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 Fox Chase Cancer Center

2. **Reporting Period (start and end date of grant award period):** 1/1/2009 – 12/31/2011

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:** 4100047634

6. **Project Number and Title of Research Project:** 1 – A Growth-Regulating Protein Tyrosine Phosphatase

7. **Start and End Date of Research Project:** 1/1/2009 – 6/30/2011

8. **Name of Principal Investigator for the Research Project:** Jonathan Chernoff, M.D., Ph.D.

9. **Research Project Expenses**.

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

   $971,592.68

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost

Chernoff	PI	20% YR01+YR02	$101,350.85
Makhlin	Scientific Technician	75% YR01 only	$33,206.26
Yip	Research Associate	80% YR02	$47,118.96
Stepanova	Scientific Technician	50% YR02 only	$21,069.12
Villamar-Cruz	Scientific Technician	35% YR03 only	$16,304.40
Chow	Research Associate	25% YR02 only	$8,465.75
Saha	Postdoctoral Associate	25% YR02 only	$14,396.27

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project
Chernoff	PI	20% YR03
Seeholzer	Director Protein Core Facility, CHOP	YR03 (consultant)
Speicher	Professor, Wistar Institute	YR03 (consultant)

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
JSAN Cell Sorter	Allowed facile separation of PTP-1B transfected cells for expression analysis and cell cycle profiling.	$187,246
Evosfl Base Microscope W/ PH/FL/LT CUBES	Enabled identification of transfected cells and assessment of cell morphology.	$27,249.67
SECTOR Imager 2400AS; sn: 1251100909201	This device was used to assess the structure of recombinant DNA constructs.	$75,000.00
(2) -86°C REVCO UXF 600BX 115V Freezers	These freezers were essential for storing biological specimens.	$21,742.05

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes___X_____ No_____

If yes, please indicate the source and amount of other funds:
(see Q11 below)

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes____X_____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Role of PTP1B in HER2 Signaling in Breast Cancer	☐NIH ☑ Other federal (specify: DOD) ☐ Nonfederal source (specify: _____)	12/2009	$523,500	$523,500
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify:		$	$

	_____)			

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

Yes____X_____ No_____

If yes, please describe your plans:

We intend to write a R01 based on this work.

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

We intend to use a combination of substrate-trapping and mass-spectroscopy methods in PTP1B-plus and PTP1B-null mammary epithelial cells to determine potential cancer-relevant substrates for this phosphatase.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____ No____X_____

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

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				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:

Sayanti Saha Ph.D., Department of Molecular Reproduction, Development and Genetics Indian Institute of Science, Bangalore, India

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 project funds enabled me to hire a new postdoctoral associate, Sayanti Saha, who was then able, based on preliminary data from this project, to obtain a grant from the DOD that allowed us to expand and continue the project.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes____X____ No____ _____

If yes, please describe the collaborations:

Collaborations initiated with Dr. David Speicher, Wistar and Dr. Steve Seeholzer, Children's Hospital of Philadelphia.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No_____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No____X_____

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

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

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the 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 Aim 1: Define the mechanism(s) by which SUMO (small ubiquitin-like modifier) modification regulates PTP1B activity.

We had previously shown that PTP1B is sumoylated on at least two sites (K335 and K347) and that sumoylation inhibited PTP1B activity (Dadke et al, NCB, **9**:80-85, 2007). We then used a variety of cell biology methods to determine the location of sumoylated PTP1B, which, in turn, has given clues as to its function.

Using both imaging and biochemical fractionation methods, we found that sumoylated PTP1B is found predominantly at an unexpected location, the inner nuclear membrane. This finding prompted us to examine if PTP1B interacts with phosphotyrosyl proteins in the inner nuclear membrane. We found that PTP1B interacts with the inner nuclear membrane proteins emerin, a lamin-binding protein that is associated with the X-chromosome-linked Emery-Dreifuss muscular dystrophy (EDMD). Several tyrosine phosphorylation sites on emerin have been identified. One tyrosine residue, Y95, is of particular interest, as small deletions that include this tyrosine residue (Δ95-99) have been found in emerin in human EDMD. To ask if PTP1B interacts with emerin, PTP1B was immunoprecipitated from a HeLa cell lysate and probed with anti-emerin antibodies. Using MEFs, we found that emerin co-immunoprecipitates with PTP1B and with a known partner, lamin A/C, but not with control IgG (Fig. 4A, Yip et al, JCS, in press). Interestingly, the same degree of binding was observed in pervanadate-treated cells and in cells transfected with catalytic inactive/ substrate trapping mutant of PTP1B (PTP1B-C215S mutant, data not shown). These results demonstrate that PTP1B and emerin interact and that this interaction requires neither phosphatase activity of PTP1B nor tyrosine phosphorylation of emerin.

To examine whether PTP1B regulates the tyrosine phosphorylation of emerin, we first asked if recombinant PTP1B could dephosphorylate emerin *in vitro*. We found that GFP-emerin, isolated from pervanadate treated cells, was readily dephosphorylated by recombinant PTP1B (data not shown). Next, we examined the levels of phosphotyrosyl emerin in cells expressing exogenous PTPT1B, PTP1B-CS or T7-SUMO-1. Expression of exogenous PTP1B reduced tyrosine phosphorylation of emerin, whereas expression of catalytic inactive mutant of PTP1B, PTP1B-CS, elevated tyrosine phosphorylation of emerin (Fig. 4B, Yip et al, JCS, in press). Interestingly, cells transfected with T7-SUMO-1 also showed increased emerin tyrosine phosphorylation. Given that sumoylation of PTP1B increases under such conditions, and that sumoylation inhibits PTP1B activity (Dadke et al., NCB, **9**:80-85, 2007), these results suggest that PTP1B may dephosphorylate emerin at the INM in a sumoylation-regulated manner.

To further demonstrate the role of PTP1B in tyrosine dephosphorylation of emerin, HeLa cells were stably transfected with a scrambled shRNA or shRNAs designed specifically to knock down PTP1B, and measured the tyrosine phosphorylation level of emerin in these cells. Scrambled shRNA had no effect on PTP1B protein levels, while one out of the two PTP1B shRNAs significantly reduced the PTP1B expression (Fig. 4C, Yip et al, JCS, in press). Lysates from the knockdown cells were subject to pTyr immunoprecipiatation and anti-emerin immunoblotting. We found that the tyrosine phosphorylation level of emerin was reciprocal to PTP1B expression level; reduced PTP1B correlated with increased PTyr-emerin (Fig. 4C, Yip et al, JCS, in press).

Sumoylation of PTP1B is associated with elevated levels of phosphotyrosyl emerin.

Since sumoylation is known to inhibit PTP1B activity (Dadke et al., 2007), we asked if sumoylation of PTP1B affects emerin tyrosine phosphorylation. HeLa cells were transfected with HA-PTP1B-WT or HA-PTP1B-K4R alone or in combination with T7-SUMO-1, followed by measurement of the relative tyrosine phosphorylation level of emerin in these cells. As expected, we found that PTP1B-WT, but not the PTP-K4R mutant, was sumoylated when the cells were co-transfected with T7-SUMO-1 (Fig. 5, Yip et al, JCS, in press). To measure the tyrosine phosphorylation level of emerin, cell lysates were subjected to anti-pTyr (PY20) immunoprecipitation followed by anti-emerin immunoblot. Cells expressing PTP1B-WT plus T7-SUMO showed markedly increased tyrosine phosphorylation of emerin (Fig. 5, Yip et al, JCS, in press), whereas cells expressing a non-sumoylatable form of PTP1B (PTP1B-KR), showed much lower levels of emerin tyrosine phosphorylation (Fig. 5, Yip et al, JCS, in press), suggesting that PTP1B regulates the tyrosine phosphorylation of emerin in a sumoylation-dependant manner.

Sumoylation of PTP1B is regulated in a cell-cycle dependent manner, correlating with tyrosine phosphorylation of emerin.

We have previously shown that PTP1B sumoylation can be augmented by growth factors such as insulin (Dadke et al., 2007). To determine if intrinsic signals regulate SUMO modification of PTP1B, we asked whether PTP1B sumoylation levels change during the cell cycle. We transfected *Ptp1b*-null MEFs with PTP1B-WT and T7-SUMO-1, and synchronized the cell cycle using thymidine treatment, followed by a release to overnight nocodazole block to achieve G2/M arrest. These mitotically blocked cells were then washed and released into nocodazole-free media for indicated time, and cell lysates were subjected to anti-PTP1B immunoprecipitation followed by anti-T7 immunoblot. We found that PTP1B sumoylation markedly increases as the cells enter mitosis (Fig. 3, Yip et al, JCS, in press). Upon release from mitotic block, PTP1B sumoylation levels drop to a low level within 30 min. These results show that PTP1B sumoylation is temporally regulated in a cell-cycle dependent manner. Interestingly, the tyrosine phosphorylation levels of emerin follow a similar pattern: increasing in mitotic cells and reverting to basal levels as cells exit mitosis into G1 (Fig. 6, Yip et al, JCS, in press).

Specific Aim 2: Determine the role(s) of PTP1B in ErbB2 signaling.

We have shown that PTP-1B has a paradoxical positive effect on HER2-induced transformation of human breast epithelial cells. Using human breast epithelial MCF-10A cells grown in a three-dimensional matrix, we found that PTP-1B, but not the closely related enzyme T-cell PTP, is required for ErbB2 transformation *in vitro*. Activation of ErbB2, but not ErbB1, increases PTP1B expression, and increased expression of PTP1B activates Src and induces a Src-dependent transformed phenotype. Activation of Src by PTP1B depended on the SH3-binding motif located in the C-terminus of PTP1B. These findings identify a molecular mechanism by which PTP1B links an important oncogenic receptor tyrosine kinase to signaling pathways that promote aberrant cell division and survival in human breast epithelial cells. Our paper describing these results was published in Cancer Research (Arias-Romero et al, *Cancer Res.* **69**:4582-4588, 2009) and is described below.

To establish the functions of PTP1B in human breast epithelial cells, we examined the effects of this phosphatase in ErbB2 signaling in MCF-10A cells grown in three-dimensional conditions. MCF-10A cells are immortalized, nontransformed cells derived from a reduction mammoplasty, which form organized acini when grown within three-dimensional matrices such as reconstituted basement membrane. In MCF-10A cells that stably express an AP1510-activatable, chimeric form of ErbB2 (10A.ErbB2 cells), treatment with AP1510 caused characteristic changes in acinar morphogenesis, proliferation, and luminal apoptosis, resembling those seen in human ductal carcinoma of the breast. Using siRNA to knockdown endogenous PTP-1B, we had found (in 2008) that this phosphatase is required for the phenotypic effects of ErbB2 on acinar development.

To supplement these siRNA data using an independent approach, in 2009, we carried out similar experiments using two different, highly specific small-molecule inhibitors of PTP1B, compounds II and III. Compounds II and III are cell-permeable analogues of the most potent and selective PTP1B inhibitor reported to date, which displays a Ki value of 2.4 nmol/L for PTP1B and exhibits several orders of magnitude of selectivity in favor of PTP1B against a panel of PTPs. As with siRNA, chemical inhibition of PTP-1B suppressed the multiacinar effects of ErbB2 (Fig. 1B, Arias-Romero, Can Res 69:4582-4588, 2009). Together with the siRNA data, these experiments show that PTP1B function is required by ErbB2 to induce a multiacinar phenotype. Molecular pathways affected by PTP1B in MCF-10A cells. We next tested if PTP1B links ErbB2 to Src in MCF-10A cells. First, we assessed Src activity in response to ErbB2. Three-dimensional cultures of 10A.ErbB2 cells were treated with AP1510 and Src activity assessed by immunoblot using phosphospecific antibodies directed against Tyr416 in Src. As expected, activation of ErbB2 induced activation of Src (Fig. 3, Arias-Romero, Can Res 69:4582-4588, 2009). In contrast, in cells treated with siRNA against PTP1B, or a small molecule PTP1B inhibitor, Src activation by ErbB2 was markedly suppressed as assessed by decreased Tyr416 and increased Tyr527 phosphorylation (Fig. 3, Arias-Romero, Can Res 69:4582-4588, 2009). Similar results were seen regarding two other important signaling molecules that are activated by Src, Akt and ERK. Also, the effects of PTP1B on ErbB2 signaling were not confined to 10A.ErbB2 cells. As in 10A.ErbB2 cells, addition of the specific PTP1B inhibitor compound II to the ErbB2-expressing human breast cancer cell lines BT-474, MDA-MB-231, or SUM190 resulted in marked loss of ERK activity.

Activated Src bypasses the requirement for PTP1B in ErbB2-mediated transformation. Treatment of 10A.ErbB2 cells with the Src inhibitor PP2 blocked the effects of ErbB2 activation on acinar morphology (Fig. 4, Arias-Romero, Can Res 69:4582-4588, 2009). If Src activation downstream of ErbB2 and PTP1B mediates the effects of ErbB2 on signal transduction, then a constitutively active form of Src should bypass the need for either ErbB2 or PTP-1B in signaling, and loss of Src should block the actions of these enzymes. We transduced 10A.ErbB2 cells with SrcY527F, which lacks the inhibitory site of tyrosine phosphorylation in the COOH terminus and is therefore constitutively active. These cells display aberrant acini and elevated Akt and ERK activity even in the absence of activated ErbB2 (Fig. 4, Arias-Romero, Can Res 69:4582-4588, 2009). In addition, these effects were also seen in Src-expressing cells treated with an inhibitor of PTP1B. Overexpression of

PTP1B distorts acinar development via activation of Src. Interestingly, we found that the expression level of PTP1B increased markedly after treatment with AP1510 (Fig. 5, Arias-Romero, Can Res 69:4582-4588, 2009). Similar results were seen in MCF-7 cells expressing the same AP1510-activatable form of ErbB2 (data not shown), indicating that the effects on PTP1B are not confined to a single type of breast epithelial cell line. These results are in line with previous observations that ErbB2-transformed cells have elevated PTP1B expression and suggest a causal relationship between these events. In contrast, PTP1B expression was not altered in 10A.ErbB1 cells following activation of ErbB1, indicating that the effect on PTP1B expression was specific to ErbB2 and not a general response to growth stimuli.

If Src activation by PTP1B plays a role in ErbB2 signaling, then activation or overexpression of PTP1B should affect acinar development in a Src-dependent manner. To test this idea, we examined the effects of PTP1B overexpression in 10A.ErbB2 cells. These cells were infected with a retrovirus encoding no insert, wild-type PTP1B, PTP1B-PA (a mutant that cannot bind Src homology 3-domain containing proteins, including Src), or PTP1B-DA (a catalytically dead mutant). In all cases, 3-fold elevation in PTP1B expression was observed, comparable with the degree of PTP1B expression in cells following AP1510 treatment (Fig. 5, Arias-Romero, Can Res 69:4582-4588, 2009). Overexpression of wild-type PTP1B, but not the PTP1B mutants, was associated with a multilaminar phenotype (Fig. 5C, Arias-Romero, Can Res 69:4582-4588, 2009). The effects of wild-type PTP1B were blocked by the Src inhibitor PP2 (Fig. 5D, Arias-Romero, Can Res 69:4582-4588, 2009), consistent with the idea that Src represents a key target of PTP1B in breast epithelial cells

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, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

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

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

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

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Activation of Src by Protein Tyrosine Phosphatase (PTP)1B is required for ErbB2 transformation of breast epithelial cells.	Arias-Romero, L.E., Saha, S., Villamar, O., Yip, S.-C., Ethier, S.P., Zhang, Z-Y., and Chernoff, J.	*Cancer Res.*	06/2010	☐Submitted ☐Accepted ☑ Published
2. Sumoylated protein tyrosine phosphatase 1B localizes to the inner nuclear membrane and regulates the tyrosine phosphorylation of emerin	Yip, S.C., Cotteret, S., and Chernoff, J	*J. Cell Sci.*	07/2011	☐Submitted ☑ Accepted ☐Published
3.				☐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 plan to follow up the Arias-Romero Cancer Research paper with a study of the cancer relevant substrates of PTP1B in MCF10A-ErbB2 cells. This is being done by using phosphoproteomics to assess differences in tyrosine phosphorylation in ErbB2-transformed breast epithelial cells that lack or contain PTP1B, as manipulated by shRNA.

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.

While there is no direct impact as yet, we do expect that our findings will ultimately change our view, and perhaps our treatment of, certain forms of breast cancer. In particular, our work identifies two potential therapeutic targets in ErbB2-positive breast cancer: PTP1B itself, and the PTP1B target Src.

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.

As above, our major discovery was that PTP1B, acting through Src, is required for transformation by ErbB2. Both PTP1B and Src are suitable therapeutic targets; indeed, in the case of Src, clinical inhibitors already exist.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No____X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
   Yes_____ No____
   If yes, indicate number of patent, title and date issued:
   Patent number:
   Title of patent:
   Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

   If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

   If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No__X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

Biosketches are included for Drs. Chernoff, Chow, Saha, and Yip.

BIOGRAPHICAL SKETCH

Provide the following information for the 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
Chernoff, Jonathan, M.D., Ph.D.	Vice President, Scientific Director Stanley P. Reimann Chair in Oncology Research
eRA COMMONS USER NAME chernoff	

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
Yale College, New Haven, CT	B.A.	1978	Molecular Biophysics /Biochemistry
Mount Sinai School of Medicine, New York, NY	M.D., Ph.D.	1984	Biochemistry

A. PERSONAL STATEMENT

I have a background in both clinical medicine and in basic science. Following my M.D., Ph.D. training and my Internal Medicine Residency and Medical Oncology Fellowship, I trained in the area of signal transduction with Ray Erikson. At Fox Chase Cancer Center (FCCC), I serve as Co-Leader (with Joe Testa) of the Cancer Biology Program. My laboratory's overarching interest is in carcinogenesis, with a particular emphasis on phosphorylation-dependent signaling. We were the first to purposely clone a protein tyrosine phosphatase (PTP) and my group remains deeply engaged in oncogenic and tumor suppressor activities of this and similar PTPs. My laboratory's strengths are in signal transduction, cell biology, and mouse models of cancer.

B. POSITIONS

Resident, Dept. of Internal Medicine, University Health Center of Pittsburgh, PA	1984-1987
Clinical Fellow, Dept. of Med. Onc., The Johns Hopkins Oncology Center, Baltimore, MD	1987-1988
Clinical Fellow, Hematology/Oncology, Beth Israel Hospital, Boston, MA	1988-1990
Postdoctoral Fellow, Department of Cellular and Developmental Biology, Harvard University, Cambridge, MA	1988-1991
Assistant Professor, Fox Chase Cancer Center, Philadelphia, PA	1991-1997
Associate Professor, Fox Chase Cancer Center, Philadelphia, PA	1997-2002
Professor, Fox Chase Cancer Center, Philadelphia, PA	2002-present
Program Leader, Cancer Biology Program, FCCC, Philadelphia, PA	1999-present
Vice President, Deputy Scientific Director, FCCC, Philadelphia, PA	2008-2010
Stanley P. Reimann Chair in Oncology Research, FCCC, Philadelphia, PA	2008-present
Chief Scientific Officer, FCCC, Philadelphia, PA	2010-present

OTHER EXPERIENCE AND PROFESSIONAL MEMBERSHIPS

Journal of Biological Chemistry (2000-2005); Molecular Biology of the Cell (2006-present)

HONORS

B.S. cum laude, Yale University (1978); Pfizer Traveling Fellow 1992; Leukemia Society of America Scholar Award, (1997-2002); Dozor Lecturer, Ben-Gurion University of the Neg'ev, Israel (2007); Faculty of 1000 (2007-present); Chair, GRC "Mechanisms of Cell Signaling (2007); Stanley P. Reimann Chair in Oncology research (2008-present). American Cancer Society Southeast PA Division, Scientific Research Award (2010).

C. SELECTED PEER-REVIEWED PUBLICATIONS – CHERNOFF, Jonathan, M.D., Ph.D. *(from a total of 113 – H index = 47)*

1. **Chernoff, J.,** Schievella, A.G., Jost, C.J., Erikson, R.L., Neel, B.G. Cloning of the cDNA of a major human protein-tyrosine-phosphatase. *Proc. Natl. Acad. Sci. U.S.A.* **87**:2735-2739, 1990.
2. Ottilie, S., **Chernoff, J.,** Hannig, G., Hoffman, C.S., Erikson, R.L. A fission yeast gene encoding a protein with features of protein-tyrosine-phosphatases. *Proc. Natl. Acad. Sci. U.S.A.* **88**:3455-3459, 1991.
3. Ottilie, S., **Chernoff, J.,** Hannig, G., Hoffman, C.S. Erikson, R.L. The fission yeast genes *pyp1* and *pyp2* encode protein tyrosine phosphatases that negatively regulate mitosis. *Mol. Cell. Biol.* **12**:5571-5580, 1992.
4. Vambutas, V., Kaplan, D.R., Sells, M.A., **Chernoff, J.** NGF stimulates tyrosine phosphorylation and activation of SH-PTP1 in PC12 cells. *J. Biol. Chem.* **270**:25629-25634, 1995.
5. Liu, F., Hill, D.E., **Chernoff, J.** Direct binding of the proline rich region of Protein Tyrosine Phosphatase 1B to the Src homology 3 domain of $p130^{Cas}$. *J. Biol. Chem.* **271**:31290-31295, 1996.
6. Bandyopadhyay, D., Kusari, A., Kenner, K., Liu, F., **Chernoff, J.**, Gustafson, T.A., Kusari, J. Protein Tyrosine Phosphatase 1B binds to the insulin receptor *in vivo* and is tyrosine phosphorylated in the presence of insulin. *J. Biol. Chem.* **272**:1639-1645, 1997.
7. Liu, F., **Chernoff, J.** Protein tyrosine phosphatase 1B interacts with epidermal growth factor receptor in cultured cells. *Biochem. J.* **327**:139-145, 1997.
8. Liu, F., Sells, M.A., **Chernoff, J.** Transformation suppression by protein tyrosine phosphatase 1B requires a functional SH3-ligand. *Mol. Cell. Biol.* **18**:250-259, 1998.
9. Liu, F., Sells, M.A., **Chernoff, J.** Protein tyrosine phosphatase 1B negatively regulates integrin signaling. *Curr. Biol.* **8**:173-176, 1998.
10. **Chernoff, J.** Protein tyrosine phosphatases as negative regulators of mitogenic signaling. *J. Cell. Physiol.* **180**:173-181, 1999.
11. Dadke, S., Kusari, J., **Chernoff, J.** Down-regulation of insulin signaling by Protein Tyrosine Phosphatase (PTP) 1B is mediated by an N-terminal binding region. *J. Biol. Chem.* **275**:23642-23647, 2000.
12. Dadke, S., **Chernoff, J.** Interaction of protein tyrosine phosphatase (PTP) 1B with its substrates is influenced by two distinct binding domains. *Biochem. J.* **364**:377-383, 2002.
13. Dadke, S., **Chernoff, J.** Protein-tyrosine phosphatase 1B mediates the effects of insulin on the actin cytoskeleton in immortalized fibroblasts. *J. Biol. Chem.* **278**:40607-40611, 2003.
14. Li, S., Depetris, R.S., Barford, D., **Chernoff, J.**, Hubbard, S.R Crystal structure of a complex between protein tyrosine phosphatase 1B and the insulin receptor tyrosine kinase. *Structure* **13**:1643-1651, 2005.
15. Bartholomew, P.J., Jones, C.W., Benware, A., **Chernoff, J.**, LaFlamme, S.W. Regulation of the catalytic activity of PTB1B: roles for cell adhesion, tyrosine residue 66, and proline residues 309 and 310. *Exp. Cell Res.* **311**:294-306, 2005.
16. Dadke, S., Cotteret, S., Yip, S.-C., Jaffer, Z.M., Haj, F., Ivanov, A., Rauscher III, F., Shuai, K., Ng, T., Neel, B.G., **Chernoff, J.** Regulation of protein tyrosine phosphatase (PTP) 1B by sumoylation. *Nat. Cell Biol.*, **9**:80-85, 2007.
17. Arias-Romero, L.E., Saha, S., Villamar, O., Yip, S.-C., Ethier, S.P., Zhang, Z-Y., and **Chernoff, J.** Activation of Src by Protein Tyrosine Phosphatase (PTP)1B is required for ErbB2 transformation of breast epithelial cells. *Cancer Res* **69**:4582-4588, 2009.
18. Yip, S.C., Saha, S., Chernoff, J. PTP1B: a double agent in metabolism and oncogenesis. *Trends Biochem Sci*. **35**:442-449, 2010.

BIOGRAPHICAL SKETCH

Provide the following information for the 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
Hoi Yee, Chow, Ph.D.	Research Associate
eRA COMMONS USER NAME	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
The Chinese University of Hong Kong, China	B.S.	1997-2000	Biology
The Chinese University of Hong Kong, China	M.S.	2000-2003	Molecular Biology
The University of Hong Kong, China	Ph.D.	2003-2007	Medicine

A. PERSONAL STATEMENT

Since my father has been diagnosed and died of cancer, I decided to shift my research specialties from RNA study in plant biology to proteomic analyzing proteins that associated with anti-cancer drug resistance. At Fox Chase Cancer Center, I got an insight on the area of signal transduction in cancer related signaling with Dr. Jonathan Chernoff and these experiences launched my specialties further to translational research using transgenic mouse models to study the physiological effects of gene targeting with small molecule inhibitors. All graduate and postdoctoral trainings are able me to compose a relevant research plan and work on hypothesis-driven research.

B. POSITIONS

Teaching Assistant, Department of Biology, The Chinese University of Hong Kong, China	2002-2002
Technician, Department of Clinical Oncology, The Chinese University of Hong Kong, China	2002-2003
Research Assistant I, Department of Clinical Oncology, The University of Hong Kong, China	2006-2007
Teaching Associate, Department of Applied Science, The Hong Kong Institute of Vocational Education	2007
Assistant Technical Manager, Department of Pathology, The University of Hong Kong, China	2007
Postdoctoral Associate, Fox Chase Cancer Center, Philadelphia, Pennsylvania	2007-2011
Research Associate, Fox Chase Cancer Center, Philadelphia, Pennsylvania	2012-date

HONORS AND AWARDS

Student Travel Award, Offered by University of California, San Francisco, CA	2005
Conference Grants for Research Students	2005-2006
Postdoctoral Traineeship Award (Department of Defense Neurofibromatosis Research Program)	2010-2012

C. PEER-REVIEWED PUBLICATIONS

1. **Chow, H.Y.**, Guan, X.Y., Sham, J.S.T. Identification of drug resistant proteins in nasopharyngealcarcinoma by proteomics. *Mol. Cell. Proteomics* **4**:S479, 2005.
2. Fu, L., Qin, Y.R., Xie, D., **Chow, H.Y.,** Ngai, S.M., Kwong, D., Li, Y., Guan, X.Y. Identification of Alpha-Actinin 4 and 67KDa Laminin receptor as stage-specific markers in esophageal cancer via proteomic approaches. *Cancer* **110**(12):2672-2681, 2007.
3. **Chow**, **H.Y.**, Sham, J.S.T., Zhang, M.Y. Chow, L.W.C. Chua, D.T.T., Ma, N.F., Xie, D., Bi, J.. Loo, W.T.Y., Fung, J.M.W., Yiu, C.C.P., Li, Y., Wang, Q. Zhan, W.H., Guan, X.Y. Increased expression of Annexin I provide the drug-resistant ability in a cisplatin-resistant NPC cell line. *Proteomics Clin. Appl.* **3**(6): 654-662, 2009.
4. Fung, W.Y., **Chow, H.Y**., Law, T.W., Dong, B., Kwan, H.S. Development of a low-cost PCR-based method for studying differentially expressed genes in developing rice leaves. *Journal of Integrative Plant Biology* **51**(6): 614-621, 2009
5. **Chow, H.Y**., Stepanova, D., Koch, J.N., Chernoff, J. p21-activated kinases are required for transformation in a cell-based model of Neurofibromatosis type 2. *PLoS One* **5**(11):e13791, 2010
6. **Chow, H.Y**., Jubb, A.M., Koch, J.N., Jaffer, Z.M., Stepanova, D., Campbell, D.A., Duron, S.G., O'Farrell, M., Cai, Q., Klein-Szanto, A.J., Gutkind, J.S., Hoeflich, K.P., Chernoff, J. p21-activated kinase 1 is required for tumor formation and progression in a Ras-mediated skin cancer model. Submitted to PNAS, 2012

BIOGRAPHICAL SKETCH

Provide the following information for the 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
Sayanti Saha, Ph.D.	Postdoctoral Associate
eRA COMMONS USER NAME (credential, e.g., agency login)	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Panjab University, Chandigarh (U.T.), India	B.S.	1998-2001	Biochemistry
M.S. University, Baroda, Gujarat, India	M.Sc.	2001-2003	Biotechnology
Indian Institute of Science, Bangalore, India	Ph.D.	2003-2008	Biochemistry

A. PERSONAL STATEMENT

I completed my Ph.D. from Indian Institute of Science, Bangalore, India, where I specialized in the fields of protein biochemistry and cell biology. As a graduate student, I worked on signal transduction by receptor guanylyl cyclases and cGMP signaling. At present, I am undergoing postdoctoral training in the laboratory of Dr. Jonathan Chernoff at the Institute for Cancer Research (ICR) in Fox Chase Cancer Center (FCCC), Philadelphia. My interest in signaling pathways underlying the progression of cancer encouraged me to join FCCC. Under the guidance of Dr. Chernoff, I expect to get high-quality research training, and generate important, interesting, and clinically relevant publications. The primary focus of my postdoctoral work is to understand the role of protein tyrosine phosphatase 1B (PTP1B) mediated signaling pathways in breast cancer. The expertise and training that I have already gained during my Ph.D. along with an additional postdoctoral training will help me develop the skills and build up my knowledge in order to pursue a successful career in cancer research.

B. POSITIONS

Postdoctoral Associate, Fox Chase Cancer Center, Philadelphia, PA	2008-present
Graduate Researcher, Indian Institute of Science (IISc), Bangalore, Karnataka, India	2003-2008

HONORS

Minaxi Lalit Science Awards, Gujarat Science Academy, Ahmedabad, India	2001 & 2002
University Grants Commission-National Eligibility Test Lectureship	2002
Scientific Officer, Bhabha Atomic Research Centre, Mumbai, India	2003
Scholarship for Graduate Studies, Indian Institute of Science, Bangalore, India	2003-2008
Postdoctoral Fellowship from Department of Defense (DOD)	2010-2013
Best Ph.D. Thesis Award	2009
Graduate Studies Scholarship, Indian Institute of Science (IISc)	2003-2008
Travel Fellowship, Department of Science & Technology, India	2007
Travel Fellowship, Council for Scientific & Industrial Research, India	2007

C. PEER-REVIEWED PUBLICATIONS

1. Basu, N., **Saha, S.,** Visweswariah, S.S. Signaling via guanylyl cyclase C: cGMP, Src and P21. BMC Pharmacology, 2011
2. Yip, S.C., **Saha, S.,** Chernoff, J. PTP1B: A double agent in metabolism and oncogenesis. Trends Biochem Sci. 35(8):442-449, 2010.
3. Arias-Romero, L.E., **Saha, S.,** Villamar-Cruz, O., Yip, S.C., Ethier, S.P., Zhang, Z.Y., Chernoff, J. Activation of Src by protein tyrosine phophatase 1B is required for ErbB2 transformation of human breast epithelial cells. Cancer Res. 69:4582-4588, 2009.
4. **Saha, S.,** Biswas, K.H., Kondapalli, C., Isloor, N., Visweswariah, S.S. The linker region in receptor guanylyl cyclases is a key regulatory module: mutational analysis of guanylyl cyclase E. J. Biol. Chem. 284:27135-27145, 2009.
5. **Saha, S.,** Ramakrishnan, P., Viswewariah, S.S. "That which we call a rose by any other name would smell as sweet": How the Nose knows! *Resonance* 10:28-34, 2005
6. Jaleel, M., **Saha, S.**, Shenoy, A.R., Visweswariah, S.S. The kinase homology domain of receptor guanylyl cyclase C: ATP binding and identification of an adenine nucleotide sensitive site. *Biochemistry* **45**:1888-1898, 2006.

BIOGRAPHICAL SKETCH

Provide the following information for the 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
Yip, Shu-chin Jenny, Ph.D.	Research Scientist
eRA COMMONS USER NAME SCJYIP	

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
Albert Einstein College of Medicine, Bronx, NY	Ph.D.	2005	Biomedical Science
SUNY Binghamton University, Binghamton, NY	B.S.	1998	Biochemistry

A. Personal Statement

Obesity, diabetes and cancers are the growing epidemics that stride a lot of research interest in the discovery and the development of a drug-able target to eliminate the threats of diseases. My research focus is not to find the magic pill, but has been focused on the understanding of the signal pathways leading to the pathogenesis of these human diseases. An essential part of graduate and postdoctoral trainings is to be able to compose a relevant research plan, and be able to direct a hypothesis-driven research.

My research specialties has been evolved from cell-based assays analyzing growth factor/receptor mediated tumor metastasis/oncology to translational research using transgenic mouse models to study the physiological effects of gene targeting, small molecule inhibitors, and dietary restriction on the particular sets of metabolic and cancer related signalings. I have implemented and executed project protocols for identification and validation of these biomarkers, which will facilitate the discovery and development of therapeutic treatments in obesity, diabetes and cancers.

B. Positions and Honors

Research Scientist, Venenum Biodesign	10/11 – present
Postdoctoral Associate, Fox Chase Cancer Center	4/06 – 10/11
Research Technician, Albert Einstein College of Medicine	8/98 – 8/00
Summer Research Assistant, CUNY Queens College	6/95 – 8/95

Academic and Professional Honors

Howard Hughes Medical Institute, Undergraduate Summer Research	1995
Keystone Associate, Cell Migration and Adhesion Scholarship	2005

C. Publications

1) **Yip, S.C.,** S. Cotterret, and Chernoff, J. (2011). Sumoylated protein tyrosine phosphotase 1B localized to the inner nuclear membrane and regulates the tyrosine phosphorylation of emerin. *J Cell Sci (Epub ahead).*

2) **Yip, S.C.,** Saha, S. and Chernoff, J. (2010). PTP1B: a double agent in metabolism and oncogenesis. *Trends Biochem Sci* **35**, 442-9.
3) Arias-Romero, L.E., S. Saha, O. Villamar-Cruz, **S.C. Yip**, S.P. Ethier, Z.Y. Zhang, and J. Chernoff. 2009. Activation of Src by protein tyrosine phosphatase 1B Is required for ErbB2 transformation of human breast epithelial cells. *Cancer Res*. 69:4582-8.
4) El-Sibai, M., Pertz, O., Pang, H., **Yip, S.C**., Lorenz, M., Symons, M., Condeelis, J.S., Hahn, K.M., and Backer, J.M. (2008). RhoA/ROCK-mediated switching between Cdc42- and Rac1-dependent protrusion in MTLn3 carcinoma cells. Exp Cell Res *314*, 1540-1552.
5) **Yip, S.C.,** Eddy, R.J., Branch, A.M., Pang, H., Wu, H., Yan, Y., Drees, B.E., Neilsen, P.O., Condeelis, J., and Backer, J.M. (2008). Quantification of PtdIns(3,4,5)P(3) dynamics in EGF-stimulated carcinoma cells: a comparison of PH-domain-mediated methods with immunological methods. Biochem J *411*, 441-448.
6) van Rheenen, J., Song, X., van Roosmalen, W., Cammer, M., Chen, X., Desmarais, V., **Yip, S.C.,** Backer, J.M., Eddy, R.J., and Condeelis, J.S. (2007). EGF-induced PIP2 hydrolysis releases and activates cofilin locally in carcinoma cells. J Cell Biol *179*, 1247-1259.
7) **Yip, S.C.,** El-Sibai, M., Coniglio, S.J., Mouneimne, G., Eddy, R.J., Drees, B.E., Neilsen, P.O., Goswami, S., Symons, M., Condeelis, J.S., and Backer, J.M. (2007). The distinct roles of Ras and Rac in PI 3-kinase-dependent protrusion during EGF-stimulated cell migration. J Cell Sci *120*, 3138-3146.
8) Dadke, S., Cotteret, S., **Yip, S.C**., Jaffer, Z.M., Haj, F., Ivanov, A., Rauscher III, F., Shuai, K., Ng, T., Neel, B.G., and Chernoff, J. (2007). Regulation of Protein Tyrosine Phosphatase (PTP) 1B by sumoylation. Nat Cell Biol. 9: 80-85. ***Featured article of the month.***
9) Shekar, S.C., H. Wu, Z. Fu, **S.C. Yip**, Nagajyothi, S.M. Cahill, M.E. Girvin, and J.M. Backer. 2005. Mechanism of Constitutive Phosphoinositide 3-Kinase Activation by Oncogenic Mutants of the p85 Regulatory Subunit. *J Biol Chem*. 280:27850-5.
10) **Yip, S.C**., M. El-Sibai, K.M. Hill, H. Wu, Z. Fu, J. Condeelis, and J.M. Backer. 2004. Over-Expression of the P110β But Not P110α Isoform of PI 3-Kinase Inhibits Motility in Breast Cancer Cells. *Cell Motility and the Cytoskeleton.* 59: 180-188.
11) Kempiak, S.J., **S.C. Yip**, J.M. Backer, and J.E. Segall. 2003. Local signaling by the EGF receptor. *J Cell Biol*. 162:781-7.
12) Mouneimne, G., L. Soon, V. DesMarais, M. Sidani, X. Song, S.C. Yip, M. Ghosh, R. Eddy, J.M. Backer, and J. Condeelis. 2004. Phospholipase C and cofilin are required for carcinoma cell directionality in response to EGF stimulation. *J Cell Biol*. 166:697-708.
13) Hill, K.M., Y. Huang, **S.C. Yip**, J. Yu, J.E. Segall, and J.M. Backer. 2001. N-terminal domains of the class ia phosphoinositide 3-kinase regulatory subunit play a role in cytoskeletal but not mitogenic signaling. *J Biol Chem*. 276:16374-8.
14) Hill, K., S. Welti, J. Yu, J.T. Murray, **S.C. Yip**, J.S. Condeelis, J.E. Segall, and J.M. Backer. 2000. Specific requirement for the p85-p110alpha phosphatidylinositol 3-kinase during epidermal growth factor-stimulated actin nucleation in breast cancer cells. *J Biol Chem*. 275:3741-4.
15) Christoforidis, S., M. Miaczynska, K. Ashman, M. Wilm, L. Zhao, **S.C. Yip**, M.D. Waterfield, J.M. Backer, and M. Zerial. 1999. Phosphatidylinositol-3-OH kinases are Rab5 effectors. *Nat Cell Biol*. 1:249-52.