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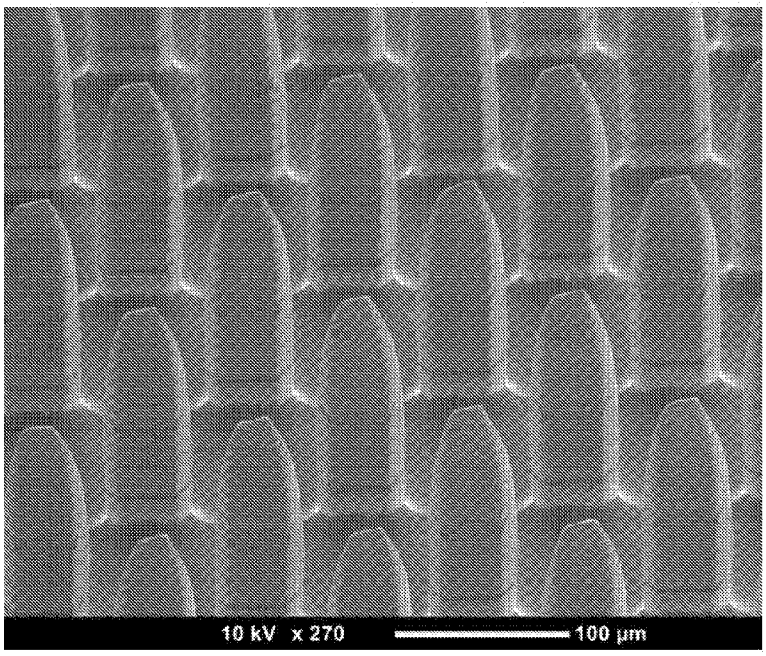


Fig. 1

(57) Abstract: A microprojection array comprising a substrate with a plurality of microprojections protruding from the substrate wherein the microprojections have a tapering hexagonal shape and comprise a tip and a base wherein the base has two substantially parallel sides with a slight draught angle of approximately 1 to 20 degrees up to a transition point at which point the angle increases to from about 20 degrees to about 70 degrees.

WO 2017/045031 A1

MICROPROJECTION ARRAYS WITH MICROPROJECTIONS HAVING LARGE SURFACE AREA PROFILES

Background of the Invention

[0001] The invention is generally directed to devices and methods for intradermal delivery of active agents into the skin, more particularly, the invention is directed to devices and methods for improving the immunogenicity of vaccine preparations by intradermal delivery of the vaccine via a microprojection array in which the geometry of the projections have been designed to improve skin penetration.

Description of the Prior Art

[0002] In recent years, attempts have been made to devise new methods of delivering drugs and other bioactive materials, for vaccination and other purposes, which provide alternatives that are more convenient and/or enhanced in performance to the customary routes of administration such as intramuscular and intradermal injection. Limitations of injection include: cross-contamination through needle-stick injuries in health workers; injection phobia from a needle and syringe; and most importantly, as a result of its comparatively large scale and method of administration, the needle and syringe cannot target key cells in the outer skin layers. This is a serious limitation to many existing and emerging strategies for the prevention, treatment and monitoring of a range of untreatable diseases.

[0003] In response to the problems of needle and syringe, multiple devices and methods were developed to deliver active agents intradermally. Depending on the device the desired active agent can be applied either as a liquid formulation or as solid, powdered vaccine particles. The process of intradermal injection employs micron-sized needles that are inserted 1.5mm perpendicularly into the skin, and which inject approximately 100-200µl of a liquid vaccine formulation into the dermal skin layers. Microneedle arrays are made of coated solid microneedles or biodegradable microneedles. These are inserted into the dermal layers of the skin where either the coating is dissolved, or the microneedle itself dissolves in place.

[0004] In particular, the delivery of vaccines intradermally has presented challenges as the question of the ideal immune targeting location in the skin remains the subjection of debate.

For example, Langerhans cells in the viable epidermis were considered to be immune cells until recently, however the prevailing thought is that these cells are tolerogenic (Romani, et al., J. Invest. Dermatol (2012) 132, 872). Intradermal injection is routinely shown to elicit strong immune responses and microprojection arrays such as the Nanopatch™ have demonstrated that reduced dosing utilizing these devices may be as effective as large dose intramuscular injection (Fernando, et al. PLos One (2010) 5, e10266). In addition to questions surrounding the ideal immune targeting location in the skin, the level of cellular/tissue damage caused by microprojection arrays is also an issue. This damage may be a large contributing factor to the immune response and the appropriate level of damage is an issue that is being explored. The mechanism of delivery of microprojection arrays to the skin also affects the level of cellular/tissue damage caused by microprojection arrays. Finally, due to the disparity in the mechanical modulus of the skin's constituent layers precise delivery of microprojection arrays to a targeted depth in the skin can be challenging.

[0005] There have been various approaches to optimizing the microneedle arrays and the methods by which they are made. Ceyssens et al., Fabrication process for tall, sharp, hollow high aspect ratio polymer microneedles on a platform, J. Micromech. and Microeng. 23 (2013) 075023 describes a process based on a combination of molding and UV lithography yielding hollow needles with record aspect ratio and sharpness that are monolithic with a platform, and feature a maximum needle length of over one millimeter while at the same time being suitable for mass fabrication. US Patent Publication No. 2009/0292254 disclose biocompatible and biodegradable microneedles having various shapes and geometries. US Patent No. 7,497,980 describes the manufacture of moulds for microneedles arrays are triangular as well as pyramidal and include microneedles that are solid as well as those through which a channel courses or those with grooves carved therein. US Patent No. 7,591,806 describes microblades or microdevices that are used as biological delivery devices that will puncture the skin. US Patent No. 6,537,264 discloses blade-type microneedles that are used to sample bodily fluids. US Patent Publication No. 2007/0293815 discloses microprojection arrays for penetrating the skin and delivering a vaccine. US Patent No. 8,414,548 describes microneedles that are formed from cutting metal with a laser and then bending the metal to form the microneedles. Prausnitz, M.R., Coated Microneedles for Transdermal Delivery, J. Controlled Release Soc. 117.2 (2007) 227-237 describe the use of

sheet metal to fashion microneedles. US Patent Publication No. 2011/0021996 describes a microneedle array in which the microneedles have a conduit through which an active substance can be inserted into a body through the skin.

[0006] High density arrays require more energy to penetrate the skin than lower density arrays and thus modification to the shape, structure and geometry of the microprojections may be required to generate an efficient skin puncture that permits penetration of the microprojections to a greater depth within the skin. Therefore, there is a need to construct microprojection arrays with appropriate microprojection geometry coupled with an understanding of the mechanical parameters of vaccine placement, skin puncture and mechanically induced cellular damage so that a more efficient system of delivering vaccine to the skin may be provided. The microprojection arrays of the present invention provide devices with greater vaccine loading and delivery than previous designs with more precise targeting within the skin.

[0007] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that the prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Summary of the Present Invention

[0008] In a broad form the present invention seeks to provide a microprojection array comprising a substrate with a plurality of microprojections protruding from the substrate wherein the microprojections have a tapering hexagonal shape and comprise a tip and a base wherein the base has two substantially parallel sides with a slight draught angle of approximately 1 to 20 degrees up to a transition point at which point the angle increases to from about 20 degrees to about 70 degrees.

[0009] Typically the substrate is at least one of:

a) solid;

b) non-porous; and

c) non-hollow.

[0010] Typically the microprojection array includes a number of microprojections arranged in a line.

[0011] Typically the line is at least one of:

a) a straight line;

b) a curved line; and,

c) a circular line extending circumferentially around an axis.

[0012] Typically at least some of the microprojections in a line have a common base.

[0013] Typically the microprojection array includes a number of spaced apart lines.

[0014] Typically the spacing of the microprojections between adjacent lines is at least one of:

a) less than 200 μm;

b) less than 150 μm; and,

c) about 100 μm.

[0015] Typically the spacing between successive microprojections is at least one of:

a) less than 200 μm;

b) less than 150 μm;

c) less than 100 μm; and,

d) about 80 μm.

[0016] Typically the tip of each microprojection terminates in an elongate edge.

[0017] Typically the tip has a width of from about 1 μm to about 2 μm and a length of about 20 μm to about 2mm

[0018] Typically the tip has a width of about 1 μm and a length of about 20 μm.

[0019] Typically the base has a length of from about 30 μm to about 2 mm.

[0020] Typically the base has a length of about 80 μm.

[0021] Typically the base is greater in length than the tip.

[0022] Typically the base has a thickness of about 5μm to 50μm.

[0023] Typically the base has a cross sectional length:thickness aspect ratio of about 2:1 to 5:1.

[0024] Typically at least one of the microprojections is coated with a vaccine antigen.

[0025] Typically the amount of the vaccine antigen is about 10 ng to about 10 μg.

[0026] Typically the amount of vaccine antigen is about 10% to about 50% less than the amount of vaccine antigen delivered by intramuscular administration.

[0027] Typically the administration of the vaccine antigen provides a greater immunogenic response when administered to a human than a comparable amount of vaccine antigen administered by intramuscular injection.

[0028] Typically the administration of the vaccine antigen provides a greater immunogenic response when administered to a human than a comparable amount of vaccine antigen administered with a microprojection array with conical or cylindrical microprojections.

[0029] Typically the microprojections have an effective cross-sectional area which is unchanged by the addition of the coating.

[0030] In another broad form the present invention seeks to provide a method of administering a vaccine to a human comprising applying the microprojection array as described above to a human's skin.

[0031] Typically the microprojection array includes a number of microprojections arranged in a line, and wherein the method includes applying the microprojection array to a human's skin in a direction of movement including a component of movement aligned with the line.

[0032] Typically the line is a straight line and the method includes applying the microprojection array to the skin in a direction perpendicular to the skin and laterally parallel to the skin in the direction of the line.

[0033] Typically the line extends circumferentially around an axis and the method includes applying the microprojection array to the skin in a direction perpendicular to the skin whilst rotating the microprojection array around the axis.

[0034] In yet another broad form the present invention seeks to provide a microprojection array comprising a substrate with a plurality of microprojections protruding from the substrate wherein the microprojections have a tapering octagonal shape and comprise a tip and a base wherein the base has two substantially parallel sides with a slight draught angle of approximately 1 to 20 degrees up to a transition point at which point the angle increases to from about 20 degrees to about 70 degrees.

[0035] Typically the substrate is at least one of:

a) solid;

b) non-porous; and

c) non-hollow.

[0036] Typically the microprojection array includes a number of microprojections arranged in a line.

[0037] Typically the line is at least one of:

a) a straight line;

b) a curved line; and,

c) a circular line extending circumferentially around an axis.

[0038] Typically at least some of the microprojections in a line have a common base.

[0039] Typically the microprojection array includes a number of spaced apart lines.

[0040] Typically the spacing of the microprojections between adjacent lines is at least one of:

a) less than 200 μm;

b) less than 150 μm; and,

c) about 100 μm.

[0041] Typically the spacing between successive microprojections is at least one of:

a) less than 200 μm;

b) less than 150 μm;

c) less than 100 μm; and,

d) about 80 μm.

[0042] Typically the tip of each microprojection terminates in an elongate edge.

[0043] Typically the tip has a width of from about 1 μm to about 2 μm and a length of about 20 μm to about 2mm.

Brief Description of the Drawings

[0044] An example of the present invention will now be described with reference to the accompanying drawings, in which: -

[0045] Figure 1 is an SEM image of one embodiment of uncoated microprojections of the present invention;

[0046] Figure 2 is an image of skin stained to show live (green) and dead (magenta) cells following administration of one embodiment of microprojections of the present invention;

[0047] Figure 3 is a plot of anti-Influenza antibody levels of sera from C57BL/6 mice determined by indirect ELISA plotted as 50% titers;

[0048] Figure 4 is a plot of day 21 IgG Titers for 5ng, 50 ng and 500 ng influenza doses administered intramuscularly, intradermally and by microprojection array TP and NP;

[0049] Figure 5A is a schematic plan view of an example of a microprojection array;

[0050] Figure 5B is a schematic front view of a line of microprojections of the microprojection array;

[0051] Figure 6A is a schematic front view of an example of a microprojection;

[0052] Figure 6B is a schematic side view of the microprojection; and,

[0053] Figure 6C is a schematic plan view of the microprojection.

Detailed Description of the Preferred Embodiments

[0054] The present invention relates to microprojection arrays where the microprojection design provides an alternative mode of skin puncture and vaccine delivery into the skin. The microprojections of the present invention are designed to have a large surface area to frontal profile design while maintaining a high density of microprojections on the array. The microprojection arrays of the present invention have a plurality of microprojections that are located upon a base. In one embodiment the microprojection have a shape that from a top down perspective is approximately an extended octagon. In another embodiment the microprojections have a shape that from a top down perspective is approximately an extended hexagon with two parallel sides being extended to give a rectangular profile with triangular ends (Figure 1). The microprojections may be aligned in parallel lines with spacing between the edges of the microprojections. The microprojections may extend vertically to a length that will provide for drugs or vaccines to be delivered to the desired location within the skin. The microprojections of the microprojection arrays of the present invention may be solid or non-porous or contain hollow portions therein. In some embodiments the microprojections are solid and non-porous and do not contain any hollow portion therein. In preferred embodiments the devices of the present invention do not contain reservoirs.

[0055] At least a portion of the projections may be coated. Accordingly, one way of providing material for delivery to the biological subject is by providing the material within the coating. For example, the coating may include a vaccine for providing an immunological response within the subject. The coating may be provided in liquid or non-liquid forms, and may further include ingredients other than the material to be delivered, such as an adjuvant. Suitable coating formulations for use with projections patches and methods of applying such coatings to the projections are known, as described, for example, in WO/2010/042996 and WO/2009/079712.

[0056] Although any type of coating may be used, particularly advantageous embodiments of the microprojection arrays are provided with at least a portion of the projections coated with a non-liquid coating. In this regard, the term "non-liquid" coating will be understood to include a coating that is applied in a liquid form and allowed to dry or otherwise solidify to thereby form a non-liquid coating.

[0057] The non-liquid coating may act as an additional substantially solid layer of material which can be used to even further adjust the geometry of the projections by optionally causing the projections to have an effective profile of a different shape to the underlying uncoated profile of the projections as initially fabricated.

[0058] The microprojections of the present invention are less sensitive to coating thickness as it relates to skin penetration. In a standard conical projection the thickness of the coating affects the cross-sectional area of the microprojection thereby affecting the ability of the microprojection to penetrate the skin at a given velocity. In the microprojections of the present invention the effective cross-sectional area is little changed by the addition of the coating, thus the velocity required for skin penetration is relatively constant.

[0059] The microprojection arrays have a substrate with a plurality of microprojections protruding from the substrate wherein the microprojections have a tapering hexagonal shape and comprise a tip and a base wherein the base has two substantially parallel sides with a slight draught angle of approximately 1 to 20 degrees up to a transition point at which point the angle increases to from about 20 degrees to about 70 degrees. In an alternate embodiment the ends of the microprojections may be blunted to provide an extended octagonal profile. While the profiles of the microprojections of the present invention may define extended hexagonal or octagonal shapes the edges of the profiles may be somewhat rounded depending on the method of manufacture of the microprojections and microprojection arrays.

[0060] The draught angle may be between about 0 to 30 degrees or about 0 to 25 degrees or about 0 to 20 degrees or about 0 to 15 degrees or about 0 to 10 degrees, or about 1 to 30 degrees or about 1 to 25 degrees or about 1 to 20 degrees or about 1 to 15 degrees or about 1 to 10 degrees, or about 2 to 30 degrees or about 2 to 25 degrees or about 2 to 20 degrees or about 2 to 15 degrees or about 2 to 10 degrees, about 3 to 30 degrees or about 3 to 25 degrees or about 3 to 20 degrees or about 3 to 15 degrees or about 3 to 10 degrees, about 4 to 30 degrees or about 4 to 25 degrees or about 4 to 20 degrees or about 4 to 15 degrees or about 4 to 10 degrees, or about 5 to 30 degrees or about 5 to 25 degrees or about 5 to 20 degrees or about 5 to 15 degrees or about 5 to 10 degrees.

[0061] The transition point angle may be between about 20 to 70 degrees or about 20 to 65 degrees or about 20 to 60 degrees or about 20 to 55 degrees or about 20 to 50 degrees, or about 20 to 45 degrees or about 20 to 40 degrees or about 20 to 35 degrees or about 20 to 30 degrees or about 20 to 25 degrees, about 25 to 70 degrees or about 25 to 65 degrees or about 25 to 60 degrees or about 25 to 55 degrees or about 25 to 50 degrees, about 25 to 45 degrees or about 25 to 45 degrees or about 25 to 40 degrees or about 25 to 35 degrees or about 25 to 30 degrees, or about 30 to 70 degrees or about 30 to 65 degrees or about 30 to 60 degrees or about 30 to 55 degrees or about 30 to 50 degrees or about 30 to about 45 degrees or about 30 to about 40 degrees or about 30 to about 35 degrees. In preferred embodiments the transition point angle will be greater than the draught angle.

[0062] A sharp blade-like tip will allow for enhanced penetration of the microprojections into the skin while also generating an enhanced localized cell death/bystander interaction in the skin with a different profile than conical microprojection arrays. The sharp blade-like tips of the microprojections may also increase the level of danger signals and antigen to more live cells thereby increasing the physical adjuvant effect of microprojections and thereby improving immune responses. On a micro-scale, skin puncture is a function of crack formation in the skin and the subsequent expansion of these cracks. While high density microprojection arrays have each individual microprojection initiating a crack (which absorbs substantial energy), the microprojection arrays of the present invention provide a line of contact rather than a single point of contact. Thus, once the crack begins to form the microprojections may enter the skin more easily allowing internal skin surface area contract with the penetrating surface. Significantly more surface area of the protrusion can enter the skin without a large increase in energy. The microprojection profile of the microprojection arrays of the present invention is wider and thinner than current conical or circular microprojection profiles. The microprojection arrays of the present invention reduce the number of penetrations made upon entry to the skin, increase the area of the microprojection in the skin and exploit surface crack propagation to enhance overall penetration and reduce the overall energy required to puncture the skin. The microprojection array may be delivered to the skin surface by an applicator. Due to the unique design of the microprojections of the present invent invention the amount of energy required to penetrate the skin will be much less than that of other microprojection arrays. The microprojection arrays may be delivered

by direct vertical application onto skin or a lateral movement on skin which will allow the blades of the microprojections to cut the skin.

[0063] While penetration of the skin by microprojections causes cell death, the microprojection arrays of the present invention provide a higher level of cell death per projection than the standard conical microprojection and generate significantly improved immune responses compared to the standard conical microprojection. Therefore, the microprojections of the present invention provide an increased and controlled physical adjuvantation effect in the skin thereby significantly improving immunogenicity.

[0064] The tip of the microprojections of the present invention may have a width of about 0.5μm, or about 1.0μm, or about 1.5μm, or about 2.0μm, or about 2.5μm, or about 3.0μm, or about 3.5μm, or about 4.0μm, or about 4.5μm, or about 5.0μm. The tip of the microprojections of the present invention may have a width of from about 0.5μm to about 5.0μm, or from about 0.5μm to about 4.5μm, or from about 0.5μm to about 4.0μm, or from about 0.5μm to about 3.5μm, or from about 0.5μm to about 3.0μm, or from about 0.5μm to about 2.5μm, or from about 0.5μm to about 2.0μm, or from about 0.5μm to about 1.5μm, or from about 0.5μm to about 1.0μm, or from about 1.0μm to about 5.0μm, or from about 1.0μm to about 4.5μm, or from about 1.0μm to about 4.0μm, or from about 1.0μm to about 3.5μm, or from about 1.0μm to about 3.0μm, or from about 1.0μm to about 2.5μm, or from about 1.0μm to about 2.0μm, or from about 1.0μm to about 1.5μm, or from about 1.5μm to about 5.0μm, or from about 1.5μm to about 4.5μm, or from about 1.5μm to about 4.0μm, or from about 1.5μm to about 3.5μm, or from about 1.5μm to about 3.0μm, or from about 1.5μm to about 2.5μm, or from about 1.5μm to about 2.0μm, or from about 2.0μm to about 5.0μm, or from about 2.0μm to about 4.5μm, or from about 2.0μm to about 4.0μm, or from about 2.0μm to about 3.5μm, or from about 2.0μm to about 3.0μm, or from about 2.0μm to about 2.5μm, or from about 2.5μm to about 5.0μm, or from about 2.5μm to about 4.5μm, or from about 2.5μm to about 4.0μm, or from about 2.5μm to about 3.5μm, or from about 2.5μm to about 3.0μm.

[0065] The tip of the microprojections of the present invention may have a length of about 20μm, or about 30μm, or about 40μm, or about 50μm, or about 60μm, or about 70μm, or about 80μm, or about 90μm, or about 100μm, or about 150μm, or about 200μm, or about

250μm, or about 500μm, or about 1000μm, or about 1500μm, or about 2000μm. The tip of the microprojections of the present invention may have a length of from about 10μm to about 2mm, or from about 10μm to about 1.5mm, or from about 10μm to about 1mm, or from about 10μm to about 900μm, or from about 10μm to about 800μm, or from about 10μm to about 700μm, or from about 10μm to about 600μm, or from about 10μm to about 500μm, or from about 10μm to about 400μm, or from about 10μm to about 300μm, or from about 10μm to about 200μm, or from about 10μm to about 100μm, or from about 10μm to about 90μm, or from about 10μm to about 80μm, or from about 10μm to about 70μm, or from about 10μm to about 60μm, or from about 10μm to about 70μm, or from about 10μm to about 60μm, or from about 10μm to about 50μm, or from about 10μm to about 40μm, or from about 10μm to about 30μm, or from about 10μm to about 20μm, or from about 20μm to about 2mm, or from about 20μm to about 1.5mm, or from about 20μm to about 1mm, or from about 20μm to about 900μm, or from about 20μm to about 800μm, or from about 20μm to about 700μm, or from about 20μm to about 600μm, or from about 20μm to about 500μm, or from about 20μm to about 400μm, or from about 20μm to about 300μm, or from about 20μm to about 200μm, or from about 20μm to about 100μm, or from about 20μm to about 90μm, or from about 20μm to about 80μm, or from about 20μm to about 70μm, or from about 20μm to about 60μm, or from about 20μm to about 70μm, or from about 20μm to about 60μm, or from about 20μm to about 50μm, or from about 20μm to about 40μm, or from about 20μm to about 30μm, about 30μm to about 2mm, or from about 30μm to about 1.5mm, or from about 30μm to about 1mm, or from about 30μm to about 900μm, or from about 30μm to about 800μm, or from about 30μm to about 700μm, or from about 30μm to about 600μm, or from about 30μm to about 500μm, or from about 30μm to about 400μm, or from about 30μm to about 300μm, or from about 30μm to about 200μm, or from about 30μm to about 100μm, or from about 30μm to about 90μm, or from about 30μm to about 80μm, or from about 30μm to about 70μm, or from about 30μm to about 60μm, or from about 30μm to about 70μm, or from about 30μm to about 60μm, or from about 30μm to about 50μm, or from about 30μm to about 40μm.

[0066] The base of the microprojections of the present invention may have a length of about 25μm, or about 30μm, or about 35μm, or about 40μm, or about 45μm, or about 50μm, or about 55μm, or about 60μm, or about 65μm, or about 70μm, or about 75μm, or about 80μm,

or about 85μm, or about 90μm or about 100μm or about 200μm, or about 300μm, or about 350μm, or about 400μm, or about 450μm, or about 500μm, or about 550μm, or about 600μm, or about 650μm, or about 700μm, or about 750μm, or about 800μm, or about 850μm, or about 900μm or about 1000μm or about 1500 μm or about 2000 μm. The base of the microprojections of the present invention may have a length of from about 30μm to about 2mm, or from about 30μm to about 1.5mm, or from about 30μm to about 1mm, or from about 30μm to about 900μm, or from about 30μm to about 800μm, or from about 30μm to about 700μm, or from about 30μm to about 600μm, or from about 30μm to about 500μm, or from about 30μm to about 400μm, or from about 30μm to about 300μm, or from about 30μm to about 200μm, or from about 30μm to about 100μm, or from about 30μm to about 90μm, or from about 30μm to about 80μm, or from about 30μm to about 70μm, or from about 30μm to about 60μm, or from about 30μm to about 70μm, or from about 30μm to about 60μm, or from about 30μm to about 50μm, or from about 50μm to about 1.5mm, or from about 50μm to about 1mm, or from about 50μm to about 900μm, or from about 50μm to about 800μm, or from about 50μm to about 700μm, or from about 50μm to about 600μm, or from about 50μm to about 500μm, or from about 50μm to about 400μm, or from about 50μm to about 300μm, or from about 50μm to about 200μm, or from about 50μm to about 100μm, or from about 50μm to about 90μm, or from about 50μm to about 80μm, or from about 50μm to about 70μm, or from about 50μm to about 60μm, or from about 80μm to about 1.5mm, or from about 80μm to about 1mm, or from about 80μm to about 900μm, or from about 80μm to about 800μm, or from about 80μm to about 700μm, or from about 80μm to about 600μm, or from about 80μm to about 500μm, or from about 80μm to about 400μm, or from about 80μm to about 300μm, or from about 80μm to about 200μm, or from about 80μm to about 100μm, or from about 80μm to about 90μm.

[0067] The base of the microprojections of the present invention may have a thickness of about 5μm, or about 10μm, or about 15μm, or about 20μm, or about 25μm, or about 30μm, or about 35μm, or about 40μm, or about 45μm, or about 50μm, or about 55μm, or about 60μm, or about 65μm, or about 70μm, or about 75μm, or about 80μm, or about 85μm, or about 90μm or about 100μm. The base of the microprojections of the present invention may have a thickness of from about 5μm to about 100μm, or from about 5μm to about 95μm, or from about 5μm to about 90μm, or from about 5μm to about 85μm, or from about 5μm to

about 80μm, or from about 5μm to about 75μm, or from about 5μm to about 70μm, or from about 5μm to about 65μm, or from about 5μm to about 60μm, or from about 5μm to about 55μm, or from about 5μm to about 50μm, or from about 5μm to about 45μm, or from about 5μm to about 40μm, or from about 5μm to about 35μm, or from about 5μm to about 30μm, or from about 5μm to about 25μm, or from about 5μm to about 20μm, or from about 5μm to about 15μm, or from about 5μm to about 10μm, or from about 10μm to about 100μm, or from about 10μm to about 95μm, or from about 10μm to about 90μm, or from about 10μm to about 85μm, or from about 10μm to about 80μm, or from about 10μm to about 75μm, or from about 10μm to about 70μm, or from about 10μm to about 65μm, or from about 10μm to about 60μm, or from about 10μm to about 55μm, or from about 10μm to about 50μm, or from about 10μm to about 45μm, or from about 10μm to about 40μm, or from about 10μm to about 35μm, or from about 10μm to about 30μm, or from about 10μm to about 25μm, or from about 10μm to about 20μm, or from about 10μm to about 15μm, or from about 20μm to about 100μm, or from about 20μm to about 95μm, or from about 20μm to about 90μm, or from about 20μm to about 85μm, or from about 20μm to about 80μm, or from about 20μm to about 75μm, or from about 20μm to about 70μm, or from about 20μm to about 65μm, or from about 20μm to about 60μm, or from about 20μm to about 55μm, or from about 20μm to about 50μm, or from about 20μm to about 45μm, or from about 20μm to about 40μm, or from about 20μm to about 35μm, or from about 20μm to about 30μm, or from about 20μm to about 25μm, or from about 30μm to about 100μm, or from about 30μm to about 95μm, or from about 30μm to about 90μm, or from about 30μm to about 85μm, or from about 30μm to about 80μm, or from about 30μm to about 75μm, or from about 30μm to about 70μm, or from about 30μm to about 65μm, or from about 30μm to about 60μm, or from about 30μm to about 55μm, or from about 30μm to about 50μm, or from about 30μm to about 45μm, or from about 30μm to about 40μm, or from about 30μm to about 35μm.

[0068] The base of the microprojections of the present invention have a cross sectional length:thickness aspect ratio of about 3:2, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, between 3:2 to 9:1, between 3:2 to 8:1, between 3:2 to 7:1, between 3:2 to 6:1; between 3:2 to 5:1, between 3:2 to 4:1, between 3:2 to 3:1, between 2:1 to 9:1, between 2:1 to 8:1, between 2:1 to 7:1, between 2:1 to 6:1; between 2:1 to 5:1, between 2:1 to 4:1, between 3:1 to 9:1, between 3:1 to 8:1, between 3:1 to 7:1, between 3:1 to 6:1; between 3:1 to 5:1, between 3:1 to 4:1,

between 4:1 to 9:1, between 4:1 to 8:1, between 4:1 to 7:1, between 4:1 to 6:1; between 4:1 to 5:1, between 5:1 to 9:1, between 5:1 to 8:1, between 5:1 to 7:1, between 5:1 to 6:1, between 6:1 to 9:1, between 6:1 to 8:1, between 6:1 to 7:1, between 7:1 to 9:1, between 7:1 to 8:1, between 8:1 to 9:1. In this regard, a high aspect ratio can assist in having the projections penetrate the skin with minimal force. On a micro-scale, puncture is a function of crack formation and subsequent growth. The use of a high aspect ratio can assist in allowing cracks to form, thereby reducing the barrier to entry, whilst also maximising the surface area of the projections, which in turn maximises the amount of coating and hence payload that can be delivered. This means that significantly more surface area of the protrusion can enter the skin, without a large increase in energy.

[0069] The height of the microprojections of the present invention depends upon the depth of penetration required. The height of the microprojections of the present invention may have a length of from about 30μm to about 2mm, or from about 30μm to about 1.5mm, or from about 30μm to about 1mm, or from about 30μm to about 900μm, or from about 30μm to about 800μm, or from about 30μm to about 700μm, or from about 30μm to about 600μm, or from about 30μm to about 500μm, or from about 30μm to about 400μm, or from about 30μm to about 300μm, or from about 30μm to about 200μm, or from about 30μm to about 100μm, or from about 30μm to about 90μm, or from about 30μm to about 80μm, or from about 30μm to about 70μm, or from about 30μm to about 60μm, or from about 30μm to about 70μm, or from about 30μm to about 60μm, or from about 30μm to about 50μm, or from about 50μm to about 1.5mm, or from about 50μm to about 1mm, or from about 50μm to about 900μm, or from about 50μm to about 800μm, or from about 50μm to about 700μm, or from about 50μm to about 600μm, or from about 50μm to about 500μm, or from about 50μm to about 400μm, or from about 50μm to about 300μm, or from about 50μm to about 200μm, or from about 50μm to about 100μm, or from about 50μm to about 90μm, or from about 50μm to about 80μm, or from about 50μm to about 70μm, or from about 50μm to about 60μm, or from about 80μm to about 1.5mm, or from about 80μm to about 1mm, or from about 80μm to about 900μm, or from about 80μm to about 800μm, or from about 80μm to about 700μm, or from about 80μm to about 600μm, or from about 80μm to about 500μm, or from about 80μm to about 400μm, or from about 80μm to about 300μm, or from about 80μm to about 200μm, or from about 80μm to about 100μm, or from about 80μm to about 90μm.

[0070] The density of the microprojection on the microprojection arrays may be about 2000 microprojections/cm^2, or about 2500 microprojections/cm^2, or about 3000 microprojections/cm^2, or about 3500 microprojections/cm^2, or about 4000 microprojections/cm^2, or about 4500 microprojections/cm^2, or about 5000 microprojections/cm^2, or about 5500 microprojections/cm^2, or about 6000 microprojections/cm^2, or about 6500 microprojections/cm^2, or about 7000 microprojections/cm^2, or about 7500 microprojections/cm^2, or about 8000 microprojections/cm^2, or about 8500 microprojections/cm^2, or about 9000 microprojections/cm^2, or about 9500 microprojections/cm^2, or about 10000 microprojections/cm^2, or about 11000 microprojections/cm^2, or about 12000 microprojections/cm^2, or about 13000 microprojections/cm^2, or about 14000 microprojections/cm^2, or about 15000 microprojections/cm^2, or about 16000 microprojections/cm^2, or about 17000 microprojections/cm^2, or about 18000 microprojections/cm^2, or about 19000 microprojections/cm^2, or about 20000 microprojections/cm^2. The density of the microprojection on the microprojection arrays may be from about 2000 to about 20000 microprojections/cm^2, or from about 2000 to about 15000 microprojections/cm^2, or from about to about 10000 microprojections/cm^2, or from about 2000 to about 9000 microprojections/cm^2, or from about 2000 to about 8000 microprojections/cm^2, or from about 2000 to about 7500 microprojections/cm^2, or from about 2000 to about 7000 microprojections/cm^2, or from about 2000 to about 6000 microprojections/cm^2, or from about 2000 to about 5000 microprojections/cm^2, or from about 2000 to about 4000 microprojections/cm^2, or from about 3000 to about 20000 microprojections/cm^2, or from about 3000 to about 15000 microprojections/cm^2, or from about to about 10000 microprojections/cm^2, or from about 3000 to about 9000 microprojections/cm^2, or from about 3000 to about 8000 microprojections/cm^2, or from about 3000 to about 7500 microprojections/cm^2, or from about 3000 to about 7000 microprojections/cm^2, or from about 3000 to about 6000 microprojections/cm^2, or from about 3000 to about 5000 microprojections/cm^2, or from about 3000 to about 4000 microprojections/cm^2, or from about 4000 to about 20000 microprojections/cm^2, or from about 4000 to about 15000 microprojections/cm^2, or from about to about 10000 microprojections/cm^2, or from about 4000 to about 9000 microprojections/cm^2, or from about

4000 to about 8000 microprojections/cm^2, or from about 4000 to about 7500 microprojections/cm^2, or from about 4000 to about 7000 microprojections/cm^2, or from about 4000 to about 6000 microprojections/cm^2, or from about 4000 to about 5000 microprojections/cm^2, or from about 5000 to about 20000 microprojections/cm^2, or from about 5000 to about 15000 microprojections/cm^2, or from about to about 10000 microprojections/cm^2, or from about 5000 to about 9000 microprojections/cm^2, or from about 5000 to about 8000 microprojections/cm^2, or from about 5000 to about 7500 microprojections/cm^2, or from about 5000 to about 7000 microprojections/cm^2, or from about 5000 to about 6000 microprojections/cm^2.

[0071] In one embodiment of the microprojections of the present invention the microprojections have a vertical shape that has an extruded base profile with a slight draught angle of approximately 0 to 20 degrees up to a transition point at which point the upper tip of the microprojection will slope towards the tip line at a greater angle.

[0072] The microprojection arrays of the present invention are comprised of a plurality of microprojections. The microprojections may be arrayed in lines. The spacing between microprojections on a single line may be from about 10μm to about 500μm, or from about 10μm to about 450μm or from about 10μm to about 400μm of from about 10μm to about 350μm or from about 10μm to about 300μm or from about 10μm to about 250μm; or from about 10μm to about 200μm of from about 10μm to about 150μm or from about 10μm to about 100μm or from about 10μm to about 50μm; or from about 20μm to about 500μm, or from about 20μm to about 450μm or from about 20μm to about 400μm of from about 20μm to about 350μm or from about 20μm to about 300μm or from about 20μm to about 250μm; or from about 20μm to about 200μm of from about 20μm to about 150μm or from about 20μm to about 100μm or from about 20μm to about 50μm; or from about 30μm to about 500μm, or from about 30μm to about 450μm or from about 30μm to about 400μm of from about 30μm to about 350μm or from about 30μm to about 300μm or from about 30μm to about 250μm; or from about 30μm to about 200μm of from about 30μm to about 150μm or from about 30μm to about 100μm or from about 30μm to about 50μm; or from about 40μm to about 500μm, or from about 40μm to about 450μm or from about 40μm to about 400μm of from about 40μm to about 350μm or from about 40μm to about 300μm or from about

40μm to about 250μm; or from about 40μm to about 200μm of from about 40μm to about 150μm or from about 40μm to about 100μm or from about 40μm to about 50μm; or from about 50μm to about 500μm, or from about 50μm to about 450μm or from about 50μm to about 400μm of from about 50μm to about 350μm or from about 50μm to about 300μm or from about 50μm to about 250μm; or from about 50μm to about 200μm of from about 50μm to about 150μm or from about 50μm to about 100μm. The spacing between lines of microprojections 40μm to about 500μm, or from about 40μm to about 450μm or from about 40μm to about 400μm of from about 40μm to about 350μm or from about 40μm to about 300μm or from about 40μm to about 250μm; or from about 40μm to about 200μm of from about 40μm to about 150μm or from about 40μm to about 100μm; or from about 50μm to about 500μm, or from about 50μm to about 450μm or from about 50μm to about 400μm of from about 50μm to about 350μm or from about 50μm to about 300μm or from about 50μm to about 250μm; or from about 50μm to about 200μm of from about 50μm to about 150μm or from about 50μm to about 100μm; or from about 75μm to about 500μm, or from about 75μm to about 450μm or from about 75μm to about 400μm of from about 75μm to about 350μm or from about 75μm to about 300μm or from about 75μm to about 250μm; or from about 75μm to about 200μm of from about 75μm to about 150μm.

[0073] In one embodiment of the present invention the microprojection has a tapering extended hexagonal shape with a rapidly tapering tip at the distal end. The microprojections have a spacing of 100 μm between adjacent lines and 80 μm between successive microprojections on the array (density about 8000/cm^2). The tip of the protrusions tapers to a distal line of approximately 25 μm long and 1-2 μm wide.

[0074] A gas jet coating process may be used to deposit liquid vaccine material in the coating solution onto the projection array. The process parameters (i.e. jet angle, jet velocity, solution viscosity, etc.) of the coating method can affect the degree to which the coating material is localized towards the tips of the projections, rather than the base. In addition to these process parameters, coating of the liquid material to the projections can be further enhanced by modifying the surface properties of the projections relative to the liquid coating material. The coating may be applied using a gas jet coating technique as described in WO/2009/079712. The microprojection arrays of the present invention may penetrate further into the skin than

corresponding arrays with conical or cylindrical microprojections having the same length and delivered with the same energy. The microprojection arrays of the present invention may penetrate further by 10% or 20% or 30% or 40% or 50% or 60% or 70% or 80% or 90% or 100%. The microprojection arrays of the present invention may penetrate further by 10% to 200% or from 10% to 150% or from 10% to 100% or from 10% to 90% or from 10% to 80% or from 10% to 70% or from 10% to 60% or from 10% to 50% or from 10% to 40% or from 10% to 30% or from 10% to 20% or from 20% to 200% or from 20% to 150% or from 20% to 100% or from 20% to 90% or from 20% to 80% or from 20% to 70% or from 20% to 60% or from 20% to 50% or from 20% to 40% or from 20% to 30% or from 30% to 200% or from 30% to 150% or from 30% to 100% or from 30% to 90% or from 30% to 80% or from 30% to 70% or from 30% to 60% or from 30% to 50% or from 30% to 40% or from 40% to 200% or from 40% to 150% or from 40% to 100% or from 40% to 90% or from 40% to 80% or from 40% to 70% or from 40% to 60% or from 40% to 50% or from 50% to 200% or from 50% to 150% or from 50% to 100% or from 50% to 90% or from 50% to 80% or from 50% to 70% or from 50% to 60%.

[0075] The microprojection arrays of the present invention may provide greater cell death in the cells surrounding the microprojections in the skin than corresponding arrays with conical or cylindrical microprojections having the same length and delivered with the same energy. The microprojection arrays of the present invention may provide cell death that is 10% or 20% or 30% or 40% or 50% or 60% or 70% or 80% or 90% or 100% greater. The microprojection arrays of the present invention may provide greater cell death by 10% to 200% or from 10% to 150% or from 10% to 100% or from 10% to 90% or from 10% to 80% or from 10% to 70% or from 10% to 60% or from 10% to 50% or from 10% to 40% or from 10% to 30% or from 10% to 20% or from 20% to 200% or from 20% to 150% or from 20% to 100% or from 20% to 90% or from 20% to 80% or from 20% to 70% or from 20% to 60% or from 20% to 50% or from 20% to 40% or from 20% to 30% or from 30% to 200% or from 30% to 150% or from 30% to 100% or from 30% to 90% or from 30% to 80% or from 30% to 70% or from 30% to 60% or from 30% to 50% or from 30% to 40% or from 40% to 200% or from 40% to 150% or from 40% to 100% or from 40% to 90% or from 40% to 80% or from 40% to 70% or from 40% to 60% or from 40% to 50% or from 50% to 200% or from

50% to 150% or from 50% to 100% or from 50% to 90% or from 50% to 80% or from 50% to 70% or from 50% to 60%.

[0076] The microprojection arrays of the present invention may provide increased immunogenicity as compared to intramuscular administration of vaccine. The microprojection arrays of the present invention may provide increased immunogenicity as compared to corresponding arrays with conical or cylindrical microprojections having the same length and delivered with the same energy in delivering vaccines. The microprojection arrays of the present invention may provide an increased immunogenic response by 10% or 20% or 30% or 40% or 50% or 60% or 70% or 80% or 90% or 100%. The microprojection arrays of the present invention may provide an increased immunogenic response by 10% to 200% or from 10% to 150% or from 10% to 100% or from 10% to 90% or from 10% to 80% or from 10% to 70% or from 10% to 60% or from 10% to 50% or from 10% to 40% or from 10% to 30% or from 10% to 20% or from 20% to 200% or from 20% to 150% or from 20% to 100% or from 20% to 90% or from 20% to 80% or from 20% to 70% or from 20% to 60% or from 20% to 50% or from 20% to 40% or from 20% to 30% or from 30% to 200% or from 30% to 150% or from 30% to 100% or from 30% to 90% or from 30% to 80% or from 30% to 70% or from 30% to 60% or from 30% to 50% or from 30% to 40% or from 40% to 200% or from 40% to 150% or from 40% to 100% or from 40% to 90% or from 40% to 80% or from 40% to 70% or from 40% to 60% or from 40% to 50% or from 50% to 200% or from 50% to 150% or from 50% to 100% or from 50% to 90% or from 50% to 80% or from 50% to 70% or from 50% to 60%.

[0077] The ability of the microprojection arrays of the present invention to provide a greater immunogenic response allows the microprojection arrays to deliver a lesser amount of vaccine to achieve the appropriate response as compared to intramuscular or intradermal administration by a needle. The ability of the microprojection arrays of the present invention to provide a greater immunogenic response allows the microprojection arrays to deliver a lesser amount of vaccine to achieve the appropriate response as compared to corresponding arrays with conical or cylindrical microprojection. Such "dose-sparing" benefit of the microprojection arrays permits a lesser amount of vaccine to be used in each dose to achieve the same immunogenic response. The amount of vaccine used with the microprojection

arrays of the present invention may be 0.01%, 0.05%, 0.10%, 0.50%, 1%, 5% or 10% or 20% or 30% or 40% or 50% or 60% or 70% or 80% or 90% less than the amount of vaccine used in conventional vaccine administrations. The amount of vaccine used with the microprojection arrays of the present invention may be about 0.01% to 90% or from 0.01% to 80% or from 0.01% to 70% or from 0.01% to 60% or from 0.01% to 50% or from 0.01% to 40% or from 0.01% to 30% or from 0.01% to 20% or from 0.01% to 10% or from 0.01% to 1% or from 0.01% to 0.10% or from 0.05% to 90% or from 0.05% to 80% or from 0.05% to 70% or from 0.05% to 60% or from 0.05% to 50% or from 0.05% to 40% or from 0.05% to 30% or from 0.05% to 20% or from 0.05% to 10% or from 0.05% to 1% or from 0.05% to 0.10% or from 0.10% to 90% or from 0.10% to 80% or from 0.10% to 70% or from 0.10% to 60% or from 0.10% to 50% or from 0.10% to 40% or from 0.10% to 30% or from 0.10% to 20% or from 0.10% to 10% or from 0.10% to 1% or from 1% to 90% or from 1% to 80% or from 1% to 70% or from 1% to 60% or from 1% to 50% or from 1% to 40% or from 1% to 30% or from 1% to 20% or from 1% to 10% or from 5% to 90% or from 5% to 80% or from 5% to 70% or from 5% to 60% or from 5% to 50% or from 5% to 40% or from 5% to 30% or from 5% to 20% or from 5% to 10% or from 10% to 90% or from 10% to 80% or from 10% to 70% or from 10% to 60% or from 10% to 50% or from 10% to 40% or from 10% to 30% or from 10% to 20% or from 20% to 90% or from 20% to 80% or from 20% to 70% or from 20% to 60% or from 20% to 50% or from 20% to 40% or from 20% to 30% or from 30% to 90% or from 30% to 80% or from 30% to 70% or from 30% to 60% or from 30% to 50% or from 30% to 40% or from 40% to 90% or from 40% to 80% or from 40% to 70% or from 40% to 60% or from 40% to 50% or from 50% to 90% or from 50% to 80% or from 50% to 70% or from 50% to 60%.

[0078] The amount of vaccine antigen given per dose may be from about 1ng, 5ng, 10ng, 20ng, 30ng, 40ng, 50ng, 60ng, 70ng, 80ng, 90ng,100ng,250ng, 500ng, 750ng, 1µg dose, 2µg dose, 3µg dose, 4µg dose, 5µg dose, 6µg dose, 7µg dose, 8µg dose, 9µg dose, 10µg dose, 15µg dose, 20µg dose, 25µg dose, 30µg, 40µg dose, 50µg dose, 60µg dose, 70µg dose, 80µg dose may be sufficient to induce an immune response . The dose of vaccine antigen may be administered to the human within a range of doses including from about 1ng to about 10 µg, about 1 ng to about 5 µg, about 1 ng to about 1 µg, about 1 ng to about 900ng, about 1 ng to about 800ng, about 1 ng to about 700ng, about 1 ng to about 600ng, about 1 ng to about

500ng, about 1 ng to about 400ng, about 1 ng to about 300ng, about 1 ng to about 200ng, about 1 ng to about 100ng, about 1 ng to about 75ng, about 1 ng to about 50ng, about 1 ng to about 25ng, about 10ng to about 10 μg, about 10 ng to about 5 μg, about 10 ng to about 1 μg, about 10 ng to about 900ng, about 10 ng to about 800ng, about 10 ng to about 700ng, about 10 ng to about 600ng, about 10 ng to about 500ng, about 10 ng to about 400ng, about 10 ng to about 300ng, about 10 ng to about 200ng, about 10 ng to about 100ng, about 10 ng to about 75ng, about 10 ng to about 50ng, about 10 ng to about 25ng, about 0.1μg to about 500μg, 1μg to about 100μg, 1μg to about 50μg, from about 1μg to about 30μg, from about 1μg to about 25μg, from about 1μg to about 20μg, from about 1μg to about 15μg, from about 1μg to about 10μg, from about 2μg to about 50μg, 2μg to about 30μg, from about 2μg to about 20μg, from about 2μg to about 10μg, from about 2μg to about 8μg, from about 3μg to about 50μg, 3μg to about 30μg, from about 3μg to about 20μg, from about 3μg to about 10μg, from about 3μg to about 8μg, from about 3μg to about 5μg, from about 4μg to about 50μg, 4μg to about 30μg, from about 4μg to about 20μg, from about 4μg to about 10μg, from about 4μg to about 8μg, from about 5μg to about 50μg, 5μg to about 30μg, from about 5μg to about 20μg, from about 5μg to about 10μg, from about 5μg to about 9μg, and from about 5μg to about 8μg.

[0079] The microprojection array may be applied vertically, laterally or a combination thereof. A lateral application of the microprojection array will slide the microprojections along the surface of the skin to penetrate the skin in lanes.

[0080] The applicators of the present invention utilize a 'low-force, higher velocity' applicator which may use a "flying" microprojection array in which the microprojection array is discharged from the device with sufficient force to propel the array through space and into the skin. Peak stresses are associated with the penetration of projections, without the follow-through, and the higher velocity achieves the change of behavior of the skin from elastic to plastic. The use of low force, high velocity approach to penetration of the skin by the microprojection array provides advantages such as: achieving equivalent penetration in the skin, but with about only $1/10^{th}$ the Kinetic Energy; improved patient acceptability/tolerability of the penetration of the skin by the microprojection array and significantly less breakage of projections (up to about 1/10000 reduction of breakage) and

patch base. The use of low force, high velocity application of the microprojection array to the skin also provides consistent penetration of the patch from site to site, because the mechanics of penetration are not heavily reliant on variations of the subcutaneous tissue (which does vary significantly within and individual and between people in populations). The direct correlation of kinetic energy with penetration may be utilized to design an applicator and microarray projections that provides maximal efficiency in delivering material to the patient while reducing discomfort to the patient.

[0081] The speed of the microprojection array as it is projected into the skin depends at least in part upon the density of the projections in the microarray and the area of the array. The range of speeds for the microprojection array entering the skin may be from about 5 m/s to about 50 m/s or from about 5 m/s to about 40 m/s or from about 5 m/s to about 30 m/s or from about 5 m/s to about 25 m/s or from about 5 m/s to about 20 m/s or about 10 m/s to about 50 m/s or from about 10 m/s to about 40 m/s or from about 10 m/s to about 30 m/s or from about 10 m/s to about 25 m/s or from about 10 m/s to about 20 m/s or from about 20 m/s to about 50 m/s or from about 20 m/s to about 40 m/s or from about 20 m/s to about 30 m/s or from about 25 m/s to about 50 m/s or from about 25 m/s to about 40 m/s or from about 25 m/s to about 30 m/s. In preferred embodiments of the of the present invention the speed of the microprojection array is at least 15 m/s or at least 20 m/s or at least 25 m/s or at least 30 m/s.

[0082] In one embodiment the microprojections have a tapering extended hexagonal shape with a rapidly tapering tip at the distal end. The protrusions have a spacing of 100 μm between adjacent lines and 80 μm between successive protrusions (density about 8000/cm^2). The tip of the protrusions tapers to a distal line of approximately 25 μm long and 1-2 μm wide.

[0083] An example of a microprojection array 500 is shown in Figures 5A-5B. The microprojection array 500 comprises a substrate 520 with a plurality of microprojections 510 protruding from the substrate 520. The microprojection array 500 includes microprojections 510 arranged in a number of straight, spaced apart lines as shown in Figure 5B. In Figure 5A, the spacing of the microprojections 510 between adjacent lines is indicated as S_1 and the spacing between successive microprojections 510 in the same line is indicated as S_2.

[0084] Further details of one of the microprojections 510 of the microprojection array 500 are shown in Figures 6A-6C. The microprojections 510 have a tapering hexagonal shape and comprise a tip 611 and a base 612 wherein the base 612 has two substantially parallel sides 621, 622 with a slight draught angle of approximately 1 to 20 degrees (as indicated in Figure 6B by α_1) up to a transition point 613 at which point the angle increases to from about 20 degrees to about 70 degrees (as indicated in Figure 6B by α_2). Although this example depicts a distinct increase in the angle at the transition point 613, it should be noted that there may be a more gradual increase in the angle than depicted. The tip 611 of each microprojection 510 terminates in an elongate edge. The tip 611 has a width W_{tip} and a length L_{tip}. The base 612 has a length L_{base}, and is greater in length than the tip 611. The base 612 has a thickness T_{base}. The cross sectional length:thickness aspect ratio of the base 612 is defined as L_{base}:T_{base}, and is greater than 2:1 in this case. Each microprojection has an overall height H which depends upon the depth of penetration required.

[0085] In view of the above, it will be appreciated that the present invention relates to microarray projections which are designed to have a large surface area to frontal profile design while maintaining a high density configuration. The microprojection arrays of the present invention exploit the manner in which skin punctures. On a micro-scale, puncture is a function of crack formation in the skin and the subsequent growth of these cracks. While high density microneedles or microdevices perform this in a large number for every individual "needle", it necessitates a very large number of crack initiations thereby absorbing substantial energy. The devices of the present invention use a lower density of protrusions compared to some high density arrays, which have a line of contact rather than a single contact point. Once the crack in the skin starts to form, the protrusion will easily enter the skin, allowing internal skin surface area contact with penetrating surface. This means that significantly more surface area for the protrusion to enter the skin. The microprojections of the present invention may be wider and thinner than current conically or cylindrically shaped microprojections. Thus, a single line of contact may cut into the skin rather than point punctures. The results are that a larger surface may be introduced into the skin rather than individual points penetrating the skin in which each point must be opened before vaccine may be delivered.

[0086] The present invention relates to microprojection arrays where the microprojection design provides an alternative mode of skin puncture and vaccine delivery into the skin. The microprojections of the present invention are designed to have a large surface area to frontal profile design while maintaining a high density of microprojections on the array. The microprojection arrays of the present invention have a plurality of microprojections that are located upon a base. In one embodiment the microprojection have a shape that from a top down perspective is approximately an extended hexagon with two parallel sides being extended to give a rectangular profile with triangular ends. In an alternate embodiment the microprojections have a shape that from a top down perspective is approximately an extended octagon. This profile is similar to the hexagonally-shaped microprojection except that the ends of the microprojections are broadened. The microprojections may be aligned in parallel line with spacing between the edges of the microprojections. The microprojections may extend vertically to a length that will provide for drugs or vaccines to be delivered to the desired location within the skin.

[0087] The present invention relates to microprojections having a tapering extended hexagonal or octagonal shape comprising a base and a tip wherein the tip has a width of from about 0.5 μm to about 2 μm and a length of about 10 μm to about 2mm.

[0088] The present invention relates to microprojection arrays comprising a plurality of microprojections wherein the microprojections have a tapering extended hexagonal shape or octagonal and comprise a base and a tip wherein the tip has a width of from about 0.5 μm to about 2 μm and a length of about 10 μm to about 2 mm.

[0089] The present invention relates to microprojection arrays comprising a plurality of microprojections organized in lines on the array wherein the microprojections have a tapering extended hexagonal or octagonal shape and wherein the spacing of the microprojection between adjacent lines is 100μm and the spacing between successive microprojections is 80μm. The present invention relates to methods of administering a vaccine to a human comprising applying the microprojection arrays in which vaccine is coated onto the microprojections of the arrays of the present invention to a human's skin.

[0090] The present invention relates to microprojection arrays comprising a substrate with a plurality of microprojections protruding from the substrate wherein the microprojections have a tapering hexagonal or octagonal shape and comprise a tip and a base wherein the base has two substantially parallel sides with a slight draught angle of approximately 1 to 20 degrees up to a transition point at which point the angle increases to from about 20 degrees to about 70 degrees.

[0091] The present invention relates to microprojection arrays where the substrate is solid or non-porous or non-hollow. The present invention relates to microprojection arrays where the microprojection array includes a number of microprojections arranged in a line. The present invention relates to microprojection arrays where the line is a straight line or a curved line or a circular line extending circumferentially around an axis. The present invention relates to microprojection arrays where some of microprojections in a line have a common base. The present invention relates to microprojection arrays where the microprojection array includes a number of spaced apart lines. The present invention relates to microprojection arrays where the spacing of the microprojections between adjacent lines is less than 200 μm or less than 150 μm or about 100 μm. The present invention relates to microprojection arrays where the spacing between successive microprojections is less than 200 μm or less than 150 μm or less than 100 μm or about 80 μm.

Examples

Example 1

Methods

[0092] All microprojection arrays were coated in a solution of 1% methylcellulose and the required vaccine dose dissolved in injectable phosphate buffered saline solution (Chen, et al, J. Controlled Release (2009) 139, 212). Fluvax 2014® was used as the antigen. Delivered dose was measured using radioassay (Fernando, et al. PLos One (2010) 5, e10266). Specific pathogen-free female C57BL/6 mice from 6 to 8 weeks old were used in all examples. Groups of 5 mice were use in each Example. Application of all microprojection array patches were performed as described (Crichton et al., Biomaterials (2010) 31, 4562) at a velocity of 2.3 m/s. The surface area and volume of the projections entering the skin was calculated

upon models using Solid Edge® software (Siemens PLM Software, Texas, US). Imaging of microprojection array puncturing and delivery into the skin was performed by coating the microprojections with Fluorospheres (Molecular Probes, OR, US) and applying the microprojection arrays to skin for histology or excised skin for CryoSEM and imaging as described (3). Trans-Epidermal water loss (TEWL) was measured using a Tewawater® TM300 (Courage & Khazajka Electronic GmbH, Cologne, Germany). Mice had TEWL measurement taken prior to microprojection array application, immediately post-microprojection array application and at 30, 60, 90 and 120 minutes and then every hour from 3-8 hours post application of the microprojection array. Two control mice that had not had microprojection arrays used on them were also measure during these timeframes to observe any environmental baseline changes. Visible staining of the tissue and quantification of live/dead cells was performed as described (Depelsebaire et al., J. Invest. Dermatol. (2014) 134, 2361). A total of n=4-5 fields of view were acquired per sample. Skin infiltrating cells were examined by flow cytometry. Excised ear tissue was diced and incubated in 1 mg/ml collagenase IV (Life Technologies, Carlsbad, CA) and 4U DNAse I (ThermoFisher Scientific, Pittsburgh, PA) for 30 minutes at 37°C before inactivating with 200uL of fetal bovine serum. Lysates were passed through a 70 µm strainer and cells pelleted by centrifugation with an additional 4U DNAse I treatment. Cells were incubated with purified anti-CD 16/32 (Clone 93, Biolegend, San Diego, CA) for 15 minutes at 4°C before washing and staining with a cocktail of fluorescently –conjugated anti-mouse monoclonal antibodies for 30 minutes at 4°C. CD45.2 PercP Cy5.5 (clone 104), CD11c PECy7 (N418), Ly6C APC (HK1.4RUO) (all from Affymetrix, San Diego, CA) CD11b Brilliant Violet 605 (M1/70), F4/80 Brilliant Vioet 421 (BM8) (Biolegend, San Diego, CA) and Ly6G FITC (IA8), Siglec F PE (E50-2440) (Becton Dickenson, Franklin lakes, NJ). Data were acquired on a BD LSR II flow cytometer and analysed using Flowjo v9 (TreeStar, Ashland, OR). DRAQ 7 (Biostatus, Shepshed UK) was used to exclude dead cells before analysis. Doublets and debris were removed based on forward and side scatter properties before gating. Results were analysed using a one-way ANOVA with Tykey post-test in Graphpad Prism® Version 6.00. Ig titers were determined as described (Fernando, et al. J. Controlled Release (2102) 159, 215) except 5ul of K- Blue TMB substrate (ELISA systems) was added and the color reaction

was developed for 5 minutes in the dark. The reaction was stopped by the addition of 50ul of 1M phosphoric acid and the plates were read spectrophotometrically at 450 nm.

Example 2

Coating and Skin Penetration of Microprojection Arrays

[0093] One embodiment of microprojections of the present invention (TP) and cylindrically/conically shaped microprojections (NP) were coated (Chen, et al, J. Controlled Release (2009) 139, 212) and the microprojection arrays were administered to mouse ear skin (Crichton, et al., Biomaterials (2010) 31, 4562). Figure 1 shows the microprojections before coating. The coating solution is localized around the tips of the microprojections. Post-skin application imaging demonstrated that the coating on the tips of the microprojections had been removed and that the microprojections had entered the skin as evidenced by the tide mark on the microprojections' surfaces. Both TP and NP microprojections show varied penetration over the array surface indicating the complexity of penetrating a topographically variable skin surface. The TP microprojection shows a deeper penetration indicating the full dermis had been penetrated whereas the NP microprojections appear to have penetrated the epidermis and upper dermis. There appears to be a greater overall coverage of delivery by TP when an overhead view is surveyed.

Example 3

In Situ Effect of Microprojection Arrays using CryoSEM

[0094] The mechanism of surface puncture was explored using CryoSEM which involved the freezing of skin with microprojections in place and then removing or fracturing the microprojection arrays and skin to show the state of the tissue in-situ. Clear puncture marks are created by both sets of microprojection arrays and the skin is entered without a large disruption of the adjacent tissue. When the microprojection arrays are withdrawn from the skin the holes in the skin quickly closed. In observing the TP microprojection array it was determined that the major axis of the hole created by the microprojections is 36μm when the microprojection is in-situ. The hole shrinks by approximately 10 to 30% to 25 to 33μm after withdrawal of the microprojection array. The minor axis shrinks to 5-10μm after an initial

width of 20μm, a reduction of 50-75%. The data indicates much larger residual stress in opening a hole across the major axis as opposed to opening a hole along the major axis. This supports the concept that crack growth along the major axis of the microprojection will be the main driver of penetration which can serve to reduce residual stress concentrations along this axis. In contrast, cylindrical or circular holes made by microprojections where the major and minor axis are the same or similar will close from all direction with considerable residual stress from all side of the microprojection. This shape of microprojection provides no stress relief to assist the penetration process. Trans-Epidermal Water Loss was measured in skin penetrated by both TP and NP microprojections. The skin penetrated by NP microprojections healed more quickly that skin penetrated by TP microprojections consistent with view that large cracks are formed during TP microprojection penetration.

Example 4

Microprojection Arrays Depth Penetration Using Fluorescent Dye

[0095] Skin vaccine delivery depth was quantified by measuring the depth to which fluorescent dye coated onto the microprojections reached within the skin (Crichton, et al., Biomaterials (2010) 31, 4562). NP microprojections delivered to a depth of 39.9±16.4 μm (n = 5 mouse ears; 337 total measurements) and TP microprojections delivered to a depth of 59.7±20.9 μm (n = 4 mouse ears; 386 total measurements). The same amount of force was used to deliver the microprojections arrays to the skin. The TP microprojections were more successful in penetrating more deeply into the skin. A greater vaccine dose was delivered by the TP microprojections.

Example 5

Model for TP and NP Microprojection Arrays Penetration

[0096] To confirm increased penetration by TP projections a 3D model of both microprojections was constructed in Solid Edge®. The surface area and the volume of the TP and NP microprojection arrays were calculated and then scaled to account for all the microprojections on both arrays. The calculation indicated that for a single TP microprojection the volume entering the skin was 2-3 times that of an NP microprojection.

Due to the large number of microprojections on the NP array, the overall volume of the microprojections in the skin summed over the entire array is similar between the NP and TP array for a given depth of penetration. The surface area of the two arrays is also similar. The increase penetration of the TP microprojections into the skin results from a greater ability to penetrate the skin rather than the disproportionate volume or surface area penetrating into the skin at comparable depths. The increase volume of the TP microprojections indicates easier entry into the skin which appears to be due to fewer penetrating microprojection into the skin and microprojections expanding punctures through the skin surface.

Example 6

Influenza Vaccine Administration with TP and NP Microprojection Arrays

[0097] Five ng of commercial influenza vaccine (Fluvax®) was administered to pathogen-free female C57BL/6 mice from 6 to 8 weeks old using intradermal injection, administration of NP microprojection array, administration of NP microprojection array, or intramuscular injection. The results are shown in Figure 3. The immune response to the TP microprojection array which held 5 ng of antigen was equivalent to the NP microprojection array response to 50 ng of antigen which indicates a 10 fold increase in immunogenicity by altering the shape and dimensions of the microprojections. The increased immunogenicity exhibited by the TP microprojection array is similar to the inclusion of a chemical adjuvant using the NP microprojection array. The use of TP microprojection array in delivering 50 ng of vaccine proved to a potent immune enhancer more than doubling the IgG titer of the elicited by the NP at the same dose (as shown in Figures 3 and 4).

Example 7

Cell Death with TP and NP Microprojection Arrays

[0098] TP and NP microprojection arrays were applied to mouse ears and the skin stained for necrotic cell death and then imaged using confocal microscopy. An example of such an image is shown in Figure 2. With respect to the NP microprojection arrays, cell death was observed within a radius of 20-30 μm with a greater number of dead cells on the edge of the array where bridged vaccine formulation restricted penetration but allowed significant force

transmission into the skin. With respect to the TP microprojection arrays dead cells are observed primarily along the major axis of the microprojections. These extend approximately 5 -25 μm from the centerline of the microprojections indicating that this area is the area of highest stress upon insertion of the array. On the edges of the array where there is higher stress and where there is some bridging of coating between microprojections the fractures of adjacent microprojections joined to form lines of continuous surface fracture, bordered by necrotic cells. This supports the idea that stress distribution and the crack growth makes it easier for TP microprojections to enter the skin. Quantifying the level of cell death around microprojection arrays revealed that TP in the central array area had 54.7±18.6 dead cells surrounding it and NP in the central array area had 21.8±3.0 dead cells surrounding it. On the edge of the arrays, the TP field of view there was 17.6% greater cell death than in the NP array. In the central area of the arrays, the TP field of view there was 42.7% greater cell death than in the NP array. The level of cell death results in an increased level of inflammation throughout the tissue which may be a stimulating factor for an enhanced immune response. The number of neutrophils and macrophages after administration of the TP array increased as opposed to the NP array. There also was a trend toward an increase in monocytes and eosinophils as well. The inflamed microenvironment may give an improved environment for dendritic cells to uptake vaccine and subsequently enhance immunogenicity.

[0099] Ranges may be expressed herein as from about one particular value, and/or to about another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent about, it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

[0100] Throughout this specification and claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated integer or group of integers or steps but not the exclusion of any other integer or group of integers.

[0101] Within this disclosure, any indication that a feature is optional is intended provide adequate support (e.g., under 35 U.S.C. 112 or Art. 83 and 84 of EPC) for claims that include closed or exclusive or negative language with reference to the optional feature. Exclusive language specifically excludes the particular recited feature from including any additional subject matter. For example, if it is indicated that A can be drug X, such language is intended to provide support for a claim that explicitly specifies that A consists of X alone, or that A does not include any other drugs besides X. "Negative" language explicitly excludes the optional feature itself from the scope of the claims. For example, if it is indicated that element A can include X, such language is intended to provide support for a claim that explicitly specifies that A does not include X. Non-limiting examples of exclusive or negative terms include "only," "solely," "consisting of," "consisting essentially of," "alone," "without", "in the absence of (e.g., other items of the same type, structure and/or function)" "excluding," "not including", "not", "cannot," or any combination and/or variation of such language.

[0102] Similarly, referents such as "a," "an," "said," or "the," are intended to support both single and/or plural occurrences unless the context indicates otherwise. For example "a dog" is intended to include support for one dog, no more than one dog, at least one dog, a plurality of dogs, etc. Non-limiting examples of qualifying terms that indicate singularity include "a single", "one," "alone", "only one," "not more than one", etc. Non-limiting examples of qualifying terms that indicate (potential or actual) plurality include "at least one," "one or more," "more than one," "two or more," "a multiplicity," "a plurality," "any combination of," "any permutation of," "any one or more of," etc. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context.

[0103] Where ranges are given herein, the endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of

the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0104] All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

[0105] While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that the various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

[0106] Persons skilled in the art will appreciate that numerous variations and modifications will become apparent. All such variations and modifications which become apparent to persons skilled in the art, should be considered to fall within the spirit and scope that the invention broadly appearing before described.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1) A microprojection array comprising a substrate with a plurality of microprojections protruding from the substrate wherein the microprojections have a tapering hexagonal shape and comprise a tip and a base wherein the base has two substantially parallel sides with a slight draught angle of approximately 1 to 20 degrees up to a transition point at which point the angle increases to from about 20 degrees to about 70 degrees.
2) The microprojection array of claim 1, wherein the substrate is at least one of:
   a) solid;
   b) non-porous; and
   c) non-hollow.
3) The microprojection array of claim 1 or claim 2, wherein the microprojection array includes a number of microprojections arranged in a line.
4) The microprojection array of claim 3, wherein the line is at least one of:
   a) a straight line;
   b) a curved line; and,
   c) a circular line extending circumferentially around an axis.
5) The microprojection array of claim 3 or claim 4, wherein at least some of the microprojections in a line have a common base.
6) The microprojection array of any one of claims 3 to 5, wherein the microprojection array includes a number of spaced apart lines.
7) The microprojection array of claim 6, wherein the spacing of the microprojections between adjacent lines is at least one of:
   a) less than 200 μm;
   b) less than 150 μm; and,
   c) about 100 μm.
8) The microprojection array of claim 6 or claim 7, wherein the spacing between successive microprojections is at least one of:
   a) less than 200 μm;
   b) less than 150 μm;
   c) less than 100 μm; and,
   d) about 80 μm.

9) The microprojection array of any one of claims 1 to 8, wherein the tip of each microprojection terminates in an elongate edge.

10) The microprojection array of any one of claims 1 to 9, wherein the tip has a width of from about 1 μm to about 2 μm and a length of about 20 μm to about 2mm

11) The microprojection array of any one of claims 1 to 9, wherein the tip has a width of about 1 μm and a length of about 20 μm.

12) The microprojection array of any one of claims 1 to 11, wherein the base has a length of from about 30 μm to about 2 mm.

13) The microprojection array of any one of claims 1 to 11, wherein the base has a length of about 80 μm.

14) The microprojection array of any one of claims 1 to 13, wherein the base is greater in length than the tip.

15) The microprojection array of any one of claims 1 to 14, wherein the base has a thickness of about 5μm to 50μm.

16) The microprojection array of any one of claims 1 to 15, wherein the base has a cross sectional length:thickness aspect ratio of about 2:1 to 5:1.

17) The microprojection array of any one of claims 1 to 16, wherein at least one of the microprojections is coated with a vaccine antigen.

18) The microprojection array of claim 17, wherein the amount of the vaccine antigen is about 10 ng to about 10 μg.

19) The microprojection array of claim 17, wherein the amount of vaccine antigen is about 10% to about 50% less than the amount of vaccine antigen delivered by intramuscular administration.

20) The microprojection array of any one of claims 17 to 19, wherein the administration of the vaccine antigen provides a greater immunogenic response when administered to a human than a comparable amount of vaccine antigen administered by intramuscular injection.

21) The microprojection array of any one of claims 17 to 19, wherein the administration of the vaccine antigen provides a greater immunogenic response when administered to a human than a comparable amount of vaccine antigen administered with a microprojection array with conical or cylindrical microprojections.

22) The microprojection array of any one of claims 1 to 21, wherein the microprojections have an effective cross-sectional area which is unchanged by the addition of the coating.

23) A method of administering a vaccine to a human comprising applying the microprojection array of any one of claims 1 to 22 to a human's skin.

24) A method according to claim 23, wherein the microprojection array includes a number of microprojections arranged in a line, and wherein the method includes applying the microprojection array to a human's skin in a direction of movement including a component of movement aligned with the line.

25) A method according to claim 24, wherein the line is a straight line and the method includes applying the microprojection array to the skin in a direction perpendicular to the skin and laterally parallel to the skin in the direction of the line.

26) A method according to claim 25, wherein the line extends circumferentially around an axis and the method includes applying the microprojection array to the skin in a direction perpendicular to the skin whilst rotating the microprojection array around the axis.

27) A microprojection array comprising a substrate with a plurality of microprojections protruding from the substrate wherein the microprojections have a tapering octagonal shape and comprise a tip and a base wherein the base has two substantially parallel sides with a slight draught angle of approximately 1 to 20 degrees up to a transition point at which point the angle increases to from about 20 degrees to about 70 degrees.

28) The microprojection array of claim 27, wherein the substrate is at least one of:

a) solid;

b) non-porous; and

c) non-hollow.

29) The microprojection array of claim 27 or claim 28, wherein the microprojection array includes a number of microprojections arranged in a line.

30) The microprojection array of claim 29, wherein the line is at least one of:

a) a straight line;

b) a curved line; and,

c) a circular line extending circumferentially around an axis.

31) The microprojection array of claim 29 or claim 30, wherein at least some of the microprojections in a line have a common base.

32) The microprojection array of any one of claims 29 to 31, wherein the microprojection array includes a number of spaced apart lines.

33) The microprojection array of claim 32, wherein the spacing of the microprojections between adjacent lines is at least one of:

a) less than 200 μm;

b) less than 150 μm; and,

c) about 100 μm.

34) The microprojection array of claim 32 or claim 33, wherein the spacing between successive microprojections is at least one of:

a) less than 200 μm;

b) less than 150 μm;

c) less than 100 μm; and,

d) about 80 μm.

35) The microprojection array of any one of claims 27 to 34, wherein the tip of each microprojection terminates in an elongate edge.

36) The microprojection array of any one of claims 27 to 35, wherein the tip has a width of from about 1 μm to about 2 μm and a length of about 20 μm to about 2mm.

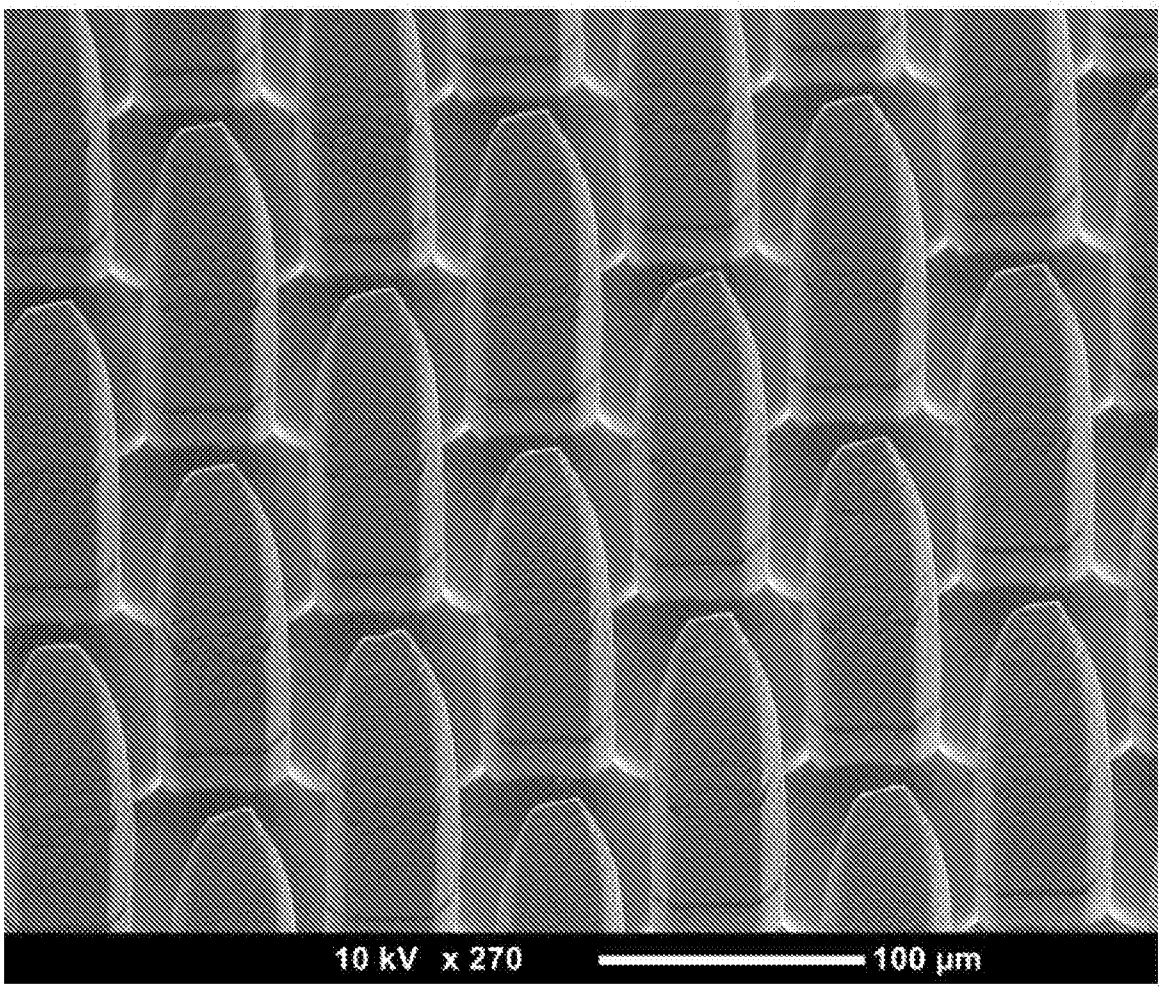


Fig. 1

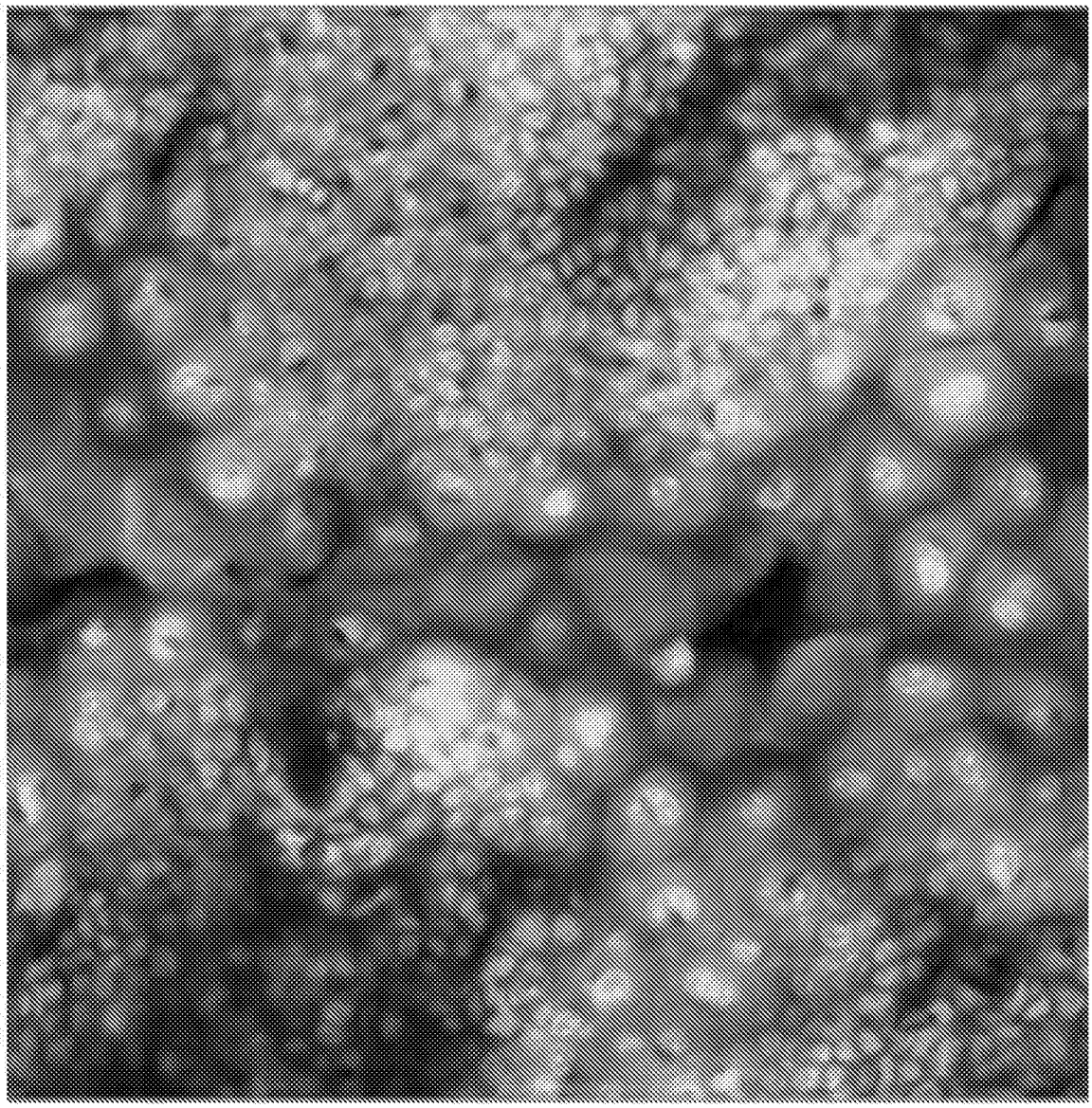
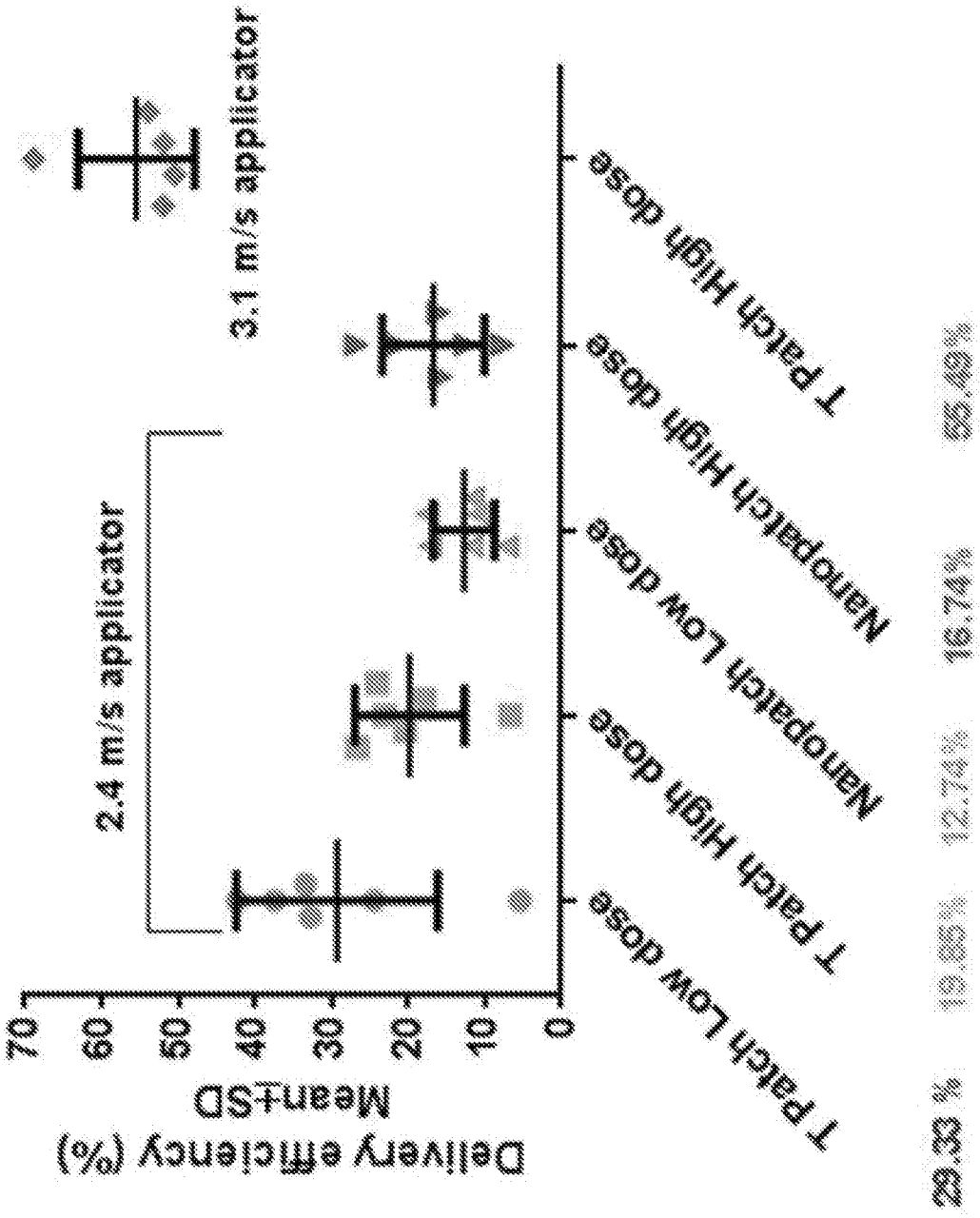


Fig. 2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50
40
30
20
10
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3.1 m/s applicator
T Patch Low dose
T Patch High dose
Nanopatch Low dose
Nanopatch High dose
T Patch High dose
28.33 %
19.65%
12.74%
16.74%
65.49%

Fig. 3

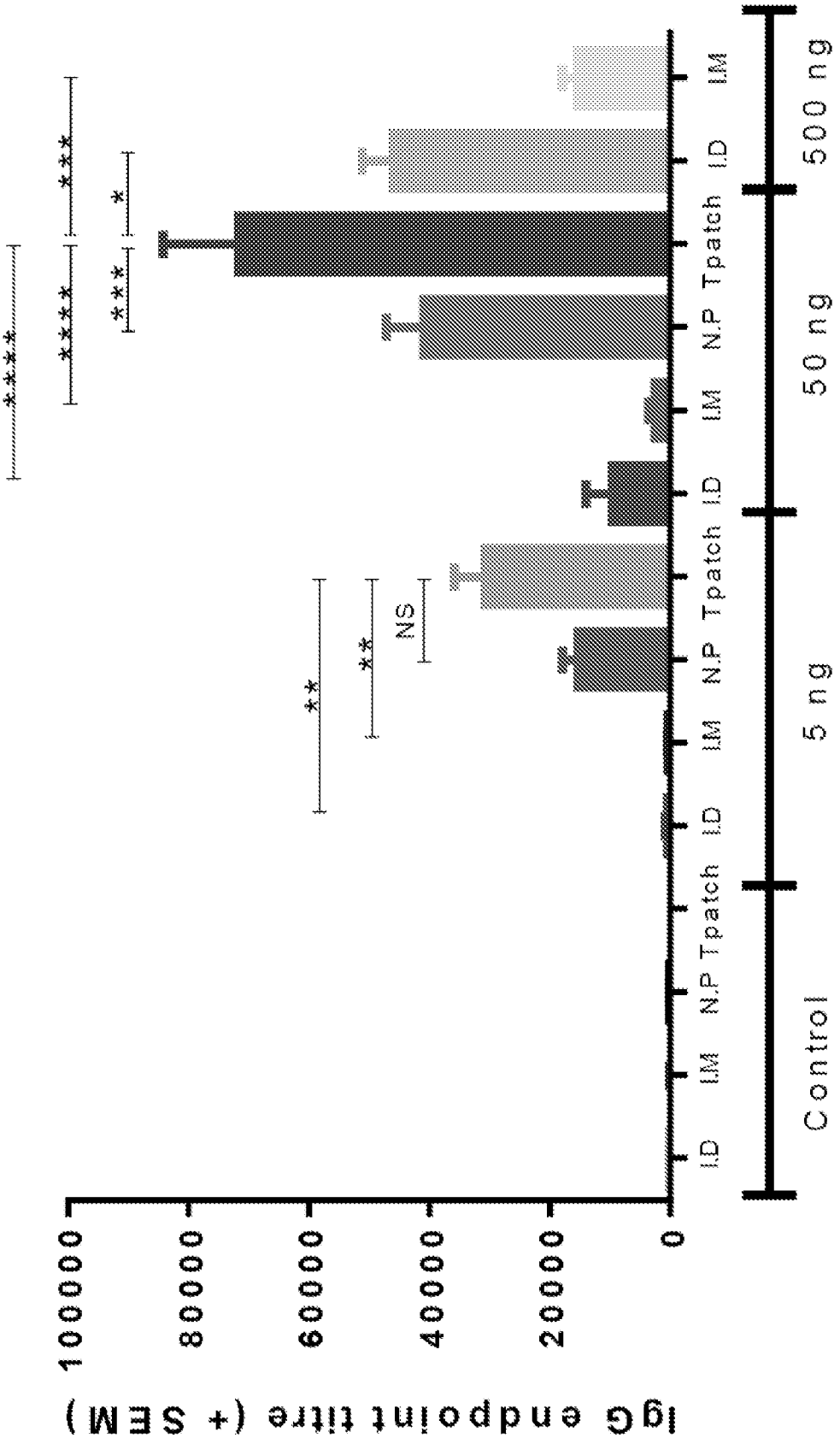
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Fig. 4

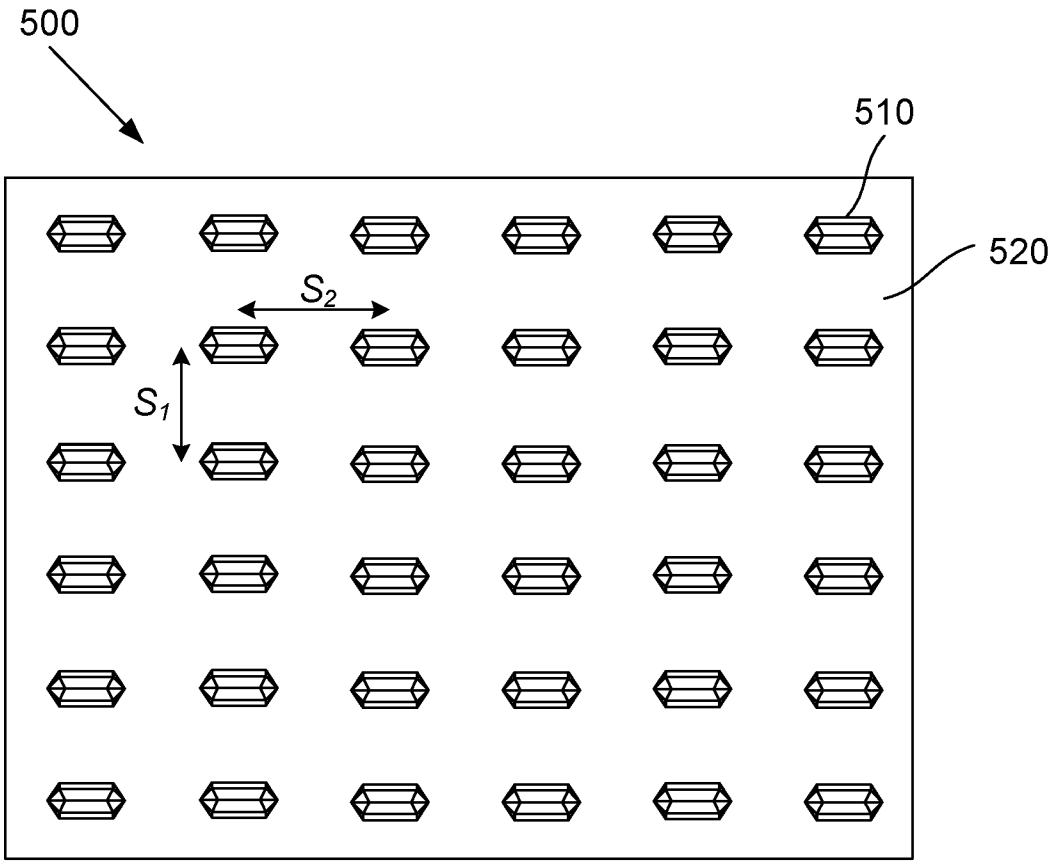

Fig. 5A

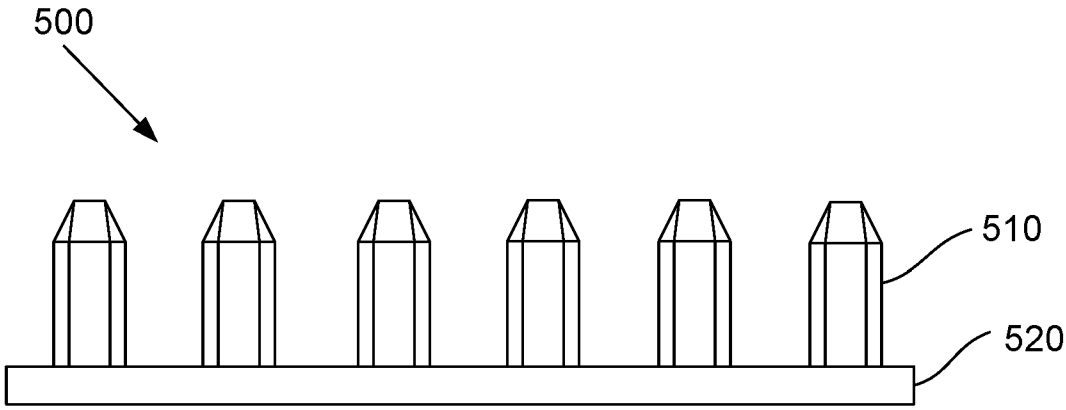

Fig. 5B

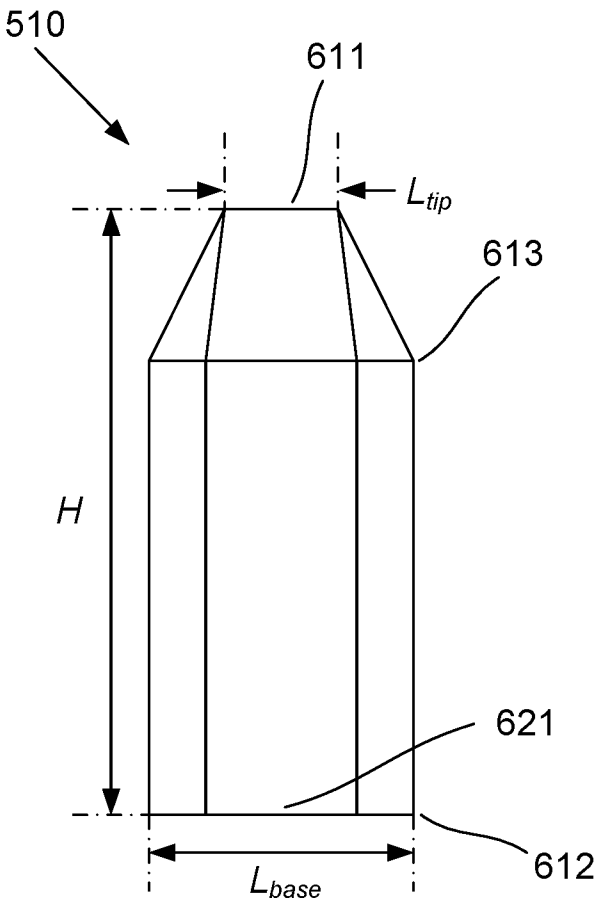

Fig. 6A

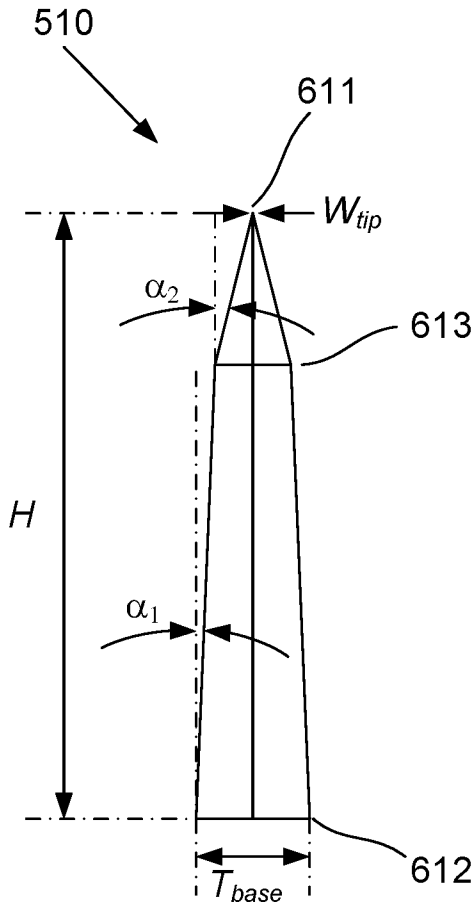

Fig. 6B

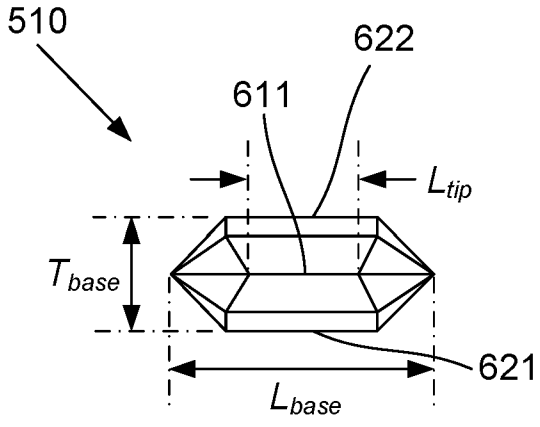

Fig. 6C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2016/050867

A. CLASSIFICATION OF SUBJECT MATTER

A61M 37/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPIAP databases limiting the search to classification index fields such as IPC and/or CPC -A61B17/-, A61M37-, A61M2037- and keywords and phrases such as microneedles, microprojections, projection, needle, penetration, vaccine delivery, micropuncture, tapering, polygonal, hexagonal, octagonal, skin puncture, intradermal and the like. MEDLINE database with keywords taper, hexagonal shape, microprojections, intradermal and the like. Google Patents and Google Scholar and databases associated with them with inventors' names in combination with keywords such as microprojection or micro projections. Applicant(s)/Inventor(s) name searched in internal databases by the International Search Authority (IP Australia).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2016	06 December 2016
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Viara Van Raad AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 62832676

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2016/050867**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	MA, B. et al. "A PZT Insulin Pump Integrated with a Silicon Micro Needle Array for Transdermal Drug Delivery," IEEE 56th Electronic Components and Technology Conference 2006, pages 677-681. Abstract, Figs. 3, 8 and 9, pages 678-680; col. 1, paragraph 2 to col. 2 end of second paragraph Entire document	1-4, 6-30, 32-36 5, 31
Y	US 2009/0292254 A1 (TOMONO) 26 November 2009 Abstract, Figs. 1, 5, 7 and 15, para[0069]-[0077], para[0088]-[0090]	1-4, 6-16, 22-30, 32-36
Y	US 2013/0131598 A1 (CORIUM INTERNATIONAL, INC.) 23 May 2013 Abstract, Fig. 5 and para[0036], para[0043]-[0048], para[0061], para[0094], claim 14.	1-4, 6-30, 32-36
Y	US 2006/0202385 A1 (XU et al.) 14 September 2006 Entire document, esp. Figs. 16A and 16H	1-4, 6-30, 32-36
Y	US 2004/0087992 A1 (CARTSTEIN et al.) 06 May 2004 Entire document, esp. Figs. 9-14	1-4, 6-30, 32-36
Y	US 6565532 B1 (YUZHAKOV et al.) 20 May 2003 Entire document, Figs. 36 and 37	1-4, 6-30, 32-36
X Y	US 2014/0257188 A1 (THE UNIVERSITY OF QUEENSLAND) 11 September 2014 Entire document, esp. Figs. 1E, 2C and para[0595], [0620], [0636], [0836]-[0851], Figs. 36C, 36D, 81B Entire document.	1-4, 6-30, 32-36 5, 31
Y	US 2013/0150822 A1 (ROSS) 13 June 2013 Entire document, esp. Figs. 8-26	5, 31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2016/050867

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Supplemental Box

Continuation of: **Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-26 are drawn to a microprojection array comprising a base and a tip , the base having parallel walls that has a small draught having varying angle between 1 to 20 degrees and further transitioning into angle between 20 to 70 degrees and hexagonal in shape. The feature of the said base and tip and the hexagonal shape is specific for this group of claims.
- Claims 27-36 drawn to a microprojection array comprising a base and a tip , the base having parallel walls that has a small draught having varying angle between 1 to 20 degrees and further transitioning into angle between 20 to 70 degrees and octagonal in shape. The feature of the said base and tip and the octagonal shape is specific for this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is that the walls of the microprojections have draught with varying angle between 1 to 20 degrees and further transitioning into angle between 20 to 70 degrees

However this feature does not make a contribution over the prior art because it is disclosed in:
D1: BIN, M. et al. "A PZT Insulin Pump Integrated with a Silicon Microneedle Array for Transdermal Drug Delivery," Microfluidics and Nanofluidics, 2006, No.2, Vol. 5, pages 417-423

Therefore in the light of this document this common feature cannot be a special technical feature. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a posteriori*.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2016/050867**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 2009/0292254 A1	26 November 2009	US 2009292254 A1	26 Nov 2009
		EP 2062611 A1	27 May 2009
		EP 2062612 A1	27 May 2009
		US 2008200883 A1	21 Aug 2008
		US 2008208134 A1	28 Aug 2008
		US 2009292255 A1	26 Nov 2009
		WO 2008020632 A1	21 Feb 2008
		WO 2008020633 A1	21 Feb 2008
US 2013/0131598 A1	23 May 2013	US 2013131598 A1	23 May 2013
		AU 2010238605 A1	24 Nov 2011
		AU 2010238605 B2	29 Oct 2015
		CA 2759850 A1	28 Oct 2010
		EP 2429627 A2	21 Mar 2012
		JP 2012524637 A	18 Oct 2012
		JP 5820805 B2	24 Nov 2015
		JP 2016025949 A	12 Feb 2016
		US 2011006458 A1	13 Jan 2011
		US 2013292886 A1	07 Nov 2013
		WO 2010124255 A2	28 Oct 2010
US 2006/0202385 A1	14 September 2006	US 2006202385 A1	14 Sep 2006
		US 7497980 B2	03 Mar 2009
		AU 2003278681 A1	26 May 2005
		CN 1691970 A	02 Nov 2005
		EP 1740256 A1	10 Jan 2007
		JP 2006513811 A	27 Apr 2006
		JP 4457229 B2	28 Apr 2010
		WO 2005044364 A1	19 May 2005
US 2004/0087992 A1	06 May 2004	US 2004087992 A1	06 May 2004
		AU 1316702 A	29 Apr 2002
		AU 1316802 A	29 Apr 2002
		AU 2002333636 A1	01 Apr 2003
		CA 2422907 A1	25 Apr 2002
		CA 2422909 A1	25 Apr 2002

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2016/050867**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		CA 2456626 A1	27 Mar 2003
		CA 2460673 A1	27 Mar 2003
		CN 1477983 A	25 Feb 2004
		CN 1665561 A	07 Sep 2005
		EP 1326673 A2	16 Jul 2003
		EP 1326673 B1	14 Feb 2007
		EP 1326674 A2	16 Jul 2003
		EP 1326674 B1	21 Sep 2005
		EP 1424928 A1	09 Jun 2004
		EP 1425064 A2	09 Jun 2004
		JP 2005502414 A	27 Jan 2005
		JP 4391818 B2	24 Dec 2009
		JP 2004521669 A	22 Jul 2004
		JP 4676128 B2	27 Apr 2011
		JP 2004516868 A	10 Jun 2004
		JP 2005503210 A	03 Feb 2005
		US 2002045907 A1	18 Apr 2002
		US 6821281 B2	23 Nov 2004
		US 2002045859 A1	18 Apr 2002
		US 7108681 B2	19 Sep 2006
		US 2002177858 A1	28 Nov 2002
		US 7131987 B2	07 Nov 2006
		US 2003220656 A1	27 Nov 2003
		US 7828827 B2	09 Nov 2010
		US 2006129174 A1	15 Jun 2006
		US 8216190 B2	10 Jul 2012
		US 2011046638 A1	24 Feb 2011
		US 8702726 B2	22 Apr 2014
		US 2005090803 A1	28 Apr 2005
		US 2006149297 A1	06 Jul 2006
		WO 0232331 A2	25 Apr 2002
		WO 0232480 A2	25 Apr 2002
		WO 03024290 A1	27 Mar 2003
		WO 03024518 A2	27 Mar 2003

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2016/050867**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 6565532 B1	20 May 2003	US 6565532 B1	20 May 2003
		AU 5727900 A	28 Dec 2000
		AU 5728000 A	28 Dec 2000
		AU 5728100 A	28 Dec 2000
		AU 6505601 A	11 Dec 2001
		CA 2376283 A1	14 Dec 2000
		CA 2376285 A1	14 Dec 2000
		CA 2376286 A1	14 Dec 2000
		CA 2591168 A1	14 Dec 2000
		CA 2689890 A1	14 Dec 2000
		EP 1183064 A1	06 Mar 2002
		EP 1183064 B1	19 Dec 2012
		EP 1183065 A1	06 Mar 2002
		EP 1183065 B1	23 Mar 2016
		EP 1183066 A1	06 Mar 2002
		EP 1183066 B1	26 Dec 2012
		JP 2003501161 A	14 Jan 2003
		JP 4436992 B2	24 Mar 2010
		JP 2003501162 A	14 Jan 2003
		JP 2003501163 A	14 Jan 2003
		TW 425294 B	11 Mar 2001
		TW 458791 B	11 Oct 2001
		TW 512067 B	01 Dec 2002
		US 6256533 B1	03 Jul 2001
		US 6312612 B1	06 Nov 2001
		US 6379324 B1	30 Apr 2002
		US 6451240 B1	17 Sep 2002
		US 2002020688 A1	21 Feb 2002
		US 6471903 B2	29 Oct 2002
		US 6652478 B1	25 Nov 2003
		US 6931277 B1	16 Aug 2005
		US 2005209565 A1	22 Sep 2005
		US 7416541 B2	26 Aug 2008
		WO 0074764 A1	14 Dec 2000
		WO 0074765 A1	14 Dec 2000

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2016/050867**

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Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		WO 0074766 A1	14 Dec 2000
		WO 0191846 A2	06 Dec 2001

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2016/050867**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 2014/0257188 A1	11 September 2014	US 2014257188 A1	11 Sep 2014
		AU 2012323782 A1	24 Apr 2014
		EP 2765927 A1	20 Aug 2014
		HK 1201136 A1	28 Aug 2015
		WO 2013053022 A1	18 Apr 2013
US 2013/0150822 A1	13 June 2013	US 2013150822 A1	13 Jun 2013
		AU 2011246879 A1	08 Nov 2012
		AU 2011246879 B2	17 Sep 2015
		AU 2011246880 A1	08 Nov 2012
		AU 2011246880 B2	29 Oct 2015
		AU 2011246881 A1	08 Nov 2012
		AU 2011246881 B2	11 Feb 2016
		AU 2011246882 A1	08 Nov 2012
		AU 2011246882 B2	25 Feb 2016
		AU 2011288209 A1	08 Nov 2012
		AU 2011288209 B2	24 Sep 2015
		AU 2011311255 A1	08 Nov 2012
		AU 2011311255 B2	08 Oct 2015
		CA 2796196 A1	03 Nov 2011
		CA 2796198 A1	03 Nov 2011
		CA 2796965 A1	12 Apr 2012
		CA 2797202 A1	16 Feb 2012
		CA 2797204 A1	03 Nov 2011
		CA 2797205 A1	03 Nov 2011
		CN 102958555 A	06 Mar 2013
		CN 102958556 A	06 Mar 2013
		CN 102958557 A	06 Mar 2013
		CN 102958557 B	03 Aug 2016
		CN 102971037 A	13 Mar 2013
		CN 102971037 B	25 May 2016
		CN 102985131 A	20 Mar 2013
		CN 102985131 B	29 Jun 2016
		EP 2563450 A2	06 Mar 2013
		EP 2563451 A2	06 Mar 2013
		EP 2563452 A2	06 Mar 2013

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2016/050867**

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Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		EP 2563453 A2	06 Mar 2013
		EP 2563454 A2	06 Mar 2013
		EP 2563455 A1	06 Mar 2013
		JP 2013524985 A	20 Jun 2013
		JP 5860032 B2	16 Feb 2016
		JP 2013532997 A	22 Aug 2013
		JP 5860033 B2	16 Feb 2016
		JP 2013524986 A	20 Jun 2013
		JP 5860453 B2	16 Feb 2016
		JP 2013529100 A	18 Jul 2013
		JP 5868953 B2	24 Feb 2016
		JP 2013524987 A	20 Jun 2013
		JP 5871907 B2	01 Mar 2016
		JP 2016055196 A	21 Apr 2016
		KR 20130058012 A	03 Jun 2013
		KR 20130058703 A	04 Jun 2013
		KR 20130058704 A	04 Jun 2013
		KR 20130094213 A	23 Aug 2013
		KR 20130094214 A	23 Aug 2013
		MX 2012012564 A	21 Nov 2012
		MX 336139 B	08 Jan 2016
		MX 2012012317 A	21 Nov 2012
		MX 2012012437 A	02 Dec 2013
		MX 2012012563 A	23 Nov 2012
		MX 2012012566 A	21 Nov 2012
		MX 2012012567 A	21 Nov 2012
		RU 2012150731 A	10 Jun 2014
		RU 2012150730 A	10 Jun 2014
		RU 2012150726 A	10 Jun 2014
		RU 2012150729 A	10 Jun 2014
		RU 2012150728 A	10 Jun 2014
		RU 2012150725 A	10 Jun 2014
		US 2011270221 A1	03 Nov 2011
		US 2012187814 A1	26 Jul 2012
		US 2013144217 A1	06 Jun 2013
		US 2013144257 A1	06 Jun 2013

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Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		US 2013158505 A1	20 Jun 2013
		US 2013165861 A1	27 Jun 2013
		WO 2011135530 A2	03 Nov 2011
		WO 2011135531 A2	03 Nov 2011
		WO 2011135532 A2	03 Nov 2011
		WO 2011135533 A2	03 Nov 2011
		WO 2012020332 A2	16 Feb 2012
		WO 2012046149 A1	12 Apr 2012

End of Annex

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