

## The African cancer drug claimed by Bristol-Myers, Novartis and Bayer

by Edward Hammond

Ixemptra (ixabepilone), a Bristol-Myers Squibb drug for breast cancer, is the product of a remarkable soil bacterium from Africa. The drug currently generates about \$120 million in annual sales for Bristol-Myers,<sup>1</sup> and both Novartis and Bayer are conducting human trials of their own versions. Yet there is no evidence that Africans are benefitting at all from this use of their biodiversity, in part because the origin of the microbe that produces ixabepilone and related drugs has been obscured by vague published information.

Numerous peer-reviewed research papers and patent documents state the bacterium comes from an unspecified location “along the banks of the Zambezi” (a river that is over 2,500 kilometres long). But the researcher who collected the microbe, who until recently was unaware that his collection had been transformed into a Bristol-Myers product, says that it actually comes from a farm located about 50 kilometres north of Bloemfontein, South Africa – nearly

1,200 kilometres south of the Zambezi River at its closest point.

In response, the German researchers who received the soil sample by mail decades ago have refined their previous statements. They now say that it was collected on the Zimbabwe side of the world-famous Victoria Falls. But the South African scientist who provided the microbe to the German researchers says that he has never been to Victoria Falls or, indeed, anywhere on the Zambezi River. The agricultural scientist, a professor in Pretoria, says he collected the sample – a mixture of soil and the dung of a small mammal called a hyrax – on his father-in-law’s farm.

This interesting case of misappropriation of African biodiversity indicates the need to conclusively determine the microbe’s origin and to implement benefit sharing by Bristol-Myers and other commercial users. As countries work on access and benefit-sharing laws

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and the Nagoya Protocol to the Convention on Biological Diversity moves towards entry into force, it is also a timely illustration of the importance of disclosure of origin of biodiversity in intellectual property applications and of ensuring that benefit-sharing rules are followed when new uses are found for microbes in *ex situ* collections.

## Ixabepilone and beyond

Life-extending treatment of breast cancer with ixabepilone may, however, only be the beginning of medical use of compounds produced by the African microbe. More drugs, developed by Novartis and Bayer, originate from the same microbe and are in advanced human trials. These may soon come to market.

Ixabepilone targets cancer tumours in a way similar to paclitaxel (taxol), by impairing the ability of cancer cells to replicate. It is approved in the United States for use in cases of breast cancer and is most often employed when tumours develop resistance to paclitaxel. The drug costs about \$18,000 a course and is the first to market of a group of anti-tumour drugs called epothilones. In addition to Bristol-Myers' approved drug, Bayer and Novartis are also testing epothilones originating from the same bacterial strain, while Bristol-Myers is trying to expand the number of cancers for which ixabepilone is approved for use.

In total, well over 100 clinical trials<sup>2</sup> for many different types of cancer have been conducted or are underway in just the United States, on epothilones originating from the South

African bacterium, dubbed Strain 90 by researchers.

## Out of Africa and into the patent office

Epothilones are produced by some strains of the myxobacterium *Sorangium cellulosum*. The strain in which they were first identified was isolated in 1985 by German researchers at the Helmholtz Institute (*Helmholtz-Zentrum für Infektionsforschung*, or HZI) in Braunschweig.<sup>3</sup>

In January 1987, HZI scientists were screening bacteria in collaboration with the company Ciba-Geigy (which later became Novartis). In the tests, interesting biological activity was produced by the strain of *S. cellulosum* that had been isolated by HZI in 1985 from a soil sample that it reported as having been collected in Africa in August 1980.

The strain, which later publications identified as coming from "along the banks of the Zambezi", was named So ce90 ("Strain 90"). From it, the compound that was later named Epothilone B was identified (and, still later, other epothilones). At the time, it was noted that epothilones had potential anti-cancer activity, but they were not viewed as sufficiently promising in this regard to merit immediate further research.<sup>4</sup>

Three years later, in 1990, Ciba-Geigy found that epothilones are active against oomycetes, a type of fungus-like microorganism. Oomycetes are the cause of a number of important crop plant diseases, including late potato blight. Upon this discovery, HZI and Ciba-

| Company                          | Current drug candidate                          | Trial cancer targets                                                              |
|----------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------|
| Bristol-Myers<br>(New York, USA) | Ixabepilone (Ixempra),<br>Epothilone B analogue | Breast (approved for use),<br>lung, cervical, uterine, colon<br>and other cancers |
| Bayer<br>(Leverkusen, Germany)   | Sagopilone (ZK-EPO),<br>Epothilone B analogue   | Breast, lung, brain, prostate<br>and other cancers                                |
| Novartis<br>(Basel, Switzerland) | Patupilone (EPO 906),<br>Epothilone B           | Ovarian, colon, breast, other<br>cancers with solid tumours                       |

Geigy moved to conduct experiments on use of the epothilones in agriculture.

Anticipating that epothilones might be valuable as fungicides, HZI quickly filed international patent applications claiming epothilone compounds as matter, claiming their use in agriculture, and also claiming their use in animal and human health.<sup>5</sup> When the agricultural experiments later failed, only the German patent application was maintained (and was later granted). The others were abandoned.

With its own experiments yielding little, in 1994 HZI sent epothilone samples to a US National Cancer Institute natural product-screening programme, where they yielded positive results. At the time, however, toxicity issues still seemed to doom the epothilones' viability as anti-cancer drugs.

Meanwhile, a Merck research programme in the United States was seeking to identify new natural products with pharmacological similarities to the drug taxol. Merck screened a US strain of *Sorangium cellulosum* called SMP44, and identified it as having taxol-like biochemical activity.<sup>6</sup> But Merck then discovered that the epothilones produced by SMP44 had already been described by HZI researchers and placed under patent claim. (This was a serendipitous discovery, as the vast majority of *S. cellulosum* strains do not produce epothilones.)

Merck's results linking epothilones to taxol-type activity on tumours<sup>7</sup> were published in 1995 and triggered huge research interest in Strain 90. Ironically, Merck reportedly terminated its own SMP44-based epothilone research because of HZI's patent, which might have interfered with it obtaining exclusive rights to epothilone drugs,<sup>8</sup> especially in view of HZI's ongoing collaboration with Novartis (and, later, Bristol-Myers).

Spurred by the widespread interest prompted by Merck's findings, HZI researchers began a "derivitization programme"<sup>9</sup> with Strain 90 epothilones, creating a number of semi-synthetic variants (derivatives) and describ-

ing the means to produce them. These were patented beginning in 1995.<sup>10</sup>

Other researchers developed pure synthetic methods to produce epothilones, after HZI provided them with the chemical structure of the original. These studies, in part financed by Novartis and Bayer, opened the door to creating still more analogues, derivative chemical "riffs" on compounds naturally produced by the African strain.<sup>11, 12</sup>

By 1997, HZI had entered into a research and development deal with Bristol-Myers. It produced Strain 90 epothilones and analogues for the company. This research eventually resulted in Bristol-Myers' commercialized drug, ixabepilone.

Meanwhile, Novartis was working in parallel. It had Strain 90 in its collection from the previous agricultural collaboration with HZI, and filed its own patent claims on methods to produce epothilones and analogues.<sup>13</sup> Ultimately, Novartis' advanced drug candidate, named patupilone, is not an analogue. It is the same as Epothilone B, which is naturally produced by Strain 90.

Bayer also began activities in the 1990s, keeping the exact structure of its epothilone analogue, called sagopilone (referred to as "ZK-EPO"), a secret until 2006. Bayer's compound is reportedly fully synthetic but, like ixabepilone, is an analogue of Epothilone B, the compound produced by Strain 90.

Patent applications and grants on epothilones, derivatives, and methods to produce and use them have now been made by numerous pharmaceutical companies and research institutes. To date, Bristol-Myers' ixabepilone is the sole epothilone drug to have been granted regulatory approval; however, a variety of other epothilones for cancer treatment are in varying stages of development.

## Patent fever

Development of a new type of cancer drug is a major commercial activity and has resulted

in aggressive patent claims by drug companies as they try to outflank one another in the process of uncovering the details of how to use epothilones to stop tumours.

As of April 2013, a stunning 609 international patent applications have been published (since 1997) that include the term “epothilone” in the patent claims. These cover a variety of items and approaches related to epothilones. Some directly claim compounds originally identified and isolated from Strain 90, derivatives of them, ways to produce epothilones and derivatives synthetically or through genetically engineering natural strains. Others cover ways to formulate and administer epothilones for medical use, for example in conjunction with other drugs, in various dosages and by various means (e.g., injected or ingested), etc.

The peak years of patent applications to date occurred in 2004 and 2005, when 64 and 63 applications were published, respectively. But new claims continue unabated: 44 applications were published in 2012. Many are classified as claims on biochemical compounds (patent class C07D, 253 claims, or 41.6%) and/or claims on medicinal preparations (patent class A61K, 375 claims, or 61.8%).

Bristol-Myers has made 110 international patent applications with epothilones mentioned in the claims, including 23 it acquired from Kosan Biosciences, which it took over in 2008. Bayer, mainly through its Schering subsidiary, has 89 patent applications. Novartis is close behind, with 85 patent applications of its own.<sup>14</sup>

Many of these applications have now been granted patents. In the United States, for example, there are 149 granted patents with the term “epothilone” in the claims. These span from a Novartis patent on production of epothilones granted in October 1999,<sup>15</sup> to a patent on methods of synthesis of epothilones granted to Bristol-Myers (Kosan) on 2 April 2013.<sup>16</sup>

Interestingly, among the 149 granted US patents, only five mention that epothilones

originally come from Africa. Four of these five patents (all from Bristol-Myers) are closely related applications on similar subject matter in which each of the patent documents repeats some of the same text. These Bristol-Myers patents (e.g., US 7,767,432) state that the bacterium was collected in 1985; however, the German scientists who isolated Strain 90 state that the sample was collected in 1980 (with isolation occurring in 1985).<sup>17</sup>

In short, the humble African myxobacterium has spurred its own research and development subsector of cancer research.

### **“The banks of the Zambezi” give way to a South African hillside?**

HZI and corporate scientists, in peer-reviewed publications and patent applications, have long stated that Strain 90 was found in a soil sample collected in 1980 on the Zambezi River. Since the Zambezi is over 2,500 kilometres long, and “along its banks” could mean any of seven different African countries,<sup>18</sup> the HZI scientists who isolated Strain 90 have never publicly identified the bacterium’s country of origin.

In a 2009 review of his 20 years of epothilone research, Gerhard Höfle, one of the primary HZI investigators, rendered the story in typical terms:<sup>19</sup> “In July 1985 *Sorangium cellulosum*, strain So ce90, the first producer of epothilone, was isolated by Hans Reichenbach from a soil sample collected at the banks of the river Zambezi in southern Africa in August 1980.”

From a benefit-sharing standpoint, the ambiguity of these statements is troubling. Under the Nagoya Protocol to the Convention on Biological Diversity, new and ongoing use of biodiversity should include benefit sharing with the provider country(ies). Whether stemming from inattention to detail or obfuscation, based on the information made public by HZI, Bristol-Myers and others, however, it was not possible to identify a provider country.

An early HZI publication on epothilones, however, offered a clue. It credited Dr. P.J.



Jooste, then at the University of Bloemfontein, for providing the soil sample that yielded Strain 90.<sup>20</sup> This somewhat obscure publication is seldom referenced today, because it stems from the period before researchers were focused on epothilones' potential as anti-tumour drugs.

Today, Piet Jooste is a research professor at the Tshwane University of Technology in Pretoria, and is a former Deputy Director of South Africa's Agricultural Research Council. Interviewed by the African Centre for Biosafety, Jooste recalls a very different origin of the Strain 90 soil sample than that published by HZI and company researchers.<sup>21</sup>

For starters, Jooste reports that he has never been to the banks of the Zambezi River, making it impossible for him to have collected a soil sample there. Jooste says he did, however, collect a sample in South Africa that he sent to Germany.

Jooste's relationship with HZI dates to the time when he was a student. While studying for his PhD at Bloemfontein in 1980, he attended a microbiology symposium held in Braunschweig, Germany, where HZI is located. There Jooste met HZI's Hans Reichenbach, who later isolated Strain 90. Reichenbach became an outside reader for Jooste's PhD thesis.

Around the time that Jooste met Reichenbach, he sent the German scientist a sample that he had collected at a *kopje* (isolated hill) on his father-in-law's farm near the town of Brandfort, about 50 kilometres north of Bloemfontein. The sample consisted of soil mixed with dung from a hyrax (a small mammal with an unusual digestive system).

In addition to his personal recollection, Jooste's files contain pertinent correspondence with HZI and others, including a late 1997 card from Reichenbach noting that "Epothilone is presently under intense study, and we hope to make an anticancer drug from it."

Information from Jooste thus indicates that it is the Brandfort, South Africa, sample from which HZI isolated *S. cellulosum* Strain 90.

In reply, HZI acknowledges that Jooste provided the sample, but the Institute continues to maintain that Strain 90 was collected at the Zambezi River. To support its case, HZI cites a page in a 1980 laboratory notebook of Hans Reichenbach and a 1985 file card, both of which state that the sample came from along the Zambezi River in "*Südafrika*", the German word for South Africa. HZI says *Südafrika* refers to the region of southern Africa and not to the country of South Africa, although in German "southern Africa" is typically written as "*südliches Afrika*". (Either way, the Zambezi River does not touch South Africa.)

HZI's Höfle claims that the notebook page and card "unequivocally" show that the soil sample "from which the strain So ce90 has been isolated was collected by Dr. P. Jooste at the banks of the river [Z]ambesi, today [Z]imbabwe, August 20, 1980."<sup>22</sup> Except HZI stakes its position on documents that were generated by the recipient of the sample, not its acknowledged originator. Nor do the HZI documents specify Zimbabwe. Instead they use the German word for South Africa, and refer to Victoria Falls (shared by Zimbabwe and Zambia). Moreover, Jooste states he's never been to the banks of the Zambezi – at Victoria Falls or anywhere else. Further, at Victoria Falls, access to the riverbank is difficult from Zimbabwe, as the Zambezi River flows there in a steep-sided and mostly inaccessible gorge.

In sum, both Jooste and HZI agree that Jooste collected the sample that yielded Strain 90 and, later, epothilone cancer drugs. Jooste's recollections of collecting the sample near Bloemfontein are specific and emphatic, and he denies ever visiting the banks of the Zambezi River. The case for a Zambezi origin of Strain 90 relies on documents generated in Germany by persons that did not collect the sample, documents whose geographic references are ambiguous and which contradict

## The Nagoya Protocol and triggers for the obligation to share benefits

The Nagoya Protocol clarifies that the negotiation of access to genetic resources and associated traditional knowledge is not what triggers an obligation for benefit sharing. Rather, it is the utilization of genetic resources or associated traditional knowledge that does so. This was born out of the understanding among developing countries that past and present biopiracy must not be rewarded by delaying the implementation of international benefit-sharing rules.

The Nagoya Protocol (in Article 5.1) says that the benefits to be shared are not only those arising from research and development (which the Protocol terms “utilization”) but also those from “subsequent applications and commercialization”. Read in conjunction with Article 2, this means that there is an obligation to share benefits from commercialization, including those from biochemical derivatives of the accessed genetic resource. This feature of the Protocol was specifically aimed at products such as drugs and cosmetics which make use of the biochemical compounds found in many organisms.

In contrast, the reference to temporal scope in Article 5.1 mainly reflects the position

of developed countries seeking to limit the Protocol’s applicability to genetic resources collected years ago, in that it suggests that the obligation to share benefits only applies when the resources were accessed in a Party to the Protocol, after its entry into force. Developed countries thus dispute the idea that sharing benefits from the continued use of genetic resources that were accessed before the entry into force of the Protocol is required by the international rules.

Article 4.4, however, says that the Protocol is the instrument for the implementation of the access and benefit-sharing provisions of the Convention on Biological Diversity. Developing countries thus maintain their broader interpretation of the temporal scope, meaning that the obligation to share benefits applies in a much wider set of circumstances.

Regardless of the outcome of these discussions, research institutions and corporations involved in the utilization and commercialization of drugs based on epothilones should clarify the origin of the genetic resources and enter into benefit-sharing agreements with the relevant government(s).

information provided by the acknowledged collector.

The weight of evidence thus favours the South African hillside; however, the matter needs further clarification to help bring about benefit sharing by those commercializing epothilones.

### **Conclusion: Archival samples, derivatives and benefit sharing**

Many countries are presently developing and refining their access and benefit-sharing (ABS) laws, including ratifying and implementing the Nagoya Protocol to the Convention on

Biological Diversity, which puts “meat on the bones” of the ABS obligations of the Convention.

In this process, pharmaceutical companies, research institutes and other entities with *ex situ* collections of biodiversity have been heard to complain that it is difficult or impossible to identify the origin of much of the biodiversity that they possess and use (an important step in setting up benefit-sharing arrangements), especially items collected years ago.

NGOs and many developing countries have replied to those claims with skepticism, noting that *ex situ* collection owners typically have

little incentive to be clear about the origin of old samples and may be overstating this problem in order to try to reduce their obligations. Even if the answer is at their fingertips, NGOs reply, companies may not try very hard to find it.

While the origin of some biodiversity that companies and others possess may truly be impossible to fully determine, the case of Strain 90 appears to be resolvable with further research, especially if supported by governments and their institutions. This should be a matter of priority, and will aid in the process of obtaining benefit sharing for Africa from Bristol-Myers, which sells over \$120 million of ixabepilone annually, as well as the other companies planning to commercialize epothilone drugs – in particular, Novartis and Bayer.

The origin of Strain 90 was never precisely represented in dozens of scientific publications and over 600 patent applications related to epothilones, yet a relatively simple investigation was quickly able to uncover important additional information pertinent to access and benefit sharing. This is thus an example of commercial beneficiaries of the use of biodiversity from developing countries failing to come forward to implement benefit sharing.

Companies and institutes can and must do more to accurately describe the origin of biological materials in scientific publications and intellectual property claims, and governments must ensure that they do so, including through the creation of robust requirements for disclosure of origin in patent applications. These requirements should include significant penalties for failure to accurately disclose, so that if patent claimants misrepresent the origin of materials, or do not show due diligence in determining and disclosing origin, they face serious consequences.

Strain 90 also highlights the importance of properly capturing derivatives in ABS law and agreements. Of the three lead compounds developed from Strain 90, only one (Novartis' patupilone) is a direct natural product of the myxobacterium. The other two, including

Bristol-Myers' commercialized drug, are derivatives of Epothilone B, chemical analogues of the natural compound. Commercialization of such derivatives requires benefit sharing under the Nagoya Protocol, and related laws, regulations and policies should clearly address this.

The record strongly suggests that Strain 90 did not come from somewhere on the Zambezi River but rather a hillside in South Africa's Free State. South Africans may now wish to achieve an appropriate benefit-sharing solution, which should involve sharing of benefits by Bristol-Myers and others who profit from epothilones. To avoid being labelled biopirates, both current and future developers of epothilone drugs, including Bayer and Novartis, will also need to commit to benefit-sharing agreements acceptable to Africans.

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*This case has been brought to the attention of the relevant South African authorities by the African Centre for Biosafety (<http://www.acbio.org.za>). The Centre also provided valuable assistance in the investigation into the case.*

*This paper was distributed at the third meeting of the Open-ended Ad Hoc Intergovernmental Committee for the Nagoya Protocol on Access and Benefit-sharing (ICNP), held in Pyeongchang, Republic of Korea, on 24-28 February 2014.*

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