

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

**Petitioner, GE Healthcare, Ltd.,
Petitioner**

v.

**Johns Hopkins University,
Patent Owner.**

**Case No. IPR2026-00069
U.S. Patent No. 11,938,201**

Second Declaration of Brian Zeglis, Ph.D.

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I. Introduction

1. I, Brian Zeglis, Ph.D., previously submitted a declaration in support of the Petition for Inter Partes Review of U.S. Patent No. 11,938,201 (“the ’201 Patent”), which was filed as Exhibit 1003 (my “First Declaration” or “Zeglis I”).

2. I was asked by counsel for Petitioner to review and respond to (a) the declaration of Dr. Henry VanBrocklin in support of Patent Owner’s Preliminary Response (EX2001, “VanBrocklin I”); (b) the declaration of Dr. VanBrocklin in support of Patent Owner’s Response (EX2047, “VanBrocklin II”); (c) the deposition testimony of Dr. VanBrocklin taken on July 29, 2026 (EX1069, “VanBrocklin Tr.”); and (d) [REDACTED]

[REDACTED].

3. I maintain all of my opinions set forth in my First Declaration remain my opinions. Nothing I reviewed in Dr. VanBrocklin’s declarations or Dr. VanBrocklin’s deposition testimony changed any of my opinions. This Declaration supplements my First Declaration, and responds to the specific opinions of Dr. VanBrocklin.

4. My qualifications, professional experience, education and compensation are set forth in ¶¶ 1–11 of my First Declaration and in my curriculum vitae attached as Appendix D to my First Declaration.

5. The materials I considered in forming my opinions in this declaration

include all of the materials that I described in my First Declaration (§ 17), along with additional materials listed in Appendix A of this Declaration.

A. Person of Ordinary Skill in the Art

6. Dr. VanBrocklin did not dispute the definition of a person of ordinary skill in the art (“skilled artisan” or “POSA”) that I set forth in my First Declaration.¹ I continue to apply that definition here.

B. Legal Principles

7. In forming my opinions, I used legal standards that were explained to me, including as set forth in §§ 18-21 of my First Declaration and below.

8. I have been informed that a claimed invention—including a claimed chemical compound—must have utility, meaning that the claimed compounds must have had a “specific” and “substantial” use that would have been credible to a person of ordinary skill in the art as of the priority date of the patent. I understand that the “specific” part of the utility requirement means that the use is particular to the claimed compound(s), rather than a general assertion that could be made of any compound or of a broad class of compounds. The “substantial” part of the utility requirement means that the use must be one that was a significant and presently available real-world use as of the priority date of the patent, rather than an object

¹ EX1003 (Zeglis I), §§ 13-15; EX2001 (VanBrocklin I), §§ 28-29; EX2047 (VanBrocklin II), § 4.

of further research or a merely hypothetical use.

9. I have been informed that the utility requirement is closely related to the enablement requirement, which requires that the specification teach a POSA how to use the claimed invention. I have been informed that the specification cannot enable the making and using of a claimed compound that lacks a specific, substantial, and credible utility. I also have been informed that if a person of ordinary skill must engage in undue experimentation to discover which of a large number of possible chemical compounds encompassed by a patent claim have a specific and substantial utility, that can render the claim not enabled.

10. I have also considered the legal standards that Dr. VanBrocklin applied in his Declaration in forming my opinions.²

II. Response to Dr. VanBrocklin's Opinions About the Claim Scope and Requirements³

11. In his declarations, Dr. VanBrocklin said that the claims are defined by their structure, not their function.⁴ He justified this by saying that B-L-A compounds can be used for “in vitro diagnostics” or “research applications,” and that all these techniques require is “direct incubation” of the compound with a

² EX2047 (VanBrocklin II), § V.

³ See, e.g., § III of my First Declaration (EX1003).

⁴ EX2047 (VanBrocklin II), ¶¶ 22, 29; EX2001 (VanBrocklin I), ¶ 35.

sample.⁵ At his deposition, he conceded the B-L-A compounds had to bind FAP but disputed they had to *selectively* bind FAP. Some examples of his statements include the following:

...the utility of these are then ultimately defined by the ability to bind these molecules to FAP. It's not prescribed in here what quantity of FAP binding it must have. It just says it's a FAP-targeting molecule.⁶

PREP is not — I don't see PREP in the — in that description, in the claims, I don't see PREP, I don't see that it has to have a particular selectivity, right, in this — in this application.⁷

I would go so far as to say that any molecule that has FAP-targeting capabilities for A would be — could — could be armed with a linker and put on a imaging group, an imaging moiety, and... it has a FAP group, a FAP-targeting group, it has a linker, it has a B, so therefore, it would fall under the claims as stated in the patent.⁸

12. I do not agree with Dr. VanBrocklin. Based on the legal standards that have been explained to me, I understand that what the claims define is determined by the words used in the claims read in view of the patent specification

⁵ EX2047 (VanBrocklin II), ¶ 28. See EX1001 (US-201), 37:40-43, 36:1-6 (discussing ex vivo and in vitro methods).

⁶ EX1069 (VanBrocklin Tr.), 227:21-228:4.

⁷ EX1069 (VanBrocklin Tr.), 224:8-12.

⁸ EX1069 (VanBrocklin Tr.), 225:16-226:1.

and the prosecution history of the patent.⁹ If a POSA read these claims in view of the specification and prosecution history, she would believe that the claimed B-L-A compounds, at a minimum, must (i) have high selectivity and affinity for FAP- α , and (ii) be suitable for use in PET, SPECT or optical imaging, or in radiotherapy, for the reasons discussed below.

A. Contrary to Dr. VanBrocklin's Opinions, the Claims Are Not Defined Solely in "Structural" Terms

13. I do not agree with Dr. VanBrocklin that the B-L-A compounds being claimed in claims 1–4 are "structurally defined, not functionally defined."¹⁰ In both the claims and the specification, the "A" moiety within the B-L-A compound has to be a targeting moiety for FAP- α and must have a particular structure defined by the "X" structure, while the "B" and "L" moieties in the B-L-A compound are defined only by what they must do, without a requirement that they possess any particular chemical structure.

14. A portion of claim 1 of the '201 Patent is reproduced below that omits the definitions of R groups and variables.

⁹ EX1003 (Zeglis I), ¶ 16.

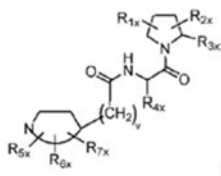
¹⁰ EX2047 (VanBrocklin II), ¶¶ 24-29.

1. A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

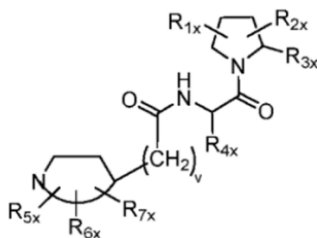
A is a targeting moiety for FAP- α , wherein A has the structure of:



B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

15. The FAP- α targeting moiety “A” is the only part of the claim that includes a chemical structure requirement. It requires the FAP- α targeting moiety to include the chemical structure, below. By contrast, the claim says that the low-molecular weight compounds have “*Formula I*” (“B-L-A”) (i.e., not “*Structure I*”). The B-L-A *formula* identifies only the relative positioning of the B, L and A moieties within the compounds (i.e., B is attached to L, L is attached to A, B is not attached directly to A).¹¹ It does not by itself impose any requirement that the compounds contain any particular chemical *structure*.



¹¹ EX1069 (VanBrocklin Tr.), 79:21-80:12; EX1003 (Zeglis I), ¶¶ 27-28; EX1009 (Jamous), 3381.

16. The claims say the “B” moiety can be “*any* optical or radiolabeled functional group *that is suitable for* optical imaging,¹² PET imaging, SPECT imaging, or radiotherapy.”¹³ This framing of what “B” moieties are is repeated throughout the specification.¹⁴ It is describing what the “B” and “L” moieties are by what they must *do* (*i.e.*, be suitable for one of three types of imaging or for radiotherapy, and form a chemical bond with each of A and the B moieties via the functional groups on either end of the linker molecule, respectively).

17. The specification does not say that “B” or “L” moieties must possess a common chemical structure. It just lists “representative” examples of two types of “B” moieties (“chelators” and “prosthetic groups”).¹⁵ Those terms also describe what those compounds must do, not particular chemical structures. For example, chelators must form three-dimensional complexes with radionuclides used in PET

¹² See EX1003 (Zeglis I), ¶ 163. For optical imaging, the chemical structure must at least have certain emission characteristics that are retained in an aqueous environment and again must form bonds that persist until detection occurs. EX1072 (Frangioni), 627 (Box 1) (listing parameters of optical imaging agents).

¹³ EX1001 (US-201), 64:46-65:63; Certificate of Correction.

¹⁴ EX1001 (US-201), 2:8-10, 8:19-24, 11:22-25, 12:43-45, 15:40-43.

¹⁵ EX1001 (US-201), 17:55-25:15; EX1003 (Zeglis I), ¶¶ 163.

or SPECT imaging devices, or in radiotherapy.¹⁶ “Prosthetic groups” are covalently bonded to an optical label or a radionuclide, and have functionalization that allows them to efficiently be attached to an existing chemical compound.¹⁷

B. The Specification Says that a B-L-A Compound Containing a FAP- α Targeting Moiety Must Be Potent and Selective

18. The specification explains that B-L-A compounds *are* both *potent* (*i.e.*, have high affinity) and *selective* for FAP- α . One passage (below) describes the exact “embodiment” being claimed by the patent:

...potent and selective low molecular weight ligands (LMW) ligands of FAP- α , *i.e.*, an *FAP- α selective inhibitor*, conjugated with *a targeting moiety* feasible for modification *with optical dyes and radiolabeling groups*, including metal chelators and metal complexes, *which enable in vivo optical imaging, nuclear imaging (optical, PET and SPECT)*, and *radiotherapy* targeting FAP- α ¹⁸

19. A POSA would recognize that the “targeting moiety” being described in the specification is a part of the overall imaging agent. The specification explains that it incorporates a “FAP- α inhibitor,” which is how the targeting moiety is able to target FAP- α . This tracks precisely how Jansen describes its

¹⁶ EX1003 (Zeglis I), ¶ 33.

¹⁷ EX1003 (Zeglis I), ¶ 34.

¹⁸ EX1001 (US-201), 7:46-54 (emphasis added).

compounds: a (2-cyano)pyrrolidine “warhead” linked to a 4-glycyl-quinolinyl group that together act as inhibitors of FAP- α .¹⁹ Dr. Pomper directed the patent examiner to this passage in his declaration to explain what the claims require.²⁰

20. Several other passages in the specification reinforce that the B-L-A compounds are potent and selective:

The presently disclosed subject matter provides, in part, *a FAP- α selective targeting moiety*....²¹

...imaging and radiotherapeutic agents *specifically targeting FAP- α* is of clinical importance.²²

The *highly potent and specific* binding moiety targeting FAP- α enables its use in nuclear imaging and radiotherapy.²³

The in vivo study showed clear tumor radiotracer uptake in mice bearing FAP- α -positive U87 tumors with minimum non-specific

¹⁹ EX1006 (Jansen), 3054, 3062. I understand that the Jansen paper is part of the disclosure of this patent because it was “incorporated by reference.” EX1001 (’201 Patent), 61:66-62:8, 63:4-9.

²⁰ EX1002 (US-201 FW), 359 (¶ 12).

²¹ EX1001 (US-201), 7:16-21.

²² EX1001 (US-201), 7:9-11 (emphasis added).

²³ EX1001 (US-201), 7:41-42 (emphasis added).

organ uptake, which allows *the specific imaging of FAP- α* expressing tumors.²⁴

C. The Prosecution History Shows JHU and Dr. Pomper Emphasized the High FAP Selectivity of the Claimed Compounds to Convince the Patent Office to Grant their Patents

1. Dr. Pomper's Declaration

21. Dr. VanBrocklin said in his declaration that “[n]owhere in the ... *prosecution history* are the claimed B-L-A compounds described solely by their ability to perform a particular function.” (emphasis added).²⁵ The prosecution history that I reviewed of the ’201 Patent, and its child ’233 Patent, clearly states the opposite.

22. During examination of the ’201 Patent, Dr. Pomper submitted a declaration in which he presented selectivity (*i.e.*, “specificity”) information for 11 compounds (the “Pomper Compounds”) that he had tested in his lab at JHU.²⁶ He

²⁴ EX1001 (US-201), 8:6-9 (emphasis added). The patent also describes the results of experiments to measure FAP specificity for the two exemplary B-L-A compounds in the specification. EX1001, 5:39-41, 59:36-67, 61:19-21.

²⁵ EX2047 (VanBrocklin II), ¶¶ 28-29.

²⁶ EX1002 (US-201 FW), 357-368. Scientists, including Dr. Pomper, use IC₅₀ values for PREP and for FAP to calculate selectivity, which is the concentration of the agent that provides 50% inhibition of the enzyme.

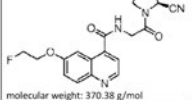
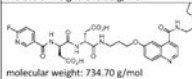
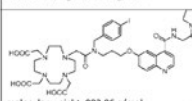
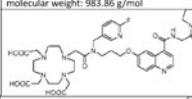
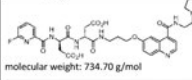
said the 11 compounds were covered by the patent claims several times (below).²⁷

The table below was annotated to provide labels for those 11 compounds (1 to 11).

15. Further, I have provided additional low molecular weight compounds of the current claims with molecular weights in the below table in paragraph 42.

42. In the process of developing FAP imaging agents, my lab tested the specificity of a number of FAP imaging agents, some of which have molecular structures covered by the pending claims of this application, and some of which have molecular structures not covered by the pending claims and which are used as reference compounds. The results are summarized in the Table below, together with the specificity data for MIP-1232 extracted from Melleta. MIP-1232 and the compounds not covered by the pending claims tested in my lab are labeled as "Reference Compound" in the table below.

43. Surprisingly, the specificity of the compounds covered by the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds. In particular, as shown in the Table below, MIP-1232, which is a compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for the representative compounds of the pending claims. I also observe that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. Such differences in specificity between the reference compounds and the compounds of the pending claims are surprising and unexpected. The higher specificity of the compounds of the pending claims certainly is beneficial for successfully developing a medical imaging agent.

Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio	
 molecular weight: 370.38 g/mol	1	779
 molecular weight: 734.70 g/mol	2	6
 molecular weight: 983.86 g/mol	3	7
 molecular weight: 1052	4	8
 molecular weight: 734.70 g/mol	5	9
 molecular weight: 761.39 g/mol		10
 molecular weight: 1282.43 g/mol		11

EX1003 (Zeglis I), ¶¶ 46-47. Accurately determining IC₅₀ values for FAP and PREP is critical to accurately measuring selectivity/specificity.

²⁷ EX1002 (US-201 FW), 360, 365-367.

23. In his declaration, Dr. Pomper identified a number of “important parameters” that the claimed B-L-A compounds had to have, including “affinity for FAP, selectivity (specificity for) FAP, ease of synthesis, and biodistribution and the like.”²⁸ These are properties I also identified in my First Declaration that a POSA would recognize as being important for FAP-targeting B-L-A compounds to be suitable for use in imaging and radiotherapy.²⁹ Dr. Pomper emphasized that it is important for the agents to have “both high affinity and high specificity,” and that the latter (high specificity) is what allows the imaging agent to bind selectively to the target protein but not other proteins. As Dr. Pomper explained:³⁰

31. There are numerous important parameters which need to be taken into consideration for successfully developing a FAP imaging agent. Those parameters include, for example, affinity for FAP, selectivity (specificity) for FAP, ease of synthesis, and biodistribution, and the like. It is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with a medical condition. The high specificity allows the imaging agent to bind selectively to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein. The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

24. Dr. Pomper repeated this point that specificity is an important parameter for imaging agents, and that high specificity of an imaging agent ensures

²⁸ EX1002 (US-201 FW), 363 (¶ 31).

²⁹ EX1003 (Zeglis I), ¶¶ 45.

³⁰ EX1002 (US-201 FW), 363 (¶ 31).

its accuracy in medical diagnoses.³¹

39. Specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a medical condition, therefore enabling the imaging agent to diagnose the medical condition more accurately.

25. He also used “specificity” interchangeably with selectivity (below).³²

For example, he used the same ratio of the ability of a compound to inhibit “prolyl peptidase (PREP) versus FAP” to define “specificity” that is used in Jansen and other papers to mean “selectivity” or the “selectivity index” (SI).³³

41. Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. In fact, Jansen I uses such a PREP/FAP ratio as a “selectivity index” for the compounds disclosed in Jansen I. See Jansen I, pages 42-51, Tables 3 and 4.

26. Dr. Pomper addressed the work reported in Meletta (EX1008) on the MIP-1232 compound, which was one of the FAP-targeting small molecule radiotracers investigated in US-633 (EX1004).³⁴ He said the low specificity

³¹ EX1002 (US-201 FW), 363 (¶ 31).

³² EX1002 (US-201 FW), 364-365 (¶ 41).

³³ EX1006 (Jansen), 3054 (“SI stands for selectivity Index (calculated as $[IC_{50}(PREP)/IC_{50}(FAP)]$).”).

³⁴ EX1002 (US-201 FW), 364. See EX1003 (Zeglis I), ¶ 95; EX1008 (Meletta), 2089-2090 (“As $[^{125}I]$ MIP-1232 *did not selectively accumulate* in the atherosclerotic tissue and as its *low FAP/PREP affinity* ratio is already

(selectivity) of MIP-1232 is what made it not suitable for the medical imaging application being investigated. He also said that Meletta demonstrated the “high unpredictability in the art” of designing imaging agents (below).

35. Accordingly, because of the low specificity MIP-1232 displayed in the testing, Meletta concluded that MIP-1232 was not suitable for the medical imaging application for the particular medical condition being tested in Meletta. *Id.* at 2095.

37. The failure of investigations with MIP-1232, which is a compound disclosed in the cited prior art, is especially telling as it demonstrates the high unpredictability of the art and lack of reasonable expectation of success by combining the prior art to arrive at the compounds of the pending claims for medical imaging applications.

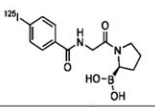
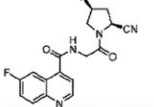
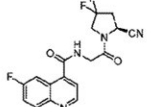
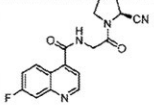
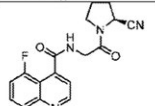
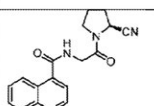
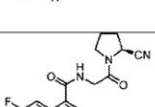
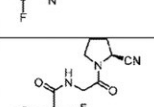
27. Dr. Pomper also referred to “testing results from my lab” and explained that his “lab tested the specificity of a number of FAP imaging agents,” including some that were not covered by the claims, which he referred to as the “reference compounds” in his declaration. The table below was annotated to provide labels for those 8 compounds (A to H).³⁵

known we did not further investigate its selectivity profile. For future studies ***more selective inhibitors are needed*** to reduce non-specific tissue accumulation.”).

³⁵ EX1002 (US-201 FW), 365-366.

38. Further, I am of the opinion that there are unexpectedly superior FAP specificities associated with the compounds of the pending claims based on the testing results from my lab.

42. In the process of developing FAP imaging agents, my lab tested the specificity of a number of FAP imaging agents, some of which have molecular structures covered by the pending claims of this application, and some of which have molecular structures not covered by the pending claims and which are used as reference compounds. The results are summarized in the Table below, together with the specificity data for MIP-1232 extracted from Melleta. MIP-1232 and the compounds not covered by the pending claims tested in my lab are labeled as "Reference Compound" in the table below.

Reference Compound Molecular Structure	PREP/FAP Ratio	Reference Compound Molecular Structure	PREP/FAP Ratio
	32 *		15.7
	152		241
	20		17
	403		3

28. Dr. Pomper directly addressed the selectivity/specificity values of the 11 Pomper Compounds (i.e., the values determined by dividing the IC₅₀ of each compound for PREP by the IC₅₀ of each compound for FAP). He said the selectivity values that his lab determined for compounds "covered by the pending claims" for FAP is generally *several orders of magnitude higher* than that of other small molecule FAP inhibitors used as reference compounds.³⁶ He points to the

³⁶ EX1002 (US-201 FW), 365-67 (¶¶ 42-43).

range of values, saying “the lowest value: for selectivity of the “representative compounds of the pending claims” was 779 and the highest value was 1,418,440.³⁷ Dr. Pomper then emphasizes that the higher specificity of the claimed compounds relative to prior art reference compounds was surprising and is what made them useful medical imaging agents (below).

43. Surprisingly, the specificity of the compounds covered by the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds. In particular, as shown in the Table below, MIP-1232, which is a compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for the representative compounds of the pending claims. I also observe that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. Such differences in specificity between the reference compounds and the compounds of the pending claims are surprising and unexpected. The higher specificity of the compounds of the pending claims certainly is beneficial for successfully developing a medical imaging agent.

2. JHU's Statements to the Patent Office

29. I understand that JHU was the patent applicant at the time these documents were filed with the Patent Office. Like Dr. Pomper, JHU told the Patent Office that the 11 Pomper Compounds were within the scope of the claims several times.³⁸ For example, it reproduced Dr. Pomper's table and described the 11 Pomper Compounds as “representative compounds of the pending claims are

³⁷ The lowest selectivity value of the 11 Pomper Compounds is actually 407 (Pomper Compound 8). EX1002 (US-201 FW), 366.

³⁸ EX1002 (US-201 FW), 408-409. These statements were made in a paper filed by JHU during examination of the parent application of the '201 Patent. See EX1002 (US-201 FW), 399-412.

provided in the table below.” As shown below, JHU repeated this point several times (e.g., “results associated with the claimed compounds,” “specificity of compounds falling under the scope of the pending claims,” (emphasis in original), selectivity of “lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims,” “compounds of the pending claims are surprising and unexpected.”).

iii. There are unexpected results associated with the claimed compounds to rebut any showing of prima facie obviousness

The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Pomper Affidavit, Paras. 38-42. As provided in the Pomper Affidavit, specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

• • •

Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 41. In fact, Jansen I uses such a PREP/FAP ratio as a “selectivity index” for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4. Representative compounds of the pending claims are provided in the table below with PREP/FAP values for comparison. Surprisingly, the specificity of compounds falling under the scope of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. Pomper Affidavit, Para. 42. In particular, as shown in the Table below, MIP-1232, which is a representative compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims. *Id.*, Para. 42. It is also notable that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. *Id.* Such differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected.

EX1002 (“201 Patent”), 408-409

30. JHU also said that the data in Dr. Pomper’s declaration showed that the compounds within the scope of the claims had surprisingly high

specificity/selectivity for FAP over PREP.³⁹ Like Dr. Pomper, JHU used selectivity and specificity interchangeably, and said “a well-accepted indicator” of selectivity is the ratio of a compound’s inhibition of PREP over its inhibition of FAP (below).

iii. There are unexpected results associated with the claimed compounds to rebut any showing of prima facie obviousness

The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. See Pomper Affidavit, Paras. 38-42. As provided in the Pomper Affidavit, specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [¹²⁵I]MIP-1232 for FAP (above section ii), the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents is shown in the current application US 2020/0330624 for the selectivity for FAP over dipeptidyl peptidase 4 (DPP4), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C). Pomper Affidavit, Para. 40.

Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 41. In fact, Jansen I uses such a PREP/FAP ratio as a “selectivity index” for the compounds disclosed in Jansen I. See Jansen I, pages 42-51, Tables 3 and 4. Representative compounds of the pending claims are provided in the table below with PREP/FAP values for comparison. Surprisingly, the specificity of compounds falling under the scope of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. Pomper Affidavit, Para. 42. In particular, as shown in the Table below, MIP-1232, which is a representative compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims. *Id.*, Para. 42. It is also notable that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. *Id.* Such differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected.

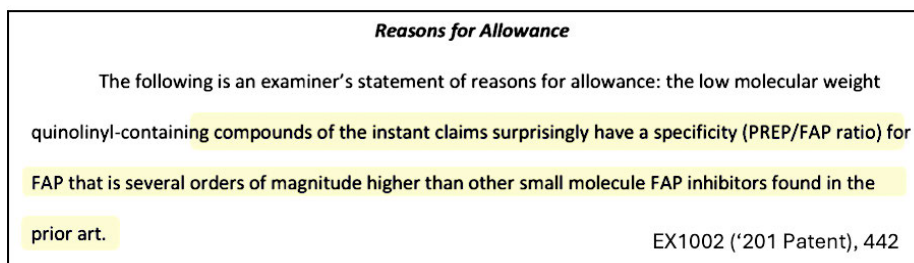
EX1002 ('201 Patent), 408-409

3. The Patent Office Relies on the Pomper Declarations and JHU’s Statements about the Claimed Compounds Having High Specificity for FAP Over PREP

31. I understand that JHU made these statements in order to convince the patent examiner to allow the patent claims in the application, which had been

³⁹ EX1002 (US-201 FW), 408-411.

rejected as being obvious.⁴⁰ After JHU made its statements, the examiner allowed their patent claims. The examiner credited the statements made by JHU and Dr. Pomper in her reasons for allowance. She said the tested compounds in the Pomper Declaration were covered by the claims being allowed, and that she believed those compounds had selectivity/specificity (“PREP/FAP ratio”) “that is several orders of magnitude higher than other small molecule FAP inhibitors found in the prior art.”⁴¹ The examiner made the identical statement in her reasons for allowance the ’201 Patent.



D. Dr. VanBrocklin Conceded the Claimed B-L-A Compounds Must Exhibit the Properties of their A, B and L Constituents

32. In his declaration, Dr. VanBrocklin said that imposing the requirements listed for the B, L and A moieties on the assembled B-L-A compound is “inconsistent with the plain language of the claims...” and that the claims do not require the assembled B-L-A compounds to retain the functional requirements of

⁴⁰ EX1002 (US-201 FW), 313-316.

⁴¹ EX1002 (US-201 FW), 408-409, 442.

each moiety.⁴² I disagree.

33. A POSA would recognize that the properties of the B, L and A moieties must persist in the assembled compound. The plain language of the claim actually requires this. It describes what the B, L and A moieties *are*, and is describing that *as they exist within the B-L-A compound* (i.e., “A *is* a targeting moiety for FAP- α when it is in the B-L-A compound, B *is* any optical or radiolabeled functional group suitable for” optical, PET or SPECT imaging, or radiotherapy.⁴³ When it is in the B-L-A compound, “L *is* a linker having bi-functionalization adapted to form a chemical bond with B and A” when it is in the B-L-A compound). The claims do not say those moieties *were only* those things before they became part of the B-L-A compound.

34. It would not make sense to read the formula-based definition of the B-L-A compounds being that the A, B and L moieties only exhibit their identified attributes when they are *not* within the B-L-A compound. Dr. VanBrocklin recognized this at his deposition. When he was asked this directly, he said:

...in order to see the targeting moiety A and where it's going, then this B has to, as indicated, have to be radiolabeled or have optical so you

⁴² EX2047 (VanBrocklin II), ¶¶ 24-25.

⁴³ EX1001 (US-201), 65:54-60.

can see where A is going, and again, this is part of the utility of this — part of the utility of this whole B-L-A compound.⁴⁴

35. That is the right conclusion. A POSA would have understood that the “A” and “B” moieties in the B-L-A compound have distinct purposes that must be preserved in the intact B-L-A compound. The purpose of the “A” moiety in the B-L-A compound is to cause the B-L-A compounds to potently and selectively bind to (*i.e.*, “target”) FAP- α expressing cells.⁴⁵ The purpose of the “B” moiety is to enable the B-L-A compounds that have selectively bound to tissue containing FAP-expressing cells to either deliver a signal detected by a device that can perform imaging, or to cause therapeutic effects in the tissue surrounding the target cells.⁴⁶ This is consistent with what the inventor, Dr. Pomper, said in the Declarations he submitted during examination to support the patentability of the

⁴⁴ EX1069 (VanBrocklin Tr.), 115:16-116:13 (emphasis added).

⁴⁵ EX1001, 7:41-42 (“The highly potent and specific binding moiety targeting FAP-a enables its use in nuclear imaging and radiotherapy.”). See also § II.C below.

⁴⁶ EX1069 (VanBrocklin Tr.), 93:5-21, 95:4-97:16; EX1001 (US-201), 7:16-21 (“The presently disclosed subject matter provides, in part, a FAP- α selective targeting moiety that can be modified with an optical dye, a radiometal chelation complex, and other radiolabeled prosthetic groups, thus providing a platform for the imaging and radiotherapy targeting FAP- α .”).

'233 Patent and its parent the '201 Patent.⁴⁷ It is also consistent with what Dr.

VanBrocklin explained at his deposition:

It is that molecule that *in its total form B-L-A* takes the signal, carries the signal from the optical, the PET or the SPECT or the gamma or the positron emission... *carries that along with it to interact with the FAP protein*.⁴⁸

36. A POSA also would have recognized that to be “suitable for” optical imaging, PET imaging or SPECT imaging, or for radiotherapy, the imaging agents must maintain their B-L-A form long enough to enable them to selectively bind to tissue and be detected by the PET/SPECT/optical device or to cause therapeutic effects.⁴⁹ This means the B-L-A compounds must be sufficiently stable to prevent it from degrading within the environment where it is being used, whether that is in the *in vivo* environment of the subject or within a tissue sample.

⁴⁷ EX1002 (US-201 FW), 363 (¶ 30 (“... the compounds of the pending claims for medical imaging applications”), ¶ 31 (“There are numerous important parameters which need to be taken into consideration for successfully developing a FAP imaging agent.”)).

⁴⁸ EX1069 (VanBrocklin Tr.), 96:22-97:16. See also, EX1069 (VanBrocklin Tr.), 95:12-96:5 (explaining that if the B moiety were cleaved from the L-A assembly, then it would “no longer be suitable for -- for its intended purpose.”).

⁴⁹ EX1069 (VanBrocklin Tr.), 95:12-96:5; EX1003 (Zeglis I), ¶ 49.

37. Dr. VanBrocklin recognized this requirement during his deposition. When he was asked if a “B” imaging moiety was cleaved from the B-L-A compound shortly after injection, would that B-L-A compound be suitable for the claimed purpose of the B moiety, he explained:

It would not be suitable for — for its intended purpose. Perhaps the signal would still be given off by the — by the molecule. The molecule, you would still see it in a optical — through imaging, optical gamma detectors, gamma counters, right, you would still see the radioactive isotope, but it would not — as you indicated, *it would not be intact.*⁵⁰

E. The Claimed FAP-Targeting Imaging and Radiotherapeutic Agents Must Distinguish FAP from Other Similar Proteins

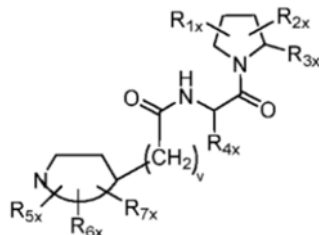
38. The claims provide a chemical structure for the “A” moiety defined by the structure below, with definitions for the various R substituents.⁵¹ But the “A” moiety is not defined *only* by its structure—the claim also states that “*A is a targeting moiety for FAP-α.*”⁵² A POSA would have understood that even if a chemical structure fell within the scope of the defined structure, it would not satisfy the claim requirement if it did not also (i) bind to FAP with high affinity

⁵⁰ EX1069 (VanBrocklin Tr.), 95:20-96:5 (emphasis added).

⁵¹ EX1001 (US-201), 64:10-46.

⁵² EX1001 (US-201), 64:10 (emphasis added).

and (ii) exhibit high selectivity in binding relative to PREP.



39. A POSA would understand that to “target” FAP the claimed FAP-inhibitor-based B-L-A compounds must *distinguish* FAP from other compounds, particularly the PREP enzyme, which requires them to exhibit high selectivity for FAP over PREP, as emphasized by the Jansen publication incorporated by reference in the patent.⁵³ If the B-L-A compound cannot do that, an imaging agent based on it will generate false positives.⁵⁴ For example, if the B-L-A compound that cannot distinguish FAP from PREP encounters a cell that only expresses PREP but not FAP, or a sample that contains only PREP, the imaging device will

⁵³ EX1001 (US-201), 62:31-37; EX1006 (Jansen), 3053.

⁵⁴ EX1003 (Zeglis-I), ¶¶ 45, 60, 117; EX1002 (US-201 FW), 363 (“The high specificity allows the imaging agent to bind selectively to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein.”).

register a “positive” signal even though there is no FAP present in the test environment. No POSA would believe that a B-L-A compound would “target FAP” or be “suitable for” “imaging or “radiotherapy” as required by the claims if it routinely generates false positive signals in tested samples or in human or animal subjects. A POSA would especially not believe a non-selective FAP compound would be suitable for radiotherapy because a non-selective radiotherapeutic would irradiate non-target tissue, causing harm to patients.

F. Dr. Pomper Explained What is Required for Compounds to Be Viable Imaging and Therapeutic Agents

40. Dr. Pomper explained in his declaration why FAP selectivity was so important for imaging agents. As he stated:

A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein.⁵⁵

41. Dr. VanBrocklin does not account for the statements made by Dr. Pomper in his declarations that were submitted during examination of the patents. In those declarations, Dr. Pomper differentiated the claimed B-L-A compounds from FAP-binding compounds described in the literature because the claimed B-L-A compounds (i) had much higher selectivity for FAP- α , and (ii) were suitable for

⁵⁵ EX1002 (US-201 FW), 363 (¶ 31).

use in “medical imaging applications.”⁵⁶

42. First, Dr. Pomper and JHU said that the claimed “B-L-A” compounds had *a level of specificity* for FAP that was not present in earlier FAP-binding compounds. As Dr. Pomper stated, “the specificity of the compounds covered by the pending claims is generally *several orders of magnitude higher* than that of other small molecule FAP inhibitors used as reference compounds.”⁵⁷ One of those reference compounds he referenced several times was MIP-1232 (reported in Meletta, EX1008), which had a FAP selectivity of ~ 32 (*i.e.*, its PREP IC₅₀ divided by its FAP IC₅₀). Taken literally, that would imply that the claimed B-L-A compounds need to have a FAP to PREP selectivity of around **32,000** (*i.e.*, several (3+) orders of magnitude). Dr. Pomper did not just say the B-L-A compounds must bind FAP, he said they must bind with *high* selectivity to FAP.⁵⁸

43. Second, Dr. Pomper explained the importance of high selectivity to a compound’s suitability for imaging:

Specificity is an important parameter for developing a medical imaging agent because *a high specificity* of the compound allows the imaging agent to *selectively bind to the target protein* associated with

⁵⁶ EX1002 (US-201 FW), 363-367 (¶¶ 30-43).

⁵⁷ EX1002 (US-201 FW), 367 (¶ 43) (emphasis added), 409.

⁵⁸ EX1002 (US-201 FW), 367 (¶ 43).

a medical condition, *therefore enabling the imaging agent to diagnose the medical condition more accurately.*⁵⁹

44. Dr. Pomper's explanation aligns with the claim requirement that the B-L-A compounds be "suitable for" use in PET, SPECT and optical imaging (which are medical imaging applications). Dr. VanBrocklin made statements at his deposition that suggest he appreciates that to be suitable for use as an imaging or radiotherapy agent, a B-L-A compound might need to do more than simply bind to FAP.⁶⁰ Dr. Pomper's statements identify what else is needed – high selectivity for FAP (at a minimum).

45. As Dr. Pomper made clear in his declarations, POSAs knew before 2017 that to be suitable for imaging or radiotherapy, radiotracers must have characteristics that enable them to bind to tissue containing the targeted cells (i.e., those that express FAP- α) and to not bind to tissue where no such cells are

⁵⁹ EX1002 (US-201 FW), 364 (¶ 39) (emphasis added).

⁶⁰ EX1069 (VanBrocklin Tr.), 216:9-22 ("...the utility of these first and foremost is that they bind to FAP... Then if you want to use them further... *they can be used as imaging agents, but you would have to look at their characteristics further...*") (emphasis added).

present.⁶¹ That is a central requirement for a radiotracer to be suitable for use in imaging and radiotherapy. For example, radiotherapy requires the administered radiotherapeutic agent to accumulate in tissue containing the targeted cells, and not other cells, which is critical to ensure that radiation is delivered to the correct location in the body and not other locations.⁶² Imaging similarly requires the B-L-A compounds to accumulate in locations where cells that express FAP are present, otherwise the imaging will generate false positives (*i.e.*, generating a positive signal even though there are no cells at the identified location that express FAP).⁶³

46. The claims also require the B-L-A compound be “suitable for” particular types of imaging devices (*i.e.*, PET, SPECT and optical imaging devices) used in medical imaging applications.⁶⁴ POSAs understood that PET, SPECT and optical imaging devices were used to measure more than just the presence of the

⁶¹ EX1001 (US-201), 35:33-45 (“The imaging methods of the invention are suitable for imaging any physiological process or feature in which FAP- α is involved, for example, identifying areas of tissues or targets which exhibit or express high concentrations of FAP- α .”), 4:27-51, 7:41-43, 7:46-56, 35:17-36:6; EX1003 (Zeglis I), ¶¶ 45-49, 60, 118.

⁶² EX1003 (Zeglis I), ¶¶ 23, 29.

⁶³ EX1003 (Zeglis I), ¶¶ 45, 60, 117.

⁶⁴ EX1002 (US-201 FW), 363 (¶¶ 30-31).

target of an imaging agent in a sample (e.g., cells expressing FAP- α). They are used to measure *the spatial distribution* of the target within a sample, as the specification explains:

Images can be generated by virtue of *differences in the spatial distribution of the imaging agents* which accumulate at a site when contacted with FAP- α . *The spatial distribution may be measured* using any means suitable for the particular label, for example, a gamma camera, a PET apparatus, a SPECT apparatus, and the like.⁶⁵

47. Dr. VanBrocklin acknowledged that measuring spatial distribution is precisely the function these imaging devices serve. As he explained at his deposition:

Images are created by the distribution of imaging agents. In — you know, as we've been talking here, a number of different circumstances, right, and by virtue — using the language there, that you're looking at the — as we even described earlier, *the differences in two different regions within whatever material it is that you are looking at* with the different imaging agent, and... alpha, would be looking for that FAP alpha interaction and *differences in different*

⁶⁵ EX1001 (US-201), 36:41-49 (emphasis added); 1:39-49 (“These characteristics make FAP- α a potential imaging and radiotherapeutic target for cancer and inflammation diseases.”).

tissues, in different cells, in different — you know, whatever the situation that you're using it in as an imaging agent.⁶⁶

48. The Meletta paper (EX1008) provides a useful illustration of a FAP-targeting imaging agent being used in an in vitro diagnostic setting. Tissue samples were isolated, prepared and then incubated with the [125I]MIP-1232 agent.⁶⁷ That particular image agent was found to exhibit insufficient selectivity for FAP in the in vitro assay—the agent bound non-specifically to targets other than FAP-expressing cells, such as hydrolases or other proteins in the tissue environment. These sources of non-specific binding are relevant to any setting in which naturally occurring materials will be evaluated.⁶⁸

⁶⁶ EX1069 (VanBrocklin Tr.), 99:6-19. Also EX1069 (VanBrocklin Tr.), 48:22-49:6 (“the scanners themselves collect decays from all angles out of the source, and so the T in each of these, PET and SPECT, refers to tomograph, right? So you end up with a three-dimensional image at the end of the day if you're — as you're collecting that data.”).

⁶⁷ EX1008 (Meletta), 2094-2905, also 2089-2090.

⁶⁸ EX1008 (Meletta), 2089-2090. See also EX2047 (VanBrocklin II), ¶ 12.

Based on our data we cannot conclude on the selectivity of [¹²⁵I]MIP-1232 for FAP. In the absence of a known selective inhibitor, we investigated specificity by blocking with the unlabeled compound itself. The relatively high amount of remaining radiotracer after blocking must, therefore, accumulate with low affinity. Lipophilicity is most probably not involved as clogP of MIP-1232 is about 0.5. The non-specific accumulation may result from interactions with highly abundant hydrolases or other proteins with affinities in the high micromolar range, considering that our blocker concentration was 100 μM. Specificity analysis of MIP-1232 was performed exclusively with FAP and PREP [29]. A conclusive evaluation of the binding affinity to dipeptidyl peptidases such as DPP-2, DPP-4, DPP-8 and DPP-9 would be required, irrespective of the fact that DPPs display in general low affinities for N blocked peptides [43,44]. As [¹²⁵I]MIP-1232 did not selectively accumulate in the atherosclerotic tissue and as its low FAP/PREP affinity ratio is already known we did not further investigate its selectivity profile. For future studies more selective inhibitors are needed to reduce non-specific tissue accumulation. To overcome limitations in specificity, novel lead structures and the use of antibodies and fusion proteins was proposed to minimize off-target effects [24,34,44].

G. “L” Moieties Are Not Defined by a Chemical Structure

49. The claims say that the “L” moiety “is a linker” “having bi-functionalization adapted to form a chemical bond with B and A.”⁶⁹ This is also a “functional” definition—it is indicating what the linker must do, not what chemical structure the L is. As a practical matter, L must be functionalized (i.e., have two reactive functional groups) that enable bond formation with atoms in each of the B and A moieties.⁷⁰ One bond will be between B and L, and the other bond will be between L and A.⁷¹

⁶⁹ EX1001 (US-201), 65:54-60 (“B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and **L is a linker having bi-functionalization adapted to form a chemical bond with B and A**”) (emphasis added).

⁷⁰ EX1003 (Zeglis I), ¶ 163; EX1001 (US-201), 65:54-60.

⁷¹ EX1069 (VanBrocklin Tr.), 79:21-80:12.

50. I note that the chemical structure of the functional group(s) that a linker had before was incorporated into any particular B-L-A compound cannot be determined by simply inspecting the assembled B-L-A compound. That is because the two functional groups on the linker before it is integrated into the B-L-A compound are typically altered by the reactions that form the two bonds. One can often infer the type of functional group was present in the linker before it is incorporated into the B-L-A compound, but there are many different functional groups that produce the same resulting bond.

H. Dr. VanBrocklin's Construction of "Low Molecular Weight" Is Incorrect and Misstates My Opinion

51. Dr. VanBrocklin said that I "did not offer a construction" for the "low molecular weight" term.⁷² That is incorrect. I explained in my First Declaration that there is no basis for reading the term "low molecular weight" as imposing a strict numerical boundary on the claimed B-L-A compounds as Dr. Pomper stated in his declaration before the Patent Office.⁷³ I also provided the following explanation what a POSA would have believed "low molecular compound" meant, based on the specification and the examination record:

⁷² EX2047 (VanBrocklin II), ¶ 30.

⁷³ EX1003 (Zeglis I), ¶¶ 170-174.

Low molecular weight radiopharmaceuticals, by contrast, are radiopharmaceuticals that use a small molecule or peptide as the targeting moiety and have molecular weights at least an order of magnitude (and often two orders of magnitude) below the molecular weight of an antibody (e.g., from a few hundred to a few thousand Daltons). Compounds in this size range have comparable pharmacokinetics (e.g., rapid uptake, rapid clearance).⁷⁴

52. Dr. VanBrocklin proposes to use Dr. Pomper's proposed definition of "low molecular weight" (i.e., a compound having a molecular weight between 50-1500 Da).⁷⁵ As I explained in my First Declaration, that is an arbitrary boundary that is not supported by the specification.⁷⁶ The papers that Dr. Pomper references also involve studies of metabolomics and metabolites, which a POSA would recognize as being a different class of molecules from the claimed B-L-A compounds.⁷⁷

I. The Claimed Genus of B-L-A Compounds is Enormous and Structurally and Chemically Heterogeneous

53. The claims of the '233 Patent, a child patent of the '201 Patent,

⁷⁴ EX1003 (Zeglis I), ¶¶ 171-174; EX1052 (Zhou), 59-60.

⁷⁵ EX2001 (VanBrocklin I), ¶¶ 36-37; EX2047 (VanBrocklin II), ¶ 30; EX1002 (US-201 FW), 360.

⁷⁶ EX1003 (Zeglis I), ¶ 174.

⁷⁷ EX1003 (Zeglis I), ¶¶ 163, 131; EX1002 (US-201 FW), 360 (¶ 17).

capture between at least $\sim 10^{27}$ to $\sim 10^{39}$ B-L-A compounds based on the parameters of the claims and possible B, L and A moieties listed as examples in the specification. The actual numbers are orders of magnitude larger because my calculations do not account for stereoisomers, differences in formulation, and possible B and L options not listed in the specification. Dr. VanBrocklin did not identify any errors in my calculations in his declaration or at his deposition.⁷⁸

54. I never portrayed the compounds captured by the A formula in the claims to be “narrow” in any aspect. Dr. VanBrocklin agreed at his deposition that I never characterized the number of A moieties as being “narrow.”⁷⁹

55. Dr. VanBrocklin testified (and I agree) that “the B and L moieties are not structurally constrained,”⁸⁰ which means there are enormous numbers of B-L-A compounds that are captured by the claims. This also contradicts his opinion that the claims define the “B” and “L” moieties in structural terms—how can those terms operate to define the B and L moieties in “structural” terms if they do not “structurally constrain” which compounds are B and L moieties?

56. Dr. VanBrocklin’s testimony reinforces that the claims capture a

⁷⁸ EX1069 (VanBrocklin Tr.), 70:4-71:15, 246:8-14.

⁷⁹ EX1069 (VanBrocklin Tr.), 247:20-248:14.

⁸⁰ EX1069 (VanBrocklin Tr.), 89:22-90:13 (“either how long or how short [the linker is] is not prescribed in the – in the claim.”).

structurally, chemically, and functionally heterogeneous set of B-L-A compounds. The choice of linker and its point of attachment can influence a variety of attributes of a B-L-A molecule, including affinity or selectivity for the target, solubility, stability, hydrophobicity / lipophilicity and pharmacokinetic profile.⁸¹ The structural heterogeneity associated with the linker option alone massively increases the unpredictability in the attributes of the claimed B-L-A compounds—without considering stereoisomer possibilities, I determined there are $\sim 5.89 \times 10^{23}$ distinct linker structures possible alone. The group of B-L-A compounds being captured by the claims is not only huge, it is structurally, chemically and functionally heterogeneous.

III. [REDACTED]

57. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁸¹ EX1018 (Fichna), 5; EX1013 (Price), 282; EX1017 (Sarko), 2668.

⁸² The full set of the documents produced by JHU are labeled JHU_000001-JHU_000271. Documents from that range that are cited in this declaration are included in the compilation that is attached as EX1071 (JHU Production Records).

[REDACTED]

[REDACTED]

[REDACTED]

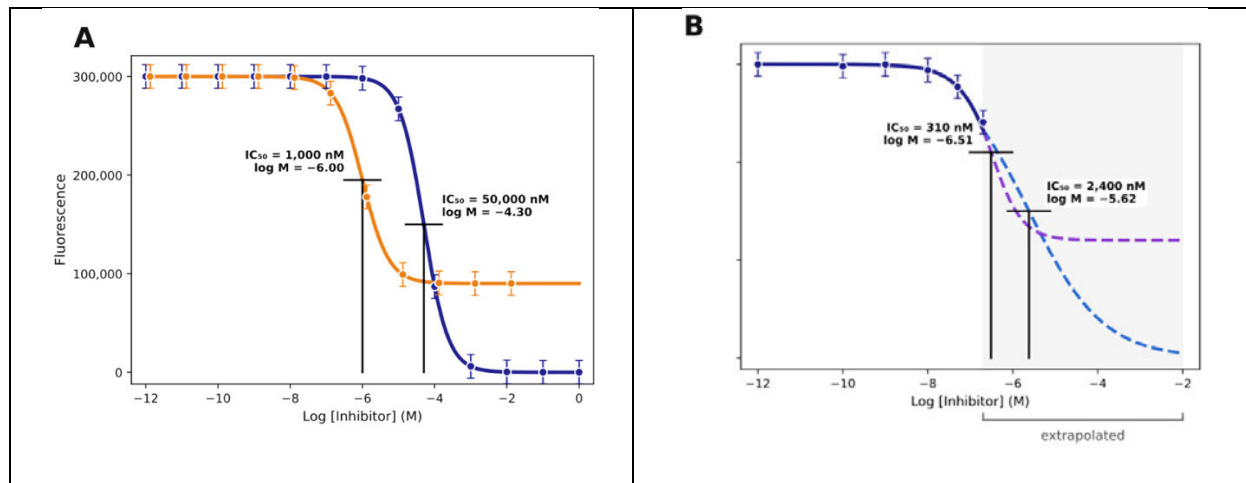
[REDACTED]

58. The reliable determination of an IC_{50} value from a dose–response assay depends on the shape of the measured curve. A well-defined inhibition curve is sigmoidal and bounded by two plateaus: an upper plateau (in which low inhibitor concentrations produce little or no inhibition) and a lower plateau (in which further increases in concentration produce no additional effect because inhibition is essentially complete). The IC_{50} value is the concentration that corresponds to the midpoint between those two plateaus, and it can be determined reliably only when the assay includes measured data points both before and after the transition that connects them.

59. Panel A (below) shows hypothetical inhibition curves for two inhibitors. Both curves are supported by data points encompassing concentrations at which no inhibition is measurable (upper plateau) as well as concentrations over which no additional inhibition is observed (lower plateau). The two curves show differences in the steepness of the transition and in the level of the lower plateau,

⁸³ See EX1002 (US-201 FW), 365-367 (¶¶ 42-43), see also 357-368.

but both remain curves from which an IC_{50} value can properly be derived because both have plateaus and an intervening transition defined by data points. In this example, the orange curve yields an IC_{50} value of 1,000 nM (log M -6.00) and the purple curve yields an IC_{50} value of 50,000 nM (log M -4.30).



60. Panel B (above) shows a hypothetical inhibition curve for one inhibitor that does not include measured data beyond the 6th measurement. The two dashed lines represent possible trajectories of the curve after the last measurement, each of which yields different yet equally plausible IC_{50} values: 310 nM (log M -6.51; purple curve) versus 2,400 nM (log M -5.62; blue curve) (*i.e.* an approximately eight-fold difference). However, without experimentally measuring the full range of concentrations to determine the lower plateau, it is possible that neither extrapolation may reflect the true plateau; a lower ‘bottom plateau’ would mean the IC_{50} value would be higher (*i.e.*, a less potent inhibitor).

61. The accuracy of the experimental determination of the IC_{50} values for

inhibition of FAP and for PREP for a compound directly influences the FAP selectivity value for that compound because FAP selectivity is simply the ratio of the PREP IC₅₀ value to the FAP IC₅₀ value. An error or unresolvable variability in the PREP IC₅₀ value thus directly influences the reported selectivity for a compound. Because an IC₅₀ value obtained from an incomplete curve cannot be treated as a reliable measurement, a selectivity value derived from it is also unreliable.

62. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

B. [REDACTED]

63. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

64. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] e.

1. [REDACTED]

65. [REDACTED]

[REDACTED]

[REDACTED]

⁸⁴ EX1071 (JHU Production Records), 7 (JHU_000114), 8 (JHU_000115), 10 (JHU_000131) (annotated), 11 (JHU_000130) (annotated), 17 (JHU_000148) (annotated), 19 (JHU_000148) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2. [REDACTED]

66. [REDACTED]

⁸⁵ EX1071 (JHU Production Records), 8 (JHU_000115) (annotated), 10 (JHU_000131) (annotated), 17 (JHU_000148) (annotated), 19 (JHU_000148) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

[REDACTED]

67. [REDACTED]

[REDACTED]

⁸⁶ EX1071 (JHU Production Records), 2 (JHU_000237) (annotated), 21 (JHU_000128) (annotated), 23 (JHU_000128) (annotated), 30 (JHU_000099) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

68.

[REDACTED]

[REDACTED]

[REDACTED]

3.

69. It is standard scientific practice for POSAs to critically evaluate outlier values in experimental data sets, especially when the data in one experiment is significantly different in scale than what is observed in comparable experiments. This examination is necessary to ensure the outlier was not the result of human or experimental error. [REDACTED]

[REDACTED]

⁸⁷ EX1071 (JHU Production Records), 25-27 (JHU_000138-140) (annotated).

⁸⁸ EX1071 (JHU Production Records), 4 (JHU_000187) (annotated).

[REDACTED]

[REDACTED]

[REDACTED].

a)

[REDACTED]

70.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED].

⁸⁹ EX1002 (US-201 FW), 365-367.

⁹⁰ EX1071 (JHU Production Records), 10 (JHU_000131) (annotated).

[REDACTED]

b)

[REDACTED]

71.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

⁹¹ EX1071 (JHU Production Records), 11 (JHU_000130) (annotated).

[REDACTED]

72. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

73. [REDACTED]

[REDACTED]

[REDACTED]

⁹² EX1071 (JHU Production Records), 28 (JHU_000211) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

[REDACTED]

74. [REDACTED]

[REDACTED]

[REDACTED].

(a) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁹³ EX1071 (JHU Production Records), 12 (JHU_000126) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

75.

[REDACTED]

[REDACTED]

⁹⁴ EX1071 (JHU Production Records), 12 (JHU_000126) (annotated).

⁹⁵ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4. [REDACTED]

76. [REDACTED]

[REDACTED]

[REDACTED]

⁹⁶ EX1002 (US-013 FW), 365.

⁹⁷ EX1002 (US-201 FW), 365 (¶ 42); EX2047 (VanBrocklin II), ¶ 108.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

C.

[REDACTED]

77.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

98

[REDACTED]

[REDACTED]

99

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

78.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁰⁰ EX1071 (JHU Production Records), 35 (JHU_000036-37), 42-45 (JHU_000043, JHU_000045-46, JHU_000048-50).

¹⁰¹ EX1001 (US-201), 1:20-25.

(12) **United States Patent**
Yang et al.

(10) Patent No.: US 12,115,233 B2
(45) Date of Patent: *Oct. 15, 2024

1
IMAGING AND RADIOTHERAPEUTICS
AGENTS TARGETING
FIBROBLAST-ACTIVATION PROTEIN- α
(FAP- α)

FEDERALLY SPONSORED RESEARCH OR
DEVELOPMENT

This invention was made with government support under 2
CA197470 awarded by the National Institutes of Health. The
government has certain rights in the invention.

79.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

1.

[REDACTED]

80. Standard experimental practices call for three replicates of
experimental assays like the FAP and PREP assays used in these experiments.
Three samples is usually the minimum number of samples required to produce
valid statistical analyses of experimental data. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁰² See, e.g., EX1071 (JHU Production Records), 15 (JHU_000044).

[REDACTED]

[REDACTED]

[REDACTED].

81. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

2. [REDACTED]

82. Scientists are trained to create contemporaneous and clear records when experiments are performed that identify experimental parameters and conditions, such as which compound was tested, in which assay, at what concentrations, and under what conditions. [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED].

¹⁰³ See, e.g., EX1071 (JHU Production Records), 35 (JHU_000036-37), 42-45 (JHU_000043, JHU_000045-46, JHU_000048-50).

83. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

84. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED].

¹⁰⁴ EX1071 (JHU Production Records), 35 (JHU_000036-37), 42-45 (JHU_000043, JHU_000045-46, JHU_000048-50).

¹⁰⁵ See EX1071 (JHU Production Records), 32 (JHU_000070) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

85.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

86.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

(a) Enzymatic potency values such as IC_{50} are comparable only when generated under the same conditions, because measured potency

¹⁰⁶ EX1071 (JHU Production Records), 33 (JHU_000236, JHU_000070) (annotated).

¹⁰⁷ EX1071 (JHU Production Records), 32 (JHU_000070) (annotated).

depends not just on the compound but on the enzyme preparation and assay used, including the substrate, its concentration relative to K_m , the buffer, and the ionic strength. Enzymes of different specific activity, or the same enzyme assayed under different conditions, will yield different potency values for the same compound unless the assay is normalized to measured activity, so a difference in enzyme source or assay format can shift the reported IC_{50} independent of the compound. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁰⁸ EX1071 (JHU Production Records), 32 (JHU_000070) (annotated).

¹⁰⁹ EX1080 (BPS FAP Assay Product Page), 3.

¹¹⁰ EX1081 (R&D FAP Assay Datasheet), 1.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

87. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED] [REDACTED] [REDACTED]

¹¹¹ EX1071 (JHU Production Records), 33 (JHU_000236) (annotated).

¹¹² See EX1071 (JHU Production Records), 16 (JHU_000044) (annotated).

[REDACTED].

[REDACTED]

3. [REDACTED]

88. It is common practice for scientists to evaluate the purity of compounds being used in experiments like enzyme inhibition assays. A failure to do that introduces significant uncertainty into the reported activity and selectivity data. For example, the determination of an IC_{50} value depends on knowing the true concentration of the inhibitor compound being tested in the assay, and that concentration can only be known if the purity of the sample has been established (*e.g.* by HPLC, mass spectrometry, or elemental analysis). If a sample is assumed to be pure but in fact contains synthetic byproducts, unreacted starting materials or degradation products, the effective concentration of the compound will be lower than the nominal concentration used to calculate the IC_{50} value, causing the compound to appear less potent than it truly is. If an impurity is present in a sample that also inhibits the target enzyme — or one of the off-target enzymes used to assess selectivity (*i.e.* PREP, DPPIV, DPP8, or DPP9) — the impurity can distort both the measured affinity of the compound as well as its calculated

selectivity index.

89.

[REDACTED]

D.

90.

[REDACTED]

91.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

[REDACTED]

92. At his deposition, Dr. VanBrocklin was asked by JHU's counsel if he had reviewed [REDACTED]

[REDACTED] and then he testified that "the data that I reviewed did not have any impact on my - on the opinions that I had in - no negative impact on the opinions that I had in the - in my

declaration, signed declarations.”¹¹³

93. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

IV. Response to Dr. VanBrocklin’s Opinions Regarding Unexpected Results

94. Dr. VanBrocklin states in his declaration that “the claimed “B-L-A” compounds exhibit a selectivity index, $SI_{FAP/PREP}$, that is orders of magnitude greater than the demonstrated selectivity of the corresponding ‘A’ compounds alone—an outcome that would have been unexpected to a person of ordinary skill in the art before 2017.”¹¹⁴ He also portrays FAP selectivity increases reported in

¹¹³ EX1069 (VanBrocklin Tr.), 268:2–4; 269:11–15.

¹¹⁴ EX2047 (VanBrocklin II), ¶ 104. Dr. VanBrocklin appears to reproduce the structure of Jansen-2013 Compound 7 in this paragraph, but the structure shown is not Compound 7, which is functionalized at the 4-position of the

Dr. Pomper's declaration for the Pomper Compounds as:¹¹⁵

- being “dramatic,” reflecting “a qualitative and unexpected shift in properties, attributable to the claimed ‘B-L-A’ structure as a whole,” and as reflecting “profoundly enhanced selectivity”;
- exhibiting selectivity that is “vastly superior to that of Meletta’s radiotracer” (MIP-1232) that “cannot be explained by the baseline properties of the underlying ‘A’ moiety”;
- showing “between ~12-fold to greater than ~44,000 fold” greater selectivity than Meletta’s MIP-1232 compound; and
- demonstrating “orders-of-magnitude improvement observed in the claimed compounds [that] cannot be attributed to the inherent selectivity of the ‘A’ moiety alone, but instead reflects an unexpected and non-linear enhancement arising from the claimed ‘B-L-A’ design.”

95. Dr. VanBrocklin also states that the reported increases in selectivity of the eleven compounds are due to conjugating a “B” and “L” moiety to the “A”

quinolinyl ring, whereas the structure Dr. VanBrocklin provided is functionalized at the 3-position.

¹¹⁵ EX2047 (VanBrocklin II), ¶¶ 107-111.

targeting moiety. Some examples of his statements include:¹¹⁶

- Stating it is the “claimed structure that gives rise to the dramatic increases in FAP/PREP selectivity”;
- “incorporation of the ‘A’ moiety into the claimed ‘B-L-A’ compounds suppresses off-target binding and produces a qualitatively different selectivity profile than that of the prior art”;
- “[t]he unexpectedly high selectivity observed for the claimed compounds is representative of, and expected across, the full scope of claims 1–3 of the ’201 patent”; and
- “the claimed compounds ... achieve an unexpected and extraordinary improvement in FAP selectivity that the prior art neither taught nor suggested.”

96. As I explain below, Dr. VanBrocklin’s opinion that all B-L-A compounds will exhibit unexpected increases in FAP-to-PREP selectivity relative to “A” moieties alone is contradicted [REDACTED]

[REDACTED].

A. The Pomper Declaration and the Pomper Compounds

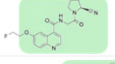
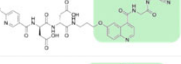
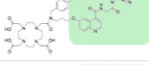
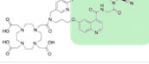
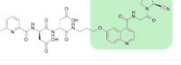
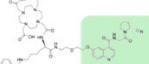
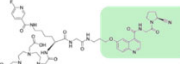
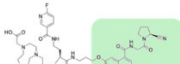
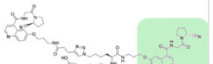
97. The Pomper Declaration compared 11 “Representative” B-L-A

¹¹⁶ EX2047 (VanBrocklin II), ¶¶ 111, 112-114.

compounds (the “Pomper Compounds”) to 8 “Reference” compounds. The 19 compounds are reproduced below with their reported selectivity ratings (*i.e.*, PREP IC₅₀/FAP IC₅₀). Labels A to H are used for Pomper Reference Compounds, and numbers are used for the 11 Pomper Compounds.

98. All 11 Pomper Compounds contain the identical “A” targeting moiety with a 4-quinolinoyl-Gly-cyanoPro core attached to the linker via an alkoxy substitution at the 6-position of the quinolinyl ring (highlighted in green below).

Pomper Reference and Representative Compounds with Annotations

Ref	Reference Compound	PREP/FAP Ratio	Pomper Compound	Representative Compound of Formula (I)	PREP/FAP Ratio
A		32*	1		4,111
B		152	2		66,084
C		20	3		>1,418,440
D		403	4		10,502
E		15.7	5		5,807
F		241	6		779
G		17	7		1,693
H		3	8		407
			9		10,694
			10		11,893
			11		1,313

B. The 11 Pomper Compounds Do Not Demonstrate Unexpected Results When Measured Against Reliable Data and Proper Comparator Compounds

99. I have been informed that counsel for JHU represented to the Board that, before submitting his declaration in this proceeding, Dr. VanBrocklin did not review any experimental information from JHU associated with the 11 Pomper compounds beyond what is contained in Dr. Pomper’s Declaration. That is

consistent with what is (and is not) in Dr. VanBrocklin's Declaration. There are no references to or discussion of any experimental records from JHU with data from testing of B-L-A compounds. There is also no reference to, or discussion of results, published in a PCT patent application, WO 2022/212958A1 (EX1057, "Pomper PCT"), that was identified by JHU as containing details of the testing of the 11 compounds in the Pomper Declaration.¹¹⁷ There are also no inhibition curves for any tested compounds, or statistical analyses of those curves to identify quality of fit or 95% confidence intervals for IC₅₀ values.

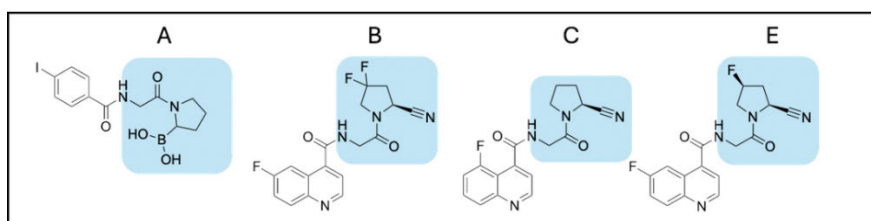
1. The Pomper Reference Compounds Are an Improper Comparator for Assessing the Pomper Compounds

100. The 8 Pomper Reference Compounds make varying changes throughout the "A" moiety. Three compounds introduced substitutions in the pyrrolidine ring A (dihydroxyboryl-), B (4-di-fluoro), E (4-fluoro). Seven introduce halogens at various positions on the quinoliny ring. Given this diversity of structures in the A moiety, a POSA would be reluctant to extrapolate selectivity results observed for a B-L-A form of one pharmacophore to the selectivity of a B-L-A form of a different pharmacophore.

101. All eight Reference compounds have low selectivity for FAP, ranging from 3 to 403, with 5 values below 50, and a geometric mean of 41. The Meletta

¹¹⁷ EX1057 (Pomper PCT), 134-141 (Table 3).

compound is one of these examples (compound A, FAP selectivity of 32), which was reported to have insufficient FAP selectivity to function as a radiotracer.¹¹⁸ A POSA familiar with the literature prior to 2017 would have believed all of these reference compounds had unacceptably low selectivity, and would not provide meaningful insights about the comparative selectivity of the 11 Pomper Compounds.



2. Dr. VanBrocklin Used the Wrong Comparator Compound to Assess B-L-A Compound Relative Selectivity

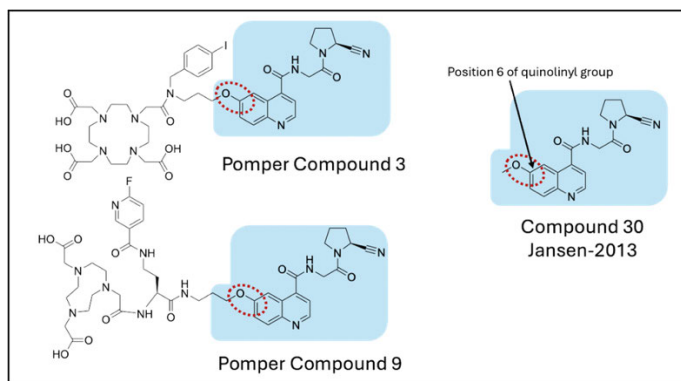
102. Dr. Pomper provides a table of information concerning the 11 Pomper Compounds.¹¹⁹ In the other tables of compounds in his declaration, Dr. Pomper reproduced the intact structure for each compound. For the 11 Pomper Compounds, Dr. VanBrocklin did not do that. Instead, he lists the “B” and “L” moieties he believed were present in the 11 Pomper Compounds separately, and then reproduces the structure of compound 7 of the Jansen 2013 paper above it.¹²⁰

¹¹⁸ EX1008 (Meletta), 2089-2090; EX1003 (Zeglis I), ¶¶ 133.

¹¹⁹ EX2047 (VanBrocklin II), ¶ 108 (pages 82-86).

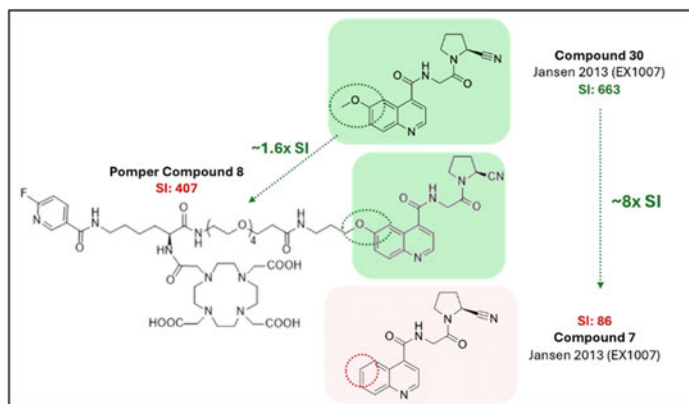
¹²⁰ EX2047 (VanBrocklin II), ¶¶ 108 (pages 82-86).

103. Dr. VanBrocklin's segregated presentation of the components of the 11 Pomper Compounds obscures an important attribute shared by all 11 Pomper Compounds—they all attach the linker via an alkoxy bond at the 6-position of the quinolinyl ring (below, Pomper Compounds 3 and 9, Compound 31, (EX1007) (Jansen-2013)).



104. Dr. VanBrocklin presents Compound 7 of Jansen-2013 as his comparator compound for the 11 Pomper Compounds. But if POSAs wanted to examine the effects of adding B and L moieties to an A moiety, they would choose the A moiety (for which there is data) that is the closest structural match to the B-L-A moieties that they have created. For the 11 Pomper compounds, that compound is **Compound 30** of Jansen-2013, **not** Compound 7. Compound 30 not only contains the same 4-quinolinoyl-Gly-cyanoPro core as all 11 Pomper Compounds, it also contains an alkoxy substitution at the 6-position of the quinolinyl ring (illustrated below) that also is present in all 11 Pomper Compounds. POSAs also would have used Compound 30 as the comparator given

that Jansen-2013 reported that adding a methoxy group at the 6-position of the quinolinyl ring caused *an 8-fold increase in selectivity* over Compound 7, which does not have that substitution (*i.e.*, **663** vs. 86, respectively).¹²¹ So Compound 30 is not only the closest structural match, it was known to be impactful to the selectivity of the pharmacophore.



105. Dr. VanBrocklin did not explain why he used Compound 7 instead of Compound 30 in his analysis of selectivity effects in the 11 Pomper Compounds. Dr. VanBrocklin was certainly aware of Compound 30 from Jansen-2013. In another part of his declaration, Dr. VanBrocklin explains that Compound 30 has a very high FAP selectivity and suggests that would have led a POSA to consider using it rather than Jansen's Compound 60, when preparing B-L-A FAP-targeting compounds.¹²² As he stated: "Many of the FAP inhibitors reported in Jansen 2013

¹²¹ See Appendix C-5, below.

¹²² EX2047 (VanBrocklin II), ¶ 60.

exhibited the same or even greater selectivity (the higher the number, the better) for FAP over PREP than Jansen's Compound 60 (with a selectivity of 562), *such as... Compound 30 (with a selectivity of 677).*"¹²³

3. Use of Compound 7 as the Comparator Artificially Inflates the Relative Selectivity of the Pomper BLA Compounds

106. Using Compound 7 as the comparator compound materially affects the magnitude and uniformity of the selectivity gains in the 11 Pomper B-L-A compounds. Using the correct comparator, Compound 30 of Jansen-2013, shows that the effects are not uniform, far more modest and even detrimental. The deficiencies in how IC₅₀ values were determined, and the flaws in several of those values also undermine the credibility of representing the effects as being significant and uniform in nature. Dr. Pomper's declaration relied on the same flawed IC₅₀ values for its comparative selectivity analysis and similarly presents results in a manner that artificially inflates the perceived increase in selectivity of the Pomper Compounds.

107. The bias introduced by use of wrong comparator compounds is illustrated using the two tables below.

¹²³ Dr. VanBrocklin's calculation of selectivity for Compound 30 is incorrect (*i.e.*, $6.1 \mu\text{M} [\text{PREP}] / 0.0092 \mu\text{M} [\text{FAP}] = 663.04$, not 677). *See* EX1007 (Jansen 2013), 493 (Table 3, right column).

- (a) The left five columns in both tables are (i) the Pomper Compound number (“X”), (ii) the JHU name of the compound, (iii) the IC₅₀ values for FAP, and (iv) the IC₅₀ values for PREP, and (v) the selectivity index value (SI PREP/FAP) for each compound, which is calculated by dividing IC₅₀[PREP] by IC₅₀[FAP]. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].¹²⁴ The cells in the fifth column are shaded to reflect [REDACTED] per § III.C above. Structures for the 11 Pomper compounds are above, ¶ 98.

- (b) In both tables, the first three rows of the sixth column provide the (i) chemical structure, (ii) selectivity index for Compound 30 of Jansen-2013 based on the published IC₅₀ values for PREP (6.1 µM) and FAP (0.0092 µM), and (iii) the % of Compound 30’s activity (which is 100%, of course).¹²⁵

¹²⁴ See ¶ 76; EX1002 (US-201 FW), 365; EX1071 (JHU Production Records), 7-8 (JHU_000114, JHU_000115).

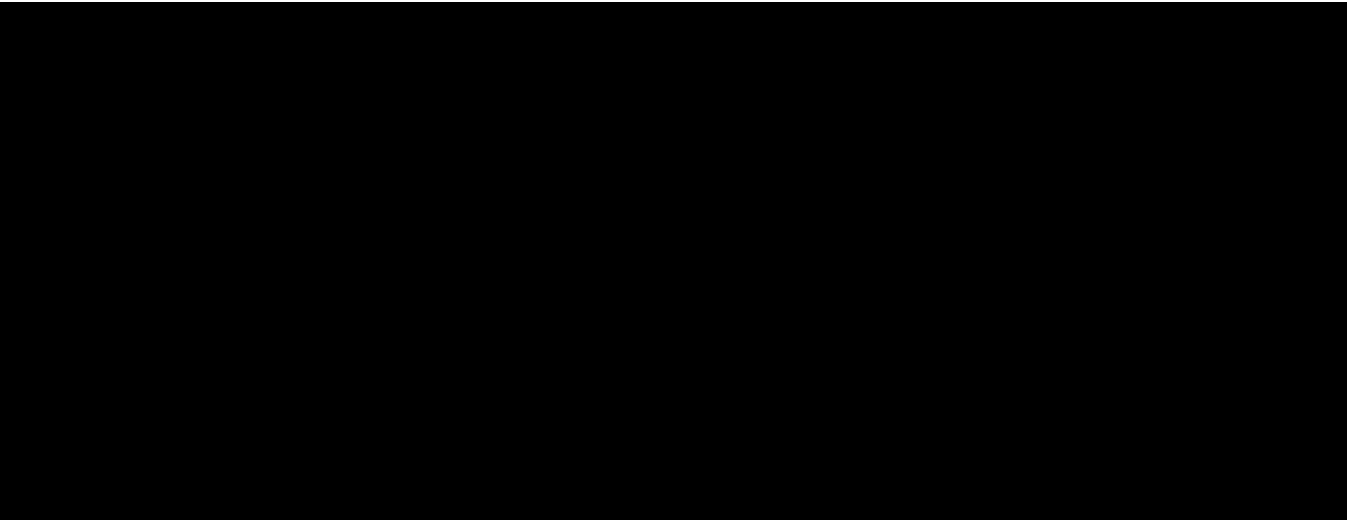
¹²⁵ EX1007 (Jansen 2013), 493; EX2047 (VanBrocklin II), ¶ 74 (pages 55-59).

- (c) In the top table, in the remaining columns contain information for Compound 7 of Jansen-2013 (EX1007) and the 8 Pomper Reference Compounds. In the first three rows are the name, structure and selectivity index for each compound. The SI for Jansen-2013 Compound 7 is based on published IC_{50} values for PREP (.86 μ M) and FAP (0.010 μ M), and values for the Pomper Compounds are from Dr. Pomper's declaration, except for Compound 2, which has been corrected per my analysis in § III.B.4.¹²⁶ The fourth row shows the percentage of the compound's SI based on the SI for compound (i.e., Jansen-2013 Compound 7 has 13.0% of the SI of Compound 30).
- (d) In the bottom table, column 6 shows the structure and SI of the MIP-1232 compound (Meletta, EX1008). Columns 7 to 12 show the designation, structure and SI values of the compounds with the top 6 selectivity indices that Dr. VanBrocklin compiled from the Jansen publications.¹²⁷ For each is shown the structure, the reported SI value from either Jansen (EX1006) or Jansen-2013 (EX1007), and the

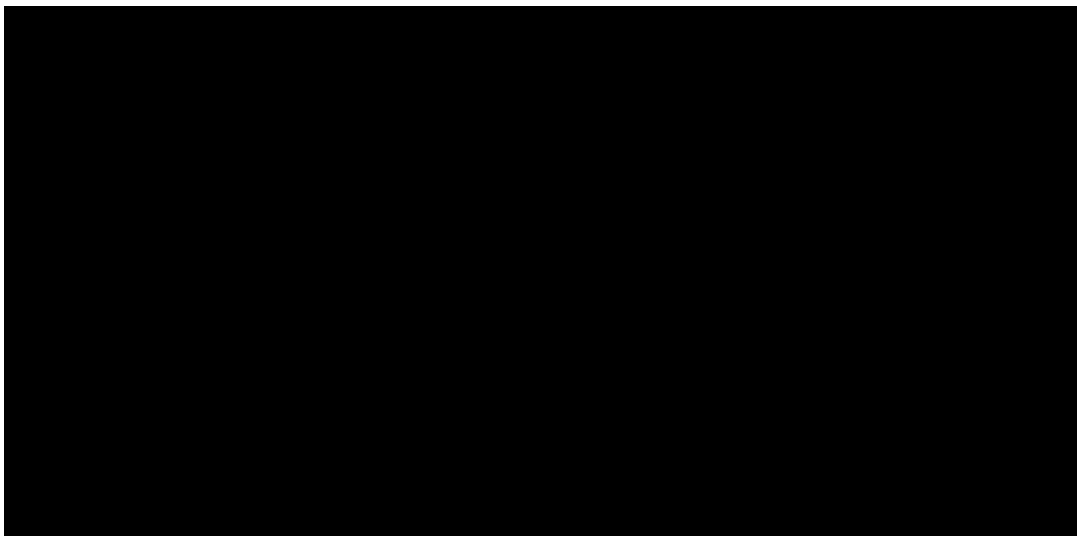
¹²⁶ EX1007 (Jansen 2013), 493; EX1002 (US-201 FW), 365-366.

¹²⁷ EX2047 (VanBrocklin II), ¶ 75.

percentage of the SI value of that compound relative to the SI value of MIP-1232.

- (e) In both tables, under each “reference compound’s” information are the ratios of the SI of the Pomper Compound (1 to 11) to the SI value of the “reference compound” (i.e., $\text{SI(Pomper)}/\text{SI(reference compound)}$). The cells are shaded with colors as follows: >10 = dark green, 2 to 10 = medium green, 1 to 2 = light green, 1 to 0.5 = light red, and <0.5 = dark red.¹²⁸
- 

¹²⁸ See Appendix C-6 and C-8, below.



108. As the upper table shows, when the 11 Pomper Compounds are compared to either Dr. Pomper’s 8 Reference Compounds or to Compound 7 from Jansen-2013, one is given the impression that *every* B-L-A compound exhibited a substantial increase in selectivity relative to an “A” compound. That is not the case when the 11 Pomper Compounds are measured against the correct comparator, Jansen-2013 Compound 30 (first comparator column), which shows more modest and non-uniform effects—Compound 8 actually showed *decreased* selectivity relative to Compound 30.

109. When the 11 Pomper Compounds are compared against other 4-quinolinoyl-Gly-cyanoPro FAP inhibitors known before 2017, the picture is very different. The second table compares the Pomper Compounds to six of the Jansen compounds with the highest FAP selectivity (*i.e.*, Compounds 60, 61 and 53 from

Jansen (EX1006), and Compounds 25, 26 and 30 from Jansen-2013 (EX1007))¹²⁹.

Each meets the requirements of the “A” moiety in the claims. Compared to these Jansen compounds, most of the Pomper Compounds show *reduced or equivalent* FAP selectivity. The effects on selectivity are also varied, not uniform.

110. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4. [REDACTED]

111. [REDACTED]

[REDACTED]

¹²⁹ EX2047 (VanBrocklin II), ¶¶ 60-61, 74-75.

¹³⁰ See §§ III.B-III.D, above.

¹³¹ See § III.B.3, above.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹³² Data, calculations and figures are compiled in Appendix C.

¹³³ See EX1057 (Pomper PCT), 134-141 (Table 3), 141-143 (Table 4). See Appendix C-9 below. See also, e.g., EX1071 (JHU Production Records), 25-27 (JHU_000138-40), 36-40 (JHU_000141, JHU_000245, JHU_000144, JHU_000085, JHU_000150).

[REDACTED]

112. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

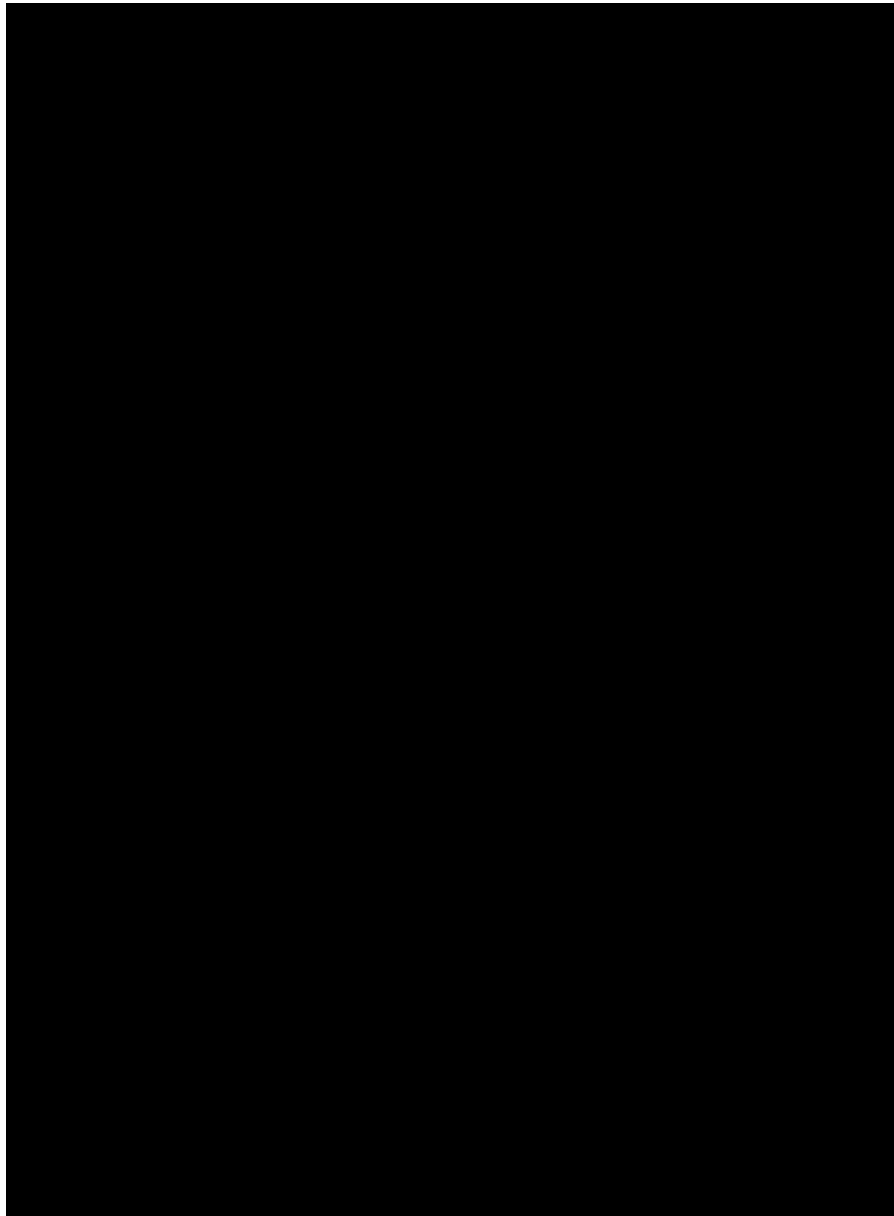
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



- (a) A POSA would expect that conjugating a targeting pharmacophore to a linker-and-reporter (B-L-) scaffold can alter its binding affinity for the target receptor by two orders of magnitude or more, and that the magnitude and direction of this change are not readily predictable. For example, Baker (EX1082) reported that attaching different fluorophores and linkers to the XAC pharmacophore (targeting the

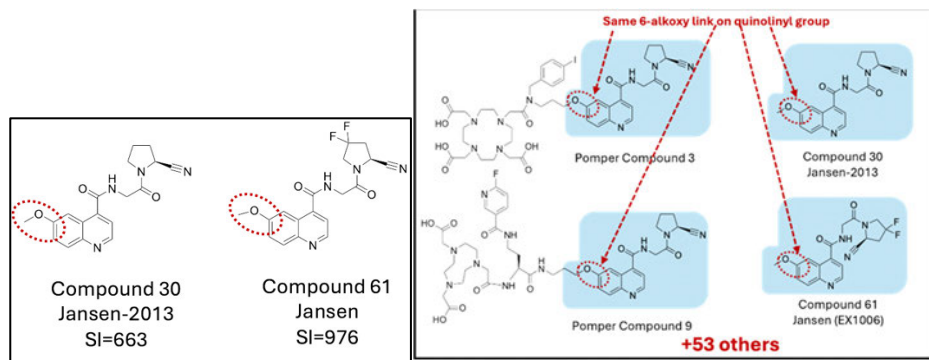
adenosine A₁-receptor) produced conjugates ranging from “at least 10-fold less potent” to approximately 128-fold less potency than the pharmacophore alone.¹³⁴ Another example is the same study’s agonist series, in which appending the optical dyes Texas Red, Cy5, EVOBlue30, or BYFL and an identical linker to the NECA-based pharmacophore ABEA “effectively abolished any measurable affinity of the agonists for the A₁ receptor,” while a BY630 conjugate of the same pharmacophore retained affinity comparable to NECA itself.¹³⁵

5. Compounds 30, 61, and Other Jansen Group 4-quinolinoyl-Gly-cyanoPro Compounds Are Within the Definition of the “A” Moiety of the Claims

113. [REDACTED]

¹³⁴ EX1082 (Baker), 778 (Table 2), 779 (reporting binding affinity K_D values for the XAC pharmacophore (42 nM) and B-L-A conjugate including: XAC-X-BY630 (38 nM) (equivalent potency) and XAC-EVOBlue30 (5370 nM) (~128-fold less potent)).

¹³⁵ EX1082 (Baker), 778 (Table 2), 779 (reporting binding affinity K_D values for the NECA pharmacophore (1072 nM) and B-L-A conjugates including: ABEA-X-BY630 (1175 nM apparent) (~5-fold more potent), AUEA-dansyl (10,715 nM apparent) (~10x less potent), and multiple compounds reported as showing no inhibition (NI) or affinity too low to quantify (K_D > ~100 μM)).

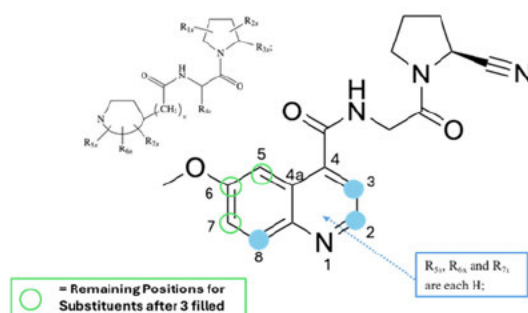


114. Dr. VanBrocklin states that Compound 61 of Jansen is not covered by the structural definition of “A” in the claims.¹³⁷ That is incorrect. The formula “X” plus the allowed parameters below that formula in claim 1 define the “A” choices permitted by the claims. As shown below, the quinolinyl ring has 10 ring atoms, of which 7 can carry a substituent. The claim requires position 4 to be used to connect the 4-quinolinoyl-Gly-cyanoPro core. The claims also require three of the positions on the quinolinyl ring to be hydrogen atoms. That leaves 3 positions at which substituents are permitted, and the claims do not restrict what substituents may be attached at those three positions. Those remaining positions must permit

¹³⁶ EX1006 (Jansen), 3082.

¹³⁷ EX2047 (VanBrocklin II), ¶ 69 (“... Compound 61 has a substituent on the quinolinyl ring (MeO-) that is not allowed by the claims.”); *see also* EX2001 (VanBrocklin I), ¶ 74.

substituents to be attached at them, because otherwise it would not be possible to make a B-L-A compound.



115. Compounds 30 and 61 fall within the A definition because (i) they attaches the glycyl(2-cyano)pyrrolidine at position 4 and (ii) hydrogens occupy five of the positions (i.e., positions 2, 3, 5, 7 and 8). Attaching the MeO- group at position 6 uses only one of the three available open positions permitted by the claim language, with multiple positions available for the attachment of the linker. All of the JHU compounds (including the 11 Pomper compounds) have a targeting moiety with an alkoxy linkage to position 6 of the quinolinyl ring and otherwise share the structure of either Compound 30 or Compound 61 (see ¶ 98 above). Following the same logic, Jansen-2013 (EX1007) Compounds 25 and 26, as well as Jansen (EX1006) Compounds 53 and 60 are also within the scope of the claims because each has no more than one substitution on the quinolinyl ring.

6.



116. Dr. Pomper and Dr. VanBrocklin each presented and relied on an

incomplete and highly biased set of B-L-A constructs and reference compounds to support the proposition that conjugating 4-quinolinoyl-Gly-cyanoPro FAP inhibitors (including those with cyano- and difluoro, cyano- substituents) to imaging (B) and linker (L) moieties will uniformly and strongly increase the FAP selectivity of those compounds. There is no credible scientific evidence that supports that proposition. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

117. [REDACTED]

[REDACTED]

[REDACTED]

¹⁴² EX1002 (US-201 FW), 367 (¶ 43); EX2047 (VanBrocklin II), ¶¶ 104, 112-113.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁴³ See § III.B.3, above. See also EX2047 (VanBrocklin II), ¶ 104; EX1071 (JHU Production Records), 10 (JHU_000131) (annotated).

¹⁴⁴ EX1002 (US-201 FW), 367 (¶ 43).

¹⁴⁵ EX2047 (VanBrocklin II), ¶¶ 105, 113.

¹⁴⁶ EX1071 (JHU Production Records), 10 (JHU_000131) (annotated).

117. Considering the claimed “A” as having the most importance due to it being the FAP-targeting moiety, the closest prior art would be Jansen 2013, which discloses the FAP-selectivity of “A”’s encompassed by the claims. Here, the claimed “B-L-A” compounds exhibit dramatic, orders-of-magnitude improvements in selectivity for FAP over PREP ($SI_{FAP/PREP}$) relative to the corresponding “A” alone. Specifically, when Jansen 2013 Compound 7, pictured below, was conjugated to a linker (“L”) and reporter moiety (“B”), the resulting claimed “B-L-A” compounds exhibited increased selectivity by several orders of magnitude compared to Compound 7, reaching values in the hundreds of thousands and, in one such “B-L-A” compound, exceeding one million. EX1002, 174–176 (Pomper Declaration, ¶42).

C. Dr. VanBrocklin Did Not Adequately Investigate the Field of the Invention Before Providing His Opinions

119. In his declaration, Dr. VanBrocklin indicated that “structural and biochemical studies” of FAP and other prolyl peptidases (e.g., PREP) are relevant to the design of FAP-targeted imaging probes.¹⁴⁷ However, at his deposition, when he was asked if he had considered published information describing the structure of the active sites of FAP and PREP, he testified that he only based his consideration of structural aspects of the two enzymes on a review of data from binding assays of the compounds.¹⁴⁸

¹⁴⁷ EX2047 (VanBrocklin II), ¶ 36.

¹⁴⁸ EX1069 (VanBrocklin Tr.), 127:17-128:9 (Q. Okay. Did you consider any differences in the PREP and FAP enzymes as to the ability of each substrate to access their active sites? A. I considered the assays that are performed to provide the inhibition data to determine the interaction of the FAP with the --

120. Before 2017, several publications had investigated the structures of the active sites of FAP and PREP and their significance to the mechanisms of action of the two enzymes. Dr. VanBrocklin cited one of them (EX2034) (Aertsgeerts), which described the active site of FAP- α as follows:

The FAP α catalytic triad is composed of residues Ser624, Asp702, and His734 and is located at the interface of the β -propeller and the α/β -hydrolase domain (Fig. 1). The active site is accessible in two ways: through a central hole formed by the eight blades of the β -propeller domain or through a cavity formed between the β -propeller and the hydrolase domain. The side opening has a diameter of ~ 24 Å in contrast to the narrower β -propeller opening (~ 14 Å).¹⁴⁹

121. An earlier paper not cited by Dr. VanBrocklin (Fulop, EX1064) investigated the structure of the active site of PREP, and the significance of it for substrate access to the PREP active site. As it stated:

The most intriguing problem of oligopeptidase activity concerns the access of substrate to the active site, which is hidden in a large cavity at the interface of the catalytic and β -propeller domains (Figures 2 and

with the enzymes. Q. But you didn't kind of look at it at a structural level of what that [access] looks like and [access] of the substrate to the different active sites. A. I reviewed the binding assays and the binding data to give me - - to assess the interaction of the FAP with the FAP and PREP enzymes.”)

¹⁴⁹ EX2034 (Aetgeerts), 19442.

6). There are two contributing factors to be considered: ***the narrow hole at the bottom of the central tunnel of the propeller***, partially covered by flexible side chains (Lys82, Glu134, His180, Asp242, Lys389, and Lys390), and the lack of “Velcro” closing between the first and last blades of the propeller (Figures 2, 4A, and 6). In the resting structure, ***the hole at the bottom of the propeller is not wide enough (~4 Å) to permit the diffusion of the substrate into the central cavity***. The entrance could be widened by the movements of these flexible side chains, enhanced by opening the propeller between its first and seventh blades. ***The opening is probably induced by the substrate, and this conformational change may be the rate-limiting step of the catalysis***, in agreement with previous results (Polgar, 1992a; Polgar et al., 1993). Such an approach of the substrate is consistent with the tunnel hypothesis put forward earlier to rationalize oligopeptidase activities (Polgar, 1992b). In this manner, ***the propeller excludes large structured peptides and proteins from the central cavity***, thus protecting them from proteolysis in the cytosol.¹⁵⁰

122. In other words, the PREP enzyme has more sterically restricted access to its active site than FAP does. FAP provides substrate access through a larger propeller opening (14Å vs. 4Å in PREP) as well as via a large (24 Å) side opening. PREP restricts access to larger, bulkier substrates and has a single and smaller “tunnel” for access to its active site. If larger or bulkier substrates have more

¹⁵⁰ EX1064 (Fulop), 167 (emphasis added).

difficulty accessing the PREP active site than they do the FAP active site, that could translate into a larger IC₅₀ value for PREP, with less of an impact on the IC₅₀ value of FAP. Mathematically, this would translate into increased selectivity for FAP for the same compound. Whether FAP and PREP do have different abilities to act on large, bulky substrates was not known by 2017. But this is an example of a possible scientific explanation as to why some larger or bulkier B-L-A compounds might, as a class, exhibit increased selectivity for FAP over PREP. As Dr. VanBrocklin explained, he did not consider these protein and substrate structural issues in forming his opinions.

V. Response to Opinions of Dr. VanBrocklin Regarding Ground 1: US-633, Jansen, and Meletta

123. As I explained in my First Declaration, the claims of the '201 Patent would have been obvious in view of US-633, Meletta, and Jansen:

- (a) Before October 2017, the literature showed there was substantial interest in FAP as a cancer-associated target for both radioimaging and radiotherapeutic applications, and POSAs were actively investigating FAP-selective small molecules to use as the targeting moieties in these radiopharmaceuticals.¹⁵¹

¹⁵¹ EX1003 (Zeglis I), ¶¶ 58-62, 106-109.

- (b) A POSA would have started with US-633, which described high FAP affinity radiotracers with a modular B-L-A structure.¹⁵²
- (c) The POSA would have recognized from Meletta that US-633's most promising radiotracer required a more selective FAP pharmacophore.¹⁵³
- (d) The POSA would have been motivated to replace US-633's boronic acid pharmacophore with Jansen's Compound 60, which was shown to be the most promising FAP inhibitor based on its FAP affinity, FAP/PREP selectivity, pharmacokinetics, stability and other physicochemical attributes.¹⁵⁴
- (e) Based on the collective guidance in US-633, Meletta, and Jansen, the POSA would have produced radiotracers that attach Compound 60 to particular B moieties suitable for PET or SPECT imaging (e.g., a DOTA for PET or DPA for SPECT) using linkers suggested by US-633 (e.g., a 3-unit diamine PEG linker). This would yield a number of specific combinations of Compound 60, PEG linkers, and chelators or

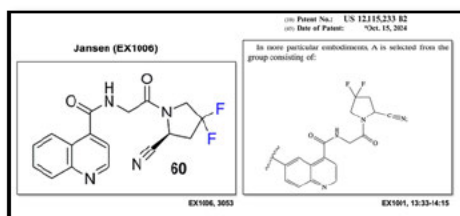
¹⁵² EX1003 (Zeglis I), ¶¶ 65-74.

¹⁵³ EX1003 (Zeglis I), ¶¶ 95-104.

¹⁵⁴ EX1003 (Zeglis I), ¶¶ 110-127.

prosthetic groups suitable for PET or SPECT imaging, all of which would have low overall molecular weights.¹⁵⁵

124. The '201 patent actually disproves Dr. VanBrocklin's opinion that a POSA would not have focused on the Jansen paper or its showcasing of Compound 60.¹⁵⁶ The '201 patent lists only two examples of FAP-targeting moieties in the specification that fall within the scope of the claims—one is Compound 60 (below)¹⁵⁷ and the other is Compound 7 of Jansen 2013 (EX1007).¹⁵⁸ It appears the Pomper group did not develop any of the FAP inhibitors it proposed to use in radiotracers outside of those known in the art.



125. I have been informed that a patent may “incorporate by reference” a publication or patent that had been published before the patent was filed, in order

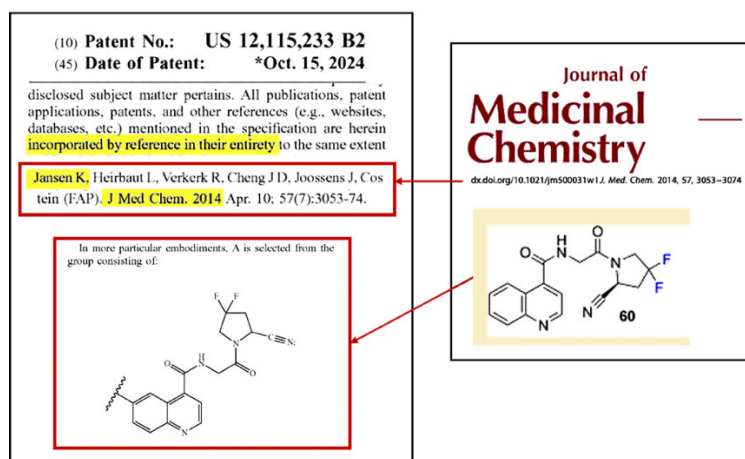
¹⁵⁵ EX1003 (Zeglis I), ¶¶ 128, 133-135, 144-145, 147-161, 217.

¹⁵⁶ EX2047 (VanBrocklin II), ¶¶ 9, 34, 55-87.

¹⁵⁷ EX1001 (US-201), 13:34-14:55; EX1003 (Zeglis I), ¶¶ 173, 169.

¹⁵⁸ EX1001 (US-201), 14:18-55; EX1007 (Jansen 2013), 493; EX2047 (VanBrocklin II), ¶ 105.

to include publicly known information as part of the patent disclosure. The '201 Patent does this with the Jansen paper that showcased Compound 60.¹⁵⁹ Jansen is one of a handful of scientific publications that the '201 Patent incorporates by reference. This signals that the inventors of the '201 Patent, including Dr. Pomper, were aware of the Jansen paper, what it was reporting, and that it had highlighted Compound 60 as one of the most promising FAP inhibitors to come out of the Jansen group's work.



A. POSAs Would Have Investigated Small-Molecule FAP Radiotracers Before 2017

126. Dr. VanBrocklin suggests that several design choices were available for the B, L, and A moieties, and therefore “the prior art did not point a POSA toward a single, predictable path leading to the claimed B-L-A compounds.”¹⁶⁰ I

¹⁵⁹ EX1001, 61:64-62:20, 63:4-10.

¹⁶⁰ EX2047 (VanBrocklin II), ¶¶ 10, also ¶¶ 6-13, 31-92.

disagree. My description of how a POSA would have approached development of a FAP-targeting radiotracer in the 2017 timeframe shows that there was substantial interest in development of small molecule radiotracers that used selective, small molecule FAP inhibitors.¹⁶¹ The literature I discussed also describes using the same modular B-L-A radiotracer design, use of the same chelator and prosthetic groups as the imaging moieties for PET and SPECT imaging, common linkers, and critically, the *identical* targeting moiety (i.e., Compound 60) that the '201 Patent proposes to use.¹⁶²

127. My obviousness analysis was based on well-established approaches for development of small molecule radiopharmaceuticals followed by POSAs before 2017. As Brennen (EX1016) observed in 2012, “the majority of FAP-based therapeutic approaches focused on the development of small-molecule inhibitors of enzymatic activity.”¹⁶³ US-633 is particularly relevant because it is focused on developing small molecule FAP-targeting radiopharmaceuticals—the same field of

¹⁶¹ EX1003 (Zeglis I), ¶¶ 59-62, 65-70, 101, 106-109.

¹⁶² EX1003 (Zeglis I), ¶¶ 27-28, 76-89, 110-115; EX1009 (Jamous), 3381; EX1004 (US-633), [0100], Tables 3, 4; EX1006 (Jansen), 3053-54, 3063-65.

¹⁶³ EX1016 (Brennen), Abstract.

research as the '201 patent.¹⁶⁴ The US-633, Meletta, and Jansen references together demonstrate an active technical path focused on small molecule, FAP-targeting radiotracer development, rather than an abandoned or speculative concept.¹⁶⁵

1. Antibody-Based Vectors Were Disfavored by 2017

128. Dr. VanBrocklin suggests that POSAs would have focused on use of antibodies as FAP-targeting moieties in radiotracers rather than small molecule FAP inhibitors in the October 2017 time frame. The pre-2017 literature shows that is not accurate.

129. One reason is the anti-FAP antibody sibrotuzumab that Dr. VanBrocklin discussed.¹⁶⁶ A radiolabeled form of sibrotuzumab was investigated in clinical trials as a cancer therapeutic. By 2017, however, it had been reported these clinical investigations were unsuccessful.¹⁶⁷ This failure of a highly specific

¹⁶⁴ EX1004 (US-633), [0002], [0005], [0007]-[0029]; EX1003 (Zeglis I), ¶¶ 65-74.

¹⁶⁵ EX1003 (Zeglis I), ¶¶ 128, 133-177.

¹⁶⁶ EX2047 (VanBrocklin II), ¶ 44.

¹⁶⁷ EX1022 (Liu), 126 (reporting sibrotuzumab “shows no beneficial effect in a phase II trial for metastatic colorectal cancer, and the antibodies did not inhibit FAP enzymatic activity.”); EX1016 (Brennen), 262 (Sibrotuzumab

FAP-targeting antibody as a human therapeutic candidate, if anything, dampened interest in antibodies as FAP-targeting agents, and drove more interest in developing small molecule FAP inhibitors as targeting moieties. That is consistent with the large volume of published work on small molecule FAP inhibitor development during the 2010-2016 time frame.¹⁶⁸

130. Experiences with using antibodies as targeting moieties before 2017 did not reduce interest in use of small molecule FAP inhibitors as targeting moieties in tumor radiotracers by 2017.¹⁶⁹ The literature between 2009 and 2017 showed there was intense interest in development of FAP inhibitors as targeting moieties for radiopharmaceuticals and radiotracers before 2017, which I explained in my First Declaration.¹⁷⁰ At his deposition, Dr. VanBrocklin agreed that “small molecules were among the many constructs that were being looked at as potential FAP agents, both as drugs and as radiopharmaceuticals at the time.”¹⁷¹

studies “observed no objective tumor response,” and in the phase II clinical study, “no responses were observed and the trial was stopped.”).

¹⁶⁸ EX1003 (Zeglis I), ¶¶ 61-62.

¹⁶⁹ EX1003 (Zeglis I), ¶¶ 22-30, 57-62; EX1001 ('201 Patent), 1:49-67.

¹⁷⁰ EX1003 (Zeglis I), ¶¶ 61-62.

¹⁷¹ EX1069 (VanBrocklin Tr.), 173:22-174:8; EX1003 (Zeglis I), ¶¶ 22-30, 59-62.

131. More generally, the literature shows that POSAs were aware that small molecules had several advantages over antibodies as targeting moieties in radiotracers for tumor imaging. As I explained in my First Declaration, antibodies were known to exhibit poor tumor penetration, have slow clearance rates and prolonged circulation, and to cause undesirable radioactivity-exposure due to off-target binding.¹⁷² Dr. Pomper described some of the reasons why in his US-121 patent that was published in 2012. As he explained:

Radioimmunotherapy based on ProstaScint™ and radiolabeled variations of this antibody are fraught with similar difficulties to the use of radiolabeled antibodies for imaging, including prolonged circulation times, poor target to nontarget tissue contrast, unpredictable biological effects and the occasional need for pre-targeting strategies, limiting the utility of these agents (Lange, P. H., Urology, vol. 57, pp. 402-406, 2001; Haseman et al., Cancer Biother Radiopharm, vol. 15, pp. 131-140, 2000; Rosenthal et al., Tech Urol, vol. 7, pp. 27-37, 2001). Furthermore, antibodies may have less access to tumor than low molecular weight agents, which can be manipulated pharmacologically.

132. Dr. VanBrocklin also published papers before 2015 identifying these drawbacks of using antibodies as the targeting moiety in radiotracers, and the

¹⁷² EX1003 (Zeglis I), ¶¶ 30, 40, 170, 186; EX1017 (Sarko), 2668-2671; EX1034 (Meyer), 2799; EX1036 (Maurer), 227; EX1053 (US-657), [0005], [0314].

relative advantages of using small molecules instead. As his 2015 paper (Ganguly 2015 (EX1065)) explained:

Even though other antibodies targeted to extracellular epitopes of PSMA have been employed successfully to deliver diagnostic and therapeutic radionuclides, the long accumulation and circulation times, poor tumor penetration, and multiple day imaging procedure result in their *suboptimal diagnostic accuracy and reduced clinical use*. In contrast, *small-molecule probes possess advantages of drug-like pharmacokinetics, high atom-economy, and reduced production costs*.¹⁷³

133. At his deposition, Dr. VanBrocklin confirmed that before 2017, these were known advantages of small molecules over antibodies in radiotracer development. As he stated:

A. That statement does describe some of the attributes of a small molecule.

Q. And those are similar to the ones that were identified in the '233 patent, right?

A. And so this -- as a class -- as a class of molecules, those on the lower -- you know, the low molecular weight side have properties that are -- make them suitable drugs, make them suitable for radiopharmaceutical labeling.¹⁷⁴

¹⁷³ EX1065 (Ganguly 2015), 780 (emphasis added).

¹⁷⁴ EX1069 (VanBrocklin Tr.), 143:21-144:13.

134. As I explained in my First Declaration, the '201 Patent recognizes these disadvantages of antibodies and advantages of small molecules for use in radiotracers for tumor imaging were known to POSAs.¹⁷⁵ The inclusion of those observations in the introduction of the '201 Patent confirms that the patent was describing what was known to POSAs before 2017.

135. Dr. VanBrocklin portrays two of my publications as showing that I believed that antibodies were more appealing targeting moieties for radiotracers than small molecules.¹⁷⁶ That mischaracterizes those papers and my beliefs before 2017. The two papers did not focus on vector selection, and each one describes known problems of using antibody-based radiotracers. In Zeglis 2015 (EX2040) we noted that the slow pharmacokinetics of antibodies force the use of “radionuclides with long physical half-lives [that] often results in high background radiation dose rates to non-target tissues,” which is why we pursued a pre-targeting method predicated on *radiolabeled small molecules*.¹⁷⁷ In Zeglis 2016 (EX2041), we observed that antibody conjugates had “stalled just short of the clinic.”¹⁷⁸ My

¹⁷⁵ EX1003 (Zeglis I), ¶ 186; EX1001 (US-201), 1:49-67.

¹⁷⁶ EX2047 (VanBrocklin II), ¶ 43 (citing EX2040 (Zeglis 2015) and EX2042 (Zeglis 2014)).

¹⁷⁷ EX2040 (Zeglis 2015), Abstract, 1; EX2027 (Zeglis Tr.), 70:4-71:8.

¹⁷⁸ EX2041 (Zeglis 2016), 3, 15.

papers thus are reinforcing the known limitations of using antibodies as targeting moieties, and relative advantages of using small molecules instead.

136. The history of radiopharmaceutical development in the United States also contradicts Dr. VanBrocklin portrayal of POSAs prioritizing antibodies as targeting moieties rather than small molecules. At his deposition, Dr. VanBrocklin testified that he was aware that “some” antibody-based molecular imaging agents had been taken off the market.¹⁷⁹ It was more than just “some” – it was nearly all of them! The table provided as Appendix B shows that since 1989, six of the eight antibody radiopharmaceuticals that received FDA approval were taken off the market by October 2017, with one of the remaining two being discontinued in 2018.¹⁸⁰ Development fared no better outside the United States—three of the four of the antibody radiopharmaceuticals that received marketing approval in the EU were off the market by October 2017, and the final molecule was withdrawn in 2018.¹⁸¹ Dr. VanBrocklin did not mention any of these antibody radiotracer product withdrawals in his declaration.

¹⁷⁹ EX1069 (VanBrocklin Tr.), 145:5-146:9.

¹⁸⁰ See Appendix B, below.

¹⁸¹ See Appendix B, below.

2. The Pre-2017 Literature Did Not Support FAP-Targeting Peptide and Liposome Vectors

137. The peptide, protein, and liposome literature cited by Dr. VanBrocklin does not establish that those vectors diminished interest small molecule-based radiotracers.¹⁸² Several simply discussed FAP biology or broad targeting concepts without reporting any particular findings about FAP radiotracers.¹⁸³ The LeBeau (EX2037) and Huang 2011 (EX2038) papers propose an emergent strategy predicated on the cleavage of peptides by FAP to release cytotoxins.¹⁸⁴ This is inherently risky for a radiopharmaceutical because the reporter moiety can then leave the tissue of interest, resulting in reduced signal or reduced therapeutic efficacy. As a result, a POSA would naturally prefer binding moieties that remain intact upon binding to FAP. The Ruger paper described use of a liposomal optical imaging agent, but there is no evidence it progressed to the clinic, and no evidence it diluted interest in small-molecule radiotracers.¹⁸⁵

¹⁸² EX2047 (VanBrocklin II), ¶¶ 44-48; EX1003 (Zeglis I), ¶¶ 57-62.

¹⁸³ EX1003 (Zeglis I), ¶¶ 57-62; EX2047 (VanBrocklin II), ¶¶ 44-48.

¹⁸⁴ EX2047 (VanBrocklin II), ¶ 48; EX2037 (LeBeau 2009), 2-3; EX2038 (Huang 2011), Abstract, 491.

¹⁸⁵ EX2047 (VanBrocklin II), ¶ 47; EX2036 (Rüger); EX1003 (Zeglis I), ¶¶ 57-62.

B. Response to Dr. VanBrocklin's Opinions Regarding the Selection of A FAP-Targeting Moiety from the Prior Art

1. The Prior Art Recognized that Compound 60 Was a Particularly Attractive Targeting Moiety

138. Dr. VanBrocklin portrays my explanation of the importance of FAP selectivity as meaning that I believed high selectivity was the sole metric that POSAs would use to identify potential targeting moieties for FAP radiotracers.¹⁸⁶ That is not correct.

139. I explained in my First Declaration that a POSA would have assessed *several* characteristics of potential targeting moieties when determining which of them should be selected for development in a radiotracer, including (i) FAP affinity, (ii) selectivity for FAP over related enzymes (particularly PREP), (iii) stability of the targeting moiety and of the assembled imaging agent, (iv) solubility, (v) toxicity, (vi) pharmacokinetics, (vii) in vivo target engagement, and (viii) maintenance of the targeting moieties affinity and selectivity for FAP in the assembled imaging agent.¹⁸⁷ Dr. Pomper identified a similar array of these characteristics as being important to selection of targeting moieties for radiotracers

¹⁸⁶ EX2047 (VanBrocklin), ¶ 9.

¹⁸⁷ EX1003 (Zeglis I), ¶¶ 45-49, 112-114, 118, 123-126; EX2027 (Zeglis Tr.), 62:18-63:5, 64:1-65:13.

to be used in medical imaging in his Declarations.¹⁸⁸ The Jansen group identified these same types of additional characteristics in their work.¹⁸⁹ What all of us are saying is that FAP binding and selectivity criteria should be used to home in on promising candidates, and then assessments of additional characteristics that are important for radiotracers should be used to further narrow that promising set of candidates.

140. The Jansen publication (EX1006) shows this process in motion. They first screened a large number of FAP inhibitors by using affinity and selectivity criteria to home in on a small subset of promising candidates. Then, they assessed additional characteristics of these promising candidates to identify those were the most promising candidates overall. As they stated, “[t]aking into account the number of low nanomolar FAP inhibitors with high FAP/PREP selectivity that we had discovered as part of this and the foregoing study, *four of the most promising compounds* were then selected for which *in vitro pharmacokinetic parameters*

¹⁸⁸ EX1002 (US-201 FW), 363 (¶ 31). See also ¶ 23, above.

¹⁸⁹ EX1006 (Jansen), 3053 (“The log D values, plasma stabilities, and microsomal stabilities of selected compounds were found to be highly satisfactory. Pharmacokinetic evaluation in mice of selected inhibitors demonstrated high oral bioavailability, plasma half-life, and the potential to selectively and completely inhibit FAP in vivo.”)

were determined (log D_{7.4}, kinetic solubility, stabilities in mouse, rat, and/or human plasma) (Table 7).”).¹⁹⁰

141. The most promising candidate Jansen identified is Compound 60. The reasons it did so were: (i) Compound 60 exhibited excellent affinity and selectivity for FAP, which placed it a small group of very promising FAP inhibitors, and (ii) relative to the other promising FAP-selective candidates, Compound 60 had the best array of additional characteristics that are important for successful radiotracers, including that it “...resulted in the most extensive and prolonged inhibition of FAP in the PK studies.”¹⁹¹ That is why Jansen showcased it in its abstract.¹⁹² Jansen is clearly reporting that Compound 60 checked the most boxes required for a successful targeting moiety in a radiotracer of its numerous candidates.¹⁹³ A POSA seeking to assemble a FAP-targeting imaging or radiotherapy agent would seek to use a targeting moiety that checks the most boxes

¹⁹⁰ EX1006 (Jansen), 3063 (emphasis added).

¹⁹¹ EX1006 (Jansen), 3063-3064. Other favorable characteristics Jansen identified included satisfactory aqueous solubility, plasma stability, microsomal stability, and lack of cellular toxicity. EX1006 (Jansen), Abstract, 3063-3064; EX1003 (Zeglis I), ¶¶ 114, 125-126.

¹⁹² EX1003 (Zeglis I), ¶¶ 112; EX1006 (Jansen), Abstract, 3063-3065.

¹⁹³ EX1006 (Jansen), Abstract, 3053, 3063-3064; EX1003 (Zeglis I), ¶¶ 111-126.

in terms of favorable attributes for different applications. I do not believe it can be seriously disputed that Jansen identified Compound 60 as a potent, selective, stable, in vivo-active FAP inhibitor with a structure amenable to conjugation.¹⁹⁴

2. Other FAP Inhibitors Described in the Art Would Not Have Led Skilled Artisans Away from Compound 60

142. Dr. VanBrocklin's ranking of FAP pharmacophores places disproportionate weight on FAP/PREP selectivity and treats compounds with different assay records as though they were fully comparable development candidates.¹⁹⁵ The Jansen and US-650 compounds with higher reported selectivity generally lacked the same combination of plasma and microsomal stability, rat pharmacokinetics, toxicity assessment, and prolonged in vivo FAP inhibition reported for Compound 60.¹⁹⁶ The absence of comparable data would not have led a POSA away from the better-characterized Compound 60.¹⁹⁷

143. The Jansen 2014 (EX2003) xanthine inhibitors cited by JHU and Dr. VanBrocklin belonged to a different scaffold series and included compounds with

¹⁹⁴ EX1003 (Zeglis I), ¶¶ 111-127, 138-143; EX1006 (Jansen), 3053-3065.

¹⁹⁵ EX2047 (VanBrocklin II), ¶¶ 56-76, 92.

¹⁹⁶ EX1003 (Zeglis I), ¶¶ 113-114, 122-126; EX1006 (Jansen), Abstract, 3063-3065; EX1007 (Jansen 2013), 491-496; EX1044 (US-650), Tables 3-4.

¹⁹⁷ EX1003 (Zeglis I), ¶¶ 122-127.

substantially weaker FAP IC₅₀ or high activity against DPPIV with no comparable *in vitro* or *in vivo* characterization work, making them inferior candidates to Compound 60.¹⁹⁸ Poplawski's (EX2024) boronic-acid series did not provide the same favorable, directly comparable *in vivo* pharmacokinetic and sustained FAP-inhibition record.¹⁹⁹ Tsai (EX1047) did not report PREP selectivity for its candidates—leading Poplawski to conclude that “it is not clear whether or not these inhibitors are truly specific and to what degree,”²⁰⁰—and described pharmacokinetic limitations for the scaffold despite favorable results for certain parameters.²⁰¹

144. The additional references Dr. VanBrocklin discusses did not say anything that would disqualify Compound 60 as being a promising candidate in the mind of a POSA. Indeed, even after his analysis, Dr. VanBrocklin agreed that “[o]f the multiple compounds” found to have “suitable FAP properties for

¹⁹⁸ EX2003 (Jansen 2014), 1701, 1703, 1706, Tables 1-4; EX1003 (Zeglis I), ¶¶ 109-112, 115-126; EX2047 (VanBrocklin II), ¶ 62.

¹⁹⁹ EX2024 (Poplawski), 3467-3477; EX1003 (Zeglis I), ¶¶ 112-115, 123-126; EX2047 (VanBrocklin II), ¶ 63.

²⁰⁰ EX2024 (Poplawski), 3; EX1047 (Tsai), Abstract, 6576-78, Tables 3-4; EX2047 (VanBrocklin II), ¶ 64.

²⁰¹ EX1047 (Tsai), Abstract, Table 2, 6578; EX2047 (VanBrocklin II), ¶ 64.

radiopharmaceuticals, I believe that compound 60 was included in those.”²⁰²

145. I did not use hindsight in my analysis.²⁰³ I followed the direct guidance and observations of the series of Jansen papers, which culminate in Jansen identifying Compound 60 as its most promising FAP inhibitor. I also did not use the claims of the ’201 patent to decide which compounds to assess—I used the information in the publications to make my assessments. Nothing in the literature I reviewed criticized Compound 60 or suggested that it would be unsuitable as a FAP-targeting moiety.

3. The Classification Scheme I Applied in My First Declaration is a More Accurate Reflection of how a POSA Would Have Approached the Design of a FAP Radiopharmaceutical

146. The Sankey diagram in my First Declaration was a transparent screening framework reflecting the sequential way a medicinal and radiopharmaceutical chemist would screen candidates.²⁰⁴ It first applied objective selectivity and affinity thresholds to eliminate inadequate candidates and then considered practical radiopharmaceutical-design factors and develop data to

²⁰² EX1069 (VanBrocklin Tr.), 184:13-22.

²⁰³ EX2047 (VanBrocklin II), ¶¶ 56-79; EX1003 (Zeglis I), ¶¶ 119-127.

²⁰⁴ EX1003 (Zeglis I), ¶¶ 117-121; EX2047 (VanBrocklin II), ¶ 66.

evaluate potential liabilities.²⁰⁵ That framework did not assume that the highest selectivity index automatically wins, and it did not require every candidate to be ranked in a single immutable order. It identified Compound 60 as one particularly strong and well-characterized choice, which is the relevant scientific point.²⁰⁶

147. Contrary to Dr. VanBrocklin's assertion, the affinity and selectivity thresholds I used were supported by the art: I cited the Mach publication (EX1033) stating that an ideal PET probe should have nanomolar affinity and greater than 100-fold selectivity for its target.²⁰⁷ Dr. VanBrocklin's competing decision diagram does not apply that full framework; it ranks compounds by FAP/PREP selectivity alone and includes compounds that do not satisfy the high-affinity threshold or that bind DPPIV much more strongly than FAP.²⁰⁸

C. The Prior Art Supported Conjugation Through a Linker

148. Dr. VanBrocklin suggests that a POSA would have preferred direct radiolabeling over using a linker to minimize structural perturbations to the small

²⁰⁵ EX1003 (Zeglis I), ¶¶ 45-48, 117-121.

²⁰⁶ EX1003 (Zeglis I), ¶¶ 110-127.

²⁰⁷ EX1033 (Mach), 140; EX1003 (Zeglis I), ¶ 119 & n.144; EX2047 (VanBrocklin II), ¶ 67; EX2001 (VanBrocklin I), ¶ 71.

²⁰⁸ EX2003 (Jansen 2014), Tables 1, 3; EX2047 (VanBrocklin II), ¶ 74.

molecule pharmacophore.²⁰⁹ I disagree.

1. Jansen's Data Justified Conjugating C⁶ or C⁷ on the Quinoliny Ring

149. Jansen's structure-activity relationship (SAR) data provided a rational basis for attaching a linker at the C⁶ or C⁷ region of the quinoline ring.²¹⁰

Substituted analogues at those positions retained useful FAP affinity and selectivity, showing that the quinoline periphery was not uniformly intolerant of modification and identified positions where a POSA could test a linker.

150. The Jansen 2013 halogen results were position- and substituent-specific; they did not establish a general rule that direct radiohalogenation was always preferred.²¹¹ C⁵-chlorine and -bromine improved FAP/PREP selectivity in that series, but other substitutions and positions produced different effects on FAP and PREP affinity.²¹² A POSA would not infer from those data that every useful

²⁰⁹ EX2047 (VanBrocklin II), ¶¶ 50-55, 80-84.

²¹⁰ EX1003 (Zeglis I), ¶¶ 138-143; EX1006 (Jansen), 3060-3063; See Appendix D, below.

²¹¹ EX1007 (Jansen 2013), 493-494; EX1003 (Zeglis I), ¶¶ 138-143.

²¹² EX1007 (Jansen 2013), Tables 3-4, 493-494 (compounds 27, 29, and 31-34 showing reduced FAP/PREP selectivity compared to C⁵-halogenated compounds); EX1006 (Jansen), 3060-3063; EX1003 (Zeglis I), ¶¶ 138-143. See also Appendix D, below.

radiotracer should place a radiohalogen directly on the pharmacophore.²¹³

151. A POSA developing a FAP radiopharmaceutical would also seek to de-risk the molecule by minimizing steric interactions between substituents on the quinolinyll ring.²¹⁴ This includes avoiding modifying a position on the heterocycle with a substitution at an adjacent carbon, as would be necessary for Jansen Compounds 51 and 61.²¹⁵

2. A POSA Would Have Preferred Linker Conjugation Over Direct Radiohalogenation

152. Linker-based conjugation was an established strategy that offered different radionuclide and physicochemical options.²¹⁶ As I previously explained, a linker can spatially separate the reporter from the binding pharmacophore, reduce steric interference, facilitate precursor and product synthesis, and provide a means to tune solubility, stability, charge, hydrophobicity, and pharmacokinetics.²¹⁷

153. Linker-based designs also permitted use of radiometals such as gallium-68 or technetium-99m through established chelators rather than limiting

²¹³ EX1003 (Zeglis I), ¶¶ 34, 53, 139; EX1007 (Jansen 2013), 493-494.

²¹⁴ EX1003 (Zeglis I), ¶ 142.

²¹⁵ EX1003 (Zeglis I), ¶ 120; EX2047 (VanBrocklin II), ¶¶ 68-69.

²¹⁶ EX1003 (Zeglis I), ¶¶ 27-28, 35-37, 86-89.

²¹⁷ EX1003 (Zeglis I), ¶¶ 35-37, 86-89.

the project to a directly attached radiohalogen.²¹⁸ That flexibility allowed POSAs to select a radionuclide whose decay properties fit the intended PET, SPECT, or therapeutic application.²¹⁹ It also avoided placing a radionuclide at a position where a particular substitution could impair affinity or selectivity.²²⁰ Dr. VanBrocklin and I also agree that the addition of a linker can de-risk concerns of additional bulk and charge created by the addition of a chelator.²²¹

154. Dr. VanBrocklin cites to a 2014 review by Sugiara (EX2028) that suggests direct radioiodination was the preferred technique in the art, but he neglects to note that Sugiara discusses radioiodination of *antibody-based radiotracers* using radioisotopes of iodine with long half-lives (4+ days), not faster-clearing small molecules.²²² Sugiara also acknowledged the benefits of using a linker, noting that an antibody conjugated with a linker and chelator-

²¹⁸ EX1003 (Zeglis I), ¶¶ 32, 35-36, 42-43, 147-155.

²¹⁹ EX1003 (Zeglis I), ¶¶ 39-43, 78-80, 147-161.

²²⁰ EX1003 (Zeglis I), ¶¶ 34-37, 138-143; EX2027 (Zeglis Tr.), 100:15-101:11, 111:2-12.

²²¹ EX1003 (Zeglis I), ¶ 36; EX2047 (VanBrocklin II), ¶ 54; EX1069 (VanBrocklin Tr.), 243:20-244:20.

²²² EX2047 (VanBrocklin II), ¶ 82; EX2028 (Sugiara 2014), Abstract, 2136, 2145-46.

radionuclide matrix exhibited a favorable safety profile and better *in vivo* stability over direct radioiodination.²²³

3. PEG Linkers Were Well-Characterized and Established in the Art

155. PEG-containing linkers were well known before 2017 and were expressly included among US-633's tether options.²²⁴ Commercial short PEG diamines provided readily available bifunctional building blocks for connecting a targeting ligand to a chelator or prosthetic group. My three-monomer PEG examples were illustrative species within that known class, not an opinion that PEG₃ was the only linker a POSA could choose.²²⁵

156. My discussion of roughly 10 to 20 bonds-length described a practical design range for reducing reporter-pharmacophore interference, not a categorical rule that shorter or longer linkers could never work.²²⁶ Radiopharmaceutical chemists routinely evaluate a small series of linker lengths because linker effects

²²³ EX2028 (Sugiara 2014), 2142, 2146.

²²⁴ EX1004 (US-633), [0130]-[0133]; EX1003 (Zeglis I), ¶¶ 72, 88, 149-152.

²²⁵ EX1003 (Zeglis I), ¶¶ 149-152.

²²⁶ EX1003 (Zeglis I), ¶¶ 88, 151; EX2027 (Zeglis Tr.), 181:16-182:20.

are context-dependent.²²⁷ That ordinary optimization does not negate the reason to begin with an established linker class disclosed by the prior art.

157. The Siwowska (EX2030) study cited by Dr. VanBrocklin involved albumin-binding radiofolates and compared specific linker constructs in that different molecular system.²²⁸ A context-specific finding that one long PEG-linked radiofolate had lower tumor uptake or greater kidney retention does not establish that PEG linkers generally were disfavored. It instead confirms the ordinary expectation that linker identity and length should be evaluated for the selected pharmacophore and reporter of any radiopharmaceutical.²²⁹

158. Dr. Pomper's own work confirms a POSA would have used short-length PEG linkers for FAP radiopharmaceuticals—the Pomper PCT (EX1057) published in October 2022 shows that Dr. Pomper synthesized multiple FAP-targeting compounds incorporating spacers of between two to four PEG monomer

²²⁷ EX1003 (Zeglis I), ¶¶ 35-37, 86-89, 149-152; EX1069 (VanBrocklin Tr.), 161:16-162:19.

²²⁸ EX2030 (Siwowska), Abstract, 823, 830; EX2047 (VanBrocklin II), ¶ 90.

²²⁹ EX1003 (Zeglis I), ¶¶ 35-37, 45-49, 86-89; EX1069 (VanBrocklin Tr.), 161:16-162:19.

units between the reporter and targeting moieties.²³⁰

D. Response to Dr. VanBrocklin's Opinions Regarding the Disclosure of US-633

159. As I explained in my First Declaration, US-633 identifies several reasons to add and vary a linker (“tether”) between the radiolabeling and FAP-binding portions of a radiotracer.²³¹ US-633 states that altering tether length can modify FAP affinity and selectivity and that incorporating heteroatoms into the tether can modify the pharmacokinetic properties of the resulting complex and identifies commercially available short PEG diamines that can be readily incorporated into the complexes.²³² In discussing his own 2016 work, Dr. VanBrocklin testified that radiopharmaceutical chemists routinely alter molecular structures and linker lengths to optimize imaging-agent properties.²³³ That is precisely what US-633 teaches.

160. JHU and Dr. VanBrocklin's division of US-633 compounds into “B-

²³⁰ EX1057 (Pomper PCT), 112, 125-126 (Schemes 4-5), 134-143 (Tables 3 and 4).

²³¹ EX1003 (Zeglis I), ¶¶ 86-89; EX1004 (US-633), [0051], [0101], [0130]-[0133].

²³² EX1004 (US-633), [0101], [0130]-[0133]; EX1003 (Zeglis I), ¶¶ 87-89.

²³³ EX1069 (VanBrocklin Tr.), 161:16-162:19; EX1066 (Dannoon 2016), Abstract, 5865.

A” and “B-L-A” categories on the grounds that a carbonyl is not a linker turns on where one draws a conceptual boundary within a continuous chemical structure.²³⁴ His minimum-distance premise is inconsistent with his deposition testimony that the claim “does not prescribe any length” or “how long or how short” L must be.²³⁵ US-633 itself teaches tethered reporter-targeting constructs and does not direct a POSA to reject a tether whenever the tether is short or incorporated into the radiolabeling moiety.²³⁶ Dr. VanBrocklin also agreed at his deposition that the only requirement of the claimed linker “is that it has the bi-functionalization to be able to connect B to A.”²³⁷ The carbonyl of US-633 Formula II satisfies that requirement by having a carbon with two bonds—one attaching to the B moiety and the other to the A moiety—which connects the B and A together.²³⁸

161. In US-633’s Compound 1024, the amide carbonyl lies between the radioiodinated prosthetic group and the glycine-pyrrolidine FAP warhead and thus forms part of the covalent connection bridging those portions in the completed

²³⁴ EX2001 (VanBrocklin I), ¶¶ 41-59.

²³⁵ EX1069 (VanBrocklin Tr.), 88:10-22, 89:22-90:13.

²³⁶ EX1004 (US-633), [0049]-[0051], [0100]-[0133]; EX1003 (Zeglis I), ¶¶ 71-72, 86-89.

²³⁷ EX1069 (VanBrocklin Tr.), 88:9-14.

²³⁸ EX1003 (Zeglis I), ¶¶ 71-72; EX1004 (US-633), [0008], [0021].

molecule.²³⁹ US-633 expressly permits V in Formula I and Y in Formula II to be “a bond,” and it permits q in Formula II to be zero, confirming that US-633 does not require every connecting structure to contain a multicarbon chain or a PEG-length spacer.²⁴⁰ A covalent bond places the atoms it joins at a finite internuclear distance, and therefore a one-bond or one-carbon connection can provide spatial separation even though that separation is small.²⁴¹

162. Contrary to Dr. VanBrocklin’s assertion, US-633’s Table 2 does not establish that adding a linker generally reduces FAP affinity because the compared compounds are not matched pairs that differ only in linker presence or length.²⁴² The structures differ in aryl groups, bond types, and other features that can independently affect binding. Table 2 also does not report the PREP selectivity, stability, or pharmacokinetic data needed for a complete radiotracer comparison.²⁴³ US-633 reported approximately 4 nM FAP inhibition for longer-tether compound

²³⁹ EX1004 (US-633), [0175]; EX2001 (VanBrocklin I), ¶ 43.

²⁴⁰ EX1004 (US-633), [0012], [0025]-[0027].

²⁴¹ EX1004 (US-633), [0012], [0025]-[0027]; EX1003 (Zeglis I), ¶ 37; EX1069 (VanBrocklin Tr.), 90:5-13.

²⁴² EX1004 (US-633), [0174]-[0185], Table 2; EX1003 (Zeglis I), ¶ 91; EX2001 (VanBrocklin I), ¶¶ 52-54.

²⁴³ EX1004 (US-633), Table 2; EX1003 (Zeglis I), ¶¶ 45-48, 91.

1020, which is in the same low-nanomolar range as the approximately 3 nM result reported for compound 1024.²⁴⁴ That result is inconsistent with a categorical rule that tethered structures were unsuitable for further work. A POSA instead would have treated tether structure as a variable to optimize while improving the targeting moiety.

E. The Exemplary Compounds and Reasonable Expectation of Success

163. In my First Declaration, I illustrated four Compound 60-based radiotracers using prior-art combinations of radionuclides, chelators or prosthetic groups, and PEG linkers that meet all of the requirements of the claims.²⁴⁵ Compounds A1 and A2 used radiometal-chelator reporter systems, while A3 and A4 used radiohalogenated prosthetic groups.²⁴⁶ Each example contains one qualifying B, one bifunctional L, and Compound 60 as the claimed A moiety, and each falls within the low-molecular-weight range relevant to this proceeding.²⁴⁷

164. Dr. VanBrocklin did not dispute that these examples meet all the claim requirements. He also testified at his deposition that Compound 60-based

²⁴⁴ EX1004 (US-633), Table 2; EX1003 (Zeglis I), ¶ 91.

²⁴⁵ EX1003 (Zeglis I), ¶¶ 146-178 (exemplary compounds A1-A4).

²⁴⁶ EX1003 (Zeglis I), ¶¶ 164-178.

²⁴⁷ EX1003 (Zeglis I), ¶¶ 164-178.

examples A3 and A4 had a high likelihood of continuing to target FAP.²⁴⁸ His disagreement concerns why a POSA would choose Compound 60 and the illustrated linkers, not whether the completed structures satisfy the claim language and will retain FAP binding properties of Compound 60.²⁴⁹ The prior art supplied a reason for both choices.²⁵⁰

1. Dr. VanBrocklin Testified that a Working A Moiety Would Have Given Skilled Artisans Reasonable Expectation of Success In Assembling a Claimed B-L-A Compound

165. Dr. VanBrocklin testified that if a POSA took an “A” moiety with “very good binding affinity to FAP, and even selectivity,” and “you put it into the molecules that are of the B-L-A design, you had some reasonable expectation that your molecules were going to bind to FAP, and they might even contain that selectivity that was borne in by the molecules that you used as your A group.”²⁵¹ The combination of a validated FAP-targeting moiety in compound 60, coupled with validated conjugated positions at the C⁶ and C⁷ positions, would have given a skilled a reasonable expectation of successfully assembling the claimed B-L-A

²⁴⁸ EX1069 (VanBrocklin Tr.), 236:19-238:11.

²⁴⁹ EX2047 (VanBrocklin II), ¶¶ 11, 56-91; EX1003 (Zeglis I), ¶¶ 164-178.

²⁵⁰ EX1003 (Zeglis I), ¶¶ 110-178.

²⁵¹ EX1069 (VanBrocklin Tr.), 217:2-218:18.

compound with the desired affinity and selectivity profile.

2. Meletta's Isolated Failure Would Not Have Led Skilled Artisans to Abandon Small Molecule-Based FAP Radiopharmaceuticals

166. Contrary to Dr. VanBrocklin's opinion, Meletta's plaque experiment would not have extinguished the interests of POSAs in FAP as a target for small molecule radiotracers.²⁵² Meletta did not suggest that MIP-1232 lacked all FAP binding or that small-molecule FAP radiotracers were categorically nonviable.²⁵³ Dr. VanBrocklin agreed at deposition that Meletta's "conclusion was not that [MIP-1232] was not a viable agent for FAP" and that the results were "not conclusive in any way, shape or form that [MIP-1232] did not bind to FAP . . . it just did not work in this particular example that they put here."²⁵⁴ Meletta's own oncology xenograft results were "promising towards the imaging of FAP to support FAP-targeted therapy in oncology," and its proposed next step was to use a more selective inhibitor.²⁵⁵ Compound 60 directly answered that identified need.²⁵⁶

²⁵² EX2047 (VanBrocklin II), ¶¶ 93-94.

²⁵³ EX1008 (Meletta), 2088-2095; EX1003 (Zeglis I), ¶¶ 99-104.

²⁵⁴ EX1069 (VanBrocklin Tr.), 52:7-53:11.

²⁵⁵ EX1008 (Meletta), 2095, 2090; EX1003 (Zeglis I), ¶¶ 102-104.

²⁵⁶ EX1003 (Zeglis I), ¶¶ 110-113.

167. Dr. VanBrocklin's own published work demonstrates that he continued studying the development of small molecule radiotracers despite a long history of documented failure. In Huang 2020 (EX1077), Dr. VanBrocklin co-wrote a paper describing the development of a PET radioligand targeting glucocorticoid receptor (GR) despite "over 3 decades" of unsuccessful attempts due to "low-yielding radiosynthesis, poor in vivo stability, or limited evidence of specific receptor binding in vivo."²⁵⁷ Instead of being discouraged by these past failures, Dr. VanBrocklin continued to work in this space and made a "promising nonsteroidal radioligand...that appears to overcome these challenges."

168. In Vasdev 2011 (EX1078), Dr. VanBrocklin described developing a small molecule ¹⁸F-labeled radiotracer with a quinazoline scaffold for imaging epidermal growth factor receptor (EGFR) expression,²⁵⁸ despite a prior study published in 2008 that said of a radiotracer with a differently-substituted quinazoline pharmacophore: "uptake levels of radiolabeled gefitinib, both in vivo and in vitro, did not correlate with EGFR expression levels or functional status. This unexpected observation was due to high nonspecific, nonsaturable cellular

²⁵⁷ EX1077 (Huang 2020), 723.

²⁵⁸ EX1078 (Vasdev 2011), 2959.

uptake of gefitinib.”²⁵⁹ Also, “the highly nonspecific cellular binding of [¹⁸F]gefitinib may preclude the use of this imaging probe for noninvasive assessment of EGFR receptor status in patients.”

169. In each example, Dr. VanBrocklin continued to develop radiotracers even though the compounds and approaches that preceded him produced unsuccessful results. That is exactly the course of conduct his declaration says a POSA would not undertake. His own body of work therefore confirms that a POSA would not be deterred from developing a promising radiotracer merely because earlier work fell short.

VI. Response to Dr. VanBrocklin’s Opinions Regarding Obviousness of the ’231 Patent Claims Over US-121 and Jansen (Ground 2)

170. Dr. VanBrocklin criticizes my opinions because I did not explain how US-121 would have led a POSA to select an “A” targeting moiety in the scope of the claims. I did not suggest that US-121 would have led a POSA to the particular FAP-binding moiety that I referenced (i.e., Compound 60). I said that Jansen would have led the POSA to Compound 60, for many of the reasons I explained in connection with US-633.²⁶⁰ Dr. VanBrocklin does not address most of the other

²⁵⁹ EX1079 (Su 2008), 1089.

²⁶⁰ EX2047 (VanBrocklin II), ¶¶ 99-101; EX1003 (Zeglis I), ¶¶ 199-203, 205-208.

observations I made about what the US-121 and Jansen publications teach the POSA.

171. As I explained in my First Declaration, a POSA developing a new cancer-targeted radiotracer would have considered successful small-molecule radiotracer designs directed to other tumor-associated proteins.²⁶¹ US-121 is one example. It describes low molecular weight, modular radiotracers directed to PSMA.²⁶² As I explained, US-121 provides extensive guidance to the POSA, including low-molecular-weight radiotracer architectures, use of particular chelator-linker combinations, radionuclide-selection principles, and methods for substituting one validated targeting ligand for another.²⁶³ US-121 also describes particular examples of combinations of specific linkers and specific imaging moieties. Those examples would help reduce the number of variables that would have to be resolved in developing a new radiotracer to be used in tumor imaging by providing tested linker-chelator combinations that could be paired with a similarly sized, validated FAP targeting moiety.²⁶⁴ Using an established architecture in this

²⁶¹ EX1003 (Zeglis I), ¶¶ 179-180, 199-201.

²⁶² EX1003 (Zeglis I), ¶¶ 182-198.

²⁶³ EX1003 (Zeglis I), ¶¶ 181-209; EX1005 (US-121).

²⁶⁴ EX1003 (Zeglis I), ¶¶ 184, 187-193, 205-209; EX1005 (US-121).

way avoids recreating every reporter and linker choice from first principles.

172. Following the design principles for radiopharmaceutical development described in US-121, a POSA would have considered US-121 with Jansen to assemble low-molecular weight radiotracers incorporating Compound 60 as the targeting moiety.²⁶⁵ I also clearly explained that US-121 describes development of low molecular weight radiotracers that target a *different* cancer-specific cell surface protein, called PSMA, not FAP.²⁶⁶ I then explained that Jansen teaches the benefits of targeting FAP, and for describing highly selective FAP-targeting moieties, particularly Compound 60.²⁶⁷ I explained that a POSA would have read Jansen with US-121 because they are directed to the same field of radiotracers that target cell surface proteins to perform imaging of tumors in patients. And I explained that when the POSA did that, they would be motivated to swap out the equivalently sized PSMA small molecule targeting moiety for Compound 60, while retaining the rest of the B-L architecture taught by US-121. I then described several specific examples of Compound 60-based radiotracers that have a B-L-A design described in particular examples in US-121.

²⁶⁵ EX1003 (Zeglis I), ¶¶ 202-215.

²⁶⁶ EX1003 (Zeglis I), ¶¶ 179-183.

²⁶⁷ EX1003 (Zeglis I), ¶¶ 199-215; EX1006 (Jansen), 3053-3065.

173. The specific examples of modified US-121 compounds in my First Declaration meet the B, L, A, and low-molecular-weight limitations for the reasons stated there.²⁶⁸ The same Compound 60 affinity, selectivity, and conjugation evidence discussed for Ground 1 provided a reasonable expectation that those structures would retain FAP binding.²⁶⁹

174. Dr. VanBrocklin did not identify any inaccuracies in my analysis of what US-121 and Jansen taught the POSA. He also did not dispute that a POSA would be able to synthesize the particular examples I illustrated. He also did not suggest that the radiotracers I illustrated that use the US-121 architecture and a Compound 60 targeting moiety would not be viable FAP-targeting radiotracers.

VII. Additional Observations on Dr. VanBrocklin's Opinions

A. JHU's Expert and Inventor Agree that Imaging Agents Require More Than Just a B-L-A Structure

175. During his deposition, Dr. VanBrocklin seemed to appreciate that imaging agents did require more than just the ability to bind to FAP to be used in

²⁶⁸ EX1003 (Zeglis I), ¶¶ 207-215.

²⁶⁹ EX1003 (Zeglis I), ¶¶ 138-143, 207-215.

imaging applications.²⁷⁰ Dr. Pomper explained in his declaration what that “more” is—it is ***high selectivity for FAP relative over PREP***. As Dr. Pomper explained:

[t]here are numerous important parameters which need to be taken into consideration for successfully developing ***a FAP imaging agent***. Those parameters include, for example, affinity for FAP, ***selectivity (specificity) for FAP***, ease of synthesis, and biodistribution, and the like. ***It is important for the agent to have both high affinity and high specificity to bind to the target protein*** that is associated with a medical condition. ***The high specificity allows the imaging agent to bind selectively to the target protein*** associated with the medical condition ***but not other proteins*** unrelated to the medical condition. ***A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein.***²⁷¹

²⁷⁰ EX1069 (VanBrocklin Tr.), 216:2-22 (“As I said, as I stated, the utility of these first and foremost is that they bind to FAP, right? That’s what — that’s what this says. Then if you want to use them further, ... , ***they can be used as imaging agents, but you would have to look at their characteristics further, right, and determine from the molecules that you make*** that are first and foremost FAP-targeting agents, ***which of these then would be suitable for downstream uses beyond the FAP-targeting ability*** that the molecule has as a part of this patent.”) (emphasis added).

²⁷¹ EX1002 (US-201 FW), 363 (¶ 31) (emphasis added).

B. Dr. VanBrocklin's Testimony Confirms That Assembling a Claimed FAP-Targeting B-L-A Compound Does Not Guarantee Unexpectedly Strong Interaction with FAP

176. As I explained in my First Declaration, the B-L-A design was not new in 2017— it was a well-known design used for radiopharmaceuticals.²⁷² Dr. VanBrocklin recognized that knowledge of the well-known “B-L-A” design for a radiopharmaceutical could not help the POSA resolve the uncertainty of producing the full scope of B-L-A compounds that the claims cover. That is because, as he explained, the B-L-A design did not always improve or even retain the affinity of FAP targeting moieties. As he explained:

A. ... it was shown in data from the '633 patent that some of these structures that had larger — that had linkers actually had poorer binding affinity to — or poorer interaction with FAP, and so that is what this was in reference to.

Q. And just two parts of that question I want to clarify. So the molecule after changes might have poor binding to FAP, but it still is included in the scope of the claim, right, because it's still binding to FAP.

A. If the molecule still binds to FAP, that would be included in the scope of the -- scope of the claim.²⁷³

²⁷² EX1009 (Jamous), 3881, EX1003 (Zeglis I), ¶¶ 27-28.

²⁷³ EX1069 (VanBrocklin Tr.), 234:2-235:5.

177. I note that Dr. VanBrocklin's testimony confirms my explanations in § IV that a POSA would have believed that conversion of a FAP-targeting moiety (A) into a B-L-A form would not always increase the affinity or selectivity of the resulting B-L-A compound.

C. Jansen's SAR Data Demonstrates That Conjugation On the Quinolinyl Ring Expectedly Led to Large Variations in Selectivity

178. I explained in my First Declaration that substitutions at different positions of the quinolinyl ring of 4-quinolinoyl-Gly-cyanoPro compounds have variable effects on the affinity and selectivity of the compound for FAP.²⁷⁴ The SAR data reported in the Jansen publications and Dr. Pomper's work show that, the point of attachment of a substituent on the quinolinyl ring alone can alter FAP/PREP selectivity by several orders of magnitude, independent of any attachment of a B-L assembly.²⁷⁵

- (a) **Bromine:** C⁵ (Compound 26, SI = **4545.5**), C⁷ (Compound 32, SI = **193.5**), and C⁸ (Compound 34, SI = **1.0**).²⁷⁶

²⁷⁴ EX1003 (Zeglis I), ¶¶ 139, 142.

²⁷⁵ See Appendix D, below (Jansen SAR data).

²⁷⁶ EX1007 (Jansen 2013), 493; Appendix D, below.

- (b) **Chlorine:** C⁵ (Compound 25, SI = **1697**), C⁶ (Compound 27, SI = **60**), C⁷ (Compound 31, SI = **197.2**), and C⁸ (Compound 33, SI = **1.8**).²⁷⁷
- (c) **Methyl:** C² (Jansen 2013 Compound 19, SI = **1.0**), C⁶ (Jansen Compound 53, SI = **2116.3**), and C⁷ (Jansen Compound 52, SI = **72.5**).²⁷⁸
- (d) **Fluorine:** C³ (Pomper Ref. Compound H, SI = **3**), C⁵ (Ref. Compound C, SI = **20**), C⁶ (Ref. Compound D, SI = **403**),²⁷⁹ C⁷ (Ref. Compound F, SI = **241**), and C⁸ (Ref. Compound G, SI = **17**).²⁸⁰

179. Jansen's work also showed that affinity/selectivity could vary dramatically based on the particular stereoisomer selected—Jansen's Compounds 58 and 59 are mono-fluorinated stereoisomers, with Compound 58 bearing the 4S-fluoro configuration and Compound 59 bearing the 4R-fluoro configuration.²⁸¹ Compound 58 exhibited FAP and PREP IC₅₀ values of 0.0033 μM and 0.29 μM,

²⁷⁷ EX1007 (Jansen 2013), 493; Appendix D, below.

²⁷⁸ EX1007 (Jansen 2013), 493; EX1006 (Jansen), 3061.

²⁷⁹ Jansen-2013 reported data showing that the same compound with a C⁶-fluorine had a selectivity of 59.2 (Compound 29). EX1007 (Jansen 2013), 493; Appendix D, below.

²⁸⁰ EX1002 (US-201 FW), 365-366 (¶ 42); Appendix C-6, below.

²⁸¹ EX1006 (Jansen), 3061.

respectively, and an SI of 87.8, whereas Compound 59 exhibited FAP and PREP IC_{50} values of 1.0 μM and $>100 \mu M$, respectively, and an SI of >100 .²⁸² Although Jansen reported an SI of >100 for Compound 59 compared with 87.8 for Compound 58, Compound 59's approximately 300-fold poorer FAP affinity would have caused a POSA considering both affinity and selectivity to deprioritize Compound 59.²⁸³ The magnitude of the affinity difference between these stereoisomers demonstrates that gross structural similarity alone would not have allowed a POSA to reliably predict FAP binding activity.²⁸⁴ Dr. VanBrocklin's Declaration does not address the effect of B-L conjugation on a stereoisomer "A" moiety.

180. As I explained in my First Declaration—Jansen reported conflicting data for substitutions at the C^5 -position, which resulted in very high calculated FAP/PREP selectivity for Jansen 2013 Compounds 25 (approximately 1,697) and 26 ($>4,545$) and Jansen Compound 53 (2,116.3), but resulted in poor FAP affinity and/or selectivity for Jansen Compounds 57 (FAP IC_{50} 16.6 μM ; SI 0.08), 62 (FAP

²⁸² EX1006 (Jansen), 3062 (Table 5).

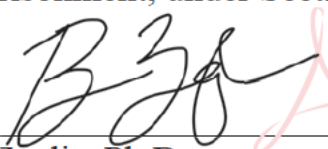
²⁸³ EX1006 (Jansen), 3062; EX1003 (Zeglis I), ¶ 118.

²⁸⁴ EX1006 (Jansen), 3061-3062; EX1003 (Zeglis I), ¶¶ 49, 139, 142.

IC₅₀ 9.0 μM; SI 1.0), and 63 (FAP IC₅₀ 7.2 μM; SI 2.3).²⁸⁵ This further demonstrates that a POSA would seek to attach a linker at position-6 of the quinolinyl ring over position-5.

²⁸⁵ EX1003 (Zeglis I), ¶¶ 139, 142; EX1007 (Jansen 2013), 493; EX1006 (Jansen), 3061-3062.

I, Brian Zeglis, do hereby declare and state, that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, under Section 1001 of Title 18 of the United States Code.


Digitally signed by Brian
Zeglis
Date: 2026.08.20 16:05:25
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Brian Zeglis, Ph.D.

Executed on: August 20th, 2026

Appendix A: Exhibit List

No.	Exhibit Description	Short Name
1001	U.S. Patent No. 11,938,201	US-201
1002	File History of U.S. Patent No. 11,938,201	US-201 FW
1003	Declaration of Dr. Brian Zeglis	Zeglis I
1004	U.S. Patent Publication 2010/0098633	US-633
1005	U.S. Patent Publication 2012/0009121	US-121
1006	Jansen et al., “Extended Structure–Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP),” J. Med. Chem, 57:3053–3074 (2014)	Jansen
1007	Jansen et al., “Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold,” ACS Med. Chem. Lett., 4:491–496 (2013)	Jansen 2013
1008	Meletta et al., “Evaluation of the Radiolabeled Boronic Acid-Based FAP Inhibitor MIP-1232 for Atherosclerotic Plaque Imaging,” Molecules, 20:2081–2099 (2015)	Meletta
1009	Jamous et al., “Synthesis of Peptide Radiopharmaceuticals for the Therapy and Diagnosis of Tumor Diseases,” Molecules, 18:3379–3409 (2013)	Jamous
1013	Price et al., “Matching chelators to radiometals for radiopharmaceuticals,” Chem. Soc. Rev., 43:260–290 (2014)	Price
1016	Brennen et al., “Rationale Behind Targeting Fibroblast Activation Protein–Expressing Carcinoma-Associated Fibroblasts as a Novel Chemotherapeutic Strategy,” Mol. Cancer Ther., 11(2):257–266 (2012)	Brennen 2012

No.	Exhibit Description	Short Name
1017	Sarko et al., “Bifunctional Chelators in the Design and Application of Radiopharmaceuticals for Oncological Diseases,” <i>Current Medicinal Chem.</i> , 19:2667–2688 (2012)	Sarko
1018	Fichna et al., “Synthesis of Target-Specific Radiolabeled Peptides for Diagnostic Imaging,” <i>Bioconjugate Chem.</i> , 14:3–17 (2003)	Fichna
1022	Liu et al., “Fibroblast activation protein, A potential therapeutic target in cancer,” <i>Cancer Biology & Ther.</i> , 13(3):123–129 (2012)	Liu
1033	Mach et al., “Challenges for Developing PET Tracers: Isotopes, Chemistry, and Regulatory Aspects,” 5(2): 131–153 (2010)	Mach
1034	Meyer et al., “Click Chemistry and Radiochemistry: The First 10 Years,” <i>Bioconjugate Chem.</i> , 27:2791–2807 (2016)	Meyer 2016
1036	Maurer et al., “Current use of PSMA-PET in prostate cancer management,” <i>Nature Reviews: Urology</i> , 13:226–235 (2016)	Maurer
1044	U.S. Patent Publication 2014/0357650	US-650
1047	Tsai et al., “Substituted 4-carboxymethylpyroglutamic Acid Diamides as Potent and Selective Inhibitors of Fibroblast Activation Protein,” <i>J. Med. Chem.</i> 53(18):6572–6583 (2010)	Tsai
1052	Zhou et al., “Radiolabeled Cyclic RGD Peptides as Radiotracers for Imaging Tumors and Thrombosis by SPECT,” <i>Theranostics</i> , 1:58–82 (2011)	Zhou
1053	U.S. Patent Publication 2011/0064657	US-657
1057	PCT/US2022/023374	Pomper PCT

No.	Exhibit Description	Short Name
1064	Fulop et al., “Prolyl Oligopeptidase: An Unusual β -Propeller Domain Regulates Proteolysis,” <i>Cell</i> , 94:161–170 (1998)	Fulop
1065	Ganguly et al., “A high-affinity [^{18}F]-labeled phosphoramidate peptidomimetic PSMA-targeted inhibitor for PET imaging of prostate cancer,” <i>Journal of Nuclear Medicine and Biology</i> , 42:780–787 (2015)	Ganguly
1066	Dannoon et al., “Structure—Activity Relationship of ^{18}F -Labeled Phosphoramidate Peptidomimetic Prostate-Specific Membrane Antigen (PSMA)-Targeted Inhibitor Analogues for PET Imaging of Prostate Cancer,” <i>Journal of Medicinal Chemistry</i> , 59:5684–5694 (2016)	Dannoon
1069	Transcript of the Deposition of Dr. Henry VanBrocklin, July, 29, 2026	VanBrocklin Tr.
1070	Second Declaration of Dr. Brian Zeglis	Zeglis II
1071	Johns Hopkins University Production Records	JHU Production Records
1072	Frangioni, “In vivo near-infrared fluorescence imaging,” <i>Current Opinion in Chemical Biology</i> , 7:626–634 (2003)	Frangioni
1074	Arruebo et al., “Assessment of Evolution of Cancer Treatment Therapies,” <i>Cancers</i> , 3:3279–3330 (2011)	Arruebo
1075	FDA and EMA Access Data	FDA and EMA Data
1076	Walsh et al., “Biopharmaceutical benchmarks 2022,” <i>Nature Biotechnology</i> , 40:1722-1760 (2022)	Walsh
1077	Huang et al., “The Synthesis and Structural Requirements for Measuring Glucocorticoid Receptor Expression In Vivo with $\pm$ ^{11}C -YJH08	Huang

No.	Exhibit Description	Short Name
	PET,” Journal of Nuclear Medicine, 62:(5) 723–731 (2020)	
1078	Vasdev et al., “Metabolic stability of 6,7-dialkoxy-4-(2-, 3- and 4-[¹⁸ F]fluoroanilino)quinazolines, potential EGFR imaging probes,” Bioorganic & Medicinal Chemistry, 19:2959–2965 (2011)	Vasdev
1079	Su et al., “Evaluation of [¹⁸ F]getfitinib as a molecular imaging probe for the assessment of the epidermal growth factor receptor status in malignant tumors,” European Journal of Nuclear Medicine and Molecular Imaging, 35:1089–1099 (2008)	Su
1080	BPS Bioscience Inc., FAP His-Tag Recombinant FAP 80100, https://bpsbioscience.com/fap-his-tag-recombinant-80100	BPS FAP Assay
1081	Biotechne R&D Systems, Recombinant Human Fibroblast Activation Protein α /FAP Catalog Number 3715-SE Product Datasheet, https://biotechne.com/p/proteins-enzymes/recombinant-human-fap-protein-cf_3715-se#product-specifications	R&D FAP Assay
1082	Baker et al., “Influence of fluorophore and linker composition on the pharmacology of fluorescent adenosine A1 receptor ligands,” British Journal of Pharmacology, 159:772-786 (2010)	Baker
2001	Declaration of Dr. Henry VanBrocklin	VanBrocklin I
2003	Jansen et al., “Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold,” Med. Chem. Comm, (2014)	Jansen 2014
2024	Poplawski et al., “Identification of Selective and Potent Inhibitors of Fibroblast Activation Protein and Prolyl Oligopeptidase,” Journal of Medicinal Chemistry, 56(9):3467-3477 (2013)	Poplawski

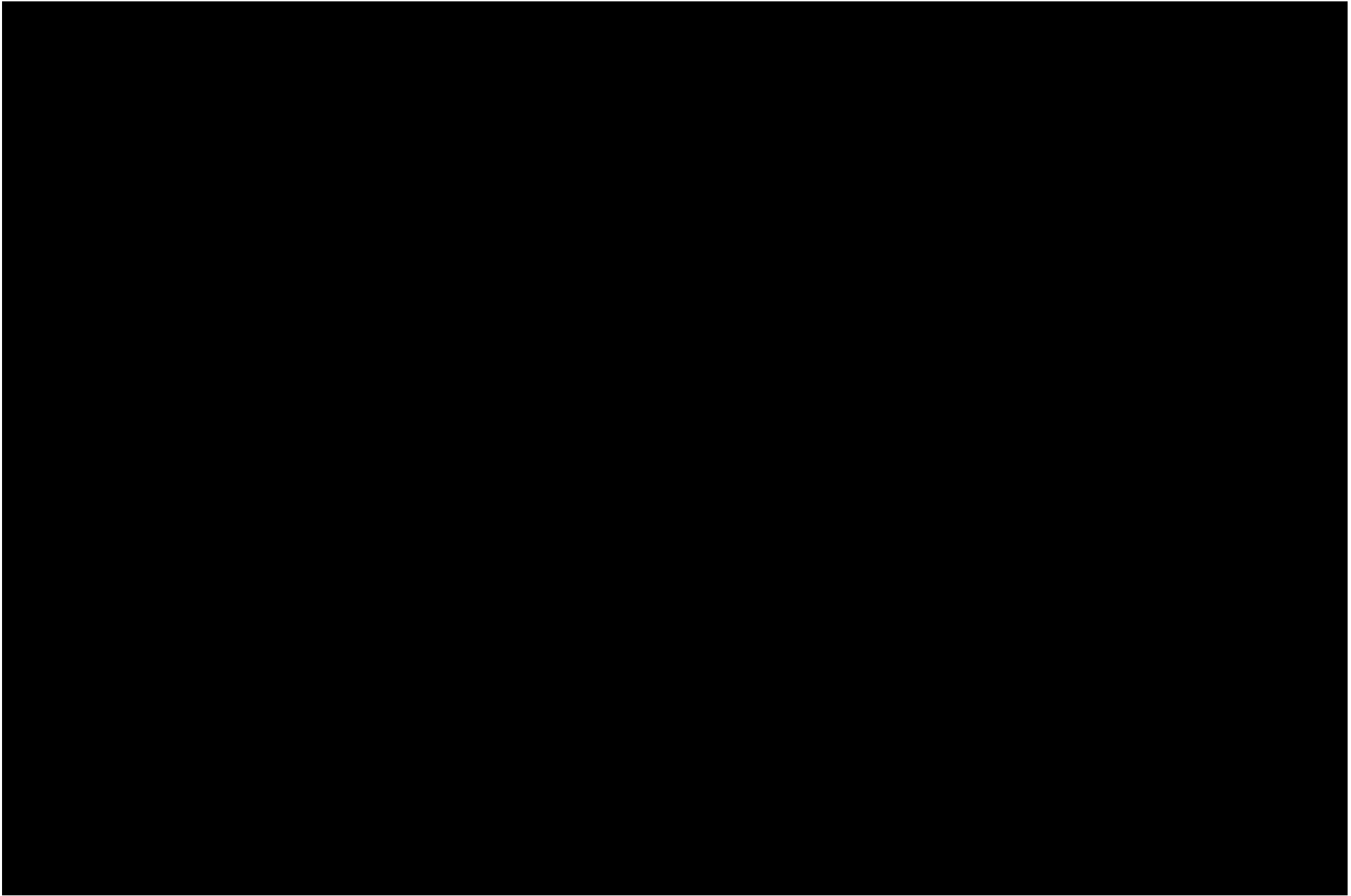
No.	Exhibit Description	Short Name
2027	Transcript of the Deposition of Dr. Brian Zeglis, March 11, 2026	Zeglis Tr.
2028	Sugiara et al., “Radiolabeling Strategies for Tumor-Targeting Proteinaceous Drugs,” Mol. 19:2132-2165 (2014)	Sugiara
2030	Siwowska et al., “Preclinical Comparison of Albumin-Binding Radiofolates: Impact of Linker Entities on the in Vitro and in Vivo Properties,” Molecular Pharmaceutics, 14(2):525-532 (2017)	Siwowska
2042	Zeglis et al., “Chemoenzymatic Strategy for the Synthesis of SiteSpecifically Labeled Immunoconjugates for Multimodal PET and Optical Imaging,” Bioconjugate Chemistry, 25(12): 2123–2128 (November 24, 2014)	Zeglis 2014
2047	Second Declaration of Dr. Henry VanBrocklin	VanBrocklin II
2034	Aetgeerts et al., “Structural and Kinetic Analysis of the Substrate Specificity of Human Fibroblast Activation Protein α ,” Journal of Biological Chemistry, 280(20):19441-19444 (2005)	Aetgeerts
2036	Rüger et al., “In vivo near infrared fluorescence imaging of FAP expressing tumors with activatable FAP-targeted single-chain Fv-immunoliposomes,” Journal of Controlled Release, 184:1-10 (2014)	Rüger
2037	LeBeau et al., “Targeting the cancer stroma with a fibroblast activation protein activated promelittin protoxin,” Molecular Cancer Therapy, 8(5): 1378-1386 (2009)	LeBeau
2038	Huang et al., “Evaluation of the tumor targeting of a FAP α -based doxorubicin prodrug,” Journal of Drug Targeting, 19(7): 487-496	Huang 2011
2040	Reiner at al., “Harnessing the Bioorthogonal Inverse Electron Demand Diels-Alder	Zeglis 2015

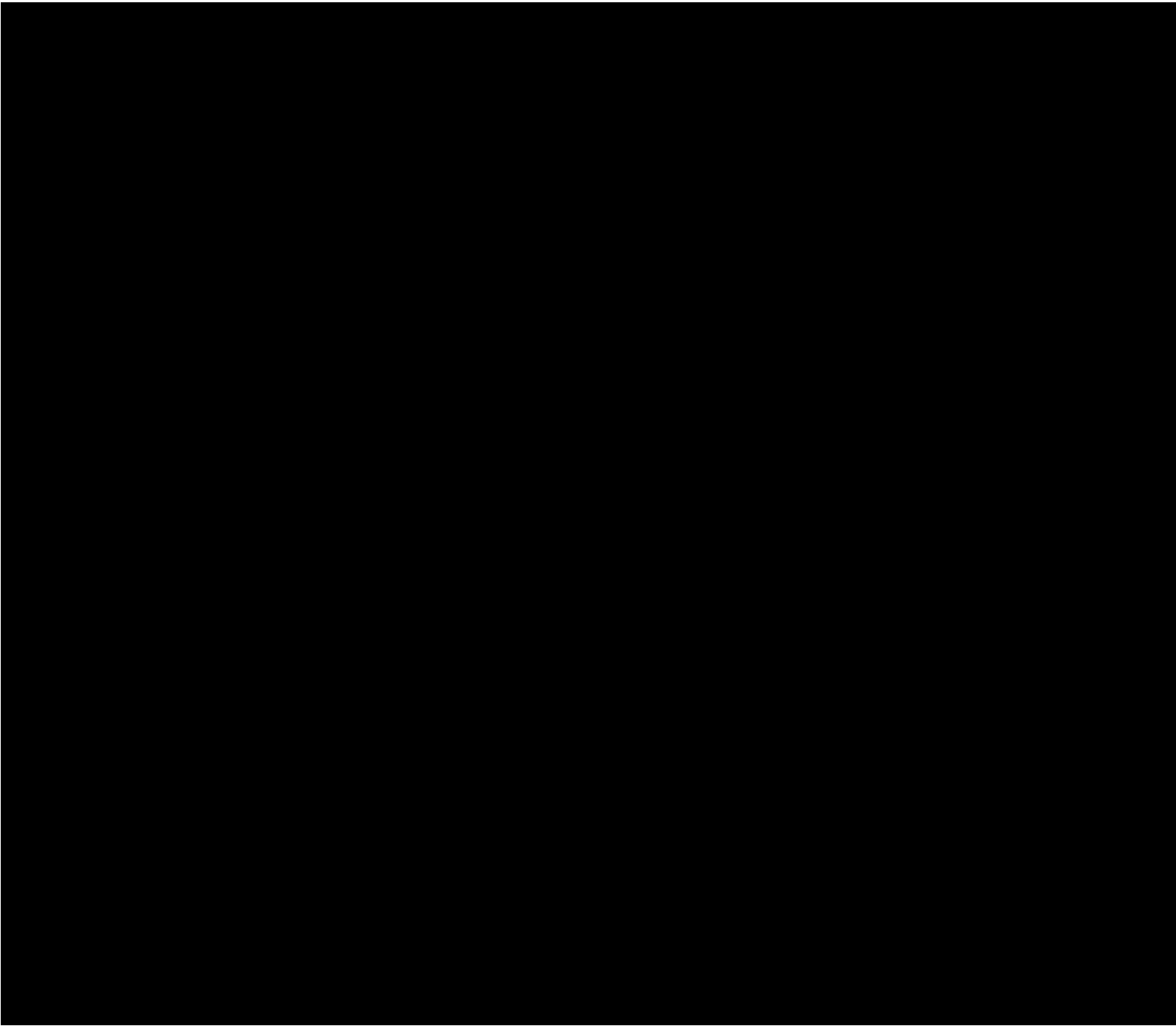
No.	Exhibit Description	Short Name
	Cycloaddition for Pretargeted PET Imaging,” Journal of Visualized Experiments, 96 (2015)	
2041	Adumeau et al., “Site-Specifically Labeled Immunoconjugates for Molecular Imaging—Part 1: Cysteine Residues and Glycans,” Molecular Imaging Biology, 18:1-17 (2016)	Zeglis 2016

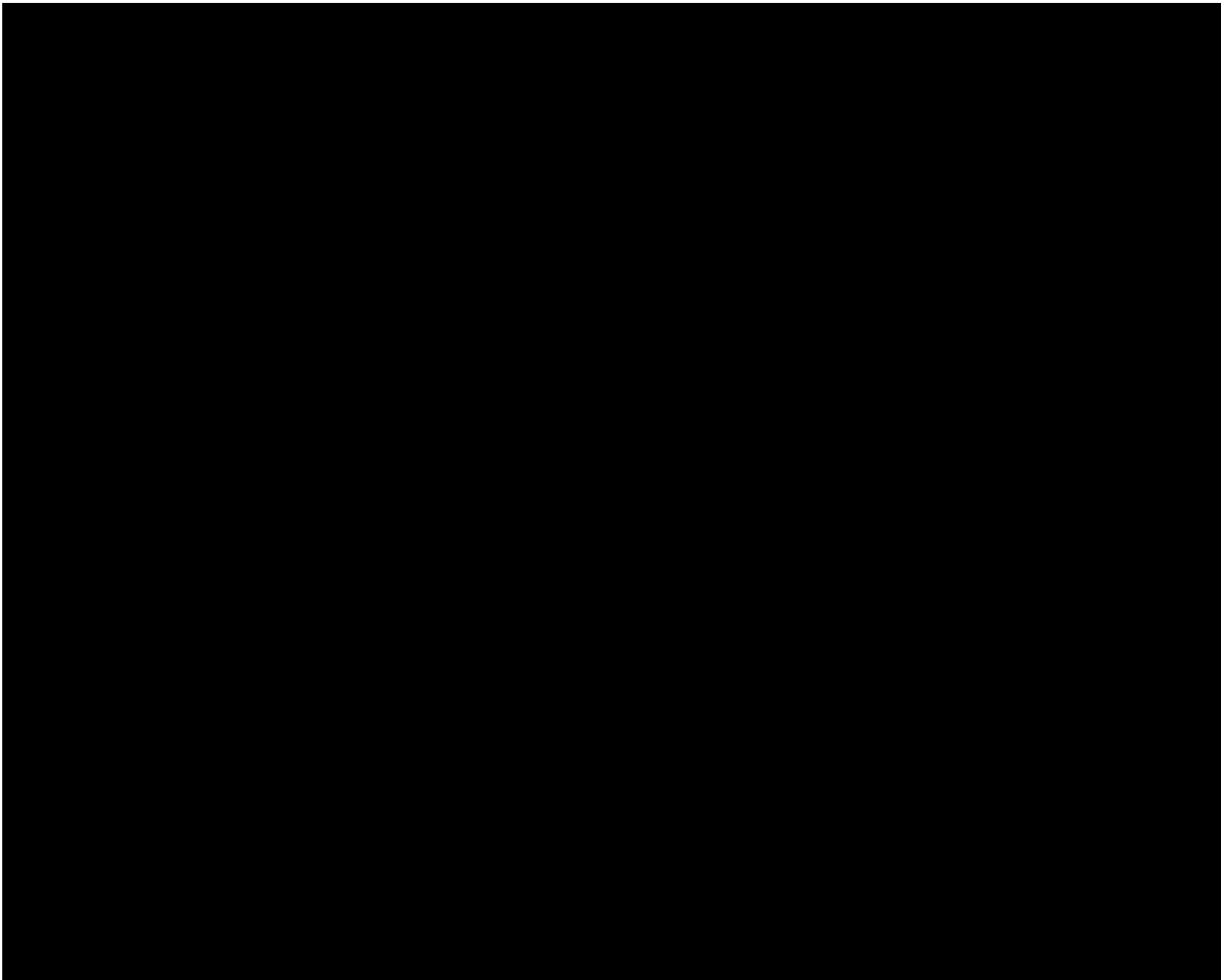
Appendix B: Antibody Product Status

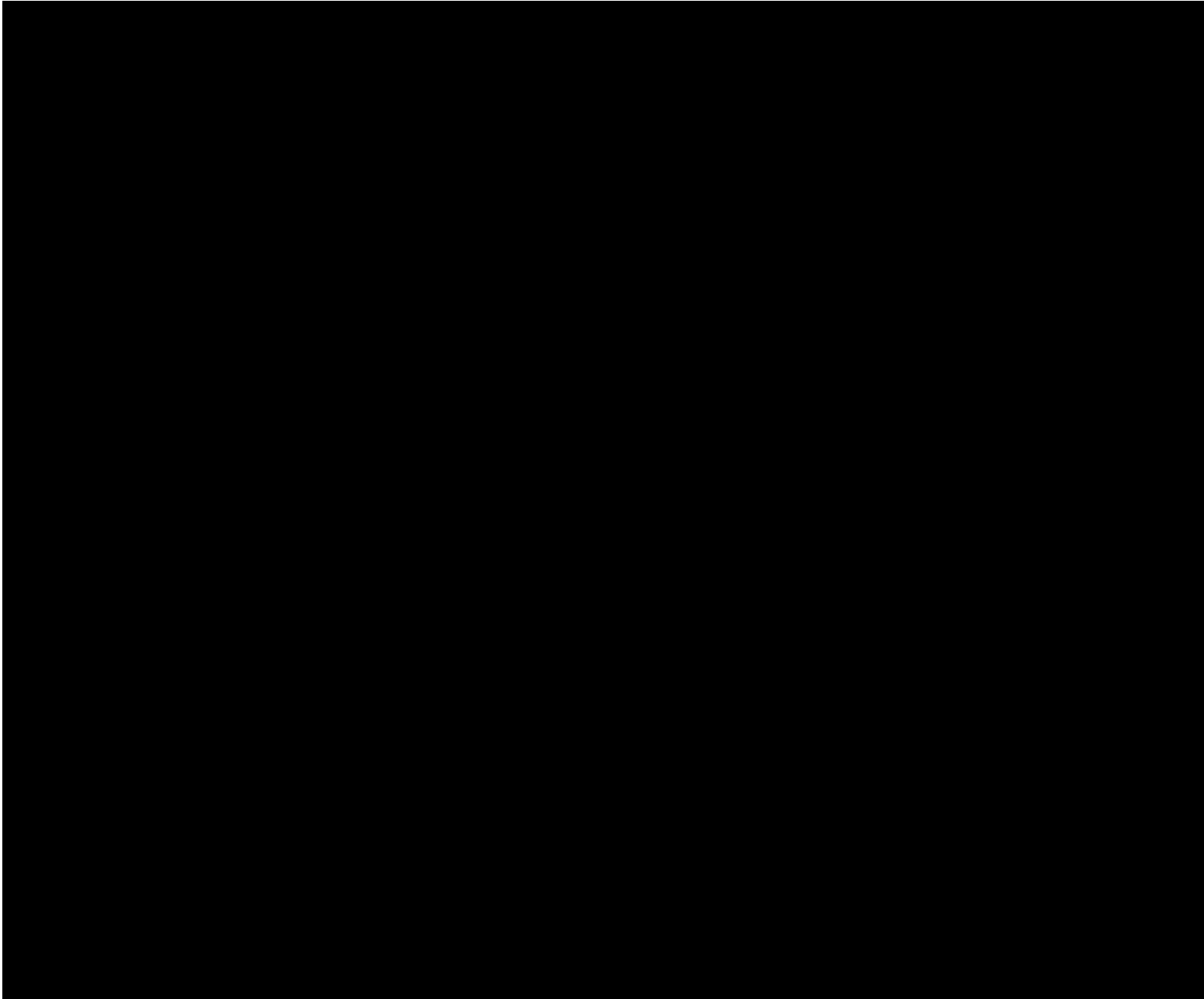
Antibody (Trade Name)	Radionuclide & Purpose	Approval Date	Withdrawal Date
Imciromab-Pentetate (MyoScint)	In-111; SPECT imaging	1989 (US)	1993
Satumomab Pendetide (OncoScint CR/OV)	In-111; SPECT imaging	1992 (US)	2002
Arcitumomab (CEA-Scan)	Tc-99m; SPECT imaging	1996 (US)	2005
Noferumomab Merpentan (Verluma)	Tc-99m; SPECT imaging	1996 (US)	1999
Capromab Pendetide (ProstaScint)	In-111; SPECT imaging	1996 (US)	2018
Ibritumomab Tiuxetan (Zevalin)	Y-90 for radiotherapy (β -emitter)	2002 (US)	N/A
Tositumomab (Bexxar)	I-131 for radiotherapy (β/γ -emitter)	2004 (US)	2013
Fanolesomab (NeutroSpec)	Tc-99m; SPECT imaging	2004 (US)	2005
Igovomab (Indimacis-125)	In-111; SPECT imaging	1996 (EU)	1999
Sulesomab (LeukoScan)	Tc-99m; SPECT imaging	1997 (EU)	2018
Votumumab (HumaSPECT)	Tc-99m; SPECT imaging	1998 (EU)	2003

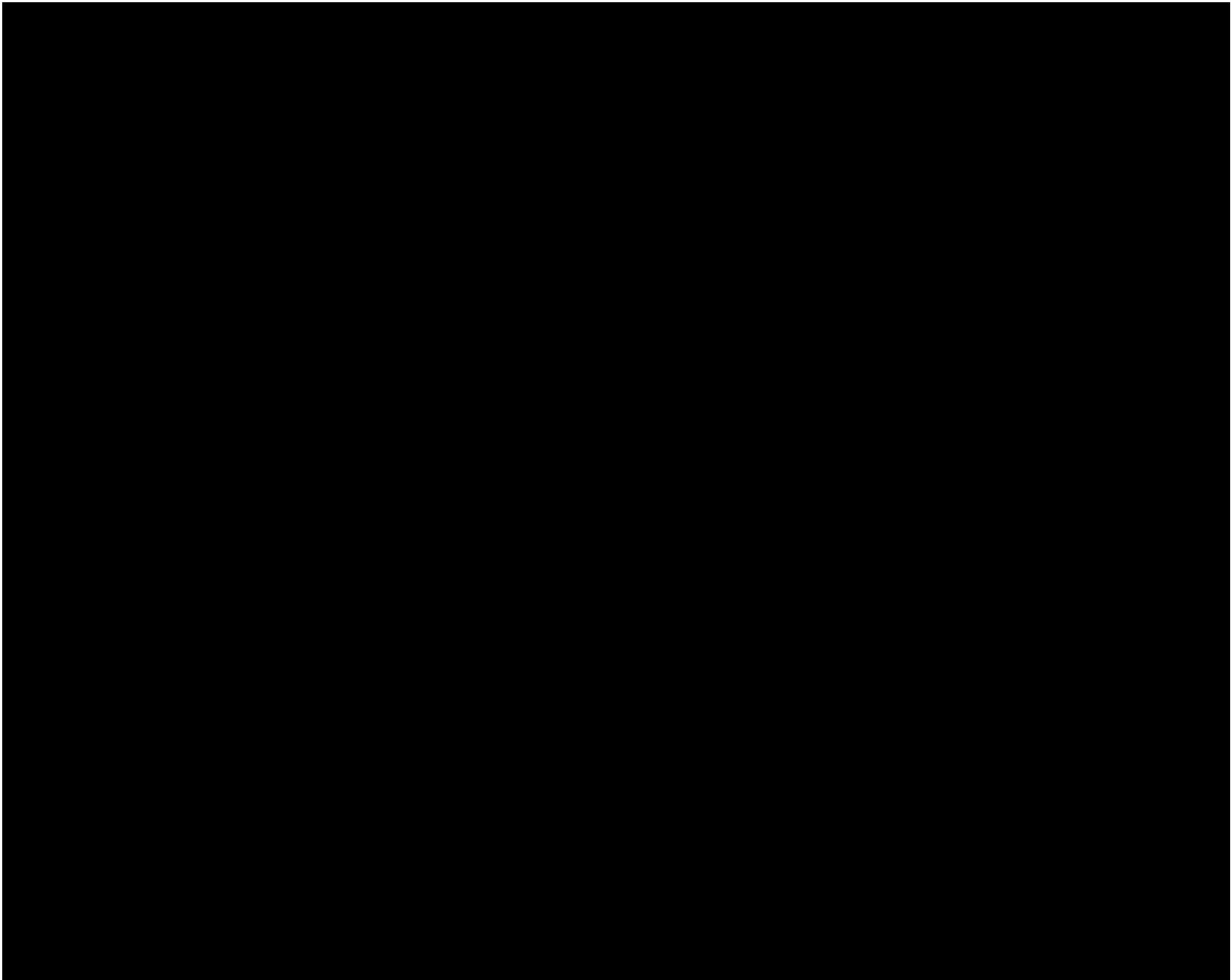
See EX1075 (FDA/EMA Data), 2 (OncoScint), 5, 39 (CEA-Scan), 8-10 (Noferumomab), 12-13 (ProstaScint), 15 (Zevalin), 36 (Bexxar), 47 (Indimacis 125), 54 (LeukoScan), 63 (HumaSPECT); EX1074 (Arruebo), 3296 (MyoScint, Zevalin, Indimacis-125), 3302 (OncoScint, LeukoScan), 3289 (CEA-Scan, ProstaScint), 3299 (Verluma), 3304 (Bexxar), 3294 (NeutroSpec), 3305 (HumaSPECT); EX1076 (Walsh), 1756 (OncoScint), 1755 (CEA-Scan, Verluma, ProstaScint, Zevalin, Bexxar, NeutroSpec, LeukoScan, HumaSPECT).

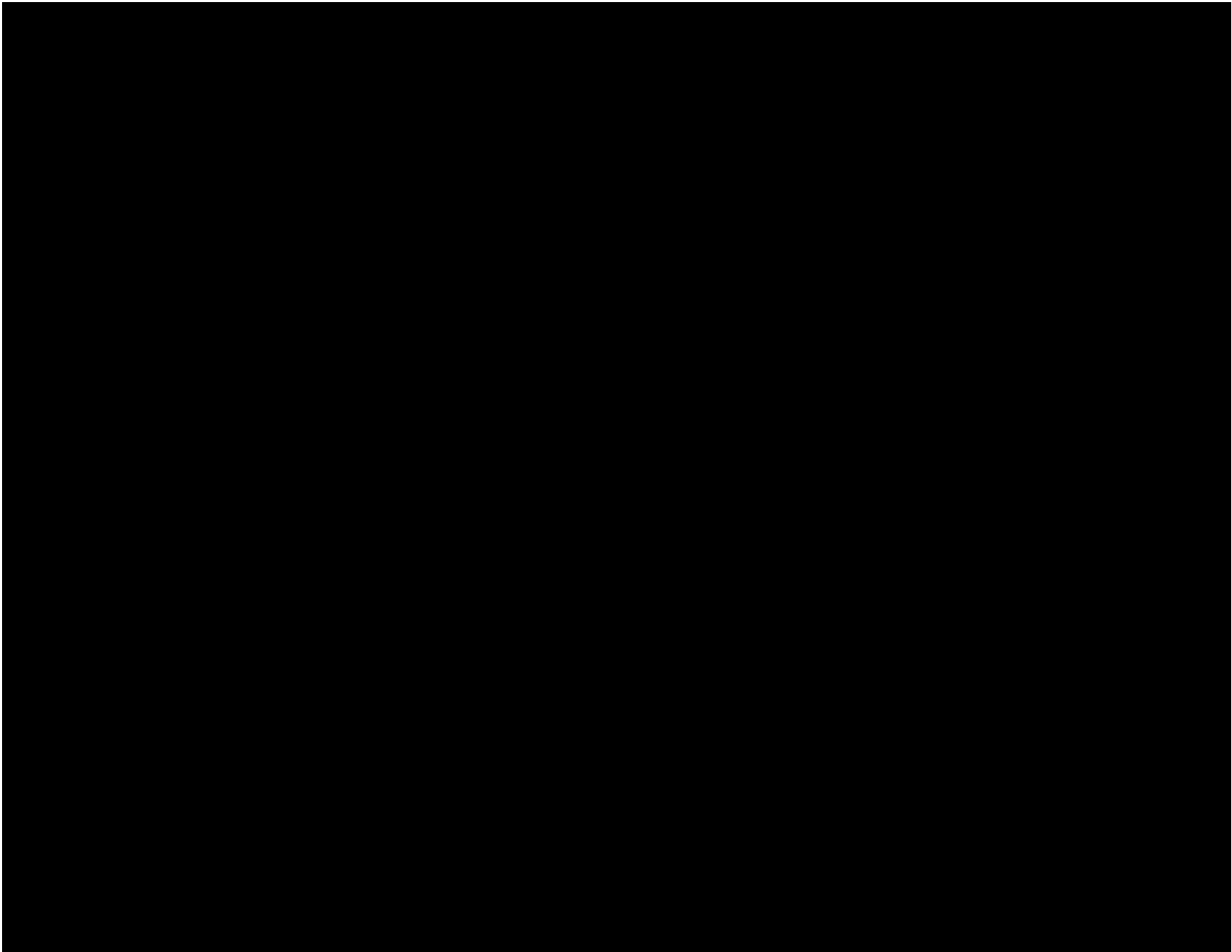




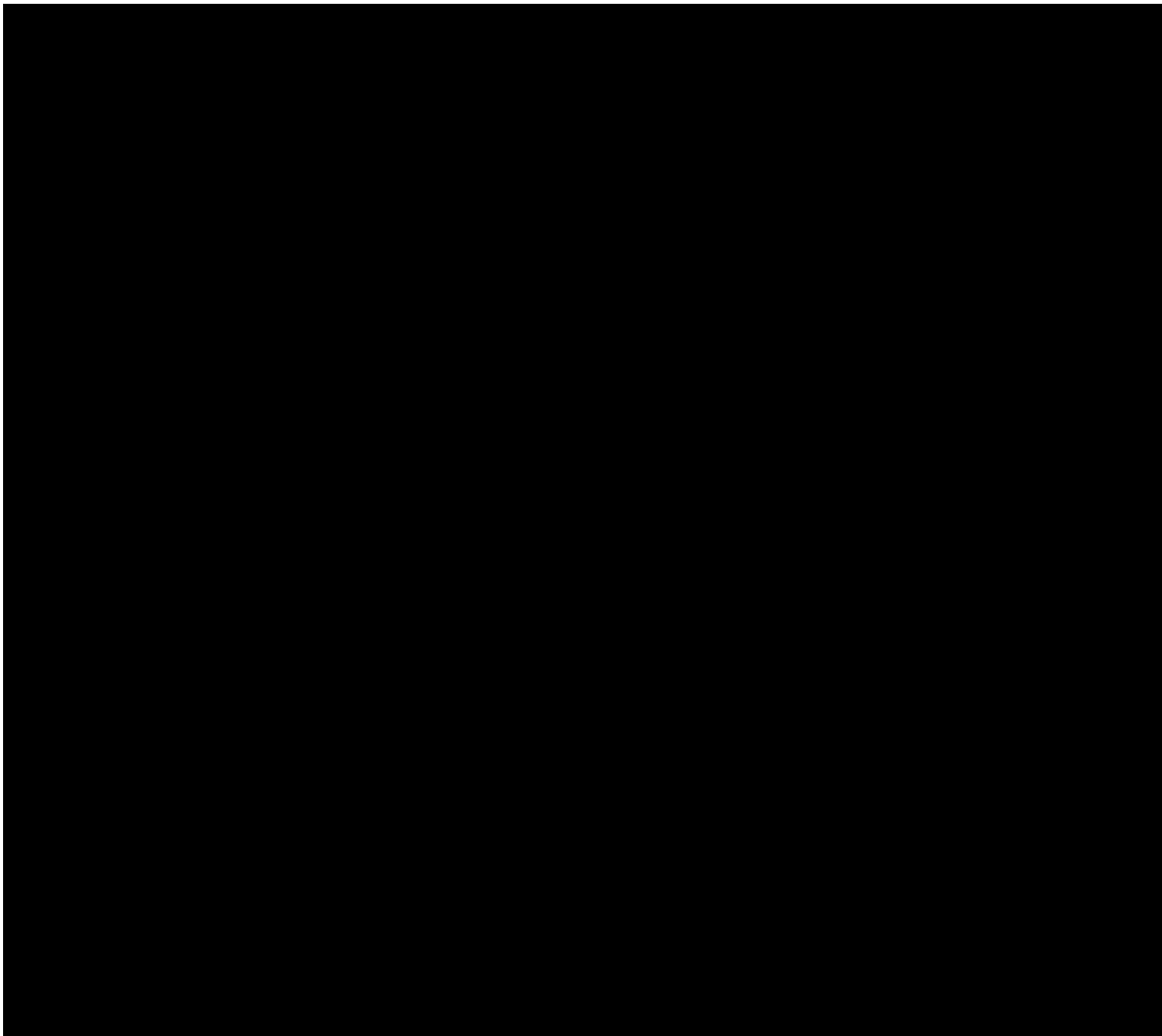


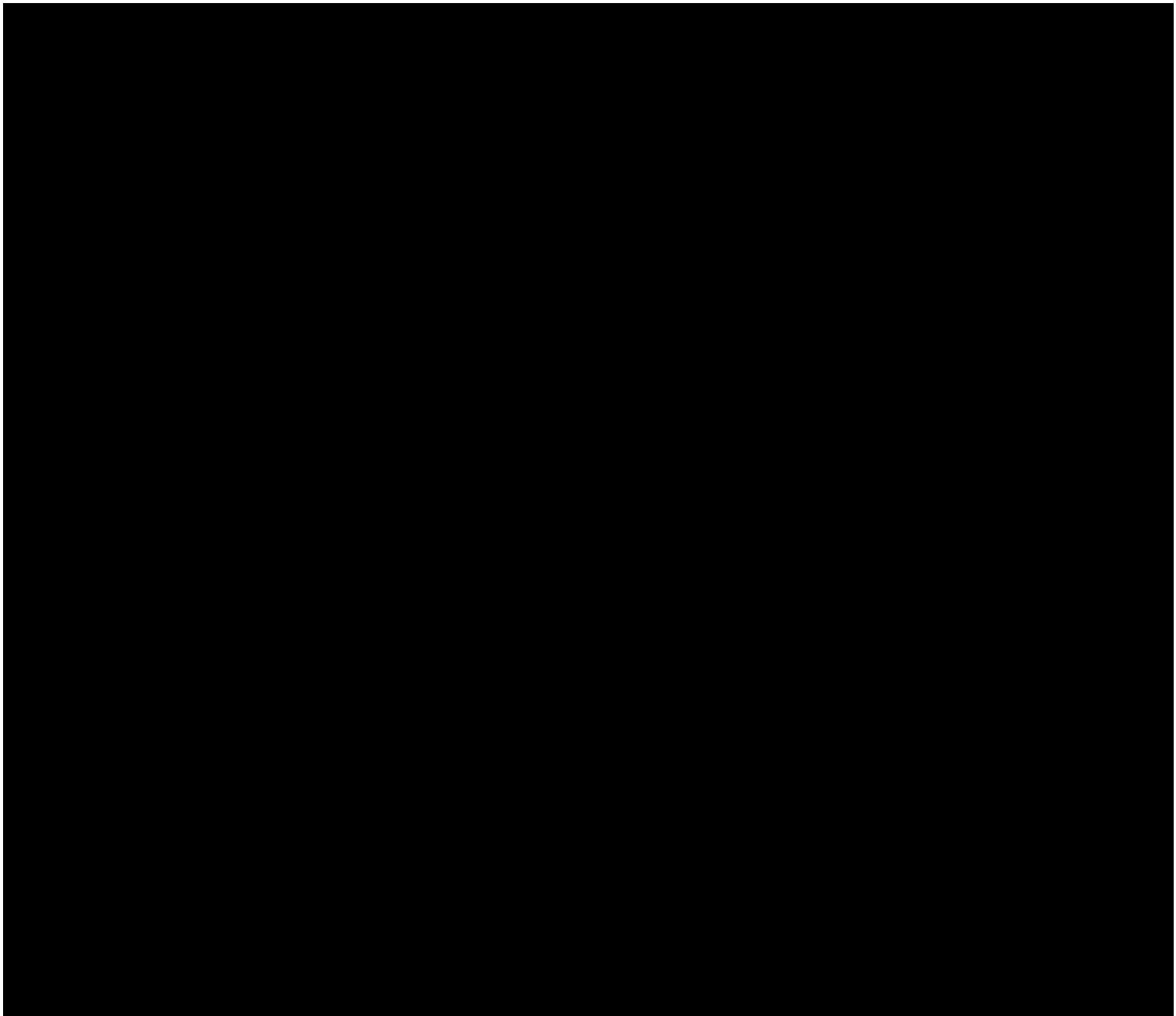


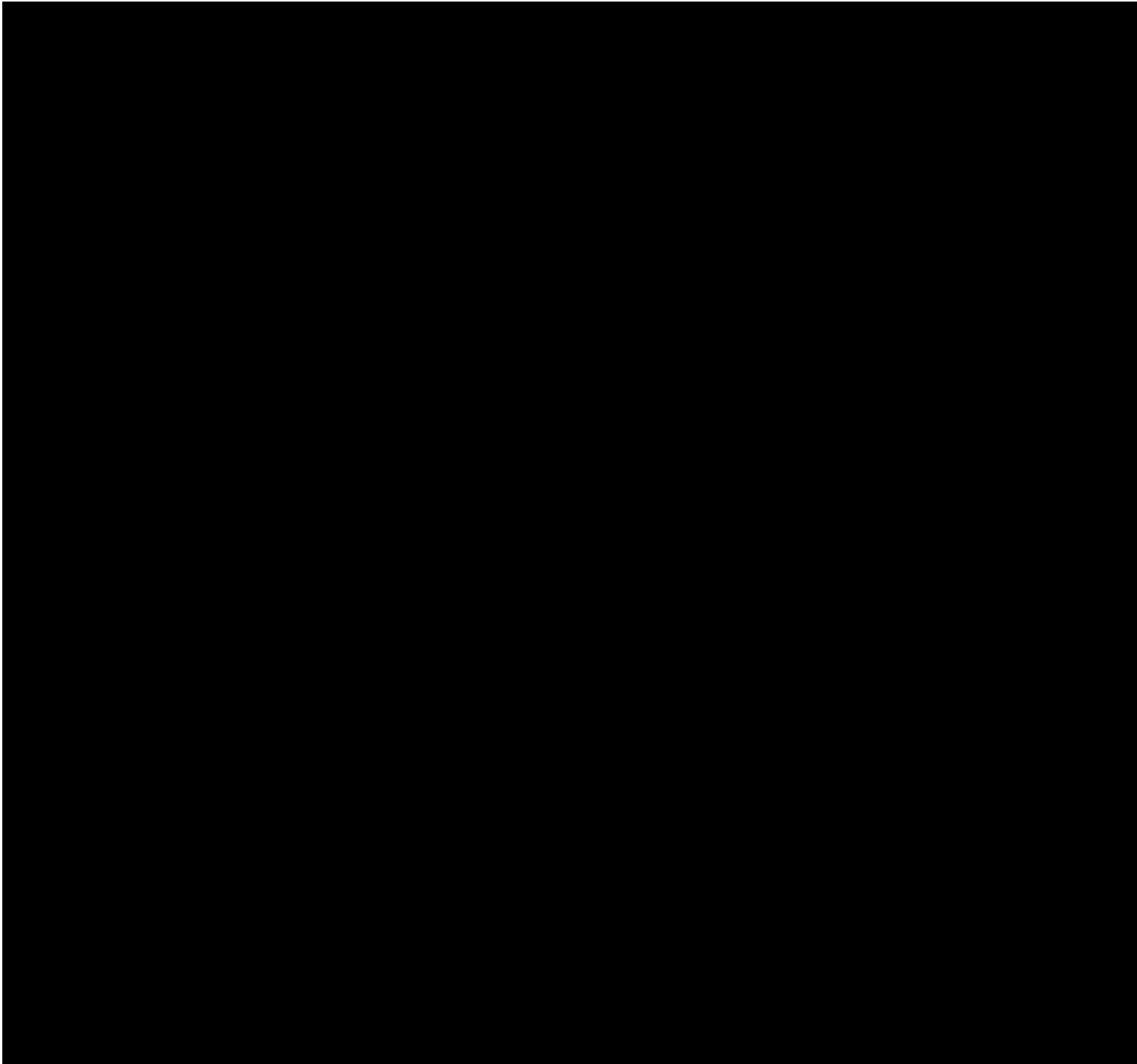


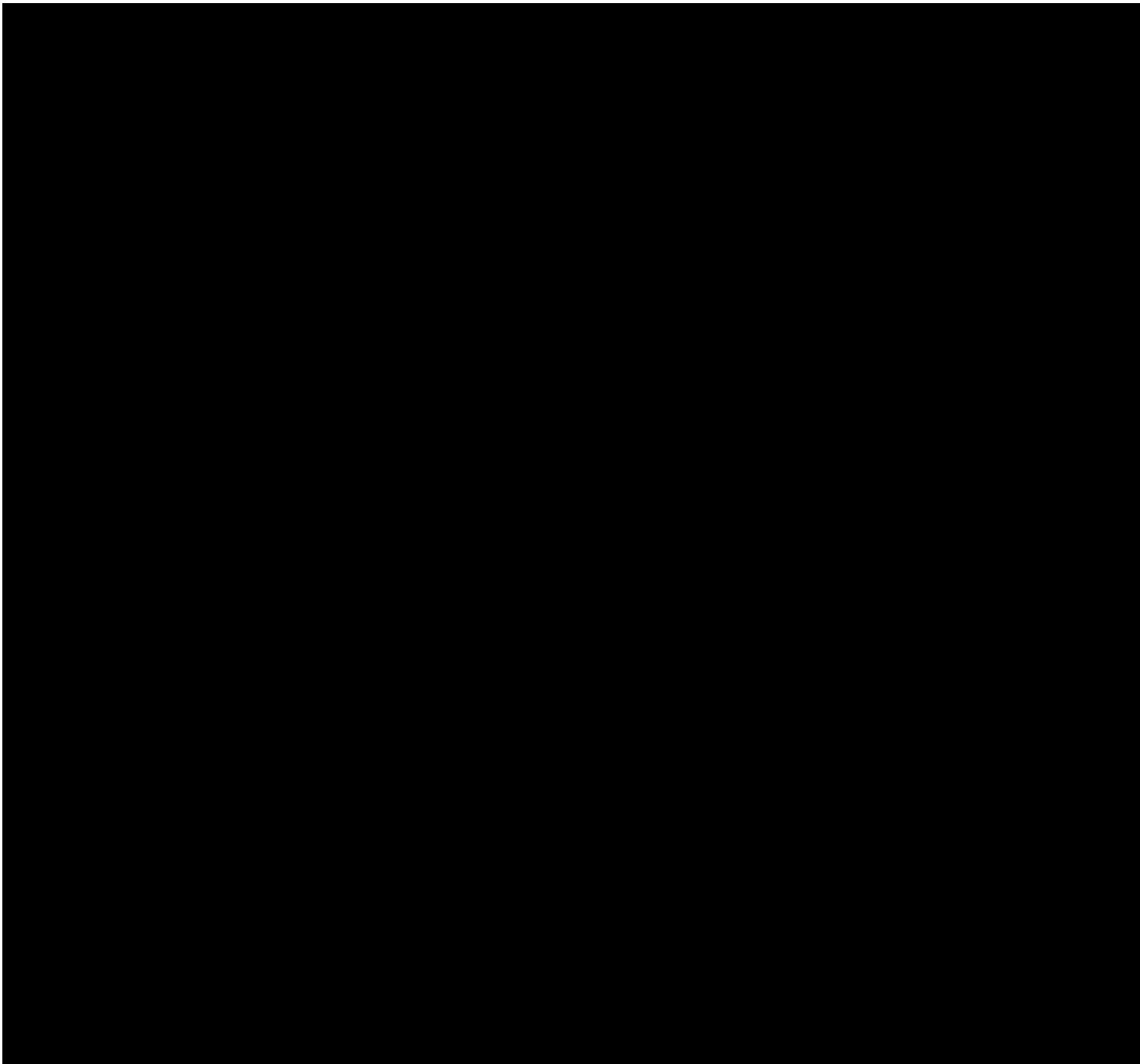




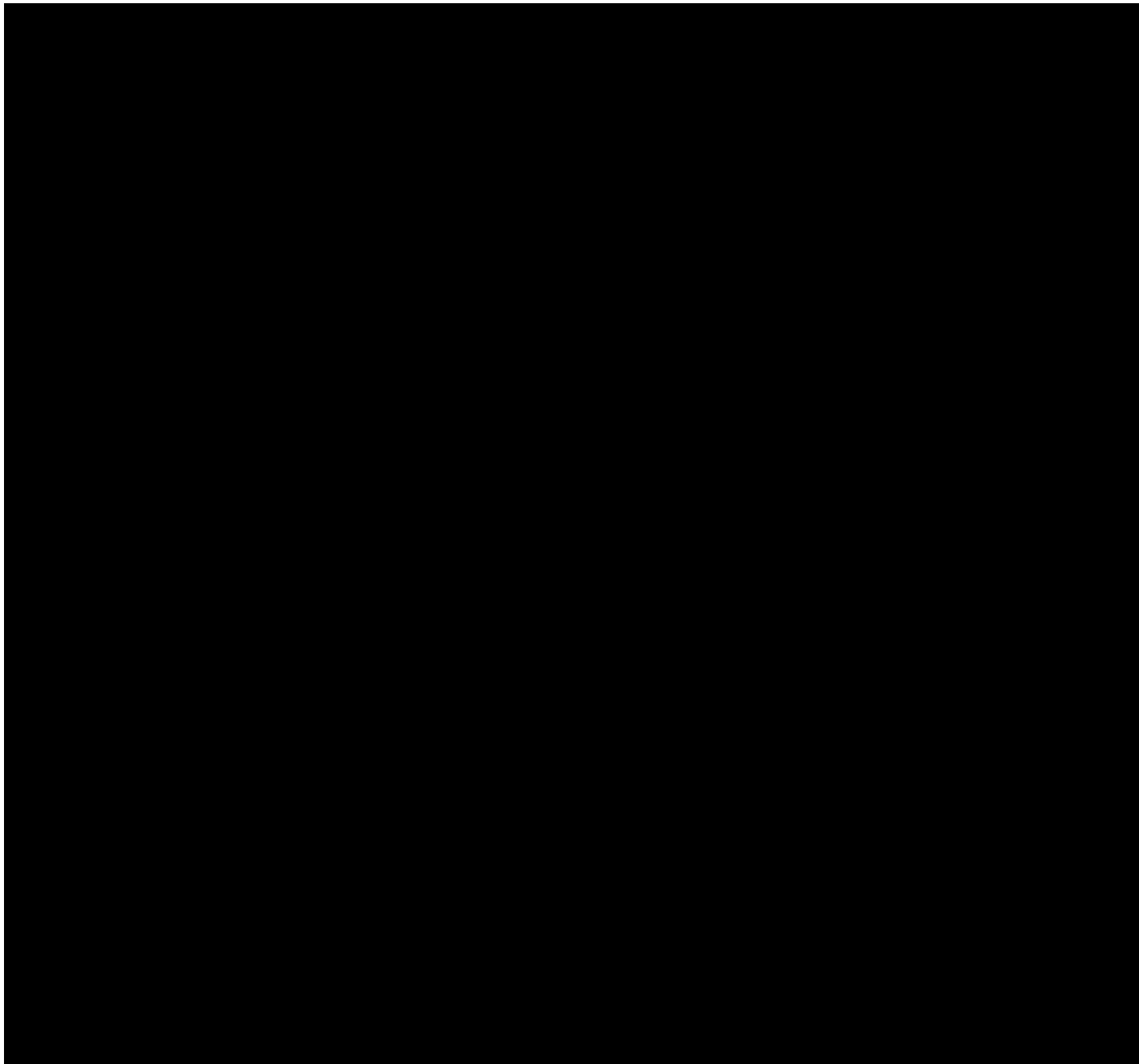


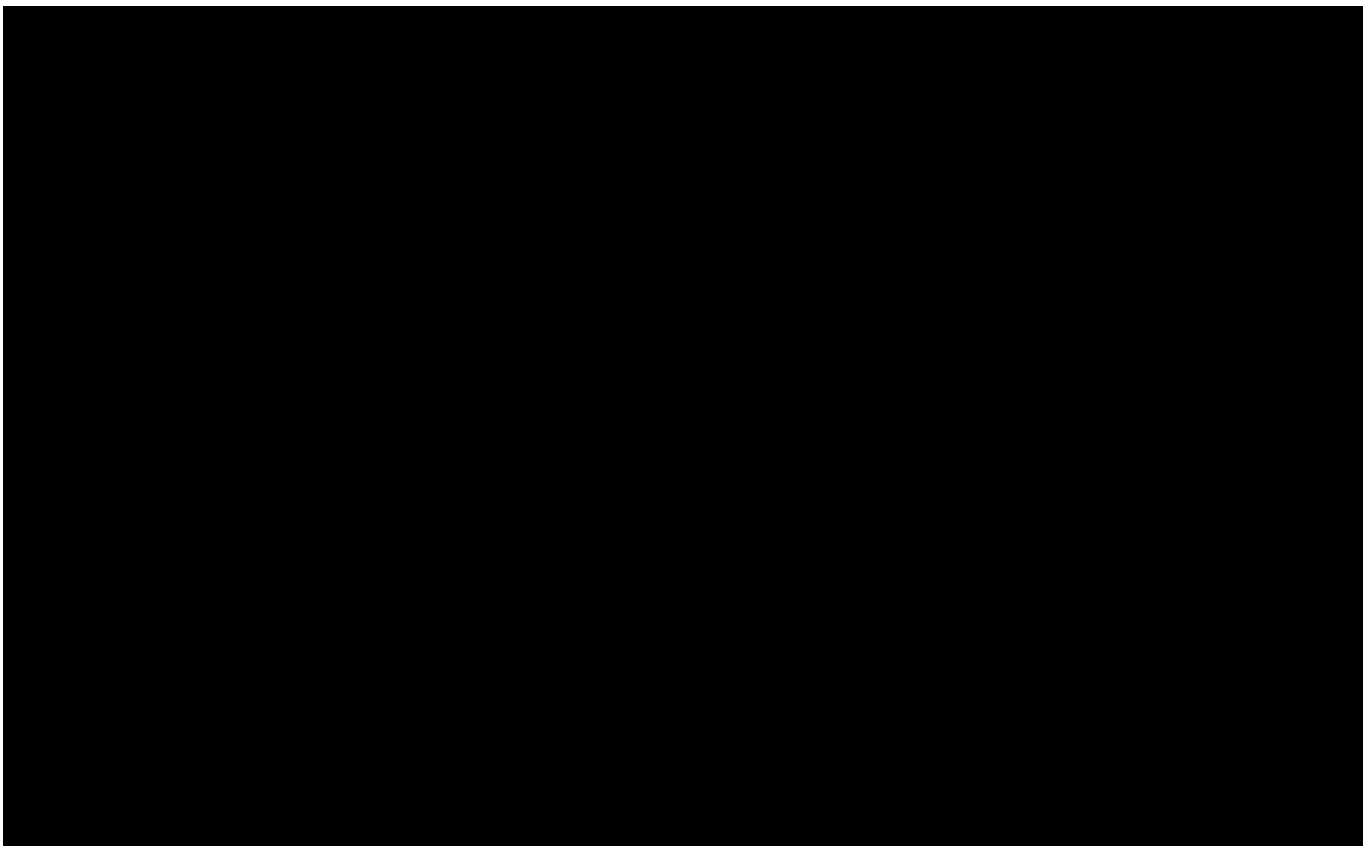


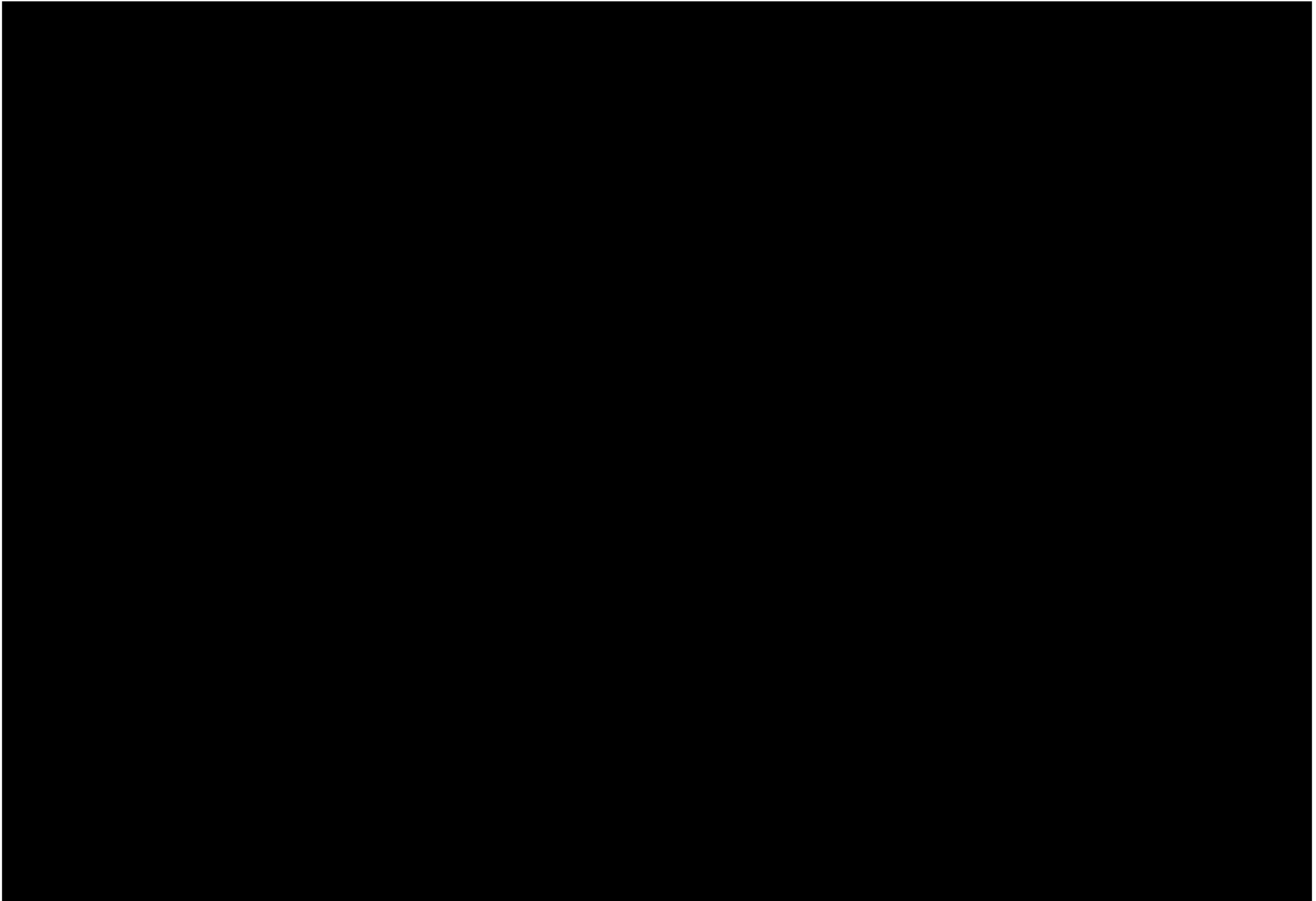


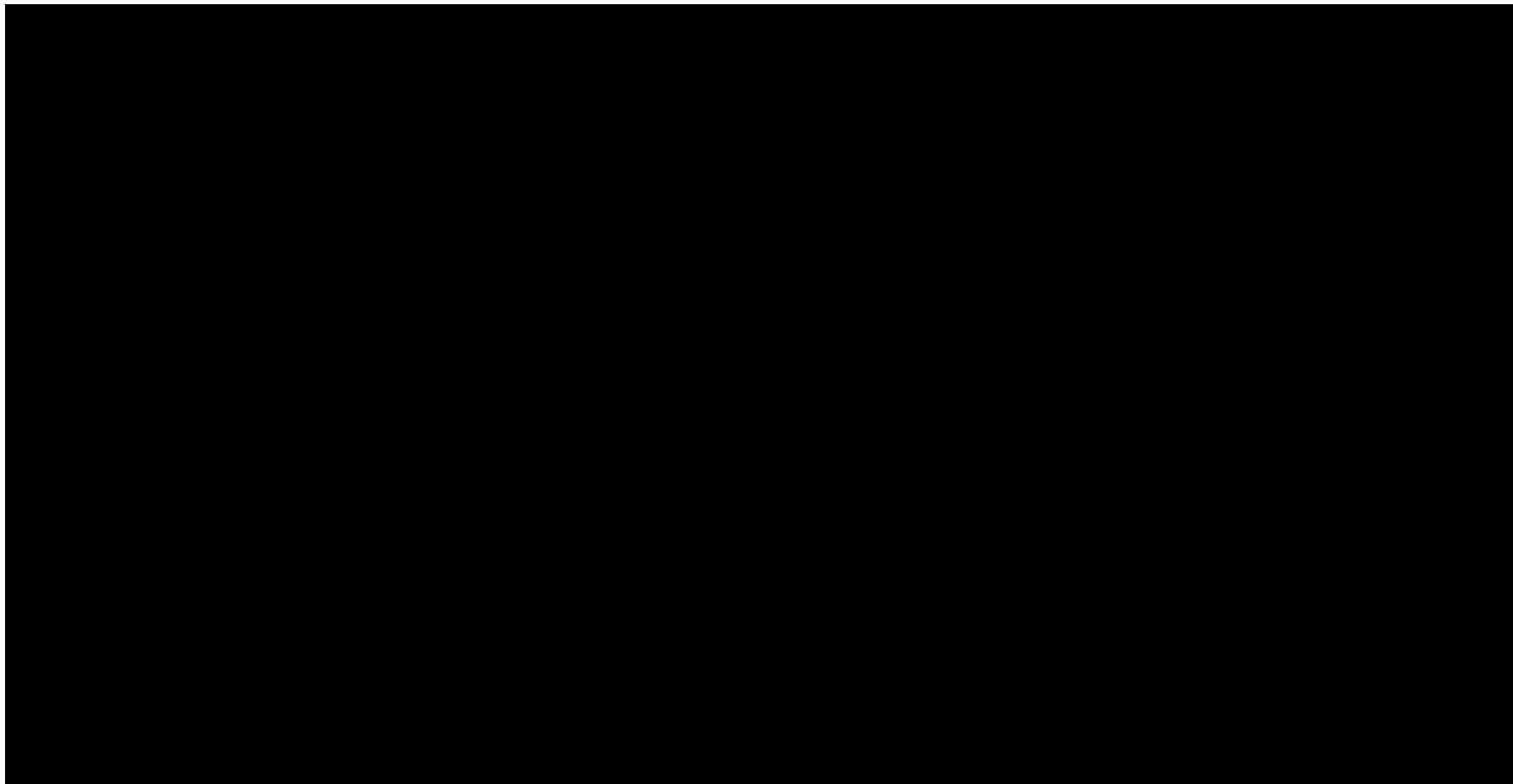


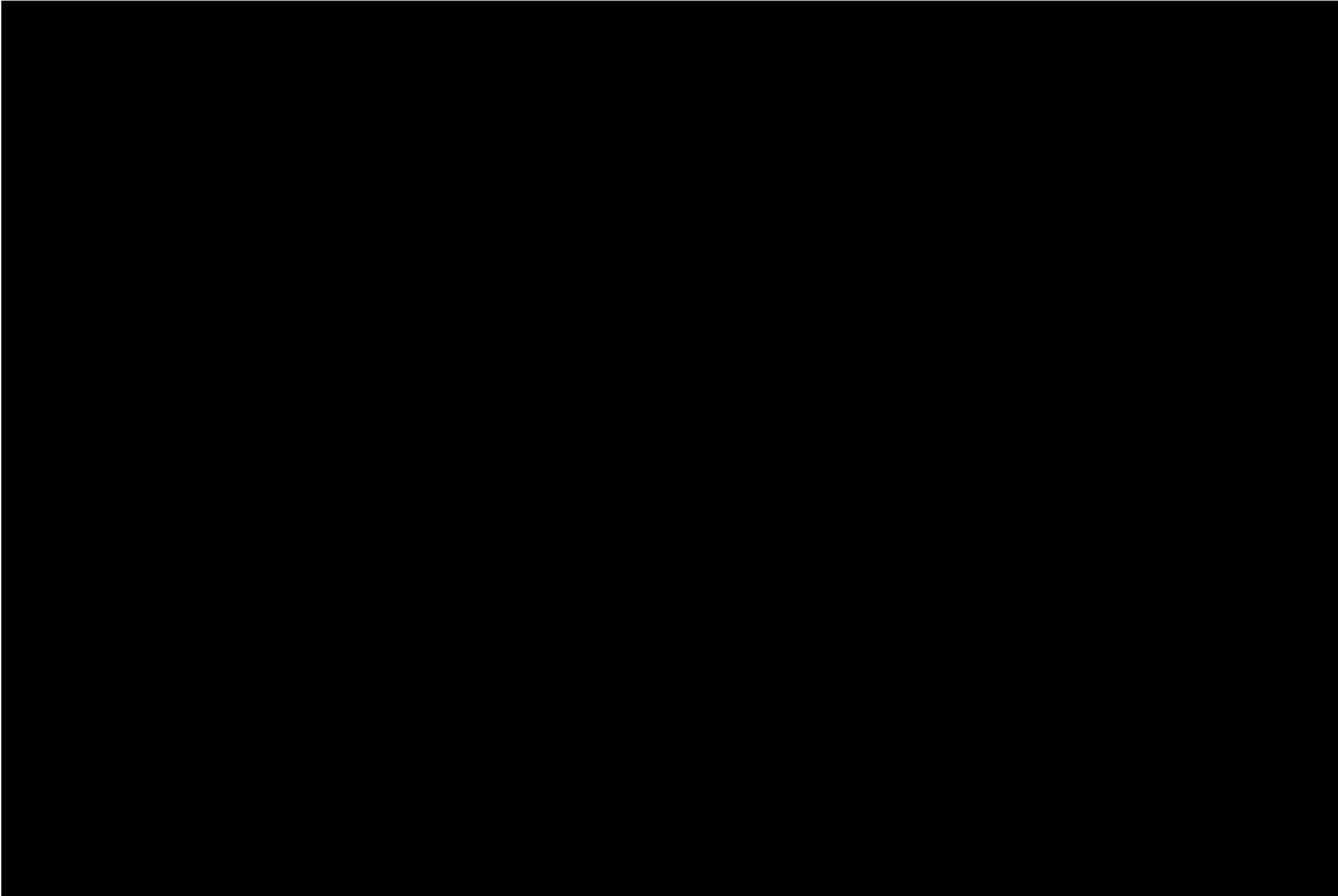


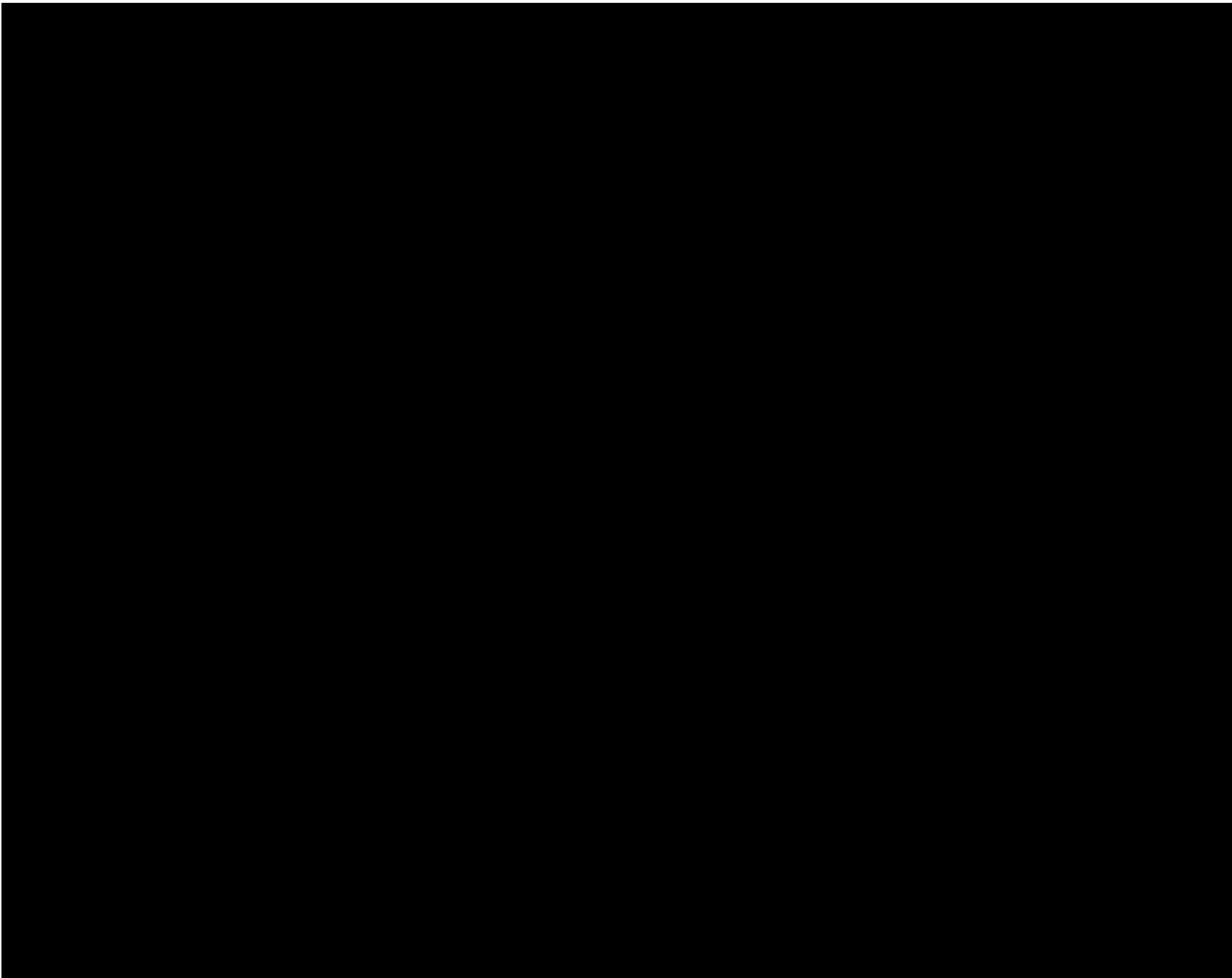


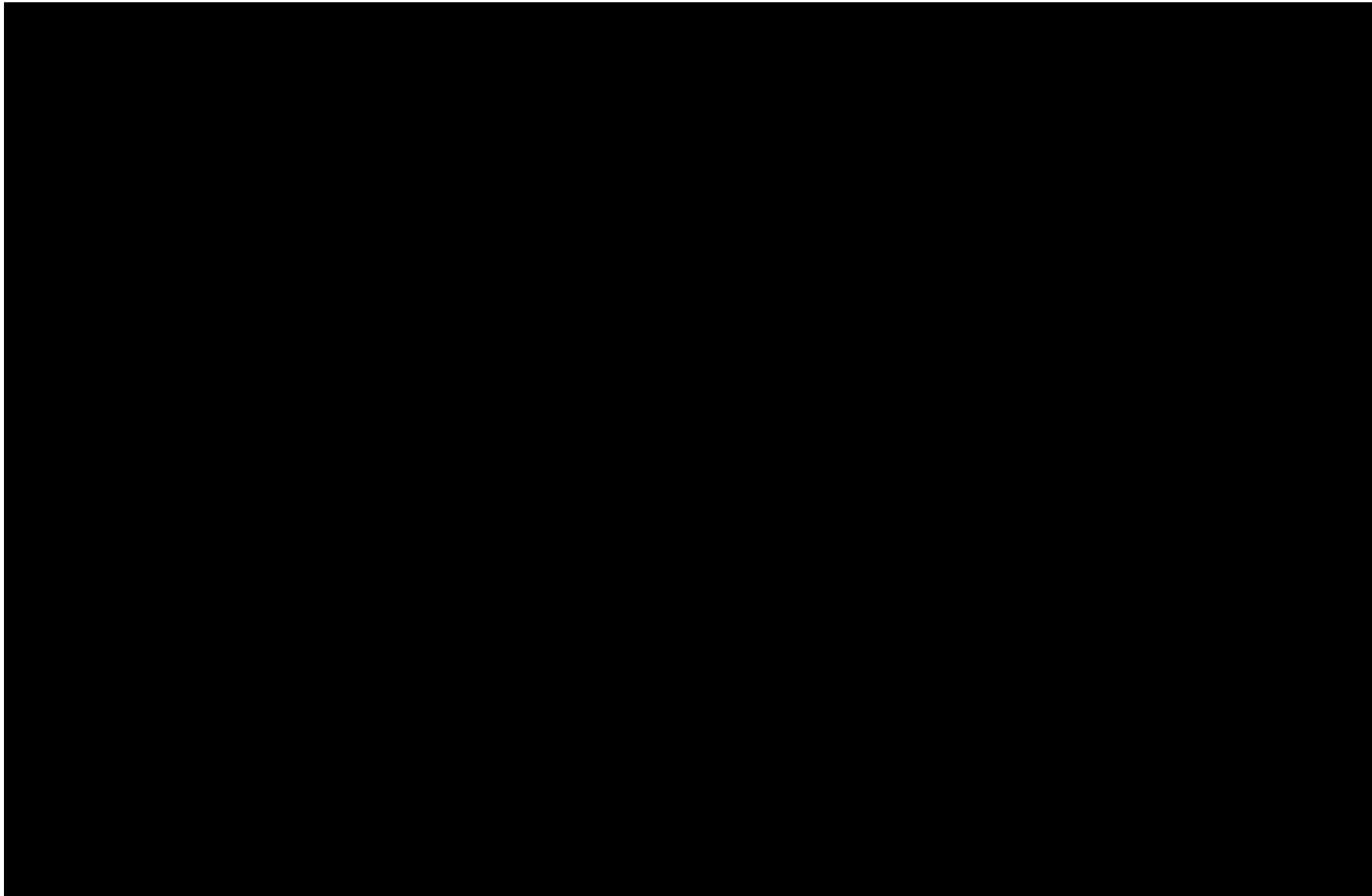


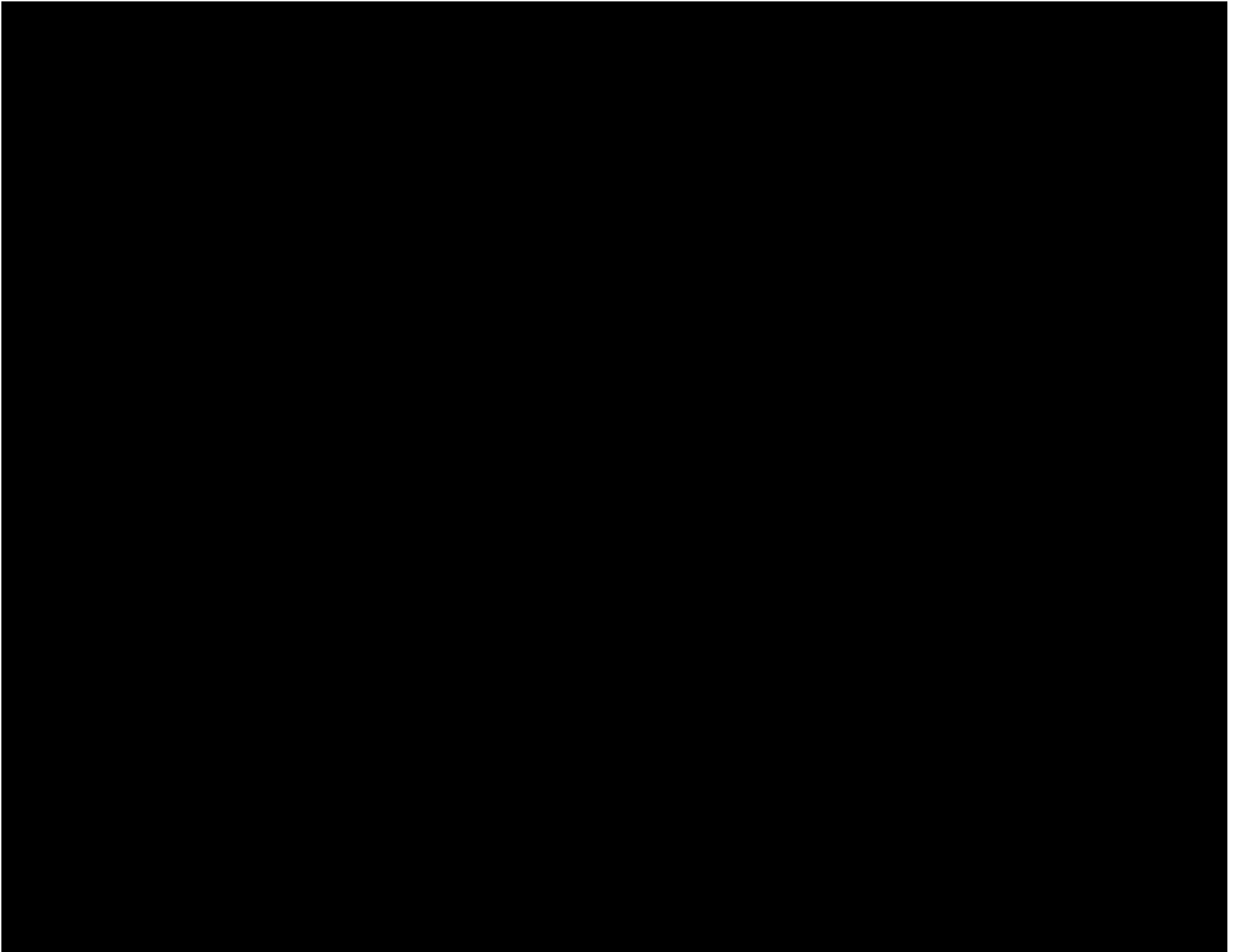


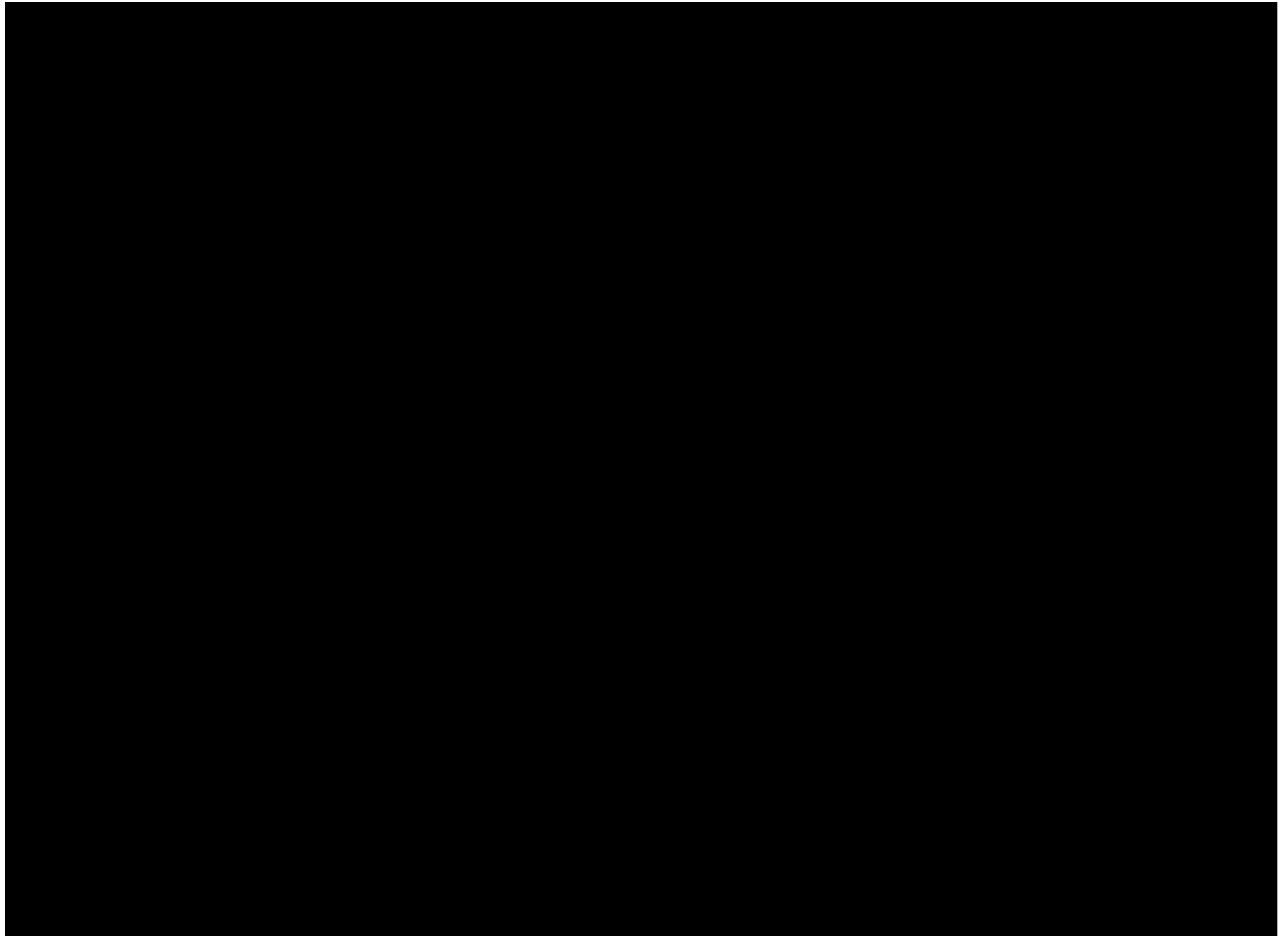


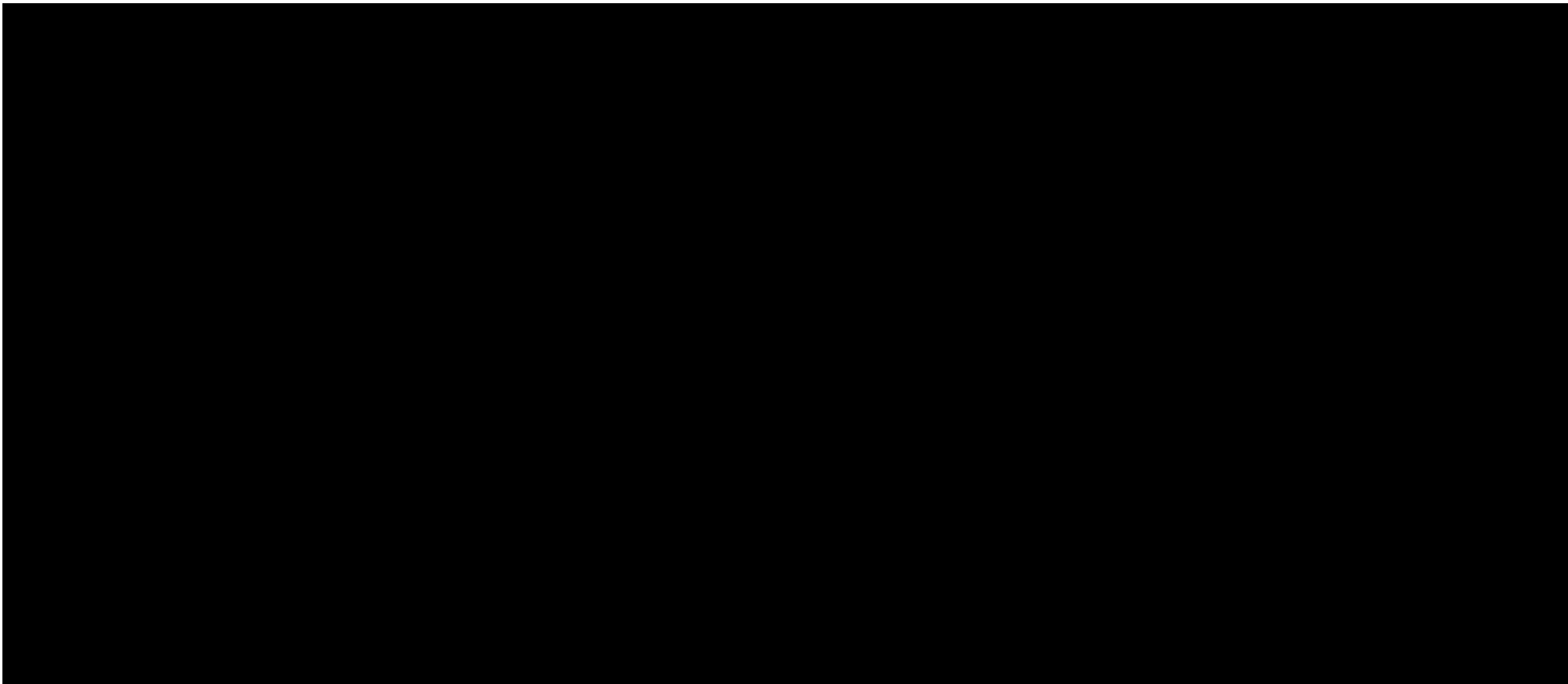






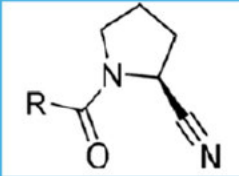
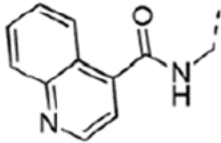
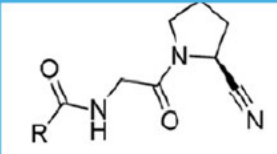


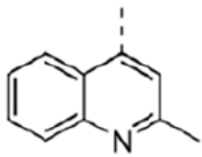
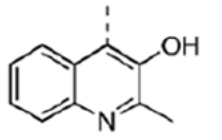
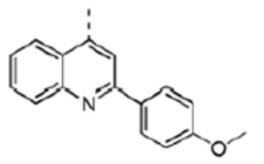
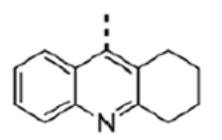
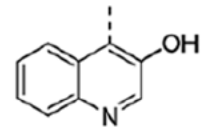
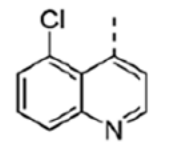


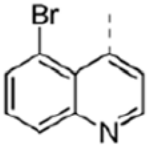
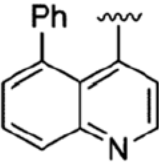
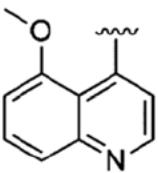
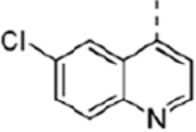
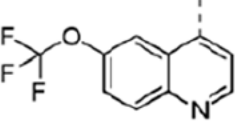


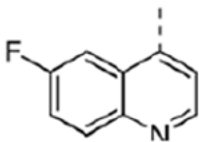
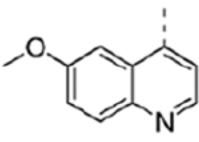
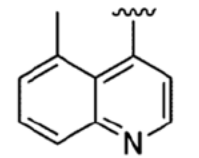
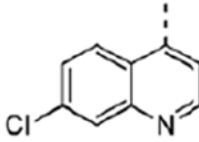
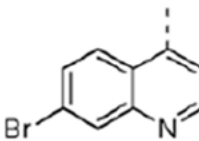
Appendix D: Jansen Publications SAR Data

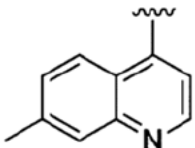
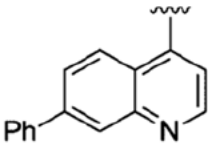
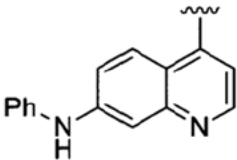
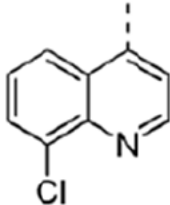
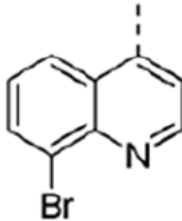
The table below shows the structure of every FAP inhibitor described in the Jansen (EX1006) and Jansen 2013 (EX1007) publications that falls within the scope of the claimed “A” moiety. The compounds are arranged by the type of chemical substitution to either the quinolinyl ring or the cyanopyrrolidine warhead. EX1006 (Jansen), 3059-62; EX1007 (Jansen 2013), 493.

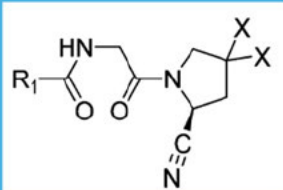
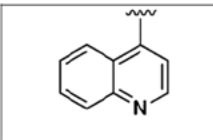
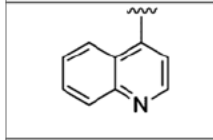
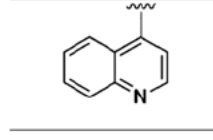
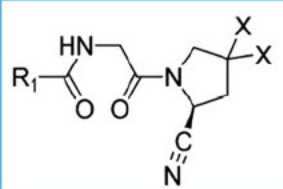
Jansen A Moiety Compound	Structure	FAP IC ₅₀ (μM)	PREP IC ₅₀ (μM)	FAP/PREP Selectivity
No Substitutions on the Quinolinyl Ring 				
Jansen 2013 Compound 7		0.0103	0.86	83.5
Substitutions on the Quinolinyl Ring 				

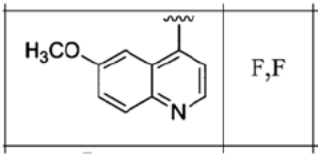
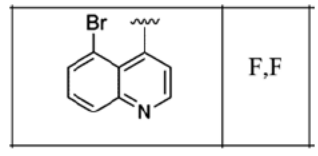
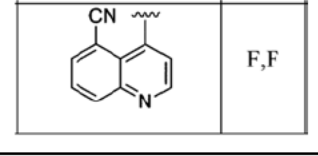
Jansen A Moiety Compound	Structure	FAP IC50 (μM)	PREP IC50 (μM)	FAP/PREP Selectivity
Jansen 2013 Compound 19		0.67	0.64	1.0
Jansen 2013 Compound 20		5.9	53.6	9.1
Jansen 2013 Compound 22		10	1	0.1
Jansen 2013 Compound 23		0.77	18.5	24.0
Jansen 2013 Compound 24		0.16	38	237.5
Jansen 2013 Compound 25		0.0099	16.8	1697.0

Jansen A Moiety Compound	Structure	FAP IC50 (μM)	PREP IC50 (μM)	FAP/PREP Selectivity
Jansen 2013 Compound 26		0.011	50	4545.5
Jansen 2014 Compound 56		0.064	8.7	135.9
Jansen 2014 Compound 57		16.6	1.28	0.1
Jansen 2013 Compound 27		0.014	0.84	60.0
Jansen 2013 Compound 28		0.012	0.71	59.2

Jansen A Moiety Compound	Structure	FAP IC50 (μM)	PREP IC50 (μM)	FAP/PREP Selectivity
Jansen 2013 Compound 29		0.0103	0.61	59.2
Jansen 2013 Compound 30		0.0092	6.1	663.0
Jansen 2014 Compound 53		0.0043	9.1	2116.3
Jansen 2013 Compound 31		0.0071	1.4	197.2
Jansen 2013 Compound 32		0.0062	1.2	193.5

Jansen A Moiety Compound	Structure	FAP IC50 (μM)	PREP IC50 (μM)	FAP/PREP Selectivity
Jansen 2014 Compound 52		0.0069	0.5	72.5
Jansen 2014 Compound 54		0.07	19.4	277.1
Jansen 2014 Compound 55		0.059	2.03	34.4
Jansen 2013 Compound 33		0.19	0.35	1.8
Jansen 2013 Compound 34		0.37	0.36	1.0

Jansen A Moiety Compound	Structure	FAP IC50 (μM)	PREP IC50 (μM)	FAP/PREP Selectivity		
Substitutions on the Pyrrolidine Warhead <table data-bbox="1045 466 1337 571"><tr><td>R₁</td><td>X</td></tr></table>					R ₁	X
R ₁	X					
Jansen 2014 Compound 58	<table data-bbox="732 604 833 742"><tr><td>H,F (S)</td></tr></table>	H,F (S)	0.0033	0.29	87.9	
H,F (S)						
Jansen 2014 Compound 59	<table data-bbox="732 782 833 920"><tr><td>H,F (R)</td></tr></table>	H,F (R)	1	100	100.0	
H,F (R)						
Jansen 2014 Compound 60	<table data-bbox="732 961 833 1099"><tr><td>F,F</td></tr></table>	F,F	0.0032	1.8	562.5	
F,F						
Substitutions on the Pyrrolidine Warhead and Quinolinyl Ring <table data-bbox="1043 1266 1344 1370"><tr><td>R₁</td><td>X</td></tr></table>					R ₁	X
R ₁	X					

Jansen A Moiety Compound	Structure	FAP IC50 (μ M)	PREP IC50 (μ M)	FAP/PREP Selectivity
Jansen 2014 Compound 61		0.0085	8.3	976.4
Jansen 2014 Compound 62		9	9.3	1.0
Jansen 2014 Compound 63		7.2	16.8	2.3