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(54) Title: USE OF IL-17- FOR MATURATION OF OOCYTES

(57) Abstract: The use of IL-17 for the *in vitro* maturation of mammalian oocytes is described. The *in vitro* matured oocytes may be used for *in vitro* fertilization protocols.

WO 2006/039592 A1

USE OF IL-17- FOR MATURATION OF OOCYTES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/614,667, filed September 30, 2004, the contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0002] The present invention is generally related to reproductive biology. More specifically, the present relates to improvements in methods of *in vitro* fertilization.

2. Description of Related Art

[0003] *In vitro* fertilization (IVF) of oocytes is a widely practiced medical technique used to overcome various forms of female and male infertility thereby providing for infertile couples. The standard IVF treatment is based on controlled ovarian hyperstimulation (COH) of female patients using exogenous hormones to induce the maturation of oocytes. The treatment is typically initiated by administering a gonadotropin releasing hormone (GnRH) agonist or antagonist to suppress the patient's own follicle stimulating hormone (FSH) and luteinizing hormone (LH). This is followed by injections of exogenous gonadotropins, e.g. FSH and/or LH, in order to ensure development of multiple preovulatory follicles. Just prior to ovulation, multiple *in vivo* matured oocytes are removed from the ovaries. The isolated mature oocytes are subsequently fertilized *in vitro* and cultured, typically for three to six days, before transferring the developed embryos back into the uterus at the 4-8 cell stage.

[0004] COH treatments are not successful in about one of five couples and are not recommended for a number of females, such as those females with polycistic ovary disease. Moreover, the exogenous hormone treatments used in COH treatments can over-stimulate follicular development and maturation of follicles. A subset of COH patients suffers from ovarian hyperstimulation syndrome (OHSS), which is a serious and potentially fatal condition. As a result, women undergoing COH

must be closely monitored by daily ultrasound examinations of the ovaries and blood hormone measurements.

[0005] Due to the limitations of standard IVF treatments using COH, various alternative protocols have been suggested. One way to alleviate the risks, side effects, and economic disadvantages of COH protocols involves the retrieval of immature oocytes followed by maturation of the oocytes *in vitro*. In this approach, the female is without stimulation, or receives reduced stimulation, and the retrieved oocytes are subjected to hormonal treatment *in vitro*. *In vitro* maturation (IVM) of oocytes would allow a reduction or elimination of the amounts of exogenous hormones typically administered, thereby reducing the problems discussed.

[0006] Despite the success of IVF, there is a significant need for improved methods of infertility treatment. In particular, there is a significant need to develop methods of maturing oocytes *in vitro*.

SUMMARY OF THE INVENTION

[0007] What the art needs are IVF protocols that reduce the occurrence of OHSS. The protocols should reduce or eliminate the amount of exogenous hormones administered to induce maturation of oocytes. The present invention satisfies these needs.

[0007a] A first aspect provides a method of maturing an oocyte *in vitro* comprising:

(a) providing an immature oocyte; and

(b) contacting the oocyte with IL-17.

[0007b] A second aspect provides an oocyte matured by the method of the first aspect.

[0007c] A third aspect provides a method of producing an embryo *in vitro* comprising treating a mature oocyte with sperm, wherein said oocyte is matured by the method of the first aspect.

[0007d] A fourth aspect provides a method of *in vitro* fertilization comprising implanting an embryo in need thereof, wherein said embryo is produced by a method comprising treating a mature oocyte with sperm, wherein said oocyte is matured by the method of the first aspect.

[0007e] A fifth aspect provides use of IL-17 for maturing an oocyte *in vitro*.

[0007f] A sixth aspect provides use of IL-17 for producing an embryo *in vitro* comprising maturing an oocyte *in vitro* using the IL-17.

[0007g] A seventh aspect provides use of IL-17 for *in vitro* fertilization comprising maturing an oocyte *in vitro* using IL-17.

[0008] An oocyte may be matured *in vitro* by providing a composition comprising an immature oocyte. IL-17 may then be added to the composition, thereby inducing maturation of the oocyte. The mature oocyte may be used to produce an embryo by contacting the mature oocyte with

sperm. The embryo may be implanted into the uterus of a female capable of carrying the embryo to term. The IL-17 may be any IL-17 type cytokine including, but not limited to, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E or IL-17F.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Figure 1 shows the percentage of cumulus-oocyte complexes expanded following treatment with the indicated concentration of AS900048-6 (IL-17-6His).

[0010] Figure 2 shows the percentage of cumulus-oocyte complexes expanded following treatment with the indicated concentration of AS900269-1 (Met-IVKA-IL-17).

[0011] Figure 3 shows the percentage of cumulus-oocyte complexes expanded following treatment with the indicated concentration of IL-17B.

[0012] Figure 4 shows the percentage of cumulus-oocyte complexes expanded following treatment with the indicated concentration of IL-17D.

[0013] Figure 5 shows the percentage of cumulus-oocyte complexes expanded following treatment with the indicated concentration of IL-17F.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention is related to the discovery that IL-17 induces the maturation of oocytes *in vitro*. By inducing the maturation of oocytes using IL-17, the amount of exogenous hormones administered in IVF treatment protocols may be reduced.

1. *In Vitro* Maturation

[0015] IL-17 may be used for the *in vitro* maturation of an oocyte.

a. Oocytes

[0016] An immature oocyte may be retrieved from a female while the oocyte is at a stage of development including, but not limited to, early antral and antral follicles.

[0017] The immature oocyte may be retrieved from a female that has not undergone external hormonal therapy. Alternatively, the immature oocyte may be retrieved from a female that has undergone external hormonal therapy. The female may have been administered hormones including, but not limited to, GnRH, FSH, LH or hCG. The hormones may have been administered in combination or sequentially in any order.

[0018] The immature oocyte may be retrieved from the female by methods including, but not limited to, echography and aspiration. The immature oocyte may be cryopreserved after isolation and thawed at a later time for *in vitro* maturation.

b. Maturation

[0019] The isolated immature oocyte may be incubated in a culture medium comprising an IL-17 cytokine. The culture medium may be any physiologically acceptable culture medium including, but not limited to, TCM 199, αMEM and Ham's F10. The culture medium may optionally further

comprise one or more other factors including, but not limited to, FSH, hCG, estradiol, cysteamine, sodium pyruvate, glutamine, and antilogous heat-inactivated serum or follicular fluid.

[0020] The immature oocyte may be incubated in the culture medium at temperatures including, but not limited to, from about 37°C to about 39°C for a period of time including, but not limited to, about 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 or 72 hours. The oocyte may be incubated until maturation has occurred as evidenced by methods including, but not limited to, visual inspection under microscope of germinal vesicle break down (GVBD), cumulus expansion, metaphase II plate formation (MII), or polar body extrusion.

c. Embryo Production

[0021] A mature oocyte may be incubated with sperm *in vitro* to produce a mammalian embryo using standard *in vitro* fertilization methods as described in Textbook of Assisted Reproductive Techniques Laboratory & Clinical Perspectives, edited by Gardner, et al., 2001 Martin Ldunetz Ltd., London, the contents of which are incorporated herein by reference. The embryo may be implanted into the uterus of a female capable of carrying the embryo to term.

2. IL-17

[0022] IL-17 is a family of structurally related cytokines. IL-17 cytokines exhibit pleiotropic biological activities on various types of cells, such as fibroblasts, endothelial cells, and epithelial cells. Representative examples of IL-17 cytokines include, but are not limited to, IL-17/IL17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. The IL-17 may also be an analog, derivative, fragment, homolog, variant, or combination thereof, of IL-17/IL-17A, IL-17B, IL-17C, IL-17D, IL-17E or IL-17F. The analog, derivative, fragment, homolog or variant may have at least 75%, 80%, 85%, 90% or 95% sequence identity with an IL-17. IL-17 cytokines may share a conserved C-terminal region but different N-terminal segments. The IL-17 cytokine may be a homodimer, which may be linked by a disulfide bond. The IL-17 may be human IL-17.

[0023] As used herein, the term "analog", when used in the context of IL-17, means a peptide or polypeptide comprising one or more non-standard amino acids or other structural variations from the conventional set of amino acids.

[0024] As used herein, the term "derivative", when used in the context of IL-17, means a peptide or polypeptide different other than in primary structure (amino acids and amino acid analogs). By way of illustration, derivatives may differ by being glycosylated, one form of post-translational modification. For example, peptides or polypeptides may exhibit glycosylation patterns due to expression in heterologous systems. If at least one biological activity is retained, then these peptides or polypeptides are derivatives according to the invention. Other derivatives include, but are not limited to, fusion peptides or fusion polypeptides having a covalently modified N- or C-terminus, PEGylated peptides or polypeptides, peptides or polypeptides associated with lipid moieties, alkylated peptides or polypeptides, peptides or polypeptides linked via an amino acid side-chain functional group to other peptides, polypeptides or chemicals, and additional modifications as would be understood in the art.

[0025] As used herein, the term "fragment", when used in the context of IL-17, means a peptide of from about 8 to about 50 amino acids in length. The fragment may be 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 amino acids in length.

[0026] As used herein, the term "homolog", when used in the context of IL-17, means a peptide or polypeptide sharing a common evolutionary ancestor.

[0027] As used herein, the term "variant", when used in the context of IL-17, means a peptide or polypeptide that differs in amino acid sequence by the insertion, deletion, or conservative substitution of amino acids, but retain at least one biological activity. For purposes of the present invention, "biological activity" includes, but is not limited to, the ability to be bound by a specific antibody.

[0028] The present invention has multiple aspects, illustrated by the following non-limiting examples.

EXAMPLES

EXAMPLE 1

Isolation Of Murine Cumulus-Oocyte Complex

[0029] PMSG (5 IU/female, Calbiochem 367222) was used to prime 7 to 8-week-old CD-1 female mice (35 total; Charles River). The mice were sacrificed 48 h later by progressive hypoxemia. Alcohol (70%) was applied to the abdominal region of the animals to clean the area and also to decrease contamination of samples with hair. A ventral incision was made to expose the abdominal cavity. The ovaries connected to oviducts were cut away from the uterine horn and the visceral adipose. The ovary/oviduct samples were placed in a 15 ml tubes (10 per tube, Corning 430052) containing 3 ml of L-15 medium (Gibco 11415-064) plus 10% fetal calf serum (FCS; Invitrogen 16000-044). The ovary/oviduct samples were maintained at 37°C.

[0030] The ovary/oviduct samples were then transferred to a Petri dish (Falcon 353004, 60x15 mm). Under a stereomicroscope (Nikon SM2-800 with thermo-plate heating stage) using a pair of scissors needle (27 gauge) mounted in a 1 ml tuberculin syringe, the ovaries and oviduct were cleaned of the fatty pad and placed in a new Petri dish filled with 2-3 ml of fresh medium (L-15 + 10% FCS). The COCs were recovered by mechanical rupture of each ovary with needles and placed in a new Petri dish filled with 2-3 ml of fresh medium (L-15 + 10% FCS).

EXAMPLE 2

Effect Of IL-17 On The *In Vitro* Cumulus Expansion Of The Cumulus-Oocyte Complex

[0031] Cumulus-intact oocytes with homogeneous cytoplasm were selected from COCs prepared as described in Example 1 using a low-power (20-30 X) stereomicroscope and transferred using mouth glass pipets to 96-well plates (2/well) containing 90 µl culture media (αMEM (Gibco 32571-036) with 10% FCS and PenStrep-Antibiotics (Invitrogen 15140-122)) per well mineral oil. Before addition of the COCs to the 96-well plate, the medium in the plate was pre-equilibrated for a period of 1 h at 37°C in a humidified incubator with 5% CO_2 in air.

[0032] Different forms of IL-17 were added to each well in a volume of 10 µl so that the final volume in each well was 100 µl. Each plate contained 4 wells of a "Negative Control" (αMEM plus 10% FCS) and 4 wells of a "Positive Control" (αMEM plus 10% FCS plus EGF (5 ng/ml,

Sigma E-9644)). Two plates, duplicates, were run per assay, providing 2 wells per test protein. Proteins were diluted 1:5 in IVM medium (αMEM plus 10% FCS) before being added to the assay plates for a final dilution of 1:50 in the assay.

[0033] The plates containing the treated COCs were incubated for 18 h at 37°C in a humidified incubator with 5% CO_2 in air. Each COC was then visually inspected using a Nikon Inverted Microscope to identify the formation of a mucoid extracellular matrix by cumulus cells, which is an indicator of cumulus expansion. The percentage of cumulus expansion was defined as the number of expanded COCs in relation to the total COCs that were used in each treatment group. As shown in Table 1 below, each of the tested forms of IL-17 induced 80% expansion of COC in the primary assay.

Table 1 - Primary COC Expansion Assay

Protein #	Protein	% Expanded
AS900231-1	IL-17-ATT-6His	80
AS900231-2	IL-17-ATT-6His	80
AS900269-1	Met-IVKA-IL-17	80
AS900048-4	IL-17-6His	80

[0034] Each of the IL-17 proteins tested in the primary assay was then retested in a reconfirmation assay. The results from the reconfirmation assays in Table 2 indicate that each of the tested forms of IL-17 induced at least 80% expansion of COCs.

Table 2 - Reconfirmation COC Expansion Assay

Protein #	Protein	% Expanded
AS900231-1	IL-17-ATT-6His	80
AS900269-1	Met-IVKA-IL-17	100
AS900048-4	IL-17-6His	100

[0035] In both the primary assay and the reconfirmation assays, the COCs in the negative controls (no EGF) or the positive controls (plus EGF) wells were always 0% or 100% expanded, respectively (data not shown).

EXAMPLE 3

Dose-Response Analysis Of IL-17

[0036] Based on the results from the preliminary and reconfirmation assays described in Example 2, dose-response analysis was performed for AS900048-6 (IL-17-6His) and AS900269-1 (Met-IVKA-IL-17). Dose-response testing was performed similar to the method described in Example 2, except 3 wells with 4-5 COCs per well were assigned to each protein concentration. Dilutions of the test proteins were made depending on the concentration of the particular proteins, which were sometimes not diluted before being added to the assay, resulting in a final concentration of 1:10.

[0037] The results of the dose-response analysis of AS900048-6 (IL-17-6His) and AS900269-1 (Met-IVKA-IL-17) appear in Figure 1 and Figure 2, respectively. Analysis with Origin 7 SR3 v7.0475 (B475) indicates that the EC_{50} for cumulus expansion with AS900048-6 (IL-17-6His) was 0.15 μg/ml whereas the EC_{50} for cumulus expansion with AS900269-1 (Met-IVKA-IL-17) was 0.45 μg/ml.

EXAMPLE 4

Analysis Of IL-17 Cytokines

[0038] Different IL-17 cytokines were tested for the ability to induce *in vitro* cumulus expansion in the manner described in Example 2. As can be seen in Tables 3-8, IL-17B, IL-17C, IL-17D, IL-E and IL-F were also able to induce *in vitro* cumulus expansion. In addition, IL-17B, IL-17D and IL-17F had similar activity to IL-17A.

Table 3 - IL-17A Expansion Assay

Protein		Expanded Oocytes	Total Oocytes	% Expanded
IL-17A	1 μg/ml	3	3	100
		3	3	100
		3	3	100
	100 ng/ml	2	3	66.7
		3	3	100
		0	3	0
	10 ng/ml	0	3	0
		0	3	0
		0	3	0

Table 4 - IL-17B Expansion Assay

Protein		Expanded Oocytes	Total Oocytes	% Expanded
IL-17B	1 μg/ml	3	3	100
		3	3	100
		3	3	100
	100 ng/ml	3	3	100
		3	3	100
		3	3	100
	10 ng/ml	1	3	33.3
		1	3	33.3
		0	3	0

Table 5 - IL-17C Expansion Assay

Protein		Expanded Oocytes	Total Oocytes	% Expanded
IL-17C	1 μg/ml	2	3	66.7
		1	3	33.3
		0	3	0.
	100 ng/ml	2	3	66.7
		1	3	33.3
		1	3	33.3
	10 ng/ml	0	3	0.
		1	3	33.3
		0	3	0

Table 6 - IL-17D Expansion Assay

Protein		Expanded Oocytes	Total Oocytes	% Expanded
IL-17D	1 μg/ml	3	3	100
		3	3	100
		3	3	100
	100 ng/ml	3	3	100
		3	3	100
		3	3	100
	10 ng/ml	3	3	100
		1	3	33.3
		1	3	33.3

Table 7 - IL-17E Expansion Assay

Protein		Expanded Oocytes	Total Oocytes	% Expanded
IL-17E	1 μg/ml	0	3	0
		1	2	50
		1	3	33.3
	100 ng/ml	1	3	33.3
		1	3	33.3
		0	3	0
	10 ng/ml	1	3	33.3
		1	3	33.3
		0	3	0

Table 8 - IL-17F Expansion Assay

Protein		Expanded Oocytes	Total Oocytes	% Expanded
IL-17F	1 □g/ml	3	3	100
		3	3	100
		3	3	100
	100 ng/ml	3	3	100
		2	3	66.7
		2	3	66.7
	10 ng/ml	1	3	33.3
		1	3	33.3
		2	3	66.7

[0039] Based on these results, dose response analysis was performed on IL-17B, IL-17D and IL-17F in the manner described in Example 3. The results of the dose-response analysis appear in Figures

3-5. Analysis with Origin 7 SR3 v7.0475 (B475) indicates that the EC_{50} for cumulus expansion with IL-17B, IL-17D and IL-17F is 12.3 ng/ml, 74 ng/ml and 50 ng/ml, respectively.

[0040] The description is not limited to the above embodiments.

[0041] In the claims which follow and in the description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

[0042] It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

CLAIMS:

1. A method of maturing an oocyte *in vitro* comprising:

(a) providing an immature oocyte; and

(b) contacting the oocyte with IL-17.

2. The method of claim 1 wherein the IL-17 is selected from the group consisting of IL17/IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F.

3. The method of claim 1 wherein the IL-17 is IL17/IL-17A or a polypeptide at least 80% identical thereto.

4. The method of any one of claims 1 to 3 wherein the immature oocyte is derived from a female that has not undergone external hormonal therapy.

5. The method of any one of claims 1 to 3 wherein the immature oocyte is derived from a female that has undergone external hormonal therapy.

6. The method of claim 5 wherein the female was administered a hormone selected from the group consisting of GnRH, FSH, LH, hCG, and a combination thereof.

7. The method of any one of claims 1 to 6 wherein the immature oocyte is provided in a culture medium comprising a factor selected from the group consisting of FSH, hCG, estrachol, cysteamine, sodium pyruvate, glutamine, autologous heat-inactivated serum, and follicular fluid.

8. An oocyte matured by the method of any one of claims 1 to 7.

9. A method of producing an embryo *in vitro* comprising treating a mature oocyte with sperm, wherein said oocyte is matured by the method of any one of claims 1 to 7.

10. A method of *in vitro* fertilization comprising implanting an embryo in need thereof, wherein said embryo is produced by a method comprising treating a mature oocyte with sperm, wherein said oocyte is matured by the method of any one of claims 1 to 7.

11. Use of IL-17 for maturing an oocyte *in vitro*.

12. Use of IL-17 for producing an embryo *in vitro* comprising maturing an oocyte *in vitro* using the IL-17.

13. Use of IL-17 for *in vitro* fertilization comprising maturing an oocyte *in vitro* using IL-17.

14. The method of any one of claims 1, 9 or 10, the oocyte of claim 8, or the use of any one of claims 11 to 13, substantially as hereinbefore described with reference to the examples and figures.

FIGURE 1

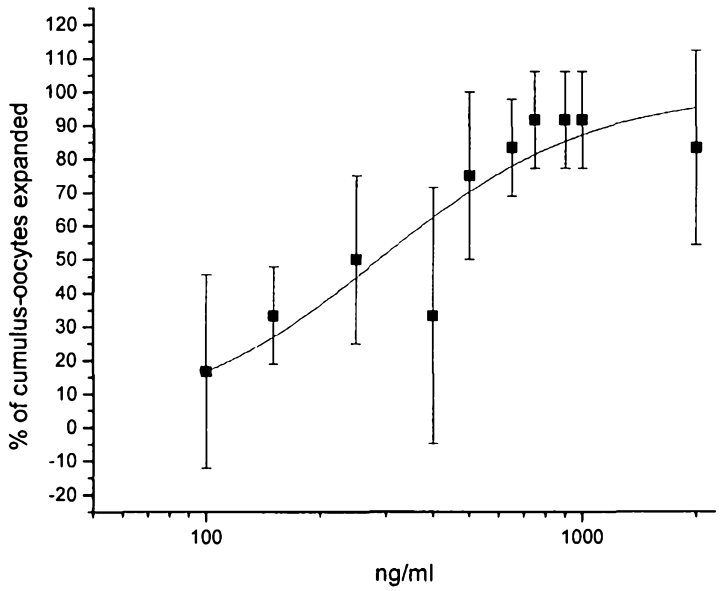

% of cumulus-oocytes expanded
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
100
1000
ng/ml

FIGURE 2

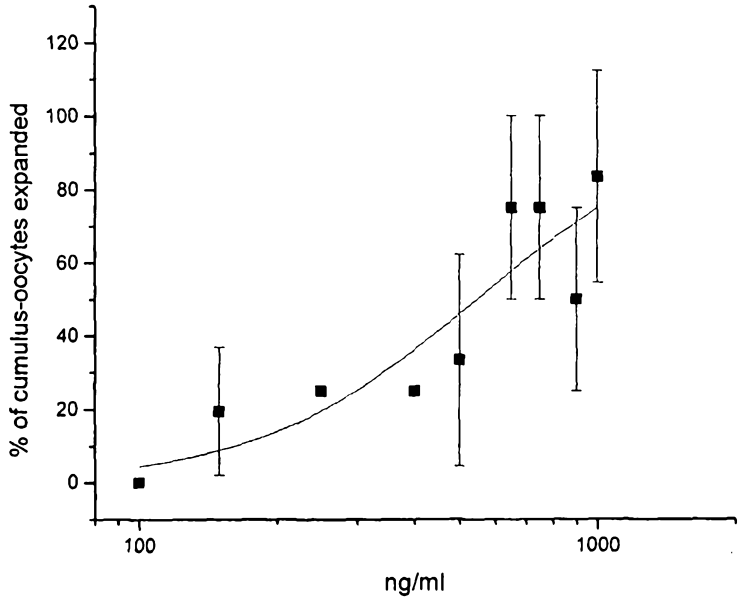

120
100
80
60
40
20
0
% of cumulus-oocytes expanded
100
1000
ng/ml

FIGURE 3

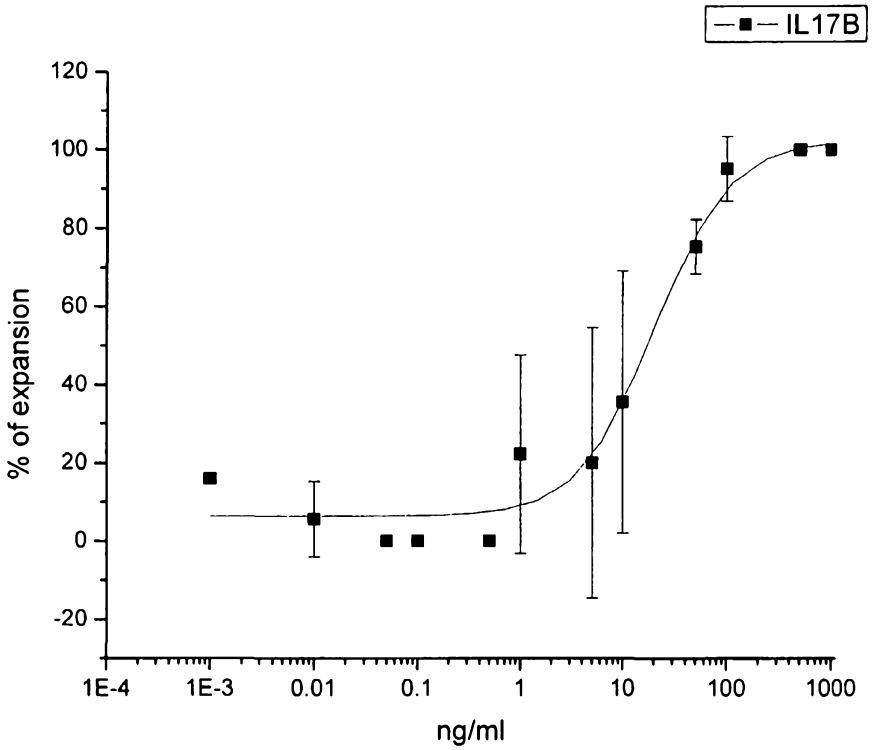

IL17B
120
100
80
60
40
20
0
-20
% of expansion
1E-4
1E-3
0.01
0.1
1
10
100
1000
ng/ml

FIGURE 4

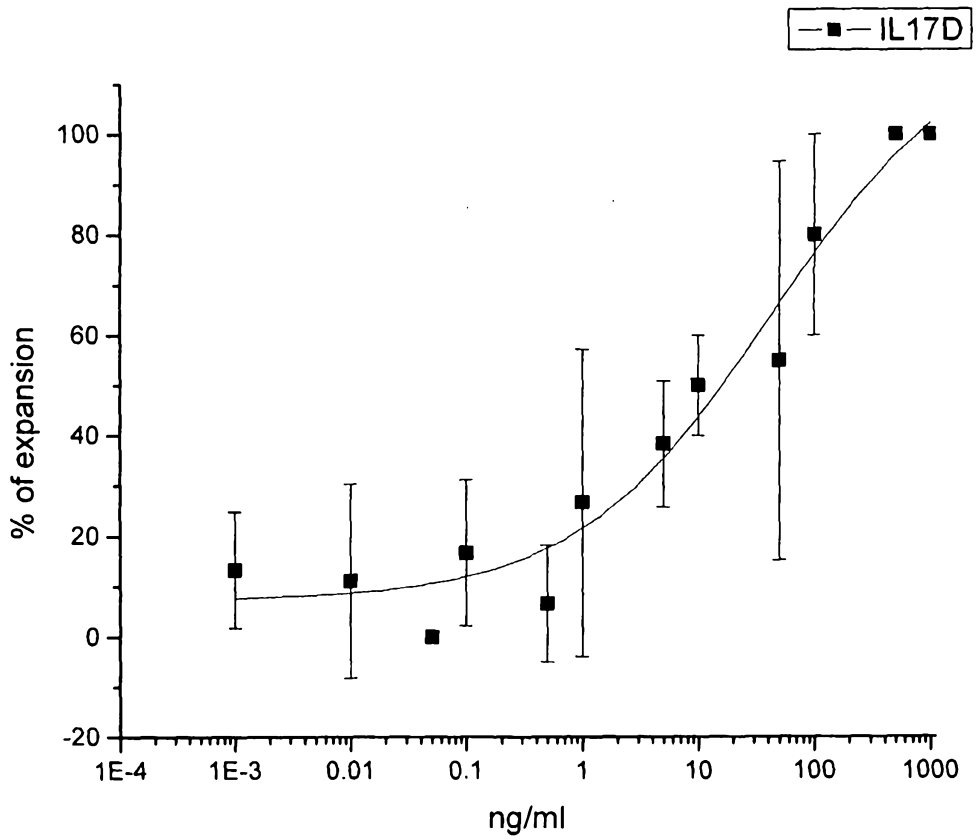
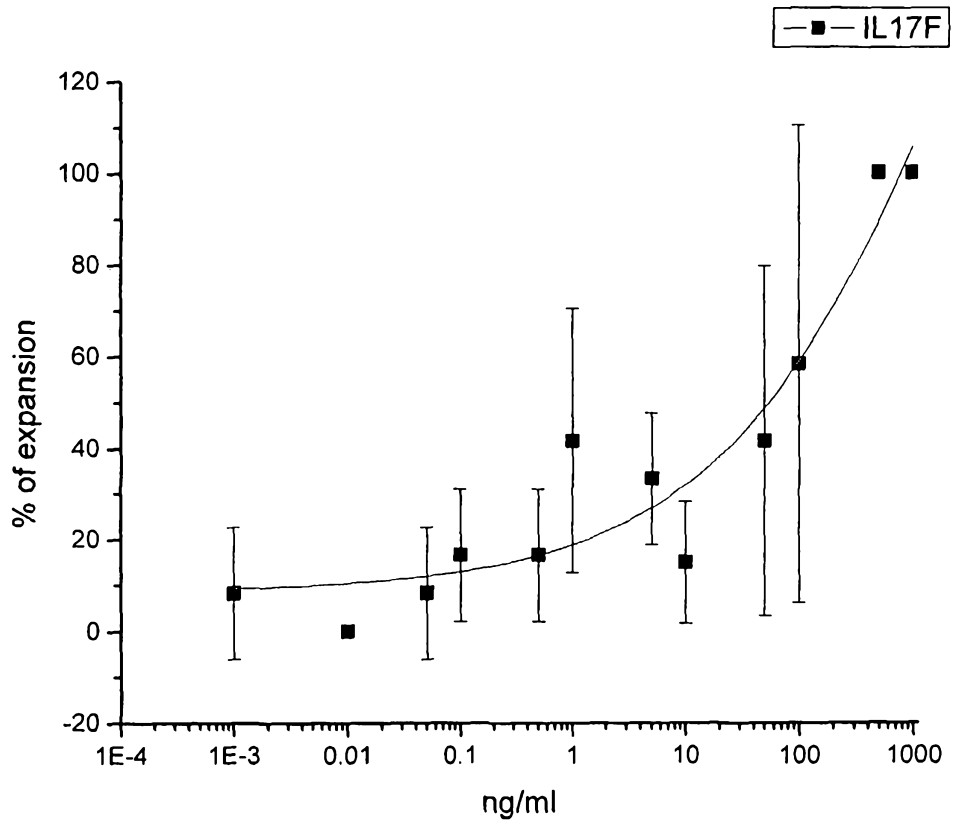

IL17D
% of expansion
100
80
60
40
20
0
-20
1E-4
1E-3
0.01
0.1
1
10
100
1000
ng/ml

FIGURE 5


IL17F
120
100
80
60
40
20
0
-20
% of expansion
1E-4
1E-3
0.01
0.1
1
10
100
1000
ng/ml