

6- Appendix

6.1- Abbreviations

°C	degree Celcius
µg	microgram
2'5'OAS	2'5'oligoadenylate synthetase
Ad5	human adenovirus type 5
Adbiluc	adenoviral vector containing the bidirectional tet-regulated promoter P _{bi-1} fused to luciferase gene
AdGH1.3	adenoviral vector containing the 1.3 overlenght HBV genome and the GFP gene under the control of CMV promoter
ALT	alanine transaminase (GTP)
cccDNA	covalently closed circular DNA
CMV	Cytomegalovirus
CTL	cytotoxic T Lymphocytes
DHBV	Duck Hepatitis B Virus
DMSO	dimethyl sulfoxide
dNTP	deoxynucleotide triphosphate
dox	doxycycline
E. coli	Escherichia coli
ELISA	enzyme-linked immunosorbent assay
FCS	fetal bovine serum
fig	figure
fmol	fetomole
GAPDH	glyceraldehyde-3-phosphate
GFP	green fluoescent protein
HBeAg	antigen of e protein as precursor of core protein of HBV
HBsAg	antigen of S envelope protein of HBV
HBV	human Hepatitis B Virus
HCV	human Hepatitis C Virus
HD	Helper-dependant adenoviral vector
HIV	Human Immunodeficiency Virus
i.p.	intraperitineous
I.U.	international unit
i.v.	intravenuous
IFN	interferon
IL	interleukin
IP10	CXC chemokine IFN γ -inducible protein-10 (IP-10/CXCL10)
kb	kilobase
kDa	kilo Dalton
LCMV	lymphocytic choriomeningitis
LDH	lactate deshydrogenase
MCMV	mouse cytomegalovirus
MHC	major histocompatibility complex
mIFN	mouse interferon
ml	milliliter

mM	millimolar
moi	multiplicity of infection
MVL	mouse
NK	natural killer cells
NKT	natural killer T cell
nm	nanometer
NPC	non-parenchymal cells
OD	optical density
OFR	open reading frame
p.i.	post infection
P _{CMV}	major immediate-early promoter of cytomegalovirus
PCR	polymerase chain reaction
PDH	primary duck hepatocytes
PHH	primary human hepatocytes
PKR	double-stranded RNA-activated protein kinase
PMH	primary mouse hepatocytes
P _{TTR}	promoter and enhancer element of transthyretin gene
rpm	rotation per minute
rtTA	reverse tetracycline-dependent transactivator
tet	tetracycline
TNF α	tumor necrosis factor alpha
tTA	tetracycline-dependent transactivator
v.p.	viral particle
WHV	Woodchuck Hepatitis Virus
wIFN	woodchuck interferon

6.2- References

- Aguilar-Cordova Estuardo; Quality control of viral vectors for clinical trials; 2001; Oral presentation at the GVPN Conference; Evry, France.
- Allen G. and Fantes KH.; A family of structural genes for human lymphoblastoid (leukocyte-type) interferon; 1980; *Nature* 287: 408-411.
- Alpini G., Phillips J.O., Vroman B. and LaRusso N.F.; Recent advances in the isolation of liver cells; 1994; *Hepatology* 20: 494-514.
- Amalfitano A., and Chamberlain J.S.; Isolation and characterization of packaging cell lines that coexpress the adenovirus E1, DNA polymerase and preterminal proteins: Implications for gene therapy; 1997; *Gene Ther.* 4: 258-263.
- Amalfitano A., Hauser M.A., Hu H., Serra D., Begy C.R. and Chamberlain J.S.; Production and characterization of improved adenovirus vectors with the E1, E2b, and E3 genes deleted; 1998; *J. Virol.* 72: 926-933.
- Amalfitano A., Hauser M.A., Hu H., Serra D., Begy C.R., and Chamberlain J.S.; Production and characterization of improved adenovirus vectors with the E1, E2b and E3 genes deleted; 1998; *J. Virol.* 72: 926-933.
- Anderson W.F.; Human gene therapy; 1998; *Nature* 392: 25-30.
- Auricchio L, Bujard H, Hillen W, Cortese R, Ciliberto G, La Monica N, Palombo F.; Regulated and prolonged expression of mIFN(α) in immunocompetent mice mediated by a helper-dependent adenovirus vector; 2001; *Gene Therapy* 8: 1817-25.
- Bai M., Harfe B. and Freimuth P.; Mutations that alter an Arg-Gly-Asp (RGD) sequence in the adenovirus type 2 pentose base protein abolish its cell-rounding activity and delay virus reproduction in flat cells; 1993; *J. Virol.* 67: 5198-5205.
- Banks K.E., Anderson A.L., Tang H., Hughes D.E., Costa R.H. and McLachlan A.; Hepatocyte nuclear factor 3 β Inhibits hepatitis B virus replication in vitro; 2002; *J. of Virol.* 76: 12974-12980.
- Baron,U., Freundlieb S., Grossen M., and Bujard H., Co-regulation of two gene activities by tetracycline via a bidirectional promoter, *Nucleic Acids Res.*, 1995, Vol. 23, No 17, 3605-3606.
- Bartenschlager R. and Schaller H.; Hepadnaviral assembly is initiated by polymerase binding to the encapsidation signal in the viral RNA genome; 1992; *EMBO J.* 11: 3413-3420.
- Bass B., Weintraub H., Cattaneo R. and Billeter M.A.; Biased hypermutation of viral RNA genomes could be due to unwinding/modification of double-stranded RNA; 1989; *Cell* 56 : 331-335.

- Belousova N., Krendelchtchikova V., Curiel D.T. and Krasnykh V.; Modulation of adenovirus vector tropism via incorporation of polypeptide ligands into the fiber protein; 2002; *J. Virol.* 76: 8621-8631.
- Benihoud K., Yeh P. and Perricaudet M.; Adenovirus vectors for gene delivery; 1999; *Curr. Opin. Biotechnol.* 10: 440-447.
- Bett A.J., Prevec L. and Graham F.L.; Packaging capacity and stability of human adenovirus type 5 vectors; 1993; *J. Virol.* 67: 5911-5921.
- Böttcher B., Wynne S.A. and Crowther R.A.; Determination of the fold of the core protein of hepatitis B virus by electron cryomicroscopy; 1997; *Nature* 386 : 88-91.
- Bruss V. and Ganem D.; The role of envelope proteins in hepatitis B virus assembly; 1991; *P.N.A.S.* 88: 1059-1063.
- Bujard H, Stueber D, Gentz R, Deuschle U, and Peschke U. ; Insertion of transcriptional elements outside the replication region can interfere with replication, maintenance, and stability of CoIE1-derived plasmids ;1985; *Basic Life Science* 30: 45-52.
- Buvoli M., Langer S.J., Bialik S. and Leinwand L.A.; Potential limitations of transcription terminators used as transgene insulators in adenoviral vectors; 2002; *Gene Ther.* 9: 227-231.
- Carloni G., Malpica Y., Michel M.L., Le Patezour A., Sobczak E., Tiollais P. and Streeter R.E.; A transformed Vero cell line stably producing the hepatitis virus surface antigen; 1984; *Gene* 31: 49-57.
- Cartmell T., Southgate T., Rees G.S., Castro M.G., Lowenstein P.R. and Luheshi G.N.; Interleukin-1 mediates a rapid inflammatory response after injection of adenovirus vectors into the brain; 1999; *J. Neurosci.* 19: 1517-1523.
- Cavanaugh V.J., Guidotti L.G. and Chisari F.V.; Inhibition of hepatitis B virus replication during adenovirus and cytomegalovirus infections in transgenic mice; 1998; *J. Virol.* 72: 2630-2637.
- Cavanaugh V.J., Guidotti L.G. and Chisari F.V.; Interleukin-12 inhibits hepatitis B virus replication in transgenic mice; 1997; *J. Virol.* 71: 3236-3243.
- Chebath J, Benech P, Revel M, Vigneron M.; Constitutive expression of (2'5')oligo A synthetase confers resistance to picornavirus infection; 1987 *Nature* 330: 587-588.
- Chisari F.V. and Ferrari C.; Hepatitis B virus immunopathogenesis; 1995; *Annu. Rev. Immunol.* 13: 29-60.
- Chisari F.V.; Hepatitis B virus transgenic mice: models of viral immunology and pathogenesis; 1996; *Curr. Top. Microbiol. Immunol.* 206: 149-173.
- Clemens M.J. and Elia A.; The double-stranded RNA-dependent protein kinase PKR: structure and function; 1997; *J. of Interferon and Cytokine Res.* 17: 503-524.

- Crowther R.A., Kiselev N.A.; Bottcher B., Berrman J.A., Borisova G.P., Ose V. and Pumpens P.; Three-dimensional structure of hepatitis B virus core particles determined by electron cryomicroscopy; 1994; *Cell* 77 : 943-950.
- Crystal R.G, Mc Elvaney N.G., Rosenfeld M.A., Chu C.S., Mastrangeli A., Hay J.G., Brody S.L., Jaffe H.A., Eissa N.T., and Danel C., Administration of an adenovirus containing the human CFTR cDNA to the respiratory tract of individuals with cystic fibrosis; 1994; *Nat. Gent.* 8:42-51.
- D'Amore P.A.; Mechanisms of endothelial growth control; 1992; *Am. J. Respir. Cell Mol. Biol.* 6: 1-8.
- De Clercq E.; Interferon induction by polynucleotides, modified polynucleotides, and polycarboxylates; 1981; *Methods Enzymol.* 78: 227-236.
- Delaney W.E.T. and Isom H.C.; Hepatitis B virus replication in human HepG2 cells mediated by hepatitis B virus recombinant baculovirus; 1998; *Hepatology* 28: 1134-1146.
- Delaney W.E.T., Miller T.G., and Isom H.C.; Use of the hepatitis B virus recombinant baculovirus-HepG2 system to study the effects of (-)- β -2'-3'-dideoxy-3'-thiacytidine on replication of hepatitis B virus and accumulation of covalently closed circular DNA; 1999; *Antimicrob. Agents Chemother.* 43: 2017-2026.
- Dong B. and Silverman R.H.; Alternative function of a protein kinase homology domain in 2'5'-oligoadenylate dependent RNase L; 1999; *Nucleic Acids Res.* 27: 439-345.
- Dong Z, Greene G, Pettaway C, Dinney CP, Eue I, Lu W, Bucana CD, Balbay MD, Bielenberg D, Fidler IJ.; Suppression of angiogenesis, tumorigenicity and metastasis by human prostate cancer cells engineered to produce interferon- β ; 1999; *Cancer Res.* 59: 872-879.
- Dumortier J., Chevallier P., Scoazec J-Y. and Biollot O; HBV reactivation in the recipient of a liver graft from an anti.HBc positive donor despite post-vaccination antibodies to hepatitis B surface antigen; 2002; *J Hepatol.* 37: 876-877.
- Elfassi E., Romet-Lemmone J.L., Essex M., Frances-McLane M. and Haseltine; Evidence of extrachromosomal forms of Hepatitis B viral DNA in bone marrow culture obtained from a patient recently infected with Hepatitis B virus; 1984; *PNAS* 81: 3526-3528.
- Engelhardt J.F., Litzky L., and Wilson J.M.; Prolonged transgene expression in cotton rat lung with recombinant adenoviruses defective in E2a; 1994; *Hum. Gene Ther.* 5: 1217-1229.
- Fallaux F.J., Kranenburg O., Cramer S.J., Houweling A., Van Ormondt H., Hoeben R.C., Van der Eb A.J.; Characterization of 911: a new helper cell line for the titration and propagation of early region 1-deleted adenoviral vectors; 1996; *Hum. Gene Ther.* 7:215-222.

Favre D., Blouin V., Provost N., Spizek R., Porrot F, Bohl D, Cherel Y., Salvetti A., Hurtel B., Heard M., Rivière Y. and Mouiller P.; Intramuscular delivery of AAV vectors in non-human primates: dissimulation, shedding and transgene regulation; 2001; Poster 26 at the GVPN Conference, Évry, France.

Ferry N. and Heard J.M.; Liver-directed gene transfer vectors; 1998; *Hum. Gene Ther.* 9: 1975-1981.

Feutren G., Lacour B. and Bach J.F.; Immune lysis of hepatocytes in culture: accurate detection by aspartate aminotransferase release measurement; 1984; *J. Immunol. Methods* 75: 85-94.

Fischler B., Lara C., Chen M., Sonnerborg A., Nemeth A. and Sallberg M.; Genetic evidence for mother to infant transmission of hepatitis G virus; 1997; *J. Infect. Dis.* 176: 281-285.

Frese M., Pietschmann T., Moradpour D., Haller O. and R. Bartenschlager; Interferon-gamma inhibits replication of subgenomic and genomic hepatitis C virus RNAs; 2001; *J. Gen. Virol.* 82: 723-733.

Freundlieb S., Schirra-Müller C. and Bujard H.; A tetracycline controlled activation / repression system with increased potential for gene transfer into mammalian cells; 1999; *J. Gene Med.* 1: 4-12.

Früh K., Gossen M., Wang K., Bujard H., Peterson P.A. and Yang Y.; Displacement of housekeeping proteasome subunits by MHC-encoded LMPs: a newly discovered mechanism for modulating the multicatalytic proteinase complex; 1994; *EMBO J.* 13: 3236-3244.

Fung W., Thomas T., Dickerson P., Aldred A.R., Milland J., Dziadek M., Powers B., Hudson P. and Schreiber G.; Structure and expression of rat transthyretin (prealbumin) gene; 1988; *J. Biol. Chem.* 263: 480-488.

Furth P.A., St. Onge L., Boger H., Gruss P., Gossen M., Kistner A. and Bujard H.; Temporal control of gene expression in transgenic mice by a tetracycline-responsive promoter; 1994; *P.N.A.S.* 91: 9302-9306.

Galibert F., Mandart E., Fitoussi F., Tiollais P., and Charnay P.; Nucleotide sequence of the hepatitis B virus genome (subtype ayw) cloned in *E. coli* ; 1979; *Nature* 281: 646-650.

Galle P.R., Hagelstein J., Kommerell B., Volkmann M., Schrank P., and Zentgraf H.; In vitro experimental infection of primary human hepatocytes with hepatitis B virus; 1994; *Gastroenterology* 106: 664-673.

Gallin J.I.; Inflammation; 1989; In W.E. Paul (edition), *Fundamental immunology*, 2nd ed. Raven Press, New York, N.Y.

Ganem D, Varmus HE.;The molecular biology of the hepatitis B viruses; 1987; *Annu Rev Biochem.* 56: 651-93.

Ganem D.; 1996; In: fields, B.N. Knipe, D.M. & Howley, P.M. (editors), *Virology*, page 2703, Lippincott-Raven publishers, Philadelphia.

Goldsby R.A., Kindt T.J. and Osborne B.A.; *Kuby Immunology*; 4th edition W.H. Freeman and Company, New York; chapter 12: Cytokines pp 3003-328.

Gorziglia M.I., Kadan M.J., Yei S., Lim J., Lee G.M., Luthra R. and Trapnell B.C.; Elimination of both E1 and E2 from adenovirus vectors further improves prospects for in vivo human gene therapy; 1996; *J. Virol.* 70: 4173-4178.

Gossen M. and Bujard H.; Tight control of gene expression in mammalian cells by tetracycline-responsive promoters; 1992; *P.N.A.S.* 89: 5547-5551.

Gossen M., Bonin A.L. and Bujard H.; Control of gene activity in higher eukaryotic cells by prokaryotic regulatory elements; 1993; *Trends Biochem. Sciences* 18: 5547-5551.

Gossen M., Freundlieb S., Bender G., Müller G., Hillen W. and Bujard H.; Transcription activation by tetracycline in mammalian cells; 1995; *Science* 268: 1766-1769.

Graham F.L., Smiley J., Russell W.C. and Nairn R.; Characteristics of a human cell line transformed by DNA from human adenovirus type 5; 1977; *J. Gen. Virol.* 36: 59-72.

Gripon P., Diot C. and Guguen-Guillouzo C.; Reproducible high level infection of cultured adult human hepatocytes by hepatitis B virus: effect of polyethylene glycol on adsorption and penetration; 1993; *Virology* 192: 534-540.

Gripon P., Diot C., Theze N., Fourel I., Loreal O., Brechot C. and Guguen-Guillouzo C.; Hepatitis B virus infection of adult human hepatocytes cultured in the presence of dimethyl sulfoxide; 1988; *J. Virol.* 62: 4136-4143.

Guidotti L. G., Matzke B., Schaller H., and Chisari F. V.; High-level Hepatitis B virus replication in transgenic mice; 1995; *J. Virol.* 69: 6158-6169.

Guidotti L.G. and Chisari F.V.; Cytokine-induced viral purging – role in viral pathogenesis; 1999; *Curr. Opin. Microbiol.* 2: 388-391.

Guidotti L.G. and Chisari F.V.; Noncytolytic control of viral infections by the innate and adaptive immune response; 2001; *Annu. Rev. Immunol.* 19: 65-91.

Guidotti L.G. and Chisari F.V.; To kill or to cure: option in host defense against viral infection; 1996; *Curr. Opin. Immunol.* 8 : 478-483.

Guidotti L.G., Borrow P., Hobbs M.V., Matzke B., Gresser I., Oldstone M.B. and Chisari F.V.; Viral cross talk: intracellular inactivation of the hepatitis B virus during an unrelated viral infection of the liver; 1996; *P.N.A.S.* 93: 4589-4594.

Guidotti L.G., Morris A., Mendez H., Koch R., Silverman R.H., Williams B.R. and Chisari F.V.; Interferon-regulated pathways that control hepatitis B virus replication in transgenic mice; 2002; *J. Virol.* 76 : 2617-2621.

Guidotti L.G., Rochford R., Chung J., Shapiro M., Purcell R. and Chisari F.V.; Viral clearance without destruction of infected cells during acute HBV infection; 1999; *Science* 284: 825-829.

Guidotti L.G.; The role of cytotoxic T cells and cytokines in the control of hepatitis B virus infection; 2002; *Vaccine* 19/20 Suppl 4: A80-82.

Guo J.T., Bichko V. and Seeger C.; Effect of alpha interferon on the hepatitis C virus replicon ; 2001; *J. Virol.* 75: 8516-8523.

Hadchouel M., Pasquinelli C., Fournier J.G., et al.; Detection of mononuclear cells expressing Hepatitis B virus in peripheral blood from HBsAg positive and negative patients by in situ hybridization; 1988; *J. Med. Virol.* 24: 27-32.

Hanahan D.; Studies on transformation of *Escherichia coli* with plasmids; 1983; *J. Mol. Biol.* 166: 557-580.

Harms JS. and Splitter GA.; Interferon-gamma inhibits transgene expression driven by SV40 or CMV promoters but augments expression driven by the mammalian MHC I promoter; 1995; *Hum. Gene Ther.* 6: 1291-1297.

Harvey B.G., Hackett N.R., El-Sawy T., Rosengart T.K., Hirschowitz E.A., Leberman M.D., Lesser M.L., and Crystal R.G.; Variability of human systemic humoral immune responses to adenovirus gene transfer vectors administered to different organs; 1999; *J. Virol.* 73: 6729-6742.

Harvey B.-G., Maroni J., O'Donoghue K.A., Chu K.W. and Jolene C.; Safety of local delivery of low- and intermediate-dose adenovirus gene transfer vectors to individuals with a spectrum of morbid conditions; 2002; *Hum Gene Ther.* 13: 15-63.

Hasan M.T., Schonig K., Berger S., Graewe W. and Bujard H.; Long-term, non-invasive imaging of regulated gene expression in living mice 2001; *Genesis* 29: 116-122.

Hatfield L. and Hearing P.; Redundant elements in the adenovirus type 5 inverted terminal repeat promote bidirectional transcription in vivo and are important for virus growth in vivo; 1991; *Virology* 184: 265-276.

He T-C., Zhou S., Costa L. T. D., Yu J., Kinzler K., and Vogelstein B.; A simplified system for generating recombinant adenoviruses; 1998; *P.N.A.S.* 95: 2509-2514.

Hearing P. and Shenk T.; The adenovirus type 5 E1A transcriptional control region contains a duplicated enhancer element; 1983; *Cell* 33: 695-703.

Heermann K.H. and Gerlich W.H.; Surface proteins of hepatitis B virus; In A. McLachlan edition, *Molecular biology of the hepatitis B virus*. CRC Press. Boca Raton, Florida, 109-144.

Hegenbach S., Gerolami R., Protzer U., Tran PL, Brechot C., Gerken F. and Knolle PA.; Liver sinusoidal endothelial cells are not permissive for adenovirus type 5; 2000; *Hum. Gene Ther.* 11: 481-486.

Heise T., Guidotti L.G. and Chisari F.V.; La autoantigen specifically recognizes a predicted stem-loop in hepatitis B virus RNA.; 1999b; *J. Virol.* 73: 5767-5776.

Heise T., Guidotti L.G., Cavanaugh V.J. and Chisari F.V.; Hepatitis B virus RNA-binding proteins associated with cytokine-induced clearance of viral RNA from the liver of transgenic mice; 1999a; *J. Virol.* 73: 474-481.

Higginbotham J.M., Seth P., Blaese M. and Ramsey W.J.; The release of inflammatory cytokines from human peripheral blood mononuclear cells in vitro following exposure to adenovirus variants and capsid; 2002; *Hum. Gene Ther.* 13: 129-141.

Hill W. and Berens C.; Mechanisms underlying expression of Tn10 encoded tetracycline resistance; 1994; *Annu. Rev. Microbiol.* 48: 345-369.

Hill W. and Wissmann A.; Topics in molecular and structural biology; 1989; eds. Saenger W. & Heinemann U. (Macmillan, London), Vol 10: 143-162.

Horke S., Reumann K., Rang A. and Heise T.; Molecular characterization of the human La protein hepatitis virus RNA-B interaction in vitro; 2002; *J. Biol. Chem.* 277: 34949-34958.

Howe J.R., Skryabin B.V., Belcher S.M., Zerillo C.A. and Schmauss C.; The responsiveness of a tetracycline-sensitive expression system differs in different cell lines; 1995; *J. Biol. Chem.* 270: 14168-14174.

Hu J. and Seeger C.; Hsp90 is required for the activity of a hepatitis B virus reverse transcriptase; 1996; *P.N.A.S.* 93:1060-1064.

Huovila A.P., Eder A.M. and Fuller S.D.; Hepatitis B surface antigen assembles in a post-ER, pre-Golgi compartment; 1992; *J Cell Biol.* 118 :1305-1320.

Isom I., Georgoff I., Salditt-Georgieff M and Darnell J.E.; Persistence of liver-specific messenger RNA in cultured hepatocytes: different regulatory events for different genes; 1987; *Cell Biol.* 105: 2877-2885.

Jackson P., Bos E. and Braithwaite AW.; Wild-type mouse p53 down-regulates transcription from different virus enhancer/promoters; 1993; *Oncogene* 8: 589-597.

Jaeckel E., Cornberg M., Wedemeyer H., Santantonio T., Mayer J., Zankel M., Pastore G., Dietrich M., Trautwein and Manns M.; Treatment of acute hepatitis C with interferon alpha-2b; 2001; *N. Engl. J. Med.* 345: 1-6.

Jaffe HA, Danel C, Longenecker G, Metzger M, Setoguchi Y, Rosenfeld MA, Gant TW, Thorgeirsson SS, Stratford-Perricaudet LD, Perricaudet M et al.; Adenovirus-mediated in vivo gene transfer and expression in normal rat liver; 1992; *Nat. Genet.* 1: 372-378.

Junker-Niepmann M., Bartenschlager R. and Schaller H.; A short cis-acting sequence is required for hepatitis B virus pregenome encapsidation and sufficient for packaging of foreign RNA; 1990; EMBO J 9: 3389-3396.

Justesen J., Hartmann R. and Kjeldgaard N.O.; Gene structure und function of the 2'-5'-oligoadenylate synthetase family; 2000; Cell. Mol. Life Science 57:1593-1612.

Kalvakolanu D.V. and Borden E.C.; An overview of the interferon system: signal transduction and mechanisms of action; 1996; Cancer Invest. 14: 25-53.

Kim J., Smith T., Idamakanti N., Mulgrew K., Kaloss M., Kylefjord H., Ryan P.C., Kaleko M. and Stevenson S. C.; Targeting adenoviral vectors by using the extracellular domain of the coxsackie-adenovirus receptor: improved potency via trimerization; 2002; J. Virol. 76: 1892-1903.

Kistner A., Gossen M., Zimmermann F., Jerecic J., Ullmer C., Lubbert H. and Bujard H.; Doxycycline-mediated quantitative and tissue-specific control of gene expression in transgenic mice; 1996; P.N.A.S. 93: 10933-10938.

Klingmüller U. and Schaller H.; Hepadnavirus infection requires interaction between the viral pre-S domain and a specific hepatocellular receptor; 1993; J. Virol. 67: 7414-7422.

Klöcker U., Schultz U., Schaller H. and Protzer U.; Endotoxin stimulates liver macrophages to release mediators that inhibit an early step in hepadnavirus replication; 2000; J. Virol. 74: 5525-5533.

Kochanek S.; High-capacity adenoviral vectors for gene transfer and somatic gene therapy; 1999; Hum. Gene Ther. 10: 2451-2459.

Kochs G. and Haller O.; Interferon-induced human MxA GTPase blocks nuclear import of Thogoto virus nucleocapsids; 1999; P.N.A.S. 96: 2082-2086.

Köck J. and Schlicht H.J.; 1993; Analysis of the earliest steps of hepadnavirus replication: genome repair after infectious entry into hepatocytes does not depend on viral polymerase activity; J. Virol. 67: 4867-4874.

Krestel H.E., Mayford M.R., Seeburg P.H. and Sprengel R.; A GFP-equipped bidirectional expression module well suited for monitoring tetracycline-regulated gene expression in mouse; 2001; Nucleic Acids Res. 29: E59.

Lanford R.E., Guerra B., Lee H., Averett D.R., Pfeiffer B., Charez D., Notvall L. and Bigger C.; Antiviral effect and virus-host interactions in response to alpha interferon, gamma interferon, poly(I)-poly(C), tumor necrosis factor alpha and ribavirin in hepatitis C virus subgenomic replicon; 2003; J. Virol. 77: 1092-1104.

Lanford RE, Chavez D, Brasky KM, Burns RB 3rd, Rico-Hesse R.; Isolation of a hepadnavirus from the woolly monkey, a New World primate: 1998; P.N.A.S. 12:5757-5761.

Lee S.B., Rodringez D., Rodringez J.R. and Esteban M.; The apoptosis pathway triggered by the interferon-induced protein kinase PKR requires the third basic domain, initiates upstream of Bcl-2 and involves ICE-like proteases; 1997; *Virology* 231: 81-88.

Lee WM.; Hepatitis B virus infection; 1997; *N. Engl. J. Med.* 337: 1733-1745.

Lenardo M.J., Fan C.-M., Maniatis T. and Baltimore D.; The involvement of NF- κ B in b-interferon gene regulation reveals its role as a widely inducible mediator of signal transduction; 1989; *Cell* 57: 287-294.

Leza MA. and Hearing P.; Cellular transcription factor binds to adenovirus early region promoters and to a cytic AMP response element; 1988; *J. Virol.* 62: 3003-3013.

Lieber A., He C.Y., Meuse L., Schowalter D., Kirillowa I., Winther B. and Kay M.A.; The role of Kupffer cell activation and viral gene expression in early liver toxicity after infusion of recombinant adenovirus vectors; 1997; *J. Virol.* 71: 8798-8807.

Lie-Injo L.E., Balasegaram M., Lopez C.G. and Herrera A.R.; Hepatitis B virus DNA in liver and white blood cells of patients with Hepatoma; 1983; *DNA* 2: 301-308.

Lin O.S. and Keeffe E.B.; Current treatment strategies for chronic hepatitis B and C; 2001; *Annu. Rev. Med.* 52: 29-49.

Liu Z.X., Govindarajan S., Okamoto S. and Dennert G.; NK cells cause liver injury and facilitate the induction of T cell-mediated immunity to a viral liver infection; 2000; *J. Immunol.* 164: 6480-6486.

Löffler-Mary H., Dumortier J., Klentsch-Zimmer C. and Prange R.; Hepatitis B virus assembly is sensitive to change in the cytosolic S loop of envelope proteins; *Virology* 270, 2000; 358-367.

Lohmann V., Korner F., Dobierzewska A. and Bartenschlager R.; Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line; 1999; *Science* 285: 110-113.

Lohrengel B., Lu M. and Roggendorf M.; Molecular cloning of the woodchuck cytokines: TNF- α , IFN- γ and IL6; 1998; *Immunogenetics* 47: 332-335.

Lu M., Lohrengel B., Hilken G., Kemper T. and Roggendorf M.; Woodchuck gamma interferon upregulates major histocompatibility complex class I transcription but is unable to deplete woodchuck hepatitis virus replication intermediates and RNAs in persistently infected woodchuck primary hepatocytes; 2002; *J. Virol.* 76: 58-67.

Luker G.D., Bardill J.P., Prior J.L., Pica C.M., Piwnica-Worms D., Leib D.A.; Noninvasive Bioluminescence imaging of herpes simplex virus type 1 infection and therapy in living mice; 2002; *J. Virol* 76:12149-12161.

Luster AD, Unkeless JC, Ravetch JV.; Gamma-interferon transcriptionally regulates an early-response gene containing homology to platelet proteins; 1985; *Nature* 315: 672-676.

Malleret G., Haditsch U., Genoux D., Jones M.W., Bliss T.V., Vanhose A.M., Weitlauf C., Kandel E.R., Winder D.G. and Mansuy I.M.; Inducible and reversible enhancement of learning, memory, and long-term potentiation by genetic inhibition of calcineurin; 2001; *Cell* 104: 675-686.

Mansuy I.M., Winder D.G., Moallem T.M., Osman M. Mayford M., Hawkins R.D. and Kanel E.R.; Inducible and reversible gene expression with the rtTA system for the study of memory; 1998; *Neuron* 21: 257-267.

Maran A., Maitra R.K., Kumar A., Dong B., Xiao W., Li G., Williams B.R., Torrence P.F. and Silverman R.H.; Blockage of NF-kappaB signaling by selective ablation of an mRNA target by 2-5A antisense chimeras; 1994; *Sciences* 265: 789-792.

Marinus MG, Morris NR; Isolation of deoxyribonucleic acid methylase mutants of *Escherichia coli* K-12; 1973; *J. Bacteriol.* 114: 1142-1150.

Marinus MG.; Location of DNA methylation genes on the *Escherichia coli* K-12 genetic map; 1973; *Mol. Gen. Genet.* 127:47-50.

Marion P.L., Oshiro L.S., Regnery D.C., Scullard G.H. and Robinson W.S.; A virus in Beechey ground squirrels that is related to hepatitis B virus of human; 1980; *P.N.A.S.* 77: 2941-2945.

Mary Ann Liebert, Inc.; Assessment of Adenoviral vector safety and toxicity: report of the National Institutes of Health recombinant DNA advisory committee; 2002; *Human Gene Therapy* 13:3-13.

Mason W.S., Seal G. and Summers J.; Virus of Pekin ducks with structural and biological relatedness to human hepatitis B virus; 1980; *J. Virol.* 36:829-836.

McClary H., Koch R., Chisari F.V. and Guidotti L.G.; Relative sensitivity of hepatitis B virus and other hepatotropic viruses to the antiviral effects of cytokines; 2000; *J. Virol.* 74: 2255-2264.

McCoy R.D., Davidson B.L., Roessler B.J., Huffnagle G.B., Janich S.L., Laing T.J. and Simon R.H.; Pulmonary inflammation induced by incomplete or inactivated adenoviral particles; 1995; *Hum. Gene Ther.* 6: 1553-1560.

McVey D., Zuber M., ETTYREDDY D., BROUGH D.E., and KOVESDI I.; Rapid construction of adenoviral vectors by Lambda phage genetics; 2002; *J. Virol.* 76: 3670-3677.

Michael M.L., Pontisso P., Sobczak E., Malpiece Y., Streeck R.E. and Tiollais P.; Synthesis in animal cells of hepatitis B surface particles carrying a receptor for polymerized human serum albumin; 1984; *P.N.A.S.* 81: 7708-7712.

Miralles VJ., Cortes P., Stone N. and Reinberg D.; The adenovirus inverted terminal repeat functions as an enhancer in a cell-free system; 1989; *J. Biol. Chem.* 264: 10763-10772.

Mittereder D.A., March G.A. and Trapnell B.C.; Evaluation of the concentration and bioactivity of adenovirus vectors for gene therapy; 1996; *J. Virol.* 70: 7498-7509.

Mizuguchi H. and Hayakawa T.; Characteristics of adenovirus-mediated tetracycline-controllable expression system; 2001; *Biochim. Biophys Acta*; 1568: 21-29.

Mizuguchi H. and Hayakawa T.; The tet-off system is more effective than the tet-on system for regulating transgene expression in a single adenovirus vector; 2002; *J. Gene Med.* 4: 240-247.

Molin M, Shoshan S., Öhman-Forslund K., Linder S and Akusjärvi G.; Two novel adenovirus vector systems permitting regulated protein expression in gene transfer experiments; 1998; *J. Virol.* 72: 8358-8361.

Muller M., Laxton C., Briscoe J., Schindler C., Improta T., Darnell J.E., Stark G.R. and Kerr I.M.; Complementation of a mutant cell line: central role of the 91 kDa polypeptide of ISGF3 in the interferon-alpha and -gamma signal transduction pathways; 1993; *EMBO J.* 12: 4221-4228.

Muruve D.A., Barnes M.J., Stillman I.E. and Liberman T.A.; Adenoviral gene therapy leads to rapid induction of multiple chemokines and acute neutrophil-dependent hepatic injury in vivo; 1999; *Hum. Gene Ther.* 10: 965-976.

Neurath A.R., Kent S.B., Strick N. and Parker K.; Identification and chemical synthesis of a host cell receptor binding site on hepatitis B virus; 1986; *Cell* 46: 429-436.

Otake K., Ennist D.L., Harrod K. and Trapnell B.C.; Nonspecific inflammation inhibits adenovirus-mediated pulmonary gene transfer and expression independent of specific acquired immune response; 1998; *Hum. Gene Ther.* 9: 2207-2222.

Pasquetto V., Wieland S.F., Uprichard S.L., Tripodi M. and Chisari F.V.; Cytokine-sensitive replication of Hepatitis B virus in immortalized mouse hepatocyte cultures; 2002; *J of Virol.* 76: 5646-5653.

Patterson J.B., Thomis D.C., Hans S.L. and Samuel C.E.; Mechanism of interferon action: double-stranded RNA-specific adenosine deaminase from human cells is inducible by alpha and gamma interferons; 1995; *Virology* 210: 508-511.

Pazzagli M, Devine JH, Peterson DO, Baldwin TO; Use of bacterial and firefly luciferases as reporter genes in DEAE-dextran-mediated transfection of mammalian cells; 1992; *Anal. Biochem.* 204: 315-323.

Peng Y., Falck-Persen E. and Elkon K.B.; Variation in adenovirus transgene expression between BALB/c and C57BL/6 mice is associated with differences in interleukin-12 and gamma interferon production and NK cell activation; 2001; *J. Virol.* 75: 4540-4550.

Perez N., Poupiot J., Gicquel E., Turbant S. and Danos O.; Performances of rAAV mediated tetracycline-dependent transgene expression into skeletal muscle compared to DNA electrotransfer; 2001; Poster 31 at the GVPN Conference, Évry, France.

Pitha P.M.; Interferon induction with insolubilized polynucleotides and their preparation; 1981; *Methods Enzymol.* 78: 236-242.

Prassolov A., Hohenberg H., Kalinina T., Schneider C., Cova L., Krone O., Fröhlich K., Will H. and Sirna H.; New hepatitis B virus of cranes that has an unexpected broad host range; 2003; *J. Virol.* 77: 1964-1976.

Prevec L, Schneider M, Rosenthal KL, Belbeck LW, Derbyshire JB, Graham FL; Use of human adenovirus-based vectors for antigen expression in animals; 1989; *J. Gen. Virol.* 70: 429-434.

Protzer U., Nassal M., Chiang P.-W., Kirschfink M. and Schaller H.; Interferon gene transfer by a hepatitis B virus vector efficiently suppresses wild-type virus infection; 1999; *PNAS* 96: 10818-10823.

Qian X., Samadani U., Porcella A. and Costa R.; Decreased expression of hepatocyte nuclear factor 3a during the acute-phase response influences transthyretin gene transcription; 1995; *Mol. Cell Biol.* 15: 1364-1376.

Qin X-Q., Beckham C., Brown J.L., Lukashev M. and Barsoum J.; Human and mouse IFN- β gene therapy exhibits different anti-tumor mechanisms in mouse models; 2001; *Mol. Ther.* 4: 356-364.

Rang A., Bruns M., Heise T. and Will H.; Antiviral activity of interferon- α against hepatitis B virus can be studied in non-hepatic cells and is dependent of MxA; 2002; *J. Biol. Chem.* 277: 7645-7647.

Rang A., Gunther S. and Will H.; Effect of interferon alpha on hepatitis B virus replication and gene expression in transiently transfected human hepatoma cells; 1999; *J. Hepatol.* 31: 791-799.

Ren S. and Nassal M.; Hepatitis B virus (HBV) virion and covalently closed circular DNA formation in primary Tupaia hepatocytes and human hepatoma cell lines upon HBV genome transduction with replication-defective adenovirus vectors; 2001; *J. Virol.* 75: 1104-1116.

Rincon M., Enslin H., Raingeaud J., Recht M., Zapton T., Su M.S., Penix L.A., Davis R.J. and Flavell R.A.; Interferon-gamma expression by Th1 effector T cells mediated by p38 MAP kinase signaling pathway; 1998; *EMBO* 17: 2817-2829.

Ritter T., Brandt C, Prosch S, Vergopoulos A, Vogt K., and Volk HD; Stimulatory and inhibitory action of cytokines on the regulation of hCMV-IE promoter activity in human endothelial cells; 2000; *Cytokine* 12: 1163-1170.

Robeck M.D., Wieland S. and Chisari F.V.; Inhibition of Hepatitis B virus replication by interferon requires proteasome activity; 2002; *J. Virol.* 76: 3570-3574.

Robertson B.H. and Margolis H.S.; Primate hepatitis B viruses- genetic diversity, geography and evolution; 2002; *Rev. Med. Virol.* 12: 133-141.

Romanno G., Pacilio C. and Giordano A.; DNA transfer technology in therapy: current applications and future goals; 1999; *Stem Cells* 17: 191-202.

Russel W.C.; Uptake on adenovirus and its vectors; 2000; *J. of General Virology* 81: 2573-2604.

Salmon P., Le Cottonnec J.Y., Galazka A., Abdul-Ahad A. and Darragh A.; Pharmacokinetics and pharmacodynamics of recombinant human interferon- β in healthy male volunteers; 1996; *J. Interferon Cytokine Res.* 16: 759-764.

Salucci V., Lu M., Aurisicchio L., La Monica N., Roggendorf M. and Palombo F.; Expression of a new woodchuck IFN-alpha gene by a helper-dependent adenoviral vector in woodchuck hepatitis virus-infected primary hepatocytes; 2002; *J. Interferon Cytokine Res.* 22: 1027-1034.

Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP and Bismuth H.; Liver transplantation in European patients with the hepatitis B surface antigen; *N Engl J Med* 1993; 329: 1842-1847.

Sawada N., Mochizuki G.-H. and Ishikawa T.; Active proliferation of mouse hepatocytes in primary culture under defined conditions as compared to rat hepatocytes; 1988; *Jpn. J. Cancer Res. (Gann)* 79: 983-988.

Schäfer S.T., Tolle T., Lottmann S. and Gerlich W.H.; Animal models and experimental systems in hepatitis B virus research; 1998; Imperial College Press, London, United Kingdom.

Schiedner G., Hertel S., Johnston M., Biermann V., Dries V., and Kochanek S.; Variables affecting in vivo performance of high-capacity adenovirus vectors; 2002; *J. Virol.* 76: 1600-1609.

Schnell M.A., Zhang Y., Tazelaar J., Gao G.P., Yu Q.C., Qian R., Chen S.J., Varnavski N., LeClair C., Raper S.E. and Wilson J.M.; Activation of innate immunity in nonhuman primates following intraportal administration of adenoviral vectors; 2001; *Mol. Ther.* 3: 708-722.

Schönig K., Schwenk F., Rajewsky K. and Bujard H.; Stringent doxycycline dependent control of CRE recombinase in vivo; 2002; *Nucleic Acids Res.* 30: E134.

Schowalter D.B., Himeda C.L., Winther B.L., Wilson C.B. and Kay M.A.; Implication of interfering antibody formation and apoptosis as two different mechanisms leading to variable duration of adenovirus-mediated transgene expression in immune-competent mice; 1999; *J. Virol.* 73: 4755-4766.

Schultz U. and Chisari F.V.; Recombinant duck interferon gamma inhibits duck hepatitis B virus replication in primary hepatocytes; 1999; *J. Virol.* 73: 3162-3168.

Schultz U., Köck J., Schlicht H.J. and Staeheli P.; Recombinant duck interferon: a new reagent for studying the mode of interferon action against hepatitis B virus; 1995; *Virology* 212: 641-649.

Seeger C., Summers J. and Mason W.S.; Viral DNA synthesis; 1991; *Curr. Top. Microbiol. Immunol.* 168: 41-60.

Sells A.M., Chen M.L. and Acs G.; Production of hepatitis B virus particles in HepG2 cells transfected with cloned hepatitis B virus DNA; 1987; *P.N.A.S.* 84, 1005-1009.

Sen GC, Ransohoff RM. Interferon-induced antiviral actions and their regulation. *Ad. Virus Res.* 1993; 42:57-102.

Shows, T. B.; Sakaguchi, A. Y.; Naylor, S. L.; Goeddel, D. V. and Lawn, R. M. ; Clustering of leukocyte and fibroblast interferon genes on human chromosome 9; 1982; *Science* 218: 373-374.

Silverman R.H.; Fascination with 2-5a-dependent RNase: a unique enzyme that functions in interferon action; 1994; *J. Interferon Res.* 14: 101-104.

Singh S.M., Yanagawa H., Hanibuchi M., Miki T., Okamura H. and Sone S.; Augmentation by interleukin-18 of MHC-nonrestricted killer activity of human peripheral blood mononuclear cells in response to interleukin-12; 2000; *Int. J. of Immunopharmacology* 22: 35-43.

Smith T.A., Mehaffey M.G., Kayda D.B., Saunders J.M., Yei S., Trapnell B.C., McClelland A., and Kaleko M.; Adenovirus mediated expression of therapeutic plasma levels of human factor IX in mice; 1993; *Nat. Genet.* 5:397-402.

Soejima K, Rollins BJ.; A functional IFN-gamma-inducible protein-10/CXCL10-specific receptor expressed by epithelial and endothelial cells that is neither CXCR3 nor glycosaminoglycan; 2001; *J. of Immunology* 167: 6576-6582.

Sprinzl M. F., Oberwinkler H., Schaller H., and Protzer U., 2001, Transfer of Hepatitis B Virus Genome by Adenovirus Vectors into Cultured Cells and Mice: Crossing the Species Barrier, *J. of Virology*, p.5108-5118.

Stark G.R., Kerr I.M., Williams B.R., Silverman R.H. and Schreiber R.D.; How cells respond to interferons; 1998; *Annu. Rev. Biochem.* 67: 227-264.

Stebbins M.J., Urlinger S., Byrne G., Bello B., Hill W. and Yin J.C.P.; Tetracycline-inducible system for *Drosophila*; 2001; *P.N.A.S.* 98: 10775-10780.

Steinwaerder DS and Lieber A.; Insulation from viral transcriptional regulatory elements improves inducible transgene expression from adenovirus vectors in vitro and in vivo; 2000; *Gene Ther.* 7: 556-567.

Summers J., Smolec J.M., and Snyder R.; A virus similar to human hepatitis B virus associated with hepatitis and hepatoma in woodchucks; 1978; *P.N.A.S.* 75: 4533-4537.

Sung V.M.-H. and Lai M.M.C.; Murine retroviral pseudotype virus containing hepatitis B virus large and small surface antigens confers specific tropism for primary human hepatocytes: a potential liver-specific targeting system; 2002; *J. Virol.* 76: 912-917.

Sureau C., Romet-Lemonne J.L., Mullins J.I. and Essex M.; Production of hepatitis B virus by a differentiated human hepatoma cell line after transfection with cloned circular HBV DNA; 1986; *Cell* 47: 37-47.

Takahashi H., Fujimoto J., Hanada S. and Isselbacher K.J.; Acute hepatitis in rats expressing human hepatitis B virus transgenes; 1995; *P.N.A.S.* 92: 1470-1474.

Talbot D., Descombes P. and Schibler U.; The 5' flanking region of the rat LAP (C/EBP beta) gene can direct high-level, position-independent, copy number-dependent expression in multiple tissues in transgenic mice; 1994; *Nucleic Acids Res.* 22: 756-766.

Tang H. and McLachlan A.; Mechanisms of inhibition of nuclear hormone receptor-dependent hepatitis B virus replication by hepatocyte nuclear factor 3b; 2002; *J. Virol.* 76: 8572-8581.

Tao N., Gao G.P., Parr M., Johnson J., Baradet T., Wilson J.M., Barsoum J. and Fawell S.E.; Sequestration of adenoviral vector by Kupffer cells leads to a nonlinear dose response of transduction in liver; 2001; *Mol. Ther.* 3: 28-35.

Taub DD, Lloyd AR, Conlon K, Wang JM, Ortaldo JR, Harada A, Matsushima K, Kelvin DJ, Oppenheim JJ.; Recombinant human interferon-inducible protein 10 is a chemoattractant for human monocytes and T lymphocytes and promotes T cell adhesion to endothelial cells; 1993; *J. Exp. Med.* 177: 1809-1814.

Terrault NA.; Hepatitis B virus and liver transplantation. In: Lee WM, Gitlin N, Eds. *Clinics in Liver Disease* Vol. 3. Philadelphia: Saunders, 1999; 389-415.

Triezenberg SJ, Kingsbury RC, McKnight SL.; Functional dissection of VP16, the transactivator of herpes simplex virus immediate early gene expression; 1988; *Genes Dev.* 2: 718-729.

Tsui L.V., Guidotti L.G., Ishikawa T. and Chisari F.V.; Posttranscriptional Clearance of Hepatitis B Virus RNA by Cytotoxic T Lymphocyte-Activated Hepatocytes; 1995; P.N.A.S. 92: 12398-12402.

Tuttleman J.S., Pourcel C. and Summer J.; Formation of the pool of covalently closed circular viral DNA in hepadnavirus-infected cells; 1986; Cell 47: 451-460.

Ueda K., Tsurimoto T. and Matsubara K.; Three envelope proteins of hepatitis B virus: large S, middle S, and major S proteins needed for the formation of Dane particles; 1991; J. Virol. 65 : 3521-3529.

Urlinger S., Baron U., Thellmann M., Hasan M., Bujard H. and Hillen W.; Exploring the sequence space for tetracycline-dependent transcriptional activators: novel mutations yield expanded range and sensitivity; 2000; P.N.A.S. 97: 7963-7968.

Vlachaki MT, Hernandez-Garcia A., Ittmann M., Chhikara M., Aguilar LK, Zhu X., The BS., Butler EB, Woos S. Thompson TC, Barrera-Saldana H. and Aguilar-Cordova E.; Impact of preimmunization on adenoviral vector expression and toxicity in a subcutaneous mouse cancer model; 2002; Mol. Therapy 6: 342-348.

Wang GH. and Seeger C.; The reverse transcriptase of hepatitis B virus acts as a protein primer for viral DNA synthesis; 1992; Cell 71: 663-670.

Watanabe Y. and Kawade Y.; Induction, production and purification of natural mouse IFN- α and - β ; 1987; p. 1-14. In M.J. Clemens, A.G. Morris and A.J.H. Gearing (ed.), Lymphokines and interferons: a practical approach. IRL Press, Oxford, England.

Weber O., Schlemmer KH., Hartmann E., Hagelschuer I, Paessens A, Graef E, Deres K, Goldmann S, Niewoehner U, Stoltefuss J, Haebich D, Ruebsamen-Waigman H and Wolhfeil S.; Inhibition of human hepatitis B virus (HBV) by a novel non-nucleosidic compound in a transgenic mouse model; 2002; Antiviral Res. 54: 69-78.

Wickham T.J., Mathias P., Cheres D.A., Nemerow GR; Integrin alpha v beta 3 and alpha v beta 5 promote adenovirus internalization but not virus attachment; 1993; Cell 73: 309-319.

Wieland S., Guidotti L.G. and Chisari F.V.; Intrahepatic induction of alpha/beta interferon eliminates viral RNA-containing capsids in hepatitis B virus transgenic mice; 2000; J. Virol. 74: 4165-4173.

Will H., Cattaneo R., Darai G., Deinhardt F., Schellekens H. and Schaller H.; Infectious hepatitis B virus from cloned DNA of know nucleotide sequence; 1985; P.N.A.S. 82: 891-895.

Wimmel A., Lucibello F.C., Sewing A., Adolph S. and Muller R.; Inducible acceleration of G1 progression through tetracycline-regulated expression of human cyclin E; 1994; Oncogene 9: 995-997.

Wood K.V.; Marker proteins for gene expression; 1995; Curr. Opin. Biotech. 6: 50-58.

Wu J.C., Merlino G. and Fausto N.; Establishment and characterization of differentiated, nontransformed hepatocyte cell lines derived from mice transgenic for transforming growth factor α ; 1993; P.N.A.S. 91: 674-678.

Wu J.C., Sundaresan G., Meera I. and Gambhir S.S.; Noninvasive optical imaging of firefly luciferase reporter gene expression in skeletal muscles of living mice; 2001; Mol. Therapy 4: 297-306.

Yang Y., Ertl H.C. and Wilson J.M.; MHC class I-restricted cytotoxic T lymphocytes to viral antigens destroy hepatocytes in mice infected with E1-deleted recombinant adenoviruses; 1994; Immunity 1: 433-442.

Yang Y., Li Q., Ertl H.C., and Wilson J.M.; Cellular and humoral immune responses to viral antigens create barriers to lung-directed gene therapy with recombinant adenoviruses; 1995; J. Virol. 69: 2004-2015.

Yang Y.-L., Reis L.F.L., Pavlovic J., Aguzzi A., Schafer R., Kumar A., Williams B.R.G., Aguet M. and Weissmann C.; Deficient signaling in mice devoid of double-stranded RNA-dependent protein kinase, PKR; EMBO 14: 6095-6106.

Yin DX, Zhu L and Schimke RT; Tetracycline-controlled gene expression system achieves high-level and quantitative control of gene expression; 1996; Anal Biochem 235: 195-201.

Zaiss A-K., Liu Q., Bowen G.P., Wong N.C.W., Barlett J.S. and Muruve D.A.; Differential activation of innate immune responses by adenovirus and adeno-associated virus vectors; 2002; J. Virol. 76: 4580-4590.

Zdanov A., Schalk-Hihi C., Menon S., Moore K.W. and Wlodawer A.; Crystal structure of Epstein-Barr virus protein BCRF1, a homolog of cellular interleukin-10; 1997; J. Mol. Biol. 268: 460-467.

Zoulim F., Saputelli J., and Seeger C.; Woodchuck hepatitis virus X protein is required for viral infection in vivo; 1994; J. Virol. 68: 2026-2030.

6.3- Curriculum vitae

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Education

2000-2003 **Ph.D program**
Center for Molecular Biology Heidelberg (ZMBH),
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1998-1999 **Diploma thesis**
Molecular Genetics, Virology
Institute for Med. Microbiology and Hygiene,
Prof. Dr. R. E. Streeck and Prof. Dr. R. Prange
University of Mainz (Germany)

1994-1997 **M.Sc. (Diplomprüfung) in Biology**
Microbiology, Molecular Genetics, Plant Biology and Computer programming
University of Mainz (Germany)

1990 **B.Sc. (D.U.T.), Applied Biology,**
Food industry and Biochemistry
Institute for Technology (I.U.T.)
University of Caen (France)

1988 **High School Diploma (Baccalauréat)**
mathematics and natural sciences
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Professional Experiences

- 2001-2003 **Research Worker**
 Institute for Hygiene, Department of Virology,
 University of Heidelberg (Germany)
 Prof. Dr. med. H.G. Kräusslich and PD Dr. med. U. Protzer
work: completion of research work for my thesis
- 1999-2001 **Research Worker**
 ZMBH,
 University of Heidelberg (Germany),
 Prof. Dr. H. Schaller and PD Dr. med. U. Protzer
work: research work for my thesis
- 1999 **Research Worker**
 Department of laboratory Medicine, Transfusion Research Program,
 University of California San Francisco (USA),
 Prof. G.N. Vyas
work: cloning of full-length genome of HBV variant extracted from
 serum of seroconverted Alaska patients (2 months)
- 1999 **Research Worker**
 Institute for Med. Microbiology and Hygiene,
 University of Mainz (Germany)
 Prof. Dr. R. E. Streeck and Prof. Dr. R. Prange
work: mutagenesis on the cytosolic loop of the S protein and effects on
 the assembly of Hepatitis B virus.
- 1999 **Transfusionszentrale**
 Johannes-Gutenberg Klinikum Mainz (Germany)
 student work at the laboratory for control, preparation and management
 of blood-donations in hospital
- 1994-1996 **SuCrest GmbH**,
 Hochheim/M (Germany)
 student work in the Research and Development laboratory
 Continuation of '90-'92 position on a part-time basis
- 1992-1994 **General Office Worker**
Union Laitière Normande Milchprodukte Germany GmbH,
 Bad Soden a. Ts. (Germany)
 In connection with civil service, worked for a major french exporter of
 dairy products in their office near Frankfurt, Germany
job position: contact with clients, place orders and resolve problems of
 transport and quality in cooperation with the marketing division of Paris
- 1990-1992 **Food Production Technician**
SuCrest GmbH, Hochheim/M (Germany)
 Work in Research and Development laboratory
 Production of new cream coatings, caramels and for the chocolate and
 confectionery industry. Manager: Mr. W. Schmedes
- 1990 **Analytical Institute of the cities Wuppertal and Solingen** (Germany),
 Practical course (2 months): inspection of norms of food quality and
 packaging in stores, analysis of soil and air samples.
- 1990 **Würzburger Hofbräu AG**, Würzburg (Germany),
 Practical course with report (2 months): production of beer and control of
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Publications

Jérôme Dumortier, Kai Schönig, Hermann Bujard and Ulrike Protzer; The Tet-system allows tight control and liver-specific gene expression *in vivo* following adenoviral gene transfer into mice; 2003; Mol. Therapy; (manuscript submitted).

M. Sprinzl, **J. Dumortier** and U. Protzer; Construction of recombinant adenoviruses that produce infectious HBV; 2003; R. Hamatke, J. Lau (eds.). Methods in Molecular Medicine. „Hepatitis B Virus Protocols“. The Human Press Inc., Totowa NJ; (in press).

Jérôme Dumortier, Andreas Limmer, Heike Oberwinkler and Ulrike Protzer; Cytokine Gene Therapy For Chronic Hepatitis B: Establishment in HBV Transgenic mice; 2002; Poster at the International Meeting for molecular Biology of Hepatitis B Viruses, Asilomar, California, USA.

Jérôme Dumortier, Kai Schönig, Hermann Bujard and Ulrike Protzer; Liver-specific and regulable gene expression following adenoviral gene transfer; 2002; Poster at the Conference for the germane society for Virology (GFV), Erlangen, Germany.

Jérôme Dumortier, Heike Oberwinkler, Andreas Limmer and Ulrike Protzer; Adenoviral Gene Transfer Of Cytokine Gene As Therapy To Repress Hepatitis B Virus Replication; 2001; Poster at the Gene Vector Production Network Conference (GVPN), Evry, France.

Dumortier J., Ritter Th., Sprinzl M., Schaller H. and Protzer U.; Expression of Interferon Type I and II following Adenoviral Gene Transfer Inhibits Hepatitis B Virus Replication; 2001; Poster at the Conference for the germane society for Virology (GFV), Dresden, Germany.

Jérôme Dumortier, Heike Oberwinkler, Thomas Ritter, Andreas Limmer, Heinz Schaller and Ulrike Protzer; Expression of Interferon Gamma After Adenoviral Gene Transfer Inhibits HBV Replication; 2000; Poster at the International Meeting for molecular Biology of Hepatitis B Viruses, Paris, France.

Heike Löffler-Mary, **Jérôme Dumortier**, Carola Klentsch-Zimmer and Reinhild Prange; Hepatitis B Virus Assembly Is Sensitive to Changes in the Cytosolic S Loop of the Envelope Proteins; 2000; Virology 270: 358-367.

Jérôme Dumortier; Untersuchung der intermolekularen Wechselwirkung zwischen dem kleinen Hüllprotein und dem Nukleokapsid bei der Morphogenese des Hepatitis B-Virus; 1999; Diploma thesis, Johannes-Gutenberg University of Mainz.

C. Hartmann-Stühler, C.E. Lambert, A. Peichl, H. Löffler-Mary, **J. Dumortier**, M. Werr and R. Prange; Hepatitis B Virus morphogenesis: Structure requirements of the envelope proteins; 1999; Recent Res. Devel. Virol., 1: 251-268.

6.4- Acknowledgement / Remerciement

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My hearty thanks go to PD Dr. med. Ulrike Protzer, the co-supervisor of this work, who introduced me into the practical aspects of adenovirus production and experiments with mice. Despite being very busy with her medical work in the diagnostic department, the preparation of her habilitation and her family, she still took time to support and advice me continuously in my work.

I also wish thank Prof. Dr. med. Hans-Georg Kräusslich for accepting to incorporate me into his Department thereby giving me the opportunity to continue the second part of this work in the new facilities of the Heidelberg Virology Department.

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I hereby confirm that this thesis entitled: “ Cytokine gene transfer by adenoviral vectors as a novel therapeutic option for hepatitis B virus infection” was entirely carried out by me and that all the materials used have been cited accordingly. This work has not been submitted to any other university.

Heidelberg, 10th February 2003

Jérôme Dumortier

Jérôme's spirit for

Science



Sport



the flying triplet

from research group for HBV



Heidelbergman triathlon
2000: 8. position
2001: 5. position
2002: 2. position

