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The Circadian System and Cancer: It's About Time!

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The 2017 Nobel Prize in Physiology or Medicine was awarded to 3 researchers who elucidated the molecular mechanism controlling circadian rhythms in humans and other organisms. Jeffrey C. Hall, Michael Rosbash, and Michael W. Young jointly received the prize for determining how the gene *period*, known since the 1970s to influence biological rhythms in fruit flies, actually works. They found that the protein PER, produced by the gene, builds up in the cytoplasm of a cell and then degrades in an approximate 24-hour rhythm. This suggested a feedback loop in which PER inhibits its own synthesis. But PER cannot enter the nucleus to access the gene and stop the synthetic process. The researchers then determined that the gene *timeless* synthesizes the protein TIM, which binds with PER to allow it to enter the cell nucleus. It can then block the activity of the *period* gene. The gene *doubletime* was also shown contribute to this system by delaying the buildup of PER enough to approximate a 24-hour rhythm. This system is at the heart of biological rhythms in all multicellular organisms and affects a multitude of bodily functions that impact health. This Nobel Prize was truly well-deserved. And as the clock turns over to a new year, this prize seems a particularly suitable subject for reflection in launching the first issue of a new volume of *Integrative Cancer Therapies*.

Hall, Rosbash, and Young performed their critical experiments on molecular mechanisms of circadian rhythms in the 1980s and early 1990s. But exploration of the clinical consequences of circadian rhythms in cancer began in the 1970s and proceeded in parallel with the molecular work. The accumulation of clinical as well as experimental work on circadian rhythms in cancer has been steadily building over the years. The circadian system is now starting to come into its own as a target for clinical interventions in cancer treatment. A recent review notes that disruptions of normal circadian rhythms of sleeping and activity are widespread in cancer patients, especially those with metastatic cancer.[1] Such disruptions manifest clinically as inability to sleep at night, excessive daytime napping, fatigue, depression, anorexia, and reduced quality of life. Alarmingly, disrupted circadian rhythms predict reduced overall survival in patients with advanced lung, kidney, breast, and colon cancer. At the cellular level, disrupted circadian rhythms are known to adversely affect angiogenesis,[2] apoptosis,[3] and many other biological processes important in cancer. It is well known that melatonin is important as a "timekeeper" for the circadian system, cuing the system to coordinate with environmental light and darkness. Many cancer patients take melatonin supplements for anticancer effects. But recent work suggests that melatonin alone does not reregulate sleep in breast cancer patients.[4] Rather, timing of meals and exercise, strategic light exposure, social support, scheduled sleep times, and potentially drugs that target circadian timing may be needed to intervene to ameliorate cancer patients' disrupted rhythms.[1,4] Nevertheless, there are studies indicating that high doses of melatonin may improve outcomes of chemotherapy, and numerous studies with melatonin demonstrate its anticancer effects. This suggests that integrative treatment approaches incorporating both lifestyle changes and melatonin may play a large role in circadian cancer therapy.

Integrative Cancer Therapies has been consistently featuring articles on circadian cancer biology since 2009. In that year, we published an entire special issue on circadian rhythms and cancer, guest edited by leading circadian researchers William Hrushesky and David Blask.[5] The special issue contains articles on topics such as tumor suppressor functions of *period* genes; circadian disruptions and cytokine secretion; circadian effects on breast tumor metabolism; clustering of circadian disruption, fatigue, and anorexia in advanced cancer patients; and practical approaches to circadian therapy.[6] A 2011 systematic review examined the effects of melatonin as an adjuvant to cancer treatment.[7] In 2013, the use of melatonin as a dietary supplement in cancer was discussed.[8] And in 2016 we published the first of a series of 3 studies of the impacts of artificial light at night, which is known to suppress melatonin levels, on the incidence of breast cancer.[9] We hope to see many more articles on the topic of circadian cancer biology published in *Integrative Cancer Therapies* and elsewhere in the coming years. Integrative therapies have, we believe, a unique role to play in improving the disrupted circadian rhythms of advanced cancer patients, potentially

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affecting treatment tolerance, response, life quality, and survival. We plan for this journal to continue to play a major role in disseminating studies and practical information on this topic.

In the first volume of each issue of *Integrative Cancer Therapies* we acknowledge the expertise and scientific wisdom of an important group of people: those who have participated in our peer review process in the past year. Journal editors know, perhaps better than most researchers, the critical role of peer review in maintaining the quality of scientific publication. The efforts of reviewers have gone for many years with minimal academic recognition, and our publication of the names of reviewers is just a small token of the true value of their time and of the work they put into article reviews. However, *Integrative Cancer Therapies* is now offering reviewers a way to track and showcase their reviews through the use of the Publons service. Publons is a website (publons.com) that allows reviewers to register each of their reviews, turning them into a measureable research output that can showcase reviewers' expertise and the influence they exert in their fields. Reviewers are now given the opportunity to seamlessly choose to register their *Integrative Cancer Therapies* reviews with Publons as a part of the review submission process. We hope our reviewers will join the more than 200 000 researchers who have already joined the Publons site, so they can better highlight their contributions to their academic colleagues.

In the meantime, we honor those who participated in our review process during 2017 by listing them below:

Douglas Abdalla, Elizabeth Addington, Carl Ade, Sabina Adorisio, Lise Alschuler, Kristina Althoff, Chelsea Anderson, Claudia Arab, Antonietta Arcella, S. Arora, Anna Arthur, Kristen Arthur, Banu Arun, Kyeore Bae, Lynda Balneaves, Louiza Béchohra, Eran Ben Arye, Hartmut Bertz, Penny Block, Stephen Bloor, Barbara Brocki, Amit Budhraja, Zhen Cai, Francesco Carli, Anitra Carr, Tracey Carr, Maëlle Carraz, Raymond Chang, Alejandro Chaoul, Jiun Liang Chen, Qi Chen, Tsai Ju Chien, Jun-Yong Choi, Kyung-Eun Choi, Marcia Ciol, Jayson Co, Colin Curtain, Debabrata Das, Jharna Datta, Niloy Ranjan Datta, Lisa Davis, Haryana Dhillon, Alexandra Dimitrova, Alberto Dionigi, Sergey Dyshlovoy, Canan Eroğlu, Xiang Fan, Yibin Feng, Giammaria Fiorentini, Michael Foley, Judith Fouladbakhsh, Michael Frass, Carlo Fremd, Katharina Gaertner, Jürgen Gailer, Kay Garcia, Sastry Gollapudi, Amir Hossein Goudarzian, Heather Greenlee, C. Guethlin, Huiru Guo, Charlotte Gyllenhaal, Amanda Hagstrom, Tibor Hajtó, Thayele Purayil Hamsa, Reid Hayward, Jacob Hill, Lara Hilton, John Hoffer, YongQiang Hua, Hua-ping Huang, David Hui, Tania Islam, Ju-Hyun Jeon, Yi Jiang, Agata Kabala-Dzik, Gülendam Karadağ, Konstantina Karatrantou, Ji-Ye Kee, Akbar Khan, Young-Kyoon Kim, Yihyun Kwon, Judith Lacey, A. Laengler, Cardella Leak, Jungtae Leem, Teresa Lesiuk, Le-Qun Li, Qinglin Li, Xiaoqian Li, Wei-Zhe Liang, Chuan-Bian Lim, Dai-Wei Liu, Jun Liu, Jun Lu, Wolfgang Marx, Hannah Matthews, Michael McCulloch, Dwight McKee, Mark Mead, Oliver Micke, Shiraz Mishra, Paola Muti, Robert Newman, Torben Nielsen, Byeongsang Oh, Oluwadamilola Olaku, Agnieszka Olchowska-Kotala, Meagan O'Neill, R. B. Oriá, Kazeem Oshikoya, Deng Pan, Siyaran Pandey, Jong-Hyock Park, Luke Peppone, Constant Pieme, Gregory Plotnikoff, Morten Quist, A. D. Rapidis, Sylvie Rapior, Marcella Renis, Mark Renneker, Ramona Ritzmann, Laura Rogers, Dan Rubin, Daniel Santa Mina, Friedemann Schad, Katherine van Schaik, Stefan Schönsteiner, Jessica Scott, Dugald Seely, Georg Seifert, Chun-Chuan Shih, Pamela Siegel, Ana Paula Simões-Wüst, Robert Slater, Judith Smith, Peter Smith, Bridget Southwell, Tobias Sprenger, Kannan Sridharan, Fiona Stacey, Leanna Standish, Fiona Streckman, Daniel Sze, Kenzaburo Tani, Caroline Terranova, Ysabella Vansebille, Erwin Wagner, Won-Bo Wang, Anna-Leila Williams, Raimond Wong, Ting-Feng Wu, Yan Fei Xin, Linhhui Xu, Jun Yan, Geliang Yang, Song Yao, Hung-Rong Yen, Seung-Gu Yeo, Hwa Seung Yoo, Seong Woo Yoon, Teresa Young, Guolin Zhang, Rong Zhang, Jian-Hong Zhong, Suzanna Zick, Philipp Zimmer and Tycho Zuzak.

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