

MIXING DEVICE AND USES THEREOF

FIELD OF THE INVENTION

5 The present invention relates to a syringe and a method of mixing low volume liquids.

BACKGROUND TO THE INVENTION

10 A syringe may be used in both medical and non-medical applications. Typically, a syringe comprises a chamber, a barrel, a plunger and a needle. Usually, the dispensed fluid is a single fluid or a mixture, in which case the syringe has a single compartment and a single needle.

15 When it has been necessary to dispense two separate and unmixed chemicals, the customary practice has been to use two separate syringes. This doubles the cost of preparing and administering the mixtures for dispensing, is worse for the environment and in certain cases doubles the pain by requiring two punctures of the patient's skin. Syringes with dual identical chambers help resolve these problems and are well known in the art. These syringes with dual identical chambers are typically used in cases
20 where two chemicals or drugs must be mixed immediately prior to the dispensing. The syringes usually have two compartments of equal volume separated by a barrier which either ruptures or opens at the time of dispensing so that the dispensed fluid is a single chemical mixture before it reaches its target point. However, the design of these syringes is usually complicated and thus expensive or the barrier which ruptures may
25 taint the mixture that is to be dispensed.

Solutions to these drawbacks to date have focused on providing more complicated syringe designs, including other features such as valves, better barriers between the two identical chambers and such. These improvements usually result in the syringe
30 being more difficult to use and/or or being more costly.

A typical mixing unit to be used in combination with a conventional syringe usually has a well into which fluids are dispensed and mixed by any means known in the art. For example, the fluids may be manually mixed using pipette action, stirring, etc., allowed
35 to mix by diffusion and/or automatically mixed with an automatic stirrer etc.,. These

mixing units known in the art usually result in high wastage of fluids during the step of mixing and/or transfer of fluids from the well to a final target point. Another drawback of the mixing units in the prior art is that the mixing is usually not optimum unless it is automatically mixed which may make the process more expensive and is more time-consuming. Also, automatic mixing is difficult with small volumes of fluids.

SUMMARY OF THE INVENTION

The present invention is defined in the appended independent claims. Some optional features of the present invention are defined in the appended dependent claims.

The syringe barrel may have a cross-section of any shape that can accommodate a plurality of chambers in any arrangement. In particular, the syringe barrel may comprise 2 to 10 chambers. Even more in particular, the syringe barrel may comprise 2, 3, 4 or 5 chambers. The chambers may be arranged adjacent to one another. In one embodiment, the chambers may be lined up beside one another within the syringe barrel. In particular, the syringe barrel may have an elliptical cross-section. An elliptical cross-section is herein defined as a rounded, oval or egg-shaped cross-section. This structure may allow for the plungers of each chamber to be arranged along a line that may easily fit along the length of a finger or part thereof that may allow for pressure to be evenly exerted on each plunger as the finger or part thereof is pushed down.

The syringe barrel may have a first end and a second end. The first end of the syringe barrel comprises the first open ends of the chambers. The second end of the syringe barrel may be configured to receive a needle. The second end of the syringe barrel may be adapted to receive a removable cap to which the needle may be attached. When the cap is removed, the syringe may be easily cleaned and reused. In another embodiment, the cap may be fixed.

The needle may be blunt or sharp. A sharp needle allows for piercing of surfaces including the skin. A blunt needle allows for release of fluids into a container (e.g. a well) without piercing the skin of a user accidentally. The syringe barrel may be adapted to comprise more than one chamber. In particular, the syringe barrel may be configured to comprise the first open ends of two chambers. This structure may prevent any fluid in

the chamber from leaking out thus reducing wastage of the fluid and increasing efficiency of any reaction and/or experiment in which the fluid may be used.

Each chamber within the syringe barrel is a hollow cylinder with the distal end open and the proximal end closed. The open distal end may be capable of receiving a plunger. The diameter of the chamber may correspond to the diameter of the plunger such that the chamber may receive the plunger in a tight fit.

In another embodiment, the chambers may be arranged within the syringe barrel to form a circular cross section. This structure may allow for the plungers to be arranged within a circle that may easily fit under a finger pulp or part thereof so that pressure may be easily and evenly spread out on each plunger when the plungers are depressed.

The volume of each chamber may be different and thus the diameter of at least two chambers within the syringe barrel may be different. In particular, the diameter of the chamber may vary depending on the volume of fluid in each chamber. More in particular, the diameter may be 0.1cm to 5cm. Even more in particular, the diameter may be 0.3cm, 0.5cm, 0.8cm, 1cm, 1.5cm or 2cm. In one embodiment, the first chamber may have a diameter of 0.5cm and the second chamber may have a diameter of 0.8cm. In another embodiment, the first chamber may have a diameter of 1cm and the second chamber may have a diameter of 1.3cm. The chamber may vary in length depending on the volume each chamber is capable of holding. In particular, the volume of the fluid in the chamber may be 10 μ l to 2ml. More in particular, the volume of the chamber may be 10 μ l, 50 μ l, 55 μ l, 95 μ l, 99 μ l, 100 μ l, 500 μ l or 1ml. The chambers, each with a different volume, allows for fluids of different amounts to be injected at the same time. For example, the first chamber may hold 1ml of fluid A and the second chamber may hold 1.5ml of fluid B. Both 1ml and 1.5ml of fluids A and B respectively may be released from the needle when the plunger is depressed. This may allow for fluid A and B to be briefly mixed before being released out of the syringe.

The closed proximal end of each chamber may further comprise an outlet. The outlet may be in fluid communication with the chamber. The outlet may be at any position on the proximal end. In one embodiment, the outlet may be at the edge of the proximal end, in the centre of the proximal end of the chamber etc. In particular, the outlet may be in fluid communication with the needle. The diameter of the outlet may vary

depending on the volume of the chamber, the viscosity of the fluid and other perimeters which may affect the speed of fluid flow. In particular, the diameter of the outlet may be 0.05cm to 1cm. More in particular, the diameter of the outlet may be 0.5cm, 0.4cm, 0.3cm or 0.1cm. In one embodiment, the outlet of each chamber may be of the same diameter. In another embodiment, the diameter of the outlet of at least two chambers may be different.

The plunger may comprise an elongate body portion, a recess along the elongate body portion and a stopper connected to the elongate body portion. The elongate body of the plunger may comprise a first end configured to enter the chamber and a second end that may comprise a holding means. The holding means may be the end arranged to be depressed by an operator of said syringe. The diameter of the elongate body portion may be complementary to the diameter of the chamber such that the plunger may fit the chamber. In one embodiment, the elongate body portion may further comprise a portion of reduced cross-sectional area configured to break upon the application of excessive axial or tensional force to the plunger rod. The diameter of the stopper may vary depending on the diameter of the chamber such that the stopper fits securely within the channel of the chamber.

In one embodiment, the holding means of each plunger may be separate such that each plunger may be depressed at different times. This arrangement may be useful when the fluids in each chamber are not to be mixed before the fluids are released from the syringe.

In another embodiment, the holding means of each plunger may be coupled to allow for both plungers to be depressed at the same time with a single finger force. This arrangement allows the fluids from the chambers to be released simultaneously thus allowing a brief mixing before the fluids exit the syringe.

The syringe may be a single use safety syringe or a multi purpose syringe. A single use syringe may have features that allow for the syringe to be used only once for health reasons and/or to prevent contamination of the fluids. The features found in a syringe that may result in it being a single use syringe may be a retractable needle, a needle that breaks after use, a plunger that is locked within the syringe once it is used and the like.

The syringe may comprise a luer taper at the outlet. The luer taper may be a luer-lok or luer-slip fitting that may be capable of connecting the syringe barrel to the needle. These fittings may allow for the fluid to pass from the chamber through the outlet and
5 out of the needle with no leakage.

In another specific expression, the present invention relates to a mixing unit comprising:

- a well with an opening adjacent to a base of the well, the opening in fluid communication with a syringe; and
- 10 - a channel configured to receive a body of the syringe.

The fluid communication may be provided by a needle of the syringe. The opening may be off centre from a vertical axis of the well. In particular, the diameter of the opening may correspond to the diameter of a tip of a needle of a syringe. This arrangement
15 allows for only the tip of the needle to enter the well via the opening and not any other part of the needle. Thus, the fluid from the needle of the syringe may be released closer to the internal wall of the well, away from the vertical axis of the well. The point of dispensing the fluid may thus be off centre from the vertical axis of the well. This arrangement may allow the fluid to produce a spiral/helical movement enabling the
20 fluids to be mixed in the well without any external mode of mixing needed.

The channel may be configured to receive a syringe of any diameter or shape. In particular, the shape of the channel may correspond with that of the body of the syringe so that the syringe may stay in place without moving and thus allowing all the fluid that
25 comes out of the needle to enter the well with minimal loss and leakage of the fluid.

The mixing unit may further comprise a needle channel adjacent to the opening capable of receiving the needle of the syringe. The diameter of the needle channel for receiving the needle of the syringe may correspond with that of the needle of the
30 syringe so that the needle may stay in place without moving. In particular, the needle channel for receiving the needle may comprise a fastening means to hold on to the needle and to keep it in position so that the tip of the needle is adjacent to the opening of the mixing unit. More in particular, the fastening means may be an elastic material capable of lining the whole or part of the needle channel. At least the part of the needle
35 channel adjacent to the opening of the mixing unit may be lined with the elastic material.

In one embodiment, the fastening means may line the circumference of the opening. In another embodiment, the fastening means may be a sleeve inserted or moulded into the needle channel or part thereof and the circumference of the opening. To this end, the internal diameter of the fastening means may represent an interference fit for the
5 needle, with the deformability of the fastening means accommodating the needle. The elastic material may be but is not limited to rubber, polypropylene, silicone, nylon, PEEK, PEBAX, polyethylene or the like.

The channel may be formed from a material that may be less elastic relative to the
10 fastening means. The relative elasticity between the materials facilitates the slight interference fit between the needle tip and the opening that creates a desired seal. The mixing unit may be made from plastic, rubber, metal or any material which may be flexible and sturdy that may not be easily punctured by the needle of the syringe and may not be easily destroyed by cleaning, heat and chemicals. More in particular, the
15 mixing unit may be made from plastic.

The well may comprise two openings, a first opening in fluid communication with a first syringe and a second opening in fluid communication with a second syringe. In particular, the first opening may be configured to receive a needle of a first syringe and
20 a second opening configured to receive a needle of a second syringe. In one embodiment, there may be at least two channels, the first channel may be configured to receive a body of the first syringe and a second channel may be configured to receive a body of the second syringe. The first syringe may be used to dispense the fluid from the first syringe into the well and the second syringe may be used to extract
25 the fluid from the well into the second syringe. The first syringe may be the syringe according to any aspect of the present invention. In this manner, the fluids from the first syringe with at least two chambers may be mixed briefly prior to being removed from the well. This arrangement may reduce the amount of fluid being lost.

30 In another embodiment, the mixing unit may comprise two wells. The well may be but not limited to conical, cylindrical, spherical, cubical, cuboidal, or pyramidal in shape. In particular, the first well may be conical in shape and the second well may be cylindrical in shape. The different shapes of the well allow for holding varying volumes thus reducing the surface area in contact with the fluid. The smaller the surface area in
35 contact with the fluid the less fluid may be left behind in the well. Some shapes of the

well for example the conical shape, may also be more useful in accommodating a tip of a pipette for extracting the fluid.

5 In one specific expression, the present invention relates to a mixing apparatus comprising a mixing unit according to any aspect of the present invention and a syringe. The syringe may be the syringe according to any aspect of the present invention. The mixing apparatus may be small and compact thus allowing it to be easily carried around and used readily.

- 10 In another specific expression, the present invention relates to a method of diagnosis of a disease in a subject, the method comprising:
- (a) providing a sample from a subject into the well of the mixing apparatus according to any aspect of the present invention;
 - (b) using the syringe of the mixing apparatus to introduce a fluid into the well;
 - 15 (c) detecting a signal produced by the interaction between the fluid and the sample;
 - (d) comparing the signal with that of a control, a difference in signal indicating the presence of the disease in the subject.

- 20 In another specific expression, the present invention relates to a method of detecting and/or quantitating the presence of, or predisposition to, and/or severity of a proliferative cell disorder in a subject, the method comprising:
- (a) providing a cyst fluid sample from a subject into the well of the mixing apparatus according to any aspect of the present invention;
 - (b) using the syringe of the mixing apparatus to introduce a fluid into the well;
 - 25 (c) determining the expression of haptoglobin protein, derivative, mutant and/or fragment thereof; and
 - (d) comparing the expression of the haptoglobin protein, derivative, mutant and/or fragment thereof with that of a control, a difference in expression indicating the presence of, or predisposition to, and/or severity of a proliferative cell disorder in the
 - 30 subject.

The control may be at least one subject not diagnosed with the cell proliferative disorder. The proliferative cell disorder may be a cancer. In particular, the proliferative cell disorder may be ovarian cancer.

In another specific expression, the present invention relates to a kit comprising the mixing apparatus according to any aspect of the present invention and instructions for use. The kit may further comprise the fluids to be used together with the apparatus.

- 5 As will be apparent from the following description, preferred embodiments of the present invention allow an optimal use of both syringe and mixing unit to take advantage of the structure and compactness and ease of use of both syringe and mixing unit where desired. This and other related advantages will be apparent to skilled persons from the description below.

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BRIEF DESCRIPTION OF THE FIGURES

Preferred embodiments of the syringe and mixing device will now be described by way of example with reference to the accompanying figures in which:

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Figure 1A is a side view of one embodiment of the syringe,

Figure 1B is a detailed side view of the syringe of Figure 1A with the internal components shown,

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Figure 2 is a side view of one embodiment of the syringe with the removable cap separated from the main body of the syringe (syringe barrel),

Figure 3A is a magnified view of the lower, needle part of the syringe with the removable cap separated from the main body of the syringe (syringe barrel),

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Figure 3B is a plan view of the lower, needle part of the syringe,

Figure 4 is a cross sectional view of the syringe showing the flow path of fluid A (light grey) and fluid B (black),

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Figure 5A is a perspective view of one embodiment of the mixing unit,

Figure 5B is a perspective view of the mixing unit of Figure 5A with the internal components shown in detail,

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Figure 5C is a top view of the mixing unit of Figure 5A,

Figure 6A is a perspective view of two wells of one embodiment of the mixing unit,

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Figure 6B is a cross-sectional view of the two wells shown in Figure 6A,

Figure 7 is a magnified view of the needle showing the swirl motion created by the fluids,

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Figure 8 is cross-sectional view of a well of one embodiment of the mixing unit showing the position of an opening adjacent to a base of the well to receive a needle of a syringe and the swirl motion created by the release of fluids from the needle;

15 Figure 9 is cross-sectional view of one embodiment of a mixing apparatus comprising at least two syringes and a mixing unit with two wells.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

20 Figures 1A and B show one embodiment of syringe 2 of the invention with an elliptical cross-section. The syringe 2 is a double chambered syringe comprising a syringe barrel 8, two chambers 10, 12 arranged within the barrel 8 and two plungers 4, 6, the first plunger 4 for movement within the first chamber 10 and the second plunger 6 for movement within the second chamber 12. The volume of the first chamber 10 is different from the volume of the second chamber 12. In particular, the volume of the first chamber is about 50 μ l and the volume of the second chamber 12 is 90 μ l. Each chamber 10, 12 comprises a first open end and a second closed end. The first open end of the chamber 10, 12 may be capable of contact with a plunger 4, 6 respectively. The second closed end of the chamber 10, 12 comprises an outlet 18, 20. The first outlet 18 is in fluid motion with the first chamber 10 and the second outlet 20 is in fluid motion with the second chamber 12. A needle 24 embedded within a removable cap 26 is attached to the end of the syringe barrel 8. Figure 2 shows the syringe 2 with the removable cap 26 separated from the syringe 2. Figure 3A is a magnified diagram of the removable cap 26. The syringe 2 is made from plastic for its durability and because it is cheap to manufacture.

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The first and second plunger 4, 6 have a first end configured to enter the chamber and a second end comprising a holding means 3. The holding means are two separate flat surfaces 3, each surface capable of receiving at least one finger or part thereof.

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When in use, fluid A 14 and fluid B 16 are placed in the first chamber 10 and the second chamber 12 respectively. The volume of fluid A 14 required in the experiment/reaction in which the chamber 10 is used is less than fluid B 16. The first plunger 4 within the first chamber 10 and the second plunger 6 within the second chamber 12 are pressed to produce a pressure that pushes the fluid A 14 and fluid B 16 out of the first outlet 18 and the second outlet 20 respectively. The two fluids 14, 16 come in contact for the first time at the entrance 22 of the needle 24. The flow path of fluid A 14 and fluid B 16 is shown in Figure 4. The lighter grey broken line shows the flow path of fluid A and the black broken line shows the flow path of fluid B from the chambers 10, 12 respectively to the entrance 22 of the needle 24 and into the needle 24 where they mix. The swirl motion created by the fluids 14, 15 allowing the fluids to briefly mix before the mixed fluid exits the needle 24 is shown in Figure 7.

Figures 5A, B and C show one embodiment of the mixing unit 100 comprising two wells 102, 104 with one opening 106, 108 adjacent to a base of each well 102, 104. The opening 106, 108 is configured to receive a tip of a needle of any syringe. The mixing unit 100 further comprises two channels 110, 112 each configured to receive a body of a syringe. The mixing unit 100 also has two needle channels 114, 116 adjacent to the opening 106, 108 that is configured to receive the remaining portion of the needle (besides the tip) of the syringe. The diameter of the opening 102, 104 corresponds to the diameter of a tip of a needle of a syringe. For example, the mixing unit 100 comprises well A 102, which comprises opening A 106 configured to receive a tip of a needle of a first syringe and a first needle channel 114 to receive the needle of the first syringe and a first body channel 110 to receive the body of the first syringe. The mixing unit 100 also comprises well B 104, which comprises opening B 108 configured to receive a tip of a needle of a second syringe and a second needle channel 116 to receive the needle of the second syringe and a second body channel 112 to receive the body of the second syringe. The ends of the needle channels 114, 116 adjacent to the openings 102, 104 are lined with an elastic material, polypropylene on the inside of the channels 114, 116. The relative elasticity between the needle channel and the

elastic material facilitates the slight interference fit between the needle tip and the openings 102, 104 that creates a desired seal. The well A 102 is conical in shape and the well B 104 is cylindrical in shape. This allows for the well to receive different volumes of fluids. In particular, as shown in Figure 6B, well A 102 is designed to have a top diameter of about 6.5mm, a bottom diameter of about 1.5mm and a depth of about 15.0mm allowing well A 102 to accommodate 140µl of fluid at any one time. Well B 104 is designed to have a top diameter of about 6.0mm, a bottom diameter of about 5.0mm and a depth of about 15.0mm allowing well B 104 to accommodate 250µl of fluid at any one time.

The position of the openings 106, 108 in the well 102, 104 allows for dispensing fluid from the syringe into the well 102, 104 wherein the point of dispensing is off centre from the vertical axis of the well 102, 104. This positioning allows for a swirl motion to be created as shown in Figure 8 by the release of fluids from the needles into the wells 102, 104 and mixing takes place. The mixing unit 100 is made from plastic for its durability and ease in moulding.

Figure 9 is a schematic showing one embodiment of a mixing apparatus. The wells 102, 104 of the mixing unit 100 and two syringes to be used in conjunction with the mixing unit are shown. One syringe 2 is the syringe as described above and the other syringe has both chambers of equal volume. Each syringe comprises a first and second plunger 4, 6 having a holding means 3 that is coupled to form a single separate flat surface 3 capable of receiving at least one finger or part thereof. The mixing apparatus may be small and compact thus allowing it to be easily carried around and used readily.

The foregoing describes preferred embodiments, which, as will be understood by those skilled in the art, may be subject to variations or modifications in design, construction or operation without departing from the scope of the claims.

For example, although the cap is shown to be removable, it does not have to be and can be fixed to the syringe. The precise dimensions of the syringe and wells of the mixing unit may be tailored for certain applications, such that a larger volume may be received by the chambers of the syringe and/or the mixing well instead of the preferred embodiment described. Similarly, the shapes of the wells need not be only conical and

cylindrical as illustrated. Also, in the mixing apparatus, one syringe having two chambers of different volumes and another syringe having chambers of equal volumes is not essential. Both the syringe may have chambers of different volumes. Similarly, the number of chambers in each syringe may not be only 2 as illustrated. Each syringe
5 may have 3, 4 or 5 chambers depending on the application (e.g. the number of fluids/reagents required in the experiment/application). Where necessary or desired, the number of chambers of the syringe may vary and the optional accompanying mixing unit may be adapted to accommodate the syringe. Skilled persons may also adapt the syringe, mixing unit and mixing apparatus accordingly for use in different
10 applications. These variations, for instance, are intended to be covered by the scope of the claims.

CLAIMS

1. A syringe comprising:
 - a syringe barrel,
 - 5 - at least two chambers arranged within the barrel, wherein the volume of each chamber is different and each chamber comprises a first open end and a second closed end, the first open end capable of contact with a plunger and the second closed end comprising an outlet; and
 - 10 - at least two plungers, the first plunger for movement within the first chamber and the second plunger for movement within the second chamber.
2. The syringe according to claim 1, further comprising a third chamber arranged within the barrel, said chamber having a first open end and a second closed end, the first open end capable of contact with a third plunger and the second closed end comprising an outlet and the third plunger for movement within the third chamber.
3. The syringe according to either claim 1 or 2, wherein the volume of the chambers is 10 μ l to 20ml.
4. The syringe according to any one of the preceding claims, wherein the volume of the chambers is 10 μ l to 100 μ l.
5. The syringe according to any one of the preceding claims, wherein the cross section of the syringe barrel has a circular or elliptical shape.
6. The syringe according to any one of the preceding claims, wherein the plungers are coupled at an end arranged to be depressed by an operator of said syringe.
7. The syringe according to any one of claims 1 to 5, wherein the plungers are separate at an end arranged to be depressed by an operator of said syringe.
8. The syringe according to any one of the preceding claims, wherein the syringe is a single use safety syringe.

9. The syringe according to any one of the preceding claims, wherein the syringe comprises a luer lock at the outlet.
10. A mixing unit comprising:
- 5 - a well with an opening adjacent to a base of the well, the opening in fluid communication with a syringe; and
- a channel configured to receive a body of the syringe.
11. The mixing unit according to claim 10, wherein the fluid communication is
- 10 provided by a needle of the syringe.
12. The mixing unit according to either claim 10 or 11, wherein the opening is off centre from a vertical axis of the well.
13. The mixing unit according to any one of claims 10 to 12, wherein the diameter
- 15 of the opening corresponds to the diameter of a tip of a needle of the syringe.
14. The mixing unit according to any one of claims 10 to 13, wherein the well
- comprises two openings, a first opening in fluid communication with a first
- 20 syringe and a second opening in fluid communication with a second syringe.
15. The mixing unit according to claim 14, comprising at least two channels, the first
- channel configured to receive a body of the first syringe and a second channel
- configured to receive a body of the second syringe.
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16. The mixing unit according to any one of claims 10 to 15, wherein the unit
- comprises two wells.
17. The mixing unit according to claim 16, wherein the first well is conical in shape
- 30 and the second well is cylindrical in shape.
18. A mixing apparatus comprising a mixing unit according to any one of 10 to 17 and a syringe.

19. The mixing apparatus according to claim 18, wherein the syringe is a syringe according to any one of claims 1 to 9.

20. A method of diagnosis of a disease in a subject, the method comprising:

- 5 (a) providing a sample from a subject into the well of the mixing apparatus according to either one of claims 18 or 19;
- (b) using the syringe of the mixing apparatus to introduce a fluid into the well;
- 10 (c) detecting a signal produced by the interaction between the fluid and the sample;
- (d) comparing the signal with that of a control, a difference in signal indicating the presence of the disease in the subject.

21. A method of detecting and/or quantitating the presence of, or predisposition to, and/or severity of a proliferative cell disorder in a subject, the method comprising:

- 15 (a) providing an ovarian cyst fluid sample from a subject into the well of the mixing apparatus according to either one of claims 18 or 19;
- (b) using the syringe of the mixing apparatus to introduce a fluid into the well;
- 20 (c) determining the expression of haptoglobin protein, derivative, mutant and/or fragment thereof; and
- (d) comparing the expression of the haptoglobin protein, derivative, mutant and/or fragment thereof with that of a control, a difference in expression
- 25 indicating the presence of, or predisposition to, and/or severity of a proliferative cell disorder in the subject.

22. The method according to claim 21, wherein the control is at least one subject not diagnosed with the cell proliferative disorder.

23. The method according to either one of claims 21 or 22, wherein the proliferative cell disorder is a cancer.

24. The method according to either claim 21 or 22, wherein the proliferative cell disorder is ovarian cancer.

25. A kit comprising the mixing apparatus according to either one of claims 18 or 19 and instructions for use.