

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MODERNA THERAPEUTICS, INC.,  
Petitioner,

v.

ARBUTUS BIOPHARMA CORPORATION  
Patent Owner.

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Case IPR2019-00554  
Patent No. 8,058,069

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**PATENT OWNER'S NOTICE OF OBJECTION TO  
DEMONSTRATIVE EXHIBITS**

## **I. INTRODUCTION**

Pursuant to the Board's trial hearing order (Paper 32, 4), Arbutus Biopharma Corporation ("Patent Owner") submits the following objections to Moderna Therapeutics, Inc. ("Petitioner")'s demonstrative slides, and any reference to or reliance on the foregoing by Petitioner. The demonstrative slides are objected to under FRE106, 401, 403, and 705. Further non-limiting discussion is provided below and is meant to illustrate the objectionable content.

## **II. OBJECTIONS**

### **1. Slides 5 and 29**

Slides 5 and 29 are improper as irrelevant to the obviousness inquiry – the '910 publication is not a grounds reference. FRE106, 401, 403. Additionally, the documents are incomplete and more prejudicial than probative. The slide 5 depiction of an Examiner's Office Action rejection in view of the '910 publication reflects an incomplete record. FRE106. Slide 29 presents only a portion of Fig. 23. Petitioner fails to mention that the Office Action challenges were overcome during prosecution or that the '910 publication specifically identifies the 30mol% cationic lipid concentration as the best concentration and that all subsequent *in vivo* testing was limited to formulations having 30% or less cationic lipid. EX1015 ¶¶335, 337-354; *see also* Surreply, 15-16; EX2043, 12:18-20, 16:6-11, 17:24-19:24.

**2. Slides 6, 7, 53, 55**

These slides are more prejudicial than probative as they falsely represent the 1:57 as one single formulation. FRE403. EX1001, 3:45-56 (defining the “1:57 formulation” as those including “a cationic lipid comprising from about 52 mol % to about 62 mol % of the total lipid present in the particle”); *see also* POR, 33-37 (detailing the ’069 patent’s testing of multiple 1:57 formulations); EX2008.

**3. Slides 10 and 11**

It was Petitioner’s witness, Dr. Janoff – not Patent Owner – that testified for limiting the claimed invention to SNALPs. EX2001, 118:19-119:4, 119:9-17, 120:5-6, 121:14-25. In the ’739 IPR, the Board confused Dr. Janoff’s interpretation with the more tempered construction advanced by Patent Owner. Slides 10 and 11 are thus irrelevant and more prejudicial than probative. FRE401, 403

**4. Slide 14**

Slide 14 is an incomplete representation of the cited evidence, and is more prejudicial than probative. FRE401, 403. Dr. Janoff’s initially proffered definition in his ’739 IPR declaration (referenced in Slide 14) was rejected at institution in the ’739 IPR and abandoned by Petitioner. During cross-examination, Dr. Janoff repeatedly testified that the claimed particle of the ’739 IPR should be defined as a SNALP. EX2001, 118:19-119:4, 119:9-17, 120:5-6, 121:14-25; *see also* POR, 10.

## **5. Slide 21**

To the extent Petitioner relies on slide 21 as supporting a phospholipid range of 5 mol % to about 90 mol %, it is irrelevant to the challenge advanced in the petition materials. FRE401. Petitioner never presented such an invalidity theory in the petition. Rather, the petition alleged that one might arrive at phospholipid ranges of 0-19.5% and 0-19% after making a series of assumptions. Pet. 39, 54. Indeed, paragraph [0152] of the '189 publication as shown on slide 21 was never relied upon in the petition.

## **6. Slides 22, 24, 26**

These slides are irrelevant to the instituted grounds and are more prejudicial than probative. FRE401, FRE 403. The petition *never* argued that the 2:40 formulation was a starting point for optimization. Tellingly, slides 22, 24, and 26 do not offer any citations to the petition and instead only point to the reply, where such arguments were first introduced.

## **7. Slide 27**

The content of this slide is irrelevant to establishing *prima facie* obviousness – the '069 patent is not prior art against itself. FRE401. Thus, to the extent that any relevance is attributed to slide 27, it supports the criticality of the claimed range and the validity of the '069 patent.

## **8. Slide 28**

Slide 28 is irrelevant to the obvious inquiry in the manner submitted.

FRE401. WO2010088537 is not a reference for any of the instituted grounds.

Indeed, it is not prior art to the '069 patent at all. To the extent that the reference is relied upon, it demonstrates post-filing data reflecting criticality of the claimed range. *See also* POR, 37-43; Surreply, 3.

## **9. Slide 30**

Slide 30 is a yet another new, attorney-generated graphical representation of unsubstantiated argument of a fabricated “trend.” Petitioner’s own witness, Dr. Anchordoquy, conceded that there were “hundreds, if not thousands” publications existing before the time of invention – none of which are identified on slide 30. EX2043, 29:25-30:4, 30:25-31:7; Surreply, 15. Further, Petitioner plots for the time on slide 30 an additional datapoint for the year 2008, presumably based on the '069 patent itself. Slide 30 is thus an incomplete and prejudicial depiction of the state of the art and, as a further extension of new arguments asserted in reply, has no relevance to the invalidity theories presented in the petition. FRE106, 401, 403.

## **10. Slide 31**

The new assertion of a “trend” to “keep PEG low” was never presented in the petition or in any of Petitioner’s briefings. Slide 31 is thus irrelevant to the obviousness theories advanced in the petition materials. FRE401. Slide 31 mischaracterizes the very evidence it cites, rendering slide 31 more prejudicial than

probative. FRE403. Paragraph 98 as depicted in slide 31 cites to EX1024, which describes conjugated lipids at 10% concentrations – far higher than the ranges claimed in the '069 patent. EX1024, 22 (citing Judge, EX2042, 335).

#### **11. Slide 32**

Slide 32 is an incomplete document as it omits Dr. Thompson's extensive testimony and corroborating evidence that higher PEG concentrations (e.g., 5-10%) were typical. EX2031, ¶¶48-49; EX1025, 57:1-7, 62:3-6, 132:9-133:23, 175:3-13; FRE106.

#### **12. Slide 33**

Slide 33 is irrelevant to the instituted grounds, as Petitioner has *never* argued that there is a trend for including non-cationic lipids. FRE401. To the contrary, Petitioner cited submitted numerous references, each at most describing non-cationic lipids (e.g. phospholipids or cholesterol) as non-required, optional components. EX1005, ¶¶12, 120 (conjugated lipid optional), ¶¶97-115 (cholesterol optional), ¶92 (neutral lipid is optionally a phospholipid); EX1004, ¶150 (conjugated lipid optional), ¶152 (cholesterol optional), ¶79 (non-cationic lipid is optionally a phospholipid); *see also* Surreply, 14.

#### **13. Slide 34**

Slide 34 is irrelevant as an argument that was never advanced in the petition materials and lacks supporting evidence. FRE401. Petitioner has failed to present

any meaningful discussion or evidence regarding an “accepted cholesterol range” or any motivation for using the range identified on slide 34.

#### **14. Slide 35**

Presenting new arguments, slide 35 is irrelevant and more prejudicial than probative. FRE106, FRE403. The petition materials never argued that there is an “accepted phospholipid range.” Indeed, slide 35 reflects Petitioner’s ever evolving position on the purported phosphide range taught by the prior art. Surreply, 9-20. The petition argued making a series of assumptions to arrive at phospholipid ranges of 0-19.5 mol% and 0-19 mol%. Pet. 39, 54. The reply changed tack, conflated non-cationic lipids with phospholipids and advanced a range of 5-90 mol%. Reply, 5. Now, for the first time in this proceeding, slide 35 alleges a phospholipid range of 0-70 mol%.

#### **15. Slide 37**

The newly annotated figures from Lin and Ahmad are erroneous and incomplete documents, and prejudicial as they mischaracterize the results reported in those references. FRE106, FRE403. In contrast, both references describe transfection efficiency plateauing below 50 mol%. EX1006, 3315; EX1007, 740. Further, slide 37 omits the more probative evidence of Petitioner’s own witness, Dr. Janoff, testifying that the overall goal of Lin and Ahmad was to *reduce* the concentration of cationic lipid in formulations. EX2002, 31:7-39:9; *see also*

EX2006, 409:3-19 (“the bottom line message of Lin and Ahmad is how to reduce cationic lipid concentration in a formulation...”), 251:3-22, 252:11-19.

**16. Slide 38**

The quotations on slide 38 are incomplete writings and prejudicial. FRE106, FRE403. Far more probative are the relevant passages from the '069 patent expressly distinguishing lipoplexes from lipid particles of the invention. EX1001, 2:8-9 (“Cationic liposome complexes are large, poorly defined systems that are not suited for systemic applications”); *see also* EX2001, 122:1-24 (Dr. Janoff testifying that lipoplex particles were fundamentally different than those described in the current specification, and outside the scope of the patent); Surreply, 6.

**17. Slide 44**

Slide 44 advances yet another new argument seeking to locate a phospholipid range, including a new argument that a phospholipid of 0-65 mol% was taught by the '554 publication, making the slide irrelevant and more prejudicial than probative. FRE401, FRE403; *see* Objections to Slide 35.

**18. Slides 47, 48 & 49**

Slides 47, 48, and 49 are irrelevant, lacking in underlying basis, and are an incomplete writing. FRE106, FRE401, FRE403. These slides omit the '069 patent's disclosure that “the 1:57 SNALP formulation ... was the most potent at reducing ApoB expression *in vivo*” EX1001, 72:21-24. Further, with respect to the error bars, the conclusions drawn on the slides are prejudicial. Dr. Janoff testified



that his conclusions were based solely on a visual inspect. EX2033, 113:2-8, 122:12-123:23 (“Q. That's based on a visual inspection of the figure? A. That's the only thing available to me here.”). Yet, he made clear that he had problems with his vision. EX2001, 19-25 (“I have difficulty with my eyesight in general now”); *see also* EX2033, 7:19-8:3. More probative is his testimony that “I have no reason not to believe the data.” EX2033, 104:8-9.

Petitioner also mischaracterizes the reported data on these slides. For instance, Petitioner fails to disclose on slide 47 that groups 2, 4, 5, and 7 are also 2:40 formulations that were clearly outperformed by the 1:57 formulation of group 11. *See e.g.*, EX1001, Table 4, Fig. 2.

## **19. Slide 52**

Slide 52 depicts Dr. Thompson’s testimony regarding the data presented in the ’069 patent itself. Thus, it is irrelevant to the obvious attack advanced in that it is not reflective of a person of ordinary skill in the art’s understanding prior to the invention. FRE401. Further, the quoted passage is incomplete. FRE106. Dr. Thompson’s testimony made clear that cationic lipids were understood to be toxic when administered *in vivo*. EX2006, 244:6-9 (“It's because the cationic lipid is toxic ... It doesn't matter whether it's protonatable or not. It's still toxic.”). Even Petitioner’s own publications provide extensive discussion about the toxicity

concerns of ionizable cationic lipids, including DLinDMA. EX2037, 21:10-12; EX2031, ¶86; *see also* POR, 29-30.

## **20. Slide 56**

Slide 56 presents incomplete testimony and is more prejudicial than probative. FRE106, FRE403. Petitioner omits Dr. Thompson's testimony regarding a difference in the perspective of a person of ordinary skill before and after the invention's disclosure. EX2006, 405:5-12 ("Q. Would the perspective of a person of ordinary skill in the art prior to the '435 patent be the same as someone in the field having studied the experimental data presented in the '435 patent? ... [A.] The individual or the experimentalist after the '435 patent would benefit from that new knowledge."). Petitioner's arguments of unpredictability undermine any belated assertions of routine optimization.

## **21. Slide 57**

Slide 57 is an incomplete document and mischaracterizes Dr. Thompson's testimony with respect to Figure 2. FRE106, FRE403. Dr. Thompson explained that "Figure 2 is an experiment that is holding ratios of conjugate lipid and cationic lipid constant across a family of cationic lipids for a direct comparison, performance comparison, at keeping of though every -- all variables but cationic lipid type constant." EX2006, 412:11-15. Thus, the conclusion presented on slide

57 misrepresents witness testimony, is more prejudicial than probative, and lacks underlying basis.

## **22. Slides 61**

The conclusory assertions on slide 61 lack underlying basis such as any supporting calculations. FRE705. Slide 51 is also an incomplete representation of the record and conflicts with the testimony of Petitioner's own witness. *E.g.* EX2003, ¶33 (Dr. Janoff explaining that "[Patisiran] ... contains 50% cationic lipid, 38.5% cholesterol, 10% DSPC and 1.5% PEG"). Further, Petitioner omits Dr. Anchordoquy's testimony that, even under his calculations, the formulations would produce a population of particles infringing the claims of the '069 patent. EX2043, 72:24-73:3 ("Q. ... with a 50 percent cationic lipid formulation, plus or minus 5 percent variability would give you a range of 45 percent to 55 percent cationic lipid; right? A. Sure"). The conclusions of slide 61 are thus irrelevant to the invalidity arguments presented in the petition, and are more prejudicial than probative. Indeed, Petitioner was well-aware of Patent Owner's arguments with respect to commercial success and chose not to address any of those arguments or supporting evidence in the petition. POPR, 1-2, 10-11; POR, 31 n.4. Accordingly, such arguments are untimely and overly prejudicial.

Dated: April 20, 2020

Respectfully submitted,

/ Michael T. Rosato /

Michael T. Rosato, Lead Counsel

Reg. No. 52,182

## **CERTIFICATE OF SERVICE**

This is to certify that I caused to be served a true and correct copy of the foregoing Patent Owner's Notice of Objection to Demonstrative Exhibits was served on April 20, 2020, on the Petitioner at the correspondence address of the Petitioner as follows:

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Respectfully submitted,

Dated: April 20, 2020

/ Michael T. Rosato /  
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