INTRODUCTION

Rosacea is a chronic dermatologic disorder that affects an estimated 16 million adults in the United States.[1] It is characterised by the presence of papules, pustules, telangiectasia, flushing and/or persistent erythema on the facial skin, and, if not effectively treated, can impair quality of life and cause social embarrassment, anxiety and depression.[2,3] The facial erythema consists of persistent redness that is usually confluent and macular in presentation, as well as perilesional redness that surrounds individual papules and pustules.[4] Although most treatments for inflammatory lesions of rosacea produce favourable effects on papules and pustules associated with rosacea, they offer no therapeutic benefit on the persistent erythema remaining after lesion clearance.[5]
Persistent facial erythema involves a complex pathophysiology of neurovascular dysregulation, enhanced immune response and alteration of the superficial cutaneous vasculature.\cite{4} Adrenergic receptors in the sympathetic nervous system play a key role in modulating the cutaneous vasculature, with individual receptor subtypes varying in tissue distribution and function.\cite{4} The $\alpha_2$-adrenoceptors are expressed postsynaptically on vascular smooth muscle cells, whereas the $\alpha_1$-adrenoceptors may be expressed presynaptically on sympathetic nerve terminals and/or postsynaptically on vascular smooth muscle and the vascular endothelium.\cite{6} The distribution of expression varies depending on the type of blood vessel. Activation of postsynaptic $\alpha_1$- and $\alpha_2$-adrenoceptors on vascular smooth muscle cells by noradrenaline or other $\alpha$-adrenoceptor agonists results in vasoconstriction.\cite{6} Activation of presynaptic $\alpha_2$-adrenoceptors inhibits noradrenaline release, and activation of $\alpha_2$-adrenoceptors in the vascular endothelium triggers nitric oxide production; both mechanisms enable or promote vasodilation and counter the postsynaptic vasoconstrictor effects.\cite{6,7,10} Patients with rosacea have higher facial skin temperatures compared with healthy individuals, reflecting the persisting facial erythema and flushing.\cite{8} Higher skin temperature reduces $\alpha_2$-adrenoceptor-mediated vasoconstrictor responses by reducing noradrenaline release, decreasing surface expression of $\alpha_2$-adrenoceptors on smooth muscle cells and increasing endothelial nitric oxide release.\cite{7,10,11,12} Therefore, for patients with rosacea, who have cutaneous vessels that have diminished $\alpha_2$-adrenoceptor-mediated vasoconstrictor capacity, the effect of an $\alpha_2$-adrenoceptor agonist on erythema associated with rosacea may be impaired, whereas the vasoconstriction effect of an $\alpha_1$-adrenoceptor agonist would not be expected to be impeded.

Currently, two $\alpha$-adrenergic products are approved by the US Food and Drug Administration for the treatment of adults with persistent facial erythema of rosacea, oxymetazoline hydrochloride cream 1.0\% (RhoFade\textsuperscript{TM}, Allergan plc, Dublin, Ireland)\cite{22} and brimonidine topical gel 0.33\% (Mirvaso\textsuperscript{®}, Galderma Laboratories, Fort Worth, TX).\cite{23}

This study compares the pharmacological mechanism of action of oxymetazoline and brimonidine on $\alpha$-adrenoceptors in vitro and in vivo. For the latter, we used a murine ultraviolet B light (UVB)-induced erythema model, recognising that UVB light is a well-known trigger of erythematosus rosacea, and induces an acute cutaneous inflammatory reaction that shares many features with rosacea including erythema, cytokine release and leukocyte infiltration.\cite{14,15}

## METHODS

### Materials

Clinical lots of oxymetazoline (Vicept cream 1\%; lots CS06722 and 11008X) and a commercial lot of brimonidine (Mirvaso gel 0.33\%, lot 101350-0813) were used in the murine erythema model. A cream vehicle was prepared at Allergan plc (Irvine, CA, USA), and used as a standard control for all experiments. A gel vehicle was not used because the composition of the vehicle used in the commercially available brimonidine gel formulation was unknown. Furthermore, in previous studies using a variety of cream and gel vehicles, effects of vehicles on erythema have not been observed (data on file; Allergan plc [Irvine, CA, USA]). Prazosin and rauwolscine were purchased from Sigma-Aldrich Corp (St Louis, MO, USA) and dissolved in water prior to use.

### 2.2 Functional $\alpha$-adrenergic receptor cellular assay

A fluorometric image plate reader (FLIPR) $Ca^{2+}$ influx assay was used to measure functional activity of the $\alpha$-adrenoceptor agonists. A transient calcium response can be induced by activation of $\alpha_1$-adrenoceptors coupled with the $G_q$ signalling protein or by activation of $\alpha_2$-adrenoceptors coupled with a chimeric $G_q$ protein that has five amino acids from the receptor recognition domain of $G_i$ (termed $G_{q5}$). HEK293 cells (ATCC, Manassas, VA, USA) stably expressing the bovine $\alpha_{1A}$-adrenoceptor or the human $\alpha_{2A}$-adrenoceptor with chimeric $G_{q5}$ were plated in poly-D-lysine-coated 384 well-plates at 15 000 to 25 000 cells per well and grown overnight in Dulbecco’s modified Eagle’s medium supplemented with 10% foetal bovine serum. For the FLIPR assay, the cells were washed two to four times with Hank’s buffered salt solution containing 20 mM 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES), pH 7.4, and then, the calcium-sensitive dye fluo-4-acetomethyl ester (Thermo Fisher Scientific Inc, Waltham, MA, USA) 4 $\mu \text{M}$, with 0.04% pluronic acid in Hank’s buffered salt solution/HEPES buffer, was added. The cells were loaded with the dye for 40 minutes at 30°C, washed four to eight times with Hank’s buffered salt solution/HEPES buffer to remove excess dye and then preincubated for 3 minutes at 37°C prior to placement into the FLIPR instrument. The transient calcium response was determined at 37°C, initiated by addition of 12.5 $\mu \text{L}$ of $\alpha$-adrenoceptor agonist to 50 $\mu \text{L}$ assay volume for a final volume of 62.5 $\mu \text{L}$. The peak height of the calcium response and concentration producing 50% of the peak height (EC$_{50}$) were determined, with noradrenaline (Sigma-Aldrich Corp, St Louis, MO, USA) utilised as the standard full agonist for evaluating $\alpha_1$- and $\alpha_2$-adrenoceptor efficacy. Comparisons between oxymetazoline and brimonidine were made using an independent samples t test.

### 2.3 Murine UVB erythema model

All animal studies were approved by the Institutional Animal Care and Use Committee and were conducted according to the NIH Guide for the Care and Use of Laboratory Animals. Male SKH1 hairless mice aged 3-5 months and weighing 25-30 g were obtained from Charles River Laboratories (Wilmington, MA, USA). To induce skin erythema, the animals were anesthetised by isoflurane inhalation, the left side of the body including head, trunk and limbs was covered with a black rubber shield to protect it from UVB light exposure, and the right side of the body was exposed to 120 $\text{mJ/cm}^2$ of UVB light (wavelength 305-315 nm) generated by a xenon arc lamp-based solar simulator (Oriel SOLIA, Newport Corp, Irvine, CA, USA). At 1.75 hours after UVB exposure, mice were injected intraperitoneally with 0.3 $\text{mg/kg}$
of the $\alpha_1$-adrenoceptor antagonist prazosin or the $\alpha_2$-adrenoceptor antagonist rauwolscine, or they received no $\alpha$-adrenoceptor antagonist treatment. Fifteen minutes later (ie, 2 hours after UVB exposure), 10 $\mu$L of oxymetazoline cream 1%, brimonidine gel 0.33% or vehicle control was applied topically to a 1-cm$^2$ area of skin (n = 6 per group) (Figure 1). Erythema was measured at baseline and for up to 6 hours after UVB exposure using a chromameter as described previously[16] and expressed as a mean haemoglobin (Hb) index. The Hb index for normal mouse skin is 1.0 to 1.3, with higher values indicating greater skin erythema. Comparisons between drug vs vehicle treatment were made using a 2-way analysis of variance with Bonferroni t tests; statistical significance was achieved at $P < .05$.

3 | RESULTS

3.1 | Functional $\alpha$-adrenoceptor activity in vitro

In the FLIPR assay, oxymetazoline induced transient Ca$^{2+}$ influx in the HEK293 cells by activating both $\alpha_1A$- and $\alpha_2A$-adrenoceptors, whereas brimonidine exhibited selectivity for $\alpha_2A$-receptors (Table 1). Oxymetazoline was approximately four times more active on $\alpha_1A$-adrenoceptors (half-maximal effective drug concentration, ie, concentration of a drug that provides half-maximal response [EC$_{50}$], 14 nM) compared with its activity on $\alpha_{2A}$-adrenoceptors (EC$_{50}$, 55 nM) and exhibited greater efficacy on $\alpha_{1A}$- than $\alpha_{2A}$-adrenoceptors when the maximum response was compared with the response achieved with the full $\alpha$-adrenoceptor agonist noradrenaline. In this in vitro assay, oxymetazoline was an $\alpha_{1A}$-adrenoceptor agonist with partial $\alpha_{2A}$-adrenoceptor activity. In contrast, brimonidine was a selective and full $\alpha_{2A}$-adrenoceptor agonist with an EC$_{50}$ of 5 nM and had only limited $\alpha_{1A}$-activity at concentrations of 600 to 2400 nM. The $\alpha_{1A}$ efficacy and potency and the $\alpha_{2A}$-efficacy of oxymetazoline and brimonidine were significantly different ($P < .001$).

### TABLE 1 Activity of oxymetazoline and brimonidine in FLIPR Ca$^{2+}$ influx assay compared with the full $\alpha$-adrenoceptor agonist norepinephrine

| Agonist       | $\alpha_{1A}$-Adrenoceptor Activity | $\alpha_{2A}$-Adrenoceptor Activity |
|---------------|-----------------------------------|-----------------------------------|
| Norepinephrine| 3.59 ± 0.66 (0.98 ± 0.01)          | 14.9 ± 1.87 (0.92 ± 0.01)         |
|               | n = 10                            | n = 20                            |
| Brimonidine$^b$| 2803 ± 640 (0.31 ± 0.04)           | 10.64 ± 0.95 (1.0 ± 0.02)         |
|               | n = 16                            | n = 20                            |
| Oxymetazoline$^b$| 14.09 ± 5.01 (0.68 ± 0.01)       | 54.94 ± 24.81 (0.49 ± 0.08)       |
|               | n = 2                             | n = 2                             |

EC$_{50}$, concentration producing 50% of the maximal response for the indicated agonist; n, number of experimental replicates; SEM, standard error of the mean.

$^b$Maximal response achieved with the indicated agonist expressed relative to the maximal response achieved with 100 nM norepinephrine, also expressed as the mean ± SEM.

$^p < .001$ for the comparison between brimonidine and oxymetazoline $\alpha_{1A}$ EC$_{50}$ and efficacy and for the comparison between brimonidine and oxymetazoline $\alpha_{2A}$ efficacy.

3.2 | Activity in murine UVB erythema model

As the efficacy of partial agonists can be exaggerated in cellular assays in which receptors and their G proteins are overexpressed, we further investigated the $\alpha$-adrenergic pharmacology of oxymetazoline and brimonidine in a mouse model of UVB-induced erythema. The maximal erythema, measured as Hb index score, was achieved at 2 hours after UVB irradiation. In animals not exposed to UVB light, the mean Hb index score remained at baseline levels through 6 hours. The difference in mean Hb index values between the UVB-exposed and non-UVB-exposed animals was approximately 0.5 and represented the magnitude of UVB-induced erythema. Mice were treated with drugs or vehicle 2 hours after UVB irradiation. Oxymetazoline cream and brimonidine gel significantly reduced UVB-induced erythema compared with vehicle when measured at 2 and 4 hours after topical application (ie, at 4 and 6 hours after UVB exposure; both $P < .01$) (Figure 2).

In four subsequent experiments, some animals were pre-treated with either the $\alpha_1$-adrenoceptor antagonist prazosin or the $\alpha_2$-adrenoceptor antagonist rauwolscine, with erythema measured at 2 hours after topical application of drug or vehicle. In animals that did not receive either antagonist, UVB-induced erythema was significantly lower (66.5%) after topical application of oxymetazoline than after application.
of vehicle in the first experiment (mean Hb index, 1.30 [standard error of the mean (SEM), 0.14] vs 1.67 [0.04] with vehicle; \( P < .01 \)). Pretreatment with prazosin impaired the ability of oxymetazoline to reduce erythema scores; the mean Hb index at 2 hours after oxymetazoline application was 1.51 (SEM, 0.05; \( P < .05 \) compared with animals not treated with prazosin) (Figure 3A). In the second experiment, UVB–induced erythema was significantly lower (61.0%) after application of oxymetazoline than after application of vehicle (mean Hb index, 1.39 [SEM, 0.07] vs 1.74 [0.16] with vehicle; \( P < .01 \)). In this experiment, pretreatment with rauwolscine did not affect the ability of oxymetazoline to reduce erythema; the mean Hb index was 1.44 (SEM, 0.09; \( P < .01 \) compared with vehicle-treated animals alone). These findings suggest that the reduction in UVB–induced erythema by oxymetazoline was primarily mediated by \( \alpha_1 \)-adrenoceptors.

Erythema was approximately 70% lower after topical application of brimonidine 2 hours post-UVB irradiation than after application of vehicle when measured 2 hours postdose (mean Hb index, 1.38 [SEM, 0.08] vs 1.75 [0.14] with vehicle in the third experiment \( P < .01 \); 1.34 [0.10] vs 1.64 [0.06] with vehicle in the fourth experiment \( P < .01 \)). Pretreatment of animals with prazosin did not impair the activity of brimonidine; the mean Hb index was 1.36 (SEM, 0.14; \( P < .01 \) compared with vehicle-treated animals). However, pretreatment of animals with rauwolscine impaired the ability of brimonidine to reduce erythema scores; the mean Hb index was 1.52 (SEM, 0.14; \( P < .01 \) compared with 1.34 [0.10] in animals not treated with rauwolscine) (Figure 4). These findings suggest that the reduction in UVB–induced erythema by brimonidine was primarily mediated by \( \alpha_2 \)-adrenoceptors.

4 | DISCUSSION

The results in the UV light–induced erythema model suggest that oxymetazoline and brimonidine cause cutaneous vasoconstriction through different \( \alpha \)-adrenergic mechanisms. Oxymetazoline caused vasoconstriction primarily by activating \( \alpha_1 \)-adrenoceptors, as demonstrated by its effect being greatly diminished in animals pretreated with prazosin but unaffected in animals pretreated with rauwolscine. Conversely, brimonidine caused vasoconstriction by activating \( \alpha_2 \)-adrenoceptors, because its effect was reduced in animals pretreated with rauwolscine but not in animals pretreated with prazosin. These in vivo profiles were mostly consistent with the functional \( \alpha \)-adrenergic activity demonstrated by these agents in the FLIPR assay in vitro, where oxymetazoline was
The efficacy and safety of oxymetazoline and brimonidine in patients with moderate to severe persistent facial erythema of rosacea were demonstrated in pivotal phase 3 trials. The agents appear to offer similar efficacy, but there may be differences in their respective safety profiles, which in turn may be related to differences in their mechanisms of action. However, no head-to-head studies have been performed. Worsening of erythema and flushing were the most common treatment-emergent adverse events in the pivotal clinical trials with brimonidine. However, flushing was not observed, and application-site erythema and worsening of erythema after cessation of treatment, or rebound effect, were observed infrequently in patients who received oxymetazoline during the treatment period of the phase 3 studies of oxymetazoline.

While UVB-induced erythema is not a model of rebound erythema, on the basis of the present experimental findings, one could speculate that flushing and worsening of erythema with brimonidine may be manifestations of its full α2-adrenoceptor agonist activity at presynaptic sympathetic nerve terminals or on the vascular endothelium, resulting in vasodilatation that counteracts the drug’s direct postsynaptic vasoconstrictive effects. Reduced surface expression of vascular smooth muscle α2-adrenoceptors in warm skin could further shift the balance towards vasodilatation. The α2-adrenoceptor agonist activity at presynaptic or endothelial sites resulting in vasodilatation has also been suggested by Docherty and colleagues as one of several potential mechanisms responsible for the paradoxical erythema seen with brimonidine. These authors suggested that high local concentrations of brimonidine in skin caused by skin barrier dysfunction could contribute to sustained activation of the presynaptic and endothelial α2-adrenoceptors or downregulation of the smooth muscle receptors. The authors also suggested activation of α2-adrenoceptors on perivascular inflammatory cells could contribute to sustained vasodilatation. Accordingly, α2-adrenoceptors on macrophages have been shown to stimulate the Gαq protein was not observed on the endogenous vascular α2-adrenoceptors.

Repetitive UVB irradiation of hairless mice has been used previously to evaluate test compounds on skin photoaging, photodamage, inflammation and tumor development. UVB-induced erythema also has been used clinically in healthy volunteers to assess the photoprotective and anti-inflammatory activity of potential therapeutic agents. In the latter studies, UVB doses of approximately one to two times the minimal erythema dose were used, with erythema measured by chromameter. In the present study, we determined experimental conditions under which brief exposure to UVB induces skin erythema without causing skin ulcerations or other obvious skin damage. The acute response to UVB exposure shares multiple features with rosacea, including skin inflammation with erythema. Whether the mechanisms underlying development of erythema in this murine model mimic those seen in patients with persistent facial erythema associated with rosacea remains to be determined. Nevertheless, the model affords the opportunity to evaluate and compare agents for their ability to produce in vivo vasoconstriction of cutaneous blood vessels.

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the release of the inflammatory mediator tumor necrosis factor-α.\textsuperscript{[34]} Oxymetazoline, however, functions primarily as an $\alpha_1$-agonist, with minimal $\alpha_2$-agonist activity that may not be sufficient for producing clinically meaningful $\alpha_2$-adrenoceptor-mediated vasodilatory effects. The consequences of this hypothesis for patients with persistent facial erythema associated with rosacea remain to be evaluated in clinical studies.

In summary, both oxymetazoline and brimonidine produce cutaneous vasoconstriction in the murine UVB light–induced erythema model, but act through different $\alpha$-adrenergic mechanisms.

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CONFLICT OF INTEREST

At the time the study was performed, E. Hsia and M. Tian were employees of Allergan plc, and D. Gil is an employee of Allergan plc, and all may own stock/stock options in that company.

AUTHOR CONTRIBUTION

E. Hsia and D. Gil designed the research study and wrote the paper. M. Tian performed the research and data analysis.

REFERENCES

\[1\] L. Drake, Rosacea Review, National Rosacea Society, Barrington, IL, 2010.
\[2\] H. E. Baldwin, J. Drugs Dermatol. 2012, 11, 725.
\[3\] F. Moustafa, R. S. Lewallen, S. R. Feldman, J. Am. Acad. Dermatol. 2014, 71, 973.
\[4\] J. Q. Del Rosso, J. Am. Acad. Dermatol. 2013, 69, 544.
\[5\] J. Q. Del Rosso, J. Clin. Aesthet. Dermatol. 2012, 5, 26.
\[6\] S. Guimaraes, D. Moura, Pharmacol. Rev. 2001, 53, 319.
\[7\] J. M. Johnson, D. L. Kellogg Jr, Front. Biosci. (Schol Ed). 2010, 2, 825.
\[8\] M. V. Dahl, A. J. Ross, P. M. Schlievert, J. Am. Acad. Dermatol. 2004, 50, 266.
\[9\] R. R. Freedman, S. C. Sabharwal, M. Moten, P. Migaly, Am. J. Physiol. 1992, 263, H1197.
\[10\] S. R. Bailey, A. H. Eid, S. Mitra, S. Flavahan, N. A. Flavahan, Circ. Res. 2004, 94, 1367.
\[11\] T. E. Wilson, J. Cui, C. G. Crandall, Auton. Neurosci. 2002, 97, 122.
\[12\] Rhofade [package insert], Allergan, Irvine, CA, 2017.
\[13\] Mirvaso [package insert], Galderma Laboratories, Fort Worth, TX, 2016.
\[14\] L. E. Rhodes, G. Belgi, R. Parslew, L. McLoughlin, G. F. Clough, P. S. Friedman, J. Invest. Dermatol. 2001, 117, 880.
\[15\] M. Steinhoff, J. Schaubner, J. J. Leyden, J. Am. Acad. Dermatol. 2013, 69, 515.
\[16\] N. Kollias, R. Gillies, J. A. McCurni, R. K. Uyeyama, S. B. Phillips, L. A. Drake, J. Invest. Dermatol. 1995, 104, 421.
\[17\] D. Piwnica, C. Rosignoli, S. T. de Monenville, T. Alvarez, M. Schuppli Nollet, O. Roye, A. Jomard, J. Aubert, J. Dermatol. Sci. 2014, 75, 49.
\[18\] J. P. Kukkonen, A. Renvaktar, R. Shariatmadari, K. E. Akerman, J. Pharmacol. Exp. Ther. 1998, 287, 667.
\[19\] C. C. Jansson, K. Pohjanoksa, J. Lang, S. Wurster, J. M. Savola, M. Scheinin, Eur. J. Pharmacol. 1999, 374, 137.
\[20\] J. R. Jasper, J. D. Lesnick, L. K. Chang, S. S. Yamanishi, T. K. Chang, S. A. Hsu, D. A. Daunt, D. W. Bonhaus, R. M. Eglen, Biochem. Pharmacol. 1998, 55, 1035.
\[21\] H. B. Pyun, M. Kim, J. Park, Y. Sakai, N. Numata, J. Y. Shin, H. J. Shin, D. U. Kim, J. K. Hwang, Prev. Nutr. Food Sci. 2012, 17, 245.
\[22\] A. Anwar, M. Gu, S. Brady, L. Qamar, K. Behbakht, Y. G. Shellman, R. Agarwal, D. A. Norris, L. D. Horwitz, M. Fujita, Photochem. Photobiol. 2008, 84, 477.
\[23\] J. G. Avila Avecedo, A. M. Espinosa Gonzalez, D. M. De Maria y Campos, C. Benitez Flores Jdel, T. Hernandez Delgado, S. Flores Maya, J. Campos Contreras, J. L. Munoz Lopez, A. M. Garcia Bores, BMC Complement Altern. Med. 2014, 14, 281.
\[24\] F. Yogianti, M. Kuniisada, E. Nakano, R. Ono, K. Sakumi, S. Oka, Y. Nakabeppe, N. Ishigiri, J. Invest. Dermatol. 2014, 134, 2610.
\[25\] M. Guarrera, C. Brusati, A. Rebora, Dermatology 2001, 203, 121.
\[26\] B. J. Hughes-Formella, K. Bohnsack, F. Rippke, G. Benner, M. Rudolph, I. Tausch, J. Gassmuelle, Dermatology 1998, 196, 316.
\[27\] L. H. Kiricik, J. Dubois, Z. D. Draelos, P. Werschler, K. Grande, F. E. Cook-Bolden, D. R. Berk, G. Ahiuvalia, Fall Clinical Dermatology Conference, Las Vegas, NV, 2016.
\[28\] L. Baumann, D. J. Goldberg, L. Stein-Gold, E. A. Tanghetti, T. Lain, J. Kaufman, D. R. Berk, G. Ahiuvalia, Fall Clinical Dermatology Conference, Las Vegas, NV, 2016.
\[29\] J. Fowler Jr, M. Jackson, A. Moore, M. Jarratt, T. Jones, K. Meadows, M. Steinhoff, D. Rudisill, M. Leoni, J. Drugs Dermatol. 2013, 12, 650.
\[30\] A. Moore, S. Kempers, G. Murakawa, J. Weiss, A. Tauscher, L. Swinney, H. Liu, M. Leoni, J. Drugs Dermatol. 2014, 13, 56.
\[31\] L. Stein-Gold, L. H. Kiricik, Z. D. Draelos, P. Werschler, J. Dubois, E. Lain, L. Baumann, D. J. Goldberg, J. Kaufman, E. A. Tanghetti, E. Weng, D. R. Berk, G. Ahiuvalia, Annual Meeting of the American Academy of Dermatology, Orlando, FL, 2017.
\[32\] Z. D. Draelos, M. H. Gold, R. A. Weiss, L. Baumann, S. K. Grekin, D. Mraz Robinson, S. E. Kempers, D. R. Berk, G. Ahiuvalia, Annual Meeting of the American Academy of Dermatology, Orlando, FL, 2017.
\[33\] J. R. Docherty, M. Steinhoff, D. Lorton, M. Detmar, G. Schafer, A. Holmes, A. Di Nardo, Adv. Ther. 2016, 33, 1885.
\[34\] R. N. Spengler, R. M. Allen, D. G. Remick, R. M. Strieter, S. L. Kunkel, J. Immunol. 1990, 145, 1430.

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