

Endometriosis : Not Just a Gynecologic Disease

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Disclosures

Contracted Research (Principal Investigators must provide information, even if received by the institution)

Abbvie, Organon

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Dot lab

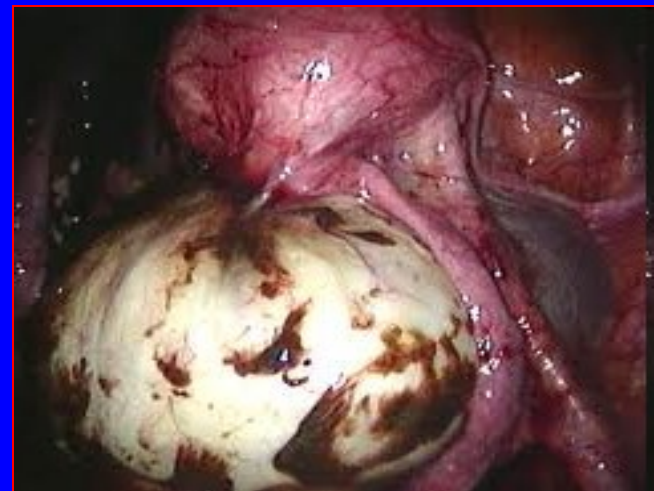
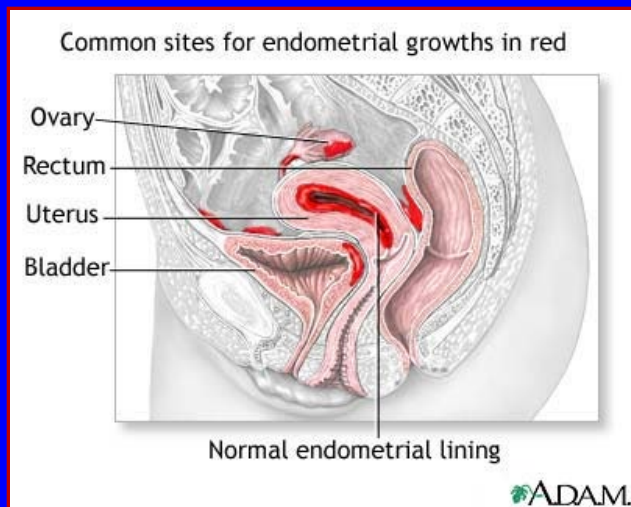
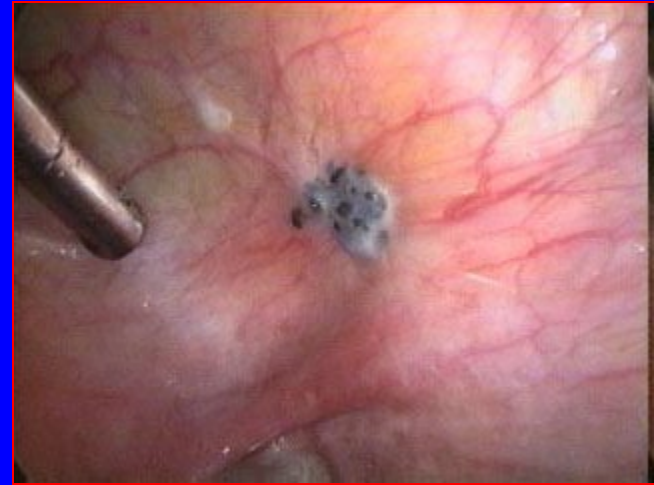
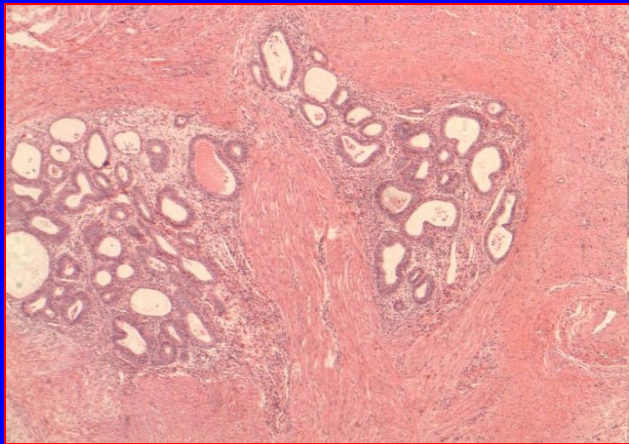
Learning Objectives

- Explain how stem cells contribute to endometriosis
- Describe how MicroRNA assists in testing for endometriosis
- List the clinical presentations of endometriosis

Endometriosis

- Prevalence: Approximately 10% of reproductive age women; 30-50% of women with infertility; 70-90% of women with pelvic pain.
- 2nd leading cause of hysterectomy in the U.S.
- Total costs: \$22 Billion in US alone

Endometriosis is Ectopic Endometrial Glands and Stroma



Clinical Presentation

- **Pain**
- **Infertility**
- **Asymptomatic**



Disease Stage does not explain pain symptoms.

Percentage at Each Stage

	Stage				
	I	II	III	IV	<i>P</i>
Dysmenorrhea	73	86	72	85	.68
Pelvic pain	38	46	36	41	.21
Dyspareunia	30	25	36	29	.91

Symptoms Associated with Endometriosis

Fatigue

Depression

Low BMI

Pain

Infertility

Cardiovascular disease

Bowel dysfunction

Inflammation

Bladder dysfunction

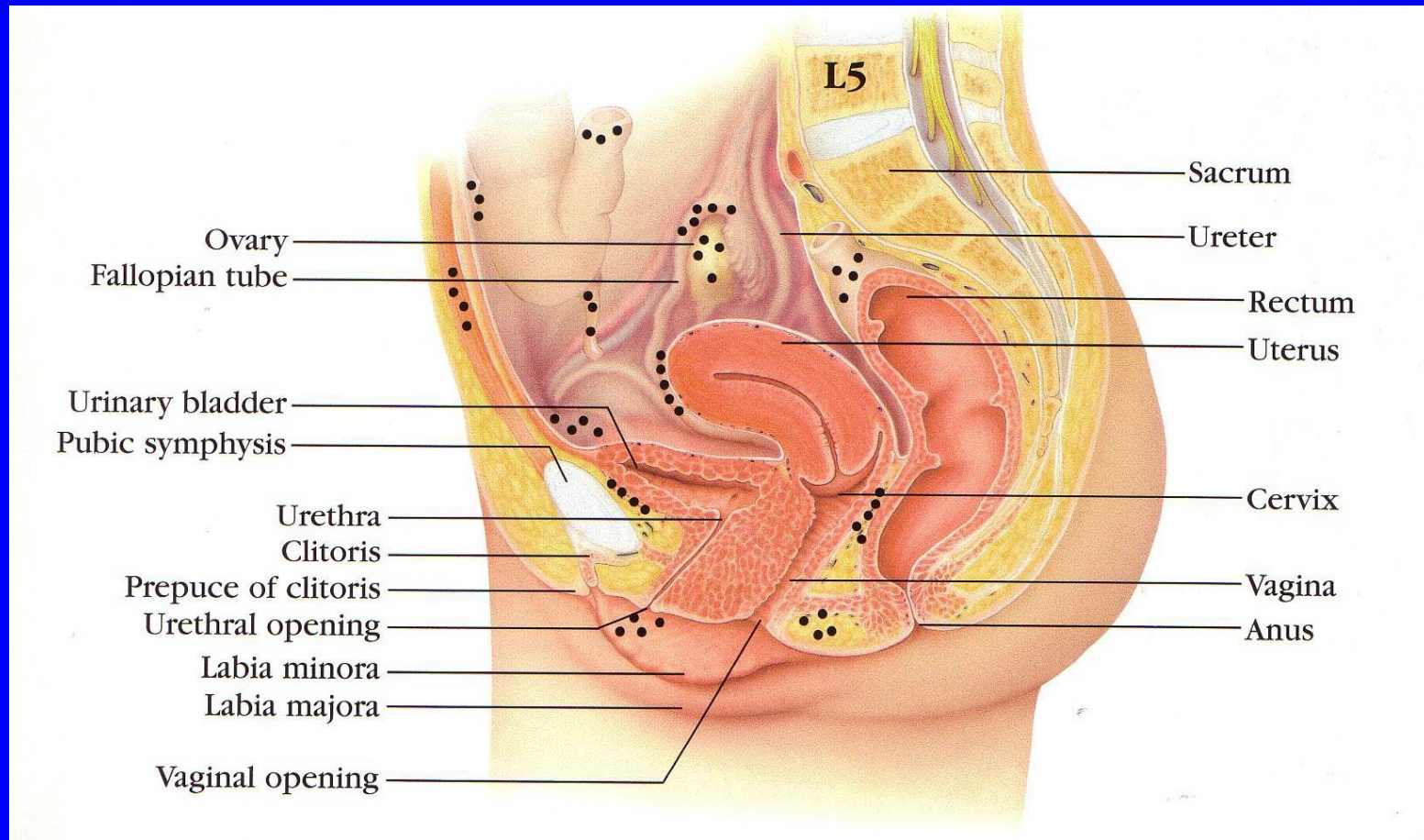
Anxiety

What you see
in the pelvis is just part
of the disease.

Endometriosis is a
systemic disease!

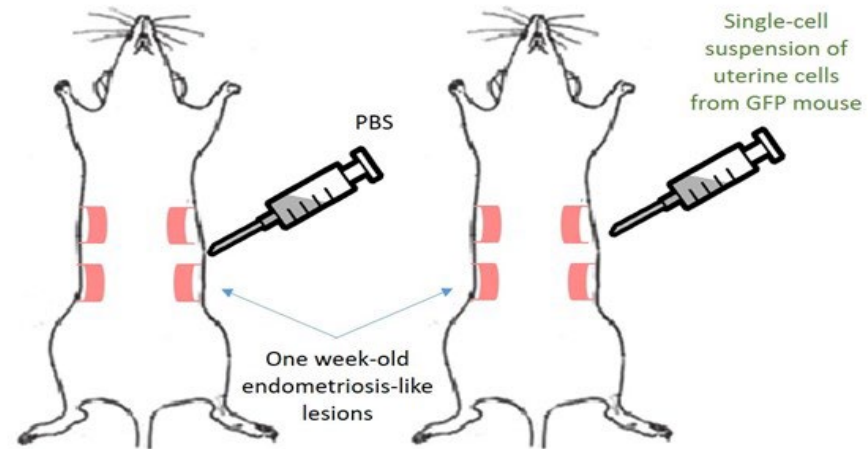
Etiology of Endometriosis

Sampson's Theory

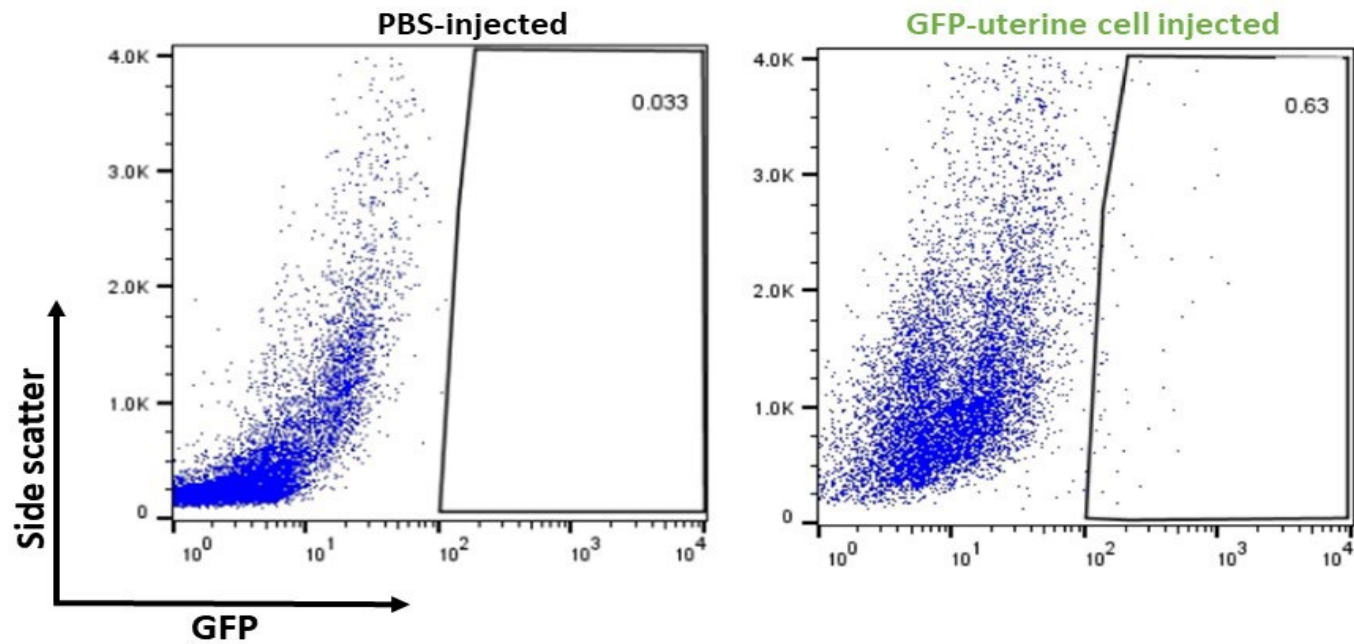


Retrograde Menstruation

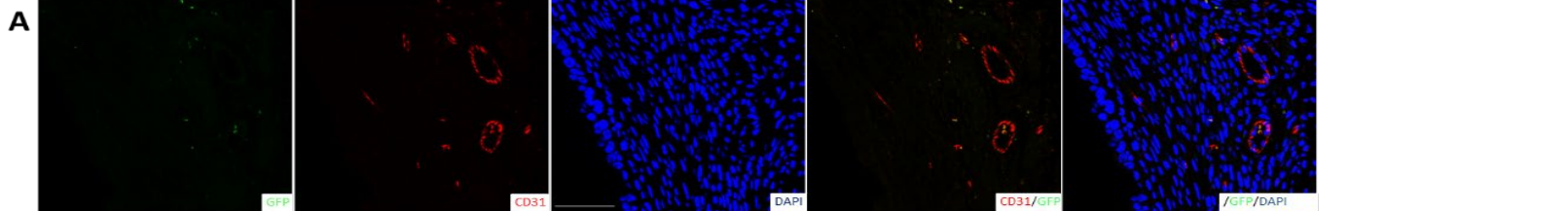
A



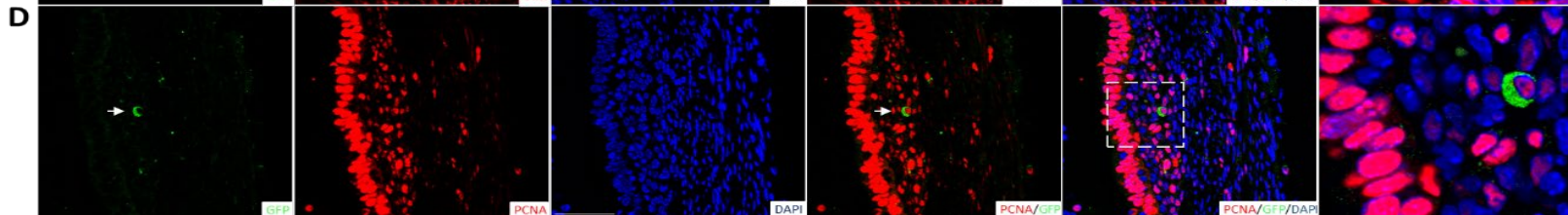
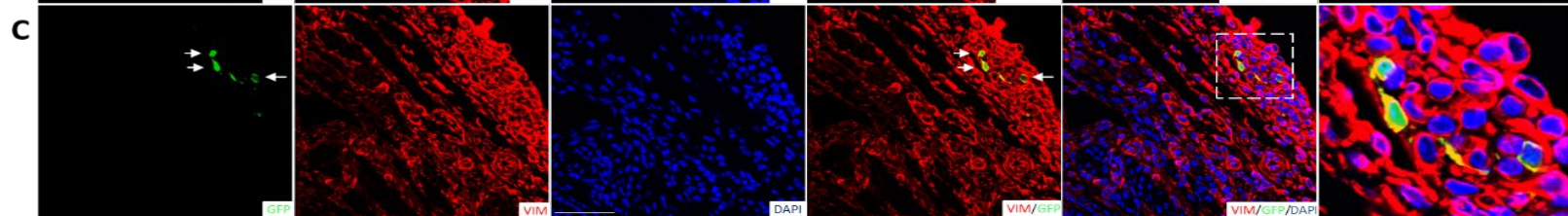
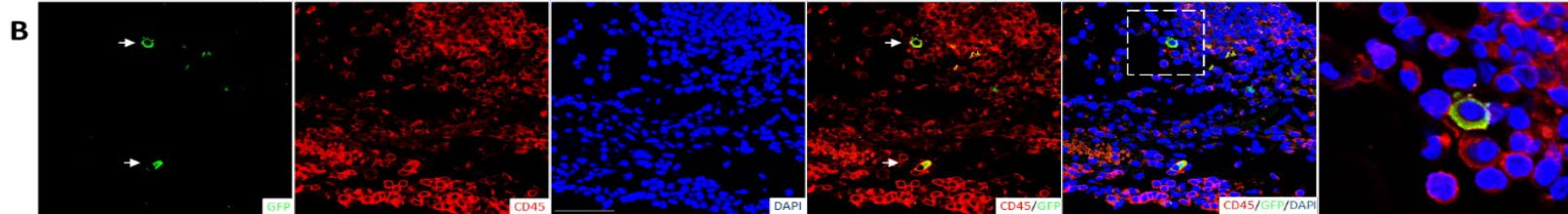
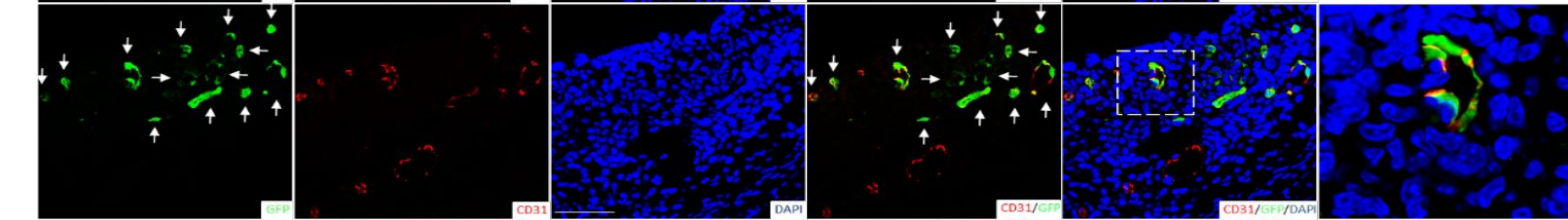
B



PBS injected

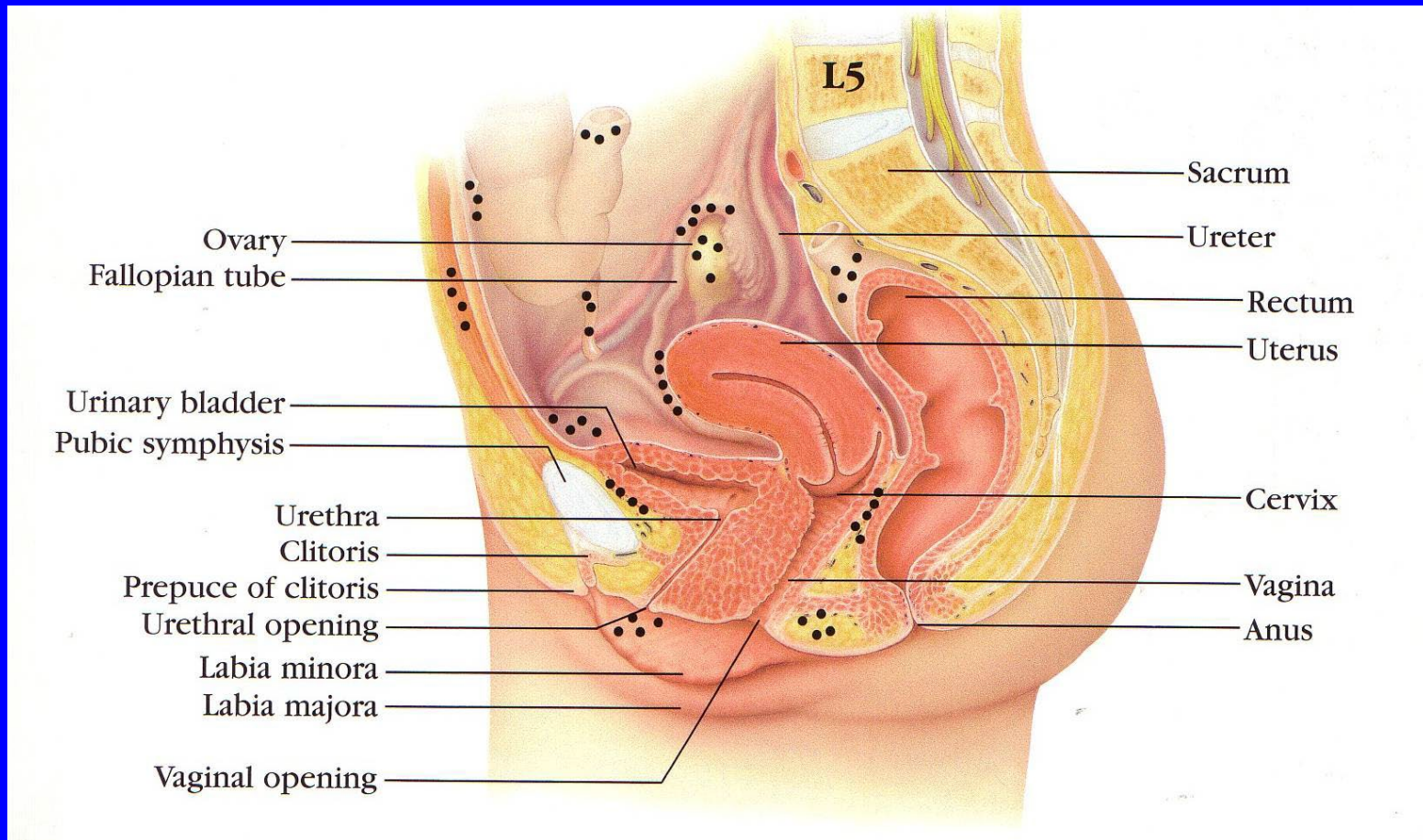


GFP-labeled uterine cell injection



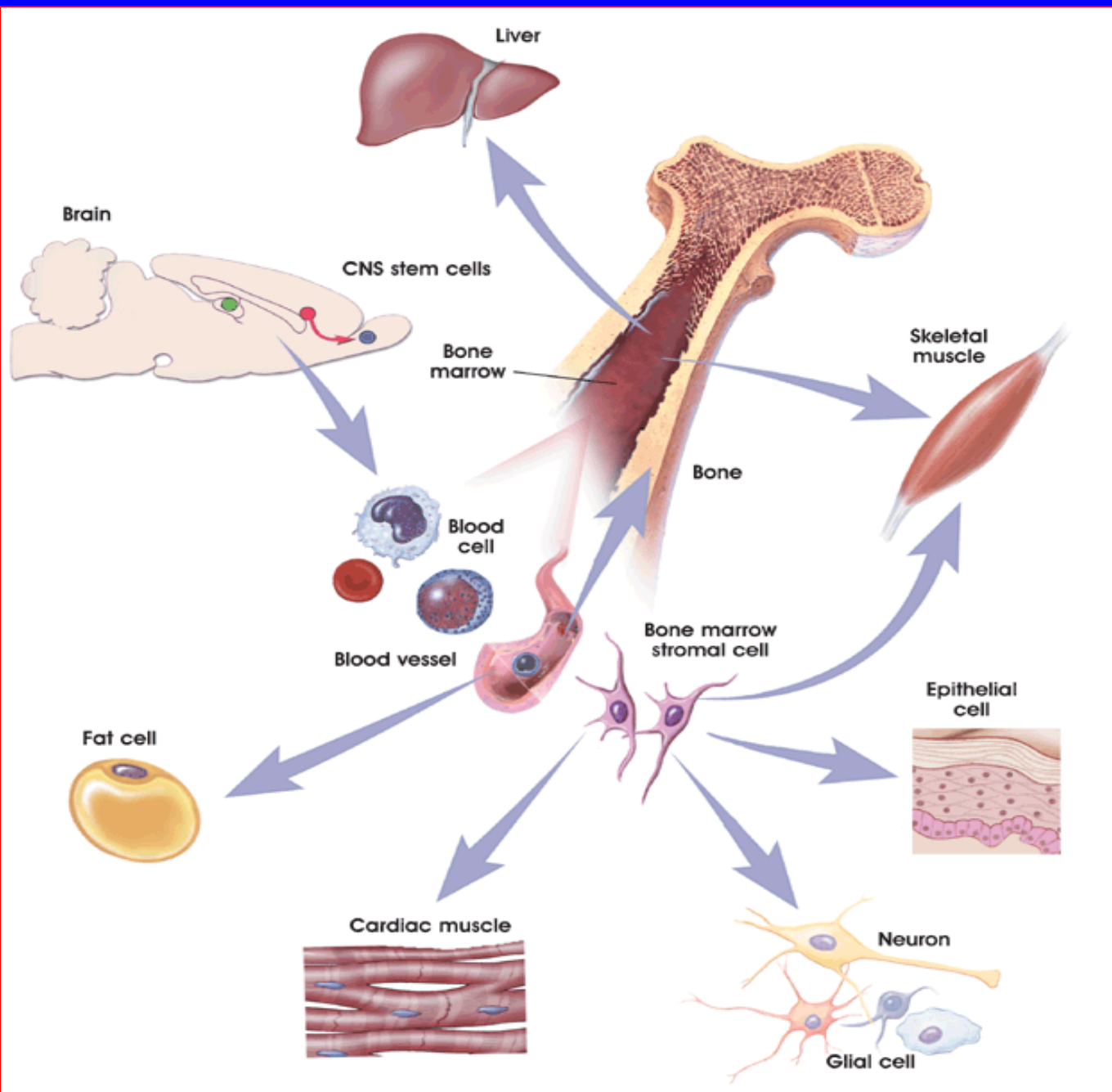
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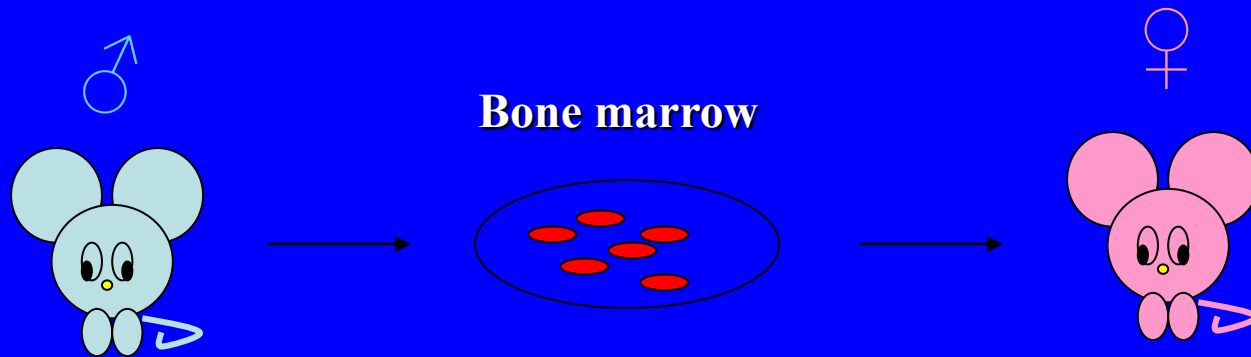


Stem Cells and Disease

Can stem cells travel and differentiate into endometrium in other locations?

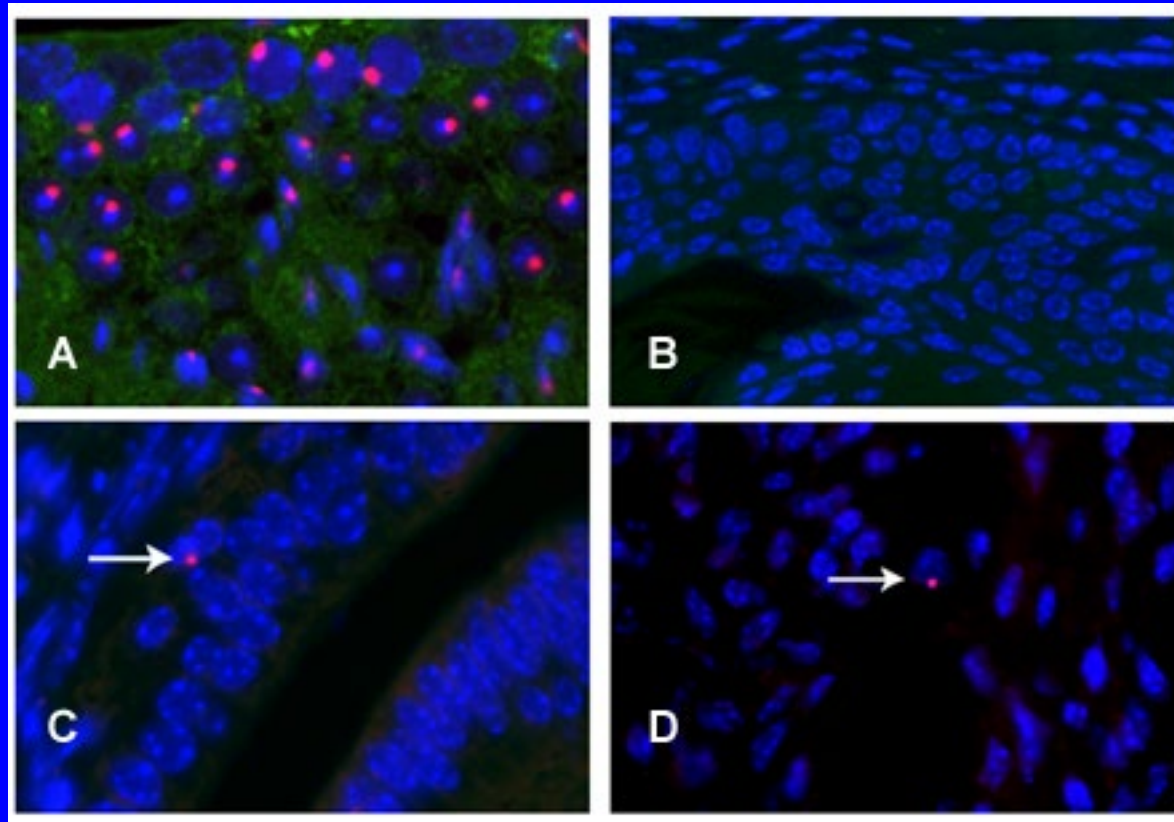


Identification of bone marrow-derived cells in murine endometrium



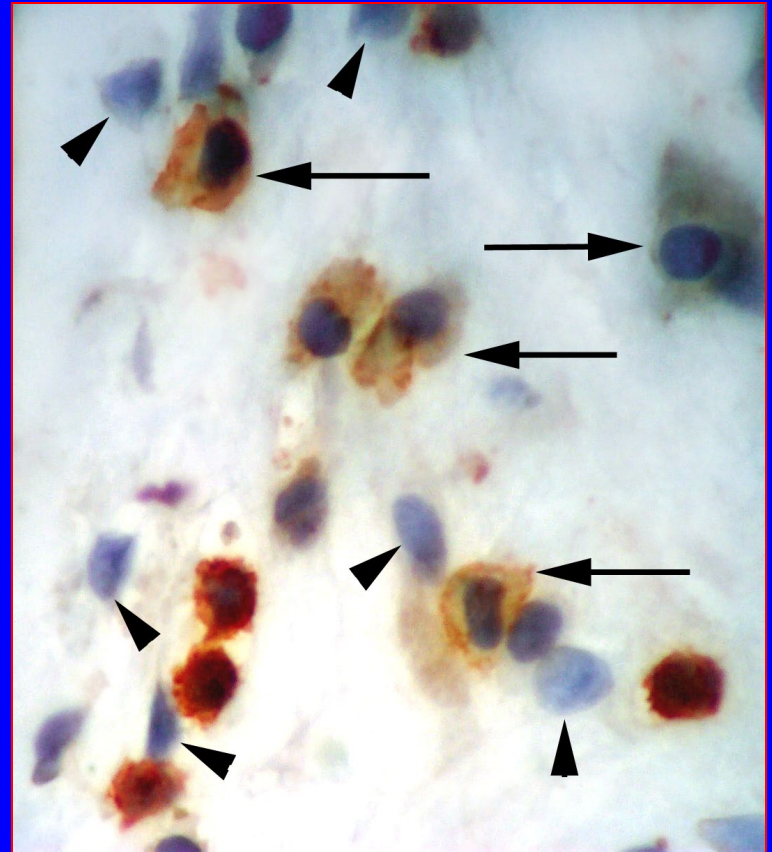
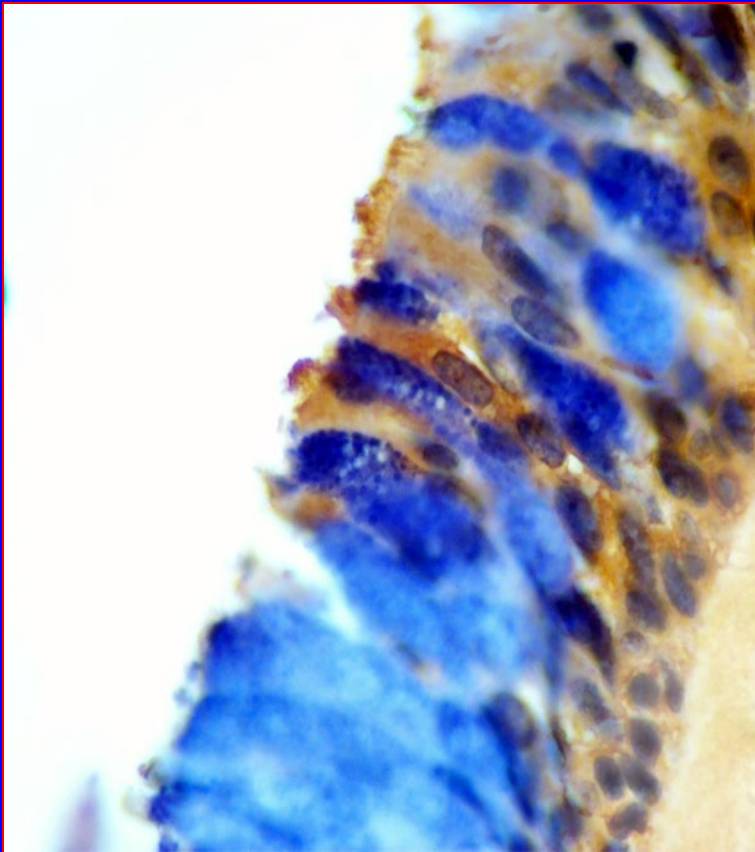
- ❑ Transplant male bone marrow into female mice
- ❑ Assess Y chromosome by FISH

Stem Cell Origin of Endometriosis

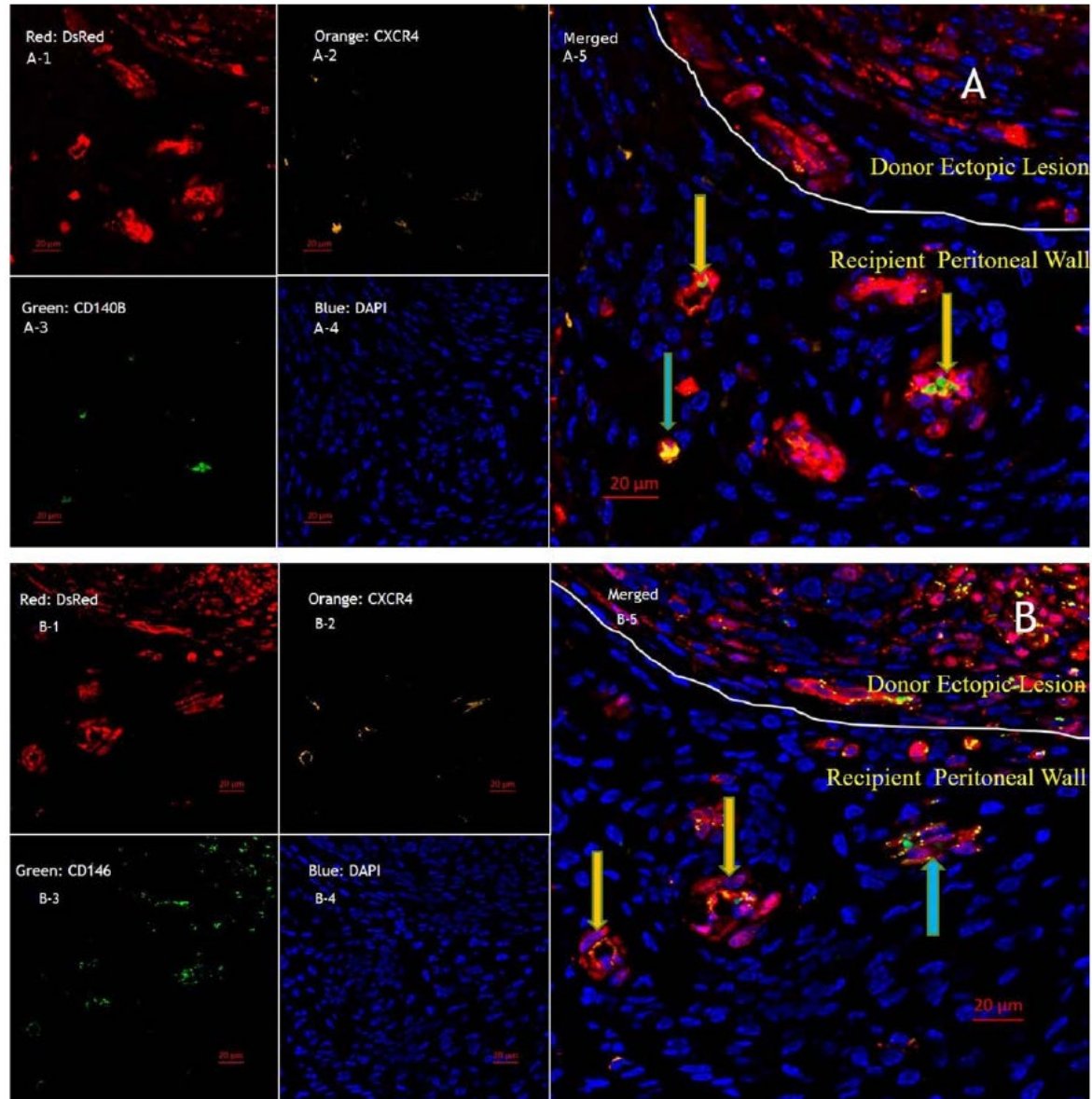


Du, H. and Taylor HS. *Stem Cells* 2007;25:2082-2086.
Taylor HS. *JAMA* 2004;292(1):81-5.

Bone Marrow Stem Cell Derived Human Endometrium



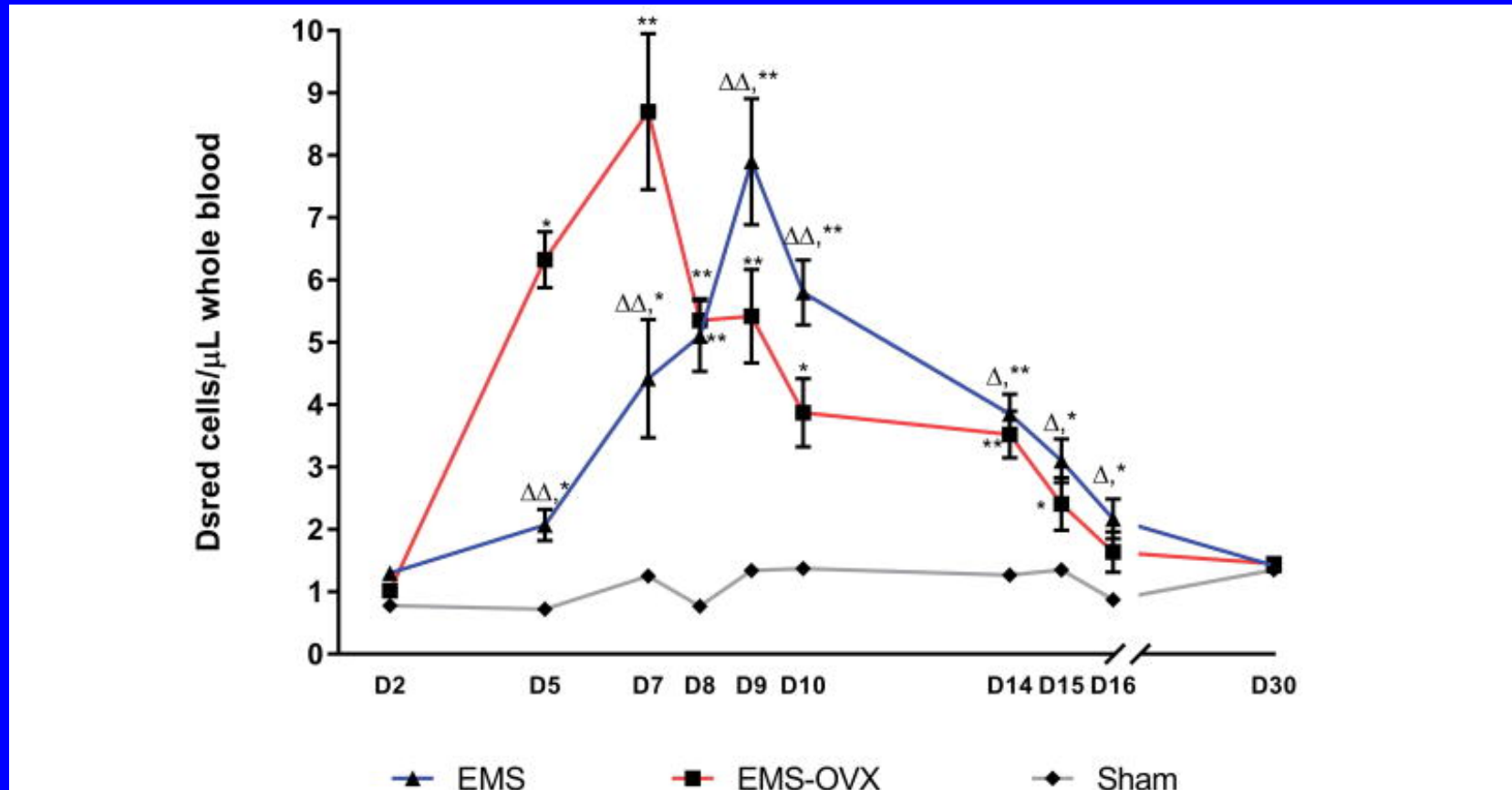
Stem Cells Contribute to Ectopic Lesions



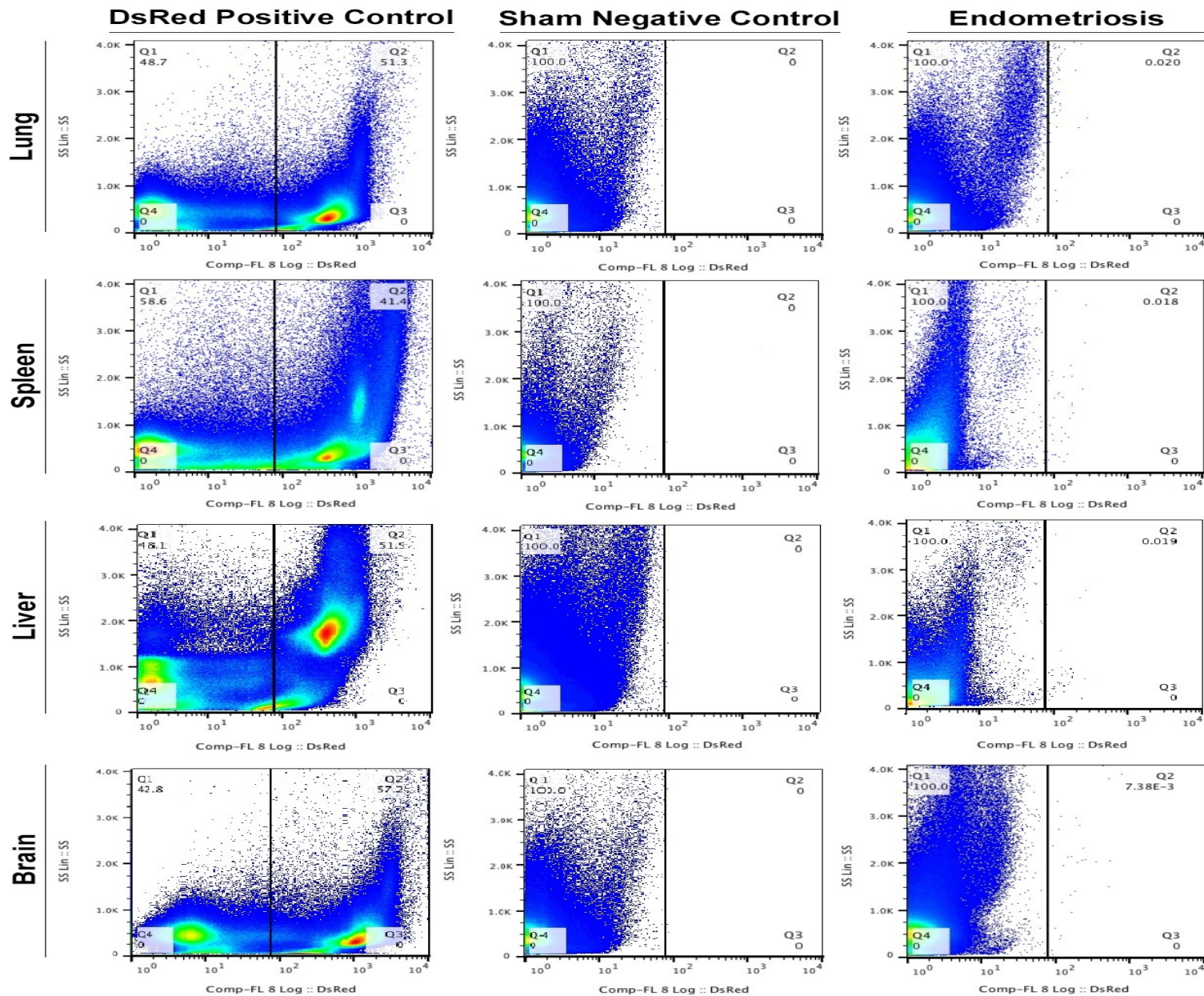
A Novel Origin of Endometriosis

- Stem cells contribute to endometriosis
- Likely accounts for endometriosis outside of the peritoneal cavity
- A novel mechanism of disease

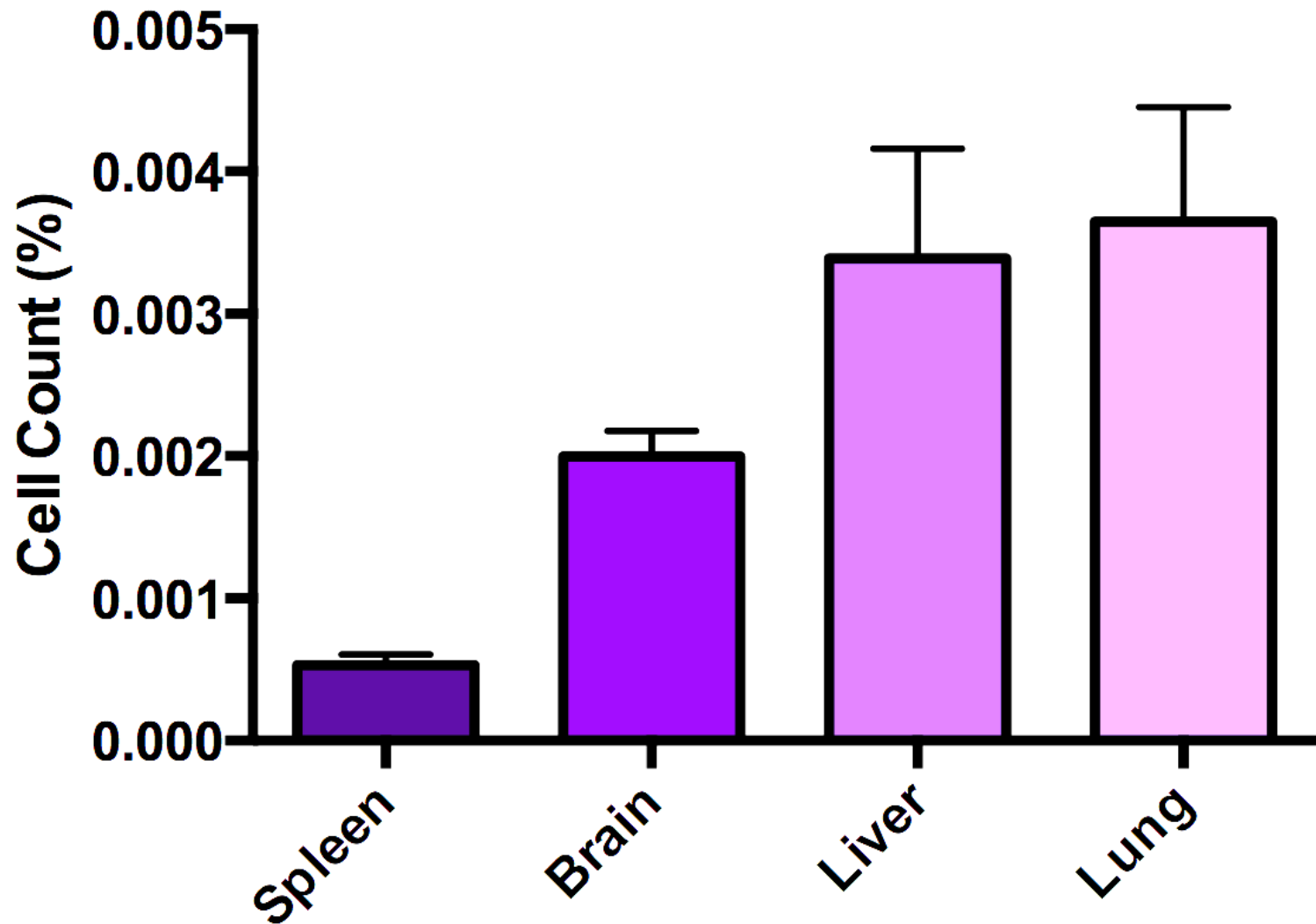
Circulating Stem Cells from Endometriosis



Frequent Micrometastasis of Endometriosis to Distant Organs

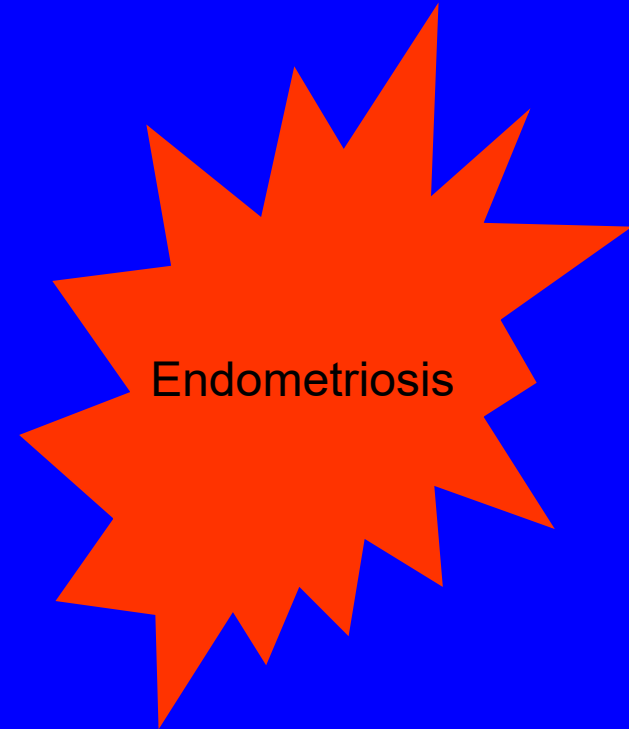
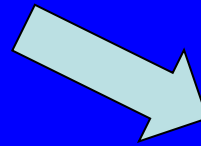


DsRed⁺ Cell Counts

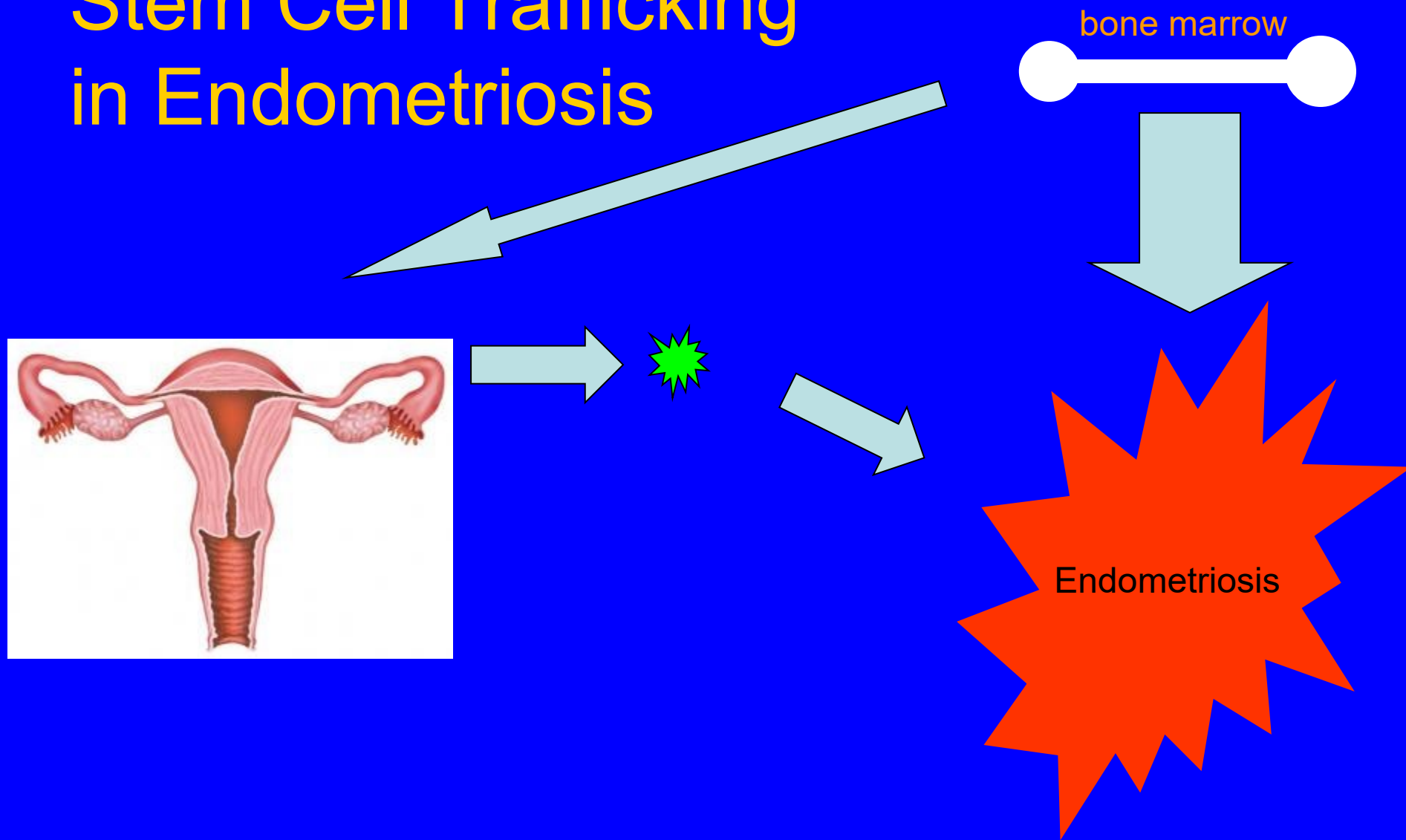


Stem Cell Trafficking in Endometriosis

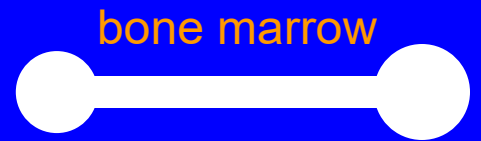
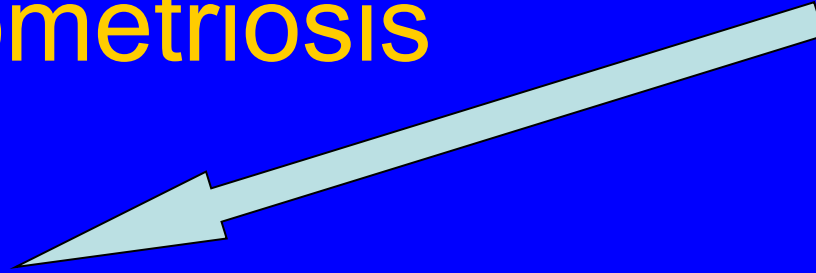
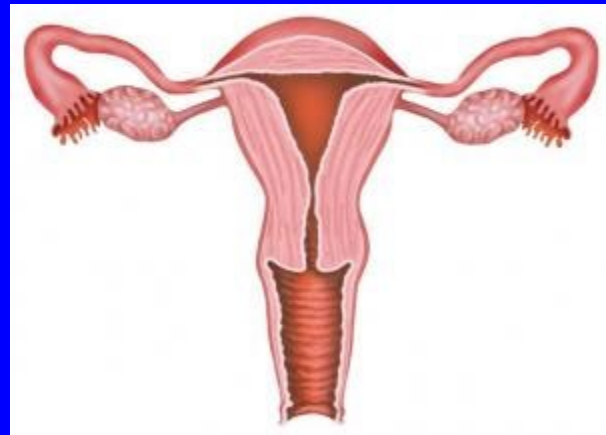
Uterus:
Retrograde
menstruation



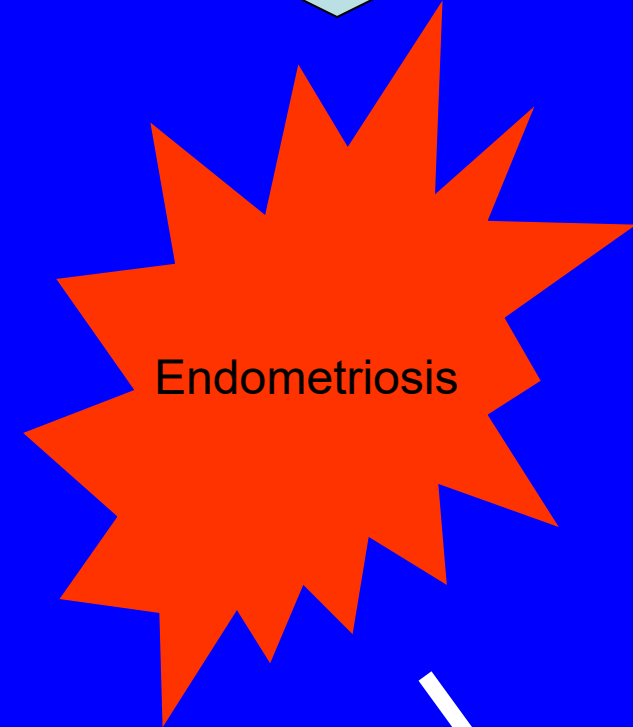
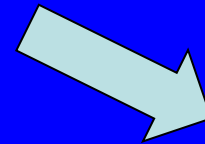
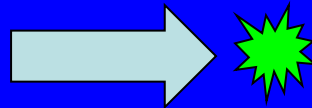
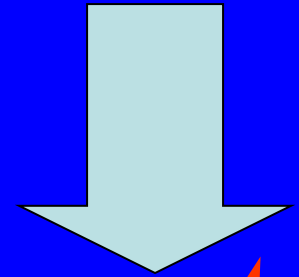
Stem Cell Trafficking in Endometriosis



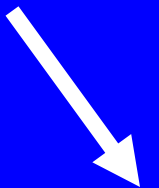
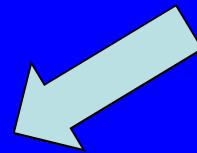
Stem Cell Trafficking in Endometriosis



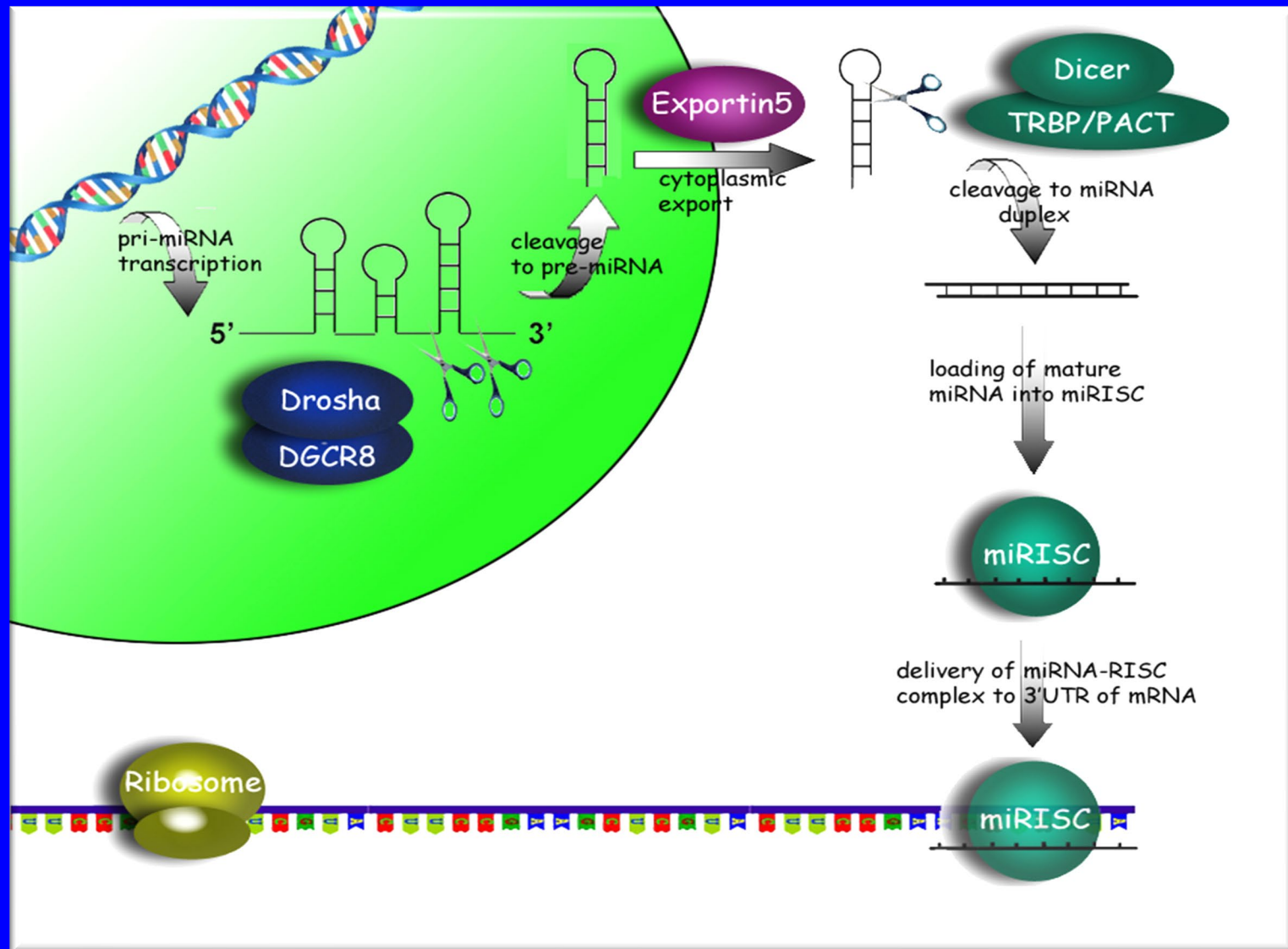
bone marrow



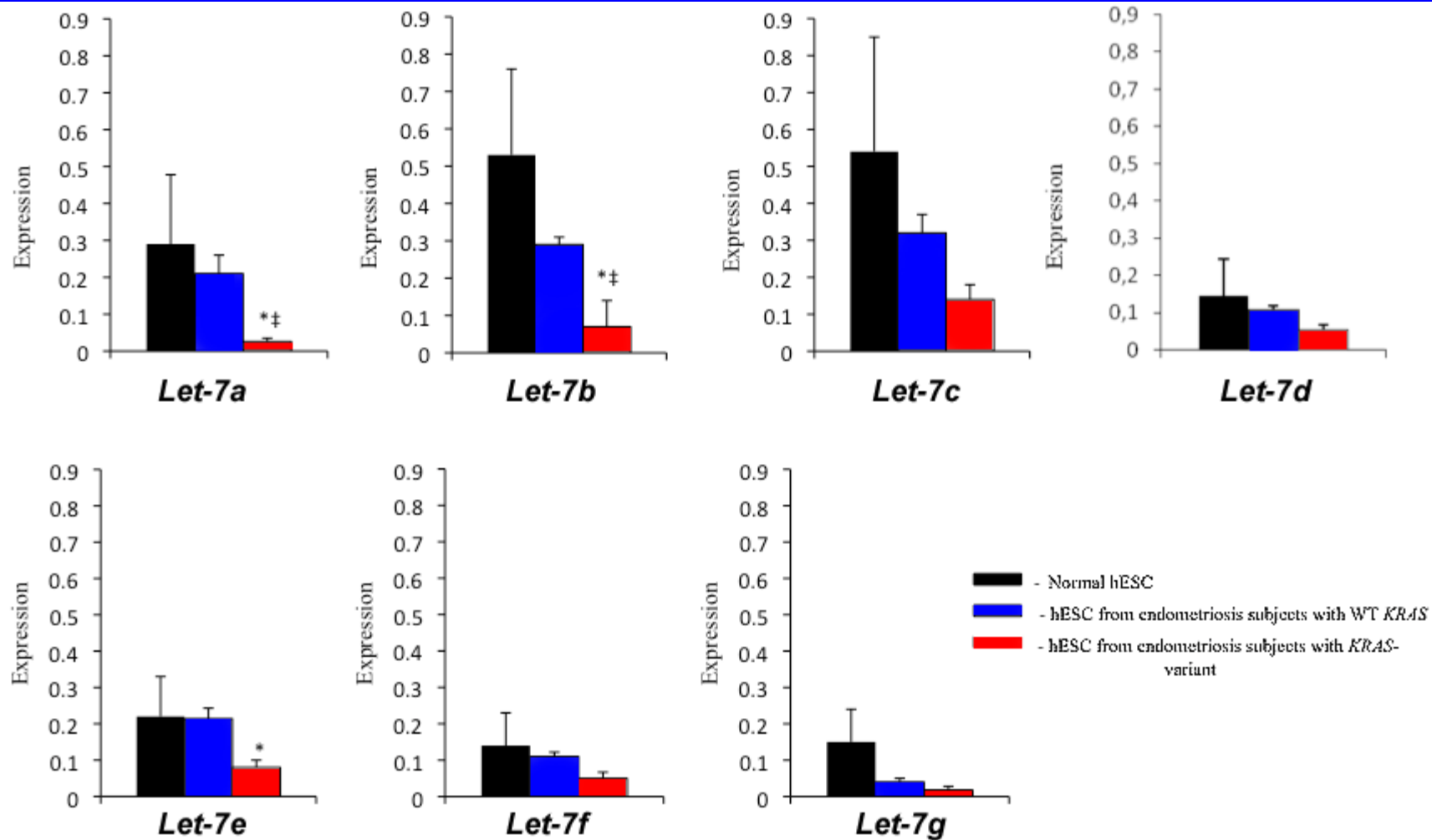
Endometriosis



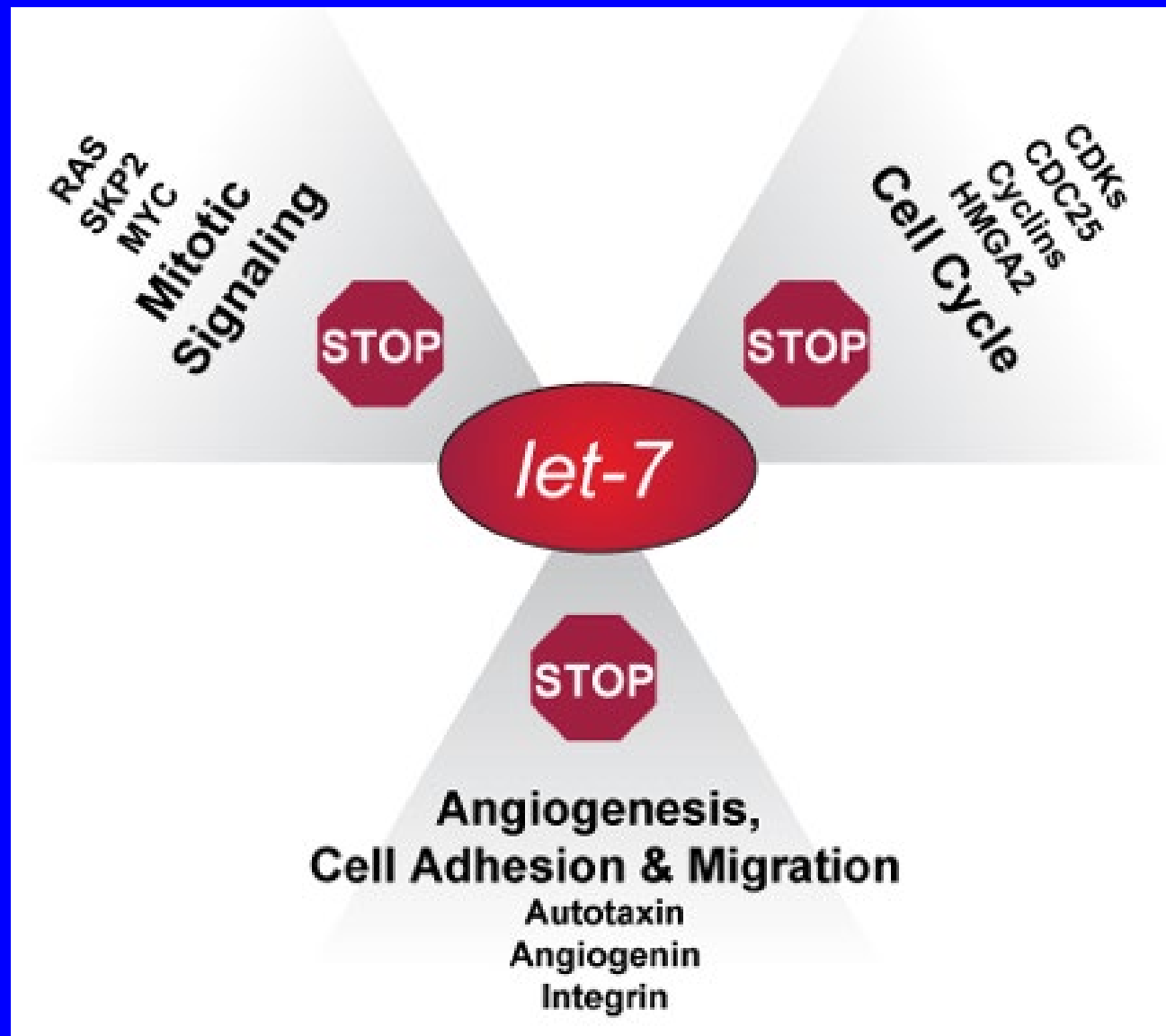
Micro RNA (MiRNA)

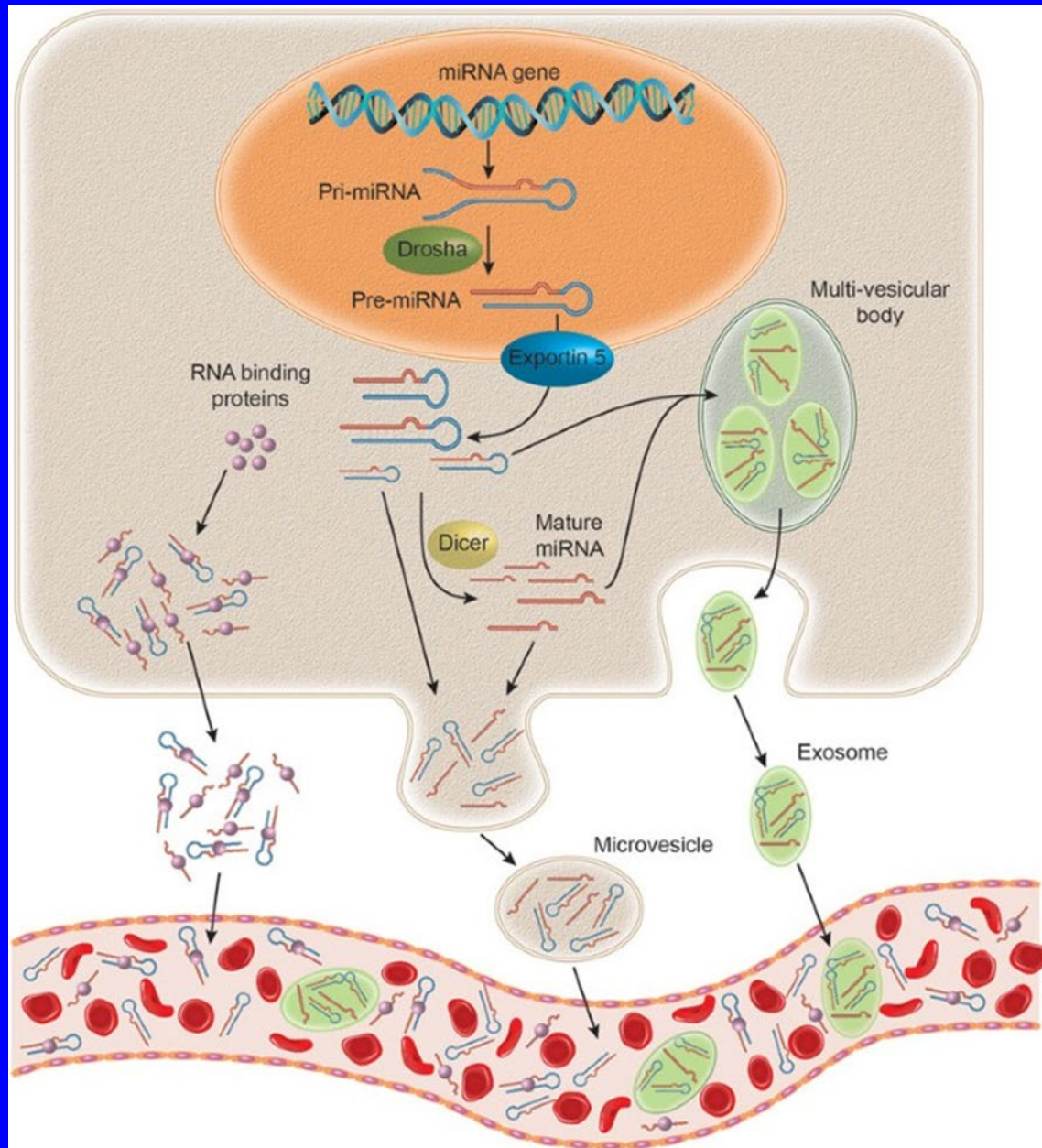


Decreased Let-7 micro RNAs in Endometriosis



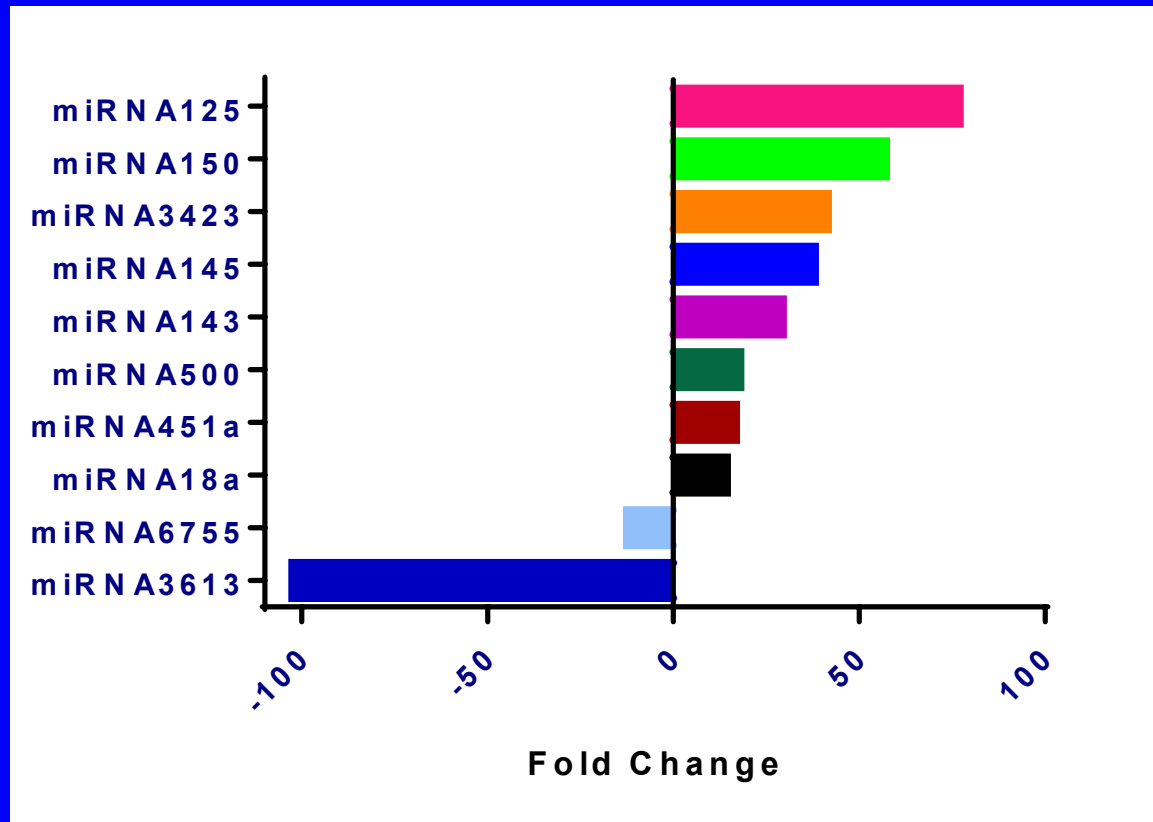
Let-7 signaling



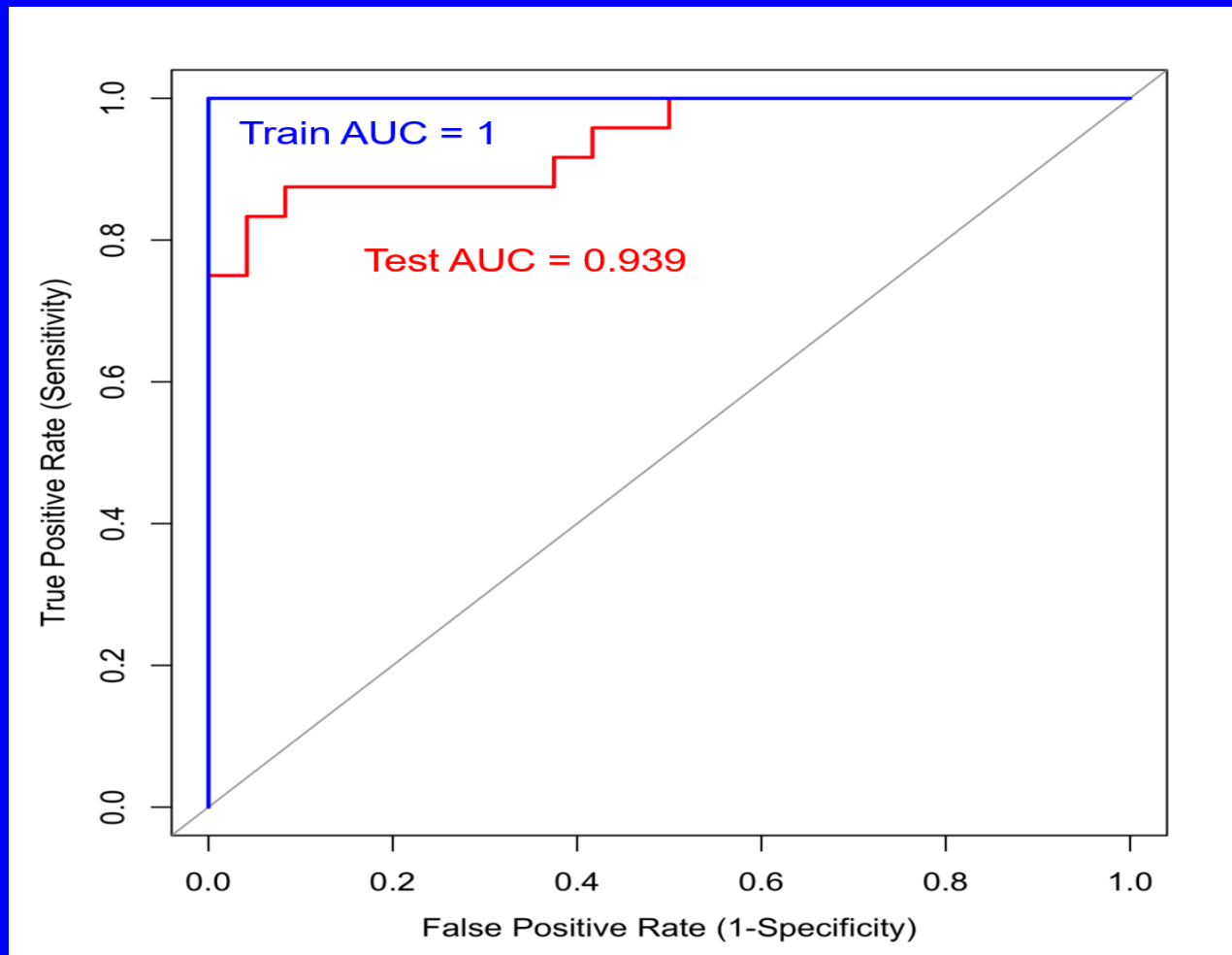


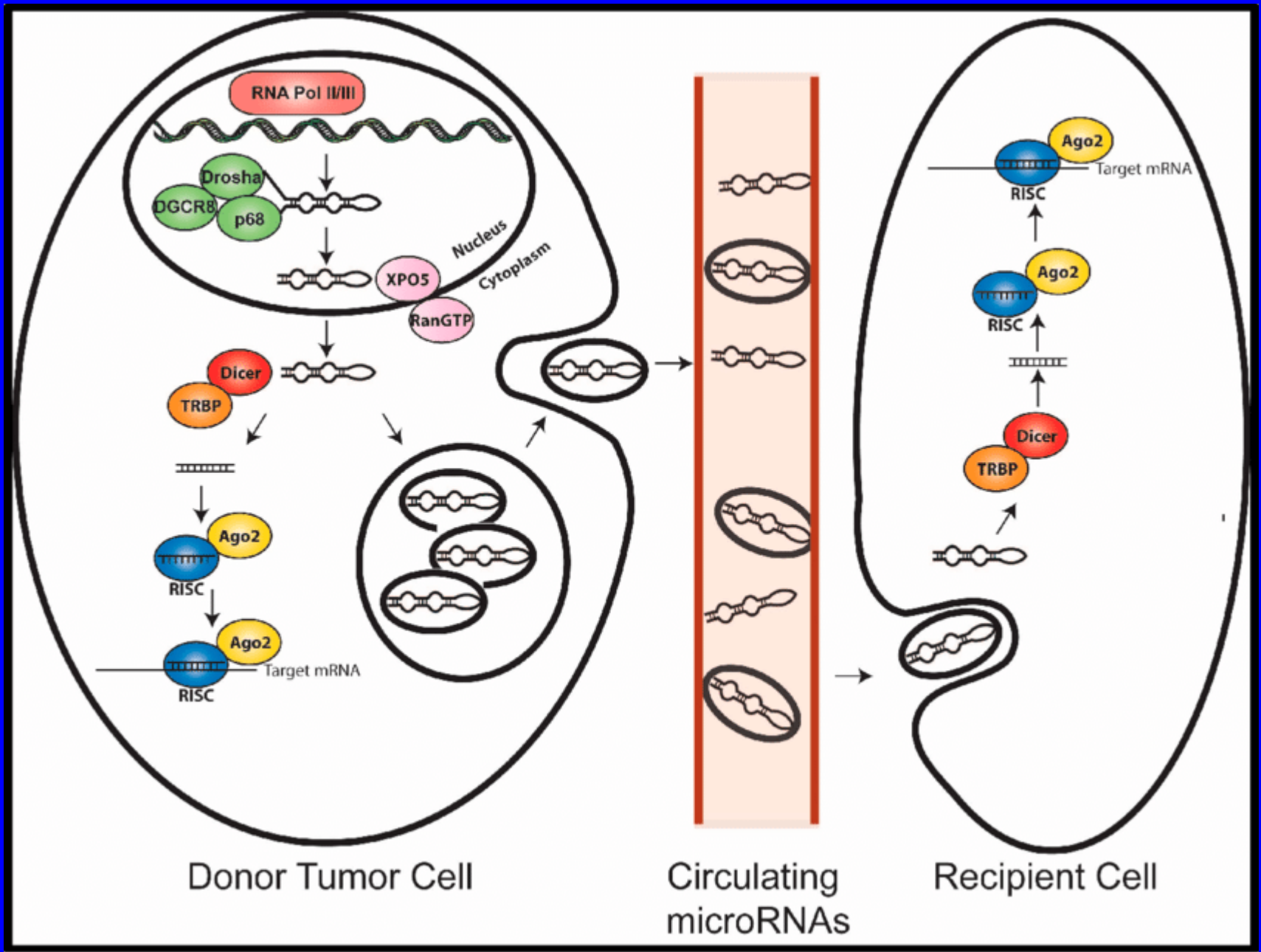
Circulating miRNAs as Serum Biomarkers of Endometriosis

Circulating MicroRNA in Endometriosis



Use of MicroRNA as a Clinical Test for Endometriosis





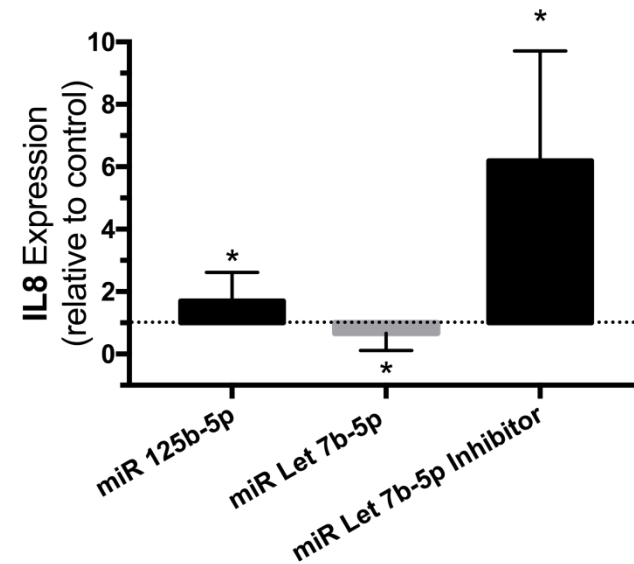
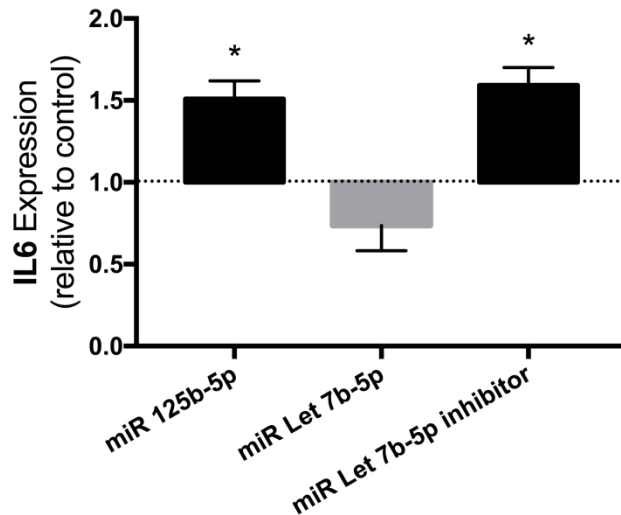
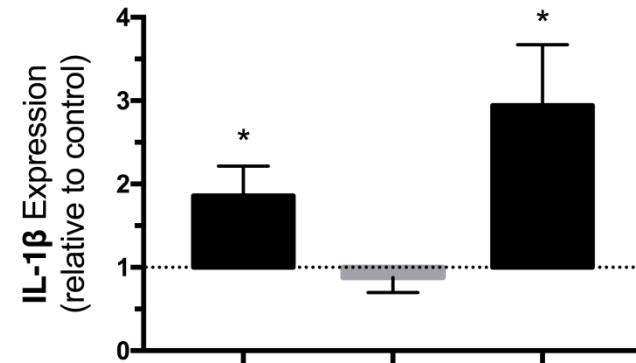
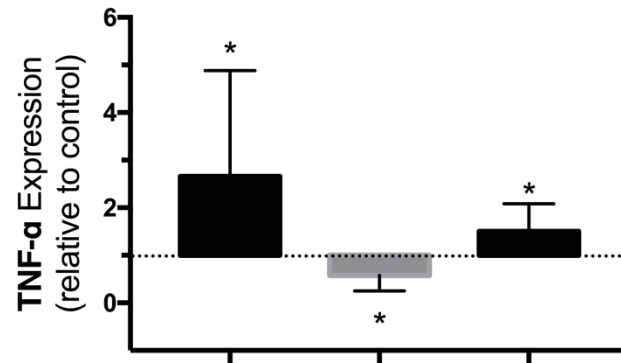
Donor Tumor Cell

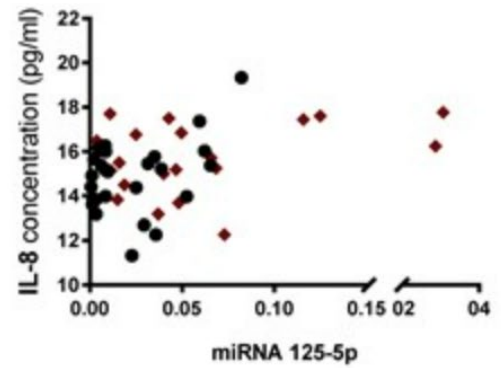
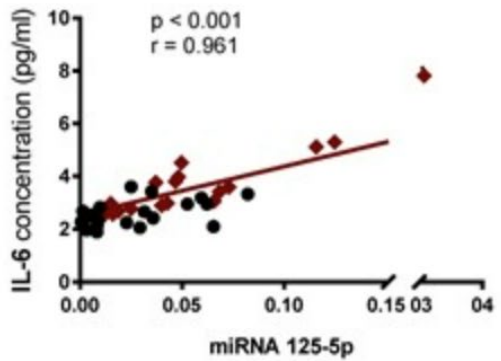
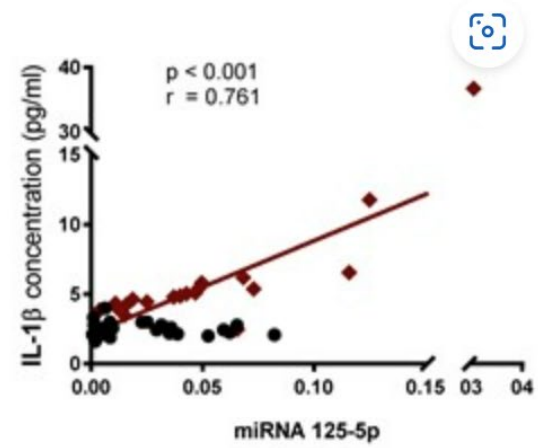
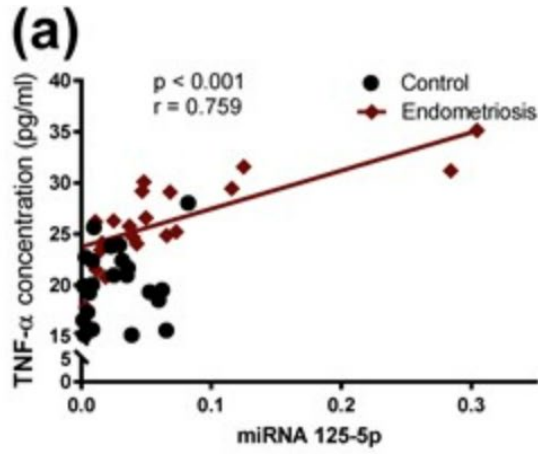
Circulating
microRNAs

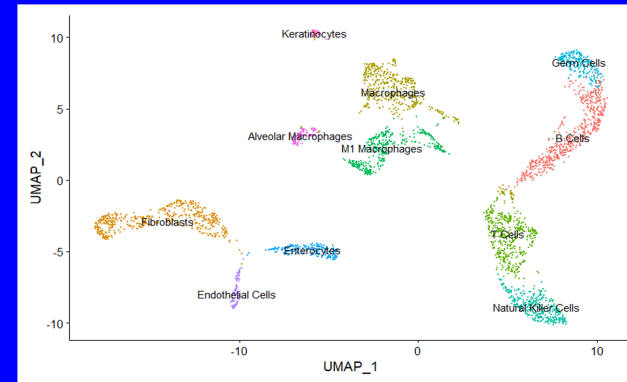
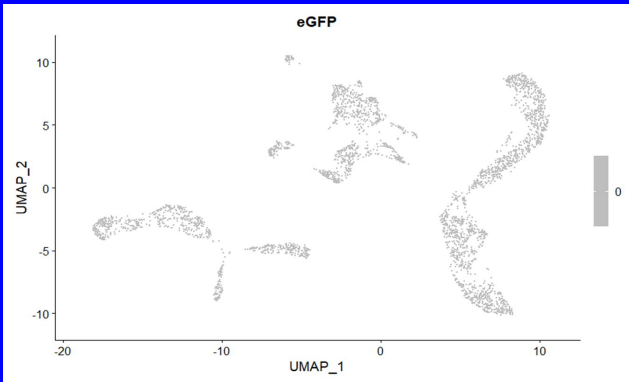
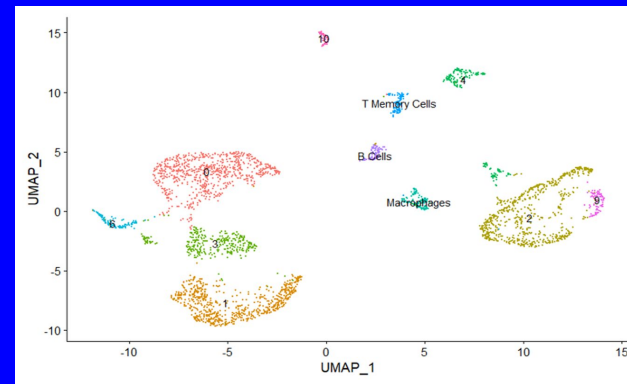
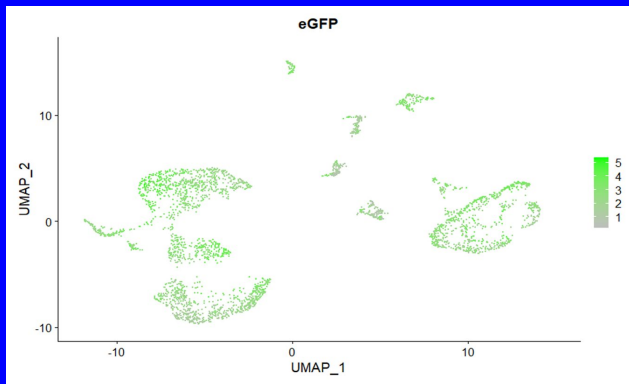
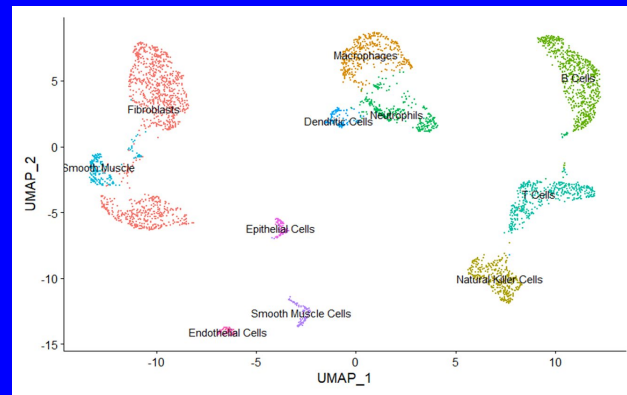
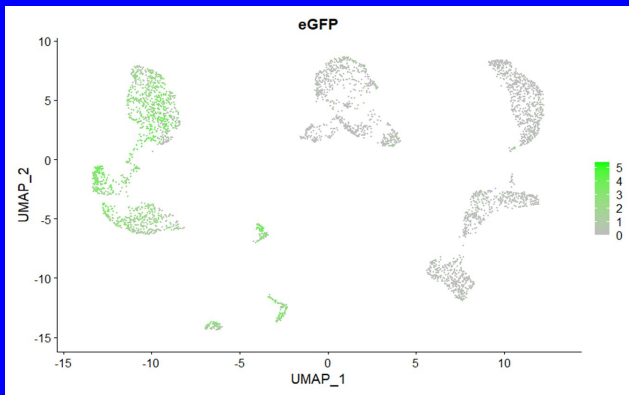
Recipient Cell

Systemic effects of microRNAs

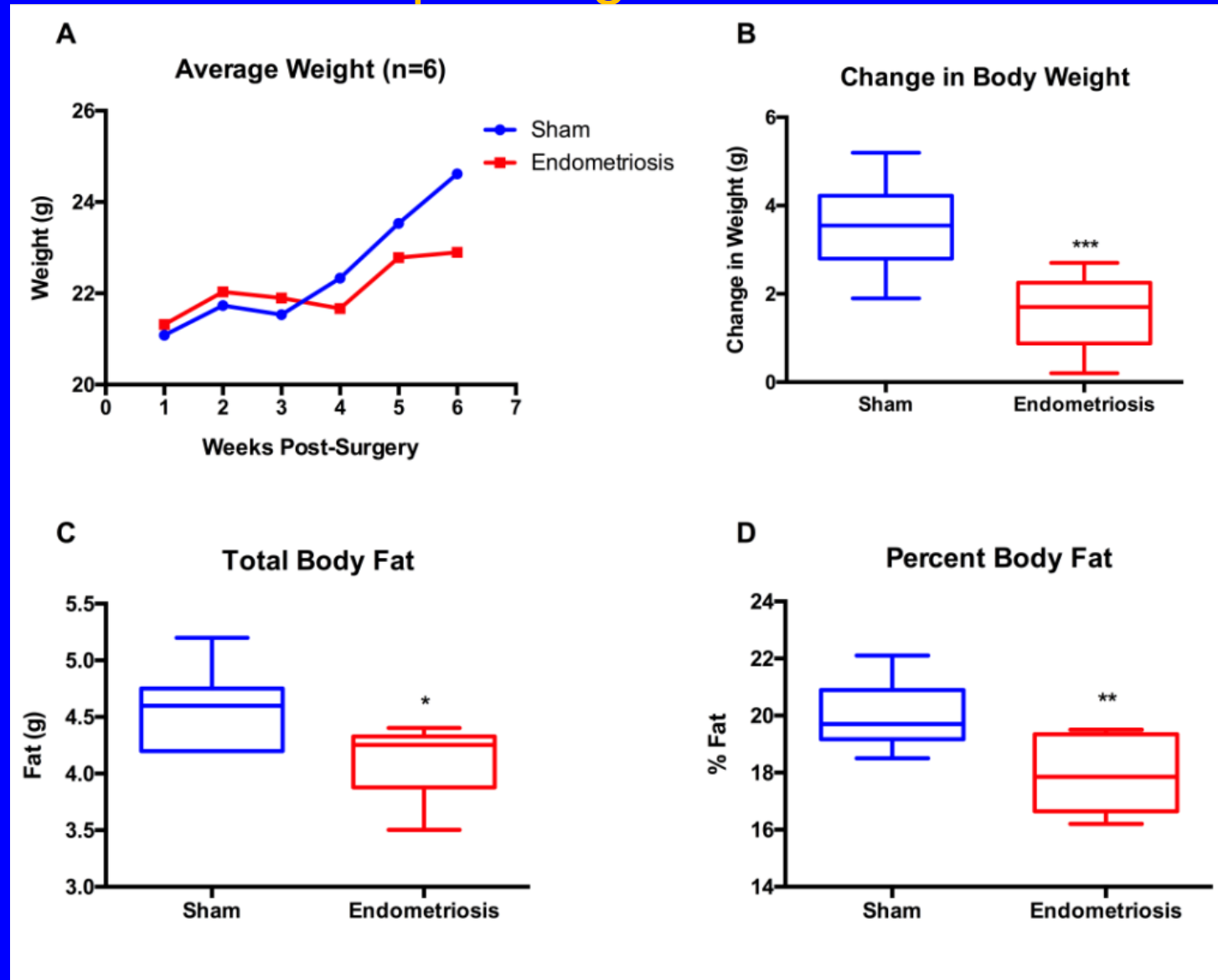
Inflammation



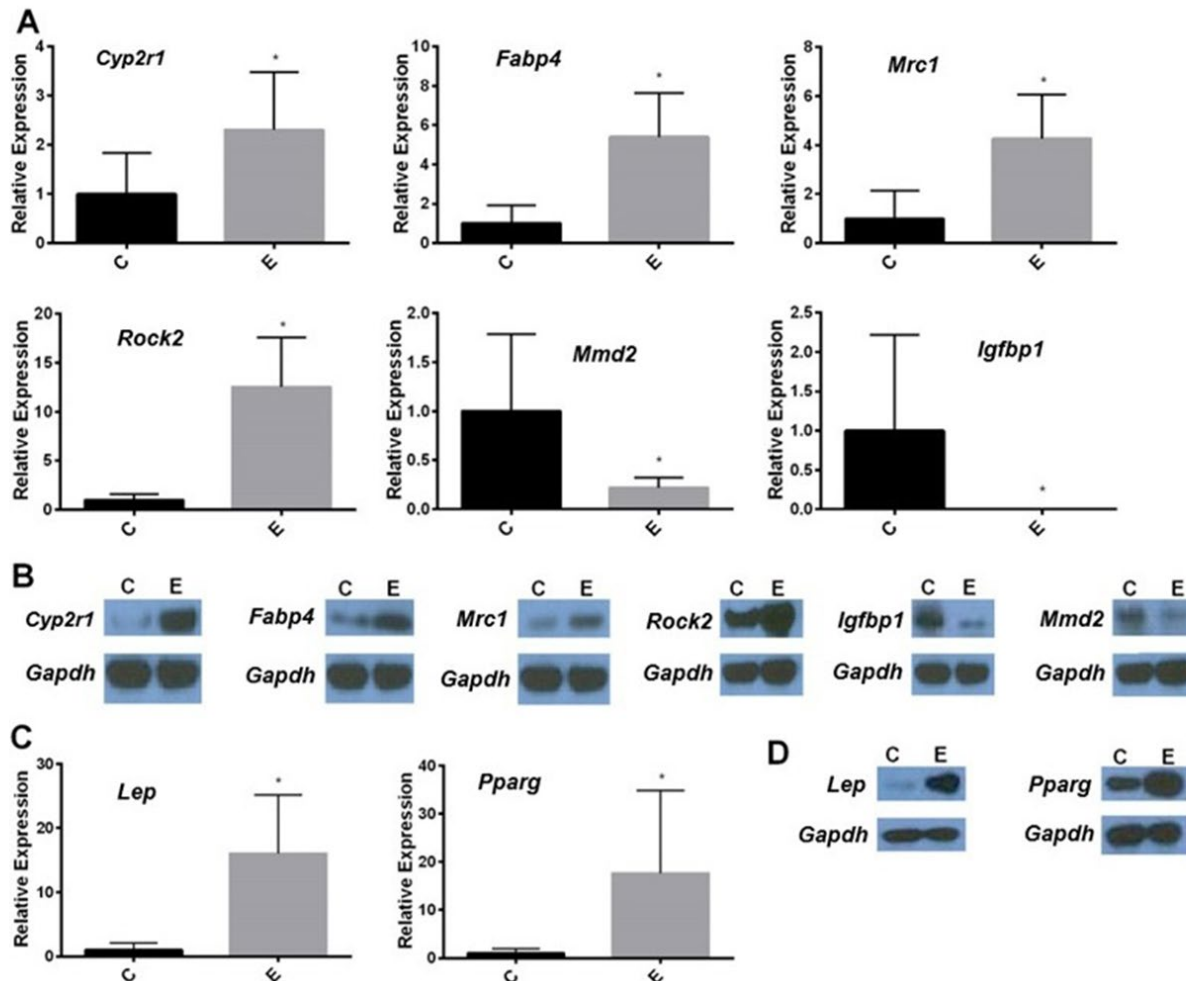




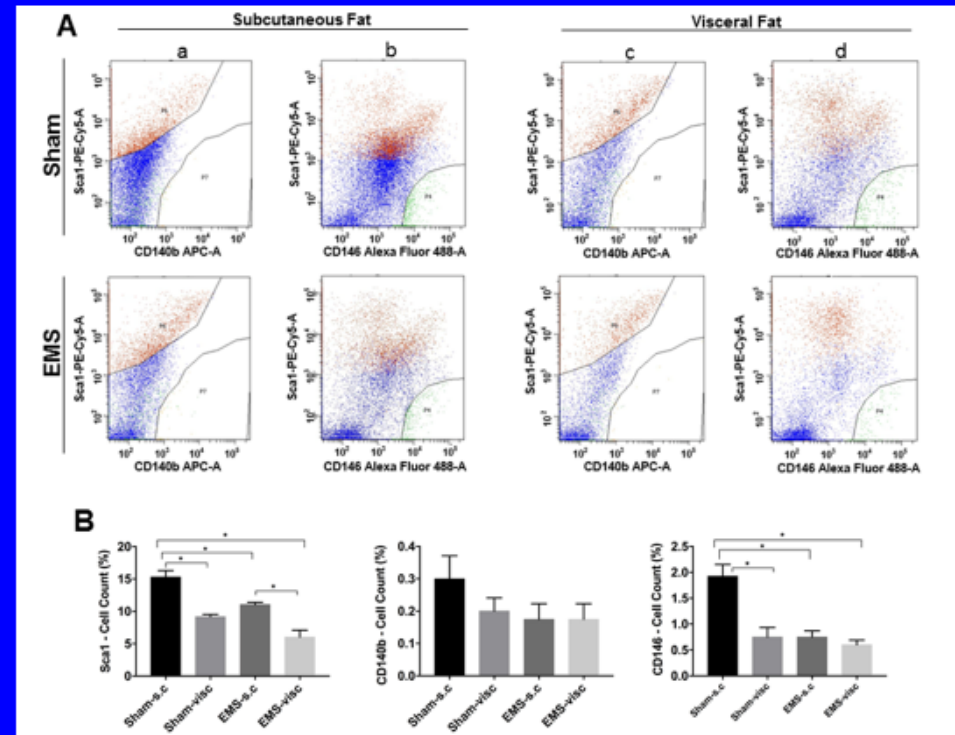
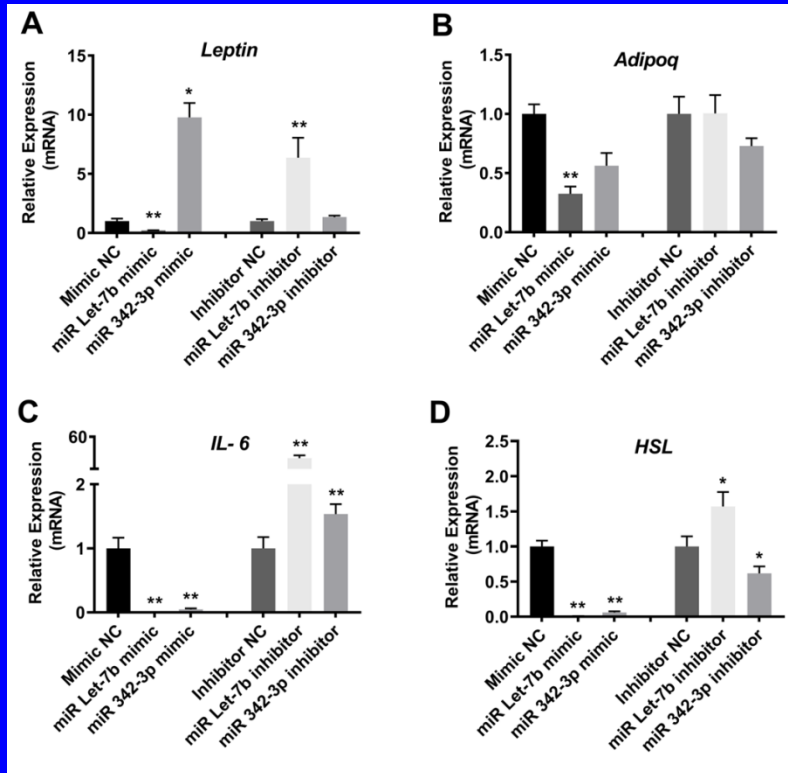
The Metabolic Phenotype of endometriosis: Explaining Low BMI



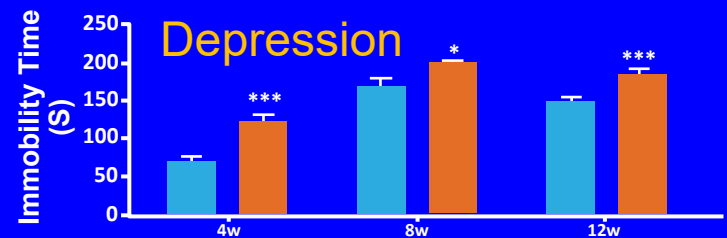
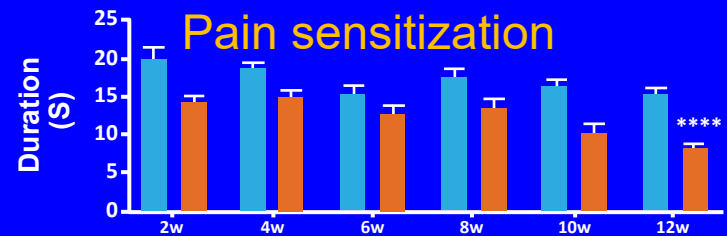
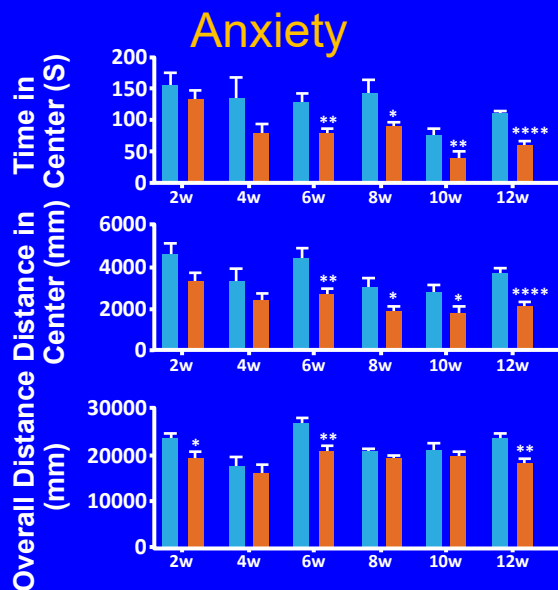
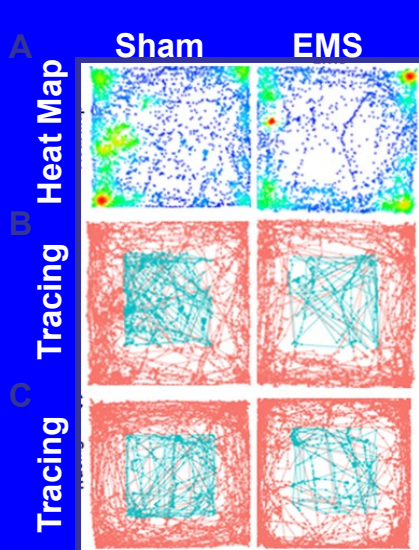
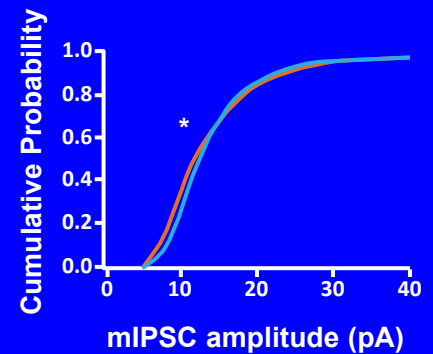
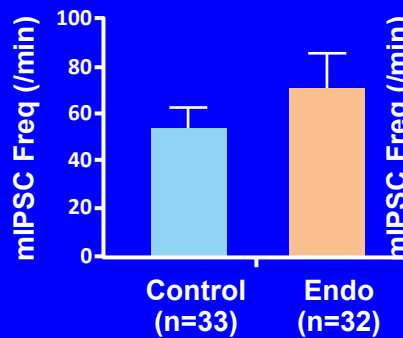
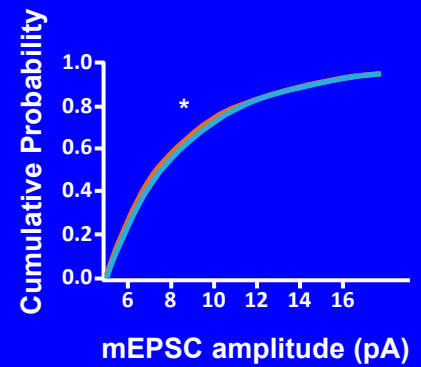
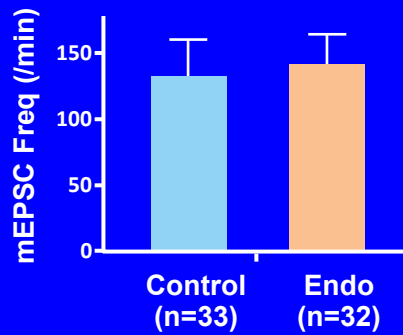
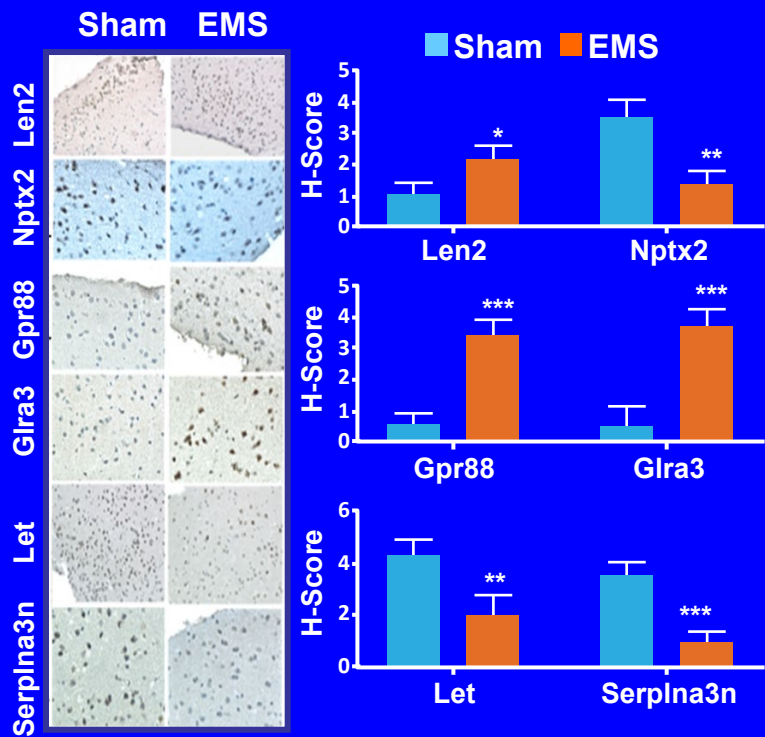
Metabolic Effect on Liver



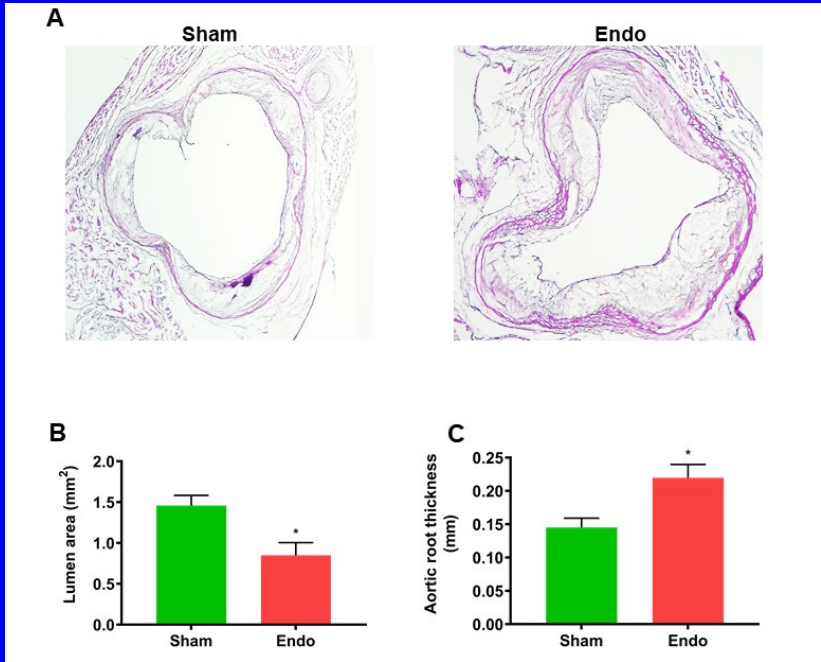
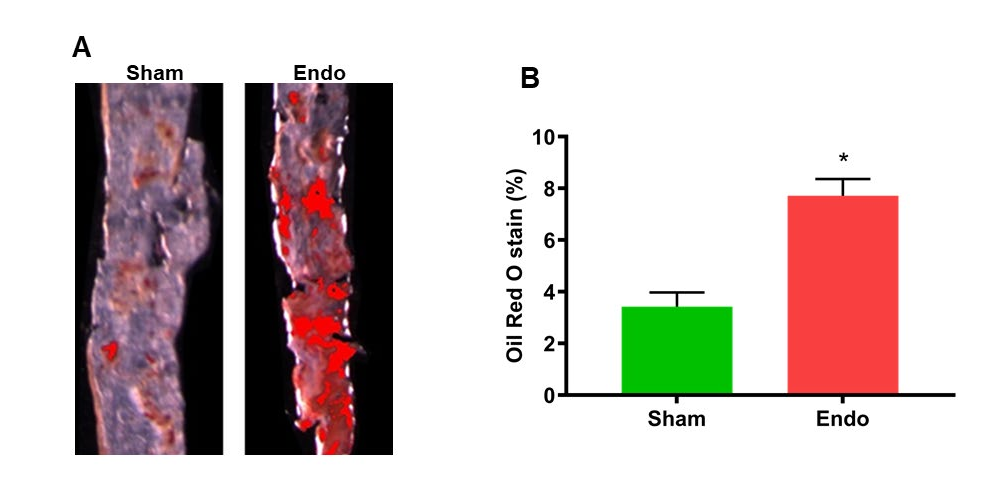
Metabolic Effect on Adipose Tissue



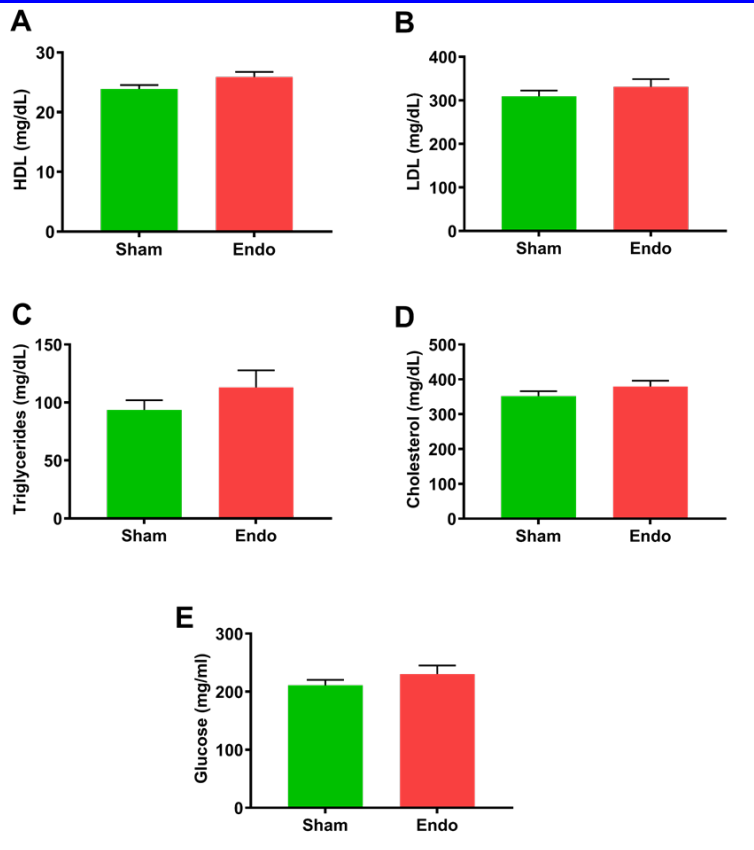
Effect on Brian and Behavior



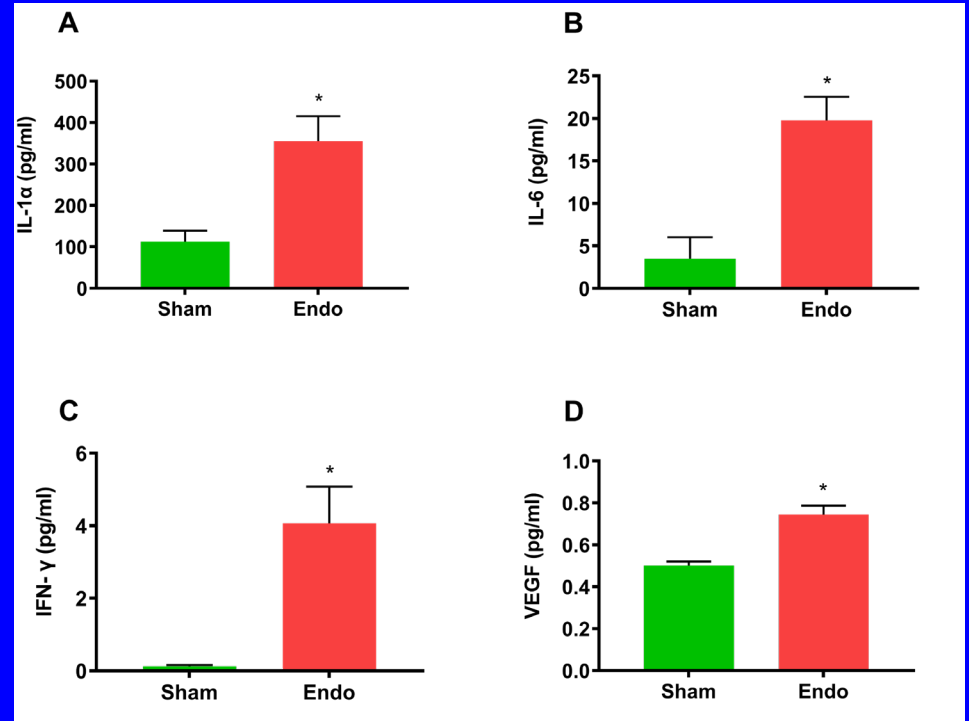
Endometriosis and Atherosclerosis



Lipids



Inflammatory Markers



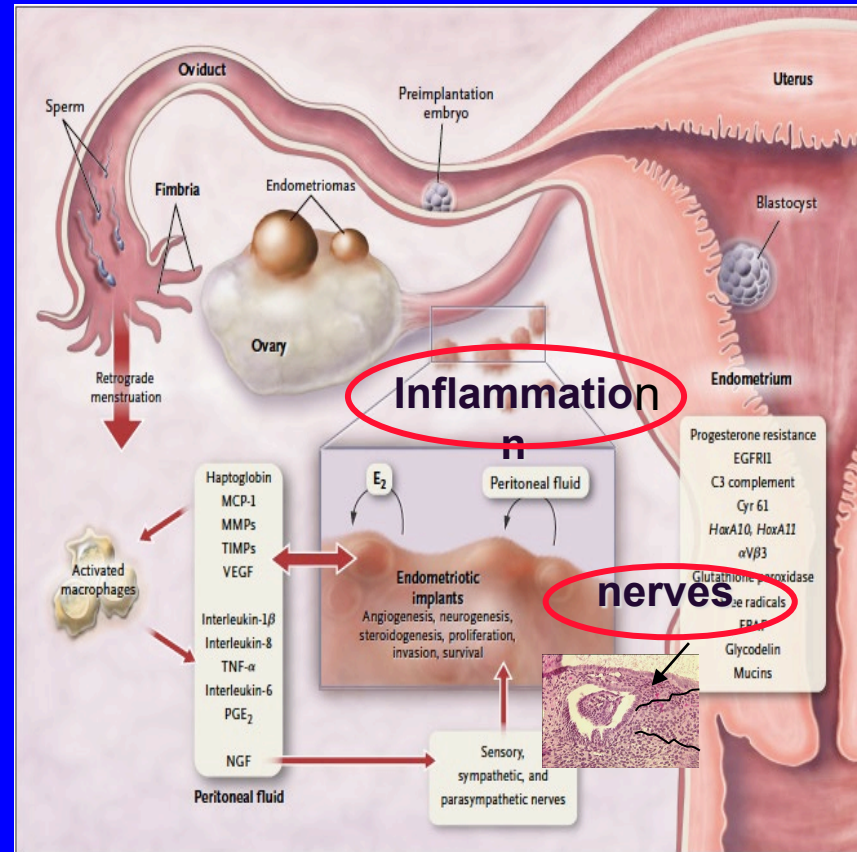


Endometriosis: A Chronic Systemic Disease

- Endometriosis is a widespread systemic disease.
- Varied presentation and diffuse symptoms have traditionally made it difficult for some practitioners to make the diagnosis.

Challenges in diagnosing endometriosis

- 6.7-11 years from symptom onset to definitive diagnosis and treatment
- Many PCPs unfamiliar with disease
- Symptoms are nonspecific or associated with other disorders
- Social norms inhibit conversation
- Pain is subjective
- Survey of n = 7,025 women
 - 65% misdiagnosed
 - 46% saw ≥ 5 MDs to get correct diagnosis



Early diagnosis and treatment can reduce uncertainty, discomfort, disease progression, and later complications

Medical Therapy

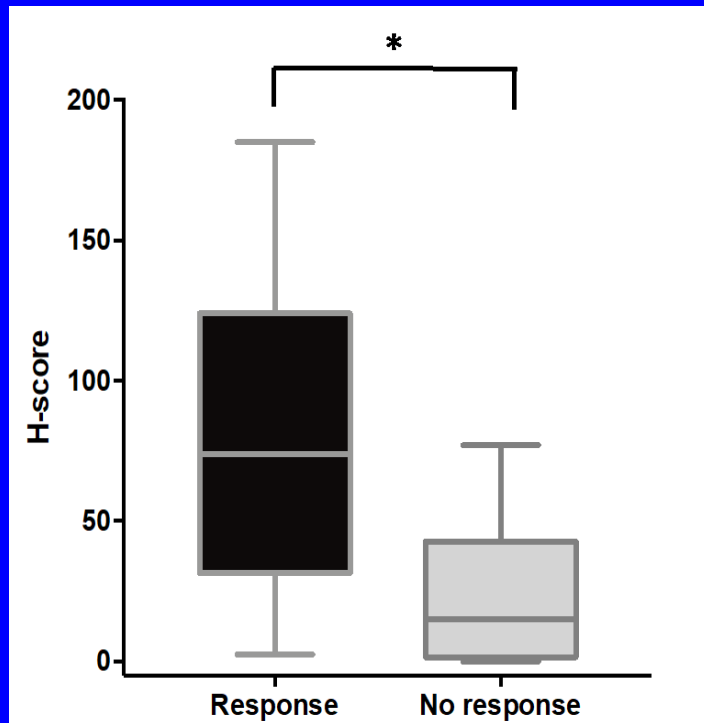


Oral Contraceptives

- Progestin effect
- Administration: cyclic or continuous
- Best for mild pelvic pain
- Also provide contraception

Progestin Resistance

Progesterone Resistance and PR



	High PR	Medium PR	Low PR
No Response	0	22	16
Response	7	6	1
Response Rate	100%	21%	6%



While complex, endometriosis is always estrogen dependent.

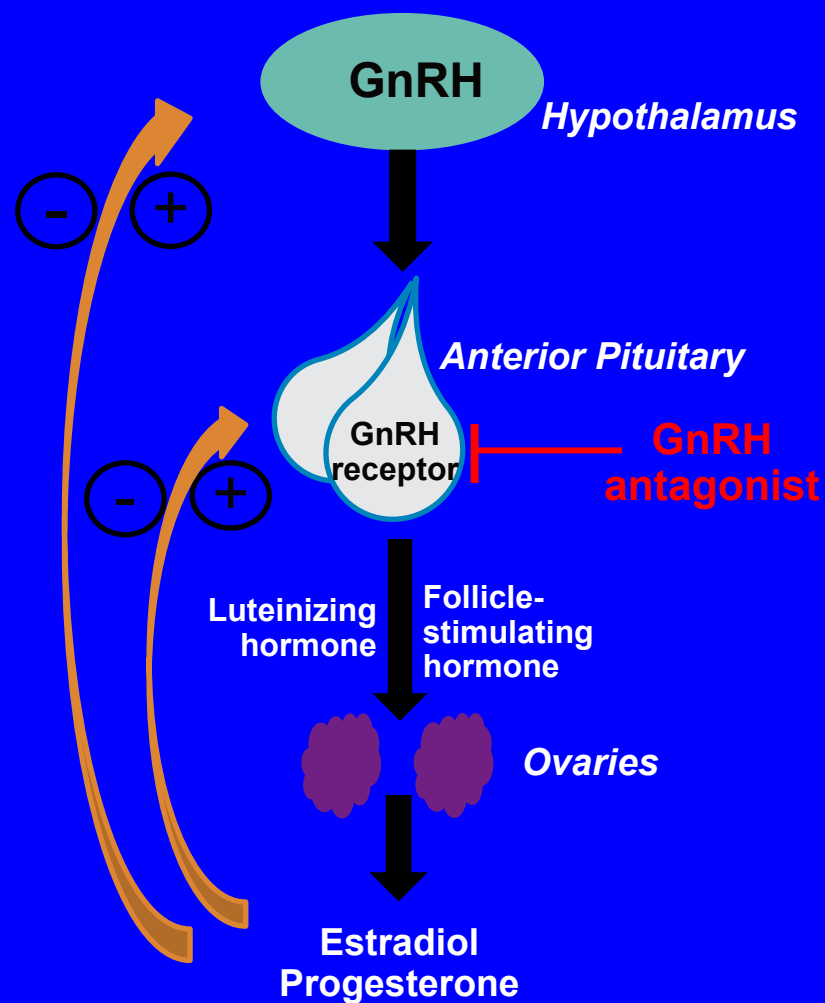
- GnRH Agonists
- Induce pseudo-menopause
- Complications: bone loss, vasomotor symptoms
- Add-back therapy (norethindrone or MHT)

Emerging Therapies for Endometriosis

Elagolix for the treatment of Endometriosis-associated Pain

Elagolix:

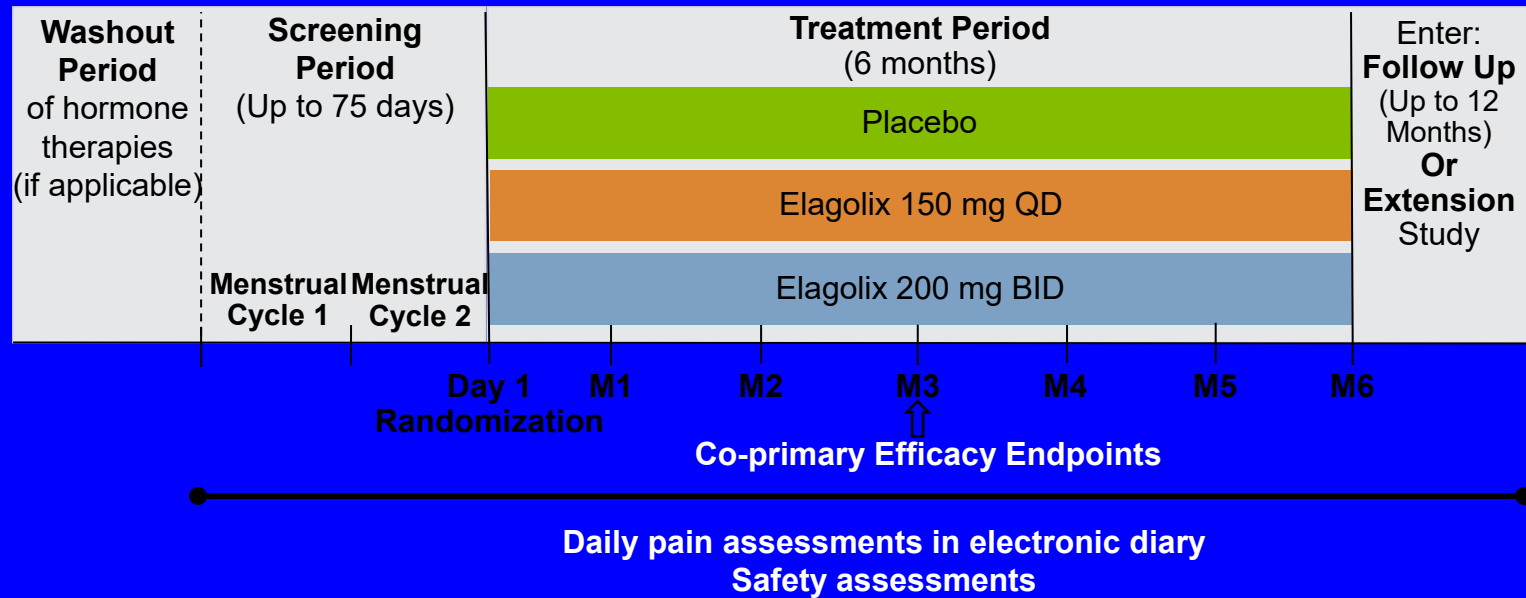
- Is an oral, non-peptide, gonadotropin-releasing hormone (**GnRH**) **antagonist**
- Results in dose dependent suppression of gonadotropins and ovarian sex steroids
- Does not desensitize or downregulate the receptor
- Hormone suppression is **rapid and reversible**



Advantages of GnRH antagonist over agonist

- Enables management of endogenous estrogen
- Allow for partial estrogen suppression
- Oral Dosing
- No flare, worsening of symptoms
- Can adjust dosage to individual patients;
personalized medicine approach

Two, Double-blind, Randomized, Placebo-controlled Studies



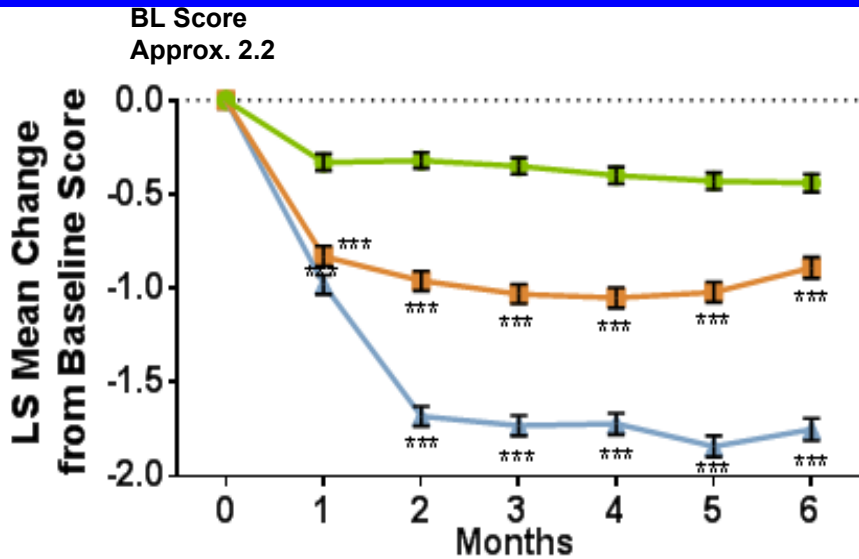
- **Elaris Endometriosis I (EM-I)** was conducted in North America (NCT01620528)
- **Elaris Endometriosis II (EM-II)** was global (NCT01931670)

Participants were:

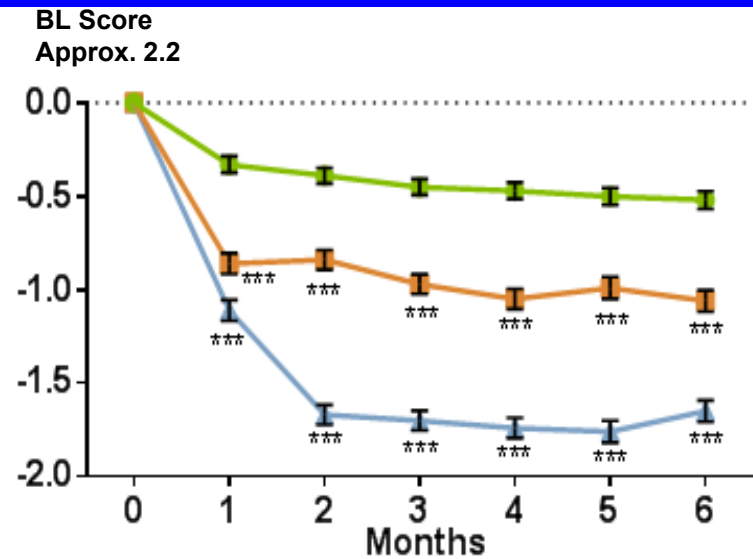
- premenopausal women (18-49 years)
- surgically diagnosed with endometriosis
- moderate/severe dysmenorrhea and non-menstrual pelvic pain

Effects of Elagolix on Dysmenorrhea

Elaris EM-I



Elaris EM-II



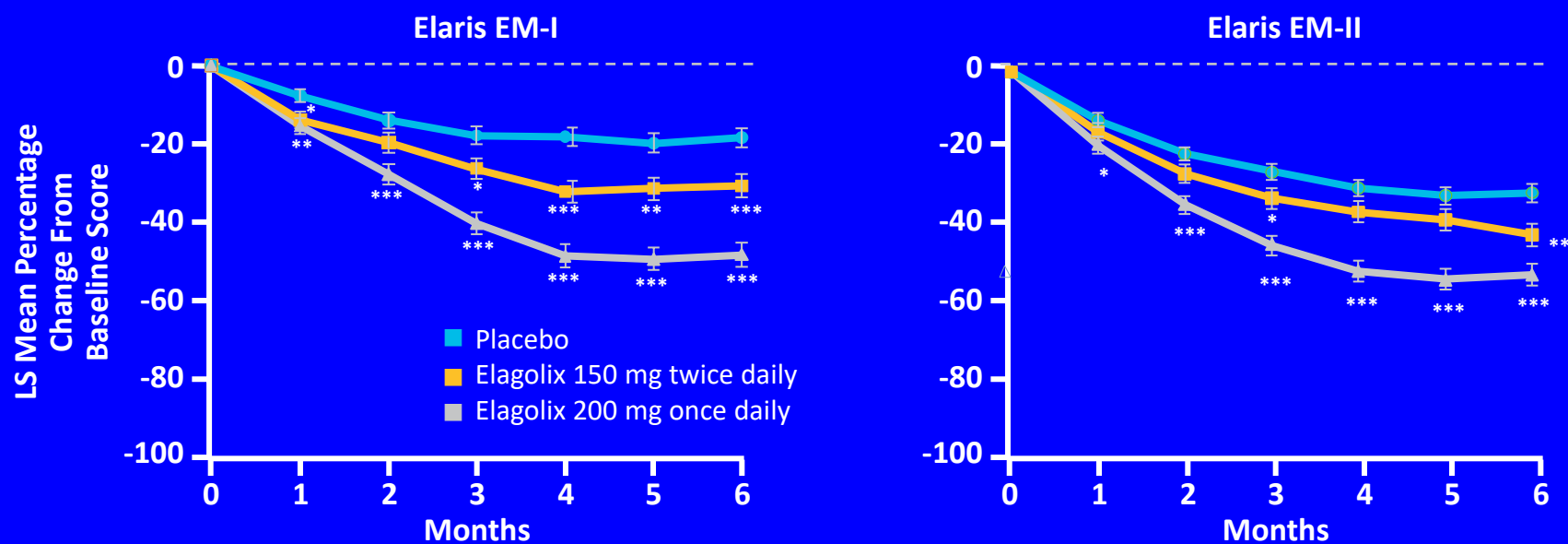
The statistical significance vs. placebo is indicated for $P < 0.05$ (*), $P < 0.01$ (**), and $P < 0.001$ (***).

Placebo

Elagolix 150 mg Once Daily

Elagolix 200 mg Twice Daily

Effects of Elagolix on Nonmenstrual Pelvic Pain



The statistical significance vs placebo is indicated for $P < .05$ (*), $P < .01$ (**), and $P < .001$ (***)

N (%)	Elaris EM-I			Elaris EM-II		
	Placebo	Elagolix		Placebo	Elagolix	
		150 mg QD	200 mg BID		150 mg QD	200 mg BID
	N=374	N=249	N=248	N=360	N=226	N=229
Any adverse event (AE)	277 (74)	201 (81)	205 (83)	260 (72)	179 (79)	194 (85)
Any serious AE	12 (3.2)	2 (0.8)	7 (2.8)	12 (3.3)	12 (5.3)	5 (2.2)
Any severe AE	56 (15)	26 (10)	43 (17)	32 (8.9)	23 (10)	21 (9.2)
Any AE leading to discontinuation	22 (5.9)	16 (6.4)	23 (9.3)	22 (6.1)	10 (4.4)	23 (10)

AEs occurring in ≥ 15% in at least 1 treatment group

Hot Flush	26 (7.0)	59 (24)***	105 (42)***	37 (10)	51 (23)***	109 (48)***
Headache	37 (9.9)	38 (15)	43 (17)**	51 (14)	42 (19)	52 (23)**
Nausea	51 (14)	25 (10)	40 (16)	41 (11)	26 (12)	36 (16)
Discontinuation due to hot flush	0	2 (0.8)	7 (2.8)	0	2 (0.9)	5 (2.2)

- The severity of hot flushes was mild in the majority (>50%) of women in each treatment group
- Discontinuation rate due to hot flushes was < 1% and <3% in each group

Relugolix CT

	Relugolix Combination Therapy	
Dose	40 mg QD	
Responder Rate (<i>placebo</i>)	SPIRIT 1	SPIRIT 2
Dysmenorrhea	74.5% (26.9%)	75.2% (30.4%)
Non-Menstrual Pelvic Pain	58.5% (39.6%)	66.0% (42.6%)
Bone Mineral Density Loss, Lumbar Spine (<i>placebo</i>)	-0.70% (0.21%)	-0.78% (0.02%)

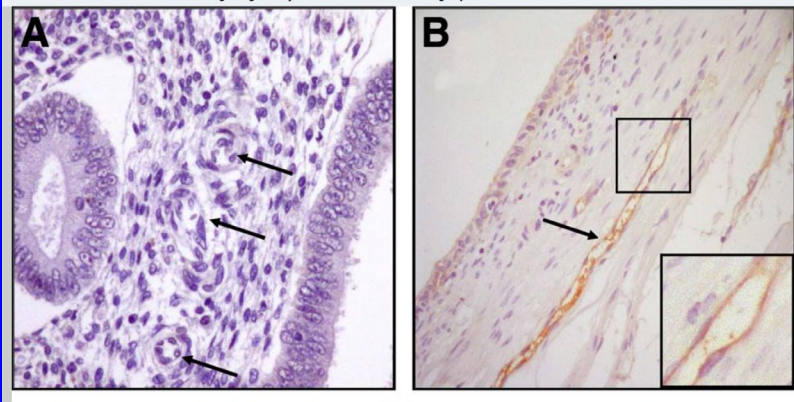
Future Targets:

Fertility sparing

Addressing the inflammation

- Micro RNAs
- Long non-coding RNAs
- Inflammation
- Fibrosis
- Angiogenesis/Tissue Factor

The Immunoconjugate “ICON” Targets Aberrantly Expressed Endothelial Tissue Factor Causing Regression of Endometriosis



L-ICON3 is composed of factor VII light chain (fVIII) fused to a truncated IgG3 hinge followed by R435H-mutated IgG3 Fc

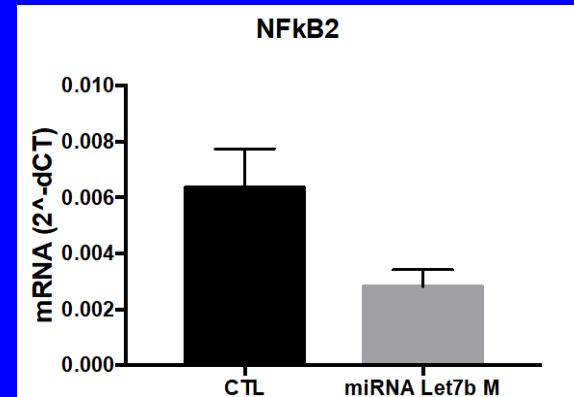
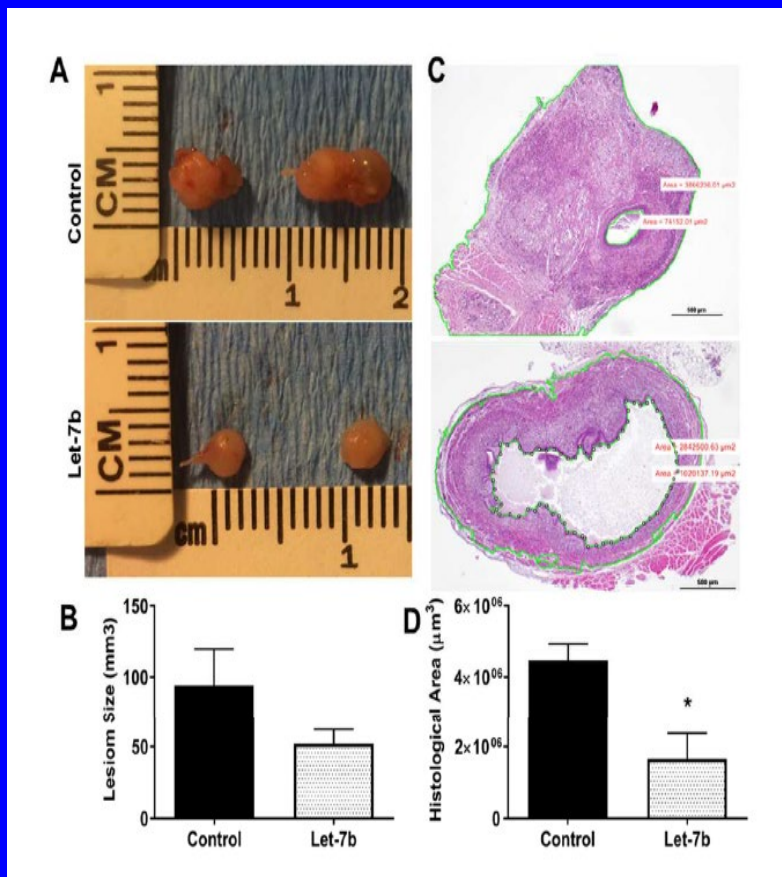
Effect of Icon Treatment on Mice with Endometriotic Lesions

Mouse Tx	Avg. vessel size (arbitrary units)	<i>P</i>	No. of mice with disease per total number	% with disease	<i>P</i>
Control	2.88		12/13	92%	
Icon (5 µg)	1.21	<0.05	7/12	58%	NS
Icon (10 µg)	1.50	<0.05	4/15	27%	<0.05

All mice were treated as described in Methods. *P* refers to the level of significance.

Mouse: Krikun G, et al. Am J Pathol. 2010;176(2):1050-6.
 Baboon: Hufnagel D, et al. Reprod Biol. 2018;18(1):109-114.

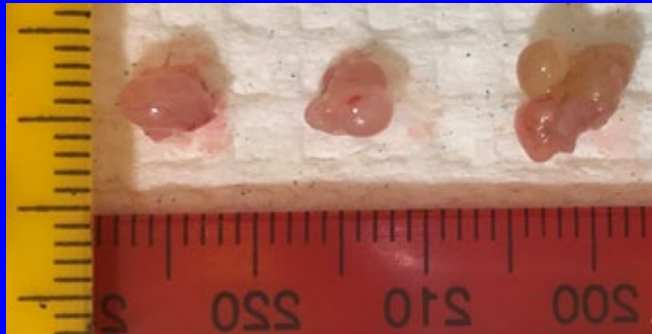
Let7 miR Therapy for Endometriosis



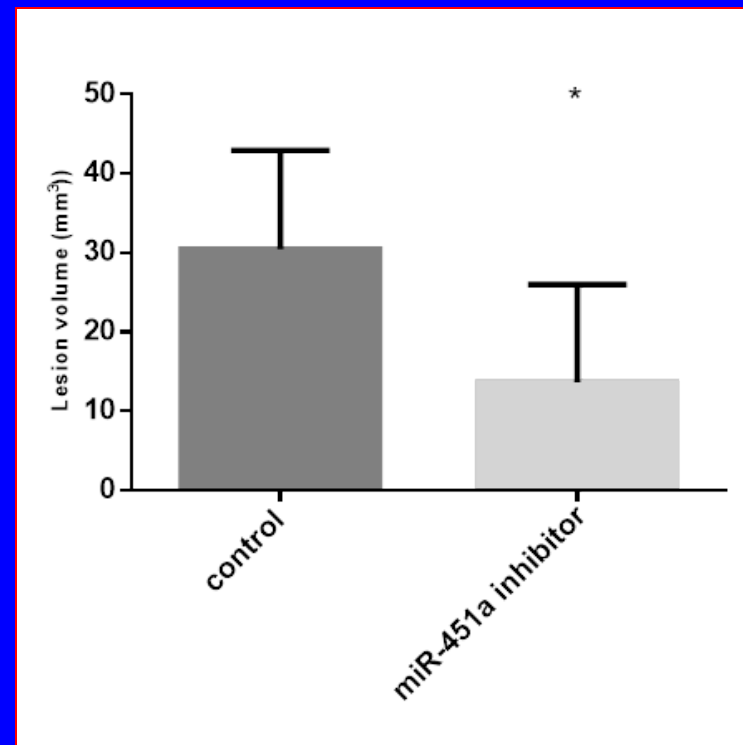
- Decreased expression of
 - Inflammatory cytokines
 - Estrogen receptors
 - Aromatase

Treatment of endometriosis with Inhibition of miR-451a

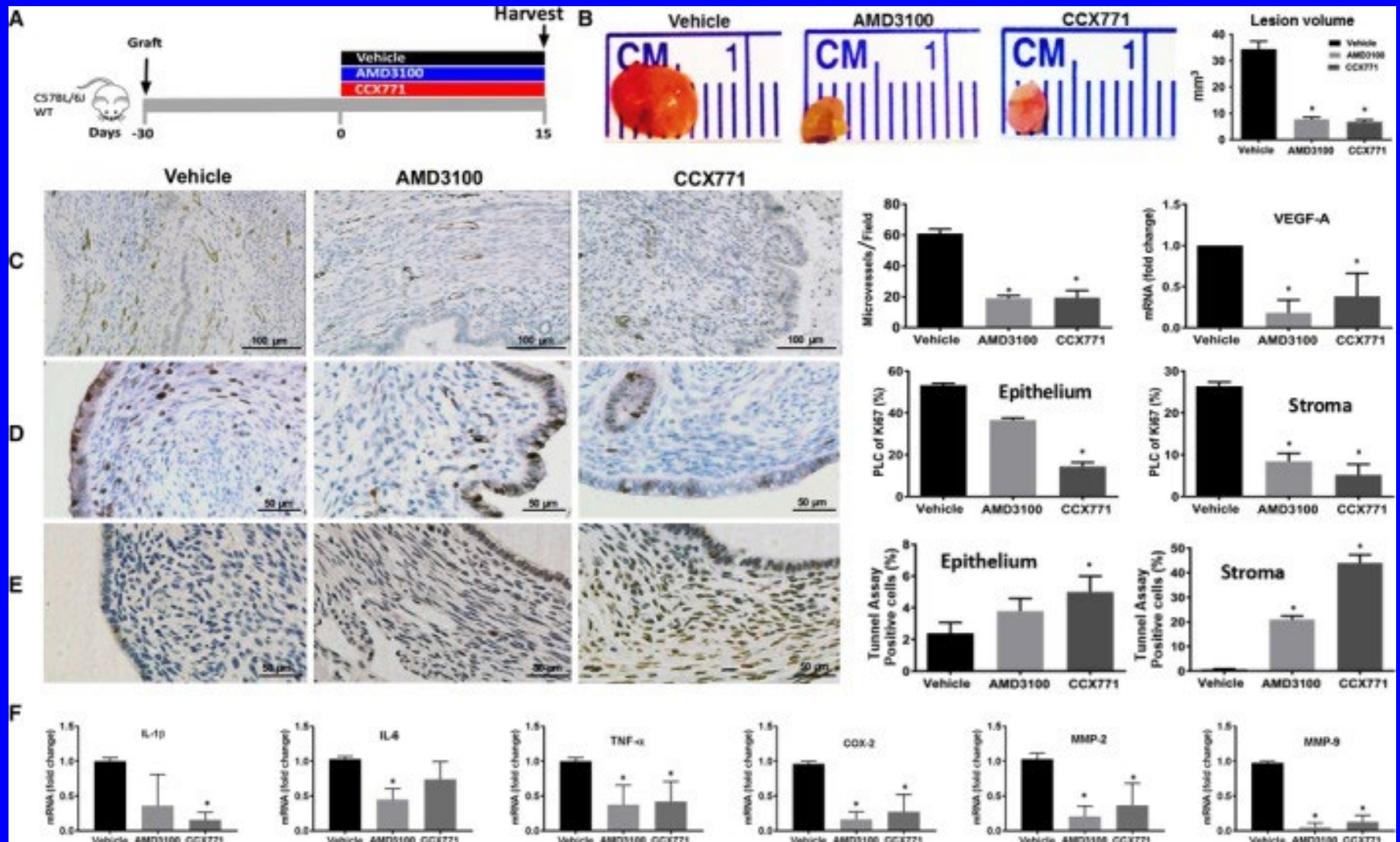
Control



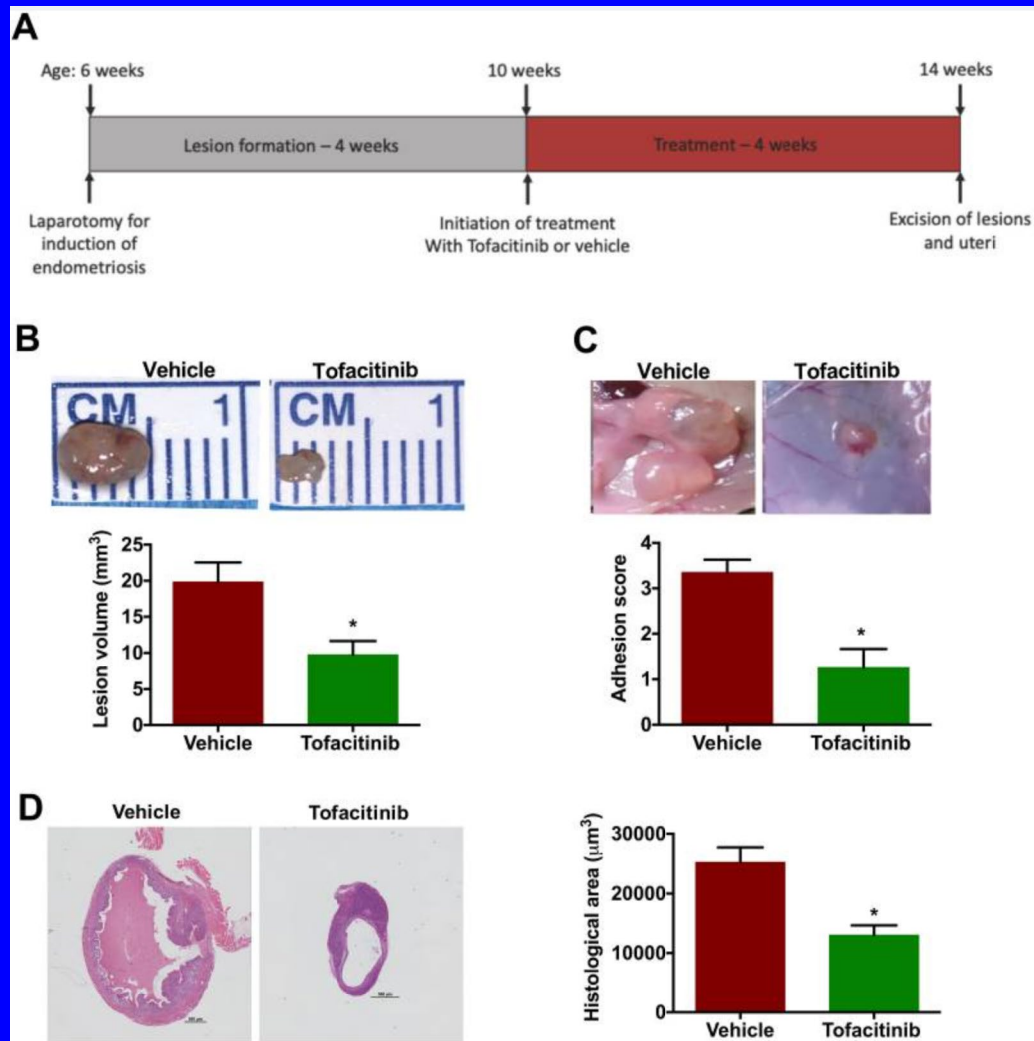
miR-451a Inhib



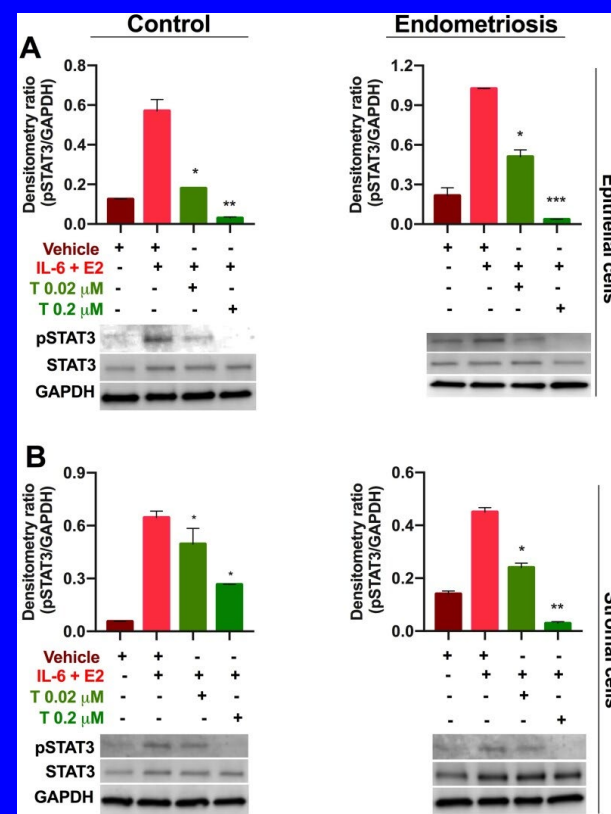
CXCR4 or CXCR7 Antagonists



Tofacitinib alters STAT3 signaling and leads to endometriosis lesion regression.



The JAK/STAT3 pathway is upregulated in endometriosis and a therapeutic target.



Endometriosis: A Chronic Systemic Disease

- Endometriosis is a widespread systemic disease.
- The systemic nature of the disease may explain the extensive symptoms often associated with endometriosis.
- Stem cells, microRNAs and inflammation are some of the mechanisms that mediate these long-range effects.

Clinical Implications for Patient Care:

- Efforts to diagnose endometriosis must include recognition of the systemic manifestations.
- While surgical therapy treats local disease, medical therapy may be needed to treat systemic manifestations.
- Future therapies will include agents that specifically target disseminated effects of the disease without hormone deprivation.

A focus exclusively on pain underestimates the true extent of endometriosis and the patient's full disability.

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