Basic mechanisms of chemotherapy-induced alopecia (CIA)

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For the record
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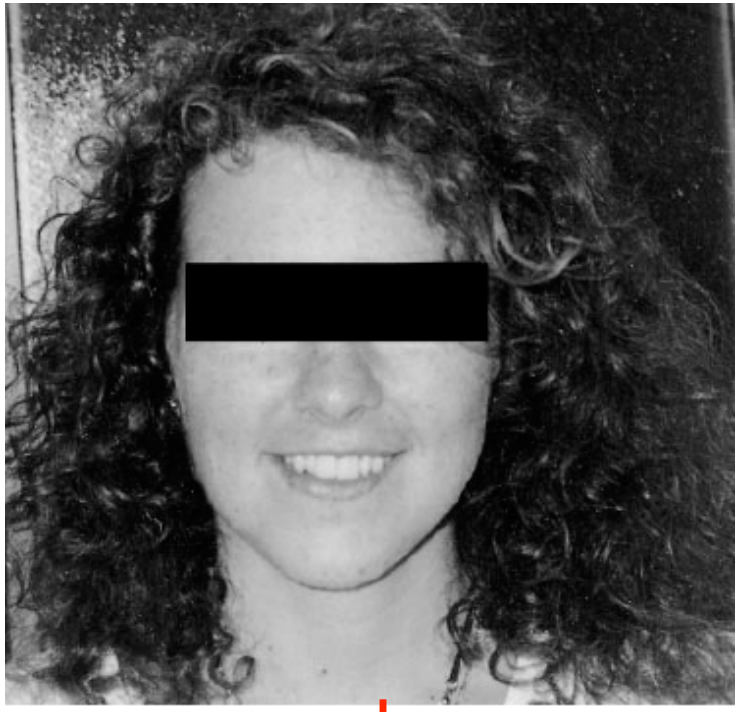
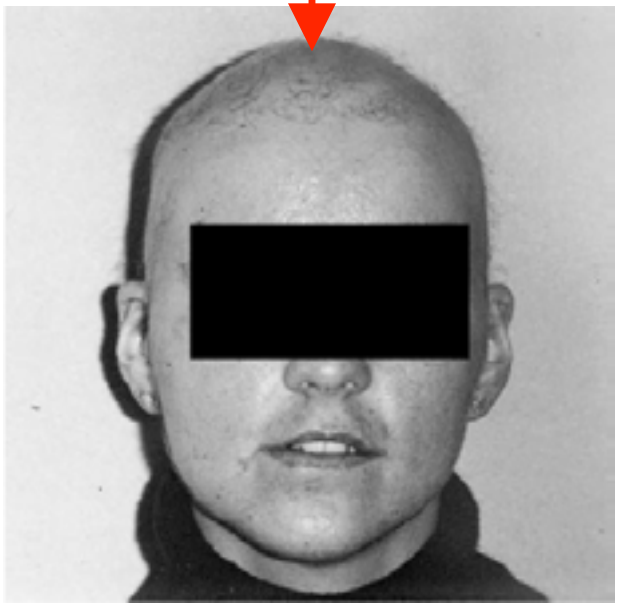
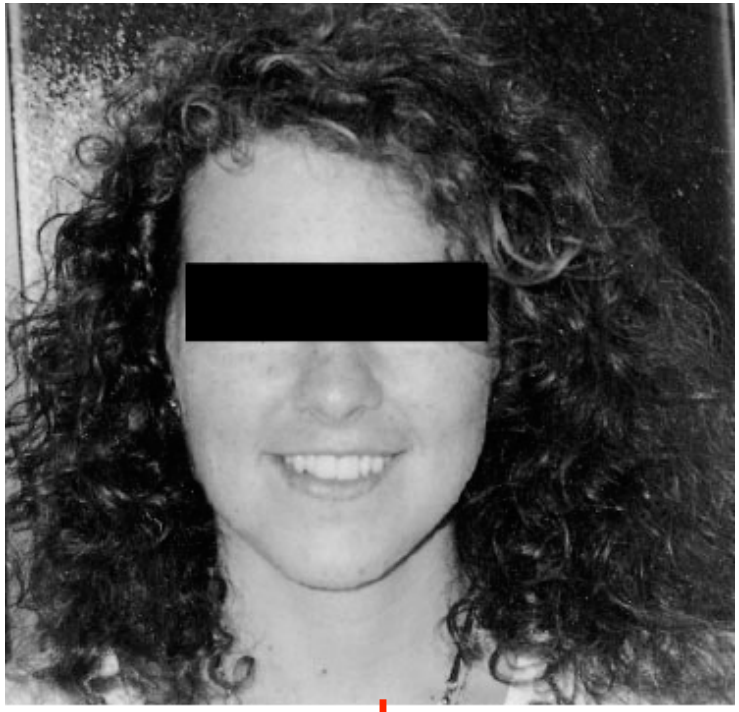
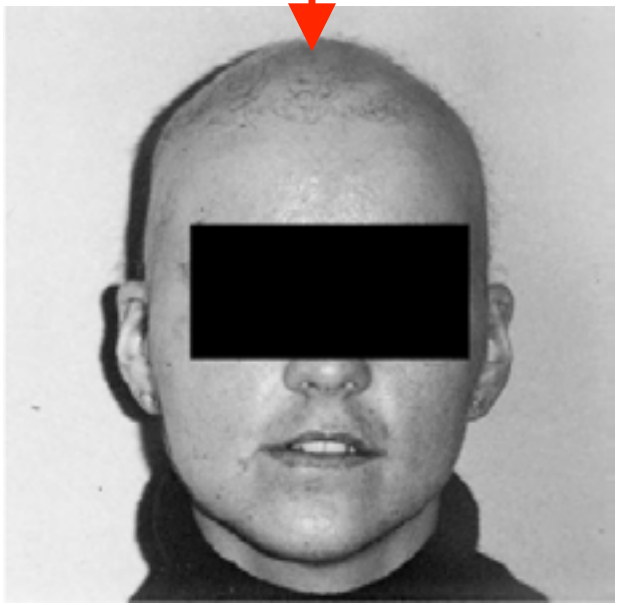




A *massive* psychoemotional Stressor !

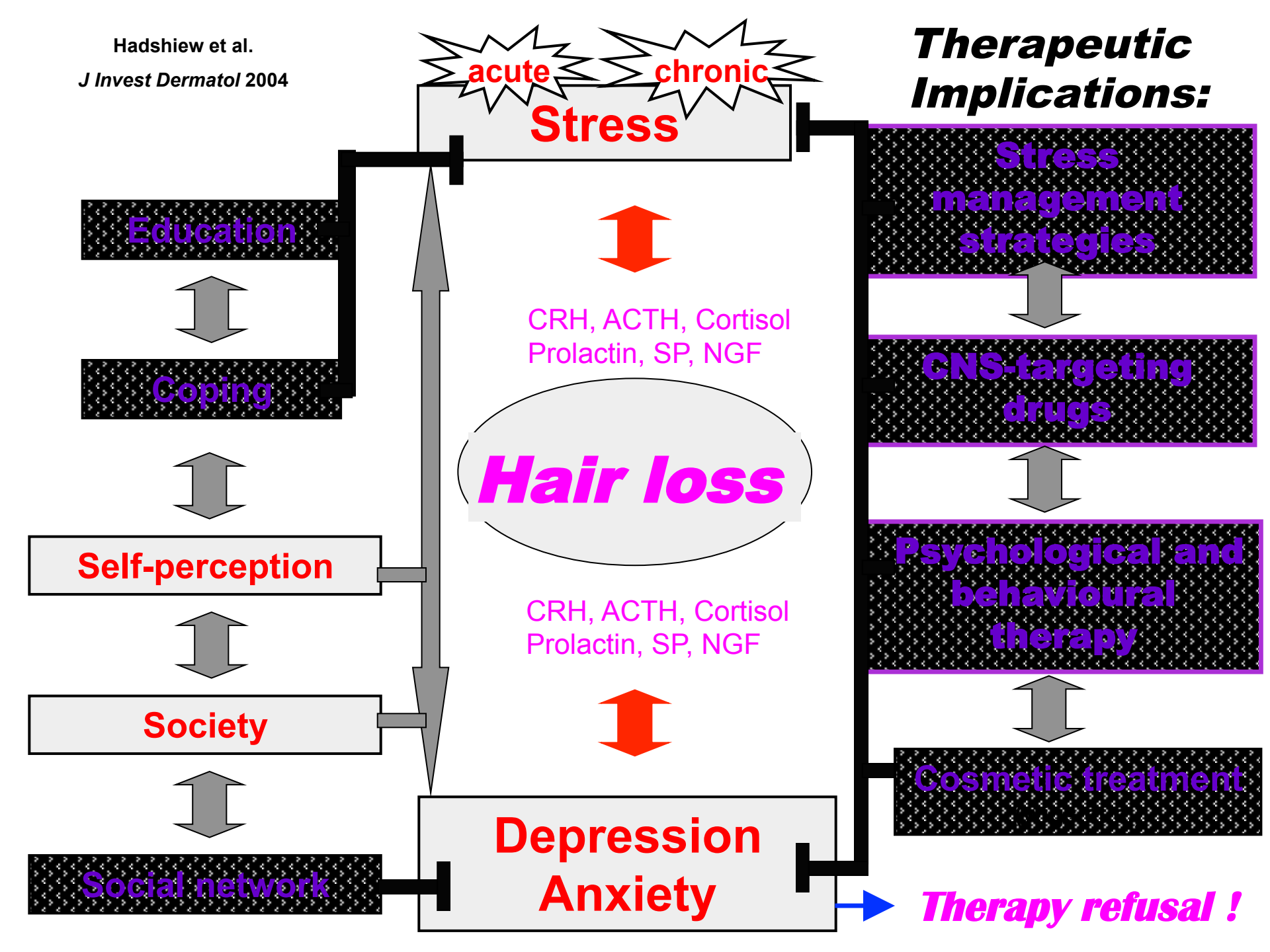
Sudden, cancer therapy-associated massive hair loss

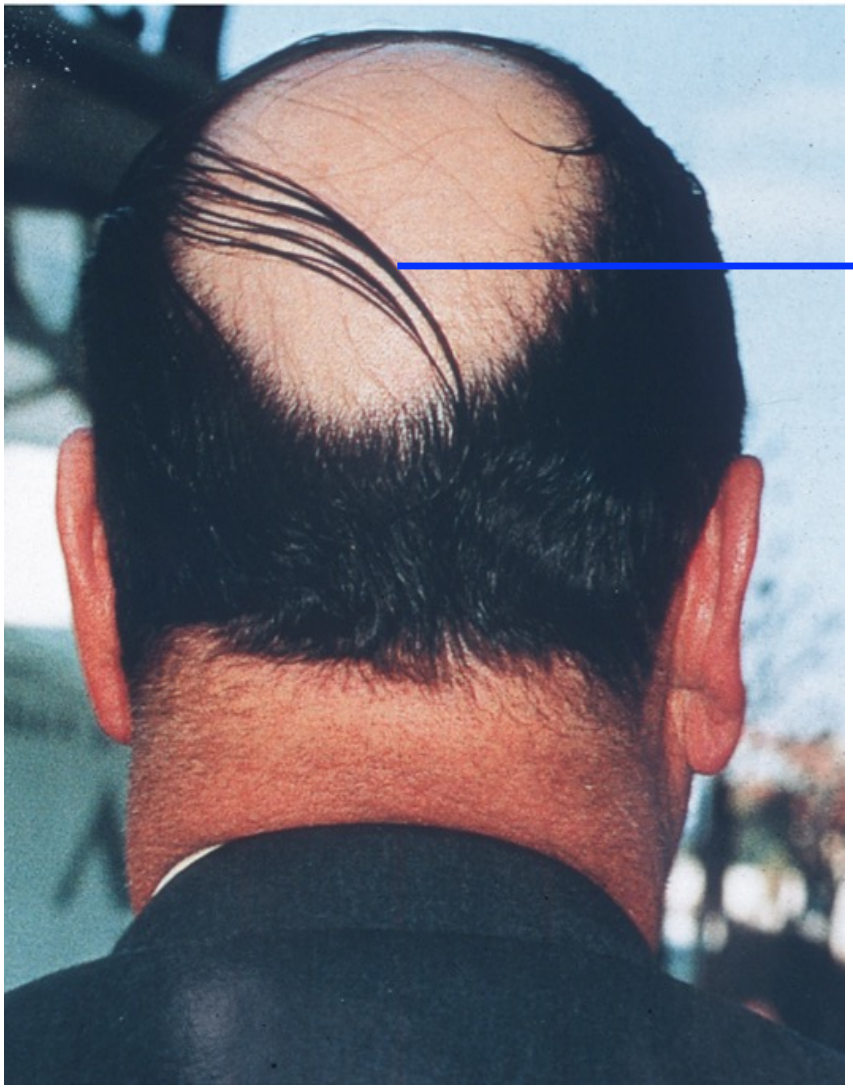




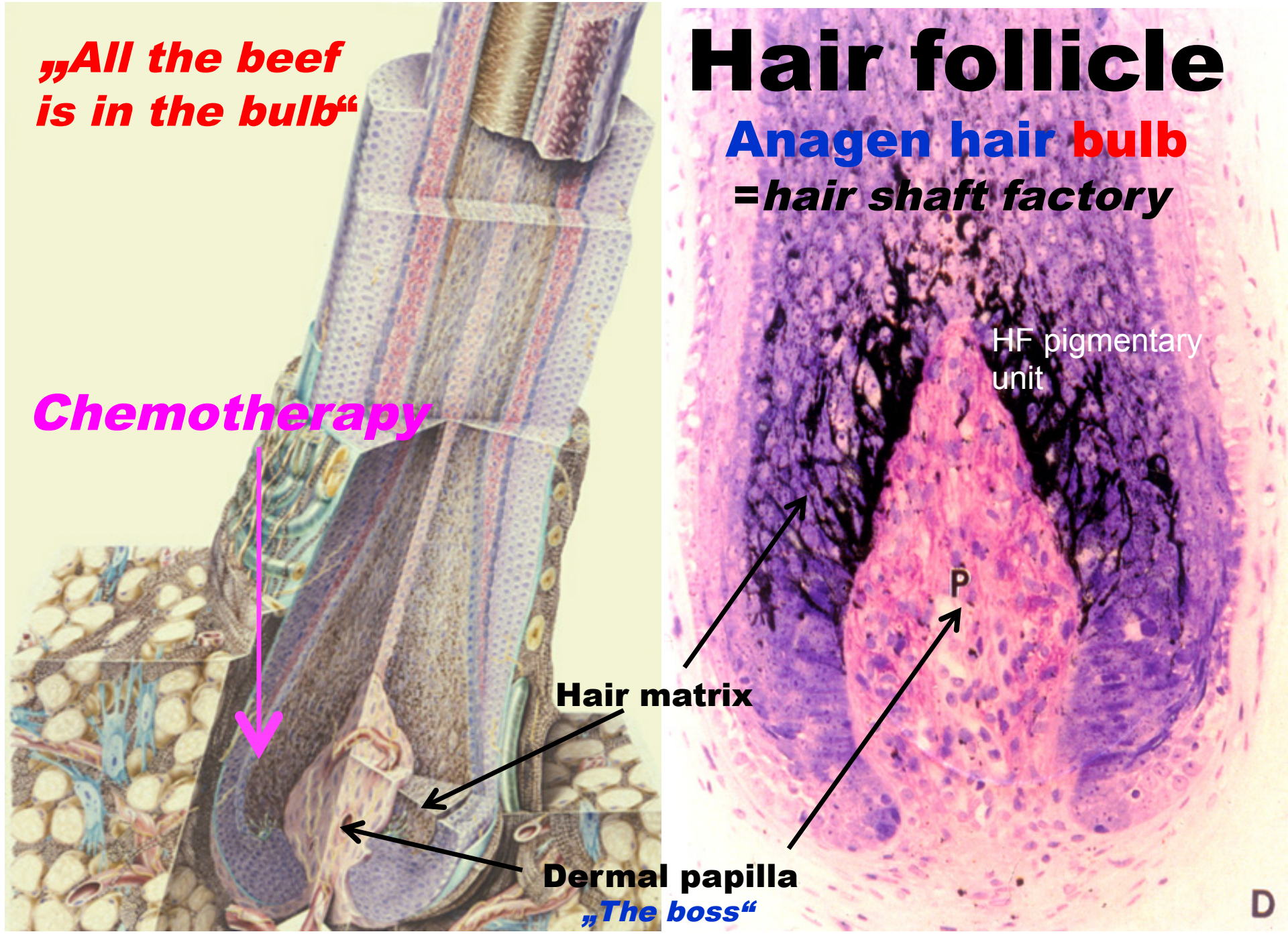
PATHO-BIOLOGY

?

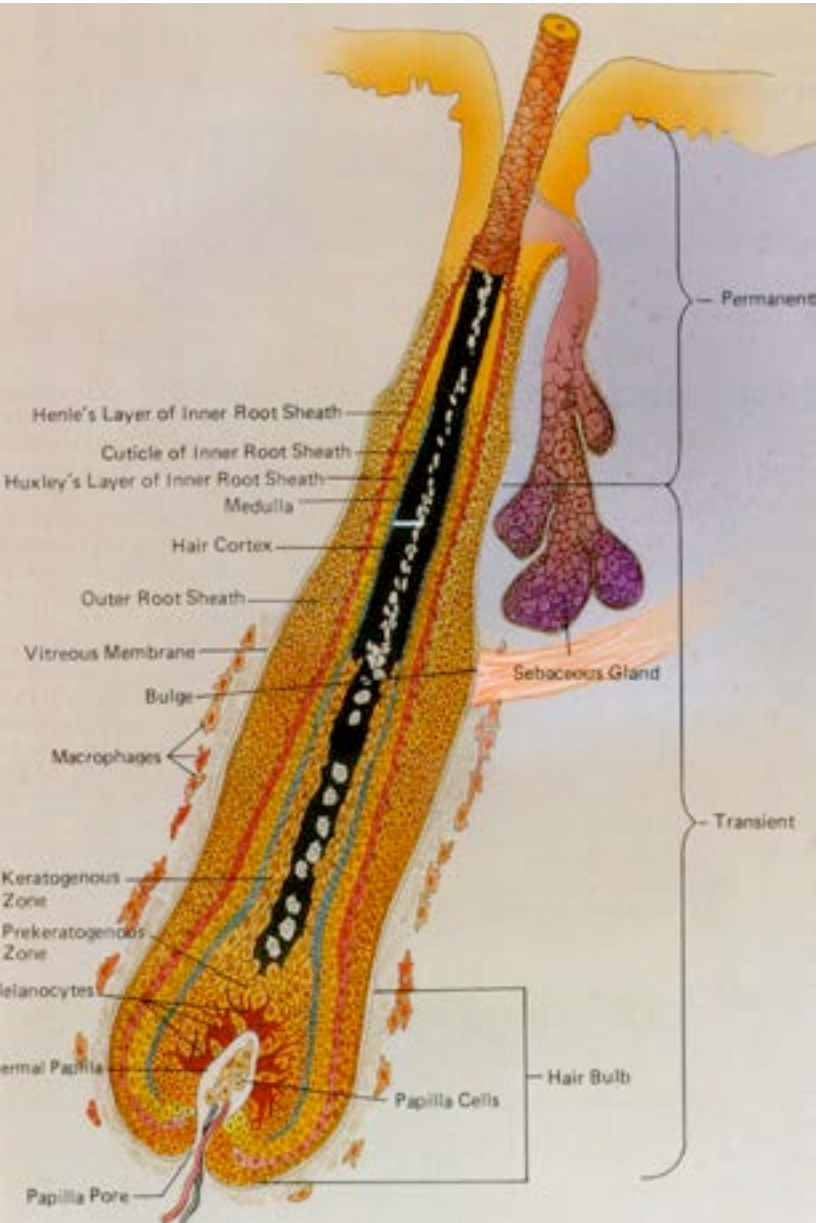

Hadshiew et al.
J Invest Dermatol 2004
acute
chronic
Stress
Education
Coping
Self-perception
Society
Social network
CRH, ACTH, Cortisol
Prolactin, SP, NGF
Hair loss
CRH, ACTH, Cortisol
Prolactin, SP, NGF
Depression
Anxiety
Therapeutic Implications:
Stress management strategies
CNS-targeting drugs
Psychological and behavioural therapy
Cosmetic treatment
Therapy refusal !



Most amazing
mini-organ
that evolution
has come up with


„All the beef is in the bulb“
Chemotherapy
Hair follicle
Anagen hair bulb
=hair shaft factory
HF pigmentary unit
P
Hair matrix
Dermal papilla
„The boss“
D

Hair follicle



ca. 5 million mini-organs
scalp: ca. 100,000 HFs

„work horse of the skin“

→ **fiber & pigment production**

→ **epidermal regeneration & repigmentation**

→**Important for wound healing, angiogenesis, innervation** etc.pp.

→ **Major hormone & protein factory**

→ ***highly sensitive to nutrients,, hormones, „stress“, drugs***

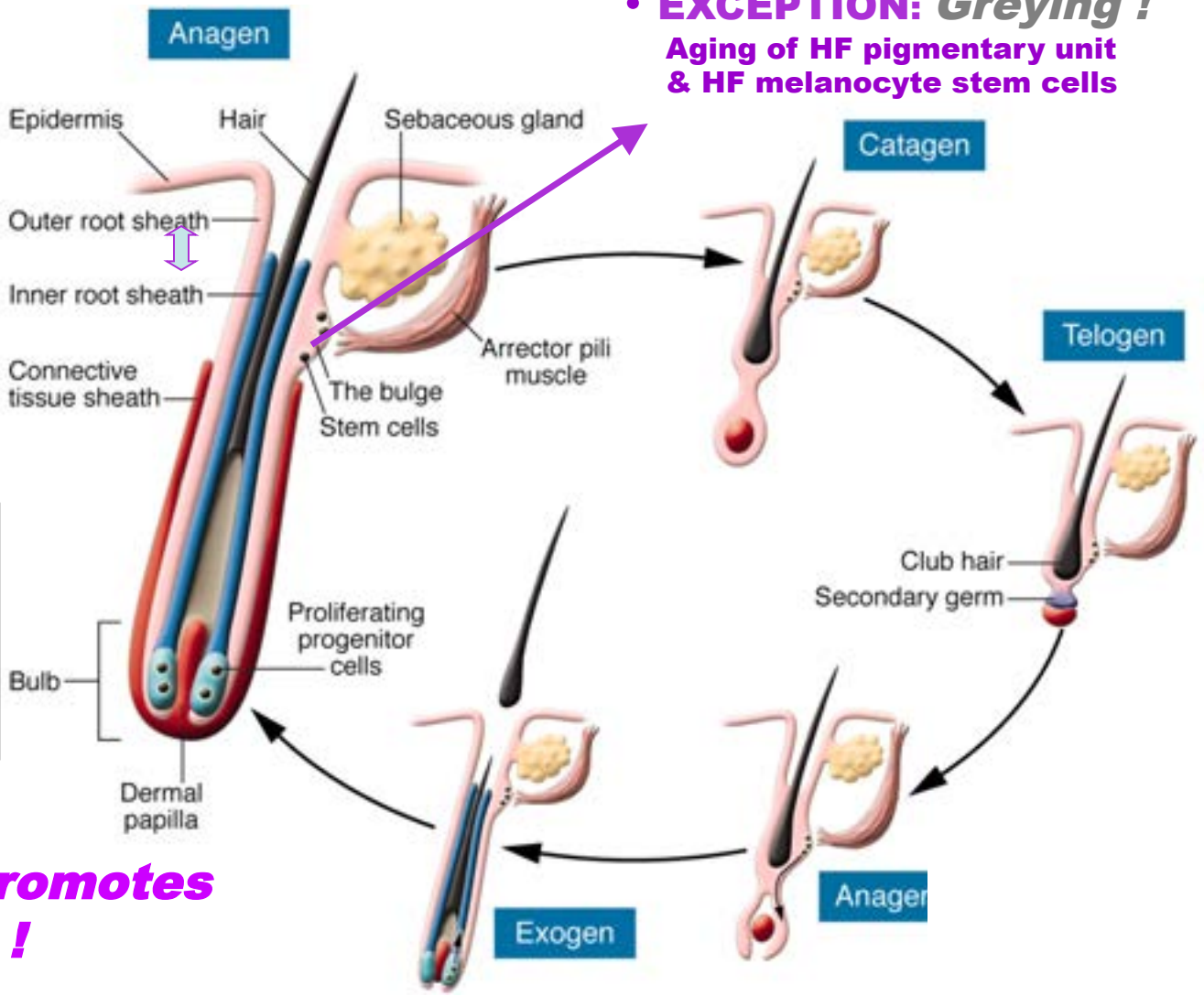
Unique feature:

Cyclic organ remodelling

HF = *regeneration miracle & anti-aging wonder*

- **HF cycles „forever“**
- **multiple stem cell pools**
-

- **EXCEPTION: *Greying !***
  Aging of HF pigmentary unit & HF melanocyte stem cells



→ **ONE organ**

to study <u>both</u>,

aging & anti-aging

→ ***Chemotherapy promotes tissue aging !***

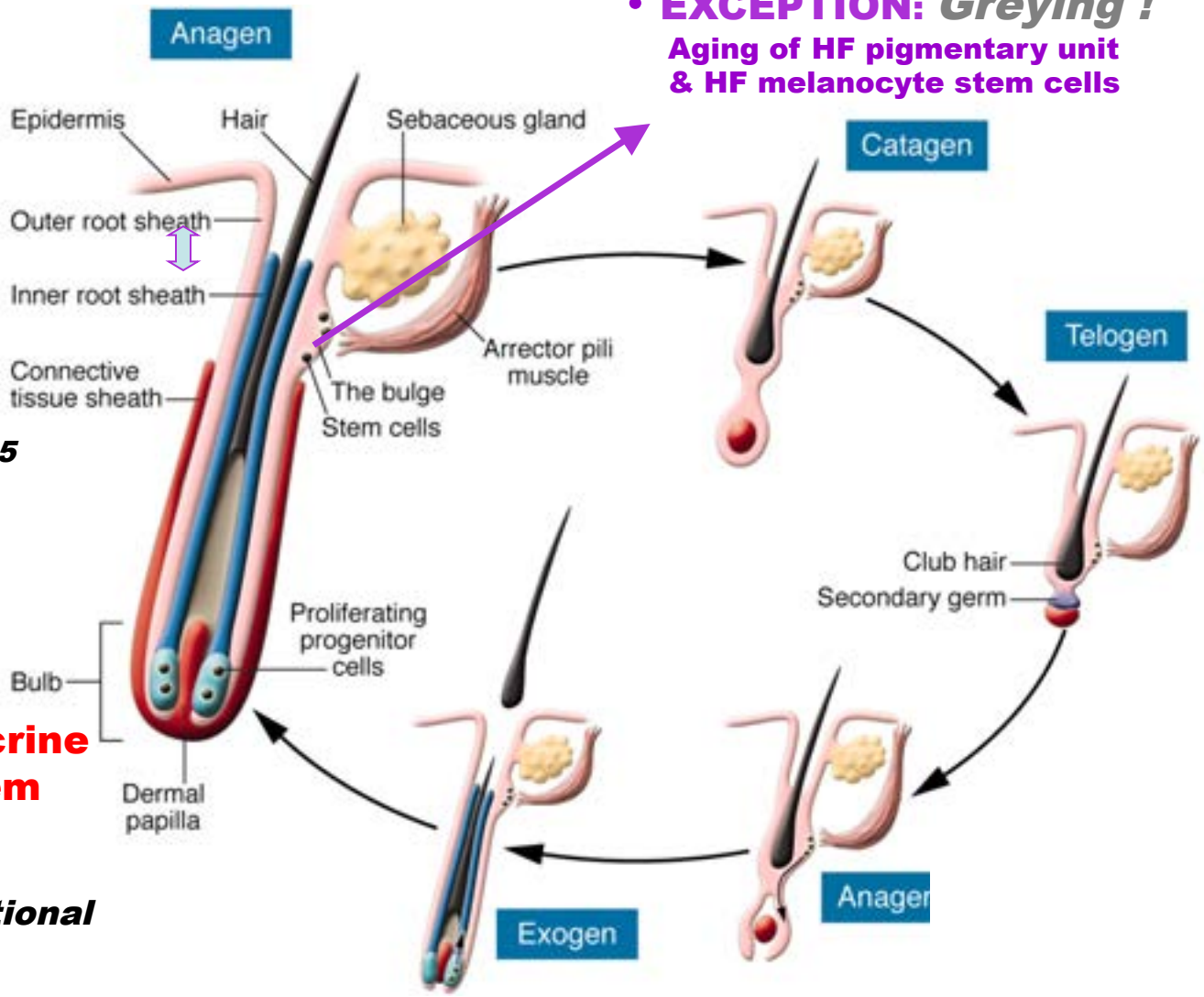
HF = *regeneration miracle & anti-aging wonder*

- **HF cycles „forever“**
- **multiple stem cell pools**
- **exc. DNA repair**
- **telomerase**
- **ROS scavenging enzymes**
- **antioxidants**
- ***Haslam et JID 2016***
- **melatonin**

Kobayashi et al. FASEB J 2005

- **EXCEPTION: *Greying !***

Aging of HF pigmentary unit & HF melanocyte stem cells



Harbors a neuroendocrine stress-response system

CRH→ACTH→cortisol

Prolactin, NGF, subst P

Responds to psychoemotional & chemical stressors

→ Hair growth inhibition

Cancer therapy-associated hair loss:
Key frontier in psychooncology

- **Sudden loss of hair as a key instrument of mammalian communication → CIA= profound psychoemotional stressor**
  → acute & chronic stress responses + depression

- **Psychoemotional „stress“ is hair growth-inhibitory !**

→ Neurogenic perifollicular inflammation (NGF→ substance P→ mast cells activation) induces premature catagen and attacks HF stem cells (bulge)

- **Hair follicles are targets & sources of key stress mediators: CRRH→ACTH→cortisol, PRL → inihibit hair growt!**

→ Enhanced intrafollicular generation of hair growth-inhibitory stress hormones by chemotherapy & CIA-associated stress ?

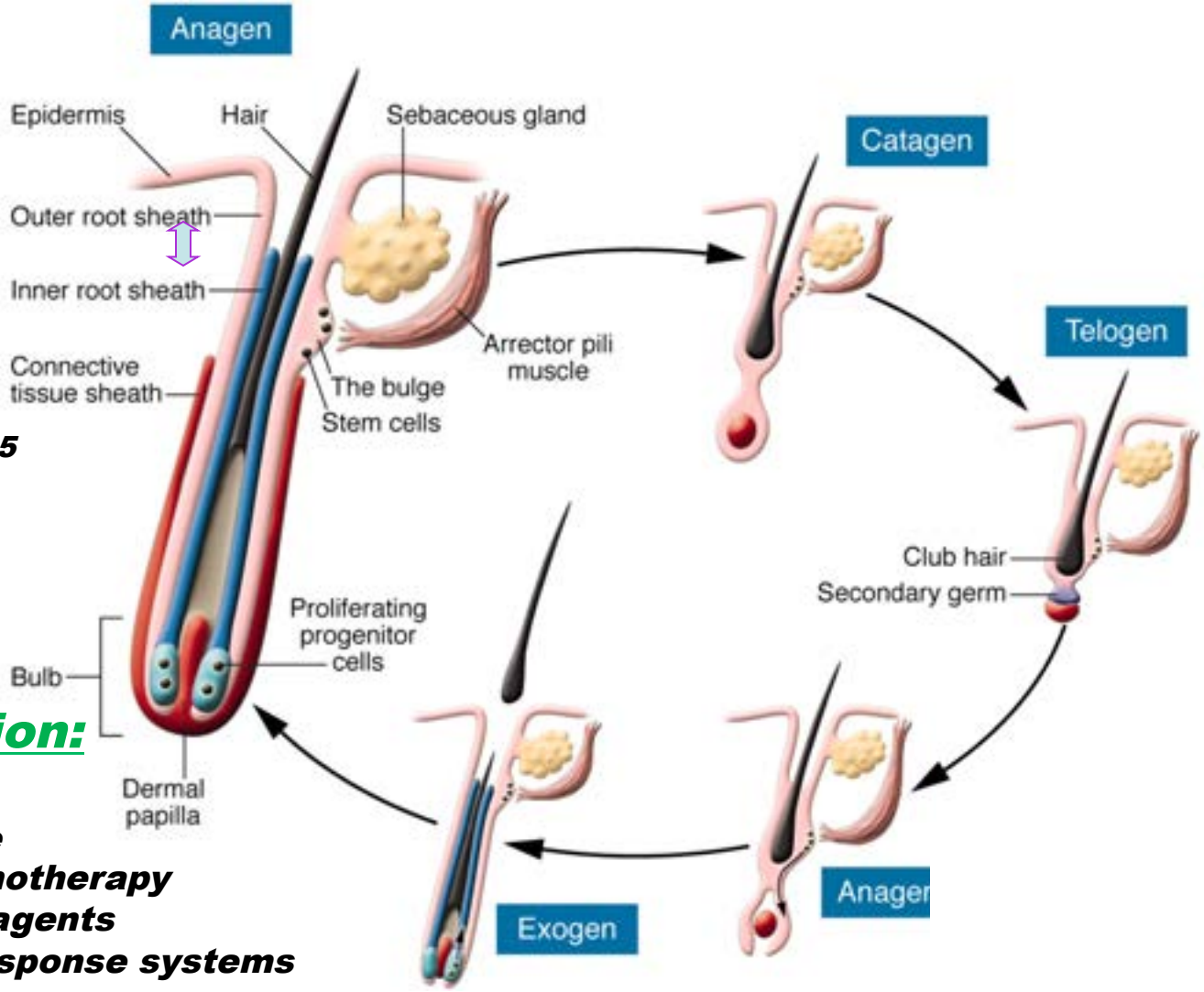
→ Psychological stress intervention: essential in CIA on multiple levels

Arck et al. *J Mol Med* 2005, Peters et al. *Am J Pathol* 2007, Paus et al. *Lancet Oncol* 2013

Why relevant in CIA ?

- **HF cycles „forever“**
- **multiple stem cell pools**
- **exc. DNA repair**
- **telomerase**
- **ROS scavenging enzymes**
- **antioxidants**
- ***Haslam et JID 2016***
- **melatonin**

Kobayashi et al. FASEB J 2005

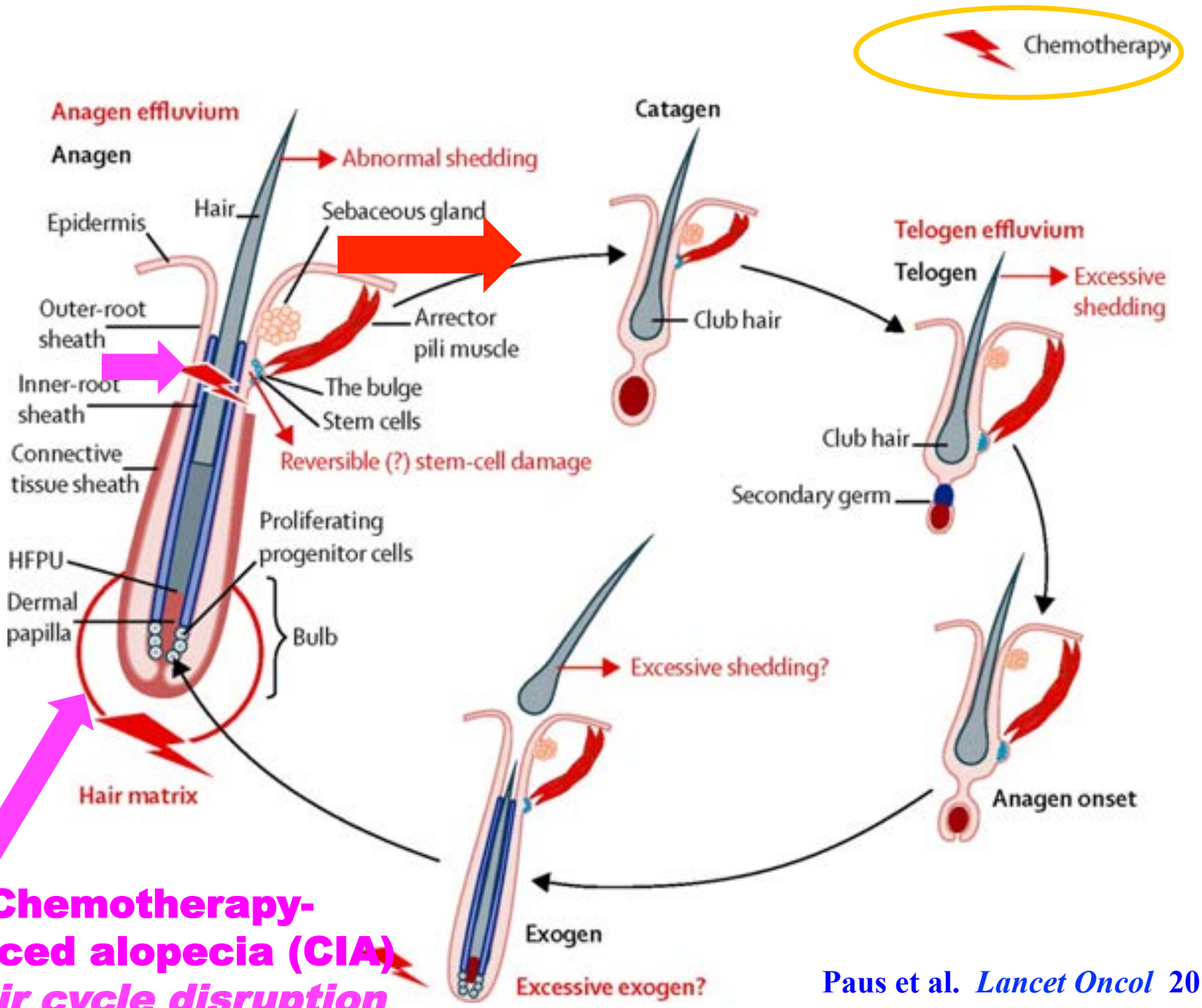


Scalp cooling ???

Future CIA management vision:

→ ***Upregulate the above before/during/after chemotherapy by HF-targeting topical agents***

→ ***Dampen HF stress response systems***



Chemotherapy-induced alopecia (CIA) = *hair cycle disruption*

Paus et al. *Lancet Oncol* 2013

Premature catagen induction:
Telogen effluvium

Trichogram

telogen =
***club* hairs**
***depigmented* tip**

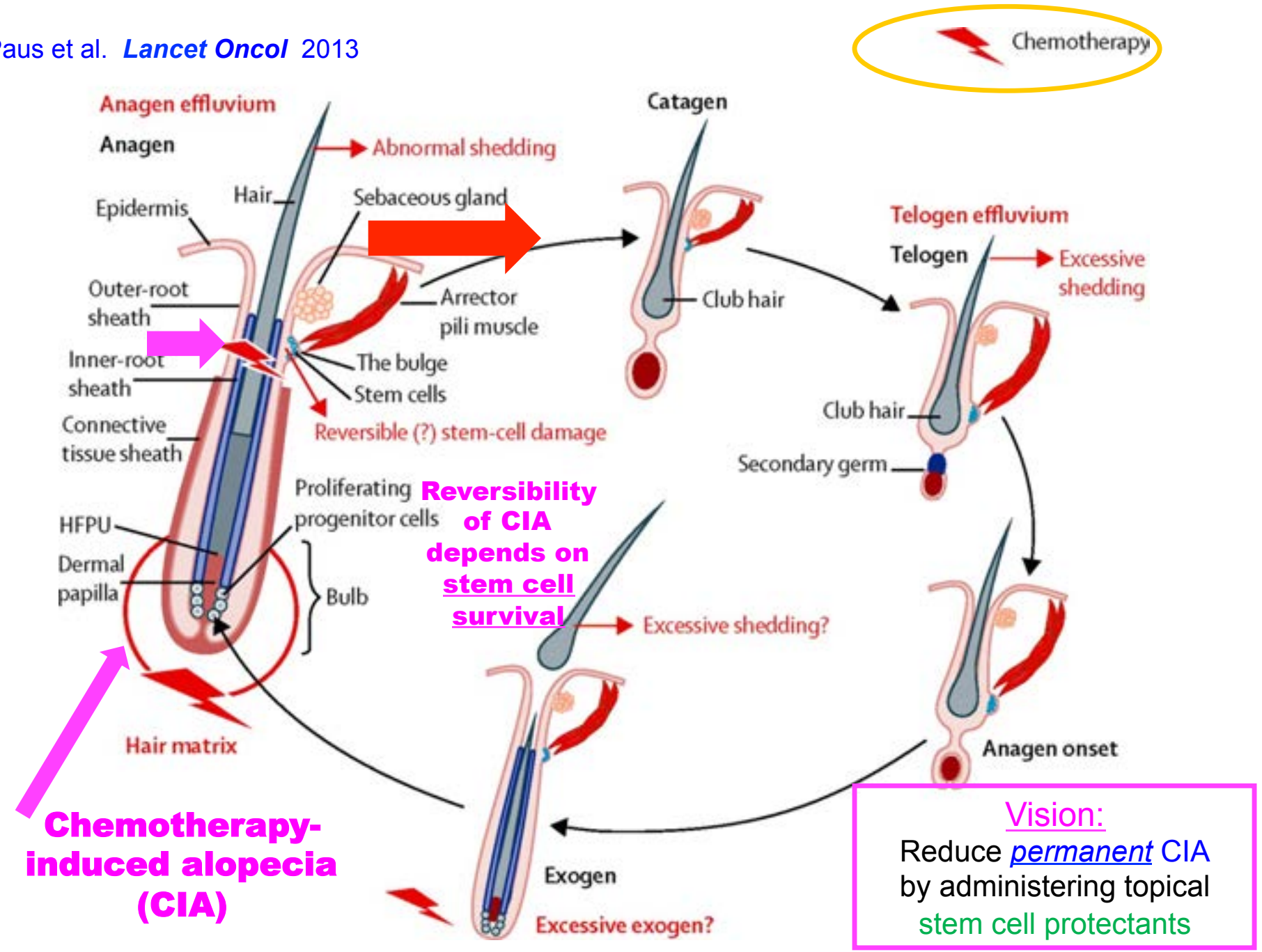
Dysruption of anagen
without normal catagen induction

anagen =
„*broom stick*“
IRS+
pigmented tip

CIA

Anagen effluvium

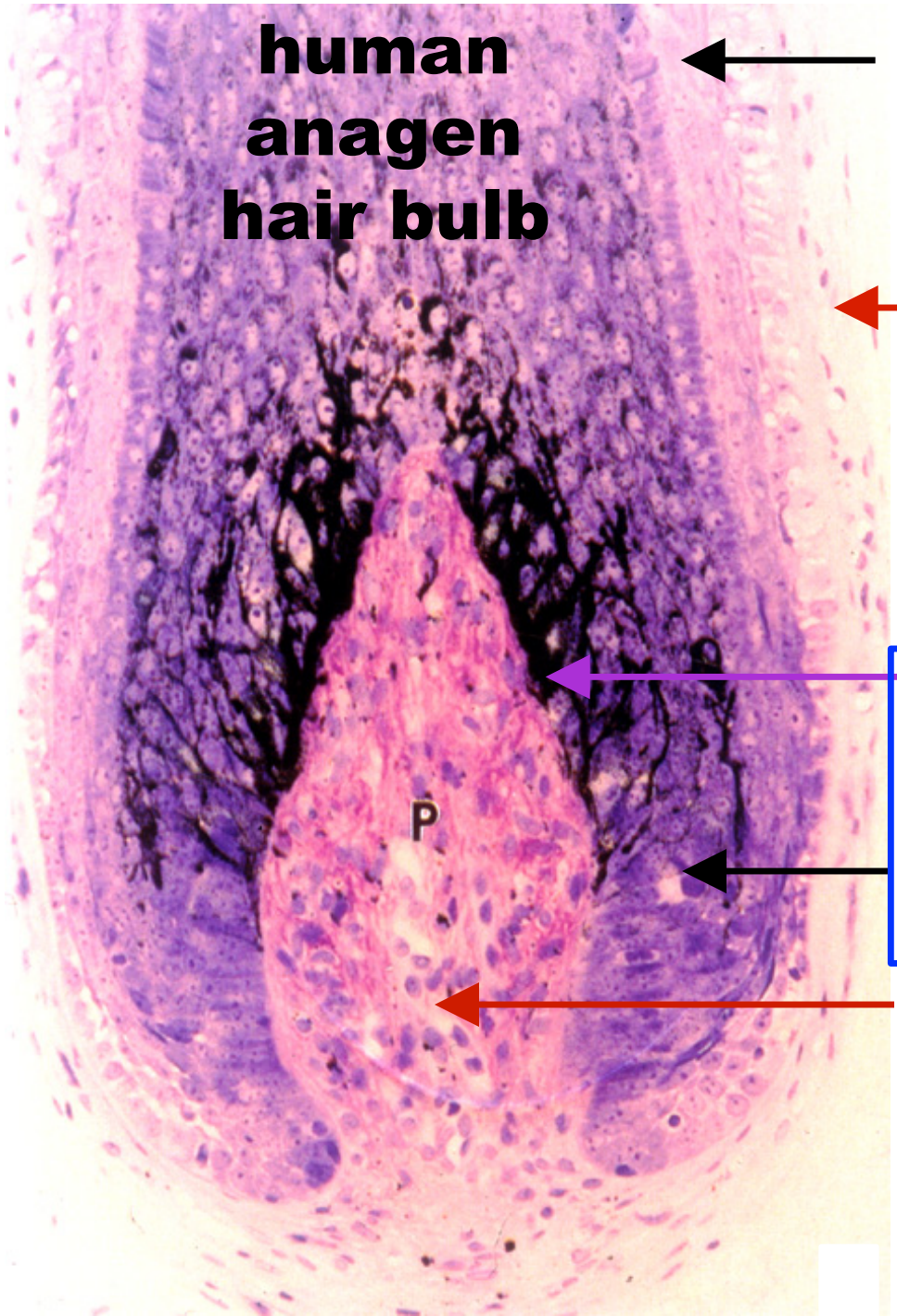
Paus et al. ***Lancet Oncol*** 2013



Chemotherapy-induced alopecia (CIA)

Vision:
Reduce *permanent* CIA by administering topical stem cell protectants

e.g. PPARg agonists, spermidine, endocannabinoids



outer root sheath

keratinocytes

amelanotic melanocytes/-blasts

T cells, Langerhans cells

connective tissue sheath

fibroblasts, mast cells,
macrophages, endothelial cells

progenitor cells

pericytes*

nestin+ cells*

Schwann cells*

*** = pluripotent progenitors

hair follicle pigmentary unit

differentiated melanocytes

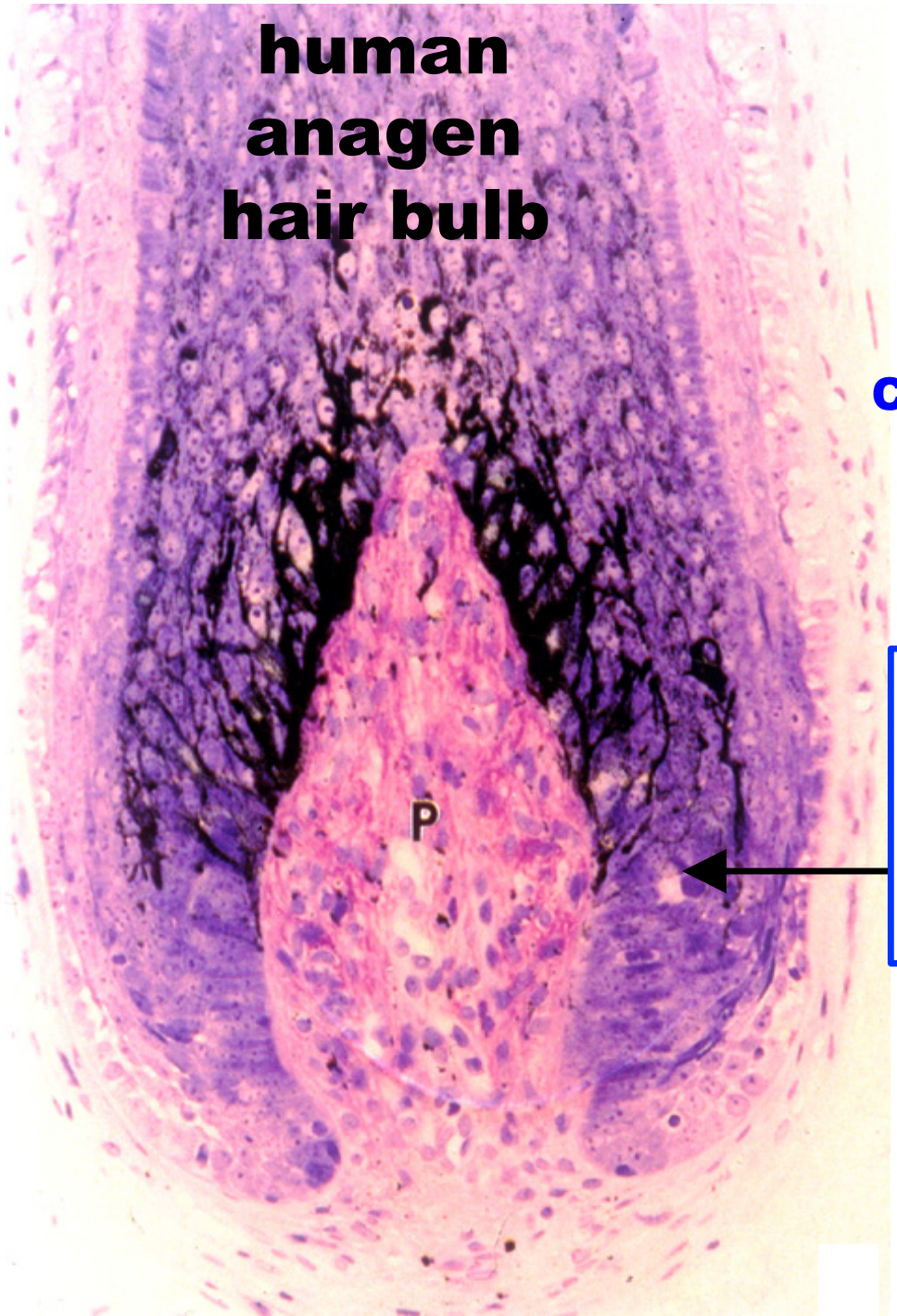
hair matrix

massively proliferating keratinocytes

follicular dermal papilla

inductive fibroblasts

Most sensitive to noxious stimuli/agents



Conventional wisdom:

Chemotherapy →

Cycling hair matrix keratinocytes

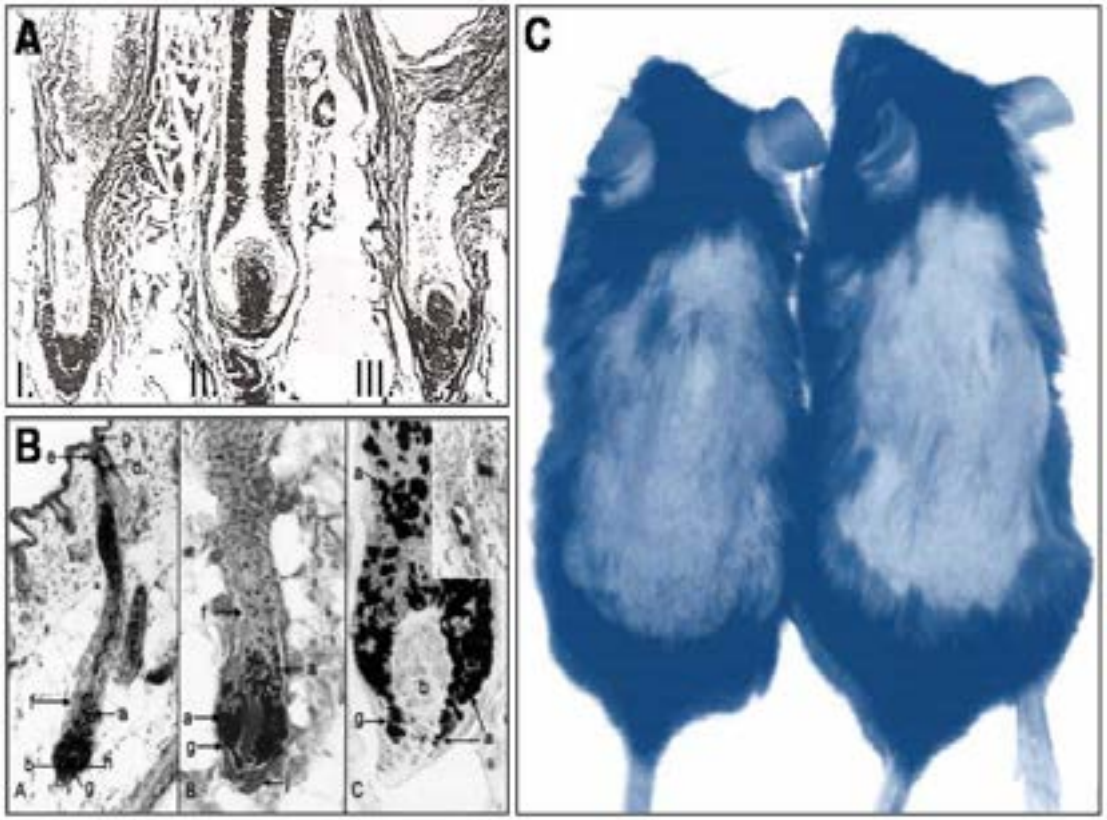
p53 → apoptosis

hair matrix

massively proliferating keratinocytes

Most sensitive to noxious stimuli/agents

Murine CIA model



Human pendant:

Scalp HF organ culture

Bodo et al. Am J Pathol 2007

Intraperitoneal injection of high-dose cyclophosphamide into adolescent/adult, darkly pigmented C57BL/6 mice with all back skin HFs in depilation-induced, early anagen VI causes massive hair matricx apoptosis, HF dystrophy and rapid alopecia,

perfectly imitating human cyclophosphamide-induced alopecia

Paus et al. ***Am J Pathol*** 1994

Botchkarev et al.
Am J Pathol 2001

- **p53 plays a key role in mediating CYP-induced massive hair matrix apoptosis and HF dystrophy**

- **Mediated via Fas (=direct p53 target!) ?**
  Sharov et al. ***Cancer Res*** 2004

Human scalp HF organ culture

→ identify hair growth promoters & inhibitors

2 Hair shaft elongation

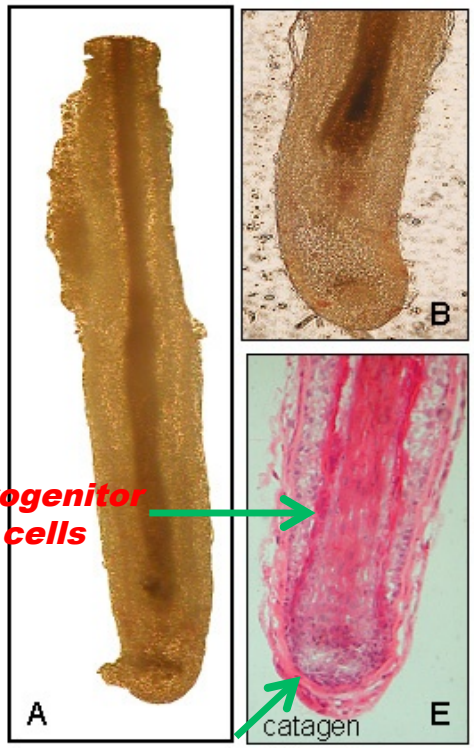
1 Anagen-catagen switch

CATAGEN

ANAGEN VI

Catagen inducers

= Hair growth inhibitors



3 Gene & protein expression profile

4 Hair matrix proliferation/ apoptosis,

5 pigmentation

Catagen inhibitors

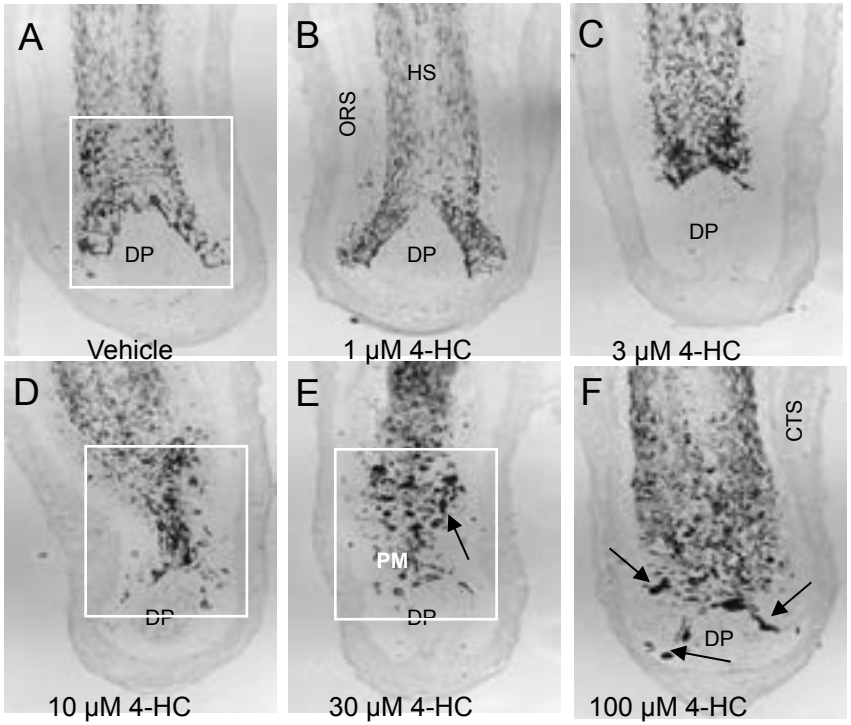
= hair growth promoters

6 Progenitor cells

7 Mast cells Macrophages

Use to test impact of chemotherapy

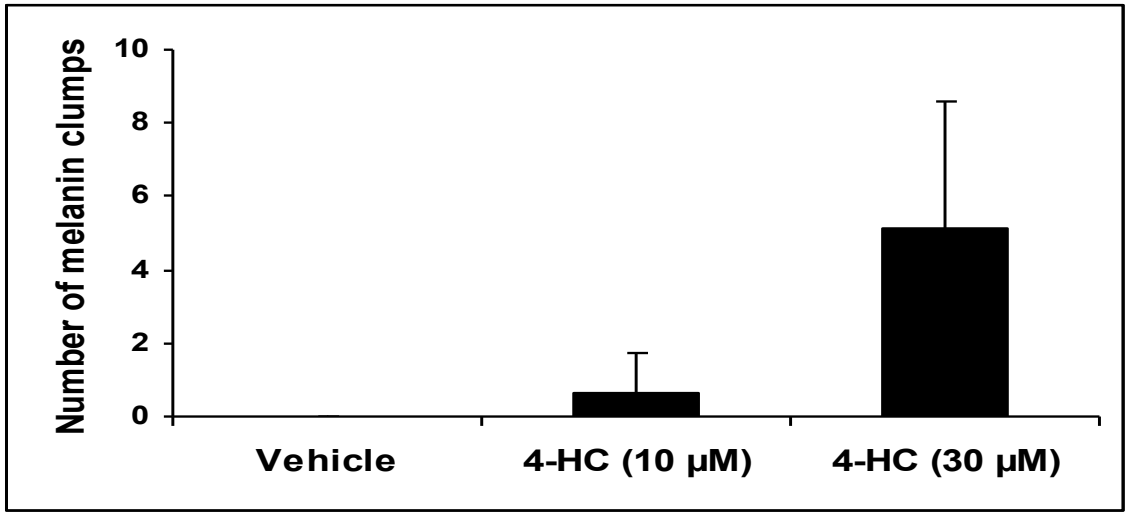
8 Gene silencing possible !



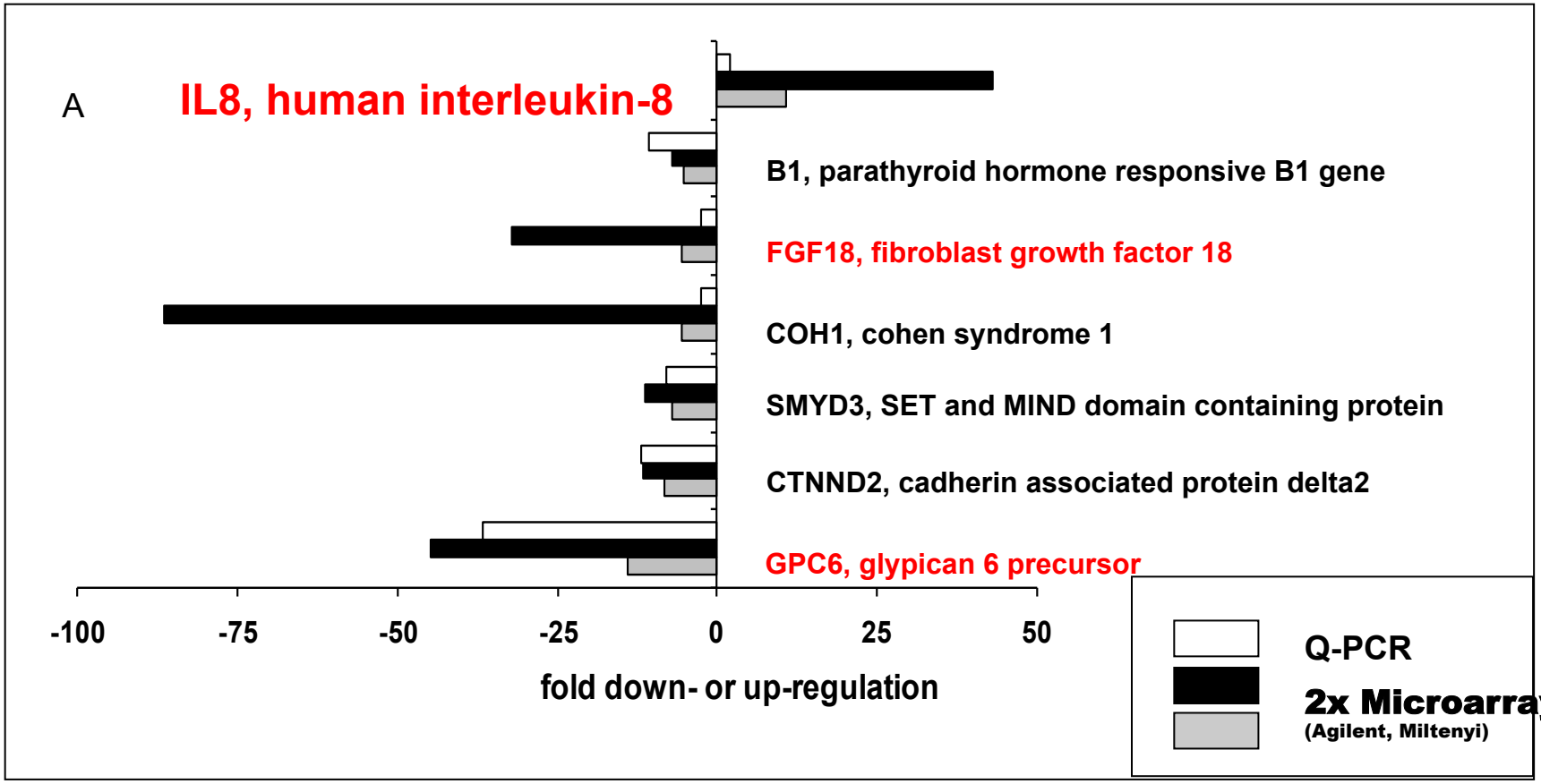
Cyclophosphamide (4-HC)
severely
disrupts HF pigmentation:

- **Ectopic melanin**
- **Melanin clumping**

→ Sensitive parameter for quantification of human HF damage level



Bodo et al.
Am J Pathol 2007



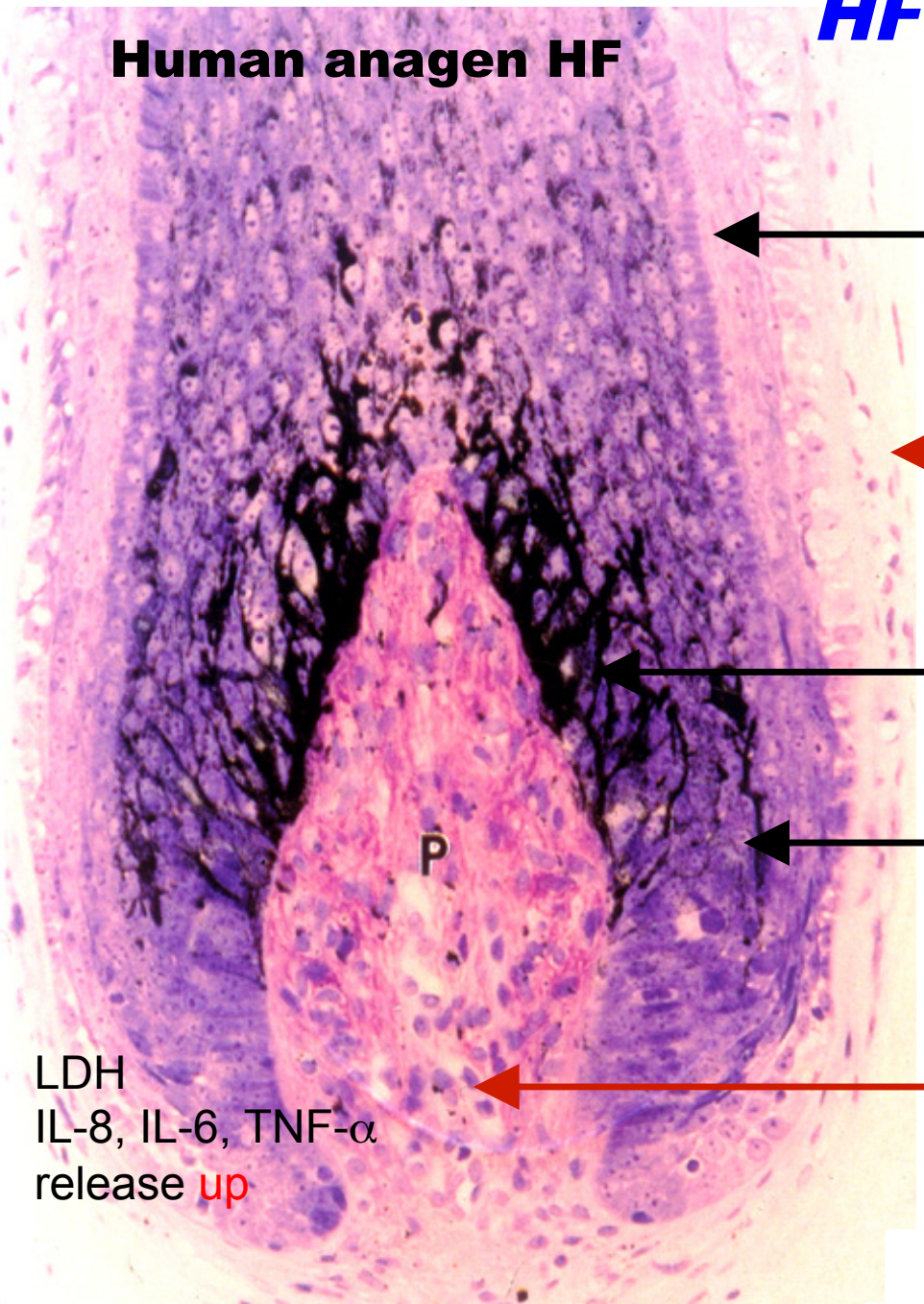
Cyclophosphamide metabolite (4-HC) induces a distinct and reproducible „ **gene expression damage profile**“ of human HFs

→ ***Define molecular damage-response profile of any chemotherapeutic agent in a living human organ !***

→ ***Candidate anti-CIA agents: „protection fingerprint“***

scalp cooling ???

HF damage responses
to chemotherapy



ORS: **TGFß1/2 up, IGF-1 down, CRH up reduced mitochondrial activity; loss of epithelial & melanocyte progenitor cells**

CTS: Mast cells degranulate, MACs activated

Disruption of HF pigmentation:
Ectopic melanin, melanin clumping, Cessation of melanogenesis

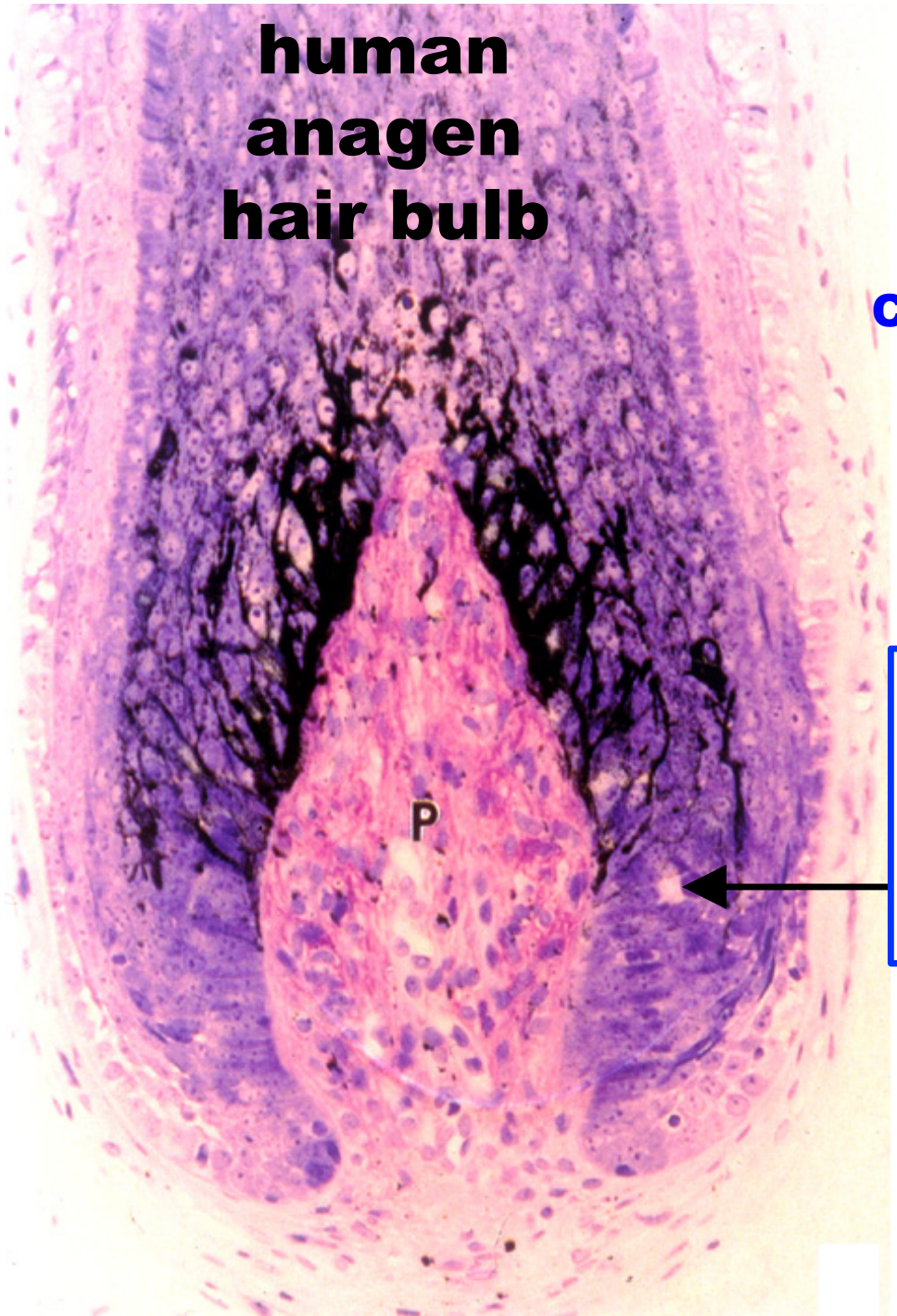
Hair matrix keratinocytes:

Increased apoptosis, reduced Proliferation; p53 up, Increased oxidative & DNA damage

Faster emigration of and reduced morphogen production by DP cells

LDH
IL-8, IL-6, TNF-α
release up

→ Premature catagen, stop of hair shaft production



Conventional wisdom:

Chemotherapy →

Cycling hair matrix keratinocytes

p53 → apoptosis

Bodo et al. AJP 207

Shh downregulation

Xie /Paus/Yie *J Invest Dermatol* 2015
& unpublished

hair matrix apoptosis

→ Vismodegib

→ *scalp cooling ???*

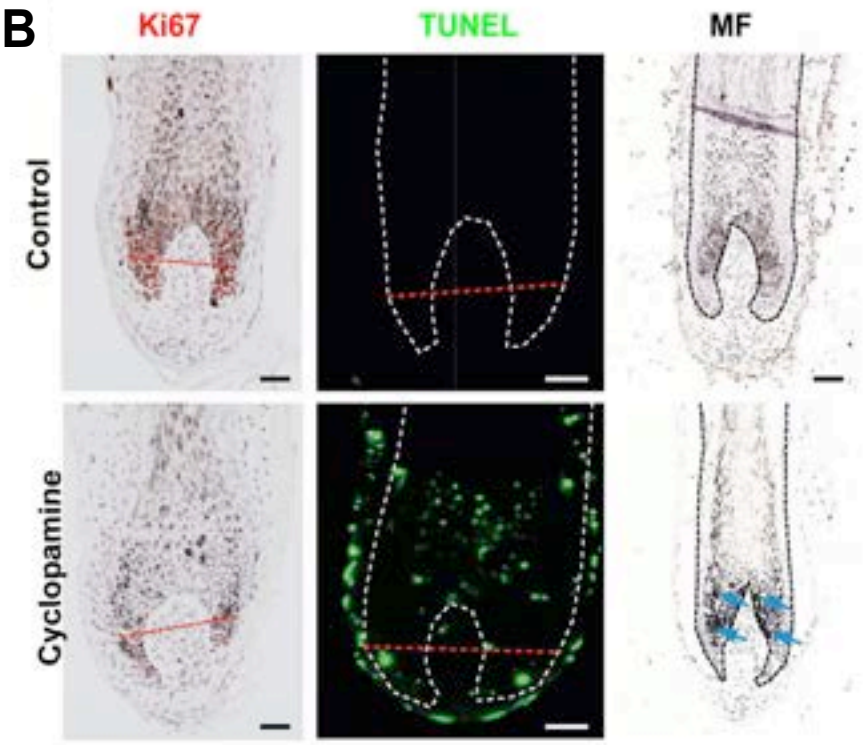
A

Case	Treatment	Hair Loss	Molecular Expression Change		
			Shh	p21	Fas
H04	Platin/Taxol	no	1.3	3.4	-4.2
L13	Taxol/Calcium forlinate/FU/Cisplatin	no	-0.5	-1.5	1.2
Y12	Vinblastine/Prednisone /Cyclophosphamide	no	2.9	1.7	-0.2
Z02	Taxol	no	1	-0.9	3.2
P16	Taxol	yes	-3.6	-0.5	8.5
T06	FU/Taxol	yes	-4.1	-0.4	-1.9
X18	Taxol	yes	-4.3	0.7	1.4
Y09	FU/Oxaliplatin/Calcium folinate	yes	-3.23	0.42	0.23
Z20	Tegafur Gimeracil	yes	-3.8	-0.8	4.6

Shh mRN downregulated in plucked hair shafts from all patients with CIA

Haslam/Paus/Yue,
•unpublished

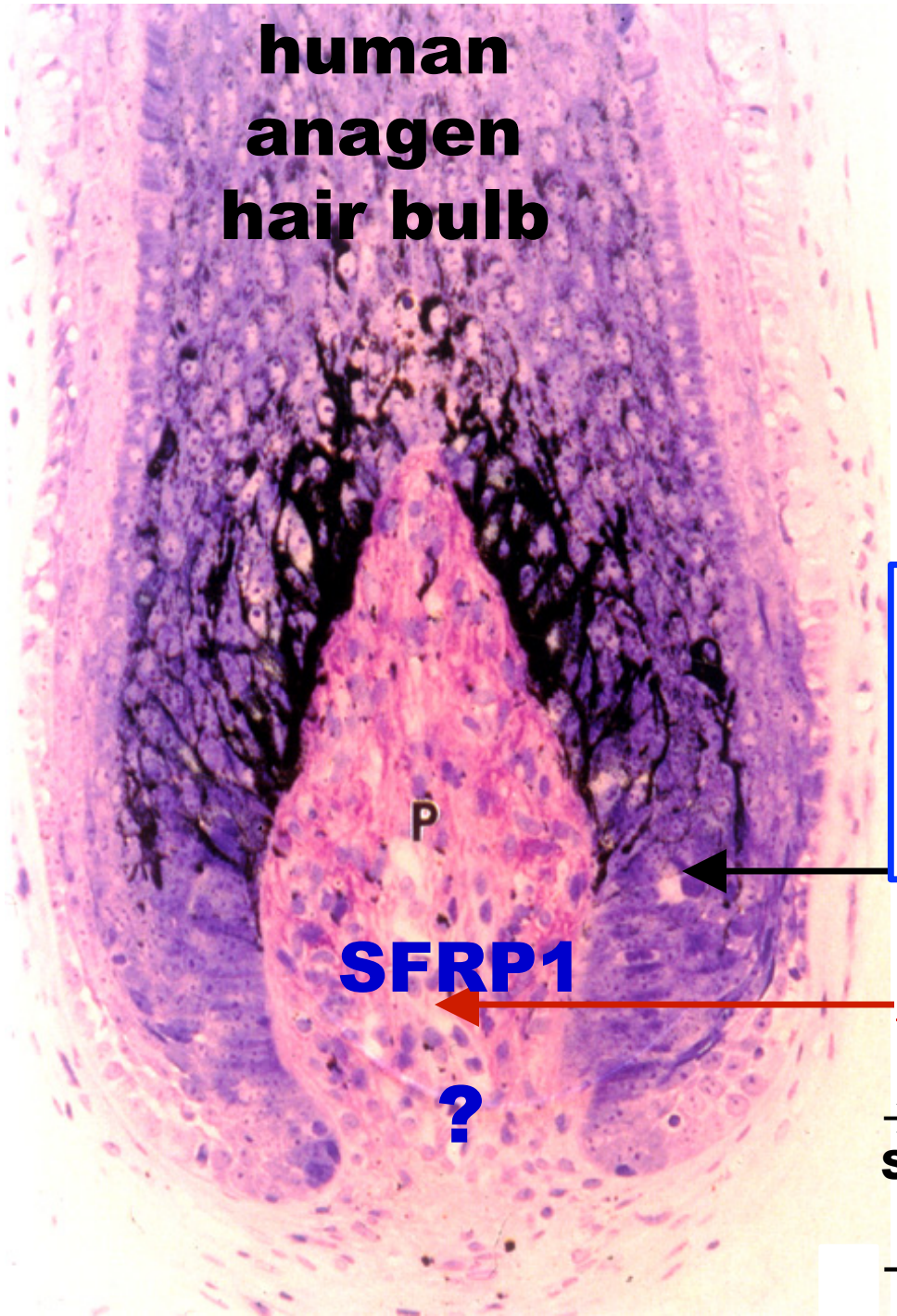
B



Cylophosphamide or Shh silencing both Inhibit proliferation & Induce apoptosis in human hair matrix

...and so does cyclopamine

CIA management vision:
Up-regulate Shh expr/activity in hair matrix



Cyclosporine A cause hypertrichosis, inhibits catagen
Hawkshaw et al. JID 2015

Cyclosporine A also Inhibits CIA in mice
Paus et al. AJP 1994 + 1997

Cyclosporine A suppresses SFRP1
Hawkshaw ert al. PloS Biol 2018

Shh → p53 → apopto**sis**

follicular dermal papilla (DP)

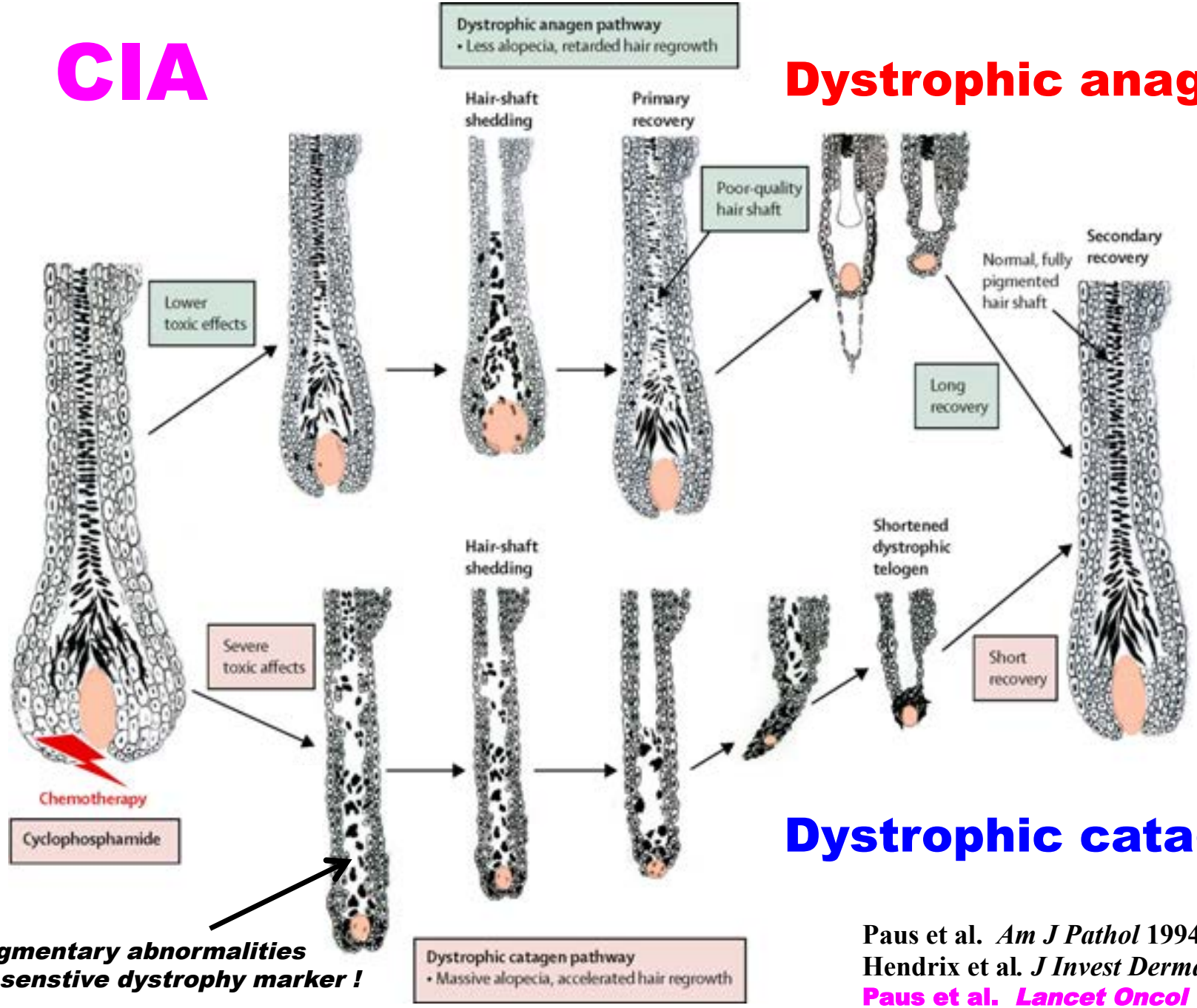
inductive **fibroblasts**

Hawkshaw et al. *PLoS Biol* 2018

→ Does chemotherapy up-regulate SFRP1-secretion from the DP ?

→ WAY-316601 suppresses SFRP1

CIA



Dystrophic anagen

Dystrophic catagen

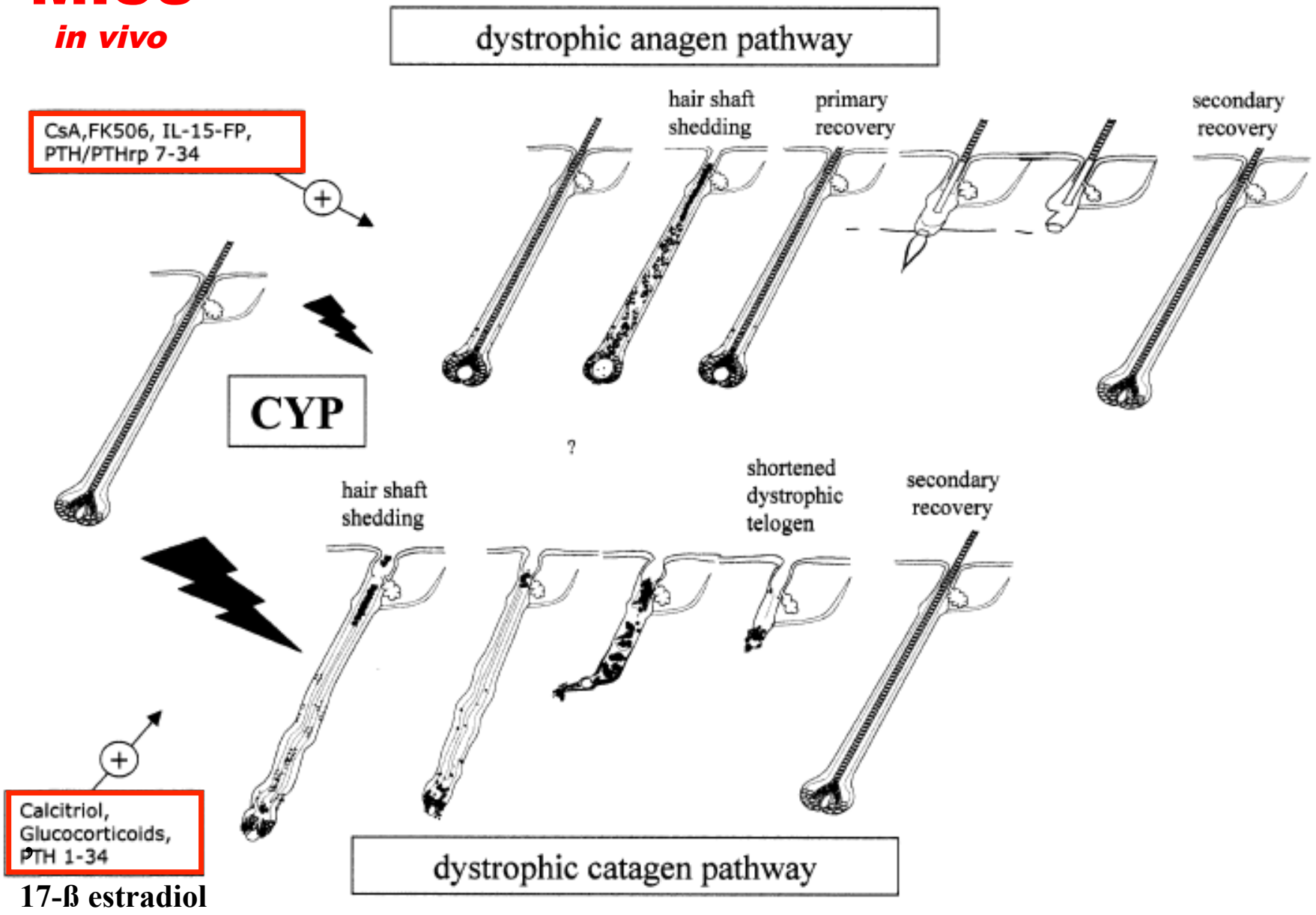
Pigmentary abnormalities
= very senstive dystrophy marker !

Paus et al. *Am J Pathol* 1994
Hendrix et al. *J Invest Dermatol* 2005
Paus et al. *Lancet Oncol* 2013

Chemotherapy-induced alopecia

Mice

in vivo



17-ß estradiol

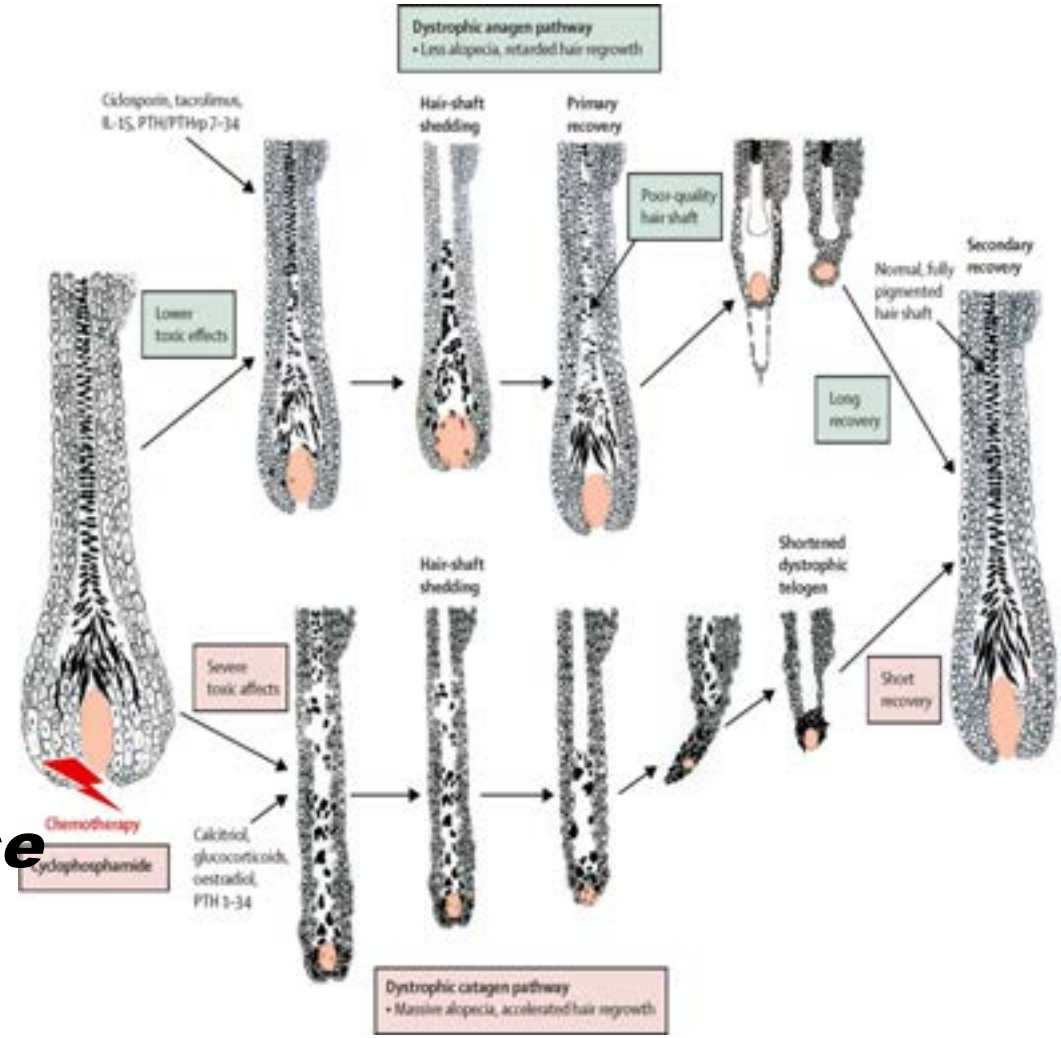
CIA

Dystrophic anagen

Conundrum:

- **Path to fastest & best hair recovery shows the most massive initial alopecia**

- ***Does it even make sense to inhibit CIA ?***

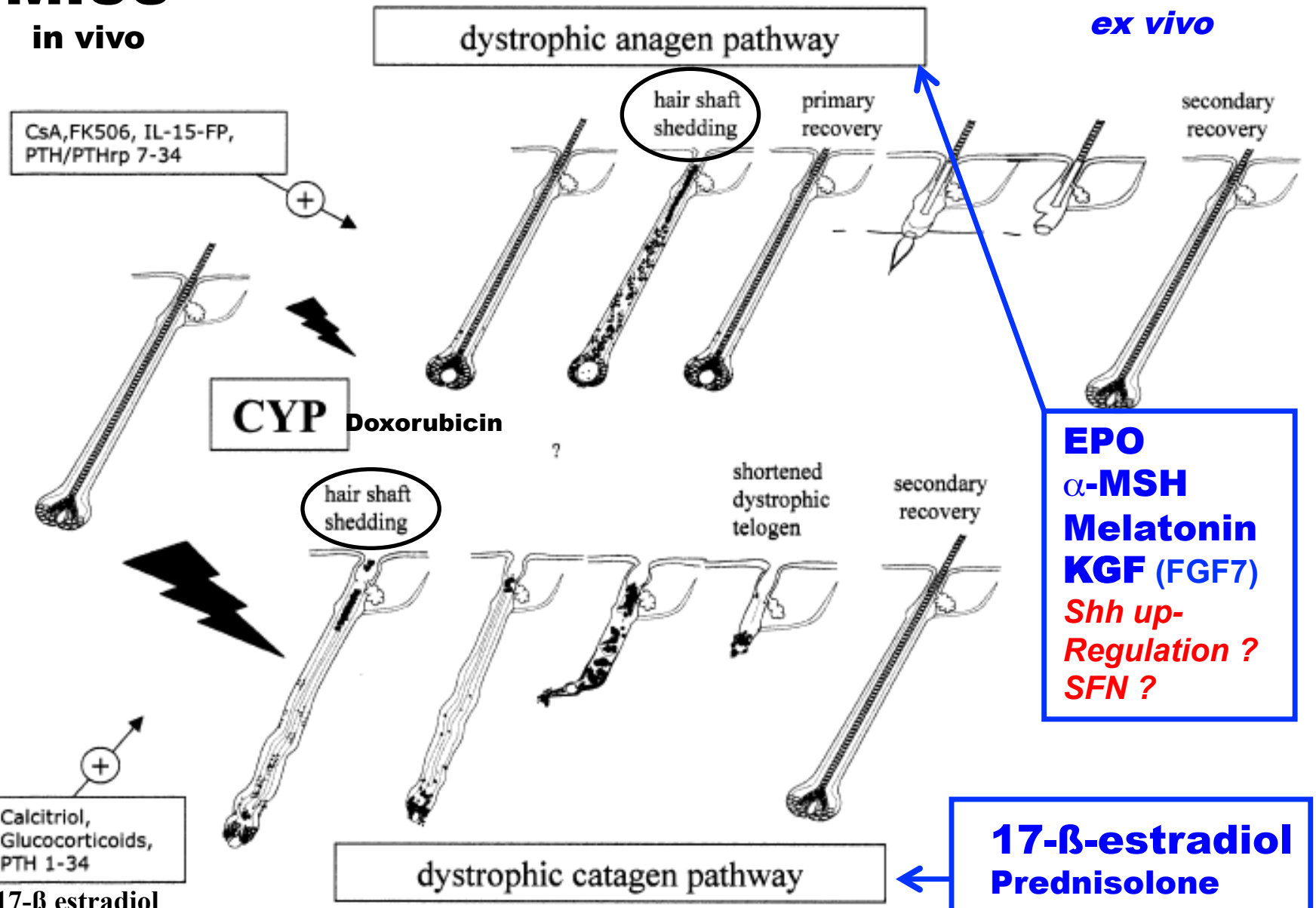


Dystrophic catagen

Mice
in vivo

CIA

Human HF
ex vivo



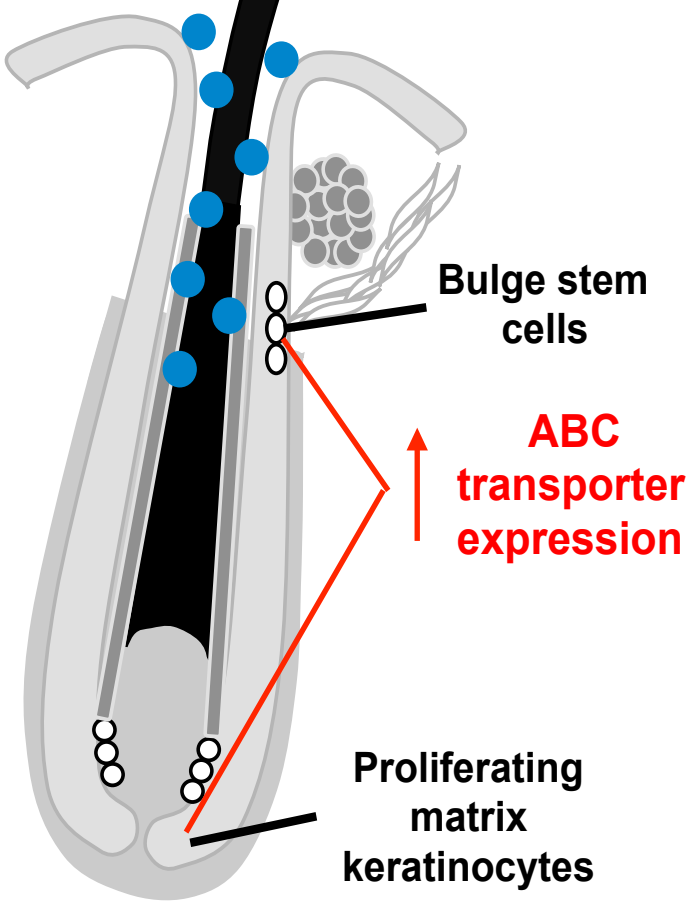
EPO
α-MSH
Melatonin
KGF (FGF7)
Shh up-Regulation ?
SFN ?

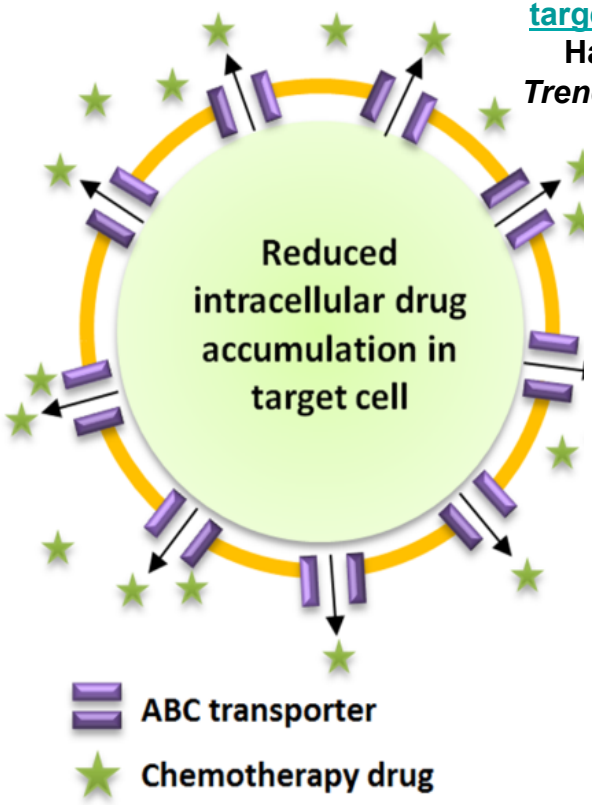
17-ß-estradiol
Prednisolone
(Vit D: calcitriol)

Generate „multi-drug resistant“ HFs

Topical ABC transporter inducing agent

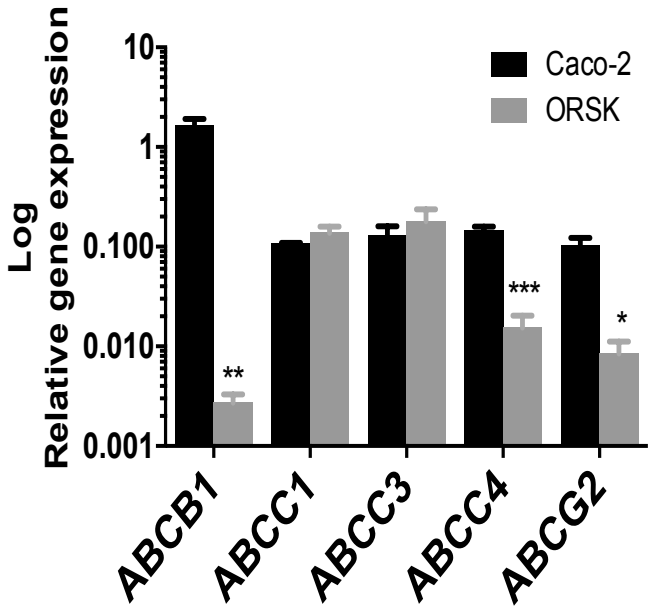
Multidrug resistant HFs





Protection against CIA: targeting ABC transporters
Haslam IS, …, **Paus** R.
Trends Pharmacol Sci. 2013

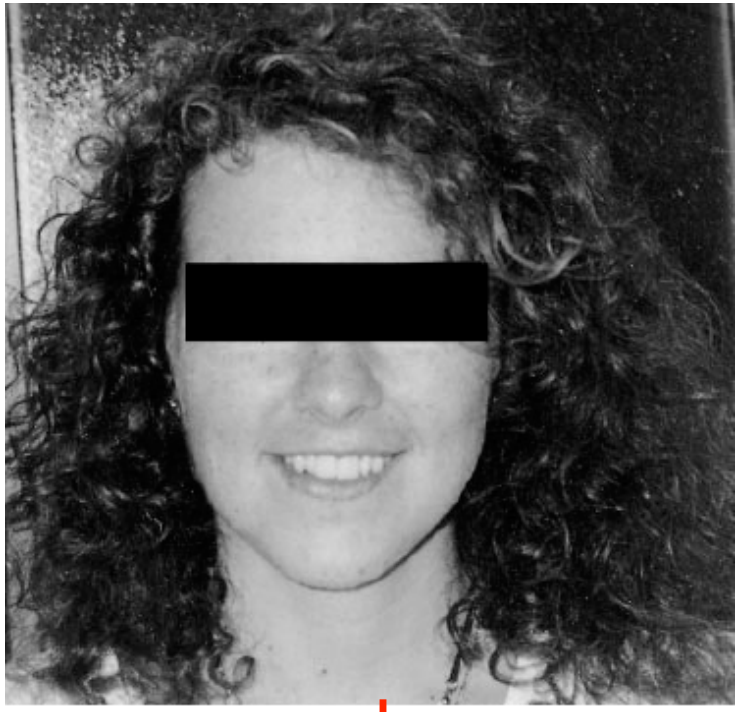
Differential expression and functionality of ATP-binding cassette transporters in the human hair follicle. Haslam IS, …, Paus R. ***Br J Dermatol.*** **2015**

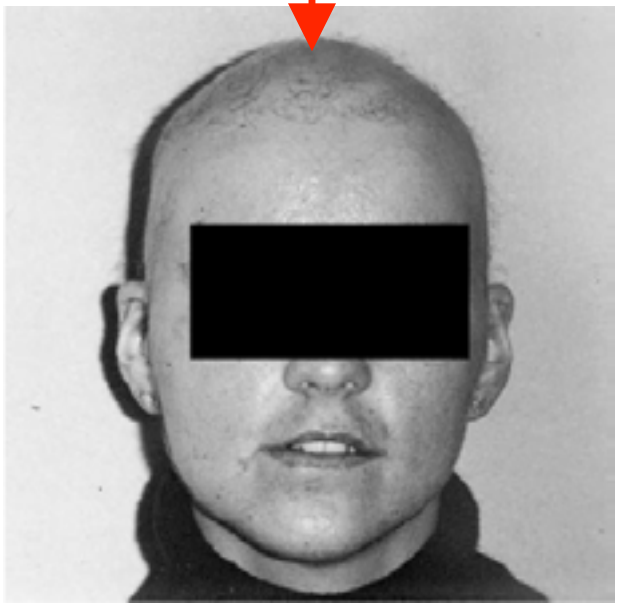


Primary human HF keratinocytes (ORS Kc) express key ABCs

Receptor	Agonist	Concentration	ABCB1	ABCC1	ABCC3	ABCC4	ABCG2
PPARg	Rosiglitazone	10μM	1.8±0.2	1.0±0.0	1.0±0.1	0.8±0.0	0.8±0.0
GR	Dexamethasone	50μM	2.1±0.6	1.0±0.0	1.2±0.2	1.0±0.1	1.6±0.5
VDR	Vitamin D	0.5μM	17.1±3.8	1.3±0.1	1.5±0.2	0.6±0.0	2.9±0.4

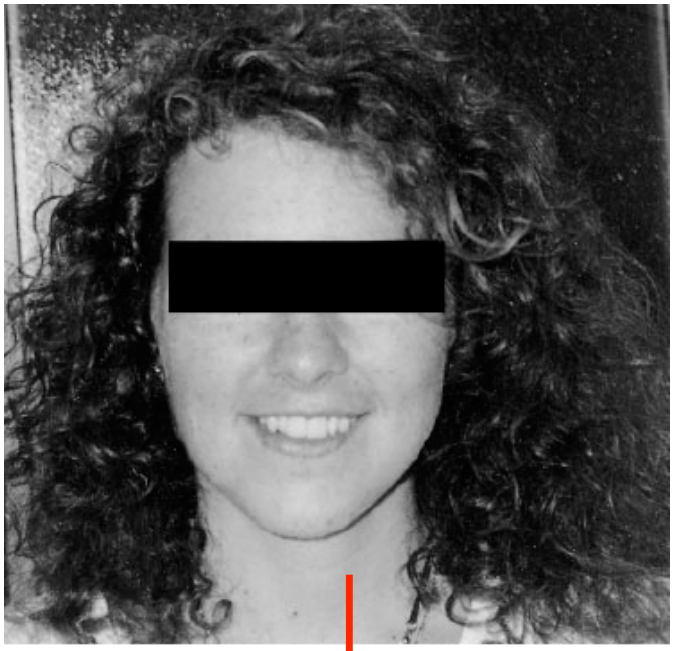
Induction of ABC transporters in human ORS keratinocytes (24 h, mRNA, qRT-PCR)

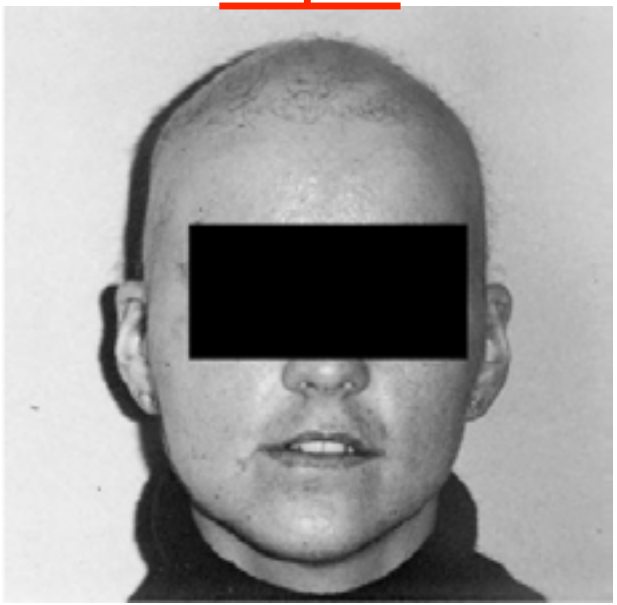




Don‘t just accept this:

Do something !





Acknowledgements

- Iain Haslam
- Zhicao Yue
- Enikö Bodo
- Boris Handjiski

We can & must do better than just scalp cooling
e.g. *explore*

How does scalp cooling work ???

EPO, α-MSH
Melatonin,KGF

Up-regulate
HF defenses against oxidate damage
Sulforaphane /Nrf2

Enhance intra-HF DNA repair & telomerase activity

Upregulate Shh
Downregulate SFRP1

Stem cell protectants
Cell cycle arrest

Make HFs „multi-drug resistant“