008-2012
Program Committee, American Association of Immunologists	2010-2013
Faculty of 1000, Leukocyte Development Section	2010-present
Elected to the Henry Kunkel Society	2013-present
Appointed as Associate Editor, Journal of Immunology	2013-present
American Cancer Society Southeastern Pennsylvania Research Award	2013

C. SELECTED PEER-REVIEWED PUBLICATIONS (From more than 78)

1. Wiest, D.L., Ashe, J.M., Abe, R., Bolen, J.B., Singer, A. ZAP70 activation is impaired in CD4+8+ thymocytes by intrathymic CD4-MHC class II interactions that diminish p56lck. Immunity 4:495-504, 1996.
2. Wiest, D.L., Ashe, J.M., Howcroft, K., Lee, H.-M, Kemper, D.M., Negishi, I., Singer, D., Singer, A., Abe, R. A spontaneously-arising mutation in the DLAARN motif of ZAP70 abrogates kinase activity and arrests thymocyte development. Immunity 6:663-671, 1997.
3. Berger, M.A., Davé, V., Rhodes, M.R., Bosma, G., Bosma, M.J., Kappes, D.J., Wiest, D.L. Subunit composition of pre-TCR complexes expressed by primary thymocytes: CD3δ is physically associated but not functionally required. J. Exp. Med. 186:1461-1468, 1997.
4. Haks, M., Lefebvre, J.M., Lauritsen, J.P.H., Carleton, M., Rhodes, M., Miyazaki, T., Kappes, D.J., Wiest, D.L. Attenuation of γδTCR signaling efficiently diverts thymocytes to the αβ lineage. Immunity 22:595-606, 2005.
5. Anderson, S.J., Lauritsen, J.P.H., Hartman, M., DiGeorge-Foushee, A.M., Gerhardt, B., Lefebvre, J.M., Oravecz, T., Wiest, D.L. Defect in ribosomal protein L22 selectively impairs αβ T cell development by activation of a p53-dependent checkpoint. Immunity 26:759-772, 2007.
6. Lauritsen, J.P.H., Kurella, S., Lee, S.Y., Lefebvre, J.M., Rhodes, Gridley, T., Alberola-Ila, J., Wiest, D.L. Egr2 is required for positive but not negative selection of CD4+8+ thymocytes. J. Immunol. 181:7778-7785, 2008.
7. Lauritsen, J.P.H., Wong, G.W., Lee, S.Y., Lefebvre, J.M., Ciofani, M., Rhodes, M., Kappes, D.J., Zúñiga-Pflücker, J.C., Wiest, D.L. Marked induction of the helix-loop protein Id3 promotes the gammadelta T cell fate and renders their functional maturation Notch independent. Immunity 31:565-575, 2009.
8. Stadanlick, J.E., Zhiqiang, Z., Lee, S.-Y., Hemann, M., Biery, M., Carleton, M.O., Zambetti, G.P., Anderson, S.J., Oravecz, T., Wiest, D.L. Developmental arrest of T cells in Rpl22-deficient mice is dependent upon multiple p53 effectors. J. Immunol. 187:664-6775, 2011.
9. Rao, S., Lee, S.Y., Gutierrez, A., Perrigoue, J., Thapa, R.J., Tu, Z., Jeffers, J.R., Rhodes, M., Anderson, S., Oravecz, T., Hunger, S.P., Timakhov, R.A., Zhang, R., Balachandran, S., Zambetti, G., Testa, J.R., Look, A.T., Wiest., D.L. Inactivation of the ribosomal protein L22 promotes transformation by induction of the stemness factor, Lin28B. Blood 120:3764-3773, 2012.
10. Zhang, Y., Duc, A.-C.E., Rao, S., Sun, X.-L., Bilbee, A.N., Rhodes, M., Li, Q., Kappes, D.J., Rhodes, J., and Wiest, D.L., Control of hematopoietic stem cell emergence by antagonistic functions of ribosomal protein paralogs. Dev. Cell 24:411-425, 2013.
11. Coffey, F., Lee, S.Y., Buus, T.B., Lauritsen, J.P., Wong, G.W., Joachims, M.L., Thompson, L.F., Zúñiga-Pflücker, J.C., Kappes, D.J., Wiest, D.L. J. Exp. Med. 211:329-343, 2014.