JOHNS HOPKINS
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Theodore DeWeese, M.D.
Dean of the Medical Faculty
CEO, Johns Hopkins Medicine
100 School of Medicine Administration

Re: Promotion of Dr. Netz Arroyo to the rank of Associate Professor

Dear Dr. DeWeese,

I am writing this letter to enthusiastically nominate Dr. Netzahualcóyotl Arroyo Currás, also known as Netz Arroyo, for promotion to the rank of Associate Professor, full time, in the Department of Pharmacology and Molecular Sciences. Dr. Arroyo's current rank is Assistant Professor in the Department of Pharmacology and Molecular Sciences. He has built a strong record of peer-reviewed research and review publications that has positioned him as a game-changing leader in the field of electrochemical biosensors. His demonstrated leadership in translational research, particularly in the space of wearable and implantable continuous molecular sensors, is recognized at both the national and international level. This is evidenced by his ~$4 million in total direct costs as PI on competitive research grants, including a single PI R01 funded by the National Institute of General Medical Sciences at the NIH. This level of funding is remarkable for a faculty member in the field of pharmacology at this career stage. Additionally, Dr. Arroyo has published 42 papers with 18 of these as first/last author. Notably, he has an H-index of 22 and his papers have 1500+ citations. Dr. Arroyo is an international leader in his field with a steep trajectory and meteoric future ahead of him. He has also demonstrated research, education, and administrative leadership within Hopkins, and has proven a strong commitment to the holistic education of trainees at all levels within our institution.

Dr. Arroyo has pioneered the use of electrochemical, aptamer-based sensors (E-ABs) for real-time monitoring of therapeutic agents and biomarkers in the body. By developing this platform, which relies on molecular affinity and not reactivity to detect analytes, Dr. Arroyo enabled continuous sensing of a large variety of molecular targets (e.g., ions, small molecules, peptides, nucleic acids, and proteins) in biological systems. To highlight how important this achievement is, I note that the only other continuous electrochemical sensing platform in existence today is the continuous glucose monitor. This technology relies on the specific chemical conversion of glucose to the metabolite gluconolactone to produce electrons, a process that cannot be replicated with many other metabolites because of its strict dependence on enzymatic reactivity. In contrast, Dr. Arroyo's platform relies on affinity interactions with nucleic acid aptamers – versatile biorecognition elements that can reversibly bind with high specificity to a vast array of molecules even in unprocessed biological fluids. Dr. Arroyo's platform is enabling the study of dynamic processes in biology with unprecedented system-relevant temporal resolution and will undoubtedly allow the development of novel medical monitors and diagnostics to further realize highly precise and personalized therapies.

INTRODUCTION

Dr. Arroyo earned his Bachelor of Science degree in Chemical Sciences from Tec de Monterrey in 2009, a premier academic institution in northern Mexico. He obtained his Ph.D. degree from The University of Texas at Austin in 2015, where he worked under the mentorship of Allen J. Bard, who is considered the father of modern electrochemistry. While in Austin, Dr. Arroyo worked on the theory and development of large-scale energy storage systems called redox flow batteries and reported the first battery operating in alkaline media. This invention was patented, the first of several patents that Dr. Arroyo has been granted to date. With support from the prestigious Otis Williams Fellowship of the Santa Barbara Foundation, Dr. Arroyo pursued postdoctoral training in bioengineering at University of California Santa Barbara, under the supervision of Kevin W. Plaxco, a world-renowned biophysicist. There, he demonstrated the first electrochemical aptamer-based sensors that could be deployed directly in vivo, in preclinical animal models to study drug pharmacokinetics in real time. His seminal work was reported in the Proceedings of the National Academy of Sciences. Based on this innovative work and his strong record of high-quality publications in leading journals, Dr. Arroyo was recruited to the Department of Pharmacology and Molecular Sciences.

RESEARCH SCHOLARSHIP

Dr. Arroyo's research focuses on developing E-AB molecular monitors that are target specific and support time-resolved molecular tracking over physiologically relevant periods. He first demonstrated the value of his technology in rat models [OR14], in which he showed the ability of E-ABs to monitor antibiotic levels in systemic circulation, providing a new tool for pharmacokinetic studies with unprecedented time resolution (i.e., one measurement every 3 s). Leveraging the sub-minute resolution of E-ABs, he also demonstrated the first in-vivo, closed-loop platform supporting real-time control over circulating drug levels [OR20], opening a new door for highly precise and personalized drug dosing.

Building from such seminal studies, in recently published work he demonstrated that his E-AB platform can support molecular monitoring in the dermis interstitial fluid [OR41], a body compartment that can be accessed noninvasively and painlessly in humans for clinical applications. Dr. Arroyo's multidisciplinary contributions go beyond bioelectrochemistry and biosensing. Aiming to facilitate broad adoption of his E-AB technology, his group developed an open access software called SACMES [OR27], which allows the real-time processing of E-AB sensor data at millisecond speed. This software is now in use by over a dozen research laboratories across the world, including academic, governmental (NASA), non-profit and industry settings, and has become the reference algorithm for processing in-vivo E-AB sensing data. The access link to the code is visited an average of 20 times per month. In addition to enabling fast processing of sensor data, the availability of SACMES allowed Dr. Arroyo to uncover a fundamental limitation of the E-AB platform: the sensor signals degrade within hours when deployed in vivo. This limitation is the last challenge that must be addressed prior to functional E-AB deployment in human subjects. E-AB degradation is driven by complex biochemical and electronic factors that Dr. Arroyo's group is now dissecting and addressing with the long-term goal of achieving multiday molecular sensing.

Dr. Arroyo recognized early on that achieving multiday molecular sensing would require astute re-engineering of the sensing platform. This is because his E-AB sensors consist of electronic conductors (e.g., gold electrodes) that are chemically functionalized with monolayers of alkylthiols and alkylthiol-modified aptamers via self-assembly. When exposed to the complex environments found in vivo, these monolayers slowly desorb from the electrode surface, limiting the operational life of E-ABs to 6 hours. Seeking to better understand this process and mitigate sensor degradation, Dr. Arroyo published a key mechanistic study in ACS Advanced Materials and Interfaces [OR30] demonstrating that the hydrophobicity of the monolayers can directly impact sensor stability over time. This study also highlighted the important observation that monolayer chemistry is not inert and, in addition to affecting sensor stability, can also affect the sensing performance of the platform. In a second mechanistic study, Dr. Arroyo's group showed that electrochemical interrogation of the E-AB interface can, by itself, accelerate sensor signal degradation [OR36]. This is because electric stimulation of the aptamer backbone can actuate the nucleic acid chain, repelling it from the sensor surface at negative voltages, thereby accelerating aptamer monolayer desorption. Finally, in work published in the Journal of Physical Chemistry C [OR38], Dr. Arroyo demonstrated that the molecular reporter used in the platform, methylene blue, is also affected by monolayer hydrophobicity, and its electrochemical activity can be modulated to improve sensor signaling and stability over time.

A common belief in the field of DNA-based sensors was that the abundance of nucleases in biological systems was the main driver of sensor degradation. In a paper published in *Langmuir* [OR37], Dr. Arroyo's group demonstrated that this is not true by showing that the rate of enzymatic hydrolysis of aptamer receptors from E-AB surfaces is much slower that the sensor decay rate observed in six different biological fluids, even when nucleases are added at supraphysiological concentrations. As part of this demonstration, his group synthesized the first E-AB sensors using left-handed DNA aptamers (Spiegelmers), which cannot be cleaved by nucleases and therefore acted as negative controls. The study showed that sensor decay is driven by loss of monolayer elements via more conventional physicochemical pathways, such as passive desorption and competitive displacement of sensor elements by naturally occurring thiolated molecules in the body.

Having established a framework to mechanistically understand the decay pathways of DNA-based sensors, including his E-AB platform, Dr. Arroyo is now pursuing alternative chemistries to eliminate sensor decay. Specifically, he is developing novel chemical strategies to covalently bind aptamer monolayers to other electronic materials to overcome the lability issues associated with the use of thiol-gold bonds. His laboratory recently reported the first chemical functionalization of carbon electrodes for E-AB sensing using electrografting of primary amines [OR40]. This transformative work is establishing a path forward for translation of E-AB sensors to carbon materials, which can be better interfaced with the body.

The broad scope of Dr. Arroyo's work has attracted funding from a diverse portfolio of agencies. His in-vivo work is funded by a single PI R01 from the National Institute of General Medical Sciences. His mechanistic and materials research work is funded by a grant jointly awarded by the Bionanomaterials Consortium at SEMI and the Air Force Research laboratory. And his work on real-time molecular sensing in interstitial fluid is funded by a >$2 million grant from the Helmsley Foundation. Given the tremendous impact of his work on biomedical and biosensing device development, and the unparalleled value of his platform for in vivo molecular monitoring, there is no doubt that Dr. Arroyo's program will continue to be robustly funded. His paradigm-changing technology will transform the way we monitor therapeutics, biomarkers, and metabolites in the body.

As a final note, it is worth highlighting that Dr. Arroyo's capacity to innovate in biosensing is not limited to the E-AB platform. Motivated to help in the control and mitigation of the current COVID-19 pandemic, Dr. Arroyo successfully obtained two internal grants to fund the development of a glucometer-based serology assay to monitor immunity in individuals that have been infected or vaccinated against SARS-CoV-2. The team he led developed a novel protein fusion reporter consisting of an anti-human IgG antibody fused to two invertases. Invertase is an enzyme that converts sucrose to glucose. Dr. Arroyo's team built plastic test strips containing SARS-CoV-2 antigens. By exposing the strips first to a patient sample (e.g., serum, saliva) and then to the fusion protein in the presence of sucrose, the team demonstrated accurate and quantitative monitoring of anti-SARS-CoV-2 antibodies in static and longitudinal clinical samples. This work was recently published in the Journal of the American Chemical Society [OR42] and has received tremendous attention from the community. With an Altmetric score of 338, it is placed in the top 5% of all papers tracked by this metric, an indication that the work will be highly cited and will advance our ability to monitor disease spread for the current and future pandemics.

TEACHING SCHOLARSHIP

Dr. Arroyo has accomplished a strong record of mentoring graduate students and postdoctoral scholars in their research training. To date, he has graduated one Masters student from the CBI program, who was the recipient of an oral presentation award from the Society of Electroanalytical Chemistry and is now a lead scientist at the diagnostics company Meso Scale Discovery. Dr. Arroyo is currently mentoring three graduate students, all recipients of travel awards from various organizations, and one of which was the recipient of an NSF GRFP fellowship. In addition, he is training three postdoctoral fellows, the most senior of which received a prestigious training fellowship from "Agencia Española Contra el Cáncer" to return to a funded research position in his home country in Spain. As evidenced by the awards granted to his trainees, Dr. Arroyo is an excellent mentor who successfully places trainees in leading positions across industry and academia.

As part of his participation in summer research programs, Dr. Arroyo has mentored one high school student and four undergraduate students from underrepresented groups. He holds a perfect record of placing these summer trainees into top academic programs, including programs at University of North Carolina – Chapel Hill, Johns Hopkins University, and The University of Texas at Austin.

In teaching, Dr. Arroyo has played a transformative role in the development of the course Primary Source Readings and Analysis that is taken by all first-year students in our Department and is also offered to students in the Department of Physiology. Dr. Arroyo has been director of this course since 2019 and created the current course structure and content, which are designed to train students in critical scientific reading and basic biostatistical analysis while also covering content on responsible conduct of research and professional development that meets requirements of our training grant. In a similar role, Dr. Arroyo is co-director of the SOM-wide course Introduction to Responsible Conduct of Research, which is offered to all trainees across the institution to meet training grant requirements. In this role, Dr. Arroyo has created the content of two modules focused on Mentor-Mentee Relationships and Data Storage and Management. This course has an enrollment of >200 students annually and is one of several core courses taken by students in several SOM graduate programs. In addition, Dr. Arroyo was the faculty organizer of the Annual Pharmacology Retreat from 2019 to 2022 and led retreat seminars in responsible conduct of research. Overall, these activities have established him as a go-to colleague for RCR mentoring and training across the SOM.

One final contribution worth mentioning is Dr. Arroyo's leadership in creating a bridge research program with a close collaborator from California State University Dominguez Hills (CSUDH), a minority serving institution. Through this program, Dr. Arroyo hosts 1-2 undergraduate trainees or faculty from CSUDH over 10 weeks each summer, with the goal of providing advanced research experiences and research training that they cannot otherwise access at their home institution. This program is entirely run and managed by Dr. Arroyo, using funds from his research grants. The success of this program can be measured by the publication of two studies [OR26, OR37] in collaboration with the CSUDH faculty lead and trainees.

CITIZENSHIP/COMMITMENT TO JOHNS HOPKINS

Dr. Arroyo's commitment to the University is demonstrated by his service to graduate education. In addition to the curriculum development activities described above, Dr. Arroyo is an active participant in Pharmacology and Molecular Sciences (PMS), Biochemistry, Cellular and Molecular Biology (BCMB), Chemistry-Biology Interface (CBI), Chemical and Biomolecular Engineering (ChemBE) and Molecular Biophysics (PMB) programs. His service to these and other programs occurs at multiple levels including administration of graduate board oral exams (16 exams), membership on thesis committees (6 committees), and admissions interviews (34 interviews). Dr. Arroyo has served as a member of the BCMB International Admissions Committee for two years. Additionally, Dr. Arroyo has served on two key School of Medicine committees: the IBBS Concept Development group and notably the COVID-19 Research Restart committee.

NATIONAL/INTERNATIONAL RECOGNITION

Dr. Arroyo's research accomplishments have been recognized at a national level with several awards. In 2019, he was the recipient of the Ralph E. Powe Junior Faculty Enhancement Award by Oak Ridge Associated Universities. In 2020, he was named a "Rising Star in Sensors" by the journal ACS Sensors from the American Chemical Society, the leading journal in the field nationally and one of the top 3 in the field internationally. As part of this recognition two of his research articles [OR18, OR28] were highlighted in a special issue of the journal. In 2022, he was one of the recipients of NIDA's Start a SUD Startup Challenge, which recognizes transformative methodologies for the management of substance abuse disorders. Finally, this year Dr. Arroyo's work on COVID-19 immunity monitoring was highlighted by the Journal of the American Chemical Society in a press release and has received attention scores that place his study in the top 5% of all papers evaluated by the Altmetric algorithm. These accomplishments clearly point at a stellar research career that has positioned Dr. Arroyo as a national and international leader in the field of biosensors.

In addition to his tremendous track record of extramural funding and recognition noted above, Dr. Arroyo's national and international reputation as a leader in the field of bioanalytical sensors is also reflected in his invited service as an ad hoc member of the NIH Enabling Bioanalytical and Imaging Technologies (EBIT) study section and his reviewer service for the European Research Commission and the Netherlands Organization for Scientific Research. He has also authored 4 review papers by invitation from national and European journals.

Dr. Arroyo frequently presents his research findings at national (13 since 2019) and international (8 since 2019) venues, including society meetings and by direct invitation to speak in university departmental seminar series and scientific webinars. He has also organized research symposia (twice) by invitation from the American Chemical Society. It is important to note that his record of scientific dissemination of knowledge is strong despite limitations imposed by the COVID-19 pandemic.

ANTICIPATED FUTURE PROGRESSION

Dr. Arroyo has established himself as a national and international leader in the field of bioanalytical sensors and in vivo sensing. Further, he is an excellent mentor with an outstanding mentoring track record. His future potential and value to the Johns Hopkins School of Medicine is incredible. Going forward, he undoubtedly will continue to receive accolades and bring great credit to the institution. His track record of generating intellectual property will continue to grow, as will the educational excellence and administrative leadership he provides to the institution. He embodies the Hopkins spirit of scientific drive, innovation, and creative and intellectual diversity that guarantees success as a researcher, innovator, and educator.

SUMMARY STATEMENT

Dr. Arroyo is a star faculty member with a meteoric trajectory. Given Dr. Arroyo’s demonstrated research success and outstanding teaching and mentoring, I believe that he is highly deserving of promotion to the rank of Associate Professor. I have the utmost regard for his scholarship and integrity and give him my highest possible recommendation.

Sincerely,

Namandjé N. Bumpus, PhD
E.K. Marshall and Thomas H. Maren Professor and Department Director