

CLAIMS

WHAT IS CLAIMED IS:

1. A method for modulating protein activity, the method comprising:
 - a) providing predetermined sequences encoding for at least about 30,000 non-identical oligonucleic acids, wherein each of the at least about 30,000 non-identical oligonucleic acids encodes for a variant codon sequence compared to a single reference sequence;
 - b) providing a structure having a surface;
 - c) synthesizing the at least about 30,000 non-identical oligonucleic acids, wherein each of the at least about 30,000 non-identical oligonucleic acids extends from the surface;
 - d) mixing the least about 30,000 non-identical oligonucleic acids with a DNA polymerase and the single reference sequence to form a library of variant nucleic acids;
 - e) transferring the library of variant nucleic acids to cells and expressing a plurality of variant proteins; and
 - f) identifying an activity associated with a variant protein of the plurality of variant proteins, wherein the activity is modulated relative to a protein encoded by the single reference sequence.
2. The method of claim 1, wherein the activity comprises cellular reproduction, growth, adhesion, death, migration, energy production, oxygen utilization, metabolic activity, cell signaling, aging, response to free radical damage, or any combination thereof.
3. The method of claim 1, wherein the cells are eukaryotic cells or prokaryotic cells.
4. The method of claim 1, wherein the cells are bacterial, plant, mouse, or primate cells.
5. The method of claim 1, wherein the library of variant nucleic acids encodes sequences for variant genes or fragments thereof.
6. The method of claim 1, wherein the variant protein is an antibody, enzyme or peptide.
7. The method of claim 1, wherein the variant protein has enhanced or reduced binding affinity for another molecule.
8. The method of claim 1, wherein the variant protein has enhanced or reduced enzymatic activity.

9. The method of claim 1, further comprising administering a single variant nucleic acid encoded by the library of variant nucleic acids to a subject in need thereof.
10. The method of claim 1, wherein the at least about 30,000 non-identical oligonucleic acids have an aggregate error rate of less than 1 in 1000 bases compared to predetermined sequences for the plurality of non-identical oligonucleic acids.
11. A method for modulating cellular activity, the method comprising:
- a) providing predetermined sequences encoding for at least about 30,000 non-identical oligonucleic acids, wherein each of the at least about 30,000 non-identical oligonucleic acids encodes for a predetermined variant sequence compared to a single reference sequence;
 - b) providing a structure having a surface;
 - c) synthesizing the at least about 30,000 non-identical oligonucleic acids, wherein each of the at least about 30,000 non-identical oligonucleic acids extends from the surface, and wherein the at least about 30,000 non-identical oligonucleic acids have an aggregate error rate of less than 1 in 1000 bases compared to predetermined sequences for the plurality of non-identical oligonucleic acids;
 - d) mixing the least about 30,000 non-identical oligonucleic acids with a DNA polymerase and the single reference sequence to form a library of variant nucleic acids;
 - e) transferring the library of variant nucleic acids to a first set of cells; and
 - f) measuring a change in a cellular activity, wherein the cellular activity is measured for the first set of cells or a second set of cells, wherein the second set of cells are treated at least one expression product isolated from the first set of cells.
12. The method of claim 11, wherein the cellular activity comprises reproduction, growth, adhesion, death, migration, energy production, oxygen utilization, metabolic activity, cell signaling, response to free radical damage, or any combination thereof.
13. The method of claim 11, wherein the first set of cells or the second set of cells are eukaryotic cells or prokaryotic cells.
14. The method of claim 11, wherein the first set of cells or the second set of cells are bacterial, plant, mouse, or primate cells.
15. The method of claim 11 wherein the library of variant nucleic acids encodes sequences for variant genes or fragments thereof.
16. The method of claim 15, further comprising translation of each of the variant genes to form a protein.
17. The method of claim 16, wherein the protein is an antibody, enzyme, or peptide.

18. The method of claim 17, wherein the library of variant nucleic acids encodes for at least a portion of a variable region or constant region of the antibody.

19. The method of claim 18, wherein the library of variant nucleic acids encodes for at least one CDR region of the antibody.

20. The method of claim 16, wherein the protein has enhanced or reduced binding affinity for another molecule, or wherein the protein has enhanced or reduced enzymatic activity.

21. The method of claim 11, wherein the library of variant nucleic acids encodes for a transcription regulatory sequence.

22. The method of claim 21, wherein the transcription regulatory sequence is a promoter, UTR, or a terminator sequence.

23. The method of claim 11, wherein the library of variant nucleic acids encodes for a sequence that, when transcribed, encodes for mRNA, miRNA, or shRNA.

24. A method for treatment or reduction of a disease state, the method comprising:

- a) providing predetermined sequences encoding for at least about 30,000 non-identical oligonucleic acids, wherein each of the at least about 30,000 non-identical oligonucleic acids encodes for a variant codon sequence compared to a single reference sequence;
- b) providing a structure having a surface;
- c) synthesizing the at least about 30,000 non-identical oligonucleic acids, wherein each of the at least about 30,000 non-identical oligonucleic acids extends from the surface;
- d) mixing the least about 30,000 non-identical oligonucleic acids with a DNA polymerase and the single reference sequence to form a library of variant nucleic acids;
- e) transferring the library of variant nucleic acids to cells obtained from a subject;
- f) identifying a reduction in harmful activity associated with a variant nucleic acid encoded by the library of variant nucleic acids; and
- g) administering the variant nucleic acid encoded by the library of variant nucleic acids to a subject in need thereof, thereby treating or reducing the disease state.

25. The method of claim 24, wherein the disease state is associated with a cell proliferative, autoimmune, viral, or bacterial disorder.

26. The method of claim 24, wherein the at least about 30,000 non-identical oligonucleic acids have an aggregate error rate of less than 1 in 1000 bases compared to predetermined sequences for the plurality of non-identical oligonucleic acids.

27. A method for nucleic acid synthesis, the method comprising:

a) providing predetermined sequences encoding for a plurality of non-identical oligonucleic acids, wherein each of the non-identical oligonucleic acids is at least 20 bases in length, and wherein the plurality of non-identical oligonucleic acids encodes for up to 19 variants for each of at least 3 codons for at least one sequence, and wherein the plurality of non-identical oligonucleic acids collectively encodes for at least one gene and variants thereof;

b) providing a structure having a surface;

c) synthesizing the plurality of non-identical oligonucleic acids, wherein each of the non-identical oligonucleic acids extends from the surface; and

d) assembling a library of variant nucleic acids from the plurality of non-identical oligonucleic acids.

28. The method of claim 27, wherein the plurality of non-identical oligonucleic acids comprises at least 75,000 non-identical oligonucleic acids.

29. The method of claim 27, wherein a subset of the plurality of non-identical oligonucleic acids collectively encodes for a single gene and variants thereof is located within a single cluster on the surface of the structure.

30. The method of claim 29, wherein the surface of the structure comprises at least 6000 of the single clusters.

31. The method of claim 30, wherein each cluster is located within a channel about 0.5 to 2 mm in diameter.

32. The method of claim 29, wherein the single cluster comprises 50 to 500 loci for nucleic acid extension.

33. The method of claim 27, wherein the plurality of non-identical oligonucleic acids collectively encode for variants of more than one gene.

34. The method of claim 27, wherein the plurality of non-identical oligonucleic acids collectively encode for variants of at least 5,000 genes.

35. The method of claim 27, wherein the library of variant nucleic acids encodes for at least a portion of an enzyme, peptide, or antibody.