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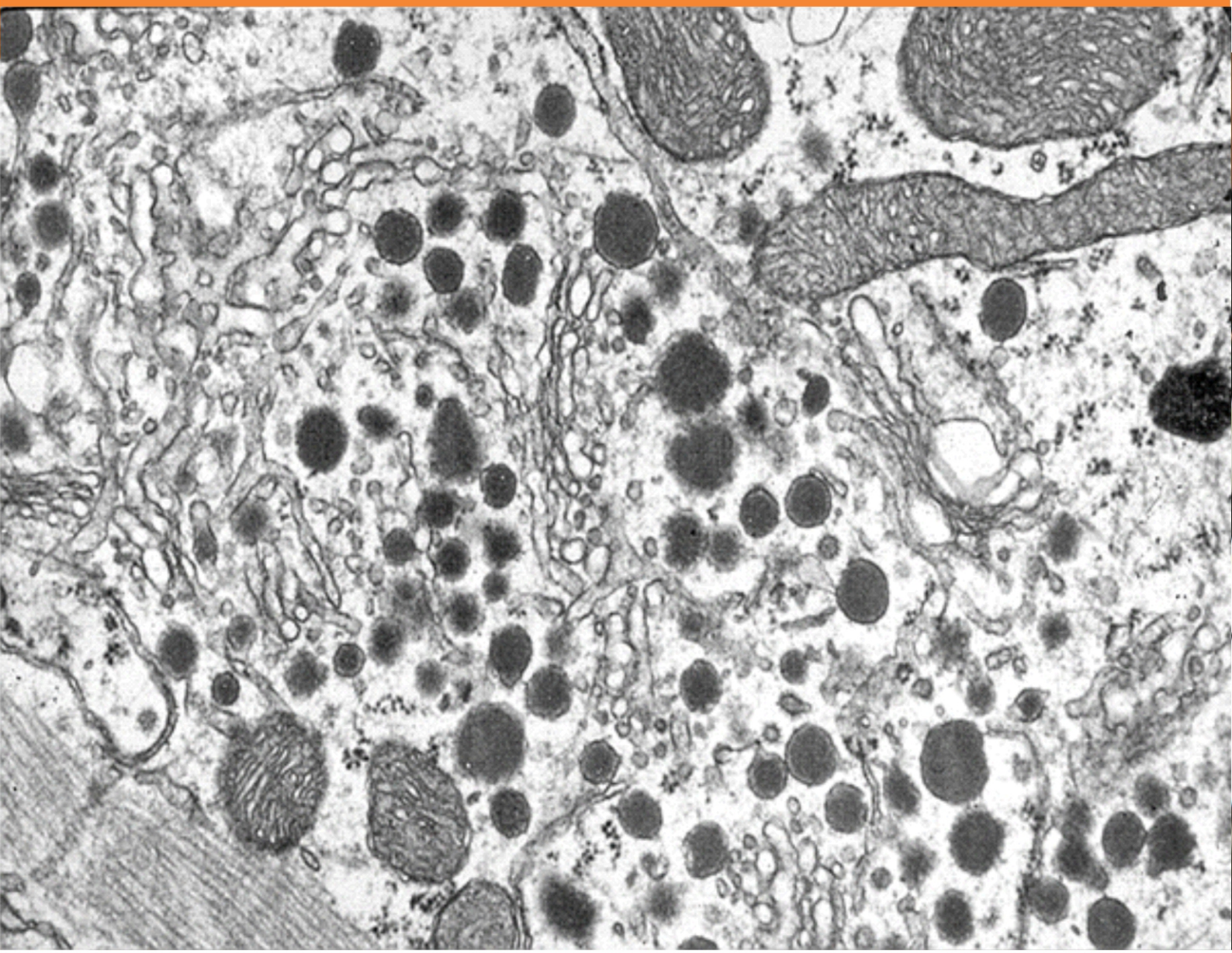

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The identification of the electrogenic nature of the Na^+/HCO_3^- cotransporter in the myocardium.

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THE IDENTIFICATION OF THE ELECTROGENIC NATURE OF THE NA^+/HCO_3^- COTRANSPORTER IN THE MYOCARDIUM.

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Abstract

Intracellular pH (pH_i) in myocardial tissue is higher than expected considering the electrochemical equilibrium for H^+. This is possible because of the existence of two acid-extruding mechanisms, the cardiac Na^+-H^+ exchanger (NHE1) and the Na^+-HCO_3^- symport (NBC), plus the possible action of a H^+/lactate cotransport under certain circumstances. The full set of pH_i regulatory mechanisms includes the acidifying Cl^--HCO_3^- anion exchanger, and probably a Cl^--OH^- exchanger, hard to differentiate from the previous one. This revision focuses on the NBC, an ubiquitous protein that was shown to be electrogenic in different cell types (stoichiometry ratio of 2 or 3 HCO_3^- to 1 Na^+), but whose electrogenicity in cardiac cells remained uncertain until its demonstration by our own research group in the 1990s decade.

Keywords: Electrogenic Na^+-HCO_3^- symport, myocardium, intracellular pH

Resumen

El pH intracelular (pH_i) del tejido cardíaco es más alcalino que lo esperable teniendo en cuenta el equilibrio electroquímico para el H^+. Esto es posible por la existencia de al menos dos mecanismos encargados de eliminar equivalentes ácidos del citosol, el intercambiador Na^+-H^+ miocárdico (NHE1) y el cotransportador Na^+-HCO_3^- (NBC), a los que podría sumarse un cotransportador H^+/lactato en determinadas circunstancias. Completan el conjunto de proteínas encargadas de mantener el pH_i miocárdico el intercambiador aniónico acidificante Cl^--HCO_3^-, y posiblemente un intercambiador Cl^--OH^-, muy difícil de diferenciar del anterior. El presente trabajo de revisión se focaliza en el NBC, proteína ubicua con características electrogénicas en diferentes tipos celulares (estequiometría de 2 o 3 HCO_3^- por cada Na^+ transportado), pero cuya electrogenicidad en células cardíacas fue motivo de controversia hasta su demostración por parte de nuestro grupo de investigación a mediados de la década de 1990.

Palabras clave: cotransportador Na^+-HCO_3^- electrogénico, miocardio, pH intracelular)

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During the first half of the 1990s decade, I was a young fellow from the National Council of Scientific Research (CONICET) of Argentine, under the expert supervision of prominent researchers in the cardiovascular area, initially Dr. Alicia Mattiazzi, and later on Drs. Horacio E. Cingolani and María C. Camilión de Hurtado. We were particularly interested in the characterization of the regulatory mechanism of pH_i in mammalian heart. As a brief introduction to the theme of this Special Edition of PMR, let me remind readers that myocardial pH_i is approximately 7.20. This value is at least 1 pH units higher than expected considering the electrochemical equilibrium for H^+, necessarily implying that acid-extruding mechanisms might contribute to maintain basal pH_i homeostasis. In this regard, two widely known alkalinizing membrane proteins are crucial for this purpose, the cardiac NHE1 [1] (only operative mechanism when experiments are performed in the absence of bicarbonate), and the NBC [2, 3], plus the possible contribution of a H^+/lactate cotransport under certain circumstances [4]. The full set of mechanisms that contribute to pH_i homeostasis also comprises the acidifying extracellular Cl^--intracellular HCO_3^- anion exchanger, and probably a Cl^--OH^- exchanger [5], extremely difficult to experimentally differentiate from the previous one. Of particular interest for the current revision is the NBC, which was one of our specific study targets 30 years ago. It was described as an electrogenic mechanism in cells from mammalian proximal tubule [6], retinal epithelium [7], smooth muscle [8], human ciliary muscle [9], and glia [10], as well as in gastric oxyntic cells [11], and hepatocytes [12], with a stoichiometry ratio of 2 or 3 HCO_3^- to 1 Na^+. However, circa 1990 when present story begins, the electrogenicity of the symport in cardiac cells was still uncertain. While studies from the Laboratory of Physiology at University of Oxford leaded by Dr. Richard D. Vaughan-Jones argued in favor of its electroneutrality [2, 3], our own laboratory at the University of La Plata strived to demonstrate its electrogenicity [13].

The electrogenicity of the Na^+/HCO_3^- cotransporter in mammalian myocardium

The main interest of our laboratory during the early 1990s was to characterizing the underlying mechanisms of the recovery of pH_i and contractility from acidosis in mammalian myocardium. In addition of focusing on the role of the NHE1, we were particularly interested in determining the contribution of bicarbonate-dependent mechanisms. For that purpose, we designed a simple acidic challenge protocol that consisted in performing a quick change of the superfusing solution of isometrically contracting isolated papillary muscles from a nominal bicarbonate-free condition (HEPES buffer) to a bicarbonate containing buffer. The first experimental observation was somewhat surprising, since following the initial acidic load (due to rapid CO_2 permeation) pH_i recovered towards control reaching a slightly higher steady sate value than in HEPES, effect that was exactly paralleled by a depress and recovery of developed force. This result was clearly challenging previous publications assuring that pH_i should be higher under bicarbonate free conditions [3, 14-17]. However, the unexpected finding was consistently observed when repeating the experimental protocol as shown in **Figure 1**.

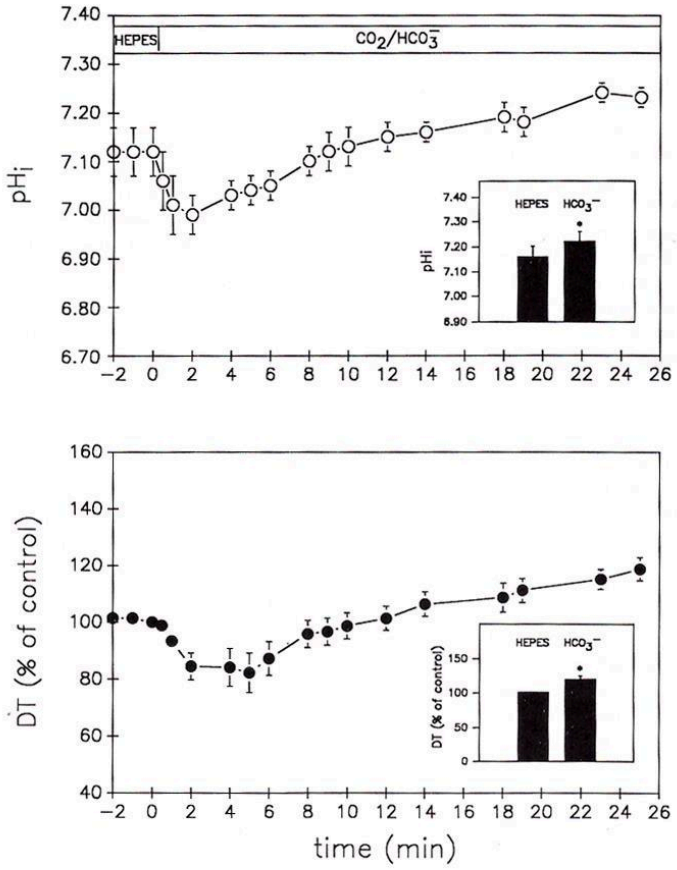

Figure 1. Time-course changes in pHi and force following an abrupt change of the superfusion solution from HEPES buffer (bicarbonate-free condition) to bicarbonate buffer. (Reproduced from J Mol Cell Cardiol, 1995. 27(1): p. 231-42).

Furthermore, using pharmacological interventions we could demonstrate that NHE1 and NBC were both necessary to fully recover pH_i after the acidic challenge, and also that their contribution was almost equal [13]. Interestingly, one of the publications proposing that pH_i should be higher in the absence of bicarbonate (from Dr. Vaughan-Jones group) also argued in favor of the NBC electroneutrality [3]. In this context of discrepancy with previous reports but absolutely confident about our own results, we decided to go further and try to identifying another possible disrupting finding, the electrogenicity of the cotransporter. At this time is when simple smart ideas emerge. Dr. Cingolani proposed me to prepare standard potassium-filled glass microelectrodes, but ultraflexible. This condition would allow reaching stable impalements of healthy isolated papillary muscles while contracting, to monitoring membrane potential during the switching protocol from HEPES- to HCO_3^--buffered solutions. Notably, the hypothesis that the NBC will carry more negative than positive charges into the cell was immediately supported by an evident hyperpolarization detected from the first measurement after changing solutions (**Figure 2**), effect that persisted despite recovery of pH_i. Additionally, 1) hyperpolarization was cancelled in the presence of the anion blocker SITS (**Figure 2**, **inset**), 2) addition of SITS to HCO_3^--buffered solution depolarized the membrane in equivalent millivolts to the hyperpolarization promoted by the physiological buffer after switching from HEPES, and 3) SITS lacked of effect on membrane potential when added to HEPES-buffer, disregarding possible non-specific effects of the compound, but also strongly supporting the notion that it was specifically suppressing negative charges entry to cardiac cells under HCO_3^- containing conditions. The certainty about the electrogenic nature of the cotransporter was further supported by the demonstration that membrane depolarization induced by high K^+ promoted a SITS-sensitive Na^+-dependent increase in pH_i compatible with Na^+-HCO_3^- co-influx.

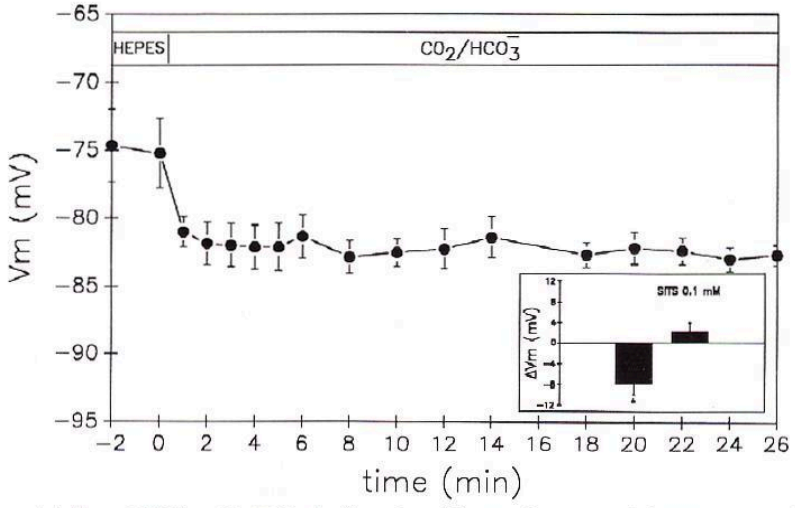

Figure 2 Immediately detected hyperpolarizing effect of bicarbonate. (Reproduced from J Mol Cell Cardiol, 1995. 27(1): p. 231-42).

Our disrupting seminal work was published in 1995 in the prestigious Journal of Molecular and Cellular Cardiology [13]. One year later we could provide additional evidence about the electrogenic property of NBC activity by demonstrating the role of the symport in promoting an increase in myocardial pH_i following an increase in heart rate (Circulation Research, 1996 [18]), and later on, Dr. Aiello et al. from our own research group accurately characterized the cotransporter current in isolated cardiac myocytes using the precise patch clamp technique (Journal of Physiology, 1998 [19]).

The progression of knowledge about cardiac NBC activity can be summarized as follows. It was originally described as an electroneutral cotransporter (nNBC) with a stoichiometry of 1 HCO_3^- to 1 Na^+ by Dr. Vaughan-Jones group [2, 3]. However, a few years later experiments from our own laboratory provided evidence that it exhibited an electrogenic behavior (eNBC) with a stoichiometry of 2 HCO_3^- to 1 Na^+ [13]. This disagreement generated a scientific controversy that lasted for several years. Fortunately, the discussion about its stoichiometry was finally resolved and it is now accepted that both variants of Na^+-HCO_3^- cotransport are present in cardiac cells [20-24]. It was demonstrated that the heart possesses at least two electrogenic isoforms called NBCe1 (also named NBC1) and NBCe2 (also named NBC4) which are encoded by different genes (SLC4A4 [22] and SLC4A5 [23], respectively), and one electroneutral isoform named NBCn1 (also named NBC3) encoded by the SLC4A7 gene [24]. Interestingly, all these important studies together with the impassioned scientific discussion about the properties of the NBC in many scientific meetings (before and after reaching the consensus), served in part as foundation stone of an important and prolific line of investigation focusing on the symport guided by Dr. Aiello in our own laboratory. In this regard, several years of research not only shed light about the function of the coexisting isoforms in mammalian myocardium, but also opened new avenues of investigation by rigorously dissecting the role played by the different isoforms in health and disease [21, 25-34].

Two short stories inside the story of this transcendent scientific discovery

A "David versus Goliath" contest

The Biblical tale of David versus Goliath is often used to describe a situation in which a small or supposedly weak person or group tries to defeat another much larger or stronger opponent. This symbolism serves to introduce the first "story inside the story".

The description as to how the electrogenic nature of the symport was identified by our group may conceivable lead readers to believe that basic science research is a "straight

forward paved way". However, actual circumstances about disrupting scientific discoveries frequently contradict such assumption. During the 1980-1990 decades, the laboratory of Physiology at the University of Oxford leaded by the prestigious researcher Richard D. Vaughan-Jones was unavoidable reference for studies on cardiac pH_i regulatory mechanisms. As stated before, his group proposed the electroneutrality of the cardiac NBC activity by publishing results that included the use of the precise patch clamp technique [2, 3]. Contemporarily, we were obtaining challenging strong evidence that the symport was indeed electrogenic using standard potassium microelectrodes. As readers may imagine, the way to publishing our disrupting results was not just a "paved way". The long journey included extremely disgusting heated discussions with Dr. Vaughan-Jones group in every scientific meeting where our advances were communicated, and as detailed in the final section of this article, a hard work to convince reviewers about the novelty when the manuscript was finally submitted for publication. Fortunately, this story had a happy end that not only included the above mentioned resolution of the scientific debate about NBC activity (once again highlighting that "absolute truth" does not exist in science), but also the closure of an initial unjustifiable hostility between both laboratory groups that finally turn into a cordial mutual scientific respect and collaboration.

The biblical interpretation of "David and Goliath" popular tale is that it teaches courage, faith, and overcoming what seems impossible. In my opinion, this is a good metaphor of what it was for us the conviction of jumping over any obstacle to demonstrating the NBC electrogenicity.

A funny (or not so funny) anecdote

The second "story inside the story" can be described as an astonishing anecdote. After obtaining enough evidence about the electrogenic nature of the NBC and despite obstacles, we enthusiastically wrote the manuscript to communicate the important disrupting discovery. However, your dreams not always turn into reality and the paper was quickly rejected by one important international scientific journal. The funny, or not so funny, anecdote is that the main objection of one reviewer was that in his/her opinion, "it was a transcendent finding that, if true, it should have been reported previously by other important laboratory", probably ("certainly" in my opinion…) referring to a laboratory from a so called "first world country". Fortunately, we ignored such unfortunate commentary and despite several months of delay the paper was finally published in the prestigious Journal of Molecular and Cellular Cardiology [13]. I am so proud to have been part of such important discovery about the NBC. Firstly, because as stated before it paved the way for further important investigations including sensitive areas of cardiovascular disease, but also because it highlighted that great discoveries often depend on smart simple ideas and optimization of research resources, no matter the place they come from. In this regard, I would like to finish this short story by transforming the popular saying "A golden cage does not improve canary's song" to "There is no need to have a golden cage to improve canary's song", which I think represents a good metaphor about doing "first world" science in developing countries like Argentine.

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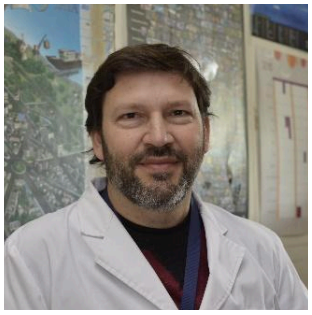

Néstor Gustavo Pérez es Licenciado en Biología (Orientación Zoología) y Doctor en Ciencias Naturales de la Facultad de Ciencias Naturales de la Universidad Nacional de La Plata (UNLP).Es Profesor Asociado con Dedicación Exclusiva (Ordinario) de la Cátedra de Fisiología y Física Biológica de la Facultad de Ciencias Médicas de La Plata (UNLP), y Miembro de la Carrera del Investigador Científico del Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) en la categoría Principal. Es además Coordinador de la Comisión de Bioseguridad e Higiene, y Miembro del Comité Académico del Departamento de Posgrado de la Facultad de Ciencias Médicas de La Plata.

Los resultados de su Tesis Doctoral sobre el acoplamiento excito-contráctil en el miocardio ventricular de ratas hipertensas y normotensas fueron publicados en la prestigiosa revista Hypertension en 1993. En 1996 obtuvo una Beca Externa Posdoctoral de CONICET para continuar con su formación profesional en el campo cardiovascular en Johns Hopkins University, Baltimore, Maryland, donde desarrolló tareas de investigación hasta obtener su ingreso a la Carrera del Investigador Científico de CONICET en 1998.

Su principal tema de investigación ha estado vinculado al estudio de los mecanismos que subyacen al desarrollo de hipertrofia e insuficiencia cardíaca de distinto origen (hipertensión arterial, post-infarto de miocardio). Se ha especializado en la caracterización de la contractilidad miocárdica en distintos contextos fisiológicos y patológicos, contando con un equipo interdisciplinario de Investigadores, Becarios y Personal Técnico que le han permitido aplicar diversas técnicas bioquímicas y de Biología y Genética Molecular a sus Proyectos, además de un seguimiento in vivo de la función cardíaca mediante ecocardiografía. Sus proyectos, principalmente de investigación básica pero con potencial impacto sobre áreas de Salud Pública, han recibido importantes subsidios del Ministerio de Salud de la Nación, de la Agencia Nacional de Promoción Científica y Tecnológica (ANPCYT), de CONICET y de la UNLP.

El Dr. Pérez es miembro activo de prestigiosas sociedades científicas nacionales e internacionales: Sociedad Argentina de Fisiología (SAFIS), Sociedad Argentina de Hipertensión Arterial (SAHA), International Society for Heart Research (ISHR), American Physiological Society y American Heart Association (AHA).

A lo largo de su carrera ha publicado 76 trabajos de investigación científica en revistas indexadas y 14 capítulos de libros, ha presentado más de 150 comunicaciones en Congresos y/o Reuniones de su especialidad habiendo sido además disertante invitado en más de 40 de ellos (tanto nacionales como internacionales), y ha recibido un total de 20 premios/distinciones entre los que se destaca el Premio a la Labor Científica, Tecnológica y Artística de la UNLP, Edición 2019.