ISCTM
International Society for CNS Clinical Trials and Methodology

Drug development in heterogeneous disorders: When to target subgroups? Case example in PTSD

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Disclosure

Consulted to Jazz Pharmaceuticals and Roche Pharmaceuticals

Case Example: Phase IIa Trial of a Selective Glucocorticoid Receptor Antagonist in the Treatment of Veterans with Posttraumatic Stress Disorder (PTSD)

- Aim 1: examine safety and tolerability of CORT108297 (Corcept) compared to placebo in Veterans with military related PTSD (N=80)
- Aim 2: examine the efficacy of CORT108297 (7 days) on PTSD symptoms in Veterans by change from baseline to week 8
- Measure biomarkers of glucocorticoid sensitivity pre and post treatment
- ***Question: Should the study sample be enriched for subjects with measurable increased glucocorticoid signaling?***

Background: HPA Axis Enhanced Negative Feedback Sensitivity in PTSD

Enhanced Suppression of Cortisol Following Dexamethasone Administration in Posttraumatic Stress Disorder

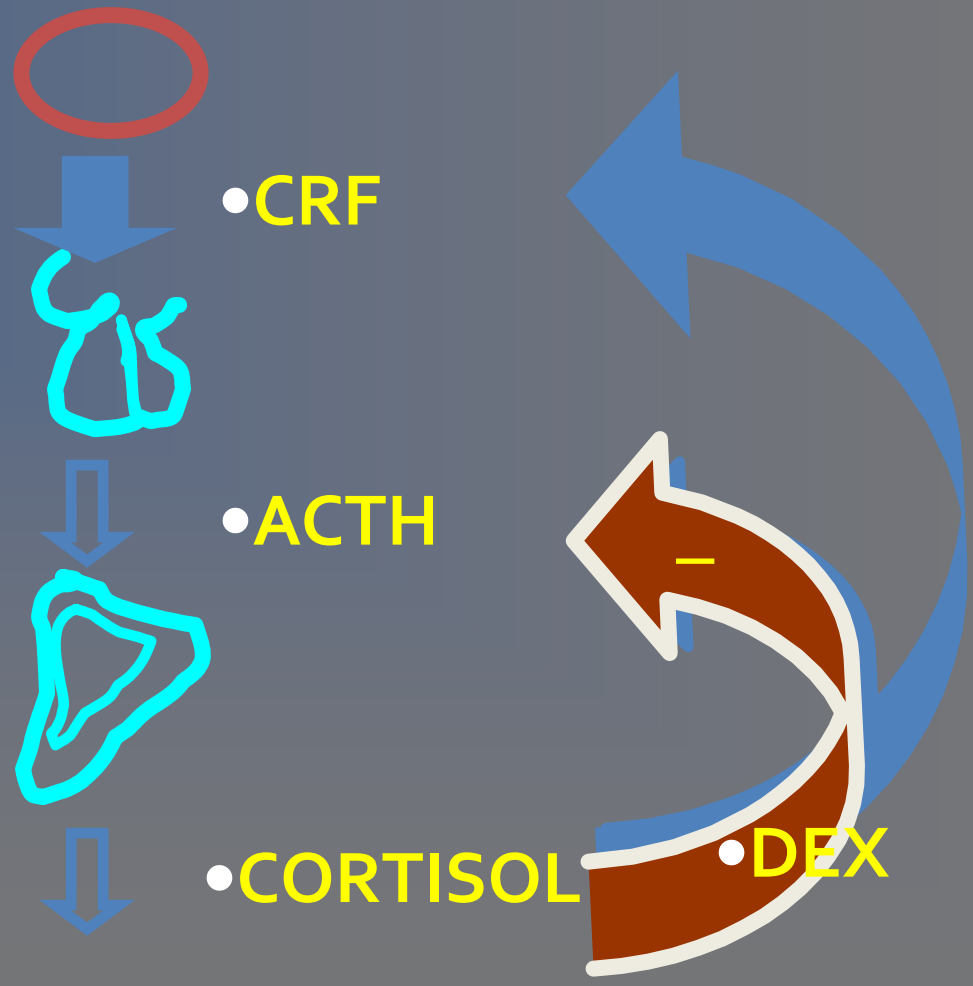
Rachel Yehuda, Ph.D., Steven M. Southwick, M.D., John H. Krystal, M.D., Douglas Bremner, M.D., Dennis S. Charney, M.D., and John W. Mason, M.D.

Objective: The authors investigated the possibility of enhanced negative feedback sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis in posttraumatic stress disorder (PTSD) by using a low dose of dexamethasone. Method: Baseline blood samples were obtained at 8:00 a.m., and 0.5 mg of dexamethasone was administered to 21 male patients with PTSD and 12 normal age-comparable men at 11:00 p.m. Cortisol and dexamethasone levels were measured 9 and 17 hours after dexamethasone administration. Results: After correction for differences in dexamethasone levels, the PTSD patients showed greater suppression of cortisol in response to dexamethasone than did the normal subjects. This was true even in patients meeting concurrent diagnostic criteria for major depression. Conclusions: The data support earlier studies showing that HPA abnormalities in PTSD are different from those seen in depression and suggest that the low-dose dexamethasone suppression test may be a potentially useful tool for differentiating the two syndromes and further exploring differences in their pathophysiology.

(Am J Psychiatry 1993; 150:83–86)

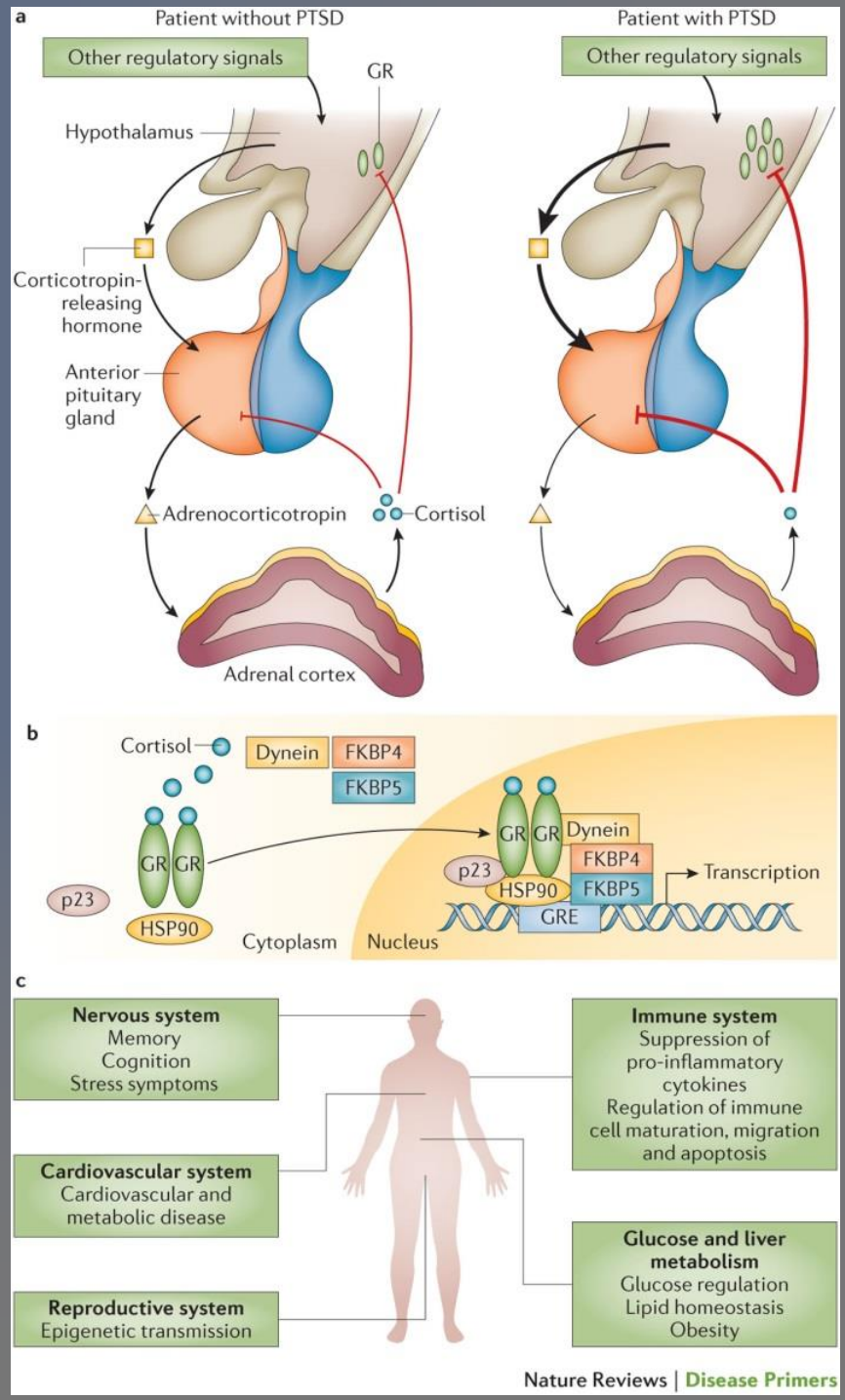
•Dexamethasone Suppression Test (DST)

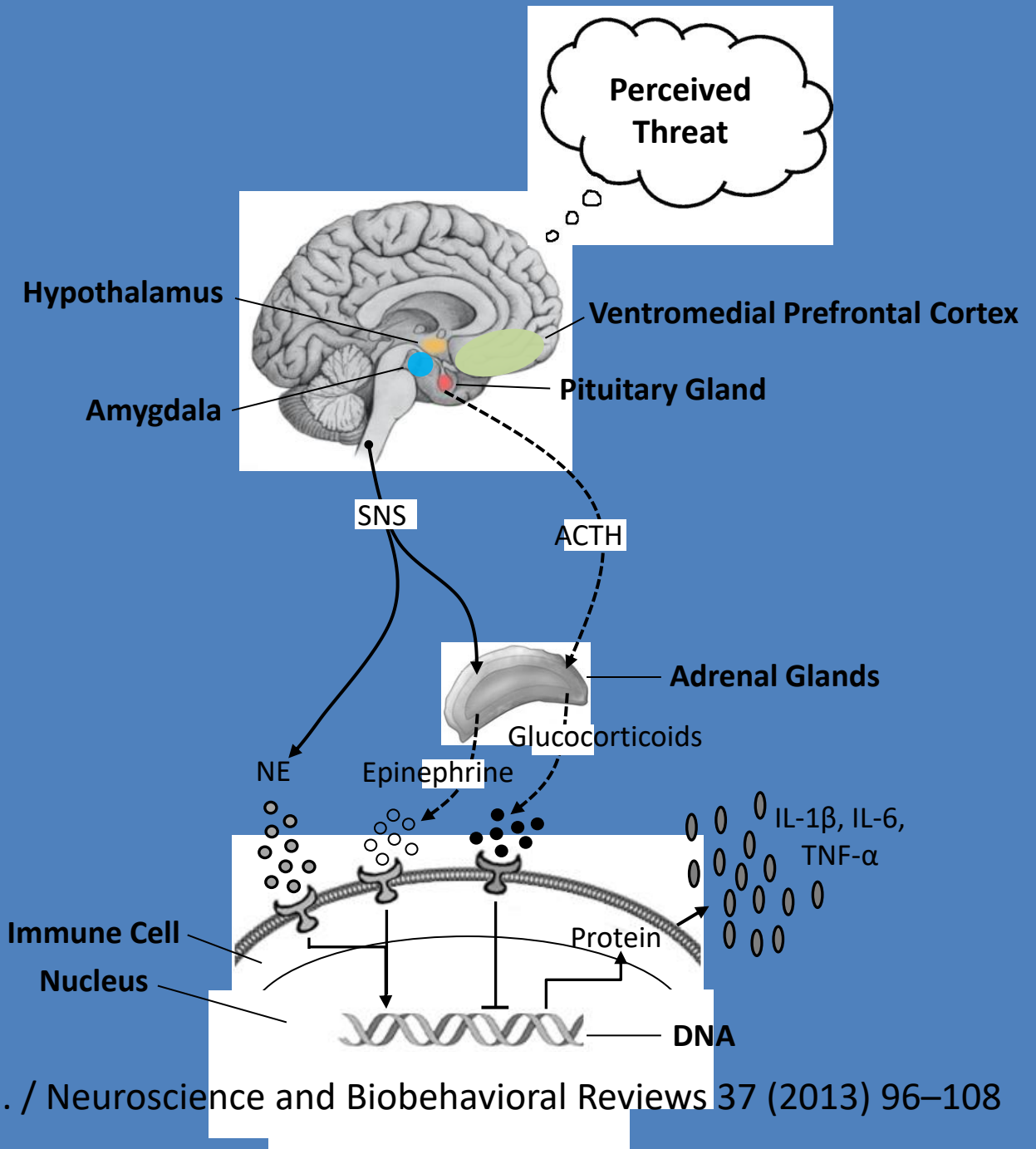
- Tests the strength of cortisol negative feedback inhibition of the HPA axis
- At low doses DEX occupies GR in the pituitary and not the CNS



Function of the HPA axis in PTSD and controls

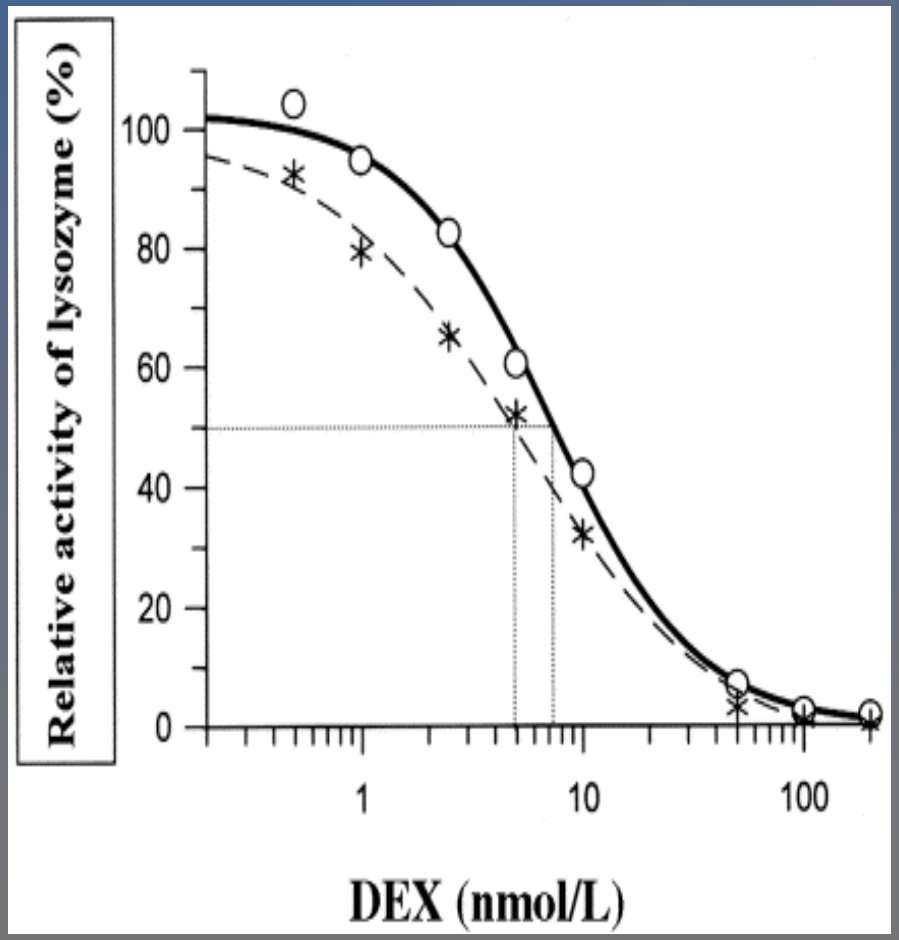
Yehuda, R. *et al*. (2015) Post-traumatic stress disorder *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.57





A. O'Donovan et al. / Neuroscience and Biobehavioral Reviews 37 (2013) 96–108

Increased Glucocorticoid Sensitivity in PTSD



Lysozyme Inhibition Test an *in vitro* measure of glucocorticoid receptor sensitivity ($IC_{50\text{-}DEX}$)

Subjects with PTSD had significantly lower mean concentration (nmol/L)) of dexamethasone at which 50% of lysozyme activity is inhibited

- IC50-DEX
- PTSD (n=26) 4.9 ± 0.5
- Controls (n=18) 7.2 ± 0.6
- F(1,41)=7.3, p=0.009, controlling for BMI

- Yehuda, Golier, Yang et al., 2004

GR Modulation as treatment for PTSD?

- PTSD associated with HPA axis dysregulation
- Distinct neuroendocrine profile from other psychiatric disorders
- Increased responsiveness of glucocorticoid receptors (GR)
- Recalibration of HPA axis with short acting medication may have benefit
- Short duration GR modulator therapy with mifepristone ‘reset’ abnormal cortisol levels in patients with bipolar disorder
- 7- day GR modulator therapy with mifepristone shows 56- day durable effect in psychotic depression

Mifepristone

- GR and PR antagonist
- No affinity for MR, ER
- Limited AR affinity
- Potential therapy in HPA axis dysregulation:
  - Cushing's Syndrome
  - Psychotic Depression
  - PTSD
  - Antipsychotic induced weight gain
  - Alzheimers disease

A Randomized Clinical Trial of Mifepristone in Veterans with PTSD

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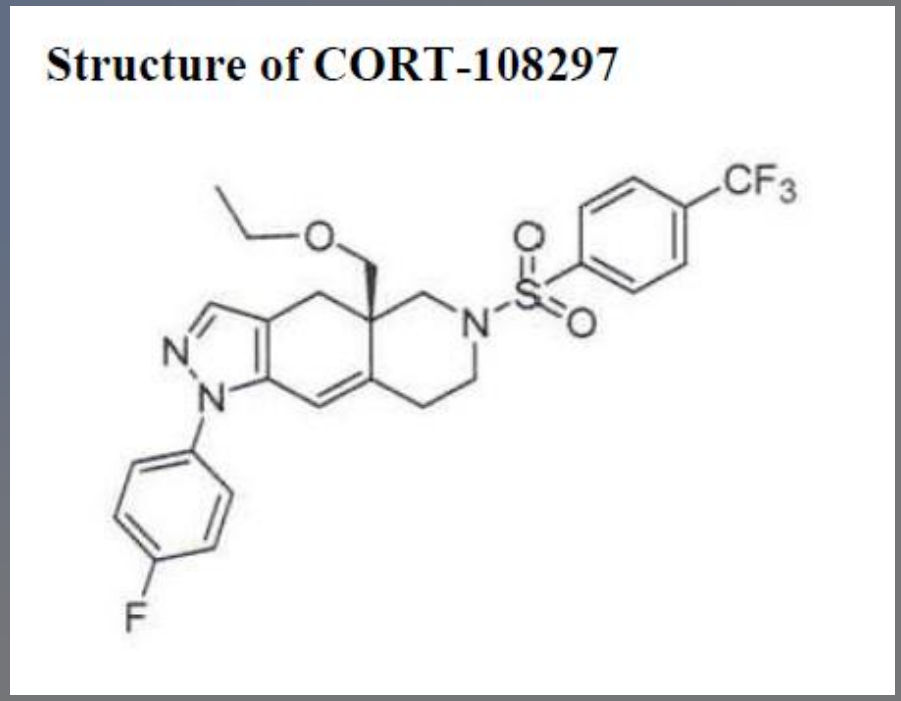
CORT108297

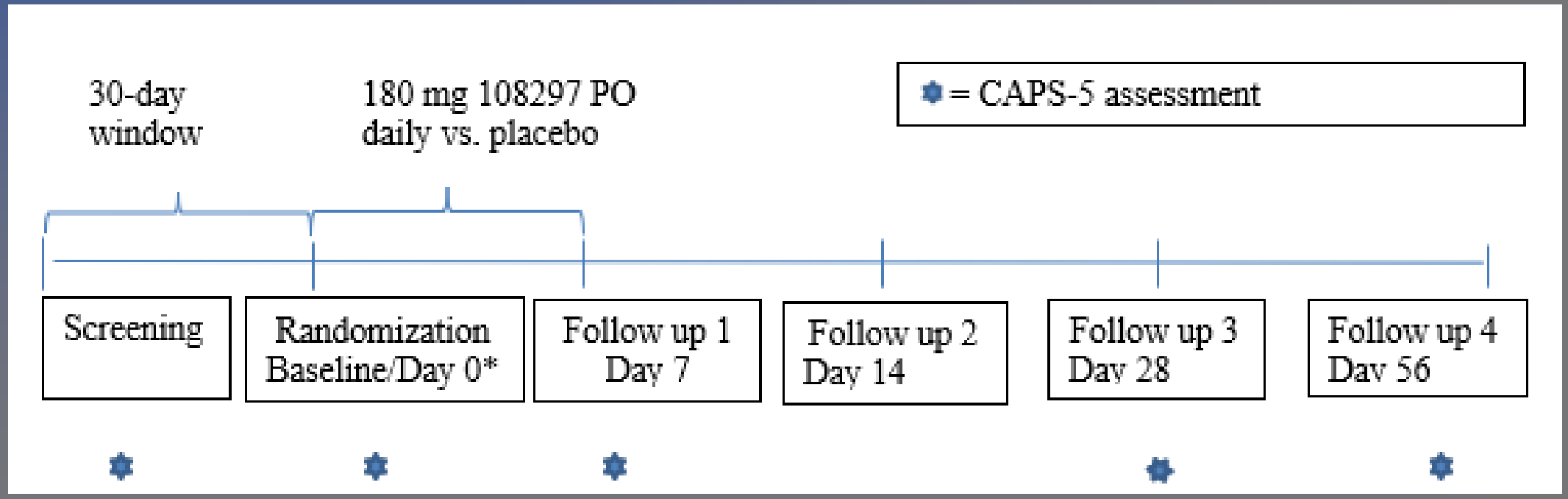
- Selective GR modulator
  - Full or partial antagonist in rat, monkey, human
  - Agonist in dog
- No affinity for PR, ER, AR, MR
- Bioavailable
- Crosses BBB
- Evaluated for safety and tolerability in healthy volunteers under US IND



CORT108297 *In Vitro* Profile

- Potent GR antagonist with > 1,000 fold selectivity compared with PR, MR, ER and AR
- Inhibits dexamethasone induced increase in TAT (tyrosine amino transferase) activity in human primary hepatocytes
- Inhibits dexamethasone induced increase in FKBP5 gene expression in human whole blood

Study Design



Design Considerations regarding targeting a homogenous subgroup

- 1) the pre-eminent need to establish safety of a novel compound not previously used in clinical patients;
- 2) Uncertainty about whether peripheral biomarkers adequately index CNS glucocorticoid receptors (e.g. validity of biomarker);
- 3) Concerns that biomarker assays are not scalable in clinical settings
- 4) Uncertainty about the direction of response to an antagonist in a highly buffered endocrine system;
- 5) Possible gain of power and discovery by allowing a heterogeneous population to be enrolled.

From the Broad Phase II Trial to Precision Oncology: A Perspective on the Origins of Basket and Umbrella Clinical Trial Designs in Cancer Drug Development

Deborah B. Doroshow, M.D., Ph.D. [Assistant Professor of Medicine]
Icahn School of Medicine at Mount Sinai

James H. Doroshow, M.D. [Director]
Division of Cancer Treatment and Diagnosis, National Cancer Institute, NIH

Cancer J. 2019 ; 25(4): 245–253

- Early phase II studies included wide range of malignancies
- Refining selection on the basis of histopathology did not markedly accelerate progress
- Molecularly-characterized disease subtypes improved outcomes
- Precision Medicine: “The right drug for the right person at the right time”

Phase II Precision Medicine Trial- example

Fumet et al. BMC Cancer (2020) 20:748
https://doi.org/10.1186/s12885-020-07253-x

BMC Cancer

STUDY PROTOCOL Open Access

Check for updates

Precision medicine phase II study evaluating the efficacy of a double immunotherapy by durvalumab and tremelimumab combined with olaparib in patients with solid cancers and carriers of homologous recombination repair genes mutation in response or stable after olaparib treatment

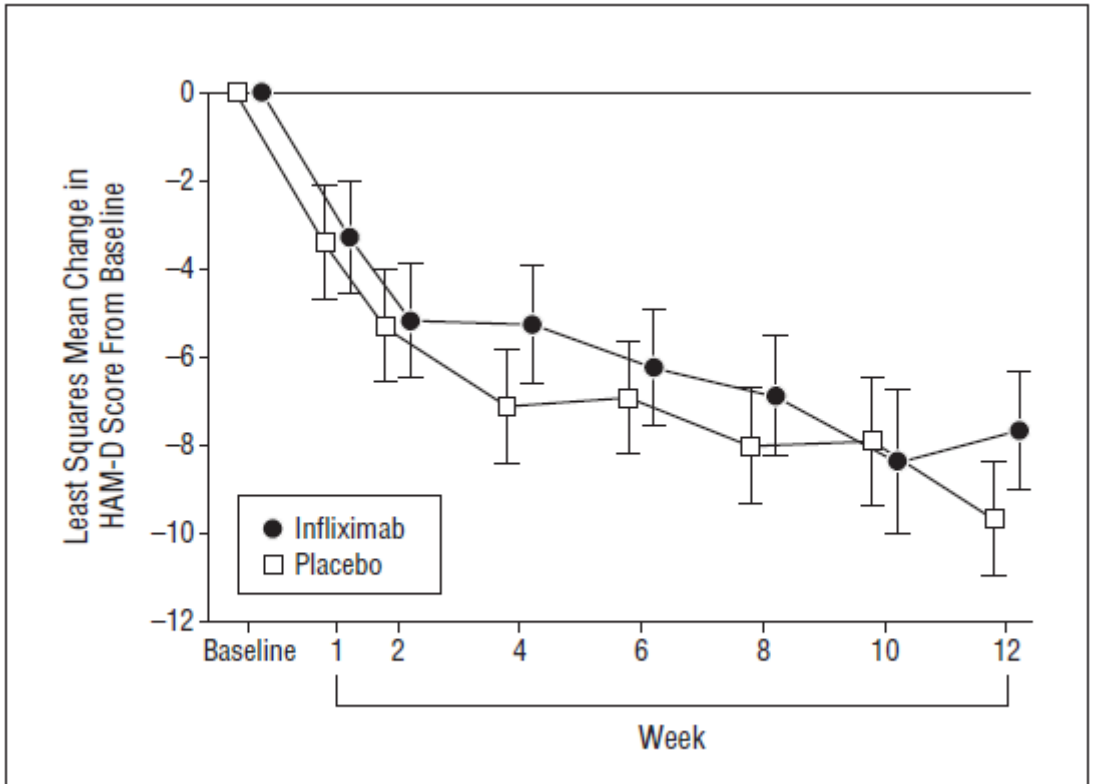
Jean-David Fumet[1,2,3,4,5*], Emeric Limagne[2,4,5], Marion Thibaudin[2,4,5], Caroline Truntzer[2,4,5], Aurélie Bertaut[6], Emilie Rederstorff[6] and Francois Ghiringhelli[1,2,3,4,5]

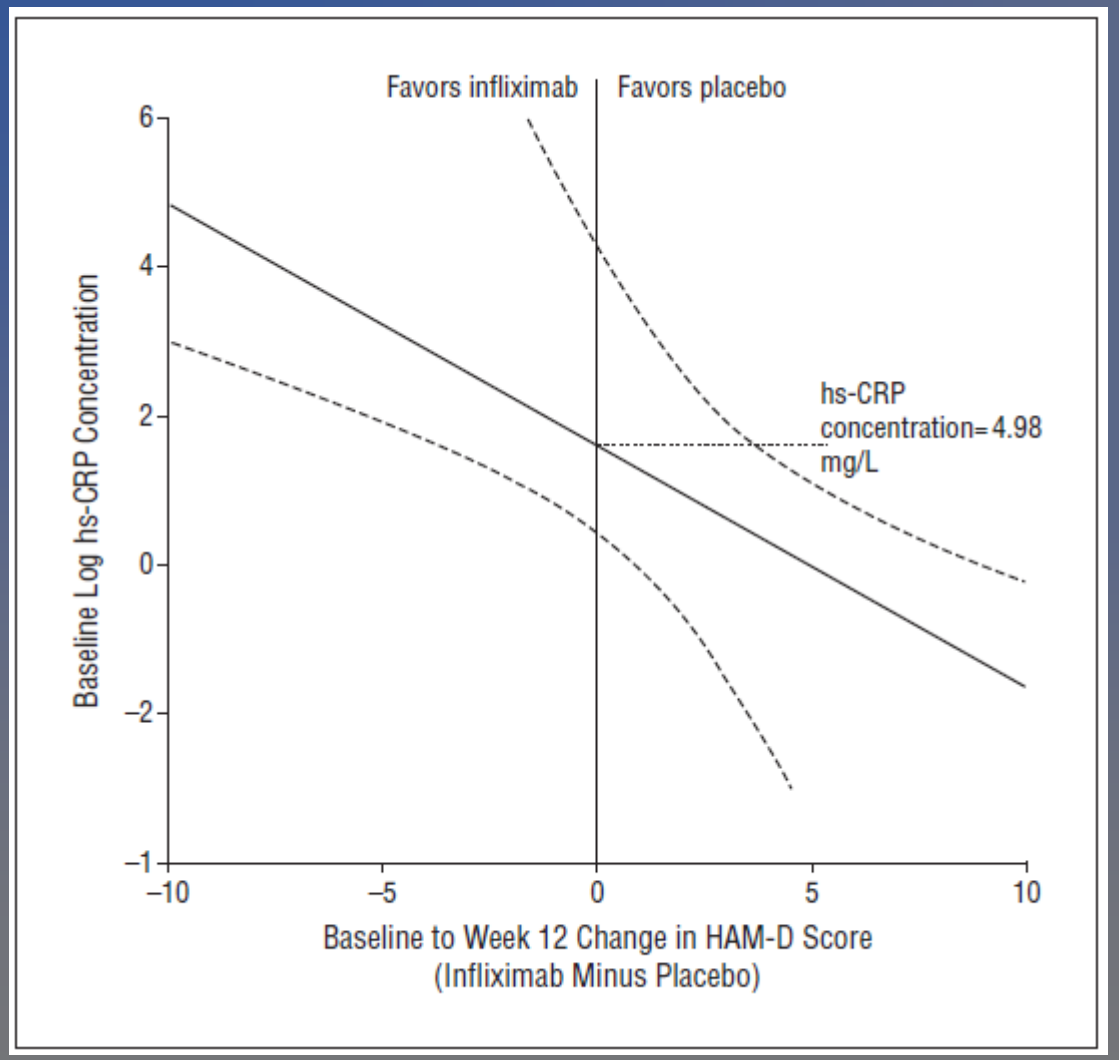
ORIGINAL ARTICLE

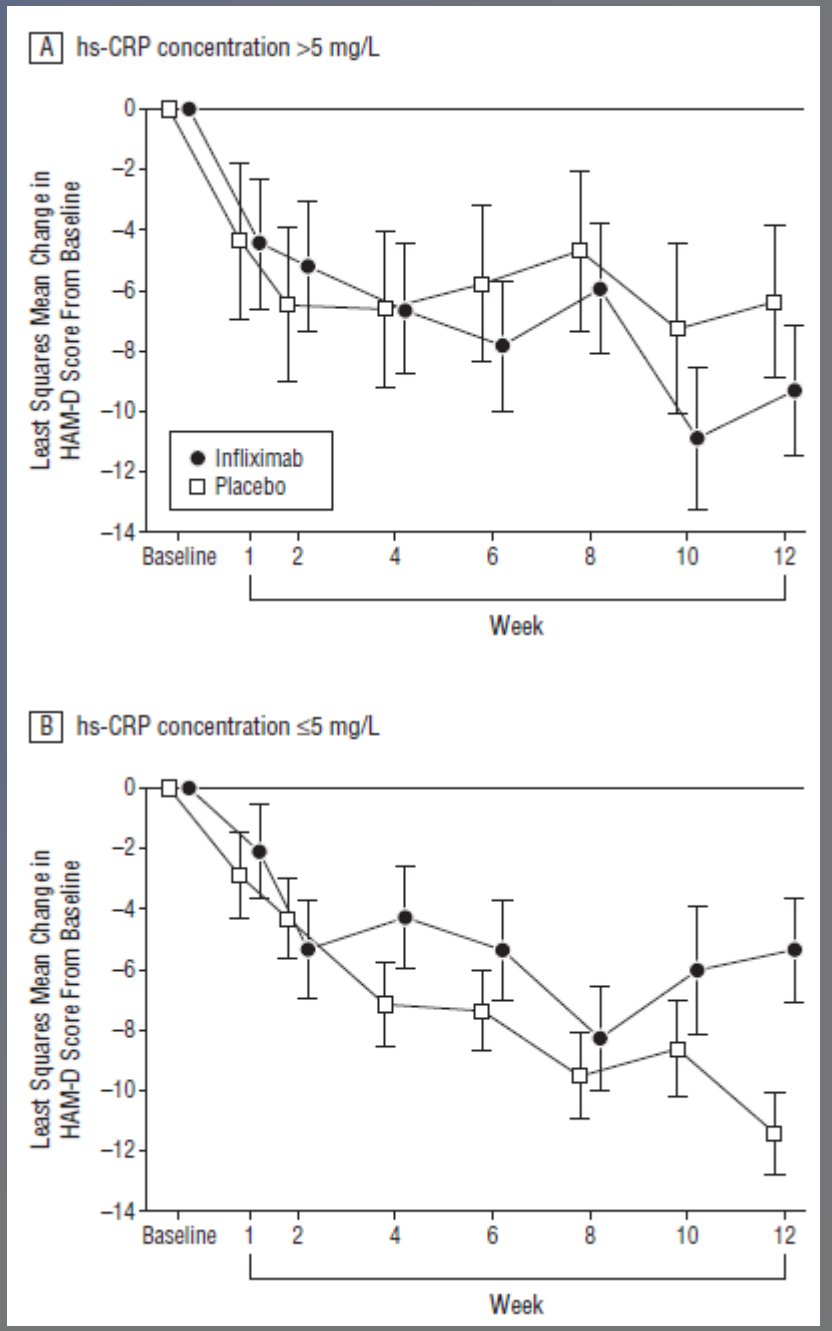
A Randomized Controlled Trial of the Tumor Necrosis Factor Antagonist Infliximab for Treatment-Resistant Depression

The Role of Baseline Inflammatory Biomarkers

Charles L. Raison, MD; Robin E. Rutherford, MD; Bobbi J. Woolwine, MSW; Chen Shuo, MS; Pamela Schettler, PhD; Daniel F. Drake, PhD; Ebrahim Haroon, MD; Andrew H. Miller, MD




Favors infliximab
Favors placebo
hs-CRP concentration= 4.98 mg/L
Baseline Log hs-CRP Concentration
6
4
2
0
−2
−1
−10
−5
0
5
10
Baseline to Week 12 Change in HAM-D Score
(Infliximab Minus Placebo)


A hs-CRP concentration >5 mg/L
Least Squares Mean Change in HAM-D Score From Baseline
0
−2
−4
−6
−8
−10
−12
−14
Infliximab
Placebo
Baseline
1
2
4
6
8
10
12
Week
B hs-CRP concentration ≤5 mg/L
Least Squares Mean Change in HAM-D Score From Baseline
0
−2
−4
−6
−8
−10
−12
−14
Baseline
1
2
4
6
8
10
12
Week

Rationale for not selecting a homogenous subgroup of PTSD in a Phase IIa trial

- 1) Safety data needed in a broad population
- 2) Biomarkers not robust for selecting a valid subpopulation
- 3) Pragmatic concerns for increasing criteria for screen failure
- 4) Possible gain of power and discovery by allowing a heterogeneous population to be enrolled.

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