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Cell Chemical Biology
Editorial

CellPress

# The Role of Chemical Biology in the Discovery and Understanding of Ferroptosis

At this unusually difficult time, when the world is faced with the challenges of COVID-19, we are pleased to welcome you to this special issue of *Cell Chemical Biology* focused on ferroptosis, which you can add to your reading list while working from home. The purpose of this piece is 2-fold. First and foremost, with the COVID-19 situation, we recognize the professional and personal challenges our scientific community is dealing with and we want to assure you on behalf of *Cell Chemical Biology*'s editorial team that we are dedicated to continuing to support and work with our authors, reviewers, and advisory board members during this extremely difficult period. Second, as we arrive at the 26th anniversary since the launch of the journal in 1994 as *Chemistry & Biology*, we wanted to take a moment to reflect on the major changes that the journal went through in the past few years.

In 1994, launching *Chemistry & Biology*, a journal focused on research that was of interest to both chemists and biologists, was a bold and novel concept. The term "chemical biology" had not yet taken hold in the scientific community and does not appear in the editorial from Schreiber and Nicolaou, though the concepts that we all appreciate today were established by then. 26 years later, the world is a different place: numerous chemical biology journals are thriving. University departments in chemical biology train the next generation of scientists, and the principles of chemical biology are applied to an increasingly diverse set of challenges. It is remarkable that, in 1994, Schreiber and Nicolaou recognized that "it is increasingly clear that chemists and biologists have an enormous amount to say to each other."

Fast forward to 2016: the journal had undergone a transformation to its current name, and the last special issue in *Cell Chemical Biology* focused on chemical biology as applied to cancer research and drug discovery. In contrast to the 1994 launch, the term "chemical biology" was now used 16 times in that editorial, reflecting the increased embracing of chemical biology as a scientific area of its own. The maturation of our field was becoming complete.

In the last few years, *Cell Chemical Biology* went through a major editorial transition. We are grateful to the long-standing former editors of *Cell Chemical Biology*, Kevan Shokat, Craig Crews, Michelle Arkin, Hiroaki Suga, and Milka Kostic, for their service and support over the years. With our new in-house editor, Mishtu Dey, we were excited to build a new editorial team, including Eranthie Weerapana and Daniel Nomura. We are also pleased to introduce a new reviews editor to the journal, Bridget Wagner. Together, we hosted an exciting Cell Press LabLinks meeting "Tools and Tricks for Drugging the Undrugged" for the Cambridge/Boston area in 2019. The meeting brought together researchers across the chemical biology, chemistry, biology, and drug development communities to discuss the state of chemical biology and the next set of challenges for the field. During this LabLinks meeting, leading scientists covered a diverse repertoire of approaches, from targeted protein degradation, to phenotypic screening, to the development of imaging agents, epigenetics, and chemoproteomics, with a common goal of discovering new therapeutics for classically difficult protein targets. This meeting was held at one of the hubs of chemical biology, and the high turnout for this event confirmed to us the enormous appetite of the community for learning more about chemical biology.

Several months ago, as we were thinking about the development and challenges of creative chemical biology approaches in understanding disease biology, the study of ferroptosis (iron-dependent non-apoptotic cell death) struck us as a great example of the importance of chemical biology tools for discovering and characterizing this important pathway. Since its discovery in 2012 by Scott Dixon and Brent Stockwell, the last 8 years have yielded rapid progress in developing novel chemical probes to understand the molecular basis of ferroptosis, identifying ferroptosis-relevant disease, and developing therapies for ferroptosis-driven diseases.

In this special issue, we provide a snapshot of recent scientific developments in the field. We included eight topics that touch upon two main themes. First, we highlight the value of chemical biology in the discovery and understanding of ferroptosis. Second, we aim to provide interesting accounts of the identification of ferroptosis-relevant disease and developments in treating ferroptosis-driven diseases.

On the discovery side, Stockwell and Jiang describe how ferroptosis was first observed upon treatment of cancer cells with chemical probes and now seen in diverse contexts. Armenta and Dixon detail how chemical biology approaches have been used to discover ferroptosis and consider some of the limitations of these approaches. Bayir et al. review ferroptotic death triggered by redox dyshomeostasis of three metabolic pathways controlled by iron, lipid, and thiols and how understanding the selectivity and specificity of these contributory pathways will aid in developing anti- and pro-ferroptotic therapies. Conrad and Proneth highlight the striking role of the selenoenzyme GPX4 in ferroptosis regulation and relate the findings in the context of the management of ferroptosis-associated diseases, such as transient ischemia/reperfusion and neurodegeneration. A mechanistic understanding of ferroptosis provides a clear opportunity to develop broad and effective therapeutics.

We transition the discussion from discovery to disease-relevant contexts and therapeutic benefits. Autophagy is a conserved cellular process by which various biological molecules and organelles are degraded through the lysosomal pathway, and ferroptosis requires the autophagy machinery. Here, Tang and colleagues describe the regulatory mechanisms and signaling pathways of autophagy-dependent ferroptosis. Chemical modulators that are currently available for triggering or blocking autophagy-dependent ferroptosis, and that may be developed for therapeutic interventions in human diseases, are

also summarized. The *in vitro*, *in vivo*, and clinical evidence of ferroptosis in disease is summarized by the group of Donna Zhang, who describe the concept of targeting upstream mediators of the ferroptosis cascade, with the NRF2 pathway as a key example, to treat ferroptosis-driven diseases. As our understanding of ferroptosis has grown over the past several years, its involvement in the pathophysiology of acute kidney injury (AKI) and AKI to chronic kidney disease (CKD) progression has emerged, which is reviewed here by Linkermann and colleagues. Specifically, they discuss ferroptosis and necroptosis as potential therapeutic targets for the treatment of AKI, nephron loss, and the AKI-to-CKD progression. In a Perspective, Zou and Schreiber present progress toward understanding and targeting ferroptosis in several distinct contexts for therapeutic benefit. Above all, we would like to thank each of the authors who contributed to this special issue, as well as the many reviewers who provided such valuable comments.

As new non-apoptotic cell pathways are emerging, we anticipate that in the coming years we will see a growing interest in applying chemical biology toolkits from a diverse group of researchers. As a journal, *Cell Chemical Biology* remains strongly interested in research articles, reviews, and perspectives in this area and beyond. Finally, we would like to thank the chemical biology community for your continued support. If your lab is involved in COVID-19-focused research, we thank you for your effort during this challenging time. We understand the hardships the COVID-19 pandemic is causing; therefore, we would like to emphasize that we are flexible with the timing for revisions, and we encourage you to reach out to us to discuss any matter. We invite you to read this special issue and share your exciting chemical biology stories.

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