

## 8 Literaturverzeichnis

- Allen, P., Worland, S. & Gold, L. (1995) Isolation of a High-Affinity RNA Ligand to HIV-1 Integrase from a Random Pool. *Virology* **209**, 327-336.
- Alzheimer, A. (1907) Über eine eigenartige Erkrankung der Hirnrinde. *Allg Z Psychiat* **64**, 146-148.
- Alzheimer Forschung International e. V. (1997) *Alzheimer Forschung Direkt* **1**, 1.
- Anderson, J. P., Esch, F. S., Keim, P. S., Sambamurti, K., Lieberburg, I. & Robakis, N. K. (1991) Exact Cleavage Site of Alzheimer Amyloid Precursor in Neuronal PC-12 Cells. *Neurosci Lett* **128**, 126-128.
- Arnold, F. H., Schofield, S. A. & Blanch, H. W. (1986) Analytical Affinity Chromatography. *J Chromatogr* **355**, 1-12.
- Asami-Odaka, A., Ishibashi, Y., Kikushi, T., Kitada, C. & Suzuki, N. (1995) Long Amyloid  $\beta$ -Protein Secreted from Wild-Type Human Neuroblastoma IMR-32 Cells. *Biochemistry* **34**, 10272-10278.
- Barrow, C. J., Yasuda, A., Kenny, P. T. M. & Zagorski, M. G. (1992) Solution Conformations and Aggregational Properties of Synthetic Amyloid  $\beta$ -Peptides of Alzheimer's Disease. Analysis of Circular Dichroism Spectra. *J Mol Biol* **225**, 1075-1093.
- Bartel, D. P. & Szostak, J. W. (1993) Isolation of New Ribozymes from a Large Pool of Random Sequences. *Science* **261**, 1411-1418.
- Baumeister R. & Haass C., The Molecular Biology of Alzheimer's Disease, C. Haass, Ed., Harwood Academic Publishers, Chur, 1998, im Druck.
- Beaucage, S. L. & Caruthers, M. H. (1981) Deoxynucleoside Phosphoramidites - A New Class of Key Intermediates for Deoxypolynucleotide Synthesis. *Tetrahedron Lett* **22**, 1859-1862.
- Beigelman, L., McSwiggen, J. A., Draper, K. G., Gonzalez, C., Jensen, K., Karpeisky, A. M., Modak, A. S., Matulic-Adamic, J., DiRenzo, A. B., Haeberli, P., Sweedler, D., Tracz, D., Grimm, S., Wincott, F. E., Thackray, V. G. & Usman, N. (1995) Chemical Modification of Hammerhead Ribozymes. *J Biol Chem* **270**, 25702-25708.
- Berzal-Herranz, A., Joseph, S. & Burke, J. M. (1992) In vitro Selection of Active Hairpin Ribozymes by Sequential RNA-Catalyzed Cleavage and Ligation Reaction. *Genes & Dev* **6**, 129-134.
- Berzal-Herranz, A., Joseph, S., Chowrira, B. M., Butcher, S. E. & Burke, J. M. (1993) Essential Nucleotide Sequences and Secondary Structure Elements of the Hairpin Ribozyme. *EMBO J* **12**, 2567-2574.
- Binkley, J., Allen, P., Brown, D., Green, L., Tuerk, C. & Gold, L. (1995) RNA Ligands to Human Nerve Growth Factor. *Nucleic Acids Res* **23**, 3198-3205.
- Blond, S. & Goldberg, M. (1987) Partly Native Epitopes are Already Present on Early Intermediates in the Folding of Tryptophan Synthase. *Proc Natl Acad Sci USA* **84**, 1147-1151.
- Bock, L. C., Griffin, L. C., Latham, J. A., Vermaas, E. H. & Toole, J. J. (1992) Selection of Single-Stranded DNA Molecules That Bind and Inhibit Human Thrombin. *Nature* **355**, 564-566.
- Brockhaus, M., Grünberg, J., Röhrlig, S., Loetscher, H., Wittenburg, N., Baumeister, R., Jacobsen, H. & Haass, C. (1998) Caspase-Mediated Cleavage is not Required for the Activity of Presenilins in Amyloidogenesis and NOTCH Signaling. *Neuroreport* **9**, 1481-1486.
- Burdick, D., Soreghan, B., Kwon, M., Kosmoski, J., Knauer, M., Henschen, A., Yates, J., Cotman, C. & Glabe, C. (1992) Assembly and Aggregation Properties of Synthetic Alzheimer's A<sub>4</sub>/ $\beta$  Amyloid Peptide Analogs. *J Biol Chem* **267**, 546-554.
- Burgstaller, P. & Famulok, M. (1994) Isolierung von RNA-Aptameren für biologische Cofaktoren durch *in vitro*-Selektion. *Angew Chem* **106**, 1163-1166.
- Carlson, J. D. & Yarmush, M. L. (1992) Antibody Assisted Protein Folding. *Bio/Technology* **10**, 86-91.
- Citron, M., Diehl, T. S., Gordon, G., Biere, A. L., Seubert, P. & Selkoe, D. J. (1996) Evidence that the 42- and 40-Amino Acid Forms of Amyloid  $\beta$  Protein are Generated from the  $\beta$ -Amyloid Precursor Protein by Different Protease Activities. *Proc Natl Acad Sci USA* **93**, 13170-13175.
- Conn, M. M., Prudent, J. R. & Schultz, P. G. (1996) Porphyrin Metallation Catalyzed by a Small RNA Molecule. *J Am Chem Soc* **118**, 7012-7013.
- Connell, G. J., Illangesekare, M. & Yarus, M. (1993) Three Small Ribonucleotides with Specific Arginine Sites. *Biochemistry* **32**, 5497-5502.

- Conrad, R., Keranen, L. M., Newton, A. C. & Ellington, A. D. (1995) Isozyme-Specific Inhibition of Protein Kinase C by RNA Aptamers. *J Biol Chem* **269**, 32051-32054.
- Cook, D. G., Forman, M. S., Sung, J. C., Leight, S., Kolson, D. L., Iwatsubo, T., Lee, V. M.-Y. & Doms, R. W. (1997) Alzheimer's A $\beta$ (1-42) Is Generated in the Endoplasmic Reticulum/Intermediate Compartment of NT2N Cells. *Nature Med* **3**, 1021-1023.
- Corder, E. H., Saunders, A. M., Risch, N. J., Strittmatter, W. J., Schmeichel, D. E., Gaskell, P. C., Jr., Rimmier, J. B., Locke, P. A., Conneally, P. M., Schmader, K. E., Small, G. W., Roses, A. D., Haines, J. L. & Pericak-Vance, M. A. (1994) Protective Effect of Apolipoprotein E Type 2 Allele for Late Onset Alzheimer Disease. *Nat Genet* **7**, 180-184.
- Crick, F. H. C. (1968) The Origin of the Genetic Code. *J Mol Biol* **38**, 367-379.
- Dai, X., De Mesmaeker, A & Joyce, G. F. (1995) Cleavage of an Amide Bond by a Ribozyme. *Science* **267**, 237-240.
- Davis, K. A., Abrams, B., Lin, Y. & Jayasena, S. D. (1996) Use of a High Affinity DNA Ligand in Flow Cytometry. *Nucleic Acids Res* **24**, 702-706.
- Davis, K. A., Lin, Y., Abrams, B. & Jayasena, S. D. (1998) Staining of Cell Surface Human CD4 with 2'-F-Pyrimidine-Containing RNA Aptamers for Flow Cytometry. *Nucleic Acids Res* **26**, 3915-3924.
- De Beuckelar, A (1998) *In vitro* Selektion antiviraler RNA-Moleküle. Dissertation, Freie Universität Berlin .
- De Strooper, B., Saftig, P., Craessaerts, K., Vanderstichele, H., Guhde, G., Annaert, W., von Figura, K. & Van Leuven, F. (1998) Deficiency of Presenilin-1 Inhibits the Normal Cleavage of Amyloid Precursor Protein. *Nature* **391**, 387-390.
- Di Luca, M., Pastorino, L., Bianchetti, A., Perez, J., Vignolo, L. A., Lenzi, G. L., Trabucchi, M., Cattabeni, F. & Padovani, A. (1998) Differential Levels of Platelet Amyloid  $\beta$  Precursor Protein Isoforms. An Early Marker for Alzheimer Disease. *Arch Neurol* **55**, 1195-1200.
- Döbeli, H., Draeger, N., Huber, G., Jakob, P., Schmidt, D., Seilheimer, B., Stüber, D., Wipf, B. & Zulauf, M. (1995) A Biotechnological Method Provides Access to Aggregation Competent Monomeric Alzheimer's 1-42 Residue Amyloid Peptide. *Bio/Technology* **13**, 988-993.
- Doudna, J. A., Cech, T. R. & Sullenger, B. A. (1995) Selection of an RNA Molecule That Mimics a Major Autoantigenic Epitope of Human Insulin Receptor. *Proc Natl Acad Sci USA* **92**, 2355-2359.
- Drolet, D. W., Moon-McDermott, L. & Romig, T. S. (1996) An Enzyme-Linked Oligonucleotide Assay. *Nature Biotechnology* **14**, 1021-1023.
- Dyrks, T., Weidemann, A., Multhaup, G., Salbaum, J. M., Lemaire, H.-G., Kang, J., Müller-Hill, B., Masters, C. L. & Beyreuther, K. (1988) Identification, Transmembrane Orientation and Biogenesis of the Amyloid A4 Precursor of Alzheimer's Disease. *EMBO J* **7**, 949-957.
- Ellington, A. D. & Szostak, J. W. (1990) *In vitro* Selection of RNA Molecules that Bind Specific Ligands. *Nature* **346**, 818-822.
- Ellington, A. D. & Szostak, J. W. (1992) Selection *in vitro* of Single-Stranded DNA Molecules that Fold into Specific Ligand-Binding Structures. *Nature* **355**, 850-852.
- Esch, F. S., Keim, P. S., Beattie, E. C., Blacher, R. W., Culwell, A. R., Oltersdorf, T., McClure, D. & Ward, P.J. (1990) Cleavage of Amyloid  $\beta$  Peptide During Constitutive Processing of its Precursor. *Science* **248**, 1122-1124.
- Famulok, M. (1994) Molecular Recognition of Amino Acids by RNA-Aptamers: An L-Citrulline Binding RNA Motif and its Evolution into an L-Arginine Binder. *J Am Chem Soc* **116**, 1698-1706.
- Famulok, M. & Hüttenhofer, A. (1996) *In vitro* Selection Analysis of Neomycin Binding RNAs with a Mutagenized Pool of Variants of the 16S rRNA Decoding Region. *Biochemistry* **35**, 4265-4270.
- Famulok, M. & Szostak, J. W. (1992) Stereospecific Recognition of Tryptophan Agarose by *in vitro* Selected RNA. *J Am Chem Soc* **114**, 3990-3991.
- Faulhammer, D. & Famulok, M. (1997) Characterization and Divalent Metal-ion Dependence of *in vitro* Selected Deoxyribozymes which Cleave DNA/RNA Chimeric Oligonucleotides. *J Mol Biol* **269**, 188-202.
- Ferris, J. P., Sanchez, R. A. & Orgel, L. E. (1968) Studies in Prebiotic Synthesis. 3. Synthesis of Pyrimidines from Cyanoacetylene and Cyanate. *J Mol Biol* **33**, 693-704.
- Games, D., Adams, D., Alessandrini, R., Barbour, R., Berthelette, P., Blackwell, C., Carr, T., Clemens, J., DonaldsonT. & Gillespie, F. (1995) Alzheimer-Type Neuropathology in Transgenic Mice Overexpressing V717F Beta-Amyloid Precursor Protein. *Nature* **373**, 523-527.
- Garzon-Rodriguez, W., Sepulveda-Becerra, M., Milton, S. & Glabe, C. G. (1997) Soluble Amyloid Abeta-(1-40) Exists as a Stable Dimer at Low Concentrations. *J Biol Chem* **272**, 21037-21044.
- Geiger, A., Burgstaller, P., von der Eltz, H., Roeder, A. & Famulok, M. (1996) RNA Aptamers that Bind L-Arginin with Sub-Micromolar Dissociation Constants and High Enantioselectivity. *Nucleic Acids Res* **24**, 1029-1036.

- Geyer, C. R. & Sen, D. (1997) Evidence for the Metal-Cofactor Independence of an RNA Phosphodiester-Cleaving DNA Enzyme. *Chem Biol* **4**, 579-593.
- Ghilardi, J. R., Catton, M., Stimson, E. R., Rogers, S., Walker, L. C., Maggio, J. E. & Mantyh, P. W. (1996) Intra-Arterial Infusion of [<sup>125</sup>I]-A<sub>β</sub>-1-40 Labels Amyloid Deposits in the Aged Primate Brain *in vivo*. *Neuroreport* **7**, 2607-2611.
- Gilbert, B. A., Sha, M., Wathen, S. T. & Rando, R. R. (1997) RNA Aptamers That Specifically Bind to a K Ras-Derived Farnesylated Peptide. *Bioorganic & Medicinal Chemistry* **5**, 1115-1122.
- Gilbert, W. (1986) The RNA World. *Nature* **319**, 618.
- Glenner, G. G. & Wong, C. W. (1984a) Alzheimer's Disease: Initial Report of the Purification and Characterization of a Novel Cerebrovascular Amyloid Protein. *Biochem Biophys Res Commun* **120**, 885-890.
- Glenner, G. G. & Wong, C. W. (1984b) Alzheimer's Disease and Down's Syndrome: Sharing of a Unique Cerebrovascular Amyloid Fibril Protein. *Biochem Biophys Res Commun* **122**, 1131-1135.
- Goate, A., Chartier-Harlin, M.-C., Mullan, M., Brown, J., Crawford, F., Fidani, L., Giuffra, L., Haynes, A., Irving, N., James, L., Mant, R., Newton, P., Rooke, K., Roques, P., Talbot, C., Pericak-Vance, M., Roses, A., Williamson, R., Rossor, M., Owen, M. & Hardy, J. (1991) Segregation of a Missense Mutation in the Amyloid Precursor Protein Gene with Familial Alzheimer's Disease. *Nature* **349**, 704-706.
- Goedert, M., Crowther, R. A. & Garner, C. C. (1991) Molecular Characterization of Microtubule-Associated Proteins Tau and MAP2. *Trends Neurosci* **14**, 193-199.
- Goedert, M., Jakes, R., Crowther, R. A., Six, J., Lübke, U., Vandermeeren, M., Cras, P., Trojanowski, J. Q. & Lee, V. M.-Y. (1993) The Abnormal Phosphorylation of Tau Protein at Ser-202 in Alzheimer Disease Recapitulates Phosphorylation During Development. *Proc Natl Acad Sci USA* **90**, 5066-5070.
- Gold, L., Polisky, B., Uhlenbeck, O. & Yarus, M. (1995) Diversity of Oligonucleotide Functions. *Annu Rev Biochem* **64**, 763-797.
- Götz, J., Probst, A., Spillantini, M. G., Schäfer, T., Jakes, R., Bürki, K. & Goedert, M. (1995) Somatodendritic Localization and Hyperphosphorylation of Tau Protein in Transgenic Mice Expressing the Longest Human Brain Tau Isoform. *EMBO J* **14**, 1304-1313.
- Green, L., Waugh, S., Binkley, J. P., Hostomska, Z., Hostomsky, Z. & Tuerk, C. (1995) Comprehensive Chemical Modification Interference and Nucleotide Substitution Analysis of an RNA Pseudoknot Inhibitor of HIV-1 Reverse Transcriptase. *J Mol Biol* **247**, 60-68.
- Griffin, L. C., Toole, J. J. & Leung, L. L. K. (1993) The Discovery and Characterization of a Novel Nucleotide-Based Thrombin Inhibitor. *Gene* **137**, 25-31.
- Guerrier-Takada, C., Gardiner, K., Marsh, T., Pace, N. & Altman, S. (1983) The RNA Moiety of Ribonuclease P is the Catalytic Subunit of the Enzyme. *Cell* **35**, 849-857.
- Haass, C. (1997) Presenilins: Genes for Life and Death. *Neuron* **18**, 687-690.
- Haass, C., Schlossmacher, M. G., Hung, A. Y., Vigo-Pelfrey, C., Mellon, A., Ostaszewski, B. L., Lieberburg, I., Koo, E. H., Schenk, D., Teplow, D. B. & Selkoe, D. J. (1992) Amyloid β-Peptide is Produced by Cultured Cells During Normal Metabolism. *Nature* **359**, 322-325.
- Hamm, J. (1996) Characterisation of Antibody-Binding RNAs Selected from Structurally Constrained Libraries. *Nucleic Acids Res* **24**, 2220-2227.
- Harada, K. & Frankel, A. D. (1995) Identification of two Novel Arginine Binding DNAs. *EMBO J* **14**, 5798-5811.
- Hartmann, T., Bieger, S. C., Brühl, B., Tienari, P. J., Ida, N., Allsop, D., Roberts, G. W., Masters, C. L., Dotti, C. G., Unsicker, K. & Beyreuther, K. (1997) Distinct Sites of Intracellular Production for Alzheimer's Disease A<sub>β</sub>40/42 Amyloid Peptides. *Nature Med* **3**, 1016-1020.
- Heidenreich, O., Benseler, F., Fahrenholz, A. & Eckstein, F. (1994) High Activity and Stability of Hammerhead Ribozymes Containing 2'-Modified Pyrimidine Nucleosides and Phosphorothioates. *J Biol Chem* **169**, 2131-2138.
- Hernault, S. W. L., Benian, G. M. & Emmons, R. B. (1993) Genetic and Molecular Characterization of the Caenorhabditis elegans Spermatogenesis-Defective Gene Spe-17. *Genetics* **134**, 769-780.
- Higgins, L. S., Holtzman, D. M., Rabin, J., Mobley, W. C. & Cordell, B. (1994) Transgenic Mouse Brain Histopathology Resembles Early Alzheimer's Disease. *Ann Neurol* **35**, 598-607.
- Hilvert, D., Hill, K., Nared, K. D. & Auditor, M.-T. M. (1989) Antibody Catalysis of a Diels-Alder Reaction. *J Am Chem Soc* **111**, 9261-9262.
- Hornung, V., Hofmann, H.-P. & Sprinzl, M. (1998) *In vitro* RNA Molecules That Bind to Elongation Factor Tu. *Biochemistry* **37**, 7260-7267.

- Howlett, D. R., Jennings, K. H., Lee, D. C., Clark, M. S. G., Brown, F., Wetzel, R., Wood, S. J., Camilleri, P. & Roberts, G. W. (1995) Aggregation State and Neurotoxic Properties of Alzheimer Beta-Amyloid Peptide. *Neurodegeneration* **4**, 23-32.
- Hsiao, K., Chapman, P., Nilsen, S., Eckman, C., Harigaya, Y., Younkin, S., Yang, F. & Cole, G. (1996) Correlative Memory Deficits, A $\beta$  Elevation, and Amyloid Plaque in Transgenic Mice. *Science* **274**, 99-102.
- Huizinga, D. E. & Szostak, J. W. (1995) A DNA Aptamer That Binds Adenosine and ATP. *Biochemistry* **34**, 656-665.
- Illangesekare, M., Sanchez, G., Nickles, T. & Yarus, M. (1995) Aminoacyl-RNA Synthesis Catalyzed by an RNA. *Science* **267**, 643-647.
- Irvine, D., Tuerk, C. & Gold, L. (1991) Selexion - Systematic Evolution of Ligands by Exponential Enrichment with Integrated Optimization by Non-Linear Analysis. *J Mol Biol* **222**, 739-761.
- Jarett, J. T., Berger, E. P. & Lansbury, P. T., Jr. (1993) The Carboxy Terminus of the  $\beta$  Amyloid Protein is Critical for the Seeding of Amyloid Formation: Implications for the Pathogenesis of Alzheimer's Disease. *Biochemistry* **32**, 4693-4697.
- Jellinek, D., Lynott, C. K., Rifkin, D. B. & Janic, N. (1993) High-Affinity RNA Ligands to Basic Fibroblast Growth Factor Inhibit Receptor Binding. *Proc Natl Acad Sci USA* **90**, 11227-11231.
- Jellinek, D., Green, L. S., Bell, C., Lynott, K., Gill, N., Vargeese, C., Kirscheheuter, G., McGee, D. P. C., Abesinghe, P., Pieken, W. A., Shapiro, R., Rifkin, D. B., Moscatelli, D. & Janic, N. (1995) Potent 2'-Amino-2'-Deoxypyrimidine RNA Inhibitors of Basic Fibroblast Growth Factor. *Biochemistry* **34**, 11363-11372.
- Jenison, R. D., Gill, S. C., Pardi, A. & Polisky, B. (1994) High-Resolution Molecular Discrimination by RNA. *Science* **263**, 1425-1429.
- Jenne, A. & Famulok, M. (1998) A Novel Ribzyme with Ester Transferase Activity. *Chem Biol* **5**, 23-34.
- Jonker, C., Schmand, B., Lindeboom, J., Havekes, L. M. & Launer, L. J. (1998) Association Between Apolipoprotein E  $\epsilon 4$  and the Rate of Cognitive Decline in Community-Dwelling Elderly Individuals with and without Dementia. *Arch Neurol* **55**, 1065-1069.
- Joyce, G. F. (1989) Amplification, Mutation and Selection of Catalytic RNA. *Gene* **82**, 83-87.
- Joyce, G. F. (1994) *In vitro* Evolution of Nucleic Acids. *Curr Opin Struct Biol* **4**, 331-336.
- Joyce G. F. & Orgel L. E., Prospect for Understanding the Origin of the RNA World, in: *The RNA World*, R. F. Gesteland & J. F. Atkins, Eds., Cold Spring Harbour Laboratory Press 1993, S. 1-25.
- Joyce, G. F., Dai, X. & De Mesmaeker, A. (1996) Amide Cleavage by a Ribozyme: Correction. *Science* **272**, 18-19.
- Kang, J., Lemaire, H.-G., Unterbeck, A., Salbaum, J. M., Masters, C. L., Grzeschik, K.-H., Multhaup, G., Beyreuther, K. & Müller-Hill, B. (1987) The Precursor of Alzheimer's Disease Amyloid A4 Protein Resembles a Cell-Surface Receptor. *Nature* **325**, 733-736.
- Khoury, J. E., Hickman, S. E., Thomas, C. A., Cao, L., Silverstein, S. C. & Loike, J. D. (1996) Scavenger Receptor-Mediated Adhesion of Microglia to  $\beta$ -Amyloid Fibrils. *Nature* **382**, 716-719.
- Kinzler, K. W. & Vogelstein, B. (1989) Whole Genome PCR: Application to the Identification of Sequences Bound by Gene Regulatory Proteins. *Nucleic Acids Res* **17**, 3645-3653.
- Kleinjung, F., Klüßmann, S., Erdmann, V. A., Scheller, F. W., Fürste, J. P. & Bier, F. F. (1998) High-Affinity RNA as a Recognition Element in a Biosensor. *Anal Chem* **70**, 328-331.
- Klüßmann, S. (1996) Spiegel-Design: Identifizierung und Charakterisierung hochaffiner L-RNA-Moleküle. *Dissertation, Freie Universität Berlin*.
- Klüßmann, S., Nolte, A., Bald, R., Erdmann, V. A. & Fürste, J. P. (1996) Mirror-Image RNA that Binds D-Adenosine. *Nature Biotechnology* **14**, 1112-1115.
- Kruger, K., Grabowski, P. J., Zaug, A. J., Sands, J., Gottschling, D. E. & Cech, T. R. (1982) Self Splicing RNA: Autoexcision and Autocatalyzation of the Ribosomal RNA Intervening Sequence of Tetrahymena. *Cell* **31**, 147-157.
- LaFerla, F. M., Troncoso, J. C., Strickland, D. K., Kawas, C. H. & Jay, G. (1997) Neuronal Cell Death in Alzheimer's Disease Correlates with ApoE Uptake and Intracellular A $\beta$  Stabilization. *J Clin Invest* **100**, 310-320.
- Lansbury, P. T., Jr. (1997) Structural Neurology: Are Seeds at the Root of Neuronal Degeneration?. *Neuron* **19**, 1151-1154.
- Lato, S. M., Boles, A. R. & Ellington, A. D. (1995) *In vitro* Selection of RNA Lectins: Using Combinatorial Chemistry to Interpret Ribozyme Evolution. *Chem Biol* **2**, 291-303.
- Lauhon, C. T. & Szostak, J. W. (1995) RNA Aptamers That Bind Flavin and Nicotinamide Redox Cofactors. *J Am Chem Soc* **117**, 1246-1257.

- Levy-Lahad, E., Wasco, W., Poorkaj, P., Romano, D. M., Oshima, J., Pettingell, W. H., Yu, C., Jondro, P. D., Schmidt, S. D., Wang, K., Crowley, A. C., Fu, Y.-H., Guenette, S. Y., Galas, D., Nemens, E., Wijsman, E. M., Bird, T. D., Schellenberg, G. D. & Tanzi, R. E. (1995) Candidate Gene for the Chromosome 1 Familial Alzheimer's Disease Locus. *Science* **269**, 973-977.
- Li, Q.-X., Evin, G., Small, D. H., Multhaup, G., Beyreuther, K. & Masters, C. L. (1995) Proteolytic Processing of Alzheimer's Disease  $\beta$ A4 Amyloid Precursor Protein in Human Platelets. *J Biol Chem* **270**, 14140-14147.
- Li, Y. & Sen, D. (1996) A Catalytic DNA for Porphyrin Metallation. *Nat Struct Biol* **35**, 743-747.
- Lin, Y., Qiu, Q., Gill, S. C. & Jayasena, S. D. (1994) Modified RNA Sequence Pools for *in vitro* Selection. *Nucleic Acids Res* **22**, 5229-5234.
- Lin, Y., Padmapriya, A., Morden, K. M. & Jayasena, S. D. (1995) Peptide Conjugation to an *in vitro*-Selected DNA Ligand Improves Enzyme Inhibition. *Proc Natl Acad Sci USA* **92**, 11044-11048.
- Lin, Y., Nieuwlandt, D., Magallanez, A., Feistner, B. & Jayasena, S. D. (1996) High-Affinity and Specific Recognition of Human Thyroid Stimulating Hormone (hTSH) by *in vitro*-Selected 2'-Amino-Modified RNA. *Nucleic Acids Res* **24**, 3407-3414.
- Lorsch, J. & Szostak, J. W. (1994) *In vitro* Evolution of New Ribozymes with Polynucleotide Kinase Activity. *Nature* **371**, 31-36.
- Lorsch, J. & Szostak, J. W. (1995) Kinetic and Thermodynamic Characterization of the Reaction Catalyzed by a Polynucleotide Kinase Ribozyme. *Biochemistry* **34**, 15315-15327.
- Macaya, R. F., Waldron, J. A., Beutel, B. A., Gao, H., Joesten, M. E., Yang, M., Patel, R., Bertelsen, A. H. & Cook, A. F. (1995) Structural and Functional Characterization of Potent Antithrombotic Oligonucleotides Possesing Both Quadruplex and Duplex Motifs. *Biochemistry* **34**, 4478-4492.
- Majerfeld, I., Yarus, M. (1994) An RNA Pocket for an Aliphatic Hydrophobe. *Nat Struct Biol* **1**, 287-292.
- Mantyh, P. W., Ghilardi, J. R., Rogers, S., DeMaster, E., Allen, C. J., Stimson, E. R. & Maggio, J. E. (1993) Aluminum, Iron, and Zinc Ions Promote Aggregation of Physiological Concentrations of  $\beta$ -Amyloid Peptide. *J Neurochem* **61**, 1171-1174.
- Martinez, L. E., Leighton, J. L., Carsten, D. H. & Jacobsen, E. N. (1995) *J Am Chem Soc* **117**, 5897-5898.
- Marx, J. (1996a) Searching for Drugs That Combat Alzheimer's. *Science* **273**, 50-53.
- Marx, J. (1996b) New 'Alzheimer's Mouse' Produced. *Science* **274**, 177-178.
- Masters, C. L., Multhaup, G., Simms, G., Pottgiesser, J., Martins, R. N. & Beyreuther, K. (1985a) Neuronal Origin of a Cerebral Amyloid: Neurofibrillary Tangles of Alzheimer's Disease Contain the Same Protein as the Amyloid of Plaque Cores and Blood Vessels. *EMBO J* **4**, 2757-2763.
- Masters, C. L., Simms, G., Weinmann, N. A., Multhaup, G., McDonald, B. L. & Beyreuther, K. (1985b) Amyloid Plaque Core Protein in Alzheimer Disease and Down Syndrome. *Proc Natl Acad Sci USA* **82**, 4245-4249.
- Mattson, M. P., Cheng, B., Culwell, A. R., Esch, F. S., Lieberburg, I. & Rydel, R. E. (1993) Evidence for Exitoprotective and Intraneuronal Calcium-Regulating Roles for Secreted Forms of the  $\beta$ -Amyloid Precursor Protein. *Neuron* **10**, 243-254.
- Matzura, O. & Wennborg, A. (1996) RNAdraw: An Integrated Program for RNA Secondary Structure Calculation and Analysis Under 32-Bit-Microsoft Windows. *CABIOS* **12**, 247-249.
- McLachlan, D. R. C., Dalton, A. J., Kruck, T. P. A., Bell, M. Y., Smith, W. L., Kalow, W. & Andrews, A. F. (1991) Intramuscular Desferrioxamine in Patients with Alzheimer's Disease. *Lancet* **337**, 1304-1308.
- Mendla, K. (1996) Die Alzheimer-Krankheit: neue Ansätze in der Pharmakotherapie. *PZ* **141**, 351-356.
- Mizuna, T. & Weiss, A. H. (1974) Synthesis and Utilization of Formose Sugars. *Adv Carbohydr Chem Biochem* **29**, 173-227.
- Moran, P. M., Higgins, L. S., Cordell, B. & Moser, P. C. (1995) Age-Related Learning Deficits in Transgenic Mice Expressing the 751-Amino Acid Isoform of Human Beta-Amyloid Precursor Protein. *Proc Natl Acad Sci USA* **92**, 53415345.
- Morris, K. N., Tarasow, T. M., Julin, C. M., Simons, S. L., Hilvert, D. & Gold, L. (1994) Enrichment for RNA Molecules That Bind a Diels-Alder Transition State analog. *Proc Natl Acad Sci USA* **91**, 13028-13032.
- Namba, Y., Kawatsu, K., Izumi, S., Ueki, A. & Ikeda, K. (1992) Neurofibrillary Tangles And Senile Plaques in Brain of Elderly Leprosy Patients. *Lancet* **340**, 978.
- Nieuwlandt, D., Wecker, M. & Gold, L. (1995) *In vitro* Selection of RNA Ligands to Substance P. *Biochemistry* **34**, 5651-5659.
- Nishikawa, F., Kawakami, J., Chiba, A., Shirai, M., Kumar, P. & Nishikawa, S. (1996) Selection *in vitro* of trans-Acting Genomic Human Hepatitis Delta Virus (HDV) Ribozymes. *Eur J Biochem* **237**, 712-718.

- Nolte, A., Klüßmann, S., Bald, R., Erdmann, V. A. & Fürste, J. P. (1996) Mirror-Design of L-Oligonucleotide Ligands Binding to L-Arginine. *Nature Biotechnology* **14**, 1116-1119.
- Orgel, L. E. (1968) Evolution of the Genetic Apparatus. *J Mol Biol* **38**, 381-393.
- Oro, J (1961) Mechanism of Synthesis of Adenine from Hydrogen Cyanide under Possible Primitive Earth Conditions. *Nature* **191**, 1193-1194.
- Pagratis, N. C., Bell, C., Chang, Y.-F., Jennings, S., Fitzwater, T., Jellinek, D. & Dang, C. (1997) Potent 2'-Amino-, and 2'-Fluoro-2'-Deoxyribonucleotide RNA Inhibitors of Keratinocyte Growth Factor. *Nature Biotechnology* **15**, 68-73.
- Pan, T. & Zhong, K. (1994) Selection of Circularly Permuted Ribozymes from *Bacillus subtilis* RNase P by Substrate Binding. *Biochemistry* **33**, 13207-13212.
- Pan, W., Craven, R. C., Qiu, Q., Wilson, C. B., Wills, J. W., Golovine, S. & Wang, J.-F. (1995) Isolation of Virus-Neutralizing RNAs from a Large Pool of Random Sequences. *Proc Natl Acad Sci USA* **92**, 11509-11513.
- Paresce, D. M., Ghosh, R. N. & Maxfield, F. R. (1996) Microglial Cells Internalize Aggregates of the Alzheimer's Disease Amyloid  $\beta$ -Protein via Scavenger Receptor. *Neuron* **17**, 553-565.
- Persidis, A. (1997) Ribozyme Therapeutics. *Nature Biotechnology* **15**, 921-922.
- Peruche, B. & Schulz, M. (1998) Donepezil, neues Mittel gegen Morbus Alzheimer. *PZ* **143**, 756-760.
- Pike, C. J., Walencewicz, A. J., Glabe, C. G. & Cotman, C. W. (1991) Aggregation-Related Toxicity of Synthetic  $\beta$ -Amyloid Protein in Hippocampal Cultures. *Eur J Pharmacol* **207**, 367-368.
- Pitsch, S., Eschenmoser, A., Gedulin, B., Hui, S. & Arrhenius, G. (1995) Mineral Induced Formation of Sugar Phosphates. *Origin Life Evol Biosphere* **25**, 297-334.
- Prudent, J. R., Uno, T. & Schultz, P. G. (1994) Expanding the Scope of RNA Catalysis. *Science* **264**, 1924-1927.
- Ribozyme Pharmaceuticals (1998) press release. <http://wwwrpicom/PresRelease/110498html>.
- Rizo, J. & Giersch, L. M. (1992) Constrained Peptides: Models of Bioactive Peptides and Protein Substructures. *Annu Rev Biochem* **61**, 387-418.
- Robertson, D. L. & Joyce, G. F. (1990) Selection *in vitro* of an RNA Enzyme That Specifically Cleaves Single-Stranded DNA. *Nature* **344**, 467-468.
- Robertson, M. P. & Miller, S. L. (1995) An Efficient Prebiotic Synthesis of Cytosine and Uracil. *Nature* **375**, 772-774.
- Rosenberg, R. N., Baskin, F., Fosmire, J. A., Risser, R., Adams, P., Svetlik, D., Honig, L. S., Cullum, M. & Weiner, M. F. (1997) Altered Amyloid Protein Processing in Platelets of Patients with Alzheimer's Disease. *Arch Neurol* **54**, 139-144.
- Roth, A. & Breaker, R. R. (1998) *Proc Natl Acad Sci USA* **95**, 6027-6031.
- Salbaum, J. M., Weidemann, A., Lemaire, H.-G., Masters, C. L. & Beyreuther, K. (1988) The Promoter of Alzheimer's Disease Amyloid A4 Precursor Gene. *EMBO J* **7**, 2807-2813.
- Sanchez, R. A., Ferris, J. P. & Orgel, L. E. (1967) Studies in Prebiotic Synthesis. II. Synthesis of Purine Precursor and Amino Acids from Aqueous Hydrogen Cyanide. *J Mol Biol* **30**, 223-253.
- Sanger, F., Nicklen, S. & Coulson, A. R. (1977) DNA Sequencing with Chain-Termination Inhibitors. *Proc Natl Acad Sci USA* **74**, 5463-5467.
- Santoro, S. W. & Joyce, G. F. (1997) A General Purpose RNA-Cleaving DNA Enzyme. *Proc Natl Acad Sci USA* **94**, 4262-4266.
- Sassanfar, M. & Szostak, J. W. (1993) An Motif That Binds ATP. *Nature* **364**, 550-553.
- Schmeichel, D. E., Saunders, A. M., Strittmatter, W. J., Crain, B. J., Hulette, C. M., Joo, S. H., Pericak-Vance, M. A., Goldgaber, D. & Roses, A. D. (1993) Increased Amyloid  $\beta$ -Peptide Deposition in Cerebral Cortex as a Consequence of Apolipoprotein E Genotype in Late-Onset Alzheimer Disease. *Proc Natl Acad Sci USA* **90**, 9649-9653.
- Schneider, D. J., Feigon, J. & Hostomsky, Z. Gold, L. (1995) High-Affinity ssDNA Inhibitors of the Reverse Transcriptase of Type 1 Human Deficiency Virus. *Biochemistry* **34**, 9599-9610.
- Schwarzman, A., Gregori, L., Vitek, M. P., Lyubski, S., Strittmatter, W. J., Enghilde, J. J., Bhasin, R., Silverman, J., Weisgraber, K. H., Coyle, P. K., Zagorski, M. G., Talafous, J., Eisenberg, M., Saunders, A. M., Roses, A. D. & Goldgraber, D. (1994) Transthyretin Sequester Amyloid  $\beta$  Protein and Prevents Amyloid Formation. *Proc Natl Acad Sci USA* **91**, 8368-8372.
- Seelig, B. & Jäschke, A. (1999) A Small Catalytic RNA motif with Diels-Alderase Activity. *Chem Biol* , in press.
- Seilheimer, B., Bohrmann, B., Bondolfi, L., Müller, F., Stüber, D. & Döbeli, H. (1997) The Toxicity of the Alzheimer's  $\beta$ -Amyloid Peptide Correlates with a Distinct Fiber Morphology. *J Struct Biol* **119**, 59-71.

- Selkoe, D. J., Podlisny, M. B., Joachim, C. L., Vickers, E. A., Lee, G., Fritz, L. C. & Oltendorf, T. (1988) Beta Amyloid Protein of Alzheimer's Disease Occurs as 110- to 135 kDa Membrane-Associated Proteins in Neuronal and Non-Neuronal Tissues. *Proc Natl Acad Sci USA* **85**, 7341-7345.
- Seubert, P., Vigo-Pelfrey, C., Esch, F., Lee, M., Dovey, H., Davis, D., Sinha, S., Schlossmacher, M., Whaley, J., Swindelhurst, C., McCormack, R., Wolfert, R., Selkoe, D., Lieberburg, I. & Schenk, D. (1992) Isolation and Quantification of Soluble Alzheimer's  $\beta$ -Peptide from Biological Fluids. *Nature* **359**, 325-327.
- Shayo, M., McLay, R. N., Kastin, A. J. & Bands, W. A. (1997) The Putative Blood-Brain-Barrier Transporter for the  $\beta$ -Amyloid Binding Protein Apolipoprotein J is Saturated at Physiological Concentrations. *Life Sci* **60**, PL115-PL118.
- Sherrington, R., Rogaev, E. I., Liang, Y., Rogaev, E. A., Levesque, G., Ikeda, M., Chi, H., Lin, C., Li, G., Holman, K., Tsuda, T., Mar, L., Focin, J.-F., Bruni, A. C., Montesi, M. P., Sorbi, S., Rainero, I., Pinessi, L., Nee, L., Chumakov, I., Pollen, D., Brookes, A., Sanseau, P., Polinsky, R. J., Wasco, W., Da Silva, H. A. R., Haines, J. L., Pericak-Vance, M. A., Tanzi, R. E., Roses, A. D., Fraser, P. E., Rommens, J. M. & St George-Hyslop, P. H. (1995) Cloning of a Gene Bearing Missense Mutations in Early-Onset Familial Alzheimer's Disease. *Nature* **375**, 754-760.
- Shoji, M., Golde, T. E., Ghiso, J., Cheung, T. T., Estus, S., Shaffer, L. M., Cai, X.-D., McKay, D. M., Tintner, R., Frangione, B. & Younkin, S. G. (1992) Production of the Alzheimer Amyloid  $\beta$  Protein by Normal Proteolytic Processing. *Science* **258**, 126-129.
- Sisodia, S. S., Koo, E. H., Beyreuther, K. & Unterbeck, A. (1990) Evidence That  $\beta$ -Amyloid Protein in Alzheimer's Disease is not Derived by Normal Processing. *Science* **248**, 492-495.
- Sisodia, S. S., Tinakaran, G., Slunt, H. H., Wong, P. C., Borchelt, D. R., Naruse, S., Zheng, H. & Price, D. L. (1998) *J Neurochem* **70**, Suppl.1, S3.
- Skolnick, A. A. (1997) Old Chinese Herbal Medicine Used for Fever Yields Possible New Alzheimer Disease Therapy. *JAMA* **277**, 776-778.
- Solomon, B., Koppel, R., Hanan, E. & Katzav, T. (1996) Monoclonal Antibodies Inhibit *in vitro* Fibrillar Aggregation of the Alzheimer  $\beta$ -Amyloid Peptide. *Proc Natl Acad Sci USA* **93**, 452-455.
- Stoks, P. G. & Schwartz, A. W. (1979) Uracil in Carbonaceous Meteorites. *Nature* **282**, 709-710.
- Sun, F., Galas, D. & Waterman, M. S. (1996) A Mathematical Analysis of *in vitro* Molecular Selection-Amplification. *J Mol Biol* **258**, 650-660.
- Suzuki, N., Cheung, T. T., Cai, X.-D., Odaka, A., Otvos Jr., L., Eckman, C., Golde, T. E. & Younkin, S. G. (1994) An Increased Percentage of Long Amyloid  $\beta$  Protein Secreted by Familial Amyloid  $\beta$  Protein Precursor ( $\beta$ APP<sub>717</sub>)Mutants. *Science* **264**, 1336-1340.
- Symensma, T. L., Giver, L., Zapp, M., Takle, G. B. & Ellington, A. D. (1996) RNA Aptamers Selected to Bind Human Immunodeficiency Virus Type 1 Rev *in vitro* are Rev Responsive *in vivo*. *J Virol* **70**, 179-187.
- Tao, J. & Frankel, A. D. (1992) Specific Binding of Arginin to TAR RNA. *Proc Natl Acad Sci USA* **89**, 2723-2726.
- Tarasow, T. M., Tarasow, S. L. & Eaton, B. E. (1997) RNA-Catalysed Carbon-Carbon Bond Formation. *Nature* **389**, 54-57.
- Tasset, D. M., Kubik, M. F. & Steiner, W. (1997) Oligonucleotide Inhibitors of Human Thrombin That Bind Distinct Epitopes. *J Mol Biol* **272**, 688-698.
- Theuring, F., Thunecke, M., Kosciessa, U. & Turner, J. D. (1997) Transgenic Animals as Models of Neurodegenerative Diseases in Humans. *Tibtech* **15**, 320-325.
- Tomiyama, T., Asano, S., Suwa, Y., Morita, T., Ktaoka, K., Mori, H. & Endo, N. (1994) Rifampicin Prevents the Aggregation and Neurotoxicity of Amyloid  $\beta$  Protein *in vitro*. *Biochem Biophys Res Commun* **204**, 76-83.
- Tsai, D. E., Kenan, D. J. & Keene, J. D. (1992) *In vitro* Selection of an RNA Epitope Immunologically Cross-Reactive with a Peptide. *Proc Natl Acad Sci USA* **89**, 8864-8868.
- Tuerk, C. & Gold, L. (1990) Systematic Enrichment of Ligands by Exponential Enrichment: RNA Ligands to Bacteriophage T4 DNA Polymerase. *Science* **249**, 505-510.
- Tuerk, C., MacDougal, S. & Gold, L. (1992) RNA Pseudoknots That Inhibit Human Immunodeficiency Virus Type 1 Reverse Transkriptase. *Proc Natl Acad Sci USA* **89**, 6988-6992.
- Unrau, P. J. & Bartel, D. P. (1998) RNA-Catalysed Nucleotide Synthesis. *Nature* **395**, 260-263.
- Virchow, R. (1854) On a New Substance Found in the Human Brain and Spinal Cord Which Reacts Chemically Like Cellulose. *Virch Arch Path Anat Physiol* **6**, 135-137.
- Wallis, M. G., von Ahsen, U., Schroeder, R. & Famulok, M. (1995) A Novel RNA Motif for Neomycin Recognition. *Chem Biol* **2**, 543-552.
- Wallis, M. G., Streicher, B., Wank, H., von Ahsen, U., Clodi, E., Wallace, S. T., Famulok, M. & Schroeder, R. (1997) *In vitro* Selection of a Viomycin-Binding RNA Pseudoknot. *Chem Biol* **4**, 357-366.

- Wang, J.-Z., Grundke-Iqbali, I. & Iqbal, K. (1996) Glycosylation of Microtubule-Associated Protein Tau: An Abnormal Posttranslational Modification in Alzheimer's Disease. *Nature Med* **2**, 871-875.
- Wang, Y. & Rando, R. R. (1995) Specific Binding of Aminoglycoside Antibiotics to RNA. *Chem Biol* **2**, 281-290.
- Weidemann, A., Paliga, K., Dürrwang, U., Czech, C., Evin, G., Masters, C. L. & Beyreuther, K. (1997) Formation of Stable Complexes Between two Alzheimer's Disease Gene Products: Presenilin-2 and Beta-Amyloid Precursor Protein. *Nature Med* **3**, 328-332.
- Wiegand, T. W., Janssen, R. C. & Eaton, B. E. (1997) Selection of RNA Amide Synthases. *Chem Biol* **4**, 675-683.
- Wild-Bode, C., Yamazaki, T., Capell, A., Leimer, U., Steiner, H., Ihara, Y. & Haass, C. (1997) Intracellular Generation and Accumulation of Amyloid  $\beta$ -Peptide Terminating at Amino Acid 42. *J Biol Chem* **272**, 16085-16088.
- Wilson, C. & Szostak, J. W. (1995) *In vitro* Evolution of a Self-Alkylating Ribozyme. *Nature* **374**, 777-782.
- Woese C., The Evolution of the Genetic Code, in: *The Genetic Code*, Haper & Row, Eds., New York 1967, S. 179-195.
- Xia, W., Zhang, J., Perez, R., Koo, E. H. & Selkoe, D. J. (1997) Interaction Between Amyloid Precursor Protein and Presenilins in Mammalian Cells: Implication for the Pathogenesis of Alzheimer Disease. *Proc Natl Acad Sci USA* **94**, 8208-8213.
- Xu, W. & Ellington, A. D. (1996) Anti-Peptide Aptamers Recognize Amino Acid Sequence and Bind a Protein Epitope. *Proc Natl Acad Sci USA* **93**, 7475-7480.
- Yaar, M., Zhai, S., Pilch, P. F., Doyle, S. M., Eisenhauer, P. B., Fine, R. E. & Gilchrist, B. A. (1997) Binding of  $\beta$ -Amyloid to the p75 Neurotrophin Receptor Induces Apoptosis. *J Clin Invest* **100**, 2333-2340.
- Yan, S. D., Fu, J., Chen, M., Zhu, H., Roher, A., Slattery, T., Zhao, L., Nagashima, M., Morser, J., Migheli, A., Nawroth, P., Stern, D. & Schmidt, A. M. (1996) RAGE and Amyloid- $\beta$  Peptide Neurotoxicity in Alzheimer's Disease. *Nature* **382**, 685-691.