

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 76171

**Title:** Milestones in the discovery of hepatitis C

**Reviewer's code:** 06084005

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

In their manuscript, authors are reviewing the literature regarding milestones in the discovery of hepatitis C. The manuscript is interesting, adheres to all journal standards and covers some important aspects. This review has certain guiding significance for future research.

**Response:** Thanks for your comments.

(see following responses)

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**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 76171

**Title:** Milestones in the discovery of hepatitis C

**Reviewer's code:** 02528485

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

This OPINION REVIEW article has summarized the milestones in the discovery of hepatitis C virus. Several suggestions:

1. The title. [Milestones in the discovery of hepatitis C virus] is suggested. Also in the entire manuscript, [hepatitis c virus] not [hepatitis c] is suggested.

#### Response:

We agree that we had used the terms hepatitis C and hepatitis C virus alternatively causing confusion. We have tried to use hepatitis C for the disease but we agree that we should specify when it is used in relation with the hepatitis C virus accordingly. We have corrected the error and added hepatitis C virus or virus when appropriate. We think we

could leave the title as originally thought in order to call the attention of gastroenterologists and hepatologists to the problem in general and not only to the parts related exclusively to the hepatitis C virus. We accept that both alternatives can work.

2. Line 2 in the Abstract section [Also in the core tip and final remark], the number should be more than [thousands of]?

**Response:**

Corrected, “thousands of” to “millions of”.

3. Page 2, line 6, [hepatitis c virus] not [hepatitis virus] is suggested. [also in the 1st line of page 3]

**Response:**

Page 2.- “ not only to cure the disease but most probably, to eliminate the problem.

This work started with Dr Harvey Alter who demonstrated that a new virus was responsible for the majority of post-transfusional hepatitis followed by Michael Houghton who cloned the virus and developed the blood test to identify those cases that carried the virus. Finally the work of Charles Rice demonstrated that a cloned hepatitis C virus produced after applying molecular biology techniques could cause long standing infection and cause the same disease as the one observed in humans.”

Page 3.- “cloned hepatitis C virus produced after applying molecular biology techniques (a virion) could cause long standing infection and cause the same disease as the one observed in humans [2].”

4. Line 15, page 3, [RNA] but not [ARN].

**Response:**

Corrected to “RNA”

5. Page 5, please rephrase the following sentences: [Nonetheless the last portion of this story took another 39 years, 14 years from the identification of non-A non-B hepatitis to the discovery of the hepatitis C virus and 25 years from the discovery of hepatitis C virus in 1989 to the approval of one of the most prescribed direct acting anti-viral agents (DAA) Sofosbuvir in 2013 for the treatment of hepatitis C]

**Response:**

Re-written: “The journey to unravel this problem took another 39 years, 14 years from the identification of non-A non-B hepatitis to the discovery of the hepatitis C virus and 25 years from the discovery of hepatitis C virus in 1989 to the approval of one of the most prescribed direct acting anti-viral agents (DAA) Sofosbuvir in 2013 for the treatment of hepatitis C [22].”

6. The last sentence in page 5, [blocking viral membrane fusion at the present time]. I do not know any DAA could block viral membrane fusion. Please check.

**Response:**

Corrected, to “ ...therapy involving the design of direct acting antivirals (DAA) that inhibit hepatitis C virus infection by blocking viral assembly and replication at the present time [22].”

7. Line 17, page 7, [to detect protein products of those clones] is miss-leading. Actually, they use these antigens to detect the antibodies in the patients’ sera.

**Response:**

Clarified, to “to detect antibodies to protein products of those clones”.

8. Page 8, The following sentence is confusing: [Confirmatory reports from various groups

worldwide all corroborated that replicons were robust in vitro replication (subgenomic HCV replication system) systems supporting complete life cycle of HCV in cell culture], if sub-genomic replicon is mentioned (ref. 28), it is not complete life cycle of HCV.

**Response:**

Corrected to: Confirmatory reports from various groups worldwide all corroborated that replicons were robust *in vitro* replication (subgenomic HCV replication system) systems that set the basis for production of infectious virus particles in cell cultures [22,32].

9. Abbreviation. The full-name [hepatitis C virus] appears for the first time and is followed by the abbreviation [(HCV)]. Then, HCV is used afterward. So is [World Health Organization (WHO)].

**Response:**

“...the hepatitis C virus (HCV) genetics...”

“...breakthroughs enabled the World Health Organization (WHO) to set the...”

10. Please cite the original article rather than the comments or review articles written by other authors. [Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989; 244:359-362.] for the clone 5-1-1; [Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T, Dienstag JL, Alter CE, Stevens CE, Tegtmeier GE, Bonino F, Colombo M, Lee WS, Kuo C, Berger K, Shuster JR, Overby LR, Bradley DW, Houghton M. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science. 1989; 244:362-364.] for the antibody detection.

**Response:**

Original references added:

26.- Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T,

Dienstag JL, Alter CE, Stevens CE, Tegtmeier GE, Bonino F, Colombo M, Lee WS, Kuo C, Berger K, Shuster JR, Overby LR, Bradley DW, Houghton M. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science*. 1989; **244**:362-364

PMID: 2496467 DOI: 10.1126/science.2496467

31.- **Choo QL**, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M.

Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989;**244**:359-362.

11. Line 5, page 3, Please add the WHO website after [by 2030].

**Response:**

Completed: World Health Organization (WHO) to set the, once unthinkable, goal for HCV elimination by 2030<sup>[3]</sup>.

3.- **World Health Organization GWHO**. Global health sector strategy on viral hepatitis 2016-2021 WHO ref. No. WHO/HIV/2016.06, june 2016

Available from: [https:// www.who.int/publications/i/item/WHO-HIV-2016.06](https://www.who.int/publications/i/item/WHO-HIV-2016.06)

12. English editing is suggested. For example, Line 5, page 3, [. apart from laying the ground work for a new approach to study infections in general and developing new antiviral agents. Moreover, we can speculate] It is difficult for me to follow.

**Response:**

Previous: The progress achieved through those scientific breakthroughs most certainly supported positively WHO decision to set the once unthinkable goal for HCV elimination by 2030 (3) apart from laying the ground work for a new approach to study infections in general and developing new antiviral agents. Moreover, we can speculate that the advances from the molecular genetic approach to the study and diagnosis of hepatitis C



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virus summarized here (Fig.1) may have benefited the current approach to deal with the new pandemics.

Re-written: These scientific breakthroughs enabled the World Health Organization (WHO) to set the, once unthinkable, goal for HCV elimination by 2030<sup>[3]</sup>. The implications of this work are not limited to hepatitis C as the new diagnostic techniques and methods of drug development may be applicable to other viral pathogens.

(The whole manuscript was reviewed by one the authors who is a native English speaker.)

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 76171

**Title:** Milestones in the discovery of hepatitis C

**Reviewer's code:** 03022180

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

was delighted to read this opinion review entitled "Milestones in the discovery of Hepatitis C." It is well written, up-to-date and brings pleasant memories to the readers dealing with viral hepatitis in the old times. I have a few minor comments that might be considered by the authors as follows:

Introduction: Session: DISCOVERY OF HEPATITIS C. INTRODUCTION The word introduction would fit better as the subtitle of this session Page 3, Line 4: Second Nobel prize: It would be interesting to point out the first one. Page 5: "mentally retarded children" could be substituted for a better term, like "children with mental disorders," maybe... There are "track changes" comments throughout the manuscript. Please delete them.

**Response:**



A)

## **“INTRODUCTION**

For those of us who grew up in the hepatology field when non-A non-B hepatitis (what a strange name!) was a common topic of discussion in the clinic and the laboratory, the...”

B) added:

(the first Nobel prize was awarded to Baruch Blumberg in 1976 for the discovery of hepatitis B virus [9].

C)

Page 5: “mentally retarded children changed to “children with mental disorders”. Page 5, 2<sup>nd</sup> paragraph.

D)

Track changes deleted accordingly.

Session: ELIMINATION OF HEPATITIS C In order to update the text, the authors could include the main drawbacks that limit hepatitis C elimination nowadays, like the SARS-COV pandemic, among others. In addition, the heterogeneity among the different continents regarding testing and HCV treatment should be emphasized.

### **Response:**

Lines added:

While there have been technical, geographic and policy limitations such as limited funding, lack of transparency and high in-country process, fragmented procurement, HCV diagnostics inefficiencies [3] and most recently the SARS-COV 2 pandemic to mention a few there have been many examples around the globe showing that the goals are feasible [35].

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 76171

**Title:** Milestones in the discovery of hepatitis C

**Reviewer's code:** 03261931

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

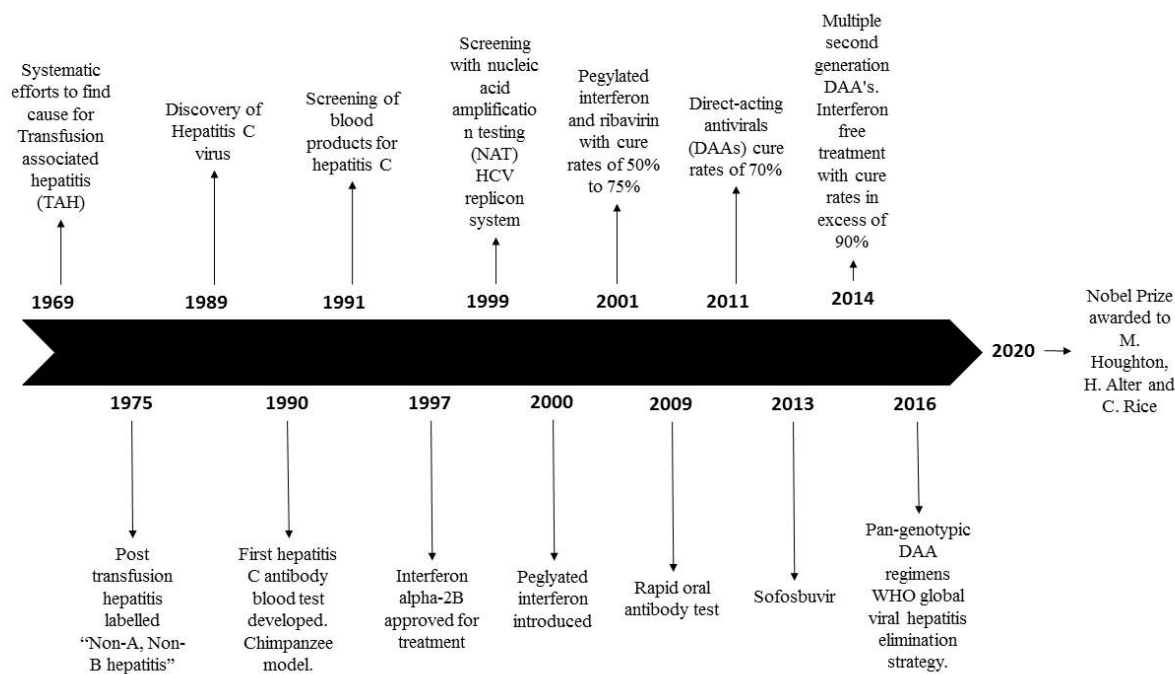
### SPECIFIC COMMENTS TO AUTHORS

The review is of clinical and scientific importance in the field of biomedical science and well written. Just only few comments.

Major comments:

1. Please provide a figure with the timeline of landmark milestones of HCV history.

**Response:**



2. Please address the unmet issues that need to be resolved currently, especially the post-SVR liver complication (Huang CF, et al. Clin Mol Hepatol. 2020 Jul;26(3):251-260.)

### Response:

Corrected Middle of 2<sup>nd</sup> paragraph page 9 :

"Patients with hepatitis C infection with cirrhosis or decompensated liver disease present special challenges such as post-SVR complications including HCV reinfection, hepatocellular carcinoma (HCC) risk, residual HCC (7,34) which should be addressed by early detection and treatment, combination and multiple DAA therapy avoiding the use of protease inhibitors and risk reduction counselling (7,20) ."

Minor comments: 3. Page 3, para 2. "entry inhibitors, protease inhibitors, polymerase inhibitors and NS5A inhibitors [3,4] the former being the most successful prodrug developed and currently used in the WHO policy for world elimination of hepatitis C". Actually, entry inhibitors are not currently available DAA in clinical practice.

**Response:**

We corrected and deleted the “entry inhibitors” part:

...attacking many targets directly (in the hepatitis C virus lifecycle) i.e., protease inhibitors, polymerase inhibitors and NS5A inhibitors [4,5,6] the former being the most successful prodrug developed and currently used in the WHO policy for world elimination of hepatitis C [6,7] aimed at either, virion processing, RNA replication and virion assembly in the liver cell [6,8].

4. Page 9, para 4. “That is a 90 % reduction in incidence and a 65 % reduction in mortality by 2020 and a new guidance was released in June 2021.” It should be “That is a 90 % reduction in incidence and a 65 % reduction in mortality by 2030 and a new guidance was released in June 2021”.

**Response:**

A)

We corrected and deleted the “entry inhibitors” part.

B)

. “...2021” has been corrected to say “...2030” Page 10, 1st paragraph.

5. The English should be reviewed by native English experts.

**Response:**

(The whole manuscript was reviewed by one of the authors who is a native English speaker.)

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 76171

**Title:** Milestones in the discovery of hepatitis C

**Reviewer's code:** 02528485

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

This revised manuscript is recommended to be accepted.

**Response:**

No comments