« ATRESIA DE LAS VIAS BILIARES: ASPECTOS INMUNOLOGICOS »

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Pour l'amour des enfants

Université de Montréal

Patients With Biliary Atresia Have Elevated Direct/ Conjugated Bilirubin Levels Shortly After Birth

AUTHORS: Sanjiv Harpavat, MD, PhD,[a] Milton J. Finego MD,[b] and Saul J. Karpen, MD, PhD[a]

[a]Division of Gastroenterology, Hepatology, and Nutrition,

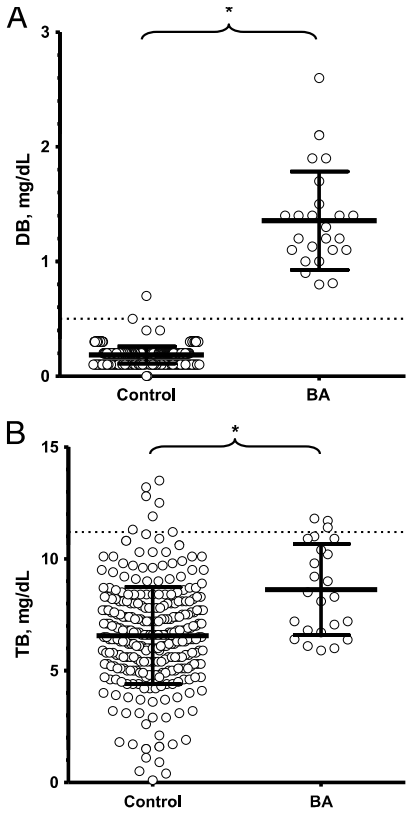


FIGURE 3

COMIENZO DE LA DESTRUCCION DE LA VIA BILIAR EN UTERO

Aetiology of biliary atresia: what is actually known?

Petersen and Davenport *Orphanet Journal of Rare Diseases* 2013, **8**:128
http://www.ojrd.com/content/8/1/128

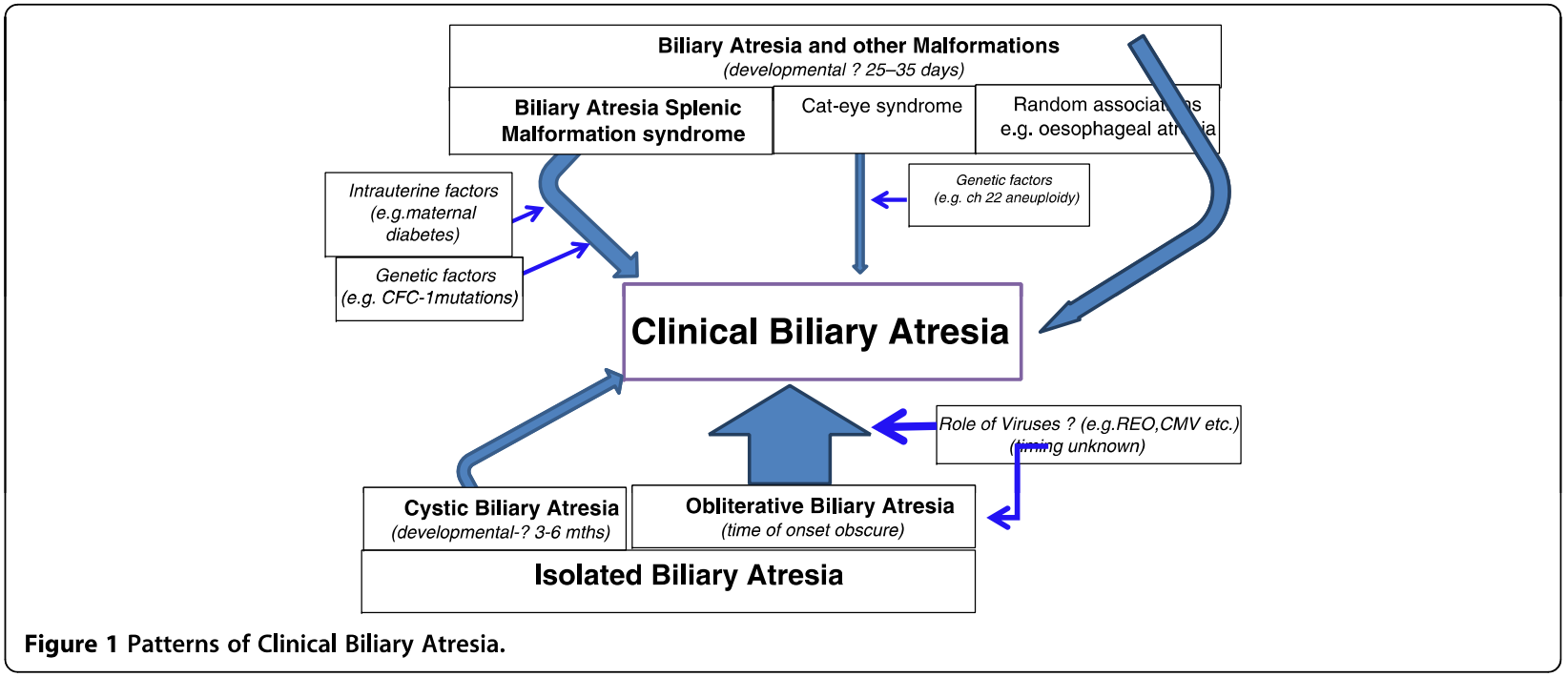
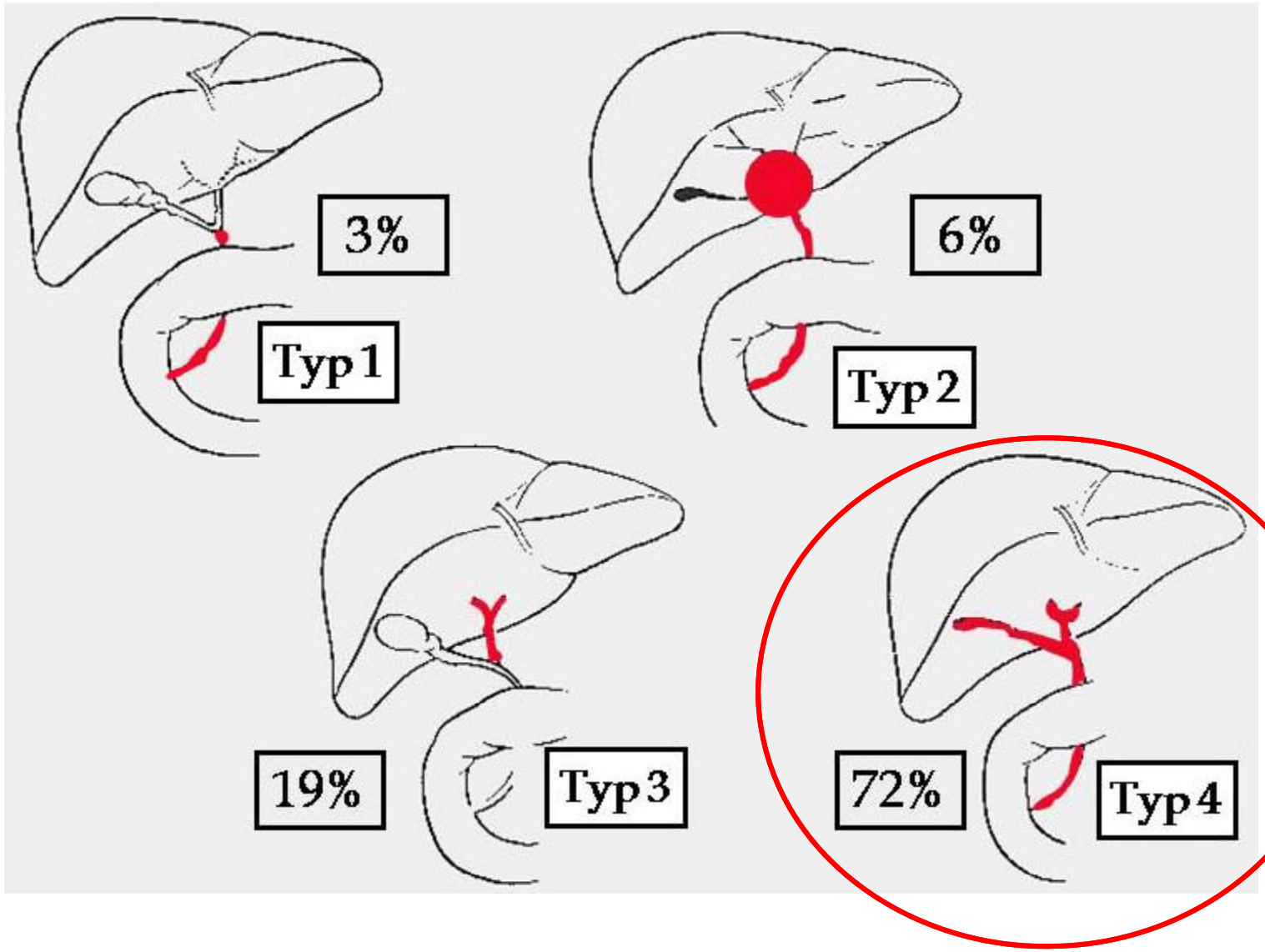


Figure 1 Patterns of Clinical Biliary Atresia.

ATRESIA DE LAS VIAS BILIARES



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Incidence of hepatotropic viruses in biliary atresia

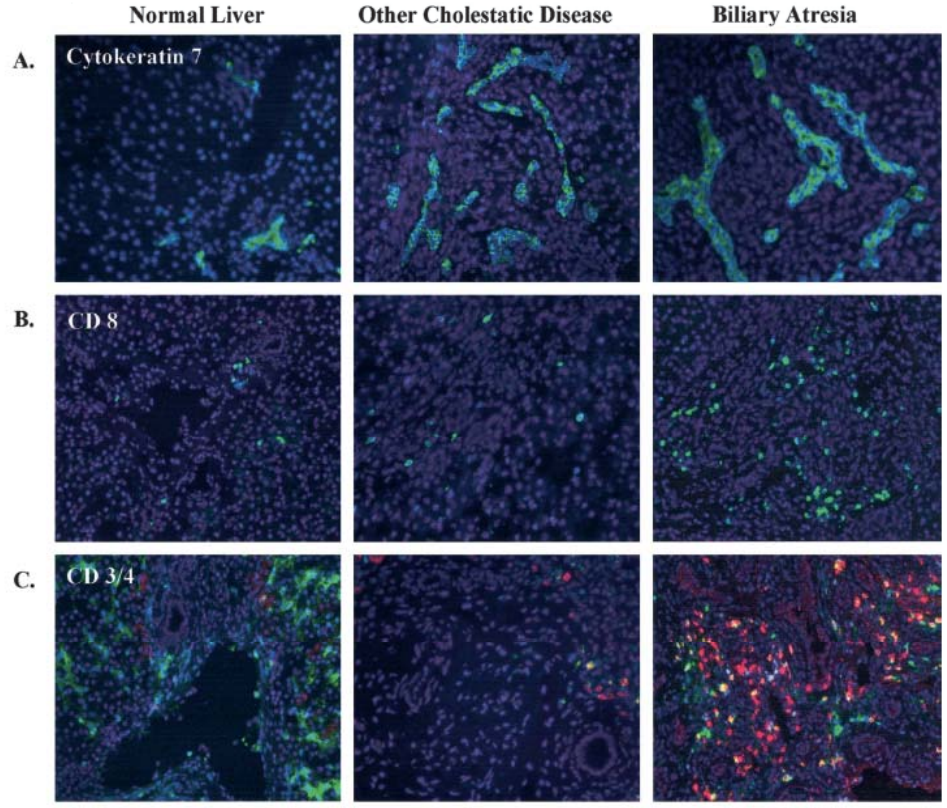
Stefan Rauschenfels · Miriam Krassmann · Ahmed N. Al-Masri · Willem Verhagen · Johannes Leonhardt · Joachim F. Kuebler · Claus Petersen

Rauschenfels et al. (present study)	2007	74	CMV	real-time PCR	8/74
		74	EBV	real-time PCR	0/74
		74	HSV	real-time PCR	0/74
		74	VZV	real-time PCR	0/74
		74	Parvo B19	real-time PCR	0/74
		74	Adenovirus	real-time PCR	1/74
		74	HPV	real-time PCR	0/74
		64	Reovirus	nested RT-PCR	21/64
		64	Coxsackie B4	nested RT-PCR	0/64
		64	Echovirus	nested RT-PCR	0/64
		64	Enterovirus 68/ 69	nested RT-PCR	1/64

ATRESIA DE LAS VIAS BILIARES

Biliary Atresia Is Associated with CD4$^+$ Th1 Cell–Mediated Portal Tract Inflammation

CARA L. MACK, REBECCA M. TUCKER, RONALD J. SOKOL, FREDERICK M. KARRER, BRIAN L. KOTZIN, PETER F. WHITINGTON, AND STEPHEN D. MILLER



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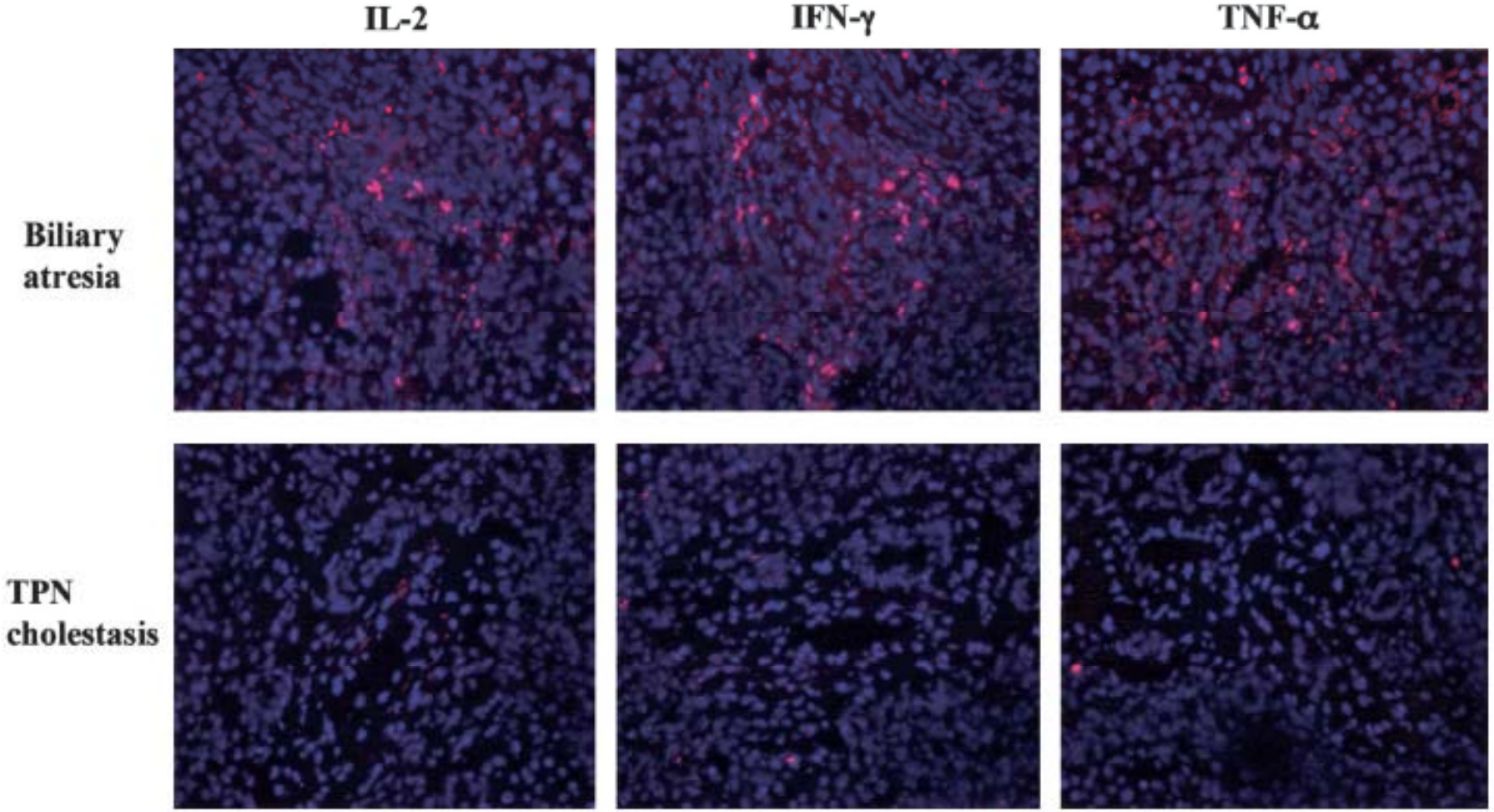
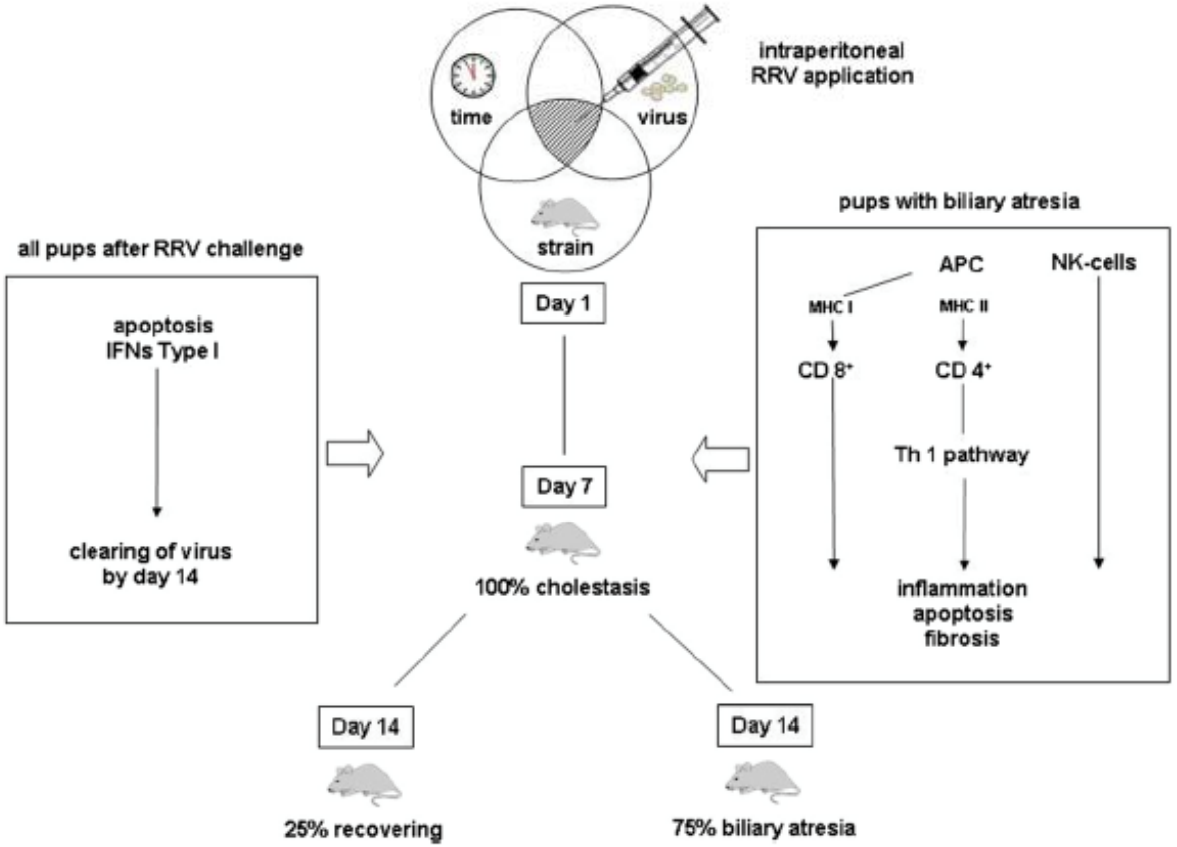


ATRESIE DES VOIES BILIAIRES-FORMES KYSTIQUES

Table 1 Characteristics of 3 children who had a choledochal cyst and biliary atresia and their outcomes at 5 years

Demographics			
Patient (gender)	1 (female)	2 (female)	3 (female)
Ethnicity	Caucasian	Caucasian	Caucasian
Presentation			
Choledochal cyst seen by ultrasound	In utero	In utero	8 weeks
Onset of jaundice	At birth	At birth	At birth
Birth weight (g) (percentile)	3,370 (50)	3,680 (75)	3,320 (43)
Age at Kasai (days)	13	11	60
5-year follow-up data			
Total bilirubin (g/dL)	0.3	0.6	0.2
Albumin (g/dL)	4.3	4.5	4.0
Weight (kg) (percentile)	20.9 (83)	21 (83)	22.2 (85)

ATRESIA DE LAS VIAS BILIARES
MODELO ANIMAL



ATRESIA DE LAS VIAS BILIARES

Group A Rotaviruses Produce Extrahepatic Biliary Obstruction in Orally Inoculated Newborn Mice

MARIE RIEPENHOFF-TALTY, KNUT SCHAEKEL, H. FRED CLARK, WOLFGANG MUELLER, INGRID UHNOO, THOMAS ROSSI, JOHN FISHER, AND PEARAY L. OGRA

Table 1. *Hepatobiliary disease after oral inoculation of neonatal BALB/c mice with different strains of rotavirus*

Virus strain	Titer/dose (pfu)	*n*	Clinical disease		Mortality	
			n	%	*n*	%
HCR-3	1.1×10^9	38	9*	24	5	13
RRV	1×10^9	62	26†	42	11	21
WI-78	4×10^8	23	0	0	0	0
Control		6	0	0	0	0

* Four of nine mice had severe disease: icterus, stunting, acholic stools, marked bilirubinuria, and oily hair effect; five of nine had mild clinical symptoms and no oily hair effect or stunting and had minimal bilirubinuria.

ATRESIA DE LAS VIAS BILIARES

New Aspects in a Murine Model for Extrahepatic Biliary Atresia

By C. Petersen, D. Biermanns, M. Kuske, K. Schäkel, L. Meyer-Junghänel, and H. Mildenberger
Hannover, Germany

NEW MURINE MODEL FOR BILIARY ATRESIA

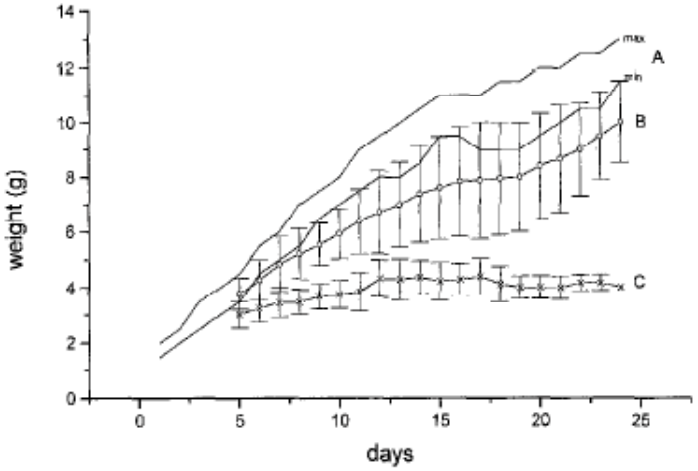


Fig 1. (A) Weight curves of 18 healthy newborn Balb/c mice. (C) Average increase in weight of infected mice with persisting symptoms and letal outcome, n = 62. (B) Spontaneous recovery, n = 10.

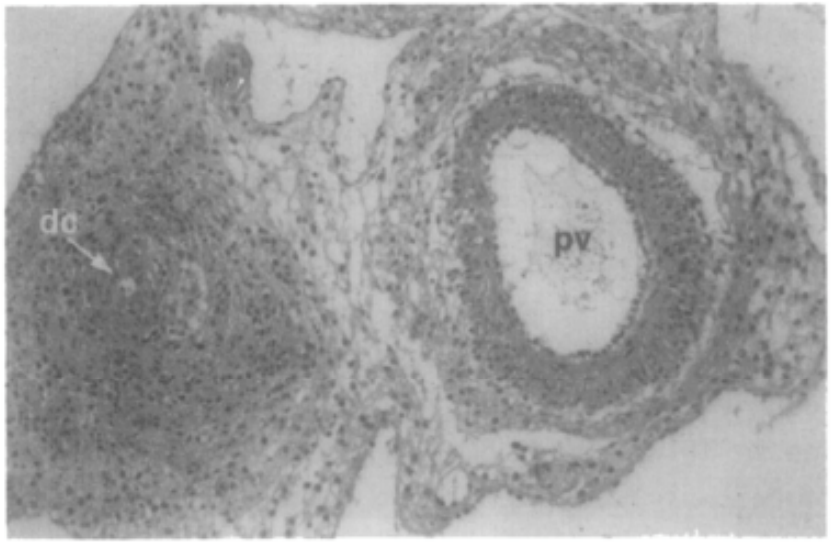


Fig 3. Nine-day-old mouse. Hepatoduodenal ligament; severe inflammation of the ductus choledochus (dc) with luminal narrowing. pv, portal vein. (H&E, original magnification ×250).

Aetiology of biliary atresia: what is actually known?

Claus Petersen[1*] and Mark Davenport[2]

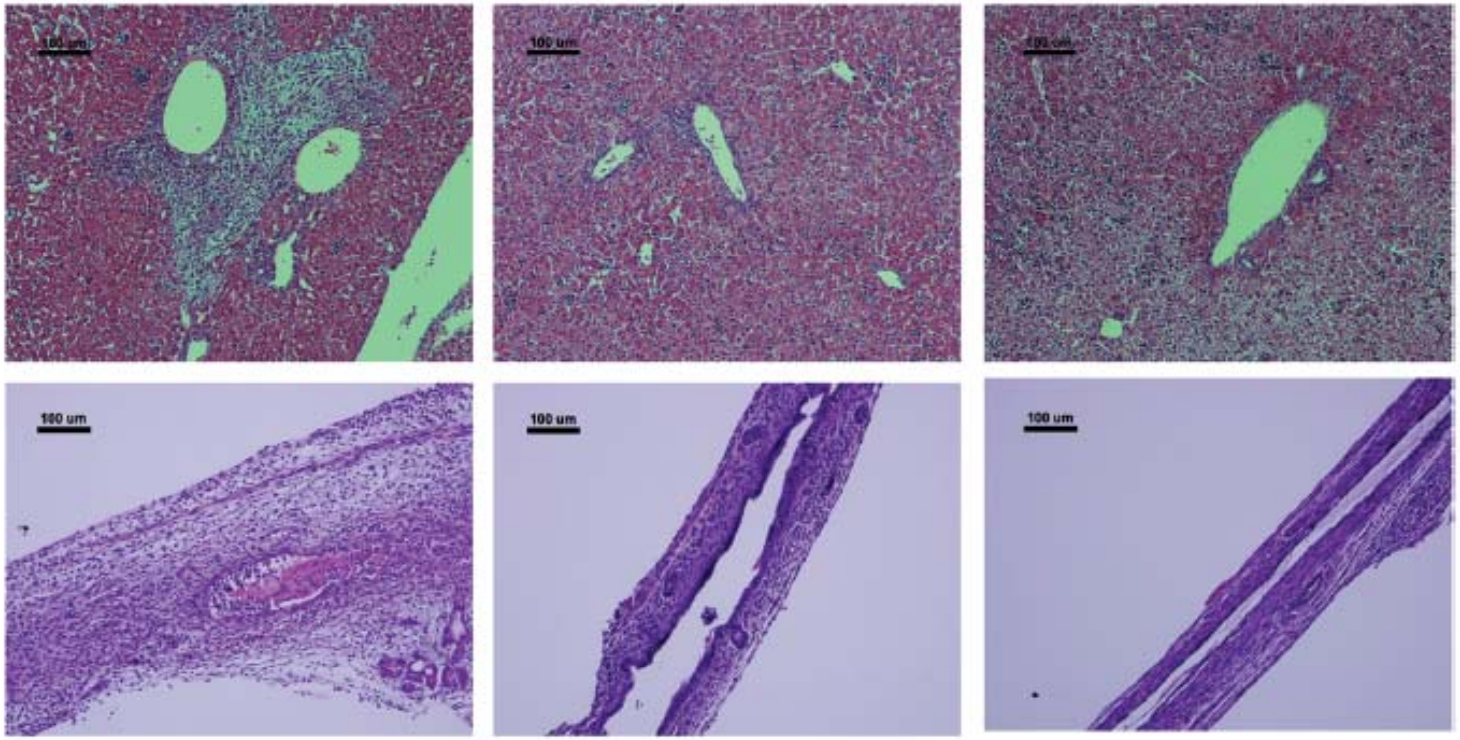
Table 1 The incidence of virally induced cholestasis and biliary atresia depends on three variable parameters, mouse strain, time (hours post partum) and dosage of Rhesus rotavirus application

Variable parameter	Cholestasis	Biliary atresia
Mouse strain		
Balb/c [55, 71]	67%-85%	67%-91%
CD [59]	33%	46%
NMRI [59]	19%	50%
C57Bl6 [67]	13%	100%
Balb/c-IFN-γ-/- [65]	90%-100%	20%
Balb/c-TNF-α-/- [68]	No data	86%
Balb/c-Mx + -A2G [71]	65%	65%
WT 129 [70]	30%	50%
A 129 IFN-α/β receptor-/- [70]	79%	96%
G 129 IFN-γ receptor-/- [70]	39%	86%
AG 129 IFN-α/β/ γ receptor-/- [70]	70%	96%
Age at infection		
12-24 hours [65, 83]	80%-86%	90%-100%
24-48 hours [55]	61%-85%	69%-91%
48-72 hours [52, 53]	13%-42%	0-17%
Infective dose		
10^{7*} pfu [62]	100%	100%
10^{6} pfu [62]	86%	100%
10^{5} pfu [62]	38%	100%
10^{4} pfu [62]	0	0

ATRESIA DE LAS VIAS BILIARES

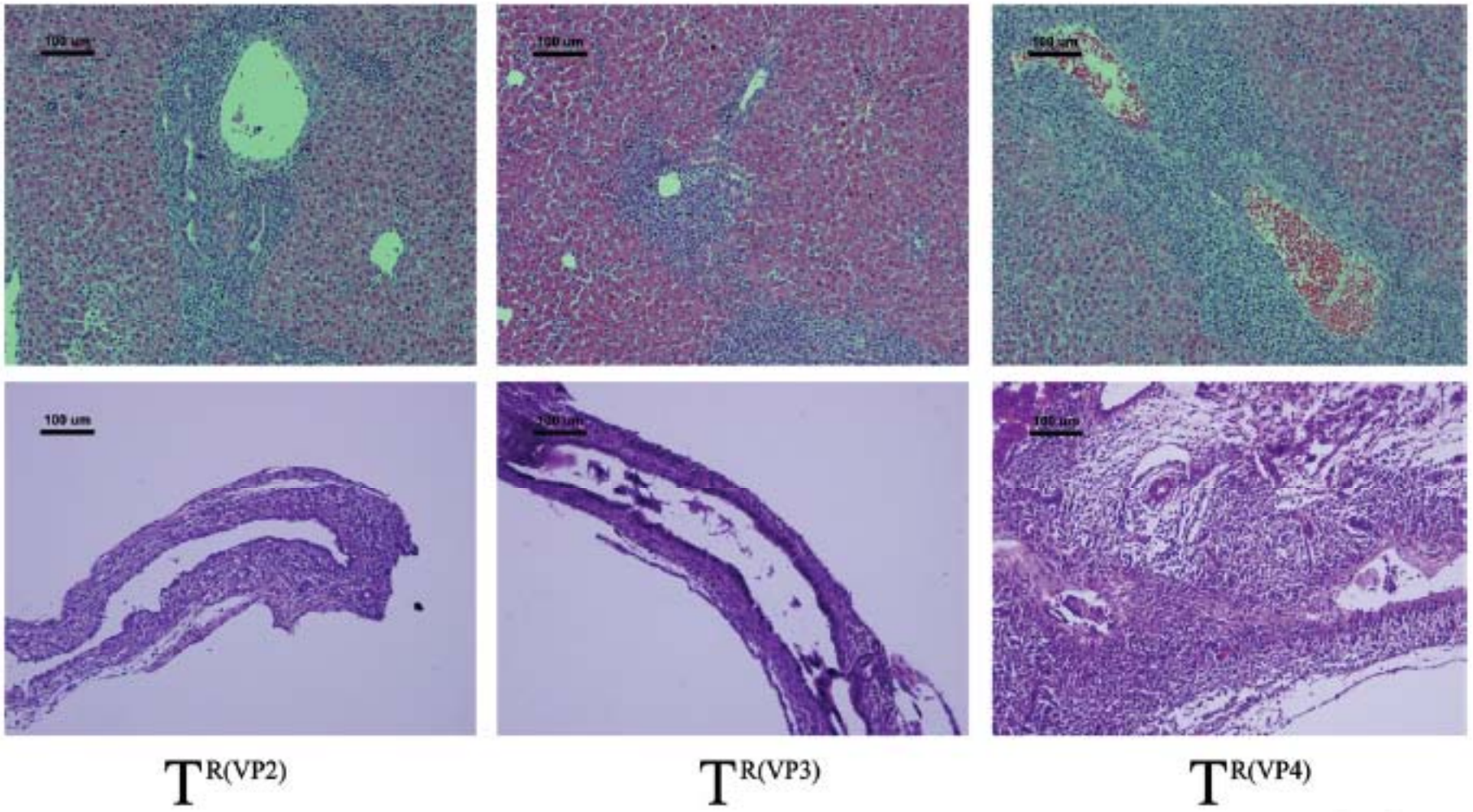
The Rhesus Rotavirus Gene Encoding VP4 Is a Major Determinant in the Pathogenesis of Biliary Atresia in Newborn Mice

Wei Wang, Bryan Donnelly, Alexander Bondoc, Sujit K. Mohanty, Monica McNeal, Richard Ward, Karol Sestak, Shan Zheng and Greg Tiao
J. Virol. 2011, 85(17):9069. DOI: 10.1128/JVI.02436-10.
Published Ahead of Print 22 June 2011.



RRV TUCH Saline

ATRESIA DE LAS VIAS BILIARES



Respuesta immune

- Tipos de respuesta immune:

»**INNATA**

»**ADAPTATIVA**

ATRESIA DE LAS VIAS BILIARES

Neonatal NK cells target the mouse duct epithelium via Nkg2d and drive tissue-specific injury in experimental biliary atresia

Pranavkumar Shivakumar, Gregg E. Sabla, [...], and Jorge A. Bezerra

Table 1

Incidence of obstruction of extrahepatic bile ducts

Experimental group	No. of mice	Obstruction (%)
Saline	10	0/10 (0%)
Saline, control serum	10	0/10 (0%)
RRV	16	16/16 (100%)
RRV, anti-NK serum, day 1[A]	25	0/25 (0%)
RRV, anti-NK serum, day 5[A]	9	6/9 (67%)
RRV, anti-NK serum, day 7[A]	10	10/10 (100%)

Results are derived from the examination of the entire duct length (from gallbladder to site of duct insertion into duodenum) using longitudinal sections stained with H&E. RRV or saline was injected i.p. on the first day of life of BALB/c mice, and ducts were harvested 12–14 days later. Control or anti-NK serum was administered daily through day 12. [A]First day of injection of anti-NK serum in relation to the time of RRV injection.

Respuesta immune

- Tipos de respuesta immune:

»**INNATA**

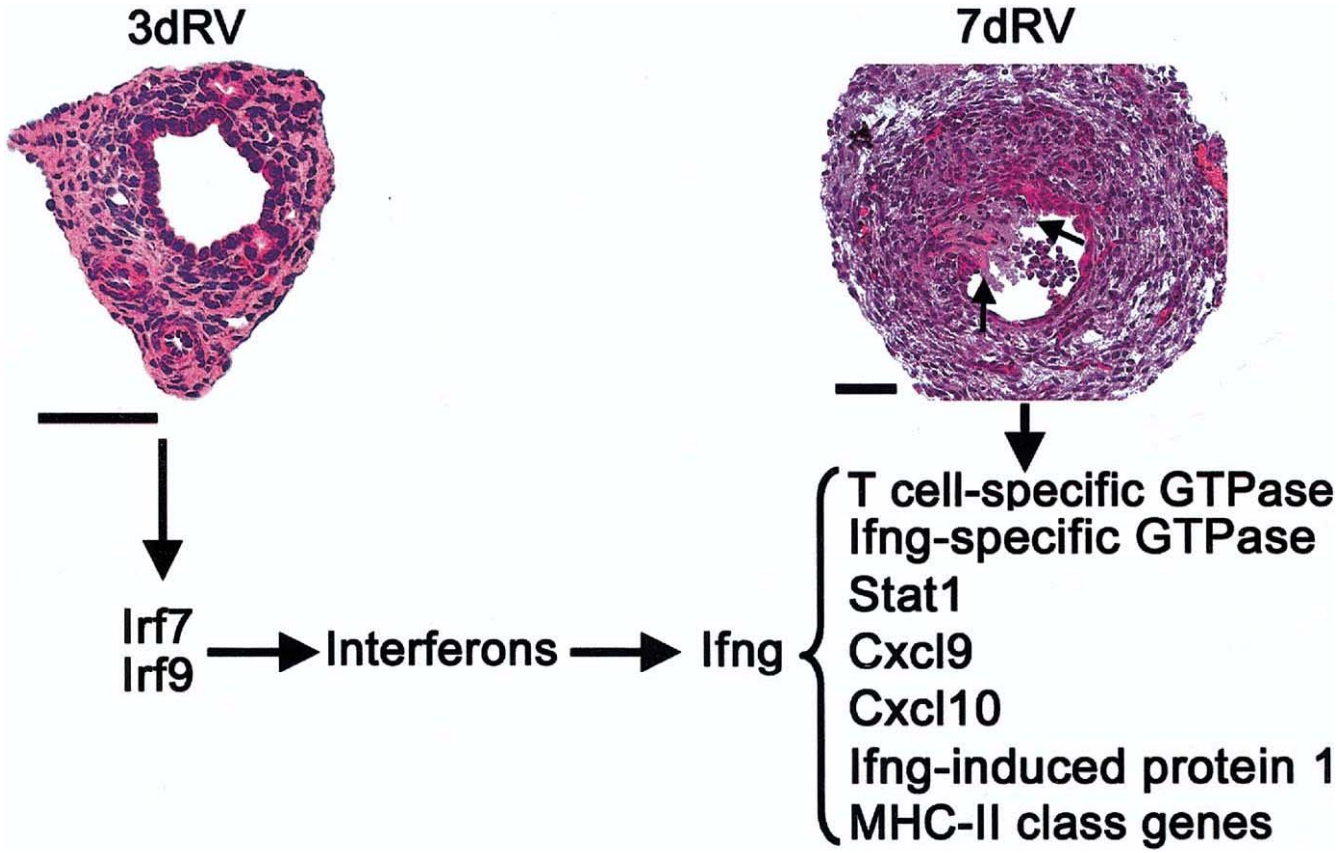
»**ADAPTATIVA**

MICROARRAYS AND OTHER NEW TECHNOLOGIES

Analysis of the Biliary Transcriptome in Experimental Biliary Atresia

ELISA CARVALHO, CONG LIU, PRANAVKUMAR SHIVAKUMAR, GREGG SABLA, BRUCE ARONOW, and JORGE A. BEZERRA

Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio

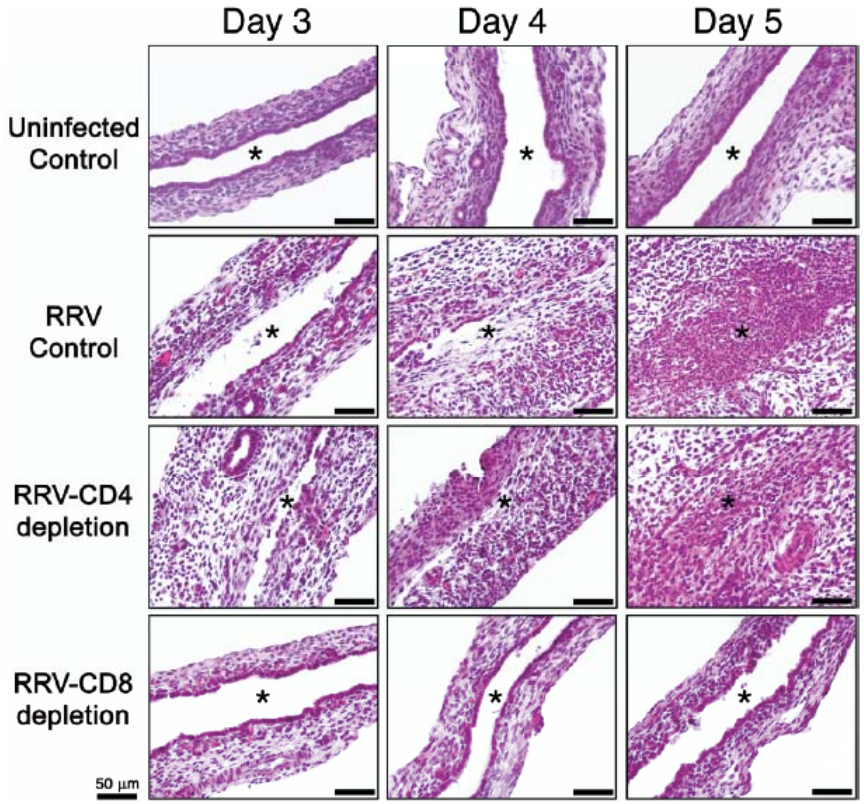


ATRESIA DE LAS VIAS BILIARES

Effector Role of Neonatal Hepatic CD8⁺ Lymphocytes in Epithelial Injury and Autoimmunity in Experimental Biliary Atresia

PRANAVKUMAR SHIVAKUMAR, GREGG SABLA, SUJIT MOHANTY, MONICA McNEAL, RICHARD WARD, KEITH STRINGER, CHARLES CALDWELL, CLAIRE CHOUGNET, and JORGE A. BEZERRA

Cincinnati Children's Hospital Medical Center and the Department of Pediatrics and Surgery at the University of Cincinnati College of Medicine, Cincinnati, Ohio



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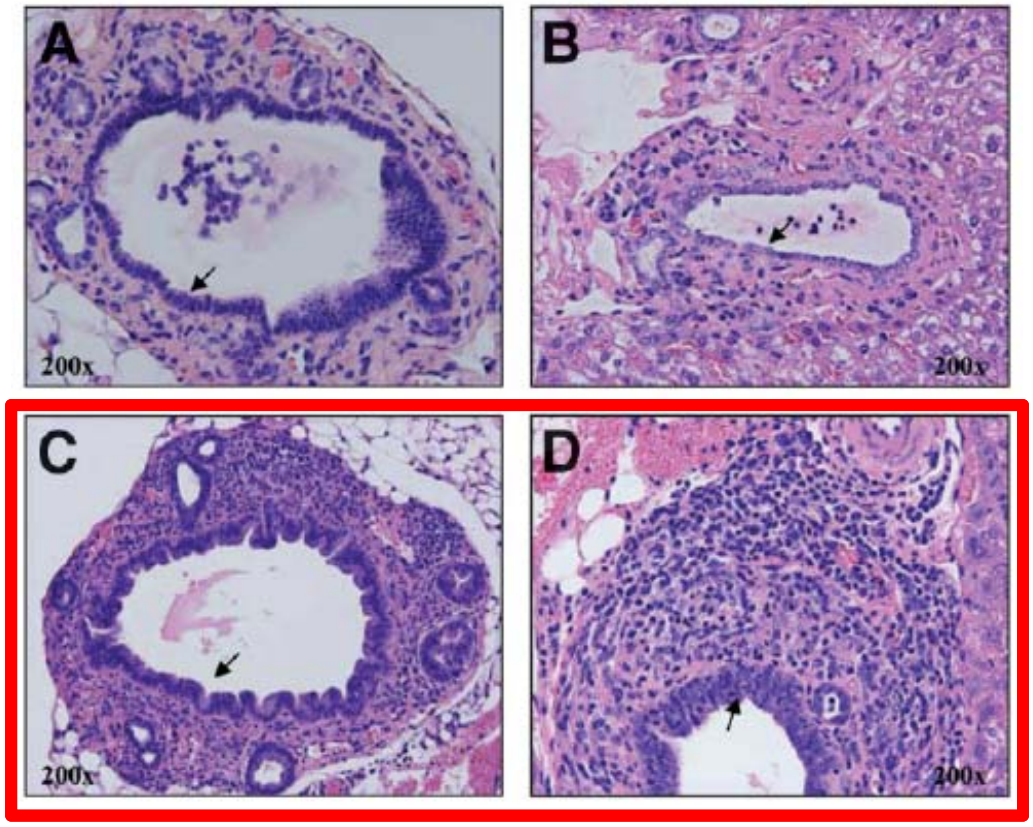
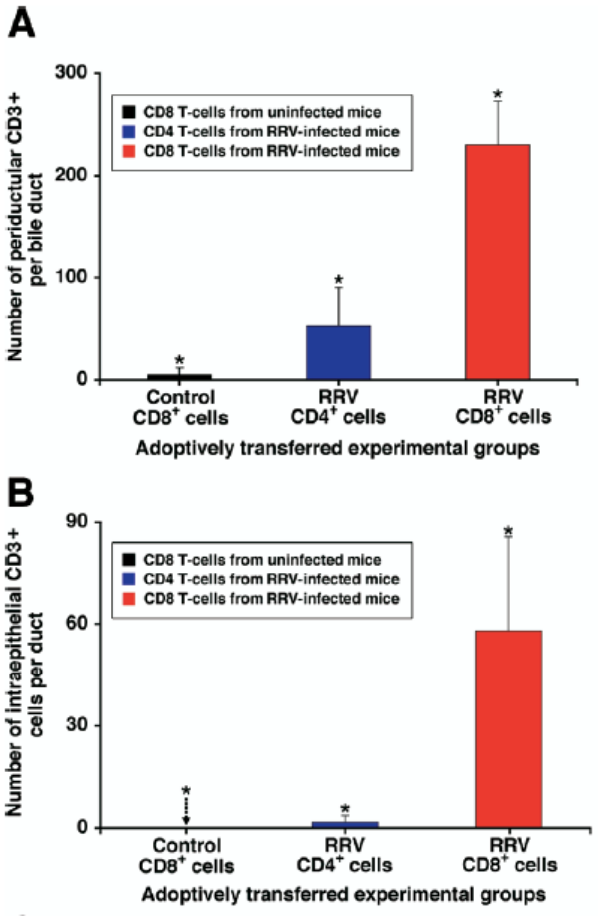
Cellular and Humoral Autoimmunity Directed at Bile Duct Epithelia in Murine Biliary Atresia

Cara L. Mack,[1,2] Rebecca M. Tucker,[2] Brandy R. Lu,[1] Ronald J. Sokol,[1] Andrew P. Fontenot,[2,3] Yoshiyuki Ueno,[4] and Ronald G. Gill[3]



Transferencia de células T

ATRESIA DE LAS VIAS BILIARES



Am J Physiol Gastrointest Liver Physiol 307: G233–G240, 2014.
First published May 29, 2014; doi:10.1152/ajpgi.00099.2014.

CD8+ T lymphocyte response against extrahepatic biliary epithelium is activated by epitopes within NSP4 in experimental biliary atresia

Shuaiyu Zheng,[1,2] Hongyi Zhang,[1] Xiaojin Zhang,[2] Fei Peng,[1] Xuyong Chen,[1] Jixin Yang,[1] David Brigstock,[3] and Jiexiong Feng[1]

[1]*Department of Pediatric Surgery, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China;* [2]*Department of Pediatric Surgery, First Affiliated Hospital of Henan University of Science and Technology, Luoyang, People's Republic of China; and* [3]*Center for Cell and Developmental Biology, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio*

Submitted 20 March 2014; accepted in final form 19 May 2014

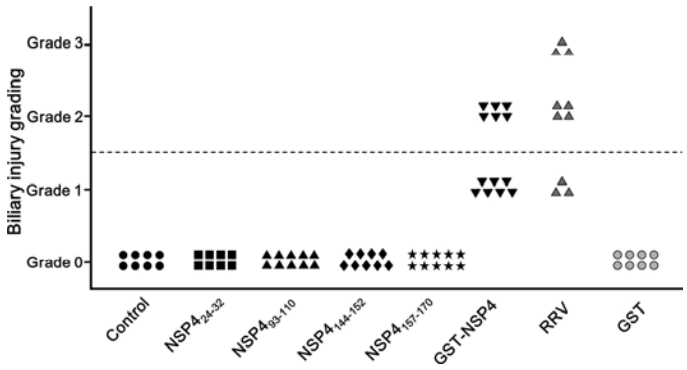


Fig. 2. Inoculation of NSP4 enhances the injury of extrahepatic bile ducts in

Am J Physiol Gastrointest Liver Physiol 307: G233–G240, 2014.
First published May 29, 2014; doi:10.1152/ajpgi.00099.2014.

CD8+ T lymphocyte response against extrahepatic biliary epithelium is activated by epitopes within NSP4 in experimental biliary atresia

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[1]*Department of Pediatric Surgery, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China;* [2]*Department of Pediatric Surgery, First Affiliated Hospital of Henan University of Science and Technology, Luoyang, People's Republic of China; and* [3]*Center for Cell and Developmental Biology, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio*

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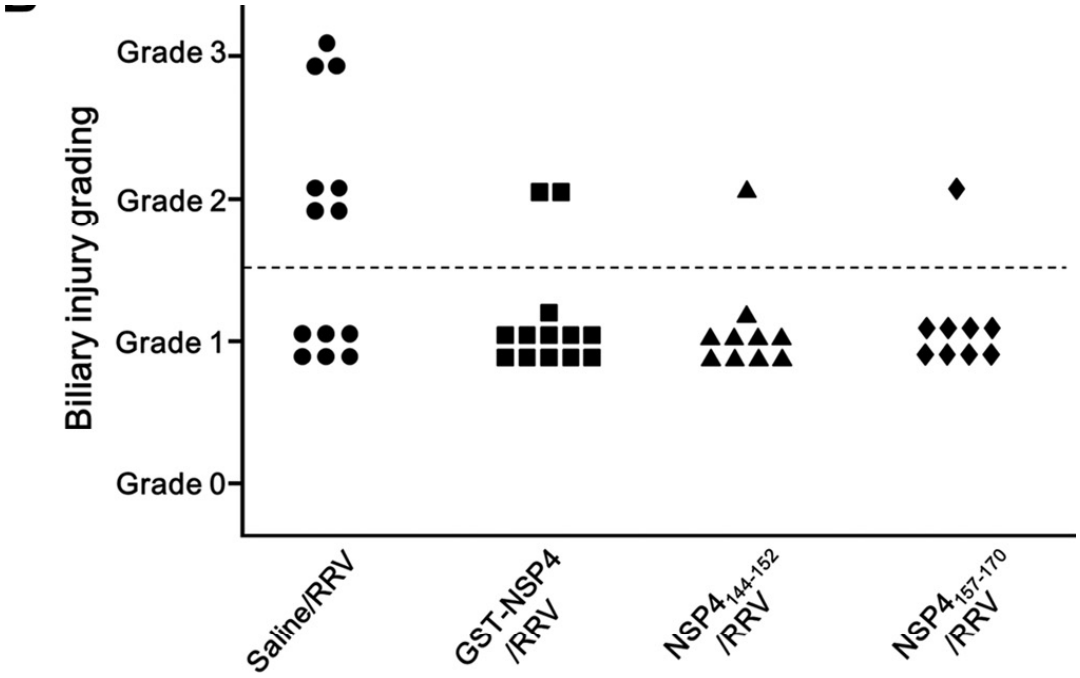

g. 7. Maternal vaccination against GST-NSP4, $NSP4_{144–152}$, or $NSP4_{157–170}$ decre

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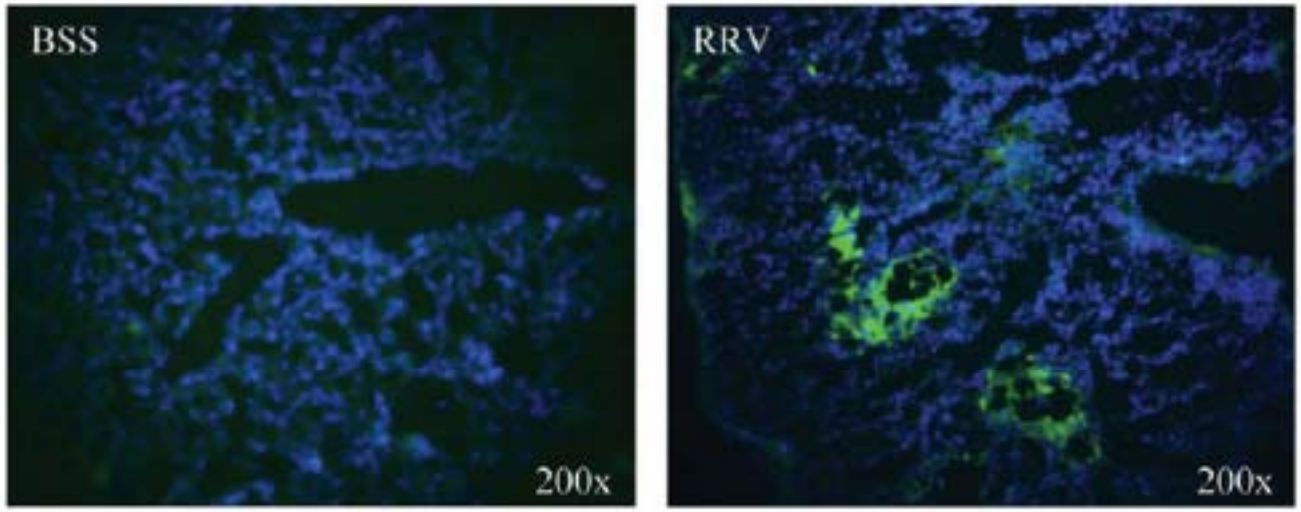
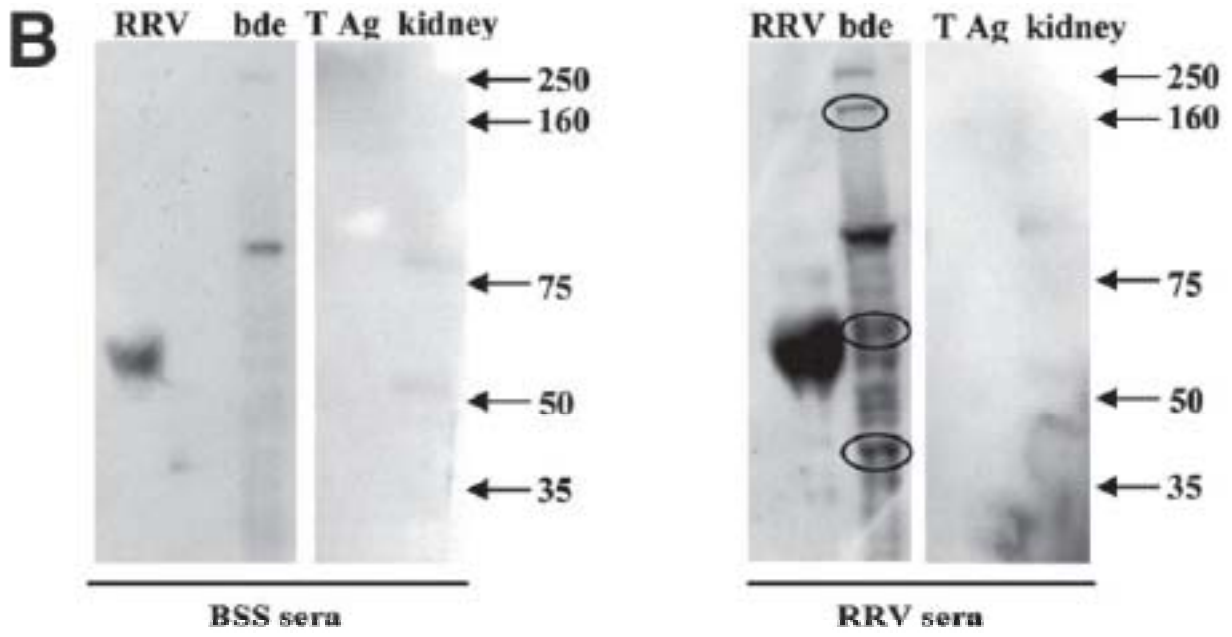


Depósito de inmunoglobulinas

ATRESIA DE LAS VIAS BILIARES



Auto-anticuerpos contra Ags biliares

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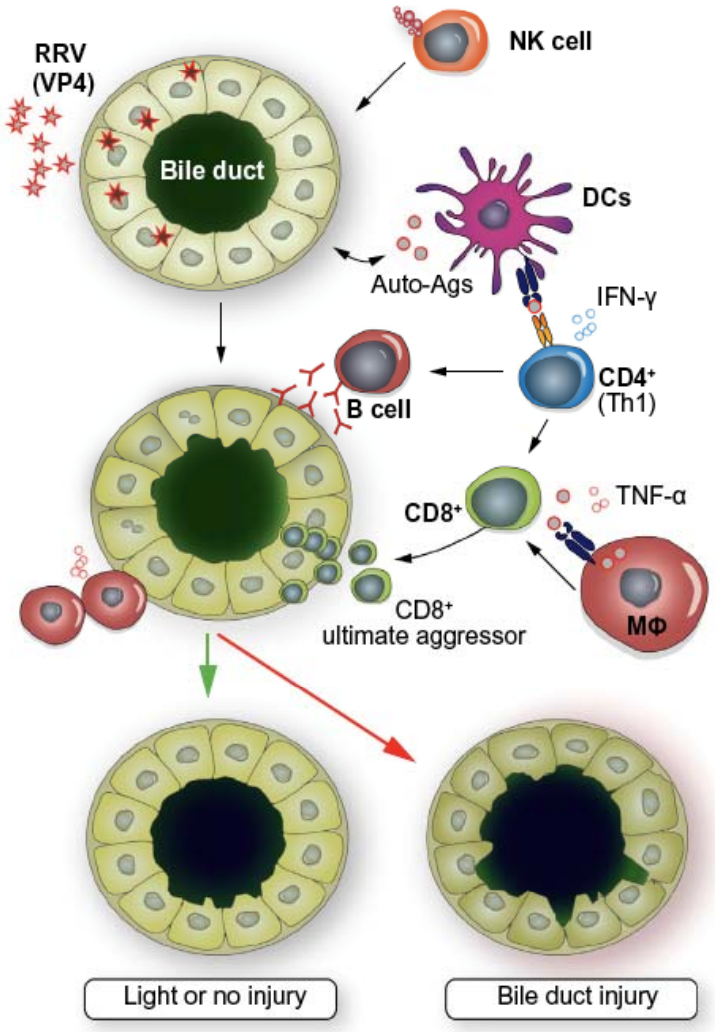
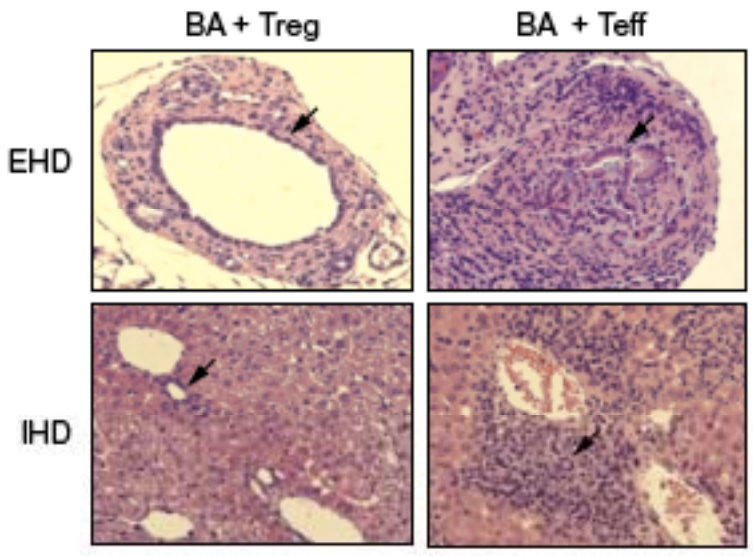


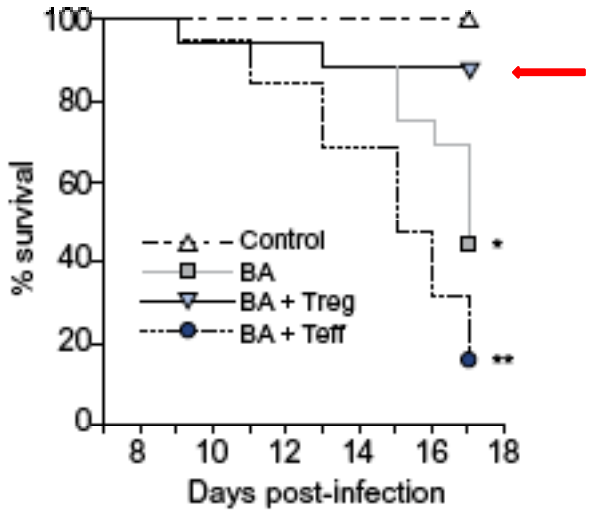
ATRESIA DE LAS VIAS BILIARES

Regulatory T cells inhibit Th1 cell-mediated bile duct injury in murine biliary atresia

Rebecca M. Tucker[1,*], Amy G. Feldman[2], Erika K. Fenner[1], Cara L. Mack[1,2]

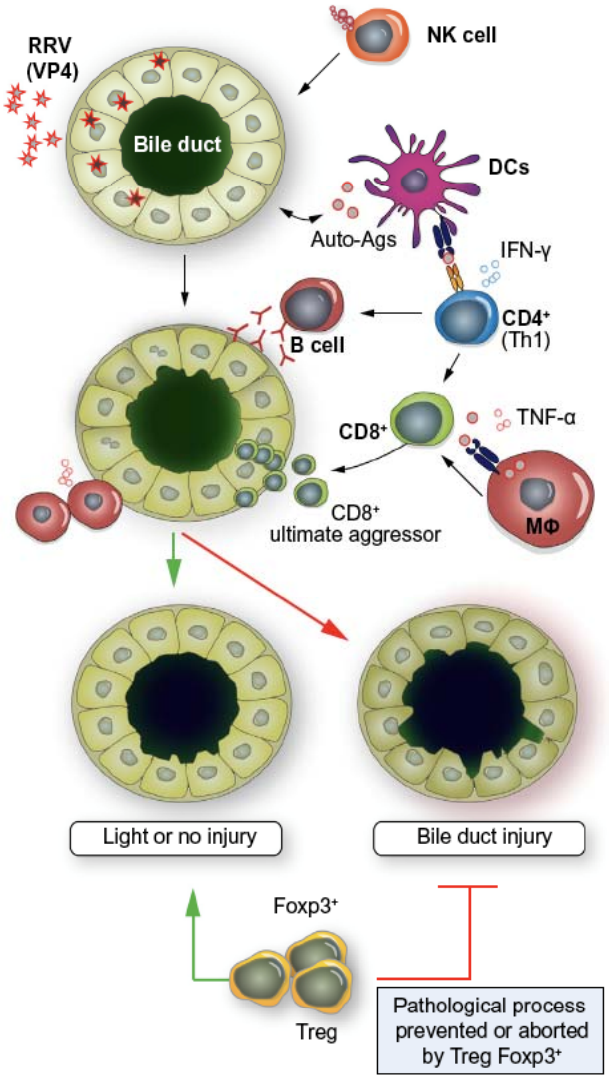
[1]*University of Colorado, Denver, United States;* [2]*Children's Hospital Colorado, Denver, United States*





TRANSFERENCIA DE Tregs MEJORA LA INFLAMACION Y LA SOBREVIDA

ATRESIA DE LAS VIAS BILIARES



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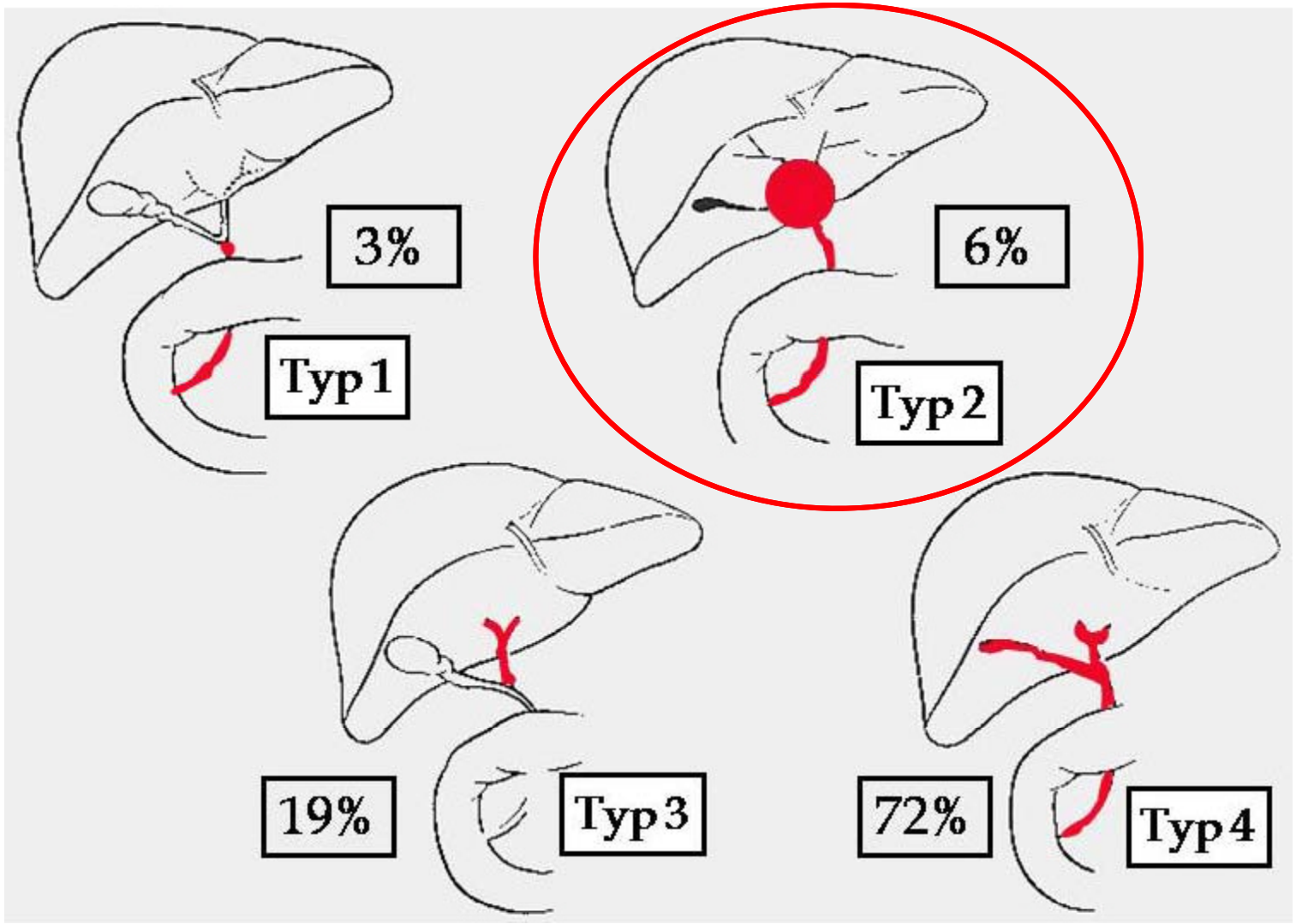
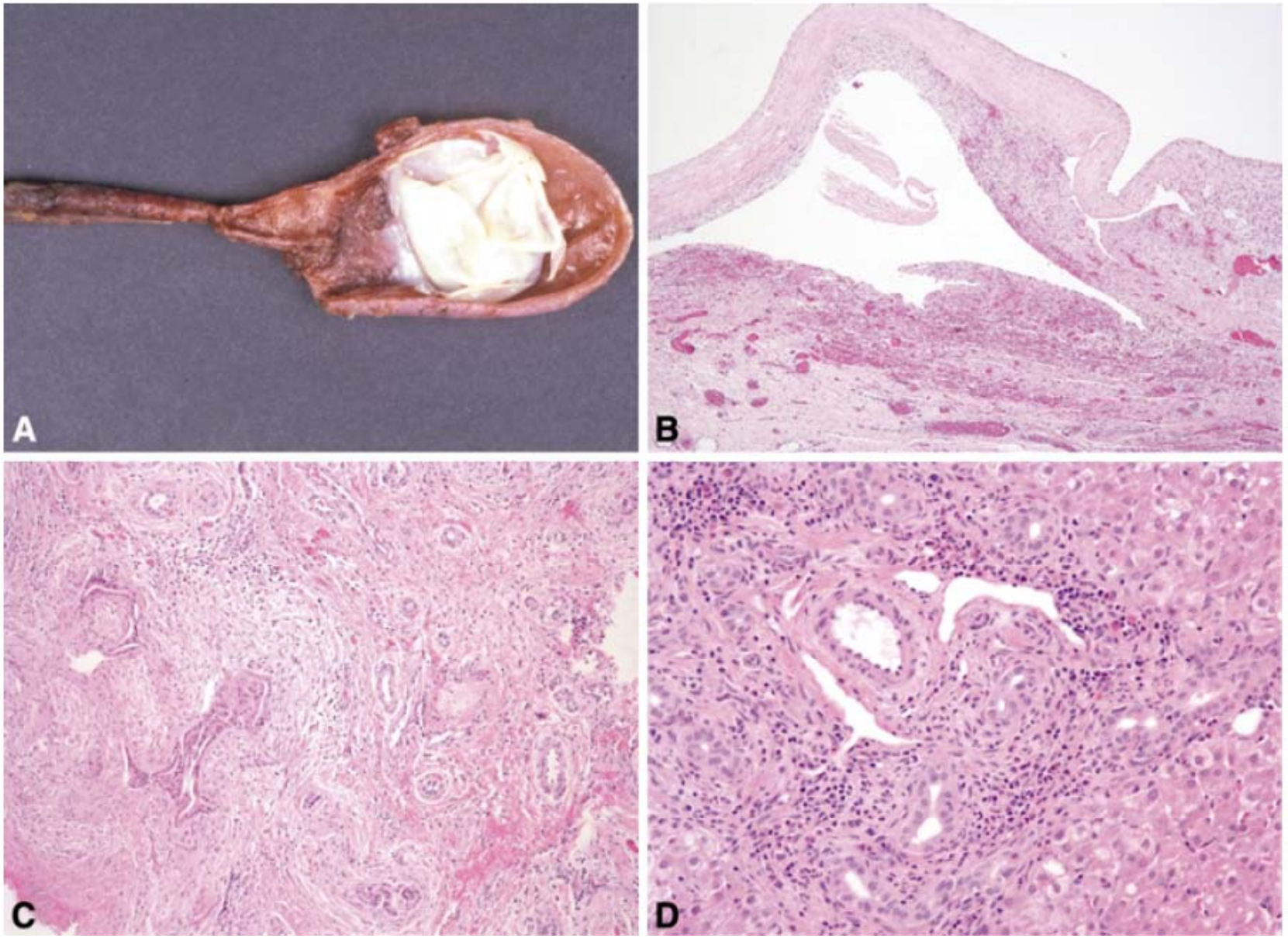


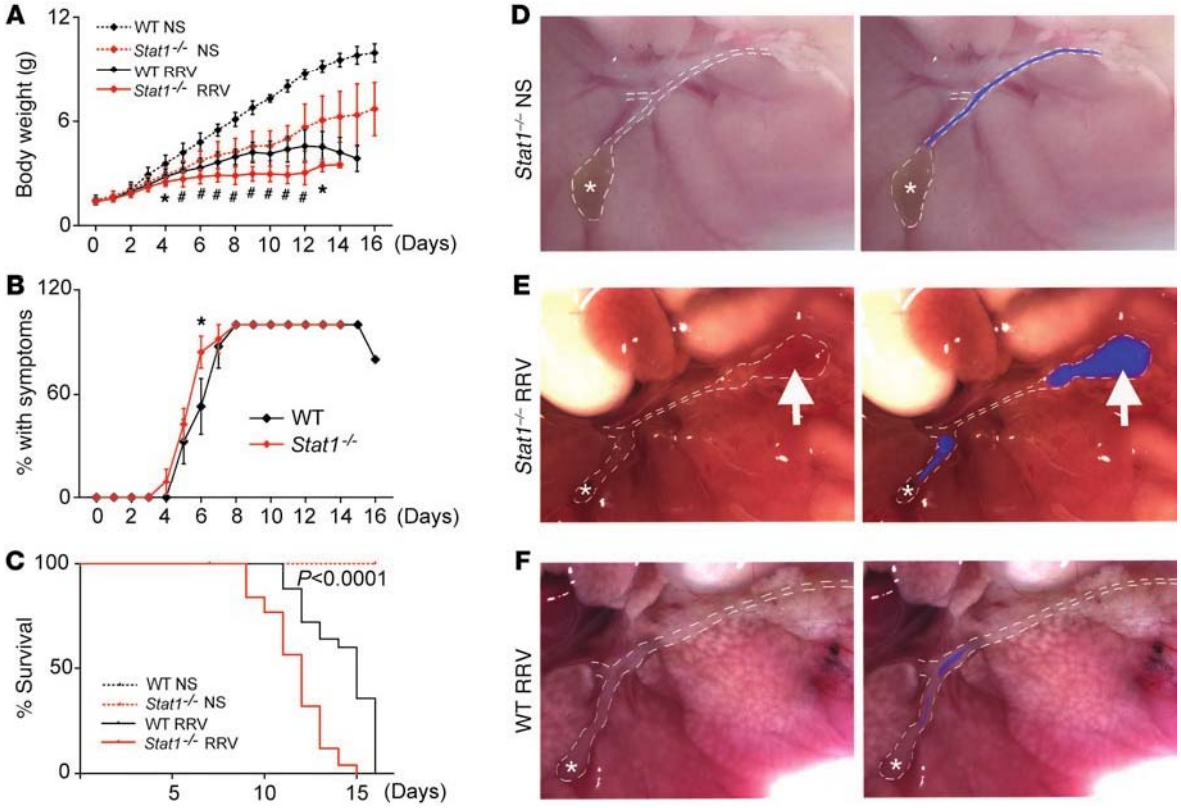
ATRESIA DE LAS VIAS BILIARES-FORMA QUISTICA



Th2 signals induce epithelial injury in mice and are compatible with the biliary atresia phenotype

Jun Li,[1] Kazuhiko Bessho,[1] Pranavkumar Shivakumar,[1] Reena Mourya,[1] Sujit Kumar Mohanty,[1] Jorge L. dos Santos,[2] Irene K. Miura,[3] Gilda Porta,[3] and Jorge A. Bezerra[1]

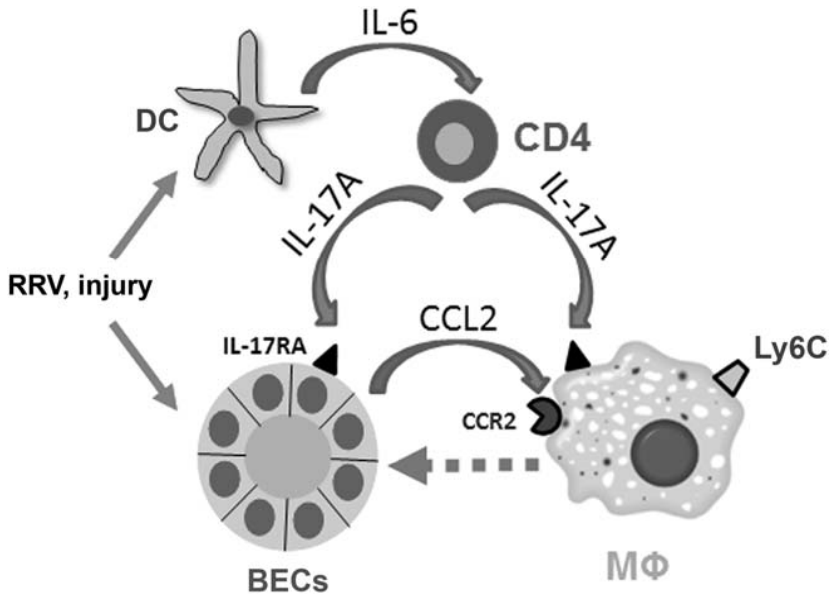
[1]Cincinnati Children's Hospital Medical Center and the Department of Pediatrics of the University of Cincinnati College of Medicine, Cincinnati, Ohio, USA.
[2]Hospital de Clínicas de Porto Alegre and Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.
[3]Hospital Sírio-Libanês e Hospital A.C. Camargo, São Paulo, São Paulo, Brazil.



HEPATOLOGY, VOL. 65, NO. 1, 2017

The Dendritic Cell–T Helper 17–Macrophage Axis Controls Cholangiocyte Injury and Disease Progression in Murine and Human Biliary Atresia

Celine S. Lages,[1] Julia Simmons,[1] Avery Maddox,[1] Keaton Jones,[2] Rebekah Karns,[1] Rachel Sheridan,[3] Shiva Kumar Shanmukhappa,[3] Sujit Mohanty,[4] Matthew Kofron,[5] Pierre Russo,[6] Yui-Hsi Wang,[7] Claire Chougnet,[8] and Alexander G. Miethke[1]



ATRESIA DE LAS VIAS BILIARES:
ASPECTOS INMUNOLOGICOS

CONCLUSIONES:

- Un agente infeccioso (o xenobiótico?) puede ser el gatillo de la respuesta inmunológica.

- Una reacción « auto » inmune continuaría el proceso inflamatorio.

- El control de esta reacción podría ser un blanco terapeútico.

ATRESIA DE LAS VIAS BILIARES

FORMAS DE AVB:

- Síndrome poli-esplenia
- Quiste extra-hepático
- Otras anomalias cromosómicas
- Malformaciones aisladas
- No malformativa

ATRESIA DE LAS VIAS BILIARES

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ATRESIA DE LAS VIAS BILIARES

SINDROME MALFORMATIVO

Table IV. Geographical Incidence of BASM

Series and Country of origin	n	Type of study/ Incidence of BA	% of BA with BASM
Europe			
Davenport (15) UK	308	Single center, n/a	9%
Vasquez (16) Spain	88	Single center, n/a	12%
McKiernan (3) UK	91	National registry, 1 in 16,700	10%
Chardot (2) France	421	National registry, 1 in 19,500	8%
Davenport UK (current)	505	Single center, n/a	10%
North America			
Karrer (27) USA	904	National registry, n/a	9%*
Carmi (4) USA	251	Multicenter, n/a	6%
Karrer (17) USA	131	Single center, n/a	12%†
Yoon (1) USA	57	Case-control, 1 in 13,700	n/a
Abramson (31) USA	112	Two centers,* n/a	9%
Asia			
Nio (32) Japan	1381	National registry, 1 in 9640	2.4%‡
Miyamoto (34) Japan	758	Autopsy study, n/a	3.7%
Tanano (5) Japan	87	Single center, n/a	6%
South Asia			
Kataria (33) India	107	Single center, n/a	5%

n/a, not applicable.
*Overall incidence of malformations only.
†Although this is the incidence quoted, if only polysplenia is used as a reference, it is 6%.
‡The overall rate for other anomalies is quoted at 19.6%, although only 33/1381 (2.4%) had polysplenia.

ATRESIA DE LAS VIAS BILIARES

SINDROME MALFORMATIVO

(10.2% DE LAS AVB)

Table I. Distribution of components of BASM

Splenic pathology	Situs inversus	Cardiac anomaly	Preduodenal portal vein
Polysplenia (n = 43)	16 (37%)*	16 (37%)	24 (56%)
Double spleen (n = 7)	3 (43%)	5 (71%)	3 (43%)
Asplenia (n = 6)	2 (33%)	4 (67%)	5 (83%)

*Observed percentage in each splenic subgroup.

ATRESIE DES VOIES BILIAIRES

SYNDROME MALFORMATIF

(10.2% DES AVB)

Table I. Distribution of components of BASM

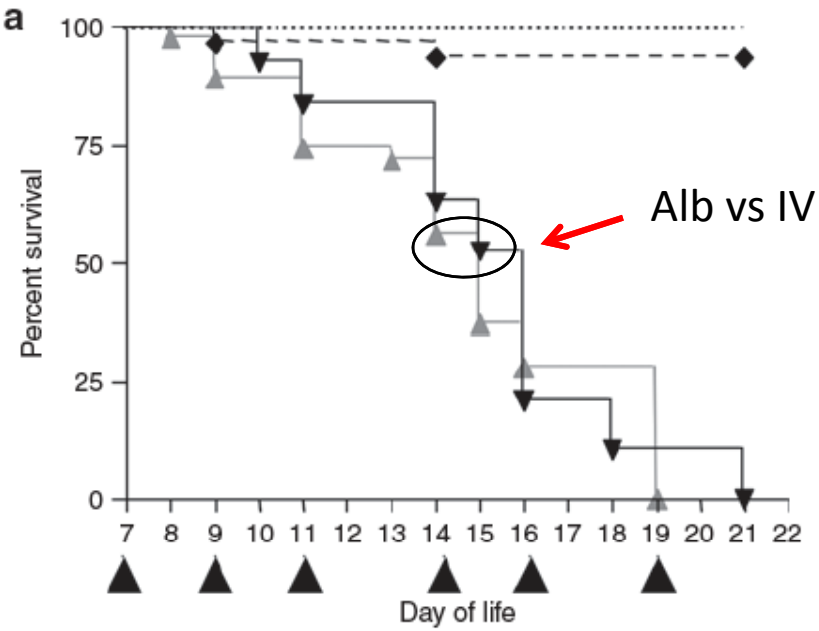
Splenic pathology	Situs inversus	Cardiac anomaly	Preduodenal portal vein
Polysplenia (n = 43)	16 (37%)*	16 (37%)	24 (56%)
Double spleen (n = 7)	3 (43%)	5 (71%)	3 (43%)
Asplenia (n = 6)	2 (33%)	4 (67%)	5 (83%)

*Observed percentage in each splenic subgroup.

ATRESIA DE LAS VIAS BILIARES

High-dose IgG therapy mitigates bile duct–targeted inflammation and obstruction in a mouse model of biliary atresia

Erika K. Fenner[1,2], Juri Boguniewicz[1], Rebecca M. Tucker[1], Ronald J. Sokol[2] and Cara L. Mack[1,2]



Alb vs IVIG: Ninguna diferencia en sobrevida

ATRESIA DE LAS VIAS BILIARES