

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MURRAY & POOLE ENTERPRISES LTD.,

Petitioner,

v.

INSTITUT DE CARDIOLOGIE DE MONTREAL,

Patent Owner.

Case IPR2023-01064

Patent 11,400,063

SUPPLEMENTAL DECLARATION OF HOSSEIN ARDEHALI,

M.D., Ph.D.

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1. I, Dr. Hossein Ardehali, M.D., Ph.D., submit this supplemental expert declaration in the above-referenced proceeding in support of Patent Owner's Response.

2. I am the same Dr. Hossein Ardehali that submitted an expert declaration in support of Patent Owner's Preliminary Response ("Opening Declaration"). EX2001. My opinions expressed in EX2001 remain unchanged and are incorporated by reference herein. A summary of my qualifications and background are described in my Declaration and a copy of my CV is attached therein as Appendix A. *See id.* at ¶¶ 3-9.

3. This declaration further demonstrates that the Petition for *inter partes* review does not support a finding that the claims of U.S. Patent No. 11,400,063 ("the '063 patent") are anticipated by the prior art and a person of ordinary skill in the art ("POSA") would not have found the claimed inventions obvious over the prior art and a POSA's knowledge.

I. INTRODUCTION

4. It is my opinion that Petitioner and Dr. Ridker's analyses of anticipation and obviousness are deficient for several reasons. Firstly, a POSA would understand that all claims of the '063 patent are supported by U.S. Provisional Patent Application No. 62/935,865 ("the '865 provisional application") filed on November 15, 2019, including specifically initiating colchicine within about 3 days of a

myocardial infarction (“MI”) and within 4 to 7 days of MI. Secondly, a POSA would understand that Dr. Tardif, the sole inventor of the ’063 patent, is the author of the Bouabdallaoui reference. Thirdly, a POSA would understand that the occurrence, prevention, and recurrence of cardiovascular (“CV”) events are multifactorial and therefore highly unpredictable. Moreover, a POSA would understand that the effectiveness of new treatment regimens for treating or preventing CV events is correspondingly highly unpredictable. Fourthly, a POSA would expect that effective treatment with colchicine would require, or at minimum have been preferred to require, a higher preloading dose. Finally, a POSA would not have had any motivation to combine disparate portions of the prior art to arrive at the colchicine treatment inventions claimed by the ’063 patent with a reasonable expectation of success.

5. I formed my opinions by applying those standards, along with my expertise in the treatment and prevention of CV disease, to analyze whether the claims of the ’063 would have been anticipated or obvious in view of the asserted prior art. In my opinion: (1) claims 1-13, 17-26, 28, 40-46, 49, and 50 are not anticipated by Bouabdallaoui, because Bouabdallaoui is not prior art; (2) claims 27, 29-36, and 39 are not anticipated by COLCOT Protocol because the reduction in risk of stroke is not disclosed and is not inherent; (3) claims 1-50 would not have been obvious to a POSA over Nidorf in view of COLCOT Protocol, ESC Guidelines, and

COLCRYs, because there was no motivation to combine the prior art with a reasonable expectation of success to arrive at claims 1-50; (4) claims 1-26, 28, and 40-50 would not have been obvious to a POSA over Bouabdallaoui in view of COLCRYs, because Bouabdallaoui is not prior art; and (5) objective indicia of nonobvious further support the surprising and unexpected inventions disclosed in the '063 patent.

II. MATERIALS CONSIDERED

6. The opinions set forth herein are based on my education, training, professional experience, documents I reviewed, the Declaration of Dr. Ridker, and information available to me at present. I have reviewed and considered the documents and materials cited in this declaration, my Opening Declaration, Patent Owner's Preliminary Response, the Petition, the declaration of Dr. Ridker, and those listed in **Appendix A**. I reserve the right to modify, expand, or otherwise amend my opinions in view of new information, and in response to any additional reports or testimony.

III. LEGAL STANDARDS

7. I am not an attorney, but I have been informed of certain patent law principles by counsel.

8. I understand from counsel that a patent's claims are interpreted from the perspective of a POSA as of the patent's priority date. I understand Dr. Ridker

has provided an opinion regarding the definition of a POSA for the '063 patent. For the reasons stated in my Opening Declaration, it is my opinion that Dr. Ridker's definition is too narrow for requiring a research background. As I stated in the Opening Declaration, in my opinion, a POSA for the '063 patent would be an M.D. with all requisite training and 3-5 years of experience in treating CV disease. Regardless of the definition the Board adopts, my opinions are unchanged.

9. I incorporate by reference the legal standards I applied for how to interpret claims, anticipation, and obviousness described in my Opening Declaration. EX2001 at ¶¶ 13-15.

10. I understand that there remains a dispute in this case regarding the priority or effective filing date of a patent. I have been informed by counsel that a patent may claim priority to a related earlier filing, such as a provisional patent application, so long as filing deadlines are met, and the claims of the issued patent are supported by the earlier filed provisional patent application.

11. I also understand from counsel that there are disputes regarding whether references qualify as prior art. I understand from counsel that a reference may be considered prior art if it meets certain criteria, including *inter alia*, is a publication that was publicly available before the effective filing date if authored by someone other than the named inventor or was publicly available for at least one year before the effective filing date if authored by the named inventor.

IV. TREATING AND PREVENTING CV EVENTS IS CHALLENGING AND UNPREDICTABLE

12. A POSA would interpret the '063 patent's inventions as being directed to the treatment and prevention of certain CV events in patients administered a regimen of low-dose colchicine shortly after a percutaneous coronary intervention ("PCI"). *See generally* EX1001. The use of colchicine in treating CV events has been investigated in the past. *See* EX2009. However, more than thirty years ago O'Keefe found that colchicine was not effective compared to placebo at preventing CV disease in the studied population. *Id.* A POSA would understand that it has been hypothesized that targeting inflammatory pathways would treat, prevent, and/or reduce CV events in patients, including with colchicine treatment which is a known anti-inflammatory. However, the body of research has shown that using colchicine to target the inflammatory pathway is not consistently effective. *See, e.g.,* EX1028 (concluding low-dose colchicine "was not associated with a significantly increased likelihood of achieving a CRP level <2 mg/L or lower absolute levels of CRP 30 days after an acute MI"); EX2054 ("[O]ur pilot study provided no evidence that colchicine 1 mg daily for 30 days compared with placebo suppresses inflammation in patients with acute coronary syndrome or acute ischemic stroke."); EX2055 ("In our study, the effect of colchicine on inflammation in the context of STEMI could not be demonstrated."); EX2056 ("The addition of colchicine to standard medical

therapy did not significantly affect cardiovascular outcomes at 12 months in patients with ACS and was associated with a high rate of mortality.”).

13. A POSA would understand that the '063 patent's field of invention is difficult and highly unpredictable. There are multiple risk factors that contribute to a patient's risk of a CV event or disease, and the treatment methods effective for each patient and risk of recurrence are also multifactorial. More specific to the inventions claimed in the '063 patent, a POSA would have understood that preventing recurrent CV events is difficult because the varied risk factors are unique to each patient, thus the same therapy may not be as effective in some patients as others. The uniqueness of each case is widely understood and even agreed by Dr. Ridker. EX2071 at 67:10-16.

14. In 2019, although it was known that the risk of recurrent CV event(s) is greater, “[p]redictors and prognosis of treatment of a recurrent MI with contemporary management are not well known.” EX2058. As recently as 2018, just one year before Dr. Tardif's surprising discovery, a POSA would have understood that the risk window for stroke post-MI was longer than previously thought, but still reported as not well-understood. EX2059. Although a POSA would not have been clueless in 2019, the unpredictability in the field is what requires physicians like me to focus on each unique patient, as well as continue to research new therapies and better understand the mechanisms that drive the risk of recurrent CV events.

15. Due to the multifactorial nature of CV events, a POSA in 2019 would have recognized that the effectiveness of any therapy, particularly a new therapy, is highly unpredictable. For example, research suggested that reducing inflammation through disrupting the inflammatory pathway without affecting lipid levels reduces the risk of CV events. However, other studies demonstrated that there may be no causal or specific relationship between high-sensitivity C-reactive protein (“hs-CRP”) levels and coronary heart disease. See EX2060; EX2061; EX2062; EX2063 (“Hs-CRP is a marker of cardiovascular risk but lowering hs-CRP for cardiovascular benefit is controversial.”). A POSA would have also known that it was reported in the prior art that hs-CRP concentration is “unlikely to be even a modest causal factor in coronary heart disease.” EX2062 at 1. Thus, while a POSA would understand there is an association between hs-CRP and CV event risk the lack of reproducible showing of causality and specificity underscores the unpredictability of the effectiveness of treatments that target protein inhibition to disrupt the inflammatory pathway for preventing or treating CV events.

16. The studies that are most relevant to the '063 patent—investigations of low-dose colchicine for the treatment or prevention of CV events—also would have informed a POSA of the unpredictability of the usefulness of colchicine. See, *e.g.*, EX2061; EX2054; EX2064; EX1020; EX1028; EX2055. From these studies, a POSA in November 2019 would have known the effectiveness of colchicine in

treating or preventing CV events was highly unpredictable. For example, O’Keefe showed that colchicine was not effective compared to placebo at reducing the risk of restenosis following plain balloon angioplasty. EX2009 at 4. However, Deftereos 2013 found that in the subset of patients that are diabetic and treated with a bare metal stent angioplasty, the risk of restenosis was reduced with colchicine. EX2064 at 7; *see also id.* at 6 (discussing negative results of O’Keefe and two other studies).

17. The unpredictability of the effectiveness of low-dose colchicine for treating or preventing CV events has continued to be displayed after the priority of the ’063 patent. Since November 2019 several studies investigated low-dose colchicine for treating or preventing CV events in different patient subsets and with slightly different treatment regimens. EX1022; EX1005; EX2065; EX2056. Tardif 2019 and Bouabdallaoui 2020 each report on the findings from the COLCOT study, as well as its post-hoc analysis. EX1022; EX1005. The COLCOT study showed that initiating patients early after MI with low-dose colchicine and no pre-loading dose reduced the risk of certain future CV events. However, the COPS trial results, which were published on the same day as Bouabdallaoui and first presented at the same conference, showed no improvement in reducing recurrent CV events and **increased** death compared to placebo when low-dose colchicine was administered to acute coronary syndrome patients. EX2056; *see also* EX2071 at 225:1-22, 233:10-17. From both the prior art and contemporary art, a POSA understands that minor

nuances in patient population or colchicine treatment regimen can substantially affect colchicine's effectiveness to treat or prevent CV events. In order for a POSA to determine precisely which patient sub-populations and treatment regimens that result in colchicine's effectiveness would require extensive and expensive clinical trials.

V. BOUABDALLAOUI DOES NOT ANTICIPATE CLAIMS 1-13, 17-26, 28, 40-46, 49, AND 50

18. I understand from counsel that for a reference to anticipate patent claims they reference must be prior art. In my opinion Bouabdallaoui is not prior art because a POSA would understand that the granted claims are supported by the '865 provisional application and that Bouabdallaoui is the work of the inventor, Dr. Tardif.

A. “Within about 3 days of the MI” and “within about 4 to 7 days of the MI” Is Supported by the '865 Provisional Application

19. Petitioner and Dr. Ridker allege that claims 1-26 and 40-50 the '063 patent are not supported by either the '865 provisional application or U.S. Provisional Application No. 63/093,988 (“the '988 provisional application”) for not disclosing initiating colchicine “within about 3 days of MI” or “within 4 to 7 days of MI.” EX1049 at ¶¶ 90-91. I disagree. The initiation time limitations of claims 1-26 and 40-50 are fully supported by the disclosure of the '865 provisional application, which is the earliest filed application related to the '063 patent.

Bouabdallaoui was published nearly one year later in August 2020, and therefore cannot be considered prior art.

1. The '865 provisional application supports the time to initiate limitations

20. As Dr. Ridker acknowledges, the '865 provisional application specification discloses “administering colchicine within 5, 10, 15, 20, or 25 days of the MI.” EX1004 at 2:32-33 (emphasis added). However, confusingly, Dr. Ridker then continues to opine that a POSA would not understand “within 5... days of the MI” would also describe administering colchicine within about 3 days of the MI or within 4 to 7 days of the MI. EX1049 at ¶ 93. Dr. Ridker provides only a cursory explanation for his position, which is the mean time to colchicine initiation in the COLCOT trial. *Id.* Dr. Ridker’s purported rationale would not make sense to a POSA.

21. A POSA would understand that the language of “within about 3 days of the MI” to mean that the colchicine should be initiated on the first, second, or third day after an MI. Similarly, a POSA would understand that the language “within 4 to 7 days of the MI” to mean that the colchicine should be initiated on the first, second, third, fourth, fifth, sixth, or seventh day after an MI. Similarly, from the '865 provisional application’s disclosure, a POSA would understand that initiating colchicine “within 5... days of MI” includes initiation on the first, second, third, fourth, and fifth day after an MI. And, the disclosure of initiating colchicine

“within... 10 days of MI” would include days one through ten after the MI. Thus, a POSA would understand that the ’865 provisional application fully discloses and supports initiating colchicine “within about 3 days of the MI” and “within 4 to 7 days of the MI.”

22. Confusingly, Dr. Ridker also alleges that because the ’865 provisional application describes the COLCOT trial, which initiated patients at a mean of 13.5 days after MI, that the disclosure of within five days does not support initiating “within about 3 days of MI.” EX1049 at ¶ 93. Critically, Dr. Ridker neglects the fact that patients were initiated at 13.5 ± 10.1 days following MI, including “25.6% of patients who were initiated between Days 0 and 3.” See EX1005 at 3. Thus, Dr. Ridker appears to not only conflate the COLCOT trial with the disclosures of the ’865 provisional application and the ’063 patent claims, but also omits critical details that were included in the trial. Thus, even if a POSA were to conflate the different sources, the disclosure of the ’865 provisional application still supports the initiation limitations of the ’063 patent claims.

23. Although the claims of the ’063 patent do not recite any requirement that the patient is also stabilized when colchicine treatment is initiated, a POSA would still understand that would not change the overlap of disclosures between “within about 3 days of the MI” and “within 4 to 7 days of the MI” on the one hand and “within 5, 10... days of the MI” on the other hand. Thus, even if there is a

stabilization requirement in the claims, a POSA would understand “within about 3 days of the MI” to include initiating treatment at stabilization up to three days after MI. Although a POSA would understand that the time it takes for a patient to become stabilized will vary based on each patient, primarily due to various comorbidities, stabilization within one to two days after the MI is very common. In my experience, many patients are stabilized within twelve hours of their MI and a large majority of patients are stabilized within twenty-four hours after MI—especially when patients are treated with PCI—and thus can be initiated with colchicine on day one. A POSA would also understand the exact same logic applies to initiating colchicine “within 4 to 7 days of the MI.”

24. Thus, a POSA would understand that initiating colchicine “within about 3 days of the MI” and “within 4 to 7 days of the MI” is fully supported by the specification of the ’865 provisional application, as well as claim 2 of the ’865 provisional application. EX1004; EX2067. Accordingly, there is no justification for concluding that the ’063 patent should receive a priority date other than November 15, 2019.

2. Bouabdallaoui was published after the filing date of the ’865 provisional application

25. Bouabdallaoui was first published on August 29, 2020. EX1005. Shortly thereafter, the data disclosed in Bouabdallaoui was presented at the European Society of Cardiology August 29, 2020 to September 1, 2020 congress.

EX1025. As described above, Dr. Ridker and Petitioner do not dispute that the '865 provisional application was filed on November 15, 2019. Additionally, as explained above, a POSA would understand that the initiation times disclosed in the '865 provisional application fully support the initiation time limitations in claims 1-26 and 40-50 of the '063 patent. Thus, a POSA would not consider Bouabdallaoui as published before the priority date of the '063 patent, and thus is not prior art.

B. Bouabdallaoui Is Not The Work of Another

26. Even if Dr. Ridker is correct that the '865 provisional application does not support the initiation limitations of claims 1-26 and 40-50, which I disagree with, Bouabdallaoui is the work of the inventor, Dr. Tardif. In my Opening Declaration I described why a POSA would understand that Dr. Tardif, the sole inventor of the '063 patent, is also the lead author of the Bouabdallaoui reference. EX2001 at ¶¶ 30-31. I understand that both Dr. Tardif and Dr. Bouabdallaoui have submitted declarations in this matter that further show that Dr. Tardif was the sole inventor of the '063 patent and the lead author of the Bouabdallaoui reference. EX2011; EX2068.

27. My experiences are entirely consistent with the statements from Dr. Tardif and Dr. Bouabdallaoui. I am a named author on more than 100 articles and book chapters, and I have served on editorial and review boards, including currently serving as the Deputy Editor of the Journal of Clinical Investigation. In my

experience, if the first named author on an article is not the corresponding author that position was given to a more junior physician or researcher in appreciation for their contribution to the project. Indeed, in my own lab for each article on which I am the lead researcher and author I do not permit any of my fellows to serve as corresponding author, because I am ultimately responsible for that work. However, they are a first named author if they are the major contributors of the project. This not only rewards their work, but also assists new researchers and clinicians develop name recognition in the field.

28. Accordingly, contrary to Petitioner's unsupported conclusions, there is nothing abnormal regarding the ordering of authors in the Bouabdallaoui reference and a POSA would recognize that Dr. Tardif was the lead author. As the lead author, a POSA would recognize the Bouabdallaoui reference as the work of Dr. Tardif, and thus not prior art to the '063 patent even if it is given the latest possible priority date of November 13, 2020, because Bouabdallaoui is the work of the inventor published less than one year before that latest priority date.

VI. COLCOT PROTOCOL DOES NOT ANTICIPATE CLAIMS 27, 29-36, AND 39

29. For the same reasons described in my Opening Declaration, the COLCOT Protocol does not anticipate claims 27, 29-36, and 39 of the '063 patent. EX2001 at ¶¶ 32. The reference that Petitioner and Dr. Ridker rely on to allege anticipation of these claims does not recite the critical reduction in risk of stroke

limitation of each of these claims. See EX1006. Indeed, the reference that Petitioner relies on is a mere summary from clinicaltrials.gov and not the type of document a POSA would rely on to understand that protocol of a trial. Here, I agree with Dr. Ridker, and it is my opinion that a POSA would rely on the actual protocol, rather than the summary. EX2071 at 135:10-16, 136:8-137:1. Regardless of the protocol reference that Petitioner relies, the protocol does not disclose the critical limitation of reducing the risk of stroke. EX1006.

30. I also disagree that the COLCOT Protocol inherently discloses the reducing of the risk of stroke limitation. As I described above, the relevant field is highly unpredictable, and the usefulness of a treatment may even differ from patient to patient. Therefore, reducing the risk of stroke is not a natural result of administering colchicine to all patients within thirty days of MI. Indeed, the data from COLCOT shows that not each and every patient experienced a reduction in the risk of stroke. EX1005 at Table 3. Thus, a POSA would not have concluded from the summary reference that the alleged prior art contains each and every limitation of claims 27, 29-36, and 39 of the '063 patent.

VII. A POSA WOULD NOT HAVE BEEN MOTIVATED TO COMBINE NIDORF, COLCOT, ESC GUIDELINES AND/OR COLCRYS WITH A REASONABLE EXPECTATION OF SUCCESS

31. For the same reasons described in my Opening Declaration, a POSA would not have found claims 1-50 obvious over Nidorf in view of COLCOT

Protocol, ESC Guidelines, and/or COLCRYST. EX2001 at Sec. VI. Moreover, as explained above, the relevant field is highly unpredictable, and thus a POSA would not have had a reasonable expectation of success in combining the prior art teachings based on the immense variety of results in administering colchicine within one month after an MI.

VIII. OBJECTIVE INDICIA SHOW THE NONOBVIOUSNESS OF THE CLAIMED INVENTIONS

32. A POSA would have found the ability to treat CV events and prevent future CV events with the administration of low-dose colchicine shortly after MI to be an unexpected benefit in the use of colchicine. Before the '063 patent's November 15, 2019 priority, a POSA would have also been skeptical that low-dose colchicine without a loading dose would be effective at reducing the risk of recurrent CV events.

A. The Reduction of Risk of Future CV Events Claimed in the '063 Patent is an Unexpected Benefit

33. As of November 15, 2019, a POSA would have understood that colchicine was an anti-inflammatory agent and that inflammation plays a role in the risk of recurrent CV events, however, due to the published research at that time, a POSA would not have expected that low-dose colchicine, without a pre-loading dose, administered shortly after MI would be effective.

34. As described above, limited research showed that low-dose colchicine was effective at lowering the risk of recurrent CV events or treating CV events. Before the priority of the '063 patent, only Nidorf 2013 and Deftereos 2013 reported such effectiveness, however, those studies differed substantially from the present invention. EX1020; EX2064. In Nidorf 2013, patients were administered low-dose colchicine after being stable for six months post-MI. EX 1020. A POSA would view those results speciously because the LoDoCo study was a non-placebo controlled, open-label study and thus at high risk of bias. EX 1020. As explained above, Deftereos 2013 investigated the usefulness of colchicine in a very narrow patient population, diabetic patients with bare metal stents. EX2064. As I described above, there were other studies, including those more relevant to the present invention that would have caused a POSA to find the benefits of the claimed invention unexpected.

35. For example, the Akodad 2017 reference describes the COLIN study. The COLIN study sought to evaluate the effectiveness of colchicine in the acute MI setting, and concluded that “[t]he lack of effect of colchicine in our study could be explained by late administration in the [ICU] after reperfusion and without loading dose.” EX2055 at 7. Thus, a POSA would understand that Akodad suggests the lack of effectiveness was due to administration initiated in the ICU after reperfusion treatment for acute MI and not using a loading dose. Those attributes contributed directly to the novelty and nonobviousness of the claims of the '063 patent, which

initiates treatment within either three, four to seven, or thirty days after MI and explicitly excludes a loading dose. See EX1001 at claims 1, 8, 27. Accordingly, a POSA would have expected that in the claimed regimen colchicine would not have been effective or reduced the risk of recurrent CV events.

36. Another study would have also led a POSA to expect that colchicine treatment within the first thirty days after MI would be ineffective to suppress inflammation compared to placebo. EX2054. In Raju 2011, the researchers sought to determine whether low-dose colchicine reduced hs-CRP in patients with acute coronary syndrome or acute stroke who were followed for 30 days. *Id.* at 1. However, that study found that “[c]olchicine given in a dose of 1 mg/day did not significantly reduce blood levels of hs-CRP when compared to placebo.” *Id.* at 6. Thus, a POSA would not have expected that colchicine could even reduce inflammation during the first thirty days when colchicine is initiated. However, Dr. Tardif surprisingly invented with the ’063 patent that initiating colchicine at 0.5 mg/daily within three, four to seven, or thirty days after MI and continued for one year reduces inflammation and the risk of recurrent CV events. Therefore, in the patient populations more relevant to the inventions of the ’063 patent, a POSA would not have expected that low-dose colchicine would reduce inflammation and the risk of recurrent CV events.

B. A POSA Would Have Been Skeptical that the Claimed Inventions Would Work

37. As described above, a POSA would not have expected that the claimed inventions would so successfully reduce inflammation and the risk of recurrent CV events. Based upon the same prior art teachings a POSA would have been skeptical that the claimed colchicine regimens would even work as claimed.

IX. CONCLUSION

38. For the foregoing reasons, and those described in my Opening Declaration, it is my opinion that the claims of the '063 patent are not anticipated and a POSA would not have found them obvious in view of the prior art.

39. This declaration is based on information known to me as of the date I signed this declaration, and I reserve the right to amend or supplement this declaration in view of any additional discovery, documents, information, declarations, and/or testimony that I receive after issuance of this declaration. I also reserve the right to rebut opinions and testimony offered by witnesses for Petitioner.

Ardehal

Hossein Ardehali, M.D., Ph.D

Dated: April 9, 2024

APPENDIX A

Exhibit	Description
2054	Nina C. Raju, et al., <i>Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial</i> , 33 J. TROMB. THROMBOLYSIS 88-94 (2011) (“Raju”)
2055	Mariama Akodad, et al., <i>COLIN trial: Value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response</i> , 110 ARCH. CARDIO. DIS. 395-402 (2017) (“Akodad”)
2056	David C. Tong & Jamie Layland, <i>Colchicine in Patients with Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial</i> , 142 CIRC. 1890-1900 (2020) (“Tong”)
2057	Abdul Q. Nawabi, et al., <i>Is Colchicine a New Game-Changer in Patients with Acute Coronary Syndrome?</i> , 14 CUREUS 1-5 (2022) (“Nawabi”)
2058	Jens Jakob Thune, et al., <i>Predictors and prognostic impact of recurrent myocardial infarction in patients with left ventricular dysfunction, heart failure, or both following a first myocardial infarction</i> , 13 EUR. J. HEART FAILURE 148-153 (2010) (“Thune”)
2059	Alexander E. Merkler, et al., <i>Duration of Heightened Ischemic Stroke Risk After Acute Myocardial Infarction</i> , 7 J. AM. HEART ASSOC. 1-6 (2018) (“Merkler”)
2060	Amit Kumar Shrivastava, et al., <i>C-reactive protein, inflammation and coronary heart disease</i> , 67 EGYPTIAN HEART J. 89-97 (2014) (“Shrivastava”)
2061	Sonia S. Anand & Salim Yusuf, <i>C-reactive protein is a bystander of cardiovascular disease</i> , 31 EUR. HEART J. 2092-2097 (2010) (“Yusuf”)
2062	BMJ, <i>Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data</i> , BMJ.COM 1-8 (2011) (“BMJ 2011”)
2063	C. Judkins, et al., <i>LoDoCo: LOw DOse COlchicine in Stable Coronary Artery Disease and the Effects on hs-CRP and Barchial Flow Mediated Dilation</i> , CSANZ Abstracts 2011, 20S HEART, LUNG, & CIRC. S36 (2011) (“Judkins”)
2064	Spyridon Deftereos, et al., <i>Colchicine Treatment for the Prevention of Bare-Metal Stent Restenosis in Diabetic Patients</i> , 61 J. AM. COLL. CARDIO. 1679-1685 (2013) (“Deftereos 2013”)

2065	S.M. Nidorf, et al., <i>Colchicine in Patients with Chronic Coronary Disease</i> , 383 N. ENG. J. MED. 1838-1847 (2020) (“Nidorf 2020”)
2066	Binita Shah, et al., <i>Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention: COLCHICINE-PCI Randomized Trial</i> , 13 CIRC. CARDIO. INTERV. 1-11 (2020) (“Shah”)
2067	As-filed Claims of U.S. Provisional Patent Application No. 62/935,865 (“the ’865 provisional application claims”)
2068	Declaration of Nadia Bouabdallaoui, M.D., Ph.D.
2069	Record History for NCT02551094 Colchicine Cardiovascular Outcomes Trial (COLCOT), https://clinicaltrials.gov/study/NCT02551094?intr=colchicine&rank=12&tab=history&a=10#oversight-card (last accessed Mar. 18, 2024)
2070	David C. Tong, et al., <i>Colchicine in Patients with Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial</i> , Circulation Online, https://doi.org/10.1161/CIRCULATIONAHA.120.050771 (2020) (“Tong Online Version”)
2071	Select Excerpts of the Deposition of Dr. Paul Ridker, M.D., M.P.H.
2073	Peter W.F. Wilson, et al., <i>An International Model to Predict Recurrent Cardiovascular Disease</i> , 125 AM. J. MED. 695-703 (2012) (“Wilson”)
2074	Sang Hun Lee, et al., <i>Predictors of recurrent acute myocardial infarction despite successful percutaneous coronary intervention</i> , 37 KOREAN J. INTERN. MED. 777-785 (2022) (“Lee”)