Name: Prof. Massimo Colombo

Country: Italy

Affiliation: Past Dpt Gastroenterology and Hepatology Policlinic Hospital University of Milan

Function: Chairman

Main expertise (1-2 lines): Diagnosis and treatment viral hepatitis and liver cancer.

VHPB meeting: Viral hepatitis in Europe's Beating Cancer Plan

Prevention and control of viral hepatitis as cancer prevention opportunities

Antwerp (Belgium), 27-28 March 2025.

A Historical Overview on the Role of Hepatitis B and C Viruses as Aetiological Factors for Hepatocellular Carcinoma

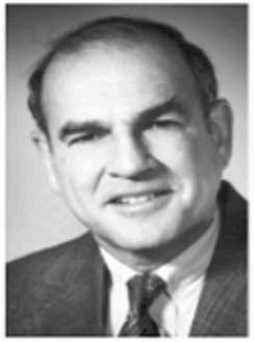
M Colombo MD , Editor Emeritus J Hepatology

Financial Disclosures 2024-2025

Advisory committees	COST, Exelixis, Agios Ph.,T arget HCC, Galapagos, Medivir-ICON
Speaking and Teaching	APASL , Improve, ESO-net European School of Oncology, GNC

1964. BS Blumberg : Digging Into Protein Polymorphysm Led to the Serendipitous Discovery of the Causative Agent of Hepatitis B

Baruch S.Blumberg



Nobel Prize in 1976 for both describing HBV and devising the novel concept of a plasma-based vaccine

1961 B.Blumberg discovered that patients who have received transfusion may develop precipitating antibodies against serum beta-lipoprotein (Ag system).

1964 B.Blumberg and H.Alter found an antibody in the serum of a transfused hemophilia patient which reacted with only one serum of an Australian aborigine in a panel of 24 against which it was tested. **"Australia antigen (AUAg)".**

1966 B.Blumberg et al. found Au Ag in leukemia, transfused , Down and in an Au Ag serocoverter patient with biopsy-confirmed icteric hepatitis.

1968 A.Prince documented the appearance of Au Ag during the incubation period of post-transfusion hepatitis.

1969 I.Millman and B.Blumberg devised and patented a concept to use HBsAg from human plasma to prepare a hepatitis B vaccine , created by M. Hilleman and licensed in 1976.

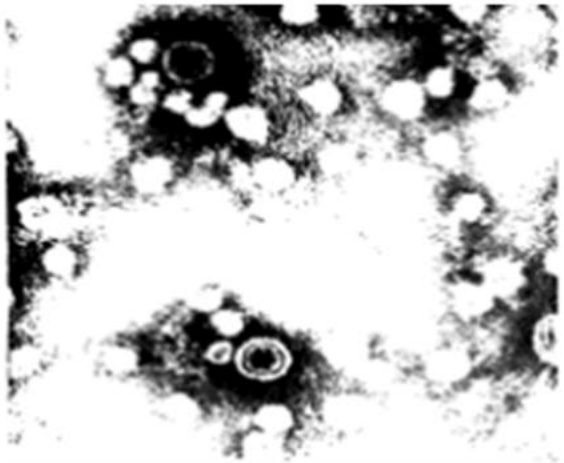
Blumberg, B. S. Bull N Y Acad Med. 1964 ; Blumberg BS and Alter HJ J Clin Invest 1965 ; Prince AM PNAS 1968

1970 -1979. From the Identification of Virus-like Particles in Au-Ag Positive Serum Specimens To Cloning of Virus DNA

THE LANCET, APRIL 4, 1970

VIRUS-LIKE PARTICLES IN SERUM OF PATIENTS WITH AUSTRALIA-ANTIGEN-ASSOCIATED HEPATITIS

D. S. DANE C. H. CAMERON
MOYA BRIGGS
Bland-Sutton Institute, Middlesex Hospital, London W.1



THE LANCET, DECEMBER 4, 1971

NEW ANTIGEN-ANTIBODY SYSTEM IN AUSTRALIA-ANTIGEN-POSITIVE HEPATITIS

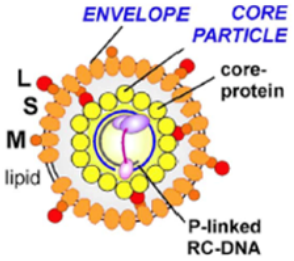
JUNE D. ALMEIDA
Department of Virology, Royal Postgraduate Medical School, London W.12

D. RUBENSTEIN E. J. STOTT
Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex

WITH ILLUSTRATIONS ON FACING PAGE

Summary After detergent treatment the 42 nm. Dane particles from the sera of patients with serum hepatitis separate into an outer coat of Australia antigen (Au-Ag) and an inner spherical 27 nm. diameter component resembling a rhinovirus. Antibody in post-hepatitic serum reacted with the inner component (but not with the outer) to yield aggregates resembling those seen in the liver of patients with serum hepatitis. Antibody to Au-Ag was not detected, before or after the attack of hepatitis. It is suggested that, in an attack of serum hepatitis, Au-Ag antibody develops but is subsequently cleared; antibody against the inner Dane component, however, persists.

Cloning of HBV virion DNA



Hepatotropic **Hepadnavirus** with a ~3,200 bp circular partially double-stranded DNA genome encoding:

- HBcAg
- HBeAg
- DNA polymerase + reverse transcriptase activity
- HBx

10 genotypes (A-J) , > 40 sub-genotypes

Host range : Human, Chimps, Great Apes

1.Tiollais P et al PNAS 1979 ; 2. Rutter WJ et al Nature 1979 ; 3. Murray K et al Nature 1979

1970's. The First Case Series Linking Hepatocellular Carcinoma With Chronic HBV Infection

THE LANCET, JUNE 13, 1970

CHRONIC LIVER DISEASE AND PRIMARY LIVER-CELL CANCER WITH HEPATITIS-ASSOCIATED (AUSTRALIA) ANTIGEN IN SERUM

SHEILA SHERLOCK R. A. FOX
S. P. NIAZI * P. J. SCHEUER
Departments of Medicine and Pathology, Royal Free Hospital, London W.C.1

- 17 patients with chronic liver disease including 5 with HCC
- Patients were from Europe ,Africa and North and south America
- All tested positive for HAA (Au Ag) by double-diffusion Ouchterlony

J. clin. Path., 1973, **26**, 217-223

Liver cell dysplasia: a premalignant condition

P. P. ANTHONY, C. L. VOGEL, AND L. F. BARKER
From The Bland-Sutton Institute of Pathology, The Middlesex Hospital Medical School, London, The Solid Tumour Centre, Uganda Cancer Institute, Kampala, Uganda, and the Division of Virology, Bureau of Biologics, Food and Drug Administration of the US Public Health Service, Rockville, Maryland, USA

The study : Au Ag tested by complement-fixation and counter electrophoresis

Prevalence of HHA in 104 cirrhotic patients with or without liver cell cancer

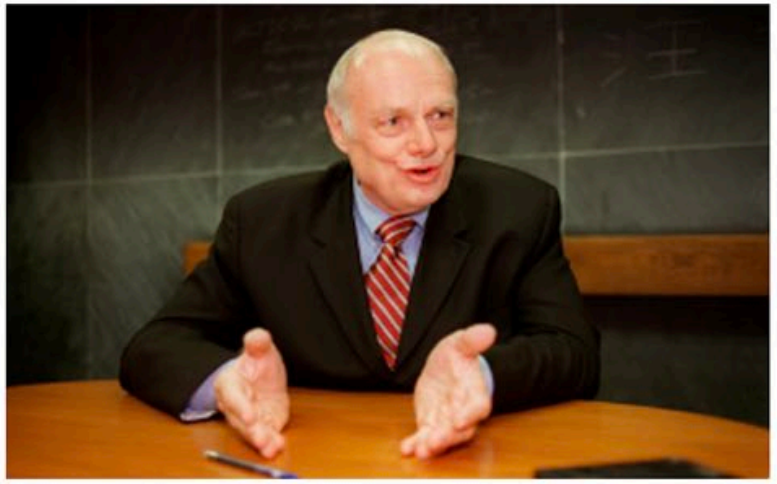
	No.	*HAA*
Dysplasia present	43	31 (72·0%)
Cirrhosis only	14	9 (64·2%)
Cirrhosis and liver cell carcinoma	29	22 (75·8%)
Dysplasia absent	61	10 (16·3%)
Cirrhosis only	46	7 (15·2%)
Cirrhosis and liver cell carcinoma	15	3 (20·0%)

1981.The Groundbreaking Prospective Study of Male Civil Servants in Taiwan Crowened
HBV as a Human Oncogenic Virus

Relative risk estimate of HCC for HBsAg carriers vs. non-carriers : 223

Prof.Palmer Beasley

University Texas School of Public Health



Status on recruitment	Cause of death			Population at risk	PHC incidence*
	PHC	Cirrhosis	Other		
Previous cirrhosis:					
* HBsAg-positive	5	7	0	40	12 500
HBsAg-negative	0	0	0	30	0
No cirrhosis:					
* HBsAg-positive	35	10	48	3414	1025
HBsAg-negative	1	2	199	19 223	5
Total	41	19	247	22 707	181

*Incidence of death from PHC per 100 000 during the time of the study.

THE LANCET, NOVEMBER 21, 1981

"PHC and cirrhosis accounted for 54·3% of the 105 deaths among HBsAg carriers but accounted for only 1·5% of the 202 deaths among non-carriers. These findings support the hypothesis that hepatitis B virus has a primary role in the aetiology of PHC."

1980's. Unravelling the Mechanisms of HBV-induced HCC . Epigenetic and Genetic Changes

- **HBV DNA integration** into the host genome occurs at early steps of clonal tumor expansion and induces both genomic instability and direct insertional mutagenesis of diverse cancer-related genes.

- Prolonged expression of the **viral regulatory protein HBx** and/or **altered versions of the preS/S** envelope proteins dysregulate cell transcription and proliferation control and sensitize liver cells to carcinogenic factors.

  - A major role is played by the HBV protein **HBx** which is recruited on cellular chromatin and modulates chromatin dynamics at specific gene loci.

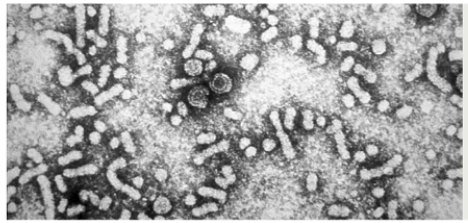
  - Accumulation of **preS1** large envelope proteins and/or **preS2/S** mutant proteins activates the unfold proteins response, that can contribute to hepatocyte transformation.

- **Epigenetic changes** targeting the expression of tumor suppressor genes occur early in the development of HCC.

Levrero M & Zucman-Rossi J J Hepatology 2016 ; Chakraborty P.R. et al Nature 1980; Brechot C et al Nature 1980

Taiwan 1983-Onwards.The POC Study of RP Beasley Paving the Way to Nationwide Campaigns of HCC Prevention Through Interruption of MTCT and Treatment of HBV

1984 The Launch of Nationwide Neonatal Hepatitis B Vaccination Campaign



A transmission electron micrograph showing the ultrastructural morphology of Dane particles — spherical HBV virions of ~42 nm in diameter. Credit: CDC.

MILESTONE 11

First recombinant DNA vaccine for HBV

In 1986, the Recombivax HB vaccine for hepatitis B was approved for human use in several countries, the culmination of research started by William Rutter, Pablo Valenzuela and colleagues in 1979 on the cloning of hepatitis B virus (HBV) antigens. It

Given the failure since its discovery to cultivate HBV in vitro, the first commercial HBV vaccine (Heptavax; licensed in 1981) was based on inactivated virus collected from the plasma of HBV-infected donors. However, plasma products at the

1992 HBV Vaccine Appointed 7th Global Vaccine by the World Health Assembly

2003 The Launch of National Antiviral Therapy Programs in HBV and HCV Patients

JAMA Netw Open. 2022 Jul 18;5(7):e2222367. doi: 10.1001/jamanetworkopen.2022.22367

Association of Nationwide Hepatitis B Vaccination and Antiviral Therapy Programs With End-Stage Liver Disease Burden in Taiwan

Chun-Ju Chiang [1,2], Jing-Rong Jhuang [1,2], Ya-Wen Yang [1,2], Bo-Zhi Zhuang [1,2], San-Lin You [3], Wen-Chung Lee [1,2,✉] Chien-Jen Chen [4,5,✉]

From 1982 -1986 to 2007-2011 birth cohort :

HCC incidence decreased by 80% , aRR, 0.20; 95% CI, 0.00-0.48

1984-2003. From IFN-alpha to Oral Nucleos(t)ides Analogues (NAs) to Treat Chronic HBV Infection

HBV-related HCC Risk Reduced Not Abolished

Meta-Analysis > Hepatol Int. 2022 Oct;16(5):1052-1063.
doi: 10.1007/s12072-022-10369-w. Epub 2022 Sep 9.

Systematic review and meta-analysis: impact of anti-viral therapy on portal hypertensive complications in HBV patients with advanced chronic liver disease

Yuanyuan Kong [1], Tingting Lv [2], Min Li [1], Lianghui Zhao [2], Tongtong Meng [2], Shanshan Wu [1]

Nucleos(t)ides(NAs) therapy & HCC

- 39 studies with 14,212 ACLD patients
- NAs associated withreduced HCC risks : RR 0.48(95% CI 0.30-0-75)
- 1st line TDF & ETV vs. non-1st line NAs : RR 0.85(95% CI 0.73-0.99)

831 with spontaneous HBsAg seroclearance 1999 - 2020,

791 did not develop HCC

40 who developed HCC after HBsAg seroclearance

Yang H et al J Hepatol 2022

1975.The Identification of PT- Non-A Non-B Hepatitis at NIH. The Role of IE Microscopy

Transfusion-Associated Hepatitis Not Due to Viral Hepatitis Type A or B

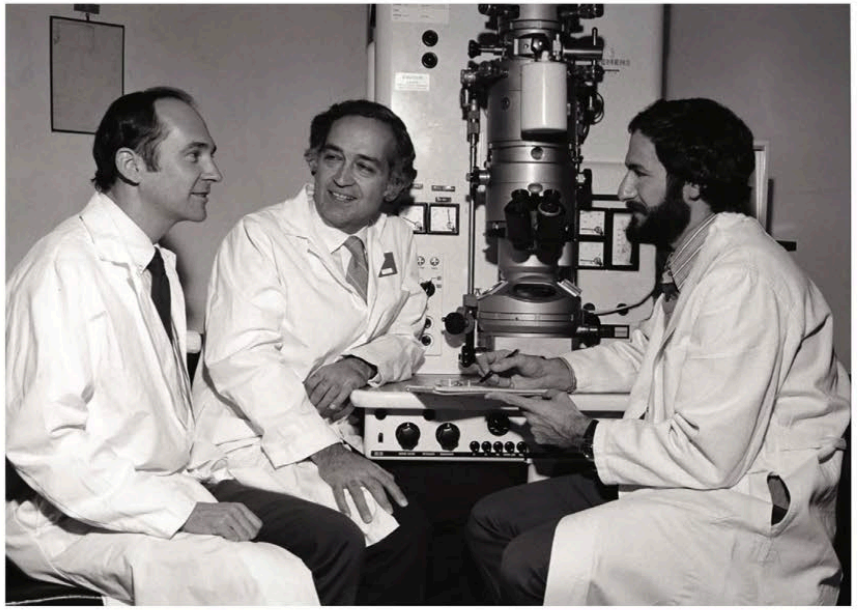
Stephen M. Feinstone MD,Albert Z. Kapikian MD,Robert H .Purcell,Harvey J .Alter MD,and Paul V. Holland MD

Published April 10, 1975 | N Engl J Med 1975;292:767-770 | DOI: 10.1056/NEJM197504102921502
VOL. 292 NO. 15

Findings

- 22 patients with HBsAg neg. transfusion-associated hepatitis
- All negative for antibodies to HAV,HBV,CMV and EBV
- None reactive at IE-microscopy for 27-nm virus-like antiHA Ag
- None developed anti HA Ag during the study period

1973 Discovery of HAV at NIH



Robert Purcell ,Albert Kapikian and Stephen Feinstone

Feinstone SM et al NEJM 1975;292:767-770

1980's. Case Series Linking Non-A,Non-B Transfusion-associated Hepatitis to HCC

› Vox Sang. 1982 Jul;43(1):45-52. doi: 10.1111/j.1423-0410.1982.tb01116.x.

The significance of blood transfusion in non-A, non-B chronic liver disease in Japan

K Kiyosawa, Y Akahane, A Nagata, Y Koike, S Furuta

PMID: 6287737 DOI: 10.1111/j.1423-0410.1982.tb01116.x

Patients with NANB type hepatitis

with a history of transfusion

42.8% of 283 patients with chronic hepatitis

37.1% of 70 patients with cirrhosis

15.1% of 53 patients with HCC

Case Reports › Dig Dis Sci. 1983 Oct;28(10):908-11. doi: 10.1007/BF01317042.

Primary hepatocellular carcinoma following non-A, non-B posttransfusion hepatitis

R H Resnick, K Stone, D Antonioli

PMID: 6193933 DOI: 10.1007/BF01317042

Case Reports › Am J Gastroenterol. 1984 Oct;79(10):777-81.

Hepatocellular carcinoma after non-A, non-B posttransfusion hepatitis

K Kiyosawa, Y Akahane, A Nagata, S Furuta

PMID: 6091443

1989. M Houghton Identified the Hepatitis C Virus, an Uncultured Infectious Agent
Chiron Co. Emeriville & Collaboration with CDC Atlanta

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY, DANIEL W. BRADLEY, MICHAEL HOUGHTON

An Assay for Circulating Antibodies to a Major Etiologic Virus of Human Non-A, Non-B Hepatitis

G. KUO, Q.-L. CHOO, H. J. ALTER, G. L. GITNICK, A. G. REDEKER, R. H. PURCELL, T. MIYAMURA, J. L. DIENSTAG, M. J. ALTER, C. E. STEVENS, G. E. TEGTMEIER, F. BONINO, M. COLOMBO, W.-S. LEE, C. KUO, K. BERGER, J. R. SHUSTER, L. R. OVERBY, D. W. BRADLEY, M. HOUGHTON

SCIENCE, VOL. 244 21 APRIL 1989

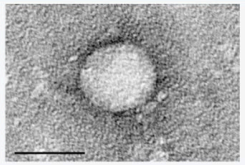
Hepatitis C virus

+SS RNA 9.6 Kb

Flaviviridae family

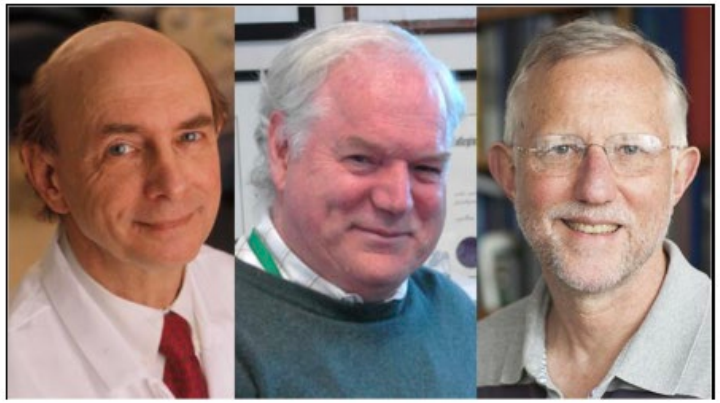
Hepacivirus genus

7 genotypes, 86 subtypes



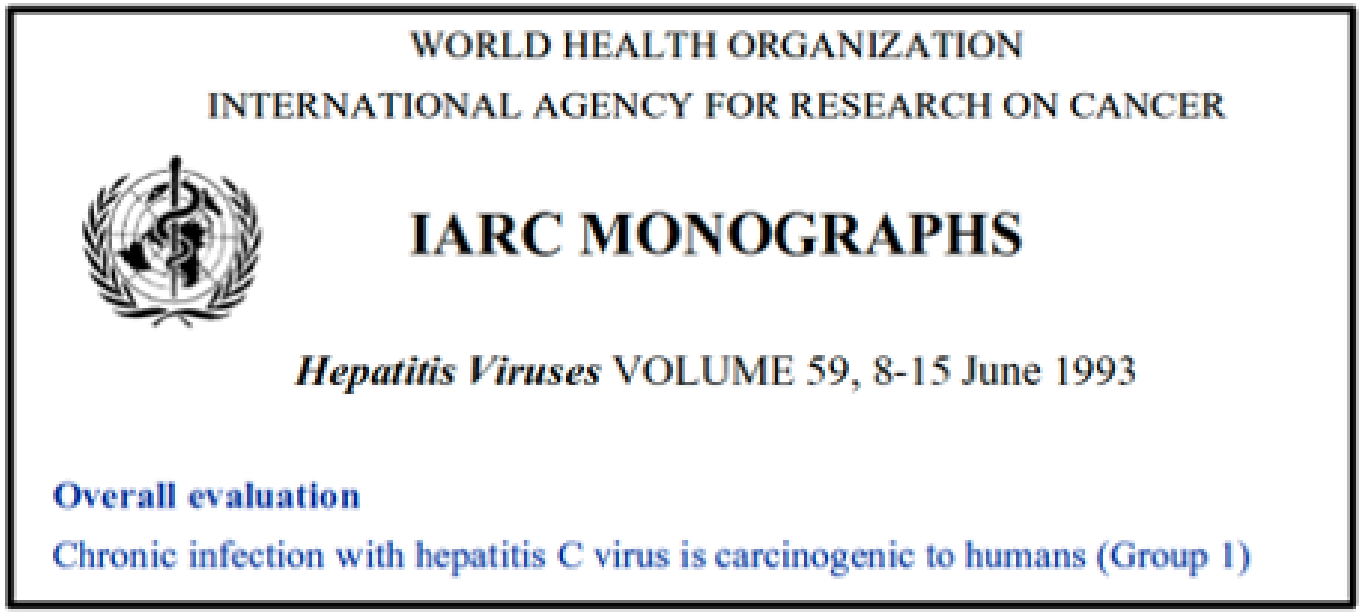
Electron micrograph of *Hepacivirus C* purified from cell culture. Scale bar = 50 nanometres

2020 Nobel Laureates for the discovery of HCV



H.J. Alter Sir M.Houghton C.M.Rice

1989. Serological Confirmation of the Role of HCV in Hepatocellular Carcinoma



WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

Hepatitis Viruses VOLUME 59, 8-15 June 1993

Overall evaluation

Chronic infection with hepatitis C virus is carcinogenic to humans (Group 1)

CTOBER 28, 1989

Anti HCV + 65.1% of 183 patients with HCC
74.0% of 186 patients with chronic hepatitis or cirrhosis

Anti HCV + 75.0% of 96 patients with HCC
55.6% of 106 patients with cirrhosis
7.3% of 177 patients without liver disease

1990 - Onwards. The Complex and Interactive Mechanisms of Liver Carcinogenesis Driven by HCV

HCV-RNA and Proteins Perturb Hepatocellular Homeostasis

Background Half-life of infection in the order of one week, affects a minority of hepatocytes. Hit-and-run mechanism surviving HCV eradication.

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Immunosuppression Many T cells with an exhausted phenotype in the infiltrates, downregulation of immune-related genes, suppression of IFN I/III and impairment of antigen presentation. Cancer cells adapt and develop strategies of immune evasion .

Fiehn F et al Curr Opin Virol 2024, 67:101423

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Fibrogenesis Associated with the secretion of growth factors, immune suppression and angiogenesis mediated by beta-catenin and YAP/TAZ .

1990's. The Complex and Interactive Mechanisms of Carcinogenesis Driven by HCV

HCV-RNA and Proteins Perturb Hepatocellular Homeostasis

Background Half-lif ...radication.

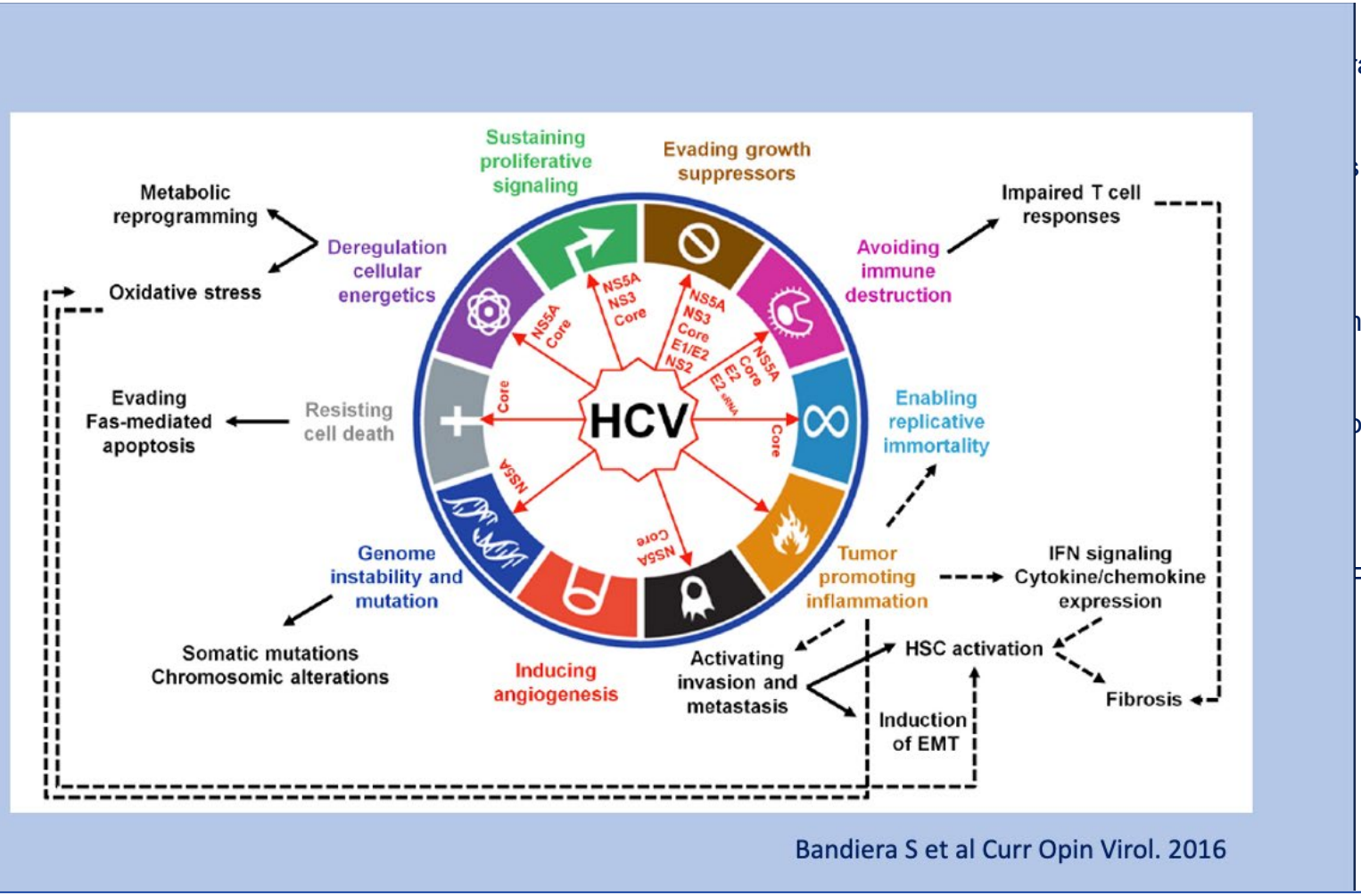
Chronic inflammatio ...s due to erroneous DNA replication, aggravate

Metabolic impact D... ...noting enviroment.

Immunosuppressior ...on of IFN I/III and impairment of ant

Fibrogenesis Assoc ...P/TAZ .

Epigenetic reprogra ... activation of Wnt/β-catenin signalling , se



Fiehn F et al Curr Opin Virol 2024, 67:101423

1984-2013. From IFN-alpha to Oral Nucleos(t)ides Analogues (NAs) in the Treatment of Chronic HCV

HCV-related HCC Risk Reduced Not Abolished

HCC risk following HCV eradication (SVR)

Study at V

- The risk of HC

Increased by 3%

Decreased with #

- The adjusted a

2.03% among pc

2.48% in LSM 10

3.22% inLSM 15-

5.07% in LSM 20

5.44% in LSM ≥25 kPa (aHR, 3.03; 95% CI, 1.74-5.26; P < .0001)

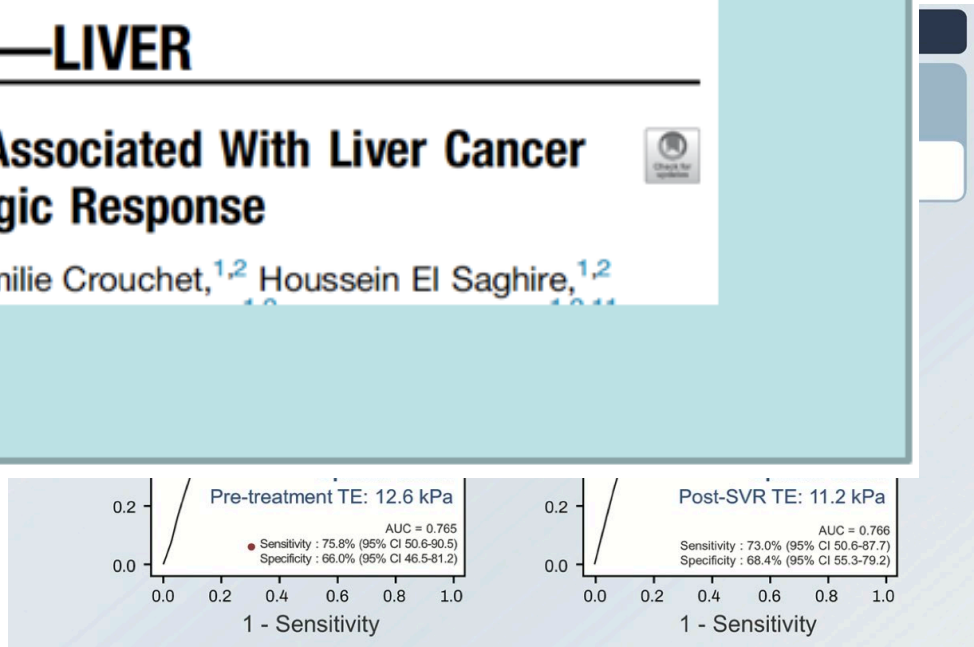
< 0.4% in LSM <5 kPa and without DM

Gastroenterology 2019;156:2313–2329

BASIC AND TRANSLATIONAL—LIVER

HCV-Induced Epigenetic Changes Associated With Liver Cancer Risk Persist After Sustained Virologic Response

Nourdine Hamdane,[1,2,*] Frank Jühling,[1,2,*] Emilie Crouchet,[1,2] Houssein El Saghire,[1,2]



John BV et al Clin. Gastroenterol Hepatol 2024

Lee HA et al Clin Molecul Hepatol 2024

Is a Protective HCV Vaccine Needed for Prevention of HCV-related HCC?

Why	Despite progress in HCV therapeutics, new infections continue to outpace cure and HCC risk is not fully eradicated in patients achieving a cure with antivirals.
The beginning	Chimps that produced a high level of anti-E1E2 were protected against challenge with homologous HCV strain (Choo et al 1994).
The way forward	Increased understanding of HCV protective immunity and HCV envelop glycoprotein structure and function is paving the way towards rational vaccine design and evolution.
Clinical protection studies	One candidate vaccine in phase I/II NCT01436357 in PWIDs,a viral vector vaccine encoding NS3-NS5B induced HCV-specific T cells, but it did not protect against chronic HCV infection (Page et al 2021).

Law M Cold Spring Harb Perspect Med 2021;11:a036962 ; Page K et al NEJM 2021

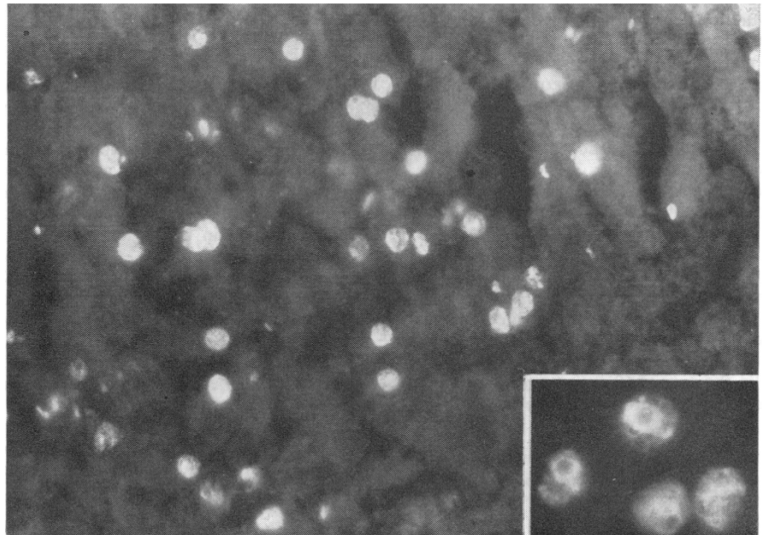
2025 IARC . Substantial Evidence for an Etiological Role of Hepatitis Delta Virus (HDV) in HCC

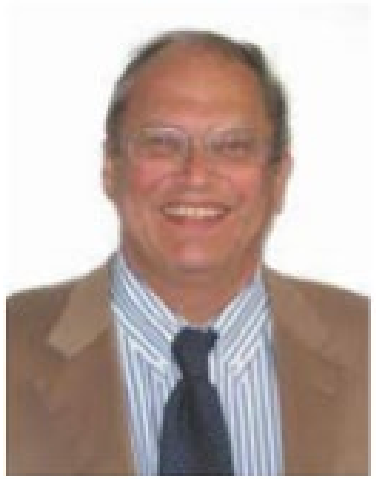
Gut, 1977, **18**, 997-100

Immunofluorescence detection of new antigen-antibody system (δ/anti-δ) associated to hepatitis B virus in liver and in serum of HBsAg carriers

M. RIZZETTO,[1] M. G. CANESE, S. ARICÒ, O. CRIVELLI, C. TREPO, F. BONINO, AND G. VERME

From the Department of Gastroenterology, Ospedale Mauriziano Umberto I, Turin, Italy, the Electron Microscopy Centre of the Faculty of Medicine, University of Turin, Italy, and INSERM U45, and Laboratory of Hygiene, University Claude Bernard, Lyon, France

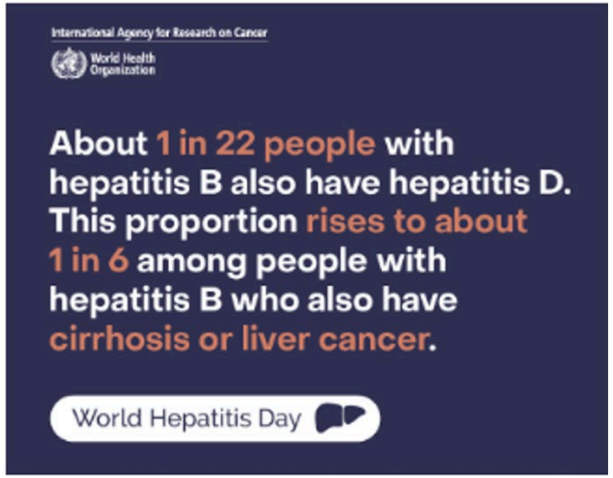




Prof.Mario Rizzetto
University of Turin,Italy

HDV Rizzetto M , New Microbiologica, 2022

- Smallest infectious agent in man : 1700 nt
- Circular,single strnded-neg.polarity RNA
- Infectious at 10^{-11} serum dilutions in HBsAg+
- Rolling circle mechanism of replication
- Self-cleaving ribozyme
- Transcription by cellular RNA polymerase



IARC WHO Report of the Advisory Group to Recommend Priorities for the IARC Monographs during 2025–2029

Report of the Advisory Group to Recommend Priorities for the IARC Monographs During 2025–2029

Hepatitis Delta Virus (HDV)

- Uncertainty on direct oncogenic effects, since HDV relies on HBV for infectivity and the machinery needed for replication (Rizzetto et al., 1977).
- HDV may enhance the effects of HBV in the development of HCC (Puigvehí et al., 2019).
- In mice, HBV–HDV coinfection elicits stronger inflammation response than HBV mono-infection (Giersch et al.,2015).
- HBV induces inflammation through activation of nuclear factor kappa ß (NF-κB); HDV activates NF-κB signalling (Park et al., 2009a).
- HDV elicits epigenetic changes : expression of DNA methyltransferase 3 β, alters DNA methylation patterns that might affect cell cycle progression (Benegiamo et al., 2013).
- In patients with HDV, dysregulation of the Y3 long non-coding RNA (lncRNA) (Zhang et al., 2016a).

Summary : Substantial evidence for an etiological role of HDV infection. The Advisory Group therefore considered an **IARC Monographs re-evaluation of HDV to be warranted**.

Recommendation : High priority and ready for evaluation within 2.5 years.

Sounding the Alarm on HCC Caused by Viral Hepatitis in European Region
WHO 2022 Estimates

- An estimated 2.08 (1.66-2.54) million and 0.49 (0.42-0.57) million people developed incident chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, respectively, across all age groups in Europe in 2019, and

  - 10.6 (6.1-19.6) million people live with hepatitis B virus (HBV) infection.
  - 8.6 (4.7-17.1) million people live with hepatitis C virus (HCV) infection.

- Primary liver cancer, is the sixth leading cause of cancer-related deaths in Europe accounting for 62,650 new cases and 54,624 deaths in 2022.

- In 2025, the IARC Monograph's programme will evaluate the carcinogenicity of hepatitis D virus (HDV) and the mechanisms by which it may cause liver cancer.

WHO— Global hepatitis report 2024: Action for access in low- and middle-income countries ; European Commission & ECDC 2024 Report

Thank you

2019-2024 Liver Societies Recommendations for HCC Surveillance in HBV Infected Individuals
Who to Screen?

	APASL 2019	EASL 2018/2024	AASLD 2023
Cirrhotics	Child Pugh A&B (C)	Child Pugh A&B (C)	Child Pugh A&B (C)
Non cirrhotics	• Asian females >50 yr • Asian males >40 yr • Africans <20yr • Family history of HCC	* PAGE B intermediate or high risk (>10 points)	• Active hepatitis (high ALT or viral load) • Family history of HCC • Africans and African Americans • Asian males >40 yr • Asian females >50 yr • PAGE B intermediate or high risk (>10 points) *
	Omata et al Hepatol Intern 2017 Kanda et al Hepatol Intern 2019	* Galle et al J Hepatol 2918 Singro et al J Hepatol 2024	Singal et al Hepatology 2023

2019-2024 Liver Societies Recommendations for HCC Surveillance in HCV Infected Individuals
Who to Screen?

	APASL 2019	EASL 2018-24	AASLD 2023
F0-F2 No/early fibrosis			
Surveillance	no	no	no
Surveillance in SVR	yes	no	no
F3 Adv fibrosis			
Surveillance	yes	yes	no
Surveillance in SVR	yes	yes	no

Kanda T et al Hepatol Intern 2019

Galle P et al JHepatol 2018
Reiberger T et al J Hepatol 2024
Sangro et al J Hepatol 2024

Singal AG et al Hepatology 2023