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:** 03-Dissecting Role of ThPOK in T Cell Development through TALEN-mediated Exon Swapping

7. **Start and End Date of Research Project:** 1/1/2012 – 12/31/2013

8. **Name of Principal Investigator for the Research Project:** Dietmar Kappes, 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:

   $ 320,857

   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
Kappes, Dietmar	PI	10% year 1	$13,211.11
Lee, Hyung-Ok	Research Associate	50% year 1	$4,741.21
Zha, Jikun	Postdoctoral Associate	50% year 1	$13,269.55
MookerjeeBasu, Jayati	Postdoctoral Fellow	50% year 1	$25,074.61

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:
R21 - Dissecting Distinct and Redundant Roles of ThPOK and LRF, Key Regulators of Hematopoiesis	☒ NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	Mar 2014	$490,875	Pending

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

Yes_____ No___X_____ (assuming above application is funded)

If yes, please describe your plans:

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

1. Further analysis of T lymphocyte development and function in knockin mice in which all ThPOK coding exons have been replaced by those of the LRF gene.

2. We have recently established additional knockin mouse lines in which individual functional domains of ThPOK (BTB, Zn finger or central domain) have been replaced by the corresponding region of LRF. These lines will be crossed to homozygosity to establish their phenotype with respect to T cell development and function.

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				1
Female				1
Unknown				
Total				**2**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				2
Unknown				
Total				**2**

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				1
Other				1
Unknown				
Total				**2**

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 project provided 2 direct benefits that enhanced capacity of research at Fox Chase: 1) Knockin mice were generated in which the coding exons of ThPOK are replaced by those of LRF. These mice were used to justify an NIH grant proposal, which recently received an excellent score. 2) The comparison of TALEN, ZFN, and CRISPR methodologies for mouse germline modification funded by the current CURE grant facilitated introduction of these cutting-edge technologies to the Fox Chase Transgenic Facility. Numerous investigators/projects at Fox Chase have subsequently benefited from application of this new technical capacity to generate important new mouse disease models.

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.

Specific Aims

Aim 1: Engineering site-specific TALENs for ThPOK gene targeting.

Currently 3 methodologies have been reported for germ-line modification directly in mouse oocytes, i.e. Zn finger nucleases (ZFNs), TALENs and most recently CRISPRs. In the course of the current research project to assess feasibility of TALEN-mediated mutagenesis, we compared the TALEN-mediated approach to both ZFN and CRISPR methodologies, and found it to be significantly less efficient/reliable than either of the latter. Consequently, we successfully utilized the ZFN approach to generate required genome editing tools for modification of the ThPOK locus.

Aim 2: Can ThPOK be functionally substituted by other POK factors?

Studies of knockout mice have shown that ThPOK and leukemia/lymphoma-related *factor* (LRF) play distinct and non-redundant roles in lymphoid development. Evidently, in the affected cell lineages the other factor is insufficient to compensate for the absence of the targeted gene. The key question is why, i.e. are they functionally distinct or do their expression levels/kinetics differ? LRF is required for hematopoeitic stem cell (HSC) maintenance, and fetal erythropoiesis, so that all LRF−/− embryos die by e16.5 of anemia. ThPOK-/- mice also display a high incidence of embryonic lethality, with only 25% of homozygous mutant mice surviving until birth, which could potentially reflect anemia. In contrast to the disruption of CD4 and iNKT development in ThPOK-/- mice, T cell-specific LRF knockout mice exhibit normal T cell development. Hence, LRF is dispensable for T cell development and cannot substitute for the absence of ThPOK, even though there is considerable LRF mRNA expression at all thymocyte stages in wt and ThPOK-/- mice. Therefore, LRF is either functionally distinct from ThPOK or is expressed at inappropriate kinetics/levels in thymocytes to allow it to substitute for ThPOK.

Although it is clear that ThPOK and LRF play critical non-redundant roles at multiple stages in hematopoiesis, including in T cell, B cell, erythroid and myeloid differentiation, the mechanistic basis for these non-redundant functions is not understood. Therefore, we have used a gene-swap strategy to generate new knockin mouse lines to test:

1. Whether non-redundant roles of ThPOK and LRF reflect inherent functional differences, not just alternative expression patterns. We have generated knockin mice in which the entire coding region of ThPOK is replaced by that of LRF, which provide strong preliminary data in favor of this hypothesis (see below).
2. Whether distinct functions of ThPOK and LRF may reflect differences in interaction with coregulators of gene expression. The BTB domain is the most likely candidate domain to encode such interaction motifs. Thus we have recently generated a second knockin mouse line in which BTB domain of ThPOK is selectively replaced by that of LRF. These mice will allow us to test whether the ThPOK BTB domain is necessary and sufficient to mediate unique functions of ThPOK, and provide the basis for further detailed mutagenesis and biochemical studies to identify the relevant interaction partners. Because of the widespread roles of ThPOK and LRF in hematopoiesis and other biological processes including cancer, these future studies will be relevant and important to many different areas of biology.

The ZFN approach was used to replace the ThPOK coding exons with those of LRF (LRK knockin mice, henceforth referred to as LKI mice). Note that the knockin construct precisely replaces the ThPOK coding exons with those of LRF, while surrounding sequences, including the small intron separating the 2 LRF coding exons, are all derived from the ThPOK gene. Note that 5' and 3' UT regions are also derived from the ThPOK gene, so that mRNA stability and translation should be similarly regulated. Hence, expression of the knockin allele should precisely replicate the levels and kinetics of endogenous ThPOK protein. RT-PCR analysis of sorted thymocyte subsets from heterozygous LKI/+ founder mice, demonstrates elevated LRF mRNA expression at the SP CD4 CD69+ stage, precisely when endogenous ThPOK is normally most highly induced. We have bred LKI founders to generate homozygous LKI/LKI mouse, which demonstrates that these animals are viable. Preliminary analysis of mature T cell composition in 4-week old homozygous LKI/LKI and heterozygous LKI/+mice reveals that 1) LKI/+ mice are phenotypically normal, indicating the knockin allele does not have a dominant effect, and 2) SP CD4 T cells are restored to about 50% of normal in LKI/LKI mice compared to ThPOK-/- mice. As a result, the relative proportions of mature SP CD4 and CD8 cells are markedly shifted towards the CD8 compartment. In addition, LKI/LKI mice exhibit unusual populations of mature CD4+8+ (DP) and SP CD4low cells. These effects presumably reflect altered development of class II-restricted thymocytes, as the knockin allele should be expressed only in the former cells, like endogenous ThPOK. We have previously reported that ThPOK is also required for development of CD4 Vα14+ iNKT cells, which are replaced by unusual CD8+ iNKT cell. In contrast, while LKI/LKI mice also fail to generate normal numbers of CD4 iNKT cells, they show elevated numbers of DN rather than SP CD8 iNKT cells. This suggests that LRF can compensate partly for ThPOK in iNKT development in preventing CD8 upmodulation, but not in promoting CD4 upmodulation. We tentatively conclude that LRF cannot substitute fully for ThPOK in development of either conventional CD4 T cells or iNKT cells, and therefore that the 2 factors must possess distinct functions.

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

19. 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.)

20. 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:

21. 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:

At least 2 publications are planned: 1) A paper reporting that that LRF cannot substitute fully for ThPOK in development of either conventional CD4 T cells or iNKT cells, and therefore that the 2 factors must possess distinct functions. 2) A report mapping the critical responsible motif/s of ThPOK using a domain swap approach. This will define functionally important motifs and identify the important ThPOK interaction partners involved in mediating its unique functions.

22. 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.

The benefit of this research on human disease outcome/diagnosis derives from the improved understanding of the function and genetic redundancy of the ThPOK and LRF transcription factors. Given their widespread roles in normal development, it is not surprising that many members of the POK gene family have been implicated in cancer, including both LRF and ThPOK. In human cancer, LRF has been implicated in tumor progression, invasion,

metastasis and therapeutic resistance in the context of other oncogenes. Hence the present study provides valuable tools to elucidate the structure-function correlation and the molecular basis of functional redundancy and specialization of ThPOK and LRF in normal development, which will eventually lead to the discovery of novel molecular interaction partners. In the context of oncogenesis, identification of such interactors may lead to both novel prognostic markers and therapeutic targets for cancer treatment.

23. 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

24. 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	POSITION TITLE
Kappes, Dietmar J., Ph.D.	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) DKAPPES	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Harvard University, Boston, MA	B.S.	06/80	Biology, Chemistry
Harvard University, Boston, MA	Ph.D.	06/88	Biology

A. PERSONAL STATEMENT

My laboratory employs genetic approaches to elucidate the signaling and transcriptional pathways that regulate thymic selection and T lymphocyte lineage commitment, as well as the molecular basis of lymphomagenesis. We have a particular interest in the control of CD4/CD8 lineage choice, arising from our identification of the transcription factor ThPOK as the "master regulator" of CD4 commitment. In my additional function as Director of the Transgenic Facility at FCCC, I take a lead role in integrating important new technologies into the facility's services, including most recently ZFN-mediated gene targeting.

B. POSITIONS

Teaching Assistant, Introductory Biology and Membrane Biology, Harvard University, Boston, MA	1982-1985
Head Teaching Fellow for undergraduate and advanced graduate courses in immunology, Harvard University, Boston, MA	1984-1987
Postdoctoral Fellow, Damon Runyon-Walter Winchell Cancer Research Fund in the group of Susumu Tonegawa, Massachusetts Institute of Technology, Cambridge, MA	1988-1992
Associate Member, Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA	1992-1999
Director, Transgenic Mouse Facility, Institute for Cancer Research, Fox Chase Cancer Center	1994-present
Member with Tenure, Institute for Cancer Research, Fox Chase Cancer Center	1999-2007
Professor, Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA	2007-present
Member, Blood Cell Development and Cancer Keystone Program, Fox Chase Cancer Center	2008-present

C. SELECTED PEER-REVIEWED PUBLICATIONS

1. Davé, V.P., Allman, D., Keefe, R., Hardy, R.R., Kappes, D.J. HD mice: a novel mouse mutant with a specific defect in the generation of CD4+ T cells. Proc. Natl. Acad. Sci. U.S.A. 95:8187-8192, 1998.
2. Davé, V.P., Allman, D., Wiest, D.L., Kappes, D.J. Limiting TCR expression leads to quantitative but not qualitative changes in thymic selection. J. Immunol. 162:5764-5774, 1999.
3. Keefe, R., Davé, V.P., Allman, D., Wiest, D., Kappes, D.J. Regulation of lineage commitment distinct from positive selection. Science 286:1149-1153, 1999.

4. Kappes, D.J., Lawrence, D.M., Vaughn, M.M., Davé, V., Belman, A.R., Rall, G.R. Protection of CD3δ knockout mice from lymphocytic choriomeningitis virus-induced immunopathology: implications for viral neuroinvasion. Virology 269:248-256, 2000.
5. Delgado, P., Fernández, E., Davé, V., Kappes, D.J., Alarcón, B. CD3δ couples T-cell receptor signalling to ERK activation and thymocyte positive selection. Nature 406:426-430, 2000.
6. Hayes, S.M., Laky, K., El Khoury, D., Kappes, D.J., Fowlkes, B.J., Love, P.E. Activation-induced modification in the CD3 complex of the γδ T cell receptor. J. Exp. Med. 196:1355-1361, 2002.
7. He, Xiao, He, Xi, Davé, V.P., Zhang, Y., Hua, X., Xu, W., Roe, B.A., Kappes, D.J. The zinc finger transcription factor TH POK regulates CD4 versus CD8 T lineage commitment. Nature 433:826-833, 2005.
8. Haks, M.C., Lebebvre, J.M., Lauritsen, J.P., Carleton, M., Rhodes, M., Miyazaki, T., Kappes, D.J.*, Wiest, D.L.* Attenuation of γδ TCR signaling efficiently diverts thymocytes to the αβ lineage. Immunity 22:595-606, 2005. *Denotes authors contributed equally.
9. He, X., Park, K., Wang, H., Zhang, Y., Hua, X., Li, Y., Kappes, D.J. CD4-CD8 lineage commitment is regulated by a silencer element at the ThPOK transcription-factor locus. Immunity 28:346-358, 2008.
10. 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-helix protein Id3 promotes the gammadelta T cell fate and renders their functional maturation Notch independent. Immunity 31:565-575, 2009.
11. Park, K., He, X., Lee, H. O., Hua, X., Li, Y., Wiest, D., Kappes, D.J. TCR-mediated ThPOK induction promotes development of mature (CD24-) γδ thymocytes. EMBO J. 29:2329-2341, 2010.
12. Engel, I., Hammond, K., Sullivan, B.A., He, X., Taniuchi, I., Kappes, D., Kronenberg, M. Co-receptor choice by V alpha14i NKT cells is driven by Th POK expression rather than avoidance of CD8-mediated negative selection. J. Exp. Med. 207:1015-1029, 2010.
13. He, X., Park, K., Kappes, D.J. The role of ThPOK in control of CD4/CD8 lineage commitment. Ann. Rev. Immunol. 28:295-320, 2010.
14. Lee, S.Y., Stadanlick, J., Kappes, D.J., Wiest, D.L. Towards a molecular understanding of the differential signals regulating αβ/γδ T lineage choice. Semin. Immunol. 22:237-246, 2010.
15. Kim, S.T., Touma, M., Takeuchi, K., Sun, Z.-Y. J., Dave, V.P., Kappes, D.J., Wagner, G., Reinherz, E.L. Distinctive CD3 heterodimeric ectodomain topologies maximize antigen-triggered activation of αβ T cell receptors. J. Immunol. 185:2951-2959, 2010.
16. de Keersmaecker, K., Real, P.J., Gatta, G.D., Palomero, T., Sulis, M.L., Tosello, V., van Vlierberghe, P., Barnes, K., Castillo, M., Sole, X., Hadler, M., Lenz, J., Aplan, P.D., Kelliher, M., Kee, B.L., Pandolfi, P.P., Kappes, D.J., Gounari, F., Petrie, H., van der Meulen, J., Speleman, F., Paietta, E., Racevskis, J., Wiernik, P.H., Rowe, J.M., Soulier, J., Avran, D., Cavé, H., Dastugue, N., Raimondi, S., Meijerink, J., Cordon-Cardo, C., Califano, A. and Ferrando, A.A. The TLX1 oncogene drives aneuploidy in T-cell transformation. Nat. Med. 16:1321-1327, 2010.
17. Kappes, D.J. Expanding roles for ThPOK in thymic development. Immunol. Rev. 238:182-194, 2010.