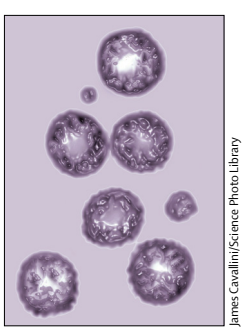
3 Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009; **374:** 979–88.
4 National Institute for Health and Clinical Excellence. Clinical guideline 107. Hypertension in pregnancy. August, 2010; modified January, 2011. https://www.nice.org.uk/guidance/cg107 (accessed Jan 25, 2015).
5 WHO. Recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: World Health Organization, 2011. http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf (accessed Feb 4, 2015).
6 Broekhuijsen K, van Baaren G, van Pampus M, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): a multicentre, open-label randomised controlled trial. *Lancet* 2015; published online March 25. http://dx.doi.org/10.1016/S0140-6736(14)61998-X.
7 Langenveld J, Broekhuijsen K, van Baaren GJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia between 34 and 37 weeks' gestation (HYPITAT-II): a multicentre, open-label randomised controlled trial. *BMC Pregnancy Childbirth* 2011; **11:** 50.
8 von Dadelszen P, Payne B, Li J, et al, for the PIERS Study Group. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet* 2011; **377:** 219–27.

Towards interferon-free treatment for all HCV genotypes

It is surely unique in modern medicine that regulatory agencies should approve seven new compounds to treat a specific disease within just 12 months. The European Commission granted marketing authorisation for sofosbuvir, a nucleotide hepatitis C virus (HCV) polymerase inhibitor, in January, 2014. Since then, the HCV protease inhibitor simeprevir (May, 2014), the NS5A inhibitor daclatasvir (August, 2014), and the single-tablet combination of the HCV NS5 inhibitor ledipasvir with sofosbuvir (November, 2014) have reached the market; followed most recently by the three-drug combination of ombitasvir (NS5A inhibitor), the ritonavir-boosted protease inhibitor paritaprevir, and the first non-nucleosidic polymerase inhibitor dasabuvir (January, 2015). Approval of these compounds was supported by phase 2 and phase 3 trial data, presented in more than 30 original papers. Almost every study described sustained virological response rates, meaning cure of HCV infection, of 90–100%. Most importantly, the new treatments allow interferon-free therapies for a broad pool of patients who could potentially benefit from these novel drugs.[1] So far, so good. But are all issues in HCV infection solved?

On closer inspection, some problems are evident. Many doctors treating HCV are realising that not every patient can be cured immediately with the new drugs. Several areas of uncertainty are emerging, including reduced efficacy of treatments in advanced cirrhosis, optimum duration of distinct combination therapies, drug–drug interactions, the role of treatment-induced or naturally occurring resistant HCV variants, the need for ribavirin, and, very importantly, drug efficacy beyond HCV genotype 1.[2] Many compounds against HCV were developed by testing against HCV genotype 1-based in-vitro replication systems,[3] and therefore show little efficacy against other HCV genotypes. Subsequently, all new direct-acting antivirals have been approved by the European Medicines Agency (EMA) and the US Food and Drug Administration for treatment of HCV genotype 1 infection, whereas only sofosbuvir and daclatasvir can theoretically be used for all seven HCV genotypes, frequently in the absence of clinical trial data. Even though HCV genotype 1 is the most prevalent genotype worldwide, more than 50% of anti-HCV-positive patients are infected with HCV genotypes 2–7.[4,5] Moreover, emerging data show that HCV genotype 1 infection could take a more benign clinical course than other HCV genotypes, with lower rates of progression to liver cirrhosis and reduced incidence of hepatocellular carcinoma.[6,7] Thus, data on efficacy of HCV drugs against non-1 HCV genotypes is urgently needed.

HCV genotype 4 accounts for 10–15% of HCV infections worldwide and represents a particular problem in north Africa. Few data for interferon-free therapies against chronic hepatitis C due to genotype 4 are available.[8] Christophe Hézode and colleagues' study[9] published in *The Lancet* is therefore of special interest. The authors investigated the single tablet formulation of ombitasvir plus paritaprevir plus ritonavir, a combination of an HCV NS5A inhibitor with a ritonavir-boosted HCV protease inhibitor. Of note and in contrast to HCV genotype 1, the regimen is used without coadministration of dasabuvir, which is effective only against HCV genotype 1. Overall, 135 patients with



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Hepatitis C virus

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HCV genotype 4 infection were studied, including 86 treatment-naive patients and 49 individuals who were not cured of HCV by a previous course of pegylated interferon alfa plus ribavirin.

Patients were treated for 12 weeks, and half of the treatment-naive and all treatment-experienced patients received ribavirin in addition. Remarkably, all but four patients had a documented sustained virological response 12 weeks after the end of therapy (100% [42/42, 95% CI 91·6–100] with the ribavirin-containing regimen, and 90·9% [40/44, 78·3–97·5] with the ribavirin-free regimen). Only three patients with virological failures occurred in the ribavirin-free group, and all of them selected distinct resistance-associated variants in the HCV NS3 and NS5A regions. Thus, so far, this trial is the largest to investigate an interferon-free regimen in HCV genotype 4 infection and show that once-daily therapy for 12 weeks with ombitasvir plus paritaprevir plus ritonavir is highly effective. On the basis of this phase 2 study, the treatment has been approved by the EMA for treatment of chronic HCV genotype 4 infection.

Several issues need to be considered, however. Most importantly, the study included only non-cirrhotic patients. Thus, there is no information about the efficacy of ombitasvir plus paritaprevir plus ritonavir in patients with HCV genotype 4-associated liver cirrhosis. Cirrhosis is well known to be associated with reduced response rates in HCV genotype 1 and 3 infection.[2] The optimum treatment for genotype 4 cirrhosis remains to be determined, and in my view ombitasvir plus paritaprevir plus ritonavir with ribavirin for 12 weeks can currently be recommended only for patients without liver cirrhosis. Moreover, whether ombitasvir plus paritaprevir plus ritonavir is similarly effective across all genotype 4 subtypes is unknown.

Genotype 4 is very heterogeneous, but Hézode and colleagues' trial[9] included mainly patients with genotypes 4a and 4d only. Of note, all three patients with virological failure had genotype 4d, and one might ask whether extended therapy beyond 12 weeks could have prevented relapse. Additionally, we do not know whether ombitasvir plus paritaprevir plus ritonavir would be of benefit if NS5A-resistant variants were present before therapy. Unfortunately, information about the baseline frequency of resistance-associated variants, for HCV genotype 4 or genotype 1, is not provided for trials including paritaprevir and ombitasvir. Finally, the role of ribavirin with ombitasvir plus paritaprevir plus ritonavir as treatment for HCV genotype 4 requires further investigation. Is ribavirin also needed for previous treatment failures? Is ribavirin required in genotype 4a? What is the optimum dose of ribavirin, because lower doses associated with fewer side-effects might be sufficient?

What should interferon-free treatments for HCV genotype look like considering the currently available data? Ombitasvir plus paritaprevir plus ritonavir with ribavirin for 12 weeks is certainly a very reasonable treatment option for non-cirrhotic patients. Boosting of ritonavir requires careful assessment of comedications, which is of major relevance because 75% of European patients with hepatitis C receive other drugs, and more than a quarter of patients take more than four additional drugs.[10] Sofosbuvir with ribavirin is also effective, but 24 weeks of treatment are needed based on a recent study.[8] The European labels also allow a combination of simeprevir plus sofosbuvir in cirrhotic patients, but in the absence of supporting data from controlled trials. More data for ombitasvir plus paritaprevir plus ritonavir plus ribavirin, ledipasvir plus sofosbuvir (NCT02081079, completed; NCT02073656, ongoing), and daclatasvir plus sofosbuvir (NCT02032888, completed; NCT02032875, ongoing; NCT02097966, data to be presented in April, 2015 at the International Liver Congress) will become available very soon. Several additional drugs from different classes are in advanced clinical development, which could further expand treatment options in the coming years.

Highly effective interferon-free therapies are now becoming available for patients infected with HCV genotypes other than genotype 1. The next step must be to fill the gaps in the HCV disease burden worldwide[11] and to ensure access to these novel therapies. HCV kills patients, but can be a curable and reversible liver disease. The drugs to eliminate HCV are now available, but only increasing treatment uptake will reduce HCV-associated morbidity and mortality.[12]

Heiner Wedemeyer
Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, 30625 Hannover, Germany
wedemeyer.heiner@mh-hannover.de

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1 Höner zu Siederdissen C, Maasoumy B, Deterding K, et al. Eligibility and safety of the first interferon-free therapy against hepatitis C in a real-world setting. *Liver Int* 2014; published online Dec 30. DOI:10.1111/liv.12774.
2 Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. *Lancet* 2015; published online Feb 13. http://dx.doi.org/10.1016/S0140-6736(14)62401-6.
3 Lohmann V, Körner F, Koch J, Herian U, Theilmann L, Bartenschlager R. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 1999; **285:** 110–13.
4 Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* 2015; **61:** 77–87.
5 Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014; **61:** S45–57.
6 van der Meer AJ, Hansen BE, Fattovich G, et al. Reliable prediction of clinical outcome in patients with chronic HCV infection and compensated advanced hepatic fibrosis: a validated model using objective and readily available clinical parameters. *Gut* 2015; **64:** 322–31.
7 Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol* 2014; **61:** S58–68.
8 Ruane PJ, Ain D, Stryker R, et al. Sofosbuvir plus ribavirin for the treatment of chronic genotype 4 hepatitis C virus infection in patients of Egyptian ancestry. *J Hepatol* 2014; published online Nov 5. DOI:10.1016/j.jhep.2014.10.044.
9 Hézode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. *Lancet* 2015; published online March 31. http://dx.doi.org/10.1016/S0140-6736(15)60159-3.
10 Maasoumy B, Port K, Calle Serrano B, et al. The clinical significance of drug–drug interactions in the era of direct-acting anti-viral agents against chronic hepatitis C. *Aliment Pharmacol Ther* 2013; **38:** 1365–72.
11 Wedemeyer H, Dore GJ, Ward JW. Estimates on HCV disease burden worldwide—filling the gaps. *J Viral Hepat* 2015; **22:** 1–5.
12 Wedemeyer H, Duberg AS, Buti M, et al. Strategies to manage hepatitis C virus (HCV) disease burden. *J Viral Hepat* 2014; **21:** 60–89.

Strategic science with policy impact

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Evidence-based policy making is an important aspirational goal, but only a small proportion of research has the policy impact it might have. Most researchers are not trained to create policy impact from their work, engagement with policy makers is not encouraged or rewarded in most settings, and the communication of scientific findings occurs within the academic community but rarely outside it. There are exceptions, but little is done to systematically link scholarship to policy.

When the broad gap between evidence and policy is addressed in academic settings, the proposed solution is generally to disseminate research findings to the media and perhaps policy makers. This approach is helpful, but overlooks the importance of information flow from the policy world into research settings. The creation of a two-way policy bridge between researchers and policy makers can help to ensure that research addresses issues relevant to policy and that research findings are communicated in real time to policy makers who often must make decisions quickly. We propose a model to create tighter interaction between research and policy domains.

We define strategic science as research designed to address gaps in knowledge important to policy decisions, derived from the reciprocal flow of information between researchers and policy makers, and communicated not only in scholarly publications but also in forms relevant to policy makers. Strategic science can complement traditional programmatic science to better realise the potential impact of scholarship on policy. We have developed a model of strategic science (figure), which we have applied to our work on nutrition policy, obesity prevention, and food systems research,[1–11] but have designed the model to be broadly applicable for other fields of research.

The first step in our model is to identify agents for change and create reciprocal information flow between researchers and these actors. Investigators can be aware of questions that are relevant to policy, but it can also be helpful to identify and seek input from individuals or institutions in a position to make policy advances. Such input can uncover important gaps in knowledge that have not been identified in

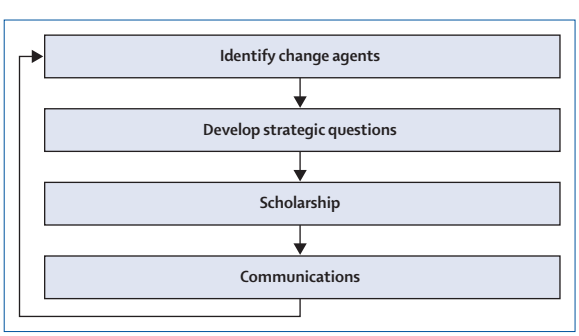

Figure: **A model of strategic science designed to enhance links between science and policy**