ABOUT COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (CCH AND CCH-AAES)

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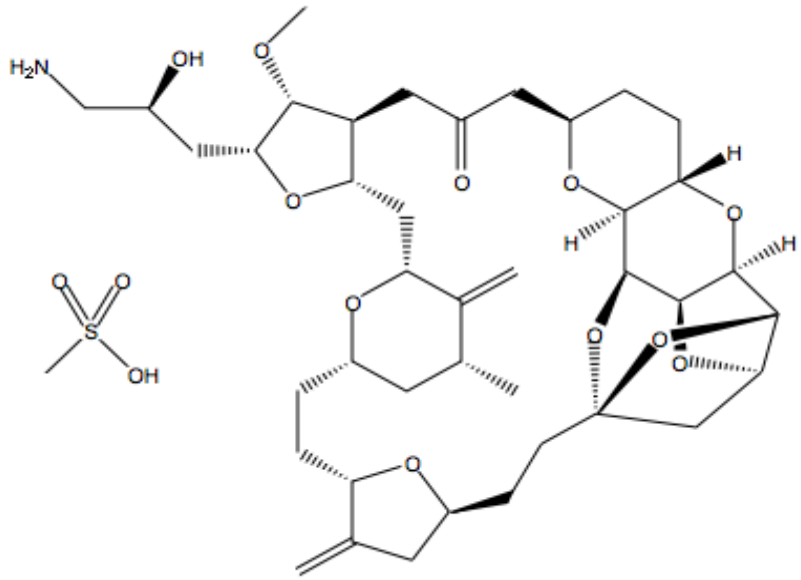
CLINICAL HISTORY OF COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (CCH)

- CCH was first approved in 2010 for the treatment of Dupuytren's contracture with a palpable cord[1]
- CCH received approval in 2013 for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy[1]
- CCH has a track record of efficacy and safety for the treatment of Dupuytren's contracture and Peyronie's disease, having been studied in over 30 studies in more than 2800 subjects[1]
- CCH-aaes received FDA approval in 2020 for the treatment of moderate to severe cellulite in the buttocks of adult women[2]
- CCH-aaes for cellulite has been studied in 11 clinical trials in a total of 1027 patients for up to 4 years[3]



References: 1. Xiaflex [package insert]. Malvern, PA: Auxilium Pharmaceuticals Inc. **2.** Qwo [package insert]. Malvern, PA: Endo Pharmaceuticals, Inc. **3.** Data on File.

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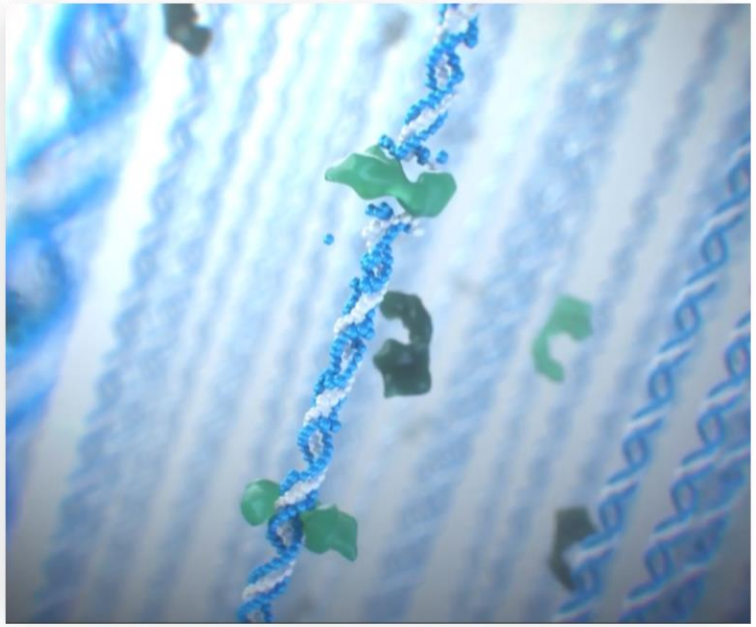
WHAT IS CCH?

- CCH consists of 2 collagenases: AUX-I and AUX-II
- AUX-I and AUX-II are isolated, purified enzymes naturally produced by the bacterium clostridium histolyticum*
- Collagen is resistant to degradation by most common proteases, except the collagenolytic proteases such as CCH[1]
- AUX-I and AUX-II degrade type I and type III collagen, which results in the generation of small peptide fragments[2,3]



CCH cleaving collagen

***The scientific community has renamed "Clostridium histolyticum" to "Hathewaya histolytica;" Endo will continue to use CCH.**

References: 1. Xiaflex [package insert]. Malvern, PA: Auxilium Pharmaceuticals Inc. **2.** Qwo [package insert]. Malvern, PA: Endo Pharmaceuticals, Inc. **3.** Data on File.

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AUX-I AND AUX-II IN COMBINATION SYNERGISTICALLY DEGRADE COLLAGEN TYPES I AND III

- **Multiple sites of collagen molecules cleaved simultaneously**
  - AUX-I, a class I collagenase, preferentially cleaves end portions of intact collagen molecules
  - AUX-II, a class II collagenase, preferentially cleaves collagen molecules centrally

DISTINCT AUX-I AND AUX-II CLEAVAGE SITES

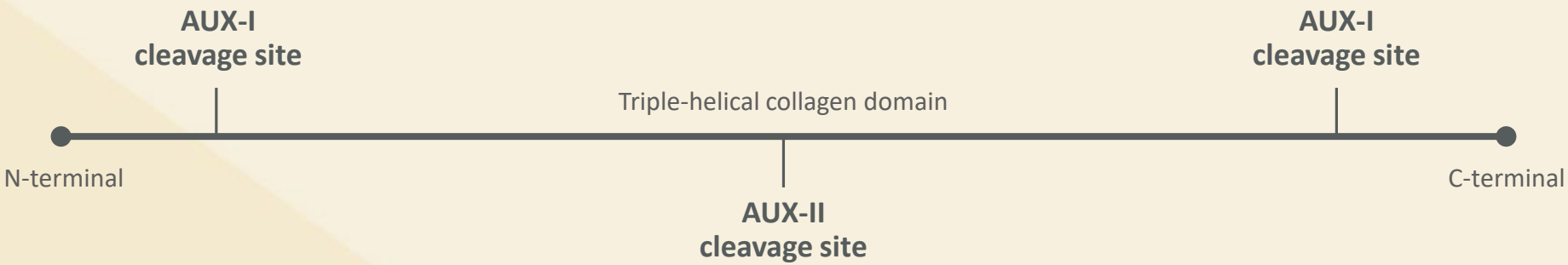

Figure adapted from: Kono T. *Biochemistry*. 1968;7(3):1106-1114.

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MORE COMPLETE AND FOCAL DIGESTION OF COLLAGEN

SYNERGISTIC EFFECT OF AUX-I AND AUX-II

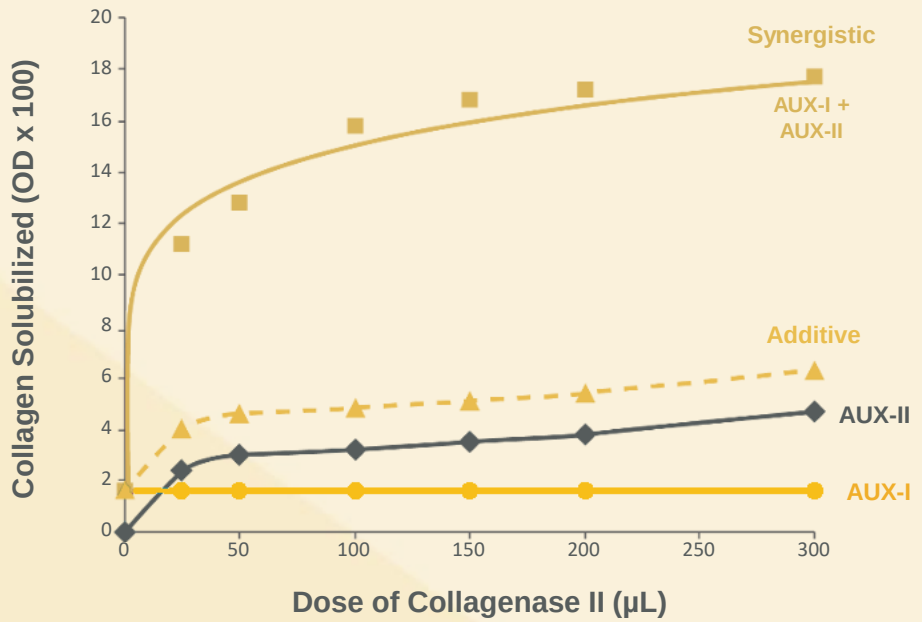

Figure adapted from: Kono T. *Biochemistry*. 1968;7(3):1106-1114.

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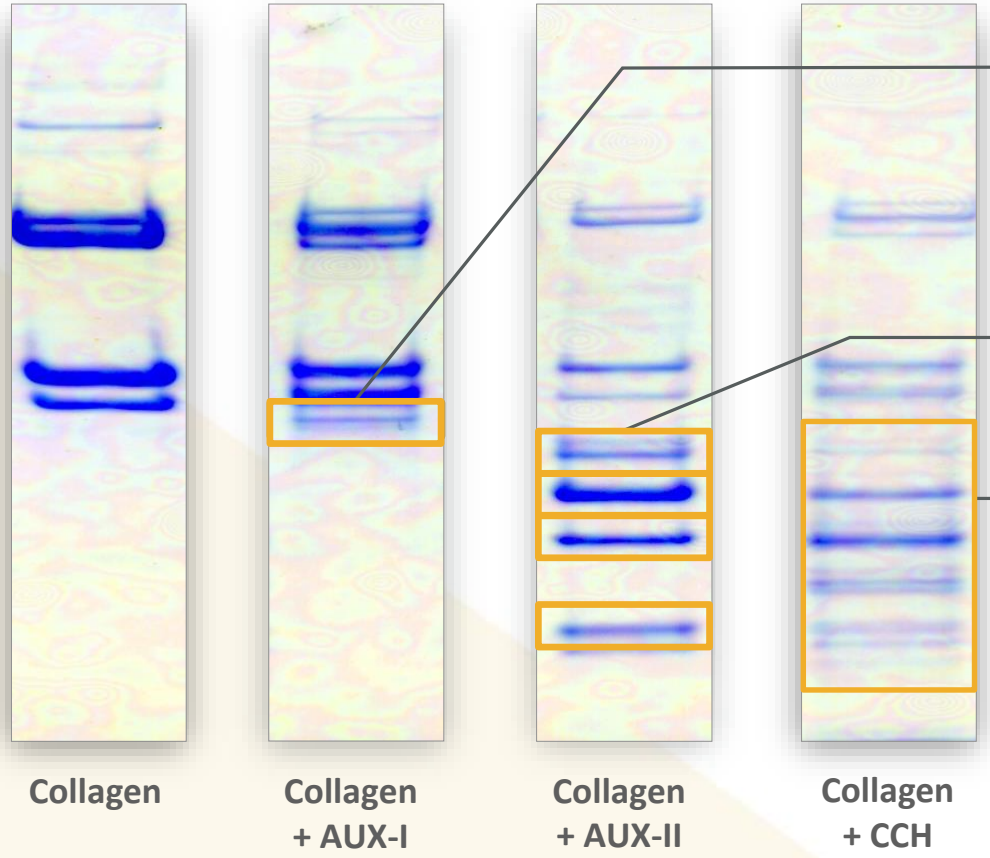
AUX-I AND AUX-II WORK TOGETHER TO DEGRADE COLLAGEN MORE COMPLETELY THAN EITHER ALONE



- AUX-I demonstrates minimal cleavage due to its preferential cleaving of the end portions of intact collagen molecules
- AUX-II demonstrates cleavage into distinct bands
- With AUX-I and AUX-II together, as found in CCH, you see multiple bands you don't see with either AUX-1 or AUX-II alone

Reference: Data on file.

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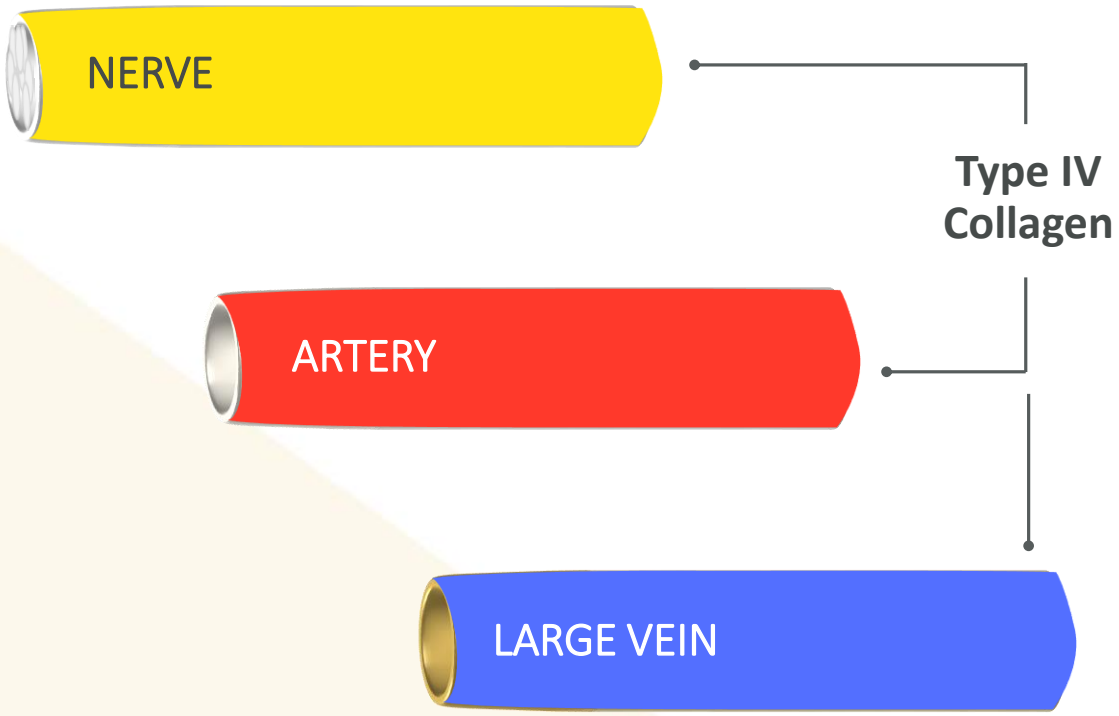
CCH TARGET SPECIFICITY: NO EVIDENCE OF STRUCTURAL OR HISTOLOGIC EFFECTS ON NERVES, ARTERIES, OR LARGE VEINS HAS BEEN OBSERVED



In vitro, at higher CCH concentration and longer durations, type IV collagen was affected, causing collagen lysis in small veins

CCH = collagenase clostridium histolyticum.

Reference: Xiaflex® (collagenase clostridium histolyticum) [package insert]. Malvern, PA: Endo Pharmaceuticals Inc.

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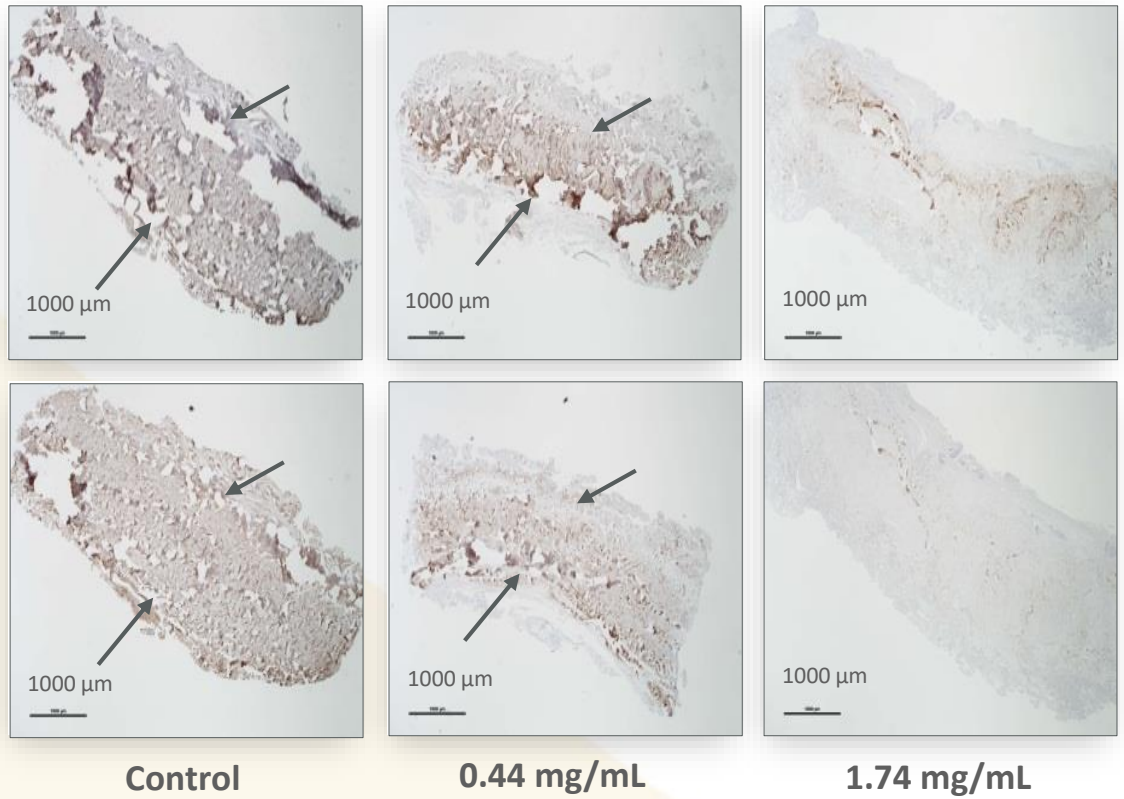
INCREASING CCH DOSAGE AND TYPE I AND III COLLAGEN DEGRADATION MAY BE CORRELATED

PD PLAQUE TISSUE EXPLANTS



*Evaluated using Xiaflex formulation.

PD = Peyronie's disease.

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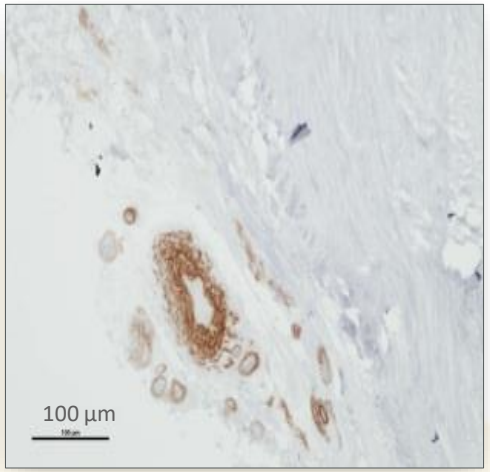
TYPE IV COLLAGEN REMAINED INTACT WHEN CCH WAS ADMINISTERED AT THERAPEUTIC LEVELS

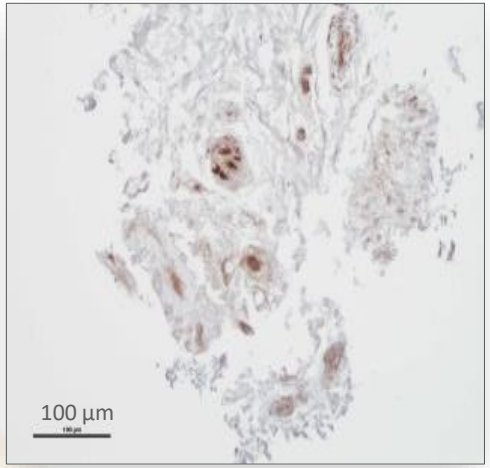
Immunostaining (20X magnification) for type IV collagen, dose-dependent degradation in PD plaque tissue explants*

Control



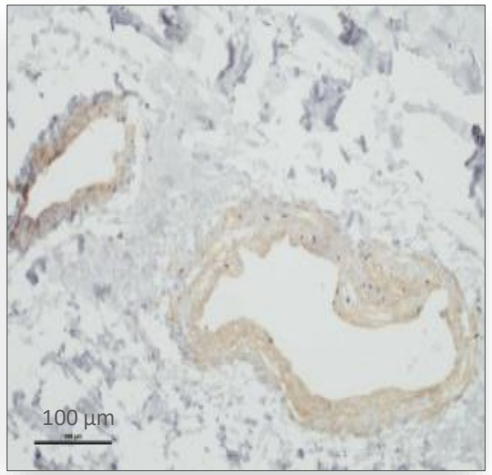
20x

0.44 mg/mL



20x

1.74 mg/mL



20x

At up to 7.5 times therapeutic levels, type IV collagen remained intact.[1]

*Evaluated using Xiaflex formulation.

PD = Peyronie's disease.

Reference: 1. Data on file.

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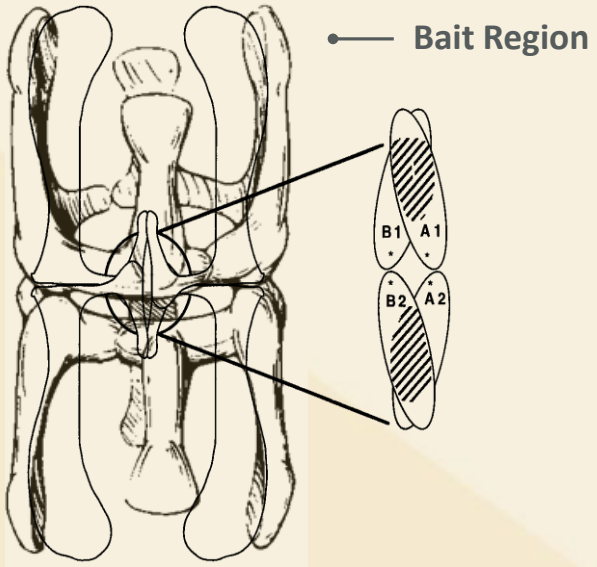
ALPHA-2-MACROGLOBULIN INACTIVATES COLLAGENASE

ALPHA-2-MACROGLOBULIN (A2M)



A2M-COLLAGENASE COMPLEX

A2M-collagenase complex

Alpha-2-macroglobulin (serum, interstitial) has bait region that cleaves collagenase

Collagenase-A2M complex cleared by liver and interstitial macrophages

References: 1. Bowen ME, Gettins PG. J Biol Chem. 1998;273(3):1825-1831. **2.** Feldman SR, et al. Proc Natl Acad Sci USA. 1985;82(17):5700-5704.

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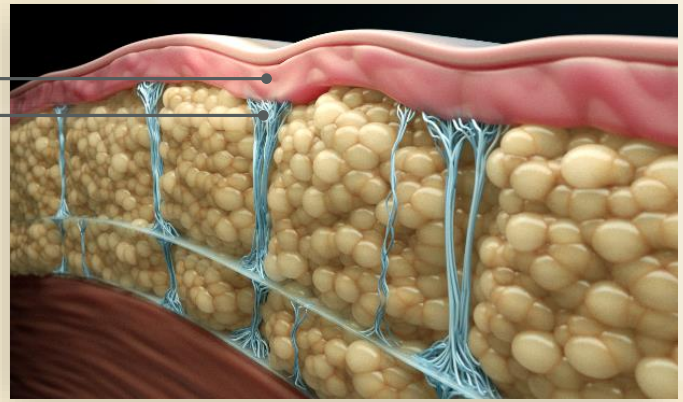
CCH-AAES IS THOUGHT TO IMPROVE THE APPEARANCE OF CELLULITE BY LYSIS OF THE FIBROUS SEPTAE

CELLULITE CONDITION

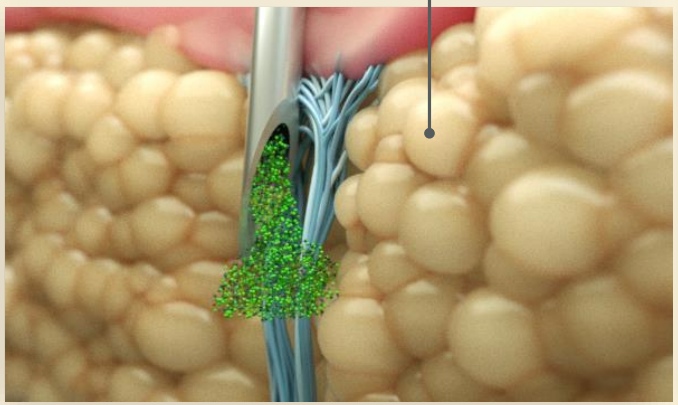
Collagen-rich subdermal fibrous septae play a role in the pathophysiology of cellulite.[1]

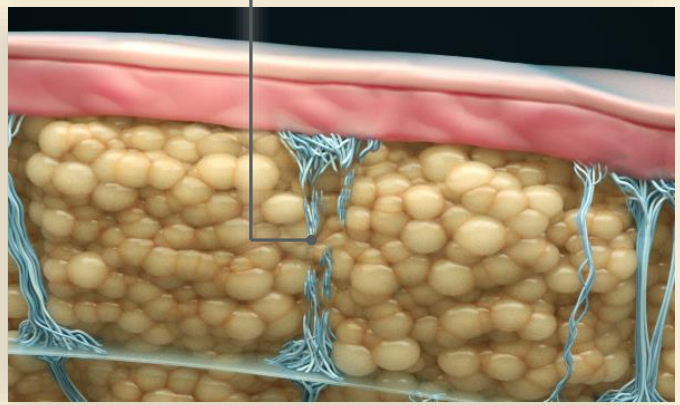
Therapeutic options that release/break fibrous septae may be effective for treating patients with cellulite.[1]



CCH-aaes MoA

When CCH-aaes is injected into the area beneath the dimple, the fibrous bands are broken.[2-4] It is thought this may release the cellulite-associated depression and smooth the surface of the skin.[5]





References: 1. Ruldolph C, et al. *Plast Reconstr Surg*. 2019;143(4):1077-1086. **2.** Rossi AM, et al. *Dermatol Clin*. 2014;32:51-59. **3.** Edkins TJ, et al. *Clin Vaccine Immunol*. 2012;19(4):562-569. **4.** Kaplan FT. *Drugs Today (Barc)*. 2011;47(9):653-667. **5.** Sadick N, et al. *Dermatol Surg*. 2019;45(8):1047-1056.

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