

# WR Tolbert & Associates, LLC

## *Pharmaceutical / Biopharmaceutical Consultation*

### Curriculum Vitae for William R. Tolbert, Ph.D.

WR Tolbert & Associates, LLC was founded in 1995. It has provided consulting expertise to over 25 firms in the area cGMP manufacturing, product development and facility design.

Prior to becoming a consultant, William R. Tolbert, Ph.D., President, managed and furnished leadership for corporate departments in the areas of Technology, Quality Assurance, Quality Control, Validation and Clinical Production.

- Dr. Tolbert's expertise is in product/process development and cGMP manufacturing of biopharmaceutical cell-based products: including rDNA proteins, monoclonal antibodies and cell/gene therapy modalities. He is an inventor on 26 patents and author of over 90 publications.
- His firm consults with academic, biotech and large pharma organizations on cGMP manufacturing issues, particularly those related to cell-based products. In addition, he assists clients in the development and implementation of process and quality systems for all phases of clinical manufacturing.
- He has designed Gene Therapy and Cell Therapy facilities for both clinical and commercial manufacturing operations and has presented several of those plans to the FDA/CBER, Division of Manufacturing and Product Quality. Plans have been prepared for Cornell Medical College, Dinny Stranahan Institute, GenVec/Warner Lambert, Memorial Sloan-Kettering Institute, Meyer Pharmaceuticals, New York Blood Center, Primedica, Progenitor Cell Therapy, North Shore University Hospital, Tulane University Health Sciences Center, Waisman Center at the University of Wisconsin and the Wake Forest University School of Medicine.
- He is a founding member of the Editorial Advisory Board for *BioPharm* and is on the Editorial Advisory Panel for *Pharmaceutical Formulation & Quality*.

### **Corporate Experience:**

Advanced Tissue Sciences, Inc.

Vice President, Process Development and Product Development

Centocor, Inc.

Vice President, Technical Affairs

Invitron Corporation

Vice President, Manufacturing, Technology Development and Technical Affairs

Monsanto Company

Group Leader, Scientist and Monsanto Fellow

### **Education:**

BS	Physics	University of Richmond, VA
MS	Physics	University of Wisconsin, Madison
Ph.D.	Biophysics	University of Wisconsin, Madison
Postdoctoral Studies		Duke University and Allegheny General Hospital, Pittsburgh

**Professional Affiliation:**

American Association for Cancer Research	American Society for Cell Biology
European Society for Animal Cell Technology	New York Academy of Sciences
Society for In Vitro Biology	Vice President 1988-1990 Member Executive Board and Council 1990-1992

## **Technology Developed:**

### **Bioreactor Design Related Patents:**

#### **Batch Suspension Bioreactor**

1. Tolbert, W.R. and Feder, J., U.S. Patent No. 4,187,149, February 5, 1980.
2. Tolbert, W.R. and Feder, J., U.S. Patent No. 4,253,684, March 3, 1981.

#### **Perfusion Suspension Bioreactor**

3. Tolbert, W.R., Feder, J. and Kimes, R.C., U.S. Patent No. 4,166,768, September 4, 1979.
4. Tolbert, W.R., Feder, J. and Kimes, R.C., U.S. Patent No. 4,178,209, December 11, 1979.
5. Tolbert, W.R., Feder, J. and Kimes, R.C., U.S. Patent No. 4,184,916, January 22, 1980.
6. Tolbert, W.R., U.S. Patent No. 4,417,861, November 25, 1983.
7. Geimer, I.R., Tolbert, W.R., U.S. Patent NO. 4,639,422, January 27, 1987.
8. Baumgartner, M.F., Tolbert, W.R. and Shanahan, J., US Patent No. 5,112,760, May 12, 1992.

#### **Perfusion Microcarrier Bioreactor**

9. Tolbert, W.R., Hitt, M.M. and Feder, J., U.S. Patent No. 4,289,854, September 15, 1981.
10. Tolbert, W.R., Hitt, M.M. Feder, J. and Kimes, R.C., U.S. Patent No. 4,335,215, June 15, 1982.

#### **Immobilized Perfusion Bioreactor**

11. Tolbert, W.R., Feder, J. and Lewis, C., U.S. Patent No. 4,537,860, August 27, 1985.
12. Applegate, D.O., Applegate, M., Baumgartner, M., Bennett, J.W., Danssaert, J., Hardin, R., Laiterman, L., Schramm, F., Tolbert, W.R., U.S. Patent No. 5,843,766, December 1, 1998.

### **Product Related Patents:**

#### **Cell Culture Methods**

13. Tolbert, W.R. and Feder, J., U.S. Patent No. 4,059,485, November 22, 1977.
14. Tolbert, W.R., U.S. Patent No. 4,059,486, November 22, 1977.

#### **Purification Methods**

15. Lewis, C., Jr., Olander, J.V. and Tolbert, W.R., U.S. Patent No. 4,533,496, August 6, 1985.

#### **Angiogenesis Factors**

16. Tolbert, W.R., Feder, J. and Kuo, M.J., U.S. Patent No. 4,209,587, June 24, 1980.
17. Tolbert, W.R., Feder, J. and Kuo, M.J., U.S. Patent No. 4,210,718, July 1, 1980.
18. Tolbert, W.R., Feder, J. and Kuo, M.J., U.S. Patent No. 4,210,719, July 1, 1980.
19. Tolbert, W.R., Feder, J., Kuo, M.J. and Folkman, J., U.S. Patent 4,217,412, August 12, 1980.
20. Tolbert, W.R., Feder, J. and Kuo, M.J., U.S. Patent No. 4,225,670, September 30, 1980.
21. Tolbert, W.R., Feder, J. and Kuo, M.J., U.S. Patent No. 4,229,531, October 21, 1980.
22. Tolbert, W.R. and Feder, J., U.S. Patent No. 4,229,532, October 21, 1980.
23. Tolbert, W.R., Kuo, M.J. and Feder, J., U.S. Patent No. 4,268,629, May 19, 1981.

24. Tolbert, W.R., Hitt, M.M. and Feder, J., U.S. Patent No. 4,273,871, June 16, 1981.

#### Tissue Plasminogen Activator (tPA)

25. Feder, J., Tolbert, W.R., Rademacher, T.W., Parekh, R.B., and Dwek, R.A., U.S. Patent No. 4,751,084, June 14, 1988.

26. Feder, J., Tolbert, W.R., Rademacher, T.W., Parekh, R.B., and Dwek, R.A., U.S. Patent No. 4,851,517, July 25, 1989.

## Publications:

#### Papers and Chapters:

1. Krigbaum, W.R., Yazgan, S. and Tolbert, W.R. Some comments on domain structure in block copolymers. *J. Polym. Sci. Polym. Phys. Ed. Biotech'88 International Conference*, London, UK, May (1988).
2. Tolbert, W.R., Large-Scale Mammalian Cell Culture, (Proceedings) *ACHEMA'88 International Meeting on Chemical Engineering and Biotechnology*, Frankfurt, Germany, June (1988).
3. Tolbert, W. R., Mammalian Cell Culture Systems, (Proceedings) *XIIth Engineering Foundation Conference*, Potosi, MO, August (1989).
4. Krigbaum, W.R., Yazgan, S. and Tolbert, W.R. Some comments on domain structure in block copolymers. *J. Polym. Sci. Polym. Phys. Ed.* 11, 511-527 (1973).
5. Tolbert, W.R., Eng, C.P., Harnaha, J.B. and Concannon, J.P. Establishment of heteroploid cell lines from mouse peritoneal exudate cells. *In Vitro* 11, 255-263 (1975).
6. Eng, C.P., Tolbert, W.R., Harnaha, J.B. and Concannon, J.P. In vitro measurement of cytotoxic antibodies in mouse-immune sera against mouse ascites tumor cells. *Can. J. Microbiol.* 20, 1681-1688 (1974).
7. Feder, J., Kimes, R.C., Tolbert, W.R., Cleveland, C., Hammond, M.E., Orenstein, N.S., Goodwin, J. and Dvorak, D.F. Plasminogen activator and MIF-like activities in Kirsten virus transformed mouse NIH culture fluids. *Biochem, Biophys. Res. Commun.* 83, 1164-1170 (1978).
8. Tolbert, W.R., Hitt, M.M. and Feder, J. Cell aggregate suspension culture for large-scale production of biomolecules. *In Vitro* 16, 486-490 (1980).
9. Tolbert, W.R., Hitt, M.M. and Feder, J. Rapid determination of cell volume density in mammalian cell suspension. *Anal. Biochem.* 106, 109-113 (1980).
10. Tolbert, W.R., Feder, J. and Kimes, R.C. Large-Scale rotating filter perfusion system for high density growth of mammalian suspension cultures. *In Vitro* 17, 885-890 (1981).
11. Tolbert, W.R., Schoenfeld, R.A., Lewis, C. and Feder, J. Large-Scale mammalian cell culture: design and use of an economical batch suspension system. *Biotech. Bioeng.* 24, 1671-1679 (1982).
12. Tolbert, W.R., and Feder, J. Sterile air shielded connectors for aseptic operations. *Biotech. Bioeng.* 24, 1885-1887 (1982).
13. Feder, J. and Tolbert, W.R. The large-scale cultivation of mammalian cells. *Sci. Am.* 248, 24-31 (1983).

14. Tolbert, W.R. and Feder, J. Large-Scale cell culture technology, in Annual Reports on Fermentation Processes 6 (G.T. Tsao and M.C. Flickinger, eds.), Academic Press, New York, pp. 35-74 (1983).
15. Feder, J. and Tolbert, W.R. Mass culture of mammalian cells in perfusion systems, *Am. Biotech. Lab.* 3, 24-36 (1985).
16. Tolbert, W.R., Lewis, C. Jr., White, P.J. and Feder, J. Perfusion culture systems for production of mammalian cell biomolecules, in Large-Scale Mammalian Cell Culture (J. Feder and W.R. Tolbert, eds.), Academic Press, New York, NY, pp.97-123 (1985).
17. Tolbert, W.R. and Feder, J. Perfusion systems for plant scale mammalian cell culture production, *Pharm. Eng.* 5, 23-27, (1985).
18. Tolbert, W.R., Flickinger, M.C., Rupp, R.G., Rice, J.M., Sato, G.H. and Van Wezel, A.L. "Overview of Animal Cells" in Research Needs in Non-Conventional Bioprocesses (D.J. Fink, L.M. Curran and B.R. Allen, eds.), Battelle Press, Columbus, OH, pp. 67-82 (1985).
19. Tolbert, W.R. and Srigley, W.R., Manufacture of Pharmacologically Active Proteins by Mammalian Cell Culture, *Biopharm Manufacturing*, 1, 42-48 (1987).
20. Tolbert, W.R., Srigley, W.R., and C.P. Prior, Perfusion culture systems for large scale pharmaceutical production, *Animal Cell Biotechnology* 3 (G. B. Griffiths, ed.), Academic Press, UK, 374-393 (1988).
21. Tolbert, W.R. and Rupp, R.G., Manufacture of Pharmaceutical Proteins from Hybridomas and other Cell Substrates, *Develop. Biol. Standard.*, 70, pp. 49-56 (S. Karger, Basel, 1989)
22. Tolbert, W.R., Application of Large Scale Perfusion Culture to Production of Biopharmaceuticals, in Trends in Animal Cell Culture Technology (H. Murakami, ed.), Kodansha, Tokyo, Weinheim, New York, pp. 9-14 (1990).
23. Hope, J., Rosenberg, M. and Tolbert, W.R., Development of Mammalian Cell Manufacturing Processes, in Production of Biologicals from Animal Cells in Culture (R.E. Spier, J.B. Griffiths, B. Meignier, eds), Butterworth, Oxford, pp. 363-369 (1991).
24. Naughton, G.K., and Tolbert, W.R., Tissue Engineering/Hybrid Cells and Tissues - Skin in 1996 Yearbook of Cell and Tissue Transplantation, W.L. Chick (ed ).
25. Tolbert, W.R., Merchant, B., Taylor, J.A., and Pergolizzi, R.G., Designing an initial gene therapy manufacturing facility, *BioPharm*, 9, 32-40 (1996).

#### Books:

26. Tolbert, W.R. Issue Editor "Mass Culture", *J. Tissue Cult. Meth.* 8, No. 4 (1983).
27. Feder, J. and Tolbert, W.R., eds. Large-Scale Mammalian Cell Culture, Academic Press, New York, NY, p.159 (1985).

#### Presented at Scientific Meetings:

28. Tolbert, W.R., Shrum, E.V., Hutcheson, E.T. and Diana, L. M. Search for evidence of positron emission in the decay of C136. *Bull. Am. Phys. Soc.* 10, 589 (1965).
29. Anderegg, J.W., Hill, W.E., Smith, W.S. and Tolbert, W.R. Small-angle x-ray scattering from E. coli ribosomes. Second International Conference on Small-Angle Scattering, Graz, Austria (1970).
30. Smith, W.S., Tolbert, W.R. and Anderegg, J.W. Small-angle x-ray scattering studies on bacterial ribosomes. *Biop. Soc. Abs.* 260 (1971).

31. Tolbert, W.R., Eng, C.P., Concannon, J.P. and Schaffer, L.M. Rabbit serum as complement source in the cytotoxicity test against mouse ascites tumors. *Fed. Proc.* 32, 1041 (1973).
32. Eng, C.P., Tolbert, W.R., Harnaha, J.B. and Concannon, J.P. Mouse ascites tumor immunotherapy with isogeneic immune serum against attenuated tumor culture cells. *Proc. Am. Assoc. Cancer Res.* 15, 28 (1974).
33. Eng, C.P., Harnaha, J.B., Tolbert, W.R. and Concannon, J.P. Locality of tumor-specific antigens in attenuated 6C3HED tumor culture cells. *In Vitro* 9, 376 (1974).
34. Tolbert, W.R., Eng, C.P. and Concannon, J.P. Concomitant increase in tumor antigenicity and decrease in transplantability of Sarcoma 180 after in vitro cultivation. *In Vitro* 9, 376 (1974).
35. Tolbert, W.R. and Feder, J. Cell Aggregate Suspension Culture for Large-Scale Production of Biomolecules. *In Vitro* 14, 379 (1978).
36. Feder, J., Kimes, R.C., Tolbert, W.R., Cleveland, C., Hammond, M.E., Orenstein, N.S., Goodwin, J. and Dvorak, H.F. (Tolbert presenting). Plasminogen activator and MIF-like activities in Kirsten virus transformed mouse NIH culture fluids, Midwest Regional Meeting, ACS, Fayetteville (1978).
37. Tolbert, W.R., Kimes, R.C. and Feder, J. Maintenance of sterility in a large-scale mammalian cell culture facility without antibiotics. Meeting of the American Association of Tissue Banks, New Orleans, LA (1979).
38. Tolbert, W.R., Feder, J. and Kimes, R.C. Large-Scale rotating filter suspension culture reactor, *In Vitro* 15, 199 (1979).
39. Tolbert, W.R., Schoenfeld, R. and Feder, J. Design of 100-liter vessels for storage of medium and growth of mammalian cell suspensions. *In Vitro* 16, 227 (1980).
40. Schoenfeld, R.A., Tolbert, W.R., Bremer, M.E. and Bartram, R.D. Use of economical 100-liter reactors for mammalian cell culture, *In Vitro* 16, 227 (1980).
41. Hitt, M.M., Tolbert, W.R. and Feder, J. Rapid determination of cell volume density in mammalian cell suspensions. *In Vitro* 16, 230 (1980).
42. Tolbert, W.R., Hitt, M.M., Kuo, M.J. and Feder, J. Production of angiogenesis stimulating activity by cell lines derived from normal human tissue. *In Vitro* 17, 234 (1981).
43. Tolbert, W.R., Kuo, M.J. and Feder, J. Production of tumor angiogenesis factor (TAF) by human tumor cell lines. *In Vitro* 17, 259 (1981).
44. Tolbert, W.R. and Feder, J. Bimolecular products from large-scale culture of anchorage dependent and independent mammalian cell lines, 2nd International Cell Culture Congress, Birmingham, AL (1981).
45. Tolbert, W.R. and Feder, J. Development of a new technology for large-scale culture of mammalian cells. Third Ohio Valley Tissue Culture Symposium and Workshop, College Corner, OH (1981).
46. Tolbert, W.R., Lewis, C., Hudson, G. and Feder, J. High density perfusion chemostat for large scale suspension culture. *In Vitro* 18, 311 (1982).
47. Tolbert, W.R. and Feder, J. Development of a new technology for the large-scale culture of mammalian cells. Roundtable session, 33rd Annual Meeting of the Tissue Culture Assoc., San Diego, CA (1982).
48. Feder, J., Tolbert, W.R. and Lewis, C., Jr. Large-Scale perfusion cell culture systems. *In Vitro* 19, 260 (1983).

49. Lewis, C., Jr., Tolbert, W.R. and Feder, J. Large-Scale perfusion culture system used for production of monoclonal antibodies, Third Annual Congress for Hybridoma Research, San Diego, CA (1984).
50. Feder, J. and Tolbert, W.R. Mass culture of mammalian cells: perfusion systems. Labcon West Symposium, Long Beach, CA (1984).
51. Tolbert, W.R. Large scale immobilized culture roundtable session, 35th Annual Meeting of the Tissue Culture Association, Houston, TX (1984).
52. Tolbert, W.R., Lewis, C., Jr., White, P.J. and Feder, J. Perfusion culture systems for production of mammalian cell biomolecules, Annual Meeting of the American Chemical Society, Division of Microbial and Biochemical Technology, Philadelphia, PA (1984).
53. Feder, J. and Tolbert, W.R. Development of a perfusion culture system for large scale mammalian cell culture. Engineering Foundation, Fourth International Biochemical Engineering Conference, Galway, Ireland (1984).
54. Tolbert, W.R. and Feder, J. Systems for large scale perfusion culture. Human Hybridoma Meeting, Kauai, Hawaii (1984).
55. Tolbert, W.R. Large-Scale culture of mammalian cells presented at the Research Association for Biotechnology, Tokyo, Japan, September (1985).
56. Tolbert, W.R. and Feder, J. Perfusion systems for commercial scale production of mammalian cell products, 3rd International Cell Culture Congress, Sendai, Japan, September (1985).
57. Tolbert, W.R. and Feder, J. Perfusion systems for plant scale mammalian cell culture production, FDA/ISPE Joint Conference, Washington, D.C., October (1985).
58. Tolbert, W.R. and Feder, J. Perfusion systems for plant scale mammalian cell culture, Biotech 85, Washington, D.C., October (1985).
59. Tolbert, W.R. Perfusion systems for monoclonal and rDNA products from mammalian cells, BIO/TECHNOLOGY Conference, New Orleans, LA, January (1986).
60. Tolbert, W.R. and Benton, C.V. Development and evolution of perfusion systems and static maintenance systems for large scale production of mammalian cell derived products, Third Annual Congress for Automation, Scale-up and the Economics of Biological Process Engineering, Baltimore, MD, January (1986).
61. Tolbert, W.R. Large scale mammalian cell culture technology for production of pharmaceutical products, Japan Management Association '86 Bioindustry Symposium, Tokyo, Japan, March (1986).
62. Tolbert, W.R. Pharmaceutical production of biological products derived from mammalian cells, Fisher Scientific Biotechnology Seminar, St. Louis, MO, May (1986).
63. Tolbert, W.R. Large scale mammalian cell culture technology, Eighth Symposium on Biotechnology for Fuels and Chemicals, Gatlinburg, TN, May (1986).
64. Tolbert, W.R. Economic concerns for production of pharmaceutical products by mammalian cultures, Society for Industrial Microbiology, San Francisco, CA, August (1986).
65. Tolbert, W.R. Pharmaceutical production of biological products derived from mammalian cells, Biotech San Francisco, San Francisco, CA, November (1986).
66. Tolbert, W.R. Economic Factors relating to large scale pharmaceutical production from mammalian cells, Fourth Annual Congress for Automation, Scale-up and The Economics of Biological Process Engineering, San Francisco, CA, March (1987).

67. Tolbert, W.R., Strigley, W.R., and Prior, C.P., Perfusion culture systems for large scale pharmaceutical production, American Institute of Chemical Engineers, St. Louis, MO, March (1987).
68. Tolbert, W.R., Strigley, W.R., and Prior, C.P., Application of large scale perfusion systems for pharmaceutical production from mammalian cells, European Society for Animal Cell Technology, Tiberias on the Sea of Galilee, Israel, April (1987).
69. Tolbert, W.R. and Prior, C.P. Perfusion Culture, NATO Advanced Research Workshop, Brussels, Belgium, September (1987).
70. Tolbert, W.R. Design of Pharmaceutical Bioreactors For Mammalian Cells, Conference on Commercial Biotechnology, Boston, MA, April (1988).
71. Tolbert, W.R. and Rupp, R.G., Manufacture of Pharmaceutical Proteins From Hybridomas and Other Cell Substrates, Continuous Cell Lines as Substrates for Biological Conference, Arlington, VA, May (1988).
72. Tolbert, W.R. and Prior, C.P., Recovery of Highly Purified Biopharmaceutical Proteins from Mammalian Perfusion Culture Systems, Biotech'88 International Conference, London, UK, May (1988).
73. Tolbert, W.R., The Economics of Manufacture - Will the Price Come Down?, Biotech'88 International Conference, London, UK, May (1988).
74. Tolbert, W.R., Large-Scale Mammalian Cell Culture,ACHEMA'88 International Meeting on Chemical Engineering and Biotechnology, Frankfurt, Germany, June (1988).
75. Tolbert, W. R., Mammalian Cell Culture Systems, XIIth Engineering Foundation Conference, Potosi, MO, August (1989).
76. Tolbert, W. R., Manufacture of Biopharmaceutical Proteins by Mammalian Cell Culture Systems, BIOTECH USA Meeting, San Francisco, CA, October (1989).
77. Tolbert, W. R., Application of Large Scale Perfusion Culture to Production of Biopharmaceuticals, JAACT Conference, Fukuoka, Japan, November (1989).
78. Tolbert, W. R., Perfusion Culture: Preferred Method for Manufacture of Protein Biopharmaceuticals, Bioprocess '90 Conference, Washington, DC, January (1990).
79. Tolbert, W. R., Mammalian Cell Products Manufacturing, Pharmaceutical Manufacturers Association - Bulk Pharmaceutical Chemicals Committee Spring 1990 Symposium, St. Louis, MO, May (1990).
80. Hope, J., Rosenberg, M. and Tolbert, W., Development of Mammalian Cell Manufacturing Processes, ESACT Meeting, Avignon, France, May (1990).
81. Tolbert, W.R., Perfusion Technology for Pharmaceutical Production, BioEast '91, Washington D.C., January (1991).
82. Tolbert, W.R., Gene Therapy - Initial Manufacturing Facility, FDA/NIH Gene Therapy Conference, Washington, DC, July (1996).
83. Tolbert, W.R., Pilot Facility Design for Gene Therapy Vector Manufacturing, Williamsburg BioProcess Conference, Williamsburg, VA, November (1996).
84. Tolbert, W.R., Development - Scale Up and Other Pitfalls, 1997 Biopharm Conference, San Francisco, May, 1997.
85. Tolbert, W.R., Conceptual Design of a Multiuse Manufacturing Facility for Gene Therapy, Williamsburg BioProcess Conference, Williamsburg, VA, November (1997).
86. Tolbert, W.R., Vision 2020: Emerging Technologies – Gene Therapy Manufacturing, IEST / PDA Contamination Control Symposium, Phoenix, AR (1998).



87. Tolbert, W.R., Design of a Large-Scale Facility for Engineered Tissue Products at The Williamsburg BioProcessing Foundation Conference, Facilities for Mammalian Cell Products: From Design Through Validation, Montreal, Canada, June (1998).
88. Tolbert, W.R., CGMP Manufacturing Issues for Cellular and Tissue-Based Products, The U.S. Biotechnology Symposium, Washington, DC, November, 1998.
89. Tolbert, W.R., Clinical Manufacturing for Cell Therapy Products – What are the Issues? at The Williamsburg BioProcessing Foundation, Cell & Tissue BioProcessing Conference, Alexandria, VA, September (1999).
90. Tolbert, W.R., cGMP Issues for Clinical Manufacturing of Cell-Based Products, INTERPHEX CA Conference, Long Beach, September (2000).
91. Tolbert, W.R., Options for CGMP Initial Manufacturing Facilities – from Recombinant Proteins to Cell and Gene Therapy, IBC Conference “Building, Constructing and Retrofitting Facilities for Biopharmaceutical Production,” San Diego, November (2001).
92. Tolbert, W.R., Cell and Gene Therapy Manufacturing Facilities – Clinical to Commercial Design Requirements and FDA Concerns, BIOPHEX Interphex California, Santa Clara, CA, October (2002).