

► Toronto, Canada, claims to be two years away from starting to extract gold, copper and other metals from a sea-floor site off Papua New Guinea.

But there is widespread scepticism of seabed mining. Lee calls the promised economic benefits “a big lie that the governments of Korea, China and India tell to their people”. Kyungsik Choi, a marine sedimentologist at Seoul National University, dismisses Nautilus Minerals and other commercial operations as not economically viable, and says that they will provide “nothing more than demonstrations”. Many in the Korean marine-science community say that KIOST itself is divided, with staff scientists chafing against the mining agenda imposed by the oceans ministry.

#### PUBLIC DEBATE

The long feud between the ministry and its critics reached a flashpoint in 2008, with the proposal to build the *Isabu*. The Korea Development Institute, a think tank in Sejong that is charged with evaluating major government projects, sided with the critics, saying that the economic benefits of sea-floor mining were uncertain. It approved the ship's construction, but on the condition that the academic community have access to it. A panel of researchers headed by Lee later recommended that the ship be managed by a committee with representatives from government, academia and industry. But in 2013, the oceans ministry transferred management to KIOST in a closed process. At the time, it was deemed most cost-effective for KIOST to both operate the vessel and direct its research, says Hyuntae Kim, director of the ministry's development division.

Disappointed by the move, Lee turned to a public forum. As one of the nation's most celebrated scientists and a well-known advocate for the rights of people with disabilities (he was paralysed from the neck down in a 2006 motor-vehicle accident), he testified in the national legislature on 24 October, accusing the oceans ministry of cutting a secret deal with KIOST. By the end of his appearance, then-minister Ju-Young Lee agreed to open up *Isabu* to the academic community, clearing a path for the merit-review process.

With the prospect of leading a major oceanographic cruise now open to him, Choi says that he hopes to take *Isabu* to the Indian Ocean. He wants to help nations in southeast Asia such as Myanmar and Bangladesh, which have extensive low-lying coastal deltas, to better understand the threat posed by sea-level rise and tsunamis.

Owing to his disability, Lee can no longer sail on cruises. But he says that he takes satisfaction in knowing that he has been able to wield his fame for a positive result. “I felt very good that, yes, this is compensation for my injury,” he says. “I felt redeemed.” ■



SCOTT HOUSTON/SYGMA/CORBIS

Special K, or ketamine, a favourite drug at raves, is being considered as a treatment for depression.

#### PHARMACEUTICALS

# Rave drug tested against depression

*Companies and clinicians turn to ketamine to treat mental-health disorder as pipeline of new drugs dries up.*

BY SARA REARDON

**K**etamine, a psychoactive ‘party drug’ better known as Special K, has pharmaceutical companies riding high. Used clinically as an anaesthetic in animals and humans, it has proved an extremely effective treatment for depression, bipolar disorder and suicidal behaviour.

It also works incredibly fast. Unlike conventional antidepressants, which generally take weeks to start working, ketamine lifts depression in as little as two hours. “It blew the doors off what we thought we knew about depression treatment,” says psychiatrist James Murrough at Mount Sinai Hospital in New York City.

Companies are racing to develop patentable forms of the drug, and researchers are battling to understand how it affects the brain. An increasing number of clinicians are prescribing ketamine off-label for their patients, even as some of their colleagues worry that too little is known about its long-term effects.

The excitement over ketamine shows how badly new depression drugs are needed, says Thomas Insel, director of the US National Institute of Mental Health (NIMH) in

Bethesda, Maryland. Many drug companies have closed their mental-health divisions in the past five years, and there have been no significant advances in medication for depression in decades.

Today's most common antidepressants target the brain's serotonin or noradrenaline pathways (some target both). Ketamine acts on the NMDA receptor, a component of the glutamate pathway, which is involved in memory and cognition. Before ketamine was studied, no one even knew that the pathway was involved in depression, Murrough says.

In 2013, his group published the largest trial of off-label ketamine carried out so far, with 73 participants. The trial found that the drug reduced depression 24 hours after treatment in 64% of patients who had tried three or more other medications with unsuccessful results. A second group received the sedative midazolam; in that case, the reduction was 28% (J. W. Murrough *et al. Am. J. Psychiatry* **170**, 1134–1142; 2013). Murrough's group is now imaging the brains of patients receiving ketamine treatment to try to dissect just how the drug works.

Murrough says that long-term studies of the

drug's effects should also be done before its use becomes widespread. And bioethicist Dominic Sisti of the University of Pennsylvania in Philadelphia worries that too many physicians already consider it a standard part of their armamentarium. The way in which ketamine should be administered still needs to be worked out, says psychiatrist Kyle Lapidus at Stony Brook University in New York. He already prescribes ketamine off-label for some patients, and guesses that dozens of physicians across the country do the same. At therapeutic doses, it often produces a dissociative, out-of-body sensation that lasts less than an hour. At higher doses, recreational users report experiencing a 'K-hole', a deeply disoriented state accompanied by vivid hallucinations.

Companies hope to profit by developing patentable variations on ketamine for treating depression. A nasal spray containing a structural variant called esketamine earned a coveted 'breakthrough therapy designation' from the US Food and Drug Administration in 2013. The designation allows its manufacturer, Johnson & Johnson in New Brunswick, New Jersey, to fast-track esketamine through the regulatory process. The company plans to release the results of a 200-person study early this year; its head neuroscience researcher, Hussein Manji, says that initial results "look very good".

Last month, a company called Naurex, based in Evanston, Illinois, released results from a 386-person trial showing that its own ketamine-like drug, GLYX-13, successfully treated depression in about half of patients, without hallucinatory side effects. Roche of

***"It blew the doors off what we thought we knew about depression treatment."***

Basel, Switzerland, is also expected to release results early this year from a 357-person trial of a drug called decoglutrant, which targets the glutamate pathway. It is unclear why ketamine's psychoactive effects are considered a drawback, Sisti says. He questions the ethics of making patients pay more for a patented, non-dissociative drug if unmodified ketamine works just as well.

Ketamine's fast action is particularly promising for suicide prevention, says Carlos Zarate of the NIMH. Instead of being committed to institutions for weeks of treatment, people who have just attempted suicide might be treated with ketamine and released in days or even hours. Zarate has found that ketamine seems specifically to affect the desire to attempt suicide, whether a person is clinically depressed or not (E. D. Ballard *et al. J. Psychiatr. Res.* **58**, 161–166; 2014). That observation suggests that suicidal behaviour might be distinct from depression.

Zarate is using ketamine to treat around 50 people with depression, some of whom have suicidal thoughts, to study these effects.

Early this year, his group will begin a multi-year study of people who have attempted suicide within the previous two weeks, imaging their brain activity and comparing them with people who attempted suicide more than a year previously and with people with depression who have never attempted suicide. Those who have recently attempted suicide will be enrolled in a clinical trial of ketamine; at the same time, Zarate hopes to learn more about what an actively suicidal brain looks like. ■

#### **CORRECTION**

The News Feature 'Keeping the lights on' (*Nature* **515**, 326–329; 2014) incorrectly stated that the Boston Biomedical Research Institute went bankrupt and closed in 2013. It closed its doors under financial duress, but did not go bankrupt. The story also states that funds for indirect costs cannot be used to support researchers who lose grants or have yet to win one. Because the money from indirect costs goes into a general fund, institutions may spend it any way they wish, but these expenses cannot be reimbursed as indirect costs.