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