

Young Career Focus: Professor Shanta Dhar (Miller School of Medicine, University of Miami, USA)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Shanta Dhar (Miller School of Medicine, University of Miami, USA).

Biographical Sketch



Prof. S. Dhar

Shanta Dhar is originally from West Bengal, India. She obtained her Bachelor of Science degree with honors in chemistry from the University of North Bengal and she was a silver medalist. She then received her Masters in Science with inorganic chemistry specialization and she was a gold medalist. She pursued her PhD at one of India's finest institutions of higher education – the Indian Institute of Science, Bangalore – under the supervision of Professor Akhil R. Chakravarty. Her thesis work in the area of Metals in Medicine received a “Best Thesis” award for chemical sciences. In 2006, she went to the other side of the globe and joined Johns Hopkins University (USA) as a postdoctoral fellow, where she worked in the area of bioorganic chemistry with Professor Marc M. Greenberg, developing fluorescent sensors for detection of DNA lesions. In 2007, she began her postdoctoral work in the group of Professor Stephen J. Lippard at the Massachusetts Institute of Technology (MIT, USA). Her postdoctoral studies as an Anna Fuller Postdoctoral Fellow of molecular oncology were focused on nanocarrier-mediated delivery of platinum-based compounds for potential applications in cancer. In 2010, she joined the Department of Chemistry at the University of Georgia (USA). In June 2016, she moved to the Department of Biochemistry and Molecular Biology, University of Miami Miller School of Medicine (USA) as an Associate Professor. She also serves as an Assistant Director of Technology and Innovation at Sylvester Comprehensive Cancer Center at Miller School of Medicine. She received the Prostate Cancer Idea Development Award from the Department of Defense, the National Scientist Development Award from the American Heart Association, the Ralph E. Powe Junior

Faculty Development Award from Oak Ridge Associated Universities, the best scientific contribution by the International Society of antioxidants in nutrition and health and the targeting mitochondria conference in 2012, one of “Georgia’s top medical researchers” by Atlanta Business Chronicle in 2014, one of Georgia’s 40 under 40 by the Georgia Trend in 2014, and the Thieme Chemistry Journals Award 2015. She also co-founded a start-up biotechnology company, Partikula LLC, and currently serves as the chair of the Scientific Advisory Board of this company.

INTERVIEW

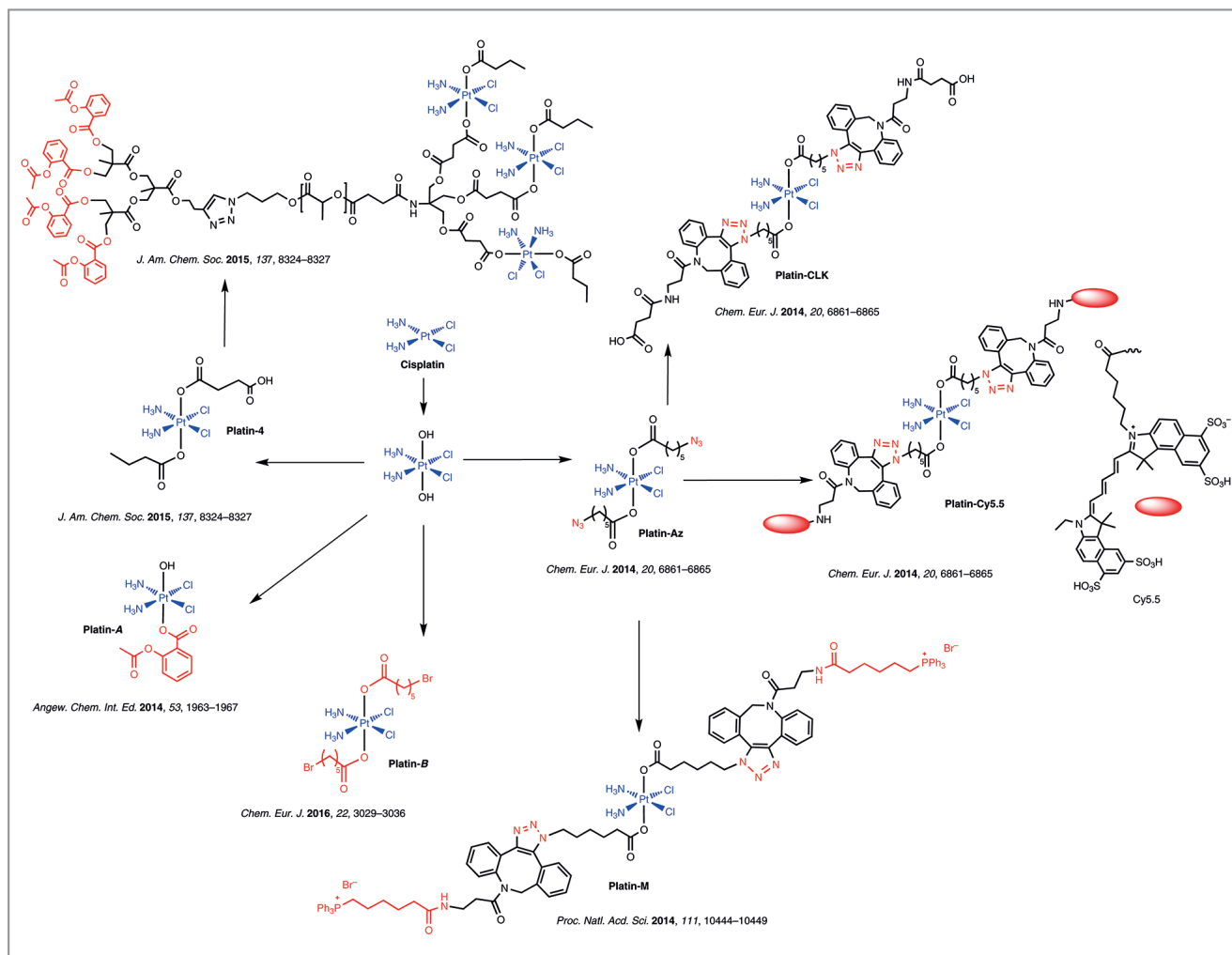
SYNFORM What is the focus of your current research activity?

Prof. S. Dhar I came across an article in *Science Illustrated* about “The top 10 challenges for the coming decade” in human health (*Science Illustrated* **2011**, page 54, Jan/Feb issue). This list included mapping the metabolic system, aging, targeted cancer therapy, obesity, malaria, etc. When I started my independent research program, this article made me think what a chemist with keen interest in solving biomedical problems can do. I looked for common connecting points for these problems to apply my expertise in chemistry, biology, and nanotechnology. I realized if I can focus at the basic level, for example, to mitochondria, which are common connecting points in all these problems, and apply my knowledge, we might have a platform technology. Mitochondrial dysfunctions are involved in most of these diseases. However, most available mitochondria-acting therapeutics face tremendous challenges in reaching the mitochondrial lumen where the therapeutic targets are located. A major focus of my research group is the study and development of nanocarriers for tar-

geted delivery of therapeutics, contrast agents, and other payloads at tunable and/or controlled rates in the mitochondrial lumen. Our work is focused in the following areas: providing new targets for platinum-based compounds using a unique combination of chemistry and nanoengineering, developing sensors and therapeutics for cardiovascular diseases, construction of cell-specific mitochondria-targeted delivery systems with the ability of multiple drug release, creation of nanovaccines, nanoparticle-based therapeutic options for brain trauma, and small-molecule-based prodrugs for cancer and inflammatory diseases.

SYNFORM When did you get interested in synthesis?

Prof. S. Dhar My love for organic synthesis started in college. I remember even trying to teach my little brother, 10 years younger than me, some organic synthesis during my college days when he was in elementary school. During my college days, one of my teachers would challenge me with organic mechanisms and organic transformations. I specialized in inorganic chemistry during my masters training and conducted my PhD in bioinorganic chemistry, and I always enjoyed organic and inorganic synthesis. In my PhD, I was synthesizing copper(II) ternary complexes, which were interpreted as difficult to synthesize. I ended up synthesizing numerous ternary complexes and was even able to get 18 such



Scheme 1 Synthesis of numerous platinum-based compounds/conjugated polymers with anti-tumor properties that were synthesized from a single FDA approved drug cisplatin as a precursor

complexes characterized by single-molecule X-ray crystallography. I love doing synthesis. I then had a one-year bootcamp organic synthesis training in Professor Greenberg's lab and I really got interested in doing organic synthesis and the new molecules one can construct using organic reactions. This training helped me to integrate organic and inorganic synthetic strategies together to create small and macromolecules. At MIT, I fell in love with synthetic aspects dealing with platinum complexes by taking advantage of different oxidation states and geometries that this precious metal offers.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. S. Dhar Being a chemist who aims to use synthetic chemistry to develop organic and inorganic molecules, nanodelivery vehicles, and combination therapeutic approaches for medical/biological applications, I would like to express my view of the role and prospects of organic synthesis by quoting the exciting comment of German chemist Friedrich Wöhler after he synthesized urea and wrote to his mentor "...I cannot, so to say, hold my chemical water, and must tell you that I can make urea, without thereby needing to have kidneys, or anyhow, an animal, be it human or dog..." Organic synthesis provides a valuable tool towards recreating biologically relevant compounds for a multitude of different purposes. In addition to traditional medicinal chemistry, organic synthesis has the power to truly transform the field of nanomedicine and bioinorganic chemistry. One of the major challenges we often observe in nanomedicine is to reproducibly construct drug-loaded materials when we consider advancing these unique technologies to the clinic. Organic synthesis has the potential to provide solutions to these problems; one can use unique organic synthetic strategies to reproducibly make these materials. Platinum complexes with anti-tumor properties are the most conspicuous representatives in medicinal inorganic chemistry and organic synthesis provided tools to modify the completely inorganic parent compound cisplatin, resulting in the platin-based subfield of bioinorganic chemistry. The impact of organic synthesis in medicine in the last two centuries has been extraordinary and this will continue to happen as organic synthetic chemists find sophisticated synthetic strategies. Organic synthesis will continue to influence the growth of nanomedicine, metal-based medicine, and other relevant fields in medicine.

SYNFORM *Your research group is active in the areas of organic synthesis, nanotechnology and biomedicine. Could you tell us more about your research and its aims?*

Prof. S. Dhar Mitochondria are not only the energy factories of cells but these dynamic organelles participate in the overall process of cellular mortality; thus, their dysfunctions lead to various diseases such as cancer, atherosclerosis, and neurodegenerative diseases in addition to conventional mitochondrial dysfunction-related diseases. To tackle these diseases, one needs to access the targets, which are located in mitochondrial lumen. Targeting mitochondria has been notoriously challenging due to their complex and dynamic nature. My lab is actively involved in generating biodegradable, tunable nanodelivery vehicles for efficacious mitochondrial delivery of therapeutics for cancer, neurodegenerative diseases, and cardiovascular diseases. As we move forward, we plan to expand the application of such nanoparticle (NP)-based platforms to other diseases where mitochondria and their abnormalities play integral roles. We also discovered that suitably optimized mitochondria-targeted NPs could distribute in the brain and we are working on the potential of mitochondria-targeted lipophilic biodegradable NPs with the ability of traversing the blood-brain barrier in neurodegenerative diseases and brain cancers.

Coronary events continue to be the leading cause of death in the United States. We are active in applying our synthetic chemistry to construct synthetic, biodegradable, mitochondria-targeted NP platforms with the ability to participate in extra- and intra-cellular lipid reduction pathways for cardiovascular diseases.

We have several programs developing alternative therapeutic platforms for cancer. One of the effective methods to tackle metastatic cancers will be to engage our immune system. We use a unique combination of mitochondrial stimulation of cancer cells using targeted NPs and light to activate the immune system. Targeting mitochondrial DNA (mtDNA) can be important for cisplatin-based chemotherapy. Cisplatin is a widely used and FDA-approved chemotherapeutic agent which is highly effective against several cancers. Therapeutic action of cisplatin relies on its ability to form interstrand and intrastrand nuclear DNA (nDNA) cross-links. Resistance to cisplatin-based chemotherapy arises from different cellular processes, one of which is accelerated DNA repair by nucleotide excision repair machinery. The absence of such repair machinery in the mitochondria and enhanced mtDNA mutation in aggressive cancers motivated us to reroute cisplatin to attack mtDNA. We are developing such technologies for nanoparticle-mediated cisplatin delivery in the form of activable prodrugs to the mitochondria of different cancer cells to attack mitochondrial genome for chemo-resistant cancers.

In the search for a successful treatment, it is evident that a single magic bullet is not enough for metastatic cancers. However, systemic administering of bolus doses of multiple therapeutics often results in intense side effects. We are engineering polymers with biodegradable dendrons at the termini through direct conjugation to incorporate anti-inflammatory drugs, chemotherapeutics along with cancer cell targeting moieties to provide an all-in-one therapeutic NP platform for metastatic cancers.

Cancer-related mitochondrial alterations such as defective oxidative phosphorylation, mitochondrial biogenesis, down-regulation of ATP synthase, and mitochondrial-reactive oxygen species provide unique targets for selective treatment modalities. Thus, engineering of small molecules known to work at different targets inside the mitochondria or developments of such molecular payloads containing mitochondria-targeted NPs have the potential to provide tumor-specific anticancer agents. We are involved in the development of mitochondria-targeted prodrugs that can be locally activated at the target sites: some examples are dichloroacetic acid, 3-bromopyruvate, Bcl-2 inhibitors.

SYNFORM *What is your most important scientific achievement to date and why?*

Prof. S. Dhar My most significant research accomplishment to date is the development of a biodegradable nanoparticle platform from Food and Drug Administration approved components for mitochondrial dysfunction-related diseases. This technology can be useful to study a wide range of human diseases where mitochondrial dysfunction is a major player. This platform technology has resulted in several other important contributions, including the first synthetic mitochondria-targeted nanoparticle that can mimic the functional behaviors of high-density lipoprotein for potential applications in coronary artery disease, the ability to generate functional immune cells in vitro for cancer vaccines, providing an alternative target to platinum-based drugs for overcoming resistance, the development of biodegradable dendron-functionalized polymeric nanoparticles for combination therapy, mitochondria-targeted metabolic reprogramming of cancer cells, and the evaluation of nanoparticle-based neuroprotection therapy for brain injury.

