HARNESSING THE UNIQUE POWER OF HUMAN BIRTH TISSUE

Supporting regenerative healing and functional recovery as the adjunct for surgical and chronic wound applications[1-16]

- **Helps facilitate wound healing**[1-16]
- **Helps manage adhesions**[9,10,13]
- **Helps manage discomfort**[11,12]
- **Helps expedite functional recovery**[8-12]

neox®

THE AMNIOX FAMILY OF CRYOPRESERVED UMBILICAL CORD ALLOGRAFTS & INJECTABLES

HELPS IMPROVE PATIENT OUTCOMES AND PATIENT SATISFACTION[2-16]

HELPS MINIMIZE COMPLICATIONS AND READMISSIONS[2-8]

HELPS REDUCE COST OF CARE[2,4-8]

clarix®

FIRST TO RECOGNIZE THE NATURAL POWER OF THE HC-HA/PTX3 COMPLEX

34 CONSECUTIVE YEARS OF NIH-FUNDED RESEARCH

OVER 360 PEER-REVIEWED PUBLICATIONS

MORE THAN 40 ISSUED PATENTS

- **First** to identify and characterize HC-HA/PTX3 as the key orchestrator in human birth tissue regenerative healing[1]
- **First** to introduce the use of cryopreserved amniotic membrane to the ophthalmic market, as part of the TissueTech family of companies
- **First** to commercialize umbilical cord tissue to support **expedited healing of surgical, acute and chronic wounds**[2-16]

AMNIOX MEDICAL

CLINICAL STUDIES REFERENCE GUIDE

www.amnioxmedical.com

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Regenerate. Restore. Recover.

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AMNIOX MEDICAL CLINICAL STUDIES REFERENCE GUIDE

*IND: Investigational New Drug
**HCT/P: Human Cells, Tissues, and Cellular and Tissue-Based Products

	Platform Technology		TTAX01	NEOX CORD 1K		CLARIX CORD 1K				CLARIX FLO	
			UC Matrix – 351 IND*	UC Matrix – 361 HCT/P**		UC Matrix – 361 HCT/P**				Injectable AM/UC – 361 HCT/P**	
	Tseng	Cooke et al.	Marston et al. (2019 & 2020)	Raphael	Caputo et al.	Bemenderfer et al.	DeMill et al.	Warner & Lasyone	Stewart	Bennett	Castellanos & Tighe
Study Focus	Biologic Science	Comparative Biology	Wagner Grade 3 & 4 Diabetic Foot Ulcers	Diabetic Foot Ulcers	DFUs with Osteomyelitis	Total Ankle Arthroplasty (TAA)	Foot and Ankle (F&A) Surgery	Foot and Ankle (F&A) Surgery	Foot and Ankle (F&A) Trauma	Facet Joint Pain	Knee Osteoarthritis
Clinical/Scientific Need	Understanding the proposed molecular action mechanism for AM tissue's innate anti-inflammatory, antiscarring and wound healing potential.	Elucidating the relative biology and structural differences of various tissue types (UC vs. AM vs. AMCh) and processing methods (dehydration vs. cryopreservation).	Complex ulcers with exposed bone, tendon, muscle, and/or joint are at particularly high risk for infection-related complications such as osteomyelitis, which has been shown to increase amputation risk fourfold. The current standard of care (SOC) for these complex foot ulcers yields poor wound healing of 30% at 12 weeks and 45% regardless of time, necessitating a safe and effective alternative.	Histopathological studies have shown a prolonged inflammatory phase in patients with diabetes, delaying the formation of mature granulation tissue and reducing wound tensile strength, making these wounds difficult for physicians to heal. Any treatment that may modulate the chronic inflammation may help improve closure of these wounds.	Deep complex ulcers in patients with multiple comorbidities including diabetes, ischemia, and underlying osteomyelitis are difficult to heal and associated with high morbidity and mortality and high rates of amputation.	Despite improvement in TAA implants, the procedure is still prone to relatively high complication rates associated with the anterior ankle incision, especially in patients with comorbidities. A direct reduction in complications will reduce the overall cost of care.	Understanding the safety profile of cryopreserved amniotic tissue used in real-world surgical procedures to assist in wound healing and adhesion prevention may better inform treatment decision of F&A surgeons and wound care specialists.	Complex reconstructive and revision procedures involving tendon and nerve are prone to adhesions and compromised functional outcomes. Multiple clinical and pre-clinical studies have suggested cUC may benefit patients undergoing reconstructive procedures, especially revisions.	The complication rate after open reduction and internal fixation (ORIF) of calcaneal fractures operated on by a lateral extensile approach range from 10 to 30%, with perioperative complications often involving tissue/bone infection and/or wound complications. This necessitates a safe and reliable means to reduce the rates of complication and readmission/reoperation.	Treatment of back pain due to facet joint syndrome has been a challenge for physicians with intra-articular injections of steroid, local anesthetics, and opioids being widely adopted despite their known shortcomings. Thus, there remains an unmet clinical need for a safer and more effective treatment.	Knee osteoarthritis (OA) is a degenerative joint disease that causes pain and decreased function for millions of Americans. Current pharmacologic therapies are limited either in their durability (steroids), adverse events (NSAIDs), addiction risk (opioids), or conflicting clinical evidence (HA). There is a need for a safe 'non opioid' treatment that improves pain and function, as well as slows progression of the disease.
Study Type	Investigational Research	Comparison Study	Prospective, multi-center clinical trial	Retrospective, single-center study	Retrospective, single-center study	Retrospective single-center study	Retrospective, consecutive case series	Retrospective single-center study	Retrospective single-center study	Single-center case series	Prospective, single-center study
Study Objective	To identify the innate biological components and mechanisms, including the pivotal role of HC-HA/PTX3 that provides cryopreserved AM the ability to control inflammation and promote wound healing.	To evaluate the different processing methods cryopreservation and dehydration affect the structural integrity and biological composition of key signaling molecules within AM, AMCh, and UC tissues.	As part of TissueTech's FDA Phase II Clinical Trial of TTAX01, this open-label pilot study was designed to estimate the efficacy of cryopreserved UC in achieving complete wound closure of complex healing DFU.	To assess the effectiveness of a cryopreserved UC allograft as an aid to promote wound healing in patients suffering from one or more DFUs of Wagner Grade 1-3.	To demonstrate the clinical effectiveness of using cryopreserved UC as an advanced adjunctive treatment modality in patients with chronic complex foot ulcers with underlying osteomyelitis.	To determine whether the local application of cryopreserved UC allograft can enhance soft tissue wound healing of the TAA anterior ankle incision in patients with and without specific risk factors for poor healing.	To report the short-term safety profile after in vivo application of cryopreserved AM/UC tissue use in foot and ankle.	To evaluate the efficacy of UC to reduce pain and improve functional outcomes in complex reconstructive and/or revision procedures involving tendon or nerve of the foot and ankle.	To assess the effects of UC applied at the time of primary ORIF of calcaneal fractures could augment soft tissue healing and decrease post-operative wound complications.	To examine the use of intra-articular UC injections in a pain management practice for patients presenting with pain caused by facet joint syndrome.	To evaluate the short-term safety and effectiveness of injections of UC particulate in managing patients with various severities of knee OA.
Patient Enrollment	N/A	N/A	32	29	31	104 (54 CLARIX, 50 control)	124	14	40 (20 CLARIX, 20 control)	9	20
Results	A novel matrix has been biochemically purified from the water-soluble extract of cryopreserved AM, termed heavy chain (HC)-hyaluron (HA)/ pentraxin 3 (PTX3) as the tissue characteristic responsible for AM's anti-inflammatory and anti-scarring effects, along with the ability to support stem cell niche quiescence.	Cryopreservation retains the native architecture of the AM/UC extracellular matrix and maintains the quantity and activity of key biological signals present in fresh AM tissue, including HC-HA/PTX3. In contrast, dehydrated tissues were structurally compromised and almost completely lacked these crucial components. Additionally, UC tissue contains quantifiably more biologic content in its thicker stromal layer than AM or AMCh.	All patients had wounds extending to muscle, fascia or bone with clinical and radiographic evidence of underlying osteomyelitis. At baseline, the wounds had an average area of 3.8 cm^2 and mean duration of 6.1 months. At initial 16 weeks endpoint, initial closure occurred in 50% of patients with an average of 1.5 applications. Mean overall time to healing for this group was 12.8 weeks. The mean reduction from baseline in wound surface area for all subjects was 91%. At one-year follow-up (2020), the overall closure rate was 86.2% vs. 45% for SOC, and only one patient went on to major amputation (3.4%).	In a total of 32 wounds in 29 patients, the average initial wound area was 10.6 cm^2. 87.5% of wounds achieved complete wound closure in an average time of 13.8 weeks with a median of 9 weeks. The average number of applications was 1.68, with 64.3% of healed wounds requiring only a single application.	In 33 complex foot ulcers in 31 patients with confirmed osteomyelitis, the average initial wound was 15.6cm^2. 78.8% of wounds healed in an average time of 16.0 weeks. Five wounds were lost to followup and one patient died, leaving an overall healing rate of 96.3% in patients with follow-up. The average number of applications was 1.24. Out of 15 wounds recommended for amputation prior to study, only one went onto BKA.	Local application of UC allograft significantly decreased the overall time to skin healing (28.5 days vs. 40 days; p=.03), with older patients (43 days vs. 28 days), smokers (51 vs. 28), and diabetics (92 vs. 57) experiencing the greatest impact. The rates of skin dehiscence (12% vs. 5.7%) and antibiotic use (22% vs 9.6%) trended lower for the UC group, though the study was inadequately powered to reveal statistical significance.	For the 124 patients with a minimum follow-up of 120 days, there was an overall wound complication rate of 5.64%. Two patients required successful irrigation and debridement of an infected wound, translating to a re-operation rate of 1.6%. This compares favorably to the historical rates of infection of 2% to 5% for foot and ankle procedures.	All patients reported improvement in outcome, namely, lessened pain intensity both on the AOFAS Ankle-Hindfoot Scale and the pain numeric rating scale, as well as improved functional status. The mean AOFAS score improved from 50 pre-operatively to 85 post-operatively, while the mean pain rating improved from 8 to 2 with a mean percent change in pain of 78%. Both outcome scoring systems showed statistically significant differences (p<.0001). There were no post-operative complications attributed to UC use.	The use of cryopreserved UC made a reduction in all wound complications, readmissions, and reoperation rates compared to our control group. The overall complication rate in the control group was 35% compared to 10% for UC, along with lower rates for infection (25% to 10%). Additionally, the readmission rate and re-operation rate in the UC group was lower than the control (10% vs. 30%).	Prior to treatment, all patients had severe pain prior to injection, with an average pain score of 8.2 ±0.8. Additionally, 44% were taking opioids. Six-months post-treatment, average pain had decreased to 0.4 ± 0.7 (p<.05), and all patients had ceased use of prescription pain medications, including opioids. No adverse events, repeat procedures, or complications were reported.	Mean knee OA pain significantly decreased from 74.3 at baseline to 45.0 at six-weeks (p<.01). This reduction was sustained and improved through 24 weeks (37.4, p<.001). Significant functional improvement in WOMAC scores was also seen in physical function (p<.05) and stiffness (p=.01). MRI evaluation also revealed an improvement for 37% of patients in the severity of bone marrow lesions, commonly described as the origin of knee OA pain, especially in patients with more severe baseline lesions. No adverse events were observed.
Conclusion	HC-HA/PTX3 can be deployed as a platform to launch new therapeutics in regenerative medicine.	Cryopreservation better preserves the structural and biological signaling molecules of placental tissues than dehydration.	Cryopreserved UC demonstrates significant improvement over SOC for the management of complex, nonhealing DFUs complicated by osteomyelitis. Additionally, it was found to be safe in long-term follow-up and associated with both a low rate of major amputation and higher than expected rates of healing.	An allograft of cryopreserved UC may be effective in improving the healing of DFU ulcers as well as potentially reducing the medical costs associated with chronic DFUs due to the low number of applications needed to achieve complete wound closure.	Adjunctive use of cryopreserved UC in conjunction with surgical debridement, resection of infected bone, open cortex and antibiotic treatement may be an effective overall treatment strategy to promote wound healing of complex foot ulcers associated with osteomyelitis.	Regenerative technology using local application of a cryopreserved UC allograft may enhance TAA outcomes by decreasing the time to healing, especially in high-risk patients.	The observed low post-op complication rates make cryopreserved UC tissue a potentially attractive option for modulating inflammation and reducing adhesion formation in several lower extremity orthopaedic applications.	The use of cryopreserved UC is both safe and effective, with post-operative measures of function and pain significantly improved in patients undergoing foot and ankle procedures with tendon and/or nerve pathologies.	The use of cryopreserved UC application directly on the bone and hardware at the time of ORIF of calcaneal fractures can decrease wound complications, re-operation rates and infection rates.	An injection of UC may be a novel, non-opioid alternative for facet joint pain, providing a safe and effective treatment without the risk of opioid abuse, dependence and addiction for highly painful conditions.	Intra-articular injections of UC particulate show preliminary safety and effectiveness in relieving pain and improving function in patients with symptomatic knee OA. A single injection on average yields benefits in nonobese patients, whereas a second injection may be warranted in obese patients.
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