



**Early Menopause
Premature Ovarian Failure
Primary Ovary Insufficiency**

Stem Cell Therapy using
Tide Motion System



Premature Ovarian Failure Cause

Primary ovarian insufficiency (POI), also called premature ovarian failure, occurs when the ovaries (the twin female organs that produce and release an egg each monthly cycle) stop working before women turns 40 years. One in 100 women underage of 40 experience this phenomenon. When the ovaries stop working, women do not ovulate or produce normal amounts of estrogen.

Many women normally experience the natural loss of ovarian function (menopause) when they are around 40 years old and above. This figure still varies among different countries and different ethnic groups.

Its prevalence among the different countries is 1 out of 250 women under 35 years and 1 out of 100 women under 40 years.

POF is characterized into two types:

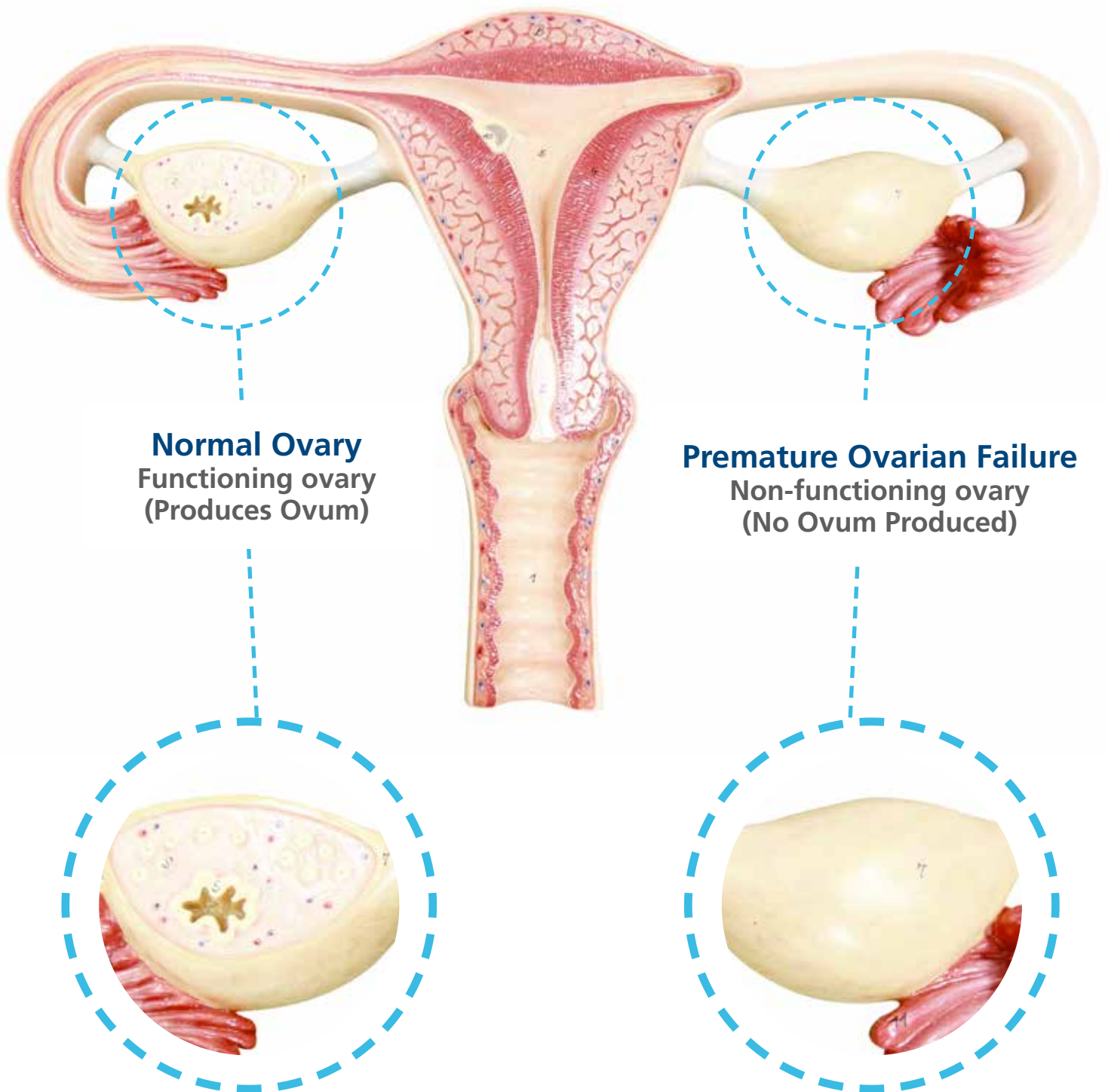
1. **Primary ovarian failure** - is when a woman never ovulates and never experiences natural menstruation
2. **Secondary ovarian failure** - it is when the menstruation occurs for months to years then stops prematurely as ovaries have failed

Histology Skin Observation	Symptoms
Infertility	Irregular or skipped periods
Osteoporosis	Difficulty getting pregnant
Depression or anxiety	Hot flashes, night sweats, vaginal dryness
Heart disease	Irritability o rdifficulty concentrating



Premature Ovarian Failure Cause

Because of different factors, the trend is increasing even more. POF can be spontaneous or induced. Many possible factors are known in the development of POF which include genes, metabolism, endocrine, paracrine and mitochondrial dysfunction-related factor, and autoimmune responses. Moreover, induced factors such as chemotherapy, radiotherapy, and pelvic surgery can also lead to this ovarian failure.

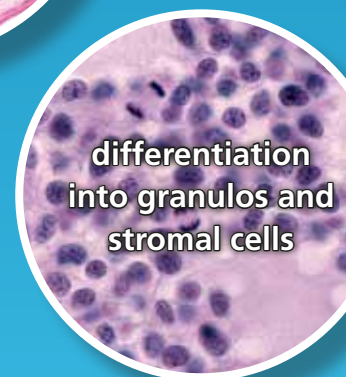
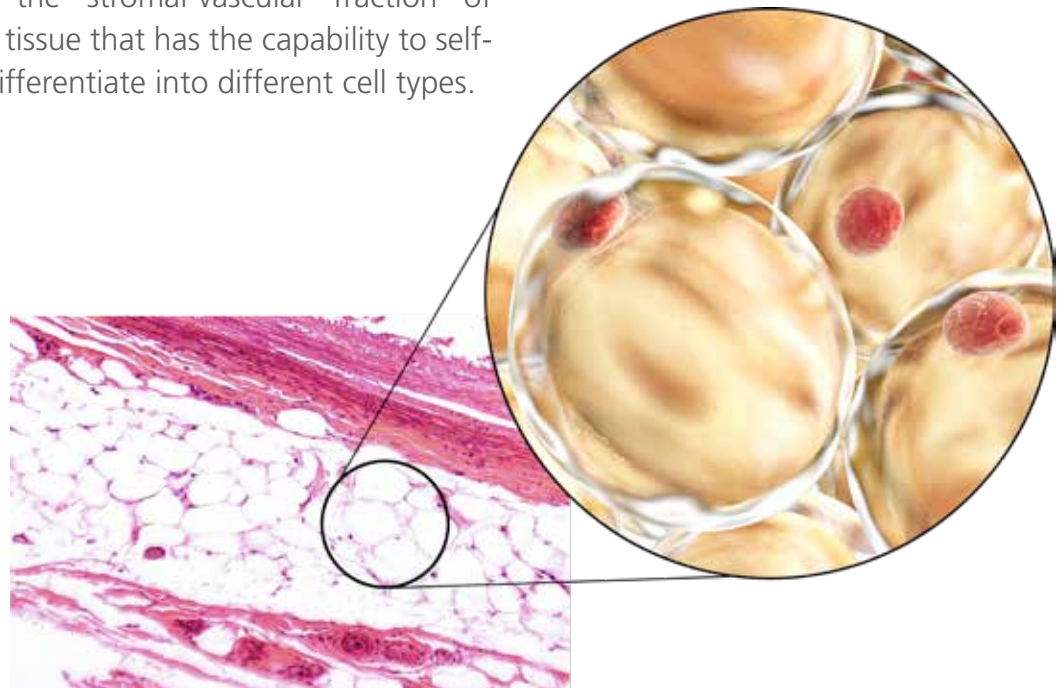


Adipose-derived Stem Cells Therapy

As a treatment option for the complexity result of POF, diverse approaches have been developed such as hormonal replacement therapy. However, this treatment does not restore the function of the ovaries. It only increases the risk of cancer due to the side effects associated with other POF and infertility treatments. Because of this scientists, have addressed the use of stem cell therapy. Because of this, scientists have addressed such concern with the use of stem cell therapy.

Is it really necessary to state this info again as it was already previously mentioned.

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



SCIENTIFIC EVIDENCES

Numerous scientific studies have verified that ADSC transplantation in women with premature ovarian failure has shown improvement for both hormone production and ovarian structure.

In a study, scientists explored the efficacy of ADSCs transplantation for the chemotherapy-induced ovarian damage in mice. The ovarian function of mice exposed to CTX injection improved after ADSC transplantation and the ovulation significantly increased. This experimental study was confirmed by another study in hormonal point of view where stem cell transplantation resulted in the improvement of hormone production and ovarian function.

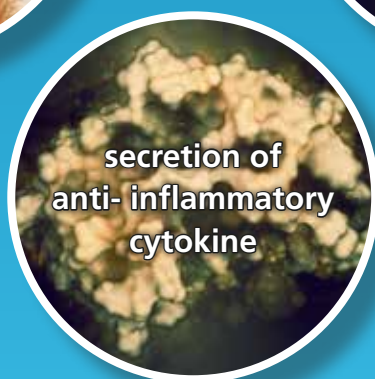
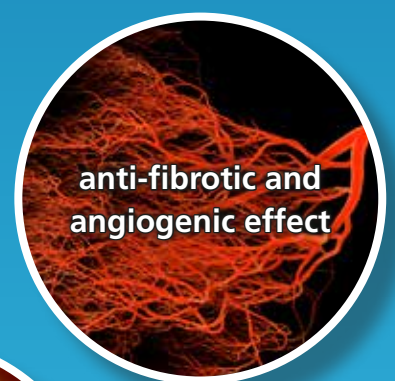
In another study, 20% of women treated with stem cell therapy regained ovarian reserve and started to experience menstruation again. The treatment allowed woman to get pregnant and give birth to a full-term healthy baby.

Lastly, a clinical trial result from ROSE (Rejuvenation of Premature Ovarian Failure with Stem Cells) showed significantly increase in estrogen levels in women treated with autologous stem cell therapy.

Menopausal symptoms were also lessened after a year of treatment and menstruation resumed six months after the injection.

1. Edessy M et al. Acta Medica International. 23-19:)1(3;2016. doi: 10.5530/ami.2016.1.7
2. Endocrine Society. 2018 Press Release. March 2018 ,18. <https://bit.ly/2JrAqz4>
3. Sun et al. Stem Cell Research & Therapy 4:80 ,2013. <http://stemcellres.com/content/80/4/4>

STEM CELLS IN ACTION



ADIPOSE-DERIVED STEM CELLS THERAPY WORKFLOW

Extraction

Centrifugation will be done to extract stem cells from fats



Expansion

Several hundreds of stem cells can be produced with the use of Tide Motion Bioreactors

Sampling

Fats are collected from the patient



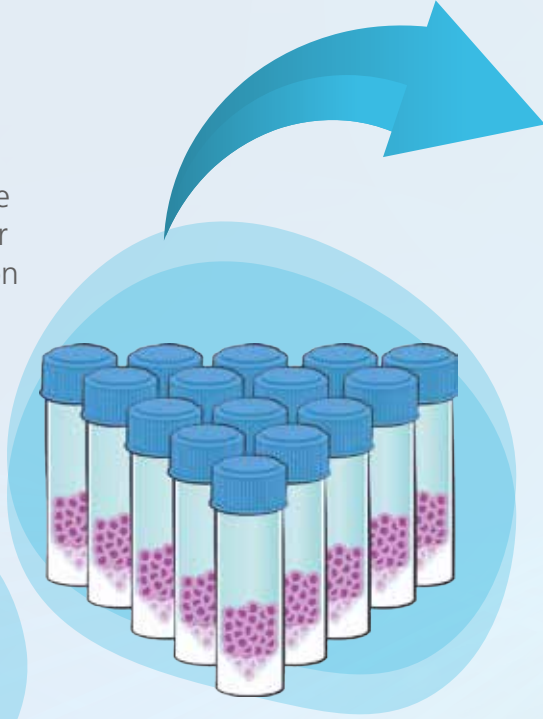
Thawing

For other additional treatment, the cryopreserved vials will be thawed and used



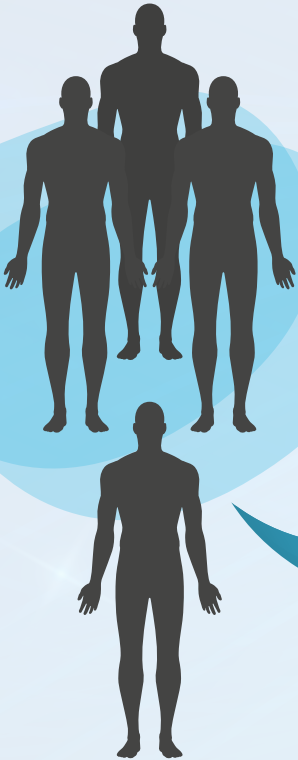
Banking

Other vials will be cryopreserved for future use



Treatment

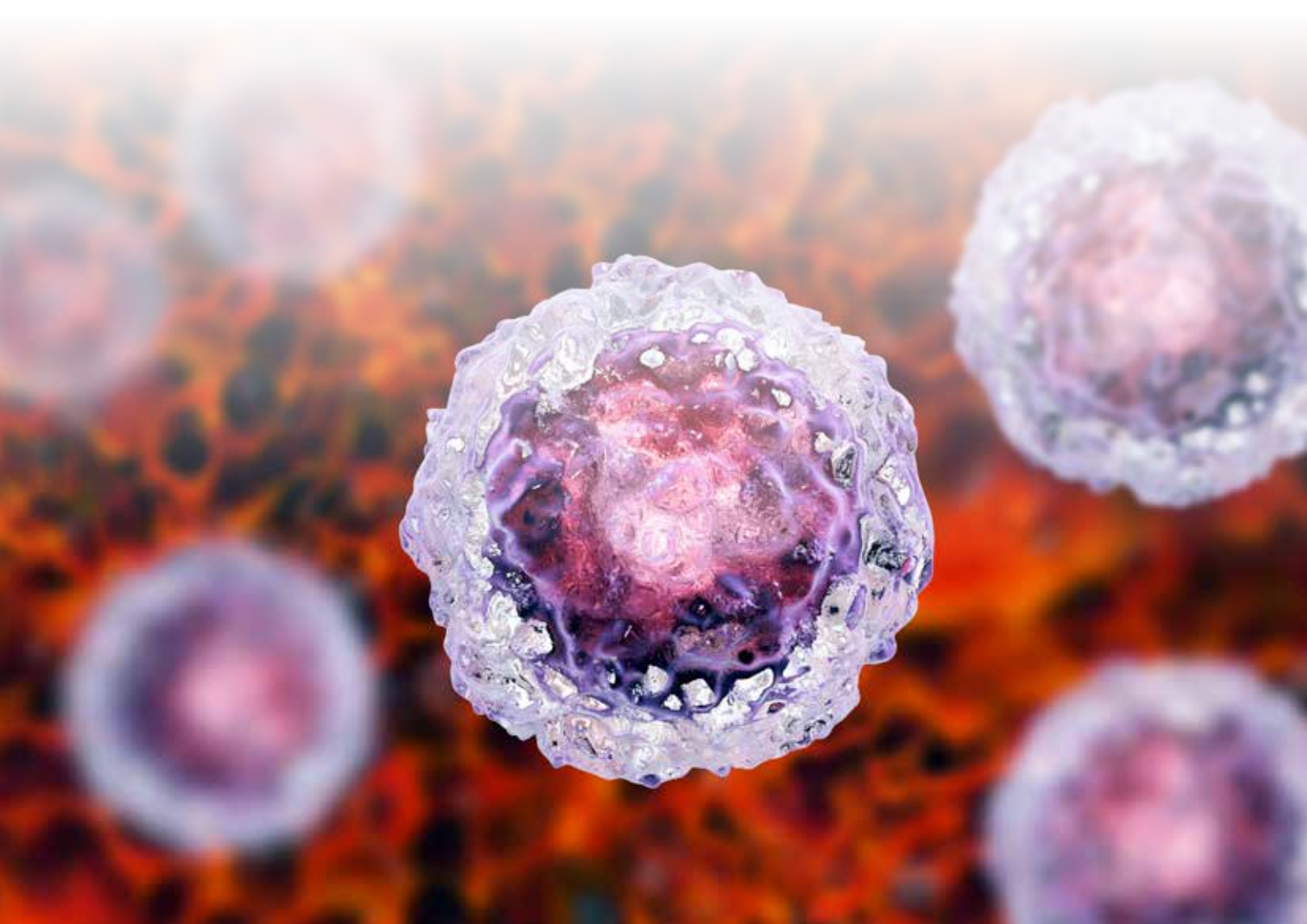
Purified stem cells will be injected to the patient or to donors after expansion



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.



ESCO LIFESCIENCES GROUP GLOBAL OFFICES

North America

USA

Esco Technologies, Inc.

Life Sciences/Medical

903 Sheehy Drive, Suite F, Horsham,
PA 19044, USA
Toll-Free USA and Canada: 1-877-479-3726
Tel: 215 441 9661
Fax: 484 698 7757
Email: eti.admin@escoglobal.com
Website: <http://escolifesciences.us>

Healthcare Division/Factory

2512 Metroprolitan Dr, Suite 120-B
Feasterville-Treose, PA 19053-6738
Tel: +1 215 322 2155
Email: eti.pharma@escoglobal.com
Website: www.escopharma.com

Europe

DENMARK

Esco Medical ApS

Kringelled 10, DK-8250 Egaa, Denmark
Tel: +45 5397 3067
Email: medical@escoglobal.com

UK

Esco GB Ltd

Unit 2 R-Evolution @ Gateway 36,
Kestrel Way, Barnsley S70 5SZ
Tel: +44 (0) 1226 360 799 (Pharma)
+44 (0) 1226 361529 (Lab)
Email: egb.info@escoglobal.com
Websites: www.escopharma.com
www.escolifesciences.co.uk

GERMANY

Esco Lifesciences GmbH

Straßheimer Straße 17
61169 Friedberg, Germany
Tel: +49 6031 6873447
Email: mail@escoglobal.com
Website www.escoglobal.de

ITALY

Esco Technologies S.r.l.

Operative and Legal office:

Via Poggio Moiano, 23,
00199, Rome, Italy
Tel: +39 06 69271849
Email: ilenia.nardolillo@escoglobal.com
Website: escolifesciences.it

RUSSIA

Esco Russia

Building 4, 8, Novovladikinskii proezd
Moscow, Russian Federation 127106
Email: esco.russia@escoglobal.com
Website: escolifesciences.ru

LITHUANIA

Esco Medical Technologies UAB

Draugystes 19
51230 Kaunas, Lithuania
Website: escomedicalgroup.com
Email: medical@escoglobal.com
support-medical@escoglobal.com

Asia Pacific

BANGLADESH

Esco Lifesciences (Bangladesh) Pvt. Ltd.

H # 662 (6th Floor), Apt. # A-6, R # 9
Mirpur DOHS, Mirpur, Dhaka-1216, Bangladesh
Tel: +8801907 700777
Email: ebd.customerservice1@escoglobal.com

CHINA

Esco Shanghai Trading Co. Ltd.

Email: mail@escolifesciences.cn
Website: www.escolifesciences.cn

Beijing

Rm.502, Tower A, Times Fortune, Sanyuanqiao
Chaoyang District, Beijing
Tel: +86 (10) 5867 7868
Fax: +86 (10) 5867 9244

Shanghai

Room1211, Jiahe International Building,
No.1, Lane 66, Huayuan Road,
Hongkou District, Shanghai
Tel: +86 (21) 6095 1955

Guangzhou

Room 901, West Block, No. 21, Huali Road
Tianhe District, Guangzhou, China 510623
Tel: +86 (20) 3837 3621

Chengdu

Rm. 1-406, Building No. 2,
Shangding International Building,
No.27 4th Block, South Renmin Road,
Chengdu City, Sichuan Province
Tel: +86 (28) 8553 6219

Qingdao

Room 23C, Fucui Building, No.135 of Yan'an Road,
Shinan District, Qingdao City,
Shandong Province
Tel: +86 (532) 8163 9321

HONGKONG

Esco Technologies (Hong Kong) Limited

Unit 904, Laurels Industrial Centre,
No.32 Tai Yau Street, San Po Kong,
Kowloon, Hong Kong
Tel : +852 3628 3986
Fax : +852 3186 2821
Email: mail@escolifesciences.hk
Website: http://escolifesciences.hk

INDONESIA

PT Esco Utama

Taman Tekno BSD Blok H6 no 10,
Serpong, Tangerang 15314
Tel: +6221 29 666 565 / 301
Fax: +6221 29 666 302
Email: eucs2@escoglobal.com
Website: http://escolifesciences.co.id

MALAYSIA

Esco Micro (M) Sdn. Bhd.

Technical Support Hotline:

1 300 88 ESCO (3726)

Selangor

No. 15, Jalan Sungai Buloh 27/101A,
Persiaran Klang, HICOM 27 Industrial Park,
40400 Shah Alam, Selangor, Malaysia
Tel: +603 5103 8480
Fax: +603 5614 3385
Email: malaysia@escoglobal.com
Website: http://my.escoglobal.com

Melaka

No. 13-1, Jalan Melaka Raya 32,
Taman Melaka Raya 1,
75000 Melaka, Malaysia
Tel: +606 284 0007
Fax: +606 283 0288
Website: http://my.escoglobal.com

MYANMAR

Esco Lifesciences Co.,Ltd

04-402B, 3-Mahar Swe Condominium,
Mahar Swe Street Hlaing Township Yangon, Myanmar
Tel: +959 423 488 984
+959 963 520 535
Email: ingyin.haymarn@escoglobal.com
csts4@escoglobal.com

PHILIPPINES

Esco Philippines, Inc.

Manila

Unit 707E, 7th floor, East Tower Four E-com
Bldg, Block 22 Seaside Cor Diokno Ave. MOA
Complex, Pasay City 1300
Direct Line: +63 (02) 8828 1527
Trunkline: +63 (02) 8478 0384
Email: philippines@escoglobal.com
Website: <http://escoglobal.com.ph>

Cebu

Blk 3 Lot 13 Mutual Homes Subd.
Pajac, Lapu-Lapu City, Cebu 6015
Tel : +63 (32) 232 5826

Davao

71-C Lupo Diaz St. cor Nicasio Torres St.,
Bo. Obrero, Davao City 8000
Tel : +63 (082) 234-0997

SINGAPORE

Esco Micro Pte Ltd

21 Changi South Street 1
Singapore 486777
Tel: +65 65420833
Fax: +65 65426920
Email: mail@escoglobal.com
Website: www.escoglobal.com

SOUTH KOREA

Esco Korea Micro Pte Ltd

#206, Byucksan Digital Valley 8-Cha, 70,
Gyeongin-ro 71-gil, Yeongdeungpo-gu, Seoul,
Republic of Korea
Tel: +82 2 830 0482
Fax: +82 2 830 0491
Email: info@escoglobal.co.kr
Website: <http://www.escoglobal.co.kr>

TAIWAN

Esco Lifesciences Taiwan

No. 122-2, Wuqing Road, Dayuan District,
Taoyuan City, Taiwan
Tel: +886 34533220
Fax: +886 34532770
Email: mail@escolifesciences.tw
Website: <http://escolifesciences.tw>

THAILAND

Esco Lifesciences (Thailand) Co.,Ltd.

8/3 Soi Rimthangduan 2, Sukhumvit Road, Bangchak,
Phrakanong , Bangkok 10260
Tel: 02 082 2029
Fax: 02 117 3746
Email: csts.th.sales1@escoglobal.com
Official Line: @escothailand
Website: <http://escolifesciences.co.th/>

VIETNAM

Esco Vietnam Company Ltd.,

Email: vietnam@escoglobal.com
Website: vn.escoglobal.com

Hanoi

7th Floor, No. 8, Alley 15,
Trung Kinh Street,
Trung Hoa Ward, Cau Giay District,
Hanoi, Vietnam
Tel: +84 24 6269 1460
+84 24 6269 1461

Ho Chi Minh

No. 14 - Lot G3, Street No. 53,
Tan Quy Dong Settlements,
Tan Phong Ward, District 7, HCMC,
Vietnam
Tel: +84 28 3776 0363

Middle East

DUBAI

Esco Lifesciences Trading LLC

1529 Tamani Arts Offices, Al Asayel St.,
Business Bay, Dubai UAE
P.O Box: 182099
Tel: (04) 770 6674
Email: alvin.heah@escoglobal.com

Africa

SOUTH AFRICA

Esco Technologies Pty Ltd

Centurion

Unit 2 Landsmark Park,
17 Landmarks Avenue,
Kosmosdal Extension 11,
Centurion 0157 South Africa
Tel : +27 (0) 11 314 3184
Mobile: +27 (0) 82 853 9655
Email : sonja.strydom@escoglobal.com
Website: <http://za.escoglobal.com>

Cape Town

Office 31, Ground Floor Liesbeek House,
River Park Gloucester Road Mowbray, 7700
Tel : +27 (0) 21 680 5061



Esco Aster Pte. Ltd.

#02-09, 67 Ayer Rajah Crescent, Singapore 139950
Tel +65 6251 9361
mail@escoaster.com • www.escoaster.com

Esco Micro Pte. Ltd.

21 Changi South Street 1, Singapore 486777
Tel +65 6251 9361 • Fax +65 6542 6920
mail@escoglobal.com • www.escoglobal.com



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