

皮毛之道及其應用： 幹細胞, 禿髮, 及演化

Cheng-Ming Chuong, M.D., Ph.D.
鍾正明

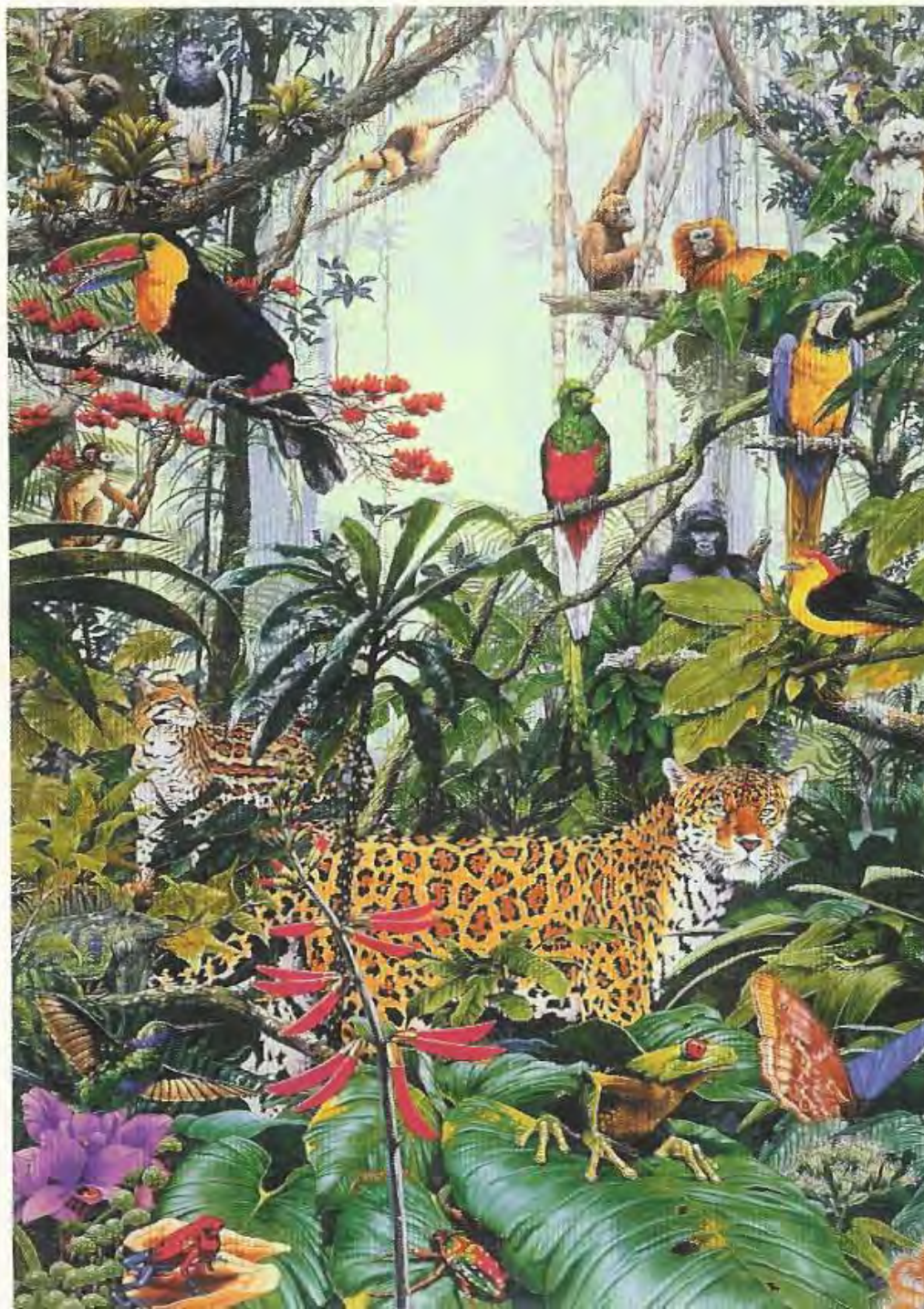
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cmchuong@usc.edu
<http://www-hsc.usc.edu/~cmchuong>*

中央研究院院士
臺灣大學榮譽研究講座教授及
發育與再生醫學研究中心榮譽主任

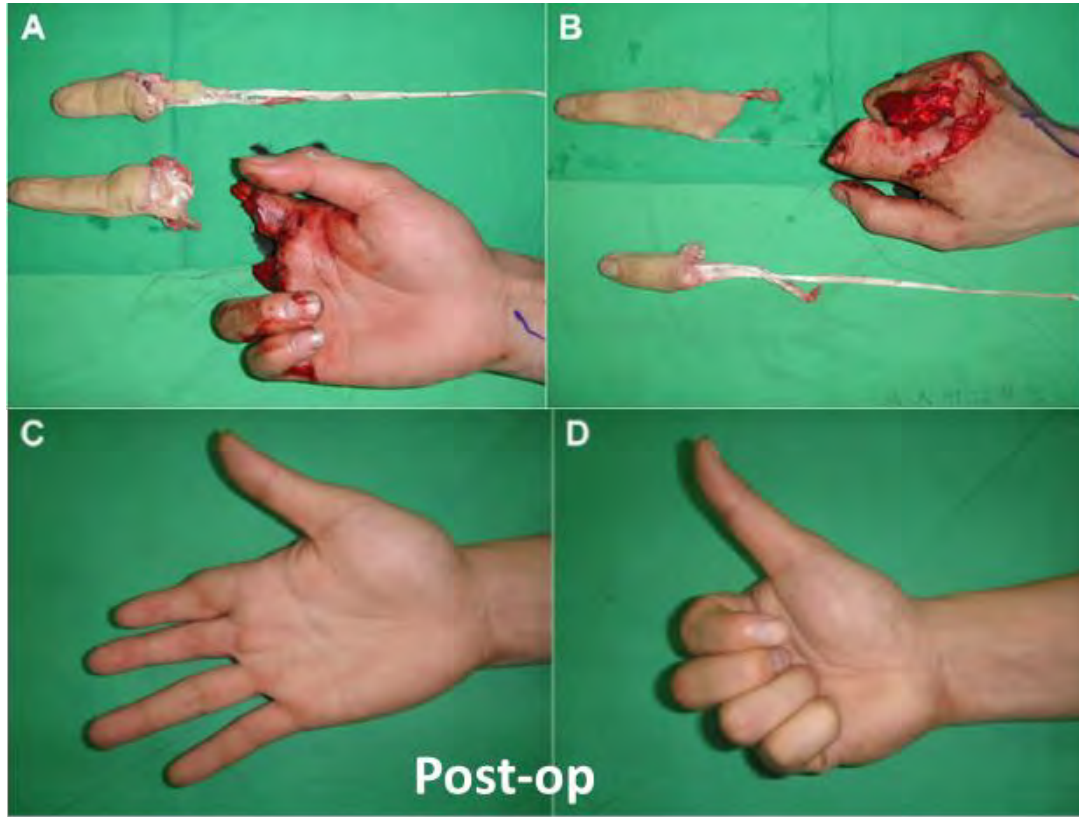
Integumentary organs:

體表器官為個體與
大自然的介面

Interface between
organisms and
environment



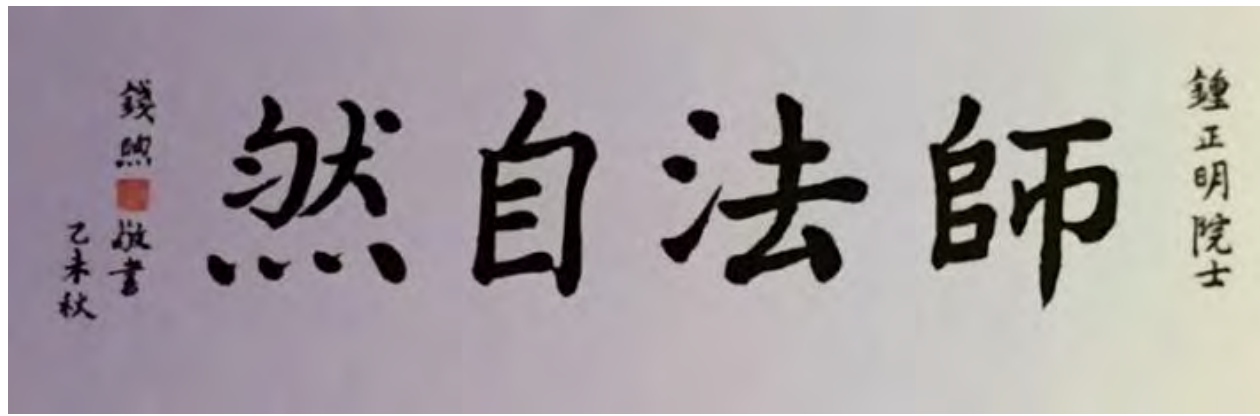
Regeneration versus Repair



If salamander and lizard can regenerate appendages, why human can not?



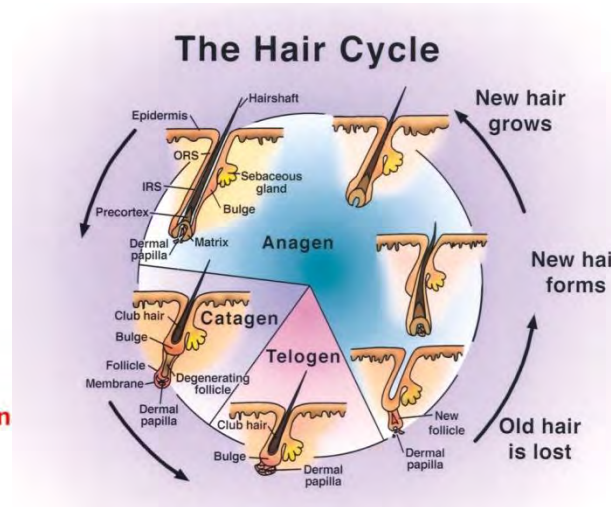
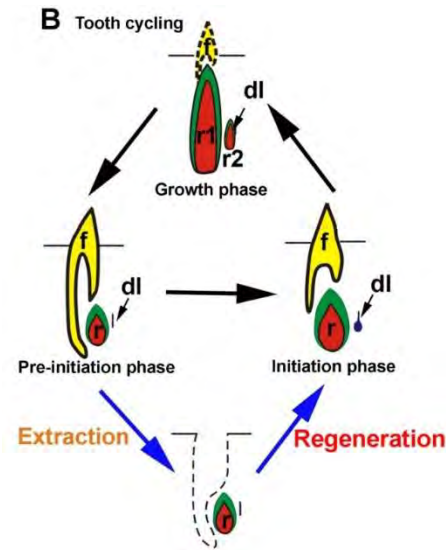
Our approach



1. Can animals regenerate certain organs?
(再生生物學)

2. How do they regenerate?
(再生之道)

3. Can human learn some of this ability and use it in medicine?
(再生醫學)

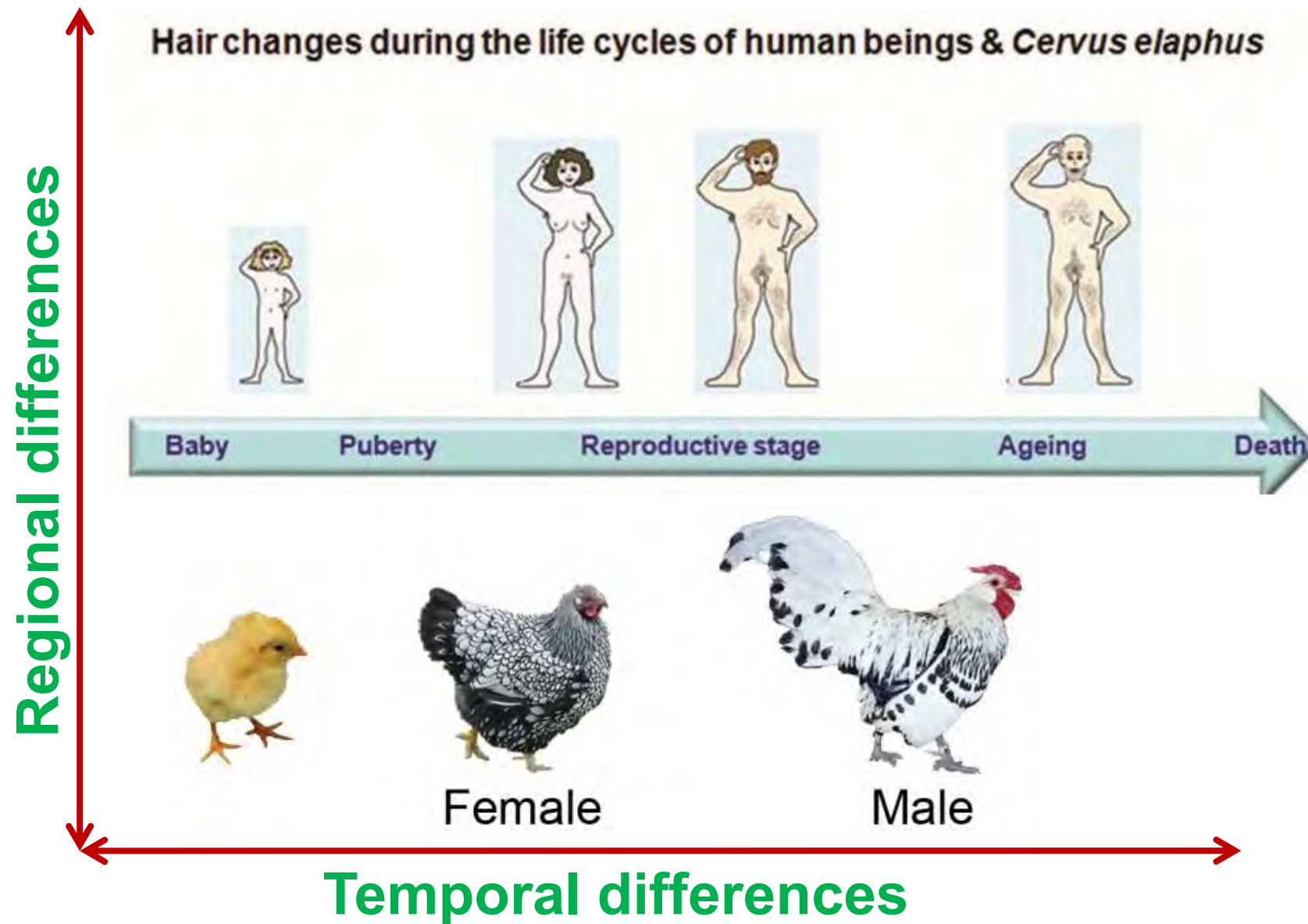




Function of feathers:
endothermy,
flight,
communication

Same follicle
Different feather types

Physiological regeneration

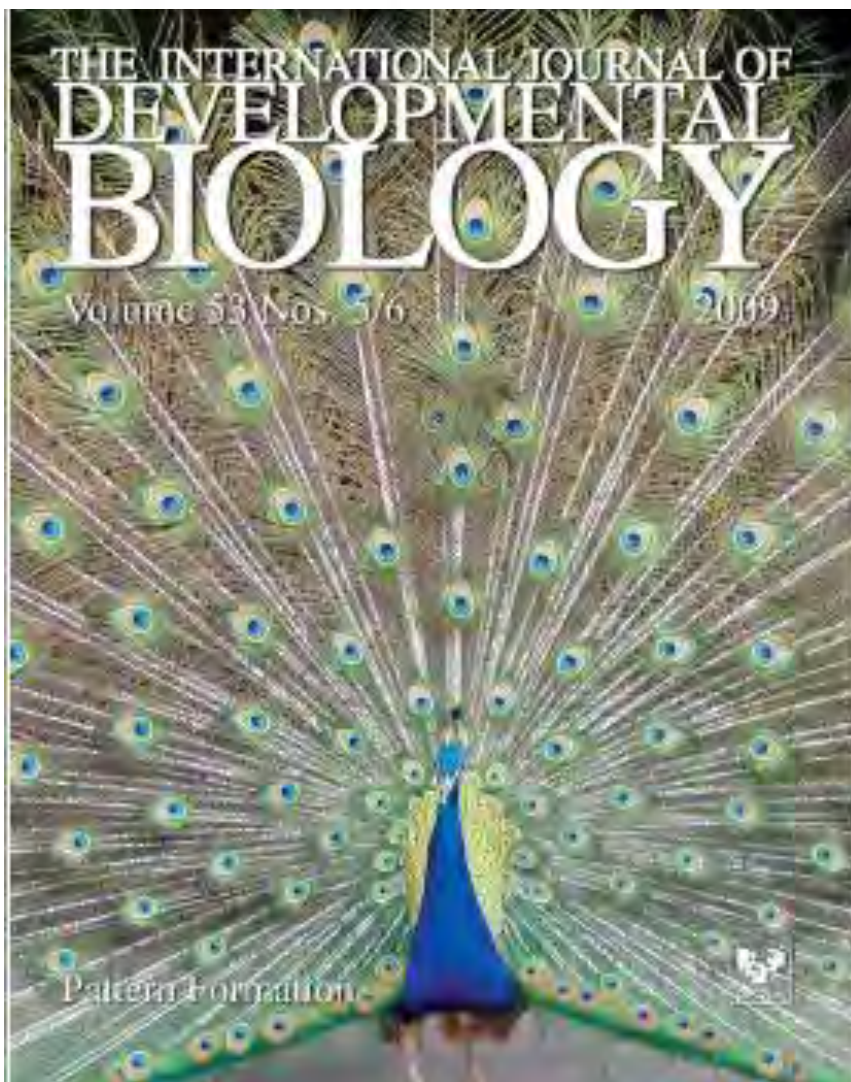


The “*tao*” of integuments

Hair follicle and sweat gland fates can be switched by morphogens at specific skin regions or developmental stages

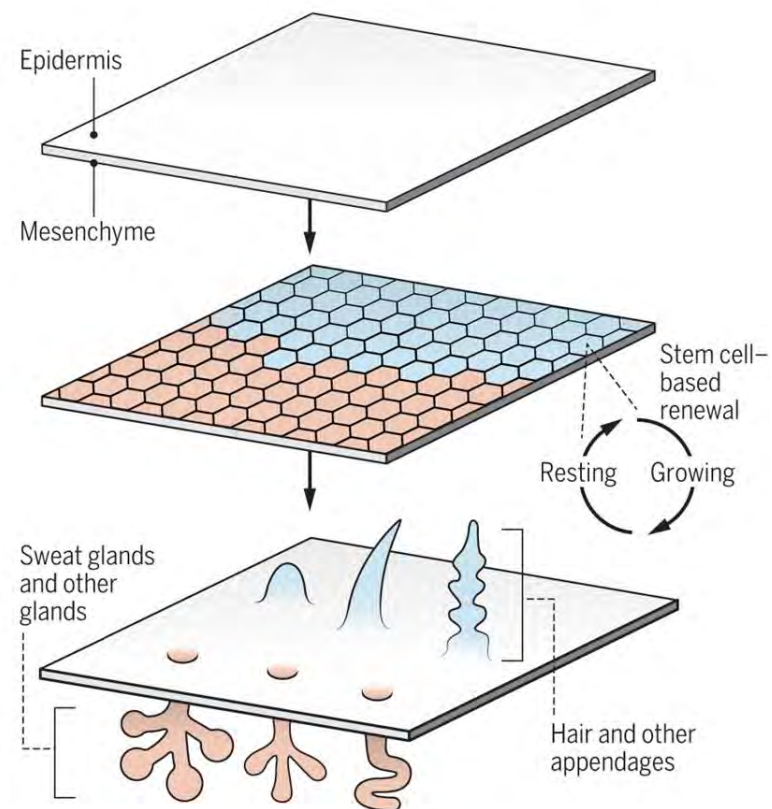
皮毛之道

Lai and Chuong, 2016,
Science



Organizing to adapt

Periodic patterning enables the formation of complex yet adaptable inte



I. Periodic patterning

II. Cyclic Renewal
周而復始

III. Temporal & Spatial diversification
多樣化

IV. In one individual or
in evolving species

STEM CELLS

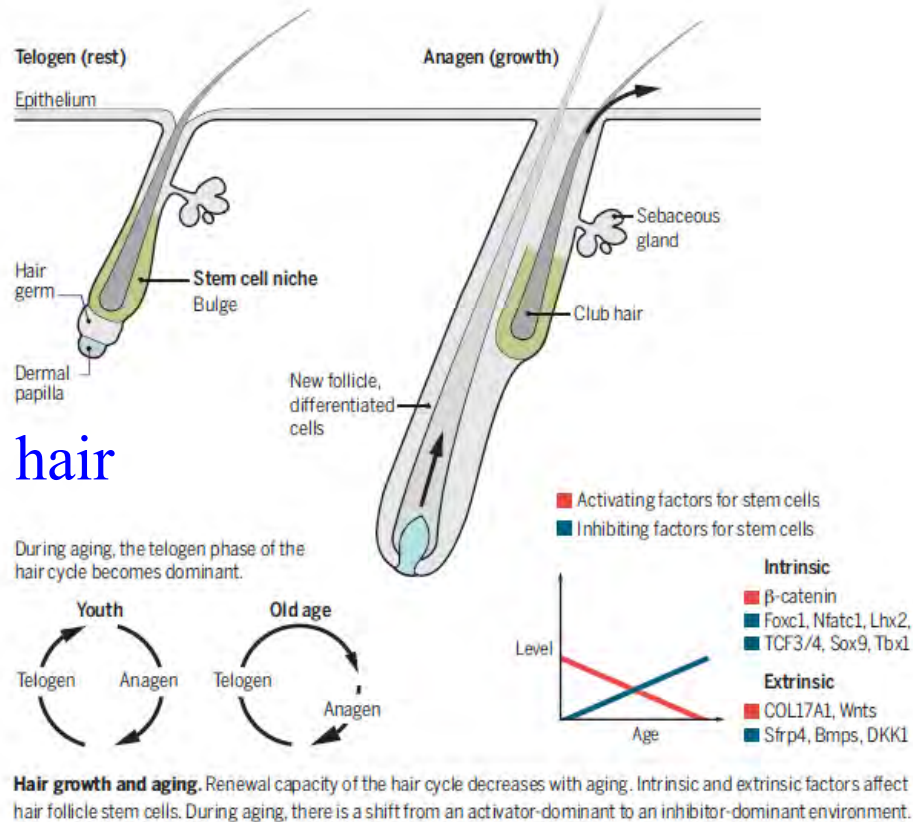
Aging, alopecia, and stem cells

Intrinsic epigenetic status and extrinsic environmental factors affect hair follicle stem cells

Lei and Chuong, 2016,
Science,

南極仙翁 福祿壽圖

INSIGHTS | PERSPECTIVES



The longer the
growth phase,
The longer the hair



Outline

鳥瞰之旅

1. Alopecia

禿髮

2. Evolution (feather, beak)

演化

3. Wound regeneration

幹細胞再生

4. Visual based cognition

對美的認知

I wish I can have more hairs!

Male pattern baldness (雄性禿) is a stem cell disease

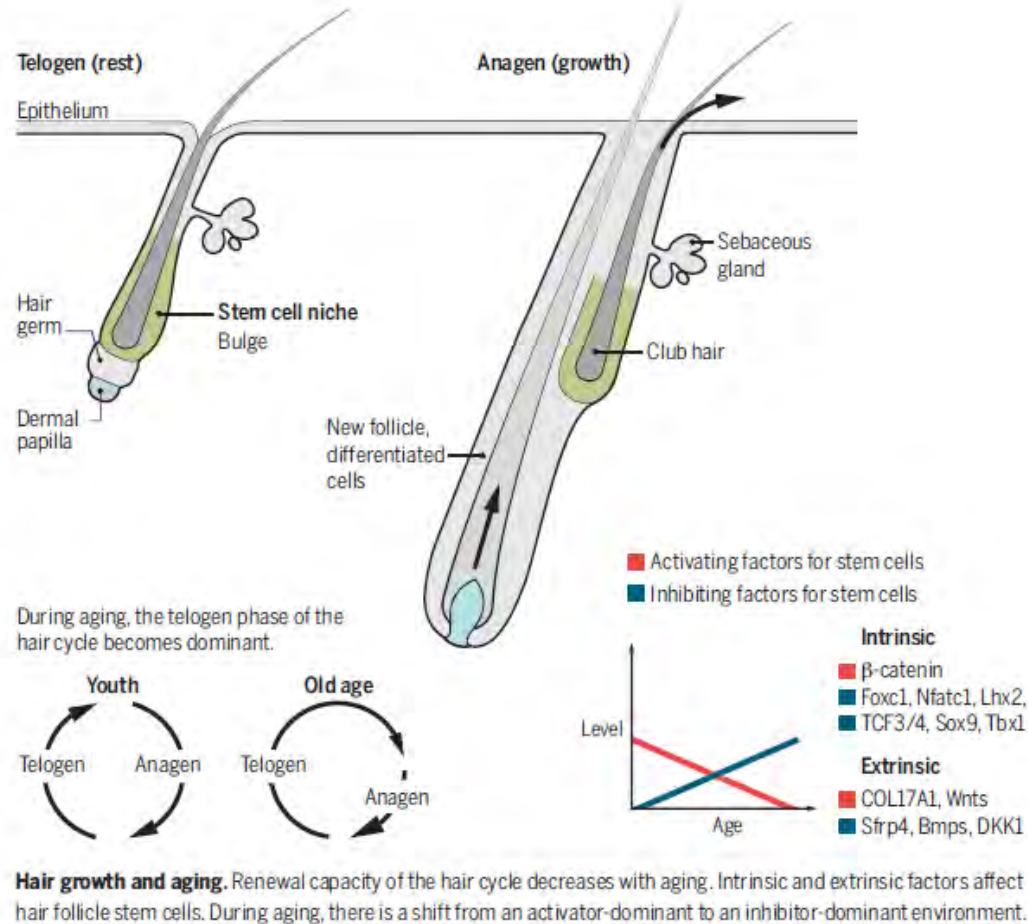


Current treatment:

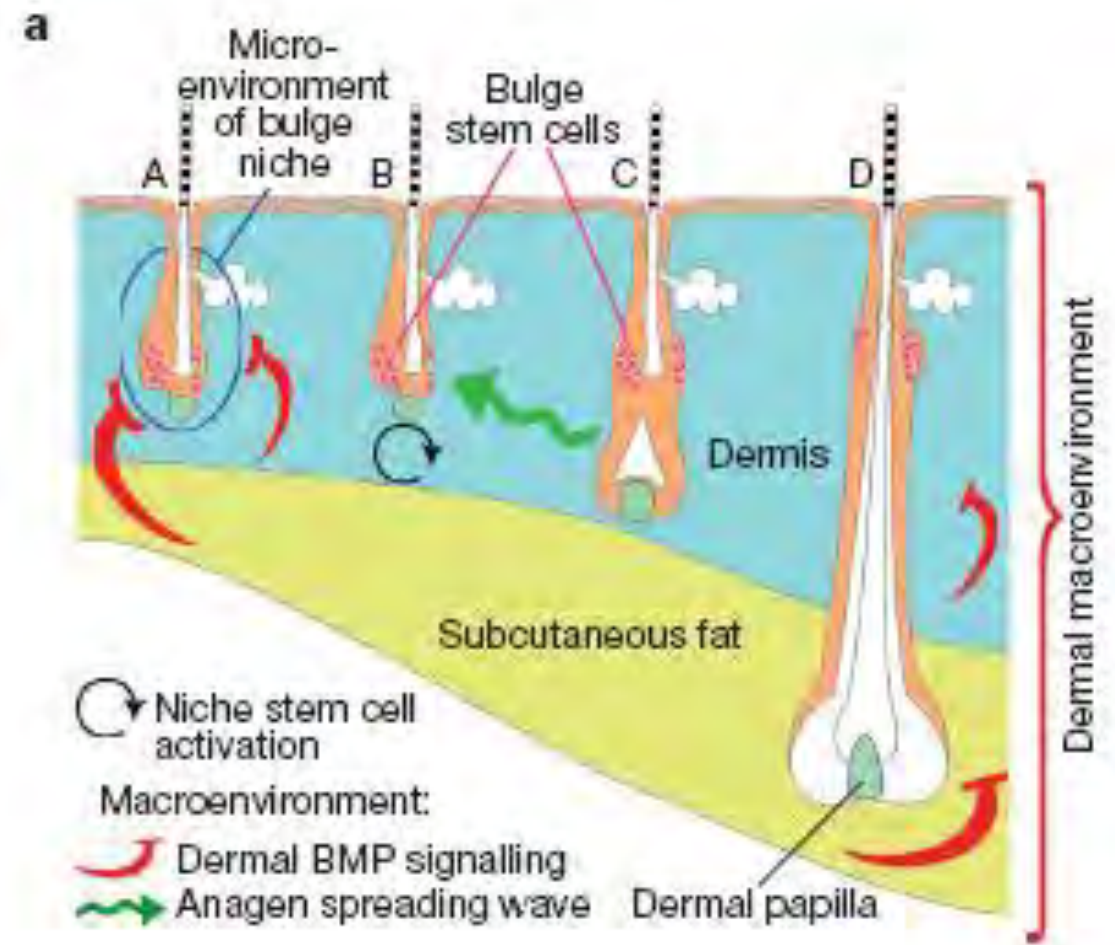
Propecia or Finasteride, prevent testosterone conversion

Rogaine or Minoxidil, vasodilation via K⁺ channel opening

Hair transplantation



Lei and Chuong, 2016,
Aging, Alopecia and Stem Cells, Science, 351:559-

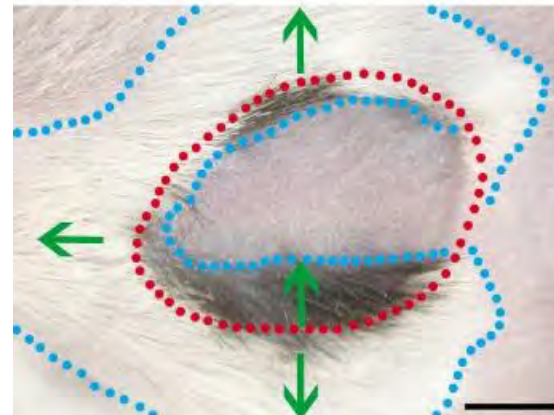
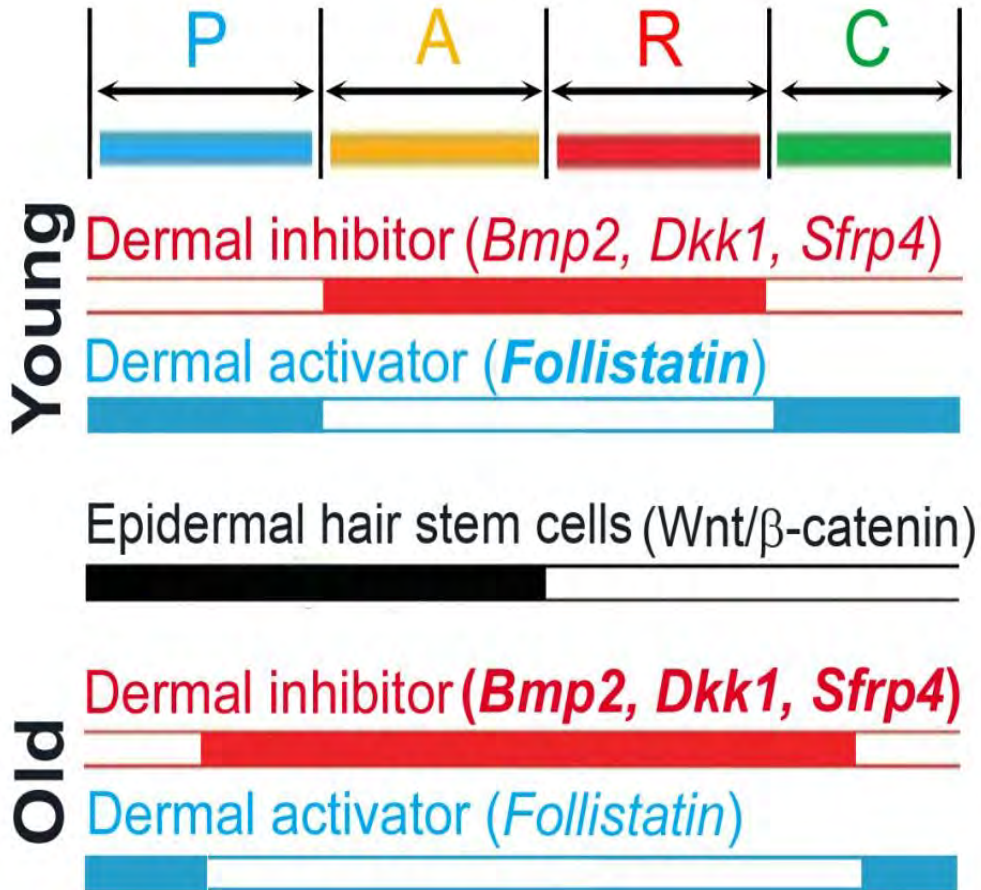


Plikus et al.,
2008, Nature
2011, Science



Aging: Changes of stem cells or local environment?

Old mice show slower regenerative hair wave



陳志強
CC Chen et al., 2014
J Invest Dermatol
Dermatologist,
Taipei VA Hospital

Old mouse hair regeneration can be rescued when the skin is transplanted to young mouse



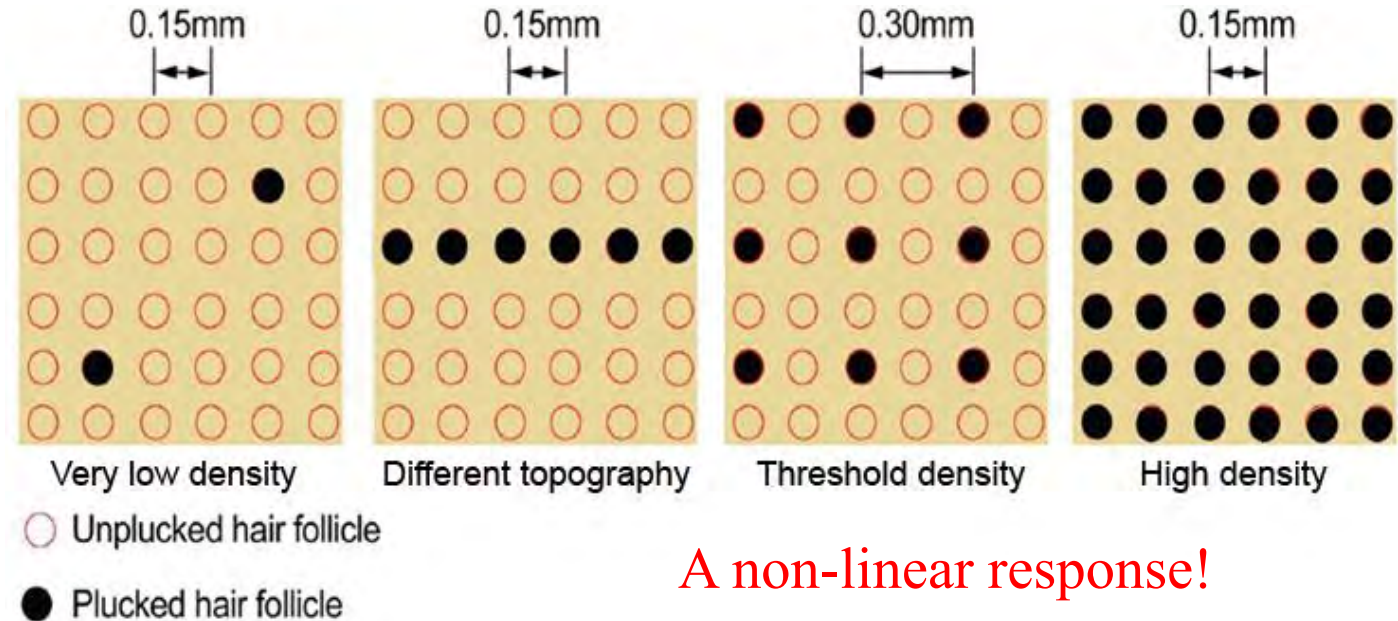
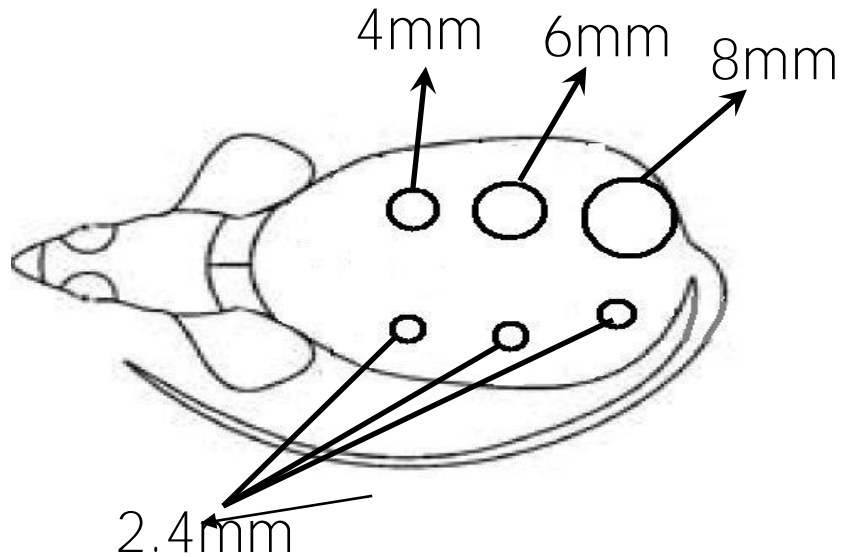
Peacock, LA aboretum, late March



Bison, Yellowstone, winter



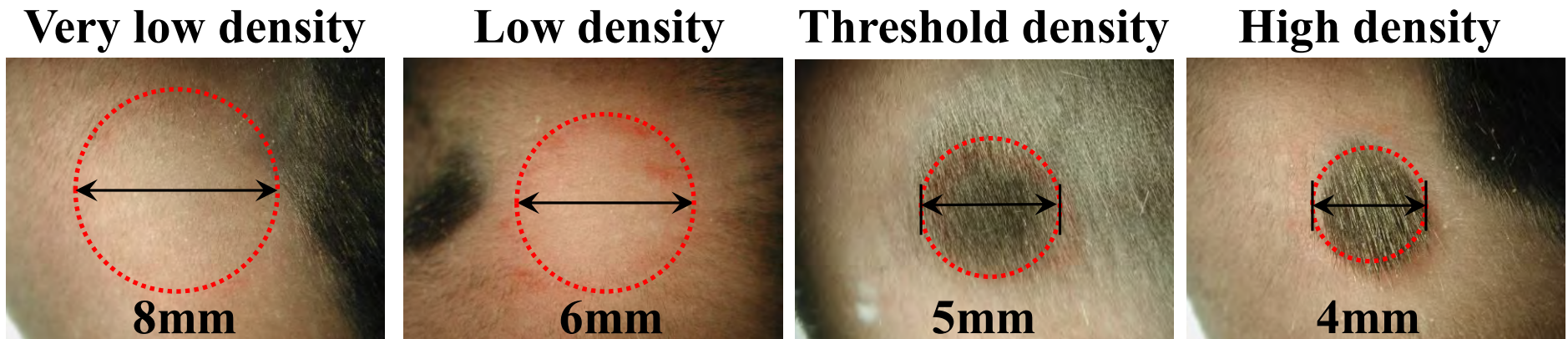
How to pluck 200 hairs and get 1000 hair follicles activated via activation of the extra-follicle **dermal environment**?



A non-linear response!

Chen et al.
2015 Cell

Quorum Sensing
dictates
organ regeneration



Organ-level quorum sensing (群體感應)

directs regeneration in
hair stem cell populations

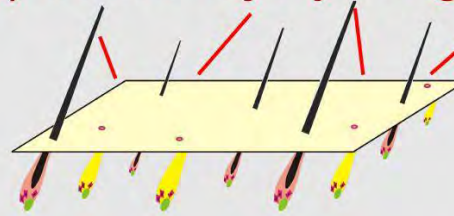
Immune environment
conducive for regeneration

Two step process:
cytokine
macrophage

Chen et al, 2015, CELL

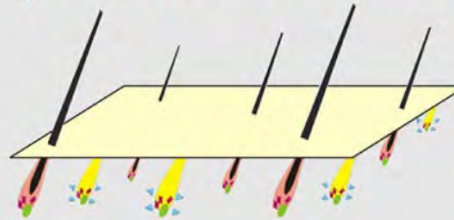
Song Tao Shi, MSC immunology, U Penn
Arthur Lander, Systems Bio Ctr, UC Irvine

(i) Micro-injury stage



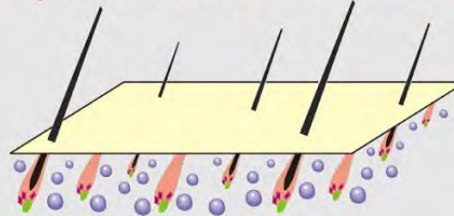
Plucking induces apoptosis
of hair keratinocytes

(ii) Distressor release stage



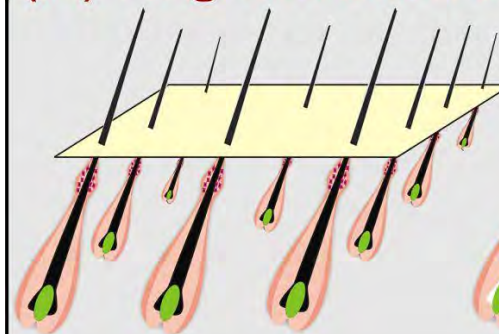
Plucked follicles secrete CCL2
that recruits macrophages
to the whole plucked region

(iii) Quorum sensing stage



TNF- α activates regeneration of
all hair follicles in the region,
plucked or not

(iv) Regeneration stage



Secondary hair growth-propagation
signal induces more hair regeneration
beyond the plucked region

Stem cells CCL2 TNF- α positive macrophages

Anagen follicles Telogen follicles Apoptotic follicles

Outline

- | | |
|-------------------------------------|-------|
| 1. Alopecia | 禿髮 |
| 2. <u>Evolution (feather, beak)</u> | 演化 |
| 3. Wound regeneration | 幹細胞再生 |
| 4. Visual based cognition | 對美的認知 |

Variation:

Single element

**Population of
elements**

**Rosetta stone to
decipher
the language of
morphogenesis**



BREAKTHROUGH OF THE YEAR (2014) : The Birth of Birds

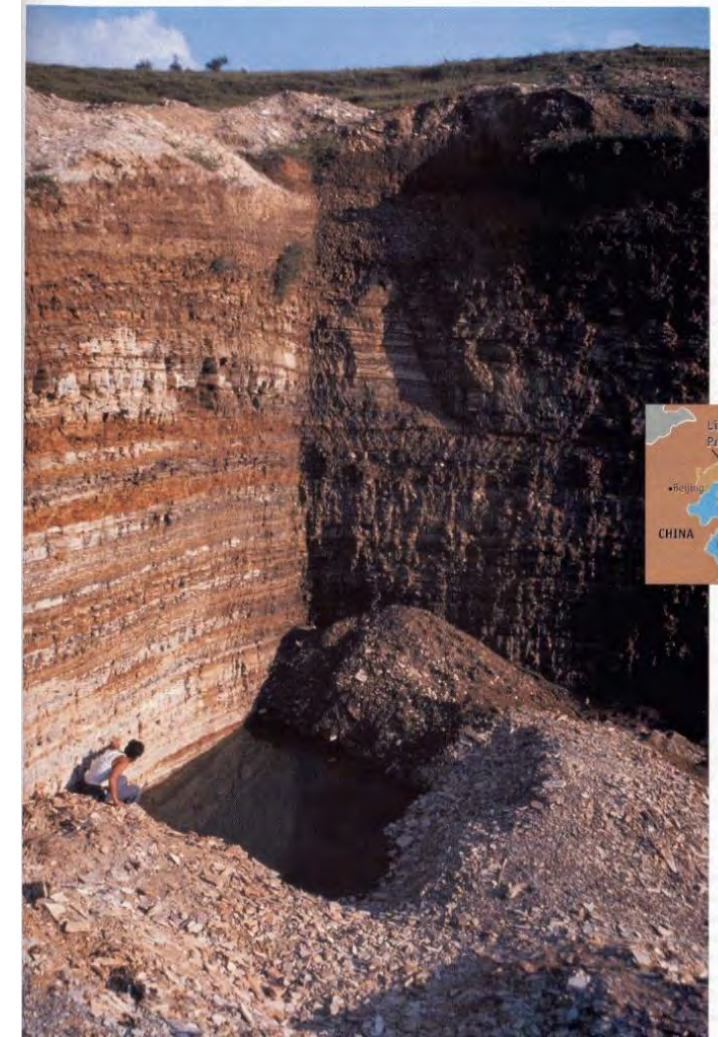
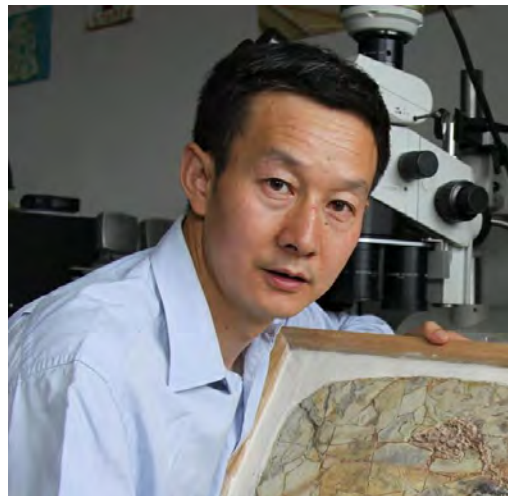
REVIEW SUMMARY

Science 2014

AVIAN EVOLUTION

An integrative approach to understanding bird origins

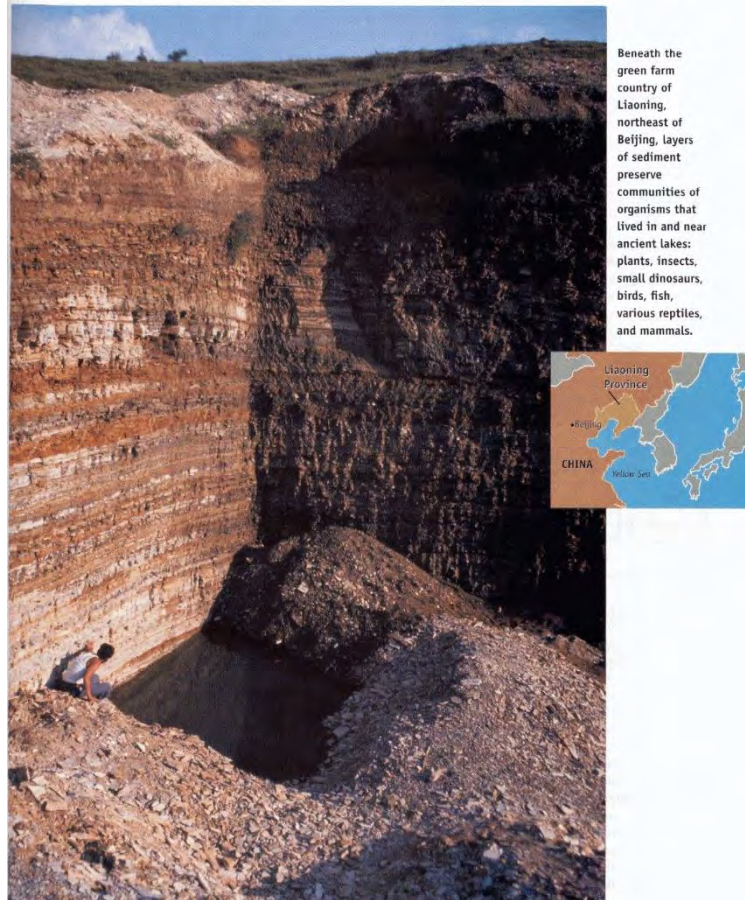
Xing Xu, Zhonghe Zhou, Robert Dudley, Susan Mackem, Cheng-Ming Chuong, Gregory M. Erickson, David J. Varricchio



Beneath the green farm country of Liaoning, northeast of Beijing, layers of sediment preserve communities of organisms that lived in and near ancient lakes: plants, insects, small dinosaurs, birds, fish, various reptiles, and mammals.



Jehol Biota,
~ 120-130 million years ago

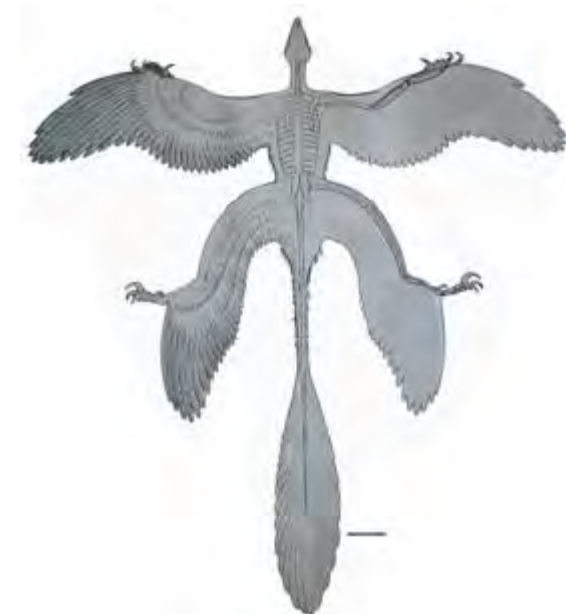
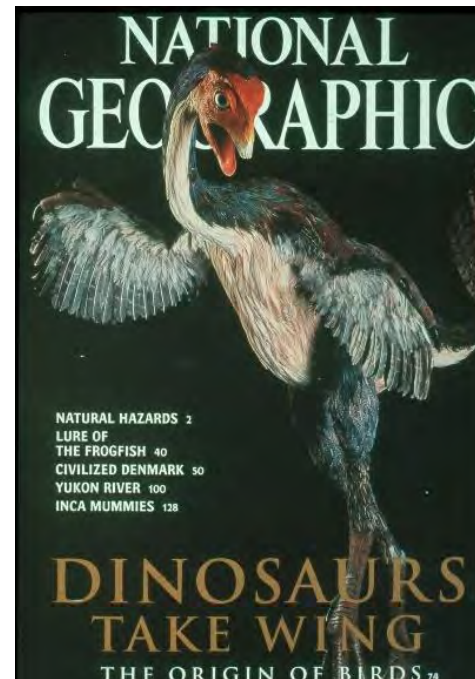


Jehol Biota, ~ 120-130 million years ago

Sinosauropteryx
(one kind of theropod)

Caudipteryx

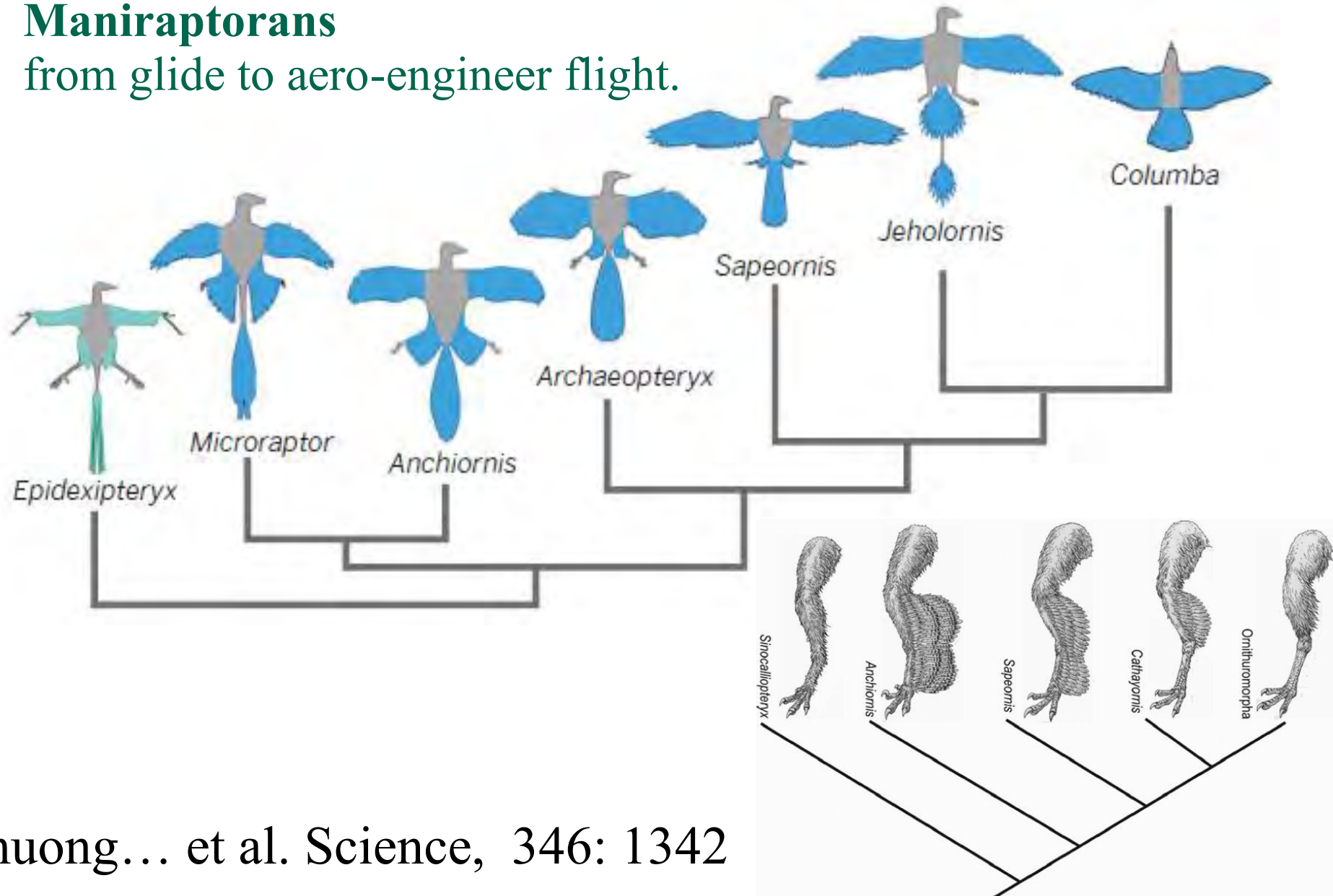
4-winged dinosaurs
(microraptor)



Evolution of Flights

Maniraptorans

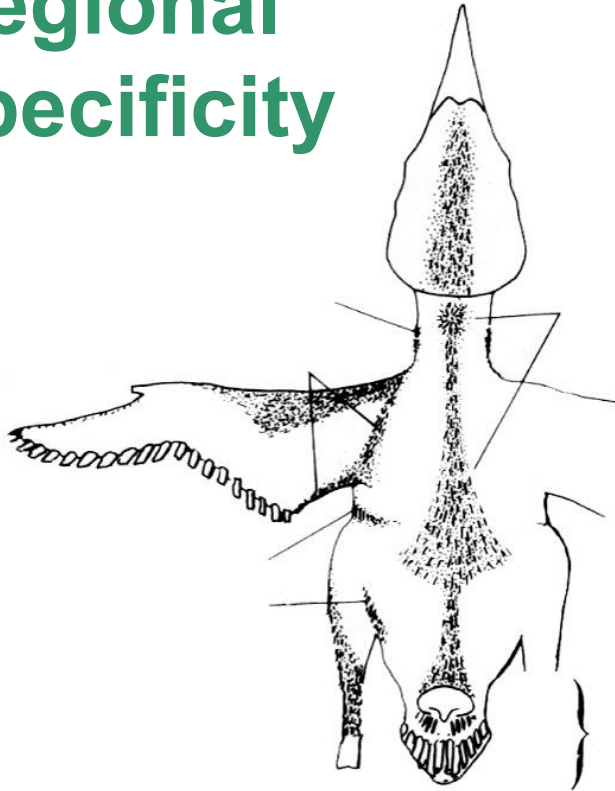
from glide to aero-engineer flight.



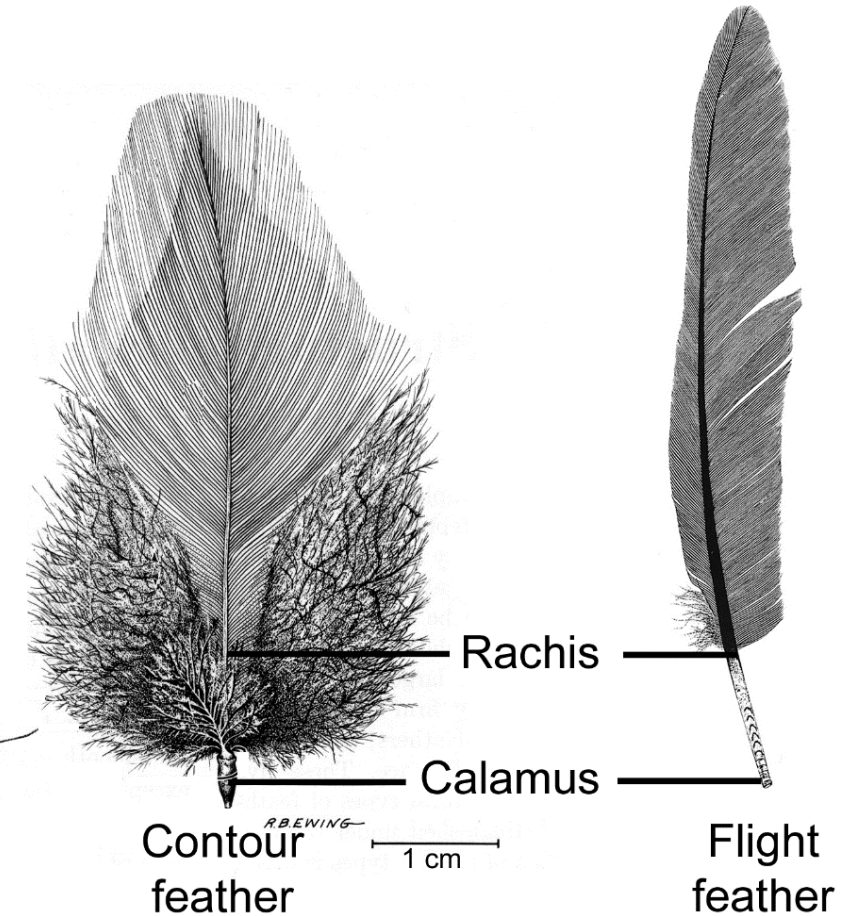
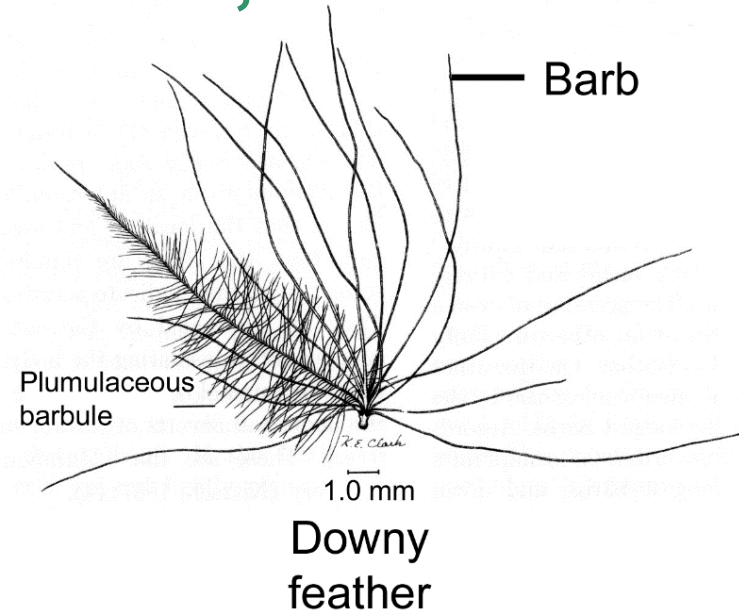
Xu, ... Chuong... et al. Science, 346: 1342

Feather shapes differ in different tracts

Regional
specificity



Shape,
Color,
Texture,

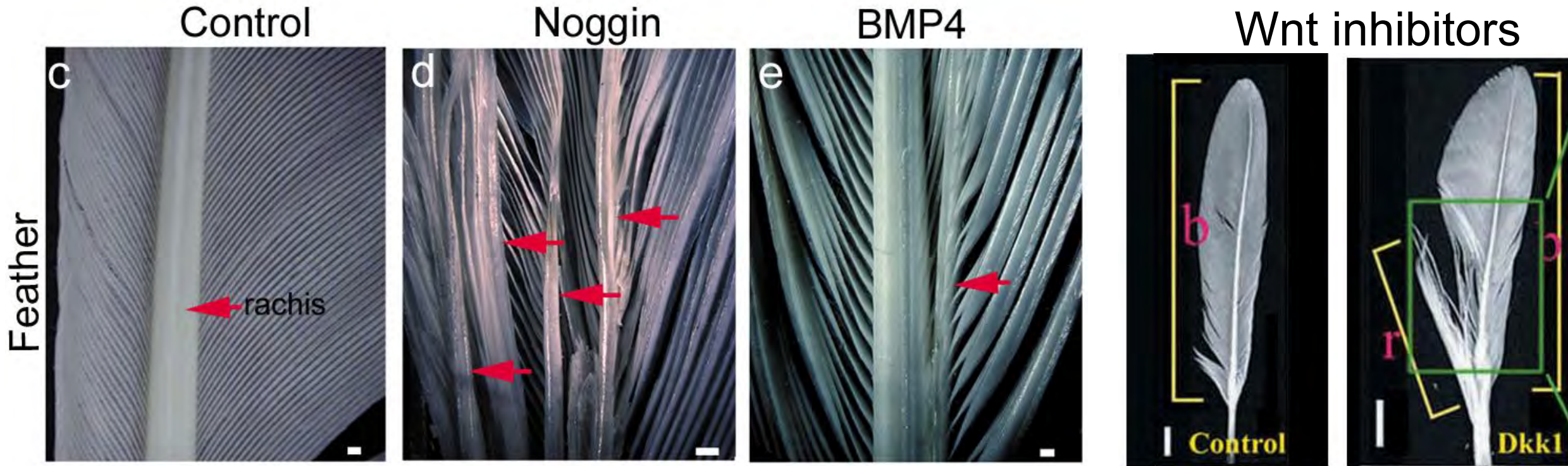


Yu et al., 2002. *Nature*
Yue et al., 2005, *Nature*,
Yue et al., 2006, *PNAS*,

Radial symmetry; Bilateral symmetry, Asymmetry

Chuong ...M Bissell, 2014, *Cell*
Li et al., 2017, *Nature Communication*

Examples of feather form perturbation via virus mediated gene mis-expression



Patterning branches

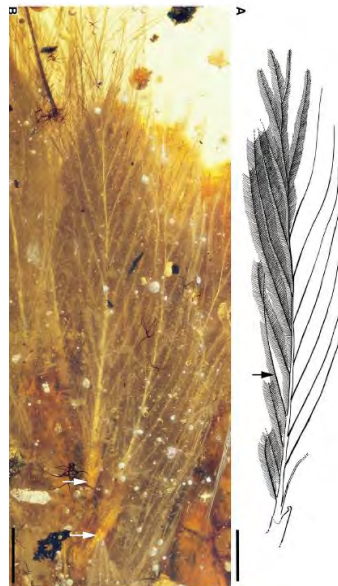
Bilateral vs
Radial symmetry

Stepwise Evolution of Feathers

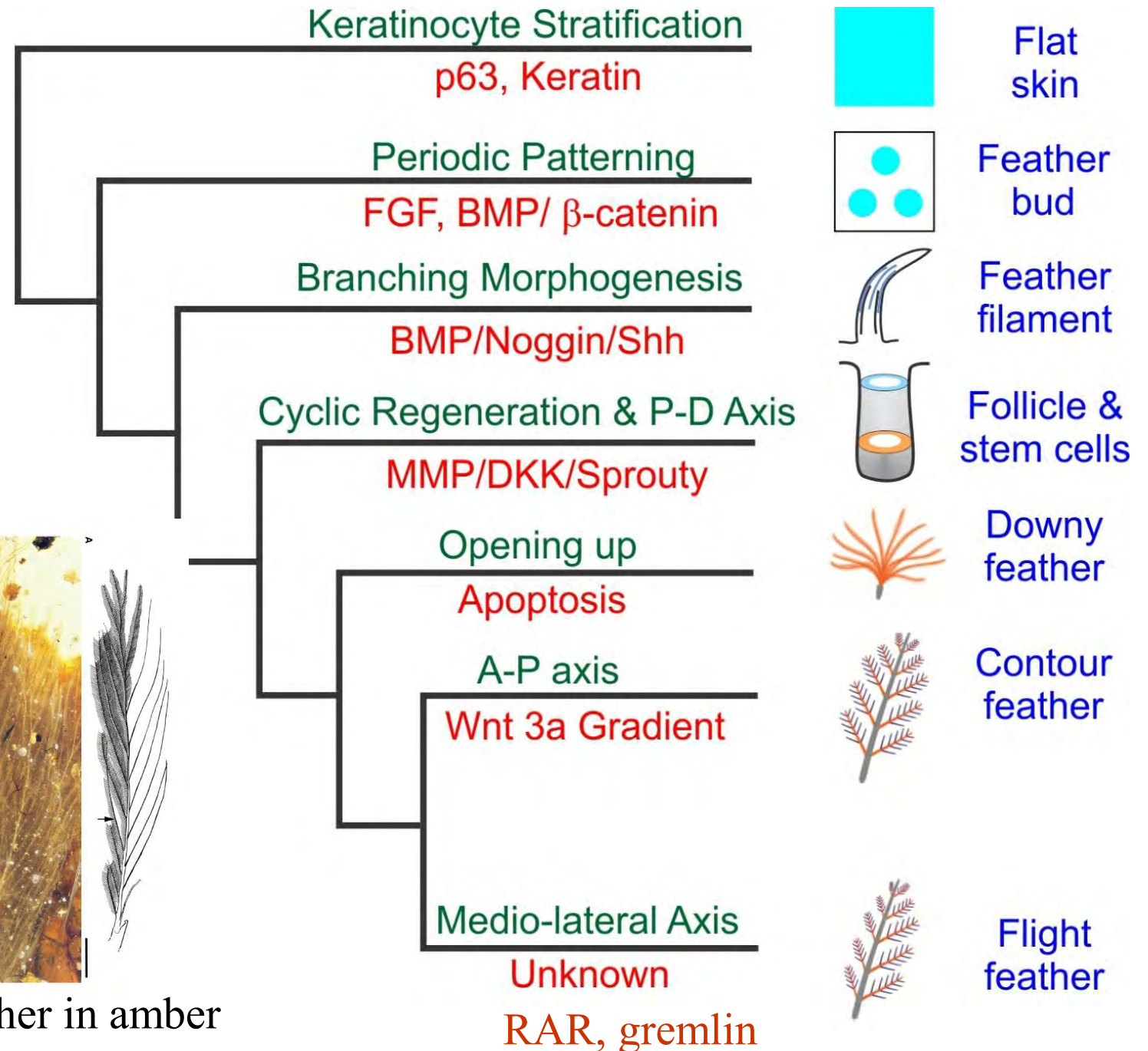
Function of feathers:
Endothermy,
Flight,
Communication

The Origin of Birds

Xu ... Chuong.... Science 2014



Feather in amber

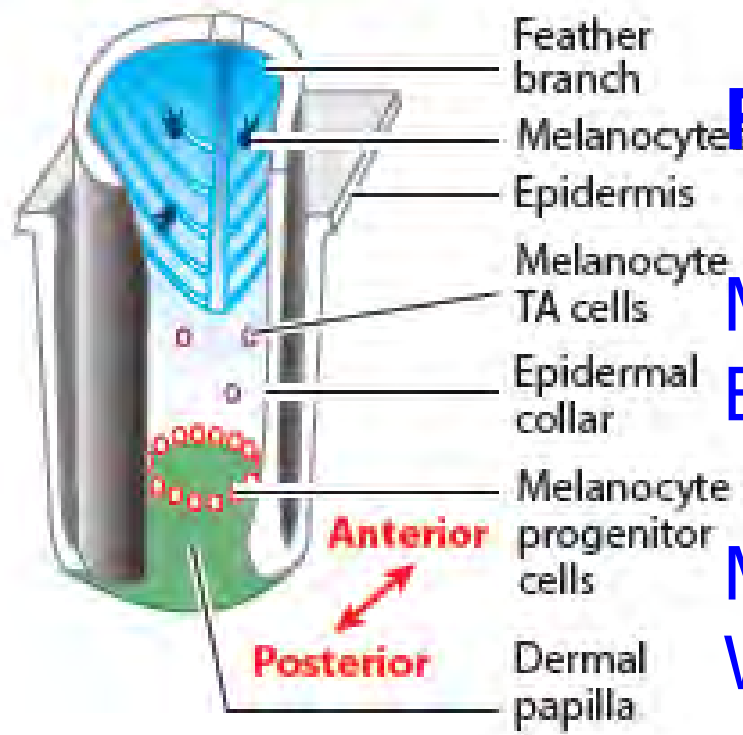


Topology of feather melanocyte progenitors niche allows complex pigment patterns to emerge

a



Growing phase



- Feather branch
- Melanocyte
- Epidermis
- Melanocyte TA cells
- Epidermal collar
- Melanocyte progenitor cells
- Dermal papilla

Anterior
Posterior

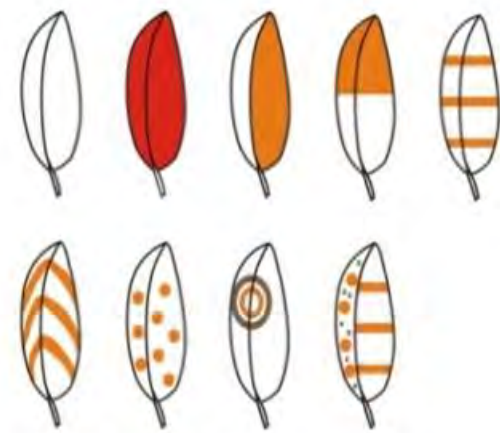
Feather Color

Macropattern

Body regions

Micropattern

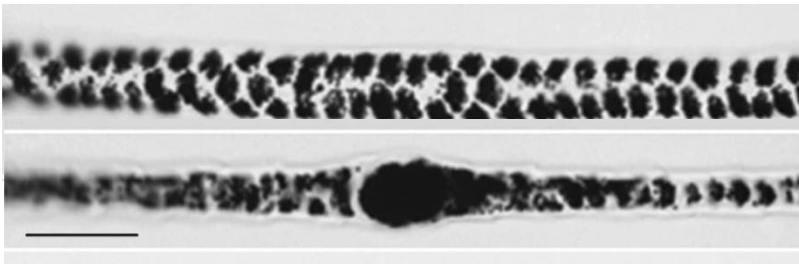
Within-feather



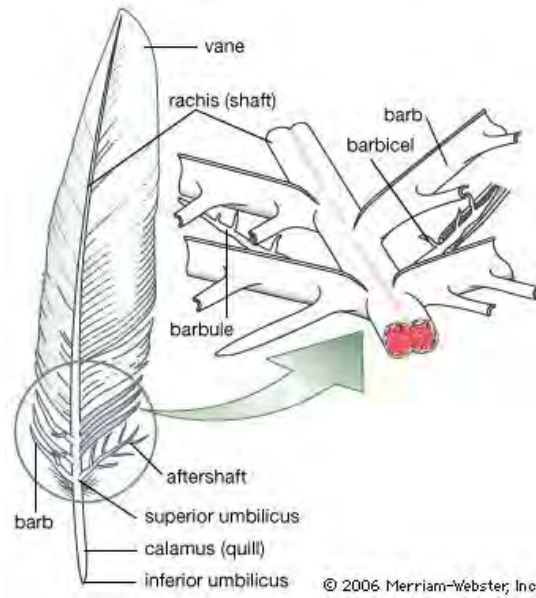
Feather Texture

Frizzle Chicken Mutation in Keratin 75

G Ng, P Wu, J Foley,,
WH Li, CM Chuong, 2012, PLOS Genetics



Mouse K75 mutant J Chen ... D Roop, 2008, JID
Human pseudo-folliculitis barbae H Winter, 2004, JID
K75, enamel and dental decay, O Duverger ..M Morasso, 2014,JCI



Frizzle

control

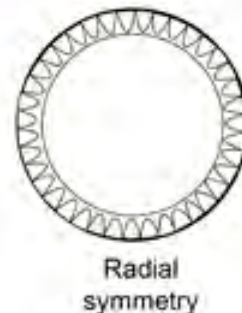
Defective
Medulla



A



- Lateral vane ■ Medial vane ■ Rachis ■ BGZ



Radial
symmetry

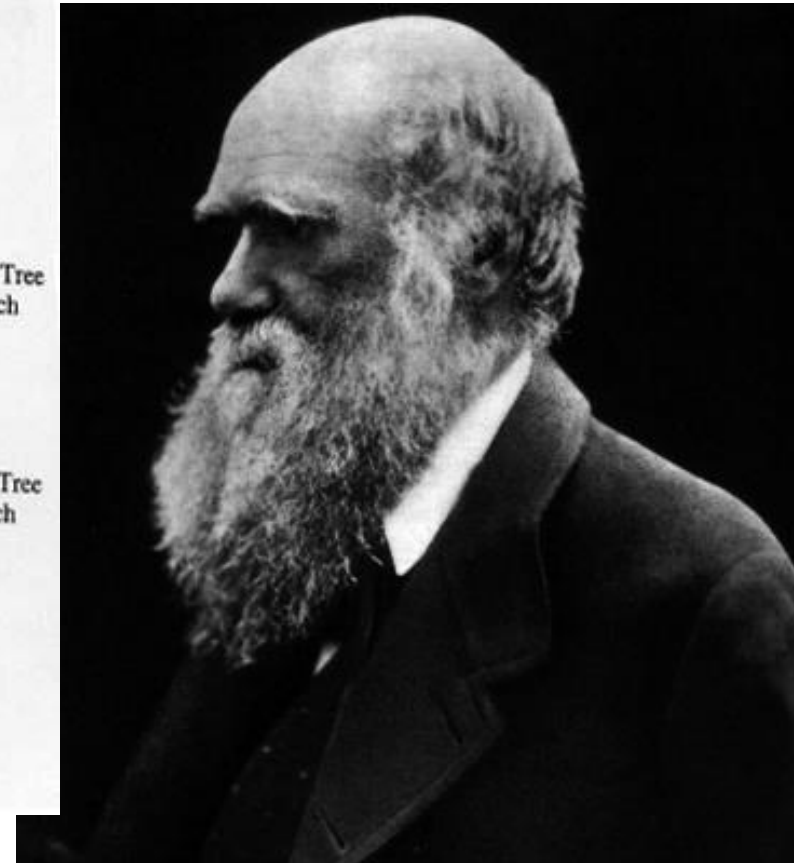
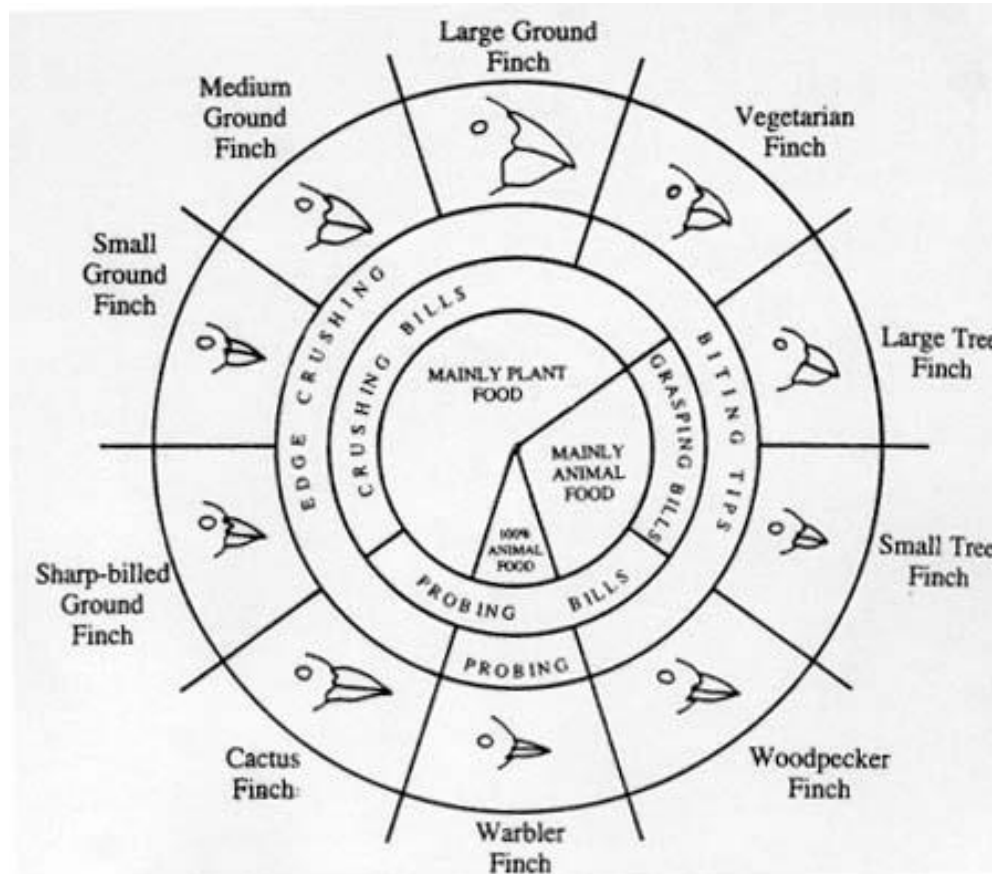
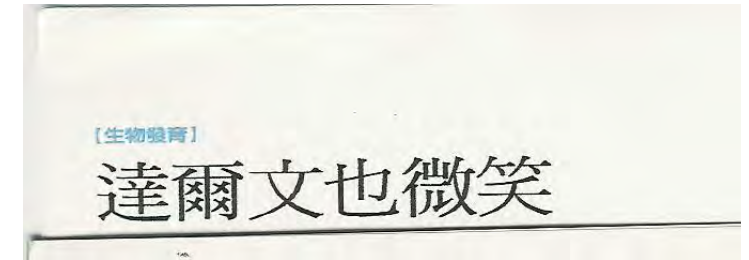
①



Stem cells respond to landscapes of signaling activities

Commentary in Science (305:1383, Sept. 2004)
on Tabin and Chuong's work of beak morphogenesis:
Darwin would be pleased.

Scientific American (Taiwan edition)



Galapagos finch beaks



A small, brown and grey finch-like bird with a yellow beak, standing on reddish-brown soil. The bird is facing right, with its head slightly turned towards the viewer. It has a compact body, short wings, and a thick, conical beak. The plumage is a mix of brown, grey, and white, with some darker streaking on the wings and back. The ground is composed of fine, reddish-brown soil with small pebbles and clumps of dried plant matter.

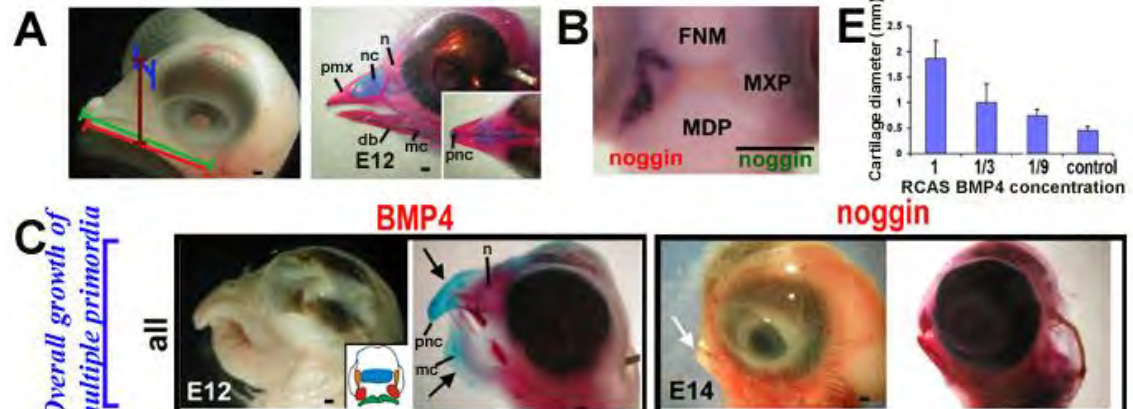
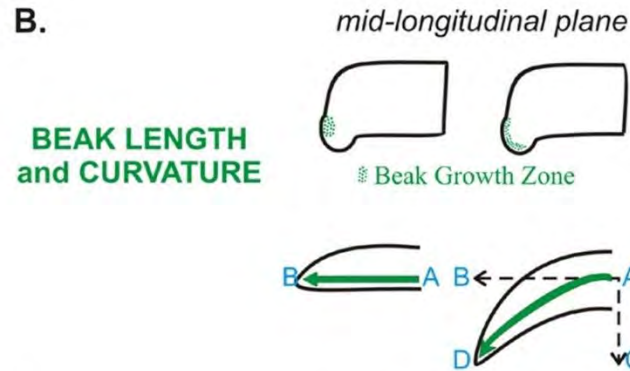
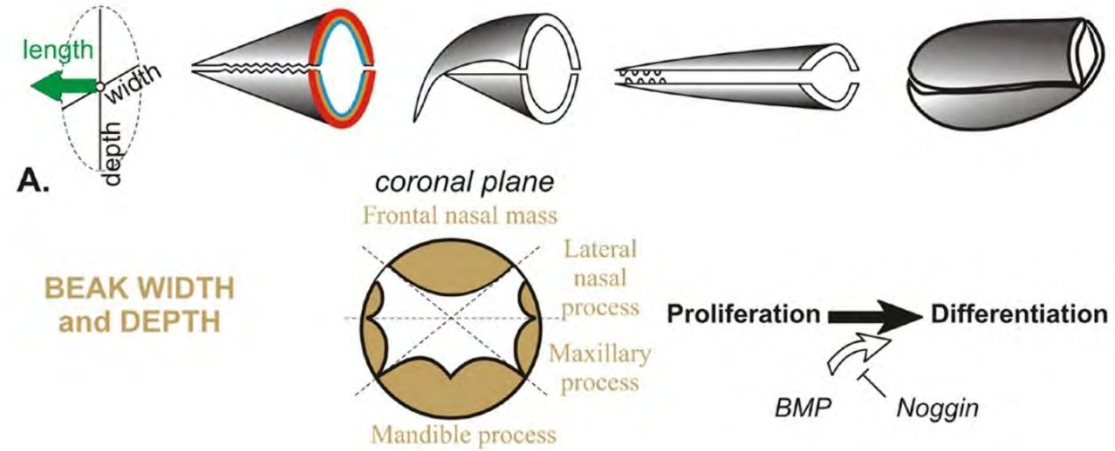
Darwin's finch



Organ ng shaping by
regulating the number, size,
position, & duration
將雞喙化爲自然界中
各種鳥喙形狀

Wu et al.,
2004,
Science

Molecular Shaping of the Organ



Macroevolution of avian beaks

Heterochronic truncation of odontogenesis

PNAS, Wang et al., 2017, Sept 25
Collaboration with Xing Xu group

The New York Times

Sept 26, 2017

Limusaurus, a theopod,
Tooth in young (right), Beak in adult

Discover SCIENCE FOR THE CURIOUS

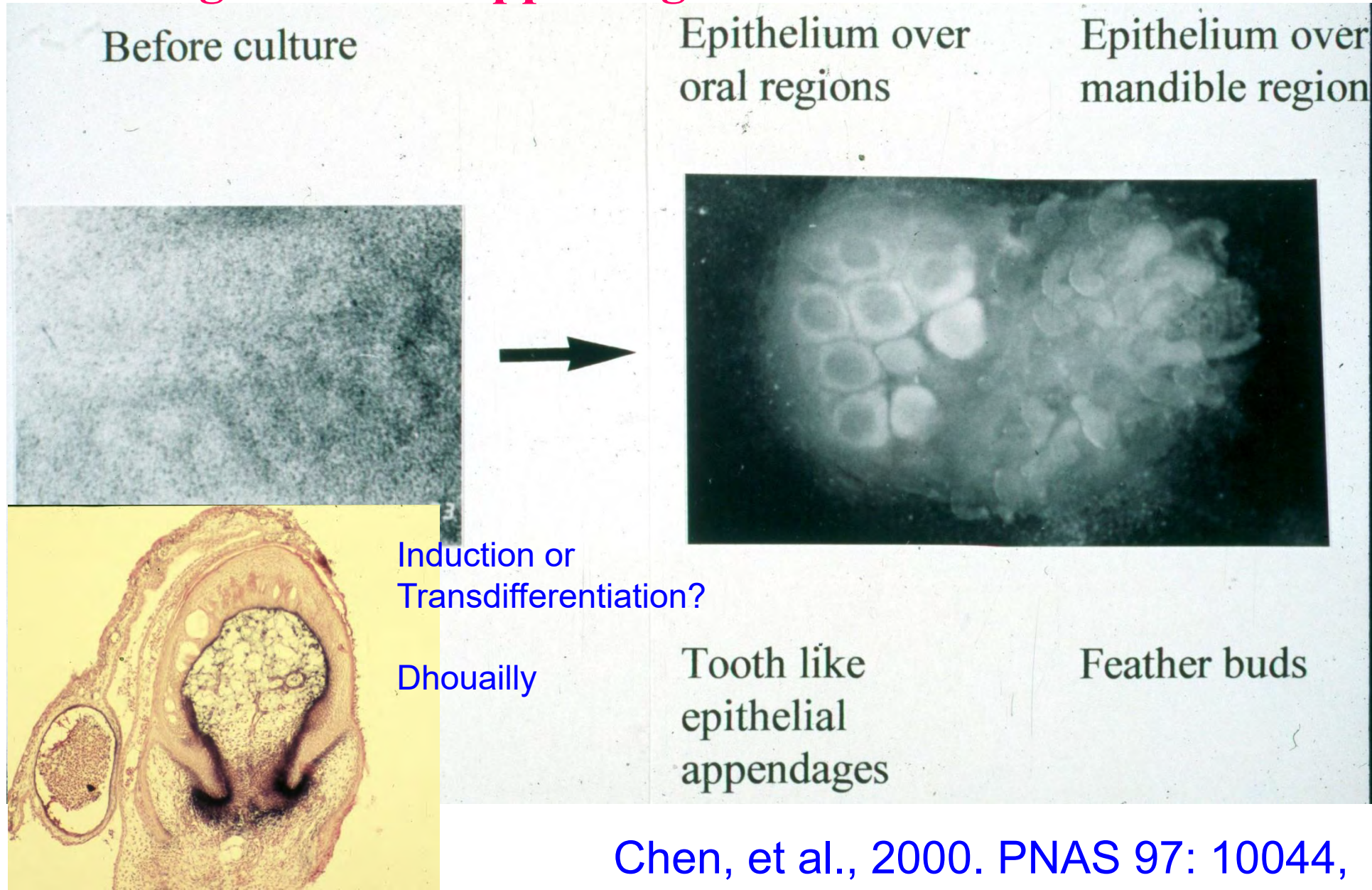
September 26, 2017

[Beak Evolution Gives New Insight Into the Beginning of Birds](#)



雞牙復生

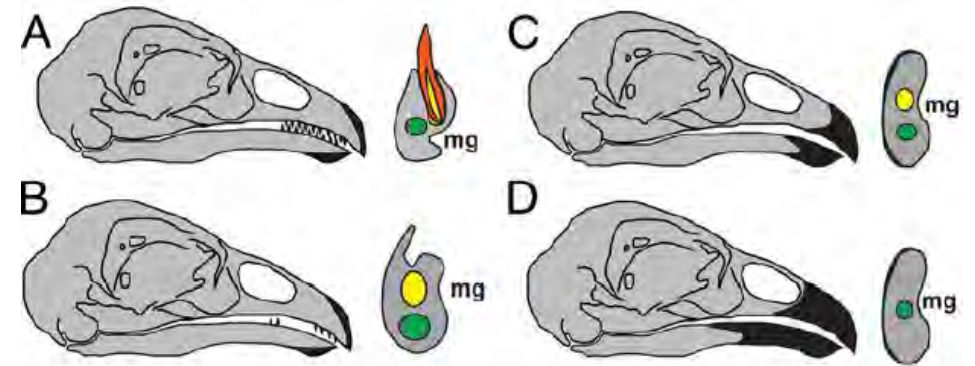
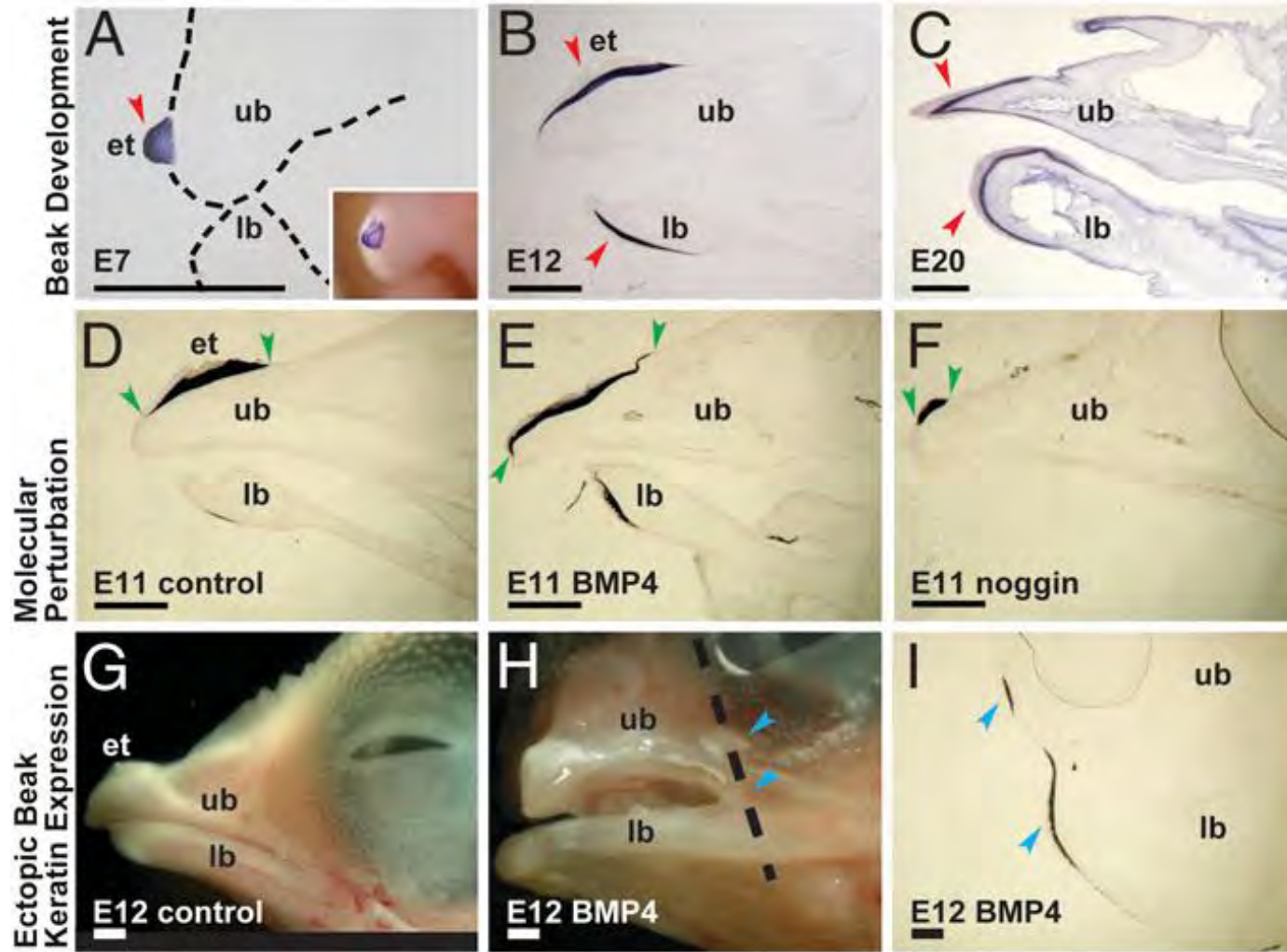
Inducing tooth like appendages from chicken oral mucosa



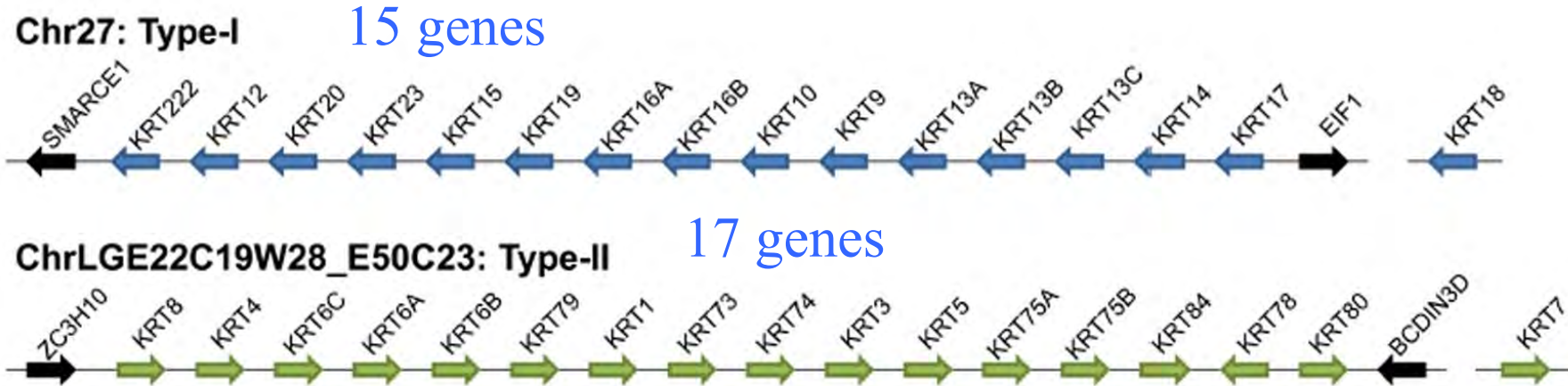
Chen, et al., 2000. PNAS 97: 10044,

Macroevolution of avian beaks

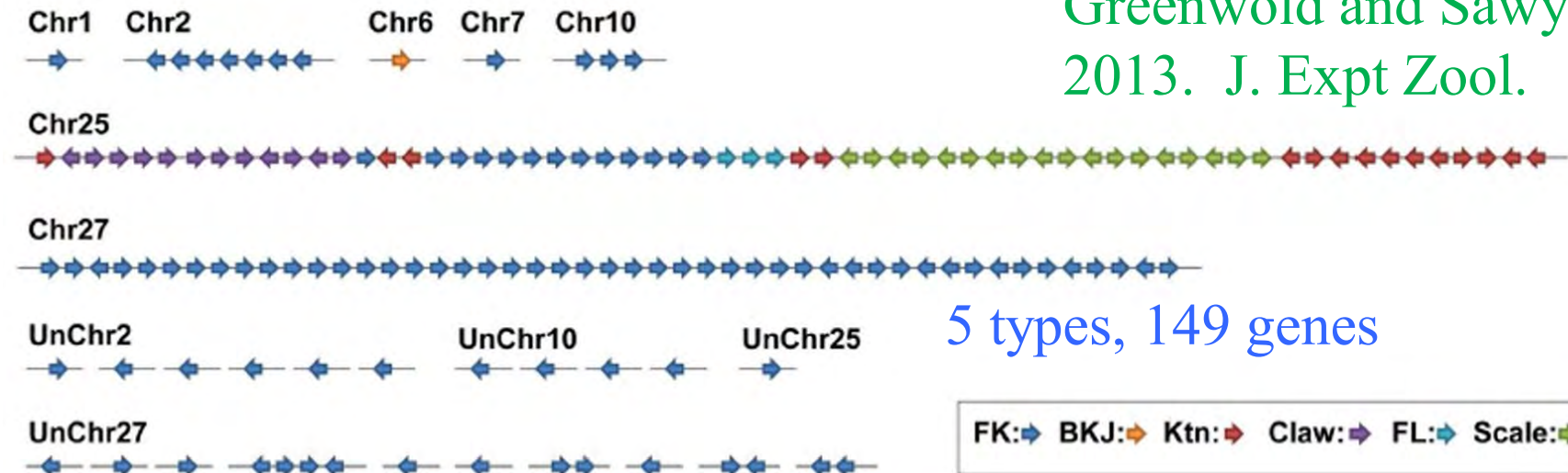
Initiation of beak keratin to form horny sheath



Alpha keratin



Beta keratin



Ng, Wu, ...Chuong, Li. 2014.
Genome Biology and Evolution
Greenwold and Sawyer 2010 BMC Evo,
2013. J. Expt Zool.

Outline

- | | |
|------------------------------|-------|
| 1. Alopecia | 禿髮 |
| 2. Evolution (feather, beak) | 演化 |
| 3. <u>Wound regeneration</u> | 幹細胞再生 |
| 4. Visual based cognition | 對美的認知 |

The Turing Model Comes of Molecular Age

Start from a homogenous state

- Properties of cell membrane
- Physicochemical properties of extracellular matrix

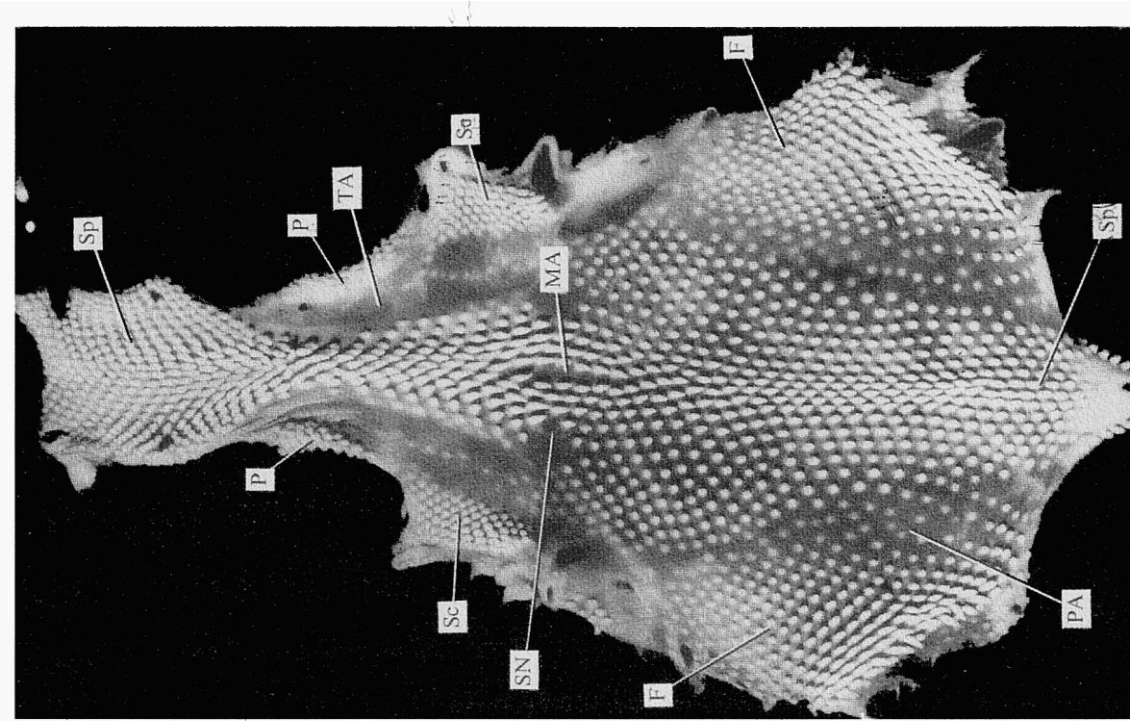
- Concentration of Activators/inhibitors
 -
- Dimension of the field

Activators:
FGF, Wnt, etc.

Inhibitor:
*BMP, Wnt
antagonists, etc.*

Developing feather buds and branches
Embryonic chicken skin, Shh

Turing activator / inhibitor, Jung et al., 1998, Dev. Biol.
Self-organization, Jiang et al., 1999, Development

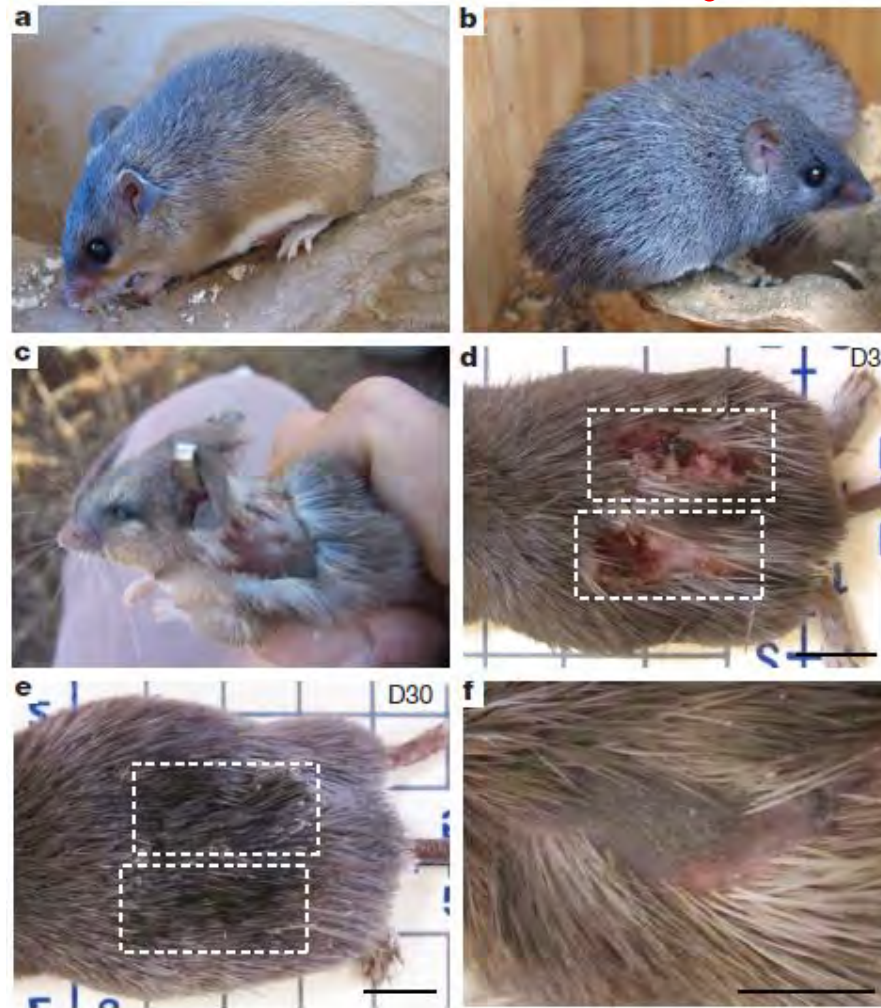


Repair versus Regeneration



Ito,.. Cotsarelis, Nature, 2007

Skin Autotomy



Skin shedding and tissue regeneration in African spiny mice (*Acomys*)

Nature, 2012, Seifert ... Maden et al

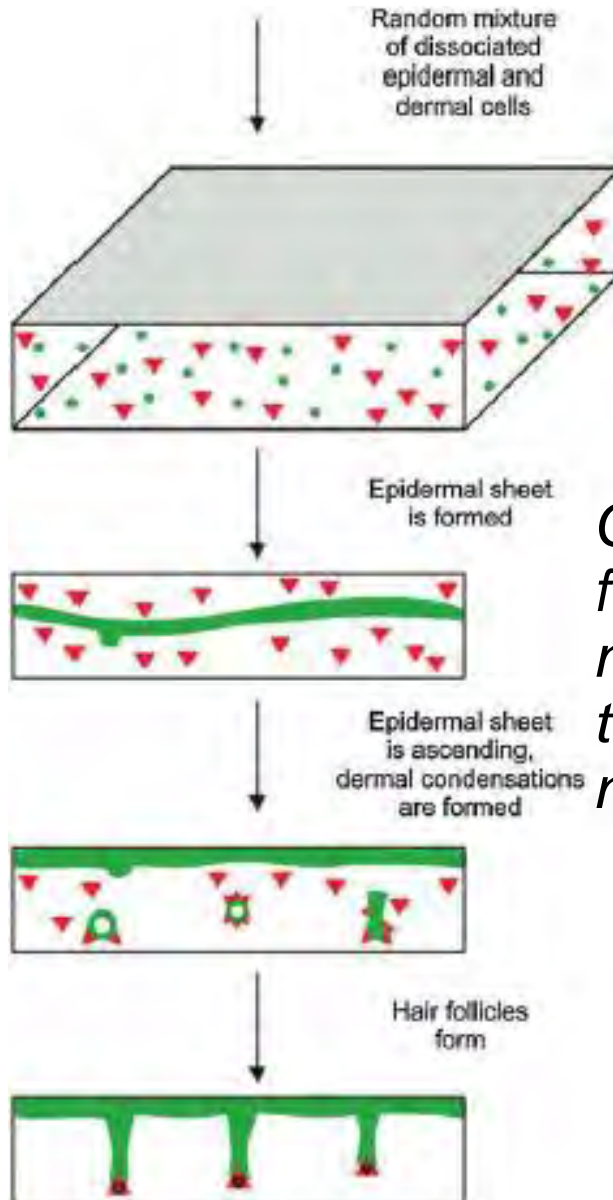
Ashley W. Seifert^{1,2,3}, Stephen G. Kiama², Megan G. Seifert^{1,3}, Jacob R. Goheen^{3,4}, Todd M. Palmer^{1,3} & Malcolm Maden¹

Dissociated
Epidermal cells
Mesenchymal cells

Rebuilding patterns after wounding

Planar hair formation leads to reconstituted skin

Chamber assay, Lichti ..Yuspa, 1995, JID,
Patch assay, Zheng .. Stenn, 2005, JID



*Cell mixture
from newborn
mouse
transplanted to
nude mice*

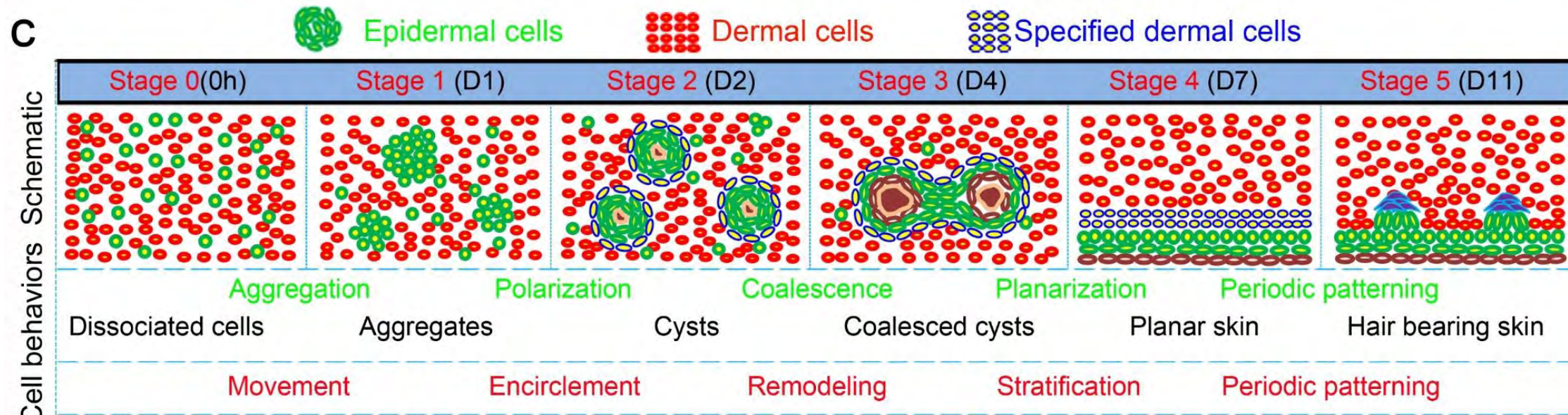
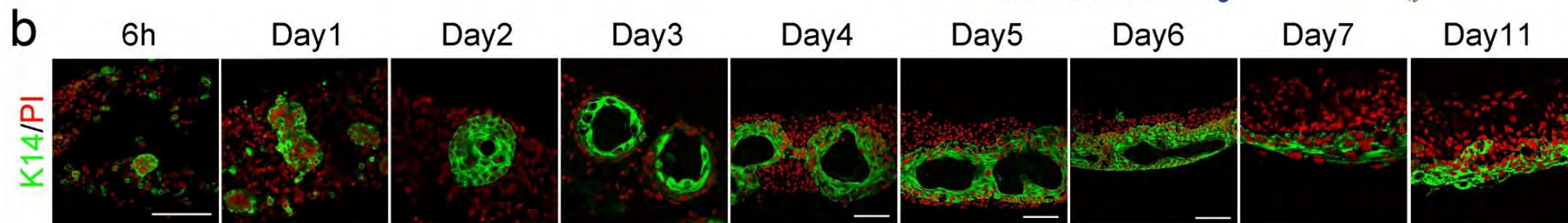
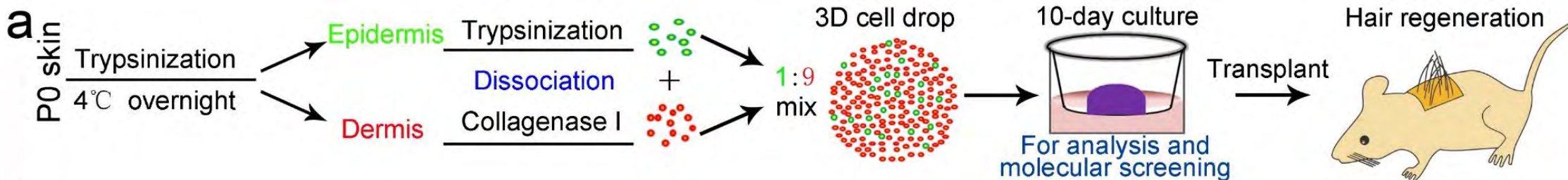
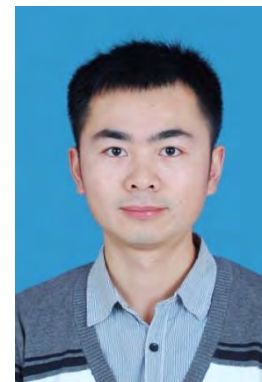


Lee et al.,2011,
Tissue Engineering



*Plastic surgeon
Resident, USC*

Self-organizing behavior of skin Organoids



Mason Lei
2017...
PNAS

Outline

1. Alopecia
2. Evolution (feather)
3. Wound regeneration
4. Visual based cognition

禿髮

演化

幹細胞再生

對美的認知

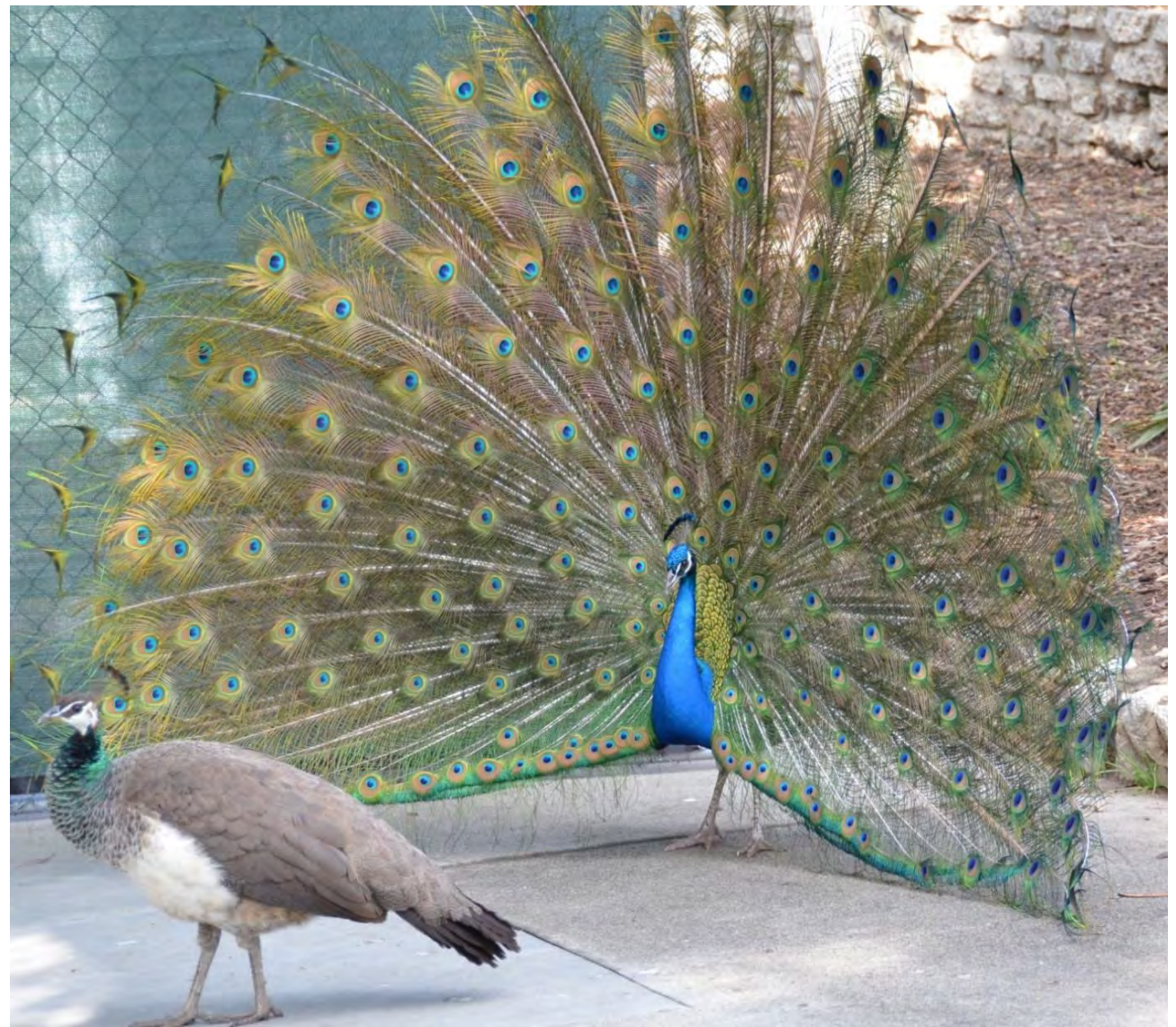
Organization principles of integumentary Organs:

I. Periodic pattering

II. Cyclic Renewal
周而復始

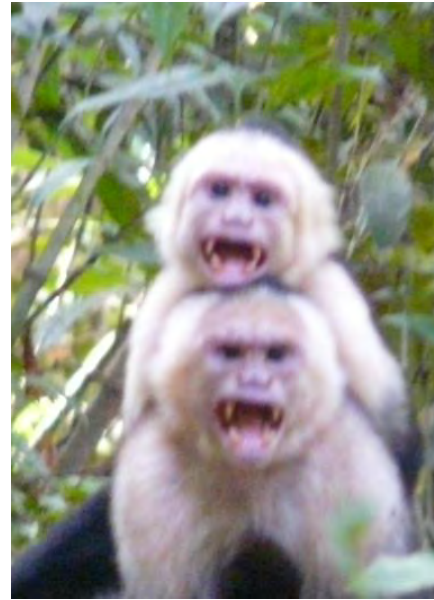
III. Temporal & Spatial
diversification 多樣化

IV. In one individua or
in evolving species



A special issue on Pattern Formation

Chuong CM & Richardson MR edit, 2009, special issue
Int J Dev. Biol. Vol 53.



**The evolution of the face
and cognition of patterns**

Regional patterning
Regional specificity



Venus of Hohle Fels,
~35,000 yrs ago,

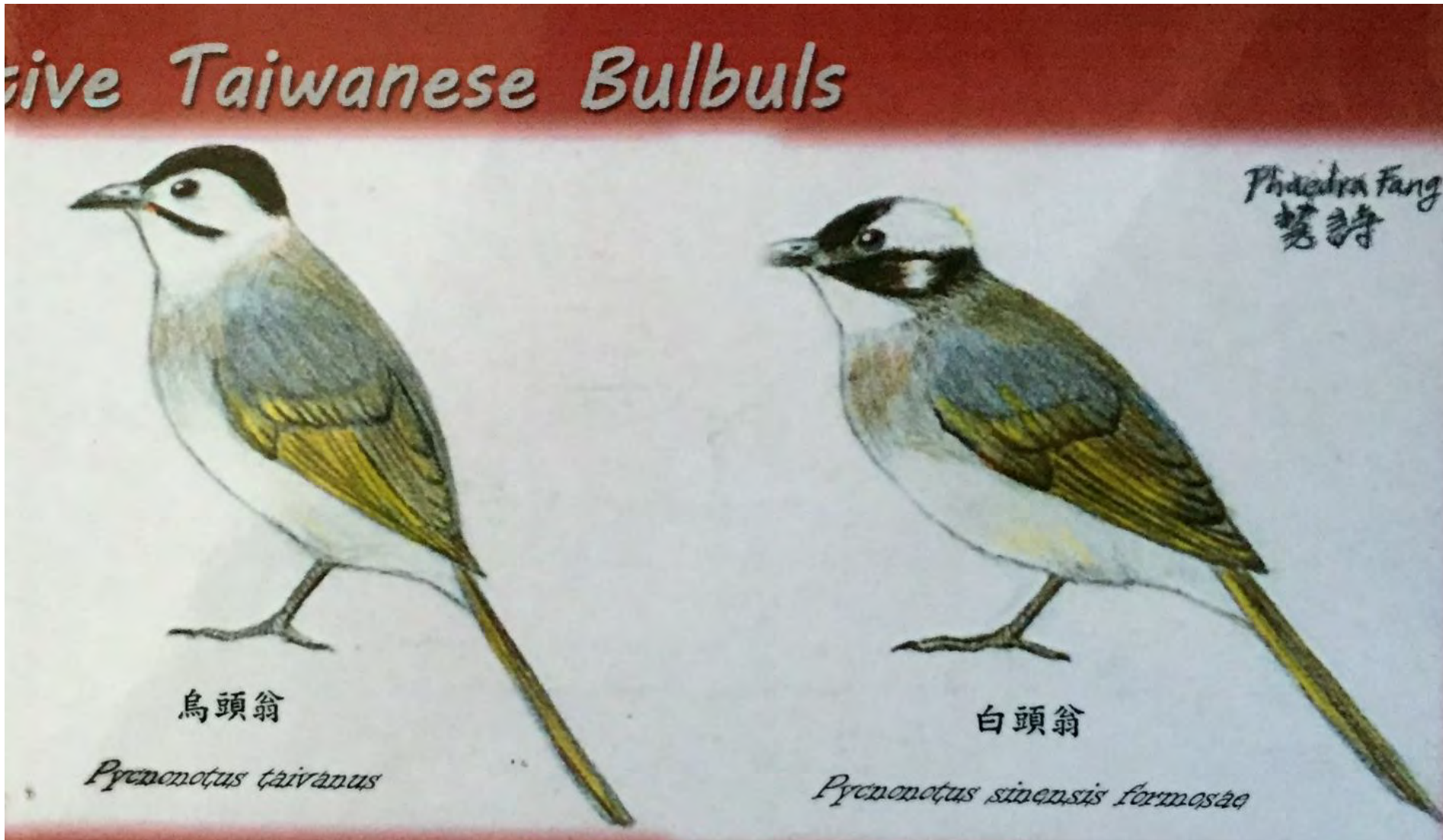


Venus of Willendorf
~25,000 yrs ago,

Botticelli, *The Birth of Venus*, ~500 yrs ago







龍門計劃:
台灣大學
中興大學
張芳嘉, 唐品琦.
于宏燦,

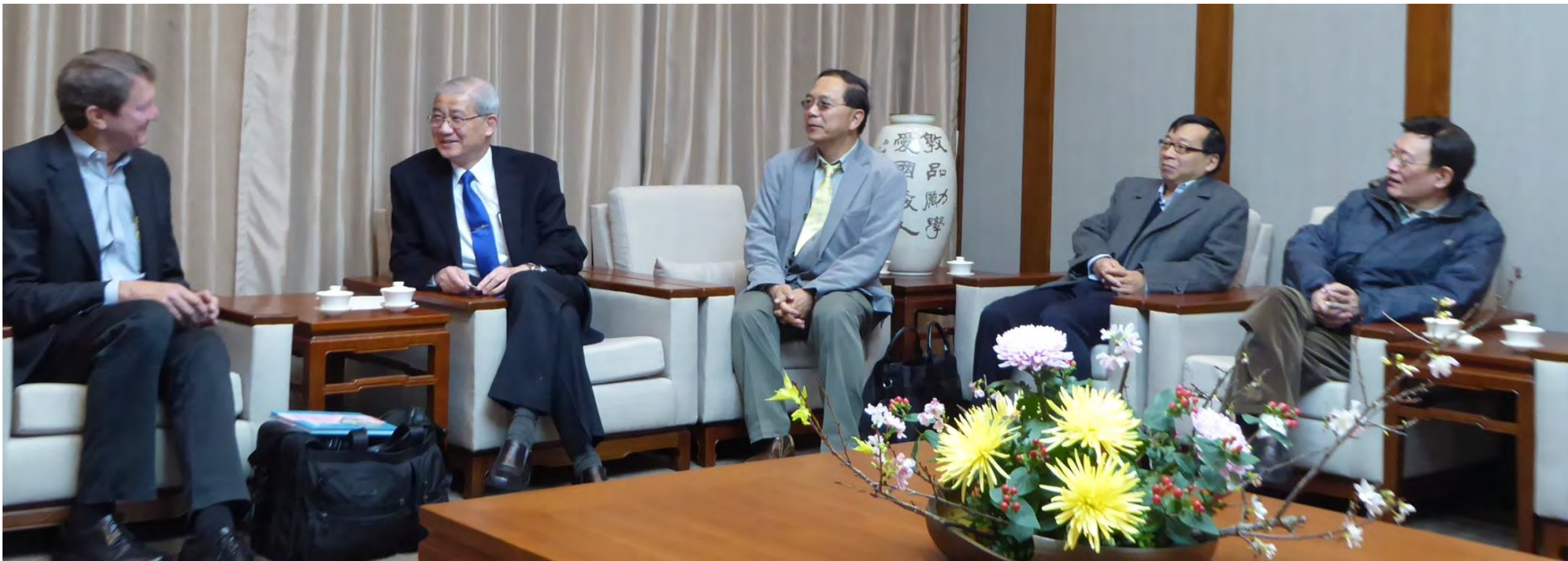
Visual based
cognition

Mating choice

Speciation

Evolution

烏頭翁, 白頭翁



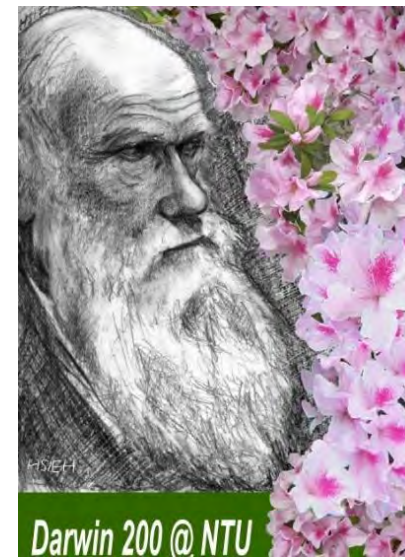
台大發育再生中心邀請南加大講座教授 **Scott Fraser**
(左一) 至台大訪問。

左二：楊泮池校長，鍾正明，楊偉勛主任，謝豐舟教授。

謝豐舟

1972 台大醫科畢業, 台灣大學名譽教授

- **Renaissance Man: Physician, Educator, Scholar, Curator, Painter, Entrepreneur**
- Midwife for the birth of:
 - Research Center of Neurobiology and Cognitive Science (2005), Bioinformatics and Systems Biology
 - **Developmental Biology and Regenerative Medicine (2010),**
 - **Dragon gate project**
- Curator: NTU Azalea Art Festival (2006-2010), 台大杜鵑花文創,





臺北市立交響樂團
Taipei Symphony Orchestra



Taipei
Symphony Orchestra

U.S. Tour

Concert

臺北市立交響樂團

美巡音樂會

Nov. 2

7:30PM THU.

Flint Center,
Cupertino, CA

Nov. 4

7:30PM SAT.

Copley Symphony Hall,
San Diego, CA

- Price 30, 55, 70, 85, 200
- Groups Of 10+ / 10% off
- Groups Of 20+ / 20% off

Tickets available at
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P Wu

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J Jiang

《景福醫訊》in press,

兩極歸來

圖文／沈慰萍、鍾正明



14

與兒子共遊北極





北極圈由美蘇。加拿大，格陵蘭，挪威等國環繞



冰河入海



北極熊母子在享用被漂流到岸邊的白鯨屍體



成群游泳的海象，複雜的鬍鬚幫助他們水中識物



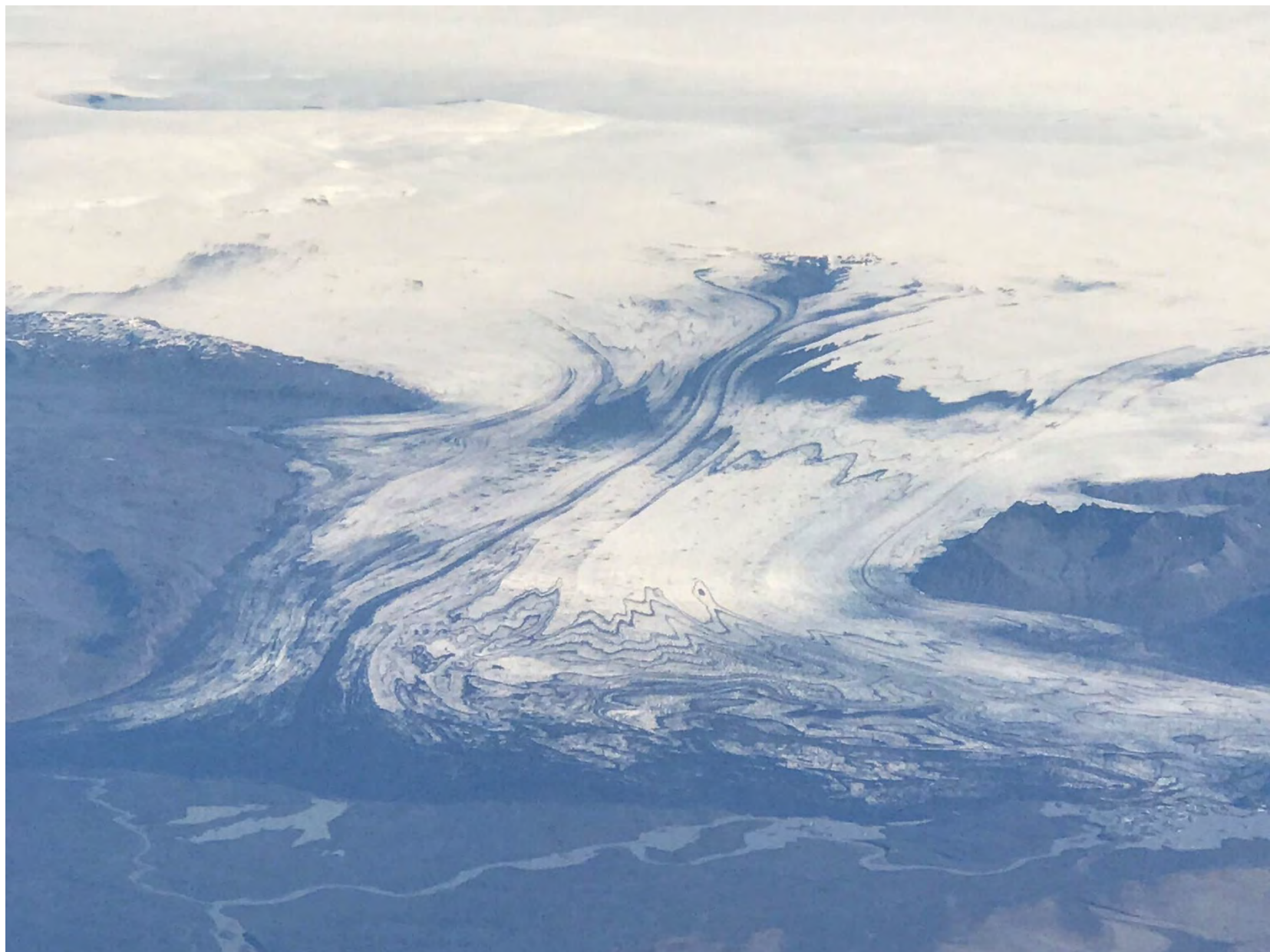
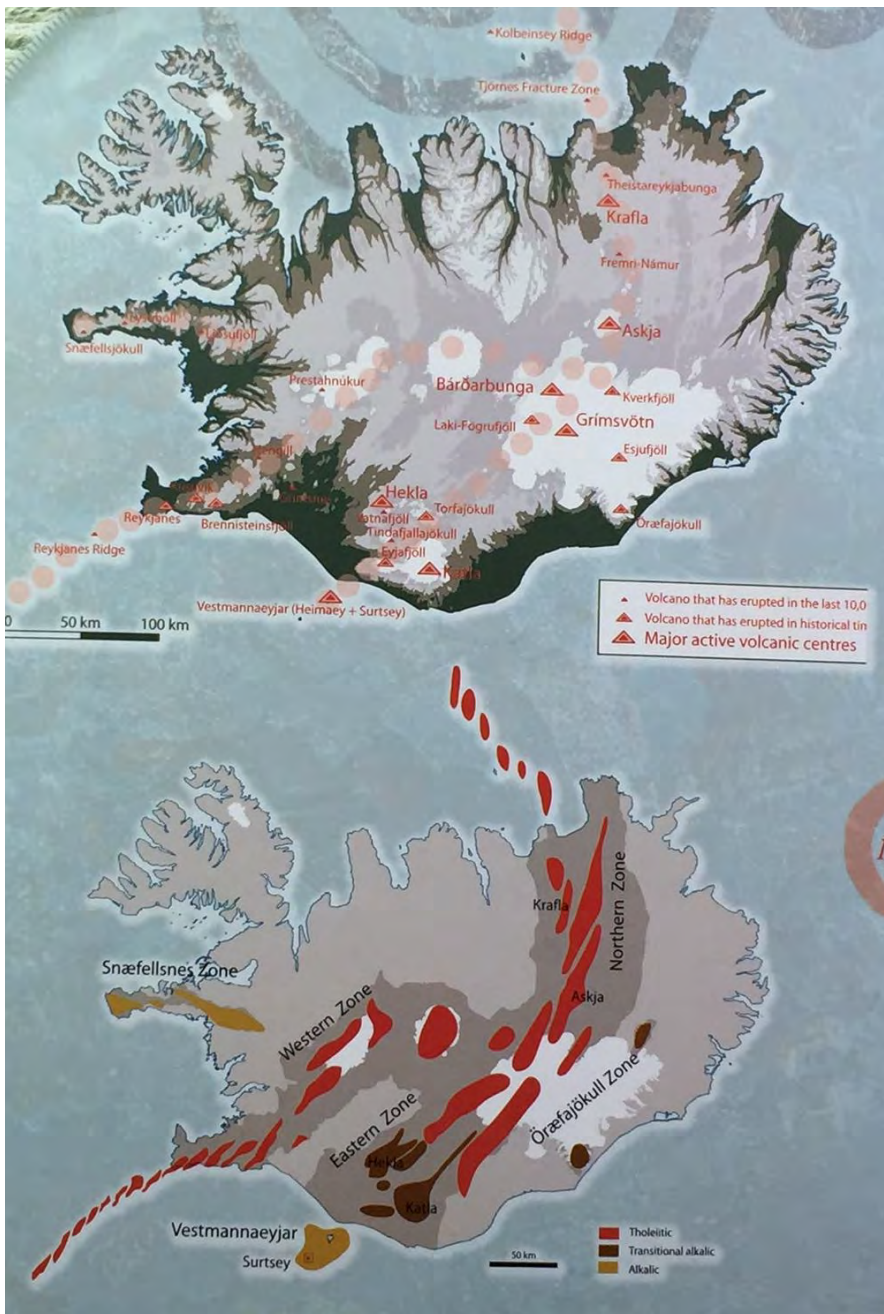


密密麻麻棲息在高層岩壁的海鳥





海冰環繞在Svalbard 群島旁





這個冰山呈現奇特規則像蜂窩般的形狀是由水流沖擊形成

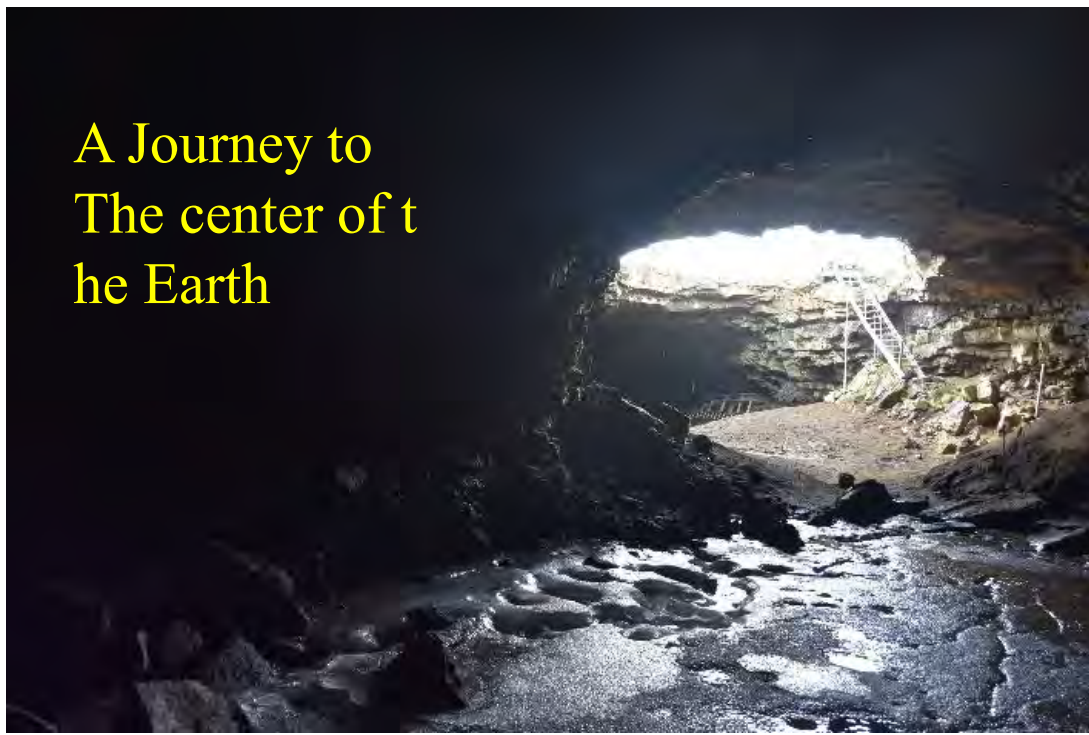








A Journey to
The center of t
he Earth





Drake Passage 南美南端到南極半島



Pass Drake strait from south Argentina to arrive in the serene Antarctica







頰帶企鵝輪流登台展現歌喉







Humpback whale

Baleen:
Tooth – Hair bundle

Thewissen





Tabular Icebergs



Low angle light reflect on different surfaces



A sunset in Antarctica



兩極歸來

