



Review Article

Progress in developing hepatitis C virus prophylactic and therapeutic vaccines

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ABSTRACT

Hepatitis C virus (HCV) has chronically infected an estimated 200 million people worldwide. This makes HCV one of the greatest public health threats of this century. Effective strategies for containment are mandatory. Significant progress has been made in the area of HCV therapy. In addition to the four DAA molecules approved by Food and Drug Administration (FDA) in 2011 and 2013, the drug development pipeline contains several compounds that hold promise to achieve the goal of a short and more tolerable therapy, and are also likely to improve treatment response rates. Nevertheless, due to issues of expected drug resistance, drug-drug interaction, and particularly because of their extremely high cost, it is questionable that new HCV drugs will markedly reduce the world's HCV infected population or the estimated global incidence of millions of new HCV infections. Hence, there is a crucial need to find other options. A prophylactic HCV vaccine can halt the spread of HCV infection, and therapeutic vaccines can help in the treatment of chronically infected patients. A plethora of approaches has been undertaken towards developing a therapeutic/prophylactic vaccine against HCV infection. These include; peptide-based vaccines, DNA-based vaccines, recombinant protein-based vaccines, virus like particles-based vaccines, viral vector-based vaccines, and dendritic cells(DCs) vaccines. Early frequent trials for making prophylactic/therapeutic HCV vaccines were met with failure. The recent progress in knowledge of immune correlates of HCV infection, combined with the demonstrated immunogenicity and protective animal efficacies of various HCV vaccine candidates have paved the way towards success. This review will discuss the most recent advances in this context, and will present future suggestions as regards HCV vaccine.

Keywords

HCV, vaccine, prophylactic vaccine, therapeutic vaccine.

Introduction

Global epidemiology of HCV infection

Nearly 2%, 3% of the world's populations are infected with HCV. In many developed countries, the prevalence of HCV infection is <2%. The prevalence is higher

(>2%) in several countries in Latin America, Eastern Europe, the former Soviet Union, and certain countries in Africa, the Middle East, and South Asia. The prevalence is

reported to be the highest (>10%) in Egypt, figure (1) (Papatheodoridis and Hatzakis, 2012).

HCV genome

HCV is a positive-stranded RNA virus, figure (2) characterized by high sequence heterogeneity. Seven HCV genotypes, numbered 1 to 7, and a large number of subtypes have been described (European Association for the Study of the Liver, 2014). Genotypes and subtypes (which are identified by lowercase letters), differ among themselves by nearly 20% - 30% of their sequence respectively.

Natural history of HCV infection

After infection with HCV, a sequence of events can occur. The natural history of HCV is presented in figure (3) (Holmes et al., 2013).

Treatment of HCV infection

Until 2011, the standard care of therapy (SOC) for chronic HCV was a combination of pegylated interferon- α (peg IFN- α) and ribavirin, (Manns et al., 2006). Response varies with different genotypes,(European Association for the Study of the Liver, 2014) In 2011, the first-generation direct-acting antivirals (DAAs), telaprevir (TVR) and boceprevir (BOC) were licensed for use in HCV genotype 1 infection in addition to a backbone of SOC. These triple therapy regimens have proven effective for treatment-naïve and for treatment-experienced patients, including previous null responders, (Sarrazin et al., 2012).In 2013, sofosbuvir, and semiprevir, (Reardon, 2013) have been approved by FDA as a pangenotypic molecules for treatment of HCV. Other DAAs at different stages of clinical development, are now investigated. (Manns and von Hahn, 2013).

The need for an HCV vaccine

Many challenges exist as regards the management of HCV infection. First of all is the low rate of diagnosis,(Holmes, 2013). Second, is that even if a certain rate of treatment can be achieved, reinfection, can still poses a problem. Third, it is established that genetic determinants in the host and the virus can prevent 100% efficacy,(Ge et al., 2009). Fourth, is the association of the SOC with many side effects. Fifth, although the DAAs represent a step forward in the treatment of HCV, other problems occur as well, e.g., the emergence of resistance. Viral resistance against Telaprevir and Boceprevir has been associated with treatment failure. (Sarrazin et al., 2012; Susser et al., 2011)Moreover, the very high costs of these new therapies means that health-care system, even in developed countries, cannot afford to treat all patients.

For all these reasons, the development of safe, effective, and affordable vaccines against HCV remain the best long-term hope for bringing the global epidemic under control. A prophylactic vaccine is essential for high risk groups and for countries where the incidence of HCV infection is high. Current data indicate that, vaccine-induced immunity may not completely prevent HCV infection but rather prevent persistence of the virus. However, this may be an acceptable goal, because chronic persistence of the virus is the main cause of pathogenesis and the development of serious liver conditions. A therapeutic vaccine approach is also sought to replace or enhance treatment. Major benefits in expenses and logistics would be gained if patients could be treated with 2–3 doses of such vaccine with/without SOC, as opposed to several months of combination drug therapy (Amer et al., 2014).The need for an HCV vaccine has been emphasized in 2011

when the US Department of Health and Human Services issued the Viral Hepatitis Action Plan (http://www.hhs.gov/ash/initiatives/hepatitis/actionplan_viral_hepatitis2011.pdf).

Challenges for developing an HCV vaccine

First of all, is the genetic heterogeneity which is a hallmark of HCV as RNA virus? Moreover, there are technical limitations in the study of HCV, mainly as regards the limited availability of convenient small animal models other than the chimpanzee, mimicking HCV infection in humans. (Murray and Rice, 2011; Welsch et al., 2012).

A successful HCV vaccine should address viral heterogeneity, cover the various genotypes and quasispecies of HCV, and must incorporate epitopes from HCV structural proteins in their correct three-dimensional conformations, to induce the production of high titers of broad nAbs. It must also incorporate HCV-specific T-cell epitopes from HCV nonstructural proteins, to elicit strong cellular responses (Houghton, 2011; Halliday et al., 2011; Torresi et al., 2011)

Vaccine target

A key question is that, which HCV antigen a vaccine should target. The envelope region may seem the obvious target for antibody-inducing vaccine, but as discussed previously, the major antigenic determinants of the envelope protein are hypervariable both between, and within, infected individuals. The HCV core protein might appear the evident candidate for a T-cell vaccine, since this is the most highly conserved region of the translated HCV. However, early studies have shown that the

core protein can interfere with innate and adaptive anti-HCV immune responses. (Large et al., 1999; Saroeb et al. 2003) Furthermore, data suggests that in persistent infection, anticore T-cell responses are frequently detected in the absence of viral escape, suggesting that these responses in particular are unable to control viral replication. (Semmo et al., 2005) The most recent strategies have focused on inducing T-cell responses to the NS HCV antigens, which are genetically conserved, and which are known to contain multiple CD4+ and CD8+ T-cell epitopes. (Halliday and Barnes, 2011) Perhaps a targeting more than one antigen seems to be the most efficient strategy. (Lechmann, 2000)

Approach for vaccine development

Both prophylactic and therapeutic vaccine candidates have been developed. The general principals pertaining to the different vaccination approaches include: peptides vaccines, DNA vaccines, recombinant protein vaccines including the recombinant yeast-based candidates, virus-like particles vaccines, viral vector vaccines, and DC-based vaccines.

Peptide-based vaccines

One of the simplest vehicles for a therapeutic vaccine is a synthetic peptide(s) that contains the T cell epitope(s). Peptide vaccines induce HCV-specific T-cell immunity through the direct presentation of vaccine peptide to the T-cell receptor via HLA molecules. However, the major limitation of this approach is that peptide vaccines are HLA-specific and, as such, coverage will be restricted to a subset of the population. Additionally, HCV peptide vaccines to date have included only a minority of peptides, and the breadth of the induced T-cell response may be insufficient

to control infection. In addition, some peptides may potentially induce tolerance of effect or cells or Treg cells rather than inducing immunity (Klade, 2008).

IC41 is a peptide vaccine currently in clinical development. It consists of synthetic peptides from core, NS3 and NS4 proteins of HCV genotypes 1 and 2, combined with the adjuvant poly-L-arginine (Firbas et al., 2010). The peptides include three CD4+ T-cell and five HLA A2-restricted CD8+ T-cell HCV epitopes. In a Phase II study, the vaccine was well tolerated with no serious adverse events. Nevertheless, weak HCV-specific T-cell response was observed. (<http://clinicaltrials.gov/ct2/show/NCT00602784>) More recently, more frequent administration has been found to induce stronger T-cell responses (Halliday et al., 2011). Another peptide vaccine composed of peptides derived from HCV core region (C35–44) with ISA51, an emulsified incomplete Freud's adjuvant, were shown to be well tolerated in HCV-infected patients (Yutani et al., 2009).

Another phase I trial with virosome-based vaccine containing NS3 peptides derived from HCV has been completed. No data from this clinical study have been released at this time. ([http://www. Clinical trials.gov/ct2/show/NCT00445419](http://www.Clinicaltrials.gov/ct2/show/NCT00445419))

DNA-based vaccines

DNA vaccine can mimic the process of the generation of the viral proteins within cells, which is the most active field of HCV experimental vaccine (Xue et al., 2014).

The first DNA-based vaccine to reach clinical trial was CICGB-230. The vaccine is combining plasmid expressing HCV structural antigens (core/E1/E2) with recombinant core protein. In a phase I trial it was shown to be safe, partially

immunogenic, and able to stabilize liver histology despite persistent detection of HCV RNA. (Alvarez -Lajonchere et al., 2009)

ChronVac C (ChronVac-C, Tripep), is the second HCV DNA-based vaccine to reach human trials. It is a therapeutic vaccine which employs electroporation to enhance the immunogenicity of intramuscular injection of plasmid expressing HCV antigens NS3/4A (Roohvand and Kossari, 2012). In a phase I clinical trial, very convenient results were obtained, which led to performing a phase II clinical study. Although vaccination did display an excellent safety profile, only transient reduction in viral load was recorded. When SOC was added, non-significant difference between treatment outcomes of the vaccinated and non-vaccinated groups was shown. (<http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=408748>).

INO-8000 is a Synthetic Consensus (SynCon) HCV multi-antigen therapeutic vaccine targeting NS3/4A, NS4B, and NS5A proteins of HCV genotypes 1a and 1b. This vaccine has been moved into a phase I/IIa clinical trial at the end of 2013 (<http://seekingalpha.com/article/1652522-the-disruptive-potential-of-inovios-syncon-dna-vaccines>). The advancement is based on outstanding results of a preclinical study, (Lang Kuhs et al., 2012) which demonstrated that it can generate robust T-cell responses not only in the blood but, more importantly, in the liver, an organ known to suppress T-cell activity.

Recombinant protein-based vaccines

In order to develop the recombinant protein for use in HCV vaccines; genes encoding HCV viral proteins are isolated and cloned into bacteria, yeast or mammalian cells. The

recombinant protein is expressed, and then purified for use. The advantage of recombinant protein vaccines is that they do not contain the pathogen or its genetic material and they do not require cultivation of the organism (Swalding et al., 2013). Recombinant proteins used for HCV vaccine development have included envelop protein, core protein, and/or non-structural proteins, with/without adjuvant. (Feinstone et al., 2012)

Frey et al., in 2010, described the safety and immunogenicity of recombinant HCV E1E2 vaccine adjuvanted with MF59 in a phase I clinical trial in healthy volunteers. However, technical difficulties in the manufacture of E1E2 protein have hampered its use. Subsequent research have proved that the vaccine provoked antibodies directed to recognized neutralizing epitopes and the sera of chosen vaccinees prohibited *in vitro* infection by HCV genotypes 1a and 2a. (Ray et al., 2010; Stamataki et al., 2011) Very recently (Law et al., 2013) antisera from Frey et al.' phase I clinical trial, (Frey et al., 2010) was assessed for cross neutralizing activity against representatives of all seven major genotypes of HCV. Very broad cross-neutralization activity was evident but not all genotypes were neutralized with similar efficiencies. When combined with the early demonstrated efficacy of similar strategy in the chimpanzee model, (Choo et al., 1994; Ralston et al.; 1993) such findings strongly encourage the further development of this and related vaccine candidates.

ISCOMATRIX is a recombinant core protein vaccine candidate produced in yeast. It was administered with a powerful T-cell adjuvant immunostimulating complex matrix. A phase I trial was conducted in 30 healthy volunteers. All vaccinees showed vaccine-induced antibodies against HCV core protein; nevertheless T cells were

demonstrable in merely 2 receiving a high dose of vaccine. Higher doses of recombinant core protein remain to be tested (Drane et al., 2009).

The use of whole heat-killed recombinant yeast that expresses targeted molecular immunogen (tarmogen) has also been evaluated. The immunotherapeutic vaccine GI-5005, has been developed by GlobeImmune Inc. It consists of recombinant *Saccharomyces cerevisiae* yeast expressing an HCV NS3-core fusion protein designed to elicit antigen-specific host CD4+ and CD8+ T-cell responses. (Habersetzer et al., 2009). In a phase II trial, GI5005 was combined with SOC in 66 chronic HCV-1 patients. An increased SVR rates in patients homozygous for the IFN- λ 3 risk alleles was reported (Pockros et al., 2010).

Virus like particles- based vaccines

The recently developed strategy of the virus like particles- based vaccines has already proved highly promising. VLPs are generated by fusing viral antigens of interest to heterologous viral structural proteins that can self-assemble into VLPs. VLPs mimic the properties of native virions, are safe and are easily manufactured. VLPs are poorly infectious or not at all (Buonocore et al., 2002). Using VLP-based strategies for the development of HCV vaccine candidates was inspired by the successful application for infections caused by hepatitis B virus and human papillomavirus (McAleer et al. 1984; Muñoz et al. 2009).

Recently, many vaccine platforms based on VLPs have been explored as prophylactic HCV vaccine candidates, with various degrees of success (Beaumont et al. 2013; Denis et al., 2007; Garrone et al., 2011; Sominskaya et al., 2010). In 2013

researchers from France, (Huret et al., 2013) have reported that immunization with plasmid DNA forming VLPs pseudotyped with HCV E1 and E2 envelope glycoproteins (HCV-specific plasmoretrovLPs) and/or displaying NS3 antigen in capsid proteins induced strong multi-genotype/ multi-specific T-cell responses.

Viral vector-based vaccines

The use of viral vectors for the delivery of HCV RNA is an appealing vaccine choice. Adenoviral (Ad) vectors are the best identified viral vectors. (Barnes et al., 2012) Adenoviral vectors have the limitation that adenoviral infection is common in humans, and preexisting high-titer anti-vector nAbs may interfere with the immunological potency. To overcome this problem, two adenoviral vectors to which humans are rarely exposed are used; human adenovirus 6 Ad6 and chimpanzee adenovirus 3 AdCh3 (Barnes et al., 2012; Colloca et al., 2012). They have been employed to create a protective HCV vaccine, which has been tried in a phase I study of healthy human volunteers (<http://www.clinicaltrials.gov/ct2/show/NCT01070407>). Upon injection, the vaccine produced a strong and high quality T-cell response against multiple HCV proteins (from genotypes 1a and 3a). It was safe and well tolerated (Barnes et al., 2012).

Modified Virus of Ankara (MVA), is immunogenic and safe compared to other strains of poxvirus. (Yu and Chiang, 2010) A therapeutic vaccine (TG4040) using MVA that expresses NS3/4/5B proteins has been evaluated in a phase II clinical trials which has been completed (<http://clinicaltrials.gov/show/NCT01055821>). A Staged Phase I/II Study is going on to assess safety, efficacy and immunogenicity of a new hepatitis C prophylactic vaccine based on

sequential use of AdCh3NSmut1 and MVA-NSmut. This study is currently recruiting participants, and is estimated to be completed by 2016 (<http://www.clinicaltrials.gov/ct2/show/NCT01436357>).

A summary of the five approaches for HCV vaccine development is shown in table 1.

Dendritic cell-based vaccines

DC vaccination holds its promises by playing a pivotal and central role in the initiation of immune responses. Several approaches involving DC-based vaccines were used as early-stage attempts for cure of, or prophylaxis against HCV infection. Some of them were being developed at the experimental level while some advanced towards clinical trials. The most recent DC-based vaccines against HCV infection are shown in table (2)

Future vaccination approaches.

The use of VLP-based vaccines has been found to improve the delivery system for HCV neutralizing antibody- and core-specific T-cell epitopes. Perhaps one of the most important applications for VLPs is the generation of a vaccine candidate against HBV and HCV infections. Cheering data have been produced by a study of a chimeric bivalent HBV-HCV prophylactic vaccine candidate. It is based on immunization with chimeric HBV-HCV envelope particles figure (4). When used to immunize New Zealand rabbits, it elicited both humoral anti-HBs response and a strong specific antibody response to the HCV and HBV envelope proteins. The antibody response had *in vitro* cross-neutralizing properties against heterologous HCV envelope proteins derived from strains of genotypes 1a, 1b, 2a and 3. (Beaumont et al, 2013) Although further studies are still required, the results

of this study, gave an impulse to the possibility of developing a bivalent HBV-HCV prophylactic vaccine candidates.(Beaumont and Roingeard, 2013).

Another future prospect to have a successful HCV vaccine, is to use a combination modality. Concerning prophylactic vaccines, such combination will provoke responses of various aspects of the immune system. It would be very interesting to investigate, in a prime-boost regimen, a combination of vaccines; the first to target nAbs formation

and the second to target cellular immune responses (Beaumont et al, 2013; Chmielewska et al., 2014). The first could be the bivalent chimeric HBV/HCV vaccine candidate, while the second could be the adenovirus-based, figure (5).This concept remains to be tested in suitable animal models and/or clinical trials. On the other hand, therapeutic vaccines can be combined with new DAAs or host targeting antivirals, to provide a boost to complement their success in combating chronic infection and to reduce time, cost and/or side effects of using the new agents.

Table.1 A summary of the five approaches for HCV vaccine development

Strategy	Approach	Examples in clinical development	Aim	Study model (Phase)	Outcome	Manufacturer	ref
Peptides	Viral peptides + adjuvants to induce humoral and cellular immune response	Virosome-formulated peptides	Therapeutic	Human Phase I	No results posted	Pevion Biotech Ltd.	http://www.clinicaltrials.gov/ct2/show/NCT00445419
		peptides derived from core (C35–44) + ISA51+ incomplete Freud’s adjuvant		Human Phase I	- Well tolerated. - CTL &IgG: better. - RNA: minimal fall. - ALT:low decrease - α -fetoprotein: moderate decrease.	InterCell AG	Yutani et al., 2009.
		IC41		Human Phase II	- Safe & well tolerated. - Specific T cell responses. - Weak viral load reduction.	InterCell AG	http://clinicaltrials.gov/ct2/show/NCT00602784 http://clinicaltrials.gov/show/NCT00601770 .
DNA vaccines	Expression of HCV protein(s) from a DNA plasmid	(CIGB-230)	Therapeutic	Human Phase I	Safe, partially immunogenic, and able to stabilize liver histology despite persistent detection of RNA	Centro de Ingeniería Genética y Biotecnología (CIGB).	Alvarez-Lajonchere, et al., 2009
		(ChronVac-c)		Human Phase II	Excellent safety profile. Elimination/reduction of HCV viral load.	Inovio	http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=408748
		INO 8000 HCV		Phase I/IIa	Preclinical study showed the multi-antigen SynCon HCV vaccine to generate robust T-cell responses in blood and in the liver.	Inovio	http://hcvadvocate.blogspot.ca/2013/01/inovio-pharmaceuticals-to-initiate.html

rProtein	MF59-adjuvanted rgpE1/gpE2	HCV E1E2/MF59C.1	Prophylactic	Human Phase I	- Anti-gpE1/gpE2 Abs - T-cell-proliferative response - High risk of escape mutants	Novartis	http://hcvadvocate.blogspot.ca/2013/01/inovio-pharmaceuticals-to-initiate.html
	recombinant gpE1/gpE2 from a single strain (HCV1 of genotype 1a)	recombinant gpE1/gpE2 vaccine	Prophylactic	Human	Minority of vaccinees, elicited broad cross- neutralization against all HCV genotypes	Novartis	Law et al., 2013
	rCore protein vaccine produced in yeast. Administered with T- cell adjuvant immunostimulating complex matrix	ISCOMATRIX	Therapeutic	Human Phase I	- Safe and well- tolerated, - Robust Ab responses to core - T-cell cytokine responses	CSL Ltd.	Drane et al., 2009
rYeast- based vaccines	Killed <i>S. cerevisiae</i> yeast expressing a fusion protein NS3 and Core + standard therapy (PEG- IFN/ribavirin)	(GI-5005)	Therapeutic	Human Phase II	Increased SVR rates in patients homozygous for the IFN- λ 3 risk alleles	GlobeImmune, Inc.	Pockros et al., 2011
Virus like particles (VLP)	Plasmid DNA forming VLPs pseudotyped with HCV E1 and E2 envelope glycoproteins	HCV-specific plasmid- retrovLPs	Prophylactic	Mice	Broad cellular and humoral immune responses.		Huret et al., 2013
Viral vector vaccines	Adenovirus-based vaccine	HAd6 and ChAdCh3, expressing nonstructural proteins of HCV	Prophylactic	Human Phase I	- Safe and well tolerated. - Highly immunogenic response, with the induction of robust, cross-reactive and sustained CD4+ and CD8+ T cell- mediated responses.	Okairos	Barnes et al., 2012
	MVA vector expressing HCV antigens including NS3, NS4, and NS5B, followed by SOC	(TG4040)	Therapeutic	Phase II	Well tolerated, decline in HCV viral load and increased early response rates of SOC.	Transgene	http://clinicaltrials.gov/show/NCT01055821 http://www.transgene.fr/index.php?option=com_press_release&task=download&id=227&l=en

Table.2 Dendritic cell-based vaccine against hepatitis C virus infection

Vaccine	Challenge inoculum	Study model	Outcome	Reference
DC transfected with adenovirus	Adenovirus encoding NS3 protein, from HCV (AdNS3)	Mice	Multi-epitopic CD4 T helper cell 1 (Th1) and CD8 T-cell responses in different mouse strains	Zabaleta et al. 2008
DC pulsed with lipopeptide	Lipopeptides contained a CD4+T cell epitope, a HLA-A2 restricted CTL epitope and the lipid Pam2Cys	Mice Patients	Specific CD8+ T cell responses in HLA-A2 transgenic mice and six patients	Chua et al., 2008; Jones, et al. 2008
DC loaded with EDA-NS3	Fusion protein EDA-NS3, poly(I:C) and anti-CD40	<i>In-vitro</i> Mice	Strong and long lasting NS3-specific CD4 and CD8 T cell responses, down-regulated intrahepatic expression of HCV-NS3 RNA	Mansilla et al. 2009
DC containing microparticles	NS5 protein-coated microparticles	Mice	Antigen-specific CTL activity in mice and significantly reduced the growth of NS5-expressing tumour cells <i>in vivo</i>	Gehring et al. 2009; Wintermeyer et al. 2010
DC transfected with lentiviral vectors (LV)	LV expressing HCV structural or non-structural gene clusters	<i>In-vitro</i>	Potent stimulation of CD4 and CD8 T-cell allogeneic and autologous responses	Jirmo et al., 2010.
DC containing microparticles	NS5 protein-coated microparticles	Mice	Antigen-specific CTL activity in mice and significantly reduced the growth of NS5-expressing tumour cells <i>in vivo</i>	Wintermeyer et al., 2010.
DC pulsed with lipopeptides	Autologous MoDC dendritic cells loaded with HCV-specific cytotoxic T cell epitopes.	Patients	Safe, induced complex immune responses <i>in vivo</i> that may or may not lead to clinical benefit.	Gowans et al., 2010 Li et al., 2012
DCs Pulsed with novel HLA-A2-restricted CTL epitopes	DCs loaded with single or multiple-peptide mixtures of novel hepatitis C virus (HCV) epitopes	Patients (<i>bioinformatics</i>)	DCs loaded with multiple-epitope peptide mixtures induced epitope-specific CTLs responses.	Guo et al., 2012
DCs pulsed with HCV pseudo particles	Bone marrow derived DCs pulsed with pseudo particles made from type 1b E1 and E2, covering a non-HCV core structure.	Mice	Humoral and cellular immune responses. T-cell responses confirmed two highly immunogenic regions in E1 and E2 outside the HVR 1.	Weignad et al., 2012

Figure.1 Global distribution of HCV infection.

(<http://www.cosmosbiomedical.com/education/virology/hepatitisvirus.shtml>)

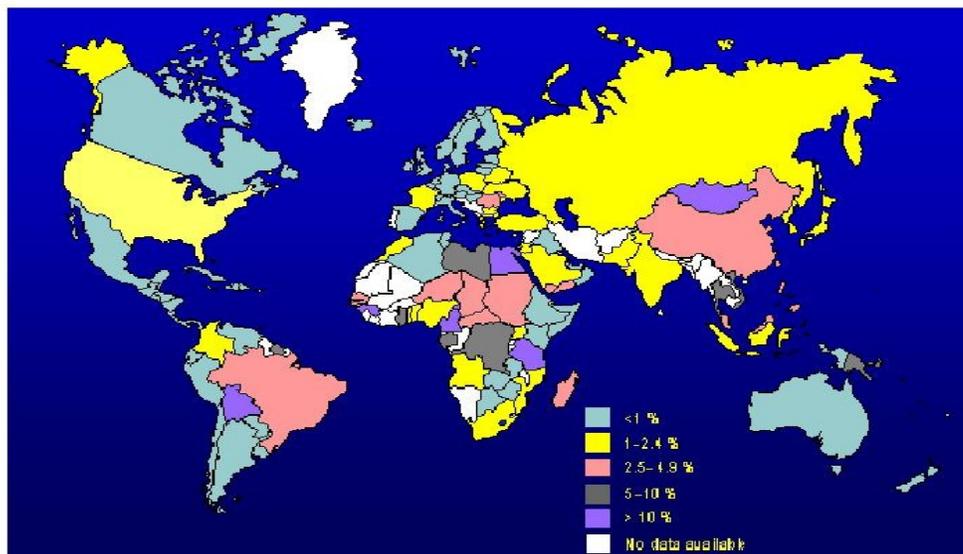


Figure.2 The hepatitis C virus (HCV) genome, adapted from Tan et al., (2002)

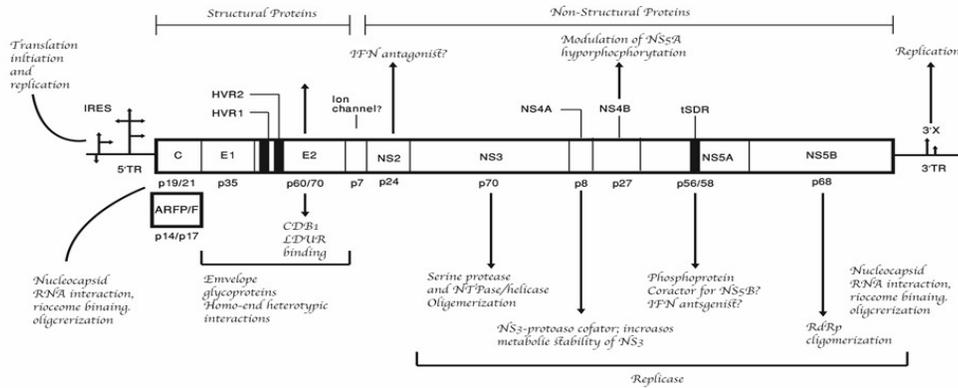


Figure.3 The natural history of HCV, adapted from Holmes et al., (2013)

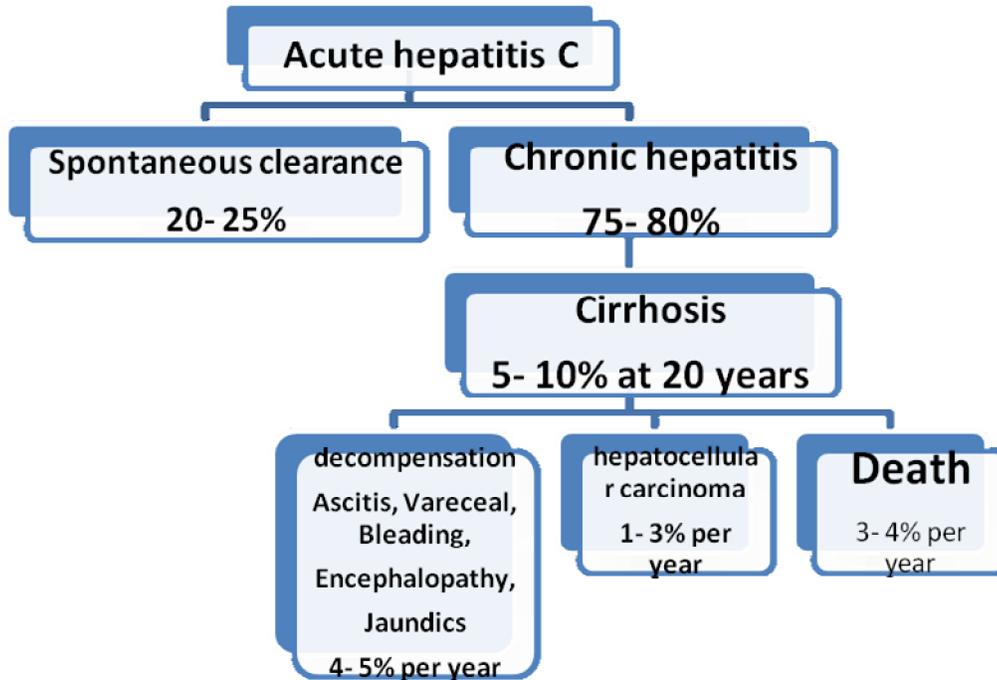


Figure.4 Transmembrane topology of the wild-type HBV S and HCV E1 and E2 envelope proteins and of the HBV–HCV E1-S and E2-S chimeric proteins used in this study. The boxes indicate the hydrophobic domains of these proteins, anchored in the ER membrane. Coassembly with HBV S refers to the ability of the HBV–HCV chimeric proteins to coassemble with the wild-type HBV S into a subviral envelope particle, following the production of the chimeric protein together with the HBV S-protein, adapted from Patient et al., (2009)

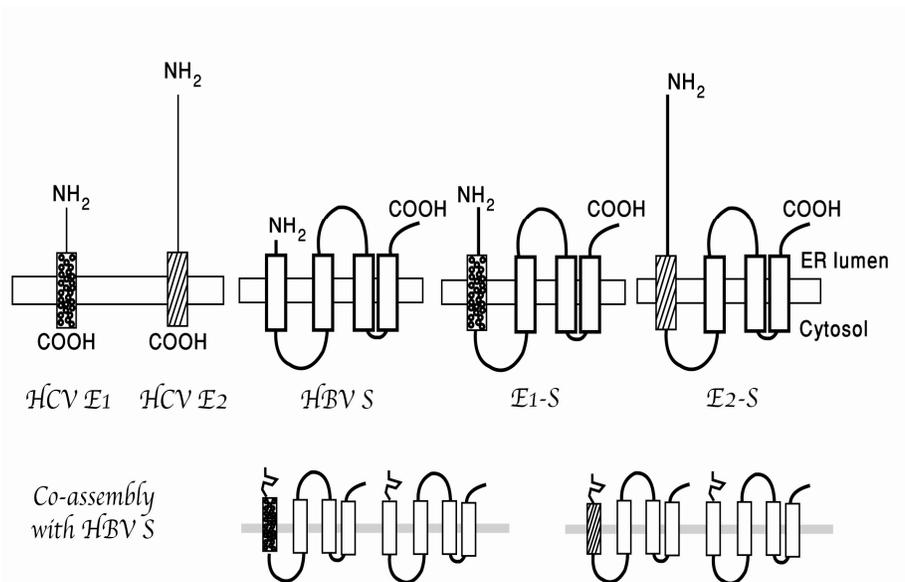
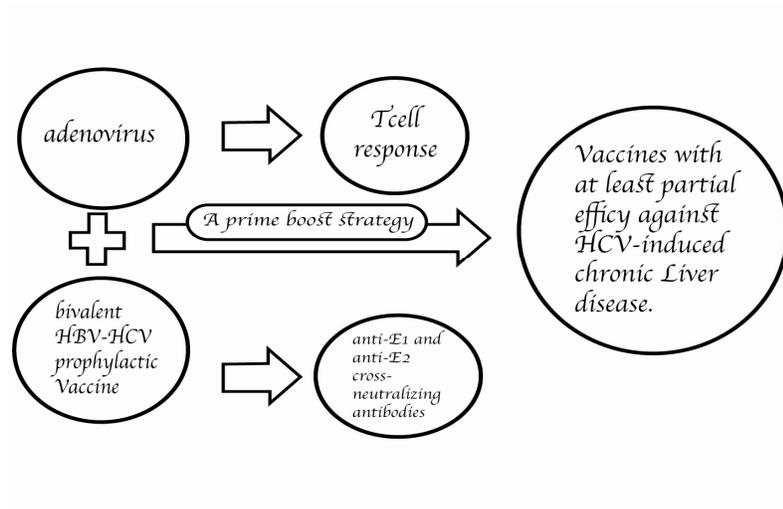


Figure.5 Suggested prime-boost regimen, to target nAbs formation and cellular immune responses for possible development of an HCV vaccine, (Amer, 2013)



Due to the global prevalence and long-term complications of chronic HCV infection, it constitutes one of the greatest challenges to human health of this decade. There have been tremendous advances in the development of antiviral therapy to treat chronic HCV infections. However, there still remains the problem of treating chronically infected persons for whom the use of antiviral drugs is impractical because of cost and logistics. Availability of therapeutic and prophylactic vaccine can provide more cost-effective alternatives.

The ultimate path to a successful vaccine requires comprehensive evaluations of all aspects of protective immunity, and innovative application of state-of-the-art vaccine technology. As moving from bench to bedside, clinical trials to test the efficacy of any vaccine candidate would have to be carefully conducted to affirm definitive endpoints of efficacy. To date, no therapeutic vaccine candidates have achieved SVRs. Furthermore, prophylactic vaccination approaches are still not finalized. However, promising results for several types of HCV vaccination in clinical trials, suggest that it should be possible to develop HCV vaccine candidates in the near future.

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