

Title for the project:

Discovery of novel expression of biomarkers for the evaluation of response to immunotherapy in bladder cancer

Name of Applicant: Dr. SAURABH GAYEN

Rank: Assistant Professor

Department: Chemistry & Physics

Total amount of funding requested: \$7500

Salary supplements for projects requiring summer work: \$6000

Cost of specialized supplies, research materials, and computer software: \$1500

Date of the application: January 15, 2021

Discovery of novel expression of biomarkers for the evaluation of response to immunotherapy in bladder cancer

Bladder cancer (BICa) is the sixth most commonly diagnosed cancer in men worldwide and the tenth when considering both the genders together [1]. Approximately 79,000 new cases of BICa are estimated in the United States in 2017, resulting in 16,870 deaths [2]. The standard treatment is transurethral resection of bladder tumors, followed by intravesical treatment with Bacillus Calmette–Guerin (BCG) or cisplatin based chemotherapy [3]. Despite advances in treatment, over the past decades treatment procedures for BICa remained relatively unchanged until the emergence of programmed cell death protein (PD-1) and programmed death ligand 1 (PD-L1) immune checkpoint therapies [4–6]. The USA FDA approvals of immunotherapy agents Atezolizumab, Nivolumab, Pembrolizumab, Avelumab, and Durvalumab represent a major paradigm shift in treating BICa. Immunotherapy has now emerged as an important treatment modality for BICa but progress towards developing novel biomarkers is a need of the hour. Standardized, reproducible biomarkers are needed to accurately guide treatment decisions to predict responders to immunotherapy. Next generation of predictive biomarkers for immunotherapy should involve targeted gene expression profile with particular attention to immune gene signatures [7].

The present study focuses to identify gene expression profiles that not only play a role in development of BICa tumors but has the potential to predict responsiveness towards Pembrolizumab based immunotherapy. Here, we will combine two publicly available microarray datasets GSE128959 [8] and GSE38264 [9], encompassing expression profiles of 10 normal bladder and 82 BICa tumor tissues, for comprehensive analysis of differential expression using the Transcriptome Analysis Console (TAC) Software (Thermo Fisher Scientific). Subsequently, Ingenuity Pathway Analysis (IPA, QIAGEN Redwood City, www.qiagen.com/ingenuity) and Gene Set Enrichment Analysis (**GSEA**) will help to delineate the essential cellular pathways involved in the development of this tumor. The expression of the identified critical genes will then be compared with the expression profile responsible for the responsiveness of the BICa patients towards Pembrolizumab immunotherapy. For this purpose, differential expression of the publicly available microarray dataset GSE111636 will be analyzed. Finally, expression of the identified markers will also be checked in the immune cells within the tumor microenvironment using the Cancer Genome Atlas (TCGA) datasets available for BICa patients [10].

References

1. Cancer Today (powered by GLOBOCAN 2018) IARC CancerBase No. 15; Ferlay, J.; Ervik, M.; Lam, F.; Colombet, M.; Mery, L.; Piñeros, M.; Znaor, A.; Soerjomataram, I.; Bray, F. (Eds.) IARC: Lyon, France, 2018; ISBN 978-92-832-0453-4.
2. Surveillance, Epidemiology, and End Results Program. SEER stat fact sheets: kidney and renal pelvis cancer. Bethesda: National Cancer Institute; 2017. at <http://seer.cancer.gov/statfacts/html/urinb.html>
3. Wołącewicz M., Hryniewicz R., Grywalska E., Suchojad T., Leksowski T., Roliński J., Niedźwiedzka-Rystwej P. Immunotherapy in Bladder Cancer: Current Methods and Future Perspectives. *Cancers (Basel)*. 2020 May 7; 12(5):1181.
4. Bellmunt J, Orsola A, Leow JJ, et al. Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014; 25(Suppl 3):iii40–8.

5. Milowsky MI, Rumble RB, Booth CM, et al. Guideline on muscle-invasive and metastatic bladder cancer (European Association of Urology guideline): American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol*. 2016; 34:1945–52.
6. Ghasemzadeh A, Bivalacqua TJ, Hahn NM, Drake CG. New strategies in bladder cancer: a second coming for immunotherapy. *Clin Cancer Res*. 2016; 22:793–801.
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8. Sjö Dahl G, Eriksson P, Patschan O, Marzouka NA et al. Molecular changes during progression from nonmuscle invasive to advanced urothelial carcinoma. *Int J Cancer* 2020 May 1; 146(9):2636-2647.
9. Maraver A, Fernandez-Marcos PJ, Cash TP, Mendez-Pertuz M et al. NOTCH pathway inactivation promotes bladder cancer progression. *J Clin Invest* 2015 Feb; 125(2):824-30.
10. Li T., Fu J., Zeng Z., Cohen D., Li J., Chen Q., Li B., X Liu SX. TIMER2.0 for analysis of tumor-infiltrating immune cells. *Nucleic Acids Res*. 2020 Jul 2; 48(W1):W509-W514.

Measurable goals and objectives

The objective of this research is to find out novel biomarker profiles. This will lead better immunotherapeutic treatment to improve survival and quality of life in Bladder cancer patients. Moreover, this will enhance our knowledge of human genomics and computational skills to tackle many more complex problems in future.

Time frame

We plan to start working on the project in Spring 2021 (4-6 hours a week) and then accelerate the work in the summer (40 hours a week for 2 months) and wrap up the proposed work by July 31, 2021.

How the project will enhance teaching and research at Lincoln University?

This project is interdisciplinary in nature. Faculties and students from different departments will get a flavor of interdisciplinary research that involves the knowledge of biological science and computational biophysics. Upon successful completion of the project, we will be able to write proposals to seek external funding that will eventually lead to more students getting involved in undergraduate research and will establish Lincoln University as one of the growing hub of research on computational biophysics. We can eventually offer a course on computational biophysics and many of our students will get an opportunity to learn new techniques in their undergraduate level.

How the success of the project will be measured?

The research outcome will be presented in a conference, published in conference proceedings and peer reviewed journals.

How, when, where, and with whom the project's outcome will be shared?

The results of this project will be presented before faculty colleagues and students in a seminar and a summary report of the project will be sent to the Center for Teaching and Learning at <http://www.lincoln.edu/departments/center-excellenceteaching-and-learning> for posting to the website.

Budget

Description	Time frame	Rate	\$ amount
Salary supplement from 06.01.2021 to 07.31.2021 of summer research work	2 months	\$3000 per month	\$6000
Software and computational support from Cancer genomics Lab, Sydney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA 19107	12 hours	\$125 per hour	\$1500
Total amount of funding requested			\$7500

(To be used only by the Applicant)

Name of the Applicant : Dr. Saurabh Gayen

Rank of the Applicant : Assistant Professor

Proposal Submission Date: 01/15/2021

Expertise Area : Theoretical condensed matter physics and computational biophysics

Prior FD Proposal Outcomes : N/A

Proposal Submission Term: Please circle one of the following

1. Spring 2021
2. Summer 2021
3. Fall 2021

Faculty Development Committee (FDC) Proposal