Project Information

1R43AI052686-01

DESCRIPTION DETAILS **RESULTS** HISTORY SUBPROJECTS

Project Number: 1R43AI052686-01
Former Number: 1R44AI052686-01
Contact PI / Project Leader: STUYVER, LIEVEN J
Title: MODIFIED NUCLEOSIDES FOR HEPATITIS C VIRUS
Awardee Organization: PHARMASSET, INC.

Abstract Text:

DESCRIPTION (provided by applicant): There are currently nearly 3 million HCV carriers in the U.S. (2% of the population) and an estimate 170 million people worldwide. The Centers for Disease Control and Prevention indicate that approximately 10,000 people died as a result of hepatitis-C infections last year and that, by 2010, the annual death toll will overtake that of HIV. The only licensed therapy for chronic hepatitis is interferon (IFN)-alpha, either alone or in combination with ribavirin. There are several side-effects related to these treatments, and the response rate is only in the range of 40%. Therefore, there is an urgent need for more therapeutic options. Using novel screening algorithms for HCV-replicon bearing Huh7 cells, two anti-HCV compounds were selected for further evaluation. These compounds inhibit the HCV replication without affecting cellular polymerases or mitochondrial functions. Funding from the combined SBIR phase 1 and 2 grant will be used to select the compound with the greatest potential for commercialization for the treatment of chronic HCV. The SBIR phase 1 component will determine the pharmacokinetics in two animal models, and will generate short-term efficacy data in chronic HCV-infected chimpanzees. Phase 2 will include advanced toxicological and early human studies.

Project Terms:

antiviral agents; drug screening /evaluation; Flaviviridae; hepatitis C virus; laboratory mouse; laboratory rat; nucleoside inhibitor; nucleosides; Pan; pharmacokinetics; replicon; virus replication

Contact PI Information:	Program Official Information:	Other PI Information:
Name: STUYVER, LIEVEN J **Email**: Click to view contact PI email address **Title**:	**Name**: Unavailable	Not Applicable

Organization:	Department / Educational Institution Type:	Congressional District:
Name: PHARMASSET, INC. **City**: TUCKER Country: UNITED STATES (US)	Unavailable Unavailable	State Code: GA District: 04

Other Information:

FOA:
Study Section: Special Emphasis Panel (ZRG1-SSS-K (10)B)
Fiscal Year: 2002 **Award Notice Date**: 30-AUG-2002
DUNS Number:
Project Start Date: 1-SEP-2002
Budget Start Date: 1-SEP-2002
CFDA Code: 856
Project End Date: 28-FEB-2004
Budget End Date: 28-FEB-2004

Administering Institutes or Centers:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Project Funding Information for 2002:

Total Funding: $162,200

Year	Funding IC	FY Total Cost by IC
2002	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$162,200

History:

Subprojects:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
No Projects information available for 1R43AI052686-01								

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC

No Subprojects information available for 1R43AI052686-01

Project Information

1R43AI056720-01

DESCRIPTION DETAILS **RESULTS** HISTORY SUBPROJECTS

Project Number: 1R43AI056720-01
Title: NOVEL CLASS OF COMPOUNDS FOR TREATMENT OF HCV INFECTIONS

Contact PI / Project Leader: PANKIEWICZ, KRZYSZTOF W
Awardee Organization: PHARMASSET, INC.

Abstract Text:

DESCRIPTION (provided by applicant): Hepatitis C virus (HCV) has already caused a global epidemic, but the worst may be to come. According to the CDC nearly 4 million people have been infected with HCV in the U.S. alone. A fourfold increase in the number of adults diagnosed with chronic HCV infection is projected up to 2015. Most persons with chronic HCV infection have yet to be diagnosed and are likely to come to medical attention in the next decade. Although about a dozen of agents have been claimed to be active against HCV, currently there is no effective treatment available. During the course of our search for nucleosides that may inhibit replication of bovine viral diarrhea virus (BVDV), used as an HCV surrogate, we discovered potent inhibitory activity of 3-beta-D-ribofuranosyl-9,5'-cyclopurine derivative, e.g. nucleoside derivative containing the bicyclo[4.2.1]nonane ring system. This compound also shows potent and selective activity in the HCV replicon system. Clearly, this compound is not an inhibitor of HCV RNA polymerase and its mechanism of action is currently unknown. SAR-based synthetic efforts are proposed by examination of 3 classes of derivatives of the lead compound with modification at the sugar moiety and/or the pyridone ring of the purine base as well as the triazole moiety. Since certain nucleosides with 2'-dehydro-2'-methyl-D-ribofuranose showed a potent anti-HCV activity the lead compound(s) will be substituted with the 2'-"beta"-(up)-methyl group. The modification of the six-membered ring and the triazole ring of the base will show the importance of the base on the anti-HCV activity of proposed compounds. It is expected that new compounds with improved anti-HCV potential will emerge from these studies and proposed SAR may help to understand the mechanism of action of this class of compounds.

Project Terms:

cytotoxicity; DNA directed RNA polymerase; drug design /synthesis /production; hepatitis C; hepatitis C virus; microorganism disease chemotherapy; nucleoside analog; pharmacokinetics; purines; replicon

Contact PI Information:	Program Official Information:	Other PI Information:
Name: PANKIEWICZ, KRZYSZTOF W **Email**: Click to view contact PI email address **Title**: SENIOR ASSOCIATE DIRECTOR	**Name**: Unavailable	Not Applicable

Organization:	Department / Educational Institution Type:	Congressional District:
Name: PHARMASSET, INC. **City**: TUCKER Country: UNITED STATES (US)	Unavailable Unavailable	State Code: GA District: 04

Other Information:

FOA:
Study Section: Special Emphasis Panel (ZRG1-SSS-L (10)B)
Fiscal Year: 2003 **Award Notice Date**: 7-JUL-2003

DUNS Number:
Project Start Date: 15-JUL-2003
Budget Start Date: 15-JUL-2003

CFDA Code: 856
Project End Date: 14-JUL-2004
Budget End Date: 14-JUL-2004

Administering Institutes or Centers:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Project Funding Information for 2003:

Total Funding: $175,000

Year	Funding IC	FY Total Cost by IC
2003	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$175,000

History:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
1R43AI056720-01		NOVEL CLASS OF COMPOUNDS FOR TREATMENT OF HCV INFECTIONS	PANKIEWICZ, KRZYSZTOF W	PHARMASSET, INC.	2003	NIAID	NIAID	$175,000

Subprojects:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC
No Subprojects information available for 1R43AI056720-01							

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Project Information

1R01DK066922-01

DESCRIPTION DETAILS **RESULTS** HISTORY SUBPROJECTS

Project Number: 1R01DK066922-01
Title: 2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS
Contact PI / Project Leader: DU, JINFA
Awardee Organization: PHARMASSET, INC.

Abstract Text:

DESCRIPTION (provided by applicant): Current therapies for chronic HCV infections are inadequate because of low response rates, toxic side effects, and unsustained viral load reductions. As with other chronic infections (HBV and HIV-1), long-term therapy with multiple drugs will most likely be required to successfully treat chronic HCV infections and significantly reduce or eliminate progressive hepatocellular damage and hepatocellular carcinoma. The only licensed therapy for chronic HCV is interferon (IFN)-alpha, either alone or in combination with ribavirin. Combination therapy with ribavirin and IFN-alpha for 6 to 12 months is currently the treatment of choice for HCV infection. The overall sustained response rate to treatment, defined as loss of HCV from serum 6 months after completion of treatment, is 40%. Thus, there is an urgent need for better agents to treat chronic HCV infections. We have designed a novel antiviral against HCV screening technology using the HCV replicon system. Using this approach we identified modified nucleoside analogues with potent and selective in vitro anti-HCV activity. In this grant proposal, we plan to design and synthesize a total of one hundred and ninety novel 2'-C- and/or 4'-C-modified nucleosides, as well as 3'-deoxynucleosides as potential anti-HCV agents. We will determine the anti-HCV activity of a series of newly designed compounds in vitro. In addition, in preparation for in vivo proof of principle studies, adequate safety and favorable pharmacokinetic (PK) profiles of candidate compounds will be determined in relevant animal models. Furthermore, potent HCV polymerase inhibitors will be used to select for drug-resistant viral mutants, and therefore, selection of HCV replicons with the proper mutations will be a relevant part of this proposal.

Project Terms:

antiviral agents; biotherapeutic agent; chemical synthesis; dosage; drug design /synthesis /production; drug screening /evaluation; enzyme inhibitors; hepatitis C; hepatitis C virus; laboratory mouse; Macaca fascicularis; nucleoside analog; pharmacokinetics; polymerase chain reaction; replicon; SDS polyacrylamide gel electrophoresis; site directed mutagenesis; tissue /cell culture; western blottings

Contact PI Information:	Program Official Information:	Other PI Information:
Name: DU, JINFA **Email**: Click to view contact PI email address **Title**:	**Name**: DOO, EDWARD **Email**: Click to view PO email address	Not Applicable

Organization:	Department / Educational Institution Type:	Congressional District:
Name: PHARMASSET, INC. **City**: TUCKER Country: UNITED STATES (US)	Unavailable Unavailable	State Code: GA District: 04

Other Information:

FOA: RFA-DK-03-011
Study Section: Special Emphasis Panel (ZRG1-GMA-2 (50)R)
Fiscal Year: 2004 **Award Notice Date**: 9-SEP-2004
DUNS Number:
Project Start Date: 15-SEP-2004
Budget Start Date: 15-SEP-2004
CFDA Code: 848
Project End Date: 31-JUL-2007
Budget End Date: 31-JUL-2005

Administering Institutes or Centers:

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Project Funding Information for 2004:

Total Funding: $189,277

Year	Funding IC	FY Total Cost by IC
2004	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES	$189,277

History:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
5R01DK066922-03		2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS	DU, JINFA	PHARMASSET, INC.	2006	NIDDK	NIDDK	$1
5R01DK066922-02		2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS	DU, JINFA	PHARMASSET, INC.	2005	NIDDK	NIDDK	$194,954

1R01DK066922-01	2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS	DU, JINFA	PHARMASSET, INC.	2004	NIDDK	NIDDK $189,277

Subprojects:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC

No Subprojects information available for 1R01DK066922-01

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Project Information

5R01DK066922-03

DESCRIPTION DETAILS **RESULTS** HISTORY SUBPROJECTS

Project Number: 5R01DK066922-03
Title: 2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS
Contact PI / Project Leader: DU, JINFA
Awardee Organization: PHARMASSET, INC.

Abstract Text:

DESCRIPTION (provided by applicant): Current therapies for chronic HCV infections are inadequate because of low response rates, toxic side effects, and unsustained viral load reductions. As with other chronic infections (HBV and HIV-1), long-term therapy with multiple drugs will most likely be required to successfully treat chronic HCV infections and significantly reduce or eliminate progressive hepatocellular damage and hepatocellular carcinoma. The only licensed therapy for chronic HCV is interferon (IFN)-alpha, either alone or in combination with ribavirin. Combination therapy with ribavirin and IFN-alpha for 6 to 12 months is currently the treatment of choice for HCV infection. The overall sustained response rate to treatment, defined as loss of HCV from serum 6 months after completion of treatment, is 40%. Thus, there is an urgent need for better agents to treat chronic HCV infections. We have designed a novel antiviral against HCV screening technology using the HCV replicon system. Using this approach we identified modified nucleoside analogues with potent and selective in vitro anti-HCV activity. In this grant proposal, we plan to design and synthesize a total of one hundred and ninety novel 2'-C- and/or 4'-C-modified nucleosides, as well as 3'-deoxynucleosides as potential anti-HCV agents. We will determine the anti-HCV activity of a series of newly designed compounds in vitro. In addition, in preparation for in vivo proof of principle studies, adequate safety and favorable pharmacokinetic (PK) profiles of candidate compounds will be determined in relevant animal models. Furthermore, potent HCV polymerase inhibitors will be used to select for drug-resistant viral mutants, and therefore, selection of HCV replicons with the proper mutations will be a relevant part of this proposal.

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antiviral agents; biotherapeutic agent; chemical synthesis; dosage; drug design /synthesis /production; drug screening /evaluation; enzyme inhibitors; hepatitis C; hepatitis C virus; laboratory mouse; Macaca fascicularis; nucleoside analog; pharmacokinetics; polymerase chain reaction; replicon; SDS polyacrylamide gel electrophoresis; site directed mutagenesis; tissue /cell culture; western blottings

Contact PI Information:	Program Official Information:	Other PI Information:
Name: DU, JINFA **Email**: Click to view contact PI email address **Title**:	**Name**: DOO, EDWARD **Email**: Click to view PO email address	Not Applicable

Organization:	Department / Educational Institution Type:	Congressional District:
Name: PHARMASSET, INC. **City**: TUCKER Country: UNITED STATES (US)	Unavailable Unavailable	State Code: GA District: 04

Other Information:

FOA: RFA-DK-03-011
Study Section: Special Emphasis Panel (ZRG1-GMA-2 (50)R)
Fiscal Year: 2006 **Award Notice Date**: 18-SEP-2006
DUNS Number:
Project Start Date: 15-SEP-2004
Budget Start Date: 1-AUG-2006
CFDA Code: 848
Project End Date: 31-JUL-2007
Budget End Date: 31-JUL-2007

Administering Institutes or Centers:

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Project Funding Information for 2006:

Total Funding: $1

Year	Funding IC	FY Total Cost by IC
2006	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES	$1

History:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
5R01DK066922-03		2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS	DU, JINFA	PHARMASSET, INC.	2006	NIDDK	NIDDK	$1
5R01DK066922-02		2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS	DU, JINFA	PHARMASSET, INC.	2005	NIDDK	NIDDK	$194,954

1R01DK066922-01	2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS	DU, JINFA	PHARMASSET, INC.	2004	NIDDK	NIDDK $189,277

Subprojects:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC
No Subprojects information available for 5R01DK066922-03							

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