Stem-cell therapy faces more scrutiny in China

But regulations remain unclear for companies that supply treatments.

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BEIJING

The Chinese Ministry of Health has implemented regulations on the clinical application of cutting-edge therapies such as stem-cell injections.

Stem-cell scientists in China contacted by *Nature* hope that the rules may help to curtail a growing trade in unproven treatments that attract patients from around the world, risking their health and potentially damaging the reputation of stem-cell research.

The new regulations, which came into effect on 1 May, designate all forms of stem-cell therapy as 'category 3' medical technologies — those deemed "ethically problematic", "high risk" or "still in need of clinical verification". The ministry will take direct responsibility for regulating all category-3 procedures, which include gene therapy, surgical treatment of mental disorders or drug addiction, and sex changes.

Institutions wishing to offer stem-cell therapies must first demonstrate safety and efficacy in clinical trials; the treatment will then be assessed by a ministry-approved regulator. Institutions failing that process must wait 12 months before reapplying. Although the penalties for not adhering to these rules have not been made explicit, institutions that transgress are likely to face fines or have their permit to practice medicine revoked, says Renzong Qiu, a bioethicist based at the Peking Union Medical College in Beijing.

"These regulations will make people understand that the Ministry of Health and many scientists in China are concerned about these unverified procedures," says Ching-Li Hu, a paediatrician and senior adviser to Shanghai Jiaotong University's medical school, and a member of the International Bioethics Committee of the United Nations Educational, Scientific and Cultural Organization.

Hu and Qiu are members of an expert panel that will deliver recommendations to the ministry later this year on how to implement the regulations effectively.

Murky area

China already has experience in regulating cutting-edge technologies by assessing clinical trials and conducting ethical reviews. It was the first country to give governmental approval for a gene-therapy treatment, one produced by SiBiono GeneTech in Shenzhen that targets head and neck cancers.

But stem-cell therapy is a murkier area. Some researchers worry that medical institutions will be able to circumvent the regulations by calling their therapies research, even though they are charging patients and not carrying out the rigorous monitoring required by clinical-trial protocols. If those institutions have sought official approval, it comes from local governments or institutional review boards, which do not have the expertise to properly assess the treatment, says Hu.

From interviews with scientists and physicians, Qiu estimates that there are 100–150 clinics claiming to offer stem-cell therapies in China. But it is not yet clear whether companies supplying the stem cells will be also be

Exome sequencing takes centre stage in cancer profiling

COLD SPRING HARBOR

To help battle their way through the stream of data coming in from human gene sequencing, major cancer-genome screening projects such as the International Cancer Genome Consortium (ICGC) seem to be choosing to simplify matters.

The ICGC aims eventually to sequence the full genomes of 25,000 tumour samples as well as those of the people from whom the tumours were taken, which would give 50,000 distinct genomes.

But in the near term, the project is doing targeted sequencing of just the 1% of the genome known to code for proteins — the 'exons' within genes.

Sequencing of the 'exome'—all the exons in the genome—involves chopping the genome into millions of pieces and capturing and sequencing only selected DNA from exon regions. It differs from transcriptome sequencing by focusing on DNA rather than the expressed RNA in a given cell, and it promises to be vastly cheaper than whole-genome sequencing. It will be a significant focus of the ICGC, which comprises ten projects from nine member countries, says Tom Hudson of the Ontario Institute for Cancer Research in Toronto and a member of the ICGC secretariat.

Last week, at the 'Biology of Genomes' meeting at Cold Spring Harbor Laboratory in New York state, some cancer researchers questioned whether exome sequencing is the most efficient way forward. They say it could represent a piecemeal half-step, and not provide a full picture of the mutations that lead to cancer.

At the conference, Michael Stratton of the Wellcome Trust Sanger Institute in Cambridge, UK, presented early results from a study of 24 breast-cancer samples that analysed more than 2,000 chromosomal rearrangements, including regions in which vast tracts of DNA were duplicated, swapped between chromosomes, inverted or otherwise adulterated.

With so many potentially deleterious rearrangements occurring in any given cancer cell, it becomes difficult to distinguish what Stratton calls the "driver" mutations, which spur and maintain cancer development, from "passenger" mutations that are just along for the ride.

Drivers might be in the coding regions of the genome, but some will presumably be in regulatory elements and other non-coding

Experts estimate that stem-cell treatments are offered by more than one hundred clinics across China.

subject to the regulations.

Shenzhen-based Beike Biotechnology is China's most prominent stem-cell therapy company, providing adult stem cells and umbilical-cord stem cells to a network of 27 clinics worldwide. The company also acts as a first point of contact for patients. Luca Ricci, the Beike representative at Zhejiang Xiaoshan Hospital in Hangzhou, told *Nature* that his job was to "work in the hospital as an interpreter, taking care of the patient before and after they arrive." Beike's medical officer, Kara Zhang, says that she visits patients to provide medical consultations.

The company claims that more than 4,000 patients have been treated for disorders including autism, cerebral palsy, multiple sclerosis and spinal-cord injury. Over the past year, several media reports have claimed that the company's stem-cell treatments have restored sight to blind children.

But the treatments have not been subject to controlled clinical trials to assess whether they are effective and safe — and they don't come cheap. Earlier this year, Beike quoted a price of US$26,300 for an initial course of six stem-cell injections to treat a patient with spinal muscular atrophy, with additional injections costing $3,500 each.

"Having the company that provides the cells interacting directly with patients at an independent hospital or institution should be prohibited," argues David Magnus, director of the Stanford Center for Biomedical Ethics in California. In his opinion, the situation seems to be "the equivalent of a drug rep selling an unproven product directly to the patients at the hospital."

Beike did not answer *Nature's* questions about the scientific evidence supporting its stem-cell treatments; their success rates; their reaction to the ministry's regulations; whether they had published any results from their procedures in a peer-reviewed journal; or whether they had conducted any clinical trials. But the company has certainly considered clinical trials. In early 2008, Beike and the Minneapolis Heart Institute Foundation in Minnesota discussed jointly pursuing clinical trials on using stem cells to mitigate certain heart disorders.

The foundation offered to help Beike set up a clinical-trial protocol that would include creating a registry of patient outcomes. Joseph Cosico, the foundation's vice-president for research operations, says that Beike declined the offer "because of their inability to fund the venture". Beike says that it decided to work with another group, partly for cost reasons, but would not provide any details of that collaboration.

"I can understand why they wouldn't want to do a trial," says cell biologist Duanqing Pei, director-general of the Guangzhou Institute of Biomedicine and Health. "They might spend millions of dollars to prove that the treatment isn't effective." ■

David Cyranoski

sequences — meaning that whole-genome sequences will ultimately be necessary, he says.

Elaine Mardis, of Washington University in St Louis, Missouri, offered a glimpse of what else could get missed by focusing on the exome with current technologies. Building on her recent whole-genome sequences of a patient with acute myeloid leukaemia (*Nature* 456, 66–72; 2008), she presented data on a second patient–tumour pair and preliminary data on a third. With hundreds of potential mutations churned up everywhere in the genome, her group focused on validating three different 'tiers' of single-nucleotide mutations, many of which lie in coding regions.

Asked why non-coding elements hadn't got more attention, she replied that her group was looking at these regions but that they would need more work to sort out, hopefully with the help of expression data and comparison with other patients. "Right now, it's not worth it," she said.

Nevertheless, Mardis remains a big fan of sequencing whole genomes. She says that the exome approach, which uses new techniques to capture the targeted DNA for sequencing, can miss as much as 20% of the coding regions.

"If the amount of data is scary, why not sequence the whole genome and then just focus on the genes?" she asks. "You could posit that is ultimately a cheaper approach than trying to get 100% of the genes, only coming up with 80%, and then going to some extraordinary measures to get the remainder that you missed."

Francis Collins, former head of the US National Human Genome Research Institute (NHGRI) in Bethesda, Maryland, agrees. "None of the methods are perfect," he says. But he predicts that in the near future, "exome sequencing is where most of the action is going to be".

And many cancer researchers see exome sequencing as a reasonable stop-gap solution until sequencing whole genomes becomes cheap enough. Lynda Chin of the Dana-Farber Cancer Institute in Boston, Massachusetts, says that exomes are a faster way in to identifying driver genes, and help accelerate better screening methods and treatments.

Chin has headed up some of the projects for the Cancer Genome Atlas (TCGA), a potentially billion-dollar-plus programme announced in 2005, and directed by the NHGRI and the National Cancer Institute. TCGA is now moving out of its pilot phase, in which it sequenced and characterized hundreds of tumours from three different types of cancer found in lungs, ovaries and brain, towards characterizing 20–25 cancer types.

In conjunction with some whole-genome sequencing, says Chin, exome sequencing will be part of the new portfolio. "We have to push the envelope," she says, "now". ■

Brendan Maher