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UNITED STATES DISTRICT COURT

DISTRICT OF ARIZONA

The Arizona Board of Regents for and on behalf of Arizona State University, Plaintiff, v. Seattle Genetics, Inc., Defendant.	No. COMPLAINT FOR INFRINGEMENT OF U.S. PATENT NO. 5,635,483 AND DEMAND FOR JURY TRIAL

Plaintiff The Arizona Board of Regents for and on behalf of Arizona State University (collectively "ASU"), on personal information as to its own acts, and on information and belief as to all others, for its complaint against Defendant Seattle Genetics, Inc. ("Seattle Genetics"), alleges as follows.

Introduction

1. Dr. Robert Pettit, an organic chemistry professor at Arizona State University, is one of the most prominent natural products chemists in the world. His life's work has focused on developing novel anticancer drugs from natural sources.

2. In 1977, Dr. Pettit isolated several potential anticancer compounds from a sea hare species found in the Indian Ocean. In 1982, he named one of the most promising compounds Dolastatin 10. Initial scientific studies carried out in Dr. Pettit's laboratory indicated that Dolastatin 10 was a potent anticancer agent and thus, over the next couple

of decades, Dolastatin 10 underwent extensive preclinical and clinical testing for the treatment of various types of cancer.

3. In an effort to continue to develop promising anticancer drugs, Dr. Pettit's laboratory synthesized a number of chemical analogues of Dolastatin 10. One class of these new Dolastatin 10 analogues named the Auristatins was the subject of U.S. Patent No. 5,635,483 (the "'483 patent"), issued to Dr. Pettit and ASU (as the assignee) on June 3, 1997. The '483 patent entitled "Tumor Inhibiting Tetrapeptide Bearing Modified Phenethyl Amides" claims a range of chemical compounds and methods for treating cancer with such chemical compounds. The chemical compounds disclosed and claimed by the '483 patent include a number of species of a chemical compound known as Auristatin E.

4. Seattle Genetics makes or has made, markets, offers to sell and sells a Food and Drug Administration ("FDA") approved antibody drug conjugate ("ADC") under the name ADCETRIS®. The cytotoxic agent, or drug, in the ADCETRIS® ADC is a chemical compound known as monomethyl Auristatin E ("MMAE"). MMAE and ADCETRIS®, which incorporates and delivers MMAE, infringe the '483 patent, as outlined more fully below.

Parties, Jurisdiction And Venue

5. Plaintiff The Arizona Board of Regents is a body corporate established under the Arizona Constitution and pursuant to A.R.S. § 15-1625 and has authority to act for and on behalf of Arizona State University. ASU is the assignee of the '483 patent, and holds all rights to the '483 patent.

6. Plaintiff is informed and believes, and therefore alleges, that Defendant Seattle Genetics is a Delaware Corporation having its principal place of business in Bothell, Washington.

7. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1 *et seq.* This Court has original subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338.

8. Seattle Genetics has ongoing and systematic contacts with the State of Arizona and this judicial district. On information and belief, Seattle Genetics is registered to conduct business in Arizona. On information and belief, Seattle Genetics is also conducting business in this state and judicial district by, among other things, selling and/or offering to sell ADCETRIS® within this district. By so doing, Seattle Genetics has infringed ASU's patent rights in Arizona. As a result, this Court has personal jurisdiction over Seattle Genetics.

9. This Court has personal jurisdiction over Seattle Genetics as it entered into a license agreement with ASU under the '483 patent, and negotiated and executed an amendment in 2004, which specifically recognized that MMAE is not one of the licensed compounds. Seattle Genetics' specific and ongoing contacts with Arizona relate to the infringement of the '483 patent. As a result, this Court has personal jurisdiction over Seattle Genetics.

10. Pursuant to 28 U.S.C. § 1391(b)(2), this Court is a proper venue for this action.

Summary Of The Controversy

11. Dr. Pettit's life work has been to find life-saving anticancer drugs. One of his most significant discoveries is Auristatin E, a powerful anticancer drug that could be linked with a monoclonal antibody to form a targeted cancer treatment called an antibody drug conjugate. ASU licensed this technology to Seattle Genetics to develop an ADC.

12. To develop its ADC, Seattle Genetics minimally modified the dimethyl form of Auristatin E and claimed that the modification is not covered by the '483 patent. Seattle Genetics' modification, however, does not allow it to avoid infringement of the '483 patent.

A. Dr. Pettit Discovered Dolastatin And Synthesized Auristatin

13. In the late 1960's, Dr. Pettit and the National Cancer Institute began a systematic study of marine plants and animals. In the fall of 1972, their research focused on animals and plants in the Western Indian Ocean. Dr. Pettit's team identified the sea

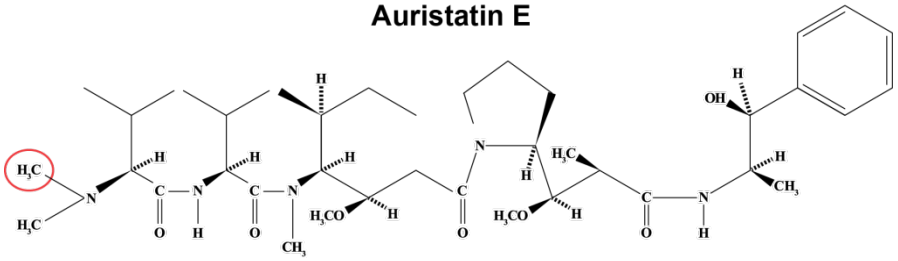
hare *Dolabella auricularia* as possessing anticancer properties, and isolated several Dolastatin compounds for further study.

14. Out of the identified compounds, Dolastatin 10 was one of the most promising anticancer drugs, because it potently interfered with cell division, a common strategy for treating cancer.

15. Over the next ten years, Dr. Pettit worked to synthesize usable Dolastatin analogues. One class of analogues he synthesized came to be known as Auristatins.

16. The chemical structure of Auristatin E, which is most relevant for this case, is:

Auristatin E



Auristatin E is a cytotoxic agent and has been shown to potently kill cancer cells. Auristatin E kills cancer cells, for example, by interfering with how such cancer cells reproduce, specifically how they divide.

17. Each normal cell in the human body contains a set of chromosomes which contain genetic information that is important in ensuring the cell functions properly. During periods of growth, when a cell divides to create new "daughter" cells, the chromosomes must be copied or "replicated" to ensure each daughter cell receives a complete set of genetic information.

18. Cellular structures known as "microtubules" physically separate each set of chromosomes to their respective daughter cell. Once normal cell division is complete, if microtubules are functioning properly, each daughter cell will have a complete set of chromosomes or genetic information.

19. In general, one of the hallmarks of cancer cells is that they divide uncontrollably, which leads to formation of tumors. Thus, a common strategy for treating cancer is to use chemical compounds that kill dividing cells.

20. Compounds claimed by the '483 patent, such as Auristatin E, kill cancer cells by, for example, disrupting microtubules. Auristatin E disrupts microtubules by binding to a protein making up microtubules called "tubulin." Much like a lock and key, Auristatin E (the key) binds to the tubulin protein at a very specific location (the lock).

21. Tubulin is a dynamic protein. In order to have properly-functioning microtubules, the tubulin protein must be able to "polymerize" or "assemble" into long linear chains.

22. When Auristatin E binds to tubulin, the tubulin protein cannot polymerize. This causes microtubules to malfunction resulting in chromosomes that are not properly separated into each daughter cell. Because each daughter cell does not have the proper number of chromosomes, each cell undergoes a process known as "apoptosis" or "programmed cell death" and the cells die.

23. Dr. Pettit applied for a patent covering his Auristatin analogues on December 3, 1992, which the United State Patent and Trademark Office issued as U.S. Patent No. 5,635,483, entitled "TUMOR INHIBITING TETRAPEPTIDE BEARING MODIFIED PHENETHYL AMIDES," on June 3, 1997 (attached as Exhibit 1). The '483 patent claims several Auristatin analogues including Auristatin E.

B. ASU Licensed Four Specific Stereoisomers In The '483 Patent To Seattle Genetics

24. Seattle Genetics had started developing ADCs but needed a potent cancer killing drug that it could link to an appropriate antibody. Recognizing the groundbreaking nature of Dr. Pettit's research, Seattle Genetics approached Dr. Pettit and began discussing the possibility of using his compounds for ADC development.

25. On August 14, 1998, Peter Senter, a scientist from Seattle Genetics, wrote Dr. Pettit seeking assistance on the use of drugs developed by Dr. Pettit at ASU. Dr. Pettit

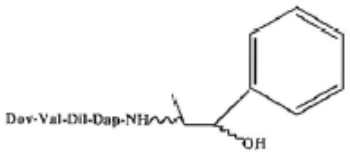
told Seattle Genetics to use Auristatin E with its then existing antibodies and linker technologies. Seattle Genetics sought to obtain from Dr. Pettit, and did in fact obtain, extensive information on the structure of the Auristatin E family, process for manufacturing it and critical information on its biological activity. Seattle Genetics received a copy of the '483 patent and reagents, including certain forms of Auristatin E and other compounds for testing and development.

26. Pursuant to a signed secrecy agreement Seattle Genetics received confidential information regarding Dr. Pettit's Auristatin E development program.

27. ASU granted Seattle Genetics a license on February 4, 2000 (the "License Agreement"). Although the class of Auristatins that Dr. Pettit discovered includes many designs, under the terms of the agreement, Seattle Genetics received a license to only four specific stereoisomers of the dimethyl version of Auristatin E. Those specific stereoisomers were defined in the agreement as "ASU's Patent Rights":

Auristatin E, Compound No. 1S2R
Auristatin E, Compound No. 1R2R
Auristatin E, Compound No. 1S2S
Auristatin E, Compound No. 1R2S

Each of which falls within the general structure shown below:



28. The '483 patent is not limited to the four stereoisomers that were licensed to Seattle Genetics under the License Agreement.

29. Seattle Genetics was required under the License Agreement to test and develop the four licensed stereoisomers, file an investigational new drug application with the FDA, and report on their development efforts.

30. Rather than use the licensed stereoisomers, however, Seattle Genetics proceeded to develop an ADC using an unlicensed version of Auristatin E. Seattle Genetics modified the structure of the dimethyl version of Auristatin E such that one

methyl (CH_3) group was replaced with a single hydrogen (H) atom, resulting in monomethyl Auristatin E ("MMAE").

31. Thus it appears, and ASU alleges on information and belief that Seattle Genetics had no intent to actually use the licensed compounds in its research. Rather, Seattle Genetics entered the agreement to obtain Dr. Pettit's confidential information related to Auristatin synthesis. Indeed, Seattle Genetics used researchers who were supposed to develop an ADC with Auristatin E to develop MMAE and ADCETRIS®.

32. In early 2004 Seattle Genetics informed ASU that it was not going to pursue an ADC using one of the four licensed stereoisomers of dimethyl Auristatin E, but instead was going to use MMAE. Seattle Genetics told ASU that its development of MMAE was completely independent of the compounds and information that it had received from Dr. Pettit's lab at ASU and that it believed MMAE was not covered by the '483 patent. ASU informed Seattle Genetics that it did not agree with Seattle Genetics' assertion that MMAE was not covered by the '483 patent, but did agree that MMAE was not one of the four licensed stereoisomers. In August 2004, Seattle Genetics and ASU amended the License Agreement to acknowledge that MMAE was not one of the four specific stereoisomers of dimethyl Auristatin E licensed under the License Agreement.

33. Seattle Genetics received FDA approval in August 2011 and began to market an ADC using MMAE under the name ADCETRIS®. Seattle Genetics infringes the '483 patent by making or having made, using, offering for sale or selling ADCETRIS®. Specifically, the cytotoxic drug in the ADC is MMAE, which infringes the '483 patent. MMAE has substantially the same structure, performs the same function in substantially the same way to achieve substantially the same results as compounds claimed in the '483 patent.

34. Seattle Genetics scientists who purported to develop MMAE have admitted that they used Dr. Pettit's inventions in the manufacture of MMAE and reviewed the '483 patent, as well as related publications by Dr. Pettit, before designing MMAE. Indeed, in

communications with Dr. Pettit, a key Seattle Genetics scientist admitted that *"there is no question that the company would not be as successful if we didn't collaborate with you."*

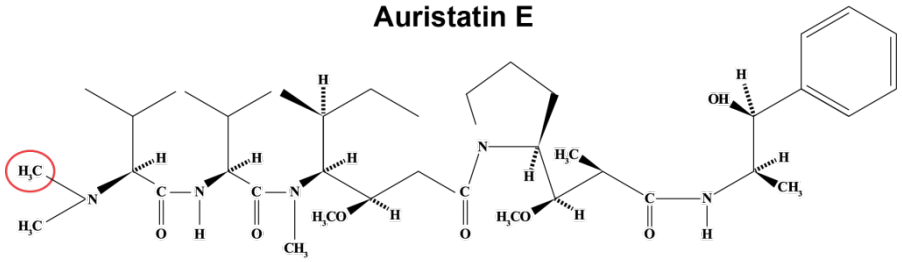
35. Seattle Genetics scientists who purported to develop MMAE have admitted that Dr. Pettit's discoveries in the '483 patent were groundbreaking and novel and that Dr. Pettit's work on Auristatin E is important. Indeed, one Seattle Genetics scientist involved in the development of MMAE, who claims that he knows "more about Dolastatins than almost everyone on the planet" stated that he regarded the '483 patent as "novel" and "valid." He testified:

> Q: Do you consider the work that Professor Pettit did on auristatin E to be important?
>
> A: Yes.

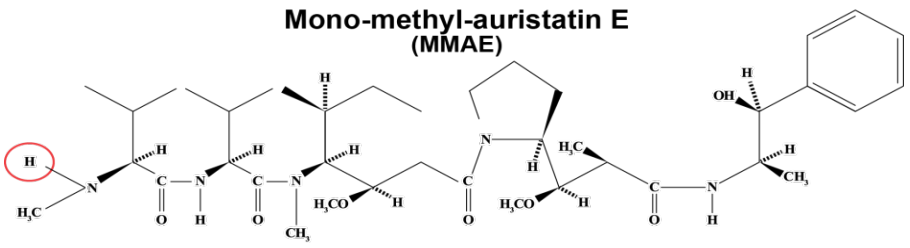
C. Monomethyl Auristatin E Infringes the '483 Patent Under the Doctrine of Equivalents

36. MMAE is identical to dimethyl Auristatin E except with respect to a single methyl group (CH3) which is replaced with a hydrogen atom (H). The respective chemical structures of dimethyl Auristatin E and MMAE are:

Auristatin E



Mono-methyl-auristatin E (MMAE)



37. The omission of a methyl group from a dimethyl Auristatin E does not alter the fact that the drugs perform the same function, in the same way to achieve the same result because of their near identity in structure except for a single methyl group, and their identity as to mechanism of action and function.

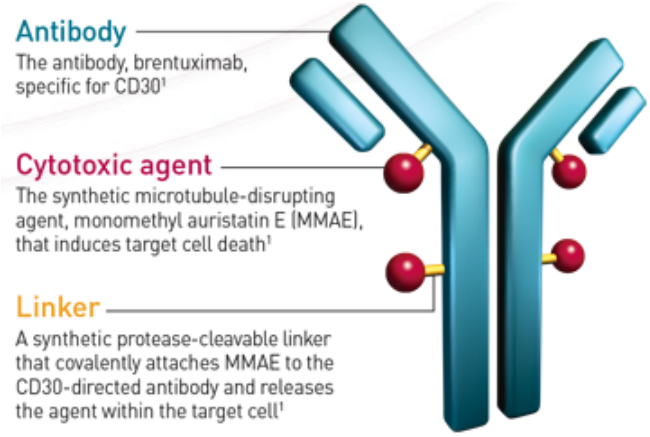
38. Seattle Genetics scientists admit that they are not aware of any differences in the mechanism of action between dimethyl Auristatin E and MMAE and admit that the drugs have the same function. Seattle Genetics scientist Brian Toki who developed MMAE provided the following testimony under oath:

> Q. *Can you think of any differences, sitting here today, in its mechanism of action*?
>
> A. Between --
>
> Q. Between auristatin E and what you describe as monomethyl auristatin E?
>
> A. *As in free drugs, I am not aware of any differences in mechanisms of action*.

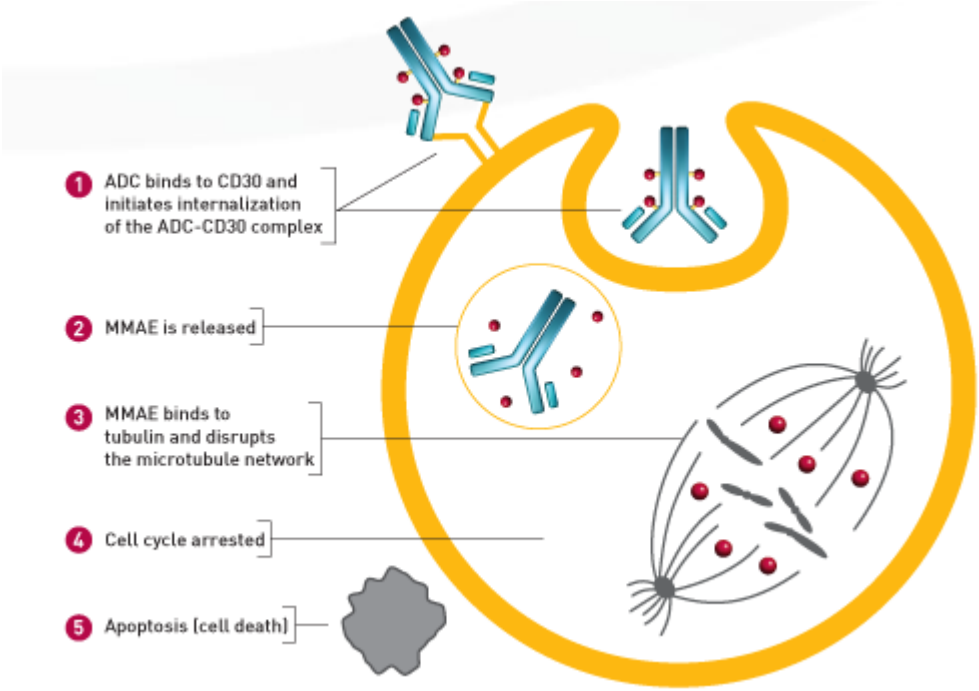
39. The omission of the methyl group from dimethyl Auristatin E is a trivial modification that does not impact the activity or mechanism of action of the drug, as demonstrated by Koichi Miyazaki, et al. *Synthesis and Antitumor Activity of Novel Dolastatin 10 Analogs*, Chem. Pharm. Bull., 43(10) 1706-1718 (1995).

40. As one example of the mechanism of action, when MMAE binds to tubulin, the tubulin protein cannot polymerize. This causes microtubules to malfunction resulting in chromosomes that are not properly separated into each daughter cell. Because each daughter cell does not have the proper number of chromosomes each cell undergoes apoptosis and the cells die.

41. Seattle Genetics combined MMAE with an antibody and a linker to form an ADC. Seattle Genetics provides the following specific illustration on its website showing how it links MMAE with an antibody to form the ADC:



ADCETRIS® binds to the cancer cell and releases MMAE in the cell. MMAE disrupts the cell cycle and the cell dies. Seattle Genetics provides the following explanation on its website of how MMAE disrupts the cell cycle, causing apoptosis:



42. ADCETRIS® was approved by the FDA on August 19, 2011. Since that time ADCETRIS® has been successfully sold in the United States. Seattle Genetics has over $300 million in ADCETRIS® sales.

Claim for Infringement of U.S. Patent No. 5,635,483

43. ASU incorporates by reference the preceding paragraphs as though fully set forth here.

44. On June 3, 1997, the United States Patent and Trademark Office issued the '483 patent, entitled "TUMOR INHIBITING TETRAPEPTIDE BEARING MODIFIED PHENETHYL AMIDES." Seattle Genetics has infringed and is infringing, directly or indirectly, the '483 patent by making or having made, using, offering to sell, and/or selling ADCETRIS® within the United States, and/or importing it into the United States without authority. Seattle Genetics has infringed and is infringing, directly or indirectly, the '483 patent by making or having made, using, offering to sell, and/or selling MMAE. Seattle Genetics also infringes the '483 patent indirectly by inducing or contributing to the infringement of claims for methods of inhibiting the growth of cancer cells by encouraging or directing the use of ADCETRIS® to inhibit the growth of cancer cells, which Seattle Genetics knows does so by delivering and engaging such cells with MMAE, which inhibits the growth of cancer cells in substantially the same way as Auristatin E.

45. ADCETRIS® infringes at least Claims 2 and 4 of the '483 patent.

46. ASU has been and continues to be damaged by Seattle Genetics' infringement of the '483 patent, in an amount to be determined at trial.

47. On information and belief, Seattle Genetics' infringement has been willful as Seattle Genetics knew of the '483 patent, and knew at least from its own research and from Koichi Miyazaki, et al. *Synthesis and Antitumor Activity of Novel Dolastatin 10 Analogs*, Chem. Pharm. Bull., 43(10) 1706-1718 (1995) that the trivial change from the dimethyl to the monomethyl version of Auristatin E did not change the effectiveness of the drug or the mechanism of action.

48. Seattle Genetics' infringement of the '483 patent is exceptional, and thus, pursuant to 35 U.S.C. § 285, entitles ASU to its reasonable attorneys' fees and costs incurred in prosecuting this action.

Prayer For Relief

WHEREFORE, ASU respectfully request that this Court grant the following relief:

A. That the Court enter judgment that Seattle Genetics has infringed the '483 patent and that such infringement was willful;

B. That ASU be awarded all damages adequate to compensate it for Seattle Genetics' infringement, such damages to be determined by a jury, and if necessary to adequately compensate ASU for the infringement, an accounting and treble damages as a result of Seattle Genetics' willful infringement;

C. That ASU be awarded pre-judgment and post-judgment interest at the maximum rate allowed by law;

D. That this case be declared exceptional within the meaning of 35 U.S.C. §285 and that ASU be awarded its reasonable attorneys' fees, expenses, and costs incurred in connection with this action; and

E. That ASU be awarded such other and further relief as this Court deems just and proper.

Demand For Trial by Jury

ASU is entitled to and demands a trial by jury of all issues so triable.

Dated: March 31, 2014

s/ C. Mark Kittredge

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