EXAMPLE 2: Developing a Therapeutic Compound for Treating Cancer

This example illustrates how inventorship is determined for claims related to Artificial Intelligence (AI)-assisted inventions in accordance with the Inventorship Guidance for AI-assisted Inventions (Inventorship Guidance).[1] *The recited drug compounds are hypothetical and are assumed to be novel. The AI systems are also hypothetical. Readers should presume that all claims are properly supported under 35 U.S.C. 112 by the specification as filed.*

Scenario 1 discusses the ideas present in guiding principles 2, 3, and 5 of the Inventorship Guidance. In this scenario, natural persons identify candidate drug compounds from the output of the AI system and take steps to synthesize a structurally modified drug compound. This scenario also includes a discussion regarding a natural person who trains and maintains an AI system but does not participate in the inventive process.

Scenario 2 discusses the ideas present in guiding principles 1 and 4 of the Inventorship Guidance. In this scenario, natural persons build and train the AI system such that the AI system creates a novel drug compound.

Background

Research plan

Marisa, a professor at the University of Cancer Research (UCR), is researching the development of a drug to treat prostate cancer. As certain types of prostate and breast cancers are primarily driven by mutations in the androgen receptor gene and protein, Marisa set out to develop a novel androgen receptor-targeted therapy that can treat prostate cancer, which limits on-target side effects (i.e., disruption of physiological androgen receptor functions in other tissues, for example, bone complications). She wants to identify lead drug compounds for prostate cancer therapy that selectively target the mutated androgen receptor protein (AR). She consulted with Raghu, UCR's AI expert, and explained that she wanted to try *in silico* drug-target interaction (DTI) prediction methods to speed up drug discovery and limit the need for traditional wet-lab experiments. She asked Raghu to identify lead drug compounds that could be used for the androgen receptor-targeted therapy.

Predictions using the Drug-target Interaction Predictor

UCR hosts a deep neural network (DNN)-based prediction model called the Drug Target Interaction Predictor (DTIP), which the university's data scientists use during drug discovery. DTIP is a ready-to-use system that can predict the interaction strength of drug-target pairs (i.e., the strength of binding between a drug compound and its target). DTIP accepts drug-target pairs as inputs, and outputs a numerical value representative of the binding affinity for that pair.

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[1] *See* Guidance: Inventorship Guidance on AI-Assisted Inventions, available at https://www.federalregister.gov/public-inspection/2024-02623/guidance-inventorship-guidance-on-ai-assisted-inventions.

Lauren, UCR's lead data scientist, trained DTIP on diverse sets of compounds and targets from previous drug-target experiments that UCR's researchers conducted. Lauren oversees DTIP's maintenance and performs regular tuning and updating to meet the system's performance expectations. DTIP only accepts a string of ASCII characters for both drug compounds and protein sequences. These strings can be generated from well-known, generally available SMILES (simplified molecular-input line-entry system) code for drug compounds and amino acid sequences for proteins.

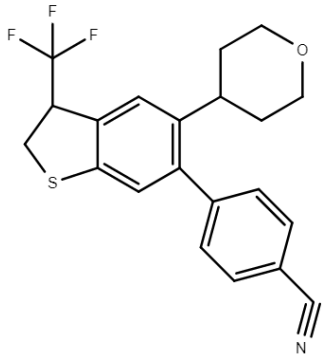
Raghu used DTIP to predict the drug compounds that had high binding affinity to a mutated AR. To do this, Marisa suggested that Raghu use well-known cancer-related compound datasets provided by the National Cancer Institute (approximately 20,000 compounds) for compound information and the mutated AR as the only target protein. For drug compound inputs, Raghu used ASCII string-representation of drug compounds. The ASCII string-representation of the amino acid sequence of a mutated AR was used as target input. Based on these inputs, the DTIP system outputted a numerical value of 0 to 1 for each drug compound, representing the binding affinity of the drug compound to the mutated AR. Raghu sorted the outputs in descending order. Marisa identified the top six drug compounds, CID_1 to CID_6, as having the highest numerical values (greater than 0.67), representing high binding affinity. Based on the high calculated binding affinity, she hypothesized that CID_1 through CID_6 would likely be therapeutic in treating prostate cancer. Marisa selected these potential candidate drug compounds for further wet-lab experiments and characterization. CID_1 has the highest numerical value representing binding affinity.

Use the Background section above as a setting for the following two different scenarios, scenario 1 and scenario 2.

Scenario 1
Drug optimization using wet-lab experiment

Naz, Marisa's postdoctoral fellow, synthesized CID_1 to CID_6. After synthesizing all six drug compounds and characterizing the binding of the drug compounds to mutated and unmutated AR, Naz identified the drug compound CID_1 as having the greatest promise of therapeutic efficacy but found that it exhibited a high degree of binding to both mutated and unmutated AR. Binding to unmutated AR has been correlated to an increased amount of on-target side effects. A higher degree of selective binding to mutated AR has been correlated to stronger anti-tumor potency and improved efficacy in treating prostate cancer. Marisa and Naz discussed the issue and determined, based on the morphology of the mutated AR, that changing the structure of the CID_1 drug compound could yield more selective binding to the mutated AR. Through a series of experiments, Marisa and Naz identified potential structural modifications of CID_1 and started the synthesis process. Naz prepared several intermediates in the synthetic preparation of CID_1 and found that one of the intermediates (CID_1-int) was more stable than the others, a characteristic that would be useful for large-scale production of the lead drug compound. Marisa found that a modified version of CID_1 (CID_1-mod), synthesized from CID_1-int, not only exhibited more selective binding to mutated AR, but also showed sufficient anti-tumor potency, indicating improved efficacy for the treatment of prostate cancer with limited on-target side effects. Based on the creation of CID_1-mod, Marisa also appreciated that the use of DTIP with

follow-on wet-lab experimentation is a valuable method of synthesizing a lead drug compound. The structure of the novel compound CID_1-mod is:



UCR files a patent application with the specification describing the use of DTIP to identify drug compounds CID_1 to CID_6. The application has two claims.

Claims

[Claim 1] A method of identifying and synthesizing a lead drug compound to treat prostate cancer, the method comprising:

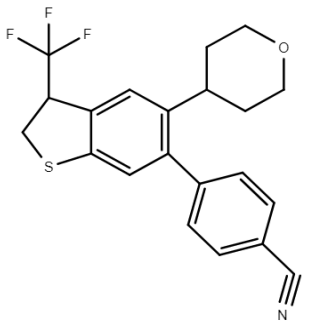
providing compound information and mutated androgen receptor protein (AR) sequence information inputs to a pre-trained Deep Neural Network (DNN); wherein the DNN outputs a numerical value representing binding affinity between the drug compound and the mutated AR;

from the output of the DNN, identifying a selected drug compound having a numeric value indicative of high binding affinity for mutated AR;

synthesizing a stable intermediate of the selected drug compound; and

synthesizing a lead drug compound by introducing structural modifications to the stable intermediate.

[Claim 2] A compound of the structural formula:



and any pharmaceutically acceptable salt thereof.

Analysis:

Inventorship is determined on a claim-by-claim basis.[2] All the inventors who contributed to at least one of the claims must be named as the inventors in the patent application.

Claim 1

Marisa and Naz are the joint inventors for the invention recited in claim 1.

Patent applications must name the natural person(s) who significantly contributed to the invention (i.e., met the *Pannu*[3] factors) as the inventor(s).[4]

A person significantly contributes to the invention recited in the claim when the person: (1) contributes in some significant manner to the conception or reduction to practice of the invention; (2) makes a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention; and (3) does more than merely explain to the real inventors well-known concepts and/or the current state of the art (*Pannu* factors).[5] Failure to meet any one of these factors precludes that person from being named an inventor.[6]

Under the first *Pannu* factor, Marisa contributed to the invention by deciding to create a treatment for prostate cancer by developing a novel androgen receptor-targeted therapy, identifying the relevant specific datasets and the sequence of the target protein for inputs to DTIP, identifying the top six drug compound candidates outputted from DTIP as potential candidates for further wet-lab experiments, determining structural modifications of CID_1 to improve selective binding affinity, identifying methodology (including identifying reagents) for preparing the structural modified CID_1, and synthesizing the modified CID_1, CID_1-mod. Naz contributed by performing wet-lab experiments on the six

A person does not lose their status as a joint inventor just because they used the services, ideas, and aid of others in the process of perfecting the invention. *See Fina Oil and Chemical Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997) (citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624 (Fed. Cir.1985). Marisa sought Raghu's help in narrowing down the number of drug compounds she could use for the next phase of the drug development. Marisa does not lose her status as a joint inventor by merely using Raghu's aid to narrow down the available compounds (approximately 20,000) to the top six highly desirable drug compounds for the anti-cancer therapy.

[2] *See Ethicon, Inc. v. United States Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir.1998).
[3] *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1351 (Fed. Cir. 1998) (*Pannu*).
[4] *See* Inventorship Guidance, sections III, IV.
[5] *See Pannu*, 155 F.3d at 1351. As discussed in the Inventorship Guidance, *Pannu*'s reference to reduction to practice as part of its first factor is an acknowledgement that simultaneous conception and reduction to practice may be applicable in certain unpredictable technologies. This doctrine is generally applicable in the context of example 2. However, reducing an invention to practice alone is not a significant contribution that rises to the level of inventorship. *See* Inventorship Guidance, section IV.A and section IV.B, principle 3.
[6] *Id.* at section IV.A.

drug compounds with the highest binding affinity scores to identify CID_1 as a promising therapeutic candidate, characterizing the drug compounds, determining that structural modifications to CID_1 that would improve the selective binding of CID_1 to mutated AR, identifying methodology (including identifying reagents) for preparing the structurally modified CID_1, and conducting synthetic methods to prepare intermediates that led to CID_1-mod, which exhibited more selective binding affinity than the unmodified form.

While some of these contributions could be characterized as simply identifying a problem or reducing the output of DTIP to practice, Marisa and Naz made significant contributions to the conception of the invention. Namely, Marisa and Naz synthesized the drug compounds identified as candidates from the output of DTIP, characterized these drug compounds, and structurally modified the lead drug compound to create a novel therapeutic drug compound. Therefore, Marisa and Naz both significantly contributed to the conception of the claimed invention. In addition, Marisa identified, based on CID_1-mod, that the use of DTIP with follow-on wet-lab experimentation is a valuable method of synthesizing a lead drug compound. Therefore, Marisa contemporaneously recognized and appreciated the invention recited in claim 1 and completed conception.

As to the second *Pannu* factor, Naz identified that CID_1 was a promising therapeutic candidate. Marisa and Naz together determined that modifying CID_1 for more selective binding affinity would provide fewer on-target side effects. As explained above, they then took the steps necessary to synthesize the structurally modified drug compound to create this novel drug compound. Their contributions are integral to the invention as claimed. The only additional limitation in the claim is providing inputs to a pre-trained DNN to output binding affinity values. This additional step is not sufficiently substantial to make the contributions of Marisa and Naz insignificant. When measured against the dimension of the full invention, the contributions of Marisa and Naz were not insignificant in quality.

Considering the third *Pannu* factor, Marisa and Naz's contributions to the invention are more than mere explanations of well-known concepts and/or the current state of the art. Instead, their contributions significantly contributed to the creation of a novel method for identifying and developing a drug compound to treat prostate cancer.

Marisa and Naz both made significant contributions to the invention and are the proper inventors of claim 1.

Raghu and Lauren are not the inventors for the invention of claim 1.

Considering the first *Pannu* factor, Raghu provided inputs to DTIP in an acceptable format to narrow down the available drug compounds to the six most likely therapeutic drug compounds, which were used by Marisa and Naz for the next phase of the drug development process. This contribution is explicitly recited in the claim and could be considered a significant contribution to conception. When analyzing Raghu's contributions under the second *Pannu* factor, these contributions were insignificant in quality when measured against the dimension of the full invention. This is because Raghu only exercised the normal skill expected of one skilled in the art to provide inputs to DTIP in the only acceptable input format (i.e., ASCII character strings)

that DTIP accepts, select the database that Marisa suggested, and sort the DTIP outputs in descending order. These activities suggest that Raghu's contributions to the invention of claim 1 are insignificant in quality.[7] The claim also recites the steps of identifying a selected drug compound as a drug compound to treat prostate cancer and synthesizing a modified version of the selected drug compound. Raghu's only contribution is prompting DTIP to identify the binding affinity of a group of drug compounds. Raghu's contribution fails to rise to the level of conception of the claimed invention in comparison to the other steps of the method developed by Marisa and Naz that led to the creation of a novel drug compound. Thus, Raghu's contribution is insignificant when compared to the full scope of the claimed invention under the second *Pannu* factor.

Lauren generally trained DTIP on a diverse set of drug compounds and targets from previous drug-target experiments conducted by UCR's researchers. Under the first *Pannu* factor, Lauren's general training of DTIP and general maintenance of the system is not a significant contribution to the conception of the invention of claim 1. These contributions were not made with a specific problem in mind (i.e., Marisa's research plan of formulating a novel androgen receptor-targeted therapy) or to elicit a particular type of output from DTIP to solve this problem. Further, a person who simply owns or oversees an AI system that is used in the creation of an invention, without making a significant contribution to the conception of the invention, is not an inventor.[8] Accordingly, Lauren is not an inventor of the invention recited in claim 1.

Raghu and Lauren fail to meet at least one of the *Pannu* factors and therefore are not the inventors of claim 1.

Claim 2

Marisa and Naz are the joint inventors for the invention recited in claim 2.

Patent applications must name the natural person(s) who significantly contributed to the invention (i.e., met the *Pannu*[9] factors) as the inventor(s).[10]

A person significantly contributes to the invention recited in the claim when the person: (1) contributes in some significant manner to the conception or reduction to practice of the invention; (2) makes a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention; and (3) does more than merely explain to the real inventors well-known concepts and/or the current state of the art (*Pannu* factors).[11] Failure to meet any one of these factors precludes that person from being named an inventor.[12]

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[7] *See Fina Oil and Chemical Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997) (citing *Sewall v. Walters*, 21 F.3d 411, 416 (Fed. Cir.1994)).
[8] *See* Inventorship Guidance, section IV.B, principle 5.
[9] *Pannu*, 155 F.3d at 1351.
[10] *See* Inventorship Guidance, sections III, IV.
[11] *Id.*.
[12] *Id*.

As explained in detail in claim 1 above, under the first *Pannu* factor, Marisa contributed to the invention by deciding to create a treatment for prostate cancer by developing a novel androgen receptor-targeted therapy, determining to structurally modify CID_1, identifying the methodology (including identifying reagents) for preparing the structurally modified CID_1, and conducting the synthesis process. Naz contributed by identifying CID_1 as a promising therapeutic candidate, determining that the structural modifications to CID_1 would improve the selective binding affinity of CID_1, and identifying the methodology (including identifying reagents) for preparing the structurally modified CID_1. Therefore, both Marisa and Naz recognized that structurally modifying CID_1 would improve its selective binding ability, and they took the steps to synthesize the claimed drug compound. These are significant contributions to the conception of the invention of claim 1. There must be a contemporaneous recognition and appreciation of the claimed invention for there to be conception.[13] Marisa recognized that the modified CID_1 resulting from the stable intermediate had the necessary properties (i.e., more selective binding affinity resulting in limited on-target side effects while still exhibiting strong anti-tumor potency and sufficient efficacy) to treat prostate cancer. Therefore, Marisa contemporaneously recognized and appreciated the invention recited in claim 2 and completed conception.

As to the second *Pannu* factor, Naz identified that CID_1 was a promising therapeutic candidate (but had issues with selective binding affinity ability), and Marisa and Naz together determined that modifying CID_1 could yield a drug compound with more selective binding ability. They took the steps necessary to synthesize the structurally modified drug compound and create this novel drug compound. These contributions are integral to the creation of the claimed drug compound. When measured against the dimension of the full invention, these contributions by Marisa and Naz were not insignificant in quality.

Guiding principle 3: A person who takes the output of an AI system and makes a significant contribution to the output to create an invention may be a proper inventor. *See Inventorship Guidance*, section IV.B, principle 3. Here, Marisa and Naz took the outputs of DTIP, i.e., CID_1 to CID_6, and made significant contributions to structurally modifying CID_1 to create the claimed compound. Therefore, Marisa and Naz are the inventors of the compound claimed in claim 2.

Considering the third *Pannu* factor, Marisa and Naz's contributions to the claimed invention are more than mere explanations of well-known concepts and/or the current state of the art. Instead, their contributions significantly contributed to the creation of a novel drug compound to treat prostate cancer.

Marisa and Naz both made significant contributions to the claimed invention and are the proper inventors of claim 2.

Finally, for at least the reasons discussed with respect to claim 1, Raghu and Lauren are not the proper inventors of claim 2.

[13] *Id.* (citing *Silvestri v. Grant*, 496 F.2d 593, 596 (CCPA 1974)).

Scenario 2

Drug optimization using Molecule Optimizer

Use the Background section above as a setting for scenario 2. Note that the facts in scenario 2 are not in addition to those in scenario 1.

Based on their past experiences with DTIP, Raghu and Marisa found that most of the drug compounds that generally had a good binding affinity with the inputted targets failed during pre-clinical and clinical trials because they had undesirable properties related to absorption, distribution, metabolism, excretion, and toxicity (ADMET). Therefore, they set out to identify and synthesize compounds that have a sufficient binding affinity to mutated AR, as well as desirable ADMET-related properties.

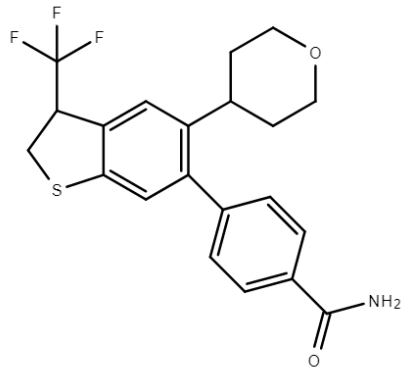
Raghu developed a new generative neural network-based AI system, Molecule Optimizer (MO), that accepts as inputs SMILES representation of a drug compound and generates an optimized drug compound (not previously synthesized), in SMILES format, for androgen receptor-targeted therapy. Marisa identified five ADMET-related properties (desirable properties) and their optimal numerical value ranges that are expected in a candidate drug compound that would have sufficient binding affinity and be successful in pre-clinical and clinical trials. She defined a scalar objective function based on the optimal ranges of these desirable properties. Raghu then trained a neural network regression model to predict the value of the objective function for a molecule, given a multi-dimensional vector representation of that molecule.

Raghu developed MO to operate in three stages. The first stage converts SMILES representation of the inputted drug compound into a multi-dimensional vector representation. The second stage performs non-convex optimization of the vector representation to maximize the scalar objective function, as approximated by the neural network regression model. The third stage converts this optimized vector representation of the drug compound back into SMILES format.

Raghu trained MO on real examples from datasets containing cancer-related drugs reviewed and approved by the Food and Drug Administration. These datasets have readily available annotations corresponding to ADMET-related properties of these synthesized drugs, along with starting compounds used for the drug synthesis/optimization. Raghu trained MO to accept SMILES inputs of drug compounds and predict desirable property values from vector representation of the drug compounds. Marisa synthesized a subset of drug compounds based on these outputs and validated the outputs for a subset of these compounds by characterizing and testing these drug compounds. Raghu fine-tuned the model based on these observations.

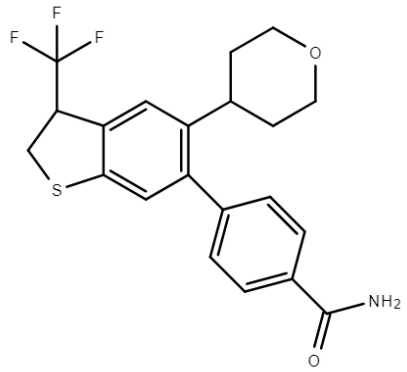
Once the training and fine-tuning was complete, Raghu inputted the SMILES format of the six drug compounds—CID_1 to CID_6 identified using DTIP, with the highest binding affinity scores (based on DTIP predictions)—to MO, which outputted structurally modified versions of the drug compounds CID_1 to CID_6—MID_1 to MID_6, respectively. Marisa synthesized and characterized MID_1 to MID_6 in her lab and determined that MID_1, which was outputted by MO, was the most viable therapeutic drug compound candidate for treating prostate cancer. The output of MO, representing the structurally modified version of CID_1, was MID_1. The novel

compound MID_1 has the structure shown below:



UCR files a patent application to patent this novel drug compound outputted by MO with the following claim (note that the numbering of the claim as "claim 3" is used for convenience).

[Claim 3] A compound with structural formula:



and any pharmaceutically acceptable salt thereof.

Raghu and Marisa are the inventors of claim 3.

Analysis:

Patent applications for AI-assisted inventions must name the natural person(s) who significantly contributed to the invention (i.e., met the *Pannu*[14] factors) as the inventor(s).[15]

A person significantly contributes to the invention recited in the claim when the person: (1) contributes in some significant manner to the conception or reduction to practice of the invention; (2) makes a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention; and (3) does more than merely explain to the real inventors well-known concepts and/or the current state of

[14] *Pannu*, 155 F.3d at 1351
[15] *See* Inventorship Guidance, sections III, IV.

the art (*Pannu* factors).[16] Failure to meet any one of these factors precludes that person from being named an inventor.[17]

Under the first *Pannu* factor, Raghu and Marisa identified the problems with synthesizing a drug directly using the drug compounds outputted by DTIP and set out to find a particular solution to synthesize a drug compound that has both selective binding affinity to mutated AR and desirable ADMET-related properties. Raghu and Marisa collaborated to train MO to generate synthetic samples of the inputted drug compounds that could be synthesized by Marisa and potentially be used to treat prostate cancer. For example, Raghu developed MO, which operates over three stages to optimize the structure of the drug compounds inputted to MO. He also identified specific datasets to train MO and worked with Marisa to fine-tune MO. Marisa identified five ADMET-related properties and developed a scalar objective function based on these properties. She also synthesized the drug compounds based on the output of MO, both to help fine-tune MO during training and to determine that MID_1 was a good candidate for the cancer therapy. Their significant contributions resulted in the creation of MO. MO, in turn, generated a novel drug compound, MID_1, which has selective binding affinity with mutated AR and desirable ADMET-related properties. Raghu and Marisa developed MO in view of a specific problem (i.e., undesirable properties of existing compounds) to generate a novel particular drug compound that does not have the specific problem. Accordingly, MO is an essential building block to the development of the claimed MID_1. Therefore, Raghu and Marisa contributed significantly to the conception of the compound recited in claim 3.

In addition, Marisa recognized that MID_1, the synthesized version of the drug compound CID_1 outputted by MO, could be used as a therapeutic drug compound for treating prostate cancer. Therefore, Marisa contemporaneously recognized and appreciated the invention recited in claim 3 and completed conception.

Guiding principle 4: The natural person(s) who designs, builds, or trains an AI system in view of a specific problem to elicit a particular solution could be an inventor, where the designing, building, or training of the AI system is a significant contribution to the invention created with the AI system. *See Inventorship Guidance*, section IV.B, principle 4. In scenario 2, Raghu and Marisa designed and trained MO to create a synthetic compound that has both high binding affinity to mutated AR and desirable ADMET-related properties to serve as an effective drug to treat prostate cancer. Here, the designing, building, and training of MO are significant contributions to the invention, i.e., the synthetic compound MID_1, which was created by MO.

Under the second *Pannu* factor, Marisa developed the scalar objective function based on the optimal ranges of the desirable properties such that the synthetic drug compound maximizes the scalar objective function. Raghu developed MO to synthesize the inputted drug compound over multiple stages, and he trained and fine-tuned MO along with Marisa. Their contributions to designing, developing, and training MO resulted in creating MID_1, the claimed compound. Without their contributions to the development of MO, MID_1 could not

[16] *See* Inventorship Guidance, section IV.A.
[17] *Id.*

have been created. When measured against the dimension of the full invention, these contributions of Raghu and Marisa were not insignificant in quality.

Considering the third *Pannu* factor, Raghu and Marisa's contributions to the invention are more than mere explanations of well-known concepts and/or the current state of the art. Instead, Raghu and Marisa significantly contributed to the development of the novel drug compound MID_1, which could be used to treat prostate cancer.

Guiding principle 1: The use of an AI system by a natural person(s) does not preclude a natural person(s) from qualifying as an inventor (or joint inventor) if the natural person(s) significantly contributed to the invention. *See Inventorship Guidance*, section IV.B, principle 1.

Raghu and Marisa made significant contributions to the invention and are the proper inventors of claim 3.

Finally, for at least the reasons discussed with respect to claim 1, Lauren is not a proper inventor of claim 3.