IN brief

Newborns sequenced at NIH

A new US National Institutes of Health (NIH) program will award $25 million over five years to study how whole-genome sequencing in newborns can be used in medical care. Under the Genomic Sequencing and Newborn Screening Disorders program, four pilot projects will investigate the medical care issues, as well as the ethical, legal and social aspects of whole-genome and exome sequencing. The projects will analyze the data for genetic diseases of Mendelian inheritance and explore whether sequencing can provide useful medical information beyond what existing newborn screening tests already provide. The National Institute of Child Health and Human Development and the National Human Genome Research Institute are funding four research teams at Brigham and Women's Hospital Boston, Children's Mercy Hospital in Kansas City, Missouri, the University of California (San Francisco) and the University of North Carolina at Chapel Hill. The blood of nearly all newborns in the US is currently screened for biochemical changes indicating certain rare disorders, such as phenylketonuria that can be controlled with diet. DNA sequencing is used as a second-tier screen, to confirm cases of cystic fibrosis, for example. As next-generation sequencing becomes quicker and cheaper, screening an infant's genome is becoming more feasible. Some genetic tests are already available, but the medical implications of routine whole-genome sequencing and the ethical challenges are unknown. "The NIH's evaluation of the risks and benefits of using this rapidly changing tool in carefully controlled studies is wise thinking," says co-investigator Richard Parad, associate professor of pediatrics at Harvard Medical School in Boston. "The right thing to do is try to generate an evidence base from which to use this rapidly developing tool." *Emma Dorey*

IN their words

"Everybody has been very happy with [the meetings] and they are getting a huge amount for very little money and they know it." Robert Dworkin of the University of Rochester, defending his practice of charging opioid manufacturers $25,000 to attend private meetings with the FDA on safety testing of painkillers. (*The Washington Post*, 6 October 2013).

"These e-mails help explain the disastrous decisions the FDA's analgesic division has made over the last 10 years. Instead of protecting the public health, the FDA has been allowing the drug companies to pay for a seat at a small table where all the rules were written." Attorney Craig Mayton, of Columbus, Ohio, who exposed the practice, after requesting and receiving hundreds of e-mails about the meetings from the University of Washington. (*The Washington Post*, 6 October 2013)

First-in-class anemia drug takes aim at Amgen's dominion

On July 31, London-based AstraZeneca committed up to $815 million to jointly develop a first-in-class anemia agent with San Francisco–based biotech FibroGen. The oral drug FG-4592 belongs to a new type of agent that inhibits hypoxia-inducible prolyl hydrolase (HIF-PH). It is currently in phase 3 trials to treat anemia in people with chronic kidney disease (CKD). Because the drug works by tapping the body's natural oxygen-sensing response system to stimulate erythropoietin (EPO), the partners are betting on its favorable side-effect profile to take a chunk out of the $3.5-billion anemia and CKD market in the US, currently dominated by Amgen's recombinant EPO Epogen (epoetin alfa).

Ashley Cooper/Alamy

Athletes use altitude training to stimulate the body's natural oxygen-sensing response to boost EPO production and gain an advantage in endurance events.

All currently available EPO-stimulating agents (ESAs) flood the body with synthetic forms of EPO at levels 100- to 100,000-fold greater than normal physiologic levels of the naturally occurring molecule, said FibroGen CEO Thomas Neff. These supraphysiologic doses have been linked to increased risk of severe adverse events such as death, stroke, myocardial infarction and hospitalization for congestive heart failure, although the molecular cause is unknown. ESAs also increase the risk of seizures and high blood pressure, and some patients experience hypersensitivity reactions; such reactions led to the market withdrawal of Omontys (peginesatide) from *Affymax* of Palo Alto, California, and its partner Takeda of Osaka in February (*Nat. Biotechnol.* **31**, 270, 2013).

By contrast, HIF-PH inhibitors work by triggering the body's natural response to hypoxia, similar to when a person is at high altitude. In a hypoxic environment, the transcription factor HIF triggers a wide range of coordinated responses in numerous tissues, namely erythropoiesis, vasculogenesis and cytoprotection, including cardioprotection, renoprotection and neuroprotection. HIF is a heterodimer, whose subunits are constantly made in nearly every cell in the body. HIF is not constantly functioning because, under normal oxygen conditions, HIF-PH puts on the brakes by degrading one of HIF's subunits. Under hypoxic conditions, as HIF-PH requires oxygen as a substrate, the brake is released, and HIF is free to function.

By blocking HIF-PH, FG-4592 allows HIF to dimerize and trigger protective responses that normally occur only under hypoxic circumstances. More specifically, the compound allows one of HIF's three isomers to dimerize, which kick-starts erythropoiesis by increasing translation of EPO in the kidneys, EPO receptor in erythroid progenitors, divalent metal transporter 1 in duodenal enterocytes, transferrin receptor in hepatocytes and possibly other tissues, ceruloplasmin in the liver and duodenal cytochrome B in the duodenum, and by decreasing hepcidin, a regulator of iron homeostasis produced in the liver. Neff believes the resulting iron mobilization and the modulation of hepcidin and endogenous EPO levels occur locally, within the normal physiologic range and in coordination with each other. "We now deliver massive doses of ESA, a wallop that is way more than what is seen in the body naturally. It works, but this is incredibly nonphysiologic," says Robert Provenzano, chief of

nephrology, hypertension and transplantation at St. John Hospital and Medical Center and clinical professor of medicine at Wayne State University, both in Detroit. "When we give the HIF-PH inhibitors, we are just allowing the body to increase hemoglobin with a natural process. It is much more physiologic," says Provenzano, previously an investigator in the FG-4592 phase 2 program.

This physiological route ushers in the potential for HIF-PH inhibitors to treat anemia without the side effects of currently marketed ESAs, and clinical data thus far point in this direction. In 73 CKD dialysis patients whose anemia was previously treated with Epogen in a phase 2 trial run by FibroGen, FG-4592 maintained hemoglobin levels to the same degree as Epogen treatment for 19 weeks. Specifically, mean changes in hemoglobin levels from baseline were −0.2 ± 1.4 g/dl for FG-4592 and 00.6 ± 1.3 g/dl for Epogen. A potential additional benefit, FG-4592 reduced total cholesterol by 20% from baseline compared with a 4% increase for patients on Epogen. Neff says this attribute could be particularly important to CKD patients given that cardiovascular events are the leading cause of death in this group and high cholesterol levels are present in >60% of patients.

The potential of this new drug class hinges on its side-effect profile. In the head-to-head trial with Epogen and in an open-label phase 2 trial in pre-dialysis CKD patients, FG-4592 resulted in stable or improved blood pressure control, with fewer of the off-target side effects that are associated with ESAs. Fibrogen's Neff says an independent data-safety monitoring committee confirmed that the adverse event profile seen in the FG-4592 treatment group was consistent with that of the overall CKD patient population, and that there were no serious adverse events attributable to the drug.

To add FG-4592 to its pipeline, AstraZeneca committed $350 million in upfront and non-contingent payments, plus up to $465 million in development-related milestones, undisclosed sales milestones and tiered royalties in the low 20% range. The deal covers the US, China and all major markets excluding Japan, Europe, the Commonwealth of Independent States, the Middle East and South Africa, which are covered by an existing agreement between FibroGen and Astellas of Tokyo. AstraZeneca will be responsible for commercializing FG-4592 in the US, whereas the partners will co-commercialize the product in China.

Not only do these novel agents appear as efficacious as and safer than EPO, but the effects also appear to work without iron supplementation, likely due to FG-4592's ability to decrease hepcidin levels. An investigator in the FG-4592 phase 2 trial, Sohan Dua, a clinical nephrologist at Valley Renal Medical Group in Northridge, California, adds that, "With EPO, if you don't give iron then it won't work. It looks like you won't need to add iron with this compound." Reducing iron supplementation reduces costs and associated adverse events, such as constipation or diarrhea.

The medical costs associated with caring for patients with CKD are high, so price is an important consideration. In 2011, Medicare introduced bundling rules, under which it pays a fixed amount for dialysis services including drugs, instead of paying for the amount of drug used (*Nat. Biotechnol.* **30**, 904, 2012). Although AstraZeneca would not publicly discuss its pricing strategies, oral drugs are generally much cheaper than injectables. "EPO is very expensive. A cheaper pill will be very attractive from a healthcare expense point of view," notes Volker Haase, associate professor of medicine and Krick-Brooks Chair in Nephrology at Vanderbilt University Medical Center in Nashville. Haase is an advisor on Cincinnati-based Akebia's clinical trials of its oral HIF-PH inhibitor, AKB-6548, which began a phase 2b trial in predialysis patients on July 24.

Oral drugs are also easier to administer than an injection, which in turn increases patient compliance. For dialysis patients, who already have a pill burden of about ten pills per day and receive infusions three times each week, the advantages of an oral drug are less clear. For this reason, FibroGen designed FG-4592 to be used on a thrice-weekly dosage regimen for dialysis patients.

Cincinnati-based Akebia takes the view that compliance is best with once-daily pills rather than on thrice-weekly tablets. Akebia CEO John Butler says the biotech is developing an oral HIF-PH inhibitor, AKB-6548, also a new molecular entity, as a once-daily pill. Provenzano believes each dosage regimen will benefit different patient populations, with once-daily pills easier for pre-dialysis patients and thrice-weekly pills for those in dialysis. FibroGen is also studying once-weekly and twice-weekly doses of FG-4592 in phase 3 trials in predialysis patients.

In CKD patients with anemia, one of the biggest problems for nephrologists is defining the right levels of hemoglobin. "When do we start treating anemia? What is the hemoglobin [level] target?" asks Haase. "Once a patient is on dialysis, it's a no-brainer; they need something to start red blood cell production. But when it's just anemia, no one knows that answer right now." Clinical guidelines recommend normalizing hemoglobin levels to 11–12 g/dl, but they do not recommend a specific hemoglobin level at which to initiate ESA use, instead stating that it depends on each individual. "A young athlete might become symptomatic at 10, and an 80-year-old woman at 7. A patient in Denver might need more hemoglobin than [one] in New York City," said Provenzano.

In nondialysis patients, frequent dosage adjustments for ESAs and the reimbursement rules for them add to the difficulties. These drugs are delivered in the outpatient setting, and under Medicare's Part B rule, physicians are reimbursed only after the drug is administered. Their high cost creates an insurmountable barrier to many doctors—especially endocrinologists and cardiologists—to be able to treat their patients with the drugs. Neff believes an oral drug obtained by prescription that is also free from the side effects associated with injectable ESAs could extend use to CKD patients who are not on dialysis. This wider target population is what primarily attracted AstraZeneca to FG-4592. Phase 3 trials in predialysis patients are under way in the US and Europe, and Fibrogen's Neff expects phase 3 studies to start in China in 2014.

At least three other HIF-PH inhibitors are under development for anemia in CKD patients. London-based GlaxoSmithKline's GSK1278863 is in phase 2 trials in dialysis and predialysis patients; BAY 85-3934 from Bayer of Leverkusen, Germany, is in phase 1 testing in predialysis patients; and JTZ-951 from Tokyo-based Japan Tobacco is in phase 1 testing.

Analysts say that although HIF-PH inhibitors could jeopardize Epogen sales, large data sets from phase 3 trials are needed before determining the magnitude of the potential threat. Eric Schmidt, managing director of Cowen & Company in New York, noted that the compounds would not pose any threat in the predialysis space, which does not see a lot of Epogen use. In the dialysis space, "At a minimum they have to show that any perceived risks are not greater than what we see with Epogen," he added. Competition from HIF-PH inhibitors also will not significantly affect growth expectations because ESA usage has been shrinking since 2011 because of safety issues, decreasing target hemoglobin levels in CKD patients and the new bundling rules (*Nat. Biotechnol.* **30**, 904, 2012). "Nobody expects Epogen to be a driver anymore," Schmidt says.

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