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I was born in Jajpur, a small town in Odisha, India, on November 1, 1955, to Manju and Prafulla Jena. My early childhood was spent in remote villages in Odisha, where my grandfather practiced medicine. The dedication of my father and grandfather to science and medicine and their service to humanity greatly influenced me to choose a career in science. I majored in Chemistry, Zoology, and Botany, for my Undergraduate studies at BJB College in Bhubaneswar, Odisha, India (B.Sc., 1975) and completed my Masters in Science with Zoology (Endocrinology) as major from Utkal University, Odisha, India (M.Sc., 1978). I graduated as the top student in the Masters of Science program and received the Prasant Ku. Memorial Prize and the Utkal University Gold Medal.

In August 1982, I joined Iowa State University, Ames, Iowa, USA on a Research Assistantship to carry out studies leading to a Ph.D. degree, first in the laboratory of Prof. John B. Balinsky (who suddenly passed away at the young age of 49) for a year, then moved to the laboratory of Prof. Joel A. Abramowitz, where I received the rest of my doctoral training. My research project in the Abramowitz lab. was to understand how receptor-mediated GTP-binding G protein signaling is turned off. I used the rabbit corpus luteum as model system for my studies. These studies resulted in the publication of four research papers **(1-4)** and several abstracts and presentations in international meetings. In December 1988, I received my Doctoral Degree in Zoology, and was awarded the Research Excellence Award by Iowa State University, for outstanding contribution in the graduate research program.

Following my doctoral studies, I joined the laboratory of Prof. James D. Jamieson, in the Department of Cell Biology, at Yale University School of Medicine, New Haven, CT, USA as a Research Associate and then as a Fellow. In the Jamieson Lab. I was introduced to the field of cell secretion, and exposed to Professor's George E. Palade and Gunter Blobel and to their thinking and approach to solving emerging questions in cellular structure-function. There were frequent discussions as to how partially empty vesicles are generated following a secretory episode, when the conventional understanding then was that secretory vesicles completely merge at the cell plasma membrane to expel their entire vesicle contents. In my four years in the Jamieson Lab. I hypothesized that there has to be a structure that served as a portal (similar to Blobel's "translocon-signal peptide hypothesis") that would allow secretory vesicles to transiently dock, fuse and release a portion of the intra-vesicular contents, and then disengage from the cell plasma membrane without compromising the integrity of either the secretory vesicle membrane or the cell plasma membrane. In my tenure in the Jamieson Lab., I published four scientific papers **(5-8)** focused on cell secretion, using the well characterized exocrine pancreas as the model system.

Following my post-doctoral training, I accepted a faculty appointment in 1994 at Yale University School of Medicine as an Assistant Professor. Immediately, after establishing my own research group, we set out to test the hypothesis that cells have a 'secretory portal' resident at the plasma membrane where secretory vesicles could dock and transiently fuse to release a portion of their contents during secretion. We had access to a new imaging modality, the Atomic Force Microscope, capable of nanoscale resolution of live cells, which we utilized to search for such a structure. We utilized the well characterized polarized cells of the exocrine pancreas as our model system, since in this slow secretory cell (secretes digestive enzymes over minutes as opposed to the neurons that secrete neurotransmitters in milliseconds). In 1995-1996, we first saw these portals, and published our exciting results in the Proceedings of the National Academy of Science, first on-line in 1996 and in print on January 1997 **(9)**. In the next two decades that followed, we characterized the secretory portal and the molecular mechanism of its function **(selected references:10-28)**, naming it the 'porosome'. We have isolated and

functionally reconstituted the porosome complex into lipid membrane (like Blobel has done for the transport of the signal peptide through the translocon) **(13,14)**, and in live cells **(18,31)**. The porosome discovery, and the elucidation of its structure-function and reconstitution, help establish a drug discovery platform to treat diseases resulting from secretory disorders like cystic fibrosis and diabetes **(29-31)**. During this period, in 2000, I moved to the Department of Physiology, at Wayne State University School of Medicine, as a tenured full Professor, and Founder-Director of the Institute of NanoBioScience. In recognition of these contributions, in 2004, I was conferred the title of Distinguished Professor, and the George E. Palade University Professor by the Board of Governors of Wayne State University. I remain the only living University Professor, and the second in Wayne State University's 160-year history. Currently, the major focus of my laboratory is to determine the distribution of proteins within the porosome complex using single particle cryoelectron microscopy, and small angle x-ray solution and neutron scattering. In the past two decades, I have been involved in institution building to bring the benefits of science and education to society.

Among the honors and awards I have received: Distinguished Scientist Award from the Society for Experimental Biology and Medicine; Elected Foreign Member of the Georgian National Academy of Science; Fellow AAAS; Elected Foreign Member of the Korea Academy of Science & Technology; Elected Foreign Member of the National Academy of Medicine, Romania; Elected to the European Union Academy of Science; the Swebelius Cancer Research Award; the Hallim Distinguished Award Lecture jointly with the Prof. Ahmed H. Zewail; Sir. Aaron Klug Award; ASAS Basic Biological Science Award; Ranbaxy Basic Research in Medical Sciences Award; George E. Palade Gold Medal; Elected to the Academy of Scholars at Wayne State University; six Honorary Doctorates including one from Babes-Bolyai University, Romania, jointly with Prof's George E. Palade and Günter Blobel; and Distinguished Visiting Professorships in a number of institutions.

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Scientific Achievements

The Jena research group has made the following contributions in cell biology and translated these contributions to application for the benefit of human health and medicine: **(1)** Discovery and characterization (chemistry, structure and functional reconstitution) of the 'porosome', the universal secretory portal in cells. **(2)** Translate porosome discovery to treat diseases resulting from secretory defects such as cystic fibrosis, diabetes and neurological disorders. **(3)** Progress in our understanding of the regulation of the bidirectional water channel Aquaporin (AQP1). **(4)** Use of quantum dots as a disease detection tool: **(a)** to determine muscle efficiency hence disease states, **(b)** identify cancer from non-cancerous tissue, and **(c)** to overcome antibiotic resistance by identifying the precise antibiotic to be used for bacterial infection in patients. **(5)** Greatly contributing to the new imaging approach of Expansion Microscopy (ExM) with the development of "Differential ExM (DiExM)".

Porosome discovery & Its translation in treating diseases: In studies conducted nearly 30 years ago, using atomic force microscopy (AFM), the Jena Laboratory identified nanoscale transmembrane cup-shaped lipoprotein secretory portals at the cell plasma membrane and named them '**porosome**' **(1-15)**. In the next decade that followed, Jena and his research team demonstrated that porosomes serve as the universal secretory machinery at the cell plasma membrane, where secretory vesicles transiently dock and fuse to release a portion of their contents during secretion. The family of proteins that compose the porosome has been biochemically identified and the mesoscale structure of the complex has been well characterized through electron microscopy and solution X-ray methods. Furthermore, the porosome has been isolated and functionally reconstituted in lipid membrane and in live cells. Defects in one or more porosome components has measurable, often highly potent effects on the regulation of secretion, establishing links between point mutations and secretion-defective disease states such as cystic fibrosis that were previously correlative and are now causative. Furthermore, the discovery of the porosome solved the conundrum of fractional discharge of intra-vesicular contents from cells during secretion, by providing an explanation for regulated graded release of intra-vesicular contents. Porosomes range in size from 15 nm in neurons, to 100-180 nm in endocrine and exocrine cells and are composed of approximately 30 proteins. In comparison, the 120 nm nuclear pore complex is composed of nearly 1,000 protein molecules. The discovery of the porosome **(2-15)**, formation of SNARE ring complex at the porosome base to establish continuity between the porosome and the secretory vesicle **(16-21)**, and the molecular mechanism of secretory vesicle volume regulation for secretion **(22-26)**, has brought about a clear and compelling understanding of the fractional intra-vesicular content release from cells during secretion. Furthermore, the discovery of the 'porosome', has provided a platform [https://www.porosome.com] for entry into a new era in drug design, development and therapy. Many diseases, such as Cystic Fibrosis (CF), Type I & Type II Diabetes (T1D, T2D), neurological disorders, immune disorders and various cancers, result from secretory defects in the porosome. These diseases can now be addressed by incorporating the native functional porosome machinery into diseased cells, or by using small molecules and nanobodies directed at porosome proteins, to modulate the cell's secretory activity and treat the disease **(11,27,24)**.

Regulation of the bidirectional transport of water through the water channel Aquaporin (AQP): Water is the most abundant molecule in living organisms, and aquaporin (AQP), the bidirectional water channel is responsible for actively transporting water from into or out of the cell or between various cellular compartments as required to sustain life. The pioneering research by the Jena group has greatly progressed our understanding of the regulated transport of water through AQP **(22-26)**. Consequently, a symposium was organized at Uppsala, Swedish Chemical Society, on this new understanding on the regulation of AQP in water transport in cells: https://kemisamfundet.se/event/minisymposium-the-molecular-regulation-of-water-gas-transport-via-aquaporins-in-cells/

Quantum dots as disease detection tools and for exploring fundamental cellular processes: Using quantum dots as nanothermometers, the Jena laboratory has developed elegant approaches to detect muscle function and efficiency for detection of various muscle disorders **(29)**, to detect cancers **(Supplementary information in ref. 29)**, approaches to overcome antibiotic resistance, and to determine energetics of fundamental process such as protein-Calcium/Magnesium ion interactions **(30)**,

Development of Differential Expansion Microscopy (DiExM) and its application: In 2015, as opposed to the invention of an imaging tool, the substrate was enlarged using an approach termed expansion microscopy (ExM) to enable nanoscale imaging using a diffraction limited light microscope. In this simple yet novel new

approach, hydration-competent polymers are used to physically expand biological specimens to be imaged at approximately 70 nanometer resolution using a diffraction limited optical microscope. Not surprisingly however, the Jena group demonstrated that different tissues, including subcellular organelles expand differently and developed a correction approach and developed protocols for up to 500-fold expansion in 3D, which was named differential expansion microscopy (DiExM) **(31)**. The Jena group has also contributed to the next generation ExM, MicroMagnify **(32).**

Two Editorials (33,34) reflect on the contributions of the Jena Laboratory.

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Twenty Important Papers

POROSOME: Discovery, Structure-Function, Composition, Reconstitution

1. Schneider SW, Sritharan KC, Geibel JP, Oberleithner H & **Jena BP**. (1997) Surface dynamics in living acinar cells imaged by atomic force microscopy: Identification of plasma membrane structures involved in exocytosis. *Proceedings of the National Academy of Sciences of the United States of America*. 94: 316-321. (published in 1996 on-line ahead of print) PMID 8990206 DOI: 10.1073/pnas.94.1.316

   (Using atomic force microscopy (AFM), 100-180 nm pores at the apical plasma membrane of live pancreatic acinar cells were observed for the first time. The pores dilated during secretion, and returned to resting size following completion of secretion. Exposure of cells to the actin depolymerizing fungal toxin cytochalasin, resulted in collapse of the pore opening and a consequent loss of secretion. These results suggested the pores to be secretory portals at the cell plasma membrane)

2. Cho SJ, Wakade A, Pappas GD & **Jena BP**. (2002) New structure involved in transient membrane fusion and exocytosis. *Annals of the New York Academy of Sciences*. 971: 254-6. PMID 12438127

   (Using AFM, a new group of plasma membrane structures (initially misnamed 'fusion pore', and later named 'porosome') in pancreatic acinar cells were found to be involved in the possible docking of secretory vesicles and their transiently fusion to release intra-vesicular contents to the outside during cell secretion)

3. Cho SJ, Jeftinija K, Glavaski A, Jeftinija S, **Jena BP** & Anderson LL. (2002) Structure and dynamics of the fusion pores in live GH-secreting cells revealed using atomic force microscopy. *Endocrinology*. 143: 1144-8. PMID 11861542 DOI: 10.1210/endo.143.3.8773

   (Immuno-AFM studies localizing antibody-conjugated gold against secreted growth hormone, demonstrate that the pores present at the cell surface of growth hormone secreting cells are secretory portals initially misnamed 'fusion pore', and later named 'porosome')

4. **Jena BP**, Cho SJ, Jeremic A, Stromer MH & Abu-Hamdah R. (2003) Structure and composition of the fusion pore. *Biophysical Journal*. 84: 1337-43. PMID 12547814 DOI: 10.1016/S0006-3495(03)74949-2

   (Immuno-AFM studies localizing amylase antibody-conjugated gold at the porosome opening to the outside. This study further demonstrates that t-SNARE is present at the base of the cup-shaped porosome complex facing the cell cytosol)

5. Jeremic A, Kelly M, Cho SJ, Stromer MH & **Jena BP**. (2003) Reconstituted fusion pore. *Biophysical Journal*. 85: 2035-43. PMID 12944316 DOI: 10.1016/S0006-3495(03)74631-1

   (Using electron microscopy, this was the first demonstration of a secretory vesicle docked and transiently fused at the porosome base in a pancreatic acinar cell. Furthermore, in this study, the structural and functional reconstitution of isolated porosomes into lipid membrane was demonstrated for the first time)

6. Cho WJ, Jeremic A, Rognlien KT, Zhvania MG, Lazrishvili I, Tamar B & **Jena BP**. (2004) Structure, isolation, composition and reconstitution of the neuronal fusion pore. *Cell Biology International*. 28: 699-708. PMID 15516328 DOI: 10.1016/j.cellbi.2004.07.004

   (Neuronal porosome complex isolated and functionally reconstituted for the first time)

7. Cho WJ, Ren G & **Jena BP**. (2008) EM 3D contour maps provide protein assembly at the nanoscale within the neuronal porosome complex. *Journal of Microscopy*. 232: 106-111. PMID 19017207 DOI: 10.1111/j.1365-2818.2008.02088.x

   (EM 3D contour map of the neuronal porosome complex confirming its 15-17 nm size, having a central plug connected to 8 protein densities at the periphery of the structure)

8. Lee JS, Jeremic A, Shin L, Cho WJ, Chen X & **Jena BP**. (2012) Neuronal porosome proteome: Molecular dynamics and architecture. *Journal of Proteomics*. 75: 3952-62. PMID 22659300 DOI: 10.1016/j.jprot.2012.05.017

   (Core proteins constituting the neuronal porosome complex in the rat brain was determined in the study)

9. Kovari LC, Brunzelle JS, Lewis KT, Cho WJ, Lee JS, Taatjes DJ & **Jena BP**. (2014) X-ray solution structure of the native neuronal porosome-synaptic vesicle complex: Implication in neurotransmitter release. *Micron (Oxford, England: 1993)*. 56: 37-43. PMID 24176623 DOI: 10.1016/j.micron.2013.10.002

   (Native neuronal porosome structure determined using solution X-ray. The X-ray solution structure of synaptic vesicles docked at porosomes present at the presynaptic membrane in isolated rat brain synaptosome was determined)

10. Naik AR, Kulkarni SP, Lewis KT, Taatjes DJ & **Jena BP**. (2015) Functional reconstitution of the insulin-secreting porosome complex in live cells. *Endocrinology*. en20151653. PMID 26523491 DOI: 10.1210/en.2015-1653

    (The porosome complex was functionally reconstituted for the first time in live cells)

SNARE COMPLEX ASSEMBLY & MEMBRANE FUSION

11. Cho SJ, Kelly M, Rognlien KT, Cho JA, Hörber JK & **Jena BP**. (2002) SNAREs in opposing bilayers interact in a circular array to form conducting pores. *Biophysical Journal*. 83: 2522-7. PMID 12414686

    (t-SNAREs and v-SNARE present in opposing bilayers interact to form a rosette or ring complex establishing a conducting channel in presence of calcium)

12. Cho WJ, Jeremic A & **Jena BP**. (2005) Size of supramolecular SNARE complex: membrane-directed self-assembly. *Journal of the American Chemical Society*. 127: 10156-7. PMID 16028912 DOI: 10.1021/ja052442m

    (t-SNAREs and v-SNAREs present in opposing bilayers interact to form a rosette or ring complex. The size of the rosette is directly proportional to the curvature of the SNARE-associated membrane, hence smaller the vesicle higher its curvature, and smaller the size of the t-/v-SNARE rosette)

13. Jeremic A, Quinn AS, Cho WJ, Taatjes DJ & **Jena BP**. (2006) Energy-dependent disassembly of self-assembled SNARE complex: observation at nanometer resolution using atomic force microscopy. *Journal of the American Chemical Society*. 128: 26-7. PMID 16390104 DOI: 10.1021/ja056286v

    (t-SNAREs and v-SNARE need to be membrane-associated to interact in a circular array to form conducting pores in the presence of calcium. This study also demonstrates that t-/v-SNARE complex requires NSF-ATP to disassemble)

14. Shin L, Cho WJ, Cook JD, Stemmler TL & **Jena BP**. (2010) Membrane lipids influence protein complex assembly-disassembly. *Journal of the American Chemical Society*. 132: 5596-7. PMID 20373736 DOI: 10.1021/ja101574d

(Smaller t-/v-SNARE ring complexes are generated when SNARE's are associated in membrane containing cholesterol. Furthermore, NSF-ATP-mediated t-/v-SNARE disassembly is negatively impacted in the absence of cholesterol)

15. Jeremic, A., Kelly, M,, Cho, J.A., Cho, S.J., Horber, J.K., **Jena, B.P.** (2004) Calcium drives fusion of SNARE-apposed bilayers *Cell Biology International* 28(1):19-31. PMID 14759765 DOI:10.1016/j.cellbi.2003.11.004.

(This study demonstrates that SNAREs and calcium are the minimal fusion machinery. Furthermore, results from the study suggests that neutralization of the negatively charged phospholipid head groups by Ca^{2+}, results in enhanced membrane–membrane interactions, formation of Ca^{2+}-phosphate bridges between opposing bilayers, freeing bilayers of inter-lamellar water, consequently resulting in lipid mixing and membrane fusion)

VESICLE VOLUME REGULATION IN CELL SECRETION

16. **Jena BP**, Schneider SW, Geibel JP, Webster P, Oberleithner H, Sritharan KC. (1997) G(i) regulation of secretory vesicle swelling examined by atomic force microscopy. *Proceedings of the National Academy of Sciences of the United States of America*. 94: 13317-13322. PMID 9371843 DOI: 10.1073/pnas.94.24.13317

(GTP-induced live secretory vesicle swelling observed at nanometer resolution in 3D using AFM)

17. Cho SJ, Sattar AK, Jeong EH, Satchi M, Cho JA, Dash S, Mayes MS, Stromer MH & **Jena BP**. (2002) Aquaporin 1 regulates GTP-induced rapid gating of water in secretory vesicles. *Proceedings of the National Academy of Sciences of the United States of America*. 99: 4720-4. PMID 11917120 DOI: 10.1073/pnas.072083499

(First demonstration that secretory vesicle volume increase is via the water channel or aquaporin, which is a GTP-mediated event)

18. Kelly ML, Cho WJ, Jeremic A, Abu-Hamdah R, & **Jena BP**. (2004) Vesicle swelling regulates content expulsion during secretion. *Cell Biology International*. 28: 709-16. PMID 15516329 DOI: 10.1016/j.cellbi.2004.07.005

(First demonstration that secretory vesicle swelling is a requirement for content release during cell secretion)

19. Jeremic A, Cho WJ & **Jena BP**. (2005) Involvement of water channels in synaptic vesicle swelling. *Experimental Biology and Medicine (Maywood, N.J.)*. 230: 674-80. PMID 16179736

(The association and involvement of water channels AQP1 and AQP6, and the heterotrimeric Go protein are associated with synaptic vesicles and participate in their swelling and release of neurotransmitters)

20. Shin L, Basi N, Jeremic A, Lee JS, Cho WJ, Chen Z, Abu-Hamdah R, Oupicky D & **Jena BP**. (2010) Involvement of vH(+)-ATPase in synaptic vesicle swelling. *Journal of Neuroscience Research*. 88: 95-101. PMID 19610106 DOI: 10.1002/jnr.22180

(Vesicle acidification is a prerequisite for AQP-6-mediated gating of water into synaptic vesicles)