1. Background

Oral head and neck cancer (OHNC) burden is very high in Africa and there are limited multimodal tools for broad-based biomonitoring, detection, prevention, and risk stratification on the continent. Socioeconomic, geographical, linguistic, and political factors, *inter alia*, have posed barriers to oral health care access in Africa. The World Health Organization identified good oral health as a crucial component of overall health and wellbeing, and systemic diseases may present with oral diagnostic clues. Risk factors such as tobacco smoking, infections, unhealthy (sugary/fatty) diet and lifestyle, as well as alcohol consumption are important in OHNC development. Also, OHNC burden is usually grossly underestimated in African people and has been estimated in our work to represent about 10% of all cancers. Poor oral hygiene and possible human papillomavirus infection have been proposed as potential key etiological factors associated with oral cancer pathogenesis in some
Africa regions. Hence, our team (comprising of investigators from University of Cape Town (UCT) University of the Western Cape (UWC) in South Africa, and University of Missouri, USA (UM)), planned to establish and sustain a multidisciplinary HPV-OHNC project through the UM/UWC Linkage Program to develop innovative in-silico data science tools for prompt detection of HPV+ OHNC in African patients.

2. Investigative Team Architecture
We assembled a team of clinician-scientists, basic scientists, bioinformaticians and data scientists from the South African and the UM USA side.

From UWC, South Africa- Prof. Henry Adeola is a clinician-scientist, precision omics and systems biology expert who sees patients at risk for OHNC and has prior experience conducting omics biomarkers research in human subjects as well as histopathological and epidemiological studies of oral cancer. Prof. Amir Afrogheh is an oral and maxillofacial pathologist whose Ph.D. focused on elucidating the role of high-risk human papillomavirus (HR-HPV) in periocular cancers. He is the current Head of Department of Oral and Maxillofacial Pathology at UWC. Prof. Haly Holmes is an oral medicine specialist with a longstanding interest in oral premalignancy, OHNC, and salivary exosomes. She is an associate professor or oral medicine at UWC. Dr Hocine Bendou is a bioinformatics expert and a software/web developer at the South African National Bioinformatics Institute (SANBI), who which uses bioinformatics to develop pipelines for genomics analysis.

From UMSL, USA- Prof. James Bashkin is a highly experienced biological chemist with experience in human antiviral agent development for human papillomavirus, green chemistry, the chemistry of DNA recognition, and the use of pyrrole-imidazole polyamides to control gene expression, exert
allosteric control on DNA, and fight viral infections. Prof. Badri Adhikari is a computer scientist with extensive experience in bioinformatics, deep learning, and other artificial intelligence tools for molecular biology.

By working together and combining their expertise, all key investigators on the collaborative HPV-OHNC project have established a synergistic relationship that will lead to an exponential output. All 6 investigators have strong interest and input in the work, assuring that the goals can and will be met. This synergistic team leadership approach will accomplish more collectively than in isolation, through calculated joint efforts and placing a high value on diversity in thought, expertise, and experience.

3. Trip Aim
The trip which took place between 7th-24th March 2023 was aimed at professionally meeting with Professor James Bashkin and members of the Bashkin Laboratory to plan, discuss and execute key aspects of the HPV-OHNC project. Also, the trip was used to discuss and develop our presentation for the precision medicine conference at the university of the western cape which hosted a trilateral guest participation from the University of Ghent, Belgium, University of the Western Cape, South Africa, and the University of Missouri, USA.

4. Objectives
The objectives mapped out to deploy our collaborative HPV-ONHC research aims include:
(a)Establish an in-silico, network-based computational pipeline to mine publicly available genomic data from The Cancer Genome Atlas’ (TCGA) OHNC patient archives.
(b) Real-time PCR analysis of saliva samples for high-risk HPV-related DNA fingerprints in prospectively collected saliva samples.
(c) Integrate both data to develop a multimodal diagnostic algorithm.

5. Achievements

(i) **Pre-visit Activities**: The first virtual meeting was initiated by Professor Rodney Uphoff, who is the Director of the UMSAEP program. This meeting was used to establish linkage between the 2 universities and to discuss the projects. Thereafter, several zoom meetings were held between the UWC and UMSL teams to discuss the project logistics and work strands that will be achieved during the visits and those that will be ongoing beyond the visit. Fortunately, our project was considered positively by the UMSAEP, and this grant solidified our bilateral interaction. The first task that we took on before the UMSL visit was to jointly write a U01 National Institute of Health (NIH) Grant. The DS-I Africa U01 is a flagship grant for data science for health discovery and innovation in Africa and it is funded through the Fogarty international NIH initiative. It is captioned “Harnessing data science technologies to develop solutions to the continent’s most pressing public health problems”. Towards the funding call, our team proposed a project entitled “Developing a multimodal, integrative, in-silico, multiomics data science approach to early detection of HPV-based biomarkers of oropharyngeal head and neck cancer”. Although the project was not sanctioned by the NIH, it was ranked in the top 50% and valuable feedback for the grant was provided. These comments are already being used to revise the grant proposal for another future call. Prior to the visit we also reached out to some colleagues (Dr Tijl Vermassen and Mathieu Struys) in Ghent University through the assistance of Professor Rodney Uphoff. Professor James Bashkin and I had 3 Zoom meetings with them, and they incorporated the
immunomodulatory role of tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs) in the microenvironment of HPV+ OHNC. This broadened the scope of the project and strengthened a trilateral collaboration between USA, Africa, and Europe. The tripartite collaboration was invited to present our collaborative project at the UMSAEp precision medicine conference at UWC between March 27-April 1, 2023. Our UM-UWC project was also selected for presentation at the conference.

(ii) **Activities during the trip:** The visit focused mostly on aspects on objective (a) due to the short duration of the trip. In collaboration with a graduate student (Ms. Jessica Thompson), we tried to identify an in-silico peptidomimetic inhibitor target for the HPV viral oncoprotein E6 ubiquitin ligase domain (E6AP). In silico inhibitors were screened from synthetic and natural compounds and synthetically modified to increase binding affinity for the E6AP domain. Among natural compounds found were Ginkgetin, Hypericin and Apigetrin, while synthetic compounds included (S)-N-((3-amino-1-(5-ethyl-7H-pyrrolo [2,3-d]pyrimidin-4-yl)pyrrolidin-3-yl)methyl)-2,4-difluorobenzamide, dihydroxyphenyl)methylidene]-7-hydroxy-4-oxochromen-5-yl acetate), N-((6-methyl-1H-benzo[d]imidazol-2-yl)methyl)-5-(thiophen-2-yl)-1H-pyrazole-3-carboxamide, and N1-(5-chloro-2-cyanophenyl)-N2-(2-hydroxy-2-(1-methyl-1H-indol-3-yl) ethyl) oxalamide. Work is still ongoing to optimize a natural flavonoid compound and a synthetic compound as inhibitors of the HPV E6AP domain with minimal toxicity in ADMET studies. We envisage physical synthesis of a novel compound using green synthesis to reduce the environmental and physiological toxicity of the novel compounds. Professor Adeola also presented a proteomics research work on hair proteomics to the Bashkin Laboratory and this presentation was shared with the department and faculty. Furthermore,
he had a mini-workshop with the students to teach them the principles of mass spectrometry and high performance liquid chromatography. He assisted graduate students with their research and participated in ongoing synthetic chemistry projects at the Bashkin Laboratory using thin layer chromatography (TLC) and nuclear magnetic resonance (NMR) spectroscopy. He also attended mock conference presentations by faculty and provided experimental workflow feedback for graduate students at Bashkin Laboratory. Prof Adeola also visited tourist attractions in St Louis such as the Gateway Arch, Union Station and Aloe Plaza.
The visit period to UMSL was used to fine-tune the oral presentation of the HPV-OHNC project by Professors Adeola and Bashkin at the Precision Medicine Conference at the University of the Western Cape, upon their return to Cape Town, South Africa.

(iii) **Post-visit activities**: Both Professors Bashkin and Adeola travelled back to South Africa and arrived in Cape Town on Saturday 25\textsuperscript{th} March 2023, ahead of the precision medicine conference. They attended the opening dinner on the 26\textsuperscript{th} of March and presented their work at the precision medicine conference on Tuesday 28\textsuperscript{th} March 2023. The conference was used for networking local within UWC and with other colleagues from Ghent University and the University of Missouri Systems. Several excellent presentations were presented at the conference, and this stimulated a lot of collaborative ideas and feedback. We continue to work on the objectives of our project and exploring additional collaboration via the bilateral and trilateral partnerships involving South Africa, Europe and the United States of America. At the conclusion of the precision medicine conference, Professor Bashkin was taken on a tour of the Dental Faculty of the UWC and other tourist attractions in Cape Town.
6. Future work
We plan to develop a rapid diagnostic test for HPV+ OHNC akin to the rapid covid tests, this will be a very useful kit for rapid screening of HPV+ OHNC cases on the African continent. Our well-resourced and skilled collaborative team is well poised to deploy innovative solutions to the pressing oral health needs of the African and European populace. We also hope to develop multimodal data-science tools that can be used for phenotyping HPV sub phenotypes among a large OHNC electronic health record and in-silico OHNC databases. Finally, we hope to find and synthesize a therapeutic intervention that can block the HPV 16 E6 AP domain which can be used effectively in the management of HPV+ OHNC on the African continent.

7. Collaborations
Beside the already established trilateral collaborations, we have recently established additional collaboration with Professor Rose Wang at the Dental School of the University of Missouri at Kansas City (UMKC) who is interested in working with our team using some of the deep learning based oral cancer diagnostic tools that she is developing. We have also leveraged various intra-UMSAEP collaboration within UWC as well as with other principal investigators at UMSL, UMKC and at Ghent University.

8. Grants leveraged.
We have recently concluded a bilateral grant application between the Ghent University Component and the University of the Western Cape. The FWO-NRF Bilateral Scientific Cooperation South Africa grant is aimed at working on the immunomodulatory role of TILs in HPV+ OHNC
microenvironment. The proposed study aims to evaluate the prevalence of HPV in a more heterogeneous population of HNC patients from different demographic regions in Africa and Europe. In addition, we propose to investigate the distribution of different HPV subtypes. This is needed to assess if the currently available nine-valent vaccine offers sufficient protection for the development of HPV-positive HNC. Lastly, the effect of HPV positivity on immune cell influx in the tumor microenvironment will be evaluated to determine novel biomarkers, specifically associated to the HNC subtype. We will hear the outcome of this grant application in December 2023. We also plan to find additional grant opportunities for our evolving collaborative research partnerships under the UMSAEP umbrella.

9. Final Reflections
The UMSAEP grant has significantly improved the collaborative potential between the African researchers such as Professor Adeola and seasoned professors within the University of Missouri systems such as Professor James Bashkin. It has also provided an environment for innovative research that focuses on the key health problems that affect Africans. It also provides a multidisciplinary platform through which research grants can be leveraged competitively to attend to the oral health needs of the African populace. Our evolving project focuses on developing innovative solutions to a problem that affects the oral health and general well-being of many indigent South Africans.