SYSTEMS AND METHODS FOR KIDNEY PERFUSION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application No. 63/575,429 filed April 5, 2024, the content of which is incorporated by reference in its entirety herein, and to which priority is claimed.

SEQUENCE LISTING

[0002] This application contains an electronic Sequence Listing which has been submitted in XML file format with this application, the entire content of which is incorporated by reference herein in its entirety. The Sequence Listing XML file submitted with this application is entitled "14648-042-228_SEQLISTING.xml", was created on April 1, 2025, and is 36,802 bytes in size.

1. FIELD

[0003] The present disclosure relates, in part, to methods and compositions for kidney perfusion.

2. BACKGROUND

[0004] There is a growing need for renal replacement therapy (dialysis & transplantation). By 2030, is it expected that 5.4 million patients will receive such therapy, up from 2.5 million in 2017. However, the demand for renal replacement therapy is severely outpacing supply. Kidneys are also frequently discarded as being unsuitable for transplantation, further complicating the shortage of available kidneys.

[0005] Machine perfusion technologies have emerged as a potential tool for addressing transplantation obstacles, such as reduced graft survival, poor post-transplant graft function, and ischaemia reperfusion injury (IRI). However, to date, such technologies remain experimental and there has not been any commercial success in developing technologies that improve transplant outcomes through delivery of therapeutic agents to repair and/or regenerate kidneys.

[0006] Thus, there is an unmet need for technology to increase the number of kidneys available for transplantation or improve transplant success rates and outcomes. Accordingly,

provided herein are perfusion systems, methods and compositions for kidney perfusion for addressing this need.

3. SUMMARY

[0007] In one aspect, provided herein is a method of *ex vivo* kidney perfusion comprising: perfusing a kidney with a therapeutic composition in a perfusion system, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and wherein the perfusion system comprises an acoustic volume sensor. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the recipient is a mammal. In some embodiments, the recipient is a human. In some embodiments, the donor is swine. In some embodiments, the swine is a miniature swine. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[0008] In another aspect, provided herein is a method of repairing kidney damage in a subject in need thereof comprising: perfusing a kidney with a therapeutic composition in a perfusion system, wherein the therapeutic composition comprises at least one agent that induces

expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and wherein the perfusion system comprises an acoustic volume sensor. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the recipient is a mammal. In some embodiments, the recipient is a human. In some embodiments, the donor is swine. In some embodiments, the swine is a miniature swine. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4, (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[0009] In yet another aspect, provided herein is a method of treating a kidney disease or disorder in a subject in need thereof comprising: perfusing a kidney with a therapeutic composition in a perfusion system, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and wherein the perfusion system comprises an acoustic volume sensor. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces OCT4,

SOX2, NANOG, and/or LIN28. In some embodiments, the recipient is a mammal. In some embodiments, the recipient is a human. In some embodiments, the donor is swine. In some embodiments, the swine is a miniature swine. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[0010] In another aspect, provided herein is a method of preserving a kidney comprising: perfusing a kidney with a therapeutic composition in a perfusion system, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and wherein the perfusion system comprises an acoustic volume sensor. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the recipient is a mammal. In some embodiments, the recipient is a human. In some embodiments, the donor is swine. In some embodiments, the swine is a miniature swine. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4,

NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[0011] In another aspect, provided herein is a method of transplanting a kidney to a recipient in need thereof, the method comprising: perfusing a kidney obtained from a donor with a therapeutic composition in a perfusion system, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and transplanting the kidney into the recipient, and wherein the perfusion system comprises an acoustic volume sensor. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the recipient is a mammal. In some embodiments, the recipient is a human. In some embodiments, the donor is swine. In some embodiments, the swine is a miniature swine. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In

some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[0012] In one aspect, provided herein is a method of genetically engineering a kidney ex vivo, the method comprising: contacting a kidney with: (a) a polynucleotide composition comprising a OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 polynucleotide, or (b) a polypeptide composition comprising a OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 polypeptide, and perfusing the kidney in a perfusion system comprising an acoustic volume sensor. In some embodiments, the composition comprises a OCT3/4, SOX2, KLF4, and/or c-MYC polynucleotide or polypeptide. In some embodiments, the composition comprises a OCT3/4, SOX2, and/or KLF4 polynucleotide or polypeptide. In some embodiments, the composition comprises a OCT4, SOX2, NANOG, and/or LIN28 polynucleotide or polypeptide.

[0013] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is configured to automatically adjust the concentration of the therapeutic composition in the perfusion system. In some embodiments, the perfusion system is transportable.

[0014] In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate.

[0015] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the

pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 milliliters. In some embodiments, the reservoir has a volume of less than about 25 milliliters. In some embodiments, the reservoir has a volume of less than about 10 milliliters. In some embodiments, the reservoir has a volume of less than about 3 milliliters.

[0016] In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone.

[0017] In another aspect, provided herein is a composition for use in a perfusion system comprising at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, wherein the perfusion system comprises an acoustic volume sensor. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof. In some embodiments, the perfusion system is a normothermic perfusion system.

[0018] In one aspect, provided herein is a perfusion system, comprising a means for perfusing a kidney with a therapeutic composition, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of OCT3/4, KLF4, c-MYC, and SOX2; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of OCT3/4, KLF4, c-MYC, and SOX2. In some embodiments, the nucleic acid is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked nucleic acid, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[0019] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is configured to automatically adjust the concentration of the therapeutic composition in the perfusion system. In some embodiments, the perfusion system is wherein the perfusion system is transportable.

[0020] In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate.

[0021] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including an acoustic volume sensor configured to measure the volume of the therapeutic composition, the

polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 milliliters. In some embodiments, the reservoir has a volume of less than about 25 milliliters. In some embodiments, the reservoir has a volume of less than about 10 milliliters. In some embodiments, the reservoir has a volume of less than about 3 milliliters.

[0022] In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone.

[0023] In one aspect, provided herein is an infusion pump comprising a means for measuring fluid volume of a therapeutic composition, wherein the therapeutic composition is suitable for ex vivo kidney perfusion. In some embodiments, the fluid volume is less than 60 milliliters. In some embodiments, the fluid volume is less than 25 milliliters. In some embodiments, the fluid volume is less than 10 milliliters. In some embodiments, the fluid volume is less than 5 milliliters. In some embodiments, the fluid volume is less than 3 milliliters. In some embodiments, the fluid volume is less than 1 milliliter.

[0024] In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT4, SOX2, NANOG, and/or LIN28.

[0025] In some embodiments, the at least one agent comprises a nucleic acid, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the nucleic acid encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28.

4. BRIEF DESCRIPTION OF THE FIGURES

[0026] **FIG. 1** depicts an example perfusion system for perfusing a tissue with the various compositions described herein. Only some of the components of the perfusion system are depicted, including an example large-volume infusion pump and an example small-volume infusion pump, and the components are not drawn to scale.

[0027] **FIG. 2** depicts a schematic representation of systemic dosing of AAV vectors using an exemplary organ perfusion system and *ex vivo* organ perfusion.

[0028] **FIG. 3** depicts a schematic representation of methods for the collection of kidney sample tissues according to the exemplary studies disclosed herein.

[0029] **FIG. 4** depicts the expression pattern of the OSK in the kidney transduced with AAV2-OSK.

[0030] **FIG. 5** depicts the percentage of cells within a given cell type that were transduced with AAV2-vector (first panel), and percentage of cells within a given cell type that were transcribed with Oct4 (second panel), Sox2 (third panel), and Klf4 (last panel).

5. DETAILED DESCRIPTION

[0031] The present disclosure is directed, in part, to perfusion systems (such as those described in Section 5.1), and methods (such as those described in Section 5.3 and Section 5.4), compositions (such as those described in Section 5.2) suitable for use with the perfusion systems.

[0032] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention pertains. Otherwise, certain terms used herein have the meanings as set forth in the specification. All patents, published patent applications and publications cited herein are incorporated by reference as if set forth fully herein. For purposes of interpreting this specification, the following description of terms will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa. In the event that any description of a term set forth conflicts with any document incorporated herein by reference, the description of the term set forth below shall control.

[0033] It should be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0034] As used herein, the terms "about" and "approximately" mean within 20%, within 15%, within 10%, within 9%, within 8%, within 7%, within 6%, within 5%, within 4%, within 3%, within 2%, within 1%, or less of a given value or range.

[0035] As used herein, the term "normothermic" is intended to mean at or around body temperature (*e.g.*, about 33-38°C).

[0036] The practice of embodiments provided herein will employ, unless otherwise indicated, conventional techniques of molecular biology, organ perfusion, and transplantation, which are within the skill of those working in the art. Such techniques are explained fully in the literature. Examples of particularly suitable texts for consultation include the following: Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Third Ed., Cold Spring Harbor

Laboratory, New York (2001); Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley and Sons, Baltimore, MD (1999); Glover, ed., DNA Cloning, Volumes I and II (1985); Freshney, ed., Animal Cell Culture: Immobilized Cells and Enzymes (IRL Press, 1986); Immunochemical Methods in Cell and Molecular Biology (Academic Press, London); Scopes, Protein Purification: Principles and Practice (Springer Verlag, N.Y., 2d ed. 1987); Kataria A, Magoon S, Makkar B, Gundroo A. Machine perfusion in kidney transplantation. Curr Opin Organ Transplant. 2019 Aug;24(4):378-384.

[0037] In an attempt to help the reader of the application, the description has been separated in various paragraphs or sections, or is directed to various embodiments of the application. These separations should not be considered as disconnecting the substance of a paragraph or section or embodiments from the substance of another paragraph or section or embodiments. To the contrary, one skilled in the art will understand that the description has broad application and encompasses all the combinations of the various sections, paragraphs and sentences that can be contemplated. The discussion of any embodiment is meant only to be exemplary and is not intended to suggest that the scope of the disclosure, including the claims, is limited to these examples. The application contemplates use of any of the applicable components in any combination, whether or not a particular combination is expressly described.

5.1 Perfusion System

[0038] Perfusion systems are important in various fields such as medicine, biotechnology, and pharmaceuticals due to their ability to mimic physiological conditions and sustain tissues outside of the body. These systems function to ensure the efficient delivery of vital nutrients, oxygen, and regulatory signals, while simultaneously eliminating waste products, thus establishing an environment that can closely resemble in vivo conditions. Perfusion systems provide an effective platform for advancing tissue engineering and regenerative medicine endeavors, facilitating the growth or maintenance of tissues intended for transplantation purposes.

[0039] FIG. 1 depicts a schematic of a perfusion system 100 (not drawn to scale) that may be used for perfusion of a tissue 132 (e.g., a kidney) in a perfusion container 130. For example, the perfusion system 100 may be used to perfuse and provide nutrition or treatment to human tissue for use in a transplantation procedure. The perfusion system 100 may function to emulate

fundamental biological processes typically occurring within the body. These processes may encompass, for example, oxygenation, carbon dioxide regulation, thermal management, and nutrient supply. In order to emulate these biological processes, the perfusion system 100 may include various additional components beyond those depicted in FIG. 1. For example, oxygenation and carbon dioxide control may be achieved using a membrane oxygenator, while a heat exchanger may be used to maintain the desired temperature of the perfusate 134. Specifically, the perfusate 134 may exit the tissue 132, pass through an oxygenator and a heat exchanger, and then be subsequently reintroduced into the tissue 132. By passing the perfusate 134 through a heat exchanger, the perfusate 134 circulated through the tissue 132 may be maintained at a desired temperature, such as a normothermic temperature. Additionally, in order to permit effective transplantation of a tissue, the perfusion system 100 may be sized and configured to be transportable, such that the tissue 132 may be safely transferred from one location to another.

[0040] In order to facilitate the fluid transfer of the perfusate 134 through the various components and the tissue 132, one or more perfusion pumps (not depicted) may be included as part of the perfusion system 100 to enable tissue perfusion and perfusate recirculation. Types of perfusion pumps that may be used include, for example, axial flow pumps, peristaltic pumps, diaphragm pumps, pumping cassettes, roller pumps, centrifugal pumps, and pulsatile pumps. As will be further discussed, nutrients, replacement perfusate solution, or various treatment or therapeutic compositions may be added to the perfusate 134 during the perfusion process, which may be introduced through one or more infusion pumps 120, 160. As will be further described, the infusion pumps 120, 160, and in some instances the perfusion pump, may be specifically designed to precisely control the flowrate of the infusible solution, and thereby control the amount of the therapeutic composition that is introduced into the perfusate 134 and experienced by the tissue. Through the use of multiple infusion pumps, such as a large-volume infusion pump 120 and a low-volume infusion pump 160, different infusible solutions may be used to manage different target concentrations in the perfusate 134.

[0041] As shown in FIG. 1, the perfusion system 100 may include a first, large-volume infusion pump 120 configured to controllably introduce a treatment solution 110 into the perfusate 134 solution that is being perfused through the tissue 132. The treatment solution 110 may include various nutrients, nutraceuticals, treatments, pharmaceuticals, inorganic compounds

or elements, organic compounds or elements, and other fluids useful for perfusion or treatment. For example, the treatment solution 110 may include water, lipids, amino acids, glucose, vitamins, hormones, antibiotics, vasodilators, vasoconstrictors, diuretics, antidiuretics, and/or anticoagulants. In this manner, the treatment solution 110 may be used to replenish the concentration of various nutrients and drugs within the perfusate 134 as they diminish over time. With the inclusion of the large-volume infusion pump 120, desired treatment concentrations within the perfusate 134 may be actively maintained and kept substantially constant throughout the perfusion process. This replenishment process may be variable, and may occur automatically via the use of sensors monitoring the perfusate 134 or a byproduct of the tissue 130 and through reactive control of the large-volume infusion pump 120. For instance, sensors may measure the consumption rate of a specific component in the perfusate 134, and that sensor data may be used to control the infusion of an infusible solution 110 containing that same medication. While the large-volume infusion pump 120 is depicted in FIG. 1 as introducing the infusible solution 110 directly into the perfusion container 130, it should be readily appreciated that the infusible solution 110 may be introduced into the perfusate 134 at various locations, including at a position along the recirculation pathway (not depicted) of the perfusion system 100 that is being used to perfuse the tissue 130. Moreover, it should be readily appreciated that additional infusion pumps beyond the two depicted may be utilized, with each pump introducing a different infusible solution. Moreover, the perfusion pump used in the perfusion system 100 may use a similar or identical pump design to the large-volume infusion pump 120.

[0042] As shown, the large-volume infusion pump 120 may specifically be a cartridge-type pump configured to integrate with a pneumatic system 140, which may permit the large-volume infusion pump 120 to remain sterile and disposable. Exemplary perfusion systems and associated perfusion and infusion pumps that may be suitable are described in U.S. Patent Publication No. 2023/0284613 entitled System And Method For Tissue Maintenance, Assessment, Maturation, And Rehabilitation, published on Sep. 14, 2023, U.S. Pat. No. 8,273,049 entitled Pumping Cassette, issued on Sep. 25, 2012, U.S. Pat. No. 9, 999,717 entitled Systems and Methods For Detecting Vascular Access Disconnection, issued on Jun. 19, 2018, the contents of each of which are hereby incorporated by reference in their entireties.

[0043] In order to effectuate the introduction of the infusible solution 110 into the perfusate 134, the large-volume infusion pump 120 may specifically have a cassette design that functions

as a membrane pump, as shown. In particular, the large-volume infusion pump 120 may include a housing 120 defining a fluid inlet 118 and a fluid outlet 119. The fluid inlet 118 and fluid outlet 119 may form a part of the fluid connection between the perfusate 134 and the infusible solution 110, which may include tubing 112, as shown. The large-volume infusion pump 120 may also include a pump chamber 122 positioned within the fluid pathway 128 of the large-volume infusion pump 120.

[0044] A membrane 124 may be positioned within the pump chamber 122, and may separate the fluid pathway section of the pump chamber 122 from an actuation section of the pump chamber 122. For example, the pump chamber 122 may be spherical in shape and the membrane 124 may extend across the pump chamber 122 to effectively create two separate semispherical sections. The membrane 124 may be flexible and configured to move within pump chamber 122 as the pressure difference between the fluid pathway and the actuation sections of the pump chamber 122 changes. In this manner, a pumping force may be created by controllably changing the pressure within the actuation section of the pump chamber 122. Thus, the membrane 124 and the pump chamber 122 may effectively create a variable-volume pumping chamber. When a vacuum is induced in the actuation section of the pump chamber 122, the membrane 124 may be drawn towards this side, facilitating fluid movement into and out of the fluid pathway section of the pump chamber 124. Conversely, when a positive pressure is applied to the actuation section of the pump chamber 122, the membrane 124 may be pushed towards the fluid pathway side, obstructing the fluid path and impeding fluid flow.

[0045] The large-volume infusion pump 120 may also include an inlet valve 129 positioned between the fluid inlet 118 and the pump chamber 122. The inlet valve 129 may be configured to controllably block the fluid pathway 128. Similarly, the large-volume infusion pump 120 may also include an outlet valve 126 positioned between the fluid outlet 119 and the pump chamber 122. The outlet valve 126 may also be configured to controllably block the fluid pathway 128. The infusion pump valves 126, 129 may permit the creation of the pump action by the pump chamber 122. For example, during an initial pump phase, a volume of the infusible solution 110 may be drawn into the pump chamber 122 with the inlet valve 129 open to permit the influx of infusible solution 110 and the outlet valve 126 closed to ensure the infusible solution is largely retained in the pump chamber 122. During a subsequent pump phase, the inlet valve 129 may then be closed and the outlet valve 126 may be opened, allowing for the infusible solution 110 to

be pumped out of the pump chamber 122 toward the fluid outlet 119. While active valves are depicted, it should be appreciated that various alternative valves may be used with such a reciprocating positive-displacement large-volume infusion pump 120.

[0046] In order to assist in the actuation of the large-volume infusion pump 120, the perfusion system 110 may include a pneumatic system 140. Generally, the pneumatic system 140 may be capable of controllably providing positive and/or negative pressurizations to the actuation section of the pump chamber 122. Among other components, the pneumatic system 140 may include a control system 142, a positive pressure source 144, and a negative pressure source 146. The control system 142 may control the pressure provided to the pump chamber 122, as well as the inlet valve 129 and the outlet valve 126. To provide this pneumatic control to the large-volume infusion pump 120, the large-volume infusion pump 120 may include a pump chamber port 123 in fluid connection with the actuation section of the pump chamber 122, as well as similar ports 121, 125 for the inlet valve 129 and the outlet valve 126, respectively. Individual tubes 141, 143, 145 or similar connectors may connect the various ports 121, 123, 125 to the pneumatic system 140.

[0047] The control system 142 may be used to adjust the flowrate of the large-volume infusion pump 120 by controlling the applied pressure, including the frequency, the duration, and the pressure amount provided for each part of the pump cycle. Various valves or similar components may also be used by the control system 142 to control the pressurizations provided to the various ports 121, 123, 125 of the large-volume infusion pump 120. The control system 142 may be in communication with various sensors of the perfusion system 100, including sensors monitoring the perfusate 134. A flow meter may be configured to measure the flowrate in the fluid pathway 128 and provide this measurement to the control system 142. The control system 142 may then use measurements received by a flow meter to adjust the flowrate of the large-volume infusion pump 120, such as to match the measured flowrate to a target flowrate. Additionally, various fluid measurement techniques may be utilized, including measuring the volume of fluid pumped through the pump chamber during 122 a stroke of the membrane 124 or detecting air in the actuation section of the pump chamber 122, such as by using a pressure transducer. For example, the control system 142 may run an end of stroke algorithm to detect when each pump stroke completes based on the measured pressure in the actuation section of the pump chamber 122.

[0048] FIG. 1 also depicts a second, small-volume infusion pump 160 for introducing small, highly-precise amounts infusible solutions into the perfusate 134, such as the various compositions described herein. Similar to the infusible solution 110 introduced by the large-volume infusion pump 120, the infusible solution introduced via the small-volume infusion pump 160 may include various nutrients, nutraceuticals, treatments, pharmaceuticals, inorganic compounds or elements, organic compounds or elements, and other fluids useful for perfusion or treatment, including the specific drug combinations described herein. In particular, for effective treatment, it may be important that the small-volume infusion pump 160 deliver an infusible solution containing the compositions described herein in precisely-controlled amounts. The small-volume infusion pump 160 may be configured to either automatically, such as by using a controller, or manually provide a given treatment fluid at a specific flow rate. For example, the small-volume infusion pump 160 may be specifically configured to receive a target injection rate value and to adjust the measured injection rate to the target injection rate value with a high degree of accuracy and precision. As will be further described, the small-volume infusion pump 160 may utilize specific volume measurement techniques to enable such an exact dosage to be provided, including the use of an acoustic volume sensor in some implementations.

[0049] The small-volume infusion pump 160 may be configured to introduce an infusible fluid (i.e., a treatment solution comprising a therapeutic composition such as a composition described in Section 5.2) into the perfusate 134. In order to provide this functionality, the small-volume infusion pump 160 may generally include a reservoir 162 to house a source of the infusible fluid, a pump assembly 164 configured to pump a quantity of the infusible fluid from the reservoir 162 along a fluid path 168 to the perfusate 134, and an acoustic volume sensor 166 configured to measure the volume of the infusible fluid that is introduced into the perfusate 134. As part of the pump assembly 164, a controller may be used to control the volumetric rate that the pump assembly 164 is pumping the infusible fluid at, and may use a one or more sensor signals when making such control determinations, including the output of the acoustic volume sensor. In other words, the small-volume infusion pump 160 may be configured so that the volume measurements produced by acoustic volume sensor 166 may be used to control, through a feedback loop, the amount of infusible fluid that is infused perfusate 134. Furthermore, the acoustic volume sensor 166 may further include a first valve assembly in the fluid path 168. The first valve assembly may be configured to fluidly isolate the acoustic volume sensor 166 from

the pump assembly 164. Likewise, a second valve assembly may also be in the fluid path 168 and configured to fluidly isolate the acoustic volume sensor 166 from the perfusate 134.

[0050] The small-volume infusion pump 160 may further include a disposable assembly which may be configured such that any components in infusion pump 160 that come in contact with the infusible fluid are contained within disposable assembly. For example, the fluid path 166 and the reservoir 162 may be positioned within disposable assembly and may be disposed of after one or more uses. The disposable nature of the disposable assembly may improve sanitation and allow for rapid reuse of the infusion pump 160. This disposable assembly may be provided separate from the infusion pump 160, and may be preloaded with a source of the infusible solution containing desired therapeutic compositions. In this manner, replacement quantities of a specific therapeutic compositions may be easily sold and provided separate from the small-volume infusion pump 160. Alternatively, the infusible solution may be added to the reservoir 162 after installation of the disposable assembly in the infusion pump 160. The disposable assembly may be specifically configured to integrate with and attach to an infusion pump that utilizes an acoustic volume sensor. For instance, in addition to a reservoir containing an infusible fluid, the disposable assembly may include a dispensing chamber with an associated membrane as part of the fluid pathway, as will be further described.

[0051] The acoustic volume sensor 166 may generally include a fixed reference chamber acoustically coupled to a speaker and a first microphone, as well as a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone. The variable chamber may be defined in part by a membrane contacting a dispensing chamber, which may be the reservoir 162. The acoustic volume sensor 166 may configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra using the first microphone and the second microphone. Pumps utilizing acoustic volume measurement technology are described in U.S. Patent Publication No. 2021/0393870 entitled Infusion Pump Assembly, published on Dec. 23, 2021, U.S. Patent No. 10,786,624 entitled Device To Determine Volume Of Fluid Dispensed, published on Sep. 29, 2020, and U.S. Pat. No. 10,126,157 entitled Volumetric Measurement Device System And Method, issued on Nov. 13, 2018, the contents of each of which are hereby incorporated by reference in their entireties.

[0052] While acoustic volume sensors are particularly suitable for the small-volume infusion of the compositions described herein (such as the compositions described in Section 5.2), it should be appreciated that other volume sensing techniques may be utilized instead of the acoustic volume sensor 166, provided that they provide sufficient accuracy and precision. Other alternative volume sensing techniques may include, for example, Doppler-based methods, the use of Hall-effect sensors in combination with a vane or flapper valve, the use of a strain beam (for example, related to a membrane over a fluid reservoir to sense deflection of the membrane), the use of capacitive sensing with plates, or thermal time of flight methods. Accordingly, in some aspects, provided herein is an infusion pump comprising a means for measuring fluid volume of a therapeutic composition, wherein the therapeutic composition is suitable for *ex vivo* kidney perfusion. In some embodiments, the fluid volume is less than about 60 milliliters (mL), less than about 50 mL, less than about 40 mL, less than about 30 mL, less than about 20 mL, less than about 25 mL, less than about 20 mL, less than about 15 mL, less than about 10 mL, less than about 9 mL, less than about 8 mL, less than about 7 mL, less than about 6 mL, less than about 5 mL, less than about 4 mL, less than about 3 mL, less than about 2 mL, or less than about 1 mL. In certain embodiments, the therapeutic composition is a composition described in Section 5.2). In some embodiments, the means for measuring fluid volume of the therapeutic composition is not an acoustic volume sensor. In some embodiments, the means for measuring fluid volume of the therapeutic composition is a volumetric sensing technique.

[0053] The acoustic volume sensor 166 may generally function by measuring fluid flow through a variable volume dispensing chamber and may provide feedback to the controller regarding volume of the dosage being delivered. The controller may include a processor and control circuitry for controlling the pump assembly 164 to pump fluid to the perfusate 134. For example, the controller may use the information provided by the acoustic volume sensor 166 to determine the rate of fluid flow, cumulative fluid flow, or both, and then use this information to control the pumping assembly, such as be reducing or increasing the pump rate to reach a target volumetric rate. As fluid enters the dispensing chamber in the fluid pathway 168, a membrane may expand into the variable volume chamber. Sound waves induced by the first microphone and may travel through the fixed volume chamber to the variable volume chamber via a port. As the membrane moves with the flow of fluid through the flow line, the volume of air in the variable volume chamber may change, and the resulting acoustic characteristic changes may be

detected by the microphones. The volume of fluid displaced in the dispensing chamber may be determined by comparing the measured volume of the variable volume chamber to an initial volume of the variable volume chamber, and the volume of infusible fluid being pumped by the pump assembly 164 may be determined. In other words, the volume of the fluid dispensed may be determined based on the acoustic response of the microphones to acoustic excitement by the speaker.

[0054] Through the use of the acoustic volume sensor 166, fluid volume sensing in the nanoliter range is possible, which can result in highly accurate and precise monitoring and delivery of an infusible solution. In particular, the reservoir 162 of the small-volume infusion pump 160 may have a volume of less than about 60 milliliters (mL), less than about 50 mL, less than about 40 mL, less than about 30 mL, less than about 20 mL, less than about 25 mL, less than about 20 mL, less than about 15 mL, less than about 10 mL, less than about 9 mL, less than about 8 mL, less than about 7 mL, less than about 6 mL, less than about 5 mL, less than about 4 mL, less than about 3 mL, less than about 2 mL, or less than about 1 mL. Moreover, the infusion pump 166 may specifically have an injection flowrate range that does not exceed 500 μL/hour. For instance, the infusion pump 160 may be configured to provide pump flowrates between about 0.5 and 300 μL/hour. The infusion pump may also have a high degree of precision. For example, the actual injection rate of the small-volume infusion pump 160 may be configured to be within 1 μL/hour, within 100 nL/hour, or within 10 nL/hour of a target injection rate. Such a small-volume infusion pump 160 may be used to enable the precise injection of specific amounts of the compositions described herein (such as in Section 5.2) into the perfusate 134.

[0055] In one aspect, provided herein is a perfusion system, comprising a means for perfusing a kidney with a therapeutic composition (such as a composition described in Section 5.2), wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney. In some embodiments, the perfusion system is configured to automatically adjust the concentration of the therapeutic composition in the perfusion system. In some embodiments, the perfusion system is transportable. In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney (such as a perfusate described in Section 5.3 and Section 5.4). In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide

composition into the perfusate, the infusion pump system including an acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 mL, less than about 50 mL, less than about 40 mL, less than about 30 mL, less than about 20 mL, less than about 25 mL, less than about 20 mL, less than about 15 mL, less than about 10 mL, less than about 9 mL, less than about 8 mL, less than about 7 mL, less than about 6 mL, less than about 5 mL, less than about 4 mL, less than about 3 mL, less than about 2 mL, or less than about 1 mL. In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone, a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone.

5.2 Compositions

[0056] Provided herein are compositions for use in a perfusion system (such as a perfusion system described in Section 5.1). In certain embodiments, provided herein are therapeutic compositions comprising at least one agent that induces expression of at least one of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In certain embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC,

KLF4, NANOG, and/or LIN28 by increasing transcription of the relevant gene. In certain embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 by increasing translation of the relevant mRNA. In certain embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 by increasing stability and/or preventing degradation of the relevant protein. In some embodiments, provided herein is a polynucleotide composition comprising a OCT3/4, a SOX2, a c-MYC, a KLF4, a NANOG, and/or a LIN28 polynucleotide. In some embodiments, provided herein is a polypeptide composition comprising a OCT3/4, a SOX2, a c-MYC, a KLF4, a NANOG, and/or a LIN28 polypeptide or fragment thereof.

[0057] Exemplary agents for use in the compositions provided herein include a gene therapy (such as a gene therapy described in Section 5.2.1), a biological therapy (such as a biological therapy described in Section 5.2.2), a small molecule therapy (such as a small molecule therapy described in Section 5.2.3), or any other pharmacological agent capable of inducing expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In certain embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a gene editing system, or any combination thereof.

[0058] In some embodiments, the composition (*e.g.*, therapeutic composition) comprises at least one agent that induces expression of OCT3/4. In some embodiments, the composition comprises at least one agent that induces expression of SOX2. In some embodiments, the composition comprises at least one agent that induces expression of c-MYC. In some embodiments, the composition comprises at least one agent that induces expression of KLF4. In some embodiments, the composition comprises at least one agent that induces expression of NANOG. In some embodiments, the composition comprises at least one agent that induces expression of LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

[0059] In some embodiments, the composition (*e.g.*, therapeutic composition) comprises at least one agent that induces expression of at least two of OCT3/4, SOX2, c-MYC, KLF4,

NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4 and SOX2. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4 and c-MYC. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4 and KLF4. In some embodiments, the composition comprises at least one agent that induces expression of SOX2 and c-MYC. In some embodiments, the composition comprises at least one agent that induces expression of SOX2 and KLF4. In some embodiments, the composition comprises at least one agent that induces expression of c-MYC and KLF4. In some embodiments, the composition comprises at least one agent that induces expression of KLF4 and NANOG. In some embodiments, the composition comprises at least one agent that induces expression of KLF4 and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of c-MYC and NANOG. In some embodiments, the composition comprises at least one agent that induces expression of c-MYC and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of SOX2 and NANOG. In some embodiments, the composition comprises at least one agent that induces expression of SOX2 and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of NANOG and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4 and NANOG. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4 and LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

[0060] In some embodiments, the composition (*e.g.*, therapeutic composition) comprises at least one agent that induces expression of at least three of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or c-MYC. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, c-MYC, and/or KLF4. In some embodiments, the composition comprises at least one agent that induces expression of SOX2, c-MYC, and/or KLF4. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4,

SOX2, and/or NANOG. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of SOX2, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, and c-MYC. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, and KLF4. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, c-MYC, and KLF4. In some embodiments, the composition comprises at least one agent that induces expression of SOX2, c-MYC, and KLF4. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, and NANOG. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, NANOG, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of SOX2, NANOG, and LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

[0061] In some embodiments, the composition (*e.g.*, therapeutic composition) comprises at least one agent that induces expression of at least four of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or NANOG. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, and LIN28. In some embodiments, the composition comprises at least one agent

that induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and NANOG. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, NANOG, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

[0062] In some embodiments, the composition (*e.g.*, therapeutic composition) comprises at least one agent that induces expression of at least five of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or NANOG. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, NANOG, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, NANOG, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, and LIN28. In some embodiments, the composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, and NANOG. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody

or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

[0063] In some embodiments, the composition (*e.g.*, therapeutic composition) comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

5.2.1 Gene Therapy

[0064] In certain embodiments, the agent comprises a gene therapy that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. For example, a gene therapy can induce the expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 by introducing a polynucleotide or polypeptide (*e.g.*, a polynucleotide or fragment thereof encoding for OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28, or a polypeptide or fragment thereof encoding for OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28). Accordingly, in some embodiments, provided herein is a polynucleotide composition comprising a OCT3/4, a SOX2, a c-MYC, a KLF4, a NANOG, and/or a LIN28 polynucleotide or fragment thereof. In some embodiments, provided herein is a polypeptide composition comprising a OCT3/4, a SOX2, a c-MYC, a KLF4, a NANOG, and/or a LIN28 polypeptide or fragment thereof. In certain embodiments, the gene therapy comprises a gene editing system (e.g., a CRISPR system) that induces the expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some the gene therapy comprises RNAi that induces the expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28.

[0065] Polypeptide and polynucleotide sequences for human OCT3/4 are known (UniProtKB No. Q01860; Table 1). OCT3/4 (also known as PO5F1 (POU domain, class 5, protein); octamer-binding protein 3 (OCT3); OCT4; OTF3) is a protein that binds to DNA and controls the expression of genes involved in embryogenesis and embryonic stem cell pluripotency. The human polypeptide and polynucleotide sequences are known for SOX2 (UniProtKB No. P48431; Table 1). Polypeptide and polynucleotide sequences for human KLF4 are known (UniProtKB No. O43474; Table 1). KLF4 (Krueppel-like factor 4), also known as EZF (epithelial zinc finger protein) and GKLF (gut-enriched krueppel-like factor), regulates the expression of proteins

during embryonic development and, in part, maintains embryonic stem cells. Polypeptide and polynucleotide sequences for human c-MYC are known (UniProtKB No. P01106; Table 1). Also known as BHLHE39 (class E basic helix-loop-helix protein 39) or protein p64, c-MYC is a protein that binds DNA in a non-specific manner and can control self-renewal of embryonic stem cells. NANOG is a transcription regulator involved in inner cell mass and embryonic stem (ES) cell proliferation and self-renewal. The polypeptide and polynucleotide sequences for human NANOG are known (UniProtKB No. Q9H9S0; Table 1). The highly conserved RNA binding protein, LIN28, comprises a family of proteins that includes two homologous members, LIN28A and LIN28B, each having similar domain structure and function. The polypeptide and polynucleotide sequences for human LIN28A (UniProtKB No. Q9H9Z2; Table 1) and human LIN28B (UniProtKB No. Q6ZN17; Table 1) are known. The LIN28 proteins influence mRNA translation, thereby regulating the self-renewal of mammalian embryonic stem cells. As used herein, "LIN28" is understood to refer to LIN28A, LIN28B, or both (LIN28A/LIN28B) interchangeably. In certain embodiments, the polynucleotide or polypeptide (*e.g.*, a polynucleotide or fragment thereof encoding for OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28, or a polypeptide or fragment thereof encoding for OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28) is a heterologous polypeptide or fragment thereof.

[0066] **Table 1: Exemplary human polypeptide and polynucleotide sequences**

	Polypeptide Sequence	Nucleotide Sequence
OCT3/4	MAGHLASDFAFSPPPGGG GDGPGGGPEPGWVVDPRTW LSFQGPPGGPGIGPGVGP GSEVWGIPPCPPPYEFCG GMAYCGPQVGVGLVPQG GLETSQPEGEAGVGVESN SDGASPEPCTVTPGAVKL EKEKLEQNPEESQDIKAL QKELEQFAKLLKQKRITL GYTQADVGLTLGVLFGK VFSQTTICREEALQLSFKN MCKLRPLLQKWVEEADN NENLQEICKAETLVQARK RKRTSIENRVRGNLENLF LQCPKPTLQQISHIAQQLG LEKDVVRVWFCNRRQKG KRSSSDYAQREDFEAAGS PFSGGPVSFPLAPGPHFGT PGYGSPHFTALYSSVPFPE GEAFPPVSVTTLGSPMHS N (SEQ ID NO: 1)	GGAAAAAAAGGAAAAGTGCACTTGGAAGAGATCCAAGTGGGCAACTTGAAGAACAAGTGCCAA ATAGCACTTCTGTCATGCTGGATGTCAGGGGCTCTTTGTCCACTTTGTATAGCCGCTGGCTTATAG AAGGTGCTCGATAAAATCTCTTGAATTTAAAAAATGAGTAAGTAACACACAAAGCACTTTATCCATT CAGTAAAGATGAGGGATAATCAATTTAAAAAAATGAGTAAGTAACACACAAAGCACTTTATCCATT CTTATGACACCTGTTACTTTTTGCTGTGTTTGTGTGATGCATGCCATGTTATAGTTTGTGGGAC CCTCAAAGCAAGCTGGGGAGAGTATATACTGAATTTAGCTTCTGAGACATGATGCTCTTCCTTT TTAATTAACCCAGAAACTTAGCAGCTTATCTATTCTCTAATCTCAAAACATCCTTAAACTGGGGG TGATACTTGAGTGAGAGAATTTTGCAGGTATTAAATGAACTATCTTCTTTTTTTTTCTTTGA GACAGAGTCTTGCTCTGTCACCCAGGCTGGAGTGCAGTGGCGTGATCTCAGCTCACTGCAACC TCCGCCTCCCGGGTTCAAGTGATTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGATTACAGGTGC GTGCCACCGTGCCCAGCTAATTTTTGTGTTTTAGTAGAGACGGGGTTTCACCATGTTGGCCAT GCTGGTCTTGAACTCCTGACCTCGTGATCTGCCCACCTCGGCCTCCCAAAGTGCTGGAATTATA GGCGTGAGCCACCGCGCCCAGCAAAGAACTTCTAACCTTCATAACCTGACAGGTGTTCTCGAG GCCAGGGTCTCTCTTTCTGTCCTTTCACGATGCTCTGCATCCCTTGGATGTGCCAGTTTCTGGG GGAAGAGTAGTCCTTTGTTACATGCATGAGTCAGTGAACAGGGAATGGGGTGAATGACATTTGT GGGTAGGTTATTTCTAGAAGTTAGGTGGGCAGCTTGGAAGGCAGATGCACTTCTACAGACTATT CCTTGGGGCCACACGTAGGTTCTTGAATCCCGAATGGAAAGGGGAGATTGATAACTGGTGTGT TTATGTTCTTACAAGTCTTCTGCCTTTTAAAATCCAGTCCCAGGACATCAAAGCTCTGCAGAAA GAACTCGAGCAATTTGCCAAGCTCCTGAAGCAGAAGAGGATCACCCTGGGATATACACAGGC CGATGTGGGGGCTCACCCTGGGGGTTCTATTTGGGAAGGTATTCAGCCAAACGACCATCTGCCG CTTTGAGGCTCTGCAGCTTACGTTCAAGAACATGTGTAAGCTGCGGGCCCTTGCTGCAGAAGTG GGTGGAGGAAGCTGACAACAATGAAAATCTTCAGGAGATATGCAAAGCAGAAACCCTCGTGC AGGCCCGAAAGAGAAAGCGAACCAGTATCGAGAACCGAGTGAGAGGCAACCTGGAGAATTT GTTCCTGCAGTGCCCGAAACCCACACTGCAGCAGATCAGCCACATCGCCCAGCAGCTTGGGCT CGAGAAGGATGTGGTCCGAGTGTGGTTCTGTAACCGGCGCCAGAAGGGCAAGCGATCAAGCA GCGACTATGCACAACGAGAGGATTTTGAGGCTGCTGGGTCTCCTTTCTCAGGGGGACCAGTGT CCTTTCCTCTGGCCCCAGGGCCCCATTTGGTACCCCAGGCTATGGGAGCCCTCACTTCACTGC ACTGTACTCCTCGGTCCCTTTCCCTGAGGGGGAAGCCTTTCCCCCTGTCTCCGTCACCACTCTG GGCTCTCCCATGCATTCAAACTGAGGTGCCTGCCCTTCTAGGAATGGGGGGACAGGGGGAGGG GAGGAGCTAGGGAAAGAAAAACCTGGAGTTTGTGTGCCAGGGTTTTTGGGATTAAGTTCTTCATTC ACTAAGGAAGAATTGGGAACACAAAGGGTGGGGGCAGGGGAGTTTGGGGGCAACTGGTTGG AGGGAAGGTGAAGTTCAATGATGCTCTTGATTTTAATCCCACATCATGTATCACTTTTTTCTTAA ATAAAGAAGCCTGGGACACAGTAGATAGACACACTTAAAAAAAAAAAA (SEQ ID NO: 2)
SOX2	MYNMMETELKPPGPQQT SGGGGGNSTAAAAGGNQ KNSPDRVKRPMNAFMV WSRGQRRKMAQENPKM	CACAGCGCCCGCATGTACAACATGATGGAGACGGAGCTGAAGCCGCCGGGCCCGCAGCAAAAC TTCGGGGGGGCGGCGGCAACTCCACCGCGGCGGCCGGCCCGGCAACCAGAAAAACAGC CCGGACCGCGTCAAGCGGCCCATGAATGCCTTCATGGTGTGGTCCCGCGGGCAGCGGCGCAA GATGGCCCAGGAGAACCCCAAGATGCACAACTCGGAGATCAGCAAGCGCCTGGGGCGCCGAGT

	HNSEISKRLGAEWKLLSE TEKRPFIDEAKRLRALHM KEHPDYKYRPRRKTKTL MKKDKYTLPGGLLAPGG NSMASGVGVGAGLGAG VNQRMDSYAHMNGWSN GSYSMMQDQLGYPQHPG LNAHGAAQMQPMHRYD VSALQYNSMTSSQTYMN GSPTYSMSYSQQGTPGM ALGSMGSVVKSEASSSPP VVTSSSHSRAPCQAGDLR DMISMYLPGAEVPEPAAP SRLHMSQHYQSGPVPGT AINGTLPLSHM (SEQ ID NO: 3)	GGAAACTTTTGTCGGAGAAGGAGGAAGCGGCCGTTCATCGACGAGGCTAAGCGGCTGCGAGCG CTGCACATGAAGGAGCACCCGGATTATAAATACCGGCCCCGGCGAAAACCAAGACGCTCATG AAGAAGGATAAGTACACGCTGCCCGGCGGGCTGCTGGCCCCGGCGGCAATAGCATGCGGAG CGGGGTCGGGGTGGGCGCCTGGGCGGGCGTGAACCAGCGCATGGACAGTTACGGCGC ACATGAACGGCTGGAGCAACGGCAGCTACAGCATGATGCAGGACCAGCTGGGCTACCCGCAG CACCCGGGCCTCAATGCGCACGGCGCAGCGCAGATGCACCCATGCACCGCTACGACGTGAG CGCCTGCAGTACAACTCCATGACCAGCTUGCAGACCTACATGAACGGCTCGCCCACCTACAG CATGTCCTACTCGCAGCAGGGCACCCCTGTGGTTACCTCTTCCCCACTCCAGGGCGCCCTGCCA GTCCGAGGCCAGCTCCAGCCCCCCTGTGGTTACCTCTTCCCCACTCCAGGGCGCCCTGCCA GGCCGGGGACCTCCGGGACATGATCAGCATGTATCTCCCCGGCGCCGAGGTGCCGGAACCCGC CGCCCCCAGCAGACTTCACATGTCCAGCACTACCAGAGCGGCCCGGTGCCCGGCACGGCCA TTAACGGCACACTGCCCCTCTCACACATGTGAGGCCGGACAGCGAACTGGAGGGGGAGAA ATTTTCAAAGAAAAACGAGGGAAATGGGAGGGGTGCAAAAGAGGAGAGTAAGAAACAGCAT GGAGAAAACCCGGTACGCTCAAAAAAAA (SEQ ID NO: 4)
KLF4	MRQPPGESDMAVSDALL PSFSTFASGPAGREKTLRQ AGAPNNRWREELSHMKR LPPVLPGRPYDLAAATVA TDLESGGAGAACGGSNL APLPRRETEEFNDLLDLD FILSNSLTHPPESVAATVSS SASASSSSSPSSSGPASAPS TCSFTYPIRAGNDPGVAP GGTGGGLLYGRESAPPPT APFNLADINDVSPSGGFV AELLRPELDPVYIPPQQPQ PPGGGLMGKFVLKASLS APGSEYGSPSVISVSKGSP DGSIPVVVAPYNGGPPRT CPKIKQEAVSSCTHLGAG PPLSNGHRPAAHDFPLGR QLPSRTTPTLGLEEVLSSR DCHPALPLPPGFHPHPGP NYPSFLPDQMQPQVPPLH YQGQSRGFVARAGEPCV CWPHFGTHGMMLTPPSSP LELMPPGSCMPEEPKPKR GRRSWPRKRTATHTCDYA	CGGGCGCAGGCCGGGACTCCGCGCCACGGCAGCCAGTCTCACCTGGCGGCACCGCCCGCCCA CCGCCCCGGCCACAGCCCCTGCGCCCACGGCAGCACTCGAGGCGACCGCGACAGTGGTGGGG GACGCTGCTGAGTGGAAGAGAGCGCAGCCGGCCACCGGACCTACTTACTCGCCTTGCTGATT GTCTATTTTTGCGTTTACAACTTTTCTAAGAACTTTTGTATACAAAGGAACTTTTTAAAAAAGA CGCTTCCAAGTTATATTTAATTCAAAGAAGGATCTCGGCCAATTTGGGGTTTTTGGGTTTTG GCTTCGTTTCTTCTTCTTCGTTGACTTTGGGGTTCAGGTGCCCCAGCTGCTTCGGGCTGCCGAGG ACCTTCTGGGCCCCCACATTAATGAGGCAGCCACCTGGCGAGTCTGATGCTGTCAGCGAC GCGCTGCTCCCATCTTTCTCCACGTTCGCGTCTGGCCCGGCGGGAAGGGAGAAGACACTGCGT CAAGCAGGTGCCCCGAATAACCGCTGGCGGAGGAGCTCTCCCACATGAAGCGACTTCCCCC AGTGCTTCCCGCCGGCCCCTATGACCTGGCGGCGACCGTGGCCACAGACCTGGAGAGCG CCGGAGCCGGTGCGGCTTGCGGCGGCTAGCAACCTGGCGCCCTACCTCGGAGAGAGCCGAG GAGTTCAACGATCTCCTGGACCTGGACTTTATTCTCTCCAATTCGCTGACCCATCCTCGGAGT CAGTGGCCGCCACCGTGTCCTCGTCAGCGTCAGCCTCCTCTTCGTCGCCGTCGAGCAGCG GCCCTGCCAGCGCGCCCTCCACCTGCAGCTTCACCTATCCGATCCGGCCGGAACGACCCGG GCGTGGCGCCGGGCACGGGCGGAGGCCTCCTCTATGGCAGGGAGTCCGCTCCCCCTCCG ACGGCTCCCTTCAACCTGGCGGACATCAACGACGTGAGCCCCTCGGGCGGCTTCGTGGCCGA GCTCCTGCCGCCAGAATTGGACCCGGTGTACATTCCGCCGCAGCAGCCGCAGGGTG GCGGGCTGATGGGCAAGTTCGTGCTGAAGGCGTCGCTGAGCGCCCCTGGCAGCGAGTACGGC AGCCCGTCGGTCATCAGCGTCACGAAAGGCAGCCCTGACGGCAGCCACCCGGTGGTGGTGGC GCCCTACAACGGCGGCCCGCCGCACGTGCCCCAAGATCAAGCAGGAGGCGGTCTCTTCGT GCACCCACTTGGGCGCTGGACCCCTCTCAGCAATGGCCACCGGCCGGCTGCACACGACTTCC CCCTGGGGCGGCAGCTCCCCAGCAGGACTACCCCGACCTGGCTCTTGAGGAAGTGCTGAGC AGCAGGGACTGTCACCCTGCCCTGCCTTCCTCCCGGCTTCCATCCCCACCCGGGGCCCAAT TACCCATCCTTCCTGCCCGATCAGATGCAGCCGCAAGTCCCGCCGCTCCATTACCAAGAGCTCA

	GCGKTYTKSSHLKAHLRT HTGEKPYHCDWDGCGW KFARSDELTRHYRKHTGH RPFQCQKCDRAFSRSDHL ALHMKRHF (SEQ ID NO: 5)	TGCCACCCGGTTCCTGCATGCCAGAGGAGCCCAAGCCAAAGAGGGAAGACGATCGTGGCCC CGGAAAAGGACCGCCACCCACACTTGTGATTACGCGGGCTGCGGCAAAACCTACACAAAGAG TTCCCATCTCAAGGCACACCTGCGAACCCACACAGGTGAGAAACCTTACCACTGTGACTGGG ACGGCTGTGGATGGAAATTCGCCCGCTCAGATGAACTGACCAGGCACTACCGTAAACACACG GGGCACCGCCCGTTCCAGTGCCAAAAATGCGACCGAGCATTTTCCAGGTCGGACCACCTCGCC TTACACATGAAGAGGCATTTTTAAATCCCAGACAGTGGATATGACCCACACTGCCAGAAGA (SEQ ID NO: 6)
c-MYC	MDFFRVVENQQPPATMPL NVSFTNRNYDLDYDSVQ PYFYCDEEENFYQQQQQS ELQPPAPSEDIWKKFELLP TPPLSPSRRSGLCSPSYVA VTPFSLRGDNDGGGGSFS TADQLEMVTELLGGDMV NQSFICDPDDETFIKNIIIQ DCMWSGFSAAAKLVSEK LASYQAARKDSGSPNPAR GHSVCSTSSLYLQDLSAA ASECIDPSVVFPYPLNDSS SPKSCASQDSSAFSPSSDS LLSSTESSPQGSPEPLVLH EETPPTTSSDSEEEQEDEE EIDVVSVEKRQAPGKRSE SGSPSAGGHSKPPHSPLVL KRCHVSTHQHNYAAPPST RKDYPAAKRVKLDSVRV LRQISNNRKCTSPRSSDTE ENVKRRTHNVLERQRRN ELKRSFFALRDQIPELENN EKAPKVVILKKATAYILSV QAEEQKLISEEDLLRKRR EQLKHKLEQLRNSCA (SEQ ID NO: 7)	AAGTGCTGGGATTACAGGTGTGAGCCACCGCGCCCAGGCTTAGATGTGGCTCTTTGGGAGATA ATTTTGTCCAGAGACCTTTCTAACGTAATTCATGCCTTGTAATTGTGTACAGCATTAATCTGGTAATTG ATTATTTTAATGTAACCTTGCTAAAGGAGTGATTTCTATTCCTTTCTTAAAGAGGAGGAACAAG AAGATGAGGAAGAAATCGATGTTGTTTCTGTGGAAAAAGAGGCAGGCTCCTGGCAAAAGGTCA GAGTCTGGATCACCTTCTGCTGGAGGCCACAGCAACCTCCTCACAGCCCACTGGTCCTCAAG AGGTGCCACGTCTCCACACATCAGCACAACTACGCAGCGCCTCCCTCCACTCGGAAGGACTAT CCTGCTGCCAAGAGGGTCAAGTTGGACAGTGTCAGAGTCCTGAGACAGATCAGCAACAACCG AAAATGCACCAGCCCCAGGTCCTCGGACACCGAGGAGAATGTCAAGAGGCGAACACACAAC GTCTTGGAGCGCCAGAGGAGGAACGAGCTAAAACGGAGCTTTTTGCCCTGCGTGACCAGAT CCCGGACGTTGGAAAACAATGAAAAGGCCCCCAAGGTAGTTATCCTTAAAAAAGCCACAGCAT ACATCCTGTCCGTCCAAGCAGAGGAGCAAAAGCTCATTTCTGAAGAGGACTTGTTGCGGAAA CGACGAGAACAGTTGAAACACAAACTTGAACAGCTACGGAACTCTTGTGCGTAAGGAAAAGT AAGGAAAACGATTCCTTCTAACAGAAATGTCCTGAGCAATCACCTATGAACTTGTTTCAAATGTC ATGATCAAATGCAACCTCACAACCTTGGCTGAGTCTTGAGGACTGAAAGATTTAGCCATAATGTA AACTGCCTCAAATTGGACTTTGGGCATAAAAGAACTTTTTATGCTTACCATCTTTTTTTTCT TTAACAGATTTGTATTTAAGAATTGTTTTTAAAAAATTTAAGATTTACACAATGTTTCTCTGTAA ATATTGCCATTAAATGTAAATAACTTTAATAAAAACGTTTATAGCAGTTACACAGAATTTCAATCCT AGTATATAGTACCTAGTATTATAGGTACTATAAAACCCTAATTTTTTTTTAATTTAAGTACATTTTGCTT TTAAAAGTTGATTTTTTTTCTATTGTTTTTAGAAAAAATAAAAATAACTGGCAAAATATATCATTGAGC CAAATCTTAAGTTGTGAATGTTTTTGTTTCGTTTCTTCCCCCTCCCAACCACCACCATCCCTGTTT GTTTTCATCAATTGCCCCTTCAGAGGGTGGTCTTAAGAAAGGCAAGAGTTTTCCTCTGTTGAA ATGGGTCTGGGGGGCCTTAAGGTCTTTAAGTTCTTGGAGGTTCTTAAGATGCTTCCTGGAGACTAT GATAACAGCCGAAGTTGACAGTTAGAAGGAATGGCAGAAGGCAGGTGAGAAGGTGAGAGGT AGGCAAAGGAGATACAAGAGGTCAAAGGTAGCAGTTAAGTACACAAAGAGGGCATAAGGGACTG GGGAGTTGGGAGGAAGGTGAGGAAGAAACTCCTGTTACTTTAGTTAACCAGTGCCAGTCCCC TGCTCACTCCAAA (SEQ ID NO: 8)
NANOG	MSVDPACPQSLPCFEASD CKESSPMPVICGPEENYPS LQMSSAEMPHTETVSPLP SSMDLLIQDSPDSSTSPKG KQPTSAEKSVAKKEDKVP VKKQKTRTVFSSTQLCVL NDRFQRQKYLSLQQMQE	GTTATTATGCAGGCAACTCACTTTATCCCAATTTCTTGATACTTTTCCTTCTGGAGGTCCTATTTC TCTAACATCTTCCAGAAAAGTCTTAAAGCTGCCTTAACCTTTTTTCCAGTCCACCTCTTAAATTT TTTCCTCCTCTTCCTCTATACTAACATGAGTGTGGATCCAGCTTGTCCCCAAAGCTTGCCTTGCT TTGAAGCATCCGACTGTAAAGAATCTTCACCTATGCCTGTGATTGTGGGCCTGAAGAAAACTA TCCATCCTTGCAAATGTCTTCTGCTGAGATGCCTCACACGGAGACTGTCTCTCCTTCCTCC TCCATGGATCTGCTTATTCAGGACAGCCCTGATTCTTCCACCAGTCCCAAAGGCAAACAACCC ACTTCTGCAGAGAATAGTGTCGCAAAAAAGGAAGACAAGGTCCCAGTCAAGAAACAGAAGA

	LSNILNLSYKQVKTWFQN QRMKSKRWQKNNWPKN SNGVTQKASAPTYPSLYS SYHQGCLVNPTGNLPMW SNQTWNNSTWSNQTQNI QSWSNHSWNTQTWCTQS WNNQAWNSPFYNCGEES LQSCMQFQPNSPASDLEA ALEAAGEGLNVIQQTTRY FSTPQTMDLFLNYSMNM QPEDV (SEQ ID NO: 9)	CCAGAACTGTGTTCTCTTCCACCCAGCTGTGTGTACTCAATGATAGATTTCAGAGACAGAAATA CCTCAGCCTCCAGCAGATGCAAGAACTCTCCAACATCCTGAACCTCAGCTACAAACAGGTGA AGACCTGGTTCCAGAACCAGAGAATGAAATCTAAGAGGTGGCAGAAAAACAACTGGCCGAA GAATAGCAATGGTGTGACCGCAGAAGGCCTCAGCACCTACCTACCCAGCCTCTACTCTTCCTA CCACCAGGGATGCCTGGTGAACCCGACTGGGAACCTTCCAATGTGGAGCAACCAGACCTGGA ACAATTCAACCTGGAGCAACCAGACCCAGAACATCCAGTCCTGGAGCAACCACTCCTGGAAC ACTCAGACCTGGTGCACCCAAICCTGGAACAATCAGGCCTGGAACAGTCCCTTCTATAACTGT GGAGAGGAATCTCTGCAGTCCTGCATGCAGTTCCAGCCAAATTCTCCTGCCAGTGACTTGGAG GCTGCTTTGGAAGCTGCTGGGGAAGGCCTTAATGTAATACAGCAGACCACTAGGTATTTAGTA CTCCACAAACCATGGATTTATTCCTAAACTACTCCATGAACATGCAACCTGAAGACGTGTGAAG ATGAGTGAAACTGATATTACTCAATTTCAGTCTGGACACTGGCTGAATCCTTCCTCTCCCCTCC TCCCATCCCTCATAGGATTTTTCTTGTTTGGAAACCACGTGTTCTGGTTTCCATGATGCCTATCC AGTCAATCTCATGGAGGGTGGAGTATGGTTGGGAGCCTAATCAGCGAGGTTTCTTTTTTTTTTT TCCTATTGGATCTTCCTGGAGAAAATACTTTTTTTTTTTTTGAGACGGAGTCTTGCTCTGTC GCCCAGGCTGGAGTGCAGTGGCGCGATCTTGGCTCACTGCAAGCTCCGCCTCCCGGGTTCAC GCCATTCTCCTGCCTCAGCCTCCCGAGCAGCTGGGACTACAGGCGCCCGCCACCTCGGCCGGC TAATATTTTGTATTTTTAGTAGAGACAGGGTTTCACTGTGTTAGCCAGGATGGTCTCGATCTCCT GACCTTGTGATCCGCCCGCCTCGGCCTCCCTAACAGCTGGGATTACAGGCGTGAGCCACCGCG CCCTGCCTAGAAAAGACATTTTAATAACCTTGGCTGCTAAGGACAACATTGATAGAAGCCGTCT CTGGCTATAGATAAGTAGATCTAATACTAGTTTGGATATCTTTAGGGTTTAGAATCTAACCTCAA GAATAAGAAATACAAGTACGAATTGGTGATGAAGATGTATTCGTATTGTTTGGGATTGGGAGGC TTTGCTTATTTTTTAAAACTATTGAGGTAAAGGGTTAAGCTGTAACATACTTAATTGATTTCTTA CCGTTTTTGGCTCTGTTTTGCTATATCCCCTAATTTGTTGGTTGTGCTAATCTTTGTAGAAAGAG GTCTTGTATTTGCTGCATCGTAATGACATGAGTACTACTTTAGTTGGTTTAAGTTCAAATGAATG AAACAAATATTTTTCCTTTAGTTGATTTTACCCTGATTTCACCGAGTGTTTCGATGAGTAAATAT ACAGCTTAAACAT (SEQ ID NO: 10)
LIN28A	MGSVSNQQFAGGCAKAA EEAPEEAPEDAARAADEP QLLHGAGICKWFNVRMG FGFLSMTARAGVALDPPV DVFVHQSKLIMEGFRSL KEGEAVEFTFKKSAKGLE SIRVTGPGGVFCIGSERRP KGKSMQKRRSKGDRCYN CGGLDHHAKECKLPPQP KKCHFCQSISIMVASCPL KAQQGPSAQGKPTYFREE EEEHSPTLLPEAQN (SEQ ID NO: 11)	CCTTTGCCTTCGGACTTCTCCGGGGCCAGCAGCCGCCGACCAGGGCGCCCGGGGCCACGGGC TCAGCCGACGACCATGGGCTCCGTGTCCAACCAGCAGTTTGCAGGTGGCTGCGCCAAGGCGG CAGAAGAGGCGCCCGAGGAGGCGCCGGAGGACGCGGCCGGGCGGCGACGAGCCTCAGCT GCTGCACGGTGCGGGCATCTGTAAGTGGTTCAACGTGCGCATGGGGTTCGGCTTCCTGTCCAT GACCGCCCGGCGCCGGGGTCGCGCTCGACCCCCCAGTGGATGTCTTTGTGCACCAGAGTAAGCT GCACATGGAAGGGTTCCGGAGCTTGAAGGAGGGTGAGGCAGTGGAGTTCACCTTTAAGAAGT CAGCCAAGGGTCTGGAATCCATCCGTGTCACCGGACCTGGTGGAGTATTCTGTATTGGGAGTG AGAGGCGGCCAAAAGGAAAGAGCATGCAGAAGCGCAGATCAAAAGGAGACAGGTGCTACAA CTGTGGAGGTCTAGATCATGCCAAGGAATGCAAGCTGCCACACCCCAGCCCAAGAAGTGCCA CTTCTGCCAGAGCATCAGCCATATGGTAGCCTCATGTCCGCTGAAGGCCCAGCAGGGCCCTAG TGCACAGGGAAAGCCAACCTACTTTCGAGAGGAAGAAGAAATCCACACAGCCCTACCCTGC GAGGAGCAGGCAGAGTGGAGAAAGTGGGAATAGGGTGCATTGGGGCTAGTTGGGCACTGCCAT GTATCTCAGGCTTGGGTTCACACCATCACCCTTTCTTCCCTCTAGGTGGGGGGAAAGGGTGAG

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CAAAGTGGCCACAAGATTGTTTAATAGGAGACGAACGAATGTAACTCCATGTTTACTGCTAAA		
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		CCATTTCTAATCATTTTTAACACAAGCTGACTCTTCCCTTCCCTTCTCCTTTCCCTGGGAAAA
		TACAATGAATAAATAAAGACTTATTGGTACGC (SEQ ID NO: 12)
LJN28B	MAEGGASKGGGEEPGKL	AATTGACAAAGTCACGTGTGCTCAGGGGGCCAGAAACTGGAGAGAGGAGAAAAAATCA
	PEPAEEESQVLRGTGHCK	AAAGAAGGAAAGCACATTAGACCATGCGAGCTAAATTGTGATCGCACAAAATCAAGATGTTA
	WFNVRMGFGFISMINREG	GATTGATGCAGAAGATCACTCCGTTCCAAAGGGAAAGTTTTCATCTCACGAGTTTGGAGCTGA
	SPLDIPVDVFVHQSKLFM	GGGCCCGTGGGGGCAACATGGCCGAAGGCGGGGCTAGCAAAGGTGGTGGAGAAGAGCCCGGG
	EGFRSLKEGEPVEFTFKK	AAGCTGCCGGAGCCGGCAGAGGAGGAATCCCAGGTTTTGCGCGGAACTGGCCACTGTAAGTG
	SSKGLESIRVTGPGGSPCL	GTTCAATGTGCGCATGGGATTTGGATTCATCTCCATGATAAACCGAGAGGGAAGCCCCTTGGAT
	GSERRPKGKTLQKRKPK	ATTCCAGTCGATGTATTTGTACACCAAAGCAAACTATTCATGGAAGGATTAGAAGCCTAAAAG
	GDRCYNCGGLDHHAKEC	AAGGAGAACCAGTGGAATTCACATTTAAAAAATCTTCCAAAGGCCTTGAGTCAATACGGGTAA
	SLPPQPKCHYCQSIMHM	CAGGACCTGGTGGGAGCCCTGTTTAGGAAGTGAAAGAAGACCCAAAGGGAAGACACTACA
	VANCPIIKNVAQPPASSQG	GAAAAGAAAACCAAAGGGAGATAGATGCTACAACTGTGGTGGCCTTGATCATCATGCTAAGGA
	RQEAESQPCTSTLPREVG	ATGTAGTCTACCTCCTCAGCCAAAGAAGTGCCATTACTGTCAGAGCATCATGCACATGGTGGCA
	GGHGCTSPPFPQEARAFIS	AACTGCCCACATAAAAATGTTGCACAGCCACCCGCGAGTTCTCAGGGAAGACAGGAAGCAGA
	ERSGRSPQEASSTKSSIAP	ATCCCAGCCATGCACTTCAACTCTCCCTCGAGAAGTGGGAGGCGGGCATGGCTGTACATCACC
	EEQSKKGPSVQKRKKT	ACCGTTTCCTCAGGAGGCTAGGGCAGAGATCTCAGAACGGTCAGGCAGGTCACCTCAAGAAG
	(SEQ ID NO: 13)	CTTCCTCCACGAAGTCATCTATAGCACCAGAAGAGCAAAGCAAAAAGGGGCCTTCAGTTCAA
		AAAAGGAAAAAGACATAACAGGTCTTCTTCATATGTTCTTTTCCTTTACCCGGTTGCAAAGTCTA
		CCTCATGCAAGTATAGGGGAACAGTATTTCACAAGCAGTAGCTGACCTGGGATTTTAACTACTA
		TTGGGGAACTGTGAATTTTTTAAACAGACAAATCACTCTAAGCAAATTACATTTGAGCAGGGT
		GTCATGTTTTAGTTAATTCAGAGAATAAGATACTATGTCTGTCAATAGTGCATGTGTGAGAGG
		GAGAGAGCCTGAGTCTGTGTGTACATGAGGATTTTTATATAGGAATGTAGACACATATATAA
		AGAGGCTTTGTCTTATATATTTGTGTATAGATCAAAGCACACACCCTCTCTCATATAATTGGATA
		TTTCCAAGAATTGAAACCCATGTGAAGCATTATAGATAGTTTTAAATTTAACCCACTGGAGTT
		TTCTTGAAATACCACTTCTTTTATATTATATAAAACTAAAAAACACGACTGTTACCTTTGTGTGA
		ACCAAAGGATACTTCAGATCTCAGAGCTGCCAATTATGGGGTACTAAAGGTTTTTAAGACATCC
		AGTTCTCCCGAATTGGGATTGCCTCTTTTTCTTGAAATCTCTGGAGTAGTAATTTTTTCCCCC
		TTTTTTGAAGGCAGTACCTTAACTTCATATGCCTCTGACTGCCATAAGCTTTTTGATTCTGGGA
		TAACATAACTCCAGAAAAGACAATGAATGTGTAATTTGGGCCGATATTTCACTGTTTTAAATTCT
		GTGTTTAATTGTAAAATTAGATGCCTATTAAGAGAAATGAAGGGGAGGATCATCTTAGTGGCTT
		GTTTTCAGTAGTATTTTAATATCAGCTTCCTTGTAACCTTTTCCATGTTGTGAGGGTTGTAAGGGA
		TTGTGTGGCAACAGCAGCTTCCCTTGGCTAACTCAATCTTCTACCCATTGCTTAGAGCAGGGAG
		CCCTCCTTATTTACTACTGAAGACCTTAGAGAACTCCAATTGTTTGGCATATATTTTGGTGGTG
		GTTTTTATTCCTCCTGGAGAGTTATCTAATTTGTTTCTAAAACAAACAAGCAGCAAAGAAATGA
		ATTAAATACTGGGGTTGAGAATTAAAATTAAGTGGATGTTCACAGTTGCCCAATATATATGACCT
		GCAAATGATACGAAAAAGTGCAGCATTTAGTGGCAGTTAACAAGAGTGACAAGCCTGGGGCA
		GAGGTACCAAACCTCTCCCACCAGAGAGCTAGAAGTATTTATACAGTAACTTGATCTTATGG
		AAGTGACCTTCAATGCTTATTCTGAAGTAACCTATATGGTGGATACAGGATGAACATTCAGTGC
		CAGGGAGAATCTTCTCAGGTTGGTTCTCGTTAGAGTGATAAACTGGCTAGGGGCCATAGTATTG
		GTCCTGTTAGGTTTCGGTCATGGGAAAAAAAAAATTATTTTGGGGTCATCCTGGCTCTAGATGTTAT

GGGCAAAATTTCTGAAACATCTGCAAGAAGGTACCAGTTAATATAGTGCTTAATATTGGGAATA		
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GCATGACTCAAATGAGACATATTCTGCTGAACAGTTTCTACTTCCTCTCCCGCCTGTCCTGTCAT		
GGGAGACGTGTATAGTTGCTGCTGTTTCAGCAAACCACCATAAGACGAAAATGCCTCAGGTTG		
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TGTAATATTTTTGTTGTTTCTTTACAGACTAGTCTACAGTCCTGCTTACTCAAAACAAACCCAAAT		
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CTGTTCCAGCCTTACAGGTGGCTGATAATTCTCTGGTACAGAACCTTTTTATCTGTATTATAAAT		
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CAACTTAAGCAAAACAGAACACGGAAGCAGTCTTAGAAGCACCACTTTGCCCAGAGGTGGAG		
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GCTCAGTTTTATTTTTGCACCAGTGCGGCCCCAAGTTACTGCTGGTTGTATTTAGTTTGTGAATAG		
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AGCATCAAACTCTGTCTTACATAGCTGTCAAACAGCCTCTTTAAGATGTGGTGGTTGTATGATCT		
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	GGCTTAACACTTGTGAGACTTACCAGCTTGAAAATGATGGTGTTGACTACCTCTTGAATCACAT CTATCAACCACTGGCACCTACCACCAAGCTGGCTTCAATTAGTATGTGTTGCTTTTGGTATTAA CAACTAACCGTACTAGAGACCAAAGTGAACCCTGATTTTTTATATGTCTTTAATAATGGTGTTTTA TCTAGTGTTTTTAAATTATCCTGTGTAGTATTTAGATTACCTCATTGTCCATTTTGACTCATGTTGT TTACAAGTGAAAATAAAAACACTTGAACTGTATGTTTTTAAAAGACAAAAAAAGGGGTAGATGT TTGGAATGCGTTTCACTCGCATGCAGTCATCTGGAGGGACTGAAGCACTGTTTGCCTTTCTGTA CACTCTGGGTTTTATATTCTCATTTCATGCCTAATGTCTTATTCTGTCAATTATGGATATGTTGAG GTTTAAAAAAATTACTTGATTAAAAATAAAACATATAACGTTGGCATTT (SEQ ID NO: 14)

(a) **Polypeptides**

[0067] In some embodiments, a gene therapy disclosed herein comprises a OCT3/4, a SOX2, a c-MYC, a KLF4, a NANOG, and/or a LIN28 polypeptide or fragment thereof. In certain embodiments, a gene therapy disclosed herein comprises at least two polypeptides or fragments thereof selected from OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In certain embodiments, a gene therapy disclosed herein comprises at least three polypeptides or fragments thereof selected from OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In certain embodiments, a gene therapy disclosed herein comprises at least four polypeptides or fragments thereof selected from OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In certain embodiments, a gene therapy disclosed herein comprises at least five polypeptides or fragments thereof selected from OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In certain embodiments, a gene therapy disclosed herein comprises at least six polypeptides or fragments thereof selected from OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28.

[0068] In certain aspects, the polypeptides provided herein can be used in a method of genetically engineering a kidney (such as a method described in Section 5.4). Accordingly, in some embodiments, the polypeptide composition comprises an OCT3/4 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a SOX2 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a c-MYC polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a KLF4 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a NANOG polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a LIN28 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises an OCT3/4, a SOX2, a c-MYC, and a KLF4 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises an OCT3/4, a SOX2, and a KLF4 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises an OCT4, a SOX2, a NANOG, and a LIN28 polypeptide or fragment thereof.

[0069] In some embodiments, the OCT3/4 polypeptide is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 1. In some embodiments, the SOX2 polypeptide is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or

100% identical to SEQ ID NO: 3. In some embodiments, the c-MYC polypeptide is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 5. In some embodiments, the KLF4 polypeptide is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 7. In some embodiments, the NANOG polypeptide is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 9. In some embodiments, the LIN28A polypeptide is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 11. In some embodiments, the LIN28B polypeptide is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 13.

(b) Polynucleotides

[0070] In some embodiments, a gene therapy disclosed herein comprises a OCT3/4, a SOX2, a c-MYC, a KLF4, a NANOG, and/or a LIN28 polynucleotide or fragment thereof. In certain embodiments, a gene therapy disclosed herein comprises at least two polynucleotides or fragments thereof selected from OCT3/4, SOX2, c MYC, KLF4, NANOG, and LIN28. In certain embodiments, a gene therapy disclosed herein comprises at least three polynucleotides or fragments thereof selected from OCT3/4, SOX2, c MYC, KLF4, NANOG, and LIN28. In certain embodiments, a gene therapy disclosed herein comprises at least four polynucleotides or fragments thereof selected from OCT3/4, SOX2, c MYC, KLF4, NANOG, and LIN28. In certain embodiments, a gene therapy disclosed herein comprises at least five polynucleotides or fragments thereof selected from OCT3/4, SOX2, c MYC, KLF4, NANOG, and LIN28. In certain embodiments, a gene therapy disclosed herein comprises at least six polynucleotides or fragments thereof selected from OCT3/4, SOX2, c MYC, KLF4, NANOG, and LIN28.

[0071] In certain aspects, the polynucleotides provided herein can be used in a method of genetically engineering a kidney (such as a method described in Section 5.4). Accordingly, in some embodiments, the polynucleotide composition comprises an OCT3/4 polynucleotide or fragment thereof. In some embodiments, the polynucleotide composition comprises a SOX2 polynucleotide or fragment thereof. In some embodiments, the polynucleotide composition comprises a c-MYC polynucleotide or fragment thereof. In some embodiments, the polynucleotide composition comprises a KLF4 polynucleotide or fragment thereof. In some embodiments, the polynucleotide composition comprises a NANOG polynucleotide or fragment

thereof. In some embodiments, the polynucleotide composition comprises a LIN28 polynucleotide or fragment thereof. In some embodiments, the polynucleotide composition comprises an OCT3/4, a SOX2, a c-MYC, and a KLF4 polynucleotide or fragment thereof. In some embodiments, the polynucleotide composition comprises an OCT3/4, a SOX2, and a KLF4 polynucleotide or fragment thereof. In some embodiments, the polynucleotide composition comprises an OCT4, a SOX2, a NANOG, and a LIN28 polynucleotide or fragment thereof.

[0072] In some embodiments, a gene therapy can comprise a polynucleotide encoding for a OCT3/4 polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 2. In some embodiments, a gene therapy can comprise a polynucleotide encoding for a SOX2 polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 4. In some embodiments, a gene therapy can comprise a polynucleotide encoding for a c-MYC polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 6. In some embodiments, a gene therapy can comprise a polynucleotide encoding for a KLF4 polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 8. In some embodiments, a gene therapy can comprise a polynucleotide encoding for a NANOG polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 10. In some embodiments, a gene therapy can comprise a polynucleotide encoding for a LIN28A polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 12. In some embodiments, a gene therapy can comprise a polynucleotide encoding for a LIN28B polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 95%, 97%, 99%, or 100% identical to SEQ ID NO: 14.

[0073] In some embodiments, a polynucleotide encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 can be introduced into an expression vector. Any method for introducing a polynucleotide sequence into an expression vector known in the art are suitable for use herein. An expression vector for use herein can include any known to one of ordinary skill in the art (*see, e.g.,* Sambrook et al., Molecular Cloning: A Laboratory Manual, Fourth Edition, Cold Spring Harbor Laboratory Press, 2012). In some embodiments, an expression vector for use herein comprises a promoter operably-linked to the polynucleotide encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, an expression vector for use herein comprises a constitutive promoter operably-linked to the polynucleotide encoding

OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, an expression vector for use herein comprises an inducible promoter (*e.g.*, a tetracycline-responsive promoter) operably-linked to the polynucleotide encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, an expression vector for use herein comprises a tissue-specific or cell type-specific promoter operably-linked to the polynucleotide encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. Non-limiting examples of a tissue-specific or cell type-specific promoter include kidney-specific, endothelial cell-specific, kidney cell-type-specific (*e.g.*, podocyte-specific, proximal tubular epithelial cell-specific).

[0074] In some embodiments, a vector can comprise at least one expression cassette encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. An "expression cassette" generally refers to a polynucleotide molecule that is capable of directing transcription (i.e., comprising at the least, a promoter or a structure functionally equivalent to a promoter). In some embodiments, a vector can comprise at least two expression cassettes encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a vector can comprise at least three expression cassettes encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a vector can comprise at least four expression cassettes encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a vector can comprise at least five expression cassettes encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a vector can comprise at least six expression cassettes encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28.

[0075] In some embodiments, a gene therapy comprises at least one expression vector encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a gene therapy comprises at least two expression vectors encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a gene therapy comprises at least three expression vectors encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a gene therapy comprises at least four expression vectors encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a gene therapy comprises at least five expression vectors encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a gene therapy comprises at least six expression vectors encoding OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28.

(c) Gene-Editing Systems

[0076] In certain embodiments, a gene therapy disclosed herein comprises a gene-editing system. A "gene-editing system" generally refers to any system that aids in adding, removing, or altering genetic material in at least one location in the genome. Non-limiting examples of such systems can include CRISPR systems (*e.g.*, Cas9), meganucleases, transcriptional activator-like effector nucleases (TALENs), zinc-finger nucleases (ZFNs), and the like.

[0077] In certain embodiments, a gene therapy disclosed herein comprises a CRISPR-system for inducing expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In certain embodiments, a gene therapy disclosed herein comprises a Type I CRISPR-system, a Type II CRISPR-system, and/or a Type III CRISPR-system for inducing expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In certain embodiments, the CRISPR-system for use herein comprises a CRISPR/Cas-based gene editing system. In certain embodiments, the CRISPR-system for use herein comprises a Cas protein or a Cas fusion protein. In some embodiments, the Cas protein is a Cas9 protein. In some embodiments, the Cas protein is a Cas12 protein (also referred to as Cpf1), such as a Cas12a protein.

[0078] In some embodiments, a Cas molecule or a Cas fusion protein disclosed herein can interact with at least one guide RNA (gRNA). A gRNA, which provides the targeting of a CRISPR/Cas-based gene editing system, is a fusion of two noncoding RNAs: a crRNA and a tracrRNA. In some embodiments, the CRISPR-system for use herein comprises at least one gRNA wherein the gRNA targets at least one DNA sequence at or near the promoter and/or enhancer region of a gene (*e.g.*, OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28) to target the Cas-transcription activation complex and drive expression of the endogenous gene. In some embodiments, the CRISPR-system for use herein comprises at least one gRNA wherein the gRNA targets at least one DNA sequence. In some embodiments, the CRISPR-system for use herein comprises at least one gRNA, wherein the gRNA targets at least two different DNA sequences. In some embodiments, the CRISPR-system for use herein comprises at least two different gRNAs, wherein the gRNAs target at least two different DNA sequences. In some embodiments, the CRISPR-system for use herein comprises at least 1 gRNA, at least 2 different gRNAs, at least 3 different gRNAs, at least 4 different gRNAs, at least 5 different gRNAs, at least 6 different gRNAs, or more than about 6 different gRNAs. In some embodiments, the

CRISPR-system for use herein comprises a vector encoding for at least 1 gRNA, at least 2 different gRNAs, at least 3 different gRNAs, at least 4 different gRNAs, at least 5 different gRNAs, at least 6 different gRNAs, or more than about 6 different gRNAs.

[0079] In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a region within or near the OCT3/4 gene, or within or near a regulatory element or promoter of the OCT3/4 gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets at least one of exons, introns, the promoter region, the enhancer region, or the transcribed region of the OCT3/4 gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets OCT3/4 or a promoter or regulatory element of the OCT3/4 gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a OCT3/4 promoter.

[0080] In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a region within or near the SOX2 gene, or within or near a regulatory element or promoter of the SOX2 gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets at least one of exons, introns, the promoter region, the enhancer region, or the transcribed region of the SOX2 gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets SOX2 or a promoter or regulatory element of the SOX2 gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a SOX2 promoter.

[0081] In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a region within or near the c-MYC gene, or within or near a regulatory element or promoter of the c-MYC gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets at least one of exons, introns, the promoter region, the enhancer region, or the transcribed region of the c-MYC gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets c-MYC or a promoter or regulatory element of the c-MYC gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a c-MYC promoter.

[0082] In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a region within or near the KLF4 gene, or within or near a regulatory element or promoter of the KLF4 gene. In some embodiments, at least one gRNA of the CRISPR-system for use

herein targets at least one of exons, introns, the promoter region, the enhancer region, or the transcribed region of the KLF4 gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets KLF4 or a promoter or regulatory element of the KLF4 gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a KLF4 promoter.

[0083] In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a region within or near the NANOG gene, or within or near a regulatory element or promoter of the NANOG gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets at least one of exons, introns, the promoter region, the enhancer region, or the transcribed region of the NANOG gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets NANOG or a promoter or regulatory element of the NANOG gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a NANOG promoter.

[0084] In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a region within or near the LIN28A/LIN28B gene, or within or near a regulatory element or promoter of the LIN28A/LIN28B gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets at least one of exons, introns, the promoter region, the enhancer region, or the transcribed region of the LIN28A/LIN28B gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets LIN28A/LIN28B or a promoter or regulatory element of the LIN28A/LIN28B gene. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a LIN28A/LIN28B promoter.

[0085] In certain embodiments, a gene therapy disclosed herein comprises a CRISPR-system for reducing expression of a least one protein involved in repression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 expression. Non-limiting examples of such proteins include DNA methyltransferases, histone deacetylases, methyl binding domain proteins, histone methyltransferases, a component of a chromatin remodeling complex, a component of the SWI/SNF complex, a component of the NuRD complex, components of the INO80 complex, and the like.

[0086] In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a repressor of OCT3/4. In some embodiments, at least one gRNA of the CRISPR-system

for use herein targets a repressor of SOX2. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a repressor of c-MYC. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a repressor of KLF4. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a repressor of NANOG. In some embodiments, at least one gRNA of the CRISPR-system for use herein targets a repressor of LIN28.

[0087] In some embodiments, the CRISPR-system stably introduces exogenous OCT3/4. In some embodiments, the CRISPR-system stably introduces exogenous SOX2. In some embodiments, the CRISPR-system stably introduces exogenous c-MYC. In some embodiments, the CRISPR-system stably introduces exogenous KLF4. In some embodiments, the CRISPR-system stably introduces exogenous NANOG. In some embodiments, the CRISPR-system stably introduces exogenous LIN28.

(d) RNAi

[0088] In certain embodiments, a gene therapy disclosed herein comprises RNA interference (RNAi). For example, a gene therapy disclosed herein can be an RNA molecule involved in sequence-specific suppression of gene expression through translational or transcriptional repression of a molecule that represses expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, a gene therapy disclosed herein comprises a short hairpin RNA (shRNA). In some embodiments, a gene therapy disclosed herein comprises a microRNA (miRNA). In some embodiments, a gene therapy disclosed herein comprises small interfering RNA (siRNA). In certain embodiments, a gene therapy disclosed herein comprises RNAi (*e.g.*, shRNA, miRNA, or siRNA) for reducing expression of a least one protein involved in transcriptional repression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 expression.

5.2.2 Biological Therapy

[0089] In certain embodiments, an agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 comprises at least one biological therapy (e.g., antibody or antibody-like molecules).

[0090] In certain embodiments, a biological therapy for use herein comprises at least one antibody. The terms "antibody" "immunoglobulin," and "Ig" are used interchangeably and in the broadest sense and encompasses, for example polyclonal antibodies, recombinant antibodies, monoclonal antibodies (including agonist antibodies, antagonist antibodies, neutralizing antibodies, or full-length monoclonal antibodies), chimeric antibodies, humanized antibodies, human antibodies, monospecific antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), or single domain antibodies (*e.g.*, VHH). "Antibodies" as used herein also include antibody fragments that retain antigen (*e.g.*, CEACAM5 and/or APLP2) binding characteristics. Non-limiting examples of antibody fragments include antigen-binding regions with or without effector regions of the antibody, *e.g.*, single chain antibody molecule, dual variable domain antibody, single variable domain, linear antibody, V region, Fab, Fab', $F(ab')_2$, Fv, scFv, $(scFv)_2$, $F(ab)_2$, Fd, Fc, diabody, di-diabody, disulfide-linked Fvs (dsFv), single-domain antibody (*e.g.*, nanobody) or other fragments (*e.g.*, fragments consisting non-covalently coupled VH and VL). Antibody variable region may include heavy and/or light variable regions in any suitable arrangement.

[0091] In certain embodiments, a biological therapy for use herein comprises at least one antibody or fragment thereof that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In certain embodiments, a biological therapy for use herein comprises at least one antibody or fragment that inhibits repression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 expression. Non-limiting examples of protein targets for antibody-medicated inhibition include DNA methyltransferases (*e.g.*, DNMT1, DNMT2, DNMT3A, DNMT3B, DMNT3L), histone deacetylases (*e.g.*, HDACs1-11, SIRT1-7), methyl binding domain proteins (*e.g.*, MBD1, MBD2, MBD3, MBD4, MeCp2), histone methyltransferases (*e.g.*, EHMT1, HDMG9A, SUV39H1, SETDB1), methyl cycle enzymes (*e.g.*, MTHFR, CBS), a component of a chromatin remodeling complex, a component of the SWI/SNF complex, a component of the NuRD complex (*e.g.*, Mi2, p70, and p32), and components of the INO80 complex (*e.g.*, Tip49A, Tip49B, the SNF2 family helicase Ino80, actin related proteins ARK ARP5, and Arp8, YEATS domain family member Taf14, HMG-domain protein, Nhp10).

5.2.3 Small Molecule Therapy

[0092] In certain embodiments, an agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 comprises at least one small molecule therapy. In certain embodiments, at least one small molecule therapy induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. Such small molecule inhibitors are known in the art, for example those described in Lin and Wu, *Stem Cells International*, (2015) Article ID 794632.

[0093] In some embodiments, a small molecule therapy for use herein comprises at least one HDAC inhibitor (*e.g.*, HC toxin; BML-210; depudecin; M-344; valproxam; valproic acid (VPA); suberoylanilide hydroxamic acid (SAHA); sodium butyrate; trichostatin A (TSA)). In some embodiments, a small molecule therapy for use herein comprises at least one DMNT inhibitor (*e.g.*, 5-azacytidine (5-aza-CR, AZA); RSC133). In some embodiments, a small molecule therapy for use herein comprises at least one retinoic acid receptor agonist (*e.g.*, AM580). In some embodiments, a small molecule therapy for use herein comprises at least one H3K4 demethylation inhibitor (*e.g.*, tranylcypromine (Parnate)). In some embodiments, a small molecule therapy for use herein comprises at least one epigenetic modulator (*e.g.*, 3-deazaneplanocin (DZNep)). In some embodiments, a small molecule therapy for use herein comprises at least one retinoic acid receptor ligand (*e.g.*, TTNPB). In some embodiments, a small molecule therapy for use herein comprises at least one ALK4, ALK5, and ALK7 inhibitor (*e.g.*, SB431542). In some embodiments, a small molecule therapy for use herein comprises at least one MEK/ERK inhibitor (*e.g.*, PD0325901). In some embodiments, a small molecule therapy for use herein comprises at least one rho-associated protein kinase inhibitor (*e.g.*, Thiazovivin; Y27632). In some embodiments, a small molecule therapy for use herein comprises at least one GSK-3β inhibitor (*e.g.*, Compound B6; LiCl). In some embodiments, a small molecule therapy for use herein comprises at least one TGF-β inhibitor (*e.g.*, A83-01). In some embodiments, a small molecule therapy for use herein comprises at least one prolyl-4-hydroxylase inhibitor (*e.g.*, N-Oxalylglycine). In some embodiments, a small molecule therapy for use herein comprises at least one ALK4 inhibitor (*e.g.*, Compound B4 (TGFb-RI)). In some embodiments, a small molecule therapy for use herein comprises at least one mTOR inhibitor (*e.g.*, rapamycin). In some embodiments, a small molecule therapy for use herein comprises at least one IP3K inhibitor (*e.g.*, Compound B8). In some embodiments, a small molecule therapy for use herein comprises at least one P38 kinase inhibitor (*e.g.*, Compound B10). In some

embodiments, a small molecule therapy for use herein comprises at least one cAMP agonist (*e.g.*, prostaglandin E2; rolipram; 8-Br-cAMP). In some embodiments, a small molecule therapy for use herein comprises at least one PDK1 activator (*e.g.*, 5-(4-chloro-phenyl)-3-phenyl-pent-2-enoic acid (PS48)). In some embodiments, a small molecule therapy for use herein comprises at least one HIF PHD1 and PHD2 inhibitor (*e.g.*, N-Oxalylglycine). In some embodiments, a small molecule therapy for use herein comprises at least one phosphofructokinase 1 activator (*e.g.*, fructose 2,6-bisphosphate). In some embodiments, a small molecule therapy for use herein comprises at least one hypoxia-inducible factor pathway activator (*e.g.*, quercetin). In some embodiments, a small molecule therapy for use herein comprises at least one oxidative phosphorylation uncoupler (*e.g.*, 2,4-dinitrophenol (DNP)). In some embodiments, a small molecule therapy for use herein comprises at least one histone demethylase inhibitor (*e.g.*, LSD1 (KIAA0601 or BHC110), flavin-dependent amine oxidase, and jumonji.). In some embodiments, a small molecule therapy for use herein comprises at least one sirtuin activator (*e.g.*, resveratrol, a polyphenol, a sirtuin activating compound, activators of SIRT1-SJRT7, and SRT-1720.)

5.3 Methods of treatment

[0094] In one aspect provided herein is a method of *ex vivo* kidney perfusion that includes perfusing a kidney with a therapeutic composition in a perfusion system, such as a perfusion system described in Section 5.1. In certain embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney. In some embodiments, the at least one agent induces expression of OCT3/4. In some embodiments, the at least one agent induces expression of SOX2. In some embodiments, the at least one agent induces expression of c-MYC. In some embodiments, the at least one agent induces expression of KLF4. In some embodiments, the at least one agent induces expression of NANOG. In some embodiments, the at least one agent induces expression of LIN28. In some embodiments, the at least one agent induces expression of at least two of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and SOX2. In some embodiments, the at least one agent induces expression of OCT3/4 and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4 and KLF4. In some embodiments, the at least one agent induces expression of SOX2 and c-MYC. In some embodiments, the at least one agent induces expression of SOX2 and KLF4. In some embodiments, the at least one agent induces expression

of c-MYC and KLF4. In some embodiments, the at least one agent induces expression of KLF4 and NANOG. In some embodiments, the at least one agent induces expression of KLF4 and LIN28. In some embodiments, the at least one agent induces expression of c-MYC and NANOG. In some embodiments, the at least one agent induces expression of c-MYC and LIN28. In some embodiments, the at least one agent induces expression of SOX2 and NANOG. In some embodiments, the at least one agent induces expression of SOX2 and LIN28. In some embodiments, the at least one agent induces expression of NANOG and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4 and LIN28. In some embodiments, the at least one agent induces expression of at least three of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of at least four of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some

embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of at least five of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the perfusion system comprises an acoustic volume sensor. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small

molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4, or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[0095] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is a hypothermic perfusion system. In some embodiments, the perfusion system is a subnormothermic system (*e.g.*, about 20 °C to about 33 °C). In some embodiments, the perfusion system is automated. In some embodiments, the perfusion system is transportable. In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is maintained at body temperature when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 33°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 39°C when perfusing the kidney. In some embodiments, the

perfusate is maintained at a temperature of about 4°C to about 10°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 6°C to about 12°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 8°C to about 14°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 10°C to about 16°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 12°C to about 18°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 15°C to about 20°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 18°C to about 23°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 22°C to about 34°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 25°C to about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 28°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 30°C to about 40°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney.

[0096] In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate. In some embodiments, the perfusate comprises oxygenated or non-oxygenated blood or an oxygen carrier. In some embodiments, the perfusate comprises oxygenated blood. In some embodiments, the perfusate has an oxygen pressure of about 100 mm Hg to about 500 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 150 mm Hg to about 400 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 200 mm Hg to about 350 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 250 mm Hg to about 300 mm Hg. In some embodiments, the perfusate comprises non-oxygenated blood. In some embodiments, the perfusate comprises autologous, allogenic, or heterologous whole

blood. In some embodiments, the perfusate comprises autologous whole blood. In some embodiments, the perfusate comprises allogenic whole blood. In some embodiments, the perfusate comprises heterologous whole blood. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes or thrombocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of thrombocytes. In some embodiments, the autologous whole blood is depleted of leukocytes. In some embodiments, the perfusate comprises an oxygen carrier. In some embodiments, the oxygen carrier comprises an artificial oxygen carrier. In some embodiments, the artificial oxygen carrier comprises a hemoglobin-based oxygen carrier (HBOC), a polymerized bovine HBOC, a pyridoxylated hemoglobin, or a pyridoxylated bovine hemoglobin, or any combination thereof. In some embodiments, the perfusate comprises acellular oxygen-carrying media. Exemplary acellular oxygen-carrying media comprises but is not limited to, Lifor, Aqix RS-I, or STEEN solution (Zulpati et al., 2021, Front. Med. 8:808719). In some embodiments, the perfusate comprises albumin or globulin. In some embodiments, the perfusate comprises a human albumin or a bovine albumin. In some embodiments, the perfusate comprises an electrolyte. In some embodiments, the perfusate has an extracellular-like Na+/K+ balance. In some embodiments, the perfusate comprise an impermeant or glucose. In some embodiments, the perfusate comprise an impermeant and glucose. In some embodiments, the perfusate comprises glucose. In some embodiments, the perfusate comprises heparin, a vasodilator, mannitol, a corticosteroid, an anticoagulant, an antibiotic, a nutrient, an amino acid, insulin, a cryoprotective agent, angiotensin, or a medication, or any combination thereof. In some embodiments, the cryoprotective agent comprises erythropoietin, metformin, doxycycline, a SUL compound, or propofol, or any combination thereof. In some embodiments, the perfusate comprises an impermeant. In some embodiments, the impermeant comprises gluconate, mannitol, lactobionate, raffinose, histidine, tryptophan, or ketoglutarate. In some embodiments, the perfusate is supplemented with a surfactant. In some embodiments, the surfactant comprises dextran 40 or dextran 70. In some embodiments, the surfactant comprises dextran 40. In some embodiments, the perfusate is removed of a cytokine and a chemokine when perfusing the kidney. In some embodiments, the removal of the cytokine and the chemokine from the perfusate comprises filtering the perfusate through a cytosorb hemadsorbtion filter. In some embodiments, the

cytosorb hemadsorbtion filter is connected to the perfusion system. In some embodiments, the cytokine comprises IL-1b, IL-1a, IL-1RA, TNFa, IL-10, IL-6, IL-8, c reactive protein (CRP), or thromboxane B2, or any combination thereof.

[0097] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 mL. In some embodiments, the reservoir has a volume of less than about 50 mL. In some embodiments, the reservoir has a volume of less than about 40 mL. In some embodiments, the reservoir has a volume of less than about 30 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 25 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 15 mL. In some embodiments, the reservoir has a volume of less than about 10 mL. In some embodiments, the reservoir has a volume of less than about 9 mL. In some embodiments, the reservoir has a volume of less than about 8 mL. In some embodiments, the reservoir has a volume of less than about 7 mL. In some embodiments, the reservoir has a volume of less than about 6 mL. In some embodiments, the reservoir has a volume of less than about 5 mL. In some embodiments, the reservoir has a volume of less than

about 4 mL. In some embodiments, the reservoir has a volume of less than about 3 mL. In some embodiments, the reservoir has a volume of less than about 2 mL. In some embodiments, the reservoir has a volume of or less than about 1 mL. In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 200 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 70 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a mean or median system pressure of about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 200 mL/min to about 500 mL/min when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 250 mL/min to about 400 mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 50 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 70 mm Hg to about 80 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 80 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0 mm Hg per mL/min to about 0.50 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.10 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.15 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.20 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney.

[0098] In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, or renal resistance, or any combination thereof. In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, and renal resistance.

[0099] In some embodiments, the perfusion lasts for about 0 hour to about 144 hours. In some embodiments, the perfusion lasts for about 0 hour to about 120 hours. In some embodiments, the perfusion lasts for up to about 24 hours. In some embodiments, the perfusion lasts for about 48 hours. In some embodiments, the perfusion lasts for up to about 2, about 4, about 6, about 8, about 10, about 12, about 14, about 16, about 18, about 20, about 22, or about 24 hours. In some embodiments, the perfusion lasts for up to about 24, about 28, about 32, about 36, about 40, about 44, or about 48 hours. In some embodiments, the perfusion lasts for a period of time sufficient to induce expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

[00100] In some embodiments, the kidney is from a subject with a chronic kidney disease, from a subject with an end-stage kidney disease, from a subject in need of kidney rejuvenation with or without any symptom of kidney failure, from an unsuitable subject, a kidney considered not viable for transplantation, a discarded kidney, an injured, damaged, or failed kidney, or from a deceased subject. In some embodiments, the kidney is from a subject with a chronic kidney disease. In some embodiments, the kidney is from a subject with an end-stage kidney disease. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with or without any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation without any symptom of kidney failure. In some embodiments, the kidney is from an unsuitable subject. In some embodiments, the kidney is a kidney considered not viable for transplantation. In some embodiments, the kidney is a discarded kidney. In some embodiments, the kidney is an injured, damaged, or failed kidney. In some embodiments, the kidney is a discarded human kidney. In some embodiments, the kidney is from a deceased subject. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human. In some embodiments, the kidney is nonhuman. In some embodiments, the kidney is from a swine or a baboon. In some

embodiments, the kidney is from a swine. In some embodiments, the kidney is from a baboon. In some embodiments, the swine or the baboon is raised in a laboratory. In some embodiments, the swine is a miniature swine.

[00101] In another aspect, provided herein is a method of repairing kidney damage in a subject in need thereof that includes perfusing a kidney with a therapeutic composition in a perfusion system, such as a perfusion system described in Section 5.1. In certain embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney. In some embodiments, the at least one agent induces expression of OCT3/4. In some embodiments, the at least one agent induces expression of SOX2. In some embodiments, the at least one agent induces expression of c-MYC. In some embodiments, the at least one agent induces expression of KLF4. In some embodiments, the at least one agent induces expression of NANOG. In some embodiments, the at least one agent induces expression of LIN28. In some embodiments, the at least one agent induces expression of at least two of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and SOX2. In some embodiments, the at least one agent induces expression of OCT3/4 and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4 and KLF4. In some embodiments, the at least one agent induces expression of SOX2 and c-MYC. In some embodiments, the at least one agent induces expression of SOX2 and KLF4. In some embodiments, the at least one agent induces expression of c-MYC and KLF4. In some embodiments, the at least one agent induces expression of KLF4 and NANOG. In some embodiments, the at least one agent induces expression of KLF4 and LIN28. In some embodiments, the at least one agent induces expression of c-MYC and NANOG. In some embodiments, the at least one agent induces expression of c-MYC and LIN28. In some embodiments, the at least one agent induces expression of SOX2 and NANOG. In some embodiments, the at least one agent induces expression of SOX2 and LIN28. In some embodiments, the at least one agent induces expression of NANOG and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4 and LIN28. In some embodiments, the at least one agent induces expression of at least three of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces

expression of OCT3/4, SOX2, and/or c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of at least four of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of

OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of at least five of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the perfusion system comprises an acoustic volume sensor. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or

LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[00102] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is a hypothermic perfusion system. In some embodiments, the perfusion system is a subnormothermic system (*e.g.*, about 20 °C to about 33 °C). In some embodiments, the perfusion system is automated. In some embodiments, the perfusion system is transportable. In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is maintained at body temperature when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 33°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 6°C to about 12°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 8°C to about 14°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 10°C to about 16°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 12°C to about 18°C when

perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 15°C to about 20°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 18°C to about 23°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 22°C to about 34°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 25°C to about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 28°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 30°C to about 40°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney.

[00103] In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate. In some embodiments, the perfusate comprises oxygenated or non-oxygenated blood or an oxygen carrier. In some embodiments, the perfusate comprises oxygenated blood. In some embodiments, the perfusate has an oxygen pressure of about 100 mm Hg to about 500 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 150 mm Hg to about 400 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 200 mm Hg to about 350 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 250 mm Hg to about 300 mm Hg. In some embodiments, the perfusate comprises non-oxygenated blood. In some embodiments, the perfusate comprises autologous, allogenic, or heterologous whole blood. In some embodiments, the perfusate comprises autologous whole blood. In some embodiments, the perfusate comprises allogenic whole blood. In some embodiments, the perfusate comprises heterologous whole blood. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes or thrombocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of

thrombocytes. In some embodiments, the autologous whole blood is depleted of leukocytes. In some embodiments, the perfusate comprises an oxygen carrier. In some embodiments, the oxygen carrier comprises an artificial oxygen carrier. In some embodiments, the artificial oxygen carrier comprises a hemoglobin-based oxygen carrier (HBOC), a polymerized bovine HBOC, a pyridoxylated hemoglobin, or a pyridoxylated bovine hemoglobin, or any combination thereof. In some embodiments, the perfusate comprises acellular oxygen-carrying media. Exemplary acellular oxygen-carrying media comprises but is not limited to, Lifor, Aqix RS-I, or STEEN solution (Zulpati et al., 2021, Front. Med. 8:808719). In some embodiments, the perfusate comprises albumin or globulin. In some embodiments, the perfusate comprises a human albumin or a bovine albumin. In some embodiments, the perfusate comprises an electrolyte. In some embodiments, the perfusate has an extracellular-like Na+/K+ balance. In some embodiments, the perfusate comprise an impermeant or glucose. In some embodiments, the perfusate comprise an impermeant and glucose. In some embodiments, the perfusate comprises glucose. In some embodiments, the perfusate comprises heparin, a vasodilator, mannitol, a corticosteroid, an anticoagulant, an antibiotic, a nutrient, an amino acid, insulin, a cryoprotective agent, angiotensin, or a medication, or any combination thereof. In some embodiments, the cryoprotective agent comprises erythropoietin, metformin, doxycycline, a SUL compound, or propofol, or any combination thereof. In some embodiments, the perfusate comprises an impermeant. In some embodiments, the impermeant comprises gluconate, mannitol, lactobionate, raffinose, histidine, tryptophan, or ketoglutarate. In some embodiments, the perfusate is supplemented with a surfactant. In some embodiments, the surfactant comprises dextran 40 or dextran 70. In some embodiments, the surfactant comprises dextran 40. In some embodiments, the perfusate is removed of a cytokine and a chemokine when perfusing the kidney. In some embodiments, the removal of the cytokine and the chemokine from the perfusate comprises filtering the perfusate through a cytosorb hemadsorbtion filter. In some embodiments, the cytosorb hemadsorbtion filter is connected to the perfusion system. In some embodiments, the cytokine comprises IL-1b, IL-1a, IL-1RA, TNFa, IL-10, IL-6, IL-8, c reactive protein (CRP), or thromboxane B2, or any combination thereof.

[00104] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic

volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 mL. In some embodiments, the reservoir has a volume of less than about 50 mL. In some embodiments, the reservoir has a volume of less than about 40 mL. In some embodiments, the reservoir has a volume of less than about 30 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 25 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 15 mL. In some embodiments, the reservoir has a volume of less than about 10 mL. In some embodiments, the reservoir has a volume of less than about 9 mL. In some embodiments, the reservoir has a volume of less than about 8 mL. In some embodiments, the reservoir has a volume of less than about 7 mL. In some embodiments, the reservoir has a volume of less than about 6 mL. In some embodiments, the reservoir has a volume of less than about 5 mL. In some embodiments, the reservoir has a volume of less than about 4 mL. In some embodiments, the reservoir has a volume of less than about 3 mL. In some embodiments, the reservoir has a volume of less than about 2 mL. In some embodiments, the reservoir has a volume of or less than about 1 mL. In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably

defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 200 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 70 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a mean or median system pressure of about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 200 mL/min to about 500 mL/min when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 250 mL/min to about 400 mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 50 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 70 mm Hg to about 80 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 80 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0 mm Hg per mL/min to about 0.50 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.10 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.15 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.20 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney.

[00105] In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, or renal resistance, or any combination thereof. In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, and renal resistance.

[00106] In some embodiments, the perfusion lasts for about 0 hour to about 144 hours. In some embodiments, the perfusion lasts for about 0 hour to about 120 hours. In some embodiments, the perfusion lasts for up to about 24 hours. In some embodiments, the perfusion lasts for about 48 hours. In some embodiments, the perfusion lasts for up to about 2, about 4, about 6, about 8, about 10, about 12, about 14, about 16, about 18, about 20, about 22, or about 24 hours. In some embodiments, the perfusion lasts for up to about 24, about 28, about 32, about 36, about 40, about 44, or about 48 hours. In some embodiments, the perfusion lasts for a period of time sufficient to induce expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

[00107] In some embodiments, the kidney is from a subject with a chronic kidney disease, from a subject with an end-stage kidney disease, from a subject in need of kidney rejuvenation with or without any symptom of kidney failure, from an unsuitable subject, a kidney considered not viable for transplantation, a discarded kidney, an injured, damaged, or failed kidney, or from a deceased subject. In some embodiments, the kidney is from a subject with a chronic kidney disease. In some embodiments, the kidney is from a subject with an end-stage kidney disease. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with or without any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation without any symptom of kidney failure. In some embodiments, the kidney is from an unsuitable subject. In some embodiments, the kidney is a kidney considered not viable for transplantation. In some embodiments, the kidney is a discarded kidney. In some embodiments, the kidney is an injured, damaged, or failed kidney. In some embodiments, the kidney is a discarded human kidney. In some embodiments, the kidney is from a deceased subject. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human. In some embodiments, the kidney is nonhuman. In some embodiments, the kidney is from a swine or a baboon. In some embodiments, the kidney is from a swine. In some embodiments, the kidney is from a baboon. In some embodiments, the swine or the baboon is raised in a laboratory. In some embodiments, the swine is a miniature swine.

[00108] In yet another aspect, provided herein is a method of treating a kidney disease or disorder in a subject in need thereof that includes perfusing a kidney with a therapeutic

composition in a perfusion system, such as a perfusion system described in Section 5.1. In certain embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney. In some embodiments, the at least one agent induces expression of OCT3/4. In some embodiments, the at least one agent induces expression of SOX2. In some embodiments, the at least one agent induces expression of c-MYC. In some embodiments, the at least one agent induces expression of KLF4. In some embodiments, the at least one agent induces expression of NANOG. In some embodiments, the at least one agent induces expression of LIN28. In some embodiments, the at least one agent induces expression of at least two of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and SOX2. In some embodiments, the at least one agent induces expression of OCT3/4 and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4 and KLF4. In some embodiments, the at least one agent induces expression of SOX2 and c-MYC. In some embodiments, the at least one agent induces expression of SOX2 and KLF4. In some embodiments, the at least one agent induces expression of c-MYC and KLF4. In some embodiments, the at least one agent induces expression of KLF4 and NANOG. In some embodiments, the at least one agent induces expression of KLF4 and LIN28. In some embodiments, the at least one agent induces expression of c-MYC and NANOG. In some embodiments, the at least one agent induces expression of c-MYC and LIN28. In some embodiments, the at least one agent induces expression of SOX2 and NANOG. In some embodiments, the at least one agent induces expression of SOX2 and LIN28. In some embodiments, the at least one agent induces expression of NANOG and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4 and LIN28. In some embodiments, the at least one agent induces expression of at least three of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or NANOG. In some embodiments, the at

least one agent induces expression of OCT3/4, SOX2, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of at least four of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of at least five of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces

expression of SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the perfusion system comprises an acoustic volume sensor. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a

virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[00109] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is a hypothermic perfusion system. In some embodiments, the perfusion system is a subnormothermic system (*e.g.*, about 20 °C to about 33 °C). In some embodiments, the perfusion system is automated. In some embodiments, the perfusion system is transportable. In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is maintained at body temperature when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 33°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 6°C to about 12°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 8°C to about 14°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 10°C to about 16°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 12°C to about 18°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 15°C to about 20°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 18°C to about 23°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C when

perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 22°C to about 34°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 25°C to about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 28°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 30°C to about 40°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney.

[00110] In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate. In some embodiments, the perfusate comprises oxygenated or non-oxygenated blood or an oxygen carrier. In some embodiments, the perfusate comprises oxygenated blood. In some embodiments, the perfusate has an oxygen pressure of about 100 mm Hg to about 500 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 150 mm Hg to about 400 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 200 mm Hg to about 350 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 250 mm Hg to about 300 mm Hg. In some embodiments, the perfusate comprises non-oxygenated blood. In some embodiments, the perfusate comprises autologous, allogenic, or heterologous whole blood. In some embodiments, the perfusate comprises autologous whole blood. In some embodiments, the perfusate comprises allogenic whole blood. In some embodiments, the perfusate comprises heterologous whole blood. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes or thrombocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of thrombocytes. In some embodiments, the autologous whole blood is depleted of leukocytes. In some embodiments, the perfusate comprises an oxygen carrier. In some embodiments, the oxygen carrier comprises an artificial oxygen carrier. In some embodiments, the artificial oxygen carrier comprises a hemoglobin-based oxygen carrier (HBOC), a polymerized bovine HBOC, a

pyridoxylated hemoglobin, or a pyridoxylated bovine hemoglobin, or any combination thereof. In some embodiments, the perfusate comprises acellular oxygen-carrying media. Exemplary acellular oxygen-carrying media comprises but is not limited to, Lifor, Aqix RS-I, or STEEN solution (Zulpati et al., 2021, Front. Med. 8:808719). In some embodiments, the perfusate comprises albumin or globulin. In some embodiments, the perfusate comprises a human albumin or a bovine albumin. In some embodiments, the perfusate comprises an electrolyte. In some embodiments, the perfusate has an extracellular-like Na+/K+ balance. In some embodiments, the perfusate comprise an impermeant or glucose. In some embodiments, the perfusate comprise an impermeant and glucose. In some embodiments, the perfusate comprises glucose. In some embodiments, the perfusate comprises heparin, a vasodilator, mannitol, a corticosteroid, an anticoagulant, an antibiotic, a nutrient, an amino acid, insulin, a cryoprotective agent, angiotensin, or a medication, or any combination thereof. In some embodiments, the cryoprotective agent comprises erythropoietin, metformin, doxycycline, a SUL compound, or propofol, or any combination thereof. In some embodiments, the perfusate comprises an impermeant. In some embodiments, the impermeant comprises gluconate, mannitol, lactobionate, raffinose, histidine, tryptophan, or ketoglutarate. In some embodiments, the perfusate is supplemented with a surfactant. In some embodiments, the surfactant comprises dextran 40 or dextran 70. In some embodiments, the surfactant comprises dextran 40. In some embodiments, the perfusate is removed of a cytokine and a chemokine when perfusing the kidney. In some embodiments, the removal of the cytokine and the chemokine from the perfusate comprises filtering the perfusate through a cytosorb hemadsorbtion filter. In some embodiments, the cytosorb hemadsorbtion filter is connected to the perfusion system. In some embodiments, the cytokine comprises IL-1b, IL-1a, IL-1RA, TNFa, IL-10, IL-6, IL-8, c reactive protein (CRP), or thromboxane B2, or any combination thereof.

[00111] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide

composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 mL. In some embodiments, the reservoir has a volume of less than about 50 mL. In some embodiments, the reservoir has a volume of less than about 40 mL. In some embodiments, the reservoir has a volume of less than about 30 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 25 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 15 mL. In some embodiments, the reservoir has a volume of less than about 10 mL. In some embodiments, the reservoir has a volume of less than about 9 mL. In some embodiments, the reservoir has a volume of less than about 8 mL. In some embodiments, the reservoir has a volume of less than about 7 mL. In some embodiments, the reservoir has a volume of less than about 6 mL. In some embodiments, the reservoir has a volume of less than about 5 mL. In some embodiments, the reservoir has a volume of less than about 4 mL. In some embodiments, the reservoir has a volume of less than about 3 mL. In some embodiments, the reservoir has a volume of less than about 2 mL. In some embodiments, the reservoir has a volume of or less than about 1 mL. In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 200 mm Hg

when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 70 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a mean or median system pressure of about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 200 mL/min to about 500 mL/min when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 250 mL/min to about 400 mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 50 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 70 mm Hg to about 80 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 80 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0 mm Hg per mL/min to about 0.50 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.10 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.15 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.20 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney.

[00112] In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, or renal resistance, or any combination thereof. In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, and renal resistance.

[00113] In some embodiments, the perfusion lasts for about 0 hour to about 144 hours. In some embodiments, the perfusion lasts for about 0 hour to about 120 hours. In some embodiments, the perfusion lasts for up to about 24 hours. In some embodiments, the perfusion lasts for about 48 hours. In some embodiments, the perfusion lasts for up to about 2, about 4, about 6, about 8, about 10, about 12, about 14, about 16, about 18, about 20, about 22, or about

24 hours. In some embodiments, the perfusion lasts for up to about 24, about 28, about 32, about 36, about 40, about 44, or about 48 hours. In some embodiments, the perfusion lasts for a period of time sufficient to induce expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

[00114] In some embodiments, the kidney is from a subject with a chronic kidney disease, from a subject with an end-stage kidney disease, from a subject in need of kidney rejuvenation with or without any symptom of kidney failure, from an unsuitable subject, a kidney considered not viable for transplantation, a discarded kidney, an injured, damaged, or failed kidney, or from a deceased subject. In some embodiments, the kidney is from a subject with a chronic kidney disease. In some embodiments, the kidney is from a subject with an end-stage kidney disease. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with or without any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation without any symptom of kidney failure. In some embodiments, the kidney is from an unsuitable subject. In some embodiments, the kidney is a kidney considered not viable for transplantation. In some embodiments, the kidney is a discarded kidney. In some embodiments, the kidney is an injured, damaged, or failed kidney. In some embodiments, the kidney is a discarded human kidney. In some embodiments, the kidney is from a deceased subject. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human. In some embodiments, the kidney is nonhuman. In some embodiments, the kidney is from a swine or a baboon. In some embodiments, the kidney is from a swine. In some embodiments, the kidney is from a baboon. In some embodiments, the swine or the baboon is raised in a laboratory. In some embodiments, the swine is a miniature swine.

[00115] In another aspect, provided herein is a method of preserving a kidney that includes perfusing a kidney with a therapeutic composition in a perfusion system, such as a perfusion system described in Section 5.1. In certain embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney. In some embodiments, the at least one agent induces expression of OCT3/4. In some embodiments, the at least one agent induces expression of SOX2. In some embodiments, the at least one agent induces expression of c-MYC. In some embodiments, the at least one agent

induces expression of KLF4. In some embodiments, the at least one agent induces expression of NANOG. In some embodiments, the at least one agent induces expression of LIN28. In some embodiments, the at least one agent induces expression of at least two of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and SOX2. In some embodiments, the at least one agent induces expression of OCT3/4 and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4 and KLF4. In some embodiments, the at least one agent induces expression of SOX2 and c-MYC. In some embodiments, the at least one agent induces expression of SOX2 and KLF4. In some embodiments, the at least one agent induces expression of c-MYC and KLF4. In some embodiments, the at least one agent induces expression of KLF4 and NANOG. In some embodiments, the at least one agent induces expression of KLF4 and LIN28. In some embodiments, the at least one agent induces expression of c-MYC and NANOG. In some embodiments, the at least one agent induces expression of c-MYC and LIN28. In some embodiments, the at least one agent induces expression of SOX2 and NANOG. In some embodiments, the at least one agent induces expression of SOX2 and LIN28. In some embodiments, the at least one agent induces expression of NANOG and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4 and LIN28. In some embodiments, the at least one agent induces expression of at least three of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and KLF4. In

some embodiments, the at least one agent induces expression of SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of at least four of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of at least five of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and LIN28. In some embodiments, the at least

one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[00116] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is a hypothermic perfusion system. In some embodiments, the perfusion system is a subnormothermic system (*e.g.*, about 20 °C to about 33 °C). In some embodiments, the perfusion system is automated. In some embodiments, the perfusion system is transportable. In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is maintained at body temperature when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 33°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of

about 36°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 6°C to about 12°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 8°C to about 14°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 10°C to about 16°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 12°C to about 18°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 15°C to about 20°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 18°C to about 23°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 22°C to about 34°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 25°C to about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 28°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 30°C to about 40°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney.

[00117] In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate. In some embodiments, the perfusate comprises oxygenated or non-oxygenated blood or an oxygen carrier. In some embodiments, the perfusate comprises oxygenated blood. In some embodiments, the perfusate has an oxygen pressure of about 100 mm Hg to about 500 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 150 mm Hg to about 400 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 200 mm Hg to about 350 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 250 mm Hg to about 300 mm Hg. In some embodiments, the perfusate comprises non-oxygenated blood. In some embodiments, the perfusate comprises autologous, allogenic, or heterologous whole blood. In some embodiments, the perfusate comprises autologous whole blood. In some embodiments, the perfusate comprises allogenic whole blood. In some embodiments, the perfusate comprises heterologous whole blood. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes or thrombocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of thrombocytes. In some embodiments, the autologous whole blood is depleted of leukocytes. In some embodiments, the perfusate comprises an oxygen carrier. In some embodiments, the oxygen carrier comprises an artificial oxygen carrier. In some embodiments, the artificial oxygen carrier comprises a hemoglobin-based oxygen carrier (HBOC), a polymerized bovine HBOC, a pyridoxylated hemoglobin, or a pyridoxylated bovine hemoglobin, or any combination thereof. In some embodiments, the perfusate comprises acellular oxygen-carrying media. Exemplary acellular oxygen-carrying media comprises but is not limited to, Lifor, Aqix RS-I, or STEEN solution (Zulpati et al., 2021, Front. Med. 8:808719). In some embodiments, the perfusate comprises albumin or globulin. In some embodiments, the perfusate comprises a human albumin or a bovine albumin. In some embodiments, the perfusate comprises an electrolyte. In some embodiments, the perfusate has an extracellular-like Na+/K+ balance. In some embodiments, the perfusate comprise an impermeant or glucose. In some embodiments, the perfusate comprise an impermeant and glucose. In some embodiments, the perfusate comprises glucose. In some embodiments, the perfusate comprises heparin, a vasodilator, mannitol, a corticosteroid, an anticoagulant, an antibiotic, a nutrient, an amino acid, insulin, a cryoprotective agent, angiotensin, or a medication, or any combination thereof. In some embodiments, the

cryoprotective agent comprises erythropoietin, metformin, doxycycline, a SUL compound, or propofol, or any combination thereof. In some embodiments, the perfusate comprises an impermeant. In some embodiments, the impermeant comprises gluconate, mannitol, lactobionate, raffinose, histidine, tryptophan, or ketoglutarate. In some embodiments, the perfusate is supplemented with a surfactant. In some embodiments, the surfactant comprises dextran 40 or dextran 70. In some embodiments, the surfactant comprises dextran 40. In some embodiments, the perfusate is removed of a cytokine and a chemokine when perfusing the kidney. In some embodiments, the removal of the cytokine and the chemokine from the perfusate comprises filtering the perfusate through a cytosorb hemadsorbtion filter. In some embodiments, the cytosorb hemadsorbtion filter is connected to the perfusion system. In some embodiments, the cytokine comprises IL-1b, IL-1a, IL-1RA, TNFa, IL-10, IL-6, IL-8, c reactive protein (CRP), or thromboxane B2, or any combination thereof.

[00118] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 mL. In some embodiments, the reservoir has a volume of less than about 50 mL. In some embodiments, the reservoir has a volume of less than about 40 mL. In some embodiments, the reservoir has a

volume of less than about 30 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 25 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 15 mL. In some embodiments, the reservoir has a volume of less than about 10 mL. In some embodiments, the reservoir has a volume of less than about 9 mL. In some embodiments, the reservoir has a volume of less than about 8 mL. In some embodiments, the reservoir has a volume of less than about 7 mL. In some embodiments, the reservoir has a volume of less than about 6 mL. In some embodiments, the reservoir has a volume of less than about 5 mL. In some embodiments, the reservoir has a volume of less than about 4 mL. In some embodiments, the reservoir has a volume of less than about 3 mL. In some embodiments, the reservoir has a volume of less than about 2 mL. In some embodiments, the reservoir has a volume of or less than about 1 mL. In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 200 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 70 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a mean or median system pressure of about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 200 mL/min to about 500 mL/min when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 250 mL/min to about 400 mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 50 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 70 mm Hg to about 80 mm Hg when perfusing the kidney. In some embodiments, the perfusion system

maintains the kidney at an arterial pressure of about 80 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0 mm Hg per mL/min to about 0.50 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.10 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.15 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.20 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney.

[00119] In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, or renal resistance, or any combination thereof. In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, and renal resistance.

[00120] In some embodiments, the perfusion lasts for about 0 hour to about 144 hours. In some embodiments, the perfusion lasts for about 0 hour to about 120 hours. In some embodiments, the perfusion lasts for up to about 24 hours. In some embodiments, the perfusion lasts for about 48 hours. In some embodiments, the perfusion lasts for up to about 2, about 4, about 6, about 8, about 10, about 12, about 14, about 16, about 18, about 20, about 22, or about 24 hours. In some embodiments, the perfusion lasts for up to about 24, about 28, about 32, about 36, about 40, about 44, or about 48 hours. In some embodiments, the perfusion lasts for a period of time sufficient to induce expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

[00121] In some embodiments, the kidney is from a subject with a chronic kidney disease, from a subject with an end-stage kidney disease, from a subject in need of kidney rejuvenation with or without any symptom of kidney failure, from an unsuitable subject, a kidney considered not viable for transplantation, a discarded kidney, an injured, damaged, or failed kidney, or from a deceased subject. In some embodiments, the kidney is from a subject with a chronic kidney disease. In some embodiments, the kidney is from a subject with an end-stage kidney disease. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with or without

any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation without any symptom of kidney failure. In some embodiments, the kidney is from an unsuitable subject. In some embodiments, the kidney is a kidney considered not viable for transplantation. In some embodiments, the kidney is a discarded kidney. In some embodiments, the kidney is an injured, damaged, or failed kidney. In some embodiments, the kidney is a discarded human kidney. In some embodiments, the kidney is from a deceased subject. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human. In some embodiments, the kidney is nonhuman. In some embodiments, the kidney is from a swine or a baboon. In some embodiments, the kidney is from a swine. In some embodiments, the kidney is from a baboon. In some embodiments, the swine or the baboon is raised in a laboratory. In some embodiments, the swine is a miniature swine.

[00122] In another aspect, provided herein is a method of transplanting a kidney to a recipient in need thereof that includes perfusing a kidney with a therapeutic composition in a perfusion system, such as a perfusion system described in Section 5.1, and transplanting the kidney into the recipient. In certain embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney. In some embodiments, the at least one agent induces expression of OCT3/4. In some embodiments, the at least one agent induces expression of SOX2. In some embodiments, the at least one agent induces expression of c-MYC. In some embodiments, the at least one agent induces expression of KLF4. In some embodiments, the at least one agent induces expression of NANOG. In some embodiments, the at least one agent induces expression of LIN28. In some embodiments, the at least one agent induces expression of at least two of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and SOX2. In some embodiments, the at least one agent induces expression of OCT3/4 and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4 and KLF4. In some embodiments, the at least one agent induces expression of SOX2 and c-MYC. In some embodiments, the at least one agent induces expression of SOX2 and KLF4. In some embodiments, the at least one agent induces expression of c-MYC and KLF4. In some embodiments, the at least one agent induces expression of KLF4 and NANOG. In some

embodiments, the at least one agent induces expression of KLF4 and LIN28. In some embodiments, the at least one agent induces expression of c-MYC and NANOG. In some embodiments, the at least one agent induces expression of c-MYC and LIN28. In some embodiments, the at least one agent induces expression of SOX2 and NANOG. In some embodiments, the at least one agent induces expression of SOX2 and LIN28. In some embodiments, the at least one agent induces expression of NANOG and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4 and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4 and LIN28. In some embodiments, the at least one agent induces expression of at least three of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and c-MYC. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of at least four of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or

NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and/or KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, and KLF4. In some embodiments, the at least one agent induces expression of at least five of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and/or NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and LIN28. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, and NANOG. In some embodiments, the at least one agent induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and LIN28. In some embodiments, the perfusion system comprises an acoustic volume sensor. In some embodiments, the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC. In some embodiments, the therapeutic composition

comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4. In some embodiments, the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof. In some embodiments, (a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28; and/or (b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of: (i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28; (ii) OCT3/4, SOX2, c-MYC, and/or KLF4; (iii) OCT3/4, SOX2, and/or KLF4; or (iv) OCT4, SOX2, NANOG, and/or LIN28. In some embodiments, the recipient is a mammal. In some embodiments, the recipient is a human. In some embodiments, the donor is swine. In some embodiments, the swine is a miniature swine. In some embodiments, the polynucleotide or fragment thereof is comprised in an expression vector. In some embodiments, the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

[00123] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is a hypothermic perfusion system. In some embodiments, the perfusion system is a subnormothermic system (*e.g.*, about 20 °C to about 33 °C). In some embodiments, the perfusion system is automated. In some embodiments, the perfusion system is transportable. In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is maintained at body temperature when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 33°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C to about 38°C when perfusing the kidney. In some

embodiments, the perfusate is maintained at a temperature of about 35°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 6°C to about 12°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 8°C to about 14°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 10°C to about 16°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 12°C to about 18°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 15°C to about 20°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 18°C to about 23°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 22°C to about 34°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 25°C to about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 28°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 30°C to about 40°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney.

[00124] In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate. In some embodiments, the perfusate comprises oxygenated or non-oxygenated blood or an oxygen carrier. In some embodiments, the perfusate comprises oxygenated blood. In some

embodiments, the perfusate has an oxygen pressure of about 100 mm Hg to about 500 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 150 mm Hg to about 400 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 200 mm Hg to about 350 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 250 mm Hg to about 300 mm Hg. In some embodiments, the perfusate comprises non-oxygenated blood. In some embodiments, the perfusate comprises autologous, allogenic, or heterologous whole blood. In some embodiments, the perfusate comprises autologous whole blood. In some embodiments, the perfusate comprises allogenic whole blood. In some embodiments, the perfusate comprises heterologous whole blood. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes or thrombocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of thrombocytes. In some embodiments, the autologous whole blood is depleted of leukocytes. In some embodiments, the perfusate comprises an oxygen carrier. In some embodiments, the oxygen carrier comprises an artificial oxygen carrier. In some embodiments, the artificial oxygen carrier comprises a hemoglobin-based oxygen carrier (HBOC), a polymerized bovine HBOC, a pyridoxylated hemoglobin, or a pyridoxylated bovine hemoglobin, or any combination thereof. In some embodiments, the perfusate comprises acellular oxygen-carrying media. Exemplary acellular oxygen-carrying media comprises but is not limited to, Lifor, Aqix RS-I, or STEEN solution (Zulpati et al., 2021, Front. Med. 8:808719). In some embodiments, the perfusate comprises albumin or globulin. In some embodiments, the perfusate comprises a human albumin or a bovine albumin. In some embodiments, the perfusate comprises an electrolyte. In some embodiments, the perfusate has an extracellular-like Na+/K+ balance. In some embodiments, the perfusate comprise an impermeant or glucose. In some embodiments, the perfusate comprise an impermeant and glucose. In some embodiments, the perfusate comprises glucose. In some embodiments, the perfusate comprises heparin, a vasodilator, mannitol, a corticosteroid, an anticoagulant, an antibiotic, a nutrient, an amino acid, insulin, a cryoprotective agent, angiotensin, or a medication, or any combination thereof. In some embodiments, the cryoprotective agent comprises erythropoietin, metformin, doxycycline, a SUL compound, or propofol, or any combination thereof. In some embodiments, the perfusate comprises an impermeant. In some embodiments, the impermeant comprises gluconate, mannitol, lactobionate,

raffinose, histidine, tryptophan, or ketoglutarate. In some embodiments, the perfusate is supplemented with a surfactant. In some embodiments, the surfactant comprises dextran 40 or dextran 70. In some embodiments, the surfactant comprises dextran 40. In some embodiments, the perfusate is removed of a cytokine and a chemokine when perfusing the kidney. In some embodiments, the removal of the cytokine and the chemokine from the perfusate comprises filtering the perfusate through a cytosorb hemadsorbtion filter. In some embodiments, the cytosorb hemadsorbtion filter is connected to the perfusion system. In some embodiments, the cytokine comprises IL-1b, IL-1a, IL-1RA, TNFa, IL-10, IL-6, IL-8, c reactive protein (CRP), or thromboxane B2, or any combination thereof.

[00125] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 mL. In some embodiments, the reservoir has a volume of less than about 50 mL. In some embodiments, the reservoir has a volume of less than about 40 mL. In some embodiments, the reservoir has a volume of less than about 30 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 25 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments,

the reservoir has a volume of less than about 15 mL. In some embodiments, the reservoir has a volume of less than about 10 mL. In some embodiments, the reservoir has a volume of less than about 9 mL. In some embodiments, the reservoir has a volume of less than about 8 mL. In some embodiments, the reservoir has a volume of less than about 7 mL. In some embodiments, the reservoir has a volume of less than about 6 mL. In some embodiments, the reservoir has a volume of less than about 5 mL. In some embodiments, the reservoir has a volume of less than about 4 mL. In some embodiments, the reservoir has a volume of less than about 3 mL. In some embodiments, the reservoir has a volume of less than about 2 mL. In some embodiments, the reservoir has a volume of or less than about 1 mL. In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 200 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 70 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a mean or median system pressure of about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 200 mL/min to about 500 mL/min when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 250 mL/min to about 400 mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 50 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 70 mm Hg to about 80 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 80 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0 mm Hg per mL/min to about 0.50 mm Hg per mL/min when perfusing the

kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.10 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.15 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.20 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney.

[00126] In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, or renal resistance, or any combination thereof. In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, and renal resistance.

[00127] In some embodiments, the perfusion lasts for about 0 hour to about 144 hours. In some embodiments, the perfusion lasts for about 0 hour to about 120 hours. In some embodiments, the perfusion lasts for up to about 24 hours. In some embodiments, the perfusion lasts for about 48 hours. In some embodiments, the perfusion lasts for up to about 2, about 4, about 6, about 8, about 10, about 12, about 14, about 16, about 18, about 20, about 22, or about 24 hours. In some embodiments, the perfusion lasts for up to about 24, about 28, about 32, about 36, about 40, about 44, or about 48 hours. In some embodiments, the perfusion lasts for a period of time sufficient to induce expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

[00128] In some embodiments, the kidney is from a subject with a chronic kidney disease, from a subject with an end-stage kidney disease, from a subject in need of kidney rejuvenation with or without any symptom of kidney failure, from an unsuitable subject, a kidney considered not viable for transplantation, a discarded kidney, an injured, damaged, or failed kidney, or from a deceased subject. In some embodiments, the kidney is from a subject with a chronic kidney disease. In some embodiments, the kidney is from a subject with an end-stage kidney disease. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with or without any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation without any symptom of kidney failure. In some

embodiments, the kidney is from an unsuitable subject. In some embodiments, the kidney is a kidney considered not viable for transplantation. In some embodiments, the kidney is a discarded kidney. In some embodiments, the kidney is an injured, damaged, or failed kidney. In some embodiments, the kidney is a discarded human kidney. In some embodiments, the kidney is from a deceased subject. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human. In some embodiments, the kidney is nonhuman. In some embodiments, the kidney is from a swine or a baboon. In some embodiments, the kidney is from a swine. In some embodiments, the kidney is from a baboon. In some embodiments, the swine or the baboon is raised in a laboratory. In some embodiments, the swine is a miniature swine.

5.4 Methods of engineering

[00129] In one aspect provided herein is a method of genetically engineering a kidney *ex vivo* that includes contacting a kidney with a polynucleotide composition comprising a OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 polynucleotide. In some embodiments, the polypeptide composition comprises an OCT3/4 polynucleotide. In some embodiments, the polynucleotide composition comprises a SOX2 polynucleotide. In some embodiments, the polynucleotide composition comprises a c-MYC polynucleotide. In some embodiments, the polynucleotide composition comprises a KLF4 polynucleotide. In some embodiments, the polynucleotide composition comprises a NANOG polynucleotide. In some embodiments, the polynucleotide composition comprises a LIN28 polynucleotide. In some embodiments, the polynucleotide composition comprises an OCT3/4, a SOX2, a c-MYC, and a KLF4 polynucleotide. In some embodiments, the polynucleotide composition comprises an OCT3/4, a SOX2, and a KLF4 polynucleotide. In some embodiments, the polynucleotide composition comprises an OCT4, a SOX2, a NANOG, and a LIN28 polynucleotide. In some embodiments, the method comprises perfusing the kidney in a perfusion system comprising an acoustic volume sensor. In some embodiments, the composition comprises a OCT3/4, SOX2, KLF4, and/or c-MYC polynucleotide. In some embodiments, the composition comprises a OCT3/4, SOX2, and/or KLF4 polynucleotide. In some embodiments, the composition comprises a OCT4, SOX2, NANOG, and/or LIN28 polynucleotide. In some embodiments, the composition further comprises a polynucleotide that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28. In some embodiments, the composition is delivered to the kidney via a delivery

system comprising a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), or a polyplex, or any combination thereof. In some embodiments, the composition is delivered to the kidney via a delivery system comprising an adeno-associated virus (AAV). In some embodiments, the AAV comprises AAV2, AAV9, AAV5, AAV6, AAV8, AAV4, AAV10, AAV11, AAV1, AAV7, or AAV12, or any combination thereof. In some embodiments, the AAV comprises AAV2 and/or AAV9. In some embodiments, the AAV comprises AAV2. In some embodiments, the AAV comprises AAV9. In some embodiments, the AAV comprises AAV2 and AAV9. In some embodiments, the AAV comprises AAV2, AAV5, AAV6, AAV8, or AAV9, or any combination thereof. In some embodiments, the AAV comprises AAV5. In some embodiments, the AAV comprises AAV6. In some embodiments, the AAV comprises AAV8.

[00130] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is a hypothermic perfusion system. In some embodiments, the perfusion system is a subnormothermic system (*e.g.*, about 20 °C to about 33 °C). In some embodiments, the perfusion system is automated. In some embodiments, the perfusion system is transportable. In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is maintained at body temperature when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 33°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C when perfusing the kidney.

In some embodiments, the perfusate is maintained at a temperature of about 6°C to about 12°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 8°C to about 14°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 10°C to about 16°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 12°C to about 18°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 15°C to about 20°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 18°C to about 23°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 22°C to about 34°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 25°C to about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 28°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 30°C to about 40°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney.

[00131] In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate. In some embodiments, the perfusate comprises oxygenated or non-oxygenated blood or an oxygen carrier. In some embodiments, the perfusate comprises oxygenated blood. In some embodiments, the perfusate has an oxygen pressure of about 100 mm Hg to about 500 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 150 mm Hg to about 400 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 200 mm Hg to about 350 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 250 mm Hg to about 300 mm Hg. In some embodiments, the perfusate comprises non-oxygenated blood. In some embodiments, the perfusate comprises autologous, allogenic, or heterologous whole blood. In some embodiments, the perfusate comprises autologous whole blood. In some

embodiments, the perfusate comprises allogenic whole blood. In some embodiments, the perfusate comprises heterologous whole blood. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes or thrombocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of thrombocytes. In some embodiments, the autologous whole blood is depleted of leukocytes. In some embodiments, the perfusate comprises an oxygen carrier. In some embodiments, the oxygen carrier comprises an artificial oxygen carrier. In some embodiments, the artificial oxygen carrier comprises a hemoglobin-based oxygen carrier (HBOC), a polymerized bovine HBOC, a pyridoxylated hemoglobin, or a pyridoxylated bovine hemoglobin, or any combination thereof. In some embodiments, the perfusate comprises acellular oxygen-carrying media. Exemplary acellular oxygen-carrying media comprises but is not limited to, Lifor, Aqix RS-I, or STEEN solution (Zulpati et al., 2021, Front. Med. 8:808719). In some embodiments, the perfusate comprises albumin or globulin. In some embodiments, the perfusate comprises a human albumin or a bovine albumin. In some embodiments, the perfusate comprises an electrolyte. In some embodiments, the perfusate has an extracellular-like Na^+/K^+ balance. In some embodiments, the perfusate comprise an impermeant or glucose. In some embodiments, the perfusate comprise an impermeant and glucose. In some embodiments, the perfusate comprises glucose. In some embodiments, the perfusate comprises heparin, a vasodilator, mannitol, a corticosteroid, an anticoagulant, an antibiotic, a nutrient, an amino acid, insulin, a cryoprotective agent, angiotensin, or a medication, or any combination thereof. In some embodiments, the cryoprotective agent comprises erythropoietin, metformin, doxycycline, a SUL compound, or propofol, or any combination thereof. In some embodiments, the perfusate comprises an impermeant. In some embodiments, the impermeant comprises gluconate, mannitol, lactobionate, raffinose, histidine, tryptophan, or ketoglutarate. In some embodiments, the perfusate is supplemented with a surfactant. In some embodiments, the surfactant comprises dextran 40 or dextran 70. In some embodiments, the surfactant comprises dextran 40. In some embodiments, the perfusate is removed of a cytokine and a chemokine when perfusing the kidney. In some embodiments, the removal of the cytokine and the chemokine from the perfusate comprises filtering the perfusate through a cytosorb hemadsorbtion filter. In some embodiments, the cytosorb hemadsorbtion filter is connected to the perfusion system. In some embodiments, the

cytokine comprises IL-1b, IL-1a, IL-1RA, TNFa, IL-10, IL-6, IL-8, c reactive protein (CRP), or thromboxane B2, or any combination thereof.

[00132] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 mL. In some embodiments, the reservoir has a volume of less than about 50 mL. In some embodiments, the reservoir has a volume of less than about 40 mL. In some embodiments, the reservoir has a volume of less than about 30 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 25 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 15 mL. In some embodiments, the reservoir has a volume of less than about 10 mL. In some embodiments, the reservoir has a volume of less than about 9 mL. In some embodiments, the reservoir has a volume of less than about 8 mL. In some embodiments, the reservoir has a volume of less than about 7 mL. In some embodiments, the reservoir has a volume of less than about 6 mL. In some embodiments, the reservoir has a volume of less than about 5 mL. In some embodiments, the reservoir has a volume of less than about 4 mL. In some embodiments, the reservoir has a volume of less than about 3 mL. In some

embodiments, the reservoir has a volume of less than about 2 mL. In some embodiments, the reservoir has a volume of or less than about 1 mL. In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 200 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 70 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a mean or median system pressure of about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 200 mL/min to about 500 mL/min when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 250 mL/min to about 400 mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 50 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 70 mm Hg to about 80 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 80 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0 mm Hg per mL/min to about 0.50 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.10 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.15 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.20 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney.

[00133] In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, or renal resistance, or any combination thereof. In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, and renal resistance.

[00134] In some embodiments, the perfusion lasts for about 0 hour to about 144 hours. In some embodiments, the perfusion lasts for about 0 hour to about 120 hours. In some embodiments, the perfusion lasts for up to about 24 hours. In some embodiments, the perfusion lasts for about 48 hours. In some embodiments, the perfusion lasts for up to about 2, about 4, about 6, about 8, about 10, about 12, about 14, about 16, about 18, about 20, about 22, or about 24 hours. In some embodiments, the perfusion lasts for up to about 24, about 28, about 32, about 36, about 40, about 44, or about 48 hours. In some embodiments, the perfusion lasts for a period of time sufficient to induce expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

[00135] In some embodiments, the kidney is from a subject with a chronic kidney disease, from a subject with an end-stage kidney disease, from a subject in need of kidney rejuvenation with or without any symptom of kidney failure, from an unsuitable subject, a kidney considered not viable for transplantation, a discarded kidney, an injured, damaged, or failed kidney, or from a deceased subject. In some embodiments, the kidney is from a subject with a chronic kidney disease. In some embodiments, the kidney is from a subject with an end-stage kidney disease. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with or without any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation without any symptom of kidney failure. In some embodiments, the kidney is from an unsuitable subject. In some embodiments, the kidney is a kidney considered not viable for transplantation. In some embodiments, the kidney is a discarded kidney. In some embodiments, the kidney is an injured, damaged, or failed kidney. In some embodiments, the kidney is a discarded human kidney. In some embodiments, the kidney is from a deceased subject. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human. In some embodiments, the kidney is nonhuman. In some embodiments, the kidney is from a swine or a baboon. In some

embodiments, the kidney is from a swine. In some embodiments, the kidney is from a baboon. In some embodiments, the swine or the baboon is raised in a laboratory. In some embodiments, the swine is a miniature swine.

[00136] In another aspect provided herein is a method of genetically engineering a kidney *ex vivo* that includes contacting a kidney with a polypeptide composition comprising a OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises an OCT3/4 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a SOX2 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a c-MYC polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a KLF4 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a NANOG polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises a LIN28 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises an OCT3/4, a SOX2, a c-MYC, and a KLF4 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises an OCT3/4, a SOX2, and a KLF4 polypeptide or fragment thereof. In some embodiments, the polypeptide composition comprises an OCT4, a SOX2, a NANOG, and a LIN28 polypeptide or fragment thereof. In some embodiments, the method comprises perfusing the kidney in a perfusion system comprising an acoustic volume sensor. In some embodiments, the composition comprises a OCT3/4, SOX2, KLF4, and/or c-MYC polypeptide or fragment thereof. In some embodiments, the composition comprises a OCT3/4, SOX2, and/or KLF4 polypeptide or fragment thereof. In some embodiments, the composition comprises a OCT4, SOX2, NANOG, and/or LIN28 polypeptide or fragment thereof. In some embodiments, the composition is delivered to the kidney via a delivery system comprising a naked polypeptide, an extracellular vesicle, a lipid nanoparticle particle (LNP), or a polyplex, or any combination thereof.

[00137] In some embodiments, the perfusion system is a normothermic perfusion system. In some embodiments, the perfusion system is a hypothermic perfusion system. In some embodiments, the perfusion system is a subnormothermic system (*e.g.*, about 20 °C to about 33 °C). In some embodiments, the perfusion system is automated. In some embodiments, the perfusion system is transportable. In some embodiments, the perfusion system further comprises a perfusate for perfusing the kidney. In some embodiments, the perfusate is maintained at body

temperature when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 33°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C to about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 35°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 37°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 39°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 6°C to about 12°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 8°C to about 14°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 10°C to about 16°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 12°C to about 18°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 15°C to about 20°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 18°C to about 23°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 22°C to about 34°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 25°C to about 36°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 28°C to about 38°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 30°C to about 40°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney. In some embodiments, the perfusate is

maintained at a temperature of about 4°C to about 10°C at the start and gradually elevated to about 20°C to about 32°C when perfusing the kidney. In some embodiments, the perfusate is maintained at a temperature of about 20°C to about 32°C at the start and gradually elevated to about 35°C to about 39°C when perfusing the kidney.

[00138] In some embodiments, the perfusate is a blood-based or red blood cell-based perfusate. In some embodiments, the perfusate comprises oxygenated or non-oxygenated blood or an oxygen carrier. In some embodiments, the perfusate comprises oxygenated blood. In some embodiments, the perfusate has an oxygen pressure of about 100 mm Hg to about 500 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 150 mm Hg to about 400 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 200 mm Hg to about 350 mm Hg. In some embodiments, the perfusate has an oxygen pressure of about 250 mm Hg to about 300 mm Hg. In some embodiments, the perfusate comprises non-oxygenated blood. In some embodiments, the perfusate comprises autologous, allogenic, or heterologous whole blood. In some embodiments, the perfusate comprises autologous whole blood. In some embodiments, the perfusate comprises allogenic whole blood. In some embodiments, the perfusate comprises heterologous whole blood. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes or thrombocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of leukocytes. In some embodiments, the autologous, allogenic, or heterologous whole blood is depleted of thrombocytes. In some embodiments, the autologous whole blood is depleted of leukocytes. In some embodiments, the perfusate comprises an oxygen carrier. In some embodiments, the oxygen carrier comprises an artificial oxygen carrier. In some embodiments, the artificial oxygen carrier comprises a hemoglobin-based oxygen carrier (HBOC), a polymerized bovine HBOC, a pyridoxylated hemoglobin, or a pyridoxylated bovine hemoglobin, or any combination thereof. In some embodiments, the perfusate comprises acellular oxygen-carrying media. Exemplary acellular oxygen-carrying media comprises but is not limited to, Lifor, Aqix RS-I, or STEEN solution (Zulpati et al., 2021, Front. Med. 8:808719). In some embodiments, the perfusate comprises albumin or globulin. In some embodiments, the perfusate comprises a human albumin or a bovine albumin. In some embodiments, the perfusate comprises an electrolyte. In some embodiments, the perfusate has an extracellular-like Na+/K+ balance. In some embodiments, the perfusate comprise an impermeant or glucose. In some embodiments, the perfusate comprise an

impermeant and glucose. In some embodiments, the perfusate comprises glucose. In some embodiments, the perfusate comprises heparin, a vasodilator, mannitol, a corticosteroid, an anticoagulant, an antibiotic, a nutrient, an amino acid, insulin, a cryoprotective agent, angiotensin, or a medication, or any combination thereof. In some embodiments, the cryoprotective agent comprises erythropoietin, metformin, doxycycline, a SUL compound, or propofol, or any combination thereof. In some embodiments, the perfusate comprises an impermeant. In some embodiments, the impermeant comprises gluconate, mannitol, lactobionate, raffinose, histidine, tryptophan, or ketoglutarate. In some embodiments, the perfusate is supplemented with a surfactant. In some embodiments, the surfactant comprises dextran 40 or dextran 70. In some embodiments, the surfactant comprises dextran 40. In some embodiments, the perfusate is removed of a cytokine and a chemokine when perfusing the kidney. In some embodiments, the removal of the cytokine and the chemokine from the perfusate comprises filtering the perfusate through a cytosorb hemadsorbtion filter. In some embodiments, the cytosorb hemadsorbtion filter is connected to the perfusion system. In some embodiments, the cytokine comprises IL-1b, IL-1a, IL-1RA, TNFa, IL-10, IL-6, IL-8, c reactive protein (CRP), or thromboxane B2, or any combination thereof.

[00139] In some embodiments, the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate. In some embodiments, the infusion pump system further includes: a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition; a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate. In some embodiments, the infusion pump system further includes: a controller configured to: receive acoustic volume sensor output; and control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output. In some embodiments, the infusion pump system further includes: a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and a second valve assembly

in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate. In some embodiments, the reservoir has a volume of less than about 60 mL. In some embodiments, the reservoir has a volume of less than about 50 mL. In some embodiments, the reservoir has a volume of less than about 40 mL. In some embodiments, the reservoir has a volume of less than about 30 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 25 mL. In some embodiments, the reservoir has a volume of less than about 20 mL. In some embodiments, the reservoir has a volume of less than about 15 mL. In some embodiments, the reservoir has a volume of less than about 10 mL. In some embodiments, the reservoir has a volume of less than about 9 mL. In some embodiments, the reservoir has a volume of less than about 8 mL. In some embodiments, the reservoir has a volume of less than about 7 mL. In some embodiments, the reservoir has a volume of less than about 6 mL. In some embodiments, the reservoir has a volume of less than about 5 mL. In some embodiments, the reservoir has a volume of less than about 4 mL. In some embodiments, the reservoir has a volume of less than about 3 mL. In some embodiments, the reservoir has a volume of less than about 2 mL. In some embodiments, the reservoir has a volume of or less than about 1 mL. In some embodiments, the acoustic volume sensor includes: a fixed reference chamber acoustically coupled to a speaker and a first microphone; a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 200 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 50 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a system pressure of about 70 mm Hg to about 150 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a mean or median system pressure of about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 200 mL/min to about 500 mL/min when perfusing the kidney. In some embodiments, the perfusion system is maintained at a flow rate of about 250 mL/min to about 400 mL/min when perfusing

the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 50 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 70 mm Hg to about 80 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at an arterial pressure of about 80 mm Hg to about 100 mm Hg when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0 mm Hg per mL/min to about 0.50 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.10 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.15 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney. In some embodiments, the perfusion system maintains the kidney at a renal resistance of about 0.20 mm Hg per mL/min to about 0.40 mm Hg per mL/min when perfusing the kidney.

[00140] In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, or renal resistance, or any combination thereof. In some embodiments, the perfusion system is capable of closed loop control for system pressure, flow rate, arterial pressure, temperature, oxygen pressure, glucose concentration, and renal resistance.

[00141] In some embodiments, the perfusion lasts for about 0 hour to about 144 hours. In some embodiments, the perfusion lasts for about 0 hour to about 120 hours. In some embodiments, the perfusion lasts for up to about 24 hours. In some embodiments, the perfusion lasts for about 48 hours. In some embodiments, the perfusion lasts for up to about 2, about 4, about 6, about 8, about 10, about 12, about 14, about 16, about 18, about 20, about 22, or about 24 hours. In some embodiments, the perfusion lasts for up to about 24, about 28, about 32, about 36, about 40, about 44, or about 48 hours. In some embodiments, the perfusion lasts for a period of time sufficient to induce expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

[00142] In some embodiments, the kidney is from a subject with a chronic kidney disease, from a subject with an end-stage kidney disease, from a subject in need of kidney rejuvenation with or without any symptom of kidney failure, from an unsuitable subject, a kidney considered

not viable for transplantation, a discarded kidney, an injured, damaged, or failed kidney, or from a deceased subject. In some embodiments, the kidney is from a subject with a chronic kidney disease. In some embodiments, the kidney is from a subject with an end-stage kidney disease. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with or without any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation with any symptom of kidney failure. In some embodiments, the kidney is from a subject in need of kidney rejuvenation without any symptom of kidney failure. In some embodiments, the kidney is from an unsuitable subject. In some embodiments, the kidney is a kidney considered not viable for transplantation. In some embodiments, the kidney is a discarded kidney. In some embodiments, the kidney is an injured, damaged, or failed kidney. In some embodiments, the kidney is a discarded human kidney. In some embodiments, the kidney is from a deceased subject. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human. In some embodiments, the kidney is nonhuman. In some embodiments, the kidney is from a swine or a baboon. In some embodiments, the kidney is from a swine. In some embodiments, the kidney is from a baboon. In some embodiments, the swine or the baboon is raised in a laboratory. In some embodiments, the swine is a miniature swine.

5.5 Assays

Assays for Measuring Gene Expression

[00143] Any assay known in the art for measuring gene expression can be used. Non-limiting examples include assessing the tissue expression levels of OCT3/4, SOX2, KLF4, c-MYC, NANOG, and/or LIN28. In certain embodiments, methods of assessing the tissue expression levels of OCT3/4, SOX2, KLF4, c-MYC, NANOG, and/or LIN28 comprise obtaining a sample from *ex vivo* perfused tissue (*e.g.*, kidney) wherein the tissue expression levels are compared to a control sample. In some embodiments, a control sample comprises a sample collected from a tissue (*e.g.*, kidney) not subjected to *ex vivo* perfusion. In some embodiments, a control sample comprises a sample collected from the tissue (*e.g.*, kidney) before it is subjected to *ex vivo* perfusion (i.e., baseline). In some embodiments, a sample is collected by tissue biopsy.

[00144] In certain embodiments, methods of assessing the tissue expression levels of OCT3/4, SOX2, KLF4, c-MYC, NANOG, and/or LIN28 in a sample comprise measuring for the gene expression of OCT3/4, SOX2, KLF4, c-MYC, NANOG, and/or LIN28. Any assay known in the

art for measuring gene expression can be used. Non-limiting examples include high-density expression array, DNA microarray, polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), real-time quantitative reverse transcription PCR (qRT-PCR), serial analysis of gene expression (SAGE), Spotted cDNA arrays, GeneChip, spotted oligo arrays, bead arrays, RNA Seq, tiling array, northern blotting, hybridization microarray, in situ hybridization, or a combination thereof. Other conventional methods can also be employed as suitable.

[00145] In certain embodiments, methods of assessing the tissue gene expression levels of OCT3/4, SOX2, KLF4, c-MYC, NANOG, and/or LIN28 in a sample comprise measuring for the protein expression of OCT3/4, SOX2, KLF4, c-MYC, NANOG, and/or LIN28. Any assay known in the art for measuring protein expression can be used. Non-limiting examples include Western blotting, enzyme-linked immunosorbent assay (ELISA), mass spectrometry, HPLC, flow cytometry, fluorescence-activated cell sorting (FACS), liquid chromatography-mass spectrometry (LC/MS), immunoelectrophoresis, translation complex profile sequencing (TCP-seq), protein microarray, protein chip, capture arrays, reverse phase protein microarray (RPPA), two-dimensional gel electrophoresis or (2D-PAGE), functional protein microarrays, electrospray ionization (ESI), matrix-assisted laser desorption/ionization (MALDI), or a combination thereof. Other conventional methods can also be employed as suitable.

5.5.1 Assays for Measuring Kidney Function and Viability

[00146] Any assay known in the art for measuring kidney function can be used. In certain embodiments, a method of the present disclosure results in a decreased occurrence of transplant rejection compared to that of current standard of care (*i.e.*, a kidney transplant). In certain embodiments, a method of the present disclosure results in a decreased occurrence of acute transplant rejection compared to that of current standard of care (*i.e.*, a kidney transplant). In certain embodiments, a method of the present disclosure results in a decreased occurrence of short-term kidney transplant rejection compared to that of current standard of care (*i.e.*, a kidney transplant). In certain embodiments, a method of the present disclosure results in about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or more than about 90% decreased occurrence of transplant rejection (*e.g.*, acute, short-term, long-term) compared to that of current standard of care (*i.e.*, a kidney transplant).

[00147] In certain embodiments, a method of the present disclosure results in a more viable kidney transplant compared to that of current standard of care (*i.e.*, a kidney transplant). In certain embodiments, a method of the present disclosure results in a kidney transplant comprising about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or more than about 90% more viability compared to that of current standard of care (*i.e.*, a kidney transplant). In certain embodiments, the viability of the kidney after *ex vivo* perfusion according to the methods disclosed herein is prolonged by about 1 to about 5, about 5 to about 10, about 10 to about 15, about 15 to about 20, about 20 to about 25, about 25 to about 30, or more than about 30 more years compared to the viability of a kidney prepared for transplant according to methods other than those of the present disclosure.

[00148] In certain embodiments, use of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in a more functional transplant compared to a kidney prepared for transplant according to methods other than those of the present disclosure. Examples of methods for assessing kidney transplant function include laboratory tests such as glomerular filtration rate, blood urea nitrogen, and serum creatinine, imaging tests (*e.g.*, ultrasound, computer tomography), and/or kidney biopsy. In certain embodiments, use of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in a transplant comprising more than about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or more than about 90% function compared to a kidney prepared for transplant according to methods other than those of the present disclosure. In certain embodiments, use of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in a transplant comprising more than about at least about or about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more than 90% function compared to a kidney prepared for transplant according to methods other than those of the present disclosure.

[00149] In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in better rate of survival of the kidney recipient as compared to the rate of survival before transplantation of the kidney to the patient. In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the

methods disclosed herein improves the rate of survival of the kidney recipient by about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or more than about 90% compared to the rate of survival before transplantation of the kidney to the patient. In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein improves the rate of survival of the kidney recipient by at least about or about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more than 90% compared to the rate of survival before transplantation of the kidney to the patient. In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein improves the rate of survival of the kidney recipient by about 3 months to about 6 months, about 6 months to about 1 year, about 1 year to about 3 years, about 3 years to about 5 years, about 5 years to about 10 years, about 10 years to about 15 years, about 15 years to about 20 years, about 20 years to about 25 years, about 25 years to about 30 years, about 30 years to about 40 years, about 40 years to about 50 years, or about more than 50 years compared to the rate of survival before transplantation of the kidney to the patient. In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein improves the rate of survival of the kidney recipient by at least about or about 3 months, 6 months, 1 year, 3 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 40 years, 50 years, or more than 50 years compared to the rate of survival before transplantation of the kidney to the patient.

[00150] In certain embodiments, a method of treating a patient (*i.e.*, a recipient) in need thereof with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein can result in reduced administration of immunosuppressive therapy to the recipient when compared to current standard of care after the transplantation of the donor organs (*i.e.*, a kidney transplant). In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in a reduced amount of immunosuppressive agents administered to the recipient when compared to the amount of immunosuppressive agents generally administered to a comparable transplant recipient (*e.g.*, a person of the same sex and of comparable age, height, and/or weight). In certain embodiments, the method provided herein results in a reduced amount of immunosuppressive agents by at least about or about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more than 90% administered to the recipient.

[00151] In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in an improvement of the corresponding disease that the transplantation aims to intervene within the kidney recipient as compared to the disease before transplantation of the kidney to the patient. In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in a greater improvement of the corresponding disease that the transplantation aims to intervene within the kidney recipient compared to that of a patient transplanted according to the current standard of care (*i.e.*, a kidney transplant) or with a kidney produced according to methods other than those of the present disclosure. One of skill in the art can appreciate that an improvement of the corresponding disease following transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein is assessed according to the disease itself, severity of the disease, the health of the patient before and after transplant, and a myriad of other factors than can be disease and/or patient specific. In certain embodiments, an improvement of the corresponding disease can include, but is not limited to, amelioration and/or ablation of at least one symptom associated with the disease, slowing progression of the disease, preventing further progression of the disease, reversing disease progression, and/or returning the kidney recipient to a healthy status (*e.g.*, comparable to a healthy, disease-free patient of comparable age, gender, and background). In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in an improvement of the corresponding disease that the transplantation aims to intervene within the kidney recipient as indicated by at least one biomarker corresponding to the disease. In certain embodiments, use of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or more than about 90% improvement of the corresponding disease compared to that of current standard of care (*i.e.*, a kidney transplant) or to the use of a kidney produced according to methods other than those of the present disclosure. In certain embodiments, use of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in at least about or about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more than 90% improvement of the corresponding disease compared to that of current standard

of care (*i.e.*, a kidney transplant) or to the use of a kidney produced according to methods other than those of the present disclosure.

[00152] In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in an improvement of kidney disease and/or at least one symptom associated with kidney disease within the kidney recipient as compared to before transplantation of the kidney to the patient. Non-limiting examples of symptoms associated with kidney disease include abnormal GFR or eGFR (*e.g.*, less than about 90 ml/min/1.73 m^2 in a middle-aged adult), proteinuria (*e.g.*, over about 150 mg protein/day), abnormal serum creatinine levels (*e.g.*, over about 1.4 mg/dl), and abnormal blood urea nitrogen (BUN) levels (*e.g.*, over about 60 mg/dl). In certain embodiments, transplantation of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in a greater improvement of kidney disease and/or at least one symptom associated with kidney disease within the kidney recipient compared to that of a patient transplanted according to the current standard of care (*i.e.*, a kidney transplant) or with a kidney produced according to methods other than those of the present disclosure. In certain embodiments, use of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or more than about 90% improvement of kidney disease and/or at least one symptom associated with kidney disease compared to that of current standard of care (*i.e.*, a kidney transplant) or to the use of a kidney produced according to methods other than those of the present disclosure. In certain embodiments, use of a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein results in at least about or about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more than 90% improvement of kidney disease and/or at least one symptom associated with kidney disease compared to that of current standard of care (*i.e.*, a kidney transplant) or to the use of a kidney produced according to methods other than those of the present disclosure.

[00153] In certain embodiments, the severity of proteinuria is reduced in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient. Proteinuria is characterized by increased levels of protein in the urine and can be a symptom of decreased kidney function and potentially renal failure. Clinically, proteinuria is defined as the

excretion of over 150 mg protein per day in the urine. In certain embodiments, the severity of proteinuria is reduced by at least about or about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or over 95% in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient. In certain embodiments, a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein does not have measurable proteinuria. In certain embodiments, a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein can experience transient proteinuria that resolves about 1, 2, 3, 3-7, 7-10, 10-14 days, or about 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8 weeks, or about 1, 2, 3, 4, 5, 6 months after the transplantation. In certain embodiments, a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein can experience urinary excretion of less than about 60 mg protein per day, less than about 80 mg protein per day, less than about 100 mg protein per day, less than about 120 mg protein per day, less than about 140 mg protein per day, less than about 160 mg protein per day, less than about 200 mg protein per day, less than about 220 mg protein per day, less than about 240 mg, per day, less than about 260 mg protein per day, less than about 280 mg protein per day, less than about 300 mg protein per day, less than about 320 mg protein per day, less than about 340 mg protein per day, less than about 360 mg protein per day, less than about 380 mg protein per day, or less than about 400 mg protein per day.

[00154] In certain embodiments, creatinine clearance is improved in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient. Creatinine clearance (often expressed as ml/min) can be determined by comparing the level of creatinine in urine with the creatinine level in blood, usually based on assessments of a 24-hour urine sample and a blood sample drawn at the end of the 24-hour period, and is used to estimate GFR (eGFR). Estimated glomerular filtration rate (eGFR) can be calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation (*See*, Inker et al., *N Engl J Med* (2021) 385(19): p. 1737-1749)). In certain embodiments, GFR or eGFR is improved in a kidney recipient who was transplanted a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient.

Normal GFR or eGFR can vary according to age, gender, and body weight. In young adults, GFR is approximately 120-130 ml/min/1.73 m^2. In certain embodiments, GFR or eGFR is improved by at least about or about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or over 95% in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient. In certain embodiments, a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein can experience a GFR or eGFR of at least about or about 15 ml/min/1.73 m^2, 20 ml/min/1.73 m^2, 25 ml/min/1.73 m^2, 30 ml/min/1.73 m^2, 35 ml/min/1.73 m^2, 40 ml/min/1.73 m^2, 45 ml/min/1.73 m^2, 50 ml/min/1.73 m^2, 55 ml/min/1.73 m^2, 60 ml/min/1.73 m^2, 65 ml/min/1.73 m^2, 70 ml/min/1.73 m^2, 75 ml/min/1.73 m^2, 80 ml/min/1.73 m^2, 85 ml/min/1.73 m^2, 90 ml/min/1.73 m^2, 95 ml/min/1.73 m^2, 100 ml/min/1.73 m^2, 105 ml/min/1.73 m^2, 110 ml/min/1.73 m^2, 115 ml/min/1.73 m^2, 120 ml/min/1.73 m^2, 125 ml/min/1.73 m^2, 130 ml/min/1.73 m^2, or more than 130 ml/min/1.73 m^2. In certain embodiments, a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein can experience a GFR or eGFR ranging from about 15 ml/min/1.73 m^2 to about 20 ml/min/1.73 m^2, about 20 ml/min/1.73 m^2 to about 25 ml/min/1.73 m^2, about 25 ml/min/1.73 m^2 to about 30 ml/min/1.73 m^2, about 30 ml/min/1.73 m^2 to about 35 ml/min/1.73 m^2, about 35 ml/min/1.73 m^2 to about 40 ml/min/1.73 m^2, about 40 ml/min/1.73 m^2 to about 45 ml/min/1.73 m^2, about 45 ml/min/1.73 m^2 to about 50 ml/min/1.73 m^2, about 50 ml/min/1.73 m^2 to about 55 ml/min/1.73 m^2, about 55 ml/min/1.73 m^2 to about 60 ml/min/1.73 m^2, about 60 ml/min/1.73 m^2 to about 65 ml/min/1.73 m^2, about 65 ml/min/1.73 m^2 to about 70 ml/min/1.73 m^2, about 70 ml/min/1.73 m^2 to about 75 ml/min/1.73 m^2, about 75 ml/min/1.73 m^2 to about 80 ml/min/1.73 m^2, about 80 ml/min/1.73 m^2 to about 85 ml/min/1.73 m^2, about 85 ml/min/1.73 m^2 to about 90 ml/min/1.73 m^2, about 90 ml/min/1.73 m^2 to about 95 ml/min/1.73 m^2, about 95 ml/min/1.73 m^2 to about 100 ml/min/1.73 m^2, about 100 ml/min/1.73 m^2 to about 105 ml/min/1.73 m^2, about 105 ml/min/1.73 m^2 to about 110 ml/min/1.73 m^2, about 110 ml/min/1.73 m^2 to about 115 ml/min/1.73 m^2, about 115 ml/min/1.73 m^2 to about 120 ml/min/1.73 m^2, about 120 ml/min/1.73 m^2 to about 125 ml/min/1.73 m^2, about 125 ml/min/1.73 m^2 to about 130 ml/min/1.73 m^2, or about 130 ml/min/1.73 m^2 to more than about 130 ml/min/1.73 m^2.

[00155] In certain embodiments, the stage of chronic kidney disease is improved in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient. The various stages of chronic kidney disease are associated with GFR or eGFR levels as follows: stage 1 (kidney damage with normal or increased GFR), GFR or eGFR greater than or equal to 90 ml/min/1.73 m^2; stage 2 (kidney damage with mild decrease in GFR), GFR or eGFR of 60-89 ml/min/1.73 m^2; stage 3 (kidney damage with moderate decrease in GFR), GFR or eGFR of 30-59 ml/min/1.73 m^2; stage 4 (kidney damage with severe decrease in GFR), GFR or eGFR of 15-29 ml/min/1.73 m2; and stage 5 (kidney failure), GFR or eGFR less than 15 ml/min/1.73 m^2. In certain embodiments, the stage of chronic kidney disease does not change in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient. In certain embodiments, the stage of chronic kidney disease is decreased in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient. In certain embodiments, the stage of chronic kidney disease is decreased by at least one stage in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to that before the transplantation of the kidney to the patient. In certain embodiments, the stage of chronic kidney disease in a kidney recipient is decreased from a stage 5, as diagnosed before kidney transplantation, to stage 4, 3, 2, or 1. In certain embodiments, the stage of chronic kidney disease in a kidney recipient is decreased from a stage 4, as diagnosed before kidney transplantation, to stage 3, 2, or 1. In certain embodiments, the stage of chronic kidney disease in a kidney recipient is decreased from a stage 3, as diagnosed before kidney transplantation, to stage 2 or 1. In certain embodiments, the stage of chronic kidney disease in a kidney recipient is decreased from a stage 2, as diagnosed before kidney transplantation, to stage 1.

[00156] In certain embodiments, biomarkers of kidney damage are measured to assess the efficiency of the methods of the present disclosure. In certain embodiments, biomarkers of kidney damage are assessed in either a tissue biopsy, a blood (*e.g.*, plasma, serum) sample, or a urine sample collected from a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein. Non-limiting examples of

biomarkers of kidney damage include IL-18, kidney injury molecule-1 (KIM-1), N-acetyl-beta-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid-binding protein (L-FABP), and osteopontin (OPN). Methods of measuring biomarkers of kidney damage are known in the art, for example, the biomarkers can be determined by ELISA. In certain embodiments, the measured level of at least one of IL-18, KIM-1, NAG, NGAL, L-FABP, and/or OPN is lower in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to a patient transplanted with a kidney prepared by methods other than those disclosed herein. In certain embodiments, the measured level of at least two of IL-18, KIM-1, NAG, NGAL, L-FABP, and/or OPN is lower in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to a patient transplanted with a kidney prepared by methods other than those disclosed herein. In certain embodiments, the measured level of at least three of IL-18, KIM-1, NAG, NGAL, L-FABP, and/or OPN is lower in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to a patient transplanted with a kidney prepared by methods other than those disclosed herein. In certain embodiments, the measured level of at least four of IL-18, KIM-1, NAG, NGAL, L-FABP, and/or OPN is lower in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to a patient transplanted with a kidney prepared by methods other than those disclosed herein. In certain embodiments, the measured level of at least five of IL-18, KIM-1, NAG, NGAL, L-FABP, and/or OPN is lower in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to a patient transplanted with a kidney prepared by methods other than those disclosed herein. In certain embodiments, the measured level of IL-18, KIM-1, NAG, NGAL, L-FABP, and OPN is lower in a kidney recipient who was transplanted with a kidney subjected to *ex vivo* perfusion according to the methods disclosed herein as compared to a patient transplanted with a kidney prepared by methods other than those disclosed herein.

6. EMBODIMENTS

[00157] The present disclosure provides the following non-limiting embodiments:

1. A method of *ex vivo* kidney perfusion comprising:

perfusing a kidney with a therapeutic composition in a perfusion system,

wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

wherein the perfusion system comprises an acoustic volume sensor.

2. A method of repairing kidney damage in a subject in need thereof comprising:

perfusing a kidney with a therapeutic composition in a perfusion system,

wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

wherein the perfusion system comprises an acoustic volume sensor.

3. A method of treating a kidney disease or disorder in a subject in need thereof comprising:

perfusing a kidney with a therapeutic composition in a perfusion system,

wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

wherein the perfusion system comprises an acoustic volume sensor.

4. A method of preserving a kidney comprising:

perfusing a kidney with a therapeutic composition in a perfusion system,

wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

wherein the perfusion system comprises an acoustic volume sensor.

5. A method of transplanting a kidney to a recipient in need thereof, the method comprising:

perfusing a kidney obtained from a donor with a therapeutic composition in a perfusion system, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

transplanting the kidney into the recipient, and

wherein the perfusion system comprises an acoustic volume sensor.

6. The method of any one of embodiments 1 to 5, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC.

7. The method of any one of embodiments 1 to 5, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4.

8. The method of any one of embodiments 1 to 5, wherein the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28.

9. The method of any one of embodiments 5 to 8, wherein the recipient is a mammal.

10. The method of any one of embodiments 5 or 9, wherein the recipient is a human.

11. The method of any one of embodiments 5 to 10, wherein the donor is swine.

12. The method of embodiment 11, wherein the swine is a miniature swine.

13. The method of any one of embodiments 1 to 12, wherein the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

14. The method of embodiment 13, wherein:

(a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28; and/or

(b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28.

15. The method of any one of embodiment 13 or 14, wherein the polynucleotide or fragment thereof is comprised in an expression vector.

16. The method of any one of embodiments 1 to 15, wherein the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

17. A method of genetically engineering a kidney *ex vivo*, the method comprising:

contacting a kidney with:

(a) a polynucleotide composition comprising a OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 polynucleotide, or

(b) a polypeptide composition comprising a OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 polypeptide, and

perfusing the kidney in a perfusion system comprising an acoustic volume sensor.

18. The method of embodiment 17, wherein the composition comprises a OCT3/4, SOX2, KLF4, and/or c-MYC polynucleotide or polypeptide.

19. The method of embodiment 17, wherein the composition comprises a OCT3/4, SOX2, and/or KLF4 polynucleotide or polypeptide.

20. The method of embodiment 17, wherein the composition comprises a OCT4, SOX2, NANOG, and/or LIN28 polynucleotide or polypeptide.

21. The method of any one of embodiments 1 to 20, wherein the perfusion system is a normothermic perfusion system.

22. The method of any one of embodiments 1 to 21, wherein the perfusion system is configured to automatically adjust the concentration of the therapeutic composition in the perfusion system.

23. The method of any one of embodiments 1 to 22, wherein the perfusion system is transportable.

24. The method of any one of embodiments 1 to 23, wherein the perfusion system further comprises a perfusate for perfusing the kidney.

25. The method of embodiment 24, wherein the perfusate is a blood-based or red blood cell-based perfusate.

26. The method of any one of embodiments 1 to 25, wherein the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate.

27. The method of embodiment 26, wherein the infusion pump system further includes:

a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition;

a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate.

28. The method of embodiment 27, wherein the infusion pump system further includes:

a controller configured to:

receive acoustic volume sensor output; and

control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output.

29. The method of embodiment 27 or 28, wherein the infusion pump system further includes:

a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and

a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate.

30. The method of any one of embodiments 27 to 29, wherein the reservoir has a volume of less than about 60 milliliters.

31. The method of embodiment 30, wherein the reservoir has a volume of less than about 25 milliliters.

32. The method of embodiment 30, wherein the reservoir has a volume of less than about 10 milliliters.

33. The method of embodiment 30, wherein the reservoir has a volume of less than about 3 milliliters.

34. The method of any one of embodiments 1 to 33, wherein the acoustic volume sensor includes:

a fixed reference chamber acoustically coupled to a speaker and a first microphone;

a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone.

35. A composition for use in a perfusion system comprising at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, wherein the perfusion system comprises an acoustic volume sensor.

36. The composition of embodiment 35, wherein the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC.

37. The composition of embodiment 35, wherein the at least one agent induces expression of OCT3/4, SOX2, and/or KLF4.

38. The composition of embodiment 35, wherein the at least one agent induces expression of OCT4, SOX2, NANOG, and/or LIN28.

39. The composition of any one of embodiments 35 to 38, wherein the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

40. The composition of embodiment 39, wherein:

(a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28; and/or

(b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28.

41. The composition of embodiment 39 or 40, wherein the polynucleotide or fragment thereof is comprised in an expression vector.

42. The composition of any one of embodiments 35 to 41, wherein the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

43. The composition of any one of embodiments 35 to 42, wherein the perfusion system is a normothermic perfusion system.

44. A perfusion system, comprising a means for perfusing a kidney with a therapeutic composition, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

45. The system of embodiment 44, wherein the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

46. The system of embodiment 45, wherein:

(a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of OCT3/4, KLF4, c-MYC, and SOX2; and/or

(b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of OCT3/4, KLF4, c-MYC, and SOX2.

47. The system of embodiment 45 or 46, wherein the nucleic acid is comprised in an expression vector.

48. The system of any one of embodiments 44 to 47, wherein the at least one agent comprises a naked nucleic acid, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

49. The system of any one of embodiments 44 to 48, wherein the perfusion system is a normothermic perfusion system.

50. The system of any one of embodiments 44 to 49, wherein the perfusion system is configured to automatically adjust the concentration of the therapeutic composition in the perfusion system.

51. The system of any one of embodiments 44 to 50, wherein the perfusion system is transportable.

52. The system of any one of embodiments 44 to 51, wherein the perfusion system further comprises a perfusate for perfusing the kidney.

53. The system of embodiment 52, wherein the perfusate is a blood-based or red blood cell-based perfusate.

54. The system of any one of embodiments 44 to 53, wherein the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including an acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate.

55. The system of embodiment 54, wherein the infusion pump system further includes:

a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition;

a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate.

56. The system of embodiment 55, wherein the infusion pump system further includes:

a controller configured to:

receive acoustic volume sensor output; and

control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output.

57. The system of embodiment 55 or 56, wherein the infusion pump system further includes:

a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and

a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate.

58. The system of any one of embodiments 55 to 57, wherein the reservoir has a volume of less than about 60 milliliters.

59. The system of embodiment 58, wherein the reservoir has a volume of less than about 25 milliliters.

60. The system of embodiment 58, wherein the reservoir has a volume of less than about 10 milliliters

61. The system of embodiment 58, wherein the reservoir has a volume of less than about 3 milliliters.

62. The system of any one of embodiments 54 to 61, wherein the acoustic volume sensor includes:

a fixed reference chamber acoustically coupled to a speaker and a first microphone;

a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone.

63. An infusion pump comprising a means for measuring fluid volume of a therapeutic composition, wherein the therapeutic composition is suitable for *ex vivo* kidney perfusion.

64. The infusion pump of embodiment 63, wherein the fluid volume is less than 60 milliliters.

65. The infusion pump of embodiment 63, wherein the fluid volume is less than 25 milliliters.

66. The infusion pump of embodiment 63, wherein the fluid volume is less than 10 milliliters.

67. The infusion pump of embodiment 63, wherein the fluid volume is less than 5 milliliters.

68. The infusion pump of embodiment 63, wherein the fluid volume is less than 3 milliliters.

69. The infusion pump of embodiment 63, wherein the fluid volume is less than 1 milliliter.

70. The infusion pump of any one of embodiments 63 to 69, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28.

71. The infusion pump of any one of embodiments 63 to 69, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC.

72. The infusion pump of any one of embodiments 63 to 69, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4.

73. The infusion pump of any one of embodiments 63 to 69, wherein the therapeutic composition comprises at least one agent that induces expression of OCT4, SOX2, NANOG, and/or LIN28.

74. The infusion pump of any one of embodiments 70 to 73, wherein the at least one agent comprises a nucleic acid, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

75. The infusion pump of embodiment 74, wherein:

(a) the nucleic acid encodes at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28; and/or

(b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28.

7. EXAMPLES

[00158] The examples in this section are offered by way of illustration, and not by way of limitation. The following examples are presented as exemplary embodiments of the invention. They should not be construed as limiting the broad scope of the invention.

7.1 Example 1: AAV gene transfer and vector kidney screening in *ex-vivo* kidneys

[00159] The exemplary study describes development of a gene delivery protocol and AAV vectors for gene delivery of Oct, Sox2, Klf4 (OSK) to *ex vivo* human kidneys (*see* **FIG. 2**). In Phase I, AAV(s) with enhanced tropism for the kidney are identified to develop an infusion protocol for systemic and localized infusion of pig and human *ex vivo* kidneys. In Phase II, using the protocol established in Phase I, human kidneys are infused with an OKS-expressing AAV vector.

Phase I: Determination of best conditions of systemic or localized infusion of pig and human *ex vivo* kidneys

[00160] In Phase I of the exemplary study, a stepwise approach establishes infusion conditions and identifies an AAV with enhanced tropism for kidney tissue.

STEP 1: AAV9-based dosing studies

[00161] *Ex vivo* perfused kidneys are transduced with different AAV-serotype (*e.g.*, AAV9, AAV2, and/or other serotypes) vectors expressing GFP. AAV9, 2, 6, and 8 vectors carry a construct with strong ubiquitous promoter (CMV) and reporter gene (*e.g.*, GFP). To transduce the kidneys, AAV vectors expressing GFP are added to the circulation or localized and best infusion conditions are established. Initial dosing studies are conducted with pig kidneys and results are confirmed in human kidneys.

(i) Preclinical vector dose Study #1

[00162] Using an AAV9-CMVGFP vector, two vector doses of capsids are tested – 5×10^{12} vector genomes per kilogram bodyweight (vg/kg) and 1×10^{13} vg/kg. After 2 or 3 days (depending on organ fitness) a macroscopic analysis of kidney for cytotoxicity (*e.g.*, bleedings,

necrosis) is performed and kidney samples are then collected as demonstrated in **FIG. 3**. In brief, six (6) serial slices approximately 3-5 mm thick are made to a kidney sample. In addition, at least four punch biopsies are collected from the renal cortex and at least three punch biopsies are collected from the renal medulla wherein the approximate size of the punch biopsy is approximately 5×3×3 mm/punch (*i.e.*, about 25 mg/punch).

[00163] The tissue samples are either snap-frozen (NO fixation) and stored at or below -70°C or the tissue samples are paraformaldehyde (PFA)-fixated. The outer section is used for glomeruli isolation (fresh tissue required). Punched samples (5×3×3 mm/punch) from cortex and medulla are snap-frozen for further analyses. For any sequencing analyses, snap-frozen tissue (not fixated tissue) is required. From all tissue samples, RNA and DNA are extracted and used to determine total viral load/cell (vg/dg) by means of droplet digital PCR (ddPCR) and/or quantitative PCR (qPCR). Fixated tissue is used for immunohistochemistry (IHC) and/or *in situ* hybridization (ISH) approaches. Tissue cryosections are microscopically analyzed for GFP expression by fluorescence microscopy, optionally using an anti-GFP antibody. Kidney cell types are counter-labeled to determine GFP co-localization.

[00164] The experiments conducted with an AAV9-CMVGFP vector are repeated with AAV2 and other AAV vectors available. The doses of capsids can be adjusted as needed to obtain an acceptable transduction protocol.

(ii) Preclinical vector dose Study #2

[00165] Two vector doses of capsids (vg/kg) are tested (*see* results of Study #1, above). Vectors are dosed in a continuous way and transduction kinetics are monitored with ddPCR. Timepoints for continuous dosing are as follows: 1, 2, 3, 4, 5, 6, 12, 24, 48, and 72 hours (h). Perfusate is collected at the above timepoints, and activity of activated complement is monitored. Vector genomes are quantified in the perfusate by means of ddPCR using GFP-specific primers.

[00166] After 2 or 3 days (depending on organ fitness) a macroscopic analysis of kidney for cytotoxicity (*e.g.*, bleedings, necrosis) is performed and kidney samples are then collected as demonstrated in **FIG. 3** (*see* Study #1). The tissue samples are either snap-frozen and stored at or below -70°C or the tissue samples are PFA-fixated. The outer section is used for glomeruli isolation (fresh tissue required). Punched samples (5×3×3 mm/punch) from cortex and medulla are snap-frozen for further analyses. For any sequencing analyses, snap-frozen tissue (not fixated

tissue) is required. From all tissue samples, RNA and DNA are extracted and used to determine total viral load/cell (vg/dg) by means of ddPCR and/or qPCR. Tissue samples are collected and subjected to single nucleus RNA sequencing (snRNA-seq) analysis to determine the transduction and expression pattern at the single cell level. Fixated tissue is used for IHC and/or ISH. Tissue cryosections are microscopically analyzed for GFP expression by fluorescence microscopy, optionally using an anti-GFP antibody. Kidney cell types are counter-labeled to determine GFP co-localization.

[00167] *Conclusions*. The AAV vector doses can result in widespread transduction and gene expression with tolerable or no signs of acute toxicology. The data can also provide the vector dose for subsequent vector dosing using different AAV serotypes.

STEP 2: Validation of infusion conditions and comparison of selected AAV capsids in human kidneys

[00168] Conclusions from STEP 1 provide the range of vector dosing and infusion conditions. AAVs with improved kidney tropism are identified using a selection of barcoded AAVs that are pooled and infused intravenously (IV) or locally. AAV9, 2, 6, and 8 vectors carrying a construct with strong ubiquitous promoter (CMV) and reporter gene (GFP or YFP), herein referred to as "AAV reporter capsids", are manufactured and supplied for dosing of an *ex vivo* perfused kidney. The AAV reporter capsids are produced in sufficient quantities to reproduce AAV9 transduction (*see* STEP 1), and to further refine dosing and infusion conditions in pig or human kidneys.

[00169] STEP 2 is pursued in two parallel tracks to reproduce the results observed in STEP 1, and to elucidate kidney tropism with a selection of suited AAVs. In parallel track 1 (PT1), *ex vivo* perfused kidneys are transduced with an AAV variant (*e.g.*, AAV2, AAV5, AAV6, AAV8, AAV9, and/or other serotypes) in a vector, wherein the vector comprises a CMV-transgene (YFP)-Barcode$_n$ expression cassette design. In parallel track 2 (PT2), the dosing of an AAV9-CMVeGFP vector is optimized for the *ex vivo* perfused kidney. A summary of the dose, route, infusion time, and end time for the experimental groups of the PT1 and PT2 *ex vivo* studies is provided in **Table 2**.

Table 2: Groups for dose, route, infusion time for *ex vivo* study

AAV	Kidney #	Route	Dose (vg/kg)	Infusion Time (min)	End Time (d)
AAV9-CMVeGFP (PT2)	2	systemic	5×10^{13}	Continuous	3
	2	systemic	Dose 2	Continuous	3
	2	systemic	Dose 3	Continuous	3
$AAV(bc)_n$ (PT1)	2	systemic	Dose 4	Continuous	3
Totals	**8**				

[00170] Vectors selected for good kidney transduction properties in non-human primates (NHP) studies are individually manufactured at high titer. For PT1, each vector expresses a CMV-YFP gene and a barcode where the vectors are mixed in an equimolar ratio. For PT2, the vector (AAV9) expresses a CMV-GFP gene. Timepoints for continuous dosing of the vectors are as follows: 1, 2, 3, 4, 5, 6, 12, 24, 48, and 72 hours (h).

[00171] Perfusate is collected at the above timepoints, and transduction kinetics are monitored following organ perfusion. The activity of activated complement is monitored in the collected perfusate. Vector genomes are quantified in the perfusate by means of ddPCR using either YFP or GFP-specific primers. Abundance of barcodes are quantified by a means of nanopore sequencing (barcode-specific amplicons) in the perfusate.

[00172] After 2 or 3 days (depending on organ fitness) a macroscopic analysis of kidney for cytotoxicity (*e.g.*, bleedings, necrosis) is performed and kidney samples are then collected as demonstrated in **FIG. 3** (*see* Study #1). The tissue samples are either snap-frozen and stored at or below -70°C or the tissue samples are PFA-fixated. The outer section is used for glomeruli isolation (fresh tissue required). Punched samples (5×3×3 mm/punch) from cortex and medulla are snap-frozen for further analyses. For any sequencing analyses, snap-frozen tissue (not fixated tissue) is required. From all tissue samples, RNA and DNA are extracted and used to determine total viral load/cell (vg/dg) by means of ddPCR and/or qPCR. Tissue samples are collected and subjected to snRNA-seq analysis to determine the transduction and expression pattern at the single cell level. Fixated tissue is used for IHC and/or ISH. Tissue cryosections are

microscopically analyzed for GFP expression by fluorescence microscopy, optionally using an anti-GFP antibody. Kidney cell types are counter-labeled to determine GFP co-localization.

[00173] *Conclusions*. The comparative vector dosing study can inform about the biodistribution of several vectors in comparison to AAV9. The study can identify a particular vector that results in widespread and significantly better transduction and gene expression with tolerable or no signs of acute toxicology. The data can provide a final vector choice for OKS gene therapy.

Phase II: Expression of epigenetic reprogramming (OSK) factors in human kidney

[00174] In Phase II, using the protocol established in Phase I, human kidneys are infused with an OKS-expressing AAV vector. Two (2) vectors expressing OCT4, SOX2, and KLF4 (OSK) are tested. In Phase II, the biologic activity of OSK expressing vectors is determined and expression as well as reprogramming activity on the genome is determined prior and post dosing. The dose amount of the two vectors is determined in Phase I. The vectors are dosed in a continuous way and vector genomes are quantified in the perfusate by means of ddPCR after 12 h, 24 h, and at the end of the study. Perfusate is collected at these timepoints and activity of activated complement is monitored.

[00175] After 2 or 3 days, kidney samples are collected as described in Phase I and the tissue samples are snap-frozen and PFA-fixated. The outer section can be used for glomeruli isolation (fresh tissue required). Punched samples (5×3×3 mm/punch) from cortex and medulla are snap-frozen for further analyses. For any sequencing analyses, snap-frozen tissue (not fixated) is required. Fixated tissue is used for IHC and ISH approaches.

[00176] The duration of the *ex vivo* kidney perfusion is maximized on an organ perfusion system, allowing for longer timepoints to be analyzed. From all tissue samples RNA and DNA are extracted and used to determine total viral load/cell (vg/dg) and expression levels of OKS factors. From all tissue samples, DNA is extracted and subjected to genome sequencing, including that for assessing chromatin modifications and determining methylation pattern analysis. Genome modification is compared to a pre-dosing state and to needle biopsies taken before dosing. Tissue cryosections are microscopically analyzed for GFP expression by fluorescence microscopy and using an anti-GFP antibody. Kidney cell types are counter-labeled to determine GFP co-localization.

[00177] *Conclusions*. The study can inform about the biological activity of the OSK expressing vectors. Data can demonstrate whether OKS expression induces epigenetic changes to kidney DNA and results in overall improvement of kidney function over time. Different constructs and gene combinations can be tested in addition to the OSK construct. Inducible gene expression as well as LNP delivery can be assessed and complement the preclinical development.

7.2 Example 2: Optimizing AAV-OSK delivery on an organ perfusion system

[00178] As a first step toward investigating the feasibility of organ-level gene therapy using an organ perfusion system, AAVs with fluorescent protein markers (AAV-GFPs) are infused during a kidney run. In brief, the kidney is on organ perfusion system for about ~6 days. The kidney is subjected to one, two, or three days of virus laden perfusate using GFP control virus to evaluate the efficiency of delivery. Once delivery time is optimized, washout times of 1, 2, 3 days are evaluated. Virus-free perfusate is monitored for appearance of virus or transduced cells. Biopsies are taken at the end of the run and viewed with confocal microscopy to see if the fluorescent proteins have been delivered into desired kidney cells using different dosing strategies. Data indicate that after two days, the fluorescence signal is detectable by confocal microscopy and the signal remains stable up to 7 days (data not shown).

[00179] OSK-based partial epigenetic reprogramming can be achieved through AAV and/or LNP based gene transfer into human kidneys not useable for conventional transplantation. AAV vectors are envelope-free viruses developed for gene transfer into tissues or cells. The technology of *ex situ* organ machine perfusion allows to test and assess the dynamics and effects of AAV-based therapies in a clinically highly translational model. In brief, the gene transfer is performed during *ex vivo* preservation using a kidney perfusion protocol for 48 h and a maximum of 5 days. The perfusion solution can be supplemented with AAV vectors/library-optimized AAV vectors and OSK expressing AAV vectors. Different AAV-vector dosages ranging from 1×10^{12} to 1×10^{13} vg/organ is applied intra-arterially with varying infusion times and volumes, with high precision assisted by the acoustic volume sensor. Deploying partial epigenetic reprogramming using AAV vectors *ex vivo* on the organ perfusion system offers a safe way of rejuvenating failing kidneys without exposing a host's other healthy tissues.

[00180] After about 6 days, the kidney is removed from the organ perfusion system and tissue samples are collected and subjected to genomic analysis. Genomics and/or measurements of rejuvenation/restoration of normal kidney function at the epigenetic (DNA methylation) or gene expression (transcriptomic) level is assessed. Multimominc readouts include, at a minimum, single cell genomics on PBMC, cfDNA, organ biopsies, spatial transcriptomics, proteomics, metabolomics.

[00181] The "leakage" of virus or transduced cells is measured "in decedo." PBMCs are monitored by qPCR and RT-qPCR for trace amounts of virus or transduced cells using probes that detect 1) viral or vector components, or 2) unique junction sequences between the factors OCT4, SOX2, and KLF4 genes and the heterologous sequences controlling their expression.

7.3 Example 3: Organ perfusion system enabled widespread transduction of human kidneys with AAV-OSK

[00182] This example demonstrates that the organ perfusion system efficiently transduced human kidneys with AAV vectors.

[00183] Briefly, AAV2 vectors containing Oct4, Sox2, and Klf4 (OSK) transgenes under the control of the CMV promoter (AAV2-CMV-OSK) were transduced into human kidneys, using the *ex-vivo* organ perfusion system. AAV2-CMV-OSK was transduced at a dose of $5x10^{13}$ vg/kg, or $3x10^{13}$ vg/kg. Before AAV treatment, the kidneys were re-perfused for 4-20 hours, which depends on the ischemia status of the kidneys. After the AAV vector particles were injected into the system, the kidneys were perfused for approximately 50 hours. The experimental conditions for each study sample were summarized in **Table 3**.

Table 3. Experimental conditions for each study sample

Sample ID	Virus Dose (vg/kg)	Reperfusion time before AAV treatment (hrs)	AAV treatment time (hrs)	Total time (hrs)
53A	$5x10^{13}$	4.10	47.83	51.93
64A	$3x10^{13}$	18.11	51.9	70.23

[00184] Kidney tissue biopsies were collected as demonstrated in **FIG. 3** (*see* STUDY #1) at two timepoint: 1) before the reperfusion (pre); and 2) approximately 2-3 days after AAV transduction (post). The collected kidney tissue samples were snap-frozen (no fixation) and stored at -70 °C. The transduction efficiency and expression pattern of OSK were determined by single nucleus RNA sequencing (snRNA-seq) analysis.

[00185] As shown in **FIG. 4**, the expression of Oct4, Sox2, and Klf4 (OSK) were widespread in the entire kidney tissue specimen with the preference of arteriole, vasa recta, capillary and glomerulus. In **FIG. 5**, through organ perfusion system, OSK was broadly expressed in the entire kidney. Up to 80% of the arteries of the kidneys were transduced with the AAV-OSK. Importantly, the AAV transduction got beyond the arteries into the tubules system of the nephron, to the magnitude of approximately 5-30%.

[00186] Taken together, the data demonstrated that the organ perfusion system enabled broad and significant transduction and gene expression of OSK with an AAV vector.

* * *

[00187] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

WHAT IS CLAIMED:

1. A method of *ex vivo* kidney perfusion comprising:

perfusing a kidney with a therapeutic composition in a perfusion system,

wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

wherein the perfusion system comprises an acoustic volume sensor.

2. A method of repairing kidney damage in a subject in need thereof comprising:

perfusing a kidney with a therapeutic composition in a perfusion system,

wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

wherein the perfusion system comprises an acoustic volume sensor.

3. A method of treating a kidney disease or disorder in a subject in need thereof comprising:

perfusing a kidney with a therapeutic composition in a perfusion system,

wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

wherein the perfusion system comprises an acoustic volume sensor.

4. A method of preserving a kidney comprising:

perfusing a kidney with a therapeutic composition in a perfusion system,

wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

wherein the perfusion system comprises an acoustic volume sensor.

5. A method of transplanting a kidney to a recipient in need thereof, the method comprising:

perfusing a kidney obtained from a donor with a therapeutic composition in a perfusion system, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, and

transplanting the kidney into the recipient, and

wherein the perfusion system comprises an acoustic volume sensor.

6. The method of any one of claims 1 to 5, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC.

7. The method of any one of claims 1 to 5, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4.

8. The method of any one of claims 1 to 5, wherein the therapeutic composition comprises at least one agent that induces OCT4, SOX2, NANOG, and/or LIN28.

9. The method of any one of claims 5 to 8, wherein the recipient is a mammal.

10. The method of any one of claims 5 or 9, wherein the recipient is a human.

11. The method of any one of claims 5 to 10, wherein the donor is swine.

12. The method of claim 11, wherein the swine is a miniature swine.

13. The method of any one of claims 1 to 12, wherein the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

14. The method of claim 13, wherein:

(a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28; and/or

(b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28.

15. The method of any one of claim 13 or 14, wherein the polynucleotide or fragment thereof is comprised in an expression vector.

16. The method of any one of claims 1 to 15, wherein the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

17. A method of genetically engineering a kidney *ex vivo*, the method comprising:

contacting a kidney with:

(a) a polynucleotide composition comprising a OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 polynucleotide, or

(b) a polypeptide composition comprising a OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 polypeptide, and

perfusing the kidney in a perfusion system comprising an acoustic volume sensor.

18. The method of claim 17, wherein the composition comprises a OCT3/4, SOX2, KLF4, and/or c-MYC polynucleotide or polypeptide.

19. The method of claim 17, wherein the composition comprises a OCT3/4, SOX2, and/or KLF4 polynucleotide or polypeptide.

20. The method of claim 17, wherein the composition comprises a OCT4, SOX2, NANOG, and/or LIN28 polynucleotide or polypeptide.

21. The method of any one of claims 1 to 20, wherein the perfusion system is a normothermic perfusion system.

22. The method of any one of claims 1 to 21, wherein the perfusion system is configured to automatically adjust the concentration of the therapeutic composition in the perfusion system.

23. The method of any one of claims 1 to 22, wherein the perfusion system is transportable.

24. The method of any one of claims 1 to 23, wherein the perfusion system further comprises a perfusate for perfusing the kidney.

25. The method of claim 24, wherein the perfusate is a blood-based or red blood cell-based perfusate.

26. The method of any one of claims 1 to 25, wherein the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including the acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate.

27. The method of claim 26, wherein the infusion pump system further includes:

a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition;

a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate.

28. The method of claim 27, wherein the infusion pump system further includes:

a controller configured to:

receive acoustic volume sensor output; and

control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output.

29. The method of claim 27 or 28, wherein the infusion pump system further includes:

a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and

a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate.

30. The method of any one of claims 27 to 29, wherein the reservoir has a volume of less than about 60 milliliters.

31. The method of claim 30, wherein the reservoir has a volume of less than about 25 milliliters.

32. The method of claim 30, wherein the reservoir has a volume of less than about 10 milliliters.

33. The method of claim 30, wherein the reservoir has a volume of less than about 3 milliliters.

34. The method of any one of claims 1 to 33, wherein the acoustic volume sensor includes:

a fixed reference chamber acoustically coupled to a speaker and a first microphone;

a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone.

35. A composition for use in a perfusion system comprising at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney, wherein the perfusion system comprises an acoustic volume sensor.

36. The composition of claim 35, wherein the at least one agent induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC.

37. The composition of claim 35, wherein the at least one agent induces expression of OCT3/4, SOX2, and/or KLF4.

38. The composition of claim 35, wherein the at least one agent induces expression of OCT4, SOX2, NANOG, and/or LIN28.

39. The composition of any one of claims 35 to 38, wherein the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

40. The composition of claim 39, wherein:

(a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28; and/or

(b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28.

41. The composition of claim 39 or 40, wherein the polynucleotide or fragment thereof is comprised in an expression vector.

42. The composition of any one of claims 35 to 41, wherein the at least one agent comprises a naked polynucleotide or fragment thereof, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

43. The composition of any one of claims 35 to 42, wherein the perfusion system is a normothermic perfusion system.

44. A perfusion system, comprising a means for perfusing a kidney with a therapeutic composition, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28 in the kidney.

45. The system of claim 44, wherein the at least one agent comprises a polynucleotide or fragment thereof, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

46. The system of claim 45, wherein:

(a) the polynucleotide or fragment thereof encodes at least one protein selected from the group consisting of OCT3/4, KLF4, c-MYC, and SOX2; and/or

(b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of OCT3/4, KLF4, c-MYC, and SOX2.

47. The system of claim 45 or 46, wherein the nucleic acid is comprised in an expression vector.

48. The system of any one of claims 44 to 47, wherein the at least one agent comprises a naked nucleic acid, a recombinant virus, a viral particle, a virus-like particle (VLP), an extracellular vesicle, a lipid nanoparticle particle (LNP), a polyplex, or any combination thereof.

49. The system of any one of claims 44 to 48, wherein the perfusion system is a normothermic perfusion system.

50. The system of any one of claims 44 to 49, wherein the perfusion system is configured to automatically adjust the concentration of the therapeutic composition in the perfusion system.

51. The system of any one of claims 44 to 50, wherein the perfusion system is wherein the perfusion system is transportable.

52. The system of any one of claims 44 to 51, wherein the perfusion system further comprises a perfusate for perfusing the kidney.

53. The system of claim 52, wherein the perfusate is a blood-based or red blood cell-based perfusate.

54. The system of any one of claims 44 to 53, wherein the perfusion system further comprises an infusion pump system configured to introduce the therapeutic composition, the polynucleotide composition, or the polypeptide composition into the perfusate, the infusion pump system including an acoustic volume sensor configured to measure the volume of the therapeutic composition, the polynucleotide composition, or the polypeptide composition that is introduced into the perfusate.

55. The system of claim 54, wherein the infusion pump system further includes:

a reservoir configured to receive the therapeutic composition, the polynucleotide composition, or the polypeptide composition;

a pump assembly configured to pump a quantity of the therapeutic composition, the polynucleotide composition, or the polypeptide composition from the reservoir along a fluid path to the perfusate.

56. The system of claim 55, wherein the infusion pump system further includes:

a controller configured to:

receive acoustic volume sensor output; and

control the volumetric rate that the pump assembly is pumping the therapeutic composition, the polynucleotide composition, or the polypeptide composition based on the acoustic volume sensor output.

57. The system of claim 55 or 56, wherein the infusion pump system further includes:

a first valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the pump assembly; and

a second valve assembly in the fluid path and configured to fluidly isolate the acoustic volume sensor from the perfusate.

58. The system of any one of claims 55 to 57, wherein the reservoir has a volume of less than about 60 milliliters.

59. The system of claim 58, wherein the reservoir has a volume of less than about 25 milliliters.

60. The system of claim 58, wherein the reservoir has a volume of less than about 10 milliliters

61. The system of claim 58, wherein the reservoir has a volume of less than about 3 milliliters.

62. The system of any one of claims 54 to 61, wherein the acoustic volume sensor includes:

a fixed reference chamber acoustically coupled to a speaker and a first microphone;

a variable volume chamber acoustically coupled to the fixed volume chamber via a first port and acoustically coupled to a second microphone, the variable chamber variably defined in part by a membrane contacting a dispensing chamber, the acoustic volume sensor configured to acoustically excite the air in the fixed chamber at a first frequency, then receive acoustic spectra with the first microphone and second microphone.

63. An infusion pump comprising a means for measuring fluid volume of a therapeutic composition, wherein the therapeutic composition is suitable for *ex vivo* kidney perfusion.

64. The infusion pump of claim 63, wherein the fluid volume is less than 60 milliliters.

65. The infusion pump of claim 63, wherein the fluid volume is less than 25 milliliters.

66. The infusion pump of claim 63, wherein the fluid volume is less than 10 milliliters.

67. The infusion pump of claim 63, wherein the fluid volume is less than 5 milliliters.

68. The infusion pump of claim 63, wherein the fluid volume is less than 3 milliliters.

69. The infusion pump of claim 63, wherein the fluid volume is less than 1 milliliter.

70. The infusion pump of any one of claims 63 to 69, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28.

71. The infusion pump of any one of claims 63 to 69, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, KLF4, and/or c-MYC.

72. The infusion pump of any one of claims 63 to 69, wherein the therapeutic composition comprises at least one agent that induces expression of OCT3/4, SOX2, and/or KLF4.

73. The infusion pump of any one of claims 63 to 69, wherein the therapeutic composition comprises at least one agent that induces expression of OCT4, SOX2, NANOG, and/or LIN28.

74. The infusion pump of any one of claims 70 to 73, wherein the at least one agent comprises a nucleic acid, a small molecule, an antibody or fragment thereof, a polypeptide or fragment thereof, a CRISPR system, or any combination thereof.

75. The infusion pump of claim 74, wherein:

(a) the nucleic acid encodes at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28; and/or

(b) the polypeptide or fragment thereof is at least one protein selected from the group consisting of:

(i) OCT3/4, SOX2, c-MYC, KLF4, NANOG, and/or LIN28;

(ii) OCT3/4, SOX2, c-MYC, and/or KLF4;

(iii) OCT3/4, SOX2, and/or KLF4; or

(iv) OCT4, SOX2, NANOG, and/or LIN28.