

# Futuristic Exploration of Addiction Neuroscience in the Genomic Era

Kenneth Blum<sup>1-7</sup>, Igor Elman<sup>8</sup>, Abdalla Bowirrat<sup>1</sup>, David Baron<sup>1</sup>, Panayotis K Thanos<sup>9</sup>, Colin Hanna<sup>9</sup>, Rajendra D Badgaiyan<sup>10</sup>, Mark S Gold<sup>11</sup>

<sup>1</sup>Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel; <sup>2</sup>Division of Addiction Research & Education, Center for Exercise Sports, Mental Health, Western University Health Sciences, Pomona, CA, USA; <sup>3</sup>Institute of Psychology, Eötvös Loránd University, Budapest, Hungary; <sup>4</sup>Department of Psychiatry, Boonshoft School of Medicine, Wright University, Dayton, OH, USA; <sup>5</sup>Department of Psychiatry, Human Integrated Services Unit, University of Vermont Center for Clinical & Translational Science, College of Medicine, Burlington, VT, USA; <sup>6</sup>Sunder Foundation, Palm Springs, CA, USA; <sup>7</sup>PEAKLOGIC, LLC., Del Mar, CA, USA; <sup>8</sup>Department of Psychiatry, Harvard College of Medicine, Cambridge, MA, USA; <sup>9</sup>Behavioral Neuropharmacology and Neuroimaging Laboratory on Addictions, Clinical Research Institute on Addictions, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biosciences, State University of New York at Buffalo, Buffalo, NY, USA; <sup>10</sup>Department of Psychiatry, Case Western Reserve University and MetroHealth System, Cleveland, OH, USA; <sup>11</sup>Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Correspondence: Kenneth Blum, Tel +1 404 234 5433, Email drd2gene@gmail.com

Addiction neuroscience is a multidisciplinary approach to treating substance and non-substance (such as eating disorders) addictive behaviors. Researchers in this field aim to understand the neural mechanisms underlying this disease.<sup>1</sup> Over the past 30 or more years, substance use disorder (SUD) research has increased significantly, as has our understanding of the neural and genetic mechanisms of addiction. New methodologies have been developed (both clinical and pre-clinical) to assess molecular and neurochemical changes in neuronal systems. In the case of SUD, it is important to remember that DNA pre-addiction antecedents and unwanted negative insults are due to epigenetics.<sup>2,3</sup> While we are not there yet, especially when we are administering opioids to treat opioid dependence as if there is an opioid deficiency,<sup>4</sup> new advancements have revealed neurogenetic and epigenetic processes by which molecular, neurobiological, and socio-spiritual factors increase vulnerability and resilience to these behaviors.<sup>5,6</sup> For example, an individual's inability to replace short-term rewards with more beneficial long-term rewards can involve neurological and behavioral disruption.<sup>7</sup> Knowledge of the combinative role of genes and environment (epigenetics) can help sway unwanted substances and behavioral addictions.<sup>8,9</sup>

Overall well-being involves numerous neurotransmitters and second messengers. Their intricate interactions regulate the release of dopamine at post-neuronal sites, such as the Nucleus Accumbens (commonly referred to as the brain's reward center).<sup>10</sup> In 1995, Kenneth Blum introduced the concept of "Reward Deficiency Syndrome" (RDS) to highlight hypo-functionality of dopaminergic brain circuits, presented clinically as a reduction in the capacity to experience pleasure and a super-sensitivity to behavioral drives.<sup>11-13</sup> It is now well known that genotypical and acquired hypodopaminergia contributes to the development of RDS.<sup>14</sup> Individuals afflicted with RDS often turn to substance abuse in an attempt to alleviate diminished reward symptoms, offering temporary relief from this deficit.<sup>15</sup>

Yet the ongoing use of such substances exacerbates the deficits over time, ultimately amplifying RDS and stress levels.<sup>16</sup> Moreover, RDS deficits can be exacerbated by negative emotions that trigger epigenetic changes. Methylation on chromosomal histones can result in substantial disruption of gene expression.<sup>17</sup> Chronic exposure to alcohol and other addictive substances can result in executive functional connectivity deficits in the brain. DRD2 methylation was negatively associated with left and right executive control network connectivity. DRD2 methylation was also associated with severity of alcohol problems, reinforcing a theoretical model in which epigenetics and neurobiology correlates of alcohol consumption and SUD. Positive and nurturing behaviors that bring about beneficial effects on gene expression can be a potential solution, lessening such deep distress to these concerns.<sup>18,19</sup> Lastly, shifting the focus from medication

prescription towards the restoration of dopaminergic homeostasis (or hedonostasis) may be a complementary therapeutic modality to treat opioid use disorder.

Opioid overdoses kill over 100,000 individuals each year.<sup>20</sup> Approximately 800 million people globally express addiction and RDS behaviors, necessitating innovative thinking to address these concerns.<sup>21</sup> We strongly believe that preaddiction trait detection through tools such as genetic testing is an essential preventative strategy.<sup>22</sup>

Currently, at least one approved FDA treatment for OUD is to prescribe powerful opioids which of course can induce unwanted dependence. One major benefit is that this successfully helps reduce harm. However, it is our responsibility as scientists and clinicians to focus on novel ways to combat drug-induced dopamine dysregulation and promote the functional balance of dopamine in the brain. This premise to induce dopamine homeostasis can be accomplished via non-pharmaceutical non-addictive and safer interventions including neuromodulation, nutraceuticals as well as cognitive and mindfulness therapies.

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KB and IE developed the first draft and AB, DB, PKT, CH, MSG and RDB edited and reviewed and inked comments. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Dr Blum is the inventor of GARS and KB220 and holds many patents thereof worldwide. Professor Kenneth Blum also reports personal fees from VNI, electronic waveform labs, Peaklogic, and Sunder Foundation. In addition, Professor Kenneth Blum has a patent 10,894,024 with royalties paid to Synapatamine. The authors report no other conflicts of interest in this work.

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