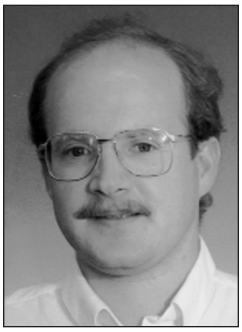
Ernst Wagner, Ph.D.

Director
Boehringer-Ingelheim Austria
Cancer Vaccines
Dr. Boehringergasse 5-11
A-1121 Vienna
Austria



1983	Diploma, Chemistry/Biochemistry, Technical University of Vienna, Austria
1985	Ph.D., Organic Chemistry, Technical University of Vienna
1985-1986	Postdoctorate, Prebiotic Chemistry, Swiss Federal School of Technology (ETH), Zurich, Switzerland
1987	Research Assistant, Federal School of Technology (ETH)
1988-1995	Group Leader, Research Institute of Molecular Pathology, Vienna, Austria
1994	Habilitation in Biochemistry, Medical Faculty, University of Vienna
1996	Professor, Biopharmaceutical Sciences, F.C. Donders Chair, Utrecht University, Utrecht, The Netherlands
1992-present	Director of Cancer Vaccines, Boehringer Ingelheim Austria, Vienna, Austria
1995-present	Group Leader, Institute of Biochemistry, Vienna University Biocenter

Polymer Based Systems for Tumor-Targeted Gene Delivery

DNA complexed with transferrin-polyethylenimine (Tf-PEI) conjugates[1,2], that combine the gene transfer efficiency of PEI[3] with the specific mechanism of receptor-mediated endocytosis, were applied. Systemic application of optimized surface-shielded Tf-PEI_{800}/DNA complexes into the tail vein of Neuro2A-bearing mice resulted in preferential gene delivery into the distantly growing subcutaneous tumors.[4,5] In contrast, application of standard DNA/Tf-PEI_{800} complexes caused gene transfer primarily to the lung and also toxicity. Biophysical parameters of the transfection complexes, such as surface charge, particle size, modification with targeting ligand, and molecular weight of the polymeric carrier (PEI_{800} vs. PEI_{25} or PEI_{22}), were found to strongly influence in vivo DNA biodistribution, toxicity, and gene transfer efficacy.

Two major mechanisms are considered to contribute to the tumor-specific targeting as found in our model: passive targeting (by shielding the surface of complexes from undesired interaction) and active targeting (by a cell surface receptor ligand such as Tf). Passive targeting can be achieved by masking the surface charge of complexes through covalent coating DNA/Tf-PEI_{800} complexes with polyethylenglycol (PEG), resulting in a reduced plasma and erythrocyte binding. Prolonged circulation in blood allows extravasation of DNA complexes into distant tumor tissue which is an area of vascular leakiness. Shielding of charges in PEI_{25} or PEI_{22} complexes by linkage of sufficient Tf ligand also leads to preferential delivery into tumors, even in the absence of PEGylation.

1. Kircheis, R. et al. *Gene Therapy* **4**, 409-418 (1997).
2. Ogris, M. et al. *Gene Therapy* **5**, 1425-1433 (1998).
3. Boussif, O. et al. *Proc. Natl. Acad. Sci. USA* **92,** 7297-301 (1995).
4. Kircheis, R. et al. *J. Gene Medicine* **1,** 111-120 (1999).
5. Ogris, M. et al. *Gene Therapy* **6,** 595-605 (1999).