

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.

On Remand from the Supreme Court of the United States

SUPPLEMENTAL BRIEF OF PLAINTIFFS-CROSS APPELLANTS INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE

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December 13, 2005

CERTIFICATE OF INTEREST

Counsel for Plaintiffs–Cross Appellants certifies the following:

1. The full names of the parties represented by us are Integra LifeSciences I, Ltd. (presently named Integra LifeSciences Corporation), and The Burnham Institute for Medical Research (formerly known as the Burnham Institute).

2. The parties listed in paragraph 1 above are the real parties in interest whom we represent.

3. All parent corporations and any publicly traded companies that own ten percent (10%) or more of the stock of the parties or amicus curiae represented by us are: LifeSciences Holding Corporation.

4. The names of all law firms and partners or associates that appeared for the parties or amicus represented by us in the trial court or that are expected to appear in this Court are the following partners of McDermott Will & Emery LLP: Mauricio A. Flores, Raphael V. Lupo, Mark G. Davis, M. Miller Baker, Richard B. Rogers, David M. Beckwith, Cathryn A. Campbell. Mr. Beckwith and I appeared at trial and before this Court as partners in the law firm of Campbell & Flores, which has since dissolved. In addition, Plaintiffs–Cross

Appellants were represented at trial by Lynn M. Brennan of Campbell & Flores.

DATED: December 13, 2005

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STATEMENT OF RELATED CASES

This appeal was previously before this Court.

1. The title and number of the earlier appeal: *Integra LifeSciences I, Ltd., The Burnham Institute, and Telios Pharmaceuticals, Inc. v. Merck KGaA, The Scripps Research Institute, and Dr. David A. Cheresh*, Nos. 02-1052, 02-1065.

2. The date of decision was June 6, 2003.

3. The panel consisted of Circuit Judges Newman, Rader, and Prost.

4. The opinion was reported as: *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003).

5. The Supreme Court vacated the judgment of this Court and remanded for further proceedings consistent with its opinion, which is reported as *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 2372 (2005).

There is no other case in this or any other court known to directly affect or be directly affected by this Court's decision in the instant appeal.

STATEMENT OF JURISDICTION

This Court has exclusive jurisdiction over this appeal pursuant to 28 U.S.C. § 1295(a)(1). The United States District Court for the Southern District of California had jurisdiction over this case pursuant to 28 U.S.C. § 1338(a).

In the District Court, Merck filed its post-trial motions prior to the entry of final judgment. On March 6, 2001, the District Court entered an order rejecting

Merck's post-trial motion for judgment as a matter of law on the FDA Exemption codified at 35 U.S.C. § 271(e)(1). A33–35. On March 26, 2001, the District Court entered final judgment disposing of all claims against all parties. Merck's post-trial motion for a new trial was denied on October 10, 2001. Merck filed its Notice of Appeal on November 7, 2001.

On June 6, 2003, this Court affirmed the District Court's denial of Merck's motion for judgment as a matter of law with regard to the FDA Exemption. *Integra Life Sciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003).

Pursuant to its jurisdiction under 28 U.S.C. § 1254(1), the United States Supreme Court vacated the judgment of this Court but declined to undertake a review of the record for the sufficiency of the evidence under a proper construction of Section 271(e)(1). *Merck KGaA v. Integra LifeSciences I*, 125 S. Ct. 2372, 2384 (2005). Accordingly, the Supreme Court remanded the case to this Court for further proceedings consistent with its opinion.

STATEMENT OF THE ISSUE

The FDA Exemption applies to otherwise infringing activities that are "reasonably related to the development and submission of information under federal law which regulates the manufacture, use, or sale of drugs . . . ." 35 U.S.C. § 271(e)(1). The Supreme Court held that the jury instruction on the FDA Exemption proposed by Integra and agreed to by Merck was "consistent with, if

less detailed than, the construction of § 271(e)(1) that we adopt today." *Merck KGaA v. Integra LifeSciences I*, 125 S. Ct. 2372 (2005). The Supreme Court's opinion was limited to the proper interpretation of Section 271(e)(1). Declining to review the record to determine the sufficiency of the evidence under Federal Rule of Civil Procedure 50(a), the Supreme Court remanded that issue for this Court to decide.

Pursuant to the Supreme Court's mandate, the sole issue presented here is whether the evidence at trial is sufficient, when considered in light of the jury instruction approved by the Supreme Court, to affirm the District Court's denial of Merck's motion for judgment as a matter of law pursuant to Federal Rule of Civil Procedure 50(a) with respect to its affirmative defense under the FDA Exemption. To prevail on this appeal, Merck must establish that it is entitled to judgment as a matter of law based on consideration of only that evidence which is favorable to the verdict and which the jury was required to believe as a matter of law.

STATEMENT OF FACTS

A. The Patented Inventions and Dr. Cheresh's Basic Research

The patented inventions of Drs. Ruoslahti and Pierschbacher were truly pioneering—they spawned an explosion of scientific research relating to RGD

peptides and the class of cell surface receptors (or integrins) to which they bind. A5465–66; Tr. 361.[1] Integrins are enormously important because they control myriad cellular functions and processes. In effect, Drs. Ruoslahti and Pierschbacher discovered the key (the RGD sequence) to a lock (the integrin cell surface receptors) that controls a wide range of cellular activity.

The patents at issue cover more than simply the compositions of RGD peptides with cell attachment activity and the cell surface receptors to which they bind. The patents also cover three distinct ways to manipulate cell interaction with the extracellular matrix: (1) promotion of cell attachment by use of an RGD peptide ('525 patent); (2) blocking cell attachment ('997 patent); and (3) disrupting existing cell attachment ('237 patent).

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[1] Integra has cited to material that was not contained in the joint appendix filed when this appeal originally came before this Court for two reasons. First, the Court has not yet ruled on Merck's motion for leave to file a supplemental appendix, and Integra therefore cites to the material as a precaution in case the Court does grant the motion. Integra believes that Merck's case is so fatally flawed that Integra should prevail even without this material, but has cited it as further evidence showing why the Court should affirm the District Court's denial of Merck's renewed JMOL motion. Second, the federal courts of appeals have recognized that an *appellee*, such as Integra, is entitled to assert any ground for affirmance that is apparent on the record as long as it does not enlarge the relief given to that appellee by the district court. *El Paso Natural Gas Co. v. Neztsosie*, 526 U.S. 473, 479 (1999); *Casey v. Moore*, 386 F.3d 896, 910 n.11 (9th Cir. 2004); *Door Sys., Inc. v. Pro-Line Door Sys., Inc.*, 83 F.3d 169, 173 (7th Cir. 1996) ("An appellee can defend the judgment appealed from on any nonwaived ground, even if the district court did not address it.").

Dr. David Cheresh was one of many scientists working in the RGD/integrin research space opened up by the pioneering inventions of Drs. Ruoslahti and Pierschbacher. In 1994, using an antibody called LM 609, Dr. Cheresh demonstrated that blocking a particular integrin claimed in Integra's '734 patent—the $\alpha_v\beta_3$ receptor—would inhibit the growth of blood vessels ("angiogenesis") in tumors, thereby depriving tumors of the blood supply they need to grow. A7152–54. Dr. Cheresh later demonstrated that blocking the $\alpha_v\beta_3$ receptor with an RGD peptide supplied by Merck had the same anti-angiogenic effect. A7157–58. Neither Scripps nor Merck discovered that RGD peptides would bind to the $\alpha_v\beta_3$ receptor—that fact was previously known. Tr. 1064–65.

By March 1994, Dr. Cheresh had filed a patent application on his discovery that inhibitors of the $\alpha_v\beta_3$ receptor, including the RGD peptide EMD-6, could be used to inhibit the growth of blood vessels in tumors. Merck Brief, p. 10. By May 1994, Dr. Cheresh had communicated his conclusion and supporting data to Merck, which had been funding his scientific research. *Id.* Dr. Cheresh advised Merck in June of 1994 that Scripps was "in a good position to develop peptide-based antagonists of angiogenesis for treatment of cancer." *Id.*

In 1995, Merck and Scripps entered into a new funding and option agreement ("1995 Agreement"). A10071–83. The 1995 Agreement provided, in

part, that Scripps would evaluate the specificity, efficacy, and toxicity of potentially anti-angiogenic compounds supplied by Merck. A10073; A10099.

The 1995 Agreement further provided that Merck would "collaborate closely with Dr. K. C. Nicolaou, to design and synthesize, non-peptide integrin antagonists for analysis . . . ." A10099. The 1995 Agreement did not identify any specific non-peptide antagonists to the $\alpha_v\beta_3$ receptor. Rather, the 1995 Agreement states prospectively that such compounds "will" be designed by Dr. Nicolaou and "examined in purified receptor assays, cell adhesion assays and angiogenesis models in vivo." A10094.

B. Scripps Attempts to Develop a Non-Peptide Inhibitor of Angiogenesis

Merck admits that eleven percent of the infringing experiments did not relate to testing RGD peptides. Merck Brief, p. 17. These experiments assessed the efficacy of the non-peptide compounds by comparing their effect to that of the Merck peptides. *Id.* These comparisons were useful precisely because the effects of the RGD peptides were already known, thereby allowing those peptides to be used as "positive controls" to determine whether the non-peptide compounds would inhibit angiogenesis. A6044; Tr. 876; *see* Lodgment of Deposition Excerpts Presented at Trial in Lieu of Live Deposition Testimony ("Video Test.") (Dist. Ct. Docket #1027), Exh. 6, pp. 29–30. Merck's objective was to develop non-peptide

compounds that have a significant inhibitory effect on angiogenesis. Video Test., Exh. 9, p. 61.

The tested non-peptide compounds were either designed by Dr. Nicolaou or were "made available" to Dr. Nicolaou by Merck, which "only offer[ed] Mr. Nicolaou the possibility of including those structures into his considerations." Video Test., Exh. 7, p. 40. Asked to explain the nature of Dr. Nicolaou's "considerations," Merck's Dr. Joncyzk explained that "Dr. Nicolaou designs structures of new substances. How he proceeds in detail, I do not know." *Id.*; *see also* A4916. Thus, it was Dr. Nicolaou's decision, and his decision alone, whether to forward these non-peptide compounds for testing in Dr. Cheresh's laboratory.

Dr. Nicolaou did not testify at trial. Therefore, the jury had no knowledge of the reasons why these particular non-peptide compounds were selected for testing. Nor was the jury told anything about the structure of these non-peptide compounds. Dr. Cheresh testified that he tested Merck's non-peptide compounds "blind," without knowledge of their structure. Tr. 2205. Dr. Cheresh told the jury that he did so because it is "always good" to perform experiments blind "so that we have no bias in looking for a particular result." *Id.* Dr. Cheresh testified that "[t]his is how most of our work is done." *Id.*

Dr. Cheresh also told the jury that in carrying out these experiments on non-peptide compounds, Scripps was "really searching for an ideal drug candidate."

A6195. Merck admitted that none of these experiments on non-peptide compounds was necessary for generating FDA-related data for the approval of a ***peptide*** drug candidate. A4919.

C. Merck Assumed Sole Responsibility for Studies Oriented to FDA Requirements

Although the 1995 Agreement states that Scripps will "examine each compound for half-life, toxicity and efficacy" (A10099), the testimony at trial indicated otherwise. Merck scientists testified that Merck, and Merck alone, performed the toxicology, pharmacology, and pharmacokinetic work necessary for FDA approval. A4894. Merck's Dr. Sombroek confirmed in a letter to Dr. Cheresh that Merck "will take care of toxicological studies once we have defined a product for the pipeline. Pharmacokinetica, pharmacodynamics and bio-distribution will be performed at our [Merck's] institute in Germany." Trial Exh. 36; *see* Tr. 2184, 2186. This evidence directly contradicts Dr. Cheresh's testimony that his work was intended to assess these FDA considerations.

There were further admissions that Merck itself did not regard Scripps' infringing experiments as oriented toward the generation of data for the FDA. Dr. Schmitges, Merck's Director of Biomedical, Research Preclinical Pharma Research, testified that Merck sharply distinguishes between research programs and drug development. Dr. Schmitges explained to the jury that Merck's development programs are focused on regulatory requirements (primarily

toxicology and clinical testing in humans), whereas its research programs are not. A4960. Further, Dr. Sombroek testified that under Merck's procedures the transition from research and development takes place with a decision by Merck's Pharma Project Steering Committee, subject to approval by Merck's Pharma Board, to proceed with the development of a specific compound. Video Test., Exh. 13, pp. 94–95.

Merck's Dr. Noll admitted that the development process for the infringing RGD compounds began in November 1996, when Merck's Pharma Board Steering Committee approved development of RGD compound EMD-8. A4949. Dr. Noll was appointed the project manager at that time (*id.*) and assumed responsibility for planning out and fitting together "all of the activities that need to be carried out preclinically and clinically . . . ." A4954. Headed by Dr. Noll, Merck's Development Project Group ("EPG") for EMD-8 met for the first time late that same month. A4952. The tasks of the EPG included toxicology, pharmacology, pharmacokinetics, clinical, and clinical development. *Id.* No one from Scripps was ever included in any of the EPG meetings or copied on any EPG team meeting minutes. A4956. In fact, Project Manager Noll never even contacted anyone at Scripps. Video Test., Exh. 10, p. 74.

Merck witnesses further admitted that the critical preclinical studies for the FDA were in fact carried out by Merck in Germany, and not by Scripps. Merck's

Dr. Grimm testified that Merck, not Scripps, performed "the specific examinations for the side affects [sic]" of the Merck RGD peptides. Video Test., Exh. 3, p. 8. Dr. Grimm also testified none of the pharmacokinetic metabolism tests were performed at Scripps. *Id.* She also testified that none of the toxicology studies were performed by Scripps. *Id.* Dr. Noll confirmed that the "orienting toxicological study" was carried out by Merck, not Scripps. A4956. Merck's Dr. Joncyzk testified that the toxicology studies done under Good Laboratory Practice ("GLP") pursuant to FDA Regulations would be done by Merck, not Scripps. A4915.

Merck's exclusive responsibility for FDA-oriented preclinical work is further substantiated by the type of experiments performed by Scripps. Of the 177 infringing experiments at issue, 93 consisted of chick CAM assays. (Appendix B to Merck's Reply Memorandum in Support of Its Motion for a New Trial on Its Section 271(e)(1) Defense, pp. 1–2 of 3 (Dist. Ct. Docket #1103), filed Dec. 7, 2000.) Merck's Dr. Joncyzk testified that he "cannot imagine" that a governmental body would permit studies on chicken embryos to be used to make inferences about human toxicity. A4932. Merck's Dr. Lukenbach agreed that the chicken embryo data would not be of any use before the FDA, noting that "[t]he FDA will afterwards get the data it requires" (A4945) and that during "the course of

development we [Merck] does all the proper testing as the FDA is asking for . . . ." Video Test., Exh. 9, p. 63.

The foregoing testimony by Merck's scientists confirmed the opinion of Integra's expert, Mr. Meyer, that chicken embryo data are not regarded by the FDA as predictive of the human experience. A8358. Given this testimony by both Merck and Integra witnesses, the jury had ample basis for concluding that the use of chicken embryo data to make inferences about the efficacy of a drug candidate in humans would be similarly unimaginable. The same is true of the *in vitro* cell adhesion studies. A8359. Considering that these two type of studies constitute over sixty-one percent of the infringing experiments at issue, these admissions alone suffice to refute Merck's contention that Scripps' work was oriented towards the FDA.

At trial, Dr. Cheresh was the only percipient witness who testified in conflict with Merck scientists, Drs. Joncyzk and Lukenbach, that the chick CAM assays and cell adhesion assays were related to safety, efficacy, and mechanism of action. Indeed, Dr. Cheresh's trial testimony in that regard conflicted not only with the testimony of Merck's scientists, but also with his own prior interrogatory responses. In those responses, Dr. Cheresh stated that all of his work done from 1985 to October 15, 1996, was basic laboratory research undertaken solely for philosophical and scholarly gratification. Tr. 1125–26; A15068–69. This response

cannot be reconciled with his trial testimony that all of his work from 1995 through 1998 was done for FDA approval.[2]

There is no evidence to support a reasonable conclusion that Scripps' infringing experiments, particularly the chick CAM assays and cell adhesion assays, could have contributed anything to the FDA process given the admittedly superior data generated by Merck's internal drug development program, which commenced in November 1996 using GLP Procedures (A4915) and approved animal models known to be predictive of the human experience. Tr. 2359. In contrast to Merck, Scripps performed the majority of the infringing experimentation on chicken eggs lacking any connection to human safety or efficacy. At no time did Merck or Scripps present any evidence as to what, if any, FDA purpose could have been reasonably believed to have been served by these Scripps experiments in light of the fact that real FDA work was being performed by Merck in Germany.

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[2] The only other witness relied upon by Merck to establish the connection between chick CAM assays and the FDA process was its expert Dr. Bynum. At trial, Dr. Bynum admitted that when he reached his conclusion that chick CAM assays are exempt, he did not even know what a chick CAM assay was. A7425–26. On the stand, Dr. Bynum was further impeached when he attempted to retract his deposition testimony that the IND application does not require any information beyond mere safety and toxicity. A7432.

Merck contends that "the federal government's leading cancer experts [at The National Cancer Institute ("NCI")] made the independent judgment that the Scripps–Merck collaboration produced exactly the sort of data that would persuade the FDA to permit clinical trials to proceed." Merck Brief, p. 19. However, there was no testimony that any federal cancer expert made any judgment about what would persuade the FDA, much less such a judgment about the infringing experiments at issue in this case. Further, the evidence that an IND application was filed was properly excluded by the District Court based on Merck's failure to comply with discovery orders. Because the IND was properly excluded from the jury's consideration—an evidentiary ruling that Merck has failed to appeal—it would not have been possible for the jury to make reasonable references based on the contents of that document.

D. Merck's Affirmative Defense Based On The FDA Exemption

There is no dispute as to the proper standard for application of the FDA Exemption. At trial,[3] the parties agreed to instruct the jury on a legal standard

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[3] Early in the case, Merck moved for partial summary judgment on the FDA Exemption with respect to one of the patents at issue. In so moving, Merck admitted that it had the burden of proving immunity under the FDA Exemption. The District Court agreed with Merck that the FDA Exemption encompassed activities reasonably related to the submission of information for an IND (continued...)

derived from *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd without op.*, 991 F.2d 808 (Fed. Cir. 1993). Dist. Ct. Docket #992, at 14 (Merck proposal for *Intermedics* legal standard). The Supreme Court stated in its decision that this instruction is "consistent with, if less detailed than, the construction of § 271(e)(1)" that it adopted in its opinion. *Merck KGaA v. Integra LifeSciences I*, 125 S. Ct. at 2384. The instruction reads, in pertinent part, as follows:

> To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

A127.

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application, but denied the motion on the basis that triable issues of fact existed as to whether the Scripps experiments beginning in September 1995 were exempt under the FDA Exemption. Order Denying Defendants' Motion for Partial Summary Judgment re 35 U.S.C. § 271(e), at 6–13 (Dist. Ct. Docket #181) (entered Sept. 12, 1997). The District Court based this ruling in part on the inconsistencies in the testimony of Dr. Cheresh and various Merck employees. *Id.* at 9–12. Significantly, the district judge who issued this ruling was not the same district judge who entered the JMOL ruling. Thus, two different district judges independently reached the same conclusion that the questions concerning the credibility of Merck's witnesses should prevent judgment as a matter of law.

The form of verdict, which Merck did not appeal, reads as follows:

> Has defendant Merck KGaA met its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA exemption?

A171.

At the close of the evidence (Dist. Ct. Docket #961) and again after trial but before final judgment was entered (Dist. Ct. Docket #1048), Merck moved pursuant to Federal Rule of Civil Procedure 50(a) for judgment as a matter of law (JMOL) based on the evidence relating to the FDA Exemption. Merck's initial and renewed Rule 50(a) motions did not challenge either the verdict form or the legal standard in the jury instructions. *Id.* The District Court denied this motion, finding that the record evidence was sufficient to uphold the verdict. A33–35. The Court cited the testimony of Integra's FDA expert, Gerald Meyer, who explained that many of the experiments in question were not reasonably related to the submission of information for an IND application because the experiments involved chicken embryos, which lack an established relationship to human safety. A34. The District Court also cited the testimony of Merck witnesses that the Scripps laboratories were not GLP-certified and that Merck did the FDA-related studies in-house. *Id.* The District Court also ruled that the evidence provided the jury with sufficient grounds to disbelieve Dr. Cheresh. A35. The District Court further concluded that "[c]onsidered as a whole, the evidence is sufficient to establish that

Merck, and not [Scripps], was responsible for conducting FDA related experiments, and that any connection between the infringing Scripps experiments and FDA review was insufficiently direct to qualify for the exem [sic]." *Id.* The District Court then denied the JMOL on the basis that, "[c]onsidering the jury's right to weigh the evidence and determine the credibility of the witnesses, the evidence, when viewed in the light most favorable to plaintiffs, was sufficient for the jury to have returned a verdict in plaintiff's favor." *Id.*

E. Proceedings on Appeal

Merck appealed to this Court on the sole grounds that (1) the District Court erred in denying its motion for judgment as a matter of law based on the FDA Exemption; (2) the District Court erred in construing various patent claims; (3) infringement of the '734 patent was not supported by substantial evidence; and (4) the jury's damage award was not supported by substantial evidence. This Court rejected the first three grounds for appeal, but vacated the damages award and remanded the case back to the District Court for consideration of that issue. The damages proceedings before the District Court have been stayed pending resolution of the present appeal before this Court.

Merck sought and obtained review by the Supreme Court of this Court's affirmance of the District Court's denial of Merck's motion for judgment as a matter of law based on the FDA Exemption. In its opinion reported at *Merck*

KGaA v. Integra LifeSciences, I, Ltd., 125 S. Ct. 2372, the Supreme Court vacated this Court's judgment and remanded the case for further proceedings consistent with its opinion. The only issue before this Court is whether the District Court erred in denying Merck's motion under Federal Rule of Civil Procedure 50(a) for judgment as a matter of law with respect to its affirmative defense under the FDA Exemption.

SUMMARY OF ARGUMENT

By failing to raise the issue either in its Rule 50(a) motion before the District Court, in its appeal to this Court, or in its petition for certiorari to the Supreme Court, Merck has thrice waived its right to complain of the verdict form, which required it to prove that ***all*** of the experiments at issue are exempt as a group. *Duro-Last, Inc. v. Custom Seal, Inc.*, 321 F.3d 1098, 1106–08 (Fed. Cir. 2003) (finding that in view of a litigant's Seventh Amendment rights, it would be constitutionally impermissible to re-examine the jury's verdict and to enter judgment on a matter of law on grounds not raised in the Rule 50(a) motion before the District Court); *United States ex rel. Totten v. Bombardier Corp.*, 380 F.3d 488, 497 (D.C. Cir. 2004) (Roberts, J.) (finding that party waived right to assert argument in second appeal that it failed to assert in an initial appeal).

Merck also fails even to attempt to meet its burden as a verdict-loser seeking judgment as a matter of law. Under the long-standing rules founded on the

constitutional right to a trial by jury, the jury is the sole and exclusive judge of the weight of the evidence and the credibility of the witnesses. Hence, to prevail Merck must establish, *based on only the evidence which the jury was required to believe*, and with all inferences in favor of the verdict, that none of the experiments could reasonably be found to fall outside the ambit of the FDA Exemption. Under the verdict form, which Merck declined to challenge on appeal, the judgment must be affirmed if only one of the infringing experiments was reasonably found to be outside the scope of the exemption. Merck has failed even to acknowledge, much less to satisfy, this heavy burden incumbent upon it as the verdict-loser.

Instead, Merck urges error upon this Court by suggesting that it would be appropriate to depart from the normal rules of deference to the jury's verdict. There is no legal basis for this extraordinary suggestion that the this Court intrude into the exclusive province of the jury. Nor is there any legal basis for Merck's flagrant disregard of those rules by its recitation of only trial evidence which supports its contentions and its steadfast disregard of the evidence that supports the verdict.

The infringing experiments at issue fall into three categories. First, there are those experiments that were conducted using RGD peptides as positive controls to assess the biological activity of certain non-peptide organic compounds. Nothing was told to the jury about the structure of these compounds or the basis upon which

they were selected for testing. The only testimony is that they were deliberately tested "blind," without any preconception as to whether they would work. Merck utterly failed to submit any evidence that it had an objective, reasonable basis to believe that any of these unknown non-peptide compounds would have the desired anti-angiogenic effect. For this reason alone, Merck failed to meet its burden of proof with respect to these experiments. And because the verdict required Merck to prove that *all* of the infringing experiments are exempt, this failure requires that Merck's entire appeal be rejected and the judgment of the District Court be affirmed.

Second, Merck was found to infringe the '734 Patent, which claims a cell surface receptor that binds to RGD peptides. Merck has not submitted any evidence or argument that this type of experiment was exempt. It simply ignores this issue. Under the verdict form, this failure alone suffices to affirm the judgment.

The third category of experiments at issue consists of those experiments that are directed to assessing the biological activity of RGD peptides. The jury's verdict that these experiments are not exempt is independently supported by two groups of evidence, and the jury had the right to disregard the testimony upon which Merck relies as not credible.

First, the jury's verdict with regard to the RGD peptides is adequately supported by the testimony of Merck's expert Dr. Bynum and Integra's expert Mr. Meyer that the FDA is concerned only with safety at the preclinical stage. The Supreme Court has determined that the FDA scope of inquiry at the preclinical stage encompasses efficacy as well as safety. However, the Supreme Court did not consider whether the expert testimony in this case that the FDA is interested only in safety should be considered in determining whether the verdict is supported by sufficient evidence. The controlling question is whether the jury had a right to consider that testimony. The testimony which Merck now seeks to excise was properly submitted, without objection, pursuant to Merck's own tactical decision. At no time did Merck seek to have the Court instruct the jury as a matter of law that the FDA considers efficacy as well as safety, and Merck neither moved for judgment as a matter of law before the District Court nor appealed to this Court on the ground that the testimony it now seeks to excise was improperly admitted. Hence, the jury had the right to consider it. Further, the contention that the expert testimony at issue was improperly admitted was not even raised in Merck's appeal to this Court. It would be fundamentally unfair, and utterly without precedent, for this Court to grant a verdict loser's motion for judgment as a matter of law based on an argument that was never advanced to the District Court, and indeed was not advanced on appeal.

Second, even if the expert testimony at issue is excised, the record supports District Court's finding that "[c]onsidered as a whole, the evidence is sufficient to establish that Merck, and not Dr. Cheresh or any other Scripps scientist, was responsible for conducting FDA-related experiments, and that any connection between the infringing Scripps experiments and FDA review was insufficient to qualify" for the exemption. A35. Merck's own scientist, Dr. Joncyzk, admitted that he "cannot imagine" that a governmental body would permit studies on chicken embryos to be used to make inferences about human safety. A4932. Integra's expert, Mr. Meyer, agreed, testifying more generally that chicken egg data is not predictive of the human experience. A8358. On this ground alone, the jury could reasonably have concluded that the chick CAM assays that constitute the majority of the infringing experiments are outside the scope of the FDA Exemption. Merck has also failed to advance any persuasive reason why the jury could not rely on expert testimony that *in vitro* cell adhesion assays similarly have no value to FDA consideration of safety or efficacy in humans. The jury was also entitled to rely on admissions by Merck scientists that Merck and Merck alone was responsible for safety, pharmacokinetic, and pharmacology studies.

In any event, the jury was within its rights to disregard the testimony of Dr. Cheresh and the other witnesses upon whom Merck relied to satisfy its burden of proof. The jury was entitled to do so, as the sole and exclusive judge of the

credibility of the witnesses, because all of these witnesses had an interest in the outcome of the litigation (Dr. Cheresh as a party and the others as employees of Scripps, which was a defendant at the time of trial). In addition, Merck's principal witnesses—Drs. Cheresh, Bynum, and Friedlander—were impeached by evidence that would support an inference of mendacity. After observing Dr. Cheresh's lengthy testimony, the District Court expressly noted that the evidence supported a jury inference that he was not credible. A35. By no stretch of the imagination can it be argued that the jury was required by law to accept the testimony of interested, impeached witnesses. If for no other reason, the judgment of the District Court should be affirmed on the ground that that Merck has failed to even articulate why the jury was *required* to believe its witnesses. As Merck had the burden of proof, the jury's disbelief of its witnesses was necessarily fatal to Merck's case.

ARGUMENT

A. MERCK'S APPEAL IS FATALLY DEFECTIVE BECAUSE IT FOCUSES ENTIRELY ON ITS OWN EVIDENCE AND IGNORES THE EVIDENCE FAVORABLE TO INTEGRA.

In considering a Rule 50(a) motion, a court must "draw all inferences in favor of the nonmoving party, and it may not make credibility determinations or weigh the evidence." *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150 (2000) (citation omitted). "Thus, although the Court should review the record as a whole, *it must disregard all evidence favorable to the moving party that the*

jury is not required to believe. That is, the court should give credence to the evidence favoring the nonmovant as well as that evidence supporting the moving party that is uncontradicted and unimpeached, at least to the extent that the evidence comes from disinterested witnesses." *Id.* at 151 (emphasis added) (citing 9A C. Wright & A. Miller, *Federal Practice and Procedure* § 2529, at 299 (2d ed. 1995)). The standard of review is the same in the trial court and on appeal. Wright & Miller, § 2524, at 251.

Merck turns these rules upside down by focusing on the evidence favorable to its position, without regard to the fact that its witnesses were both impeached and interested, and ignoring the evidence that supports the verdict. Merck's failure to cite to the evidence in support of the verdict, or to advance reasons why the jury was required to believe the evidence upon which Merck relies, is particularly egregious in light of the fact that Merck had the burden of proof with regard to the FDA Exemption, an affirmative defense.[4] "[G]ranting judgment as a matter of law for a party who bears the burden of proof is an extreme step that may be taken only

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[4] The jury instruction agreed to by Merck placed the burden on Merck to prove the applicability of the FDA Exemption. A127; *see also NLRB v. Ky. River Cmty. Care, Inc.*, 532 U.S. 706, 711 (2001) (noting the general rule of statutory construction that "the burden of proving justification or exemption under a special exception to the prohibitions of a statute generally rests on one who claims its benefits") (citation omitted).

when the evidence favoring the movant is so one-sided that, absent adequate evidentiary response by the non-movant, it could not be disbelieved by a reasonable jury." 9 J. Moore et al., *Moore's Federal Practice*, Civil § 50.05[2] (3d ed. 2004); *see also Mentor H/S, Inc. v. Medical Device Alliance, Inc.*, 244 F.3d 1365, 1375 (Fed. Cir. 2001) ("Courts grant JMOL for the party bearing the burden of proof only in extreme cases, when the party bearing the burden of proof has established its case by evidence that the jury would not be at liberty to disbelieve and the only reasonable conclusion is in its favor."); Wright & Miller, § 2535, at 328–29 (citing, *inter alia*, *Mihalchak v. Am. Dredging Co.*, 266 F.2d 875, 877 (3d Cir. 1959)).

Recognizing that it cannot possibly hope to prevail if the standards of Rule 50(a) are applied, Merck argues that the rules of deference to the jury's assessment of credibility and the weight of the evidence are not applicable in this case. Conceding that ordinarily the evidence "would be viewed through a lens of deference to the jury's verdict," Merck baldly, and without authority, asserts that "deference is of no value here" because the form of the verdict did not ask the jury to assess whether each individual experiment is exempt, or even whether categories of experiments are exempt. Merck Brief, p. 31.

This argument is based on an attack on the propriety of the form of verdict, an issue which Merck has waived ***not once but three times***. Merck first waived

this issue by not raising it in Merck's original Rule 50(a) JMOL motion and its renewed Rule 50(b) JMOL motion. Rule 50(a)(2) specifies that a motion for a judgment as a matter of law "shall specify . . . the law and the facts on which the moving party is entitled to judgment." Fed. R. Civ. P. 50(a)(2). Thus, "[c]ontentions not urged in the trial court are not available on appeal." Wright & Miller, § 2536, at 333. Merck waived the argument again by failing to raise it in its initial appeal to this Court. Merck waived it for a third time by failing to raise it in the Supreme Court in its petition for certiorari. It is now too late, in its second appearance before this Court following Supreme Court review, for Merck to belatedly attack the verdict form adopted by the District Court after review of the evidence and the final summations of counsel at trial. *United States ex rel. Totten*, 380 F.3d at 497 (finding that party waived right to assert argument in second appeal that it failed to assert in initial appeal). Indeed, the scope of the remand is limited to the sufficiency of the evidence, not the legal validity of the verdict form.

Knowing that it cannot directly attack the verdict form, Merck nevertheless asserts that it furnishes grounds on which to depart from the standards governing Rule 50(a) motions and their appellate review. This assertion is wrong. It would not be proper, under any circumstances, for this Court to invade the province of the jury as defined by Rule 50(a). To do so would violate Integra's Seventh Amendment right to a trial by jury.

Merck's second argument for ignoring Rule 50(a) is that where the jury applied a reasonableness standard, "the conduct in question [of the defendant] must be sustained unless it was arbitrary or capricious." Merck Brief, pp. 32–33. By this argument, Merck seeks to reverse the burden of proof and to force Integra to prove that Merck's and Scripps' conduct was arbitrary and capricious. Merck also seeks to avoid its required showing under Rule 50(a). But nothing in the case law cited by Merck supports a conclusion that the deference to the jury required by Rule 50(a) is somehow uniquely inapplicable in the context of the FDA Exemption. Rule 50(a) admits of no exceptions. In every case where the defendant moves for judgment as a matter of law, that motion can be granted ***only*** if the law so requires based upon facts which a reasonable jury was required to believe. It remains true in all cases, even when the jury applies a reasonableness test, that the jury is the sole judge of the credibility of the witnesses and of the weight of the evidence.

B. MERCK MISSTATES THE SUPREME COURT'S CONSTRUCTION OF SECTION 271(E)(1).

The main thrust of the Supreme Court's opinion is that Section 271(e)(1) establishes a reasonableness test. By definition, what is reasonable depends upon the circumstances. *See Black's Law Dictionary* 1265 (6th ed. 1990) (defining "reasonable" as "[f]air, proper, just, moderate, suitable under the circumstances. Fit and appropriate to the end in view."); *see also Skinner v. Ry. Labor Executives'*

Ass'n, 489 U.S. 602, 619 (1989) (finding that in the context of the Fourth Amendment's guarantee against "unreasonable" searches, "[w]hat is reasonable, of course, depends on all of the circumstances.") (internal quotation marks omitted). The exemption may apply to pre-clinical experiments if the reasonable relationship test is satisfied. Similarly, experiments are not automatically excluded from the ambit of the exemption merely because they are not submitted to the FDA, or because they are performed on compounds not submitted to the FDA, or were not performed in compliance with GLP standards.

Merck argues that the Court has articulated a two-prong test that narrows the decisional focus to certain specific considerations, to the exclusion of all others. According to Merck, the first prong of the test is whether a drug maker had a reasonable basis for believing that "a patented compound may work, through a particular biological process, to produce a particular physiological effect." 125 S. Ct. at 2383. The second putative prong is whether the drug maker uses the compound in research that "if successful, would be appropriate to include in a submission to the FDA . . . ." *Id.*

Although these "prongs" are central to the inquiry, they do not preclude consideration of the evidence that is favorable to the verdict, including Merck's admissions that it was performing FDA-oriented preclinical studies in Germany, as well as other evidence relating to the context in which the experiments at issue

were performed. This evidence is relevant to the *context* in which the infringing experiments were performed—information Merck would have this Court ignore. The breadth of the reasonableness standard works *both* ways. If the defendant is to be allowed ample latitude to introduce evidence of a reasonable relationship, then the plaintiff must be allowed equal scope to build a factual context in which to challenge the veracity of the defendants' witnesses. Nothing in the Supreme Court's opinion suggests otherwise.

C. EVEN UNDER MERCK'S ERRONEOUS TWO-PRONGED TEST, THE TRIAL COURT'S JUDGMENT MUST BE SUSTAINED BECAUSE OF MERCK'S FAILURE OF PROOF WITH RESPECT TO THE TESTING OF NON-PEPTIDE COMPOUNDS AND CELL SURFACE RECEPTORS.

Merck's appeal fails even under its own erroneous crystallization of the Supreme Court's opinion into a rigid two-part test. Under its own proposed standard, Merck assumes the burden of establishing that Scripps scientists reasonably believed at the time of the infringing experiments that the patented compounds would work, through a particular biological process, to produce a particular physiological effect. However, Merck cannot, and does not, point to any evidence to support its burden of proof with respect to those experiments directed to the evaluation of non-peptide organic molecules. With respect to these experiments, which Merck admits constitute eleven percent of the total infringing experiments, *see* Merck Brief at 17, Merck's failure of proof is total. Under the

form of verdict, which Merck failed to appeal, this failure of proof alone suffices to require that the District Court's judgment be affirmed.

The only person who evaluated the potential biologic activities of the tested non-peptide compounds, and who was solely responsible for their selection for testing, was Dr. K. C. Nicolaou. Video Test., Exh. 7, p. 39; A4916. Dr. Nicolaou did not testify at trial. No witness testified as to either the structure of the non-peptide compounds or the reasons why these particular compounds were selected for testing.

The only testimony at trial was that the scientists who performed the infringing tests had no belief, one way or the other, as to whether these compounds would work. Dr. Cheresh told the jury that these experiments were carried out "blind." Tr. 2205. Dr. Cheresh testified that he carried out the infringing experiments without knowing the structure of the non-peptide compounds he was testing. *Id.* Dr. Cheresh even went so far as to tell the jury that these experiments were carried out without having information about what was known about what the compounds do or do not do. *Id.* This lack of information and reasonable belief was deliberate. Dr. Cheresh explained that it is "always good" to perform experiments blind "so that we have no bias in looking for a particular result." *Id.* Dr. Cheresh testified that this is how "most of our work is done." *Id.*

Despite its failure to call Dr. Nicolaou to the stand, Merck contends that "there is no dispute that they [the non-peptide compounds] were designed to look and behave like Merck's peptides, and that they therefore could be expected to have similar, perhaps superior, effects in animals." Merck Brief, p. 16. In support of that contention, however, Merck cites the testimony of Integra's Dr. Pierschbacher, who had no personal knowledge of the nature of the non-peptide compounds tested at Scripps, much less the reason for their selection. Merck also cites the testimony of Integra's expert, Dr. Dedhar, who also lacks such knowledge, and who specifically testified that he did not know whether the non-peptide compounds were "mimetics or not." A6046. Finally, Merck cites the testimony of Dr. Goodman, who was involved in research at Merck on compounds which had been synthesized by Merck chemists, but who never testified as to what, if any, non-peptide compounds were sent to Scripps for testing.

Thus, Merck's assertion that the non-peptide compounds were designed to behave in the same manner as RGD peptides and could reasonably be expected to do so is nothing more than rank speculation. In effect, Merck argues that because the goal was to develop a peptide "mimetic" (*i.e.*, a compound that has the same anti-angiogenic effect as an RGD peptide) it necessarily follows that every compound tested was reasonably believed, in advance of the testing, to meet that description. If such speculation suffices to meet its burden of proof, then by

definition every experiment undertaken on every compound is exempt. Merck's reliance on such speculation, rather than calling Dr. Nicolaou to testify, was well calculated to effectively deny Integra any opportunity to cross-examine him, thereby shielding its speculation from attack.

Finally, Merck was found to infringe the '734 Patent, *see* A170, which claims a cell surface receptor that binds to RGD peptides. A364. Merck has not submitted any evidence or argument that this type of experiment was exempt. It simply ignores this issue. Under the verdict form, this failure alone suffices to affirm the judgment.

In short, Merck could have submitted evidence as to its beliefs with respect to the non-peptide compounds and the cell surface receptor that it tested, but it chose not to do so. Having made that choice, it cannot now ask that the gap in its proof be filled by speculative inferences that were shielded from cross-examination by its own decision not to produce a witness. To prevail, Merck must show that the jury was not merely permitted, ***but required by law*** to make the speculative leap that the tested peptides and cell surface receptors were reasonably believed, before testing, to be mimetics. Moreover, Merck must show that the jury was required to make this speculative leap even ***though Merck had the burden of proof***. Merely to state Merck's position is to refute it.

D. THE JURY'S VERDICT THAT MERCK FAILED TO MEET ITS BURDEN OF PROOF WITH RESPECT TO THE EXPERIMENTS DESIGNED TO TEST THE BIOLOGICAL ACTIVITY OF THE RGD PEPTIDES IS SUPPORTED BY SUBSTANTIAL EVIDENCE.

Merck's appeal is totally dependent on its assumption that the jury could not lawfully rely on expert testimony that the FDA considers only safety, and not efficacy, at the preclinical stage. As demonstrated in Subpart D.1. below, this assumption is wrong and Merck's appeal fails for that reason alone. Further, as demonstrated in Subpart D.2. below, even if this expert testimony were disregarded, the weight of the evidence, primarily admissions by Merck witnesses, is more than sufficient to sustain the verdict and judgment below. Finally, Subpart D.3. demonstrates that Merck failed to meet its burden of proof because the jury had reasonable grounds to disbelieve the testimony of the witnesses upon whom it relies.

1. The Jury Was Entitled to Rely on the Testimony of Mr. Meyer and Dr. Bynum That the FDA Is Concerned Only with Safety and Not with Efficacy at the Pre-Clinical Stage.

Merck rests its appeal on the erroneous proposition that the Supreme Court "rejected the notion that the jury was entitled to credit testimony" that the FDA is only concerned with safety at the pre-clinical stage (Merck Brief, p. 27) and that the FDA's practice is to require safety data to be based on experiments in compliance with GLP standards. *Id.* at 28; *see also* Merck Brief, p. 32 (asserting

that the jury "reached a verdict based upon 'expert' testimony and arguments that, as the Supreme Court has now held, were impermissible as a matter of law"). The Supreme Court's opinion, however, says nothing about what *testimony* the jury was or was not entitled to believe. To the contrary, the Supreme Court expressly remanded that issue for this Court to decide based on its review of the record. The controlling question for this Court is whether the testimony of Mr. Meyer was properly *admitted*. If so, then the jury was entitled to consider it.

In *Weisgram v. Marley Co.*, 528 U.S. 440 (2000), the Supreme Court held that improperly admitted expert testimony should not be considered in determining whether there is legally sufficient evidentiary basis to sustain a jury verdict. *Id.* at 453–54. The Court took pains, however, to note that the JMOL movant had objected at trial to the admission of the expert testimony in question, and reasserted those objections in JMOL motions. *See id.* at 445; *see also id.* at 456 ("In this case, for example, *although Weisgram was on notice every step of the way that Marley was challenging his experts*, he made no attempt to add or substitute other evidence") (emphasis added). The Court further predicated its holding on the premise that excision of improperly admitted evidence in review of a verdict-loser's Rule 50(a) JMOL motion would work no unfairness because "the party whose verdict is set aside will have had notice, before the close of evidence, of the alleged evidentiary deficiency." *Id.* at 454. The Court specifically pointed out that

such notice is expressly required by Rule 50(a)(2), which states that a motion for judgment as a matter of law "shall specify the law and the facts on which the moving party is entitled to judgment." *Id.* (quoting Fed. R. Civ. P. 50(a)(2)). By so doing, the Court in *Weisgram* reaffirmed the importance of the long-standing rule that failure to raise an issue in a motion for JMOL at trial waives that issue for purposes of the denial of a post-judgment Rule 50(a) motion. *Duro-Last*, 321 F.3d at 1105–07.[5]

At 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, much less seek judgment as a matter of law based on such an objection. Nor did Merck do so with respect to the testimony of Integra's expert,

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[5] To be sure, in *Weisgram*, the Supreme Court noted its prior observation in *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993), 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 or otherwise render the opinion unreasonable, it cannot support a jury's verdict.'" *Weisgram*, 528 U.S. at 454 (quoting *Brooke Group*). Notably, however, *Weisgram* cited *Brooke Group* for the proposition that "[*i*]*nadmissible* evidence contributes nothing to a legally sufficient evidentiary basis." *Id.* (emphasis added). Here, because Merck never objected that these experts' testimony was inadmissible, it failed to preserve the issue of *admissibility*. In *Brooke Group*, it was apparent that the party challenging the expert testimony had preserved that challenge from its initial JMOL motion through appeal. In contrast, Merck *failed* to challenge the admissibility of this testimony in either its initial or renewed JMOL motions or on appeal. Moreover, the indisputable facts in the record in *this* case do not contradict the opinions or otherwise render them unreasonable.

Mr. Meyer, that the FDA's "practice" is to have all safety data meet GLP requirements.

To the contrary, Merck made a deliberate tactical decision to submit these matters as issues of fact to be decided by the jury based on the testimony of its own expert witness, Dr. Bynum, and that of Integra's expert, Mr. Meyer. Merck's decision in this regard reflected a judgment that it would be to its advantage to focus the jury on expert views on how the FDA works in practice, in the context of the specific drug candidates at issue, rather than on an abstract legalistic discussion of the scope of the FDA's authority. Accordingly, Merck chose not to have the jury instructed as a matter of law on the scope of the FDA's concerns. Having made these decisions, Merck must live with their consequences. Merck cannot contend that the jury erred in considering testimony which was properly submitted without objection as a consequence of Merck's own trial strategy. The testimony having been made without objection, the jury was entitled to weigh it. *See Sartor v. Ark. Natural Gas Corp.*, 321 U.S. 620, 627 (1944) ("[I]f the court admits the testimony, then it is for the jury to decide whether, any, and if any what, weight is to be given to the testimony.") (quoting *Spring Co. v. Edgar*, 99 U.S. 645, 658 (1879)).

Merck's own expert, Dr. Bynum, testified at his deposition that the FDA does not need any information at the IND stage other than toxicity and safety data.

A7432. This deposition testimony was presented to the jury as impeachment and admission evidence when Dr. Bynum testified to the contrary at trial. Merck could not and did not object to this impeachment evidence, which was predictably admitted as a necessary consequence of Merck's decision to rely on the testimony of Dr. Bynum rather than to seek an instruction on the law from the District Court. Given that this evidence was properly admitted, it necessarily follows that the jury was entitled to consider it.

Consistent with its decision to rely on the testimony of Dr. Bynum, Merck also failed to object to the testimony of Integra's expert, Mr. Meyer, a former Acting Director of the FDA's Center for Drug Evaluation and Research who worked for that agency in various high-ranking posts for approximately 22 years.[6] Tr. 3150–53. Merck's own counsel, in front of the jury, conceded that Mr.

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[6] Merck contends that it "unsuccessfully sought to exclude Mr. Meyer as irrelevant and unreliable under a proper interpretation of the FDA exemption." Merck Brief, p. 23, n.2. But the District Court's order denying that motion indicates that Merck raised only two arguments—that Mr. Meyer's testimony was irrelevant because it did not address the ultimate legal issue and that it was based on hearsay. (Order Denying Merck's Motion in Limine #1, at 4–5 (Dist. Ct. Docket #772), entered Oct. 14, 1999.) Merck did not argue that Mr. Meyer's testimony that the FDA is concerned only with safety at the preclinical stage was inadmissible as contrary to law. In any event, the point is moot. Merck waived its right to seek to excise this testimony from Rule 50(a) review of the record by failing to object to it at trial; it further waived the argument by failing to move at trial for judgment as a matter of law on that ground; and, finally, it waived the argument yet again by failing to make this contention in Merck's appeal to this Court.

Meyer's qualifications as an expert in the FDA process are "stellar." Tr. 3159. Merck did not object to Mr. Meyer's testimony, consistent with that of Dr. Bynum at his deposition, that the FDA never bases its consideration of efficacy on animal data, only on human clinical trials. A8354. Without objection by Merck, Mr. Meyer further testified that the FDA's "***practice***" is to have all safety data meet GLP requirements. A8357. This testimony is in no way inconsistent with the Supreme Court's opinion and constituted properly admitted, relevant evidence which the jury was entitled to consider.[7]

Merck failed to argue either in its Rule 50(a) motion for directed verdict at trial, or in its renewed motion after judgment, that the foregoing testimony of Dr. Bynum and Mr. Meyer was improperly admitted. Merck's counsel specifically

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[7] Merck contends that the Supreme Court "rejected the proposition that the jury could have credited 'witnesses [who] testified that toxicology studies must be carried out in accordance with'" GLP regulations. Merck Brief, p. 28, quoting *not* from the Supreme Court's opinion but from the District Court's denial of Merck's JMOL. In fact, the Supreme Court said nothing about what testimony from witnesses regarding GLP the jury could consider. Rather, the Court merely rejected the argument that "the experiments in question here are **necessarily** disqualified from" the FDA Exemption because they were not done in conformance with GLP. 125 S. Ct. at 2381–82 (emphasis added). Nothing in the Court's opinion suggests that Mr. Meyer's testimony regarding the FDA's actual practice requiring GLP is inaccurate. Nor is this testimony irrelevant merely because it is not "necessarily" dispositive in and of itself. Common sense would indicate that evidence of how the FDA operates could be very relevant to the jury's deliberations.

referred to Mr. Meyer's testimony during oral argument of Merck's initial Rule 50(a) motion. Tr. 3378. However, there was no suggestion at argument or in Merck's memorandum that Mr. Meyer's testimony was inadmissible—not even after the District Court advised counsel of its reliance on Mr. Meyer's testimony. Tr. 3391. Thus, Integra had no notice at trial that Merck objected to the admissibility of Mr. Meyer's testimony that the FDA considered safety and not efficacy at the IND stage as being contrary to law. Had it been given such notice, Integra would have been able to seek to introduce expert testimony that the experiments at issue could not reasonably have been believed to contribute, relatively directly, to the FDA's consideration of efficacy. Absent such notice, there was no reason for Integra to add to the expense and length of a 28-day jury trial when two experts hired by both parties testified that efficacy was not an FDA consideration at the preclinical stage. To allow Merck to profit from its lack of notice would be so unfair as to violate Integra's Seventh Amendment right to a trial by jury. *Duro-Last*, 321 F.3d at 1107.

The admissibly of the testimony of Dr. Bynum and Mr. Meyer suffices to affirm the verdict. This testimony provided the jury with ample grounds on which to conclude that the preclinical experiments at issue were: (1) unrelated to efficacy considerations because, in practice, the FDA was concerned only with safety at the preclinical stage; and (2) unrelated to safety concerns because they were not done

in compliance with GLP procedures and thus had no significant value in light of the GLP safety studies which Merck planned to perform at its facilities in Germany (especially given that even the orienting toxicology study was performed by Merck and not Scripps). A4195; A4956.

2. In Any Event, the Weight of the Evidence Supports a Reasonable Conclusion That the Accused Experiments Did Not Contribute, Relatively Directly, to the Generation of the Kinds of Information Likely to be Relevant to the FDA Process.

Under the jury instruction approved by the Supreme Court, Merck had the burden of establishing that "it would have been objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, ***relatively directly***, to the generation of the kinds of information that are likely to be relevant" to the FDA process. A127 (emphasis added). Even assuming *arguendo* that the FDA is concerned with efficacy as well as safety in the preclinical stage, the evidence supports a reasonable jury inference that the infringing experiments do not have the relatively direct connection to the FDA process that Merck had the burden to prove.

Mr. Meyer testified that chicken embryo data are not regarded by the FDA as predictive of the human experience. A8358; Tr. 3240. This testimony alone is fatal to Merck's appeal. It provides the jury with a firm evidentiary foundation on which to conclude that chick CAM assays—which together comprise 93 out of 177

infringing experiments—could not reasonably be viewed as having any significant connection to the FDA's concern with how a potential drug works in humans. Nothing in the Supreme Court's opinion suggests that this testimony, to which Merck did not object at trial, is unavailable to support the jury's verdict.

Merck's response to this testimony is simply to deny its existence. Mistakenly describing Mr. Meyer's testimony as limited to safety, Merck erroneously contends that Mr. Meyer told the jury that chick CAM assays were "relevant to the 'physical, chemical and biological characteristics of the new drug,' which is as another way of saying efficacy and mechanism of action." Merck Brief, p. 15. Merck's characterization of Mr. Meyer's testimony is squarely at odds with his express testimony that "I don't think that chicken data has ever been considered to be predictive of the human experience" and that the use of chick CAM assays had been tried and rejected by the FDA as a basis for assessing the safety of bond additives. A8358.

Merck also ignores the admission of Merck's Dr. Joncyzk that he "cannot imagine" that a government body would permit studies on chicken embryos to be used to make inferences about human toxicity. A4932. It defies logic to argue that a technique that is not predictive of the human experience can be used to make inferences about efficacy and mechanism of action in humans. To argue that the jury was compelled to reach this dubious conclusion is manifestly erroneous.

For the same reason, the jury could reasonably infer that *in vitro* cell adhesion assays lacked a relatively direct connection to the FDA process. Mr. Meyer testified that cell adhesion assays would have no value in substantiating safety. A8359. Merck ignores this testimony even though nothing in the Supreme Court's opinion suggests that it is unavailable to support the verdict. Again, it defies logic to contend that an experiment of no value to safety is nevertheless capable of shedding light on efficacy or other activity in humans.

In addition to the unsuitability of chick CAM and *in vitro* cell adhesion assays for making inferences about effects on humans, the jury was entitled to rely upon the admissions of Merck scientists that directly contradicted the testimony of Drs. Cheresh and Bynum. For example, Dr. Cheresh testified that chick CAM assays related to pharmacokinetics, which is the study of how the potential drug is metabolized and distributed in a living system. Tr. 2050–51; Tr. 1832. Merck's Dr. Grimm, however, testified that none of the pharmacokinetic metabolism tests was performed at Scripps. Video Test., Exh. 3, p. 8.

Merck scientists also contradicted the testimony of Scripps witnesses that the experiments at issue were related to safety. Merck's expert Dr. Bynum testified that the terms "toxicology" and "safety" mean the same thing. Tr. 2252. Dr. Lukenbach testified that toxicology, like pharmacokinetics, was Merck's responsibility and would be performed by Merck. Tr. 2349. Merck's Dr. Joncyzk

further told the jury that the safety studies would be done by Merck, under GLP conditions. A4195. Merck's project manager for the RGD peptides, Dr. Noll, testified that none of the toxicology studies were performed by Scripps. Video Test., Exh. 3, p. 8. According to Dr. Noll, even the "orienting toxicology study" was performed by Merck, not Scripps. A4956. And Merck's Dr. Grimm confirmed that Merck, not Scripps, performed "the scientific examinations for side-effects of the Merck Peptides." Video Test., Exh. 3, p. 8.

There is much additional evidence to support the District Court's conclusion that, "[c]onsidered as a whole, the evidence is sufficient to establish that Merck, and not Dr. Cheresh or any other Scripps scientist, was responsible for conducting FDA-related experiments, and that any connection between the infringing Scripps experiments and FDA review was insufficient to qualify" for the exemption. A35. As a general matter, Merck sharply distinguishes between research programs and drug development. A4960. As explained by Dr. Schmitges, Merck's development programs are focused on regulatory requirements (primarily toxicology and clinical testing in humans), whereas its research programs are not. *Id.* It is undisputed that Merck's development process for the infringing RGD compounds began in November 1996, when Merck's Pharma Board Steering Committee approved development of RGD compound EMD-8. A4949.

It is further undisputed that the project group within Merck charged with these developmental activities, including toxicology, pharmacology, and pharmacokinetics, met for the first time that same month. A4952. No one from Scripps was ever included in any of Merck's developmental meetings or copied on any of its team meeting minutes. A4956. In fact, Merck's project manager, Dr. Noll, who was charged with coordinating all developmental activities, never even contacted anyone at Scripps. Video Test., Exh. 10, p. 74; A4954. These admissions, combined with evidence that the Scripps experiments themselves were unrelated to drug activity in humans, provide more than ample support for the jury's verdict.

3. In Any Event, Merck's Appeal Fails Because the Jury Was Entitled to Disbelieve the Testimony of Merck's Principal Witnesses.

As noted above, Federal Rule of Civil Procedure 50 required the District Court to *disregard* "all evidence favorable to the moving party [i.e., Merck] that the jury was not required to believe." *Reeves*, 530 U.S. at 151. It has been long-settled that juries are not required to believe the testimony of party witnesses, such as Dr. Cheresh, or of employees of a corporate party.[8] *See, e.g.*, *Sartor*, 321 U.S. at

[8] With the exception of Dr. Brooks, a former Scripps employee, all of the percipient witnesses upon whom Merck relies were employees of either Merck or (continued...)

628 ("[T]he mere fact that the witness is interested in the result of the suit is deemed sufficient to require the credibility of his testimony to be submitted to the jury as a question of fact.") (quoting *Sonnentheil v. Christian Moerlein Brewing Co.*, 172 U.S. 401, 408 (1899)); *Wood v. C.I.R.*, 338 F.2d 602, 605 (9th Cir. 1964) (stating that uncontradicted testimony need not be accepted where given by interested parties); *Tavoulareas v. Piro*, 759 F.2d 90, 115 n.30 (D.C. Cir.) (stating that the fact that a witness is an employee of a litigant is itself reason for discounting his evidence), *vacated in part on other grounds*, 763 F.2d 1472 (D.C. Cir. 1985); *see also Peterson v. U.S.*, 723 F.2d 43, 45 (8th Cir. 1983).

Nor was the jury required to believe the testimony of Merck's expert witnesses, Drs. Houston, Armitage, and Bynum, who by definition were also interested witnesses *See, e.g.*, *Sartor*, 321 U.S. at 627–28 (referring to expert

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Scripps at the time of their testimony. Merck did not rely on Dr. Brooks's testimony in its initial appeal to this Court. Accordingly, Merck may not rely on his testimony now. *See* Integra's Opposition to Merck's Motion for Leave to File a Supplemental Appendix (filed in this Court on October 11, 2005), and cases cited therein; *see also* Integra's Reply in Support of Its Motion for Leave to File a Surreply in Opposition to Merck's Motion for Leave to File a Supplemental Appendix (filed in this Court on October 21, 2005). In any event, Dr. Brooks's testimony that infringing experiments are indicative of effects in humans is limited to a small subset of five experiments called "tumor growth SCID-mouse" and "tumor growth mouse assays." Tr. 1638–41; Appendix A to Merck's Reply Memorandum in Support of Its Motion for a New Trial on Its Section 271(e)(1) Defense, p. 3 of 3 (Dist. Ct. Docket #1103), filed Dec. 7, 2000.

witness as "interested witness"); *see Powers v. Bayliner Marine Corp.*, 83 F.3d 789, 798 (6th Cir. 1996) (stating that jury is free to disbelieve expert testimony, even if uncontradicted).

Here, Merck's entire case relied on the testimony of party and expert witnesses whose testimony the jury, as the sole judge of the credibility of the witnesses, was entitled to disregard in its entirety based solely on their interest in the outcome of the trial. Because Merck had the burden of proof, the District Court's denial of Merck's motion for judgment as a matter of law should be affirmed on that ground alone. This is especially true because Merck has not even attempted to demonstrate why the jury was compelled to believe its witnesses.

There are additional grounds on which the testimony of the interested witness upon which Merck relies should be disregarded. The jury also had ample evidence on which to conclude that the testimony of Merck's and Scripps' witnesses was not credible. Merck's main witness, Dr. Cheresh, stated in his interrogatory responses that all of his work done from 1985 to October 15, 1996, was basic laboratory research undertaken solely for philosophical or scholarly gratification. Tr. 1125–26; A15069. At trial, however, Dr. Cheresh testified that all of his work from 1995–1998 was done for FDA approval. There is no way to reconcile these contradicting statements. In addition, Dr. Cheresh's testimony that his experiments related to safety and pharmacokinetics was expressly refuted by

the admissions of Merck witnesses. *See* discussion *supra*, Part C of Statement of Facts. No wonder the District Court, which had the opportunity to view Dr. Cheresh's demeanor and testimony over several days, expressly concluded that the evidence provided sufficient grounds to disregard Dr. Cheresh's testimony as not credible. A35.

Similarly, the jury was entitled to disbelieve the testimony of Dr. Bynum that all of Scripps' experiments were done to seek FDA approval. Dr. Bynum manifested his bias by his willingness to reach the conclusion that the FDA Exemption applied before he even looked at Scripps' laboratory notebooks or understood the nature of the accused experiments. A7424–25. Dr. Bynum admitted that when he reached his conclusion on the applicability of the FDA Exemption, he did not know what a chick CAM assay was. A7425–26. On the stand he also attempted to retract his prior sworn deposition testimony that the IND application does not require any information beyond mere safety and toxicity. A7432.

Merck's other key witnesses were similarly exposed as not credible. Dr. Friedlander had specifically sought grant funding to upgrade his laboratory to comply with the GLP requirements. Dr. Friedlander's grant application stated: "In order to proceed to Phase I clinical trials, a rigorous series of preclinical testing is necessary and must conform to good laboratory practices (GLP) standards."

A6968. At trial, however, Dr. Friedlander claimed that he was mistaken and that GLP was actually not required for FDA approval. A7006. Given these contradictions, the jury was not required to believe Dr. Friedlander.

What is particularly notable is that these discredited witnesses are the only witnesses presented by Merck in support of the argument idea that the accused experiments relate to efficacy data. As to the following categories of infringing experiments, Merck relies on the testimony of Dr. Cheresh to establish a relationship to efficacy: $\alpha_v\beta_3$-binding assay experiments (Appendix A to Merck's Reply Memorandum in Support of Its Motion for a New Trial on Its Section 271(e)(1) Defense, p. 1 of 3 (Dist. Ct. Docket #1103), filed Dec. 7, 2000); angiogenesis/chick CAM assay experiments (*id.*); angio-matrigel experiments (*id.*); cell adhesion assay experiments (*id.*); chemotaxis experiments (*id.*, p. 2 of 3); FACS experiments (*id.*); mice arthritis experiments (*id.*); tumor growth chick CAM assay experiments (*id.*); tumor growth in SCID-mouse experiments (*id.*); and tumor growth/nude mice assay experiments (*id.*). Thus, the jury was not required to accept Merck's contention that any of these experiments related to efficacy, and the District Court was therefore required to ignore all of this testimony.

Similarly, as to mice-retina-vasculo experiments (*id.*, p. 2 of 3) and rabbit cornea assay experiments (*id.*, p. 3 of 3), Merck relies on the testimony of Dr. Friedlander. As noted above, Dr. Friedlander discredited himself through

inconsistent testimony, and therefore the jury was not required to believe him and, in assessing the JMOL, the District Court was required to disregard his testimony.

CONCLUSION

For the foregoing reasons, Integra requests that this Court affirm the District Court's denial of Merck's motion for judgment as a matter of law.

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing Supplemental Brief of Plaintiffs–Cross Appellants was served via the methods indicated below on this 13th day of December, 2005, upon:

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Supplemental Brief of Plaintiffs–Cross Appellants complies with the type-volume limitations prescribed by FRAP 32(a)(7)(B) and Fed. Cir. R. 32(b). As counted by the word processing program used to prepare it, Microsoft Word 2002, the brief contains 11,616 words, which is less than the 14,000 maximum.

Dated: December 13, 2005

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