6 LITERATURVERZEICHNIS

1. Rojas, M., Yao, S. & Lin, Y.Z.
Controlling epidermal growth factor (EGF)-stimulated Ras activation in intact cells by a cell-permeable peptide mimicking phosphorylated EGF receptor.
J Biol Chem **271**, 27456–27461 (1996).
2. Derossi, D., Chassaing, G. & Prochiantz, A.
Trojan peptides: the penetratin system for intracellular delivery.
Trends Cell Biol **8**, 84–87 (1998).
3. Oess, S. & Hildt, E.
Novel cell permeable motif derived from the PreS2-domain of hepatitis-B virus surface antigens.
Gene Ther **7**, 750–758 (2000).
4. Burger, A. & Wachter, H.
Hunnius, Pharmazeutisches Wörterbuch (Walter de Gruyter & Co, Berlin; 1993).
5. Torchilin, V.P.
Drug targeting.
Eur J Pharm Sci **11 S 2**, 81–91 (2000).
6. Hunter, W.L., Burt, H.M. & Machan, L.
Local delivery of chemotherapy: a supplement to existing cancer treatments. A case for surgical pastes and coated stents.
Adv Drug Deliv Rev **26**, 199–207 (1997).
7. Jain, R.K.
Transport of molecules across tumor vasculature.
Cancer Metastasis Rev **6**, 559–593 (1987).
8. Maeda, H., Wu, J., Sawa, T., Matsumura, Y. & Hori, K.
Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review.
J Control Release **65**, 271–284 (2000).
9. Weinstein, J.N., Magin, R.L., Yatvin, M.B. & Zaharko, D.S.
Liposomes and local hyperthermia: selective delivery of methotrexate to heated tumors.
Science **204**, 188–191 (1979).
10. de Groot, F.M., Damen, E.W. & Scheeren, H.W.
Anticancer prodrugs for application in monotherapy: targeting hypoxia, tumor-associated enzymes, and receptors.
Curr Med Chem **8**, 1093–1122 (2001).
11. Alexiou, C., Arnold, W., Klein, R.J. et al.
Locoregional cancer treatment with magnetic drug targeting.
Cancer Res **60**, 6641–6648 (2000).
12. Ehrlich, P.
On immunity with special reference to cell life.
Proc R Soc **66**, 424–448 (1900).
13. Edelman, G.M., Gall, W.E., Waxdal, M.J. & Konigsberg, W.H.
The covalent structure of a human gamma G-immunoglobulin. I. Isolation and characterization of the whole molecule, the polypeptide chains, and the tryptic fragments.
Biochemistry **7**, 1950–1958 (1968).
14. Porter, R.R.
The structure of antibodies. The basic pattern of the principal class of molecules that neutralize antigens (foreign substances in the body) is four cross-linked chains. This pattern is modified so that antibodies can fit different antigens.
Sci Am **217**, 81–87 (1967).
15. Kohler, G. & Milstein, C.
Continuous cultures of fused cells secreting antibody of predefined specificity.
Nature **256**, 495–497 (1975).
16. Borchmann, P., Riethmuller, G. & Engert, A.
Monoclonal antibodies: development and clinical prospects.
Internist (Berl) **42**, 803–804, 807–814 (2001).
17. Repp, R., Valerius, T. & Bargou, R.
Bispecific antibodies in hematology and oncology.
Internist (Berl) **42**, 854–859 (2001).

18. Kratz, F., Beyer, U., Collery, P. et al.
Preparation, characterization and in vitro efficacy of albumin conjugates of doxorubicin.
Biol Pharm Bull **21**, 56–61 (1998).
19. Greenfield, R.S., Kaneko, T., Daues, A. et al.
Evaluation in vitro of adriamycin immunoconjugates synthesized using an acid-sensitive hydrazone linker.
Cancer Res **50**, 6600–6607 (1990).
20. Beyer, U., Roth, T., Schumacher, P. et al.
Synthesis and in vitro efficacy of transferrin conjugates of the anticancer drug chlorambucil.
J Med Chem **41**, 2701–2708 (1998).
21. Brusa, P., Dosio, F., Coppo, S. et al.
In vitro and in vivo antitumor activity of immunoconjugates prepared by linking 5-fluorouridine to antiadenocarcinoma monoclonal antibody.
Farmaco **52**, 71–81 (1997).
22. Gerweck, L.E. & Seetharaman, K.
Cellular pH gradient in tumor versus normal tissue: potential exploitation for the treatment of cancer.
Cancer Res **56**, 1194–1198 (1996).
23. Hamann, P.R., Hinman, L.M., Hollander, I. et al.
Gemtuzumab ozogamicin, a potent and selective anti-CD33 antibody-calicheamicin conjugate for treatment of acute myeloid leukemia.
Bioconjug Chem **13**, 47–58 (2002).
24. Kratz, F., Muller-Driver, R., Hofmann, I.I., Drevs, J. & Unger, C.
A novel macromolecular prodrug concept exploiting endogenous serum albumin as a drug carrier for cancer chemotherapy.
J Med Chem **43**, 1253–1256 (2000).
25. Kratz, F., Drevs, J., Bing, G. et al.
Development and in vitro efficacy of novel MMP2 and MMP9 specific doxorubicin albumin conjugates.
Bioorg Med Chem Lett **11**, 2001–2006 (2001).
26. Pincus, S.H.
Therapeutic potential of anti-HIV immunotoxins.
Antiviral Res **33**, 1–9 (1996).
27. Wu, M.
Are immunoconjugates useful for therapy with autoimmune diseases?
Int J Immunopharmacol **19**, 83–93 (1997).
28. Vitetta, E.S., Fulton, R.J., May, R.D., Till, M. & Uhr, J.W.
Redesigning nature's poisons to create anti-tumor reagents.
Science **238**, 1098–1104 (1987).
29. Kreitman, R.J. & Pastan, I.
Immunotoxins for targeted cancer therapy.
Adv Drug Deliv Rev **31**, 53–88 (1998).
30. Frankel, A.E., Tagge, E.P. & Willingham, M.C.
Clinical trials of targeted toxins.
Semin Cancer Biol **6**, 307–317 (1995).
31. Zündorf, I. & Dingermann, T.
New genetically engineered drugs.
Pharm Unserer Zeit **29**, 167–173 (2000).
32. Brinkmann, U.
Recombinant antibody fragments and immunotoxin fusions for cancer therapy.
In Vivo **14**, 21–27 (2000).
33. Kreitman, R.J.
Immunotoxins in cancer therapy.
Curr Opin Immunol **11**, 570–578 (1999).
34. Sutherland, R., Delia, D., Schneider, C. et al.
Ubiquitous cell-surface glycoprotein on tumor cells is proliferation-associated receptor for transferrin.
Proc Natl Acad Sci U S A **78**, 4515–4519 (1981).
35. Dautry, V.A., Ciechanover, A. & Lodish, H.F.
pH and the recycling of transferrin during receptor-mediated endocytosis.
Proc Natl Acad Sci U S A **80**, 2258–2262 (1983).
36. Bhakdi, S., Kehoe, M., Valeva, A., Weller, U. & Palmer, M.
in Guidebook to Protein Toxins and Their Use in Cell Biology.
(eds. R. Rappuoli & C. Montecucco Oxford University Press, New York; 1997) p. 5.
37. Pellizzari, R. & Rossetto, O.
in Guidebook to Protein Toxins and Their Use in Cell Biology.
(eds. R. Rappuoli & C. Montecucco Oxford University Press, New York; 1997) p. 100.
38. Harvey, A.L.
in Guidebook to Protein Toxins and Their Use in Cell Biology.
(eds. R. Rappuoli & C. Montecucco Oxford University Press, New York; 1997) p. 159.
39. Pizza, M., Fontana, M.R. & Rappuoli, R.
in Guidebook to Protein Toxins and Their Use in Cell Biology.
(eds. R. Rappuoli & C. Montecucco Oxford University Press, New York; 1997) p. 28.
40. Rappuoli, R. & Pizza, M.
in Guidebook to Protein Toxins and Their Use in Cell Biology.
(eds. R. Rappuoli & C. Montecucco Oxford University Press, New York; 1997) p. 34.
41. Hanna, P.C. & Collier, R.J.
in Guidebook to Protein Toxins and Their Use in Cell Biology.
(eds. R. Rappuoli & C. Montecucco Oxford University Press, New York; 1997) p. 91.
42. Olsnes, S., Sandvig, K., Madshus, I.H. & Sundan, A.
Entry mechanisms of protein toxins and

picornaviruses.
Biochem Soc Symp **50**, 171–191 (1985).

43. Stirpe, F.
in Guidebook to Protein Toxins and Their Use in Cell Biology.
(eds. R. Rappuoli & C. Montecucco Oxford University Press, New York; 1997) p. 57.
44. Aktories, K. & Wegner, A.
Mechanisms of the cytopathic action of actin-ADP-ribosylating toxins.
Mol Microbiol **6**, 2905–2908 (1992).
45. Yamaizumi, M., Mekada, E., Uchida, T. & Okada, Y.
One molecule of diphtheria toxin fragment A introduced into a cell can kill the cell.
Cell **15**, 245–250 (1978).
46. Eiklid, K., Olsnes, S. & Pihl, A.
Entry of lethal doses of abrin, ricin and modeccin into the cytosol of HeLa cells.
Exp Cell Res **126**, 321–326 (1980).
47. Fitzgerald, D.
Why toxins!
Semin Cancer Biol **7**, 87–95 (1996).
48. Endo, Y., Chan, Y.L., Lin, A., Tsurugi, K. & Wool, I.G.
The cytotoxins alpha-sarcin and ricin retain their specificity when tested on a synthetic oligoribonucleotide (35-mer) that mimics a region of 28 S ribosomal ribonucleic acid.
J Biol Chem **263**, 7917–7920 (1988).
49. Van Ness, B.G., Howard, J.B. & Bodley, J.W.
ADP-ribosylation of elongation factor 2 by diphtheria toxin. Isolation and properties of the novel ribosyl-amino acid and its hydrolysis products.
J Biol Chem **255**, 10717–10720 (1980).
50. Van Ness, B.G., Howard, J.B. & Bodley, J.W.
ADP-ribosylation of elongation factor 2 by diphtheria toxin. NMR spectra and proposed structures of ribosyl-diphthamide and its hydrolysis products.
J Biol Chem **255**, 10710–10716 (1980).
51. Oppenheimer, N.J. & Bodley, J.W.
Diphtheria toxin. Site and configuration of ADP-ribosylation of diphthamide in elongation factor 2.
J Biol Chem **256**, 8579–8581 (1981).
52. Chung, D.W. & Collier, R.J.
Enzymatically active peptide from the adenosine diphosphate-ribosylating toxin of Pseudomonas aeruginosa.
Infect Immun **16**, 832–841 (1977).
53. Pappenheimer, A.M.
Diphtheria toxin - I: Isolation and characterization of a toxic protein from C. diphtheriae filtrates.
J Biol Chem **125**, 543 (1937).
54. Liu, P.V.
The roles of various fractions of Pseudomonas aeruginosa in its pathogenesis - 3: Identity of lethal toxins produced in vitro and in vivo.
J Infect Dis **116**, 481–489 (1966).
55. Brooke, J.S., Cha, J.H. & Eidels, L.
Diphtheria toxin: receptor interaction: association, dissociation, and effect of pH.
Biochem Biophys Res Commun **248**, 297–302 (1998).
56. Hsu, C.T., Lin, J.Y. & Tung, T.C.
Further report on therapeutic effect of abrin and ricin on human cancers.
Taiwan Yi Xue Hui Za Zhi **73**, 526–542 (1974).
57. Fodstad, O., Kvalheim, G., Godal, A. et al.
Phase I study of the plant protein ricin.
Cancer Res **44**, 862–865 (1984).
58. Rybak, S.M., Saxena, S.K., Ackerman, E.J. & Youle, R.J.
Cytotoxic potential of ribonuclease and ribonuclease hybrid proteins.
J Biol Chem **266**, 21202–21207 (1991).
59. Deonarain, M.P. & Epenetos, A.A.
Design, characterization and anti-tumour cytotoxicity of a panel of recombinant, mammalian ribonuclease-based immunotoxins.
Br J Cancer **77**, 537–546 (1998).
60. Li, B.Y., Frankel, A.E. & Ramakrishnan, S.
High-level expression and simplified purification of recombinant ricin A chain.
Protein Expr Purif **3**, 386–394 (1992).
61. Chiron, M.F., Fryling, C.M. & FitzGerald, D.J.
Cleavage of pseudomonas exotoxin and diphtheria toxin by a furin-like enzyme prepared from beef liver.
J Biol Chem **269**, 18167–18176 (1994).
62. Collier, R.J. & Kandel, J.
Structure and activity of diphtheria toxin. I. Thiol-dependent dissociation of a fraction of toxin into enzymically active and inactive fragments.
J Biol Chem **246**, 1496–1503 (1971).
63. Drazin, R., Kandel, J. & Collier, R.J.
Structure and activity of diphtheria toxin. II. Attack by trypsin at a specific site within the intact toxin molecule.
J Biol Chem **246**, 1504–1510 (1971).
64. O'Hare, M., Roberts, L.M., Thorpe, P.E. et al.
Expression of ricin A chain in Escherichia coli.
Febs Lett **216**, 73–78 (1987).
65. Greenfield, L., Bjorn, M.J., Horn, G. et al.
Nucleotide sequence of the structural gene for diphtheria toxin carried by corynebacteriophage beta.
Proc Natl Acad Sci U S A **80**, 6853–6857 (1983).
66. Gray, G.L., Smith, D.H., Baldridge, J.S. et al.
Cloning, nucleotide sequence, and expression in Escherichia coli of the exotoxin A structural gene of Pseudomonas aeruginosa.

Proc Natl Acad Sci U S A **81**, 2645–2649 (1984).

67. Umata, T. & Mekada, E.
Diphtheria toxin translocation across endosome membranes. A novel cell permeabilization assay reveals new diphtheria toxin fragments in endocytic vesicles.
J Biol Chem **273**, 8351–8359 (1998).
68. Stenmark, H., Afanasiev, B.N., Ariansen, S. & Olsnes, S.
Association between diphtheria toxin A- and B-fragment and their fusion proteins.
Biochem J **281**, 619–625 (1992).
69. Bennett, M.J. & Eisenberg, D.
Refined structure of monomeric diphtheria toxin at 2.3 A resolution.
Protein Sci **3**, 1464–1475 (1994).
70. Allured, V.S., Collier, R.J., Carroll, S.F. & McKay, D.B.
Structure of exotoxin A of Pseudomonas aeruginosa at 3.0-Angstrom resolution.
Proc Natl Acad Sci U S A **83**, 1320–1324 (1986).
71. Hwang, J., Fitzgerald, D.J., Adhya, S. & Pastan, I.
Functional domains of pseudomonas exotoxin identified by deletion analysis of the gene expressed in E. coli.
Cell **48**, 129–136 (1987).
72. Frankel, A.E., Kreitman, R.J. & Sausville, E.A.
Targeted toxins.
Clin Cancer Res **6**, 326–334 (2000).
73. Olsen, E., Duvic, M., Frankel, A. et al.
Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma.
J Clin Oncol **19**, 376–388 (2001).
74. Kreitman, R.J.
Toxin-labeled monoclonal antibodies.
Curr Pharm Biotechnol **2**, 313–325. (2001).
75. Jain, R.K.
Delivery of molecular medicine to solid tumors.
Science **271**, 1079–1080 (1996).
76. Jain, R.K.
Vascular and interstitial barriers to delivery of therapeutic agents in tumors.
Cancer Metastasis Rev **9**, 253–266 (1990).
77. Au, J.L.-S., Jang, S.H., Zheng, J. et al.
Determinants of drug delivery and transport to solid tumors.
J Control Release **74**, 31–46 (2001).
78. Brinkmann, U. & Pastan, I.
Immunotoxins against cancer.
Biochim Biophys Acta **1198**, 27–45 (1994).
79. Keppler-Hafkemeyer, A., Kreitman, R.J. & Pastan, I.
Apoptosis induced by immunotoxins used in the treatment of hematologic malignancies.
Int J Cancer **87**, 86–94 (2000).
80. FitzGerald, D.J., Willingham, M.C., Cardarelli, C.O. et al.
A monoclonal antibody-pseudomonas toxin conjugate that specifically kills multidrug-resistant cells.
Proc Natl Acad Sci U S A **84**, 4288–4292 (1987).
81. Mickisch, G.H., Pai, L.H., Siegsmund, M. et al.
Pseudomonas exotoxin conjugated to monoclonal antibody MRK16 specifically kills multidrug resistant cells in cultured renal carcinomas and in MDR-transgenic mice.
J Urol **149**, 174–178 (1993).
82. Frankel, A.E., Hall, P.D., McLain, C. et al.
Cell-specific modulation of drug resistance in acute myeloid leukemic blasts by diphtheria fusion toxin, DT388-GMCSF.
Bioconjug Chem **9**, 490–496 (1998).
83. Perentesis, J.P., Waddick, K.G., Bendel, A.E. et al.
Induction of apoptosis in multidrug-resistant and radiation-resistant acute myeloid leukemia cells by a recombinant fusion toxin directed against the human granulocyte macrophage colony-stimulating factor receptor.
Clin Cancer Res **3**, 347–355 (1997).
84. Srinivasachar, K. & Neville, D.M., Jr.
New protein cross-linking reagents that are cleaved by mild acid.
Biochemistry **28**, 2501–2509 (1989).
85. Mueller, B.M., Wrasidlo, W.A. & Reisfeld, R.A.
Antibody conjugates with morpholinodoxorubicin and acid-cleavable linkers.
Bioconjug Chem **1**, 325–330 (1990).
86. O'Hare, M., Brown, A.N., Hussain, K. et al.
Cytotoxicity of a recombinant ricin-A-chain fusion protein containing a proteolytically-cleavable spacer sequence.
Febs Lett **273**, 200–204 (1990).
87. Goyal, A. & Batra, J.K.
Inclusion of a furin-sensitive spacer enhances the cytotoxicity of ribotoxin restrictocin containing recombinant single-chain immunotoxins.
Biochem J **345 Pt 2**, 247–254 (2000).
88. Claus, V., Jahraus, A., Tjelle, T. et al.
Lysosomal enzyme trafficking between phagosomes, endosomes, and lysosomes in J774 macrophages. Enrichment of cathepsin H in early endosomes.
J Biol Chem **273**, 9842–9851 (1998).
89. Conner, G.E.
in Handbook of Proteolytic Enzymes.
(eds. A.J. Barrett, N.D. Rawlings & J.F.

Woessner Academic Press, London and San Diego; 1998) pp. 828–836.

90. Rejmanova, P., Kopecek, J., Duncan, R. & Lloyd, J.B.
Stability in rat plasma and serum of lysosomally degradable oligopeptide sequences in N-(2-hydroxypropyl) methacrylamide copolymers.
Biomaterials **6**, 45–48 (1985).
91. Vasey, P.A., Kaye, S.B., Morrison, R. et al.
Phase I clinical and pharmacokinetic study of PK1 [N-(2-hydroxypropyl)methacrylamide copolymer doxorubicin]: first member of a new class of chemotherapeutic agents-drug-polymer conjugates.
Clin Cancer Res **5**, 83–94 (1999).
92. Denault, J.B. & Leduc, R.
Furin/PACE/SPC1: a convertase involved in exocytic and endocytic processing of precursor proteins.
FEBS Lett **379**, 113–116 (1996).
93. Thornberry, N.A. & Lazebnik, Y.
Caspases: enemies within.
Science **281**, 1312–1316. (1998).
94. Ehlert, J.E. & Kubbutat, M.H.
Apoptosis and its relevance in cancer therapy.
Onkologie **24**, 433–440 (2001).
95. Morimoto, H. & Bonavida, B.
Diphtheria toxin- and pseudomonas A toxin-mediated apoptosis. ADP ribosylation of elongation factor-2 is required for DNA fragmentation and cell lysis and synergy with tumor necrosis factor-alpha.
J Immunol **149**, 2089–2094 (1992).
96. Kochi, S.K. & Collier, R.J.
DNA fragmentation and cytolysis in U937 cells treated with diphtheria toxin or other inhibitors of protein synthesis.
Exp Cell Res **208**, 296–302 (1993).
97. Keppler-Hafkemeyer, A., Brinkmann, U. & Pastan, I.
Role of caspases in immunotoxin-induced apoptosis of cancer cells.
Biochemistry **37**, 16934–16942 (1998).
98. Houchins, J.P.
Immunotoxin-induced apoptosis.
Stem Cells **18**, 384–385 (2000).
99. Gansauge, S., Gansauge, F., Yang, Y. et al.
Interleukin-1 beta converting enzyme (caspase-1) is overexpressed in the adenocarcinoma of the pancreas.
Cancer Res **58**, 2703–2706 (1998).
100. Krajewski, S., Gascoyne, R., Zapata, J. et al.
Immunolocalization of ICE/Ced-3-family protease, Cpp32 (Caspase-3) in non-Hodgkin's lymphomas, chronic lymphocytic leukemias, and reactive lymph nodes.
Blood **89**, 3817–3825 (1997).
101. Thornton, K., Wang, Y., Weiner, H. & Gorenstein, D.G.
Import, processing, and two-dimensional NMR structure of a linker-deleted signal peptide of rat liver mitochondrial aldehyde dehydrogenase.
J Biol Chem **268**, 19906–19914. (1993).
102. Zhou, J., Bai, Y. & Weiner, H.
Proteolysis prevents in vivo chimeric fusion protein import into yeast mitochondria. Cytosolic cleavage and subcellular distribution.
J Biol Chem **270**, 16689–16693 (1995).
103. Lindgren, M., Hallbrink, M., Prochiantz, A. & Langel, U.
Cell-penetrating peptides.
Trends Pharmacol Sci **21**, 99–103. (2000).
104. Schwarze, S.R. & Dowdy, S.F.
In vivo protein transduction: intracellular delivery of biologically active proteins, compounds and DNA.
Trends Pharmacol Sci **21**, 45–48 (2000).
105. Vives, E., Brodin, P. & Lebleu, B.
A truncated HIV-1 Tat protein basic domain rapidly translocates through the plasma membrane and accumulates in the cell nucleus.
J Biol Chem **272**, 16010–16017 (1997).
106. Elliott, G. & O'Hare, P.
Intercellular trafficking and protein delivery by a herpesvirus structural protein.
Cell **88**, 223–233 (1997).
107. Lin, Y.Z., Yao, S.Y., Veach, R.A., Torgerson, T.R. & Hawiger, J.
Inhibition of nuclear translocation of transcription factor NF-kappa B by a synthetic peptide containing a cell membrane-permeable motif and nuclear localization sequence.
J Biol Chem **270**, 14255–14258 (1995).
108. Lindgren, M., Gallet, X., Soomets, U. et al.
Translocation properties of novel cell penetrating transportan and penetratin analogues.
Bioconjug Chem **11**, 619–626 (2000).
109. Oehlke, J., Scheller, A., Wiesner, B. et al.
Cellular uptake of an alpha-helical amphipathic model peptide with the potential to deliver polar compounds into the cell interior non-endocytically.
Biochim Biophys Acta **1414**, 127–139 (1998).
110. Scheller, A., Oehlke, J., Wiesner, B. et al.
Structural requirements for cellular uptake of alpha-helical amphipathic peptides.
J Pept Sci **5**, 185–194 (1999).
111. Scheller, A., Wiesner, B., Melzig, M., Bienert, M. & Oehlke, J.
Evidence for an amphipathicity independent cellular uptake of amphipathic cell-penetrating peptides.
Eur J Biochem **267**, 6043–6050 (2000).
112. Caron, N.J., Torrente, Y., Camirand, G. et al.
Intracellular delivery of a Tat-eGFP fusion

protein into muscle cells.
Mol Ther **3**, 310–318 (2001).

113. Dignam, J.D., Martin, P.L., Shastry, B.S. & Roeder, R.G.
Eukaryotic gene transcription with purified components.
Methods Enzymol **101**, 582–598 (1983).
114. Ciechanover, A., Schwartz, A.L., Dautry, V.A. & Lodish, H.F.
Kinetics of internalization and recycling of transferrin and the transferrin receptor in a human hepatoma cell line. Effect of lysosomotropic agents.
J Biol Chem **258**, 9681–9689 (1983).
115. Laemmli, U.K.
Cleavage of structural proteins during the assembly of the head of bacteriophage T4.
Nature **227**, 680–685 (1970).
116. Heukeshoven, J. & Dernick, R.
Improved silver staining procedure for fast staining in PhastSystem Development Unit. I. Staining of sodium dodecyl sulfate gels.
Electrophoresis **9**, 28–32 (1988).
117. Kreitman, R.J. & Pastan, I.
Recombinant toxins containing human granulocyte-macrophage colony- stimulating factor and either pseudomonas exotoxin or diphtheria toxin kill gastrointestinal cancer and leukemia cells.
Blood **90**, 252–259 (1997).
118. Li, B.Y. & Ramakrishnan, S.
Recombinant hybrid toxin with dual enzymatic activities. Potential use in preparing highly effective immunotoxins.
J Biol Chem **269**, 2652–2658 (1994).
119. Fritzer, M., Barabas, K., Szuts, V. et al.
Cytotoxicity of a transferrin-adriamycin conjugate to anthracycline- resistant cells.
Int J Cancer **52**, 619–623 (1992).
120. Ueno, Y., Umemori, K., Niimi, E. et al.
Induction of apoptosis by T-2 toxin and other natural toxins in HL-60 human promyelotic leukemia cells.
Nat Toxins **3**, 129–137 (1995).
121. Carroll, S.F. & Collier, R.J.
NAD binding site of diphtheria toxin: identification of a residue within the nicotinamide subsite by photochemical modification with NAD.
Proc Natl Acad Sci U S A **81**, 3307–3311 (1984).
122. Larsson, R., Nygren, P., Ekberg, M. & Slater, L.
Chemotherapeutic drug sensitivity testing of human leukemia cells in vitro using a semiautomated fluorometric assay.
Leukemia **4**, 567–571 (1990).
123. Mosmann, T.
Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays.
J Immunol Methods **65**, 55–63 (1983).
124. Larsson, R., Kristensen, J., Sandberg, C. & Nygren, P.
Laboratory determination of chemotherapeutic drug resistance in tumor cells from patients with leukemia, using a fluorometric microculture cytotoxicity assay (FMCA).
Int J Cancer **50**, 177–185 (1992).
125. Ross, D.D., Joneckis, C.C., Ordonez, J.V. et al.
Estimation of cell survival by flow cytometric quantification of fluorescein diacetate/propidium iodide viable cell number.
Cancer Res **49**, 3776–3782 (1989).
126. Passador, L. & Iglewski, W.
ADP-ribosylating toxins.
Methods Enzymol **235**, 617–631 (1994).
127. Iglewski, B.H. & Kabat, D.
NAD-dependent inhibition of protein synthesis by Pseudomonas aeruginosa toxin.
Proc Natl Acad Sci U S A **72**, 2284–2288 (1975).
128. Zhang, J.
Use of biotinylated NAD to label and purify ADP-ribosylated proteins.
Methods Enzymol **280**, 255–265 (1997).
129. Moskaug, J.O., Sletten, K., Sandvig, K. & Olsnes, S.
Translocation of diphtheria toxin A-fragment to the cytosol. Role of the site of interfragment cleavage.
J Biol Chem **264**, 15709–15713 (1989).
130. Denault, J.B., Claing, A., D'Orleans-Juste, P. et al.
Processing of proendothelin-1 by human furin convertase.
FEBS Lett **362**, 276–280 (1995).
131. Kawooya, J.K., Treat, J.C., Kirschner, R.J. et al.
The expression, affinity purification and characterization of recombinant pseudomonas exotoxin 40 (PE40) secreted from Escherichia coli.
J Biotechnol **42**, 9–22 (1995).
132. Lu, Z., DiBlasio-Smith, E.A., Grant, K.L. et al.
Histidine patch thioredoxins. Mutant forms of thioredoxin with metal chelating affinity that provide for convenient purifications of thioredoxin fusion proteins.
J Biol Chem **271**, 5059–5065 (1996).
133. Hanahan, D.
Studies on transformation of Escherichia coli with plasmids.
J Mol Biol **166**, 557–580 (1983).
134. Birnboim, H.C. & Doly, J.
A rapid alkaline extraction procedure for screening recombinant plasmid DNA.
Nucleic Acids Res **7**, 1513–1523 (1979).
135. Sanger, F., Nicklen, S. & Coulson, A.R.
DNA sequencing with chain-terminating

inhibitors.
Proc Natl Acad Sci U S A **74**, 5463–5467 (1977).

136. Ciechanover, A., Schwartz, A.L. & Lodish, H.F.
The asialoglycoprotein receptor internalizes and recycles independently of the transferrin and insulin receptors.
Cell **32**, 267–275 (1983).
137. McGraw, T.E., Greenfield, L. & Maxfield, F.R.
Functional expression of the human transferrin receptor cDNA in Chinese hamster ovary cells deficient in endogenous transferrin receptor.
J Cell Biol **105**, 207–214 (1987).
138. Schneider, C., Sutherland, R., Newman, R. & Greaves, M.
Structural features of the cell surface receptor for transferrin that is recognized by the monoclonal antibody OKT9.
J Biol Chem **257**, 8516–8522 (1982).
139. Gordon, V.M., Klimpel, K.R., Arora, N., Henderson, M.A. & Leppla, S.H.
Proteolytic activation of bacterial toxins by eukaryotic cells is performed by furin and by additional cellular proteases.
Infect Immun **63**, 82–87 (1995).
140. Ogata, M., Chaudhary, V.K., Pastan, I. & FitzGerald, D.J.
Processing of pseudomonas exotoxin by a cellular protease results in the generation of a 37,000-Da toxin fragment that is translocated to the cytosol.
J Biol Chem **265**, 20678–20685 (1990).
141. Chaudhary, V.K., Xu, Y.H., FitzGerald, D., Adhya, S. & Pastan, I.
Role of domain II of pseudomonas exotoxin in the secretion of proteins into the periplasm and medium by Escherichia coli.
Proc Natl Acad Sci U S A **85**, 2939–2943 (1988).
142. Skerra, A., Pfitzinger, I. & Pluckthun, A.
The functional expression of antibody Fv fragments in Escherichia coli: improved vectors and a generally applicable purification technique.
Biotechnology (N Y) **9**, 273–278 (1991).
143. Wunderlich, M. & Glockshuber, R.
In vivo control of redox potential during protein folding catalyzed by bacterial protein disulfide-isomerase (DsbA).
J Biol Chem **268**, 24547–24550 (1993).
144. Topell, S., Hennecke, J. & Glockshuber, R.
Circularly permuted variants of the green fluorescent protein.
FEBS Lett **457**, 283–289 (1999).
145. Burns, J.A., Butler, J.C., Moran, J. & Whitesides, G.M.
Selective reduction of disulfides by tris(2-carboxyethyl)phosphine.
J Org Chem **56**, 2648–2650 (1991).
146. Ariansen, S., Afanasiev, B.N., Moskaug, J.O. et al.
Membrane translocation of diphtheria toxin A-fragment: role of carboxy - terminal region.
Biochemistry **32**, 83–90 (1993).
147. Kuderova, A., Nanak, E., Truksa, M. & Brzobohaty, B.
Use of rifampicin in T7 RNA polymerase-driven expression of a plant enzyme: rifampicin improves yield and assembly.
Protein Expr Purif **16**, 405–409 (1999).
148. de Smit, M.H., Hoefkens, P., de Jong, G. et al.
Optimized bacterial production of nonglycosylated human transferrin and its half-molecules.
Int J Biochem Cell Biol **27**, 839–850. (1995).
149. Hoefkens, P., de Smit, M.H., de Jeu-Jaspars, N.M. et al.
Isolation, renaturation and partial characterization of recombinant human transferrin and its half molecules from Escherichia coli.
Int J Biochem Cell Biol **28**, 975–982. (1996).
150. Zak, O., Trinder, D. & Aisen, P.
Primary receptor-recognition site of human transferrin is in the C-terminal lobe.
J Biol Chem **269**, 7110–7114 (1994).
151. Lee, J.H., Engler, J.A., Collawn, J.F. & Moore, B.A.
Receptor mediated uptake of peptides that bind the human transferrin receptor.
Eur J Biochem **268**, 2004–2012 (2001).
152. Ponka, P., Beaumont, C. & Richardson, D.R.
Function and regulation of transferrin and ferritin.
Semin Hematol **35**, 35–54 (1998).
153. Testa, U., Pelosi, E. & Peschle, C.
The transferrin receptor.
Crit Rev Oncog **4**, 241–276 (1993).
154. Stoorvogel, W., Geuze, H.J., Griffith, J.M. & Strous, G.J.
The pathways of endocytosed transferrin and secretory protein are connected in the trans-Golgi reticulum.
J Cell Biol **106**, 1821–1829 (1988).
155. Ippoliti, R., Lendaro, E., D'Agostino, I. et al.
A chimeric saporin-transferrin conjugate compared to ricin toxin: role of the carrier in intracellular transport and toxicity.
Faseb J **9**, 1220–1225. (1995).
156. Fujimori, K., Covell, D.G., Fletcher, J.E. & Weinstein, J.N.
A modeling analysis of monoclonal antibody percolation through tumors: a binding-site barrier.
J Nucl Med **31**, 1191–1198 (1990).
157. Sung, C., Dedrick, R.L., Hall, W.A., Johnson, P.A. & Youle, R.J.

The spatial distribution of immunotoxins in solid tumors: assessment by quantitative autoradiography.
Cancer Res **53**, 2092–2099 (1993).

158. Csoka, K., Larsson, R., Tholander, B. et al.
Cytotoxic drug sensitivity testing of tumor cells from patients with ovarian carcinoma using the fluorometric microculture cytotoxicity assay (FMCA).
Gynecol Oncol **54**, 163–170 (1994).
159. Riordan, H.D., Riordan, N.H., Meng, X., Zhong, J. & Jackson, J.A.
Improved microplate fluorometer counting of viable tumor and normal cells.
Anticancer Res **14**, 927–931 (1994).
160. Chang, T.M. & Chang, C.H.
Study on the variables affecting toxicity of hybrid toxins. The effect of different target cell receptor distribution and toxin binding chain.
Biochim Biophys Acta **1013**, 239–246 (1989).
161. Chung, D.W. & Collier, R.J.
The mechanism of ADP-ribosylation of elongation factor 2 catalyzed by fragment A from diphtheria toxin.
Biochim Biophys Acta **483**, 248–257 (1977).
162. Epinat, J.C. & Gilmore, T.D.
In vitro-translated diphtheria toxin A chain inhibits translation in wheat germ extracts: analysis of biologically active, caspase-3-resistant diphtheria toxin mutants.
Biochim Biophys Acta **1472**, 34–41 (1999).
163. Langer, M., Rothe, M., Eck, J., Mockel, B. & Zinke, H.
A nonradioactive assay for ribosome-inactivating proteins.
Anal Biochem **243**, 150–153 (1996).
164. Chang, M.P., Bramhall, J., Graves, S., Bonavida, B. & Wisnieski, B.
Internucleosomal DNA cleavage precedes diphtheria toxin-induced cytolysis.
J Biol Chem **264**, 15261–15267 (1989).
165. Schwarze, S.R., Ho, A., Vocero-Akbani, A. & Dowdy, S.F.
In vivo protein transduction: delivery of a biologically active protein into the mouse.
Science **285**, 1569–1572 (1999).
166. Wawrzynczak, E.J., Cumber, A.J., Henry, R.V., Parnell, G.D. & Westwood, J.H.
Structural factors influencing the pharmacokinetics and stability of immunotoxins.
Biochem Soc Trans **20**, 738–743 (1992).
167. Trail, P.A., Willner, D., Knipe, J. et al.
Effect of linker variation on the stability, potency, and efficacy of carcinoma-reactive BR64-doxorubicin immunoconjugates.
Cancer Res **57**, 100–105 (1997).
168. Arpicco, S., Dosio, F., Brusa, P., Crosasso, P. & Cattel, L.
New coupling reagents for the preparation of disulfide cross-linked conjugates with increased stability.
Bioconjug Chem **8**, 327–337 (1997).
169. Bayer, M.E., Bayer, M.H., Lunn, C.A. & Pigiet, V.
Association of thioredoxin with the inner membrane and adhesion sites in Escherichia coli.
J Bacteriol **169**, 2659–2666 (1987).
170. Rubartelli, A., Bajetto, A., Allavena, G., Wollman, E. & Sitia, R.
Secretion of thioredoxin by normal and neoplastic cells through a leaderless secretory pathway.
J Biol Chem **267**, 24161–24164 (1992).
171. vanderSpek, J.C. & Murphy, J.R.
Fusion protein toxins based on diphtheria toxin: selective targeting of growth factor receptors of eukaryotic cells.
Methods Enzymol **327**, 239–249 (2000).
172. Huber, O. & Huber-Wunderlich, M.
in Protein Liquid Chromatography. (ed. M. Kastner Elsevier Science Ltd, Oxford; 1999) pp. 557–586.
173. Rosenthal, J.A., Levandoski, M.M., Chang, B. et al.
The functional role of positively charged amino acid side chains in alpha-bungarotoxin revealed by site-directed mutagenesis of a His-tagged recombinant alpha-bungarotoxin.
Biochemistry **38**, 7847–7855. (1999).
174. Tang, W., Sun, Z.Y., Pannell, R., Gurewich, V. & Liu, J.N.
An efficient system for production of recombinant urokinase-type plasminogen activator.
Protein Expr Purif **11**, 279–283. (1997).
175. Molloy, S.S., Anderson, E.D., Jean, F. & Thomas, G.
Bi-cycling the furin pathway: from TGN localization to pathogen activation and embryogenesis.
Trends Cell Biol **9**, 28–35 (1999).
176. Tsuneoka, M., Nakayama, K., Hatsuzawa, K. et al.
Evidence for involvement of furin in cleavage and activation of diphtheria toxin.
J Biol Chem **268**, 26461–26465 (1993).
177. Xiang, Y., Molloy, S.S., Thomas, L. & Thomas, G.
the PC6B cytoplasmic domain contains two acidic clusters that direct sorting to the distinct trans-Golgi network/endosomal compartments.
Mol Biol Cell **11**, 1257–1273 (2000).
178. Wise, R.J., Barr, P.J., Wong, P.A. et al.
Expression of a human proprotein processing enzyme: correct cleavage of the von Willebrand factor precursor at a paired basic amino acid site.

Proc Natl Acad Sci U S A **87**, 9378–9382 (1990).

179. Matsuo, E., Sampei, G., Mizobuchi, K. & Ito, K.
The plasmid F OmpP protease, a homologue of OmpT, as a potential obstacle to E. coli-based protein production.
FEBS Lett **461**, 6–8 (1999).
180. Kaup, M., Dassler, K., Reinecke, U. et al.
Cleavage processing of human transferrin receptor at distinct positions within the stalk region by neutrophil elastase and cathepsin G.
Biol Chem, in press (2002).
181. Rutledge, E.A., Root, B.J., Lucas, J.J. & Enns, C.A.
Elimination of the O-linked glycosylation site at Thr 104 results in the generation of a soluble human-transferrin receptor.
Blood **83**, 580–586 (1994).
182. Larsen, A.K., Escargueil, A.E. & Skladanowski, A.
Resistance mechanisms associated with altered intracellular distribution of anticancer agents.
Pharmacol Ther **85**, 217–229 (2000).
183. Zhang, J.T.
The multi-structural feature of the multidrug resistance gene product P-glycoprotein: implications for its mechanism of action (hypothesis).
Mol Membr Biol **18**, 145–152 (2001).
184. Falnes, P.O., Wesche, J. & Olsnes, S.
Ability of the Tat basic domain and VP22 to mediate cell binding, but not membrane translocation of the diphtheria toxin A-fragment.
Biochemistry **40**, 4349–4358 (2001).
185. Feder, J.N., Gnirke, A., Thomas, W. et al.
A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis.
Nat Genet **13**, 399–408 (1996).
186. Bennett, M.J., Lebron, J.A. & Bjorkman, P.J.
Crystal structure of the hereditary haemochromatosis protein HFE complexed with transferrin receptor.
Nature **403**, 46–53 (2000).
187. Lebron, J.A., Bennett, M.J., Vaughn, D.E. et al.
Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor.
Cell **93**, 111–123 (1998).
188. Plank, C., Oberhauser, B., Mechtler, K., Koch, C. & Wagner, E.
The influence of endosome-disruptive peptides on gene transfer using synthetic virus-like gene transfer systems.
J Biol Chem **269**, 12918–12924 (1994).
189. Lorenzetti, I., Meneguzzi, A., Fracasso, G. et al.
Genetic grafting of membrane-acting peptides to the cytotoxin dianthin augments its ability to de-stabilize lipid bilayers and enhances its cytotoxic potential as the component of transferrin-toxin conjugates.
Int J Cancer **86**, 582–589 (2000).
190. Subbarao, N.K., Parente, R.A., Szoka, F.C., Jr., Nadasdi, L. & Pongracz, K.
pH-dependent bilayer destabilization by an amphipathic peptide.
Biochemistry **26**, 2964–2972 (1987).