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- Research Associate (2002-2005), The Scrips Research Institute (With Prof. M G Finn)
- Alexander Von Humboldt Fellow (2005-2006), Technical University of Munich, Germany (With Prof. Thomas Schiebel)
- Scientist, CSIR-National Chemical Laboratory, Pune (2006-2016)
- Associate Professor, Indian Institute of Science Education and Research, Kolkata (2016-2021)
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TEACHING ASSISTANTSHIP:

- Teaching Assistant for **"CH2101-Elements of Chemistry II"**- 2nd Year UG Students
- Teaching Assistant for **"CH4201-Bioinorganic Chemistry"**- 4th Year UG Students
- Teaching Assistant for **"CH5106-Sustainability and Chemistry"**- 5th Year UG Students
- Online Teaching at **Jawahar Navodaya Vidyalaya (JNV), Kalyani**, Nadia- XIth and XIIth Students
- Teaching Assistant for **"CH1101-Elements of Chemistry"**- 1st Year UG Students
- Teaching Assistant for **"CH1102-Chemistry Lab I"**- 1st Year UG Students
- Online Teaching at NPTEL for the course **"Chemical Process Intensification"**
- Practical demonstration of cool scientific experiments at **"Garden High School"**

RESEARCH INTEREST:

Organic Synthesis, Polymer Synthesis, Bio-inspired Materials, Drug Delivery, Anti-cancer agents, Bio-medical Applications

EDUCATIONAL BACKGROUND:

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1	10th	BOARD OF SECONDARY EDUCATION	UNVERSITY HIGHER SECONDARY SCHOOL, BHANJABIHAR	2011	92.5 %
2	12th	COUNSIL OF HIGHER SECONDARY EDUCATION	KHALLIKOTE JUNIOR COLLEGE, BERHAMPUR	2013	85.83 %
3	B.Sc.	KHALLIKOTE UNIVERSITY	KHALLIKOTE AUTONOMOUS COLLEGE, BERHAMPUR	2018	9.24 CGPA
4	Int. PhD	I.I.S.E.R. KOLKATA	I.I.S.E.R. KOLKATA	2018-PRESENT	1st SEM 9.17 2nd SEM 9.33 3rd SEM 10 4th SEM 9.5 5th SEM 10 6th SEM 10 TOTAL 9.7CGPA

AWARDS & ACHIEVEMENTS:

- Junior Merit Scholarship from 2011-2013
- Kishore Vaigyanik Protshahan Yojana (KVPY) from Aug 2016-July 2018
- JAM Qualified- AIR 670 in 2018 (Joint Admission Test for M.Sc)
- Joint CSIR-UGC NET JRF Qualified- AIR 32 in June 2019
- 1st Rank Holder in the University during B.Sc
- GATE 2020 and 2021 Qualified AIR 505
- Prime Minister's Research Fellow (May 2020)
- Chemical Science Best Poster Prize at ChemSci2020

EXPERIMENTAL and TECHNICAL SKILLS:

- Spectrophotometry (UV-Vis, Fluorescence), Spectroscopy (FTIR, NMR), Spectrometry (Mass), Electron Microscopy (SEM, TEM, AFM), Rota Vapor, Schlenck Line, Glove Box etc.
- Softwares of ChemDraw, Origin, ACD NMR, MesterNova, Adobe Illustrator

- Chromatographic Techniques (TLC and Column), Solvent Distillation
- N-carboxyanhydride (NCA) synthesis and their Polymerization
- Gel electrophoresis such as SDS-PAGE and Agarose

PUBLICATION:

- Mondal, B.; Pandey, B.; Parekh, N.; Panda, S.; Dutta, T.; **Padhy, A.**; Sen Gupta, S*. **Amphiphilic mannose-6-phosphate glycopolypeptide-based bioactive and responsive self-assembled nanostructure for controlled and targeted lysosomal cargo delivery**. *Biomater. Sci.* **2020**, *8*, 6322-6336.
- B. Mondal, T. Dutta, **A. Padhy**, S. Das, S. Sen Gupta*, **Lysosome Targeting Strategy using Polypeptides and Chimeric Molecules,** *ACS Omega* **2022**, *7*, 1, 5–16.

- B. Mondal#, **A. Padhy#**, S. Maji#, A. Gupta*, S. Sen Gupta*, **Dual Stimuli Responsive Photo Cross-linked Nanogel from Amphiphilic M6P Functionalized ABC tri-Block Copolymer for Lysosomal Cell Death**, *Biomater. Sci.* **2023**, *11*, 1810-1827. (# equal contribution)

- **A. Padhy**, S. Sen Gupta*, **Delivery of Functional Lysosomal Enzymes by using polypeptide or liposomal carriers for the treatment of Lysosomal storage disorder.** *(Manuscript under preparation)*

PICTURES ABOUT RESEARCH:

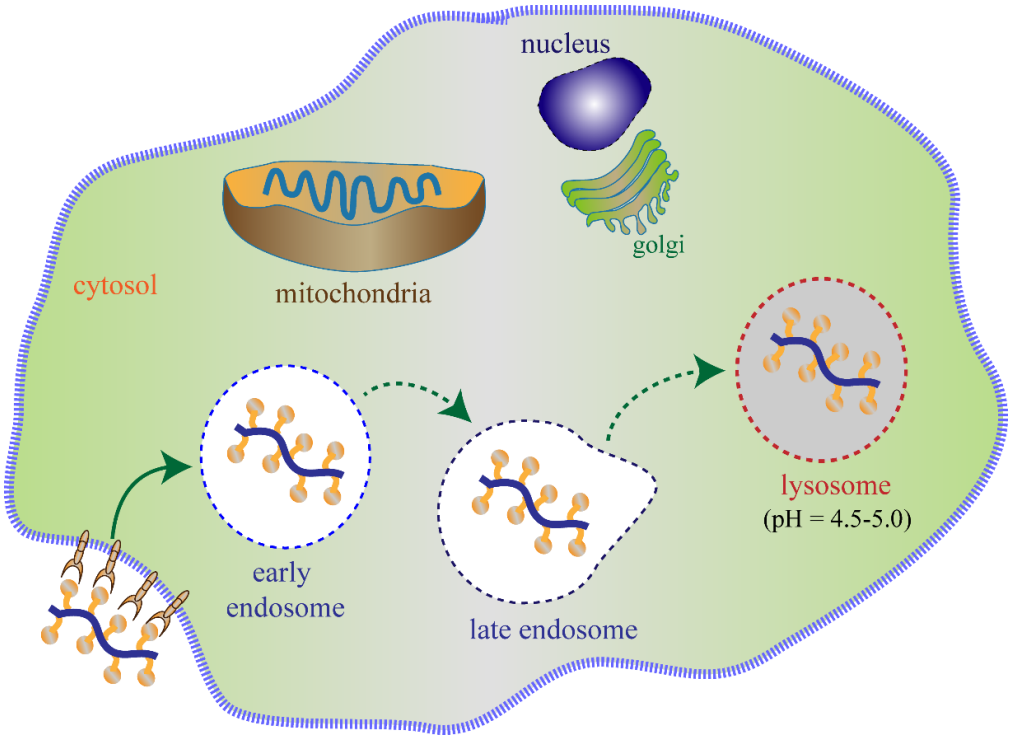

Fig: Schematic representation of Lysosome Targeting using specific Ligands

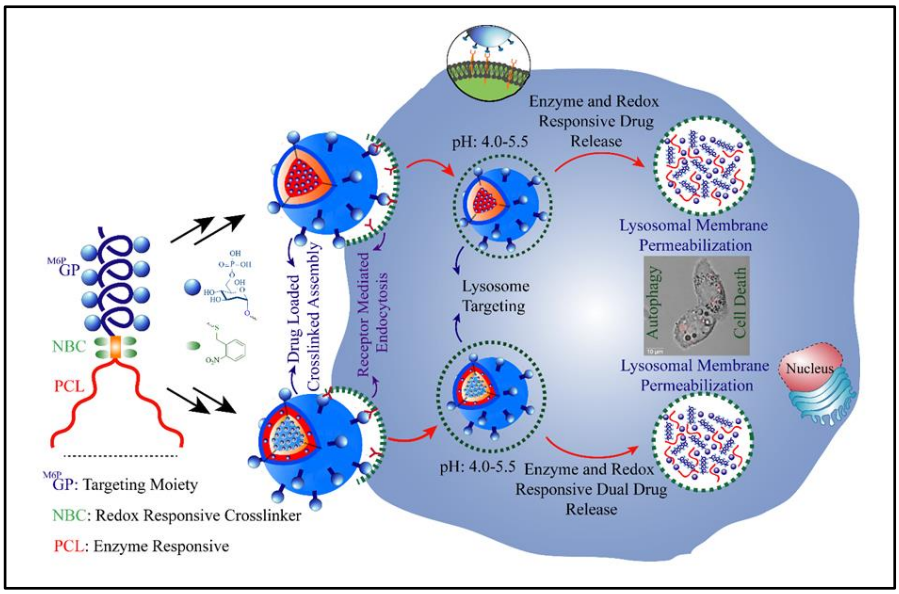

Fig: Lysosomal Membrane Permeabilization by delivering Lysosomotropic agents using cross-linked drug delivery vehicles fabricated from Amphiphilic block-copolymers

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Amphiphilic mannose-6-phosphate glycopolypeptide-based bioactive and responsive self-assembled nanostructures for controlled and targeted lysosomal cargo delivery†

Basudeb Mondal, ‡[a] Bhawana Pandey, §‡[b,c] Nimisha Parekh, ‡[b,c] Sidharth Panda, [a] Tahiti Dutta, [a] Abinash Padhy [a] and Sayam Sen Gupta *[a]

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Receptors of carbohydrate mannose-6-phosphate (M6P) are overexpressed in specific cancer cells (such as breast cancer) and are also involved in the trafficking of mannose-6-phosphate labeled proteins exclusively onto lysosomes *via* cell surface M6P receptor (CI-MPR) mediated endocytosis. Herein, for the first time, mannose-6-phosphate glycopolypeptide (^{M6P}GP)-based bioactive and stimuli-responsive nanocarriers are reported. They are selectively taken up *via* receptor-mediated endocytosis, and trafficked to lysosomes where they are subsequently degraded by pH or enzymes, leading to the release of the cargo inside the lysosomes. Two different amphiphilic M6P block copolymers $^{M6P}GP_{15}$-$^{A}PPO_{44}$ and $^{M6P}GP_{15}$-$(PCL_{25})_2$ were synthesized by click reaction of the alkyne end-functionalized $^{M6P}GP_{15}$ with pH-responsive biocompatible azide end-functionalized acetal PPO and azide end-functionalized branched PCL, respectively. In water, the amphiphilic M6P-glycopolypeptide block copolymers self-assembled into micellar nanostructures, as was evidenced by DLS, TEM, AFM, and fluorescence spectroscopy techniques. These micellar systems were competent to encapsulate the hydrophobic dye rhodamine-B-octadecyl ester, which was used as the model drug. They were stable at physiological pH but were found to disassemble at acidic pH (for $^{M6P}GP_{15}$-$^{A}PPO_{44}$) or in the presence of esterase (for $^{M6P}GP_{15}$-$(PCL_{25})_2$). These ^{M6P}GP based micellar nanoparticles can selectively target lysosomes in cancerous cells such as MCF-7 and MDA-MB-231. Finally, we demonstrate the clathrin-mediated endocytic pathway of the native FL-^{M6P}GP polymer and RBOE loaded ^{M6P}GP micellar-nanocarriers, and selective trafficking of MCF-7 and MDA-MB-231 breast cancer cell lysosomes, demonstrating their potential applicability toward receptor-mediated lysosomal cargo delivery.

Introduction

Synthetic glycopolypeptide-based nanostructures are widely being explored as mimics of natural glycoproteins which are involved in several cellular functions such as extracellular recognition, adhesion, cell growth regulation, cancer cell metastasis, and inflammation.[1–6] Their specificity towards function results from the multiple carbohydrate groups present on their surface which polyvalently interact with their complementary receptor proteins present on the cell surface.[1–3] Among these glycopolypeptides, those containing the carbohydrate mannose-6-phosphate (M6P) are especially interesting, since their analogous glycoproteins containing M6P bind specifically to the M6P receptor (M6PR), a cation-independent (CI) transmembrane multifunctional glycoprotein whose principal function is sorting out of lysosomal enzymes and their transport from the cell surface or Trans-Golgi network (TGN) to lysosomes.[7–9] Hence M6P containing glycopolypeptides (^{M6P}GPs) tend to specifically target the lysosomes *via* cell surface M6P receptor (CI-MPR) mediated endocytosis,[9,10] thus generating much interest in their use as vehicles for lysosome targeted therapy of various diseases such as the lysosomal storage disease (LSD).[11,12] Additionally, these M6P receptors are overexpressed in some cancer cells (*e.g.*, breast cancer) and thus could be used for targeted drug delivery during cancer therapy.[13,14] This could be a double-edged sword since deliver-

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Perspective

Lysosome-Targeting Strategy Using Polypeptides and Chimeric Molecules

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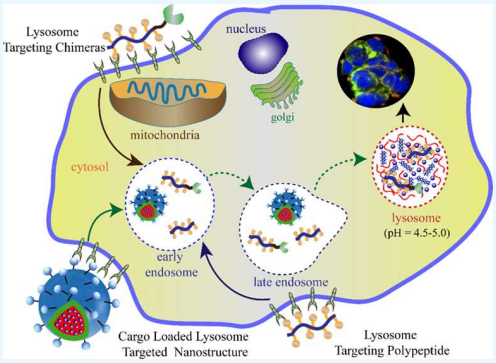
ABSTRACT: Lysosomes are membranous compartments containing hydrolytic enzymes, where cellular degradation of proteins and enzymes among others occurs in a controlled manner. Lysosomal dysfunction results in various pathological situations, such as several lysosomal storage disorders, neurodegeneration, infectious diseases, cancers, and aging. In this review, we have discussed different strategies for synthesizing peptides/chimeric molecules, their lysosome-targeting ability, and their ability to treat several lysosomal associated diseases, including lysosomal storage diseases and cancers. We have also discussed the delivery of cargo molecules into the lysosome using lysosome-targeting ligand-decorated nanocarriers. The introduction of a protein-binding ligand along with a lysosome-targeting ligand to manufacture a chimeric architecture for cell-specific protein (extracellular and membrane protein) degradation ability has been discussed thoroughly. Finally, the future applications of these lysosome-targeting peptides, nanocarriers, and chimeric molecules have been pointed out.



LYSOSOME AND ITS FUNCTION

Lysosomes are membrane-bound acidic cellular organelles containing hydrolytic enzymes that degrade various biomacromolecules such as carbohydrates, nucleic acids, proteins, fats, and cellular components.[1,2] Belgian biologist Christian de Duve discovered these organelles, a part of the endomembrane system, and coined the term "lysosome," for which he was awarded the Nobel Prize in Medicine in 1974.[1] This acidic environment (pH ∼ 4.5−5.0) is maintained by a *vacuolar* ATPase that actively pumps protons in-between the cytoplasm and lysosome.[3] Highly glycosylated lysosome-associated membrane proteins Lamp-1 and Lamp-2 protect the internal lysosomal environment from the cytoplasmic environment. These lysosomal membrane components play diverse and crucial roles in lysosome homeostasis.[2] Apart from the degradation of biomacromolecules and biogenesis, the primary function of the lysosome is controlling cellular responses to nutrients. A lysosomal membrane kinase protein complex, mammalian target of rapamycin complex 1 (mTORC1), regulates cellular responses such as nutrient/energy/redox sensing and controls protein synthesis inside the cell.[4,5] Lysosomes are spatially linked with mTOR autophagy-dependent protein degradation and recycling, allowing new building blocks to maintain several cellular functions.[6] The role of lysosomes and autophagy appears to be related to programmed cell death.[6] Thus, lysosomes play different roles during development and differentiation, detecting morphogen gradients, remodeling intracellular components during the cell differentiation, and participating in cell demise, either by directly inducing cathepsin-dependent cell death or degrading apoptotic cells.[7,8] All the above evidence suggests that lysosomes are essential and active players in controlling several cellular responses to nutritional stress.

LYSOSOMAL DYSFUNCTION

The cell types and their environment influence the functioning of the lysosome. The change of any lysosomal function causes several disorders, including neurodegenerative disorders, cancers, and metabolic disorders. Lysosomes protect any damage to the cells from immune regulation.[8] However, genetic defects, environmental factors, and deficiency of any one enzyme in the lysosomes may impair its function, and as a result, accumulation of the substrates occurs, causing widespread harm to cells.[8] Metabolic machinery may be impaired, and other cell organelles such as mitochondria and peroxisomes may be dysfunctional. Lysosomal Storage Disorder (LSD) is an example of lysosomal dysfunction (Table 1).[7,9−11] The complete absence or insufficiency of any

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Dual stimuli-responsive cross-linked nanoassemblies from an amphiphilic mannose-6-phosphate based tri-block copolymer for lysosomal membrane permeabilization†

Basudeb Mondal, ‡§[a] Abinash Padhy, §[a] Saptarshi Maji, §[b] Arnab Gupta *[b] and Sayam Sen Gupta *[a]

Stimuli-responsive cross-linked nanocarriers that can induce lysosomal cell death (LCD) *via* lysosomal membrane permeabilization (LMP) represent a new class of delivery platforms and have attracted the attention of researchers in the biomedical field. The advantages of such cross-linked nanocarriers are as follows (i) they remain intact during blood circulation; and (ii) they reach the target site *via* specific receptor-mediated endocytosis leading to the enhancement of therapeutic efficacy and reduction of side effects. Herein, we have synthesized a mannose-6-phosphate (M6P) based amphiphilic ABC type tri-block copolymer having two chains of FDA-approved poly(ε-caprolactone) (PCL) as the hydrophobic block, and poly(*S*-(*o*-nitrobenzyl)-L-cysteine) (NBC) acts as the photoresponsive crosslinker block. Two different tri-block copolymers, $[(PCL_{35})_2$-*b*-NBC_{20}-*b*-$^{M6P}GP_{20}]$ and $[(PCL_{35})_2$-*b*-NBC_{15}-*b*-$^{M6P}GP_{20}]$, were synthesized which upon successful self-assembly initially formed spherical uncross-linked "micellar-type" aggregates (UCL-M) and vesicles (UCL-V), respectively. The uncross-linked nanocarriers upon UV treatment for thirty minutes were covalently crosslinked in the middle PNBC block giving rise to the di-sulfide bonds and forming interface cross-linked "micellar-type" aggregates (ICL-M) and vesicles (ICL-V). DLS, TEM, and AFM techniques were used to successfully characterize the morphology of these nanocarriers. The dual stimuli (redox and enzyme) responsiveness of the cross-linked nanocarriers and their trafficking to the lysosome in mammalian cells *via* receptor-mediated endocytosis was probed using confocal microscopy images. Furthermore, the addition of a chloroquine (CQ, a known lysosomotropic agent) encapsulated cross-linked nanocarrier (CQ@ICL-V) to non-cancerous (HEK-293T) cells and liver (HepG2), and breast cancer cells (MDA-MB-231) was found to initiate lysosomal membrane permeabilization (LMP) followed by lysosomal destabilization which eventually led to lysosomal cell death (LCD). Due to the targeted delivery of CQ to the lysosomes of cancerous cells, almost a 90% smaller amount of CQ was able to achieve similar cell death to CQ alone.

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Introduction

Lysosomal cell death (LCD) *via* lysosomal membrane permeabilization (LMP) triggers a cascade of events that culminate in cell death.[1–3] LMP is induced by lysosomal destabilization followed by translocation of cathepsins from the lysosomal lumen to the cytoplasm. Although occurring less frequently, several small molecule drugs and antibodies can destabilize the lysosomes to permeabilize the lysosomal membrane, which destroys the cancer cells *via* LCD.[4–6] The critical factor of LCD is the release of proteases through the lysosomal membrane, resulting in lysosomal membrane permeabilization (LMP) and subsequent cell death.[6–15] LCD may be convenient for cancer treatment, provided that small molecule drugs or antibodies that function as lysosomotropic reagents can be delivered into cancer cell lysosomes specifically and destabilize the lysosomal membrane to initiate LMP. In this context, mannose-6-phosphate is being explored as a targeting ligand to deliver therapeutics specifically inside the lysosomes. Mannose-6-phosphate receptors (MPR) are insulin-like growth

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