Award Number: W81XWH-11-1-0731

TITLE: Modulation of Estrogen-Depurinating DNA Adducts by Sulforaphane for Breast Cancer

PRINCIPAL INVESTIGATOR: Dr. Li Yang

CONTRACTING ORGANIZATION: University of Pittsburgh
PITTSBURGH, PA 15213-3320

REPORT DATE: October 2012

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Sulforaphane (SFN), a bioavailable phytochemical found in young broccoli, is a potent inducer of detoxification enzymes such as NAD(P)H:quinone oxidoreductase (NQO1) and glutathione-S-transferase (GST) via the Kelch-like ECH-associated protein 1 (Keap1) - Nuclear Factor- E2-related factor (Nrf2) signaling pathway. To test the hypothesis that SFN may be an ideal chemoprevention agent to block estrogen-mediated carcinogenesis, we treated the ER-negative, nontumorigenic human breast epithelial MCF10A cell line with either vehicle or SFN (10µM) and E2 or 4-OHE2. Results show that NQO1 was up-regulated at the mRNA (~2fold), protein (~3fold) and activity levels (~3fold) by SFN treatment. Estrogen metabolites and depurinating DNA adducts in the cell culture medium were partially purified by solid phase extraction and then analyzed by UHPLC- ESI-MS/MS. Following E2 treatment, the depurinated adducts 4-OHE1/2-1-N3Ade and 4-OHE 1/2-1-N7Gua were significantly lower in SFN treated cells compared to vehicle (0.03±0.01 versus 0.07±0.02 pmole/10^6cell, p=0.0294); 4-OHE1/2-glutathione conjugates were significantly higher following SFN treatment (1.54±0.37 versus 0.83±0.19 pmole/10^6cell, p=0.0015) as were 4-OCH3E1/2 (5.36 ± 0.16 versus 1.81±0.20pmole/10^6cell,p<0.0001) levels. Following treatment with the proximate metabolite 4-OHE2, 4-OHE1/2-1-N3Ade and 4-OHE 1/2-1-N7Gua were again significantly lower in SFN treated cells compared to vehicle (0.59±0.11 versus 1.42±0.16 pmole/10^6cell, p=0.0028) while 4-OHE1/2-glutathione-conjugates (4.44±0.52 versus 0.87±0.03 pmole/10^6cell,p=0.0001) and 4-OCH3E4/12 levels were significantly higher (195.00±12.33 versus 58.05±1.77pmole/10^6cell, p<.00001).
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Introduction
My long-term career goal is to be a leader in basic and translational breast cancer research, and have an impact on the prevention of breast cancer. To achieve the goal of this journey, a valuable postdoctoral training in breast cancer research in a setting with experienced, well established investigators is very important. The BC103928 Postdoc Fellowship Award granted me the opportunity to deepen my understanding of the mechanisms and underlying role of estrogens in the process of carcinogenesis leading to breast cancer. The goal of this study is to investigate the modulation of estrogen-depurinating DNA adducts by sulforaphane for breast cancer chemoprevention. I am under the supervision of a Mandatory Career Development Committee composed of Dr. Thomas Kensler (mentor), Dr. Nancy Davidson (co-mentor), Dr. Bruce Freeman and Dr. Kala Visvanathan. With this training, I will gain further experience in cell culture, animal models, clinical samples, mass spectrometry and estrogen metabolism at University of Pittsburgh. In addition to learning laboratory techniques, I will attend local, national and international meetings and workshops, classes and seminars that relate to mass spectrometry and clinical trial methods and practice. I have the opportunity to receive guidance from both my meetings with the Career Development Committee and from communications with other senior experts in breast cancer research in the Department of Pharmacology such as Dr. Steffi Oesterreich and Dr. Adrian Lee. In summary, this is a comprehensive and personalized training program to ensure the highest productivity and to effectively facilitate my career goal of transitioning into an independent breast cancer researcher.

Body
In the past year, I have been working on research and training tasks according to the original schedule.
I have established a solid phase extraction method to partially purify estrogen metabolites and depurinating DNA adducts from cell culture medium. I have developed a UHPLC-MS/MS method to separate and quantify estrogen metabolites and depurinating DNA adducts and used this method to quantify levels in MCF-10A cell culture media treated with vehicle or sulforaphane and E2 or 4-OHE2.
Sulforaphane (SFN) is a potent inducer of detoxification enzymes such as NAD(P)H:quinone oxidoreductase (NQO1) and glutathione-S-transferase (GST) via the Kelch-like ECH-associated protein 1 (Keap1) - Nuclear Factor- E2-related factor (Nrf2) signaling pathway. NQO1 reduces the carcinogenic estrogen metabolite, Catechol Estrogen-3,4-Quinone (CE-3,4-Q), to catechols while GSTs detoxify it through nucleophilic addition. CE-3,4-Q can bind with DNA to form depurinating DNA adducts, leading to DNA damage via an estrogen receptor (ER) independent pathway. Thus, SFN may be an ideal chemoprevention agent to block estrogen-mediated carcinogenesis.
To test the above hypothesis, I have treated MCF10A cells with either vehicle or SFN (10 µM) and E2 (10µM) or 4-OHE2(10µM). The results show that NQO1 was up-regulated at the mRNA (~2fold), protein (~3fold) and activity levels (~3fold) by SFN treatment. Estrogen metabolites and depurinating DNA adducts in the cell culture medium were partially purified by solid phase extraction and then analyzed by UHPLC- ESI-MS/MS. Following E2 treatment, the depurinated adducts 4-OHE1/2-1-N3Ade and 4-OHE 1/2-1-N7Gua were significantly lower in SFN treated cells compared to vehicle (0.03±0.01 versus 0.07±0.02 pmole/10⁶cell, p=0.0294); 4-OHE1/2- glutathione-conjugates were significantly higher following SFN treatment (4.44± 0.52 versus 0.87±0.03 pmole/10⁶cell, p<0.0001) and 4-OCH3E1/2 levels were significantly higher (195.00±12.33 versus 58.05±1.77pmole/10⁶cell, p<.00001). In summary of the past one year work, SFN can modulate estrogen metabolism leading to diminished formation of estrogen-DNA adducts.
For the training tasks, I have completed task 1 and 2. I attended “TSQ Family Operations MASS Spectrometry training” at Thermo Scientific in 10/24/2011 – 10/27/2011 in Florida. I have also learned course “Clinical Trials: Methods and Practice” at Graduate School of Public Health in spring 2012 (auditing).

In addition to completing the research and training tasks according to the schedule, I have attended the 24th University of Pittsburgh Cancer Institute 2012 Scientific Retreat in June at Greensburg, PA. I also attended the University of Pittsburgh Cancer Institute 2012 Satellite Conference in June at Greensburg, PA.

Key Research Accomplishments

In the MCF-10A cell study, I found that SFN can modulate estrogen metabolism leading to diminished formation of estrogen-DNA adducts by up-regulating NQO1 and GST via Keap1-Nrf2 pathway. The manuscript is under preparation.

Reportable Outcomes

- 2012, the 1st place poster award for clinical/translational cancer research, the 24th University of Pittsburgh Cancer Institute 2012 Scientific Retreat, Greensburg, PA. Abstract: Modulation of estrogen metabolism and estrogen depurinating DNA adducts via activation of Nrf2 signaling by sulforaphane in human breast epithelial cells. (Poster). Yang, L; Zahid, M., Cavalieri, E.; Rogan, E., Kensler T.
- 2012, the 2nd place poster award in cancer epidemiology, prevention and control program, University of Pittsburgh Cancer Institute 2012 Satellite Conference, Greensburg, PA. Abstract: Modulation of estrogen metabolism and estrogen depurinating DNA adducts via activation of Nrf2 signaling by sulforaphane in human breast epithelial cells. (Poster). Yang, L; Zahid, M., Cavalieri, E.; Rogan, E., Kensler T.
- Poster presentation at Women’s cancer research center Retreat in Farmington, PA in Sep. 2012 (poster title: Modulation of estrogen metabolism and estrogen depurinating DNA adducts via activation of Nrf2 signaling by sulforaphane in human breast epithelial cells.)
- Invited oral presentation at UPCI seminar series in Pittsburgh PA in Sep, 2012 (Title: Pharmacological and genetic activation of Nrf2 signaling in MCF-10A cell for modulation of estrogen depurinating DNA adducts).
- One manuscript is under preparation (Title: Pharmacological and genetic activation of Nrf2 signaling in MCF-10A cell for modulation of estrogen depurinating DNA adducts.).
- Received the training in TSQ MASS SPECTROMETRY at Thermo
- Learned course - Clinical Trials: Methods and Practice
- Review papers for the following journals: Biomarker Insights; Carcinogenesis; Breast cancer: Basic and Clinical Research; Nutrition and Metabolic Insights; Clinical Medicine Insights: Women’s Health
- Judge for Intel International Science & Engineering Fair 2012. Pittsburgh, PA, USA

Conclusion

SFN can modulate estrogen metabolism leading to diminished formation of estrogen-DNA adducts via Keap1-Nrf2 pathway in breast epithelial cells. The findings support that SFN, a food-derived natural product, could be a novel breast cancer chemoprevention agent.

References

N/A

Appendices

See the attached.
Curriculum vitae

Li Yang, PhD.

July 2012
Li Yang, PhD.
Department of Pharmacology & Chemical Biology,
University of Pittsburgh School of Medicine,
Pittsburgh, PA, 15261
TEL: (412) 760-6249 (cell)
E-mail: liyang@pitt.edu

Education

PhD in Environmental Toxicology, 2010
Department of Environmental, Agricultural and Occupational Health
College of Public Health, UNMC, Omaha, NE, USA

PhD Dissertation
Estrogen metabolism and risk of breast cancer and prostate cancer: Detection of potential early biomarkers from case-control studies

M.S. in Biology, 2002
Department of Biology Science
College of Biology, China Agricultural University, Beijing, China

B.S. in Plant Protection, 1995 (plant pathology, pesticides)
Department of Horticulture
Inner Mongolia Agricultural University, Inner Mongolia, China

Working Experience
Postdoc. Associate, June 2010 - present:
Department of Pharmacology & Chemical Biology, University of Pittsburgh School of Medicine
PhD student, Aug 2004 – May 2010:
Department of Environmental, Agricultural and Occupational Health
College of Public Health, UNMC, Omaha, NE, USA
Research Associate, July. 2002 - Aug. 2004:
Department of Pesticide, School of Science, China Agricultural University, Beijing, China

**Honors/Awards**

2012, Award for the 1st place best poster presentation for clinical study, 24th University of Pittsburgh Cancer Institute Scientific Retreat 2012, Greensburg, PA.

2012, Award for the 2nd place best poster presentation, University of Pittsburgh Cancer Institute Satellite Conference 2012, Greensburg, PA.


2007-2010, UNMC graduate school, Fellowship Award

2009, Award for the 2nd place best abstract, American Association of Chinese in Toxicology (AACT), Baltimore, Maryland.

2009 Award for Graduate Student Travel Support for 2009 National Environmental Public Health Conference, Atlanta, GA.

2008, Award for the 3rd place poster presentation, 39th Midwest Student Biomedical Research Forum, Omaha, Nebraska.


2008, Representative of UNMC graduate students for International Student Research Forum. Omaha, Nebraska.

2007, Award for best poster presentation, Central States Society of Toxicology Meeting. Iowa City, Iowa.

2004, Special award for contribution to the pesticides research, Society of Pesticide Res., Beijing, China.

**Research Presentations**

breast epithelial cells. (Poster). **Yang, L;** Zahid, M., Cavalieri, E.; Rogan, E., Kensler T.


biomarkers for risk of prostate cancer: results from a case-control study. **Yang L**, Cavalieri E. L. and Rogan E. G.


Note: Even though the title of the above posters might be the same or similar, the contents of above posters are different because the sample size increased with time and all the data were presented with updated data.
Membership

- Active Member, American Association of Cancer Research (AACR), 2011-present
- Member, American Society for Mass Spectrometry, 2011-present
- Member, Women in Toxicology (WIT) SIG, 2010 – present
- Member, American Association of Chinese in Toxicology (AACT) Special Interest Group (SIG), 2009 - present
- Full Member, Society of Toxicology (SOT), 2011 – present
- Graduate student SOT member, 2008 - 2011

Publication

Yang L, Kensler T, Cavalieri E., Rogan E., Zahid M. Pharmacological and genetic activation of Nrf2 signaling in MCF-10A cell for modulation of estrogen depurinating DNA adducts. (in preparation).


Research and Laboratory Skills

- Chemical analysis: UPLC/MS-MS; HPLC; MALDI-TOF; Chiral pesticides separation
- Statistical software: PAWS; SPSS; SAS; Prizm
- Biology: Cell culture; western blotting; PCR; Animal model
- Epidemiology: design and execution of studies (cohort, case control, and cross-sectional studies); environmental epidemiology of cancer, epidemiological data analysis
- Purification of biological fluid samples (including serum, urine and cell culture medium)
- Solid phase extraction technique

Teaching Experience

- Teaching Assistant in the course: Plant cell anatomy (Sep. 2000 – May, 2001. China Agricultural University, 33 undergraduate student, major in plant protection)
- English teacher (Aug. 2000. – May, 2001, Peking PeiLi ZhiYe College, 30 undergraduate student, major in English)

Information Technology Skills

- Molecular Modeling software
- Microsoft Word, Excel, and PowerPoint
• Basic Internet skills

Invited Presentations

2008. Novel serum biomarkers for assessing breast cancer risk: results from a case-control study. For Breast Cancer Training Program at Eppley Cancer Center, UNMC, Omaha, NE.


Invited Reviews

2011-2012. Biomarker Insights. (Four times)
2011. Carcinogenesis (One time)
2011-2012. Breast cancer: Basic and Clinical Research (Three times)

Invited Judgment

Dear Li YANG:

This is your course confirmation! We would like to thank you for enrolling in the following course(s):

TSQ Family Operations
10/24/2011: 9:00 AM - 5:00 PM
10/25/2011: 9:00 AM - 5:00 PM
10/26/2011: 9:00 AM - 5:00 PM
10/27/2011: 9:00 AM - 5:00 PM

Location: West Palm Beach
1400 North Point Parkway Suite 10 West Palm Beach, Florida 33407
Room: Key Largo

Enrollment Status: Enrolled

Thank you! If you are paying by credit card, please call 1-800-532-4752.

Please note by the submission of your on-line Pre-Registration you agree to adhere to our cancellation, Weather Related and refund policy that is listed below:

Cancellation Policy:
- We reserve the right to cancel any course, 30 calendar days prior to the scheduled start date, due to insufficient enrollment.
- We reserve the right to change the venue of the course, 30 calendar days prior to the scheduled start date. Travel arrangements should not be made more than 30 calendar days in advance, as the venue is subject to change.
- In the event of a venue change, you will be notified by a Thermo representative. Thermo will not be responsible for expenses incurred (for example, non-refundable airline reservations) if the course is cancelled or moved.
- Cost for courses is quoted in U.S. dollars.
- Payment in full is due upon course commencement.
- Attendee substitutions may be made at any time (call us first to determine if course is appropriate).
- Enrollment in your desired training course(s) is not guaranteed until receipt of this form, the pre-course questionnaire (if applicable), and confirmed method of payment.

Weather Related Cancellation:
- We reserve the right to cancel any course, by 2pm Eastern time the Friday prior to the course start date.
- Thermo will not be responsible for expense incurred (for example, non-refundable airline reservations).
- If a customer arrives to the area in advance and the course is cancelled by 2pm Eastern the Friday prior to the course start date, Thermo is not responsible for expenses incurred.
- For weather advisories, please contact us at 800-532-4752 and speak directly with the registrar.

Refund Policy:
- 100% refund for cancellations received 15+ business days prior to course date.
- 50% refund for cancellations received 10-15 business days prior to course date.
- No refund for cancellations received fewer than 10 business days prior to course date.
- No refund for no-shows.

If you have any questions or need further information please feel free to contact us.
BIOSTATISTICS 2062

Clinical Trials: Methods and Practice

Lecture Schedule
Spring Term, 2012 (12-2)
Class Times: Thursday, 9:00 am - 11:50 am
Room: A425 Crabtree Hall, GSPH

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Spring Break - March 5-9, 2012

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Dear Li Yang,

It was a pleasure to have you in the class. Your contributions as an auditor were important. I hope that you will keep in touch and let me know about how your career and other activities progress over time. If you should need a statistical collaborator or consultant at some time in the future, please feel free to contact me. If I am not able to assist directly, I will try to recommend someone to you.

Best wishes and warm regards,

Carol Redmond

Dr. Carol K. Redmond

Distinguished Service Professor of Public Health

318A Parran Hall, University of Pittsburgh

130 DeSoto Street

Pittsburgh, PA 15261

Telephone: 1-412-624-0765 Fax: 1-412-624-2183

http://www.biostat.pitt.edu/redmond.htm


rom: "Redmond, Carol K" <ckr3@pitt.edu>

Subject: RE: hello from li yang

Date: Fri, April 27, 2012 3:49 pm

To: "Yang, Li" <liyang@pitt.edu>
Welcome

Dear WOMEN'S CANCER RESEARCH CENTER MEMBERS:

We are pleased to invite you to attend the 2nd Annual WCRC Retreat on September 7 and 8, 2012 at Nemacolin Woodlands Resort (1001 Lafayette Drive, Farmington, PA). The goals of the Retreat are to showcase exciting research which is currently performed in labs of WCRC members, to further enhance interaction, and foster collaboration among the stimulating program in the area of women's cancer research, covering basic, clinical, and translational areas of investigations.

The Retreat will begin Friday September 7th at noon, with a presentation by Dr Lee, Director of the WCRC, entitled “Two years of WCRC - what have we accomplished?”. For the afternoon, we have scheduled presentations on breast and ovarian cancer topics (including presentations by last year's WCRC Pilot grant awardees). We will conclude with dinner and entertainment. The Keynote Address will be given by Dr Bill Hahn, Associate Professor, Department of Medicine, Harvard Medical School Cancer Genome Discovery, Dana-Farber Cancer Institute. Dr Hahn is an expert in cancer genomics (including breast and ovarian cancer), and high-throughput functional genomics.

Saturday session will include a short morning session for all and then interested faculty can participate in a brainstorming session dealing with programmatic issues.

We very much look forward to your attendance and participation in this retreat. We especially encourage you to bring students and fellows, as our trainees are so important in the current and future research endeavors! We will need to limit the number of attendees at the Retreat, and therefore encourage you to register soon. Should we reach that number, the Retreat committee will make decisions based on active participation in WCRC activities.

All information, including a preliminary program, and forms regarding the WCRC Retreat can be found at http://www.upci.upmc.edu/WCRC/retreat. Please use the abstract submission forms for this year's event. The deadline for registration (including abstract submission) will be July 10th at 5 pm. For questions regarding the Retreat, please contact Steffi Oesterreich, oesterreichs@upmc.edu.

Adrian V Lee, PhD
Director, WCRC

Bob Edwards, MD
Co-Director, WCRC
Congratulations! Your abstract has been accepted for display and presentation at the Women’s Cancer Research Center Retreat on September 7, 2012. You will be notified of your poster number the week before the retreat.

If you have any questions regarding your abstract submission or the UPCI Scientific Retreat, please contact Kathleen Pater at kpater@magee.edu.
Dear Li, Erica and Qingming,

As the winners of the Clinical Science Poster competition that was held during this year's UPCI retreat, Dr. Nancy Davidson invites you to participate in our UPCI seminar series. You are each invited to deliver a 15 minute oral presentation at noon on 25th September 2012.

Dr. Davidson will introduce you personally. I suggest we use the following order:

12.00-12.15
1st place: Li Yang et al. “Modulation of estrogen metabolism and estrogen depurinating DNA adducts via activation of Nrf2 signaling by sulforaphane in breast epithelial cells” (senior author Dr. Thomas Kensler)

12.20-12.35
2nd place: Erica Nakajima et al. “Diverse metabolite consumption by head and neck squamous cell carcinoma cells” (senior author Dr. Ben Van Houten)

12.40-12.55
3rd place: Qingming Fang et al. “Complex formation regulates the stability and degradation of PolB and XRCC1” (senior author Dr. Robert Sobol)

I am copying Dr. Freeman because I note that the Department of Pharmacology and Chemical Biology is well represented, to say the least, in these winning posters.

Please save this date for your seminar presentation.

Sincerely,

Chris Bakkenist
Invited review Records:

From: "Jan McIver" <jan.mciver@la-press.com>
Subject: Your Completed Peer Review
Date: Mon, July 9, 2012 7:00 pm
To: liyang@pitt.edu

Dear liyang,

On behalf of the Editor in Chief as well as the authors, I would like to thank you for completing your review for Combining mTOR Inhibitors With Chemotherapy and Other Targeted Therapies in Advanced Breast Cancer: Rationale, Clinical Experience, and Future Directions.

The effort you have put into this is most appreciated by us and will be of great value to the authors.

Completing the peer reviewer survey takes less than one minute of your time. Your responses will be anonymous.

Complete the 2 minute survey:

Regards,
Jan

Libertas Academica
la-press.com
(+64-9) 476-3930

From: "Jan McIver" <jan.mciver@la-press.com>
Subject: You Are Invited to Review a Paper [10071]
Date: Tue, June 26, 2012 10:47 pm
To: liyang@pitt.edu

Dear Dr liyang,

I would like to invite you to undertake a peer review of "Combining mTOR Inhibitors With Chemotherapy and Other Targeted Therapies in Advanced Breast Cancer: Rationale, Clinical Experience, and Future Directions", a manuscript submitted by Dr Yardley to Breast Cancer: Basic and Clinical Research.

If you are able to do this I need to receive your review comments by 09 July 2012. Please go to http://la-press.com/review.php?f=YDoXDA7oClKuiYZAnBdPA6YS71575 to accept or decline to undertake this review. Please also read the peer review guidelines in this email. The guidelines may be different to those of other journals.

Please confirm your willingness to undertake this review as soon as possible using
the link given above. If you have any questions please email me for assistance.

You were sent this invitation either because you have previously joined the journal's editorial board, peer reviewer pool or because you were identified as being suitable through Pubmed. If you do not want to receive further peer review invitations click here to opt-out: http://la-press.com/disable_peer_review.php?fp=zoom993&u=liyang2

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How to use My LA to undertake this peer review:
1. Click on the link above as soon as possible after receiving this email.
2. Click on "View Files" to access the abstract and check that you have the expertise to peer-review the paper.
3. Click on "Agree to Review" or "Decline to Review" the manuscript
4. Click "View Files" to read the manuscript files.
5. Click "Review" to write your review comments.

NB: Peer review comments can only be accepted online via My LA. We do not accept downloaded manuscript files that you have annotated or modified in any way.

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Before you start writing your peer review it is essential that you read the guidance here. The guidance is updated regularly:


Other information about the peer review process is available here:


Plagiarism:

All submissions are scanned with plagiarism detection software. If you become aware of plagiarism issues with the paper please inform me immediately and also include it in your report. The journal applies COPE guidelines on plagiarism.


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You may not have been aware of Breast Cancer: Basic and Clinical Research, which is a new journal. To learn more about it go to http://la-press.com/t.php?i=journalist.

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Dear Dr liyang

On behalf of the Editor in Chief as well as the authors, I would like to thank you for completing your review for Insulin-like growth factor 1 gene polymorphism and breast cancer risk among Arab Omani women: A case-control study.

The effort you have put into this is most appreciated by us and will be of great value to the authors.

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Subject: Your Completed Peer Review
Date: Wed, April 4, 2012 1:37 pm
To: liyang@pitt.edu

Dear Dr liyang

On behalf of the Editor in Chief as well as the authors, I would like to thank you for completing your review for Circulating immune complex levels are associated with disease severity and seasonality in children with malaria from Mali.

The effort you have put into this is most appreciated by us and will be of great value to the authors.

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Regards,
Jan
Dear Dr Liyang,

I would like to invite you to undertake a peer review of "Circulating immune complex levels are associated with disease severity and seasonality in children with malaria from Mali", a manuscript submitted by Dr Bolaji N. Thomas to Biomarker Insights.

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Dear Dr Liyang,

I would like to invite you to undertake a peer review of “The prognostic value of suPAR compared to other inflammatory markers in patients with severe sepsis”, a manuscript submitted by Mrs Gustafsson to Biomarker Insights.

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Subject: Your Completed Peer Review
Date: Tue, January 10, 2012 12:31 am
To: liyang@pitt.edu

Dear Dr liyang

On behalf of the Editor in Chief as well as the authors, I would like to thank you for completing your review for Evaluation of ischemia-modified albumin and C-reactive protein in type 2 diabetics with and without ketosis.

The effort you have put into this is most appreciated by us and will be of great value to the authors.

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Dear Dr liyang,

I would like to invite you to undertake the peer-review of "Evaluation of ischemia-modified albumin and C-reactive protein in type 2 diabetics with and without ketosis". This paper has been submitted by Dr Ma to Biomarker Insights.

If you are able to do this I need to receive your review comments by 09 January 2012.

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Dear Dr liyang,

On behalf of the Editor in Chief as well as the authors, I would like to thank you for completing your review for Safety profile of a dietary supplement containing 1,3-dimethylamylamine: a 10-week intervention study.

The effort you have put into this is most appreciated by us and will be of great value to the authors.

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Dear Dr liyang,

I would like to invite you to undertake the peer-review of "Safety profile of a dietary supplement containing 1,3-dimethylamylamine: a 10-week intervention study". This paper has been submitted by Dr Bloomer to Nutrition and Metabolic Insights.

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Subject: Your Completed Peer Review
Date: Tue, October 18, 2011 10:20 pm
To: liyang@pitt.edu
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From: "Jan Mciver" <jan.mciver@la-press.com>

Subject: You are invited to review a paper [8513]

Date: Mon, October 3, 2011 5:36 pm

To: liyang@pitt.edu

Dear Dr liyang,

I would like to invite you to undertake the peer-review of "Sustainable long-term delivery microRNA with polylysine nanoparticles for inhibition of breast cancer invasion". This paper has been submitted by Dr Jin to Breast Cancer: Basic and Clinical Research.

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From: carcinogenesis.editorialoffice@oup.com
Subject: Thank you for submitting your review of manuscript ID CARCIN-2011-00715.R1 for Carcinogenesis
Date: Mon, October 31, 2011 11:25 am
To: liyang@pitt.edu

31-Oct-2011

Dear Ms Yang

Thank you for reviewing manuscript CARCIN-2011-00715.R1 entitled "Catechol-<i>O</i>-methyltransferase-mediated metabolism of 4-hydroxyestradiol inhibits the growth of human renal cancer cells through the apoptotic pathway" for Carcinogenesis.

On behalf of the Editors of Carcinogenesis, we appreciate the voluntary contribution that each reviewer gives to the Journal. We thank you for your participation in the online review process and hope that we may call upon you again to review future manuscripts.

Yours sincerely
Dr Thomas Kensler
Editor
Carcinogenesis

From: carcinogenesis.editorialoffice@oup.com
Subject: Carcinogenesis MS - CARCIN-2011-00715
Date: Tue, August 30, 2011 1:41 pm
To: liyang@pitt.edu

30-Aug-2011
Dear Li:

A manuscript entitled "Catechol-O-methyltransferase-mediated metabolism of 4-hydroxyestradiol inhibits the growth of human renal cancer cells through the apoptotic pathway," with Dr Yuichiro Tanaka as corresponding author, has been submitted to Carcinogenesis, and we are writing to ask whether you could assess it for us. The abstract is shown below. We appreciate that there are many demands on your time, but would greatly value your evaluation of this article.

Could you please let us know whether you would be willing to review this paper for Carcinogenesis, bearing in mind that we would hope to receive the assessment within 2-3 weeks? If you are unable to review this manuscript, we would be grateful for any suggestions for suitable alternative referees, including senior members of your laboratory.

To record your reply automatically, click on the appropriate link below. Details of how to view the manuscript and submit your review will be e-mailed to you as soon as you have agreed.

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Alternatively, please reply by return e-mail to carcinogenesis.editorialoffice@oup.com within 24 hours if at all possible, so that we can continue to provide a timely review process for the research community.

Yours sincerely

Dr Thomas Kensler
Editor
Carcinogenesis

Catechol-O-methyltransferase-mediated metabolism of 4-hydroxyestradiol inhibits the growth of human renal cancer cells through the apoptotic pathway - CARCIN-2011-00715
Corresponding Author: Dr Yuichiro Tanaka
Contributing Authors: Chang, Inik; Liu, Jan; Majid, Shahana; Saini, Sharanjot; Zaman, Mohd; Yamamura, Soichiro; Shahryari, Varamah; Chiyomaru, Takeshi; Deng, Guoren; Dahiya, Rajvir; Tanaka, Yuichiro

Abstract

Long-term exposure to estrogen and its metabolites may play an important role in renal cell carcinogenesis. Catechol-O-methyltransferase (COMT) participates in the estrogen metabolism pathway by neutralizing toxic substances. Although reduced COMT activity has been suggested to be a risk factor for estrogen-associated cancers, no studies have investigated the biological significance of COMT in the pathogenesis of human renal cell cancers (RCC). We initially found that COMT levels are significantly decreased in human RCC tissues and cells suggesting it plays a suppressive role in tumor development. However, transient over-expression of COMT has no functional effect on RCC cell lines. In contrast, when cells over-expressing COMT are treated with its substrate 4-hydroxyestradiol (4-OHE\textsubscript{2}), growth is inhibited by apoptotic cell death. We also found that COMT over-expression combined with 4-OHE\textsubscript{2} induces up-regulation of growth arrest- and DNA damage-inducible protein \(\alpha\) (GADD45\(\alpha\)). We further show that down-regulation of GADD45\(\alpha\) by a siRNA-mediated approach inhibits cell death, indicating the essential role of GADD45\(\alpha\) in the underlying mechanism of COMT action in response to 4-OHE\textsubscript{2}. Finally, 4-methoxyestradiol (4-ME) fully reproduces the anti-proliferative function of COMT with 4-OHE\textsubscript{2} prevents RCC cell proliferation by enhancing apoptosis, and that GADD45\(\alpha\) plays a critical role in the COMT-mediated inhibition of RCC.
Thank you for agreeing to serve as a Grand Awards judge at the Intel International Science & Engineering Fair 2012. Please allow this email to serve as a reminder of your commitment as well as general information about the logistics of Tuesday, May 15 and Wednesday, May 16.

**SCHEDULE:**
Please remember that the time commitment for Grand Awards judging is from Tuesday, May 15, through the evening of Wednesday, May 16. We need you to register in the David L. Lawrence Convention Center no later than 5:00 pm on Tuesday.

Once registered, you should check-in at your category room, pick-up a category ribbon and then spend the time prior to 5:30 p.m. reviewing the projects within your category on the exhibit hall floor. The exhibit hall opens at noon with no finalists present. At 5:30 p.m. all judges will be asked to go back to their respective category rooms for a buffet dinner and brief orientation by the category co-chairs. There will then be a Welcome and training session for all judges from 6:30 - 8:00 p.m. in Hall A. Following this session, the co-chairs will meet their judges in the exhibit hall within their category area to distribute the specific judging interview schedules for the next morning.

On Wednesday, the Exhibit Hall will be open to judges at 7:00 a.m. and all judges are asked to report to their category rooms by 8:30 for final attendance verification and to receive their score cards. Judging and post-interview category deliberations will occupy all of Wednesday. The detailed schedule for your judging as well as the Judging Guide that explains the complete process is available on the SSP site at http://www.societyforscience.org/page.aspx?pid=290

**PARKING:**
Parking has been arranged for judges and volunteers on Tuesday and Wednesday at the Grand Street Parking Lot between 11th and 12th Streets and Penn and Liberty. A map is available at the website address above. Those that park will need to ask their category co-chair for a chaser card to provide when exiting the garage each day.

**MEALS:**
All meals will be provided from dinner Tuesday, breakfast-lunch-dinner Wednesday. These will be in the judge’s meeting area.

**QUESTIONS:**
Send all inquiries to: Judging@societyforscience.org

Thank you again for your commitment to science education and young scientists. We look forward to working with you.

Sincerely,

Chuck
24th Annual UPCI Scientific Retreat

POSTER ABSTRACTS

June 21-22, 2012

University of Pittsburgh at Greensburg
Modulation of estrogen metabolism and estrogen depurinating DNA adducts via activation of Nrf2 signaling by sulforaphane in human breast epithelial cells

Li Yang(1), Muhammad Zahid(2), Eleanor G. Rogan(2,3), Ercole L. Cavalieri(3), Thomas W. Kensler(1*)

1) Department of Pharmacology & Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15213; 2) Environmental, Agricultural and Occupational Health, College of Public Health, and 3) Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE 68198.

Sulforaphane (SFN) is a potent inducer of detoxification enzymes such as NAD(P)H:quinone oxidoreductase (NQO1) and glutathione-S-transferase (GST) via the Kelch-like ECH-associated protein 1 (Keap1)- Nuclear Factor- E2-related factor (Nrf2) signaling pathway. NQO1 reduces the carcinogenic estrogen metabolite, Catechol Estrogen-3,4-Quinone (CE-3,4-Q), to catechols while GSTs detoxify it through nucleophilic addition. CE-3,4-Q can bind with DNA to form depurinating DNA adducts, leading to DNA damage via an estrogen receptor (ER) independent pathway. Thus, SFN, a bioavailable phytochemical found in young broccoli plants, may be an ideal chemoprevention agent to block estrogen-mediated carcinogenesis. For this study we used the ER-negative, nontumorigenic human breast epithelial MCF10A cell line. MCF10A cells were treated with either vehicle or SFN (10 μM) and E2 or 4-OHE2. NQO1 was up-regulated at the mRNA (~2fold), protein (~3fold) and activity levels (~3fold) by SFN treatment. Estrogen metabolites and depurinating DNA adducts in the cell culture medium were partially purified by solid phase extraction and then analyzed by HPLC-ESI-MS/MS. Following E2 treatment, the depurinated adducts 4-OHE1/2-1-N3Ade and 4-OHE 1/2-1-N7Gua were significantly lower in SFN treated cells compared to vehicle (0.03±0.01 versus 0.07±0.02 pmole/106cell, p=0.0294); 4-OHE1/2-glutathione conjugates were significantly higher following SFN treatment (1.54±0.37 versus 0.83±0.19 pmole/106cell, p=0.0015) as were 4-OCH3E1/2 (5.36 ± 0.16 versus 1.81±0.20 pmole/106cell, p<0.0001) levels. Following treatment with the proximate metabolite 4-OHE2, 4-OHE1/2-1-N3Ade and 4-OHE 1/2-1-N7Gua were again significantly lower in SFN treated cells compared to vehicle (0.59±0.11 versus 1.42±0.16 pmole/106cell, p=0.0028) while 4-OHE1/2-glutathione-conjugates (4.44±0.52 versus 0.87±0.03 pmole/106cell, p=0.0001) and 4-OCH3E1/2 levels were significantly higher (195.00±12.33 versus 58.05±1.77 pmole/106cell, p<0.0001). Follow-up studies are examining the effects of genetic activation of Nrf2 signaling though disruption of Keap1 as well as targeted silencing of key metabolic genes. In conclusion, SFN can modulate estrogen metabolism leading to diminished formation of estrogen-DNA adducts.

Supported by DOD BCRP Postdoctoral Fellowship 103928.
Director's Award
for Scientific Excellence
University of Pittsburgh
Cancer Institute
2012 Scientific Retreat
1st PLACE POSTER AWARD
FOR CLINICAL/TRANSLATIONAL CANCER RESEARCH
Presented to
Li Yang
June 22, 2012
Annual UPCI Scientific Retreat
Satellite Conference

POSTER ABSTRACTS

June 20, 2012

University of Pittsburgh
at Greensburg
Modulation of estrogen metabolism and estrogen depurinating DNA adducts via activation of Nrf2 signaling by sulforaphane in human breast epithelial cells

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Sulforaphane (SFN) is a potent inducer of detoxification enzymes such as NAD(P)H:quinone oxidoreductase (NQO1) and glutathione-S-transferase (GST) via the Kelch-like ECH-associated protein 1 (Keap1) - Nuclear Factor- E2-related factor (Nrf2) signaling pathway. NQO1 reduces the carcinogenic estrogen metabolite, Catechol Estrogen-3,4-Quinone (CE-3,4-Q), to catechols while GSTs detoxify it through nucleophilic addition. CE-3,4-Q can bind with DNA to form depurinating DNA adducts, leading to DNA damage via an estrogen receptor (ER) independent pathway. Thus, SFN, a bioavailable phytochemical found in young broccoli plants, may be an ideal chemoprevention agent to block estrogen-mediated carcinogenesis. For this study we used the ER-negative, nontumorigenic human breast epithelial MCF10A cell line. MCF10A cells were treated with either vehicle or SFN (10 μM) and E2 or 4-OHE2. NQO1 was up-regulated at the mRNA (~2fold), protein (~3fold) and activity levels (~3fold) by SFN treatment. Estrogen metabolites and depurinating DNA adducts in the cell culture medium were partially purified by solid phase extraction and then analyzed by HPLC-ESI-MS/MS. Following E2 treatment, the depurinated adducts 4-OHE1/2-1-N3Ade and 4-OHE1/2-1-N7Gua were significantly lower in SFN treated cells compared to vehicle (0.56±0.03 pmole/100cells±0.00007 pmole/100cells). 4-OHE1/2-glutathione conjugates were significantly higher following SFN treatment (1.54±0.37 pmole/100cells versus 0.83±0.19 pmole/100cells) as were 4-OCH3E1/2 (5.36±0.46 pmole/100cells versus 1.81±1.04 pmole/100cells) levels. Following treatment with the proximate metabolite 4-OHE2, 4-OHE1/2-1-N3Ade and 4-OHE 1/2-1-N7Gua were again significantly lower in SFN treated cells compared to vehicle (0.59±0.14 pmole/100cells versus 1.42±0.16 pmole/100cells) while 4-OHE1/2-glutathione conjugates (1.36±0.03 pmole/100cells versus 0.69±0.09 pmole/100cells) and 4-OCH3E1/2 levels were significantly higher (195.00±2293 versus 5.96±1.72 pmole/100cells) in SFN treated cells. Follow-up studies are examining the effects of genetic activation of Nrf2 signaling though disruption of Keap1 as well as targeted silencing of key metabolic genes. In conclusion, SFN can modulate estrogen metabolism leading to diminished formation of estrogen-DNA adducts.

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