

Special Issue: Biomarkers of Substance Abuse

## Editorial

# Finding the Roots: Molecularly Tracking Substance Addiction

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We are in the midst of a substance abuse crisis worldwide. A clear and alarming example is the current opioid addiction and overdose epidemic, representing a serious global health problem as well as a significant social and economic burden. One way to promote reaching better solutions to tackling and treating these health-threatening disorders is to present new ideas and findings on the most recent research on substance abuse. Indeed, a major goal is to gain a vantage point on detecting risk, prognosis, and danger of relapse of drug-seeking behavior, as well as any associated complications.

Our themed issue on 'Biomarkers of Substance Abuse' summarizes the state of current research in the fields of opioid, cannabis, nicotine, cocaine, and alcohol addiction. Describing novel findings and molecular details, the issue highlights and proposes avenues of investigation that may lead to improved, well-characterized peripheral biomarkers of substance abuse disorders (SUDs) in humans. On this occasion, *Trends in Molecular Medicine* has hosted two guest editors, Drs. Jonathan Pollock and Kristopher Bough, from the National Institute on Drug Abuse/NIH, who have spearheaded the conception of this informative issue. With the advent of new concepts and methodologies in the field of addiction, the collection explores experimental and modeling approaches geared towards gaining genomic and mechanistic insight into SUD biology that may lead to the discovery of more accurate predictive measures (biomarkers) of diagnosis, prognosis, and ultimately, personalized treatment of SUDs.

We begin our special issue with a spotlight article showcasing exciting new research in animal models: Alexander Smith and Paul Kenny describe how histone deacetylase 5 can epigenetically play a role in regulating gene expression pathways that influence cocaine-seeking behavior, and which enable the formation of drug reward memories in mice.

Kristopher Bough and Jonathan Pollock provide an informative overview describing the urgent need to develop peripheral biomarkers of SUDs and summarizing key points delivered from the contributors of this issue. It is imperative to identify novel SUD biomarkers, as well as to improve and exquisitely refine ones that may already exist. Laura Kwako, David Goldman, and Warren Bickel discuss the reliance on the Addictions Neuroclinical Assessment – encompassing epidemiologic, genetic, clinical, and treatment addiction measurements across populations – to further define candidate biomarkers of SUDs. They propose that behavioral reinforcer pathology, common across various addictions, might be used as a potential biomarker, poised to be behaviorally altered in the course of an addiction.

Neuroimaging is another approach that may inform future SUD biomarker discovery; Matthew Sutherland and Elliot Stein focus on tobacco use and offer a brain systems-level neuroimaging perspective for identifying neurocircuitry that may mediate distinct facets of substance abuse. They posit that this strategy may enable the characterization of novel therapeutic targets, and define biomarkers that might facilitate stratifying SUD patients.

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In terms of alcohol use disorder (AUD), Eric Gross and colleagues expand on the knowledge that the genetic variant of aldehyde dehydrogenase 2 predisposes millions of individuals to aldehyde-induced toxicity with alcohol use. They suggest that measuring aldehyde-induced DNA and protein adducts generated during alcohol metabolism may allow an earlier detection of AUD – including duration and intensity – compared to (or as a complement to) currently used measures for diagnosis/prognosis. Adducts might also inform on the risk of developing AUD-associated complications such as esophageal cancer.

With the recent medicalization and legalization of marijuana use, accurately quantifying exposure, time of use, frequency of use, relapse, withdrawal, as well as predicting the effects of cannabis use, seem imperative. Marilyn Huestis and Michael Smith provide an informative account of this type of cannabis and synthetic cannabinoid quantification of intake and its biomarker potential.

Rajita Sinha and Verica Milivojevic focus on the effects of stress on the pathophysiology of SUDs, and examine peripheral and central stress responses associated with the hypothalamus–pituitary–adrenal axis, the autonomic nervous system, as well as central structural and functional brain modifications. They propose that these response measures might also bear predictive biomarker utility in identifying the development, progression, and relapse of SUDs.

Rachel Tyndale and Laura Bierut discuss the genomic contribution of *CHRNA5* and *CYP2A6* as strong genetic risk factors for tobacco use disorder and smoking-related diseases. They also illustrate how *CYP2A6* variants can lead to differential nicotine metabolite ratios (3-hydroxycotinine: cotinine) that gauge the enzymatic activity of nicotine metabolism in smokers. They propose exploiting the expression of these genes as biomarkers for elevated disease risk and diagnosis, which might enable personalizing smoking cessation treatments.

Biochemical analyses of bodily fluids and excreta can yield a significant amount of information on drug addiction profiles. Susan Sumner and Reza Ghanbari outline the possibility of relying on epigenetic as well metabolomic alterations to define addicted states, using this measure as a biomarker of drug dependence, withdrawal, relapse, and treatment.

An important concern in SUD biomarker discovery is being able to probe opioid function in peripheral tissues. Pierre-Eric Lutz and colleagues describe the neurobiology of  $\mu$ ,  $\delta$  and  $\kappa$  opioid receptors and examine how assessing these molecular pathways may improve and guide SUD diagnosis. Accordingly, they suggest that these pathways should be further investigated for potential pharmacotherapeutic interventions.

Mathematical modeling and high-throughput omics methodologies are being increasingly used to analyze data generated during SUD investigations. However, high-dimensional data are not commonly used. We end our line-up with an article by James Baurley, Andrew Bergen *et al.* highlighting strategies aimed at identifying biomarkers and biosignatures from high-dimensional data types using statistical learning. In their approach, various statistical methods are considered that may help characterize and combine biomarkers of SUDs.

The collection includes updated information on emerging technologies and approaches to explaining the molecular roots of SUDs. It is imperative to molecularly track changes in substance abuse and to build on this knowledge by examining how to apply these analytical tools across different SUDs and for different substances. A plethora of questions flourish from

previous laid-out queries, yet, important research efforts are already here, and exciting progress is just on the horizon. We hope you will enjoy and be informed by this special issue in which we have assembled some of the current trends, and left some provocative ideas to ponder upon. Many thanks to all authors and reviewers for their contribution and insight, and my apologies to the many scientists whose work in the field we were unable to add to this collection. We'd love to hear from our readers: please send your comments to [tmm@cell.com](mailto:tmm@cell.com) or [@TrendsMolecMed](https://twitter.com/TrendsMolecMed). In the meantime, keep on reading!