Transcript

Thank you very much, Professor Allen Selman, for your kind introduction. Good evening, ladies and gentlemen, dear colleagues. It's my great honor to be here to share you about the journey toward the SGV elimination in Taiwan. First of all, I would like to thank Professor He's well organized and invited me to share the experience for the audience. Before my talk, I would like to share you the short video to introduce the Kaushan Medical University.

Not just a school, they are the starting point of Kaushan's modern health care. They exist for medicine, science, and humanity. Knowledge lives only when it is questioned and practiced. So, what can a curious mind imagine? A light of hope. A whisper in the laboratory. Relentless questions about life. Again and again. The respect for life. The pursuit of truth. Technology is only a tool until it finds answers that can change lives. Every research project, every experience, Every moment we come together, it is the wonder born from the collision of the known and the unknown. A beam of light connecting the past, the future, and the present. At Cowshaw Medical University, we do more than study medicine. To treat as a healer, one must first be humane, and we put it into practice.

Okay, I would like to stop my talk with the very typical question report in the 1980s. Many of the patients would debate my jaundice, nausea, followed by elevated alloted level just three months after blood transfusion for major surgery. And at the time, most of these patients were negative for marker for hepatitis A and hepatitis B, as well as the other such as CMV and EBV. So, when following this patient, you will find the patient will suffer from a continuous abnormal liver function, and also the histology show the chronic portal intervention with stem cell infiltration. So, it was designated as a lung A lung B hepatitis, accounted for about 80% of the post-change fusion cases in the late 1970s and 1980s. So, Doctor from the NIH first reported the so-called acute and chronic lung A lung B hepatitis in 1972, and thereafter a lot of research Later, many teams tried to isolate the potential infectious agents responsible for the hepatitis. So, Doctor Michael Hilton in the Corporation led our team and eventually they isolate successfully the genome of hepatitis C virus, which was responsible for 80% of non-A long-V hepatitis in 1989. the year I graduated from the middle school. And after that, the Charles Rice, Professor Charles Rice from Rockefeller, demonstrates using the engineer viral genome can induce the hepatitis as fallible and chronic. So the 2020 Nobel Prize in Physiology and of Medicine were awarded to these three outstanding researchers. So, hepatitis is a global disease burden that threats more than 70 million

people in the world, especially in Egypt and Mongolia. So, today I will show you 4 stories that I try to answer, focus on the firstly, the HCV epidemiology, the efficacy of anti-HCV therapy, The long-term outcome after the anti-therapy and the HGV-related extrahepatitis manifestations. The question one come from my colleagues. He's a cardiologist. He said there are high rates of liver cancer in his hometownship, the Massago, despite the absence of the HBV marker and alcohol history among the residents. So, it is possible that SGB is driving the liver cancer cluster in 1994, and there soon later Doctor Chu is the member of the public health at the Cultural Medical University also said that in her recent community surveillance program at the Zhuguan, why many participants had abnormal liver function test but negative for HBB markers. So, these two questions peak our curiosity whether HCB play an important role in the abnormal test in the southern Taiwan. Usually we know that it's hypoendemia for hepatitis B, not hepatitis C. So we conducted 2 large-scale community survey and found an unbelievable high anti-HCB punish rates in these two areas, 67% in Masago and 38% in Zubuan. which were fully confirmed by the Homebrew PCR. So, my mentor, Professor decided to found the Taiwan Liver Research Foundation in 1999, dedicated on the communal survey education and prevention of liver disease in Taiwan. Here, I would like to show you a brief video at the 20 anniversary of Tawa Niba Research Foundation in 2019. . . . So after accumulating the so many community survey data, we eventually figure out the Taiwan HCV map. It's about 3.2% of anti-HCV penetrate around the adult population. So it is estimated around 400,000 of the people living in Taiwan are infected with the virus. Especially you can see there are many area hyper-endemic for the HCV. Let's move to the second question that I try to answer is to answer the class of antiviral therapy in two stages. The stage one is in the interferon era, the second one is in the interferon-free antiviral era. So this is the nature cause of HGV infection. Once acquired the virus, we have developed acute hepatitis. and around 25% of the patients will clear the virus spontaneously. But the remaining 75% of the patients will suffer from continuous HCV infection, progress to chronic hepatitis, and eventually develop liver cirrhosis after 20 to 30 years of infection. Once the cirrhosis is established, there are around 1 to 4% of the patients will develop hepatocellular carcinoma every year. And eventually, around 20% of the patients will develop a so-called liba failure. So how can we stop this phenomenon? So we can do nothing for the prevention of HIV infection because there are no vaccines available so far. So what we can do is to block the colonic infection of the virus is to eradicate the virus from the human body. So the interferon is the only approved anti-SGV agent until 2014. He had known, he had two tumours of aging, including the direct inhibition of viral identification and also the immune system elimination of the infected cells. So the treatment of the C is to achieve the goal also called sustained biological response or SVR. It's defined as undetectable HCV RNA through twenty-four weeks after antivirus therapy. Achieve the goal can ensure that the patient will not really have experienced the HCV after achieving the goal. However, with the conventional interferon is 3 million units subcutaneous,

three times a week. For 24 weeks, we just can cure around 6% to 12% of the patients. Even in Southern Taiwan, we have more patients infected with SGV genotype than A, than one. This genotype is responsive to the interferon better than the genotype one, but the SVR rate just can achieve thirty-one percent. In 1996, there are a study show that aiding the ribarin is an analog to the conventional interferon could increase the SVR rate from 6% to forty-three percent. I think it's a Denmark study. And soon later, the introduction of new formulation of the interferon, so-called the interferon is a long interferon, and it's just only once a week, plus the can further increase the SBR rate to fifty-five percent. So, in the second decade of the SEB battle, it moved to the interferon plus the and Because we are curious whether use of the PEG interferon plus ribovaluin, we can have a different regimen to cure the correct genotype, because, as I say, genotype long one have a much better response to the conventional interferon. So, this phase four study randomized the patient into receive twenty-four weeks or forty-eight weeks regimen of PEG ribo. with low dose of ribarin, 800 milligram per day, or standard dose of ribarin, 1000 to 1200 milligram per day. And as you can see, for genotype one, the SBR rate was highest to 52% if they received 48 weeks of peg interferon plus standard dose of ribarin. But for genotype 2, for the treatment duration, for the dose of ribarin, the SBR rate was in average 82%. So, in 2004, the HEB treatment moved to the so-called genotype-guided therapy. Genotype one patient was assigned to 48 weeks, and the genotype two or three patients were assigned to receive 24 weeks. They can achieve the highest SVR rate. However, the PegRIBA still have many challenges, especially there are many patients suffer from the adverse events such as for relaxing zone, depression, pain cytopenia, and hemolytic anemia. So around the 5% to 20% of patients will discontinue the treatment early. So in one conference, Professor in the National Taiwan University, he asked me a question, how about the outcome of your patient who discontinued early from the treatment? So I summarize, I try to summarize the outcome of my patients. Thirty-two patients withdraw the PEGRIBAR before 20 weeks, and we found interesting. Five of these thirty-two patients still achieve an SVR, even they have received only four weeks to 20 weeks of the PEGRIBAR. And all these five patients are genotype 2. and had undetectable at the treatment week four. We call this patient a super responder because they achieved so-called rapid biology response at the week four. So we are curious that can we further tailor the patients by the rapid biology response to shorter treatment duration without compromising the treatment efficacy? Because the cost is very high, the advance events is very high. So, we conduct two large-scale study, the genotype one patient to receive either twenty-four weeks or forty-eight weeks, and the genotype 2 patient to 16 weeks or twenty-four weeks, and try to evaluate the impact of the treatment response on treatment response at the and the on the treatment efficacy in these four groups. So, here's the result. For genotype one patient who had a low baseline viral load less than 400,000 IU per mil, they can achieve a ninety-six percent with the SBR rate with twenty-four weeks regimen if they achieve the rapid biological response at the treatment week four. These are compatible to 100%

in the forty-eight weeks regimen. And again, for the genotype 2 patient, if the patient achieve an rapid biological response, At the week of fall, 16 weeks of regimen could achieve an SBR rate at 100%, which was comparable to the standard 24 weeks regimen at 98%. And if the patient cannot have early biological response, we can extend the treatment duration from 24 weeks to 48 weeks, and we can have a better SBR rate from 46% to 70%. So, with this evidence, we try to figure out concept or so-called personalized HGV therapy is this road map based on the baseline biology genotype, genotype one or four, genotype two or three, and the untreatment biology response at the with four and with 12. If the patient was super responder, we can show the treatment duration to 24 or 16 weeks for genotype one and four and genotype 2-3 patients respectively. And if the patient have a normal response to the PET/RIBAR, we remain use the 48 weeks and the 24 weeks for this patient population. But if the patient have a slow responder, we might extend the treatment duration to 72 weeks and the 48 weeks for genotype 4 and 2/3 patients respectfully. But if the patient have a very low response at the treatment with 4 and 12, We have to stop the treatment for this patient population as early as possible, because there are only 3% of 3% chance to achieve an SVR. So, this so-called response-guided therapy was there, was referenced at the HGB press guideline in 2008 by Taiwan Association for the Study of Liver and 2011 by the ESO, the European Association for the Study of Lieber, and by the parts of the Asian Pacific Society, and also the smooth-guided therapy concept successfully change the policy of the reimbursement in Taiwan. So, I think it is the second decade of the HGV battle is quite important milestone that moved to the so-called response-guided therapy. And later on, completely understanding the HGV life cycle could help us to develop the direct antiviral targeting the specific sites during the life cycle. For example, the non-structured protein 3-4-A protease inhibitor It inhibits the translation and polyprotein processing, and the NSFIB polymerase inhibitor inhibiting the RNA replication, and the NSFIA inhibitor blocking the replication complex formation and by the assembly. So, by combining two or three classes of this DAA, there are many regimens that have been developed with a very high SBR rate of ninety-five percent or more. simpler dosing, one target to three target a day, and the shorter treatment duration, just only 8 to 12 weeks, and the very high safety profile. Almost all the patients are eligible for the DAA, interferon-free DAA regimen. And currently, there are three pangenotic regimen available in the world, widely available, including the SOLVEL and GLIP for TRP-9 patients, and SOLVEL VAS for TRP-9 patients. So, in 2016, the WHO set the goal of the so-called wild hepatitis elimination, that is to reduce 90% of knee infection and reduced 65% of annual deaths from the viral hepatitis by 2030 through the achievement of 90% of the patients being diagnosed and 80% of diagnosed patients being treated. That means that the community effectiveness should be 72% or more. So the Taiwan government set the nation's hepatisis program office immediately at the end of 2016, with a very ambitious goal to achieve the SGB elimination in Taiwan by 2025, five years ahead of the lobby or go. Based on the three major strategies, the first one is

treatment as prevention, the second is scoring to scale up the treatment, and the final is the prevention to consolidate effectiveness. However, to achieve HCV elimination, there are several gaps within the HCV care cluster that need to be addressed, including the screening rates by HCV antibody, the HCV tested to diagnosis, and the rate of the care provider, and finally, what regimen the government will provide. So, we have to close all of the gap in each HGB care casket. But we have to know before the strategy have been met. So the first step we try to know where we are in HGB console in 2016. So we conducted this model to evaluate the rate of disease awareness, diagnosis, accessibility, treatment rates, and the clinical advocacy in Taiwan at the time. So we found that just only 48% have disease awareness, and just only 19% of patients have been accessed to a doctor, and just only 14% of the patients have been recommended to receive the interferon-based therapy at the time. And even with such high clinical efficacy with the so-called response-guided therapy, we can achieve the clinical efficacy at 80%. We just cure only 11% of our HG population. So it's a huge gap because a lot of patients are ineligible to the interferon-based therapy and a lot of patients are fear of the adverse events. So To achieve the goal of HCV animation by 2025, we have to increase the rate of diagnosis awareness, accessibility, and introduce a new advanced DA therapy with high cure rates and safety profile. So the first step is that we have to close the gap in the HCV RNA diagnosis, because even a lot of patients have been tested screening by anti-HCV. Even they are positive anti-SCB, a lot of these patients still lost to receive the RNA testing. Because that traditionally, they need three visits to complete the diagnosis. The first is test the anti-SCB, the second is test the HVRNA if the patient is positive for anti-SCB, and the third, if the patient is positive on HVRNA, we do the HVB via genotyping. So, we try to develop a so-called automatic testing by just only using one sample. We set the IT that can spontaneously put the sample into the RNA testing with the sample positive anti-SCB, and then if the sample positive RNA is spontaneously put a sample to detect the HGB genotyping. So it's the one visit for timing and accurate diagnosis. And you also implemented the so-called real-time automatic point system and also the late-core-backed system by the way of training coordination with the patient missing back to the clinic. So use this so-called RNA model, we successfully increased the RNA loss rate from 23% to 100%. and the children's rates increased from 27% to 74%. So the national health insurance in Taiwan approved the HVRNA refreshing testing as a clinical routine practice and also reimburse the payment. So the second gap we have to close is to increase the screening rate and also increase the rate of dental care. by using a so-called micro-elimination approach and the decentralization to make the elimination goal attainable. The micro-elimination approach break down the national so-called elimination target into the smaller, more manageable goal for individual population, especially for the population at high risk of HCB infection, such as people who live in the HCB harbor in Demi area, people under regular dialysis, people who are injecting drugs. So we organize an outreach-integrated HCV team with the on-site screening and treatment to target the HCV micro-image. We

send a treatment, including the hepatologist, nursing, technician, and pharmacist, to the rural area to the hematodialysis center. So, here I would like to share you 4 programs we implement. The first one is RASC. It's a mass screening program with on-site group therapy to facilitate the SGV micro-immunition in hemodialysis center. We collaborate with 18 hemodialysis centers, implement the SGV rephasing test, and then refer the patient by linked to local care or treat the patient on-site, and And also very important, we're treating all the eligible patients as well as the care providers in each HD center at the same time. So overall, more than 2,300 patients and 350 health care providers join these programs with a screening rate at 100%, diagnosis rate at 98%, and the chip Linked to care and the treatment rate at ninety-four percent, including linked to care or on-site treatments, and eventually 90% of patients were cured. So, with this ERASHC program, we successfully achieved the goal of HEV micro-immunitions, successfully decreased the HEV rate from 7.7% to just only 0.6%. And three years later, we found that the annual incidence of new HC infection decreased from more than 1% per year to just only 0.1% per year. So these results prove the concept of so-called treatment as prevention. The second program is a compact. It's an outreach mobile model of the care in SGV hyper-endemic area, the Zuba areas. We collect with the local health care authority and provide them a mobile point of care screening and also we provide the universal effective DAA and using the social media to increase the disease awareness. I mean that because it's conducted during the COVID-19 pandemic. So more than 5,700 patients resident joined the programs and the HCB viremia was diagnosed. As you can see, there are very high anti-HCB presence rate at 19% in this area and the RNA positive rate was 40% among anti-HCB positive residents. Even in the COVID-19 pandemic, we successfully revolved around the 80% to linked care and 100% receiving the DA therapy, 99% computer treatments, and the 99% cured, with eventually community effectiveness at 76%. The third one is the mountain and remote area. It's micro-immunation or SGV conducted in the mountainous and rural areas of Taiwan. It's outreach, decentralizing community-based care systems from screening to DS therapy. So among the more than 8,200 registered residents who walk or live in the four mountainous area partitioning this program, 94% of the subjects accessible was screened. and the RNA testing rate was 94 percent. As you can see in this area, the anti-ACV penis rate remained very high at 14 percent. The RNA pulse rate was 15 percent among the anti-ACV positive patients. And 94 percent of RNA positive patients were treated with an SBR rate at 96 percent. So eventually, the community effectiveness achieved 81 percent in this four rural area. The final one is a SGB micro immunization program for the prison at Permian Pu Island. Among this, among the Permian Pu prisoners, around more than half of the prisoners are PWID. So it's a very special population. So we conduct an in-prison, five-days mass screening for HBV, HCV, and HDV by reflection test. and the provider in-prison on-site treatment with the penicillin DA regimen. So, two-thirds of the prisoners adjoined the screening with an anti-ICV, anti-ICV prince rate at thirty-five percent and the ICV on the post rate at fifty-three

percent, and 90% of the RNA participation received treatment with the SBR rate 100%. So the overall effectiveness was around 60% in the prisoners. And the final gap we have to close is the children's regimen. As I mentioned earlier, in the DAA era, we have a pan-generic regimen with very high SBR rate and high safety profile. So we do see a light at the end of the tunnel. There are no problem to animate the SGB from Taiwan. However, it's no more medical barrier, but we have to think about they still have a so-called long medical barrier in the DA era because of the DAA costs are very high. Along the 11,000 to 80,000 US dollars of cost. So it will have a very huge impact if we treat all the patients at the same time. And the other challenge, non-medical challenge, is we know that we just cure 11% of the patients. They still have 90% of patients waiting for the DR regimen. So we have a huge impact on the professional brain power. So how to deal with this problem? So, we have to try to evaluate the cost-effectiveness of the DAA and try to prioritizing our patients by the stability to the DAA. So, the question is, what cost is it worth to cure patients? So, we try to evaluate the cost-effectiveness with the traditional PEG in the variant plus ribarin. by linking a real-world cohort to the nation health insurance database as a reference for the DAA policy-making. So, we take all the costs, not only the anti-virus, but also the non-development for the, you know, for the adverse events or the intervention and labor consultants. We eventually find that the adjust price is US dollars around 8050. Dollars to achieve an SVR by after waiting the distribution of one and two, and also the proportion of two and experience. So, the National Health Insurance Administration Taiwan approved to reimburse US dollars of 8300 pay by success. I think it's the first ever The health reimbursement is paid by successful treatment. You can know it's the ability of the Taiwan National Health Insurance Administration is very hard. You have the ability to negotiate with the big pharma. And the final question we I want to answer is how to prioritize the patient to receive a DAA. So, in this study, we try to evaluate the impact of successful biologic response on the risk of liver cancer, specified by the disease of severity, the liver fibrosis status. As you can see in the left side panel, for fibrosis 0 and 1 patients, low fibrosis, mild fibrosis, there are no difference. in the long-term HCCC risk, however achieving an SVR or not during the 15 years follow-up. But in the right side panel, you can see if the patient have advanced fibrosis, stage two to four, achieving the SVR could remarkably reduce the HCC incidence. So this data highlights the urgence to cure the patients with advanced liver fibrosis. So the nation's highest health insurance approach to the inverse DEA regimen for patients who had fibrosis status three and four. First, after cure, almost cure of this patient population, there extended the reimbursement to the less fibrosis patients. So to reduce the budget impact in the short term. And how about how to deal with the manpower shortage? There are around 2,000 GI and liver specialists in Taiwan. It's not enough. to deal with such many patients in the short term. So we have to do so-called task sharing to empower lung specialist. So we develop a simplified anti-SCV algorithm with the lung specialist care. Even the patients have a complicated condition, such as history of hepatic decompensation, history of

hepatocellular carcinoma, HBV or HIV colon infection, who fail to prior DAA or history of organ transplantation, or they have a current presence. They have to be referred to the specialist's care. But if not, they can be treated by the non-specialist. But if the patient has a risk associated with significant adverse events from our study, such as patient, the EGFR less than 60, or baseline bilubin level 21.2. They have been referred to the specialist for consultation. And if it's no problem, then we will go back to the non-specialist. So, and then we think it's very important to know the real-time status of the HCV elimination in each county as well as in each special population. So we set up the website to trace the real-time progress in the HCV elimination program.

Welcome to the tutorial for Taiwan Hepatitis C Elimination Roadmap webpage. The goal of this interactive webpage is to provide the latest view of Taiwan HCV elimination status. In the right-hand side, you can see illumination status for all Taiwanese population and how it compares against WHO's targets. These data are being updated on a quarterly basis. To further drill down by geography, you can easily move your cursor over the map and click on the counting of interest to obtain data. The different color shades shows the execution rate. Darker means more percentage achieved. This bar graph provides the number of estimated and treated HCV patients by each counting. You can also explore by counting illumination status for various high-risk populations, including HIV, ESRD, and Pee Wee, who receive methadone replacement therapy. The setup is similar to the map in the home page.

So the website also shows the Taiwan commitment to imminent HEV after the lobby HEO goal. including a strategy of decentralization, integration, task sharing, and also the rapid diagnosis testing. So by the end of 2025, the Taiwan government announced by the president of Taiwan, Dr. Lai, announced that Taiwan successfully achieved the leverage of gold-tier programmatic a target for HCV intervention, five years ahead of the global 2030 timeline. So here is the news. Overall, we cure more than 182,000 people, spend around $28 billion new term dollars. Let's move my third story is the question on the long-term outcome after antivirus therapy. The question came from one of my mentors, Professor Yuan Liao. Actually, he's the, you know, the godfather of the hepatitis B in the world. He asked me any long-term effect on the liver complications of antivirus therapy for HCV. So, we tried to organize a big cohort by implementing A tassel HCV registry program and since 2018 and By the end of 2024, there are around 15,000 of the intervalent-based therapy patients and around the 44,000 of the DA-based therapy patients have been registered in this platform from the 21 tertiary hospital and 727 community hospital and the five primary care clinics. Here I summarize all the data we have published. We found that the achievement of sustainable response gradually reduced the long-term both of the intra-hepatic and extra-hepatic complications, including cirrhosis, less than 61% decrease, the risk of hepatocellocarcinoma, even the risk of gastric cancer and the lymphoma, and also the all-cause mortality. However, we observed a substantial of patients still at the risk of HCC development. And in this

study, we found we used to think patients at the risk of HCC is those who had already advanced fibrosis. But in this cohort, we found around near half of the patients, just only fibrosis stage one and two, but eventually they developed hepatocyte carcinoma after eradicated the virus. So, we are curious whether they have a so-called wild-host interaction at the genetic or epigenetic level. They are responsible for the persistent hepatocarcinogenesis of the wild re-assifications. So, we collaborated with Professor Gail Tanami in by Ilan Isseres, and you found that the SGV infection could induce the epigeneic change in the histone 3 isolated on lysine lines and the sub the downstream gene expressions and interesting the downstream gene expression, the eight gene signature was associated with the risk of hepatocellular carcinoma in human. So, but interesting when you try to use the DAA to eradicate the virus, we cannot see any change in the epigenetic label as well as in the genetic label. And we follow found that the SGV-induced epigenetic and the associated messenger signature cannot be reverted by the DAA, but can be reverted by DAA plus specific inhibitors such as the C646 is a histone osteotransferase. inhibitor or such as the allotamine is a specific EGFR inhibitor. And at the same time, similar results are also reported by a team in French. They are focused on the histone 3 isolated lysine 27. So taken together, these two studies demonstrates that the HGV-induced epigenetic scar associated with liver cancer persist, be changed after SVR. So this study, this data implicate, there might be a so-called hit-and-run scenario involving the HCG development after the virus eradication. We also want to know how to prevent the HCC risk of the SV achievement. So we use the big data, try to evaluate the results better, to look at who are at the risk of HCC and who can have the benefit of lower HCC. Because there are reports not for HCV but for the fatty liver, the use of metformin for diabetes patients have a chance to reduce the HCC. So, we collected more than 7,000 HGV patients who achieved SVR and followed all these patients for more than 10 years. And we found that if the patient have diabetes but without a metformin administration, the five-year cumulative risk rate was around 11%, which was significantly higher than the patient without diabetes, only 3%. But with the diabetes patients, Also, hypermetformin in the control of diabetes, the risk of ICC decline to around only 2.6% during five years. So it's very interesting. Here is another unfavorable risk, including the liver cirrhosis, the old age, the male, and obesity. And also interesting, you find that hyperlipidemia did not correlate any risk of hepatocepicarcinoma. But if the patient received the sterling, it will decrease the risk of HCC. So it's quite interesting. So recently we started to plan to have a new choice, randomized process control with the study to prevent the HCC development in the muscle D patient, the fatty liver. The final question that we are we want to answer is the HCV manifestation. It's quite interesting. In our conference, one of my colleagues, he's a nephrologist and endocrinologist, he said many of his patients have abnormal liver function test, but positive for anti-HCV. Does HCV infection induce diabetes? So, this question started our journey to explore the mystery between the virus and the diabetogenesis. First of all, we conducted an epidominous study, we found if

the patient positive HCV RNA, the diabetes rates were very high at 18% compared to only 12% for the patient without viral hepatitis or for the patient with hepatitis B. And for this phenomenon, this observation for not confirmed by using the oral glucose tolerance test, you can see HGV patients have remarkably high rates of diabetes and as well as the pre-diabetes at 38% and 72%. When stratifying the patient into different patient age group, you can see the HGV not only increase the risk of diabetes, but also accelerate the onset of the glucose abnormality early in the 20s and 30 years old. So we are curious whether we can find any correlation between the virus and the diabetes. So it's the rationale that we know. the assessed hepatic glucose output, so-called hepatic gluconeogenesis, is one of the key drivers for type 2 diabetes. So we hypothesis that HCB might affect the key regulator of the hepatic gluconeogenesis. So this is a study design. We obtained the liver tissue from the chronic HCB patients, and the phenotype by OGT glucose oral glucose test stratify the patient into use glycemia, normal glycemia, pre-diabetes, and sub-clinical diabetes, and using the chip for the gene expression screening and try to find the candidate gene, and they use the cell model or SGB infected cell model and the long SGB cell model to explore the pathway, and then set and design the **** model to look at whether the the kinetic gene have a preventive or therapeutic effect on the development of type 2 diabetes, and eventually we have a gene. May we take this opportunity to have a new drug discovery. So, here's I showed you review our recent the results. The screening panel includes 11 patients, because you know the liver biology is very hard to obtain. So, We found that there are 82 genes differentially expressed between the patients with normal glycaemia and glucose abnormality, PDM and DM. And we identified the 10 top plots, which were differentially expressed among the three groups with p-value less than 0.002 and at least 1.54 change. And around this probe, only two genes were selected because this is a functional gene, the gene S2 and the CSCL4. And in the validation panel, we continue to find that gene S2 downregulates in the patients with abnormal glucose metabolism. Especially in the validation panel, we include four patients, the red dots. This for patient is diabetes under the oral hypoglycemic aging control with a well controlled diabetes. You can see even the sugar is well controlled, the gene still don't regulate. So indicated the gene is not a downstream or the glucose metabolism, maybe the onstream, the tough stream regulator for the so-called glucose neogenesis. So, we conducted a series of cell model. We found that the SGB could down-regulate the gene S2, and with complement down-regulator of the phosphovalidation of phospho-1. You know the phospho-1 is the key transcription factor for the glucose neogenesis gene, the BEPCKNP6PS. And also down-regulates the gene S2 also have the down-regulation of glucose transporter. And we found that the down-regulation of the gene S2 is through the interaction between the virus down-structure protein 5A and the FASTA2. The FASTA2 is the transcription factor of gene S2. The interaction will induce the so-called perinuclein correlation and Also, we found a dose-dependent manner of the down regulation, and if we use the DAA to block to inhibit the we can install the gene S2

expression and also suppress the gluconeogenesis thereafter, and if we direct introduce the gene S2 over expression in the cell SGB model, we also can restore the genus 2 and also down-regulate the intracranuclear phosphor 1 and also the gluconeogenesis gene expression. And interesting, in the lung HCB model, there are no HCB infection, just only down-regulate the genus 2. We also observed a similar result, indicates this gene might play very important in the hepatic gluconeogenesis. So, we conducted another model use the highway dye to produce the DNA mice and with or without the genus to avoid expression introduction immediately at the highway dye or the delay the introduction of the genus to avoid expression after the establishment of the DNA model. And, as you can see, The highway dye induce the diabetes and also suppress the gene S2 expression, even there are no virus and also you can see they induce the gluconeogenesis and introduction of the over-expression plasmin or gene S2 immediately or late could restore the suppress the gene S2 expression and also. Restore the unregulated PPCK and G6PS. So, in the functional study by the glucose tolerant, you can see why the immediate or the late introduction of the gene S2 is over-expressing can restore the glucose abnormality in the green or the orange bar. So, this is the model that must be over expression of gene as to could prevent or to treat the high fetal-induced diabetes mass non-HCB model. So, is the summary or is interesting data we show that the colony HCB infection increase the risk and assert the onset of diabetes and gene as to might serve as a key regulator associated with the glucose metabolin in hepatocyte, which is suppressed by either SGBNSYA protein or by the high-fat diet-induced DNA mice. And correction of the suppressed gene S2 expression could reverse the phytogenes, however, in the SGB model or in the high-fat model. So we think that gene S2 might serve as a normal SGBT target for type 2 diabetes. So, ladies and gentlemen, the story of our HCV study demonstrates that by using by the patient-centric stress translation research empowers us to identify the normal stress for targeting HCV imaging, decode the high-risk barriers, the so-called point of normal return for facing the advanced disease progression, and uncover the new pathway for managing metabolic diseases. So, from the slow beginning of the HCV journey to rapid advancement, the HCV management has transformed in the past 30 years. So, let's make the first take the final chamber of the HCV fighting. Finally, I will ask all of the patients and the family and our collaborator and the team in Kosher Medical University, and thank you very much for your attention. I'm happy. I'm happy to take the questions from the audience. Thank you. Thank you.