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Research Note
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*This note, the basis of a forthcoming research paper, provides background on the development of new cancer drugs from a bacteria collected in southern Africa. These promising drugs, called epothilones, include a breast cancer treatment sold by Bristol Myers. Commercial development of epothilones illustrates important questions about how to achieve more equitable sharing of benefits from use of biodiversity and, in particular, how governments should implement their obligations under the Convention on Biological Diversity and its Nagoya Protocol on access and benefit sharing.*

*Few of the hundreds of patents that have been filed on the products of this remarkable bacterium (and how to produce and use them) mention its African origin. Those that do only identify a region, not a specific country or place where it was collected. This obscuration of the bacteria's African origin highlights the importance of requiring patent applicants to divulge the origin of the materials they claim.*

*Many of the same patent applications also claim synthetic or semi-synthetic variants of chemical compounds first discovered in the African microbe. Although some of these drug variants are now made in biotechnological processes and not directly produced by the microbe, these drugs originate with and are all closely derived from the African bacteria. Patenting and utilization of these derivatives also requires benefit sharing under the Nagoya Protocol. This case shows some of the complexities of benefit sharing with derivatives, and the need to address these scenarios in law and policies.*

# Promising African Cancer Drugs Claimed by Pharma Giants[1]

Ixempra (ixabepilone), a Bristol Myers Squibb drug for breast cancer, owes its existence to a soil bacterium reportedly taken from banks of the Zambezi River in southern Africa. In 2012, the drug generated about US $120 million in sales,[2] but

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[2] EvaluatePharma (2013). Ixempra Worldwide Overview (web page). URL: http://www.evaluatepharma.com (accessed 19 March 2013).

there's no evidence that Africans are benefitting at all from this use of their biodiversity.

Ixabepilone is administered by injection. The drug targets cancer tumors a similar way as the blockbuster drug paclitaxel (taxol), impairing the ability of cancer cells to replicate. It is approved for use against breast cancer, and is most often used in cases where tumors have developed resistance to taxol treatment. The drug costs about US $18,000 a course in North America (where it is mainly used).

Life-extending treatment of breast cancer with ixabepilone may, however, only be the beginning of medical use of compounds produced by the African microbe.

Ixabepilone comes from a compound produced by a strain of the bacterium *Sorangium cellulosum.* This strain, collected in Africa, is not only the source of Bristol Myers' drug, but of an entire new class of anti-cancer compounds called epothilones. The strain was isolated in 1985 by German researchers at the *Helmholtz-Zentrum für Infektionsforschung* in Braunschweig (formerly called the *Gesellschaft fur Biotechnologische Forschung).*

Ixabepilone is the first epothilone to market. Giant companies Novartis and Bayer are also testing epothilone drugs originating from the same bacterial strain, and Bristol Myers is seeking to expand the types of cancers for which its drug is used.

In total, well over 100 clinical trials[3] for many different types of cancer have been conducted or are underway in just the United States, all of them on epothilones originating, in inadequately explained circumstances, "along the banks of the Zambezi."

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

[3] US National Institutes of Health (2013). Studies Matching "Epothilone" at clinicaltrials.gov (web site). URL: http://www.clinicaltrials.gov/ct2/results?term=epothilone (accessed 19 March 2013).

**Out of Africa and into the Patent Office**

In January 1987, German scientists at the *Gesellschaft fur Biotechnologische Forschung* (GBF)[4] in Braunschweig were screening bacteria in collaboration with Ciba Geigy (later Novartis). In the tests, interesting biological activity was produced by a strain of *Sorangium cellulosum.* This interesting bacterium had recently (July 1985) been isolated by GBF researchers from a soil sample that was collected in Africa in August 1980.

The strain, which according to later publications was collected "along the banks of the Zambezi", was named So ce90 ("Strain 90"). And from it the compounds that were later named Epothilone A and B were first identified [5] (and, still later, other epothilones). At the time, it was noted that the compounds had potential anti-cancer activity, but they were not viewed as sufficiently promising in this regard to merit immediate further research.

In 1990, Ciba-Geigy, which had access to Strain 90 from the screening collaboration, found that epothilones had activity against oomycetes, a kind of fungus-like microorganism. Oomycetes are the cause of a number of important plant diseases, including late potato blight. Upon this discovery, GBF and Ciba-Geigy moved to conduct experiments on use of the epothilones in agriculture.

Thinking epothilones could prove to be a valuable fungicide, GBF quickly filed international patent applications claiming epothilone compounds as matter, as well as their use in agriculture, animal and human health.[6] When the agricultural experiments later failed, only the German patent application was maintained (and later granted). The others were abandoned.

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

Meanwhile, a Merck research program in the United States was seeking to identify new natural products with pharmacological similarities to taxol. Merck screened a US strain of *Sorangium cellulosum* called SMP44, and it was identified as having taxol-like biochemical activity.[7] On further investigation, Merck discovered that the

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[4] GBF is now known as Helmholtz-Zentrum für Infektionsforschung (HZI), however, because it used the name GBF for most of the timeframe discussed by this paper, it is referred to here by its older name.

[5] Höfle G (2009). General Aspects, in Kinghorn AD et al (eds). The Epothilones: An Outstanding Family of Anti-Tumor Agents (Progress in the Chemistry of Organic Natural Products v. 90).

[6] Hofle G et al (1993). Epothilones, Process for Preparing the Same and their Use as Medicaments and as Plant Protecting Agents. PCT patent publication WO1993010121.

[7] Kosan Biosciences, later acquired by Bristol Myers, opened a research program using SMP44 and semi-synthetic compounds derived from it. This resulted in a candidate drug, now owned by Bristol Myers, which does not appear to be moving to commercialization. Bristol Myers commercialized drug, ixabepilone, arose from the company's collaboration with GBF, using epothilones and analogs generated from Strain 90.

epothilones produced by SMP44 had already been described by GBF researchers and placed under the German patent claim. (This was an unanticipated and serendipitous discovery, as the vast majority of *S. cellulosum* strains do not produce epothilones.)

Merck's results linking epothilones to taxol-type biological activity[8] were published in 1995 and triggered huge research interest in Strain 90. Ironically, Merck terminated its own SMP44-based epothilone research, reportedly after it discovered GBF's patent, which would have interfered with Merck obtaining exclusive rights to epothilone drugs.[9]

Spurred by the widespread interest prompted by Merck's findings, GBF researchers began a "derivitization program"[10] with Strain 90 epothilones, creating a number of semi-synthetic variants (derivatives) and the means to produce them, which they patented beginning in 1995.[11]

Other researchers developed pure synthetic methods to produce epothilones, after GBF provided them with the chemical structure of the original. These studies, in part financed by Novartis and Bayer, opened the door to create still more chemical analogs, "riffs" on the compounds naturally produced by the African strain.[12] [13]

By 1997, GBF had entered into a research and development deal with Bristol Myers, producing Strain 90 epothilones and analogs for the company. This research eventually resulted in the Bristol Myers' commercialized drug, ixabepilone.

Meanwhile Novartis, which had Strain 90 from the previous agricultural collaboration with GBF, was working in parallel, filing its own patent claims on methods to produce epothilones and epothilone chemical analogs.[14] Ultimately, Novartis' current drug candidate, which is named patupilone, is not an analog. It is the same compound as Epothilone B, produced by Strain 90.

Bayer began activities at about this time, keeping the exact structure of its epothilone analog, called sagopilone (referred to as "ZK-EPO") a secret until 2006. Bayer's compound is reportedly fully synthetic but, like ixabepilone, is an analog derived from Epothilone B 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 Squibb's ixabepilone is the sole

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[8] Bollag DM et al (1995). Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action. Cancer Res. 1995 Jun 1;55(11):2325-33.
[9] Höfle G and H Reichenbach (2011). Epothilone, A Myxobacterial Metabolite with Promising Antitumor Activity, in Cragg DJ et al (eds). Anticancer Agents from Natural Products, Second Edition.
[10] Höflle G (2009), p. 9.
[11] Höfle G and M Kiffe (1996). Epothilone Derivatives, Preparation and Use. PCT patent publication WO/1997/019086.
[12] Höflle G (2009), p. 9.
[13] Schinzer D (1999). Total Synthesis of (-)-Epothilone A. Chem. Eur. J. 1999, 5, No. 9.
[14] These begin with PCT publications WO1998008849 and WO1998025929 and continue to this day.

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 class of cancer drugs is a major commercial activity and has resulted in aggressive intellectual property claims by drug companies as they use patents to try to outflank one another in the process of uncovering the details of how to use epothilones to stop tumors.

As of 4 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 compounds originally identified and isolated from Strain 90, derivatives of them, ways to produce epothilones and derivatives synthetically or through genetically engineering natural strains. These patent claims also cover ways to formulate epothilones for medical use, administer them 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: Forty four applications were published in 2012, and six thus far this year.

Many of these patent applications were classified as either or both 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%).

The largest patent claimant, Bristol Myers, owns 110 international patent applications with epothilones mentioned in the claims (this includes 23 it acquired from Kosan Biosciences, which Bristol Myers took over in 2008). Bayer, mainly through its Schering subsidiary, is second, with 89 patent applications. Novartis is close behind, with 85 of its own applications.[15]

A large number of these applications have been granted as 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,[16] through a patent on methods of synthesis of epothilones granted to Bristol Myers (Kosan), on 2 April 2013.[17]

Interestingly, among the 149 granted US patents, only five (3%) mention that epothilones originally come from Africa. And four of these five patents (all from Bristol Myers) are closely related claims on very similar subject matter in which each of the patent documents repeats some of the same text. These Bristol Myers patents (e.g. 7,767,432) state that the bacteria was collected in 1985, however, the

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[15] Information on international patent applications from the World Intellectual Property Organization Patentscope Database (http://patentscope.wipo.org), accessed 4 April 2013.
[16] Schinzer D et al (1999). US Patent 5,969,145.
[17] Chen Y and Li Y (2013). US Patent 8,410,305.

German scientists who isolated Strain 90 state that the sample was collected in 1980 (with isolation occurring in 1985).[18]

## "Along the banks of the Zambezi" – What does it mean?

The GBF scientists who isolated Strain 90 have never publicly named its country of origin. Instead, they have repeatedly stated that it was found in a soil sample collected in 1980 "along the banks of the Zambezi", a terribly imprecise indication of the strain's origin.

In a 2009 chapter reviewing his 20 years of epothilone research, Gerhard Höfle, one of the primary GBF investigators, rendered the story in typical terms:[19]

> *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 Zambesi in southern Africa in August 1980.*

One of Africa's great rivers, the Zambezi (Zambesi) rises in northern Zambia, briefly borders Congo (DR), and then passes through eastern Angola. It then returns to Zambia, flowing southward, before turning east and forming Zambia's southern border, first in short sections with Namibia and Botswana, and then a longer border with Zimbabwe (including Victoria Falls). Before emptying into the Indian Ocean, both banks of the final lengths of the river are found in Mozambique.

**Course of the Zambezi River**


Thus, "along the banks of the Zimbabwe" might mean any of seven different countries: Angola, Botswana, Congo (DR), Mozambique, Namibia, Zambia, or Zimbabwe.[20]

While the precise origin of Strain 90 remains a secret, it seems certain that it originates in southern Africa.

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[18] Höflle G (2009), p. 9.
[19] Höflle G (2009), p. 6.
[20] To complicate matters further, in at least one publication, the German researchers refer to the sample as having been collected "along the banks of the Zambezi" in South Africa. In fact, the banks of the Zambezi River don't touch South Africa. This might be attributable to a translation error or limited geographic knowledge.