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(54) **Titre : PROCEDES POUR LA GENERATION DE NOUVEAUX FOLLICULES CAPILLAIRES, DE TRAITEMENT DE LA CALVITIE, ET L'ELIMINATION DE POILS**
(54) **Title: METHODS FOR GENERATING NEW HAIR FOLLICLES, TREATING BALDNESS, AND HAIR REMOVAL**



(57) **Abrégé/Abstract:**

The present invention provides methods of treating baldness in a subject and generating new hair follicles, comprising epidermal disruption and administration of a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell. The present invention also provides methods for hair removal and inducing hair pigmentation.

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(54) Title: METHODS FOR GENERATING NEW HAIR FOLLICLES, TREATING BALDNESS, AND HAIR REMOVAL



(57) Abstract: The present invention provides methods of treating baldness in a subject and generating new hair follicles, comprising epidermal disruption and administration of a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell. The present invention also provides methods for hair removal and inducing hair pigmentation.

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**METHODS FOR GENERATING NEW HAIR FOLLICLES, TREATING BALDNESS,
AND HAIR REMOVAL**

FIELD OF INVENTION

5 [0001] The present invention provides methods of treating baldness in a subject and generating new hair follicles, comprising epidermal disruption and administration of a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell. The present invention also provides methods for hair removal and inducing hair pigmentation.

BACKGROUND OF THE INVENTION

10 [0002] Follicular neogenesis is defined as the generation of new hair follicles (HF) after birth. Humans are born with a full complement of HF, which can change in size and growth characteristics as in early baldness or can ultimately degenerate and disappear as in late stages of baldness or in permanent scarring (cicatricial) alopecias. Therefore, the generation of new HF is desirable in the treatment of common baldness as well as less common hair loss conditions, such as discoid lupus
15 erythematosus, congenital hypotrichosis, lichen planopilaris and other scarring alopecias.

SUMMARY OF THE INVENTION

[0003] The present invention provides methods of treating baldness in a subject and generating new hair follicles (HF), comprising epidermal disruption and administration of a compound that
20 promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell. The present invention also provides methods for hair removal and inducing hair pigmentation.

[0004] In one embodiment, the present invention provides a method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting the epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region
25 with a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell, thereby generating a hair follicle in a scalp, eyebrow, or scarred region of a subject.

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[0005] In another embodiment, the present invention provides a method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting the epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell, thereby generating a hair follicle in a scalp, eyebrow, or scarred region of a subject.

[0006] In another embodiment, the present invention provides a method for treating baldness in a scalp, eyebrow, or scarred region, comprising the steps of: (a) disrupting the epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle (HF) cell, thereby treating baldness in a scalp, eyebrow, or scarred region.

[0007] In another embodiment, the present invention provides a method for treating baldness in a scalp, eyebrow, or scarred region, comprising the steps of: (a) disrupting the epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell, thereby treating baldness in a scalp, eyebrow, or scarred region. In another embodiment, the baldness is an androgenetic alopecia (AGA)-induced baldness. Each possibility represents a separate embodiment of the present invention.

[0008] In another embodiment, the present invention provides a method for removal of an HF from a skin or scalp of a subject, comprising the steps of: (a) disrupting an epidermis of the skin or scalp; and (b) contacting the skin or scalp with either: (i) an EGF protein; (ii) an EGF receptor; (iii) a nucleotide encoding an EGF protein or EGF receptor; or (iv) a compound or factor that activates a EGF protein or EGF receptor, thereby removing an HF from a skin or scalp of a subject.

[0009] In another embodiment, the present invention provides a method for increasing a size of a hair follicle in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a compound or factor that promotes a differentiation of an

uncommitted epidermal cell into a hair follicle cell, thereby increasing a size of a hair follicle in a scalp, eyebrow, or scarred region of a subject.

[00010] In another embodiment, the present invention provides a method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a)

5 disrupting an epidermis of said scalp, eyebrow, or scarred region; and (b) contacting said scalp, eyebrow, or scarred region with a cell selected from (a) a precursor cell that is capable of differentiation into a hair follicle cell; (b) an inductive cell that is capable of inducing differentiation of an uncommitted epidermal cell into a hair follicle cell; or (c) a hair follicle or portion thereof, thereby generating a hair follicle in a scalp, eyebrow, or scarred region of a
10 subject. In another embodiment, step (b) is performed 3-12 days after step (a). Each possibility represents a separate embodiment of the present invention.

[00011] In another embodiment, the present invention provides a method for treating an AGA in a scalp, comprising the steps of: (a) disrupting an epidermis of said scalp; and (b) contacting said

15 scalp with a cell selected from (a) a precursor cell that is capable of differentiation into a hair follicle cell; (b) an inductive cell that is capable of inducing differentiation of an uncommitted epidermal cell into a hair follicle cell; or (c) a hair follicle or portion thereof, thereby treating an AGA in a scalp. In another embodiment, step (b) is performed 3-12 days after step (a). Each possibility represents a separate embodiment of the present invention.

[00011a] In another embodiment, there is provided a method for stimulating hair growth in a

20 balding scalp of a human subject using a compound or factor that enhances the size of a hair follicle cell comprising: contacting a disrupted area of the balding scalp of said human subject with minoxidil, wherein the disrupted area comprises perforated epidermis or epidermal layers of the balding scalp of said human subject.

[00011b] In another embodiment, there is provided use of a compound or factor that enhances

25 the size of a hair follicle cell for stimulating hair growth in a balding scalp of a human subject, comprising: contacting a disrupted area of the balding scalp of said human subject with minoxidil, wherein the disrupted area comprises perforated epidermis or epidermal layers of the balding scalp of said human subject.

BRIEF DESCRIPTION OF THE FIGURES

5 [00012] Figure 1: Epidermal abrasion results in *de novo* hair follicle (HF) formation. HF at progressive stages of development are depicted in the left, center, and right panels. The arrow in the left panel indicates a hair germ. The dark stained cells are progeny of HF stem cells in the bulge.

[00013] Figure 2: BrdU labeling of HF following epidermal abrasion. HF at progressive stages of development are depicted in the left, center, and right panels.

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[00014] Figure 3. The wound site did not contain HF immediately after re-epithelialization. Top view (left panel) and tissue section (right panel) of the site 10 days after wound induction.

[00015] Figure 4. Appearance of hair germs 12 days after wound induction. Arrow indicates hair germ.

5 [00016] Figure 5. Epidermal Disruption-Induced HF neogenesis (EDIHN)-induced hair germs express K17. Two different hair germs are depicted in the left and right panels.

[00017] Figure 6. EDIHN-induced hair germs contain dermal papilla (DP) cells, as evidenced by alkaline phosphatase (AP) staining. Arrows indicate DP cells. Left panel: hair germs. Right panel: HF at a further developmental stage.

10 [00018] Figure 7. Histological comparison between EDIHN-induced and embryonic HF. Top left, second from left, third from left, and right panels: Progressive stages of EDIHN-induced HF development. Bottom left, center, and right panels: Progressive stages of and embryonic HF development.

15 [00019] Figure 8. Induction of several markers of embryonic HF development, *Lef1* (left panel), *wingless/int (Wnt) 10b* (center panel), and *sonic hedgehog (Shh)* (right panel), by EDIHN. HF structures are indicated by arrowheads.

[00020] Figure 9. Proliferative activity during EDIHN, as evidenced by BrdU pulse-labeling. Progressive stages of HF development are depicted in the left, center, and right panels.

20 [00021] Figure 10. Induction of HF markers S100A3 (left panel; tissue section parallel to HF axis) and S100A6 (right panel; cross-sectional view of follicle) by EDIHN.

[00022] Figure 11. New hair growth 25 days (left panel) and 45 days (right panel) after wound induction.

[00023] Figure 12. Schematic of whole-mount EDIHN assay.

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[00024] Figure 13. Repopulation of stem cells in the bulge of EDIHN-induced HF, as evidenced by retention of BrdU label following a chase period. Left panel: lower magnification: 50 X. Right panel: higher magnification: 400 X.

5 [00025] Figure 14. A. Stem cells in EDIHN-induced HF express K15. Left top panel: Top view of wound site. Bottom, far left panel: epidermis whole mount; bottom, second from left panel: same as [bottom, far left] panel but viewed under white light; right panel: tissue sections. B. Neogenesis HF proceed to next hair cycle.

[00026] Figure 15. Schematic of creation of new HF by EDIHN.

10 [00027] Figure 16. No new HF are evident 11 days after wound induction in 21-day-old mice. Top panel: macroscopic examination; bottom left panel: AP staining of the dermis; bottom right panel: K17 staining of the epidermis.

[00028] Figure 17. 14 days after wound induction, new HF have begun to form as evidenced by AP staining of the dermis (left panel) and K17 staining of the epidermis (right panel). Main panels: 10 X magnification. Inserts: 80 X magnification.

15 [00029] Figure 18. 17 days after wound induction, new HF are more developed. Left panel: AP staining of the dermis; right panel: K17 staining of the epidermis. Main panels: 10 X magnification. Inserts: 80 X magnification.

20 [00030] Figure 19. Wounds closed similar in mice subjected to depilation, then wounding (left 3 mice in each panel) vs. wounding alone (right 4 mice in each panel). Left panel: immediately following wounding. Right panel: 10 days following wounding.

[00031] Figure 20. Anagen induction by depilation prior to wounding enhances the efficiency of EDIHN. A. Top panel: lower left panel AP staining of the dermis; lower right panel: K17 staining of the epidermis. B. Graphical representation of enhancement of EDIHN by depilation.

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- [00032] Figure 21. A. EDIHN in human skin grafted to immunodeficient (scid) mice, seven days after induction of an excisional wound. Arrows indicate new HF. B. Dermal abrasion of human skin grafts results in EDIHN. Human adult skin (W) was grafted onto mice, abraded, and examined seven days later, by staining for S100A6 (first, second, and fourth rows) or S100A4 (third row). Hair germs (HG) and dermal papilla (DP) are indicated. Human fetal skin (F) with normal developing hair follicles is shown for comparison. Mouse skin 17d post wounding was included as a control (top left panel).
- 10 [00033]
- [00034] Figure 22. Pigmented hair follicle neogenesis observed in the skin of Dkk1-expressing mice following EDIHN A. 3.2x magnification. B. 8x magnification.
- [00035] Figure 23. Control mice lacked pigmented HF.
- 15 [00036] Figure 24. EGF inhibits HF formation by EDIHN. A. K17 staining of wounded skin of representative mouse treated with EGF. Magnification is 4x. B. High magnification view (10x) of skin depicted in (A). C. K17 staining of wounded skin of representative control mouse that received no EGF after wounding. Magnification is 4x. D. Higher magnification view (10X) of skin depicted in (D).
- 20 [00037] Figure 25 Administration of an EGF receptor inhibitor (AG1478) leads to generation of more and larger HF compared with controls. A. Top: skin of 2 control mice. Outer dashed line indicates the extent of the wounded area after contraction and healing; inner dashed line indicates the area of neogenesis. Bottom: skin of 2 treated mice, in which the wounded area and area of neogenesis largely coincide, with the exception of a small area on the left side of the encircled area
- 25

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in each panel. B. Large hair follicles developed in the wounded area in the AG1478-injected mice. Left panel: epidermis stained for K17, with three large hair follicles next to each other. Right panel: dermis stained for AP with large coalescing DP areas. Scale Bars: 200 μ m.

[00038] Figure 26. A. Increased hair follicle formation in K14-Wnt7a mice. Left panel: Wnt7a transgenic mice. Right panel: control (wild-type) mice. B. Quantitation of experiment with 4 week old mice. C. Quantitation of experiment with 3 week old mice

DETAILED DESCRIPTION OF THE INVENTION

[00039] The present invention provides methods of treating baldness in a subject and generating new HF, comprising epidermal disruption and administration of a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell. The present invention also provides methods for hair removal and inducing hair pigmentation.

[00040] In one embodiment, the present invention provides a method for generating a hair follicle (HF) in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a compound that promotes a differentiation of an uncommitted epidermal cell into an HF cell, thereby generating an HF in a scalp, eyebrow, or scarred region of a subject.

[00041] In another embodiment, the present invention provides a method for generating an HF in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a factor that promotes a differentiation of an uncommitted epidermal cell into an HF cell, thereby generating an HF in a scalp, eyebrow, or scarred region of a subject.

[00042] In another embodiment, the present invention provides a method for generating a new HF in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell, thereby generating a new HF in a scalp, eyebrow, or scarred region of a subject.

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[00043] In another embodiment, the present invention provides a method for increasing the number of HF in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a compound or factor that promotes a differentiation of an uncommitted epidermal cell into an HF cell, thereby increasing the number of HF in a scalp, eyebrow, or scarred region of a subject.

[00044] In another embodiment, the present invention provides a use of a compound or factor that promotes a differentiation of an uncommitted epidermal cell into an HF cell, for the preparation of a pharmaceutical composition for use in a method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the compound or factor.

[00045] In another embodiment, the present invention provides a use of a compound or factor that promotes a differentiation of an uncommitted epidermal cell into an HF cell, for the preparation of a pharmaceutical composition for use in a method for treating baldness in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the compound or factor.

[00046] In another embodiment, the present invention provides a use of a compound or factor that promotes a differentiation of an uncommitted epidermal cell into an HF cell, for the preparation of a pharmaceutical composition for use in a method for treating AGA in a scalp of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp with the compound or factor.

[00047] In another embodiment, the present invention provides a method for increasing a size of a hair follicle in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a compound or factor that promotes a differentiation of an

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uncommitted epidermal cell into an HF cell, thereby increasing a size of a hair follicle in a scalp, eyebrow, or scarred region of a subject. In another embodiment, the factor is an inhibitor of an EGF protein or an EGFR. In another embodiment, the factor is a Hedgehog protein, a nucleotide encoding same or an activator of same. In another embodiment, the factor is an androgen antagonist. In another embodiment, the factor is any other compound or factor that promotes a differentiation of an uncommitted epidermal cell into an HF cell. Each possibility represents a separate embodiment of the present invention.

[00048] In another embodiment, the present invention provides a method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting an epidermis of said scalp, eyebrow, or scarred region; and (b) contacting said scalp, eyebrow, or scarred region with a cell selected from (a) a precursor cell that is capable of differentiation into a hair follicle cell; (b) an inductive cell that is capable of inducing differentiation of an uncommitted epidermal cell into a hair follicle cell; or (c) a hair follicle or portion thereof, thereby generating a hair follicle in a scalp, eyebrow, or scarred region of a subject. In another embodiment, step (b) is performed 3-12 days after step (a). Each possibility represents a separate embodiment of the present invention.

[00049] The precursor cell of methods and compositions of the present invention, is, in another embodiment, a HF stem cell. In another embodiment, the precursor cell is an epidermal cell. In another embodiment, the precursor cell is a dermal papilla cell. In another embodiment, the precursor cell is a connective tissue sheath cell. In another embodiment, the precursor cell is any other type of cell known in the art that is capable of differentiation into a hair follicle cell. Each possibility represents a separate embodiment of the present invention.

[00050] In another embodiment, the present invention provides a method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting an epidermis of said scalp, eyebrow, or scarred region; and (b) contacting said scalp, eyebrow, or scarred region with a precursor cell that is capable of differentiation into a hair follicle cell, thereby generating a hair follicle in a scalp, eyebrow, or scarred region of a subject.

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[00051] In another embodiment, the present invention provides a method for treating an AGA in a scalp, comprising the steps of: (a) disrupting an epidermis of said scalp; and (b) contacting said scalp with a cell selected from (a) a precursor cell that is capable of differentiation into a hair follicle cell; (b) an inductive cell that is capable of inducing differentiation of an uncommitted epidermal
5 cell into a hair follicle cell; or (c) a hair follicle or portion thereof, thereby treating an AGA in a scalp. In another embodiment, step (b) is performed 3-12 days after step (a). Each possibility represents a separate embodiment of the present invention.

[00052] In another embodiment, the present invention provides a method for treating an AGA in a scalp, comprising the steps of: (a) disrupting an epidermis of said scalp; and (b) contacting said
10 scalp with a precursor cell that is capable of differentiation into a hair follicle cell, thereby treating an AGA in a scalp.

[00053] In another embodiment, the inductive cell is a mesenchymal cell. In another embodiment, the inductive cell is any other type of inductive cell enumerated herein. In another embodiment, the inductive cell is any other type of inductive cell known in the art. Each possibility represents a
15 separate embodiment of the present invention.

[00054] "Contacting" as used herein refers, in another embodiment, to bringing the scalp, eyebrow, etc, into to contact with the compound, factor, cell, etc. In another embodiment, the term refers to embedding the compound, factor, cell, etc into the scalp, eyebrow, etc. In another embodiment, the term refers to injecting the compound, factor, cell, etc into the scalp, eyebrow, etc. In another
20 embodiment, term refers to any other type of contacting known in the art. Each possibility represents a separate embodiment of the present invention.

[00055] "Promotes a differentiation" refers, in another embodiment, to the act of increasing the percentage of cells that will differentiate as indicated. In another embodiment, the term refers to increasing the number of cells per unit area of skin that will differentiate. In another embodiment, the
25 promoter of differentiation is active in the milieu of the skin. Each possibility represents a separate embodiment of the present invention.

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[00056] "Uncommitted epidermal cell" refers, in another embodiment, to an epidermal stem cell. In another embodiment, the epidermal cell is a bulge cell. In another embodiment, the epidermal cell is a bulge-derived cell. In another embodiment, the epidermal cell is any other type of cell known in the art that can be induced to differentiate into an HF cell.

5 [00057] The "HF cell" that results from the differentiation is, in another embodiment, an HF stem cell. In another embodiment, the HF cell is a dermal papilla cell. In another embodiment, the HF cell is a bulb cell. In another embodiment, the HF cell is a matrix cell. In another embodiment, the HF cell is a hair shaft cell. In another embodiment, the HF cell is an inner root sheath cell. In another embodiment, the HF cell is an outer root sheath cell. In another embodiment, the HF cell is a
10 melanocyte stem cell. In another embodiment, the HF cell is a melanocyte. Each type of uncommitted epidermal cell and HF cell represents a separate embodiment of the present invention.

[00058] In another embodiment, the present invention provides a method for treating baldness in a scalp, eyebrow, or scarred region, comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a
15 compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle (HF) cell, thereby treating baldness in a scalp, eyebrow, or scarred region. In another embodiment, the baldness is an androgenetic alopecia (AGA)-induced baldness. Each possibility represents a separate embodiment of the present invention.

[00059] In another embodiment, the present invention provides a method for treating baldness in a
20 scalp, eyebrow, or scarred region, comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with a factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell, thereby treating baldness in a scalp, eyebrow, or scarred region. In another embodiment, the baldness is an androgenetic alopecia (AGA)-induced baldness. Each possibility represents a separate embodiment
25 of the present invention.

[00060] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is administered in a solution. In another embodiment, the

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compound or factor is administed in a cream. In another embodiment, the compound or factor is administed in an ointment. In another embodiment, the compound or factor is administed in a slow release formulation. In another embodiment, the compound or factor is administed in a liposome encapsulated formulation. In another embodiment, the compound or factor is directly injected. In another embodiment, the compound or factor is administed by any other method known in the art. Each possibility represents a separate embodiment of the present invention.

[00061] The compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is, in another embodiment, an inhibitor of an Epidermal Growth Factor (EGF). In another embodiment, the compound or factor is an inhibitor of an EGF receptor. Each possibility represents a separate embodiment of the present invention.

[00062] As provided herein (Example 11), activating one or more pathways in which EGF is involved (by injection of EGF) blocks the formation of HF. Thus, antagonizing the pathway increases HF formation, as demonstrated in Example 12.

[00063] In another embodiment, the inhibitor of an EGF or an EGF receptor is panitumumab. In another embodiment, the inhibitor is AG1478. In another embodiment, the inhibitor is nimotuzumab. In another embodiment, the inhibitor is an antibody that binds EGF or EGFR. In another embodiment, the inhibitor is HuMax-EGFR® (Genmab, Copenhagen, Denmark). In another embodiment, the inhibitor is cetuximab. In another embodiment, the inhibitor is IMC 11F8. In another embodiment, the inhibitor is matuzumab. In another embodiment, the inhibitor is SC 100. In another embodiment, the inhibitor is ALT 110. In another embodiment, the inhibitor is PX 1032. In another embodiment, the inhibitor is BMS 599626. In another embodiment, the inhibitor is MDX 214. In another embodiment, the inhibitor is PX 1041. In another embodiment, the inhibitor is any other inhibitor of an EGF or an EGF receptor known in the art. Each possibility represents a separate embodiment of the present invention.

[00064] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is an inhibitor of a tyrosine kinase activity of an EGF receptor. In another embodiment, the inhibitor is gefitinib. In another embodiment, the inhibitor is

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erlotinib. In another embodiment, the inhibitor is canertinib. In another embodiment, the inhibitor is leflunomide. In another embodiment, the inhibitor is A77 1726. In another embodiment, the inhibitor is pelitinib. In another embodiment, the inhibitor is ZD 1839. In another embodiment, the inhibitor is CL 387785. In another embodiment, the inhibitor is EKI 785. In another embodiment, the inhibitor is vandetanib. In another embodiment, the inhibitor is any other inhibitor of a tyrosine kinase activity of an EGF receptor known in the art. Each possibility represents a separate embodiment of the present invention.

[00065] In another embodiment, the EGF or EGFR antagonist is a carboxypeptidase inhibitor from potato (PCI) protein or a homologue, fragment or mimetic thereof. In another embodiment, the EGF or EGFR antagonist is a sprouty protein or a homologue, fragment or mimetic thereof. In another embodiment, the EGF or EGFR antagonist is an Argos protein or a homologue, fragment or mimetic thereof. In another embodiment, the EGF or EGFR antagonist is a lefty protein or a homologue, fragment or mimetic thereof. In another embodiment, the EGF or EGFR antagonist is an antibody that recognizes EGF or EGFR, or a fragment or mimetic thereof. In another embodiment, the EGF or EGFR antagonist is small molecule inhibitor that binds and reduces the activity of EGF or EGFR. In another embodiment, the EGF or EGFR antagonist is CRM197. In another embodiment, the EGF or EGFR antagonist is IMC-C225 (ImClone Systems, New York, NY). In another embodiment, the EGF or EGFR antagonist is any other antagonist of EGF or EGFR known in the art. Each possibility represents a separate embodiment of the present invention.

[00066] In another embodiment, the present invention provides a use of an inhibitor of an EGF protein or an EGF receptor for the preparation of a pharmaceutical composition for use in a method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the inhibitor of an EGF protein or an EGF receptor.

[00067] In another embodiment, the present invention provides a use of an inhibitor of an EGF protein or an EGF receptor for the preparation of a pharmaceutical composition for use in a method

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for treating baldness in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the inhibitor of an EGF protein or an EGF receptor.

[00068] In another embodiment, the present invention provides a use of an inhibitor of an EGF protein or an EGF receptor for the preparation of a pharmaceutical composition for use in a method for treating AGA in a scalp of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp with the inhibitor of an EGF protein or an EGF receptor.

[00069] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is a β -catenin protein. In another embodiment, the compound or factor is a nucleotide that encodes a β -catenin protein. In another embodiment, the compound or factor is an activator of a β -catenin protein. In another embodiment, the compound or factor is an inhibitor of a protein that suppresses an activity of the β -catenin protein. Each possibility represents a separate embodiment of the present invention.

[00070] In another embodiment, the present invention provides a use of (a) a β -catenin protein; (b) a nucleotide encoding a β -catenin protein; or (c) a compound or factor that activates a β -catenin protein, for the preparation of a pharmaceutical composition for use in a method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the β -catenin protein, nucleotide, compound or factor.

[00071] In another embodiment, the present invention provides a use of (a) a β -catenin protein; (b) a nucleotide encoding a β -catenin protein; or (c) a compound or factor that activates a β -catenin protein, for the preparation of a pharmaceutical composition for use in a method for treating baldness in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the β -catenin protein, nucleotide, compound or factor.

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[00072] In another embodiment, the present invention provides a use of (a) a β -catenin protein; (b) a nucleotide encoding a β -catenin protein; or (c) a compound or factor that activates a β -catenin protein, for the preparation of a pharmaceutical composition for use in a method for treating AGA in a scalp of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp with the β -catenin protein, nucleotide, compound or factor.

[00073] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is a fibroblast growth factor (FGF) protein. In another embodiment, the compound or factor is a nucleotide that encodes an FGF protein. In another embodiment, the compound or factor is an FGF receptor. In another embodiment, the compound or factor is a nucleotide that encodes an FGF receptor. In another embodiment, the compound or factor is an activator of an FGF protein. In another embodiment, the compound or factor is an activator of FGF receptor. In another embodiment, the compound or factor is an inhibitor of a protein that suppresses an activity of the FGF protein or FGF receptor. In another embodiment, the protein that is inhibited is an FGF binding protein. In another embodiment, the protein that is inhibited is FGF-bp1. Each possibility represents a separate embodiment of the present invention.

[00074] Is provided herein, FGF and its receptor are upregulated, under the conditions utilized herein, upon HF stem cell differentiation (Example 9). Moreover, FGF-bp1 is downregulated, under the conditions utilized herein, upon HF stem cell differentiation. Thus, FGF and its receptor promote differentiation of uncommitted epidermal cells into HF cells.

[00075] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is an ectodysplasin protein (referred to, in another embodiment, as "eda"; in another embodiment, as "ectodermodyplasin protein.") In another embodiment, the ectodysplasin protein is Eda-A1. In another embodiment, the compound or factor is an ectodysplasin receptor (referred to, in another embodiment, as "edar"). In another embodiment, the compound or factor is an activator of an ectodysplasin protein. In another embodiment, the compound or factor is an activator of an ectodysplasin receptor. In another embodiment, the

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compound or factor is an inhibitor of a protein that suppresses an activity of the ectodysplasin protein or ectodysplasin receptor. Each possibility represents a separate embodiment of the present invention.

[00076] In another embodiment, the eda protein of methods and compositions of the present invention has the sequence:

MGYPEVERRELLPAAAPRERGSQGC GCGGAPARAGEGNSCLLFLGFFGLSLALHLLTLCC
YLELRSELRRERGAESRLGGSGTPGTSGTLSSLGGLDPDSPITSHLGQPSPKQQPLEPGEAAL
HSDSQDGHQMALLNFFFPDEKPYSEEESSRRVRRNKRSKSNEGADGPVKNKKKGKKAGPP
GPNGPPGPPGPPGPQGPPGIPGIPGIPGTTVMGPPGPPGPPGPQGPPGLQGPPSGAADKAGTR
10 ENQPAVVHLQGQGSIAIQVKNDLSGGVLNDWSRITMNPKVFKLHPRSGELEVLVDGTYFIY
SQVEVYYINFTDFASYEVVVDEKPFLLQCTRSIETGKTNYNTCYTAGVCLLKARQKIAVKM
VHADISINMSKHTTFFGAIRLGEAPAS (GenBank Accession No: NM_001399; SEQ ID No:
274). In another embodiment, the eda protein has a sequence selected from the sequences set forth
in GenBank entries NM_001005609, NM_001005610, NM_001005611, NM_001005612,
15 NM_001005613, NM_001005614, NM_001005615, AF040628, AF061194, AF061193,
AF061192, AF061191, AF061190, AF061189, and AF060999. In another embodiment, the eda
protein is encoded by a nucleic acid molecule having a sequence set forth in the one of the above
GenBank entries. In another embodiment, a biologically active fragment of an Eda protein is
utilized in a method of the present invention. Each possibility represents a separate embodiment of
20 the present invention.

[00077] In another embodiment, the edar protein of methods and compositions of the present invention has the sequence:

MAHVGDCCTQTPWLPVLVVSLMCSARAEYSNCGENEYYNQTTGLCQECPPCGPGGEEPYLS
CGYGTKDEDYGCVP CPAEKFSKGGYQICRRHKDCEGFFRATVLT PGDMENDAECGPCLP
25 GYYMLENRPRNIYGMVCYSCLLAPPNTKECVGATSGASANFP GTSGSSTLSPFQHAHKELS
GQGH LATALIAMSTIFIMAIIVLIMFYILKTKPSAPACCTSHPGKSVEAQVSKDEEKKEAP
DNVVMFSEKDEFEKL TATPAKPTKSENDASSENEQLLSRSVDSDEEPAPDKQGSPELCLLS

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LVHLAREKSATSNNKSAGIQSRRKKILDVYANVCGVVEGLSPTELPFDCLEKTSRMLSSSTYN
SEKAVVKTWRHLAESFGLKRDEIGGMTDGMQLFDRISTAGYSIPELLTKLVQIERLDAVES
LCADILEWAGVVPPASQPHAAS (GenBank Accession No: BC093872; SEQ ID No: 275). In
another embodiment, the edar protein has a sequence selected from the sequences set forth in
5 GenBank entries BC093870; BC034919; NM_021783; NM_022336; AY152724; AF298812;
AH008077; AF130996; AF130988. In another embodiment, the edar protein is encoded by a
nucleic acid molecule having a sequence set forth in the one of the above GenBank entries. In
another embodiment, a biologically active fragment of an Edar protein is utilized in a method of
the present invention. Each possibility represents a separate embodiment of the present invention.

10 [00078] In another embodiment, the compound or factor that promotes a differentiation of an
uncommitted epidermal cell into a HF cell is a Noggin protein. In another embodiment, the
compound or factor is a nucleotide encoding a Noggin protein. In another embodiment, the
compound or factor is an activator of a Noggin protein. In another embodiment, the compound or
factor is an inhibitor of a protein that suppresses an activity of the Noggin protein. Each possibility
15 represents a separate embodiment of the present invention.

[00079] In another embodiment, the Noggin protein of methods and compositions of the present
invention has the sequence:

MERCPSLGVTLYALVVVLGLRATPAGGQHLYHIRPAPSDNLPLVDLIEHPDPIFDPKEKDLNE
TLLRSLGGHYDPGFMATSPPEDRPGGGGGAAGGAEDLAELDQLLRQRPSGAMPSEIKGLE
20 FSEGLAQGKKQRLSKKLRRKLQMWLWSQTFCPVLYAWNDLGSRFWPRYVKVGSCFSKRS
CSVPEGMVCKPSKSVHLTVLRWRCQRRGGQRCGWIPYIPISECKCSC (GenBank Accession
No: NM_005450; SEQ ID No: 276). In another embodiment, the Noggin protein has a sequence
selected from the sequences set forth in GenBank entries BC034027 and U31202. In another
embodiment, the Noggin protein is encoded by a nucleic acid molecule having a sequence set forth
25 in the one of the above GenBank entries. In another embodiment, a biologically active fragment of a
Noggin protein is utilized in a method of the present invention. Each possibility represents a separate
embodiment of the present invention.

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[00080] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is a Hedgehog protein. In another embodiment, the compound or factor is a nucleotide encoding a Hedgehog protein. In another embodiment, the compound or factor is an activator of a Hedgehog protein. In another embodiment, the compound or factor is a sonic Hedgehog protein. In another embodiment, the compound or factor is a nucleotide encoding a sonic Hedgehog protein. In another embodiment, the compound or factor is an activator of a sonic Hedgehog protein. Each possibility represents a separate embodiment of the present invention.

[00081] In another embodiment, the Hedgehog protein of methods and compositions of the present invention has the sequence set forth in GenBank Accession No. NM_000193. In another embodiment, the Hedgehog protein has a sequence selected from those set forth in GenBank entries L38518 and NP_000184. In another embodiment, the Hedgehog protein has any other Hedgehog sequence known in the art. In another embodiment, the Hedgehog protein has any other sonic Hedgehog sequence known in the art. Each possibility represents a separate embodiment of the present invention.

[00082] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is a Transforming Growth Factor (TGF)-beta1 protein. In another embodiment, the compound or factor is a nucleotide encoding a TGF-beta1 protein. In another embodiment, the compound or factor is an activator of a TGF-beta1 protein. In another embodiment, the compound or factor is a TGF-beta3 protein. In another embodiment, the compound or factor is a nucleotide encoding a TGF-beta3 protein. In another embodiment, the compound or factor is an activator of a TGF-beta3 protein. In another embodiment, the compound or factor is an antagonist of a TGF-beta1 protein. In another embodiment, the compound or factor is an antagonist of a TGF-beta3 protein. Each possibility represents a separate embodiment of the present invention.

[00083] In another embodiment, the TGF-beta1 protein of methods and compositions of the present invention has the sequence set forth in GenBank Accession No. BC000125. In another embodiment, the Hedgehog protein has a sequence selected from those set forth in GenBank entries BC001180,

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BC022242, and NM_000660. In another embodiment, the TGF-beta1 protein has any other TGF-beta1 sequence known in the art. Each possibility represents a separate embodiment of the present invention.

[00084] In another embodiment, the TGF-beta3 protein of methods and compositions of the present invention has the sequence set forth in GenBank Accession No. J03241. In another embodiment, the Hedgehog protein has a sequence selected from those set forth in GenBank entries NM_003239, BC018503, BT007287 and X14149. In another embodiment, the TGF-beta3 protein has any other TGF-beta3 sequence known in the art. Each possibility represents a separate embodiment of the present invention.

[00085] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell acts directly on the uncommitted epidermal cell. In another embodiment, the compound or factor acts on the uncommitted epidermal cell via a mesenchymal cell. Each possibility represents a separate embodiment of the present invention.

[00086] In another embodiment, the mesenchymal cell is a dermal condensate cell. In another embodiment, the mesenchymal cell is a DP cell. In another embodiment, the mesenchymal cell is another cell type or differentiation stage in the dermal condensate-DP lineage. In another embodiment, the mesenchymal cell is any other type of mesenchymal cell known in the art. Each possibility represents a separate embodiment of the present invention.

[00087] The EGFR of methods and compositions of the present invention has, in another embodiment, the sequence:

MRPSGTAGAALLALLAALCPASRALEKKVCQGTSNKLTQLGTFEDHFLSLQRMFNNCEV
VLGNLEITYVQRNYDLSFLKTIQEVAGYVLIALNTVERIPLNLQIIRGNMYEYNSYALAVL
SNYDANKTGLKELPMRNLQEILHGAVRFSNNPALCNVESIQWRDIVSSDFLSNMSMDFQN
HLGSCQKCDPSCPNGSCWGAGEENCQKLTKIICAQQCSGRCRGKSPSDCCHNQCAAGCTG
PRESCLVCRKFRDEATCKDTCPLMLYNPTTYQMDVNPEGKYSFGATCVKKCPRNYVV
TDHGSCVRACGADSYEMEEDGVRKCKKCEGPCRKVCNGIGIGEFKDSLSINATNIKHFKN

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CTSISGDLHILPVAFRGDSFTHTPPLDPQELDILKTVKEITGFLLIQAWPENRTDLHAFENLEII
 RGRTKQHGQFSLAVVSLNITSLGLRSLKEISDGDVHISGNKNLCYANTINWKKLFGTSGQKT
 KIISNRGENSCKATGQVCHALCSPEGCGWPEPRDCVSCRNVSRGRECVDKCNLLEGEPRF
 VENSECIQCHPECLPQAMNITCTGRGPDNCIQCAHYIDGPHCVKTCPAGVMGENNTLVWK
 5 YADAGHVCHLCHPNCTYGCTGPGLEGCPNGPKIPSIATGMVGALLLLLVVALGIGLFMR
 RRHIVRKRTLRRLLQERELVEPLTPSGEAPNQALLRILKETEFKKIKVLGSGAFGTVYKGLW
 IPEGEKVKIPVAIKELREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTVQLITQLMP
 FGCLLDYVREHKDNIGSQYLLNWCVQLAKGMNYLEDRLVHRDLAARNVLVKTPQHVKI
 TDFGLAKLLGAEEKEYHAEGGKVPIKWMALESILHRIYTHQSDVWSYGVTVWELMTFGS
 10 KPYDGIPASEISSILEKGERLPQPPICTIDVYMIMVKCWMIDADSRPKFRELIIEFSKMARDPQ
 RYLVIQGDERMHLPSPTDSNFYRALMDEEDMDDVDDADEYLIPQQGFFSSPSTSRTPLLS
 LSATSNNSTVACIDRNLQSCPIKEDSFLQRYSSDPTGALTEDSIDDTFPLVPEYINQSVPKR
 PAGSVQNPVYHNQPLNPAPSRDPHYQDPHSTAVGNPEYLNTVQPTCVNSTFDSPAHWAAQ
 KGSHQISLDNPDYQQDFFPKEAKPNGIFKGSTAENAEYLRVAPQSSEFIGA (GenBank
 15 Accession No: NM_005228; SEQ ID No: 277). In another embodiment, the EGFR has a sequence
 selected from the sequences set forth in GenBank entries NM_201282, NM_201283, NM_201284,
 BC094761, AF288738, AY588246, AY573061, X17054, AF125253, U48722, K03193, and
 AY698024. In another embodiment, the EGFR is encoded by a nucleic acid molecule having a
 sequence set forth in the one of the above GenBank entries. In another embodiment, a biologically
 20 active fragment of an EGFR is utilized in a method of the present invention. Each possibility
 represents a separate embodiment of the present invention.

[00088] The EGF of methods and compositions of the present invention has, in another embodiment, the sequence:

MLLTLIILLPVVSKFSFVSLAPQHWSCPEGTLAGNGNSTCVGPAPFLIFSHGNSIFRIDTEGTN
 25 YEQLVVDAGVSVIMDFHYNEKRIYWVDLERQLLQRVFLNGSRQERVCNIEKNVSGMAINW
 INEEVIWSNQQEGHITVTDMKGNNSHILLSALKYPANVAVDPVERFIFWSSEVAGSLYRADL
 DGVGVKALLETSEKITA VSLDVLDKRLFWIQYNREGSNSLICSCDYDGGSVHISKHPTQHNL
 FAMSLFGDRIFYSTWKMKTIWIANKHTGKDMVRINLHSSFVPLGELKV VVHPLAQPKAEDDT

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WEPEQKLCKLRKGNCSSSTVCGQDLQSHLCMCAEGYALSRDRKYCEDVNECAFWNHGCTL
 GCKNTPGSYYCTCPVGFVLLPDGKRCHQLVSCPRNVSECSHDCVLTSEGPLCFCPEGSVLER
 DGKTCSGCSSPDNGGCSQLCVPLSPVSWECDCFPGYDLQLDEKSCAASGPQPFLLFANSQDI
 RHMHFDDGTDYGTLLSQQMGMVYALDHDPVENKIYFAHTALKWIERANMDGSQRERLIEE
 5 GVDVPEGLAVDWIGRRFYWTDRGKSLIGRSDLNGKRSKIITKENISQPRGIAVHPMAKRLFW
 TDTGINPRIESSSLQGLGRLVIASSDLIWPSGITIDFLTDKLYWCDAKQSVIEMANLDGSKRRR
 LTQNDVGHFPAVAVFEDYVWFSDWAMPSVIRVKNKRTGKDRVRLQGSMLKPSSLVVVHPL
 AKPGADPCLYQNGGCEHICKKRLGTAWCSCREGFMKASDGKTCLALDGHQLLAGGEVDL
 KNQVTPLDILSKTRVSEDNITESQHMLVAEIMVSDQDDCAPVGCSMYARCISEGEDATCQC
 10 LKGFAGDGKLCSDIDECMGVPVCPPASSK.CINTEGGYVCRCSEGYQGDGIHCLDIDECQLG
 VHSCGENASCTNTEGGYTCMCAGRLSEPGLICPDSTPPPHLREDDHHYSVRNSDSECPLSHD
 GYCLHDGVCMYIEALDKYACNCVVG YIGERCQYRDLKWWELRHAGHGQQQKVIVVAVC
 VVVLVMLLLLSLWGAHYRTQKLLSKNPKNPYEESSRDVRSRRPADTEDGMSSCPQPWFV
 VIKEHQDLKNGGQPVAGEDGQAADGSMQPTSWRQEPQLCGMGTEQGCWIPVSSDKGSCP
 15 QVMERSFHMPSTGTQTLGGVEKPHSLLSANPLWQQRALDPPHQMELTQ (GenBank
 Accession No: NM_001963; SEQ ID No: 278). In another embodiment, the EGF has a sequence
 selected from the sequences set forth in GenBank entries BC093731, AY548762, and X04571. In
 another embodiment, the EGF is encoded by a nucleic acid molecule having a sequence set forth in
 the one of the above GenBank entries. In another embodiment, a biologically active fragment of an
 20 EGF is utilized in a method of the present invention. Each possibility represents a separate
 embodiment of the present invention.

[00089] The beta-catenin protein of methods and compositions of the present invention has, in
 another embodiment, the sequence:

MATQADLMELDMAMEPDRKAAVSHWQQQSYLD SGIHSGATTTAPSLSGKGNPEEEDVDT
 25 SQVLYEWEQGFSSFTQE QVADIDGQYAMTRAQRVRAAMFPETLDEGMQIPSTQFDAAHP
 TNVQRLAEPQMLKHAVVNLINYQDDAELATRAIPELTKLLNDEDQVVVNKAAMVHQLS
 KKEASRHAIMRSPQMVSIVRTMQNTNDVETARCTAGTLHNLSHHREGLLAIFKSGGIPAL
 VKMLGSPVDSVLFYAITTLHNLLHQEGAKMAVRLAGGLQKMVALLNKTNVKFLAITTDC

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LQILAYGNQESKLILASGGPQALVNIMRTYTYEKLLWTTSRVLKVLSVCSSNKPAIVEAGG
 MQALGLHLTDPSQRLVQNCLWTLRNLSDAATKQEGMEGLLGTLVQLLGSDDINVVTCAAG
 ILSNLTCNNYKNKMMVCQVGGIEALVRTVLRAGDREDITEPAICALRHLSRHQEAEMAQN
 AVRLLHYGLPVVVKLLHPPSHWPLIKATVGLIRNLALCPANHAPLREQGAIPRLVQLLVRAHQ
 5 DTQRRRTSMGGTQQQFVEGVRMEEIVEGCTGALHILARDVHNRI VIRGLNTIPLFVQLLYSPIE
 NIQRVAAGVLCELAQDKEAAEAIEAEGATAPLTELLHSRNEGVATYAAAVLFRMSEDKPQD
 YKKRLSVELTSSLFRTEPMAWNETADLGLDIGAQGEPLGYRQDDPSYRSFHSGGYGQDALG
 MDPMMEHEMGGHHPGADYPVDGLPDLGHAQDLMDGLPPGDSNQLAWFDTDL (GenBank

Accession No: NM_001904; SEQ ID No: 279). In another embodiment, the beta-catenin protein has
 10 a sequence selected from the sequences set forth in GenBank entries BC058926, X87838,
 AF130085, AB062292, Z19054, and NP_001895. In another embodiment, the beta-catenin protein
 is encoded by a nucleic acid molecule having a sequence set forth in the one of the above GenBank
 entries. In another embodiment, a biologically active fragment of a beta-catenin protein is utilized in
 a method of the present invention. Each possibility represents a separate embodiment of the present
 15 invention.

[00090] The Wnt protein of methods and compositions of the present invention has, in another
 embodiment, the sequence:

MNRKARRCLGHLFLSLGMVYLRIGGFSSVVALGASII CNKIPGLAPRQRAICQSRPD AII VIGE
 GSQMGLDECQFQFRNGRWNC SALGERTVFGKELKVGSREAAFTYAIIAAGVAHAITAACT
 20 QGNLSDCGCDKEKQGQYHRDEGWKWGGCSADIRYGIGFAKVFVDAREIKQNARTLMNLH
 NNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEPVRA
 SRNKRPTFLKIKKPLSYRKPM DTLVYIEKSPNYCEEDPVTGSGVTQGRACNK TAPQASGC
 DLMCCGRGYNTHQYARVWQCNCKFHWCCYVKCNTCSERTEMYTCK (GenBank Accession
 No: BC008811; SEQ ID No: 280). In another embodiment, the Wnt protein has a sequence selected
 25 from the sequences set forth in GenBank entries NM_004625, D83175, U53476, and NP_004616.
 In another embodiment, the Wnt protein is a Wnt7 protein. In another embodiment, the Wnt protein
 is a Wnt7a protein. In another embodiment, the Wnt protein is Wnt1 protein. In another
 embodiment, the Wnt protein is a Wnt3 protein. In another embodiment, the Wnt protein is a Wnt3a

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protein. In another embodiment, the Wnt protein is a Wnt10 protein. In another embodiment, the Wnt protein is a Wnt10a protein. In another embodiment, the Wnt protein is a Wnt10b protein. In another embodiment, the Wnt protein is encoded by a nucleic acid molecule having a sequence set forth in the one of the above GenBank entries. In another embodiment, a biologically active
5 fragment of a Wnt protein is utilized in a method of the present invention. In another embodiment, a biologically active fragment of a Wnt7 protein is utilized in a method of the present invention. In another embodiment, a biologically active fragment of a Wnt7a protein is utilized in a method of the present invention. Each possibility represents a separate embodiment of the present invention.

[00091] In another embodiment, the compound or factor that promotes a differentiation of an
10 uncommitted epidermal cell into a HF cell is a protein encoded by a ribonucleic acid (RNA) molecule having a sequence selected from the sequences set forth in SEQ ID No: 1-232. In another embodiment, the compound or factor is an RNA molecule having a sequence selected from SEQ ID No: 1-232. In another embodiment, the RNA molecule is homologous to a sequence selected from SEQ ID No: 1-232. In another embodiment, the RNA molecule is an isoform of a sequence selected
15 from SEQ ID No: 1-232. In another embodiment, the compound or factor increases an activity of a protein encoded by an RNA molecule having a sequence selected from SEQ ID No: 1-232. In another embodiment, the compound or factor increases an expression or level of a protein encoded by an RNA molecule having a sequence selected from SEQ ID No: 1-232. Each possibility represents a separate embodiment of the present invention.

[00092] As provided herein, the transcripts depicted in Table 3 (Example 8; SEQ ID No: 1-232), the proteins they encode, and the pathways in which the proteins participate contribute significantly to HF stem cell activation. Accordingly, under the conditions utilized herein, anagen can be induced by activation of these transcripts, proteins, and pathways. Activation of the transcripts, proteins, and pathways depicted in Table 3 is thus a method for enhancing EDIHN. In another embodiment,
20 activation of these transcripts, proteins, and pathways represents a method for enhancing hair growth in a subject.
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[00093] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is a protein encoded by an RNA molecule having a sequence selected from the sequences set forth in SEQ ID No: 233-257. In another embodiment, the compound or factor is an RNA molecule having a sequence selected from SEQ ID No: 233-257. In another embodiment, the RNA molecule is homologous to a sequence selected from SEQ ID No: 233-257. In another embodiment, the RNA molecule is an isoform of a sequence selected from SEQ ID No: 233-257. In another embodiment, the compound or factor increases an activity of a protein encoded by an RNA molecule having a sequence selected from SEQ ID No: 233-257. In another embodiment, the compound or factor increases an expression or level of a protein encoded by an RNA molecule having a sequence selected from SEQ ID No: 233-257. Each possibility represents a separate embodiment of the present invention.

[00094] As provided herein, the transcripts depicted in Table 4 (Example 9; SEQ ID No: 233-257), the proteins they encode, and the pathways in which the proteins participate, contribute significantly, under the conditions utilized herein, to induction of epidermal cells to differentiate into HF stem cells. Activation of the transcripts, proteins, and pathways depicted in Table 4 is thus a method for enhancing EDIHN. In another embodiment, activation of these transcripts, proteins, and pathways represents a method for enhancing hair growth in a subject.

[00095] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is a compound or factor that decreases an activity of a protein encoded by an RNA molecule having a sequence selected from the sequences set forth in SEQ ID No: 258-273. In another embodiment, the compound or factor decreases an expression or level of a protein encoded by an RNA molecule having a sequence selected from SEQ ID No: 258-273. Each possibility represents a separate embodiment of the present invention.

[00096] As demonstrated by findings of the present invention, the transcripts depicted in Table 5 (Example 9; SEQ ID No: 258-273), the proteins they encode, and the pathways in which the proteins participate, contribute significantly, under the conditions utilized herein, to preventing induction of epidermal cells to differentiate into HF stem cells. Inhibition of the transcripts, proteins, and

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pathways depicted in Table 5 is thus a method for enhancing EDIHN. In another embodiment, inhibition of these transcripts, proteins, and pathways represents a method for induction of hair growth in a subject.

[00097] In one embodiment, the compound that modulates a protein encoded by an RNA molecule having a sequence selected from the sequences set forth in SEQ ID No: 233-273 or the nucleic acid encoding same is administered before the compound that modulates a protein encoded by an RNA molecule having a sequence selected from the sequences set forth in SEQ ID No: 1-232 or the nucleic acid encoding same. In another embodiment, the two compounds are administered simultaneously. Each possibility represents a separate embodiment of the present invention.

[00098] In one embodiment, a protein encoded by an RNA sequence selected from SEQ ID No: 1-273, or a compound that modulates the protein, is administered before other proteins encoded by same or compounds that modulate them, in order to further enhance their effect in generating an HF or stimulating hair growth. In another embodiment, the wnt pathway is stimulated before the hedgehog pathway. In another embodiment, the two pathways are stimulated in an overlapping fashion. In another embodiment, the two pathways are stimulated simultaneously. Each possibility represents a separate embodiment of the present invention.

[00099] In another embodiment, activating or decreasing expression of an RNA transcript in methods of the present invention occurs via a transcription mechanism (e.g. activation of expression of the RNA). In another embodiment, activating or decreasing expression of the RNA transcript occurs via a translational mechanism. In another embodiment, activating or decreasing expression of the RNA transcript occurs via a post-translational mechanism. Each possibility represents a separate embodiment of the present invention.

[000100] In another embodiment, the nucleic acid molecule utilized in methods of the present invention is a deoxyribonucleic acid (DNA) molecule that encodes an RNA molecule having a sequence selected from the sequences set forth in the present invention.

[000101] In one embodiment, an RNA molecule of the present invention encodes a protein that plays

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a role in HF regeneration. In another embodiment, the RNA molecule is itself catalytically active, e.g., a ribozyme, etc. Each possibility represents a separate embodiment of the present invention.

[000102] In another embodiment, the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell is a compound or factor that promotes placodal cell fate.

5 As provided herein, factors that promote placodal cell fate enhance EDIHN, as exemplified in the Examples herein. In another embodiment, the compound or factor acts at the placode stage of HF development.

[000103] In another embodiment, the compound or factor inhibits a biological factor that inhibits a differentiation of an uncommitted epithelial cell into an HF cell.

10 [000104] In another embodiment of methods and compositions of the present invention, a composition comprising one of the above compounds or factors is administered. Each of the above types of compounds, factors, and compositions represents a separate embodiment of the present invention.

[000105] In one embodiment, the present invention provides a method for generating an HF in a scalp, 15 eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with minoxidil, thereby generating an HF in a scalp, eyebrow, or scarred region of a subject.

[000106] In one embodiment, the present invention provides a method for treating baldness in a scalp, 20 eyebrow, or scarred region of a subject, comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with minoxidil, thereby treating baldness in a scalp, eyebrow, or scarred region of a subject.

[000107] In another embodiment, the present invention provides a use of minoxidil for the preparation of a pharmaceutical composition for use in a method for an HF in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, 25 eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the minoxidil.

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[000108] In another embodiment, the present invention provides a use of minoxidil for the preparation of a pharmaceutical composition for use in a method for treating baldness in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the minoxidil.

[000109] In another embodiment, the present invention provides a method for removal of an HF from a skin or scalp of a subject, comprising the steps of: (a) disrupting an epidermis of the skin or scalp; and (b) contacting the skin or scalp with either: (i) an EGF protein; (ii) an EGF receptor; (iii) a nucleotide encoding an EGF protein or EGF receptor; or (iv) a compound or factor that activates a EGF protein or EGF receptor, thereby removing an HF from a skin or scalp of a subject.

[000110] In another embodiment, the present invention provides a method for hair removal from a skin or scalp of a subject, comprising the steps of: (a) disrupting an epidermis of the skin or scalp; and (b) contacting the skin or scalp with either: (i) an EGF protein; (ii) an EGF receptor; (iii) a nucleotide encoding an EGF protein or EGF receptor; or (iv) a compound or factor that activates a EGF protein or EGF receptor, thereby removing hair from a skin or scalp of a subject. In another embodiment, the epidermal disruption is light dermabrasion. In another embodiment, the epidermal disruption is a non-scarring method. In another embodiment, administration of the EGF protein, EGF receptor, nucleotide, compound, or factor suppresses HF formation. In another embodiment, the EGF protein, EGF receptor, nucleotide, compound, or factor is administered within several days of healing. In another embodiment, the EGF protein, EGF receptor, nucleotide, compound, or factor is administered within about 1 day of healing. In another embodiment, the EGF protein, EGF receptor, nucleotide, compound, or factor is administered according to any of the timing embodiments enumerated herein for Dkk1 protein. Each possibility represents a separate embodiment of the present invention.

[000111] In another embodiment, the present invention provides a use of either: (i) an EGF protein; (ii) an EGF receptor; (iii) a nucleotide encoding an EGF protein or EGF receptor; or (iv) a compound or factor that activates a EGF protein or EGF receptor, for the preparation of a pharmaceutical composition for use in a method for removal of an HF from a skin or scalp of a

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subject, the method comprising the steps of: (a) disrupting an epidermis of the scalp, eyebrow, or scarred region; and (b) contacting the scalp, eyebrow, or scarred region with the EGF protein, EGF receptor, nucleotide, compound, or factor.

[000112] In another embodiment, a composition or method of the present invention is utilized on human skin. In another embodiment, the composition or method is utilized on an area of unwanted hair growth. In another embodiment, the area is the face. In another embodiment, the area is the bikini area. In another embodiment, the area is the legs. In another embodiment, the area is the arms. In another embodiment, the area is the chest.

[000113] An “inhibitor” utilized in methods and compositions of the present invention is, in another embodiment, an antibody that binds the protein or biological factor that is the target of the inhibitor. In another embodiment, the inhibitor is a pharmacologic inhibitor. In another embodiment, the inhibitor is any other type of inhibitor known in the art. Each possibility represents a separate embodiment of the present invention.

[000114] The step of disrupting the epidermis in methods of the present invention is performed, in another embodiment, by abrading the scalp, eyebrow, or scarred region. In another embodiment, the term “abrading” refers to an act of creating an abrasion. In another embodiment, “abrading” refers to rubbing. In another embodiment, “abrading” refers to wearing away by friction. As provided herein (Example 1), epidermal abrasion causes, under the conditions utilized herein, *de novo* HF neo-genesis. In another embodiment, the epidermal layer is disrupted.

[000115] In one embodiment, “abrasion” has the same meaning as “abrading.” In another embodiment, “abrasion” refers to an area of the scalp or skin from which the epidermis is removed. In another embodiment, “abrasion” refers to an area of the scalp or skin from which the epidermis and dermis are removed. Each definition of “abrading” and “abrasion” represents a separate embodiment of the present invention.

[000116] As provided herein, under the conditions utilized, epidermal disruption by a method of the present invention converts the skin back, in another embodiment, to an embryonic-like state, in which the follicle regenerates. In another embodiment, a subsequent window of opportunity is

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created, during which the number and size of new HF in the skin can be manipulated. In another embodiment, the administration of a compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell during this window causes regeneration of larger and more numerous HF. The morphology of HF in abraded skin is similar to that of embryonic HF (Example 1-2 and subsequent Examples), and the markers expressed are similar as well.

[000117] In another embodiment, the present invention provides a method of stimulating hair growth in a scalp, eyebrow, or scarred region of a subject, comprising performing a method of present invention, thereby stimulating hair growth in a scalp, eyebrow, or scarred region of a subject. As demonstrated in Example 3, EDIHN-induced HF are capable of generating hairs. Thus, methods of the present invention can be used to stimulate hair growth.

[000118] "EDIHN," in another embodiment, refers to HF neogenesis induced by disruption of the epithelial layer. In another embodiment, the term refers to HF neogenesis induced by abrasion. In another embodiment, the term refers to HF neogenesis induced by wounding. In another embodiment, the term refers to HF neogenesis induced by disruption of the epithelial layer, followed by administration of a compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell. Each possibility represents a separate embodiment of the present invention.

[000119] In another embodiment, the present invention provides a method of testing an ability of a compound to modulate HF generation *in vivo*, comprising (a) disrupting an epithelial layer of a first scalp, eyebrow, or scarred region, whereby the first scalp, eyebrow, or scarred region has been contacted with the compound; (b) measuring a first HF generation in the first scalp, eyebrow, or scarred region; (c) disrupting an epithelial layer of a second scalp, eyebrow, or scarred region, wherein the second scalp, eyebrow, or scarred region is a scalp, eyebrow, or scarred region of the first subject or a second subject, whereby the second scalp, eyebrow, or scarred region has not been contacted with the compound; (d) measuring a second HF generation in the second scalp, eyebrow, or scarred region; and (e) comparing the first HF generation to the second HF generation, whereby a difference between the first HF generation and the second HF generation indicates that the

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compound modulates an HF generation *in vivo* (Examples).

[000120] In another embodiment, the present invention provides a method of testing an ability of a compound to stimulate hair growth *in vivo*, comprising disrupting an epithelial layer of a first scalp, eyebrow, or scarred region, whereby the first scalp, eyebrow, or scarred region has been contacted
5 with the compound; measuring a first HF generation in the first scalp, eyebrow, or scarred region; disrupting an epithelial layer of a second scalp, eyebrow, or scarred region, whereby the second scalp, eyebrow, or scarred region has not been contacted with the compound; measuring a second HF generation in the second scalp, eyebrow, or scarred region; and comparing the first HF generation to the second HF generation, whereby a difference between the first HF generation and
10 the second HF generation indicates that the compound stimulates a hair growth *in vivo*.

[000121] In one embodiment, the methods of the present invention of testing a compound are repeated using a plurality of subjects, until a statistically significant sample has been tested.

[000122] In another embodiment of methods for testing compounds of the present invention, the first scalp, eyebrow, or scarred region is a scalp, eyebrow, or scarred region of a first subject. In another
15 embodiment, the subject is a subject in need of generation of a new HF. The second scalp, eyebrow, or scarred region, in another embodiment, is a scalp, eyebrow, or scarred region of the first subject. In another embodiment, the second scalp, eyebrow, or scarred region is a scalp, eyebrow, or scarred region of a second subject. Each possibility represents a separate embodiment of the present invention.

20 [000123] In another embodiment, the excisional wounds of methods of the present invention are created using a surgical tool. In one embodiment, the surgical tool is a dermal biopsy punch (Example 2). In another embodiment, the excisional wounds are induced by freezing or cryoinjury. The use of freezing or cryoinjury is well known in the art, and is used, for example by dermatologists to injure skin. In one embodiment, the freezing or cryoinjury results in a blister. In
25 another embodiment, the blister is used as a "chamber" to introduce drugs and or cells into the reepithelialized area. Each possibility represents a separate embodiment of the present invention.

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[000124] In another embodiment, the excisional wounds of methods of the present invention are not surgically closed. In another embodiment, the excisional wounds are not contacted with a bandage or dressing before they heal or during a period of time after wound induction. In another embodiment, the excisional wounds are not contacted with an ointment before they heal or during a
5 period of time after wound induction. In another embodiment, the excisional wounds are allowed to heal by secondary intention. Each possibility represents a separate embodiment of the present invention.

[000125] The subject of methods of the present invention, is, in another embodiment, a human. As provided herein (Example 7) human skin responds to EDIHN in the same manner as mouse skin. In
10 another embodiment, the subject is a male. In another embodiment, the subject is a female. In another embodiment, the subject is any other type of subject known in the art. Each possibility represents a separate embodiment of the present invention.

[000126] In another embodiment, the subject is an adult. In one embodiment, "adult" refers to an age greater than about 18 years. In another embodiment, "adult" refers to an age greater than about 20
15 years. In another embodiment, "adult" refers to an age greater than about 25 years. In another embodiment, "adult" refers to an age greater than about 30 years. In another embodiment, "adult" refers to an age greater than about 35 years. In another embodiment, "adult" refers to an age greater than about 40 years. In another embodiment, "adult" refers to an age greater than about 45 years.

[000127] In another embodiment, the subject is elderly. In one embodiment, "elderly" refers to an age
20 greater than about 45 years. In another embodiment, "elderly" refers to an age greater than about 50 years. In another embodiment, "elderly" refers to an age greater than about 55 years. In another embodiment, "elderly" refers to an age greater than about 60 years. In another embodiment, "elderly" refers to an age greater than about 65 years. In another embodiment, "elderly" refers to an age greater than about 70 years.

25 [000128] In another embodiment, the first subject, or, where applicable, both the first subject and the second subject, is a laboratory animal. In another embodiment, the subject(s) is/are mice. In another embodiment, the subject(s) is/are rats. In another embodiment, the subject(s) is/are gerbils. In

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another embodiment, the subject(s) is/are hamsters. In another embodiment, the subject(s) is/are guinea pigs. In another embodiment, the subject(s) is/are rabbits. In another embodiment, the subject(s) is/are pigs. In another embodiment, the subject(s) is/are dogs. In another embodiment, the subject(s) is/are cats. In another embodiment, the subject(s) is/are primates. In another embodiment, the subject(s) is/are any other laboratory animal known in the art. Each possibility represents a separate embodiment of the present invention.

[000129] In another embodiment, the subject(s) has a disease or disorder comprising balding. In another embodiment, the subject(s) does not have a disease or disorder comprising balding. In another embodiment, the disease or disorder is androgenetic alopecia (AGA). In another embodiment, the disease or disorder is male pattern baldness. In another embodiment, the disease or disorder is female pattern baldness. In another embodiment, the disease or disorder is a discoid lupus erythematosus. In another embodiment, the disease or disorder is a congenital hypotrichosis. In another embodiment, the disease or disorder is a lichen planopilaris. In another embodiment, the disease or disorder is a scarring alopecia. In another embodiment, the disease or disorder is any other disease or disorder comprising balding known in the art.

[000130] In another embodiment, the scalp, eyebrow, or scarred region(s) has a majority of HF in the telogen stage of the hair cycle. The findings of Examples 5-6 show that (a) EDIHN can restore hair growth to the scalp, eyebrow, or scarred region at the telogen stage; and (b) the efficiency of EDIHN at the telogen stage can be enhanced by depilation prior to abrasion or wound induction. In another embodiment, the scalp, eyebrow, or scarred region(s) has more than about 60% of HF in the telogen stage of the hair cycle. In another embodiment, the scalp, eyebrow, or scarred region(s) has more than about 70% of HF in the telogen stage of the hair cycle. In another embodiment, the scalp, eyebrow, or scarred region(s) has more than about 80% of HF in the telogen stage of the hair cycle. In another embodiment, the scalp, eyebrow, or scarred region(s) has more than about 90% of HF in the telogen stage of the hair cycle. In another embodiment, the scalp, eyebrow, or scarred region(s) does not have a majority of HF in the telogen stage of the hair cycle. Each possibility represents a separate embodiment of the present invention.

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[000131] In another embodiment of methods and compositions of the present invention, the first step (e.g. epithelial disruption) is performed 3-12 days prior to the second step (e.g. addition of an active compound, factor, cell, etc). In another embodiment, the interval is 4-12 days. In another embodiment, the interval is 5-12 days. In another embodiment, the interval is 4-11 days. In another embodiment, the interval is 6-11 days. In another embodiment, the interval is 6-10 days. In another embodiment, the interval is 6-9 days. In another embodiment, the interval is 6-8 days. In another embodiment, the interval is 7-8 days. In another embodiment, the interval is 5-11 days. In another embodiment, the interval is 5-10 days. In another embodiment, the interval is 7-10 days. In another embodiment, the interval is about 1 week. Each possibility represents a separate embodiment of the present invention.

[000132] In another embodiment, a method of the present invention further comprises the step of suppressing an activity or expression of a Wnt protein in the scalp, eyebrow, or scarred region. As provided herein, suppressing Wnt activity induces pigmentation in HF generated by methods of the present invention. In another embodiment, the step of suppressing Wnt activity or expression is performed within about 10 days of epidermal disruption. In another embodiment, the step of suppressing Wnt activity or expression is performed prior to the second step (e.g prior to addition of a compound or factor that promotes HF cell differentiation. Each possibility represents a separate embodiment of the present invention.

[000133] In another embodiment, the present invention provides a method for inducing pigmentation of a hair, comprising suppressing expression of a Wnt protein in a follicle of the hair. In another embodiment, the Wnt protein is Wnt1. In another embodiment, the Wnt protein is a Wnt7. In another embodiment, the Wnt protein is a Wnt7a. In another embodiment, the Wnt protein is a Wnt3. In another embodiment, the Wnt protein is a Wnt3a. In another embodiment, the Wnt protein is a Wnt10. In another embodiment, the Wnt protein is a Wnt10a. In another embodiment, the Wnt protein is any other Wnt protein known in the art. Each possibility represents a separate embodiment of the present invention.

[000134] In another embodiment, the present invention provides a method for inducing growth of a

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pigmented scalp hair or eyebrow of a subject, comprising generating a hair follicle in the scalp, eyebrow, or scarred region according to a method of the present invention and suppressing expression of a Wnt protein in the hair follicle, thereby inducing a growth of a pigmented scalp hair or eyebrow of a subject.

5 [000135] In another embodiment, the step of suppressing expression of a Wnt protein comprises inducing an expression of a Dkk1 protein. In another embodiment, the step of suppressing expression of a Wnt protein comprises inducing an expression of any other Wnt inhibitor known in the art. In another embodiment, the step of suppressing expression of a Wnt protein is performed immediately or shortly after epidermal disruption. In another embodiment, the step of inducing
10 expression of a Dkk1 protein is performed immediately or shortly after epidermal disruption. In another embodiment, the step of suppressing expression of a Wnt protein is performed at the time of epidermal disruption. In another embodiment, the step of inducing expression of a Dkk1 protein is performed at the time of epidermal disruption. In another embodiment, the step of suppressing expression of a Wnt protein is performed several days before generation of the follicle. In another
15 embodiment, the step of inducing expression of a Dkk1 protein several days before generation of the follicle. Each possibility represents a separate embodiment of the present invention.

[000136] In another embodiment, the step of suppressing expression of a Wnt protein is performed for about 8 days. In another embodiment, the step of inducing expression of a Dkk1 protein is performed for about 8 days. In another embodiment, the step of suppressing expression of a Wnt
20 protein is performed for about 9 days. In another embodiment, the step of inducing expression of a Dkk1 protein is performed for about 9 days. In another embodiment, the step of suppressing expression of a Wnt protein is performed for about 10 days. In another embodiment, the step of inducing expression of a Dkk1 protein is performed for about 10 days. In another embodiment, the step of suppressing expression of a Wnt protein is performed for about 12 days. In another
25 embodiment, the step of inducing expression of a Dkk1 protein is performed for about 12 days. In another embodiment, the step of suppressing expression of a Wnt protein is performed during the period of re-epithelialization. In another embodiment, the step of inducing expression of a Dkk1 protein is performed during the period of re-epithelialization. In another embodiment, expression of

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a Dkk1 protein is halted after several days. In another embodiment, halting expression of Dkk1 protein after several days induces, or enables induction of Wnt protein expression. In another embodiment, the expression of a Wnt protein is induced about 9 days after the abrading or wounding. In another embodiment, the expression of a Wnt protein is induced following the period
5 of re-epithelialization. In another embodiment, induction of Wnt protein expression is necessary for formation of new HF. Each possibility represents a separate embodiment of the present invention.

[000137] In another embodiment, "several" refers to about 1 day. In another embodiment, "several" refers to about 2 days. In another embodiment, "several" refers to about 3 days. In another embodiment, "several" refers to about 5 days. In another embodiment, "several" refers to about 7
10 days. In another embodiment, "several" refers to about 10 days. In another embodiment, "several" refers to about 12 days. Each possibility represents a separate embodiment of the present invention.

[000138] In another embodiment, the step of contacting in methods of the present invention comprises directly contacting the scalp, eyebrow, or scarred region with the compound, RNA, protein, etc. In another embodiment, the step of contacting comprises indirectly contacting the scalp, eyebrow, or
15 scarred region via contacting another site or tissue of the subject, after which the compound, RNA, or protein is transported to the scalp, eyebrow, or scarred region by a biological process; e.g., diffusion, active transport, or circulation in a fluid such as the blood, lymph, interstitial fluid, etc. Each possibility represents a separate embodiment of the present invention.

[000139] In another embodiment, the epidermal disruption in methods of the present invention further
20 removes dermal tissue from the scalp, eyebrow, or scarred region. In another embodiment, the epidermal disruption does not remove dermal tissue from the scalp, eyebrow, or scarred region. Each possibility represents a separate embodiment of the present invention.

[000140] "Disrupting" an epidermis or epidermal layer refers, in another embodiment, to removing part of the epidermis or epidermal layer. In another embodiment, the term refers to disturbing the
25 intactness of the epidermis or epidermal layer. In another embodiment, the term refers to perforating the epidermis or epidermal layer. In another embodiment, only part of the the epidermal layer need be removed. In another embodiment, the entire epidermal layer is removed. In another embodiment,

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the term refers to abrading the epidermis or epidermal layer (Examples). In another embodiment, the term refers to wounding the epidermis or epidermal layer (Examples). Each possibility represents a separate embodiment of the present invention.

[000141] In another embodiment, the epidermal disruption is performed with a tool that comprises
 5 sandpaper. In another embodiment, the epidermal disruption is performed with a laser. In another
 embodiment, the laser is a FraxelTM laser. In another embodiment, the laser is a CO₂ laser. In another
 embodiment, the laser is an excimer laser. In another embodiment, the laser is any other type of laser
 capable of inducing trans-epithelial injury. In another embodiment, the epidermal disruption is
 performed with a felt wheel. In another embodiment, the epidermal disruption is performed with a
 10 surgical tool. In another embodiment, the epidermal disruption is performed with any other tool
 known in the art that is capable of epidermal disruption. In another embodiment, the epidermal
 disruption comprises use of a micro-dermabrasion device. In another embodiment, the epidermal
 disruption comprises a burn treatment.

[000142] In another embodiment, the epidermal disruption comprises a disruption of a follicle of said
 15 epidermis and a disruption of an interfollicular region of said epidermis. In another embodiment, the
 epidermal disruption comprises a disruption of a follicle of said epidermis and does not comprise a
 disruption of an interfollicular region of said epidermis. Each possibility represents a separate
 embodiment of the present invention.

[000143] In another embodiment, the epidermal disruption comprises a light-based method. In another
 20 embodiment, the epidermal disruption comprises irradiation with visible light. In another
 embodiment, the epidermal disruption comprises irradiation with infrared light. In another
 embodiment, the epidermal disruption comprises irradiation with ultraviolet radiation. In another
 embodiment, the epidermal disruption comprises orthovoltage irradiation. In another embodiment,
 the epidermal disruption comprises X-ray irradiation. In another embodiment, the epidermal
 25 disruption comprises any other type of irradiation known in the art.

[000144] In another embodiment, the epidermal disruption is performed by mechanical means. In
 another embodiment, "mechanical means" refers to abrading. In another embodiment, the term

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refers to wounding. In another embodiment, the term refers to ultrasound. In another embodiment, the term refers to radio-frequency. In another embodiment, the term refers to an electrical process or the use of an electrical current. In another embodiment, the term refers to electroporation. In another embodiment, the term refers to excision. In another embodiment, the term refers to tape-stripping. In another embodiment, the term refers to microdermabrasion. In another embodiment, the term refers to the use of peels. In another embodiment, the term refers to any other type of mechanical means known in the art. Each possibility represents a separate embodiment of the present invention.

[000145] In another embodiment, the epidermal disruption comprises chemical treatment. In another embodiment, the chemical is phenol. In another embodiment, the chemical is trichloroacetic acid. In another embodiment, the chemical is ascorbic acid. In another embodiment, the chemical is any other chemical capable of epidermal disruption that is known in the art.

[000146] Each method or type of method of epidermal disruption represents a separate embodiment of the present invention.

[000147] In another embodiment, epidermal trauma is utilized in a method of the present invention.

[000148] Each type of epidermal abrasion and epidermal trauma represents a separate embodiment of the present invention.

[000149] In another embodiment, the epidermal disruption of methods of the present invention creates an abrasion at least about 1-1.5 centimeters (cm) in width. In another embodiment, the abrasion is at least about 1 cm in width. In another embodiment, the abrasion is at least about 1.5 cm in width. In another embodiment, the abrasion is at least about 2 cm in width. Each type of abrasion represents a separate embodiment of the present invention.

[000150] In another embodiment, the scalp, eyebrow, or scarred region is not contacted with a bandage or dressing following the epidermal disruption. In another embodiment, the scalp, eyebrow, or scarred region is not contacted with an ointment following the epidermal disruption. In another embodiment, the scalp, eyebrow, or scarred region is allowed to heal for a period of time without being contacted by any substance, device, ointment, etc., that is ordinarily administered to an

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abrasion or wound to facilitate healing. In another embodiment, the scalp, eyebrow, or scarred region is allowed to heal for a period of time without being contacted by any substance, device, ointment, etc., that is ordinarily administered to an abrasion or wound to prevent infection. In another embodiment, the period of time is the time it takes the epidermal disruption to heal. In
5 another embodiment, the period of time is any time or range of times between 2 days and 3 weeks. Each possibility represents a separate embodiment of the present invention.

[000151] In one embodiment, "following" refers to a period of time of about 2 days. In another embodiment, "following" refers to a period of time of about 3 days. In another embodiment, "following" refers to a period of time of about 4 days. In another embodiment, "following" refers to
10 a period of time of about 5 days. In another embodiment, "following" refers to a period of time of about 7 days. In another embodiment, "following" refers to a period of time of about 10 days. In another embodiment, "following" refers to a period of time of about 2 weeks. In another embodiment, "following" refers to a period of time of about 3 weeks. Each possibility represents a separate embodiment of the present invention.

15 [000152] In another embodiment, a method of the present invention further comprises the step of depilating the scalp, eyebrow, or scarred region. As provided herein, the findings of Example 6 show that the efficiency of EDIHN can be enhanced by depilation prior to abrasion or wound induction.

[000153] In another embodiment, the depilation is epilation. In another embodiment, the depilation
20 comprises the step of waxing. In another embodiment, the depilation comprises the step of plucking. In another embodiment, the depilation comprises the use of an abrasive material. In another embodiment, the depilation comprises the use of a laser. In another embodiment, the depilation comprises the use of electrolysis. In another embodiment, the depilation comprises the use of a mechanical device. In another embodiment, the depilation comprises the use of thioglycolic acid. In
25 another embodiment, the depilation comprises the use of any other method of depilation or epilation known in the art. Each possibility represents a separate embodiment of the present invention.

[000154] In another embodiment, a method of the present invention further comprises the step of

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administering a topical retinoid to the scalp, eyebrow, or scarred region. In one embodiment, the topical retinoid induces resting (telogen) HF in the scalp, eyebrow, or scarred region to enter anagen. Each possibility represents a separate embodiment of the present invention.

[000155] In another embodiment, the additional step (depilation or administration of a retinoid) is performed prior to the step of disrupting the epidermis. In another embodiment, the additional step is performed following the step of disrupting the epidermis, but prior to the addition of the compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell. In another embodiment, the additional step is performed concurrently with the addition of the differentiation-promoting compound or factor. In another embodiment, the additional step is performed following the addition of the differentiation-promoting compound or factor. Each possibility represents a separate embodiment of the present invention.

[000156] In another embodiment, the additional step is performed between about two days and about three weeks before the step of abrading. In another embodiment, the additional step is performed about two days before the step of abrading. In another embodiment, the additional step is performed about three days before the step of abrading. In another embodiment, the additional step is performed about four days before the step of abrading. In another embodiment, the additional step is performed about one week before the step of abrading. In another embodiment, the additional step is performed about ten days before the step of abrading. In another embodiment, the additional step is performed about two weeks before the step of abrading. In another embodiment, the additional step is performed about three weeks before the step of abrading. Each possibility represents a separate embodiment of the present invention.

[000157] In another embodiment, the methods of the present invention further comprise the step of contacting the scalp, eyebrow, or scarred region with an inductive cell capable of inducing an epidermal cell to differentiate into an HF cell. In another embodiment, the HF cell is an HF stem cell. Each possibility represents a separate embodiment of the present invention.

[000158] In another embodiment, the inductive cell is a dermal papilla cell. In another embodiment, the inductive cell is a follicular papilla cell. In another embodiment, the inductive cell is a dermal

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sheath cell. In another embodiment, the inductive cell is a cell that has been genetically modified; for example, with a gene encoding a factor that activates one of the proteins or pathways shown in the present invention to be up-regulated in HF stem cells. In one embodiment, the factor is hedgehog. In another embodiment, the factor is a DP cell protein. In another embodiment, the factor is wingless/ int (wnt). In another embodiment, the factor is a Noggin protein. In another embodiment, the factor is a bone morphogenic protein (BMP). In another embodiment, the factor is a fibroblast growth factor (FGF). In another embodiment, the factor is a transforming growth factor beta (TGF-beta) protein. In another embodiment, the factor is sonic hedgehog protein. In another embodiment, the factor is a neurotrophin. In another embodiment, the factor is any other factor known in the art that can contribute to induction of an epidermal cell to differentiate into an HF cell. Each possibility represents a separate embodiment of the present invention.

[000159] In another embodiment, the inductive cell has been genetically modified with a gene encoding a factor that represses one of the proteins or pathways shown in the present invention to be down-regulated in HF stem cells. In another embodiment, the inductive cell has been genetically modified with a gene encoding a factor that activates one of the proteins or pathways shown in the present invention to be up-regulated in HF stem cells upon their activation.

[000160] In another embodiment, the inductive cell is an autologous cell. In another embodiment, the inductive cell is an allogenic cell.

[000161] In another embodiment, the inductive cell is derived from a mesenchymal stem cell. In another embodiment, the inductive cell is derived from a mesodermal progenitor cell. In another embodiment, the inductive cell is derived from a hematopoietic stem cell. In another embodiment, the inductive cell is derived from an embryonic stem cell. In another embodiment, the inductive cell is derived from an embryonic carcinoma cell. In another embodiment, the inductive cell is one of the cell types disclosed in United States Patent Application No. 2003/0201815. In another embodiment, the inductive cell is any other type of cell known in the art with inductive properties for an epidermal cell. Each type of inductive cell represents a separate embodiment of the present invention.

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[000162] In another embodiment, the epidermal cell (e.g. the epidermal cell that is induced to differentiate into an HF cell) is an epidermal stem cell. In another embodiment, the epidermal cell is a bulge cell. In another embodiment, the epidermal cell is any other type of cell known in the art that can be induced to differentiate into an HF stem cell. Each possibility represents a separate
5 embodiment of the present invention.

[000163] In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with an anti-androgen compound. In one embodiment, the anti-androgen compound is finasteride. In another embodiment, the anti-androgen compound is Fluridil®. In another embodiment, the anti-androgen compound is dutasteride. In
10 another embodiment, the anti-androgen compound is spironolactone. In another embodiment, the anti-androgen compound is cyproterone acetate. In another embodiment, the anti-androgen compound is bicalutamide. In another embodiment, the anti-androgen compound is flutamide. In another embodiment, the anti-androgen compound is nilutamide. In another embodiment, the anti-androgen compound is an inhibitor of an androgen receptor. In another embodiment, the anti-
15 androgen compound is any other anti-androgen compound known in the art. Each possibility represents a separate embodiment of the present invention.

[000164] In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with an estrogen compound. In another embodiment, a method of the present invention further comprises the step of contacting the scalp,
20 eyebrow, or scarred region with an estrogen receptor agonist. In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with an estrogen analogue. In one embodiment, the estrogen analogue is estradiol. In another embodiment, the estrogen analogue is 17 beta-estradiol. In another embodiment, the estrogen analogue is 17 alpha-estradiol. In another embodiment, the estrogen analogue is ZYC3. In another
25 embodiment, the estrogen compound, estrogen receptor agonist, or estrogen analogue is any other estrogen compound, estrogen receptor agonist, or estrogen analogue known in the art. Each possibility represents a separate embodiment of the present invention.

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[000165] In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with an inhibitor of an EGF protein. In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with an inhibitor of an EGFR. In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with a compound that reduces an expression of an EGF protein or an EGFR. Each possibility represents a separate embodiment of the present invention.

[000166] In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with a Hedgehog protein. In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with a nucleotide encoding a Hedgehog protein. In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with an activator of a Hedgehog protein. Each possibility represents a separate embodiment of the present invention.

[000167] In one embodiment, a scalp is treated by a method of the present invention. In another embodiment, an eyebrow is treated. In another embodiment, any other hair-bearing area or region of the skin is treated. Each possibility represents a separate embodiment of the present invention.

[000168] In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with a lithium compound. In one embodiment, the lithium compound contains a lithium ion. In another embodiment, the lithium compound contains a lithium atom.

[000169] In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with (2'Z,3'E)-6-bromoindirubin-3'-oxime (BIO). In another embodiment, a method of the present invention further comprises the step of contacting the scalp, eyebrow, or scarred region with any other compound known in the art that is capable of inducing an epidermal cell to differentiate into an HF stem cell. Each compound represents a separate embodiment of the present invention.

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[000170] In one embodiment, the compound administered as part of methods of the present invention is administered systemically. In another embodiment, the compound is administered topically. In another embodiment, the compound is administered to the site of the abrasion. In another embodiment, the compound is administered to the site of the wound induction. In another embodiment, the compound is administered to the site of the depilation. In another embodiment, the compound is administered during wound healing. In another embodiment, the compound is administered prior to HF neo-genesis. In another embodiment, the compound is administered during HF neo-genesis. Each possibility represents a separate embodiment of the present invention.

[000171] In another embodiment, the present invention provides a method of inducing formation of an HF stem cell, comprising performing a method of the present invention. In another embodiment, the present invention provides a method of inducing formation of a DP cell, comprising performing a method of the present invention. Each possibility represents a separate embodiment of the present invention.

[000172] In another embodiment, homologues and variants of transcripts and proteins of the present invention are administered in methods of the present invention. In another embodiment, homologues and variants of transcripts and proteins of the present invention are targeted in methods of the present invention. Each possibility represents a separate embodiment of the present invention.

[000173] The terms "homology," "homologous," etc, when in reference to any protein or peptide, refer in one embodiment, to a percentage of amino acid residues in the candidate sequence that are identical with the residues of a corresponding native polypeptide, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology, and not considering any conservative substitutions as part of the sequence identity. Methods and computer programs for the alignment are well known in the art.

[000174] In another embodiment, the term "homology," when in reference to any nucleic acid sequence similarly indicates a percentage of nucleotides in a candidate sequence that are identical with the nucleotides of a corresponding native nucleic acid sequence.

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[000175] In another embodiment, "homology" refers to identity of greater than 70%. In another embodiment, "homology" refers to identity of greater than 75%. In another embodiment, "homology" refers to identity of greater than 80%. In another embodiment, "homology" refers to identity of greater than 82%. In another embodiment, "homology" refers to identity of greater than 85%. In another embodiment, "homology" refers to identity of greater than 87%. In another embodiment, "homology" refers to identity of greater than 90%. In another embodiment, "homology" refers to identity of greater than 92%. In another embodiment, "homology" refers to identity of greater than 95%. In another embodiment, "homology" refers to identity of greater than 97%. In another embodiment, "homology" refers to identity of greater than 98%. In another embodiment, "homology" refers to identity of greater than 99%. In another embodiment, "homology" refers to identity of 100%.

[000176] Protein and/or peptide homology for any amino acid sequence listed herein is determined, in one embodiment, by methods well described in the art, including immunoblot analysis, or via computer algorithm analysis of amino acid sequences, utilizing any of a number of software packages available, via established methods. Some of these packages may include the FASTA, BLAST, MPsrch or Scanps packages, and may employ the use of the Smith and Waterman algorithms, and/or global/local or BLOCKS alignments for analysis, for example. Each method of determining homology represents a separate embodiment of the present invention.

[000177] In another embodiment, the present invention provides a kit, comprising a tools and/or a compound suitable for performing a method of the present invention.

[000178] In another embodiment, the present invention provides a device, comprising a tool suitable for epidermal disruption and a means of delivering a compound or factor that promotes a differentiation of an uncommitted epidermal cell into a HF cell.

[000179] In other embodiments, the present invention provides a method of treating any disease, disorder, or symptom associated with balding. In other embodiments, the present invention provides a method of treating any disease, disorder, or symptom associated with balding. In other embodiments, the present invention provides a method of treating any disease, disorder, or symptom

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associated with balding. Each disease, disorder, or symptom represents a separate embodiment of the present invention.

Pharmaceutical Compositions

[000180] In another embodiment, methods of the present invention comprise administering a pharmaceutical composition comprising the HF stem cell-inducing or -activating compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or any combination thereof; and a pharmaceutically acceptable carrier. Each possibility represents a separate embodiment of the present invention.

[000181] The pharmaceutical compositions containing the HF stem cell-inducing or -activating compound can, in another embodiment, be administered to a subject by any method known to a person skilled in the art, such as topically, parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitoneally, intraventricularly, intracranially, intravaginally or intratumorally. Each possibility represents a separate embodiment of the present invention.

[000182] In another embodiment, the pharmaceutical compositions are administered orally, and are thus formulated in a form suitable for oral administration, i.e. as a solid or a liquid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment of the present invention, the HF stem cell-inducing or -activating compounds are formulated in a capsule. In another embodiment, the compositions of the present invention comprise, in addition to the HF stem cell-inducing or -activating compound active compound and the inert carrier or diluent, a hard gelating capsule.

[000183] In another embodiment, the pharmaceutical compositions are administered topically to body surfaces and are thus formulated in a form suitable for topical administration. Suitable topical formulations include gels, ointments, creams, lotions, drops and the like. For topical administration, the HF stem cell-inducing or -activating compound or its physiologically tolerated derivatives such

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as salts, esters, N-oxides, and the like are prepared and applied as solutions, suspensions, or emulsions in a physiologically acceptable diluent with or without a pharmaceutical carrier.

[000184] In another embodiment, the pharmaceutical compositions are administered by subcutaneous implantation of a pellet. In another embodiment, the pellet provides for controlled release of HF
5 stem cell-inducing or –activating compound agent over a period of time.

[000185] For liquid formulations, pharmaceutically acceptable carriers are, in another embodiment, aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include, in another embodiment, water, alcoholic/aqueous solutions, emulsions or
10 suspensions, including saline and buffered media. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil.

[000186] In one embodiment, the pharmaceutical compositions are controlled-release compositions, i.e. compositions in which the HF stem cell-inducing or –activating compound is released over a
15 period of time after administration. Controlled- or sustained-release compositions include, in another embodiment, formulation in lipophilic depots (e.g. fatty acids, waxes, oils). In another embodiment, the composition is an immediate-release composition, i.e. a composition in which all the HF stem cell-inducing or –activating compound is released immediately after administration.

EXPERIMENTAL DETAILS SECTION

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EXAMPLE 1

DEPILATION AND EPIDERMAL ABRASION CAUSES DE NOVO HAIR FOLLICLE FORMATION

MATERIALS AND EXPERIMENTAL METHODS

Depilation and epidermal abrasion

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[000187] Mice were anesthetized with an injection of sodium pentobarbital before the hair on the back was clipped and depilated with Nair™ (Carter-Wallace, New York, NY), then epidermis was removed using a rotating felt wheel as described by Argyris T, J Invest Dermatol, 75: 360-362, 1980). After scrubbing with 70% ethanol and drying under an incandescent lamp, the basal and supra-basal layers in an area of (1.5 cm)² cm of the inter-follicular epidermis were removed by careful abrasion with a felt wheel mounted on a Dremel Moto-tool (Racine, WI). After abrasion, the skin was shiny and smooth, and there was no blood. One day later, the abraded area was covered by a fibrin crust, which fell off after 3–7 days, exposing the newly regenerated epidermis. A group of control mice was sacrificed immediately after abrasion to confirm microscopically the complete removal of the interfollicular epidermis.

Immunohistochemistry

[000188] Skin samples were fixed in PBS-buffered 10% formalin. Six-micron thick paraffin sections were cut and stained, where applicable, with antibodies.

BrdU labeling

[000189] The protocol described by Bickenbach and colleagues (Bickenbach et al, Cell Tiss Kinet 19: 325-333, 1986; Bickenbach et al, Exp Cell Res 244, 184-195, 1998) was used. Mice were injected with 50 milligrams per kilogram (mg/kg) bodyweight 5-bromo-2'-deoxyuridine (BrdU) every 12 hours for a total of four injections.

RESULTS

[000190] An area of the backs of 50-day old mice was subjected to depilation and removal of the epidermis using a rotating felt wheel. Fifteen days later, HF placodes, hair germs and other signs of follicle neogenesis were present (Figure 1; arrow indicates a hair germ). Morphology of the follicles was similar to embryonic follicle development. To further characterize proliferation in the new follicles, the skin was labeled with BrdU 60 minutes before sacrifice. As depicted in Figure 2, the proliferation pattern was similar to developing follicles in the embryo.

[000191] These findings demonstrate that (a) disruption of the epidermis causes generation of new

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HF, and that this generation of new HF can occur (b) in adult subjects and (c) during telogen (50-day-old mice are in the second telogen stage of the hair cycle).

EXAMPLE 2

INDUCTION OF A LARGE EXCISIONAL WOUND, BUT NOT A SMALL PUNCH

WOUND, CAUSES DE NOVO HAIR FOLLICLE FORMATION

MATERIALS AND EXPERIMENTAL METHODS

Punch wound and excisional wound induction

[000192] The backs of 21-day-old mice were depilated as described for Example 1 and sterilized with alcohol, followed by 1% iodine solution. Punch wounds, 4 mm in diameter, were induced using a dermal biopsy punch, down to, but not through, the muscle fascia. Excisional wounds were full thickness and 1 cm in diameter; skin and panniculus carnosus was excised using fine surgical scissors.

RESULTS

[000193] To test whether wounding could induce HF formation, punch wounds or excisional wounds were induced in mice. Both types of wounds exhibited contraction and re-epithelialization following wound induction; however, unlike the mice receiving punch wounds, the mice receiving excisional wounds also exhibited scar formation within 10 days of wound induction (Figure 3, left panel). No follicles were evident at this time point (Figure 3, right panel). 12 days after wound induction, hair germs, with similar morphology to fetal hair germs, were observed in the wound site, following BrdU pulse labeling (Figure 4). Several markers were used to verify that the observed structures were HF. The structures exhibited staining with anti-keratin 17 (K 17), an HF marker (Figure 5), and staining with anti-alkaline phosphatase at the 12 day time point verified that the structures had dermal papilli containing fibroblasts, as expected for HF (Figure 6; HF at earlier and later stages are depicted in the left and right panels, respectively).

[000194] The HF generated by wound induction were further characterized by morphological

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comparison to embryonic HF, following BrdU staining; a clear correspondence in morphology was observed at various stages (Figure 7). In addition, several markers of embryonic HF development, namely Lef1, wingless/ int (Wnt) 10b, and sonic hedgehog (Shh), were also induced in the epidermal disruption-induced HF neogenesis (EDIHN) (Figure 8). Additional BrdU staining (Figure 9) and staining for HF markers S100A3 and S100A6 (Figure 10; left panel: tissue section parallel to HF axis; right panel: cross-sectional view of follicle) provided further verification that the development of the EDIHN follicles closely paralleled embryonic HF development.

[000195] These findings provide further evidence that disruption of the epidermis causes generation of new HF, and that this generation of new HF can occur (b) in adult subjects and (c) during telogen (21-day-old mice are in the first telogen stage of the hair cycle).

EXAMPLE 3

EDIHN-INDUCED HAIR FOLLICLES GENERATE HAIRS

[000196] At 25 and 45 days after wound induction, wound sites contained new hairs (Figure 11, left and right panels, respectively). New hairs appeared to lack pigmentation, except when the wnt pathway was inhibited, using Dkk-1 (Dickkopf-1) during the first nine days after wounding (see Example 10).

[000197] These findings indicate that EDIHN-induced HF function normally; i.e. are capable of generating hairs.

EXAMPLE 4

EDIHN HAIR FOLLICLES RETAIN THE ABILITY TO ENTER INTO CYCLICAL HAIR GROWTH

MATERIALS AND EXPERIMENTAL METHODS

BrdU labeling

[000198] 50 mg/kg bodyweight BrdU (Sigma) was injected twice per day for 3 days beginning 20

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days after wounding. BrdU was detected 40 days after wounding (17 day chase).

Whole mounting and immunofluorescence

[000199] HF whole mounts were obtained by incubating fresh skin with EDTA (20mM in PBS) at 37 °C overnight, then separating the epidermis and dermis. Epidermis was then fixed in 10% formalin for 10 min, room temperature (RT). Dermis was fixed in acetone overnight, RT. After rinsing with PBS, whole mounts were stained with antibodies for immunohistochemistry (schematically depicted in Figure 12) and were imaged using a Leica confocal microscope.

RESULTS

[000200] To determine whether EDIHN-induced HF contain normal levels of HF stem cells, mouse skin was examined for the presence of label-retaining cells at 21 days after wound induction. Retention of BrdU during a long chase period is, under these conditions, one of the hallmarks of HF stem cells. Normal numbers and placement of label-retaining cells (in the bulge of the HF) were observed (Figure 13). To verify that the label-retaining cells were HF stem cells, K15-eGFP mice were utilized. In these mice, eGFP (enhanced green fluorescent protein) is expressed from the K15 promoter; thus, expression of eGFP identifies HF stem cells. As depicted in Figure 14A, eGFP-expressing cells were observed in in tissue sections (right side) of newly formed hair follicles 35 days following wound induction. eGFP-expressing cells were also seen in the epidermis whole mounts (bottom, far left panel) indicating the conversion of epidermal cells into cells with hair follicle stem cell characteristics. ([bottom, second from left] panel is same as [bottom, far left] panel but viewed under white light) This finding shows that the observed label-retaining cells exhibited HF stem cell properties.

[000201] To determine whether EDIHN-induced HF cycle normally, mounts were prepared from additional mice at 35, 38 and 45 days after wounding. As depicted in Figure 14B, the EDIHN-induced HF entered the resting phase, telogen, and then re-entered a new anagen stage.

[000202] In summary, the findings of this Example show that EDIHN-induced HF contain HF stem cells, as do embryonically generated HF. The presence of the HF stem cells shows that EDIHN-

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induced HF retain the ability to enter into cyclical hair growth in the same manner as embryonically generated HF. The findings also show that wounding induces epidermal cells to assume a hair follicle stem cell state (expressing K15-eGFP). This model is shown schematically in Figure 15. The findings of Examples 2, 3, and 4 show that EDIHN-induced HF are fully functional and thus able to restore hair growth to a subject in need.

EXAMPLE 5

EDIHN-INDUCES NEW HAIR FOLLICLES IN MICE AT THE TELOGEN STAGE OF THE HAIR CYCLE

[000203] To determine whether EDIHN was induced new hair follicles in mice wounded at the telogen stage of the hair cycle, 21-day-old mice were subjected to EDIHN using a 1-cm excisional wound, as described in Example 2. Skin was then examined by whole-mount assay for indications of new HF. As depicted in Figure 16, after 11 days, new HF were not evident by macroscopic examination (top panel), AP staining of the dermis (bottom left panel), or K17 staining of the epidermis (bottom right panel). After 14 days, as depicted in Figure 17, dermal papilla cells were detected in the dermis (left panel) and HF stem cells in the epidermis (right panel), demonstrating that new follicles were being formed. After 17 days, the new follicles were more developed, as shown by examination of the dermis and epidermis (Figure 18, left and right panels, respectively). This method induced formation of an average of 49 new follicles in the wound, a number that was consistent over three separate experiments, as depicted in Table 1.

[000204] Table 1. Results of three separate experiments performed on 21-day-old mice.

Sample	Expt 1	Expt 2	Expt 3		
1	24	70	55		
2	29	52	25		
3	27	85	53		
4	102	25	80		
5	53	27	23	Avg of expts	Std dev of expts

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Average	47	51.8	47.2	48.67	2.71
Std dev	32.8	26.3	23.7		

[000205] The findings of this Example demonstrate that EDIHN is capable of inducing formation of new HF in mice at the telogen stage of the hair cycle, despite that fact that these mice do not contain HF at the anagen stage during wounding.

EXAMPLE 6

5 IN ADULT MICE, INDUCTION OF ANAGEN INCREASES THE EFFICIENCY OF EDIHN

[000206] The experiment described in Example 5 was repeated with mice of different ages, and therefore at different stages of the hair cycle. To ensure that wound scarring occurred, larger wounds were induced in the older mice. As depicted in Table 2, adult mice at telogen, such as 8-week-old mice, exhibited lower efficiencies of HF formation by EDIHN.

[000207] Table 2. Efficiency of HF formation by EDIHN in adult mice at various stages of the hair cycle.

Age	Wound size	Days after wound	Mice exhibiting EDIHN	Hair cycle
3 wk	1 cm	20	25/25 (100%)	Telogen
4 wk	1 cm	20	5/5 (100%)	Early anagen
5 wk	1 cm	20	1/2 (50%)	Anagen
8 wk	1.5 cm	30	16/35 (46%)	Telogen
14 wk	1.5 cm	30	1/2 (50%)	N/A*
20 wk	1.5 cm	30	2/2 (100%)	N/A*

* The second telogen lasts approximately 40 days in mice. Thus, 14-week-old and 20-week-old mice contained a mixture of telogen and anagen HF.

15 [000208] To determine whether experimental induction of anagen increased the efficiency of EDIHN,

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8-week-old mice were depilated several days prior to wound induction. As depicted in Figure 19, the wounds closed similarly whether or not they were preceded by depilation. As depicted in Figure 20A-B, the depilated mice exhibited enhanced EDIHN relative to the non-depilated mice depicted in the previous Example by a factor of 11-fold.

- 5 [000209] The findings of this Example demonstrate that anagen induction enhances EDIHN. In addition, these findings show that EDIHN is capable of not only forming new HF, but also of activating anagen in pre-existing HF in the telogen stage.

EXAMPLE 7

EDIHN-INDUCES NEW HAIR FOLLICLES IN HUMAN SKIN

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MATERIALS AND EXPERIMENTAL METHODS

Grafting

[000210] Discarded human adult scalp from the preauricular area obtained from plastic surgery was grafted onto immunodeficient (scid) mice. The graft was bandaged and allowed to heal, then was used in the wound healing study 3 months after grafting.

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RESULTS

[000211] To determine whether human skin responded to EDIHN as did mouse skin, human skin was grafted onto SCID (immuno-deficient) mice and subjected to depilation by plucking and wound induction three days later. Seven days following wound induction, formation of new HF was observed in the human skin (Figure 21A; arrows indicate new HF) by hematoxylin and eosin staining of paraffin embedded tissue sections.

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[000212] In additional experiments, adult human skin was grafted onto mice, abraded, and examined at 7 days post-abrasion. New HF were generated in the human skin, which mimicked normal hair follicle formation during fetal development, as evidenced by staining for S100A6 or S100A4 (Figure 21B).

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[000213] The results of this Example show that EDIHN can be used to generate hair growth in human skin as for mouse skin.

EXAMPLE 8

MOLECULAR PATHWAYS ACTIVATED DURING HF STEM CELL ACTIVATION

5

MATERIALS AND EXPERIMENTAL METHODS

Isolation and activation of HF stem cells

[000214] K15-eGFP mice were depilated in order to induce formation of new HF. Activated hair follicle stem cells were isolated from K15-eGFP mice using fluorescence-activated cell sorting (FACS) two days after depilation and 5 µg (micrograms) total RNA from the cell population was isolated, reverse-transcribed and hybridized to an Affymetrix (Santa Clara, California) array MG_U74v2 chip. Scanned chip images were analyzed using Affymetrix Microarray Suite 5.0 and GeneSpring software (Silicon Genetics) to detect fold-change differences between activated HF stem cells (HFSCs) and non-activated (telogen) HFSCs. Values were normalized before computing fold-changes and differences between non-activated "bs-line" and activated ("expt") samples.

15

RESULTS

[000215] To identify molecular pathways up-regulated during HF stem cell activation, activated HF stem cells were isolated, and the gene expression patterns of the cells were analyzed to detect up-regulated transcripts. The transcripts depicted in Table 3 were up-regulated at least 2-fold in the activated HF stem cells relative to the cells prior to activation. In some cases, the sequence in Table 3 is a genomic sequence that contains the sequence of the transcript. Data pertaining to the up-regulation of the transcripts and further information about them is provided in Tables A through C below.

[000216] Table 3. RNA transcripts up-regulated during HF stem cell activation.

SEQ ID No:	Access. #	Sequence

[illegible]

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3	M26005	gcgccaguccuccgauagacugagucgcccggguacccguguucucauaaaagccucuu cuguuugcauccgaaucguggucucgcugguccuugagagggucuccucagauugauugac uaccacgucgggggucuuucauuuggaggccccagcgagauuuggagacccugcccagg accaccgacccccgucgggagguaagcuggccagcgguucguuucgugucugucucugucuu cgugcguguuugugccggcauuuauguuugcgccugcgucuguaacuaguuagcuaacuag aucuguaucuggcgguuccgcggaagaacugacgaguucguauucccgccgcagccccugg gagacguccagcgccucggggggccguuuuguggccauucuguaucaguaaccaccga gucggacuuuuuggagcuccgccacugacguggcuuuugugggggacgagagacagagac acuucccgccccgucugaauuuuugcuuucgguuuuacgccgaaaccgcgccgcgcgucug auuuguuuuguuucuuuuguuucuuucguuaguuuuucuuucugucuuuaaguguuuuucgag aucaugggacagaccguaacuacccucugaguuuuaaccuugcagcacugggggagauucca gcgcauugcauccaaccagucuguggauguaagaagaggcgucggauuaccuucuguuccg cugaauaggccaacuucuaaugugggauggccucaggauugguacuucuaauuaaguuau cucucagguuaagucuaagaguuuuuguccuggucccccacggacacccggauccagguccau auaucgucaccugggaggcacuuigccuauagacccccuccgugggucaaaccguuuugucuu ccuaaacuuccuccucgcccagacgucuccgucuccgcccggucuuucugcgcaaccuccg ucccgauucgcccuuuaccucgcccuuacccccucuaaaaguccaaaccuccuaagccccag guucucccugauagcgggcgacccucuaugaccuucucacagaggaccucccgccguacgg agcacaaccuuccuccucugccagagagaacgauaaagaagaggcgccaccaccuccgaggu uuccccccuucccauggugucucgacugcggggaaggagagaccucccgagcggaacu ccaucaucuccaggaucuccacuccgcaugggggggagauggccagcuucaguacuggccg uuuuccuccucugauuuuaaccuuccuuucugaagaaccagguaauugacggccuuga
4	AA681998	gacguagagccccuugcgcccgguuuccugaucccgcuuacuccucugcgcgccggcaggau ggcccacaagcagaucuaacuacagacaaguacuucgaugagcacuacgaguaccggcaugu cauguuaccagagaacucucuaaacaaguacccaaaacucaucugauguccgaagaggagug gaggagacuugguguccaacagagucuaaggauuggguucauuacaugauuacagagccagaac cgcauauucuuucuuuagacgaccucuuccaaaagaacaacaaaaugaagugcagcuggga ucaucuaaucuuuuucaauuuuaauguaauauguguaauuaagguaguauucagugaauacu ugaaaaguguacaaaccuuucauccauaccugugcaugcgcuuauucacagcaacaga gcucagucaaaugcaacugcaaguagg

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[illegible]

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8	AV374591	aaccaaauggggaauugggguccccaacnuuncugugguaccagccggguuucucuugcauug gaaacaaacaccuuuguaggcauuugcguaauucgugaagagacuguuuuauagaucaccucu uagauuuauuaauuaaccuaaguuguugaaguuuucuguuucuccuuaagagaaaauaaca aaauucaacauugaagcauaguuuucuguuuuucuguuugucaaaauaguaauaauugugcugug auguuuaugcuuaauucauaaagauguuuuacuuuuuaguguaaaguuauguucuuuuuaaca uuauuuugcuuaaaauuugaauauggcccgacaagaauauuuuugcuuugauuuauacacug auucuuugugacaaaauagacccauuaaaaauggccuuuaauagacuaacuuaaccuuuugua gcuagguacucauguucuuuuuuuaaagaugcccuuuggauuggauuggauugaucauguu uaacucagcguauuuuauuggaugaaagcuaaaauacagauuuuuggcaucucuaagguggaau gagcccacuccacacacugauaaaaaucaugcauaguuuuuuaaauagaacauuaauaaacucaug uugucuu
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21	U57524	Sequence below.

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26	M21285	See above (same Accession Number).

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 5 cuaaagucuaauuuuaagauguguuuuguguguguguguuuugacuauuuuauugaaucauuuaagua

30	U19118	Sequence below
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 10 cugccaucggauuguccucugcgcuaggagucaguuaccgucaacaacagaccccuggagauugucagucaccaagucugaggcg
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 20 uauugcuuucuaagaaaauugcuguucugucccagaauagacugugcauaggguauccguuucagagccugguguugugcuau
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 gaacaaaaccuggua

		uuuuuuuuuuuuuuuuuugcugauaagaauucuuuuuauuguuauucgaauaaaaauaca uucauacagaaaauuaacaauucugcaaaaaacaauuucaaaauaaaaucuuuguuaaaacaaa auuuuacaaaaaucuuacaagaauucuuuagauaacaggguugcucaaaaaaaaagaaau aaagaaauucacuaauagaaauuuuuuuuuuuuauuuucaagcaaaaguuccugcuugau ugaggcucaguugucaccugaccagaauaggacugcuuaguauuaaaguuaacagcaucgac acggacggcaccagccccagccaguccagcaacgucgcuguguuuucauaagugagacgc gccagcacaaguuuuccucucucuuucuguuuuaccuucuuacuuaauggaaauugcuauggau 31 1 aagcacacagcagggccaaaaaaggaguuuuuccaaaauccagcaaaucagug
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32	M93275	uaguggugaucuggaccgugcggacuugcucguccucagcucuccuguuaggcgucucu uuucuccaggaggaaaaauggcagcagcaguaguggauccgcaacagagcguggugaug agaguggccaaccugcccuuggugagcucuaccuacgaccuuguguccuccgcuuauguc aguacaaaggaucaaguacccguauuugagauccgugugugagauggccgagaaggggcgug aagaccgugaccucugcggccaugacaagugcccuugcccaucauccagaagcuggagcca caauuugcggguugccaauaccuaugccugcaagggggcuagacaggauaggaggaagacug ccuauucugaaccagccaacguccgagauuuguugccagugccagaggugccguaacuggg gcgaaggauugggugacgacuaccauaggcuggagccaaggauucuguagccagcacaguc ucagggguggguggaauaagaccaaaggagcagugacuggcagcguggaaaggaccaagucu guggucaauggcagcaucaauacaguuuuggggauaggugcaguucaugaacaguggagua gauaaugccaucaccaagucgggagauugcugguagaccaguacuucccucucacucaggag gagcuggagauaggaaagcaaaaagguggaaggauuugauauugguucagaagccgagcaac uauaagggcuggagucccugucuaccaagcucugcucucggggcuuaucaccagggcucuc agcaggguuaaagaggccaaaacaaaagagccaggagaccauuucucagcuccacuccacu guccaccugauuugaauucgccaggaagaauaugcacagugccaaccagaaaauucagggu gcucaggauaagcucuaugucucguggguggaguggaagagaagcaucggcuacgacgac accgaugagucccacuguguugagcacaucgagucacguacucuggcuaucccccgaac cugaccagcagcuccagacuacaugccagacuguccuggucaacgcccaggguuacca cagaacauucaagaucaggccaaacacuugggggugauggcagggcgacaucaucuccgua uuccgcaaugcugccuccuuuaagggaaguguccgauggcguccucacaucaagcaagggg cagcugcagaaaaugaagggaauccuuagaugaaguuauggauuacuuguuuacaacacg ccucucaacuggcugguagguccuuuuauccucagucuaaccaggguagaacaaggccagc cugaagguccagcagucugaggucuaaagcucaguaaaccuccuugucaccagagcaug auguugcuggccagauagacccuuuugcuguauugaaauaacuugguagauggcuuuaag cuuagaaaagcagcuucuuagaaccaaggggccuauuauaggucacucacagcucaguuau ggucuugccccagcuggcccgaggagguucucuuaccuggcuggugaguggccugu guuagucuugugaggaccuggaggaaccuaaaagcucagaugcacuuacagucuugucug uggccuuuguauuuguuauuggcuguaaacgucugucuggaccgaauaaagauucacguga
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		ggcacgagggagcugcaguguucgcgcguugguagcuggugcaucggacucagcuggcuuu gugucccugagggcucaccgaaaaacacuuucucagcccucugacuccagagagagagaga gagagguacuuuuuguggucaccgacuuugaccccugcagaggcugagcgauggcgucua ugggacuacagguccuggggaucuccuuggcaguccugggcuggcuggggaucauccuga guugugcgcuccccaugugggcgggugaccgccuucaucggcagcaacaucgucacggcac agaccagcuggggagggccucuggaugaacugcguggugcagagcacaggucagaugcagu gcaagauguacgacucgaugcucgcccugccgcaggaccugcaggccgcccagcccua ugguacucagcauacugugggugcucugggggaugcuucucucagugguaggggggcaagu gcaccaacugcauggaggagcagaccgucaaggccaagaucagaucaccgcccggaggccg uguucaucguggcaagcaugcugauuauggugcccuguccuggaccgcucacaacguca uccgcgacuucuaacaaccuauugguggcuccggggcagaagagggaauggggggccucgc uuuacgucggcuggggcgccuccgggcugcugcuccugggaggaggccuccucugcugca guugcccaccucguagcaacgacaagccuacucggccaaguacuccgcccgcgcucug uccccgcccagcaacuauguguaaggugggccacucuguccacaaugccuuuguuuuuu uuucggauugagcucuaaacagccuguggccccucacaauuccaggaccugcccugcua uggggccacuaacugcuugcuggggacaggcaaaccggacugugcaaaguuacuagcccg uagcucuuggggcugcuccacauggcuccuuacggccggcaagauggauguaaaaaauuc uugcugcuuacauccaaauugcgguggaugaugggcugaaggcagaagcagcugggaaggg caguagaggcgcaagcuggguccugcuggccgggggagcucagcugugacuugggacucg gaguggauguccucauguuagcaaacguccacuguccuuucucuaucucccucacucage cuacacguuacuccagcgcuaucuuugccauuacgccccguguuuccgagcacagcuggu ccuaccccaagucauggugugcugagugacugaugaggggccauugagagccggugggcu cugccauggaaccuuuccguugauuagcaaugacugugcuugaccaccaccuaccua cuaaugaauuucuguagaguggaugggacggguuugagggaagaaggguagguggauu aaacugguuuggggaggggcuggggaccuagaagcagcccaguguguccccacccuuucc gcacugucuuugcuauuguucugaucacugugcgccccuccucucucagaaggaccugg gccucuuagauuggccccucugaguucccuccuuugcccauuucaaggacaccggccag ucugcggaaggaagguacgggggggggggggggggggugauggcauuguaccaggggaguc uccuggacuccccugccuucucugugguuucuuuguuuuguauuaaggucuguucacagc uguaauuaauuaauuuuucuaaauaauggcaccugcauacag
33	AB000713	
34	U20735	See above (same Accession Number).

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[illegible]

P-7628-PC

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37	U88328	
38	X82786	Sequence below.

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[illegible]

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41	L07264	cggccgccagaccuucaggcugaggaguggacgcgcggaccgacucugaacagacagacg aaccgcggccgcaagguucccagacaggauucacccagaggcaggcagcggacagugcc uuaguggaaccucgcuguccuccaccgccuggccccggugcaggcguccaguggccgccg cauccaaagugaucgcugccuccccgucuccgccagcucgggaccaugaagcugcugccg ucggugaugcugaagcucuuucuggccgcaguguuguccgcguuggugaccggugagagu cuggagcggcuucggagaggucuggcggcagcaaccagcaaccugaccucccacugga uccacaaaccagcugcuaccacgggaggugaucgugcucaggggguccaggacuuggaa gggacagaucugaaccuuucaaaguugcuuucuccuccaagccacaaggccuggccacc ccaagcaaagaaaggaaugggaaaaagaagaagaaggaaaggguuagggaagaagaga gaccuagccucaggaaauacaaggacuacugcauccacggggagugcagauaccugcag gaguuccguacuccucuuugcaauugccucccugguuaccacggacacaggugucauggg cugacucuaccaguggagaaucuccuauacacauaugaccacacuacagucuuggcugug guggcuguaguacugucguccgucugucuuuugucaucgugggacuucucauguuuag guaccacaggagaggagguuauagacuuggaaagugaagagaaagugaaguugggcguggc uagucccacugaggaggaccugagcuauaggaaccuucagaggcuacuucugagacagug guucguuacacguucuaacauagaggagaaaauuuucaccagcagccaugaaaacgucuuc auucauuuccaguugcuaccucgacuggggccuccuguaau
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42	M15668	ucgaccucacgggucuuugccaaaugucgcuuuccaacaagcugacuauuggacaagcugga cgugaaggggaagcgggucgugaugaggguggacuuaacguuccuangaagaacaacca gauaacaacaaccaaaggaucaaggcugcuguuccaagcaucaaauucugcuuggacaa uggagccaacuccguuguccuuaugagccaccuuggggccggccugaugguguucccaugcc ugacaaguacuccuuaugagccaguugcugcugaacucaaaucucugcugggcaaggau ucuguuucuaaggauguguguggggccagaagucgagaauccugugccaaccagcggc ugggacugucauccugcuggaaaaccuccgcuuucauguagaggaagaagggaaggga agaugcuucugggaacaagguaaagcugagccggccaaaauugaugcuuuccgagccuc acuguccaaaacaggagaugucuaugucaauaugcuuuugggacugcacaccgagccca uagcuccauggguggugugaauccugccacagaaggcuggguggauuuuugaugaagaagga gcugaacuacuauugccaaggcuuuggagaguccugagcggaccuuccuggcuaucuuggg agggcguaaaguugcagacaagaauccagcugaucauaauaugcuagacaaagucuauga gaugaucauugggugguggaauaggccuuuaccuuccuuaagguccucaacaauaggagau uggcacauucucuguaugaugaagaaggagccaagauugucaaaagaucucauguccaaagc ugagaaaaauaggugugaagauuaccuugccugugacuauugucacugcugacaaaauuga ugagaaugccaaagacuggccaagcuacuguggccucugguauaccugcuggcuggauggg cuuggacugugguacugagagcagcaagaaauugccgaggcugugggucgagcuaagca gauuguuuggaaugguccuguuugggguaauuugaauagggaagccuuugccagggggaacca gucacucauggaugagguggugaaagccacuucuaagggguugcaucacuaucuaaggugg uggagacacugccacuugcugugccaaauggaacacagaggauaaagucagccaugugag cacuggggggcgugccagucuaagagcuccuggaagguaaaguccuuccugggguggaugc ucucagcaauguuuaguauuuuucuuuccugccuuugguuccugugcuccuaagcuaaccu gcuguuuuccacauuccauuugguguuagcgcaagauucagcuaguggcugagaugugg cacagaccuuuacagugcaagcaucucagcucgucuuacugcaucagaugcugguucuc aagaucuccauuuuuuuuccuuaugugacuaaaaaccauugugcauuguagagggcgucua uauauucugccugagaaagggaagugagcuguaaaggcugagcucucucucugacguaugu agccucugguuagcuucgucacucacugucuuugacucagcaugggcaaucugaugaaau ccagcuguaagucugcagaaauuuccgaauuc
43	AI047508	uuuuuuuuuuuuuuuuucauguuuaauaguuuuauuuuucuuuuuuguuugcuuauaucuuc aaauaaucuuuuugcagguuuuuguuacagauuuuugauaagccaacucaaguacugauuu uucauccucucugaaaguuuuuaaccagggaaggaaaacguuccaugggaauccaucuuca cauggugaugagucacauaacaucuccaacaauucugaagccgcuugacauacauagauccauc aucucuuaaggacaucauacuggcaagugaugauauaggucuuagguaaauaugcaauau auugucauuggccaacagaggggcaugccuucacaucaugaaccuggaauacuuuugagc cagcucagaacuaccaggagugggaaauuuuuguaaacgggacuuuuucuuuguaucucagc gagcaaggaacuccaauucacaaacuguaacaaguggcuagauuccauggguacauguug guuga
44	AJ001418	Sequence below.

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[illegible]

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47	X80417	Sequence below.
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 20 ggguguggguguuuggcguggguggggggugaugggugugaggaggccagacccaaauuggggcuuaggguucaagcucuca
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 25 gucuucgguuuagguugcugacaagcugcugaaguggucuguccaaauccagcugagccugaguccagucgcagggguug
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65	AF064088	Sequence below.
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30 gacagcggagcgcggugggcugcagcucuaugugucucagugcucccgucuguggcuuacuaagcagccagcagccaggcagc
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[illegible]

-90

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 u

69	AI854358	cggacgcugcagaccugaccgacgugcugugcgaguucgacgcggugcuggccgacuucg cgucgcccuccacgagcgcacuuccacuauaggagcaccuagagcgcgaugaagcggcg cagcagcggcagcgucagcgcagcagcggcuucagcgcagucggagagugcagacucagu guacagggacagcuucaccuucagugaugagaagcugaauucuccaaccaacuccucucc agcucuccugcccuccgcugucacuccucggaaagccaaauaggugacacuaaagagcu cgaagacuucuuugccgaucuggacaggaccuuagcauguaugugaagcaaggaguugg gguc
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70	X67668	ccgggcccaggagaagucugcaaaacaaggaggcuggggauugccuuagcgagaaucagu ucucuuaggagguuagggaaggaagucuuucucuggaggucugagggaagcgucuguc agaugcccggguugucauggguaaggugaccccaucaagccgcuggggcaaauguccucu uacgccuuuuuugugcagaccugccgggaggagcacaagaagaagcaucccaauucgucg gucaacuucgccgagaucccaagaaaugcuccaagagauggaagaccaugucugcaaag gaaaacucgaaguuugaagauuuggccaagagcgacaaagcuuguuuuacaggggagau aagaacuauguuucucccaaaggugauaagaaaggaaaagaaaaagauccaaugcuccg aagagaccaccgucugccuucugccuguuuugcucugaaaaucgcccagaaucaaaaau gaauacccggggccugucuaauugggagauacugcgaaagaaacugggugagauguggucugag cagucugccaaagagaaacaaccguauagagcagaaagcagcuaaacuaaaggagaaguau gaaaaggauuuugcugcauaccgugucaaggggcaaaagugaagcaggaaagaaggguccu gguaaggccagcaggcucaaagaagaugacucagaagaugaggaaagaagaaggaggaa gaugaagaggggggaagaaggaggaugaagaauaaguggcuauccuaaaguguggaguauau gugcucaggcaguuuuuugcuaagaauuucaagcgagcucaacauuagcucca guaggaa
71	K02236	aucacgcuccuagaacucuucaaacccgaucucucgucgaucuucaa ccgccgccuccacucgccauaggaccccaacugcuccuguccuccgguaagggggacugc ugacggggaauucugggagagcuagacaggcuuuuuggccccuccuuuaguaauuacuuua aggguacgaccggcuaccccuuccgaauugaauucugaagcacuccugcuccuuuaacua guccuugagauaguggcucgccuacccgggugauuuugccucaccuuccuaggagaacagc guucagguacucccgggucccacucaaccgcgcucacugacugccuucuaauuuuagaug gauccugcuccugcgucggcgccugcaaaugcaaacaaugcaaauguacuuccugcaaga aaaguaaguuggauucucucugccauuuucccgucacucuccugggguccuagccccgc gcgccgcgccuucccucccgggagcguucaggugguuguccucugacaagguuucucgcu cacguucaacucucucuccccacaggcugcugcuccugcugccccgugggucugcgaa gugcucccagggcugcaucugcaaaagaggcuuccgacaagugcagcugcuguccugaag ggggggcgagggggucuccacaucuguguaaaauagaccauguagaagccuagccuuuuug uacaaccugacucguucuccauaauuuuuuauaaaagcauguaacugacaauaaaagc cguugacuugauu
72	X51829	Sequence below.

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76	AI121305	ccaauaccacagccgugaccacagccaagaccacagccaaaagccuggccauccgcacuc ucggcagccccuggcagugcccuccauauccugcuuguuuuucacauuaguaaaacuccu cuucuaaaagaaaacugggggaagcagaucccaaccuccaggucuccuccgagcucuu ucaggccagugcuuaaacaauaccgaugaagguuuuauuguccucaguccgcagcuccac caccuuggaccacagaccugcaacacuagugcacuugagggaucacaaugcuugccugga ucuucaggggcacaauuccgcuucuuuguaaaauacuuauguccauccauccugcgugua
77	U35374	auaggagaacgaguucacauacgaagaauuauagagaccacugccaaguggcuucugcaacac acugaauaucgaccucaaguggcagugaucugugguuccggcuuaggaggggcugacugcu cacuuuaaggaggcucagaucuuugacuacaauagagauaccaacuuccccaaagcaca gugcaaggucacgcagggccgacugguguuuggauugcugaauggcagaugcugugugaug augcaaggccgguuuccauauguaugaaggauacucacugucuaaaggugacauucccagug agaguuuuccaucuucugggugugggaaacuuggguggucaccaaugcugcuggaggacuc aaccccaauuuugaaguuggagauuuauugcugauccgugaucacaucaaccuaccuggu uucugugggccagaaccucuccgggggccccaacgaugaaagguuuggaguucguuuuccu gccaugucugaugcuuauagaccgggaugaugaggcagaaggcuucagugccuggaaacaa auggggggagcaacgaaagcuacaagaaggcaccuacugugauguuggcaggccccaacuuu gagacuguggcagagagucgucugcuaaaagauugcugggggagcagaugcuguuggcaugagc acaguucccagaaguuaucgucgcaaggcagugugggcuccgugucuuugguuucucacuc auuacgaacaagguuugucauggauuauagagaacuuggagaaggccaaucaauggaagu cuggaugccgggaaagcagcugcacagacauuggaaagguuugucuccauucuuauaggag agcauuccacucccggaucguggcagcuga
78	X15643	Sequence below.

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20 uggcuagucuuuccagagaaccagggucauccagcacucacaaggcagcuugugagcugauacuauucuguauauuucaguccua
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[illegible]

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79	AI849109	uuuuuuuuuuuuuuuuuuuuuaagcguccaggcugacuuaauuuuacacaagugggugggcccc agaaccacagggacaugaccuggagaguaggcacagugccugaggcugcaagagccaaaaua cagggauucaugccuucuccuugggucccaugaccaaauuaaaaaaaaaaaaaaacaacaa aucacacagcacacaucgccacaccauucccuccuuccuucagcaacagccaauucag cuuucuaagccaaagacaguggcuacaacugaauuuacagagaaccaugcagccaagaaac cagagccacggagggggagaggcuugcgugacuucccacauugugcugucccauagcagcu gagugacccccacca
80	U70132	agaaagauaaggggccagcaaggaaagaauagggauguggggcgccgaggaccgguccaaga agaagcgggcaacgccggcagaggacucauuucacuagccagcagcugcaggagcuggaag ccacuucccagagaaaaccgcuaccagacauguccacucgcgaagaaucgccgugugga ccaaccuuacggaagcccaguccggguuuggguucaagaauccggcgccaaauggagaa agcggggaacgcaaccagcaggccgagcugugcaagaauggcuuuggggccgcaguucaacg ggcucaugcagcccuacgaugacauguacccccggcuauucguacaacaauuggggcugcca agggccucacgucagcgcucucuguccaccaagagcuuccccuucuucaacuccaугааcг ucaaucccccuguccucucagaguauuuuuccccgcccacuccaucucaucuaugagua ugucguccagcaugggugcccuccgcggugaccggcgucccgggcuccagccucaauagcc ugaauaacuugaacaaccugagcagcccгucgcugaauuccgcggugcccacgcccgccu guccuuacgcgcccggcaguccuccguacguuuauagggacacaугааacucgagccugg ccagccugagacugaaagcaaagcagcacuccagcuucggcuacgccagcgugcagaacc cgggccuccaaccugagugcuuugccaguaugcagucgaccggcgccggugugaaccgcgcccc gggcgcgggggauccgaggacugucggagugggcaacucugccccagaaagacugagaauu gugcuagaaguuugugcgcacuauggggaagggaaggagggggaaaaaгаucagaggaaaa gaaaccacugaauucaaaagagagagcggccuuугаuuucaaaagggaauuccccaagugucu acgucuuucgcuaaгaгуаuuucccaacaguuggaggacgcгуacgcccacaaauгуuuга cuggauaugacaauuuuaacauuacuauaagcuuguuauuuuuuaaguuuagcauугuuaa cauuaaaaugacugaaagggaугаuuauauaucgaaaugucaaaauuaauuuuauaaaagca guuguuaguacuaucacuacaguguuuuuuaaaggcuaggcuuuuaaaauaaagcaугуuuau acagaaucaguuaaggauuuuucgcuugcgagcaaagggaугаuuauuacuaaaugccacac угаугуuuucuaacauuuauuuuu

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81	M13805	cugagagggccagguggggcggaaucaacguggagauuggaugccgcucccguguggac cugagccgcauccugucagagaugcgugaucaguacgagaagauggcggaagaaccgc aaggauGCCgaagacugguucucagcaagaccgaggagcugaaccgcgagguggccacc aacagcgagcuggugcagagcggcaagagcgagaucuccgagcucagggcgaccaugcag gcccuggagauugagcugcagucccagcucagcaugaaagcaucucuggaggggcagccug gcagagacagagaaccgcuacugcgugcagcugucucagauccaggggcuagucggcagu guggaggagcagcuggcucagcugcgugcgagauggagcagcagaaccaggaguacaag auccugcuggaugugaagacaaggcuggagcaggagaucgccaccuaccgccgucugcug gaggagagggaugcccaccugacucaguacaagccaaaagaaccugugaccaccgccag gugcgaccuauuguggaagaaguucaggauuggcaaggucaucucaucccggaacaggug caccagaccaccgguuaaggacucagcuccuuccgccaguucccaggcugcagagag gcagcuucccucuccgcuccggcaucaccuccugcuacagccucucccagcauuccua ugcuugagaccauuuaagcuugcugaccugaagugaacuguggccuuuguucugaacacu gaaauaaugaccauggugac
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83	K02927	Sequence below.

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10 uacaagaagugcuccugggcugaucacgaacuugaccuacuuccccgagacggugccucgggagcucguggugccggugggca
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114	AA980204	ggcagcgagacgagcucacggucgaggauacgggugaagcgggacaggagcaggagccgg agccggggccaaagcagaaggugcaggucggcgccggcgguuggggcangaccagucaagc cggacagugaggagcggauagcagacggcacgaccauggccacgauggugcuuccucgaga ggagaagcugagucaggacgagauagugcuggggcaccaaggcgguuaguccaggguuuaga gaccugagagggggagcaucgugcccugcuagcucccuagcuucucaugaagcaggcgga ggcugagcggggcucacaggagcgcugccuccuccugcgccgcucccuggaggccaucgag cuggggcuugggggaggcucaggugauccuggcauuaucaagccaucuggggggcuguggag ucagagaagcagaagcugcgggcucaggugcgcccgguacaagagaacagugguugcg ugaggagcuggcaggggacacagcagaagcucagcgcagugaacaggcgguuggcucagcug gagaagagagcagcacauu
115	AI843232	ggcagcgagacgagcucacggucgaggauacgggugaagcgggacaggagcaggagccgg agccggggccaaagcagaaggugcaggucggcgccggcgguuggggcangaccagucaagc cggacagugaggagcggauagcagacggcacgaccauggccacgauggugcuuccucgaga ggagaagcugagucaggacgagauagugcuggggcaccaaggcgguuaguccaggguuuaga gaccugagagggggagcaucgugcccugcuagcucccuagcuucucaugaagcaggcgga ggcugagcggggcucacaggagcgcugccuccuccugcgccgcucccuggaggccaucgag cuggggcuugggggaggcucaggugauccuggcauuaucaagccaucuggggggcuguggag ucagagaagcagaagcugcgggcucaggugcgcccgguacaagagaacagugguugcg ugaggagcuggcaggggacacagcagaagcucagcgcagugaacaggcgguuggcucagcug gagaagagagcagcacauu
116	U59807	Sequence below.

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 15 guuuccggggcgggccacaagugugacuggggagcuggggggucugggauucugguuuggaagauucaggggccgggaacugggggc
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 20 gagggggguggaccuuggggccugggcgucuccuuccugugacuguuagcagagcagagauucaguacaagguaggggggagggu
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117	AI152659	gaaaauuuuagagccaucaaaauucuggauauuuugcuaggaaaaugaaauucacacu uauuuuuuguagacuuuuuuuaaauugcuguuuuacauaauuuguauuuuuggaaaaauuu auacugugcaccucugaugcaugaagugauuuuauguauggucugcuauuguggcagag gucaccuuauuccuaugaucuggaauuguuuuacuuucuaaaaagaaagcuuuguggggau uuugcuuucuuuuucuuuguagcugauguuuuuuaccaggugugcagcaggaauuacac cacuguguggaauuaauaauacaucccaugugca
118	AI850090	uuuuuuuuuuuuuuuuuccuggugaauuuuuuuuuuagaggugacaguuuccaggugac aguuuuucccaaggaagcaauucucugcgucuaauaagggaagaccacagaaccuucacu ugaauuuuaccuguguaauuuuauccaagaacacagcagcaauugcuuuauugguacu cugaccuuuagaaacaaguuguuaacagaaaaacacaucaaaacaaaaggauaauucucuaa uuaucaagucagccauacagcuuuucuuaggagagagagagagagugugugugugugug ugugugugugugugugugucugucugucugucugucuggguaucccacuuaggggccaugu gcauguuagguaaaugcuccaccacugagcuguuucuuagccgcacuuucucagauuuc agguuuuguuuuguuuuguuuuguuuuuuuuacuaaggcaugaaaauaaacuucacuuaaa u
119	AF064635	See above sequence (AI850090).
120	AI843106	uuuuuuuuuuuuuuuuuguggaaaauacucuuuauugaaaaauaccaguaauacugacag acuucaaaaaucauuuacgguuccagaauacaaaguacuuauuacauuuuuuuccaaacc uguuuuguauucuaaaguuaagcauuuuuguuaaucaagauacaaauaugauaacuucacua aaauuuuuuccagcuuuuauucuuuaaggagcuguauaaccuucuaagucagggucccgag gucagcagggcauggggcagaauugcaccuggccacucccugugcagcagacugcaaccaca uu

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121	AF033186	augggccagcuuucccccgagggguuaacgagaaagagaucgugagaucacguacuauaggg gaacucuuggcuccagcagcuccuuuugacaagaaauguggugggugagaacuggacgguu gcuuuugcuccugaugguuccuacuugcguggucacaaggauaucgcauagugaagcuu gucccgugguccagugccguaagaacuucuuuugcaugguuccaaaaauguuaccaau ucaagcugucuaaaaauuggcaagacaaaacaguaauggugggucagaaaaacaagccuccu gagcacguuauagacuguggagacauagucuggagucuuugcuuuugggucuuucaguucca gaaaaacagagucguugcguaauauagaauaggcaucgguuuccgauuuggacaggauag cuacuccuugccacaggauuaaacaauaggucgcaucaaaaucuggggauguauauacagga aaacuccuccuuauuuugguagaccacauugaaaugguuagagauuuuacuucucca gaugggagcuuacuccuuguaucagcuucaagagacaaaacucuaagagugugggaccug aaagaugauggaaacauggugaaaguauugcgggcacaucagaauuggguguacaguugu gcauucucucccgacuguuuauugcuguguuucaguuggcgccaguaaagcaguuuuccuu uggaauauggaaauaacaccaugauuaggaagcuggaaggucaucaccaugauguugua gcuugugacuuuucuccugaugggagcauugcuagcuacugcauccuauagacacucgugug uauugcugggauccacacaauaggagaccuucugauggaguuuugggcaccuguuuccucg cccacuccaauauuugcuggaggagcaaaugaccgaugggugagagcugugucuuucagu caugauggacugcauguugccagccuugcugaugauaaauggugagguucuggagaauuc gaugaggauuguccgguaacaaguugcaccuuugagcaauaggucuuugcugugccuuuuc acugauggcaguguuuagcugcugggacacauugauggaaguguguauuuuugggccacu ccaaggcaagucccuagccuucacauauaugucgcaugucaauccgaagagugaugucc accaagaaguccaaaaacugccuguuuccuuccaaaaauuuggcguuucucuccuaccgc gguuag
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122	Z50159	auggccagcuuucccccgaggguuaacgagaaagagauugugagauacguacuauaggg gaacucuuggcuccagcagcuccuuuugacaagaaugugguggugagaacuggacgguu gcuuuugcuccugaugguuccuacuugcguggucacaaggauaucgauagugaagcuu gucccgugguccagugccguaagaacuuucuuuugcaugguuccaaaaauguuaccaau ucaagcugucuaaaaauuggcaagacaaaacaguaaugguggucagaaaaacaagccuccu gagcacguuauagacuguggagacauagucuggagucuuugcuuuugggucuuucaguucca gaaaaacagagucguugcguaauauagaauaggcaucggauuccgauuuggacaggauacag cuacuccuugccacaggauuaaacaauggucgcaucaaaaucugggauguauauacagga aaacuccuccuuuaauuugguagaccacauugaaauggguuagagauuuuacuuuugcucca gauggggagcuuacuccuuguaucagcuucaagagacaaaacucuaagagugugggaccug aaagaugauggaaacauuggugaaaguauugcgggcacauagaaauuggguguaacaguugu gcauucucucccgacugucuaugcugugucaguuggcgccaguaaagcaguuuuccuu uggaauauggauaaaacaccaugauuaggaagcuggaaggucaucaccaugauguugua gcuugugacuuuucuccugaugggagcauugcuagcuacugcauccuauagacacucgugug uauugcugggauccacacaauaggagaccuucugauuggaguuuugggcaccuguuucccucg cccacuccaauauuugcuggaggagcaauugaccgauggggugagagcugugucuuucagu caugauggacugcauguugccagccuugcugaugauaaaugggugagguuucuggagaauuc gaugaggauuuguccgguacaaguugcaccuuugagcaauuggucuuugcugugccuuuuc acugauggcaguguuuagcugcugggacacaugauggaaguguguaauuuuggggccacu ccaaggcaagucccuagccuuaacauauaugucgcaugucaauccgaagagugaugucc accaagaaguccaaaaacugccuguuuccuuccaaaaauuuggcguuucucuccuaccgc gguuag
123	X78683	Sequence below.

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15 gccagcucggggucaagcacagcccaccugccccaggcaucaugugauggacuuuucuguaucugcccucuuuggauuaagg
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124	X68193	acccaccgggcuuucgggaccaugggccaaccucgagcguaccuucuuugccaaucaagccaga uggcgugcagcgcggccugguugggcgagaucauaaacggguucgagcagaaggggguuccg ccugguuggccaugaaguuccuucgggcccucugaagaacaccugaagcagcauuacaucga ccugaaaagaccguccuuuucuccggggcuggugaaguacaugaacucggggggccguggu ggccauggucuggggaggggcucaaugugggugaaaacggggccgagugaugcugggggagac caauccagcugauucaaaaaccaggcaccuuccgugggggaauucugcauuaaguuggcag gaacaucauucauggcagugauucagugggagagugcugagaaagagauccaucugugguu uaagcccgaagaacugaucgacuacaagucuuugugcccgaugacuggguguacgaguagac augaagaaaccagaauccuuuucagcacuacugaugggguuucuggacagagcucuucauc ccacugacaggauggaucaucuuuucuaaaaacaauaaagacuuggaacugaaaaaaaaa aaaaaaaaaaaaa
125	AA062013	uuuuugcuuucacaugacagaugccgcuguguccuucgccaaggacuucuuuggccggugg aguggccgcagcaucuccaagacagcggucacaccaucgagagggucaagcugcugcugc aggugcacaugccagcaagcaaaucacgggcagauaagcaauacaagggcaucauagacug cgugguucguauccccaaggaacagggagugcucugguccuuuggggcgugggaaccgggc caaugucaucagauacuuccccaccaaggcucucaacuuggccuucuaaaguuaauuccaa gcagaucuuucugggugguugacaagaggaccaguuucugggcgcuaucuuugcagggga accuggcaucaggugguugccgcuggggcuacauccuuggggcuuuguguaccucuuugau uuuuugccgguaaccgucuaagcagcugaugugggcaagcugggagcuaaagggaauucaaggg ccuuggggacugccugguaagacuucuaucugauggggauaagggcuguac
126	AI465965	auccgggacccccacggcccccuuugcagcuugccacaagguucugagccccuuggaauac uuccgccaauguguguaugacaugugugcccuaaaggguagacaaagccuaucucugccgu agccugggcugcuuauacugcagccugucaggcagcugggggcagcagugaagcccuggagg acagacagcgucugcccucuccaguguccugcccacagccacuacuccaucugcacccgc uccugccaggggcuuccugugcugcucucucucuggccucacugggcugcaccac
127	U50413	Sequence below.

[illegible]

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 10 gucccccacacaguccccaccuguaauuaccuguuacuugucaccuuucaauaaagcauaucaaauguugau

130	U60020	Sequence below.
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 25 ggaggccuuggcuuacgucgcugaagucuggaccagagugucucgggaaugcugcugaaggugggaaauucuguaccuggg
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 35 uggcaaccagcuacggguccagcgggcuccuguaugagagccccaagcggggcuucucggagcgguuucuuuacaccagcag
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131	L32752	gaaauccggggccgcucucuccggcaggauccgcccgauggccgccagggagagccgca gguccaguucaaggucguccuggggcgacggcgccaccggaaagacgacauucaugaa gcgccacuugaccggagaguuuagagaaggagauauguagccaccucggggcguggaggugca cacauuagucuuccauaccaacagaggaccuaucaaguucaauguguggggacacagccgg ucaggagaaguucgggggggcugcgcgauggcuacuauccaagcccagugugccauuau aauguuugacguaacaaucaagaguuaacuuaagaauugugccuagcugggcauaaagauc agugcgugugugugaaaaacauccccauuguauuuguguggcaacaaaguggauguuaaaga caugaaagugaaggcaaaaccuauucucuccaccgaaagaagaucuuucaguacuaua cauuucugccagaaguaacuacaacuugaaaagccuuucucuggcuugccagaaagcu cauuggagauccuaacuuggaguuucguugccaugccugcucuuugcccaccugagguagu cauggaccagcuuuggcagcacaguacgagcaugauuuagagguugcucagacgacugc ucucccagaugaggaagaugaccugugagaaagugaagcuggagcccugcgucagaaguc uauuuuaggcaacuguccugugaugccagccagcggugcaguguguguccaccuuuuu agcuaaaggagauugcgaauucauuggggaugcugaaggagauaauugggcuucggagug aauguggcaguuaaaauacaccuucuuuuuuuggacuugcguaauuagccccuggaac agaguugucuggauuucaagauaagacugcuaccguagcaucacaauagucaguggug accggaauuc
132	AI840013	uuuuuuuuuuuuuuuuuugauuuuugaaaaguuuuauuuuaucauacugugaagaauuc aucauaauugcuacguuaaucaaggaaaaggcacagagaagcaugugucguuuaguccu cgauacuggaccucccagcccagcucccuauagaggagucuaagcugcuguggugguuc acagcuuugguuuucuggagacgaagcucaugauugcguucaugcacuccucugacagcc accuugcuugcagaguagugcacucuuacagcguugacugcguaagagcuuuucuuuc uuuuucugauuaacucuuuggaaaauucucauuggguuuuggcgggagcuucgcauu
133	AB020424	ucgggaauugauugagagaccgcgaaccuguaaacggauugauaccgagucggggcaggcgu uaugccagcccaacucgggaccucgcaucauguccgcggcuaccuuagaguguuucggga augauuuugcgguggaugaacgaaaccccgguacguccugugccaaggagcauauugcagg acggacgcucguuaauugccucaguggguggggcaacguucgcucucuaucuaauacgacuc cgacaauuggauaucucgggcucucgcaucgaugaagaacguagcgaaaugcgauacuuggu gugaauugcagaauccugugaaccaucgagucuuugaacgcaaguugcgcccagggccuu ucggguugagggcacgccugccugggcgucacgccuuguuuugcucugugcccugcucuu ucggggggcggucauggaugcggaugauuggcccuccuguccugugugcgggcgguuaag cgcggggugucggcgucgggaaggggcacgacgagugggagcaggagcaccagcaggau uguggucccccugaccuuuagggggcucaagagaccgggacuaggcgagccgcgcucgu aagaggaggggcgagcugucucgcauu
134	AI848453	uuuuuuuuuuuuuuuuuugaaguugcugccccuuuauugggugacccgggcaaguuuuagga gaacaacauuaaagcacacaaaguguaucacagcucuaaccaggaggagugagg gucacggcaggguucuccauugguuaagaaaaucaacgcaauuucacacaccoguuac uuuccaaguuuacgaaccgauaagaaaagaauucuccuuuaaauacgacaaguacaauguac auguacauuauuuggaauuaauuuuauuuuacuuuuaaccucaagauacaacuauuuuuaaga ccauuuuuuuuuaaggaacggauccuuacaaaaccaaauuuaacccauuauagcacgagguug guuuagccuuuucuuucuuuucuuuacaaaacgugcaccacauguuuucaguagcaaggccgau gccauuggauaugagagcugugauuugcagggaccaaccacaucuaagaaccggggaggcca aucanacgguggguu

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135	AU040563	cccuuggaggauaguuuuauugacaagucgaguuaagguuuuagaguaaacuuuuauacacc ccagucaggcccccucccaggggaggcucgcugguagcucagauggccuuggugggggc agauuguuguaguugucuuccuggccuccagcaggcuucgggagguggcuaucuccugc uccagccuggacuugauguccaguagcugcuuauacuccggguucuggcgcucuaugugc ggcacgcaggugcngcg
136	X89749	Sequence below.

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 uguaaguuaaccgggagcacuaguauaggaggaggaucaucgacuaccuccccgccacuccacggcugcuggcuccuagaaacc
 ccagcuucaccucucacuggggacucgaguuccagaaugaaaaagcaagaaggguuuuguugcagcaucaggcagugacucuga
 5 ggauagaagacagcauggacaguccccuggaccuuuccucaucagcagccucuggcaugagaaggaggagaggcaaucugccc
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 15 ggggugauggcaagagaugcauuuuuuauauuuuuuuc

137	AW12539 0	uuuuuuuuuuuuuuuuuuggugguuaucaagugcacuuuauugaauccacuguggauagau aaugaguguuacaccugcguguagggaggggcaaggaggggacgcagcugcggagggguga agcacuucaggaccgggaagucggaauccucuauuaagugugaaggguuuugagcguuaaga acaugaugaugacacuaacaauaggugauaacaaccaucaggauugcugaggaccaaggug cugauguucaggcacuuagcaguggaggcguaaggccugggcuccagucacauaccacc aucuuccgaucccuagacuucacggaguaggcauaggcuauagaagcccaggcagcagaag uucaugaagaguguauugaacagggaccagaccacauggucaggcaccgacaccucucug ggcauguugaucacaguaguucugacagaagccga
138	X05862	Sequence below.

aagcuucaggauacagugcacacucguaaaauaaaaacuacaggcugcugcgaauuauuuucaacugaccggagaggcaaag
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 uccaaggcaagagaagcgucacuaauaaccacgcaugugcaacagcuuuuccagaggaaagguguggguggcucuuaaaaga
 gccuuugaguuaaggagugugaguuaaacgagcucacuuggagcugguuacuuggugacugccuuggugcccuccgacacc
 20 gcgugcuuggccagcuccccgggcagcagcaggcgccacggccgucuggaucucccgggacgugauggucgagcgcuuguug
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139	AW04618 1	
140	U10118	Sequence below.

10 gaggcugcucaagagcugcgguugggucaccgcuucauguuucucugccgauucuggggaaagauggcaacgaauaugcu
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 gagaagcauuuugcaggcaacaugagagaagaaaagaaacuucgaguugaaaaugcuaaaacugaaaaagaaauagaaga
 gcuaaagcaagagcugauucuggcagaaaucauaacggagugggagcaagugcguguucgauugaguacuccacugcagacg
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 15 cgggagaagaaaagaaggugaaagagaagacugaaaagaaaggagagaaaaaggagaagcagcagucggcagcagcaaguacu
 gacuccaagccuauccgacgcacugcgucuggaucuuucgaauugguuuauuguuuacugccaagaagcaccucgaugcagau
 ucacuguauguggaggaaguagaugugggagaagcagccccgcgcacggucgucagcgggcuggugaaucauguuccucua
 gaacagaugcaaaucguauugguuguuuacucuguaauucugaagccugcaaaagauccggggaguuucugucuaagccaug
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 20 gaugcuuuuccuggagagccugacaaggagcuaaaccuagaagaagauucuggggagcagaucagccugaccugcacacca
 augcugaguguguggccacauacaaaggagcucccuuugaggguagaagggggaaggaguuugcagagcccaaaccauggccaa
 uaguggaaauuaaauaagugcucuguaacugaaagacauuggcgaaaacuuuaaacaauaaagagaaguguguuuuacacuu
 acauau

		ggccuuguuuuugguuugcauuuaagaguauuucuuuaaaaggcacauuuuuguuuaauag gcaguuccccuccugccucuuuccuuuugagcaguguaucugcauccuagaaacauuuagca 141 aagcagcccuuagccuccccgaccccuuuccuccuccuccagca
	AW21277 5	
		uuuuuuuuuuuuuuuuuaaacaugacgccguuuuauuuuaaauguuuacucccagaaaua uagauauaaaaaaaaaaaaaagacaauuaacagcacuaaaccaggcaccuuaaccgaau cccaccauccucguuaacucccuuccuguuaccuuuuguaugaccagaagauuucagg agccccuggacagccagagugguuccugcccaggggcuucccgccuuccuccuguccuaga gcuucccgugggaaagcuugggugagaauuuuagccuaaaggagggggcuugggccggg 142 cacuuugcgcucauccacugcagg
142	AI846302	
143	M22998	Sequence below.

acaggguacaguugugcgucagggcguggaggucuggcgaggagacgcauaguuaacagcgcguccguuccgucucgcagc

[illegible]

144	X64837	Sequence below.
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147 1465 Sequence below:

ccgggcucgaaucucuaagacucgaguuuagagaauucgagcucuccaguuuuaaagcaaaaauuuggacugugaagcaa
ggcacuggggcaaacacaacauuggccuccccggcugacagcuguauccaguuuacccgggcacgcuagugauguucuuucaac
cuuaaucgccuccgggagucgggacaucuugacggacguugucaucguggugagccgugagcaguuuagagcccuaaagaca
20 gugcucaugggccugcagcggccuuguucuaacaguaucuuacugaccaguuugaaaugcaaccuuaguguaaucaaucauagauc
cugaaaucagcccugagggguuuugcauccuccuggacuucauguacacaucuaggcucaaccugaggggaaggcaauaucau
ggcggugaugaccacagccauguaaccugcagauggagcauguugucgacacaugcaggaaguucaucaaggccagugaagca
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gaggucgugaggucguggagaacaauaugccacugagaaauacucccgggugugagagcagagcuuuugcuccuccucugu
25 acagugggccugucaaacaccaccagccucuuaucuccauguacagccaucucccgucagcaccuuccucuucucugaugagga
gcuccgagaugccccccgaaugccugugggccaaccuuuuuccaaggagcggugcccuccccugcgacagugccaggcaaguc
ccuaaugaguauagcagggccagccauggaggguucccccaguuugugucacagcaacaucuacucgcccgaaggaggcagucc
cagaggaggcucggagugacauacacuacagugugccugaggggccccaagccugcugucccuucugcucggaaugcuccaua
cuuccccugugacaaagccagcaaagaagaagagagaccuuucucggagggaugagauugcccugcauuucgagcccccaau
30 gcacccuugaaccgggaaggguucgguuaguccccagaguccccagaaauccgacugccagcccaacucacccacagaguccug
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5 cagagaugugccuccauacugcuggggccacguucccgaggagaugggggaaaccagucagaguauucggauucuaagcu
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10 auccacacugggagagaagccguaccuccugugaaaucugugggcacucgcuuuccggcaccuucagacucugaagagccaucugc
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[illegible]

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 15 aagaucuuuugagggaauuaaaaaaaaaaagaaagaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa

155	AI604314	uuauuaauuaaaaaacaauuuauugaaaaagaguagugcuuuguacaaauucccauugca gccccagauaucaacugaucucuuuccagcuuugguaguaggguauaaaaaucaaaa cuagguaaguucugauguaagauuucuaugggaaauuuuagaauauauagauuugugua guuuggcaaguaucuuucuaugcauuuacauuacauauuaagcacagaauucuguggcaa aacaucuuugcaugauuacuuuacacacacaaaauauaguaaaaacuacauaguacaaaau cacauaagacuccauucugucuaauaacuucacuccauugguuuuaccaugaauuaauu cuuaaccucuccuauaacugucagcuuccauuuuuuugaagauacacucacaaaaga gcacuucuuugcuuuuagaguauacauagacu
156	AI845121	cggccgccaagaaguauaacaugcgcaguggaagacuacgagccauaccccgauauggca ugggguauggcgacuacccgaugcucccaaccgaucacagcaugagagggaucgguggu aucagugggaccacucagaacucaggaugaacuggggugaaccgauacacugggaccuag acauguacaucaaggaaucguguggacacgucaccuaccccuuguguccugngaugucaugu guaaacauucucugggcuuuguggcuuucaugguuuuauuguucuggguagggcacgugu ucccuuccuaccagccuguggguccgaagcaguaccuuacaaaaucuguaccuggagc g
157	AW04775 6	uuuuuuuuuuuuuuuuugaugcaaaugucuuuauuuuccacuuuaacaaguuuuccuuuu gcacuggccuguggcacaaaacagauggcugggugggugacauuaacugucaaguuaaguga gaugcagagauggugagacacugcauuugagugcuaauaacuuuuauuccagaggaacgc caugcagcccaguuacaccuuuaggucagaaaggcugaugcgcugaccagccucuauugcc ucccuugguaagaaggaccacaaagugcagaguccaacaagaugcuggcucugagcugaac ucagggcuuuccauuaccacuuucuuucacuuacacaggggccugcucagauguccuu uuuacaacuccauaagcccuuuggccaaagucccugcaguguuuuggggaggaccuuccca ccuucaccagucagugucugaucugguggag

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[illegible]

g c g c c c g a a c g u c u a g c a g a g u a c c u g c u g c u g u a a g c u u g u c g u c u g g g c u g c a c c g c c c g u c u u a a c c c a u u c u c g a c u u
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c u c g c a u g c a g c g a g g u g g c u u g c g a c u c c a c c g g a g u c u g c a g c u a u c c c u c g u u a u g c g c a g c g c u c g a g a g c u c u a c c u
c u c a g c c a a g g u a g a a g c c c a c c a g c c c g a g u u c c c g c c a u c c c g c a g g g c u c u u g a c c c u c g c c u g c a c c c g c c g c g g g a a g
5 c c g a a g u u g c a g u g g a a g u a g c g u c c c c c g a a g c c g u g c a g c c u c c g g a g c c c a u g g a u a c g c a a g a g g a a g u g c u g c g a g u
c c a g g a g a c c c c u g c g c u c u g u g a c c c g c c c c c g c u a g a g u c a g c c g c a a g c g c c g g a g c a g c a g c g a u u u g a g c g a c a g u a
g u g a u g c c g g a c u g g u a c c a a g c a a g a a g g c c c g u c u a g a a g a g g u g g a g g g g a g g c g a c g u c g g a g g u u c c c g a u c g c c
u g c a g c u u c c u c c g g c a c a a a g c g a a g g u g c c u u c c c u a a c c u c g c c c g c g u c c u c c a a a g g c g c u u c u c c a g u c u c c u g a a c
u g u g g a c c c g c c g u g c c c c c g c c g a c g c c c c c a c g u g c g a g g c c a a g c c a g c c u g c c g c c c g g c c g a c a u a u g c u c a a c g u
10 g c u g g u g c g a g c u g u g g u g g c c u u c u g a g a g c u c u g g u g g c u u c u u u c g a g c g g c g c c a c c g g a g c g g a g a a c g c a c a c c c
g a g g c g a a g g c c g g c g g g g g c c g u g a a g a a g a g c c g c g g c c c g a g c u g c c g a g a g g c c a g g g c a a g g a c u g a g g a g c g a g g g
g c g c g g g c g c c u u c u c c c a g a c g u g c g u c c a u a g g u g c u a u u a a a g g a c u g u c c c u u c c u u g g c u u g g a g a a g g g a c a c c u
a g a u c u u g a a u c u c a g g g u c g a a c u c u c u a g g g g c c a g g c u g c c c u u u c a a g g c c g u u u c a c u a c c a u u c g c g u u u c g g c c
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15 u g u g g g g c c u g g g a g g a g g c c a g g g u g u g g a c c c g c c c u a g g g a c u g g g a a g u g a c u u g a g u c a c c u c g c c c c c a c a g g c u
g c u g u g g g u g a g c c u g a a c u g a a c c a u c a a a u c u g c g c a g a g u u g a a g u g g c u g g a g a c c c c g g g a c u g g u c a a c c u a g a u
g a u c g c c u g g c g u g g a c c a c c g c g g g a c g g g u g g g c c g c u g g u c g u a g u u g c u g c c g u a g a c a c a g c u u c u u c g g g c a g g a
a a g a a a u u u u u u u u u u a c c a g c g u g u u u a a g a a a g u c u g u u u a c u u u u c c c a c g g u g g g u u g u u u a a u u a g c a a c u a c c u
g g a g u u u u a c a a u g u c a g c u a g g a a a u a a a g a c c a u c g g u g u

[illegible]

163	X53157	gucucgggcgagauaggcuucaaggguuacuucgcgggagugggcgcuuuggcgggcgagggcc cugagggcgacggcccguaggcgcgggccgugacccgcuccaugggcuucuggaggugguguc cccacugaugaggagcaggcuacugggcuggagaggaggagaucaugauagcagcacagaag ggacuggacccauacaauaugcuaccuccaaaggcagcuucaggcaccaagggaagaccu aaucuaagucccguccaucagcaacaagagaauagugggcugcaucugugaaggaggacaac uguacugucaucugguuuuggcugcacaaggcgagagucagcgaugccccaacugugga acccaauacaagcuggugccccaccaaugggccacugagccccuguguuauuuuucag aauguaaagaaaaacuucucucuaauaaaagacuagccaauugcaccugcuccuccc
164	U19118	See above (same Accession Number).
165	AF062071	Sequence below.

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		augacagaugccgcuguguccuucgccaaggacuucugccggugggagugggcgagcc aucuccaagacagcggugagcaccuagagagggucaagcugcugcugcaggugcagcau gccagcaagcaaaucacggcagauaagcaauacaagggaucacugcugguucgu auccccaaggaacaggaggaguccuguccuucugggcuggggaaccuggccaugucacaga uacuuccccaccaggcucucaacuugccuucuaaagauaaaauacaagcagauuuucug gguggugugggacaagaggaccaguuucugggcgcuaacuugcagggaaccuggcaucaggu ggugccgcugggggcuacauccuugugcuuuguguacccuucugauuuugcccguaaccgu cuagcagcugaugugggcaaagcuggagcugaaagggaauucaaaaggccuuggugacugc cugguuagaucuaaaaucugaugggauuaaggggcuguaaccaaggcuuuuauuguguca guacagggcuaaucaucuaaccagcugccuacuugguaucaugacacugcaaaggga augcuccagaucccaagaauacucacauucuaucagcuggaugauugcacagucuguc acugcugucgcugggcugacuuccuauccuuuugacacggucgucgugaugaugaug cagucuggacgcaaagggaacugauaucauguacacaggcacgcuugacugcugggcggaag aucgcgcgcgaugaaggaggcaaggcuuuuuucaaggggcgauagguccaacguucucaga ggcauggggugggcgccuuugugcuugucuuugauaugagaaucaagaaauacacauaa
166	U10404	
167	U07634	Sequence below.

5 cguagaaguugucucugucggcgggcgggcgggcaggauuggggcaccgagaccggcgugcggacagcagggaucgcggggg
 agcgagggggugcggauggagcuccgggcagucgguuucugccugggcgugcuguggggungcgcgugggcgggcgggc
 ggcacagggaaggaaguuguuuuguggacuucgcagcaaugaaggagagcucggcugggcucacgcaccccuauaggcaaa
 10 ggguggggaccugaugcagaacaucauggacgacauccuaucauacugacugcugcaacuggguaucggcgaccag
 gacaacuggcuccgcaccaacuggguguaaccgggaggaggccgagcgcacuuuuauugagcucaaguucacggugcgagacu
 guaacagcuucccgggugggcgcccaugccugcaaaagagaccuuaaccuacuaugcagagucagaugggacuauaggcac
 caacuuccagaagcgccaguuacccaagaauugacaccaucgccccugacgagauacaggucagcagugacuucgaggcucgca
 acgucaagcugaacguagaggagcgcauggugggggcccuuacccgggaaggggcuuacucugggccuuccaggacauccggcg
 15 cugcgugcgggcugcucuccguucgcgucuaacaagaagugucccgagauugcugcagagcuuggccugcuuccccgagacc
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 ggcgagggggcucucaugcacugcacgguggauggcgagugggcugggcgauccgagugccugugccagggaaggcuacgag
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 gagcauaccugccauccacagaggguccaccuccugccagugugaagaaggcuauuucaggggcaccugaggaccacug
 20 ccaugucuuugcacacguccaccucugccccuaacuaccucacggcaugcaugggugccaaaguagaacugcgauuggacagc
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 gccugugaggccacggugcgcuauucagaaccuccucacggccugacccgcagagugugacagucagugaccugggagccc
 cacaugaacuauaccuucgcugucgaagcacgcaauggcgucucaggccugggugacuagccgaagcuuccggacugccagcg
 ucaguauuaaccaaagagcccccaagugaggcugggaggaccgaagcaccaccuccugagugucaccaggagcaucccg
 25 gugucacagcagagccguguguggaaguacgaagucaccuaccgcaagaagggggaugccaacagcuauaauggccgcccga
 cggaaggcuucuccgugacccuggaugaccuugcuccggauaccacguaccugggugcaggugcaggcauggacgcaggagg
 gccaaaggagccggcagcaagugcacgaguuccagacgcuguccacgggaaggauucgcaacauggcgguagucggcggu
 ggcuguagguguuuuugcuucugguacugggcaggaguuuggccuucuaucgaagaggagggaaccugcgggcuc
 gccaguccucugaggauuguccguuuuuccaagucagaacaacuaaagccccugaagaccuauuggauccucacacuuacga
 agaccccaaccaggcuuacucaaguuuaccaccgagaucacccauccugugugggcaaggcagaaggucuuuggagcagga
 gaguuuggagaggucuaauaaaggacgcugaaggcauccucgggggaagaaggagauaccggugggccaucaagacacugaaag
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169	X61232	Sequence below.
5	ggcagacaaaagaggccggcagugcagcucgcgggacgcauggccgggcgcgaggacgggugcugcuggcgugugucc gcgcuggguggccggcgggugggcugcugacgcgugaagcccaggagcccggggcgccagcggcugggcaugaggcgccggc cggcuccagcaagaggacggcaucuccuucgaguaccaccgcuauccagagcugcgcgaggcgugggugucgguauggcugc agugcaccgccaucagcagaauacuacacaguggggcgccagcuucgagggcggggagcuccugggucaucgagcugucugacaa ccccgggguccaugagccgggugaaccugaaauuaaauacaucgggaacaugcauggcaaugaggcgguuggacgggaauu gcucauuuucuuuggcccaguccuguguaacgaguaccagaaaggcaaugagacaauugucaaccugauccacagcaccgga auucauaucaugcccuccuugaacccccgacggcuuugagaaaaggccgauggcagcccggggcagcugaaggacugguuugg ggcgagcaacgcccagggaauagaucugaaccguaacuuccagaccuggacagggaucguauauguuuaugagaaagagg cggucccaacaaccaccugcugaagaauucugaagaaaauugggacaaaaaucaaagcuugcccccgagaccaaggcuguca 10 uucacuggaucauggacauuccauuugugcuuucugccaauucgacggaggagaccuuguggcuauuacccauaugaug agacacggagcgguacugcucacgaauacaguuccugcccugaugacgcauuuuccaaagcuuggcucgcgcguacucuuc uuucaaccagucaugucugaccccaauccgaccuccugcugcaagaauagacgaugacagcagcuuugaugauggaacgacc aauggugggugcaugguacagcguccccgguggaauagcaagacuuaauuaccugagcagcagcaacugcuuugagauacug uggagcuuacgugugagaaguucccaccugaagagacucuaaaagcuacugggaagauaacaacuuuccucaucaacuac 15 cuggagcagauacaccgagguguaaaggguuuguccgugaccuucaggguuacccgaaugccaacgcaaccaucucugugg augggauagaccaugaugucaccucggcuuaaggauuggggauuacugggcgauugcuugcuccuggaaacuauaaacuacag ccuccgauccugggcuaccugggcauacacaaagaaagguggcaguuccuuuagcccugcuguuugggguggacuugagcuug agucuuucucugaaagggaaggaggaggaaggaagaaauugauggagugggaaaauaugucagaaacuugaauuuuu aagaaaggcuucuaacuaauugcuuucaucuauuagacuguaagaaugcaauugggcucuuuucuuuuagguugug 20 ugcaguuugauuuuaacauugauuuuuuugaucauuuaguuacuaaauacacguaaaauacacccggacagaaaua uaauggcuggacauucuaucuaucacauuucgcuuaaaucauucgaagccuuaaagcuuaauggggugacaauugucac uugacagaugcaugagagucacgaauuagcugacugugaccucgacugcauacacauaguuuccauuaaguuguccuagu cucuugugcugauuacuguaauaagcaugauccugguaaugcacuuuggauggggaagaaaanguacgucuuuucagaggg gcucugaacagaauagaaaccuaguucuuugcguguacuugaagauggaauuguaauagucagcuguuaauggccacuua 25 gaaguuuugggguuuugucuuugauuguagauugg	

170	X14309	Sequence below.
30	gccacggagccucucugaacggggauccaggcaggauuagagcugccucacugacuacaggccgugucgugucaccguuuc ugcaggcaccaugagccaggacaccgaaguggacaugaaagauguggagcugaacgagcuagaaccggagaagcagcccaug aaugcagcgggacggggcgcgggccggggagaagaacggucuggugaagaaucaaggugggcggaggacgagacggaggccggg gucaaguucaccggcuuaaccaaggaggagcuacugaagguagcggggcagcccuggcugggugcgccaccgcugggcgug 30 cugcugcucuuucggcucggguuggcugggcaugcugggcgggcgccgugguuaucaucguucggggcgccgcugccguga gcugccuguaacagaggugggugggcacaaggggcgccuucacggcgaccuucaggccuuuguaggccggggaugcggg aggcauagcuggucugaagagccaucuggaguacuugagcaccuugaaggugaaggggcugguuaggcccaauucacaa gaaccagaaggauagaaaucaauagaaaccgaccugaaacagaauuaauccacuuaugggcucccagggaagauuuuaaagaccuuc uacaaagugccaagaaaaagagcauucacaucauuuuggaccucacucccaacuaccaggggccagaauugcugguuccuccu 35 gcucaggcugacauuguagccacaaaaugaagggaagcucugaguucuuuggcugcaggacgguguggaugguuuccaauuc cgggaugugggaaagcugaugaauagcaccuuuguacuuggcugaguggcagaauuacacaaagaacuaaagugaggacagg cuuuugauugcagggacugaguccucugaccugcagcaaaauugucaacauacuugaauccaccagcgaccugcuguugacca gcuccuaccugucaaaauccacuucacuggggagcguaucugaaucccuagucacuagguuuuugaaugccacuggcagcca auggugcagcuggagugugucgcaagcaggacuccucgagacuuaauaccggaccauucuccgacucuaaccagcugcug 40 cucuucacucugccagggacuccuuguuuuagcuacggggauagagcuuggccuucaggguugcccuuccuggacagccugcg aaggccccacuaugccguggaauagaguccagcauucacaucccaagaccuguaagccucaacaugacagugaaggggcca	

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171	U42386	Sequence below.
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172	U51126	Sequence below.
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ucuacucuaaaguauacacuuauucuaacaauacagacaacaaauaugacuuuuuccuaugaaagagugauaaagauacugu
aucagucugcuuugacucaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa

173	AF093853	Sequence below.
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5 uggaauaggugcuaggugaaggcuuuguugaucaggauugcugagcugguguuuuacagguccagauaugaugagcugg
 aguuuugguaggcccagguaccuccuccaaaauugaccacauaaauuggucacaaaucaggccuccacagauacaaaaauuu
 gaaauaucccaugcauccugucugaucaccacagacuaaggcugaucuucuaaauaacaacauaaaaauagaaagccagguuca
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 acuuugaggccaauaccaccaucggccgcauccgcuuccacgaauuuccugggagauucaugggggcauucucuuuuccaccc
 acgggacuuuaccccagugugcaccacagaacuuggcagagcugcaaagcuggcgccagaguucgccaagaggaauuuuag
 uugauugcucuuucaauagacaguguugaggaucauucugccuggagcaaggacaucaaugcuuacaauuggugaaacaccca
 10 cggaaaaguugccauuucccaucauugaugauaaaggcagggaccuugccauccuuuuggggcauguuggauccagucgaga
 aggacgaauaacaauccugugacggcccugugguuucuuuuggcccugacaagaaacugaagcugucuaucucuc
 acccugccaccacgagcaggaacuugaugagauucucagagugguugacucucuccagcugacaggcacaaagccgguugc
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 uagaauaugaaacaccuuuuguaugcuuuccgaacggaaucuuucuguuacccauuuuuggagagcacugacauggggagaag
 20 cuuucuuuuguaauuuuaguaaaauaaaguggggacagccgggagaauucuuacaggggaucuaauuguaaguuucuaucg
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 25 ccacaacauacccaaacuuaugggacacaaugaaggcauuucuaagaggaaaacucuaugcccugagugcauccaaaggaaaa
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 ccuaauuaacaaaucagaacugaaaaggagacauaacaacagauccugaagaaauccaaaacaccaccagauccucuaaaaa
 30 aggcuaucucaacaaaacuggaaaaccuggauggaaaggaaaagcuucuaagacaga

174	Z19521	Sequence below.
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35 augagcaccgcggaucugaugcugcugggucaucgcccugcuccuugcugcugccggaguugcaguagaagacucaggc
 agcaggaacgaguuccaguguagagacggaaaugcaucgcuagcaagugggugugcgauggcagccccagugcccggau
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 40 ggcgaggcagacugcaaggacaagucagaugaggagcacugcgcgguggccaccugccgaccugaauuccagugugcag
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 25 uauuuauugucugggacagaaaaggcuacugggcugugcuugaaaauucga

175	U04354	Sequence below.
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-144

[illegible][illegible]

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 145

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 145

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

Claims:

1. A method for stimulating hair growth in a balding scalp of a human subject using a compound or factor that enhances the size of a hair follicle cell comprising:
 contacting a disrupted area of the balding scalp of said human subject with minoxidil,
 wherein the disrupted area comprises perforated epidermis or epidermal layers of the balding scalp of said human subject.
2. The method of claim 1, wherein said disruption is induced by a tool that comprises sandpaper, a laser, a FRAXEL™ laser, a CO₂ laser, an excimer laser, a felt wheel, a dermabrasion device, a light-based method, irradiation with visible light, irradiation with infrared light, irradiation with ultraviolet radiation, orthovoltage radiation, x-ray radiation, or is induced by a burn treatment or chemical treatment.
3. The method of claim 2, wherein said dermabrasion device is a micro-dermabrasion device.
4. The method of claim 1, wherein said disruption is induced by dermabrasion.
5. The method of any one of claims 1 to 4, wherein said disruption comprises perforated epidermis and dermis of the area of the scalp.
6. The method of any one of claims 1 to 5, in which only a portion of the epidermal layer is perforated in said disrupted area.
7. The method of any one of claims 1 to 6, further comprising contacting a precursor cell with an inductive cell.
8. The method of any one of claims 1 to 7, wherein the compound or factor is contacted to a disrupted area of scalp of said human subject, wherein said area of the scalp region is further contacted with a precursor cell, an inductive cell, or a hair follicle or a portion thereof.
9. The method of claim 8, wherein the compound or factor is contacted to a disrupted area of scalp of said human subject, wherein said area of the scalp is further contacted with an antagonist of an androgen or an antagonist of an androgen receptor.
10. The method of claim 9, wherein the antagonist of an androgen or antagonist of an androgen receptor is finasteride, Fluridil®, dutasteride, spironolactone, cyproterone acetate, bicalutamide, flutamide, nilutamide, an inhibitor of an androgen receptor, an androgen antagonist, or an anti-androgen.

11. The method of any one of claims 1 to 10, wherein the androgen or an antagonist of an androgen receptor and/or minoxidil is for administration as a cream, gel, lotion, emulsion, suspension, oil, non-aqueous solution, aqueous solution, or drop, or by direct injection, or is encapsulated in a liposome.
12. The method of any one of claims 2 to 11, wherein said area of the scalp is subjected to depilation or administration of a retinoid prior to said disruption.
13. The method of claim 12, wherein said depilation is induced by plucking, waxing, abrasion, laser, electrolysis, or administration of thioglycolic acid on said area of the scalp.
14. The method of any one of claims 1 to 13, wherein said disrupted area is not contacted with a bandage, dressing, or ointment that facilitates healing for a period of time following said disruption.
15. The method of claim 14, wherein said period of time is within about 2 days, about 3 days, about 4 days, about 5 days, about 7 days, about 10 days, about 11 days, about 14 days, about 17 days, or about 3 weeks.
16. The method of any one of claims 1 to 15, wherein said disrupted area of scalp is allowed to heal by secondary intention.
17. The method of any one of claims 1 to 16, wherein said disrupted area of scalp is contacted with a gel, cream, lotion, emulsion, suspension, oil, non-aqueous solution, aqueous solution, or drop following said disruption.
18. The method of any one of claims 1 to 17, wherein said disruption was performed prior to between 3-12 days, 4-12 days, 5-12 days, 4-11 days, 6-11 days, 6-10 days, 6-9 days, 6-8 days, 7-8 days, 5-11 days, 5-10 days, 7-10 days, or about 1 week of said contacting step.
19. The method of any one of claims 1 to 18, wherein the treatment of a balding scalp is in a subject with male pattern baldness or female pattern baldness.
20. The method of any one of claims 1 to 19, which results in an increase in markers of hair follicle proliferation, hair follicle differentiation or hair follicle embryonic development.
21. The method of any one of claims 1 to 20, which results in an increase in the amount of pigmented hair or an increase in hair follicle size.

22. The method any one of claims 1 to 21, which results in differentiation of an uncommitted epidermal cell into a hair follicle cell.
23. The method of any one of claims 1 to 22, which results in generation of a hair follicle in the scalp of the subject.
24. Use of a compound or factor that enhances the size of a hair follicle cell for stimulating hair growth in a balding scalp of a human subject, comprising:
contacting a disrupted area of the balding scalp of said human subject with minoxidil,
wherein the disrupted area comprises perforated epidermis or epidermal layers of the balding scalp of said human subject.
25. The use of claim 24, wherein said disruption was induced by a tool that comprises sandpaper, a laser, a FRAXEL™ laser, a CO₂ laser, an excimer laser, a felt wheel, a dermabrasion device, a light-based method, irradiation with visible light, irradiation with infrared light, irradiation with ultraviolet radiation, orthovoltage radiation, x-ray radiation, a surgical tool, a dermal biopsy punch, or was induced by a burn treatment or chemical treatment.
26. The use of claim 25, wherein said dermabrasion device is a micro-dermabrasion device.
27. The use of claim 24, wherein said disruption was induced by dermabrasion.
28. The use of any one of claims 24 to 27, wherein said disruption comprises perforated epidermis and dermis of the area of the scalp.
29. The use of any one of claims 24 to 28, in which only a portion of the epidermal layer is perforated in said disrupted area.
30. The use of any one of claims 24 to 29 in combination with an inductive cell.
31. The use of any one of claims 24 to 29, in combination with use of a precursor cell, an inductive cell, or a hair follicle or a portion thereof.
32. The use of claim 31, in combination with an antagonist of an androgen or an antagonist of an androgen receptor.

33. The use of claim 32, wherein the antagonist of an androgen or antagonist of an androgen receptor is finasteride, Fluridil®, dutasteride, spironolactone, cyproterone acetate, bicalutamide, flutamide, nilutamide, an inhibitor of an androgen receptor, an androgen antagonist, or an anti-androgen.

34. The use of any one of claims 24 to 33, wherein the androgen or an antagonist of an androgen receptor and/or minoxidil is for administration as a cream, gel, lotion, emulsion, suspension, oil, non-aqueous solution, aqueous solution, or drop, or by direct injection, or is encapsulated in a liposome.

35. The use of any one of claims 25 to 34, wherein said area of the scalp was subjected to depilation or administration of a retinoid prior to said disruption.

36. The use of claim 35, wherein said depilation was induced by plucking, waxing, abrasion, laser, electrolysis, or administration of thioglycolic acid on said area of the scalp.

37. The use of any one of claims 24 to 36, wherein said disrupted area of scalp was not surgically closed, or not contacted with a bandage, dressing, or ointment that facilitates healing for a period of time following said disruption.

38. The use of claim 37, wherein said period of time was within about 2 days, about 3 days, about 4 days, about 5 days, about 7 days, about 10 days, about 11 days, about 14 days, about 17 days, or about 3 weeks.

39. The use of any one of claims 24 to 38, wherein said disrupted area of scalp is allowed to heal by secondary intention.

40. The use of any one of claims 24 to 39, wherein said disrupted area of scalp was contacted with a gel, cream, lotion, emulsion, suspension, oil, non-aqueous solution, aqueous solution, or drop following said disruption.

41. The use of any one of claims 24 to 40, wherein the disruption was performed prior to between 3-12 days, 4-12 days, 5-12 days, 4-11 days, 6-11 days, 6-10 days, 6-9 days, 6-8 days, 7-8 days, 5-11 days, 5-10 days, 7-10 days, or about 1 week of said contacting step.

42. The use of any one of claims 24 to 41, for stimulating hair growth in a balding scalp of a human subject with androgenetic alopecia (AGA), scarring alopecia, male pattern baldness, female pattern baldness, discoid lupus erythematosus, or lichen planopilaris.

43. The use of any one of claims 24 to 42, which results in an increase in markers of hair follicle proliferation, hair follicle differentiation or hair follicle embryonic development.
44. The use of any one of claims 24 to 43, which results in an increase in the amount of pigmented hair or an increase in hair follicle size.
45. The use any one of claims 24 to 44, which results in differentiation of an uncommitted epidermal cell into a hair follicle cell.
46. The use of any one of claims 24 to 45, which results in generation of a hair follicle in the scalp of the subject.

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Figure 1

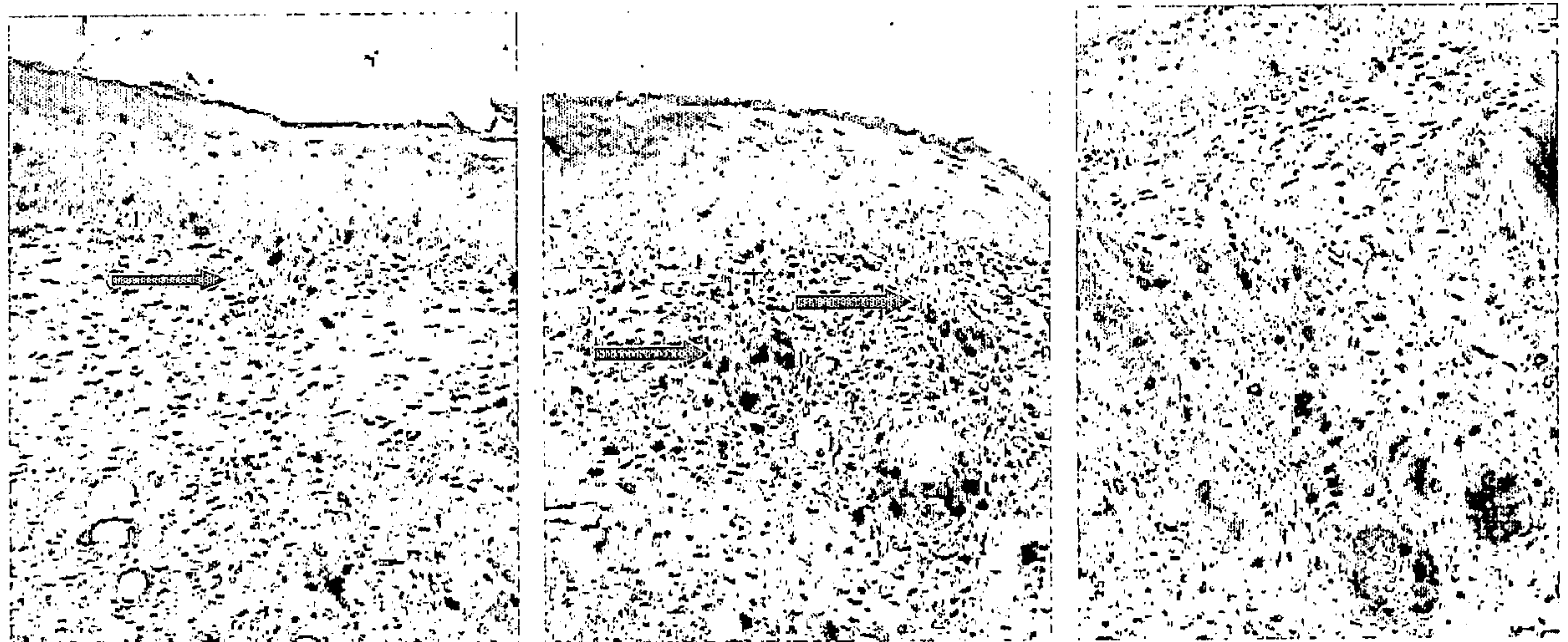


Figure 2

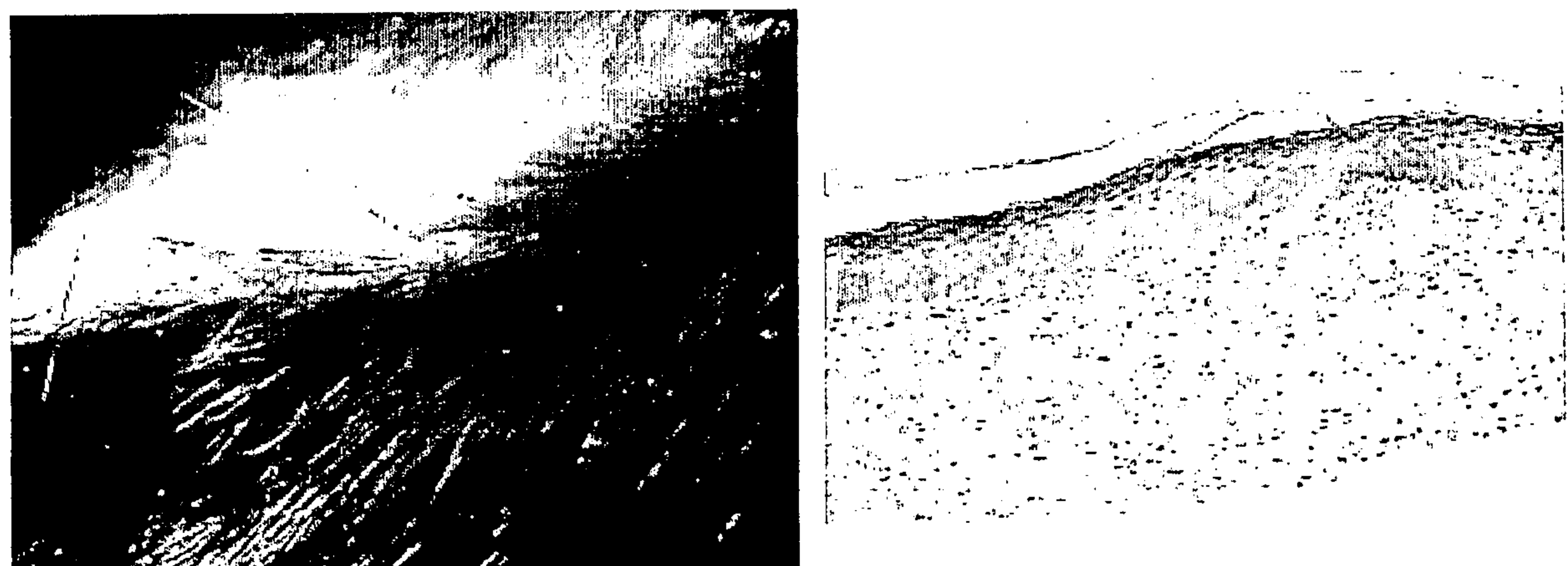


Figure 3

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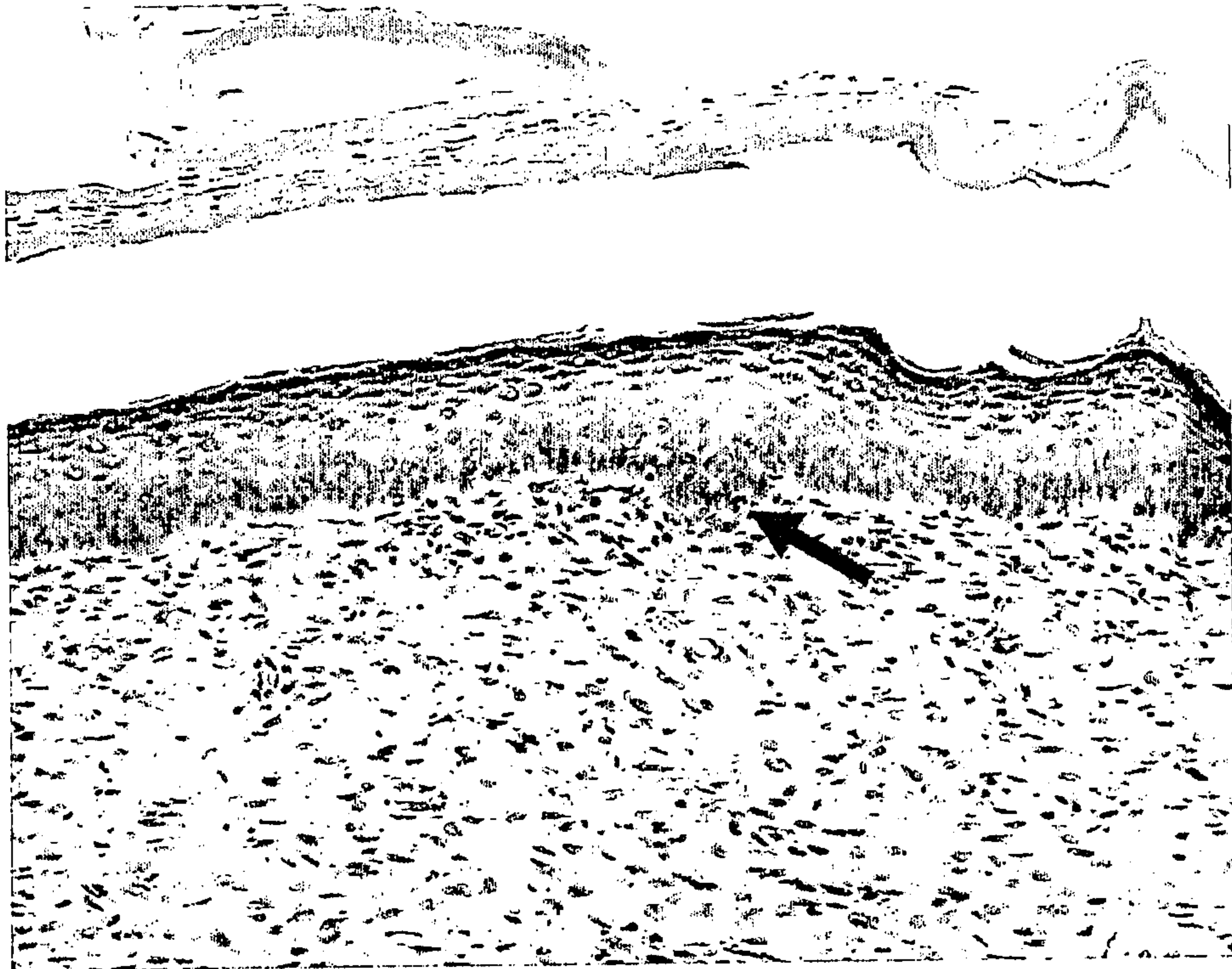


Figure 4

K 17 immuno-stain

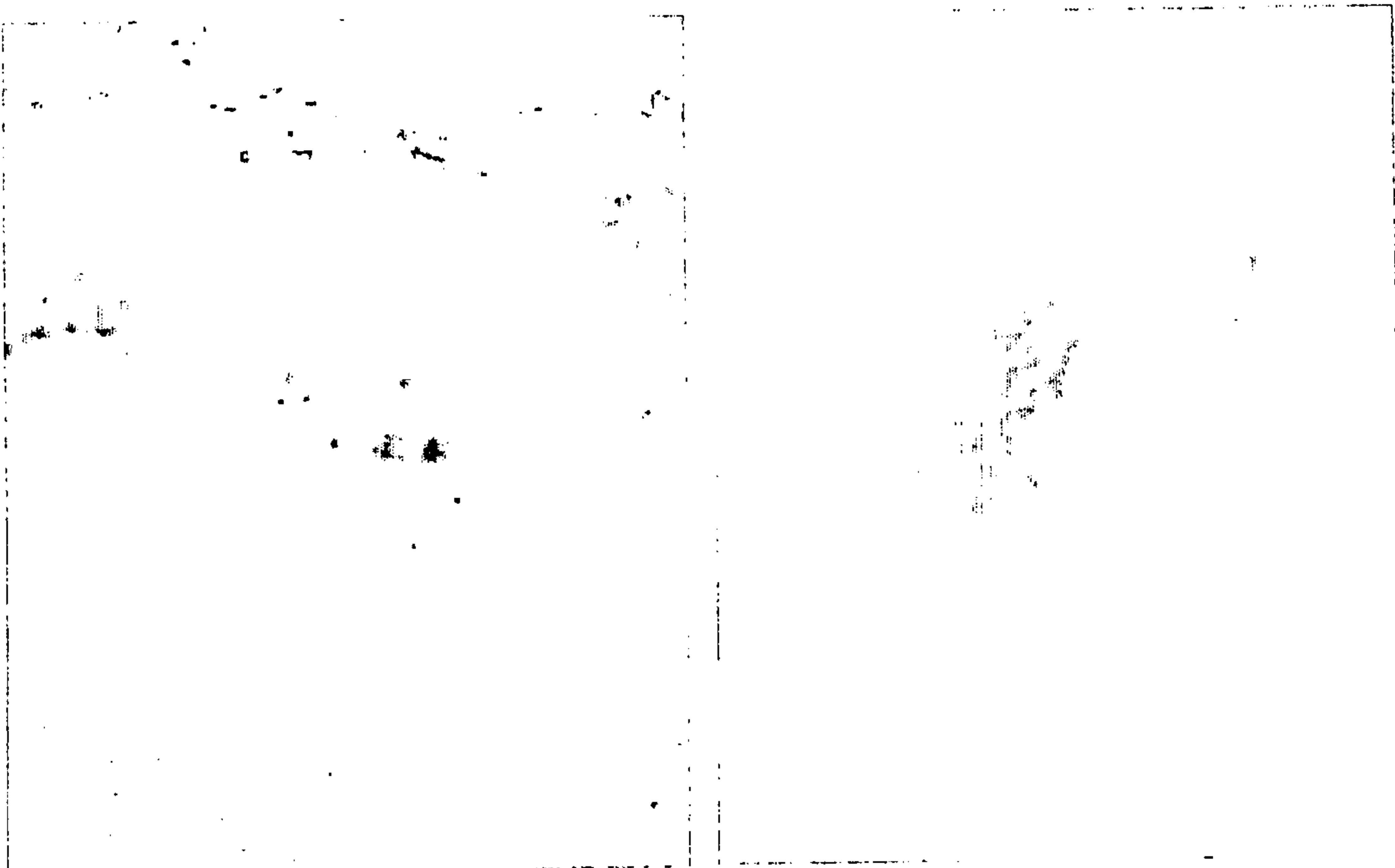


Figure 5

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Alkaline Phosphatase

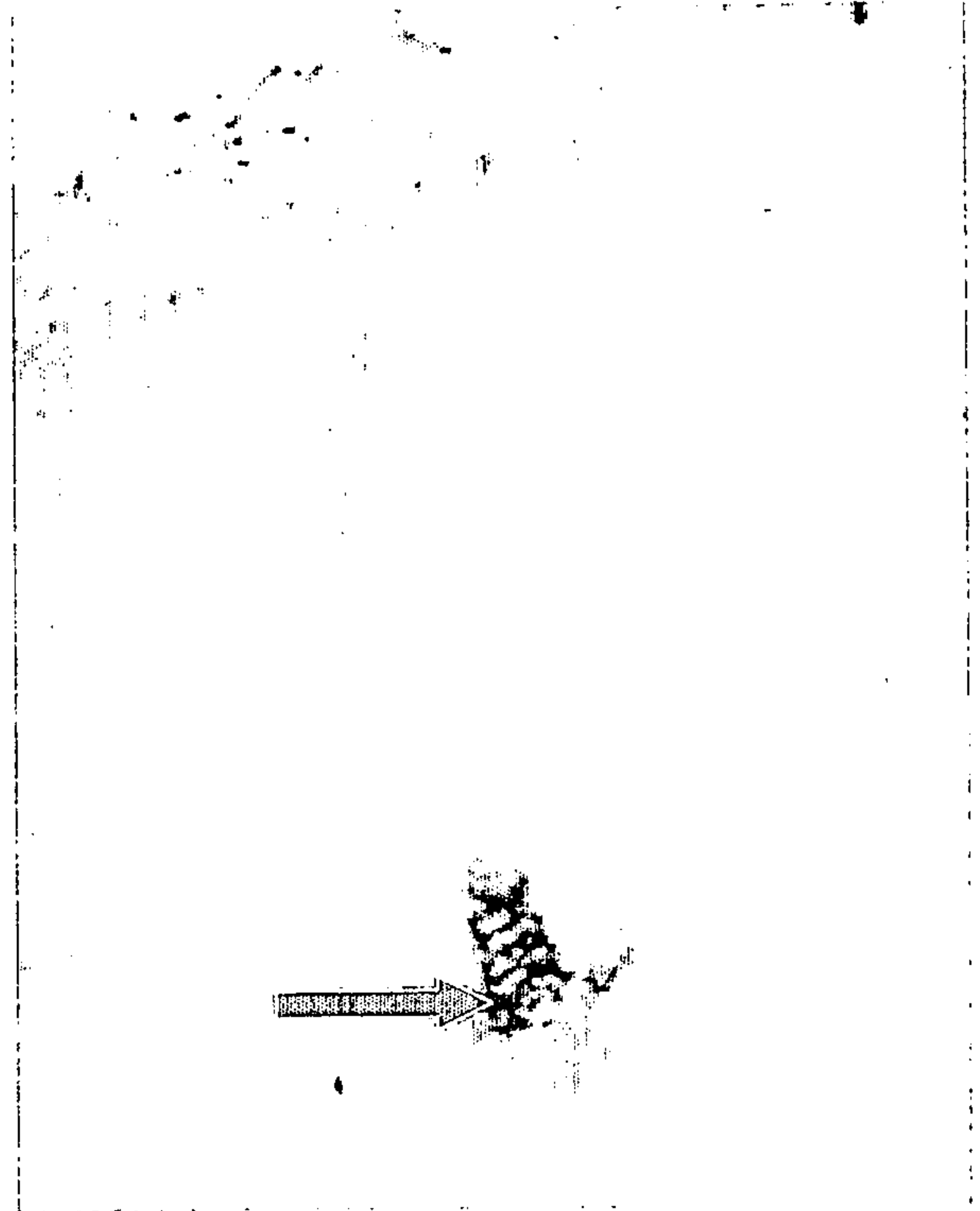


Figure 6

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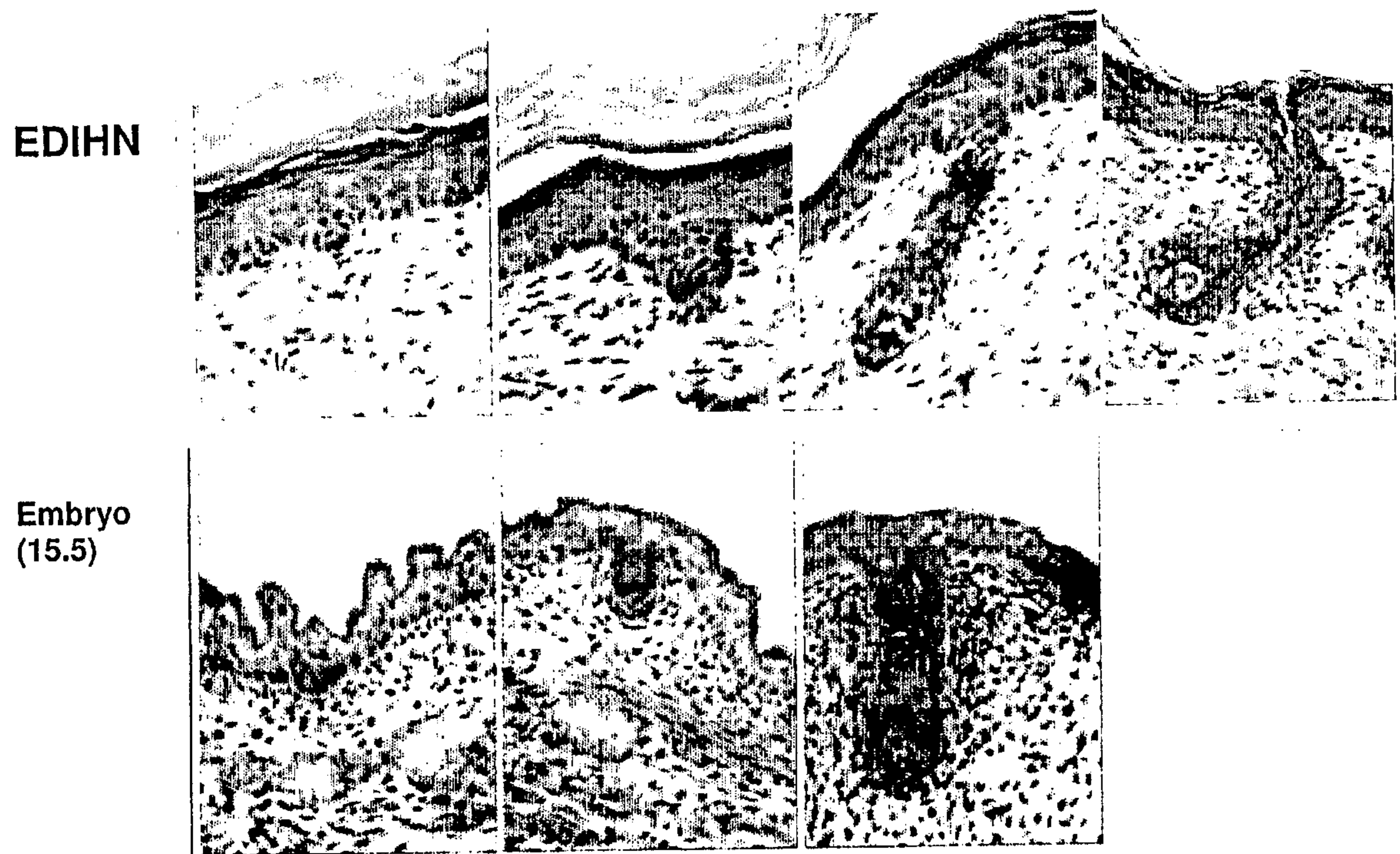


Figure 7

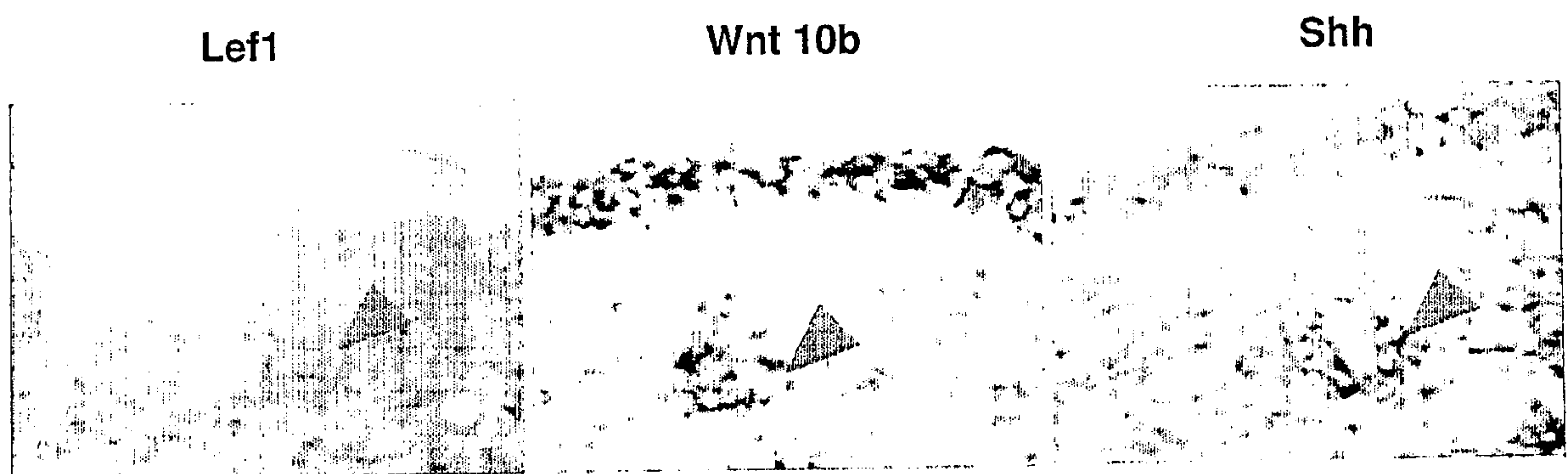


Figure 8

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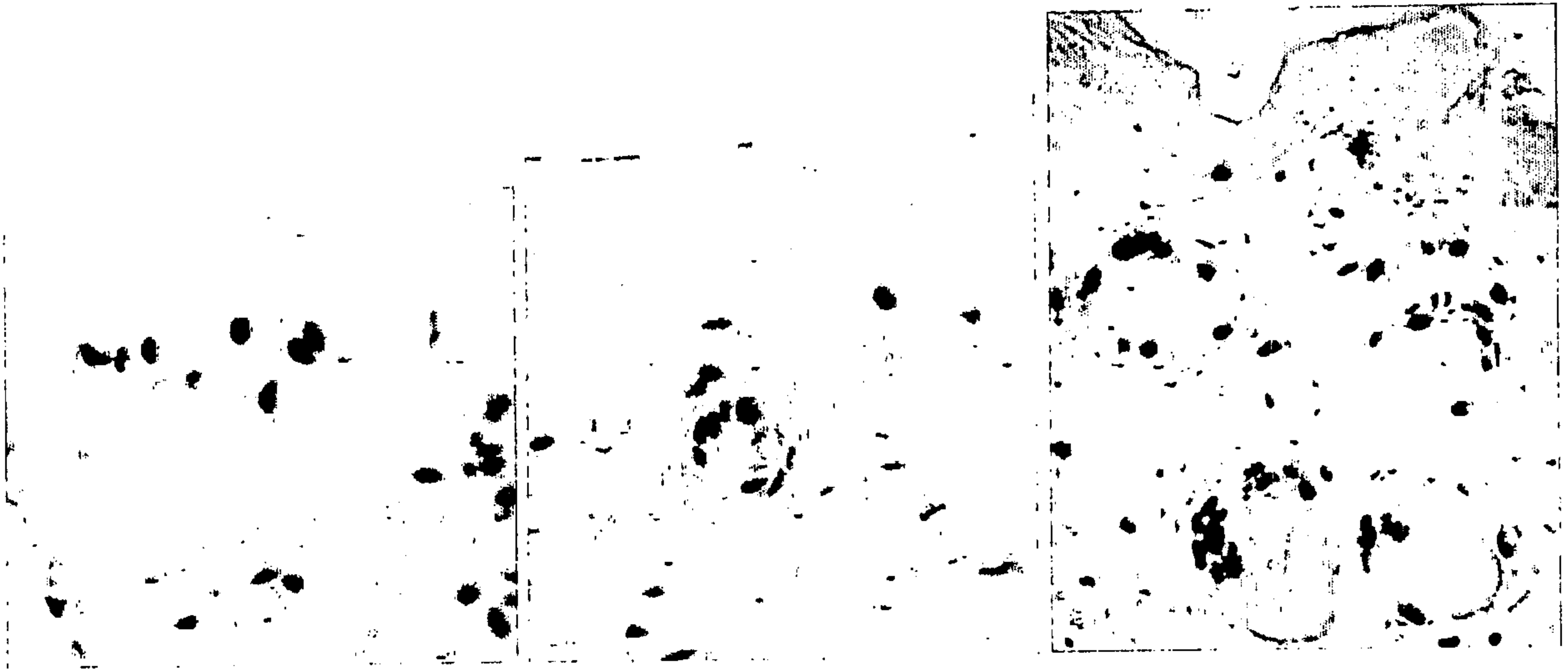


Figure 9

Cuticle , cortex : S100A3

IRS, medulla: S100A6

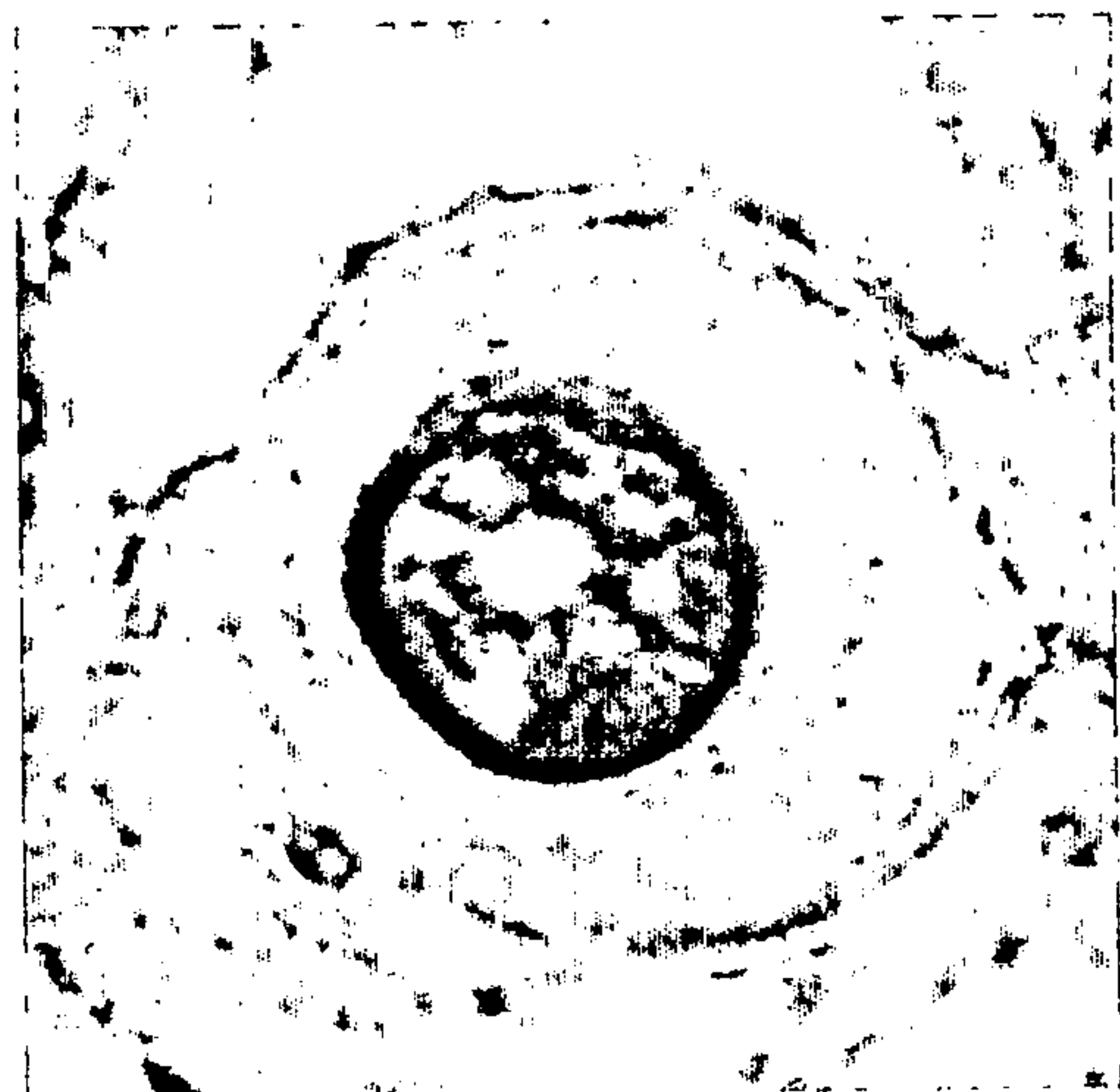


Figure 10

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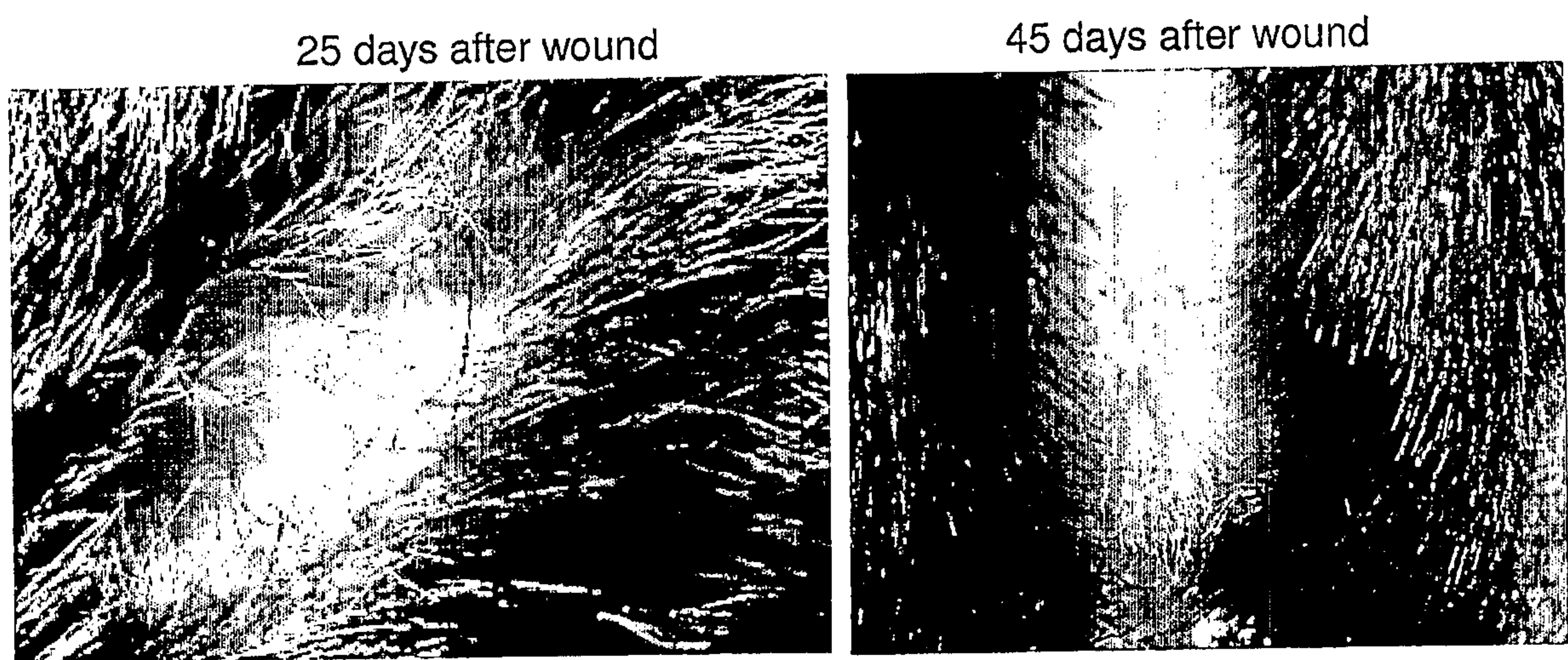


Figure 11

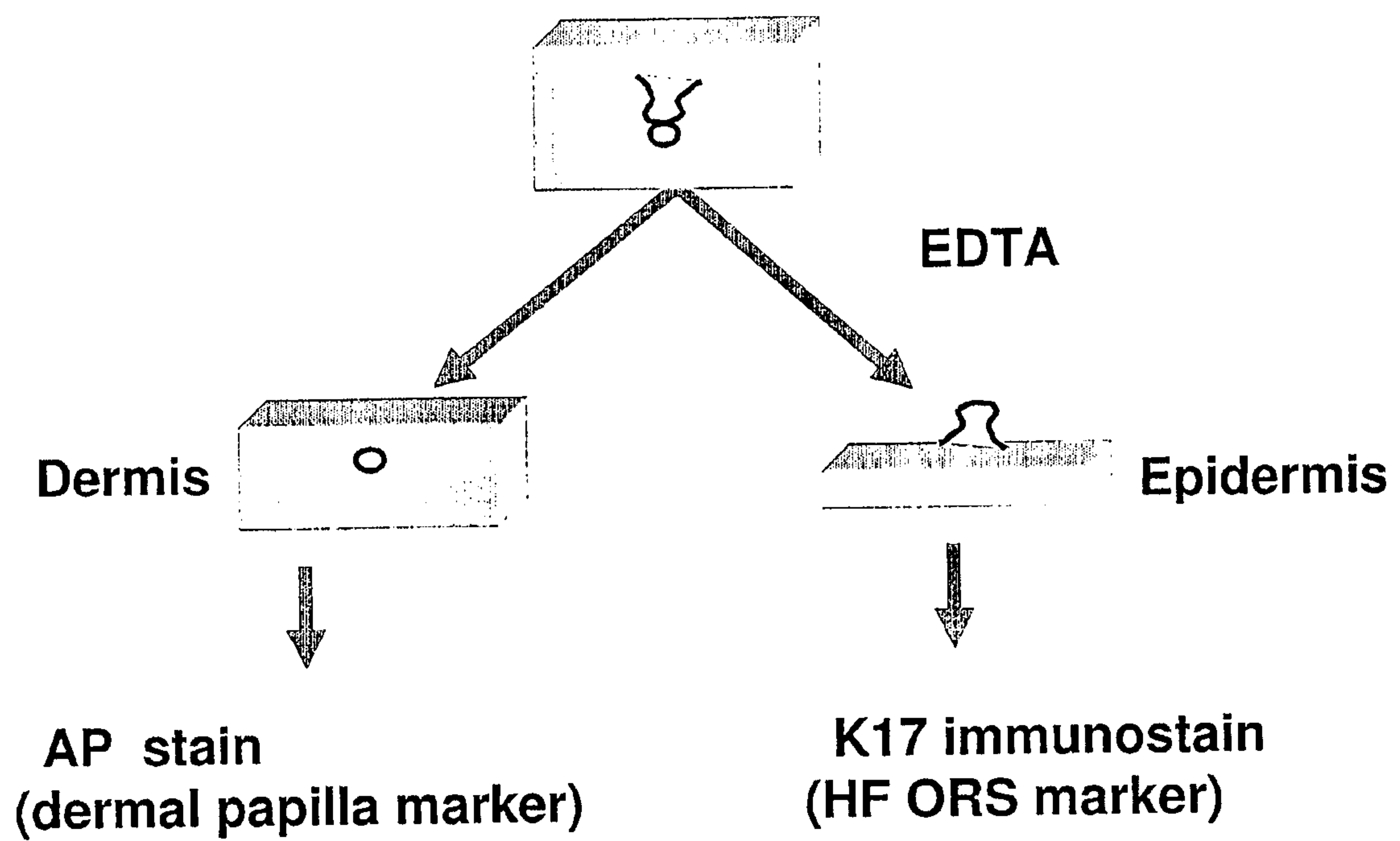


Figure 12

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Label retaining cells

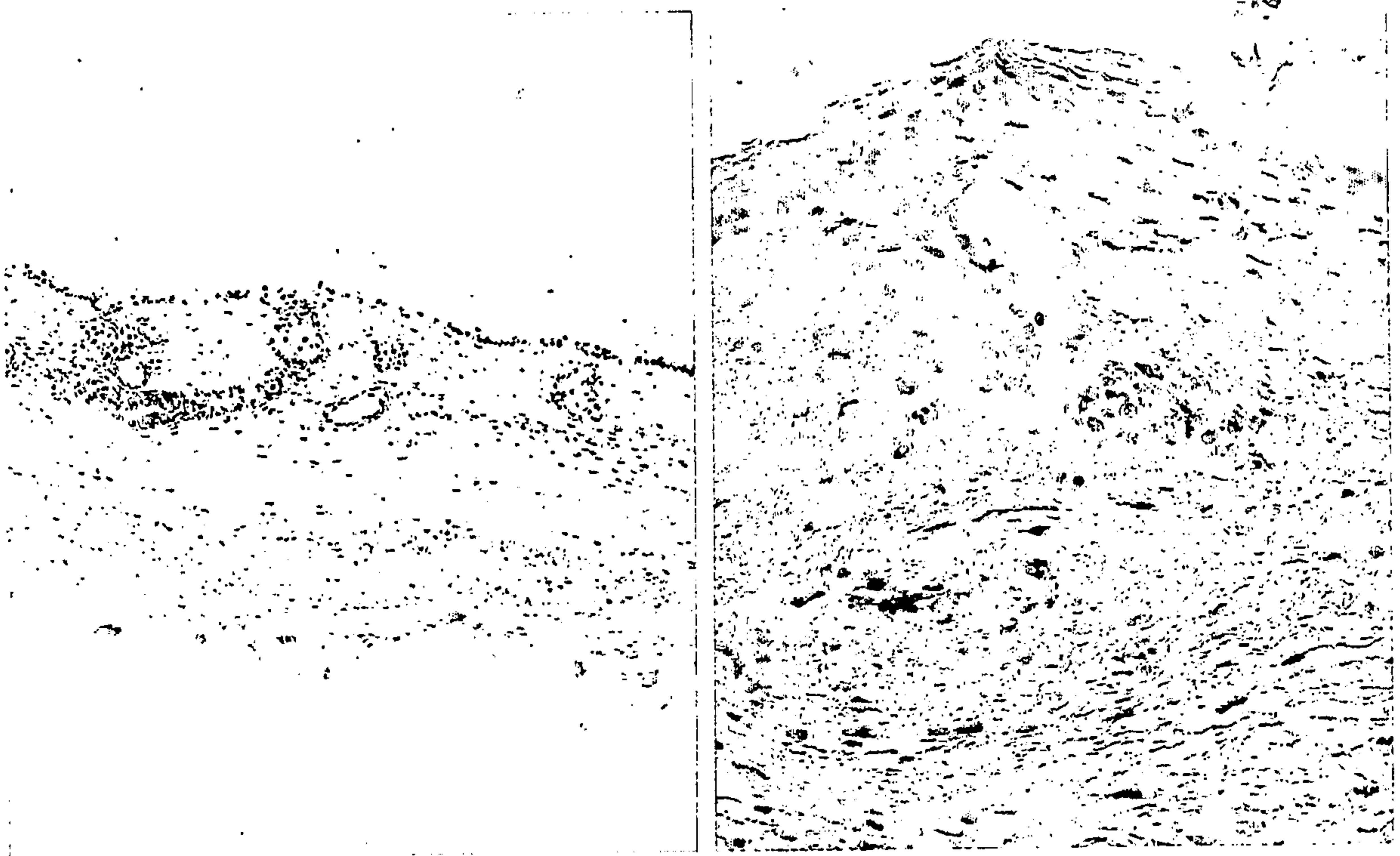
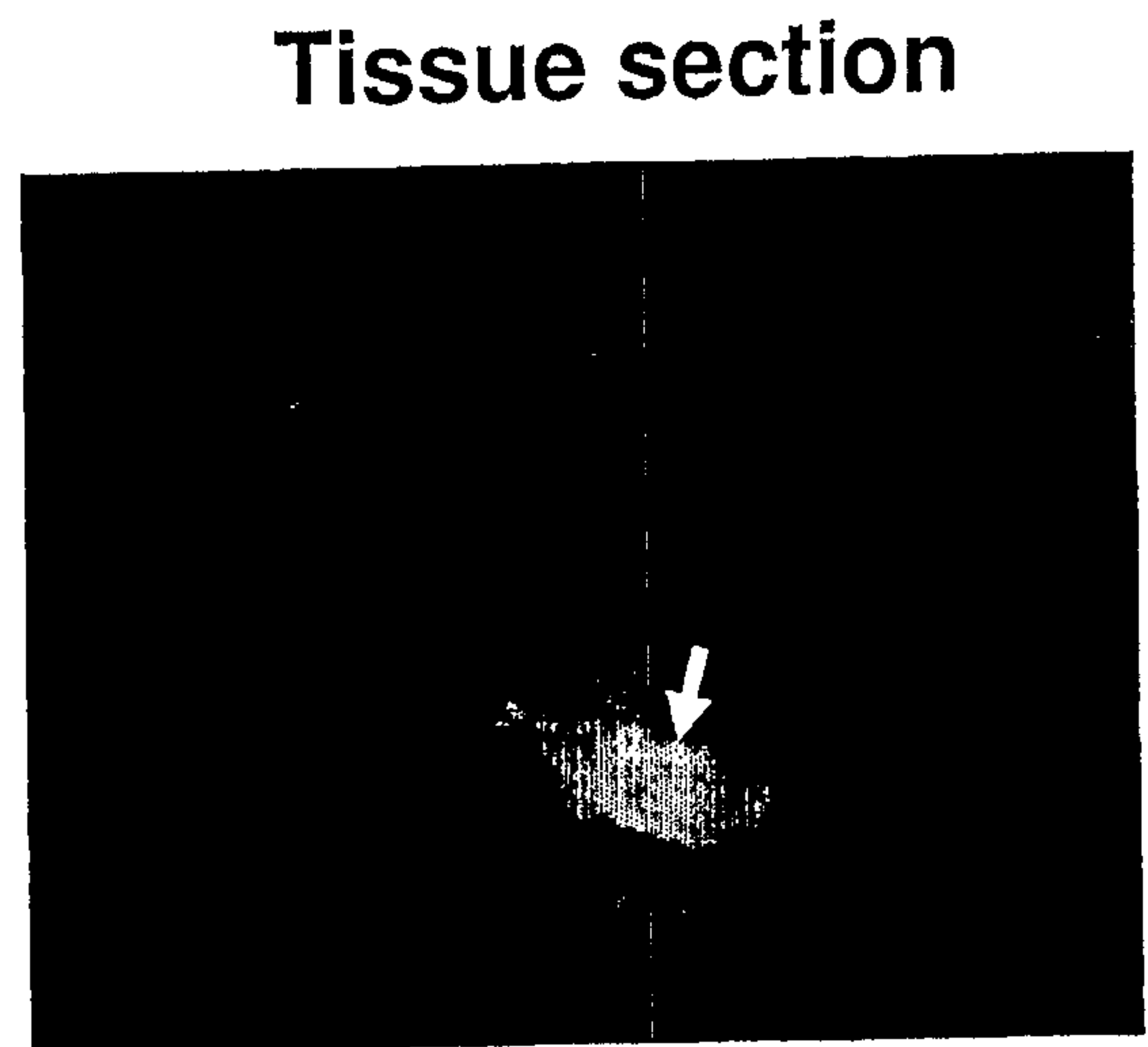
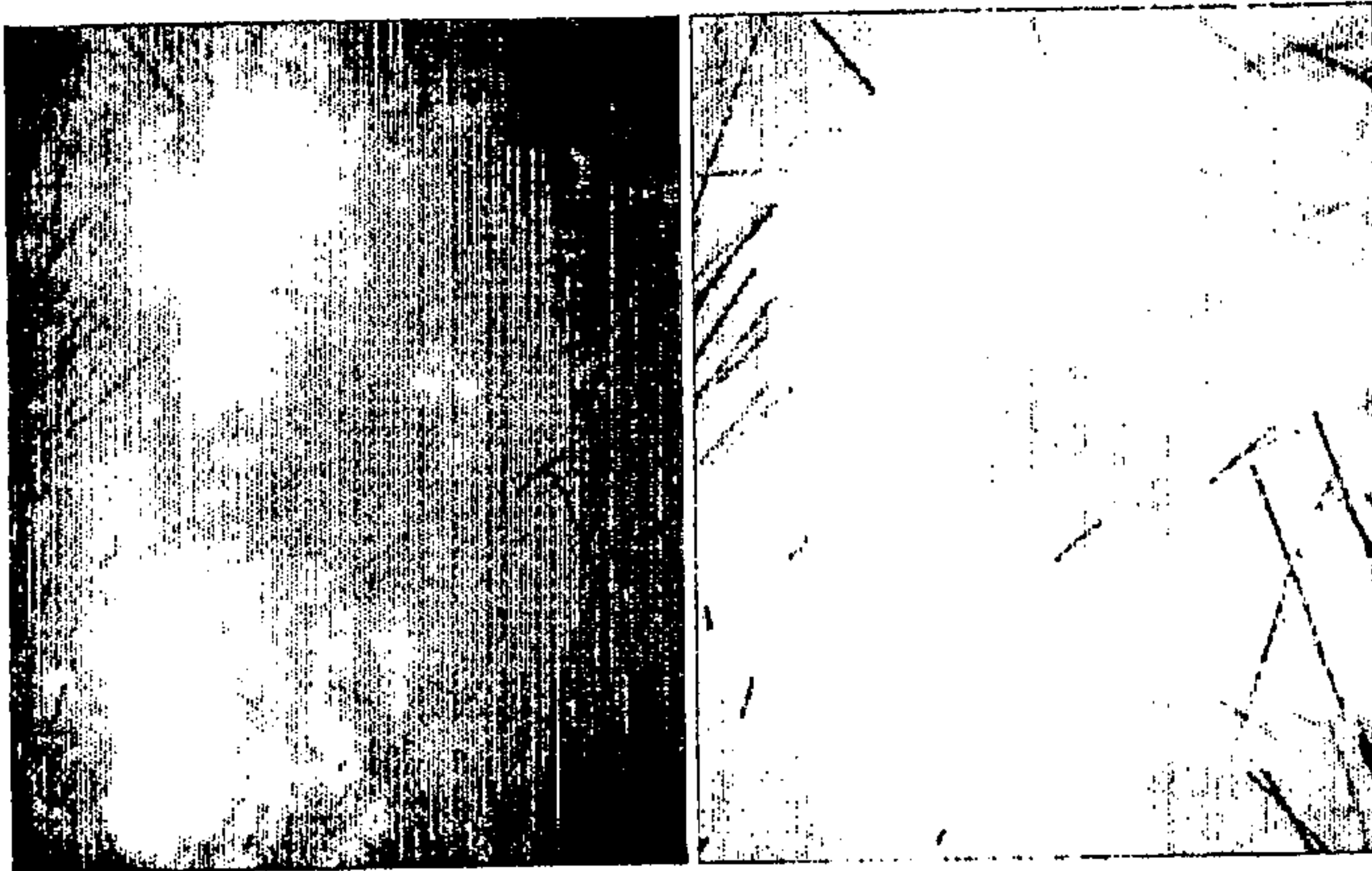
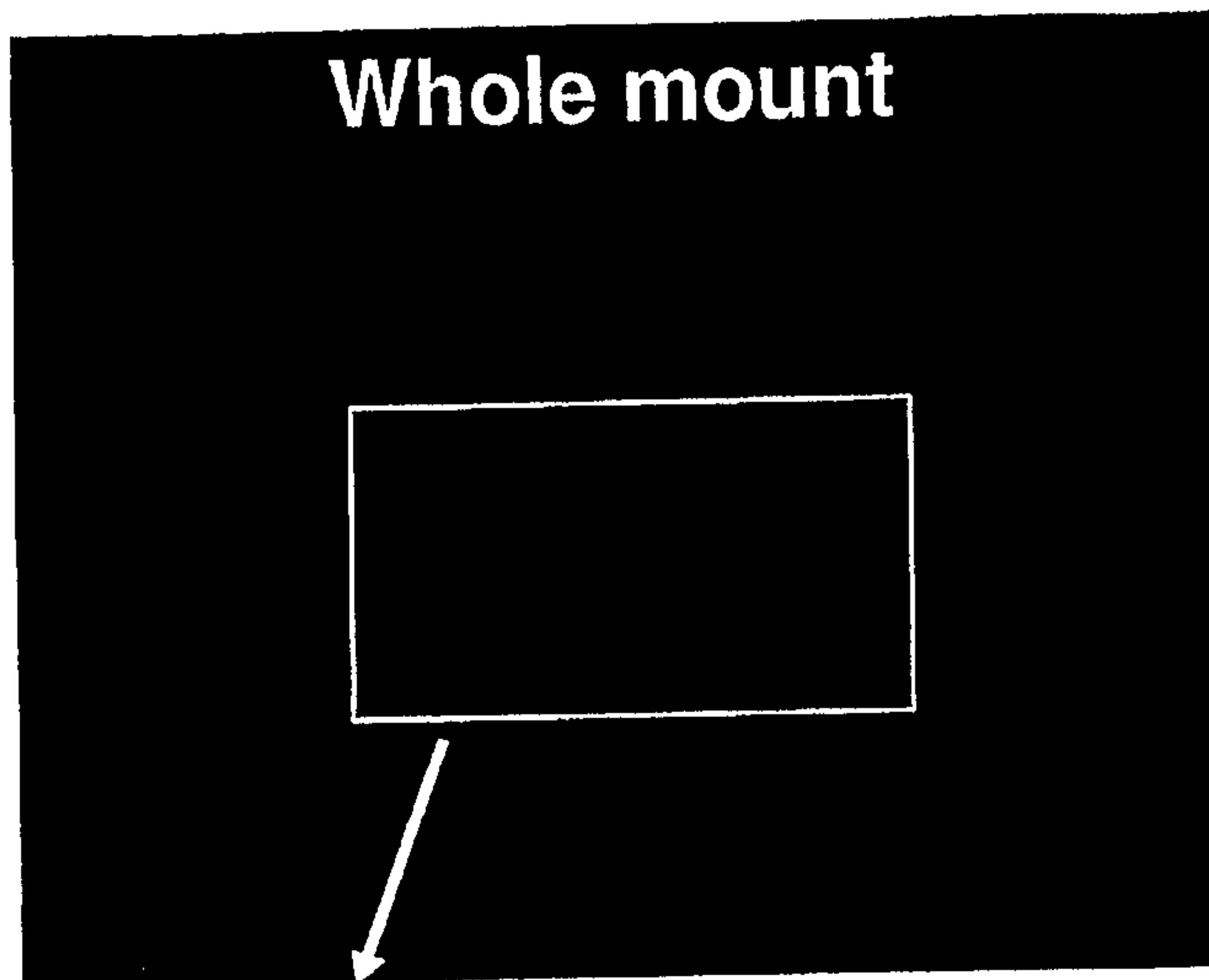


Figure 13

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35d after wound

Figure 14A

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Neogenesis hair follicles go to next hair cycle

35 d after wound



38 d after wound



45 d after wound



Figure 14B

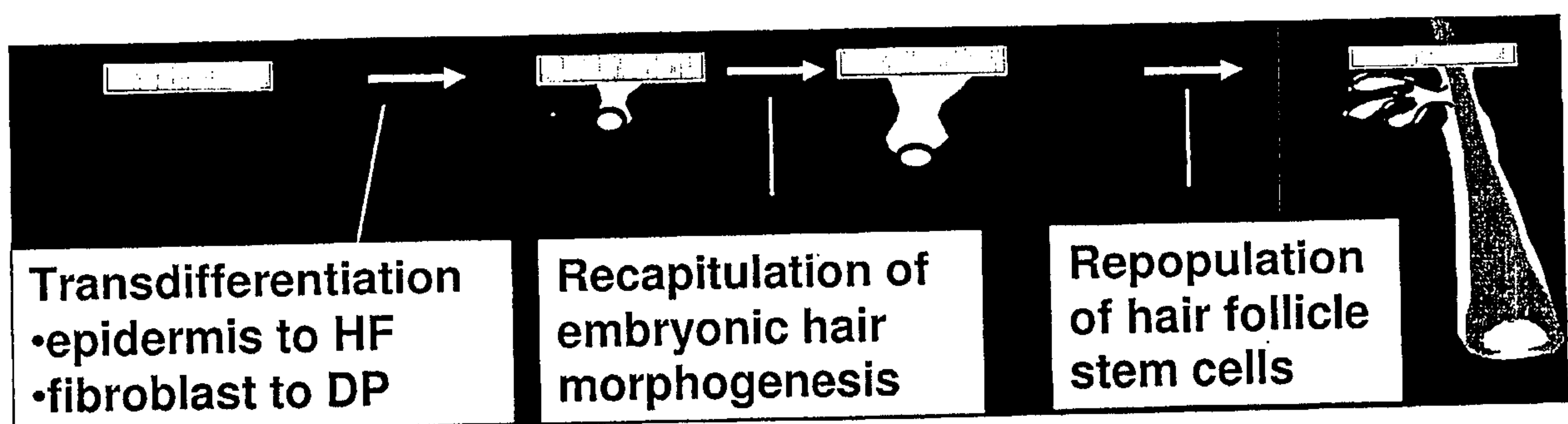
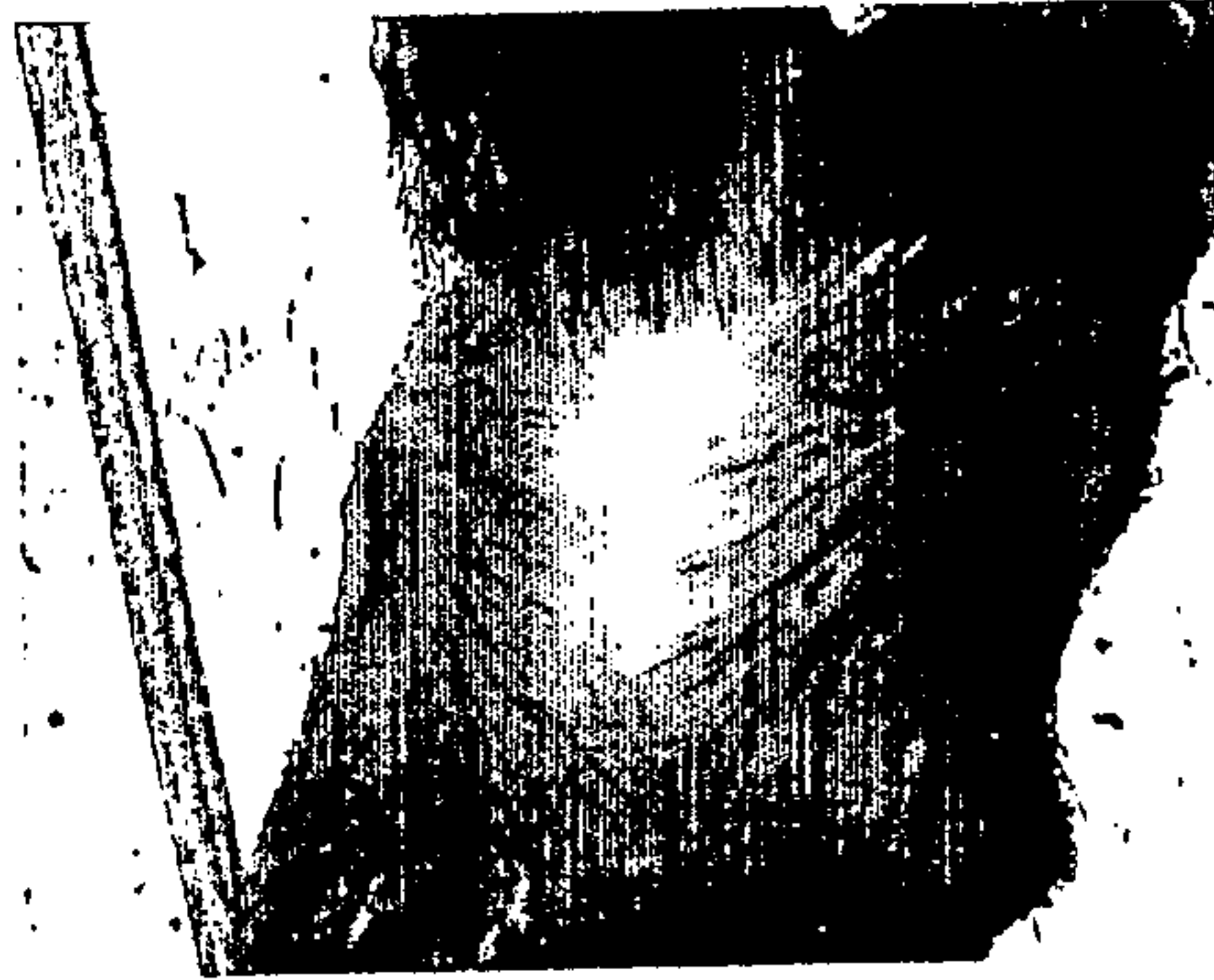


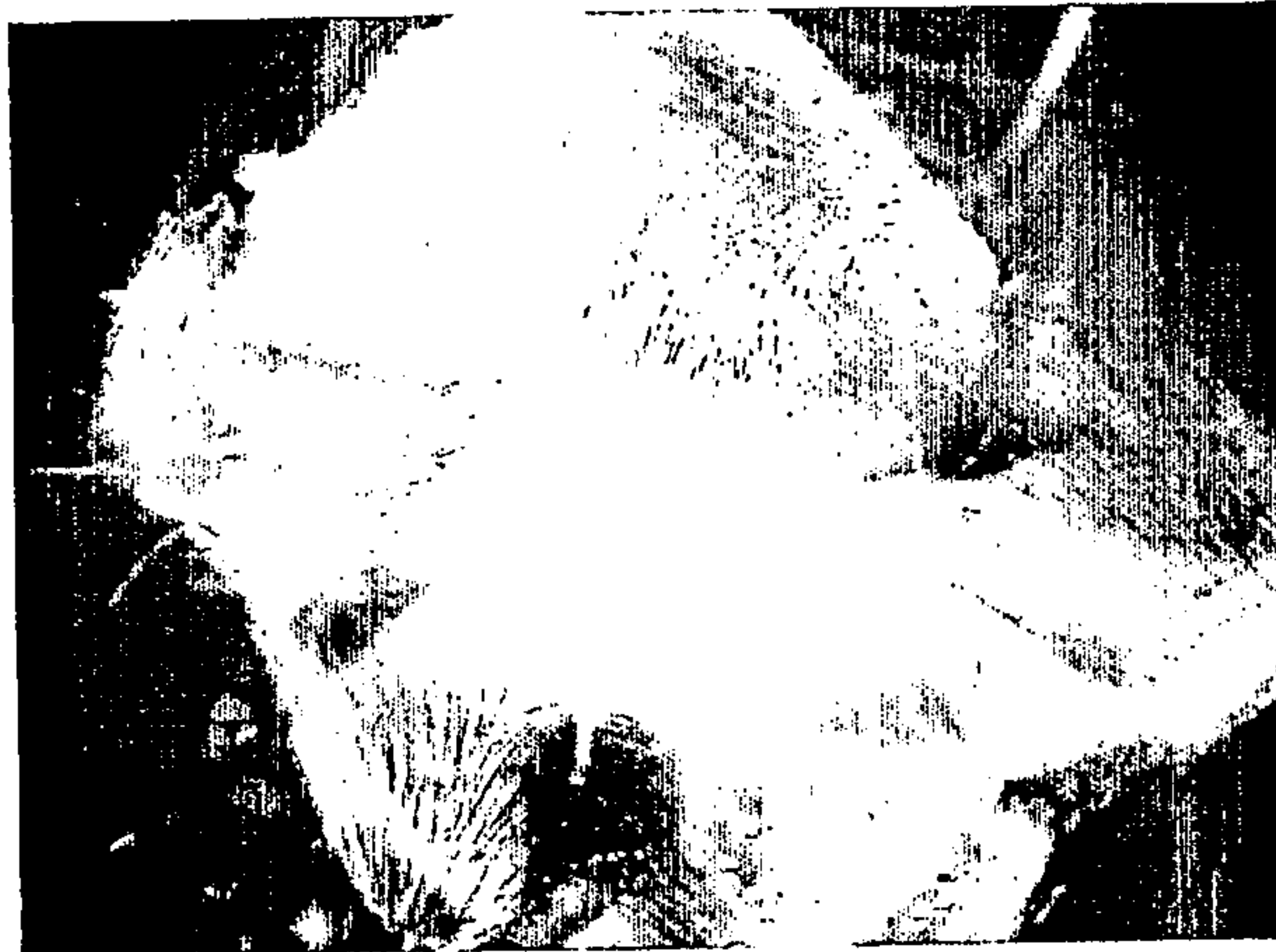
Figure 15

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11 days after wound



AP stain



K17 immunostain

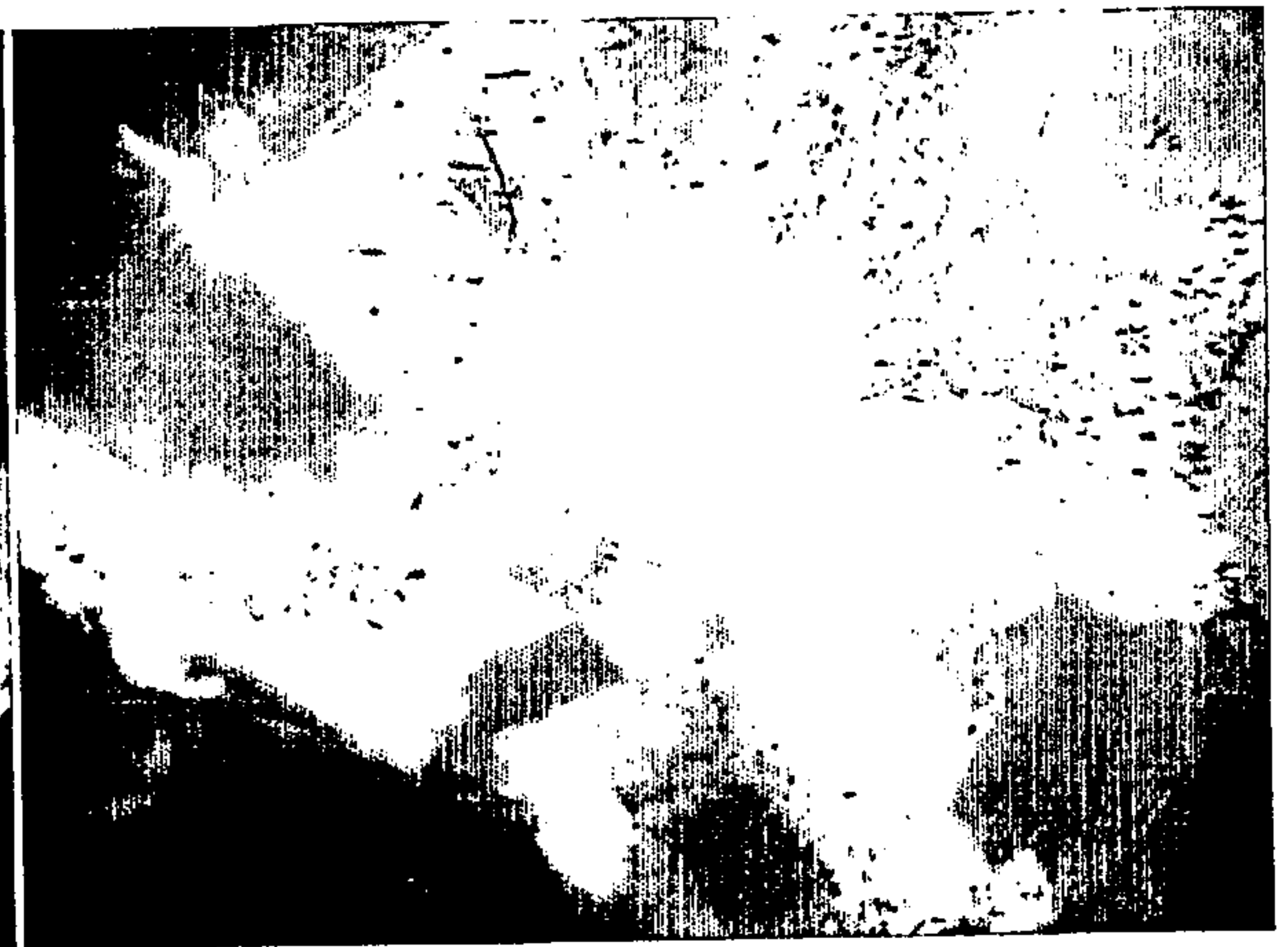


Figure 16

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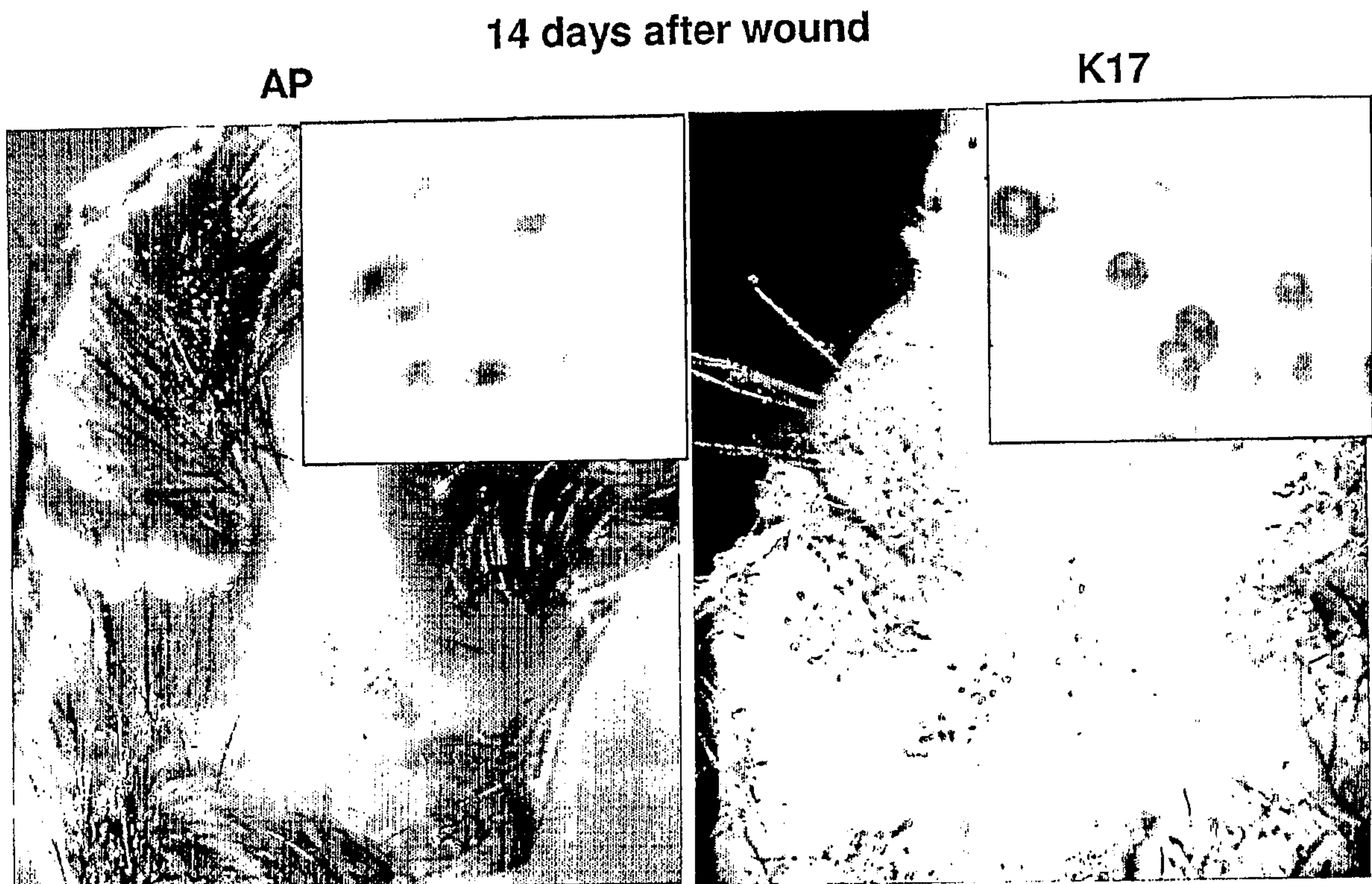


Figure 17

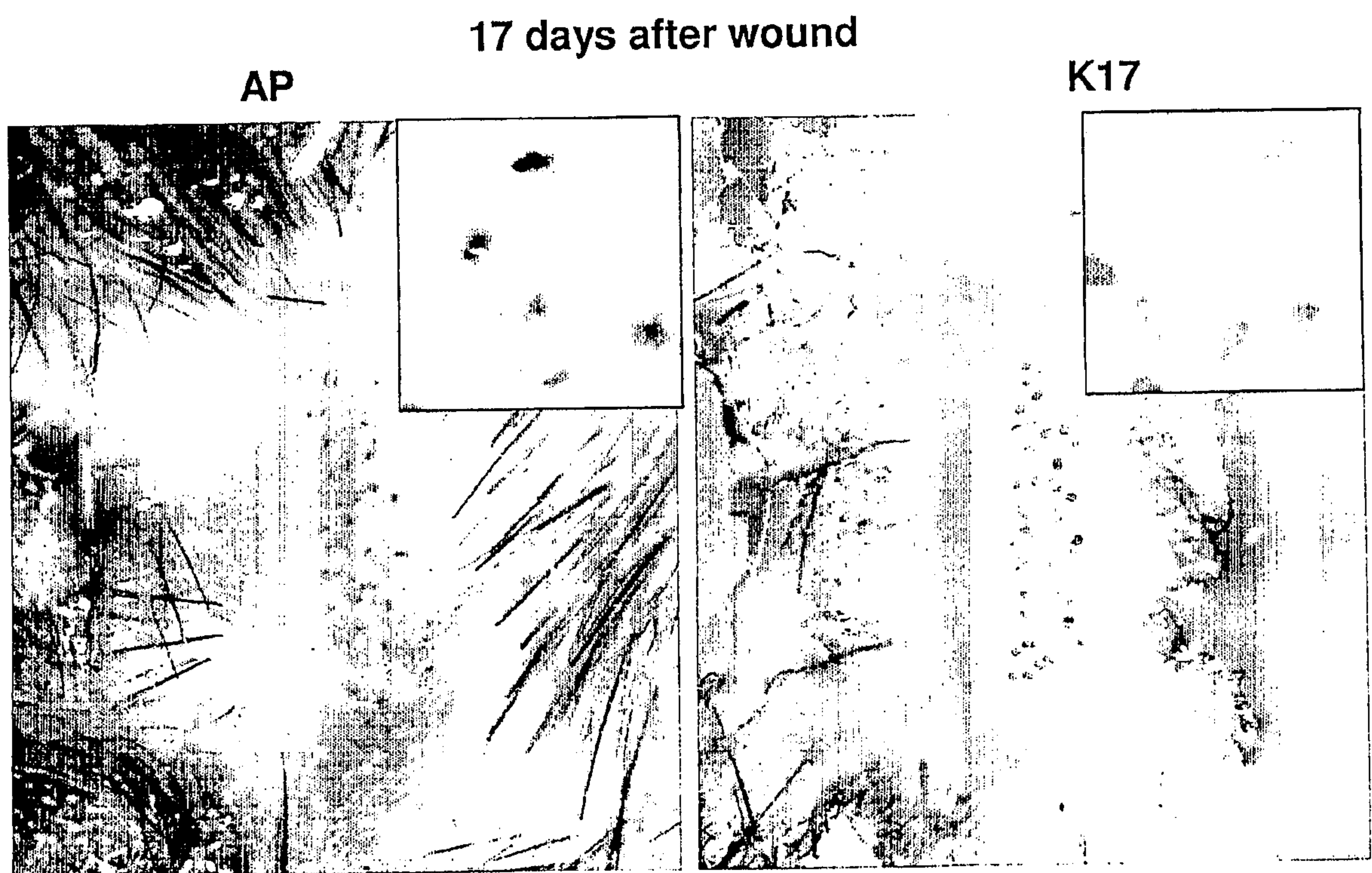


Figure 18

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8 weeks old mice (2nd telogen)

Depilation x Wound wound

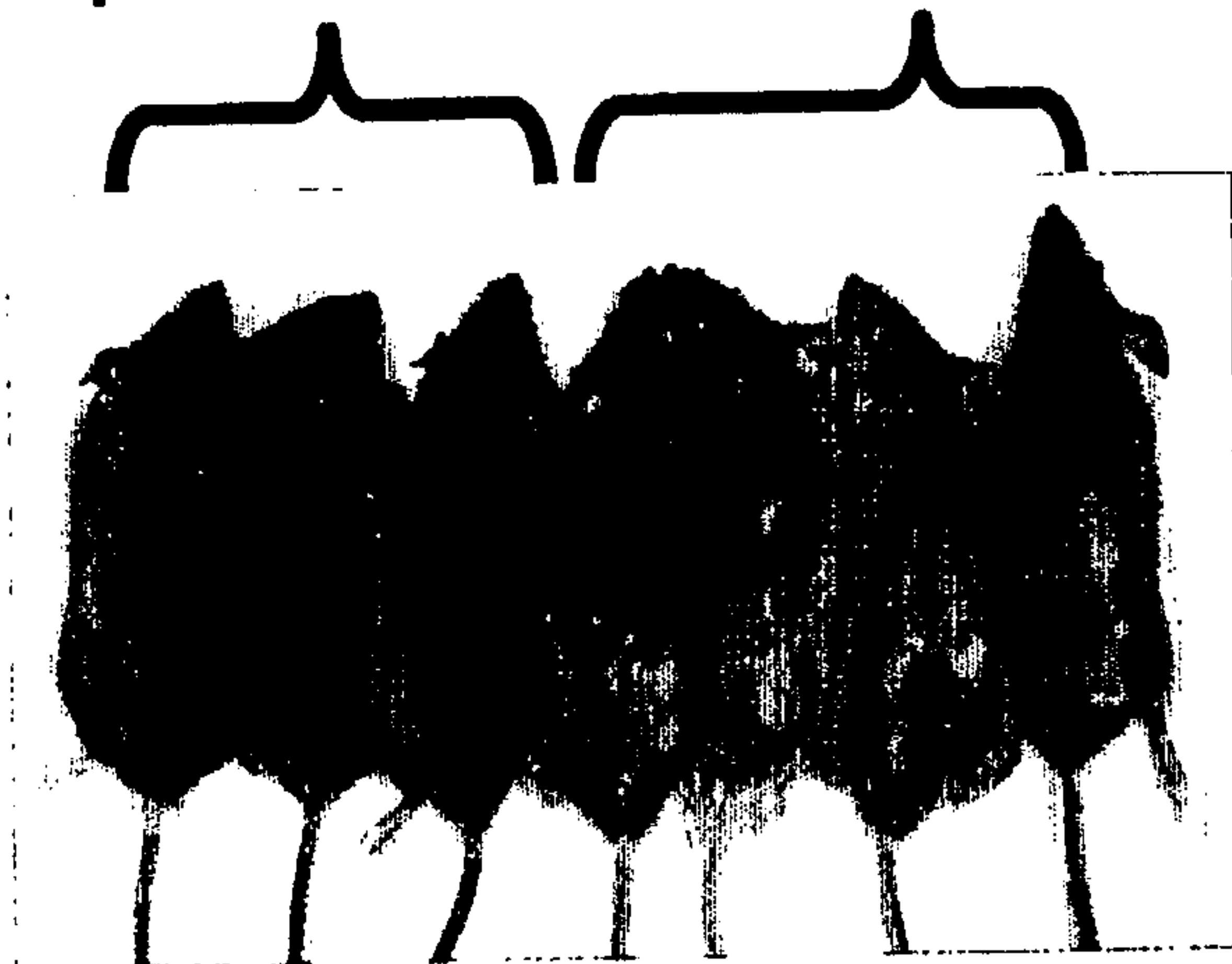
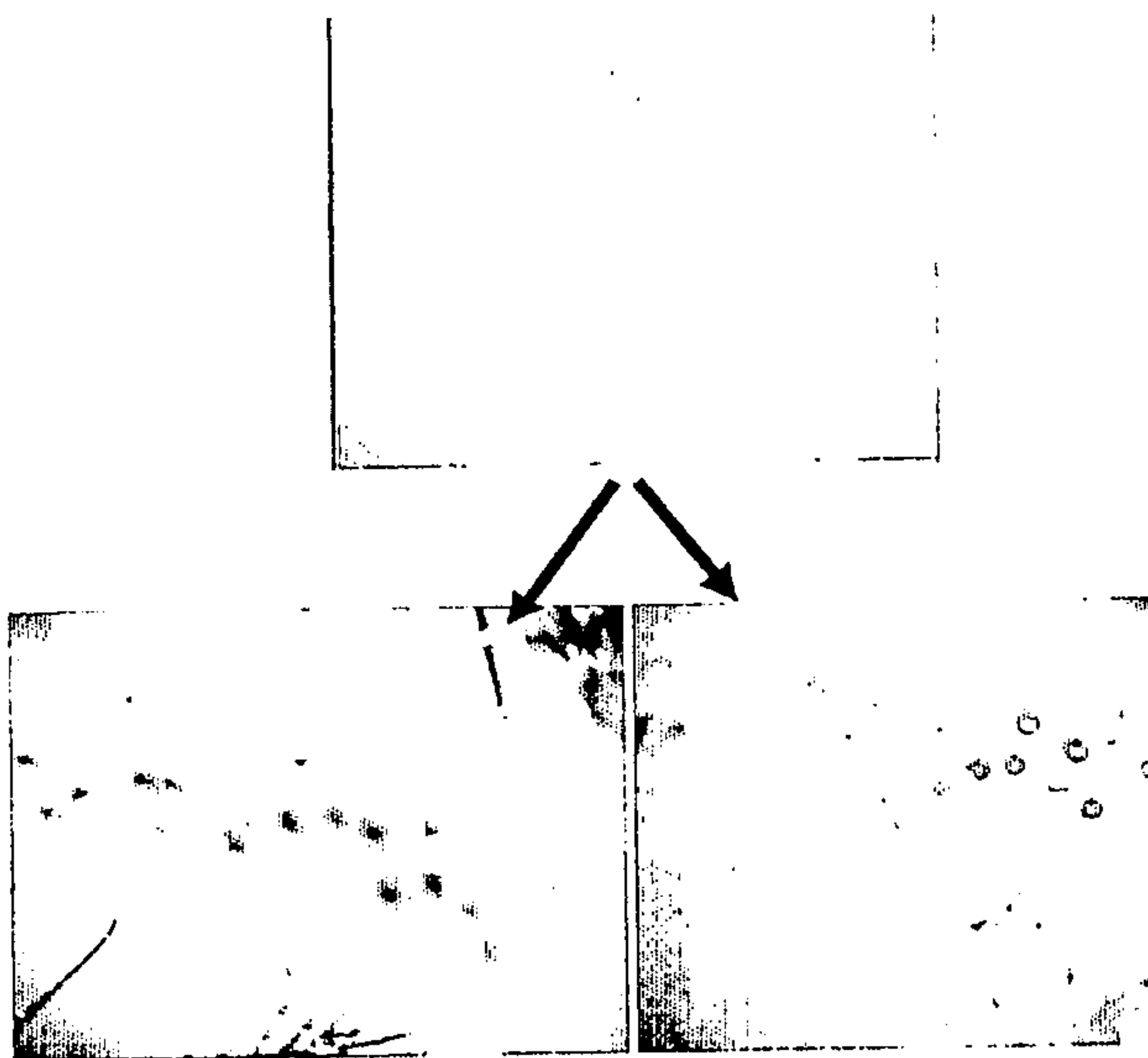


Figure 19

A.**AP****K17****B.**

WIHN assay :30 days after wound

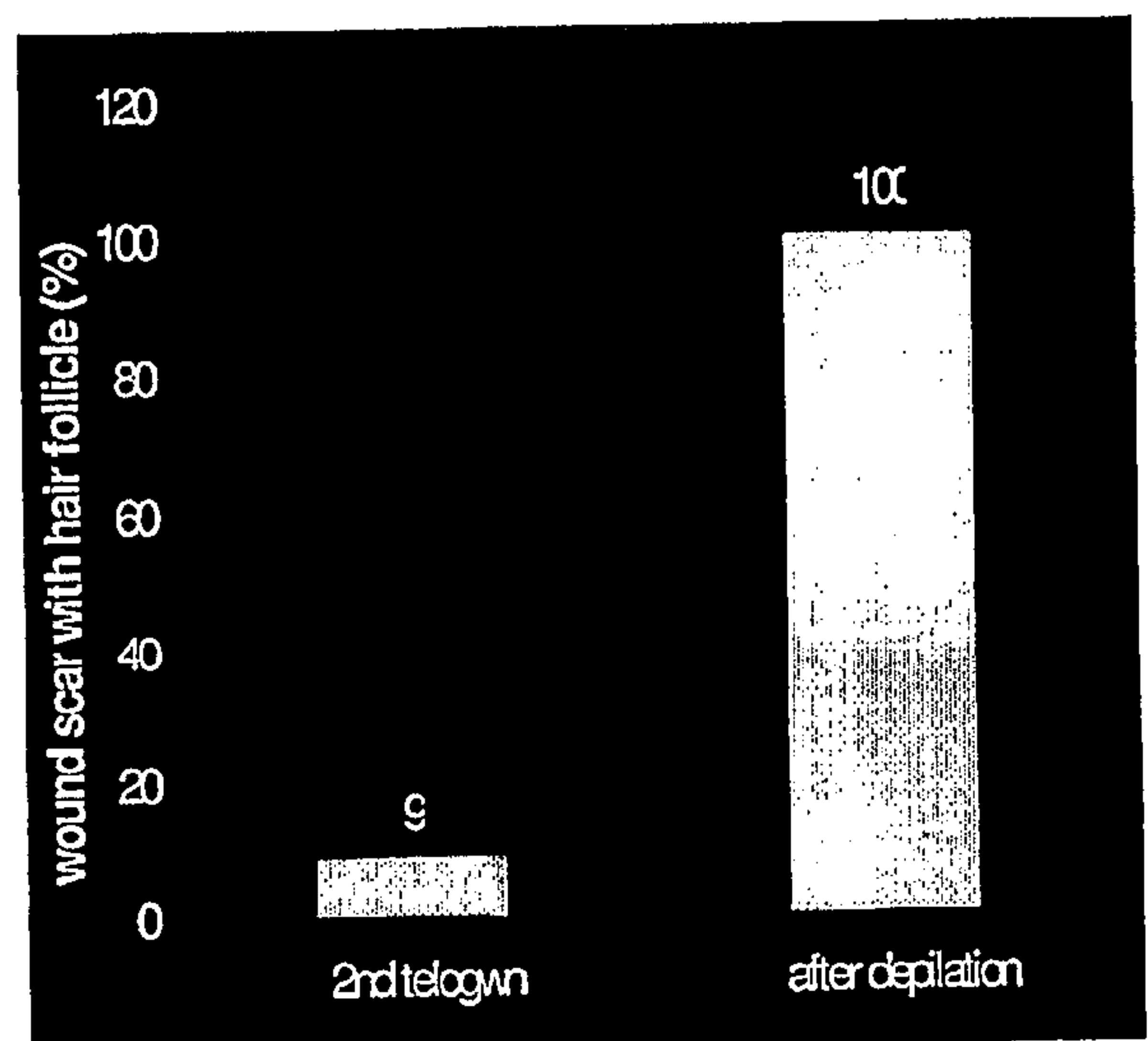


Figure 20

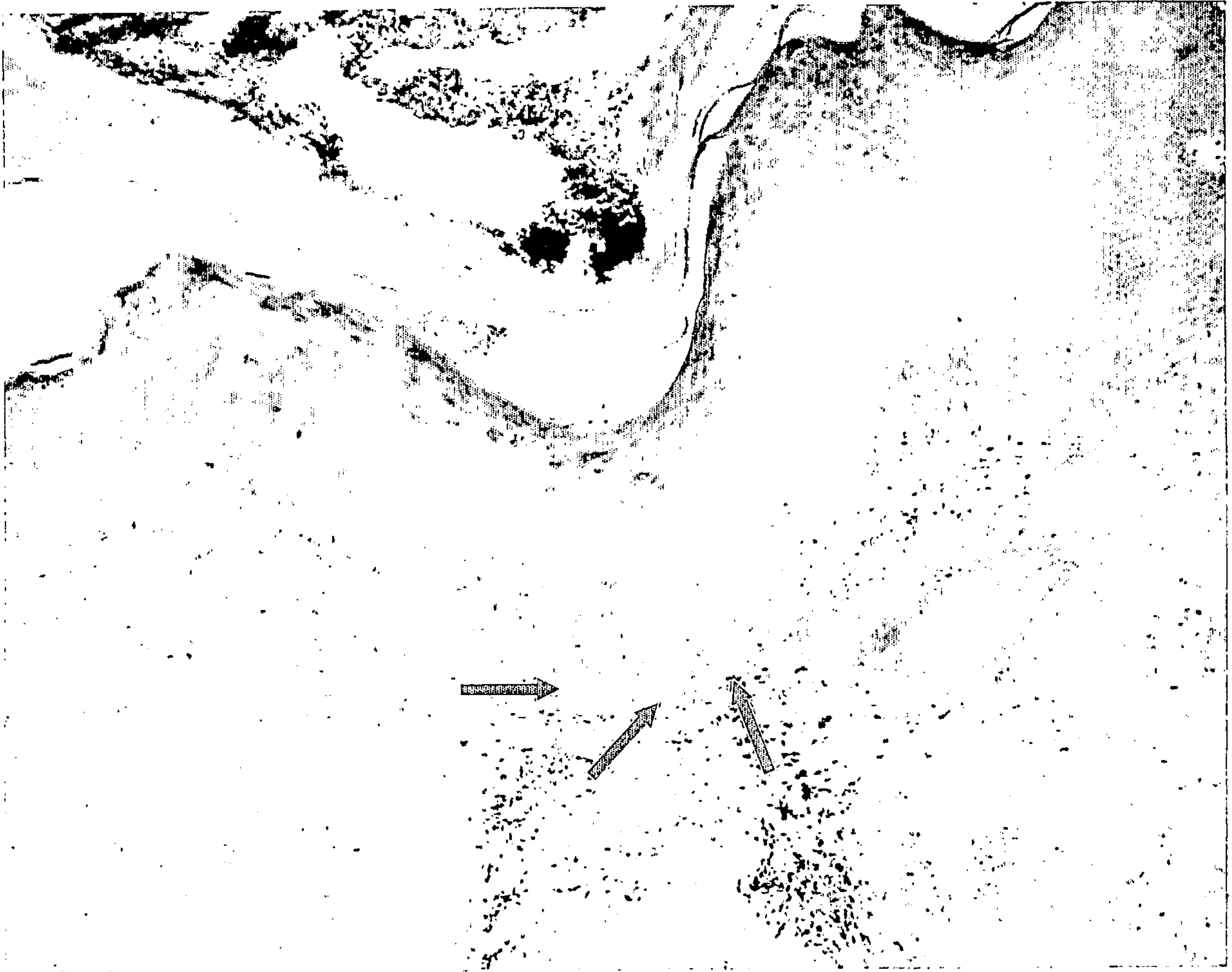


Figure 21A

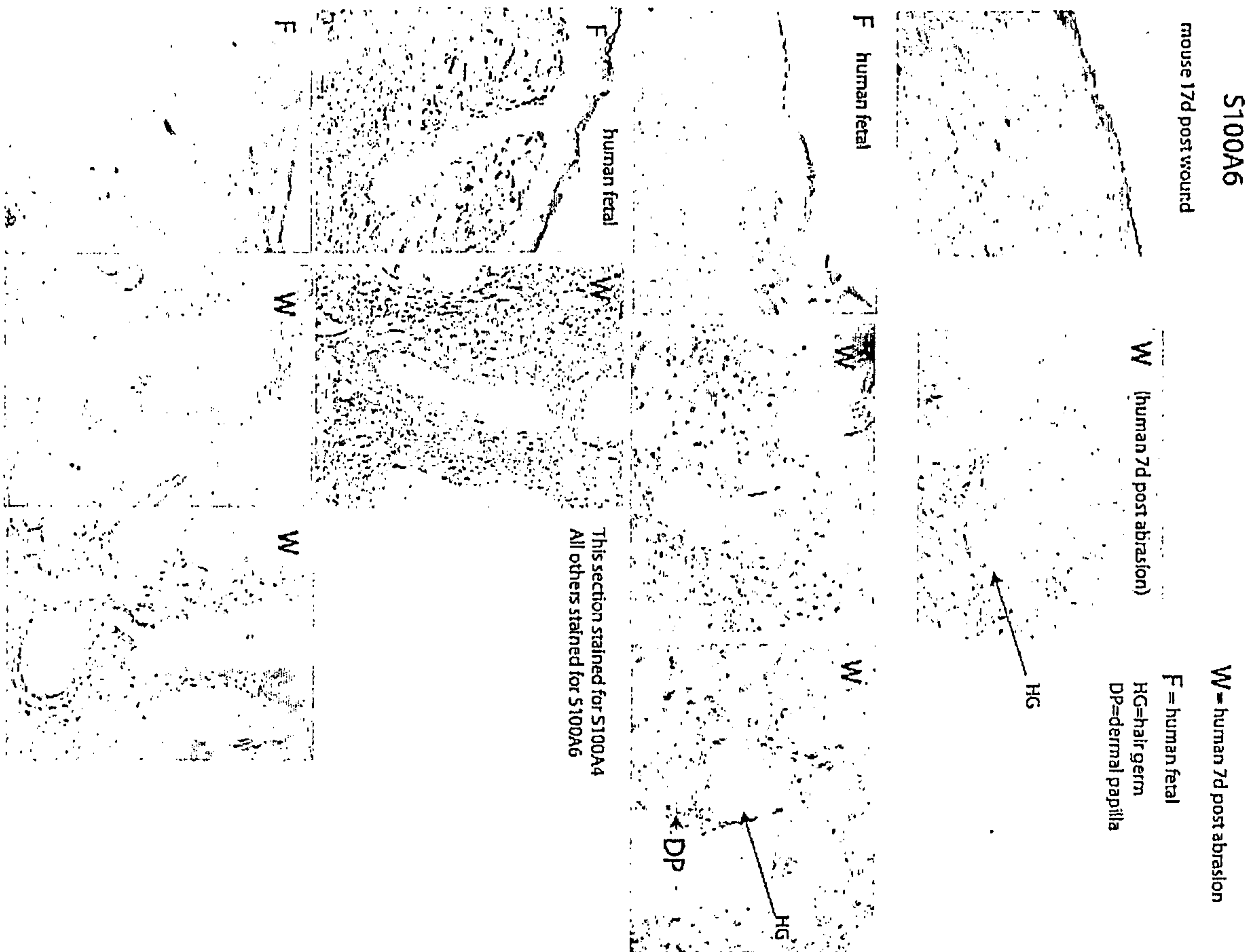


Figure 21B

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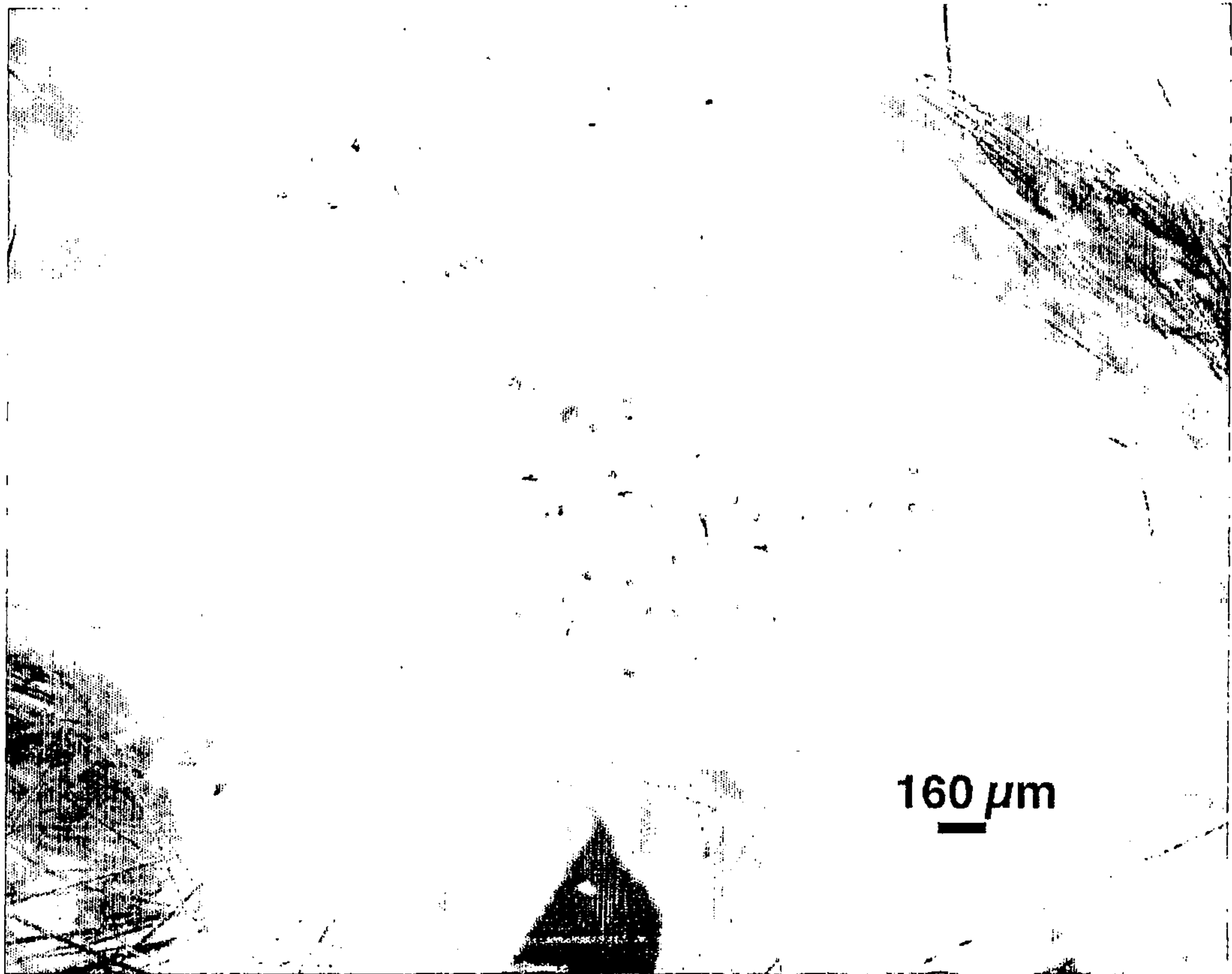


Figure 22A

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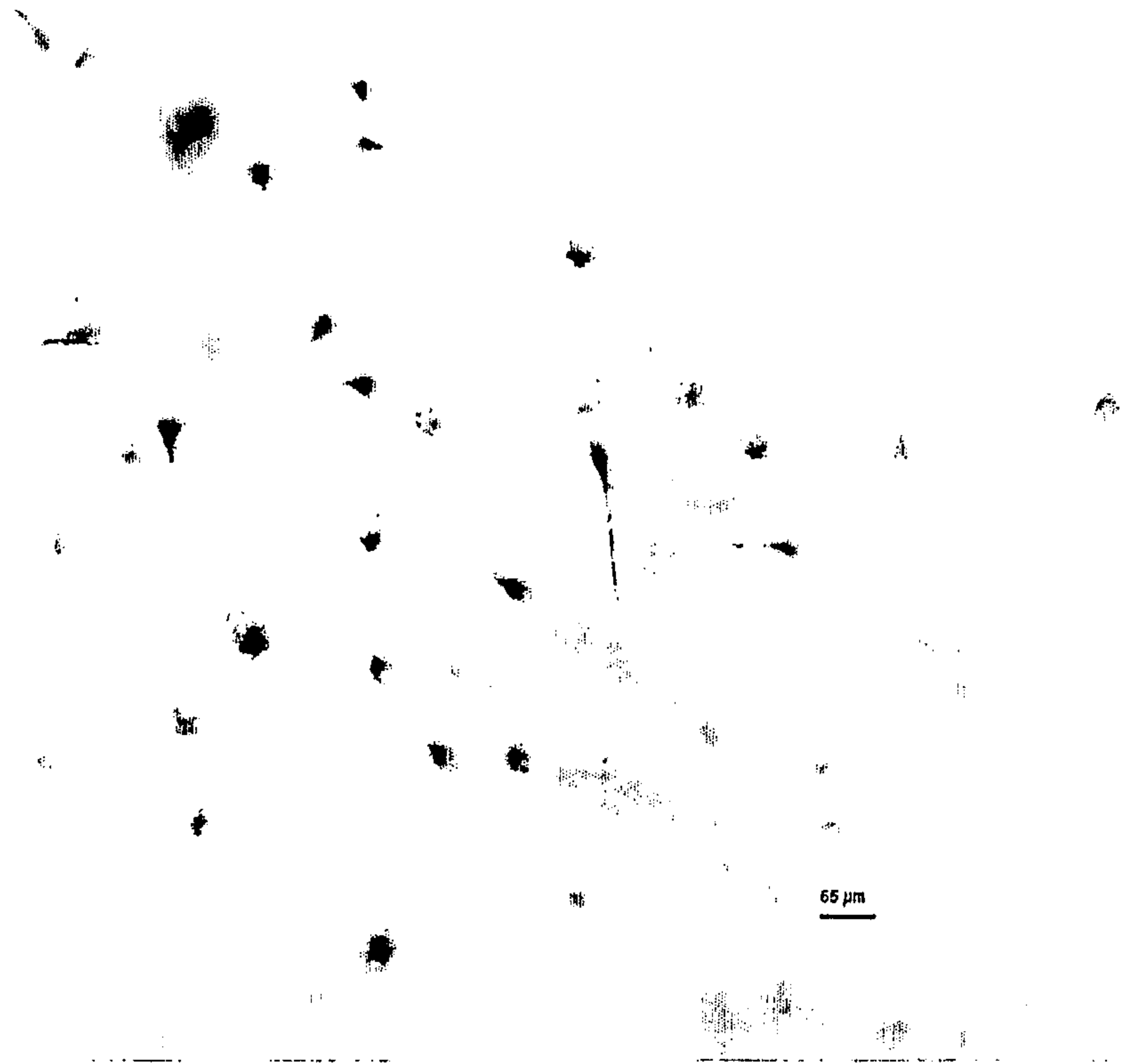


Figure 22B



Figure 23

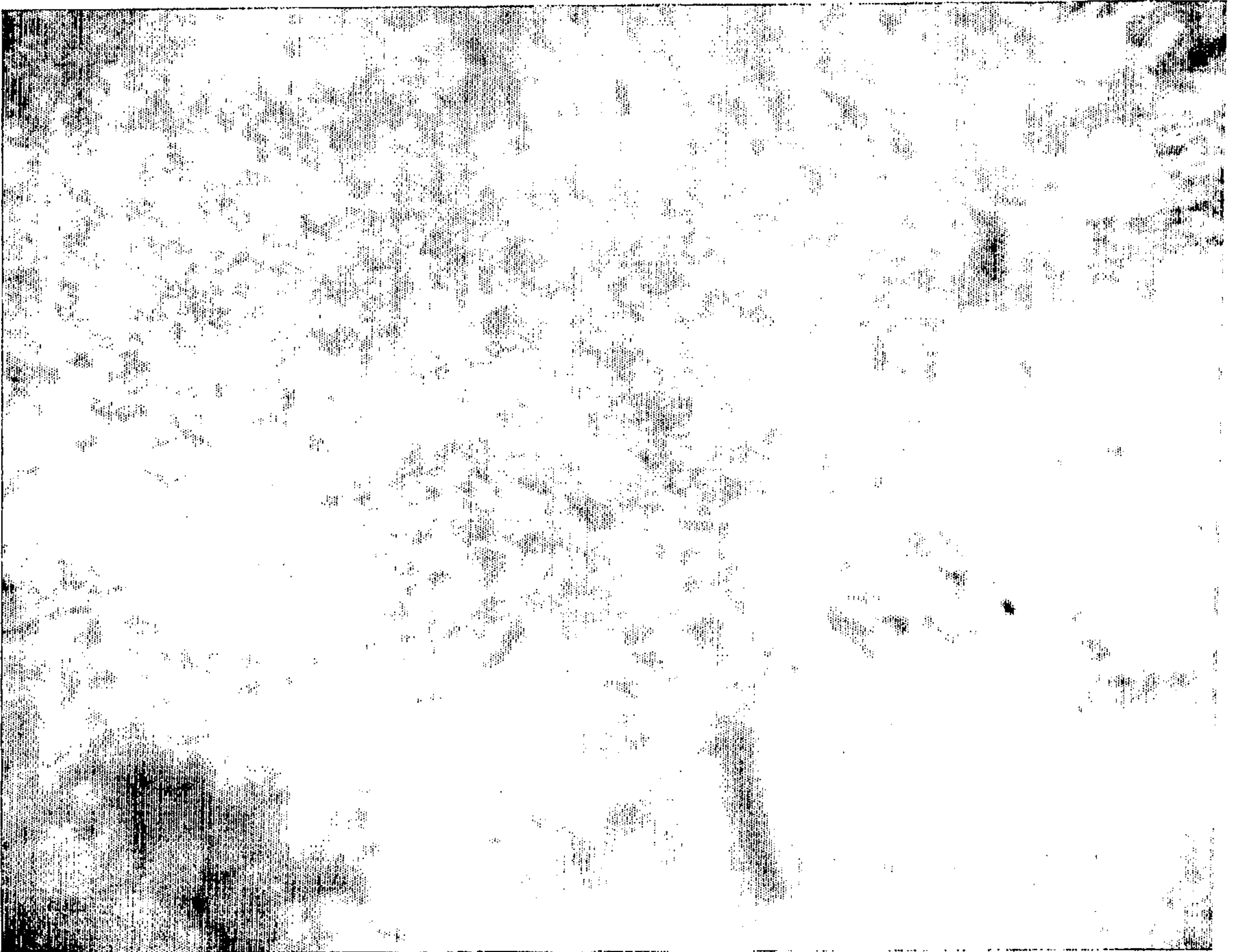


Figure 24A

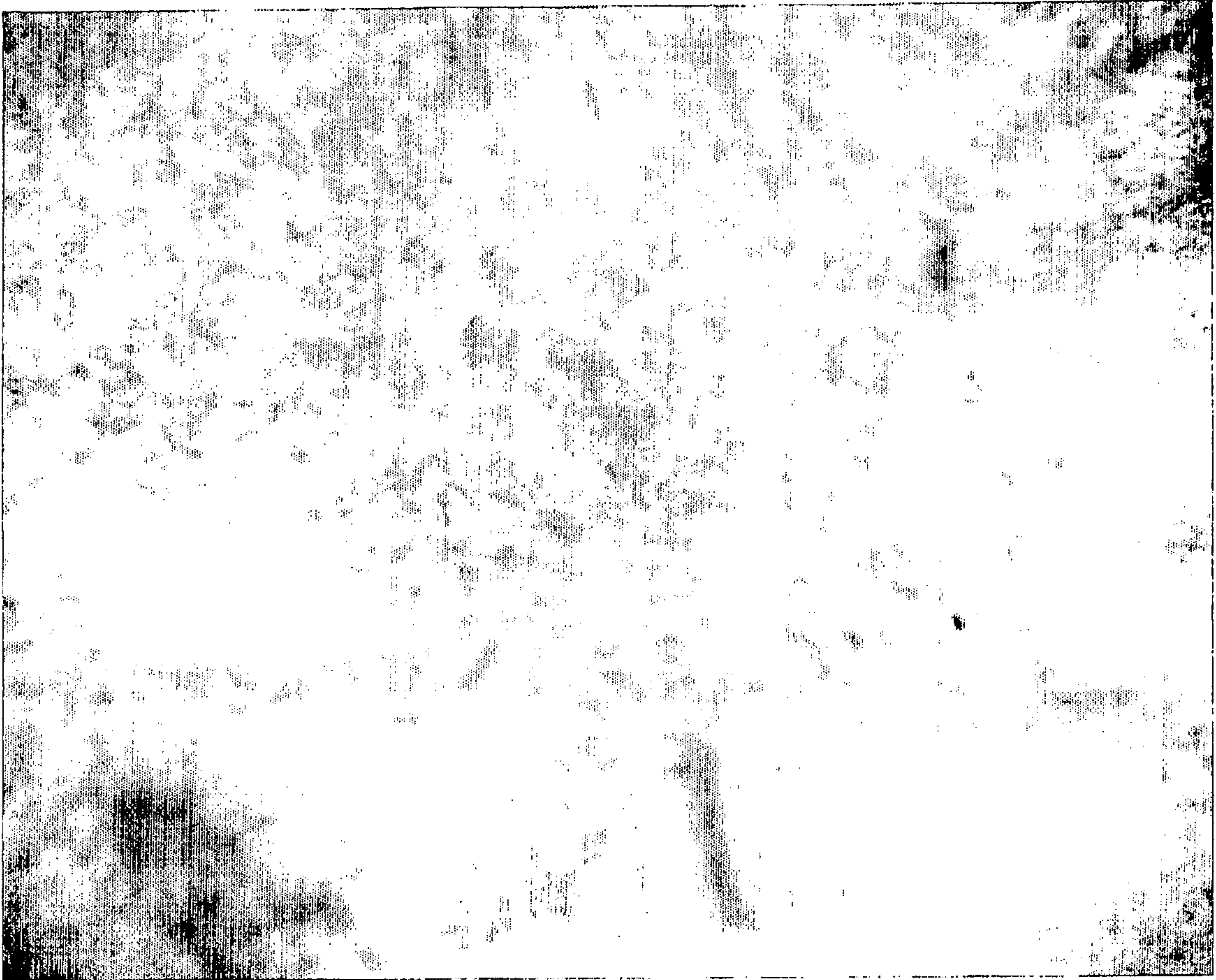


Figure 24B



Figure 24C



Figure 24D

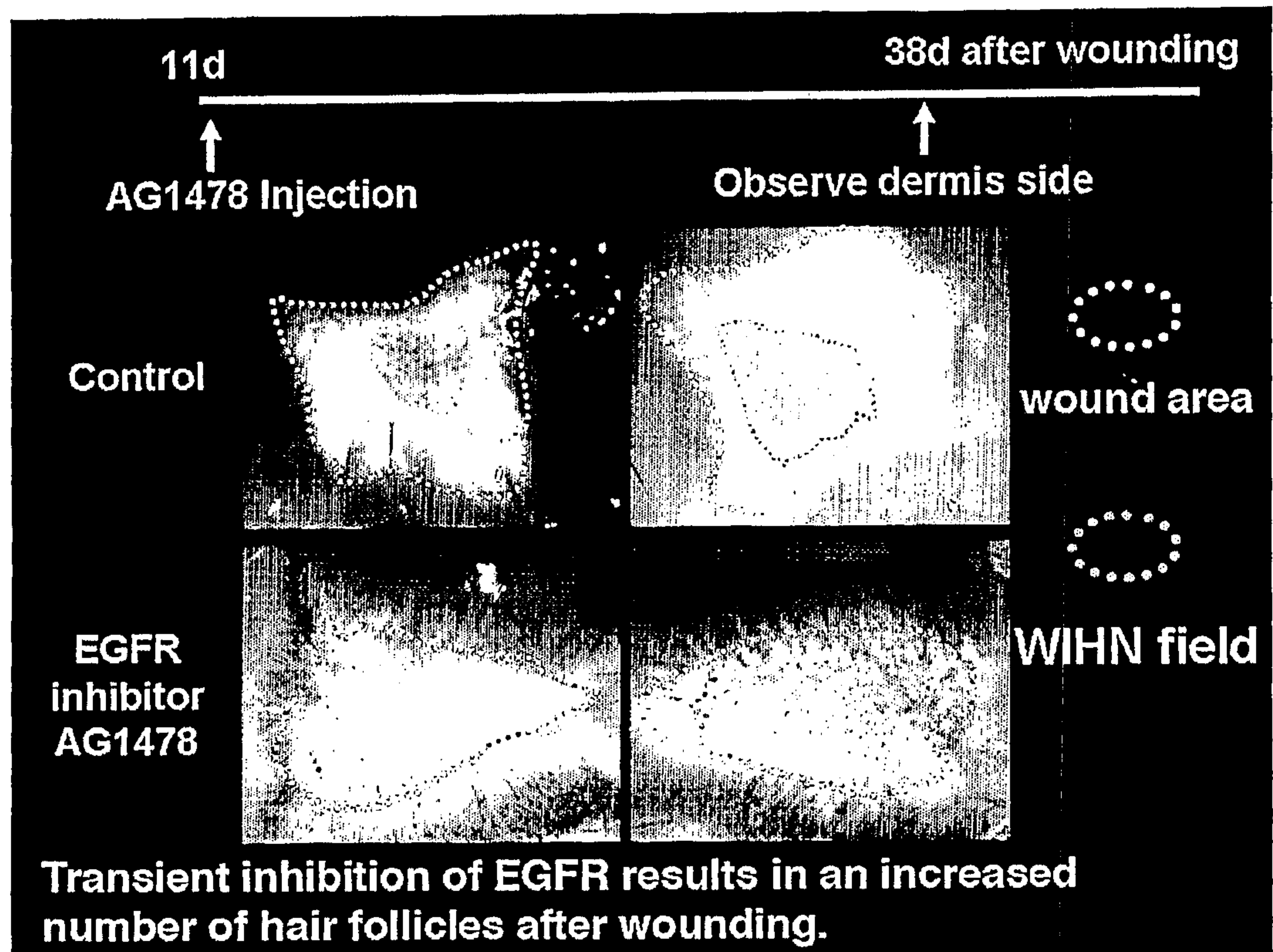


Figure 25A

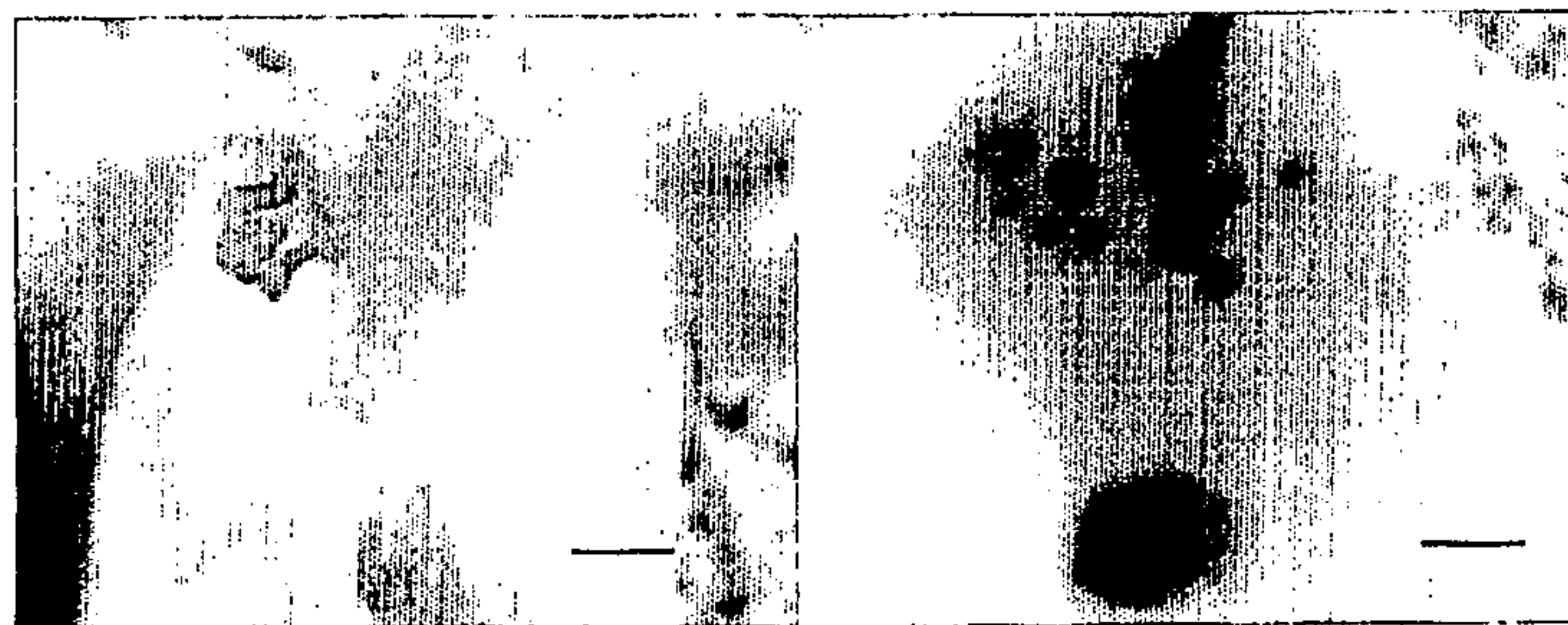


Figure 25B

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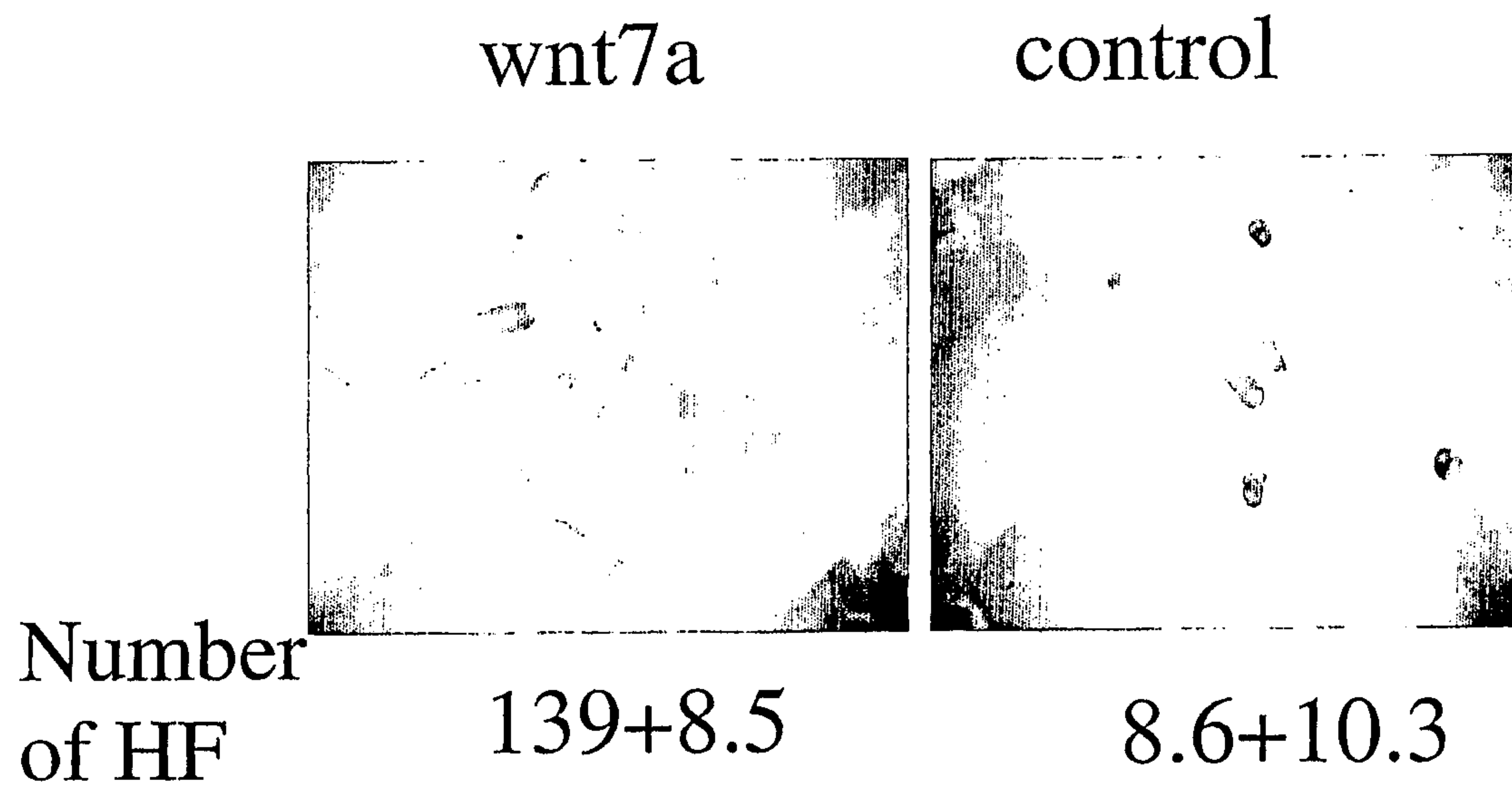


Figure 26A

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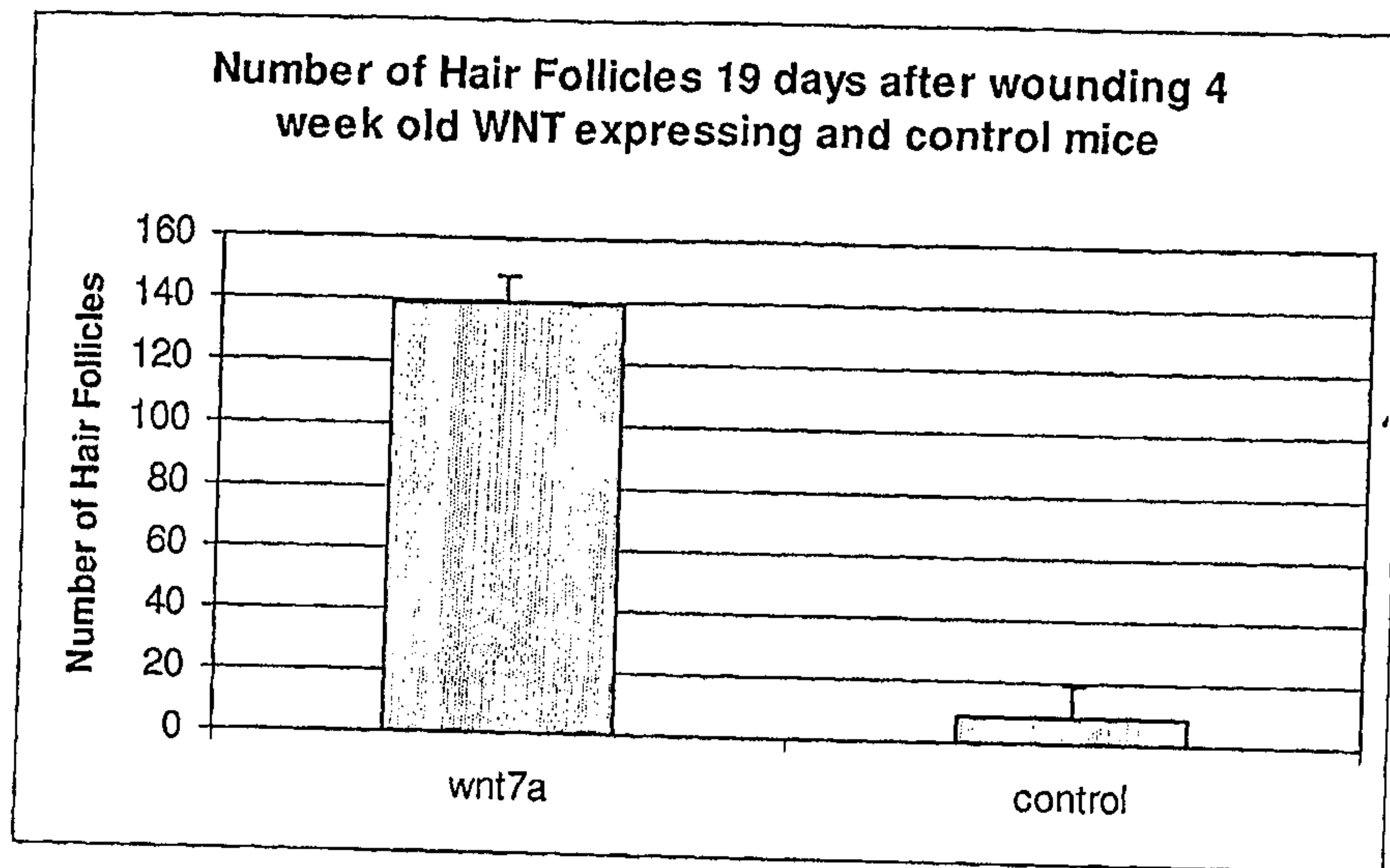


Figure 26B

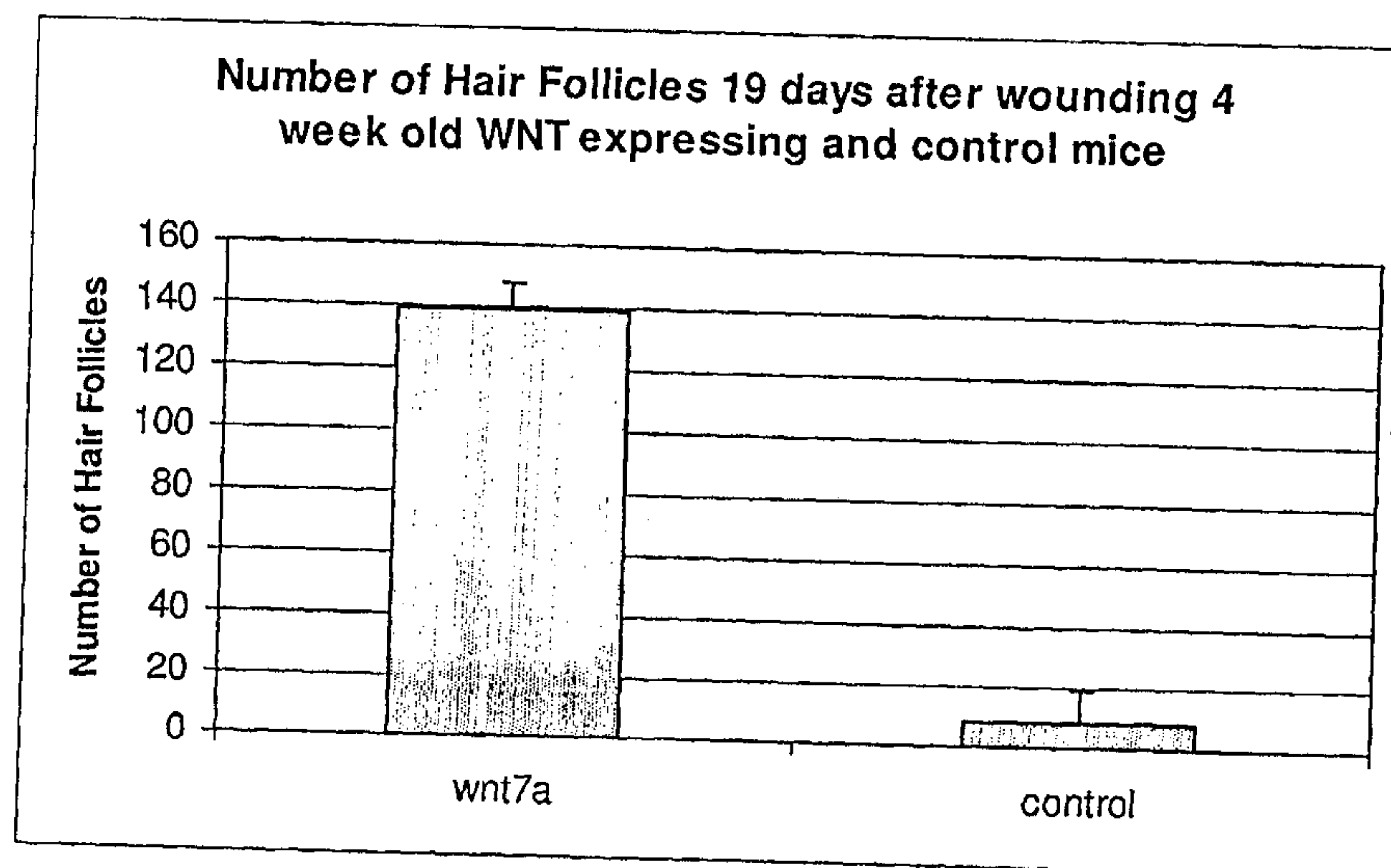


Figure 26C

