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Gastroenterology & Hepatology
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JOHNS HOPKINS MEDICINE

Spring 2013

For Hepatitis C Therapy Worth the Wait

"When patients now tell me they want to get blood tests prior to hepatitis C therapy, that they want to be *ready*, it's a new experience," says hepatologist **Saleh Alqahtani** who's unused to enthusiasm for treatment. Though present medication for the degenerative disease cures roughly 75 percent of patients who stay with it, "eager" isn't a usual patient descriptor.

"The side effects of the drugs significantly alter quality of life for a number of patients. They stop medication prematurely or decline it altogether," Alqahtani says, "especially if they're asymptomatic."

But major change is on its way, as he and colleague **Mark Sulkowski** are well aware. Long part of the drug-development pipeline through its clinical trials, Johns Hopkins is now waiting for a virtual outpouring of new, more patient-friendly hepatitis C antiviral agents, some as soon as this year. Already, Sulkowski, an infectious disease expert who directs the institution's hepatitis trials, and Alqahtani, who oversees pre- and post-liver transplant patients, face new treatment protocol and policy questions.

For a decade, therapy has meant a combo of interferon and the broad antiviral, ribavirin. The regimen clears hepatitis C virus (HCV) in about half of those able to take it. Then, in 2011, companion drugs arrived. The first oral *protease inhibitors*—direct-acting drugs aimed at HCV's reproducing machinery—added to what came before to raise cure rate dramatically, to some 80 percent.

Still, the benefit has come at a price. Patients face rashes and anemia from the newer drugs, fatigue and depression from the interferon.

So the good news from yet more pharma research last year was welcome. Researchers heralded a second generation of better protease inhibitors, all fresh from phase II and III trials. On top of that came *sofosbuvir*, a drug metabolized in the liver to yield an agent both potently disruptive of HCV and comparatively gentle to patients—even those with advanced liver disease.

The present standard of care for hepatitis C will soon take a back seat, says Saleh Alqahtani. "We all know patients who call their drugs *chemotherapy* because of side effects. Now they won't be able to say that anymore."

After Sulkowski's report of a late-phase trial of sofosbuvir plus one of the new protease inhibitors last fall at national meetings, the place was abuzz. More than 95 percent of patients tested negative for the virus. "HCV normally outruns the immune system, but now we can catch it and hold it down," he says. "We can actually clear the virus to cure the disease."

And, says Alqahtani, "for the first time in history, that cure doesn't have to involve interferon."

Progress is moving so fast for this and other combos that FDA approval should come (see box) within two or three years. Optimism shines as never before. The only immediate cloud is having to settle which new patients can safely wait for therapy until the government OK.

"That decision is especially complex for patients facing liver transplant for the disease," Alqahtani explains. "You can't reverse frank liver failure. And though hepatitis C is now the number one reason for U.S. liver transplants, the disease unfortunately recurs some time after transplant. What's wonderful now is that data suggest clearing the virus *before* transplant makes that risk very small. Knowing that an interferon-free protocol is likely coming that's both easier on patients and keeps their transplants healthy—it's worth the wait." ■

New HCV protocols—tested in Johns Hopkins trials—should soon see the light of day.

- sofosbuvir + ribavirin for genotypes 2,3 (2013)
- interferon + ribavirin + sofosbuvir for genotype 1 (2013)

— Courtesy Mark Sulkowski

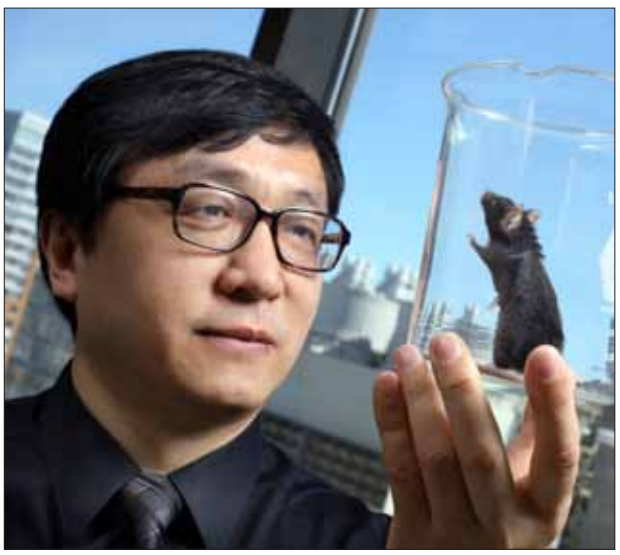
Casting the Proteome Net for IBD

Four years ago, **Xuhang Li** devised rapid ways to screen the blood serum of patients with inflammatory bowel disease for antibodies—his search for renegade molecules to tie to ulcerative colitis or Crohn's disease. His lab netted a cache of antibodies not found in healthy children or adults. Now benefits for patients—in diagnosis or prognosis—are closer.

Li expected to find red herrings. But true biomarkers were possible as well. The *good* antibodies could be tested for in a drop of patient blood and would signal generalized bowel inflammation. The *best* could distinguish Crohn's from ulcerative colitis or other bowel conditions.

Now Li's lab has patents on three IBD and Crohn's biomarkers that lean toward "best." They come from patient immune responses—outpourings of reactive proteins like cytokines or antibodies called forth by yeasts or gut bacteria.

There's more. Using both variations on the standard laboratory ELISA assay and new ways of analysis, the group hopes to predict therapeutic benefit. "If we knew beforehand the 30 percent who won't respond to the current IBD therapy, infliximab, we could save suffering," says Li. Typically, it takes six weeks for the agent to help *any* patient. "That's a long time for a nonresponder to lose." An NIH grant is helping the researchers single out patients who do improve.



A new way of studying an old mouse model of IBD is helping Xuhang Li's lab decipher the disease's earliest chemistry.

Li also hasn't forgotten IBD's extreme complications. "About 50 percent of patients undergoing IBD-related surgery at Johns Hopkins have painful strictures in the bowel," he explains. "Fistulas, with their dangerous leakages, are also a concern." Even a small idea of who's at risk could prompt earlier, more aggressive treatment. Fortunately, Li's group has unique biomarkers in hand, candidates to be tested in a larger patient cohort.

The most basic use of their "proteomic nets" aims to reveal IBD's early biology. By regularly sampling proteins in a standard mouse model of IBD, the researchers revealed molecular activity well before the disease appears. At three months, for example, the IL-10 gene-knockout mouse that mirrors human disease has obvious diarrhea. But early as a month after birth, its proinflammatory cytokines start climbing.

Both mice and humans generate cytokines from an *inflammasome*, a "death star" of immune activity activated fast at bodily threats. One of its cytokine products, interleukin-1-beta, is key to the decline that follows. "How do we know?" asks Li. "We shot down the 'death star.' The cytokine disappeared. Mice had a much healthier gut.

"For therapies, you want to go upstream as far as possible. That's what we believe we've done." ■

Pay Attention to Vitamin D

Hepatologist **Esteban Mezey** doesn't fail to check the box 25-dihydroxyvitamin D3 for his patients' blood studies. Those with alcoholic liver disease, chronic hepatitis or fatty liver are invariably deficient in the fat-soluble vitamin, especially when liver fibrosis is severe.

Recently, however, studies by Mezey, the basic scientist, give added motivation for checking vitamin D. He's found a mechanism—how and where the active form of the vitamin damps an abnormally high output of type I collagen by hepatic cells. Type I collagen is essential in shifting a healthy liver to one occupied with scar-making fibrosis.

Fibrosis, of course, is part of healing, part of the body's natural injury response. Its dark side comes, however, when chronic injury sends it into overdrive. Not a passive process as was once thought, fibrosis following chronic liver inflammation is a relentless cascade. It typically leads to cirrhosis, then end-stage liver disease or cancer. "The steps are all related," says Mezey, "each increasing the risk of the next."

In understanding the remodeling, Mezey has focused on the liver's *stellate cells*—a key to the organ's fine balance between collagen release and its breakdown. Normally, stellate cells hold that balance through quiet, molecular cross-talk with their surroundings. Prolonged injury, however, changes the conversation.

Preventing fibrosis is Mezey's goal. And he's turned to the fat-soluble vitamins.

"Hepatitis patients are really low in vitamins A, D and E," he explains. It's partly diet: The "fat solubles" are among vitamins that many cirrhosis patients fail to eat. Also, patients' intestinal absorption of them is poor. But disease is also at work. Stellate cells normally store the fat solubles, Mezey says, unless they're secreting collagen.

Might supplemental fat-soluble vitamins help? Mezey has shown that's the case. Vitamin A clearly lowers collagen output in mouse models of fibrosis. So does vitamin E, especially in the company of selenium. Now this newest work with vitamin D shows that it, too, reins in collagen-secretion by stellate cells. The vitamin acts directly to inhibit stellate cells' collagen genes, Mezey's found.

He's encouraged: "We're hoping this form of vitamin D will prevent progression of fibrosis in patients at risk." Larger patient studies to come will tell. For now, "the message is that we have to pay attention to these vitamins, especially D."

Esteban Mezey and Mark Donowitz

Mezey's work adds to the broadening perspective on fibrosis, says colleague **Mark Donowitz**, who heads a Johns Hopkins' Conte center for digestive diseases' basic and translational research. "It's amazing," he says. "We'd all studied inflammation and fibrosis in the esophagus, liver and intestine, thinking we were seeing specific diseases. Now we realize it's the *same* process."

To help get out that word, the researchers have organized a rare gathering of top national scientists on GI and liver fibrosis and its aftermath.

Learn more at the Conte symposium. *See page 4.*

No Depending on Depends

"Ten years ago," muses gastroenterologist **Ellen Stein,** "about all we could therapeutically offer patients with fecal incontinence (FI) were the extremes." On one hand were suggestions that patients adopt diets geared to bulk up the stool or arrange a morning enema before setting out—mild tactics, certainly. On the other, in rare, extreme cases of FI—the sort that might come after, say, neurological damage or cancer—there was colostomy.

Now that's changed significantly. And as clinicians who treat a condition that's fraught with psychological or social shame, Stein says, she and colleagues with the Johns Hopkins motility service "are relieved."

Two recently FDA-approved approaches now offered as outpatient procedures improve quality of life for patients. One uses a sterile, injectable gel to bulk up the perianal area. The gel is a natural oligosaccharide, long a workhorse in plastic surgery practice.

"We see a lot of younger women with FI who've had difficult deliveries and suffered obstetric trauma," says gastroenterologist **Patrick Okolo**, who introduced the technique for FI to Baltimore. Injected into the submucosal layer of the anal canal, the gel closes the gap between the canal and buttocks, a common site of obstetric injury. "The extra 'tissue' improves a patient's ability to grip with the sphincter, even with limited strength, and get to the bathroom," says Stein. She, like Okolo, is certified in the procedure.

"The gel resists breaking down, so treatment typically lasts a year or two," Okolo says. "It offers an extra level of control and restores a measure of natural strength to sphincter action. It's not a panacea. But the gel is extremely effective when part of comprehensive treatment."

The other new therapy, sacral nerve stimulation, is a surgical procedure originally developed for urinary incontinence. "But many patients reported it worked better for their *rectal* problems," says **Susan Gearhart,** the service's colorectal surgeon. "With the tactic, patients can get 100 percent control." She cites a study that shows 80 percent of patients have FI episodes reduced at least by half. And in 40 percent of those, they stop altogether. Like the injectable gel, placement of the "interstim" device is an outpatient procedure that is safe and well-tolerated.

Gastroenterologist Ellen Stein and colorectal surgeon Susan Gearhart team with colleagues on new tactics to counter fecal incontinence. Gearhart has implanted more than 20 sacral nerve stimulators since recent FDA approval.

To reach the target nerve, Gearhart eases an electrode into a small incision in the buttocks. She feeds it under the skin and guides it by fluoroscopy through a pelvic foramen to rest on the S3 nerve overseeing the sphincter. Because permanently securing the attached battery pack means implanting it in the buttocks, patients first get a two-week trial of neurostimulation with an external pack.

Nothing happens for either therapy without what Okolo calls "a short but deep evaluation" because patients with FI are so heterogeneous. Disease history will tell who needs anorectal manometry or ultrasound to verify sphincter strength. Stein may also ask patients to keep a bowel habits diary. It helps alert her to patients "who resort to intuitive but unhelpful behaviors like overusing muscles to retain stool."

"We work together," adds Okolo, "to keep patients from depending on Depends." ■

Why Us?

If you ever needed reasons why academic medical centers need to be kept strong and impervious to the winds of sequesters, Medicare caps and NIH cutbacks, they're in this issue of Inside Tract.

Our clinician-scientists offered the know-how in designing and running clinical trials that helped bring a breakthrough—we don't use that word lightly—in therapy for hepatitis C. As you read this, they're considering how to adapt the bounty of more effective drugs for all of our patients, in every stage of the disease that's receptive.

Esteban Mezey's decade of research on fat-soluble vitamins fits into his new molecular findings to suggest that tapping a natural brake on liver cirrhosis is possible and worth large-scale testing. Xuhang Li's lab is on its way to useful biomarkers that not only point out a patient's subtype of inflammatory bowel disease but also report who risks serious complications.

And even though we weren't on the discovery end of newer, patient-friendly tactics for fecal incontinence, our clinicians have been quick to make them their own and alert patients who'd otherwise suffer.

We invite you to call on us to learn how we can contribute to your practice.

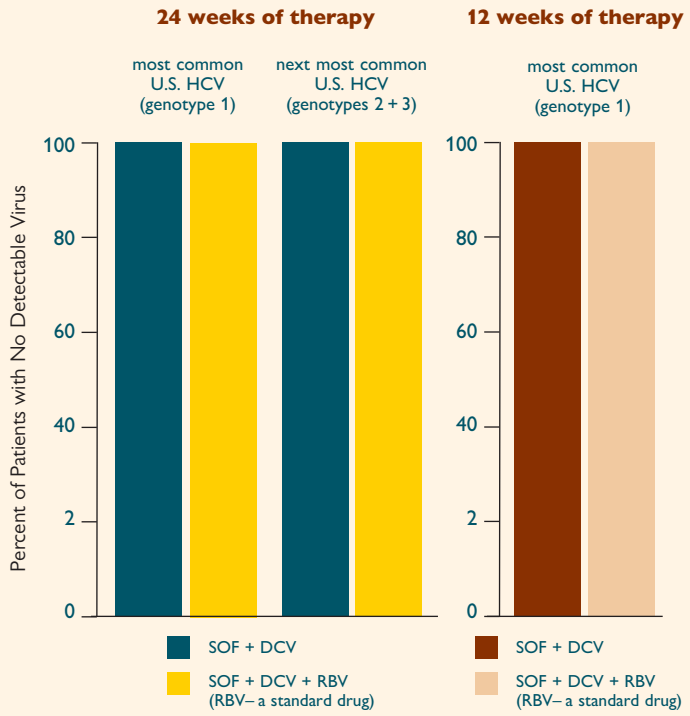
Anthony N. Kalloo, M.D.
Director,
Johns Hopkins Division of Gastroenterology and Hepatology

Image Gallery

A Picture of Hepatitis C Virus on the Run

We've pulled the best bits from a bar graph that infectious disease expert Mark Sulkowski presented at last November's annual meetings of the American Association for the Study of Liver Diseases. In the phase II trial Sulkowski led, the two newest—and gentler—direct-acting antiviral drugs, sofusbuvir and declatasvir, taken together, "disappeared" measureable virus from patients—across the usual subtypes, whether on a half-year or three month schedule.

Yes, we know there's a sameness with all the bars here hitting 100 percent—a welcome sight.



Mark Your Calendar

The Annual Symposium: Hopkins Conte Digestive Diseases Basic & Translational Research Core Center

Inflammation, Fibrosis and Cancer in Gastrointestinal and Liver Diseases

June 13, 2013
8:00 a.m. to 5:30 p.m.
The Johns Hopkins Medical Campus, Turner Auditorium

The symposium features new findings by the field's key scientists/clinicians that inflammation can lead to fibrosis and cancer.

For information:
410-955-9675

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Johns Hopkins' Division of Gastroenterology is pleased to offer brief videos via email, highlighting its innovations in endoscopy. To keep updated on cutting-edge technologies, email GIInnovations@jhmi.edu.

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Inside Tract is one of many ways the Johns Hopkins Division of Gastroenterology and Hepatology seeks to recognize and enhance its partnership with its thousands of referring physicians. Comments, questions and thoughts on topics you would like to see covered in upcoming issues are always welcome.

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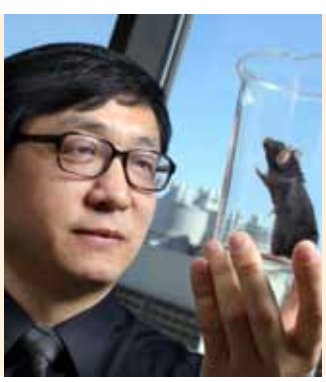

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