Department of Biological Engineering
MIT Superfund Research Program
Center for Environmental Health Sciences

June 25, 2023

Dr. Roger W. Giese
Dept. of Pharmaceutical Sciences
Northeastern University
Boston, MA 02115

Dear Roger,

I am writing to you about your proposed CaSe assay for DNA adductomics. Thank you for the information that you sent, and I enjoyed our recent phone conversation about it.

In a word, I find your assay to be exciting! In fact, we would use it today in our research involving animal studies with NDMA if it were available. The lack of detailed adduct information in these studies is a gap, and currently there is no good way to fill it. Indeed, throughout the world, many researchers are conducting animal or cell culture experiments in which DNA adductomics should be measured. This is a major application for your technology, in my opinion.

In regard to applications of your assay to cancer patients, I suggest that you first talk to oncologists, who can advise you and ultimately inform their patients.

For both animal and human studies, we need advances in discovery and measurement of DNA repair, a major theme in my laboratory. Your assay would enable adduct ratios to be measured, such as O^6MeG to N7MeG, that can change with certain variations in DNA repair. Various adducts could selected for ratioing to help define the repair status of a person, for example as a red flag to signal a repair deficiency. This in turn should help to guide drug dosage in chemotherapy, and impact lifestyle to help minimize cancer risk for an individual with compromised DNA repair, for example take advantage of chemoprevention as this area emerges.

About half of cancer patients receive radiation. It is important to give the right dose to optimally balance efficacy and toxicity. Testing a urine or blood sample by CaSe the day after treatment could provide a good assessment,

Your assay could lead to tort cases. For example, there are many ongoing cases due to contamination of drugs with nitrosamines. Cancer as an injury takes years to build up enough cases to go to court as you know. Your assay could provide immediate evidence of injury in the form of DNA adducts that establish an increased risk for cancer and thereby enable a toxic tort class action. Upstream your assay could help the pharmaceutical industry to minimize genotoxic contaminants in the first place in their drug products.

Department of Biological Engineering

There is a need for better assays for oxidative stress. A profile of urinary oxidative DNA adducts could be a valuable biomarker for this, especially if the adduct patterns help to define the tissue of origin. Tissues of course vary in their biochemistry, making this a reasonable hypothesis.

As you know, an advanced comet assay has emerged in recent years from my laboratory for assessing DNA damage in a high throughput and multiplexed way (now commercialized as the “CometChip” by Trevigen). Combining this assay with CaSe would be of great interest for us, and we would be delighted to work mutually on projects in this area, such as selecting chemotherapy, or adding scope to cohort studies of cancer incidence.

Our labs are nearby, and we share a research interest in common in the area of damage to DNA and its repair. I look forward to collaboration with you as your CaSe assay emerges.

Sincerely yours,

Bevin Engelward

Bevin P. Engelward, *Sc.D*.
Professor of Biological Engineering
Director, MIT Superfund Research Program
Center for Environmental Health Sciences
Department of Biological Engineering
Massachusetts Institute of Technology

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

David E. Fisher, M.D., Ph.D.

Chief, Department of Dermatology
Director, Melanoma Program, MGH Cancer Center
Director, Cutaneous Biology Research Center
Massachusetts General Hospital
Edward Wigglesworth Professor of Dermatology
Harvard Medical School
Bartlett Hall, Room 604
Boston, MA 02114
Telephone 617-643-5428
Fax 617-643-6588

April 26, 2023

Professor Roger Giese
ECRP, Northeastern University
Boston, MA 0215

Dear Roger,

I am writing to express my enthusiasm towards our continuing to study skin cancer with you by DNA adductomics. While COVID interrupted our studies, it is compelling to continue. Your emerging CaSe assay could bring on key advantages of testing very small amounts of skin (from people patch-painted with sunscreen prior to liposection, as we collaborated before, and obtained some interesting results), and providing global adduct detection. This would allow us to follow up reports in the literature that some sunscreens actually might contribute to increased cancer while also protecting against the harmful rays from the sun. Potentially the work could lead to safer sunscreens by knowing what impurities or ingredients to change in general or for certain people. Many people certainly tend to slather on lots of sunscreen on themselves and their children, and perhaps at least some, such as those having a defect in DNA repair, or with other complications, might be better off with a different sunscreen lotion. In principle, the CaSe assay could be powerful for studying this.

Please keep me informed, and looking forward to our continued collaboration.

Sincerely,

David E. Fisher

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

April 18, 2023

Dr. Roger Giese
Northeastern University
Boston, MA

Dear Roger,

I very much enjoyed our discussion about your emerging CaSe Test. As described, a successful CaSe Test would be a real asset in the broad field of environmental toxicology, with a great diversity of applications as you propose. The use of environmental chemical specific DNA adduct measurements in exposure, dose and risk analysis has been in stasis for the past decade and new methods are very much needed. One of the pioneers of this concept was Bernard Weinstein, who (along with many others) pushed the idea of this test. It is remarkable that 40+ years have gone by and still there is nowhere in the world where one can send a biosample and obtain a broad- scope DNA adductomics test: the Weinstein vision continues to be a unfulfilled. The recent train catastrophe in Ohio is an evident example of the use of such a metric. Our studies on the aflatoxin DNA adduct in urine were successful, as you know, but that was a single analyte test.

As we discussed, I especially advise you to get the CaSe Test into NHANES testing at the CDC (testing of 100K people every two years) to help build up the interpretation. A minor suggestion is to obtain cumulative samples (e.g. a urine every other day which are then, in part, pooled) to deal with episodic exposures as needed. Some of my initial, favorite applications for your CaSe Test: drug nitrosamines, first responders, toxic torts, dietary supplements, climate change wildfires, and cannabis safety. Further as mentioned before the application of this method to real-time disasters would be an enabler for public health.

Thank you for the invitation to collaborate. I accept with enthusiasm, and also hope that you will continue to count me as an advisor to your project.

Sincerely yours,

John D. Groopman, PhD
Edyth H. Schoenrich Professor in Preventive Medicine

John D. Groopman, Ph.D.
Edyth H. Schoenrich Professor of Preventive Medicine
Department of Environmental Health and Engineering
Johns Hopkins Bloomberg School of Public Health
Associate Director for Population Sciences
Sidney Kimmel Comprehensive Cancer Center
615 North Wolfe Street
Baltimore, MD 21205
Telephone: 410-955-3900; FAX: 410-955-0617
e-mail: jgroopm1@jhu.edu; web site: https://www.jhsph.edu/faculty/directory/profile/282/john-groopman

Memorial Sloan Kettering
Cancer Center

May 23, 2023

Dr. Roger Giese
Northeastern University
Boston, MA

Dear Roger,
We look forward to continuing our collaboration with you on monitoring chemotherapy by measuring DNA adducts with mass spectrometry. As before, the goal is to optimize personalized chemotherapy. Sufficient damage to DNA is needed to stop the cancer, but avoiding over-dosing that excessively raises the risk for side effects and secondary cancer is important. Towards this goal, the more practical and comprehensive assay that you have designed would be of great benefit.
Of initial interest are chemotherapeutics that target blood-based cancers. Examples of these drugs, in addition to melphalan treatment for multiple myeloma that we are continuing to study with you, are as follows: busulfan, treosulfan, and cyclophosphamide. We seek to test both blood (target tissue) and urine (convenience) in these studies. Indeed, it would be interesting to monitor remission by testing urine for oxidative DNA adducts arising from inflammation, as a red flag for return of the cancer.
Hopefully your method can be extended to chemotherapy for solid tumors. While it is unrealistic to expect many biopsy samples in this area (to furnish target tissues), liquid biopsy samples already are being studied for monitoring chemotherapy mainly for tissue cancers. Potentially such monitoring could become more specific by measuring the DNA adducts in the liquid biopsy samples. Here the ultrasensitivity of your new method would be important. We would be delighted to explore this area as well with you.
Please let me know when you are ready to receive more samples for measuring DNA adducts to improve chemotherapy.

Sincerely,

Gunjan L. Shah, MD MS
Assistant Attending Physician
Adult Bone Marrow Transplant Service
Memorial Sloan Kettering Cancer Center

530 East 74th Street
New York, NY 10021
T 646.608.3734 | F 929.321.8166

Dana-Farber Cancer Institute | HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Timothy R. Rebbeck, Ph.D.
Vincent L. Gregory, Jr. Professor of Cancer Prevention

Director
Zhu Family Center for Global Cancer Prevention
Harvard TH Chan School of Public Health

Director
Center for Cancer Equity and Engagement
Dana-Farber Harvard Cancer Center

Dana Building 1101, 450 Brookline Avenue
Boston, Massachusetts 02215-5450

T: 617.632.6128
F: 617.632.2270
E: Timothy_Rebbeck@dfci.harvard.edu

May 30, 2022

Roger Giese, PhD
Professor, Chemistry and Biomedical Science
Director, Environmental Cancer Research Program
Bouvé College of Health Sciences, Northeastern University
Boston, MA 02115

Dear Roger,

I am writing to express my great interest in the new technology that you have designed for DNA adductomics. I worked in this area early in my career and have maintained a keen interest in this topic because of its potential to become a significant tool in cancer prevention. The emphasis of your proposed technology to develop and implement an approach that can be used by epidemiologists and clinicians will have a great impact on the field.

I am pleased that we have started to collaborate, and I look forward to helping you to recruit participants from our patient population to facilitate your method development and application. I am enthusiastic about organizing epidemiological studies to evaluate DNA adductomics for personalized cancer prevention.

I also look forward to presenting a seminar for OneNIght, a group of cancer prevention specialists from the Boston area hospitals and academic centers. Best of luck with your grant proposal.

Sincerely,

Timothy R. Rebbeck, PhD
Vincent L. Gregory, Jr. Professor of Cancer Prevention

TRR/bf

Superfund Research Center
Oregon State University, 1011
Agriculture and Life Sciences
Building, Corvallis, Oregon 97331
P 541-737-3608
F 541-737-4371
Robyn.tanguay@oregonstate.edu

5/22/2023

Dr. Roger Giese
Northeastern University
Boston, MA

Dear Roger,
Thank you for attending my recent webinar on high through put toxicology studies using the zebrafish. I very much enjoyed learning about your emerging DNA adduct technology in a subsequent zoom conversation.

As you know, we do zebrafish exposure studies to model human exposures, towards a long-term goal of translating such discoveries to the clinic. We have exposed zebrafish to thousands of chemicals and mixtures including PAHs, dioxins, flame retardants, nicotine, pesticides, pharmaceuticals and complex environmental mixtures through the years. For a while we measured benzo[a]pyrene DNA adducts by ^{32}P-postlabeling in collaboration with Bill Baird, but, as you know, the assay is not specific. It was also onerous and slow, so we abandoned it. Currently we are using the functional assays of Bevan Engelward at MIT, but these assays also are not specific. We need to know adduct structures, not just that something has damaged the DNA.

The CaSe assay that you described would fill an enormous data gap in our research program. Not only would it enable us to learn what is happening in detail to the DNA in our experiments, but also to more fully characterize the exposures including their impact on the overall biology. Indeed, the entire field of exposure studies with animal and cell culture studies severely needs an assay with the properties of CaSe.

I look forward to collaboration with you when your assay emerges, and please keep me informed of your progress.

Sincerely yours,

Robyn Leigh Tanguay

Robyn Leigh Tanguay, Ph.D.
University Distinguished Professor
Director of the Superfund Research Program at Oregon State University