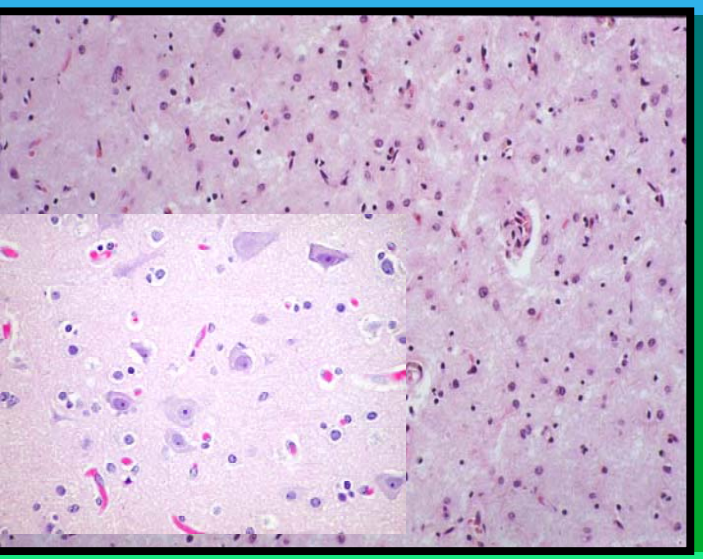
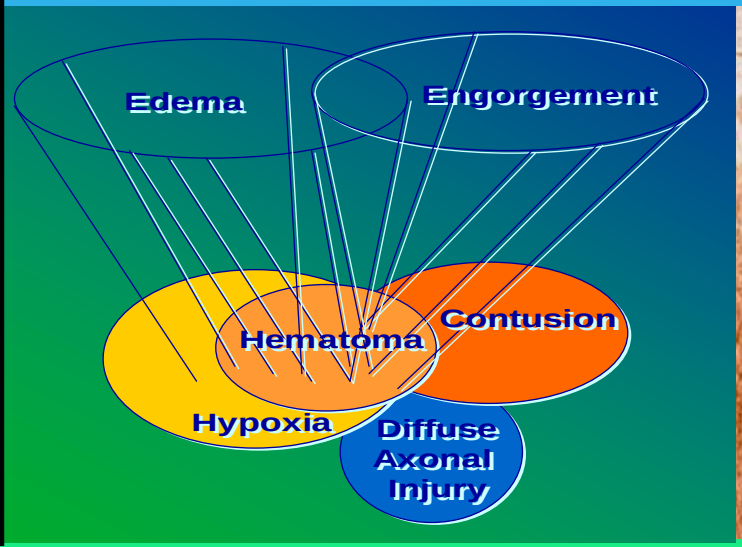
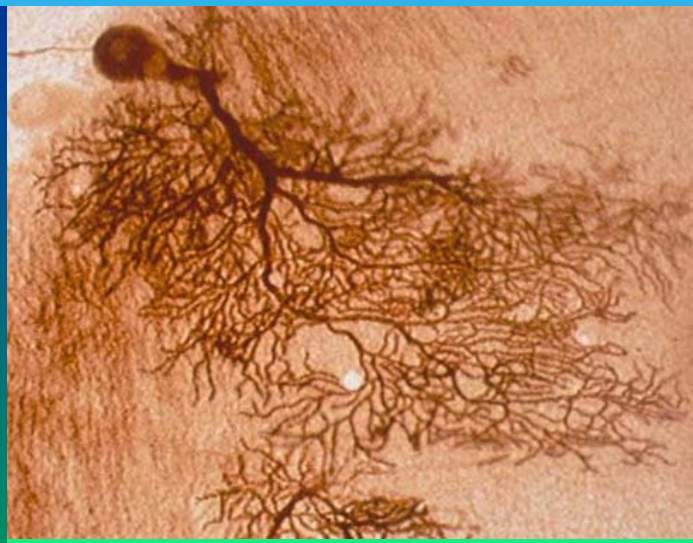
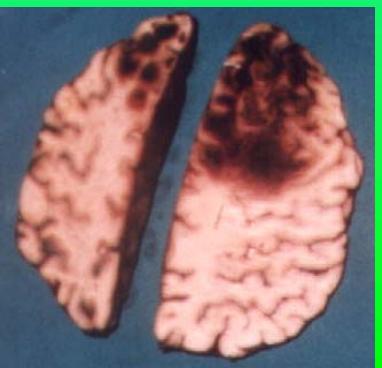
How do we OPTIMISE NEUROTRAUMA TRIAL Design: WHERE DO WE GO FROM HERE?



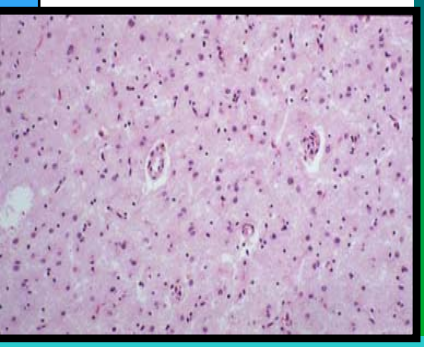


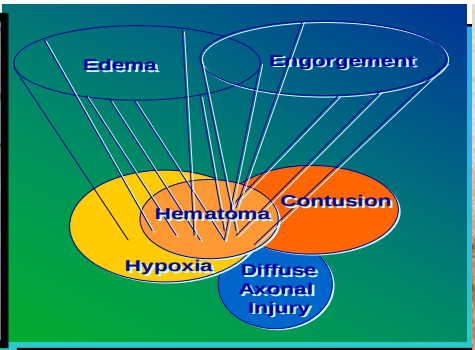


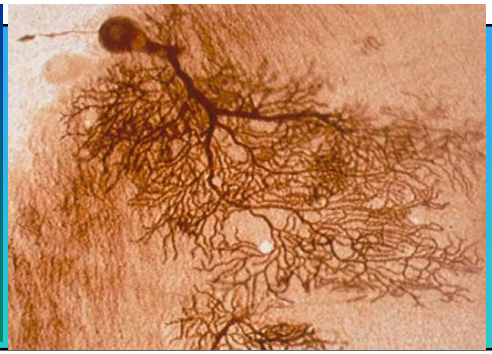


Ross Bullock, MD, PhD.
Director, Neurotrauma,-
University of Miami /Jackson Memorial Hospital, Miami.

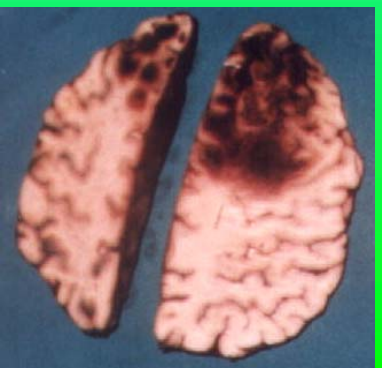
How to Optimize the design of NEUROTRAUMA TRIALS…







- History of Severe TBI trials…
- Current trials
- Reasons for failure..
- NIH approaches…
- TBI trials consortia..
- The problems of Mild/Moderate TBI
- Statistical issues…

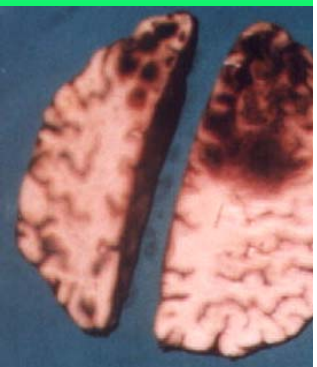


2007…

PRODUCTS IN DEVELOPMENT FOR TRAUMATIC BRAIN INJURY AND SPINAL CORD INJURY

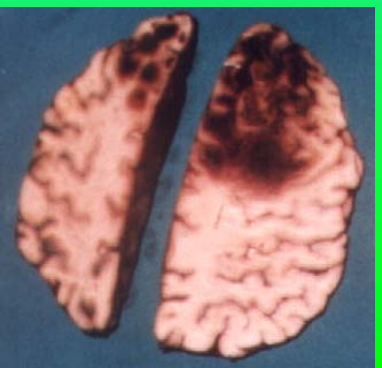
Product	Company	Status	Mechanism	Comment
CP101-606	Pfizer	Phase II/III	NMDA receptor antagonist	400 patient TBI trial complete; data being analyzed
Repinotan	Bayer	Phase II/III	5HT1A receptor agonist	Blocks nerve damage, increases perfusion in TBI
Dexanabinol	Pharmos	Phase II/III	Cannabinoid; mild NMDA antagonist	Anti-inflamatory; reduces ICP in TBI
Cyclosporin	Maas BiolAB	Phase IIA	Immunophilin and mitochondrial pore blocker	Neuroprotectant; neurotrophic compound for TBI and SCI
AIT-082	NeoTherapeutics	Phase II	Neurotrophic factors	Stimulates nerve regeneration in SCI
Fampridine SR	Acorda	Phase II	Potassium channel blocker	Allows nerve pulses to travel farther in SCI
BAY 38-7271	Bayer	Phase I	Cannabinoid receptor agonist	Neuroprotectant for TBI
Macrophages	ProNeuron	Phase I	Activated Macrophages	Stimulates regrowth of spinal cord nerve cells in SCI
NS1209	Shire/NeuroSearch	Phase I	AMPA receptor antagonist	Protects both white and gray matter in rodent stroke models of TBI and SCI
Porcine Stem Cell Transplants	Diacrin	Phase I	Porcine Stem Cells	Replaces axons and nerve cells in TBI and SCI
S-1746	Shionogi/GlaxoSmithKline	Phase I	AMPA receptor antagonist	Part of Shionogi/GlaxoSmithKline joint venture; for TBI
ARR-15896AR	AstraZeneca	Pre-clinical	NMDA receptor antagonist	Originally for stroke; now in testing for TBI and other CNS disorders
BAY 44-2041	Bayer	Pre-clinical	Adenosine re-uptake inhibitor	Increases perfusion in TBI
FKBP Immunophilins	Guilford	Pre-clinical	Immunophilin	Neuroprotectant; novel neurotrophic compounds; for TBI and SCI
NAALADase Inhibitors	Guilford	Pre-clinical	NAALADase inhibitor	Neuroprotectant; works presynaptically; for TBI and SCI
T-Cell Therapy	ProNeuron	Pre-clinical	T-cells	Neuroprotectant for secondary damage in SCI
Neramexane	Forest Labs/Merz	Unknown	NMDA receptor antagonist	Several neurological applications

Source: SG Cowen, company data



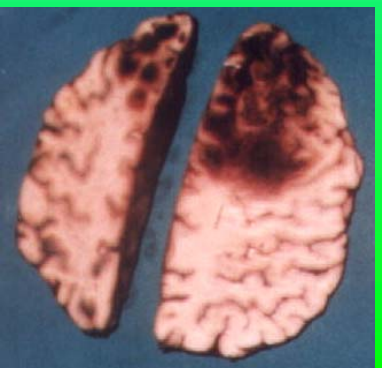
TBI Clinical Trials….2009

- Cyclosporin –ABIC/UK
- Solvay SL339…endothelin antagonist..
- Progesterone … “NETT”?
- Factor VII..Novonordisk
- Hypertonic saline –prehospital/ER…NHLB consortium..
- Citicholine “COBRIT” NICHD consortium..
- Neuren NNZ 2566
- Decompressive craniotomy…
- Cooling..”NABISH “COOL KIDS, ”B-HYPO” Japan..
- Oxycyte….Perfluorocarbon…
- CALSOLAC..Innogene ..
- Stem cells?
- HBO--Minneappolis



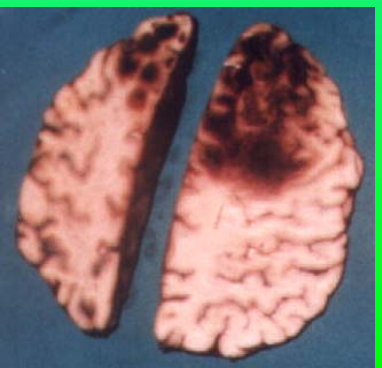
Completed "Neuroprotection" Clinical Trials in Severe TBI

Investigator/year	Agent	Patients / Country	Outcome/comments
Ward et al 1954	Scopalamine	940 us	Uncontrolled no benefit
Six Authors	Corticosteroids	365 various	Some controlled, no net benefit
Schwartz et al, 1985	Mannitol vs pentobarbital	59 Canada	randomised crossover Mannitol more beneficial
Ward et al, 1985	Barbiturates(Prophylaxis)	53 US	DBPCRT, no benefit
Eisenburg et al 1988	Barbiturates(Therapeutic)	73 US	Barbs lower ICP-no benefit on outcome
Wolf et al 1993	THAM , Hyperventilation	149 US	DBCRT - No benefit on outcome Hypervent harmful
Teasdale et al 1992	Nimodipine (Hit 1)	255 UK & Finland	DBPCRT, no benefit



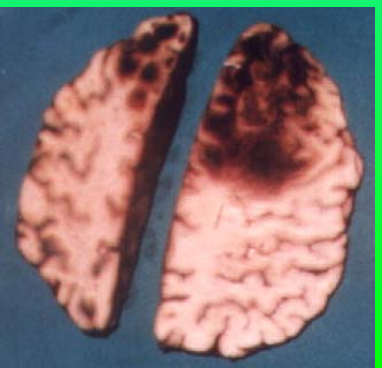
Completed "Neuroprotection" Clinical Trials in Severe TBI

Investigator/year	Agent	Patients / Country	Outcome/comments
Brakman 1993	Nimodipine (HIT II)	840 EU	DBPCRT, No benefit
Muzelaar et al 1993	PEG-SOD Free Radial scavenger	94 US	DBPCRT,ICP lower
Muzelaar et al, 1993	PEG SOD RAD Scavenger	463 US	Outcome better (p<0.057)
Bullock et al, 1995	CGS19755 (Glutamate NMDA Antagonist)	113 US UK	DBPCRT, Outcome 9 % in drug vs Placebo (p=0.15)
Allves & Jane 1995	Trilazad	1170 US & Canada	DBPCRT, ICP Lower-no benefit
Marshall 1995	Trilazad	1128 EU Austr	DBPCRT, No benefit
Cohadon et al 1996	Synthelabo Eliprodil (SL, 82)Phase II	453 France	DBPCRT, better outcome in brain swelling patients (p=<0.01)
Harders et al 1996	Nimodpine (L-channel antagonist) Phase II	123 Germany (only traumatic SAH patients	DBPCRT, 59 %relative reduction in bad Outcome at 6 mo (p<0.002)
Nichols 1997	Bradycor (Bradykinin Receptor)	133US	DBPCRT, no benefit but 10% Trend Toward better outcome
Novartis 1998	SDZ EAA 494 NMDA antagonist	800EU	DBPCRT No benefit



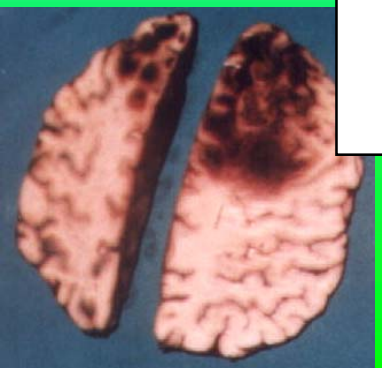
Severe TBI Clinical Trials prematurely terminated…..

Company	Agent/treatment	Phase	Patients/country	Mechanism/class/comment
NIH	Moderate Hypothemia	III	-500 US	5 Support Pilot studies
Parke Davis	SNX-111	III	-600 US	N-Calcium channel blocker
Bayer	Bayer X3702	II	-100 EU	5-HT1A Agonist /ion blocker
Ciba geigy	Selfotel CGS 19755	III	260US and Israel 426 EU and Australia	NMDA Receptor antagonist
Cambridge	Cerestat (CNS 1102)	III	512US and EU	non competitive NMDA antagonist



Stroke Academia –Industry Roundtable…

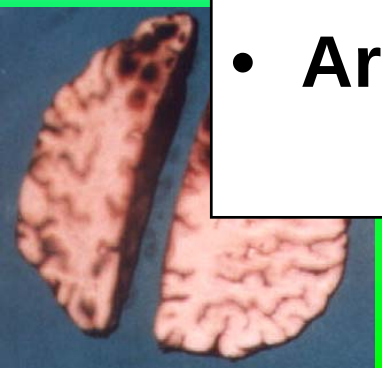
- **Potential approaches to reducing sample sizes and costs of phase 3 stroke trials**
  - **Utilize more sensitive and less variable outcome measures**
  - **Develop new methods of analysis of study data**
  - **Incorporate novel study designs and focus patient population to improve homogeneity**



What are the lessons for TBI?

Why do many TBI and Stroke trials fail in phase 3?-

- ~22 Severe TBI trials..~180 stroke trials…>600 AIDS/HIV TRIALS.!
- Was the Preclinical data bad?
- Did the drug penetrate the brain?
- Was Data from Phase 2 trials flawed?
- Were populations studied too variable?
- Were numbers enrolled too small?
- Are the indications too risky for “big Pharma?”



The New England
Journal of Medicine

Volume 333 DECEMBER 14, 1995 Number 24

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

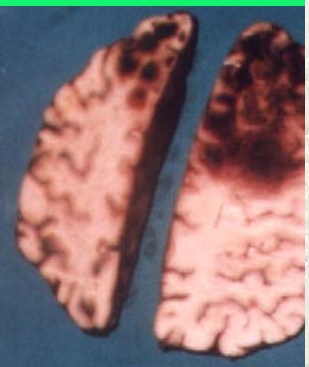
THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

Abstract *Background.* Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

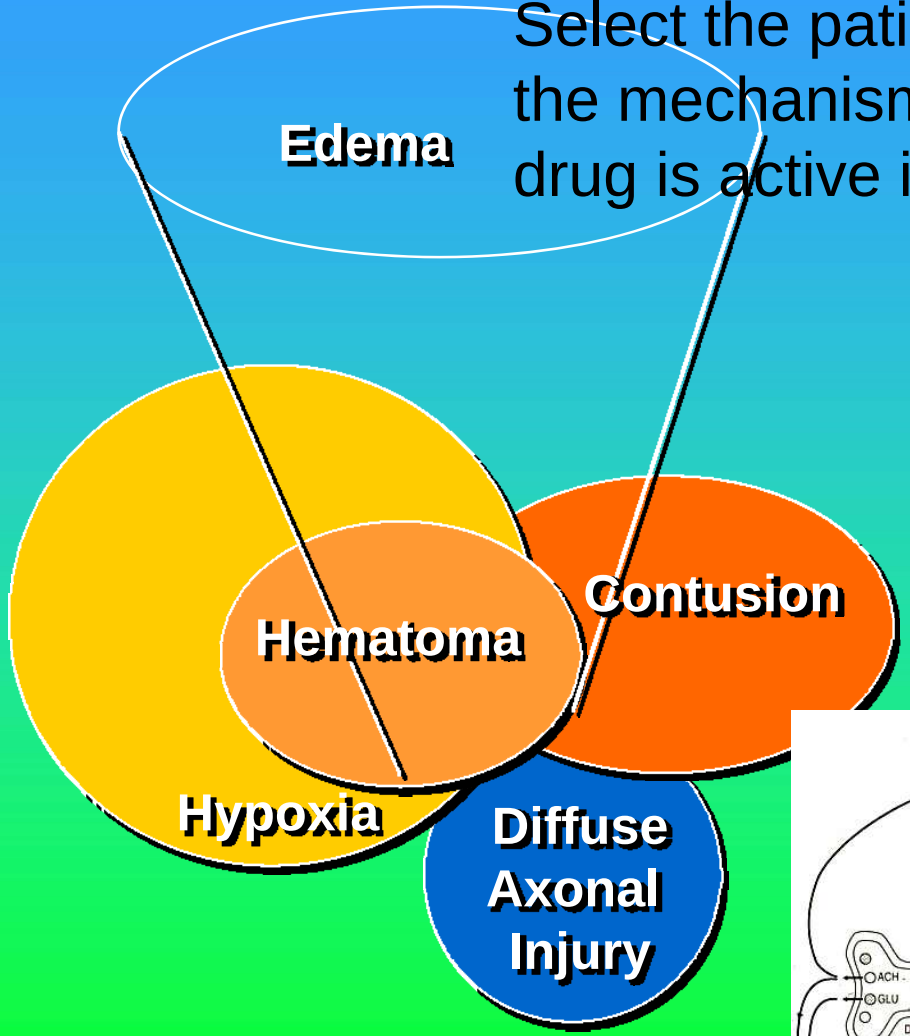
Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo ($P<0.001$). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group ($P=0.30$).

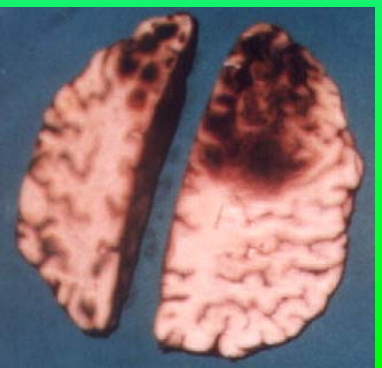
Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)

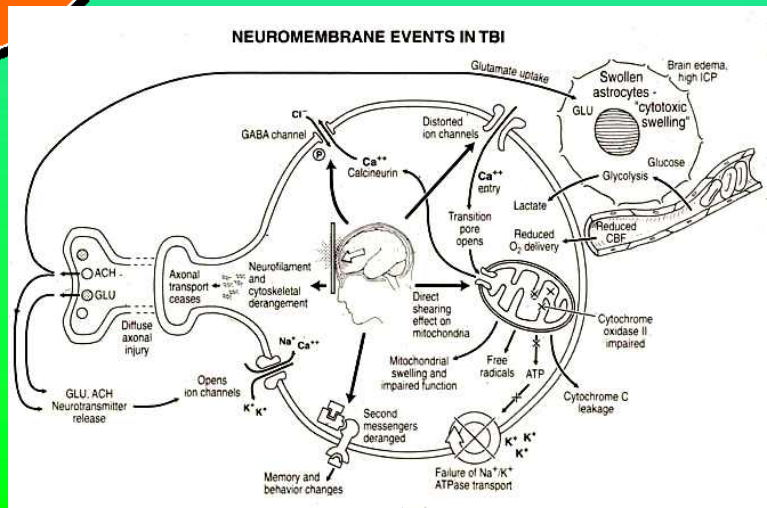


The Targetted Pathophysiology concept…

Select the patients showing the mechanism for which the drug is active in preclinical studies..

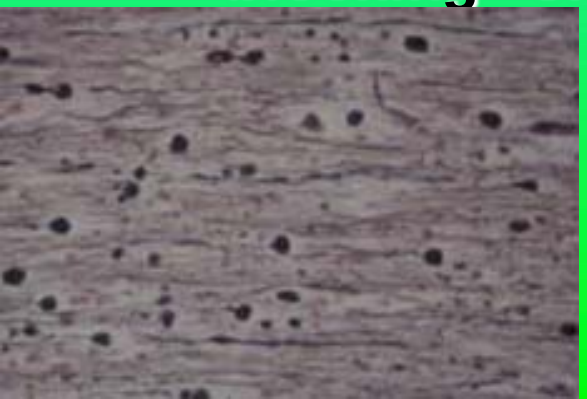


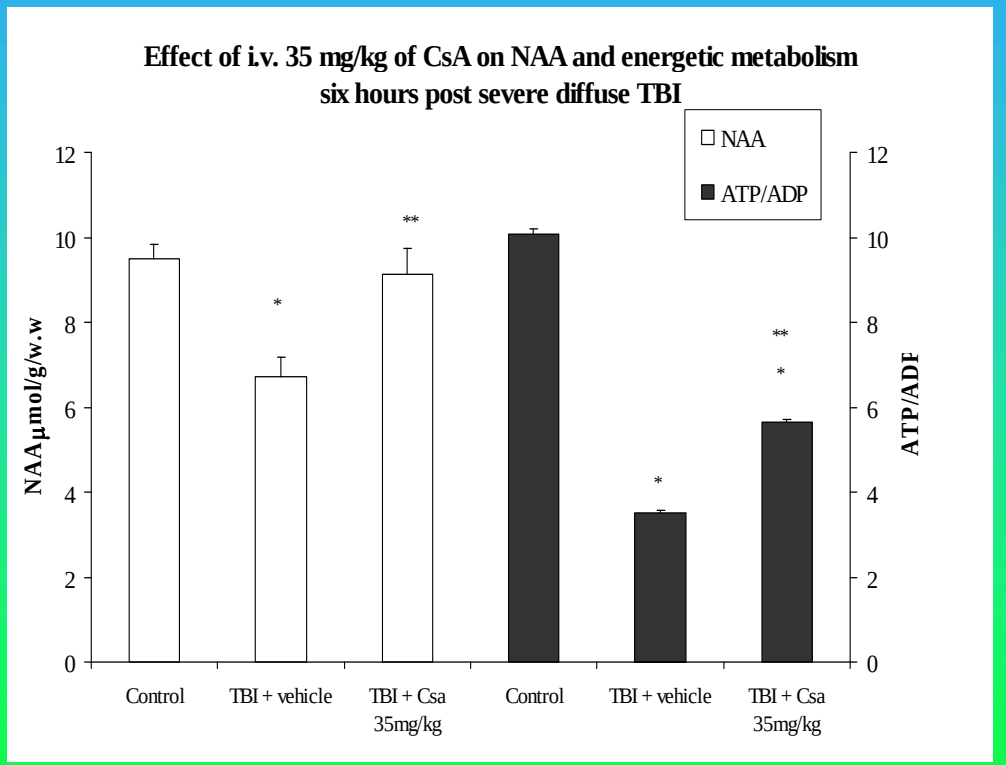




Can we protect mitochondria --Why Cyclosporin A?

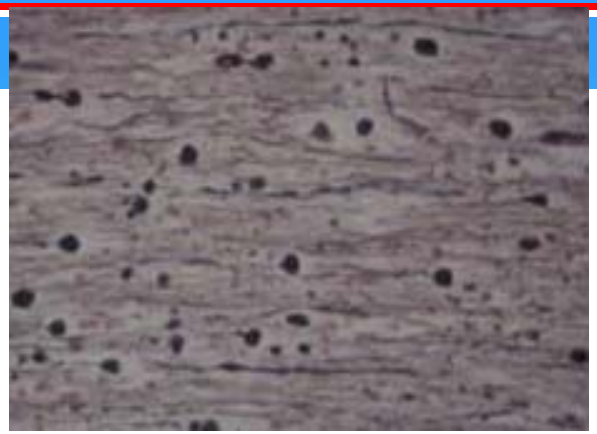
- **Advantages….**
- Safe, in many thousands of patients…FDA approved
- Cheap, available..
- Good animal model data..
- **Disadvantages..**
- Poor brain penetration..
- Weak “Mitochondrial pore blocking” effect..

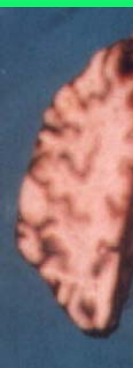


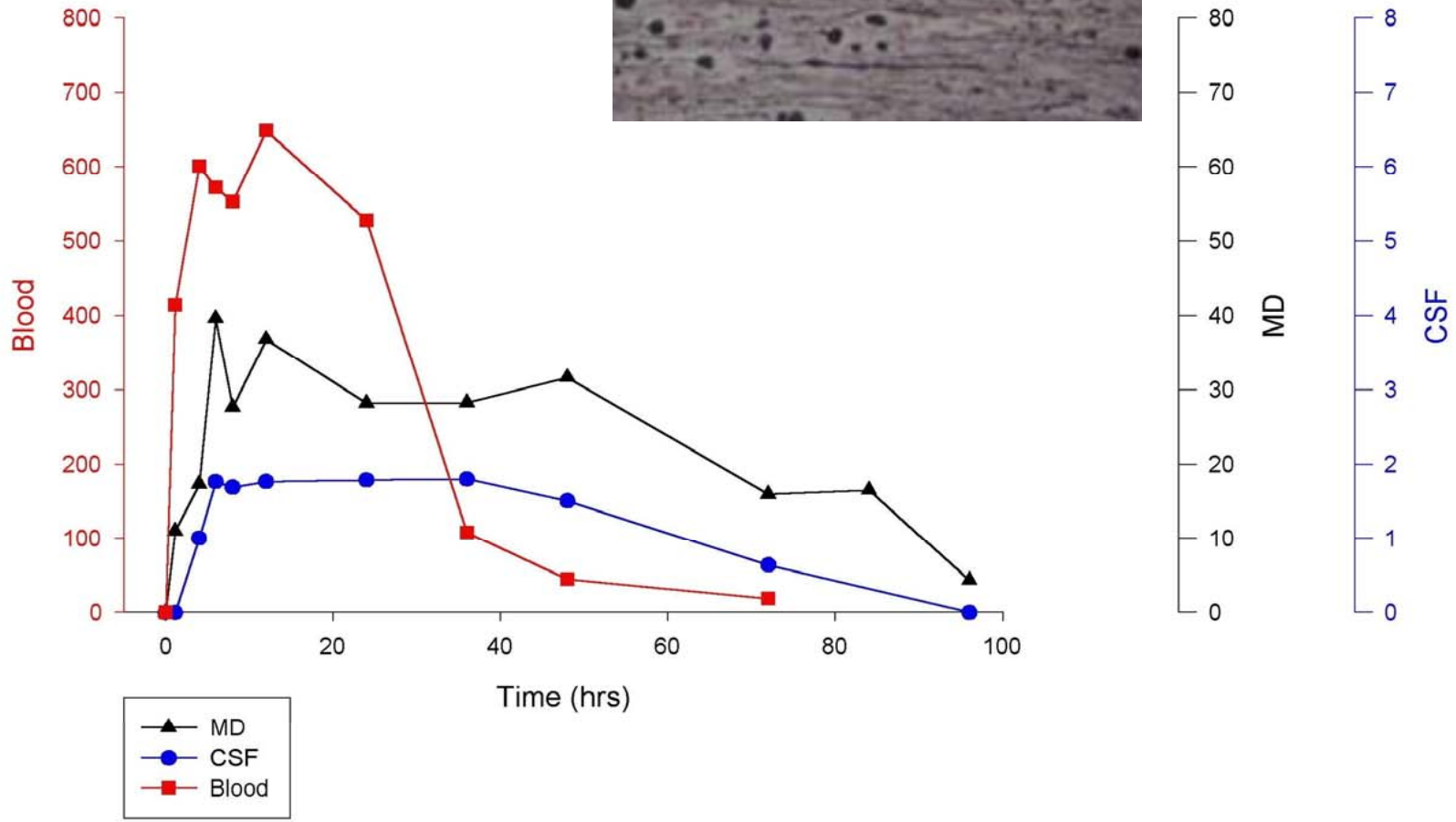


Brain Cyclosporin concentration, measured by Microdialysis, in Human TBI patients..

The CASTBI Trial…

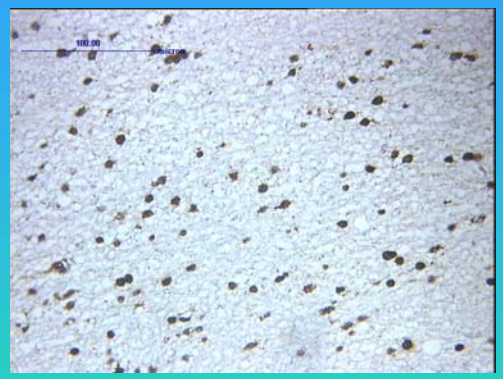


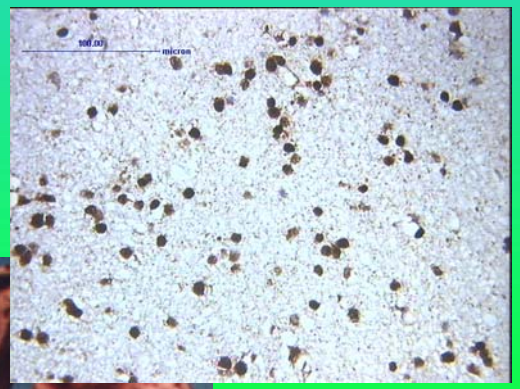




Apoptotic markers, in Human Contusion material...(Nathoo et al...Fiscum et al,)

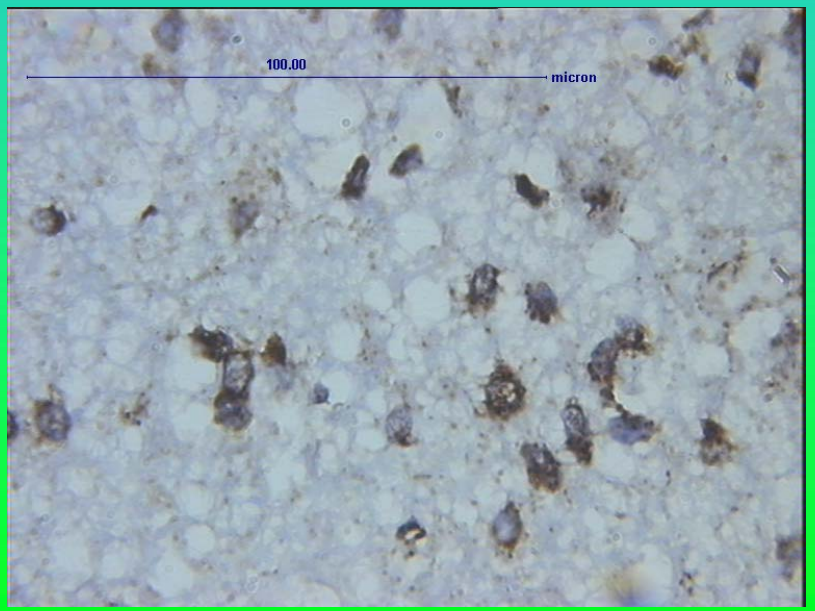
Cyclin E





Retinoblastoma protein

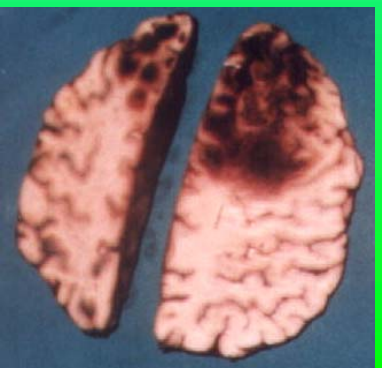
Solvay SL 334…



HIGH POWER

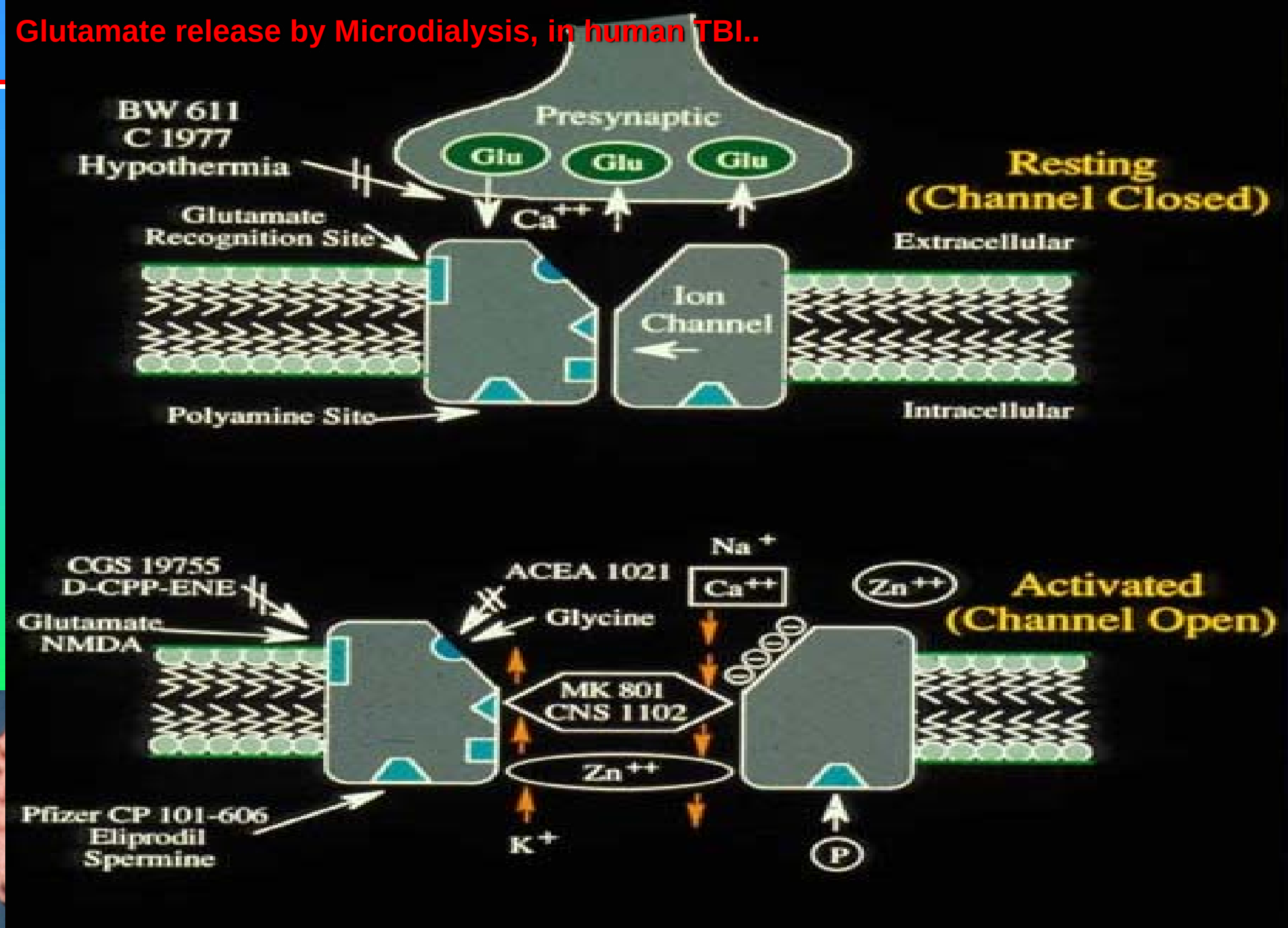
How can we improve TBI clinical Trials?

“Those who do not learn from the lessons of History, are Doomed to repeat the mistakes of the past”



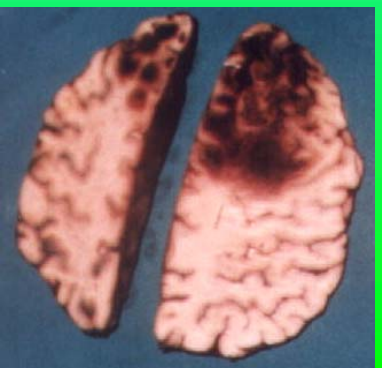
Winston Churchill

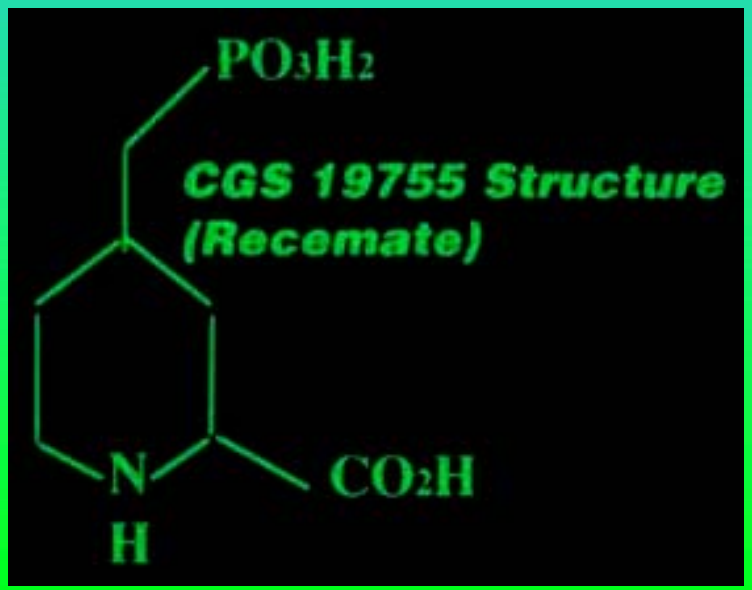
Glutamate release by Microdialysis, in human TBI..

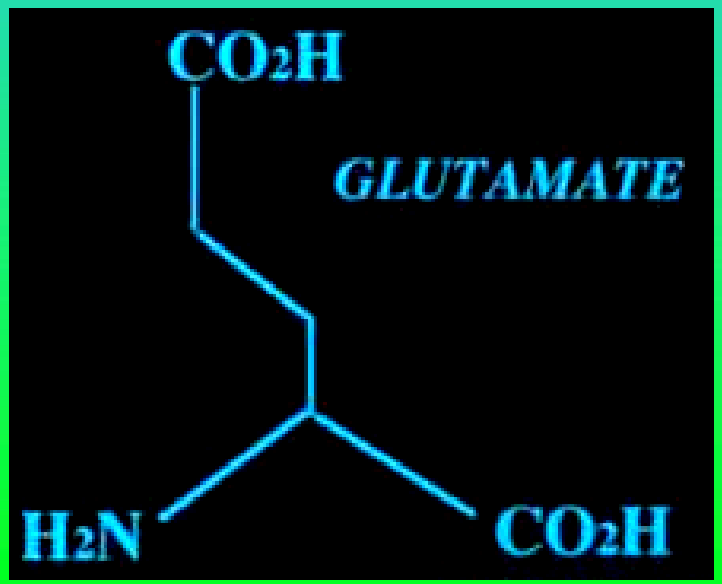


Selfotel -CGS 19755

- **First commercially developed glutamate antagonist “Neuroprotectant”**
- **Competitive NMDA glutamate site antagonist**

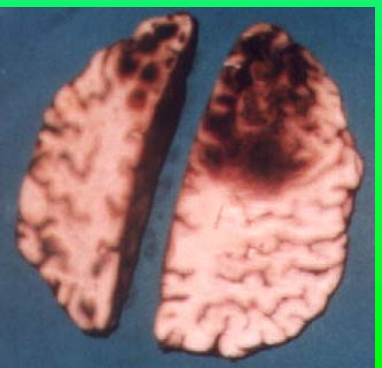






The Selfotel Development Plan

1. Animal Studies
   - Efficacy - TBI, Stroke
   - Safety, Toxicity, Behavior
2. Phase I Volunteers - 2mg/kg/24 hr max dose
3. Phase II
   - TBI - Glasgow n=32. ICP effect
   - Stroke - Houston - Grotta
4. Phase “IIb” - TBI ABIC - USA/UK n=108
   - Never fully analyzed!
5. Phase III - 4 trial -USA + Europe, Australia
   - TBI - 5 mg/kg/day - n~1200



J Neurosurg 91:737–743, 1999

Failure of the competitive *N*-methyl-D-aspartate antagonist Selfotel (CGS 19755) in the treatment of severe head injury: results of two Phase III clinical trials

Gabrielle F. Morris, M.D., Ross Bullock, M.D., Ph.D., Sharon Bowers Marshall, B.S.N., Anthony Marmarou, Ph.D., Andrew Maas, M.D., the Selfotel Investigators, and Lawrence F. Marshall, M.D.

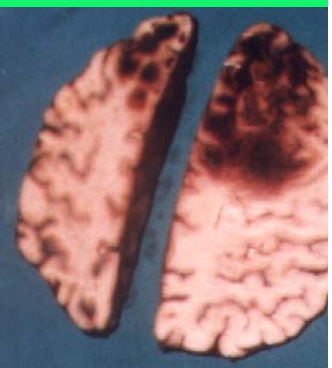
Division of Neurological Surgery, University of California, San Diego, California; Division of Neurosurgery, Medical College of Virginia, Richmond, Virginia; Division of Neurosurgery, University Hospital, Rotterdam, The Netherlands; and Ciba Geigy Pharmaceuticals, Basel, Switzerland and Summit, New Jersey

Object. Excessive activity of excitatory amino acids released after head trauma has been demonstrated to contribute to progressive injury in animal models and human studies. Several pharmacological agents that act as antagonists to the glutamate receptor have shown promise in limiting this progression. The efficacy of the *N*-methyl-D-aspartate receptor antagonist Selfotel (CGS 19755) was evaluated in two parallel studies of severely head injured patients, defined as patients with postresuscitation Glasgow Coma Scale scores of 4 to 8.

Methods. A total of 693 patients were prospectively enrolled in two multicenter double-blind studies. Comparison between the treatment groups showed no significant difference with regard to demographic data, previous incidence of hypotension, and severity of injury. As the study progressed, the Safety and Monitoring Committee became concerned about possible increased deaths and serious brain-related adverse events in the treatment arm of the two head injury trials, as well as deaths in the two stroke trials being monitored concurrently. The Selfotel trials were stopped prematurely because of this concern and because an interim efficacy analysis indicated that the likelihood of demonstrating success with the agent if the studies had been completed was almost nil.

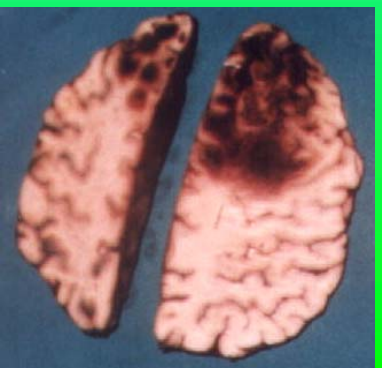
Conclusions. Subsequently, more complete data analysis revealed no statistically significant difference in mortality rates in all cases between the two treatment groups in the head injury trials. In this report the authors examine the studies in detail and discuss the potential application of the data to future trial designs.

Key Words • severe head injury • clinical trial design • *N*-methyl-D-aspartate • Selfotel • glutamate receptor antagonist • excitatory amino acid



What can we learn from the SELFOTEL trials

- Prematurely terminated due to mortality excess in stroke trials (n=693 for TBI)
- No evidence of efficacy for drug in any trauma subgroup at 3 and 6 months
- Lowest overall mortality rates for any severe head injury Phase III study (17%; 19%)
-



The Selfotel Programme Conclusions

What should be done better next time

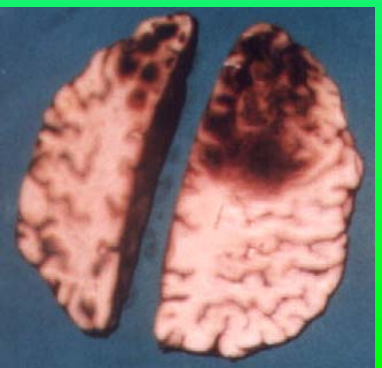
1) Pharmacokinetics

2) Receptor occupancy post glutamate loading

(most effective in pre-treatment animal paradigms)

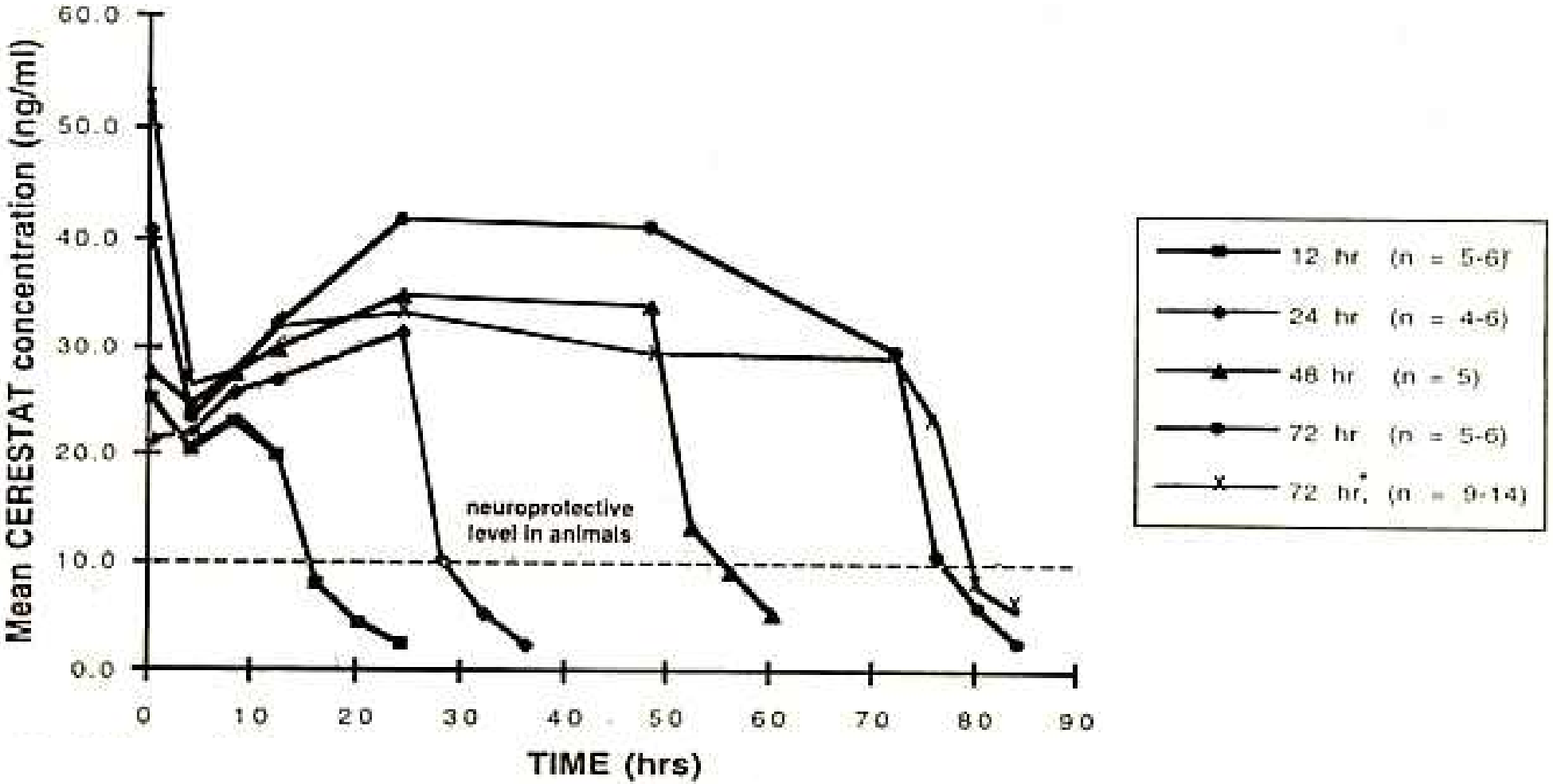
3) Complete Phase II analysis before Phase III

4) Better quality control of centers?



Plasma Levels of CERESTAT® in TBI Patients

*100μg/kg Bolus + Various Durations of 40μg/kg/hr i.v.**



*The last group received non-weighted adjusted I.v. doses of 15 mg + 3mg/hr

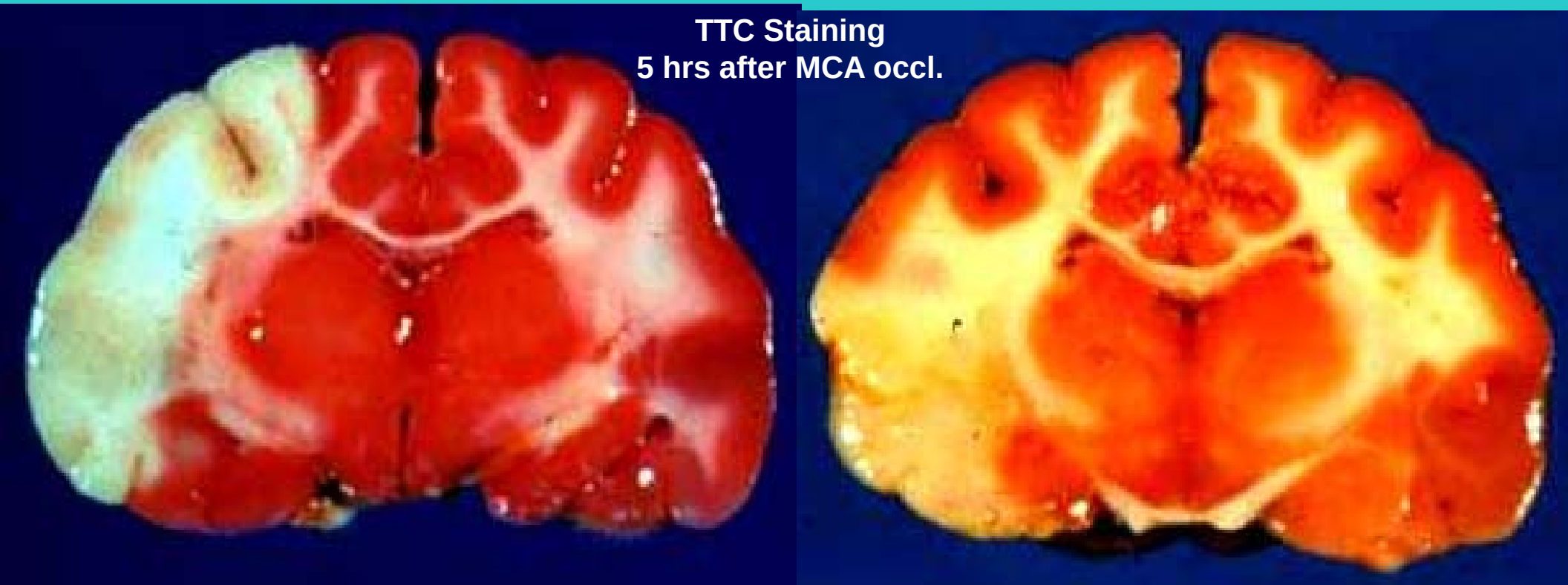
Hundreds of successful Laboratory studies With EAA antagonists..more than any other "Neuroprotective" strategy…

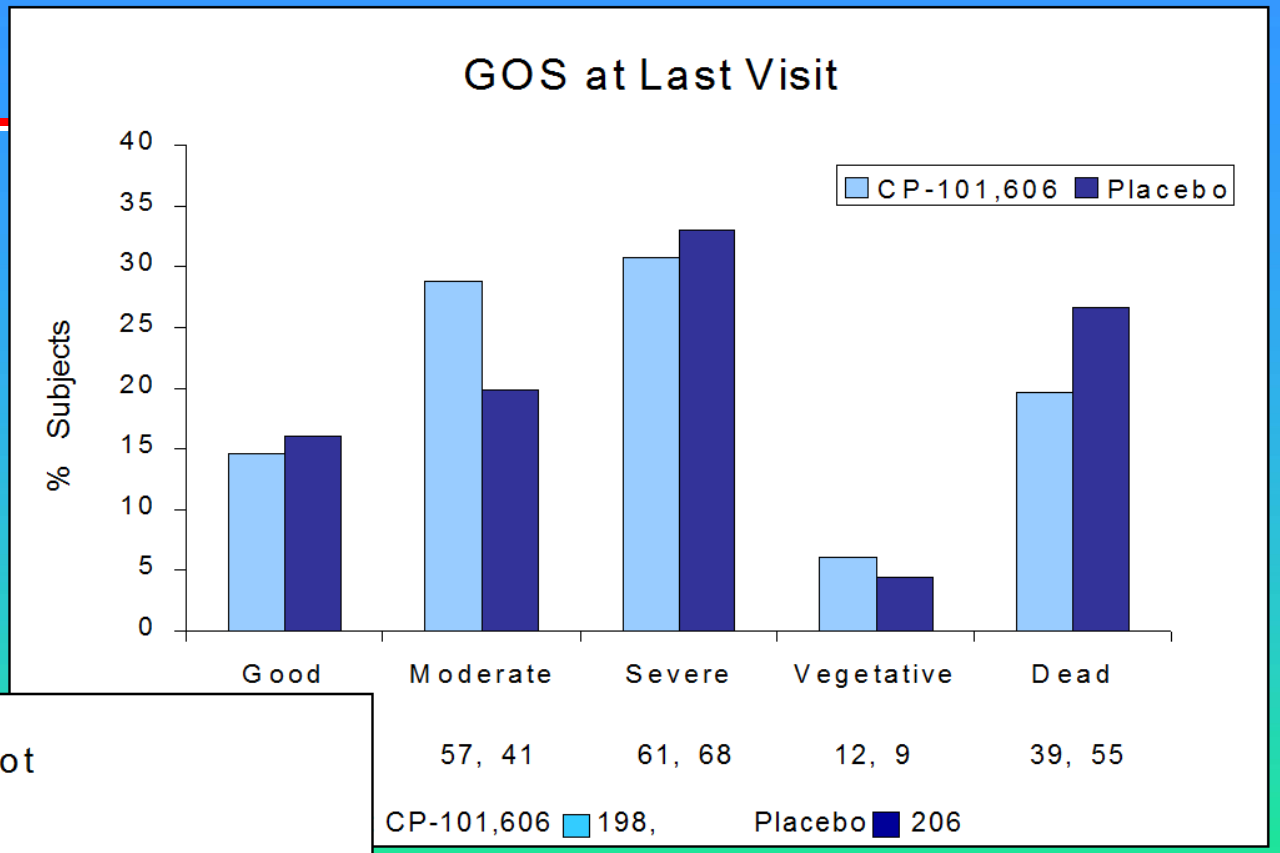
"Traxprodil"

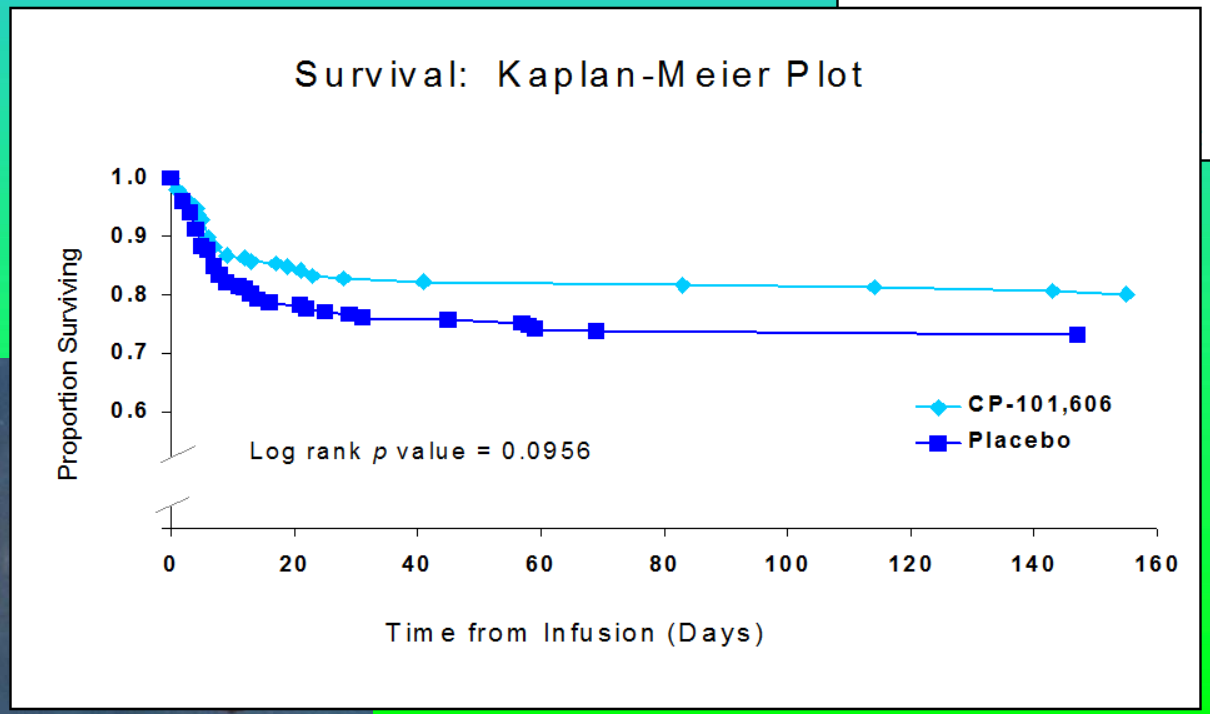
Cat no. s8
Control group

Cat no. P9-3
CP101. 606-treated

TTC Staining
5 hrs after MCA occl.




GOS at Last Visit
% Subjects
40
35
30
25
20
15
10
5
0
CP-101,606
Placebo
Good
Moderate
Severe
Vegetative
Dead
57, 41
61, 68
12, 9
39, 55
CP-101,606 198,
Placebo 206


Survival: Kaplan-Meier Plot
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
Log rank p value = 0.0956
CP-101,606
Placebo
0
20
40
60
80
100
120
140
160
Time from Infusion (Days)

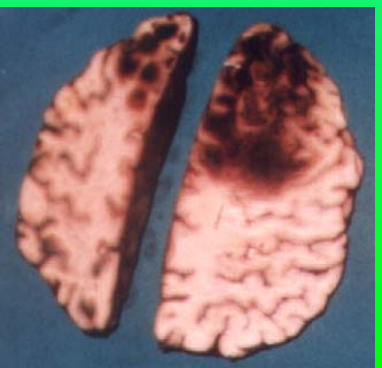
Traxprodil improved outcome 11%, in males

GOS at Last Visit by Gender

	N		% Favorable*			OR	95% CI**
Gender	**All**	**(Trax./Pbo)**	**Trax**	**Pbo**	**delta**		
Male	298	(146/152)	46.6	35.5	11.1	1.73	1.07, 2.80
Female	106	(52/54)	34.6	37.0	-2.4	0.85	0.37, 1.93

*Raw percentages, i.e. n Favorable/ N randomized

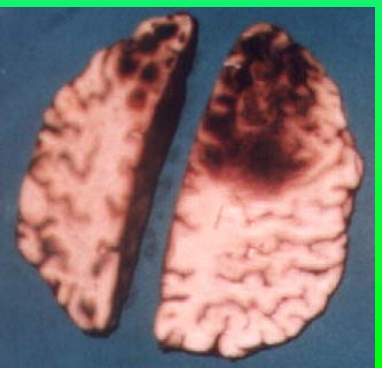
**Estimate of Odds Ratio (OR) and 95% CI are based on a logistic regression model with the following terms: baseline motor score strata, treatment, gender and treatment by gender interaction.



Failure of Phase III Trials in Neurotrauma - Possible Solutions

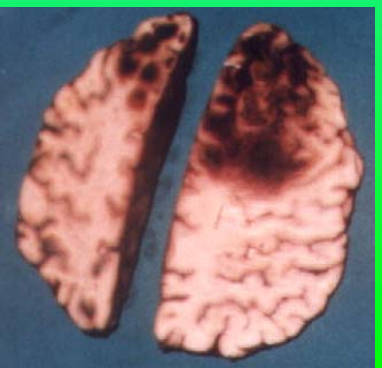
Better animal studies
Better Phase II mechanism studies

Brain Pharmacokinetics -
Phase II mechanism & dose finding
Better Outcome measures…
“biomarkers” ,
Synergistic therapies…NIH RFA..

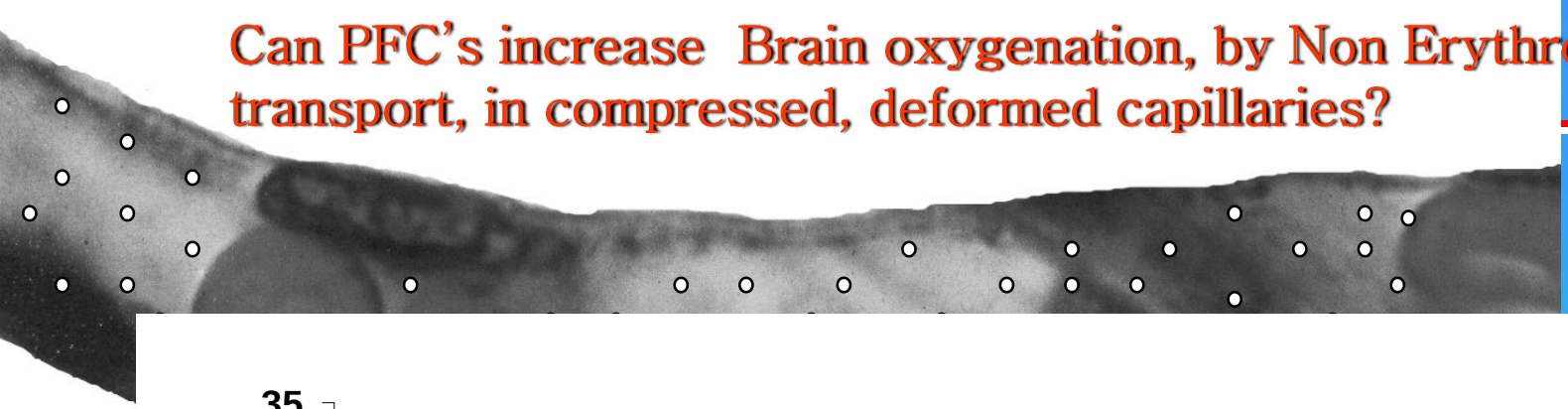


Requirement for successful TBI Trials-
The 6 “Koch’s Postulates”…

- Mechanism demonstrated in animal models
- Drug / agent reverses damage in animal models
- mechanism shown in human TBI
- brain penetration
- Safety/tolerability in humans with TBI
- Use drug sensitive end points

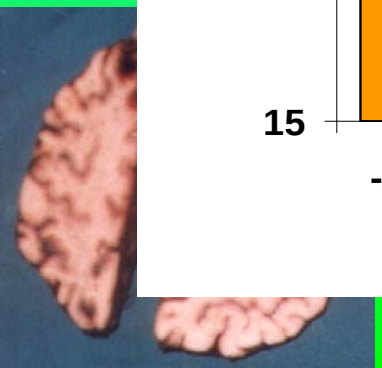


Can PFC's increase Brain oxygenation, by Non Erythrocyte Oxygen transport, in compressed, deformed capillaries?



RB

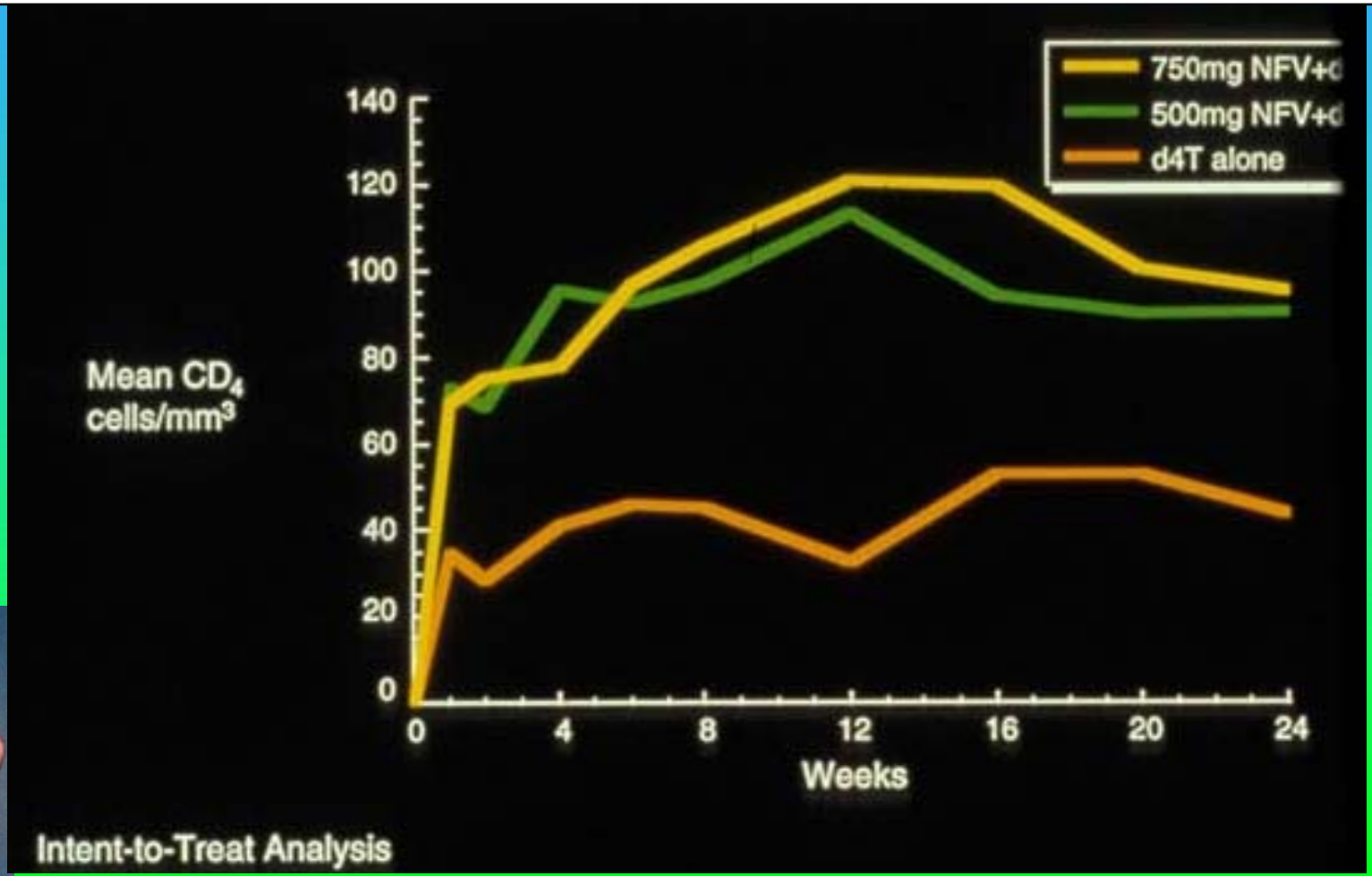
Scher
capilla

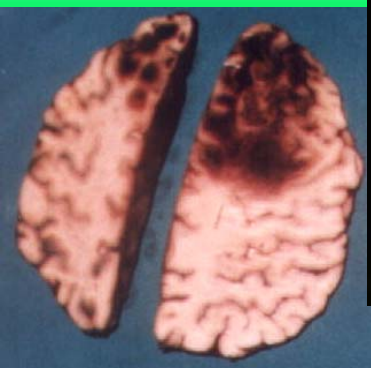


– a PFC
ies 40 ml
er 100ml

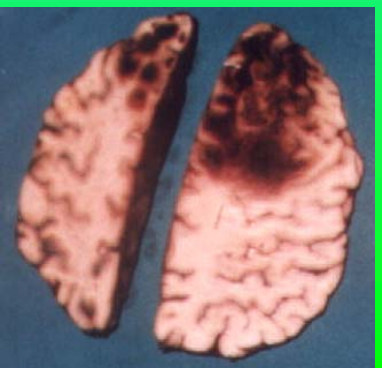
We need “Biomarkers” to better detect drug effect, in TBI…

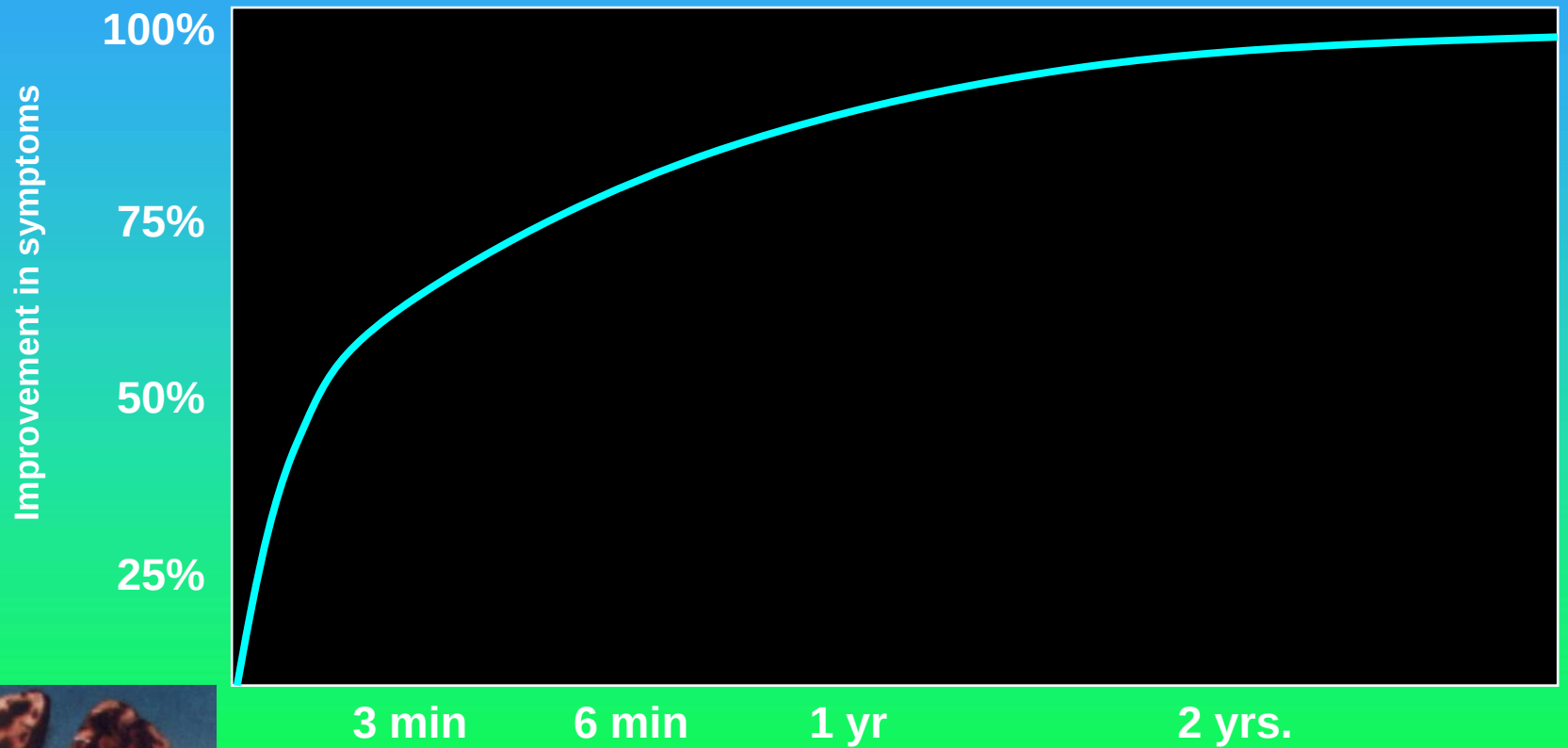
~600 efficacy trials, in HIV/AIDS…!



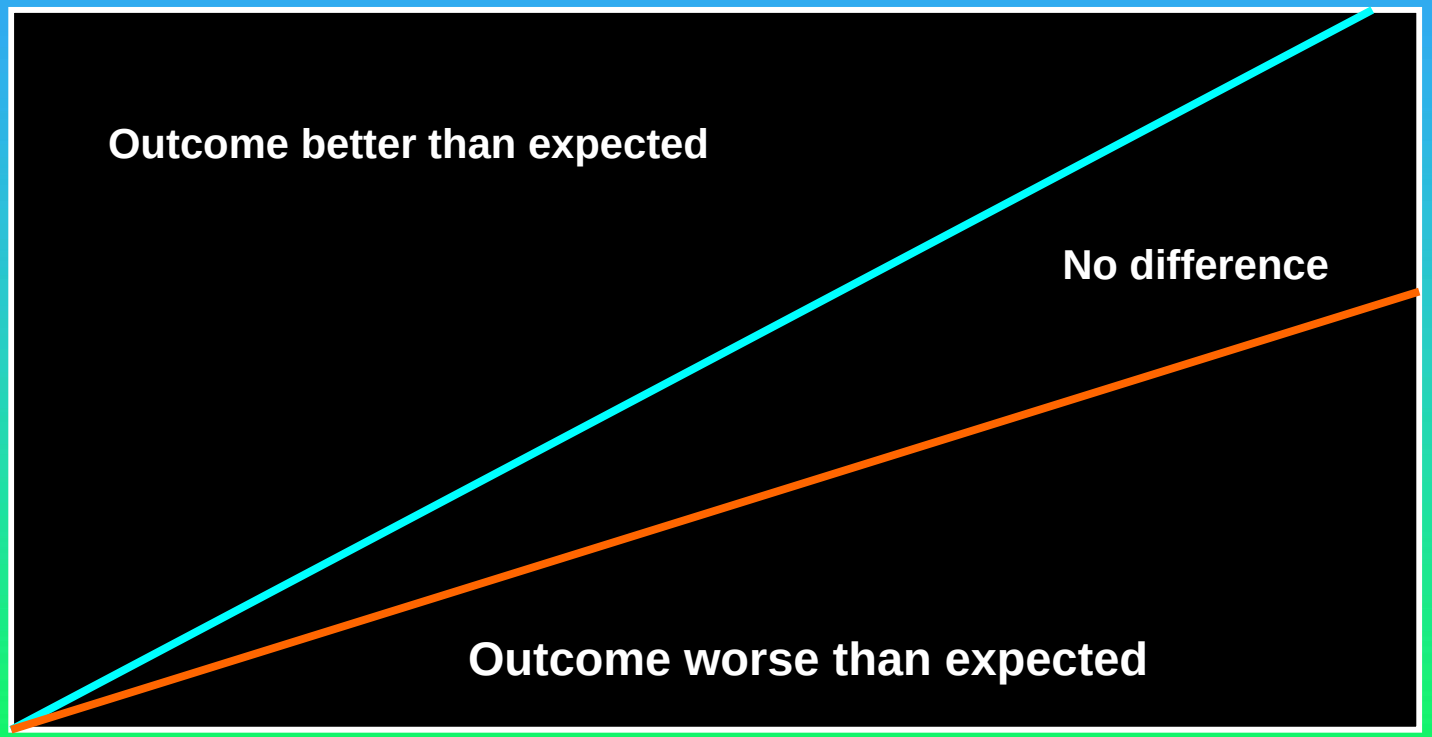


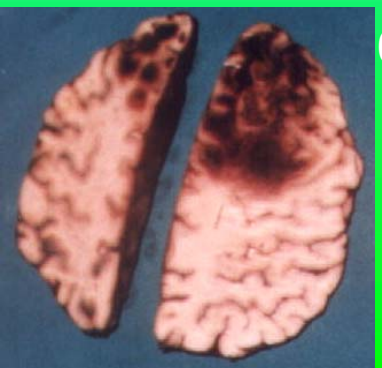
The recovery curve - severe TBI





Sequential analysis, and "Sliding Dichotomy"

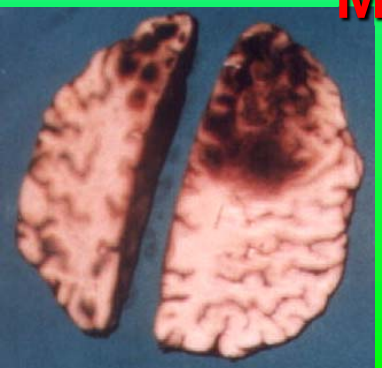




Novel Therapeutic Strategies

for Traumatic Brain Injury

- Better designed trials with existing drugs
- ALL TBI trials UNDERPOWERED ~ 1,200 patients,
- Should be powered for “Delta” of -- 5% - 3,000 patients per arm. - Less data complexity, lower cost.. ?
- Should we perform large, simple trials, first, in “”TBI RICH” Countries?
- Synergistic therapies… –eg SOD-like radical scavengers, Mild HYPOTHERMIA and drugs, ..



6 Major Consortia for TBI trials….Over 270 centers…

NICHD TBI trials Cosortium…CDP choline trial-8 centers
NETT…… progesterone “Protect “ trial-~17major centers..
NHLBI ….Hypertonic saline, prehospital
DOD new PTSD/TBI Consortium.. 10 centers…

“Per Ardua ad Virtutam”

European
Brain Injury
Consortium