

90 mg version - 100%
FDA COMMENTS-RND 2



PMS Orange 021
4/C Orange- 0.53.100.0

GPSG Global Pharmaceutical Supply Group

PRODUCT NAME Stelara COMPONENT TYPE Label

COMP. NUMBER AW_52954 ARTWORK VERSION 2

SOFTWARE USED Illustrator VERS. CS2 UPGRADE ☒

MODIFIED DATE 06/18/09 DESIGNER Kim DePaola

Date/Comment: TITLE BLOCK PROOFED ☐ NO ☒ YES

04/14/09: V1: CR created from 10139900 with revs per PDF.
06/18/09: V2: KD made revs per marked up PDF

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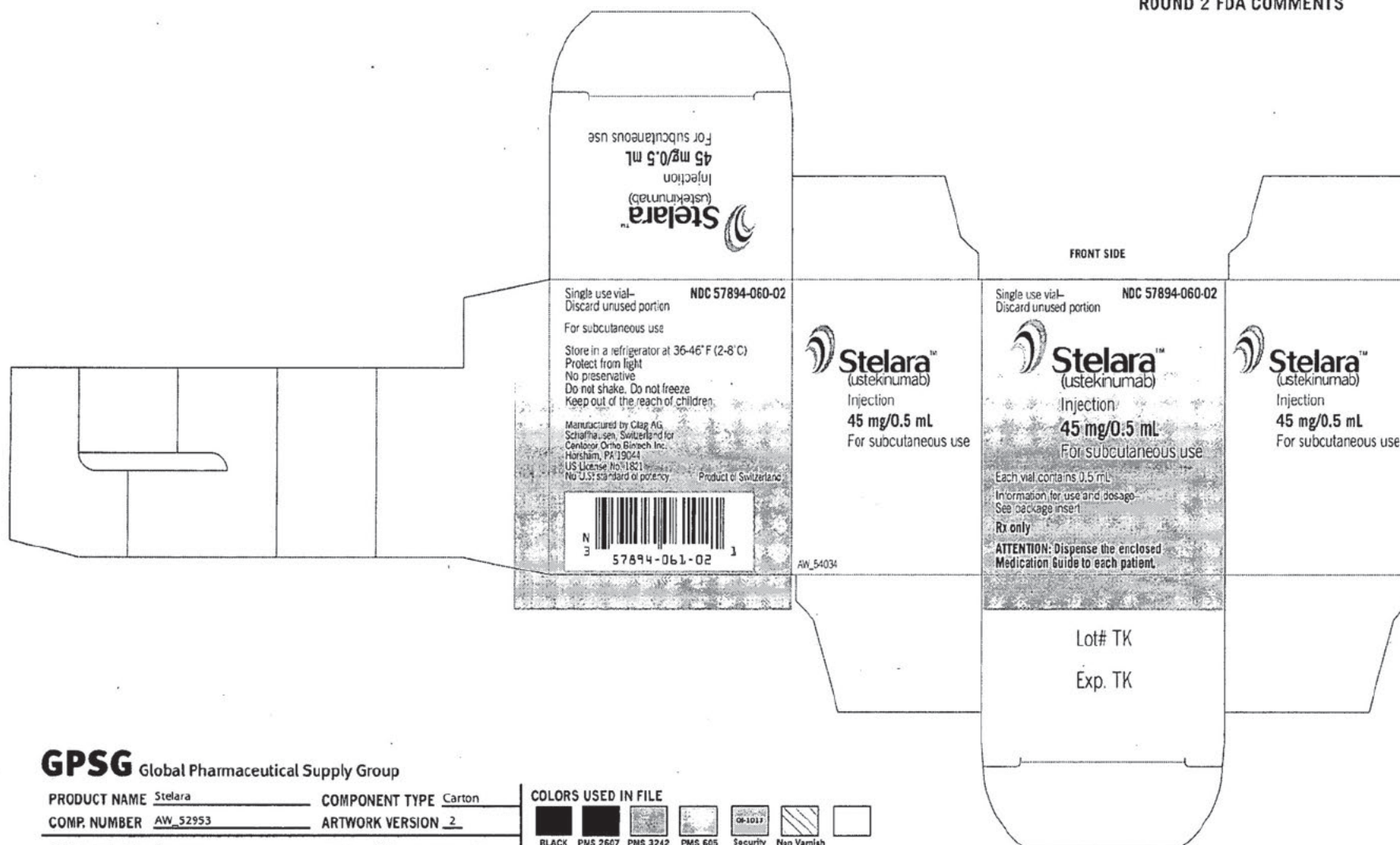


BLACK PMS 2607 PMS 3242 PMS 605 Security LPI-1013 Non Varnish Indication

DIMENSIONS 2-13/64" x 21/32"

DWG # R/L/81924/V1 OUTPUT % 100%

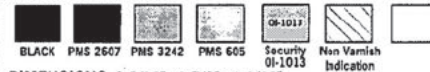
SPEC # 81877 ePM Order # 52954

45 mg-100%
ROUND 2 FDA COMMENTS**GPSG** Global Pharmaceutical Supply GroupPRODUCT NAME Stelara COMPONENT TYPE CartonCOMP. NUMBER AW_52953 ARTWORK VERSION 2SOFTWARE USED Illustrator VERS. CS2 UPGRADE ☐MODIFIED DATE 06/18/09 DESIGNER Kim DePaolaDate/Comment: TITLE BLOCK PROOFED ☐ NO ☒ YES

04/14/09: V1: CR created document from 10139701 with changes per PDF

06/18/09: V2: KD used die and layout from AW_54034 per LS and made changes per marked up PDF

COLORS USED IN FILE

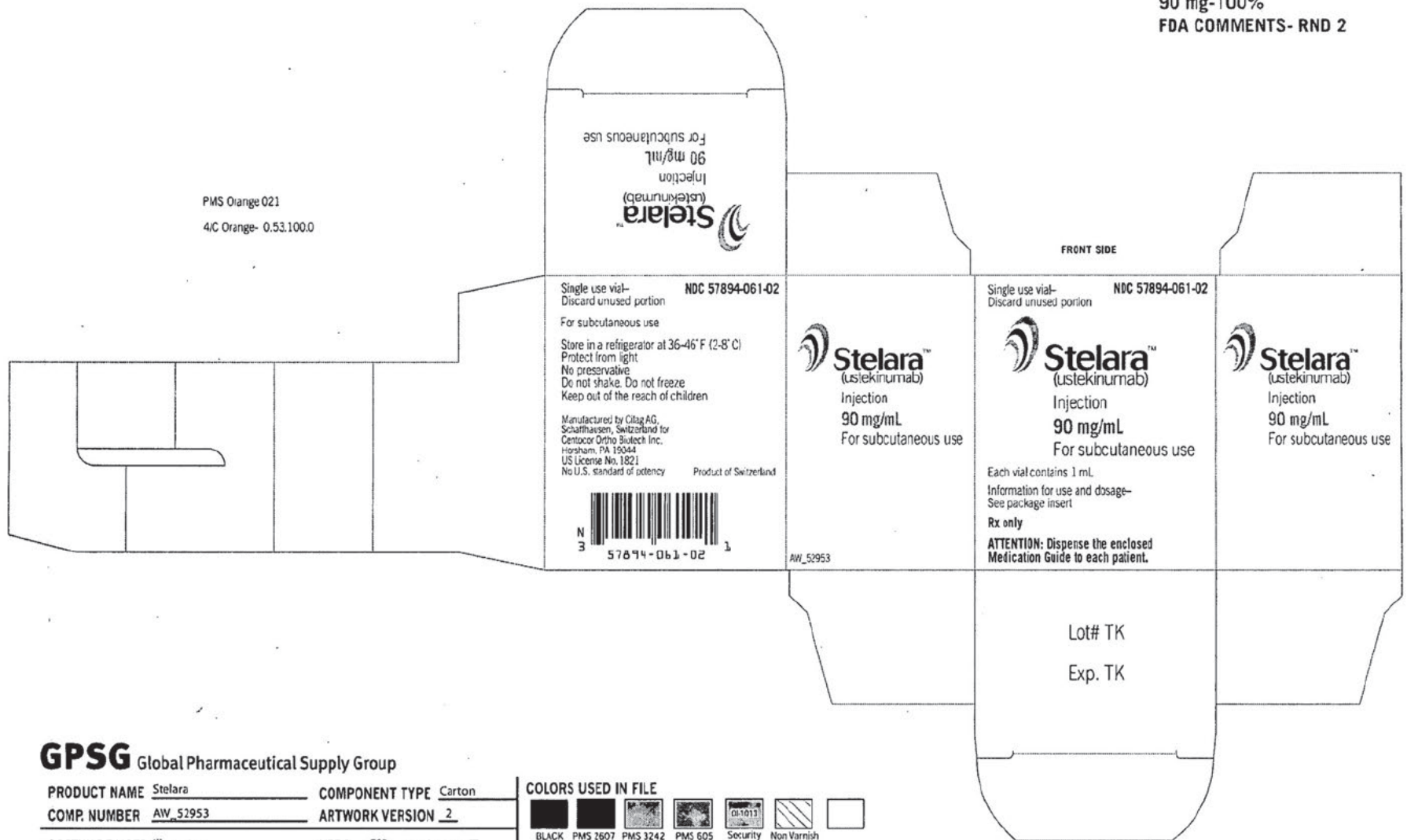


DIMENSIONS 3-3/16" x 1-7/8" x 1-1/16"

DWG # NA OUTPUT % 100%SPEC # NA ePM Order # 52953

PMS Orange 021
4/C Orange- 0.53.100.0

90 mg-100%
FDA COMMENTS- RND 2



GPSG Global Pharmaceutical Supply Group

PRODUCT NAME	Stelara	COMPONENT TYPE	Carton
COMP. NUMBER	AW_52953	ARTWORK VERSION	2
SOFTWARE USED	Illustrator	VERS.	CS2
MODIFIED DATE	06/18/09	DESIGNER	Kim DePaola
Date/Comment:		TITLE BLOCK PROOFED ☐ NO ☒ YES	

COLORS USED IN FILE	
BLACK	PMS 2607
PMS 3242	PMS 605
Security 01-1013	Non Varnish Indication

DIMENSIONS	3-3/16" x 1-7/8" x 1-1/16"
DWG #	NA
OUTPUT %	100%
SPEC #	NA
oPM Order #	52953

04/14/09: V1: CR created document from 10139701 with changes per PDF
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Appendix A. REMS Document

BLA 125261 STELARA™ (ustekinumab)

Human interleukin 12 and 23 antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

To evaluate and mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) associated with STELARA™ by:

- alerting and warning healthcare providers and patients about the risks
- informing and educating healthcare providers about the Psoriasis Longitudinal Assessment and Registry (PSOLAR) voluntary disease-specific patient registry

II. REMS ELEMENTS

A. MEDICATION GUIDE

In accordance with 21 CFR 208.24, a Medication Guide will be appended to the package insert and will be provided by Centocor Ortho Biotech Inc. and/or its affiliates by either:

1. Providing Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product; or
2. Providing the means to produce Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product.

Medication Guides will be included in each single unit carton containing one vial and dispensed in accordance with 21 CFR 208.24.

The Medication Guide will also be available on the STELARA™ patient and professional websites.

Please see appended Medication Guide (Attachment A).

B. COMMUNICATION PLAN

Centocor Ortho Biotech Inc. will implement a communication plan to the following healthcare providers:

- Dermatologists and dermatology healthcare providers (HCPs) who are likely to prescribe and/or inject STELARA™
- Oncologists who may treat malignancies potentially associated with the use of immunosuppressants for chronic inflammatory and autoimmune disease and will need to ascertain cases of malignancy after a long latency period
- Rheumatologists who may co-manage with dermatologists moderate to severe psoriasis patients with psoriatic arthritis
- Infectious disease specialists and gastroenterologists who may be consulted about infections and will need to understand the potential for infectious complications of IL-12/IL-23 blockade
- Neurologists who may treat RPLS

The communication plan will provide for the dissemination of risk information about serious infection, malignancy, and RPLS, and encourage patient participation and physician referral to PSOLAR investigator sites (a voluntary psoriasis registry).

Elements of the communication plan:

1. A Dear Healthcare Professional letter (see Attachment B) will be distributed to dermatologists, oncologists, rheumatologists, infectious disease specialists, gastroenterologists, and neurologists. This will be distributed within 60 days of STELARA™ approval.

A Professional Label and a copy of the Medication Guide will also be distributed in this communication.
2. A Dear Pharmacist letter (see Attachment C) will be distributed to pharmacists. This will be distributed within 60 days of STELARA™ approval.

A Professional Label and a copy of the Medication Guide will also be distributed in this communication.
3. Dissemination of information about serious infection, malignancy, and RPLS to health care providers through certain dermatology, oncology, rheumatology, infectious diseases, and gastroenterology professional societies' journals:
 - 1) For display as a panel/poster and distribution as printed material at all dermatology and oncology scientific meetings where the company has a sponsored booth
 - 2) For quarterly presentation as a printed information piece in the *Journal of the American Academy of Dermatology* and the *Archives of Dermatology* for 3 years

- 3) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* and *Blood* for 5 years
- 4) For twice yearly presentation as a printed information piece in *Arthritis and Rheumatism*, the *Journal of Infectious Disease*, the *American Journal of Gastroenterology*, and *Gastroenterology* for 3 years

The REMS Journal Information Piece is appended to this document (see Attachments D, E, F, G, and H).

4. Centocor Ortho Biotech Inc. will enhance participation in PSOLAR, a voluntary, disease-specific registry (which is comprised of patients receiving systemic therapies including other biologic agents), by outreach to dermatologic societies, inclusion of PSOLAR contact information in communication materials, and proactively educating dermatologists about PSOLAR.

C. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Centocor Ortho Biotech Inc. will submit REMS Assessments to the FDA according to the table below. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Centocor Ortho Biotech Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

<u>Assessment Submission</u>	<u>Timing Interval Relative to Approval of the REMS</u>	<u>Date of Submission to the FDA (month/year)</u>
1st Assessment	18 months after approval	March, 2011
2nd Assessment	3 years after approval	September, 2012
3rd Assessment	7 years after approval	September, 2016

Attachment A Medication Guide

MEDICATION GUIDE

STELARA™ (stel ar' a)

(ustekinumab)

Injection

Read this Medication Guide before you start taking STELARA™ and each time before you get an injection. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment with STELARA™.

What is the most important information I should know about STELARA™?

STELARA™ is a medicine that affects your immune system. STELARA™ can increase your chances of having serious side effects, including:

Serious Infections: STELARA™ may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections while taking STELARA™, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.

- Your doctor should check you for TB before starting STELARA™.
- If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with STELARA™ and during treatment with STELARA™.
- Your doctor should watch you closely for signs and symptoms of TB during treatment with STELARA™.

You should not start taking STELARA™ if you have any kind of infection unless your doctor says it is okay.

Before starting STELARA™, tell your doctor if you think you have an infection or have symptoms of an infection such as:

- fever, sweats, or chills
- muscle aches
- cough
- shortness of breath
- blood in your phlegm
- weight loss

- warm, red, or painful skin or sores on your body
- diarrhea or stomach pain
- burning when you urinate or urinate more often than normal
- feel very tired
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have TB, or have been in close contact with someone who has TB.

After starting STELARA™, call your doctor right away if you have any symptoms of an infection (see above).

STELARA™ can make you more likely to get infections or make an infection that you have worse.

People who have a genetic problem where the body does not make any of the proteins interleukin 12 (IL-12) and interleukin 23 (IL-23) are at a higher risk for certain serious infections. These infections can spread throughout the body and cause death. It is not known if people who take STELARA™ will get any of these infections, because of the effects of STELARA™ on these proteins in your body.

Cancers:

STELARA™ may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your doctor if you have ever had any type of cancer.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS):

RPLS is a rare condition that affects the brain and can cause death. The cause of RPLS is not known. If RPLS is found early and treated, most people recover. Tell your doctor right away if you have any new or worsening medical problems including:

- headache
- seizures
- confusion
- vision problems

What is STELARA™?

STELARA™ is a prescription medicine used to treat adults 18 years and older with moderate or severe psoriasis that involves large areas or many areas of their body, who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).

STELARA™ may improve your psoriasis but may also lower the ability of your immune system to fight infections. This may also increase your risk for certain types of cancer.

It is not known if STELARA™ is safe and effective in children.

It is not known if taking STELARA™ for more than 2 years is safe and effective.

What should I tell my doctor before receiving STELARA™?

Before receiving STELARA™, tell your doctor if you:

- have any of the conditions or symptoms listed in the section “What is the most important information I should know about STELARA™?”
- have recently received or are scheduled to receive an immunization (vaccine). People who take STELARA™ should not receive live vaccines. Tell your doctor if anyone in your house needs a vaccine. The viruses used in some types of vaccines can spread to people with a weakened immune system, and can cause serious problems. **You should not receive the BCG vaccine during the one year before taking STELARA™ or one year after you stop taking STELARA™.**
- receive phototherapy for your psoriasis.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if STELARA™ will harm your unborn baby. You and your doctor should decide if you will take STELARA™.
- are breast-feeding or plan to breast-feed. It is thought that STELARA™ passes into your breast milk. You should not breast-feed while taking STELARA™ without first talking with your doctor.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- other medicines that affect your immune system.
- certain medicines that can affect how your liver breaks down other medicines.

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive STELARA™?

- STELARA™ is given by injection under the skin (subcutaneous injection).
- STELARA™ should only be given by a healthcare provider as directed by your doctor.
- Your doctor will decide the right dose of STELARA™ for you and how often you should receive it.

- Be sure to keep all of your scheduled follow-up appointments.

What should I avoid while receiving STELARA™?

You should not receive a live vaccine while taking STELARA™. See “What should I tell my doctor before taking STELARA™?”

What are the possible side effects of STELARA™?

STELARA™ can increase your chances of having serious side effects. See “What is the most important information I should know about STELARA™?”

Common side effects of STELARA™ include:

- upper respiratory infections
- headache
- tiredness

These are not all of the possible side effects of STELARA™. Tell your doctor about any side effect that bothers you or that does not go away. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about STELARA™

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about STELARA™. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about STELARA™ that was written for healthcare professionals. For more information, go to www.STELARAinfo.com or call 1-800-457-6399.

What are the ingredients in STELARA™?

Active ingredient: ustekinumab

Inactive ingredients: sucrose, L-histidine, and polysorbate 80.

Manufactured by Cilag AG,
Schaffhausen, Switzerland
for

Centocor Ortho Biotech Inc.
Horsham, PA 19044

Revised September 2009

This Medication Guide has been approved by the U.S. Food and Drug Administration.

U.S. License No. 1821

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Attachment B Dear Healthcare Professional Letter



Centocor Ortho Biotech Inc.

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

The purpose of this letter is to inform you of important safety information for STELARA™ (ustekinumab), a new human monoclonal antibody which has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. STELARA™ targets interleukin-12 (IL-12) and interleukin-23 (IL-23). FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for STELARA™ to ensure that the benefits of the drug outweigh the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS).

IMPORTANT SAFETY INFORMATION FOR POTENTIAL RISKS OF SERIOUS INFECTIONS AND MALIGNANCIES, AND RPLS

The following information is important for healthcare professionals and patients treated with STELARA™:

Infections

- STELARA™ may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections, some requiring hospitalization, were observed in patients receiving STELARA™. STELARA™ should not be given to patients with a clinically important active infection and should not be administered until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. Exercise caution when considering use of STELARA™ in patients with a chronic infection or a history of recurrent infection.

Theoretical Risk for Vulnerability to Particular Infections

- Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria, salmonella, and *Bacillus Calmette-Guérin* (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.
- It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA™ will be susceptible to these types of infections. Appropriate diagnostic testing should be considered as dictated by clinical circumstances.

Pre-Treatment Evaluation of Tuberculosis (TB)

- Evaluate patients for TB infection prior to initiating treatment with STELARA™. Do not administer STELARA™ to patients with active TB. Initiate treatment of latent TB before administering STELARA™.
- Consider anti-tuberculosis therapy prior to initiation of STELARA™ in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.
- Patients receiving STELARA™ should be monitored closely for signs and symptoms of active TB during and after treatment.

Malignancies

- STELARA™ (ustekinumab) is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA™ in clinical studies.

- The safety of STELARA™ has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- One case of RPLS has been reported in a STELARA™-treated subject.
- RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. It has been associated with preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy.
- If RPLS is suspected, discontinue STELARA™ and administer appropriate treatment.

REPORTING PATIENT ADVERSE EVENTS

It is important that you report all serious adverse events that occur in patients using STELARA™. If you have a patient who develops a serious infection or RPLS while being treated with STELARA™, or if you have a patient with cancer at any time after receiving STELARA™ therapy, it is important that you report the case even if you do not think there is a causal relationship.

The information that you can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA™ manufacturer or directly to FDA.

- Centocor Ortho Biotech Inc. at 1-800-457-6399
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

VOLUNTARY REGISTRY INFORMATION

PSOLAR (PSoriasis Longitudinal Assessment and Registry) is a Centocor Ortho Biotech Inc.-sponsored voluntary psoriasis registry that will be available to enroll patients treated with STELARA™. Please call 1-888 PSOLAR-5 or go to www.clinicaltrials.gov for more information.

Please see the enclosed:

- STELARA™ package insert, and
- Medication Guide

Please Note: This letter does not include a comprehensive description of the serious and significant risks associated with the use of STELARA™. Please read the accompanying Full Prescribing Information and Medication Guide for a complete description of the serious and significant risk that may be associated with the use of STELARA™. You are advised to discuss the risks that may be associated with STELARA™ therapy with patients and their caregivers. We have enclosed a copy of the STELARA™ Medication Guide, which is required to be provided to patients with every filled prescription. This Medication Guide contains information that can be used to facilitate discussions about the potential risks of therapy.

Sincerely,



Peter Callegari, MD
Vice President, Medical Affairs

Enclosures

Attachment C Dear Pharmacist Letter



Centocor Ortho Biotech Inc.

IMPORTANT DRUG WARNING

Dear Pharmacist:

The purpose of this letter is to inform you of important safety information for STELARA™ (ustekinumab), a new human monoclonal antibody which has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. STELARA™ targets interleukin-12 (IL-12) and interleukin-23 (IL-23). FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for STELARA™ to ensure that the benefits of the drug outweigh the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS).

FDA requires that a copy of the enclosed STELARA™ Medication Guide be distributed to each patient (or agent such as a caregiver) who fills a prescription for STELARA™. A copy of the STELARA™ Medication Guide will be packaged with every vial of STELARA™.

Should you require additional copies of the STELARA™ Medication Guide, you may

- Request copies from Centocor Ortho Biotech Inc. by calling the toll-free medical information line at 1-800-457-6399
- Print copies of the Medication Guide from the STELARA™ website www.stelarainfo.com
- Request copies from your drug supplier
- Photocopy the enclosed Medication Guide, after confirming that it is the most current version.
- Call the toll-free medical information line at the number above

IMPORTANT SAFETY INFORMATION FOR POTENTIAL RISKS OF SERIOUS INFECTIONS AND MALIGNANCIES, AND RPLS

Important Safety Information is listed in the Warnings and Precautions sections of the Prescribing Information for STELARA™ and Medication Guide for patients.

Infections

- STELARA™ may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections, some requiring hospitalization, were observed in patients receiving STELARA™. STELARA™ should not be given to patients with a clinically important active infection and should not be administered until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. Exercise caution when considering use of STELARA™ in patients with a chronic infection or a history of recurrent infection.

Theoretical Risk for Vulnerability to Particular Infections

- Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria, salmonella, and *Bacillus Calmette-Guerin* (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.
- It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA™ (ustekinumab) will be susceptible to these types of infections. Appropriate diagnostic testing should be considered as dictated by clinical circumstances.

Pre-Treatment Evaluation of Tuberculosis (TB)

- Evaluate patients for TB infection prior to initiating treatment with STELARA™. Do not administer STELARA™ to patients with active TB. Initiate treatment of latent TB before administering STELARA™.
- Consider anti-tuberculosis therapy prior to initiation of STELARA™ in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.
- Patients receiving STELARA™ should be monitored closely for signs and symptoms of active TB during and after treatment.

Malignancies

- STELARA™ is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA™ in clinical studies.
- The safety of STELARA™ has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- One case of RPLS has been reported in a STELARA™-treated subject.
- RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. It has been associated with preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy.
- If RPLS is suspected, discontinue STELARA™ and administer appropriate treatment.

REPORTING PATIENT ADVERSE EVENTS

It is important that you report all serious adverse events that occur in patients using STELARA™. If you are aware of a patient who develops a serious infection or RPLS while being treated with STELARA™, or if you are aware of a patient with cancer at any time after receiving STELARA™ therapy, it is important that you report the case even if you do not think there is a causal relationship. The information that you can provide may inform therapy and monitoring decisions.

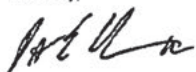
Reporting is easy and maintains patient confidentiality. The patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.*

You can report cases to the STELARA™ manufacturer or directly to FDA.

- Centocor Ortho Biotech Inc. at 1-800-457-6399
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please Note: This letter does not include a comprehensive description of the serious and significant risks that may be associated with the use of STELARA™. Please read the accompanying Full Prescribing Information and Medication Guide for a complete description of the serious and significant risk that may be associated with the use of STELARA™.

Sincerely,



Peter Callegari, MD
Vice President, Medical Affairs

Enclosures

Attachment D Journal Information Piece for Dermatologists

Important Information for Dermatologists about the Potential Risks of Serious Infections and Malignancy, and RPLS with STELARA™ for Psoriasis Therapy

STELARA™ (ustekinumab) is a new human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA™ targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models and humans genetically deficient for components of IL-12 and IL-23 pathways, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for serious infections, including mycobacterial and recurrent salmonella infections**. In addition, data from rodent models suggest there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for malignancies**.

One case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in a STELARA™-treated patient in clinical trials. RPLS is a neurological disorder which is not caused by demyelination or a known infectious agent, and can present with headache, seizures, confusion and visual disturbances.

If you have a patient that develops a serious infection or RPLS while being treated with STELARA™, or if you have a patient with cancer at any time after receiving STELARA™ therapy, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as a STELARA™ prescribing dermatologist, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA™ manufacturer or directly to FDA.

- Centocor Ortho Biotech Inc. at 1-800-457-6399
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

PSOLAR (Psoriasis Longitudinal Assessment and Registry) is a **voluntary, disease-specific registry**, developed by Centocor Ortho Biotech Inc., that collects information from psoriasis patients and their treating physicians. Since this registry will continue for 10 years, it will help us better understand the risk of long-latency serious events, such as malignancies, that can occur after exposure to a product such as STELARA™.

For more information on PSOLAR and how to include patients in this voluntary registry, call 1-888-PSOLAR5 (1-888-776-5275) or access www.clinicaltrials.gov and search for PSOLAR.

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 Centocor Ortho Biotech Inc.

Attachment E Journal Information Piece for Oncologists

Important Information for Oncologists About Potential Malignancy Risk With STELARA™ for Psoriasis Therapy

STELARA™ (ustekinumab) is a new human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA™ targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for malignancies.**

If you are consulted to see a patient with cancer at any time after receiving STELARA™ therapy, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as an oncologist, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.*

You can report your cases to the STELARA™ manufacturer or directly to FDA.

- Centocor Ortho Biotech Inc. at 1-800-457-6399
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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 Centocor Ortho Biotech Inc.

Attachment F Journal Information Piece for Rheumatologists

Important Information for Rheumatologists about the Potential Risks of Serious Infections and Malignancy, and RPLS with STELARA™ for Psoriasis Therapy

STELARA™ (ustekinumab) is a new human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA™ targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models and humans genetically deficient for components of IL-12 and IL-23 pathways, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for serious infections, including mycobacterial and recurrent salmonella infections**. In addition, data from rodent models suggest there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for malignancies**.

One case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in a STELARA™-treated patient in clinical trials. RPLS is a neurological disorder which is not caused by demyelination or a known infectious agent, and can present with headache, seizures, confusion and visual disturbances.

If you have a patient that develops a serious infection or RPLS while being treated with STELARA™, or if you have a patient with cancer at any time after receiving STELARA™ therapy, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as a rheumatologist that may co-manage patients receiving STELARA™ therapy, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA™ manufacturer or directly to FDA.

- Centocor Ortho Biotech Inc. at 1-800-457-6399
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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Attachment G Journal Information Piece for Infectious Disease Specialists

**Important Information for Infectious Disease Specialists
About Potential Serious Infection Risk
With STELARA™ for Psoriasis Therapy**

STELARA™ (ustekinumab) is a new human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA™ targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models and humans genetically deficient for components of IL-12 and IL-23 pathways, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for serious infections, including mycobacterial and recurrent salmonella infections.**

If you are consulted to see a patient that develops a serious infection while being treated with STELARA™, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as an infectious disease specialist, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.*

You can report your cases to the STELARA™ manufacturer or directly to FDA.

- Centocor Ortho Biotech Inc. at 1-800-457-6399
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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 Centocor Ortho Biotech Inc.

Attachment H Journal Information Piece for Gastroenterologists

Important Information for Gastroenterologists About Potential Serious Infection Risk With STELARA™ for Psoriasis Therapy

STELARA™ (ustekinumab) is a new human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA™ targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models and humans genetically deficient for components of IL-12 and IL-23 pathways, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for serious infections, including mycobacterial and recurrent salmonella infections.**

If you are consulted to see a patient that develops a serious infection while being treated with STELARA™, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as a gastroenterologist, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA™ manufacturer or directly to FDA.

- Centocor Ortho Biotech Inc. at 1-800-457-6399
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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 Centocor Ortho Biotech Inc.

Exhibit 2

Copy of U.S. Patent No. 6,902,734



US006902734B2

(12) **United States Patent**
Giles-Komar et al.

(10) **Patent No.:** **US 6,902,734 B2**

(45) **Date of Patent:** **Jun. 7, 2005**

(54) **ANTI-IL-12 ANTIBODIES AND COMPOSITIONS THEREOF**

(75) **Inventors:** **Jill Giles-Komar**, Downingtown, PA (US); **David M. Knight**, Berwyn, PA (US); **David Peritt**, Bala Cynwyd, PA (US); **Bernard Scallon**, Collegeville, PA (US); **David Shealy**, Downingtown, PA (US)

(73) **Assignee:** **Centocor, Inc.**, Malvern, PA (US)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 360 days.

(21) **Appl. No.:** **09/920,262**

(22) **Filed:** **Aug. 1, 2001**

(65) **Prior Publication Data**

US 2003/0124123 A1 Jul. 3, 2003

Related U.S. Application Data

(60) Provisional application No. 60/236,827, filed on Sep. 29, 2000, and provisional application No. 60/223,358, filed on Aug. 7, 2000.

(51) **Int. Cl.⁷** **C07K 16/24; A61K 39/395**

(52) **U.S. Cl.** **424/145.1; 424/130.1; 424/139.1; 530/387.1; 530/387.9; 530/388.23; 530/389.2**

(58) **Field of Search** **530/387.1, 387.9, 530/388.23, 389.2; 424/130.1, 139.1, 145.1**

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Primary Examiner—Prema Mertz

(74) *Attorney, Agent, or Firm*—Eric A. Dichter; Guy Kevin Townsend

(57) **ABSTRACT**

The present invention relates to at least one anti-IL-12 antibody, including isolated nucleic acids that encode at least one anti-IL-12 antibody, IL-12, vectors, host cells, transgenic animals or plants, and methods of making and using thereof, including therapeutic compositions, methods and devices.

4 Claims, 12 Drawing Sheets

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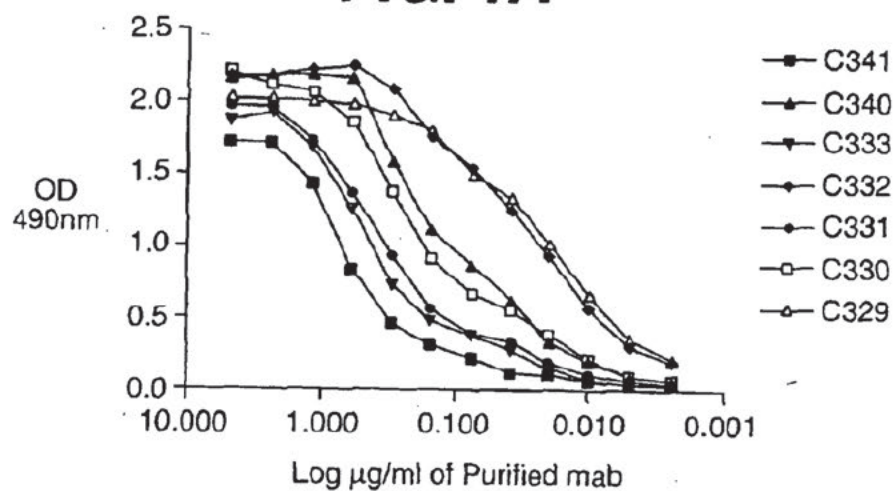
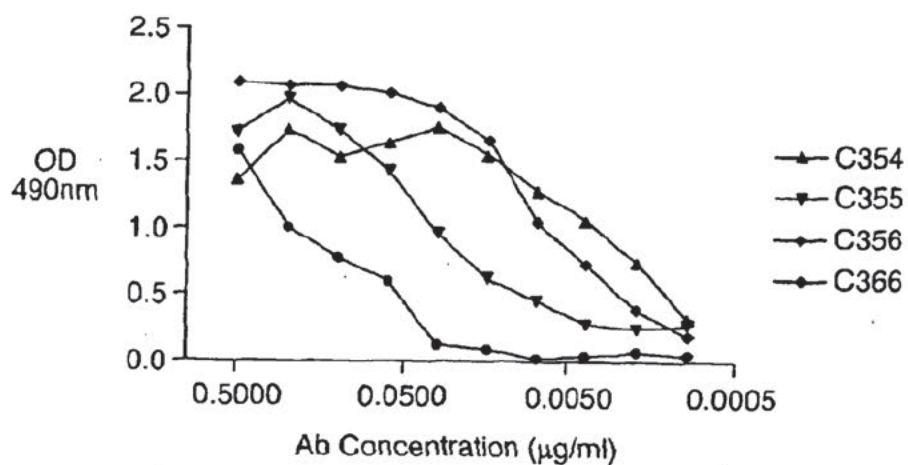
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FIG. 1A**FIG. 1B**

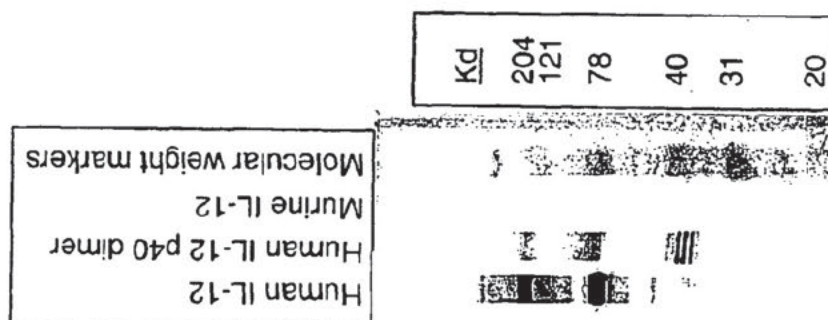


FIG. 2B

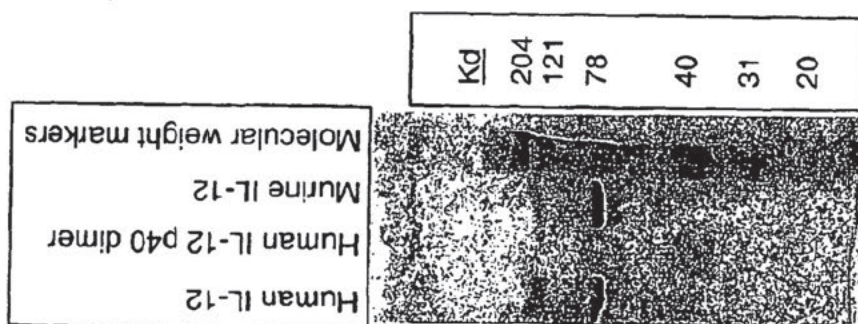


FIG. 2A

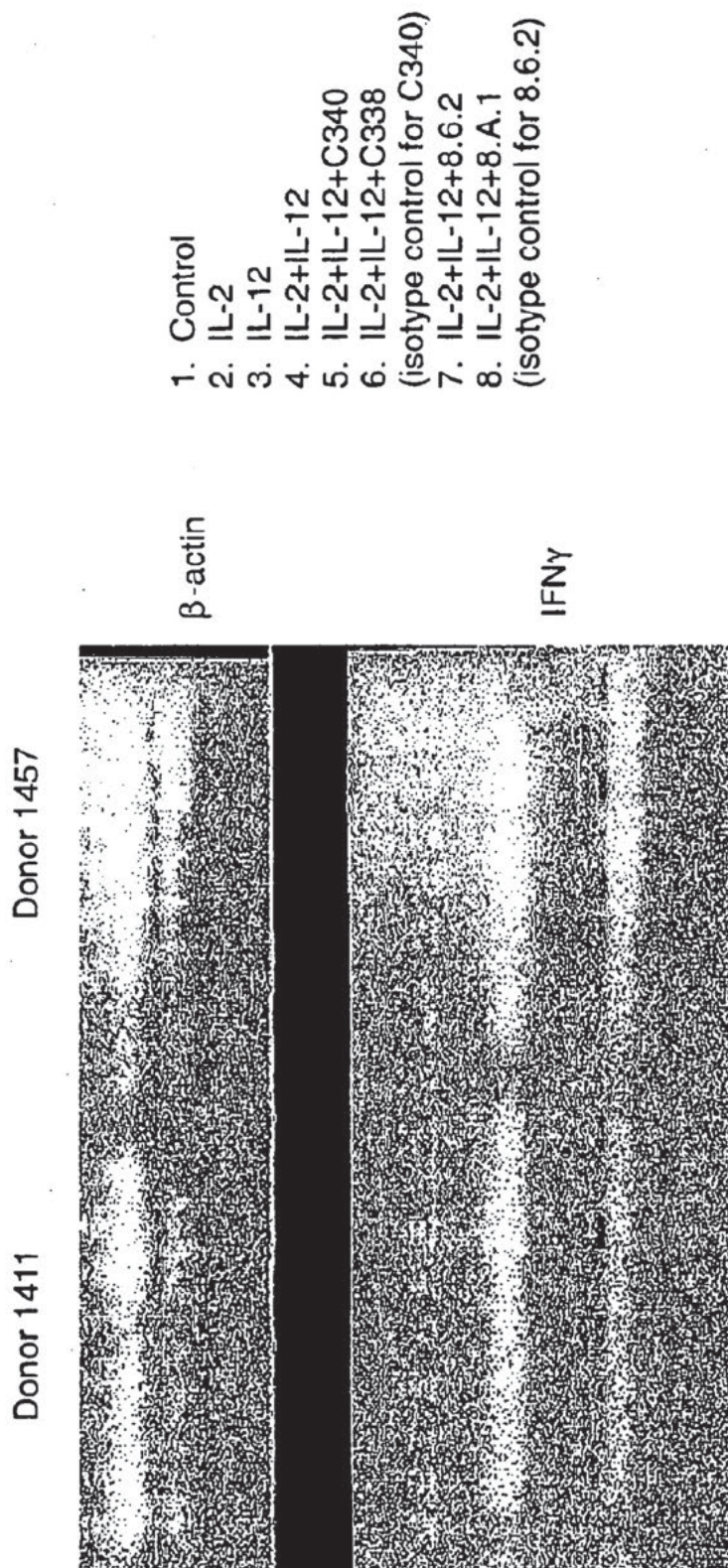
FIG. 3

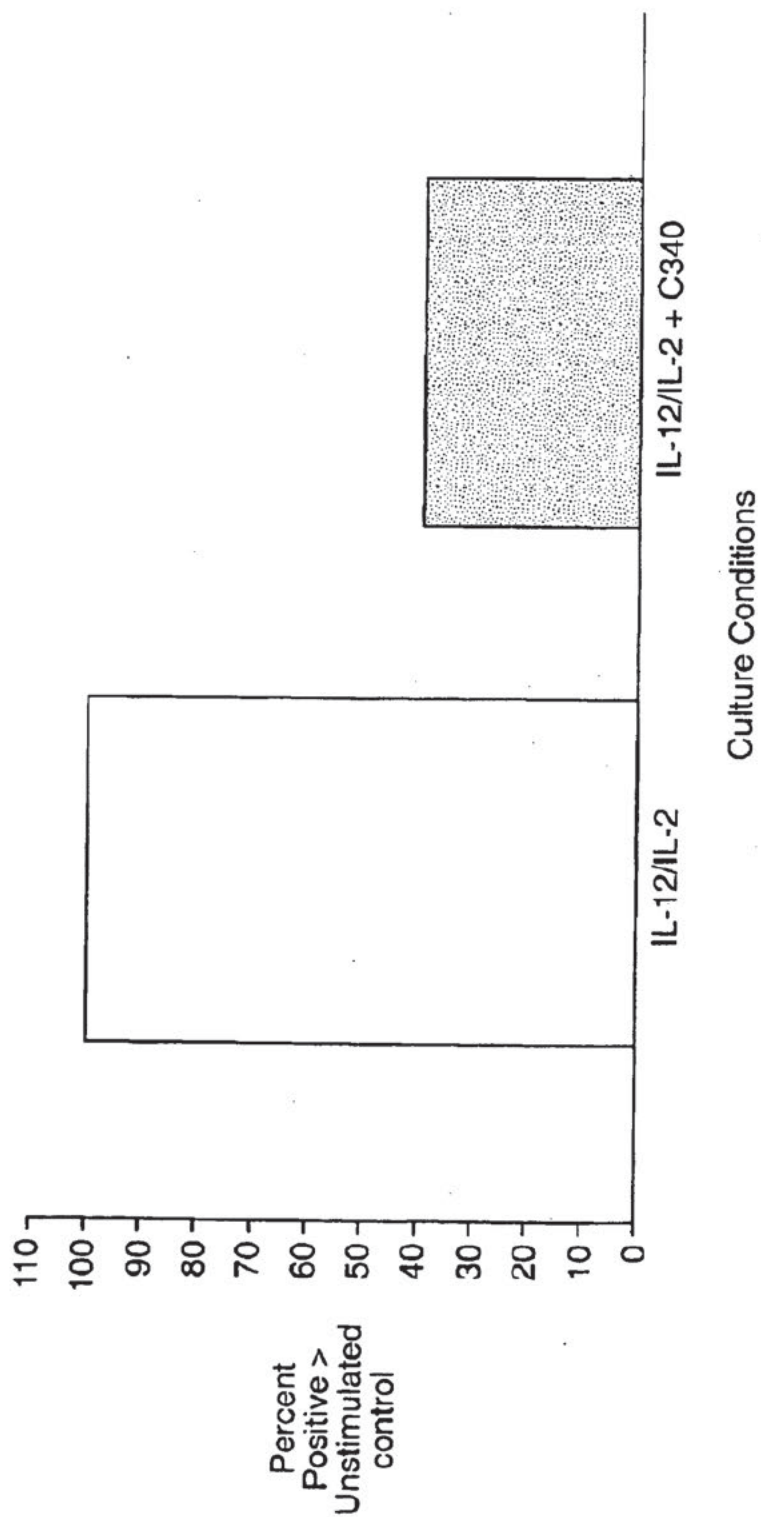
FIG. 4

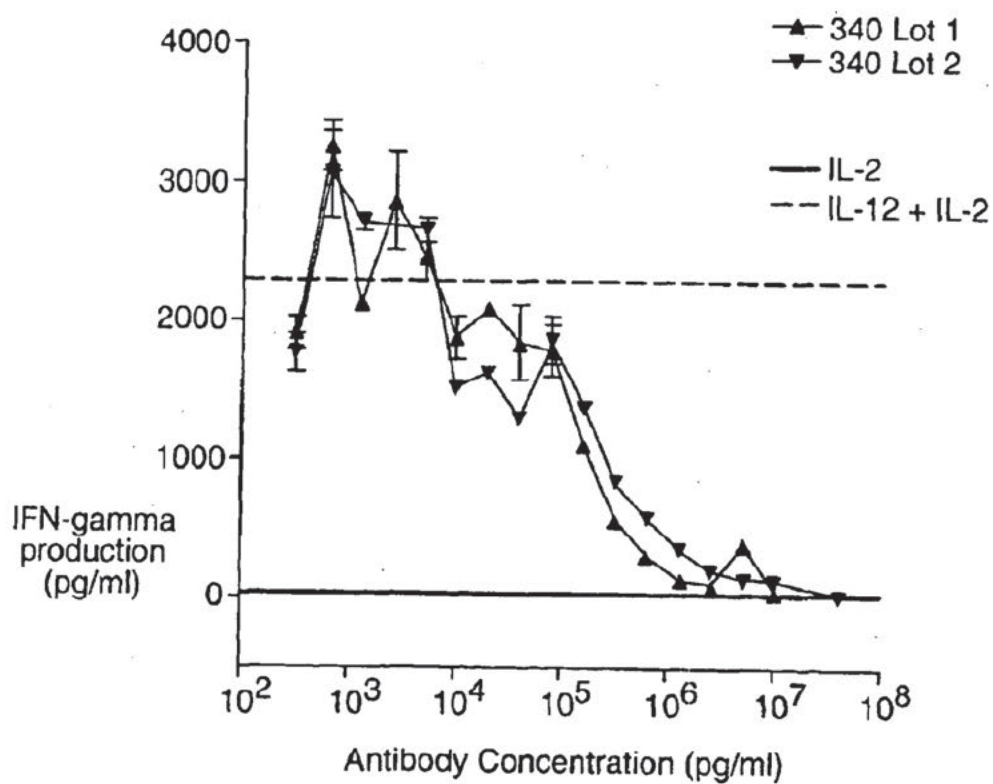
FIG. 5

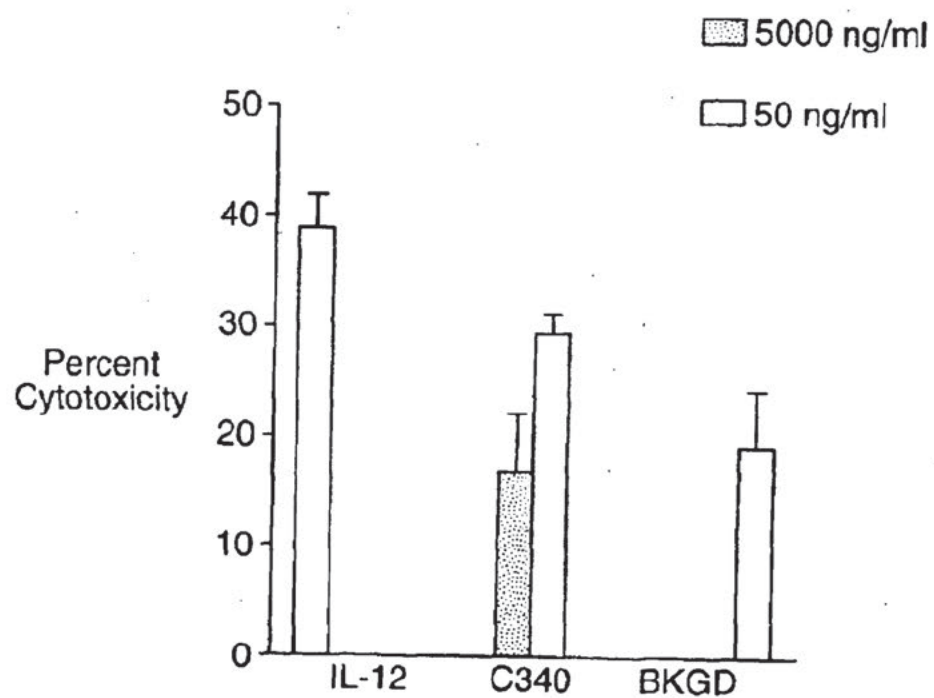
FIG. 6

FIG. 7A

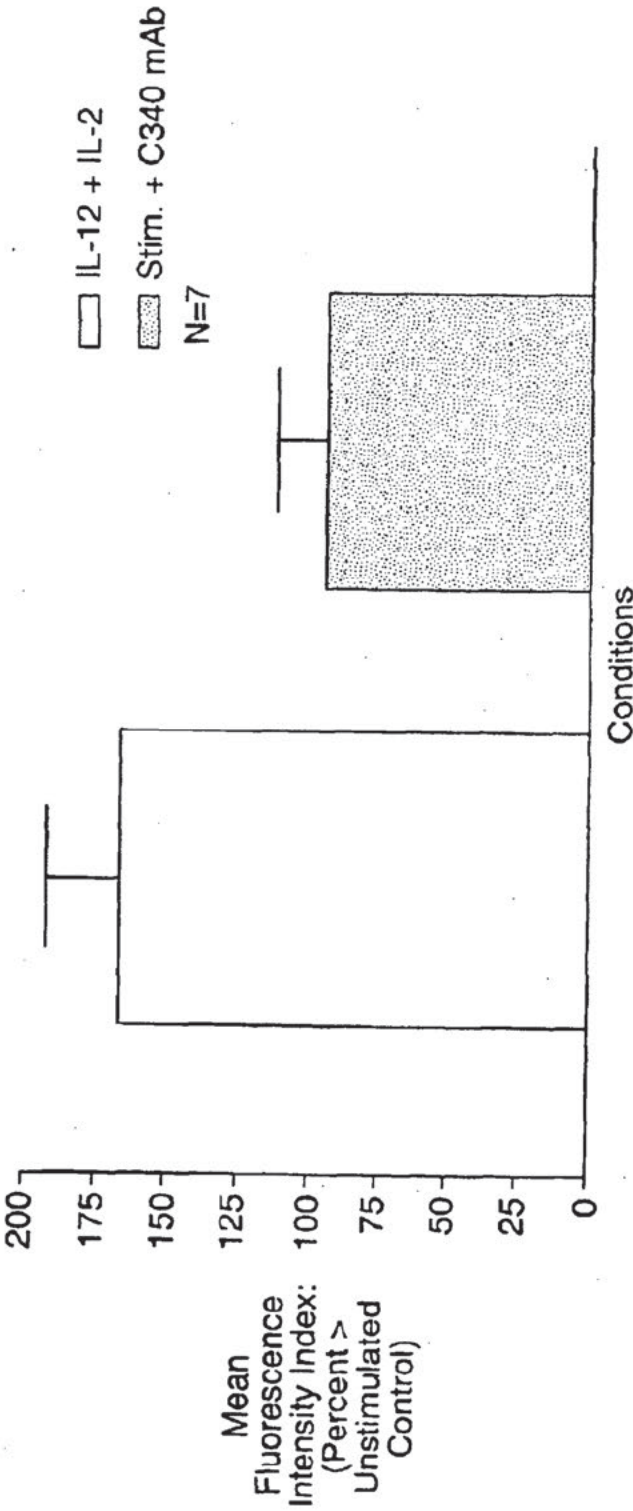


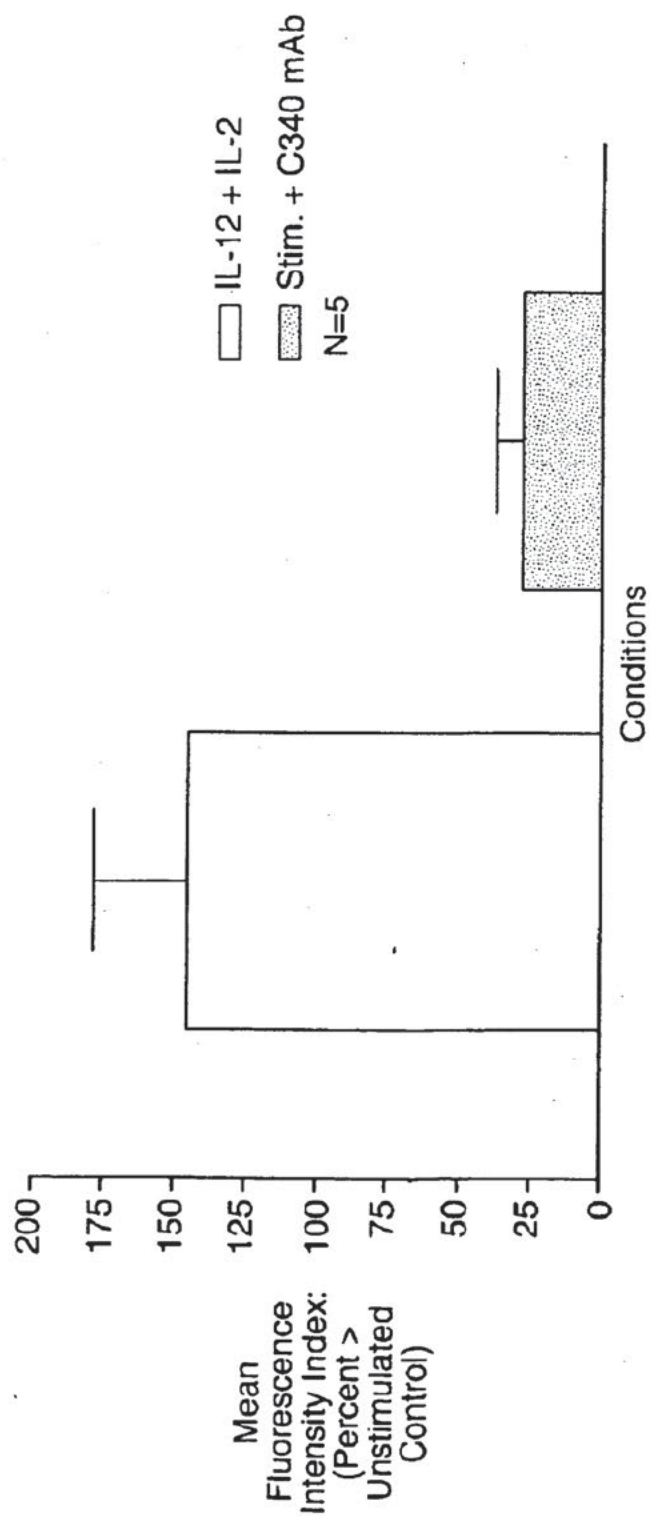
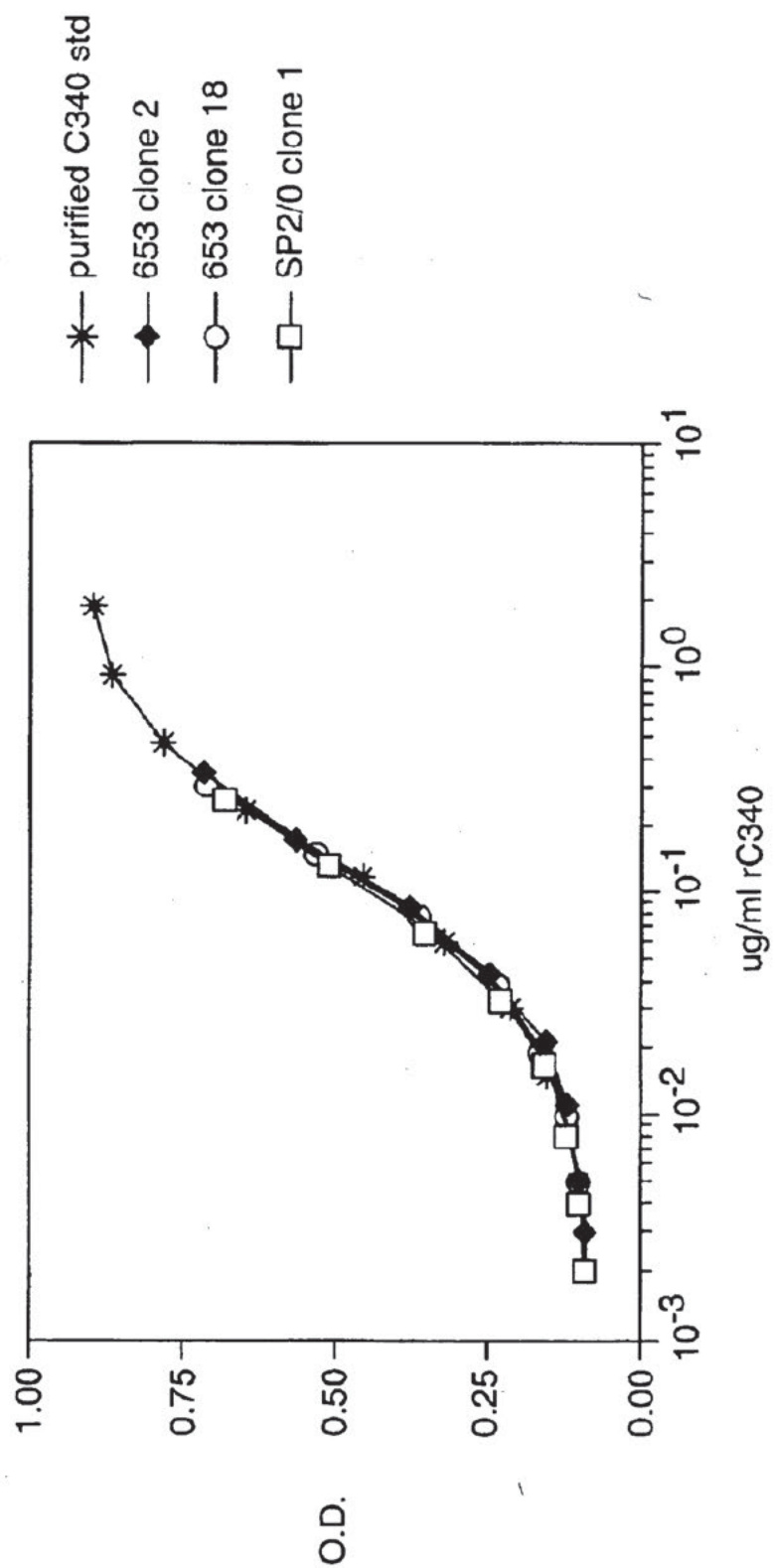
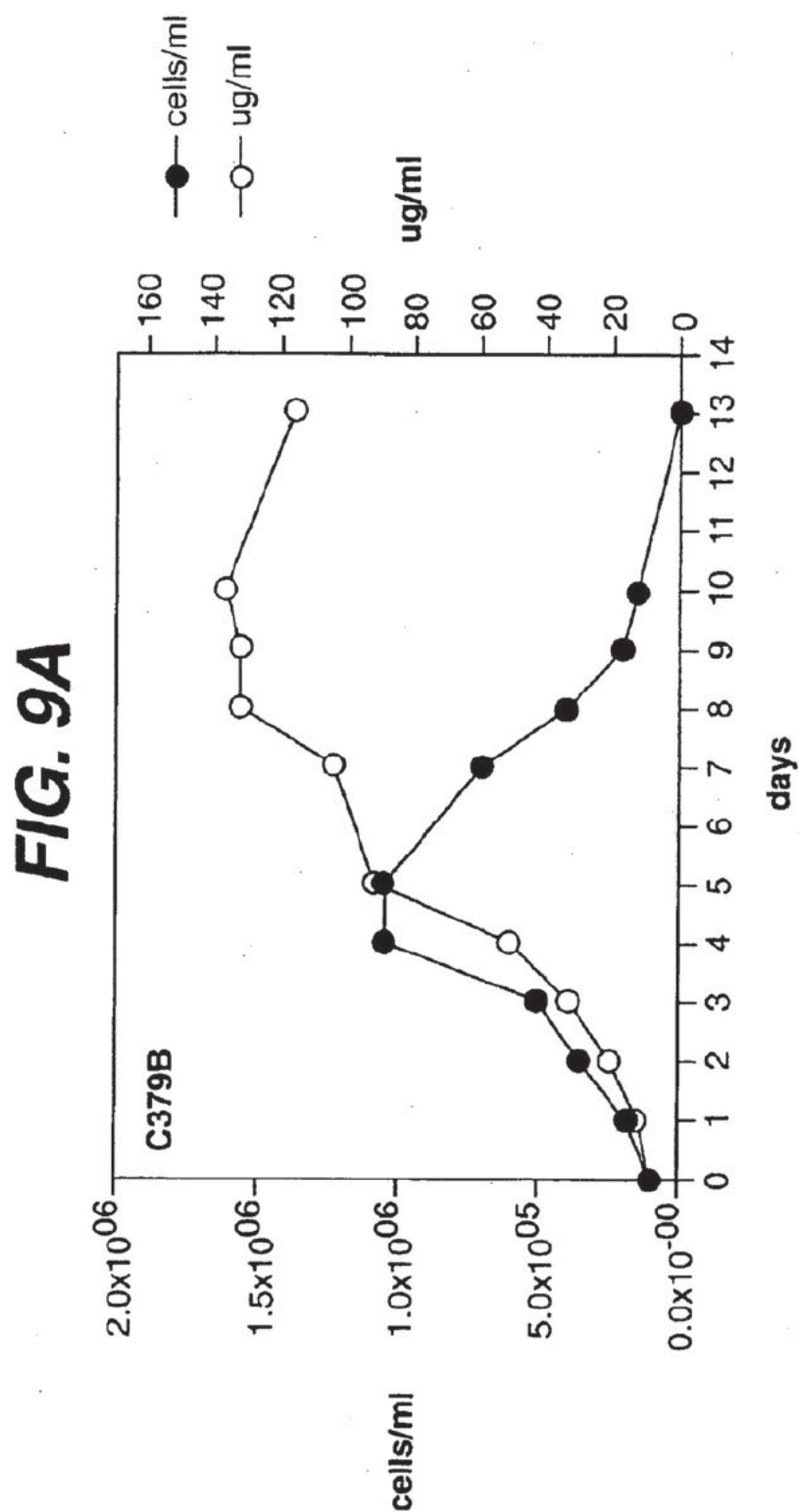
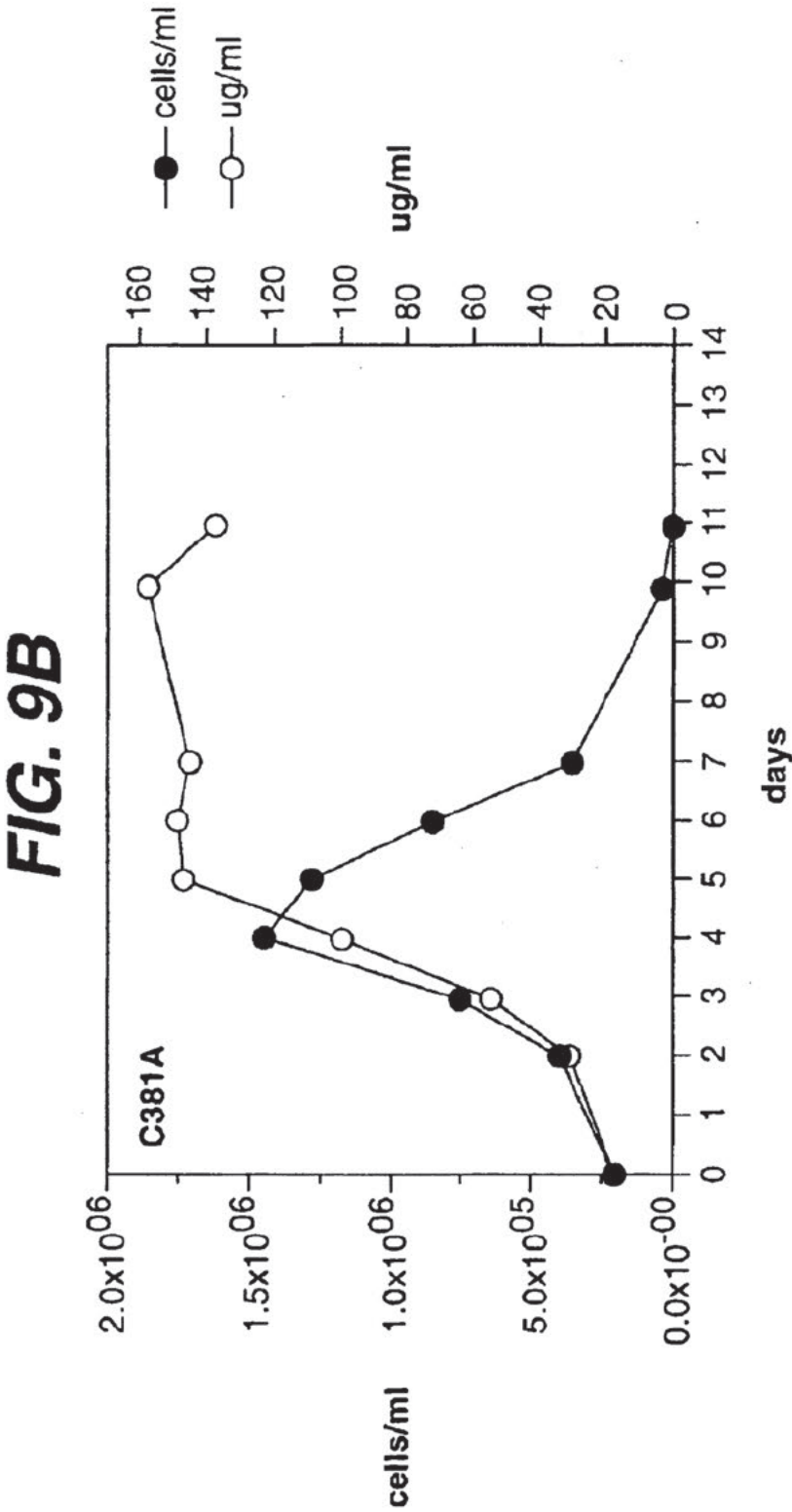
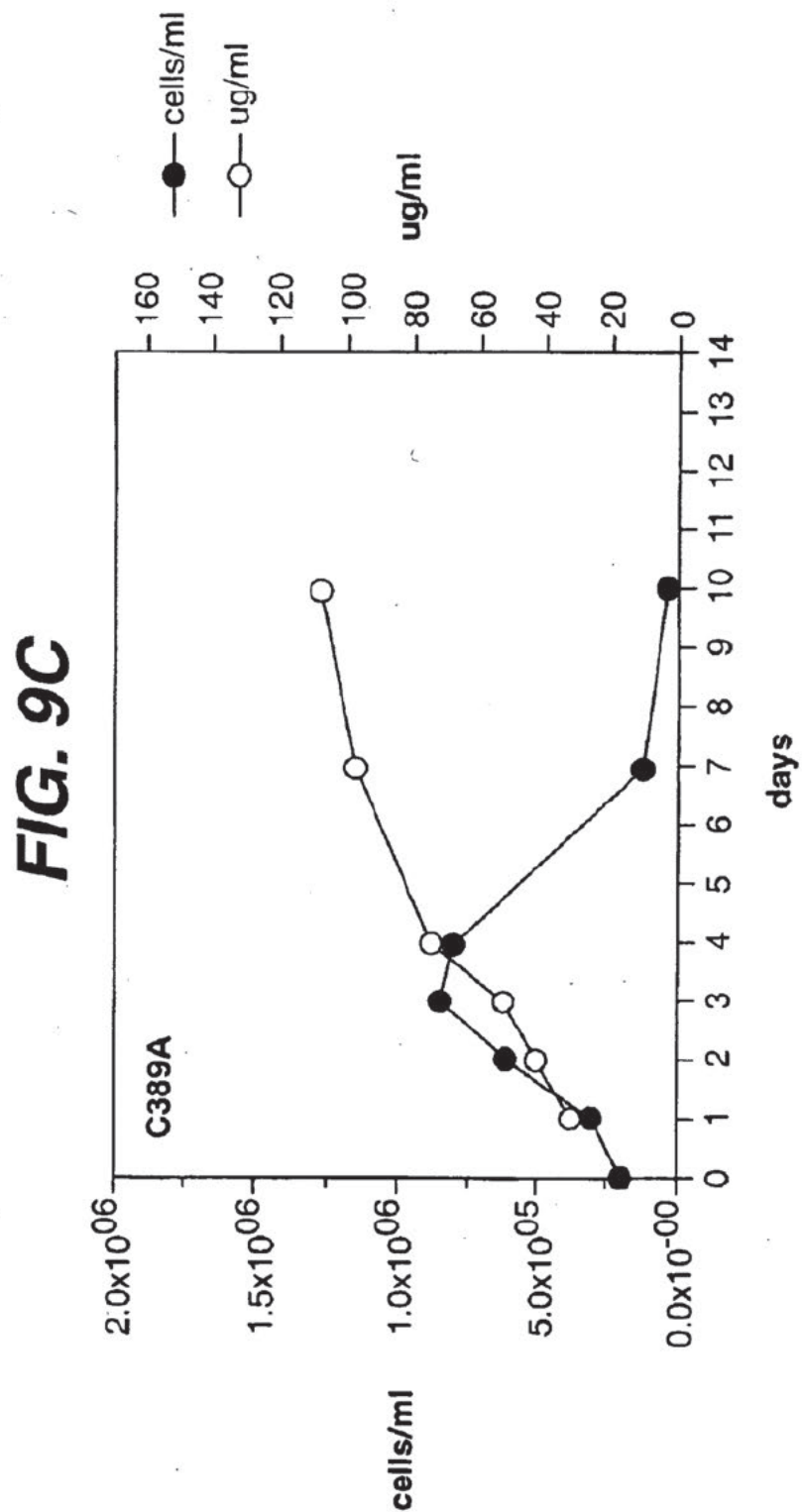
FIG. 7B

FIG. 8







ANTI-IL-12 ANTIBODIES AND COMPOSITIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

This application is based in part on, and claims priority to, U.S. Provisional Application Nos. 60/223,358 filed Aug. 7, 2000 and 60/236,827 filed Sep. 29, 2000, each of which is entirely incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to antibodies, including specified portions or variants, specific for at least one Interleukin-12 (IL-12) protein or fragment thereof, as well as nucleic acids encoding such anti-IL-12 antibodies, complementary nucleic acids, vectors, host cells, and methods of making and using thereof, including therapeutic formulations, administration and devices.

2. Related Art

Interleukin-12 (IL-12) is a heterodimeric cytokine consisting of glycosylated polypeptide chains of 35 and 40 kD which are disulfide bonded. The cytokine is synthesized and secreted by antigen presenting cells including dendritic cells, monocytes, macrophages, B cells, Langerhans cells and keratinocytes as well as natural killer (NK) cells. IL-12 mediates a variety of biological processes and has been referred to as NK cell stimulatory factor (NKSF), T-cell stimulating factor, cytotoxic T-lymphocyte maturation factor and EBV-transformed B-cell line factor (Curfs, J. H. A. J., et al., *Clinical Microbiology Reviews*, 10:742-780 (1997)).

Interleukin-12 can bind to the IL-12 receptor expressed on the plasma membrane of cells (e.g., T cells, NK cell), thereby altering (e.g., initiating, preventing) biological processes. For example, the binding of IL-12 to the IL-12 receptor can stimulate the proliferation of pre-activated T cells and NK cells, enhance the cytolytic activity of cytotoxic T cells (CTL), NK cells and LAK (lymphokine activated killer) cells, induce production of gamma interferon (IFN GAMMA) by T cells and NK cells and induce differentiation of naive Th0 cells into Th1 cells that produce IFN GAMMA and IL-2 (Trinchieri, G., *Annual Review of Immunology*, 13:251-276 (1995)). In particular, IL-12 is vital for the generation of cytolytic cells (e.g., NK, CTL) and for mounting a cellular immune response (e.g., a Th1 cell mediated immune response). Thus, IL-12 is critically important in the generation and regulation of both protective immunity (e.g., eradication of infections) and pathological immune responses (e.g., autoimmunity) (Hendrzak, J. A. and Brunda, M. J., *Laboratory Investigation*, 72:619-637 (1995)). Accordingly, an immune response (e.g., protective or pathogenic) can be enhanced, suppressed or prevented by manipulation of the biological activity of IL-12 in vivo, for example, by means of an antibody.

Non-human mammalian, chimeric, polyclonal (e.g., antisera) and/or monoclonal antibodies (Mabs) and fragments (e.g., proteolytic digestion or fusion protein products thereof) are potential therapeutic agents that are being investigated in some cases to attempt to treat certain diseases. However, such antibodies or fragments can elicit an immune response when administered to humans. Such an immune response can result in an immune complex-mediated clearance of the antibodies or fragments from the circulation, and make repeated administration unsuitable for therapy, thereby reducing the therapeutic benefit to the

patient and limiting the readministration of the antibody or fragment. For example, repeated administration of antibodies or fragments comprising non-human portions can lead to serum sickness and/or anaphylaxis. In order to avoid these and other problems, a number of approaches have been taken to reduce the immunogenicity of such antibodies and portions thereof, including chimerization and humanization, as well known in the art. These and other approaches, however, still can result in antibodies or fragments having some immunogenicity, low affinity, low avidity, or with problems in cell culture, scale up, production, and/or low yields. Thus, such antibodies or fragments can be less than ideally suited for manufacture or use as therapeutic proteins.

Accordingly, there is a need to provide anti-IL-12 antibodies or fragments that overcome one more of these problems, as well as improvements over known antibodies or fragments thereof.

SUMMARY OF THE INVENTION

The present invention provides isolated human, primate, rodent, mammalian, chimeric, humanized and/or CDR-grafted anti-IL-12 antibodies, immunoglobulins, cleavage products and other specified portions and variants thereof, as well as anti-IL-12 antibody compositions, encoding or complementary nucleic acids, vectors, host cells, compositions, formulations, devices, transgenic animals, transgenic plants, and methods of making and using thereof, as described and enabled herein, in combination with what is known in the art.

The present invention also provides at least one isolated anti-IL-12 antibody as described herein. An antibody according to the present invention includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, that can be incorporated into an antibody of the present invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, or any combination thereof, and the like.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding specific anti-IL-12 antibodies, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said anti-IL-12 antibody nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such antibody nucleic acids, vectors and/or host cells.

At least one antibody of the invention binds at least one specified epitope specific to at least one IL-12 protein, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of said protein, which epitope is preferably comprised of at least 1-5 amino acids of at least one portion thereof, such as but not limited to, at least one functional, extracellular, soluble, hydrophilic, external or cytoplasmic domain of said protein, or any portion thereof.

The at least one antibody can optionally comprise at least one specified portion of at least one complementarity determining region (CDR) (e.g., CDR1, CDR2 or CDR3 of the

heavy or light chain variable region) and/or at least one constant or variable framework region or any portion thereof. The at least one antibody amino acid sequence can further optionally comprise at least one specified substitution, insertion or deletion as described herein or as known in the art.

The present invention also provides at least one isolated anti-IL-12 antibody as described herein, wherein the antibody has at least one activity, such as, but not limited to: (i) inhibition of IL-12 induced IFN-gamma secretion; (ii) inhibition of LAK cell cytotoxicity; (iii) inhibition of IFN gamma mRNA transcription; (iv) inhibition of intracellular IFN gamma CD3+ cells; and/or (v) CD95 expression. See, e.g., Chan, et al., (1992) J. Immunol. 148(1): 92-98; Chan, et al., (1991) J. Exp. Med. 173(4): 869-79; Chehimi, et al., (1992) J. Exp. Med. 175(3): 789-96; Medvedev, et al., (1997) Cytokine 9(6): 394-404. A(n) anti-IL-12 antibody can thus be screened for a corresponding activity according to known methods, such as but not limited to at least one biological activity towards a IL-12 protein.

The present invention further provides at least one IL-12 anti-idiotypic antibody to at least one IL-12 antibody of the present invention. The anti-idiotypic antibody includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, that can be incorporated into an antibody of the present invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, and the like.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding at least one IL-12 anti-idiotypic antibody, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said IL-12 anti-idiotypic antibody encoding nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such anti-idiotypic antibody nucleic acids, vectors and/or host cells.

The present invention also provides at least one method for expressing at least one anti-IL-12 antibody, or IL-12 anti-idiotypic antibody, in a host cell, comprising culturing a host cell as described herein under conditions wherein at least one anti-IL-12 antibody is expressed in detectable and/or recoverable amounts.

The present invention also provides at least one composition comprising (a) an isolated anti-IL-12 antibody encoding nucleic acid and/or antibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known carriers or diluents. The composition can optionally further comprise at least one further compound, protein or composition.

The present invention further provides at least one anti-IL-12 antibody method or composition, for administering a therapeutically effective amount to modulate or treat at least one IL-12 related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as described herein.

The present invention also provides at least one composition, device and/or method of delivery of a thera-

peutically or prophylactically effective amount of at least one anti-IL-12 antibody, according to the present invention.

The present invention further provides at least one anti-IL-12 antibody method or composition, for diagnosing at least one IL-12 related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as described herein.

The present invention also provides at least one composition, device and/or method of delivery for diagnosing of at least one anti-IL-12 antibody, according to the present invention.

DESCRIPTION OF THE FIGURES

FIGS. 1A and 1B are graphs showing concentration-dependent binding of human anti-IL-12 mAbs to immobilized human IL-12. Anti-IL-12 antibodies were serially diluted in 1% BSA/PBS and incubated on rhIL-12 coated plates for 1 hour at 37° C. Plates were washed twice with 0.02% Tween 20 (polyoxyethylene (20) sorbitan monolaurate), 0.15M saline and then probed with horse radish peroxidase (HRP) labeled goat anti-human IgG kappa specific antibody for 1 hour at room temperature. Plates were again washed, developed with o-phenylenediamine (OPD) substrate and the optical density (OD) of each well was measured at 490 nm.

FIG. 2: Lanes from left to right in Figures A and B contain human IL-12, human IL-12 p40, murine IL-12, and prestained molecular weight markers. FIG. 2A shows bands stained from total protein. The primary bands in each lane are human IL-12 (75 kd), p40 human IL-12 (40 kd), and murine IL-12 (75 kd). FIG. 2B shows a western blot prepared from a gel identical to that shown in FIG. 2A. Blot was reacted with C340 followed by HRP labeled goat anti-human IgG and specifically detected human IL-12 (monomer and multimers) and human IL-12 p40 only. A control blot (not shown) reacted with HRP labeled goat anti-human IgG did not display any bands.

FIG. 3: Reverse transcription-PCR analysis of IFN γ gene expression in human PBL's treated with IL-2, IL-12, IL-2+IL-12 with and without anti-IL-12 antibody C340, 8.6.2, isotype control antibody. Total RNA was reverse transcribed, amplified by PCR using gene-specific primers. The level of β -actin mRNA in each sample was also determined which served as a control for mRNA integrity and content.

FIG. 4 is a histogram showing that human anti-IL-12 mAb (C340) inhibits production of interferon- γ (IFN γ) by monocyte depleted CD3+ peripheral blood mononuclear cells (PBMC) stimulated with IL-2 plus IL-12. PBMC were cultured for five hours in control media (no added cytokines), media supplemented with IL-12 (0.1 ng/ml) plus IL-2 (50 IU/ml) (IL-12/IL-2), control media containing mAb C340 (10 μ g/ml) and IL-12/IL-2 media containing mAb C340 (10 μ g/ml). Intracellular IFN γ was measured by two color immunostaining with CD3-PE and IFN γ -FITC. Data are shown for one donor.

FIG. 5 is a graph showing dose-dependent inhibition of IFN γ secretion by IL-2 plus IL-12 stimulated peripheral blood lymphocytes with two different lots of a human anti-IL-12 mAb (C340). Human PBL (8 $\times$ 10⁶/ml) were cultured for 24 hours with 10 U/ml IL-2, IL-2 plus 400 pg/ml IL-12, or IL-2 plus IL-12 and mAb C340 as indicated. The culture supernatants were removed and assayed for IFN γ by EIA.

FIG. 6 is a histogram showing dose-dependent inhibition of IL-12 plus IL-2 induced LAK cell cytotoxicity by a

human anti-IL-12 mAb (C340). LAK effector cells (human PBL, 8×10^6 /ml) were cultured for 24 hours with IL-12 (400 pg/ml) plus IL-2 (10 U/ml) and mAb C340 (5000 ng/ml or 50 ng/ml as indicated). The LAK effector cells were washed and cultured with ^{51}Cr labeled Raji target cells for four hours at an effector to target (E:T) ratio of 80:1, and the quantity of ^{51}Cr released into the media upon Raji cell lysis was measured. Results are expressed as the mean of three normal donors standard error. IL-12 positive control (IL-12) is effector cells incubated with IL-12 and without antibody. Background (BKGD) is effector cells incubated without IL-12 or antibody.

FIGS. 7A and 7B are histograms showing that IL-12 plus IL-2-induced expression of CD95 on CD3+ peripheral blood mononuclear cells is inhibited by human anti-IL-12 mAb (C340). PBMC were cultured for 72 hours in media containing 0.1 ng/ml IL-12 and a suboptimal dose of IL-2 (50 IU/ml) in the presence or absence of mAb C340 (10 μg /ml). CD95 expression was measured flow cytometry of cells stained with anti-CD95-FITC. Gating was performed using two-color analysis (CD3 or CD56-PE vs. CD95-FITC) and forward vs. orthogonal light scatter.

FIG. 8 is a graph showing that recombinant human anti-human IL-12 antibodies (rC340) bind to immobilized IL-12 in a manner that is indistinguishable from purified mAb C340. The concentration of rC340 in the supernatants of three rC340-producing recombinant cell lines was determined, and the supernatants were evaluated for IL-12 binding in an ELISA. Plates were coated with 2 μg /ml human IL-12 and incubated with purified mAb C340 from the original hybridoma (standard) or the supernatants of recombinant cell lines. IL-12-bound antibody was detected using alkaline phosphatase-conjugated goat anti-human IgG (heavy chain+light chain).

FIGS. 9A-9C are graphs showing growth kinetics and the quantity of antibody secreted by three independently-derived rC340-producing recombinant cell subclones (FIG. 9A, subclone C379B; FIG. 9B, subclone C381A; FIG. 9C, subclone C389A). Recombinant cells were seeded into T75 flasks at a starting density of 2×10^5 cells/ml in standard media. At various times, cells were resuspended and the number of live cells and the quantity (μg /ml) of rC340 in the media were determined.

DESCRIPTION OF THE INVENTION

The present invention provides isolated, recombinant and/or synthetic anti-IL-12 human, primate, rodent, mammalian, chimeric, humanized or CDR-grafted, antibodies and IL-12 anti-idiotypic antibodies thereto, as well as compositions and encoding nucleic acid molecules comprising at least one polynucleotide encoding at least one anti-IL-12 antibody or anti-idiotypic antibody. The present invention further includes, but is not limited to, methods of making and using such nucleic acids and antibodies and anti-idiotypic antibodies, including diagnostic and therapeutic compositions, methods and devices.

As used herein, an "anti-Interleukin-12 antibody," "anti-IL-12 antibody," "anti-IL-12 antibody portion," or "anti-IL-12 antibody fragment" and/or "anti-IL-12 antibody variant" and the like include any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof,

or at least one portion of an IL-12 receptor or binding protein, which can be incorporated into an antibody of the present invention. Such antibody optionally further affects a specific ligand, such as but not limited to where such antibody modulates, decreases, increases, antagonizes, agonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one IL-12 activity or binding, or with IL-12 receptor activity or binding, in vitro, in situ and/or in vivo. As a non-limiting example, a suitable anti-IL-12 antibody, specified portion or variant of the present invention can bind at least one IL-12, or specified portions, variants or domains thereof. A suitable anti-IL-12 antibody, specified portion, or variant can also optionally affect at least one of IL-12 activity or function, such as but not limited to, RNA, DNA or protein synthesis, IL-12 release, IL-12 receptor signaling, membrane IL-12 cleavage, IL-12 activity, IL-12 production and/or synthesis. The term "antibody" is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian IL-12. For example, antibody fragments capable of binding to IL-12 or portions thereof, including, but not limited to Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and F(ab')₂ (e.g., by pepsin digestion), fabc (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, Immunology, supra).

Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a F(ab')₂ heavy chain portion can be designed to include DNA sequences encoding the CH₁ domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques.

As used herein, the term "human antibody" refers to an antibody in which substantially every part of the protein (e.g., CDR, framework, C_L, C_H domains (e.g., C_H1, C_H2, C_H3), hinge, (V_L, V_H)) is substantially non-immunogenic in humans, with only minor sequence changes or variations. Similarly, antibodies designated primate (monkey, baboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pig, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies include any combination of the above. Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans or other species relative to non-modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies. For example, an Fv can comprise a linker peptide, such as two to about eight glycine

or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for at least one IL-12 protein, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, *Nature* 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, U.S. Pat. Nos. 6,210,668, 6,193,967, 6,132,992, 6,106,833, 6,060,285, 6,037,453, 6,010,902, 5,989,530, 5,959,084, 5,959,083, 5,932,448, 5,833,985, 5,821,333, 5,807,706, 5,643,759, 5,601,819, 5,582,996, 5,496,549, 4,676,980, WO 91/00360, WO 92/00373, EP 03089, Trautnecker et al., *EMBO J.* 10:3655 (1991), Suresh et al., *Methods in Enzymology* 121:210 (1986), each entirely incorporated herein by reference.

Anti-IL-12 antibodies (also termed IL-12 antibodies) useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to IL-12 and optionally and preferably having low toxicity. In particular, an antibody, specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low immunogenicity, is useful in the present invention. The antibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double antigen enzyme immunoassay) (see, e.g., Elliott et al., *Lancet* 344:1125-1127 (1994), entirely incorporated herein by reference).

Utility

The isolated nucleic acids of the present invention can be used for production of at least one anti-IL-12 antibody or specified variant thereof, which can be used to measure or effect in a cell, tissue, organ or animal (including mammals and humans), to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one IL-12 condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified IL-12 related condition.

Such a method can comprise administering an effective amount of a composition or a pharmaceutical composition

comprising at least one anti-IL-12 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation, prevention, or reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.001 to 500 mg/kg per single (e.g., bolus), multiple or continuous administration, or to achieve a serum concentration of 0.01-5000 µg/ml serum concentration per single, multiple or continuous administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

Citations

All publications or patents cited herein are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats. The following references are entirely incorporated herein by reference: Ausubel, et al., ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., NY, N.Y. (1987-2001); Sambrook, et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor, N.Y. (1989); Harlow and Lane, *Antibodies, a Laboratory Manual*, Cold Spring Harbor, N.Y. (1989); Colligan, et al., eds., *Current Protocols in Immunology*, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., *Current Protocols in Protein Science*, John Wiley & Sons, New York, N.Y., (1997-2001).

Antibodies of the Present Invention

At least one anti-IL-12 antibody of the present invention can be optionally produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as well known in the art. See, e.g., Ausubel, et al., ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., New York, N.Y. (1987-2001); Sambrook, et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor, N.Y. (1989); Harlow and Lane, *Antibodies, a Laboratory Manual*, Cold Spring Harbor, N.Y. (1989); Colligan, et al., eds., *Current Protocols in Immunology*, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., *Current Protocols in Protein Science*, John Wiley & Sons, New York, N.Y., (1997-2001), each entirely incorporated herein by reference.

Human antibodies that are specific for human IL-12 proteins or fragments thereof can be raised against an appropriate immunogenic antigen, such as isolated and/or IL-12 protein or a portion thereof (including synthetic molecules, such as synthetic peptides). Other specific or general mammalian antibodies can be similarly raised. Preparation of immunogenic antigens, and monoclonal antibody production can be performed using any suitable technique.

In one approach, a hybridoma is produced by fusing a suitable immortal cell line (e.g., a myeloma cell line such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1, L.5, >243, P3X63Ag8.653, Sp2 SA3, Sp2 MA1, Sp2 SS1, Sp2 SA5, U937, MLA 144, ACT IV, MOLT4, DA-1, JURKAT, WEHI, K-562, COS, RAJI, NIH 3T3, HL-60, MLA 144, NAMAIWA, NEURO 2A, or the like, or heteromyelomas, fusion products thereof, or any cell or fusion cell derived therefrom, or any other suitable cell line as known in the art. See, e.g., www.atcc.org, www.lifetech.com, and the like, with antibody producing cells, such as, but not limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell containing cells, or any other cells expressing heavy or light

chain constant or variable or framework or CDR sequences, either as endogenous or heterologous nucleic acid, as recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian, fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA, cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA, tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof. See, e.g., Ausubel, supra, and Colligan, Immunology, supra, chapter 2, entirely incorporated herein by reference.

Antibody producing cells can also be obtained from the peripheral blood or, preferably the spleen or lymph nodes, of humans or other suitable animals that have been immunized with the antigen of interest. Any other suitable host cell can also be used for expressing heterologous or endogenous nucleic acid encoding an antibody, specified fragment or variant thereof, of the present invention. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).

Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a peptide or protein library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, RNA, cDNA, or the like, display library; e.g., as available from Cambridge antibody Technologies, Cambridgeshire, UK; MorphoSys, Martinsreid/Planegg, DE; Biovation, Aberdeen, Scotland, UK; BioInvent, Lund, Sweden; Dyax Corp., Enzon, Affymax/Biosite; Xoma, Berkeley, Calif.; Ixsys. Sec., e.g., EP 368,684, PCT/GB91/01134; PCT/GB92/01755; PCT/GB92/002240; PCT/GB92/00883; PCT/GB93/00605; U.S. Ser. No. 08/350,260 (May 12, 1994); PCT/GB94/01422; PCT/GB94/02662; PCT/GB97/01835; (CAT/MRC); WO90/14443; WO90/14424; WO90/14430; PCT/US94/1234; WO92/18619; WO96/07754; (Scripps); EP 614 989 (MorphoSys); WO95/16027 (BioInvent); WO88/06630; WO90/3809 (Dyax); U.S. Pat. No. 4,704,692 (Enzon); PCT/US91/02989 (Affymax); WO89/06283; EP 371 998; EP 550 400; (Xoma); EP 229 046; PCT/US91/07149 (Ixsys); or stochastically generated peptides or proteins—U.S. Pat. Nos. 5,723,323, 5,763,192, 5,814,476, 5,817,483, 5,824, 514, 5,976,862, WO 86/05803, EP 590 689 (Ixsys, now Applied Molecular Evolution (AME), each entirely incorporated herein by reference) or that rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al., Microbiol. Immunol. 41:901-907 (1997); Sandhu et al., Crit. Rev. Biotechnol. 16:95-118 (1996); Eren et al., Immunol. 93:154-161 (1998), each entirely incorporated by reference as well as related patents and application) that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein. Such techniques, include, but are not limited to, ribosome display (Hanes et al., Proc. Natl. Acad. Sci. USA, 94:4937-4942 (May 1997); Hanes et al., Proc. Natl. Acad. Sci. USA, 95:14130-14135 (November 1998)); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (U.S. Pat. No. 5,627,052, Wen et al., J. Immunol. 17:887-892 (1987); Babcook et al., Proc. Natl. Acad. Sci. USA 93:7843-7848 (1996)); gel microdroplet and flow cytometry (Powell et al., Biotechnol. 8:333-337 (1990); One Cell Systems, Cambridge, Mass.; Gray et al., J. Imm. Meth. 182:155-163 (1995); Kenny et al., Bio/Technol.

13:787-790 (1995)); B-cell selection (Steenbakkers et al., Molec. Biol. Reports 19:125-134 (1994); Jonak et al., Progress Biotech, Vol. 5, In Vitro Immunization in Hybridoma Technology, Borrebaeck, ed., Elsevier Science Publishers B. V., Amsterdam, Netherlands (1988)).

Methods for engineering or humanizing non-human or human antibodies can also be used and are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid residues from a source which is non-human, e.g., but not limited to mouse, rat, rabbit, non-human primate or other mammal. These human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence. Known human Ig sequences are disclosed, e.g., www.ncbi.nlm.nih.gov/entrez/query.fcgi; www.atcc.org/phage/hdb.html; www.sciquest.com/; www.abcam.com/; www.antibodyresource.com/onlinecomp.html; www.public.iastate.edu/~pedro/research_tools.html; www.mgen.uni-heidelberg.de/SD/IT/IT.html; www.whfreeman.com/immunology/CH05/kuby05.htm; www.library.thinkquest.org/12429/Immune/Antibody.html; www.hhmi.org/grants/lectures/1996/vlab/; www.path.cam.ac.uk/~mrc7/mikeimages.html; www.antibodyresource.com/; mcb.harvard.edu/BioLinks/Immunology.html; www.immunologylink.com/; pathbox.wustl.edu/~hcenter/index.html; www.biotech.ufl.edu/~hcl/; www.pebio.com/pa/340913/340913.html; www.nal.usda.gov/awic/pubs/antibody/; www.mchime-u.ac.jp/~yasuhito/Elisa.html; www.biodesign.com/table.asp; www.icnet.uk/axp/facs/davies/links.html; www.biotech.ufl.edu/~fccl/protocol.html; www.isac-net.org/sites_geo.html; aximtl.imt.uni-marburg.de/~rek/AEPStart.html; baserv.uci.kun.nl/~jraats/links1.html; www.recab.uni-hd.de/immuno.bmc.nwu.edu/; www.mrc-cpe.cam.ac.uk/imt-doc/public/INTRO.html; www.ibt.unam.mx/vir/V_mice.html; imgt.cnusc.fr:8104/; www.biochem.ucl.ac.uk/~martin/abs/index.html; antibody.bath.ac.uk/; abgen.cvm.tamu.edu/lab/wwwabgen.html; www.unizh.ch/~honegger/AHOseminar/Slide01.html; www.cryst.bbk.ac.uk/~ubcg07s/; www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm; www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html; www.ibt.unam.mx/vir/structure/stat_aim.html; www.biosci.missouri.edu/smithgp/index.html; www.cryst.bioc.cam.ac.uk/~fmolina/Web-pages/Pept/spottech.html; www.jerini.de/fr/_products.htm; www.patents.ibm.com/ibm.html. Kabat et al., Sequences of Proteins of Immunological Interest, U.S. Dept. Health (1983), each entirely incorporated herein by reference. Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art. Generally part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions are replaced with human or other amino acids. Antibodies can also optionally be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, humanized antibodies can be optionally prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin