BIOGRAPHICAL SKETCH

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NAME: **LABHASETWAR, Vinod**

eRA COMMONS USER NAME (credential, e.g., agency login): LABHASETWAR.VINOD

POSITION TITLE: Professor of Biomedical Engineering and Director, Nanomedicine Program

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Dept. Pharmaceutical Sciences, India	B. Pharm.	06/82	Pharmacy
Dept. Pharmaceutical Sciences, India	M. Pharm.	06/84	Pharmaceutics
Dept. Pharmaceutical Sciences, India	Ph.D.	02/90	Pharmaceutics
University of Michigan, Ann Arbor, MI	Postdoc	1990-93	Drug and Gene Delivery

A. Personal Statement: My laboratory's primary research focus over the past 25+ years has been on nanoparticle-mediated drug delivery to translational and clinical medicine, particularly focusing on disease conditions where there are no effective treatments. Our specific interests are in developing effective treatments for cancer therapy (drug resistance and metastasis), cardiovascular diseases (particularly inhibition of restenosis), and facilitating the repair mechanisms in stroke and spinal cord injury. Recently we began investigation in two new areas: retinitis pigmentosa with the goal to slow down the progression of photoreceptor degeneration and transplantation research with the objective to extend organ preservation time window. Laboratory's basic research involves understanding of biophysics/biomechanics of nanoparticle-cell membrane lipid interactions and their implications for intracellular uptake and trafficking and targeting. Our projects involve clinical collaborators and industry partners with the aim to moving the technologies developed in clinical practice. I have published over 160 peer-reviewed articles and book chapters. I am listed among the 2014 and 2015 Highly Cited Researchers by Thomson Reuters, based on the top 1% of citations during the past 10 years. I have over 25 issued US and international patents and 4 provisional US patents filed/pending. I also received *Mahatma Gandhi* Gold Medal for my contribution to science at a function held at House of Lords, London, UK.

B. Positions and Honors

1988-90	Staff Scientist, National Institute of Immunology, New Delhi, India
1993-97	Assist. Research Professor, University of Michigan Medical School, Ann Arbor, MI
1997-2007	Associate Professor, Dept. of Pharmaceutical Sciences and Dept. of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE
2001-07	Associate Professor (courtesy), Department of Biological Systems Engineering, College of Engineering and Technology, University of Lincoln, Lincoln, NE
2007-pres.	Full Staff (equivalent to Full Professor), Dept. of Biomedical Engineering and Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH
2008-pres	Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland Clinic, Cleveland, OH
2007-09	Adjunct Professor, Dept. of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE
2008-pres.	Director, NanoMedicine Program (joint program of Dept. of Biomedical Engineering and Taussig Cancer Institute), Cleveland Clinic, Cleveland, OH
2008-pres.	Adjunct Professor, Dept. of Chemical and Biomedical Engineering, Cleveland State University, Cleveland, OH

2009-pres. Adjunct Professor, Dept. of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
2011-pres. Adjunct Professor, Integrated Bioscience, University of Akron, Akron, OH
2011-pres Director of the collaborative Graduate Program between University of Akron and Lerner Research Institute, Cleveland Clinic, Cleveland, OH
2012-pres. Member, Advanced Platform Technology (APT) Center, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH

Honors & Awards

1989 Best Research Award, National Institute of Immunology, New Delhi (Dipstick DOT-EIA for the Diagnosis of Typhoid)
1996 Outstanding Young Clinical Investigator, Dept. of Pediatrics, University of Michigan (Nanoparticles- A Novel Nonviral Method of Gene Transfer)
1996,-97,-98 Technology Award, University of Michigan, for Patents and Technology Transfer
2005-2008 Editor-in-Chief, *Journal of Biomedical Nanotechnology* (American Scientific Publishers, Valencia, CA)
2006 Distinguished Scientist, University of Nebraska Medical Center
2007 Innovator Award, University of Nebraska Medical Center
2008 Fellow of the American Association of Pharmaceutical Scientists
2009 Guest Editor, Special Issue on nanotechnology for therapy, imaging, and diagnosis, *Molecular Pharmaceutics*, Vol. 6, Issue 5, 2009 (American Chemical Society, ACS Publications)
2010-pres. Founding Editor-in-Chief, *Drug Delivery and Translational Research* (An Official Journal of the Controlled Release Society)
2012, -13 -14 Innovator Award, Cleveland Clinic
2013 Cover Story, Nanoparticles offer "infinite" possibility for cancer treatment, in HemOnc Today, May 10, 2013.
2013 Cover Story, Nanotechnology: Small Particles Make Huge Impact on Cancer Medicine, in Spring Issue of Cancer Consult.
2014 Quoted in Wall Street Journal in article published on April 8, 2014 titled "Paraplegics Show Gains in Study of Spinal-cord Stimulation".
2014- Mahatma Gandhi *Pravasi Samman* Gold Medal that recognizes the people of Indian origin for their significant contributions in their respective field and service of the wider global community. The award was given at House of Lords, London, UK on Oct 9, 2014.
2014, 15 Thomson Reuters Highly Cited Researchers based on top 1% by citation during 10 years (2002-12) in the respective field; total 3215 investigators are listed globally from all 21 areas of research; the list is published once in every 10 years. (http://highlycited.com/).
2014, 15 Listed as Thomson Reuters Most Influential Mind in Science
2015 Lerner Research Institute Chairman's Innovation Research Award, Cleveland Clinic
2016 Fellow, Controlled Release Society. It is given to individuals who made outstanding contributions to the field of delivery science and technology.

Other Experience and Professional Memberships

2008-10 Organizer, Nanomedicine Summit, Cleveland, OH
2009- Member of the External Advisory Committee, NIH-RCMI Program, Xavier University, New Orleans
2011-14 **NIH:** Regular Member, NANO Study Section
2011 Organizer, Indo-US Joint Symposium, Nanomedicine: Prospects and Challenges, Mumbai, India
2011-14 Chair, Committee for Selection of Outstanding Transdermal Abstract, Controlled Release Society
2011- Member, Committee for Selection of Outstanding Research Paper Published in *Drug Delivery and Translational Research*

Intellectual Property (US Patents issued)

2002 6,143,037: Compositions and methods for coating medical devices
2004 6,814,980: Microspheres containing condensed polyanionic bioactive agents and methods for their production
2008 7,332,159: Method and composition for inhibiting reperfusion injury in the brain

2010 7,727,554: Sustained-release nanoparticle compositions and methods for using the same
2012 8,182,807: Method for inhibiting reperfusion injury in the brain
2013 8,507,437: Apoptosis-modulating p53 protein therapy for vascular disorders and nanoparticles containing the same
2014 8,865,216: Surface-modified nanoparticles for intracellular delivery of therapeutic agents and compositions for making same
2015 9,138,416: Sustained-release nanoparticle compositions and methods using the same

C. Contribution to Science (Total publications over 160, including 130 peer-reviewed publications, 25 book chapters, 5 editorials, and one edited book, Total Citations ~18,240, h index 54. Source: Google Scholar)

Neuroprotective nanoparticles for treating CNS injuries: My laboratory began investigating the efficacy of unique neuroprotective nanoparticles in CNS injuries, particularly in stroke and spinal cord injury (SCI). We recently expanded my research into the area of blast wave-associated traumatic brain injury (bTBI), a significant issue for the military. Our overall therapeutic strategy is to inhibit the progression of the secondary injury cascades of degenerative events that follow the primary injury and promote endogenous brain-repair mechanisms. Our recent and ongoing studies have demonstrated that delivery of neuroprotective nanoparticles at the time of reperfusion in a stroke model is effective in minimizing the damage due to ischemia/reperfusion injury, leading to neuronal regeneration and functional recovery over time. We have made similar progress in SCI model. The data show significant locomotive recovery following treatment with neuroprotective nanoparticles.

Selected Publications

1. Reddy MK, **Labhasetwar V**. Nanoparticle-mediated delivery of superoxide dismutase to the brain: an effective strategy to reduce ischemia-reperfusion injury. *FASEB J* 2009;23:1384-95.
2. Hayder J, Adjei, **Labhasetwar V.** Optical imaging to map the blood-brain barrier leakage. Sci Rep. 2013 Nov 1;3:3117. doi: 10.1038/srep03117.
3. Kabu S, Jaffer H, Petro M, Dudzinski D, Stewart D, Courtney A, Courtney M, **Labhasetwar V**. Blast-associated shock waves result in increased brain vascular leakage and elevated ROS levels in a rat model of traumatic brain injury. *PLoS One* 2015;10:e0127971. PMCID: PMC4449023
4. Petro M, Jaffer H, Yang J, Kabu S, Morris VB, **Labhasetwar V.** Tissue plasminogen activator followed by antioxidant-loaded nanoparticle delivery promotes activation/mobilization of progenitor cells. Biomaterials 2016, 81, 169-180. PMID: 26735970

Epigenetic cancer nanotherapy: We have been studying nanoparticles for cancer nanomedicine, particularly as a drug-/gene-delivery system to overcome resistance to chemotherapy drugs. Our laboratory's recent focus has been on understanding the role of epigenetic changes in cancer drug resistance and tumor metastasis. The goal is also to determine the link between epigenetics and breast cancer stem cells, and testing the approach of reprogramming them with epigenetic drugs to make them susceptible to conventional anticancer drugs.

Selected Publications

1. Peetla C, Bhave R, Vijayaraghavalu S, Stine A, Kooijman E, **Labhasetwar V**. Drug resistance in breast cancer cells: Biophysical characterization of and doxorubicin interactions with membrane lipids. *Mol Pharmaceutics* 2010;7:2334-48. PMCID: PMC2997943
2. Prabha S, Sharma B, **Labhasetwar V**. Inhibition of tumor angiogenesis and growth by nanoparticle-mediated p53 gene therapy in mice. *Cancer Gene Ther* 2012;19:530-7. PMCID: PMC3400709
3. Vijayaraghavalu S, **Labhasetwar V**. Efficacy of decitabine-loaded nanogels in overcoming cancer drug resistance is mediated via sustained DNA methyl transferase 1 (DNMT1) depletion. *Cancer Lett* 2013;331:122-9. PMCID: PMC3572331
4. Vijayaraghavalu S, Peetla C, Lu S, **Labhasetwar V**. Epigenetic modulation of the biophysical properties of drug-resistant cell lipids to restore drug transport and endocytic functions. *Mol Pharmaceutics* 2012;9:2730-42. PMCID: PMC3433581

Cellular uptake and intracellular trafficking of nanoparticles: My laboratory has extensively investigated the mechanism of cellular uptake of nanoparticles (NPs) and their intracellular trafficking. We first discovered that poly lactic *co*-glycolic acid (PLGA) NPs rapidly escape endosomes following their cellular uptake, but a major fraction (85%) of these internalized NPs remains in recycling endosomes and undergoes exocytosis. This observation led us to further understand the role of NP surface characteristics on cellular uptake,

endosomal escape, and retention. This understanding will help us develop rationale for formulating NPs for efficient intracellular delivery of therapeutics.

Selected Publications

1. Panyam J, Zhou WZ, Prabha S, Sahoo SK, **Labhasetwar V**. Rapid endo-lysosomal escape of poly(D,L-lactide-*co*-glycolide) nanoparticles: implications for drug and gene delivery. *FASEB J* 2002;16:1217-26.
2. Panyam J, **Labhasetwar V**. Dynamics of endocytosis and exocytosis of poly(D,L-lactide-*co*-glycolide) nanoparticles in vascular smooth muscle cells. *Pharm Res* 2003;20:212-20.
3. Vasir JK, **Labhasetwar V**. Quantification of the force of nanoparticle-cell membrane interactions and its influence on intracellular trafficking of nanoparticles. *Biomaterials* 2008;29:4244-52. PMCID: PMC2570224
4. Morris VB, **Labhasetwar V.** Arginine-rich polyplexes for gene delivery to neuronal cells. *Biomaterials* 2015, 60, 151-160.

Role of biophysics of membrane lipids in drug delivery: We found that biophysical interactions of nanoparticles (NPs) depend on both biophysical (e.g., membrane fluidity) properties of membrane lipids and NP characteristics (interfacial properties). Recently, we determined that biomechanics (bending force) and thermodynamics ("Gibbs free energy") of interactions of NPs with cell membrane lipids play an important role in endocytosis and escape of NPs from endosomes. We also found that selective biophysical interaction of NPs with the membrane lipids of cancer cells vs. normal cells could be developed as a new targeting approach for drug/gene delivery. We are also exploring the approach of modulating characteristics of NPs for targeted drug delivery, particularly to bone marrow to treat bone metastasis which is a significant issue in prostate and breast cancers.

Selected Publications

1. Adjei IM, Sharma B, Peetla C and Labhasetwar V: Inhibition of bone loss with surface–modulated, drug-loaded nanoparticles in an intraosseous model of prostate cancer. J. Controlled Release 213, 83-92, 2016. PMID: 27090164
2. Peetla C, **Labhasetwar V**. Effect of molecular structure of cationic surfactants on biophysical interactions of surfactant-modified nanoparticles with a model membrane and cellular uptake. *Langmuir* 2009;25:2369–77. PMCID: PMC2653596
3. Sharma B, Peetla C, Adjei IM, **Labhasetwar V**. Selective biophysical interactions of surface modified nanoparticles with cancer cell lipids improve tumor targeting and gene therapy. *Cancer Lett* 2013;334:228-36. PMCID: PMC3669664
4. Peetla C, Jin S, Weimer J, Elegbede A, **Labhasetwar V.** Biomechanics and thermodynamics of nanoparticle interactions with plasma and endosomal membrane lipids in cellular uptake and endosomal escape. *Langmuir* 2014;30:7522-32. PMCID: PMC4079324

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40575741/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01NS092033 **PI:** Labhasetwar V **Dates:** 04/01/2015 – 03/31/2020
Efforts: 2.4 Months
Source: NIH/NINDS
Title: Neuronal Protective NanoParticles for Treating Acute SCI
Main objective is to demonstrate robust preclinical efficacy with Pro-NPs in an animal model of spinal cord injury.

Type: 1 R01 CA206189-01 **PI:** Labhasetwar V, **Dates:** 05/1/16- 03/30/21
Efforts: 1.2 Months
Source: NIH/NCI
Title: Nanoparticle-mediated treatment for bone metastasis
The objective is to evaluate surface-charge modulated nanoparticles (NPs) in prostate cancer model of bone metastasis.

Type: W81XWH-16-1-0786 **PI:** Labhasetwar V, **Dates:** 09/30/16- 09/29/19
Efforts: 1.2 Months

Source: DOD
Title: Developing Pro-NP™ for Acute Spinal Cord Injury
The proposal is an academia-industry partnership focused on developing Pro-NP™ for the treatment for acute spinal cord injury (SCI).

Type: 2R01 NS048837 **PI:** Ghorpade, A. **Dates:** 02/01/2004 – 04/30/2019
Efforts: 0.6 Months
Source: NIH/NINDS
Title: Neuronal Survival, HIV-1 and Astrocyte-TIMP-1
The goal is to address key issues regarding regulation of Tissue Inhibitor of Metalloproteinase-1 in HIV-1-associated dementia and in other inflammatory diseases. Role: Co-Investigator

Type: 1R01EY026340 Multi-**PI:** Labhasetwar and Yu **Dates:** 10/1/16- 09/31/19
Efforts: 1.2 Months
Source: NIH/NEI
Title: Nanoparticle-based therapy for photoreceptor degeneration
The application is aimed at evaluating nano-SOD/CAT – a unique combination of antioxidant enzymes loaded in biodegradable nanoparticles – to slow-down the progression of photoreceptor degeneration in retinitis pigmentosa.

Source: Lerner Research Institute Chair's Innovation Award, **PI:** Labhasetwar V. **Dates:**07/01/2015-06/30/2017
Title: Nanoparticle-based therapy for photoreceptor degeneration
The proposal is to generate preliminary data for the hypothesis that nano-SOD/CAT will be effective in slowing the rate of photoreceptor cell death for many genetic forms of retinal pigmentosa (RP).

Source: Cleveland Clinic Innovation **PI:** Labhasetwar V. **Dates:** 02/01/17- 05/35/17
Title: Nanoparticle composition for drug eluting balloon
To develop drug-loaded nanoparticle coated balloon for vascular delivery for testing in porcine model by Cook Medical.

Completed Research Support

1R01NS070896 **PI:** Labhasetwar, V. 08/15/2010 – 05/31/2016 (with no-cost extension).
NIH/NINDS
Stroke Therapy
The goal is to extend the window of treatment for use of t-PA in stroke and prevent reperfusion injury.

1R01 CA149359 **PI:** Labhasetwar, V. 05/10/2010 – 03/31/2016 (with no-cost extension)
NCI/NIH
Drug Resistance in Cancer Therapy
The goal is to overcome drug resistance in cancer therapy by modulating the membrane properties of drug-resistant cells with epigenetic drugs to facilitate drug transport/nanoparticle delivery.

1R01 DK102020-01 **PI:** Yakubenko, V.P. 07/15/2014 – 04/30/2015
NIH/NIDDK
Role of β_2 integrins in macrophage retention and egress during inflammation.
The goal is to test the role of leukocyte migratory receptors, integrins $\alpha_M\beta_2$ and $\alpha_D\beta_2$, in the retention and egress of macrophages within the site of inflammation. Role: Co-Investigator

Industrial **PI:** Labhasetwar, V. 08/1/012 – 06/30/14
ProTransit Nanotherapy, LLC, Omaha, NE
Feasibility Study: PLGA Nanoparticle targeting oxidative stress in skin condition
The goal was to evaluate PLGA nanoparticle for transdermal delivery of antioxidants to test their protective effect from UV radiation.