

**[0007]** In an aspect, the present application provides a biochip, the biochip carrying a chemical entity and a code, wherein the code has a unique corresponding relationship with the chip.

**[0008]** In another aspect, the present application provides a method for preparing the biochip of the application, and the method comprising the following steps:

**[0009]** 1) coding the biochip;

**[0010]** 2) pretreating the biochip;

**[0011]** 3) performing silanization treatment on the surface of the biochip;

**[0012]** 4) chemically modifying the surface of the biochip; and

**[0013]** 5) optionally, detecting or quantitatively analyzing the chemical modification.

**[0014]** In another aspect, the present application provides use of the biochip of the application in synthesis of a biomacromolecule such as DNA, RNA and polypeptide.

**[0015]** In another aspect, the present application provides use of the biochip of the application in biological detection.

#### **Brief description of the drawings**

**[0016]** Fig. 1 schematically depicts an example of a recognizable 2-dimensional bar code chip according to the application.

**[0017]** Fig. 2 schematically depicts a process of DNA synthesis using a chip according to the application.

**[0018]** Fig. 3 schematically depicts a process of polypeptide synthesis using a chip according to the application.

**[0019]** Fig. 4A shows an HPLC chromatogram of a T30 product synthesized in experiment 1 in Example 3.

**[0020]** Fig. 4B shows an HPLC chromatogram of a T30 product synthesized in experiment 2 in Example 3.

**[0021]** Fig. 4C shows an HPLC chromatogram of a T30 product synthesized in experiment 3 in Example 3.

**[0022]** Fig. 4D shows an HPLC chromatogram of a T30 product synthesized in experiment 4 in Example 3.

**[0023]** Fig. 4E shows an HPLC chromatogram of a T30 product synthesized in experiment 5 in Example 3.

**[0024]** Fig. 4F shows an HPLC chromatogram of a standard sample of T30 in Example 3.

**[0025]** Fig. 5 shows a gel electrophoretogram of a product synthesized in Experiment 6 in

Example 3, wherein, Ctrl: standard synthetic primer control; lanes 1-3: Mix1-3.

### **Detailed description**

**[0026]** In the present application, unless otherwise defined, all technical and scientific terms used herein have the meanings generally understood by those skilled in the art of the present application. In the embodiments of the present application, methods and materials similar to or equivalent to those described herein may be used, and only illustrative and suitable methods and materials are described below. All public publications, patent applications, patents and other references are incorporated herein for reference. Furthermore, the materials, methods and embodiments are only exemplary and not restrictive. Meanwhile, in order to better understand the invention, the application also provides definitions and explanations of related terms. In case of any conflict between the definitions and explanations of the terms provided in this application and the meanings generally understood by ordinary technical personnel in the field of this application, the definitions and explanations of the terms provided in this application shall be prevailed.

### **[0027]** Biochip

**[0028]** In an aspect, the present application provides a biochip, the biochip carrying a chemical entity and a code, wherein the code has a unique corresponding relationship with the chip.

**[0029]** As known by those skilled in the art, the substrate of the chip is made of any materials suitable for the chip, and the materials have no adverse effect on the activity of the reaction reagent or has undesired side reaction with the reaction reagent. Preferably, the chip is made of an inert material. In some preferred embodiments, the chip is made of a material selected from silicon wafer (silicon crystal), glass sheet (bead), ceramics, sheet metal, plastic sheet (bead), gel, nylon membrane or any combination thereof, preferably silicon wafer. In one embodiment, the chip is made of porous glass, which has a particle size being any one of 5  $\mu\text{m}$ -2000  $\mu\text{m}$ , more preferably, any one of 25  $\mu\text{m}$ , 50  $\mu\text{m}$ , 100  $\mu\text{m}$ , 200  $\mu\text{m}$  and 500  $\mu\text{m}$ ; which has a pore diameter being any one of 200 $\text{\AA}$ -5000 $\text{\AA}$ , more preferably, any one of 500 $\text{\AA}$ , 1000 $\text{\AA}$ , 1500 $\text{\AA}$ , 2000 $\text{\AA}$  and 3000 $\text{\AA}$ . The chips may have any desired shapes. For example, the chip may be in a form of flake, cuboid, cylinder, sphere and the like, preferably, the chip is in a form of square flake. In a specific embodiment, the biochip is a microchip for DNA synthesis, which has a size of 2 mm\*2 mm, even 1 mm\*1 mm, 0.5 mm\*0.5 mm or less. In some preferred embodiments, the chip of the application is reused.

### **[0030]** Code

## Claims

1. A biochip carrying a chemical entity and a code, wherein the code has a unique corresponding relationship with the biochip.

2. The biochip according to claim 1, wherein the chemical entity is capable of reacting with a reaction reagent, thereby linking a monomer in the reaction reagent to a terminal of the chemical entity.

3. The biochip according to claim 2, wherein the chemical entity is a linker molecule capable of initiating a DNA/RNA synthesis reaction, preferably a linker molecule having a functional group reacting with an amino group on a beginning end and having hydroxyl protected with an acid-labile protecting group on a terminal, more preferably Universal Linker.

4. The biochip according to claim 2, wherein the chemical entity is a linker molecule capable of initiating a polypeptide synthesis reaction, preferably a linker molecule having a functional group reacting with an amino group on a beginning end and having a functional group coupling with carboxyl of an amino acid monomer on a terminal and capable of being dissociated when in acid treatment finally after the polypeptide synthesis reaction is finished, more preferably 4-hydroxymethyl benzoic acid.

5. The biochip according to claim 1, wherein the biochip carries a specific antigen for screening an antibody; or the biochip carries a specific antibody for detecting an antigen.

6. The biochip according to any one of claims 1~5, wherein the code is a specific characterization for the identity of the biochip, comprising a number, a symbol, a graph and/or an identification code; preferably, the code is a 2-dimensional bar code.

7. The biochip according to any one of claims 1~6, wherein  
the biochip is selected from a non-polished single-sided 2-dimensional bar code chip, a non-polished double-sided 2-dimensional bar code chip, a single-polished single-sided

2-dimensional bar code chip, a single-polished double-sided 2-dimensional bar code chip, a double-polished single-sided 2-dimensional bar code chip and a double-polished double-sided 2-dimensional bar code chip.

8. The biochip according to any one of claims 1~7, wherein the biochip has a size of less than 2 mm\*2mm, preferably 0.5 mm\*0.5mm.

9. The biochip according to any one of claims 1~8, wherein the biochip is made of a material selected from silicon wafer (silicon crystal), glass sheet (bead), ceramic, sheet metal, plastic sheet (bead), gel, nylon membrane or any combination thereof, preferably silicon wafer.

10. The biochip according to any one of claims 1~9, wherein the biochip is made of porous glass, and the porous glass has a particle size of 5  $\mu\text{m}$ ~2000  $\mu\text{m}$ ; the porous glass has a pore diameter of 200 $\text{\AA}$ -5000 $\text{\AA}$ .

11. The biochip according to any one of claims 1~10, wherein the biochip is in a form of flake, cuboid, cylinder or sphere, preferably, the biochip is in a form of square flake.

12. The biochip according to any one of claims 1~11, wherein the biochip is selected from a 100 nm silicon oxide wafer, a 300 nm silicon oxide wafer, a frosted quartz chip or a transparent quartz chip; preferably, the biochip is a transparent quartz chip.

13. The biochip according to any one of claims 1~12, wherein the biochip has a surface treated with a silanizing reagent, preferably, the silanizing reagent is selected from APTMS or APTES, more preferably, the silanizing reagent is a 50% silanizing reagent.

14. A method for preparing the biochip according to any one of claims 1~13, the method comprising the following steps:

- 1) coding the biochip;
- 2) pretreating the biochip;
- 3) performing silanization treatment on the surface of the biochip;
- 4) chemically modifying the surface of the biochip; and
- 5) optionally, detecting or quantitatively analyzing the chemical modification.

15. The method according to claim 14, wherein the pretreating comprises acid treatment, alkali treatment, ultrasonic treatment, plasma cleaning, acetone washing or a combination thereof, wherein the acid is selected from sulfuric acid, hydrochloric acid, phosphoric acid and piranha liquid, the alkali is selected from sodium hydroxide and potassium hydroxide; preferably, the pretreatment method is acid treatment followed by plasma cleaning; more preferably, the pretreatment method is sodium hydroxide treatment followed by plasma cleaning and acetone washing.

16. The method according to claim 14, wherein chemical modification on the surface of the biochip is achieved by linking the chemical entity on the surface of the biochip.

17. The method according to claim 14, wherein a 2-dimensional bar code is printed on the biochip by means of laser printing, preferably, coding is carried out using red laser through a dot 2-dimensional bar code mode.

18. The method according to claim 14, wherein silanization treatment is performed on the surface of the biochip by soaking the biochip in a silanizing reagent and carrying out ultrasonic treatment, preferably, the silanizing reagent comprises APTES and PTES.

19. The method according to claim 18, wherein the silanizing reagent is a 50% silanizing reagent.

20. Use of the biochip according to any one of claims 1~13 or the biochip prepared by using the method according to any one of claims 14~19 in synthesis of a biomacromolecule.

21. The use according to claim 20, wherein the biomacromolecule is a nucleic acid or a polypeptide.

22. Use of the biochip according to any one of claims 1~13 or the biochip prepared by using the method according to any one of claims 14~19 in antigen- or antibody detection.

23. A method for synthesizing a nucleic acid, comprising the following steps:

(1) providing the biochip according to any one of claims 1~13 or the biochip prepared by using the method according to any one of claims 14~19, wherein the code carried on the biochip corresponds to a sequence of the nucleic acid to be synthesized;

(2) providing four reaction tanks which are respectively used for addition of deoxyribonucleotides A, T, C and G or ribonucleotides A, U, C and G, and for deprotection, capping, oxidation and washing in each of the reaction tanks;

(3) recognizing the code carried on the biochip, and determining the deoxyribonucleotide or ribonucleotide to be added according to the sequence corresponding to the code, and sorting the biochips with the same deoxyribonucleotide or ribonucleotide to be added into the same reaction tank;

(4) adding a deprotection reagent in the reaction tank, soaking the biochip in the reaction tank for deprotection, and discharging the deprotection reagent after the reaction is completed;

(5) adding a coupling reagent of corresponding deoxyribonucleotide or ribonucleotide into the reaction tank, soaking the biochip in the reaction tank for coupling reaction, and discharging the coupling reagent after the reaction is completed;

(6) adding a capping reagent in the reaction tank, soaking the biochip in the reaction tank for capping reaction, and discharging the capping reagent after the reaction is completed;

(7) adding an oxidizing reagent in the reaction tank, soaking the biochip in the reaction tank for oxidizing reaction, and discharging the oxidizing reagent after the reaction is completed, thereby completing addition of one nucleotide;

(8) according to the sequence of nucleic acid to be synthesized corresponding to the code, repeating steps (3)~(7) once or more times, thereby generating a nucleic acid having a predetermined sequence on the biochip;

optionally, the method further comprises the following steps:

(9) cutting the nucleic acid from the biochip, thereby obtaining the nucleic acid.

24. The method according to claim 23, wherein before the nucleic acid synthesis and after the biochip is sorted to the reaction tank, the capping reagent is added in the reaction tank, and the biochip is soaked in the reaction tank for capping reaction.

25. The method according to claim 23 or 24, wherein a plurality of chips are simultaneously used to perform synthesis reaction.

26. A method for high-throughput screening of an antibody, wherein the method comprises the following steps:

(1) mixing a plurality of chips, wherein the chip is the biochip according to any one of claims 1~13 or the biochip prepared by the method according to any one of claims 14~19, and each chip is modified with a specific antigen and carries a unique code;

(2) soaking the plurality of chips in a sample solution to be detected and sufficiently reacting;

(3) removing the sample solution and washing the chip;

(4) recognizing the code carried on each of the chips, and separating each of the chips from each other according to the code; and

(5) desorbing the antibody binding to the chip from the antigen on the chip, and identifying to the obtained antibody.

27. A method for high-throughput detection of an antigen, comprising the following steps:

(1) mixing a plurality of chips, wherein the chip is the biochip according to any one of claims 1~13 or the biochip prepared by the method according to any one of claims 14~19, and each chip is modified with a specific antibody and carries a unique code;

(2) soaking the chip in a sample solution to be detected and sufficiently reacting;

(3) removing the sample solution and washing the chip;

(4) recognizing the code carried on each of the chips, and separating each of the chips from each other according to the code; and

(5) desorbing the antigen binding to the chip from the antibody on the chip, and identifying the obtained antigen.

28. The method according to claim 26 or 27, wherein in step (4), the biochip is sorted by recognizing the code carried on each biochip, and each chip is moved to a different reaction container through a drive device being configured to drive the movement of the chip.

29. The method according to claim 28, wherein a desorption reagent is added into the reaction container containing the sorted chip to cause desorption of the antigen and the antibody.