

IL-13 blockade reduces lung inflammation after *Ascaris suum* challenge in cynomolgus monkeys

Andrea Bree, BS, Franklin J. Schlerman, BS, Michael Wadanoli, DVM, Lioudmila Tchistiakova, PhD, Kimberly Marquette, BS, Xiang-Yang Tan, MD, PhD, Bruce A. Jacobson, PhD, Angela Widom, MS, Timothy A. Cook, BS, Nancy Wood, BS, Suresh Vunnum, PhD, Rustem Krykbaev, PhD, Xin Xu, PhD, Debra D. Donaldson, MD,* Samuel J. Goldman, PhD, Joseph Sypek, PhD, and Marion T. Kasaian, PhD *Cambridge, Mass*

Background: Airway inflammation is a hallmark feature of asthma and a driver of airway hyperresponsiveness. IL-13 is a key inducer of airway inflammation in rodent models of respiratory disease, but a role for IL-13 has not been demonstrated in primates.

Objective: We sought to test the efficacy of a neutralizing antibody to human IL-13 in a cynomolgus monkey model of lung inflammation.

Methods: Using cynomolgus monkeys (*Macaca fascicularis*) that are sensitized to *Ascaris suum* through natural exposure, we developed a reproducible model of acute airway inflammation after segmental *A suum* antigen challenge. This model was used to test the *in vivo* efficacy of mAb13.2, a mouse mAb directed against human IL-13, and IMA-638, the humanized counterpart of mAb13.2. Bronchoalveolar lavage (BAL) cells and BAL fluid were collected before and after antigen challenge and assayed for cellular content by means of differential count.

Results: Total BAL cell count, eosinophil number, and neutrophil number were all reduced in animals treated with mAb13.2 or IMA-638 compared with values in control animals that were untreated, given saline, or treated with human IgG of irrelevant specificity. In addition, levels of eotaxin and RANTES in BAL fluid were reduced in anti-IL-13-treated animals compared with levels seen in control animals.

Conclusion: These findings support a role for IL-13 in maintaining lung inflammation in response to allergen challenge in nonhuman primates.

Clinical implications: IL-13 neutralization with a specific antibody could be a useful therapeutic strategy for asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Cytokines, inflammation, cynomolgus monkey, asthma, *Ascaris suum*

As an inducer of airway hyperreactivity and lung pathology, IL-13 represents a key target for the treatment of asthma.¹ In human asthmatic subjects, bronchoalveolar lavage (BAL) fluid collected after segmental allergen challenge contains IL-13 protein,² *IL13* mRNA,³ and IL-13–producing T cells,⁴ strongly implicating an association of IL-13 with the human disease. Furthermore, polymorphisms in genes encoding IL-13,⁵ IL-13 receptor components,⁶ or the IL-13 receptor–associated signaling molecule signal transducer and activator of transcription 6 (STAT6)⁷ are all associated with high levels of serum IgE and the development of atopic disease in human populations.

Data from animal models support the potential utility of IL-13 neutralization as a therapeutic approach. Neutralization of IL-13 bioactivity prevents airway hyperresponsiveness and other asthmatic changes in rodents.^{8–10} Nonhuman primate (NHP) models of allergic respiratory disease more closely resemble human asthmatic responses.¹¹ In cynomolgus monkeys, IL-13 has been implicated in mediating airway eosinophilia and hyperresponsiveness to respiratory syncytial virus infection,¹² but the contribution of IL-13 to asthmatic responses has not been previously reported.

In the current model, a single administration of *Ascaris suum* antigen directly to the lungs of sensitized cynomolgus monkeys induced an inflammatory response characterized by increased numbers of eosinophils and neutrophils in BAL fluid. We tested the efficacy of mouse anti-human IL-13 mAb13.2 and the humanized form of this antibody, IMA-638, in reducing lung inflammation in this model. Both antibodies were effective, establishing a role for IL-13 in contributing to asthmatic changes in cynomolgus monkeys.

From Wyeth Research, Cambridge, Mass.

*Dr Donaldson is currently affiliated with Millennium Pharmaceuticals, Cambridge, Mass.

Disclosure of potential conflict of interest: M. T. Kasaian, A. Bree, F. J. Schlerman, M. Wadanoli, N. Wood, S. Vunnum, and X. Xu own stock in and are employed by Wyeth. L. Tchistiakova, K. Marquette, X.-Y. Tan, A. Widom, T. A. Cook, S. J. Goldman, and J. Sypek are employed by Wyeth. B. A. Jacobson has received grant support from and is employed by Wyeth. R. Krykbaev owns stock in, has received grant support from, and is employed by Wyeth. D. D. Donaldson has patent licensing arrangements with Wyeth. The nucleotide sequence for cynomolgus monkey *IL-13* was submitted to Genbank, accession number DQ679797.

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Reprint requests: Marion T. Kasaian, PhD, Wyeth Research, 200 Cambridge Park Dr, Cambridge, MA 02140. E-mail: mkasaian@wyeth.com. 0091-6749/\$32.00

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Abbreviations used

BAL: Bronchoalveolar lavage
 IP-10: IFN- γ -inducible protein 10
 IVIG: Intravenous immunoglobulin
 NHP: Nonhuman primate
 STAT6: Signal transducer and activator of transcription 6

METHODS**Test and control articles**

Antibody 13.2 (IgG1, κ) was cloned from BALB/c mice immunized with human IL-13. The humanized version of this antibody, IMA-638, was generated at Wyeth Research (Cambridge, Mass) by grafting the V_H and V_L complementarity-determining region of mAb13.2 onto the most highly homologous human V_H and V_L germ-line genes. IMA-638 (IgG1, κ) was formulated in 10 mmol/L histidine, pH 6, containing 5% sucrose. Carimune NH immune globulin intravenous (human intravenous immunoglobulin [IVIG]; ZLB Bioplasma, Inc, Berne, Switzerland) was depleted of non-Ig components by means of passage over a protein A column and formulated in 10 mmol/L histidine, pH 6, containing 5% sucrose. A *suum* extract (Greer Diagnostics, Lenoir, NC) was diluted to 82,000 protein nitrogen units per milliliter in PBS. Dexamethasone (American Pharmaceutical Partners, Schaumburg, Ill) was diluted to 4 mg/mL in PBS.

Animals

Adult male cynomolgus monkeys (*Macaca fascicularis*; Charles River BRF, Inc, Houston, Tex) weighing 6 to 10 kg were singly or pair housed and cared for according to the American Association for Accreditation of Laboratory Animal Care guidelines. The Wyeth Institutional Animal Care and Use Committee approved all aspects of this study.

Study design

Antibody was administered by means of intravenous infusion 24 hours before A *suum* challenge. Two separate studies were performed. In the first study groups of animals treated with saline control ($n = 4$) or mAb 13.2 (8 mg/kg; $n = 6$) were challenged with 0.5 μ g of A *suum* antigen. In the second study groups of animals treated with (1) saline control ($n = 4$); (2) dexamethasone, given in 2 intramuscular injections of 1 mg/kg administered 24 hours and 30 minutes before A *suum* challenge ($n = 3$); (3) IVIG (10 mg/kg; $n = 5$); or (4) IMA-638 (10 mg/kg; $n = 5$) were challenged with 0.75 μ g of A *suum* antigen.

BAL procedure and segmental antigen challenge

Twenty-four hours after antibody administration, baseline BAL was performed. Atropine (0.02-0.05 mg/kg administered intramuscularly; Phoenix Scientific, Inc, St Joseph, Mo) was administered to reduce salivation, and animals were chemically restrained with ketamine hydrochloride (8-10 mg/kg administered intramuscularly). Immediately before the BAL procedure, the anesthetic propofol (3-5 mg/kg; Propofol; Abbot Labs, N Chicago, Ill) was administered, followed by a saline flush. Each monkey was placed in a supine position, and Cetacaine (Benzocaine/butamben/tetracaine Hcl; Cetylite Industries, Inc, Pennsauken, NJ) was applied to the epiglottis to prevent tracheal spasms. After 1 minute, a veterinary bronchoscope (VFS-10; Schott Fiber Optics, Swiss Precision Products, Inc, Spencer, Mass) was guided past the carina and wedged into the third- or fifth-generation bronchus of the left lung. Three 20-mL aliquots of warm sterile saline were instilled into the lung, gently aspirated, and pooled (baseline BAL).

Baseline BAL was followed by segmental allergen challenge. The bronchoscope was retracted, repositioned, and wedged in the right lung, and a 5-mL aliquot of sterile saline containing the dose of A *suum* was instilled. Twenty-four hours later, a second lavage was performed on the challenged lung. Animals were observed until they were fully recovered. Study animals were prescreened for A *suum* responsiveness, characterized as increased total BAL cell counts after A *suum* challenge, composed of greater than 15% eosinophils.

Blood sample procedure

Under ketamine sedation, the femoral area was cleaned with povidone-iodine (Betadine; Purdue Frederick Co, Norwalk, Conn) prep solution followed by alcohol. Blood samples were drawn before the study and at day 0, day 1, week 1, and week 8 after A *suum* challenge. EDTA-anticoagulated blood was run on the Cell-Dyn 3500 hematology analyzer (Abbott Labs) for generation of a 15-parameter complete blood count and white cell differential.

Quantitation of BAL inflammation and cytokine levels

The BAL fluid was filtered through a 70- μ m cell strainer and centrifuged at 2000 rpm for 15 minutes to pellet cells. The cell fraction was analyzed for total leukocyte count, spun onto microscope slides (Cytospin; Thermo Shandon, Pittsburgh, Pa), and stained with Diff-Quick (Dade Behring, Inc, Newark, Del) for differential analysis. BAL fluid was concentrated approximately 16-fold with Centriprep-YM3 concentrators (Millipore, Billerica, Mass). IL-5 and eotaxin were quantitated by means of ELISA specific for human proteins (Biosource International, Camarillo, Calif). The limit of assay sensitivity for these assays was 7.8 pg/mL. IFN- γ -inducible protein 10 (IP-10), monocyte chemoattractant protein 1, RANTES, and IL-8 were quantitated by using a cytometric bead array kit (BD PharMingen, San Diego, Calif) with human-specific reagents. The limit of assay sensitivity ranged from 0.2 pg/mL (IL-8) to 2.8 pg/mL (IP-10).

ELISA for detection of IMA-638 in NHP plasma

ELISA plates (MaxiSorp; Nunc, Rochester, NY) were coated with anti-FLAG M2 (Sigma, St Louis, Mo), blocked with 0.5% gelatin, and washed in PBS containing 0.05% Tween-20 (PBS-Tween). In a separate uncoated plate, biotinylated mAb13.2 or IMA-638 was preincubated for 2 hours at room temperature with NHP IL-13-FLAG (Wyeth Research) in the presence of unlabeled anti-IL-13 standard or NHP plasma. Anti-IL-13 present in the plasma competed with biotinylated antibody for binding to IL-13-FLAG. This mixture was transferred to the anti-FLAG-coated ELISA plate and incubated for 2 hours at room temperature. Binding of biotinylated antibody was detected with horseradish peroxidase (HRP)-streptavidin (Southern Biotechnology Associates, Inc, Birmingham, Ala) and Sure Blue substrate (KPL, Inc, Gaithersburg, Md). The sensitivity of the assay was approximately 30 ng/mL.

Cloning of cynomolgus monkey IL-13

Cynomolgus monkey splenocytes were stimulated with A *suum* antigen (44 hours) or with concanavalin A (24 hours) in RPMI containing 10% heat-inactivated FCS, 50 U/mL penicillin, 50 μ g/mL streptomycin, and 2 mmol/L L-glutamine (complete RPMI) in a 37°C incubator at 5% CO₂. On days 4 and 7, dead cells were removed by means of centrifugation over Ficoll Hypaque, and cells were replated in 10% conditioned media. On day 9, cells were stimulated with 100 ng/mL phorbol 12-myristate 13-acetate (Sigma) and 2 μ g/mL ionomycin (Sigma). On day 11, cells were harvested for RNA extraction.

Primers that matched the 5' and 3' untranslated regions of both pigtailed macaque (accession no. DQ645391) and human (accession

no. U31120) *IL-13* sequences were used for the amplification. The product was reamplified with internal primers for human *IL-13*, which were derived from a highly conserved region of *IL-13* from multiple species, and the sequence was confirmed. Eight independent amplification reactions, 4 from each of 2 monkeys, were done with 5' and 3' untranslated region primers. These full-length PCR fragments were cloned, sequenced, and reamplified by means of nested PCR. Thirteen clones were compared to determine a consensus sequence. The *IL-13* was expressed in *Escherichia coli*, purified, and refolded. Anti-*IL-13* binding activity was quantitated by means of surface plasmon resonance analysis, performed as described previously.¹³

Cell-based assays for IL-13

The monocyte CD23 expression assay was performed with human PBMCs, as previously described.¹³ The STAT6 phosphorylation assay was performed with HT-29 human colonic epithelial cells (American Type Culture Collection, Manassas, Va), as previously described.¹³ Antibodies to CD11b, CD23, and phosphorylated STAT6 were purchased from BD Biosciences, San Jose, Calif. Cells were analyzed with a FACScan and CellQuest software (BD Biosciences).

Statistical analysis

Treatment effects were compared by using paired or unpaired Student *t* tests, as indicated. Significance was defined as a *P* value of less than .05 in 2-tailed analysis.

RESULTS

Cloning and expression of cynomolgus monkey IL-13

Cynomolgus monkey *IL-13* was cloned from splenocytes stimulated with *A suum* antigen or with concanavalin A. The consensus *IL-13* sequence (accession no. DQ679797) had 76% nucleotide identity (data not shown) and 94% amino acid identity (Fig 1)¹⁴ with human *IL-13*. A comparison of the cynomolgus monkey *IL-13* amino acid sequence with other known primate *IL-13* sequences is shown in Fig 1. The 4 potential N-linked glycosylation sites are conserved. Position 110 is GLN in the cynomolgus monkey *IL-13* sequence and GLN or ARG in the other NHP sequences. The R110Q variation is a polymorphism in human populations.^{5,15}

The bioactivity of *E coli*-expressed NHP *IL-13* was tested in 2 different bioassay formats. The first quantitated expression of the low-affinity IgE receptor CD23 on primary human monocytes. In the second assay *IL-13*-induced STAT6 phosphorylation was measured in the HT-29 human epithelial cell line. In both bioassays the activity of NHP *IL-13* was comparable with that of human *IL-13* (Fig 2, A and B).

Binding and neutralization of cynomolgus monkey IL-13 bioactivity by anti-human IL-13 antibodies

Antihuman *IL-13* antibody mAb13.2 (IgG1, κ) was produced in mice and was humanized to generate IMA-638 (IgG1, κ). Both mAb13.2 and IMA-638 bound to human and NHP *IL-13* with high affinity. As determined by using surface plasmon resonance analysis, dissociation constants for mAb13.2 and IMA-638 were 4.55×10^{-9} mol/L and 1.08×10^{-10} mol/L, respectively, for human

IL-13. Dissociation constants were 7.05×10^{-11} mol/L and 9.87×10^{-12} mol/L, respectively, for NHP *IL-13*. Both antibodies efficiently neutralized the bioactivity of human and NHP *IL-13* (Fig 2, C and D).

Anti-IL-13 effects on *A suum*-induced lung inflammation in cynomolgus monkeys

The *in vivo* efficacy of antihuman *IL-13* antibodies was evaluated in a cynomolgus monkey model of lung inflammation. A single airway challenge with *A suum* antigen resulted in a reproducible pulmonary inflammation 24 hours later, with increased total BAL cell counts (Fig 3, A) consisting primarily of eosinophils (Fig 3, B) and neutrophils (Fig 3, C). Increased numbers of monocytes/macrophages were also found (Fig 3, D).

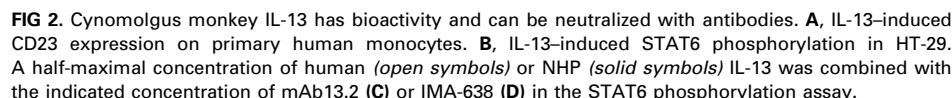
The murine (mAb13.2) and humanized (IMA-638) antibodies to *IL-13* were tested in 2 separate studies, as outlined in the Methods section. In the first, cynomolgus monkeys received mAb13.2 (8 mg/kg administered intravenously) or an equivalent volume of saline. Twenty-four hours later, a baseline BAL sample was collected from the left lung, and *A suum* antigen was instilled into the right lung with a bronchoscope. Twenty-four hours after *A suum* challenge, BAL fluid was collected from the right lung, and inflammation was analyzed by using differential counting. The second study followed the same design, with IMA-638 administered at 10 mg/kg intravenously. Additional groups included human IgG of irrelevant specificity (IVIG, 10 mg/kg). Dexamethasone, which is known to block *A suum*-induced lung inflammation in cynomolgus monkeys,¹⁶⁻¹⁸ was administered as a positive control anti-inflammatory agent. All agents, including mAb13.2 and IMA-638, were well tolerated. For analysis, results from the 2 studies were combined as follows. The control group included data from saline-treated animals from both studies (*n* = 7) and the IVIG-treated animals (*n* = 5). The anti-*IL-13*-treated group included data from mAb13.2-treated animals (*n* = 6) and IMA-638-treated animals (*n* = 5). None of the groups that were combined for analysis differed significantly from each other in any parameter of the study.

Before challenge, total cell numbers and differential cell counts in BAL fluid were comparable for all groups (data not shown). The anti-*IL-13* treatment reduced total lung inflammation compared with that seen in control animals (*P* < .05), resulting in a 69% reduction in median total BAL cell count. Dexamethasone produced an 86% reduction in total BAL inflammation compared with that seen in control animals (Fig 3, A). The anti-*IL-13* treatment also reduced median eosinophil numbers in BAL fluid by 89% (*P* < .05; Fig 3, B), median neutrophil numbers by 73% (*P* < .01; Fig 3, C), and median monocyte/macrophage numbers by 67% (*P* < .05; Fig 3, D). Inflammation was unaffected by IVIG.

Effects of IMA-638 on BAL chemokine levels after *A suum* challenge

BAL fluid was concentrated approximately 16-fold and assayed for several cytokines and chemokines by using

FIG 1. Comparison of primate IL-13 amino acid sequences. The human (U31120) and cynomolgus monkey (DQ679797) amino acid sequences are 94% identical. Amino acid differences are shaded. Potential N-linked glycosylation sites are boxed. The R110Q polymorphism is indicated by an *asterisk*. The *arrow* indicates the N-terminus of the mature protein. Accession numbers are as follows: chimpanzee, AY480012; Pere David's macaque, AY849927; rhesus monkey, AY244790; and pigtailed macaque, DQ645391. The owl monkey partial sequence was reported in Bost et al.¹⁴



chemoattractant protein 1 levels were high in BAL fluid (median, approximately 5 $\mu\text{g/mL}$) but did not change after *A. suum* challenge (data not shown). Eotaxin, RANTES,

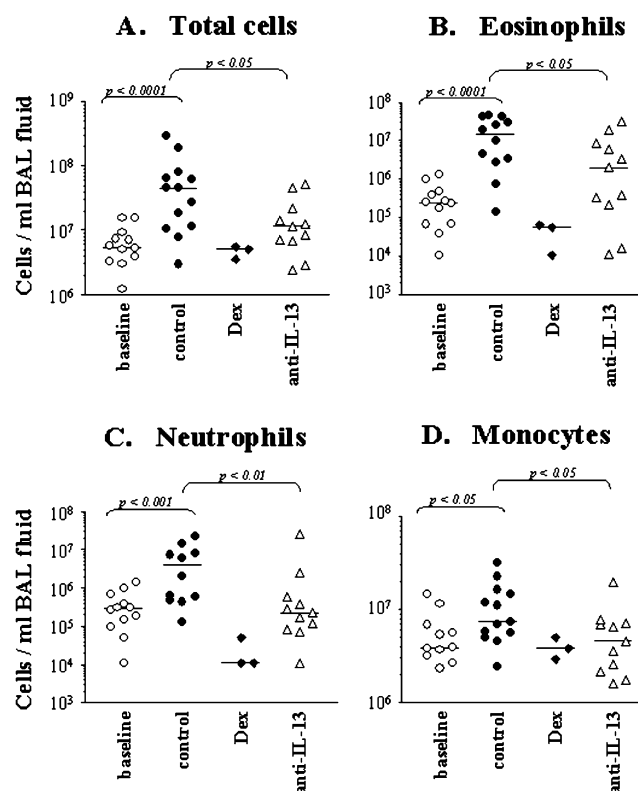


FIG 3. Anti-IL-13 antibody reduced total BAL inflammation in response to *A suum* challenge. Animals were given IVIG or saline (*control*), dexamethasone (*DEX*), or anti-IL-13 (mAb13.2 or IMA-638). Twenty-four hours later, they were challenged with *A suum* antigen. BAL fluid was collected 24 hours after the challenge. **A**, Total cells; **B**, eosinophils; **C**, neutrophils; **D**, monocytes/macrophages. Median values are indicated. *P* values were determined by using the 2-tailed *t* test.

IP-10, and IL-8 were detectable in most BAL fluid samples before *A suum* challenge and increased significantly after challenge. Anti-IL-13 treatment prevented the *A suum*-induced increases in BAL levels of eotaxin and RANTES (Fig 4) but did not significantly reduce the median levels of IP-10 or IL-8 (data not shown). The *A suum*-induced increases in all chemokine levels were reduced by dexamethasone.

Serum levels of IMA-638

Sera were collected at various time points after *A suum* challenge for analysis of mAb13.2 or IMA-638 levels with an IL-13-binding ELISA (data not shown). Serum half-lives of mAb13.2 and IMA-638 were estimated to be less than 5 days and 14.2 days, respectively (data not shown).

BAL levels of IL-13

BAL levels of IL-13 were assayed after *A suum* challenge by using an ELISA that was designed to detect IL-13 in the presence or absence of IMA-638 (data not shown). BAL IL-13 levels in all groups were less than the limits of assay sensitivity (100 pg/mL) both before and 24 hours after allergen challenge. IL-13 transcript levels in BAL cells were assayed by means of real-time PCR by using the primer sequences AAGGTCTCAGCTGGCAGTTT (forward), AAAGTCTG

GGCCACCTCGATT (reverse), and CCAGCTTGCATGT CCGAGACACCA (probe). IL-13 transcript could be detected before challenge and increased approximately 15- to 20-fold in BAL cells collected 24 hours after challenge. The anti-IL-13 antibody did not affect the magnitude of this increase relative to control values (data not shown).

DISCUSSION

IL-13 neutralization is an effective strategy for the prevention or treatment of respiratory pathology in rodent models of asthmatic disease.^{1,8,10} The goal of the present study was to evaluate the efficacy of IL-13 neutralization in a cynomolgus monkey model of lung inflammation in response to *A suum* challenge by using mAb13.2, a neutralizing murine antibody to human IL-13, and IMA-638, a humanized version of the same antibody. IMA-638 has recently been shown to block *A suum*-induced late bronchial responses and airway hyperresponsiveness in a sheep model of allergic asthma.¹³ These antibodies represent novel strategies for the neutralization of human IL-13.

IL-13 was cloned from cynomolgus monkey splenocytes and expressed recombinantly in *E coli* to evaluate the ability of mAb13.2 and IMA-638 to neutralize endogenous IL-13 in NHP. The cynomolgus monkey IL-13

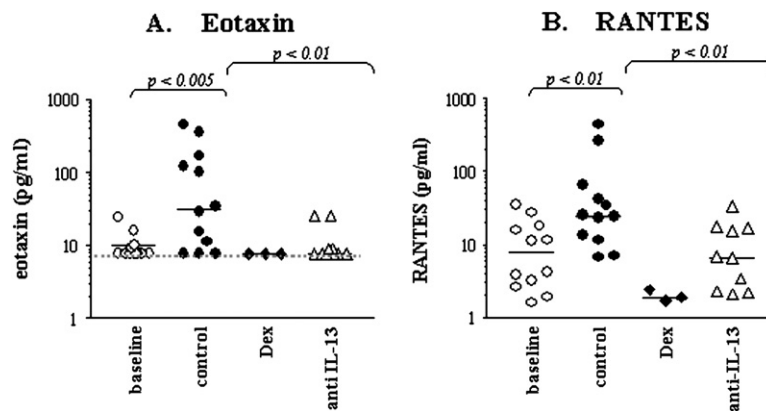


FIG 4. Anti-IL-13 reduces BAL chemokine levels after *A suum* challenge. Animals were given IVIG or saline (*control*), dexamethasone (*DEX*), or anti-IL-13 (mAb13.2 or IMA-638). Twenty-four hours later, they were challenged with *A suum* antigen. BAL fluid was collected 24 hours after the challenge and assayed for eotaxin (**A**; dashed line indicates limit of sensitivity, 7.8 pg/mL) and RANTES (**B**). *P* values were determined by using the paired 2-tailed *t* test.

sequence contained 8 amino acid differences from the human sequence, including a GLN for ARG substitution at position 110. R110Q is a human polymorphic variant expressed at an allele frequency of approximately 20%, which has been associated with increased concentrations of serum IgE and increased risk of atopy in different populations throughout the world.^{5,15} The IL-13 sequences of both chimpanzees and rhesus monkeys contain ARG at position 110, whereas the IL-13 sequences of Pere David's macaques and pigtailed macaques contain the variant GLN residue. Current data do not allow us to distinguish whether the GLN110 found in the cynomolgus monkey sequence is a polymorphic variant or is conserved in this species. Both mAb13.2 and IMA-638 efficiently bound to and neutralized the bioactivity of recombinant cynomolgus monkey IL-13 *in vitro*.

Cynomolgus monkeys that become sensitized through natural exposure to the roundworm parasite *A suum* can be used to develop animal models of asthma. A single airway inhalation challenge with aerosolized *A suum* antigen leads to transient increases in airway resistance and inflammation, whereas multiple challenges can establish chronic airway hyperresponsiveness and eosinophilia.¹⁷⁻²⁰ The current model is novel in that animals were given a segmental lung challenge with *A suum* antigen delivered by using a bronchoscope rather than by means of inhalation challenge. In human subjects segmental lung antigen challenge has been found to induce a more profound airway inflammation response than aerosol challenge.²¹ Segmental challenge protocols are a valuable tool for investigation of inflammatory mechanisms in human asthma²² and have been instrumental in efficacy analysis for every major class of asthma therapeutic.²³⁻²⁶ The adaptation of this technique for use with cynomolgus monkeys represents a useful advance.

The most robust and reproducible end point of the current model was an acute and transient airway inflammation characterized by influx of eosinophils and neutrophils. Airway eosinophilia is a characteristic feature of

asthma,²⁷ but in severe disease neutrophils can become the predominant cell type infiltrating the lung.²⁸ Interestingly, the clinical efficacy of anti-human IgE (omalizumab [Xolair], Genentech, Inc, South San Francisco, Calif) in reducing asthma exacerbations was accompanied by decreased airway inflammation, but not lung function tests, in treated subjects.²⁹ This suggests that under appropriate conditions, modulation of lung inflammation can drive therapeutic efficacy.

IL-13 is a key driver of airway inflammation in rodent models. Mice in which IL-13 is transgenically targeted to the lung exhibit IL-13-dependent airway eosinophilia,³⁰ whereas mice deficient in IL-13 fail to mount a strong inflammatory response to lung antigen challenge.³¹ IL-13 blockade prevents or reduces ongoing lung inflammation in murine asthma models,^{8,9} and a humanized antibody to human IL-13 was recently found to reduce lung inflammation induced by administration of human IL-13 to mice.³² The current demonstration that anti-IL-13 antibody treatment significantly reduced total lung inflammation, eosinophilia, and neutrophilia in cynomolgus monkeys confirms that IL-13 is a driver of lung inflammation not only in rodent models but also in primates.

Proinflammatory cytokines and chemokines are important mediators of lung inflammation. Microarray analysis has detected transcripts encoding these agents in cells recovered from BAL fluid or from lung tissue in this (Donaldson and Goldman, unpublished observations) and similar models.³³ In the current study levels of eotaxin and RANTES were increased in response to *A suum* challenge, and these increases were prevented by antibodies to IL-13. Eotaxin, produced in the airway in response to IL-13, is a major chemokine driving eosinophilic inflammation after allergen challenge.^{34,35} RANTES also mediates eosinophil recruitment to the lung³⁶ and has been consistently observed in human BAL samples after allergen challenge.³⁷ The reduced levels of eotaxin and RANTES in BAL fluid of antibody-treated animals after *A suum*

challenge is consistent with the reduced BAL eosinophilia seen in these animals.

The current findings support a role for IL-13 in mediating airway inflammation in cynomolgus monkeys after segmental lung challenge with *A suum*. This is the first demonstration of the efficacy of IL-13 antagonism in NHPs. In human asthmatic subjects airway inflammation is associated with reduced lung function, contributes to airway remodeling and disease progression, and is a characteristic and important clinical feature of the asthmatic response.^{28,38} Given the pivotal role of airway inflammation, our results support the utility of IL-13 antagonism as a therapeutic approach for the treatment of asthma.

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