

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. PGR2025-00059
U.S. Patent No. 12,115,233**

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 Post-Grant Review of U.S. Patent No. 12,115,233 (“the ’233 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 (EX2029, “VanBrocklin II”); (c) the deposition testimony of Dr. VanBrocklin taken on July 29, 2026 (EX1069, “VanBrocklin Tr.”); and (d) [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 (§ 18), along with additional materials listed in Appendix A of this Declaration.

A. Person of Ordinary Skill in the Art

6. Dr. VanBrocklin applied the same 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 §§ 19-30 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), §§ 14-16; EX2001 (VanBrocklin I), § 29; EX2029 (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 “do not contain any functional requirements” and 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

² EX2029 (VanBrocklin II), § V.

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

⁴ EX2029 (VanBrocklin II), ¶ 25; EX2001 (VanBrocklin I), ¶¶ 26, 91.

is “direct incubation” of the compound with a 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 EX2029 (VanBrocklin II), ¶¶ 43, 127, 137, 158. See EX1001 (US-233), 37:22-25, 35:46-52 (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 ’233 Patent is reproduced below that omits the definitions of R groups and variables for structure X.

⁹ EX1003 (Zeglis I), ¶ 20.

¹⁰ EX2029 (VanBrocklin II), ¶¶ 41-44.

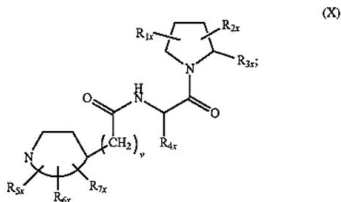
1. A low molecular weight compound of Formula (I):

B-L-A

(I)

wherein:

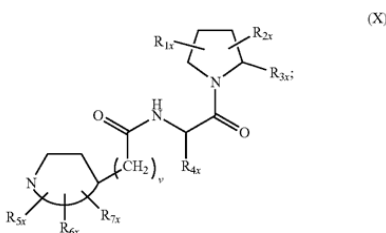
A is a targeting moiety for FAP- α , wherein A has the structure of:



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 “X” (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), ¶¶ 37-38; 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

¹² See EX1003 (Zeglis I), ¶ 75. 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-233), 64:5-61; Certificate of Correction.

¹⁴ EX1001 (US-233), 2:1-3, 8:19-23, 11:20-23, 12:43-45, 15:44-46.

“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 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

¹⁵ EX1001 (US-233), 17:56-25:15; EX1003 (Zeglis I), ¶¶ 75, 88-89.

¹⁶ EX1003 (Zeglis I), ¶ 43.

¹⁷ EX1003 (Zeglis I), ¶ 44.

¹⁸ EX1001 (US-233), 7:46-54 (emphasis added).

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 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

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 (’233 Patent), 61:27-36, 62:31-36

²⁰ EX1002 (US-233 FW), 168 (¶ 12).

²¹ EX1001 (US-233), 7:16-21.

²² EX1001 (US-233), 7:9-11 (emphasis added).

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 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 and '233 Patents clearly states the opposite.

22. During examination of the '233 Patent, Dr. Pomper submitted a declaration in which he presented selectivity (*i.e.*, “specificity”) information for 11

²³ EX1001 (US-233), 7:41-42 (emphasis added).

²⁴ EX1001 (US-233), 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, 5:40-42, 58:61-59:25, 60:45-47.

²⁵ EX2029 (VanBrocklin II), ¶ 43. See also EX2029, ¶¶ 26, 44.

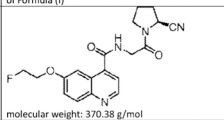
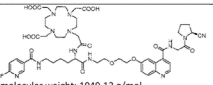
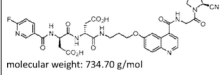
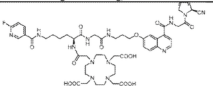
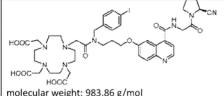
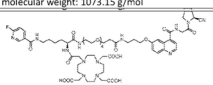
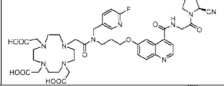
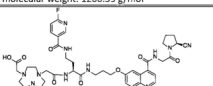
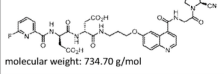
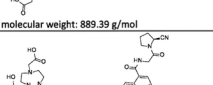
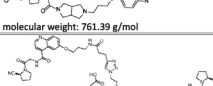
compounds (the “Pomper Compounds”) that he had tested in his lab at JHU.²⁶ He said the 11 compounds were covered by the patent claims several times (below).²⁷

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

<p>15. Further, I have provided additional low molecular weight compounds of the current claims with molecular weights in the below table in paragraph 42.</p> <p>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.</p> <p>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.</p> <p>EX1002 (‘233 Patent), 169, 174-176.</p>
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²⁶ EX1002 (US-233 FW), 166-177; EX1031 (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. EX1003 (Zeglis I), ¶¶ 56-57. Accurately determining IC₅₀ values for FAP and PREP is critical to accurately measuring selectivity/specificity.

²⁷ EX1002 (US-233 FW), 169, 174-176.

Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio	
 molecular weight: 370.38 g/mol	4,111	 molecular weight: 1049.13 g/mol
 molecular weight: 734.70 g/mol	66,084	 molecular weight: 1073.15 g/mol
 molecular weight: 983.86 g/mol	>1,418,440	 molecular weight: 1266.39 g/mol
 molecular weight: 10,502	10,502	 molecular weight: 889.39 g/mol
 molecular weight: 734.70 g/mol	5,807	 molecular weight: 761.39 g/mol
		 molecular weight: 1282.43 g/mol

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

²⁸ EX1002 (US-233 FW), 172 (¶ 31).

²⁹ EX1003 (Zeglis I), ¶¶ 55, 275.

³⁰ EX1002 (US-233 FW), 172 (¶ 31).

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.

EX1002 ('233 Patent FW), 172

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

EX1002 ('233 Patent), 173-174

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

³¹ EX1002 (US-233 FW), 172 (¶ 31).

³² EX1002 (US-233 FW), 173-74 (¶ 41).

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

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.

EX1002 ('233 Patent), 173-174

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 (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.

EX1002 ('233 Patent), 173

27. Dr. Pomper also referred to “testing results from my lab” and

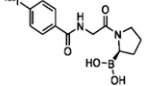
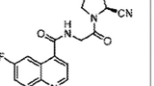
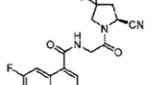
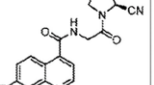
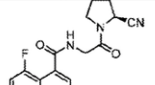
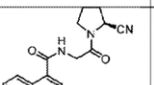
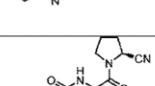
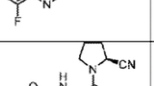
³⁴ EX1002 (US-233 FW), 173. See EX1003 (Zeglis I), ¶ 129; EX1008 (Meletta), 2089-2090 (“As [¹²⁵I]MIP-1232 *did not selectively accumulate* in the atherosclerotic tissue and as its *low FAP/PREP affinity* ratio is already known we did not further investigate its selectivity profile. For future studies *more selective inhibitors are needed* to reduce non-specific tissue accumulation.”)

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

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.

EX1002 (‘233 Patent), 173-174

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

³⁵ EX1002 (US-233 FW), 174-175.

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 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.

EX1002 ('233 Patent), 174-176

2. JHU's Statements to the Patent Office

29. I understand that JHU was the patent applicant at the time these

³⁶ EX1002 (US-233 FW), 174-176 (¶¶ 42-43).

³⁷ The lowest selectivity value of the 11 Pomper Compounds is actually 407 (Pomper Compound 8). EX1002 (US-233 FW), 175.

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 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.")

³⁸ EX1031 (US-201 FW), 408-409. These statements were made in a paper filed by JHU during examination of the parent application of the '233 Patent, the '201 Patent. EX1031 (US-201 FW), 399-412.

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).

³⁹ EX1031 (US-201 FW), 408-411.

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 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

⁴⁰ EX1031 (US-201 FW), 313-316.

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 for both patents.

<i>Reasons for Allowance</i>	
The following is an examiner’s statement of reasons for allowance: the low molecular weight quinolinyl-containing compounds of the instant claims surprisingly have a specificity (PREP/FAP ratio) for FAP that is several orders of magnitude higher than other small molecule FAP inhibitors found in the prior art.	
	EX1002 (‘201 Patent), 442

<i>Reasons for Allowance</i>	
The following is an examiner’s statement of reasons for allowance: the low molecular weight quinolinyl-containing compounds of the instant claims surprisingly have a specificity (PREP/FAP ratio) for FAP that is several orders of magnitude higher than other small molecule FAP inhibitors found in the prior art.	
	EX1002 (‘233 Patent), 213

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 each moiety.⁴² I disagree.

⁴¹ EX1031 (US-201 FW), 408-409, 442; EX1002 (US-233 FW), 213.

⁴² EX2029 (VanBrocklin II), ¶¶ 41, 125-126.

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 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

⁴³ EX1001 (US-233), 64:47-52.

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

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

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-233), 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 .”).

⁴⁷ EX1002 (US-233 FW), 172 (¶ 30 (“... the compounds of the pending claims for medical imaging applications”), ¶ 31 (“There are numerous important

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.

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

parameters which need to be taken into consideration for successfully developing a FAP imaging agent.”)); EX1031 (US-201 FW), 363 (¶¶ 30-31).

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), ¶¶ 59, 275.

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

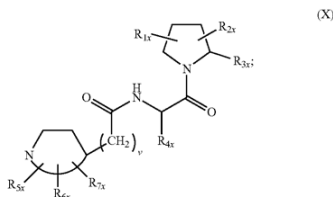
E. The Claimed FAP-Targeting Imaging and Radiotherapeutic Agents Must Distinguish FAP from Other Similar Proteins

38. The claims provide a chemical structure for the “A” moiety defined by the structure (X) (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 “(X)”, it would not satisfy the claim requirement if it did not also (i) bind to FAP with high affinity and (ii) exhibit high selectivity in binding relative to PREP.

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

⁵¹ EX1001 (US-233), 64:10-46.

⁵² EX1001 (US-233), 64:10 (emphasis added).



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 register a “positive” signal even though there is no FAP present in the test

⁵³ EX1001 (US-233), 62:31-37; EX1006 (Jansen), 3053.

⁵⁴ EX1003 (Zeglis-I), ¶¶ 55, 70, 151; EX1002 (US-233 FW), 172 (“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.”)

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-233 FW), 172 (¶ 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

⁵⁶ EX1002 (US-233 FW), 172-76 (¶¶ 30-43).

⁵⁷ EX1002 (US-233 FW), 176 (¶ 43) (emphasis added); EX1031 (US-201 FW), 409.

⁵⁸ EX1002 (US-233 FW), 176 (¶ 43).

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*.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-233 FW), 173 (¶ 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-233), 35:12-24 (“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, 34:63-35:52; EX1003 (Zeglis I), ¶¶ 55-59, 70, 152, 275.

⁶² EX1003 (Zeglis I), ¶¶ 33, 39.

⁶³ EX1003 (Zeglis I), ¶¶ 55, 70, 151.

⁶⁴ EX1002 (US-233 FW), 172 (¶¶ 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-233), 36:21-29 (emphasis added); 1:34-43 (“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), 2094-2095, also 2089-2090.

⁶⁸ EX1008 (Meletta), 2089-2090. See also EX2029 (VanBrocklin II), ¶ 22.

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-233), 64:47-52 (“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), ¶¶ 75-76; EX1001 (US-233), 64:47-52.

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 EX2029 (VanBrocklin II), ¶ 45.

⁷³ EX1003 (Zeglis I), ¶¶ 79-83.

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

⁷⁴ EX1003 (Zeglis I), ¶¶ 80-83; EX1052 (Zhou), 59-60.

⁷⁵ EX2001 (VanBrocklin I), ¶¶ 47-48; EX2029 (VanBrocklin II), ¶ 45; EX1002 (US-233 FW), 169.

⁷⁶ EX1003 (Zeglis I), ¶ 83.

⁷⁷ EX1003 (Zeglis I), ¶¶ 75-76, 165; EX1002 (US-233 FW), 169 (¶ 17).

I. There Is No Dispute That the Claimed Genus of B-L-A Compounds is Enormous and Structurally and Chemically Heterogeneous

53. In my First Declaration, I determined that claims 1-4 of the '233 patent 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.⁷⁸ I also explained that 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.⁷⁹ Dr. VanBrocklin did not identify any errors in my calculations in his declaration or at his deposition.⁸⁰

54. In his declaration, Dr. VanBrocklin states that I “acknowledge[d] the narrow nature of the claimed A moiety.”⁸¹ That is incorrect. 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.”⁸²

⁷⁸ EX1003 (Zeglis I), ¶¶ 84-96.

⁷⁹ EX1003 (Zeglis I), ¶¶ 95-96.

⁸⁰ EX1069 (VanBrocklin Tr.), 70:4-71:15, 246:8-14.

⁸¹ EX2029 (VanBrocklin II), ¶ 158.

⁸² EX1069 (VanBrocklin Tr.), 247:20-248:14.

55. Dr. VanBrocklin testified (and I agree) that “the B and L moieties are not structurally constrained,”⁸³ 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 my opinion that the claims capture a structurally, chemically, and functionally heterogeneous set of B-L-A compounds. As I explained in my declaration, 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.⁸⁴ 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

⁸³ EX2029 (VanBrocklin II), ¶ 192; EX1003 (Zeglis I), ¶¶ 75-76, 85-90. See also EX1069 (VanBrocklin Tr.), 89:22-90:13 (“either how long or how short [the linker is] is not prescribed in the – in the claim.”).

⁸⁴ EX1003 (Zeglis I), ¶¶ 45-46, 270-272, 276; EX1018 (Fichna), 5; EX1013 (Price), 282; EX1017 (Sarko), 2668.

alone.⁸⁵ The group of B-L-A compounds being captured by the claims is not only huge, it is structurally, chemically and functionally heterogeneous.⁸⁶

[REDACTED]

57. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

58. The reliable determination of an IC₅₀ value from a dose-response

⁸⁵ EX1003 (Zeglis I), ¶ 86.

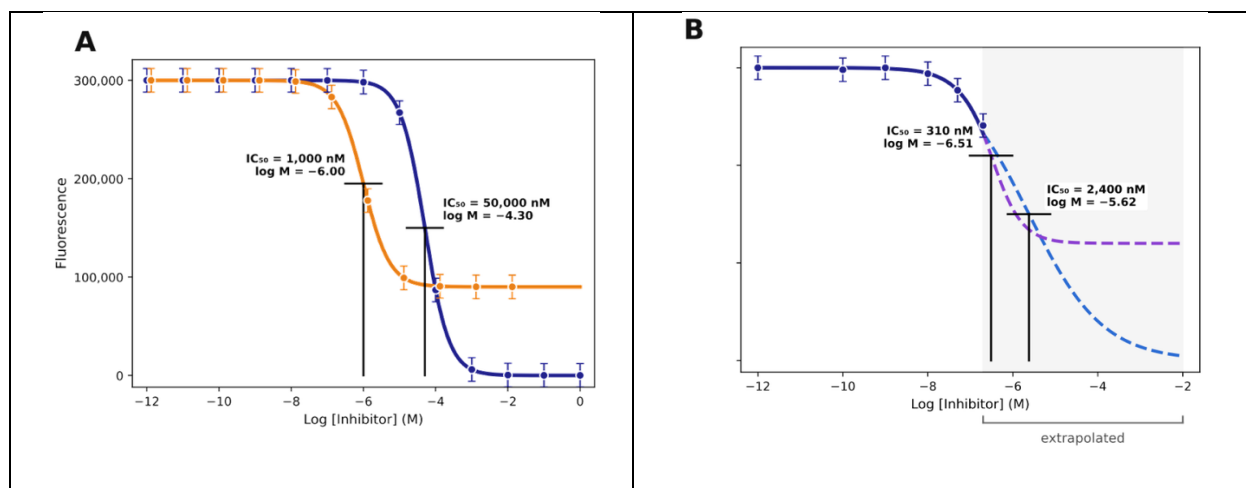
⁸⁶ EX1003 (Zeglis I), ¶¶ 45-46, 96-97, 270-272, 276, 291.

⁸⁷ 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).

⁸⁸ See EX1002 (US-233 FW), 174-176 (¶¶ 42-43), see also 166-177.

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, 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 IC_{50} value to the FAP IC_{50} value. An error or unresolvable variability in the PREP IC_{50} value thus directly influences the reported selectivity for a

compound. Because an IC_{50} 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]

[REDACTED].

64. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

1. [REDACTED]

65. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁸⁹ 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]

2. [REDACTED]

66. [REDACTED]

[REDACTED]

⁹⁰ EX1071 (JHU Production Records), 8 (JHU_000115) (annotated), 10 (JHU_000131) (annotated), 17 (JHU_000148) (annotated), 19 (JHU_000148) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

67. [REDACTED]

[REDACTED]

[REDACTED]

⁹¹ EX1071 (JHU Production Records), 2 (JHU_000237) (annotated), 21 (JHU_000128) (annotated), 23 (JHU_000128) (annotated), 30 (JHU_000099) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

68. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3. [REDACTED]

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]

[REDACTED]

⁹² EX1071 (JHU Production Records), 25-27 (JHU_000138-140) (annotated).

⁹³ EX1071 (JHU Production Records), 4 (JHU_000187) (annotated).

⁹⁴ EX1002 (US-233 FW), 174-176.

[REDACTED]

[REDACTED]

a)

[REDACTED]

70.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁹⁵ EX1071 (JHU Production Records), 10 (JHU_000131) (annotated).

b)

71.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

72.

[REDACTED]

⁹⁶ EX1071 (JHU Production Records), 11 (JHU_000130) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

73.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

⁹⁷ EX1071 (JHU Production Records), 28 (JHU_000211) (annotated).

⁹⁸ EX1071 (JHU Production Records), 12 (JHU_000126) (annotated).

[REDACTED]

74. [REDACTED]

[REDACTED]

[REDACTED].

(a) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

(b) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

75. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁹⁹ EX1071 (JHU Production Records), 12 (JHU_000126) (annotated).

¹⁰⁰ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

4. [REDACTED]

76. [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED].

¹⁰¹ EX1002 (US-233 FW), 174.

¹⁰² EX1002 (US-233 FW), 174 (¶ 42); EX2029 (VanBrocklin II), ¶ 118.

¹⁰³ [REDACTED]

[REDACTED]

[REDACTED]

C. [REDACTED]

77. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁰⁴ [REDACTED]
[REDACTED]

¹⁰⁵ EX1071 (JHU Production Records), 35 (JHU_000036-37), 42-45 (JHU_000043, JHU_000045-46, JHU_000048-50).

78.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(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]

¹⁰⁶ EX1001 (US-233), 1:20-22.

[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]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

81. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁰⁷ See, e.g., EX1071 (JHU Production Records), 15 (JHU_000044).

[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]

83. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁰⁸ See, e.g., EX1071 (JHU Production Records), 35 (JHU_000036-37), 42-45 (JHU_000043, JHU_000045-46, JHU_000048-50).

¹⁰⁹ EX1071 (JHU Production Records), 35 (JHU_000036-37), 42-45 (JHU_000043, JHU_000045-46, JHU_000048-50).

[REDACTED]

[REDACTED].

84. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

85. [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

¹¹⁰ See EX1071 (JHU Production Records), 32 (JHU_000070) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

¹¹¹ EX1071 (JHU Production Records), 33 (JHU_000236, JHU_000070) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

86.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

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

¹¹² EX1071 (JHU Production Records), 32 (JHU_000070) (annotated).

compound.

115

ot

¹¹³ EX1071 (JHU Production Records), 32 (JHU_000070) (annotated).

¹¹⁴ EX1080 (BPS FAP Assay Product Page), 3.

¹¹⁵ EX1081 (R&D FAP Assay Datasheet), 1.

¹¹⁶ EX1071 (JHU Production Records), 33 (JHU_000236) (annotated).

[REDACTED]

[REDACTED]

[REDACTED]

87. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

[REDACTED]

3. [REDACTED]

88. It is common practice for scientists to evaluate the purity of

¹¹⁷ See EX1071 (JHU Production Records), 16 (JHU_000044) (annotated).

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]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

D.

[REDACTED]

90.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

91.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

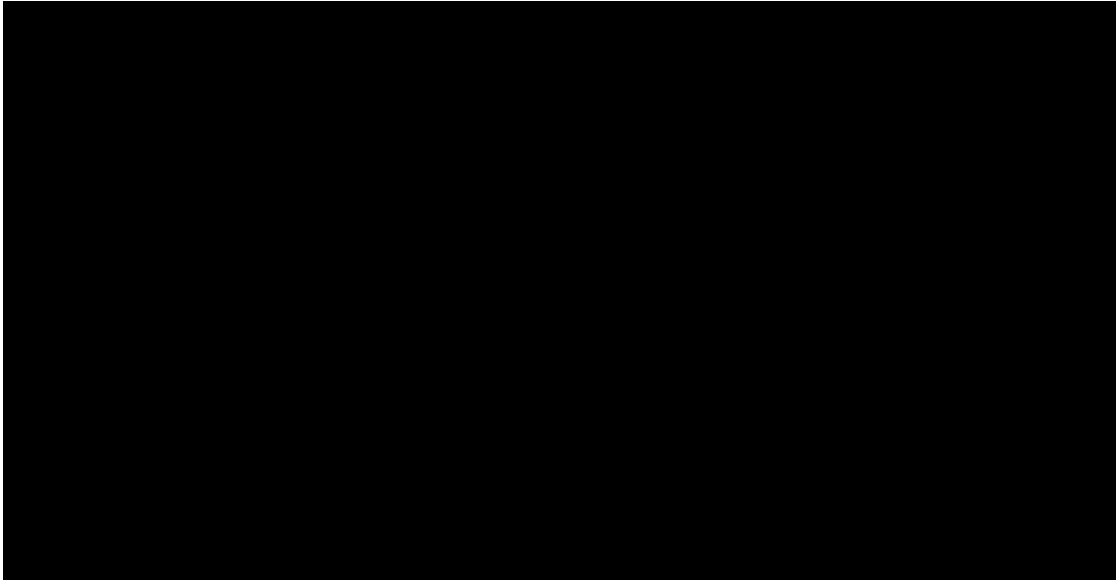
[REDACTED]

[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.”¹¹⁸

93. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

¹¹⁸ EX1069 (VanBrocklin Tr.), 268:2–4; 269:11–15.

[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.”¹¹⁹ He also portrays FAP selectivity increases reported in Dr. Pomper's declaration for the Pomper Compounds as:¹²⁰

- 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

¹¹⁹ EX2029 (VanBrocklin II), ¶ 117. 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 quinolinyl ring, whereas the structure Dr. VanBrocklin provided is functionalized at the 3-position.

¹²⁰ EX2029 (VanBrocklin II), ¶¶ 119-121.

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” targeting moiety. Some examples of his statements include:¹²¹

- 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

¹²¹ EX2029 (VanBrocklin II), ¶¶ 121, 123-124

compounds is representative of, and expected across, the full scope of claims 1–4 of the '233 patent”; and

- “the claimed compounds ... achieve an unexpected and extraordinary improvement in FAP selectivity that the prior art neither taught nor suggested.”

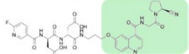
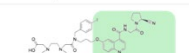
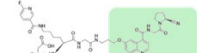
96. As I explain below, Dr. VanBrocklin’s opinion that all B-L-A compounds will exhibit unexpected increases in FAP-to-PREP selectivity relative to “A” moieties alone is contradicted [REDACTED]
[REDACTED].

A. The Pomper Declaration and the Pomper Compounds

97. The Pomper Declaration compared 11 “Representative” B-L-A 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
Ref	Reference Compound	PREP/FAP Ratio	Pomper Compound	Representative Compound of Formula (I)	PREP/FAP Ratio
G		17	7		1,683
H		3	8		407
			9		10,684
			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.¹²² 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

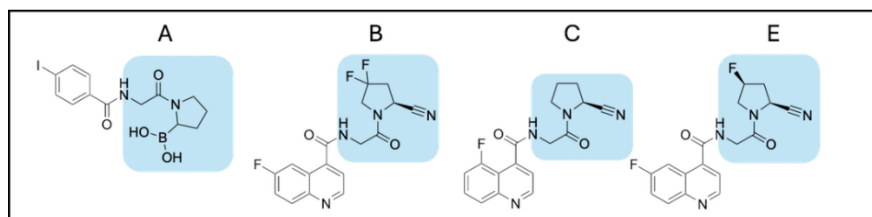
100. The 8 Pomper Reference Compounds make varying changes throughout the “A” moiety. Three compounds introduced substitutions in the pyrrolidine ring A (dihydroxyboryl-), B (4-di-fluoro), E (4-fluoro). Seven introduce halogens at various positions on the quinolinyl ring. Given this diversity of structures 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 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.¹²³ 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

¹²² EX1057 (Pomper PCT), 134-141 (Table 3).

¹²³ EX1008 (Meletta), 2089-2090; EX1003 (Zeglis I), ¶¶ 287-288.

meaningful insights about the comparative selectivity of the 11 Pomper Compounds.



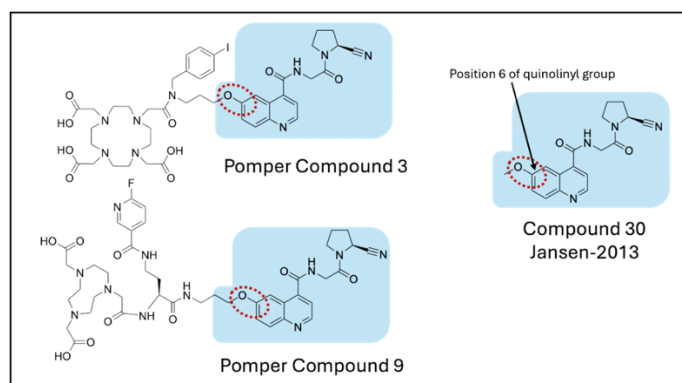
2. Dr. VanBrocklin Used the Wrong Comparator Compound to Assess B-L-A Compound Relative Selectivity

102. Dr. Pomper provides a table of information concerning the 11 Pomper Compounds.¹²⁴ 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.¹²⁵

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)).

¹²⁴ EX2029 (VanBrocklin II), ¶ 149 (pages 114-117).

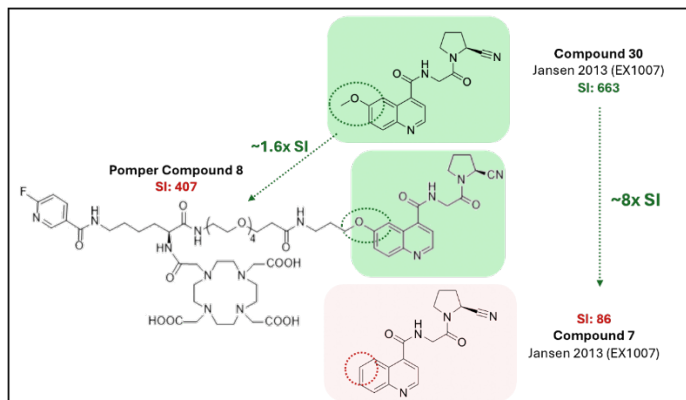
¹²⁵ EX2029 (VanBrocklin II), ¶¶ 117-118 (page 88).



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).¹²⁶ So Compound 30

¹²⁶ See Appendix C-5, below.

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.¹²⁷ As he stated: "Many of the FAP inhibitors reported in Jansen 2013 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*

¹²⁷ EX2029 (VanBrocklin II), ¶ 74.

as... Compound 30 (with a selectivity of 677).’’¹²⁸

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.

- (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

¹²⁸ 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).

values for FAP, and (iv) the IC_{50} values for PREP, and (v) the selectivity index value (SI PREP/FAP) for each compound, which is calculated by dividing $IC_{50[PREP]}$ by $IC_{50[FAP]}$. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]¹²⁹ 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 IC_{50} values for PREP (6.1 μ M) and FAP (0.0092 μ M), and (iii) the % of Compound 30's activity (which is 100%, of course).¹³⁰
- (c) In the top table, in the remaining columns contain information for Compound 7 of Jansen-2013 (EX1007) and the 8 Pomper Reference

¹²⁹ See ¶ 76; EX1002 (US-233 FW), 174; EX1071 (JHU Production Records), 7-8 (JHU_000114, JHU_000115).

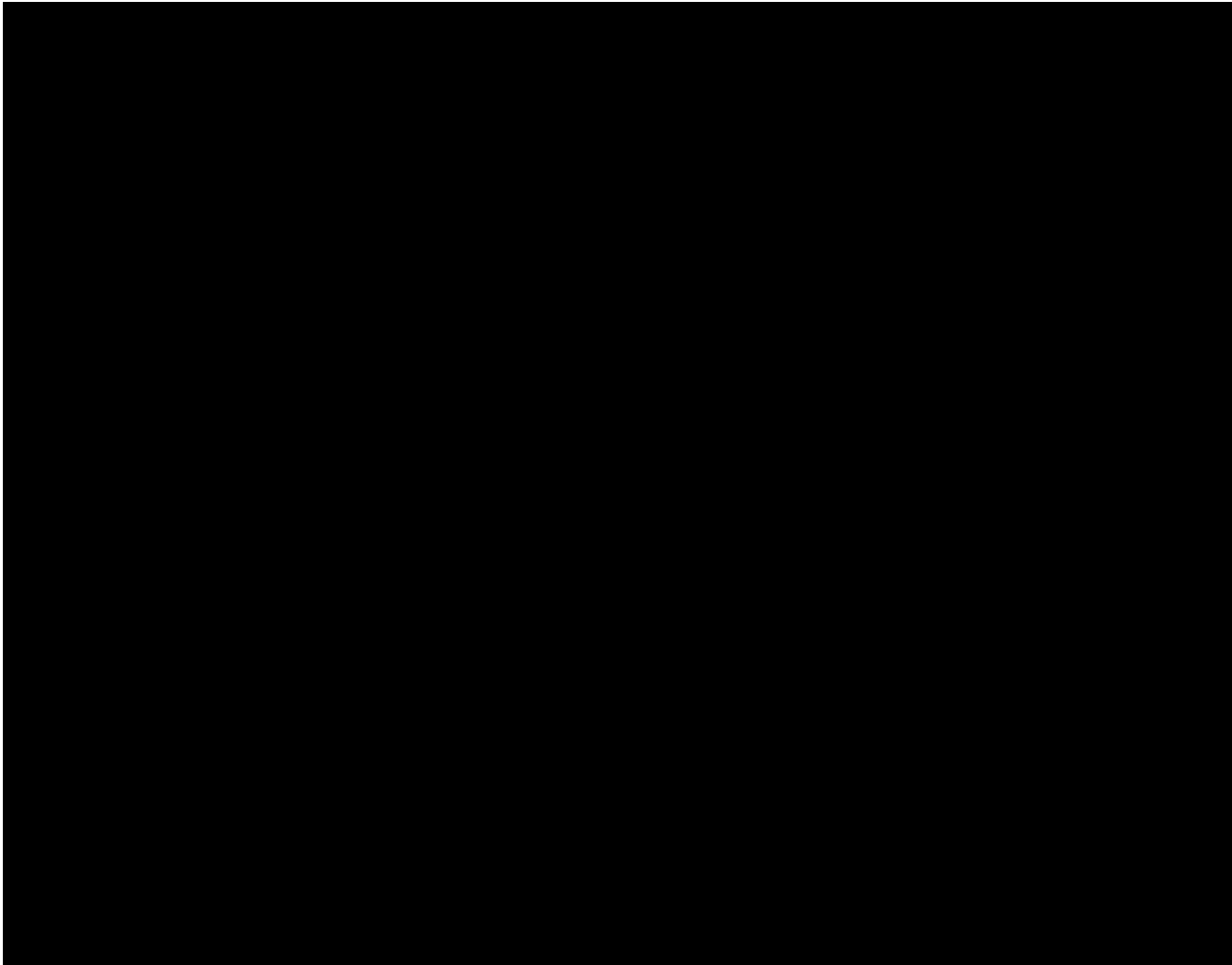
¹³⁰ EX1007 (Jansen 2013), 493; EX2029 (VanBrocklin II), ¶88 (page 65).

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 IC₅₀ values for PREP (.86 µM) and FAP (0.010 µM), 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.4.¹³¹ 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.¹³² For each is shown the structure, the reported SI value from either Jansen (EX1006) or Jansen-2013 (EX1007), and the percentage of the SI value of that compound relative to the SI value of MIP-1232.

¹³¹ EX1007 (Jansen 2013), 493; EX1002 (US-233 FW), 174-175.

¹³² EX2029 (VanBrocklin II), ¶ 89.

- (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.¹³³
- 

¹³³ See Appendices C-6 (top) and C-8 (bottom), below; see also Appendices C-5 and C-7, below (showing Pomper Compound structures).

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))¹³⁴. 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]

¹³⁴ EX2029 (VanBrocklin II), ¶¶ 74-75, 88-89.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.

[REDACTED]

111.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] 8

¹³⁵ See §§ III.B-III.D, above.

¹³⁶ See § III.B.3, above.

¹³⁷ Data, calculations and figures are compiled in Appendix C.

¹³⁸ See EX1057 (Pomper PCT), 134-141 (Table 3), 141-143 (Table 4). See Appendices C-2 and C-9, below. See also, e.g., EX1071 (JHU Production

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

112. [REDACTED]

[REDACTED]

Records), 25-27 (JHU_000138-40), 36-40 (JHU_000141, JHU_000245, JHU_000144, JHU_000085, JHU_000150).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

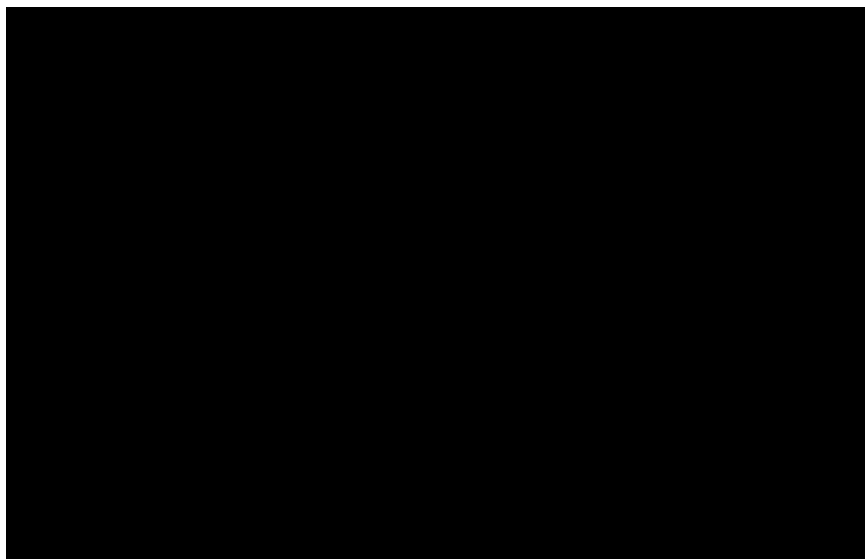
[REDACTED]

[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.¹³⁹ Another example is the same study’s agonist

¹³⁹ EX1082 (Baker), 778 (Table 2), 779 (reporting binding affinity KD 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)).

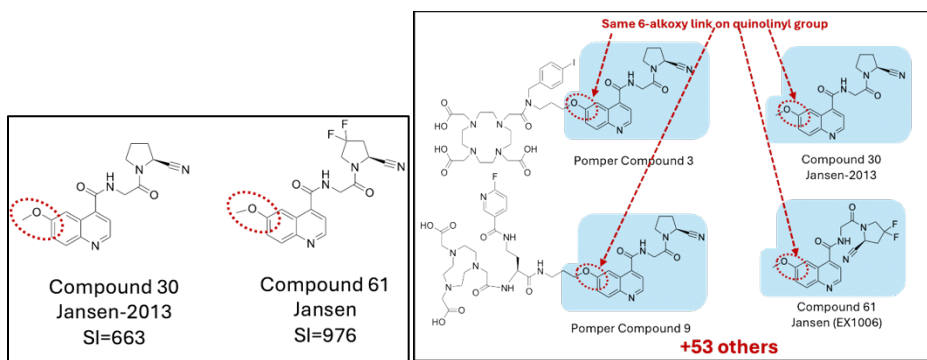
series, in which appending the optical dyes Texas Red, Cy5, EVOBlue30, or BYFL and an identical linker to the NECA-based pharmacophore ABEA “effectively abolished any measurable affinity of the agonists for the A₁ receptor,” while a BY630 conjugate of the same pharmacophore retained affinity comparable to NECA itself.¹⁴⁰

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]

[REDACTED]

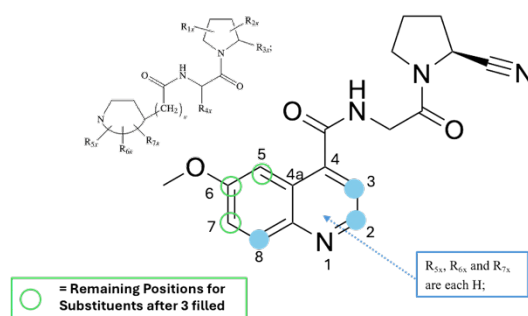
[REDACTED]



¹⁴⁰ 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)).

¹⁴¹ EX1006 (Jansen), 3082.

114. Dr. VanBrocklin states that Compound 61 of Jansen is not covered by the structural definition of “A” in the claims.¹⁴² 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 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 glycyloxy(2-cyano)pyrrolidine at position 4 and (ii) hydrogens occupy

¹⁴² EX2029 (VanBrocklin II), ¶ 83 (“... Compound 61 has a substituent on the quinolinyl ring (MeO-) that is not allowed by the claims.”); *see also* EX2001 (VanBrocklin I), ¶ 81.

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. [REDACTED]

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].

117. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁴³ See Appendix C-1, below.

¹⁴⁴ EX1057 (Pomper PCT), 134 (FAP1-04); EX1071 (JHU Production Records), 41 (JHU_000269) (Ga-JHU152263); Appendix C-1 below.

[REDACTED]

[REDACTED]¹⁴⁶

118. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹⁴⁵ EX1003 (Zeglis I), ¶¶ 175, 178.

¹⁴⁶ EX1003 (Zeglis I), ¶ 91.

¹⁴⁷ EX1002 (US-233 FW), 176 (¶ 43); EX2029 (VanBrocklin II), ¶¶ 117, 122-123.

¹⁴⁸ See § III.B.3, above. See also EX2029 (VanBrocklin II), ¶ 117; EX1071 (JHU Production Records), 10 (JHU_000131) (annotated).

¹⁴⁹ EX1002 (US-233 FW), 176 (¶ 43).

¹⁵⁰ EX2029 (VanBrocklin II), ¶¶ 118, 123.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

<p>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).</p>	[REDACTED]
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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.¹⁵² 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

¹⁵¹ EX1071 (JHU Production Records), 10 (JHU_000131) (annotated).

¹⁵² EX2029 (VanBrocklin II), ¶ 51.

consideration of structural aspects of the two enzymes on a review of data from binding assays of the compounds.¹⁵³

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 (EX2032) (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).¹⁵⁴

¹⁵³ 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 -- 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.”)

¹⁵⁴ EX2032 (Aertsgeerts), 19442.

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 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 ($\sim 4 \text{ \AA}$) 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.¹⁵⁵

¹⁵⁵ EX1064 (Fulop), 167 (emphasis added).

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 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 '233 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.¹⁵⁶

- (b) A POSA would have started with US-633, which described high FAP affinity radiotracers with a modular B-L-A structure.¹⁵⁷
- (c) The POSA would have recognized from Meletta that US-633's most promising radiotracer required a more selective FAP pharmacophore.¹⁵⁸
- (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.¹⁵⁹
- (e) Based on the collective guidance in US-633, Meletta, and Jansen, the POSA would have produced radiotracers that attach Compound 60 to

¹⁵⁶ EX1003 (Zeglis I), ¶¶ 68-72, 140-143.

¹⁵⁷ EX1003 (Zeglis I), ¶¶ 99-108.

¹⁵⁸ EX1003 (Zeglis I), ¶¶ 129-138.

¹⁵⁹ EX1003 (Zeglis I), ¶¶ 144-161.

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 prosthetic groups suitable for PET or SPECT imaging, all of which would have low overall molecular weights.¹⁶⁰

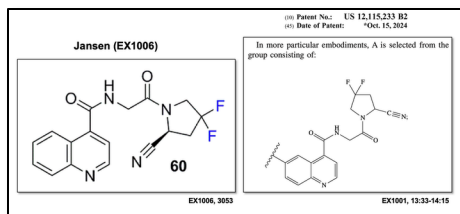
124. The '233 patent actually disproves Dr. VanBrocklin's opinion that a POSA would not have focused on the Jansen paper or its showcasing of Compound 60.¹⁶¹ The '233 patent lists only two examples of FAP-targeting moieties in the specification that fall within the scope of the claims—one is Compound 60 (below)¹⁶² and the other is Compound 7 of Jansen 2013 (EX1007).¹⁶³ 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.

¹⁶⁰ EX1003 (Zeglis I), ¶¶ 162, 167-171, 180-181, 183-197, 204.

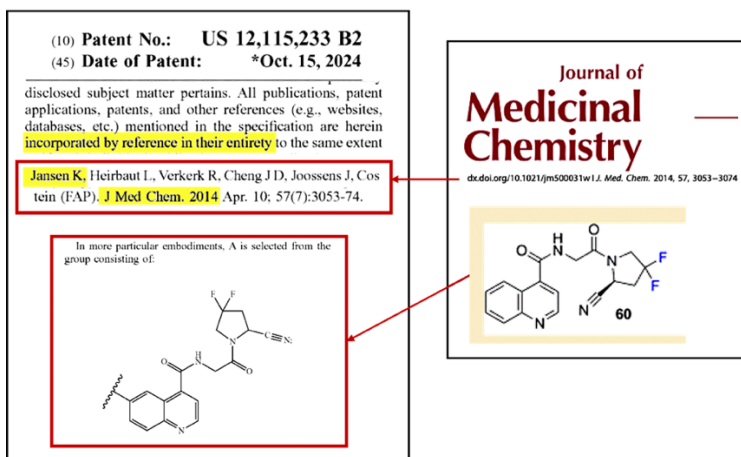
¹⁶¹ EX2029 (VanBrocklin II), ¶¶ 19, 49, 70-101.

¹⁶² EX1001 (US-233), 13:33-14:55; EX1003 (Zeglis I), ¶¶ 82, 203.

¹⁶³ EX1001 (US-233), 14:18-55; EX1007 (Jansen 2013), 493; EX2029 (VanBrocklin II), ¶ 118.



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 to include publicly known information as part of the patent disclosure. The ’233 Patent does this with the Jansen paper that showcased Compound 60.¹⁶⁴ Jansen is one of a handful of scientific publications that the ‘233 Patent incorporates by reference. This signals that the inventors of the ’233 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.



¹⁶⁴ EX1001, 61:25-47, 62:31-37.

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.”¹⁶⁵ I 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.¹⁶⁶ 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 '233 Patent proposes to use.¹⁶⁷

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

¹⁶⁵ EX2029 (VanBrocklin II), ¶ 20, also ¶¶ 16-23, 46-106.

¹⁶⁶ EX1003, ¶¶ 69-72, 99-104, 135, 140-143.

¹⁶⁷ EX1003 (Zeglis I), ¶¶ 37-38, 110-123, 144-149; EX1009 (Jamous), 3381; EX1004 (US-633), [0100], Tables 3, 4; EX1006 (Jansen), 3053-54, 3063-65.

therapeutic approaches focused on the development of small-molecule inhibitors of enzymatic activity.”¹⁶⁸ US-633 is particularly relevant because it is focused on developing small molecule FAP-targeting radiopharmaceuticals—the same field of research as the ’233 patent.¹⁶⁹ 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.¹⁷⁰

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.¹⁷¹ A radiolabeled form of sibrotuzumab was investigated in clinical trials as a cancer therapeutic. By 2017, however, it had been reported

¹⁶⁸ EX1016 (Brennen), Abstract.

¹⁶⁹ EX1004 (US-633), [0002], [0005], [0007]-[0029]; EX1003 (Zeglis I), ¶¶ 99-108.

¹⁷⁰ EX1003 (Zeglis I), ¶¶ 162, 167-205.

¹⁷¹ EX2029 (VanBrocklin II), ¶ 59.

these clinical investigations were unsuccessful.¹⁷² This failure of a highly specific 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.¹⁷³

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 2017.¹⁷⁴ 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.¹⁷⁵ At his deposition, Dr. VanBrocklin agreed that “small

¹⁷² 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 studies “observed no objective tumor response,” and in the phase II clinical study, “no responses were observed and the trial was stopped.”).

¹⁷³ EX1003 (Zeglis I), ¶¶ 71-72.

¹⁷⁴ EX1003 (Zeglis I), ¶¶ 32-40, 67-72; EX1001 ('233 Patent), 1:43-61.

¹⁷⁵ EX1003 (Zeglis I), ¶¶ 71-72.

molecules were among the many constructs that were being looked at as potential FAP agents, both as drugs and as radiopharmaceuticals at the time.”¹⁷⁶

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.¹⁷⁷ 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

¹⁷⁶ EX1069 (VanBrocklin Tr.), 173:22-174:8; EX1003 (Zeglis I), ¶¶ 32-40, 69-72.

¹⁷⁷ EX1003 (Zeglis I), ¶¶ 40, 50, 79, 214; EX1017 (Sarko), 2668-2671; EX1034 (Meyer), 2799; EX1036 (Maurer), 227; EX1053 (US-657), [0005], [0314].

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 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*.¹⁷⁸

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?

¹⁷⁸ EX1065 (Ganguly 2015), 780 (emphasis added).

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.¹⁷⁹

134. As I explained in my First Declaration, the '233 Patent recognizes these disadvantages of antibodies and advantages of small molecules for use in radiotracers for tumor imaging were known to POSAs.¹⁸⁰ The inclusion of those observations in the introduction of the '233 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.¹⁸¹ 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 (EX2039) we noted that the slow pharmacokinetics of antibodies force the use of “radionuclides with long physical half-lives [that] often results in high background

¹⁷⁹ EX1069, 143:21-144:13.

¹⁸⁰ EX1003 (Zeglis I), ¶ 214; EX1001 (US-233), 1:43-61.

¹⁸¹ EX2029 (VanBrocklin II), ¶ 58 (citing EX2039 (Zeglis 2015) and EX2040 (Zeglis 2016)).

radiation dose rates to non-target tissues,” which is why we pursued a pre-targeting method predicated on *radiolabeled small molecules*.¹⁸² In Zeglis 2016 (EX2040), we observed that antibody conjugates had “stalled just short of the clinic.”¹⁸³ My 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.¹⁸⁴ 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 2018.¹⁸⁵ Development fared no better outside the United States—three of the four of the antibody radiopharmaceuticals that received marketing approval in the EU

¹⁸² EX2039 (Zeglis 2015), Abstract, 1; EX2023 (Zeglis Tr.), 70:4-71:8.

¹⁸³ EX2040 (Zeglis 2016), 3, 15.

¹⁸⁴ EX1069 (VanBrocklin Tr.), 145:5-146:9.

¹⁸⁵ See Appendix B, below.

were off the market by October 2017, and the final molecule was withdrawn in 2018.¹⁸⁶ Dr. VanBrocklin did not mention any of these antibody radiotracer product withdrawals in his declaration.

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.¹⁸⁷ Several simply discussed FAP biology or broad targeting concepts without reporting any particular findings about FAP radiotracers.¹⁸⁸ The LeBeau (EX2036) and Huang 2011 (EX2037) papers propose an emergent strategy predicated on the cleavage of peptides by FAP to release cytotoxins.¹⁸⁹ 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

¹⁸⁶ See Appendix B, below.

¹⁸⁷ EX2029 (VanBrocklin II), ¶¶ 59-63; EX1003 (Zeglis I), ¶¶ 67-72.

¹⁸⁸ EX1003 (Zeglis I), ¶¶ 67-72; EX2029 (VanBrocklin II), ¶¶ 59-63.

¹⁸⁹ EX2029 (VanBrocklin II), ¶ 63; EX2036 (LeBeau 2009), 2-3; EX2037 (Huang 2011), Abstract, 491.

imaging agent, but there is no evidence it progressed to the clinic, and no evidence it diluted interest in small-molecule radiotracers.¹⁹⁰

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.¹⁹¹ That is not correct.

139. I explained in my Opening 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

¹⁹⁰ EX2029 (VanBrocklin II), ¶ 62; EX2035 (Rüger); EX1003 (Zeglis I), ¶¶ 67-72.

¹⁹¹ EX2029 (VanBrocklin), ¶ 19.

assembled imaging agent.¹⁹² Dr. Pomper identified a similar array of these characteristics as being important to selection of targeting moieties for radiotracers to be used in medical imaging in his Declarations.¹⁹³ The Jansen group identified these same types of additional characteristics in their work.¹⁹⁴ 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

¹⁹² EX1003 (Zeglis I), ¶¶ 55-59, 146-148, 152, 157-160; EX2023 (Zeglis Tr.), 62:18-63:5, 64:1-65:13.

¹⁹³ EX1002 (US-233 FW), 172 (¶ 31). See also ¶ 23, above.

¹⁹⁴ 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.”)

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* were determined (log D_{7.4}, kinetic solubility, stabilities in mouse, rat, and/or human plasma) (Table 7).”).¹⁹⁵

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.”¹⁹⁶ That is why Jansen showcased it in its abstract.¹⁹⁷ Jansen is clearly reporting that Compound 60 checked the most boxes required for a successful targeting moiety in a radiotracer of its numerous

¹⁹⁵ EX1006 (Jansen), 3063 (emphasis added).

¹⁹⁶ 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), ¶¶ 148, 159-160.

¹⁹⁷ EX1003 (Zeglis I), ¶¶ 146; EX1006 (Jansen), Abstract, 3063-3065.

candidates.¹⁹⁸ A POSA seeking to assemble a FAP-targeting imaging or radiotherapy agent would seek to use a targeting moiety that checks the most boxes 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.¹⁹⁹

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.²⁰⁰ 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 60.²⁰¹ The absence of comparable data would not have led

¹⁹⁸ EX1006 (Jansen), Abstract, 3053, 3063-3064; EX1003 (Zeglis I), ¶¶ 145-160.

¹⁹⁹ EX1003 (Zeglis I), ¶¶ 145-161, 174-179; EX1006 (Jansen), 3053-3065.

²⁰⁰ EX2029 (VanBrocklin II), ¶¶ 71-90, 106.

²⁰¹ EX1003 (Zeglis I), ¶¶ 147-148, 156-160; EX1006 (Jansen), Abstract, 3063-3065; EX1007 (Jansen 2013), 491-496; EX1044 (US-650), Tables 3-4.

a POSA away from the better-characterized Compound 60.²⁰²

143. The Jansen 2014 (EX2003) xanthine inhibitors cited by JHU and Dr. VanBrocklin belonged to a different scaffold series and included compounds with 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 60.²⁰³ Poplawski's (EX2020) boronic-acid series did not provide the same favorable, directly comparable *in vivo* pharmacokinetic and sustained FAP-inhibition record.²⁰⁴ 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,”²⁰⁵—and described pharmacokinetic limitations for the scaffold despite favorable results for certain parameters.²⁰⁶

²⁰² EX1003 (Zeglis I), ¶¶ 156-161.

²⁰³ EX2003 (Jansen 2014), 1701, 1703, 1706, Tables 1-4; EX1003 (Zeglis I), ¶¶ 143-146, 149-160; EX2029 (VanBrocklin II), ¶ 76.

²⁰⁴ EX2020 (Poplawski), 1-14; EX1003 (Zeglis I), ¶¶ 146-149, 157-160; EX2029 (VanBrocklin II), ¶ 77.

²⁰⁵ EX2020 (Poplawski), 3; EX1047 (Tsai), Abstract, 6576-78, Tables 3-4; EX2029 (VanBrocklin II), ¶ 78.

²⁰⁶ EX1047 (Tsai), Abstract, Table 2, 6578; EX2029 (VanBrocklin II), ¶ 78.

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 radiopharmaceuticals, I believe that compound 60 was included in those.”²⁰⁷

145. I did not use hindsight in my analysis.²⁰⁸ 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 ‘233 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 Opening 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 Opening Declaration was a transparent screening framework reflecting the sequential way a medicinal and

²⁰⁷ EX1069 (VanBrocklin Tr.), 184:13-22.

²⁰⁸ EX2029 (VanBrocklin II), ¶¶ 71-93; EX1003 (Zeglis I), ¶¶ 153-161.

radiopharmaceutical chemist would screen candidates.²⁰⁹ It first applied objective selectivity and affinity thresholds to eliminate inadequate candidates and then considered practical radiopharmaceutical-design factors and develop data to evaluate potential liabilities.²¹⁰ 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.²¹¹

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.²¹² 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.²¹³

²⁰⁹ EX1003 (Zeglis I), ¶¶ 151-155; EX2029 (VanBrocklin II), ¶ 80.

²¹⁰ EX1003 (Zeglis I), ¶¶ 55-58, 151-155.

²¹¹ EX1003 (Zeglis I), ¶¶ 144-161.

²¹² EX1033 (Mach), 140; EX1003 (Zeglis I), ¶ 153 & n.163; EX2029 (VanBrocklin II), ¶ 81; EX2001 (VanBrocklin I), ¶ 78.

²¹³ EX2003 (Jansen 2014), Tables 1, 3; EX2029 (VanBrocklin II), ¶ 88.

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 molecule pharmacophore.²¹⁴ 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.²¹⁵ 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.²¹⁶ C⁵-chlorine and -bromine improved FAP/PREP selectivity in that series, but other substitutions and positions produced different effects on FAP

²¹⁴ EX2029 (VanBrocklin II), ¶¶ 65-70, 94-98.

²¹⁵ EX1003 (Zeglis I), ¶¶ 174-179; EX1006 (Jansen), 3060-3063; See Appendix D, below.

²¹⁶ EX1007 (Jansen 2013), 493-494; EX1003 (Zeglis I), ¶¶ 174-179.

and PREP affinity.²¹⁷ A POSA would not infer from those data that every useful radiotracer should place a radiohalogen directly on the pharmacophore.²¹⁸

151. A POSA developing a FAP radiopharmaceutical would also seek to de-risk the molecule by minimizing steric interactions between substituents on the quinoliny ring.²¹⁹ 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 61.²²⁰

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.²²¹ 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

²¹⁷ 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), ¶¶ 174-179. See also Appendix D, below.

²¹⁸ EX1003 (Zeglis I), ¶¶ 44, 63, 175; EX1007 (Jansen 2013), 493-494.

²¹⁹ EX1003 (Zeglis I), ¶ 178.

²²⁰ EX1003 (Zeglis I), ¶ 154; EX2029 (VanBrocklin II), ¶¶ 82-83.

²²¹ EX1003 (Zeglis I), ¶¶ 37-38, 45-47, 120-123.

to tune solubility, stability, charge, hydrophobicity, and pharmacokinetics.²²²

153. Linker-based designs also permitted use of radiometals such as gallium-68 or technetium-99m through established chelators rather than limiting the project to a directly attached radiohalogen.²²³ That flexibility allowed POSAs to select a radionuclide whose decay properties fit the intended PET, SPECT, or therapeutic application.²²⁴ It also avoided placing a radionuclide at a position where a particular substitution could impair affinity or selectivity.²²⁵ 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.²²⁶

154. Dr. VanBrocklin cites to a 2014 review by Sugiara (EX2024) 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

²²² EX1003 (Zeglis I), ¶¶ 45-47, 120-123.

²²³ EX1003 (Zeglis I), ¶¶ 42, 45-46, 52-53, 183-191.

²²⁴ EX1003 (Zeglis I), ¶¶ 49-53, 112-114, 183-197.

²²⁵ EX1003 (Zeglis I), ¶¶ 44-47, 174-179; EX2023 (Zeglis Tr.), 100:15-101:11, 111:2-12.

²²⁶ EX1003 (Zeglis I), ¶ 46; EX2029 (VanBrocklin II), ¶ 69; EX1069 (VanBrocklin Tr.), 243:20-244:20.

faster-clearing small molecules.²²⁷ Sugiara also acknowledged the benefits of using a linker, noting that an antibody conjugated with a linker and chelator-radionuclide matrix exhibited a favorable safety profile and better *in vivo* stability over direct radioiodination.²²⁸

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.²²⁹ 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.²³⁰

156. My discussion of roughly 10 to 20 bonds-length described a practical design range for reducing reporter-pharmacophore interference, not a categorical

²²⁷ EX2029 (VanBrocklin II), ¶ 96; EX2024 (Sugiara 2014), Abstract, 2136, 2145-46.

²²⁸ EX2024 (Sugiara 2014), 2142, 2146.

²²⁹ EX1004 (US-633), [0130]-[0133]; EX1003 (Zeglis I), ¶¶ 106, 122, 185-188.

²³⁰ EX1003 (Zeglis I), ¶¶ 185-188.

rule that shorter or longer linkers could never work.²³¹ Radiopharmaceutical chemists routinely evaluate a small series of linker lengths because linker effects are context-dependent.²³² That ordinary optimization does not negate the reason to begin with an established linker class disclosed by the prior art.

157. The Siwowska (EX2026) study cited by Dr. VanBrocklin involved albumin-binding radiofolates and compared specific linker constructs in that different molecular system.²³³ 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.²³⁴

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-

²³¹ EX1003 (Zeglis I), ¶¶ 122, 187; EX2023 (Zeglis Tr.), 181:16-182:20.

²³² EX1003 (Zeglis I), ¶¶ 45-47, 120-123, 185-188; EX1069 (VanBrocklin Tr.), 161:16-162:19.

²³³ EX2026 (Siwowska), Abstract, 823, 830; EX2029 (VanBrocklin II), ¶ 104.

²³⁴ EX1003 (Zeglis I), ¶¶ 45-47, 55-59, 120-123; EX1069 (VanBrocklin Tr.), 161:16-162:19.

targeting compounds incorporating spacers of between two to four PEG monomer units between the reporter and targeting moieties.²³⁵

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

159. As I explained in my Opening Declaration, US-633 identifies several reasons to add and vary a linker (“tether”) between the radiolabeling and FAP-binding portions of a radiotracer.²³⁶ 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.²³⁷ In discussing his own 2016 work, Dr. VanBrocklin testified that radiopharmaceutical chemists routinely alter molecular structures and linker lengths to optimize imaging-agent properties.²³⁸ That is precisely what US-633 teaches.

²³⁵ EX1057 (Pomper PCT), 112, 125-126 (Schemes 4-5), 134-143 (Tables 3 and 4).

²³⁶ EX1003 (Zeglis I), ¶¶ 120-123; EX1004 (US-633), [0051], [0101], [0130]-[0133].

²³⁷ EX1004 (US-633), [0101], [0130]-[0133]; EX1003 (Zeglis I), ¶¶ 121-123.

²³⁸ EX1069 (VanBrocklin Tr.), 161:16-162:19; EX1066 (Dannoon 2016), Abstract, 5865.

160. JHU and Dr. VanBrocklin’s division of US-633 compounds into “B-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.²³⁹ 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.²⁴⁰ 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.²⁴¹ 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.”²⁴² 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.²⁴³

161. In US-633’s Compound 1024, the amide carbonyl lies between the radioiodinated prosthetic group and the glycine-pyrrolidine FAP warhead and thus

²³⁹ EX2001 (VanBrocklin I), ¶¶ 50-67.

²⁴⁰ EX1069 (VanBrocklin Tr.), 88:10-22, 89:22-90:13.

²⁴¹ EX1004 (US-633), [0049]-[0051], [0100]-[0133]; EX1003 (Zeglis I), ¶¶ 105-106, 120-123.

²⁴² EX1069 (VanBrocklin Tr.), 88:9-14.

²⁴³ EX1003 (Zeglis I), ¶¶ 105-106; EX1004 (US-633), [0008], [0021].

forms part of the covalent connection bridging those portions in the completed molecule.²⁴⁴ 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.²⁴⁵ 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.²⁴⁶

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.²⁴⁷ 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.²⁴⁸

²⁴⁴ EX1004 (US-633), [0175]; EX2001 (VanBrocklin I), ¶ 52.

²⁴⁵ EX1004 (US-633), [0012], [0025]-[0027].

²⁴⁶ EX1004 (US-633), [0012], [0025]-[0027]; EX1003 (Zeglis I), ¶ 47; EX1069 (VanBrocklin Tr.), 90:5-13.

²⁴⁷ EX1004 (US-633), [0174]-[0185], Table 2; EX1003 (Zeglis I), ¶ 125; EX2001 (VanBrocklin I), ¶¶ 60-62.

²⁴⁸ EX1004 (US-633), Table 2; EX1003 (Zeglis I), ¶¶ 55-58, 125.

US-633 reported approximately 4 nM FAP inhibition for longer-tether compound 1020, which is in the same low-nanomolar range as the approximately 3 nM result reported for compound 1024.²⁴⁹ 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.²⁵⁰ Compounds A1 and A2 used radiometal-chelator reporter systems, while A3 and A4 used radiohalogenated prosthetic groups.²⁵¹ 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.²⁵²

164. Dr. VanBrocklin did not dispute that these examples meet all the

²⁴⁹ EX1004 (US-633), Table 2; EX1003 (Zeglis I), ¶ 125.

²⁵⁰ EX1003 (Zeglis I), ¶¶ 182-206 (exemplary compounds A1-A4).

²⁵¹ EX1003 (Zeglis I), ¶¶ 198-206.

²⁵² EX1003 (Zeglis I), ¶¶ 198-206.

claim requirements. He also testified at his deposition that Compound 60-based examples A3 and A4 had a high likelihood of continuing to target FAP.²⁵³ 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 60.²⁵⁴ The prior art supplied a reason for both choices.²⁵⁵

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.”²⁵⁶ 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

²⁵³ EX1069 (VanBrocklin Tr.), 236:19-238:11.

²⁵⁴ EX2029 (VanBrocklin II), ¶¶ 21, 71-105; EX1003 (Zeglis I), ¶¶ 198-206.

²⁵⁵ EX1003 (Zeglis I), ¶¶ 144-206.

²⁵⁶ EX1069 (VanBrocklin Tr.), 217:2-218:18.

skilled a reasonable expectation of successfully assembling the claimed B-L-A 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.²⁵⁷ Meletta did not suggest that MIP-1232 lacked all FAP binding or that small-molecule FAP radiotracers were categorically nonviable.²⁵⁸ 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."²⁵⁹ 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.²⁶⁰ Compound 60 directly answered that identified

²⁵⁷ EX2029 (VanBrocklin II), ¶¶ 107-108.

²⁵⁸ EX1008 (Meletta), 2088-2095; EX1003 (Zeglis I), ¶¶ 133-138.

²⁵⁹ EX1069 (VanBrocklin Tr.), 52:7-53:11.

²⁶⁰ EX1008 (Meletta), 2095, 2090; EX1003 (Zeglis I), ¶¶ 136-138.

need.²⁶¹

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."²⁶² 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,²⁶³ 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.

²⁶¹ EX1003 (Zeglis I), ¶¶ 144-147.

²⁶² EX1077 (Huang 2020), 723.

²⁶³ EX1078 (Vasdev 2011), 2959.

This unexpected observation was due to high nonspecific, nonsaturable cellular uptake of gefitinib.”²⁶⁴ 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 ’233 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

²⁶⁴ EX1079 (Su 2008), 1089.

connection with US-633.²⁶⁵ Dr. VanBrocklin does not address most of the other 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.²⁶⁶ US-121 is one example. It describes low molecular weight, modular radiotracers directed to PSMA.²⁶⁷ 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.²⁶⁸ 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

²⁶⁵ EX2029 (VanBrocklin II), ¶¶ 113-114; EX1003 (Zeglis I), ¶¶ 227-231, 233-236.

²⁶⁶ EX1003 (Zeglis I), ¶¶ 207-208, 227-229.

²⁶⁷ EX1003 (Zeglis I), ¶¶ 210-226.

²⁶⁸ EX1003 (Zeglis I), ¶¶ 209-237; EX1005 (US-121).

sized, validated FAP targeting moiety.²⁶⁹ Using an established architecture in this 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.²⁷⁰ 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.²⁷¹ I then explained that Jansen teaches the benefits of targeting FAP, and for describing highly selective FAP-targeting moieties, particularly Compound 60.²⁷² 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

²⁶⁹ EX1003 (Zeglis I), ¶¶ 212, 215-221, 233-237; EX1005 (US-121).

²⁷⁰ EX1003 (Zeglis I), ¶¶ 230-243.

²⁷¹ EX1003 (Zeglis I), ¶¶ 207-211.

²⁷² EX1003 (Zeglis I), ¶¶ 227-243; EX1006 (Jansen), 3053-3065.

several specific examples of Compound 60-based radiotracers that have a B-L-A design described in particular examples in US-121.

173. The specific examples of modified US-121 compounds in my Opening Declaration meet the B, L, A, and low-molecular-weight limitations for the reasons stated there.²⁷³ The same Compound 60 affinity, selectivity, and conjugation evidence discussed for Ground 1 provided a reasonable expectation that those structures would retain FAP binding.²⁷⁴

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. Response to Dr. VanBrocklin's Opinions Regarding Written Description and Enablement

175. In his declaration, Dr. VanBrocklin disputed my description of the challenges of producing viable radiotracers and radiotherapeutic agents. That appears to be because he believed that the claims do not require the B-L-A compounds to meet any requirement other than they contain a B moiety, an A

²⁷³ EX1003 (Zeglis I), ¶¶ 235-243.

²⁷⁴ EX1003 (Zeglis I), ¶¶ 174-179, 235-243.

moiety and an L moiety arranged in the order B-L-A.²⁷⁵ I explained why that is not correct in § II above.

176. The problem is that the claims reference an immense number of possible B+L+A combinations, but only some unknowable number of them will be B-L-A compounds with sufficient FAP- α selectivity over PREP and will be suitable for use in PET, SPECT or optical imaging, or in radiotherapy.²⁷⁶ Failed attempts to make FAP-targeting and other radiotracers before 2017 told POSAs that not all B+L+A combinations will yield a compound that is suitable for imaging or radiotherapy.²⁷⁷ The size, shape, and chemical character of the appended B+L moieties, and their positioning relative to the FAP-targeting pharmacophore, can each disrupt FAP binding in unpredictable ways that reduce selectivity for FAP over PREP.²⁷⁸ Certain combinations of components may degrade in physiological or other experimental conditions that are used in imaging and radiotherapy.²⁷⁹ The description is a research plan that requires the POSA to

²⁷⁵ See EX2029 (VanBrocklin II), ¶¶ 41, 43, 125-128; EX2001 (VanBrocklin I), ¶¶ 44-46, 89-92.

²⁷⁶ EX1001 (US-233), 7:41-57.

²⁷⁷ EX1008 (Meletta), 2089-2090; EX2029 (VanBrocklin II), ¶ 189.

²⁷⁸ EX1003 (Zeglis I), ¶¶ 59(b); 175.

²⁷⁹ EX1003 (Zeglis I), ¶ 64.

perform an impossible scale of experimentation to make and assess combinations to know which ones will or will not yield viable imaging or radiotherapeutic agents.²⁸⁰

177. My opinions were not restricted to *in vivo* uses of the claimed compounds.²⁸¹ The properties I identified in my Opening Declaration, such as that the assembled B-L-A compound retain sufficient FAP affinity and selectivity and a functioning optical or radioactive label, are required for the compounds to be suitable for all of the imaging and therapeutic applications the patent describes. *See* ¶¶ 40-46 above.²⁸² A compound that does not retain sufficiently high selectivity for FAP over PREP after conjugation would render the “B” moiety (and thus the entire compound) **unsuitable** for PET, SPECT or optical imaging, or for radiotherapy, whether performed *in vivo* or “*in vitro*.” That is because the compound will not do the most basic thing it needs to—differentiate a sample that contains the FAP- α target from one that does not.²⁸³

²⁸⁰ EX1003 (Zeglis I), ¶ 277-278.

²⁸¹ EX2023 (Zeglis Tr.), 38:20-39:10, 62:18-63:5, 80:9-15.

²⁸² EX1003 (Zeglis I), ¶¶ 251, 270, 274.

²⁸³ EX1003 (Zeglis I), ¶¶ 270, 275.

A. Response to Dr. VanBrocklin's Opinions on Written Description Issues

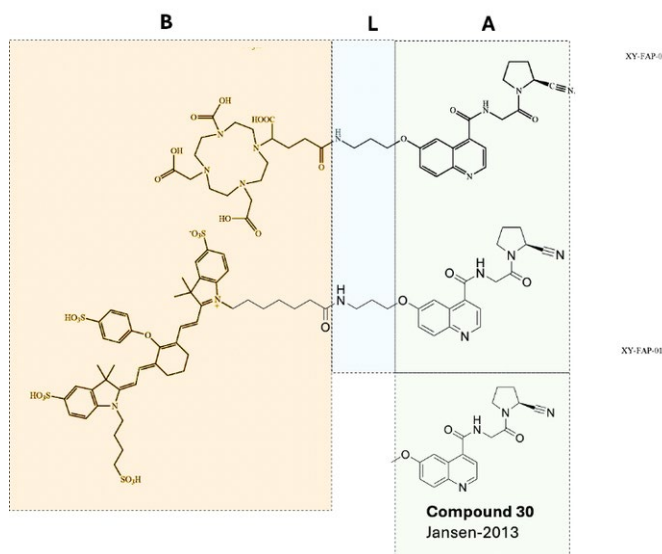
1. The Two Examples of B-L-A Compounds Do Not Demonstrate Possession of the Claimed B-L-A Compounds

178. As I explained in my First Declaration, the patent describes only two examples of compounds having the “B-L-A” design. One is the optically labelled compound “XY-FAP-01” and the other is an ¹¹¹In-labelled compound “XY-FAP-02” for SPECT imaging. The two compounds contain the same “A” moiety and the same “L” moiety (below). Both examples also use the same ether attachment at C⁶ of the quinolinyl ring of the A moiety.²⁸⁴ The only difference is the imaging moiety (“B”): XY-FAP-01 is a dye, and XY-FAP-02 is a chelator (DOTA).²⁸⁵ There are no other examples in the patent of a complete, specific B-L-A compound. There also are no examples of assembled B-L-A radiotracers suitable for PET imaging or that incorporates a radiolabeled prosthetic group.²⁸⁶

²⁸⁴ EX1001 (US-233), 53:1-15, 53:48-50, 57:37-60; EX1003 (Zeglis I), ¶¶ 249-250. EX1069 (VanBrocklin Tr.), 195:18-197:9, 197:15-21; EX1067 (XY-FAP-01); EX1068 (XY-FAP-02).

²⁸⁵ EX1067 (XY-FAP-01), EX1068 (XY-FAP-02).

²⁸⁶ EX1001 (US-233), 53:1-15, 53:48-50, 57:37-60; EX1003 (Zeglis I), ¶¶ 248-249. See also Appendix E, below (chart of the disclosed examples against the variables spanned by the claimed genus).



179. An important omission in the patent is the IC_{50} and selectivity values for XY-FAP-02. This means a POSA cannot assess the impact on selectivity of the B and L choices in XY-FAP-02 using the criteria Dr. Pomper said were how one knows if a B-L-A compound has sufficiently high selectivity to differentiate it from the prior art reference compounds.²⁸⁷

180. Dr. VanBrocklin believes these two examples are “representative” of the entire claimed genus because they share the B-L-A formula.²⁸⁸ I disagree.

- (a) The “B-L-A” *formula* does not identify any chemical attributes of B and L moieties or which “A” compounds meeting the structure “X” definition will yield specific B-L-A compounds with sufficient

²⁸⁷ EX1002 (US '233 FW), 171-176.

²⁸⁸ EX2001 (VanBrocklin I), ¶ 93; EX2029 (VanBrocklin II), ¶¶ 132, 135.

selectivity over PREP to function as a “FAP- α targeting” moiety, both independently and within the assembled B-L-A compound. It also does not describe specific chemical structures or types of chemical bonds that must be used or chemical attributes of the compounds being joined. A POSA cannot visualize the precise chemical structures in any particular compound from the B-L-A design.²⁸⁹ The “B-L-A” formula is just a conceptual description of the arrangement of parts of a chemical compound.

- (b) The two examples interrogated only one variable - the imaging moiety (“B”). The A and L moieties were identical in both examples. No POSA would portray these two examples to be representative of all possible combinations.
- (c) The claims do not include in their definitions of “B” and “L” moieties any language that identifies chemical structures each moiety must possess to be suitable for PET, SPECT, optical imaging or radiotherapy. The specification also does not define “B” or “L” with particular required chemical structures. It just lists known examples of

²⁸⁹ EX1003 (Zeglis I), ¶¶ 247-48, 253-54, 259-260, 270-72.

imaging groups (“B”) and linkers (“L”), but emphasizes those are just “representative” examples that do not restrict B or L choices.²⁹⁰

181. Dr. VanBrocklin incorrectly equates my observations that the B-L-A design is “modular” (EX1003, ¶ 37) and “flexible” (EX1003, ¶ 38) as meaning it increases the ability of a POSA to know *which* B and L moieties can be combined with a FAP-targeting moiety to yield FAP-targeting B-L-A compounds that can be used in imaging and radiotherapeutic applications.²⁹¹ A modular architecture is useful for organizing a research plan, but it does not *identify* any successful combinations of the moieties, or suggest that all B, L and A moiety choices are interchangeable and will yield successful combinations. Certainly, the two B-L-A examples in the specification are not representative of every combination that the claim parameters permit.²⁹²

182. As I explain in ¶¶ 241-245 below, empirical evidence from Jansen and JHU’s own B-L-A data demonstrates that minor structural modifications lead to unpredictable effects on physicochemical properties such as affinity, selectivity

²⁹⁰ EX1001 (US-233), 17:58-69 (“Representative radiolabeled prosthetic groups include, but are not limited to...”); 19:8-10 (“Representative chelating agents include, but are not limited to:”).

²⁹¹ EX2029 (VanBrocklin II), ¶ 135.

²⁹² EX1003 (Zeglis I), ¶¶ 37-47, 248-251, 270-272.

and stability. A POSA therefore could not determine imaging or therapeutic suitability for a B-L-A compound from a conceptual, general arrangement of the imaging, linker and targeting moieties alone. Changing a reporter, linker, attachment site, or targeting moiety clearly can change the compound's physicochemical properties in unpredictable ways.²⁹³ Shared modular labels do not describe specific structures of the B-L-A compounds within the claim's scope that are FAP-targeting B-L-A compounds suitable for imaging or radiotherapy.²⁹⁴

2. The Patent Does Not Describe the Full Range of Types of B-L-A Compounds that JHU Says Are in the Claim Scope

183. In his declaration, Dr. VanBrocklin says that a “POSA with experience in developing and evaluating radiotracers would have known how to combine known ‘A,’ ‘B,’ and ‘L’ moieties as disclosed in the ’233 patent specification.”²⁹⁵ But what Dr. VanBrocklin references are the two examples plus the option of a POSA picking and choosing individual A, B and L moieties listed in the patent.²⁹⁶

184. Dr. VanBrocklin illustrates how a POSA would identify particular “B-

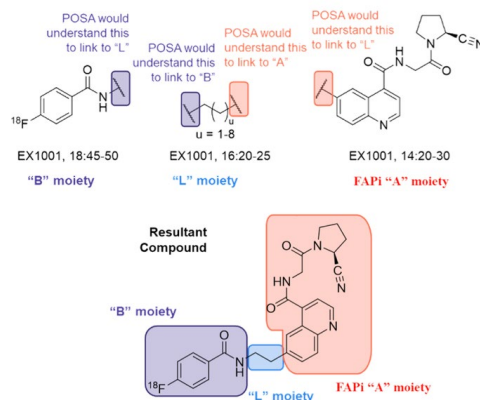
²⁹³ EX1003 (Zeglis I), ¶¶ 43-47, 221, 270, 276, 280-286.

²⁹⁴ EX1003 (Zeglis I), ¶¶ 247-48, 251, 253, 255, 260, 270-73.

²⁹⁵ EX2029 (VanBrocklin II), ¶ 131.

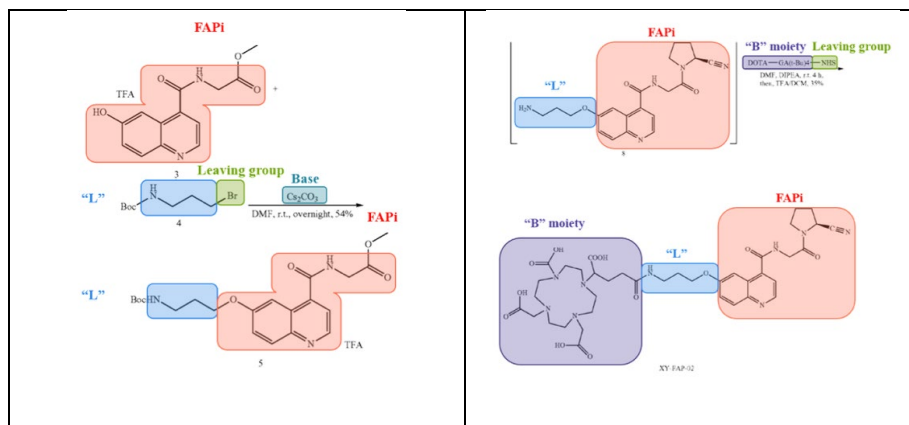
²⁹⁶ EX2029 (VanBrocklin II), ¶¶ 131; *See also* ¶¶ 25, 98, 129, 135, 141, 174.

L-A” compounds using the information in the patent: “I have taken three disclosed ‘B’, ‘L’ and ‘A’ moieties from the ‘233 patent and annotated them, in color, the way a POSA would have understood.”²⁹⁷ Then he provides the below illustration.



185. Dr. Van Brocklin then illustrates how the specification describes producing a B-L-A compounds in a sequence of steps. He explains that first a A-L intermediate is produced by linking one A group to one linker. The other end of the linker part of this A-L intermediate has a protecting group on its other functional group (e.g., a “Boc” group that protects the terminal amine). The A-L-intermediate is linked to a single B group.

²⁹⁷ EX2029 (VanBrocklin II), ¶ 131.



186. Dr. VanBrocklin's explanations and illustrations show what a POSA would understand the B-L-A language in the specification to be defining: a compound that has one "B" moiety linked to one "L" moiety, and one A moiety linked to the other end of that "L" moiety. This yields a B-L-A compound with a 1:1:1 relationship of the B, L and A moieties, and where one linker has two bonds that join the three components.

187. At his deposition, Dr. VanBrocklin confirmed this is how he understood the specification to be describing the structure of the claimed B-L-A compounds. His testimony is reproduced below.

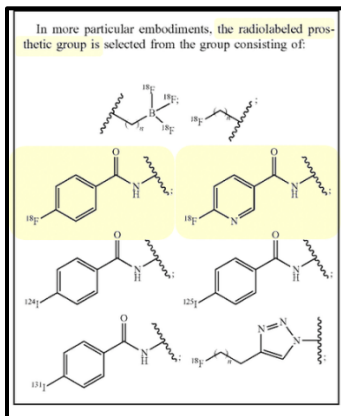
Q. Okay, so let me make sure I understand that. So you have the B moiety, and the L attaches on one side of L to the B moiety, right?

A. That's -- yes.

Q. And then you have an A moiety, and the other side of the L attaches to the A.

A. That's correct, it is a bi -- as described here, a bifunctional molecule, so it means it can interact with the A and interact with -- react with A, react with B, and form the full structure.²⁹⁸

188. I explained in my First Declaration that the patent specification lists a variety of examples of “B” and “L” moieties. It lists two general types of “B” moieties, chelators and prosthetic groups.²⁹⁹ The specification describes the following chemical structures as being “radiolabeled prosthetic groups.” The highlighted group includes the common ¹⁸F-fluorobenzamide and ¹⁸F-fluoropyridinecarboxamide prosthetic groups.



189. Dr. VanBrocklin used this “prosthetic group” nomenclature in the same way in his own work. For example, at his deposition he identified the ¹⁸F-fluorobenzamide moiety in one of the radiotracers he was investigating as a

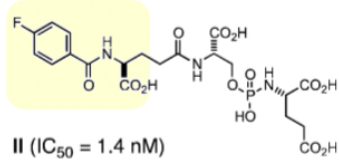
²⁹⁸ EX1069 (VanBrocklin Tr.), 85:14-86:1.

²⁹⁹ EX1003 (Zeglis I), ¶¶ 252-253.

“prosthetic group” (below).³⁰⁰

Structure–Activity Relationship of ¹⁸F-Labeled Phosphoramidate Peptidomimetic Prostate-Specific Membrane Antigen (PSMA)-Targeted Inhibitor Analogues for PET Imaging of Prostate Cancer

Shorouk Dannoon,^{1,2} Tanushree Ganguly,^{1,2} Hendry Cahaya,¹ Jonathan J. Geruntho,³ Matthew S. Galliher,² Sophia K. Beyer,¹ Cindy J. Choy,² Mark R. Hopkins,² Melanie Regan,⁴ Joseph E. Blecha,¹ Lubica Skultetyova,³ Christopher R. Drake,¹ Salma Jivan,² Cyril Barinka,³ Ella F. Jones,^{1,2} Clifford E. Berkman,^{1,2,3,4} and Henry F. VanBrocklin^{1,2,3}



II (IC₅₀ = 1.4 nM)

Figure 1. Phosphoramidate-based PSMA inhibitors and radiolabelling precursors.

17 Q So just tell me what -- tell me what 1 and

18 2 are.

19 A One is a phosphoramidate molecule that

20 binds to PSMA, and 2 is the fluorobenzamide

21 version of that PSMA molecule, same PSMA molecule.

22 Q And the fluorobenzamide unit is a

1 prosthetic group that can be used as your

2 radiolabel, right?

3 A In this case, we introduced this as a

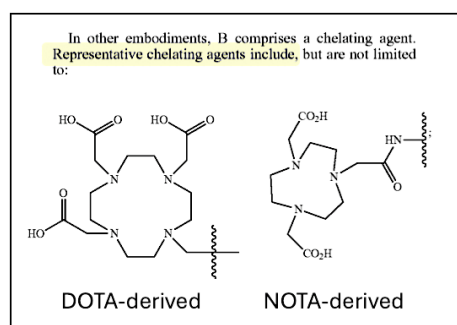
4 prosthetic group.

5 Q Okay, and when you make it a radioactive

6 version of it, you use ¹⁸F?

7 A That is correct.

190. The specification states that each of the following chemical structures is a “chelating group”:



191. In ¶ 149 of his second Declaration,³⁰¹ Dr. VanBrocklin described the 11 Pomper Compounds that were listed in Dr. Pomper’s declaration as “additional working examples disclosed during the prosecution of the ’233 Patent” and being an “additional 11 species fall within the scope of the claims.” He says these

³⁰⁰ EX1066 (Dannoon), 5684-5685; EX1069 (VanBrocklin Tr.), 156:22-157:3; 158:17-159:7.

³⁰¹ EX2029 (VanBrocklin II), ¶ 149.

“working examples” “provide additional enabling disclosure” and that they “have a diverse set of ‘B’ and ‘L’ moieties.” In the table below paragraph ¶ 149, Dr. VanBrocklin includes a column that identifies the “B function” for all of the compounds and indicates all of the halogens in the compounds are radiohalogens (below). Those are Pomper Compounds 1 to 9.

Citation	“B” Moiety Structure	“L” Moiety Structure	B-L-A MW (g/mol)	B Function	B MW (g/mol)	Citation	“B” Moiety Structure	“L” Moiety Structure	B-L-A MW (g/mol)	B Function	B MW (g/mol)
EX1002, 174 (Pomper Decl., ¶42)			370	Radiohalogen (F)	19.0	EX1002, 175 (Pomper Decl., ¶42)			1049	Dual 3-membered chelator (DOTA) / radiohalogen (F)	652.7
EX1002, 174 (Pomper Decl., ¶42)			734	Radiohalogen (F)	369.3	EX1002, 175 (Pomper Decl., ¶42)			1073	Dual 3-membered chelator (DOTA) / radiohalogen (F)	711.4
EX1002, 174 (Pomper Decl., ¶42)			983	Dual 3-membered chelator (DOTA) / radiohalogen (I)	620.4	EX1002, 175 (Pomper Decl., ¶42)			1266	Dual 3-membered chelator (DOTA) / radiohalogen (F)	888.4
EX1002, 174 (Pomper Decl., ¶42)			876	Dual 3-membered chelator (DOTA) / radiohalogen (F)	502.4	EX1002, 175 (Pomper Decl., ¶42)			889	Dual 2-membered chelator (NOTA) / radiohalogen (F)	525.3
EX1002, 175 (Pomper Decl., ¶42)			734	Radiohalogen (F)	369.3						

192. The 11 compounds are not described in the disclosure of the '233 Patent. They are also not described in document that was incorporated by reference by the '233 Patent. They are instead described and discussed in a PCT application that JHU filed in 2021 (WO 2022/212958) (the “Pomper PCT”) (EX1057), several years after the applications that led to the '233 patent were first

filed (2017).³⁰²

193. The Pomper PCT describes the 11 Pomper Compounds as having “Formula (III)” (below right). It presents this formula using the same style that the ’233 Patent uses to describe the B-L-A compounds (“Formula (I)”) (below left).³⁰³ As can be seen the two formulae depict structurally distinct classes of compounds.

'233 Patent	Pomper PCT Formula (III)	Pomper PCT Formula (IV) ³⁰⁴
<p style="text-align: center;">B-L-A</p> <p style="text-align: center;">(I)</p>	$ \begin{array}{c} C_1 \\ \\ L_{c1} \\ \\ A-L_a - \text{---} L_b - B \\ \\ L_{c2} \\ \\ C_2 \end{array} \quad (III); $	$ \begin{array}{c} C \\ \\ L_c \\ \\ A-L_a - \text{---} L_b - B \end{array} \quad (IV); $

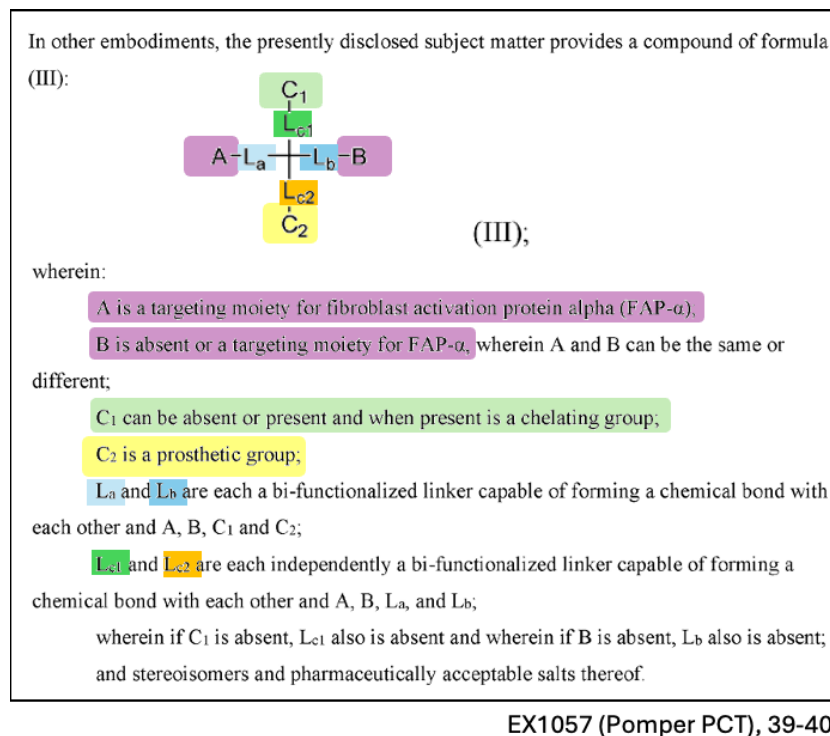
194. The Pomper PCT provides a description of the components of

³⁰² EX1057 (Pomper PCT), 39:16-40:12.

³⁰³ EX1001 (US-233), 1:65-67; EX1057 (Pomper PCT), 3:1-14.

³⁰⁴ The compounds of Formula (IV) contain both FAP- and PSMA-targeting moieties. EX1057 (Pomper PCT), 55:6-17. Table 4 of the Pomper PCT identifies exemplary compounds that fall under the scope of formula (IV). EX1057 (Pomper PCT), 141:2-143:1. Each heterobivalent FAP/PSMA-targeting compound listed in Table 4 was among the list of compounds for which JHU separately produced data. See, e.g., EX1071 (JHU Production Records), 46 (JHU_000270).

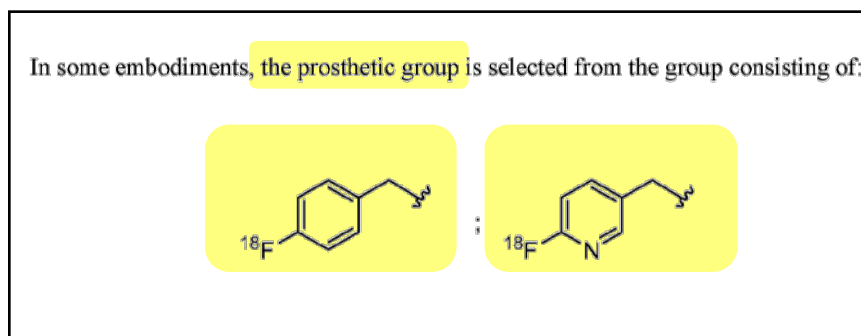
Formula III. An annotated description showing how each component corresponds to the parts of Formula III is shown below.



195. The Pomper PCT identifies many of the same chemical structures as being “prosthetic groups” according to C₂ (below) that were defined to be prosthetic groups in the ’233 Patent.³⁰⁵ As can be seen, the Pomper PCT identifies these structures, including the ¹⁸F-fluoropyridinecarboxamide, as being “prosthetic groups.” The Pomper PCT also identifies as C₁ groups the DOTA-derived and NOTA-derived structures shown in the ’233 Patent.³⁰⁶

³⁰⁵ EX1057 (Pomper PCT), 42.

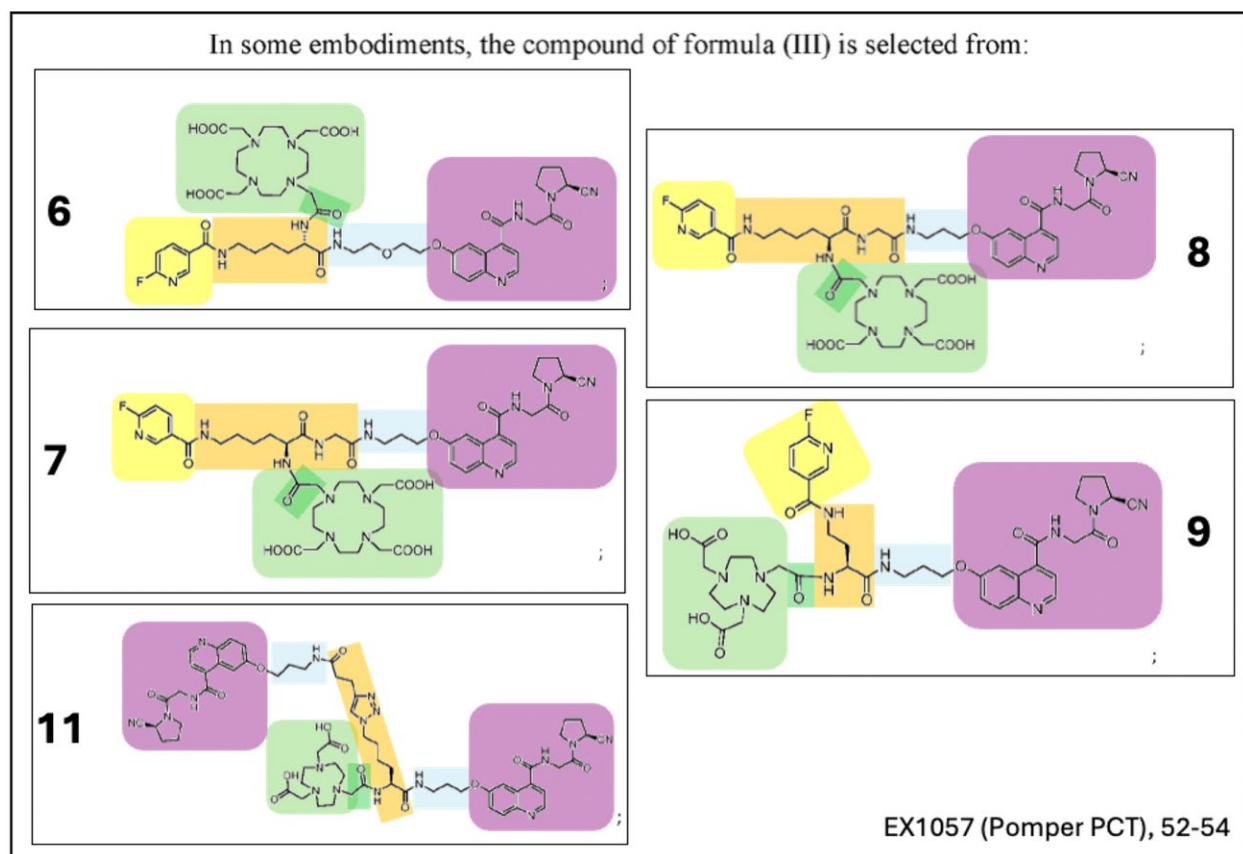
³⁰⁶ EX1057 (Pomper PCT), 43-44.



196. The Pomper PCT describes a variety of structurally distinct classes of radiotracer compounds relative to the simple B-L-A formula discussed in the '233 Patent. Formula III depicts those compounds having (i) one or two target binding moieties "A" and "B" (*e.g.*, two FAP-targeting moieties, one FAP-targeting plus one PSMA-targeting), (ii) one chelating group C₁, (iii) one prosthetic group C₂, and (iv) four linkers that connect the various components.

197. The Pomper PCT lists Pomper Compounds 2, 3, 4, 6, 7, 8, 9, 10, and 11 as examples of its Formula III compounds.³⁰⁷ Pomper Compounds 6, 7, 8, 9 and 11 are annotated using the color scheme for Formula III in ¶ 194.

³⁰⁷ EX1057 (Pomper PCT), 52-54. The Pomper PCT also identifies Pomper Compounds 2, 3, 4, and 10 as Formula III compounds.



198. As Dr. VanBrocklin points out in his declaration, each of Pomper Compounds 3, 4, and 6 to 9 has **two radiolabeled imaging moieties**: (i) one chelator moiety and (ii) one radiohalogenated prosthetic group.³⁰⁸ Compound 11, by contrast, shows a structure that has **two FAP-targeting moieties** attached to the compound, with a chemical linkage to a NOTA-derived chelating group positioned

³⁰⁸ EX2029 (VanBrocklin II), ¶ 149. I note that Dr. VanBrocklin classified the benzylamine of Pomper Compound 3 and pyridine of Pomper Compound 4 as prosthetic groups because they are attached to a radiohalogen. In my experience, those two structure would be very difficult prosthetic groups to use because they are attacked via alkylation to a secondary amine.

between them.

199. Dr. Pomper and his co-inventors addressed some of the shortcomings of prior forms of radiotracers, as well as new functionalities and capabilities associated with the more structurally complex radiotracers covered by the formulae in the Pomper PCT. Some examples included (all citations to EX1057 (Pomper PCT) with emphasis added):

- (a) “*To date*, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP- α ,” (9:27-28).
- (b) “The highly potent and specific binding moiety targeting FAP- α enables its nuclear imaging and radiotherapy. Herein, *the first synthesis* of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to FAP- α for nuclear imaging is described,” (120:10-13).
- (c) “The presently disclosed subject matter provides *the first synthesis* of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to FAP- α and PSMA,” (10:25-27).
- (d) “A platform targeting both PSMA and FAP- α simultaneously would not only be able to image, but if suitably functionalized with therapeutic agents, also would be able to treat cancers associated with

PSMA and FAP- α *in a superior fashion to any one agent alone*”

(1:16-19).

- (e) “Without wishing to be bound to any one particular theory, it was thought that a heterobivalent agent targeting fibroblast activation protein alpha (FAP) and PSMA, as both are abundantly expressed within the TME, and the latter on prostate tumor cells, may enhance cancer detection and therapy,” (108:15-18).
- (f) “A dual-targeting approach has the advantage of managing two biologically disparate targets and could lead to synergy,” (115:22-23).

200. A POSA would have viewed the examples of Formula III compounds described in the Pomper PCT in Dr. Pomper’s Declaration to be both structurally and functionally distinct from the simpler, B-L-A formula described in the ’233 Patent. The way those are described in the Pomper PCT also reinforce that they are materially different designs and compounds than the ones being described in the ’233 Patent.

201. There is no description in the ’233 Patent of radiotracer designs or formulae other than the “B-L-A” one that is a 1:1:1 structure (one B, one L, one A, in that order). There are no statements in the patent that suggest that one B-L-A compound should incorporate multiple or distinct imaging moieties (“B”) or more than one copy of the targeting moiety. There are no examples of compounds that

include more than one targeting or imaging moiety. The patent also explains that the linker L is one that has “bi-functionalization adapted to form a chemical bond with B and A.”³⁰⁹ This reinforces that there is one B and one A being joined by a linker structure in the assembled compounds. The patent does show use of a linker that contains multiple linker subunits joined together, but that linker design yields a linear linker with only two functional groups on it, one at the start and one at the end of the linker sequence.

202. I do not believe a POSA could have read the '233 patent and concluded the inventors were describing B-L-A compounds that incorporate more than one imaging moiety or more than one targeting moiety. I see nothing in the patent would have led a POSA to conclude from its description that the inventors were in possession of the Pomper Compounds, or compounds that have the more complex formulae in the Pomper PCT, when they first filed that patent application in October of 2017.

3. The Specification Does Not Adequately Describe Unpredictable Chelator-Radionuclide Pairings

203. Dr. VanBrocklin treats the listing of chelator options as describing

³⁰⁹ EX1001 (US-233), 2:3-5, 8:22-24. *See also* EX1001 (US-233), 3:5-11 (stating anchor figure “indicates a point of attachment of *the* FAP- α binding ligand to *the* linker, L, or *the* reporter moiety, B”).

particular chelator-based radiopharmaceutical compounds, including for claim 4.³¹⁰

As I explained in my First Declaration, this overlooks that the claimed B moiety includes not merely a chelator but a chelator paired with a compatible radionuclide, and that such pairing is not guaranteed to be stable.³¹¹ Price (EX1013) confirmed that chelator-radionuclide compatibility may be unpredictable and often must be tested and confirmed, and that even widely used chelators such as DOTA and NOTA require investigation to assess compatibility for particular radionuclides.³¹² The claims cover *all* chelator-radionuclide pairings, including those considered to be unstable or that had not been verified as being stable in the prior art, and the specification does not acknowledge this unpredictability, let alone provide guidance for how to pair chelators with radionuclides.³¹³

4. Lists of Possible Components to Combine Do Not Describe Assembled B-L-A Compounds

204. Dr. VanBrocklin correctly notes that the specification devotes several columns of options for A, B, and L.³¹⁴ However, most appear only as separate

³¹⁰ EX2029 (VanBrocklin II), ¶¶ 129-135.

³¹¹ EX1003 (Zeglis I), ¶¶ 261-267.

³¹² EX1003 (Zeglis I), ¶¶ 262-265; EX1013 (Price), 263-266, 267-268, 272.

³¹³ EX1003 (Zeglis I), ¶¶ 261-267.

³¹⁴ EX2029 (VanBrocklin II), ¶¶ 129, 135; EX2001 (VanBrocklin I), ¶ 94.

formulae, generic classes, or laundry lists.³¹⁵ These passages tell a POSA which bins of components might be explored. They do not identify the covalent structures, attachment chemistry, radionuclide loading, or completed-compound properties for the vast majority of combinations.³¹⁶ Dr. VanBrocklin's description of selecting one item from each column and putting them together is a design instruction rather than a description of particular examples of B-L-A compounds.³¹⁷

205. A squiggly attachment line on an isolated B, L, or A drawing indicates a possible connection point, as Dr. VanBrocklin notes.³¹⁸ It does not identify which counterpart is attached, which bond is formed, or whether the resulting B-L-A structure was made or characterized.³¹⁹

³¹⁵ EX1001 (US-233), 8:13-32:45; EX1003 (Zeglis I), ¶¶ 251-267.

³¹⁶ EX1003 (Zeglis I), ¶¶ 251-267, 270-272.

³¹⁷ EX1069 (VanBrocklin Tr.), 236:6-11 ("These are a couple -- I mean, there's multiple choices one could make here. I mean, you could pick one from column A, pick one from column B and pick one from column L and put them together, right? So these are just one or two of the choices that -- yeah, that could be made, yes."); EX1003 (Zeglis I), ¶¶ 251, 267.

³¹⁸ EX2029 (VanBrocklin II), ¶¶ 129-135; EX2001 (VanBrocklin I), ¶¶ 99-101; EX1003 (Zeglis I), ¶¶ 251-253.

³¹⁹ EX1001 (US-233), 14:20-30, 16:14-20:25, 18:35-65.

206. A POSA would have understood that combining a known chelator, a known radionuclide, a known linker, and the A moiety does not always predictably yield a FAP-targeting B-L-A compound that is suitable for imaging or radiotherapy, because each individual choice can affect binding, stability, and complex formation.³²⁰

207. A POSA would have understood that the choice of linker—its length, rigidity, hydrophobicity, and size—can affect the compound's ability to engage its target with retained affinity and selectivity, which Dr. VanBrocklin does not dispute in his declaration.³²¹ A compound with the same A moiety but a different linker could have a very different character and would not necessarily be expected to exhibit comparable binding or selectivity. Aside from a single alkyl linker, the working examples do not illustrate how the many other linker options would perform.³²²

³²⁰ EX1003 (Zeglis I), ¶¶ 270, 279-302 (Exemplary Compounds C-1 through C-9). See also ¶¶ 220, 222-225 below.

³²¹ EX1003 (Zeglis I), ¶ 270.

³²² EX1003 (Zeglis I), ¶¶ 250, 271-272.

B. Response to Dr. VanBrocklin’s Opinions Regarding Enablement**1. The Claims Require B-L-A Compounds that Bind Selectively to FAP**

208. In his declaration, Dr. VanBrocklin stated that the specification enables the claimed set of B-L-A compounds because it “teaches a POSA how to make and use the claimed low-molecular weight B-L-A compounds.”³²³ He then states “[t]hese claims do not require any function.”³²⁴ But at his deposition, Dr. VanBrocklin testified that the claimed B-L-A compounds did have functional requirements. As he testified:

[i]n order for this molecule to have utility, *it has to bind to the FAP alpha*, and again, can be used in a number of applications in the nuclear imaging and radiopharmaceutical space, including in vitro applications as well.³²⁵

209. Dr. VanBrocklin also recognized this is required by the claims from the “targeting moiety for FAP- α ” language in the claims, and that is a requirement of the claimed B-L-A compounds. When Dr. VanBrocklin was asked what that

³²³ EX2029 (VanBrocklin II), ¶ 137.

³²⁴ EX2029 (VanBrocklin II), ¶137, see also ¶ 87, ¶ 125 (“...the claims do not require that the claimed ‘B-L-A’ *compounds* have this functionality.”) (emphasis in original).

³²⁵ EX1069 (VanBrocklin Tr.), 82:4-13 (emphasis added).

phrase meant, he testified:

A. ...in the context of this patent, the targeting moiety of FAP alpha is describing *the utility of this molecule once it is combined with a linker L and a imaging tag B.*

Q Okay, and that is — that utility is based on the ability of the A moiety to bind to FAP alpha; is that right?

A The ability of the binding moiety to bind to FAP alpha in vitro, in vivo applications.³²⁶

210. 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 imaging applications.³²⁷ 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*.

³²⁶ EX1069, 80:20-81:8.

³²⁷ EX1069: 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, 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).

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.*³²⁸

211. Dr. Pomper's description is true for any imaging agent, whether it is to be used for *in vivo* imaging of a patient or in “*in vitro*” imaging applications. The central requirement of any imaging agent is that when it creates a positive signal on the imaging device, that signal corresponds to binding of the imaging agent to its target (e.g., FAP- α) and not something else.

212. It was well known before 2017 that many small molecule inhibitors of FAP also inhibit PREP and other prolyl peptidase enzymes.³²⁹ This well-known cross-reactivity is why the primary focus of experimentation on FAP inhibitors

³²⁸ EX1002, 172 (¶ 31) (emphasis added).

³²⁹ EX1006 (Jansen), Abstract, 3053; EX1007 (Jansen 2013), 491; EX1024 (Hamson), 457; EX1003 (Zeglis I), ¶¶ 70-72.

concerned their ability to *selectively* bind to FAP relative to other proteins, particularly PREP. Some examples of observations on this point include the following:

Additionally, selectivity for FAP with respect to prolyl oligopeptidase (PREP) is reported. Not unexpectedly, the latter data suggest significant overlap in the pharmacophoric features that define FAP or PREP-inhibitory activity and *underscore the importance of systematically evaluating the FAP/PREP-selectivity index for inhibitors* of either of these two enzymes.³³⁰

The challenge has been in identifying inhibitors that are selective for FAP over both the dipeptidyl peptidases (DPPs), with which it shares exopeptidase specificity, and prolyl oligopeptidase (PREP), with which it shares endopeptidase specificity.³³¹

A major hurdle in the study of FAP as a potential disease biomarker is the inability to specifically measure FAP enzyme activity.³³²

2. Discovering Which B-L-A Compounds Bind Selectively to FAP and Are Suitable for Imaging and Radiotherapy Was Not Predictable

213. A major challenge to creating an imaging agent based on highly selective FAP inhibitors, such as the 4-quinolinoyl-Gly-cyanoPro compounds at

³³⁰ EX1029 (Ryabtsova), 3412 (emphasis added).

³³¹ EX2020 (Poplawski), 3467.

³³² EX1024 (Hamson), 457.

issue here, is unpredictability. The Jansen papers showed that very modest chemical changes to the quinolinyl ring of unpredictability altered both the affinity and selectivity of 4-quinolinoyl-Gly-cyanoPro-based compounds.³³³ See ¶¶ 240-244, below. The unpredictability is relevant to the claims in this case because they encompass BLAs that can use ~31,000 different FAP-targeting “A” moieties. Which of those choices retain FAP binding or sufficiently selective binding to FAP is unknown. Discovering which ones are would entail an impossible scale of experimentation.

214. Dr. Pomper emphasized the unpredictability in the field of the claimed invention in his declaration, stating:

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.³³⁴

The *unpredictability of the art* is clearly manifested by the documented failure of a compound disclosed in Zimmerman.³³⁵

³³³ EX1003, ¶¶ 175, 178, 298-302; Appendix D, below.

³³⁴ EX1002 (US-233 FW), 172 (¶ 31) (emphasis added).

³³⁵ EX1002 (US-233 FW), 172 (¶ 32) (emphasis added).

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.³³⁶

215. Even when one has a selective FAP inhibitor in hand, some amount of unpredictability remains. As I explained in my First Declaration, there are a number of linker-imaging agent combinations that have been used successfully radiotracers. The claims, however, capture every choice that exists for imaging and linker moieties. The claims capture B-L-A compounds that include any “B” imaging moiety that is “suitable for” PET/SPECT/optical imaging or radiotherapy. As the claims recognize, not every one or every combination of B and L will preserve the selectivity needed for a B-L-A compound to be used in imaging or radiotherapy.

216. The specification does not provide any meaningful guidance to the POSA to overcome the unpredictability surrounding identification of A moieties that sufficiently and accurately target FAP- α , and creating B-L-A forms of them that are suitable for imaging or therapy.

- It describes only two examples of B-L-A compounds, which vary only

³³⁶ EX1002 (US-233 FW), 173 (¶ 37) (emphasis added).

in the B portion of the compounds, and does not report the affinity or selectivity for one of them (XY-FAP-02).³³⁷

- It provides lists of known chelators, prosthetic groups, linkers and even FAP-targeting moieties. But it presents all these options as being equivalently plausible choices for any combination.
- It instructs that the three components are to be assembled into the formula “B-L-A.” This is a design that has been used for decades in radiopharmaceutical development and is perhaps the simplest conceptual way of combining three components of a radiopharmaceutical.

217. The guidance in the specification leaves the POSA with about $\sim 10^{27}$ to $\sim 10^{39}$ possible B-L-A combinations to evaluate (§§51-53).³³⁸ What the specification does not provide is any guidance on making selections among these possible combinations, or experimental insights that might help the POSA navigate this immense array of choices. That means the POSA must decide which combinations to make and evaluate driven by their own investigations and

³³⁷ See §§ 178-181, above.

³³⁸ EX1003 (Zeglis I), §§ 94, 96. Actual numbers likely much larger, as my calculation does not include other B and L moieties, different radionuclides, enantiomers, diastereomers, tautomers, racemates, salts, and solvates.

decisions. Even a one-in-a-million sampling of the smallest calculated set of B-L-A combinations captured by the claims would require evaluation, synthesis and testing of $\sim 10^{21}$ compounds—an immense level of effort, time, money, and experimentation.³³⁹

218. 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.³⁴⁰ 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.

³³⁹ EX1003 (Zeglis I), ¶¶ 273-278.

³⁴⁰ EX1009 (Jamous), 3381, EX1003, ¶¶ 37-38

A. If the molecule still binds to FAP, that would be included in the scope of the -- scope of the claim.³⁴¹

219. I also note that Dr. VanBrocklin's testimony also 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.

220. Structural modifications or changes to the A, B, and L moieties can alter important physicochemical attributes of the B-L-A molecule, including its affinity, selectivity, hydrophobicity, stability, and other attributes. The resulting work required by the claims is an open-ended screening program caused by the absence of predictive direction, not simply the cumulative time required to repeat a known path.³⁴² I believe this imposes an undue amount of experimentation on the POSA, even if one does not even consider the need to identify which of the resulting B-L-A compounds possess the ability to target FAP and are suitable for use in optical, PET or SPECT imaging, or in radiotherapy.

221. I have been informed that the standard for enablement was established in *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023), which explained that the specification must enable the full breadth of the claimed invention. In his

³⁴¹ EX1069 (VanBrocklin Tr.), 234:2-235:5.

³⁴² EX1003 (Zeglis I), ¶¶ 251, 270-278, 287-302.

declaration, Dr. VanBrocklin goes through what he calls the *Wands* factors.³⁴³ I understand that those factors are relevant to the question of whether the claims require undue experimentation, and I have considered those factors in my assessment of why the claims lack enablement, as explained below.

3. The '233 Patent Does Not Teach a POSA How to Make and Use the Full Scope of Claimed B-L-As

222. Contrary to Dr. VanBrocklin's statements, my opinions on enablement do not depend solely on the compounds being used in *in vivo* applications.³⁴⁴ As I explained in my Opening Declaration, a POSA would have understood that the identities of the A, B, and L moieties—and the point and manner of their attachment—affect the completed B-L-A compound's FAP affinity, selectivity, stability, and solubility, all of which influence whether a compound will be suitable for the any of the imaging or therapeutic uses of B-L-A compounds.³⁴⁵ For the patent's *in vivo* applications, those variables can also affect the compound's pharmacokinetic profile and bioavailability.³⁴⁶

³⁴³ EX2029 (VanBrocklin II), ¶¶ 34-35, 173-195.

³⁴⁴ EX2029 (VanBrocklin II), ¶¶ 157, 165-169; EX2001 (VanBrocklin I), ¶¶ 105-109.

³⁴⁵ EX1003 (Opening Decl.) ¶¶ 55, 274-302.

³⁴⁶ EX1003 (Opening Decl.) ¶¶ 46, 51, 59, 275-302.

223. A POSA would understand that for the claimed compounds to have the required FAP imaging use, the completed compound must produce a detectable signal that both binds tightly to FAP and can differentiate tissue expressing FAP from non-target tissue, and those requirements do not disappear merely because the tissue is examined after removal from the body *in vitro*.³⁴⁷

224. Dr. VanBrocklin suggests that attributes of B-L-A compounds that make them suitable for use in *in vivo* applications are not relevant their use in *in vitro* applications.³⁴⁸ I disagree. Many of the chemical and physicochemical properties of B-L-A compounds that make them viable *in vivo* imaging agents are important to them being viable in *in vitro* imaging applications. A POSA would not ignore issues like instability or excessive charge or hydrophobicity characteristics of the compound when evaluating it for use even in simple *in vitro* detection applications.

225. The same core stability and solubility requirements apply when FAP-expressing tissue or cells are examined outside the body because the completed B-L-A compound must remain sufficiently intact through incubation and washing, retain its optical or radioactive reporter, and freely interact with and preserve FAP

³⁴⁷ EX1003 (Zeglis I), ¶¶ 35, 39, 41, 55, 102-104, 274-276, 287-290; EX1008 (Meletta), 2081-83, 2089-90.

³⁴⁸ EX2029 (VanBrocklin II), ¶¶ 25-26, 43, 157.

binding long enough for the detected signal to correspond to the location of FAP-expressing material rather than to degradation products or non-specific accumulation.³⁴⁹ Consistent with those requirements, Meletta incubated tissue sections with [¹²⁵I]MIP-1232 in HEPES buffer at physiological pH 7.4 for 60 minutes, washed the sections repeatedly, and then quantified the retained radioactive signal.³⁵⁰

226. PET and SPECT imaging devices are almost exclusively used to perform imaging on patients or animals, which involves administering the B-L-A compound to the subject and then imaging portions of the body in which the B-L-A compound accumulates. PET, SPECT and optical imaging devices also can be used to image tissue samples obtained from human patients or animals.³⁵¹ To be suitable for imaging in those applications, the B-L-A compounds must still transit through the tissue and selectively accumulate at locations where cells expressing

³⁴⁹ EX1003 (Zeglis I), ¶¶ 41-43, 45, 174, 275-279; EX1008 (Meletta), 2089-90, 2094-95.

³⁵⁰ EX1008 (Meletta), 2094-95; EX1003 (Zeglis I), ¶¶ 41, 275.

³⁵¹ See, e.g., EX1001 (US-233), 5:40-62 (measuring B-L-A uptake by cell lines); EX1001, 7:66-8:3 (using with cell line and implanted tumor from same cell line); 35:47-52 (in vitro assays of body fluids (e.g., blood, urine), cells and tissue samples from humans and animals); 37:22-35 (describing in vitro and ex vivo, and in vivo uses); 60:48-55 (testing XY-FAP-02 against cell line).

FAP are located.³⁵²

227. Dr. VanBrocklin suggests that the claimed B-L-A compounds could be used by mixing them with cells or tumors in a tube.³⁵³ However, as I explained above, the specification and Dr. VanBrocklin both confirm that “imaging” entails measuring the spatial distribution of a target of interest within a particular sample.³⁵⁴ Certain types of samples (e.g., fluid samples like blood or urine) do not maintain a static three-dimensional structure. While it would be possible to detect the presence of a B-L-A compound in such a sample, it would not be possible to derive any type of spatial distribution information about the B-L-A compound in such samples using PET, SPECT or optical imaging devices. A POSA would not read the claims as encompassing use of the B-L-A compounds to perform PET, SPECT or optical imaging on those types of fluid samples.

4. Contrary to Dr. VanBrocklin’s Opinions, FAP Selectivity is Crucial for In Vitro Uses

228. Selectivity affects whether the observed signal can be interpreted as

³⁵² EX1003 (Zeglis I), ¶¶ 34, 48, 104, 275; EX1004 (US-633), [0005].

³⁵³ EX2029 (VanBrocklin II), ¶ 165.

³⁵⁴ EX1001 (US-233), 36:21-29; EX1069 (VanBrocklin Tr.), 99:6-19, 48:22-49:6. See ¶¶ 46-47, above.

FAP-specific over off-target substrates.³⁵⁵ A POSA would not attribute a positive signal specifically to FAP when the probe could also bind an off-target enzyme like PREP, generating a “false positive” result.³⁵⁶ Dr. VanBrocklin also testified that non-specific binding for a radiopharmaceutical “happens quite often” and occurs “because the structure of the molecule has some characteristic that it interacts with other proteins in there.”³⁵⁷ Meletta’s inability to distinguish plaque from normal tissue illustrates that detectable binding alone may not provide the proposed diagnostic information.³⁵⁸ Although the claims do not recite a numerical selectivity threshold, the patent’s asserted FAP-targeted diagnostic and research uses still require sufficient specificity for an interpretable result in the relevant assay context.³⁵⁹ Dr. Pomper acknowledged the importance of FAP/PREP

³⁵⁵ EX1003 (Zeglis I), ¶¶ 55, 70, 151, 275; EX1006 (Jansen), 3053-3054; EX1008 (Meletta), 2083, 2089-2090.

³⁵⁶ EX1003 (Zeglis I), ¶¶ 55-58, 277-278, 287-302.

³⁵⁷ EX1069 (VanBrocklin Tr.), 37:19-39:12.

³⁵⁸ EX1008 (Meletta), 2088-2090; EX1003 (Zeglis I), ¶¶ 133-139, 275.

³⁵⁹ EX1001 (’233 Patent), 7:46-54, 35:47-52; EX1003 (Zeglis I), ¶¶ 55, 70, 274-278; EX1069 (VanBrocklin Tr.), 223:7-228:4.

selectivity for the claimed FAP imaging agents during prosecution.³⁶⁰

229. Dr. VanBrocklin suggests that FAP/PREP selectivity may be irrelevant in a biopsy or other sample that contains only FAP and no material amount of PREP or another off-target enzyme.³⁶¹ Given the ubiquitous expression of PREP across many healthy tissues in the body, such a scenario is highly unlikely (below).³⁶² Further, Dr. VanBrocklin's proposed use presupposes that the sample and the relevant competing targets have already been characterized. Dr. VanBrocklin testified that while the initial characterization assays place FAP and PREP in separate samples, further evaluation is necessary to see if the agent would be "suitable for downstream uses beyond the FAP-targeting ability that the molecule has as a part of this patent."³⁶³ If the *only* asserted utility of a B-L-A compound is that it produces a detectable binding signal in a sample already known to contain nothing but FAP, then the compound is functioning as a research

³⁶⁰ EX1002 (US-233 FW), 172 ("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.").

³⁶¹ EX2029 (VanBrocklin II), ¶ 168.

³⁶² EX1083 (Protein Atlas), 1-2.

³⁶³ EX1069 (VanBrocklin Tr.), 215:1-216:22.

reagent whose sole use is to interrogate a target that has already been fully characterized. The only benefit to this assay would be a benefit to further research the downstream uses Dr. VanBrocklin described in his deposition, which would include the ability to generate a detectable optical or radioactive signal.³⁶⁴ I understand that a mere research plan that requires further testing to identify compounds having the full utility of the claimed compounds is insufficient to satisfy the enablement requirement.³⁶⁵



5. Routine Bond-Forming Chemistry Does Not Always Predict the Properties of the Completed Compound

230. Dr. VanBrocklin claims that the patent's modular architecture, SN2 chemistry, peptide coupling, NHS or activated-ester coupling, aldehyde chemistry,

³⁶⁴ EX1069 (VanBrocklin Tr.), 215:1-216:22; EX1003 (Zeglis I), ¶¶ 33, 273-278.

³⁶⁵ EX1003 (Zeglis I), ¶¶ 28, 273-278.

Fmoc chemistry, and click chemistry teach a POSA how to assemble the claimed compounds.³⁶⁶ That knowledge may allow a POSA to synthesize a selected candidate, but it does not enable them to predict whether the resulting molecule will bind FAP, distinguish FAP from PREP, hold its radionuclide, remain stable and soluble, or produce a usable signal.³⁶⁷ The synthesis evidence therefore addresses the mechanics of making candidates and not than the type of experimentation required to identify viable B-L-A compounds across the full scope of the claims.³⁶⁸

231. Dr. VanBrocklin relies on my statements that US-633 used conventional synthesis and selection of B and L moieties was straightforward.³⁶⁹ Those statements concern the construction of specific designs *after* the components and intended radionuclide have been selected; they do not state that the properties of every claimed combination are predictable.³⁷⁰ My Opening

³⁶⁶ EX2029 (VanBrocklin II), ¶¶ 139-148, 153-156; EX1001, 51:22-48, cols. 55-56.

³⁶⁷ EX1003 (Zeglis I), ¶¶ 41-47, 55-59, 270-278, 287-302.

³⁶⁸ EX1003 (Zeglis I), ¶¶ 273-302; EX2029 (VanBrocklin II), ¶¶ 129-158, 166-192.

³⁶⁹ EX2029 (VanBrocklin II), ¶¶ 139, 156; EX1003 (Zeglis I), ¶¶ 121, 172.

³⁷⁰ EX1003 (Zeglis I), ¶¶ 120-123, 172-179, 247-278.

Declaration separately explains that the reporter-linker attachment must not compromise binding strength or specificity and that linker length and composition can alter affinity, selectivity, solubility, stability, and other properties.³⁷¹ It is for this same reason that the claimed B-L-A architecture does not necessarily make the genus suitable for in vitro use—that architecture is a structural format, not a predictive structure-function relationship.³⁷²

232. Dr. VanBrocklin also contends that structurally analogous linkers, leaving groups, and reporters could be substituted without changing the overall synthetic approach.³⁷³ A POSA would understand that retaining the same bond-forming approach does not always retain the same completed-compound properties, because each added optical dye, prosthetic group, chelator, radionuclide, and linker changes size, charge, rigidity, hydrophobicity, and other chemical features.³⁷⁴ Dr. VanBrocklin likewise testified that adding a reporter can enhance or detract from binding, that chelation introduces bulk, charge, and rigidity that can alter physicochemical and biological properties, and that a linker is

³⁷¹ EX1003 (Zeglis I), ¶¶ 45-47, 121, 174, 270-272.

³⁷² EX2029 (VanBrocklin II), ¶¶ 180, 187, 191-193.

³⁷³ EX2029 (VanBrocklin II), ¶¶ 143-148.

³⁷⁴ EX1003 (Zeglis I), ¶¶ 41-47, 59, 121, 174, 251, 270-278.

one possible mitigation strategy rather than a guarantee of preserved binding.³⁷⁵

233. Radionuclide selection introduces an additional enablement variable because the physical half-life and emission type must fit the intended imaging or therapeutic use and the behavior of the carrier molecule.³⁷⁶ A short-lived PET nuclide, a longer-lived SPECT nuclide, and an alpha-emitting therapeutic nuclide place different timing and stability demands on the same B-L-A scaffold.³⁷⁷ The patent does not provide a predictive framework for matching the enormous set of claimed structures with the many permitted radionuclides.³⁷⁸

234. The optical branch is also broad because the specification lists dyes with widely different sizes, charges, absorption and emission properties, and

³⁷⁵ EX1069, (VanBrocklin Tr.), 232:7-232:12 (“when you incorporate the radioactive isotope, or in this case the optical imaging agent, right? That adds another component to your overall molecule, and that can enhance or detract from the binding of your molecule.”), 242:2-245:9 (“I was agreeing with Dr. Zeglis here that this introduces -- that adding on an L and a B, and especially in the case of metallic radionuclides, introduces structural changes, bulk to the molecule, and -- and would potentially have a adverse effect on interaction of the molecule with the intended target.”); EX2029 (VanBrocklin II), ¶ 69.

³⁷⁶ EX1003 (Zeglis I), ¶¶ 49-53, 275-278.

³⁷⁷ EX1003 (Zeglis I), ¶¶ 49-53, 258-267, 275-278.

³⁷⁸ EX1003 (Zeglis I), ¶¶ 258-267, 273-302.

hydrophobic characteristics.³⁷⁹ Attaching a large near-infrared dye can affect a small FAP inhibitor differently from attaching a compact radiolabeled prosthetic group.³⁸⁰ The single optical example does not provide guidance sufficient to predict the performance of every claimed dye-linker-A combination.³⁸¹

6. Using Routine Assays to Practice the Claims Imposes Undue Experimentation

235. Dr. VanBrocklin stated that the experiments required to characterize a FAP-targeting B-L-A are routine or generally straightforward because the same types of tests appear in Jansen, US-121, US-633, and Meletta.³⁸² The undue burden for this patent arises because there are ~31,000+ molecules within the scope of the “X” structure for the “A” moiety in the claims for which no information exists. A meaningful portion of that set would have to be selected, synthesized, purified, and tested for its affinity and selectivity for FAP. Then, if it had sufficient binding and selectivity properties, it would have to be incorporated into different B+L frameworks, labeled when appropriate, and tested. For this

³⁷⁹ EX1001 (’233 Patent), 24:1-29:53; EX1003 (Zeglis I), ¶¶ 88-90, 251, 270-278.

³⁸⁰ EX1003 (Zeglis I), ¶¶ 43-47, 55-59, 270-278, 280-286.

³⁸¹ EX1003 (Zeglis I), ¶¶ 248-251, 270-302.

³⁸² EX2029 (VanBrocklin II), ¶¶ 170-175; EX1003 (Zeglis I), ¶ 277.

portion of the claim scope, the patent provides no guidance about predicting successful structures.³⁸³ Certainly, not every compound in the claim scope raises these types of questions. But the scale of the claims makes exploring even a modest fraction of the entire scope of *entirely uncharacterized* B-L-A compounds being claimed imposes an incredible volume of experimental work, that I believe would be undue. Calling those assays routine does not convert an open-ended discovery program into a predictable path across the claimed genus.³⁸⁴

236. Jansen illustrates the empirical scale of the work that a POSA would perform to assess new FAP-targeting compounds. That group synthesized ~60 new inhibitors after an earlier series and advanced only a small subset into more extensive stability, pharmacokinetic, toxicity, and *in vivo* studies.³⁸⁵ The study's detailed SAR did not yield a simple rule that predicted all tolerated substitutions or all *in vivo* candidates.³⁸⁶ The patent provides far less guidance.³⁸⁷

237. Dannon (EX1066), coauthored by Dr. VanBrocklin, illustrates the

³⁸³ EX1003 (Zeglis I), ¶¶ 251, 270-278, 287-302.

³⁸⁴ EX1003 (Zeglis I), ¶¶ 273-302.

³⁸⁵ EX1006 (Jansen), 3054-3065; EX1003 (Zeglis I), ¶¶ 145-160.

³⁸⁶ EX1006 (Jansen), 3055-3065; EX1003 (Zeglis I), ¶¶ 174-179, 276.

³⁸⁷ EX1003 (Zeglis I), ¶¶ 84-96, 247-278.

breadth of work involved in developing and comparing even a focused three-member series of radiolabeled targeting agents built on a common scaffold. The development program involved multistep preparation and characterization of nonradioactive reference standards, followed by a separate synthesis, purification, and quality-control run for each corresponding fluorine-18 analog; although the compounds shared a common late-stage labeling strategy, different linker variants required different precursor-building and deprotection sequences.³⁸⁸ The authors then measured potency and mode of inhibition, assessed uptake in target-positive and target-negative cells and internalization in target-positive cells across replicates and time points, and used X-ray co-crystal structures to investigate binding geometry. Those studies revealed material differences among close analogs that were not reliably predicted by linker length or affinity alone.³⁸⁹ Identifying operable compounds throughout the scope of the $\sim 10^{30}$ claimed B-L-A compounds would require extensive, iterative synthesis and testing, not a single routine screen.³⁹⁰ Again, while the individual techniques are conventional, performing them for even a fraction of the universe of B-L-A compounds covered

³⁸⁸ EX1066 (Dannoon), 5685-86, 5690-95, Schemes 1-2.

³⁸⁹ EX1066 (Dannoon), Abstract, 5685-89, 5692, Table 1.

³⁹⁰ EX1003 (Zeglis I), ¶¶ 94-96, 247.

by the claims implicates an immense scale of experimentation that I believe would be undue.³⁹¹

238. Dr. VanBrocklin characterizes the C-series examples I illustrated in my Opening Declaration as readily recognizable problem compounds and any remaining testing as optimization.³⁹² Several of those examples cannot be resolved by inspection, and Jansen's conflicting data for closely related 5-substituted compounds show that structural similarity does not reliably predict affinity or selectivity.³⁹³ The testing I described determines whether a claimed member has the FAP interaction, selectivity, stability, and reporter behavior needed for the proposed use, rather than merely selecting the best conditions for a member already known to work.³⁹⁴

7. The Breadth of A and the Attachment-Site Choices Remain Empirical

239. I disagree with Dr. VanBrocklin that the variable substituents are on the pyrrolidine ring and pyrrolidine building blocks can be exchanged through

³⁹¹ EX1003 (Zeglis I), ¶¶ 276-278.

³⁹² EX2029 (VanBrocklin II), ¶ 171.

³⁹³ EX1003 (Zeglis I), ¶¶ 298-302; EX1006 (Jansen), 3060-3063.

³⁹⁴ EX1003 (Zeglis I), ¶¶ 275-278, 287-302.

routine coupling chemistry.³⁹⁵ Commercial availability of a building block and the ability to form an amide bond establish that a candidate can be synthesized; they do not establish that the resulting A, or the completed B-L-A, will retain useful FAP affinity, selectivity, and signal.³⁹⁶

240. A POSA would struggle to navigate the enormous structural heterogeneity of the claimed B-L-As because he or she could not predict which combinations of structures in a candidate molecule correlate to a compound's ability to be used in imaging or therapy without experimentally testing it.³⁹⁷ Because the selection of the A, B, and L moieties and the point of attachment can impact the physicochemical attributes of a B-L-A compound, a POSA would be unable to discern from the structure alone particular choices for the compound will yield a B-L-A form with the necessary properties to be a viable imaging or therapeutic agent.³⁹⁸

³⁹⁵ EX2029 (VanBrocklin II), ¶¶ 152-158, 191; EX1003 (Zeglis I), ¶¶ 91, 94.

³⁹⁶ EX1003 (Zeglis I), ¶¶ 91, 247, 251, 273-278, 288-302.

³⁹⁷ EX1003 (Zeglis I), ¶¶ 247, 273, 277-278.

³⁹⁸ EX1003 (Zeglis I), ¶¶ 45-46, 221, 270-272, 276, 280-286; EX1004 (US-633), [0101] (describing how tether length and composition can modify affinity, selectivity, and pharmacokinetic properties).

8. The Jansen Publications Demonstrate Substantial Unpredictability for Almost the Entire FAP-Targeting Population of Compounds Being Claimed

241. The Jansen publications demonstrate that structural modifications to FAP pharmacophores falling within the claimed “A” genus can produce large and sometimes unexpected changes in FAP affinity and FAP/PREP selectivity.³⁹⁹ A table of the FAP pharmacophores reported in Jansen’s publications is provided in Appendix D below.

242. I explained in my Opening Declaration that substitutions at different positions of the quinolinyl ring of 4-quinolinoyl-Gly-cyanoPro compounds unpredictably affect the affinity and selectivity of FAP binding.⁴⁰⁰ 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 magnitudes:⁴⁰¹

- (a) **Bromine:** C⁵ (Compound 26, SI = **4545.5**), C⁷ (Compound 32, SI = **193.5**), and C⁸ (Compound 34, SI = **1.0**).⁴⁰²

³⁹⁹ EX1006 (Jansen), 3060-3062; EX1007 (Jansen 2013), 492-494; EX1003 (Zeglis I), ¶¶ 288-291.

⁴⁰⁰ EX1003 (Zeglis I), ¶¶ 178, 298-302.

⁴⁰¹ See Appendix D, below (Jansen SAR data).

⁴⁰² 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**).⁴⁰³
- (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**).⁴⁰⁴
- (d) **Fluorine:** C³ (Pomper Ref. Compound H, SI = **3**), C⁵ (Ref. Compound C, SI = **20**), C⁶ (Ref. Compound D, SI = **403**),⁴⁰⁵ C⁷ (Ref. Compound F, SI = **241**), and C⁸ (Ref. Compound G, SI = 17).⁴⁰⁶

243. 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.⁴⁰⁷ Compound 58 exhibited FAP and PREP IC₅₀ values of 0.0033 μM and 0.29 μM,

⁴⁰³ EX1007 (Jansen 2013), 493; Appendix D, below.

⁴⁰⁴ EX1007 (Jansen 2013), 493; EX1006 (Jansen), 3061.

⁴⁰⁵ 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.

⁴⁰⁶ EX1002 (US-233 FW), 174-175 (¶ 42) (EX1002); Appendix C-6, below.

⁴⁰⁷ 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 .⁴⁰⁸ 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 59.⁴⁰⁹ 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.⁴¹⁰

244. As I explained in my Opening Declaration—Jansen reported conflicting data for substitutions at the C5-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 IC_{50} 9.0 μM ; SI 1.0), and 63 (FAP IC_{50} 7.2 μM ; SI 2.3).⁴¹¹

245. A POSA developing a FAP imaging or radiotherapy agent would

⁴⁰⁸ EX1006 (Jansen), 3062 (Table 5).

⁴⁰⁹ EX1006 (Jansen), 3062; EX1003 (Zeglis I), ¶ 152.

⁴¹⁰ EX1006 (Jansen), 3061-3062; EX1003 (Zeglis I), ¶¶ 290-291.

⁴¹¹ EX1003 (Zeglis I), ¶¶ 178, 298-302; EX1007 (Jansen 2013), 493; EX1006 (Jansen), 3061-3062.

prioritize tight and specific FAP binding because those properties govern accurate target localization and selective delivery of the reporter moiety or radionuclide.⁴¹² Otherwise, high non-specific binding could lead to potential false positive results and irradiation of non-target tissue.⁴¹³ In the absence of correlation data between the claimed B-L-A architecture and its chemical attributes, a POSA could not reliably predict the imaging or therapeutic function from the structure alone.⁴¹⁴

9. The Pomper Compounds Do Not Correspond to the Structural Diversity of the B-L-A Compound Genus

246. Dr. VanBrocklin relies on the eleven post-filing Pomper Compounds, claiming they teach how to make a “broad set” of compounds.⁴¹⁵ JHU’s own comparison notes that all eleven compounds had the same A and linker moieties at the same attachment site, with only a variable B, and do not evaluate the other 31,751 “A” structures, the range of attachment sites, and vast set of linkers.⁴¹⁶ A POSA would not understand these compounds to enable how to make and test a

⁴¹² EX1003 (Zeglis I), ¶ 287.

⁴¹³ EX1003 (Zeglis I), ¶¶ 39, 70.

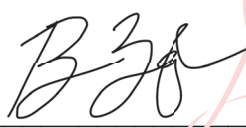
⁴¹⁴ EX1003 (Zeglis I), ¶¶ 273, 290-291.

⁴¹⁵ EX2029 (VanBrocklin II), ¶¶ 150, 187, 192; EX1002 (US-233 FW), 174-176.

⁴¹⁶ EX2029 (VanBrocklin II), ¶¶ 118-121, 149-150; EX1007 (Jansen 2013), 493 (Table 2); EX1003 (Zeglis I), ¶¶ 85-95.

“broad set” of the claimed compounds, and would require going to information that was not available in the patent disclosure or from public sources in October of 2017.

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
09:22:16 -04'00'

Brian Zeglis, Ph.D.

Executed on: August 20, 2026

Appendix A: Exhibit List

No.	Exhibit Description	Short Name
1001	U.S. Patent No. 12,115,233	US-233
1002	File History of U.S. Patent No. 12,115,233	US-233 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
1024	Hamson et al., “Understanding fibroblast activation protein (FAP): Substrates, activities, expression and targeting for cancer therapy,” <i>Proteomics Clin. Appl.</i> , 8:454–463 (2014)	Hamson
1029	Ryabtsova et al., “Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity,” <i>Bioorganic & Medicinal Chemistry Letters</i> , 22(10):3412–3417 (2012)	Ryabtsova
1031	File History of U.S. Patent No. 11,938,201	US-201 FW
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	Tsai

No.	Exhibit Description	Short Name
	Activation Protein,” J. Med. Chem. 53(18):6572–6583 (2010)	
1052	Zhou et al., “Radiolabeled Cyclic RGD Peptides as Radiotracers for Imaging Tumors and Thrombosis by SPECT,” Theranostics, 1:58–82 (2011)	Zhou
1053	U.S. Patent Publication 2011/0064657	US-657
1057	PCT/US2022/023374	Pomper PCT
1064	Fulop et al., “Prolyl Oligopeptidase: An Unusual β -Propeller Domain Regulates Proteolysis,” Cell, 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,” Journal of Nuclear Medicine and Biology, 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,” Journal of Medicinal Chemistry, 59:5684–5694 (2016)	Dannoon
1067	Dr. VanBrocklin Annotation of XY-FAP-01	XY-FAP-01
1068	Dr. VanBrocklin Annotation of XY-FAP-02	XY-FAP-02
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,” Current Opinion in Chemical Biology, 7:626–634 (2003)	Frangioni

No.	Exhibit Description	Short Name
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 PET,” <i>Journal of Nuclear Medicine</i> , 62:(5) 723–731 (2020)	Huang
1078	Vasdev et al., “Metabolic stability of 6,7-dialkoxy-4-(2-, 3- and 4- [^{18}F]fluoroanilino)quinazolines, potential EGFR imaging probes,” <i>Bioorganic & Medicinal Chemistry</i> , 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,” <i>European Journal of Nuclear Medicine and Molecular Imaging</i> , 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	Baker

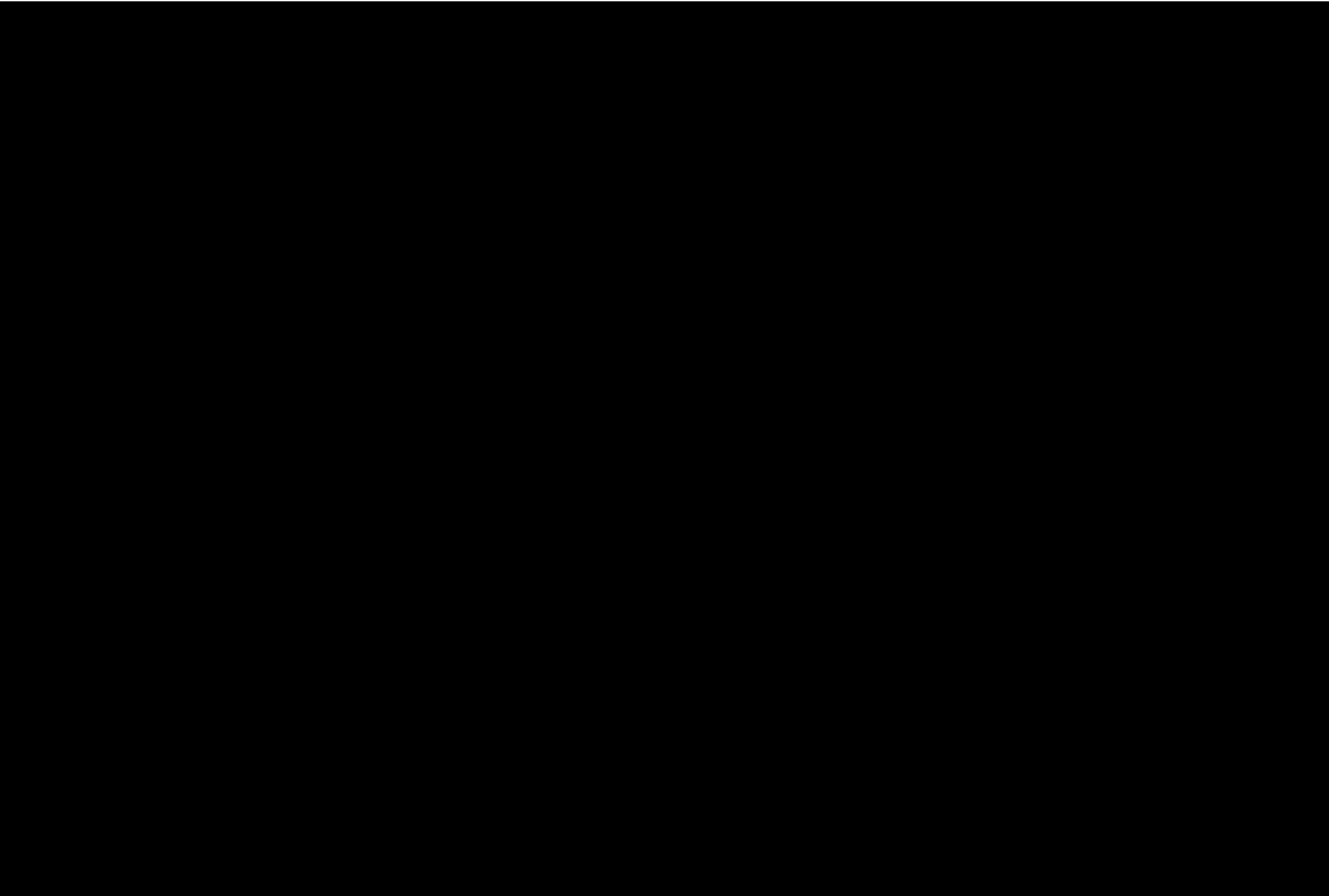
No.	Exhibit Description	Short Name
	adenosine A1 receptor ligands,” British Journal of Pharmacology, 159:772-786 (2010)	
1083	PREP Tissue, The Human Protein Atlas, https://www.proteinatlas.org/ENSG00000085377-PREP/tissue	Protein Atlas
2001	Declaration of Dr. Henry VanBrocklin	VanBrocklin I
2003	Jansen et al., “Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold,” Med. Chem. Comm, (2014)	Jansen 2014
2020	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
2023	Transcript of the Deposition of Dr. Brian Zeglis, March 11, 2026	Zeglis Tr.
2024	Sugiara et al., “Radiolabeling Strategies for Tumor-Targeting Proteinaceous Drugs,” Mol. 19:2132-2165 (2014)	Sugiara
2026	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
2029	Second Declaration of Dr. Henry VanBrocklin	VanBrocklin II
2032	Aertsgeerts 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)	Aertsgeerts
2035	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

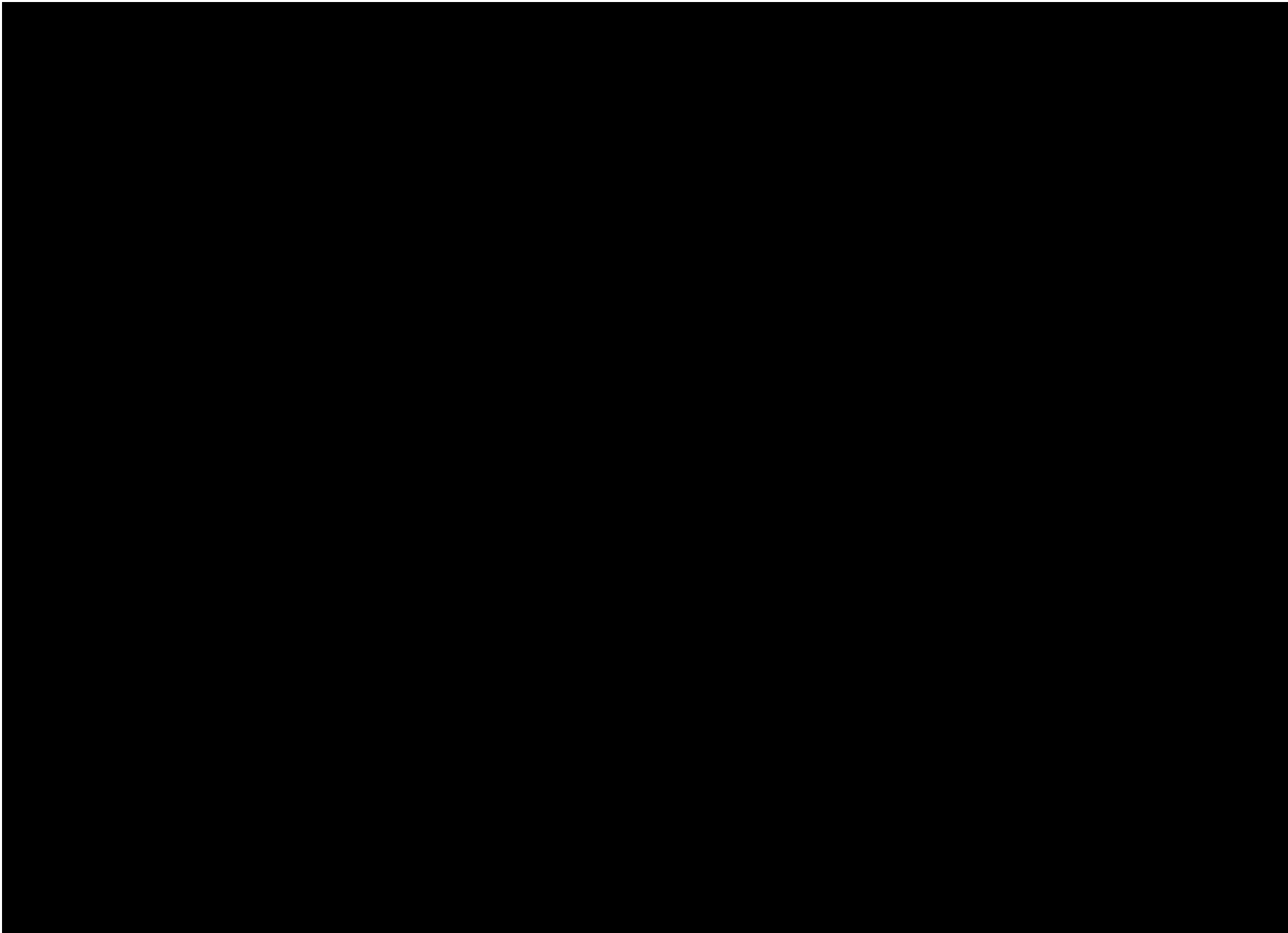
No.	Exhibit Description	Short Name
2036	LeBeau et al., “Targeting the cancer stroma with a fibroblast activation protein activated promelittin protoxin,” <i>Molecular Cancer Therapy</i> , 8(5): 1378-1386 (2009)	LeBeau
2037	Huang et al., “Evaluation of the tumor targeting of a FAP α -based doxorubicin prodrug,” <i>Journal of Drug Targeting</i> , 19(7): 487-496	Huang 2011
2039	Reiner et al., “Harnessing the Bioorthogonal Inverse Electron Demand Diels-Alder Cycloaddition for Pretargeted PET Imaging,” <i>Journal of Visualized Experiments</i> , 96 (2015)	Zeglis 2015
2040	Adumeau et al., “Site-Specifically Labeled Immunoconjugates for Molecular Imaging—Part 1: Cysteine Residues and Glycans,” <i>Molecular Imaging Biology</i> , 18:1-17 (2016)	Zeglis 2016

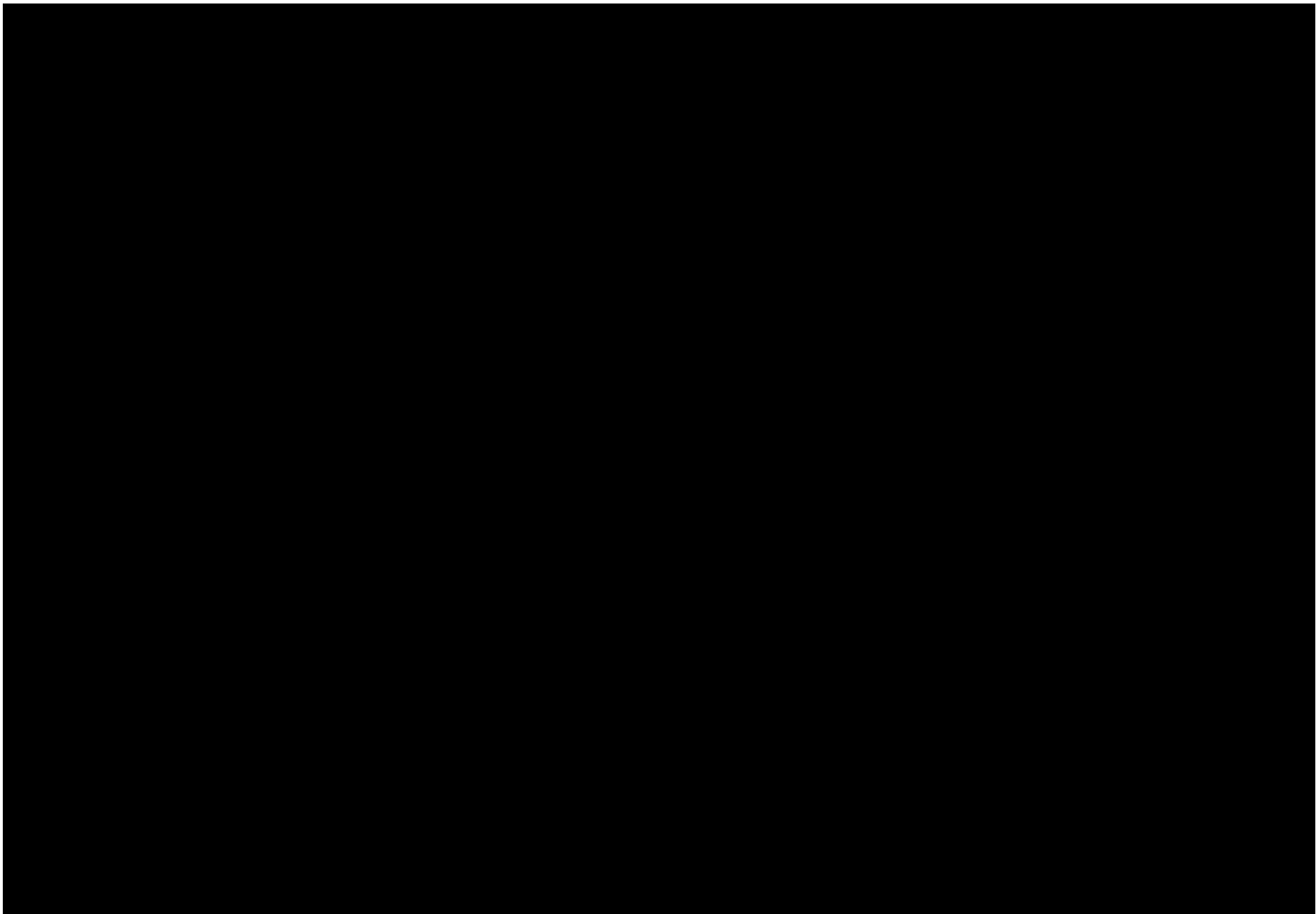
Appendix B: Antibody Product Status

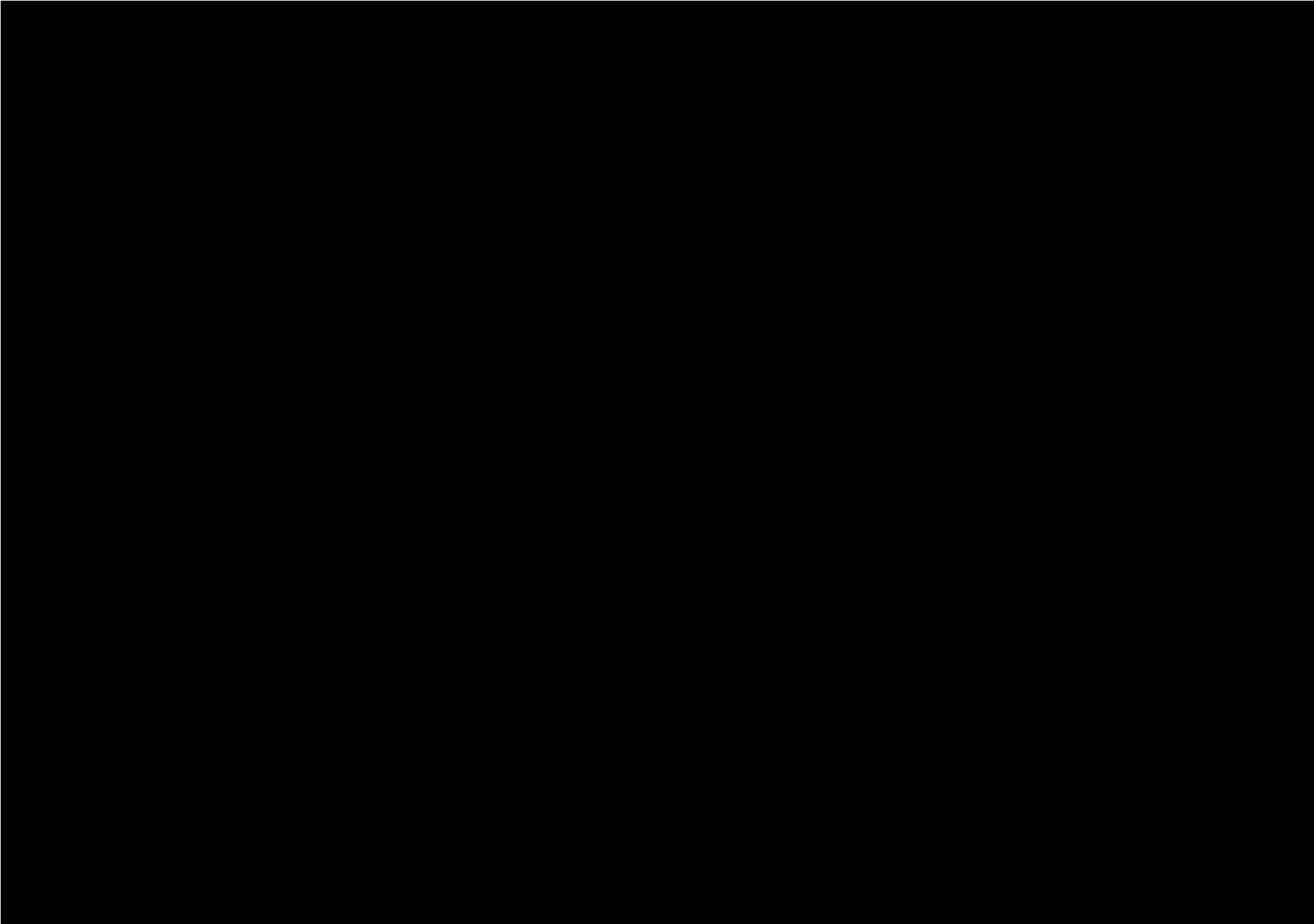
Antibody (Trade Name)	Radionuclide & Purpose	Approval Date	Withdrawal Date
Imciromab-Pentetate (MyoScint)	In-111; SPECT imaging	1989 (US)	1993
Satumomab Pendetide (OncoScint CR/OV)	In-111; SPECT imaging	1992 (US)	2002
Arcitumomab (CEA-Scan)	Tc-99m; SPECT imaging	1996 (US)	2005
Noferumomab Merpentan (Verluma)	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

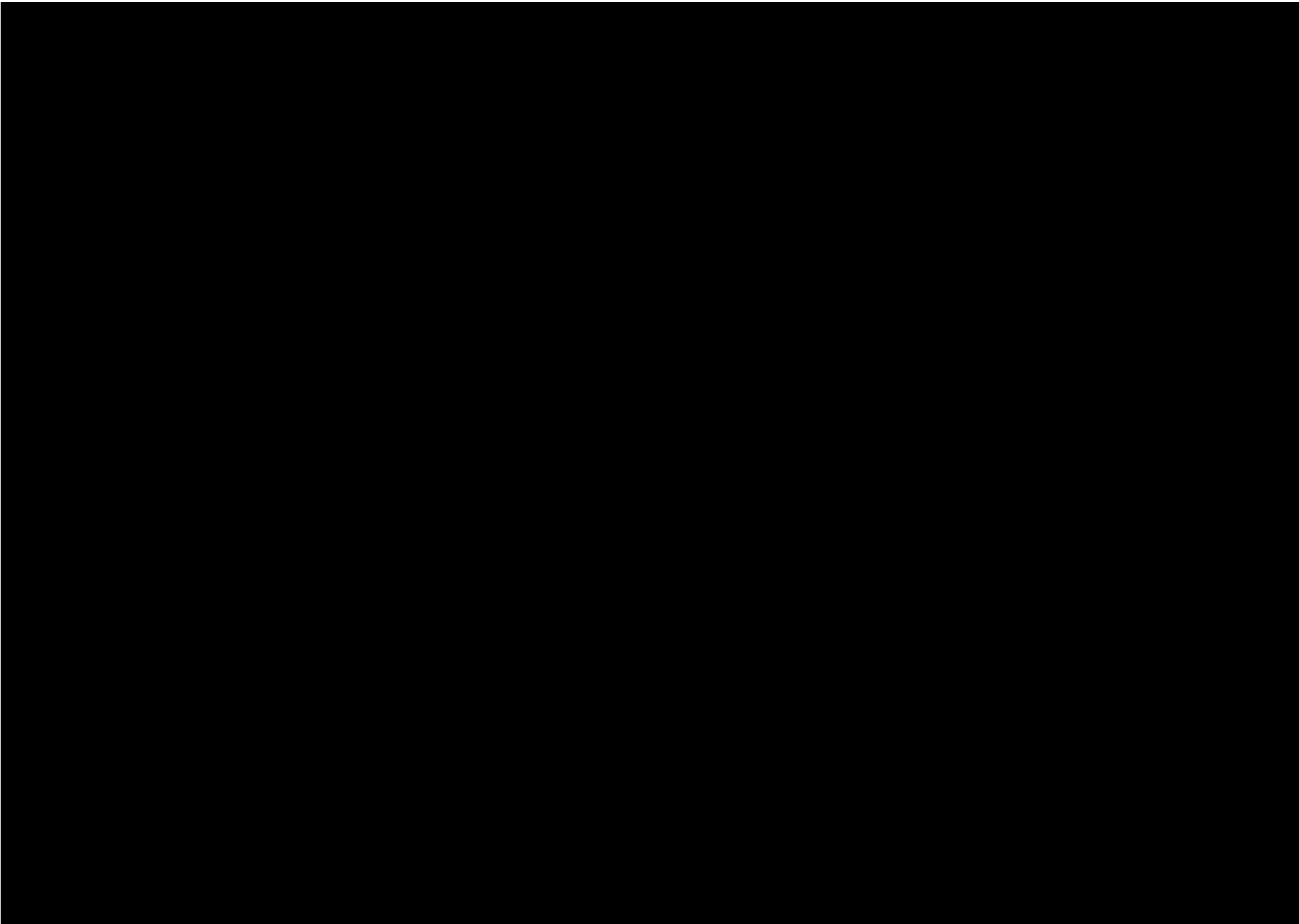
See EX1075 (FDA/EMA Data), 2 (OncoScint), 5, 39 (CEA-Scan), 8-10 (Noferumomab), 12-13 (ProstaScint), 15 (Zevalin), 36 (Bexxar), 47 (Indimacis 125), 54 (LeukoScan), 63 (HumaSPECT); EX1074 (Arruebo), 3296 (MyoScint, Zevalin, Indimacis-125), 3302 (OncoScint, LeukoScan), 3289 (CEA-Scan, ProstaScint), 3299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

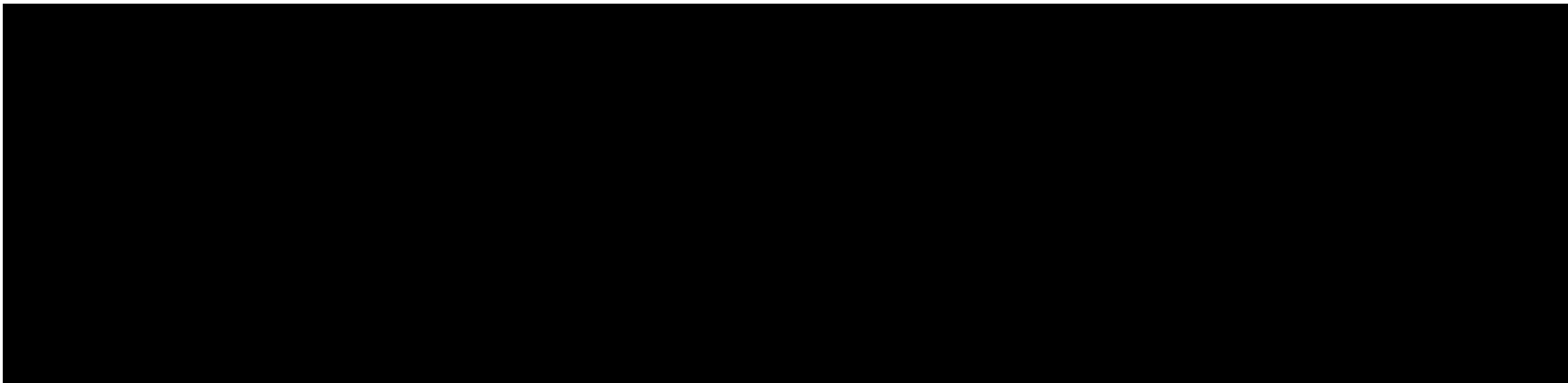


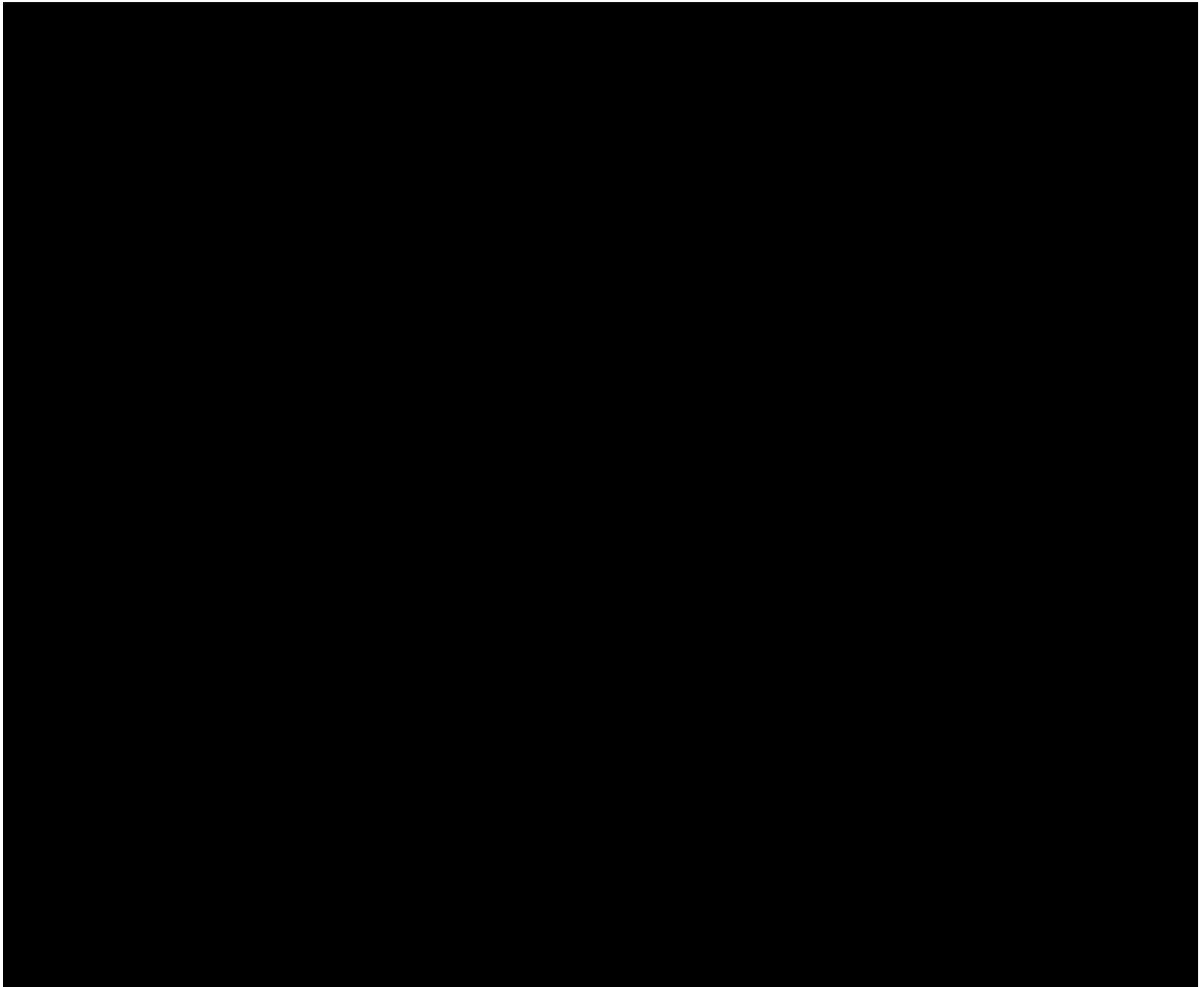


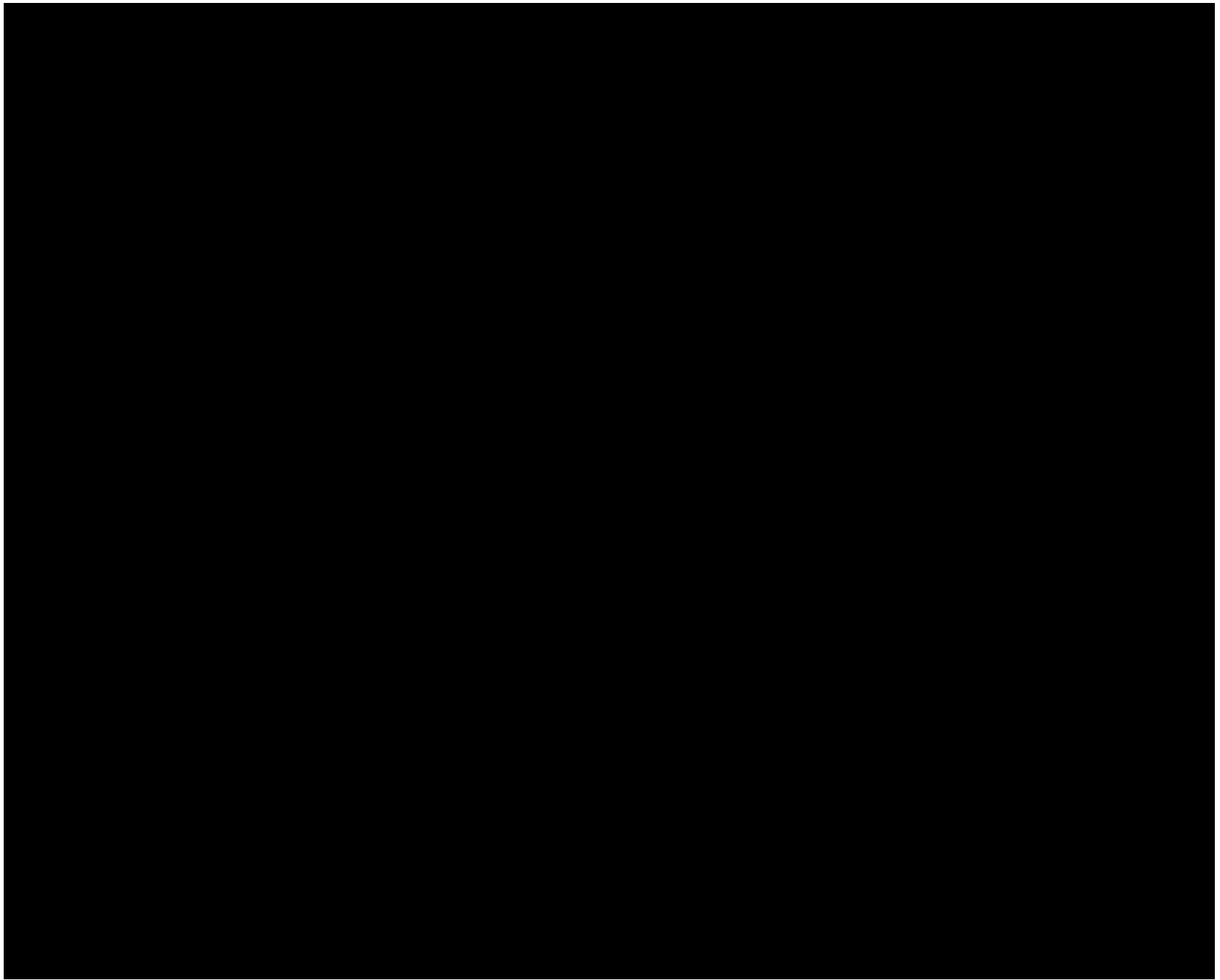


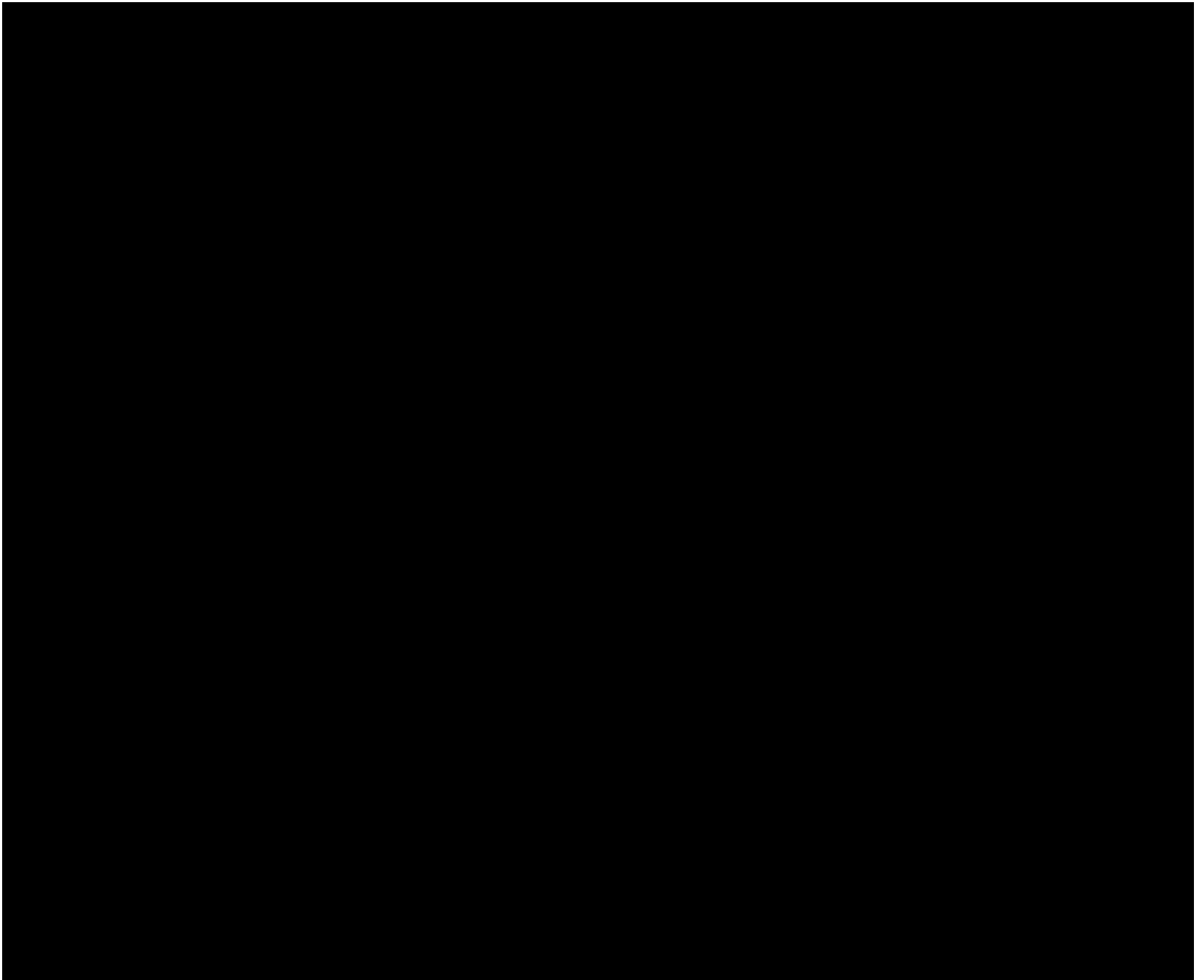


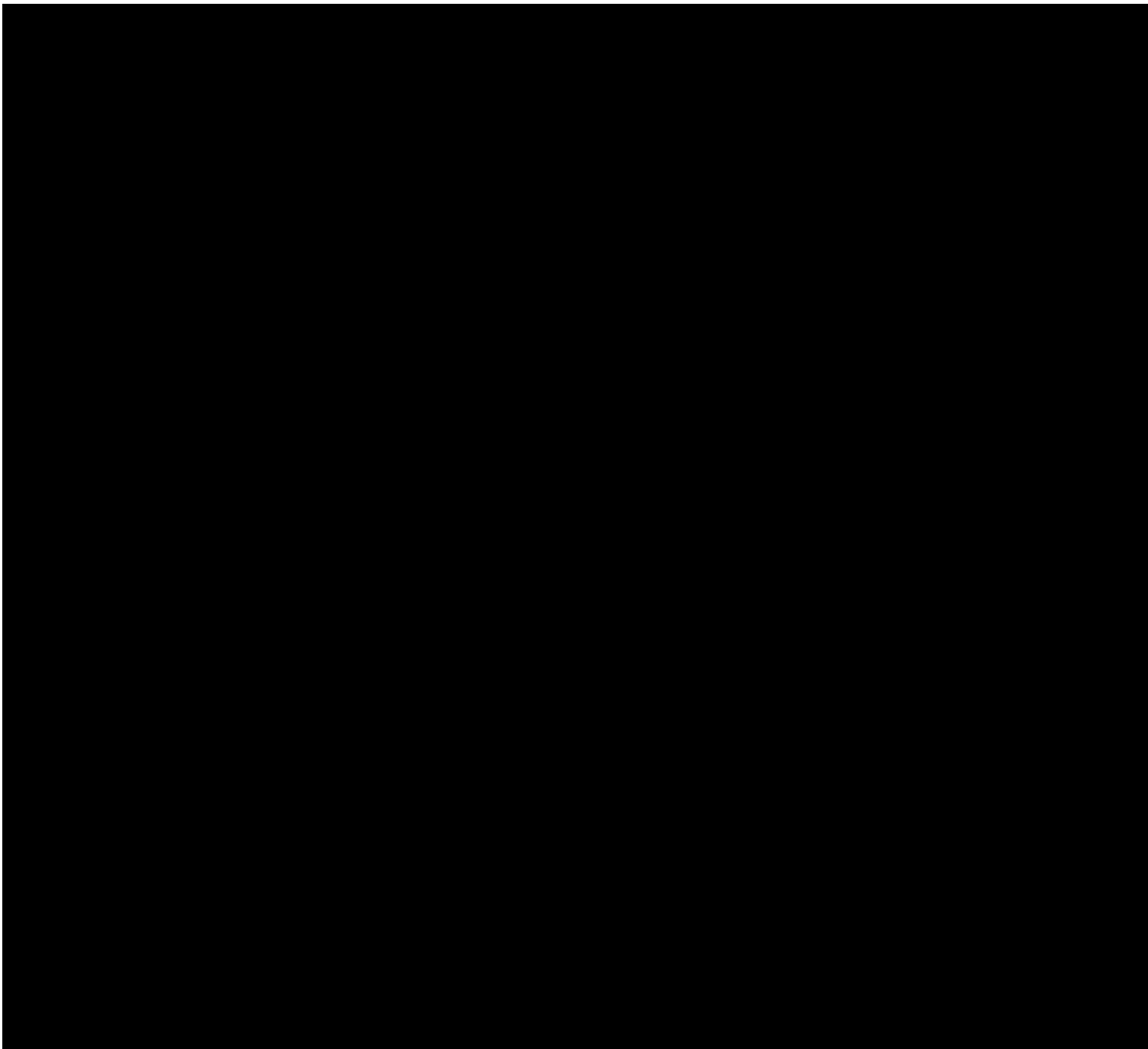


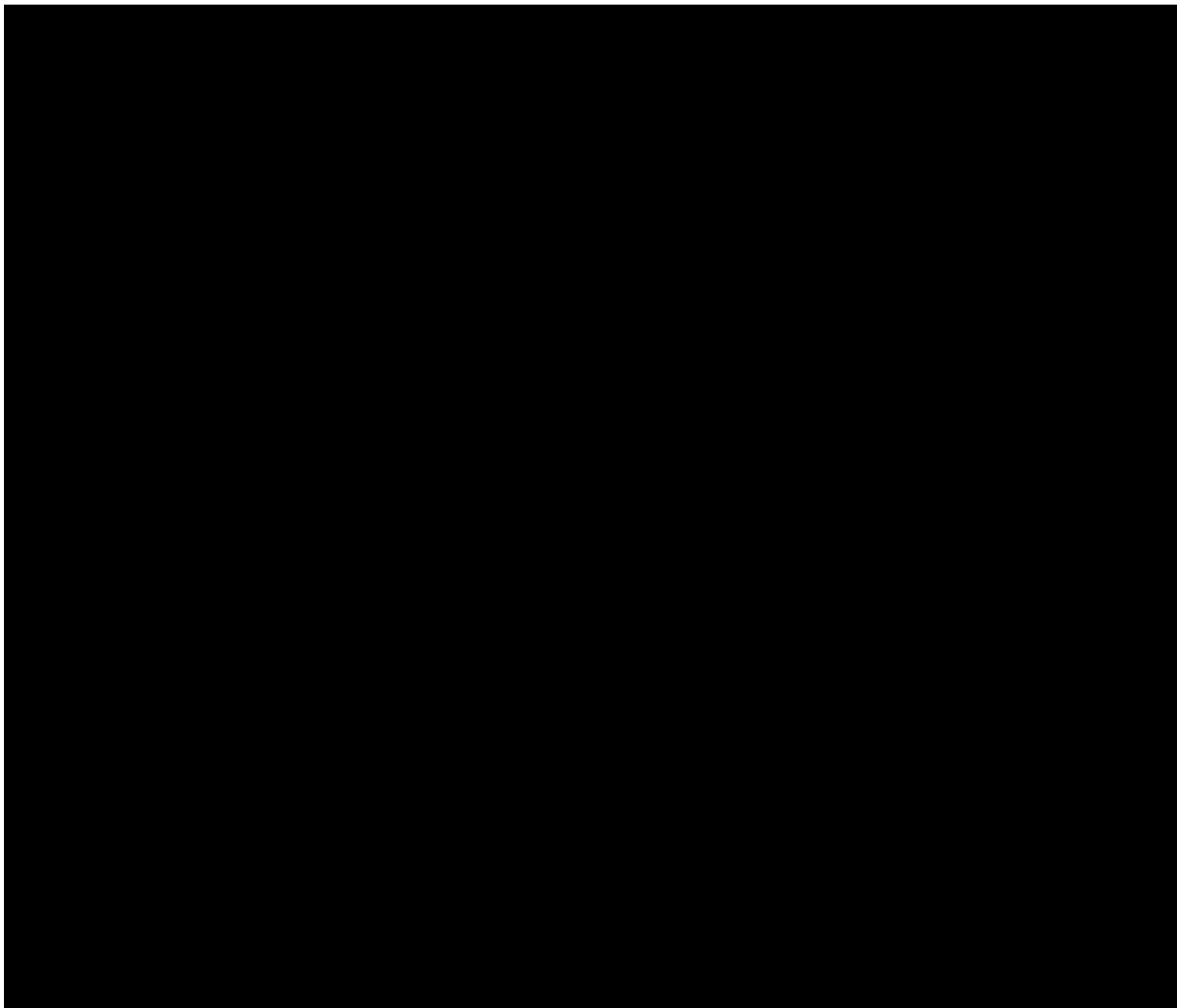


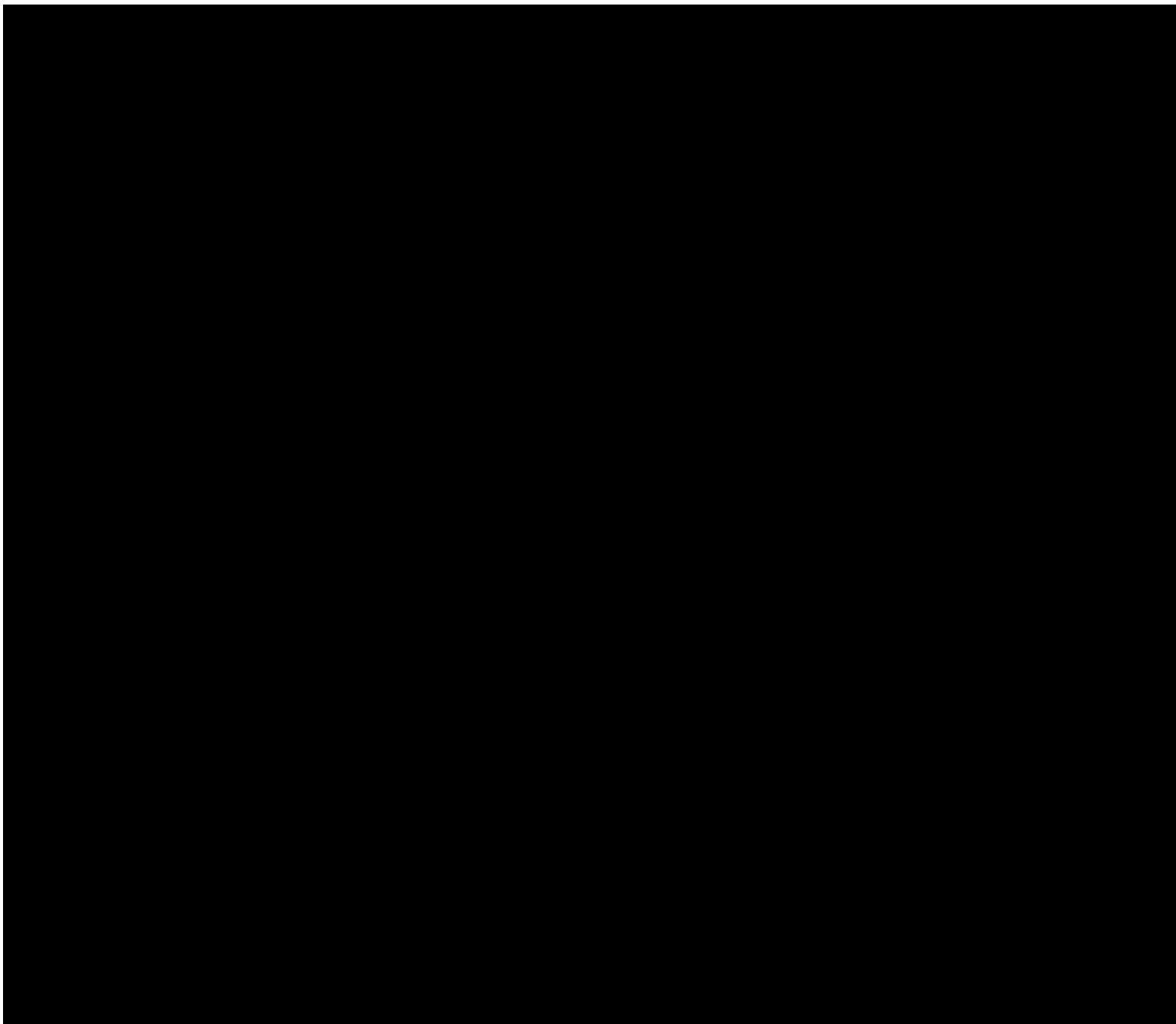


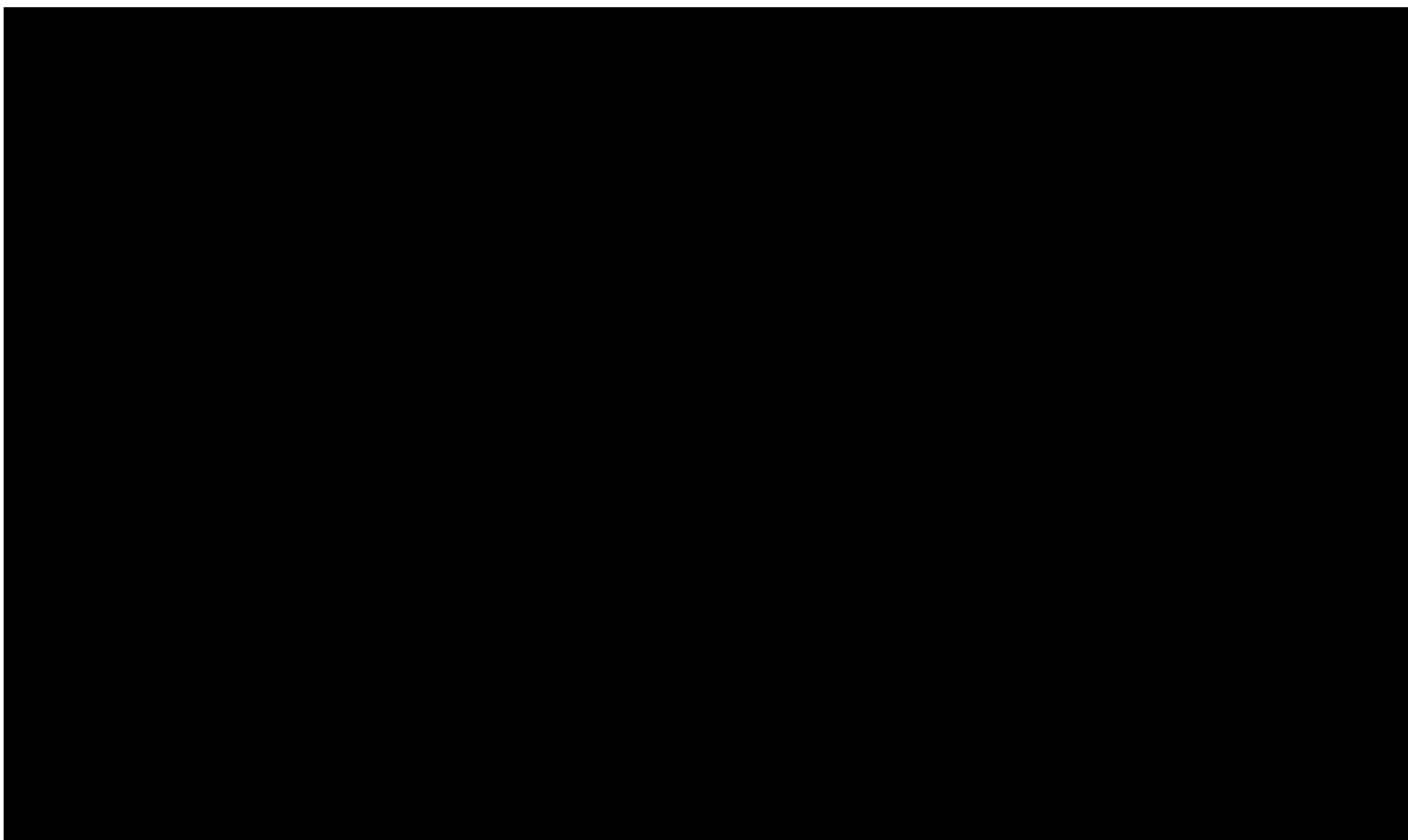


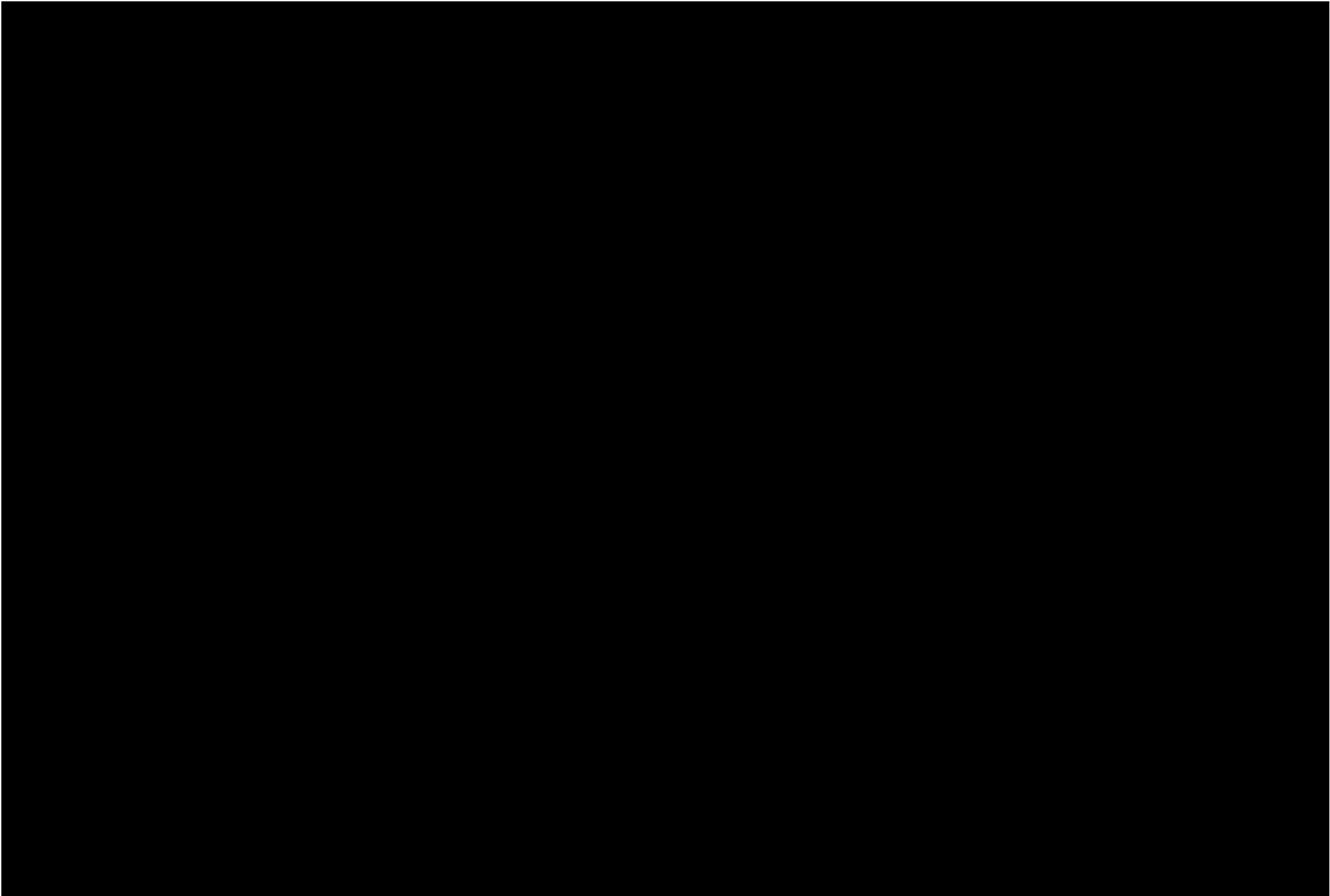


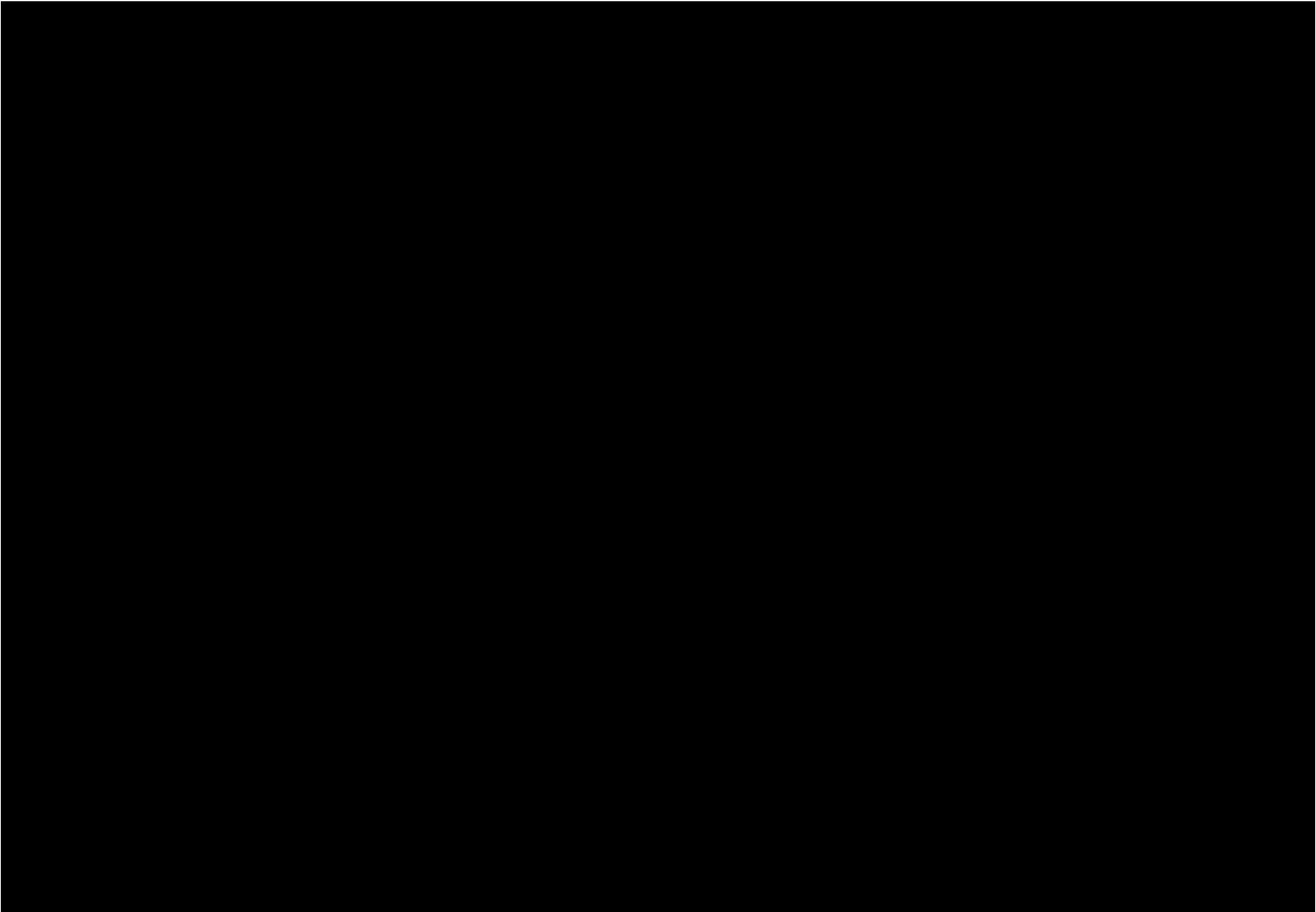


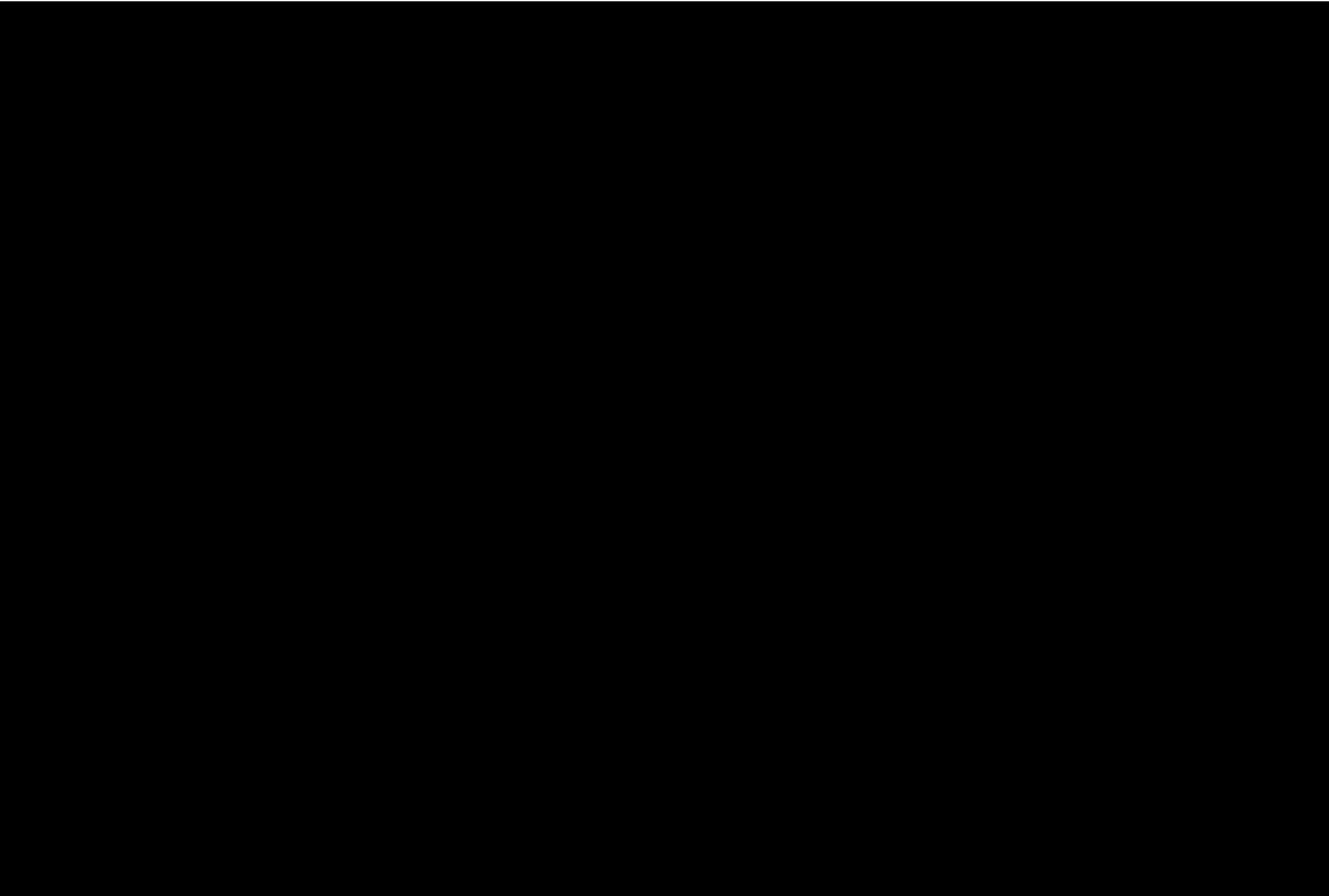


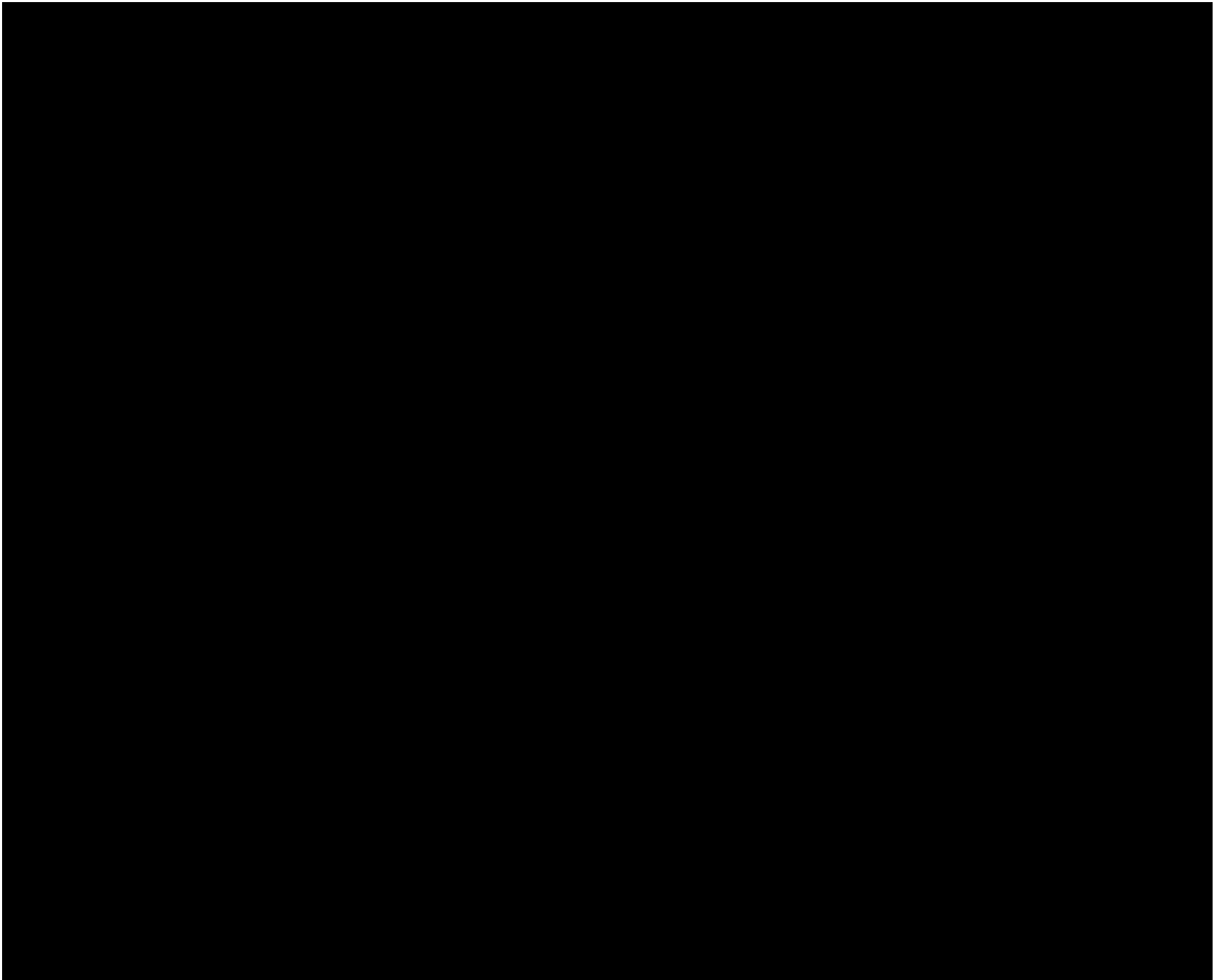


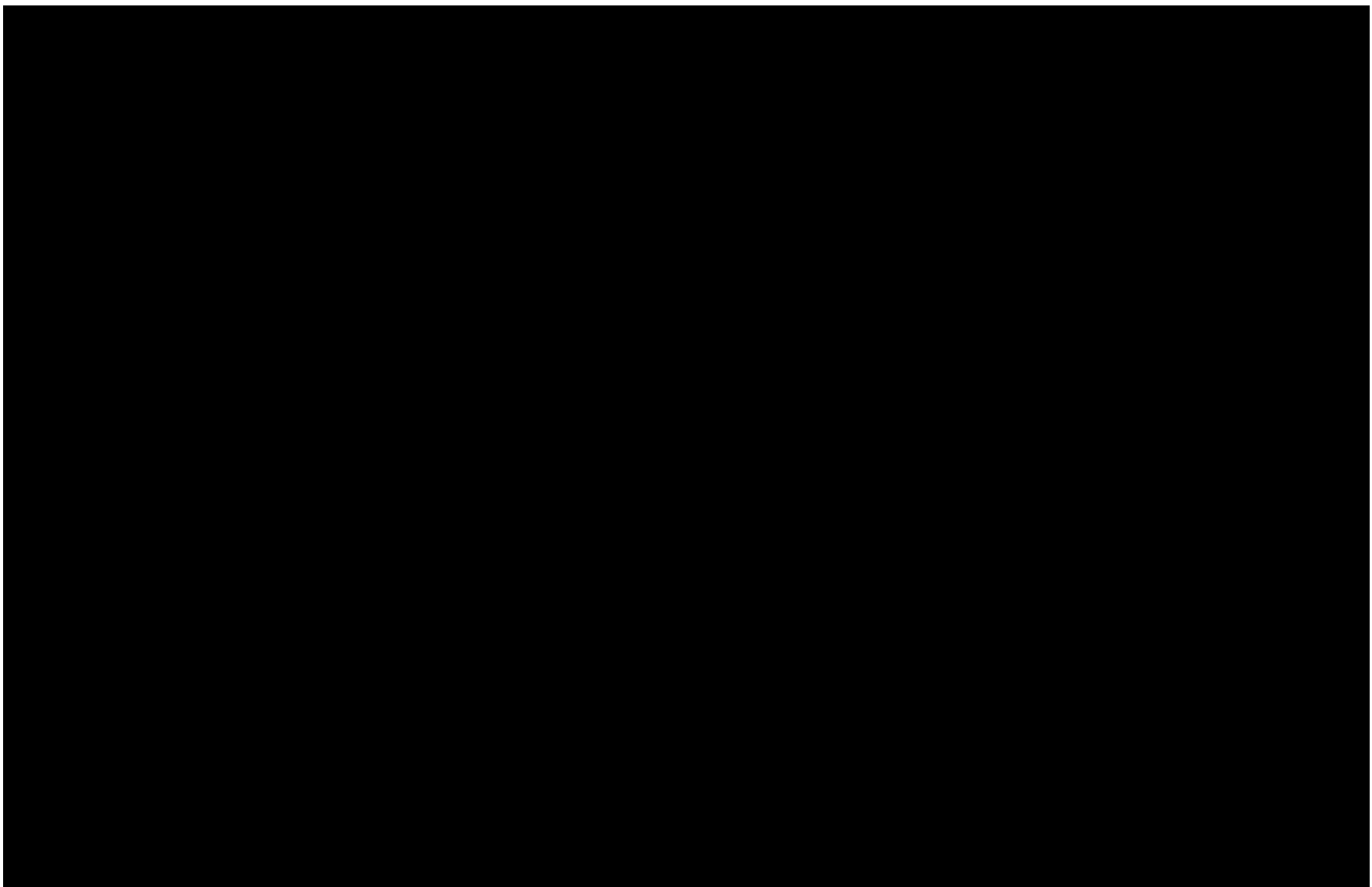


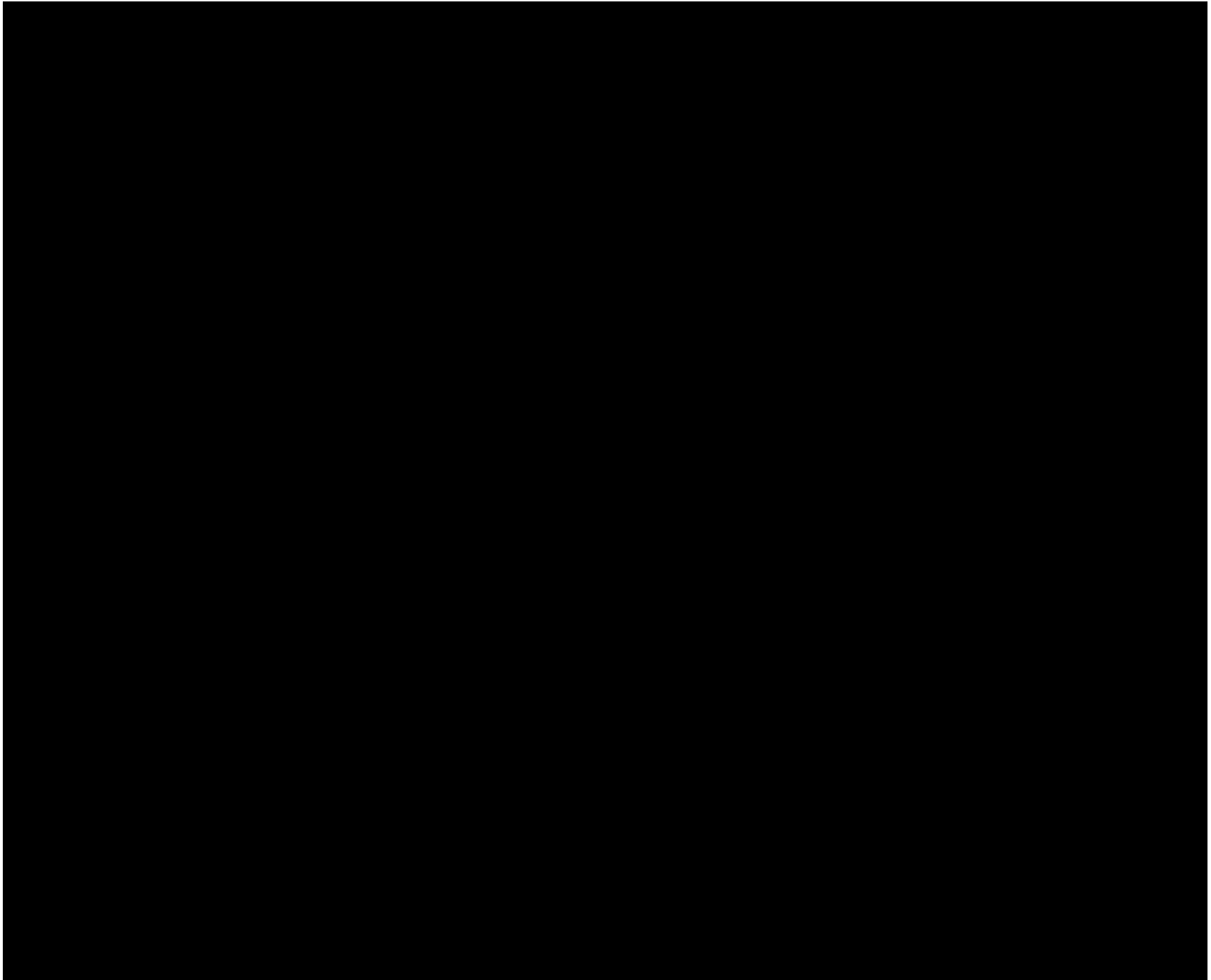


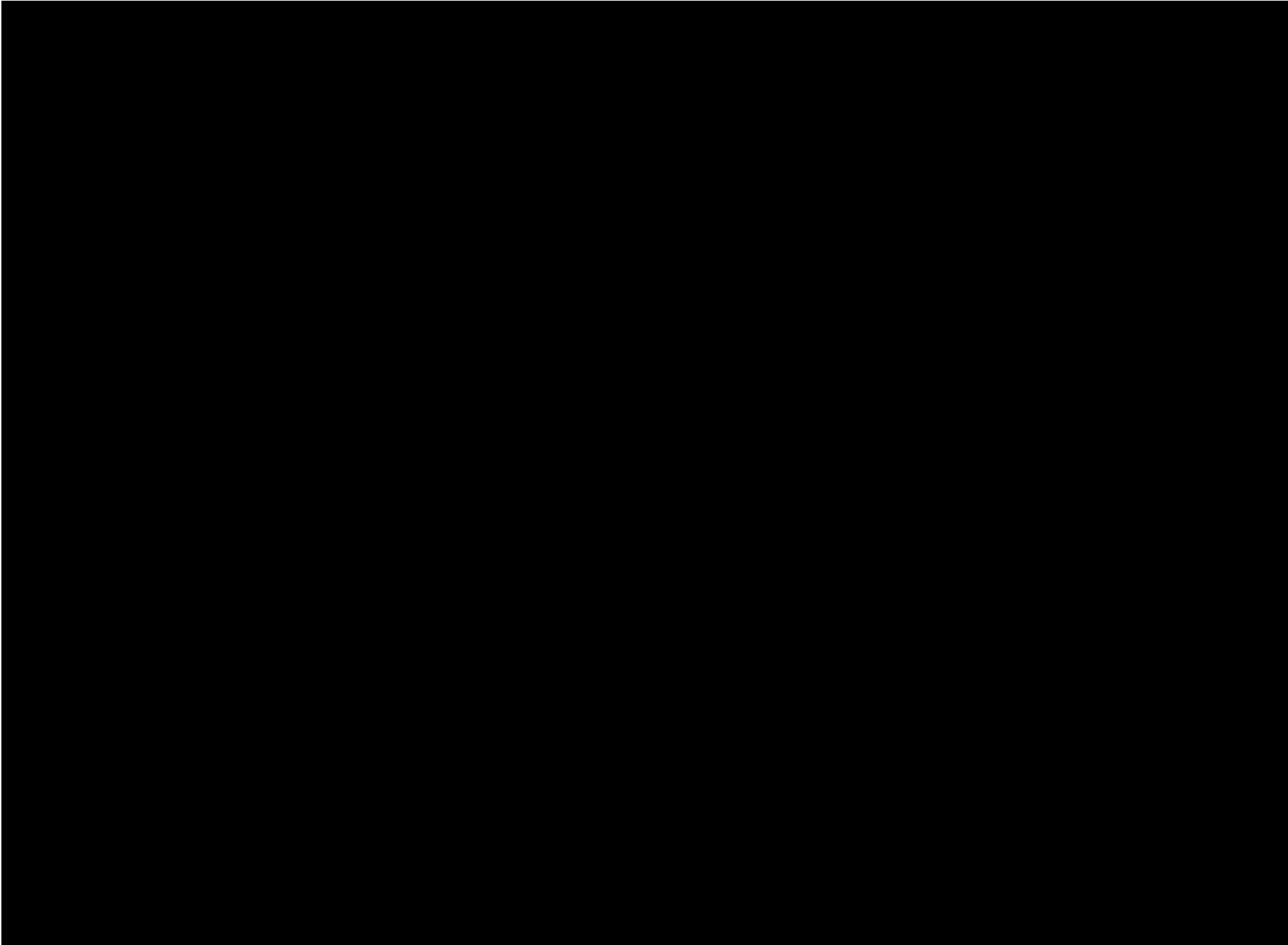


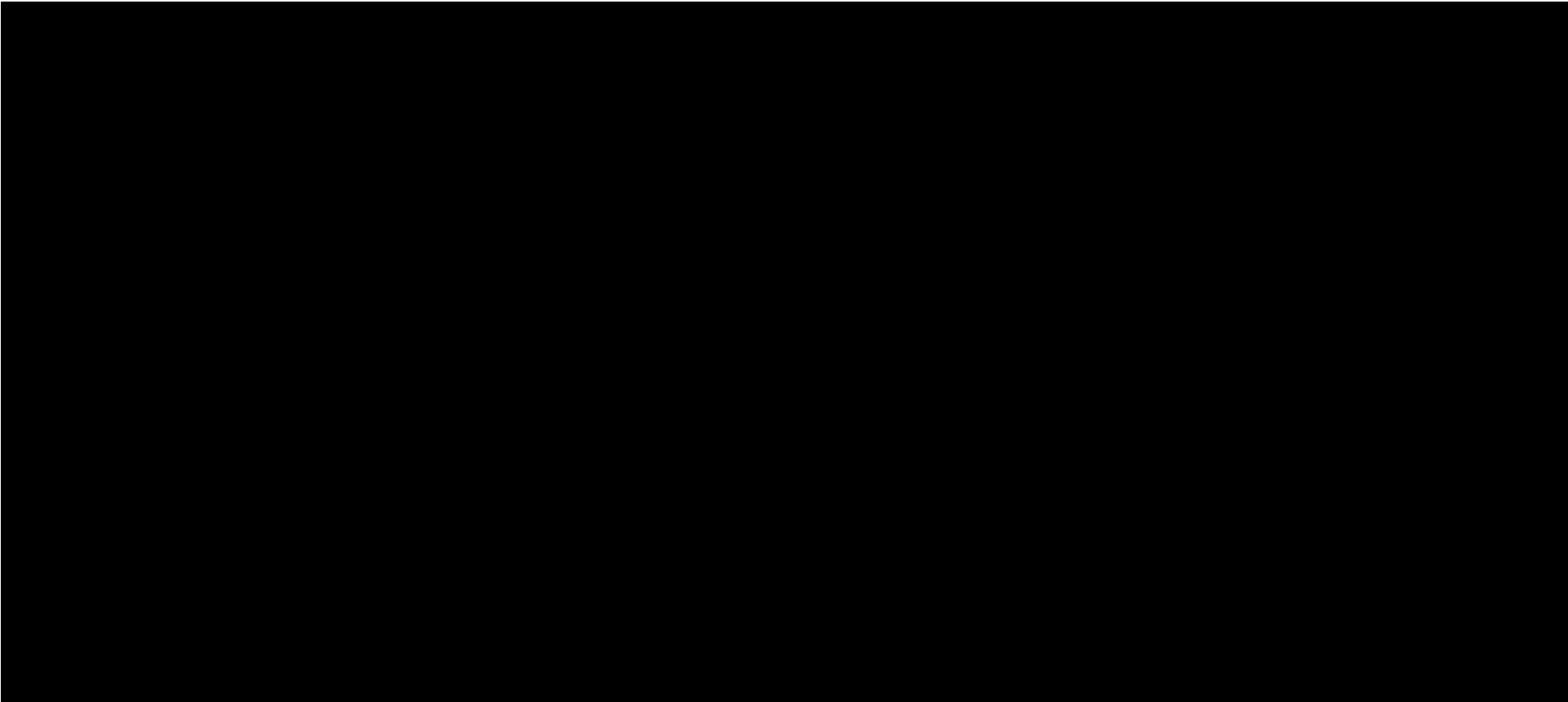






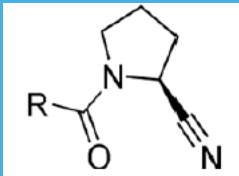
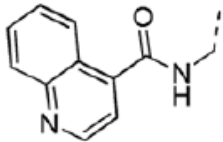
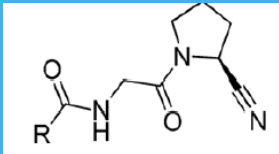


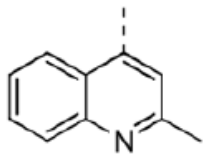
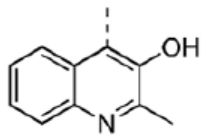
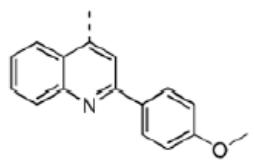
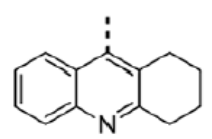
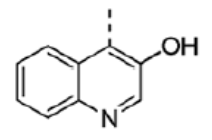
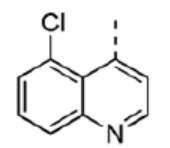


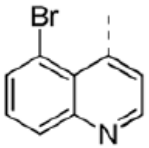
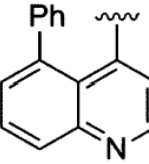
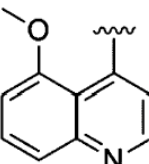
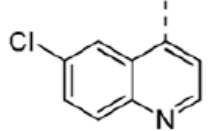
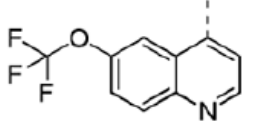


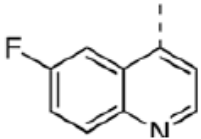
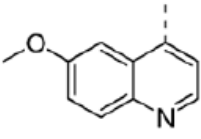
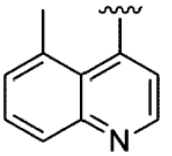
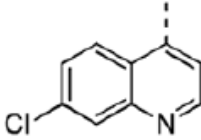
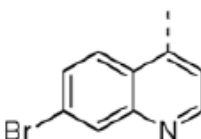
Appendix D: Jansen Publications SAR Data

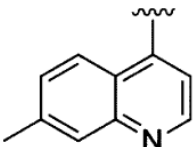
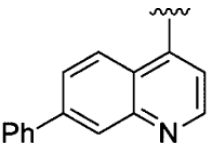
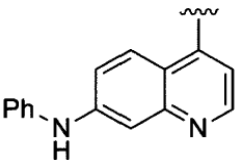
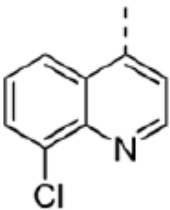
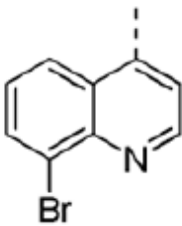
The table below shows the structure of every FAP inhibitor described in the Jansen (EX1006) and Jansen 2013 (EX1007) publications that falls within the scope of the claimed “A” moiety. The compounds are arranged by the type of chemical substitution to either the quinolinyl ring or the cyanopyrrolidine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

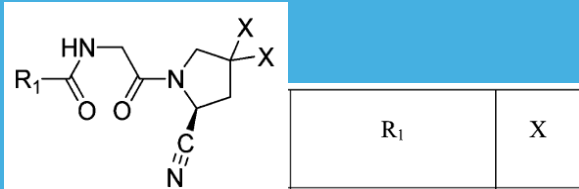
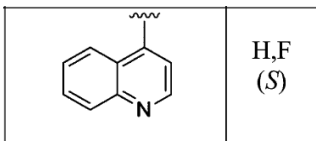
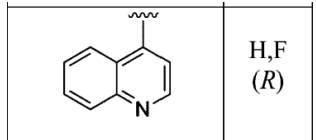
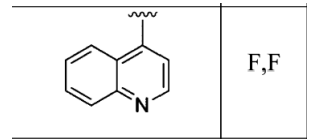
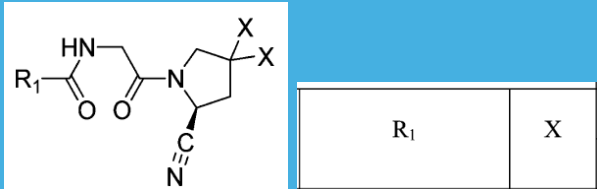
Jansen A Moiety Compound	Structure	FAP IC50 (uM)	PREP IC50 (uM)	FAP/PREP Selectivity
No Substitutions on the Quinolinyl Ring <div>  </div>				
Jansen 2013 Compound 7		0.01	0.86	86
Substitutions on the Quinolinyl Ring <div>  </div>				

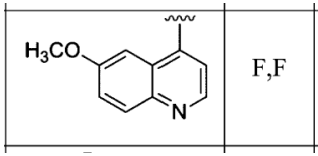
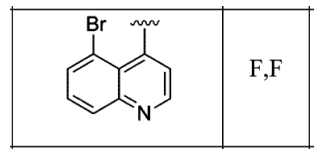
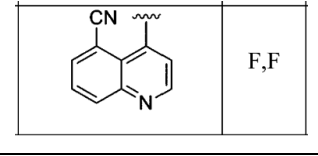
Jansen A Moiety Compound	Structure	FAP IC50 (uM)	PREP IC50 (uM)	FAP/PREP Selectivity
Jansen 2013 Compound 19		0.67	0.64	1.0
Jansen 2013 Compound 20		5.9	53.6	9.1
Jansen 2013 Compound 22		10	1	0.1
Jansen 2013 Compound 23		0.77	18.5	24.0
Jansen 2013 Compound 24		0.16	38	237.5
Jansen 2013 Compound 25		0.0099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

Jansen A Moiety Compound	Structure	FAP IC50 (uM)	PREP IC50 (uM)	FAP/PREP Selectivity
Jansen 2013 Compound 26		0.011	50	4545.5
Jansen Compound 56		0.064	8.7	135.9
Jansen 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 (uM)	PREP IC50 (uM)	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 (uM)	PREP IC50 (uM)	FAP/PREP Selectivity
Jansen Compound 52		0.0069	0.5	72.5
Jansen Compound 54		0.07	19.4	277.1
Jansen 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 (uM)	PREP IC50 (uM)	FAP/PREP Selectivity
<div>Substitutions on the Pyrrolidine Warhead</div> <div><div></div></div>				
Jansen Compound 58	<div></div>	0.0033	0.29	87.9
Jansen Compound 59	<div></div>	1	100	100.0
Jansen Compound 60	<div></div>	0.0032	1.8	562.5
<div>Substitutions on the Pyrrolidine Warhead and Quinolinyl Ring</div> <div><div></div></div>				

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

Appendix E: Written Description Deficiency Chart

Non-Exhaustive B-L-A Component and Design Factors					
Possible Prosthetic Groups					
Possible Chelators	NOTA [1 of 8 in '233 Below] 	DOTA [1 of 10 in '233 Below] 	DTPA [1 of 5 in '233 Below] 	DACH [1 of 8 in '233 Below] 	HBED ['233 Example Below]
Possible Linkers					
Parameters for A Moieties	R1x, R2x includes but not limited to H, OH, 5 Halogen options, C1-6 alkyl 	R3x includes but not limited to H, CN, B(OH)2, -C(O)alkyl, -C(O)aryl 	Orientations of R1x, R2x (6 relative orientations) 	R4x is Hydrogen 	R5x, R6x, R7x includes H at 3 of the positions on the quinolinyl ring
Possible Positions for Linker Attachment	<p style="text-align: center;">Pyrrolidine (C2, C3, C4, C5); Quinolinyl (C2, C3, C5, C6, C7, C8)</p>				