reprogramming factors, and culturing the non-hepatocyte cell under conditions suitable for reprogramming a non-hepatocyte cell to an induced hepatocyte, thereby producing an induced hepatocyte from the non-hepatocyte cell.

In another aspect, there is provided a method for producing a human induced hepatocyte from a human fibroblast cell, the method comprising providing a human fibroblast cell, introducing into the human fibroblast cell a nucleic acid or protein preparation which encodes or provides a combination of reprogramming factors, wherein the combination of reprogramming factors comprise FOXA1, FOXA2, FOXA3, HNF1A, and HNF4A, and culturing the human fibroblast cell under conditions suitable for reprogramming a human fibroblast cell to a human induced hepatocyte, thereby producing a human induced hepatocyte from the human fibroblast cell.

Disclosed is a method for producing an induced hepatocyte from a non-hepatocyte cell, the method comprising providing a non-hepatocyte cell, introducing into the non-hepatocyte cell a nucleic acid or protein preparation which encodes or provides one or more reprogramming factors, and culturing the non-hepatocyte cell under conditions suitable for reprogramming a non-hepatocyte cell to an induced hepatocyte, thereby producing an induced hepatocyte from the non-hepatocyte cell.

~~In another aspect, there is provided a cell population comprising human induced hepatocytes obtained by any of the methods described herein.~~

Disclosed is a cell population comprising induced hepatocytes obtained by the methods as described herein.

~~In another aspect, there is provided an isolated human induced hepatocyte obtained by any of the methods described herein.~~

Disclosed is an isolated induced hepatocyte obtained by the methods as described herein.

In another aspect, there is provided a composition comprising a nucleic acid preparation, wherein the composition is capable of reprogramming a human fibroblast cell to a human induced hepatocyte when the composition is introduced into the human fibroblast cell, wherein the nucleic acid preparation comprises nucleic acid molecules encoding a combination of reprogramming factors, wherein the combination of reprogramming factors is selected from the group consisting of a combination comprising FOXA1, FOXA3, and HNF1A; a combination comprising FOXA1, FOXA2, and HNF1A; a combination comprising FOXA2, FOXA3, and HNF1A; a combination comprising FOXA1, HNF1A, and HNF4A; a combination comprising FOXA2, HNF1A, and HNF4A; and a combination comprising FOXA3, HNF1A, and HNF4A.

In another aspect, there is provided a composition comprising a nucleic acid preparation, wherein the composition is capable of reprogramming a human fibroblast cell to a human induced hepatocyte when the composition is introduced into a human fibroblast cell, wherein the nucleic acid preparation comprises nucleic acid molecules encoding a combination of reprogramming factors, where the combination of reprogramming factors comprises FOXA1, FOXA2, FOXA3, HNF1A, and HNF4A.

Disclosed is a composition comprising a nucleic acid preparation, wherein the composition is capable of reprogramming a non-hepatocyte cell to an induced hepatocyte when the composition is introduced into a non-hepatocyte cell.

~~In another aspect, there is provided a method of screening a test compound, the method comprising contacting the human induced hepatocyte obtained by any of the methods described herein with a test compound, and determining the effect of the test compound on the human induced hepatocyte.~~

Disclosed is a method of screening a test compound, the method comprising contacting an induced hepatocyte obtained by the methods as described herein with a test compound, and determining the effect of the test compound on the induced hepatocyte.

The methods and compositions provided herein are useful for reprogramming a starting cell or starting cell population (*e.g.*, a non-hepatocyte cell or non-hepatocyte cell population) to an induced hepatocyte or a population of induced hepatocytes with high efficiency. In some

WHAT IS CLAIMED IS:

1. A method for producing a human induced hepatocyte from a human fibroblast cell, the method comprising providing a human fibroblast cell, introducing into the human fibroblast cell a nucleic acid or protein preparation which encodes or provides a combination of reprogramming factors, wherein the combination of reprogramming factors is selected from the group consisting of a combination comprising FOXA1, FOXA3, and HNF1A; a combination comprising FOXA1, FOXA2, and HNF1A; a combination comprising FOXA2, FOXA3, and HNF1A; a combination comprising FOXA1, HNF1A, and HNF4A; a combination comprising FOXA2, HNF1A, and HNF4A; and a combination comprising FOXA3, HNF1A, and HNF4A, and culturing the human fibroblast cell under conditions suitable for reprogramming a human fibroblast cell to a human induced hepatocyte, thereby producing a human induced hepatocyte from the human fibroblast cell.

2. The method of claim 1, wherein the combination of reprogramming factors is the combination comprising FOXA1, FOXA3, and HNF1A; the combination comprising FOXA1, FOXA2, and HNF1A; or the combination comprising FOXA2, FOXA3, and HNF1A, the combination further comprising HNF4A.

3. The method of claim 1 or claim 2, wherein the one or more reprogramming factors is selected from the group consisting of FOXA1, FOXA2, FOXA3, HNFIA, HNF4A, and GATA4.

4. The method of claim 1 or claim 2, wherein the reprogramming factors comprise CEBPA, GATA6, HHEX, HNFIB, HNF6A, FOXA1, FOXA2, FOXA3, GATA4, HNFIA, and HNF4A.

5. The method of claim 1 or claim 2, wherein the reprogramming factors comprise FOXA1, FOXA2, FOXA3, HNFIA, HNF4A, and GATA4.

6. A method for producing a human induced hepatocyte from a human fibroblast cell, the method comprising providing a human fibroblast cell, introducing into the human fibroblast cell a nucleic acid or protein preparation which encodes or provides a combination of reprogramming factors, wherein the combination of reprogramming factors comprise FOXA1, FOXA2, FOXA3, HNF1A, and HNF4A, and culturing the human fibroblast cell under conditions suitable for reprogramming a human fibroblast cell to a human induced hepatocyte, thereby producing a human induced hepatocyte from the human fibroblast cell.

7. The method of claim 6, wherein the combination of reprogramming factors further comprises GATA4.

8. A cell population comprising human induced hepatocytes obtained by the method of any of claims 1 to claim 7.

9. An isolated human induced hepatocyte obtained by the method of any of claims 1 to claim 7.

10. A composition comprising a nucleic acid preparation, wherein the composition is capable of reprogramming a human fibroblast cell to a human induced hepatocyte when the composition is introduced into the human fibroblast cell, wherein the nucleic acid preparation comprises nucleic acid molecules encoding a combination of reprogramming factors, wherein the combination of reprogramming factors is selected from the group consisting of a combination comprising FOXA1, FOXA3, and HNF1A; a combination comprising FOXA1, FOXA2, and HNF1A; a combination comprising FOXA2, FOXA3, and HNF1A; a combination comprising FOXA1, HNF1A, and HNF4A; a combination comprising FOXA2, HNF1A, and HNF4A; and a combination comprising FOXA3, HNF1A, and HNF4A.

11. The composition of claim 10, wherein when the nucleic acid preparation comprises nucleic acid molecules encoding the combination of reprogramming factors comprising FOXA1, FOXA3, and HNF1A; the combination comprising FOXA1, FOXA2, and HNF1A; or the combination comprising FOXA2, FOXA3, and HNF1A, the combination further comprises nucleic acid molecules encoding HNF4A.

12. A composition comprising a nucleic acid preparation, wherein the composition is capable of reprogramming a human fibroblast cell to a human induced hepatocyte when the composition is introduced into a human fibroblast cell, wherein the nucleic acid preparation comprises nucleic acid molecules encoding a combination of reprogramming factors, where the combination of reprogramming factors comprises FOXA1, FOXA2, FOXA3, HNF1A, and HNF4A.

13. The composition of claim 12, wherein the composition further comprises nucleic acid molecules encoding GATA4.

14. A method of screening a test compound, the method comprising contacting the human induced hepatocyte obtained by the method of any of claims 1 to 7 with a test compound, and determining the effect of the test compound on the human induced hepatocyte.

WHAT IS CLAIMED IS:

1. A method for producing a human induced hepatocyte from a human fibroblast cell, the method comprising providing a human fibroblast cell, introducing into the human fibroblast cell a nucleic acid or protein preparation which encodes or provides a combination of reprogramming factors, wherein the combination of reprogramming factors is selected from the group consisting of a combination comprising FOXA1, FOXA3, and HNF1A; a combination comprising FOXA1, FOXA2, and HNF1A; a combination comprising FOXA2, FOXA3, and HNF1A; a combination comprising FOXA1, HNF1A, and HNF4A; a combination comprising FOXA2, HNF1A, and HNF4A; and a combination comprising FOXA3, HNF1A, and HNF4A, and culturing the human fibroblast cell under conditions suitable for reprogramming a human fibroblast cell to a human induced hepatocyte, thereby producing a human induced hepatocyte from the human fibroblast cell.

2. The method of claim 1, wherein the combination of reprogramming factors is the combination comprising FOXA1, FOXA3, and HNF1A, wherein the combination further comprises HNF4A; the combination comprising FOXA1, FOXA2, and HNF1A, wherein the combination further comprises HNF4A; or the combination comprising FOXA2, FOXA3, and HNF1A, wherein the combination further comprises HNF4A.

3. The method of claim 1 or claim 2, wherein the reprogramming factors comprise FOXA1, FOXA2, FOXA3, HNFIA, HNF4A, and GATA4.

4. The method of claim 1 or claim 2, wherein the reprogramming factors comprise CEBPA, GATA6, HHEX, HNFIB, HNF6A, FOXA1, FOXA2, FOXA3, GATA4, HNFIA, and HNF4A.

5. The method of claim 1 or claim 2, wherein the reprogramming factors comprise FOXA1, FOXA2, FOXA3, HNFIA, HNF4A, and GATA4.

6. A method for producing a human induced hepatocyte from a human fibroblast cell, the method comprising providing a human fibroblast cell, introducing into the human fibroblast cell a nucleic acid or protein preparation which encodes or provides a combination of reprogramming factors, wherein the combination of reprogramming factors comprise FOXA1, FOXA2, FOXA3, HNF1A, and HNF4A, and culturing the human fibroblast cell under conditions suitable for reprogramming a human fibroblast cell to a human induced hepatocyte, thereby producing a human induced hepatocyte from the human fibroblast cell.

7. The method of claim 6, wherein the combination of reprogramming factors further comprises GATA4.

8. A composition comprising a nucleic acid preparation, wherein the composition is capable of reprogramming a human fibroblast cell to a human induced hepatocyte when the composition is introduced into the human fibroblast cell, wherein the nucleic acid preparation comprises nucleic acid molecules encoding a combination of reprogramming factors, wherein the combination of reprogramming factors is selected from the group consisting of a combination comprising FOXA1, FOXA3, and HNF1A; a combination comprising FOXA1, FOXA2, and HNF1A; a combination comprising FOXA2, FOXA3, and HNF1A; a

combination comprising FOXA1, HNF1A, and HNF4A; a combination comprising FOXA2, HNF1A, and HNF4A; and a combination comprising FOXA3, HNF1A, and HNF4A.

9. The composition of claim 8, wherein when the nucleic acid preparation comprises nucleic acid molecules encoding the combination of reprogramming factors comprising FOXA1, FOXA3, and HNF1A, wherein the combination further comprises nucleic acid molecules encoding HNF4A; the combination comprising FOXA1, FOXA2, and HNF1A, wherein the combination further comprises nucleic acid molecules encoding HNF4A; or the combination comprising FOXA2, FOXA3, and HNF1A, wherein the combination further comprises nucleic acid molecules encoding HNF4A.

10. A composition comprising a nucleic acid preparation, wherein the composition is capable of reprogramming a human fibroblast cell to a human induced hepatocyte when the composition is introduced into a human fibroblast cell, wherein the nucleic acid preparation comprises nucleic acid molecules encoding a combination of reprogramming factors, where the combination of reprogramming factors comprises FOXA1, FOXA2, FOXA3, HNF1A, and HNF4A.

11. The composition of claim 10, wherein the composition further comprises nucleic acid molecules encoding GATA4.