

RAVI V. J. CHARI

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CAREER SUMMARY

- Experienced in leading a team of scientists, from laboratory research to clinical product development in a biotechnology setting
- Proficient in the design and synthesis of novel chemotherapeutic drugs.
- Broad range of experience in: drug design, multi-step organic synthesis, enzymology and inhibitor design, medicinal chemistry, drug delivery, antibody purification, antibody conjugation, protein biochemistry.
- Extensive involvement in the transformation of laboratory results into clinically usable products.
- Strong organizational skills
- Prolific in patent filings and publishing research articles
- Inventor on 101 Issued U. S Patents
- Leadership role in coordinating efforts of diverse research groups
- Research innovation in several scientific areas.

EXPERIENCE

Oct 2019 - Present **Chief Scientific - Full-Life Technologies**
Design, research and development of radionuclide conjugates of nanobodies and small molecular weight binders to tumor cells, for targeted cancer therapy.

July 2019 - Present **RChari Consulting – Biotechnology Consultant**
Consultation on all aspects of antibody-drug conjugates (ADCs): chemistry, biochemistry, pharmacology. Design, research and development of ADCs, including patents and technology evaluation

1988 to 2019 **ImmunoGen Inc., Waltham, MA,**
A biotechnology company engaged in the development of novel pharmaceuticals for cancer therapy

Last Position **Vice President, Chemistry & Biochemistry**
Distinguished Research Fellow

- Member of the Senior Management Team

- Fellow of the American Institute for Medical and Biological Engineering (AIMBE)
- Directed the chemistry and biochemistry research efforts of the company. Formulated a research program for the targeted delivery of chemotherapeutic agents for cancer.
- Led the efforts of a multidisciplinary team consisting of chemists, biochemists, cell biologists and pharmacologists.
- Inventor on the U.S. Composition of Matter Patent on the FDA-approved product Kadcyła® for treatment of breast cancer
- Well-versed in drafting patent applications and responding to office actions
- Experienced in the design and synthesis of highly potent compounds, such as potent maytansinoids, doxorubicins, CC-1065 analogs and other potent DNA-targeted agents, taxane drugs, for use in antibody-drug conjugates
- Developed effective tumor-specific anti-cancer agents based on the targeted delivery of potent cytotoxic drugs: Clinical proof of concept achieved with the approval of Kadcyła® for metastatic breast cancer
- Experienced in the design and synthesis of novel linkers and protein modifying agents for the conjugation of drugs to targeting agents.
- Experienced in the modification and purification of monoclonal antibodies, peptide growth factors and drug conjugates.
- Member of the Editorial board of the journals MABs and ChemMedChem
- Invited speaker at several national and international conferences
- Author on >60 peer-reviewed scientific publications

1986 - 1987 Harvard Medical School Boston, MA.
& Dana Farber Cancer Institute
Research Scientist

- Initiated a research project funded by ImmunoGen Inc., for the targeted delivery of cytotoxic drugs and protein toxins to tumor cells.
- Developed highly potent and antigen-specific immunotoxins and antibody-drug conjugates as potential anti-cancer agents.
- Synthesized highly cytotoxic drugs, modified and purified monoclonal antibodies and protein toxins.

1985 University of Maryland, College Park, MD
Department of Chemistry
Research Scientist
 Research project on enzyme mechanisms, inhibitor design and stereochemistry.

1980 - 1984 Yale Medical School New Haven, CT
Department of Pharmacology

Yale-Celanese Research Fellow

- Elucidated the mechanism and stereochemistry of the glyoxalase enzyme.
- Identified a new catalytic activity for the enzyme.
- Deduced the mechanism and absolute stereochemistry of the carboxymuconate lactonizing enzymes.
- Designed, synthesized and evaluated a variety of mechanism based enzyme inhibitors. Synthesized radiolabeled substrate analogs as mechanistic probes
- Studied isotope effects on enzyme reactions. Isolated and purified enzymes, used enzymes for the synthesis of optically pure organic compounds, studied enzyme kinetics and inhibition.

EDUCATION

Ph.D. Chemistry, University of Detroit, Detroit, MI, 1979

Thesis: Synthesis of β,γ -unsaturated amino acids as potential, irreversible enzyme inhibitors

- Synthesized and evaluated several novel amino acid substrate analogs as irreversible inhibitors ('suicide substrates') of enzymes of clinical importance in disorders such as phenylketonuria and Parkinson's disease.
- Developed a new, general method for the synthesis of α,β -unsaturated aromatic amino acids.

M. Phil. Life Sci., Jawaharlal Nehru University, New Delhi, India, 1975

Thesis: Adsorption profile of native and irradiated DNA at solid-liquid interface.

M.Sc. Chemistry, University of Delhi, India, 1973

B.Sc. Chemistry (Honors), University of Delhi, India, 1971

HONORS AND AWARDS

- NIH-SBIR Phase II \$750,000 grant awardee 1997-1999
- NIH-SBIR Phase II \$750,000 grant awardee 1995-1997
- NIH-SBIR Phase I grant awardee 1993
- NIH-SBIR Phase I grant awardee 1992
- American Cancer Society Research Grant (1982-1983)
- Celanese Corporation Fellowship (1982-1984)
- Boston Business Journal "Champions in Health Care" award (2013)
- Inducted into the AIMBE College of Fellows (2016)
- World ADC award for "Longstanding Contribution" to the field (2018)

PUBLICATIONS

1. R. Singh, E.E. Reid, L. Harris, P.L. Salomon, M.L. Miller, R.V.J. Chari and T.A. Keating (2020) Antibody–Drug Conjugates with Indolinobenzodiazepine Dimer Payloads: DNA-Binding Mechanism of Indolinobenzodiazepine Dimer Catabolites in Target Cancer Cells *Mol. Pharmaceutics* **17**; 1, 50–58
2. J.F. Ponte, L. Lanieri, E. Khera, R. Laleau, O. Ab, C. Espelin, N. Kohli, B. Matin, Y. Setiady, M.L. Miller, T.A. Keating, R. Chari, J. Pinkas, R. Gregory and G. M. Thurber (2020) Antibody Co-Administration Can Improve Systemic and Local Distribution of Antibody Drug Conjugates to Increase In Vivo Efficacy. *Mol. Cancer Ther.*, DOI: 10.1158/1535-7163.MCT-20-0451
3. C. Bai, E. E. Reid, A. Wilhelm, M. Shizuka, E. K. Maloney, R. Laleau, L. Harvey, K. E. Archer, D. Vitharana, S. Adams, Y. Kovtun, M. L. Miller, R. Chari, T. A. Keating and N. C. Yoder (2020) Site-Specific Conjugation of the Indolinobenzodiazepine DGN549 to Antibodies Affords Antibody–Drug Conjugates with an Improved Therapeutic Index as Compared with Lysine Conjugation, *Bioconj. Chem.*, **91**; 93-103.
4. P. L. Salomon, E. E. Reid, K. E. Archer, L. Harris, E. K. Maloney, A. J. Wilhelm, M. L. Miller, R. V. J. Chari, T. A. Keating, and R. Singh (2019) Optimizing Lysosomal Activation of Antibody–Drug Conjugates (ADCs) by Incorporation of Novel Cleavable Dipeptide Linkers, *Mol. Pharm.*, **16**; 12, 4817-4825
5. J. A. Costoplus, K. H. Veale, Q. Qiu, J. F. Ponte, L. Lanieri, Y. Setiady, L. Dong, A. Skaletskaya, L. M. Bartle, P. Salomon, R. Wu, E. K. Maloney, Y. V. Kovtun, O. Ab, K. Lai, R. V. J. Chari, and W. C. Widdison (2019) Peptide-Cleavable Self-immolative Maytansinoid Antibody–Drug Conjugates Designed To Provide Improved Bystander Killing *ACS Med. Chem. Lett.*, **10**; 10, 1393-1399
6. W. Li, K. H. Veale, Q. Qui, K. W. Sinkevicius, E. K. Maloney, J. A. Costoplus, J. Lau, H. L. Evans, Y. Setiady, O. Ab, S. M. Abbott, J. Lee, S. Wisitpitthaya, A. Skaletskaya, L. Wang, T. A. Keating, R. V. J. Chari, and W. C. Widdison (2019) Synthesis and Evaluation of Camptothecin Antibody–Drug Conjugates *ACS Med. Chem. Lett.*, **10**; 10, 1386-1392
7. K.E. Archer, E. E. Reid, M. Shizuka, J. Woods, L. Harris, E.K. Maloney L.M. Bartle, O. Ab, A. Wilhelm, Y. Setiady, J.F. Ponte, R. Singh, T.A. Keating, R.V.J. Chari, M.L. Miller (2019) Synthesis of highly potent N-10 amino-linked DNA-alkylating indolinobenzodiazepine antibody-drug conjugates (ADCs). "Effect of linker stereochemistry on the antitumor activity of antibody-drug conjugates (ADCs). *ACS Med. Chem. Lett.* **10**; 8, 1211-1215
8. E. E. Reid, K.E. Archer, M. Shizuka, A. Wilhelm, N.C. Yoder, C. Bai, N.E. Fishkin, L. Harris, L. Maloney, E. K. P. Salomon, E. Hong, R. Wu, O. Ab, S. Jin, K.C. Lai, S. Sikka, R.V.J. Chari, M.L. Miller (2019). "Effect of linker stereochemistry on the antitumor activity of antibody-drug conjugates (ADCs) containing indolinobenzodiazepine payloads" *ACS Med. Chem. Lett.* **10**; 8, 1193-1197
9. E. E. Reid, K.E. Archer, K. E. M. Shizuka, M.A. McShea, E.K. Maloney, O. Ab, L. Lanieri, A. Wilhelm, J.F. Ponte, N.C. Yoder, C. Bai, Wilhelm, N.C. Yoder, R.V.J. Chari, M.L. Miller (2019) "Design, synthesis and evaluation of novel, potent DNA alkylating agents and their antibody-drug conjugates (ADCs), *BioOrg. Med. Chem. Lett.* **29**; 17, 2455-2458

10. Y. Kovtun, G. E. Jones, S. Adams, L. Harvey, C. A. Audette, A. Wilhelm, C. Bai, L. Rui, R. Laleau, F. Liu, O. Ab, Y. Setiady, N. C. Yoder, V. S. Goldmacher, R. V. J. Chari, J. Pinkas, and Chittenden (2018) A CD123-targeting antibody-drug conjugate, IMGN632, designed to eradicate AML while sparing normal bone marrow cells. *Blood Advances* **2**; 848-858.
11. M. Miller, M. Shizuka, A. Wilhelm, P. Salomon, E. Reid, L. Lanieri, S. Sikka, E. Maloney, L. Harvey, Q. Qiu, K. Archer, C. Bai, D. Vitharana, L. Harris, R. Singh, J. Ponte, N. Yoder, Y. Kovtun, K. Lai, O. Ab, J. Pinkas, T. Keating and R. V. J. Chari (2018). A DNA-Interacting Payload Designed to Eliminate Cross-Linking Improves the Therapeutic Index of Antibody-Drug Conjugates (ADCs). *Mol Cancer Ther.* **17**; 650-660
12. X. Sun, J. Ponte, N. Yoder, R. Laleau, J. Coccia, L. Lanieri, Q. Qiu, R. Wu, E. Hong, M. Bogalhas, L. Wang, L. Dong, Y. Setiady, E. Maloney, O. Ab, X. Zhang, J. Pinkas, T. Keating, R. Chari, H. Erickson, and J. Lambert (2017). Effects of Drug-Antibody Ratio on Pharmacokinetics, Biodistribution, Efficacy, and Tolerability of Antibody-Maytansinoid Conjugates. *Bioconj. Chem.*, **28**; 1371-81.
13. R. V. J. Chari (2016) Expanding the Reach of Antibody-Drug Conjugates. *ACS Med Chem Lett.*, **7**; 974-6.
14. M. Miller, N. Fishkin, W. Li, K. Whiteman, Y. Kovtun, E. Reid, K. Archer, E. Maloney, C. Audette, M. Mayo, A. Wilhelm, H. Modafferi, R. Singh, J. Pinkas, V. Goldmacher, J. Lambert, and R. Chari (2016). A New Class of Antibody-Drug Conjugates with Potent DNA Alkylating Activity. *Mol. Cancer Ther.* **15**; 1970-8.
15. J. Ponte, X. Sun, N. Yoder, N. Fishkin, R. Laleau, J. Coccia, L. Lanieri, M. Bogalhas, L. Wang, S. Wilhelm, W. Widdison, T. Keating, R. Chari, H. Erickson, and J. Lambert (2016). Understanding How the Stability of the Thiol-Maleimide Linkage Impacts the Pharmacokinetics of Lysine-linked Antibody-Maytansinoid Conjugates. *Bioconj. Chem.* **27**; 1588-98.
16. R. Singh, Y. Setiady, J. Ponte, Y. Kovtun, K. Lai, E. Hong, N. Fishkin, L. Dong, G. Jones, J. Coccia, L. Lanieri, K. Veale, J. Costoplus, A. Skaletskaya, R. Gabriel, P. Salomon, R. Wu, Q. Qiu, H. Erickson, J. Lambert, R. Chari, and W. Widdison (2016), A New Tripeptide Linker for Antibody-Drug Conjugates (ADCs) with Improved Targeted Killing of Cancer Cells. *Molecular Cancer Therapeutics*, **15**; 1311-1320.
17. W. Widdison, S. Wilhelm, K. Veale, J. Costoplus, G. Jones, C. Audette, B. Leece, L. Bartle, Y. Kovtun and R. Chari (2015), Metabolites of Antibody-Maytansinoid Conjugates: Characterization and in vitro potencies, *Molecular Pharmaceutics*, **12**; 1762-1773.
18. W. Widdison, J. Ponte, J. Coccia, L. Lanieri, Y. Setiady, L. Dong, A. Skaletskaya, E. Hong, R. Wu, Q. Qiu, R. Singh, P. Salomon, N. Fishkin, L. Harris, E. Maloney, Y. Kovtun, K. Veale, S. Wilhelm, C. Audette, J. Costoplus, and R. V. J. Chari (2015). Development of Anilino-Maytansinoid ADCs that Efficiently Release Cytotoxic Metabolites in Cancer Cells and Induce High Levels of Bystander Killing, *Bioconj. Chem.*, **26**; 2261-2278
19. K. Lai, J. Deckert, Y. Setiady, P. Shah, L. Wang, R. Chari & J. Lambert (2015). Evaluation of Targets for Maytansinoid ADC Therapy Using a Novel Radiochemical Assay, *Pharm Res.*, **32**; 3593-3603.

20. R.V.J. Chari, M.L. Miller and W.C. Widdison (2014), Antibody-Drug Conjugates: An Emerging Concept in Cancer Therapy, *Angew Chem. Intl. Ed.*, **53**; 3796-3827.
21. M. Lambert and R.V.J. Chari (2014), Ado-trastuzumab Emtansine (T-DM1): An Antibody-Drug Conjugate (ADC) for HER2-Positive Breast Cancer (2014) , *J. Med. Chem.* **57**; 6949-6964.
22. Wayne C. Widdison and Ravi V.J. Chari (2013) Factors Involved in the Design of Cytotoxic Payloads for Antibody-Drug Conjugates in Antibody-Drug Conjugates and Immunotoxins: From Pre-Clinical Development to Therapeutic Applications, Humana press, New York, Ed. G. L. Phillips, pp 93-116.
23. R. Singh, J.M. Lambert and R.V.J. Chari (2013), Antibody-Drug Conjugates (ADCs): in New Frontier in Cancer Therapeutics, Wiley 2014
24. R.Y. Zhao, H. E. Erickson, B.A. Leece, E. Reid, B. A. Leece, V. S. Goldmacher, , J. M. Lambert, and R. V. J. Chari (2012) Synthesis and Biological Evaluation of Antibody Conjugates of Phosphate Prodrugs of Cytotoxic DNA Alkylators for the Targeted Treatment of Cancer, *J. Med. Chem.*, **55**; 766-782.
25. V. S. Goldmacher, T. Chittenden, R.V.J. Chari, Y. V.Kovtun, J. M. Lambert, Antibody-Drug Conjugates for Targeted Cancer Therapy. In Manoj C. Desai, editor: Annual Reports In Medicinal Chemistry, Vol. 47, Academic Press, 2012, pp. 349-366.
26. R.Y. Zhao, S. D. Wilhelm, C. Audette, G. Jones, B. A. Leece, A. C. Lazar, V. S. Goldmacher, R. Singh, Y. Kovtun, W. C. Widdison, J. M. Lambert, and R. V. J. Chari (2011) Synthesis and Evaluation of Hydrophilic Linkers for Antibody-Maytansinoid Conjugates, *J. Med. Chem.*, **54**; 3606-3623.
27. B.A. Teicher and R.V.J. Chari (2011), Antibody Conjugate Therapeutics: Challenges and Potential, *Clin Cancer Res.*, **17**; 6389-6397.
28. X. Sun, W. Widdison, M. Mayo, S. Wilhelm, B. Leece, R. Chari, R. Singh, and H. Erickson (2011), Design of Antibody-Maytansinoid Conjugates Allows for Efficient Detoxification via Liver Metabolism, *Bioconj. Chem.*, **22**; 728-735.
29. N. Fishkin, E. K. Maloney, R. V. J. Chari and R. Singh (2011) A novel pathway for maytansinoid release from thioether linked antibody-drug conjugates (ADCs) under oxidative conditions. *Chem. Commun.*, **47**; 10752-10754
30. B. A. Kellogg, L. Garrett, Y. Kovtun, K. C. Lai, B. Leece, M. Miller, G. Payne, R. Steeves, K. R. Whiteman, W. Widdison, H. Xie, Rajeeva Singh, R.V.J. Chari, J.M. Lambert and R.J. Lutz, Disulfide-Linked Antibody-Maytansinoid Conjugates: Optimization of In Vivo Activity by Varying the Steric Hindrance at Carbon Atoms Adjacent to the Disulfide Linkage, *Bioconj. Chem.*, **22**; 717-727.
31. E. Oroudjev, M. Lopus, L. Wilson, C. Audette, C. Provenzano, H. Erickson, Y. Kovtun, R. Chari, and M.A. Jordan (2010) Maytansinoid-Antibody Conjugates Induce Mitotic Arrest by Suppressing Microtubule Dynamic Instability. *Mol. Cancer Ther.* **9**; 2700-13.
32. M. Lopus, E. Oroudjev, L. Wilson, S. Wilhelm, W. Widdison, R. Chari, and M.A. Jordan (2010), Maytansine and Cellular Metabolites of Antibody-Maytansinoid Conjugates Strongly Suppress Microtubule Dynamics by Binding to Microtubules, *Mol. Cancer Ther.* **9**; 2689-2699.
33. Y. V. Kovtun, C. A. Audette, M. F. Mayo, G. E. Jones, H. Doherty, E.K. Maloney, H.K. Erickson, X. Sun, S. Wilhelm, O. Ab, K. C. Lai, W. C. Widdison, B. Kellogg, H. Johnson, J. Pinkas, R. J. Lutz, R. Singh, V. S. Goldmacher, and R, V.J. Chari (2010)

- Antibody-Maytansinoid Conjugates Designed to Bypass Multidrug Resistance, *Cancer Res* **70**: 2528-2537.
34. R. V. J. Chari, (2008) Targeted Cancer Therapy: Conferring Specificity to Cytotoxic Drugs, *Acc. Chem. Res.*, **41**; 98-107.
 35. G. D.L. Phillips G. Li, D.K. Dugger, L.M. Crocker, K.L. Parsons, E. Mai, W.A. Blattler, J.M. Lambert, R.V.J. Chari, R.J. Lutz, W.L. Wong, F.S. Jacobson, H. Koeppen, R.H. Schwall, S.R. Kenkare-Mitra, S.D. Spencer, M.X. Sliwkowski MX, (2008) Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res* **68**: 9280-90.
 36. J. A. Reddy, E. Westrick, H. K. Santhapuram, S. J. Howard, M. L. Miller, M. Vetzal, I. Vlahov, R. V.J. Chari, V. S. Goldmacher, and C. P. Leamon, (2007), Folate Receptor-Specific Antitumor Activity of EC131, a Folate-Maytansinoid Conjugate, *Cancer Res.*, **67**; 6376-6382.
 37. W. C. Widdison, S. D. Wilhelm, E. Cavanagh, K. R. Whiteman, B. A. Leece, Y. Kovtun, V. S. Goldmacher, H. Xie, R. M. Steeves, R. J. Lutz, R. Zhao, L. Wang, W. A. Blattler, and R. V. J. Chari (2006) Semisynthetic Maytansine Analogues for the Targeted Treatment of Cancer *J. Med. Chem.*, **49**; 4392-3408.
 38. E. Baloglu, M. L. Miller, E. Cavanagh, T. Marien, E. E. Roller, and R. V. J. Chari (2005) Synthesis and biological evaluation of novel taxoids designed for targeted delivery to tumors, *Synlett*, **5**; 817-818.
 39. E. Baloglu, M. L. Miller, E. E. Roller, E. Cavanagh, B. A. Leece, V. S. Goldmacher and R. V. J. Chari (2004) Synthesis and biological evaluation of novel taxoids designed for targeted delivery to tumors, *BioOrg. Med. Chem. Lett.*, **14**; 5885-5888.
 40. M. L. Miller, E. E. Roller, X. Wu, B. A. Leece, V. S. Goldmacher, R.V.J. Chari and I. Ojima, (2004) Synthesis of potent taxoids for tumor-specific delivery using monoclonal antibodies, *BioOrg. Med. Chem. Lett.*, **14**; 4079-4082.
 41. M. L. Miller, E. Roller, R. Zhao, B. A. Leece, O. Ab, E. Baloglu, V. S. Goldmacher, and R.V. J. Chari (2004) Synthesis of taxoids with improved cytotoxicity and solubility for use in tumor-specific delivery, *J. Med. Chem.*, **47**, 4802-4805.
 42. A.W. Tolcher, L.Ochoa, L.A. Hammond, A. Patnaik, T. Edwards, R.V.J.Chari, J.Lambert and E.K. Rowinski, (2003). Cantuzumab mertansine, a maytansinoid immunoconjugate directed to the CanAg antigen: A phase I, pharmacokinetic, and biologic correlative study, *J. Clin. Oncol.*, **21**, 211-222.
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49. R. V. J. Chari, B. A. Martell, J. L. Gross, S. B. Cook, S. A. Shah, W. A. Blättler, S. J. McKenzie, and V. S. Goldmacher, (1992) Immunoconjugates containing novel maytansinoids: Promising anticancer drugs, *Cancer Research*, **52**; 127-31.
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51. C. F. Scott, V. S. Goldmacher, J. M. Lambert, R. V. J. Chari, S. Bolender, M. N. Gauthier and W. A. Blättler, (1987) The antileukemic efficacy of an immunotoxin composed of a monoclonal anti Thy-1 antibody disulfide linked to the ribosome-inactivating protein gelonin. *Cancer Immunol. Immunother.*, **25**; 31.
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