WHAT IS CLAIMED:

1. A method for simultaneously integrating a plurality of (n) exogenous nucleic acids into a plurality of (n) target sites of a host cell genome, wherein n is at least two, the method comprising:

(a) simultaneously contacting a host cell with:

(i) said plurality of exogenous nucleic acids, wherein:

x is an integer that varies from 1 to n, and for each integer x, each exogenous nucleic acid $(ES)_x$ comprises a first homology region $(HR1)_x$ and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of $(ES)_x$ at a target site $(TS)_x$ selected from said plurality of (n) target sites of said host cell genome; and

(ii) for each said target site $(TS)_x$, a nuclease $(N)_x$ capable of cleaving at $(TS)_x$, whereupon said cleaving results in homologous recombination of $(ES)_x$ at $(TS)_x$;

and

(b) recovering a host cell wherein each exogenous nucleic acid $(ES)_x$ has integrated at its selected target site $(TS)_x$.

2. A host cell comprising:

(a) a plurality of (n) genomic target sites, wherein n is at least two;

(b) a plurality of (n) exogenous nucleic acids, wherein x is an integer that varies from 1 to n, and for each integer x, each exogenous nucleic acid $(ES)_x$ comprises a first homology region $(HR1)_x$ and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of $(ES)_x$ at a target site $(TS)_x$ selected from said plurality of (n) genomic target sites; and

(c) for each said target site $(TS)_x$, a nuclease $(N)_x$ capable of cleaving at $(TS)_x$, whereupon said cleaving results in homologous recombination of $(ES)_x$ at $(TS)_x$.

3. The method of claim 1, or the host cell of claim 2, wherein $(HR1)_x$ is homologous to a 5' region of $(TS)_x$, and $(HR2)_x$, is homologous to a 3' region of $(TS)_x$.

4. The method of claim 1, or the host cell of claim 2, wherein $(N)_x$ is capable of cleaving at a region positioned between said 5' and 3' regions of $(TS)_x$.

5. The method of claim 1, or the host cell of claim 2, wherein a single nuclease is capable of cleaving each $(TS)_x$.

6. The method or host cell of any one of claims 1 to 5, wherein n= 3, 4, 5, 6, 7, 8, 9 or 10.

7. The method of any one of claims 1 and 3 to 6, wherein said recovering does not require integration of a selectable marker.

8. The method of any one of claims 1 and 3 to 6, wherein said recovering occurs at a higher frequency as compared to not contacting the host cell with a nuclease capable of cleaving at said target site.

9. The method of any one of claims 1 and 3 to 6, wherein said recovering occurs at a frequency of about one every 10, 9, 8, 7, 6, 5, 4, 3, or 2 contacted host cells, or clonal populations thereof, screened.

10. The method or host cell of any one of claims 1, 2, and 3 to 9, wherein $(N)_x$ is capable of cleaving an endogenous genomic sequence within $(TS)_x$.

11. The method or host cell of any one of claims 1, 2, and 3 to 9, wherein $(N)_x$ is capable of cleaving an exogenous sequence within $(TS)_x$.

12. The method or host cell of claim 11, wherein the exogenous sequence is a recognition sequence for a homing endonuclease.

13. The method or host cell of claim 12, wherein the homing endonuclease is F-cphI.

14. The method or host cell of any one of claims 1 to 13, wherein $(ES)_x$ further comprises a nucleic acid of interest $(D)_x$ positioned 3' of $(HR1)_x$ and 5' of $(HR2)_x$.

15. The method or host cell of claim 14, wherein $(D)_x$ is selected from the group consisting of a selectable marker, a promoter, a nucleic acid sequence encoding an epitope tag, a gene of interest, a reporter gene, and a nucleic acid sequence encoding a termination codon.

16. The method or host cell of any one of claims 1 to 15, wherein $(ES)_x$ is linear.

17. The method or host cell of any one of claims 1, 2, and 3 to 16, wherein $(N)_x$ is provided as an expression vector comprising a nucleic acid sequence encoding $(N)_x$.

18. The method or host cell of any one of claims 1, 2, and 3 to 17, wherein $(N)_x$ is selected from the group consisting of an endonuclease, a zinc finger nuclease, a TAL-effector DNA binding domain-nuclease fusion protein (TALEN), a transposase, and a site-specific recombinase.

19. The method or host cell of claim 18, wherein the endonuclease is modified to specifically bind an endogenous genomic sequence, wherein the modified endonuclease no longer binds to its wild type endonuclease recognition sequence.

20. The method or host cell of claim 18 or 19, wherein the endonuclease is a homing endonuclease selected from the group consisting of: an LAGLIDADG homing endonuclease, an HNH homing endonuclease, a His-Cys box homing endonuclease, a GIY-YIG homing endonuclease, and a cyanobacterial homing endonuclease.

21. The method of or host cell of claim 18 or 19, wherein the endonuclease is derived from an endonuclease selected from the group consisting of: H-DreI, I-SceI, I-SceII, I-SceIII, I-SceIV, I-SceV, I-SceVI, I-SceVII, I-CeuI, I-CeuAIIP, I-CreI, I-CrepsbIP, I-CrepsbIIP, I-CrepsbIIIP, I-CrepsbIVP, I-TliI, I-PpoI, Pi-PspI, F-SceI, F-SceII, F-SuvI, F-CphI, F-TevI, F-TevII, I-AmaI, I-AniI, I-ChuI, I-CmoeI, I-CpaI, I-CpaII, I-CsmI, I-CvuI, I-CvuAIP, I-DdiI, I-DdiII, I-DirI, I-DmoI, I-HmuI, I-HmuII, I-HsNIP, I-LlaI, I-MsoI, I-NaaI, I-NanI, I-NclIP, I-NgrIP, I-NitI, I-NjaI, I-Nsp236IP, I-PakI, I-PboIP, I-PcuIP, I-PcuAI, I-

PcuVI, I-PgrIP, I-PobIP, I-PorI, I-PorIIP, I-PbpIP, I-SpBetaIP, I-ScaI, I-SexIP, I-SneIP, I-SpomI, I-SpomCP, I-SpomIP, I-SpomIIP, I-SquIP, I-Ssp68031, I-SthPhiJP, I-SthPhiST3P, I-SthPhiSTe3bP, I-TdeIP, I-TevI, I-TevII, I-TevIII, i-UarAP, i-UarHGPAIP, I-UarHGPA13P, I-VinIP, I-ZbiIP, PI-MgaI, PI-MtuI, PI-MtuHIP PI-MtuHIIP, PI-PfuI, PI-PfuII, PI-PkoI, PI-PkoII, PI-Rma43812IP, PI-SpBetaIP, PI-SceI, PI-TfuI, PI-TfuII, PI-ThyI, PI-TliI, or PI-TliII.

22. The method or host cell of any one of claims 1 to 21, wherein the host cell is selected from the group consisting of a fungal cell, a bacterial cell, a plant cell, and an animal cell.

23. The method or host cell of any one of claims 1 to 22, wherein the host cell is a yeast cell.

24. The method or host cell of claim 23, wherein the yeast cell is a *Saccharomyces cerevisiae* cell.

25. A method for simultaneously integrating a plurality of (n) exogenous nucleic acids into a plurality of (n) target sites of a host cell genome, wherein n is at least two, the method comprising:

(a) simultaneously contacting a host cell with:

(i) a plurality of libraries, wherein x is an integer that varies from 1 to n, and for each integer x, each library $(L)_x$ comprises a plurality of exogenous nucleic acids, wherein each exogenous nucleic acid comprises, in a 5' to 3' orientation, a first homology region $(HR1)_x$, any nucleic acid of interest selected from the group $(D)_x$, and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of said selected exogenous nucleic acid at a target site $(TS)_x$ of said host cell genome; and

(ii) for each said target site $(TS)_x$, a nuclease $(N)_x$ capable of cleaving at $(TS)_x$, whereupon said cleaving results in homologous recombination of an exogenous nucleic acid from $(L)_x$ at $(TS)_x$;

and

(b) recovering a host cell wherein an exogenous nucleic acid from each library $(L)_x$ has integrated at each selected target sequence $(TS)_x$.

26. A host cell comprising:

(a) a plurality of (n) genomic target sites, wherein n is at least two;

(b) a plurality of libraries, wherein x is an integer that varies from 1 to n, and for each integer x, each library $(L)_x$ comprises a plurality of exogenous nucleic acids, wherein each exogenous nucleic acid comprises, in a 5' to 3' orientation, a first homology region $(HR1)_x$, any nucleic acid of interest selected from the group $(D)_x$, and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of said selected exogenous nucleic acid at a target site $(TS)_x$ of said host cell genome; and

for each said target site $(TS)_x$, a nuclease $(N)_x$ capable of cleaving at $(TS)_x$, whereupon said cleaving results in homologous recombination of an exogenous nucleic acid from $(L)_x$ at $(TS)_x$.

WHAT IS CLAIMED:

1. A method for simultaneously integrating a plurality of (n) exogenous nucleic acids into a plurality of (n) target sites of a host cell genome, wherein n is at least two, the method comprising:

(a) simultaneously contacting a host cell with:

(i) said plurality of exogenous nucleic acids, wherein:

x is an integer that varies from 1 to n, and for each integer x, each exogenous nucleic acid $(ES)_x$ comprises a first homology region $(HR1)_x$ and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of $(ES)_x$ at a target site $(TS)_x$ selected from said plurality of (n) target sites of said host cell genome; and

(ii) for each said target site $(TS)_x$, a nuclease $(N)_x$ capable of cleaving at $(TS)_x$, whereupon said cleaving results in homologous recombination of $(ES)_x$ at $(TS)_x$;

and

(b) recovering a host cell wherein each exogenous nucleic acid $(ES)_x$ has integrated at its selected target site $(TS)_x$.

2. A host cell comprising:

(a) a plurality of (n) genomic target sites, wherein n is at least two;

(b) a plurality of (n) exogenous nucleic acids, wherein x is an integer that varies from 1 to n, and for each integer x, each exogenous nucleic acid $(ES)_x$ comprises a first homology region $(HR1)_x$ and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of $(ES)_x$ at a target site $(TS)_x$ selected from said plurality of (n) genomic target sites; and

(c) for each said target site $(TS)_x$, a nuclease $(N)_x$ capable of cleaving at $(TS)_x$, whereupon said cleaving results in homologous recombination of $(ES)_x$ at $(TS)_x$.

3. A host cell comprising:

~~(a) a plurality of (n) genomic target sites, wherein n is at least two; and~~

(b) a plurality of (n) exogenous nucleic acids, wherein x is an integer that varies from 1 to n, and for each integer x, each exogenous nucleic acid $(ES)_x$ comprises a first homology region $(HR1)_x$ and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of $(ES)_x$ at a target site $(TS)_x$ selected from said plurality of (n) genomic target sites;

wherein each said genomic target site $(TS)_x$, comprises a double-strand break.

4. The method of claim 1, or the host cell of claim 2 or 3, wherein $(HR1)_x$ is homologous to a 5' region of $(TS)_x$, and $(HR2)_x$, is homologous to a 3' region of $(TS)_x$.

5. The method of claim 1, or the host cell of claim 2, wherein $(N)_x$ is capable of cleaving at a region positioned between said 5' and 3' regions of $(TS)_x$.

6. The method of claim 1, or the host cell of claim 2, wherein a single nuclease is capable of cleaving each $(TS)_x$.

7. The method or host cell of any one of claims 1 to 6, wherein n= 3, 4, 5, 6, 7, 8, 9 or 10.

8. The method of any one of claims 1 and 4 to 7, wherein said recovering does not require integration of a selectable marker.

9. The method of any one of claims 1 and 4 to 7, wherein said recovering occurs at a higher frequency as compared to not contacting the host cell with a nuclease capable of cleaving at said target site.

10. The method of any one of claims 1 and 4 to 7, wherein said recovering occurs at a frequency of about one every 10, 9, 8, 7, 6, 5, 4, 3, or 2 contacted host cells, or clonal populations thereof, screened.

11. The method or host cell of any one of claims 1, 2, and 4 to 10, wherein $(N)_x$ is capable of cleaving an endogenous genomic sequence within $(TS)_x$.

12. The method or host cell of any one of claims 1, 2, and 4 to 10, wherein $(N)_x$ is capable of cleaving an exogenous sequence within $(TS)_x$.

13. The method or host cell of claim 12, wherein the exogenous sequence is a recognition sequence for a homing endonuclease.

14. The method or host cell of claim 13, wherein the homing endonuclease is F-cphI.

15. The method or host cell of any one of claims 1 to 14, wherein $(ES)_x$ further comprises a nucleic acid of interest $(D)_x$ positioned 3' of $(HR1)_x$ and 5' of $(HR2)_x$.

16. The method or host cell of claim 15, wherein $(D)_x$ is selected from the group consisting of a selectable marker, a promoter, a nucleic acid sequence encoding an epitope tag, a gene of interest, a reporter gene, and a nucleic acid sequence encoding a termination codon.

17. The method or host cell of any one of claims 1 to 16, wherein $(ES)_x$ is linear.

18. The method or host cell of any one of claims 1, 2, and 4 to 17, wherein $(N)_x$ is provided as an expression vector comprising a nucleic acid sequence encoding $(N)_x$.

19. The method or host cell of any one of claims 1, 2, and 4 to 18, wherein $(N)_x$ is selected from the group consisting of an endonuclease, a zinc finger nuclease, a TAL-effector DNA binding domain-nuclease fusion protein (TALEN), a transposase, and a site-specific recombinase.

20. The method or host cell of claim 19, wherein the endonuclease is modified to specifically bind an endogenous genomic sequence, wherein the modified endonuclease no longer binds to its wild type endonuclease recognition sequence.

~~21. The method or host cell of claim 19 or 20, wherein the endonuclease is a homing~~ endonuclease selected from the group consisting of: an LAGLIDADG homing endonuclease, an HNH homing endonuclease, a His-Cys box homing endonuclease, a GIY-YIG homing endonuclease, and a cyanobacterial homing endonuclease.

22. The method of or host cell of claim 19 or 20, wherein the endonuclease is derived from an endonuclease selected from the group consisting of: H-DreI, I-SceI, I-SceII, I-SceIII, I-SceIV, I-SceV, I-SceVI, I-SceVII, I-CeuI, I-CeuAIIP, I-CreI, I-CrepsbIP, I-CrepsbIIP, I-CrepsbIIIP, I-CrepsbIVP, I-TliI, I-PpoI, Pi-PspI, F-SceI, F-SceII, F-SuvI, F-CphI, F-TevI, F-TevII, I-AmaI, I-AniI, I-ChuI, I-CmoeI, I-CpaI, I-CpaII, I-CsmI, I-CvuI, I-CvuAIP, I-DdiI, I-DdiII, I-DirI, I-DmoI, I-HmuI, I-HmuII, I-HsNIP, I-LlaI, I-MsoI, I-NaaI, I-NanI, I-NclIP, I-NgrIP, I-NitI, I-NjaI, I-Nsp236IP, I-PakI, I-PboIP, I-PcuIP, I-PcuAI, I-PcuVI, I-PgrIP, I-PobIP, I-PorI, I-PorIIP, I-PbpIP, I-SpBetaIP, I-ScaI, I-SexIP, I-SneIP, I-SpomI, I-SpomCP, I-SpomIP, I-SpomIIP, I-SquIP, I-Ssp68031, I-SthPhiJP, I-SthPhiST3P, I-SthPhiSTe3bP, I-TdeIP, I-TevI, I-TevII, I-TevIII, i-UarAP, i-UarHGPAIP, I-UarHGPA13P, I-VinIP, I-ZbiIP, PI-MgaI, PI-MtuI, PI-MtuHIP PI-MtuHIIP, PI-PfuI, PI-PfuII, PI-PkoI, PI-PkoII, PI-Rma43812IP, PI-SpBetaIP, PI-SceI, PI-TfuI, PI-TfuII, PI-ThyI, PI-TliI, or PI-TliII.

23. The method or host cell of any one of claims 1 to 22, wherein the host cell is selected from the group consisting of a fungal cell, a bacterial cell, a plant cell, and an animal cell.

24. The method or host cell of any one of claims 1 to 23, wherein the host cell is a yeast cell.

25. The method or host cell of claim 24, wherein the yeast cell is a *Saccharomyces cerevisiae* cell.

26. A method for simultaneously integrating a plurality of (n) exogenous nucleic acids into a plurality of (n) target sites of a host cell genome, wherein n is at least two, the method comprising:

(a) simultaneously contacting a host cell with:

(i) a plurality of libraries, wherein x is an integer that varies from 1 to n, and for each integer x, each library $(L)_x$ comprises a plurality of exogenous nucleic acids, wherein each exogenous nucleic acid comprises, in a 5' to 3' orientation, a first homology region $(HR1)_x$, any nucleic acid of interest selected from the group $(D)_x$, and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of said selected exogenous nucleic acid at a target site $(TS)_x$ of said host cell genome; and

(ii) for each said target site $(TS)_x$, a nuclease $(N)_x$ capable of cleaving at $(TS)_x$, whereupon said cleaving results in homologous recombination of an exogenous nucleic acid from $(L)_x$ at $(TS)_x$;

and

(b) recovering a host cell wherein an exogenous nucleic acid from each library $(L)_x$ has integrated at each selected target sequence $(TS)_x$.

27. A host cell comprising:

(a) a plurality of (n) genomic target sites, wherein n is at least two;

(b) a plurality of libraries, wherein x is an integer that varies from 1 to n, and for each integer x, each library $(L)_x$ comprises a plurality of exogenous nucleic acids, wherein each exogenous nucleic acid comprises, in a 5' to 3' orientation, a first homology region $(HR1)_x$, any nucleic acid of interest selected from the group $(D)_x$, and a second homology region $(HR2)_x$, wherein $(HR1)_x$ and $(HR2)_x$ are capable of initiating host cell mediated homologous recombination of said selected exogenous nucleic acid at a target site $(TS)_x$ of said host cell genome; and

for each said target site $(TS)_x$, a nuclease $(N)_x$ capable of cleaving at $(TS)_x$, whereupon said cleaving results in homologous recombination of an exogenous nucleic acid from $(L)_x$ at $(TS)_x$.