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Modified polynucleotides for the production of oncology-related proteins and peptides

Abstract

The invention relates to compositions and methods for the preparation, manufacture and therapeutic use of oncology-related polynucleotides, oncology-related primary transcripts and oncology-related mmRNA molecules.

Images (4)



Classifications

■ **C07K14/535** Granulocyte CSF; Granulocyte-macrophage CSF

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US9587003B2

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Inventor: [Stephane Bancel](#), [Tirtha Chakraborty](#), [Antonin de Fougerolles](#), [Sayda M. Elbashir](#), [Matthias John](#), [Atanu Roy](#), [Susan Whoriskey](#), [Kristy M. Wood](#), [Paul Hatala](#), [Jason P. Schrum](#), [Kenechi Ejebe](#), [Jeff Lynn Ellsworth](#), [Justin Guild](#)

Current Assignee : [ModernaTx Inc](#)

Worldwide applications

2015 · [US](#) [US](#) [US](#) 2016 · [US](#) [US](#) [US](#) [US](#) 2017 · [US](#) [US](#) 2019 · [US](#) [US](#) 2020 · [US](#)

Application US15/015,684 events

2012-04-02 · Priority to US201261618868P

2016-02-04 · Application filed by ModernaTx Inc

2016-06-02 · Publication of US20160152678A1

2017-03-07 · Publication of US9587003B2

2017-03-07 · Application granted

Scroll down to page 51 in the file

51 of 304



Automatic Zoom



The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing file entitled MNC2USCON6SQLST.txt, created on Feb. 4, 2016 which is 91,364,237 Bytes in size. The information in electronic format of the sequence listing is incorporated by reference in its entirety.

REFERENCE TO LENGTHY TABLE

The specification includes a lengthy Table 6. Lengthy Table 6 has been submitted via EFS-Web in electronic format as follows: File name: MNC2TBL.txt, Date created: Feb. 4, 2016; File size: 538,729 Bytes and is incorporated herein by reference in its entirety. Please refer to the end of the specification for access instructions.

that avoid one or more of the problems in the art.

SUMMARY OF THE INVENTION

Described herein are compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of modified mRNA (mmRNA) molecules encoding at least one oncology-related polypeptide of interest.

The present invention provides a method of treating a disease, disorder and/or condition in a subject in need thereof by increasing the level of an oncology-related polypeptide of interest comprising administering to said subject an isolated polynucleotide encoding said oncology-related polypeptide. The disease, disorder and/or condition may

LENGTHY TABLES

The patent contains a lengthy table section. A copy of the table is available in electronic form from the USPTO web site (<http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US09587003B2>). An electronic copy of the table will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).


Open the link under the heading
that says “LENGTHY TABLES”

LENGTHY TABLES

The patent contains a lengthy table section. A copy of the table is available in electronic form from the USPTO web site (<http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US09587003B2>). An electronic copy of the table will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

Enter the patent number into this box, then click on “By Number” to access the sequence





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➡

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Enter sequence number 11652 in this box, then click on "Submit"

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Supplemental Data Results for **Patent # 9587003B2**

Modified polynucleotides for the production of oncology-related proteins and peptides

Summary of Information	
Number of Sequences	33915 
Number of Lengthy Tables	1 

Supplemental Results Section(s)

This document has 33915 sequences associated with it. If you would like to view one or more of these sequences, then indicate which numeric sequence or range of numeric sequences you would like to view in the text box below. For instance, let's say the document has 400 sequences. You can select any one of them for viewing by ordinal (say, "327"), or you can specify a range (e.g., "57-94"). Note that a large range may take a while to process; we recommend keeping ranges as small as possible. You can always hit "Back" and try a new sequence ID.

Enter Sequence ID or Range (1-33915)

→ →

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Viewing Sequence(s): 11652 of 33915 for Document # **9587003B2**

Search Format

View Sequence ID No:

[View Sequence](#)

SEQ ID NO 11652

LENGTH: 3387

TYPE: DNA

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence: Synthetic
coding sequence

SEQUENCE: 11652

Highlight then copy this 19-letter
sequence found in the 2760 region

ctgcaggaga	tcagaaagat	cctgaagaac	cccagcgccc	agtacgtgac	cgtgagcggc	2220
caggagttca	tgatcgagat	caagaacagc	gccgtgagct	gcatccccac	cgactgggtg	2280
aaggtgggca	gcaccaaggc	cgtgagcaga	ttccacagcc	ccttcatcgt	ggagaactac	2340
agacacctga	accagctgag	agagcagctg	gtgctggact	gcagcgccga	gtggctggac	2400
ttcctggaga	agttcagcga	gcactaccac	agcctgtgca	aggccgtgca	ccacctggcc	2460
accgtggact	gcatcttcag	cctggccaag	gtggccaagc	agggcgacta	ctgcagaccc	2520
accgtgcagg	aggagagaaa	gatcgtgatc	aagaacggca	gacaccccgt	gatcgacgtg	2580
ctgctgggcg	agcaggacca	gtacgtgccc	aacaacaccg	acctgagcga	ggacagcgag	2640
agagtgatga	tcatcaccgg	ccccaacatg	ggcggcaaga	gcagctacat	caagcaggtg	2700
gccctgatca	ccatcatggc	ccagatcggc	agctacgtgc	ccgcccagga	ggccaccatc	2760
ggcatcgtgg	acggcatctt	caccagaatg	ggcgccgccg	acaacatcta	caagggccag	2820
agcaccttca	tggaggagct	gaccgacacc	gccgagatca	tcagaaaggc	caccagccag	2880

Open a new browser instance, then proceed to open NIH's database of gene sequences

https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn&PAGE_TYPE=BlastSearch&LINK_LOC=blasthome

Your page will appear like this

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Standard Nucleotide BLAST

blastn blastp blastx tblastn tblastx

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Enter Query Sequence

Enter accession number(s), gi(s), or FASTA sequence(s) [?](#) [Clear](#)

Query subrange [?](#)

From

To

Or, upload file [?](#)

No file chosen

Job Title

Enter a descriptive title for your BLAST search [?](#)

☐ Align two or more sequences [?](#)

Place cursor in the “Enter Query Sequence” box indicated and paste copied sequence

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COVID election news employment fauci RGV colleges RGV life utilities evidence cares act autism contagion contact Moderna 1,000 'woke' com...

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blastn blastp blastx tblastn tblastx

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Enter accession number(s), gi(s), or FASTA sequence(s) [?](#) [Clear](#)

ctacgtgccccgcgaggag

Query subrange [?](#)

From

To

Or, upload file No file chosen [?](#)

Job Title

Enter a descriptive title for your BLAST search [?](#)

☐ Align two or more sequences [?](#)

Scroll down to the bottom and then click on “BLAST”

Program Selection

Optimize for

- ☒ Highly similar sequences (megablast)
- ☐ More dissimilar sequences (discontiguous megablast)
- ☐ Somewhat similar sequences (blastn)

Choose a BLAST algorithm ?



BLAST

Search database Nucleotide collection (nr/nt) using Megablast (Optimize for highly similar sequences)

☐ Show results in a new window

+ Algorithm parameters

The search may take 5 minutes. Be patient!

The screenshot shows the NCBI BLAST Nucleotide Sequence Search results page. The browser address bar shows the URL `blast.ncbi.nlm.nih.gov/Blast.cgi`. The page header includes the NIH logo and the text "U.S. National Library of Medicine National Center for Biotechnology Information". A "Log in" button is visible in the top right. A banner for "COVID-19 Information" is displayed, with links to "Public health information (CDC)", "Research information (NIH)", "SARS-CoV-2 data (NCBI)", "Prevention and treatment information (HHS)", and "Español". The main heading is "BLAST® » blastn suite » results for RID-1F9XBDS4013". Navigation links include "Home", "Recent Results", "Saved Strategies", and "Help". Below the heading, there are links for "< Edit Search", "Save Search", "Search Summary", "How to read this report?", "BLAST Help Videos", and "Back to Traditional Results Page". A message states: "Your search parameters were adjusted to search for a short input sequence." The left sidebar contains a table with search parameters:

Job Title	Nucleotide Sequence
RID	1F9XBDS4013 <small>Search expires on 02-25 22:43 pm</small> Download All ▼
Program	BLASTN ? Citation ▼
Database	nt See details ▼
Query ID	lcl Query_33799
Description	None
Molecule type	nucleic acid
Query Length	19
Other reports	Distance tree of results MSA viewer ?

The right sidebar is titled "Filter Results" and contains the following options:

- Organism**: only top 20 will appear ☐ exclude. A text box for "Type common name, binomial, taxid or group name" and a link "+ Add organism".
- Percent Identity**: Two input boxes separated by "to".
- E value**: Two input boxes separated by "to".
- Query Coverage**: Two input boxes separated by "to".
- Buttons: "Filter" and "Reset".

Your page will eventually appear like this

Scroll down and you will find links to all nucleotide sequences uploaded to NIH

Sequences producing significant alignments

[Download](#)[New](#)[Select columns](#)[Show](#)

100

☒ select all 100 sequences selected[GenBank](#)[Graphics](#)[Distance tree of results](#)[New](#)[MSA Viewer](#)

	Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/AZ-CDC-LC0527810/2022 O...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29232	OM724686.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1821/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29849	OM725650.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1813/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29831	OM725649.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1808/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29837	OM725648.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1807/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29827	OM725647.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1783/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29837	OM725646.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1782/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29823	OM725645.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1781/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29856	OM725644.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1780/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29835	OM725643.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1779/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29830	OM725642.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1777/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29830	OM725641.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1776/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29835	OM725640.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1774/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29827	OM725639.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1772/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29823	OM725638.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1770/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29819	OM725637.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1763/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29815	OM725636.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1695/...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29815	OM725635.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1671-...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29833	OM725634.1
<input checked="" type="checkbox"/>	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/SouthAfrica/NHLS-UCT-GS-1653-...	Severe acute res...	38.2	38.2	100%	4.4	100.00%	29874	OM725633.1

This is a sample of what you might see if you open one of these sequence links

NCBI Blast:Nucleotide Sequence x US9216205B2 - Modified polynucleotide The USPTO Publication Site for Issu +

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Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/IL-19193710/2021, complete genome
Sequence ID: [MZ576208.1](#) Length: 29789 Number of Matches: 1

Range 1: 23548 to 23566 [GenBank](#) [Graphics](#) [Next Match](#) [Previous Match](#)

Score	Expect	Identities	Gaps	Strand
38.2 bits(19)	3.2	19/19(100%)	0/19(0%)	Plus/Minus

Query 1 CTACGTGCCCCGCCGAGGAG 19
Sbjct 23566 CTACGTGCCCCGCCGAGGAG 23548

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Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/DOM/UNIBE004/2021 ORF1ab polyprotein (ORF1ab), ORF1a polyprotein (ORF1ab), surface glycoprotein (S), ORF3a protein (ORF3a), envelope protein (E), membrane glycoprotein (M), ORF6 protein (ORF6), ORF7a protein (ORF7a), and ORF7b (ORF7b) genes, complete cds; ORF8 gene, complete sequence; nucleocapsid phosphoprotein (N) gene, complete cds; and ORF10 protein (ORF10) gene, partial cds
Sequence ID: [MZ576192.1](#) Length: 29602 Number of Matches: 1

Range 1: 23538 to 23556 [GenBank](#) [Graphics](#) [Next Match](#) [Previous Match](#)

Score	Expect	Identities	Gaps	Strand
38.2 bits(19)	3.2	19/19(100%)	0/19(0%)	Plus/Minus

Query 1 CTACGTGCCCCGCCGAGGAG 19
Sbjct 23556 CTACGTGCCCCGCCGAGGAG 23538


Query 1 CTACGTGCCCCGCCGAGGAG 19
Sbjct 23556 CTACGTGCCCCGCCGAGGAG 23538

What is the significance of these results?

1. In 2013 Moderna applied to patent a “modified polynucleotide” that contains a 19-base sequence that is the reverse complement of a 19-base sequence in the COVID-19 virus.
2. This 19-base sequence does not occur in any other virus listed in the NIH database
3. This 19-base sequence contains the “furin cleavage site”(PRRAR)
4. The furin cleavage site plays a key role facilitating entry of the COVID-19 virus into human cells
5. The probability that the same 19-base sequence appeared in the virus by means of natural selection is 1 out of 3.6 trillion.

ACKNOWLEDGMENTS:








The power point is based on information provided in the following article:

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Emerging and Reemerging Viruses

MSH3 Homology and Potential Recombination Link to SARS-CoV-2 Furin Cleavage Site

 **Balamurali K. Ambati**¹,  **Akhil Varshney**²,  **Kenneth Lundstrom**^{3*},  **Giorgio Palú**⁴,  **Bruce D. Uhal**⁵,  **Vladimir N. Uversky**⁶ and  **Adam M. Brufsky**⁷

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<https://www.frontiersin.org/articles/10.3389/fviro.2022.834808/full>