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## Nitrite and Nitrate: from Bench to Bedside

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This special issue represents recent proceedings and developments in the fields of nitrite and nitrate chemistry, biology and therapeutics that were discussed at the biannual international meeting entitled “Approaching the Clinic: Nitrite and Nitrate Pathophysiology and Therapy Conference”. This conference represents the fourth installment of this meeting series that has served as a unique forum where investigators from diverse backgrounds have come together to better understand the chemical biology of nitrite and nitrate with an emphasis on therapeutic utility of nitrite and nitrate for various disease conditions.

Over the three-day meeting, new information was shared regarding the biological importance of nitrite and nitrate mediated nitric oxide (NO) formation for numerous aspects of physiological homeostasis and disease states. Initial studies regarding nitrite biology and function elucidated biochemical mechanisms involved in nitrite reduction to NO under specific conditions such as tissue ischemia [1]. However, meeting presentations demonstrated that therapeutic benefits of nitrite might be more broadly beneficial than previously considered for several cardiovascular pathologies such as vascular intimal hyperplasia and vascular aging, and chemotherapeutic cardiotoxicity [2; 3; 4]. New findings were also discussed regarding the relationship between myoglobin and mitochondrial function with respect to hypoxia and nitrite/NO metabolism that are further discussed in this issue [5; 6]. Lastly, clinical and translational studies were discussed regarding the safety and efficacy of nitrite therapy for peripheral vascular diseases that are currently under way [7].

Nitrate and nitrite work in coordination with nitric oxide synthase (NOS) enzymes to establish a unique and dynamic NO endocrine system that is operational throughout the body [8; 9]. Data was presented showing that nitrate consumption augments vascular compliance but did not alter flow-mediated vasodilation in healthy subjects [10]. Presentations also discussed biochemical and physiological similarities and differences between various organic versus inorganic nitrates and nitrites as it is now clear that these compounds are metabolized in diverse ways and can elicit different biological responses that could be harnessed for various therapeutic uses [11; 12].

With a significant theme of the conference focused on translational and therapeutic implications of nitrite and nitrate, both novel uses and potential limitations were actively

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### Conflicts of Interest

C.G.K. and D.J.L. are listed on intellectual property using nitrite for ischemia and cardiovascular disease. C.G.K. has a commercial interest in TheraVase Inc.

discussed. New evidence has emerged that exogenous nitrite can stimulate significant biological responses in different cell types under normal oxygen tensions. In particular, nitrite enhances lung epithelial cell activation under normoxic conditions through redox signaling pathways [13]. Evidence was also presented demonstrating that nitrite therapy is neuroprotective after cardiac arrest reinforcing its utility as a cytoprotective agent [14]. Conversely, safety concerns surrounding nitrite and nitrate were also discussed based on previous and recent studies [15]. Careful comparison and evaluation across multiple areas of investigation further revealed that nitrite/nitrate adverse effects and toxicity to be significantly above therapeutic amounts that have been used by numerous investigators [8; 9]. Nonetheless, it was acknowledged that close evaluation and monitoring of adverse events and toxicity are critical for therapeutic studies moving forward.

In summary, results from the 4<sup>th</sup> biannual Nitrite and Nitrate meeting provided important and unique insight into the different therapeutic directions that are emerging. Significant interest on this and other biochemical and pathophysiological topics from both academic and industry sectors highlight that the field of Nitrite and Nitrate chemical biology is continuing to mature and progressing toward the realization of useful therapeutics for numerous disease conditions involving dysfunctional NO metabolism and bioavailability.

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