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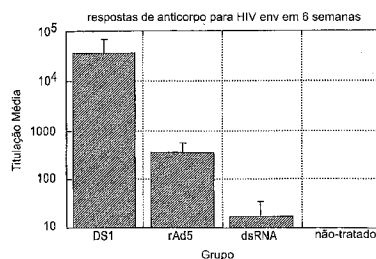
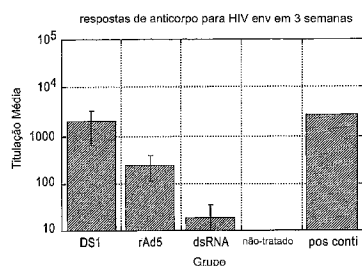
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(57) Resumo: VETORES ADENOVIRAIS QUIMÉRICOS. A presente invenção refere-se a vetores adenovirais quiméricos e métodos para uso dos vetores para induzir uma resposta imune a um anti- geno de interesse.



Relatório Descritivo da Patente de Invenção para "VETORES
ADENOVIRAIS QUIMÉRICOS".

REFERÊNCIAS CRUZADAS A PEDIDOS DE PATENTE RELACIONADOS

O presente pedido de patente reivindica prioridade ao Pedido de
5 Patente Provisório dos Estados Unidos N° 60/778.026, depositado em 28 de
fevereiro de 2006, Pedido de Patente Provisório dos Estados Unidos N°
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dos N° 60/846.658, depositado em 22 de setembro de 2006, e Pedido de
Patente Provisório dos Estados Unidos N° 60/848.195, depositado em 28 de
setembro de 2006), as descrições dos quais são, desse modo, incorporadas
por referência em sua totalidade para todas as propostas.

15 DECLARAÇÃO AOS DIREITOS A INVENÇÃO FEITA SOB PESQUISA E
DESENVOLVIMENTO FEDERALMENTE PATROCINADOS

Não aplicável.

Antecedentes da Invenção

As vacinas são um meio importante para prevenir e/ou tratar um
20 número de doenças e enfermidades (por exemplo, infecção viral, infecção
bacterial, e câncer). As vacinas baseadas em ácido nucléico têm várias van-
tagens sobre vacinas de proteína ou vacinas vivas atenuadas. A introdução
de um ácido nucléico que expressa um antígeno em uma célula-alvo permite
rápido desenvolvimento de vacina que gera uma resposta imune contra um
25 antígeno de interesse. Para vacinas de proteína, um método eficaz e eficien-
te de purificação de proteína necessita ser desenvolvido cada vez que uma
nova vacina é criada. Para vacinas vivas, um método de atenuação necessi-
ta ser identificado que não cessa completamente o crescimento da patoge-
nia, ainda se comprovando ser completamente seguro em seres humanos.
30 O desenvolvimento de metodologias de purificação e atenuação são proces-
sos de consumo de tempo extremo. Em contraste, muitas vacinas baseadas
em ácido nucléico podem ser fabricadas muito rapidamente usando-se as

mesmas técnicas de fabricação cada vez com apenas uma mudança rápida no ácido nucléico que codifica o antígeno de interesse. A replicação incompetente do adenovírus é um sistema de vacina baseado em ácido que é rápida, prognóstica e não-custosamente feita em alta titulação [Polo, J.M. e Dubensky, T. W., Jr., *Drug Discov Today*, 7(13), 719-727 (2002)]. Contudo, a eficiência da resposta específica de antígeno em seguida a administração de vetores adenovirais conhecido na técnica é baixa. Desse modo, existe uma necessidade na técnica de novos vetores adenovirais que possam ser usados para induzir eficientemente uma resposta imune contra um antígeno de interesse. A presente invenção satisfaz estas e outras necessidades.

Sumário da Invenção

A presente invenção refere-se a vetores adenovirais quiméricos compreendendo ácidos nucléicos que codificam um polipeptídeo heterólogo, e métodos para indução de uma resposta imune contra o polipeptídeo heterólogo.

Uma concretização da invenção proporciona vetores de expressão adenovirais quiméricos compreendendo um cassete de expressão compreendendo (a) um primeiro promotor operavelmente ligado a um ácido nucléico que codifica um agonístico de receptor-3 (TLR-3) similar a toll; e (b) um segundo promotor operavelmente ligado a um ácido nucléico que codifica um polipeptídeo heterólogo. Em algumas concretizações, o ácido nucléico que codifica o agonístico TLR compreende uma seqüência selecionada a partir de SEQ ID N^{os}: 3, 7, 8, 9, 10, 11 e 12. Em algumas concretizações, o polipeptídeo heterólogo é selecionado de um polipeptídeo envelope de HIV (por exemplo, gp41, gp120 e gp160), e polipeptídeo de gripe HA. Em algumas concretizações, o primeiro promotor e o segundo promotor são os mesmos. Em algumas concretizações, as primeira e segunda concretizações são diferentes. Em algumas concretizações, os promotores são selecionados a partir do promotor beta actinae o promotor de CVM. A invenção também proporciona composições imunogênicas compreendendo o vetor de expressão.

Uma concretização adicional da invenção proporciona métodos

de indução de uma resposta imune contra o polipeptídeo heterólogo pela administração de uma quantidade imunologicamente eficaz das composições a um indivíduo mamífero (por exemplo, um roedor, tal como um camundongo, um rato, ou porquinho-da-índia, ou um primata, tal como um chimpanzé, uma macaca rhesus, ou um ser humano). Em algumas concretizações, o vetor é administrado via qualquer via não-parenteral (por exemplo, oral, intranasal e mucosalmente). Em algumas concretizações, o polipeptídeo heterólogo é expresso em uma célula selecionada a partir de uma célula dendrítica, uma célula de microdobra, e uma célula epitelial intestinal.

Uma concretização adicional da invenção proporciona composições imunogênicas compreendendo: (a) um vetor de expressão adenoviral quimérico compreendendo um promotor operavelmente ligado a um ácido nucléico que codifica um polipeptídeo heterólogo; (b) um agonístico TLR-3 (por exemplo, um dsRNA). Em algumas concretizações, o agonístico TLR-3 é codificado por um ácido nucléico. A invenção também proporciona métodos de indução de uma resposta imune pela administração das composições a um indivíduo mamífero (por exemplo, um roedor, tal como um camundongo, um rato, ou um porquinho-da-índia, ou um primata, tal como um chimpanzé, uma macaca rhesus, ou um humano), via qualquer via não-parenteral (por exemplo, oral, intranasal, ou mucosal).

Outra concretização da invenção proporciona um ácido nucléico isolado compreendendo a sequência colocada em SEQ ID N^{os}: 1, 2, 6, 7, 13, 14, 15, 16 ou 17.

Breve Descrição dos Desenhos

A Figura 1 ilustra dados demonstrando que um vetor adenoviral quimérico da invenção (isto é, DS1), em combinação com um agonístico TLR-3, é mais eficaz do que um vetor adenoviral padrão (isto é, rAd5) na indução de uma resposta imune específica de antígeno em seguida a distribuição do vetor oral. A Figura 1A ilustra dados representando a titulação de anticorpo para proteína envelope de HIV (isto é, gp120) em 3 semanas em seguida a distribuição oral dos vetores adenovirais. A Figura 1B ilustram dados representando a titulação de anticorpo para proteína envelope de HIV

(isto é, gp120) em 6 semanas em seguida a distribuição oral dos vetores adenovirais.

A Figura 2 ilustra dados demonstrando que um vetor adenoviral quimérico da invenção (isto é, DS1b ou DS1c), em combinação com um agonístico TLR-3, é mais eficaz na indução de uma resposta imune específica de antígeno do que um vetor adenoviral padrão (isto é, rAd5). A Figura 2A ilustram dados representando a titulação de anti-GFP IgG em 3 semanas em seguida a distribuição oral dos vetores. A Figura 2B ilustram dados representando a resposta de CD8+ célula T para GFP em 10 semanas em seguida a administração do vetor em 0, 4 e 8 semanas. A Figura 2C ilustra dados representando a titulação de anticorpo anti-HA em 3 semanas em seguida a administração oral dos vetores.

A Figura 3 ilustra dados demonstrando que os vetores adenovirais quiméricos da invenção são superiores para indução de respostas imunes quando administrados não-parenteralmente. A Figura 3A ilustram dados representando a titulação de anticorpo anti-gp 120 3 semanas em seguida a administração intramuscular de DS1. A Figura 3B ilustra dados representando a titulação de anticorpo anti-HA três semanas em seguida a administração intranasal de DS1c.

A Figura 4 ilustra dados demonstrando que os agonísticos TLR-3 ligante expressos podem induzir ativação de células apresentando antígeno. A Figura 4A ilustra dados representando ativação de célula dendrítica pelo dsRNA ILR-3 agonístico luc1 expresso. A Figura 4B ilustra dados representando a ativação de célula dendrítica pelos dsRNA TLR-3 agonísticos luc1 e m1.

A Figura 5 é uma ilustração gráfica dos vetores adenovirais quiméricos da invenção, isto é, vetores adenovirais quiméricos compreendendo ácidos nucleicos que codificam agonísticos ds RNA TLR-3.

A Figura 6 ilustra dados demonstrando que os vetores adenovirais quiméricos da invenção são eficazes na indução de uma resposta imune específica de antígeno em seguida a distribuição oral. A Figura 6 ilustra dados representando titulação de anticorpo anti-gp120 3 semanas em seguida

a administração oral de um adenoviral quimérico compreendendo seqüência de ácido nucléico que codifica o dsRNA TLR-3 agonístico luc1.

A Figura 7 ilustra dados demonstrando que agonísticos TLR-7/8 têm eficiência pobre na indução de uma resposta imune específica de antígeno.

A Figura 8 ilustra dados demonstrando que os vetores adenovirais quiméricos da invenção são eficazes na indução de uma resposta imune específica de antígeno em seguida a distribuição oral. A Figura 8A ilustra dados representando titulação de anticorpo anti-HA 4 semanas em seguida a administração oral de um adenoviral quimérico compreendendo uma seqüência de ácido nucléico que codifica o dsRNA TLR-3 agonístico luc1. A Figura 8B ilustra dados representando a titulação de anticorpo anti-HA 4 semanas ou 7 semanas em seguida a administração de um adenoviral quimérico compreendendo uma seqüência de ácido nucléico que codifica o dsRNA TLR-3 agonístico luc1. A Figura 8C ilustra dados representando titulação de anticorpo anti-HA 3 semanas em seguida a administração oral ou administração intranasal de um adenoviral quimérico compreendendo uma seqüência de ácido nucléico que codifica o dsRNA TLR-3 agonístico luc1.

Breve Descrição das Seqüências

SEQ ID Nº:1 coloca a seqüência de nucleotídeo para o vetor adenoviral quimérico DS1.

SEQ ID Nº:2 coloca a seqüência de nucleotídeo para o vetor adenoviral quimérico DS2.

SEQ ID Nº:3 coloca uma seqüência de nucleotídeo que codifica um agonístico TLR-3.

SEQ ID Nº:4 coloca uma seqüência de nucleotídeo que codifica um agonístico TLR-3.

SEQ ID Nº:5 coloca uma seqüência de nucleotídeo que codifica um agonístico TLR-3.

SEQ ID Nº:6 coloca uma seqüência de nucleotídeo para um vetor adenoviral quimérico compreendendo um ácido nucléico que codifica HA de gripe e um ácido nucléico que codifica um agonístico TLR-3 (luc), no qual

o HA de gripe e o agonístico TLR-3 estão na mesma orientação.

SEQ ID Nº:7 coloca uma sequência de nucleotídeo para um vetor adenoviral quimérico compreendendo um ácido nucléico que codifica HA de gripe e um ácido nucléico que codifica um agonístico TLR-3 (luc), no qual
5 o HA de gripe e o agonístico TLR-3 estão na orientação oposta.

SEQ ID Nº:8 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto. Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

10 SEQ ID Nº:9 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto (g1). Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

SEQ ID Nº:10 coloca uma sequência de nucleotídeo que codifica
15 ca um agonístico RNA TLR-3 em forma de grampo de cabelo curto (luc). Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

SEQ ID Nº:11 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto (m1).
20 Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

SEQ ID Nº:12 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto. Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.
25

SEQ ID Nº:13 coloca a sequência de nucleotídeo para o vetor adenoviral quimérico DS1c. A sequência compreende um nucleotídeo que codifica HA(PR8/34).

SEQ ID Nº:14 coloca a sequência de nucleotídeo para o vetor
30 adenoviral quimérico DS2beta-luc. O vetor compreende uma sequência que codifica o agonístico TLR-3 luc sob o controle do promotor beta actin. O vetor também compreende locais de clonagem abertos para inserção de se-

seqüência(s) de ácido nucléico que codificam o antígeno de interesse.

SEQ ID Nº:15 coloca a seqüência de nucleotídeo para o vetor adenoviral quimérico DS2beta-luc. O vetor compreende uma seqüência que codifica o agonístico TLR-3 luc sob o controle do promotor de CMV. O vetor
5 também compreende locais de clonagem abertos para inserção de seqüência(s) de ácido nucléico que codificam o antígeno de interesse.

SEQ ID Nº:16 coloca a seqüência de nucleotídeo para o vetor pshuttle compreendendo uma seqüência de ácido nucléico que codifica o agonístico TLR-3 luc sob o controle do promotor de CMV e uma seqüência
10 de ácido nucléico que codifica HA (gripe aviária) sob o controle de um promotor de CMV separado.

SEQ ID Nº:17 coloca a seqüência de nucleotídeo para o vetor adenoviral quimérico ND1.1 214. O ácido nucléico que codifica o antígeno heterólogo está em um texto em negrito, e é flanqueado por um local de re-
15 conhecimento ClaI na extremidade 5', e um local de reconhecimento Not 1 na extremidade 3'. A seqüência de ácido nucléico que codifica os agonísticos TLR-3 está em itálico, com a seqüência articuladora em negrito.

Descrição Detalhada da Invenção

I. Introdução

20 A presente invenção proporciona novos vetores adenovirais quiméricos que podem ser administrados não-parenteralmente para induzir uma resposta imune contra um antígeno de interesse. Os vetores adenovirais quiméricos da invenção compreendem um ácido nucléico que codifica um polipeptídeo heterólogo, e um ácido nucléico que codifica um agonístico
25 TLR-3. Os vetores adenovirais quiméricos induzem respostas imunes fortes e eficazes específicas para o polipeptídeo heterólogo, particularmente quando aplicado via uma rota não-parenteral (por exemplo, oral, intranasal, ou mucosamente).

A invenção é baseada na descoberta surpreendente que a
30 administração de agonísticos dsRNA TLR-3 são adjuvantes específicos quando administrados em conjunto com vetores virais. De fato, o uso de dsRNA como um adjuvante para vetores virais seria contra-intuitivo,

considerando-se que a maior utilidade proposta do dsRNA mimético poli I:C era um agente antiviral [Nemes, *et al.*, *Proc. Soc Exp Biol Med.* (1969) 132:776; Schafer *et al*, *Nature* (1970) 226:449; Fenje, *et al.*, *Nature* (1970) 226:171].

5 II. Definições

O termo "quimérico" ou "recombinante", conforme aqui usado, com referência a, por exemplo, um ácido nucléico, proteína, ou vetor, indica que o ácido nucléico, proteína ou vetor, foi modificado pela introdução de um ácido nucléico ou proteína heteróloga, ou a alteração de um ácido nucléico ou proteína nativa. Desse modo, por exemplo, vetores quiméricos e recombinantes incluem seqüências de ácido nucléico que não são encontradas dentro da forma nativa (não-quimérica ou não-recombinante) do vetor. Um vetor de expressão adenoviral quimérico se refere a um vetor de expressão adenoviral compreendendo uma seqüência ácido nucléico que codifica um polipeptídeo heterólogo.

Um "vetor de expressão" é um constructo de ácido nucléico, gerado recombinante ou sinteticamente, com uma série de elementos de ácido nucléico específicos que permitem transcrição de um ácido nucléico particular em uma célula hospedeira. O vetor de expressão pode ser parte de um plasmídeo, vírus, ou fragmento de ácido nucléico. Tipicamente, o vetor de expressão inclui um ácido nucléico a ser transcrito operavelmente ligado a um promotor.

Os termos "promotor" e "seqüência de controle de expressão" são aqui usados para se referir a uma série de seqüências de controle de ácido nucléico que direcionam transcrição de uma ácido nucléico. Conforme aqui usado, um promotor inclui seqüências de ácido nucléico necessárias perto do local de partida de transcrição, tais como, no caso de um promotor tipo polimerase II, um elemento TATA. Um promotor também inclui opcionalmente elementos intensificadores ou repressores distais, que podem estar localizados tanto quanto vários milhares de pares de base a partir do local de partida de transcrição. Os promotores incluem promotores constitutivos e inducíveis. Um promotor "constitutivo" é um promotor que é ativo sob

5 muitas condições ambientais e de desenvolvimento. Um promotor "inducível" é um promotor que é ativo sob regulação ambiental e de desenvolvimento. O termo "operavelmente ligado" se refere a uma ligação funcional entre uma seqüência de controle de expressão de ácido nucléico (tal como um promotor, uma série de locais de ligação de fator de transcrição), e uma segunda seqüência de ácido nucléico, no qual a seqüência de controle de expressão direciona transcrição do ácido nucléico correspondente à segunda seqüência.

10 O termo "agonístico TLR" ou "agonístico receptor similar a Troll", conforme aqui usado, se refere a um composto que liga e estimula um receptor similar a Troll, incluindo, por exemplo, TLR-2, TLR-3, TLR-6, TLR-7, ou TLR-8. Os agonísticos TLR são revistos em MacKichan, *IAVI Report*. 9:1-5 (2005) e Abreu *et al.*, *J. Immunol*, 174(8), 4453-4460 (2005). Os agonísticos incluem transdução de sinal em seguida a ligação a seu receptor.

15 O termo "agonístico TLR-3" ou "agonístico receptor 3 similar a Troll", conforme aqui usado, se refere a um composto que liga e estimula o TLR-3. Os agonísticos TLR-3 foram identificados incluindo RNA de filamento duplo, dsRNA viralmente derivado, vários análogos quimicamente sintetizados para RNA de filamento duplo incluindo ácido (poli I:C), poliinosinapolicitidílico – ácido (poli A:U) poliadenílico poliuridílico e (poli I:poli C, e anticorpos (ou reticulação de anticorpos) para TLR-3 que conduz a produção de IFN-beta [Matsumoto, M, *et al.*, *Biochem Biophys Res Commun* 24:1364 (2002), de Bouteiller, *et al.*, *J Biol Chem* 18:38133-45 (2005)]. Os agonísticos TLR-3 também incluem dsRNA expresso (por exemplo, dsRNA codificado por um ácido nucléico compreendendo um seqüência colocada em SEQ ID NOS: 3, 7, 8, 9, 10, 11 ou 12).

30 O termo "agonístico TLR-7/8" ou agonístico 7/8 receptor similar a Toll", conforme aqui usado, se refere a um composto que liga e estimula os receptores TLR-7 ou TLR-8; estes receptores reconhecem vários dos mesmos ligantes. Vários agonísticos TLR-7/8 foram identificados tais como um RNA viral de trançado simples, imiquimod, loxribina, ácido poliuridílico, ou resiquimod.

O termo "heterólogo" quando usado com referência a porções de um ácido nucléico indica que o ácido nucléico compreende duas ou mais subsequências que não são encontradas no mesmo relacionamento uma em relação à outra na natureza. Por exemplo, o ácido nucléico é típica e recombinantemente produzido, tendo duas ou mais sequências de genes não-relacionadas para produzir um novo ácido nucléico funcional, por exemplo, um promotor de uma fonte, e uma região de codificação de outra fonte. Similarmemente, uma proteína heteróloga indica que a proteína compreende duas ou mais subsequências que não são encontradas no mesmo relacionamento uma em relação à outra na natureza (por exemplo, uma proteína de fusão).

Os termos "ácido nucléico" e "polinucleotídeo" são usados permutavelmente aqui para se referirem a deoxirribonucleotídeos e ribonucleotídeos e polímeros destes na forma de filamento simples ou duplo. O termo envolve ácidos nucléicos contendo análogos de nucleotídeo conhecidos, ou resíduos de estruturas principais modificadas ou ligações, que são sintéticas, que ocorrem naturalmente, e não ocorrem naturalmente, que têm propriedades de ligação similares como o ácido nucléico de referência, e que são metabolizados em uma maneira similar aos nucleotídeos de referência. Exemplos de tais análogos incluem, sem limitação, fosforotioatos, fosforamidatos, fosfonatos de metila, fosfonatos de quiral-metila, ribonucleotídeos de 2-O-metila, ácidos peptídeo-nucléico (PNAs).

A menos que de outro modo indicado, uma sequência de ácido nucléico particular também envolve variantes conservativamente modificadas desta (por exemplo, substituições de códon degeneradas) e sequências complementares, bem, como a sequência explicitamente indicada. Especificamente, substituições de códon degeneradas podem ser alcançadas pela geração de sequências nas quais a terceira posição de um ou mais (ou todos) códons é substituída com base de mistura e/ou resíduos de deoxinosina (Batzer *et al.*, Nucleic Acid REs. 19:5081 (1991); Ohtsuka *et al.*, J. Biol. Chem. 260:2605-2608 (1985); Rossolini *et al.*, Mol. Cell. Probes 8:91-98 (1994)). O termo ácido nucléico é usado permutavelmente com gene, cDNA, mRNA, oligonucleotídeo, e polinucleotídeo.

Antígeno se refere a uma proteína ou parte de uma cadeia de polipeptídeo que pode ser reconhecida por receptores de célula T e/ou anticorpos. Tipicamente, os antígenos são derivados de proteínas bacteriais, virais ou fungais.

- 5 Uma "dose ou quantidade imunologicamente eficaz" das composições da presente invenção é uma quantidade que induz ou modula uma resposta imune específica para o polipeptídeo heterólogo. As respostas imunes incluem respostas imunes humorais e respostas imunes mediadas por célula. Uma composição imunogênica pode ser usada terapêutica ou profilaticamente para tratar ou prevenir doença em qualquer estágio.

"Respostas imunes humorais" são mediadas por componentes livres de célula do sangue, isto é, plasma ou soro; transferência do soro ou plasma de um indivíduo para outra imunidade de transferências.

- 15 "Respostas imunes mediadas por célula" são mediadas por linfócitos específicos de antígeno; transferência dos linfócitos específicos de antígeno de um indivíduo para outra imunidade de transferências.

- Uma "dose terapêutica" ou "quantidade terapeuticamente eficaz" ou "quantidade eficaz" de um vetor adenoviral quimérico, ou uma composição compreendendo um vetor adenoviral quimérico, é uma quantidade do
20 vetor ou composição compreendendo o vetor que previne, alivia, abate, ou reduz a severidade de sintomas de doenças e enfermidades associadas com a fonte do polipeptídeo heterólogo (por exemplo, um vírus, uma bactéria, um parasita, ou um câncer).

- Anticorpo se refere a um polipeptídeo codificado por um gene de
25 imunoglobulina ou fragmentos deste que se liga especificamente e reconhece um antígeno. Os genes de imunoglobulina reconhecidos incluem genes de região constante kappa, lâmbda, alfa, gama, delta, épsilon e mu, bem como genes de região variável de imunoglobulina miríade. As cadeias leves são classificadas como ou kappa ou lâmbda. As cadeias pesadas são classifi-
30 cadas como gama, mu, alfa, delta, ou épsilon, que, por sua vez, define as classes de imunoglobulina IgG, IgM, IgA, IgD e IgE, respectivamente.

Células T se referem a uma classe particular de linfócitos que

expressam um receptor específico (receptor de célula T) codificado por uma família de genes. Os genes de receptor de célula T reconhecidos incluem receptores alfa, beta, delta, e gama, de loci, e os receptores de célula T (mas não universalmente) tipicamente reconhecem uma combinação de MHC mais um peptídeo curto.

Resposta imune adaptativa se refere a reconhecimento de célula T/de anticorpo de antígeno.

Células de apresentação de antígeno (APCs), conforme aqui usadas, se referem a células que são capazes de apresentar peptídeos imunogênicos ou fragmentos destes de células T para ativar ou aumentar uma resposta imune. APCs incluem células dendríticas, células B, monócito e outras células que podem ser projetadas para serem APCs eficientes. Tais células podem, mas não necessitam, serem geneticamente modificadas para aumentar a capacidade de apresentação de antígeno, para aperfeiçoar a ativação e/ou manutenção da resposta de célula T, para ter efeitos antitumor por si, e/ou para ser imunologicamente compatível com o recebedor (isto é, haplótipo HLA equiparado). APCs podem ser isolados de qualquer de uma variedade de fluidos biológicos e órgãos incluindo tutano de osso, sangue periférico, tumor e tecidos peritumorais, e podem ser células autólogas, alogênicas, singenéticas ou xenogênicas. APCs tipicamente utilizam um receptor a partir do local de maior histocompatibilidade (MHC) para apresentar polipeptídeos curtos para células T.

Adjuvante é um intensificador de resposta imune não-específica. Adjuvantes adequados incluem, por exemplo, toxina de cólera, monosfífil lipídeo A (MLP), Adjuvante Completo de Freund, Adjuvante Incompleto de Freund, Quil A, e Al(OH). Os adjuvantes podem também ser aquelas substâncias que causam ativação de APC e apresentação aumentada de células T através de moléculas de sinalização secundárias. Exemplos de receptores similares a Toll que reconhecem RNA de filamento duplo, flagelante bacteriana, LPS, CpG DNA, e lipopeptídeo bacteriano (Revisto recentemente em [Abreu *et al.*, *J. Immunol*, 174(8), 4453-4460 (2005)]).

Os termos "polipeptídeo", "peptídeo" e "proteína" são usados

permutavelmente aqui para se referirem a um polímero de resíduos de aminoácido. Os termos se aplicam a polímeros de aminoácido nos quais um ou mais resíduos de aminoácido é um mimético químico artificial de um aminoácido que ocorre naturalmente correspondente, bem como a polímeros de aminoácido que ocorrem naturalmente, e polímeros de aminoácido que não ocorrem naturalmente.

O termo "aminoácido" se refere a aminoácidos que ocorrem naturalmente e sintéticos, bem como análogos de aminoácido e miméticos de aminoácido que funcionam em uma maneira similar aos aminoácidos que ocorrem naturalmente. Os aminoácidos que ocorrem naturalmente são aqueles codificados pelo código genético, bem como aqueles aminoácidos que são mais tarde modificados, por exemplo, hidroxiprolina, γ -carboxiglutamato, e O-fososerina. Análogos de aminoácido se referem a compostos que têm a mesma estrutura química básica como um aminoácido que ocorre naturalmente, isto é, um γ carbono que é ligado a um hidrogênio, um grupo carboxi, um grupo amino, e um grupo R, por exemplo, homoserina, norleucina, metionina sulfóxido, metionina metil sulfônio. Tais análogos têm grupos R modificados (por exemplo, norleucina), ou suportes de peptídeo modificados, mas retêm a mesma estrutura química básica como um aminoácido que ocorre naturalmente. Miméticos de aminoácido se referem a compostos químicos que têm uma estrutura que é diferente da estrutura química geral de um aminoácido, mas que funciona em uma maneira similar a um aminoácido que ocorre naturalmente.

Os aminoácidos podem ser referidos aqui por, ou seus símbolos de três letras comumente conhecidos, ou por símbolos de uma letra recomendados pela IUPAC-IUB Biochemical Nomenclature Commission. Os nucleotídeos, do mesmo modo, podem ser referidos por seus códigos de letra simples comumente aceitos.

"Variantes conservativamente modificadas" se aplicam a ambas seqüências de aminoácido e de ácido nucléico. Com relação a seqüências de ácido nucléico particulares, variantes conservativamente modificadas se referem aqueles ácidos nucléicos que codificam seqüências de aminoácido

idênticas, ou essencialmente idênticas, ou onde o ácido nucléico não codifica uma seqüência de aminoácido, para seqüências essencialmente idênticas. Devido à degeneração do código genético, um grande número de ácidos nucléicos funcionalmente idênticos codifica qualquer dada proteína. Por exemplo, os códons GCA, GCC, GCG e GCU todos codificam o aminoácido alanina. Desse modo, em toda posição onde uma alanina é especificada por um códon, o códon pode ser alterado para qualquer dos códons correspondentes descritos sem alterar o polipeptídeo codificado. Tais variações de ácido nucléico são "variações mudas", que são uma espécie de variações conservativamente modificadas. Toda seqüência de ácido nucléico aqui que codifica um polipeptídeo também descreve toda variação muda possível do ácido nucléico. Um versado no assunto reconhecerá que cada códon em um ácido nucléico (exceto AUG, que é ordinariamente o único códon para metionina, e TGG, que é ordinariamente o único códon para triptofan), pode ser modificado para produzir uma molécula funcionalmente idêntica. Consequentemente, cada variação muda de um ácido nucléico que codifica um polipeptídeo é implicada em cada seqüência descrita.

Como para seqüências de aminoácido, um versado reconhecerá que substituições individuais, retiradas ou adições a um ácido nucléico, peptídeo, polipeptídeo, ou seqüência de proteína que alteram, adicionam ou retiram um aminoácido simples ou em uma percentagem pequena de aminoácidos na seqüência codificada é uma "variante conservativamente modificada", onde a alteração resulta na substituição de um aminoácido com um aminoácido quimicamente similar. Tabelas de substituição conservativa proporcionando aminoácidos funcionalmente similares são bem-conhecidas na técnica. Tais variantes conservativamente modificadas são em adição a e não excluem variantes polimórficas, homólogos inter-espécie, e alelos da invenção.

Os seguintes oito grupos cada contém aminoácidos que são substituições conservativas para uma outra:

- 1) Alanina (A), Glicina (G);
- 2) Ácido aspártico (D), Ácido glutâmico (E);

- 3) Asparagina (N), Glutmina (Q);
 - 4) Arginina (R), Lisina (K);
 - 5) Isoleucina (I), Leucina (L), Metionina (M), Valina (V);
 - 6) Fenilalanina (F), Tirosina (Y), Triptofan (W);
 - 7) Serina (S), Treonina (T); e
 - 8) Cisteína (C), Metionina (M);
- (vide, por exemplo, Creighton, *Proteins* (1984)).

A frase "seletivamente (ou especificamente) hidrolisa para" se refere à ligação, duplexação, ou hibridização de uma molécula somente a uma seqüência de nucleotídeo particular sob condições de hibridização es-

10 tringentes quando esta seqüência está presente em uma mistura complexa (por exemplo, DNA ou RNA celular total ou de biblioteca).

A frase "condições de hibridização estringentes" se refere a condições sob as quais uma sonda hibridizará para sua seqüência-alvo, tipicamente em uma mistura de complexo de ácido nucléico, mas não para outras seqüências. As condições estringentes são dependentes da seqüência, e serão diferentes em circunstâncias diferentes. Seqüências mais longas hibridizam especificamente em temperaturas mais altas. Um guia extensivo à hibridização de ácidos nucléicos é encontrado em Tijssen, *Techniques in*

15 *Biochemistry and Molecular Biology-Hybridization with Nucleic Probes*, "Visão geral de princípios de hibridização e a estratégia de ensaios de ácido nucléico" (1993). Geralmente, condições estringentes são selecionadas para serem cerca de 5-10°C mais baixas do que o ponto de fusão térmico T_m para a seqüência específica em uma resistência iônica definida Ph . A T_m é a temperatura (sob resistência iônica definida, Ph , e concentração nucléica) na qual

20 50% das sondas complementares ao alvo hidrolisam para a seqüência-alvo em equilíbrio (à medida que as seqüências de alvo estão presentes em excesso, em T_m , 50% das sondas estão ocupadas em equilíbrio). As condições estringentes serão aquelas nas quais a concentração de sal é menos do que

25 cerca de 1,0 M de íon sódio, tipicamente cerca de 0,01 a 1,0 M de concentração de íon sódio (ou outros sais) em pH 7,0 a 8,3, e a temperatura é pelo menos cerca de 30°C para sondas curtas (por exemplo, 10 a 50 nucleotí-

30

deos), e pelo menos cerca de 60°C para sondas grandes (por exemplo, maior do que 50 nucleotídeos). As condições estridentes podem também serem alcançadas com a adição de agentes desestabilizantes, tal como formamida. Para hibridização seletiva ou específica, um sinal positivo é pelo menos duas vezes antecedente, opcionalmente 10 vezes antecedente a hibridização. Condições de hibridização estridentes exemplares podem ser conforme se segue: 50% de formamida, e 1% de SDS, incubando a 42°C, ou, 5xSSC, 1% de SDS, incubando a 65°C, com lavagem em 0,2xSSC, e 0,1% de SDS a 65°C.

Os ácidos nucléicos que não hidrolisam um ao outro sob condições estridentes são ainda substancialmente idênticos se os polipeptídeos que eles codificam são substancialmente idênticos. Isto ocorre, por exemplo, quando uma cópia de um ácido nucléico é criada usando-se a degeneração de códon máxima permitida pelo código genético. Em tais casos, os ácidos nucléicos tipicamente hibridizam sob condições de hibridização moderadamente estridentes. "Condições de hibridização moderadamente estridentes" exemplares incluem uma hibridização em um tampão de 40% de formamida, 1M de NaCl, 1% de SDS a 37°C, e uma lavagem em 1XSSC a 45°C. Uma hibridização positiva é pelo menos duas vezes antecedente. Aqueles versados na técnica reconhecerão prontamente que hibridização alternativa e condições de lavagem podem ser utilizadas para proporcionar condições de estridência similares.

"Anticorpo" se refere a um polipeptídeo compreendendo uma região de estrutura de um gene de imunoglobulina ou fragmentos deste que liga especificamente e reconhece um antígeno. Os genes de imunoglobulina reconhecidos incluem genes de região constante kappa, lâmbda, alfa, gama, delta, épsilon, e mu, bem como os genes de região variável de imunoglobulina miríades. As cadeias leves são classificadas como, ou kappa ou lâmbda. As cadeias pesadas são classificadas como gama, mu, alfa, delta ou épsilon, que, por sua vez, definem as classes de imunoglobulina, IgG, IgM, IgA, IgD e IgE, respectivamente.

Uma unidade estrutural (anticorpo) de imunoglobulina exemplar

compreende um tetrâmero. Cada tetrâmero é composto de dois pares idênticos de cadeias de polipeptídeo, cada par tendo uma cadeia "leve" (cerca de 25 kDa) e uma cadeia "pesada" (cerca de 50-70 kDa). O terminal N de cada cadeia define uma região variável de cerca de 100 a 110 ou mais aminoácidos principalmente responsáveis pelo reconhecimento do antígeno. Os termos cadeia leve variável (V_L) e cadeia pesada variável (V_H) se referem àquelas cadeias leves e pesadas, respectivamente.

A frase "ligar especificamente (ou seletivamente)" a um anticorpo ou "especificamente (ou seletivamente) imunorreativo com", quando se referindo a uma proteína ou peptídeo, se refere a uma reação de ligação que é determinativa da presença da proteína em uma população heterogênea de proteínas e outras biológicas. Desse modo, sob condições de imunoensaio designadas, os anticorpos especificados se ligam a uma proteína particular pelo menos duas vezes de fundo e não se liga substancialmente em uma quantidade significativa a outras proteínas presentes na amostra. Ligações específicas a um anticorpo sob tais condições podem requerer um anticorpo que é selecionado para sua especificidade para uma proteína particular. Por exemplo, anticorpos policlonais ocorridos de proteínas de fusão podem ser selecionados para obter somente aqueles anticorpos policlonais que são especificamente imunorreativos com proteína de fusão, e não com componentes individuais das proteínas de fusão. Esta seleção pode ser alcançada pela subtração de anticorpos que reagem em cruzamento com os antígenos individuais. Uma variedade de formato de imunoensaio pode ser usada para selecionar anticorpos especificamente imunorreativos com uma proteína particular. Por exemplo, imunoensaios ELISA de fase sólida são rotineiramente usados para selecionar anticorpos especificamente imunorreativos com uma proteína (vide, por exemplo, Harlow & Lane, *Antibodies, A Laboratory Manual* (1988), para uma descrição de formatos de imunoensaio, e condições que podem ser usadas para determinar imunorreatividade específica). Tipicamente uma reação específica ou seletiva será pelo menos duas vezes sinal ou ruído de fundo, mais tipicamente mais do que 10 a 100 vezes de fundo.

Os polinucleotídeos podem compreender uma sequência nativa

(isto é, uma sequência endógena que codifica um polipeptídeo individual, ou dsRNA, ou uma porção deste), ou pode compreender uma variante de tal sequência. As variantes de polinucleotídeo podem conter uma ou mais substituições, retiradas, e/ou inserções, tais que a atividade biológica do polipeptídeo codificado não é diminuída, relativo a um polipeptídeo compreendendo antígenos nativos. As variantes de polinucleotídeo podem conter uma ou mais substituições, adições, retiradas, e/ou inserções, tal que a atividade de agonístico de TLR-3 do dsRNA codificado não é diminuída, relativa a um dsRNA que não contém substituições, adições, retiradas, e/ou inserções. As

5 variantes preferivelmente exibem pelo menos cerca de 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, para uma sequência de polinucleotídeo que codifica um polipeptídeo nativo ou uma porção deste, ou para uma sequência de polinucleotídeo que codifica um dsRNA com atividade agonística de TLR-3.

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15 Os termos "idêntico" ou "identidade" por cento, no contexto de dois ou mais ácidos nucleicos (por exemplo, um dsRNA que é um agonístico de TLR-3), ou sequências de polipeptídeo, se referem a duas ou mais sequências ou subsequências que são as mesmas, ou têm uma percentagem especificada de resíduos de aminoácido ou nucleotídeos que são as mesmas

20 mas (isto é, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, ou mais identidade sobre uma região especificada), quando comparada e alinhada para correspondência máxima sobre uma janela de comparação, ou região designada conforme medida usando um dos seguintes algoritmos de comparação de sequência, ou

25 por alinhamento manual e inspeção visual. Tais sequências são, em seguida, referidas para serem "substancialmente idênticas". Esta definição também se refere ao cumprimento de uma sequência de um teste. Opcionalmente, a identidade existe sobre uma região que é pelo menos 10 a cerca de 100, cerca de 20 a cerca de 75, cerca de 30 a cerca de 50 aminoácidos

30 ou nucleotídeos de comprimento.

Para comparação de sequência, tipicamente uma sequência age como uma sequência de referência, a cujas sequências de teste são compa-

radas. Quando se usa um algoritmo de comparação de seqüência, as seqüências de teste e de referência são admitidas em um computador, coordenadas de subseqüência são designadas, se necessário, e parâmetros de programa de algoritmo de seqüência são designados. O algoritmo de comparação de seqüência em seguida calcula a percentagem de identidades de seqüência para as seqüências de teste relativo à seqüência de referência, baseado nos parâmetros do programa.

Uma "janela de comparação", conforme aqui usado, inclui referência a um segmento de qualquer um do número de posições contíguas de cerca de 10 a cerca de 500, cerca de 25 a cerca de 200, 50 a cerca de 150, em que uma seqüência pode ser comparada a uma seqüência de referência do mesmo número de posições contíguas após as duas seqüências serem otimamente alinhadas. Os métodos de alinhamento de seqüência para comparação são bem-conhecidos na técnica. O alinhamento ótimo de seqüências para comparação pode ser conduzido, por exemplo, pelo algoritmo de homologia local de Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), pelo algoritmo de alinhamento de homologia de Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), pela pesquisa para método de similaridade de Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA.* 85-2444 (1988), por implementações computadorizadas destes algoritmos (GAP, BESTFIT, FASTA, e TFASTA no Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), ou por alinhamento manual e inspeção visual (*vide, por exemplo, Current Protocols in Molecular Biology* (Ausubel *et al.*, eds. 1995 suplemento)).

Um exemplo de um algoritmo útil é PILEUP. PILEUP cria um alinhamento de seqüência múltiplo de um grupo de seqüências relacionadas usando alinhamentos em pares progressivos para mostrar relacionamento e percentagem de identidade de seqüência. Ele também assinala uma árvore ou dendograma mostrando os relacionamentos de agrupamento usados para criar o alinhamento. PILEUP usa uma simplificação do método de alinhamento progressivo de Feng & Doolittle, *J. Mol. Evol.* 35:351-360 (1987). O método usado é similar ao método descrito por Higgins & Sharp, CABIOS

5:15-153 (1989). O programa pode alinhar até 300 seqüências, cada uma de um comprimento máximo de 5.000 nucleotídeos ou aminoácidos. O procedimento de alinhamento múltiplo começa com o alinhamento de par das duas seqüências mais similares, produzindo um grupo de duas seqüências alinhadas. Este grupo é, em seguida, alinhado à próxima seqüência mais relacionada, ou grupo de seqüências alinhadas. Dois grupos de seqüências são alinhados por uma extensão simples do alinhamento de par de duas seqüências individuais. O alinhamento final é alcançado por uma série de alinhamentos de par progressivo. O programa é operado pela designação de seqüências específicas e suas coordenadas de aminoácido ou nucleotídeo para regiões de comparação de seqüência, e pela designação dos parâmetros do programa. Usando-se PILEUP, uma seqüência de referência é comparada a outras seqüências de teste para determinar a percentagem do relacionamento de identidade de seqüência usando-se os seguintes parâmetros: peso de intervalo padrão (3.00), peso de comprimento de intervalo padrão (0.10), e folgas terminais pesadas. PILEUP pode ser obtido a partir de acondicionamento de software de análise de seqüência de GCG, por exemplo, versão 7.0 (Devereaux *et al.*, *Nuc. Acids Res.* 12:387-395 (1984).

Outro exemplo de algoritmo que é adequado para determinar percentagem de identidade de seqüência e similaridade de seqüência são os algoritmos BLAST e BLAST 2.0, que são descritos em Altschul *et al.*, *Nuc. Acids Res.* 25:3389-3402 (1977) e Altschul *et al.*, *J. Mol. Biol.* 215:403-410 (1990), respectivamente. O software para realização de análise de BLAST é publicamente disponível através do Centro Nacional de Informação de Biotecnologia (<http://www.ncbi.nlm.nih.gov/>). Este algoritmo envolve primeiro identificação de pares de seqüência de alta classificação (HSPs) por identificação de palavras curtas de comprimento W na seqüência de consulta, que ou se equipara ou satisfaz alguma contagem T de limite de valor positivo quando alinhada com uma palavra do mesmo comprimento em uma seqüência de base de dados. T é referido como o limite de contagem de palavra vizinha (Altschul *et al.*, *supra*). Estes ataques de palavra vizinha inicializam como sementes para iniciação de pesquisas para encontrar HSPs

mais longos contendo-as. Os ataques de palavra são estendidos em ambas as direções ao longo de cada sequência tanto quanto a contagem de alinhamento cumulativo pode ser aumentada. Contagens cumulativas são calculadas usando, para seqüências de nucleotídeo, os parâmetros M (contagem de recompensa de um par de resíduo de equiparação; sempre >0) e N (contagem de penalidade para resíduos de desequiparação; sempre <0). Para seqüências de aminoácido, uma matriz de classificação é usada para calcular a contagem cumulativa. A extensão dos ataques de palavra em cada direção é cessada quando: a contagem de alinhamento cumulativo declina pela quantidade X de seu valor máximo alcançado; a contagem cumulativa vai à zero ou abaixo, devido ao acúmulo de um ou mais alinhamentos de resíduo de classificação negativa; ou a extremidade de sua seqüência é alcançada. Os parâmetros de algoritmo BLAST W, T e X determinam a sensibilidade e velocidade do alinhamento. O programa BLAST (para seqüências de nucleotídeo) usa como padrão um comprimento de palavra (W) de 11, uma expansão (E) ou 10, $M=5$, $N=4$, e uma comparação de ambas as resistências. Para seqüência de aminoácido, o programa BLASTP usa como padrão um comprimento de palavra de 3, e expressão (E) de 10, e alinhamentos de matriz de classificação BLOSUM62 (B) (vide Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989) de 50, expectativa (E) de 10, $M=5$, $N=4$, e uma comparação de ambas resistências.

O algoritmo BLAST também realiza uma análise estatística da similaridade entre duas seqüências (vide, por exemplo, Karlin & Altschul, *Proc. Nat'l Acad. Sci. USA* 90:5873-5787 (1993). Uma medida de similaridade provida pelo algoritmo BLAST é a menor probabilidade de soma ($P(N)$), que proporciona uma indicação da probabilidade pela qual uma equiparação entre duas seqüências de nucleotídeo ou aminoácido ocorreria por chance. Por exemplo, um ácido nucléico é considerado similar a uma seqüência de referência se a probabilidade de soma menor em uma comparação do ácido nucléico de teste para o ácido nucléico de referência é menor do que 0,2, mais preferivelmente menor do que 0,0,1 e, mais preferivelmente, menor do que cerca de 0,001.

III. Composições da Presente Invenção

A invenção proporciona composições compreendendo vetores adenovirais quiméricos. Em algumas concretizações, os vetores adenovirais quiméricos da invenção compreendem um primeiro promotor operavelmente
5 ligado a um ácido nucléico que codifica um polipeptídeo heterólogo, e um segundo promotor operavelmente ligado a um ácido nucléico que codifica um agonístico TLR-3. Os primeiro e segundo promotores podem ser os mesmos ou diferentes. Em algumas concretizações, os primeiro e segundo promotores são independentemente selecionados de: o promotor beta actinae o promotor de CMV.
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Em algumas concretizações, o vetor adenoviral quimérico compreende o genoma adenoviral (menos o genes E1 e E3), e um ácido nucléico que codifica um gene que ativa IRF-3 e outras moléculas de sinalização a jusante de TLR-3. O vetor quimérico pode ser administrado a uma célula que
15 expressa gene Ad's, E1 tal que adenovírus recombinante (rAd) é produzido pela célula. Este rAd pode ser colhido e é capaz de uma etapa simples de infecção que distribuirá a composição transgênica para outra célula dentro de um mamífero de modo a induzir respostas imunes ao polipeptídeo heterólogo.

20 A. Vetores Adenovirais Adequados

Em algumas concretizações, o vetor adenoviral é adenovírus 5, incluindo, por exemplo, Ad5 com retiradas das regiões E1/E3, e Ad5 com uma retirada da região E4. Outros vetores adenovirais adequados incluem cepas 2, cepas oralmente testadas 4 e 7, adenovírus entéricos 40 e 41, e
25 outras cepas (por exemplo, Ad34) que são suficientes para distribuição de um antígeno e indução de uma resposta imune adaptativa ao antígeno transgene [Lubeck *et al.*, *Proc Natl Acad Sci USA*, 86(17), 6763-6767 (1989); Shen *et al.*, *J. Virol*, 75(9), 4297-4307 (2001); Bailey *et al.*, *Virology*, 202(2), 695-706 (1994)]. Em algumas concretizações, o vetor adenoviral é um vetor
30 adenoviral incompetente de replicação, vivo (tais como rAd5 retirado E1 e E3), vetor adenoviral atenuado e vivo (tais como vírus de retirada E1B55K), ou um vetor adenoviral vivo com uma replicação tipo selvagem.

As seqüências de controle transcricionais e translacionais nos vetores de expressão a serem usadas na transformação de células vertebradas *in vivo* podem ser providas por fontes virais. Por exemplo, promotores comumente usados e intensificadores são derivados, por exemplo, de

5 beta actin, adenovírus, vírus simian (SV40), e citomegalovírus humano (CMV). Por exemplo, vetores que permitem expressão de proteínas sob a direção do promotor de CMV, promotor anterior SV40, promotor posterior SV40, promotor metalotionein, promotor de vírus de tumor mamário de murina, promotor de vírus de sarcoma de Rous, promotor transdutor, ou outros

10 promotores mostrados eficazes para expressão em células mamíferas, são adequados. Promotor genômico viral adicional, seqüências de controle e/ou de sinal podem ser usadas, provido que tais seqüências de controle são compatíveis com a célula hospedeira escolhida.

B. Polipeptídeos Heterólogos

15 Os ácidos nucléicos que codificam polipeptídeos heterólogos adequados podem ser derivados de antígenos, tais como, por exemplo, antígenos virais, antígenos bacteriais, antígenos de câncer, antígenos fungais, ou antígenos parasitas.

Os antígenos virais podem ser derivados de, por exemplo, vírus

20 de imunodeficiência humana (por exemplo, gag (p55 e p160), pol, env (gp120 e gp41), conforme colocado em Shiver *et al.*, *Nature* 415(6869):331 (2002); as seqüências genômicas de HIV colocadas nos Acessos no Banco de Gene Nºs EF363127; EF363126; EF363125; EF363124; EF363123; EF363122; EF192592; e EF192591; as seqüências gag de HIV colocadas

25 nos Acessos no Banco de Gene Nºs EF396891; EF396890; EF396889; EF396888; EF396887; EF396886; EF396885; EF396884; EF396883; EF396882; EF396881; EF396880; EF396879; EF396878; EF396877; EF396876; EF39687; EF396874; EF396873; e EF396872; as seqüências pol de HIV colocadas nos Acessos no Banco de Gene Nºs

30 EF396810; EF396809; EF396808; EF396807; EF396806; EF396805; EF396804; EF396803; EF396802; EF396801; EF396800; EF396799; EF396798; EF396797; EF396796; EF396795; EF396794; EF396793;

EF396792; e EF396791; e as seqüências env de HIV colocadas nos Acessos no Banco de Gene N^{os} 9: EF367234; EF367233; EF367232; EF367231; EF367230; EF367229; EF367228; EF367227; EF367226; EF367225; EF367224 e EF367223, vírus papilloma humano (por exemplo, proteína L1 capsid, conforme descrita em, por exemplo, Donnelly *et al.*, *J Infect Dis.* 173:314 (1996), e as seqüências colocadas nos Acessos no Banco de Gene N^{os} EF362755; EF362754; NC_001694; NC_001693; NC_001691; NC_001690; NC_005134; NC_001458; NC_001457; NC_001354; NC_001352; NC_001526; e X94164), vírus Epstein Barr, vírus simplex d

10 herpes, vírus da herpes humano, rinovírus, cocksackievírus, enterovírus, hepatite A, B, C e E (por exemplo, antígeno de superfície de hepatite B conforme descrito em, por exemplo, Lubeck *et al*, *PNAS USA* 86:6763 (1989), e as seqüências colocadas nos Acessos no Banco de Gene N^{os} AB236481; AB236471; AB206501; AB206489; AB206487; AB221788; AB221777;

15 AB221773; AR933671; AR933670; AB236514; AB236513; AB236512; AB236511; AB236510; AB236509; AB236508; AB236507); hepatite C NS5 (vide, por exemplo, Acessos no Banco de Gene N^{os} X59609; DQ911563; S71627; S70787; S70786; S70341; S6220; S70790; S70789; S70788; e AB204642)), vírus mumps, vírus rubella, vírus measles, poliovírus, vírus

20 smallpox, vírus rabies, e vírus Variella-zoster. O antígeno da gripe inclui, por exemplo, hemagglutinin (HA), proteína matriz 1 (M1), e nucleoproteína (NP) (vide, por exemplo, Donnelly, *et al*, *Vaccine* 15:865 (1997) e as seqüências de HA de gripe colocadas no Acesso no Banco de Genes N^{os} AB294219; AB294217; AB294215; AB294213; EF102944; EF102943; EF102942;

25 EF102941; EF102940; EF102939; EF102938; EF102937; EF102936; EF102935; EF102934; EF102933; DQ643982; DQ464354; CY019432; CY019424; CY019416; CY019408; CY019400; CY019392; CY019384; CY019376; CY019368; CY019360; CY019352; EF124794; EF110519; EF110518; EF165066; EF165065; EF165064; e EF165063; as seqüências

30 de M1 de gripe colocadas nos Acessos no Banco de Gene N^{os} AB292791; CY019980; CY019972; CY019964; CY019956; CY019948; CY019940; CY019628; CY019652; CY019644; CY019932; CY019924; CY019916;

CY019908; CY019900; CY019892; CY019884; CY019876; CY019868; CY019860; e as seqüências de NP de gripe colocadas nos Acessos no Banco de Gene N^{os} AB292790; CY019461; CY019974; CY019966; CY019958; CY019950; CY019942; CY019630; CY019654; CY019934; CY019926; 5 CY019918; CY019910; CY019902; CY019894; CY019886; CY019878; CY019870; e CY019862.

Antígenos virais adequados também incluem, por exemplo, proteínas não-estruturais virais. O termo "Proteína não-estrutural viral", conforme aqui usado, se refere a proteínas codificadas por ácido nucléico viral que 10 não codifica para polipeptídeos estruturais, tais como aqueles que produzem capsid ou a proteína que circunda um vírus. As proteínas não-estruturais incluem aquelas que promovem replicação de ácido nucléico viral e expressão de gene viral tais como, por exemplo, proteínas não-estruturais , 2, 3 e 4 (NS1, NS2, NS3 e NS4, respectivamente) de encefalite Eqüina Venezuelana 15 (VEE), EEE, ou vírus Semiliki Forest [Dubensky *et al.*, *J Virol*, 70(1), 508-519 (1996); Petrakova *et al J Virol* 2005 79(12): 7595-608; Patente dos Estados Unidos N^{os} 5.185.440; 5.739.026; 6.566.093; e 5.814.482. Vários exemplos representativos de alfavírus adequados incluem Aura (ATCC VR-368), vírus Bebaru (ATCC VR-600, ATCC VR-1240), Cabassou (Acesso no Banco de 20 Genes N^{os} AF398387, ATCC VR-922), vírus chikungunya (ATCC VR-64, ATCC VR-1241), vírus de encefalomielite eqüina do oeste (Acesso no Banco de Genes N^{os} AY705241, AY705240, ATCC VR-65, ATCC VR-1242), Fort Morgan (ATCC VR-924), vírus Getah (ATCC VR-369, ATCC VR-1243), Kyzylgach (ATCC VR-927), Mayaro (ATCC VR-66), vírus Mayaro (ATCC VR- 25 1277), Middleburg (ATCC VR-370), vírus Mucambo (ATCC VR-580, ATCC VR-1244), Ndumu (ATCC VR-371), vírus Pixuna (ATCC VR-372, ATCC VR-1245), vírus Ross River (ATCC VR-373), ATCC VR-1246), Semliki Forest (Acesso no Banco de Genes N^{os} AJ251359, ATCC VR-67, ATCC VR-1247), vírus Sindbis (Acesso no Banco de Genes N^{os} J02363, ATCC VR-68, ATCC 30 VR-1248), Tonate (ATCC VR-925), Trinita (ATCC VR-469), Una (ATCC VR-374), encefalomielite eqüina venezuelana (ATCC VR-69), vírus de encefalomielite eqüina venezuelana (Acesso no Banco de Genes N^{os} AY986475,

AY973944, NC 001449, ATCC VR-923), ATCC VR-1250, ATCC VR-1249, ATCC VR-532), encefalomielite eqüina do oeste (ATCC VR-70, ATCC VR-1251, ATCC VR-622, ATCC VR-1252), Whatoroa (ATCC VR-926), e Y-62-33 (ATCC VR-375).

- 5 Os antígenos bacteriais podem ser derivados de, por exemplo, *Staphylococcus aureus*, *Staphylococcus epidermis*, *Helicobacter pylori*, *Streptococcus bovis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Corynebacterium diphtheriae*, *Borrelia burgdorfi*, *Bacillus anthracis*, *Bacillus*
- 10 *cereus*, *Clostridium botulinum*, *Clostridium difficile*, *salmonella typhi*, *Vibrio cholerae*, *Haemophilus influenza*, *Bordetella pertussis*, *Yersinia pestis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, *Mycoplasma* sp., *Neisseria ransducer* s, *Legionella pneumophila*, *Rickettsia typhi*, *Chlamydia trachomatis*, e *Shigella dysenteriae*, *Vibrio cholera* (por exemplo, Cholera toxin subunidade B conforme colocada no Acesso no Banco de Genes N^{os} U25679; A09803; EF158842; X76391; AF390572; cholera toxin-pilus co-regulado (TCP), conforme descrito em Wu *et al.*, *Infection and Immunity* Vol. 69(12):7695 (2001), e conforme colocado no Acesso no Banco de Gene N^{os} NC_002505 e A-E004169); *Helicobacter pylorii* (VacA, conforme colocado no Acesso no Banco de Gene N^{os} AY848858; AF042737; AF042736; AF042735; AF042734; NC_000921; CagA, conforme colocado no Acesso no Banco de Gene N^{os} AF043490; AF043489; AF043488; AF043487; NAP conforme colocado no Acesso no Banco de Gene N^{os} AF284121; AF284120; AF284119; AF284118; AF284117; AF284116; AB045143; AB045142; AF227081; AF227080; AF227079; AF227078; AF227077; AF227076; AF227075; AF227074; Hsp ou catalase, conforme colocado no Acesso no Banco de Gene N^{os} NC_000921; urease, conforme colocado no Acesso no Banco de Gene N^{os} AM417610; AM417609; AM417608; AM417607; AM417606; AM417605; AM417604; AM417603; AM417602; AM417601; e AM417600; antígenos de *E. coli*, conforme colocado no Acesso no Banco de Gene N^{os} NC_000913; U00096; NC_002655; BA000007; AE014075; incluindo antígenos finbrial de *E. coli* conforme colocado no Acesso no Banco de Gene N^{os}

AB214865; AB214864; AB214863; AB214862; enteroxina instável a calor conforme colocado no Acesso no Banco de Gene N^{os} X83966; V00275; X83966; J01646; V00275; M35581; M17873; M17874; K01995; M61015; M178894; M17101; K00433.

- 5 Antígenos de parasita podem ser derivados de, por exemplo, *Giardia lamblia*, *Leishmania sp.*, *Trypanosoma sp.*, *Trichomonas sp.*, *Plasmodium sl.* (por exemplo, antígenos de proteína de superfície *P. falciparum*, tais como seqüências pfs25, conforme colocado no Acesso no Banco de Gene N^{os} XM_001347551; AF193769; AF179423; AF154117; e AF030628,
- 10 seqüências pfs28, conforme colocado no Acesso no Banco de Gene N^{os} L25843, seqüências pfs45, conforme colocado no Acesso no Banco de Gene N^{os} EF158081; EF158079; EF158078; EF158076; EF158075; e EF158085, seqüências pfs84, pfs48/45, conforme colocadas no Acesso no Banco de Gene N^{os} AF356146; AF356145; AF356144; AF356143; AF356142;
- 15 AF356141; AF356139; AF356138; AF356137; AF356136; AF356135; AF356134; AF356133; AF356132; AF356131; AF356130; AF356129; AF356128; AF356127; seqüências pfs 230, conforme colocadas no Acesso no Banco de Gene N^{os} NC_000910; XM_001349564; AE001393; L22219; L08135; e AF269242, antígenos *P. virax*, tais como seqüências Pvs25, con-
- 20 forme colocadas no Acesso no Banco de Gene N^{os} DQ641509; DQ641508; DQ641507; AY639971; AY639970; AY639969; AY639968; AY639967; AY639966; e AY639965; e seqüências Pvs28, conforme colocadas no Acesso no Banco de Gene N^{os} AB033364; AB033363; AB033362; AB033361; AB033360; AB033359; AB033358; AB033357; AB033356; AB033355;
- 25 AB033354; AB033353; AB033352; AB033351; AB033350; AB033349; AB033348; AB033347; AB033346; e AB033345), *Schistosoma sp.*, *Mycobacterium tuberculosis* (por exemplo, seqüências Ag85, conforme colocadas no Acesso no Banco de Gene N^{os} AX253506; AX253504; AX253502; e AX211309; MPT64, ESAT-6, CFP10, R8307, MTB-32 MTB-39, CSP, LSA-1,
- 30 LSA-3, EXP1, SSP1, SSP-2, SALSA, STARP, GLURP, MSP-1, MSP-2, MSP-3, MSP-4, MSP-5, MSP-8, MSP-9, AMA-1, proteína de membrana integral tipo 1, RESA, EBA-175, e seqüências DBA conforme colocadas no A-

cesso no Banco de Gene N^{os} BX842572; BX842573; BX842574; BX842575; BX842576; BX842577; BX842578; BX842579; BX842580; BX842581; BX842582; BX842583; BX842584; e NC_000962, seqüências HSP65, conforme colocadas no Acesso no Banco de Gene N^{os} AY299175; AY299174; 5 AY299144; AF547886; e AF547885).

Antígenos de câncer incluem, por exemplo, antígenos expressos, por exemplo, em câncer de cólon, câncer de estômago, câncer pancreático, câncer de pulmão, câncer de ovário, câncer de próstata, câncer de seio, câncer de pele (por exemplo, melanoma), leucemia, linfoma, ou mieloma, 10 antígenos de câncer exemplares incluem, por exemplo, HPV L1, HPV L2, HPV E1, HPV E2, fosfatase alcalina placentar, AFP, BRCA1, Her2/neu, CA 15-3, CA 19-9, CA-125, CEA, Hcg, ativador de plasminogênio tipo uroquinase (Upa), inibidor de ativador de plasminogênio.

Antígenos fungais podem ser derivados de, por exemplo, *Tinea* 15 *pedis*, *Tinea corporis*, *Tinea cruris*, *Tinea unguium*, *Cladophorium carionii*, *Coccidioides immitis*, *Cândida sp.*, *Aspergillus fumigatus*, e *Pneumocytis carinii*.

Os ácidos nucléicos que codificam polipeptídeos imunogênicos são tipicamente produzidos por métodos de DNA recombinante (vide, por 20 exemplo, Ausubel, *et al*, ed. (2001) *Current Protocols in Molecular Biology*). Por exemplo, as seqüências de DNA que codificam o polipeptídeo imunogênico podem ser montadas de fragmentos de cDNA e ligantes de oligonucleotídeo curtos, ou de uma série de oligonucleotídeos, ou amplificadas de cDNA usando iniciadores apropriados para proporcionar um gene sintético que é 25 capaz de ser inserido em um vetor de expressão recombinante (isto é, um vetor de plasmídeo, ou um vetor viral), e expresso em uma unidade transcricional recombinante. Uma vez que o ácido nucléico que codifica um polipeptídeo imunogênico é produzido, ele pode ser inserido em um vetor de expressão recombinante que é adequado para expressão *in vivo* ou *ex-vivo*.

30 Os vetores de expressão recombinantes contêm uma seqüência de DNA que codifica um polipeptídeo imunogênico operavelmente ligado a elementos regulatórios transcricionais ou translacionais adequados deriva-

dos de genes de mamíferos ou virais. Tais elementos regulatórios incluem um promotor transcricional, uma sequência operadora opcional para controlar transcrição, uma sequência que codifica locais de ligação ribossomal de mRNA adequados, e sequências que controlam a terminação de transcrição e translação. Uma origem de replicação e um marcador selecionável para facilitar reconhecimento de transformantes podem adicionalmente serem incorporados. Os genes utilizados nos vetores de expressão recombinantes podem ser divididos entre mais do que um vírus, tal que os produtos de gene estão em dois vetores diferentes, e os vetores são usados para co-transdução para proporcionar todos os produtos de gene em trans. Existem razões que dividem os produtos de gene, tais como limitações de tamanho para inserção, ou toxicidade dos produtos de gene combinados para as linhas de célula produzirem vírus.

C. Agonísticos TLR

De acordo com os métodos da invenção, os agonísticos TLR são usados para aumentar a resposta imune ao polipeptídeo heterólogo. Em algumas concretizações, os agonísticos TLR-3 aqui descritos podem ser distribuídos simultaneamente com o vetor de expressão que codifica um antígeno de interesse, ou distribuídos separadamente (isto é, temporariamente ou espacilmente) a partir do vetor de expressão que codifica um antígeno de interesse. Por exemplo, o vetor de expressão pode ser administrado via uma via não-paralela (por exemplo, oralmente, intranasalmente, ou mucosamente), enquanto o agonístico TLR é distribuído por uma via parenteral (por exemplo, intramuscular, intraperitoneal, ou subcutaneamente).

1. Agonísticos TLR

Em uma concretização preferida da presente invenção, um agonístico TLR-3 é usado para estimular reconhecimento imune de um antígeno de interesse. Os agonísticos TLR-3 incluem, por exemplo, RNA em forma de grampo de cabelo curto, RNA viralmente derivado, segmentos curtos de RNA que podem formar filamentos duplos, ou RNA em forma de grampo de cabelo curto, e RNA de interferência curto (siRNA). Em uma concretização da invenção, o agonístico TLR-3 é dsRNA viralmente derivado, tal como, por

exemplo, um ds-RNA derivado de um vírus Sindbis, ou intermediários virais de dsRNA [Alexopoulou *et al.*, *Nature* 413:732-8(2001)]. Em algumas concretizações, o agonístico TLR-3 é um RNA em forma de grampo de cabelo curto. Sequências de RNA em forma de grampo de cabelo curto tipicamente compreendem duas seqüências complementares unidas por uma seqüência ligante. A seqüência ligante particular não é um aspecto crítico da invenção. Qualquer seqüência ligante apropriada pode ser usada, considerando-se que ela não interfira com a ligação das duas seqüências complementares para formar um dsRNA.

Em algumas concretizações, o RNA em forma de grampo de cabelo curto compreende uma seqüência colocada em SEQ ID N^{os}: 3, 4, 5, 8, 9, 10, 11 ou 12, uma seqüência com identidade substancial para uma seqüência colocada em SEQ ID N^{os}: 3, 4, 5, 8, 9, 10, 11 ou 12, ou uma variante de uma seqüência colocada em SEQ ID N^{os}: 3, 4, 5, 8, 9, 10, 11 ou 12. Em certas concretizações, dsRNA que é um agonístico TLR-3 que não codifica um polipeptídeo particular, mas produz uma citocina pró-inflamatória (por exemplo, IL-6, IL-8, TLF-alfa, IFN-alfa, IFN-beta) quando contactado com uma célula respondidora (por exemplo, uma célula dendrítica, um célula mononuclear de sangue periférico, ou um macrófago) *in vitro*, ou *in-vivo*. Em alguns casos, o ácido nucléico que codifica o agonístico TLR-3 (por exemplo, um dsRNA expresso) e o vetor adenoviral quimérico compreendendo um ácido nucléico que codifica um antígeno heterólogo são administrados na mesma formulação. Em outros casos, Em alguns casos, o ácido nucléico que codifica o agonístico TLR-3 e o vetor adenoviral quimérico compreendendo um ácido nucléico que codifica um polipeptídeo heterólogo são administrados em formulações diferentes. Quando o ácido nucléico que codifica o agonístico TLR-3 e o vetor adenoviral quimérico compreendendo um ácido nucléico que codifica um antígeno heterólogo são administrados em formulações diferentes, sua administração pode ser simultânea ou seqüencial. Por exemplo, o ácido nucléico que codifica o agonístico TLR-3 pode ser administrado primeiro, seguido pelo vetor adenoviral quimérico (por exemplo, 1, 2, 4, 8, 12, 16, 20 ou 24 horas, 2, 4, 6, 8 ou 10 dias mais tarde). Alternativamente,

o vetor adenoviral pode ser administrado primeiro, seguido pelo ácido nucléico que codifica o agonístico TLR-3 (por exemplo, 1, 2, 4, 8, 12, 16, 20 ou 24 horas, 2, 4, 6, 8 ou 10 dias mais tarde). Em algumas concretizações, o ácido nucléico que codifica o agonístico TLR-3 e o ácido nucléico que codifica o antígeno heterólogo estão sob o controle do mesmo promotor. Em outras concretizações, o ácido nucléico que codifica o agonístico TLR-3 e o ácido nucléico que codifica o antígeno heterólogo estão sob o controle de promotores diferentes.

Sete análogos quimicamente sintetizados para RNA de filamento duplo são comercialmente disponíveis. Estes incluem poliinosina ácido policitidílico (poli I:C), ácido poliadenílico:poliuridílico (poli A:U), e poli I:poli C. Anticorpos (ou reticulação de anticorpos) para TLR-3 podem também conduzir a IFN-beta, ou produção de citocina pró-inflamatória [Matsumoto *et al*, *Biochem. Biophys. Res. Commun.* 24:1364(2002), de Bouteiller *et al*, *J. Biol. Chem.* 18:38133-45 (2005). Segmentos de siRNA comercialmente disponíveis de qualquer sequência podem também serem obtidos através de fontes, tal como Invitrogen.

2. Agonísticos TLR7/8

Em algumas concretizações, os agonísticos TLR são agonísticos TLR7/8. Ligantes TLR7/8 são tipicamente RNA derivado viralmente de filamento duplo. Devido aos receptores serem expressos em compartimentos intracelulares, tais como o endossoma, nem todos os segmentos curtos de RNA dispararão a cascata de sinalização de TLR7/8 porque eles necessitam alcançar o compartimento correto. Alguns ligantes que foram mostrados não disparar esta adição exógena são ácido poliuridílico, resiquimod, e imiquimod [Westwood, *et al.*, *Vaccine* 24:1736-1745(2006)].

IV. Composições Farmacêuticas

Composições farmacêuticas compreendendo os vetores aqui descritos podem também conter outros compostos, que podem ser biologicamente ativos ou inativos. Polipeptídeos podem, mas não necessitam, serem conjugados a outras macromoléculas conforme descrito, por exemplo, nas Patentes dos Estados Unidos N^{os} 4.372.945 e 4.474.757. As composi-

ções farmacêuticas podem geralmente serem usadas para proposta profilática e terapêutica. As composições farmacêuticas podem ser compostas de métodos para proteger contra degradação do estômago, tal que o vetor adenoviral quimérico administrado pode alcançar as localizações desejadas.

5 Para o ambiente oral, vários destes são disponíveis, incluindo os sistemas de liberação Eudragit e TimeClock, bem como outros métodos especificamente designados para adenovírus [Lubeck *et al.*, *Proc Natl Acad Sci USA*, 86(17), 6763-6767 (1989); Chourasia e Jain, *J. Pharm. Sci.*, 6(1), 33-66 (2003)]. Existem também vários métodos já descritos para microencapsula-

10 mento de DNA e fármacos para distribuição oral (vide, por exemplo, Publicação de Patente dos Estados Unidos Nº 2004043952). Em algumas concretizações, o sistema Eudragit será usado para distribuir o vetor adenoviral quimérico ao intestino delgado inferior. Contudo, a distribuição para outros locais do intestino delgado deve também operar.

15 Conforme notado acima, os vetores adenovirais quiméricos na invenção podem ser distribuídos usando-se quaisquer sistemas de distribuição conhecidos àqueles versados na técnica. Numerosas técnicas de distribuição de gene são bem-conhecidas na técnica, tais como aquelas descritas por Rolland (1998) *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, e

20 referências aqui citadas.

Será aparente que composições imunogênicas podem conter sais farmaceuticamente aceitáveis dos polinucleotídeos que codificam os polipeptídeos heterólogos (por exemplo, polipeptídeos imunogênicos). Tais

25 sais podem ser preparados de bases não-tóxicas farmaceuticamente aceitáveis, incluindo bases orgânicas (por exemplo, sais de aminas primária, secundária e terciária, e aminoácidos básicos), e bases inorgânicas (por exemplo, sais de sódio, potássio, lítio, amônia, cálcio e magnésio). Alguns exemplos particulares de sais incluem solução salina tamponada por fosfato, e solução salina para injeção.

30 Qualquer veículo adequado conhecido àqueles versados na técnica pode ser empregado nas composições farmacêuticas desta invenção. Veículos adequados incluem, por exemplo, água, solução salina, álcool, uma

gordura, um cera, um tampão, um veículo sólido, tais como manitol, lactose, amido, estearato de magnésio, sacarina de sódio, talco, celulose, glicose, sacarose, e carbonato de magnésio, ou microesferas biodegradáveis (por exemplo, polilactto poliglicolato). Microesferas biodegradáveis adequadas
 5 são descritas, por exemplo, nas Patentes dos Estados Unidos Nºs 4.897.268; 5.075.109; 5.928.647; 5.811.128; 5.820.883. O polipeptídeo imunogênico e/ou vírus veículo podem ser encapsulados dentro da microesfera biodegradável, ou associados com a superfície da microesfera.

Tais composições podem também compreender tampões (por exemplo, solução salina tamponada neutra, ou solução salina tamponada por fosfato), carboidratos (por exemplo, glicose, manose, sacarose e dextranos), manitol, proteínas, polipeptídeos ou aminoácidos, tais como glicina, antioxidantes, bacteriostats, agentes quelatantes, tais como EDTA ou glutathionina, adjuvantes (por exemplo, hidróxido de alumínio), solutos que tornam
 10 a formulação isotônica, hipotônica ou fracamente hipertônica com o sangue de um recipiente, agentes de suspensão, agentes de espessamento e/ou conservantes. Alternativamente, as composições da presente invenção podem ser formuladas como um liofilisato. Os compostos podem também ser encapsulados dentro dos lipossomas usando-se tecnologia bem-conhecida.

Em algumas concretizações da presente invenção, as composições compreendem adicionalmente um adjuvante. Adjuvantes adequados incluem, por exemplo, os compostos de lipídeos e não-lipídeos, cholera toxin (CT), CT subunidade B, CT derivativo CTK63, enterotoxina instável a calor de E. coli (LT), derivado de LT LTK63, $Al(OH)_3$, e ácidos orgânicos poliiônicos conforme descritos em, por exemplo, WO 04/020592, Anderson e Crowle, *Infect. Immun.* 31(1):413-418 (1981), Roterman *et al.*, *J. Physiol. Pharmacol.*, 44(3):212-32 (1993), Arora e Crowle, *J. Reticuloendothel.* 24(3):271-86(1978), e Crowle e May, *Infect. Immun.* 38(3):932-7 (1982)). Ácidos orgânicos poliiônicos adequados incluem, por exemplo, 6,6'-[3,3'-dimetil[1,1'-bifenil]-4,4'-diil]bis(azo)bis[ácido
 25 4-amino-5-hidróxi-1,3-naftaleno-dissulfônico](Evans Blue) e 3,3'-[1,1'-bifenil]-4,4'-diilbis(azo)bis[ácido 4-amino-1-naftalenossulfônico] (Congo Red). Será apreciado por aqueles ver-

sados na técnica que os ácidos orgânicos poliiônicos podem ser usados para qualquer método de vacinação genética em conjunto com qualquer tipo de administração.

5 Outros adjuvantes adequados incluem imunomoduladores tópicos, tais como, membros da família imidazoquinolina, tais como, por exemplo, imidaquimod e resiquimod (vide, por exemplo, Hengge *et al.*, *Lancet Infect. Dis.* 1(3):189-98 (2001). Agonísticos TLR-3 expressos (por exemplo, dsRNA) e agonísticos TLR-7 (por exemplo, ssRNA), podem também serem usados com a invenção.

10 Adjuvantes adequados adicionais são comercialmente disponíveis como, por exemplo, adjuvantes baseado em alum adicionais (por exemplo, Alhydrogel, Rehydragel, fosfato de alumínio, Algammulin); adjuvantes baseado em óleo (Adjuvante Incompleto e Adjuvante Completo de Freund (Difco Laboratories, Detroit, Mich), Specol, RIBI, TiterMax, Montanide ISA 50
15 ou Seppic MONTANIDE ISA 720); adjuvantes baseados em copolímero de bloco não-iônico, citoquinas (por exemplo, GM-CSF ou Flat3 ligante); Adjuvante Merck 65 (Merck and Company, Inc., Rahway, N.J.); AS-2 (SmithKline Beecham, Philadelphia, Pa); sais de cálcio, ferro ou zinco; uma suspensão insolúvel de tirosina acilatada; açúcares acilatados; polissacarídeos cationicamente ou anionicamente derivatizados; polifosfozenos; microesferas biodegradáveis; monofosforil lipídeo A e Quil A. Citoquinas, tais como GM-CFS
20 ou interleukin-2, -7, ou -12, são também adjuvantes adequados. Hemocianins (por exemplo, hemocianin de lapa) e hemoeritrins podem também serem usados na invenção. Adjuvante de polissacarídeo tais como, por exemplo,
25 chitin, chitosan, e chitin deacetilado são também adequados como adjuvantes. Outros adjuvantes adequados incluem muramil dipeptídeo (MDP, N acetilmuramil L alanil D isoglutamina) peptidoglicans bacteriais e seus derivados (por exemplo, threonil-MDP, e MTPPE). BCG e esqueleto de parede de célula de BCG (CWS) podem também serem usados como adjuvantes na
30 invenção, com ou sem trehalose dimicolato. Trehalose dimicolato pode ser usado (vide, por exemplo, Patentes dos Estados Unidos Nº 4.579.945). Endotoxins detoxificados são também úteis como adjuvantes apenas, ou em

combinação com outros adjuvantes (vide, por exemplo, Patente dos Estados Unidos N^{os} 4.866.034; 4.435.386; 4.505.899; 4.436.727; 4.436.728; 4.505.900; e 4.520.019. Os saponins QS21, QS17, QS7 são também úteis como adjuvantes (vide, por exemplo, Patente dos Estados Unidos N^{os} 5.057.540; EP 0362 279; WO 96/33739; e WO 96/11711). Outros adjuvantes adequados incluem Montanide ISA 720 (Seppic, França), SAF (Chiron Calif, United States), ISCOMS (CSL), MF-59 (Chiron), a série SBAS de adjuvantes (por exemplo, SBAS-2, SBAS-4 ou SBAS-6 ou variantes destes, disponíveis de SmithKline Beecham, Rixensart, Bélgica), Detox, Hamilton, Mont.), e RC-529 (Corixa, Hamilton, Mont).

Superantígenos são também contemplados para uso como adjuvantes na presente invenção. Superantígenos incluem *Staphylococcus exoproteínas*, tais como α , β , γ e Δ enterotoxins de *S.aureus* e *S. epidermidis*, e α , β , γ e Δ exotoxins *E. coli*. *Staphylococcus* enterotoxins comum são conhecidos como *staphylococcal* enterotoxin A (SEA) e *staphylococcal* enterotoxin B (SEB), com enterotoxins através de E (SEE) sendo descritas (Rott et al., 1992). *Streptococcus pyogenes* B (SEB), *Clostridium perfringes* enterotoxin (Bowness et al., 1992), proteína associada a membrana citoplásmica (CAP) de *S. pyogenes* (Sato et al., 1994) e toxin de síndrome de choque térmico 1 (TSST 1) de *S. aureus* (Schwab et al., 1993) são superantígenos úteis adicionais.

Dentro das composições farmacêuticas aqui providas, a composição adjuvante pode ser designada para induzir, por exemplo, uma resposta imune predominantemente do tipo Th1 ou Th2. Altos níveis de citocinas tipo Th1 (por exemplo, IFN-gama, TNF-alfa, IL-2 e IL-3) tendem a favorecer a indução de respostas imunes mediadas de célula para um antígeno administrado. Em contraste, altos níveis de citocinas tipo Th2 (por exemplo, IL-4, IL-5, IL-6 e IL-10) tendem a favorecer a indução de repostas imunes humorais. Seguindo distribuição oral de uma composição compreendendo um polipeptídeo imunogênico conforme provido aqui, uma resposta imune que inclui respostas tipo Th1 e Th2 será tipicamente induzida.

As composições aqui descritas podem ser administradas como

parte de uma formulação de liberação sustentada (isto é, uma formulação tal como uma cápsula ou esponja que efetua uma liberação lenta de composto em seguida a administração). Tais formulações podem geralmente ser preparadas usando-se tecnologias conhecidas (vide, por exemplo, Coombes *et al* (1996) *Vaccine* 14:1429-1438). Formulações de liberação sustentada podem conter um polipeptídeo, polinucleotídeo ou anticorpo disperso em uma matriz transportadora, e/ou contidas dentro de um reservatório circundado por uma membrana de controle de taxa.

Os veículos para uso dentro de tais formulações são biocompatíveis, e podem ser biodegradáveis; preferivelmente as formulações proporcionam um nível relativamente constante de liberação de componente ativo. Tais veículos incluem micropartículas de poli(lactídeo-co-glicolídeo), bem como poliacrilato, látex, amido, celulose e dextrano. Outros veículos de liberação retardada incluem biovetores supramoleculares, que compreendem um núcleo hidrofílico não-líquido (por exemplo, um polissacarídeo reticulado ou oligossacarídeo) e, opcionalmente, uma camada externa compreendendo um composto anfifílico (vide, por exemplo, WO94/20078; WO94/23701 e WO96/06638). A quantidade de composto ativo contida dentro de uma formulação de liberação sustentada depende do local de implantação, da taxa e da duração esperada de liberação e da natureza da condição a ser tratada ou prevenida.

As composições farmacêuticas podem ser apresentadas em recipientes de dose única ou de dose múltipla, tais como ampolas vedadas ou frascos. Tais recipientes são preferivelmente hermeticamente vedados para preservar a esterilidade da formulação até uso. Em geral, formulações podem ser armazenadas como suspensões, soluções ou emulsões em veículos oleosos ou aquosos. Alternativamente, uma composição farmacêutica pode ser armazenada por uma condição secada por armazenamento requerendo somente a adição de um veículo líquido estéril imediatamente antes do uso.

V. Usos Terapêuticos da Invenção

Um aspecto da presente invenção envolve o uso das composi-

ções imunogênicas aqui descritas para induzir uma resposta imune específica de antígeno de um indivíduo ou paciente com uma doença tal como, por exemplo, uma infecção viral, infecção bacterial, uma infecção parasítica, uma infecção funga, ou câncer. Conforme aqui usado, um "indivíduo" ou um

5 "paciente" se refere a qualquer animal de sangue quente, tal como, por exemplo, um roedor, um felino, um canino, ou um primata, preferivelmente um ser humano. As composições imunogênicas podem ser usadas em qualquer estagio da doença, isto é, no pré-câncer, câncer, ou estados metastáticos, ou para prevenir doença. Por exemplo, as composições aqui descritas po-

10 dem ser usadas para tratar uma doença viral, tal como HIV, ou hepatite, ou a prevenção ou tratamento de câncer. Dentro de tais métodos as composições farmacêuticas são tipicamente administradas a um paciente. O paciente pode ou não pode ser afligido com a doença ou enfermidade (por exemplo, uma infecção viral, uma infecção bacterial, ou câncer). Conseqüentemente,

15 as composições farmacêuticas acima podem ser usadas para prevenir o desenvolvimento de uma doença ou enfermidade (por exemplo, uma infecção viral, uma infecção bacterial ou câncer), ou tratar um paciente afligido com a doença ou enfermidade (por exemplo, uma infecção viral, uma infecção bacterial ou câncer). A doença ou enfermidade pode ser diagnosticada usando-

20 se critérios geralmente aceitos na técnica. Por exemplo, a infecção viral pode ser diagnosticada pela medição da titulação viral em uma amostra do paciente, a infecção bacterial pode ser diagnosticada pela detecção da bactéria em uma amostra do paciente, e o câncer pode ser diagnosticado pela detecção da presença de um tumor maligno. As composições farmacêuticas po-

25 dem ser administradas, ou antes, ou, em seguida a remoção cirúrgica de tumores primários e/ou tratamento, tal como administração de radioterapia ou fármacos quimioterapêuticos convencionais.

A imunoterapia é tipicamente imunoterapia ativa, em que o tratamento ocorre na estimulação *in vivo* do sistema imune hospedeiro endó-

30 geno para reagir contra, por exemplo, tumores ou células bacterial ou viralmente infectadas, com a administração de agentes de modificação de resposta imune (composições compreendendo ácidos nucleicos que codificam

polipeptídeos imunogênicos conforme aqui providos).

A frequência de administração das composições profiláticas ou terapêuticas aqui descritas, bem como a dosagem, variará de indivíduo para indivíduo, e pode ser prontamente estabelecida usando-se técnicas padrão.

- 5 Frequentemente entre 1 e 10 doses podem ser administradas sobre um período de 51 semanas. Tipicamente 3 doses são administradas, em intervalos de um mês, mais tipicamente 2-3 doses são administradas todo 2-3 meses, é possível que os intervalos sejam mais de uma vez por ano para certas terapias. Vacinações em grupo podem ser dadas periodicamente em seguida.
- 10 Protocolos alternados podem ser apropriados para pacientes individuais e doenças e enfermidades particulares. Uma dose adequada é uma quantidade de um composto que, quando administrada conforme descrito acima, é capaz de promover, por exemplo, uma resposta imune antitumor, antiviral ou antibacterial, e é pelo menos 10-50% do nível basal (isto é, não tratado). Tal
- 15 resposta pode ser monitorada pela medição dos anticorpos antitumor em um paciente, ou por geração dependente de vacina de células T citolíticas capazes de matar, por exemplo, as células tumorais do paciente, as células viralmente infectadas do paciente, ou as células bacterionalmente infectadas do paciente *in vitro*. Tais vacinas devem também serem capazes de causar uma
- 20 resposta imune que conduz a um efeito clínico aperfeiçoado (por exemplo, remissões mais frequentes, sobrevivência livre de doença completa ou parcial ou mais longa) em pacientes vacinados, conforme comparado a pacientes não vacinados. Tipicamente a quantidade das titulações virais estará entre $1,0 \times 10^4$ pfu/animal e $1,0 \times 10^{15}$ pfu/animal. Os tamanhos da dose a-
- 25 dequados variarão com o tamanho do paciente, mas tipicamente variará de cerca de 0,01 ml a cerca de 10 ml, mais tipicamente de cerca de 0,025 ml a cerca de 7,5 ml, mais tipicamente de cerca de 0,05 ml a cerca de 5 ml. Aqueles versados na técnica apreciarão que o tamanho da dose pode ser
- 30 ajustado baseado no paciente particular, ou na doença particular ou enfermidade sendo tratada. Para a administração oral, o vetor adenoviral quimérico pode ser convenientemente formulado em uma pílula.

Em geral, uma dosagem apropriada e regime de tratamento

proporciona o(s) composto(s) em uma quantidade suficiente para proporcionar benefício terapêutico e/ou profilático. Tal resposta pode ser monitorada pelo estabelecimento de um efeito clínico aperfeiçoado (por exemplo, remissões mais freqüentes, sobrevivência livre de doença completa ou parcial ou mais longa) em pacientes tratados, conforme comparado a pacientes não tratados. Tais respostas imunes podem geralmente serem avaliadas usando-se proliferação padrão, citotoxicidade ou ensaios de citocina descritos acima, que podem ser realizados usando-se amostras obtidas de um paciente antes e após tratamento.

- 10 Por exemplo, a detecção de imunocomplexos formados entre polipeptídeos imunogênicos e anticorpos no fluido corpóreo que são específicos para polipeptídeos imunogênicos, pode ser usada para monitorar a eficiência de terapia, que envolve um polipeptídeo imunogênico particular, para uma doença ou enfermidade em que o polipeptídeo imunogênico é associado. As amostras de fluido corpóreo tomadas de um indivíduo antes e subsequente a iniciação de terapia podem ser analisadas para os imunocomplexos pelas metodologias descritas acima. Brevemente, o número de imunocomplexos detectado em ambas as amostras é comparado. Uma mudança substancial no número de imunocomplexos na segunda amostra (iniciação de pós-terapia), relativa à primeira amostra (pré-terapia), reflete terapia bem-sucedida.

A. Administração das Composições da Presente Invenção

- De acordo com os métodos da presente invenção, uma composição compreendendo o vetor adenoviral quimérico é administrada por qualquer via não-parenteral (por exemplo, oral, intranasal ou mucosalmente via, por exemplo, a vagina, pulmões, glândulas salivares, cavidades nasais, intestino delgado, cólon, reto, amígdala, ou emplastos de Peyer). A composição pode ser administrada sozinha, ou com um adjuvante conforme descrito acima. Em algumas concretizações, os adjuvantes são codificados por uma sequência de ácido nucléico (por exemplo, um ácido nucléico que codifica IL-2, GM-CSF, IL-12, ou flagellin bacterial). Em algumas concretizações da presente invenção, o adjuvante é administrado ao mesmo tempo, conforme

a composição. Em outras concretizações da presente invenção, o adjuvante é administrado após a composição, por exemplo, 6, 12, 18, 24, 36, 48, 60 ou 72 horas após administração da composição.

B. Detecção de uma Resposta Imune a Antígenos de Interesse

5 Uma resposta imune ao polipeptídeo heterólogo pode ser detectada usando-se qualquer meio conhecido na técnica, incluindo, por exemplo, detecção de ativação específica de células T CD4⁺ ou CD8⁺, ou pela detecção da presença de anticorpos que se ligam especificamente ao polipeptídeo.

10 A ativação específica de células T CD4⁺ ou CD8⁺ associada com uma resposta imune mediada por mucosal, humoral ou célula, pode ser detectada em uma variedade de modos. Os métodos de detecção de ativação de célula T específica incluem, mas não estão limitados a, detecção da proliferação de células T, a produção de citocinas (por exemplo, linfoquinas), ou
15 a geração de atividade citolítica (isto é, geração de células T citotóxicas específicas para o polipeptídeo imunogênico). Para células T CD4⁺, um método preferido para detecção de ativação de célula T específica é a detecção da proliferação de células T. Para células T CD4⁺, um método preferido para detecção de ativação de célula T específica é a detecção da proliferação de
20 células T. Para células T CD8⁺, um método preferido para detecção de ativação de célula T específica é a detecção da geração de atividade citolítica usando-se ensaios de liberação de ⁵¹Cr (vide, por exemplo, Brossat e Bevan, *Blood* 90(4):1594-1599 (1997) e Lenz *et al.*, *J. Exp. Med.* 192(8):1135-1142 (2000)).

25 A detecção da proliferação de células T pode ser efetuada por uma variedade de técnicas conhecidas. Por exemplo, a proliferação de célula T pode ser detectada pela medição da taxa de síntese de DNA. As células T que foram estimuladas a proliferarem exibem uma taxa aumentada de síntese de DNA. Um modo típico de medir a taxa de síntese de DNA é, por
30 exemplo, por culturas de pulso-etiquetamento de células T com timidina tritiatada, um precursor de nucleosídeo que é incorporado em um DNA recentemente sintetizado. A quantidade de timidina tritiatada incorporada pode ser

determinada usando-se um espectrofotomedidor de cintilação líquida. Outros modos para detectar proliferação de célula T incluem medição do aumento na produção de interleukin-2(IL-2), fluxo de Ca^{2+} , ou percepção de corante, tal como 3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolium. Alternativamente, a síntese de linfoquinas (por exemplo, interferon-gama) pode ser medida, ou o número relativo de células T que pode responder ao polipeptídeo imunogênico pode ser quantificado.

As respostas imunes de anticorpo (Respostas imunes humorais aka ou respostas de célula B), incluindo respostas de anticorpo mucosal, podem ser detectadas usando-se imunoensaios conhecidos na técnica [Tucker *et al.*, *Mol. Therapy*, 8, 392-399 (2003); Tucker *et al.*, *Vaccine*, 22, 2500-2504 (2004)]. Imunoensaios adequados incluem a técnica de imunoensaio de intercalamento de anticorpo monoclonal duplo de David *et al* (Patente dos Estados Unidos Nº 4.376.110); ensaios de intercalamento de anticorpo monoclonal-policlonal (Wide *et al.*, em Kirkham e Hunter, eds., *Radioimmunoassay Methods*, E e S. Livingstone, Edinburgh (1970)); o método de "western blot" de Gordon *et al.* (Patente dos Estados Unidos Nº 4.452.901); imunoprecipitação de ligante etiquetado (Brown *et al* (1980) *J. Biol. Chem.* 255:4980-4983); ensaios imunoabsorventes ligado por enzima (ELISA) conforme descrito, por exemplo, por Raines *et al.* (1982) *J. Biol. Chem.* 257:5154-5160; técnicas imunocitoquímicas, incluindo o uso de fluorocromos (Brooks *et al.* (1980) *Clin. Exp. Immunol.* 39:477); e neutralização de atividade (Bowen-Pope *et al.* (1984) *Proc. Natl. Acad. Sci. USA* 81:2396-2400). Em adição aos imunoensaios descritos acima, um número de outros imunoensaios são disponíveis, incluindo aqueles descritos nas Patentes dos Estados Unidos Nºs 3.817.827; 3.850.752; 3.901.654; 3.935.074; 3.984.533; 3.996.345; 4.034.074; e 4.098.876.

Exemplos

Os seguintes exemplos são pretendidos para ilustrarem, mas não limitarem a presente invenção.

Exemplo 1: Construção de um Vetor Adenoviral Quimérico (DSI)

Para demonstrar que agonistas TLR-3 podem aperfeiçoar res-

postas imunes adaptativas a antígenos expressos de interesse, vários vetores adenovirais quiméricos diferentes foram construídos, que compreendem seqüências de ácido nucléico que codificam vários antígenos diferentes de interesse. Neste exemplo, o ácido nucléico que codifica gp 120 (a partir do Programa de Reagente de Referência NIH AIDS) foi colocado sob controle de um promotor de CMV com um pequeno intron imediatamente a montante do códon de partida no vetor de lançadeira (pShuttle, Qbiogene). Uma calda poli A de bGH foi colocada a jusante do ácido nucléico que codifica gp120. A seqüência de vetor é colocada em SEQ ID Nº:1. A recombinação homóloga com o vetor pAd (Qbiogene) foi realizada para gerar um vetor capaz de produzir Ad recombinante (E1/E2 retirado), que contém o ácido nucléico que codifica gp120. DSI foi gerado pela transferência do constructo de expressão pAd-CMV-gp120 nova em 293 células. As titulações foram medidas por métodos padrões.

15 Exemplo 2: DSI (vetor mais agonístico TLR-3) é superior a rAd5 padrão para indução de uma resposta imune específica de antígeno

Para determinar se a adição de agonístico TLR-3 podia aperfeiçoar respostas imunes adaptativas, 10×10^7 PFU de ou rAd-CMV-gp120 mais 5 ug/ml de poli I:C (DSI), ou rAd-CMV-gap-120 somente (rAd5), foram administrados a animais por administração oral nas semanas 0 e 3. Ambos os vetores expressam HIV gp120 sob controle do promotor de CVM e usam adenovírus tipo 5 retirado de recombinante E1/E3. Titulações de anticorpo a gp120 foram medidas no plasma 3 e 6 semanas após a administração inicial por anti-gp120 IgG ELISA, conforme descrito em Tucker, *et al.*, *Mol. Ther* 8:392 (2004)). Conforme mostrado na Figura 1, DSI se portou significante-mente melhor do que rAd5 na indução de respostas de anticorpo para gp120 ambos em 3 e 6 semanas pós administração oral inicial. Em particular, a titulação de anticorpo média para gp120 foi 100 vezes melhor com o grupo DSI do que com o grupo rAd5 na semana 6. Parece também que o grupo DSI foi agrupado por re-administração na semana 4 em que a titulação média aumentou mais do que 20 vezes entre as semanas 3 e 6 onde o grupo rAd5 mostrou somente um leve aumento na titulação de anticorpo média. Os re-

sultados demonstraram que a adição de um agonístico TLR-3 pode aperfeiçoar grandemente respostas de anticorpo mediadas por Ad5 a antígenos de interesse em seguida a administração oral de um vetor adenovírus quimérico compreendendo um ácido nucléico que codifica o antígeno de interesse.

- 5 Como um controle positivo para o ensaio, soro de um animal injetado subcutaneamente com gp120 mais Adjuvante Completo de Freund foi também medido no anti-gp120 ELISA na semana 3. Os animais não-tratados e animais administrados com o análogo dsRNA somente (dsRNA) serviram como controles negativo e antecedentes respectivamente para a ELISA. Cada grupo contém 6 animais.

Exemplo 3: Construção de Um Segundo Vetor Adenoviral Quimérico (DS1b) e um Terceiro Vetor Adenoviral Quimérico (DS1c)

- Um ácido nucléico que codifica proteína fluorescente verde (GFP) foi inserido em pShuttle-CMV (Qbiogene) usando-se digestões de enzima de restrição padrão. O plasmídeo pShuttleCMV-GFP foi combinado por recombinação homóloga com o vetor pAd(Qbiogene), conforme descrito antes, de modo a gerar um vetor capaz de produzir recombinante Ad(E1/E3 retirado) compreendendo uma seqüência de ácido nucléico que codifica GFP. Um ácido nucléico que codifica hemaglutinin (HA) de gripe A/PR/8/34 foi clonado e colocado no vetor pShuttle-CMV (Qbiogene) (SEQ ID Nº:13). O plasmídeo pShuttleCVM-HA (PR/8) foi combinado por recombinação homóloga com o vetor pAd(Qbiogene), conforme descrito antes, de modo a gerar um vetor capaz de produzir recombinante Ad(E1/E3 retirado) compreendendo uma seqüência de ácido nucléico que codifica HA. O recombinante Ad foi gerado por transfecção do novo constructo de expressão de pAd-CMV-GFP e pAd-CMV-HA em 239 células. As titulações foram medidas por métodos padrões.

- Exemplo 4: DS1B (Ad-CMV-GFP mais agonístico LTR-3) e DS1c (Ad-CMV-HA mais agonístico TLR-3) é superior a rAd5 padrão para indução de uma resposta imune específica de antígeno.

$1,0 \times 10^7$ PFU de ou Ad-CMV-GFP mais 5 ug/ml de poli I:C (DS1b), ou Ad-CMV-GFP (rAd5), foram administrados a animais por admi-

nistração oral na semana 0. Ambos os vírus expressam o GFP sob controle do promotor de CVM e usam adenovírus tipo 5 retirado de recombinante E1/E3. Titulações de anticorpo para GFP foram medidas no plasma 3 semanas após a administração de vírus inicial por anti-GFP IgG ELISA. Conforme mostrado na Figura 2, o grupo DS1b se portou significativamente melhor do que rAd5 na indução de respostas de anticorpo para GFP em 3 semanas pós administração oral inicial.

As respostas de célula T CD8⁺ para GFP foram medidas por tratamento de manchamento de esplenócitos. Os animais foram vacinados nas semanas 0, 4, 8, e os baços foram colhidos na semana 10. Os esplenócitos foram manchados com CD8-FITC, e o tetrâmero que reconhece o epítipo imunodominante para GFP em Balb/c camundongos. Os resultados mostram que administração oral do vetor DS1b foi estatisticamente melhor do que rAd sozinho na indução de células CD8 de tetrâmero (Figura 2b).

1,0x10⁷ PFU de ou Ad-CMV-HA mais 5 ug/ml de poli I:C (DS1c), ou Ad-CMV-HA (rAd5), foram administrados a animais por administração oral na semana 0. Ambos os vírus expressam HA sob controle do promotor de CVM e usam adenovírus tipo 5 retirado de recombinante E1/E3. Titulações de anticorpo para HA foram medidas no plasma 3 semanas após a administração de vírus inicial por anti-PR8/34 IgG ELISA. O procedimento para medição de respostas de anticorpo é similar àquele descrito antes, com a exceção que as placas de ELISA foram revestidas com 5 ug/ml de lisato A/PR8/34 total (Advanced Biotechnology Incorporated, Gaithersburg, MD). Conforme mostrado na Figura 2C, o grupo DS1c se portou significativamente melhor (aproximadamente 100 vezes melhor) do que rAd5 na indução de respostas de anticorpo para gripe em 3 semanas pós administração oral inicial. Os resultados destes estudos demonstraram também que a aproximação de usar-se agonístico TLR-3 junto com um vetor adenoviral recombinante quimérico pode ser geralmente aplicada a antígenos heterólogos diferentes múltiplos, com um aperfeiçoamento de 100 vezes na titulação de anticorpo.

Exemplo 5: As Vias Não-Parenterais de Distribuição São Superiores a Vias Parenterais

A distribuição intramuscular foi testada por injeção diretamente de $1,0 \times 10^7$ pfu de pAd-CMV-gp120 (DS10+/-poli I:C em 5 ug/ml nos quadripes de animais. Titulações de IgG de soro de plasma para GFP foram medidas conforme descrito acima. Cada grupo continha 6 animais. Conforme mostrado na Figura 3A, titulações de anticorpo significantes em gp120 foram observadas em 3 semanas pós administração no grupo com agonístico TLR-3 (i.m. rAd+PI). (Figura 3A).

A administração intranasal foi testada por administração de 20 ul de $1,1 \times 10^6$ pfu de DS1c+/5 ug/ml de poli I:C na cavidade nasal de camundongos. Os camundongos foram levemente anestesiados com isoflurano antes da administração do vírus formulado em solução salina estéril. Os resultados mostram que o rAd-CMV-HA mais poli I:C (DS1c) tinham titulações de anticorpo levemente mais altas comparadas a animais dado o padrão rAd-CMV-HA. Os resultados são plotados como animais individuais para os grupos DS1c (N=6) e rAd (N=5). Animais não-tratados (N=4) são usados para controles negativos.

Exemplo 6: Construção de um agonístico TLR-3 expresso.

Um segmento curto de 45 bp de DNA foi sintetizado por ordenação de oligos de DNA que quando recozidos juntos formam um segmento de 45 bp designado para produzir um grampo de cabelo de RNA de filamento duplo (GAAACGATATGGGCTGAATACGGATCCGTATTCAGCCCATATCGTTTC) (SEQ ID Nº:10). Este segmento curto (denominado luc1) foi clonado no plasmídeo pSK contendo o promotor beta actinahumano e uma cauda A poli BGH. Este plasmídeo é denominado pSkLuc1.

Exemplo 7: As funções pSK-luc1 em culturas de célula dendrítica similares a poli I:C, os efeitos de poli I:C e rAd são aditivos.

Para determinar se o agonístico TLR-3 expresso do Exemplo 6 acima pode funcionar como um indutor de citocinas pró-inflamatórias e maturação de célula dendrítica similares a poli I:C ligante de TLR-3, um agonístico dsTLR-3 expresso foi testado em culturas de célula dendrítica. Tutanos

de osso de fêmures de camundongos Balb/c foram cultivados com ligante fti-3 (200 ng/ml), 5% de soro, em meio DMEM de modo a produzir culturas de célula dendrítica primária. Cinco dias após as culturas de tutano de osso primária serem assentadas, 293 células foram transfectadas com, ou pSK-luc1, pSK-beta 2 (um segmento longo de beta galactosidase que forma um grampo de cabelo de 200 bp), ou pcDNA3 (vetor de expressão vazio). No dia 6, as células transfectadas foram tratadas por irradiação UV (20 segundos a 40 kJ/cm²) para causar apoptose, e estas células foram dadas para as células dendríticas. Ou poli I:C (1 µg/ml), rAd (1 pfu/célula), rAd + poli I:C, células transfectadas pSK-luc1, células transfectadas pSK-beta2, ou células transfectadas pcDNA3, foram dados para as células dendríticas, e cultivadas durante toda a noite. Conforme mostrado na Figura 4A, células transfectadas pSK-luc1 podem aperfeiçoar significativamente ativação de célula dendrítica conforme medida pelo camundongo IL-6 ELISA. Os resultados deste experimento também mostram que a combinação de rAd mais ligante de TLR-3 (poli I:C) juntos pode aperfeiçoar grandemente a atividade da célula dendrítica.

Ligantes adicionais também foram testados. O agonístico TLR-3 colocado em SEQ ID Nº:11 (ml) também forma um grampo de cabelo de ds-RNA de aproximadamente o mesmo tamanho como luc1. Estes foram produzidos por sobreposição de oligonucleotídeos e recozimento dos mesmos juntos antes de clonagem no vetor pSK sob controle do promotor beta actina humano. Os vetores foram transfectados em 293 células e dados às células dendríticas primárias, conforme descrito antes. Conforme mostrado na Figura 4B, estes ligantes adicionais podem ativar células dendríticas similares às aquelas do ligante luc1 (Figura 4B).

Exemplo 8: Construção de um Quarto Vetor Adenoviral Quimérico (DS2) e vetores de clonagem rápida (DS2beta-luc e DS2C-luc).

Um ácido nucléico que codifica gp120 (do Programa de Reagente de Pesquisa e Referência de NIH AIDS) foi colocado sob controle de um promotor de CVM com um pequeno intron imediatamente a montante do códon de partida no vetor de lançadeira (pShuttleCMV, Qbiogene). Uma cauda

A poli A de bGH foi colocada a jusante do ácido nucléico que codifica gp120. O agonístico dsRNA TLR-3 luc1 sob o controle do promotor beta actinahumano e poli A (descrito no exemplo 5 acima) foi inserido no vetor gp120 p-Shuttle, tal que ambos o ácido nucléico que codifica gp120 e o ácido nucléico que codifica agonístico TLR-3 estavam contidos em um vetor simples sob o controle de dois promotores separados. A orientação da expressão do ácido nucléico que codifica o antígeno de interesse e a expressão do agonístico TLR-3 é ilustrada na Figura 5.

Dois vetores de lançadeira genéricos denominados DS2beta-luc (SEQ ID Nº:14) e DS2-luc (SEQ ID Nº:15) foram também construídos tal que o ácido nucléico que codifica qualquer antígeno de interesse podia ser inserido sob o promotor de CMV e, ou o promotor beta actinahumano ou o promotor de CMV, é usado para acionar expressão de um agonístico dsRNA TLR-3. Em particular, o vetor DS2-luc tem um local Kpn 1 único que um ácido nucléico que codifica um antígeno de interesse pode facilmente ser clonado. A proposta destes vetores é produzir construção de vetor subsequente mais fácil porque um ácido nucléico que codifica qualquer antígeno de interesse podia ser inserido no local de clonagem para manufaturar rapidamente um vetor capaz de induzir anticorpo e respostas de célula T contra o antígeno de interesse. Recombinação homóloga de DS2 com o vetor pAd (Qbiogene) foi realizada como antes de modo a gerar um vetor capaz de produzir recombinante Ad (E1/E3 retirado) que continha um ácido nucléico que codifica GFP e um ácido nucléico que codifica o agonístico dsRNA LR-3 luc1. O recombinante Ad foi gerado por transfecção do novo constructo de expressão de pAd-betaactin-luc1-CMV-gp120 em 293 células. As titulações foram medidas por métodos padrões.

Exemplo 9: Indução de uma reposta imune específica de antígeno em seguida a distribuição oral de DS2.

$1,0 \times 10^7$ PFU de, ou pAd-CMV-gp120 mais o agonístico TLR-3 luc1 (DS2), ou pAd-CMV-gp120 (rAd5), foram administrados a animais por administração oral na semana. Ambos os vírus expressam gp120 sob controle do promotor de CVM e usam adenovírus tipo 5 retirado de recombinan-

te E1/E3. Titulações de anticorpo para gp120 foram medidas no plasma 3 semanas após a administração de vírus por anti-gp120 IgG ELISA. O protocolo ELISA foi descrito antes (Tucker, *et al*, *Mol. Therapy* 8:392 (2004)). Os resultados demonstraram que DS2 pode induzir aproximadamente um aperfeiçoamento de 2 log na titulação de anticorpos para gp120, o antígeno heterólogo usado no experimento. O vetor DS2 compreende uma sequência de ácido nucléico que codifica expressão de gp120 e uma sequência de ácido nucléico que codifica expressão de um agonístico dsRNA TLR03. Como um controle positivo para o ensaio, soro de dois animais injetados subcutaneamente com 10 microgramas de proteína de gp120 mais Adjuvante Completo de Freund, foi também medido no anti-gp120 ELISA. Os animais não-tratados serviram como controles negativos para ELISA. Cada grupo continha 6 animais. Os resultados são ilustrados na Figura 6.

Exemplo 10: Indução de um resposta imune específica de antígeno em seguida a distribuição oral de DS3.

1,0x10⁷ PFU de, ou pAd-CMV-HA de gripe (de A/PR/8/34) mais o ácido poliuridílico ligante TLR7/8 (DS3), ou pAd-CMV-HA (rAd5), foram administrados a animais por administração oral na semana 0. Ambos os vírus expressam HA de gripe sob controle do promotor de CVM e usam adenovírus tipo 5 retirado de recombinante E1/E3. Titulações de anticorpo para HA foram medidas no plasma 3 semanas após a administração de vírus por HA de anti-gripe IgG ELISA. Cada grupo continha 6 animais. Os resultados são ilustrados na Figura 7.

Exemplo 11: Construção de um quinto, sexto e sétimo vetor adenoviral quimérico para, e (DS2b, DS2b e ND1.1 214).

O gene de HA de gripe (A/Indo/5/2005) foi sintetizado por Cel-Tek (Nashville, TN), e colocado no vetor pShuttleCMV (Qbiogene) que tinha um promotor de CMV com um pequeno intron imediatamente a montante do códon de partida no vetor de lançadeira. O luc1 DNA com promotor beta actin humano e poli A (descrito no exemplo 5) foram colocados no vetor a jusante do antígeno, na orientação mostrada na figura 5 para DS2b. A sequência de luc1 é (GAAACGATATGGGCTGAATACGGATCCGTATTCAGCCCATATCGTTTC)

(SEQ ID Nº:10), e o vetor pShuttle completado é colocado em SEQ ID Nº:6. Uma orientação alternativa de luc1 com promotor em um vetor de lançadeira é descrita como SEQ ID Nº:7, e é designada DS2b-for. Nós também construímos outro vetor pShuttle (denominado DS2bC-HA) (SEQ ID Nº:16) que

5 compreende dois promotores separados que acionam expressão do agonístico TLR-3 luc1 e HA de gripe acima descrito. A recombinação homóloga com o vetor pAd (Qbiogene) foi realizada como antes de modo a gerar vetores capazes de produzir recombinante Ad (E1/E3 retirado) que continha o ácido nucléico que codifica HA e o agonístico TLR-3 luc1 sob promotores

10 separados. O recombinante Ad foi gerado por transfecção do novo construído pAd em 293 células. As titulações foram medidas por métodos padrões. O vetor pAD completado contendo DS2C-luc foi denominado ND1.1 214 e depositado no depósito de patente ATCC em 22 de fevereiro de 2007 (Manassus, VA). A sequência de ácido nucléico deste vetor adenoviral quimérico

15 é colocada em SEQ ID Nº:17. O ácido nucléico que codifica o antígeno heterólogo está no texto em negrito, e é flanqueado por um local de reconhecimento Cla I na extremidade 5', e um local de reconhecimento Not I na extremidade 3'. A sequência de ácido nucléico que codifica os agonísticos TLR-3 está em itálico, com a sequência ligadora em negrito. Uma sequência

20 de ácido nucléico que codifica qualquer antígeno de interesse, e uma sequência de ácido nucléico que codifica qualquer agonístico TLR-3 expresso, podem ser inseridas no vetor adenoviral quimérico.

Exemplo 12: Indução de uma resposta imune específica de antígeno em seguida a distribuição oral de DS2b.

25 1,0x10⁷ PFU de, ou pAd-CMV-HA mais os agonísticos TLR-3 luc1 na orientação reversa (DS2b-for), ou orientação de avanço (DS2b), ou pAd-CMV-HA (rAd5), foram administrados a animais por administração oral na semana 0. Estes vírus expressam HA de gripe de antígeno sob controle do promotor de CVM, e usam adenovírus tipo 5 retirado de recombinante

30 E1/E3. Titulações de anticorpo para HA foram medidas no plasma 3 semanas após a administração de vírus por HA de anti-HA IgG ELISA. Os resultados demonstraram que o vetor DS2b induziu respostas de anticorpo para

proteína HA maior do que o vetor rAd padrão (rAd5). O vetor DS2b contém rAd5 que expressa HA, bem como expressa um agonístico de receptor 3 similar a toll (TLR-3), um grampo de cabelo de RNA de filamento duplo, demonstrando que o uso do ligante de dsRNA pode aperfeiçoar respostas imunes adaptativas a antígenos de interesse. Conforme mostrado na Figura 8A e Figura 6, dsRNA expresso pode aperfeiçoar respostas imunes adaptativas a antígenos heterólogos diferentes múltiplos. Os animais não-tratados serviram como controle negativo para ELISA. Cada grupo continha 6 animais.

Os vetores na orientação oposta (DS2for) foram examinados para respostas de anticorpo em seguida, ou a administração oral, ou intramuscular de $1,0 \times 10^7$ pfu de vírus por animal nas semanas 0 e 5. As respostas de anticorpo para HA foram medidas nas semanas 4 e 7 pós administração inicial. Conforme mostrado na Figura 8B, o vetor de orientação oposta pode também induzir respostas de anticorpo substanciais para antígenos heterólogos. Os vetores DS1b e DS1bfor induzem respostas similares para HA no ponto de tempo de semana 4. Significativamente, o efeito de agrupamento da resposta de anticorpo foi demonstrado com o vetor DS1for, e mostrou que doses múltiplas podiam ser usadas para aumentar as respostas de anticorpo ao antígeno heterólogo. Outro exemplo de potencial da aproximação de vetor adenoviral quimérico foi demonstrado também. O vetor ND1. 1 214 foi dado a animais por administração oral ($1,0 \times 10^7$ pfu) ou intranasal (3×10^6 pfu), e as respostas de anticorpo ao antígeno heterólogo foram medidas na semana 3. Conforme mostrado na Figura 8C, respostas de anticorpo substanciais para HA foram medidas em seguida a administração oral, bem além dos valores típicos de uma administração oral simples de vetor rAd.

Todas as publicações, publicações de patente, patentes, pedidos de N^ºs de Acesso no Banco de Genes citados neste relatório descritivo são aqui incorporados por referência em sua totalidade para todas as propostas como se cada publicação individual, publicação de patente, ou patentes, fossem especificamente e individualmente indicadas para serem incorporados por referência.

Listagem de Sequência Informal

SEQ ID NO:1 (DS1)

taacatcatc aataatatac cttatttttg attgaagcca atatgataat
 gagggggtg agtttgtgac gtggcgcggt gcgtgggaac ggggcgggtg
 acgtagtagt gtggcggaag tgtgatgttg caagtgtggc ggaacacatg
 taagcgacgg atgtggcaaa agtgacgttt ttggtgtgag ccggtgtaca
 caggaagtga caattttcgc gcggttttag gcggatgttg tagtaaattt
 gggcgtaacc gagtaagatt tggccatttt cgcgggaaaa ctgaataaga
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 GGTACTGGCCAcagagcttggcccattgcatacgttgtatccatatacataatattgtacattt
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 CATCACAATTTTACAAATAAAGCATTTTTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAAAC
 TCATCAATGTATCTTATCATGTCTGgatctggg cgtgggtaag

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<211> 10153

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<400> 6

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ccctcattat catattggtc tcaatccaaa ataaggata ttattgatga tnnnnnttaa 39300
t 39301

REIVINDICAÇÕES

1. Vetor de expressão adenoviral quimérico, referido vetor compreendendo um cassete de expressão compreendendo os seguintes elementos:

- 5 (a) um primeiro promotor operavelmente ligado a um ácido nucleico que codifica um agonístico de receptor-3 (TLR-3) similar a toll; e
 (b) um segundo promotor operavelmente ligado a um ácido nucleico que codifica um polipeptídeo heterólogo.

10 2. Vetor de expressão adenoviral quimérico, de acordo com a reivindicação 1, no qual o ácido nucleico que codifica o agonístico TLR-3 compreende um ácido nucleico que codifica um dsBNA.

 3. Vetor de expressão adenoviral quimérico, de acordo com a reivindicação 1, no qual o ácido nucleico que codifica o agonístico TLR-3 compreende uma seqüência selecionada a partir do grupo consistindo em:
15 SEQ ID N^{os}: 3, 4, 5, 8, 9, 10, 11 e 12.

 4. Vetor de expressão adenoviral quimérico, de acordo com a reivindicação 1, no qual o polipeptídeo heterólogo é um polipeptídeo de HIV env.

20 5. Vetor de expressão adenoviral quimérico, de acordo com a reivindicação 4, no qual o polipeptídeo de HIV env é selecionado a partir do grupo consistindo em: gp41, gp120 e gp160.

 6. Vetor de expressão adenoviral quimérico, de acordo com a reivindicação 1, no qual o polipeptídeo heterólogo é um polipeptídeo de gripe HA.

25 7. Vetor de expressão adenoviral quimérico, de acordo com a reivindicação 1, no qual o primeiro promotor e o segundo promotor são os mesmos.

 8. Vetor de expressão adenoviral quimérico, de acordo com a reivindicação 7, no qual o primeiro promotor e o segundo promotor são cada um promotor de CMV.

30 9. Composição imunogênica compreendendo o vetor de expressão como definido na reivindicação 1, e um veículo farmacologicamente aceitável.

10. Método para induzir uma resposta imune, referido método compreendendo administrar uma quantidade imunologicamente eficaz do vetor como definido na reivindicação 1, a um indivíduo mamífero, no qual a resposta imune é dirigida contra os polipeptídeos heterólogos, e no qual a
5 via de administração é selecionada a partir do grupo consistindo em: oral, intranasal e mucosal.

11. Método, de acordo com a reivindicação 10, no qual o polipeptídeo heterólogo é expresso em uma célula selecionada a partir do grupo consistindo em: uma célula dendrítica, uma célula de microdobra, e uma cé-
10 lula epitelial intestinal.

12. Método, de acordo com a reivindicação 10, no qual referido mamífero é um ser humano.

13. Composição imunogênica, referida composição compreendendo:

15 (a) um vetor de expressão adenoviral quimérico compreendendo um promotor operavelmente ligado a um ácido nucleico que codifica um polipeptídeo heterólogo;

(b) um agonístico TLR-3; e

(c) um veículo farmacêuticamente aceitável.

20 14. Composição, de acordo com a reivindicação 13, no qual o promotor é um CMV.

15. Composição, de acordo com a reivindicação 13, no qual o agonístico TLR-3 é selecionado a partir do grupo consistindo em: dsRNA e poli I:C.

25 16. Composição, de acordo com a reivindicação 13, no qual o polipeptídeo heterólogo é um polipeptídeo de HIV env.

17. Composição, de acordo com a reivindicação 16, no qual o polipeptídeo de HIV env é selecionado a partir do grupo consistindo em: gp41, gp120 e gp160.

30 18. Composição, de acordo com a reivindicação 13, no qual o polipeptídeo heterólogo é um polipeptídeo de gripe HA.

19. Composição, de acordo com a reivindicação 13, no qual o

agonístico TLR-3 é administrado dentro de 48 horas da administração do polipeptídeo heterólogo.

20. Composição, de acordo com a reivindicação 13, no qual o agonístico TLR-3 é um ácido nucléico compreendendo uma sequência selecionada a partir do grupo consistindo em: SEQ ID N^{os}: 3, 4, 5, 8, 9, 10, 11 e 12.

21. Método para induzir uma resposta imune, referido método compreendendo administrar a um indivíduo mamífero

(a) um vetor de expressão adenoviral quimérico compreendendo um promotor operavelmente ligado a um ácido nucléico que codifica um polipeptídeo heterólogo;

(b) um agonístico TLR-3;

no qual a resposta imune é dirigida contra o polipeptídeo heterólogo.

22. Método, de acordo com a reivindicação 21, no qual o promotor é selecionado a partir do grupo consistindo no: promotor de CMV e o promotor beta actina humana.

23. Método, de acordo com a reivindicação 21, no qual o polipeptídeo heterólogo é um polipeptídeo de HIV env.

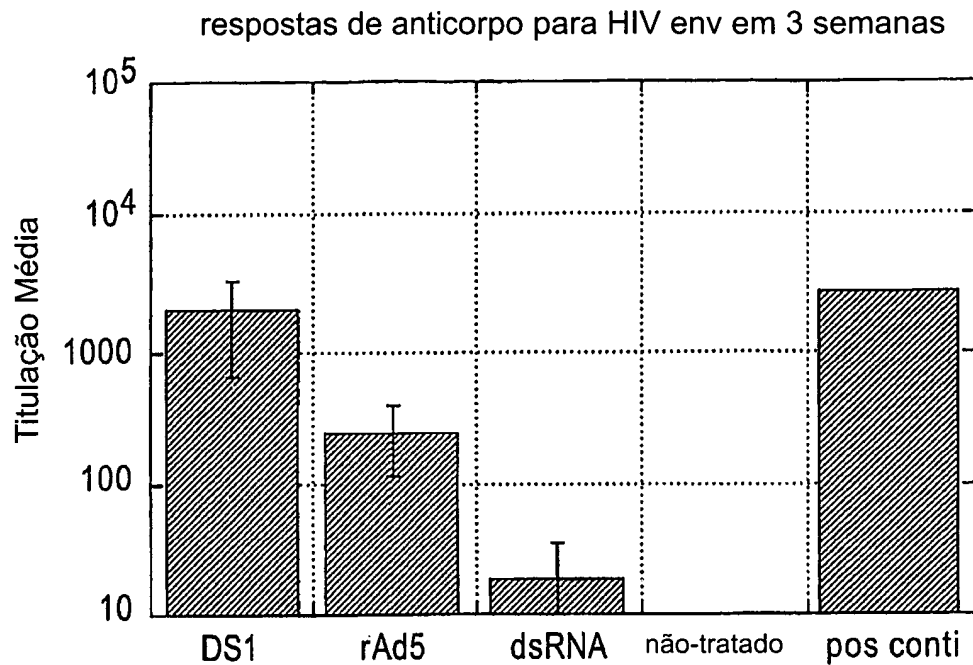
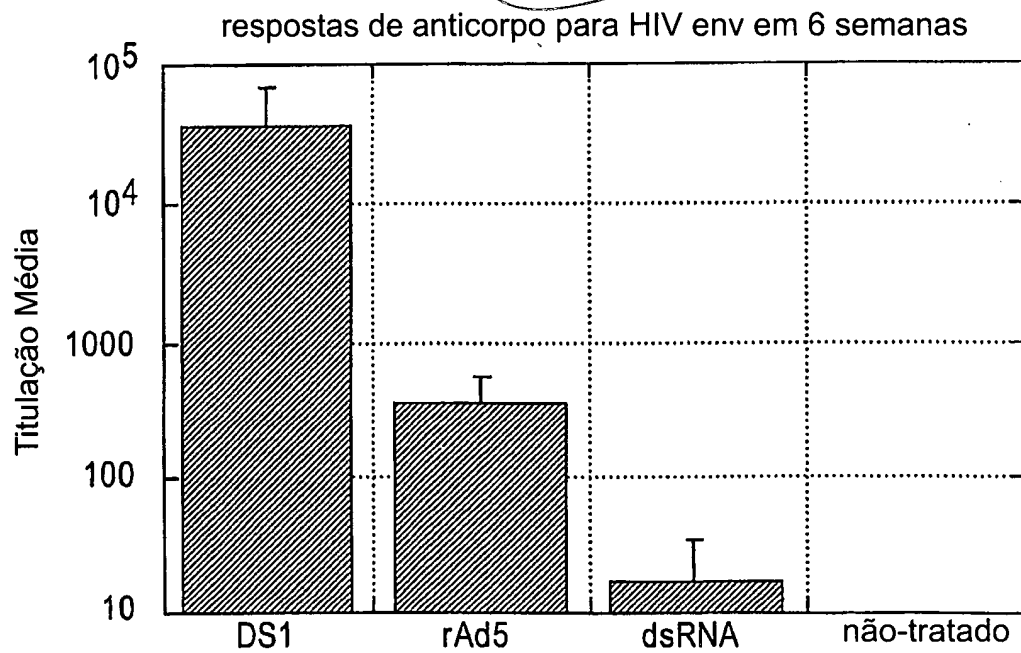
24. Método, de acordo com a reivindicação 23, no qual o polipeptídeo de HIV env é selecionado a partir do grupo consistindo em: gp41, gp120 e gp160.

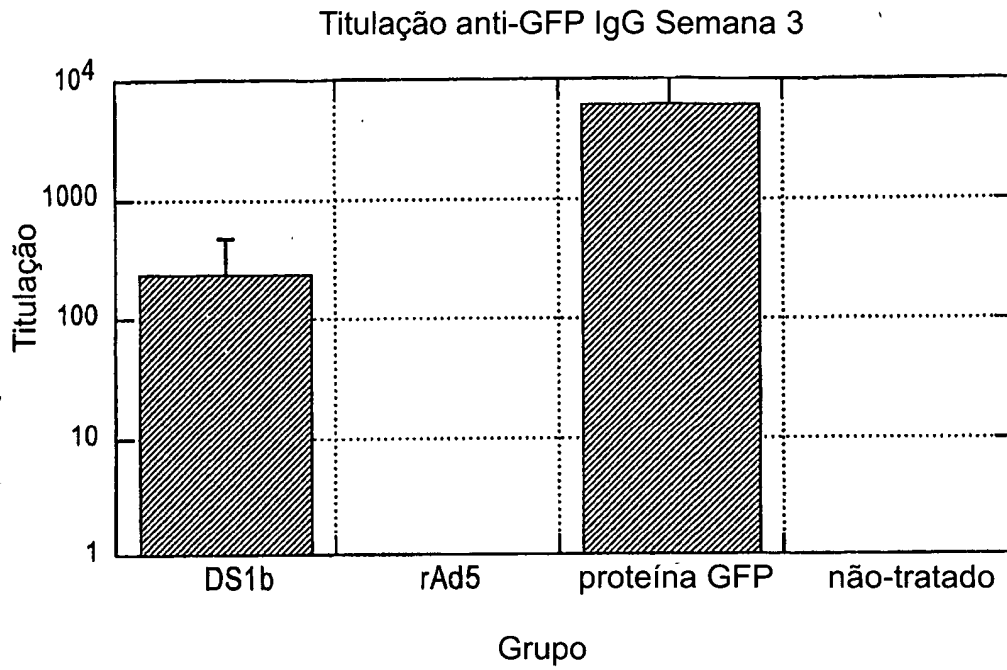
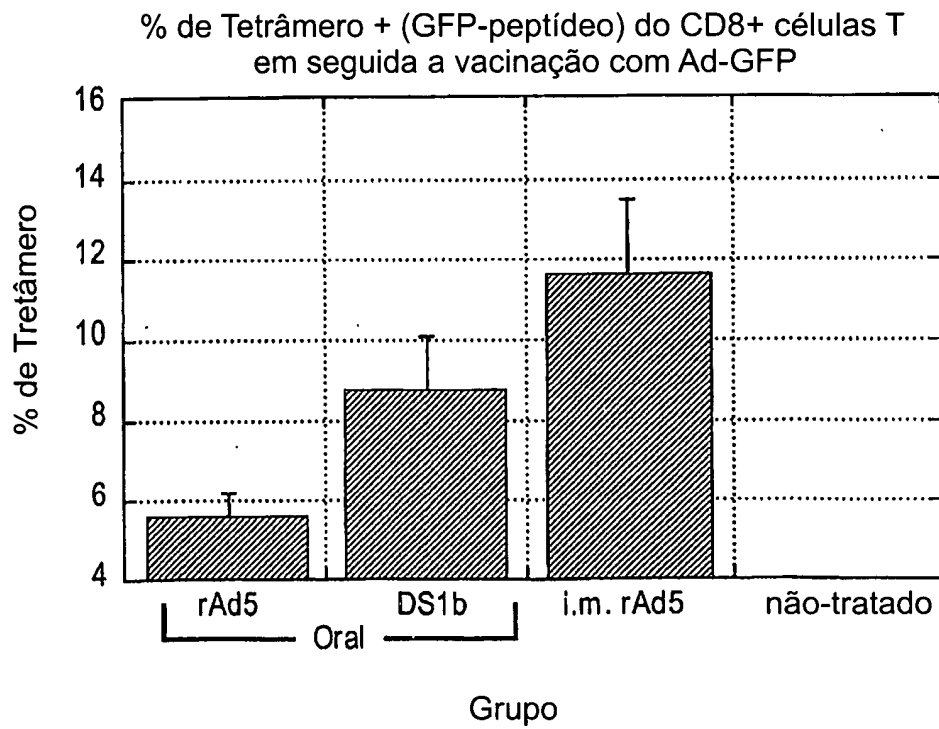
25. Método, de acordo com a reivindicação 21, no qual o polipeptídeo heterólogo é um polipeptídeo de gripe HA.

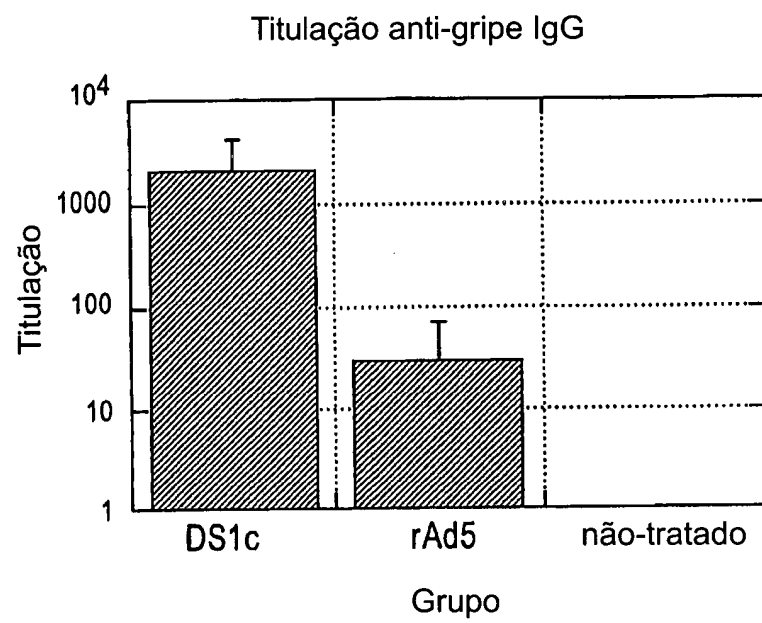
26. Método, de acordo com a reivindicação 21, no qual o agonístico TLR-3 é um dsRNA.

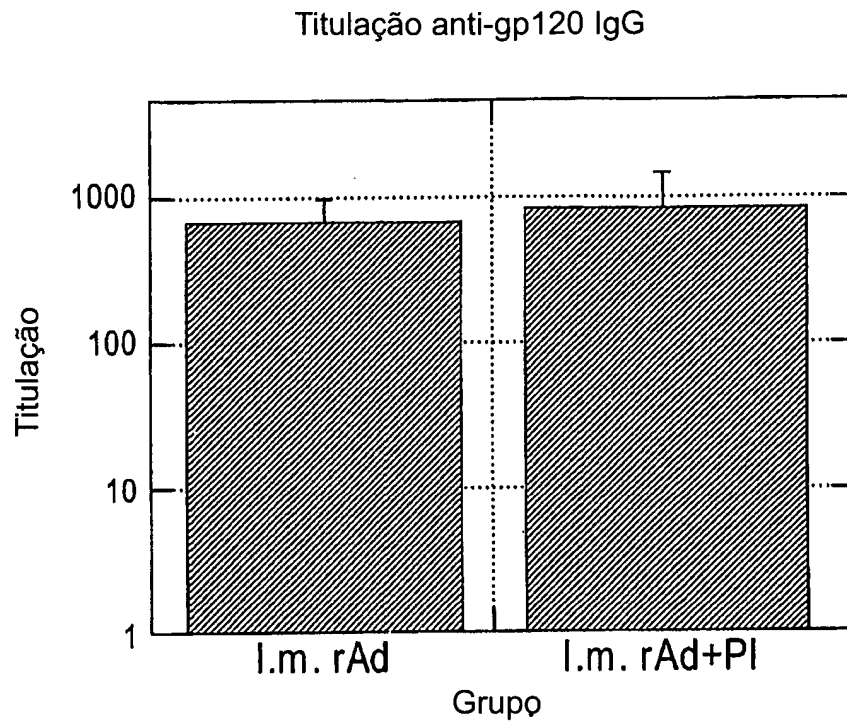
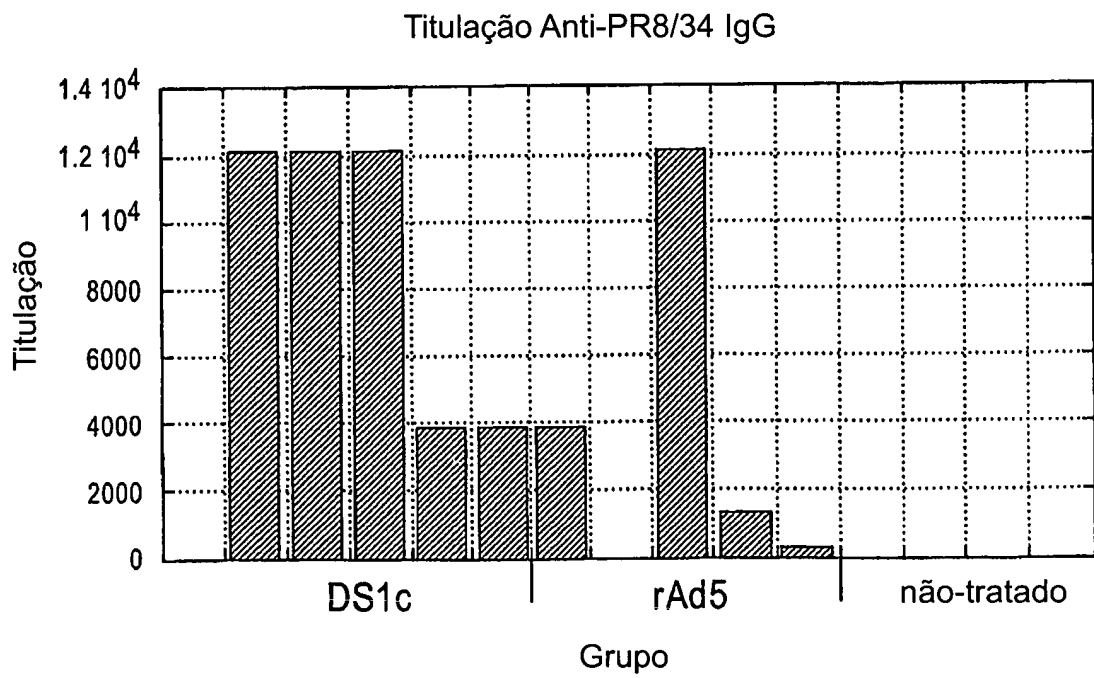
27. Método, de acordo com a reivindicação 21, no qual o agonístico TLR-3 é administrado dentro de 48 horas da administração do vetor de expressão adenoviral quimérico.

28. Ácido nucléico isolado compreendendo a sequência colocada em SEQ ID N^{os}: 1, 2, 3, 7, 14, 15, 16 ou 17.

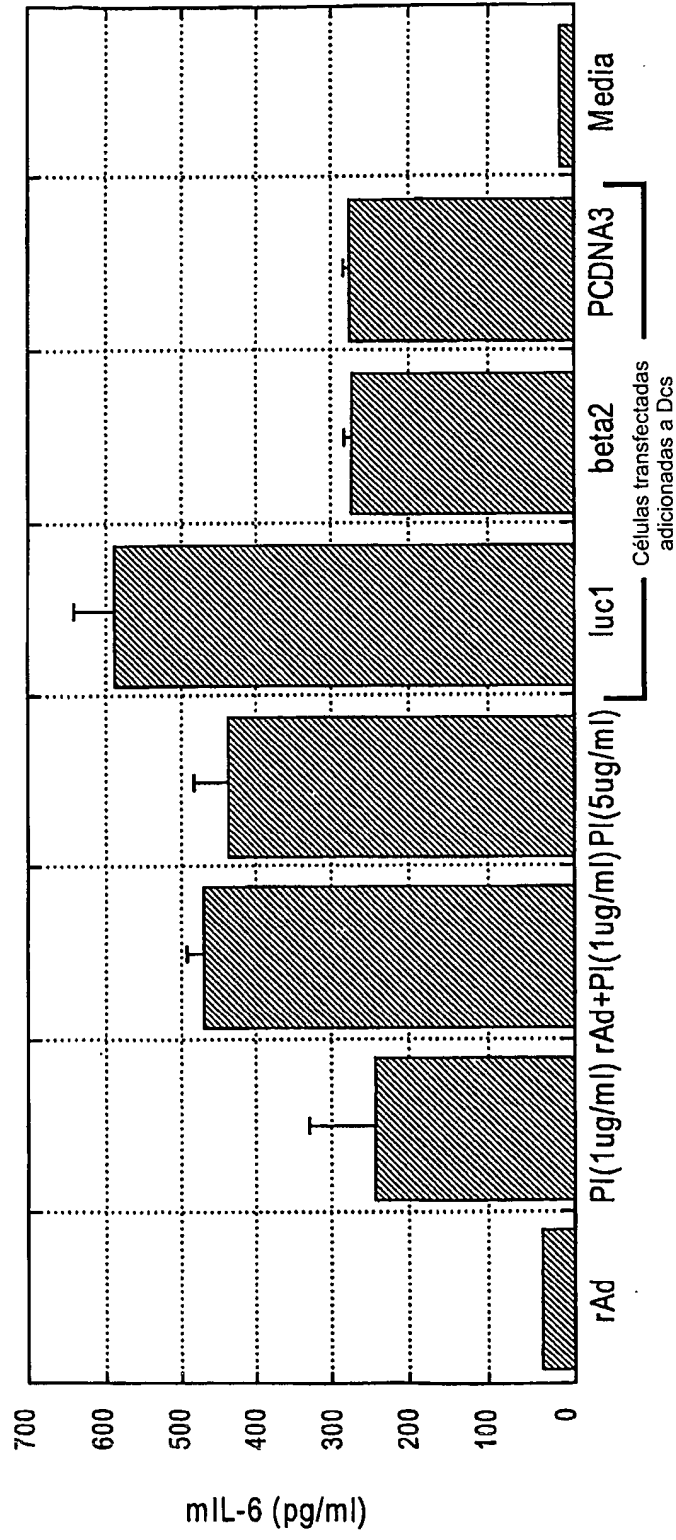
**FIG. 1A****FIG. 1B**

**FIG. 2A****FIG. 2B**

**FIG. 2C**

**FIG. 3A****FIG. 3B**

Secreção de célula dendrítica de IL-6 em resposta a estímulo



Grupo

FIG. 4A

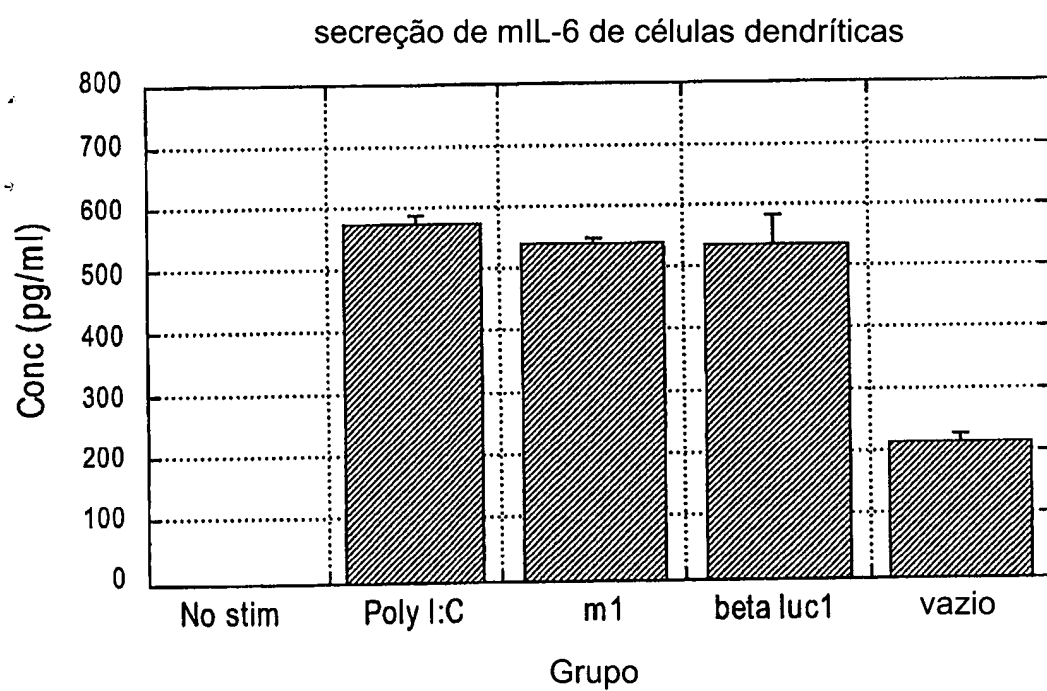
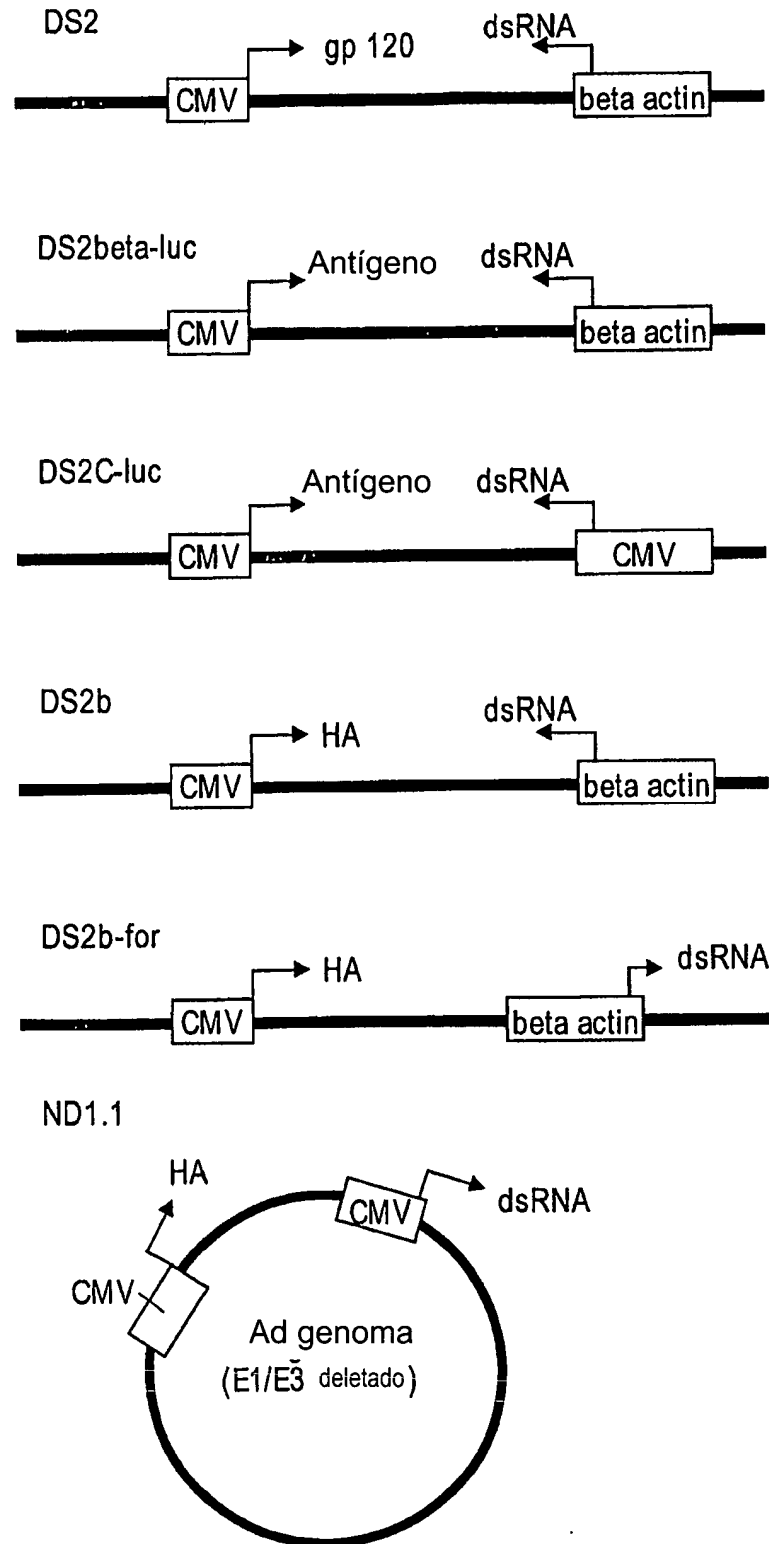
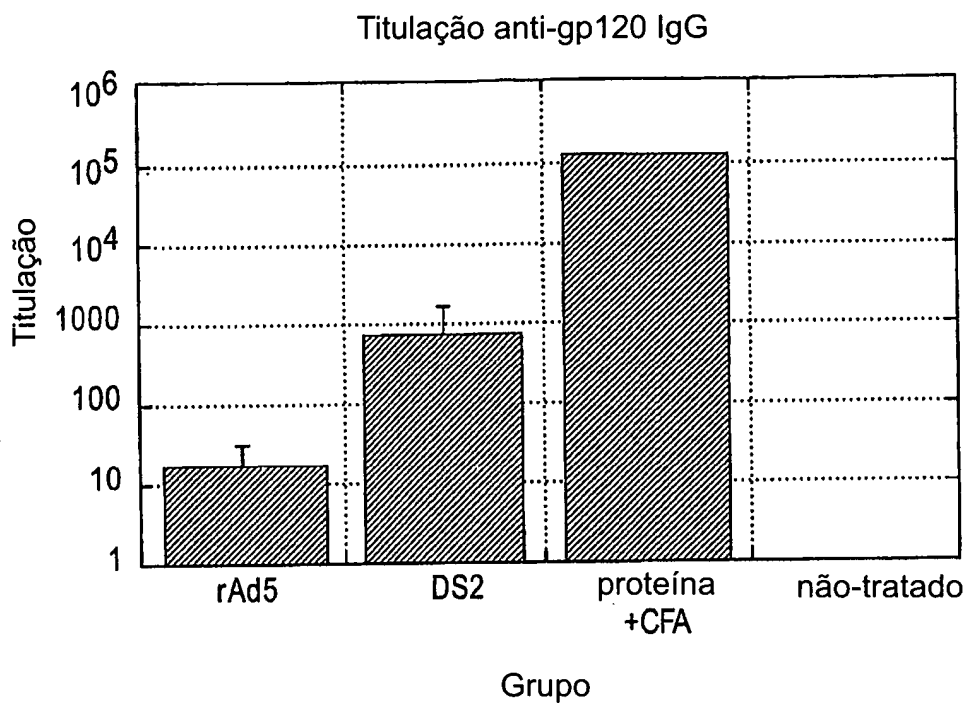
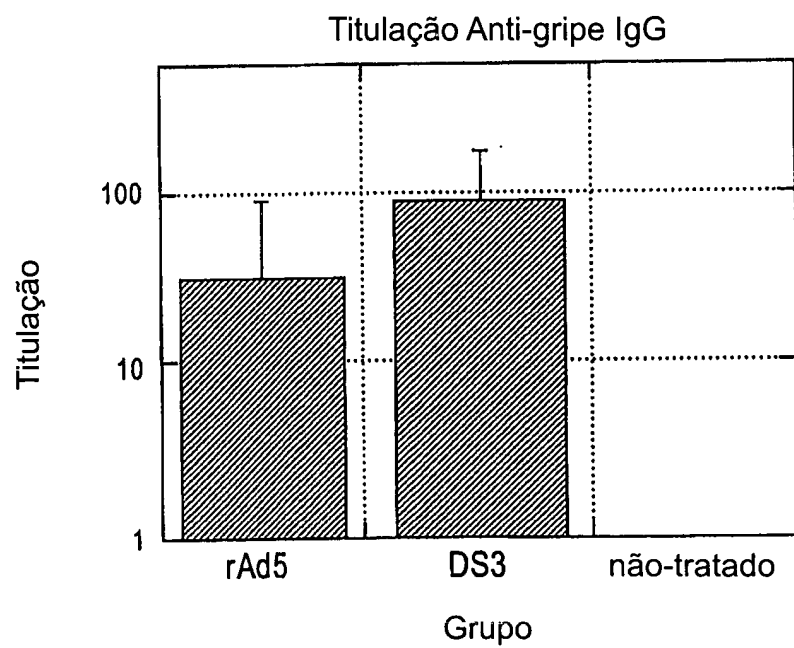
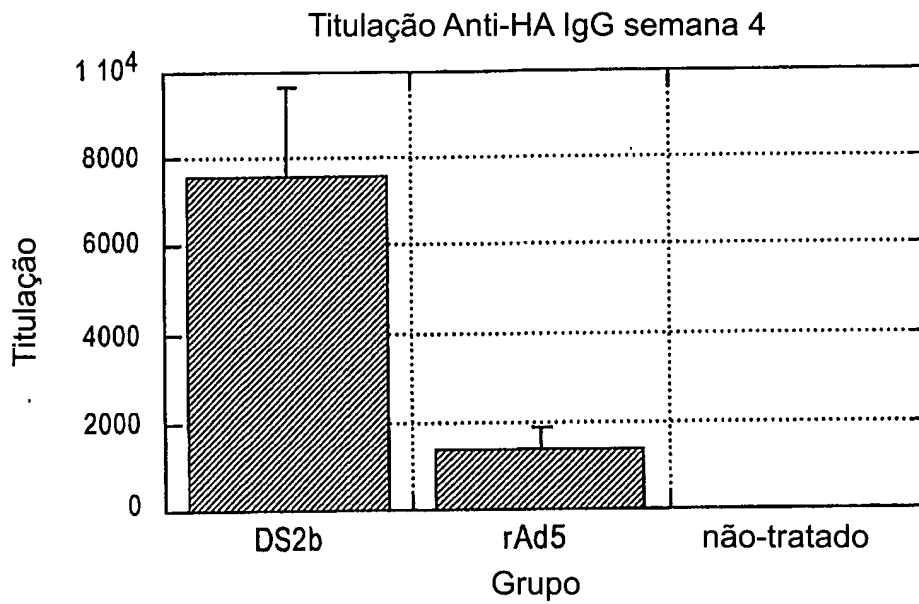
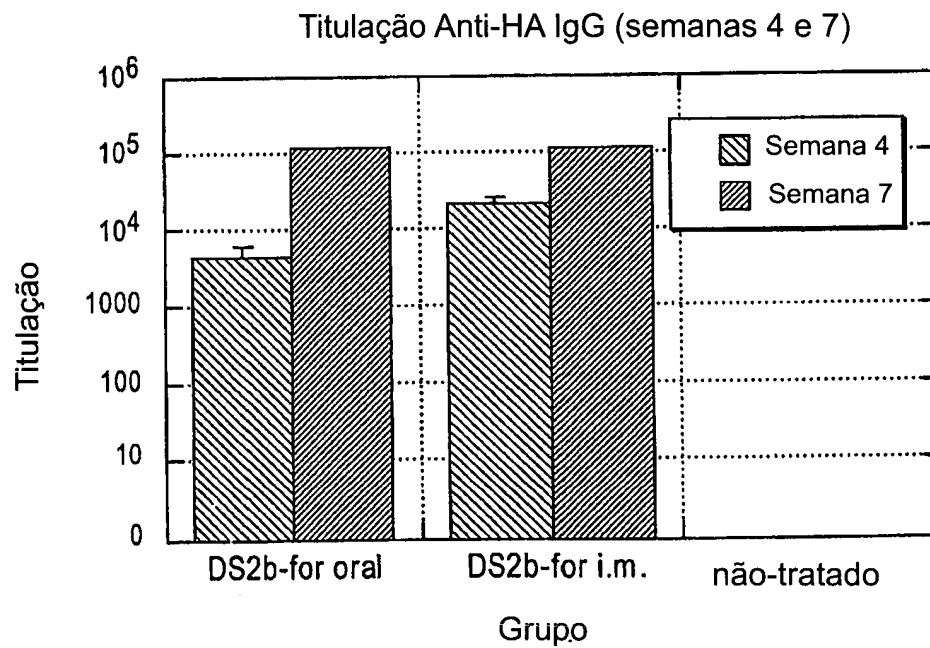
**FIG. 4B**

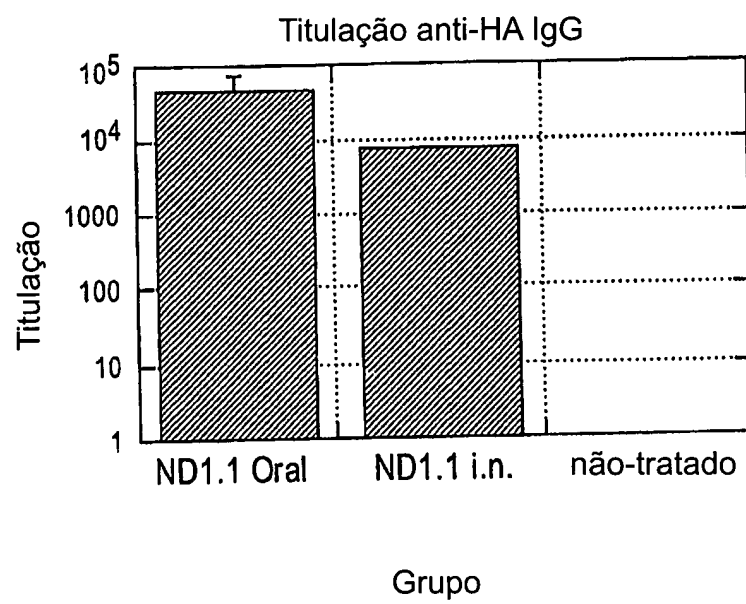
FIG. 5

Construções de dsRNA expressas



**FIG. 6****FIG. 7**

**FIG. 8A****FIG. 8B**

**FIG. 8C**

RESUMO

Patente de Invenção: "VETORES ADENOVIRAIS QUIMÉRICOS".

A presente invenção refere-se a vetores adenovirais quiméricos e métodos para uso dos vetores para induzir uma resposta imune a um antígeno de interesse.

Novas páginas 6-7, 41-43 e 47 do relatório descritivo para processamento na Fase Nacional Brasileira.

o HA de gripe e o agonístico TLR-3 estão na mesma orientação.

SEQ ID Nº:7 coloca uma sequência de nucleotídeo para um vetor adenoviral quimérico compreendendo um ácido nucléico que codifica HA de gripe e um ácido nucléico que codifica um agonístico TLR-3 (luc), no qual
5 o HA de gripe e o agonístico TLR-3 estão na orientação oposta.

SEQ ID Nº:8 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto. Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

10 SEQ ID Nº:9 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto (g1). Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

15 SEQ ID Nº:10 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto (luc). Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

20 SEQ ID Nº:11 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto (m1). Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

25 SEQ ID Nº:12 coloca uma sequência de nucleotídeo que codifica um agonístico RNA TLR-3 em forma de grampo de cabelo curto. Porções complementares da sequência são mostradas em letras maiúsculas e a sequência articuladora é mostrada em letras de caso inferiores.

SEQ ID Nº:13 coloca a sequência de nucleotídeo para o vetor adenoviral quimérico DS1c. A sequência compreende um nucleotídeo que codifica HA(PR8/34).

30 SEQ ID Nº:14 coloca a sequência de nucleotídeo para o vetor adenoviral quimérico DS2beta-luc. O vetor compreende uma sequência que codifica o agonístico TLR-3 luc sob o controle do promotor beta actin. O vetor também compreende locais de clonagem abertos para inserção de se-

qüência(s) de ácido nucléico que codificam o antígeno de interesse.

SEQ ID Nº:15 coloca a seqüência de nucleotídeo para o vetor adenoviral quimérico DS2beta-luc. O vetor compreende uma seqüência que codifica o agonístico TLR-3 luc sob o controle do promotor de CMV. O vetor
5 também compreende locais de clonagem abertos para inserção de seqüência(s) de ácido nucléico que codificam o antígeno de interesse.

SEQ ID Nº:16 coloca a seqüência de nucleotídeo para o vetor pShuttle compreendendo uma seqüência de ácido nucléico que codifica o agonístico TLR-3 luc sob o controle do promotor de CMV e uma seqüência
10 de ácido nucléico que codifica HA (gripe aviária) sob o controle de um promotor de CMV separado.

SEQ ID Nº:17 coloca a seqüência de nucleotídeo para o vetor adenoviral quimérico ND1.1 214. O ácido nucléico que codifica o antígeno heterólogo está em um texto em negrito, e é flanqueado por um local de reconhecimento ClaI na extremidade 5', e um local de reconhecimento Not 1
15 na extremidade 3'. A seqüência de ácido nucléico que codifica os agonísticos TLR-3 está em itálico, com a seqüência articuladora em negrito.

Descrição Detalhada da Invenção

I. Introdução

20 A presente invenção proporciona novos vetores adenovirais quiméricos que podem ser administrados não-parenteralmente para induzir uma resposta imune contra um antígeno de interesse. Os vetores adenovirais quiméricos da invenção compreendem um ácido nucléico que codifica um polipeptídeo heterólogo, e um ácido nucléico que codifica um agonístico
25 TLR-3. Os vetores adenovirais quiméricos induzem respostas imunes fortes e eficazes específicas para o polipeptídeo heterólogo, particularmente quando aplicado via uma via não-parenteral (por exemplo, oral, intranasal, ou mucosamente).

A invenção é baseada na descoberta surpreendente que a
30 administração de agonísticos dsRNA TLR-3 são adjuvantes específicos quando administrados em conjunto com vetores virais. De fato, o uso de dsRNA como um adjuvante para vetores virais seria contra-intuitivo,

determinada usando-se um espectrofotomedidor de cintilação líquida. Outros modos para detectar proliferação de célula T incluem medição do aumento na produção de interleukin-2(IL-2), fluxo de Ca^{2+} , ou percepção de corante, tal como 3-(4,5-dimetiltiazol-2-il))-2,5-difeniltetrazolium. Alternativamente, a síntese de linfoquinas (por exemplo, interferon-gama) pode ser medida, ou o número relativo de células T que pode responder ao polipeptídeo imunogênico pode ser quantificado.

As respostas imunes de anticorpo (Respostas imunes humorais aka ou respostas de célula B), incluindo respostas de anticorpo mucosal, podem ser detectadas usando-se imunoensaios conhecidos na técnica [Tucker *et al.*, *Mol. Therapy*, 8, 392-399 (2003); Tucker *et al.*, *Vaccine*, 22, 2500-2504 (2004)]. Imunoensaios adequados incluem a técnica de imunoensaio de intercalamento de anticorpo monoclonal duplo de David *et al* (Patente dos Estados Unidos Nº 4.376.110); ensaios de intercalamento de anticorpo monoclonal-policlonal (Wide *et al.*, em Kirkham e Hunter, eds., *Radioimmunoassay Methods*, E e S. Livingstone, Edinburgh (1970)); o método de "western blot" de Gordon *et al.* (Patente dos Estados Unidos Nº 4.452.901); imunoprecipitação de ligante etiquetado (Brown *et al* (1980) *J. Biol. Chem.* 255:4980-4983); ensaios imunoabsorventes ligado por enzima (ELISA) conforme descrito, por exemplo, por Raines *et al.* (1982) *J. Biol. Chem.* 257:5154-5160; técnicas imunocitoquímicas, incluindo o uso de fluorocromos (Brooks *et al.* (1980) *Clin. Exp. Immunol.* 39:477); e neutralização de atividade (Bowen-Pope *et al.* (1984) *Proc. Natl. Acad. Sci. USA* 81:2396-2400). Em adição aos imunoensaios descritos acima, um número de outros imunoensaios são disponíveis, incluindo aqueles descritos nas Patentes dos Estados Unidos Nºs 3.817.827; 3.850.752; 3.901.654; 3.935.074; 3.984.533; 3.996.345; 4.034.074; e 4.098.876.

Exemplos

Os seguintes exemplos são pretendidos para ilustrarem, mas não limitarem a presente invenção.

Exemplo 1: Construção de um Vetor Adenoviral Quimérico (DS1)

Para demonstrar que agonistas TLR-3 podem aperfeiçoar res-

postas imunes adaptativas a antígenos expressos de interesse, vários vetores adenovirais quiméricos diferentes foram construídos, que compreendem seqüências de ácido nucléico que codificam vários antígenos diferentes de interesse. Neste exemplo, o ácido nucléico que codifica gp 120 (a partir do Programa de Reagente de Referência NIH AIDS) foi colocado sob controle de um promotor de CMV com um pequeno intron imediatamente a montante do códon de partida no vetor de lançadeira (pShuttle, Qbiogene). Uma calda poli A de bGH foi colocada a jusante do ácido nucléico que codifica gp120. A seqüência de vetor é colocada em SEQ ID Nº:1. A recombinação homóloga com o vetor pAd (Qbiogene) foi realizada para gerar um vetor capaz de produzir Ad recombinante (E1/E2 retirado), que contém o ácido nucléico que codifica gp120. DS1 foi gerado pela transferência do constructo de expressão pAd-CMV-gp120 nova em 293 células. As titulações foram medidas por métodos padrões.

Exemplo 2: DS1 (vetor mais agonístico TLR-3) é superior a rAd5 padrão para indução de uma resposta imune específica de antígeno

Para determinar se a adição de agonístico TLR-3 podia aperfeiçoar respostas imunes adaptativas, 10×10^7 PFU de ou rAd-CMV-gp120 mais 5 ug/ml de poli I:C (DSI), ou rAd-CMV-gap-120 somente (rAd5), foram administrados a animais por administração oral nas semanas 0 e 3. Ambos os vetores expressam HIV gp120 sob controle do promotor de CVM e usam adenovírus tipo 5 retirado de recombinante E1/E3. Titulações de anticorpo a gp120 foram medidas no plasma 3 e 6 semanas após a administração inicial por anti-gp120 IgG ELISA, conforme descrito em Tucker, *et al.*, *Mol. Ther* 8:392 (2004)). Conforme mostrado na Figura 1, DSI se portou significativamente melhor do que rAd5 na indução de respostas de anticorpo para gp120 ambos em 3 e 6 semanas pós administração oral inicial. Em particular, a titulação de anticorpo média para gp120 foi 100 vezes melhor com o grupo DSI do que com o grupo rAd5 na semana 6. Parece também que o grupo DSI foi agrupado por re-administração na semana 4 em que a titulação média aumentou mais do que 20 vezes entre as semanas 3 e 6 onde o grupo rAd5 mostrou somente um leve aumento na titulação de anticorpo média. Os re-

sultados demonstraram que a adição de um agonístico TLR-3 pode aperfeiçoar grandemente respostas de anticorpo mediadas por Ad5 a antígenos de interesse em seguida a administração oral de um vetor adenovírus quimérico compreendendo um ácido nucléico que codifica o antígeno de interesse.

- 5 Como um controle positivo para o ensaio, soro de um animal injetado subcutaneamente com gp120 mais Adjuvante Completo de Freund foi também medido no anti-gp120 ELISA na semana 3. Os animais não-tratados e animais administrados com o análogo dsRNA somente (dsRNA) serviram como controles negativo e antecedentes respectivamente para a ELISA. Cada grupo contém 6 animais.

Exemplo 3: Construção de Um Segundo Vetor Adenoviral Quimérico (DS1b) e um Terceiro Vetor Adenoviral Quimérico (DS1c)

- Um ácido nucléico que codifica proteína fluorescente verde (GFP) foi inserido em pShuttle-CMV (Qbiogene) usando-se digestões de enzima de restrição padrão. O plasmídeo pShuttleCMV-GFP foi combinado por recombinação homóloga com o vetor pAd(Qbiogene), conforme descrito antes, de modo a gerar um vetor capaz de produzir recombinante Ad(E1/E3 retirado) compreendendo uma sequência de ácido nucléico que codifica GFP. Um ácido nucléico que codifica hemaglutinin (HA) de gripe A/PR/8/34 foi clonado e colocado no vetor pShuttle-CMV (Qbiogene) (SEQ ID Nº:13). O plasmídeo pShuttleCVM-HA (PR/8) foi combinado por recombinação homóloga com o vetor pAd(Qbiogene), conforme descrito antes, de modo a gerar um vetor capaz de produzir recombinante Ad(E1/E3 retirado) compreendendo uma sequência de ácido nucléico que codifica HA. O recombinante Ad foi gerado por transfecção do novo constructo de expressão de pAd-CMV-GFP e pAd-CMV-HA em 239 células. As titulações foram medidas por métodos padrões.

- Exemplo 4: DS1b (Ad-CMV-GFP mais agonístico LTR-3) e DS1c (Ad-CMV-HA mais agonístico TLR-3) é superior a rAd5 padrão para indução de uma resposta imune específica de antígeno.

$1,0 \times 10^7$ PFU de ou Ad-CMV-GFP mais 5 ug/ml de poli I:C (DS1b), ou Ad-CMV-GFP (rAd5), foram administrados a animais por admi-

A poli A de bGH foi colocada a jusante do ácido nucléico que codifica gp120. O agonístico dsRNA TLR-3 luc1 sob o controle do promotor beta actinahumano e poli A (descrito no exemplo 5 acima) foi inserido no vetor gp120 p-Shuttle, tal que ambos o ácido nucléico que codifica gp120 e o ácido nucléico que codifica agonístico TLR-3 estavam contidos em um vetor simples sob o controle de dois promotores separados. A orientação da expressão do ácido nucléico que codifica o antígeno de interesse e a expressão do agonístico TLR-3 é ilustrada na Figura 5.

Dois vetores de lançadeira genéricos denominados DS2beta-luc (SEQ ID Nº:14) e DS2-luc (SEQ ID Nº:15) foram também construídos tal que o ácido nucléico que codifica qualquer antígeno de interesse podia ser inserido sob o promotor de CMV e, ou o promotor beta actinahumano ou o promotor de CMV, é usado para acionar expressão de um agonístico dsRNA TLR-3. Em particular, o vetor DS2-luc tem um local Kpn 1 único que um ácido nucléico que codifica um antígeno de interesse pode facilmente ser clonado. A proposta destes vetores é produzir construção de vetor subsequente mais fácil porque um ácido nucléico que codifica qualquer antígeno de interesse podia ser inserido no local de clonagem para manufaturar rapidamente um vetor capaz de induzir anticorpo e respostas de célula T contra o antígeno de interesse. Recombinação homóloga de DS2 com o vetor pAd (Qbiogene) foi realizada como antes de modo a gerar um vetor capaz de produzir recombinante Ad (E1/E3 retirado) que continha um ácido nucléico que codifica GFP e um ácido nucléico que codifica o agonístico dsRNA TLR-3 luc1. O recombinante Ad foi gerado por transfecção do novo constructo de expressão de pAd-betaactin-luc1-CMV-gp120 em 293 células. As titulações foram medidas por métodos padrões.

Exemplo 9: Indução de uma reposta imune específica de antígeno em seguida a distribuição oral de DS2.

$1,0 \times 10^7$ PFU de, ou pAd-CMV-gp120 mais o agonístico TLR-3 luc1 (DS2), ou pAd-CMV-gp120 (rAd5), foram administrados a animais por administração oral na semana. Ambos os vírus expressam gp120 sob controle do promotor de CVM e usam adenovírus tipo 5 retirado de recombinan-