Bhabatarak Bhattacharyya (1944–2021)

Professor Bhabatarak Bhattacharyya, fondly known by his nickname 'Bablu', passed away on 6 May 2021. He was a distinguished biophysicist and made stellar contributions in understanding the biophysical and pharmacological properties of tubulin, the eukaryotic cell division protein. Originally a chemist, Bhattacharyya set out to build his career on applying biochemical and biophysical techniques to address the fascinating mysteries of biology, specifically the eukaryotic cytoskeleton. For more than four decades, he led the investigation of several aspects of the cytoskeletal protein tubulin primarily on tubulin–drug interactions, folding and unfolding pathways of tubulin, and chaperone-like activity of tubulin.

Bhattacharyya had both Bachelor's and Master's degrees in Chemistry from Calcutta University, West Bengal. Intrigued by biology, yet drawn to chemistry, he went on to pursue his doctoral work – investigating the interaction of small molecules with DNA, under the guidance of Umashankar Nandi (whose lab was first at the Indian Association for the Cultivation of Science, Jadavpur and then at Indian Institute of Science, Bangalore). He then joined the laboratory of J. Wolff at the National Institutes of Health, Bethesda, USA as a postdoctoral fellow. Bhattacharyya utilized his physical chemistry expertise to understand colchicine–tubulin interaction. Colchicine is a widely used antimitotic agent for understanding mitosis and the role of microtubules in cell division. He discovered that colchicine strongly fluoresces upon binding to tubulin. Using the development of colchicine fluorescence upon tubulin binding, he elucidated several interesting characteristics of colchicine binding to tubulin. This provided a method to study tubulin–colchicine interaction without using radioactivity. Even today, researchers use this technique to discover colchicine analogs and to understand the interactions of colchicine site agents with tubulin. He was also able to purify and polymerize membrane tubulin. This discovery of the polymerization of the membrane tubulin was published in *Nature*. Even with all the prospects of a full-time research career in the USA, Bhattacharyya did not deviate from his long-term dream of nurturing the development of science and research in India. He established his lab at the Biochemistry Department of Bose Institute, Kolkata, India. His lab was the first tubulin laboratory in the country and he was lovingly known as the microtubule-organizing centre of India. Several of his graduate students are now leading microtubule laboratories in India. Microtubules formed by the polymerization of the tubulin dimer of alpha and beta subunits, provide the structural framework to the cells to carry out important processes such as cell division, cell polarity and cell motility. He showed that the C-terminal tails of tubulin, previously

thought only to associate with microtubule-associated proteins (MAPs), also had an important role in the association between alpha and beta-tubulin subunits.

Tubulin is an important drug target. A large number of anti-cancer drugs, such as vincristine, target tubulin. Bhattacharyya studied the interaction of several of such drugs with tubulin, including analogs of colchicine. He and his group published a detailed study of the thermodynamics of B-ring analogs of colchicine–tubulin interactions to understand the role of the C-7 substituent on the B-ring of the colchicinoids for tubulin–colchicine binding. Colchicine exerts its antimitotic property upon binding to a high-affinity site on the tubulin heterodimer. It is composed of a trimethoxybenzene ring (A-ring), a methoxytropone ring (C-ring) and a seven-membered ring (B-ring), which anchors the A- and C-rings. His structure–activity studies indicated that the A- and C-rings of colchicine comprise the minimum structural features of the molecule necessary for its high-affinity binding to tubulin. The role of C-7 substituents on the B-ring was not known. His group determined the thermodynamic parameters for the binding reactions of four B-ring analogs of colchicine with tubulin: deacetamidocolchicine (DAAC), 1 deacetylcolchicine (NH2-DAAC), demecolcine (NHMeDAAC) and N-methyldemecolcine (NMe2-DAAC) using steady-state fluorescence spectroscopy. The study indicated that the presence of B-ring per se did not affect the entropic contribution significantly, as bindings of both AC and DAAC were enthalpy-driven reactions. It is the amino substituent at the C-7 position in the B-ring that converts an enthalpy-driven reaction into an entropy-driven reaction. Thermodynamic data of colchicinoid–tubulin interactions suggest that the C-7 substituent on the B-ring of the colchicinoids studied here make additional contact(s) with the dimeric tubulin molecule.

Bhattacharyya is well-known for his research on the pharmacological properties of tubulin. However, one of his significant contributions to tubulin research was the discovery of the chaperone-like activity of tubulin. Molecular chaperones are specialized classes of proteins that assist the folding of cellular proteins by protecting their structures under stress conditions. Only a small number of molecular chaperones have been identified in eukaryotic cells so far and they are known to assist the folding of only a limited subset of proteins. Therefore, it is an open question how the vast majority of proteins are folded in cells. Tubulin is a highly abundant multi-subunit protein with several hydrophobic patches and unstructured regions. These features are commonly found in many chaperones. Bhattacharyya conceptualized the idea that tubulin could play important roles in protecting cellular proteins during their structural organization or folding. His group convincingly demonstrated that mammalian tubulin stabilizes several proteins and enzymes from heat or chemically induced aggregation. Tubulin assists other cellular proteins to refold and restore their biological activities

during renaturation. His work also demonstrated that tubulin interacts with the substrate proteins in their unfolding or refolding intermediate states. Interestingly, his work also revealed that charged C-terminal tails of tubulin play an important role in imparting this function. These findings could have meaningful and far-reaching implications. Protein misfolding and aggregation are causal factors for numerous diseases, including Alzheimer's, Parkinson's and cancer. Functions of several well-established molecular chaperones have been implicated to be closely linked to tubulin and microtubules. For example, heat shock protein 90 (HSP90), an abundant chaperone in mammalian cells, functions in concert with microtubules/tubulin and is trafficked along the microtubule. Interestingly, later studies from the Bhattacharyya lab revealed that microtubule-associated protein MAP2 also possesses chaperone-like activity. It will be interesting to investigate whether or not the chaperone activities of microtubule proteins are exhibited *in vivo*, the answer of which may uncover new cellular pathways of protein folding.

Bhattacharyya's contributions were recognized by several awards and fellowships of several Academies. He received the Shanti Swarup Bhatnagar award in 1989 from the Council of Scientific and Industrial Research (CSIR), Government of India. He was an elected fellow of National Academy of Sciences, Indian Academy of Sciences, Indian National Science Academy, and a fellow of The World Academy of Sciences. He also received the prestigious Ramanna fellowship.

Bhattacharyya contributed immensely to the growth of protein science in India. However, we must not fail to acknowledge his caring side and highly effective mentorship. His peers would describe Bablu Bhattacharyya as a kind and friendly person while his 24 graduate students – several are now faculty members in several top institutes like IITs, IISERs and renowned universities – would unanimously agree about his inspiring demeanor. He was an excellent researcher, philosopher, and most importantly an inspirational teacher. One of his good qualities was that he truly appreciated good research, irrespective of the status of the person who was doing it. He encouraged young people to do good science. He was instrumental in making Bose Institute a prominent centre of biophysical research. We will deeply miss Bablu, and he will always be in our memories for his patience, simplicity and pleasant personality. He is survived by his wife and two daughters.

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