HEPATITIS C – TRI DECENIJE PUTA OD OTKRIĆA DO NOBELOVE NAGRADE

UVODNIK

EDITORIAL

HEPATITIS C – THREE DECADES OF THE PATH FROM DISCOVERY TO THE NOBEL PRIZE

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UVOD

Ove godine, Nobelova nagrada za medicinu dodeljena je trojici naučnika koji su pre 31 godinu identifikovali novi, krvlju prenosivi primarno-hepatotropni virus (engl. *blood born virus-BBV*). Bio je to hepatis C virus (HCV), uzročnik istoimene infekcije i globalnog zdravstvenog problema koji se povezuje sa teškim komplikacijama, cirozom jetre i hepatocelularnim karcinomom (HCK). Zbog ovog velikog otktića trojice laureta ovogodišnje Nobelove nagrade – Harvija Altera, Majkla Hotona i Čarlsa Rajsa, kojim su zadužili čitavo čovečanstvo, nezamislivo je da se, u godini kada im je dodeljeno najprestižnije priznanje za otkrića u nauci, ne osvrnemo na njihov rad [1].

Hepatitis C virus je nova paradigma za identifikaciju i kontrolu virusnih infekcija, a njegovo otkriće je postalo prekretnica u borbi protiv virusnih bolesti tokom 20. veka. Od trenutka kada je HCV, kao novi BB hepatotropni virus identifikovan, pokrenuta je era naglog razvoja veoma osetljivih laboratorijskih testova za njegovo dokazivanje, što je uslovilo da posttransfuzijski hepatitis C u velikom delu, posebno razvijenog sveta, bude iskorenjen, a tendencija je da se i u ostatku sveta, prevalencija posttransfuzijske HCV infekcije svede na zanemarljive procente [2]. Takođe, ovo otkriće je dovelo do napretka u lečenju HCV infekcije, dizajniranjem veoma efikasnih antivirusnih lekova, kojima se HCV infekcija u potpunosti stavlja pod kontrolu, daje

INTRODUCTION

This year, the Nobel Prize in Medicine was awarded to the three scientists who, 31 years ago, identified a new, blood-borne, primarily hepatotropic virus (BBV). This was the hepatitis C virus (HCV) that causes the infection with the same name, which is a global health problem linked to serious complications, such as liver cirrhosis and hepatocellular carcinoma (HCC). Because of this major discovery achieved by this year's laureates of the Nobel Prize – Harvey Alter, Michael Houghton and Charles M. Rice, a discovery which the whole world has these scientists to thank, it is quite natural that, in the year when they are awarded this most prestigious prize, we should pay tribute to their work [1].

The hepatitis C virus is a new paradigm for the identification and control of viral infections, and its discovery has become a milestone in the fight against viral diseases in the 20th century. From the moment the HCV, as a new BB hepatotropic virus, had been identified, an era of rapid development of very sensitive laboratory tests for its detection started, which in turn, resulted in posttransfusion hepatitis C being eradicated in a large part of the developed world, with a tendency of decreasing the prevalence of posttransfusion HCV infection in the rest of the world to negligible percentages [2]. Also, this discovery has brought about advancements in the treatment of HCV infection, through the design of very efficient antiviral drugs, which completely put the HCV

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se šansa koja bi mogla da dovede do izlečenja i po prvi put postoji nada da će doći do iskorenjavanja HCV iz svetske populacije. Ipak, ovaj cilj je globalan i zahteva međunarodne napore kako bi se testiranje na HCV kao i savremena anti-virusna terapija novim, direktno delujućim anti HCV lekovima učinili dostupnim širom sveta. Ovo je imperativ koji su Alter, Hoton i Rajs postavili kao cilj koji treba da reše novi timovi naučnika [3].

NOVI, NEPOZNATI VIRUS UZROČNIK HEPATITISA – KAKO JE SVE POČELO

Već u prvoj polovini 20. veka bilo je jasno da postoje dve vrste hepatitisa virusne etiologije. Prvi otkriveni uzročnik virusnog hepatitisa bio je hepatitis A virus (HAV), koji se prenosi putem kontaminirane hrane, vode ili prljavim rukama i uspostavlja samo akutnu infekciju bez težih i dugoročnih sekvela po zdravlje ljudi. 60-tih godina istog veka je Baruh Blumberg identifikovao novi hepatitis virus koji se prenosi krvlju i drugim telesnim tečnostima. Bio je to hepatitis B virus (HBV), koji, pored akutne, može da uspostavi i hroničnu infekciju [4]. Utvrđeno je da HBV obično uspostavlja hroničnu infekciju tiho i neprimetno, te se infekcija često dijagnostikovala kada su nastajale teške kliničke forme ili komplikacije hronično uspostavljene infekcije, kao što su ciroza jetre i hepatocelularni karcinom. Blumberg je, 1976. godine, za identifikaciju novog virusnog patogena, dobio Nobelovu nagradu za medicinu. Otkriće HBV je vrlo brzo pokrenulo niz daljih istraživanja, koja su uslovila rad na osetljivim dijagnostičkim testovima za rano otkrivanje HBV infekcije, kao i istraživanja na polju prevencije i terapije. Ova istraživanja su rezultovala otkrivanjem veoma uspešnih antivirusnih lekova sa visokom genetičkom barijerom za nastanak virusne rezistencije, što ih čini izuzetno delotvornom terapijom kod pacijenata sa hroničnim B hepatisom. Takođe, dizajnirana je efikasna anti-HBV vakcina od koje se u skorijoj budućnosti očekuje da će dovesti do iskorenjivanja HBV iz svetske populacije [5].

KAKO SE SKLAPALA SLAGALICA O NOVOM BB VIRUSU, UZROČNIKU HEPATITISA C

U periodu između 60-tih i 70-tih godina 20. veka, Alter je radio zajedno sa Blumbergom na usavršavanju metodologije za dokazivanje HBsAg, glikoproteina u omotaču HBV, koji kasnije postaje glavni kandidat za razvoj uspešne anti-HBV vakcine. Ranih 70-tih godina, Alter sa svojim naučnim timom, primećuje učestalu pojavu hepatitisa kod pacijenata koji su primili transfuzije krvi, iako su već u to vreme postojali serološki testovi za dokazivanje HBV, koji su mogli da eliminišu HBV kao potencijalnog uzročnika posttransfuzijskog hepatitisa.

infection under control, providing a chance that can lead to a cure and, for the first time, offering hope that the HCV will be eradicated from the world population. However, this goal is global and requires international efforts in order to make HCV testing as well as up-to-date antiviral therapy with new, direct-acting anti-HCV drugs, accessible all over the world. This is an imperative which has been set as a goal before new teams of researchers by Alter, Houghton and Rice [3].

THE NEW UNKNOWN VIRUS CAUSING HEPATITIS – HOW IT ALL BEGAN

As early as the first half of the 20th century it became clear that there were two types of hepatitis of viral etiology. The first viral hepatitis pathogen to be discovered was the hepatitis A virus (HAV), which is transmitted by contaminated food, water and unclean hands and it causes only an acute infection without serious long-term consequences to people's health. In the 1960s, Baruch Blumberg identified a new hepatitis virus transmitted by blood and other bodily fluids. This was the hepatitis B virus (HBV), which, in addition to acute, can also cause chronic infection [4]. It was established that HBV usually develops chronic infection quietly and imperceptibly, which is what caused the infection to be often diagnosed only when serious clinical forms or complications occurred, such as liver cirrhosis and hepatocellular carcinoma. In 1976, Blumberg was awarded the Nobel Prize in Medicine, for identifying this new viral pathogen. The discovery of HBV very quickly initiated a series of further research, which necessitated the work on sensitive diagnostic tests for early HBV infection detection, and sparked research in the area of prevention and therapy. This research resulted in the discovery of very efficient antiviral drugs with a high genetic barrier for the development of viral resistance, which makes these drugs exceptionally effective therapy in patients with chronic hepatitis B. Also, an efficient anti-HBV vaccine was developed, and it is expected to bring about the eradication of HBV from the world population in the near future [5].

HOW THE PUZZLE OF THE NEW BB VIRUS, THE COUSE OF HEPATITIS C, WAS PIECED TOGETHER

In the period between the 1960s and the 1970s, Alter worked together with Blumberg on perfecting the methodology for detecting the HBsAg, a glycoprotein in the HBV capsule, which was later to become the main candidate for the development of an effective anti-HBV vaccine. In the early 1970s, Alter and his research team noticed a frequent incidence of hepatitis in patients who had received blood transfusions, although, at the time, there were serological tests for detecting HBV, which were able to eliminate HBV as a potential cause

Takođe, ni drugi poznati hepatotropni A virus nije bio povezan sa pojavom novog posttransfuzijskog hepatitisa. Bilo je jasno da se radi o novom patogenu, povezanim sa krvlju, koji je dovodio do zapaljenja jetre [6]. U to vreme nepoznati BBV koji se povezivao sa hepatitisom, nazvan je non-A, non-B (NANB). Ovo svoje zapažanje Alter i saradnici su morali da dokažu, što je i bio njihov sledeći istraživački korak, odnosno cilj je bio da se pokaže povezanost NANB sa hepatitisom koji je nastajao nakon transfuzija krvi [7]. Tokom 1975. godine, Alter i saradnici su, u odsustvu drugih *in vitro* laboratorijskih postupaka za dokazivanje novog NANB virusa, svoje istraživanje nastavili na životinjskom modelu. Oni su na eksperimentalnom modelu šimpanzi pokazali da, nakon inokulacije seruma osoba sa kliničkim slikama novog virusnog NANB hepatitisa, u količinama ekvivalentnim transfuziji krvi kod ljudi, dolazi do razboljevanja životinja. Već nakon prve infekcije postigli su uspeh, jer je pet od pet šimpanzi razvilo povećanje alaninaminotransferaze (ALT).

Prvi uspesi su ohrabrili naučni tim u daljim istraživanjima, te su se eksperimenti nastavili sa titriranjem inokuluma dobijenog iz krvi, sada pacijenata sa teškim kliničkim slikama NANB hepatitisa, što je koreliralo sa drastičnim povećanjima nivoa ALT kod eksperimentalnih životinja. Iz obolelih životinja je izolovan novi filtrabilni patogen. Bio je ovo dokaz da se radi o novom virusu [5,8]. Radilo se o malim virusnim partikulama, prečnika 30 - 70 nm, sferičnog izgleda sa lipidnim omotačem, koje su bile osetljive na organske rastvarače [9]. Novi virus, uzročnik hepatitisa koji je povezivan sa transfuzijama krvi, nazvan je NANB. Prema morfologiji, bio je sličan virusima iz porodice togavirusa i/ili flavivirusa, pa je u početku i trertiran kao toga/flavi-nalik partikula (engl. *toga/flavi-like particle*). Tek kasnije će dobiti svoje taksonomsko mesto u porodici flavivirusa, rod *Hepacivirus*. Alterova istraživanja su takođe donela još jedno veoma važno zapažanje a to je, da se u toku infekcije razvijaju neutrališuća anti –NANB antitela, koja su visoko specifična za soj virusa, ali koja nisu u stanju da neutrališu virusne genetičke varijante (kvazispecijese). Ovo će se tek kasnije pokazati kao jedna od veoma važnih karakteristika HCV, kao visoko varijabilnog virusa, koja dovodi do uspostavljanja trajne doživotne infekcije, čak i u prisustvu specifičnih antitela [4].

Sledeći korak u dokazivanju novog virusa hepatitisa bio je da se dešifruje genom virusa, odnosno da se izdvoji genomska sekvenca koja je odgovorna za sintezu virusnih produkata – antigena virusa, koji senzibilišu sintezu specifičnih anti-HCV antitela. Ovakvu zamisao, da se pomoću seruma pacijenata sa kliničkim slikama novog virusnog hepatitisa dokaže određena genom-

of posttransfusion hepatitis. The other known hepatotropic A virus was also not linked to the occurrence of the new posttransfusion hepatitis. It was clear that there was a new, blood-related pathogen, which was causing hepatitis [6]. At the time, the new BBV linked to hepatitis was named non-A, non-B (NANB). Alter and his associates had to prove their finding, which was the next step in their research, i.e. the goal was to demonstrate the link between NANB and hepatitis developing after blood transfusion [7]. During 1975, in the absence of other *in vitro* laboratory procedures for proving the existence of the new NANB virus, Alter and his associates continued their research on the animal model. On the experimental model of chimpanzees, they demonstrated that, after the inoculation of the serum taken from people with the clinical presentation of the new viral NANB hepatitis, in amounts equivalent to the blood transfusion performed in people, the animals got sick. They achieved success immediately after the first infecting procedure, since five out of the five chimps developed an increase in alanin-aminotransferase (ALT).

The initial success encouraged the research team to continue their studies, so the experiments were then continued with the titration of the inoculum obtained from the blood taken from patients which had serious clinical presentation of NANB hepatitis, which correlated with drastic increase in the level of ALT in the experimental animals. A new filtrated pathogen was isolated from the samples obtained from the sick animals [5,8]. What they isolated were small viral particles, 30 - 70 nm in diameter, spherical in appearance, with a lipid envelope, which were sensitive to organic solvents [9]. The new virus causing hepatitis, which was linked to blood transfusions, was named NANB. As to its morphology, it was similar to the viruses belonging to the togavirus and/or flavivirus family, and was therefore, initially, treated as a toga/flavi-like particle. It was only later that it received its place in the taxonomy of the flavivirus family, genus *Hepacivirus*. Alter's research resulted also in a very important finding, that during the infection, neutralizing anti-NANB antibodies developed, which were highly specific to the strain of the virus, but were not capable of neutralizing the viral genetic variants (quasispecies). This would only later prove to be a very important characteristic of the HCV, as a highly variable virus, as it is what leads to the establishing of permanent life-long infection, even with the presence of specific antibodies [4].

The next step in proving the existence of the new hepatitis virus was to decipher the virus genome, i.e. to identify the genome sequence responsible for the synthesis of viral products – virus antigens, which cause the synthesis of specific anti-HCV antibodies. Such an idea, to use the serum of patients with clinical presentations of the new viral hepatitis to prove the existence of a particular

ska sekvenca, tačnije njeni produkti, bila je naučna ideja Majkl Hotona, koji je osamdestih godina prošlog veka bio istraživač u farmaceutskoj kompaniji Širon, iz Kalifornije, SAD.

Kako su tradicionalne tehnike za izolovanje virusa bile limitirane, a eksperiment na majmunskom modelu je doneo jasnu povezanost virusa sa novim NANB hepatitisom, sledeći nedostajući deo slagalice, koja se zove hepatits C, bila je molekularna identifikacija novog virusa. Hoton i njegovi saradnici su, 1982. godine, stvorili kolekciju DNK fragmenata od nukleinskih kiselina ekstrahovanih iz uzoraka krvi zaraženih šimpanzi. Većina ovih fragmenata pripadala je genomu same šimpanze, ali su Hoton i sradnici pretpostavili da će barem neka sekvenca biti poreklom od genetičkog materijala novog NANB virusa. Pod pretpostavkom da će anti-virusna antitela biti prisutna u krvi uzetoj od pacijenata sa hepatitisom, naučnici su koristili serume pacijenta za identifikaciju kloniranih virusnih fragmenata komplementarne DNK (cDNK) koji kodiraju virusne proteine. Nakon mnogo izvedenih testiranja, pronađen je jedan pozitivan klon. Dalji rad pokazao je da je ovaj klon izveden iz novog RNK virusa koji pripada porodici *Flaviviridae*. Molekularna identifikacija HCV bila je vrhunac timskog napora, koji je trajao 7 godina, te je, 1989. godine, NANB virus promenio naziv u današnje ime virusa, odnosno virus hepatitisa C [10].

Tako je Hoton, zajedno sa dvojicom kolega Ki Lim Čuom i Džordžom Kuom, postao prvi naučnik koji je identifikovao virus i formalno mu dodelio ime virus hepatitisa C. Takođe, njihov naučni rad rezultirao je dizajniranjem dijagnostičkog testa za identifikaciju virusa u krvi, koji je omogućio lekarima da, po prvi put, uvedu rutinski skrining na hepatitis C, testiranjem i davaoca i primaoca transfuzija krvi. Dr Angela Rasmusen, virusolog koja je svoje postdoktorske studije radila u timu dr Hotona na otkrivanju hepatitis C virusa, opisuje HCV kao intrigantni i lukavi patogen sa kojim je inspirativno da se radi. Naučno otkriće dr Hotona, koji je izolovao genetsku sekvencu HCV, jasno je ukazalo da je otkriven novi virus, uzročnik novog hepatitisa, koji se pridružio već do tada poznatim hepatotropnim virusima A i B [11].

Istraživanja Altera i Hotona bila su od presudnog značaja u otkriću hepatitisa C. Ipak, nedostajao je još jedan suštinski deo „HCV slagalice", koji je trebalo da pruži odgovor na pitanje: Da li HCV može sam da izazove hepatitis? Čarls Rajs, istraživač na Univerzitetu Vašington u Sent Luisu, zajedno sa drugim naučnim timovima koji su radili sa različitim RNK virusima, pretpostavio je da bi region na 5' kraju HCV genoma, mogao da bude važan za otpočinjanje virusne

genome sequence, more precisely its products, was the scientific idea conceived by Michael Houghton, who, during the 1980s, worked as a researcher at the pharmaceutical company *Chiron Corporation* in California, USA.

As the traditional techniques for isolating viruses were limited, and the experiment on the monkey model had clearly indicated the link between the virus and the new NANB hepatitis, the next missing piece of the hepatitis C puzzle was the molecular identification of the new virus. In 1982, Houghton and his associates created a collection of DNA fragments from nucleic acids extracted from blood samples of infected chimpanzees. Most of these fragments belonged to the genome of the chimpanzees themselves, however Houghton and his team believed that at least some sequence would originate from the genetic material of the new NANB virus. Under the assumption that anti-viral antibodies would be present in the blood taken from patients with hepatitis, the scientists used the patients' serum for identifying cloned viral fragments of complementary DNA (CDNA) encoding viral proteins. After many tests, one positive clone was found. Further work showed that this clone was derived from a new RNA virus belonging to the *Flaviviridae* family. The molecular identification of HCV was the climax of the team's effort which lasted 7 years, and in 1989, as a result, the name of the NANB virus was changed to what it is called today, i.e. the hepatitis C virus [10].

In this way, Houghton, together with two of his colleagues, Qui-Lim Choo and George Kuo, became the first scientist to identify the virus and to formally name it the hepatitis C virus. Additionally, their research resulted in the designing of a diagnostic test for the identification of the virus in the blood, which enabled doctors to introduce, for the first time, routine hepatitis C screening, by testing both the donor and the recipient of blood transfusion. Dr. Angela Rasmussen, a virologist who carried out her postdoctoral studies in Dr. Houghton's team, working on discovering the hepatitis C virus, described the HCV as an intriguing and cunning pathogen which was inspirational to work on. The scientific discovery achieved by Dr. Houghton's, who isolated the genetic sequence of the HCV, very clearly indicated that a new virus, which was the cause of a new type of hepatitis, had been discovered, thus joining the group of already known hepatotropic viruses, A and B [11].

Research carried out by Alter and Horton was of crucial importance in discovering the hepatitis C virus. However, another, key component of the HCV puzzle was missing, which needed to provide an answer to the question: Can HCV cause hepatitis on its own? Charles Rice, a researcher at the Washington University in St. Louis, together with other research teams working on different

replikacije [12]. Rajs je takođe primetio da određeni drugi regioni HCV genoma, svojim genskim produktima mogu da suprimiraju virusnu replikaciju, jer vrše inhibiciju genomske sekvence koja je započinje [13]. Metodama genetskog inžinjeringa, Rajs je dizajnirao HCV RNK, koja je obuhvatala region odgovoran za inicijaciju replikacije, uklonivši regione koji su je suprimirali. Kada je ovako modelirana HCV RNK ubrizgana direktno u jetru šimpanze, replikacijom su nastajali virioni koji su dokazani u krvi životinje, a takođe su primećene i patološke promene slične onima koje su viđene kod pacijenata sa hroničnim hepatitisom C [14].

Ovo je bio konačni dokaz da virus hepatitisa C može sam da prouzrokuje BB hepatitis.

TRIDESET GODINA KASNIJE – ŠTA SE DANAS ZNA O HCV

Tokom tri decenije od otkrića do danas, o HCV govorimo kao visoko varijabilnom, pozitivno jednolančanom RNK virusu sa visokom stopom mutacija. Ova biološka karakteristika je posledica njegovog životnog ciklusa i uloge virusne RNK-zavisne RNK polimeraze, enzima uključeng u virusnu replikaciju, koji nema mehanizme za ispravljanje slučajno nastalih grešaka. To obezbeđuje stvaranje različitih genomskih varijanti unutar inficiranog organizma – kvazispecijesa, ali i različitih antigenskih varijanti [15]. Upravo antigenska varijabilnost HCV-a obezbeđuje da on vešto izbegava imunski odgovor domaćina, te pomaže uspostavljanje perzistentne infekcije, a istovremno predstavlja problem za razvoj uspešne vakcine. Razlika od 30% na dužini celog genoma uslovila je podelu na danas poznatih 8 HCV genotipova, dok još manja genomska razlika dalje klasifikuje HCV na 90 subtipova i 9 rekombinantnih formi [16]. Genotipovi HCV se međusobno značajno razlikuju u odgovoru na terapiju, te je njihovo dokazivanje deo rutinskog laboratorijskog protokola kod pacijenata koji su kandidati za otpočinjanje antivirusne terapije [17].

HCV može da uspostavi i akutnu i hroničnu infekciju. Oko 30% pacijenata (15% − 45%) spontano izluči virus unutar 6 meseci od infekcije i u odsustvu specifične terapije. Ipak, ~ 70% pacijenata (55% − 85%) razvije hroničnu bolest sa rizikom od nastanka ciroze jetre ili HCK, u visokom procentu od 15% do 30%, unutar dvadesetogodišnjeg perioda [18].

Noviji podaci procenjuju da danas u svetu ima oko 110 miliona ljudi sa dokazom prethodne HCV infekcije (prisustvo anti-HCV antitela), dok je 71 milion hronično inficiranih [19]. HCV infekcija je jedna od retkih infektivnih bolesti čiji mortalitet raste u

RNA viruses, speculated that the region at the 5'terminus of the HCV genome could be important for the initiation of virus replication [12]. Rice also noticed that certain other regions of the HCV genome can suppress virus replication with their gene products, as they inhibit the genome sequence that initiates it [13]. Through methods of genetic engineering, Rice designed HCV RNA, which included the region responsible for replication initiation, eliminating the regions suppressing it. When thus designed HCV RNA was injected directly into the liver of a chimpanzee, virions were replicated, which were detected in the blood of the animal, and pathological changes were also noted, similar to those observed in patients with chronic hepatitis C [14]. This was final proof that the hepatitis C virus could cause BB hepatitis on its own.

THIRTY YEARS LATER – WHAT IS KNOWN ABOUT THE HCV TODAY

During the thirty years since its discovery until now, HCV has been known as a highly variable, single-stranded, positive-sense RNA virus, with a high mutation rate. This biological characteristic is the result of its life cycle and the role of the viral RNA-dependent RNA polymerase, an enzyme involved in virus replication, which lacks the repair mechanism for correcting accidental mistakes. This enables the creation of different genome variants within the infected organism – quasispecies, but also different antigen variants [15]. It is this antigen variability of the HCV that enables it to skillfully avoid the immune response of the host, which, in turn, facilitates the establishing of persistent infection, at the same time posing a problem to the development of a successful vaccine. Due to a 30% difference in the length of the entire genome, a categorization into 8 different HCV genotypes, known today, has been made, while an even smaller genome difference classifies the HCV into 90 subtypes and 9 recombinant forms [16]. HCV genotypes differ amongst themselves significantly in their response to therapy, which is why their detection is a part of the routine laboratory protocol in patients who are candidates for antiviral therapy [17].

HCV can cause both acute and chronic infection. Around 30% of patients (15% − 45%) spontaneously eliminate the virus within 6 months of infection even without specific therapy. However, ~ 70% of patients (55% − 85%) develop chronic illness with a high risk (15% − 30%) of developing liver cirrhosis or HCC within a 20-year period [18].

More recent data estimate that there are around 110 million people in the world with proven previous HCV infection (detected anti-HCV antibodies) and 71 million chronically infected patients [19]. HCV infection is one of the rare infectious diseases whose mortality

poslednjim decenijama. Prema dostupnim podacima, mortalitet je od 2000. godine porastao 22% i procenjuje se da danas godišnje od komplikacija HCV infekcije umre oko 700.000 pacijenata. Da bi se ovakav trend zaustavio, neophodno je uvesti efikasnu terapiju hronične HCV infekcije, koja prema najnovijim preporukama Svetske zdravstvene organizacije, predlaže tretman pangenotipskim direktno delujućim antivirusnim lekovima (DAA). Radi se o novoj *interferon free* terapiji, koja efikasno suprimira virusnu replikaciju i za relativno kratko vreme od 8 do 12 nedelja, uspostavlja stabilan virusološki odgovor (nedetektabilna HCV–RNK) i to kod čak 95% pacijenata [20]. U zavisnosti od genotipa i subgenotipa virusa, prisustva ili odsustva ciroze, HCV terapijski protokoli sa novim DAA su različiti, odnosno radi se o različitoj kombinaciji lekova [21].

Sa više testiranja i uz obezbeđivanje dostupnosti nove anti-HCV terapije, smatra se da će u narednoj deceniji biti moguće iskoreniti HCV infekciju, čak i u odsustvu vakcine. Veliki deo HCV slagalice je dešifrovan. Korake, bez kojih se dalje ne bi moglo ići, napravili su Alter, Hoton i Rajs. Ipak, HCV je još uvek intrigantan patogen i do momenta njegove eradikacije zaokupljaće pažnju stručnih i naučnih timova.

KRATKE BIOGRAFIJE LAURETA NOBELOVE NAGRADE ZA MEDICINU 2020. GODINE

Harvi Dž. Alter je rođen 1935. godine u Njujorku. Diplomirao je na Medicinskom fakultetu Univerziteta u Ročesteru, a internu medicinu je stažirao u bolnici *Strong Memorial Hospital* i u Univerzitetskim bolnicama u Sietlu. 1961. pridružio se Nacionalnom institutu za zdravlje (*NIH*) kao klinički asistent. Proveo je nekoliko godina na Univerzitetu u Džoržtaunu (Alberta), pre nego što se 1969. vratio u *NIH* kako bi se pridružio Odeljenju za transfuzijsku medicinu Kliničkog centra, kao viši naučni saradnik.

Majkl Hoton je rođen u Velikoj Britaniji. Doktorirao je 1977. na fakultetu *King's College* u Londonu. Kao naučnik istarživač, 1982. počeo je da radi u farmaceutskoj korporaciji Širon u Emervilu, Kalifornija. Od 2010. godine postaje rukovodilac naučnog tima za virusologiju na Univerzitetu u Alberti, gde ostaje sve do danas. Takođe je i profesor virusologije na Univerzitetu u Alberti, i direktor Instituta za primenjenu virusologiju, takođe u Alberti.

Čarls M. Rajs je rođen 1952. godine u Sakramentu. Doktorirao je 1981. godine na Kalifornijskom tehnološkom institutu, gde se takođe usavršavao kao post-doktorand između 1981-1985. godine. Svoju istraživačku grupu osnovao je 1986. godine na Medicinskom fakultetu Univerziteta Vašington u St. Luisu. Redovni

rate has been rising in the past decades. According to available data, mortality has risen since the year 2000, by 22%, and it is estimated that around 700,000 patients die, every year, as the result of HCV infection complications. In order to put a stop to this trend, it is necessary to establish efficient therapy for chronic HCV infection, which, according to the latest recommendations of the World Health Organization, proposes treatment with pan-genotypic direct-acting antiviral drugs (DAA). This is a new, interferon free regimen, which efficiently suppresses viral replication and, within a relatively short time period of 8 to 12 weeks, establishes a stabile virologic response (undetectable HCV-RNA) in as many as 95% of patients [20]. Depending on the subgenotype of the virus, the presence or absence of cirrhosis, HCV therapy protocols with the new DAA are different, i.e. the combinations of drugs vary [21].

With more testing, and with new anti-HCV therapy being made available, it is believed that, within the next decade, it will be possible to irradicate HCV infection, even without a vaccine. A large part of the HCV puzzle has been pieced together. The steps, without which there would be no other steps further, were made by Alter, Houghton and Rice. However, the HCV remains an intriguing pathogen, and, until it is eradicated, it will be the object of attention of expert and research teams.

SHORT BIOGRAPHIES OF THE 2020 NOBEL PRIZE IN MEDICINE LAUREATES

Harvey J. Alter was born in 1935, in New York City. He graduated from the University of Rochester Medical School and was a resident in internal medicine at Strong Memorial Hospital and the University Hospitals of Seattle. In In 1961, he joined the National Institutes of Health (NIH) as a clinical associate. He spent several years at the University of Georgetown. Alberta, before returning to the NIH, in 1969, where he joined the Clinical Center's Department of Transfusion Medicine as a senior investigator.

Michael Houghton was born in the United Kingdom. He earned his doctoral degree in 1977, at King's College, London. In 1982, he started working as a scientist-researcher at the pharmaceutical company Chiron Corporation, in Emeryville, California. In 2010 he became the head of a virology research team at the University of Alberta, where he remains to this day. He is also a Professor of Virology at the University of Alberta and the Director of the Applied Virology Institute, also in Alberta.

Charels M. Rice was born in 1952. in Sacramento. In 1981 he received his PhD from the California Institute of Technology, where he also remained for postdoctoral research between 1981-1985. He formed his research group in 1986 at the Washington University School of

professor postaje na istom fakultetu 1995. godine. Od 2001. godine, profesor je na Univerzitetu *Rockefeller* u Njujorku. U periodu od 2001 - 2018. godine bio je naučni i izvršni direktor Centra za proučavanje hepatitisa C, na Univerzitetu *Rockefeller*, gde je i danas aktivni istraživač.

Sukob interesa: Nije prijavljen.

Medicine in St. Louis. In 1995, he became Full Professor at the same University. Since 2001, he is also Professor at the Rockefeller University in New York City. Between 2001 and 2018, he was the Scientific and Executive Director of the Center for the Study of Hepatitis C at the Rockefeller University, where he remains an active researcher to this day.

Conflict of interest: None declared.

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