Currently established manufacturing processes for RNA molecules approved by regulatory authorities implement many separate manufacturing steps. Particularly, the respective manufacturing steps are performed by several different devices. Further, various separate quality controls are performed on DNA level and RNA level as described in detail in WO2016/180430A1.

A critical step in RNA production is the generation of a suitable DNA template, which at industrial scale is a major cost factor. Currently, DNA templates can only be used for a single RNA in vitro transcription reaction and need subsequently be destroyed by DNAse digestion and eventually removed by RNA purification in order to ensure efficacy and safety of the RNA-based therapeutics.

Manufacturing of RNA requires a large degree of manual handling in a GMP-regulated laboratory executed by well-trained technical staff. In consequence, current established manufacturing processes are time consuming, cost intensive, and require a lot of laboratory space and laboratory equipment.

Summary

As outlined above, there is the problem associated with common manufacturing devices and processes that RNA in vitro transcription currently requires a large degree of manual handling of well- trained technical staff. Thus, there is a need for providing an improved bioreactor for RNA in vitro transcription and an automated apparatus for RNA production to save time, space, equipment and personal.

An advantage of an improved bioreactor may be that it may allow for repetitive use of DNA templates in several RNA production processes which reduces the costs as less starting material (that is DNA template) has to be used and DNAse treatment can be omitted or substantially minimized. Moreover, an improved bioreactor may allow for the robust production of RNA with a higher purity profile (no residual DNAse, no residual DNA fragments in final RNA product). Advantages of an automated apparatus for RNA production are that the whole manufacturing process may be more robust and reliable (due to minimizing human error) and that the production of RNA may be accelerated.

Further, an acceleration of RNA manufacturing would be highly advantageous and of major importance for public health, especially in the context of pandemic scenarios. Further advantageous in that context would be the production of the RNA therapeutics in the region of the outbreak which would, however, require a portable RNA production apparatus.

The above problems are solved by the subject-matter of the independent claims, wherein further examples are incorporated in the dependent claims. It should be noted that the features of the disclosure described in the following apply equally to the bioreactor for RNA in vitro transcription, the method for RNA in vitro transcription, the module for transcribing DNA into RNA, the automated apparatus for RNA manufacturing and to the uses described herein.

In one aspect, the present disclosure refers to bioreactor (1) for RNA in vitro transcription comprising: (a) a reaction vessel (2) suitable to hold magnetic particles, DNA templates, a DNA immobilization buffer, DNA magnetic particles and an IVT master mix, wherein the DNA magnetic particles are DNA templates immobilized on the free-floating magnetic particles, and wherein the IVT master mix comprises ribonucleoside triphosphates and DNA dependent RNA polymerase, (b) a magnet unit (3) positioned at the reaction vessel, wherein the magnet unit (3) is configured to capture the magnetic particles and the DNA magnetic particles or to introduce a movement ~~of~~ into the magnetic particles and the DNA magnetic particles, wherein the magnet unit (3) is ring-shaped and encircles the reaction vessel (2).

In a first example, the present disclosure is directed to a bioreactor for RNA in vitro transcription comprising:

- a reaction vessel, and
- a magnet unit positioned at the reaction vessel.

CLAIMS

1. A bioreactor (1) for RNA in vitro transcription comprising:

(a) a reaction vessel (2) suitable to hold magnetic particles, DNA templates, a DNA immobilization buffer, DNA magnetic particles and an IVT master mix, wherein the DNA magnetic particles are DNA templates immobilized on the free-floating magnetic particles, and wherein the IVT master mix comprises ribonucleoside triphosphates and DNA dependent RNA polymerase, and

(b) a magnet unit (3) positioned at the reaction vessel,

wherein the magnet unit (3) is configured to capture the magnetic particles and the DNA magnetic particles or to introduce a movement into ~~of~~ the magnetic particles and the DNA magnetic particles~~.~~,

wherein the magnet unit (3) is ring-shaped and encircles the reaction vessel (2).

2. Bioreactor (1) according to claim 1, wherein an inner surface of the reaction vessel (2) has an ellipsoid~~,~~ or an oval inner geometry ~~or an egg-shape inner geometry~~, wherein the inner surface of the reaction vessel (2) has a shape without edges.

3. Bioreactor (1) according to claim 1 or 2, wherein the magnet unit (3) is a permanent magnet or an electromagnet movable in a longitudinal direction (362) along a longitudinal axis of the reaction vessel (2) and/or a transversal direction (363) towards and apart from the reaction vessel (2).

4. Bioreactor (1) according to one of the preceding claims, wherein the magnet unit (3) is configured to rotate around the longitudinal axis of the reaction vessel (2), and wherein a rotation direction of the magnet unit (3) is switchable during mixing.

~~5. Bioreactor (1) according to one of the preceding claims, wherein the magnet unit (3) comprises a magnetic ring (31), and wherein the magnetic ring (31) is designed to surround the reaction vessel (2).~~

~~6.~~5. Bioreactor (1) according to ~~the preceding~~ claim 1, wherein the magnetic ring (31) comprises at least a first rod (320) and a second rod (322) extending from an inner circumference (34) of the magnetic ring (31) to a centre (33) of the magnetic ring (31), so that free ends (321, 323) of the first and second rod (320, 322) face each

other, and wherein the free end (321) of first rod (320) comprises a magnet with an N pole and the free end (323) of the second rod (322) comprises a magnet with an S pole.

~~7.~~6. Bioreactor (1) according to one of the preceding claims, wherein the reaction vessel (2) is paramagnetic or is configured to allow penetration of a magnetic field for withholding magnetic particles and DNA magnetic particles on the reaction vessel wall.

~~8.~~7. Bioreactor (1) according to one of the preceding claims, wherein a mechanical motion for the reaction vessel is introduced by an orbital shaker.

~~9.~~8. Bioreactor (1) according to one of the preceding claims, wherein the reaction vessel (2) comprises at least one flow breaker (4) arranged at least partially along an inner surface (21) of the reaction vessel (2) in a longitudinal direction of the reaction vessel (2).

~~10.~~9. Bioreactor (1) according to one of the preceding claims, wherein a temperature element (5) is positioned between the inner surface (21) and the outer surface (23) of the reaction vessel (2) for adjusting a temperature of the reaction vessel (2), wherein the temperature element (5) comprises a heat exchange channel (51) at least partially helically surrounding the reaction vessel (2) in a radial direction of the reaction vessel (2).

~~11.~~10. Bioreactor (1) according to one of the preceding claims 1 to ~~9~~8, wherein the reaction vessel (2) further comprises a temperature element (5), which comprises a heating wire (54) at least partially helically surrounding the reaction vessel (2) in a radial direction of the reaction vessel (2), wherein the heating wire (54) is at least partially integrated in an outer surface of the reaction vessel (2) or at least partially coated on the outer surface of the reaction vessel (2).

~~12.~~11. Bioreactor (1) according to one of the preceding claims, wherein the reaction vessel (2) is configured for an uptake of at least 20 ml of fluid, preferably 20 ml to 100 ml or 20 ml to 50 ml of fluid.

~~13.~~12. Bioreactor (1) according to one of the preceding claims, further comprising valve means (60) with a multi position valve (62) positioned downstream a magnetic trap

(61) and configured to direct a cleaning gas or cleaning fluid through the port (24) to remove magnetic particles and DNA magnetic particles from the port (24) and/or wherein the multi position valve (62) is configured to direct a process gas or process fluid into the reaction vessel (2) to mix the DNA magnetic particles.

~~14.~~13. A method for RNA in vitro transcription, wherein the method comprises the following steps:

- providing magnetic particles, DNA templates, a DNA immobilisation buffer in a reaction vessel of a bioreactor (1) according to any one of claims 1 to 12 (S1),
- mixing the magnetic particles, the DNA templates and the DNA immobilisation buffer by means of a cooperation of the magnetic particles and a magnet unit of the bioreactor to obtain DNA magnetic particles, which are the DNA templates immobilized on the free-floating magnetic particles (S2),
- providing DNA magnetic particles and IVT master mix in the reaction vessel of the bioreactor (1), wherein the IVT master mix comprises ribonucleoside triphosphates and DNA dependent RNA polymerase,
- mixing free-floating DNA magnetic particles with the IVT master mix by means of a cooperation of the DNA magnetic particles and the magnet unit to obtain RNA (S3).

~~15.~~14. Use of a bioreactor (1) according to any one of claims 1 to ~~13~~ 12 in a method according to claim 14.

~~16.~~15. An automated apparatus for RNA manufacturing, comprising a bioreactor (1) according to any one of claims 1 to ~~13~~12, the apparatus further comprising at least one of:

- a module for DNA synthesis (T), and
- a module for RNA formulation (F).