Practical and Regulatory Issues in EU and US
Examples with Research Molecules

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Recent Issues SPRMs
Ph3 rejections were surprise

- Asoprisnil
  - endometrial “hydroplasia”
  - Poorly understood pathological finding
  - Regulatory agencies – If unusual, and unexplained, - “adverse”; needs duration of exposure for safety to be defined
- Proellex
  - liver enzymes
  - Safety issue is primary concern, exposure and toxicity relationship
  - Fertility issue becomes secondary concern (although drug reduces chance of spontaneous conception while on therapy)

Learning Objectives

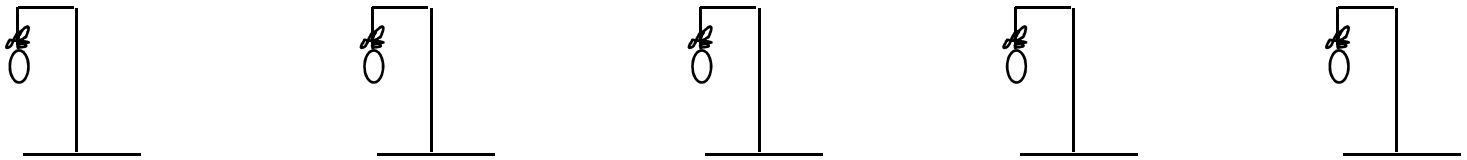
- When does Regulatory Affairs become involved in Drug Development and with Agencies?
- What roles do Regulatory Affairs have in Drug Development?
- How do Regulatory Affairs Obtain guidelines

- Why was the drug I worked on not continued into Development?
  - examples

When Does RA Influence Process?

Drug Development Overview

Discovery	Preclin	Ph1	Ph2	Ph3	Reg & L
$5M	$10M	$15M	$60M	$200M	$40M
$20M	$30M	$40M	$160M	$300M	
Experiments designed to meet intended claims in Ph3	Safety & Tox Disease model Clinical Biomarker	Safety & Exposure PK Initial PD Biomarker in Patients	Dose in Patients Initial Efficacy to determine Ph3 trial	Efficacy in Patients	**Proof they were involved**



When - Post Registration

- Launch and Pre-marketing activity
  - All statements for marketing are reviewed and approved by marketing
  - Any statements comparing current product with competitor product must be matched with supportive clinical results
- Sales messaging
  - All statements for marketing are reviewed and approved by marketing
  - Any statements comparing current product with competitor product must be matched with supportive clinical results
- Phase IV – post approval plans
  - Market expansion – studies that support extended claims in existing indication
  - Market expansion – studies that support new indications with medical field
  - Approval of studies in new indications that could compromise existing claims and field of use

How are Regulatory Requirements and Success Determined

- Previous drug approvals
  - Path to registration is well defined
  - They like this best
- Related drug approval process
  - Path to registration has reasonable comparisons with previous drugs
  - This is OK, but make them frown
- No precedent
  - Path to registration is undefined
  - They just say no

What Roles Do RA Have in Drug Development

- Preclinical & Clinical Experiments need to support intended regulatory claim (endometriosis)
  - If desired claim is pain relief, then clinical studies need to focus on reduction in pain
    - Preclinical models: pain or inflammation
    - Biomarkers of inflammation are surrogates of therapeutic outcome in inflammation
    - Intended therapy must have no impact on natural fertility, & fecundity (no reprotoxicity), or development plan manages risk of conception while on therapy
  - Marketed indications need to match with clinical results and regulatory approval [several examples of pharma fines for off-label claims]

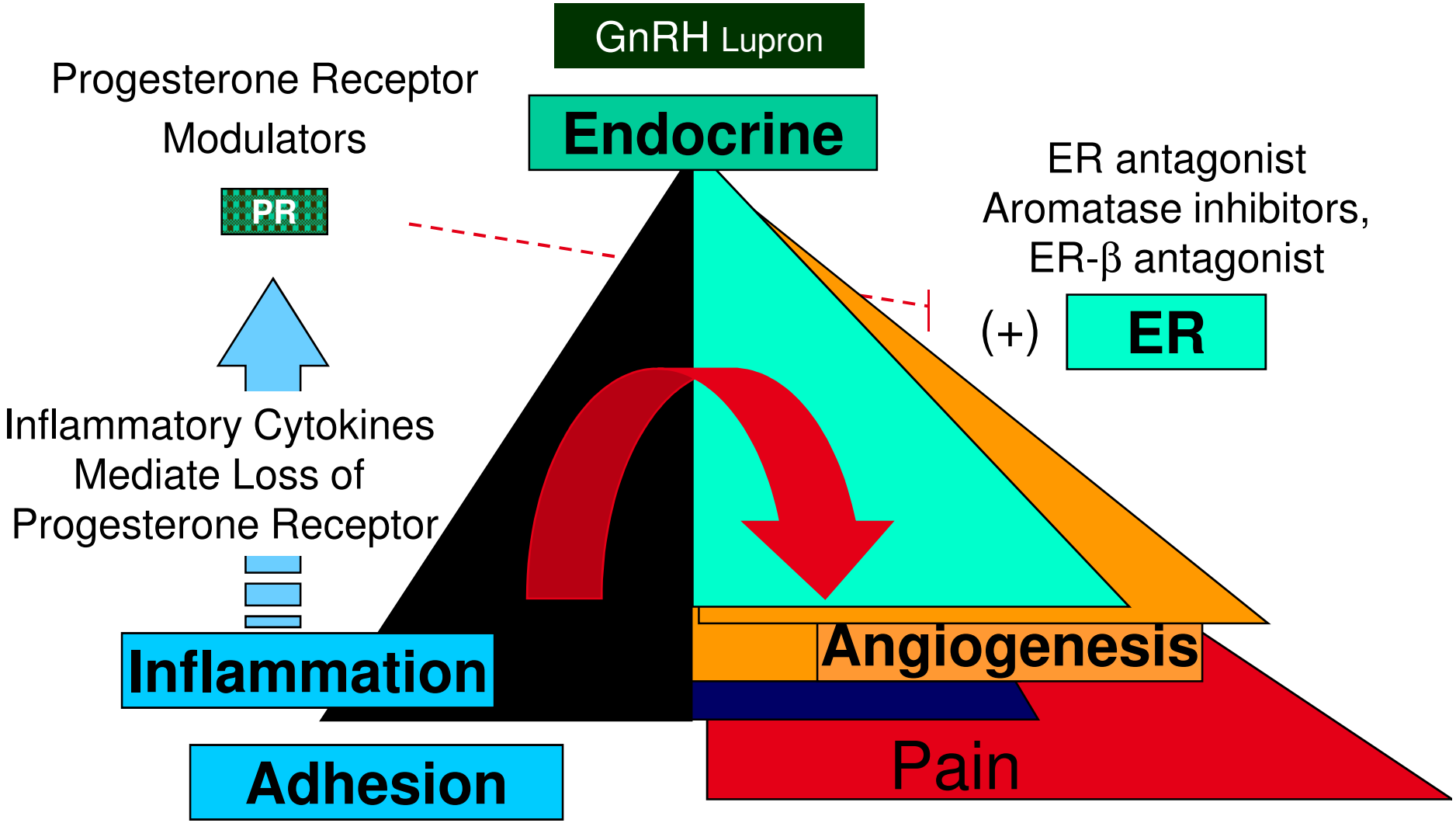
State the Obvious

- Experiments support intended regulatory claim
  - If desired claim is fertility, the clinical studies need to demonstrate reduction in disease and matching improvement in pregnancy outcomes
    - Confirmed by laparascope
    - Intended therapy must be safe for mother, embryo & fetus
      - must have no impact on natural fertility, (preconception)
      - Or inhibits natural fertility and minimizes risk of therapy affecting simultaneous pregnancy
      - reproductive toxicity evaluation (postconception), requires contraception to manage reprotox risk.
  - Combination therapies must demonstrate superior effect relative to any of individual therapies
    - Safety
    - efficacy

Route of Administration & Changes to Drug Formulation

- Local administration vs systemic administration
  - Differential drug exposure and activity - results match claims
    - Aromatase inhibitor – local lesion vs pituitary gonadotropins
    - GnRH antagonist – local lesion vs pituitary gonadotropins
- Claims of superiority or equivalence –
  - results match claims
  - To claim superiority, must be backed by clinical results
  - Includes formulation or route of administration: bioequivalence
  - Comparative clinical efficacy trials are risky, but worthwhile if your drug or formulation or route proves superior

Progesterone Suppression of ER Diminishes, Inflammatory Axis Amplified in Endometriosis



Hypothesis

- Endometriosis affects sensory nerves (pain) in an analogous manner as multiple sclerosis affects motor neurons (loss of function):
  - Aberrant attachment of cells initiates inflammatory cascade
  - Inflammation leads to exacerbation of disease
    - Endometriosis – pain perception by sensory nerves
    - Multiple sclerosis – degeneration of motor neurons

- Therapeutic agents with proven efficacy in models of multiple sclerosis should be effective in treatment of endometriosis
  - Register drug in indication with more tolerant regulatory position (MS)
  - Repurpose drug into endometriosis once established safety record in primary indication
    - Control of ovulation & pregnancy (OC) is accepted practice in MS;
    - apply combination with OC in endometriosis

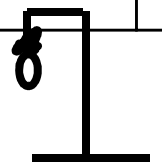
Examples from EMD-SRI

- TBP : Safety issue
  - Tumor necrosis factor binding protein
  - Soluble TNFR-1
- TBP-ihCG: Comparison of efficacy
  - 2 Molecules of TBP fused with hCG (to alpha and beta chains)
- JNK – safety marginal
  - Repurpose molecule from multiple sclerosis drug discovery
  - Need for combination therapy; superior efficacy

TBP: Onercept

Safety at clinical dose achieved: pain reduction unknown

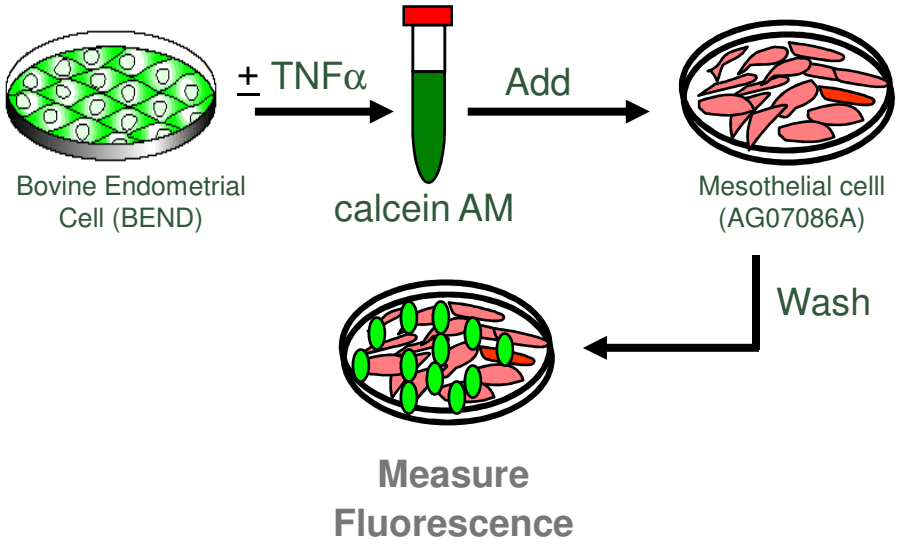
Discovery	Preclin	Ph1	Ph2	Ph3	Reg & L

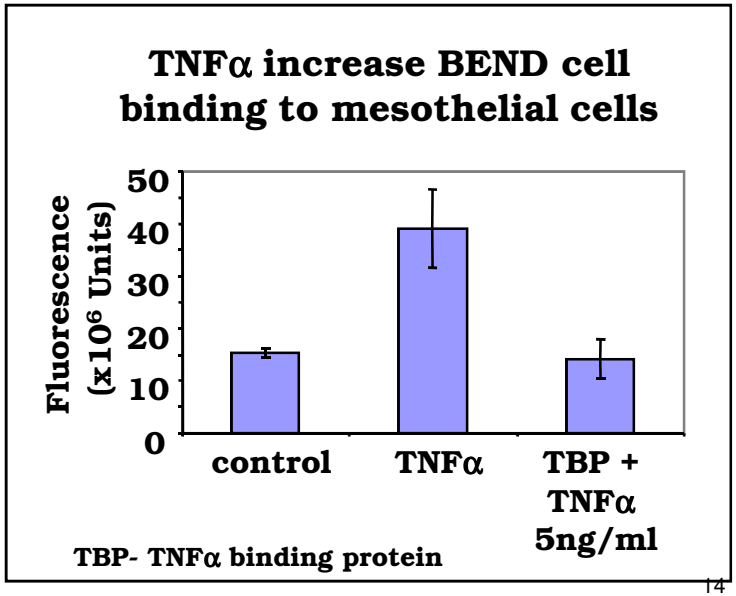


- Primary indication: Psoriasis
  - TNF neutralizing therapies patients have increased susceptibility to develop sepsis
- Secondary indication - endometriosis
  - effective on lesion size
    - rodent model of endometriosis in 1994; D'Antonio et al., 2001
    - baboon model of endometriosis; D'Hooghe et al., 2006
- Related marketed or tested drugs
  - Infliximab – no effect on pain in women (2008; Koninckx et al)
  - Etanercept - baboon; (Barrier et al., 2004)
  - c5N – baboon effective on lesions, conception while on drug, no increase in fecundity (Falconer, et al., 2006, 2007

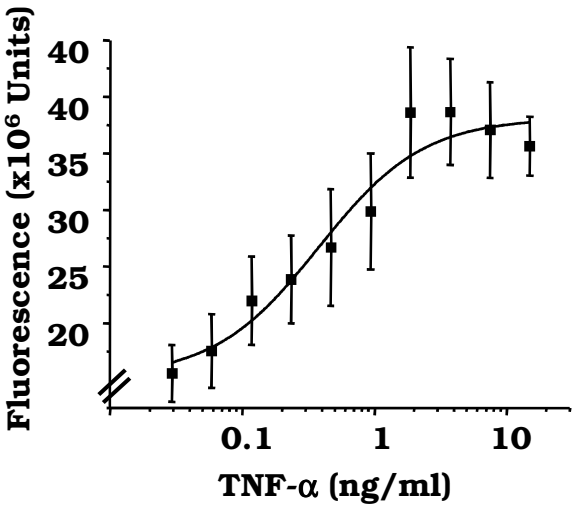
TBP is Useful Research Tool
Adhesion of Endometrium to Peritoneum

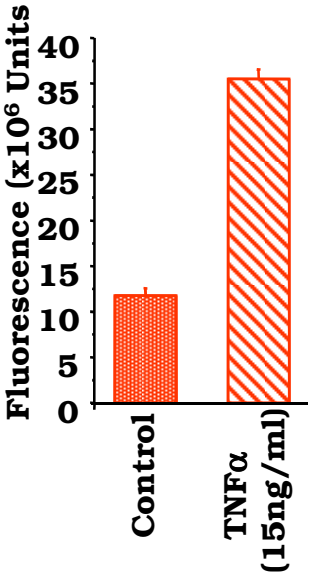
- **Endometrial cell adhesion to peritoneum is mediated by the interaction of**
  - endometrial integrin to the ECM in peritoneal mesothelium
  - Homophilic interaction of cadherins
- **TNFα increase binding of endometrial cells to mesothelium**
- **Inhibition of endometrial cell attachment to peritoneum - prevention of endometriosis progression**

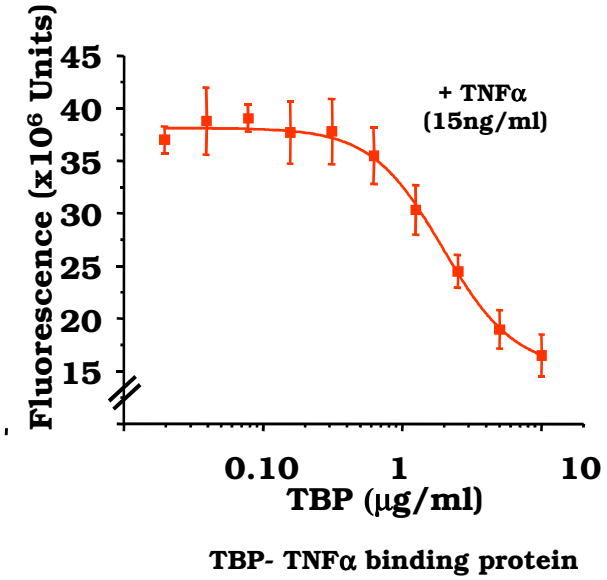




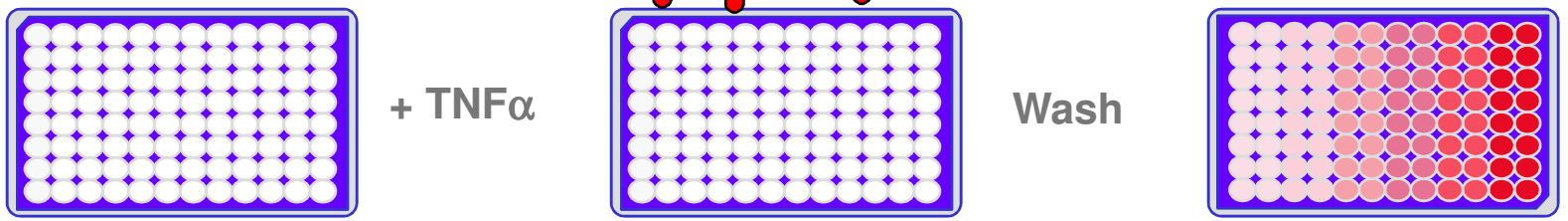
TNFα Increases Binding of Fibronectin to Endometrial Cells





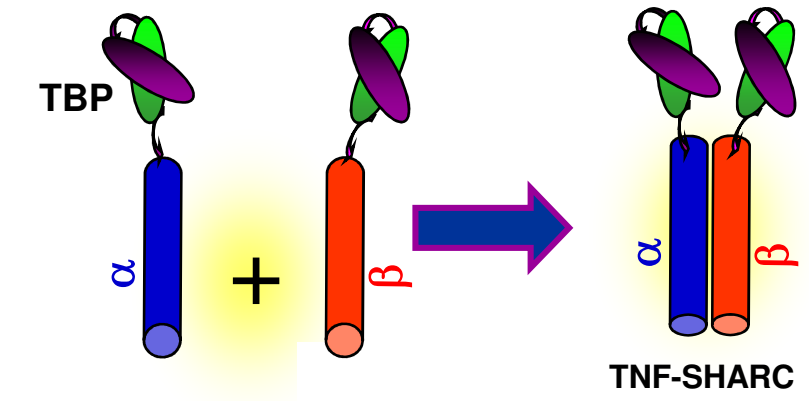


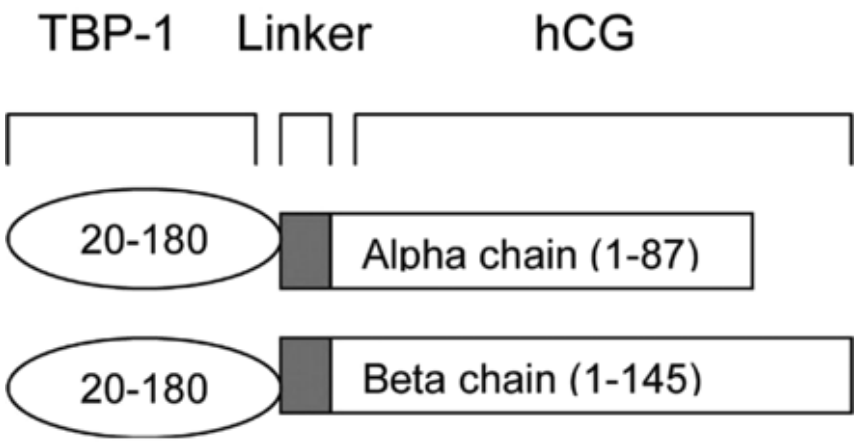
TBP- TNFα binding protein



Innovative treatment for Endometriosis: Comparative Efficacy

- TNFα binding protein (TBP) an effective therapy for treating endometriosis in animal models (rodent and baboon)
- hCG is inactive
- Requires very high concentration
- Regulatory advantage – single molecule with only 1 set of phramacological set properties

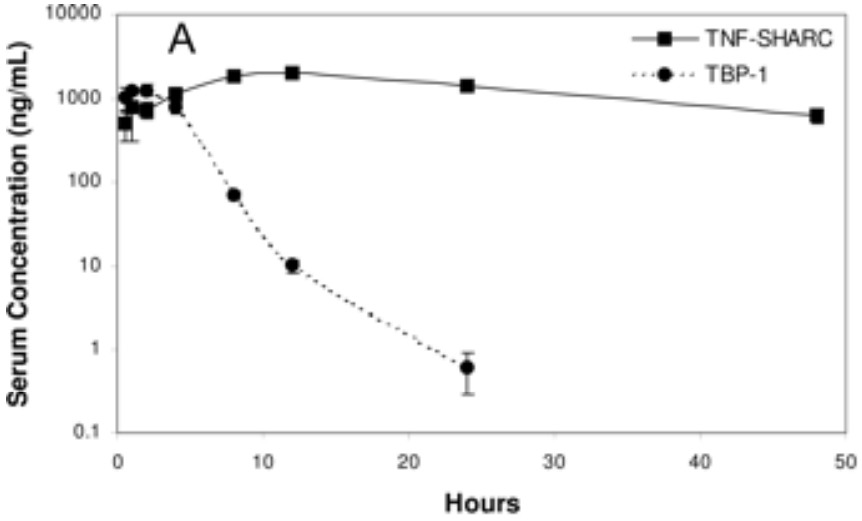


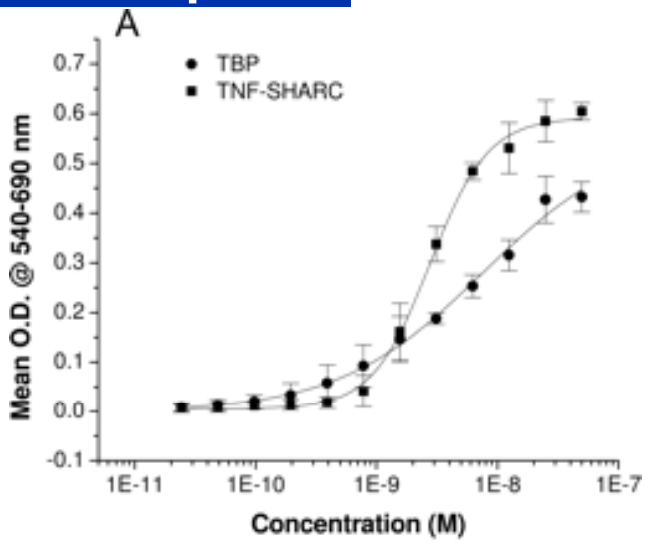


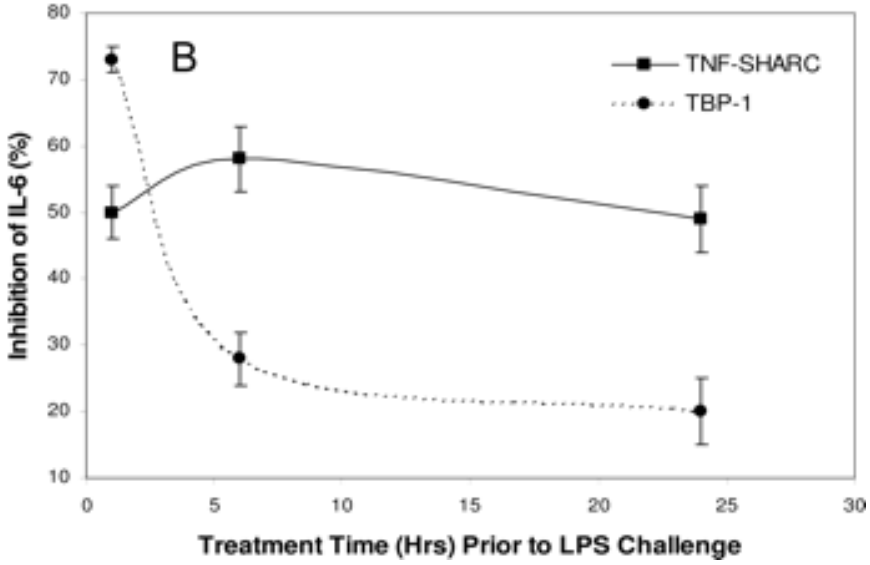
TNF-SHARC
(**S**oluble **H**eterodimeric **A**ntigen **R**eceptor **C**omplex)

Soluble Dimeric TNF Receptor Superior Half-Life In Vivo and Prolonged Suppression of Inflammatory Response:

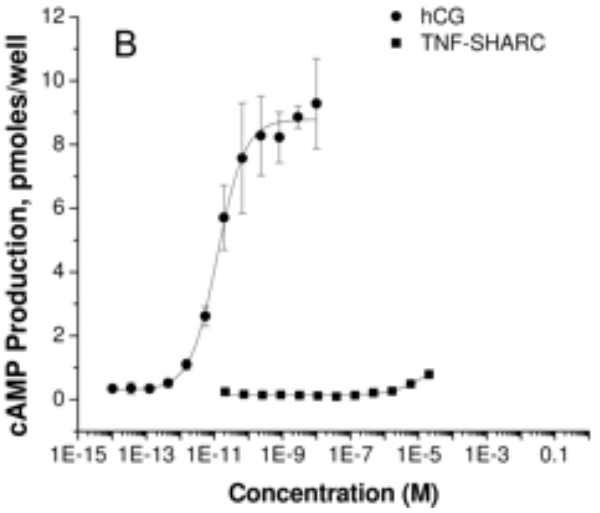
Neither Safety or Efficacy Tested Because of Onercept





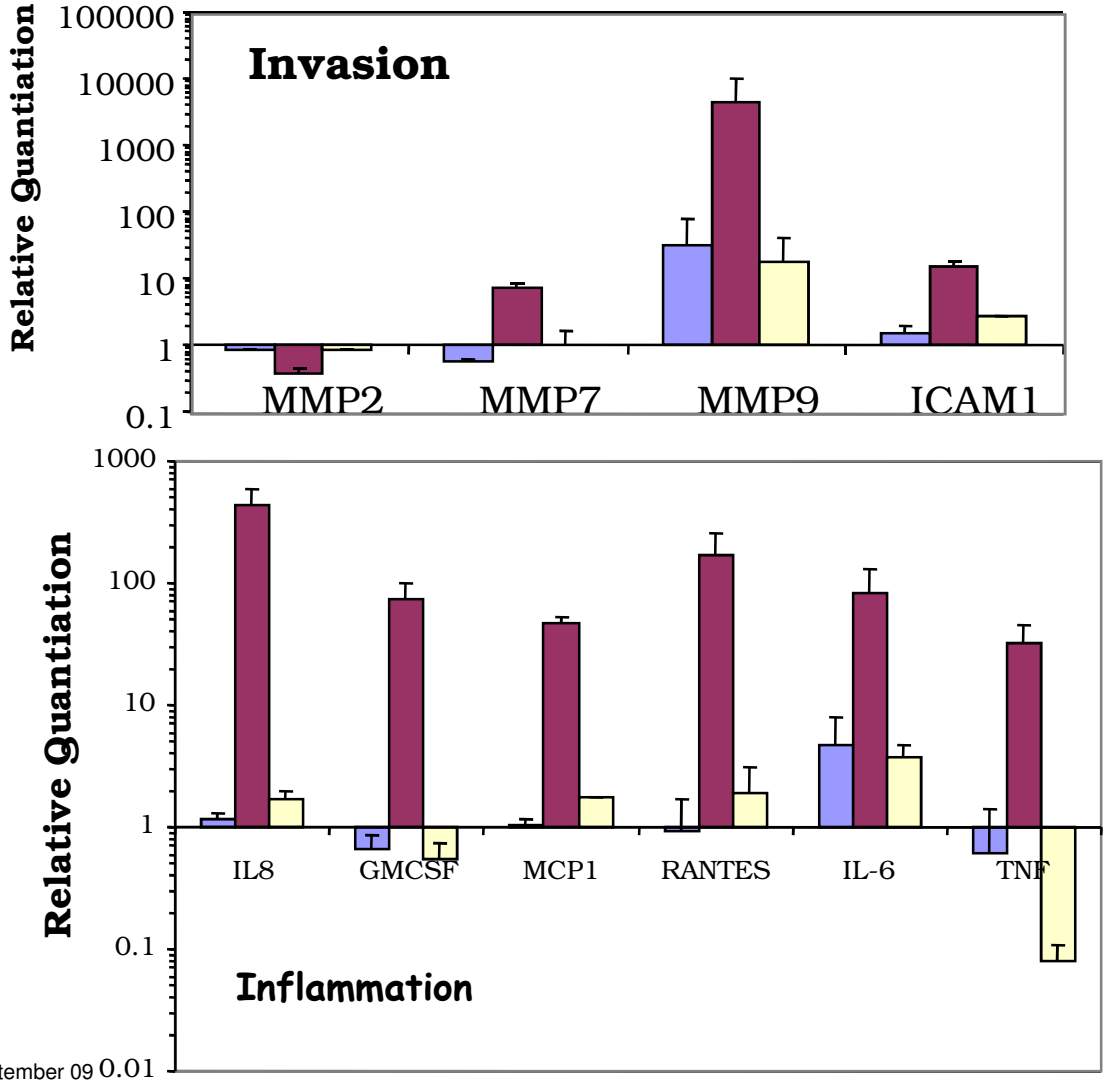


J Pharmacol Exp Ther
2007, 322:822-828

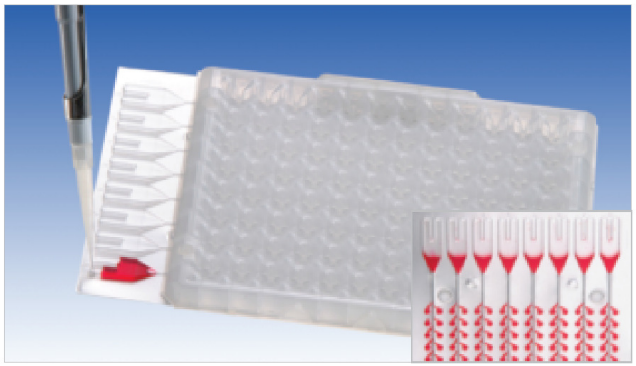


Genes modulated by TNFα in 12Z cells-LDA

(12Z immortalized human endometriotic cells from A. Starzinsky-Powitz)

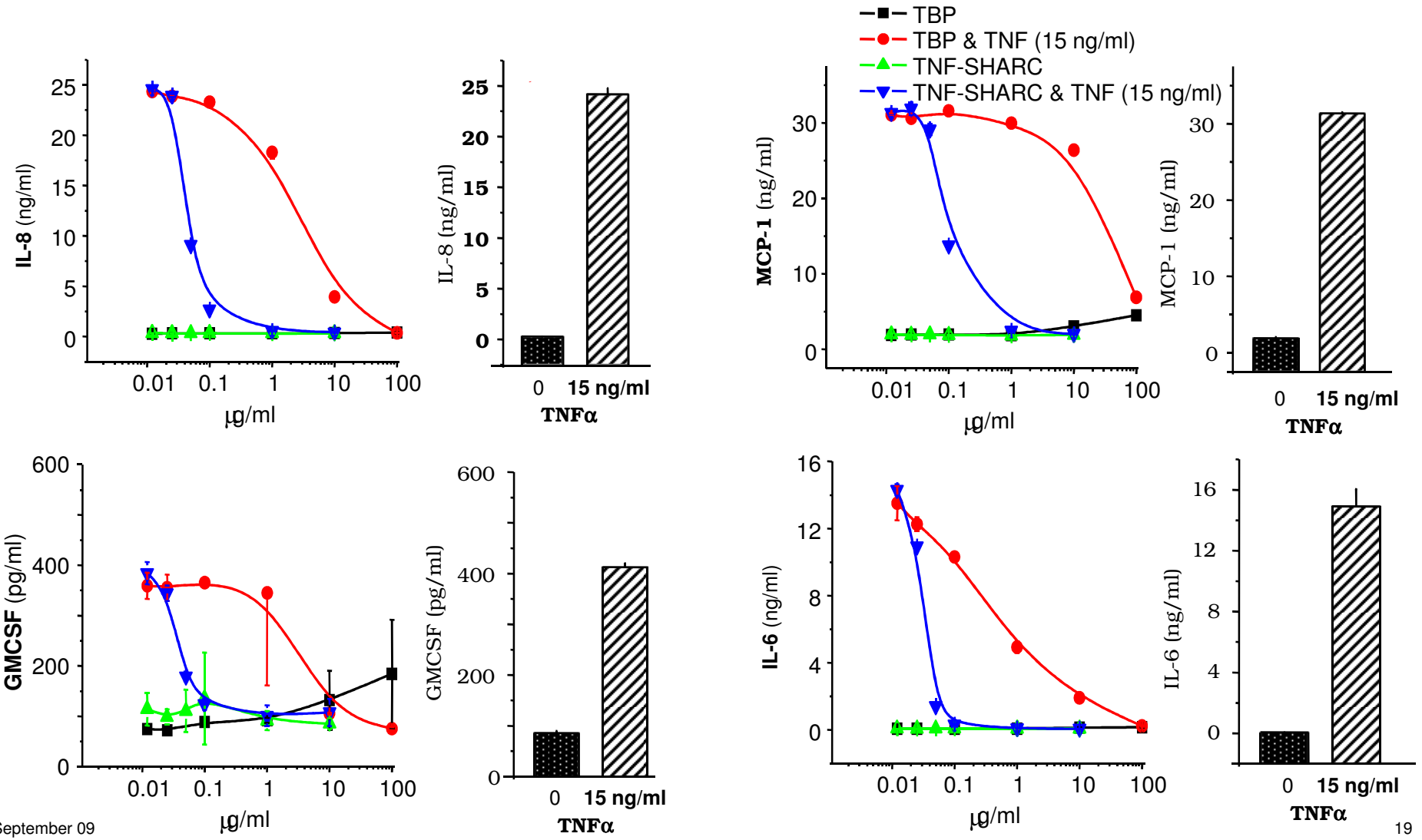


qRT-PCR



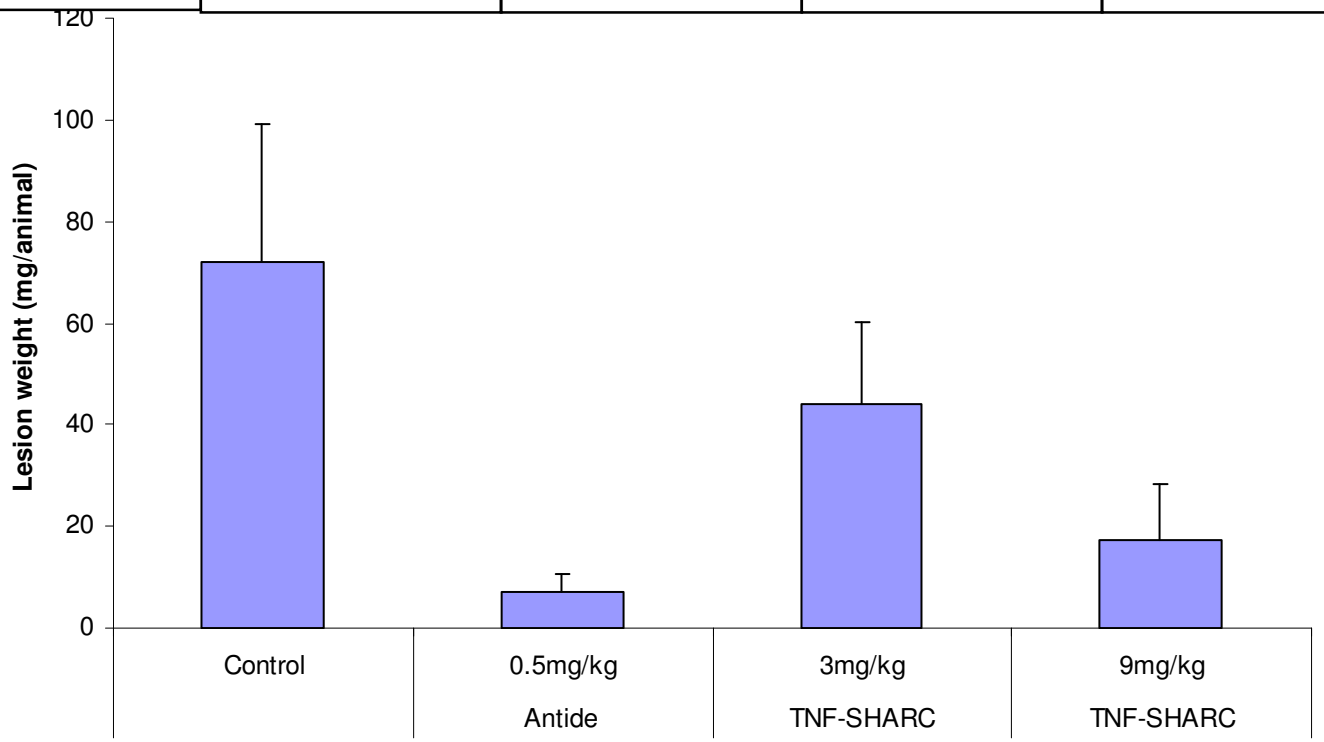
Soluble Dimeric TNF Receptor Inhibits TNFα Response in 12Z cells

ELISA



TNF-SHARC Causes Regression of Lesion in WT mouse model of injected endometriosis

Discovery	Preclin	Ph1	Ph2	Ph3	Reg & L



Drug substance required 1000-fold higher than needed for pharmaceutical efficacy & cost:revenue margin

Stopped before preclinical development

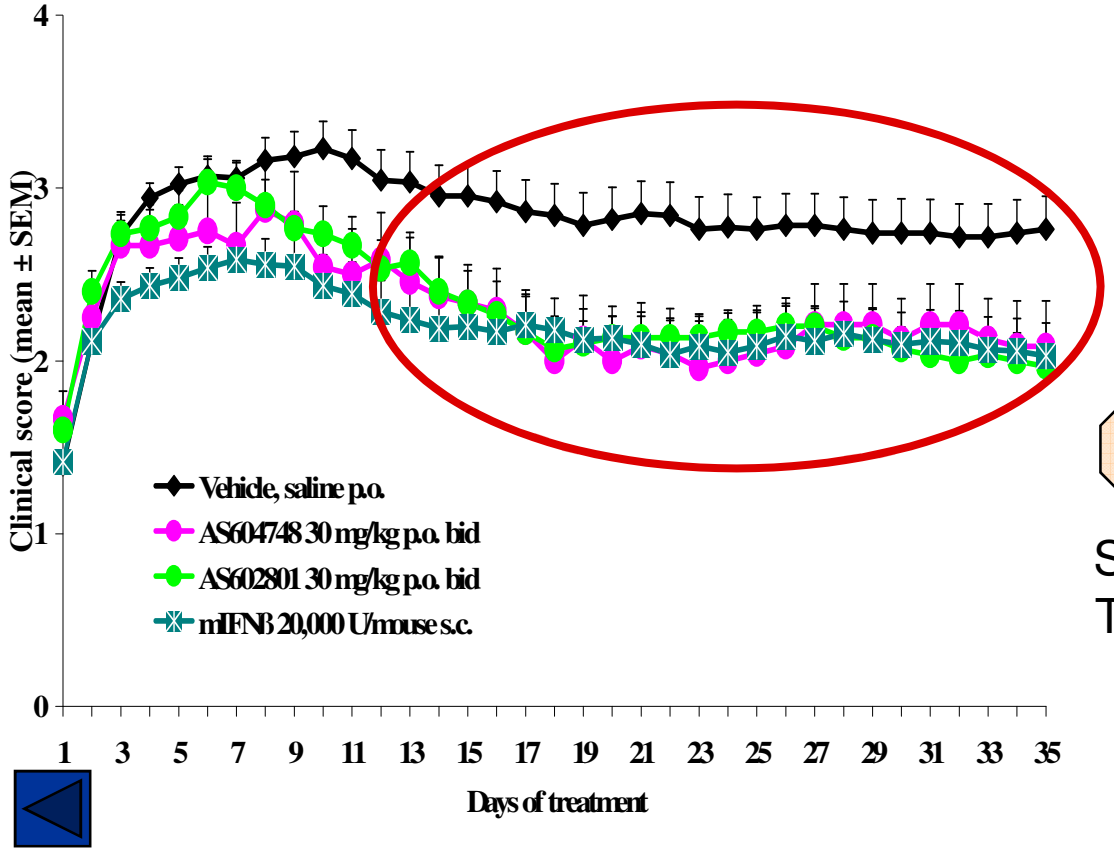
c-Jun-N-terminal Kinase Inhibitor JNK-I

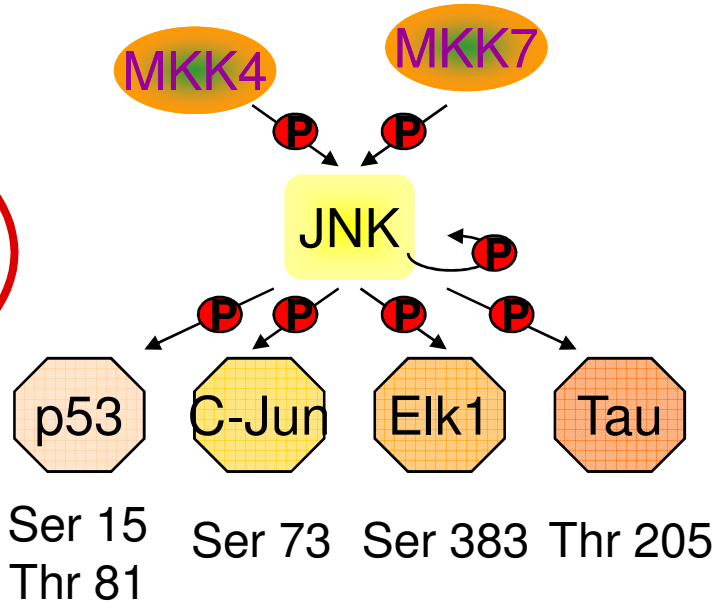
- Primary indication –
  - Multiple Sclerosis
  - Similar reduction in lesions in EAE model as current therapy (Rebif)
  - Orally bioavailable
  - Similar efficacy as Rebif

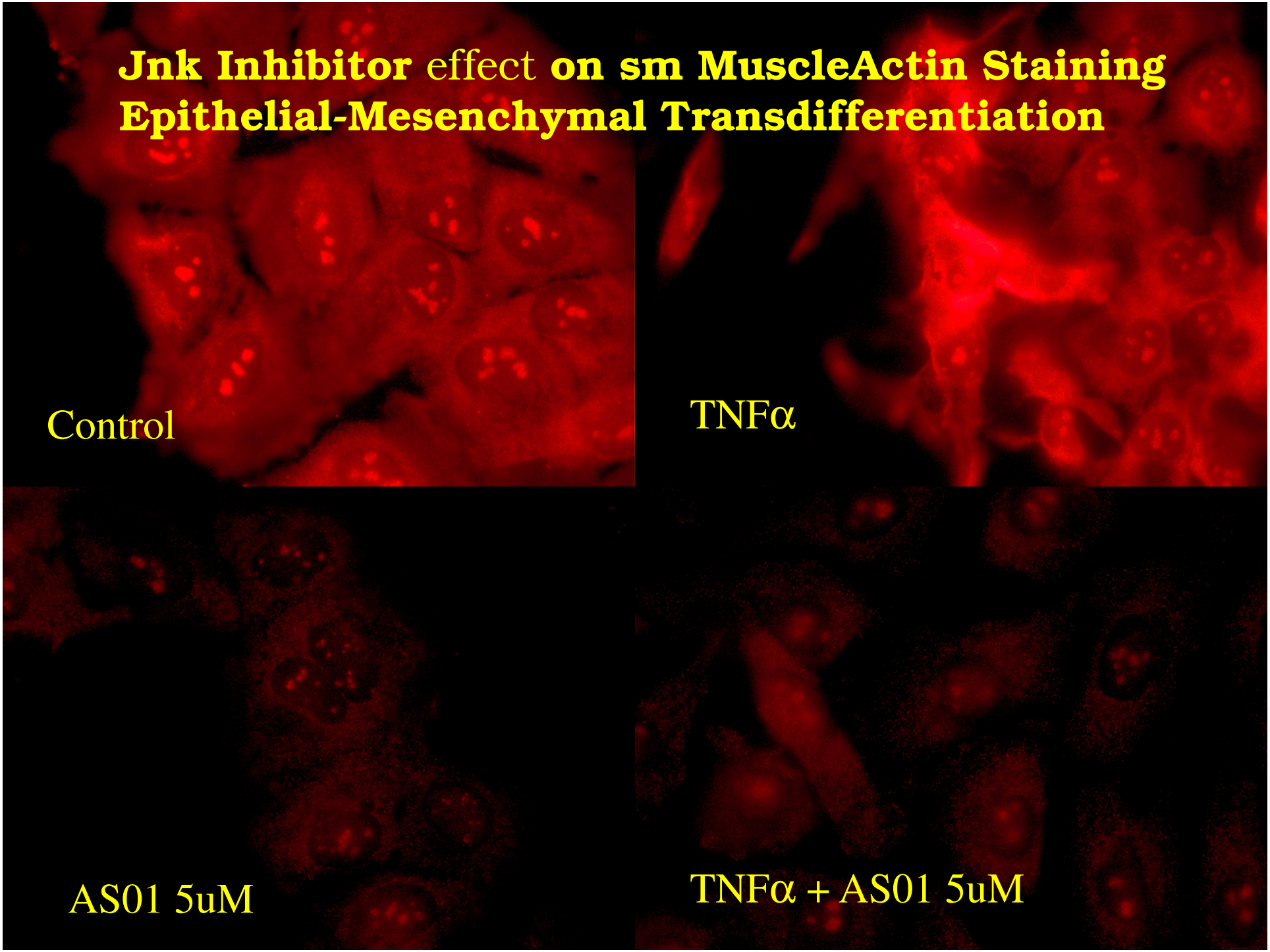
- Secondary indication –
  - endometriosis – best therapeutic response of all diseases
    - Fibrosis, multiple sclerosis, pulmonary fibrosis, CI-arthritis
  - reduced lesion size in 3 rodent models of endometriosis
  - Reverses epithelial-mesenchymal changes (12Z) induced by TNF-α
  - effective on lesion number in baboon model of endometriosis

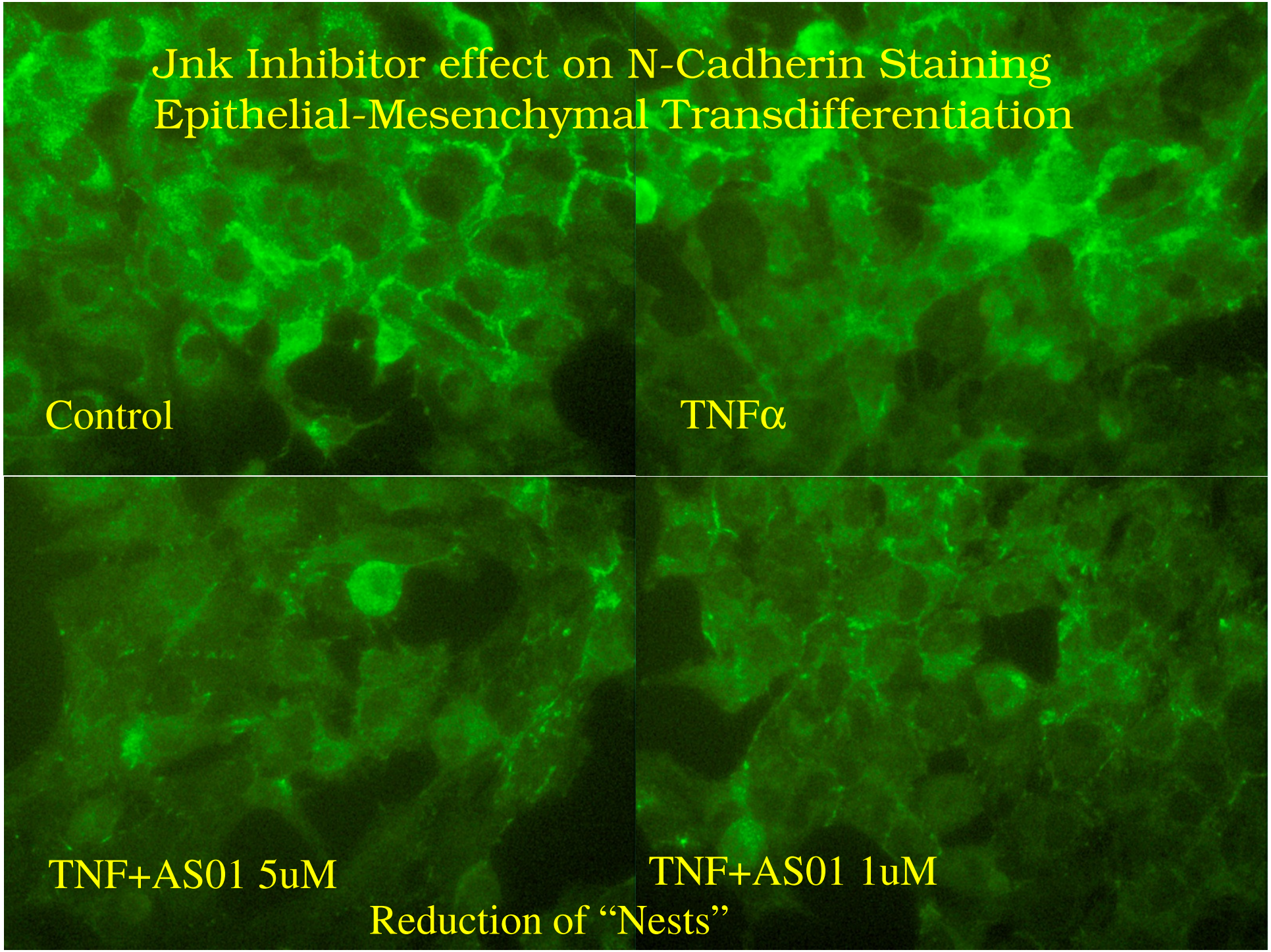
AS602801: a potent, selective ATP-competitive inhibitor of c-Jun-N-terminal Kinase

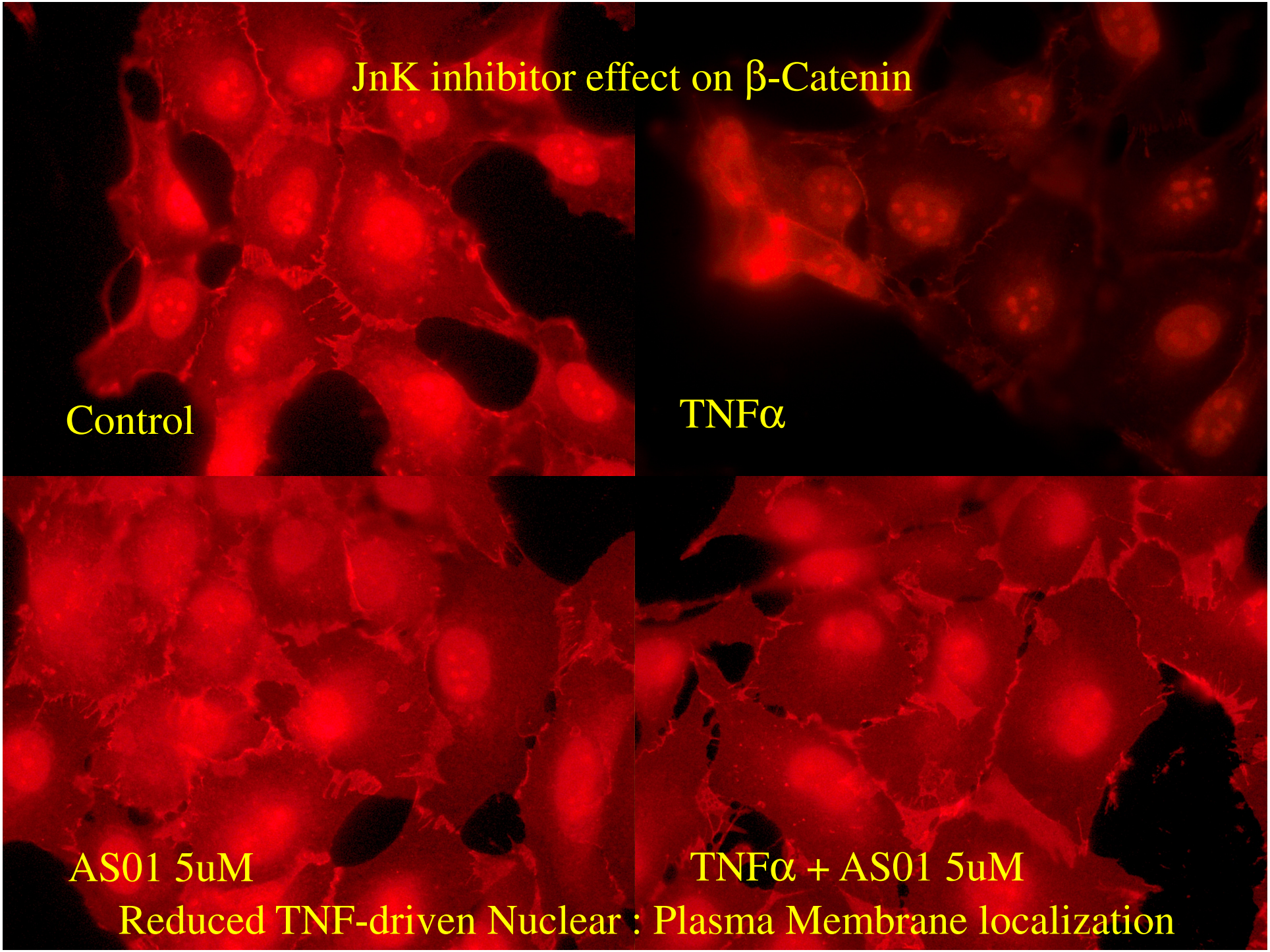
Inhibits TNF-α – mediated inflammatory pathways






Jnk Inhibitor effect on sm MuscleActin Staining
Epithelial-Mesenchymal Transdifferentiation
Control
TNFα
AS01 5uM
TNFα + AS01 5uM

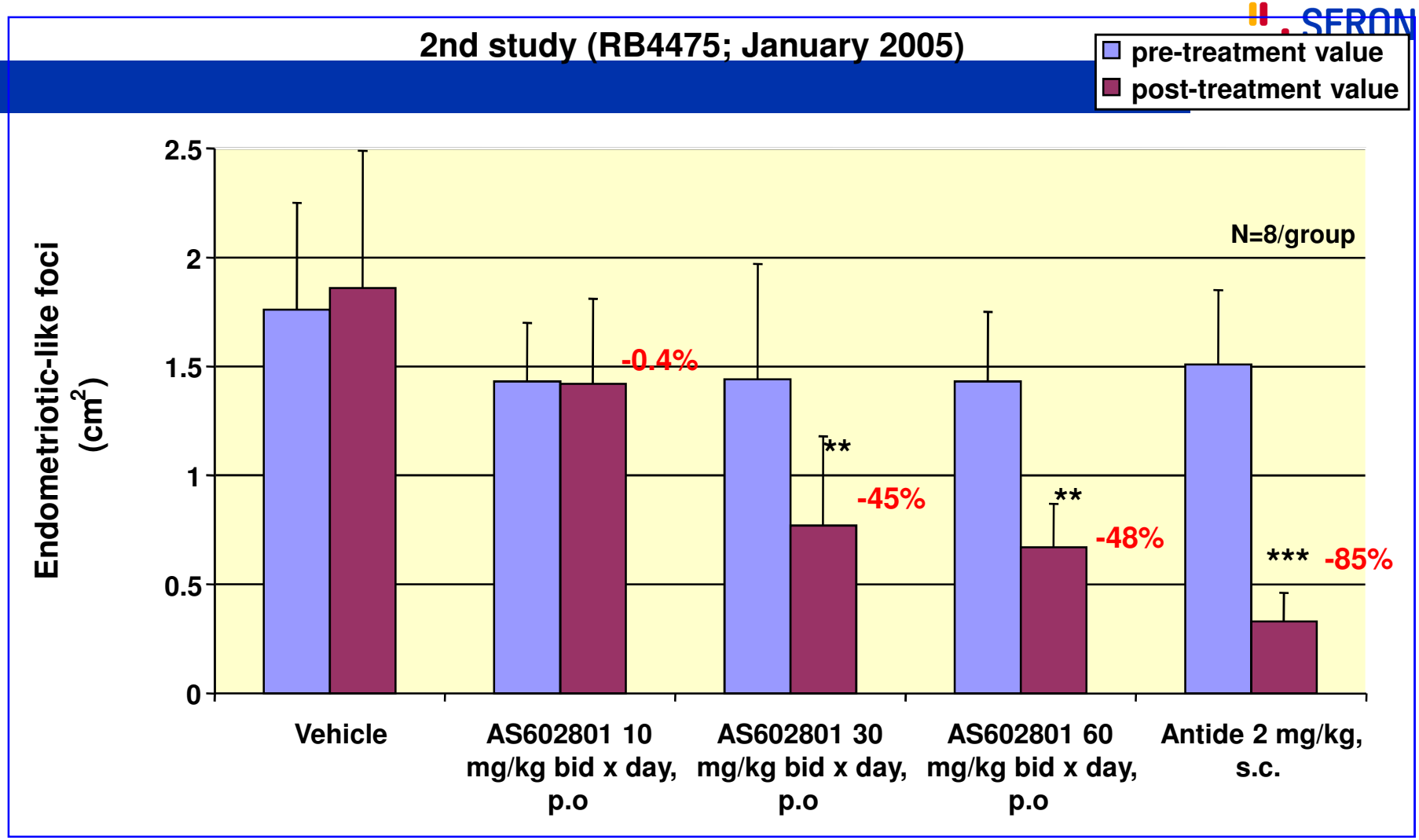

Jnk Inhibitor effect on N-Cadherin Staining
Epithelial-Mesenchymal Transdifferentiation
Control
TNFα
TNF+AS01 5uM
TNF+AS01 1uM
Reduction of "Nests"


JnK inhibitor effect on β-Catenin
Control
TNFα
AS01 5uM
TNFα + AS01 5uM
Reduced TNF-driven Nuclear : Plasma Membrane localization

Preclinical Pharmacology Models That Simulate Processes of Endometriosis

- Surgically induced endometriosis in rats
- Nude mouse human endometrial xenograft
- Wild type mouse – disrupted endometrial preparation
- Baboon

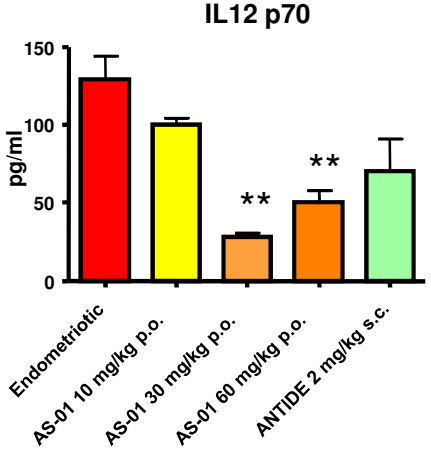
Size of endometriotic-like foci

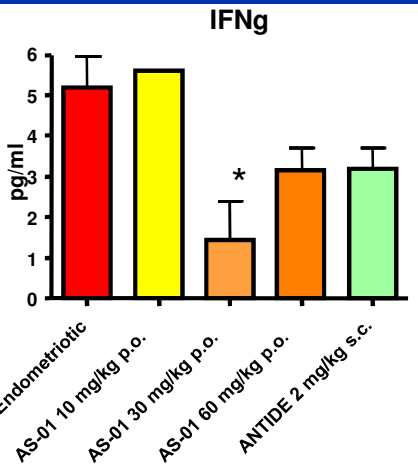


No treatment-related effects on body weight gain

Experimental endometriosis in rats:Cytokines in endometriotic-like foci

MP
IL12p70
T cells
NK cells

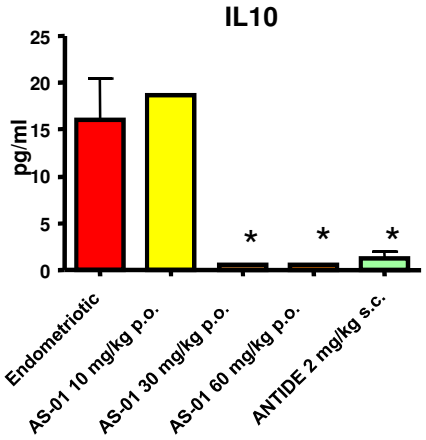


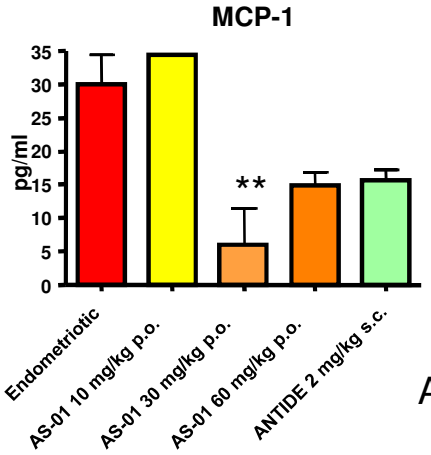


T cells
NK cells
IFNg
T & B cells
MP

T cells

MP
IL10
B cells



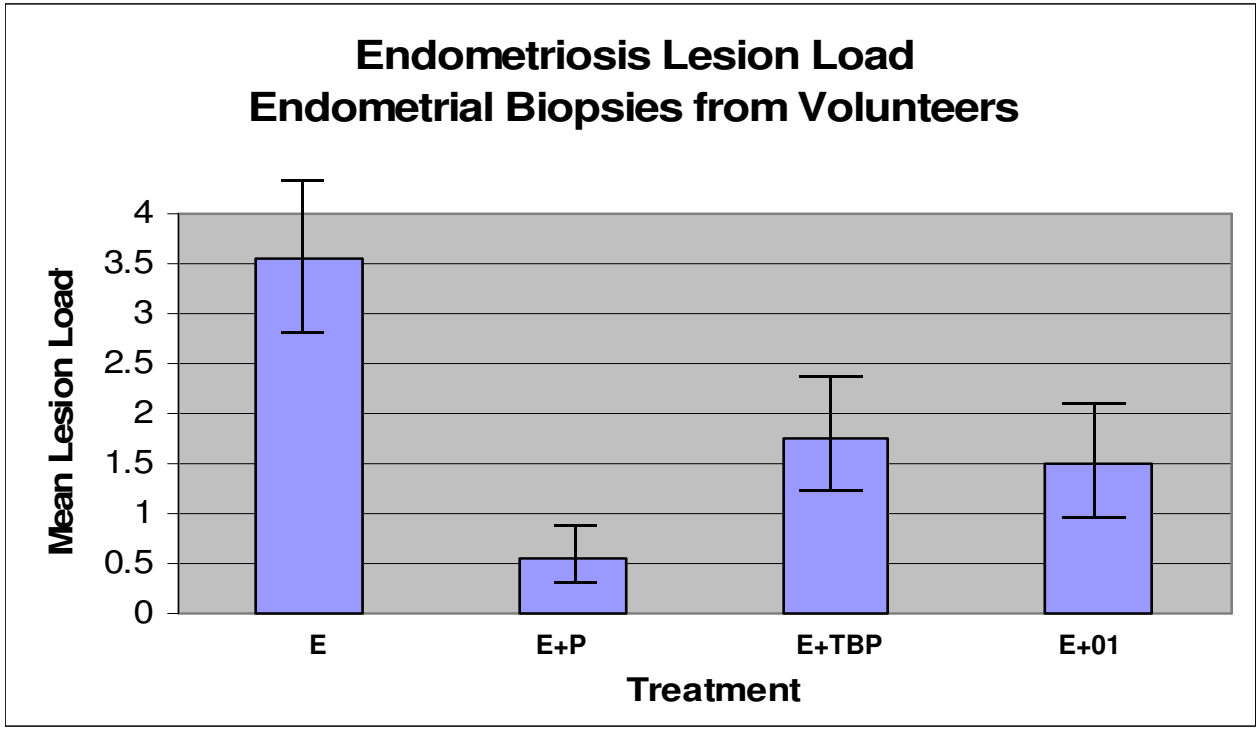


Endothelial cells
Smooth muscle
MCP-1
MO, BA, NK
T cells, DC

n=3
*p<0.05; **p<0.01
ANOVA followed by
Tukey test

AS-01 reduced inflammatory cytokines in endometriotic-like foci

JNK Inhibitors Cause Regression of Endometriosis in Curative Model of Disease in Nude Mice

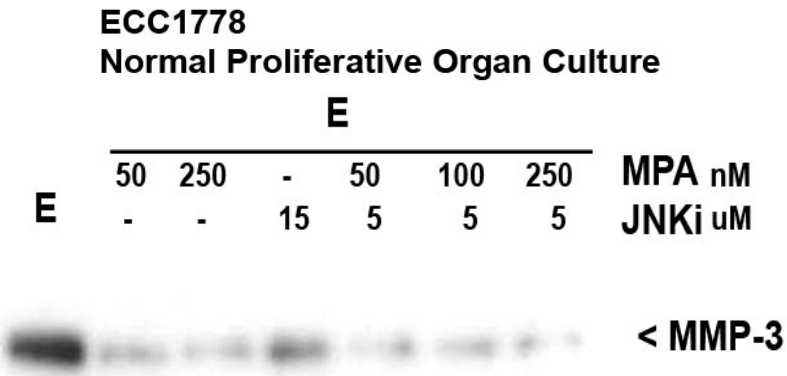


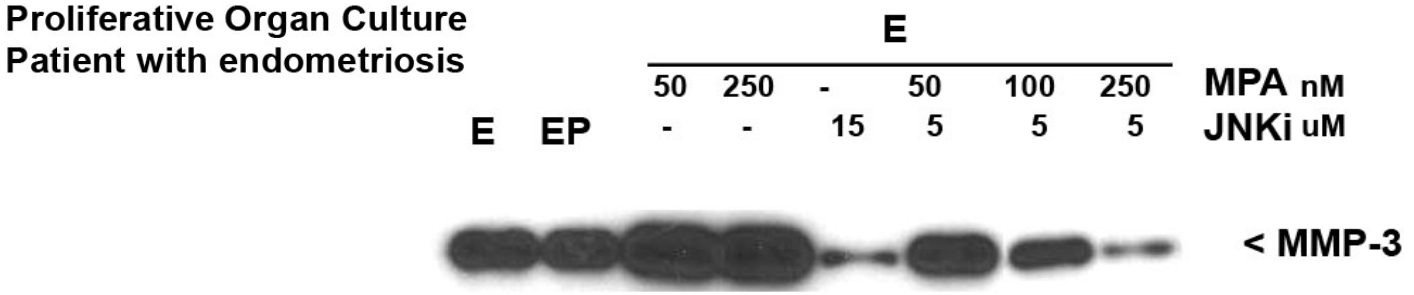
2 JNK Inhibitors Effective
Cause Regression of Established Lesions
25% Have Complete Elimination of Disease

4 independent experiments
n=4 mice / group / experiment
AS01 As Effective As TBP
Causes Regression of Established Lesions
25% Have Complete Elimination of Disease

–Kaylon Bruner-Tran; Kevin Osteen, Vanderbilt Univ

Synergy of JNK Inhibitor with Endocrine Modulator (MPA) in Endometriosis – In Vitro





Progesterone Resistance
Same for MMP-7

JNK Summary –

- Cellular Models
  - 3 systems – model aspects of endometriosis
  - Screening for medicaments that modify process of endometriosis
  - Opportunity to understand therapeutic modulation of disease
  - Test hypotheses and create new focus for drug discovery

- Animals models
  - 4 various models explored – all confirm therapeutic value of repurpose MS drugs to endometriosis
  - Create new biomarkers for disease regression as opposed to academic focus of biomarkers of disease presence.

Regulatory Review of JNK

- Safety pharmacology
  - Phototoxicity (patient exposure to sunlight generates adverse metabolite)
  - Fetal malformations if given during pregnancy – managed by OC
  - No malformations if given prior to conception
- General pharmacology OK
- Non-Clinical Pharmacology
  - Poor drug distribution due to high protein binding specific to humans
    - Not seen in rodents or primates
    - Unexplained; resolve in future analogs
  - Unable to develop plasma biomarker demonstrating decrease of JNK activity
    - Requires elevated plasma TNF-α to see biomarker response
    - (ex-vivo)

Acknowledgement

Selva Nataraja
Daniel de Matos
Deborah Denis
Melis Altan
Sriraman Venkataraman
David Kagan
Anh Tran

External Collaborators:

Asgi Fazleabas
Susana Strakova
University of Illinois at Chicago
Anna Starzinski-Powitz
Frankfurt, Germany
Kaylon-Bruner Tran
Kevin Osteen
Vanderbilt University
Thomas D'Hooghe
Leuven, Belgium

EMD SRI

Effect of AS602801 on Gene Expression in Human Endometrial Xenografts

Proposed Mechanism

Progesterone receptor function compromised in endometriosis

Steroid receptor co-activators augment and co-repressors suppress progesterone receptor activity*

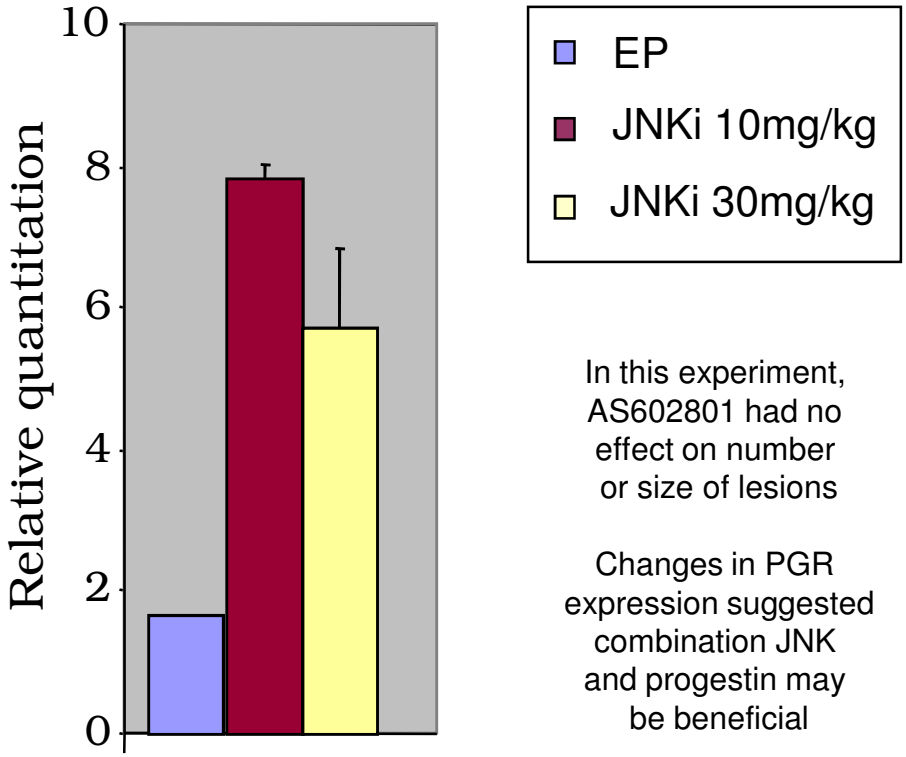
JNK phosphorylates co-repressors and co-activators of progesterone and estrogen receptor*

Co-factor imbalance of progesterone and estrogen receptor function contributes to progression of endometriosis

JNK inhibitor restores progesterone receptor sensitivity (previous slide) and increases progesterone receptor expresssion (this slide)

Proposed therapy – combination JNK and progesterone modulator treats disease, and protects against pregnancy

TaqMan Primers – human-specific
Biopsies obtained from women with disease

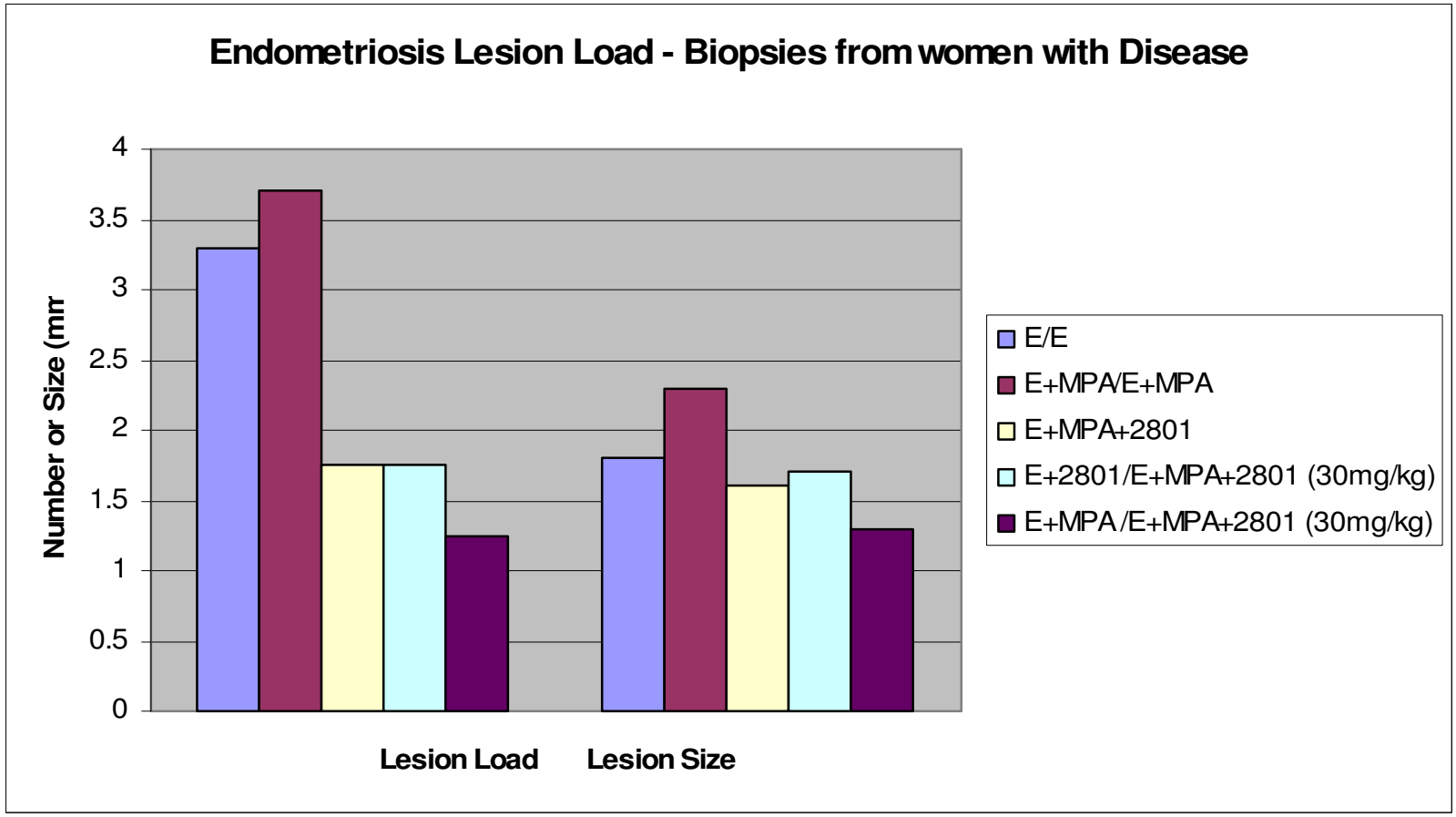


In this experiment, AS602801 had no effect on number or size of lesions

Changes in PGR expression suggested combination JNK and progestin may be beneficial

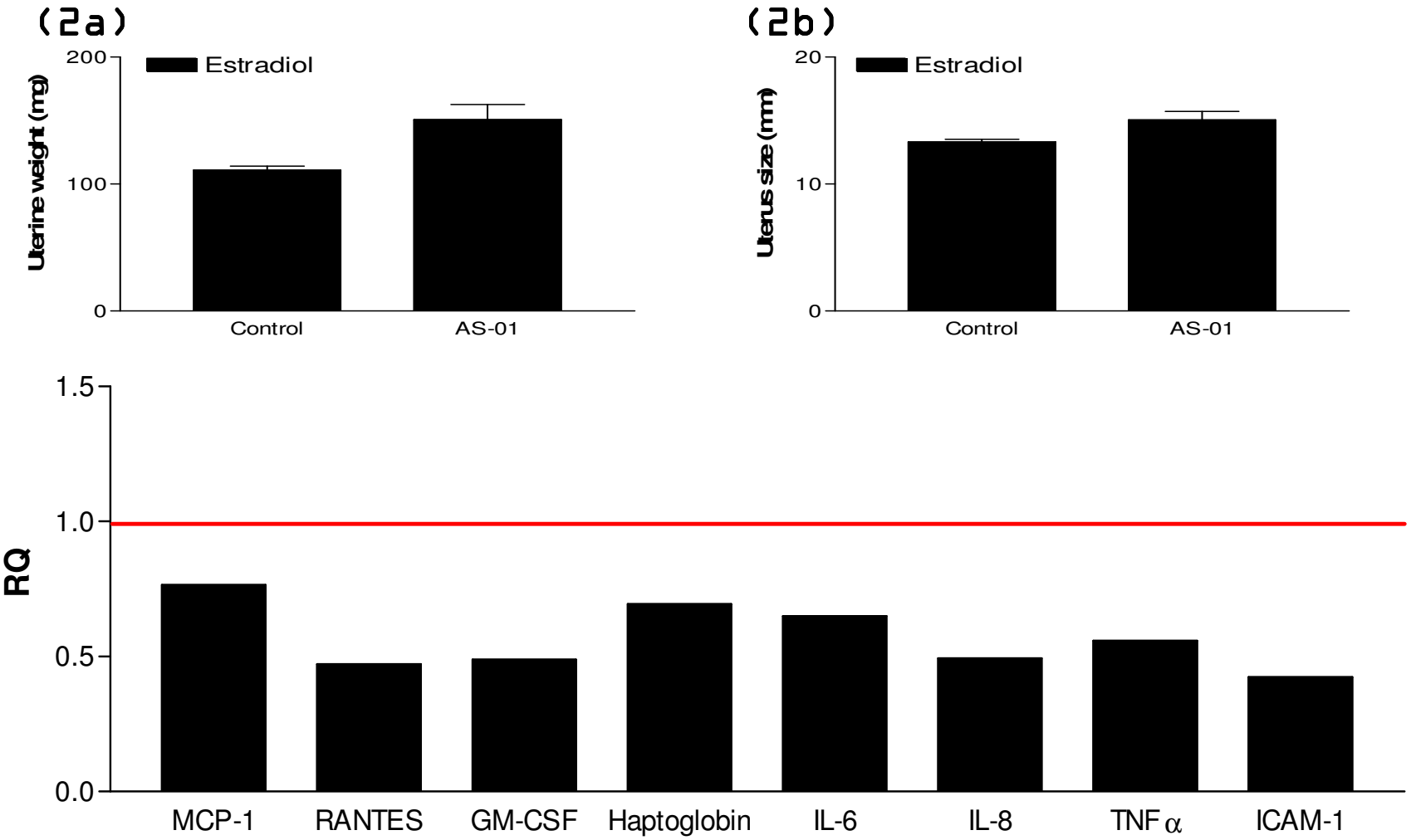
*Feng et al., 2001; Kino et al., 2004

JNK Inhibitor AS01 Restores Progesterone Sensitivity Superior Efficacy Compared Progesterone Alone *In Vivo*



- Confirmed response in biopsies from women with disease
- Results are mean of 2 independent experiments (2 biopsies; n=4/trt)

JNK inhibitor does not affect uterine weight, but reduces expression of inflammatory genes: Human-specific primers



Enzymes that regulate tissue remodeling and angiogenesis are suppressed by AS602801