Chemical Biology of nucleic acid modifications – Celebrating the groundbreaking contributions of Chuan He

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We are excited to present this special issue of the Israel Journal of Chemistry, which is dedicated to the prestigious Wolf Prize in Chemistry 2023 awarded to Chuan He for his "*pioneering work elucidating the chemistry and functional consequences of RNA modification*". In honor of Chuan's remarkable achievements, this special issue features contributions from a number of his past trainees, collaborators, and colleagues. Focusing on "Chemical Biology of nucleic acid modifications," this collection underscores Chuan's pioneering work in epigenetics and epitranscriptomics, which has transformed our understanding of DNA and RNA modifications, unlocking new paths for diagnostics and treatments.[1, 2] We present a collection of 15 Research and Review Articles that demonstrate the wide-ranging impact of Chuan's work across chemical biology, nucleic acid chemistry, biology, epigenetics, biochemistry, and genomics.

The diverse chemical modifications in cellular DNA and RNA, as Chuan has shown, add new dimensions to gene regulation that are crucial throughout development and disease progression. Chuan has been a trailblazer in applying chemical biology tools to mapping and understanding these modifications. This special issue opens with a research article from Chuan's lab, which presents a quantitative sequencing method for 5-formylcytosine (f^5C) in RNA (R. Lyu *et al.* https://doi.org/10.1002/ijch.202300111). f^5C is found in human tRNA and yeast mRNA, however, its transcriptome-wide distribution in mammals remained unexplored. Chuan's lab developed f^5C-seq based on pic-borane reduction to map f^5C transcriptome-wide and advanced our understanding of f^5C in human and mouse cells. The research paper on f^5C sequencing is complemented by a review from Cheng and coworkers, summarizing recent advances in f^5C detection methods through selective chemical labeling, enrichment, and sequencing (X. Wang *et al.* https://doi.org/10.1002/ijch.202300178).

N^6-methyladenosine (m^{6}A) is the most common mRNA modification in eukaryotes. Chuan's lab made a landmark discovery in 2011 by identifying the first RNA demethylase, FTO, which removes the methyl group from m^{6}A.[3] This discovery unveiled the concept of reversible RNA methylation and led to the birth of the epitranscriptomics field. Today, m^{6}A has become the most extensively studied RNA modification. Reflecting its prevalence, five articles in this issue are dedicated to m^{6}A, including two complementary review papers offer a comprehensive look at m^{6}A research. The review by Tang and coworkers is centered on m^{6}A detection methods (R. Ge *et al*. ijch.202300181R1, accepted), while the review by Zhao and coworkers focuses on the biological functions of m^{6}A in gene regulation and cellular diversity (S. Fei *et al*. ijch.202400014, in revision). Wang and coworkers further detailed one particular type of m^{6}A detection techniques involving nitrite-mediated deamination, which holds promise to become the gold standard for quantitative analysis of m^{6}A (W. Shen *et al*. https://doi.org/10.1002/ijch.202300180). Jia and coworkers, on the other hand, reviewed the regulatory role of m^{6}A in plants, which has shown huge potential for improving crop traits, such as increased biomass and enhanced stress resistance (S. Tayier *et al*. ijch.202400029, under review). Completing the m^{6}A segment, a research paper by Yang and coworkers described the synthesis of inhibitors for the m^{6}A demethylase FTO based on 2-(arylthio)benzoic acid, demonstrating their potential therapeutic applications in the treatment of acute myeloid leukemia (AML) (C. Yan *et al*. https://doi.org/10.1002/ijch.202300166).

In addition to m^{6}A, cellular RNA contains over 150 structurally distinct post-transcriptional modifications, which play pivotal roles in a wide range of biological processes due to their chemical diversity and dynamic regulation. Yang and coworkers reviewed RNA methylation broadly, covering m^{6}A, 5-methylcytidine (m^{5}C), *N*^{1}-methyladenosine (m^{1}A), *N*^{7}-methylguanosine (m^{7}G), and *N*^{6},2'-O-dimethyladenosine (m^{6}Am), summarizing their regulatory proteins, distribution pattern, and biological function (G.-G. Song *et al.* ijch.202400003R1, accepted). They further outlined the advantages and limitations of the key sequencing techniques, discussing challenges and future directions in the RNA epitranscriptomics field. Yu and coworkers discussed the two other prevalent RNA modifications, pseudouridine (Ψ) and 2'-O-methylation (2'-O-Me), focusing on the mechanism and function of RNA-guided pseudouridylation and 2'-O-methylation, and the potential therapeutic opportunities for site-specific pseudouridylation and 2'-O-methylation (H. Adachi *et al.* https://doi.org/10.1002/ijch.202400005). Complementing this, a research article from Burrows and coworkers reported nanopore direct RNA sequencing for various uridine modifications, including Ψ, N^1-methylpseudouridine ($m^1Ψ$), 5-bromouridine (BrU), and 5-ethynyluridine (EU) (A. Fleming *et al.* https://doi.org/10.1002/ijch.202300177). $m^1Ψ$ is the key modification used in mRNA vaccines while BrU and EU are widely used for cellular metabolic labelling. Their work laid a foundation for improving nanopore sequencing for these important RNA modifications.

Several articles in this special issue explore both DNA and RNA modifications. Zhou and coworker discussed the use of DNA and RNA modifications to study nucleic acid function and metabolism within cells through cellular metabolic labelling of nucleic acid, a key technique for revealing the dynamic nature of nucleic acid metabolism (Z, He *et al.* https://doi.org/10.1002/ijch.202300165). Their review offers a comprehensive summary of recent advances in metabolic labeling for DNA and RNA and their applications in cellular imaging and sequencing. Focusing on the detection of rare DNA and RNA modification, which may have significant roles, Luo and coworkers discussed the challenges and strategies for their precise detection and mapping, given their scarcity and chemical complexity (R.-J. Luo *et al.* ijch.202400024, in revision). Song and coworkers presented the chemical tools they developed to detect DNA and RNA modifications in a direct, quantitative, and base-resolution manner (H. Xu *et al.* ijch.202400007, under review). These tools include borane reduction chemistry for DNA methylation sequencing, cytosine modification oxidation chemistry for enhanced detection of DNA hydroxymethylation, and bromoacrylamide cyclization chemistry for sequencing RNA pseudouridylation.

Concluding the special issue, two review articles in this special issue highlighted two emerging areas in nucleic acid biology. Dickinson and coworkers' review on engineered RNA-binding proteins offered an overview of the toolkit for creating synthetic RNA regulators (R. Sinnott *et al.* https://doi.org/10.1002/ijch.202300169). These innovative tools can alter RNA sequence composition or fate and are explored for their diverse applications in both basic research and therapeutic settings. Crucially, much of the foundational work, including the elucidation of the writer, eraser, and reader proteins for m^6A, was conducted by Chuan, further underscoring his influence on the field. Wang and coworkers introduced the exciting new area of spatially resolved transcriptomics to map the regulatory events throughout the RNA life cycle, including kinetics, translation, and RNA-protein interactions, at single-cell resolution (Q. Zhou *et al.* ijch.202400028, under review). Finally, they highlighted the recent development in single-cell and spatially resolved epitranscriptomics, with a focus on m^6A. These advancements hold the promise of advancing our understanding of RNA-centered regulatory dynamics across the intricate network of cellular and tissue architecture. It is exciting to envision the new biological discoveries that may arise from spatially resolved epigenomics and epitranscriptomics, especially with the prospects of spatial multi-omics.

Together, this collection of contributions celebrates the transformative power of chemical biology in nucleic acid modification research, a field where Chuan’s pioneering work has made profound contributions. Beyond the broad reach of Chuan’s research, his role as a mentor has been invaluable, inspiring young scientists with his dedication and innovative approach to science. As four of Chuan's previous trainees, we have been deeply inspired Chuan's relentless energy and passion for science. We are thrilled to celebrate Chuan's well-deserved recognition with the Wolf Prize in Chemistry 2023. We express our gratitude to all the authors to this special issue, and we hope that it will spark further interest and advancement in the vibrant frontier of chemical biology.

References

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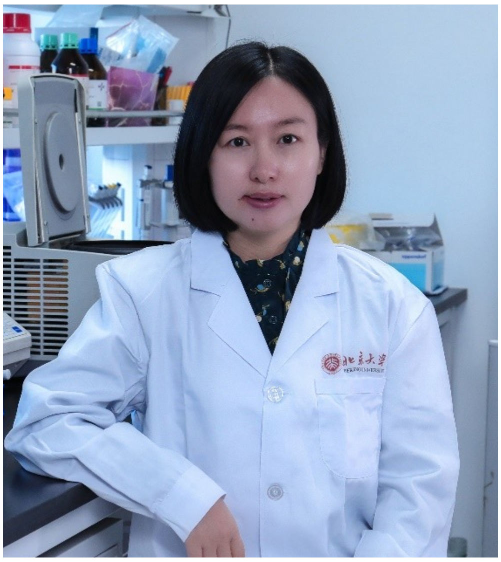
Chun-Xiao Song is an Associate Professor at the University of Oxford. He obtained his B.S. from Peking University in 2008 and completed his PhD at the University of Chicago in Prof. Chuan He’s lab in 2013. After postdoctoral research at Stanford, he started his independent career at Oxford in 2016, where his lab has been developing novel epigenetic sequencing chemistry for understanding chemical modifications in the genome and transcriptome.



Guifang Jia received her B.S. and Ph.D. from China Agricultural University in 2002 and 2008, respectively. She became a visiting student at the University of Chicago to study chemical biology under the guidance of Prof. Chuan He in 2007, and continued her postdoctoral research with Chuan (2007-2012). In 2012, she joined Peking University and currently leads a research group focused on the function of RNA epigenetics in human and plants.

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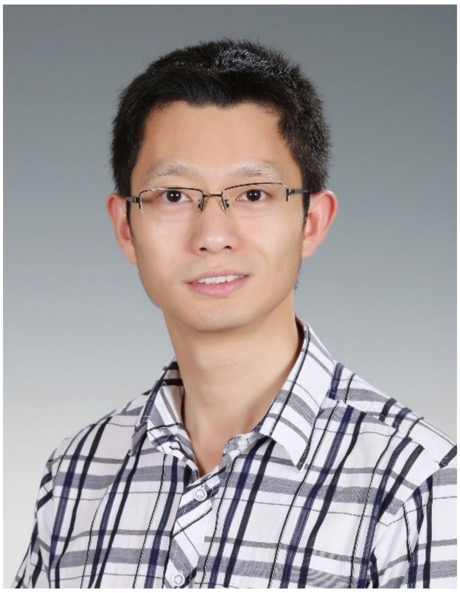

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