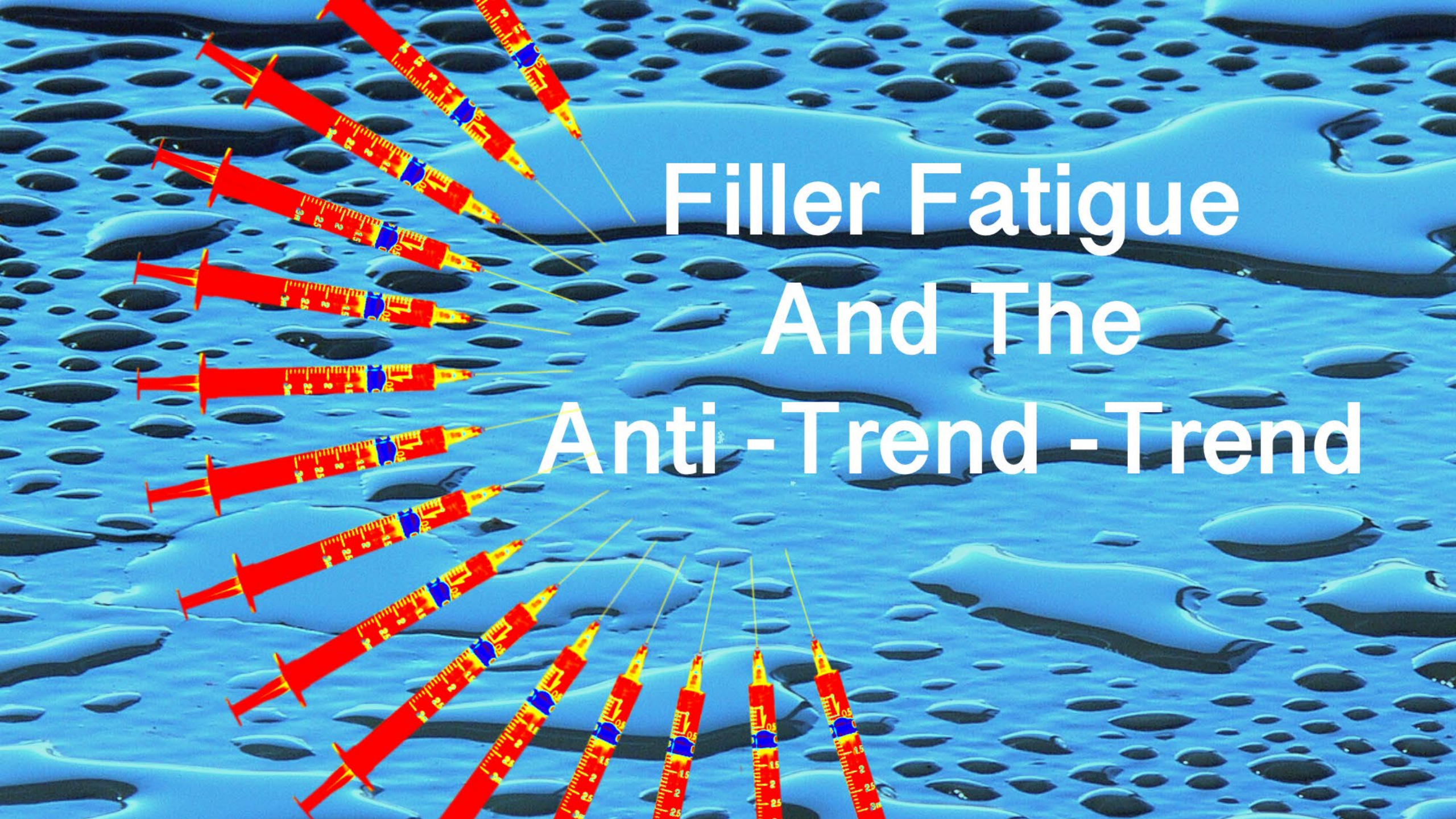
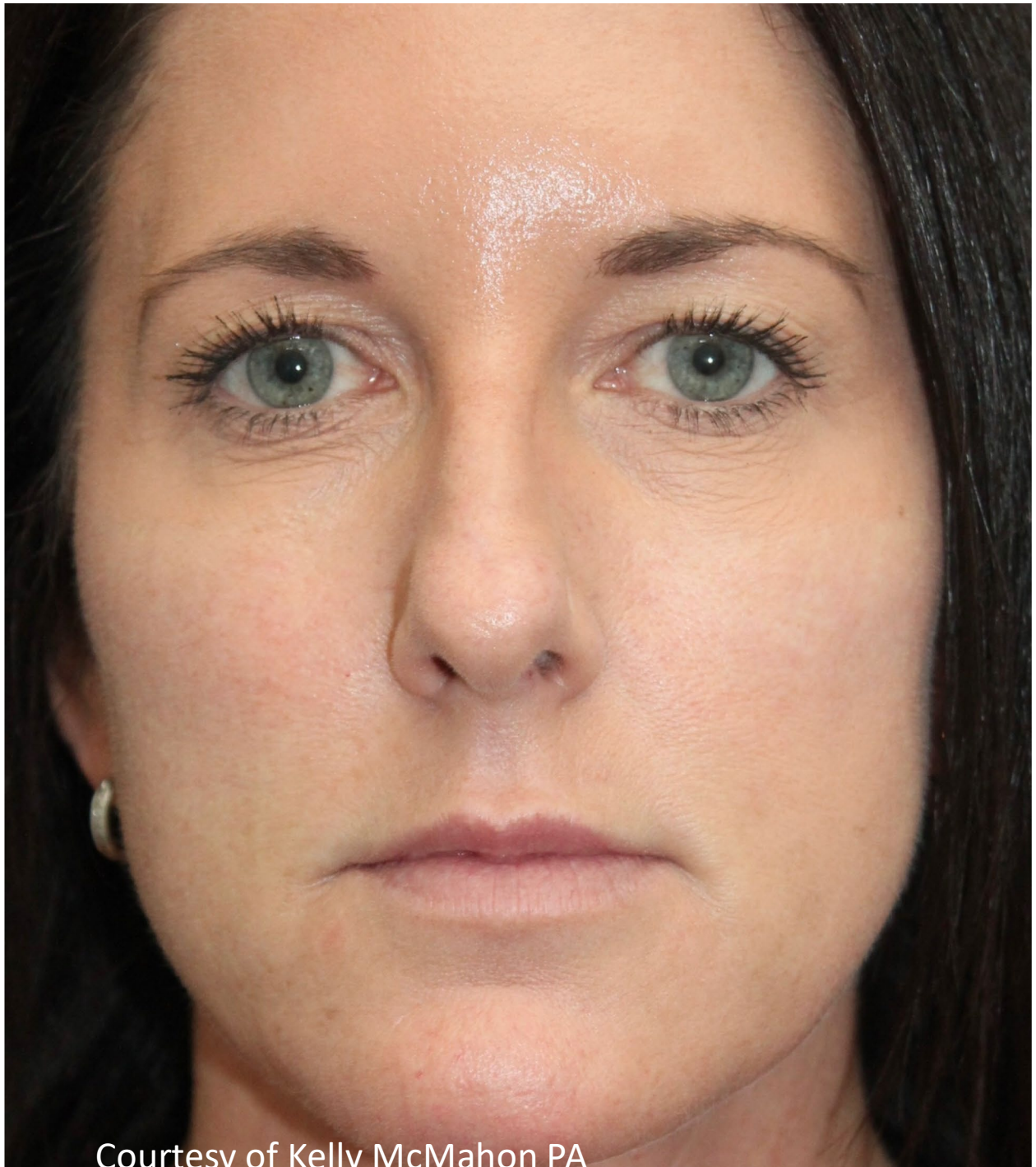
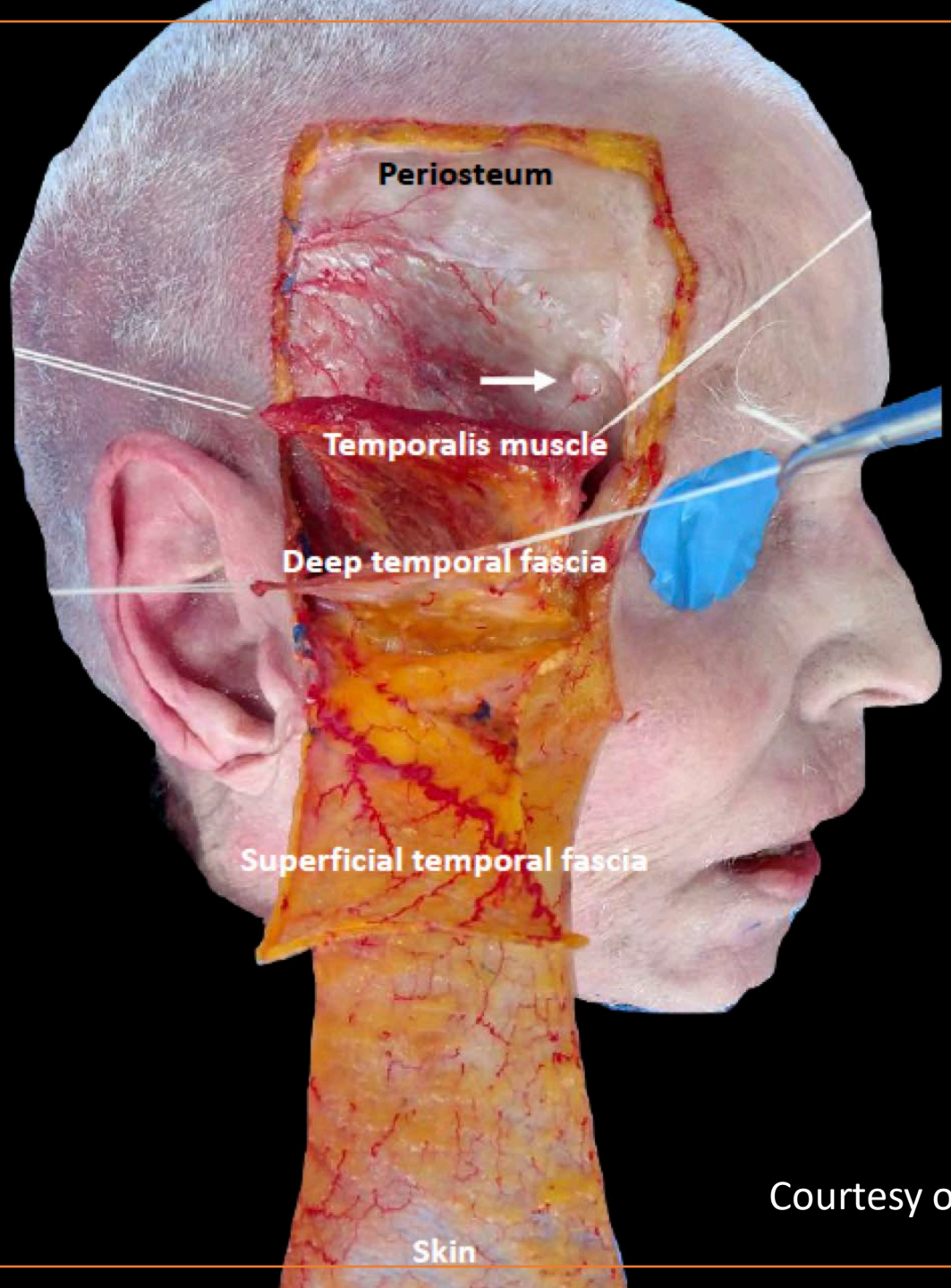

Filler Fatigue
And The
Anti-Trend-Trend

Grateful for them

H.A. Fillers



Courtesy of Kelly McMahon PA



Courtesy of professor Sebastian Cotofana MD

Daily Mail

WEDNESDAY, JANUARY 11, 2023 — Daily newspaper of the year — 90p — 65p to subscribers

Page 20 — Daily Mail, Wednesday, January 11, 2023

INVESTIGATION
by Alice Hart-Davis

ALICE, 59, HADN'T HAD DERMAL FILLER FOR THREE AND A HALF YEARS

...BUT IT WAS CLEARLY VISIBLE IN HER CHEEKS, LIPS AND CHIN

It's meant to dissolve over two years. But shock any woman tempted by tweakments, in an investigation that will Alice's MRI scan revealed...

I've got 20 years of filler stuck in my face

The doctor was 'astonished' to see so much left

AS THE grainy images from the MRI scan of my face resolved into 3D shapes on screen, my mind froze in disbelief. 'So, all the coloured parts that are showing,' I ventured, 'is that *all* filler?'

'Yes,' said Dr Simon Morley, the consultant radiologist who was talking me through the results. 'I'd say there's about 35ml of it altogether.'

I stared, alarmed, at the patches across my cheeks, along my jawline, in my chin, under my eyes, in my nose-to-mouth lines and lips. Dr Morley pressed a few buttons and helpfully deleted the underlying image of my face on the screen, leaving a framework of filler like a macabre mask. It didn't make sense.

'But if there's 35 millilitres there... that's more than all the fillers I've had put together. And I haven't had any for nearly four years!'

To say I was stunned was putting it mildly.

Over the past couple of years, I had heard stories of hyaluronic acid (HA) fillers lasting much longer than they were supposed to and not dissolving properly. And even though I've only ever trusted my face to Britain's leading cosmetic practitioners, I'd began to wonder if I might be affected too.

But to this mind-blowing extent? That ghostly imprint on the screen, an accumulation of years-old filler, was simply not supposed to be there.

As a journalist, I've been reporting on tweakments for more than two decades — I turn 60 this year — and in that time I've had a good deal of filler (probably about 30ml) injected into my face. I've had it put into my temples, cheeks, lips, nose-to-mouth lines, jawline and chin, in the 'tear trough' grooves below my eyes and in the tails of my eyebrows.

The idea is to soften the tell-tale signs of ageing, replace lost volume and add structure to your face as you move through your 40s and 50s, although nowadays women as young as 20 are using injectable fillers too, mostly in their lips.

It has, of course, become huge business. Since the first hyaluronic acid fillers were launched in 1996, thousands of people in the UK — and millions worldwide — have had injectable fillers (and you can have it injected anywhere, from your face to your hands, earlobes or even genitals). Last year, the world's leading filler brand celebrated the manufacture of a milestone 100 million syringes of filler.

But, along with the rest of the world, I had always understood that these dermal fillers were temporary treatments, lasting for a year or most before being absorbed into the body and effectively disappearing.

If you want to maintain those plumped lips or that enhanced jawline beyond the year-long limit, you need to 'be re-treated', most aesthetic clinics book patients back in every six to 12 months for reassessment, to 'refresh' their fillers and keep their faces looking on point.

Yet, quietly, thanks to a pioneering aesthetic radiologist I met Dr Mobin Master, based in Melbourne, Australia, evidence has been mounting that fillers may stick around for a good deal longer.

'I probably first saw this issue in mid-2019,' he tells me. That was when cosmetic surgeons started sending patients to him wondering if the swelling around their eyes was the result of old filler. And, yes, 'many of these cases showed residual filler, some of which was from two years to 12 years old'.

Filler apparently lasting for 12 years was a worrying discovery.

'Certainly, it was surprising,' continues Dr Master. 'The general understanding is that hyaluronic acid dermal filler is temporary and should self-dissolve over a period of, at most, two years.'

From my research, particularly in the mid-face and around the eyes, filler seems to last a lot longer than we initially expected.

Having followed Dr Master's work, I decided to see what an MRI of my face might reveal. So, at a point when — apart from one scrap of lip filler — I'd had no HA injected into my face for more than three and a half years, at the recommendation of London-based aesthetic practitioner Dr Sophie Shotter, I booked in for a scan.

Analysing filler using an MRI is a specialised, painstaking process. Dr Morley is usually to be found working as a consultant head and neck radiologist at University College Hospital, but in his private work he is fielding an increasing number of requests from aesthetic doctors and surgeons to identify filler in faces where it may be causing lumps, or has migrated or drifted from its original position.

He admits he was 'completely astonished' to see the extent of filler in my face — he is normally looking at problematic filler, not at someone whose face looks fine on the surface. I seem to recall the phrase 'blown away' being bandied about as he, Dr Shotter and I pored over the images together.

I had wanted a 'baseline' image of a filler-free face. This was so far beyond what I was expecting, I found it hard to take in.

I asked how the imaging worked. 'HA fillers attract water,' Dr Morley explained. 'So you can depict the filler against the fatty tissue in the cheeks, then by nulling the signal from the fat, you're left with an image of the filler.'

So the 8ml of fat I had transferred from my thighs to my face in 2019 wouldn't be showing up in these images? No, said Dr Morley.

And what about all the Sculptra that I had injected into my face about 15 years ago? Sculptra is a 'stimulating' filler that encourages your face to grow more of its own collagen. Could that be showing?

Again, no, because the carrier gel with which the Sculptra is mixed is not HA and leaves the face very quickly.

I can see that actually I'm lucky, as that framework of filler has stayed exactly where it was placed in my face. None has migrated.

But three rather urgent questions occurred to me.

First, superficially, how ancient would my face look if that filler wasn't in there? Heavens, here I was imagining that, when I looked in the mirror, I was looking at my real almost-60-year-old, filler-free face, when in fact it was still held up by 35ml of hyaluronic acid.

Secondly, I wondered why there is apparently more filler than I have had injected. That is hard to say. Dr Morley suggests it may be because HA attracts water, so it appears as a larger volume on the scan. Dr Shotter wonders if it is because, over time, the filler has integrated with my facial tissues, so the scan is picking up filler that has become part of my face — so, excuse the grimness of the description, filler-plus-flesh — as well as the filler that is just still there.

It's also hard to say exactly what the HA in my face is, and when it dates from. I've tried fillers from all the major brands over the years and been very happy with them.

Much of what is showing will be from a 10ml-in-one-go treatment in early 2018 — but Dr Morley detected filler in my tear trough area, which hasn't been touched since 2018, and my nose-to-mouth lines, which I can't recall having had done in well over a decade.

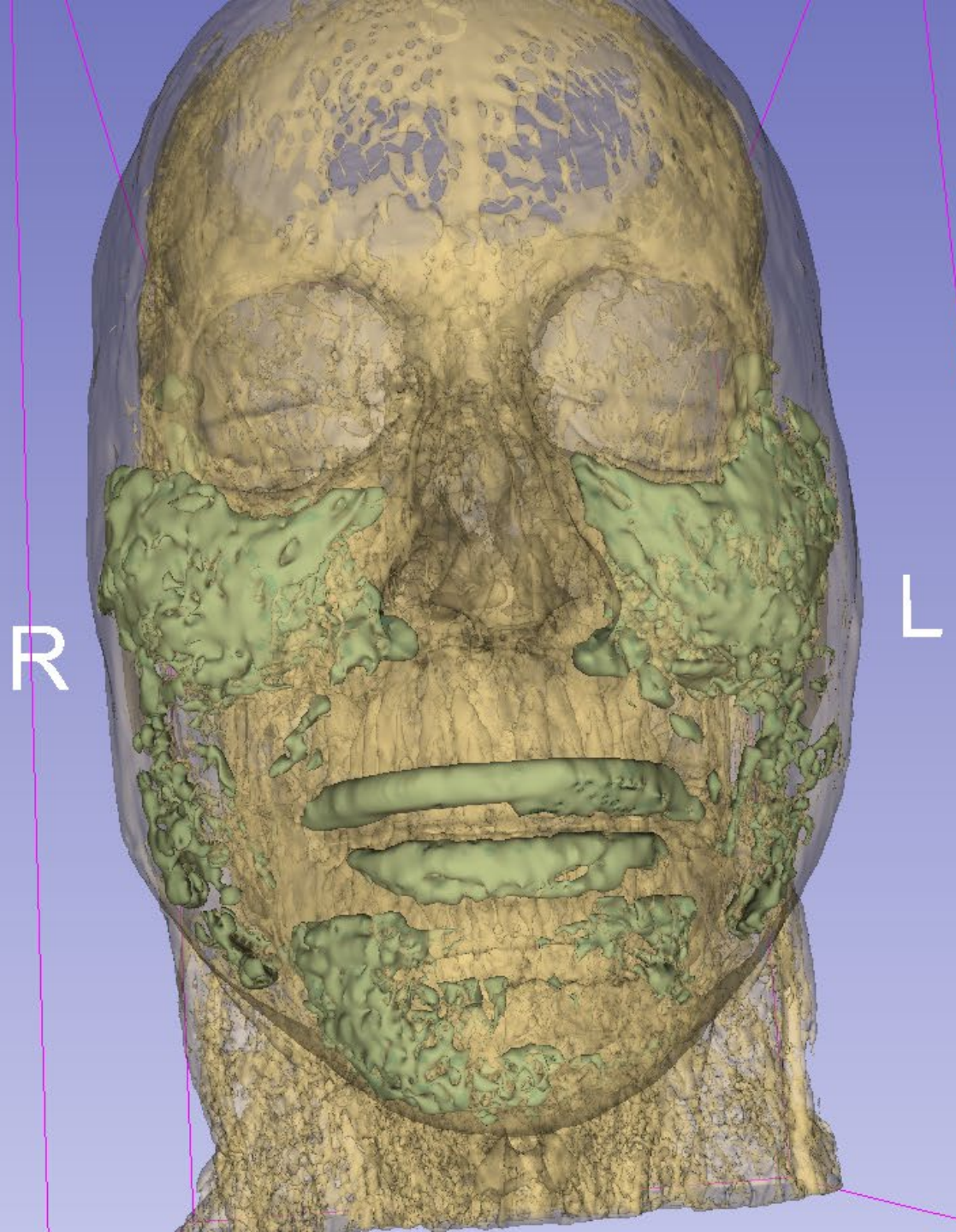
But the third question is perhaps the most important of all. What effect, if any, is all this undiscovered — indeed, hitherto undetected — residual filler having on my health?

The truth is, no one knows definitively — but it's unlikely to be bad. 'At this stage,' says Dr Master, 'we don't know of any adverse effects of longevity. But injectables have been around for more than two decades and there is little or no reporting of health concerns.'

If we were going to hear of effects on health, we would have done so by now, he thinks. Yet it is clearly an area that merits more study. Individual consumers can't be expected to find out for themselves whether their face is still full of filler after all. MRI scans are very expensive — I paid £700 for mine.

The person who keeps Dr Morley busiest with requests for filler MRIs is leading oculoplastic surgeon Daniel Ezra. 'When patients come to him to discuss

Courtesy of Alice Hart-Davis



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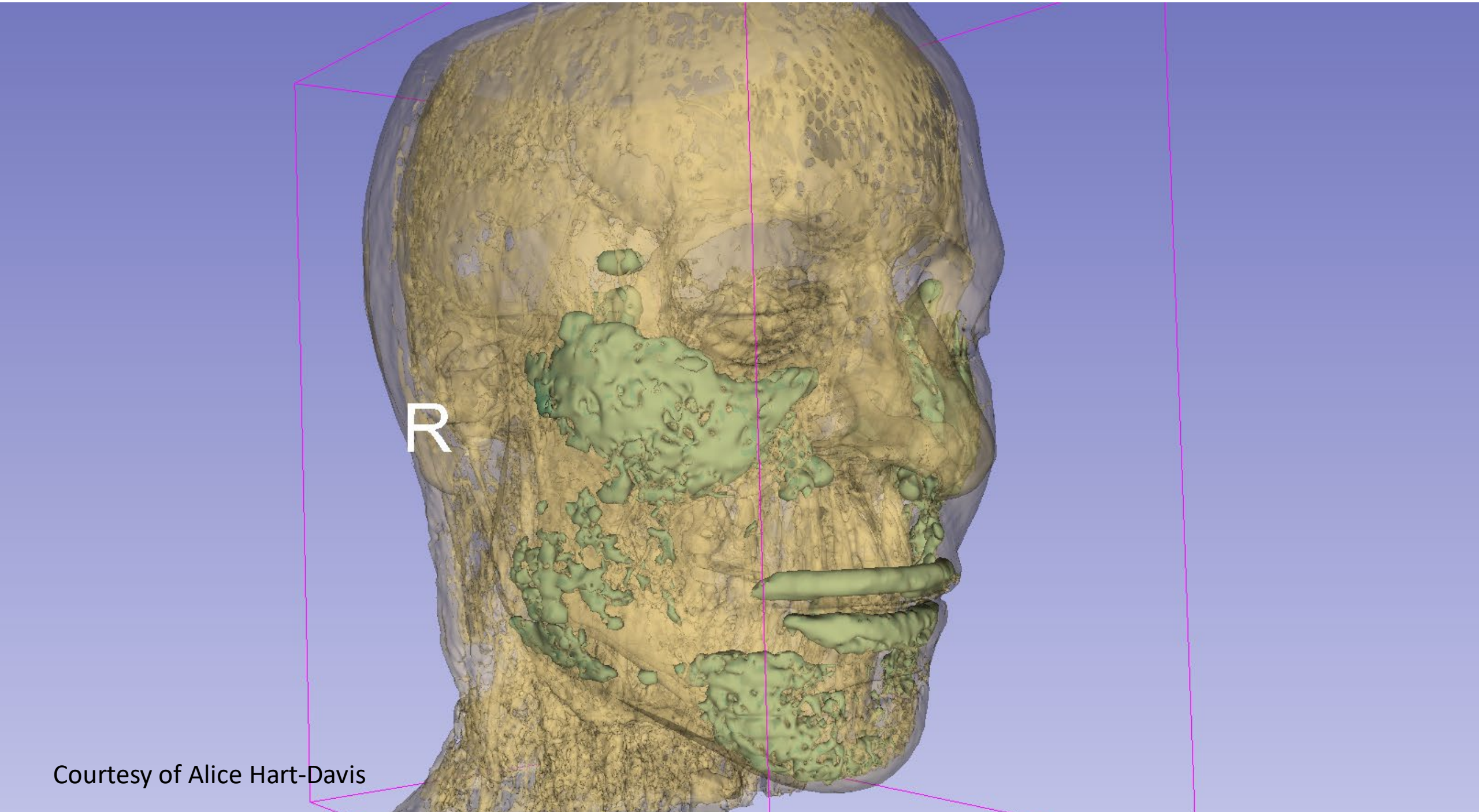

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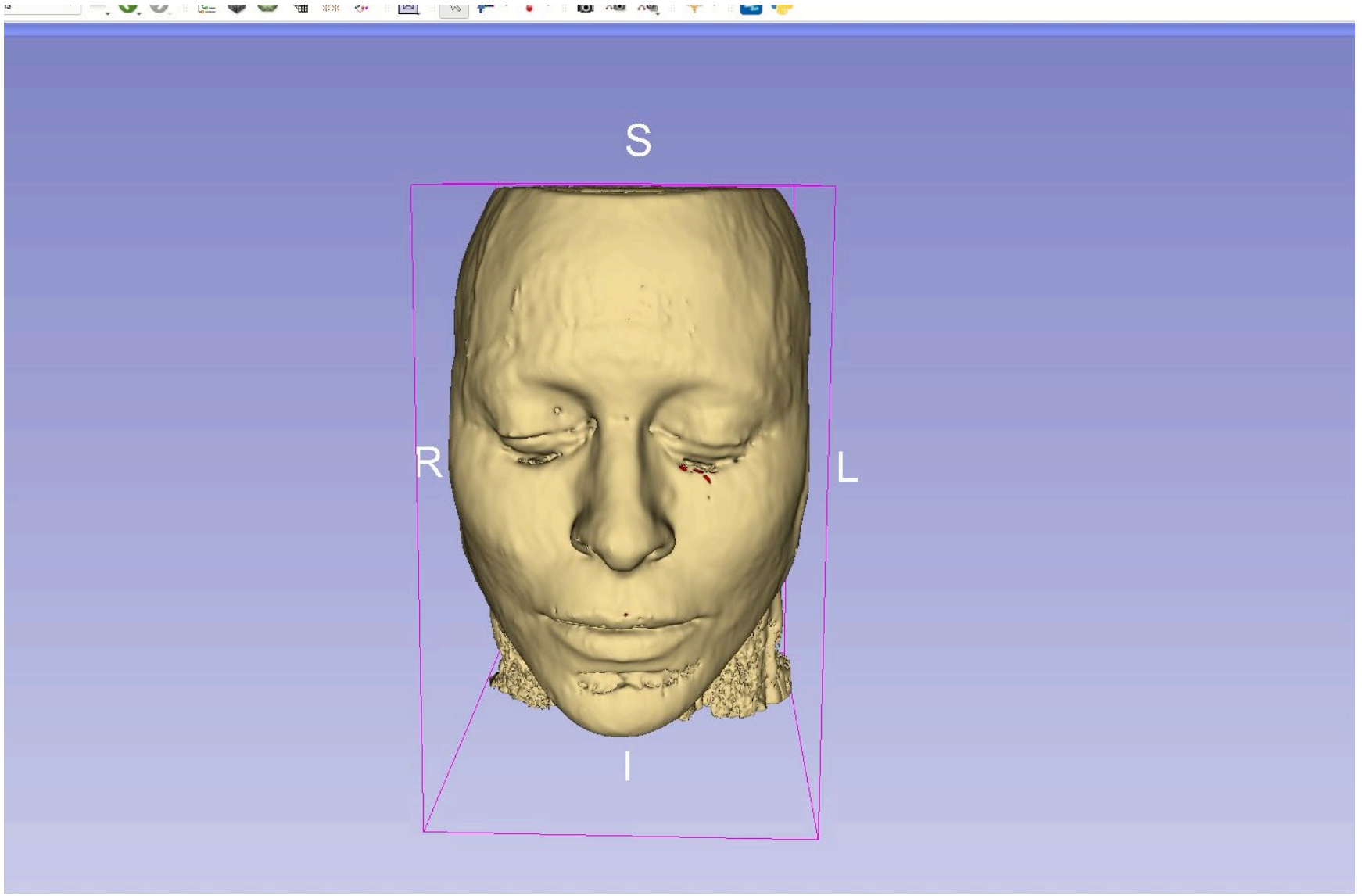

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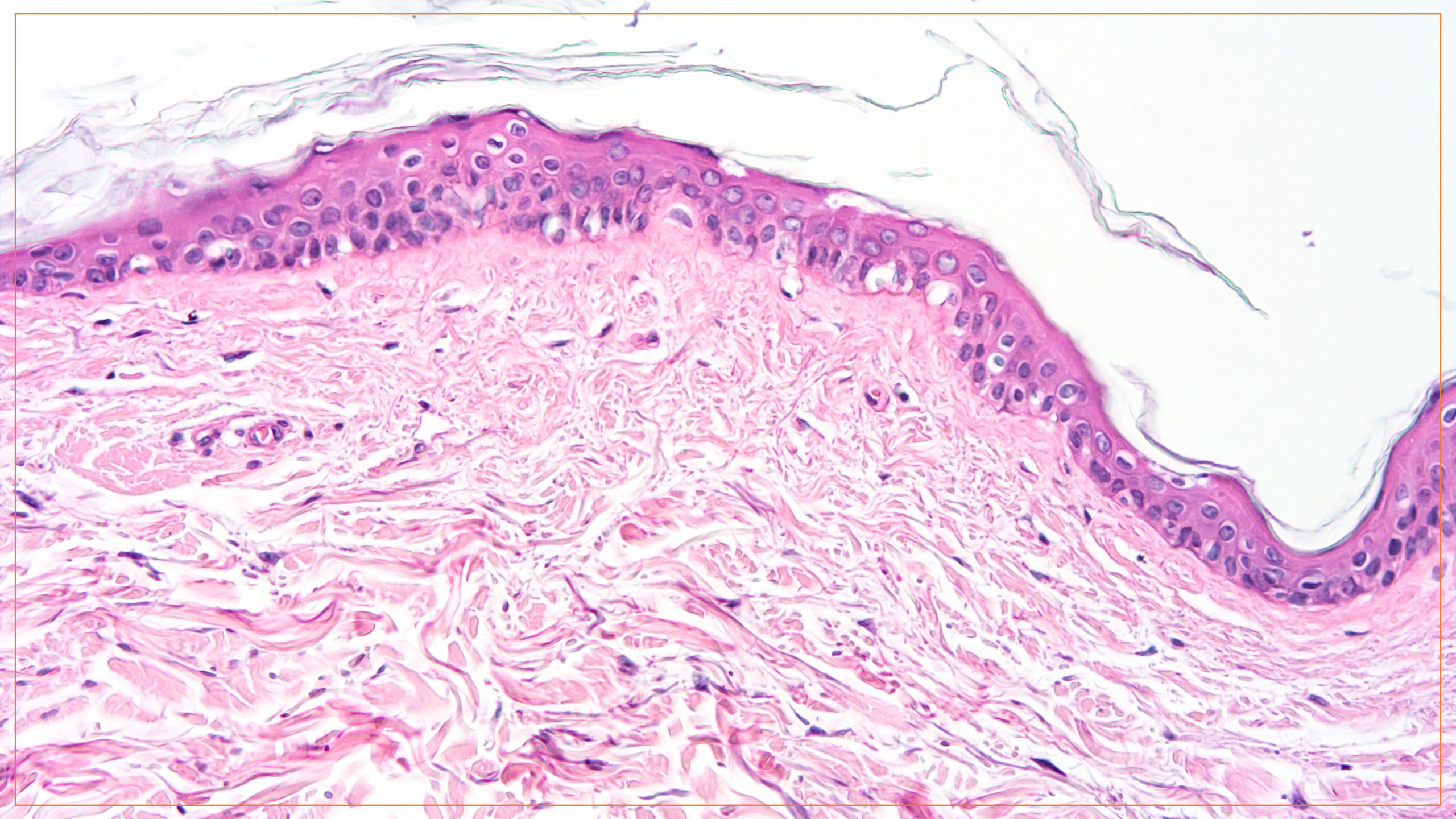

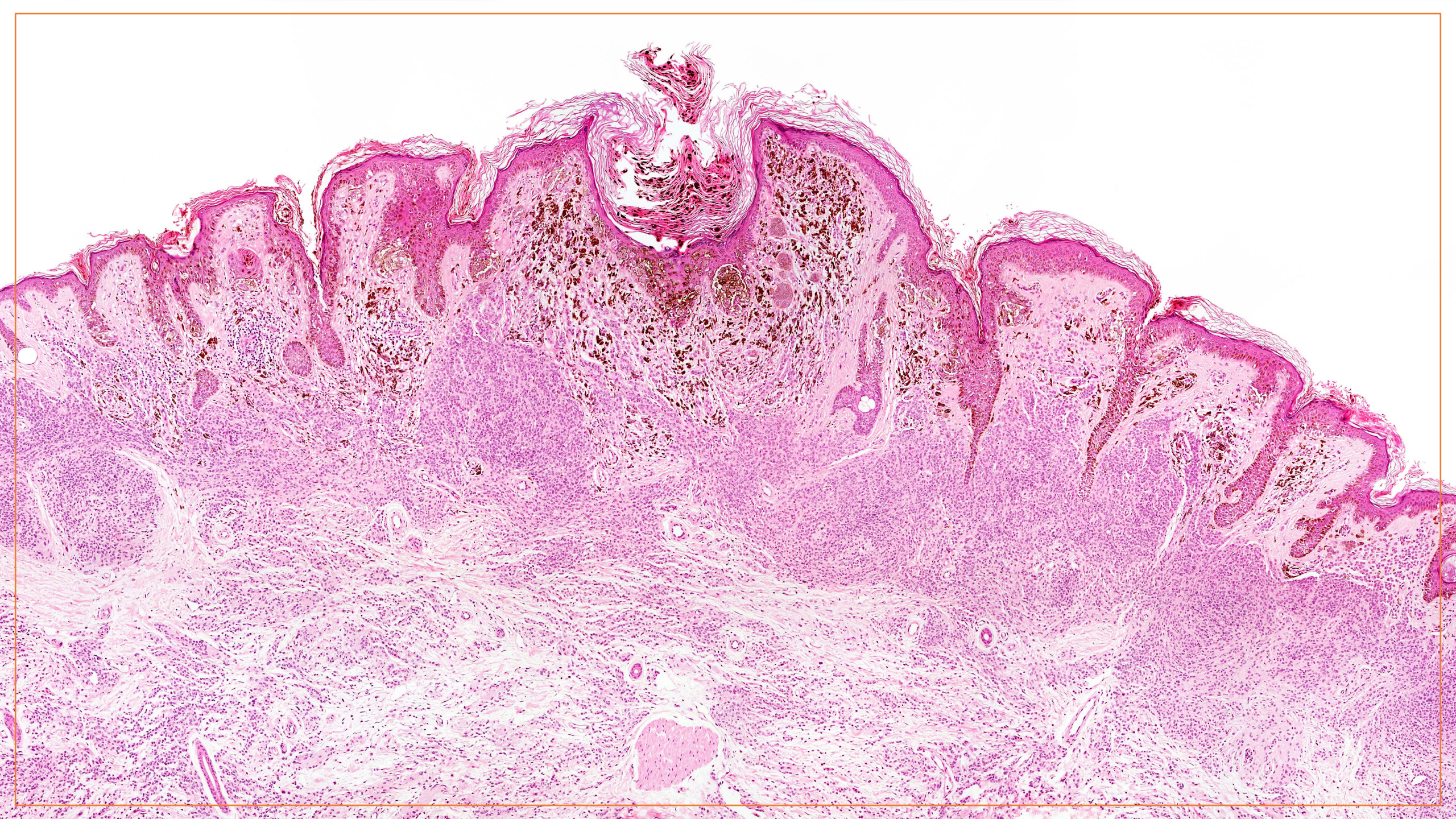

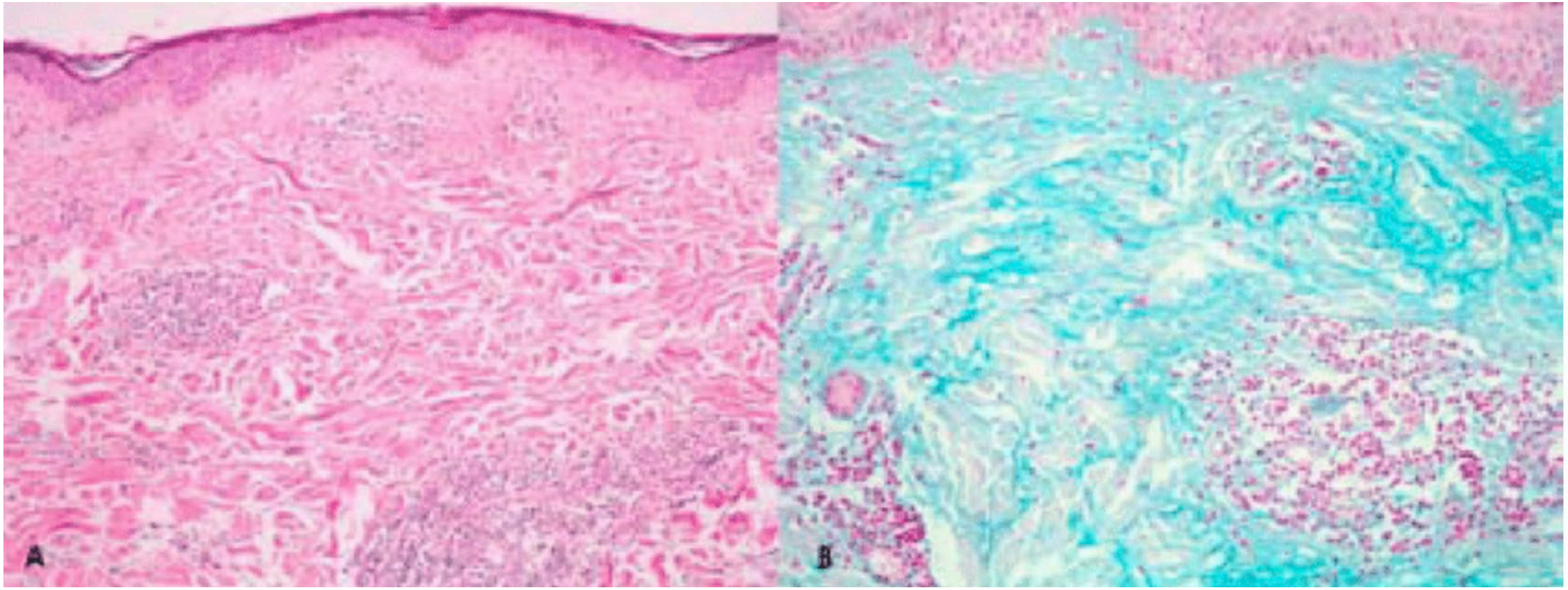
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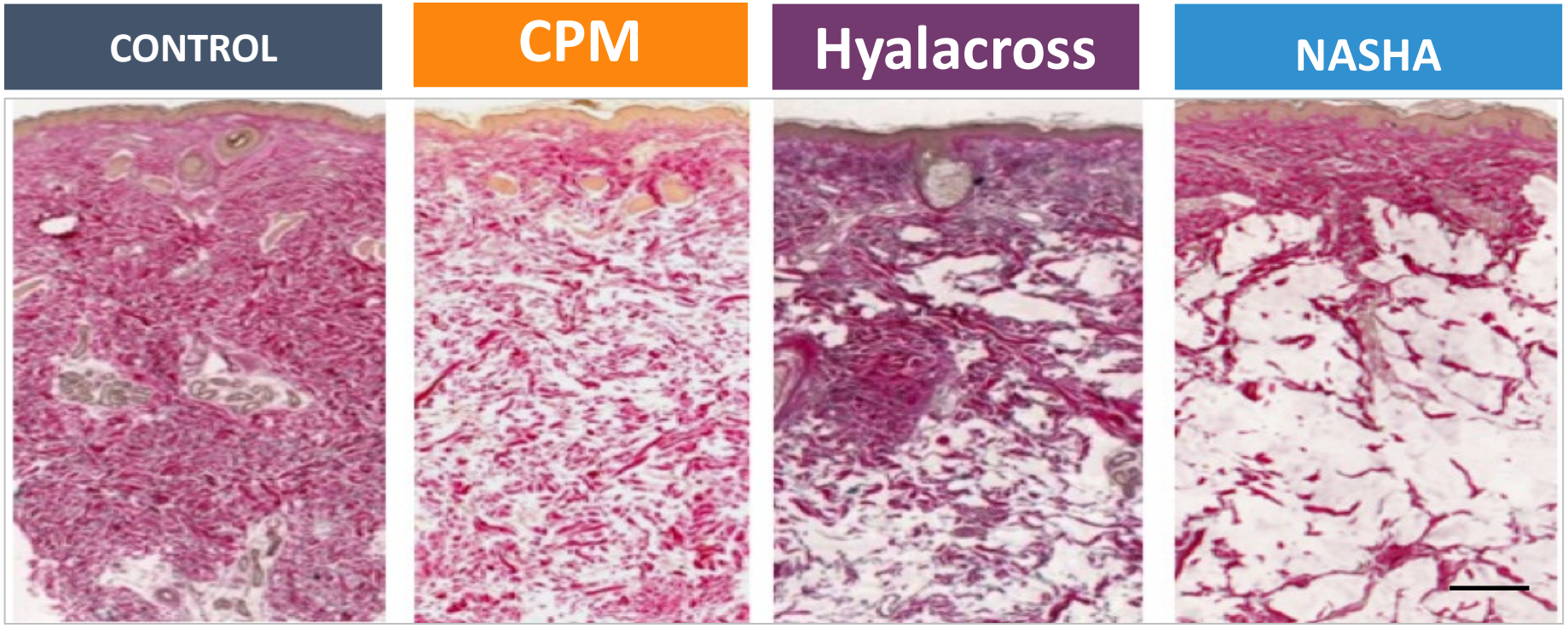
Histology Demonstrates Minimal to Pronounce Dermal Disruption with injectable fillers Fillers



Day 8: Hyaluronic Acid (White) and Van Gieson Staining for Elastin and Collagen (Red)

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Tran C, et al. *Dermatology*. 2014;228(1):47-54

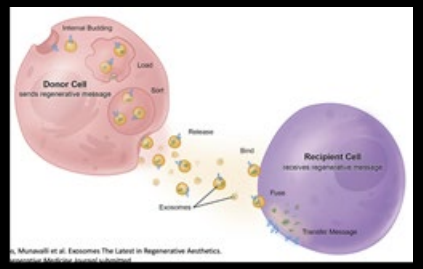

REGENERATIVE
the future of aesthetics

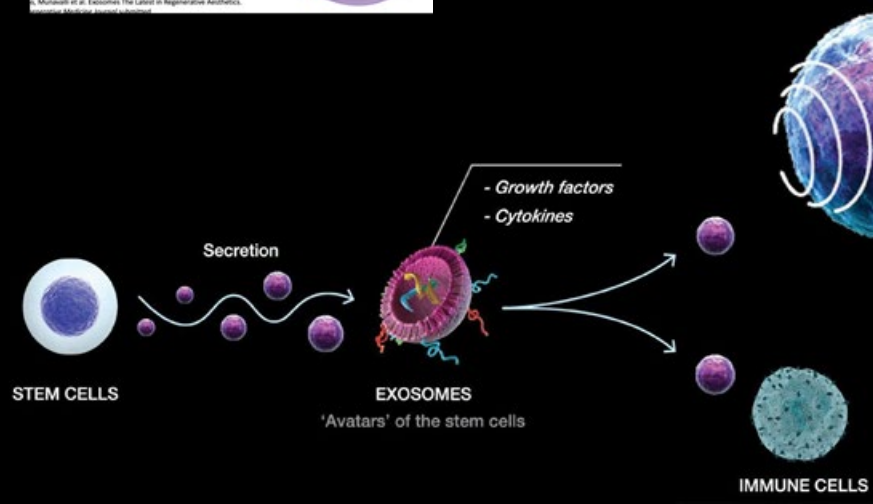
Regenerative Medicine

Cell Talk - The Power of Exosomal Communication

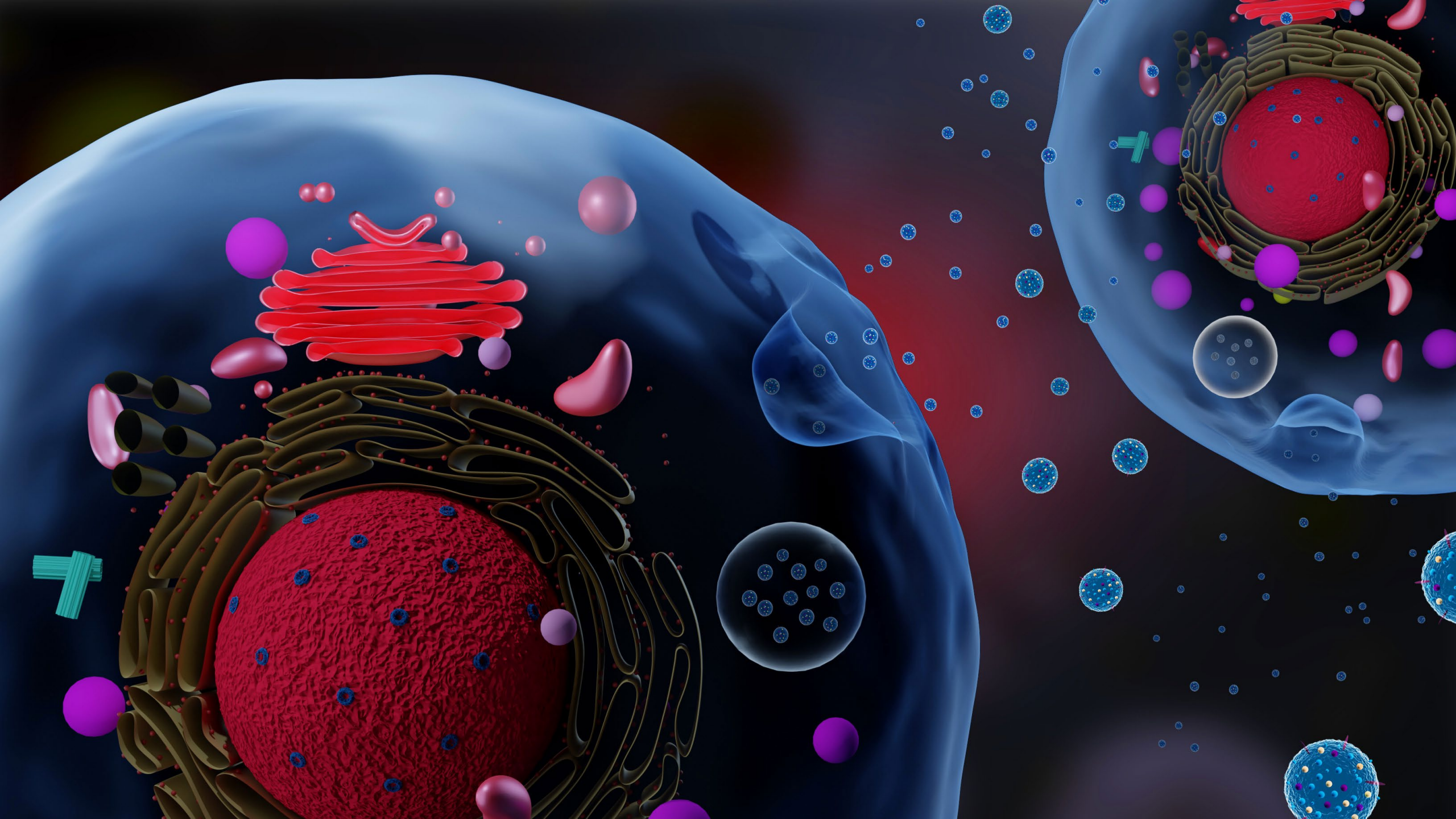
r:

Shino Bay
DO, FAOCD





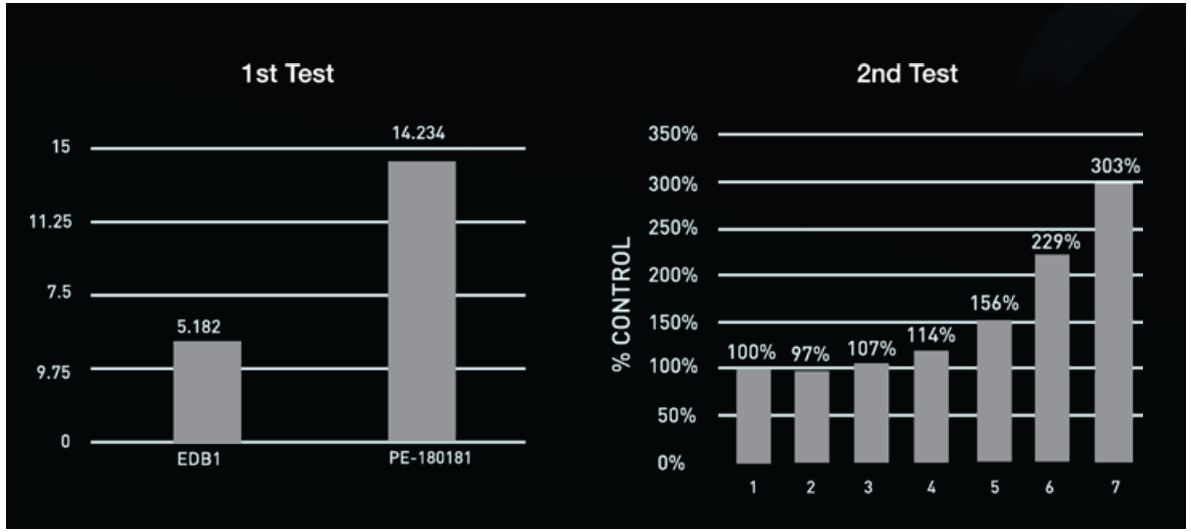
Data Coding Avatars & Cell to Cell Communicator



EXOSOME TECHNOLOGY

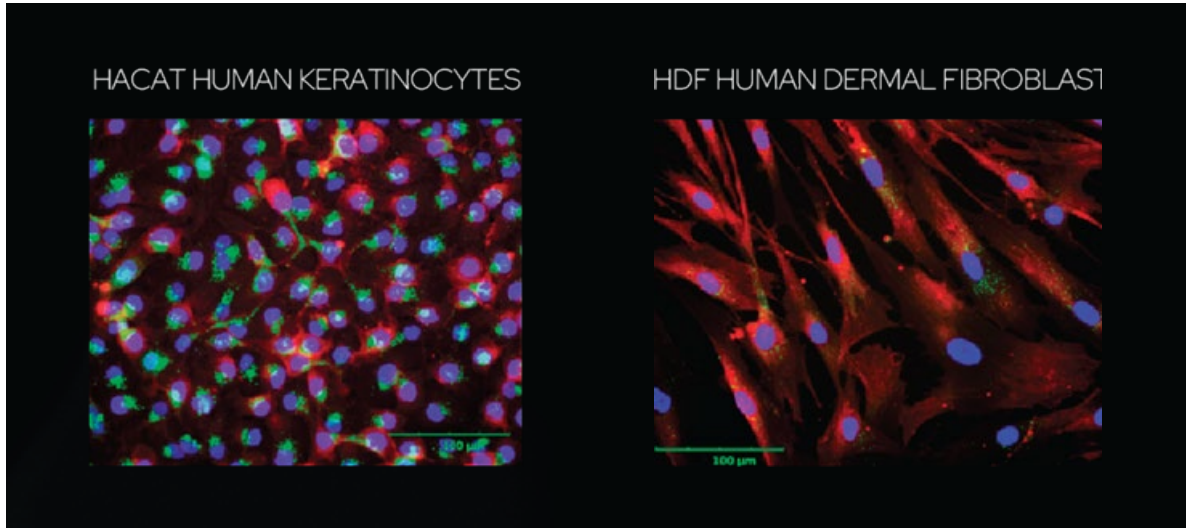
ELASTIN INCREASE BY ExoSCRT™

Exosome products powered by ExoSCRT™ may Increase the elastin amount of human dermal fibroblasts up to 300% in vitro.



CELLULAR UPTAKE OF EXOSOMES

Human skin cells easily uptake Exosome products powered by which means that stem cell-derived exosomes can message skin cells to “Do Something”.



Courtesy of BENEV

Platelet Rich Fibrin

FIGURE 2 Centrifuge used: Remi R4C (Remi Sales & Engineerin Ltd, Mumbai)

FIGURE 3 Injectable PRF obtained after centrifuga yellow orange fluid on top in the tube, below which RB plasma layer is seen

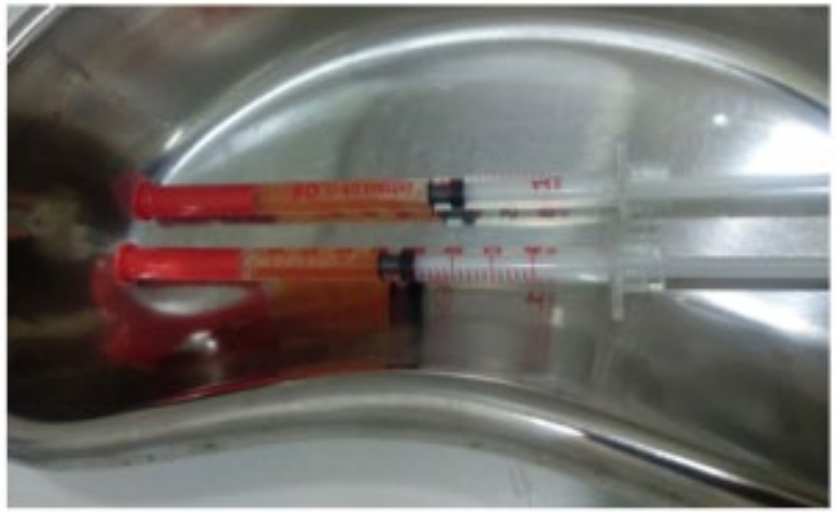


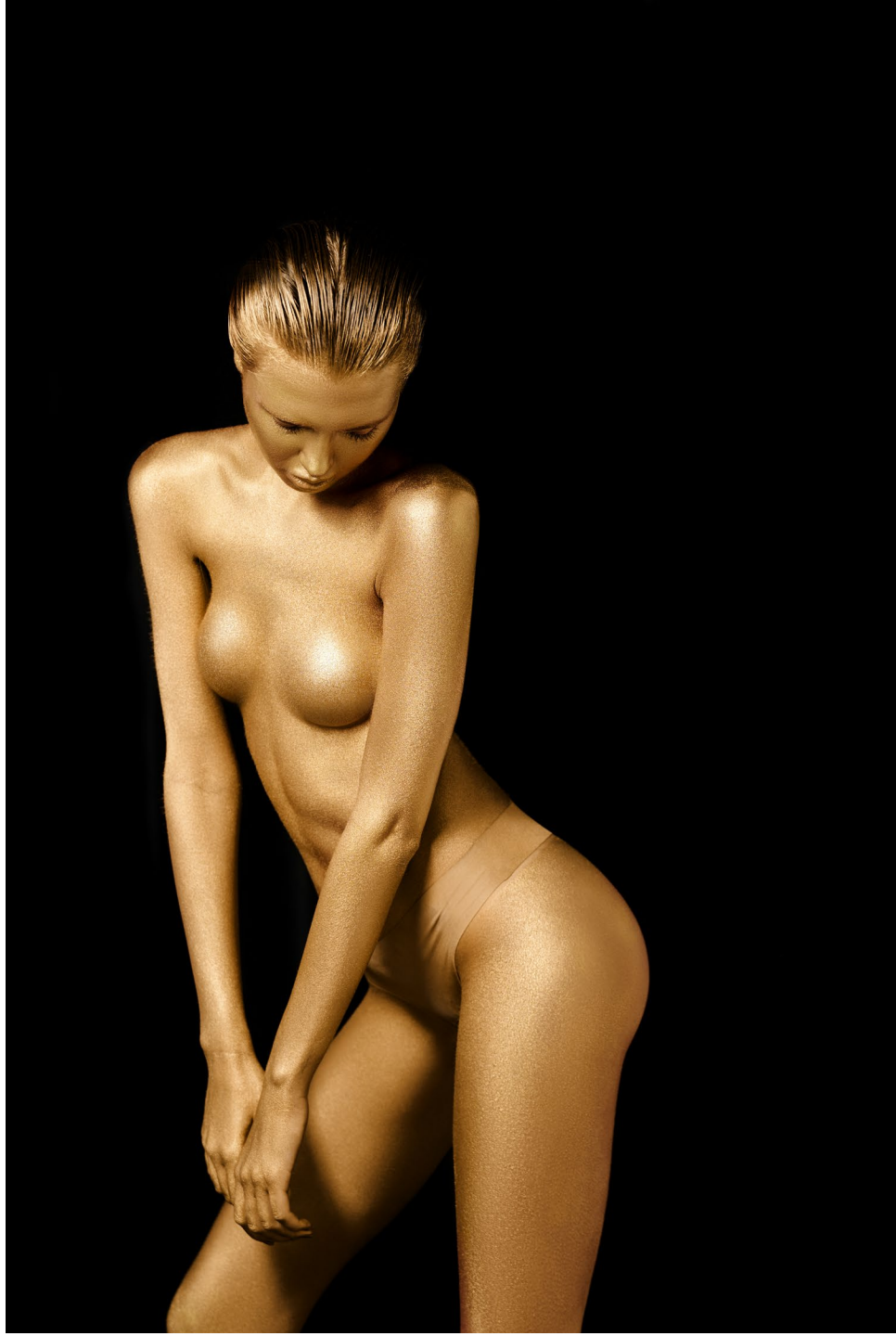
FIGURE 4 Ready to be injected product filled in insulin syringes

FIGURE 5 Injectable PRF may form a semi solid to gel-like material in vitro, if not injected at the earliest

Shashank B, Bhushan M. Injectable Platelet-Rich Fibrin (PRF): The newest biomaterial and its use in various dermatological conditions in our practice: A case series. J Cosmet Dermatol. 2021 May;20(5):1421-1426. doi: 10.1111/jocd.13742. Epub 2020 Oct 12. PMID: 32996229.

Polynucleotides

The power of DNA



Polynucleotide

- Purified and sterilized DNA molecules extracted from salmon trout germ cells
- Injectable monotherapy or in combination with hyaluronic acid or lasers
- induce cellular migration and collagen synthesis from fibroblasts
- the viscoelasticity of the long DNA fragments in polynucleotide fillers allows for a temporary medium that allows steady regeneration for a more natural repair to the skin

Polynucleotide

JOURNAL OF DERMATOLOGICAL TREATMENT
2022, VOL. 33, NO. 1, 254–260
https://doi.org/10.1080/09546634.2020.1748857

ARTICLE

Comparison of the effects of polynucleotide and hyaluronic acid fillers on periocular rejuvenation: a randomized, double-blind, split-face trial

Ye Jin Lee[a*], Hak Tae Kim[b], You Jin Lee[b], Seung Hwan Paik[b], Young Seon Moon[b], Woo Jin Lee[b], Sung Eun Chang[b], Mi Woo Lee[b], Jee Ho Choi[b], Joon Min Jung[b†] and Chong Hyun Won[b†]

[a]Department of Dermatology, Kyunghee University Hospital at Gangdong, Seoul, Republic of Korea; [b]Department of Dermatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

ABSTRACT

Background: Filler injection has become an extremely popular method for facial skin rejuvenation, including the periorbital area. In the recent years, new polynucleotide (PN)-containing filler products have been used for esthetic purposes.

Aim: We aimed to investigate the efficacy and safety of PN filler injection in the periorbital area.

Patients/methods: A total of 27 subjects were enrolled in this randomized, pair-matched, and active-controlled study. Each subject received filler injections thrice with two-week intervals, with a PN filler

ARTICLE HISTORY
Received 8 March 2020
Accepted 23 March 2020

KEYWORDS
Polynucleotide; hyaluronic acid; face; rejuvenation

- 27 subjects , randomized, controlled study.
- 3 Tx, with two-week intervals, with a PN filler injection on one side and a non-crosslinked hyaluronic acid (HA) filler injection on the contralateral side of the periorbital area.

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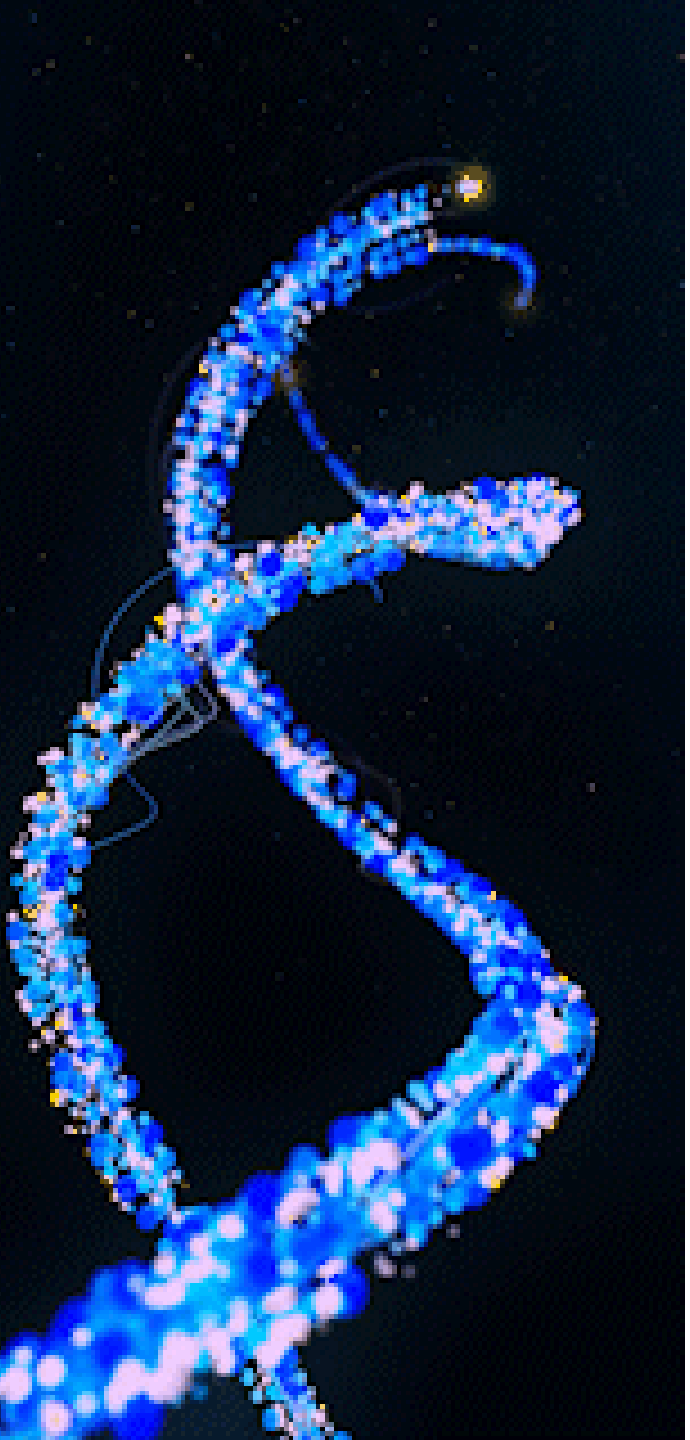

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The power of Polynucleotides associated with the stimulating strength of synthetic exosomes, enriched with biomimetic peptides


BEFORE
AFTER


BEFORE
AFTER

One treatment with Aquagold

One treatment with Aquagold

One treatment with RF Microneedling

ISSN: 1545 9616 September 2023 • Volume 22 • Issue 9

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

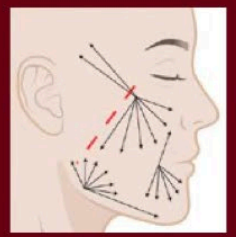

Image credit page 927

SPECIAL TOPIC:
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doi:10.36849/JDD.7405

September 2023 925 Volume 22 • Issue 9

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Optimizing Skin Regenerative Response to Calcium Hydroxylapatite Microspheres Via Poly-Micronutrient Priming

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Viviana Perico MD,[c] Shino Bay Aguilera DO FAAD[d]

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[d]Shino Bay Cosmetic Dermatology, Plastic Surgery & Laser Institute, Fort Lauderdale, FL

ABSTRACT

Regenerative aesthetics aims to restore the structure and function of aging skin. Two products, Radiesse (CaHA) and NCTF 135 HA (micronutrient mesotherapy) have been established as minimally invasive treatments that restore the structure and function of various skin components. It has been anecdotally observed by the authors, however, that some patients respond suboptimally to regenerative treatments without a clear indication as to why. It was hypothesized that micronutrient deficiencies in some patients may contribute to their lack of responsiveness and that a concurrent delivery of amino acids and co-enzymes may create a nutritional reservoir necessary for optimal protein synthesis. Noting that CaHA is known to drive the regeneration of extracellular matrix proteins, the aim of this case series was to investigate if "priming" the skin with NCTF 135 HA could lead to enhanced clinical effects of CaHA. The combination treatment resulted in improvements in panfacial aesthetics, skin laxity, wrinkle severity, skin luminosity, hyperpigmentation, and in skin and subcutis thicknesses in 100% of patients following a single treatment. This study is the first to introduce skin priming via diluting a regenerative biostimulator treatment with an amino acid-based diluent.

J Drugs Dermatol. 2023;22(9):925-934. doi:10.36849/JDD.7405

INTRODUCTION

Like many pathologies, skin aging is complex. The well-balanced, youthful architecture of young skin relies on the structure of dermis, via a "bed base" supporting youthful skin while fibroblasts are the "craftsmen", producing collagen, hyaluronic acid (HA), and regulating molecules that control skin pigmentation.[1,2] Dermal fibroblasts interact with extracellular matrix (ECM) fibers to produce healthy, elastic, hydrated, and unblemished skin.[3] Age-related alterations of the structural and mechanical support of the skin's ECM are the driving pathomechanisms of aging skin. Therefore, fibroblasts play a vital role in the skin aging process, and if untreated during intrinsic or extrinsic aging, can contribute to loose, saggy skin with uneven tone. Previous studies have shown that fibroblasts are reduced in numbers and their proliferative and metabolic functions slow with aging.[1,4,5] Simultaneously, matrix metalloproteinase concentrations increase with aging and enzymatically contribute to the degradation of the ECM and phenotypic changes associated with aging skin.[6,7] Recent findings suggest that senile fibroblasts can be revived and their functions restored, particularly by restoring mechanical tension and cell-substrate contact.[8-10] Targeting fibroblast activity, restoring ECM structure and mechanical tension, or mitigating degradative enzyme activity may be ideal targets for anti-aging therapy.[11]

In recent years, cosmetic dermatology has borrowed many ideas from regenerative medicine, which is loosely defined as the restoration of damaged or diseased tissues and their functions via biochemical or biomechanical cues, and has resulted in the emergence of regenerative aesthetics.[12] Several bioregenerative treatments, including calcium hydroxylapatite (CaHA; Radiesse®/Radiesse® (+) (which includes integral lidocaine), Merz Aesthetics), polylactic acid (PLLA; Sculptra®, Galderma), polymethyl methacrylate (PMMA; Bellafill®, Suneva Medical) have been implemented in clinics and have demonstrated the ability to induce synthesis of some endogenous ECM components for contouring tissue in aesthetic indications.[10,13,14] Specifically and uniquely among these fillers, CaHA has demonstrated the ability to restore fibroblast function in aged or damaged skin, synthesize type I and type III collagens, elastin, and proteoglycans, and is a promising regenerative aesthetic treatment.[14-16]

Since its introduction in the aesthetic market in 2006, CaHA has been an efficacious and safe injectable treatment for improving global panfacial volume loss and skin rejuvenation.[17] CaHA injectable filler consists of 25-45 um synthetic, immunologically inert, and mechanically-stimulating microspheres suspended in an aqueous gel preparation containing carboxymethyl cellulose

Skin Priming

Viviana Perico MD

- Aesthetic Medicine specialist, Bogota, Colombia
- Speaker and trainer for Zaneo, Globaltee, Zaneo and Fillmed.

Dr. Elina Theodorakopoulou MD, PhD

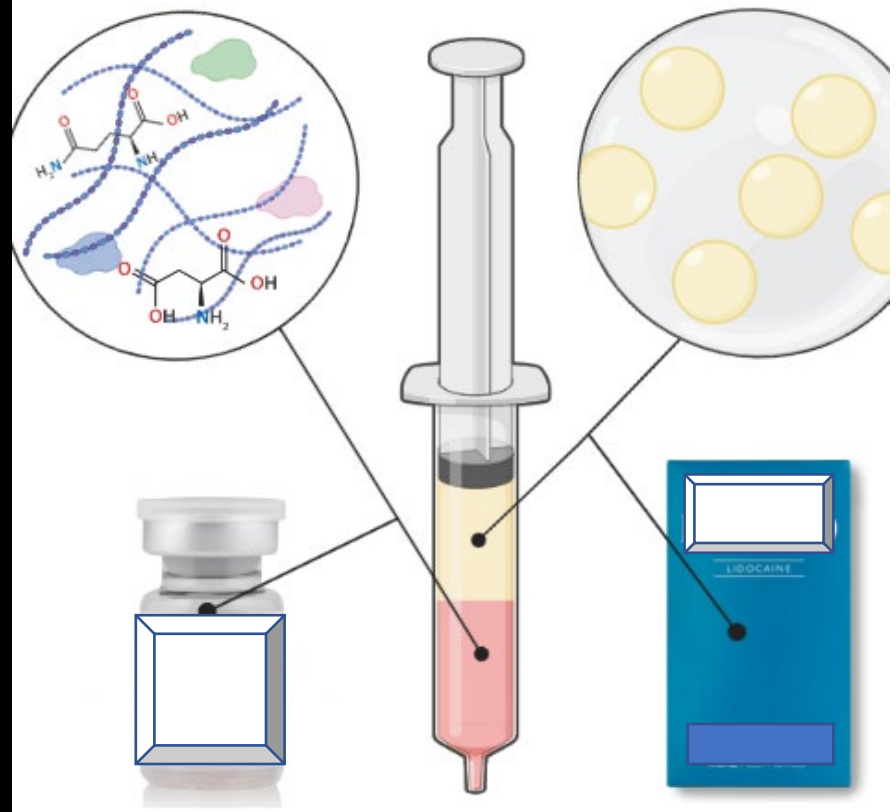
- Greek & Dubai licensed Dermatologist
- Founder of Pretty You Dermatology Clinic, Greece
- Visiting Dermatologist at 11/11 Aesthetic & Dermatology Clinic, Dubai
- PhD on Psoriasis
- Facial Ultrasound holder
- Investigator & Researcher
- Published Author & trainer

Alec McCarthy PhD

- Dr. of Bioregenerative Medicine and Bioengineering
- Medical Science Liaison at Merz Aesthetics

Ferial Fanian MD PH

- Dermatologist, Laserist, Confocalist
- M.D, PhD in life and health science at Center for Study and Research on the Integument (CERT)
- Besançon, Franche-Comté, France
- *Scientific and Medical Director FILLMED Laboratories Paris, France*



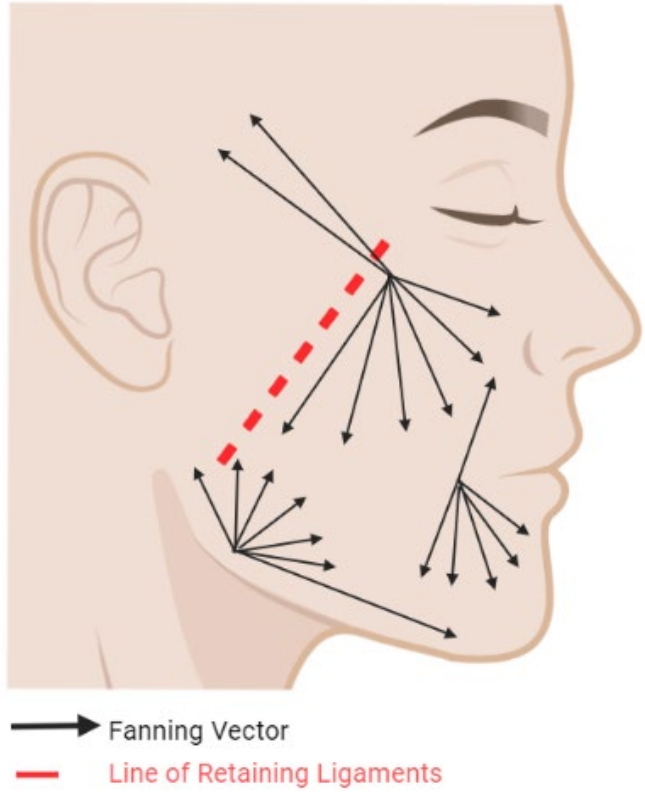
Skin priming components

. 1:1 ratio of CaHa and bioregenerative injectable solution

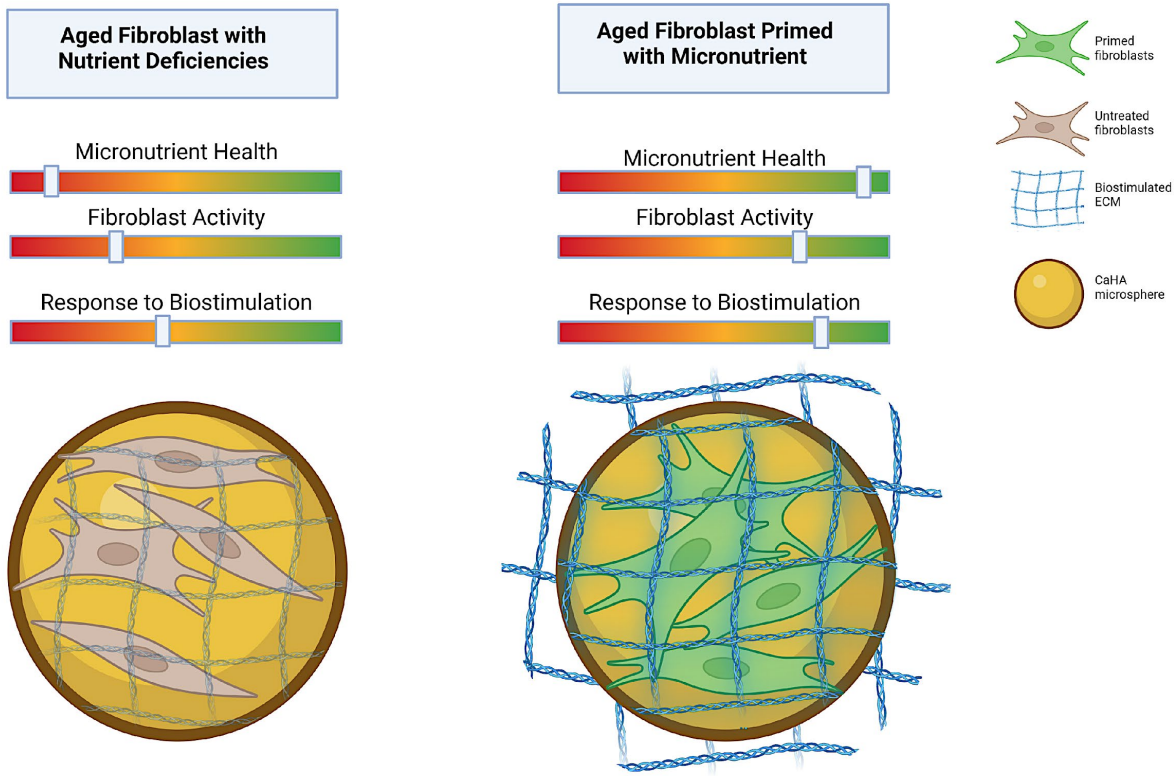
CaHA microspheres in CMC gel

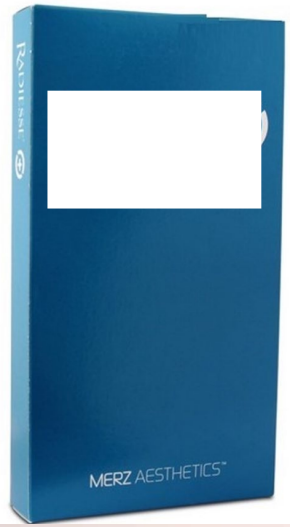
Bioregenerative injectable solution = amino acids, uncrosslinked HA, coenzymes, nucleotides

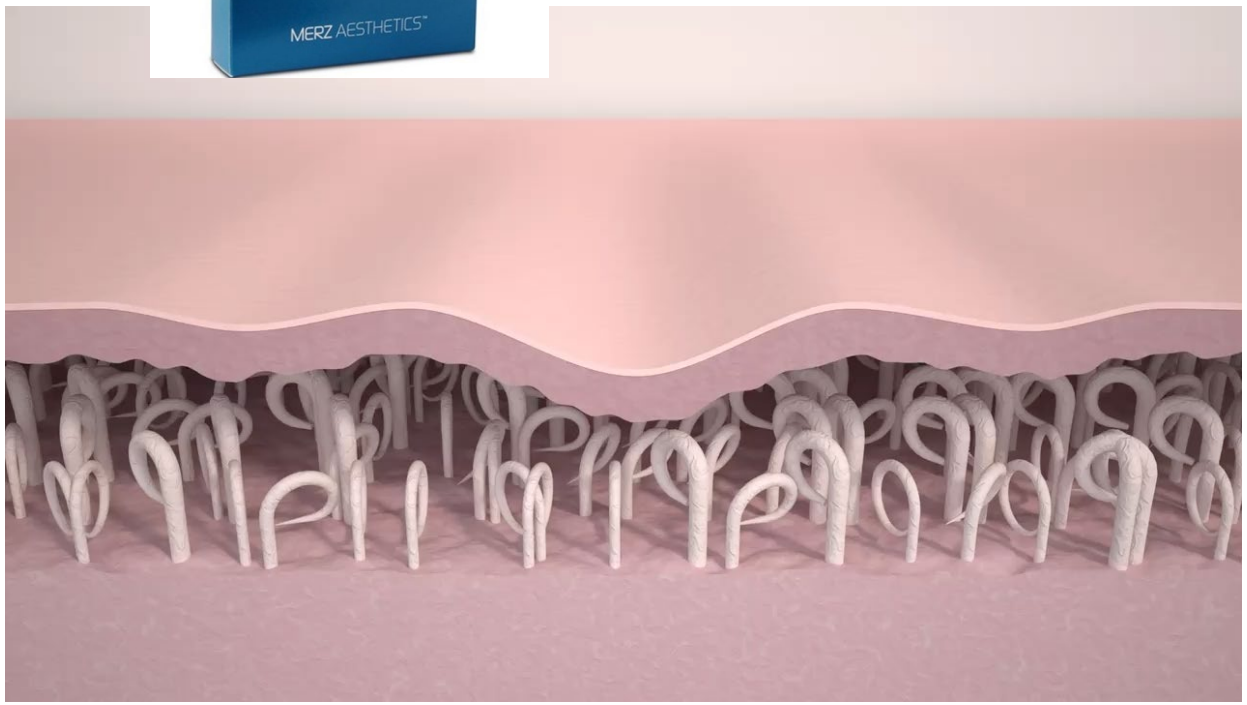
SKIN PRIMING: INJECTION TECHNIQUE



SKIN PRIMING: BACKGROUND







Courtesy Elina Theodorakopoulou MD, Alec McCarthy PhD

SKIN PRIMING: U/S RESULTS

Skin thickness increased by

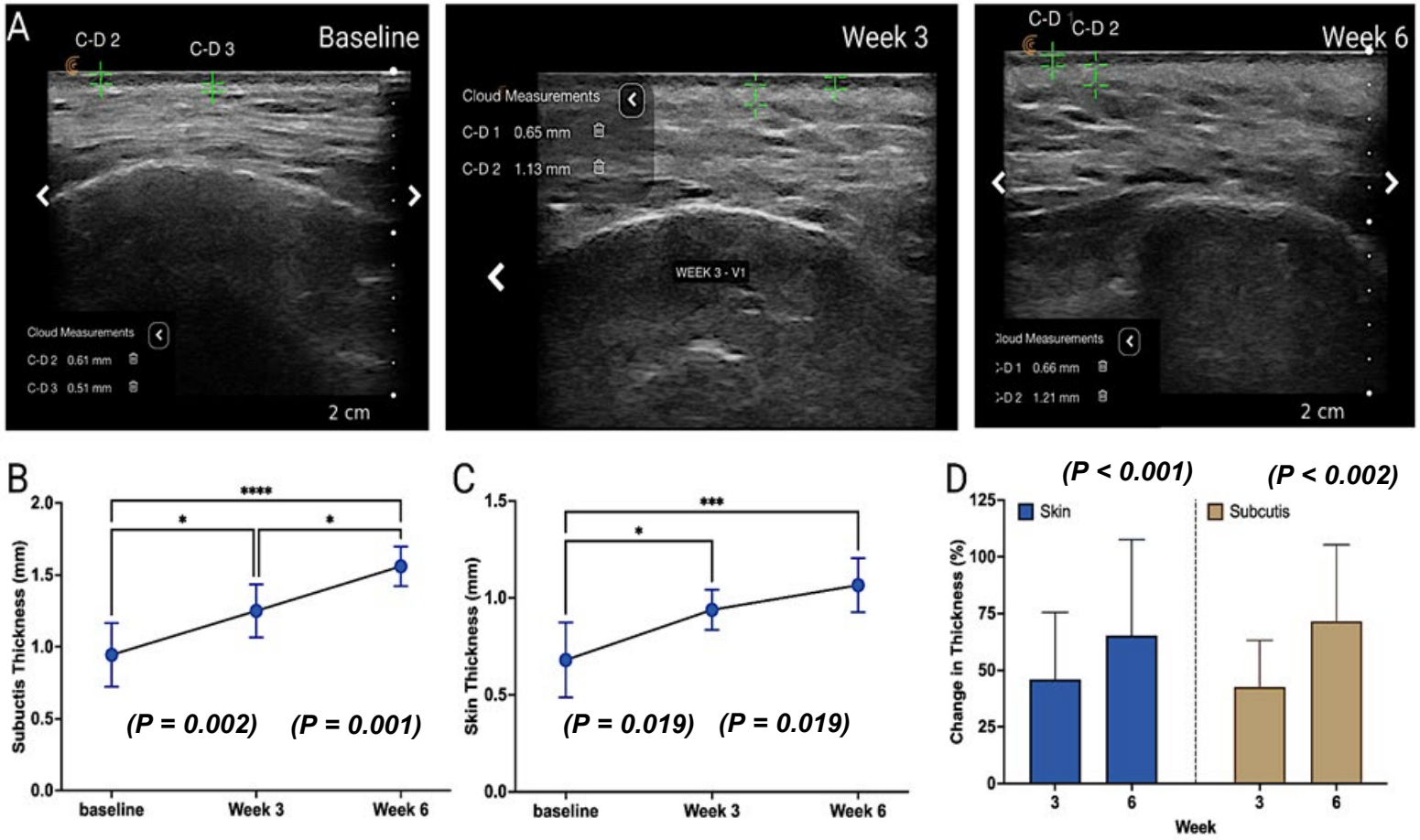
45.89% ± **29.60** between baseline & wk 3

65.31% ± **42.29** between baseline & wk 6

Subcutis thickness

42.56% ± **20.52**

71.53% ± **33.71%**

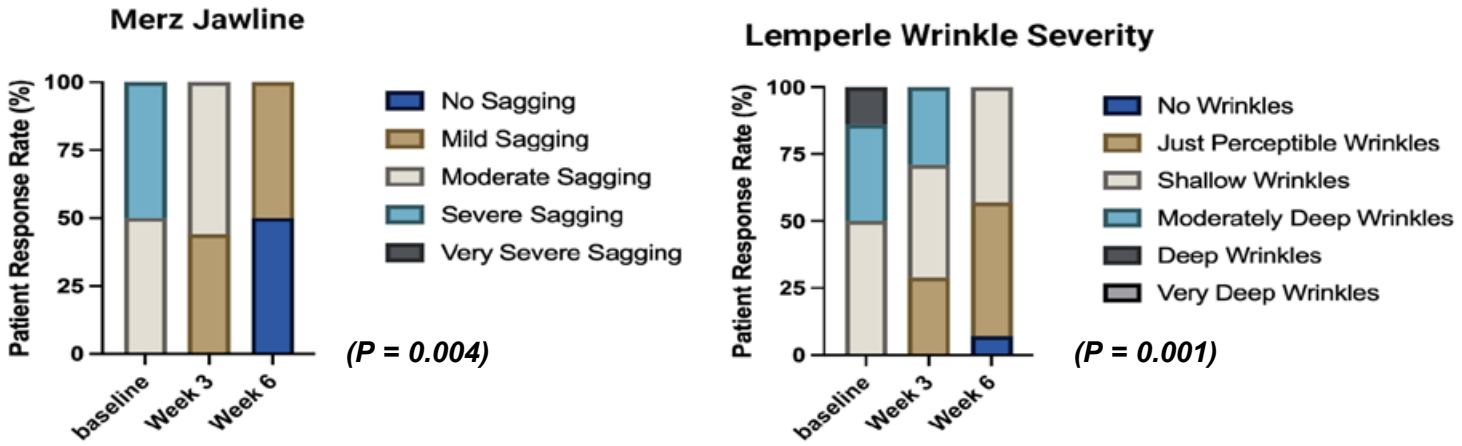


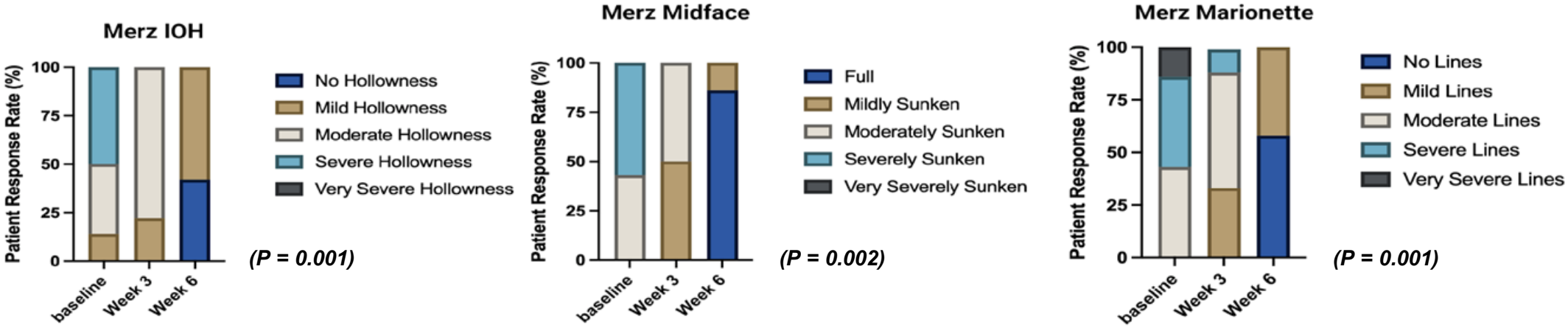
Courtesy Elina Theodorakopoulou MD, Alec McCarthy PhD

SKIN PRIMING: CLINICAL RESULTS

Significant improvements in:

- Jawline
- Wrinkle
- Infraorbital Hollowness (IOH)
- Midface
- Marionette





Courtesy Elina Theodorakopoulou MD, Alec McCarthy PhD


9/13/22 4:59 PM
10/5/22 12:17 AM

9/13/22 4:59 PM

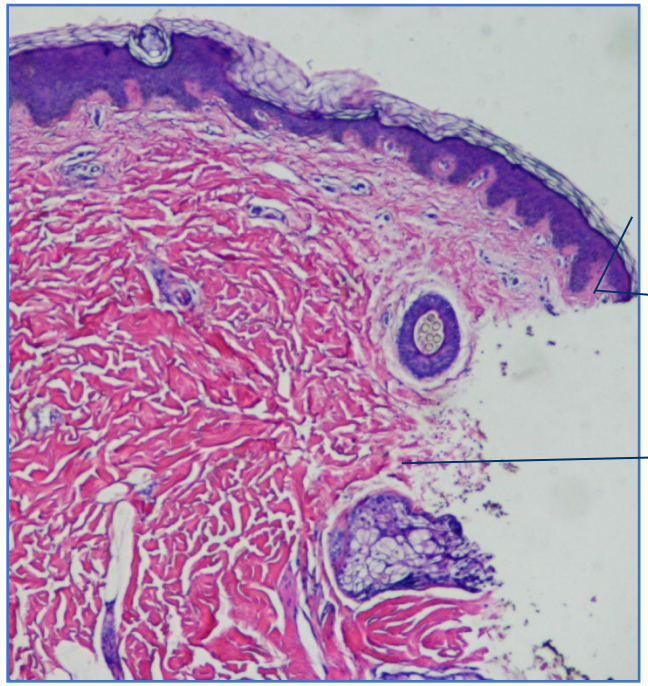
10/5/22 12:17 AM


Before
3 weeks


Before
3 weeks


6 weeks
One year and 6 months

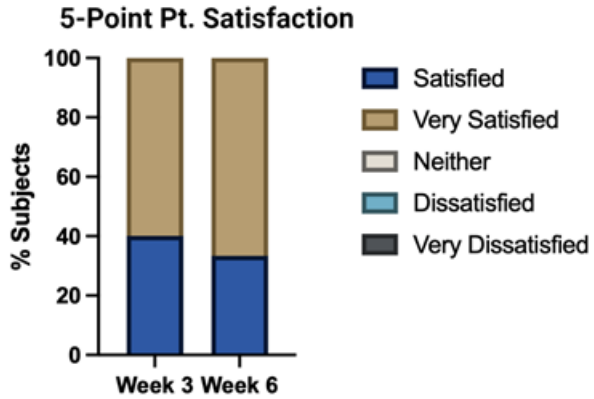
Cross section of 50 year old skin

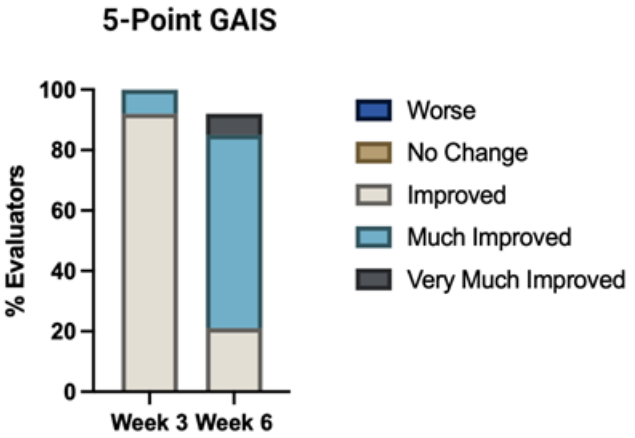


Cross section of 18 year old skin

SKIN PRIMING: MORE RESULTS

- 100% of patients were at least 1-point responders by wk 3 & wk 6
- 100% of patients recommended treatment
- **Patient satisfaction** was either “satisfied” or “very satisfied” at wk 3 & 6
- Most common adverse event: erythema, which spontaneously resolved within 3 days





- 56 y/o male complaining of sagginess on the neck

- One treatmet of CaHa with 6cc polymicronutrients 1:4 dilution
- This is the result after 3 weeks

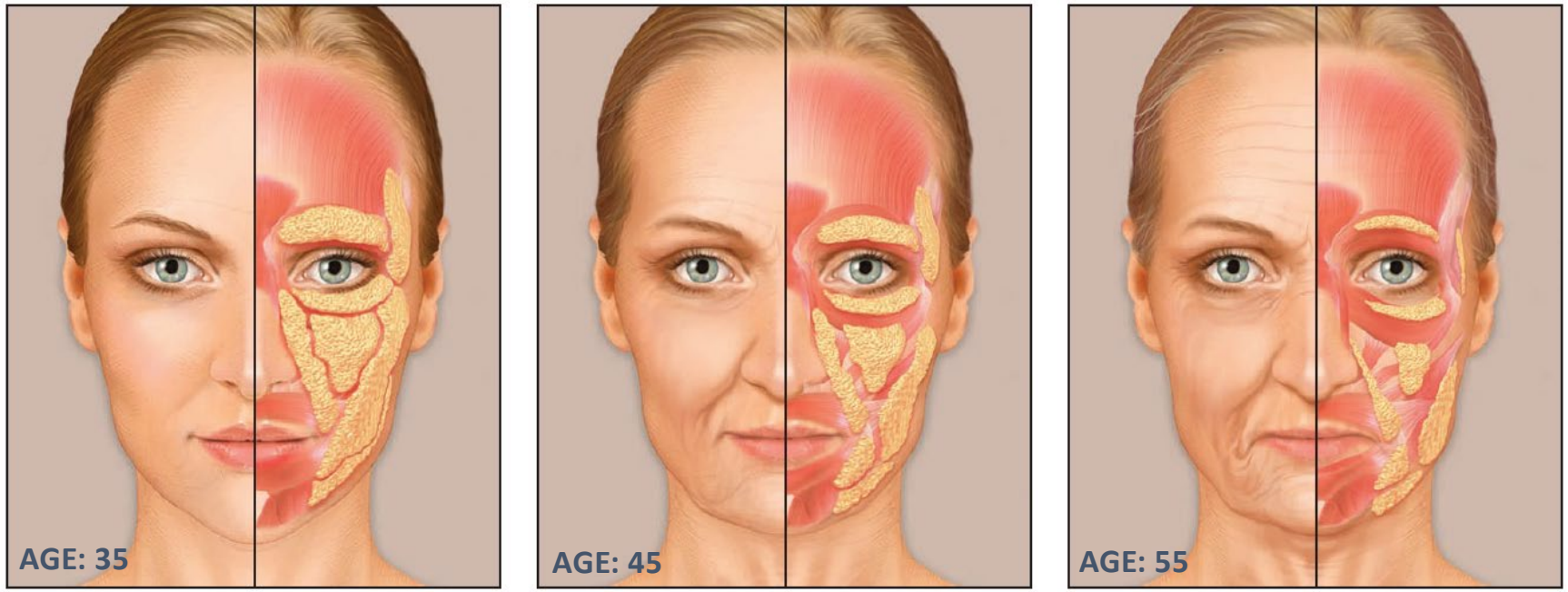
Treatment was done with a full syringe RADIESSE® (+) hyper-diluted with 9cc NCTF 135

TYLSTIN
MED-SPA

@tylstinmedspa
Vaughan ON, Canada

Fat

A youthful look depends on having the right amount of facial fat in the right places. Redistribution, accumulation, and atrophy of fat lead to facial volume loss.[1,2,4,5]



- Some areas lose fat. Examples are the forehead and cheeks.
- Other areas gain fat. Examples are the mouth and jaw.
- Modification of the fat pads leads to contour deficiencies.[2-5]

1.Goldberg D, Guana A, Volk A, Daro-Kaftan E. Single-arm study for the characterization of human tissue response to injectable poly-L-lactic acid. *Dermatol Surg*. 2013;39:915-922.
2. Mayo Clinic. Facial fillers for wrinkles. Available at https://www.mayoclinic.org/tests-procedures/facial-fillers/about/pac-20394072. Accessed February 5, 2019.

allograft adipose matrix

is not a Filler

Off-the-shelf allograft adipose derived matrix

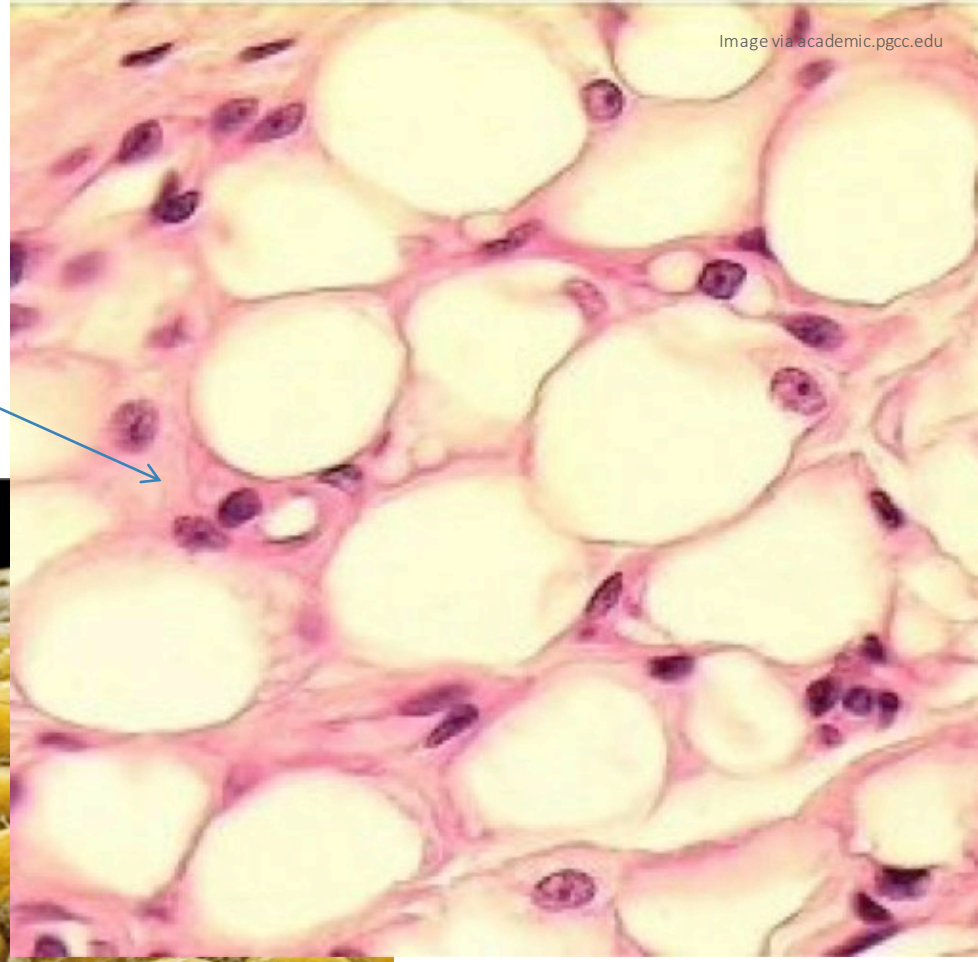
- contains the same matrix proteins and components found in native adipose tissue
- Designed to obtain similar results to fat grafting procedures
- Eliminates need for surgery and downtime
- Minimal prep time <5 mins. prior to treatment
- Little to no downtime
- Easy to store
  15-month shelf life

Courtesy of MTF Biologics

This is…

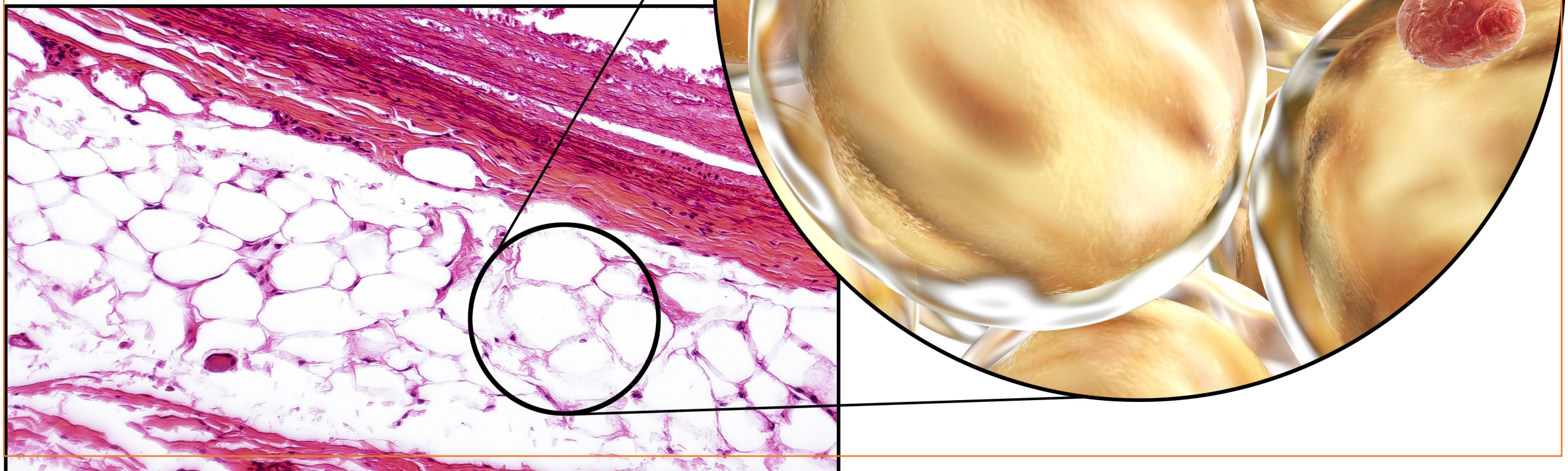
Aseptically processed adipose ECM

Adipose ECM
(eventually Renuva™)

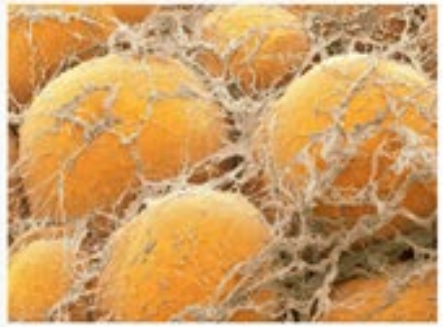


Human adipose H&E

Courtesy of MTF Biologics



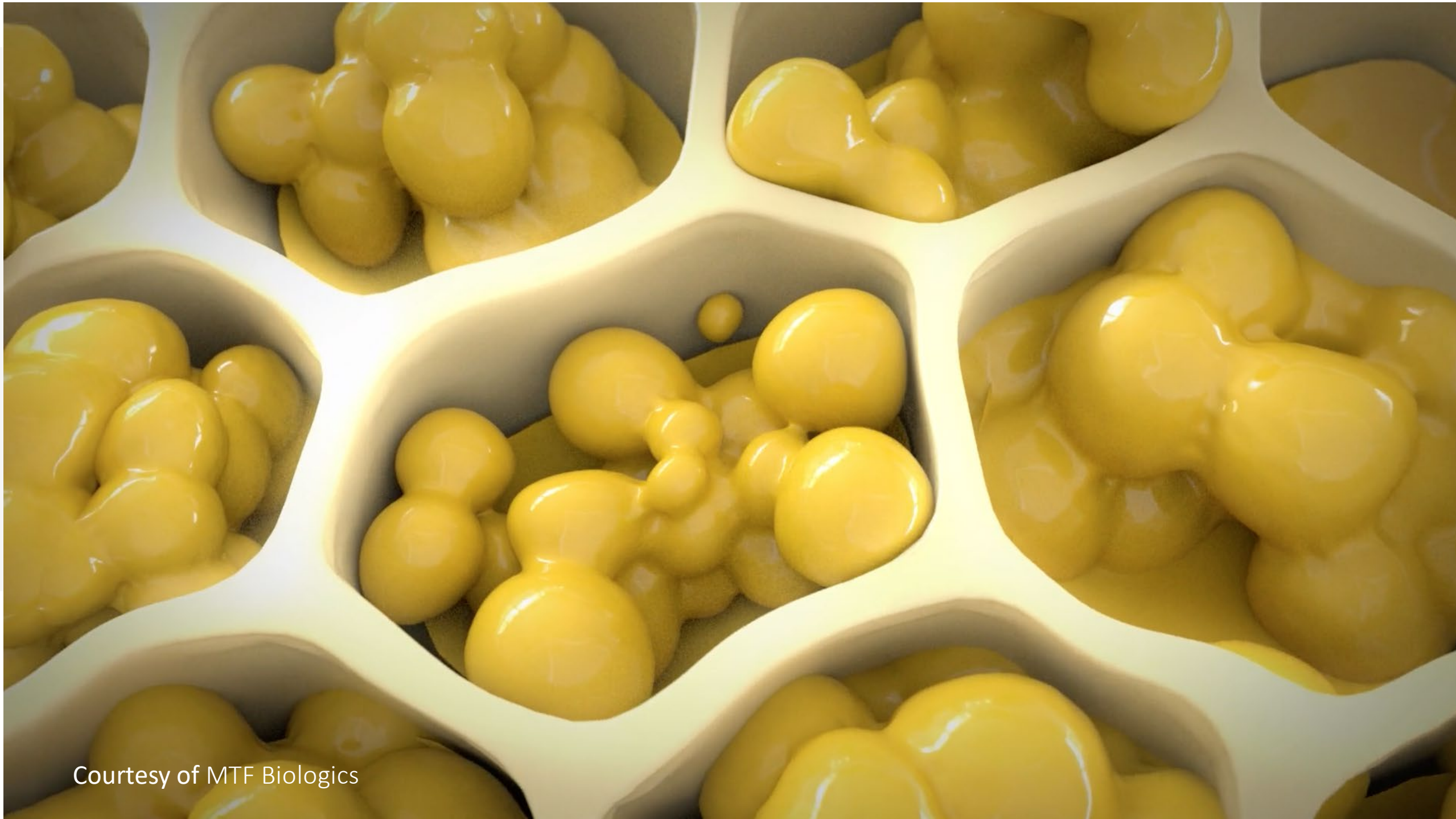
Think of a Honeycomb…



Host Adipose

Donor Adipose

Courtesy of MTF Biologics


Courtesy of MTF Biologics

Patient Results

Courtesy of Trevor Larsen, RN

Age: 24

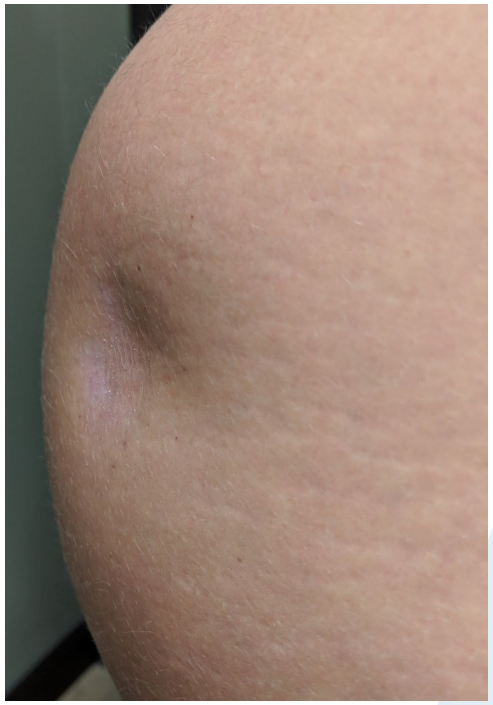
Depressed area

Treatment area: Buttocks

quantity: 3 ccs
injected in each side

Number of treatments: One

After photos: 3 months
post procedure



Before

After

Courtesy of MTF Biologics

Patient Results

Case Courtesy of Alan Durkin, MD

Age: 72

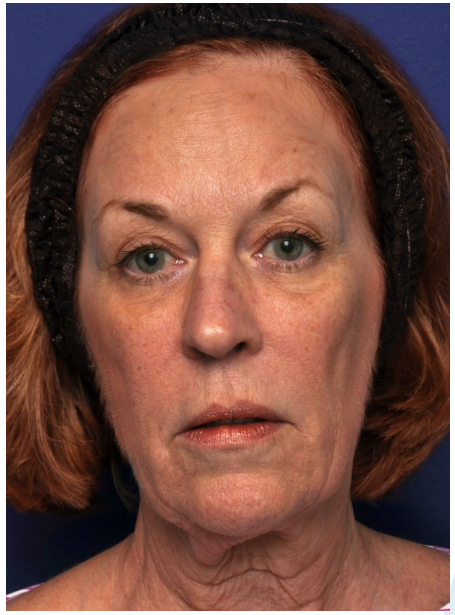
Age-related volume loss

quantity: 3 ccs injected in each side

Treatment area:
Malar, Sub-Malar & Nasolabial

Number of treatments: One

After photos: 6 months post procedure



Before

After

Courtesy of MTF Biologics

Patient Results

Courtesy of Leif Rogers, MD, FACS

Age: 54

Treatment area: Neck

Age-related volume loss

quantity: 4.5 ccs injected in each side

Number of treatments: One

After photos: 8 months post procedure

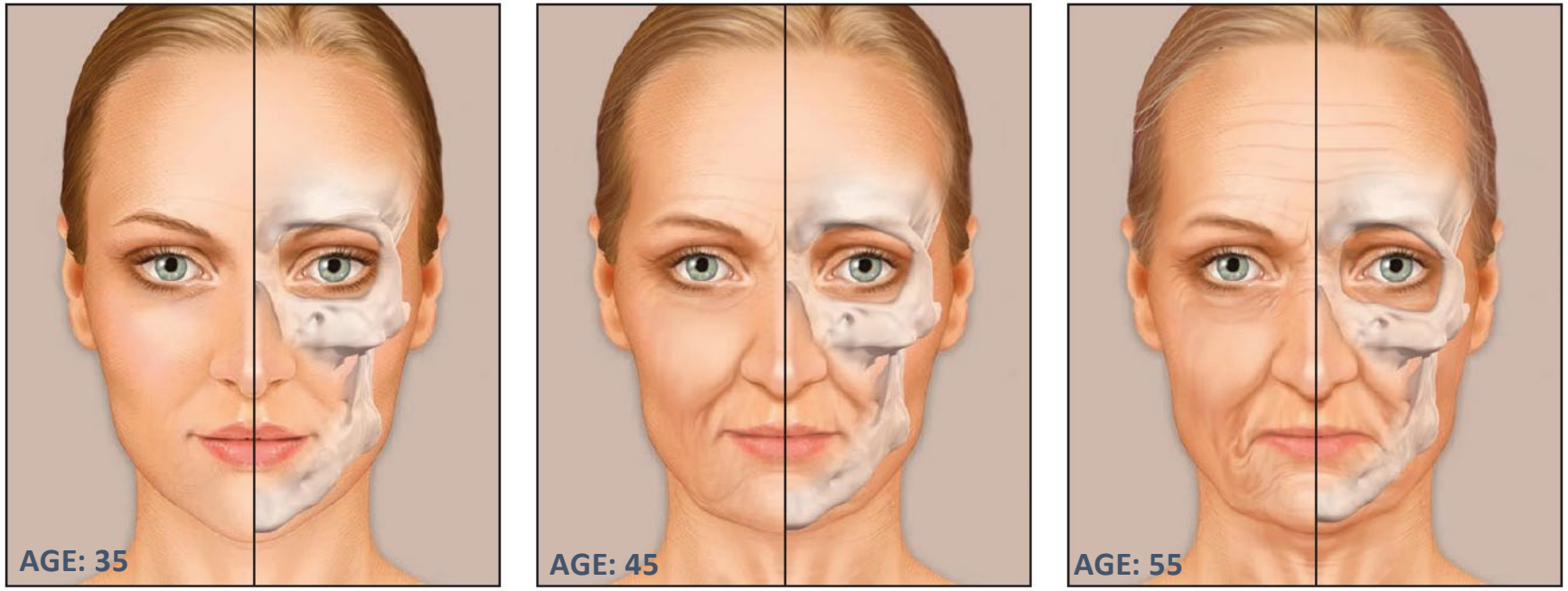
Before

After

Courtesy of MTF Biologics

Bone

There is a significant loss of facial bone with age.[4] Aging of the craniofacial skeleton may be due to changes in the relative dynamics of bone expansion and bone resorption. Bone resorption leads to biometric volume loss.[2,4]

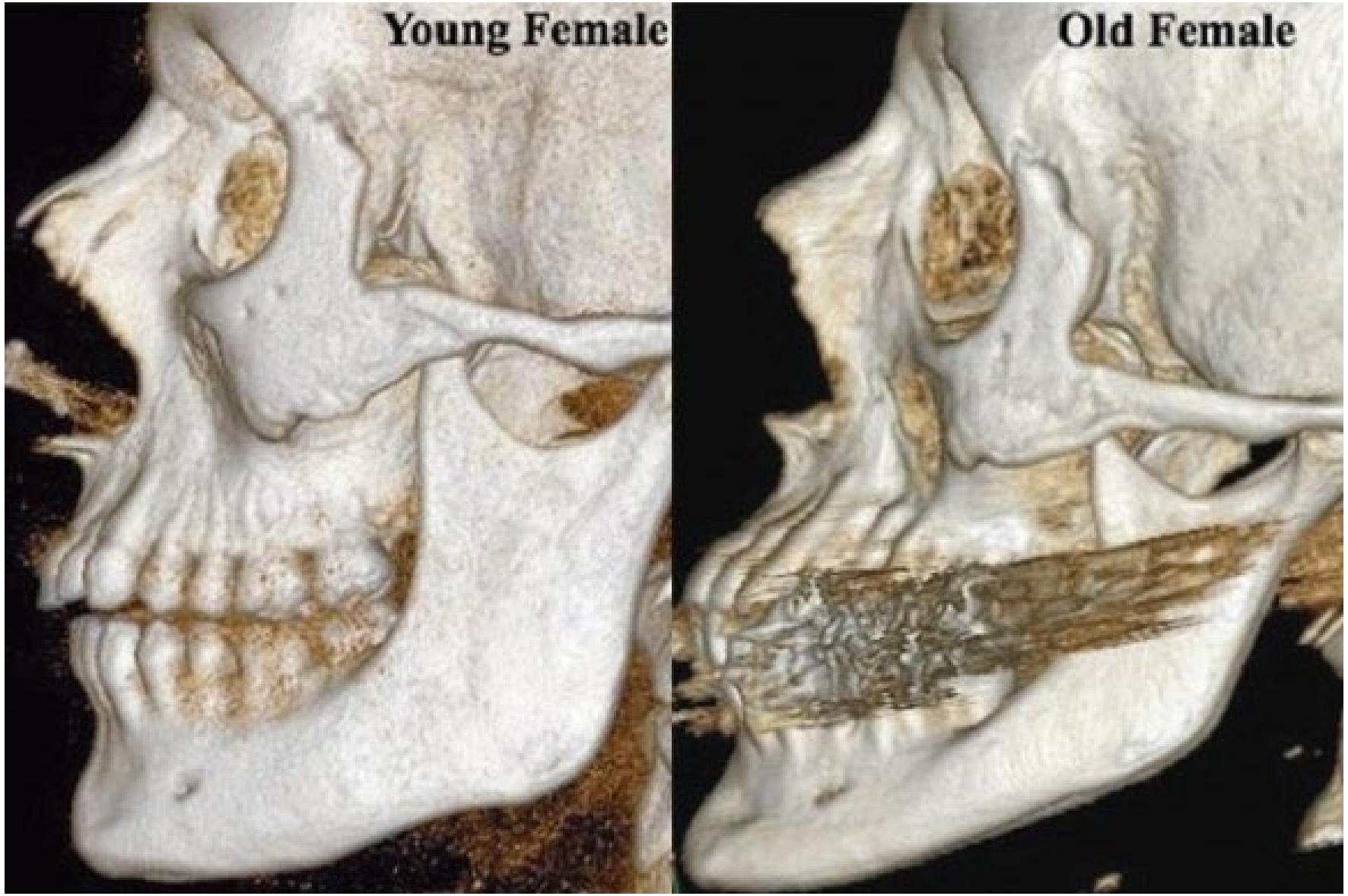


Without the structural support of bone, there are noticeable changes in the other layers of overlying soft tissue and skin.[3,4]

1.Goldberg D, Guana A, Volk A, Daro-Kaftan E. Single-arm study for the characterization of human tissue response to injectable poly-L-lactic acid. *Dermatol Surg*. 2013;39:915-922.
2. Mayo Clinic. Facial fillers for wrinkles. Available at https://www.mayoclinic.org/tests-procedures/facial-fillers/about/pac-20394072. Accessed February 5, 2019.

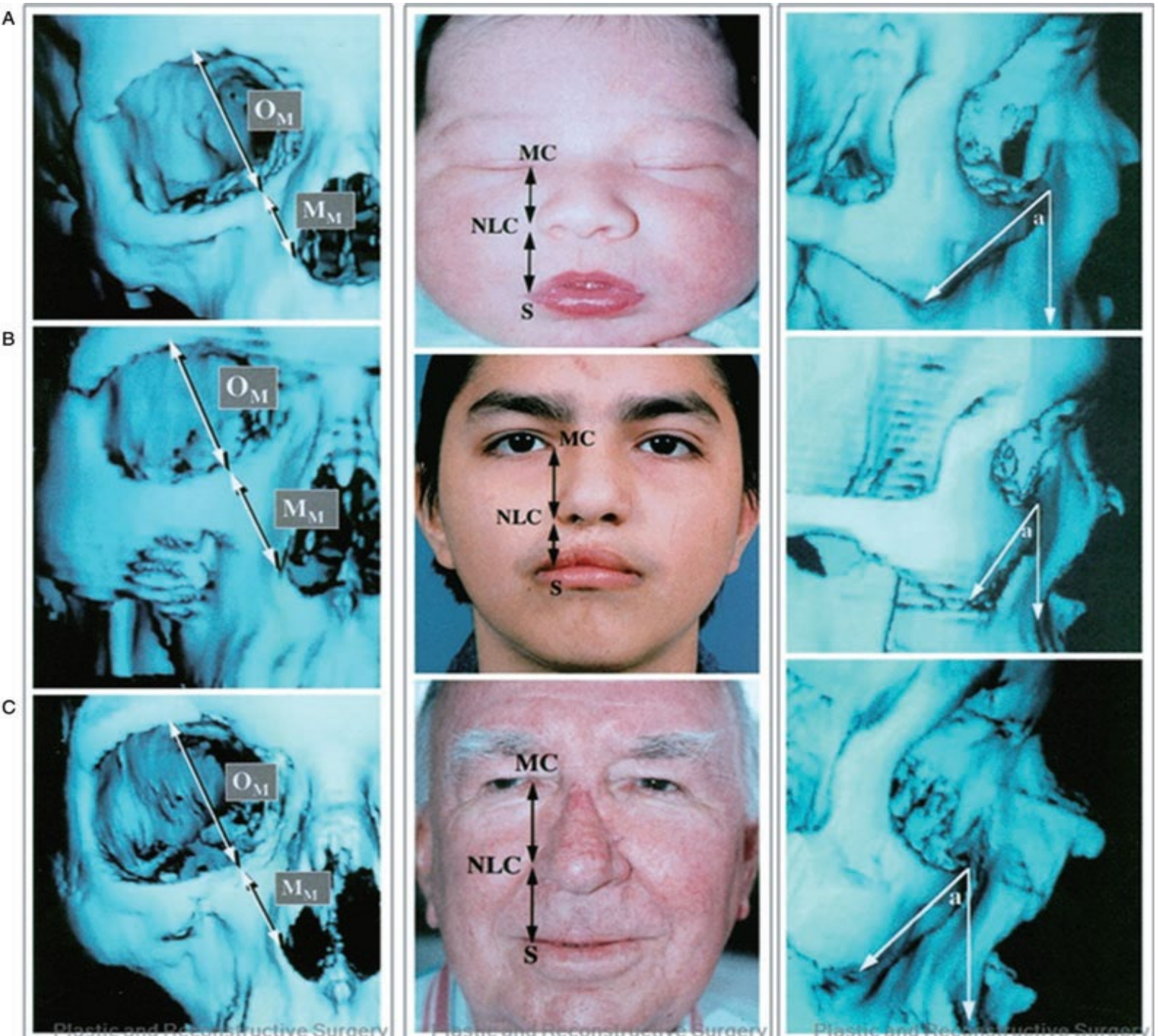
Craniofacial bone remodeling

Courtesy of Fitzgerald and Vleggaar *Dermatologic Therapy, Vol. 24, 2011, 2–27*


Young Female
Old Female

CRANIOFACIAL SKELETAL SUPPORT & FACIAL SHAPE

Courtesy of Fitzgerald and Vleggaar *Dermatologic Therapy, Vol. 24, 2011, 2–27*



Concertina Effect

Courtesy of Fitzgerald and Vleggaar Dermatologic Therapy, vol 24, 2011, 2-27

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

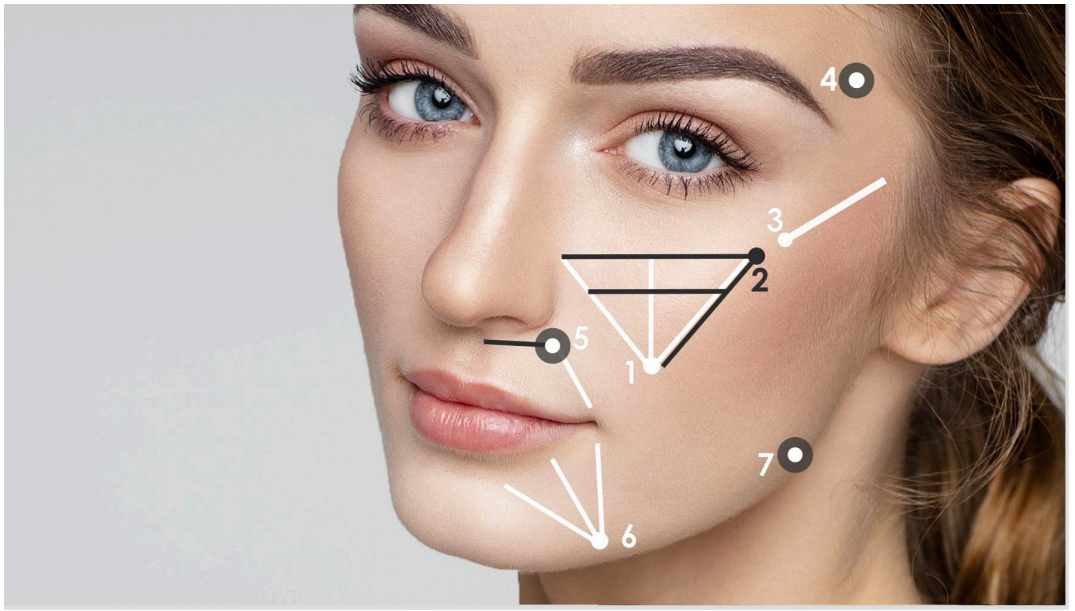
Optimizing Injections of Poly-L-lactic Acid: The 6-Step Technique

Shino Bay Aguilera DO FAAD,[a] Sean Branch DO FAAD,[b] and Luis Soro DO FAAD[a]

[a]Shino Bay Cosmetic Dermatology, Plastic Surgery &Laser Institute, Fort Lauderdale, FL [b]Henghold Skin Health &Surgery Group, Pensacola, FL

ABSTRACT

The authors present a reproducible and effective technique utilizing poly-L-lactic acid for panfacial revolumization. The variable dilution ratios, reconstitution times, injection techniques and rates of nodule formation with poly-L-lactic acid can be intimidating to even experienced injectors. While there is no single cookie-cutter approach to facial volumization, this 6-step “Precise Sculpt” technique can be used as a template to reliably achieve optimal results while minimizing the risk of adverse events. J Drugs Dermatol. 2016;15(12):1550-1556.



7 points Now

Before

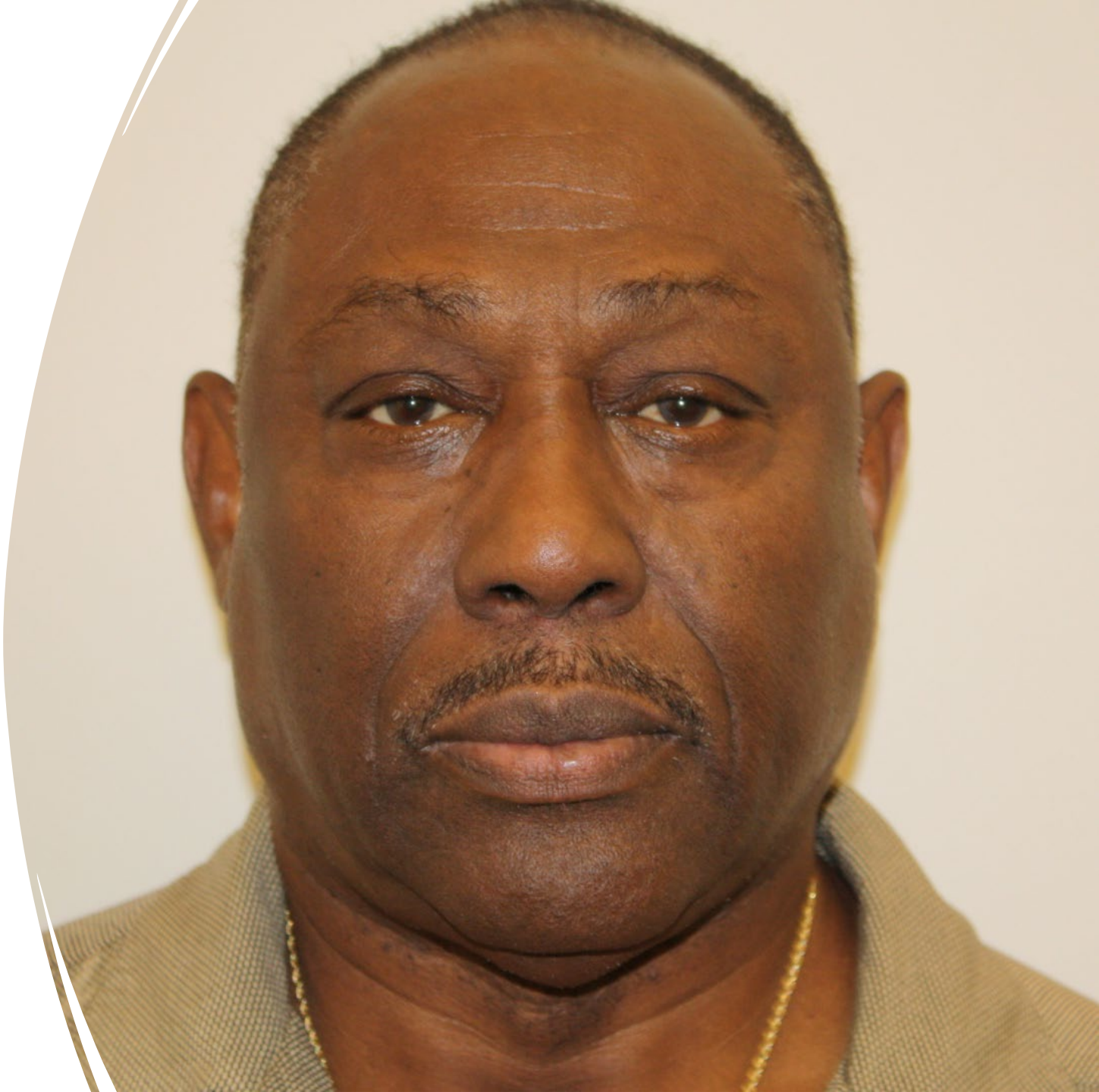
- 75 y/o male
- Looking to look younger
- Wife looking like his daughter now.

After one session

- 2 vials Sculptra per session
- Supraperiosteal technique (7points)
- 8 weeks later
- Decided to do another session 2 more vials.

After 2 sessions

- 8 weeks after the second session
- Observe how the soft tissue fits better on the ticker periosteum.



Before

- 72 year old male
- Looking tired and older wants to look refreshed

After one session

- Two vials

Before

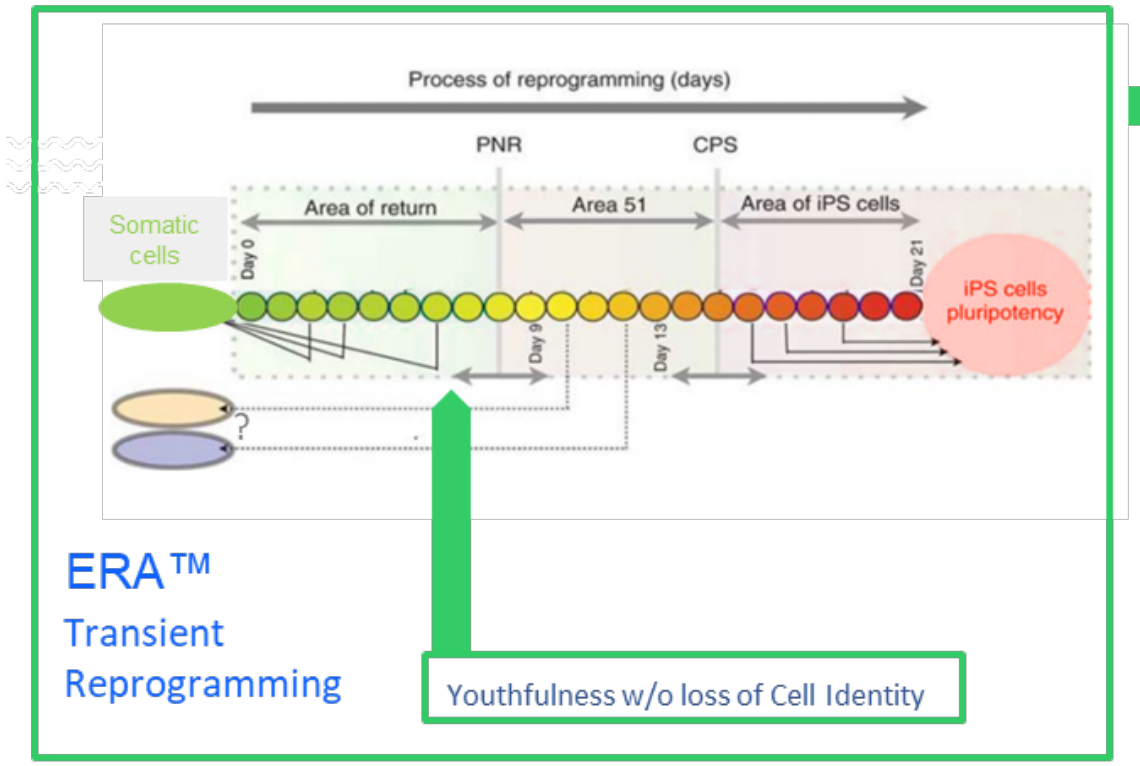
- 49 y/o male post weight loss
- Looking for facial rejuvenation

After two sessions

- 2 vials per session
- 8 weeks apart per session


THE DAWN
OF A
NEW ERA
0:09.33

Epigenetic Reprogramming of Aging (ERA): Cellular Restoration



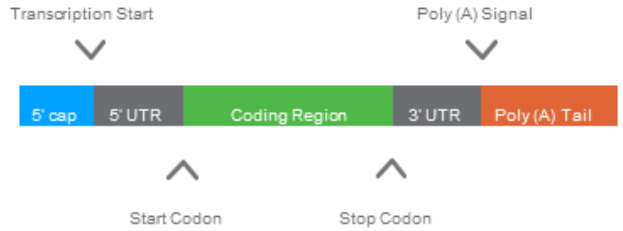
ERA™

Transient Reprogramming

Youthfulness w/o loss of Cell Identity

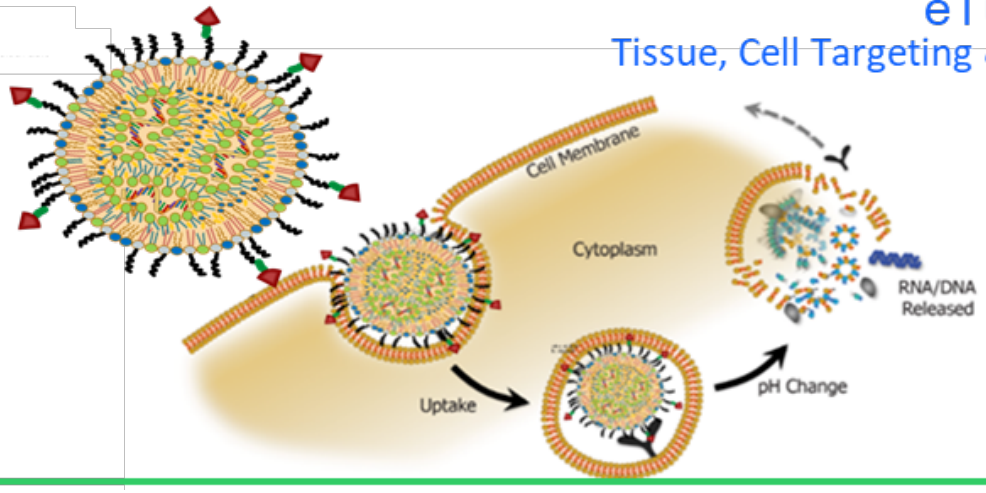
Proprietary mRNA

Cell Transfection & Reprogramming



eTurna™

Tissue, Cell Targeting & Delivery



Sarkar et al., 2020, Nature Communications

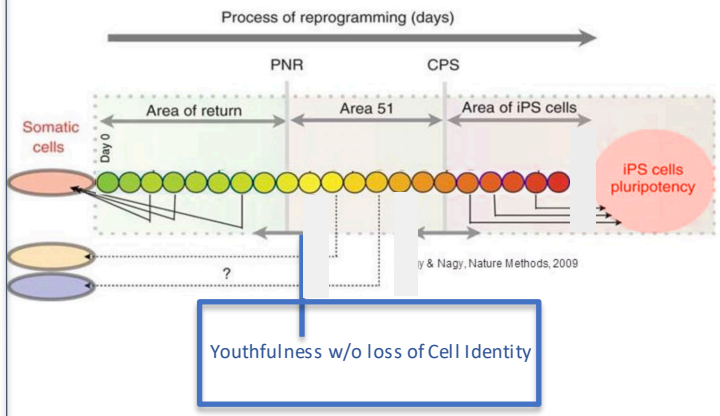
Nagy & Nagy, Nature Methods, 2009

Disease Targeted Precision Medicine

ERA™ and eTurna™

ERA™ mRNA PLATFORM

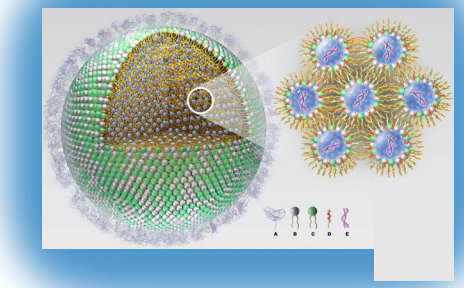
Epigenetic Reprogramming



Cellular Reprogramming

eTurna™ PROPRIETARY PLATFORM

Novel Nano-Carriers



Targeted Cell & Tissue Delivery

FORMULATIONS BY TARGET TISSUE

Cell Rejuvenation

Courtesy of TurnBio

How Can We Restore the Functionality of Aged Cells?

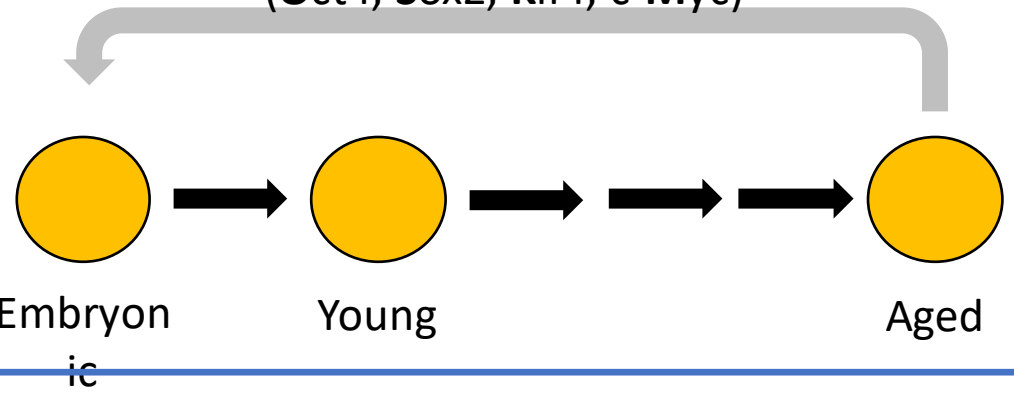
Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]
[1] Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2] CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
*Contact: yamanaka@frontier.kyoto-u.ac.jp
DOI 10.1016/j.cell.2006.07.024

Cell 126, 663–676, August 25, 2006

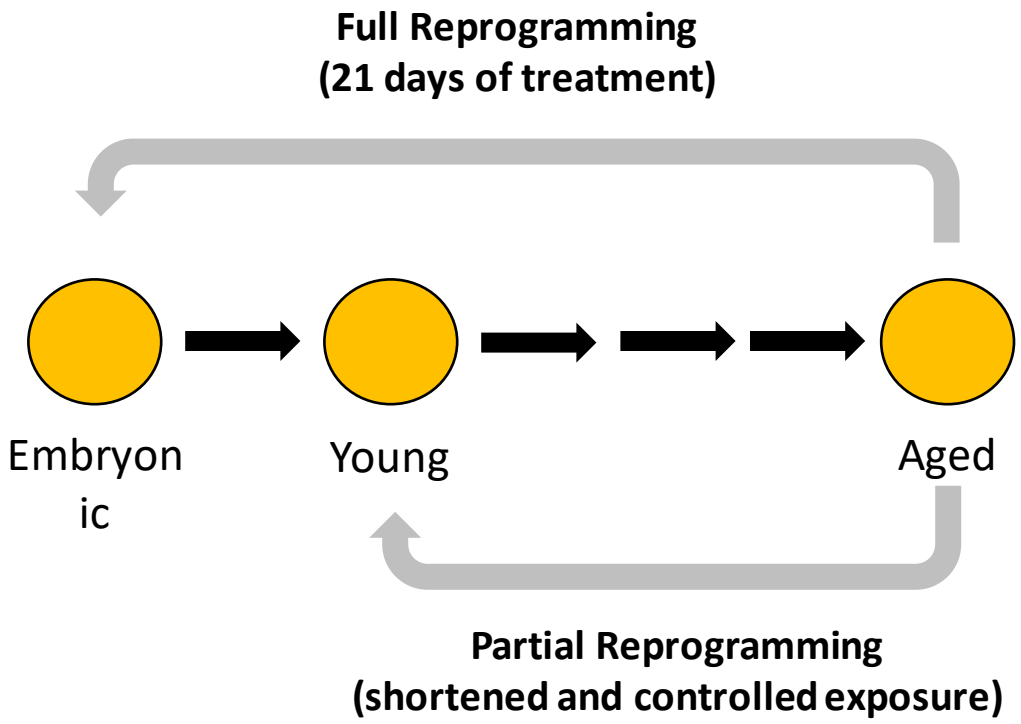
Shinya Yamanaka (2012)

OSKM aka "Yamanaka Factors"
(**O**ct4, **S**ox2, **K**lf4, c-**M**yc)



- Aged cells can be fully reprogrammed back to an embryonic state ("iPSC")
- Minimum of 4 protein transcription factors needed → "Yamanaka Factors"

Partial (or Transient) Reprogramming Restores Youthfulness Without Changing the Cell's Identity



Full vs. Partial Reprogramming

- Can use the same transcription factors, but the difference is in the duration of treatment
- Partial reprogramming rejuvenates cells but does not change the cell's identity
- Full reprogramming requires redifferentiation and has the potential to form tumors

ERA™ in Dermatology:
The Future of Skin

Wrinkles
Texture
Thickness
Elasticity
Scars
Discoloration
Volume loss
Purpura (vessels)
Wounds

ERA works in all layers of the skin:
epidermis, dermis, hypodermis, muscle

- Proven effective in over 40+ cell types

ERA-mediated rejuvenation

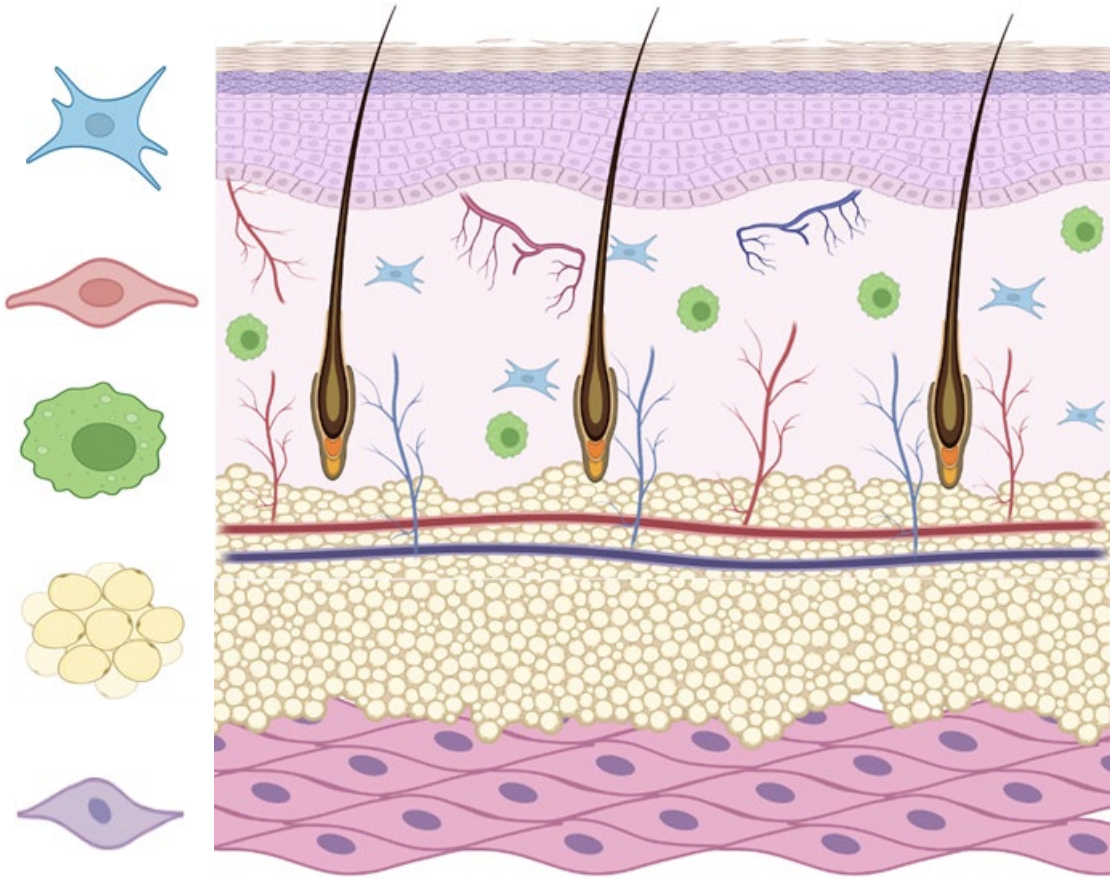
Fibroblasts (Connective tissue, ages 70-80 yrs)

Endothelial Cells (Blood vessel, ages 45-60 yrs)

Macrophages (Blood, ages 55-65 yrs)

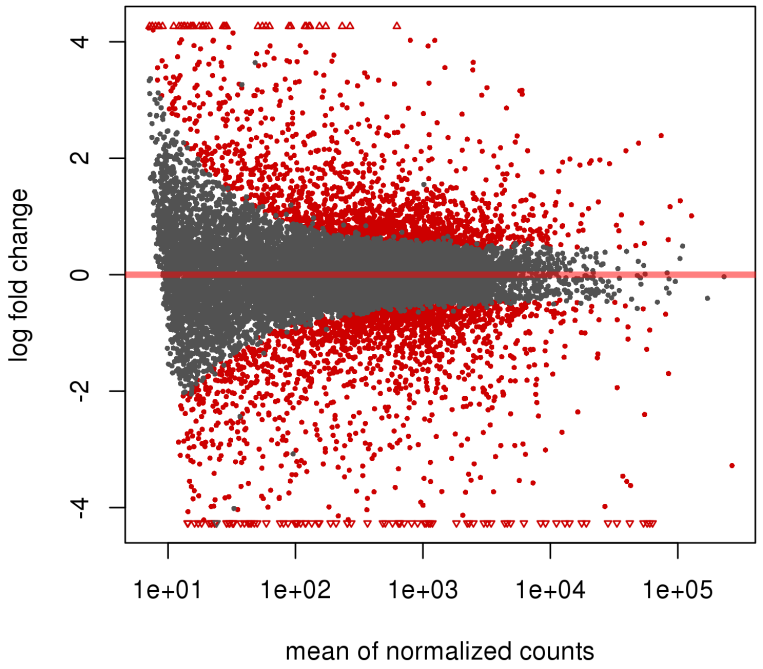
MSCs, Adipocytes Progenitor Cells (lipoaspirate, ages 50-70)

Satellite Cells (Muscle, ages 70-90 yrs)

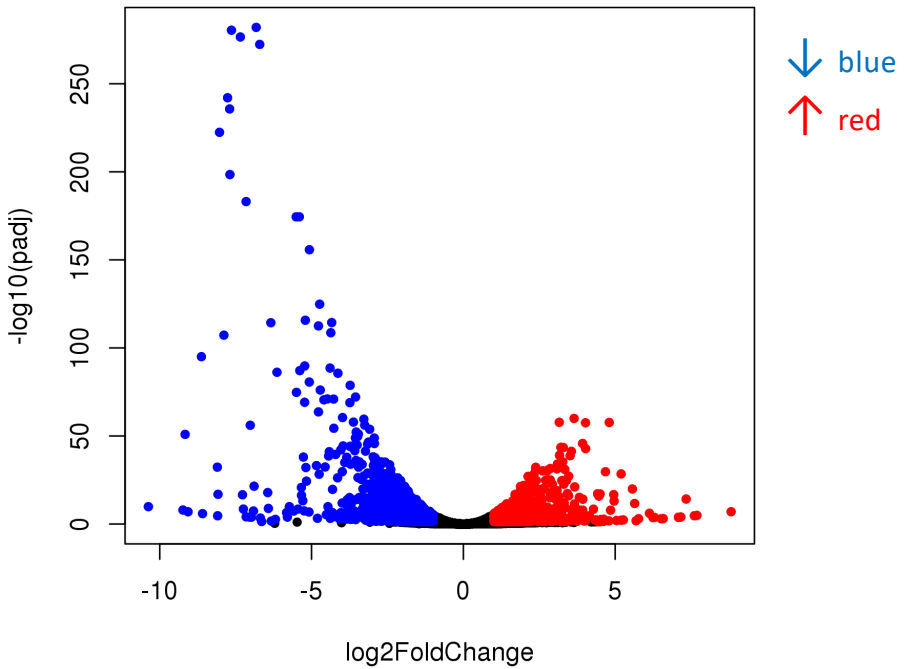


ERA restores balance and youthful function in all cells

ERA™ Has a Strong Global Transcriptional Effect on Adult Dermal Fibroblasts



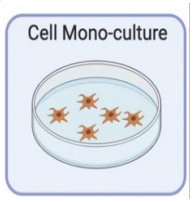
MA Plot: genes in red are differentially expressed



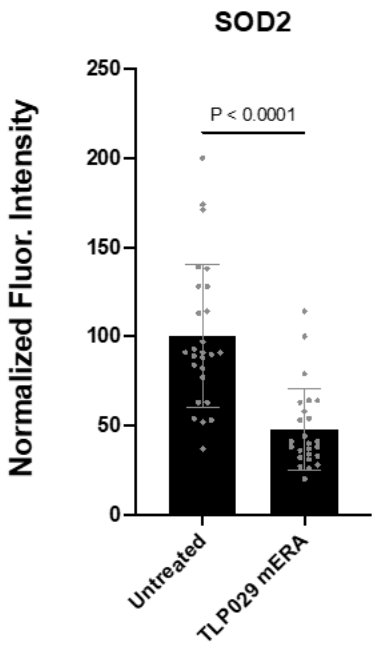
Volcano Plot: distribution of significant (2-fold) genes

- With ERA treatment, many significant differentially expressed genes are associated with extracellular matrix (ECM) remodeling and inflammation
- Gene ontology analysis showed that ERA-induced changes amount to an overall enrichment of ECM protein deposition and downregulation of cytokine signaling

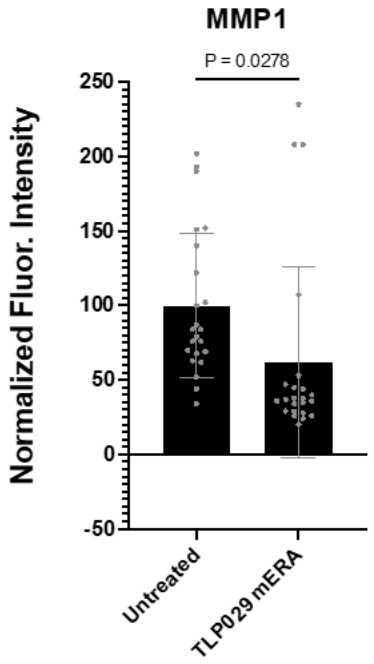
Treatment with ERA Results in a Broad Panel of Changes Related to Aging and Skin Quality

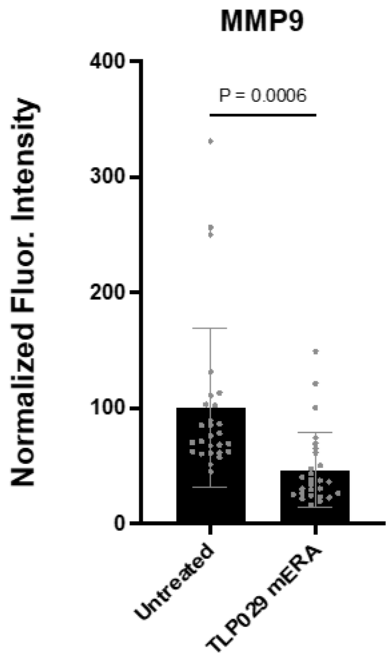


↓ Oxidative Stress

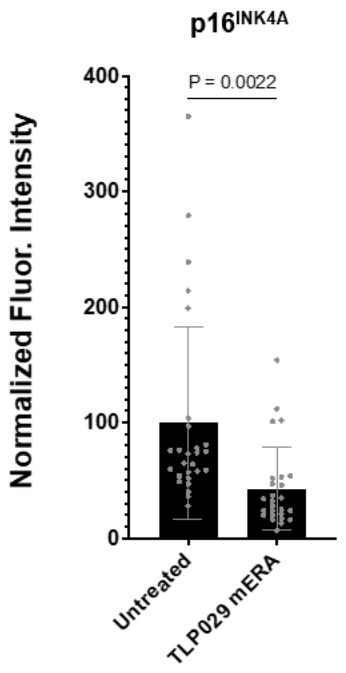


↓ MMPs

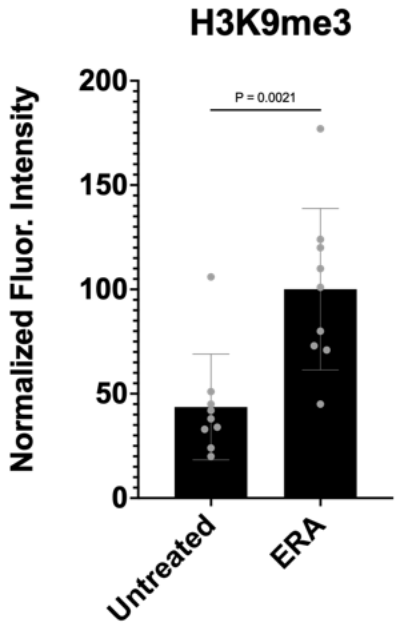




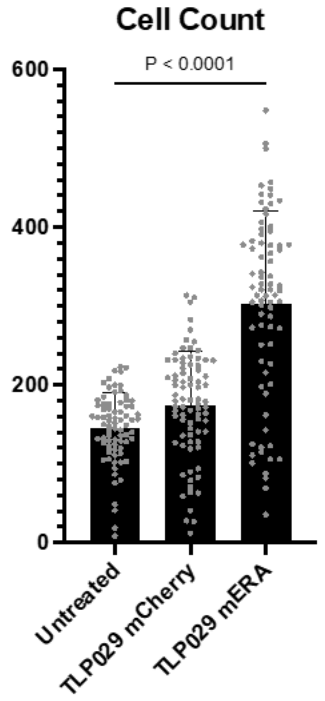
↓ Senescence



↑ Rejuvenation

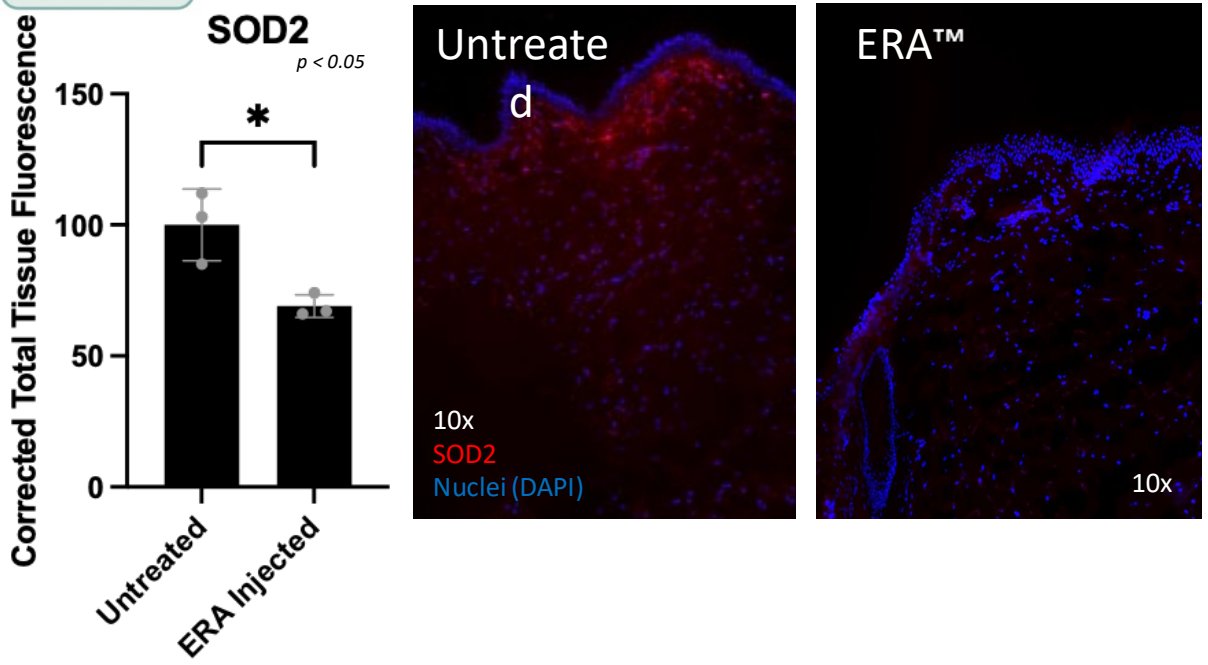


↑ Proliferation

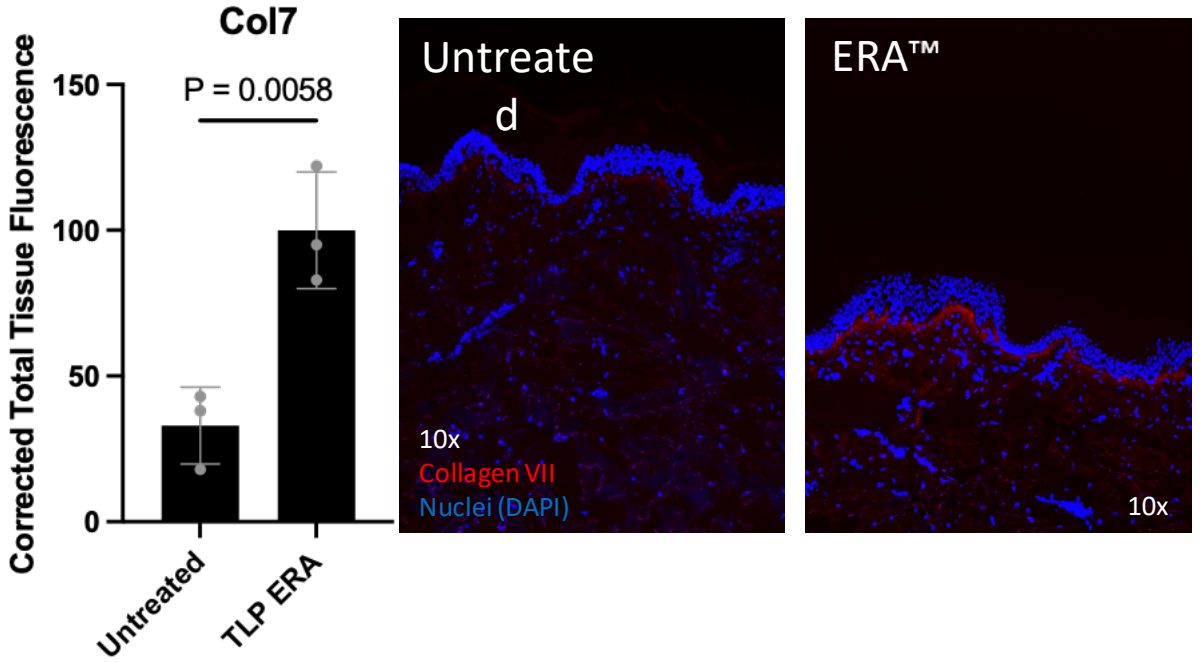


ERA™ Rejuvenates Ex Vivo Human Skin Cultures

Decreased Oxidative Stress



Increased Collagen VII



- Consistent with cellular studies, the oxidative stress marker, SOD2, is also decreased with ERA treatment at the tissue level
- Collagen VII, a key ECM protein that maintains the integrity of the dermal-epidermal junction that is known to decrease with age, is increased with ERA treatment

Path Forward to the Clinic

INTERACT Meeting with FDA

- Positive feedback from FDA discussions provides guidance for clinical trial design

***In vivo* Efficacy (ongoing)**

- Human skin mouse xenograft model
- Wound healing models (mouse and pig)

Development

- Formulation optimization
- IND-enabling studies

V15LA80782