



**Developing Novel Solutions for
Women's Health and Cancer Therapy**

Selective Estrogen Receptor beta Agonists Mechanism of Action and Clinical Applications in Women's Health and Cancer

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NASDAQ: BNVI

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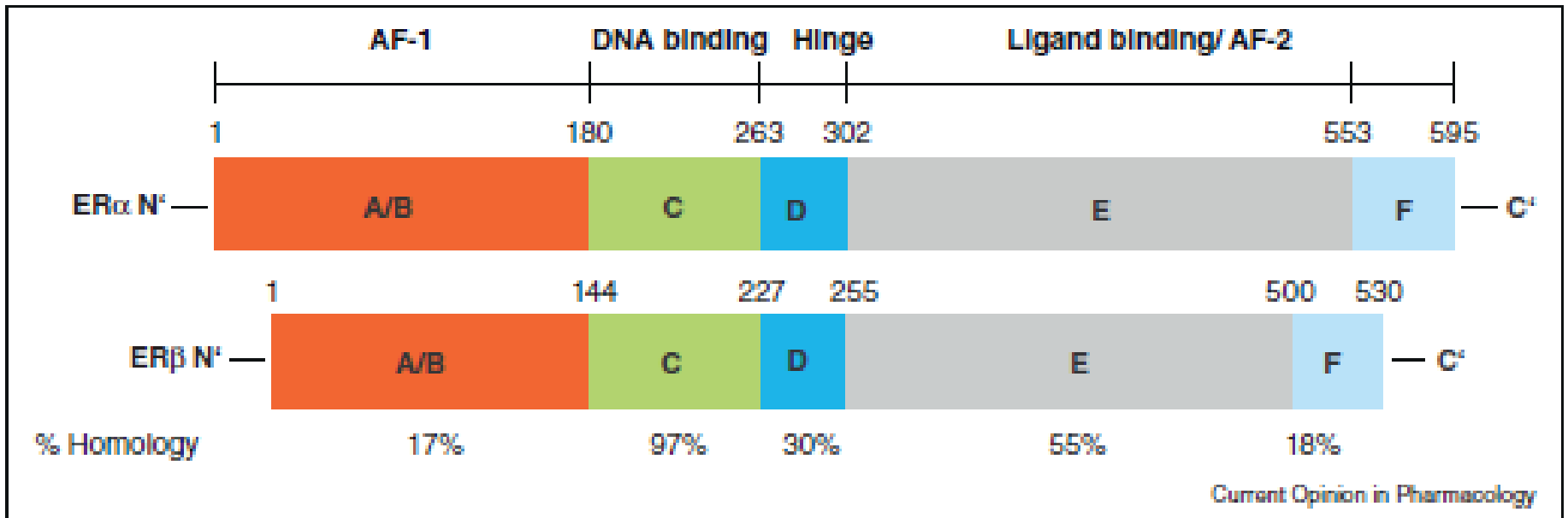
Estrogens and Estrogen Receptors: The Problem for Drug Discovery

- Estrogen- Estrogen Receptor Physiology and Pathophysiologic Conditions
 - Age- Development
 - Reproduction
 - Abnormalities related to estrogen biosynthesis and Receptor Morphology
 - Menopause- Estrogen Deficiency

- Differences in ER α and ER β Function

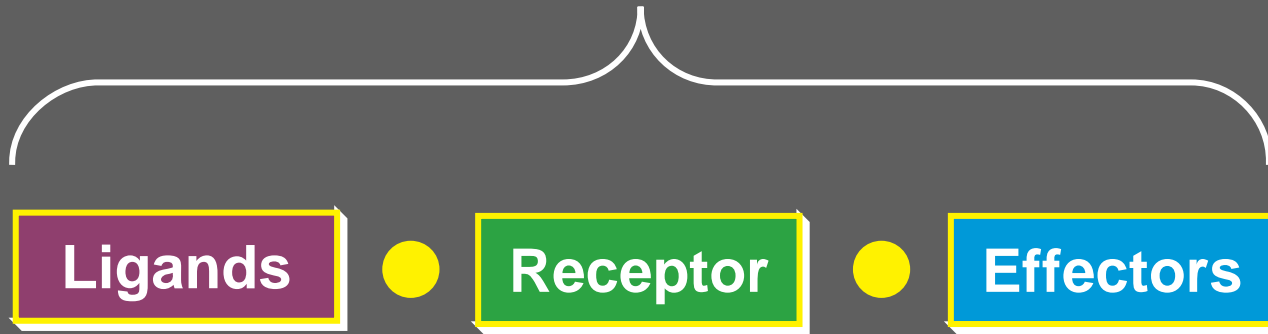
- ER- Ligand Mechanism of Action
 - Genomic and Non-Genomic effects
 - Tissue distribution
 - Obligatory effectors (Co-regulatory proteins, Transcription factors, Response elements etc.)

Biological Effects of Estrogens Are Mediated by ER α and β



Complexities of Estrogen Receptor Biology

“Interactions”



Ligands

- natural
- synthetic
- environmental

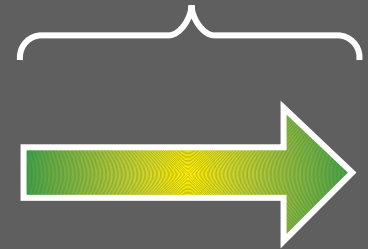
Receptor

- subtypes
- isoforms
- splice variants

Effectors

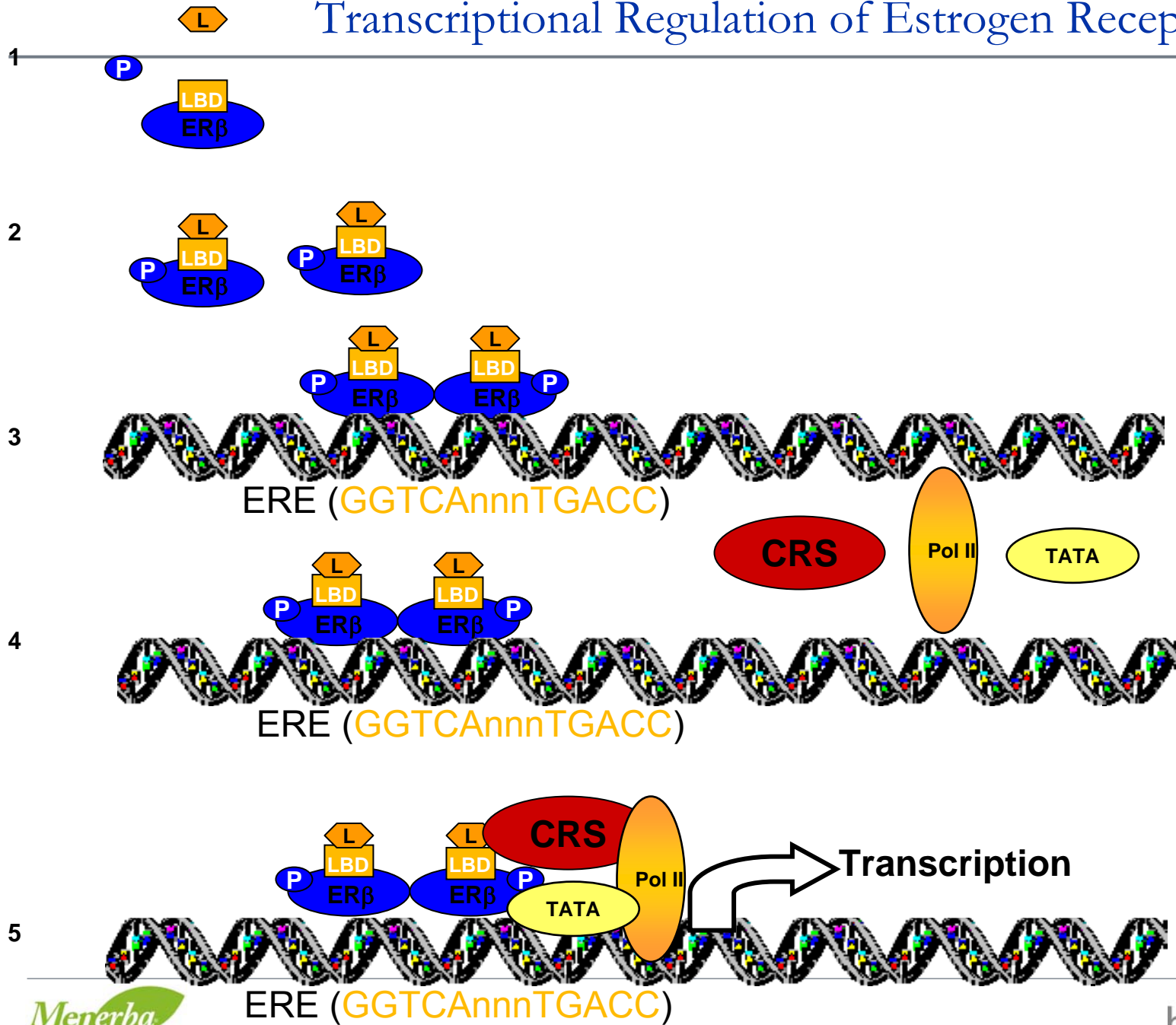
- DNA response elements
- Co-regulators
activators
repressors
- Other TFs • REs

“Actions”

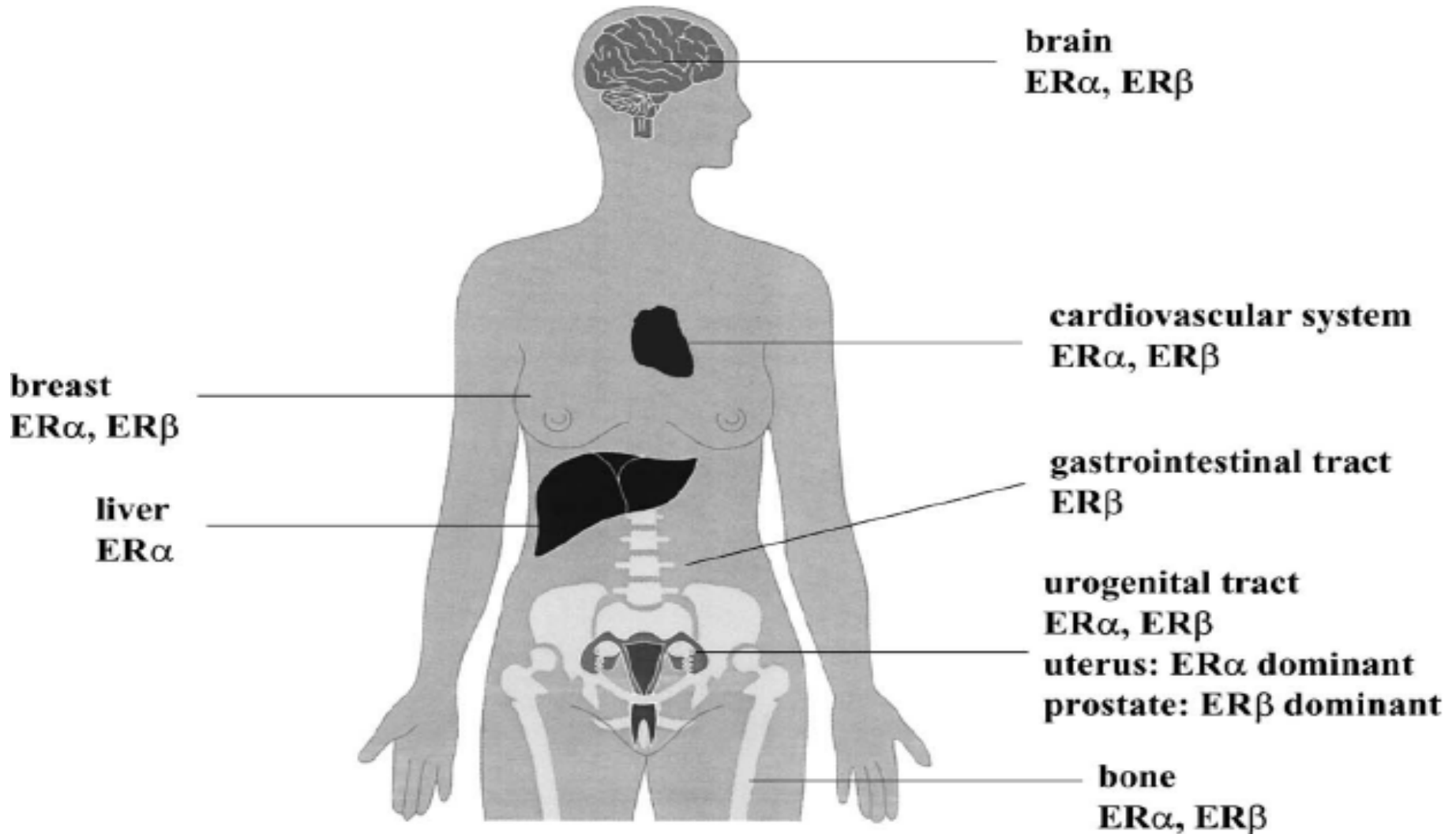


**TRANSCRIPTION
OTHER Actions**

Transcriptional Regulation of Estrogen Receptor β



Tissue distribution of ER α and ER β



Discovering Drugs for Menopause

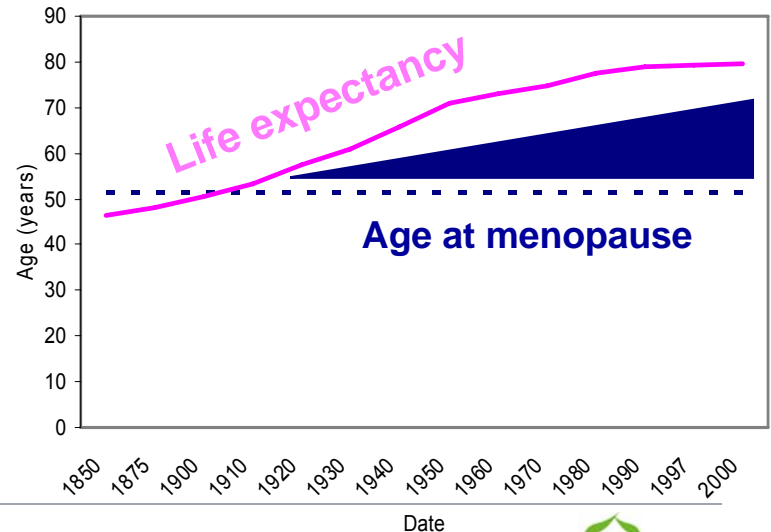
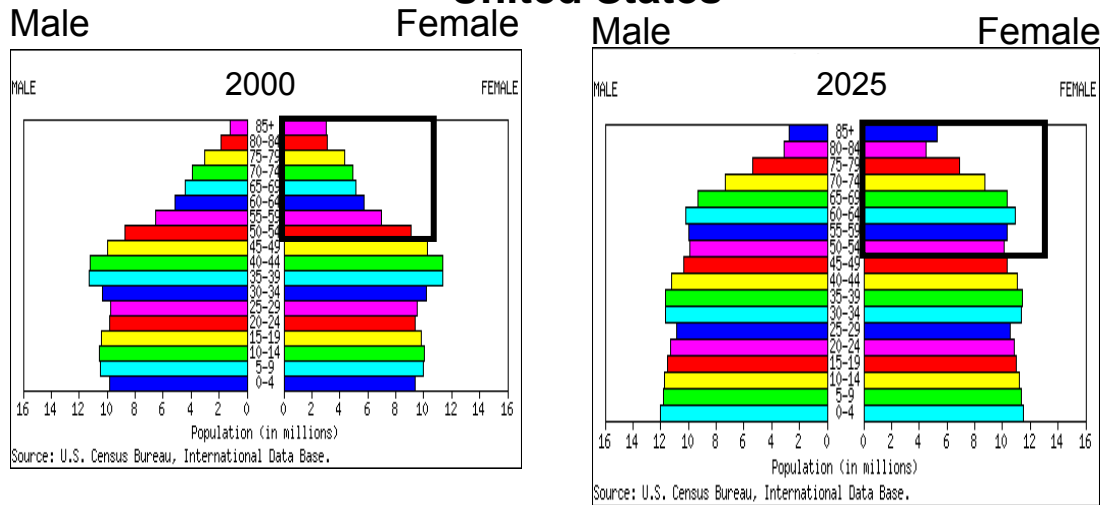
■ Symptom Management

- Hot flashes
- Urogenital atrophy
- Depression
- Insomnia

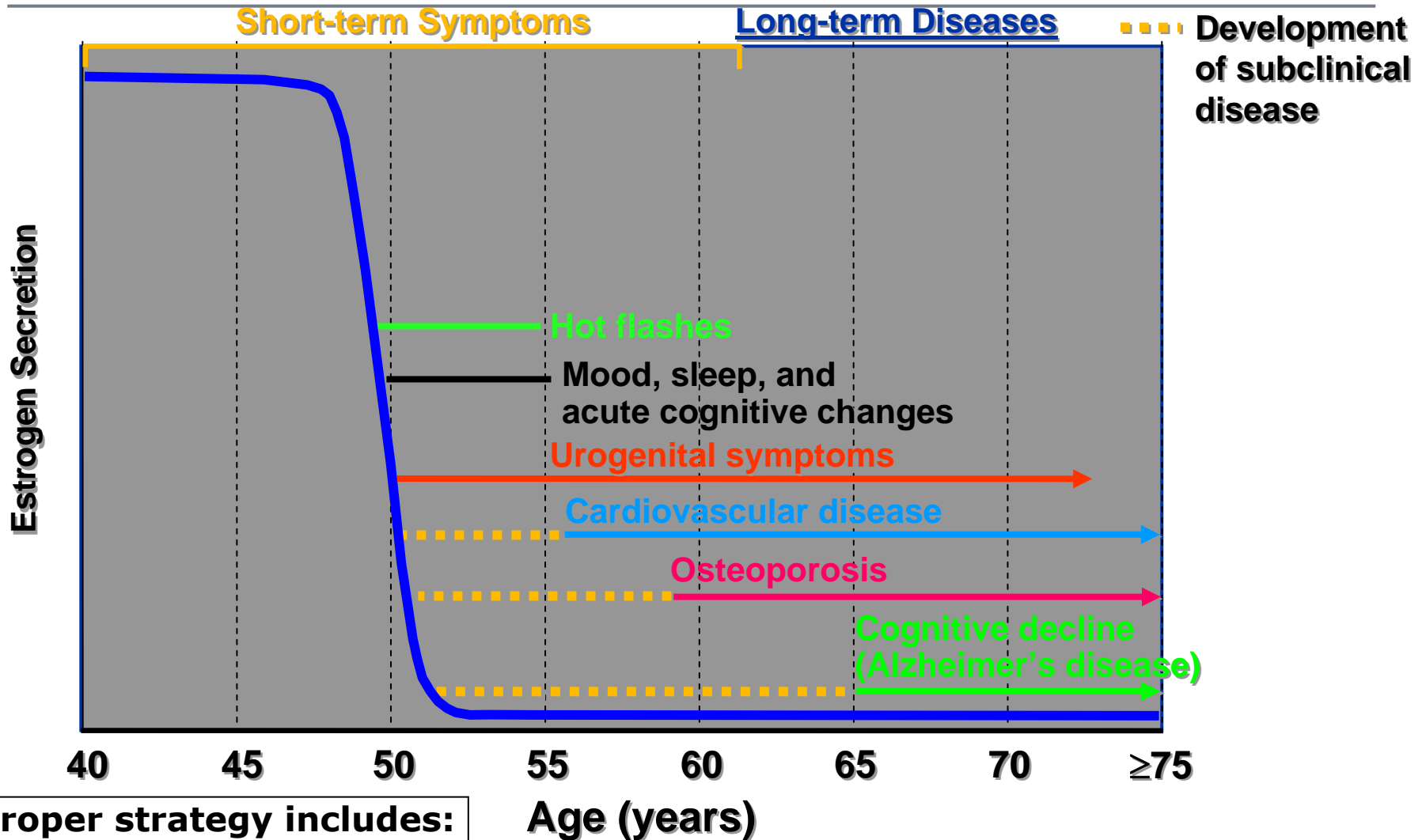
■ Post menopausal increased risk

- Breast cancer
- Cardiovascular disease
- Metabolic syndrome/ Type 2 Diabetes
- Dementia/ Alzheimer's disease
- Osteoporosis

United States



Age and the Menopausal Transition



Proper strategy includes:

- Symptom management
- Treatment of Disease
- Prevention of Disease

Example: Menopause and Insomnia

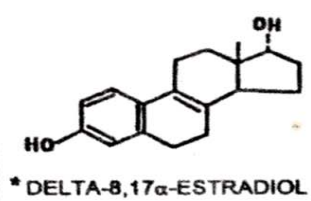
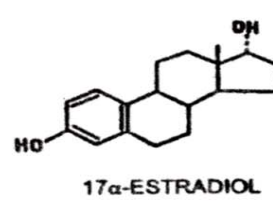
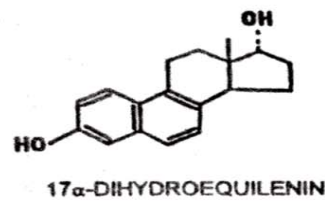
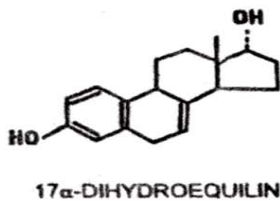
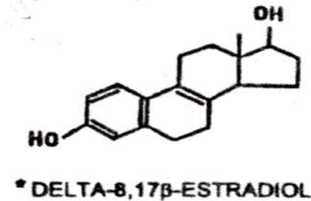
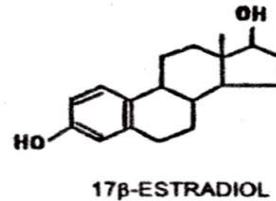
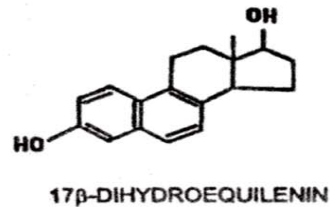
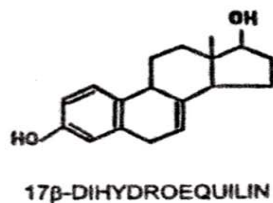
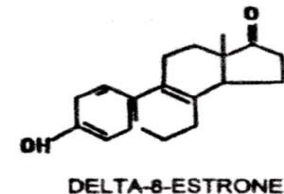
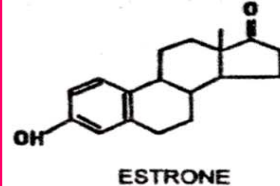
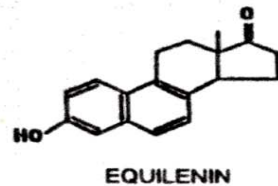
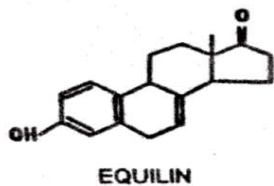
- 95% of menopausal women suffer from sleep difficulties and 85% suffer from night sweats (Berg et al. 2008).
- Menopausal women who suffered from insomnia related to night time awakenings experienced a significantly greater proportion of impairment in their daily activities. These women experienced an average of 47.8% activity impairment compared to women without night time awakenings ($P < 0.001$) (Bolge et al. 2010).
- It has also been estimated that menopausal women who suffered from insomnia related to night time awakenings had more Emergency Department visits in a 6-month period than did those who did not experience insomnia. (Bolge et al. 2010).
- Menopausal women who suffered from insomnia related to night time awakenings also had 16% greater work productivity loss than did those who did not experience insomnia. This 16% equated to a loss of 6.4 hours of work during a 40-hour work week and 8 weeks of lost productivity per year per person (Bolge et al. 2010).
- In a recently reported economic translation within one Canadian province, Quebec, with a population of just more than 7.5 million, data was obtained from 948 adults, 60% women, mean age, 43.7 years. Insomnia was estimated to cost \$6.6 billion CAD. The largest proportion of annual expenses (76%) was attributed to insomnia-related work absences (\$970.6 million CAD) and reduced productivity (\$5.0 billion CAD) (Daley et al. 2009).

Example: Menopause and Cardiovascular Disease

- Cardiovascular disease is the primary cause of death in women in Western countries.
- Among 411 women in the Study of Women's Health Across the Nation (SWAN), hot flashes were related to concurrently assessed carotid intima media thickening (IMT) at baseline and follow-up. Moreover, women reporting hot flashes at both study visits had significantly increased follow-up IMT relative to women reporting no hot flashes at either visit. Results indicate that hot flashes are associated with increased carotid intima media thickening, a marker of subclinical CVD.
- Women in the SWAN study who were in the early postmenopause were twice as likely to have LDL cholesterol levels higher than national recommended guidelines for healthy cholesterol levels, compared to premenopausal women (Derby et al. 2009). By the time of their final menstrual period, close to one-third of SWAN women had the metabolic syndrome, a cluster of heart disease risk factors (Janssen et al. 2008).
- In the SWAN Heart Study which evaluated 492 women 45 to 58 years, hot flashes were associated with significantly lower flow-mediated dilation and greater coronary artery and aortic calcification in age- and race-adjusted models. Significant associations between hot flashes and flow-mediated dilation and aortic calcification remained in models adjusted for cardiovascular disease risk factors and estradiol (Thurston et al. 2008).
- In a Swedish population-based sample of 5,857 women aged 50-64 years women with symptoms of hot flashes had a statistically higher BMI, waist hip ratio, total cholesterol level, LDL level, triglycerides level, glucose level, systolic and diastolic blood pressure. These findings demonstrate that women with vasomotor symptoms have a less favorable cardiovascular risk profile (Gast et al. 2010).
- In 302 women participating in the Healthy Women Study, a longitudinal study of cardiovascular risk during perimenopause and postmenopause, among women using hormone therapy, a longer history of reported hot flashes was associated with increased aortic calcification, controlling for traditional cardiovascular risk factors (Thurston et al. 2010).

Menopause Hormone Therapy- Steroidal Estrogens

- Premarin- equine estrogens from pregnant mare's urine
- 17β -estradiol
- Ethynil- estradiol
- Estrone, Estriol, 17β -estradiol mixtures



Risks Associated with Hormone Therapy

Outcome	Relative Risk	Publication
Coronary heart disease	1.29 (E+P)	Writing Group for the WHI Investigators. <i>Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the WHI Randomized Controlled Trials</i> . JAMA. 2002; 288 (3): 321-333.
Coronary heart disease Death	1.18 (E+P)	WHI Paper
Nonfatal myocardial infarction	1.32 (E+P)	WHI Paper
Stroke	1.41(E+P)	WHI Paper
Venous thromboembolic disease	2.11 (E+P)	WHI Paper
Cancer	1.03 (E+P)	WHI Paper
Invasive breast cancer	1.26 (E+P)	WHI Paper
Ovarian cancer	1.58 (E+P)	Anderson GL; Judd HL; et al. <i>Effects of Estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: The WHI randomized Trial</i> . JAMA. 2003 Oct 1; 290 (13): 1739-48.
Endometrial cancer	2.30 (E) 9.50 (E) >10 yr	Grady; Gebretsadik T; Kerlikowski K; et al. <i>Hormone replacement therapy and endometrial cancer risk: a meta-analysis</i> . Obstet Gynecol. 1995 Feb;85(2):304-13
Global index*	1 .15 (E+P)	WHI Paper
Dementia	2.05 (E+P)	Shumaker, S; Legault C; Rapp S; et al. <i>Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the WHI memory study: a randomized controlled trial</i> . JAMA. 2003; 289(20): 2651-2662.
Urinary incontinence (stress)	1.87(E alone)	Hendrix, S; Cochrane, B; Nygaard, I. <i>Effects of Estrogen with and without Progestin on Urinary Incontinence</i> . JAMA. 2005; 293(8): 935-948.

*Global index: the first event for each participant from among the following types: CHD, stroke, PE, breast cancer, endometrial cancer, colorectal cancer, hip fracture and death due to other causes.

Risks Associated with Hormone Therapy, Continued

Outcome	Relative Risk	Publication
Lung cancer incidence	1.23 (E+P)	Chlebowski, R; Schwartz, AG, Wakelee, H, et al. <i>Oestrogen plus progestin and lung cancer in postmenopausal women (WHI trial): a post-hoc analysis of a randomised controlled trial</i> . Lancet. 2009 Oct 10; 374 (9697): 1243-51.
NSCLC (non-small lung cancer)	1.28 (E+P)	Chlebowski, R; Schwartz, AG, Wakelee, H, et al. <i>Oestrogen plus progestin and lung cancer in postmenopausal women (WHI trial): a post-hoc analysis of a randomised controlled trial</i> . Lancet. 2009 Oct 10; 374 (9697): 1243-51.
SCLC (small lung cancer)	1.58 (E)	Chlebowski, R; Anderson, G; Manson, JE. ; et all. <i>Lung Cancer Among Postmenopausal Women Treated with Estrogen Alone in the WHI Randomized Trial</i> . J Natl Cancer Inst 2010; 102: 1413-1421
Death from lung cancer	1.71 (E+P)	Chlebowski, R; Schwartz, AG, Wakelee, H, et al. <i>Oestrogen plus progestin and lung cancer in postmenopausal women (WHI trial): a post-hoc analysis of a randomised controlled trial</i> . Lancet. 2009 Oct 10; 374 (9697): 1243-51.
Death from NSCLC	1.87 (E+P)	Chlebowski, R; Schwartz, AG, Wakelee, H, et al. <i>Oestrogen plus progestin and lung cancer in postmenopausal women (WHI trial): a post-hoc analysis of a randomised controlled trial</i> . Lancet. 2009 Oct 10; 374 (9697): 1243-51.
Death from SCLC	2.11 (E)	Chlebowski, R; Anderson, G; Manson, JE. ; et all. <i>Lung Cancer Among Postmenopausal Women Treated with Estrogen Alone in the WHI Randomized Trial</i> . J Natl Cancer Inst 2010; 102: 1413-1421
Increase in invasive breast cancer	1.25 (E+P)	Chlebowski, R; Anderson G; Gass, M, et al. <i>Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women</i> . JAMA. 2010; 304(15): 1684-1692.
Increase in deaths of breast cancer	1.96 (E+P)	Chlebowski, R; Anderson G; Gass, M, et al. <i>Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women</i> . JAMA. 2010; 304(15): 1684-1692.
Cholecystitis (gallbladder attack)	2.1 (HRT)	Grodstein F; Colditz GA; Stampfer MJ. <i>Postmenopausal hormone use and cholecystectomy in a large prospective study</i> . Obstet Gynecol. 1994 Jan; 83(1):5-11.
Nephrolithiasis (kidney stones)	1.21 (HRT)	Maalouf N; Sato, A; Welch B; et al. <i>Postmenopausal hormone use and the risk of Nephrolithiasis</i> . Arch Intern Med. 2010; 170(18): 1678-1685

THE IDEAL ESTROGEN:

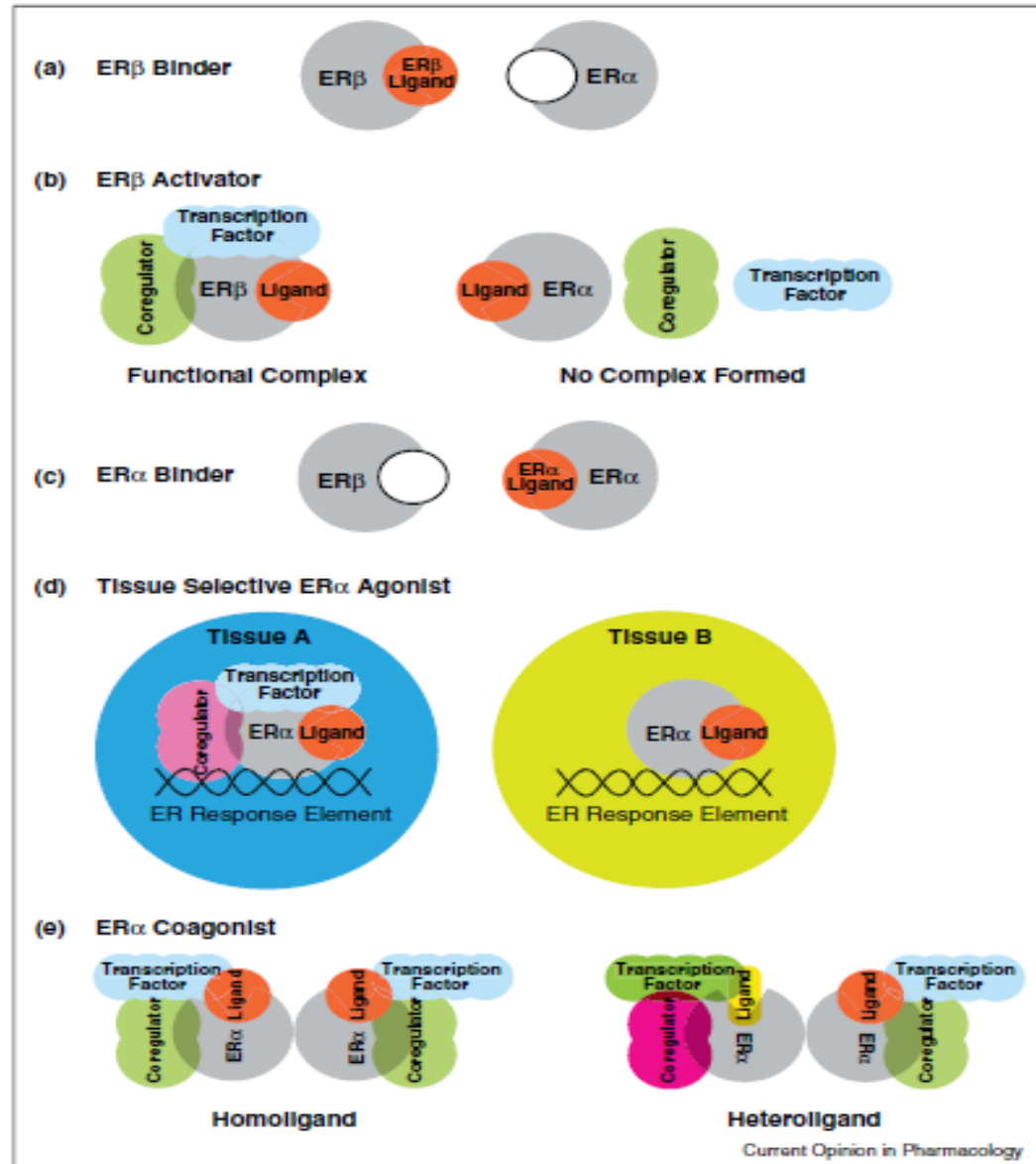
	Bone +	Breast +	Uterus +	Brain +	Liver +	CV +
	Prevents Osteoporosis	Prevents Breast Cancer	No Endometrial Cancer	Prevents Hot flushes	No Clotting	No Stroke, CHD
Estradiol	+	-	-	+	-	-
Raloxifene	+	+	+	-	-	-
Tamoxifen	+	+	-	-	-	-

+ Positive Effect

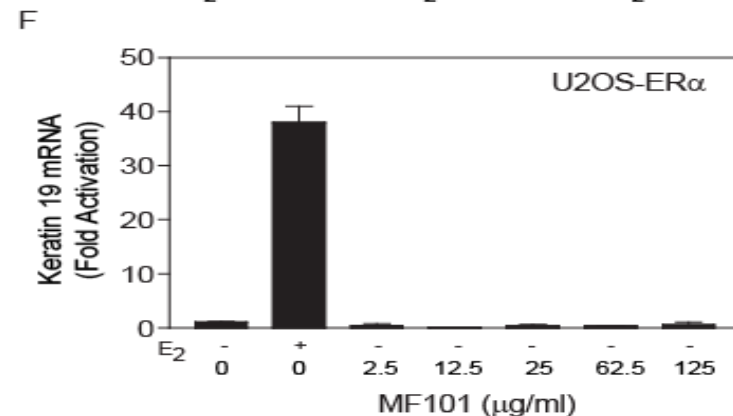
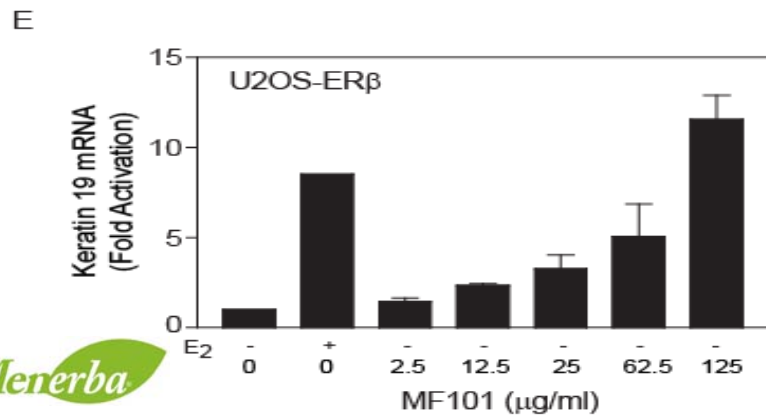
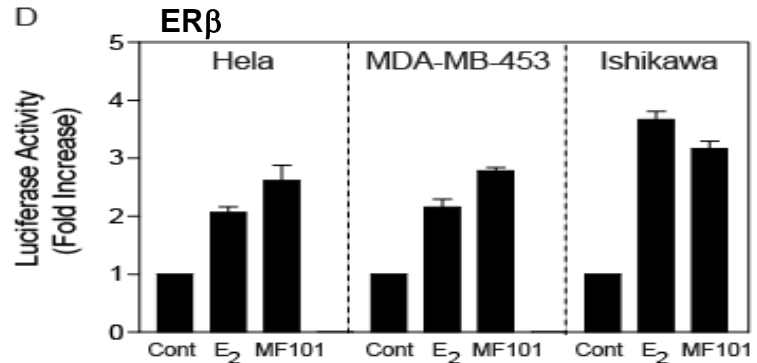
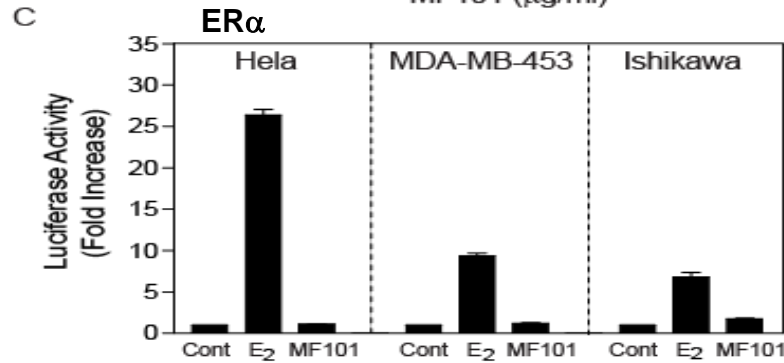
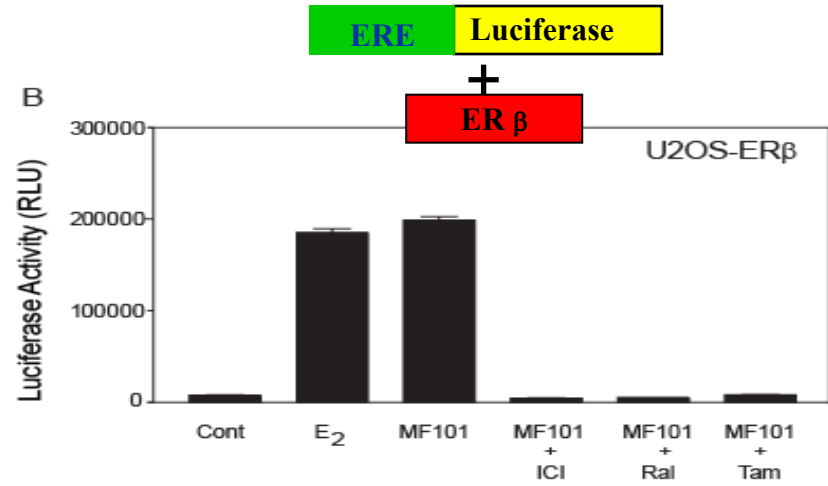
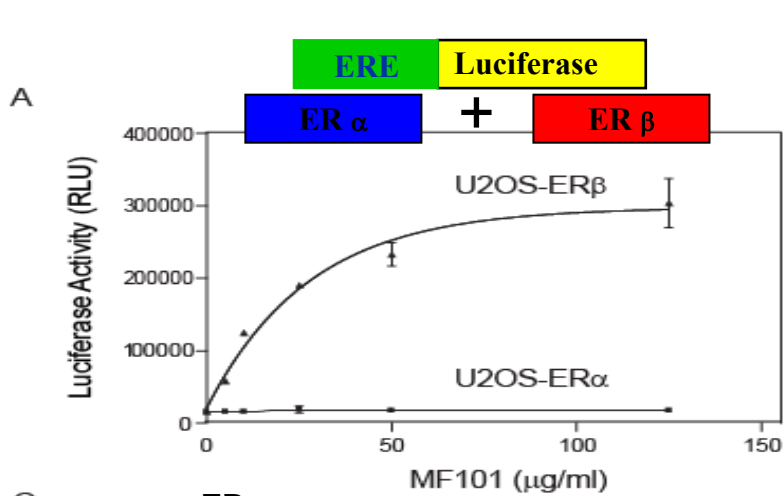
- Negative Effect

Classes of ER Selective Agonists

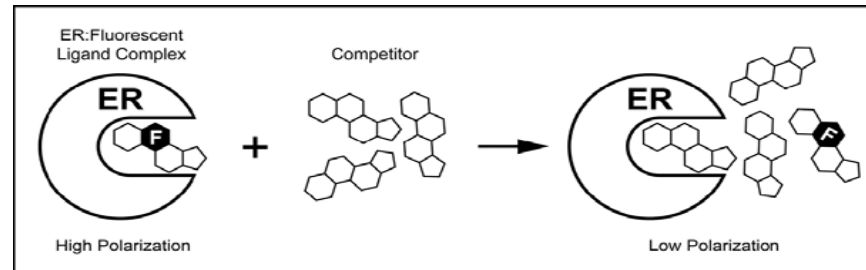
- Binding selectivity to each receptor subtype
- Selective recruitment of effectors
- Tissue selective transactivation
- Co- agonist activity



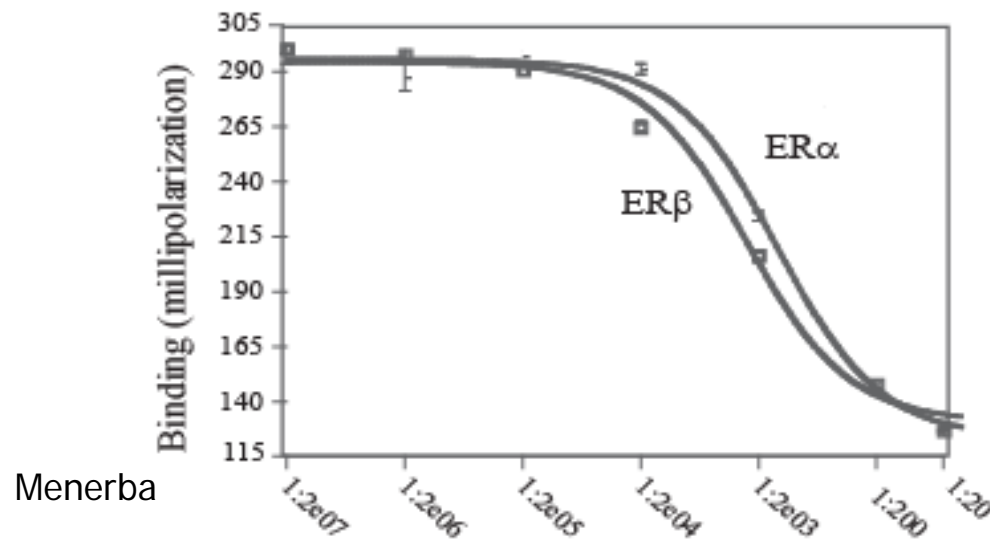
Menerba transcriptional regulation is dependant on ERb expression



Menerba Binds Equally to ER α and ER β



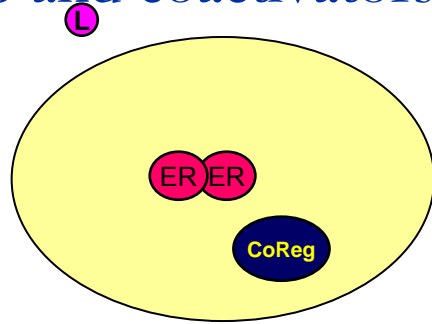
fluorescence polarization based method



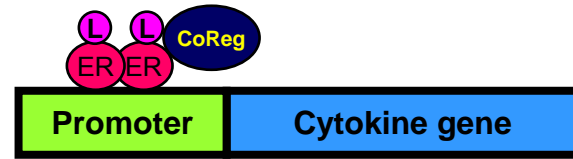
DL2

Surprisingly, The binding data shows that MF101 Binds Equally to ERa and ERb
Dale Leitman, 3/11/2006

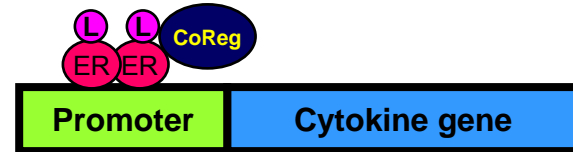
Menerba is ER β -selective because it only recruits ER β and coactivators to target genes



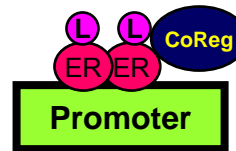
Assemble complex at promoter



Cross-link with Formaldehyde



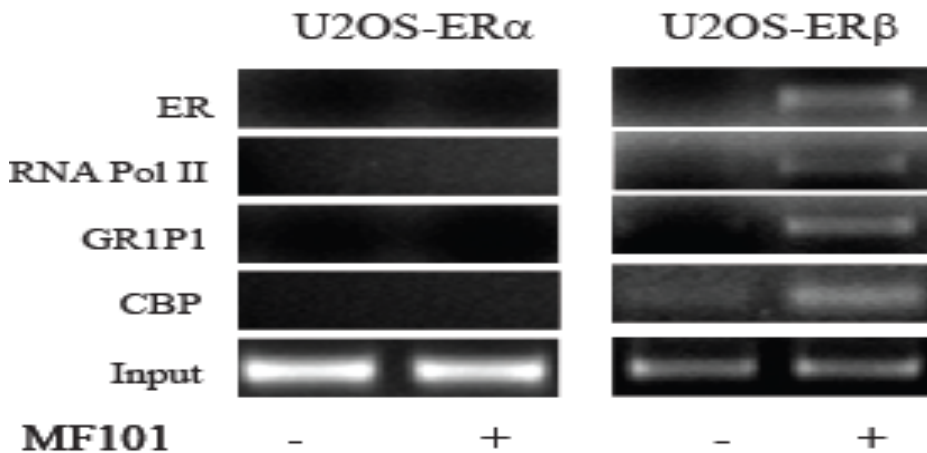
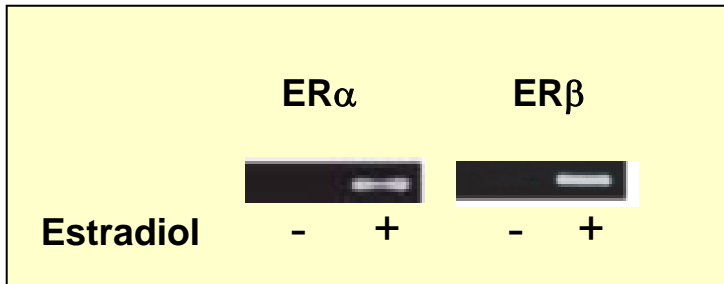
Shear DNA into 200-500 bp



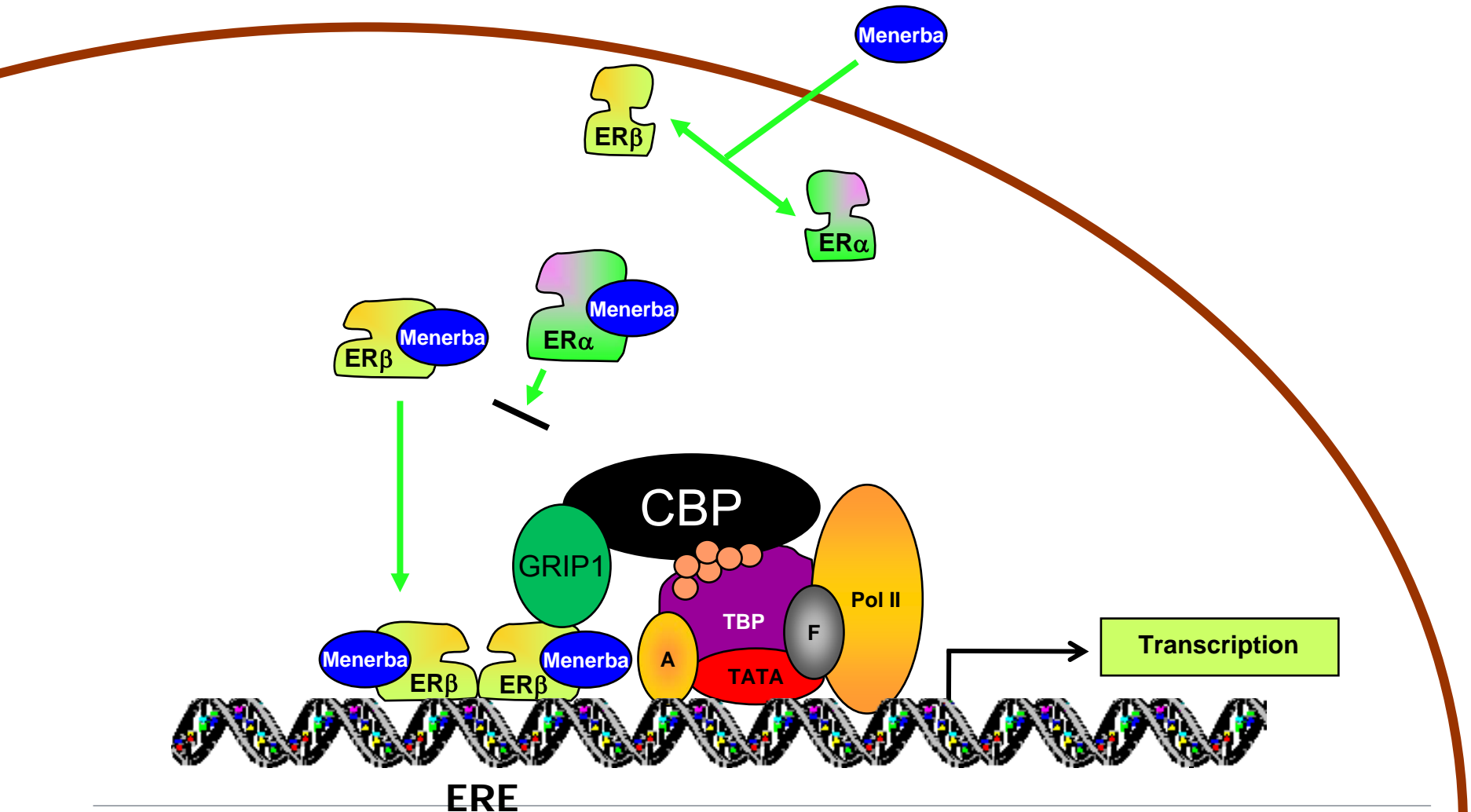
Immunoprecipitate with antibodies to ER or CoReg



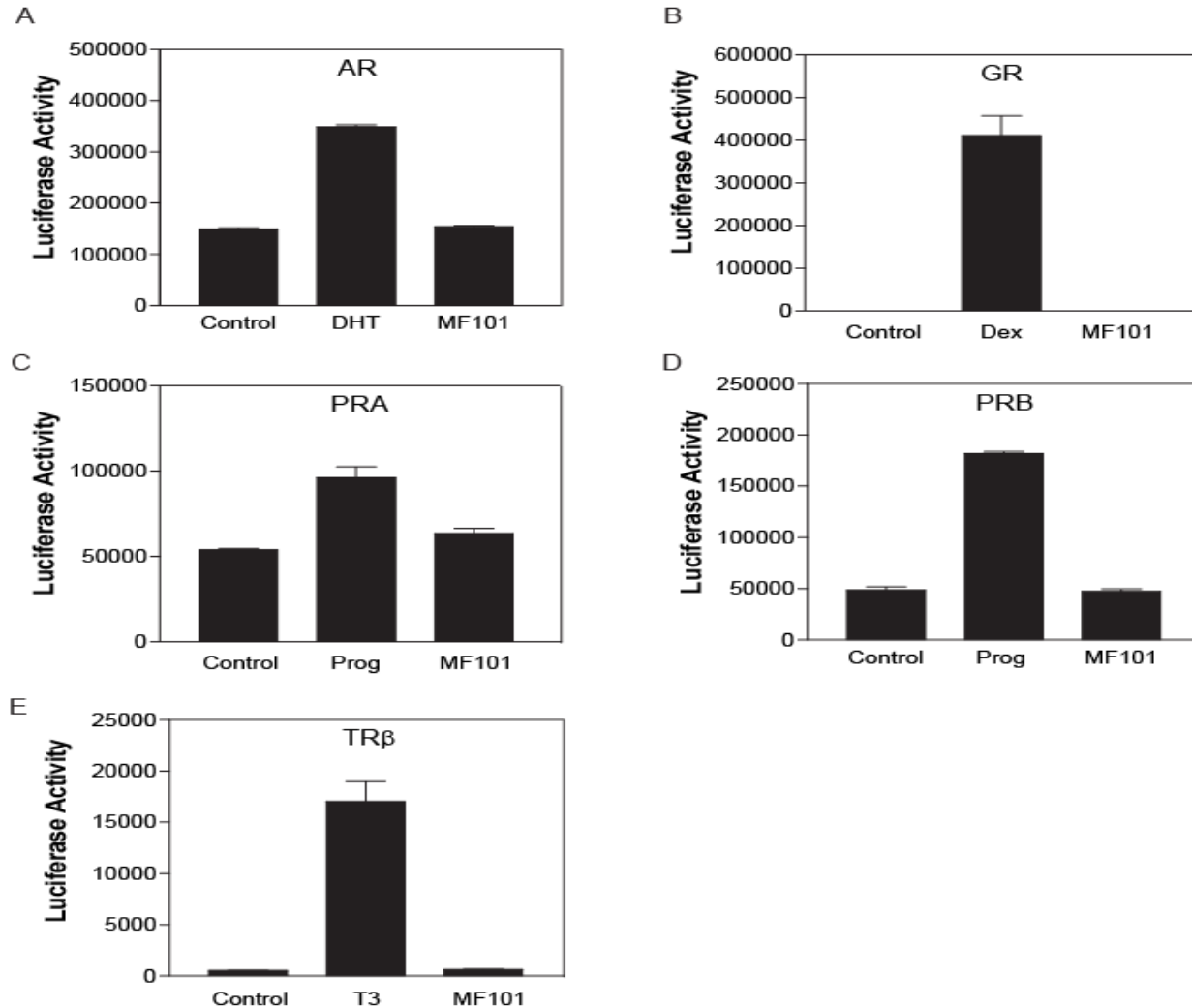
Reverse cross-links



Menerba Selectively Recruits ERβ and Coactivators to Target Genes



Menerba Does NOT Activate Other Steroid Nuclear Receptors

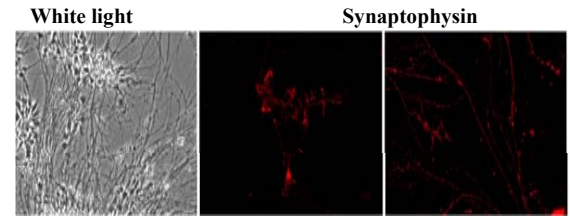
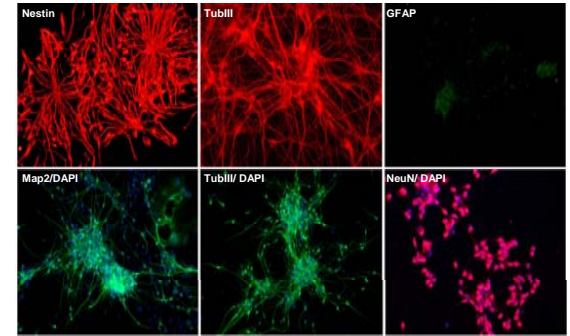


hES Derived Primary Neurons: Screening for ER Functional Selectivity

Mouse ES cells

Embryoid Bodies

Neurons

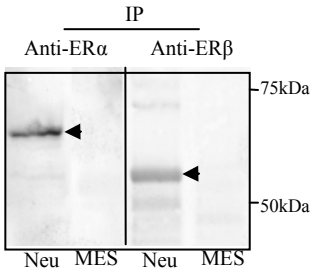


Retinoic Acid

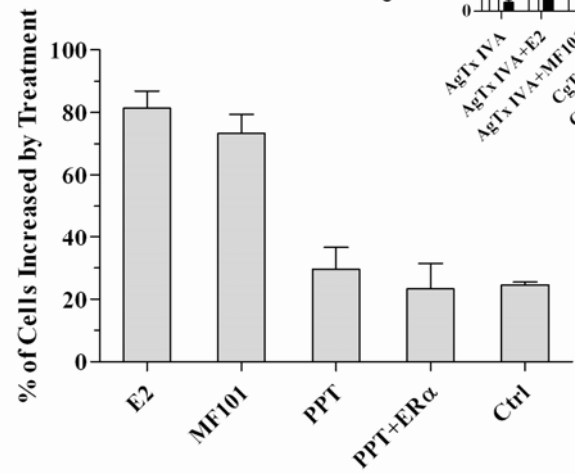
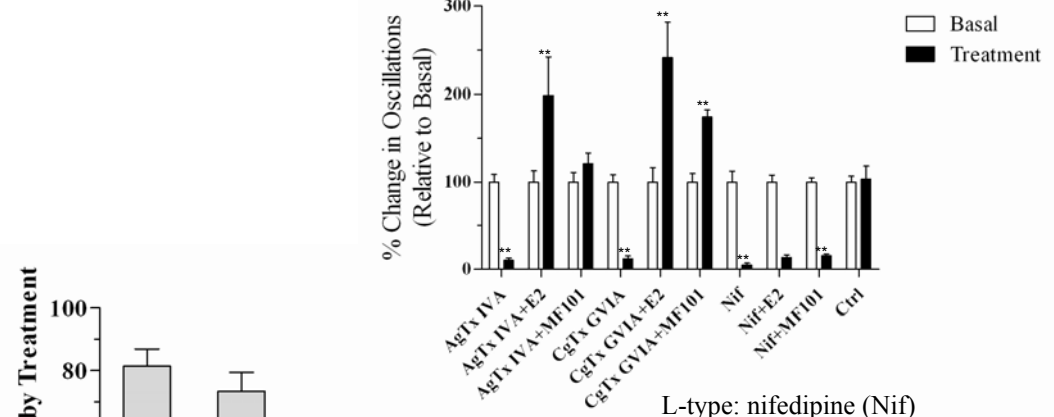
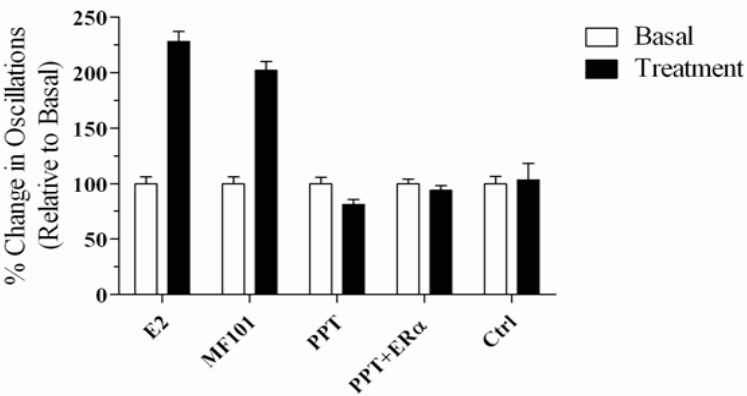
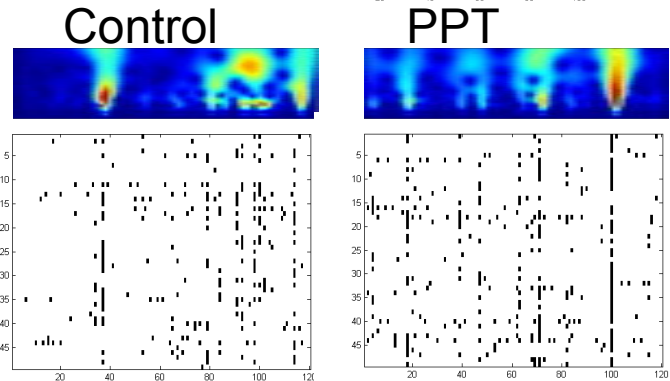
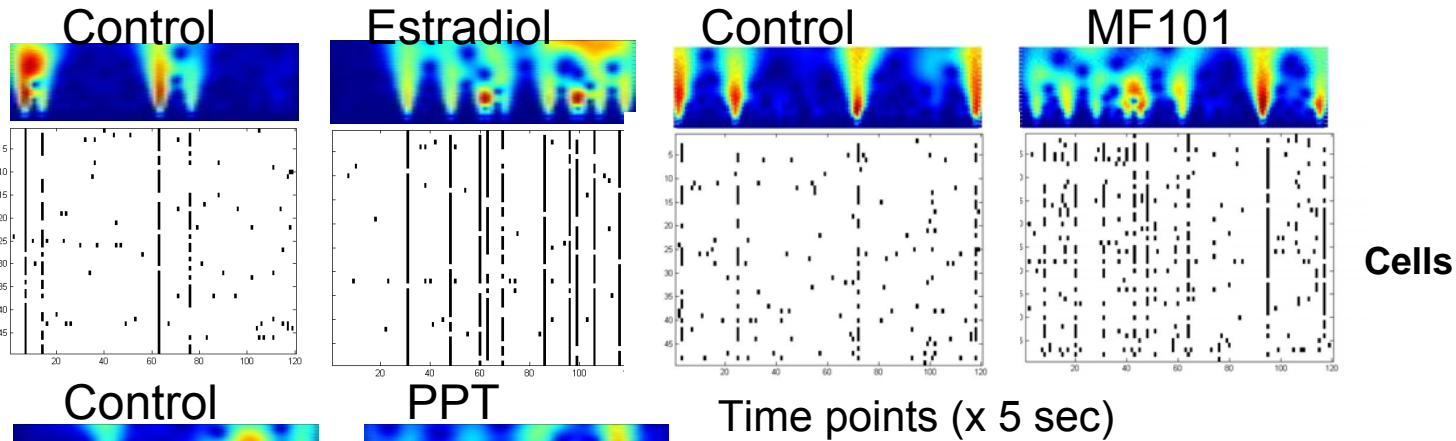
Non-selective estrogen (E2)
ER α -selective estrogen (PPT)
ER β -selective estrogens (MF101)

- Characterization**
- Neuronal Markers
 - Electrophysiology
 - ER α and ER β
 - Coactivators

- Non-Genomic Responses**
- Calcium Oscillations
 - Protein Kinase Assays



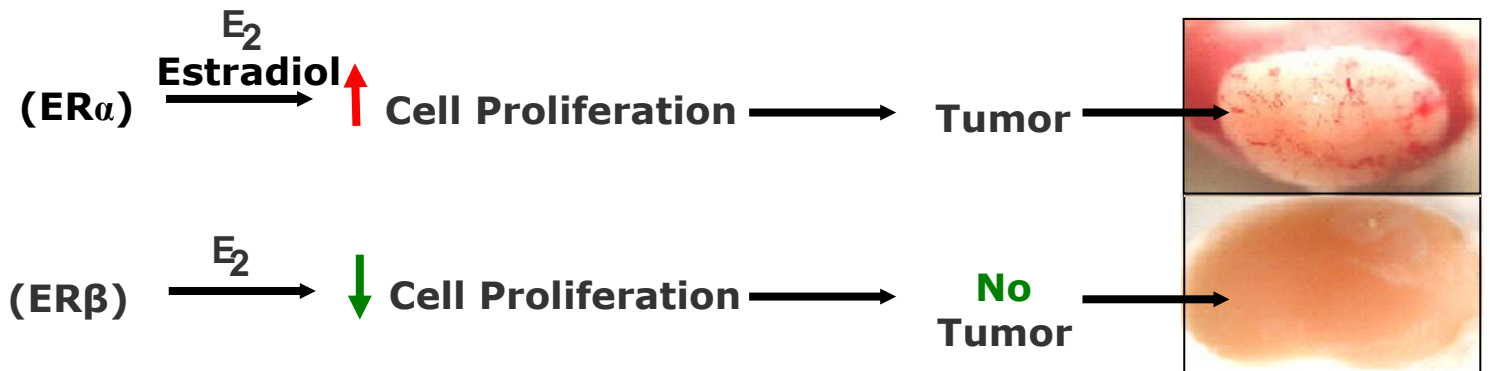
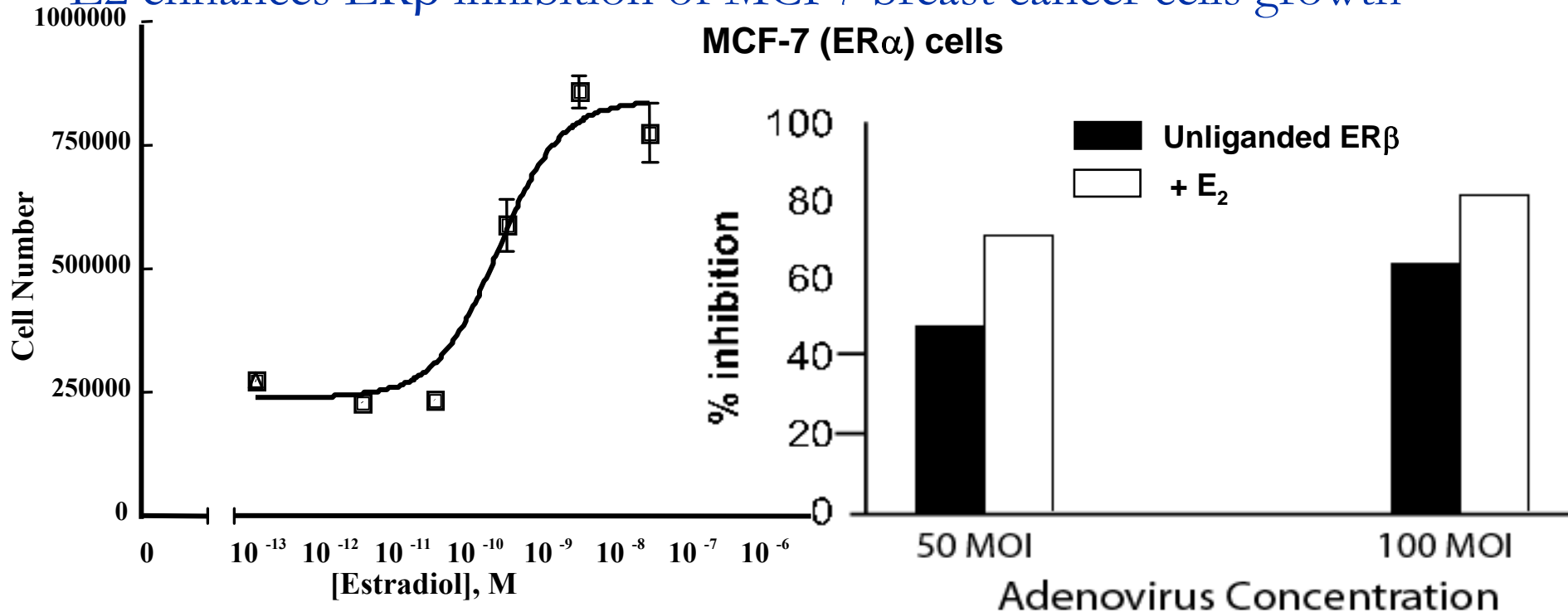
Menerba and E2 Regulate Calcium Oscillations through ERb



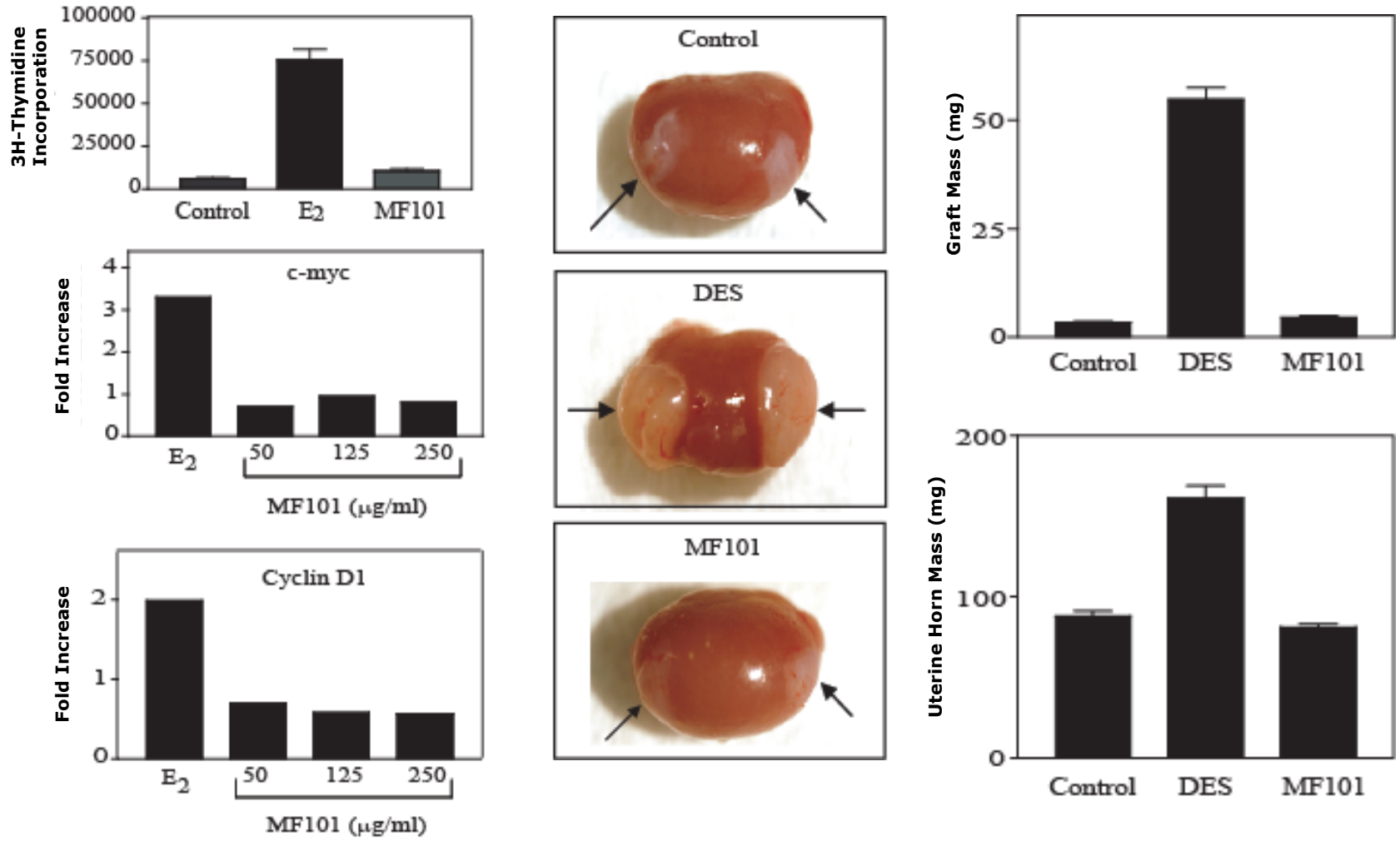
L-type: nifedipine (Nif)
 N-type: ω -conotoxin GVIA (CgTx GVIA)
 P-type: ω -agatoxin IVA (AgTx IVA)

ER α mediates cell proliferation

E2 enhances ER β inhibition of MCF7 breast cancer cells growth

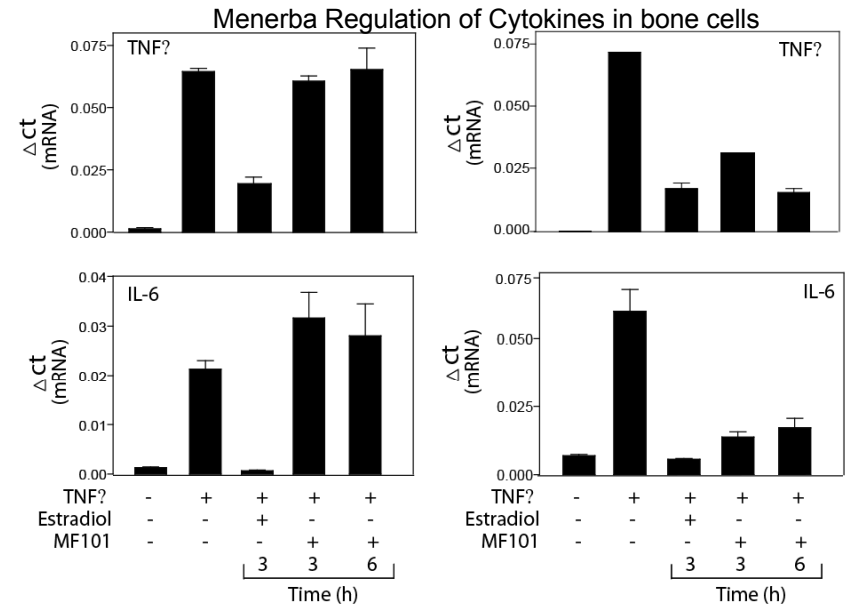
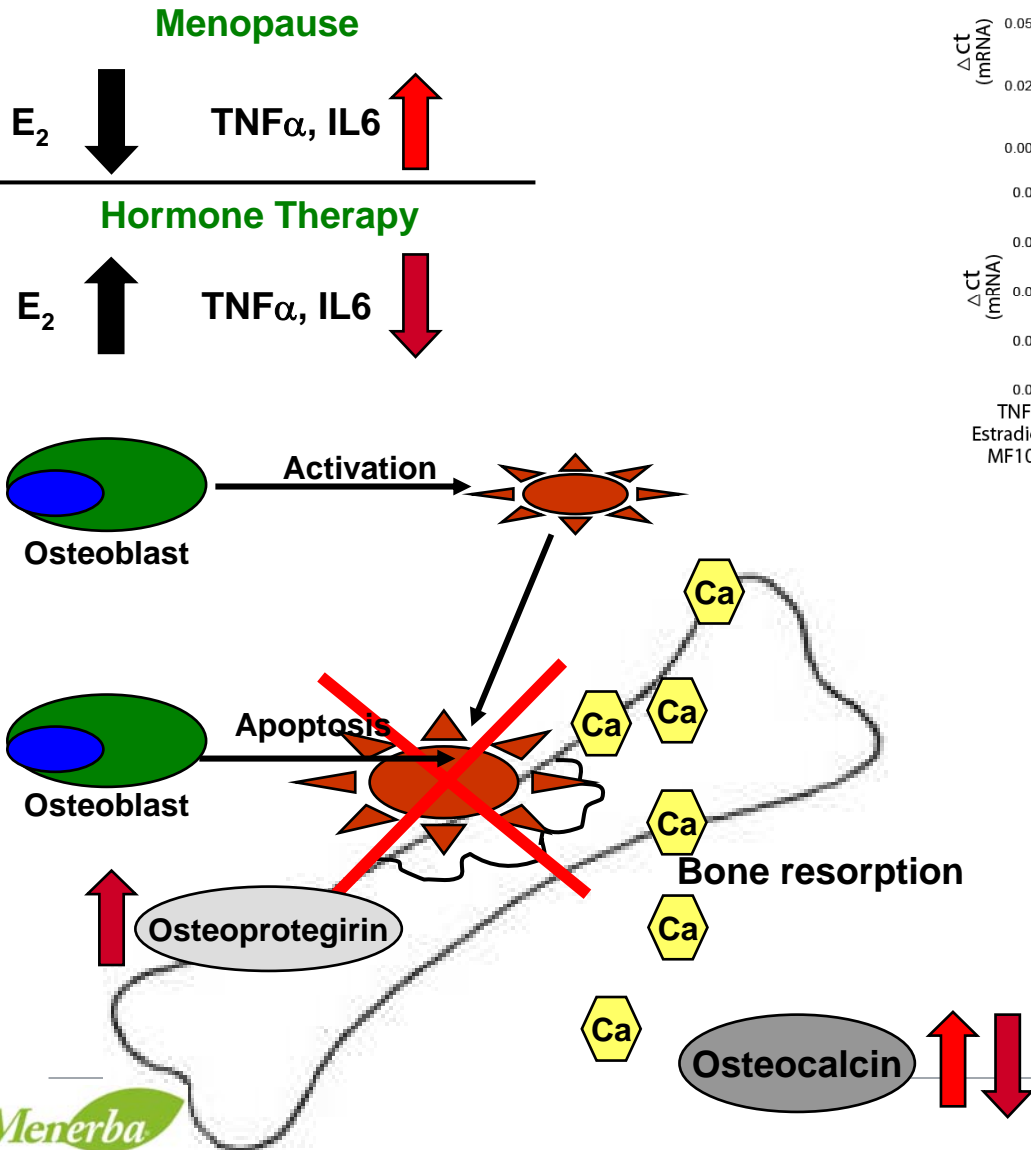


Menerba Does NOT Stimulate Cell Proliferation

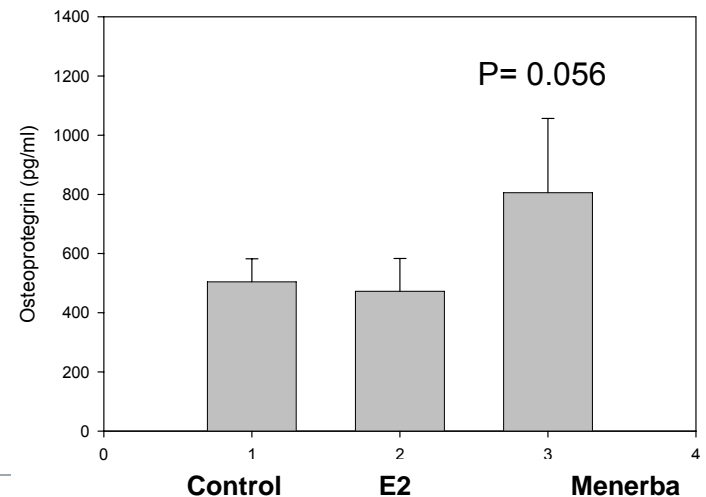


Source: Cvoro A, Endocrinology. November 9, 2006.

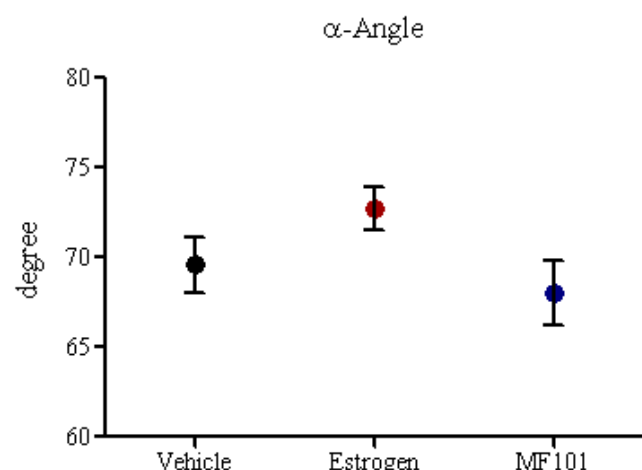
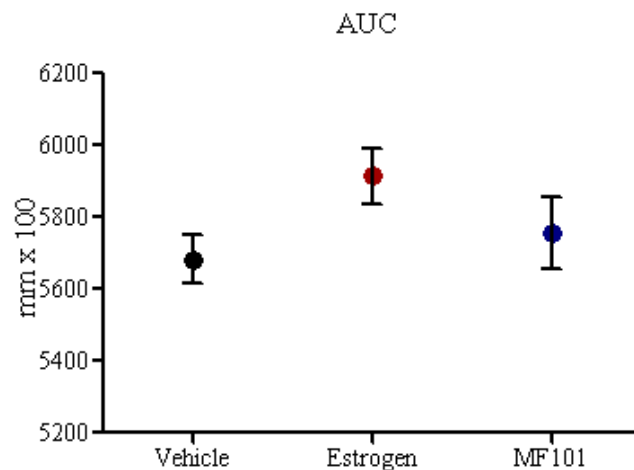
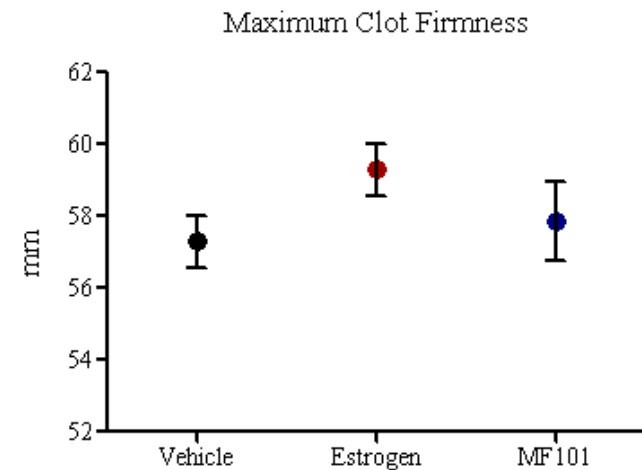
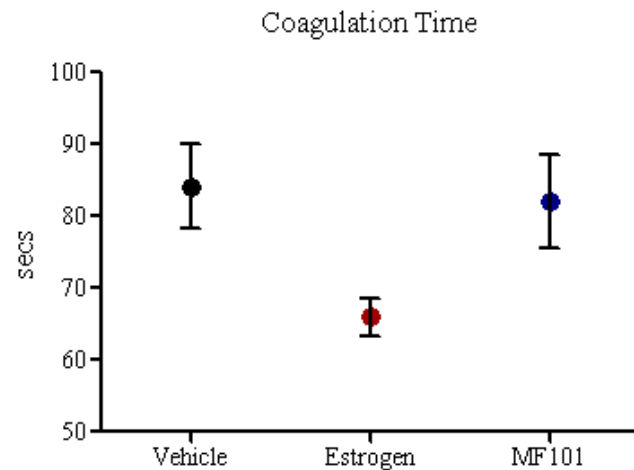
Menerba Effect on Inflammation and Bone



Osteoprotegerin Levels in OVX mice after 32 days of Treatment

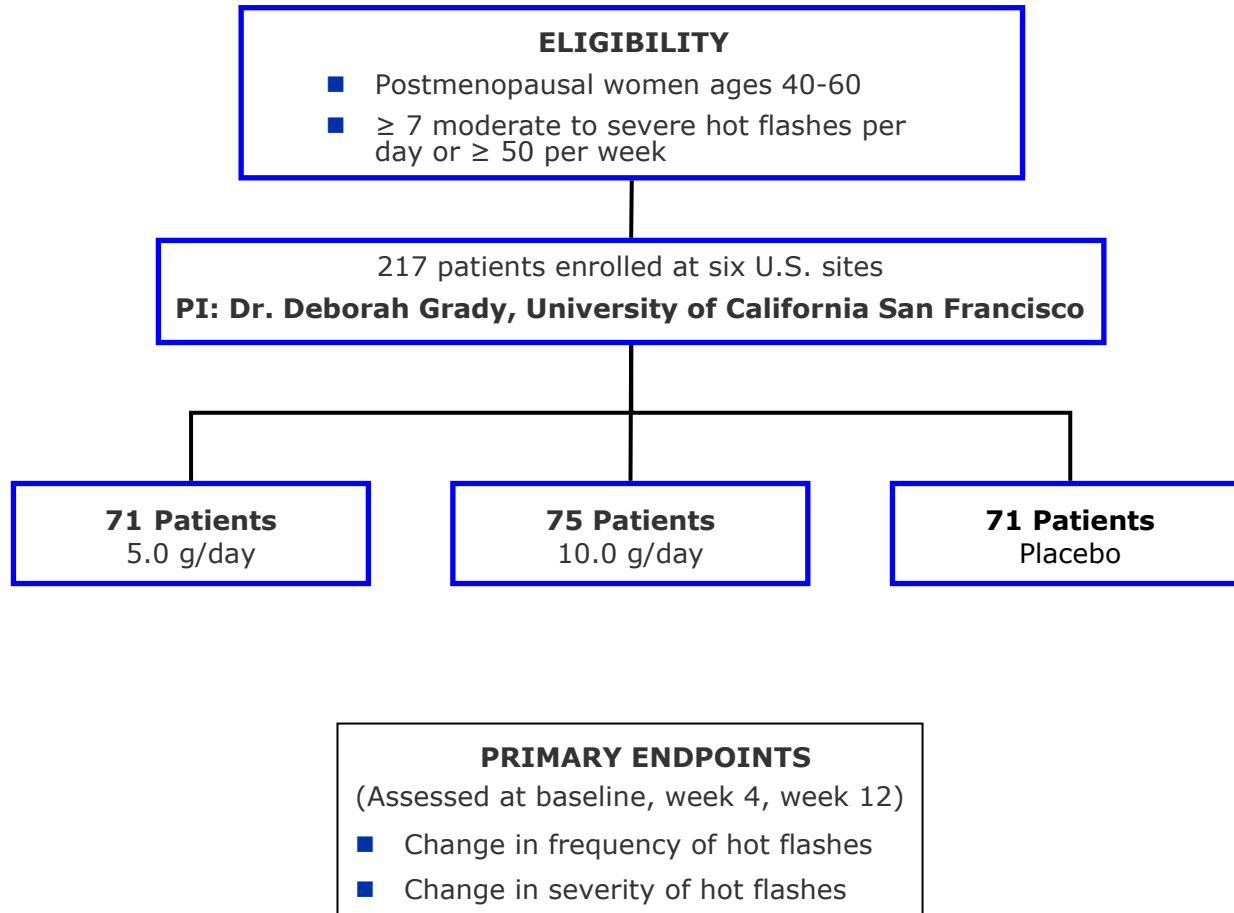


Results: Unlike E2, Menerba does NOT Cause Clotting Changes



mean +/-SEM

Completed Menerba Phase 2 Clinical Trial Design



Note: Dose defined by total amount, not active ingredient.

Phase 2 Baseline Characteristics

Variable	Number (%) / Mean (\pmSD)
Total No. of Participants	217
Age, years, mean (SD)	53.7 (2.8)
Ethnicity, %	
White/Caucasian	174 (80)
Black/African American	28 (13)
Asian	4 (2)
Latina/Hispanic	4 (2)
Native American/American Indian	3 (1)
Multi-ethnic/Mixed Race	1 (0)
Other/Don't know	3 (1)
Education Level, %	
High school or less	38 (18)
Some college/AA degree	70 (32)
College degree or more	109 (50)

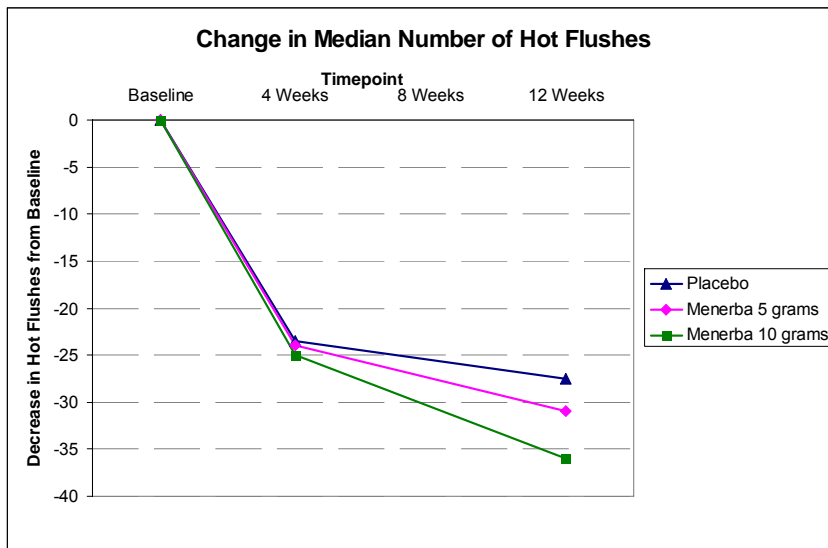
Phase 2 Baseline Characteristics, cont.

Variable	Number (%) / Mean (\pmSD)
Age at Menopause, years, mean (SD)	50.1 (4.3)
Both Ovaries Removed, %	23 (11)
Hysterectomy, %	53 (24)
Endometrial Thickness on TVUS, mm, median (range)	3 (1 - 5)
Prior Estrogen User, %	76 (35)
Follicle Stim. Hormone, mIU/mL, mean (SD)	89.8 (29.9)
Estradiol, pg/mL, mean (SD)	4.4 (9.0)
Total number of hot flashes	9.8 (3.7)
Total number of moderate-severe hot flashes	7.2 (4.0)

Phase 2 Clinical Trial Results

Efficacy

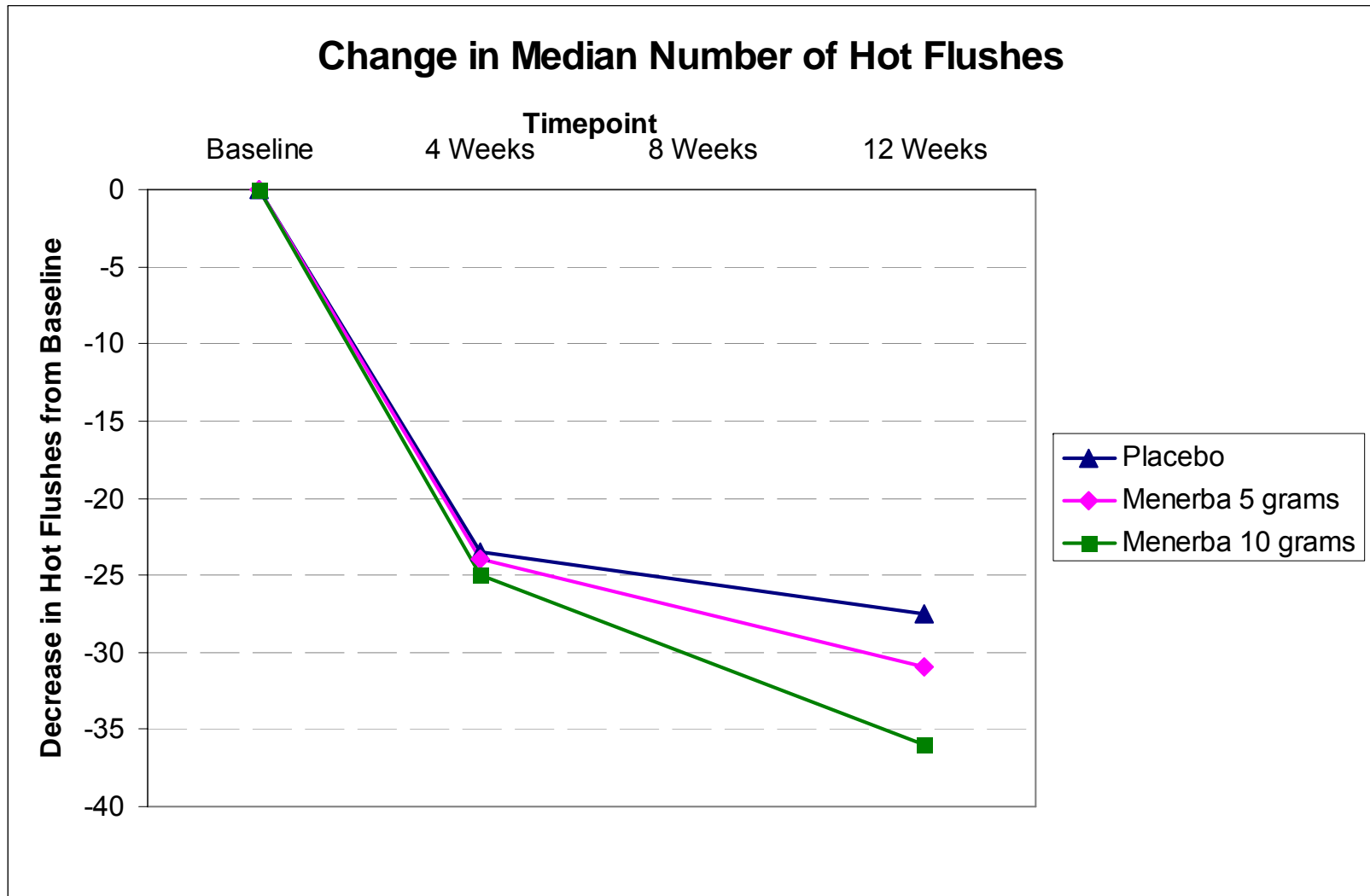
- Menerba demonstrated statistically significant ($p=0.04$) results in the high dose group
- 62% reduction in moderate to severe hot flashes
- Odds ratio of 60% reduction on Menerba vs. placebo was 2.4 ($p=0.02$)
- Menerba exhibits a clear dose response curve
- Higher dose (3x) to be included in Phase 3 trial



Safety

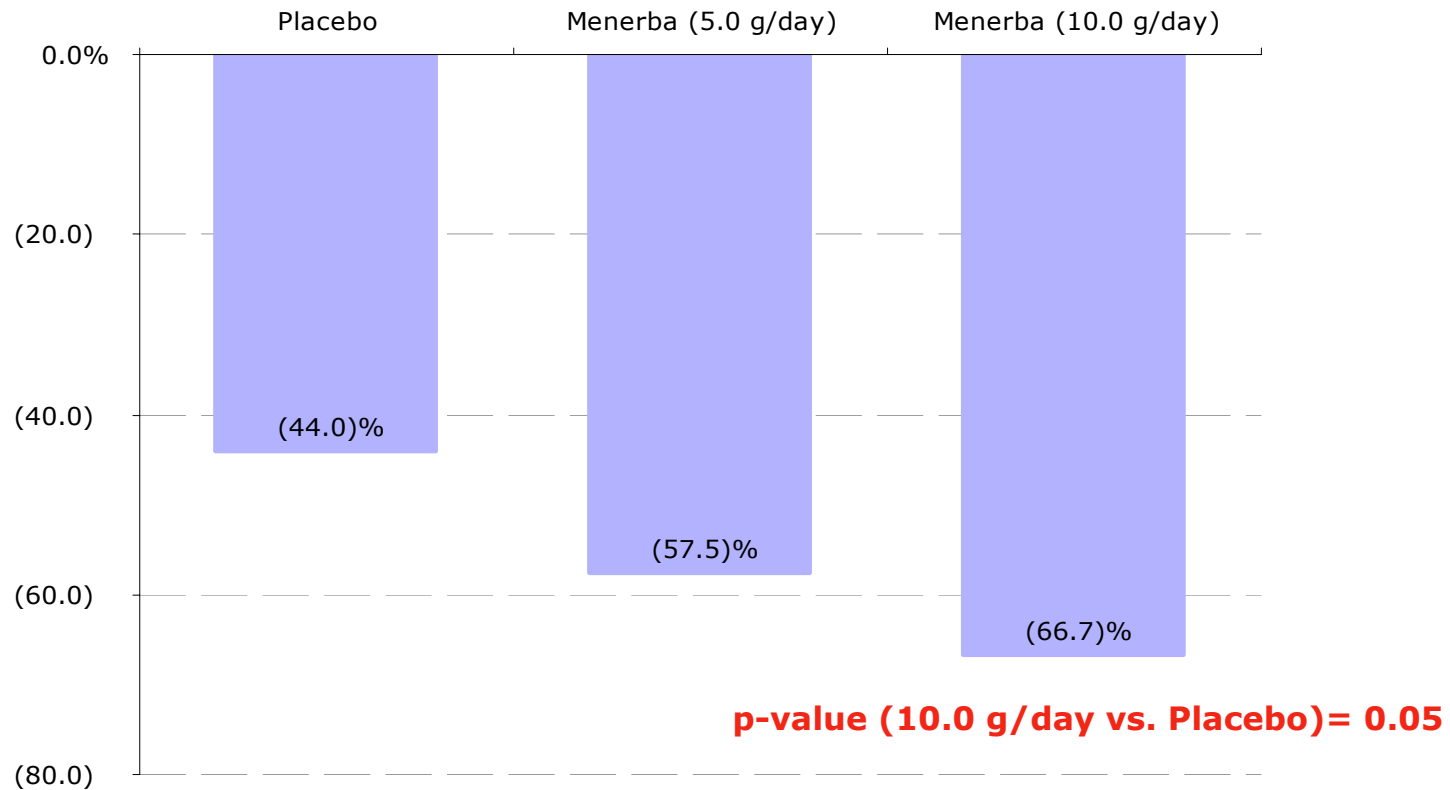
- No difference in the number of uterine bleeding episodes between treatment and placebo
- No cases of endometrial hyperplasia
- “Transient loose stools” was the only side effect (12.0% vs. 3.0% for placebo)
 - Benefit from reduced constipation on Menerba vs. placebo (1.3% vs. 4.0%)
- Statistically significant reduction in weight ($p=0.04$) and BMI ($p=0.05$) on Menerba versus placebo
- Trend toward reduction in blood pressure
- 91.0% of participants used greater than 75.0% of study medication during the 12 week period
 - Low drop out rate (2.0%)

Phase 2 Reduction in Number of Hot flashes per Week



Phase 2 Reduction in Nighttime Awakenings

(Median % Reduction at 12 Weeks)

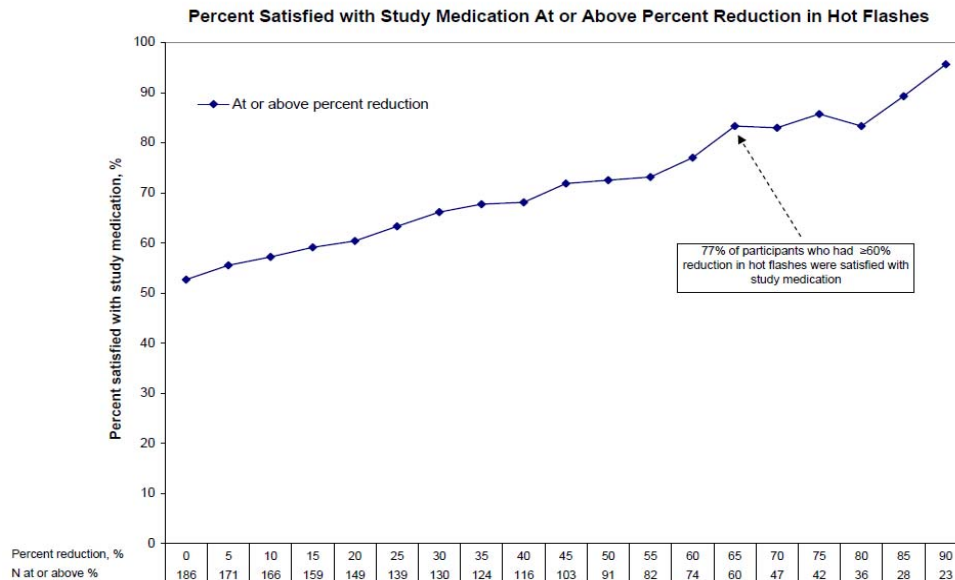


Data from Phase 2 Clinical Trial

Phase 2 Results: Clinical Relevance

Intent to treat responder analysis linked to anchoring question regarding subject satisfaction to determine clinically meaningful efficacy

Phase II Efficacy Menerba 10g/d versus Placebo	Odds Ratio (95% CI)	P value
50% Reduction in HF at 12 weeks	2.3 (1.1 - 4.7)	0.03
60% Reduction in HF at 12 weeks	2.4 (1.1 - 5.3)	0.02



Question at 12 Weeks:

Were you satisfied enough with the study medication that you would like to continue taking it for hot flashes?

Phase 2 Summary

■ Safety

- No difference in the number of uterine bleeding episodes between treatment and placebo.
- No cases of endometrial hyperplasia.
- “Transient loose stools” was most common side effect (12.0% vs. 3.0% for placebo).
 - Benefit from reduced constipation on Menerba (1.3% vs. 4.0% for placebo).
 - Benefit from lower BMI and lower blood pressure.

■ Tolerability

- 91% of participants took > 75.0% of study medication at 12 weeks.
 - Very low drop out rate (2.0%).

■ Efficacy

- Menerba demonstrated statistically significant results in the high dose group, Menerba 10 g/day.
- Menerba exhibited a clear dose response curve, but has yet to reach a maximal tolerated dose.
- An ineffective dose was identified.

Phase 3A Dose-Ranging Clinical Trial Design

40 U.S. Clinical Sites Approved and Trained
PI: Wulf Utian, M.D., Ph.D., Founder and President Emeritus of the North American Menopause Society (NAMS)

ELIGIBILITY

- Postmenopausal women ages 40-60
- ≥ 7 moderate to severe hot flashes per day or ≥ 50 per week

RANDOMIZATION

- 1,200 patients
- 3 months of treatment

400 Participants
5.0 g/day

400 Participants
10.0 g/day

400 Participants
Placebo

PRIMARY ENDPOINT

- Change in frequency of moderate-to-severe hot flashes

Phase 3B Clinical Trial Design

20 U.S. Clinical Sites Approved and Trained
PI: Wulf Utian, M.D., Ph.D., Founder and President Emeritus of the North American Menopause Society (NAMS)

ELIGIBILITY

- Postmenopausal women ages 40-60
- ≥ 7 moderate to severe hot flashes per day or ≥ 50 per week

RANDOMIZATION

- 680 patients
- 52 weeks of treatment

340 Participants
Menerba Xg/day for 12 weeks

340 Participants
Placebo for 12 weeks

680 Participants
Menerba Xg/day for the remaining 40 weeks

PRIMARY ENDPOINTS

- Change in frequency of moderate-to-severe hot flashes after 12 weeks of treatment
- Endometrial safety after 52 weeks of treatment

Vaginal Atrophy is a significant unmet need

- 75% of middle-aged women report that sex is moderately to extremely important
- 55% of post menopausal women have vaginal dryness
- 41% of post menopausal women experience painful intercourse
- 40% of women taking oral hormone replacement have persistent vaginal dryness

Vaginal Epithelium expresses both ER α and ER β

Human Vagina

A



ER α

B



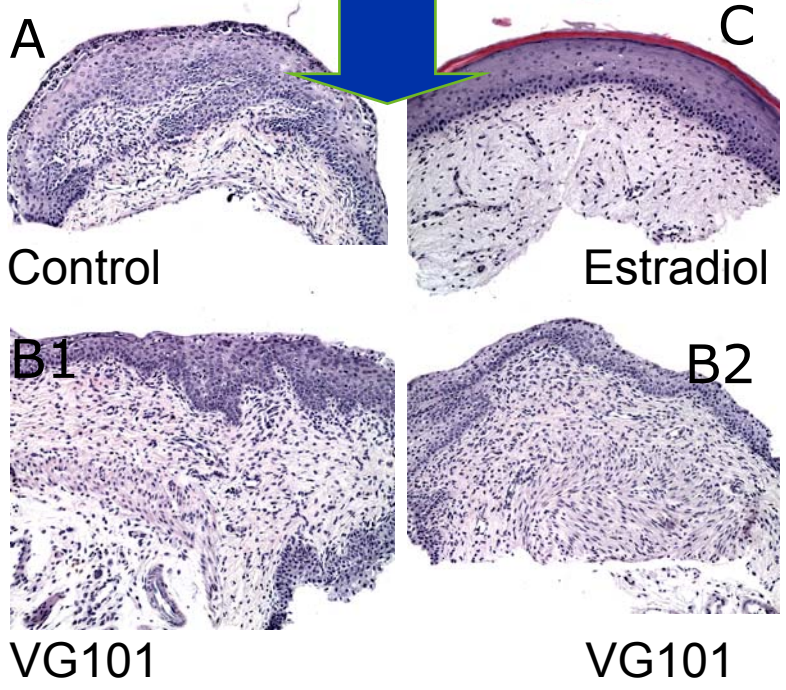
ER β

Formalin fixed vaginal wall tissue slides were tested using immunohistochemistry stains for ER α and ER β . Dako 5 antibody was used for ER α and two mouse monoclonal antibodies were used for ER β (Genetex 14C8 and 7B10.7, 1:600 each).

VG101 is Safer and Effective

Uterine Tissue

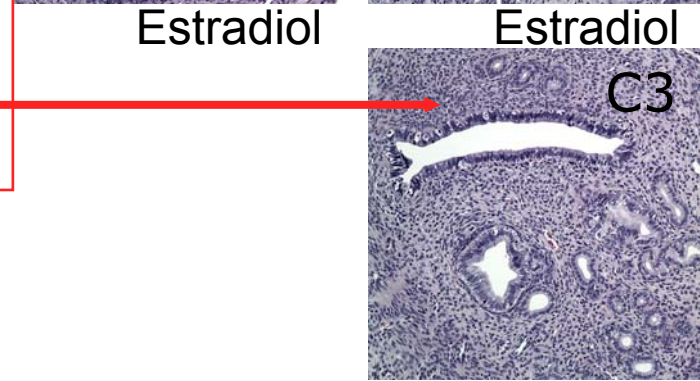
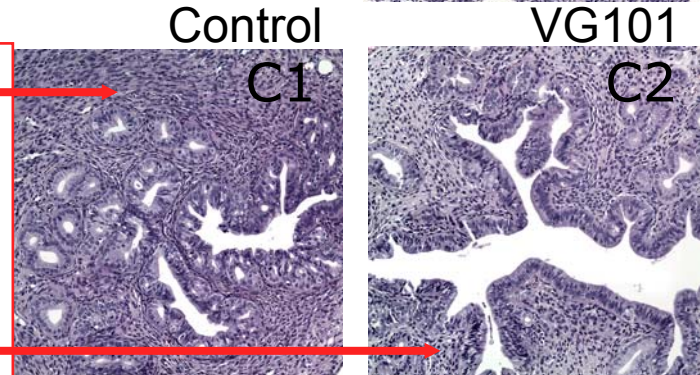
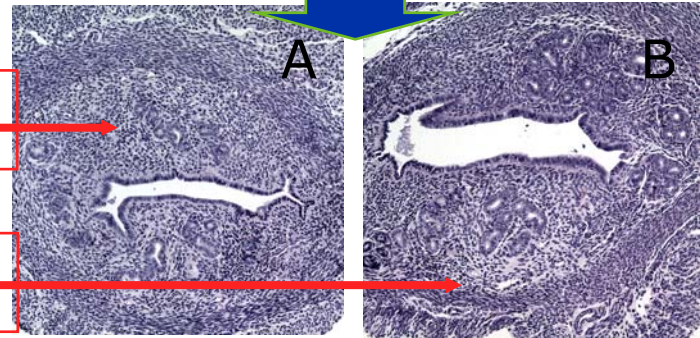
Vaginal Tissue



A. Normal atrophied endometrium

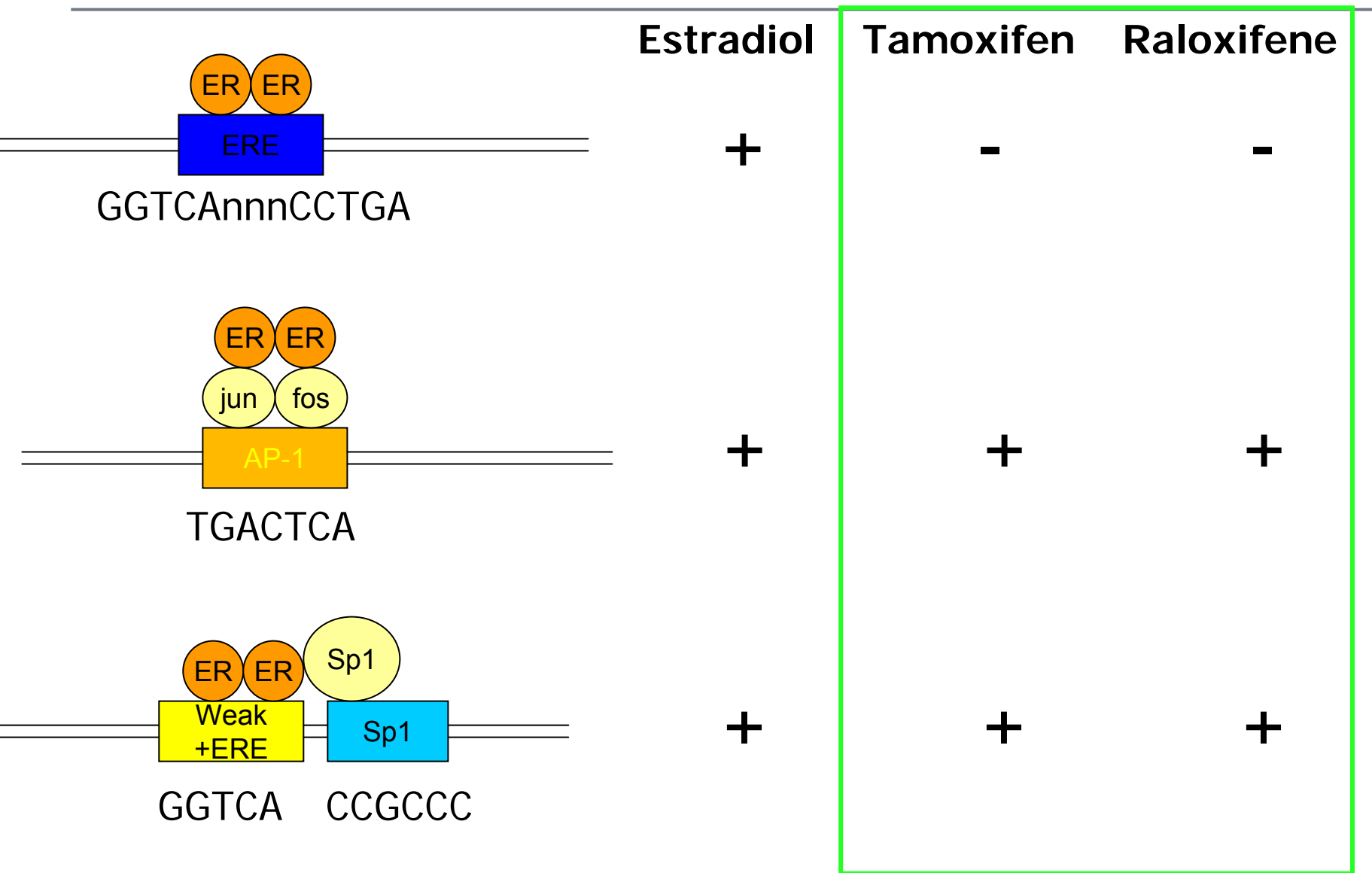
B. Normal luteal phase endometrium

C. Endomyometrium (the equivalent of complex atypical hyperplasia in women, worrisome for in situ carcinoma). The glands form back to back without intervening stroma. Numerous mitotic figures, markedly atypical nuclei with nucleoli.

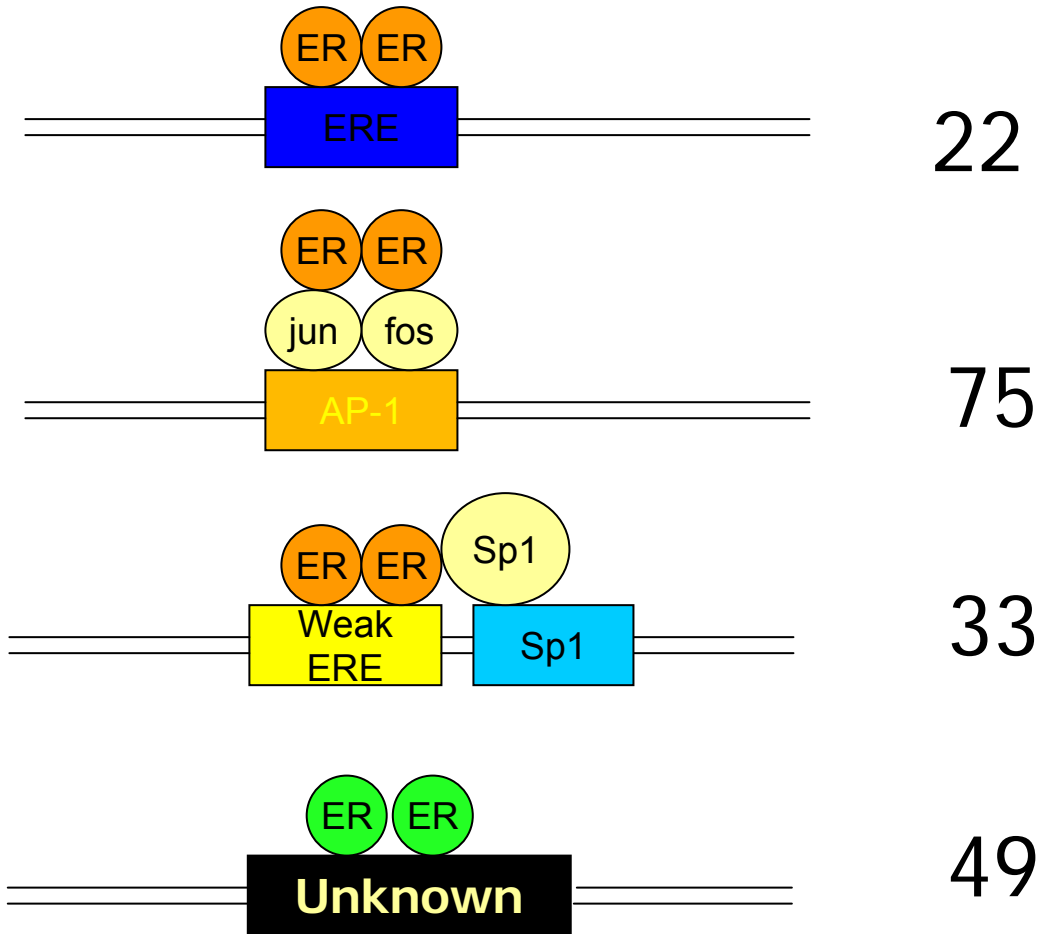


10 tx of 0.5mg/day VG101
or 0.1mg/day E2 over 14 days
In female OVX mice

ER Regulation Depends on Unique Reporters



Number of Genes



BONE-U2OS							CERVICAL-Hela						BREAST-MDA-453						ENDOMETRIAL-ishikawa								
ER-alpha			ER-beta				ER-alpha			ER-beta			ER-alpha			ER-beta			ER-alpha			ER-beta					
clone	E2	TAM	RAL	E2	TAM	RAL	clone	E2	TAM	RAL	E2	TAM	RAL	clone	E2	TAM	RAL	E2	TAM	RAL	clone	E2	TAM	RAL	E2	TAM	RAL
23	0.6	1.0	0.9	0.5	3.1	4.5	23	0.88	1.18	1.24	0.88	6.14	12.97	23	1.29	1.03	1.07	1.08	0.96	1.06	23	0.92	1.94	1.38	0.79	2.64	5.17
32	0.5	1.5	1.3	0.3	6.4	9.0	32	1.32	1.09	1.13	0.95	0.43	0.64	32	1.36	1.47	1.41	0.92	0.95	0.85	32	1.12	3.77	1.74	0.44	1.15	1.34
43	0.9	0.9	1.0	0.6	4.5	6.2	43	1.1	0.9	1.0	0.9	1.3	1.7	43	0.7	1.04	0.93	0.88	1.13	0.5	43	1.22	4.1	1.18	0.87	4	3.32
45	0.9	1.6	2.0	0.9	8.4	9.7	45	1.04	1.18	1.21	0.87	1.47	1.80	45	1.67	1.08	1.24	1.00	1.27	1.52	45	1.05	2.05	1.74	0.53	2.75	3.56
49	1.1	7.4	2.9	0.9	4.3	7.2	49	0.79	0.94	1.19	0.66	1.56	2.28	49	1.04	1.17	0.94	0.75	0.94	0.88	49	0.79	1.24	0.89	0.97	4.05	3.26
92	1.0	0.9	0.8	1.3	3.4	4.9	92	1.25	1.72	1.85	0.55	7.58	17.07	92	1.08	0.9	1.04	1.23	0.92	0.94	92	2.3	5.18	1.86	0.49	1.36	1.87
93	218.9	5.1	2.5	29.2	0.8	1.4	93	5.37	1.06	0.63	2.95	1.67	1.78	93	3.75	2.34	1.02	1.42	0.73	0.79	93	8.60	3.11	1.66	1.68	1.04	1.41
99	1.2	2.3	3.1	0.6	3	4.5	99	1.29	1.44	1.06	0.82	2.41	5.35	99	2.16	1.74	1.46	0.86	1.10	0.83	99	3.08	5	4.13	0.93	3.02	3.36
131	1.0	2.6	2.0	0.4	2.4	3.9	131	1.55	2.61	1.40	1.06	4.11	6.07	131	2.97	1.62	1.67	0.92	1.05	0.94	131	0.76	2.3	1.25	0.78	3.33	4.04
136	1.1	2.9	3.1	0.3	1.7	2.7	136	0.95	1.43	1.15	0.94	4.53	7.33	136	3.41	3.59	4.34	1.26	0.74	0.78	136	1.14	2.07	1.55	1.05	1.4	1.8
144	1.1	1.2	1.1	1.0	1.6	1.6	144	0.81	0.84	0.92	1.08	3.06	6.57	144	1.43	1.35	1.05	0.7	1.27	0.93	144	1.78	3.16	1.5	0.96	2.43	3.82
154	1.0	2.5	2.1	0.4	2.6	3.6	154	1.25	1.62	1.08	0.97	5.32	7.94	154	9.40	2.06	1.73	1.29	0.73	0.96	154	1.67	5.26	2.15	0.83	2.02	1.26
193	24.6	2.5	1.5	0.3	4.1	5.1	193	2.23	1.63	1.00	1.04	1.32	1.17	193	5.08	1.92	1.16	1.62	0.68	0.73	193	1.59	1.48	1.17	1.31	2.96	3.5
218	0.5	0.8	1.1	0.6	3.5	5.1	218	0.75	0.82	0.89	1.00	1.65	0.83	218	1.7	1.29	1.15	1.31	2.01	1.8	218	0.62	1.47	1.15	0.74	7.04	7.715
219	0.5	1.3	1.7	0.4	5.6	11.6	219	0.7	1.0	1.0	1.0	1.5	2.3	219	1.46	1.09	1.17	0.98	1.26	1.65	219	0.66	2.3	1.17	0.58	7.85	10.73
229	0.6	1.2	1.3	0.4	1.8	2.5	229	1.22	1.24	1.46	0.73	5.94	15.57	229	3.07	1.37	1.29	1.49	1.30	1.41	229	0.89	0.95	1.01	0.89	1.47	1.6
262	0.3	0.7	0.7	0.6	3.4	4	262	0.81	0.7	0.85	0.59	4.56	11.02	262	1.29	1.2	1.21	1.09	0.96	1.07	262	0.67	2.17	0.93	1.48	3.86	5.94
280	0.8	1.1	0.9	0.5	3.0	3.5	280	0.98	1.12	0.90	0.92	8.12	11.96	280	1.19	1.21	1.36	1.58	0.93	1.03	280	1.22	3.8	1.31	0.28	5.87	5.18
367	0.8	2.0	1.4	0.4	3.3	4.4	367	1.11	1.59	1.61	1.73	16.4	24.05	367	1.36	1.06	0.96	1.14	1.03	0.89	367	0.62	2.57	1.15	0.45	5.56	4.5
371	0.4	1.1	1.1	0.8	4.8	6.5	371	0.86	0.92	0.95	0.34	1.21	2.51	371	1.2	0.92	0.94	0.93	0.86	0.62	371	0.6	1.28	0.72	1.24	3.46	3.66
396	0.7	2.0	1.7	0.4	3.4	6.9	396	1.1	1.0	0.8	1.1	1.5	1.7	396	1.15	0.77	0.81	1.01	0.91	1.07	396	0.71	1.74	1.16	0.5	3.9	9.36
403	7.1	2.2	2.0	2.9	1.5	2.5	403	2.72	1.43	1.03	2.76	5.35	10.49	403	2.77	2.04	1.47	1.08	1.05	1.04	403	1.63	3.59	1.51	1.37	2.6	3.82
414	0.6	1.4	1.4	0.3	2.4	3	414	0.88	0.85	0.94	1.58	5.67	14.58	414	1.15	1.10	1.85	0.97	0.94	0.86	414	0.54	1.72	1.97	0.79	4.38	6.16
421	0.9	1.9	2.2	0.4	2.9	2.8	421	1.32	1.70	1.61	0.85	3.55	8.16	421	4.66	4.03	6.88	0.92	1.05	0.94	421	0.83	1.93	1.38	1.35	1.29	1.71
424	0.9	1.7	1.4	0.4	3.5	5.8	424	1.01	0.66	0.44	0.78	2.79	4.18	424	2.76	2.45	3.03	1.08	0.80	0.70	424	0.84	2.68	1.54	0.8	7.42	10.37
430	1.0	1.5	1.2	0.6	2.6	4.1	430	1.18	1.86	1.77	0.67	3.10	6.13	430	1.12	1.12	0.9	0.93	0.88	0.89	430	1.56	1.19	1.04	1.1	3.59	4.52

Summary

- There are at least 3 types of ER β regulators
- Tissue selectivity is dependent on varying effectors
- Selective ER β regulators do not result in similar activity
- In a Phase 2, randomized clinical trial, the selective ER β agonist Menerba resulted in statistically significant reduction of hot flashes
- It also resulted in statistically significant reduction in night time awakening, weight loss and BMI
- Menerba did not cause increase in abnormal uterine bleeding episodes or resulted in endometrial hyperplasia
- VG101, an ER β selective agonist, is effective for the treatment of menopausal vaginal atrophy in oopherctomized mice

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