干细胞治疗法令引发科学家的恐慌
Stem-cell Ruling Riles Researchers

【动态】 无论在哪个国家，那些提供尚未证实的干细胞治疗的诊所都常会和卫生监管部门玩猫捉老鼠的游戏。然而，意大利则颁布了干细胞治疗的官方处理方式。其卫生部长 Renato Balduzzi 颁布命令，称可以对 32 例临终患者继续进行干细胞治疗，这其中大部分是儿童患者，并且所应用的干细胞也不是按照意大利安全标准法制造的。

3 月 21 日，科学家被这个让人始料不及的决定吓坏了，他们认为这种疗法从未经过严格的测试，是很危险的。在米兰大学干细胞研究者 Elena Cattaneo 看来，这就是点石成金式的炼金术。

该决定是在接连数周媒体报道允许干细胞疗法同情使用的压力下出台的，该疗法是由 Brescia-based Stamina 基金会开发的，在过去 6 年中历经数次禁止。现在，患者群体呼吁将该疗法对所有身患无法治愈疾病的患者进行普及。3 月 23 日，数百人在罗马举行抗议。

Stamina 基金会总裁、乌迪内大学的心理学家 Davide Vannoni 表示，对干细胞疗法的宣传已经为其赢得了 9000 名新患者。他希望法律能进一步完善，让他可以扩大该疗法的应用。1 个月前，The Hyena 的一期电视调查节目曾报道一些身患绝症（如脊髓性肌萎缩症）的儿童患者被拒绝给予可能具有疗效的治疗，意大利商界名流也参与呼吁放宽干细胞疗法的政策。

在帕维亚大学从事科学与法律的教授 Amedeo Santosuosso 表示，在意大利，未经证实的疗法可在临终患者无他选择的紧急情况下酌情使用，且国家卫生服务部门必须免费提供这种治疗。法律规定，卫生行政部门应认可这些疗法的质量，但某些条款不是很明确，这已经成为 Stamina 瓦解的潜在问题了。Stamina 基金会治疗的案例并没有明确表示治疗有效，所以在他们看来同情使用是不合法的。

Vannoni 说他是 2004 年在俄罗斯成功治疗病毒引发的面瘫后才发现的这种疗法，并邀请了俄罗斯和乌克兰的科学家至都灵共同开发这种疗法。此外，Vannoni 称 Stamina 已经治疗 80 例左右的患者，包括帕金森患者、阿尔茨海默氏症以及肌肉萎缩的患者，但他并未公开其利用骨髓间质干细胞进行治疗的结果或该疗法的详细资料。他的治疗方案是从患者身上提取细胞，经实验室培养操作后再注入患者体内。

Vannoni 承认，他虽没有公布其成果，但这种方法绝不是炼金术。每次治疗都会使用 5 种类型的细胞来更换受损组织或分泌能减少炎症、抗感染的分子或促进血管生长。不管是什么病，总会有某种类型的细胞会发挥正确的效果。

2007 年欧盟颁布一项法规，要求干细胞疗法必须遵循药品安全性和有效性法规，之后，Vannoni 将他的实验室搬至圣马力诺共和国，那里有关干细胞疗法的法规不那么严格。但他的研究受到都灵检察官 Raffaele Guariniello 的关注，根据他的调查得出结论：“Vannoni 的实验对公众是有害的。”Vannoni 表示，Guariniello 是借国际压力阻止他在圣马力诺工作，于是，他又搬至雅斯特，但是在这里 Guariniello 再次阻止了他的工作。

从那以后，Vannoni 迁移至布雷西亚的公立医院。去年 5 月，由一家意大利药品局（AIFA）、国际空间站（ISS）以及国家卫生部研究所组成的代表团参观了布雷西亚实验室，并报道了实验室的混乱状况：道德委员会之所以会做出如此评论主要是基于信息不足、没有详细的操作规程、没有患者随访等。AIFA 关闭了实验室，称实验室设施不具备生产无污染制剂的可信度。
患者和家属开始寻求法律帮助以期可以继续酌情使用这种疗法。许多法院得出的结论是：接受治疗服务是患者的权利，医疗卫生部门必须提供，且在某些情况下，布雷西亚实验室可再次提供细胞治疗。

到目前为止，只有那些被迫接受治疗的临床结果被公布了。雅斯特 Burlo Garafalo 儿童医院的临床医生治疗了5个患I型脊肌萎缩症的婴儿，并于去年10月公布了结果。他们发现治疗并未改变疾病的发展进程。Vannoni 认为治疗之所以失败是因为医生使用他精制的细胞“鸡尾酒”。

3月7日，卫生部长 Balduzzi 批准为患有异染性脑白质营养不良症（一种致死性疾病）的3岁儿童进行干细胞治疗（确保干细胞生成符合 GMP 标准），Balduzzi 此举有违他所在的监管机构的规定，激怒了科学家们，包括 Cattaneo 和 Santosuosso 在内的13位学者联合发表了一封公开信，警告 Balduzzi 这一做法的危险性。

罗马大学干细胞科学家 Paolo Bianco 参与署名了这封公开信。他表示这种授权糟糕透顶：“现任部长正在允许违反 GMP 标准，称一个未经授权、未公开发表和未经实践证实的行为为‘疗法’。”

Balduzzi 的这项法令有可能是他在意大利政府换届前的最后一项立法，科学家希望他的继任者能尊重 AIFA 及其他科学机构。AIFA 总裁 Luca Pani 拒绝对该政治决定发表评论，但表示他的机构坚持关于布雷西亚干细胞制剂的安全性和有效性的声明，“我们依旧坚守这一禁令”。

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【News】 Clinics that offer unproven stem-cell treatments often end up playing cat and mouse with health regulators, no matter which country they operate in. In Italy, however, one such treatment now has official sanction. The country’s health minister, Renato Balduzzi, has decreed that a controversial stem-cell treatment can continue in 32 terminally ill patients, mostly children—even though the stem cells involved are not manufactured according to Italy’s legal safety standards.

The unexpected decision on 21 March has horrified scientists, who consider the treatment to be dangerous because it has never been rigorously tested. In the opinion of stem-cell researcher Elena Cattaneo of the University of Milan: “It is alchemy”.

The decision followed weeks of media pressure to authorize compassionate use of the therapy, which was developed by the Brescia-based Stamina Foundation and has been repeatedly banned in the past six years. Now, patient groups are pushing for the treatment to be available to anyone with an incurable illness. Hundreds protested in Rome on 23 March, including a naked woman with pro-Stamina slogans painted on her skin.

Stamina Foundation president Davide Vannoni, a psychologist at the University of Udine, says that the publicity around the treatment has won him 9,000 new patients. He hopes that further modifications to the law will allow him to expand the therapy.

A month ago, an investigatory television programme, The Hyena, reported that children with incurable diseases such as spinal muscular atrophy were being denied supposedly important treatment, and Italian show-business personalities joined the call to relax rules on stem-cell treatment.

In Italy, the compassionate use of as-yet-unapproved therapies is allowed on an emergency basis for dying individuals who have no other options, and the national health service must provide them for free. The law requires that health authorities approve the quality of such therapies, but some of its terms are ambiguous, says Amedeo Santosuosso, a Milanese judge and a professor at the University of Pavia who specializes in science and law. “That has been the underlying problem in the Stamina debacle,” he says. “In the case of the Stamina Foundation therapy, there is no suggestion that it might be efficacious, so in my opinion compassionate use is not legitimate.”

Vannoni says that he developed the therapy after having successful stem-cell treatment for a virus-induced facial paralysis in 2004 in Russia. He invited a Russian and a Ukrainian scientist to Turin to develop the method and says that Stamina
has since treated 80 or so patients—including people with Parkinson’s disease, Alzheimer’s and muscle-wasting disorders. He has not published the outcomes or precise details of his therapy, which uses the mesenchymal stem cells from bone marrow that differentiate into bone, fat and connective tissue. In his protocol, the cells are extracted from patients, manipulated in the laboratory and then re-infused.

Vannoni acknowledges that he has not published outcomes but says that the method is far from alchemy. Each treatment uses five types of cell, he explains, with their claimed characteristics tuned to replace damaged tissue or to secrete molecules that could reduce inflammation, fight infection or promote blood-vessel growth. “Whatever the disease, one of the types of cell is going to have the right effect,” he says.

When a 2007 European Union regulation required that stem-cell therapies follow the same safety and efficacy rules as pharmaceuticals, Vannoni moved his lab to the republic of San Marino. “There, rules were not so strict,” he says.

But his work had drawn the attention of a Turin prosecutor, Raffaele Guariniello, whose investigations concluded that Vannoni’s operation could be “dangerous to public health”. Vannoni says that Guariniello marshalled international pressure to stop him working in San Marino, so he moved to Trieste, where he says Guariniello again stopped his work.

From there, Vannoni moved to a public hospital in Brescia. Last May, a delegation including representatives of the Italian Medicines Agency (AIFA) and the ISS, the health ministry’s national institute, visited the Brescia lab and reported chaotic conditions; ethics-committee approvals had been based on inadequate information, and there were no detailed protocols or patient follow-up, for example. The AIFA closed the lab, stating that the facilities could not be trusted to produce contamination-free preparations.

Patients and families turned to the legal system to allow treatments to continue as compassionate use; many of the courts concluded that it was a patient’s right to receive treatment and that health services must offer it, and in some cases the Brescia lab once again supplied cells.

Some of the compelled treatments led to the only publication of clinical results so far. Clinicians at the Burlo Garafalo Children’s Hospital in Trieste treated five babies with type I spinal muscular atrophy and published the results last October (M. Carrozz et al. Neuromuscul. Disord. 22, 1032 – 1034; 2012). They found that “the treatment did not change the course of the disease”, says co-author Marco Carrozz. Vannoni argues that the therapy failed because the clinicians did not use his exact cocktail of cells.

Setting himself against his own regulatory agencies, Balduzzi had earlier angered scientists when, on 7 March, he authorized continued therapy for a three-year-old child with the deadly disease metachromatic leukodystrophy—provided that the stem cells were created in a good manufacturing practice (GMP) facility. Thirteen academics, including Cattaneo and Santosuosso, published an open letter to Balduzzi warning him of the dangers (see go.nature.com/pb1wdl; in Italian).

That authorization was bad enough, says Paolo Bianco, a stem-cell scientist at the University of Rome who co-signed the letter. “Now the minister is allowing the non-GMP version and saying that an unauthorized, unpublished, unknown practice is a ‘treatment’.”

Balduzzi’s decree is likely to be his last legislative act in Italy’s outgoing government, and scientists hope that his successor will respect the role of the AIFA and other science-based agencies. AIFA president Luca Pani declined to comment on the political decision but says that his agency is sticking to its statements on the safety and efficacy of the stem-cell preparations from Brescia. “Our ban holds,” he says.

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