

9 Literaturverzeichnis

- 1 Adler S, Pellizzer C, Paparella M, Hartung T, und Bremer S. The effects of solvents on embryonic stem cell differentiation. *Toxicol In Vitro* 2006; 20:265-271.
- 2 Ahlfeld JF. Die Missbildungen des Menschen. F. W. Grunow 1880;
- 3 Alsdorf R und Wyszynski DF. Teratogenicity of sodium valproate. *Expert Opin Drug Saf* 2005; 4:345-353.
- 4 Ardinger HH, Atkin JF, Blackston RD et al. Verification of the fetal valproate syndrome phenotype. *Am J Med Genet* 1988; 29:171-185.
- 5 Barroso I, Benito B, Garci-Jimenez C et al. Norepinephrine, tri-iodothyronine and insulin upregulate glyceraldehyde-3-phosphate dehydrogenase mRNA during Brown adipocyte differentiation. *Eur J Endocrinol* 1999; 141:169-179.
- 6 Basson CT, Bachinsky DR, Lin RC et al. Mutations in human TBX5 [corrected] cause limb and cardiac malformation in Holt-Oram syndrome. *Nat Genet* 1997; 15:30-35.
- 7 Basson CT, Huang T, Lin RC et al. Different TBX5 interactions in heart and limb defined by Holt-Oram syndrome mutations. *Proc Natl Acad Sci U S A* 1999; 96:2919-2924.
- 8 Biometrischer Abschlussbericht. Biometrischer Abschlussbericht zum Verbundprojekt: Weiterentwicklung eines in vitro Embryotoxizitätstests mit embryonalen Stammzellen: Verwendung molekularer marker zur Erfassung verschiedener Differenzierungsendpunkte. 2004;
- 9 Bodmer R. The gene tinman is required for specification of the heart and visceral muscles in *Drosophila*. *Development* 1993; 118:719-729.
- 10 Boheler KR, Czyz J, Tweedie D et al. Differentiation of pluripotent embryonic stem cells into cardiomyocytes. *Circ Res* 2002; 91:189-201.
- 11 Bojic U, Elmazar MM, Hauck RS, und Nau H. Further branching of valproate-related carboxylic acids reduces the teratogenic activity, but not the anticonvulsant effect. *Chem Res Toxicol* 1996; 9:866-870.
- 12 Brown NA. Selection of test chemicals for the ECVAM international validation study on in vitro embryotoxicity tests. European Centre for the Validation of Alternative Methods. *Altern Lab Anim* 2002; 30:177-198.
- 13 Brown NA, Spielmann H, Bechter R et al. Screening Chemicals for Reproductive Toxicity: the Current Alternatives. *ATLA* 1995; 23:868-882.
- 14 Brulet P, Babinet C, Kemler R, und Jacob F. Monoclonal antibodies against trophectoderm-specific markers during mouse blastocyst formation. *PNAS* 1980; 77:4113-4117.
- 15 Bruneau BG. Transcriptional regulation of vertebrate cardiac morphogenesis. *Circulation Research* 2002; 90:509-519.
- 16 Bruneau BG, Logan M, Davis N et al. Chamber-specific cardiac expression of Tbx5 and heart defects in Holt-Oram syndrome. *Dev Biol* 1999; 211:100-108.
- 17 Bruneau BG, Nemer G, Schmitt JP et al. A murine model of Holt-Oram syndrome defines roles of the T-box transcription factor Tbx5 in cardiogenesis and disease. *Cell* 2001; 106:709-721.

- 18 Budihardjo II, Walker DL, Svingen PA et al. 6-Aminonicotinamide sensitizes human tumor cell lines to cisplatin. *Clin Cancer Res* 1998; 4:117-130.
- 19 Bustin SA. Absolute quantification of mRNA using real-time reverse transcription polymerase chain reaction assays. *J Mol Endocrinol* 2000; 25:169-193.
- 20 Bustin SA. Quantification of mRNA using real-time reverse transcription PCR (RT-PCR): trends and problems. *J Mol Endocrinol* 2002; 29:23-29.
- 21 Cao D, Wang Z, Zhang CL et al. Modulation of smooth muscle gene expression by association of histone acetyltransferases and deacetylases with myocardin. *Mol Cell Biol* 2005; 25:364-376.
- 22 Carden MJ, Trojanowski JQ, Schlaepfer WW, and Lee VM. Two-stage expression of neurofilament polypeptides during rat neurogenesis with early establishment of adult phosphorylation patterns. *J Neurosci* 1987; 7:3489-3504.
- 23 Charron F und Nemer M. GATA transcription factors and cardiac development. *Semin Cell Dev Biol* 1999; 10:85-91.
- 24 Charron F, Paradis P, Bronchain O, Nemer G, und Nemer M. Cooperative interaction between GATA-4 and GATA-6 regulates myocardial gene expression. *Mol Cell Biol* 1999; 19:4355-4365.
- 25 Chaube S, Kreis W, Uchida K, und Murphy ML. The teratogenic effect of 1-beta-D-arabinofuranosylcytosine in the rat. Protection by deoxycytidine. *Biochem Pharmacol* 1968; 17:1213-1216.
- 26 Cohen SS. The mechanisms of lethal action of arabinosyl cytosine (araC) and arabinosyl adenine (araA). *Cancer* 1977; 40:509-518.
- 27 Colofiore JR, Stolfi RL, Nord LD, und Martin DS. Biochemical modulation of tumor cell energy. IV. Evidence for the contribution of adenosine triphosphate (ATP) depletion to chemotherapeutically-induced tumor regression. *Biochem Pharmacol* 1995; 50:1943-1948.
- 28 Crissman HA, Gadbois DM, Tobey RA, und Bradbury EM. Transformed mammalian cells are deficient in kinase-mediated control of progression through the G1 phase of the cell cycle. *Proc Natl Acad Sci U S A* 1991; 88:7580-7584.
- 29 Cserjesi P, Brown D, Lyons GE, und Olson EN. Expression of the novel basic helix-loop-helix gene eHAND in neural crest derivatives and extraembryonic membranes during mouse development. *Dev Biol* 1995; 170:664-678.
- 30 Dagg CP. Sensitive stages for the production of developmental abnormalities in mice with 5-fluorouracil. *Am J Anat* 1960; 106:89-96.
- 31 Dagg CP. Combined action of fluorouracil and two mutant genes on limb development in the mouse. *J Exp Zool* 1967; 164:479-489.
- 32 Dansky LV und Finnell RH. Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades; 2: Human studies. *Reprod Toxicol* 1991; 5:301-335.
- 33 Diehl SR und Erickson RP. Genome scan for teratogen-induced clefting susceptibility loci in the mouse: evidence of both allelic and locus heterogeneity distinguishing cleft lip and cleft palate. *Proc Natl Acad Sci U S A* 1997; 94:5231-5236.
- 34 DiLiberti JH, Farndon PA, Dennis NR, und Curry CJ. The fetal valproate syndrome. *Am J Med Genet* 1984; 19:473-481.
- 35 Doetschman T, Eistetter H, Katz M, Schmidt W, und Kemler R. The in vitro development of blastocyst-derived embryonic stem cell lines: formation of visceral yolk sac, blood islands and myocardium. *J Embryol Exp Morphol* 1985; 87:27-45.

- 36 Dono R, Scalera L, Pacifico F et al. The murine *cripto* gene: expression during mesoderm induction and early heart morphogenesis. *Development* 1993; 118:1157-1168.
- 37 Edwards DR und Denhardt DT. A study of mitochondrial and nuclear transcription with cloned cDNA probes. Changes in the relative abundance of mitochondrial transcripts after stimulation of quiescent mouse fibroblasts. *Exp Cell Res* 1985; 157:127-143.
- 38 Ehlers K, Sturje H, Merker HJ, und Nau H. Spina bifida aperta induced by valproic acid and by all-trans-retinoic acid in the mouse: distinct differences in morphology and periods of sensitivity. *Teratology* 1992a; 46:117-130.
- 39 Ehlers K, Sturje H, Merker HJ, und Nau H. Valproic acid-induced spina bifida: a mouse model. *Teratology* 1992b; 45:145-154.
- 40 Eluma FO, Sucheston ME, Hayes TG, und Paulson RB. Teratogenic effects of dosage levels and time of administration of carbamazepine, sodium valproate, and diphenylhydantoin on craniofacial development in the CD-1 mouse fetus. *J Craniofac Genet Dev Biol* 1984; 4:191-210.
- 41 Erickson RP, Karolyi IJ, und Diehl SR. Correlation of susceptibility to 6-aminonicotinamide and hydrocortisone-induced cleft palate. *Life Sci* 2005; 76:2071-2078.
- 42 Evans MJ und Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. *Nature* 1981; 292:154-156.
- 43 Finley MF, Kulkarni N, und Huettner JE. Synapse formation and establishment of neuronal polarity by P19 embryonic carcinoma cells and embryonic stem cells. *J Neurosci* 1996; 16:1056-1065.
- 44 Förster A. Die Missbildungen des Menschen. Mauke 1861; Jena.
- 45 Fraichard A, Chassande O, Bilbaut G et al. In vitro differentiation of embryonic stem cells into glial cells and functional neurons. *J Cell Sci* 1995; 108 (Pt 10):3181-3188.
- 46 Fraser FC und Fainstat TD. Production of congenital defects in the off-spring of pregnant mice treated with cortisone; progress report. *Pediatrics* 1951; 8:527-533.
- 47 Fraser FC, Kalter H, Walker BE, und Fainstat TD. The experimental production of cleft palate with cortisone and other hormones. *J Cell Physiol* 1954; 43:237-259.
- 48 Fujinaga M, Park HW, Shepard TH, Mirkes PE, und Baden JM. Staurosporine does not prevent adrenergic-induced situs inversus, but causes a unique syndrome of defects in rat embryos grown in culture. *Teratology* 1994; 50:261-274.
- 49 Genschow E, Spielmann H, Scholz G et al. Validation of the embryonic stem cell test in the international ECVAM validation study on three in vitro embryotoxicity tests. *Altern Lab Anim* 2004; 32:209-244.
- 50 Genschow E, Scholz G, Brown N et al. Development of Prediction Models for Three *In Vitro* Embryotoxicity Tests in an ECVAM Validation Study. *in vitro & molecular toxicology* 2000; 13:51-65.
- 51 Genschow E, Spielmann H, Scholz G et al. The ECVAM international validation study on in vitro embryotoxicity tests: results of the definitive phase and evaluation of prediction models. European Centre for the Validation of Alternative Methods. *ATLA* 2002; 30:151-176.
- 52 Ghelli A, Porcelli AM, Zanna C, und Rugolo M. 7-Ketocholesterol and staurosporine induce opposite changes in intracellular pH, associated with distinct types of cell death in ECV304 cells. *Arch Biochem Biophys* 2002; 402:208-217.
- 53 Glaser T und Brustle O. Retinoic acid induction of ES-cell-derived neurons: the radial glia connection. *Trends Neurosci* 2005; 28:397-400.

- 54 Gorzelniak K, Janke J, Engeli S, und Sharma AM. Validation of endogenous controls for gene expression studies in human adipocytes and preadipocytes. *Horm Metab Res* 2001; 33:625-627.
- 55 Gossler A, Doetschman T, Korn R, Serfling E, und Kemler R. Transgenesis by means of blastocyst-derived embryonic stem cell lines. *Proc Natl Acad Sci U S A* 1986; 83:9065-9069.
- 56 Gottlicher M, Minucci S, Zhu P et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J* 2001; 20:6969-6978.
- 57 Gough NM, Williams RL, Hilton DJ et al. LIF: a molecule with divergent actions on myeloid leukaemic cells and embryonic stem cells. *Reprod Fertil Dev* 1989; 1:281-288.
- 58 Grafton TF, Bazare JJ, Jr., Hansen DK, und Sheehan DM. The in vitro embryotoxicity of 5-fluorouracil in rat embryos. *Teratology* 1987; 36:371-377.
- 59 Gregg NM. Congenital cataract following German measles in the mother. *Trans Ophthalmol Soc Aust* 1941; 3:35-46.
- 60 Guan K, Furst DO, und Wobus AM. Modulation of sarcomere organization during embryonic stem cell-derived cardiomyocyte differentiation. *Eur J Cell Biol* 1999; 78:813-823.
- 61 Hakuno D, Takahashi T, Lammerding J, und Lee RT. Focal adhesion kinase signaling regulates cardiogenesis of embryonic stem cells. *J Biol Chem* 2005; 280:39534-39544.
- 62 Hale F. The relation of Vitamin A to Anophthalmos in Pigs. *American Journal of Ophthalmology* 1935; 18:1087-1091.
- 63 Hanson JW und Smith DW. Fetal hydantoin syndrome. *Lancet* 1976; 1:692.
- 64 Harvey RP. Patterning the vertebrate heart. *Nat Rev Genet* 2002; 3:544-556.
- 65 Heid CA, Stevens J, Livak KJ, und Williams PM. Real time quantitative PCR. *Genome Res* 1996; 6:986-994.
- 66 Heikinheimo M, Scandrett JM, und Wilson DB. Localization of transcription factor GATA-4 to regions of the mouse embryo involved in cardiac development. *Dev Biol* 1994; 164:361-373.
- 67 Hescheler J. Embryonic stem cells: a model to study structural and functional properties in cardiomyogenesis. *Cardiovasc Res* 1997; 36:149-162.
- 68 Hirooka Y und Shimokawa H. Therapeutic potential of rho-kinase inhibitors in cardiovascular diseases. *Am J Cardiovasc Drugs* 2005; 5:31-39.
- 69 Horb ME und Thomsen GH. Tbx5 is essential for heart development. *Development* 1999; 126:1739-1751.
- 70 Jalava A, Heikkila J, Lintunen M, Akerman K, und Pahlman S. Staurosporine induces a neuronal phenotype in SH-SY5Y human neuroblastoma cells that resembles that induced by the phorbol ester 12-O-tetradecanoyl phorbol-13 acetate (TPA). *FEBS Lett* 1992; 300:114-118.
- 71 Johnson SE, Rothstein JL, und Knowles BB. Expression of epidermal growth factor family gene members in early mouse development. *Dev Dyn* 1994; 201:216-226.
- 72 Karolyi J, Erickson RP, und Liu S. Genetics of susceptibility to 6-aminonicotinamide-induced cleft palate in the mouse: studies in congenic and recombinant inbred strains. *Teratology* 1988; 37:283-287.
- 73 Kauffman FC und Johnson EC. Cerebral energy reserves and glycolysis in neural tissue of 6-aminonicotinamide-treated mice. *J Neurobiol* 1974; 5:379-392.
- 74 Kawamura T, Ono K, Morimoto T et al. Acetylation of GATA-4 is involved in the differentiation of embryonic stem cells into cardiac myocytes. *J Biol Chem* 2005; 280:19682-19688.

- 75 Kemler R, Brulet P, Schnebelen MT, Gaillard J, und Jacob F. Reactivity of monoclonal antibodies against intermediate filament proteins during embryonic development. *J Embryol Exp Morphol* 1981; 64:45-60.
- 76 Kitajima S, Inoue T, und Saga Y. MesP1 and MesP2 are essential for the development of cardiac mesoderm. *Development* 2000; 127:3215-3226.
- 77 Kochhar DM. Teratogenic activity of retinoic acid. *Acta Pathol Microbiol Scand* 1967; 70:398-404.
- 78 Kohler E, Barrach H, und Neubert D. Inhibition of NADP dependent oxidoreductases by the 6-aminonicotinamide analogue of NADP. *FEBS Lett* 1970; 6:225-228.
- 79 Koshiba-Takeuchi K, Takeuchi JK, Matsumoto K et al. Tbx5 and the retinotectum projection. *Science* 2000; 287:134-137.
- 80 Kuo CT, Morrisey EE, Anandappa R et al. GATA4 transcription factor is required for ventral morphogenesis and heart tube formation. *Genes Dev* 1997; 11:1048-1060.
- 81 Lammer EJ, Chen DT, Hoar RM et al. Retinoic acid embryopathy. *N Engl J Med* 1985; 313:837-841.
- 82 Lau C, Mole ML, Copeland MF et al. Toward a biologically based dose-response model for developmental toxicity of 5-fluorouracil in the rat: acquisition of experimental data. *Toxicol Sci* 2001; 59:37-48.
- 83 Lee SH, Lumelsky N, Studer L, Auerbach JM, und McKay RD. Efficient generation of midbrain and hindbrain neurons from mouse embryonic stem cells. *Nat Biotechnol* 2000; 18:675-679.
- 84 Lenz W. Fragen aus der Praxis: kindliche Missbildungen nach Medikament Einnahme während der Graviditat? *Dtsche Med Wochenschr* 1961; 86:2555-2556.
- 85 Li QY, Newbury-Ecob RA, Terrett JA et al. Holt-Oram syndrome is caused by mutations in TBX5, a member of the Brachyury (T) gene family. *Nature Genetics* 1997; 15:21-29.
- 86 Lin Q, Schwarz J, Bucana C, und Olson EN. Control of mouse cardiac morphogenesis and myogenesis by transcription factor MEF2C. *Science* 1997; 276:1404-1407.
- 87 Lints TJ, Parsons LM, Hartley L, Lyons I, und Harvey RP. Nkx-2.5: a novel murine homeobox gene expressed in early heart progenitor cells and their myogenic descendants. *Development* 1993; 119:419-431.
- 88 Little SA und Mirkes PE. Teratogen-induced activation of caspase-9 and the mitochondrial apoptotic pathway in early postimplantation mouse embryos. *Toxicol Appl Pharmacol* 2002; 181:142-151.
- 89 Lombet A, Zujovic V, Kandouz M et al. Resistance to induced apoptosis in the human neuroblastoma cell line SK-N-SH in relation to neuronal differentiation. Role of Bcl-2 protein family. *Eur J Biochem* 2001; 268:1352-1362.
- 90 Lyons GE, Ontell M, Cox R, Sassoon D, und Buckingham M. The expression of myosin genes in developing skeletal muscle in the mouse embryo. *J Cell Biol* 1990a; 111:1465-1476.
- 91 Lyons GE, Schiaffino S, Sassoon D, Barton P, und Buckingham M. Developmental regulation of myosin gene expression in mouse cardiac muscle. *J Cell Biol* 1990b; 111:2427-2436.
- 92 Maltsev VA, Rohwedel J, Hescheler J, und Wobus AM. Embryonic stem cells differentiate in vitro into cardiomyocytes representing sinusnodal, atrial and ventricular cell types. *Mech Dev* 1993; 44:41-50.
- 93 Maltsev VA, Wobus AM, Rohwedel J, Bader M, und Hescheler J. Cardiomyocytes differentiated in vitro from embryonic stem cells developmentally express cardiac-specific genes and ionic currents. *Circ Res* 1994; 75:233-244.

- 94 Mansur NR, Meyer-Siegler K, Wurzer JC, und Sirover MA. Cell cycle regulation of the glyceraldehyde-3-phosphate dehydrogenase/uracil DNA glycosylase gene in normal human cells. *Nucleic Acids Res* 1993; 21:993-998.
- 95 Martin GR. Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proc Natl Acad Sci U S A* 1981; 78:7634-7638.
- 96 Matsumoto M, Rey DA, und Cory JG. Effects of cytosine arabinoside and hydroxyurea on the synthesis of deoxyribonucleotides and DNA replication in L1210 cells. *Adv Enzyme Regul* 1990; 30:47-59.
- 97 McBride WG. Thalidomide and congenital abnormalities. *Lancet* 1961; 2:1358.
- 98 Menegola E, Broccia ML, Nau H et al. Teratogenic effects of sodium valproate in mice and rats at midgestation and at term. *Teratog Carcinog Mutagen* 1996; 16:97-108.
- 99 Miller-Hance WC, LaCorbiere M, Fuller SJ et al. In vitro chamber specification during embryonic stem cell cardiogenesis. Expression of the ventricular myosin light chain-2 gene is independent of heart tube formation. *J Biol Chem* 1993; 268:25244-25252.
- 100 Minty AJ, Alonso S, Caravatti M, und Buckingham ME. A fetal skeletal muscle actin mRNA in the mouse and its identity with cardiac actin mRNA. *Cell* 1982; 30:185-192.
- 101 Molkentin JD, Lin Q, Duncan SA, und Olson EN. Requirement of the transcription factor GATA4 for heart tube formation and ventral morphogenesis. *Genes Dev* 1997; 11:1061-1072.
- 102 Morimoto M, Takahashi Y, Endo M, und Saga Y. The Mesp2 transcription factor establishes segmental borders by suppressing Notch activity. *Nature* 2005; 435:354-359.
- 103 Mullis KB und Faloona FA. Specific synthesis of DNA in vitro via a polymerase-catalyzed chain reaction. *Methods Enzymol* 1987; 155:335-350.
- 104 Murphy CL und Polak JM. Differentiating embryonic stem cells: GAPDH, but neither HPRT nor beta-tubulin is suitable as an internal standard for measuring RNA levels. *Tissue Eng* 2002; 8:551-559.
- 105 Nau H. Teratogenicity of isotretinoin revisited: species variation and the role of all-trans-retinoic acid. *J Am Acad Dermatol* 2001; 45:S183-S187.
- 106 Nichols J, Branko Z, Anastassiadis K et al. Formation of Pluripotent Stem Cells in the Mammalian Embryo Depends on the POU Transcription Factor Oct4. *Cell* 1998; 95:379-391.
- 107 Niwa H, Miyazaki J, und Smith AG. Quantitative expression of Oct-3/4 defines differentiation, dedifferentiation or self-renewal of ES cells. *Nat Genet* 2000; 24:372-376.
- 108 Nomura-Kitabayashi A, Takahashi Y, Kitajima S et al. Hypomorphic Mesp allele distinguishes establishment of rostrocaudal polarity and segment border formation in somitogenesis. *Development* 2002; 129:2473-2481.
- 109 Nord LD, Stolfi RL, Alfieri AA et al. Apoptosis induced in advanced CD8F1-murine mammary tumors by the combination of PALA, MMPR and 6AN precedes tumor regression and is preceded by ATP depletion. *Cancer Chemother Pharmacol* 1997; 40:376-384.
- 110 O'Rahilly R und Müller F. *Embryologie und Teratologie des Menschen*. Verlag Hans Huber 1999;
- 111 Oberdisse E, Hackenthal E, und Kuschinsky K. *Pharmakologie und Toxikologie*. Springer-Verlag 2002; Berlin Heidelberg New York.
- 112 Oh J, Wang Z, Wang DZ et al. Target gene-specific modulation of myocardin activity by GATA transcription factors. *Mol Cell Biol* 2004; 24:8519-8528.

- 113 Oikarinen A, Makela J, Vuorio T, und Vuorio E. Comparison on collagen gene expression in the developing chick embryo tendon and heart. Tissue and development time-dependent action of dexamethasone. *Biochim Biophys Acta* 1991; 1089:40-46.
- 114 Okabe S, Forsberg-Nilsson K, Spiro AC, Segal M, und McKay RD. Development of neuronal precursor cells and functional postmitotic neurons from embryonic stem cells in vitro. *Mech Dev* 1996; 59:89-102.
- 115 Omtzigt JG, Los FJ, Grobbee DE et al. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology* 1992; 42:119-125.
- 116 Ortega A, Puig M, und Domingo JL. Maternal and developmental toxicity of low doses of cytosine arabinoside in mice. *Teratology* 1991; 44:379-384.
- 117 Parisi S, D'Andrea D, Lago CT et al. Nodal-dependent Cripto signaling promotes cardiomyogenesis and redirects the neural fate of embryonic stem cells. *J Cell Biol* 2003; 163:303-314.
- 118 Parker WB und Cheng YC. Metabolism and mechanism of action of 5-fluorouracil. *Pharmacol Ther* 1990; 48:381-395.
- 119 Parlakian A, Tuil D, Hamard G et al. Targeted inactivation of serum response factor in the developing heart results in myocardial defects and embryonic lethality. *Mol Cell Biol* 2004; 24:5281-5289.
- 120 Parman T, Wiley MJ, und Wells PG. Free radical-mediated oxidative DNA damage in the mechanism of thalidomide teratogenicity. *Nat Med* 1999; 5:582-585.
- 121 Pease S und Williams RL. Formation of germ-line chimeras from embryonic stem cells maintained with recombinant leukemia inhibitory factor. *Exp Cell Res* 1990; 190:209-211.
- 122 Pellizzer C, Adler S, Corvi R, Hartung T, und Bremer S. Monitoring of teratogenic effects in vitro by analysing a selected gene expression pattern. *Toxicol In Vitro* 2004; 18:325-335.
- 123 Pennica D, King KL, Shaw KJ et al. Expression cloning of cardiotrophin 1, a cytokine that induces cardiac myocyte hypertrophy. *Proc Natl Acad Sci U S A* 1995; 92:1142-1146.
- 124 Perea-Gomez A, Shawlot W, Sasaki H, Behringer RR, und Ang S. HNF3beta and Lim1 interact in the visceral endoderm to regulate primitive streak formation and anterior-posterior polarity in the mouse embryo. *Development* 1999; 126:4499-4511.
- 125 Peterkin T, Gibson A, Loose M, und Patient R. The roles of GATA-4, -5 and -6 in vertebrate heart development. *Semin Cell Dev Biol* 2005; 16:83-94.
- 126 Phiel CJ, Zhang F, Huang EY et al. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J Biol Chem* 2001; 276:36734-36741.
- 127 Risau W, Sariola H, Zerwes HG et al. Vasculogenesis and angiogenesis in embryonic-stem-cell-derived embryoid bodies. *Development* 1988; 102:471-478.
- 128 Robbins J, Gulick J, Sanchez A, Howles P, und Doetschman T. Mouse embryonic stem cells express the cardiac myosin heavy chain genes during development in vitro. *J Biol Chem* 1990; 265:11905-11909.
- 129 Robertson E, Bradley A, Kuehn M, und Evans M. Germ-line transmission of genes introduced into cultured pluripotential cells by retroviral vector. *Nature* 1986; 323:445-448.
- 130 Rodriguez-Esteban C, Tsukui T, Yonei S et al. The T-box genes Tbx4 and Tbx5 regulate limb outgrowth and identity. *Nature* 1999; 398:814-818.
- 131 Rohwedel J, Guan K, und Wobus AM. Induction of cellular differentiation by retinoic acid in vitro. *Cells Tissues Organs* 1999; 165:190-202.

- 132 Rohwedel J, Maltsev V, Bober E et al. Muscle cell differentiation of embryonic stem cells reflects myogenesis in vivo: developmentally regulated expression of myogenic determination genes and functional expression of ionic currents. *Dev Biol* 1994; 164:87-101.
- 133 Rote Liste. Rote Liste. ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH 2005; Aulendorf.
- 134 Russell WMS und Burch RL. *The Principles of Humane Experimental Technique*. Methuen, London 1959;
- 135 Saga Y. Genetic rescue of segmentation defect in MesP2-deficient mice by MesP1 gene replacement. *Mech Dev* 1998; 75:53-66.
- 136 Saga Y, Hata N, Kobayashi S et al. MesP1: a novel basic helix-loop-helix protein expressed in the nascent mesodermal cells during mouse gastrulation. *Development* 1996; 122:2769-2778.
- 137 Saga Y, Hata N, Koseki H, und Taketo MM. Mesp2: a novel mouse gene expressed in the presegmented mesoderm and essential for segmentation initiation. *Genes Dev* 1997; 11:1827-1839.
- 138 Saga Y, Miyagawa-Tomita S, Takagi A et al. MesP1 is expressed in the heart precursor cells and required for the formation of a single heart tube. *Development* 1999; 126:3437-3447.
- 139 Sanchez A, Jones WK, Gulick J, Doetschman T, und Robbins J. Myosin heavy chain gene expression in mouse embryoid bodies. An in vitro developmental study. *J Biol Chem* 1991; 266:22419-22426.
- 140 Sassoon DA, Garner I, und Buckingham M. Transcripts of alpha-cardiac and alpha-skeletal actins are early markers for myogenesis in the mouse embryo. *Development* 1988; 104:155-164.
- 141 Sauer H, Neukirchen W, Rahimi G et al. Involvement of reactive oxygen species in cardiotrophin-1-induced proliferation of cardiomyocytes differentiated from murine embryonic stem cells. *Exp Cell Res* 2004; 294:313-324.
- 142 Schmitt RM, Bruyns E, und Snodgrass HR. Hematopoietic development of embryonic stem cells in vitro: cytokine and receptor gene expression. *Genes Dev* 1991; 5:728-740.
- 143 Schmittgen TD und Zakrajsek BA. Effect of experimental treatment on housekeeping gene expression: validation by real-time, quantitative RT-PCR. *J Biochem Biophys Methods* 2000; 46:69-81.
- 144 Schnier JB, Gadbois DM, Nishi K, und Bradbury EM. The kinase inhibitor staurosporine induces G1 arrest at two points: effect on retinoblastoma protein phosphorylation and cyclin-dependent kinase 2 in normal and transformed cells. *Cancer Res* 1994; 54:5959-5963.
- 145 Scholer HR, Dressler GR, Balling R, Rohdewohld H, und Gruss P. Oct-4: a germline-specific transcription factor mapping to the mouse t-complex. *EMBO J* 1990; 9:2185-2195.
- 146 Scholz G. STANDARD OPERATING PROCEDURE EMBRYONIC STEM CELL TEST (EST) FINAL VERSION ZEBET . 1998.
- 147 Scholz G, Genschow E, Pohl I et al. Prevalidation of the Embryonic Stem Cell Test (EST) - A New *In Vitro* Embryotoxicity Test. *Toxicology in vitro* 1999; 675-681.
- 148 Schultheiss TM, Burch JB, und Lassar AB. A role for bone morphogenetic proteins in the induction of cardiac myogenesis. *Genes Dev* 1997; 11:451-462.
- 149 Schumacher A, Arnhold S, Addicks K, und Doerfler W. Staurosporine is a potent activator of neuronal, glial, and "CNS stem cell-like" neurosphere differentiation in murine embryonic stem cells. *Mol Cell Neurosci* 2003; 23:669-680.
- 150 Secrest RJ, Williams P, Bonjouklian R et al. Hypotensive properties of the protein kinase inhibitor, staurosporine, in normotensive and spontaneously hypertensive rats. *Clin Exp Hypertens A* 1991; 13:219-234.

- 151 Seiler A, Visan A, Buesen R, Genschow E, und Spielmann H. Improvement of an in vitro stem cell assay for developmental toxicity: the use of molecular endpoints in the embryonic stem cell test. *Reprod Toxicol* 2004; 18:231-240.
- 152 Shah RM und MacKay RA. Teratological evaluation of 5-fluorouracil and 5-bromo-2-deoxyuridine on hamster fetuses. *J Embryol Exp Morphol* 1978; 43:47-54.
- 153 Sheng Z, Pennica D, Wood WI, und Chien KR. Cardiotrophin-1 displays early expression in the murine heart tube and promotes cardiac myocyte survival. *Development* 1996; 122:419-428.
- 154 Shepard TH und Lemire RJ. *Catalog of Teratogenic Agents*. Johns Hopkins University Press 2004; Baltimore and London.
- 155 Shuey DL, Lau C, Logsdon TR et al. Biologically based dose-response modeling in developmental toxicology: biochemical and cellular sequelae of 5-fluorouracil exposure in the developing rat. *Toxicol Appl Pharmacol* 1994; 126:129-144.
- 156 Sirover MA. New insights into an old protein: the functional diversity of mammalian glyceraldehyde-3-phosphate dehydrogenase. *Biochim Biophys Acta* 1999; 1432:159-184.
- 157 Smith AG, Heath JK, Donaldson DD et al. Inhibition of pluripotential embryonic stem cell differentiation by purified polypeptides. *Nature* 1988; 336:688-690.
- 158 Speckmann und Wittkowski. *Bau und Funktionen des menschlichen Körpers*. Urban & Schwarzenberg 1994; München.
- 159 Spielmann H, Pohl I, Döring B, Liebsch M, und Moldenhauer F. The Embryonic Stem Cell Test, an *In Vitro* Embryotoxicity Test Using Two Permanent Mouse Cell Lines: 3T3 Fibroblasts and Embryonic Stem Cells. *In Vitro Toxicology* 1997; 10:119-127.
- 160 Spielmann H, Genschow E, Scholz G et al. Preliminary results of the ECVAM validation study on three in vitro embryotoxicity tests. *Altern Lab Anim* 2001; 29:301-303.
- 161 Srivastava D, Cserjesi P, und Olson EN. A subclass of bHLH proteins required for cardiac morphogenesis. *Science* 1995; 270:1995-1999.
- 162 Srivastava D, Thomas T, Lin Q et al. Regulation of cardiac mesodermal and neural crest development by the bHLH transcription factor, dHAND. *Nat Genet* 1997; 16:154-160.
- 163 Stolfi RL, Colofiore JR, Nord LD, Koutcher JA, und Martin DS. Biochemical modulation of tumor cell energy: regression of advanced spontaneous murine breast tumors with a 5-fluorouracil-containing drug combination. *Cancer Res* 1992; 52:4074-4081.
- 164 Street JC, Alfieri AA, und Koutcher JA. Quantitation of metabolic and radiobiological effects of 6-aminonicotinamide in RIF-1 tumor cells in vitro. *Cancer Res* 1997; 57:3956-3962.
- 165 Strubing C, Ahnert-Hilger G, Shan J et al. Differentiation of pluripotent embryonic stem cells into the neuronal lineage in vitro gives rise to mature inhibitory and excitatory neurons. *Mech Dev* 1995; 53:275-287.
- 166 Takeuchi JK, Koshiba-Takeuchi K, Suzuki T et al. Tbx5 and Tbx4 trigger limb initiation through activation of the Wnt/Fgf signaling cascade. *Development* 2003a; 130:2729-2739.
- 167 Takeuchi JK, Ohgi M, Koshiba-Takeuchi K et al. Tbx5 specifies the left/right ventricles and ventricular septum position during cardiogenesis. *Development* 2003b; 130:5953-5964.
- 168 Tamaoki T, Nomoto H, Takahashi I et al. Staurosporine, a potent inhibitor of phospholipid/Ca⁺⁺dependent protein kinase. *Biochem Biophys Res Commun* 1986; 135:397-402.

- 169 Toumadje A, Kusumoto K, Parton A et al. Pluripotent differentiation in vitro of murine ES-D3 embryonic stem cells. *In Vitro Cell Dev Biol Anim* 2003; 39:449-453.
- 170 Tyson RL, Perron J, und Sutherland GR. 6-Aminonicotinamide inhibition of the pentose phosphate pathway in rat neocortex. *Neuroreport* 2000; 11:1845-1848.
- 171 Uehata M, Ishizaki T, Satoh H et al. Calcium sensitization of smooth muscle mediated by a Rho-associated protein kinase in hypertension. *Nature* 1997; 389:990-994.
- 172 Ueyama T, Kasahara H, Ishiwata T, Nie Q, und Izumo S. Myocardin expression is regulated by Nkx2.5, and its function is required for cardiomyogenesis. *Mol Cell Biol* 2003; 23:9222-9232.
- 173 Wang D, Chang PS, Wang Z et al. Activation of cardiac gene expression by myocardin, a transcriptional cofactor for serum response factor. *Cell* 2001; 105:851-862.
- 174 Wei L, Roberts W, Wang L et al. Rho kinases play an obligatory role in vertebrate embryonic organogenesis. *Development* 2001; 128:2953-2962.
- 175 Werling U, Siehler S, Litfin M, Nau H, und Gottlicher M. Induction of differentiation in F9 cells and activation of peroxisome proliferator-activated receptor delta by valproic acid and its teratogenic derivatives. *Mol Pharmacol* 2001; 59:1269-1276.
- 176 White PH, Farkas DR, McFadden EE, und Chapman DL. Defective somite patterning in mouse embryos with reduced levels of Tbx6. *Development* 2003; 130:1681-1690.
- 177 Williams RL, Hilton DJ, Pease S et al. Myeloid leukaemia inhibitory factor maintains the developmental potential of embryonic stem cells. *Nature* 1988; 336:684-687.
- 178 Winer J, Jung CK, Shackel I, und Williams PM. Development and validation of real-time quantitative reverse transcriptase-polymerase chain reaction for monitoring gene expression in cardiac myocytes in vitro. *Anal Biochem* 1999; 270:41-49.
- 179 Winn LM und Wells PG. Phenytoin-initiated DNA oxidation in murine embryo culture, and embryo protection by the antioxidative enzymes superoxide dismutase and catalase: evidence for reactive oxygen species-mediated DNA oxidation in the molecular mechanism of phenytoin teratogenicity. *Mol Pharmacol* 1995; 48:112-120.
- 180 Wobus AM, Kaomei G, Shan J et al. Retinoic acid accelerates embryonic stem cell-derived cardiac differentiation and enhances development of ventricular cardiomyocytes. *J Mol Cell Cardiol* 1997; 29:1525-1539.
- 181 Wobus AM, Wallukat G, und Hescheler J. Pluripotent mouse embryonic stem cells are able to differentiate into cardiomyocytes expressing chronotropic responses to adrenergic and cholinergic agents and Ca²⁺ channel blockers. *Differentiation* 1991; 48:173-182.
- 182 Xu C, Liguori G, Adamson ED, und Persico MG. Specific arrest of cardiogenesis in cultured embryonic stem cells lacking Cripto-1. *Dev Biol* 1998; 196:237-247.
- 183 Xu C, Liguori G, Persico MG, und Adamson ED. Abrogation of the Cripto gene in mouse leads to failure of postgastrulation morphogenesis and lack of differentiation of cardiomyocytes. *Development* 1999; 126:483-494.
- 184 Yamada M, Revelli JP, Eichele G, Barron M, und Schwartz RJ. Expression of chick Tbx-2, Tbx-3, and Tbx-5 genes during early heart development: evidence for BMP2 induction of Tbx2. *Dev Biol* 2000; 228:95-105.
- 185 Yamashita J, Itoh H, Hirashima M et al. Flk1-positive cells derived from embryonic stem cells serve as vascular progenitors. *Nature* 2000; 408:92-96.

-
- 186 Ying QL, Stavridis M, Griffiths D, Li M, und Smith A. Conversion of embryonic stem cells into neuroectodermal precursors in adherent monoculture. *Nat Biotechnol* 2003; 21:183-186.
- 187 Zackheim HS. Treatment of psoriasis with 6-aminonicotinamide. *Arch Dermatol* 1975; 111:880-882.
- 188 Zackheim HS. Topical 6-aminonicotinamide plus oral niacinamide therapy for psoriasis. *Arch Dermatol* 1978; 114:1632-1638.
- 189 zur Nieden NI, Kempka G, und Ahr HJ. In vitro differentiation of embryonic stem cells into mineralized osteoblasts. *Differentiation* 2003; 71:18-27.
- 190 zur Nieden NI, Kempka G, und Ahr HJ. Molecular multiple endpoint embryonic stem cell test--a possible approach to test for the teratogenic potential of compounds. *Toxicol Appl Pharmacol* 2004; 194:257-269.
- 191 zur Nieden NI, Kempka G, Rancourt DE, und Ahr HJ. Induction of chondro-, osteo- and adipogenesis in embryonic stem cells by bone morphogenetic protein-2: effect of cofactors on differentiating lineages. *BMC Dev Biol* 2005; 5:1.
- 192 zur Nieden NI, Ruf LJ, Kempka G, Hildebrand H, und Ahr HJ. Molecular markers in embryonic stem cells. *Toxicol In Vitro* 2001; 15:455-461.