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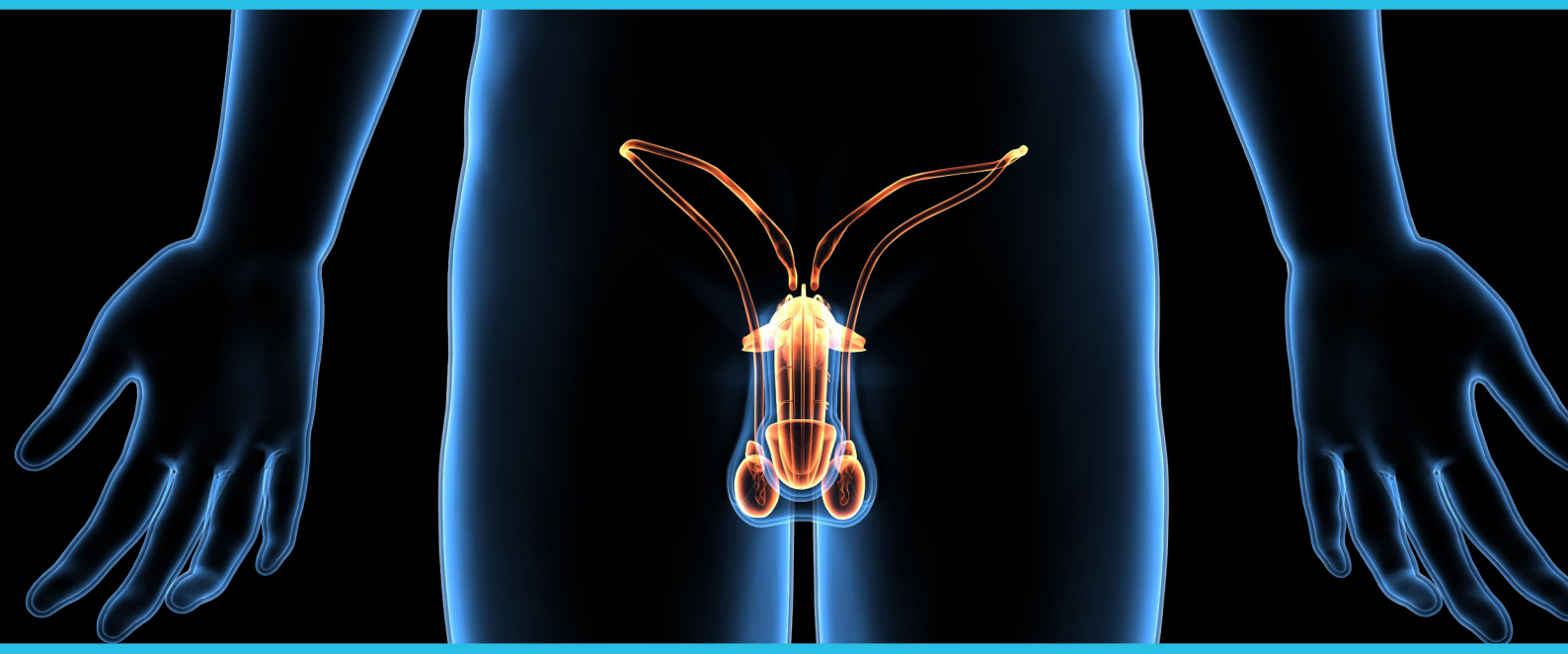


Erectile Dysfunction

Stem Cell Therapy using Tide Motion System

Introduction

Erectile dysfunction (ED) is a common problem affecting sexual function in men. Studies have shown that about 5% of men that are 40 years old have complete erectile dysfunction, and that number increases to about 15% at age of 70.

Erectile dysfunction can occur at any age, but it is more common among older men. They are more likely to have health illnesses that require medication, which can impede erectile function. Moreover, as men age, they may need more stimulation to get an erection and more time between erections.

ED is a compound condition that may involve any one or more of several different organic causes. Contrarily, it may also be psychogenic.

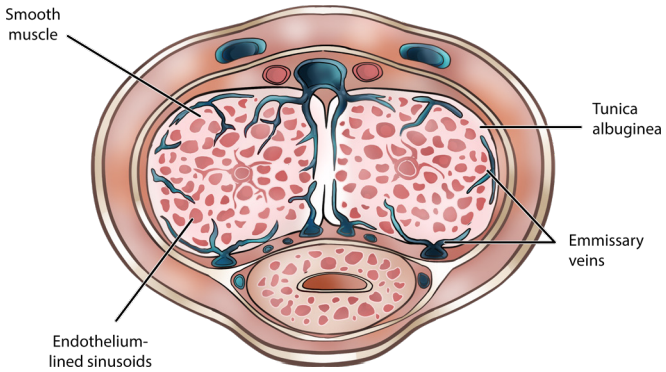
What is Erectile Dysfunction or ED?

Erectile dysfunction (ED) or impotence is mostly defined as the inability to obtain or maintain a penile erection sufficient enough for satisfactory sexual intercourse. This may be accompanied by ejaculatory problems, i.e. either ejaculating too early or too late, with decreased pleasure derived from the ejaculation.

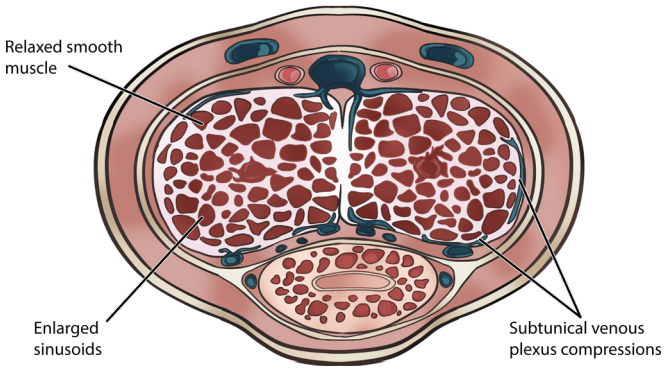
Achieving an erection is a complex process involving the brain, hormones, nerves, muscles, and blood circulation. If something interferes with this process, the result conceivably is erectile dysfunction.

Furthermore, it can confines several different conditions of reproductive health. It is a very common condition, but is also a very emotional and sensitive topic to discuss.

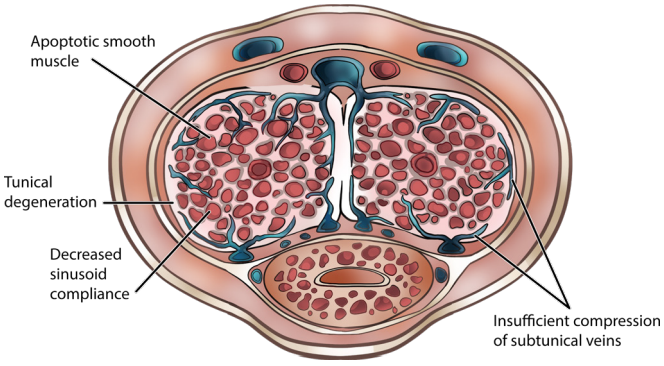
CROSS SECTION OF THE PENILE ANATOMY



Normal Flaccid State



Normal Erect State



On Erectile Dysfunction State

What Causes Erectile Dysfunction?

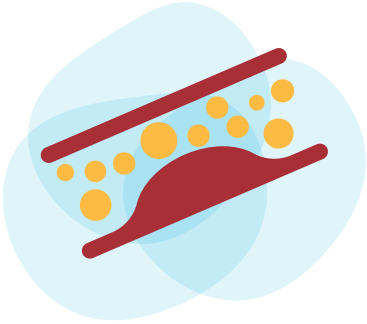
Many factors can affect a man's ability to get and keep an erection and several factors may be present at one time. Commonly there is a combination of physical and psychological factors. Sometimes there is no clear reason for the erectile dysfunction; however, most cases have a physical cause. Some of the causes are shown below:

Psychosocial Problems

- Depression
- Psychiatric disorders
- Performance anxiety
- Sexual attitudes and upbringing

Neurological Injuries / Damage

- Central Nervous System (CNS) damage
- Diabetic neuropathy
- Pelvic surgery
- Multiple sclerosis



Restricted Blood Flow

- Causes of restricted blood flow to the penis includes health conditions like:
  - atherosclerosis
  - diabetes
- Smoking
- Sleep apnea

Urological Problems

- Pelvic Trauma
- Peyronie's disease

Endocrine Problems

- Hypogonadism (low testosterone levels)
- Acromegaly
- Hyperprolactinemia (high proclactin levels)
- Abnormal thyroid hormone levels

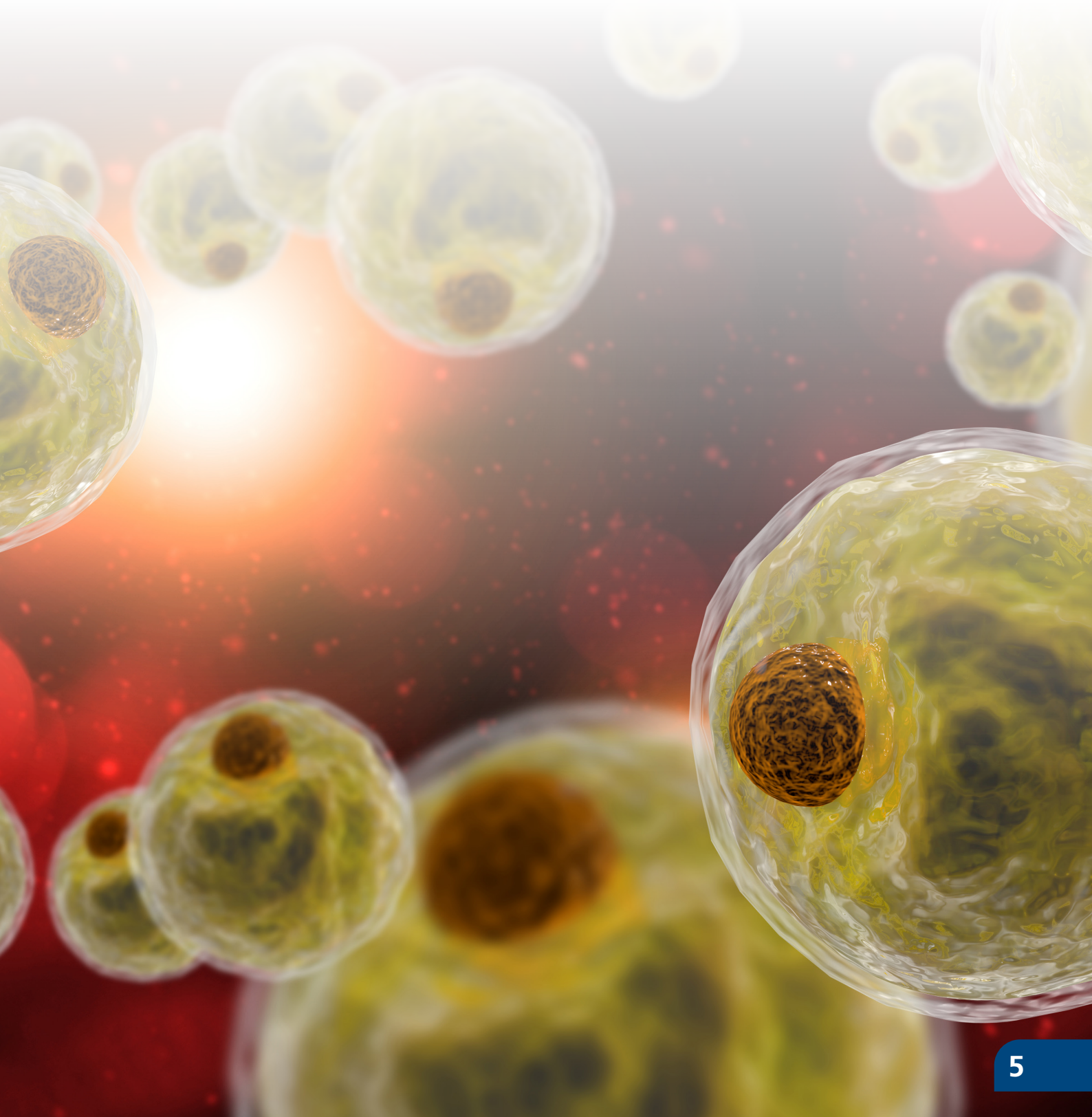
Alcohol / Drug-Induced

- Alcohol and drug abuse
- Some medicines used to treat:
  - hypertension
  - hyperlipidemia (high cholesterol or triglyceride levels in blood)
  - psychiatric disorders
  - prostatic carcinoma

Adipose-derived Stem Cell Therapy

Erectile dysfunction is both a common and complex disease process. Current treatments for ED focus on relieving its symptoms and therefore tend to provide a temporary solution rather than a cure or reversing the cause. Recently, therapies based on stem cells (SCs) especially adipose-derived stem cells (ADSCs), have had increasing attention as a treatment option to restore erectile function.

Adiposed-derived stem cells (ADSCs) - mesenchymal stem cells found in the stromal-vascular fraction of subcutaneous adipose tissue that have a capability to self-renew and to differentiate into different cell types.



Scientific Evidences

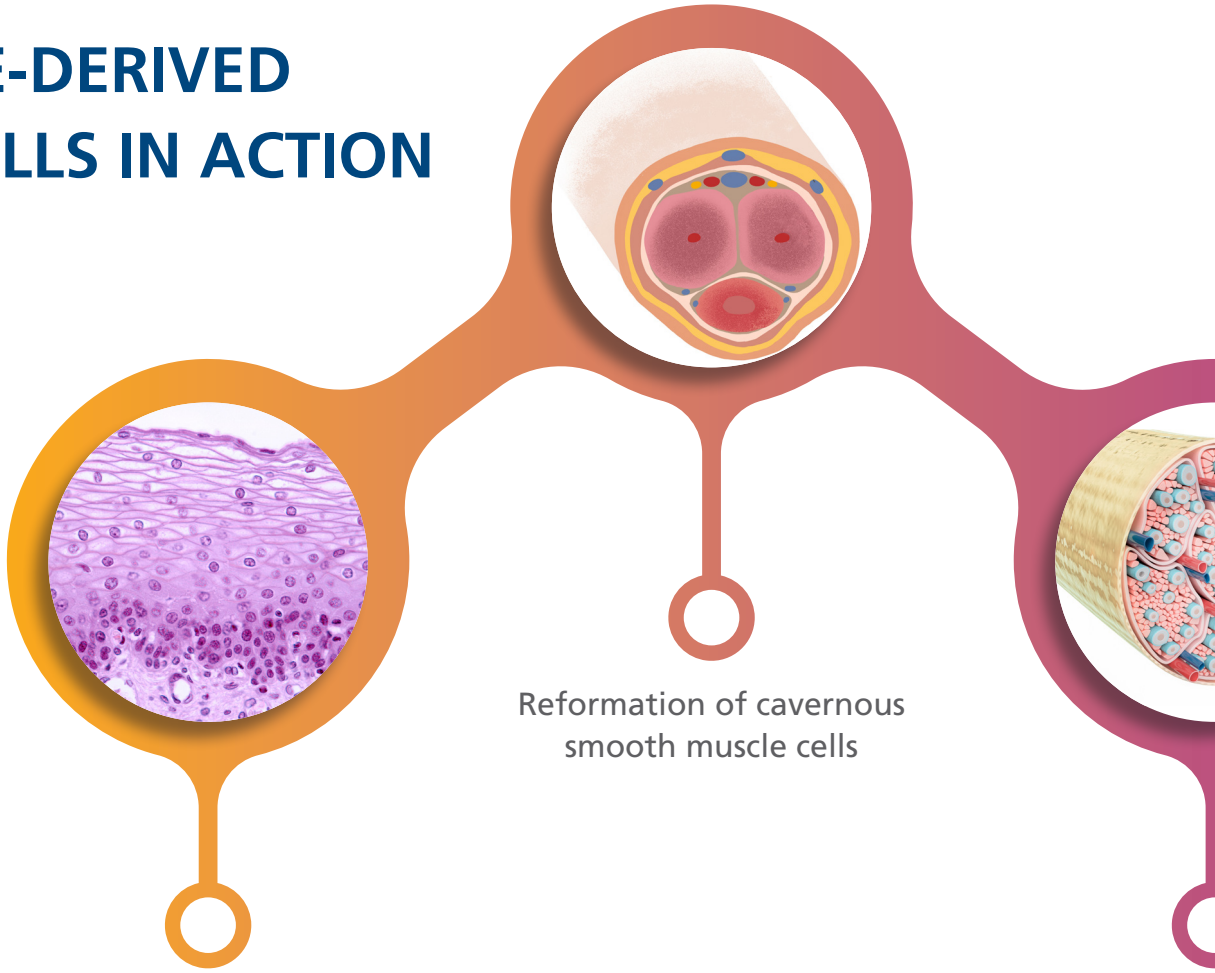
Research led by Dr. Haahr, of Odense University Hospital in Denmark, and colleagues found that within 6 months of the procedure, 8 of the 21 men treated were able to engage in an unforced and spontaneous sexual intercourse.

In their phase I trial, they tested adipose-derived stem cell therapy on 21 men who had ED as a result of undergoing radical prostatectomy for prostate cancer. None of the men had responded to standard medical intervention for ED.

Before the stem cell procedure, 6 months, and 12 months after, the participants' erectile function was assessed using the International Index of Erectile Function (IIEF) questionnaire. An IIEF score of 5-7 represents severe erectile dysfunction, 12-16 is mild to moderate erectile dysfunction, and 22-25 is no erectile dysfunction. All 21 men saw their erectile function improve with stem cell therapy: their IIEF score increased from 6 before treatment to 12 at 6 months after treatment.

Eight of the men reported that they had been able to engage in spontaneous sexual activity 6 months after stem cell therapy, and this outcome persisted 12 months after treatment. These men saw their IIEF score rise from 7 to 14 with ADSC therapy.

ADIPOSE-DERIVED STEM CELLS IN ACTION



Regeneration of the host's own epithelial cells

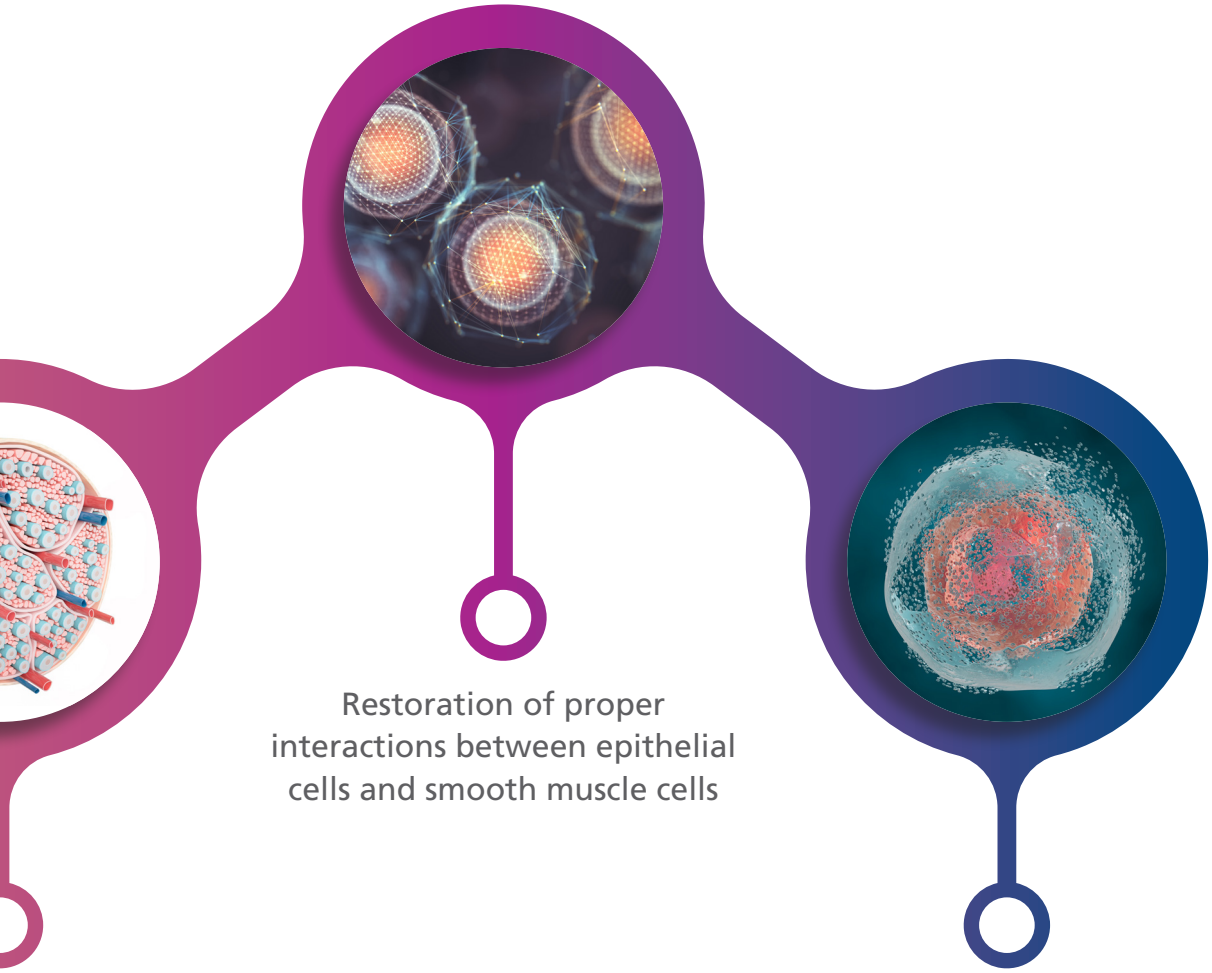
Reformation of cavernous smooth muscle cells

Restoration
cavernou

Another study suggests that other animal models using ADSCs indicate that paracrine action might be an important means by which stem cells play a vital role in the regeneration of endothelial and smooth muscle cells. Albersen et al. documented evidence of a paracrine mechanism of ADSCs in a neurogenic rat model with cavernous nerve (CN) crush injury when they found comparable functional recovery in rats treated with ADSCs and ADSC-derived lysate despite having no live stem cells injected or identified upon inspection in the latter group.

References:

1. *Albersen, M, Fandel, TM, Lin, G, et al. Injections of adipose tissue-derived stem cells and stem cell lysate improve recovery of erectile function in a rat model of cavernous nerve injury. J Sex Med 2010; 7: 3331–3340.*
2. *Haahr MK, et al. Safety and potential effect of a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial. EBioMedicine. 2016;5:204–210.*



Restoration of proper interactions between epithelial cells and smooth muscle cells

of damaged
us nerves

Decreased apoptosis of cavernosal cells

Adipose-derived Stem Cell Therapy Workflow

1 Adipose Tissue Collection

Body fat is collected via liposuction.

2 Cell Processing

Collected fat tissues are then processed in a cGMP lab to isolate ADSCs.

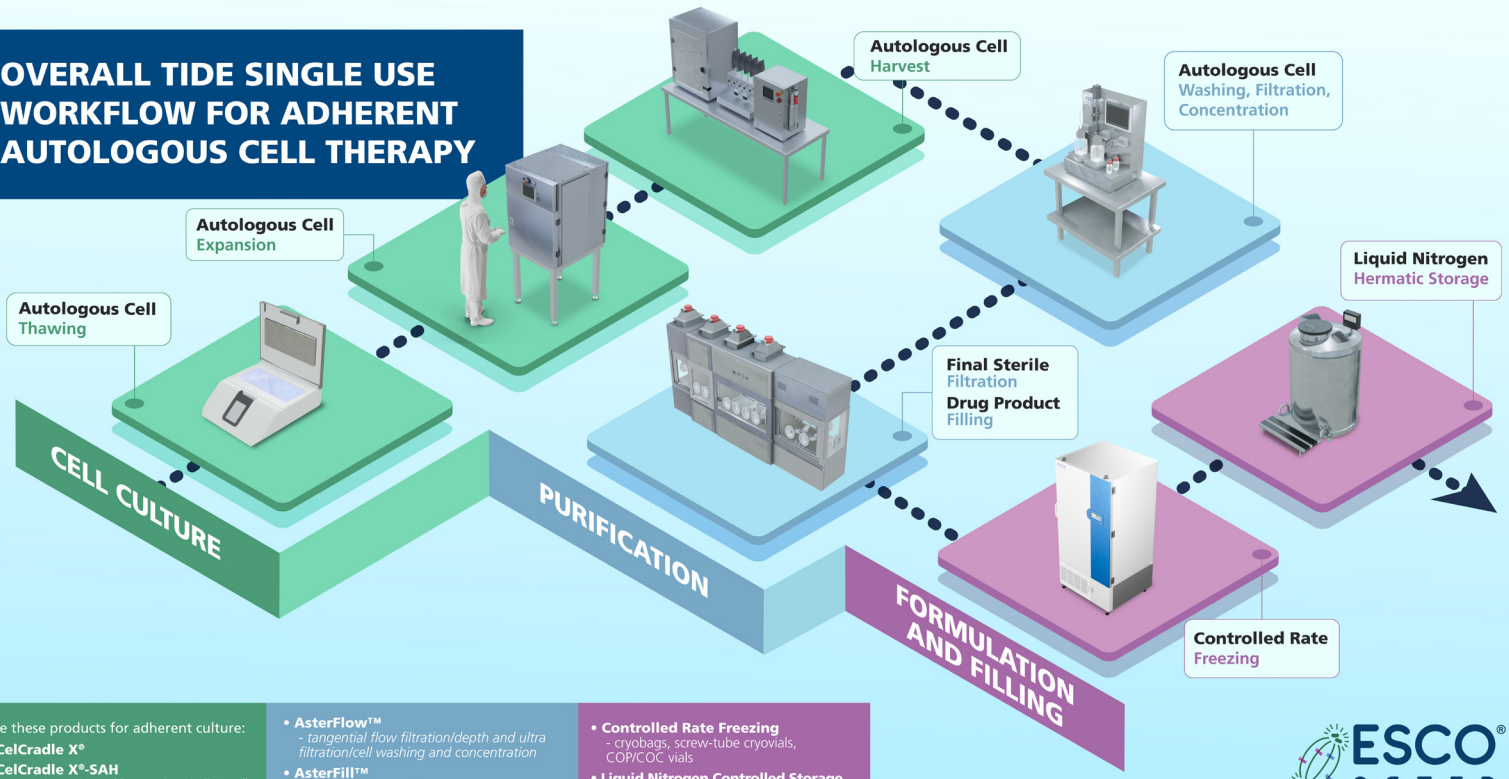
3 Expansion

ADSCs are then expanded using our proprietary Tide Motion bioreactor systems.

4 Treatment

Purified ADSCs will be directly injected to the patients or to other donors.

OVERALL TIDE SINGLE USE WORKFLOW FOR ADHERENT AUTOLOGOUS CELL THERAPY



Use these products for adherent culture:

- **CelCradle X®**
- **CelCradle X®-SAH**
  - a semi-automated harvesting, in line cell washing concentration and filling into cryobags

- **AsterFlow™**
  - tangential flow filtration/depth and ultra filtration/cell washing and concentration
- **AsterFill™**
  - auto formulation for upstream processing with optional cryopreservation, single use tubing, excipients and filling; in-built autoclave (for change parts) filling into screw tube cryovials of COP/COC vials

- **Controlled Rate Freezing**
  - cryobags, screw-tube cryovials, COP/COC vials
- **Liquid Nitrogen Controlled Storage**
  - long term storage at autologous cGMP site or within cell processing facility in hospital/medical centre.

ESCO ASTER

Cell Banking

A clinical-grade portion of ADSCs are cryopreserved for future use.

5

Thawing

Cryopreserved ADSCs will be thawed and used for additional treatment.

6

Disclaimer:

These are potential applications of the Tide Motion system for Autologous Cell Therapy.

Esco Aster under an investigator-initiated clinical trial can perform adipose-derived stem cells (ADSCs) isolation, banking, and expansion to the filled product within our cGMP compliant facility in Singapore.

Esco Aster does not make claims and warrants that the treatment is medically effective and such complementary and alternative medicine are to be performed under strict clinical advice from the patient's clinician/physician.

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The future of stem cell therapy demands high quantities of mesenchymal stem cells (MSCs) ranging from 10 million to more than 200 million cells per dosage. Conventional expansion of MSCs on plasticwares (2D culture systems) become impractical when large dosages of more than 50 million cells are required. The use of bioreactors which combines scaling-up ability, process control, and automation is the primary solution for this need. Many bioreactors are facing issues in supporting MSC cultures due to complications in balancing the need for proper mixing of media with the need to extremely low shear stress as well as the inability to separate cells from micro/macrocarriers with high cell yield and viability.

ESCO® ASTER has leveraged on the use of Esco VacciXcell's Tide Motion bioreactors to establish a robust and scalable platform using macrocarriers to meet the demands for future clinical therapies. MSCs isolated from different tissues sources were seeded and allowed to expand within PET macroporous carriers. Throughout culture periods, cell culture conditions were monitored, with bioprocess parameters such as glucose consumption and pH levels measured to ensure proper scale-up. Key issues such as cell seeding densities, media culturing conditions and improved bioprocess parameters needed for optimal stem cell systems were studied in our system. Overall, we present our process optimization with quality controls and release criteria of functional and phenotypic characteristics for the translation of academic/industrial R&D into bench scale for future clinical trials and commercialization process.

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