AGGIORNAMENTI in EMATOLOGIA

TREVISO, 25-26 Novembre 2016

LA BARRIERA EMATO-ENCEFALICA

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✓100 miliardi di capillari
✓ 600 Km di lunghezza
✓ 20 m² di superficie

LA BARRIERA EMATOENCEFALICA

CARATTERISTICHE DELL'ENDOTELIO DEL SNC

- assenza di fenestrature
- scarsa endocitosi (o pinocitosi)
- ricchezza in mitocondri
- elevata resistenza elettrica, che limita il passaggio di molecole polarizzate e di ioni, valutata in 1000-2000 Ohm/cm^2 (nei capillari periferici è circa pari a 10 Ohm/cm^2)
- assai bassa espressione di molecole di adesione leucocitaria
- tight junctions

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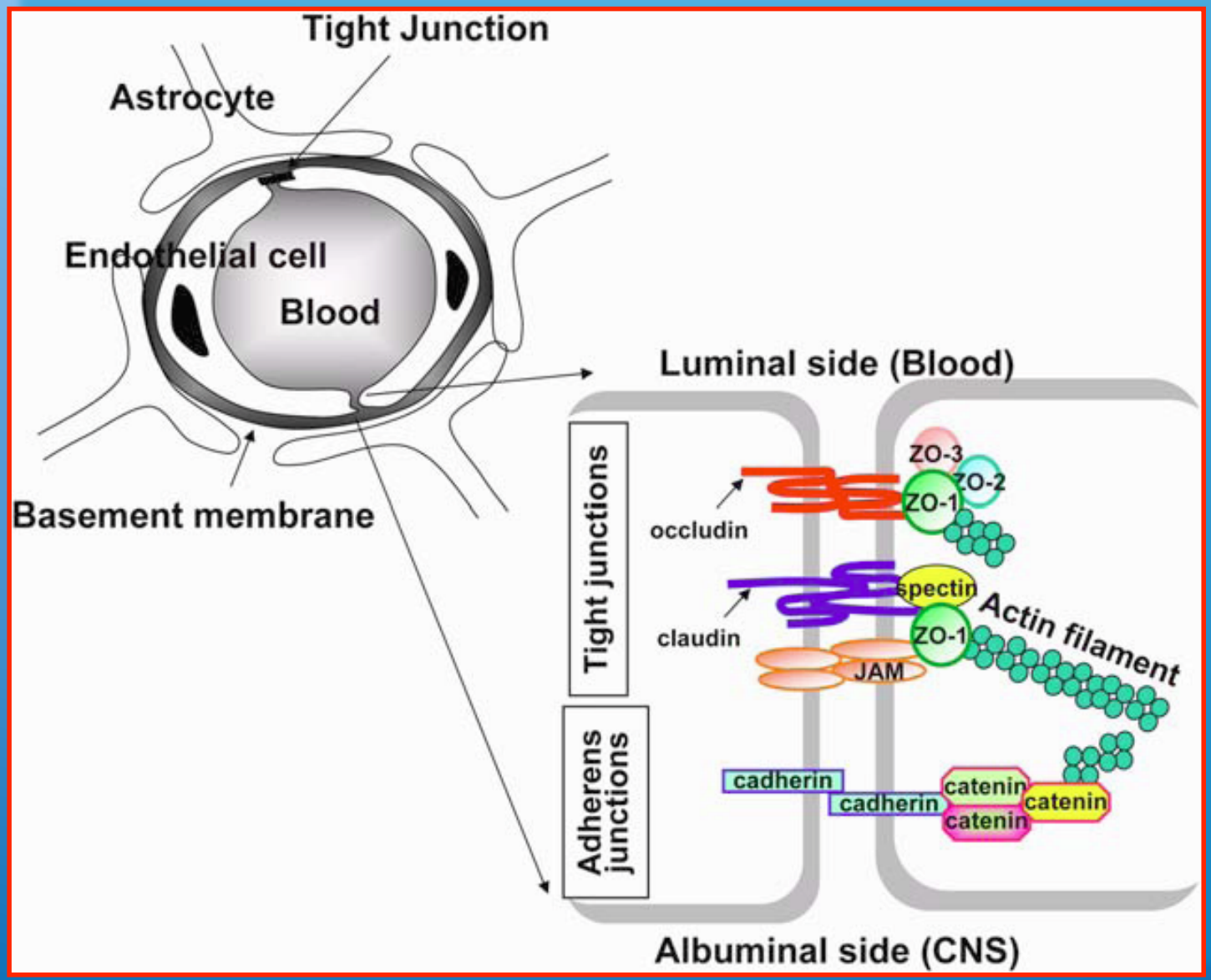

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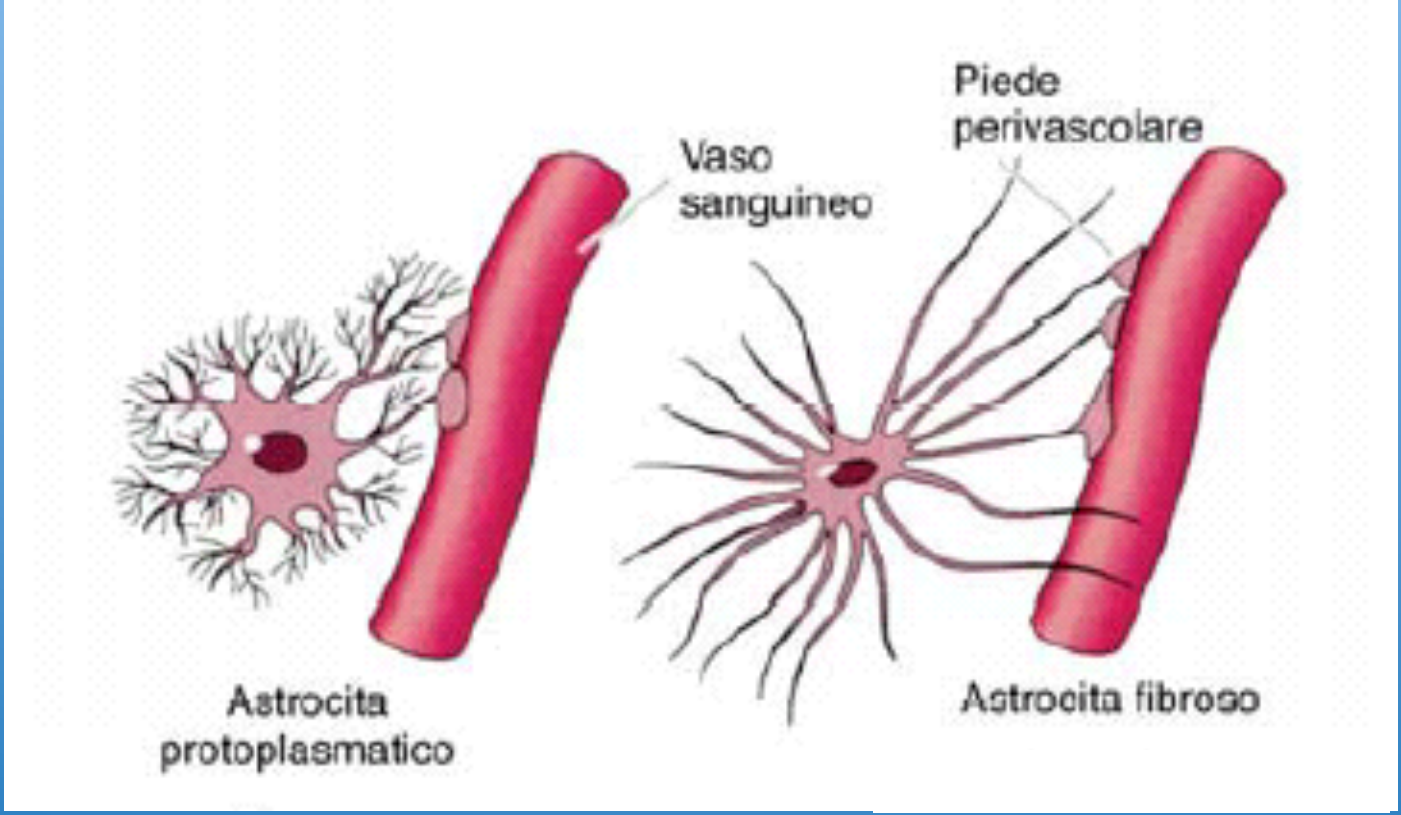

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ASTROCITI

- Non solo funzione di supporto ("collante del SNC") e funzione trofica, ma anche ruolo nei processi di sinaptogenesi e di controllo del tono vascolare del SNC.

- Rappresentano il link cellulare tra il circuito neuronale e i vasi sanguigni regolando il flusso ematico in risposta all'attività neuronale.

- Capacità di produzione di fattori umorali necessari per l'impermeabilità della barriera emato-encefalica (angiopoietina-1, trombospondina-1, bFGF).

- La co-coltura di astrociti e cellule endoteliali non-neurali è in grado di indurre proprietà di barriera (Hayashi, 2011).

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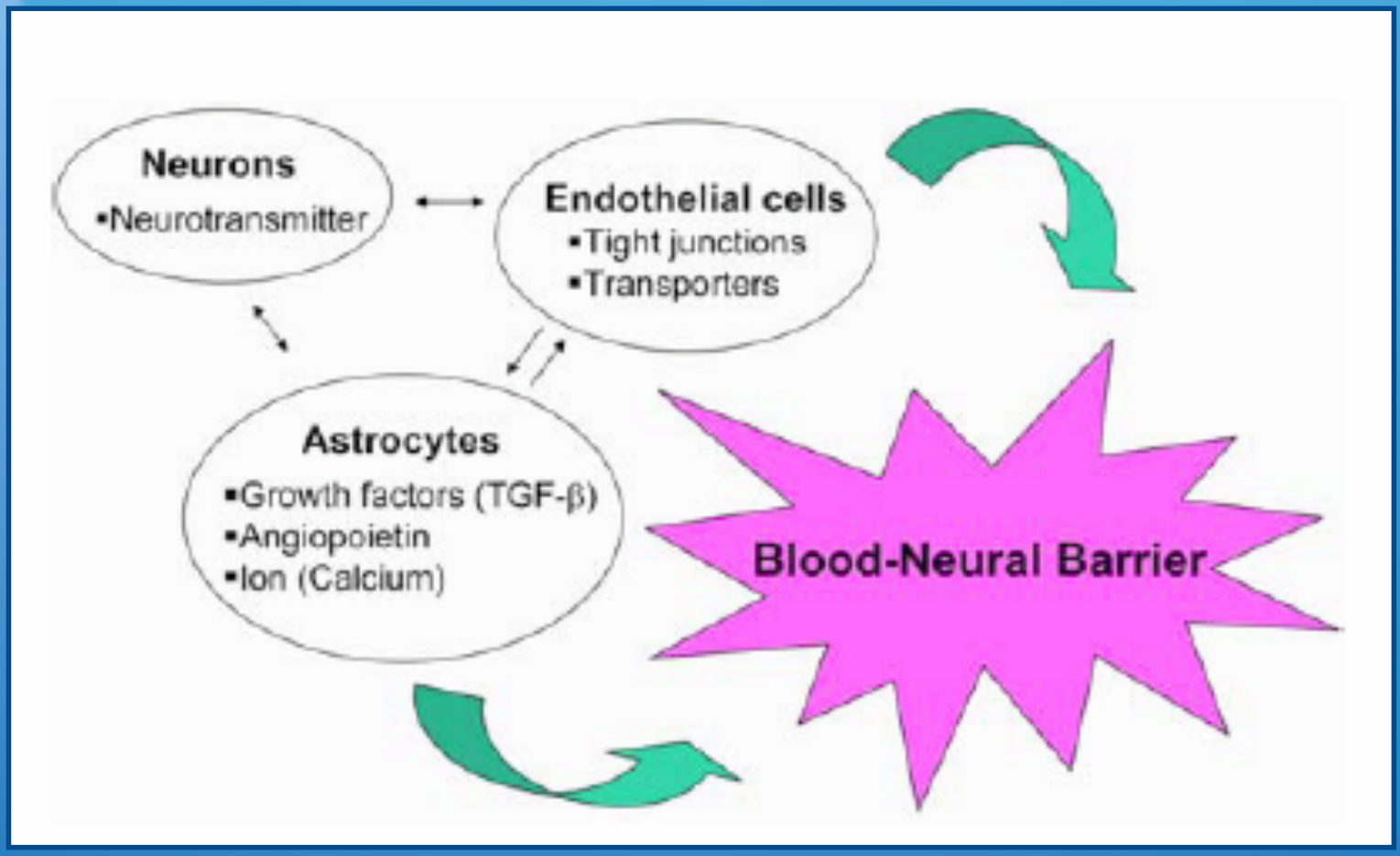

LA BARRIERA EMATOENCEFALICA

FUNZIONI DELLA BARRIERA

1) Consentire che il SNC sia un compartimento protetto in cui la composizione dei fluidi extracellulari deve essere quanto più precisamente regolata in termini di concentrazione dei soluti (ad esempio: sindrome da demielinizzazione osmotica)

Table 1
A comparison of the concentration of some solutes in CSF and plasma

Solute	CSF	Plasma
Total amino acids (mM)	0.89	2.89
Glucose (mM)	5.38	7.19
Albumin (mg/mL)	0.155 ± 0.039	28.4–53.8
IgG (mg/mL)	0.012 ± 006	9.87 ± 2.2
Total protein (mg/mL)	0.433 ± 790	70.00
Osmolarity (mOsmol)	298.5	305.2
HCO_3^- (mM)	22.0	25.0
pH	7.27	7.46

Begley DJ et al. Pharmacology & Therapeutics 2008

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2) Funzione neuroprotettiva di limitazione dell'accesso al SNC di molecole potenzialmente tossiche

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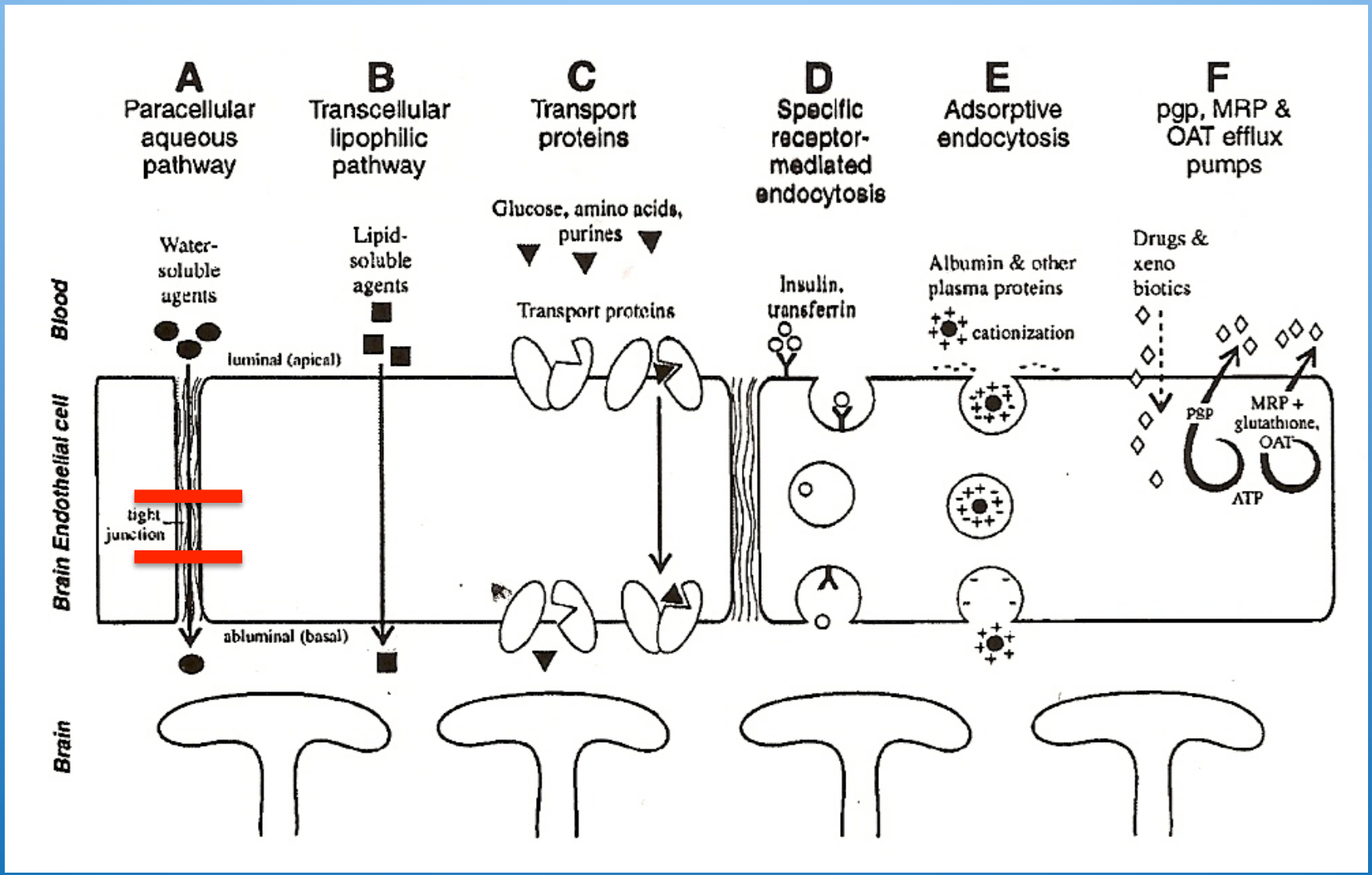

LA BARRIERA EMATOENCEFALICA

PRINCIPALI FATTORI CHE REGOLANO IL PASSAGGIO DI UN FARMACO ATTRAVERSO LA BARRIERA

1) **IL LEGAME CON LE PROTEINE PLASMATICHE.** Unicamente la frazione libera del farmaco nel plasma può attraversare la barriera. Molti agenti chemioterapici (Chlorambucil, Etoposide, Melphalan, Vincristina, Paclitaxel) sono legati per oltre il 90% alle proteine plasmatiche.

2) **LE DIMENSIONI DEL FARMACO, OVVERO IL SUO PESO MOLECOLARE.**

LA BARRIERA EMATOENCEFALICA

PESO MOLECOLARE DI ALCUNI FARMACI ANTIBLASTICI

FARMACO	P.M. (g/mol)
ARACYTIN	243.22
METHOTREXATE	454.45
IDARUBICINA	497.49
DOXORUBICINA	543.51
ETOPOSIDE	588.00
VINCRISTINA	824.95

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2) **LE DIMENSIONI DEL FARMACO, OVVERO IL SUO PESO MOLECOLARE.**

3) **LA LIPOSOLUBILITÁ.** Solo le molecole altamente solubili nei lipidi possono attraversare le membrane della barriera mediante il pathway transcellulare

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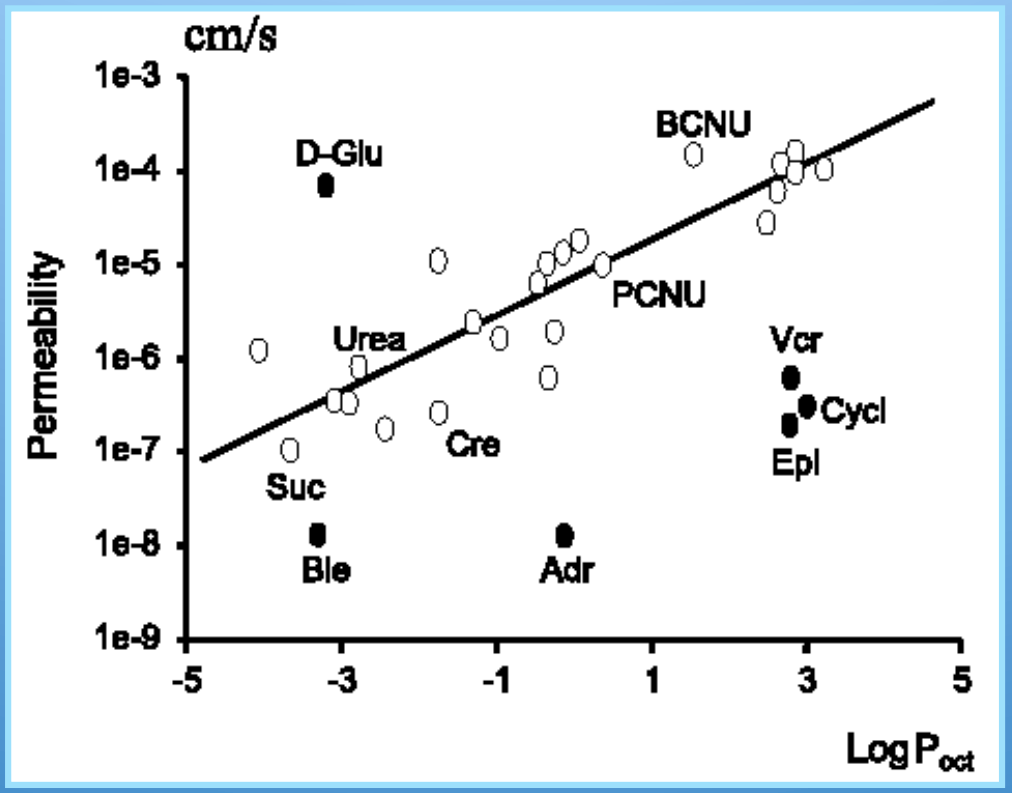

Fig. 4. Graph of BBB permeability (cm/sec) for several solutes plotted against lipid solubility determined in an octanol/water partition system. For many of these solutes (open points), there is a clear correlation between lipid solubility and BBB penetration. There are several outliers shown as filled points. Glucose has a greater BBB penetration than its lipid solubility would suggest as the result of its facilitated transport across the cerebral endothelium. The filled points well below the regression line are all substrates for efflux transporters, principally Pgp.

Begley DJ et al. Pharmacology & Therapeutics 2008

LA BARRIERA EMATOENCEFALICA

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4) **POMPE DI EFFLUSSO**

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MECCANISMI DI TRASPORTO ATTIVO DI EFFLUSSO DI MOLECOLE DAL SNC

- Pgp (P170 , codificata da un gene posto sul cromosoma 7)

- MRP multi-drug resistance protein

- MOAT multi-specific organic anion transporter

- Breast cancer-resistance protein

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NORMAL TISSUES EXPRESSING *MDR1*

LEVEL OF EXPRESSION		
HIGH	**MODERATE**	**LOW**
Brain[1]	Adrenal medulla	Skin
Kidney[2]	Trachea	Skeletal muscle
Liver[3]	Lung (major bronchi)	Heart
Placenta	Prostate	Spleen
Colon		Esophagus
Small bowel		Stomach
Adrenal cortex		Ovary
Testis[1]		Spinal cord
Pancreas[4]		Bone marrow[5]

[1]endothelial cells. [2] renal proximal tubule. [3] billiary lining. [4] epitelial cells. [5] CD34+ pregenitor cells

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CHEMIOTERAPICI E RESISTENZA MDR MEDIATA

CROSS-RESISTANT

Vinca alkaloids
- vincristine
- vinblastine
- vinorelbine

Anthracyclines
- doxorubicin
- daunorubicin
- idarubicin

Epipodophillotoxins
- etoposide (VP-16)
- docetaxel

Other
- dactinomycin
- mithramycin
- mitomycin C

NON-CROSS-RESISTANT

Platimun derivatives
- cisplatin
- carboplatin

Antimetabolites
- methotrexate
- fluoruracil
- cytarabine (ara-C)

Alkylating agents
- carmustine
- cyclophosphamide
- chlorambucil
- melphalan

Other
- bleomycin

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Distribution of STI-571 to the Brain Is Limited by P-Glycoprotein-Mediated Efflux

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Department of Pharmaceutics, University of Minnesota, Minneapolis, Minnesota (H.D., W.F.E.); Novartis Pharma AG, Preclinical Safety, Basel, Switzerland (P.M., M.L.); and Novartis Pharma, East Hanover, New Jersey (M.H.)

Received October 7, 2002; accepted November 25, 2002

ABSTRACT

The adequate distribution of STI-571 (Gleevec) to the central nervous system (CNS) is critical for its effective use in CNS tumors. P-glycoprotein-mediated efflux in the blood-brain barrier may play a role in the CNS delivery of this drug. Whether STI-571 is a substrate of P-glycoprotein was determined by examining the directional flux of [^{14}C]STI-571 in parental and MDR1-transfected Madin-Darby canine kidney (MDCK) II epithelial cell monolayers. The basolateral-to-apical flux of STI-571 was 39-fold greater than the apical-to-basolateral flux in the MDR1-transfected cells and 8-fold greater in the parental cell monolayers. This difference in directional flux was significantly reduced by a specific P-glycoprotein inhibitor (2*R*)-anti-5-{3-[4-(10,11-difluoromethanodibenzo-suber-5-yl)piperazin-1-yl]-2-hydroxypropoxy}quinoline trihydrochloride (LY335979). The role of P-glycoprotein in the CNS distribution of STI-571 was examined in vivo, using wild-type and mdr1a/b (−/−) knockout mice that were orally administered 25 mg/kg [^{14}C]STI-571. In the wild-type mice, the brain-to-plasma STI-571 concentration ratio at all time points was low (1–3%); however, there was an 11-fold greater brain partitioning of STI-571 at 1 h postdose in the mdr1a/b (−/−) mice compared with the wild-type mice. When 12.5 mg/kg STI-571 was given intravenously, the brain-to-plasma ratio of STI-571 in the mdr1a/b (−/−) mice was approximately 7-fold greater than that of wild-type mice up to 120 min postdose. These data indicate that STI-571 is a substrate of P-glycoprotein, and that the inhibition of P-glycoprotein affects the transport of STI-571 across MDCKII monolayers. Moreover, P-glycoprotein plays an important role in limiting the distribution of STI-571 to the CNS.

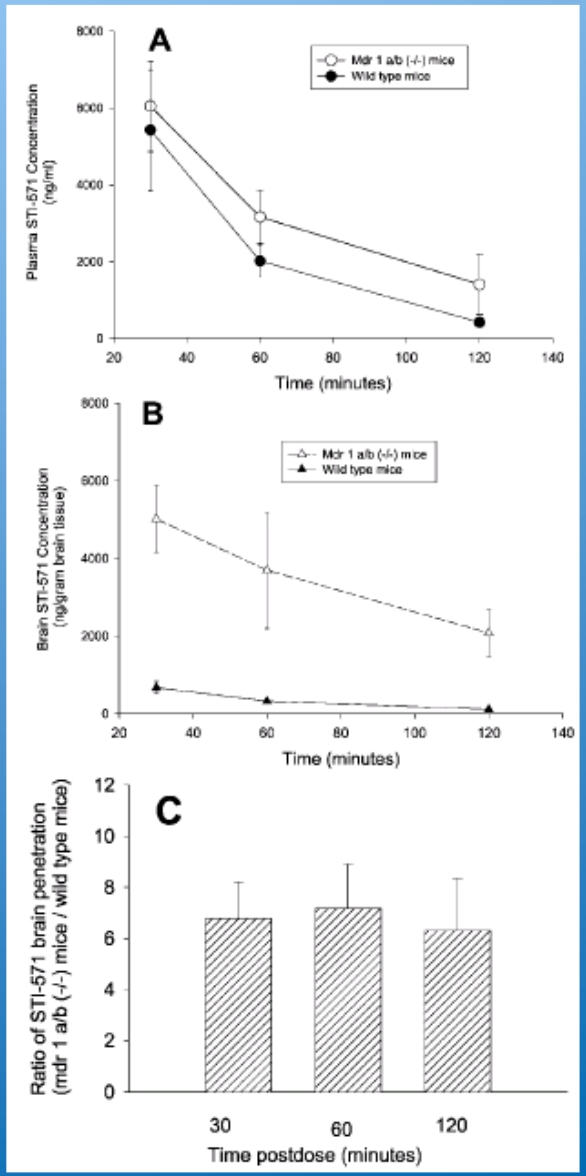

Fig. 6. Brain distribution of STI-571 in the mdr1a/b (−/−) knockout and wild-type mice after intravenous dosing. The mdr1a/b (−/−) knockout and wild-type mice received 12.5 mg/kg STI-571 via tail vein injection. The plasma and total brain tissue were collected at different times (30, 60, and 120 min postdose, $n = 4$ each) and analyzed for STI-571 using LC-MS. A, plasma concentration of STI-571 versus time in mdr1a/b (−/−) knockout and wild-type mice. B, brain concentration of STI-571 versus time in mdr1a/b (−/−) knockout and wild-type mice. C, ratio of brain penetration of STI-571 in mdr1a/b (−/−) knockout mice versus wild-type mice at different time points. The values are presented as mean ± S.D.

LA BARRIERA EMATOENCEFALICA

La concentrazione tissutale cerebrale dei diversi farmaci antiblastici può dipendere inoltre da:

- via di somministrazione e velocità di infusione
- tipo di tumore
- metabolismo del farmaco, interazioni con altri farmaci
- dose (Methotrexate)

Circa il 98% di tutti i potenziali farmaci per il SNC non attraversano la barriera

Methotrexate area under the curve is an important outcome predictor in patients with primary CNS lymphoma: A pharmacokinetic–pharmacodynamic analysis from the IELSG no. 20 trial

Joerger M. et al
British Journal of Cancer (2010) 102.

Table 3 Predictors for event-free and overall survival using multivariate Cox regression analysis

Covariate	HR	95% CI	*P*-value
Event-free survival			
Patient gender			
Female	Ref		
Male	1.12	0.52–2.40	0.77
IELSG score			
0–1 *vs* 2–3 *vs* 4–5 points	1.71	1.04–2.81	0.03
Treatment group			
HD-MTX	Ref		
HD-MTX/AraC	0.65	0.34–1.25	0.19
$AUC_{HD\text{-}MTX}$			
Per 100 $\mu mol\,l^{-1}\,h$ increase	0.82	0.69–0.98	0.03
Overall survival			
Patient gender			
Female	Ref		
Male	1.77	0.76–4.10	0.19
IELSG score			
0–1 *vs* 2–3 *vs* 4–5 points	1.82	1.00–3.31	0.05
Treatment group			
HD-MTX	Ref		
HD-MTX/AraC	0.80	0.39–1.65	0.54
$AUC_{HD\text{-}MTX}$			
Per 100 $\mu mol\,l^{-1}\,h$ increase	0.73	0.59–0.89	0.002

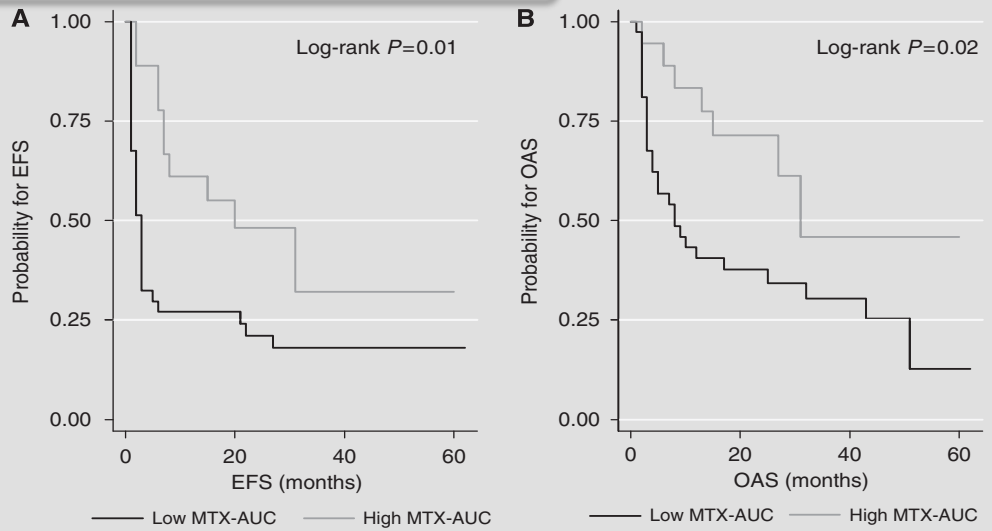

Figure 2 Kaplan–Meier plots for event-free survival (**A**) and overall survival (**B**) grouped according to the highest $AUC_{HD\text{-}MTX}$ tertile (>980 $\mu mol^{*}l^{-1}\,h$) and the lower two tertiles of $AUC_{HD\text{-}MTX}$ (<980 $\mu mol^{*}l^{-1}\,h$).

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MALATTIE DEL SNC ASSOCIATE CON DISFUNZIONE DI BARRIERA

- **MALATTIE NEOPLASTICHE** — tumori benigni o maligni del SNC
- **MALATTIE VASCOLARI** — ischemia, ipertensione, malformazioni
- **MALATTIE METABOLICHE** — diabete
- **MALATTIE INFIAMMATORIE** — sclerosi multipla, meningo-encefaliti
- **TRAUMI** — danni meccanici o chimici, irradiazione

LA BARRIERA EMATOENCEFALICA

SE LA BARRIERA IN UN TUMORE CEREBRALE É ALTERATA, PERCHÉ I FARMACI ANTITUMORALI NON RIESCONO A RAGGIUNGERE IN QUANTITÁ ADEGUATA IL TUMORE?

- La neoangiogenesi tumorale è disordinata ed eterogenea, il tumore spesso utilizza la pre-esistente rete vascolare cerebrale con una barriera in gran parte integra

- L'entità della permeabilità vascolare tumorale varia sia spazialmente sia temporalmente all'interno del tumore, essendo la permeabilità maggiore nel "core" tumorale e molto minore nella porzione tumorale più periferica di crescita del tumore ("brain adjacent to tumor")

- Parallelamente alla crescita del tumore, la distanza intra-capillare aumenta e cresce lo spazio di diffusione del farmaco per raggiungere la cellula neoplastica

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SE LA BARRIERA IN UN TUMORE CEREBRALE É ALTERATA, PERCHÉ I FARMACI ANTITUMORALI NON RIESCONO A RAGGIUNGERE IN QUANTITÁ ADEGUATA IL TUMORE?

- anche in presenza di una barriera compromessa, l'accumulo del farmaco è limitato a causa di una elevata pressione interstiziale intratumorale (che può arrivare a 50 mmHg rispetto a 2 mmHg nel tessuto cerebrale normale)

- l'edema peri-tumorale comporta un ulteriore aumento della pressione idrostatica nel parenchima cerebrale adiacente al tumore e riduce la possibilità di diffusione dei farmaci all'interno del tessuto tumorale

- l'integrità della barriera tende a ristabilirsi rapidamente

- si parla perciò di blood-tumor barrier che preclude una efficace erogazione di farmaci antiblastici nei tumori cerebrali attraverso la via ematica

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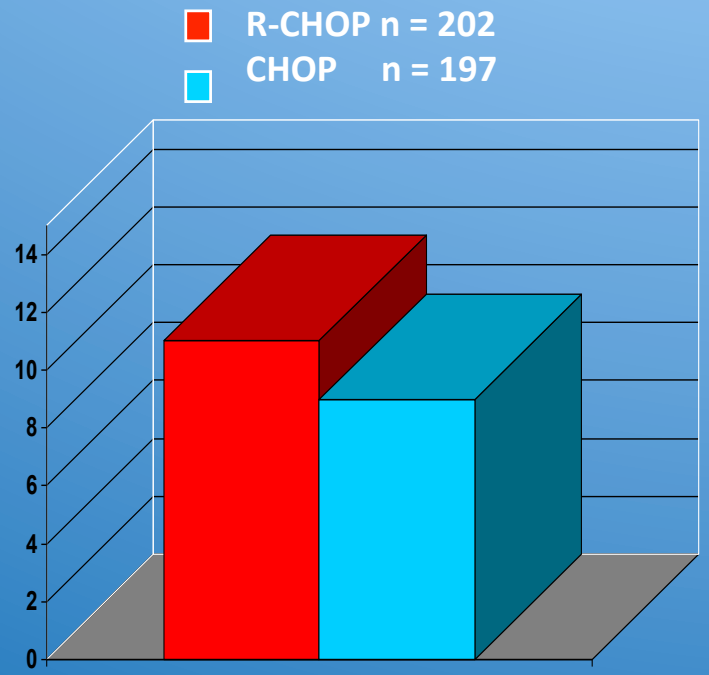
- **GELA 98.5**



- **No efficacy of systemic Rituximab**

Feugier P *et al. Ann Oncol* 2004; 15: 129-133

- **CSF concentrations of systemic rituximab (375 mg/sqm) ~ 0.1% of serum levels**

Table 1. CSF levels in patients with CNS lymphoma who were treated intravenously with rituximab plus high-dose methotrexate or Ara-C

Patient no.	Week	Serum rituximab	CSF rituximab
1	4	345.7 μg/mL	0.44 μg/mL
2	8	—	0.6 μg/mL
3	1	355.4 μg/mL	0.48 μg/mL
4*	1	273.8 μg/mL	LTR†

Patients received rituximab at 375 mg/m² intravenously weekly for 8 treatments. Rituximab levels were determined in serum and atraumatic CSF specimens collected simultaneously at the completion of the rituximab infusion.

— indicates not available.

*Patient no. 4 had malignant CSF cytology but no contrast-enhancing lesions on MRI.

†The assay result was less than the reportable limit.

- **Il Rituximab passa in misura molto ridotta la barriera emato-encefalica**

Rubenstein JL *et al. Blood* 2003; 101: 466-468

RITUXIMAB MONOTHERAPY FOR PATIENTS WITH RECURRENT PRIMARY CNS LYMPHOMA

Batchelor TT et al, Neurology 2011

12 pazienti affetti da "recurrent or refractory PCNSL" trattati fino a 8 dosi di Rituximab (375 mg/mm^2)

Table Patient characteristics

Characteristics	Values
Median age, y (range)	64 (31-81)
Male:female	7:5
Median KPS score (range)	85 (60-100)
Median MMSE score (range)	29 (18-30)

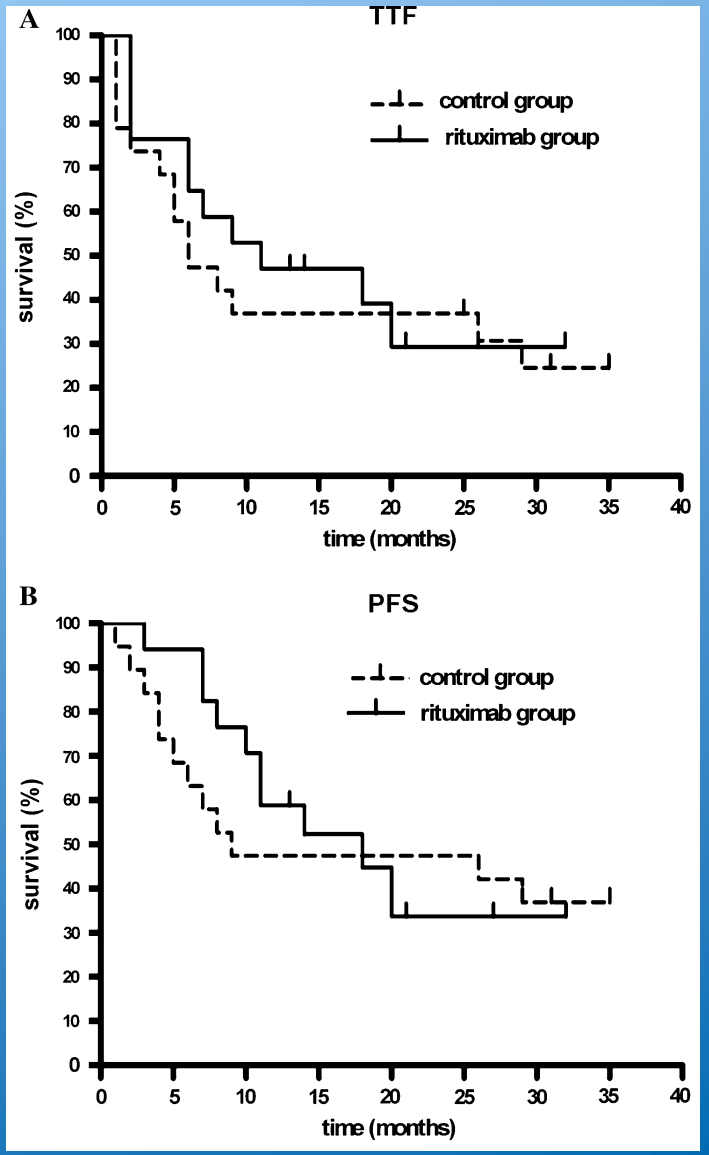
Abbreviations: KPS = Karnofsky Performance Scale; MMSE = Mini-Mental State Examination.

RESULTS :

- 3 CR, 1 PR (33%) by MRI
- median PFS 57 days
- median OS 20.9 months (47 months for patients achieving a confirmed radiographic response)

Rituximab significantly improves complete response rate in patients with primary CNS lymphoma

	Control group (MTX + IFO)	Rituximab group (MTX + IFO + R)	*p*
Response to chemotherapy			
CR/uCR, *n* (%)	13/19 (68.4)	17/17 (100)	0.02
CR, *n* (%)	11/19 (57.9)	10/17 (58.8)	
uCR, *n* (%)	2/19 (10.5)	7/17 (41.2)	
PR, *n* (%)	4/19 (21.1)	0/17 (0)	
SD, *n* (%)	0/19 (0)	0/17 (0)	
PD, *n* (%)	1/19 (5.3)	0/17 (0)	
n.a. (%)	1/19 (5.3)	0/17 (0)	
PFS-6 (%)	12/19 (63.2)	16/17 (94.1)	0.04
WBI adjuvant, *n* (%)	5/19 (26.3)	1/17 (5.9)	0.18
WBI anytime, *n* (%)	8/19 (42.1)	5/17 (29.4)	0.5
Relapses following CR to chemotherapy only, *n* (%)	6/12 (50)	8/16 (50)	



Birnbaum T et al. J Neurooncol 2012

"HIGH-DOSE METHOTREXATE WITH OR WITHOUT RITUXIMAB IN NEWLY DIAGNOSED PRIMARY CNS LYMPHOMA"

ABSTRACT

Objective: To evaluate the efficacy of rituximab (R) when added to high-dose methotrexate (HD-MTX) in patients with newly diagnosed immunocompetent primary CNS lymphomas (PCNSLs).

Methods: Immunocompetent adults with newly diagnosed PCNSL treated at The Johns Hopkins Hospital between 1995 and 2012 were investigated. From 1995 to 2008, patients received HD-MTX monotherapy (8 g/m^2 initially every 2 weeks and after complete response [CR] monthly to complete 12 months of therapy). From 2008 to 2012, patients received the same HD-MTX with rituximab (375 mg/m^2) with each HD-MTX treatment. CR rates and median overall and progression-free survival were analyzed for each patient cohort in this single-institution, retrospective study.

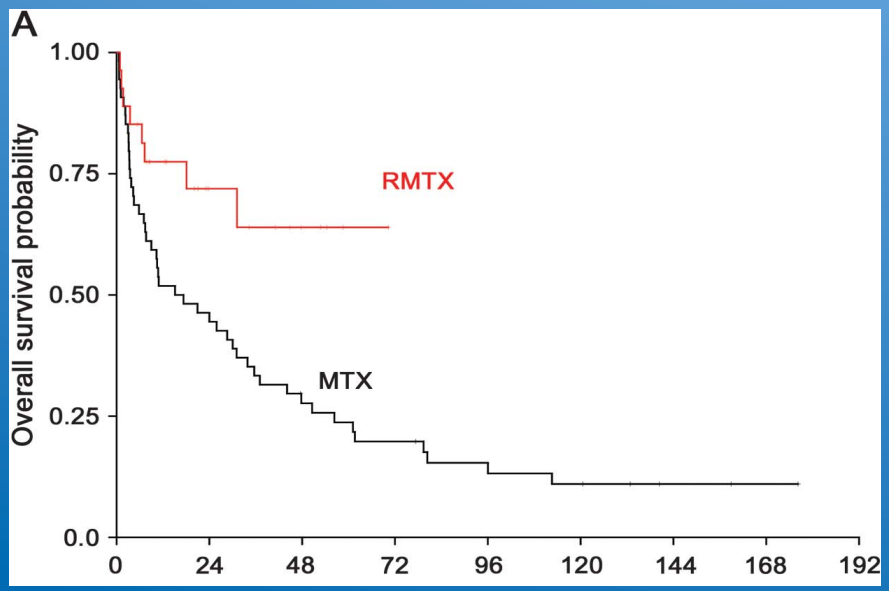
Results: A total of 81 patients were identified: 54 received HD-MTX (median age 66 years) while 27 received HD-MTX/R (median age 65 years). CR rates were 36% in the HD-MTX cohort and 73% in the HD-MTX/R cohort ($p = 0.0145$). Median progression-free survival was 4.5 months in the HD-MTX cohort and 26.7 months in the HD-MTX/R cohort ($p = 0.003$). Median overall survival was 16.3 months in the HD-MTX cohort and has not yet been reached in the HD-MTX/R cohort ($p = 0.01$).

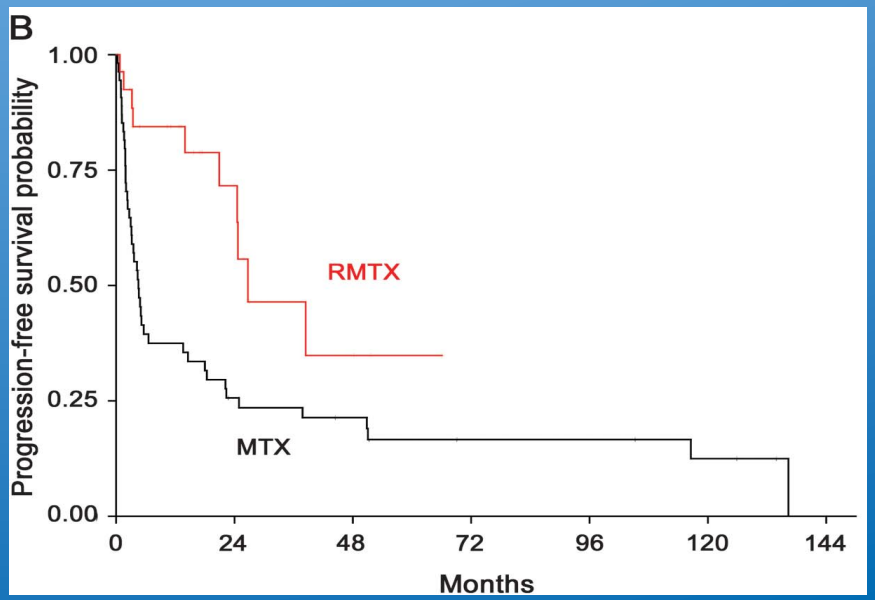
Conclusions: The addition of rituximab to HD-MTX appears to improve CR rates as well as overall and progression-free survival in patients with newly diagnosed PCNSL. Comparisons of long-term survival in the 2 cohorts await further maturation of the data.

Classification of evidence: This study provides Class III evidence that in immunocompetent patients with PCNSL, HD-MTX plus rituximab compared with HD-MTX alone improves CR and overall survival rates. *Neurology®* 2014;83:235–239

Table Demographics

	HD-MTX/R (n = 27)	HD-MTX (n = 54)
Median age at diagnosis, y (range)	65 (44-85)	66 (32-79)
Age distribution, n (%)		
30-45 y	1 (4)	7 (13)
46-55 y	4 (15)	8 (15)
56-65 y	8 (29)	14 (26)
66-75 y	11 (41)	17 (31)
Older than 75 y	3 (11)	8 (15)
Sex, % male	56	50
ECOG scores 0-2, %	67	65





Holdhoff M, et al. Neurology 2014

R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma

Antonio Omuro,[1] Denise D. Correa,[1] Lisa M. DeAngelis,[1] Craig H. Moskowitz,[2] Matthew J. Matasar,[2] Thomas J. Kaley,[1] Igor T. Gavrilovic,[1] Craig Nolan,[1] Elena Pentsova,[1] Christian C. Grommes,[1] Katherine S. Panageas,[3] Raymond E. Baser,[3] Geraldine Faivre,[1] Lauren E. Abrey,[1] and Craig S. Sauter[2]

[1]Department of Neurology, [2]Department of Medicine, and [3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Table 1. Patient characteristics (N = 32)

Characteristic	Value
Median age (range)	57 (23-67)
Age <60	21 (66%)
Age <50	11 (34%)
Median KPS (range)	80 (40-100)
KPS <70	6 (19%)
KPS <50	1 (3%)
Women	15 (47%)
Men	17 (53%)
MSK RPA	
Class I	11 (34%)
Class II	15 (47%)
Class III	6 (19%)
DLBCL	32 (100%)
CSF cytology*	
Positive	1 (3%)
Suspicious	2 (6%)
Not performed	1 (3%)
Ocular involvement	3 (9%)
Median product of tumor diameters (range)	6 cm^2 (0-20 cm^2)

MSK RPA, Memorial Sloan-Kettering prognostic score determined by recursive partitioning analysis (I, age <50; II, age ≥50 and KPS ≥70; III, age ≥50 and KPS <70).

*Conventional cytology; flow cytometry not performed.

Table 3. Response status after R-MPV and following transplant

	CR/CRu	PR	SD	PD
Response after 5 R-MPV cycles (N = 32)	14 (44%)	16 (50%)	1* (3%)	1 (3%)
Best response to R-MPV induction chemotherapy (5 or 7 cycles) (N = 32)	21 (66%)	9 (28%)	1* (3%)	1 (3%)
Pretransplant response status in the transplanted patients (N = 26)	18 (69%)	7 (27%)	1* (4%)	0 (0)
Best response after transplant (N = 26)	21 (81%)	3 (11%)	1* (4%)	1 (4%)

*This 1 patient had no measurable disease at start of R-MPV because of complete resection, remained stable after 7 cycles of R-MPV and underwent HDC-ASCT, and was considered nonevaluable for objective response rate assessment.

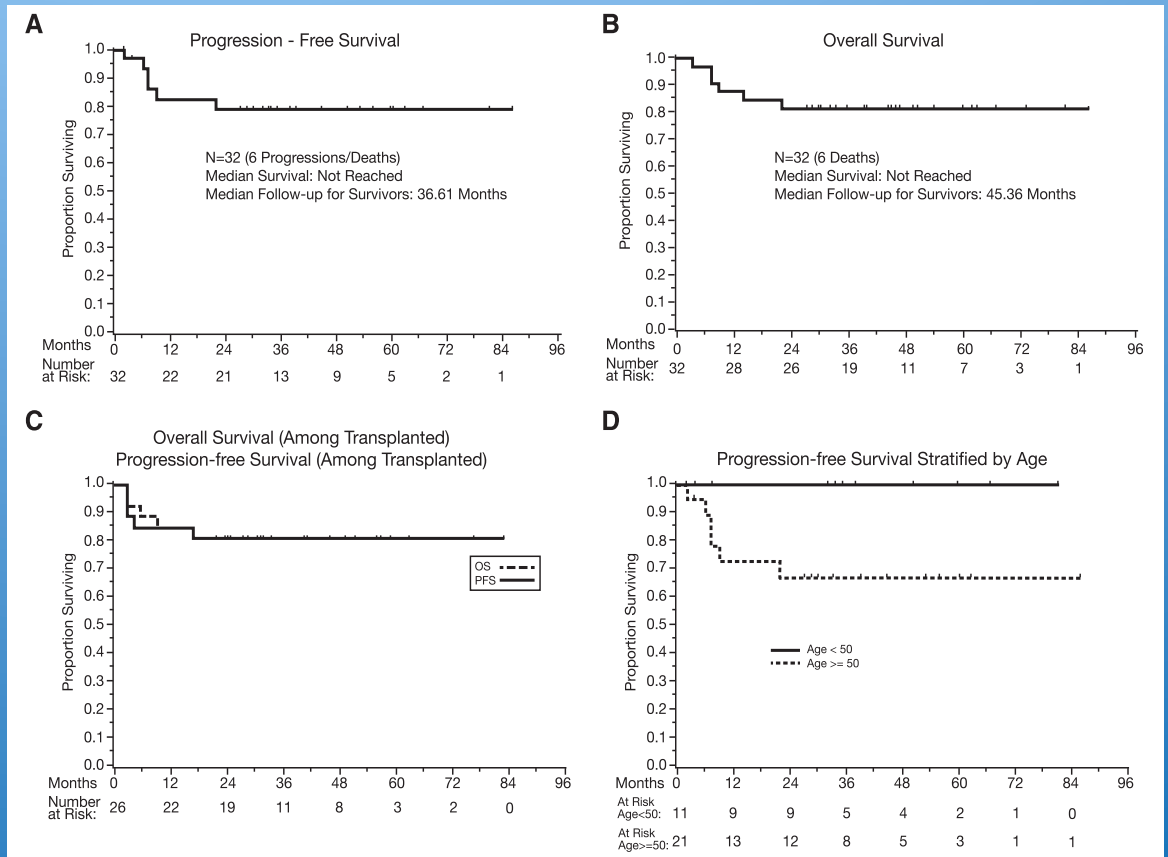


Figure 1. PFS and OS. (A) PFS, all patients (N = 32). (B) OS, all patients (N = 32). (C) PFS and OS in transplanted patients. (D) PFS according to age (above 50 vs 50 and under). *P* = .05.

Blood 2015

How I treat CNS lymphomas

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" in summary, given the data from a number of prospective trials as well as clinical series that document activity of rituximab in the setting of CNS lymphomas, as monotherapy and in combination with MTX-based induction regimens, we recommend the incorporation of intravenous Rituximab in CD20+ CNS lymphoma-directed therapies."

Trial for Patients With Newly Diagnosed Primary Central Nervous System (CNS) Lymphoma

This study is ongoing, but not recruiting participants.

Sponsor:
International Extranodal Lymphoma Study Group (IELSG)

Information provided by (Responsible Party):
International Extranodal Lymphoma Study Group (IELSG)

ClinicalTrials.gov Identifier:
NCT01011920

First received: November 9, 2009
Last updated: July 26, 2016
Last verified: July 2016
History of Changes

Purpose

This is a multicenter open label randomized phase II trial.

Enrolled Primary Central Nervous System Lymphoma (PCNSL) patients will be stratified according to the IELSG score and randomized to receive one of the follows as primary chemotherapy:

- Arm A: Methotrexate (MTX) + Cytarabine (Ara-C)
- Arm B: MTX + Ara-C + rituximab
- Arm C: MTX + Ara-C + rituximab + thiotepa.

Chemotherapy will be administered every three weeks. The maximum number of chemotherapy induction courses will be 4. Patients in Stable Disease (SD) or better after two courses will receive two more courses of the same primary chemotherapy regimen. Stem-cells harvest will be performed in the three arms after the second course. After 4 courses response assessment will be performed.

Patients who will not achieve SD or better after the 4th course, as well as those who will experience Progressive Disease (PD) at any time and those who will not achieve a sufficient stem cell harvest, will receive Whole Brain Radiation Therapy (WBRT) 36-40 Gy +/- tumor bed boost of 9 Gy.

Patients who will achieve SD or better after the 4th course will be stratified according to objective response to primary chemotherapy and to primary chemotherapy regimen and randomly allocated to receive as consolidation therapy one of the follows:

- Arm D: WBRT 36 Gy +/- boost 9 Gy
- Arm E: Carmustine (BCNU) + Thiotepa + Autologous Peripheral Blood Stem Cell Transplant (APBSCT) Patients in Complete Response (CR) after WBRT or APBSCT will remain in follow-up. Patients who will not achieve a CR after WBRT will be managed according to physician's preferences. Patients who will not achieve a CR after APBSCT will be referred to WBRT.

LA BARRIERA EMATOENCEFALICA

STRATEGIE PER SUPERARE LA BARRIERA

1) Rottura dell'integrità della barriera su BASE OSMOTICA

LA BARRIERA EMATOENCEFALICA

ROTTURA DELLA BARRIERA SU BASE OSMOTICA

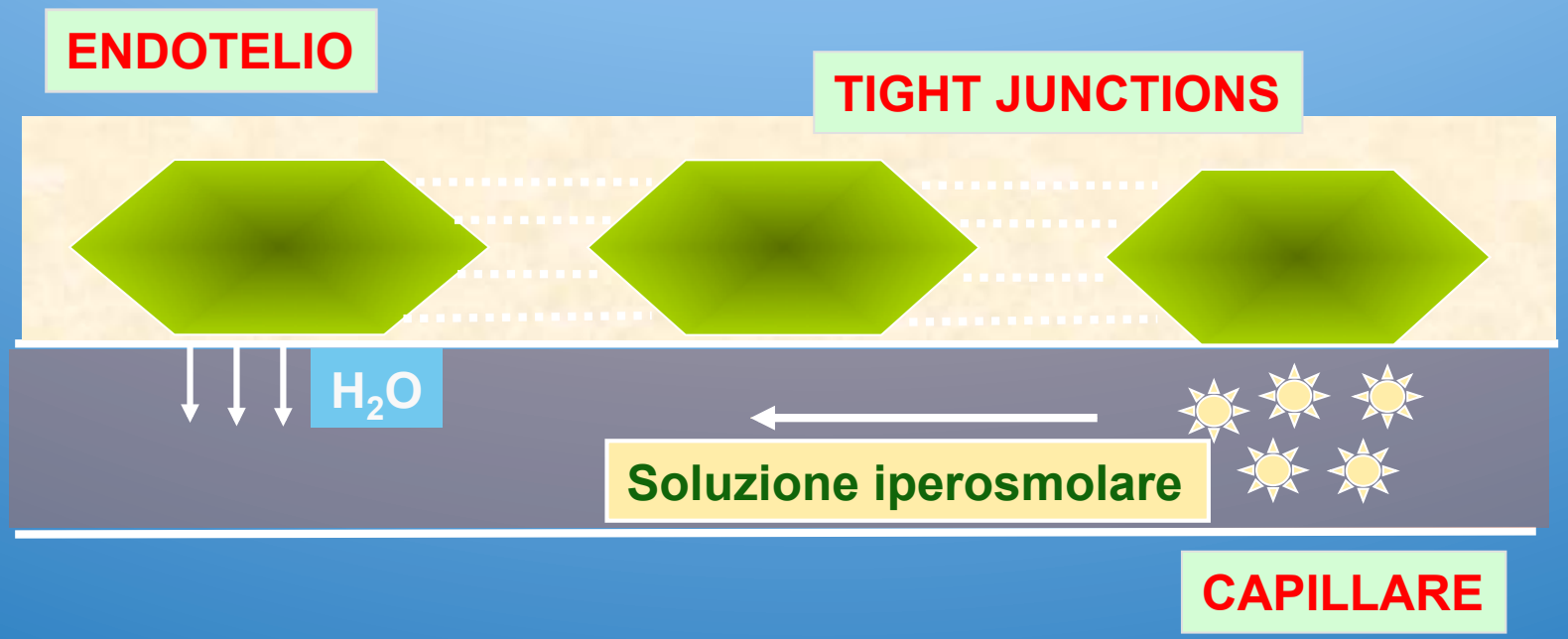
- una transitoria e reversibile rottura della barriera si può ottenere attraverso l'infusione per via intra-arteriosa di un agente iperosmolare (mannitolo), che può indurre le cellule endoteliali a ritirarsi, consentendo così l'apertura delle tight junctions

- studi farmacocinetica nell'animale hanno mostrato che la permeabilità al methotrexate raggiunge il suo massimo entro 15 minuti dopo l'infusione del mannitolo e ritorna a livelli preinfusione entro 2 ore

- l'infusione arteriosa del mannitolo consente una "delivery" intracerebrale del methotrexate da 10 a 100 volte superiore rispetto all'infusione endovenosa

LA BARRIERA EMATOENCEFALICA

ROTTURA DELLA BARRIERA SU BASE OSMOTICA



LA BARRIERA EMATOENCEFALICA

PROCEDURA DI ROTTURA OSMOTICA DELLA BARRIERA

- anestesia generale
- premedicazione con anticonvulsivante (nel 6% circa delle procedure si possono manifestare crisi convulsive, generalmente focali)
- infusione di atropina per la prevenzione della bradicardia
- posizionamento di un catetere per via transfemorale nella arteria carotide interna (a livello di C1-C2) o in arteria vertebrale (a livello di C4-C5), a seconda della sede del tumore
- infusione del mannitolo al 25% in sede intra-arteriosa alla velocità di 4-10 mL/secondo per 30 secondi, monitorando il flow-rate in fluoroscopia

LA BARRIERA EMATOENCEFALICA

ROTTURA DELLA BARRIERA SU BASE OSMOTICA

- a tutt'oggi nell'uomo sono state riportate oltre 8000 procedure di rottura osmotica della barriera, senza un significativo eccesso di eventi tossici, comunque controllabili
- riportata CR 58%, PFS a 5 anni 31% con accettabile morbidità e neurotossicità (Angelov L, JCO 2009)
- la reale efficacia della procedura è difficile da valutare, sia per la mancanza di studi prospettici, sia soprattutto per la invasività e per la delicatezza delle manovre, che richiedono competenze e abilità multidisciplinari

"I do not expect that BBB disruption and intra-arterial chemotherapy will be used worldwide in the next years…"
(Andrès Ferreri, Blood 2011)

LA BARRIERA EMATOENCEFALICA

ALTRE TECNICHE PER INDURRE LA ROTTURA DELLA INTEGRITÁ DELLA BARRIERA

- infusione di solventi (dimetilsulfossido, etanolo) o di metalli (alluminio)
- irradiazione ad alte energie
- induzione di situazioni patologiche, come ipossia, ipercapnia o ipertensione
- somministrazione di farmaci, come il metrazolo, che può transitoriamente aumentare la permeabilità della barriera, associandosi tuttavia alla induzione di marcate convulsioni
- MRI-guided focused ultrasound

LA BARRIERA EMATOENCEFALICA

STRATEGIE PER SUPERARE LA BARRIERA

2) Uso dei sistemi di trasporto endogeni

Table 2
Drug entry into the CNS via endogenous transporters

Medium-chain fatty acid carrier
Valproic acid
Docosahexanoic acid (DHA-) taxol
DHA-ddC
Large neutral amino acid carrier
L-DOPA
α-Methyl-DOPA
Melphalan
Baclophen
Gabapentin
Acivicin
D,L-NAM
Phosphonoformate-tyrosine conjugate
Nitrosoarginine derivatives
Monocarboxylic acid carrier
Active metabolites of simvastin and lovastatin (with carboxylic acid groups)
Basic drugs: cation transporter (OCT)
Mepyramine
Diphenhydramine
Diphenylpyraline
Lidocaine
Imipramine
Propranolol
Purine carrier
Oxazolamine COR3224
Nucleoside carrier
Abacivir
Hexose carrier
Dehydroascorbic acid
Glycosylated morphine

DHA-ddc, docosahexanoic acid-2′ ,3′ -dideoxycytidine.

LA BARRIERA EMATOENCEFALICA

STRATEGIE PER SUPERARE LA BARRIERA

3) Inibizione dei sistemi di trasporto di efflusso extra-SNC del farmaco

Table 3
Modulators of ABC transporters

First generation Inhibitors	Target
Probenecid	MRP1/2
Sulfinpyrazone	MRP1/2
Benzbromarone	MRP1/2
Verapamil	Pgp
Quinidine	Pgp
Cyclosporin A	Pgp
Second generation Inhibitors	
SDZ-PSC833	Pgp
Third generation Inhibitors	
GF120918	Pgp/BCRP
LY335979	Pgp
V-104	Pgp
Pluronic L-61	Pgp
Fumitremorgin C	BCRP

LA BARRIERA EMATOENCEFALICA

STRATEGIE PER SUPERARE LA BARRIERA

4) Modificazioni della struttura del farmaco per aumentare la lipofilia

Formazione di liposomi e immunoliposomi peghilati

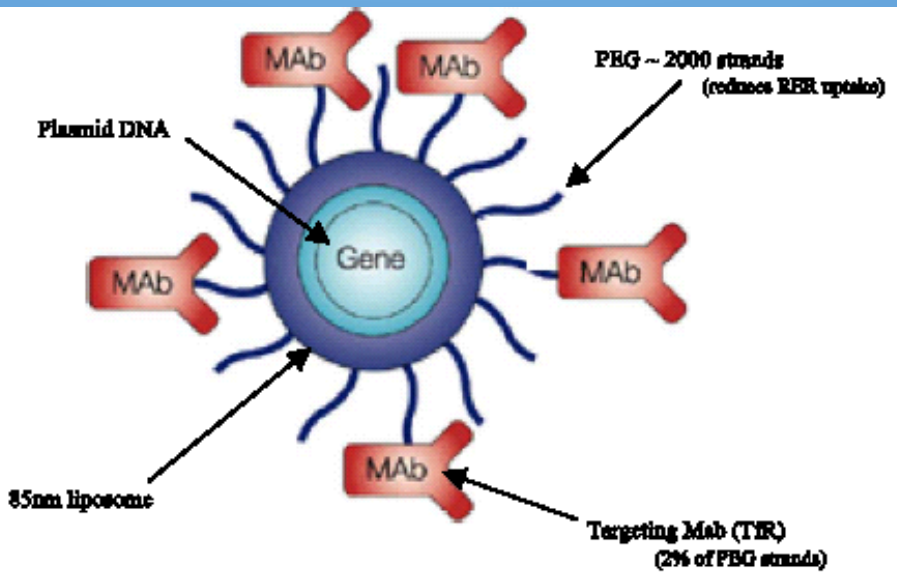


Fig. 7. An immunoliposome. A plasmid DNA containing a gene is packaged into the center of an 85 nm diameter liposome. The surface of the liposome is coated with ~2000 strands of PEG, which reduces uptake by the RER. Between 1% and 2% of these strands are conjugated to the transferrin receptor targeting mAb. From Pardridge (2002).

LA BARRIERA EMATOENCEFALICA

STRATEGIE PER SUPERARE LA BARRIERA

6) Nanobiotecnologie

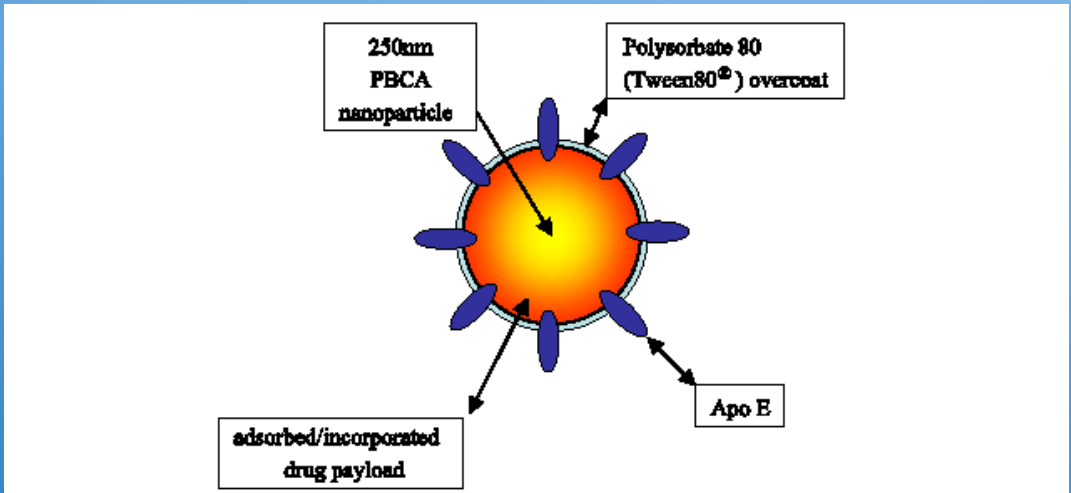


Fig. 8. A PBCA nanoparticle. A drug can be incorporated into the 250 nm diameter nanoparticle during polymerization or absorbed onto the surface of the preformed particle. The particle is then coated with polysorbate 80 (Tween 80), which further binds Apo-E in the bloodstream.

Poligenic nanoparticles, liposomas, solid-lipid nanoparticles, micelles, nanogels, dendrimers.

NANONEUROMEDICINE

- "Surface engineering of nano-sized carriers, that are able to remain stable in the bloodstream, protect the drug from metabolic reactions, promote the long-lasting release of the drug and directly interact with the transport systems present at the BBB endothelial cells."

- Concerns:
  - Biocompatibility
  - Selectivity
  - Safety


La barriera emato-encefalica non deve essere considerata unicamente come barriera anatomica statica alla libera diffusione di molecole, ma come un sistema altamente complesso che interagisce con multipli fattori di provenienza ematica e con segnali prodotti nel SNC, che ne regolano l' attività e la funzione di barriera.
Impegno della ricerca scientifica per nuove strategie capaci di direzionare efficacemente il farmaco al compartimento cerebrale, tutelandone al contempo la delicata omeostasi chimico-fisica.