**SUPPLEMENTARY INFORMATION**

**miR-Synth: a computational resource for the design of multi-site multi-target synthetic miRNAs**

Alessandro Laganà1,#,\*, Mario Acunzo1,#, Giulia Romano1, Alfredo Pulvirenti2, Dario Veneziano1,2, Luciano Cascione3, Rosalba Giugno2, Pierluigi Gasparini1, Dennis Shasha4, Alfredo Ferro2 & Carlo Maria Croce1,\*

1Department of Molecular Virology, Immunology and Medical Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA

2Department of Clinical and Molecular Biomedicine, University of Catania, Italy

3IOR - Institute of Oncology Research, Bellinzona, Switzerland

4Department of Computer Science, Courant Institute of Mathematical Sciences, New York University, New York, NY, USA

#These Authors equally contributed to the work.

\*Corresponding Authors

**S1. The miR-Synth pipeline**

miR-Synth is a computational tool for the design of multi-site multi-target artificial miRNAs available through a web interface. It accepts up to 8 target sequences and returns a list of synthetic miRNAs potentially able to target simultaneously the input sequences or subsets of them, together with details about the predicted interactions.

The miR-Synth pipeline consists of the following three steps: (i) Identification and filtering of repeated patterns, (ii) Design and filtering of miRNA sequences, (iii) Scoring and ranking of the designed miRNAs. A detailed description of these steps is given below.

*(i) Identification and filtering of repeated patterns*

Input sequences are screened for repeated patterns of 6 or 7 nucleotides, which will constitute the seed binding regions: 6 nt for 6mer and 7mer-A1 matches, 7 nt for 7mer-m8 and 8mer matches.

These binding sites are then filtered based on the following user-provided specifications:

* A site must appear at least *n* times on each target (Default: n=2).
* A site must be present in every target (Default: NO).
* Users can also provide a list of sequences that must not be targeted. In this case, all the seed sites that appear at least once in any of the provided sequences will be removed.

*(ii) Design and filtering of miRNA sequences*

For each seed site identified in the previous phase, all its instances are aligned together and an anti-complementary miRNA seed is created. The rest of the sequence is constructed by computing a consensus sequence through a simple profile technique, as depicted below. The miRNA sequences thus obtained will be 22 nt long.

*seed site*

…5’-**AA**TT**GA**CC**GAAG**CAG**TAGCAATA**TT-3’… mRNA-site1

…5’-**A**T**AGGAGTGA**T**GA**TA**TAGCAAT**CTG-3’… mRNA-site2

…5’-**A**G**A**A**GAGTGAAG**G**CCTAGCAATA**TT-3’… mRNA-site3

…5’-**A**\***A**\***GAGTGAAG**\*\*\***TAGCAATA**..-3’… Consensus.

---------------------------------- \_

…3’-TTTCCTCACTTCTGG**ATCGTTA**T-5’ miRNA\_\_\_\_\_

The seed region and its binding sites are in red, the matches in the 3’ region are in blue. Here below are the detailed interactions of the designed miRNA with each binding site.

…5’-AATTGACCGAAGCAG**TAGCAAT**ATT-3’… mRNA-site1

|| || |||| **|||||||**| \_

…3’-TTTCCTCACTTCTGG**ATCGTTA**T-5’ miRNA\_\_\_\_\_

…5’-ATAGGAGTGATGATA**TAGCAAT**CTG-3’… mRNA-site2

| |||||||| || **|||||||** \_

…3’-TTTCCTCACTTCTGG**ATCGTTA**T-5’ miRNA\_\_\_\_\_

…5’-AGAAGAGTGAAGGCC**TAGCAAT**ATT-3’… mRNA-site3

| | |||||||| ||**|||||||**| \_

…3’-TTTCCTCACTTCTGG**ATCGTTA**T-5’ miRNA\_\_\_\_\_

The designed miRNAs are then filtered based on their nucleotide composition. In particular:

* Sequences with GC content out of the user's specified range will be discarded (Default: 23% - 78%) (See section S2).
* Sequences containing stretches of six or more nucleotides of the same kind are discarded (See section S2).
* Sequences sharing a seed with an endogenous miRNA are discarded.

*(iii) Scoring and ranking of the designed miRNAs*

We developed a scoring function based on six different features of miRNA/target interactions coming from the literature. For any given miRNA, each feature is assigned a score ranging from 0 to 1. The features and the computation of the related scores is here described.

***Seed type***. We assigned a score to each of the 4 types of canonical seeds, based on the degree of repression typically yielded: 8mer = 1.0, 7mer-m8 = 0.7, 7mer-A1 = 0.5, 6mer = 0.4. Then, for each designed miRNA, the average seed score on its binding sites is computed.

***Degree of pairing of the miRNA 3' region***. This is simply computed as the fraction of paired bases in the miRNA/target duplex, excluding the seed area. Then, for each designed miRNA, the average 3’ match score on its binding sites is computed.

***AU content of the binding site and its surrounding regions***. This is computed as the fraction of A and U bases in the region which spans from 5 nt upstream to 5 nt downstream of the whole binding site. Then, for each designed miRNA, the average AU score on its binding sites is computed.

***miRNA nucleotide composition***. We assigned a score to the base pairs on each position of the miRNA/target duplex, based on the frequency of base pairs observed on a set of validated miRNA/target duplexes retrieved from the database Tarbase. For each miRNA binding site, this score is computed as the average value over the seed region.

***Structural accessibility of the binding sites***. For each binding site, local structural accessibility is calculated on a 160 nt window centered on the site, by using the program RNAplfold from the Vienna RNA Package1 with the following parameters: *W*=80, L=402,3 and *u*=4. *W* is the sliding window size, *L* is the maximum base pairing distance, and *u* is the stretch of consecutive nts within the target site for which the accessibility is computed. We consider the probability of 4 nt sub-sequences to be unpaired and compute the average value over the bases of the binding site4. Then, for each designed miRNA, the average accessibility score on its binding sites is computed.

***Presence of ARE and CPE motifs upstream of the binding sites***. For each binding site, the fraction of ARE (sequence: AUUUA) and CPE (sequence: UUUUUAU) motifs in the upstream region is computed. For each designed miRNA, the ARE/CPE score is computed as the average value over its binding sites.

***Repression Score***. For each designed miRNA, the total score is calculated by using the tree-based learning systems M5P and CTree, based on the scores of the 6 features described above. Both systems were trained on a set of publicly available gene expression profiles following the over-expression of nine individual endogenous human miRNAs5 (miR-9-5p, miR-7-5p, miR-181a-5p, miR-148b-3p, miR-142-5p, miR-133a, miR-132-3p, miR-128 and miR-122-5p). In particular, binding sites on down-regulated genes were predicted for each transfected miRNA, then feature scores were calculated. The gene expression fold change after 24h was used as a measure of the degree of repression induced by the miRNA. Thus, lower values mean stronger down-regulation of the target. Only transcripts with single binding sites for the transfected miRNAs were considered in order to reduce the chances of indirect effects. According to the M5P tree, the most discriminant features were the nucleotide composition of the miRNA, the type of seed and the AU content of the binding site. Depending on the values of these three, six different sets of weights were assigned to all of the features. Only the seed type and the nucleotide composition of the miRNA were considered as discriminant features by CTree. Fig. 1d and tables st1 contains details about the generated M5P tree and the corresponding sets of feature weights. Fig.1e describes the generated CTree and the score classes.

***Ranking of the designed miRNAs***. The miRNA produced by miR-Synth are first ranked according to the CTree score and subsequently by the M5P score. In particular, CTree splits the miRNAs into major classes, while M5P is used to rank miRNAs within each class.

**In-silico validation of the miR-Synth scoring function**

We validated the scoring function by using a database of experimentally validated human miRNA/target interactions called miRTarBase as a test set6. This dataset contains 495 cases of proven direct interactions, 490 cases of down-regulated genes for which direct binding wasn’t verified and 71 negative cases.

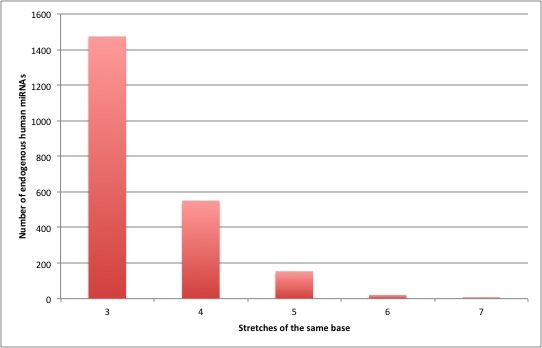
We randomly created 1,000 groups with 71 proven direct and 71 proven negative cases. For each group, we found that the top 10 interactions, as ranked by our approach, always contained a higher number of true direct interactions compared to 10,000 sets of 10 cases randomly chosen (P<0.0001). We obtained the same result when we considered random groups with 71 proven direct, 71 indirect and 71 proven negative cases and counted the number of proven direct interactions in the top 10 cases (P< 0.0001).

**S2. Basic miRNA and 3’ UTR descriptive statistics**

We performed some basic statistics on endogenous human mature miRNA sequences in order to identify typical values to be used by filters in the artificial miRNA selection process.

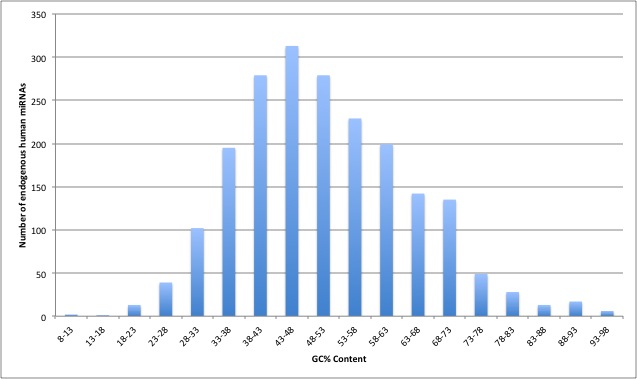
*Stretches of nucleotides of the same kind*

General siRNA guidelines recommend to avoid sequences with long stretches of the same kind of nucleotide. Endogenous human miRNAs commonly present stretches of 3 or 4 nucleotides of the same kind (72.2% and 26.9%, respectively), while stretches of 5, 6 and 7 nucleotides are more rare (7.5%, 1% and 0.4%, respectively) (Ref. miRBase Rel. 19 – 2042 mature sequences)7 (See chart below). We set 5 nt as the threshold for stretches of the same kind allowed for an artificial miRNA.



*GC content*

General siRNA guidelines recommend to avoid sequences with GC content <30% and >60%. GC content in endogenous human miRNAs vary from 8.69% to 100% (Ref. miRBase Rel. 19 – 2042 mature sequences)7. However, only 4% of them have GC content less than 23% and greater than 78%. We set 23%-78% as default range for artificial miRNAs’ GC content.



*Repeated patterns in human 3’ UTR sequences*

In order to appropriately set the maximum number of sequences that can be accepted as input to miR-Synth, we performed basic statistics on repeated patterns in the whole set of 40,110 human 3’ UTR sequences downloaded from the UCSC Genome Browser. We randomly picked 10,000 subsets of 2, 3, 4 and 5 sequences respectively, and counted how many of them shared at least a common 7mer. The results show that 64.3% pairs of sequences share at least a 7mer, with an average of 44.03 common 7mers. The table here below summarizes the results for all the groups.

|  |  |  |
| --- | --- | --- |
| **Group cardinality** | **% of groups sharing a 7mer** | **Average number of common 7mers** |
| 2 | 64.31% | 44.03 |
| 3 | 16.07% | 4.86 |
| 4 | 2.61% | 1.63 |
| 5 | 0.08% | 1 |

Based on these statistics and considering highly homologous sequences and the fact that users might also be interested in 6mer seeds, we decided to set a maximum threshold of 8 target sequences that users can provide as input to the system. We believe this is not a real limitation, since 8 is already a considerable number of targets, unlikely to be practical in most applications.

**References**

1. Lorenz, R. *et al.* ViennaRNA Package 2.0. *Algorithms for molecular biology : AMB* **6,** 26 (2011).

2. Tafer, H. *et al.* The impact of target site accessibility on the design of effective siRNAs. *Nat Biotechnol* **26,** 578–583 (2008).

3. Marín, R. M. & Vanícek, J. Efficient use of accessibility in microRNA target prediction. *Nucleic Acids Res* (2010). doi:10.1093/nar/gkq768

4. Long, D. *et al.* Potent effect of target structure on microRNA function. *Nat Struct Mol Biol* **14,** 287–294 (2007).

5. Grimson, A. *et al.* MicroRNA targeting specificity in mammals: determinants beyond seed pairing. *Mol Cell* **27,** 91–105 (2007).

6. Hsu, S. D. *et al.* miRTarBase: a database curates experimentally validated microRNA-target interactions. *Nucleic Acids Res* **39,** D163–D169 (2010).

7. Kozomara, A. & Griffiths-Jones, S. miRBase: integrating microRNA annotation and deep-sequencing data. *Nucleic Acids Res* **39,** D152–D157 (2010).

**Table S1**. Sets of feature weights assigned by M5P tree (see fig. 1d)

|  |  |  |
| --- | --- | --- |
| Group (leaf) | Feature | Weight |
| G1 | Seed Match | + 0.004 |
| 3’ Match | + 0.0071 |
| AU Content | + 0.0164 |
| Nucleotide Composition | + 1.3323 |
| Structural Accessibility | + 0.0732 |
| ARE/CPE motifs | + 0.0005 |
| Constant | - 0.8396 |
| G2 | Seed Match | + 0.004 |
| 3’ Match | + 0.0071 |
| AU Content | + 0.0164 |
| Nucleotide Composition | + 1.0936 |
| Structural Accessibility | + 0.0525 |
| ARE/CPE motifs | + 0.0005 |
| Constant | - 0.6601 |
| G3 | Seed Match | + 0.004 |
| 3’ Match | + 0.0032 |
| AU Content | + 0.0078 |
| Nucleotide Composition | + 2.5724 |
| Structural Accessibility | + 0.0066 |
| ARE/CPE motifs | + 0.0005 |
| Constant | - 1.3783 |
| G4 | Seed Match | + 0.0075 |
| 3’ Match | + 0.0034 |
| AU Content | - 0.0465 |
| Nucleotide Composition | + 0.3517 |
| Structural Accessibility | + 0.0074 |
| ARE/CPE motifs | - 0.0162 |
| Constant | - 0.2045 |
| G5 | Seed Match | - 0.0044 |
| 3’ Match | 0 |
| AU Content | + 0.0007 |
| Nucleotide Composition | + 0.3131 |
| Structural Accessibility | + 0.0009 |
| ARE/CPE motifs | + 0.0002 |
| Constant | - 0.3749 |
| G6 | Seed Match | - 0.2156 |
| 3’ Match | 0 |
| AU Content | + 0.0007 |
| Nucleotide Composition | + 0.2042 |
| Structural Accessibility | + 0.0009 |
| ARE/CPE motifs | + 0.0002 |
| Constant | - 0.1842 |

**Table S2.** Synthetic miRNAs for c-MET

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Rank** | **ID** | **Sequence** | **Sites** | **M5P score** | **Ctree score** |
| 1 | 60 | UUUGAAACGGAGGCUGUCUAGA | 3 | -0.26149351 | -0.224881716 |
| 2 | 118 | UUUAUAAAGUCGAUACGUGUUU | 3 | -0.260479749 | -0.224881716 |
| 3 | 181 | UUCUUUCUAAGGACGGGGCCGU | 2 | -0.253428787 | -0.224881716 |
| 4 | 176 | UCAGUACAAAACCUUGUGGCUU | 2 | -0.246296285 | -0.224881716 |
| 5 | 108 | UAAAUAUUAGACGACGAAUAAG | 3 | -0.242355599 | -0.224881716 |
| 6 | 165 | UUCCACAGUCGGGAGCUUCUCU | 2 | -0.240768881 | -0.224881716 |
| 7 | 167 | UGCACUAUGGCGGAGCUUGCAG | 2 | -0.234875889 | -0.224881716 |
| 8 | 35 | UAUAUGACUCCUGUGUUGUCCC | 2 | -0.231553603 | -0.224881716 |
| 9 | 53 | UUGAGUUUAGCUUUAACAAAAC | 3 | -0.231103438 | -0.224881716 |
| 10 | 81 | UACAAACAACGUGAGGGGUCUG | 2 | -0.230296126 | -0.224881716 |
| 11 | 140 | UUUGAGUUAGGGUGUGACACAC | 2 | -0.229173718 | -0.224881716 |
| 12 | 13 | UCAAGUCCACAUGUUGUGCUGU | 2 | -0.226153654 | -0.224881716 |
| 13 | 89 | UUGCAGUGAAGUCGGGGCCGAA | 3 | -0.225760484 | -0.224881716 |
| 14 | 173 | UUCAUGCUCAGGUCCCUGGCAG | 2 | -0.225516386 | -0.224881716 |
| 15 | 128 | UUAUUUCAACGUGACUUUCUUA | 2 | -0.225290884 | -0.224881716 |
| 16 | 36 | UCAAGUUUACCACUCGCAUACG | 2 | -0.223165296 | -0.224881716 |
| 17 | 43 | UUCCUGCUAGUCUUUCCCGCUG | 2 | -0.222018082 | -0.224881716 |
| 18 | 69 | UGUAAUGACCCUGGGGUGUGUC | 2 | -0.216304624 | -0.224881716 |
| 19 | 152 | CCAAUUGCGACCGUGGUGGGUU | 2 | -0.213761756 | -0.224881716 |
| 20 | 178 | UAGUCCUGAACAUGGGAUGUGG | 2 | -0.211142676 | -0.224881716 |
| 21 | 124 | UGUACAUUAGGUCCUGGCCAUU | 2 | -0.210068602 | -0.224881716 |
| 22 | 161 | UAAUAGCUCCCCUGUUCAAUUG | 2 | -0.20750942 | -0.224881716 |
| 23 | 164 | UCCACAGACGCGAGCUUCUCUU | 2 | -0.205812794 | -0.224881716 |
| 24 | 22 | UUUCCUUACGCCCCUGUACUGU | 2 | -0.204985723 | -0.224881716 |
| 25 | 41 | GGCUUCAACAGCCGAUGUGGUA | 2 | -0.202127102 | -0.224881716 |
| 26 | 61 | UUUUGAAAGGGUGGCUGUCUAG | 3 | -0.201722794 | -0.224881716 |
| 27 | 155 | UUUUGUUUGGUAUGGCUGGCGU | 2 | -0.200881894 | -0.224881716 |
| 28 | 143 | UCAUGCUGACAUUUCUCCCAGU | 2 | -0.20029129 | -0.224881716 |
| 29 | 21 | CCUUAGAACGGUGUCUUUCUCC | 2 | -0.197161863 | -0.224881716 |
| 30 | 141 | UAUUACUUCAGUCAUUUUGGGU | 2 | -0.196153669 | -0.224881716 |
| 31 | 38 | CAGAAUUCAUCUUGUGGGGCCC | 2 | -0.195643221 | -0.224881716 |
| 32 | 131 | UAGCAUCAGAGUGUUCCGGUGG | 2 | -0.194422456 | -0.224881716 |
| 33 | 67 | CCAUACAAGAGUCCUUAGUGUC | 2 | -0.190860619 | -0.224881716 |
| 34 | 136 | UGUUCACACACCUGUGUUCUGG | 2 | -0.190305003 | -0.224881716 |
| 35 | 11 | GCCUAUAAAACUGCUUCCUUGG | 2 | -0.189374926 | -0.224881716 |
| 36 | 112 | UAUUGCCUAAAUCUUUUGUUCC | 2 | -0.189195173 | -0.224881716 |
| 37 | 135 | GUUCACAUACGUGUGUUCUGAG | 2 | -0.18825176 | -0.224881716 |
| 38 | 126 | UACAAAUUAGGUGUCUGUCUUC | 2 | -0.184152565 | -0.224881716 |
| 39 | 68 | AAAAUGUUGUGGGCGACACAAC | 3 | -0.183729956 | -0.224881716 |
| 40 | 154 | UUUGUUUCGUUUGGCUGGCGUG | 2 | -0.18348581 | -0.224881716 |
| 41 | 179 | UCUAUUGACCGGCUGUGGGUCU | 2 | -0.181952092 | -0.224881716 |
| 42 | 39 | UUAUGAAAGCCCGUGGUUCGGG | 2 | -0.179847408 | -0.224881716 |
| 43 | 153 | UUGUUUCCGGCUGCUCGCGCGG | 2 | -0.179749929 | -0.224881716 |
| 44 | 10 | CGCAAUUUACCGUCGUGGAAAG | 2 | -0.179455174 | -0.224881716 |
| 45 | 56 | UGUCCUGACCUUGUCUUGCGGG | 2 | -0.176768878 | -0.224881716 |
| 46 | 184 | GGACAAGUAAGUAAUUCGCAGA | 2 | -0.175046667 | -0.224881716 |
| 47 | 175 | GUACAUUUGGCUAUCGGCAUUU | 2 | -0.175019209 | -0.224881716 |
| 48 | 77 | UACAUUUAACUGGGGGCGUUUU | 2 | -0.17496555 | -0.224881716 |
| 49 | 117 | UAUAAACAACAUUUGUGUGAUG | 2 | -0.172624901 | -0.224881716 |
| 50 | 110 | UAUAAAUACGGUUCGUGCCUUU | 2 | -0.172598868 | -0.224881716 |
| 51 | 172 | UCAUUAAUGGGAGGCCGAGUUU | 2 | -0.172256161 | -0.224881716 |
| 52 | 114 | UACAUGUUGACUGUGAUGCGAU | 2 | -0.171576103 | -0.224881716 |
| 53 | 5 | GCCAUUGGAGGGUGGGCGGUGG | 2 | -0.213069622 | -0.192354835 |
| 54 | 4 | GACAAAGUCGCGCCCGGGGCGG | 2 | -0.21303433 | -0.192354835 |
| 55 | 122 | GUCCUGUUCUAGGGUUGUCUCG | 2 | -0.210619715 | -0.192354835 |
| 56 | 130 | GUUCUCAACGUGGGGGUUUCUA | 2 | -0.207090962 | -0.192354835 |
| 57 | 129 | GACUAAAUAAAUCCUGACGACU | 2 | -0.204147926 | -0.192354835 |
| 58 | 32 | GGCUGCAGCGGUUGGGUGCGUG | 2 | -0.203230939 | -0.192354835 |
| 59 | 26 | GAUGCUCUCCGCGCUGGGAGAG | 2 | -0.202700524 | -0.192354835 |
| 60 | 113 | GUGUAUUGCGAAUCAGUACUCU | 2 | -0.201519939 | -0.192354835 |
| 61 | 24 | CAAUUCCUACCGUCCCCGGGUU | 2 | -0.200488314 | -0.192354835 |
| 62 | 72 | AUGUUUACCAGGUGGGUGCCUG | 2 | -0.200111258 | -0.192354835 |
| 63 | 145 | GAAUGUAUGGAGCUGUGCGUAG | 2 | -0.199036351 | -0.192354835 |
| 64 | 116 | AUAAACAUCAAUUGUGUGAUGC | 2 | -0.196067856 | -0.192354835 |
| 65 | 64 | ACACACAAUUCUGCUUCGUGUC | 2 | -0.194817406 | -0.192354835 |
| 66 | 80 | ACAAACAUCGAGAGGGGUCUGU | 2 | -0.194775336 | -0.192354835 |
| 67 | 14 | AUACAAGUCGCUUGUCCGGGCG | 2 | -0.194211864 | -0.192354835 |
| 68 | 100 | AAAAUACAGUGAUUAGCCGGGG | 2 | -0.192455249 | -0.192354835 |
| 69 | 168 | GUCAUUAAAGGCAGUCUGUCUU | 2 | -0.188782353 | -0.192354835 |
| 70 | 138 | CAUGUUCAGUCUGCUGUGUUCU | 2 | -0.188472869 | -0.192354835 |
| 71 | 109 | CUAAAUAUAGGUCGAUGCCUAG | 2 | -0.186946414 | -0.192354835 |
| 72 | 16 | CAAUACAACAGCUAGCCGGGGG | 2 | -0.182203855 | -0.192354835 |
| 73 | 66 | CAACACACGGAAGUGCUUUGUA | 2 | -0.180580894 | -0.192354835 |
| 74 | 12 | CAAGUCCUCAAGUUGUGCUGUG | 2 | -0.178653125 | -0.192354835 |
| 75 | 103 | GAGGUGGGACCCUGCCUCGGGG | 2 | -0.178390727 | -0.192354835 |
| 76 | 50 | CUCAAGAACCGCUCUACAUGUG | 2 | -0.178213915 | -0.192354835 |
| 77 | 163 | GAGGGUGGCCAGUCCUGGCAGG | 2 | -0.177917914 | -0.192354835 |
| 78 | 27 | GUGAUGCUGACUCGGAUCUGUG | 2 | -0.173280732 | -0.192354835 |
| 79 | 132 | GAGUAGCAACGUCCUCAUUCCG | 2 | -0.17101295 | -0.192354835 |
| 80 | 144 | CUUUACAAAGGUGCGGGGUUUU | 2 | -0.069237272 | -0.192354835 |
| 81 | 23 | AAUUCCUUCCCUCCCCGGGUUU | 2 | -0.41024469 | -0.175175976 |
| 82 | 105 | CAUUUAUAUCCGCGGGGCGCGG | 2 | -0.395943892 | -0.175175976 |
| 83 | 55 | GUCUUCUGCCAUGUCUGUGCUC | 2 | -0.3751398 | -0.175175976 |
| 84 | 171 | CAUUAAUCGGUGGCCGAGUUUC | 2 | -0.331313964 | -0.175175976 |
| 85 | 125 | UUGUCAUCGUGGUUCUUCACUU | 2 | -0.310409533 | -0.175175976 |
| 86 | 45 | UUUUCCUGGAACAACUGCCCAU | 2 | -0.294615584 | -0.175175976 |
| 87 | 90 | GUUGCAGUCACCUCUGGUCUGU | 2 | -0.293919674 | -0.175175976 |
| 88 | 146 | CUUUCUUUCGACAGCCCAGAUU | 3 | -0.288951912 | -0.175175976 |
| 89 | 58 | GCCUGUUCACCGGCUGCCGCGC | 2 | -0.278983644 | -0.175175976 |
| 90 | 149 | CCAUCCACGGAUUCCUUGCCCC | 2 | -0.278349633 | -0.175175976 |
| 91 | 147 | CCUUUCUUACGUCUGCGCAGGU | 2 | -0.275113467 | -0.175175976 |
| 92 | 71 | CCCUAAUGCCAGAUUGACCCCC | 2 | -0.270184291 | -0.175175976 |
| 93 | 115 | CAAACAUGGACUGUGUGCUGCU | 2 | -0.238706749 | -0.175175976 |
| 94 | 88 | CACACCACACCCCCUCUGCCGU | 2 | -0.234691371 | -0.175175976 |
| 95 | 57 | CUCCUGUCGGCAGCAUCACUCU | 2 | -0.211722458 | -0.175175976 |
| 96 | 180 | GUUCUUUCGUGUGAGGCGUUCU | 2 | -0.207660043 | -0.175175976 |
| 97 | 85 | CUGGCAACUCCGCGAGACCCCG | 2 | -0.196272954 | -0.175175976 |
| 98 | 79 | CAAACAUUAAAAUGGGAAUGUU | 2 | -0.185803729 | -0.175175976 |
| 99 | 52 | CUCUGUGAAGAAGUAGCCCUCA | 2 | -0.172565783 | -0.175175976 |
| 100 | 47 | AAUAUUUCGACCUGCCUUUUCC | 2 | -0.171902699 | -0.175175976 |
| 101 | 40 | CUUCAAUUCGGCUUUUGAUUUG | 2 | -0.167104685 | -0.175175976 |
| 102 | 160 | GUUUCUAAUCAGUGCUCUGCGC | 2 | -0.152025812 | -0.175175976 |
| 103 | 1 | GCUUUGACACAGUUGCCGCUCU | 2 | -0.148885354 | -0.175175976 |
| 104 | 19 | CAUUUAAAUUUGAAUACACACC | 3 | -0.145943715 | -0.175175976 |
| 105 | 95 | GGCUAUUCCCCCGGGGUGAGCC | 2 | -0.139559865 | -0.175175976 |
| 106 | 157 | CACACCCUGAAGGUAGCUUGCU | 2 | -0.112879723 | -0.175175976 |
| 107 | 46 | CAUUUCCUCGACGCAUUUCCCA | 2 | -0.112134257 | -0.175175976 |
| 108 | 18 | CUUUAAAUCAGUACGCCGGCCC | 2 | -0.074502814 | -0.175175976 |
| 109 | 137 | AUGUUCACUCAGCUGUGUUCUG | 2 | -0.071339198 | -0.175175976 |
| 110 | 34 | AUAUGACACCAGUGUUGUCCCG | 2 | -0.070561764 | -0.175175976 |
| 111 | 83 | GAUCCUGUGGGUUUAUACACAC | 2 | -0.05988612 | -0.056348738 |

**Table S3.** Synthetic miRNAs for EGFR

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Rank** | **ID** | **Sequence** | **Sites** | **M5P score** | **Ctree score** |
| 1 | 3 | UGUGGCUUCACCUCCUGUAUCG | 3 | -0.241109911 | -0.224881716 |
| 2 | 106 | UGUGUGACACUGCGUAAGGGGG | 2 | -0.237930433 | -0.224881716 |
| 3 | 25 | CAAAUGCUCGAGAGUCCGAUGU | 2 | -0.229263136 | -0.224881716 |
| 4 | 83 | UAACAAUGCACUGGGGGCCCUG | 2 | -0.227948932 | -0.224881716 |
| 5 | 80 | GUUUACAAUCCUCUGCCGUUGG | 2 | -0.215213766 | -0.224881716 |
| 6 | 30 | CUCUUGCUCCAUGCGUGUCUGC | 2 | -0.213776638 | -0.224881716 |
| 7 | 11 | GCUGUGGGGGAUUGGGCCAAUG | 2 | -0.213676632 | -0.224881716 |
| 8 | 99 | UCUGAUCUCCCCGCCAAAGGUC | 2 | -0.213178355 | -0.224881716 |
| 9 | 87 | UGAUUUCACCCCAGCUUGACUG | 2 | -0.210567041 | -0.224881716 |
| 10 | 34 | UGAUAAAUACCUGGGGGUGGGG | 2 | -0.209980431 | -0.224881716 |
| 11 | 29 | UCUUGCUGCAAGCGUGUCUGCA | 2 | -0.203586399 | -0.224881716 |
| 12 | 101 | UAAAGGAGUAAUCUGUGCUGCU | 2 | -0.203327846 | -0.224881716 |
| 13 | 18 | UGACAAAGCCAUGGGAGGGGGC | 2 | -0.200018437 | -0.224881716 |
| 14 | 39 | UAUACUUUGAAUUCUUUGCUGU | 2 | -0.194319957 | -0.224881716 |
| 15 | 13 | UAACCAGUGACGGGGCCGGGGA | 2 | -0.188424699 | -0.224881716 |
| 16 | 49 | UUUGAAGUCUUGUUCAAGGGGG | 2 | -0.188173837 | -0.224881716 |
| 17 | 79 | UUUACAAACCACUGCCGUUGGC | 2 | -0.186924671 | -0.224881716 |
| 18 | 95 | UAGGAGAUAGCUGUGCGGGUGC | 2 | -0.185762278 | -0.224881716 |
| 19 | 21 | GGAAGACAUUCGAGUGCGUCUU | 2 | -0.183769423 | -0.224881716 |
| 20 | 84 | GAGUUUCAAUACUACGGCCUGG | 2 | -0.182995268 | -0.224881716 |
| 21 | 5 | UGCUGUGGCGAGGUGGUGGGUA | 2 | -0.175358928 | -0.224881716 |
| 22 | 53 | UUCUUCCUACAUGGAUGGGCCG | 2 | -0.174828175 | -0.224881716 |
| 23 | 68 | GGCCAUGAGCCGCUUCUGGGCC | 2 | -0.172446058 | -0.224881716 |
| 24 | 52 | UCUUCCUUCAAGGAUGGGCCGG | 2 | -0.057443635 | -0.224881716 |
| 25 | 97 | GAUUAGGACUAACGGUGGGGCG | 2 | -0.21222741 | -0.192354835 |
| 26 | 12 | AACCAGUCACCGGGCCGGGGAG | 2 | -0.20811832 | -0.192354835 |
| 27 | 66 | GAACCACUCCACCCUCGGUGGG | 2 | -0.206795205 | -0.192354835 |
| 28 | 59 | CAUCCUCUCCAGGUGUUGUGGC | 2 | -0.204106947 | -0.192354835 |
| 29 | 19 | AAGACAAACUUGUGAGACUUCC | 3 | -0.203066258 | -0.192354835 |
| 30 | 75 | GAAUUCCAGGGCCCCCGUUUCG | 2 | -0.203044354 | -0.192354835 |
| 31 | 109 | GAAGGAACAAAUUGCCUGCGUG | 2 | -0.20129902 | -0.192354835 |
| 32 | 77 | CAGUCUAACCGUGAUGUCCGGC | 2 | -0.195392425 | -0.192354835 |
| 33 | 9 | GAGGACCUCGAGCGGCUCGGCC | 2 | -0.194200831 | -0.192354835 |
| 34 | 10 | GGUCUAAGCCGGAAUGCGGGCC | 2 | -0.194120035 | -0.192354835 |
| 35 | 15 | CAAAGGAAGCGUUCGUCCGUGU | 2 | -0.193665793 | -0.192354835 |
| 36 | 27 | GCGUUUCUCGAUUGGCCUGGCA | 2 | -0.186045989 | -0.192354835 |
| 37 | 31 | AAGGGACACACUGGCUGCUGGU | 2 | -0.185644896 | -0.192354835 |
| 38 | 41 | ACAUAUACAGAUUGUGUUUUUC | 2 | -0.185605154 | -0.192354835 |
| 39 | 105 | GGGAACAUAAAGUCUGUGUGUG | 2 | -0.18253095 | -0.192354835 |
| 40 | 98 | CAAAGGACGCCUGGCAUCCCGU | 2 | -0.181851227 | -0.192354835 |
| 41 | 46 | GAAGUAAAUCCCGAUAGCGACC | 2 | -0.179760435 | -0.192354835 |
| 42 | 16 | ACAAAGGAGACCAGGUACCCAA | 3 | -0.176861267 | -0.192354835 |
| 43 | 40 | CAUAUACUGAAUGUGUUUUUCG | 2 | -0.047420846 | -0.192354835 |
| 44 | 74 | GUUUCUUCGAAGCCCAGGUGGG | 2 | -0.386216637 | -0.175175976 |
| 45 | 51 | CUUCCUUGAACGAUGGGCCGGG | 2 | -0.25020063 | -0.175175976 |
| 46 | 57 | GUUGUGGCGACUGCUGCUUGCG | 2 | -0.201286859 | -0.175175976 |
| 47 | 22 | GUUUGAAGACUAGGGAAUGGAG | 2 | -0.199922587 | -0.175175976 |
| 48 | 35 | CUCUUUGACACAUAAGCUUCUG | 2 | -0.173773465 | -0.175175976 |
| 49 | 92 | CAAUGCUGAACGGGCCCUGGCG | 2 | -0.168048984 | -0.175175976 |
| 50 | 72 | GCUACUGUGGGUGGCACGUGUU | 2 | -0.166946483 | -0.175175976 |
| 51 | 102 | AUCUUCCAAAAGUAGCGCAAUC | 2 | -0.163898438 | -0.175175976 |
| 52 | 94 | UAUUCCACUGACCCCGCUGUGG | 2 | -0.162939094 | -0.175175976 |
| 53 | 104 | GGAACAUAAGGGCUGGGUGUAA | 2 | -0.157510275 | -0.175175976 |
| 54 | 33 | GAUAAAUUCCAGGGGGUGGGGA | 2 | -0.127141007 | -0.175175976 |
| 55 | 44 | CAAUCAAUUCGGACCCUGACAU | 2 | -0.076113199 | -0.175175976 |
| 56 | 71 | CCAUGACUCCUUACCGCUGGGC | 2 | -0.074602147 | -0.056348738 |
| 57 | 108 | CUGUUGUGCGGGGAGCUGCAAG | 2 | -0.074028151 | -0.056348738 |
| 58 | 17 | GACAAAGGUGAGCUGCUUCCCA | 2 | -0.064169449 | -0.056348738 |
| 59 | 43 | AAUCAAUACGCACCCUGACAUA | 2 | -0.061562959 | -0.056348738 |

**Table S4.** Synthetic miRNAs for c-MET and EGFR

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Rank** | **ID** | **Sequence** | **Sites on c-MET** | **Sites on EGFR** | **M5P score** | **Ctree score** |
| 1 | 141 | UUCCAAUUCGAGGGGAGGUGGG | 1 | 1 | -0.262121054 | -0.224881716 |
| 2 | 23 | UCAAUUUCGGUCCCGAGUUCCA | 1 | 1 | -0.258085949 | -0.224881716 |
| 3 | 140 | UCCAAUUGGACGGGAGGUGGGU | 1 | 1 | -0.249811547 | -0.224881716 |
| 4 | 106 | UUUCAUGAGCCCUAGACUGGGG | 1 | 1 | -0.246390682 | -0.224881716 |
| 5 | 196 | UGAGUUUCUCAGCGACGGACCG | 1 | 1 | -0.241071036 | -0.224881716 |
| 6 | 98 | UUUCUUAAGCACGCCGUUGGGG | 1 | 1 | -0.23874806 | -0.224881716 |
| 7 | 204 | UGUCAUCCAGGCUUGCCGAUUC | 1 | 1 | -0.234493846 | -0.224881716 |
| 8 | 137 | UACCUGCCUGCGCGUGAGAGGG | 1 | 1 | -0.232062736 | -0.224881716 |
| 9 | 18 | GACCUGAUCGAUUUCAUCUGCG | 1 | 1 | -0.231204838 | -0.224881716 |
| 10 | 24 | UUCAAUUUGGGACCCGAGUUCC | 1 | 1 | -0.2289542 | -0.224881716 |
| 11 | 134 | UUCCAUCCGGGCCGUCUCUGCU | 1 | 1 | -0.228564665 | -0.224881716 |
| 12 | 55 | UUGCAGUGAAGUCGUGGCAGAA | 3 | 1 | -0.228046307 | -0.224881716 |
| 13 | 194 | UGUGUGACUCUGCGUAAGUGUA | 1 | 2 | -0.225800008 | -0.224881716 |
| 14 | 66 | GGAAACCACGCGUGGCUCCGUG | 1 | 1 | -0.225675946 | -0.224881716 |
| 15 | 105 | UGAUGACUGUUGGCUGUGACAC | 1 | 1 | -0.225395337 | -0.224881716 |
| 16 | 104 | GAAAUUAUAAGAGGCAGGUUCU | 1 | 1 | -0.220162553 | -0.224881716 |
| 17 | 33 | UACUAUCUGGGCUGAGUUUCCC | 1 | 1 | -0.219504707 | -0.224881716 |
| 18 | 6 | UUCCUUAGCAACCCGUCAUUCU | 1 | 1 | -0.218806489 | -0.224881716 |
| 19 | 119 | UCAAAUUACCAGUCUCGUUUUG | 1 | 1 | -0.217631437 | -0.224881716 |
| 20 | 127 | GUUUACAAUUCUCUGUGGUUAA | 2 | 2 | -0.215926957 | -0.224881716 |
| 21 | 182 | GUCAUUGACUGUCAUGCCGUCU | 1 | 1 | -0.214027874 | -0.224881716 |
| 22 | 139 | CUUGCGAGCACGGAAGCGGCGC | 1 | 1 | -0.213417504 | -0.224881716 |
| 23 | 190 | CUUUGUAGGGAGCUGGGCUAUG | 1 | 1 | -0.21275742 | -0.224881716 |
| 24 | 5 | UGAAUCCACACUGGGCUGGAAC | 1 | 1 | -0.2123791 | -0.224881716 |
| 25 | 1 | GGACAAAGCCAGGGGAGUUGCU | 1 | 2 | -0.21178937 | -0.224881716 |
| 26 | 199 | UGUCUUCUCCACUGUGCCCGCA | 1 | 1 | -0.20861562 | -0.224881716 |
| 27 | 123 | GAUCUUUACACUUUUGCAGCGG | 1 | 1 | -0.20765557 | -0.224881716 |
| 28 | 44 | CAAUGAAAUUGGCCAUGGUCCC | 1 | 1 | -0.205235717 | -0.224881716 |
| 29 | 50 | GACAAACAACACAAGGUAACUG | 2 | 1 | -0.203109841 | -0.224881716 |
| 30 | 210 | GGAUGCGUAGGUGCUCUUGCCC | 1 | 1 | -0.202085781 | -0.224881716 |
| 31 | 149 | UAUUCCAUGGGGGCGGUUUCGC | 1 | 1 | -0.200549294 | -0.224881716 |
| 32 | 111 | CCACAUUCAGAGGUGCGGGGUA | 1 | 1 | -0.200046043 | -0.224881716 |
| 33 | 169 | CACUUUAAUACCUUACGGCGCC | 1 | 1 | -0.197034181 | -0.224881716 |
| 34 | 207 | CAGAGACACAACUUGCGUGCCA | 1 | 1 | -0.196664641 | -0.224881716 |
| 35 | 211 | CCCGAGUUGAAUCUUGUGGUGC | 1 | 1 | -0.196288461 | -0.224881716 |
| 36 | 131 | UUCUUUGCGGAGGCUGGGAGCG | 1 | 1 | -0.196200539 | -0.224881716 |
| 37 | 16 | CAGAAUUCGUCCUGCGGGGUCU | 2 | 1 | -0.195419698 | -0.224881716 |
| 38 | 29 | CUGAGUUUGGUUUUAACAAAAU | 3 | 1 | -0.194295453 | -0.224881716 |
| 39 | 60 | CUGAGCCUCCCAGGUGGAGGUU | 1 | 1 | -0.193240516 | -0.224881716 |
| 40 | 85 | UCUUCCAAGGCUAGGGAUGUCU | 1 | 1 | -0.192665497 | -0.224881716 |
| 41 | 151 | GGGCUAUUCCACCUAGGGGUGA | 1 | 1 | -0.192460042 | -0.224881716 |
| 42 | 187 | CUGCUGGGCGGACGCUGGGCUU | 1 | 1 | -0.192256358 | -0.224881716 |
| 43 | 126 | UUUACAAACCAGCGGCGUUAGC | 1 | 2 | -0.186986322 | -0.224881716 |
| 44 | 181 | CCAUUGAACAACAUGCCGUCAG | 1 | 1 | -0.186901168 | -0.224881716 |
| 45 | 43 | AAAAUGUUCAGGACGCAAUAUC | 3 | 1 | -0.183772168 | -0.224881716 |
| 46 | 3 | UACAAGUCGCACUAUCGCGCAU | 1 | 1 | -0.183220195 | -0.224881716 |
| 47 | 195 | GAGUUUCACUCUGACGGACUGG | 1 | 2 | -0.182550608 | -0.224881716 |
| 48 | 4 | UUAACAAUCGAGGUGGGGCUCU | 1 | 1 | -0.178444851 | -0.224881716 |
| 49 | 202 | UAUACUCUCACAGUUAGUAGCU | 1 | 1 | -0.17390764 | -0.224881716 |
| 50 | 46 | UCCAUCAGACCGGAGUAAGGUC | 1 | 1 | -0.173460973 | -0.224881716 |
| 51 | 42 | UUAUUGACGUCGCGAGUCUCAA | 1 | 1 | -0.173403994 | -0.224881716 |
| 52 | 150 | GUAUUCCAGGAUGGCGGCUGUG | 1 | 1 | -0.214676798 | -0.192354835 |
| 53 | 121 | CAUAUUUAGGUCCUGAUUUCCU | 1 | 1 | -0.214215256 | -0.192354835 |
| 54 | 90 | CAAUAUUCAACCUGGCUGCGGU | 1 | 1 | -0.213315585 | -0.192354835 |
| 55 | 37 | GAAACACUCCAUUCCUAGGUGU | 1 | 1 | -0.211610023 | -0.192354835 |
| 56 | 19 | GUACCUGAAAACCACACUACUC | 1 | 1 | -0.209476917 | -0.192354835 |
| 57 | 198 | GGUAAGUCAGAGGACGAUCUGC | 1 | 1 | -0.208297186 | -0.192354835 |
| 58 | 143 | AAAACUCCGGCAUCGCCUUGCU | 1 | 1 | -0.205182651 | -0.192354835 |
| 59 | 161 | GAAUUCCAGUGCAUGCAUCAUG | 1 | 2 | -0.203956341 | -0.192354835 |
| 60 | 117 | AAAUUACUACACUUGCUUUGGG | 1 | 1 | -0.203833332 | -0.192354835 |
| 61 | 179 | GCUGUCAUAGCCCCCUGUCUGA | 1 | 1 | -0.199636827 | -0.192354835 |
| 62 | 128 | CCAAUGAAGGACUCCGUGAUCC | 1 | 1 | -0.199015364 | -0.192354835 |
| 63 | 68 | GAGUUUGAUCGCAGCGGUGGGC | 1 | 1 | -0.198809637 | -0.192354835 |
| 64 | 51 | ACAAACAACGGUGUCUAAGGGU | 1 | 1 | -0.198105301 | -0.192354835 |
| 65 | 175 | GUUCACAGACGGGUGUCUUUGG | 1 | 1 | -0.194653159 | -0.192354835 |
| 66 | 80 | AAGGAAUGGGACUUCCCAAAUU | 1 | 1 | -0.193807589 | -0.192354835 |
| 67 | 82 | CAAAGGAAACACUCUUCCGAAA | 1 | 2 | -0.193715957 | -0.192354835 |
| 68 | 63 | CAAAUUAGCGCGGGCGGGUGGG | 1 | 1 | -0.193548681 | -0.192354835 |
| 69 | 177 | CCCAGUCUCACGGUCCUUGUGC | 1 | 1 | -0.192488442 | -0.192354835 |
| 70 | 164 | GGUAGCAACGCCUACCUGCCAG | 1 | 1 | -0.189526401 | -0.192354835 |
| 71 | 48 | CAAAGGGAGACUUUUCCUGCUG | 1 | 1 | -0.186758484 | -0.192354835 |
| 72 | 129 | GAGCUGUGCCGGGUUGGUCCGA | 1 | 1 | -0.184923686 | -0.192354835 |
| 73 | 67 | AGUUUGAACGGAGCGGUGGGCA | 1 | 1 | -0.184721793 | -0.192354835 |
| 74 | 83 | CCAAAGGAGACCAUGUACCCAA | 1 | 3 | -0.181226913 | -0.192354835 |
| 75 | 112 | AAACAUCUCGUUGUGCUGUGUC | 1 | 1 | -0.179846756 | -0.192354835 |
| 76 | 118 | CAAAUUACAACUCUUGCUUUGG | 1 | 1 | -0.179833043 | -0.192354835 |
| 77 | 57 | GAGGUGGACCAUGCUGCGGGCU | 1 | 1 | -0.177332532 | -0.192354835 |
| 78 | 70 | GUGGAUUUGAAGGGCCCAGGCG | 1 | 1 | -0.173363013 | -0.192354835 |
| 79 | 135 | GGACAGAGCCCCUUCUCCUCCU | 1 | 1 | -0.17316924 | -0.192354835 |
| 80 | 81 | AAAGGAAUCGGUCUUCCCAAAU | 1 | 1 | -0.172564314 | -0.192354835 |
| 81 | 197 | GUAAGUCUGACGACGAUCUGCG | 1 | 1 | -0.171923146 | -0.192354835 |
| 82 | 100 | GUUUCAUAGAAACUUCCUGAAU | 1 | 1 | -0.636826091 | -0.175175976 |
| 83 | 107 | AUUUCAUGUGCGCUAGACUGGG | 1 | 1 | -0.61727485 | -0.175175976 |
| 84 | 97 | GUGUCAUCGUGGCUUGCUAAUU | 2 | 1 | -0.593206114 | -0.175175976 |
| 85 | 99 | CUUUCUUAUGCUCGCCGUUGGG | 1 | 1 | -0.417249477 | -0.175175976 |
| 86 | 115 | CUUUGAGUAAACAGCUUUUGAA | 1 | 1 | -0.394743264 | -0.175175976 |
| 87 | 160 | AAUUCCACUCAAUGAAGCAUGG | 1 | 2 | -0.382526629 | -0.175175976 |
| 88 | 32 | GUCUUCUGUAGUGUCUCUGAAC | 2 | 1 | -0.371348388 | -0.175175976 |
| 89 | 113 | AAAACAUCACGAUGUGCUGUGU | 1 | 1 | -0.354712867 | -0.175175976 |
| 90 | 133 | CCUUUCUUACGACUGCGGAGGG | 2 | 1 | -0.348274732 | -0.175175976 |
| 91 | 76 | GGCUCAUGGGAGGAAUCCUCGG | 1 | 1 | -0.323637775 | -0.175175976 |
| 92 | 28 | GUUUCUGUCUACGCGUCGCCGU | 1 | 1 | -0.318472847 | -0.175175976 |
| 93 | 178 | CUGUCAUUGCGCCCUGUCUGAC | 1 | 1 | -0.300834678 | -0.175175976 |
| 94 | 56 | GUUGCAGUCCCCUCCGGGAAGC | 2 | 1 | -0.295746177 | -0.175175976 |
| 95 | 215 | GUCUAAGGUGCAGUUCCUUCCC | 1 | 1 | -0.289242383 | -0.175175976 |
| 96 | 157 | GAAGCAUCGGGUGGUUGUGCUG | 1 | 1 | -0.283672502 | -0.175175976 |
| 97 | 13 | CAUUGGUCGCAGGGCUGUGGGA | 1 | 1 | -0.276685141 | -0.175175976 |
| 98 | 45 | CCAUCAGUCCCGAGUAAGGUCC | 1 | 1 | -0.275227159 | -0.175175976 |
| 99 | 166 | GAUACAGUUCGGAGCCGGCCUG | 1 | 1 | -0.274337558 | -0.175175976 |
| 100 | 10 | GCCUCUGGAACUGUUGCGGCGU | 1 | 1 | -0.265060228 | -0.175175976 |
| 101 | 201 | CUUCCUUGAACGAUGGGGUGAG | 1 | 2 | -0.249959324 | -0.175175976 |
| 102 | 20 | GGUACCUGGGAUGUCUUGAUUC | 1 | 1 | -0.248825674 | -0.175175976 |
| 103 | 183 | UUUUCCUUGAGGCACUUCUGCG | 1 | 1 | -0.242047438 | -0.175175976 |
| 104 | 69 | GAUUUCUUCGCUGCUGGAGUGG | 1 | 1 | -0.227626176 | -0.175175976 |
| 105 | 96 | GAUCUAUGGGGCUUAGGUCCUG | 1 | 1 | -0.215919214 | -0.175175976 |
| 106 | 188 | CUUGCUGGCACCGCCCCUGGCU | 1 | 1 | -0.207794047 | -0.175175976 |
| 107 | 213 | CCCUGUUGACCGGAGGGCUGCC | 1 | 1 | -0.206015154 | -0.175175976 |
| 108 | 173 | GUUGUGGCGACAGCUGCUUGUU | 1 | 2 | -0.198492211 | -0.175175976 |
| 109 | 186 | GGUUAACCGCAGGGGUCACGGG | 1 | 1 | -0.188473609 | -0.175175976 |
| 110 | 142 | CUUCCAAUACGUGGGGAGGUGG | 1 | 1 | -0.178464233 | -0.175175976 |
| 111 | 86 | AUCUUCCAUGGGUAGGAAAAUC | 1 | 2 | -0.1783074 | -0.175175976 |
| 112 | 84 | CCCAAAGGUGGGGCUGCACUUC | 1 | 1 | -0.17819961 | -0.175175976 |
| 113 | 147 | GCUUAACAAACCUGUCGGGGCU | 1 | 1 | -0.160963016 | -0.175175976 |
| 114 | 209 | GAUGCGUUGGAGCUCUUGCCCC | 1 | 1 | -0.154353507 | -0.175175976 |
| 115 | 145 | GCUAAUGCCCCCUUGGCCGCCG | 1 | 1 | -0.14778502 | -0.175175976 |
| 116 | 61 | GUGUAGUCGACUGGAUUGGGGG | 2 | 1 | -0.147318953 | -0.175175976 |
| 117 | 185 | UCCUGAUGGACUUCUGCGGGGG | 1 | 1 | -0.143788441 | -0.175175976 |
| 118 | 116 | AAUUACUUCAGACAUUUAGGGA | 2 | 1 | -0.139345459 | -0.175175976 |
| 119 | 132 | CUUCUUUGGGGUGGCUGGGAGC | 1 | 1 | -0.136639271 | -0.175175976 |
| 120 | 2 | GAACCAUUCCACCCUGGGUGGA | 1 | 1 | -0.133880309 | -0.175175976 |
| 121 | 88 | AUAUUCUUCGAGGCUGCGGUUC | 1 | 1 | -0.127301118 | -0.175175976 |
| 122 | 170 | GACACUUUAACUGUGUCCGUGG | 1 | 1 | -0.110378135 | -0.175175976 |
| 123 | 189 | UCUUGCUGCCAUCAUGCCUGGA | 1 | 2 | -0.086690594 | -0.175175976 |
| 124 | 168 | AAACCAGUGUCGGUACCGGACA | 1 | 2 | -0.075914566 | -0.175175976 |
| 125 | 171 | CAAAUAUAGGACUUUGAAUGUU | 1 | 1 | -0.061478711 | -0.056348738 |

**Table S5.** Mutagenesis’ primers for c-MET and EGFR.

|  |  |  |
| --- | --- | --- |
| **Primer name** | **Target gene** | **Sequence** |
| M-60-mut1 FW | c-MET | 5'-ccactcatttagaattctagtgaacacttttgtgtgttgtatgg-3' |
| M-60-mut1 RV | c-MET | 5'-ccatacaacacacaaaagtgttcactagaattctaaatgagtgg-3' |
| M-60-mut2 FW | c-MET | 5'-tgttgccaaggctggactcctggactcaag-3' |
| M-60-mut2 RV | c-MET | 5'-cttgagtccaggagtccagccttggcaaca-3' |
| M-60-mut3 FW | c-MET | 5'-gaatatttataggcaatacagtcaaagaatagcatcacacaaaacatgtttata-3' |
| M-60-mut3 RV | c-MET | 5'-tataaacatgttttgtgtgatgctattctttgactgtattgcctataaatattc-3' |
| ME-196-mutM FW | c-MET | 5'-gagggtgtgtcacactgaatagttgagtttggct-3' |
| ME-196-mutM RV | c-MET | 5'-agccaaactcaactattcagtgtgacacaccctc-3' |
| E-3-mut1 FW | EGFR | 5'-tcgatacccaggaccaagcaggtcctcc-3' |
| E-3-mut1 RV | EGFR | 5'-ggaggacctgcttggtcctgggtatcga-3' |
| E-3-mut2 FW | EGFR | 5'-tgtgagcaaggagcacaaagtcttccagaggatg-3' |
| E-3-mut2 RV | EGFR | 5'-catcctctggaagactttgtgctccttgctcaca-3' |
| E-3-mut3 FW | EGFR | 5'-gtcatggcaggtacagtaggatatctgtcccttcc-3' |
| E-3-mut3 RV | EGFR | 5'-ggaagggacagatatcctactgtacctgccatgac |
| ME-196-mutE FW | EGFR | 5'-tccattccattgttttgagtatgctgcccctgtc-3' |
| ME-196-mutE RV | EGFR | 5'-gacaggggcagcatactcaaaacaatggaatgga-3' |