 Appeal Nos. 02-1052, -1065

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Plaintiffs-Cross-Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGAA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

Defendants.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF CALIFORNIA IN 96-CV-1307, SENIOR JUDGE JAMES M. FITZGERALD

SUPPLEMENTAL REPLY BRIEF OF DEFENDANT-APPELLANT

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INTRODUCTION

Reality matters in litigation.

The reality is that the Supreme Court held that JMOL must be granted so long as Merck satisfied two prongs: If it was reasonable for Merck to believe (1) that the compounds being tested could stunt the growth of blood vessels; and (2) that every accused experiment would yield information relevant to efficacy, mechanism of action, pharmacokinetics, or pharmacology. Yet, Integra argues that the Supreme Court held the opposite.

The reality is that the Supreme Court addressed at length, and rejected, Integra's argument that the jury verdict could be sustained because an expert incorrectly testified that the FDA cares only about safety at the IND stage and will consider only GLP studies. But Integra contends that the Supreme Court did not decide the argument Integra presented, and then tries to persuade this Court to consider the exact same argument and reach the opposite conclusion.

The reality is that, throughout this litigation, Integra never disputed the two propositions the Supreme Court has identified as central, having staked its litigation strategy on the assertion that these points were irrelevant. Yet, Integra argues now, for the first time ever in this litigation, that the jury's verdict could be sustained on the ground that there was conflicting evidence on the propositions it chose not to contest.

The reality is that there was no conflicting evidence on these two propositions, precisely because Integra chose not to dispute them. So Integra tries to manufacture disputes that do not exist. Integra then insists that the jury was free to disregard the explicit and consistent testimony of ten witnesses, without regard to whether the witnesses were impeached, cross-examined, disputed, or interested. These efforts fail because the rules contemplate a reasonable jury, not a runaway jury.

The reality is that Merck never wavered from the view it repeatedly pressed to the District Court, that the sufficiency of the evidence on the FDA exemption must be assessed as to each experiment individually. But Integra now claims that Merck waived the issue, and that the immunity evaporates as to all experiments so long as Integra can show that the exemption could reasonably be rejected as to any single one.

Faced with a reality that is inauspicious, Integra is not entitled to substitute an alternate reality, a Carrollean world where the case was litigated on different grounds, objections vociferously made were never uttered, explicit testimony evaporates or transforms into a grotesque caricature of itself, rulings from on high mean the opposite of what they say, and juries ignore a parade of witnesses for no reason at all.

ARGUMENT

A. The Supreme Court Adopted A Two-Pronged Test And Rejected Integra's Effort To Defend The Verdict Based On Expert Testimony That Was Incorrect As A Matter Of Law.

Integra's argument on remand is premised on the position that the Supreme Court decision means the opposite of what that Court expressly held. Integra first contradicts the rule of decision the Supreme Court laid down, and then contends that the Supreme Court never addressed arguments that it in fact attributed to Integra and rejected at length.

Rule of decision. Integra does not dispute that the passage from the Supreme Court's opinion block-quoted on page 30 of Merck's opening brief prescribes the rule of decision for this appeal. *See* 125 S. Ct. at 2383 [S75]. The form of the holding is: "At least where Condition 1 and Condition 2 are satisfied, Consequence C attaches." Yet, Integra contends that Merck is incorrectly interpreting this as a "two-prong test that narrows the decisional focus to certain specific considerations to the exclusion of all others." Resp. 27.[1] Integra is only half right. On the one hand, when the Court said that the FDA exemption applies "[a]t least" in the circumstances described, it was allowing that there could be *additional* circumstances where an experiment

[1] Merck's Opening Supplemental Brief before this Court will be cited as "OB," and Integra's will be cited as "Resp."

might fall within the safe harbor even though the two conditions are not met. On the other hand, there is no room to interpret the Supreme Court's holding, as Integra does, as allowing for a circumstance where those two conditions *are* met but the consequence—JMOL—nevertheless does not attach. If that is what the Supreme Court had meant, it would have started the passage with the words "at times," rather than "at least," and it would have offered the courts—or at least the panel addressing *this* case—a hint about what the superseding considerations might be.

Integra's alternative grounds rejected. Integra next asserts that it is entitled to defend the verdict with testimony that is inconsistent with this rule of decision: "[1] that the FDA is only concerned with safety at the pre-clinical stage ... and [2] that the FDA's practice is to require safety data to be based on experiments in compliance with GLP standards." Resp. 32 (citations omitted). The Supreme Court went out of its way to reject what "Respondent [Integra] argue[d]" on both propositions, as a matter of law. 125 S. Ct. at 2381[S73]; *see id.* at 2381-82 [S73-74] (rejecting what "Respondent contends"). Yet, Integra tries to evade the Court's ruling by insisting that the jury could rely on a witness who testified to those legally erroneous propositions, because "[t]he Supreme Court says nothing about what *testimony* the jury was or was not entitled to believe." Resp. 33 (emphasis in original).

Integra's position depends upon two premises, both of which are false. First, Integra asserts that "[t]he controlling question for this Court" is different from the question the Supreme Court decided. *Id.* To the contrary, the Supreme Court said it was addressing *Integra's* arguments—which were exactly the arguments Integra now advances. The section in Integra's Supreme Court brief directed at efficacy began with this introductory sentence: "Merck's argument that certain of Scripps' preclinical experiments relate to efficacy fails *because of* Mr. Meyer's testimony that the FDA relies solely on clinical data to determine efficacy." S189 (emphasis added). Similarly, Integra's argument about GLP was that "Integra's expert, Mr. Meyer, testified that the FDA's practice is to require that preclinical data for an IND comply with GLP regulations." S186. The Supreme Court rejected both arguments.

Second, Integra insists that "[a]t no time during trial, or in its initial appeal to this Court, did Merck object to expert testimony that the FDA considers only safety and not efficacy at the preclinical stage" or "that the FDA's 'practice' is to have all safety data meet GLP requirements." Resp. 34-35. The very cases Integra cites adopt no such requirement, holding, without noting any exception, that "[w]hen an expert opinion is not supported by sufficient facts to validate it in the eyes of the law, or when indisputable record facts contradict it or otherwise render the opinion unreasonable, it cannot

support a jury's verdict." *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993); *Weisgram v. Marley Co.*, 528 U.S. 440, 454 (2000).

More importantly, even if there were such an exception, Merck did object—vehemently and often—both to the District Court and on appeal. Before trial Merck moved to exclude Mr. Meyer's testimony in its entirety. *See* Docket #596 (in limine motion); Docket #712 (reply). Merck asserted that Mr. Meyer's "opinion ... fails the threshold requirement of Rule 702, as well as the relevance requirements of Rule 401 and the reliability requirement of *Daubert/Kumho*." S619-20. More specifically, Merck asserted that "Mr. Meyer ignored all of the FDA approval process *except* the safety data submitted in an IND application." S617 (emphasis in original); *see* S629-30. The motion even presented an "overview of all the various sorts of (non-safety-related) information that should be included in an IND." S618 n.9; *see* S621-25. Merck summed up its position as follows: "Allowing [Mr. Meyer] to testify that Defendants do not meet a 'test' that is *not* the governing legal standard would only confuse and mislead the jury and unfairly prejudice Defendants." S620 (emphasis in original).

Merck repeated—and even expanded upon—these points in both its JMOL motions and its contemporaneous motion for a new trial. *See* S720-22,

886, 894-95, 902-03, 1107 n.2. In its appeal to this Court, Merck also disputed Mr. Meyer's testimony, refuting, as a matter of law, Integra's position that only safety data are relevant to FDA approval and only data obtained through GLP strictures. *See* S564-65. Merck took pains specifically to "[r]efut[e] Integra's FDA expert's testimony," by pointing out that "the Code of Federal Regulations clearly provides that an IND application requires much more than *in vivo* GLP safety data." S564. In short, the only way to turn Integra's assertion that "[a]t no time ... did Merck object" into a truthful statement is with an Exacto knife and copious amounts of Wite-Out.

B. Having Opted Not To Contest The Factual Questions Integra Now Admits Are "Central," Integra May Not Now Defend The Verdict By Contesting Those Facts.

While insisting that the Supreme Court did not adopt a two-pronged test, Integra concedes at least that the two "'prongs' [the Supreme Court identified] are *central to the inquiry*" under the FDA exemption. Resp. 27 (emphasis added). Yet, Integra does not contradict Merck's representation that Integra *never disputed either of the conditions* it now admits are "central."

Integra does not point to a shred of testimony in which any of its witnesses disagreed with either proposition; to the contrary, Integra acknowledges that it did not "introduce expert testimony" on these subjects. *Id.* at 38. Integra does not point to any cross-examination casting doubt on these

propositions, or to a single instance in which it urged the jury to reach the opposite conclusion, in opening or in summation. Integra does not cite a single sentence, in the extensive summary judgment briefing or two rounds of JMOL briefing on the FDA exemption, where it made such an argument. Integra does not cite to any point on appeal—either to this Court or to the Supreme Court—where it disputed Merck's position on those "central" factual points. Only now that the Supreme Court has rejected Integra's very different approach has Integra tried to contest the factual points that Merck has always tried to put at center stage.

Now is too late. As Integra acknowledges, "[c]ontentions not urged in the trial court are not available on appeal," Resp. 25 (citation omitted), which means that it may defend the verdict based only on "'any *nonwaived* ground,'" *id.* at 4 n.1 (citation omitted; emphasis added). The rule that generally "appellate courts do not consider *a party's* new theories, lodged first on appeal," *Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1426 (Fed. Cir. 1997) (emphasis added), applies with equal force to *both* parties, *see Pannu v. Iolab Corp.*, 155 F.3d 1344, 1351 (Fed. Cir. 1998). And it applies fully to efforts to defend the sufficiency of the evidence before the jury. *See id.*

For this reason alone, this Court should vacate the verdict and award Merck judgment as a matter of law.

C. Any Reasonable Juror Would Have To Accept The Undisputed Evidence That The Accused Experiments Fell Within The Safe Harbor.

Should the Court deem it appropriate to address a sufficiency-of-the-evidence argument that Integra strategically avoided throughout the litigation, it will immediately confront another ripple of that strategy: Merck, alone, presented evidence bearing on the two questions Integra now admits are "central." Integra's problem is not that "Merck turns the[] rules upside down by focusing on the evidence favorable to its position," Resp. 23, nor that "Merck seeks to reverse the burden of proof," *id.* at 26. It is that there is no other evidence to consider.

Even now, as to most of the categories of experiments, Integra does not claim to have produced any evidence bearing directly on the "central" prongs the Supreme Court identified. *See id.* at 27-28. As to a handful of categories, Integra argues that Merck produced no evidence on one of these conditions, and as to another few categories, it tries to manufacture a dispute of fact by distorting the obvious meaning of a single sentence of testimony. These efforts are addressed in Point C.2. Beyond that, Integra tries to squeeze material issues of fact out of two species of irrelevant evidence that, by its own description, are ancillary to the "central" questions. *Id.* We address this unsuccessful effort in Point C.3. We then address Integra's last-ditch argument that the jury was free

to ignore *all* the relevant and undisputed testimony of ten witnesses, without regard to whether they were impeached, interested, or disputed. *See infra* Point C.4.

But before demonstrating that *all* the experiments fell within the FDA exemption as a matter of law, we begin with an important threshold point: The judgment must be reversed as to *any* experiment that was exempt, even if there were some experiments this Court concludes were not exempt as a matter of law.

1. The verdict must be reversed as to any single experiment that fell within the safe harbor.

Integra does not dispute that the District Court was required to assess the FDA exemption with respect to each "use," which is to say, each experiment. Nor does Integra dispute that Merck lodged a series of timely objections to the verdict sheet erroneously directing the jury to reject the FDA exemption as to all 180 experiments so long as it found that a single experiment fell outside the safe harbor. *See* S650-51, 688-94, 750-51, 758-64, 8655-67, 8690, 8912-16. Nevertheless, Integra takes the curious position that the patent infringement verdict must be upheld in its entirety—as to all 180 accused experiments—so long as a reasonable juror could find that a single one of them fell outside the safe harbor. *See, e.g.,* Resp. 17, 19, 31.

The law dictates that sufficiency of the evidence must be judged by the correct legal standard. *See Doctor's Assocs., Inc. v. Weible*, 92 F.3d 108, 115 (2d Cir. 1996); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 975 n.5 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). The rule in this Circuit is so robust that it would apply even if Merck had never lodged its objections and, indeed, even if it had originally embraced the incorrect legal standard. *Markman*, 52 F.3d at 975 n.5; *see Boyle v. United Tech. Corp.*, 487 U.S. 500, 513-14 (1988). Integra does not mention, much less distinguish, this controlling precedent, but simply offers two different waiver theories that defy it.

At points, Integra argues that Merck's JMOL position "is based on an attack on the propriety of the form of verdict," which Merck cannot press because it did not appeal the point separately. Resp. 24; *see id.* at 25, 29. To the contrary, Merck is not attacking the *verdict form*; it is attacking the *verdict*, and insisting that the evidence before the jury must be assessed by the correct legal standard. Merck would be insisting on the same legal standard whether or not the District Court had heeded its request to instruct the jury properly. To be sure, Merck *could have* asked this Court for a new trial (as it did below) on the ground that the verdict sheet led the jury astray. But Merck is not now interested in enduring the expense and distraction of another six-week trial, and

had no obligation to seek one in order to secure its right to a directed verdict under the correct legal standard.

At other points, Integra's waiver argument amounts to the equally erroneous position that Merck "thrice waived its right" to apply the correct standard by failing to call attention to the correct legal standard in its JMOL motions or on appeal to this Court and the Supreme Court. *Id.* at 17. This position, too, is inconsistent with this Court's precedents governing JMOL review. It is also based upon a misreading of the rules, which allow a party to lodge a timely objection under Fed. R. Civ. P. 51(d), as Merck did, without having to repeat the objection multiple times. *See Lear v. Equitable Life Assurance Soc'y*, 798 F.2d 1128, 1133 (8th Cir. 1986). But law aside, Integra's factual premise is triply false, for Merck invoked the correct legal standard at every level.

Merck filed its post-verdict JMOL motion contemporaneously with a motion for a new trial, and *both* objected to the verdict sheet. *See* Docket #1048 (post-verdict JMOL motion); Docket #1051 (motion for new trial). The latter objected that "the jury verdict form improperly combined sixteen categories of accused experiments, thus preventing the jury from evaluating independently each of the experiment categories accused of infringement." S977; *see also* S982-83. Merck's JMOL motion reiterated the point. S1105 n.1. In keeping

with the correct legal standard, Merck then proceeded to address the FDA exemption category-by-category. S882-83 n.1-2. Merck even parsed Integra's arguments based upon which category of experiments they applied to. S892.

Merck never abandoned the position on appeal. Merck's initial brief before this Court cited the scientists' particularized category-by-category testimony. S364. Likewise, on appeal to the Supreme Court, Merck took pains to point out that "instead of directing the jury to decide whether each experiment fell within the safe harbor, the verdict form directed the jury to reject the FDA exemption if it found that *any one* experiment fell outside the safe harbor." S108; *see also* S221 & n.2. Merck then emphasized in bold and italics, as one of four key principles governing the case, that: "***Every use is individually assessed***," which, as Merck explained at length, means that "the JMOL ruling cannot be sustained as to any experiment that falls within the safe harbor." S221 (emphasis in original). If the point took less prominence in the earlier rounds of appellate briefs, the explanation is straightforward: Integra defended the verdict based on theories that transcended the specific categories, and both the District Court and this Court took Integra's lead, painting with an equally broad brush.

Certainly, this Court was not under any misimpression that Merck waived the proper legal standard. At oral argument before this Court, Integra insistently floated exactly the argument it makes here, S606, and the Court chided:

> COURT: You're not going to get an interpretation of law to go your way on the technicality that there was an instruction that may have been inconsistent with the law, are you? I can't understand why you continue to push that point. We've told you three times it's not going to work.
>
> MR. FLORES: Okay. Then I will not push that point any further.

S607. Yet, now, before the very same panel, Integra does not just "push that point ... further," but builds its entire appellate stance around the point.

2. Merck presented undisputed evidence that all the experiments were directed at topics that are FDA-relevant.

The undisputed evidence was that the accused experiments fell into 16 categories, based upon the experimental model. It was Integra's expert who devised this taxonomy, which both parties embraced throughout trial. *See, e.g.*, S6018-19. In a display of the disconnect between Integra's strategy to secure the initial verdict and its current effort to salvage it, Integra now adopts a completely different taxonomy of experiments, an awkward cross-section of the 16 categories that no one considered until now. For the sake of argument, we adopt Integra's re-classification, and address each class in turn: (1) "experiments that are directed to assessing the biological activity of RGD peptides"; (2) a total of two experiments involving a purified "cell surface

receptor that binds to RGD peptides";[2] and (3) experiments that compared the activity of RGD peptides with mimetics. Resp. 18-19.

That is not the order in which Integra addresses the classes, which brings us to yet another symptom of the disconnect. Integra treats the first class of experiments as an afterthought, even though it was by far the largest—encompassing nearly 90% of all the experiments. We address this large class of studies first, because they were central to the damages analyses in this case. Integra would never have brought a patent infringement case to collect royalties for the use of a patented compound to help test 15 to 20 drug candidates that animal testing showed to be inferior (Class 3) or for two receptor binding assays (Class 2).

RGD peptide studies. At least as to this dominant class of experiments, Integra does not dispute that Merck satisfied the first "central" inquiry, for it was undisputed that RGD peptides yielded the desired physiological effect. *See* OB 34-35. As to the second prong, Integra does not deny that Merck presented a massive amount of evidence in support of the proposition that these experiments all bore on FDA-relevant topics, other than safety: efficacy, mechanism of

[2] The summary chart, which tracks the testimony of Integra's expert Dr. Dedhar, lists 15 experiments in this category. *See* Resp., App. at 1. In fact, the District Court excluded 13 of those experiments from the case, based upon the experimental use exception. *See* S714-16, 1231-83, 8596-603, 8619.

action, pharmacology, or pharmacokinetics. Rather, Integra's effort to bolster the jury verdict consists of grasping for some material dispute of fact on this latter prong. The entire effort revolves around a single sentence in the testimony of the now-discredited Mr. Meyer.

Before addressing the sentence, let us be clear about the very limited scope of experiments the purported dispute could possibly affect. Integra's Class 1 covers 15 of the 16 categories of experiments (every category except the purified receptor assay), encompassing a total of 165 experiments. Nine of those categories were performed on mammals, specifically, mice and rabbits. *See generally* OB, App. A. But Mr. Meyer did not testify about these mammalian experiments, nor about most of the other categories. He testified only about *three* out of the 15 categories of experiments in Class 1. The testimony Integra invokes was limited only to two types of chicken CAM experiments and a cell adhesion assay. A8357-59. So JMOL is appropriate as to all the other 12 categories of experiments on RGD peptides, without regard to this purported factual dispute.

Moreover, what Mr. Meyer said about the three categories of experiments does not undermine the otherwise undisputed testimony that these experiments related at least to efficacy, mechanism of action, pharmacokinetics, or some combination of these topics. That much is evident upon reading the one

sentence Integra highlights (italicized below) in the context of the numerous signals (bolded below) limiting the comment to considerations of safety:

> Q. Is data from a chick CAM assay acceptable to the FDA **to bear on safety issues** relating to an IND application?
>
> A. I do not believe that data would have any value **in substantiating the safety** of a substance in an IND application, sir.
>
> Q. And would you explain the basis of your opinion?
>
> A. Well, *I don't think that chicken data has ever been predictive of the human experience.* And, in addition, we actually tried—we actually had some staff who some years ago tried to use that assay as a test **for safety** of food additives, and it was just—just didn't work. We just discontinued it. It's considered by—to be a **useful** discovery screening kind of tool **to evaluate the ability to stimulate and inhibit blood vessel growth**.

A8358 (emphasis added). The questioning turned next to cell adhesion studies, and Mr. Meyer's testimony on that topic was limited to this single sentence: "I don't believe they would have any value, again, **in substantiating the safety** of a compound to be submitted for the possibility of evaluating it in man." A8359 (emphasis added).

This was not, as Integra contends, a pronouncement that chicken models and cell adhesion assays have no bearing on any FDA-related topic, including efficacy and mechanism of action. If that were what Mr. Meyer meant, he would not have said, on the same page, that chicken CAM experiments are "useful ... *to evaluate the ability to stimulate and inhibit blood vessel growth.*" A8358. That is why Integra acknowledged to the Supreme Court and to this

Court that Mr. Meyer was commenting only on the value of these models "to substantiate human safety." S188 (Supreme Court brief uses the words "safety" or "toxicity" five times in the two paragraphs characterizing the same testimony); *see* S481-82 (initial brief to this Court discusses same testimony as limited to "relationship to human safety").

Ultimately, Integra's position turns not on any testimony that these three categories of experiments were unrelated to efficacy and mechanism of action, but on a logical construct, first devised on appeal, which no witness ever embraced. According to counsel, "It defies logic to argue that a technique that is not predictive of human experience [on toxicity] can be used to make inferences about efficacy and mechanism of action in humans." Resp. 40; *see id.* at 41 (making same point on cell adhesion assays). In other words, Integra imagines a jury that would conclude—without prompting from any witness—that it is illogical for a scientist to hold the following two views simultaneously: (1) the FDA would not deem a drug safe enough to administer to humans based on nothing more than evidence that it has not killed chicken embryos; but (2) the FDA would at least *consider* experiments demonstrating that a drug stops blood vessel growth and starves tumors in chicken CAMs in evaluating whether it might conceivably have the same effect on human blood vessels.

It is hard enough to imagine any juror who could reach that conclusion faced with an avalanche of testimony, including testimony that Ixsys, a completely separate entity, made the independent judgment to commission chicken CAM and cell adhesion experiments for its IND submission. But it is downright inconceivable that an entire jury could have reached that conclusion here, because Integra premised its case at trial on the opposite proposition. As we shall see, all the comparisons between RGD peptides and mimetics were conducted in these same experimental models. *See* OB, App. A at 1 (three rows designated with "m"). Integra repeatedly stressed that those comparative studies were directed at finding the "best drug candidate," meaning that the experiments were directed at assessing efficacy. *E.g.*, S8844; *see also* A6993. Even now, that is exactly how Integra describes the experiments: "*These experiments assessed the efficacy* of the non-peptide compounds by comparing their effect to that of the Merck peptides." Resp. 7 (emphasis added). It would have been nonsensical for a jury to have concluded that these very same categories of experiments had no bearing on efficacy when conducted on RGD peptides alone.

Purified receptor assays. Integra is wrong when it asserts that "Merck has not submitted *any* evidence or argument that [the purified receptor assay] was exempt." *Id.* at 31 (emphasis in original). Dr. Cheresh testified about

exactly what the assay demonstrated: the "alpha-v-beta-3 binding assay ... simply *speaks to the idea of efficacy*. It allows you to pick the best peptide and really describe with precision how active the peptide might be with regard to this target." A7177 (emphasis added). Various other witnesses included this assay in their assessment that *all* the experiments were directed at the FDA-relevant topics of efficacy, mechanism of action, pharmacology, and pharmacokinetics. *See* OB 44-46.

To the extent that Merck did not focus on this category in the last round of briefing, it is because Integra "simply ignored" the issue throughout the case, Resp. 31, never suggesting to any witness, to the District Court, to the jury, to this Court, or to the Supreme Court that the two experiments with purified receptor had a legal status that was any different from any of the others. Even now, Integra merely mentions that this particular category of experiment is subject to a different patent, but offers no reason to treat it differently under the FDA exemption.

Comparisons of RGD peptides to mimetics. Integra's argument as to the comparative experiments with mimetics (Integra's Class 3) is different, but equally flawed. This final class of experiments is a cross-section of only three categories of experiments—two varieties of chicken CAM experiments and a cell adhesion assay, *see* OB, App. A; A6043-44, the same three categories that

were the subject of Mr. Meyer's testimony above. *See supra* at 16-18. Scripps ran most of the experiments in these three categories with RGD peptides alone. But it ran a few of those experiments with RGD peptides alongside other compounds designed to mimic the activity of the peptides.

As noted above, Integra cannot plausibly claim that these experiments yielded no information on efficacy of the mimetics, since Integra admits (and has maintained throughout the litigation) that "[t]hese experiments assessed the *efficacy* of the non-peptide compounds." Resp. 6. Integra argues, instead, that the moment Scripps included a mimetic in one of the experiments, the experiment lost the protection it would otherwise have had. According to Integra, there was no evidence "that the non-peptide compounds"—i.e., the *non*-patented compounds—"were designed to behave in the same manner as RGD peptides and could reasonably be expected to do so." *Id.* at 30.

Without the slightest hint as to why this focus is permissible when the Supreme Court's test asks whether the "*patented* compound produced a particular physiological effect," 125 S. Ct. at 2383 [S75] (emphasis added), Integra challenges Merck's assertion that "'there is no dispute'" on this factual point. Resp. 30 (quoting OB 16). Until now, there *was* no dispute; Integra disputes the point for the first time on remand. Integra never suggested either in its opening, cross-examination, summation, or any JMOL brief or appellate brief

to this Court or the Supreme Court that there was any question that these "mimetics" were designed to *mimic* RGD peptides. *See, e.g.*, S466 (Integra's initial brief to this Court acknowledges that the purpose of the comparisons was to assess: "would a nonpeptide compound that mimics an RGD peptide ('a mimetic') be a better candidate?"). Had Integra ever disputed that the mimetics were, indeed, designed to mimic, Merck would have fleshed out the record.

As it stands, though, the undisputed record is perfectly clear. Dr. Cheresh was not screening thousands of random compounds with unknown properties. S7302-05. He tested 15 to 20 *select* compounds carefully designed to mimic the activity of the RGD peptides. *See, e.g.*, A4887, 10107; S2011, 5816-17, 6674-75 . Most of them came from Merck. *See* S7332-33. Integra does not focus on the Merck mimetics, presumably because the testimony was unequivocal that Merck sent Dr. Cheresh these compounds only after confirming that they displayed the relevant physiological potential. A4887, 10106-08; S1444-48, 2011, 5816-17. Integra spotlights only the few compounds that Dr. Nicolaou of Scripps synthesized. *See* Resp. 28-29.

There was no dispute that Merck contracted with Dr. Nicolaou with the "Specific Aim[]" to "*design[] specific non-peptide mimetic antagonists of integrin avB-3 and/or avB-5*," the cell surface receptors involved in angiogenesis. A10094 (emphasis added). Nor was there any dispute that the

contract was premised on the understanding that "Dr. K.C. Nicolaou ... *has already designed*" some mimetics, S1410; *see also* S1423, or that his job was to "modify" those "chemical structures ... to obtain the most potent, specific, non-toxic inhibitors of angiogenesis in vivo," A10094. Contrary to Integra's suggestion, the jury *did* have evidence about the structure of mimetics Dr. Nicolaou synthesized, and so did Integra and its experts. *Compare* Resp. 28. They were drawn in the laboratory notebooks admitted into evidence, and the jury could see for itself that they did, indeed, resemble RGD peptides. S1301-04.

Even without the benefit of these drawings, it does not take "rank speculation" for a jury to conclude that Dr. Nicolaou, the Chairman of the Chemistry Department at Scripps, supplied what Merck paid him over a million dollars to supply, A10109, rather than trying to pass off a test tube of, say, baking soda as a mimetic. Resp. 30; *see* S1423 (Dr. Nicolaou undertakes commitment). And even a juror who might have speculated that Dr. Nicolaou was inept at chemistry would still have no basis to conclude that it was unreasonable for Dr. Cheresh and Merck to believe they were getting what they ordered.

In any event, Integra's argument on the comparative experiments misses a fundamental point: These experiments, like Integra's Class 1 experiments, were

experiments "directed to assessing the biological activity of *RGD peptides*." Resp. 19 (emphasis added). The testimony—which Integra, again, chose not to dispute—reveals that every time Scripps scientists conducted any experiment on RGD peptides alongside another candidate, they learned more about the *RGD peptides*. *See* A6195-96, 6993; S6801-02, 8844. Integra did not adduce any evidence to challenge the proposition that every step in the search for the "best possible compound" gave Merck more information about the drug candidate that took the lead. A6195-96, 6993; S262, 268-71, 8281-82.

3. The ancillary evidence Integra invokes does not undermine the conclusion that all the experiments on the RGD peptides were directed at FDA-relevant topics.

Having failed to adduce any evidence directly relevant to the "central" inquiries, Integra resorts to ancillary evidence of purported "admissions" and "other evidence relating to the context in which the experiments ... were performed." Resp. 27-28. None of this undermines Merck's showing.

Claimed "admissions." The "admissions" Integra invokes amount to nothing but distortions of testimony about the rough division of labor that Merck and Integra had worked out over the four years of collaboration at issue in this case. It shows only that, as a general matter, Merck and Scripps agreed that Merck would conduct the toxicological studies requiring GLP certification and limited pharmacokinetic studies, but Scripps would conduct the studies relating

to efficacy and mechanism of action, and most of the pharmacology. But Integra describes these general statements—which it studiously avoids quoting—as categorical proof that no experiment performed at Scripps could have yielded any evidence relevant to safety or to pharmacokinetics. *See* Resp. 41-42. A closer look confirms that no one ever testified to any such airtight separation.

Integra devotes most of its energies to demonstrating that "Merck scientists contradicted the testimony of Scripps witnesses that certain experiments at issue were related to *safety*." *Id.* at 41 (emphasis added). But as a quick scan of the summary table reveals, not a single experiment was justified as relevant to safety alone. *See* OB, App. A. Of the 16 categories of experiments, 13 were justified as relevant to efficacy or mechanism of action, or both—and all witnesses agreed that these topics were within Scripps' area of responsibility. So Integra's purported factual dispute has no bearing on these 13 categories, which encompassed all but nine of the 180 experiments.

The Scripps scientists justified the remaining few experiments as relevant to pharmacokinetics. *See* OB, App. A. They all consisted of injecting an animal with an RGD peptide and then periodically sampling the blood or tissues to measure the rate of absorption or elimination of the drug. *See* A6993-94, 6998-99, 7184-85; S6959-60 . Integra never disputed that these experiments were

classic pharmacokinetic exercises, and, indeed, introduced no testimony about them at all. Integra's effort to dispute the proposition now is based upon the assertion that "Merck's Dr. Grimm, however, testified that *none of the pharmacokinetic metabolism* tests was performed at Scripps." Resp. 41 (emphasis added). That assertion is based upon an answer to a single question: "*Turning to M02846*, were any of the pharmacokinetic metabolism tests performed at ... Scripps?" A4894; S2018 (emphasis added). When Dr. Grimm answered no, she was answering a question about a specific page of a report she had prepared, reflecting two specific sorts of metabolic studies performed on mice and monkeys. *See* S1478, 2016-18. Dr. Grimm did not testify—there, or anywhere else—that none of the Scripps experiments were related to pharmacokinetics. She was obviously not contradicting the testimony of several witnesses that three entirely different categories of Scripps experiments bore on pharmacokinetics. No reasonable juror could have concluded otherwise.

Evidence of "context." The rest of Integra's contextual evidence fixates upon a label Merck used for purposes of internal administration and public disclosure. Integra points out that Merck "distinguishes between research programs and drug development," arguing that the latter "are focused on regulatory requirements (primarily toxicology and clinical testing in humans), whereas its research programs are not." Resp. 42 (citing A4960). Integra also

observes that "[i]t is undisputed" that Merck's official "development process for the infringing RDG compounds began in November 1996." *Id.* From these two facts, Integra suggests that a reasonable juror could draw the conclusion that no experiments before that date could have yielded evidence relevant to the FDA.

Accepting this analysis, then, two years' worth of accused research—from November 1996 through 1998—was categorically and "undisputed[ly]" within the FDA safe harbor, and the verdict must be overturned at least as to that period.

More importantly, the FDA exemption depends upon the specific "use"—the experiment—not upon some label that is affixed to research for corporate administrative purposes. Merck's decision to label as "drug development" the experiments demanding the greatest financial investment—covering "primarily toxicology and clinical testing in humans"—has no bearing on whether experiments leading up to that phase will be relevant to the FDA's consideration of efficacy and mechanism of action. Indeed, the very witness Integra invokes confirmed that "[t]he transition between research and development are often flowing transitions, and in the pre-phase it may have been a development project but not officially." A4950. Notably, several Merck officials confirmed that data prior to that formal designation are routinely inputted into the official corporate database that is intended for the FDA. S7500-01, 7507-08, 7902-03, 7912-13.

In the end, all the evidence Integra tries to pass off as "admissions" and "context" really boils down to an unsuccessful effort to show that some official or another at Merck was not certain that a particular sort of data would be relevant to the FDA. Even if Integra had succeeded in proving that modest point, these sorts of subjective impressions have no bearing on the objective standard, which focuses on comparing what the experiments actually accomplished to the topics of the FDA's known regulatory interest. *See* OB 54-57.

4. Integra cannot sweep away the undisputed testimony of ten witnesses just by positing that the jury was not required to believe any of them.

Integra's last-ditch effort is the assertion "that juries are not required to believe the testimony of party witnesses, such as Dr. Cheresh, or of the employees of a corporate party," Resp. 43 (footnote omitted), "[n]or was the jury required to believe the testimony of Merck's [independent] expert witnesses ... , who by definition were also interested witnesses," *id.* at 44. With these sweeping pronouncements, Integra wipes away the consistent—and undisputed—testimony of nine witnesses. It also glides over, without explanation, the testimony of a tenth witness, Dr. Houston, the independent Ixsys consultant, who was called as a *fact* witness to testify only to the sorts of

studies a completely separate entity commissioned and included in its IND application. *See* OB 45.

Contrary to Integra's assertion, *see* Resp. 47, these ten witnesses all agreed, based upon their review of experimental protocols and results, that all the experiments were relevant to efficacy, mechanism of action, pharmacokinetics, or pharmacology. *See* OB 40-46. Four of the witnesses—the outside experts and Dr. Brooks—were not interested witnesses in any normal sense of the term. As we have seen, these independent witnesses confirmed that "the CAM test and *all the tests*" were "designed to understand the basis upon which the cyclic peptide compounds might have application to human medicine," S8270, and that they went "to the heart of the mechanism by which [the drug in question] might work," S8240-44. Integra does not even claim to have tried to challenge the credibility of seven out of the ten witnesses. And Integra does not point to a single effort to challenge any witness on the specific point relevant here, that the experiments were directed at efficacy and the other non-safety issues that the FDA considers in an IND application.

There are limits to the principle that a jury is entitled to make credibility determinations. It is not enough to pronounce, "the jury was not required to believe" it, and call it a day. Resp. 43; *see McAnally v. Gildersleeve*, 16 F.3d 1493, 1500 (8th Cir. 1994) ("we cannot accord the jury with the benefit of

unreasonable inferences, or those at war with the undisputed facts.") (internal quotations omitted).

Integra's effort to do just that is emblematic of an approach that pervades its brief. Integra imagines a remarkable jury. A jury that would have reached a series of conclusions Integra never pressed. A jury that, for no reason, would have rejected the testimony of ten witnesses who confirmed that the Scripps experiments did indeed satisfy the relevant conditions. A jury that would have reached this untenable result only by rejecting Integra's own central position that Merck was performing all these experiments to identify the "best drug candidate"—i.e., the one that is most effective—an exercise that can be conducted only if the experiments say something about efficacy. S8844 (internal quotation marks omitted).

Nothing in the rules governing sufficiency-of-the-evidence review requires this Court to indulge Integra's fantasy of a jury so unwilling to assess the evidence. *See Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1569 (Fed. Cir. 1993). The rules contemplate a jury of reasonable persons, not a jury of risible partisans.

CONCLUSION

For these reasons, this Court should grant judgment as a matter of law dismissing Integra's claims of patent infringement.

DATED: January 3, 2006

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