

Final Progress Report for Research Projects Funded by Health Research Grants

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

1. **Grantee Institution:** Trustees of the University of Pennsylvania
2. **Reporting Period (start and end date of grant award period):** 1/1/2011 – 12/31/2014
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Gearline Robinson-Hall, BSF
4. **Grant Contact Person’s Telephone Number:** 215-746-6821
5. **Grant SAP Number:** 4100054874
6. **Project Number and Title of Research Project:** 10 - CD40 and Notch as Novel Therapeutic Targets of Pancreatic Carcinoma
7. **Start and End Date of Research Project:** 1/1/2011 – 6/30/2013
8. **Name of Principal Investigator for the Research Project:** Robert H. Vonderheide, MD, DPhil
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:

\$ 200,825.95

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
Beatty, Gregory	Assistant Professor A	5% Yr 1	6,250.00
Mirek, Emily	Research Specialist 1	27% Yr2	8,088.71

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
Vonderheide, Robert	Principal Investigator	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 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:
Stand Up 2 Cancer Dream Team Award in Pancreatic Cancer	<input type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify:____) <input type="checkbox"/> Nonfederal source (specify: Stand Up 2 Cancer-AACR__)	January 2014	\$249K per year for each of three years	\$747,000

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:

Dr. Stanger and I will apply for a multi-PI R01 from the NCI within two years.

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

Our goal is to use the genetic murine model of pancreatic cancer to screen for novel therapies for this disease that can be brought rapidly to the clinic with sound scientific rationale and biomarker plan.

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
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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.

We established a pancreatic cancer “mouse hospital” which is a shared facility in our vivarium that maintains the KPC colony and performs treatment studies using ultrasound guided serial tumor measurements and survival as the primary endpoints.

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 (β) should not print as boxes (\square) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

This project has been completed. There are several findings:

1. Pancreatic ductal adenocarcinoma (PDA) is a highly aggressive cancer that is resistant to most treatments, and more than 90% of patients with metastatic PDA die within five years of diagnosis. Nanoparticle albumin bound-Paclitaxel (nab-Paclitaxel, nP) was recently approved as a new standard of care with gemcitabine (Gem) for patients with metastatic PDA, as the combination improved the overall survival of patients in clinical trials. However, the benefits were short-lived as all tumors eventually progressed. Given the potential synergy between chemotherapy and immune stimulation to create an anti-tumor vaccine, we administered agonistic CD40 monoclonal antibody with combined Gem/nP chemotherapy activate the immune response and reverse immunosuppression in the PDA microenvironment. Using the $Kras^{G12D+/-}; Trp53^{R172H+/-}; Pdx-1\ Cre$ (KPC) genetically engineered mouse model of PDA, we found that 37.5% of mice treated with Gem/nP/CD40 therapy had tumor regressions or stable disease, compared to only 9% of mice receiving Gem/nP without CD40. Furthermore, when mice were depleted of CD8 T cells, the tumor regressions were completely ablated. To study this mechanism further, we injected PDA cell lines generated from KPC tumors subcutaneously in to C57Bl/6 mice, and found that more than 50% of mice treated with Gem/nP/CD40 experienced T cell dependent tumor regressions compared to only rare regressions in Gem/nP or CD40 treated mice ($p < 0.0001$). The proportion of T regulatory cells in the tumor was reduced 6.9-fold after Gem/nP/CD40 ($p < 0.05$, versus Gem/nP or CD40 alone), with a concurrent 1.75-fold increase in activated CD4 T cells ($p < 0.01$). Additionally, the proportions of IFN-gamma and TNF-alpha producing CD4 and CD8 T cells were significantly increased (by 2 to 4-fold) in Gem/nP/CD40 treated mice compared to other cohorts. The loss of the immunosuppressive tumor microenvironment was detectable 24 hours after Gem/nP/CD40 treatment, when CD11b⁺ and CD11c⁺ cells in the tumor reduced production of IL-10 and TGF-beta by 1.3 to 5-fold (compared to Gem/nP treatment), and increased production of IL-12 (35% versus 23% in CD40 treated mice), concurrent with increased expression of of both CD86 and MHCII (37% versus 10% in control group). Surprisingly, responses to Gem/nP/CD40 were independent of the IFNAR, MyD88, and TLR4 pathways, which have previously been reported as critical mediators of the anti-tumor immune response generated with chemotherapy. These studies highlight the clinical potential of adding CD40 activation to standard-of-care chemotherapy as a novel strategy for PDA, and underscore an emerging hypothesis that T cells can mediate destruction of this otherwise highly immunosuppressive tumor if triggered by robust vaccination.

2. Disabling the function of immune checkpoint molecules can unlock T cell immunity against cancer, yet despite remarkable clinical success with mAb that block PD-1 or CTLA-4, resistance remains common and essentially unexplained. To date, pancreatic carcinoma is fully refractory to these antibodies. Using a genetically engineered mouse model of pancreatic ductal adenocarcinoma in which spontaneous immunity is minimal, we found that PD-L1 is prominent in the tumor microenvironment, a phenotype confirmed in patients; however, tumor PD-L1 was found to be independent of IFN- γ in this model. Tumor T cells expressed PD-1 as prominently as T cells from chronically infected mice, but treatment with PD-1 mAb, with or without CTLA-4 mAb, failed in well-established tumors, recapitulating clinical results. Agonist CD40 mAb with chemotherapy induced T cell immunity and reversed the complete resistance of pancreatic tumors to PD-1 and CTLA-4. The combination of α CD40/chemotherapy plus PD-1 and/or CTLA-4 induced regression of subcutaneous tumors, improved overall survival, and conferred curative protection from multiple rechallenges, consistent with immune memory not otherwise achievable. Combinatorial treatment nearly doubled survival of mice with spontaneous pancreatic cancers although no cures were observed. Our findings suggest that in pancreatic carcinoma, a non immunogenic tumor, baseline refractoriness to checkpoint inhibitors can be rescued by the priming of a T cell response with α CD40/chemotherapy.

3. PDA is characterized by a dense desmoplastic stroma which begins to accrue during the formation of precursor PanIN lesions. One of the mediators of the desmoplastic reaction which we believe may co-regulated with Notch signaling is Sonic hedgehog (Shh), a secreted ligand that is overexpressed from epithelial cells in pancreatic cancer and sends a proliferative signal to nearby stromal cells. Although acute inhibition of the Hedgehog pathway effector Smoothed (Smo) depletes pancreatic stroma, facilitates drug delivery and extends overall survival in KPC mice, Smoothed inhibitors have not exhibited efficacy in Phase I clinical trials, and may even result in a worse clinical outcome. Thus, there is considerable uncertainty regarding the role of this pathway, and its suitability as a target for therapy, in PDA. To better understand its role in malignant progression, we deleted Shh in a well-defined mouse model of PDAC. As predicted, Shh-deficient tumors had reduced stromal content. Surprisingly, such tumors were more aggressive and exhibited undifferentiated histology, increased vascularity, and heightened proliferation--features that were fully recapitulated in control mice treated with a Smoothed inhibitor. Furthermore, administration of VEGFR blocking antibody selectively improved survival of Shh-deficient tumors, indicating that Hedgehog-driven stroma suppresses tumor growth in part by restraining tumor angiogenesis. Together, these data demonstrate that some components of the tumor stroma can act to restrain tumor growth.

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
 No

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

- Yes
 No

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

20. Articles Submitted to Peer-Reviewed Publications.

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

publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

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

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

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

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

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

Yes X No _____

If yes, please describe your plans:

Yes, we intend to submit manuscripts that include part of the data reported above sometime later in 2015.

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.

1. The addition of CD40 activation to standard-of-care chemotherapy has potential as a novel strategy for PDA, underscoring the emerging hypothesis that T cells can mediate destruction of this otherwise highly immunosuppressive tumor if triggered by robust vaccination.
2. Baseline refractoriness of PDA to checkpoint inhibitors can be rescued by the priming of a T cell response with α CD40/chemotherapy
3. Administration of VEGFR blocking antibody selectively improves survival of Shh-deficient tumors in mice, indicating that Hedgehog-driven stroma suppresses tumor growth in part by restraining tumor angiogenesis.

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 VONDERHEIDE, Robert H.	POSITION TITLE Professor of Medicine; Hanna Wise Professor in Cancer Research		
eRA COMMONS USER NAME (credential, e.g., agency login) VONDER			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Notre Dame, Notre Dame, IN	BSc	1985	Chemical Engineering
Oxford University, England	DPhil	1989	Immunology
Harvard Medical School, Boston, MA	MD	1993	Medicine
Intern and Resident in Medicine, Massachusetts General Hospital, Boston, MA		1993-96	Internal Medicine
Clinical Fellow, Dana-Farber Cancer Institute, Boston, MA		1996-98	Oncology-Hematology

A. Personal Statement: Dr. Vonderheide's laboratory combines efforts in both basic research and clinical investigation to advance the understanding of tumor immunology and to develop novel immunotherapies for cancer. His basic research includes deciphering the immunobiology of novel genetically engineered mouse models of cancer, including the regulation of immune surveillance and the tumor microenvironment by CD40 and other pathways, and with a focus on melanoma and pancreatic cancer. His translational work tests novel approaches such as vaccines, antibodies, and adoptive T cells for the treatment of patients with melanoma, pancreatic cancer and other cancers. He has studied 'universal' tumor antigens such as hTERT and immune modulatory pathways involving CD40, GM-CSF, PD-1, CTLA-4, and CD25.

B. Positions and Honors:

Positions and Employment

1989-1993 Research Fellow, Center for Blood Research, Harvard Medical School, Boston, MA
 1998-2001 Instructor in Medicine, Dana-Farber Cancer Institute, Boston, MA
 2001-2008 Assistant Professor of Medicine, University of Pennsylvania School of Medicine
 2001- Investigator, Abramson Family Cancer Research Institute, Philadelphia, PA
 2008-2014 Associate Professor of Medicine, University of Pennsylvania School of Medicine
 2008- Program Co-Leader, Immunobiology Program, Abramson Cancer Center, Phila., PA
 2011- Associate Director for Translational Research, Abramson Cancer Center, Phila., PA
 2013- Leader, Cancer Immunology, Institute for Immunology, University of Pennsylvania
 2014- Professor of Medicine, Perelman School of Medicine, University of Pennsylvania
 2014- Hanna Wise Professor of Cancer Research, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
 2014- Vice Chief for Research, Hematology-Oncology Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Other Experience and Professional Memberships

2003- Editorial Board Member, *Clinical Cancer Research*
 2007- Editorial Board Member, *Journal of Clinical Oncology*
 2008- Editorial Board Member, *Journal of Translational Medicine*
 2010- Editorial Board Member, *Cancer Immunology Immunotherapy*
 2009- Member, Immunotherapy Task Force, NCI Investigational Drug Steering Committee
 2011-15 Chair, Steering Committee, Cancer Immunology Working Group, AACR
 2011-17 Member, Scientific Advisory Board, Pancreatic Cancer Action Network.
 2012- Member, Clinical Advisory Board, Lustgarten Foundation for Pancreatic Cancer
 2012-18 Standing member, Cancer Immunopathology and Immunotherapy study section, NIH

2012- Deputy Editor, *Cancer Immunology Research* (AACR)
2014-15 Co-Chairperson, 2015 AACR Annual Meeting Program Committee

Honors

1985 Rhodes Scholar
1985 *Summa cum laude*, University of Notre Dame
1993 Shipley Prize and *Magna cum laude*, Harvard Medical School
1999 Doris Duke Charitable Foundation Clinical Scientist Award
2000 Clinical Investigator Award of the Damon Runyon-Cancer Research Foundation
2007- American Society of Clinical Investigation (elected); Elected Councilor, 2014
2013- American Association of Physicians (elected)

C. Selected Peer-Reviewed Publications (in chronological order) from over 110 publications:

1. **Vonderheide RH**, Hahn WC, Schultze JL, Nadler LM. The telomerase catalytic subunit is a widely expressed tumor-associated antigen recognized by cytotoxic T lymphocytes. *Immunity*, 1999, 10:673-679.
2. **Vonderheide RH**, Flaherty KT, Khalil M, Stumacher MS, Bajor DL, Hutnick NA, Sullivan P, Mahaney JJ, Gallagher M, Kramer A, Green SJ, O'Dwyer PJ, Running KL, Huhn RD, Antonia SJ. Clinical activity and immune modulation in cancer patients treated with CP-870,893, a novel CD40 agonist monoclonal antibody. *J Clin Onc*, 2007, 25:876-883.
3. Domchek SM, Recio A, Mick R, Clark CE, Carpenter EL, Fox KR, DeMichele A, Schuchter LM, Leibowitz MS, Wexler MH, Vance BA, Beatty GL, Veloso E, Feldman MD, **Vonderheide RH**. Telomerase-specific T-cell immunity in breast cancer: impact of vaccination on tumor immunosurveillance, *Can Res*, 2007, 67: 10546-55.
4. **Vonderheide RH**, LoRusso PM, Khalil M, Gartner EM, Khaira D, Soulieres D, Dorazio P, Trosko JA, Ruter J, Mariani GL, Usari T, Domchek SM. Tremelimumab in combination with exemestane in patients with advanced breast cancer and treatment-associated modulation of ICOS expression on patients T cells. *Clin Cancer Res*, 2010, 16:3485-94.
5. Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, Huhn RD, Song W, Li D, Sharp LL, Torigian DA, O'Dwyer PF, **Vonderheide RH**. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science*, 2011, 331:1612-6. PMID: PMC3406187.
6. Sorenmo KU*, Krick E, Coughlin CM, Overley B, Gregor TP, **Vonderheide RH***, Mason NJ*. CD40-activated B cell cancer vaccine improves second clinical remission and survival in privately owned dogs with non-Hodgkin's lymphoma. *PLoSOne*, 2011, 6:e24167. PMID: PMC3164165.
7. Rech AJ, Mick R, Martin S, Recio A, Aqui NA, Powell Jr DJ, Colligon TA, Trosko JA, Leinbach LI, Pletcher CH, Tweed CK, DeMichele A, Fox KR, Domchek SM, Riley JL, **Vonderheide RH**. CD25 blockade depletes and selectively reprograms regulatory T cells in concert with immunotherapy in cancer patients. *Science Transl Med*, 2012, 4: 132-147.
8. Bayne LJ, Beatty GL, Jhala N, Clark CE, Rhim AD, Stanger BZ, **Vonderheide RH**. Tumor-derived granulocyte-macrophage colony stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. *Cancer Cell*, 2012, 21:822-35. PMID: PMC3575028
9. Reshef R, Luger SM, Hexner EO, Loren AW, Frey NV, Nasta SD, Goldstein SC, Stadtmauer EA, Smith J, Bailey S, Mick R, Heitjan DF, Emerson SG, Hoxie JA, **Vonderheide RH***, Porter DL*. Blockade of lymphocyte chemotaxis in visceral graft-versus-host disease. *New England Journal of Medicine*, 2012, 367:135-45. PMID: PMC3568501
10. **Vonderheide RH**, Burg JM, Mick R, Trosko JA, Li D, Shaik MN, Tolcher AW, Hamid O. Phase I study of CD40 antibody CP-870,893 in combination with carboplatin and paclitaxel in patients with advanced solid tumors *OncoImmunology*, 2013, 2: e23033. PMID: PMC3583942
11. Beatty GL, Torigian DA, Chiorean EG, Saboury B, Brothers A, Alavi A, Troxel AB, Sun W, Teitelbaum UR, **Vonderheide RH**, O'Dwyer P. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. *Clin Can Res*, 2013, 19:6286-95. PMID: PMC3834036.