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# Clinical Functions and Bioactivities of Hyaluronan and its Fragments: A Minireview

**Mizhou Hui[1] , Jessica Hui[1], Munkh-Amgalan Gantumu[3] and Dylan Treger[2]**

[1]*Hynaut Group, Qingdao, PRC*

[2]*Miller school of medicine, university of Miami,1120 NW 14th St Miami, FL 33136, United States*

[3]*Nakhia impex pharmaceutical co. ltd, #39A, 21 th Khoroo, Khan-Uul district, Ulaanbaatar, Mongolia*

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***Corresponding author**: Mizhou Hui, Hynaut Group, Qingdao, PRC

## Abstract

High molecular weight gel-like hyaluronan injectable solution or gels has been marketed for local injection more than a half century, including joint cavity injectable solution, eye surgery gel, dermal filler gel and anti-adhesive gel for abdominal surgery, solutions for bladder painful syndrome and dry eyes. No clearly definated bioactivities or clinical functions and action mechanisms were confirmed due to the poor tissue permeability of high molecular weight hyaluronan and the poor access to its cell surface binders or receptors deep inside of human tissues. Recent studies in Nature and Science indicated that naked mole rat having 6% tissue content of hyaluronan, and its fragments has extremely long-life span and nature of cancer resistance, inflammation resistance and pain resistance. Recent study in Nature by using tissue permeable gene transfer method again demonstrated its variety of bioactivities of hyaluronan and its fragments, including life span promotion, cancer resistance, inflammation resistance and pain resistance. Previous study in Nature Communication also demonstrated that hyaluronan inhibited pain ion channel TRPV1. Previous studies indicated that average 35kDa hyaluronan fragment HA35 was made in human breast colostrum where human testis hyaluronidase PH20 gene has expressed. Our previous studies demonstrated human testis and bovine testis hyaluronidase PH20 cleaved high molecular weight hyaluronan into narrowly distributed average 35kDa hyaluronan fragment which made pharmaceutical grade HA35 injection and topical used HA35 commercially available.

By using this tissue permeable HA35, we have demonstrated that topically used HA35 were effective in treatment of gingivitis, pharyngitis, laryngitis, lazer-induced skin wound, and scald wound. Again, by using this tissue permeable HA35, we have also demonstrated that injectable solution of HA35 is a promising injection drug candidate for pain killing, including inflammatory pain (neck pain, shoulder pain and back pain), neuropathic pain (herpes zoster related pain and diabetic foot related pain), cancer pain (lung cancer pain and rectal cancer pain) and wound pain. It is also a promising drug candidate for wound healing (scald wound and vascular inflammation related chronic wound). The mechanism studies suggested that hyaluronan and its fragments promoted human mononuclear cells including lymphocyte and microglia diffused from the "inflammation site". The mechanism studies also indicated that HA35 promoted lymphocyte "homing", thus strengthening immunity. Taking together, HA35 is potentially a billion-dollar drug for inflammatory pain, neuropathic pain, cancer pain and wound pain. Most probably, it has therapeutic action for pain due to its anti-clinical inflammation action.

**Keywords:** 35kDa Hyaluronan fragment; HA35; Inflammatory pain; Neuropathic pain; Cancer pain; Radiation therapy; Chronic wound pain; Wound healing

## Minireview

High molecular weight gel-like hyaluronan [1,2,3] injectable solutions or gels have been marketed for local injection more than a half century, including joint cavity injectable solution [4], eye surgery gel [5] dermal filler gel [6] and anti-adhesive gel for abdominal surgery [7], solutions for bladder painful syndrome [8,9] and dry eyes [10]. The clinical applications of these products also suggested that hyaluronan might have some anti-inflammation [4,7,10] and pain killing [4,8,9] functions except for its confirmed physical activities of lubrication, hydration and space fillings. HA and its constantly degraded fragments [1,2,3] have a variety of cell surface binders [11,12] or receptors, including CD44 [13], LYVE-1 [14], RHAMM [15], HARE [16,17] Siglec-9

[18], TLR2 [19], CEMIP [20] and TMEM2 [21], again suggesting their wide range of bioactivities and clinical functions including regulation of inflammation [13,14,18,19] and pain [11,12]. Interestingly, no clearly definated bioactivities and functions were confirmed due to the poor tissue permeability of high molecular weight hyaluronan and the poor access to its cell surface binders or receptors deep inside of human tissues.

Recent studies in Nature and Science indicated that naked mole rat having 6% tissue content of hyaluronan and its fragments has extremely long life span, cancer resistance, inflammation resistance and pain resistance [22-24]. These studies suggested that hyaluronan synthase 2 is a long life-span gene. Importantly, a recent study in Nature by using tissue permeable gene transfer method again demonstrated its variety of bioactivities of hyaluronan and its fragments, including life-span promotion, cancer resistance, inflammation resistance and pain resistance [25]. This study further suggested that clinical application of a hyaluronan gene transfer-based medicine or tissue permeable hyaluronan fragment-based medicine is clinically important in multiple therapeutic areas, which might have Lasker Award potential.

Previous studies in Nature Communication and Channel demonstrated that hyaluronan modulates TRPV1 channel opening, reducing peripheral nociceptor activity and pain [11,12], suggesting that TRPV1 channel modulation by hyaluronan reduces pain. In other words, hyaluronan and its low molecular weight fragments might be a drug candidate for pain therapy. A patent (US 920510 B2) together with case studies at https://www.medcentral.com/pain/chronic/cross-linked-hyaluronic-acid-injection-neuropathic-pain reported that local injection of hyaluronan directly at nerve trunk significantly reduced neuropathic pain. Other studies [4,8,9,26,27] also suggested that hyaluronan plays an important role in pain treatment.

Previous studies indicated that average 35kDa hyaluronan fragment HA35 was made in human female breast colostrum [28] where A human male testis hyaluronidase PH20 gene has expressed [29]. Human Pilot study (NCT02867605 at www.clinicaltrials.com) indicated that HA35 is safe for human use for promoting intestinal health [30]. Our previous studies demonstrated human testis and bovine testis hyaluronidase PH20 cleaved high molecular weight hyaluronan into narrowly distributed average 35kDa hyaluronan fragment which made pharmaceutical grade HA35 injection and topical used HA35 commercially available(Novel application and manufacturing method for hyaluronic acid fragment WO/2021/180252; Use of human and bovine hyaluronidase PH20 and hyaluronan for treatment of diseases, Chinese patent application# 202211138082.7). Take together, it is shown that both human male testis and female breast contain same hyaluronidase PH20 gene which cleaved high molecular weight hyaluronan into average 35kDa hyaluronan fragment HA35 which is <220 nanometer tissue permeable nanoparticle (Hyaluronic acid injection and applications thereof, WO/2017/185383) [28,31,32]. In clinical trials, tissue permeable topical used HA35 and HA35 injection were prepared by mixing hyaluronidase extracted from bovine testis (Hyaluronidase for injection, H31022111, PRC) and high molecular weight hyaluronan(Sodium hyaluronate for injection, H20174089, PRC) at room temperature for 20 minutes [33-39] (NCT05756595 and NCT05764226 at www.clinicaltrials.gov). Tissue permeable HA35 or B-HA injection(Ministry of Health, Registration number L20200708MP07707) was also manufactured by cleaving high molecular weight hyaluronan(Bloomage Biotech, PRC) for 5 hours at 37°C with a recombinant human hyaluronidase PH20 (Huihui Technology Inc, PRC) for clinical study(Hyaluronic acid injection and applications thereof, WO/2017/185383) (NCT05852002 at www.clinicaltrials.gov).

By using the above tissue permeable hyaluronan fragment HA35 [31,32] (Novel application and manufacturing method for hyaluronic acid fragment, WO/2021/180252), we demonstrated that topical used 35kDa hyaluronan fragment HA35 were effective in treatment of gingivitis [33,34] (A toothpaste containing bioactive hyaluronan fragment B-HA or HA35, CN201510067326.0), pharyngitis [35] (A compound formulation containing hyaluronan fragment B-HA or HA35, Chinese patent# CN201510333526.6) , Laryngo-pharyngeal Reflux [36] (A compound formulation containing hyaluronan fragment B-HA or HA35, CN201510333526.6) and laser-caused skin wound [37] and skin scald wound [38] (A manufacturing method and its clinical applications of hyaluronan fragment B-HA or HA35, Chinese patent# CN105018547A). Taken together, these studies suggested that HA35 not only effectively reduce the symptoms of itcheness and discomfort caused by the above surface inflammatory diseases, but also has therapeutic action on these inflammatory diseases [33-39].

Again by using this tissue permeable HA35, we also demonstrated that injectable solution of HA35 is a promising injection drug candidate for pain treatment, including inflammatory pain (neck pain, shoulder pain and back pain) (NCT05756595 at www.clinicaltrials.gov) [32], neuropathic pain (herpes zoster related pain and diabetic foot related pain) (NCT05756595 at www.clinicaltrials.gov) [32] and lung cancer pain(NCT05852002 at www.clinicaltrials.gov). It is also a promising drug candidate for wound healing (acute and chronic inflammatory wound(NCT05764226 at www.clinicaltrials.gov) [32,37,38] and rectal cancer pain after radiation therapy) NCT06209970 at www.clinicaltrials.gov [39]. By employing large numbers of beagle dogs, we demonstrated that high dose 200mg of HA35 intravenous one-time injection did not cause any noticed harmful effects [40].

The mechanism studies [31,32,41,42] suggested that hyaluronan and its fragments promoted freshly extracted human mononuclear cells including lymphocyte and microglia diffused from the “inflammation site”, namely an experimental gel drop. In this study, the molecular imaging results of radiolabelled HA35 suggested inflammatory lymphocytes diffused through


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lymphatic vessels and nodes from "inflammation site", namely foot subcutaneous injection sites, where traditionally "clinical inflammation" was thought be diffused through blood vessels. The mechanism studies also indicated that HA35 promoted lymphocyte "homing", thus possibly strengthing immunity [31,32,41].

## Conclusion

Taking together, 35kDa hyaluronan fragment HA35 is potentially a billion-dollar drug for multiple types of pain including inflammatory pain, neuropathic pain, cancer pain and wound pain. Most probably, it has therapeutic action for pain due to its anti-clinical inflammation action. 35kDa hyaluronan fragment HA35 injection is possibly a first in class novel drug ever developed in mainland China and Mongolia.

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