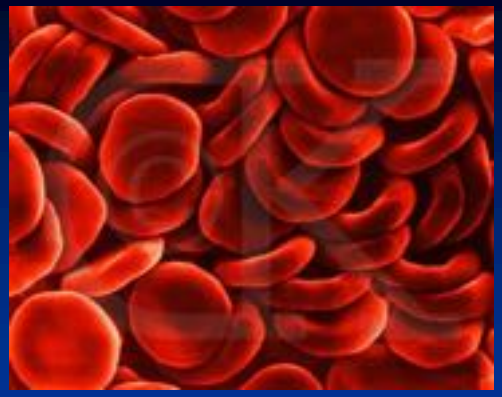


Università degli Studi di Urbino
"Carlo Bo"

Utilizzo di globuli rossi ingegnerizzati come nuova strategia per la veicolazione di farmaci

Pesaro
22 settembre 2007

Prof. Luigia Rossi
luigia.rossi@uniurb.it

USO DI FARMACI INTELLIGENTI

O

USO INTELLIGENTE DI FARMACI?

LE NUOVE SFIDE TERAPEUTICHE ALLA LUCE DELL'USO RAZIONALE DEI FARMACI

PERCHÈ UTILIZZARE "CARRIERS" PER FARMACI

- aumentarne l'efficacia terapeutica
- ridurne la tossicità

- Maggiore stabilità in circolo
- Riduzione del dosaggio
- Riduzione della frequenza di somministrazione
- Riduzione degli effetti collaterali

Targeting specifico

PERCHÈ I GLOBULI ROSSI

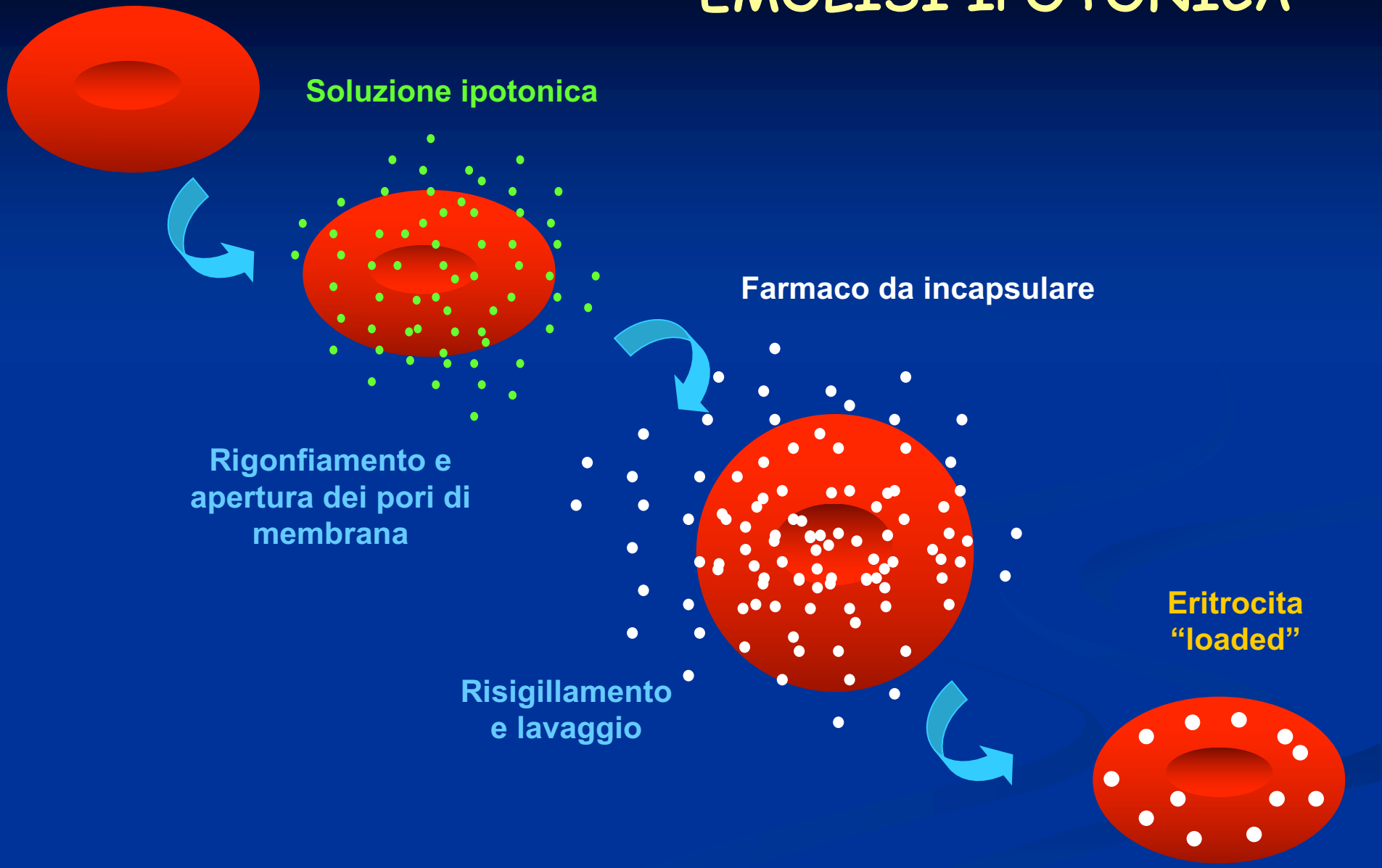
- ottenibili in grandi quantità
- biodegradabili
- non tossici nè immunogenici
- grande volume cellulare quindi elevata capacità
- possono circolare per lunghi periodi di tempo (mesi)
- possiedono corredo enzimatico in grado di attivare profarmaci incapsulati
- la procedura di incapsulamento (LOADING) non ne altera le proprietà morfologiche, immunologiche e biochimiche

TECNICHE DI LOADING

- ELETTROPORAZIONE
- ENDOCITOSI INDOTTA DA FARMACI
- METODO DEL PULSE OSMOTICO
- EMOLISI IPOTONICA

  - DILUTIONAL
  - PRESWELL DILUTIONAL
  - DIALYSIS
  - PRESWELL DILUTIONAL WITH CONCENTRATION

EMOLISI IPOTONICA



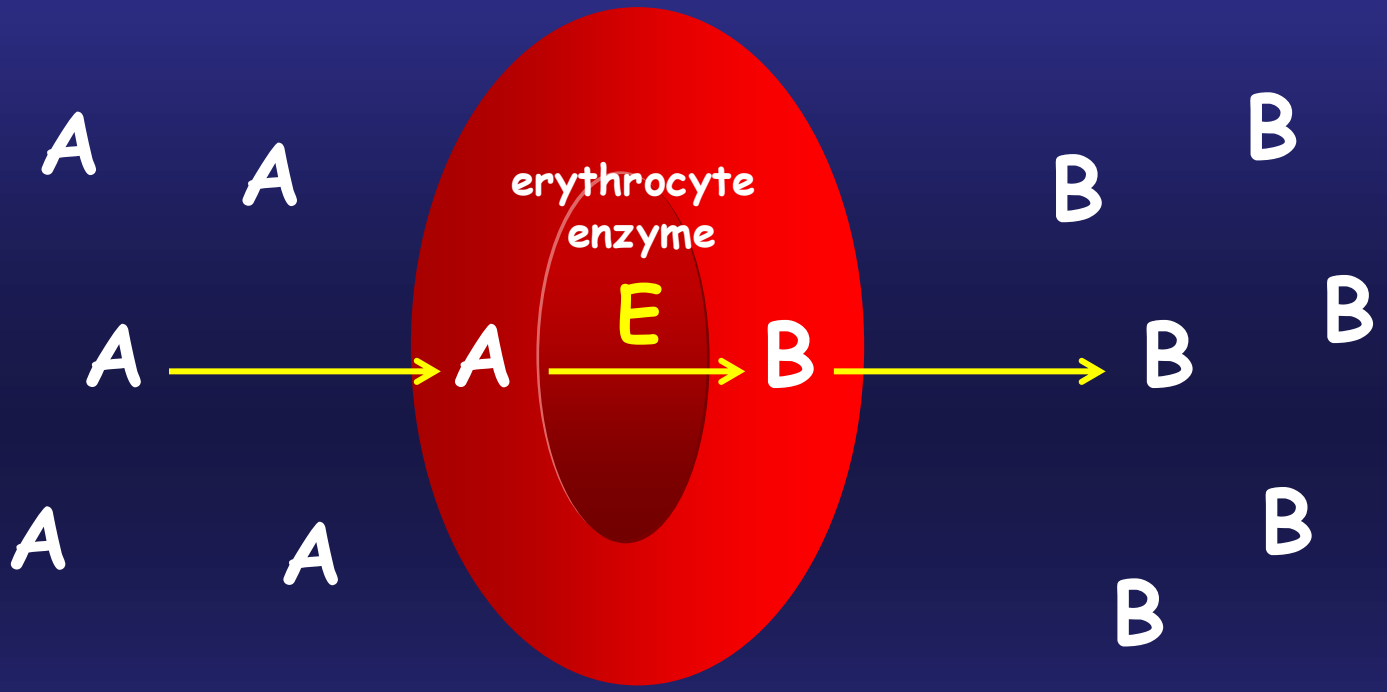
APPLICAZIONI BIOMEDICHE DEGLI RBC "LOADED"

A) Bioreattori circolanti con enzimi incapsulati

B) Bioreattori circolanti per un lento rilascio in circolo di farmaci

C) Targeting selettivo di farmaci a cellule macrofagiche

Bioreattori circolanti con enzimi incapsulati



Es:

- loading di adenosina deaminasi nella SCID (sindrome di immunodeficienza grave combinata)
- loading di asparaginasi nella leucemia linfoblastica acuta

ERYtech Pharma offers a new solution for the use of therapeutic enzymes by increasing their half life and reducing their toxicity.

Therapeutic enzymes are very often characterized by their toxicity. Thanks to their encapsulation into red blood cells, enzymes are **active only inside the erythrocyte**. The development of neutralizing antibodies, which may decrease the effectiveness of the treatment, is prevented.

Moreover, enzymes have a very short half life, going from a few minutes to a maximum of a few days. **Encapsulated enzymes' half life is increased up to that of the erythrocyte;** they become active longer than under their free form – up to one month – and at a lower dosage – dosages are reduced about 100 fold.

ERYtech Pharma®

The Therapeutic Red Cell Company

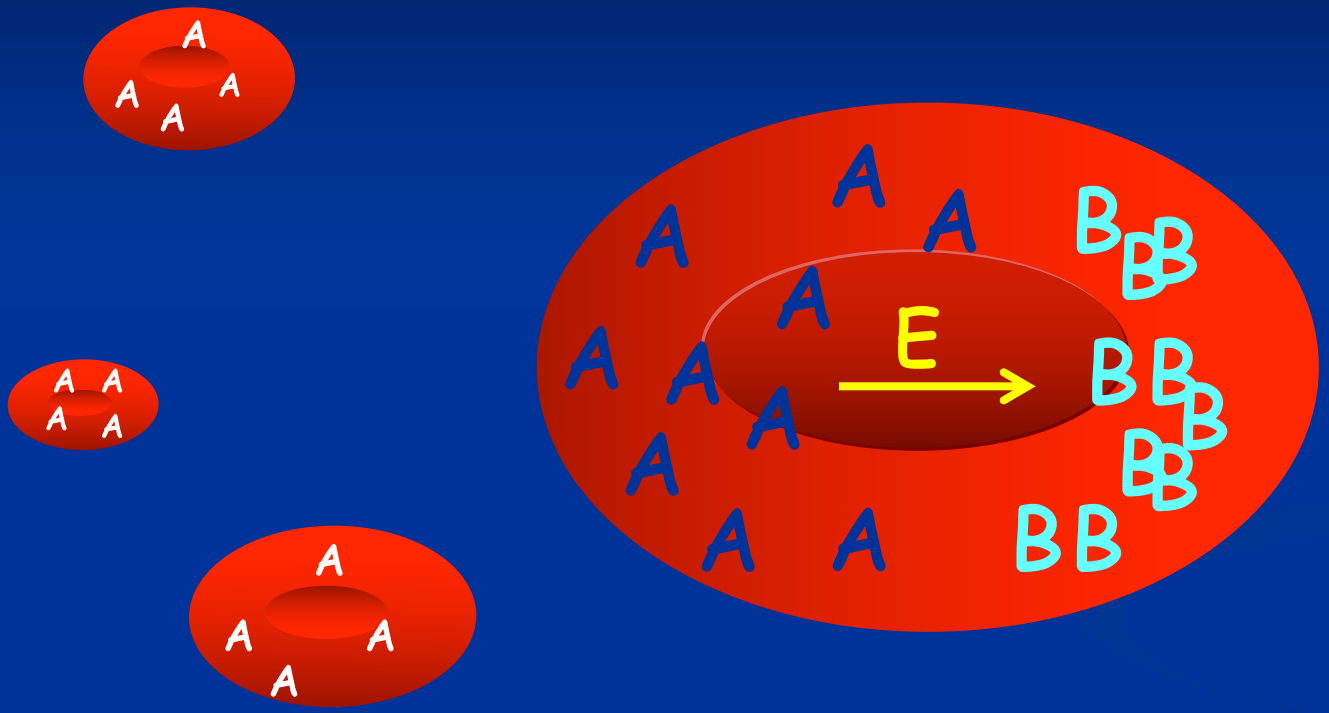
BIOREATTORI CIRCOLANTI PER UN LENTO RILASCIO IN CIRCOLO DI FARMACI

ERITROCITI CARICATI CON PROFARMACI NON DIFFUSIBILI

BIOREATTORI PER IL RILASCIO DI FARMACI DIFFUSIBILI E ATTIVI

Il globulo rosso caricato con il farmaco di interesse agisce come un bioreattore

Vaso sanguigno

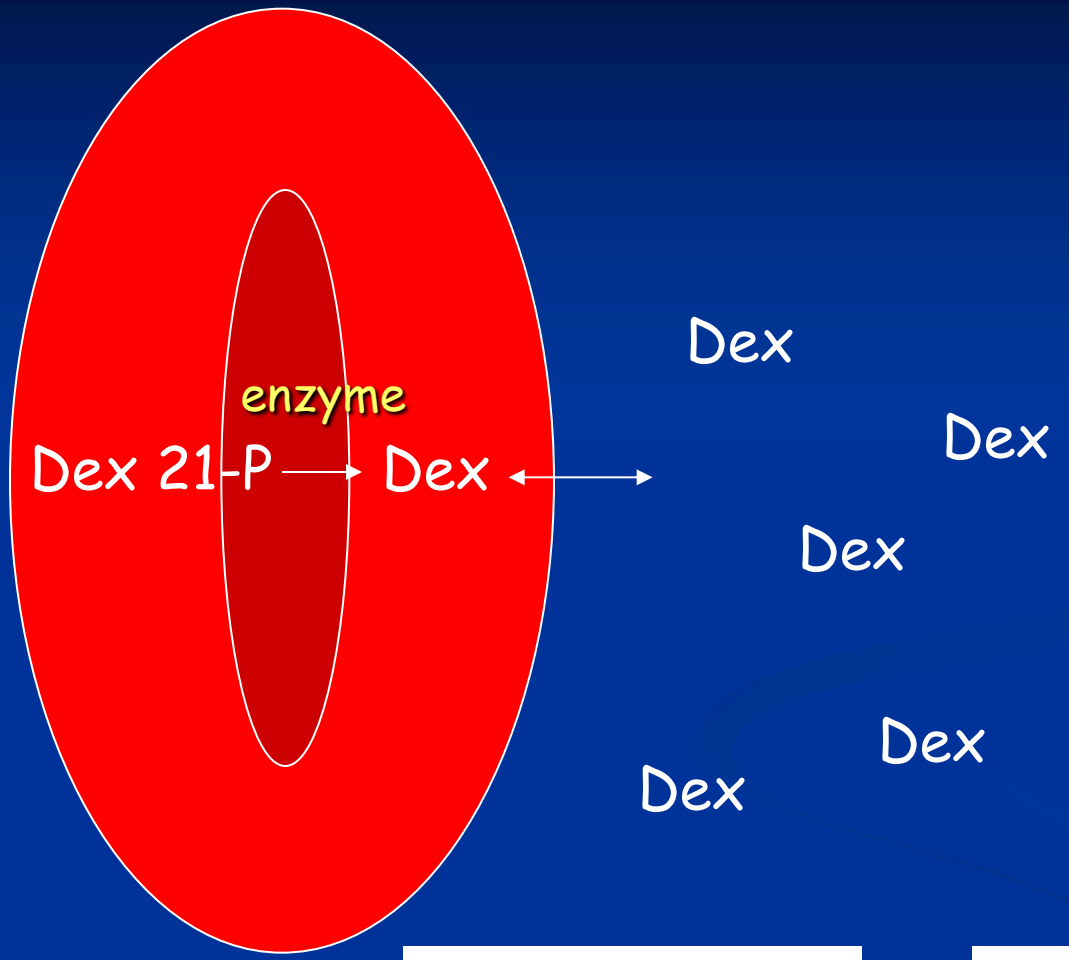


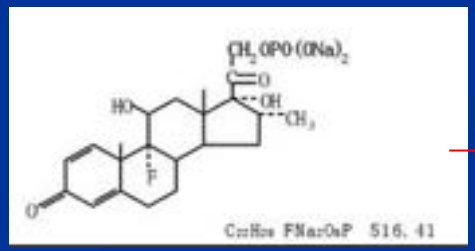
A: profarmaco

B: farmaco attivo

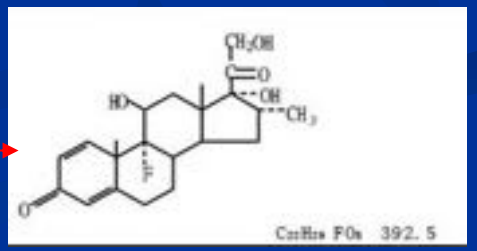
E: enzimi del globulo rosso

ERITROCITA COME BIOREATTORE PER UN LENTO E COSTANTE RILASCIO IN CIRCOLO DELL'ANAOGO GLUCOCORTICOIDE DESAMETASONE (DEXA)





dexamethasone 21-phosphate



dexamethasone

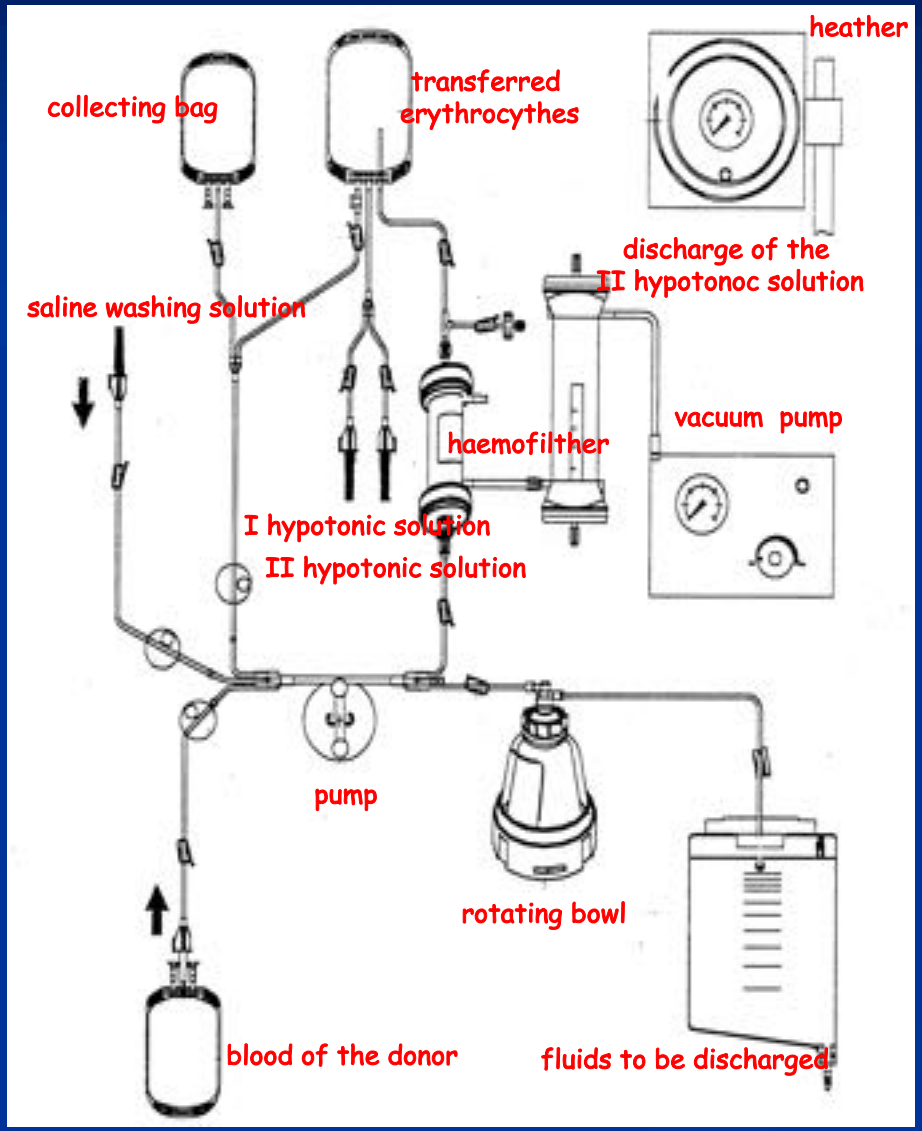
Perchè il Desametasone ?

The highest anti-inflammatory potency together with no mineralcorticoid activity candidate dexamethasone as the elective choice for low dose/long term treatment such as needed in chronic inflammatory status of patients

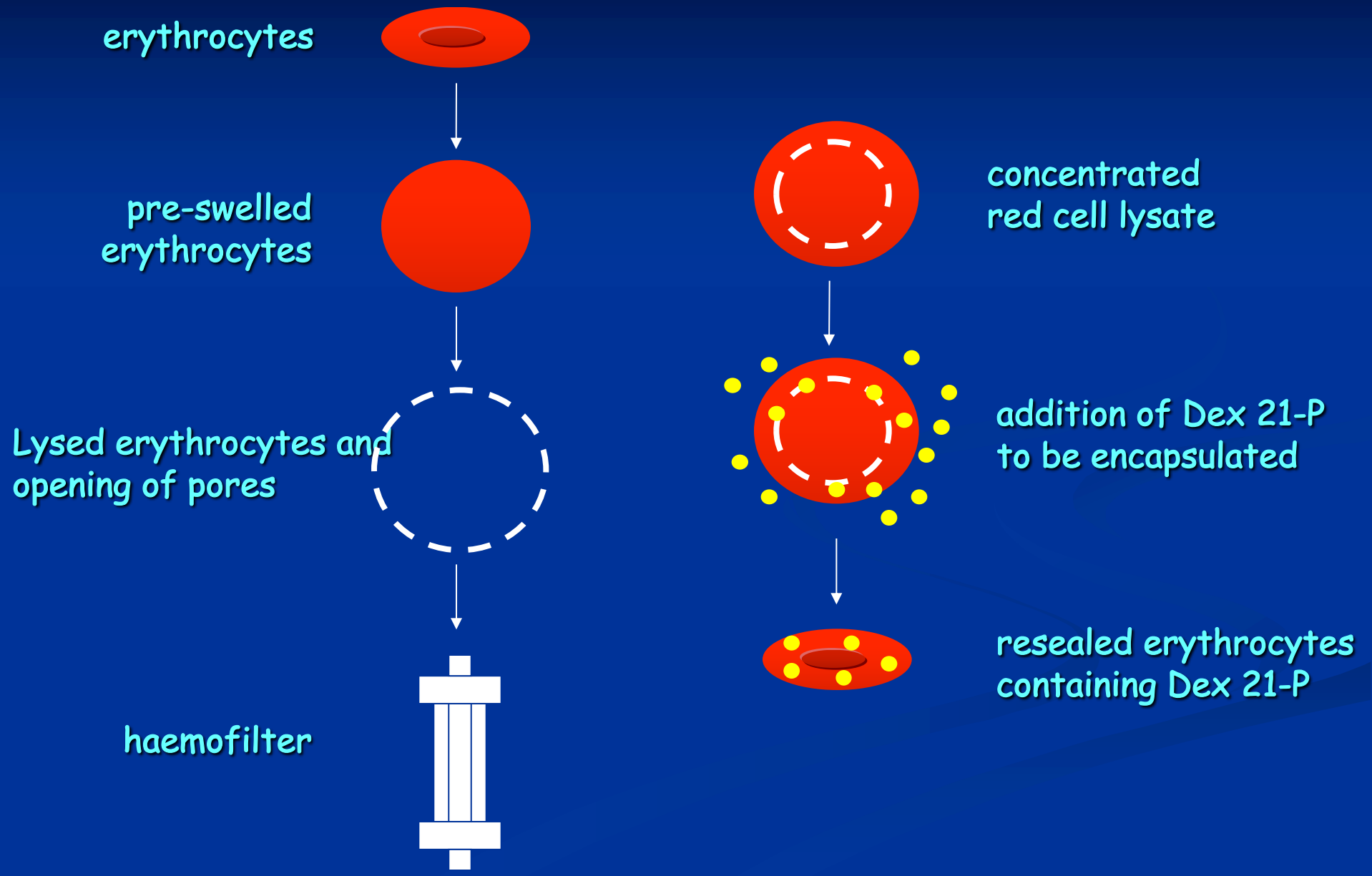
COMPOUND	Anti-inflammatory potency	Na+ retaining potency	Duration of action	Equivalent Dose mg
Cortisol	1	1	Short	20
Cortisone	0,8	0,8	Short	25
Fludrocortisone	10	125	Short	-
Prednisone	4	0,8	Intermediate	5
Prednisolone	4	0,8	Intermediate	5
Methyprednisolone	5	0,5	Intermediate	4
Triamcinolone	5	0	Intermediate	4
Betamethasone	25	0	Long	0,75
Desamethasone	25	0	Long	0,75

Extracted from Goodman Gilman "Pharmacological Basis of Therapeutics"

RED CELL LOADER disposable



Caricamento di desametasone 21-P in eritrociti tramite il Red Cell Loader



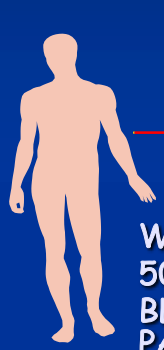
Desametasone 21-P e nuovo modo di somministrazione

- Solution of Dexamethasone sodium phosphate (250mg/10ml)
- Red Cells Loader (Compact Advanced)
- Red Cells disposable kit
- Hypotonic Solutions 1&2
- Hypertonic Solution (PIGPA)

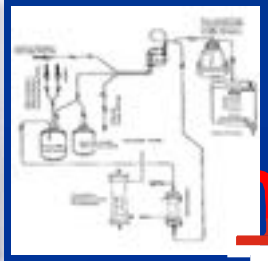
CE Marked Medical Device

COMPACT + KIT COD. 04154 + HYPOTONIC SOLUTIONS & PIGPA

STEP 1

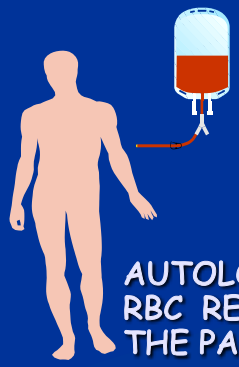


WITHDRAWAL OF 50 ml OF WHOLE BLOOD FROM THE PATIENT



STEP 2

RBC LOADING WITH DEXAMETHASONE 21-P



AUTOLOGOUS LOADED RBC REINFUSION TO THE PATIENT

STEP 3

Sperimentazioni cliniche

BPCO
in collaborazione con:
Ospedale "S. Maria della Misericordia"
Urbino

Morbo di Crohn e Colite ulcerosa
in collaborazione con:
Ospedale "Bambin Gesù" Roma
Ospedale "Casa Sollievo della Sofferenza"
San Giovanni Rotondo

Fibrosi cistica
in collaborazione con:
Ospedale "Bambin Gesù"
Roma

BPCO: VALUTAZIONE CLINICA

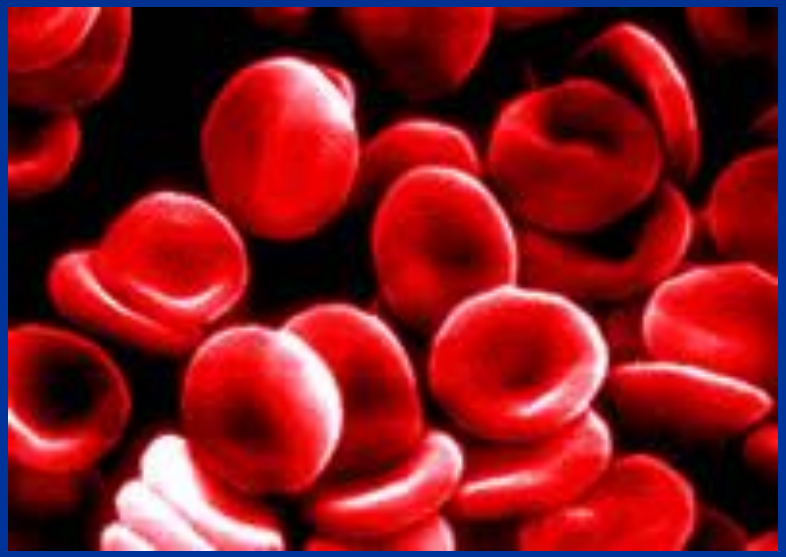
Gruppi	Pazienti	Età	Dexa 21-P (mg)	Giorni senza corticosteroidi	Giorni senza beta$_2$ agonisti
Gruppo A	1	72	0.78	> 11	> 11
	2	45	1.96	4	4
	3	75	3.93	> 10	> 10
	4	71	4.28	12	> 10
	5	75	8.78	> 13	> 13
Gruppo B 2 sommin. a distanza di 2 settiimane	6	72	1 somm. 4.39 2 somm. 6.25	10 > 30	10 > 30
	7	75	1 somm. 3.49 2 somm. 5.32	10 > 30	10 > 30
	8	63	1 somm. 3.48 2 somm. 6.50	> 30	> 30
Gruppo C	9	65	2.00	30	30
	10	83	2.84	> 10	> 10

Farmacocinetica

Rossi L. et al BAB 2001

GLOBULI ROSSI COME DRUG CARRIERS

APPLICAZIONE CLINICA IN PEDIATRIA



UNITÀ OPERATIVA DI GASTROENTEROLOGIA

OSPEDALE PEDIATRICO BAMBINO GESÙ-ROMA

IRCCS

Eritrociti Dex 21-P-loaded e Fibrosi Cistica

- La Fibrosi Cistica si manifesta con infezioni broncopolmonari croniche, maldigestione ed eccessiva risposta infiammatoria.

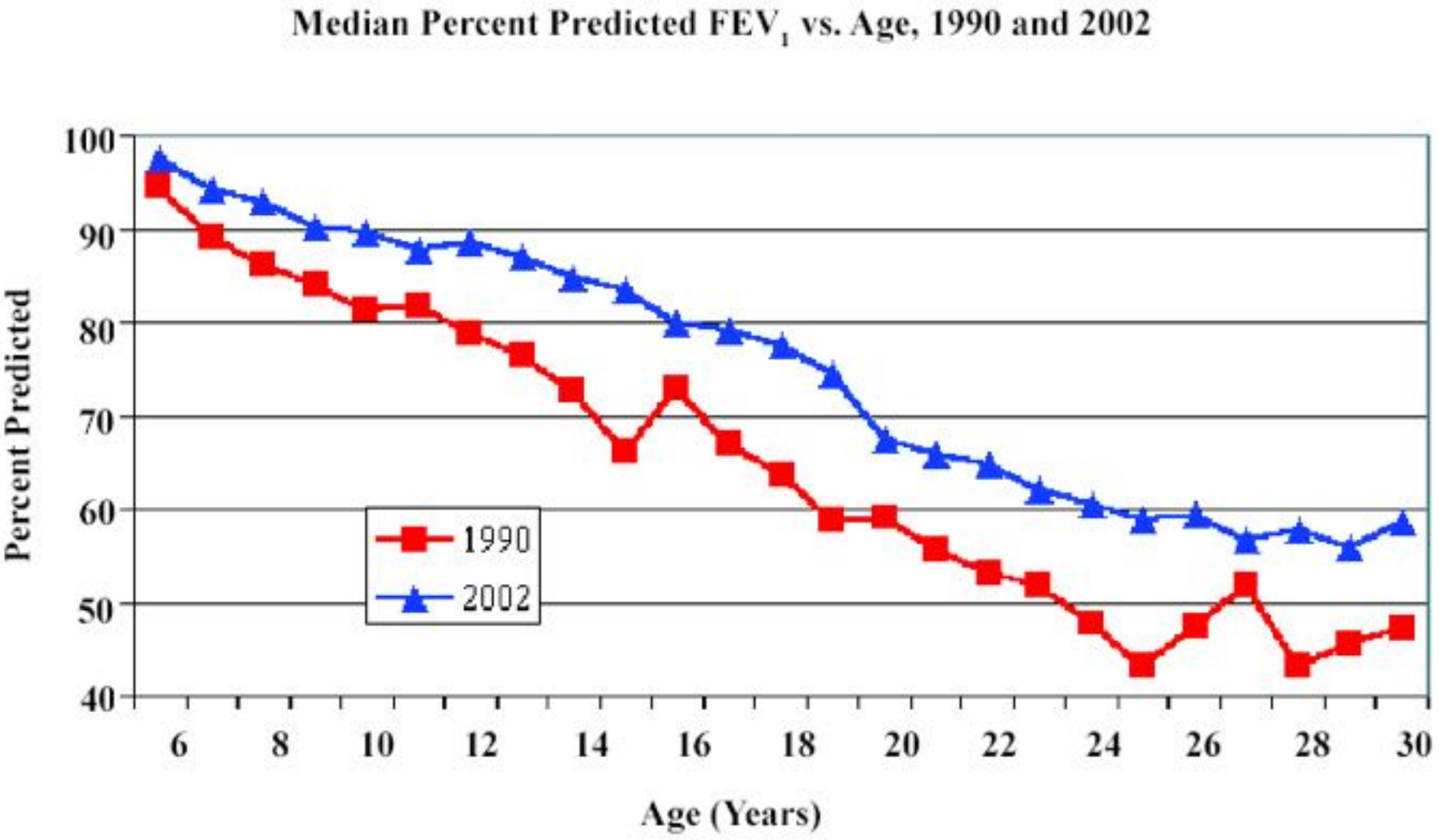
- Una terapia antinfiammatoria prolungata è in grado di rallentare l'evoluzione del danno polmonare.

- I glucocorticoidi agiscono come efficaci farmaci antinfiammatori ma non sono privi di effetti collaterali

Caratteristiche dei pazienti FC

- 17 CF patients homozygous for ΔF508 deletion*
- Age: ranging from 12 to 26 years
- Forced expiratory volume in one second (FEV_1) at least 35% of the predicted value
- Presence of chronic suppurative pulmonary disease
- Colonization by *Pseudomonas aeruginosa*

* Braccio lungo cromosoma 7



Cystic Fibrosis Foundation, Patient Registry 2002 Annual Report, Bethesda, Maryland

FOLLOW UP CLINICO

Parametri valutati

- Sicurezza
- Riproducibilità
- Funzionalità respiratoria (FEV_1)
- Riacutizzazioni infettive da *Pseudomonas aeruginosa*

1st Follow-up Clinico
Safety

- Otto pazienti FC hanno ricevuto una somministrazione di eritrociti caricati con desametasone 21-P a concentrazioni crescenti (1.19 to 14.5 mg)

Group	Patients	Dex 21-P (mg)
A	1*	1.19
B	2*	2.26
	3	2.28
C	4*	5.0
	5	6.07
	6	6.57
	7	6.69
D	8	14.5

I pazienti sono stati suddivisi in 4 gruppi (A, B, C, D) sulla base della quantità di farmaco somministrato

- Parametri valutati: pressione arteriosa, parametri ematochimici, cortisolo urinario → non è stato registrato alcun segno di tossicità

*patients underwent to pharmacokinetic studies

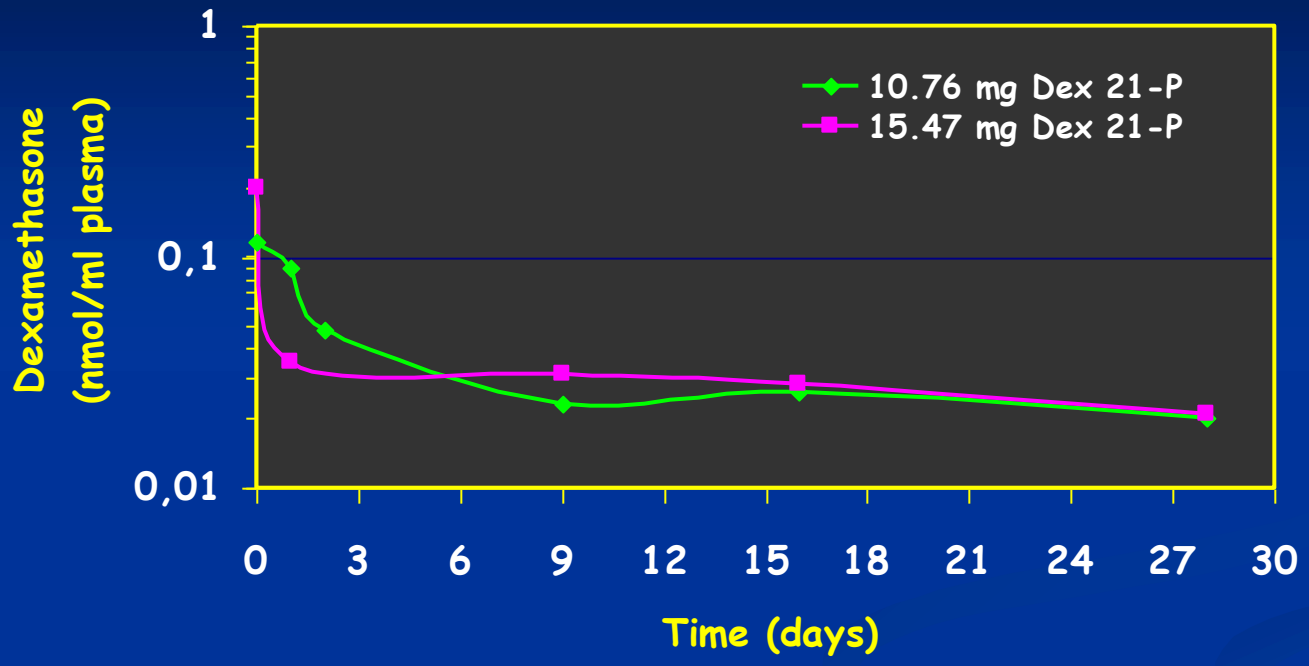
1st Follow-up Clinico
Sicurezza e riproducibilità

- Condizione selezionata: grouppo C (6.07 ± 0.7 mg Dex 21-P)

- Gli otto pazienti ricevettero 2 ulteriori somministrazioni di eritrociti carichi a distanza di tre settimane (16 infusionsi in totale)

- ✓ nessun effetto collaterale registrato → safety confermata
- ✓ 6.09 ± 3.26 mg somministrati → riproducibilità ottenuta

CONCENTRAZIONI PLASMATICHE DI DESAMETASONE



Semilogarithmic plot of plasma concentration of Dexamethasone in patient n. 9 at times 0 (immediately post infusions) and 1, 9, 16 and 28 days post two successive infusions of erythrocytes loaded with 10.76 and 15.47 mg of Dex 21-P, respectively.

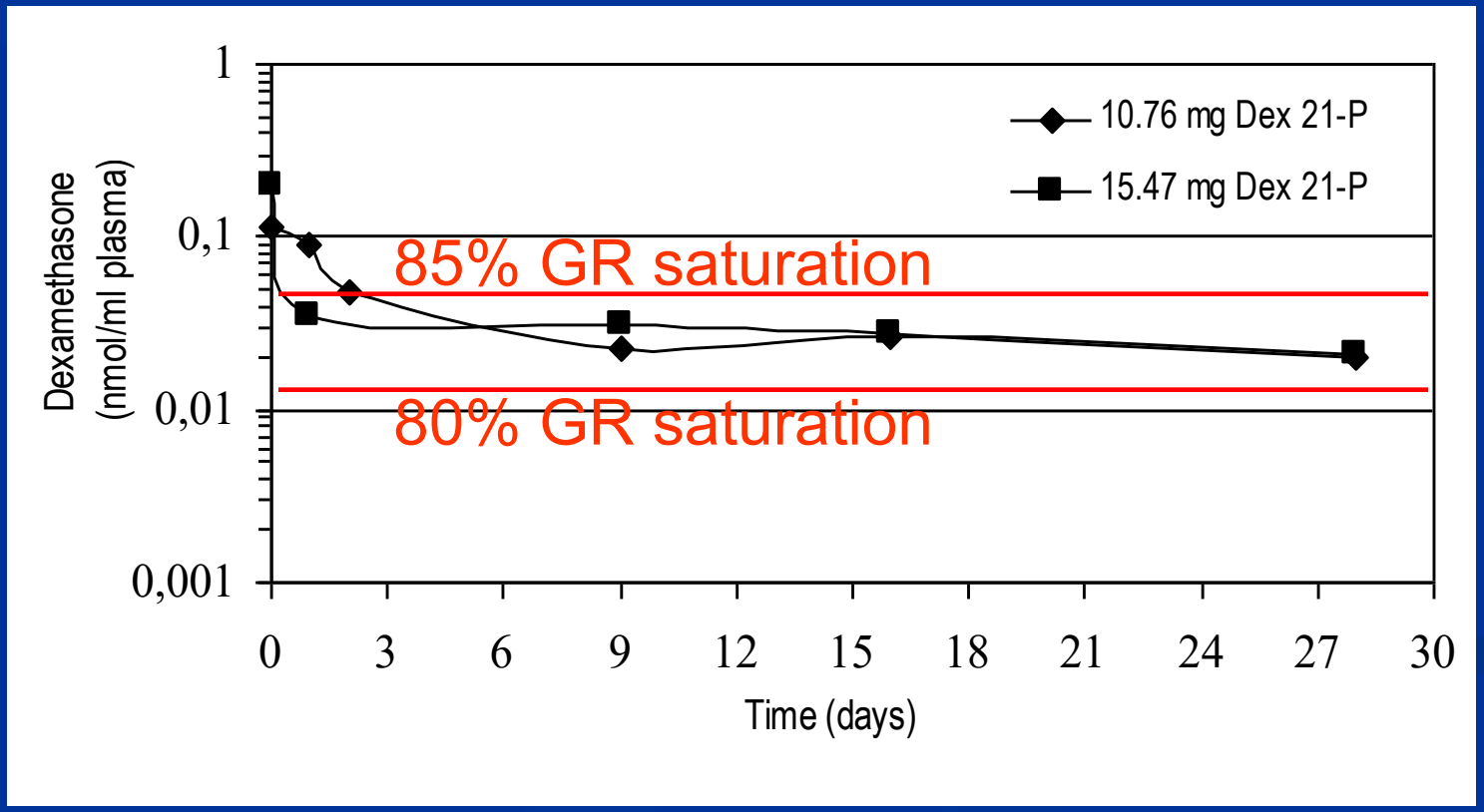
Rossi L. et Blood Cells, Molecules and diseases, 2004 2005

Vantaggi del nuovo metodo di somministrazione

The Glucocorticoid Receptor % saturation at steady state is:

$$\theta = [L]*100 / (Kd + [L])$$

dissociation constant (Kd) of GR (glucocorticoid receptor) for dexamethasone on lymphocytes is 5,5 nM and dexamethasone plasma concentration [L] at steady state is 0,025 nmol/ml.



No soppressione del cortisolo plasmatico

The Lipworth systematic review "*Systemic Adverse Effects of Inhaled Corticosteroid Therapy*" (Lipworth, 1999), shows suppression of 8 AM plasma cortisol level caused by inhaled and oral administration of corticosteroids (fluticasone, budesonide, triamcinolone and prednisolone).

Below 0.3 mg/day in case of inhaled corticosteroids and **below 4 mg/day in case of oral corticosteroids** there is no evident cortisol suppression for any considered corticosteroid.

Considering the average of Dex 21-P loaded in erythrocytes (8.9 mg) as constantly delivered in plasma by red blood cells along 28 days, the theoretical daily dose of intra-erythrocytic dexamethasone is 0.3 mg/day. Hence, the IED administered dose was supposed not to cause cortisol inhibition and therefore highly safe for patients.

This conclusion was confirmed by the normal plasma cortisol level measured in 9 CF patients receiving intra-erythrocytic dexamethasone for 15 months during the preliminary clinical trial (Rossi et al.).

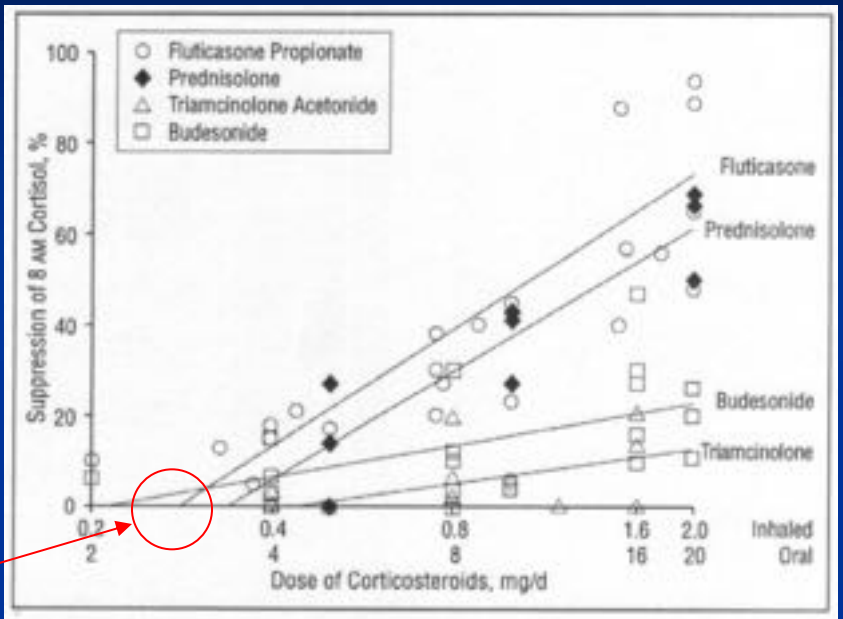


Figure 2. *Meta-analysis of 13 studies that evaluated effects on 8 AM plasma and serum cortisol levels.† For the purposes of clarity, the scale was plotted on a putative dose equivalence of 10:1 mg for oral vs inhaled corticosteroid (shown as doubling doses). Multiple regression analysis showed a significant difference in slope gradients (shown as line of best fit) between fluticasone propionate vs budesonide (P<.001) or triamcinolone acetonide (P<.005). There was also a significant difference in slope between prednisolone vs budesonide (P<.05) or triamcinolone (P<.05). The slope for prednisolone was not significantly different (P = .76) from that of fluticasone.*

Systemic adverse effects are related to both dose and duration of treatment. Doses lower than 4 mg/day of oral corticosteroids cause no suppression of plasma cortisol.

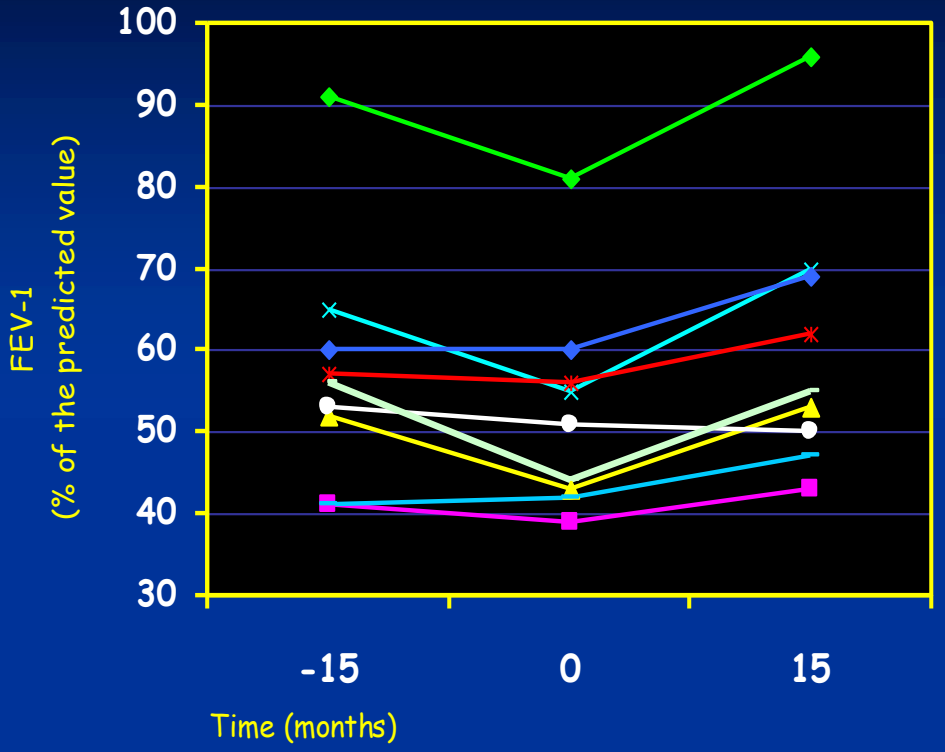
2nd Follow-up Clinico
efficacia

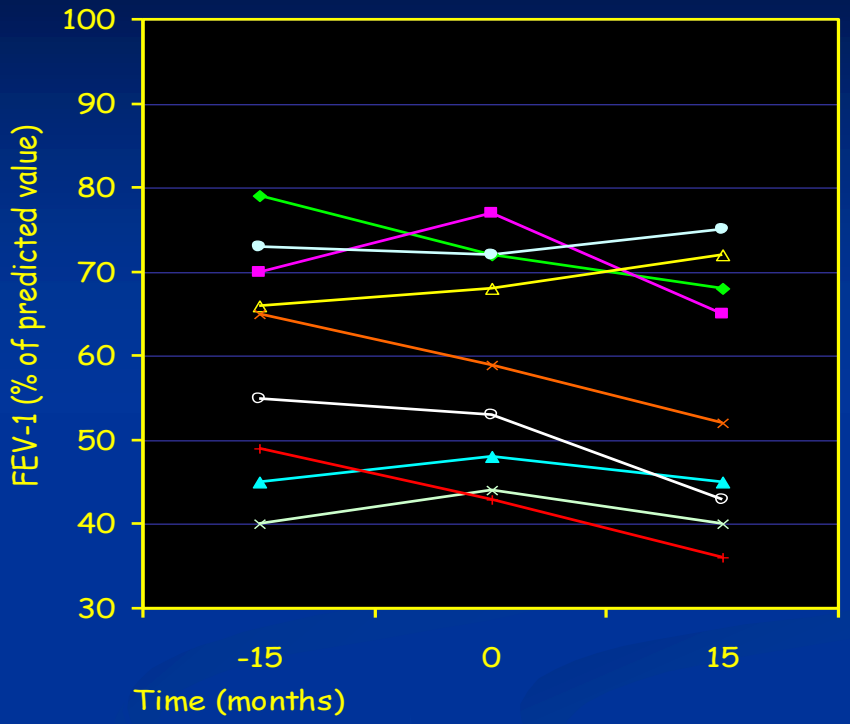
- Nove pazienti hanno ricevuto eritrociti con incapsulati mediamente 8.9 ± 3.8 mg di Dex 21-P ad intervalli mensili per 15 mesi

- Parametri valutati durante il trattamento e nei 15 mesi precedenti :
  - FEV_1
  - infective relapses by *Pseudomonas aeruginosa*
  - body mass index (BMI)

- Parametri valutati durante il trattamento :
  - plasma level of IL-8
  - plasma level of TNF-α

SOMMINISTRAZIONE DI RBC CON INCAPSULATO DEX 21-P E FUNZIONALITA' RESPIRATORIA





TRATTATI

Forced expiratory volume in one second (FEV_1) in nine CF patients that received erythrocytes loaded on the average with 8.9±3.8 mg of Dex 21-P at 1 month interval.

P=0.03; Friedman's test

CONTROLLI

Forced expiratory volume in 1 second (FEV_1) in nine control CF patients submitted to usual therapeutic protocols.

ΔFEV P=0.0002; Mann-Whitney U test between the two groups

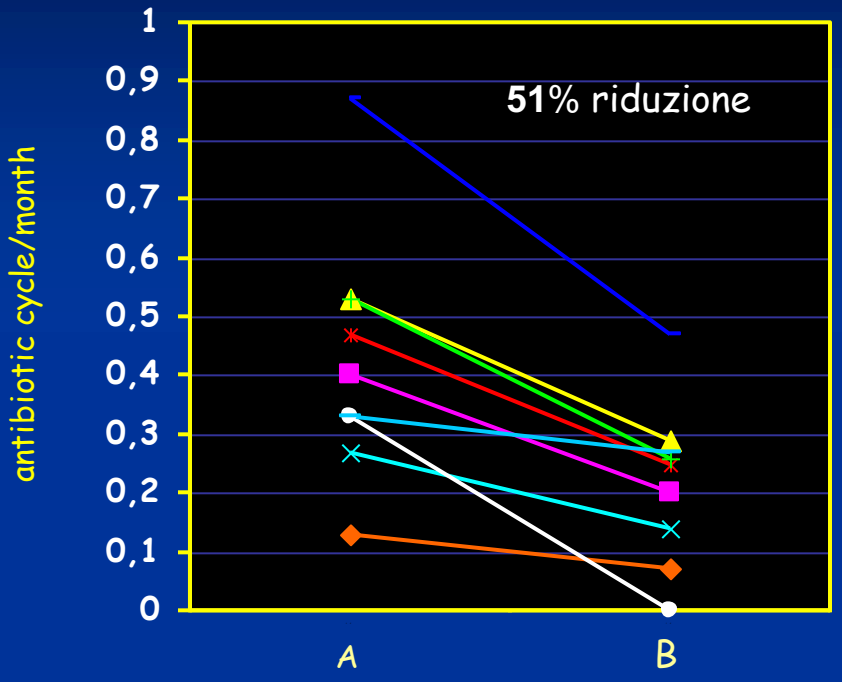
VALORI FEV1 NEI SINGOLI PAZIENTI

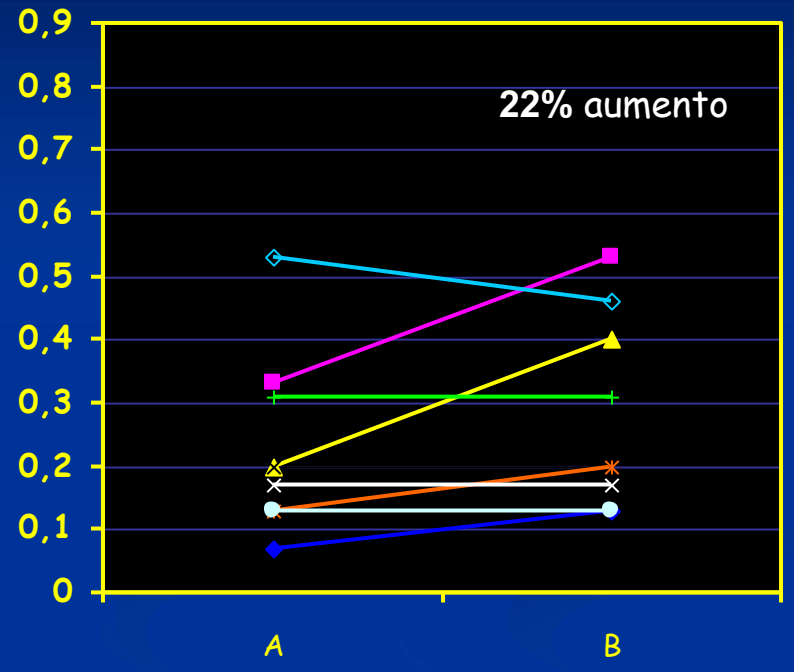
Intra-erythrocytic Dexamethasone Plus Conventional Therapy			
Patients (No.)	FEV_1 (%)		Δ FEV_1 (%)
	T=0	T=15	
1	81	96	+15
2	60	69	+9
3	56	62	+6
4	55	70	+15
5	51	50	-1
6	45	55	+10
7	43	53	+10
8	41	47	+6
9	39	43	+4
Mean			+8.22
Range			+15, -1

Conventional Therapy alone (Control)			
Patients (No.)	FEV_1 (%)		Δ FEV_1 (%)
	T=0	T=15	
1	77	65	-12
2	73	75	+2
3	73	68	-5
4	68	72	+4
5	59	55	-4
6	53	44	-9
7	48	45	-3
8	44	40	-4
9	43	36	-7
Mean			-4.22
Range			+4, -12

SOMMINISTRAZIONE DI RBC CON INCAPSULATO DEX 21-P E CICLI DI ANTIBIOTICO-TERAPIA

Infective relapses by *Pseudomonas aeruginosa* were monitored by registering the frequency of antibiotic therapy cycles



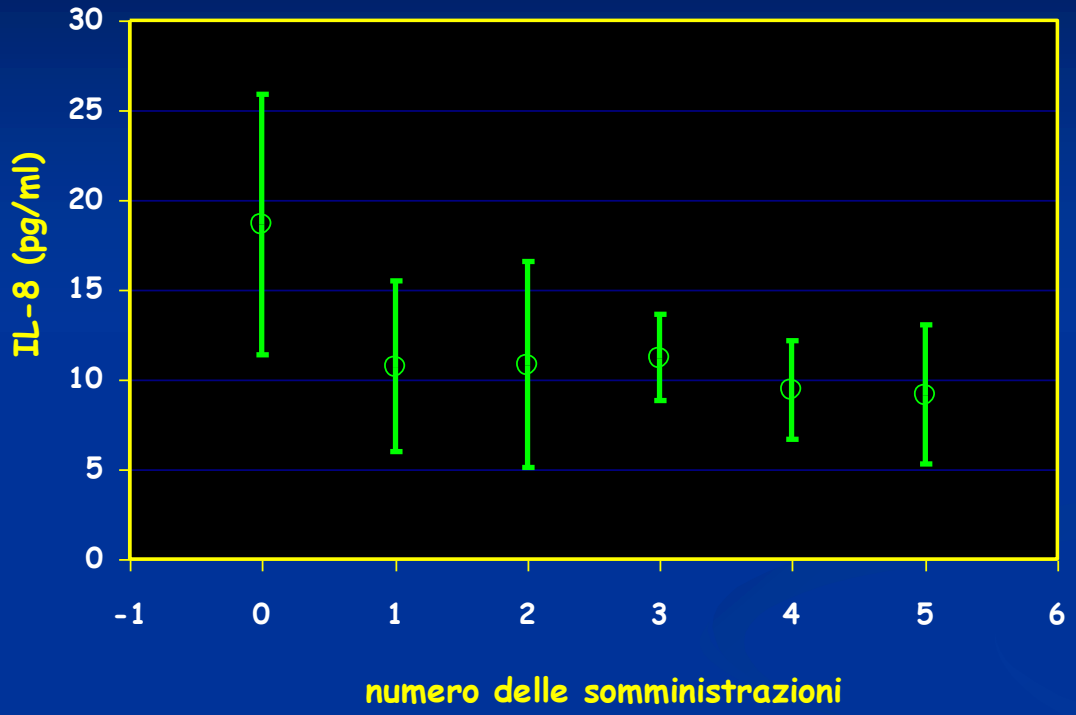


TRATTATI
Antibiotic cycles per month in nine CF patients in 15 months precending Dex 21-P loaded RBC adiministrations (A) and in 15 months following Dex 21-P-loaded RBC administrations (B)

CONTROLLI
Antibiotic cycles per month in nine control CF patients in a 30 months period.
A first 15 months; B second 15 months

P=0.0002; Mann-Whitney U test between the two groups

LIVELLO PLASMATICO DI IL-8



Mean IL-8 values in plasma samples of three CF patients (n. 10, 12 and 13) during a five months period of treatment with Dex 21-P-loaded erythrocytes at one month interval. IL-8 was evaluated immediately before starting therapy (time 0) and about one week post each infusion. Normal Values = 0-8.1 pg/ml

CONCLUSIONI

- Tramite il red Cell Loader è possibile incapsulare il profarmaco desametasone 21-P nei globuli rossi autologhi di pazienti FC

- La procedura di incapsulamento è riproducibile ed il trattamento è privo di effetti collaterali

- Gli eritrociti con il profarmaco incapsulato una volta reinfusi nei pazienti rilasciano il desametasone lentamente in circolo per almeno 28 giorni

- Le basse concentrazioni di Desametasone somministrate tramite gli eritrociti sono state in grado di rallentare la progressione della patologia (almeno 10 volte inferiori a quelle somministrate in 2 settimane di terapia classica)


European Medicines Agency (EMEA) granting of orphan medicinal product designation (EMEA/OD/39/04)

Patologie infiammatorie intestinali (IBD)
e
RBC ingegnerizzati

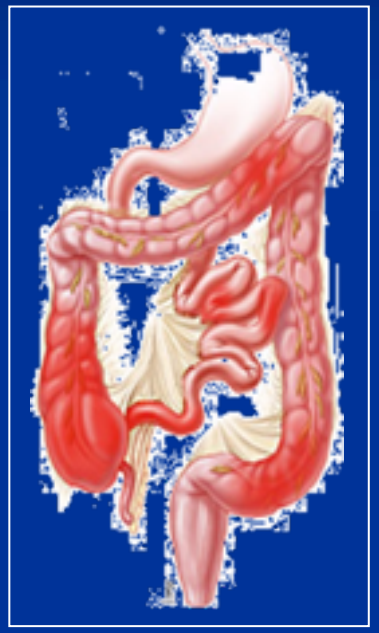
in collaborazione con

Ospedale "Casa Sollievo della Sofferenza" San Giovanni Rotondo

Ospedale "Bambino Gesù" Roma

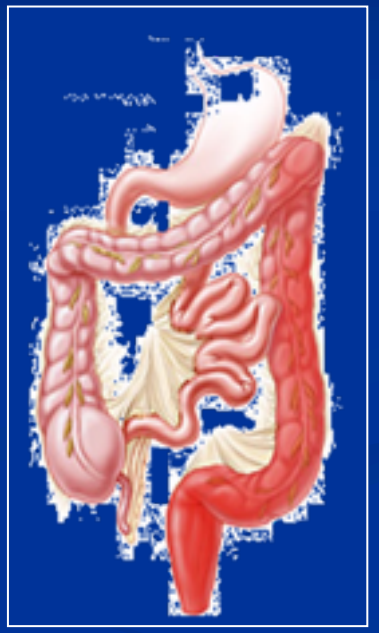
PATOLOGIE INFIAMMATORIE INTESTINALI (IBD)

MORBO DI CROHN



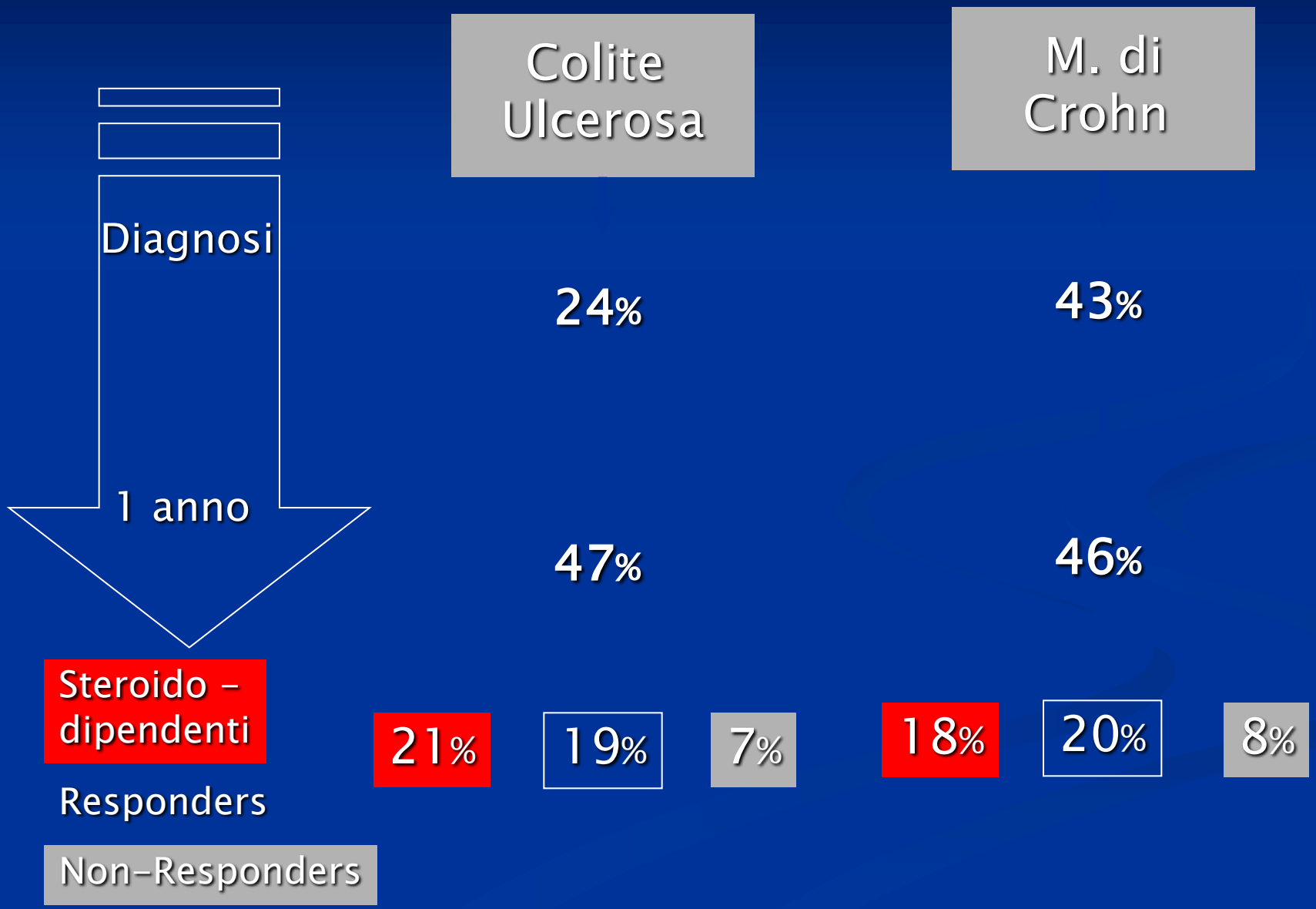
- INFIAMMAZIONE CRONICA DI TUTTI GLI STRATI DELLA PARETE INTESTINALE
- FORMAZIONE DI FISTOLE E ASCESSI

COLITE ULCEROSA



- INFIAMMAZIONE DELLA MUCOSA
- SVILUPPO DI ULCERE MULTIPLE

Storia naturale e terapia steroidea



Globuli rossi con desametasone incapsulato in pazienti con m. di Crohn (CD) e Colite Ulcerosa (UC)

SCOPI

- Verificare efficacia in queste malattie nell'induzione della remissione e mantenimento della remissione
- Ridurre il fabbisogno steroidi sistemici
- Evitare effetti indesiderati da steroidi

Il trattamento nell'adulto del m. di Crohn e Colite Ulcerosa con Desametazone incapsulato in globuli rossi

Unità Operativa di Gastroenterologia
Ospedale IRCCS "Casa Sollievo della Sofferenza"
San Giovanni Rotondo

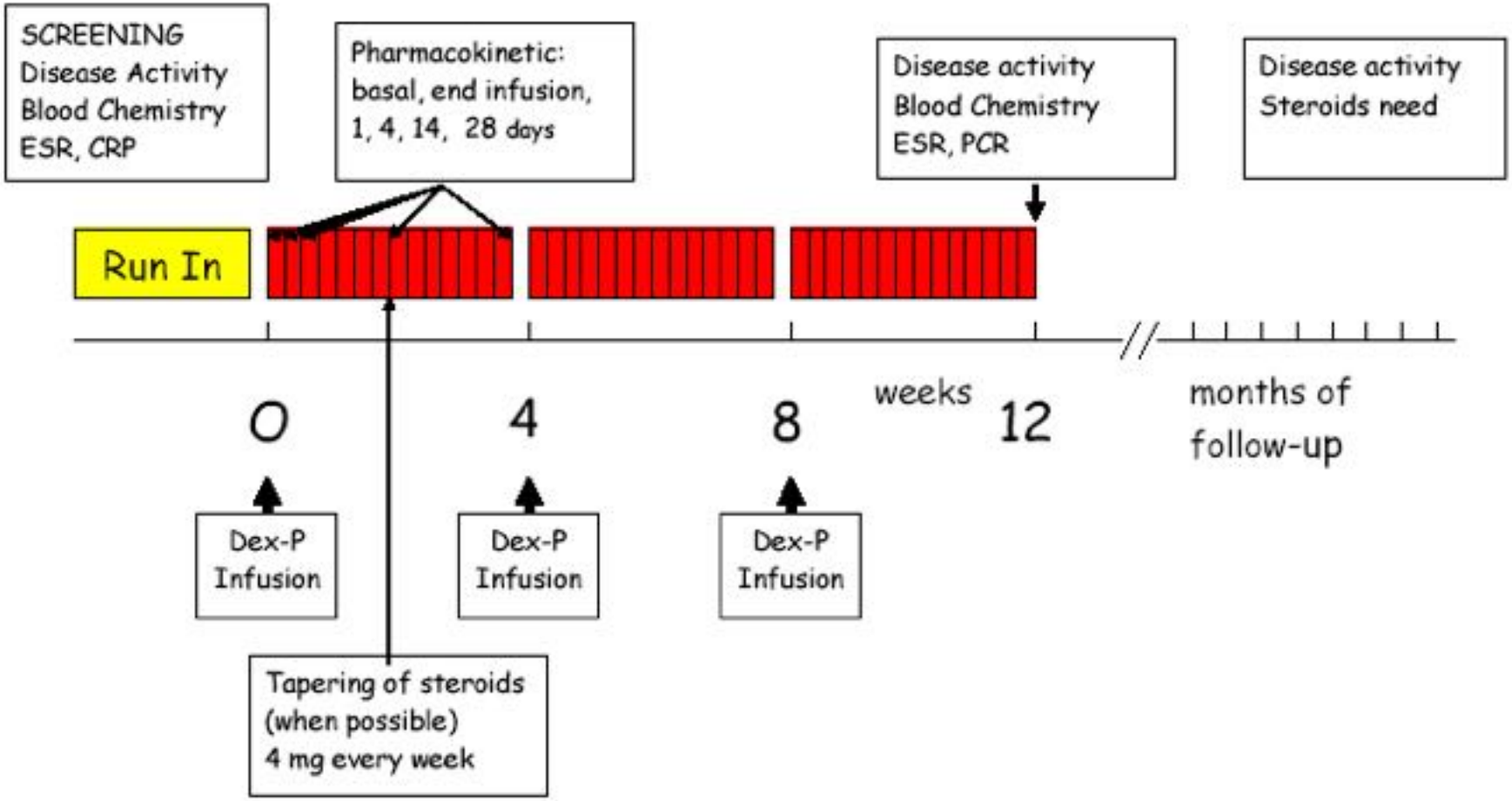
Caratteristiche cliniche dei pazienti inseriti nello studio pilota

Cases	Age, sex (yrs)	Disease	Site	Clinical activity	Endo. activity	Duration of the disease (months)	Duration of steroids therapy (months)	Dosage of Prednisolone (mg)	Azat/ 6-MP* (mg/Kg)
1	36, m	UC	Left Colon	Remis	Mild	48	14	20	1.25*
2	40, m	UC	Pan-colitis	Remis	Mild	108	43	16	2
3	62, m	UC	Left colitis	Mild	Remis	20	14	20	Intol.
4	28, m	UC	Left colitis	Remis	Mild	41	12	24	2.5
5	28, f	UC	Pan-Colits	Remis	Mild	142	13	16	2
6	29, m	CD	Colon	Remis	Mild	60	12	8	2.5
7	30, f	CD	Colon	Mild	Mild	16	9	20	1.25*
8	30, m	CD	Colon	Remis	Mild	60	60	8	2.5
9	33, m	CD	Colon	Mild	Mild	72	30	16	2
10	44, m	CD	Colon	Remis	Mild	96	8	8	Intol.

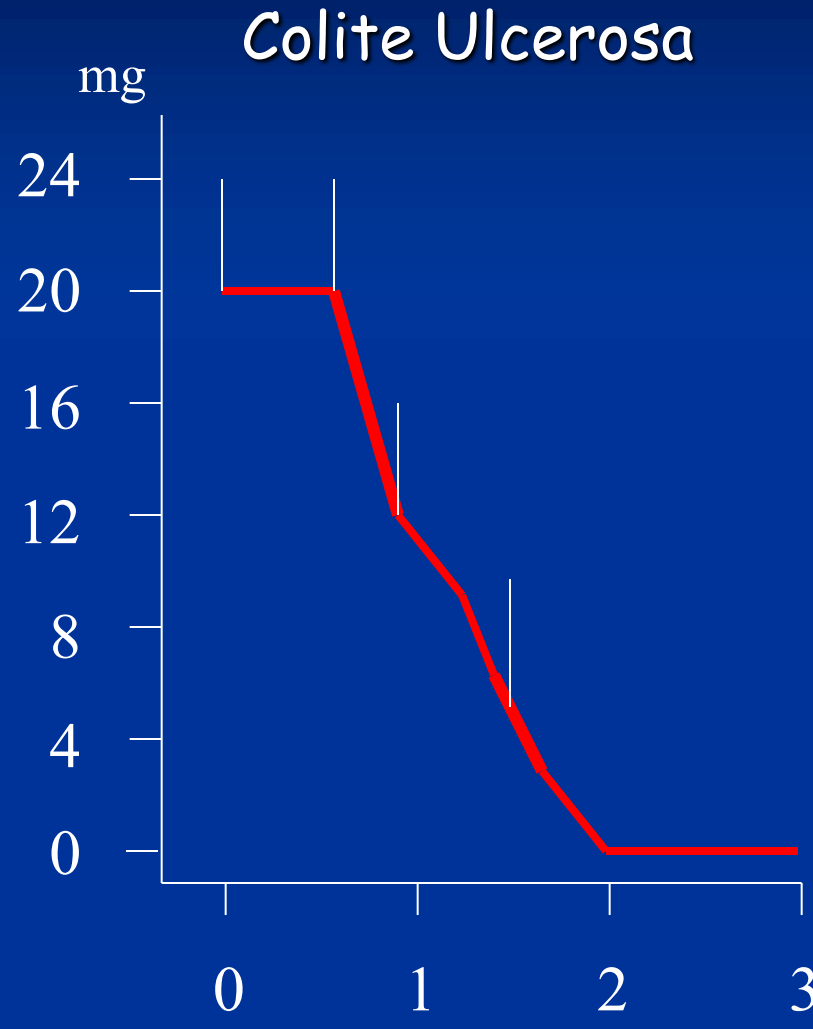
* patients under 6-Mercaptopurine

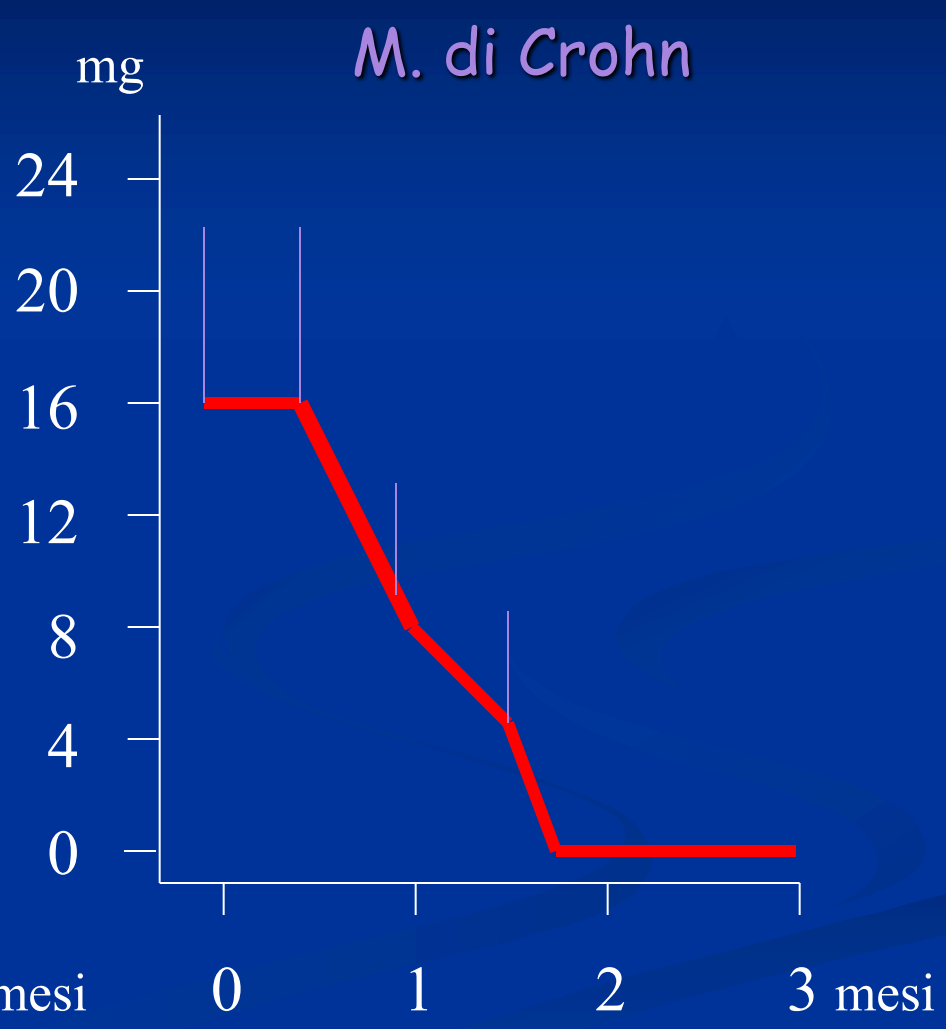
✓ Azathioprine (AZA) or 6-Mercaptopurine (6-MP) are widely used as steroid-sparing, however, in one third of patients they are ineffective or not tolerated

Protocollo clinico



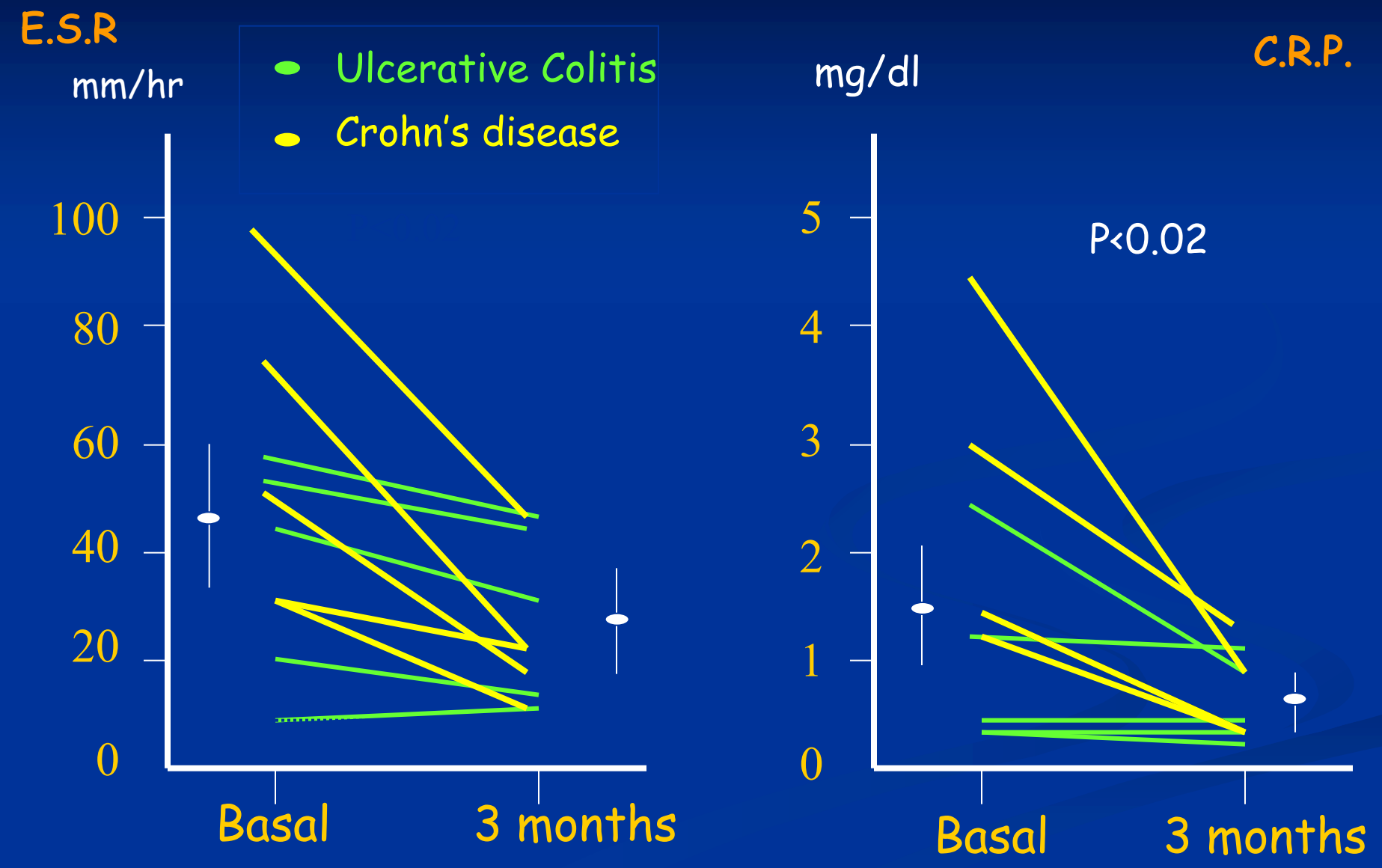
Riduzione fabbisogno steroidi





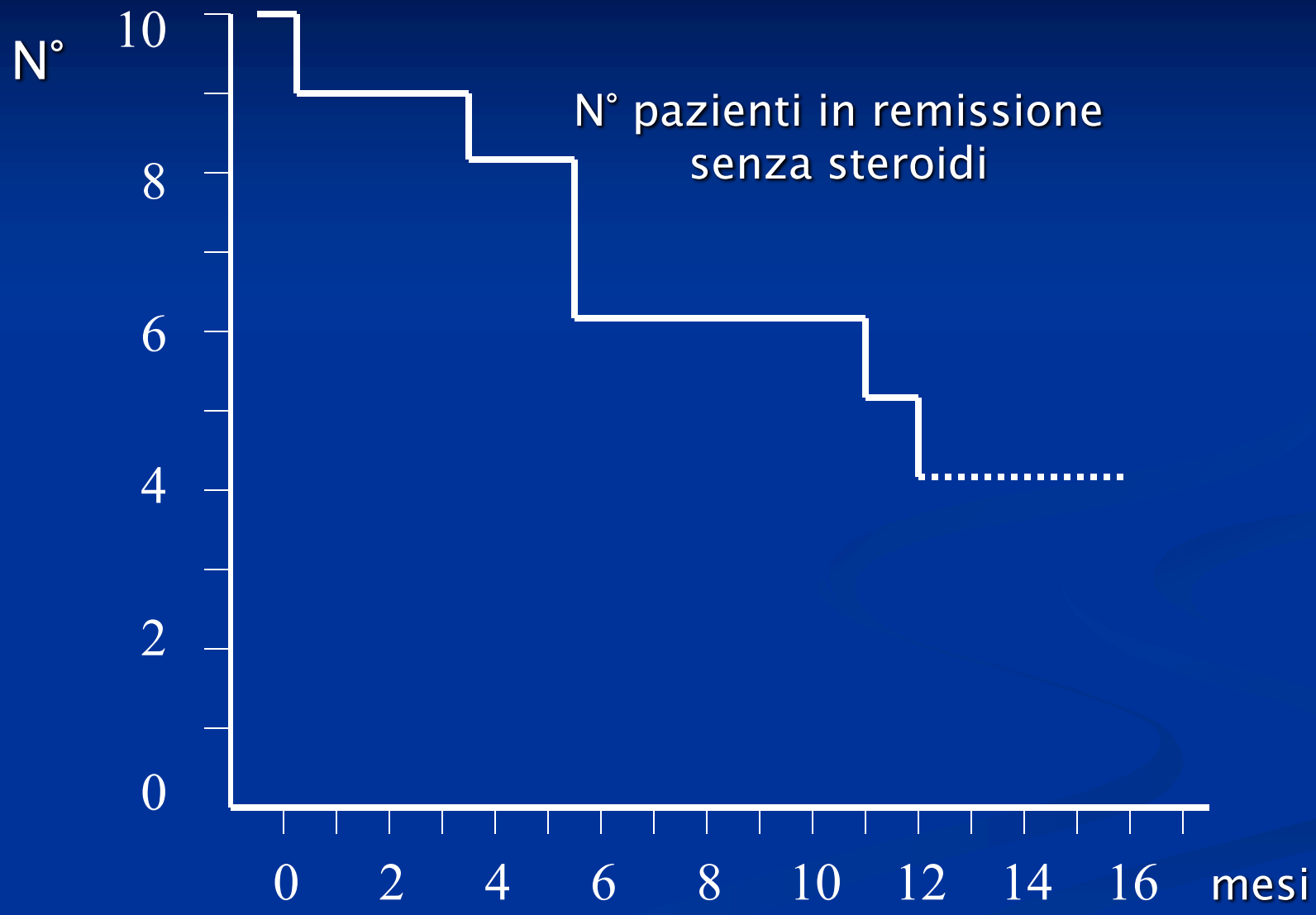
Annese V. et al Am J Gastro 2005

Velocità di eritrosedimentazione (ESR) e livelli plasmatici della proteina C reattiva (CRP)



Dotted lines represent upper limit of normal values (12 mmHr for ESR and 0.5 mg/dl for CRP).

Follow-up dopo 3 infusioni di Dex



RBC CARICATI E MORBO DI CROHN

- 12 PAZIENTI (5-18 anni) CORTICODIPENDENTI
- PERIODO DI OSSERVAZIONE:24 MESI

PARAMETRI VALUTATI

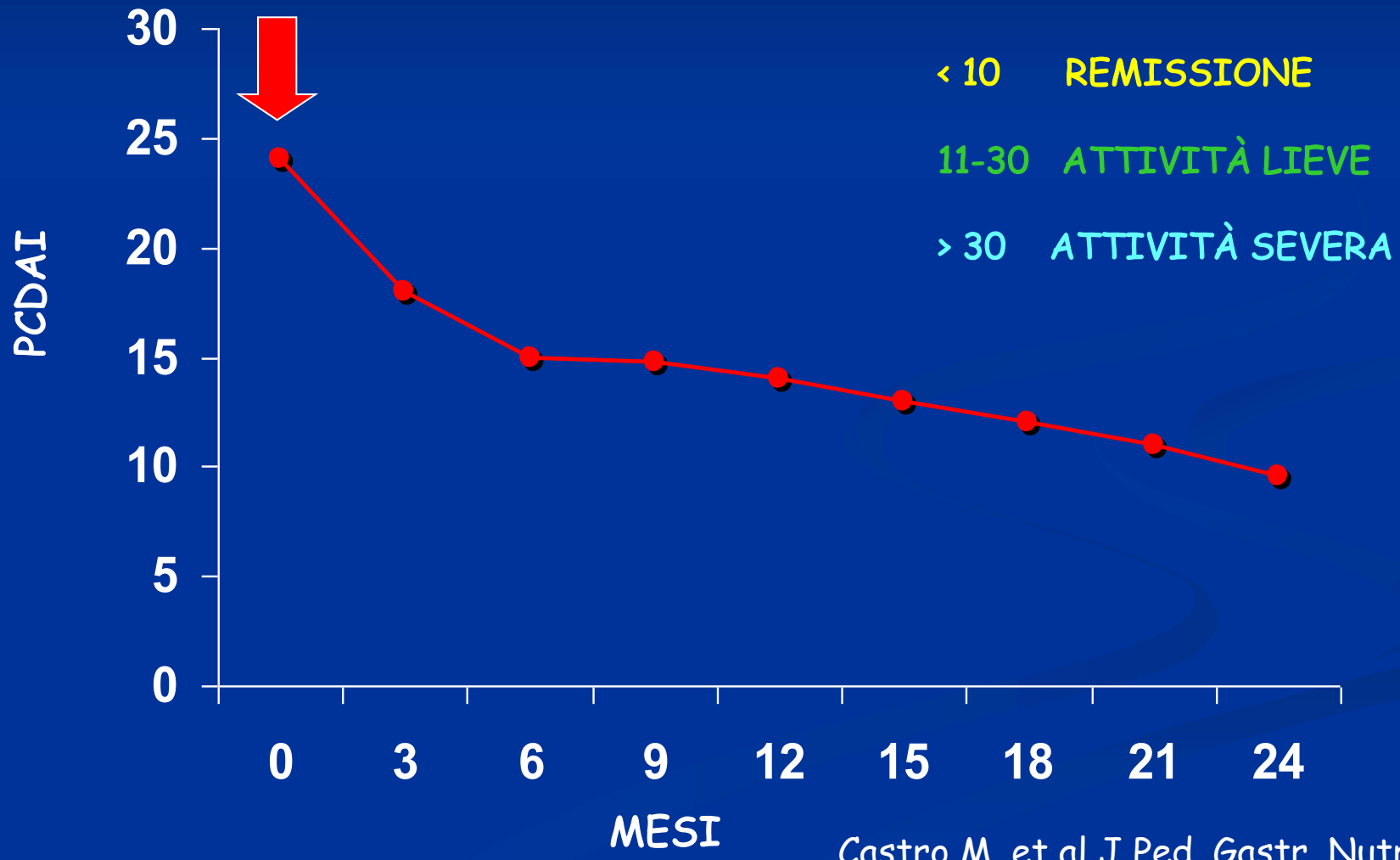
- Assunzione di cortisone per bocca
- Pediatric Crohn's Disease Activity Index (pCDAI)
- Indice di Massa Corporea (IMC)
- Giorni di permanenza in ospedale
- Mineralometria Ossea Computerizzata (MOC)
- Altri effetti collaterali dei glucocorticoidi (facies lunare, *striae rubrae*, ipertensione….)

RBC CARICATI E MORBO DI CROHN
EFFICACIA

VARIABILI	Media prima del trattamento	Media a 24 mesi	Significatività statistica
pCDAI	23.8	9.6	p<0.05
Steroidi/die	11.10 mg	2.9 mg	p<0.05
IMC	20.5	20.4	n.s.
Giorni osp./anno	30.15	13.9	p<0.02

MOC: 33% di miglioramento in 6 pazienti e nessuna variazione negli altri

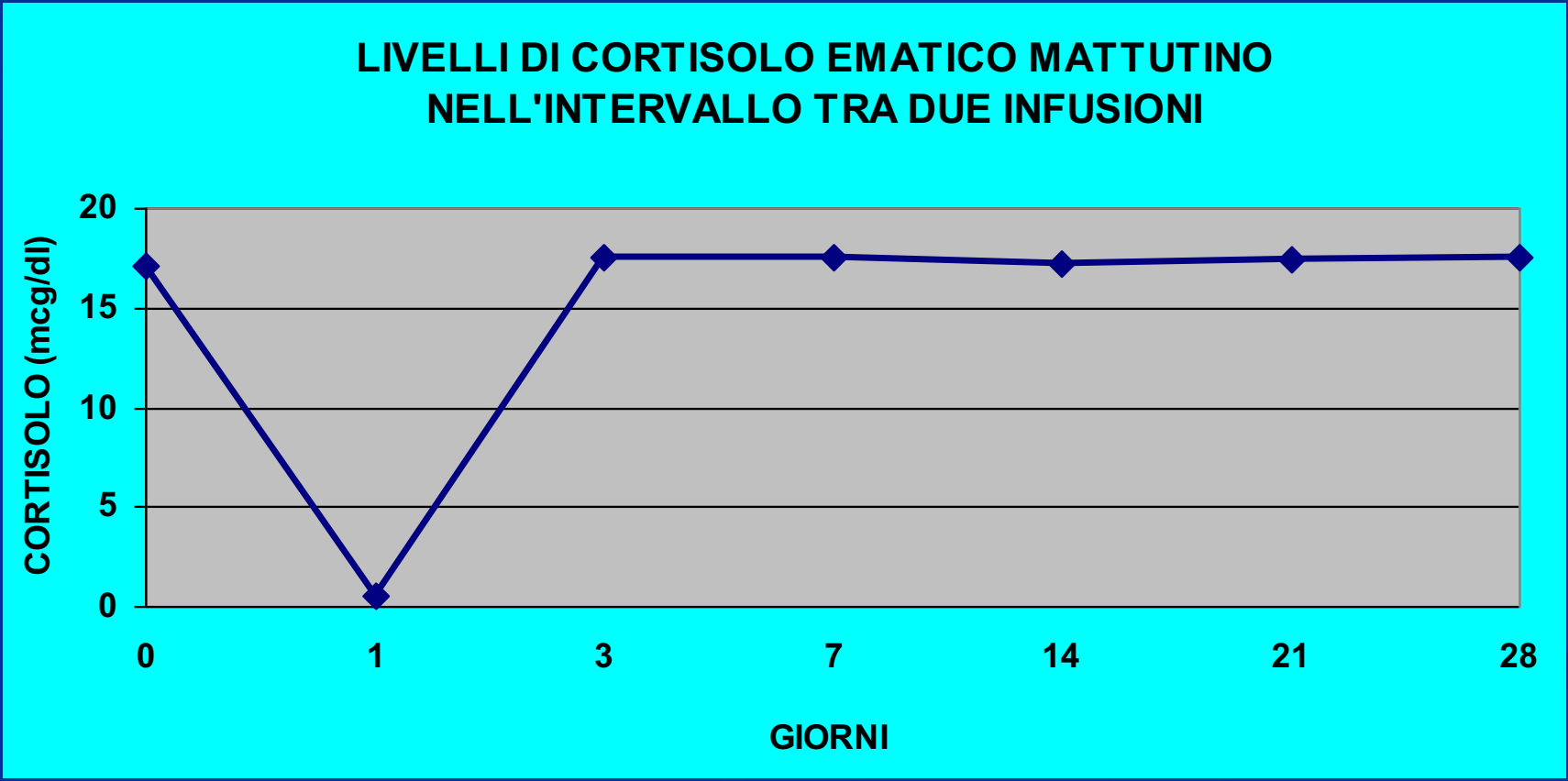
ANDAMENTO ATTIVITA' DI MALATTIA NEL M. DI CROHN



Castro M. et al J Ped. Gastr. Nutr. 2007

GR CARICATI E MORBO DI CROHN
SICUREZZA

LIVELLI DI CORTISOLO EMATICO



GR CARICATI E RETTOCOLITE ULCEROSA

TUTTI CORTICODIPENDENTI

INDICE CLINICO UTILIZZATO: CAI (Colitis Activity Index)

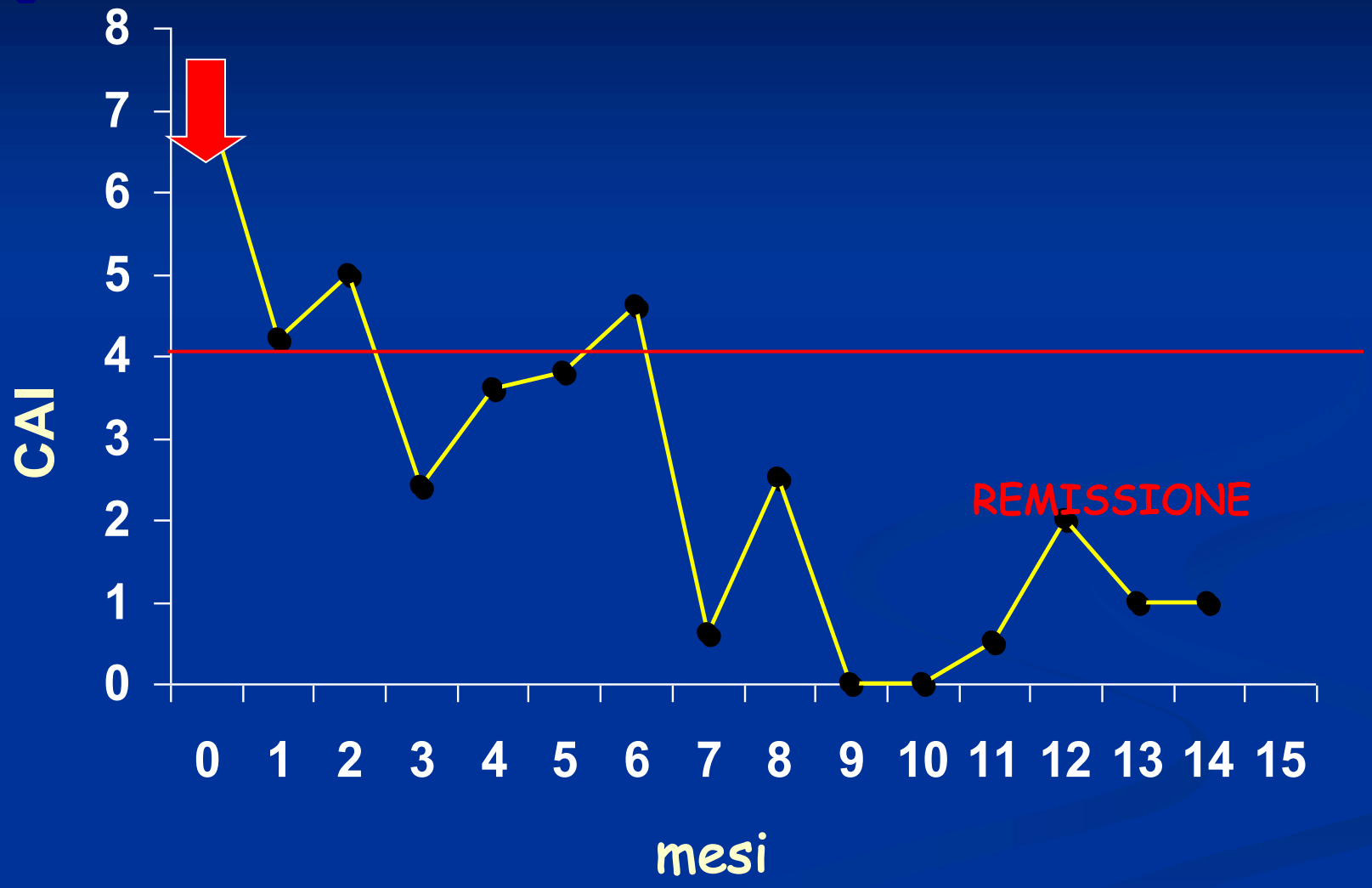
(Rachmilewitz et al, BMJ 1989; 298: 82-86)

TOTALE PAZIENTI TRATTATI: 8

PAZIENTI ATTUALMENTE IN TRATTAMENTO: 7

NUMERO INFUSIONI TOTALI: 67

ANDAMENTO ATTIVITA' DI MALATTIA NELLA UC



- .....NESSUN PAZIENTE HA ASSUNTO CORTISONE PER BOCCA

TOTALE INFUSIONI

"Bambino Gesù" Pediatric Hospital (Rome)

Numero di infusioni di eritrociti con incapsulato il desametasone 21-P in pazienti FC e IBD fino a tutto il 2006

1423

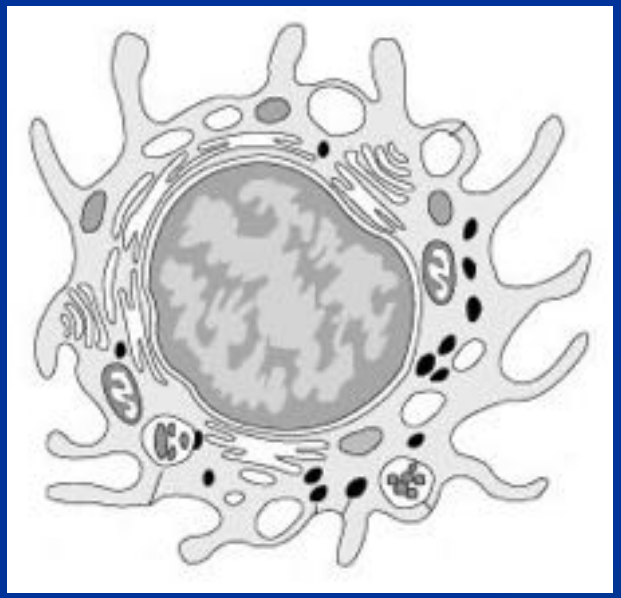
"Casa Sollievo della Sofferenza" Hospital (S. Giovanni Rotondo)

Numero di infusioni di eritrociti con incapsulato il desametasone 21-P in pazienti IBD fino a tutto il 2006

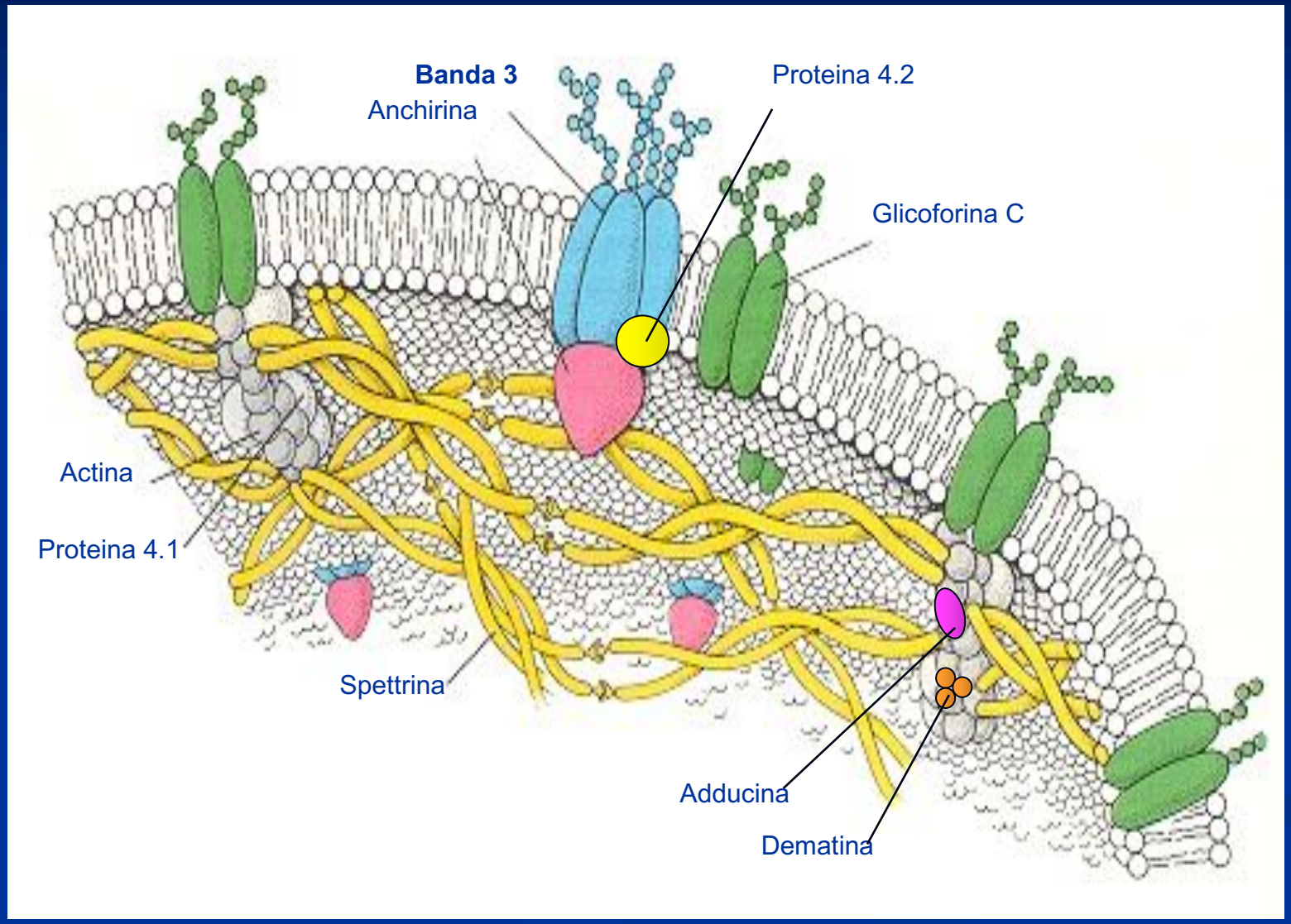
234

TOTALE 1657

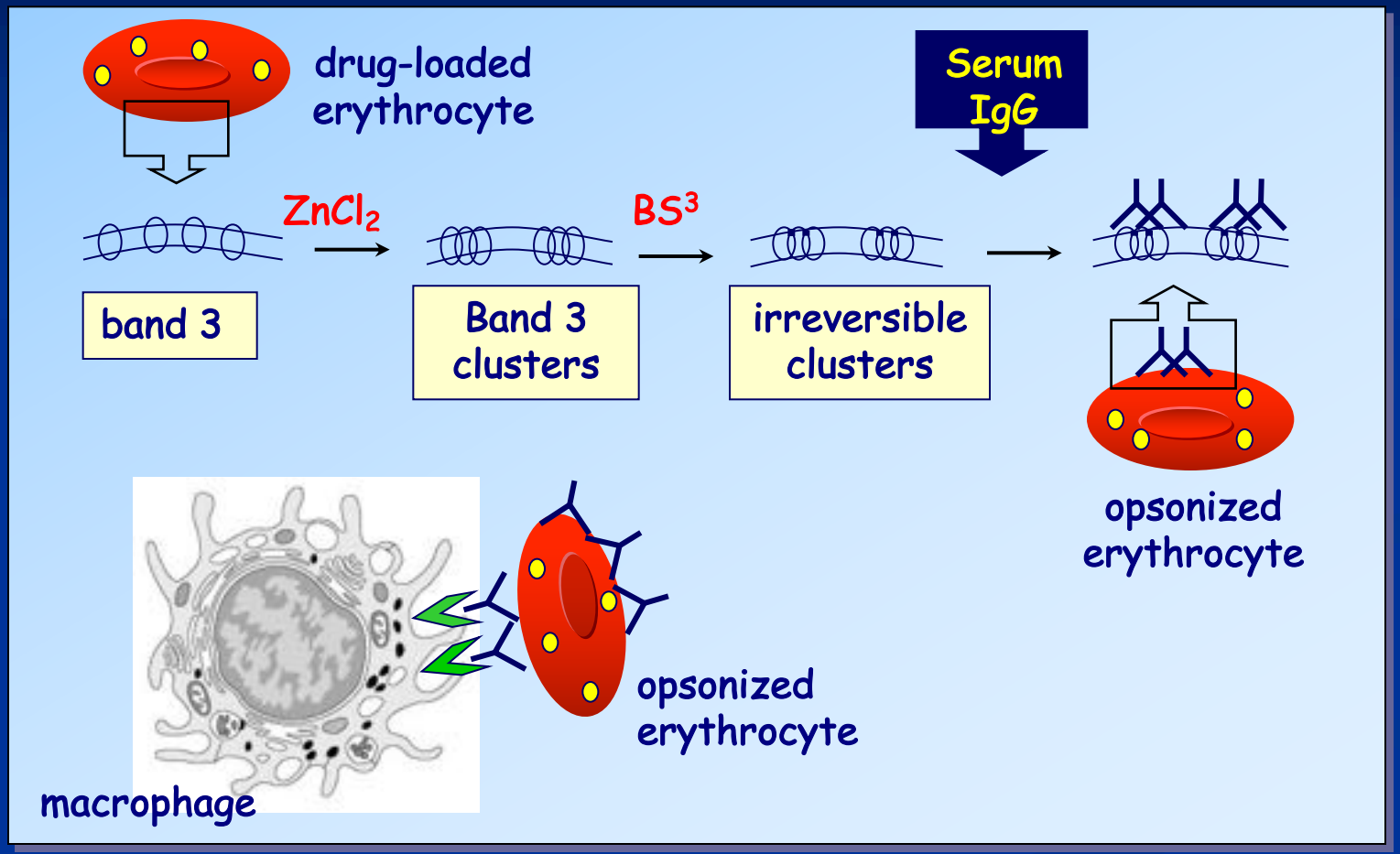
RBC e Targeting



RBC e Banda 3


Banda 3
Anchirina
Proteina 4.2
Glicoforina C
Actina
Proteina 4.1
Spettrina
Adducina
Dematina

Targeting selettivo di farmaci a cellule macrofagiche



Alcuni patogeni con tropismo macrofagico

Listeria Monocytogenes	Batterio
Brucella spp.	"
Salmonella spp.	"
Mycobacteria spp.	"
Herpes simplex	Virus
Varicella zoster	"
Cytomegalovirus	"
HIV-1	"
Candida spp.	Fungo
Toxoplasma gondii	Protozoo

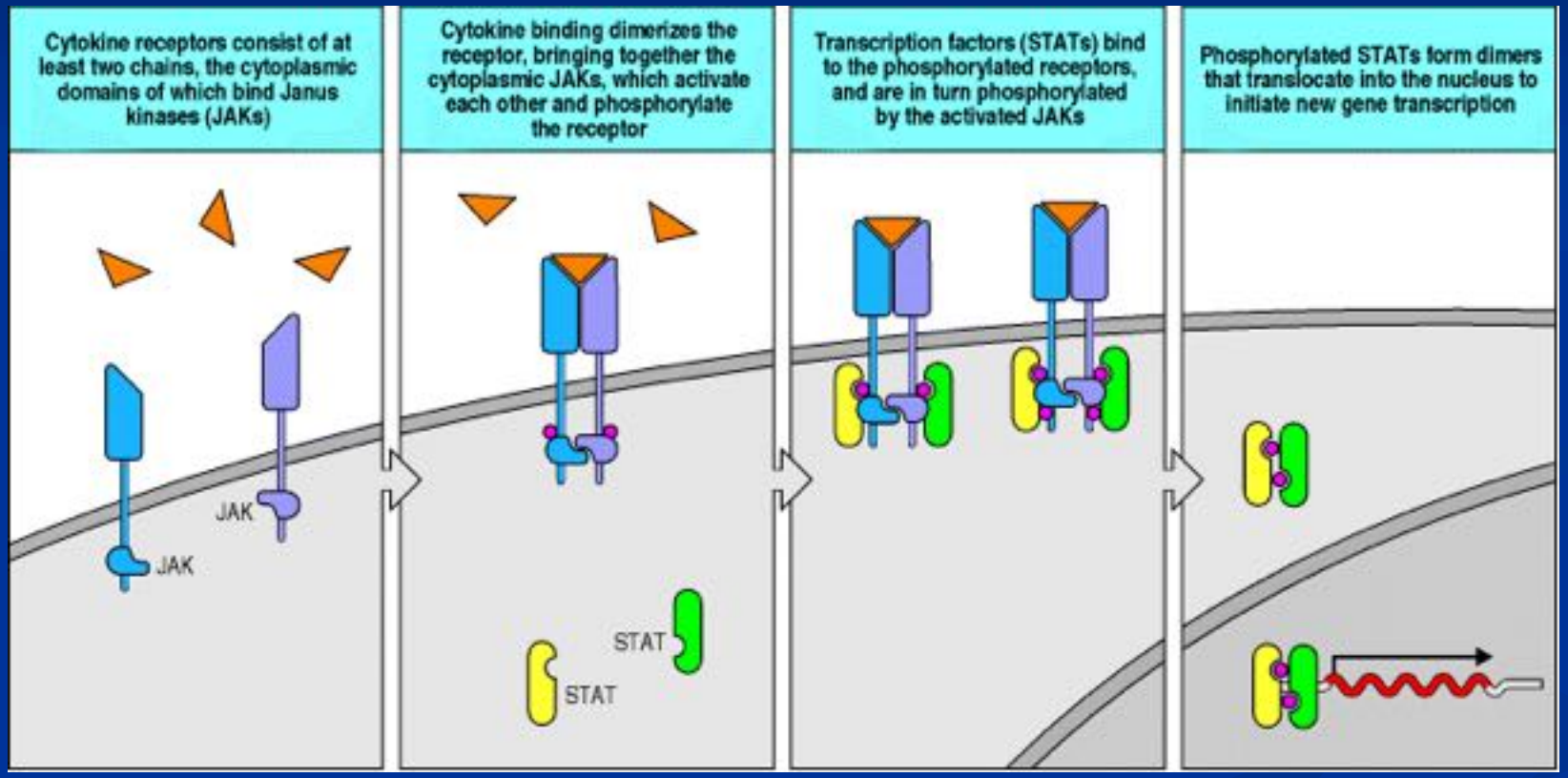
TARGETING DI FLUDARABINA A MACROFAGI INFETTATI CON HIV-1 TRAMITE ERITROCITI

obiettivo

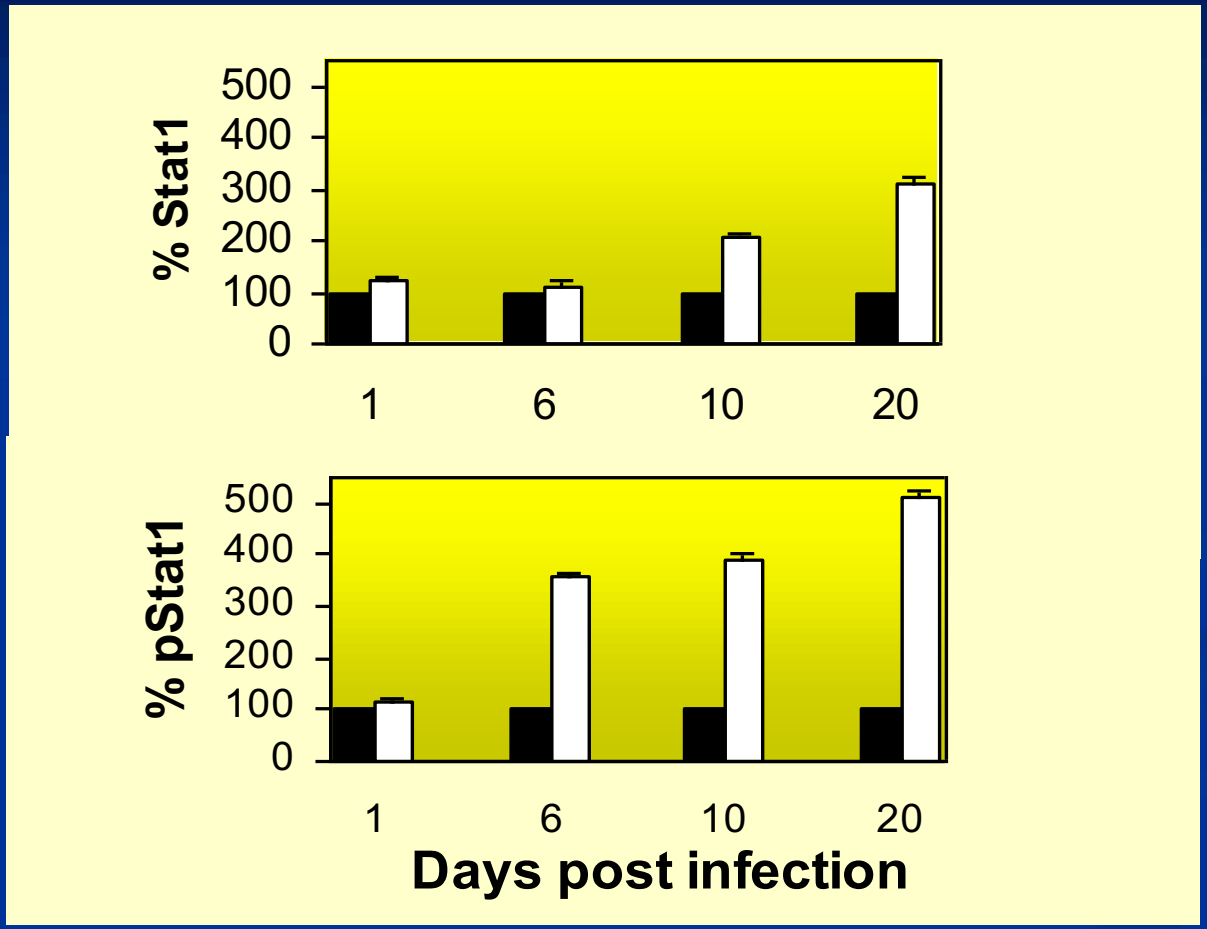
Deplezione selettiva di macrofagi infettati

Fludarabine
(9-β-D-arabinofuranosyl-2-fluoroadenine-5'-monophosphate)

JK/STAT PATHWAY



Analisi quantitativa dei livelli di STAT-1 e pSTAT1



Magnani M. et al. J. Leuk. Biol. 2003

La somministrazione di eritrociti con incapsulata Fludarabina ha eliminato i macrofagi infettati da HIV-1

controlli trattati **infettati trattati**

A: Uninfected macrophages+UL-RBC;
B: Infected macrophages+UL-RBC;
C: Uninfected macrophages+L-RBC;
D: Infected macrophages+L-RBC.
Pictures have been taken after a single 18-hours treatment with RBC.

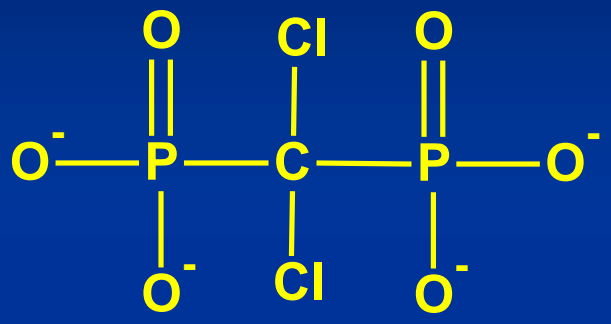
COSA C'E' DI NUOVO?

Studi preclinici di globuli rossi con farmaci nel trapianto di isole pancreatiche

Federico Bertuzzi
Istituto Scientifico San Raffaele, Milano

MECCANISMO D'AZIONE DEI NONAMINOBISFOSFONAT

I nonaminobisfosfonati sono metabolicamente incorporati in analoghi nucleotidici



Clodronate $pCCl_2p$

Aminoacido + ATP ⟵ aminoacido-AMP + PPi

Aminoacido-AMP + $pCCl_2p$ ⟶ aminoacido + $AppCCl_2p$

↓

analogo di ATP tossico per le cellule

Macrophage depletion induced by clodronate-loaded erythrocytes

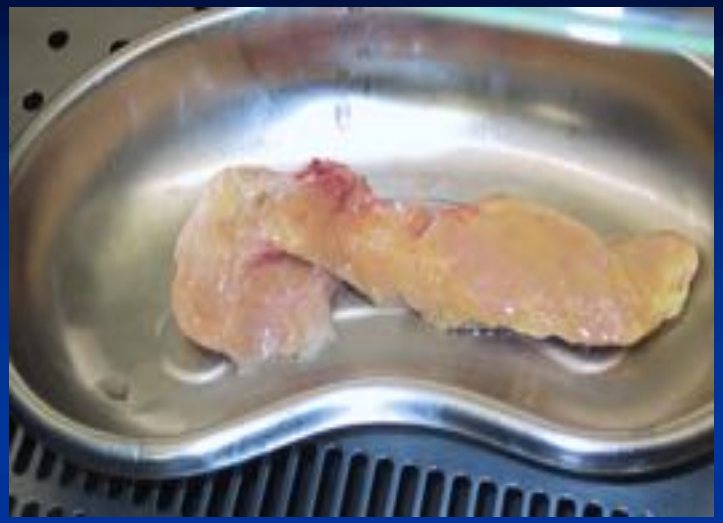
LUIGIA ROSSI[2], SONJA SERAFINI[2], ANTONELLA ANTONELLI[2], FRANCESCA PIERIGÈ[1], ANDREA CARNEVALI[2], VALERIA BATTISTELLI[1], MANUELA MALATESTA[3], EMANUELA BALESTRA[4], RAFFAELE CALIÒ[4], CARLO-FEDERICO PERNO[4], & MAURO MAGNANI[1]

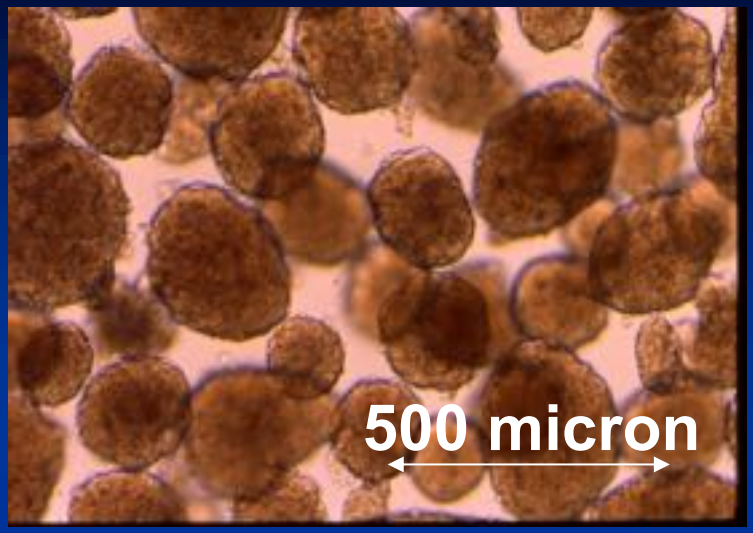
Journal of Drug Targeting, February 2005; 13(2): 99–111

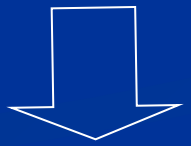
PROSPETTIVE CLINICHE DEGLI ERITROCITI CON CLODRONATE INCAPSULATO

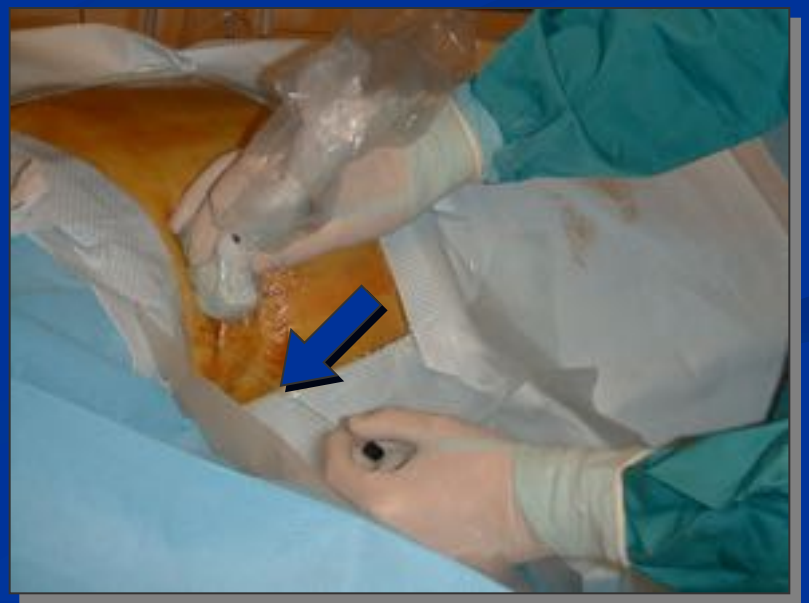
- Somministrazione di RBC-clodronate nei trapianti
- Somministrazione di RBC-clodronate nelle patologie autoimmuni
- Somministrazione di RBC-clodronate nelle patologie infiammatorie
- Somministrazione di RBC-clodronate nelle patologie causate da patogeni con tropismo macrofagico (HIV-1, *Mycobacteria spp.*, *Listeria monocytogenes*, *Herpes simplex virus*, etc.)

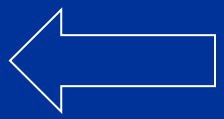
IL TRAPIANTO DI ISOLE

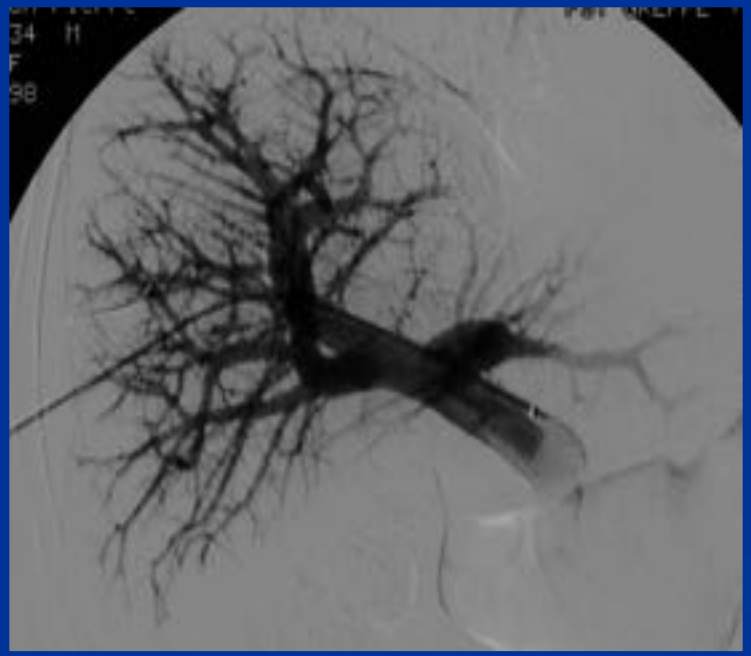




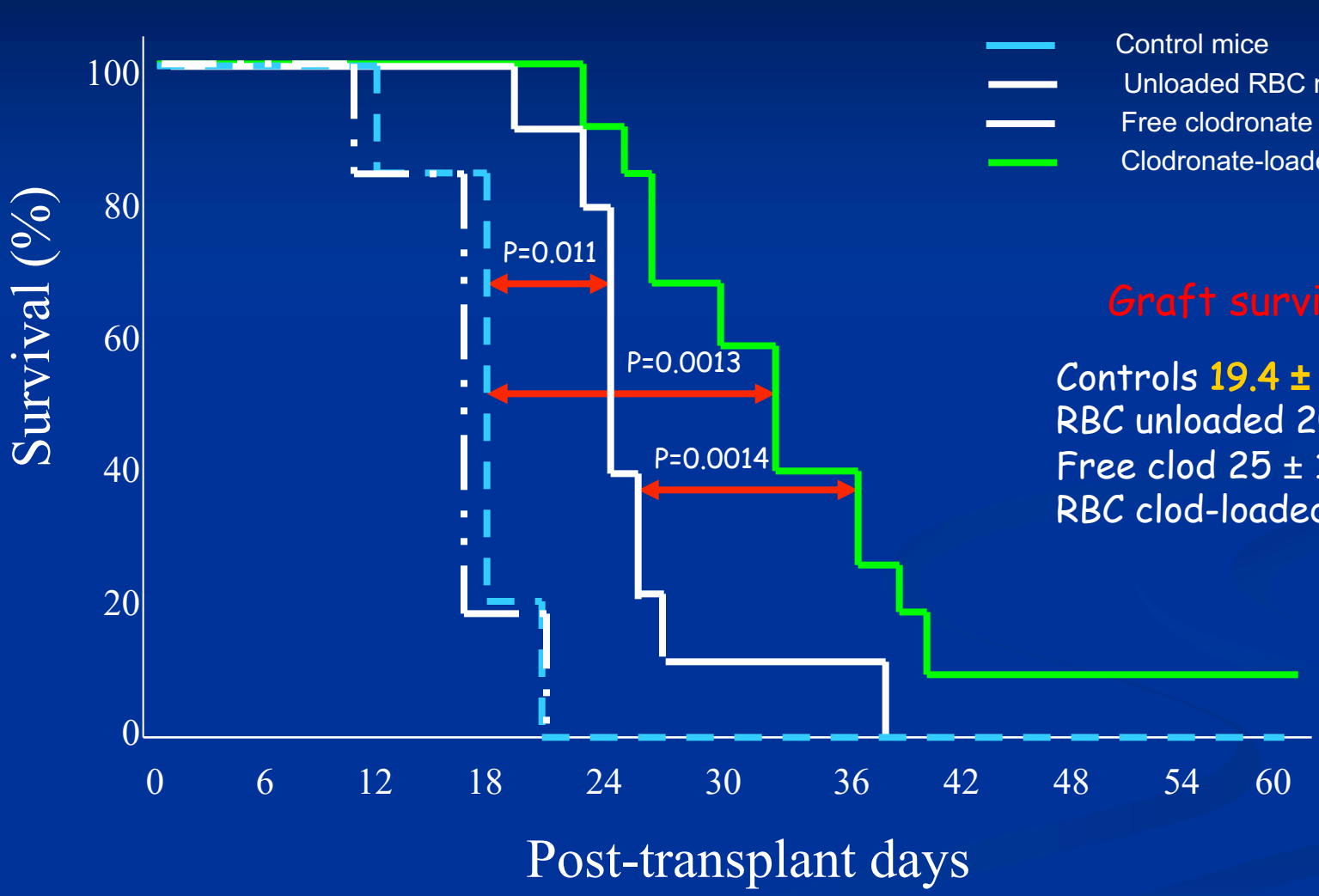








Strategie per ridurre la reazione infiammatoria: Ruolo degli eritrociti caricati con clodronato



Graft survival

Controls 19.4 ± 0.9 days
RBC unloaded 20 ± 2 days
Free clod 25 ± 1.9 days
RBC clod-loaded 35 ± 6 days

Rejection occured when 3 consecutive blood glycemic values after transplantation were found over 250 mg/dl

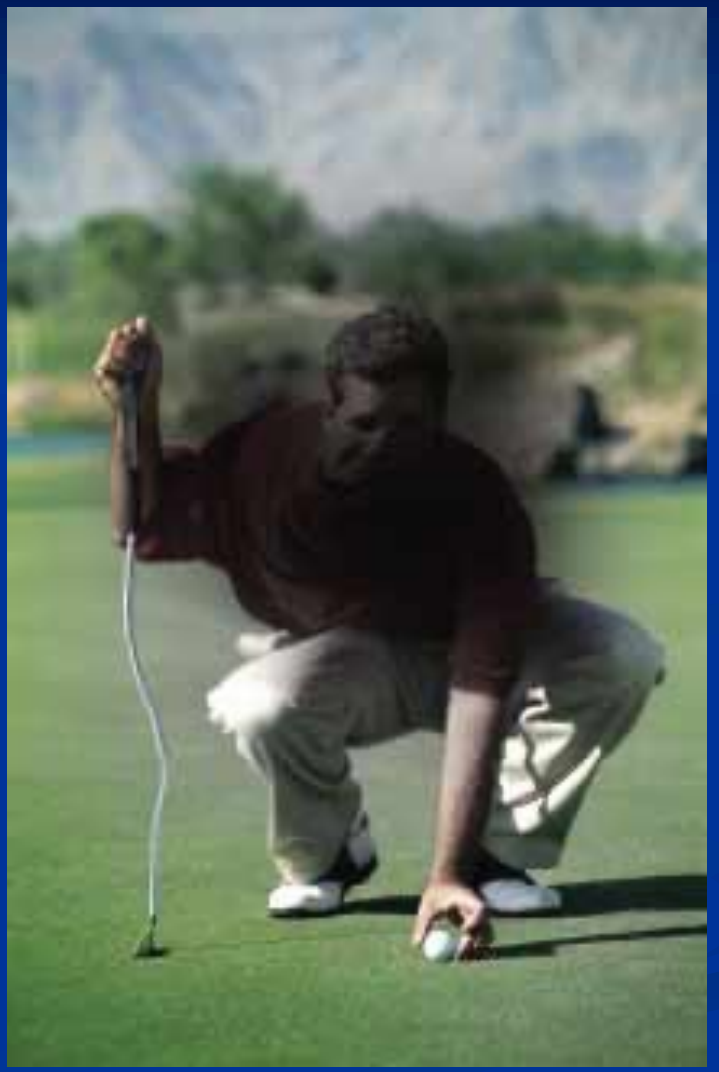
Prospettive future

Carriers di agenti di contrasto nell'IR

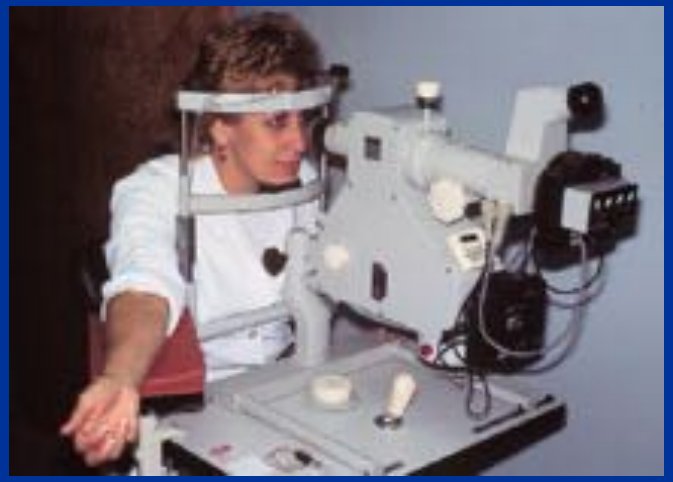
Carriers di nanoparticelle magnetiche

AMD DISEASE

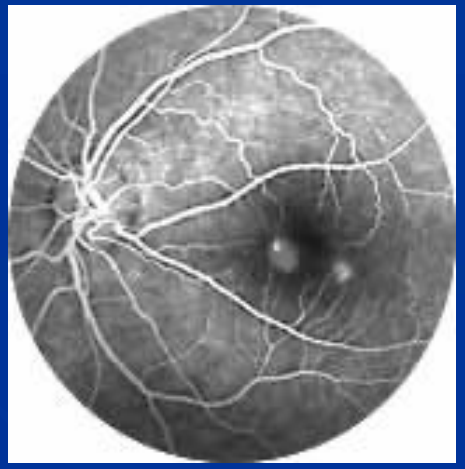
Choroidal neovascular membrane (CNVM) is a problem that is related to a wide variety of retinal diseases, but is most commonly linked to age-related macular degeneration.



Fluorescein angiography (fluorescein - the type of dye that is used; angiogram - a study of the blood vessels) is an extremely valuable test that provides information about the circulatory system and the condition of the back of the eye. FAs are useful for evaluating many eye diseases that affect the **retina**.



Retinal photograph of a patient complaining of decreased vision.

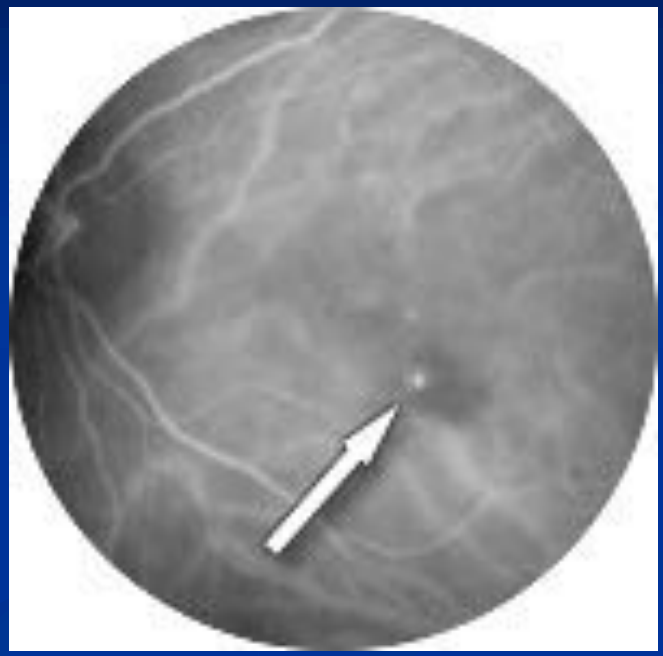


Fluorescein angiogram indicating fluid leakage within the retina.

Riesce ad identificare i neovasi sottoretinici solo nel 15% dei casi

Indocyanine Green Dye Study

An Indocyanin Green study (ICG) is a special dye test used to evaluate the circulatory system of the choroid, the layer just behind the retina. ICG reacts to light with a longer wavelength than fluorescein dye, allowing the doctor to pinpoint the location of leaking vessels deeper within the eye that may not be apparent with fluorescein angiography.

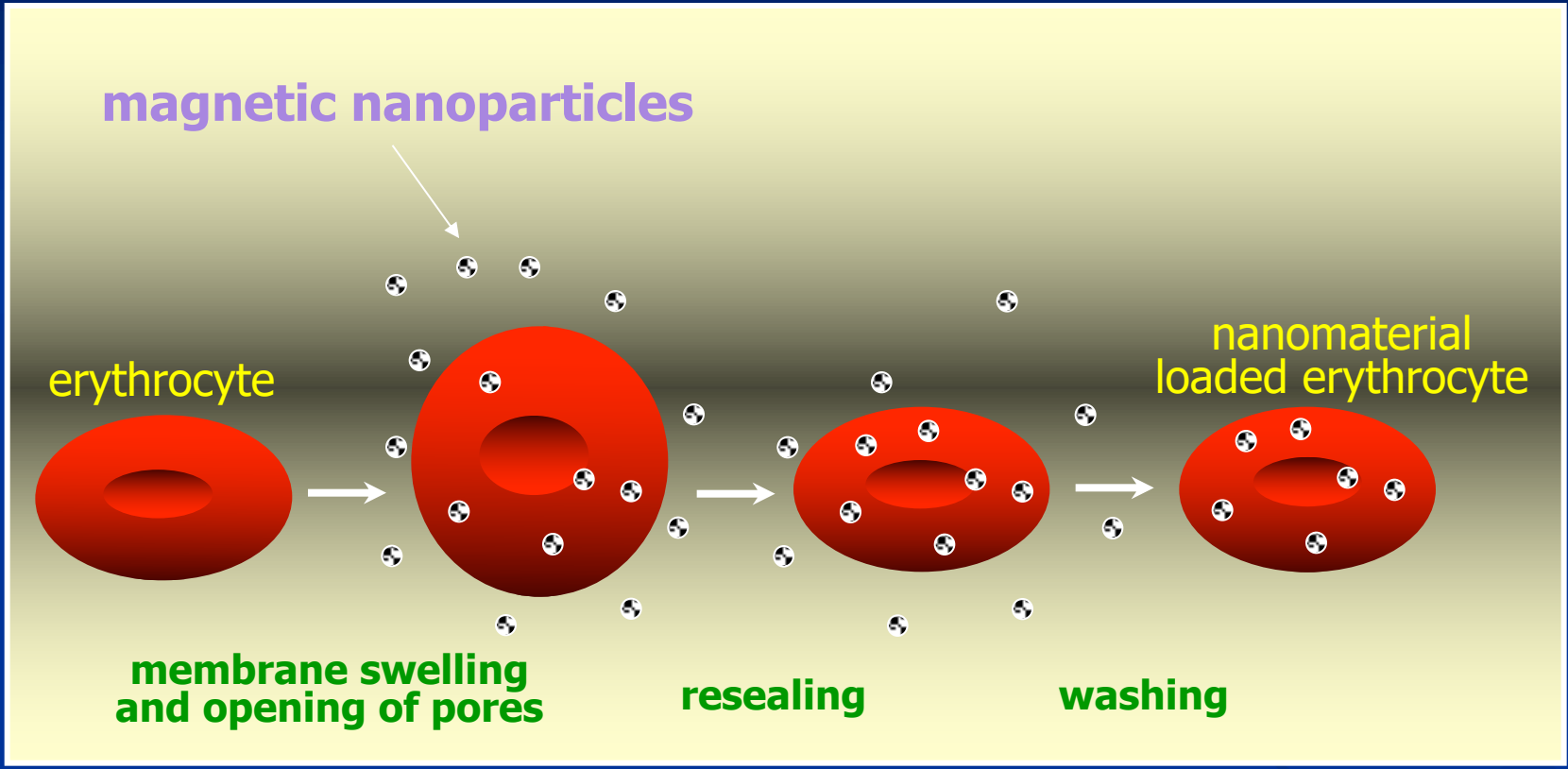


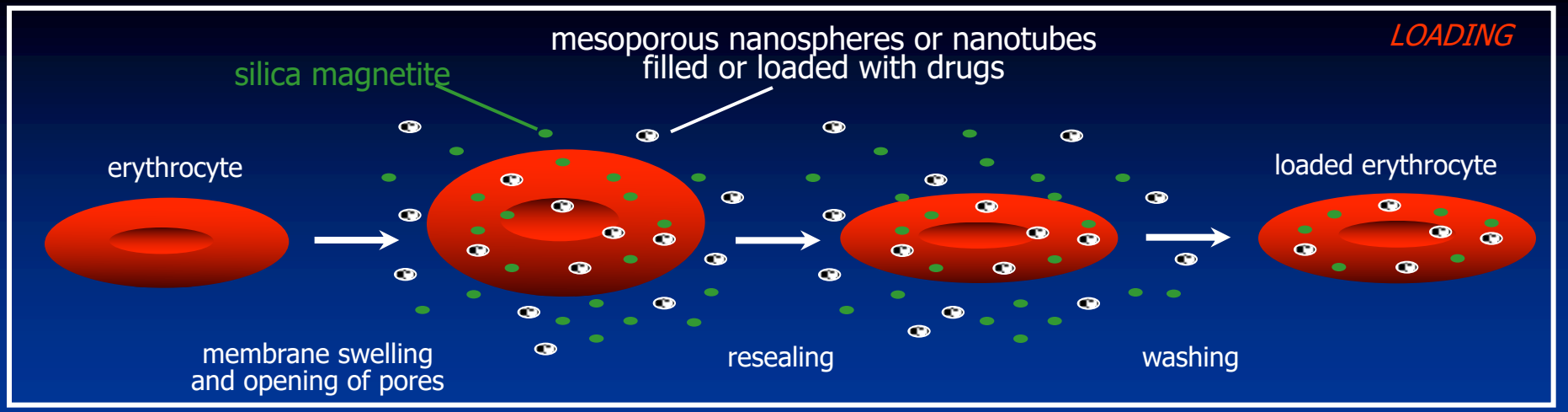
Sfrutta emissione dell'ICG nell'infrarosso, cosa che permette di visualizzare la coroide consentendo di evidenziare circa il 60-70% dei vasi occulti

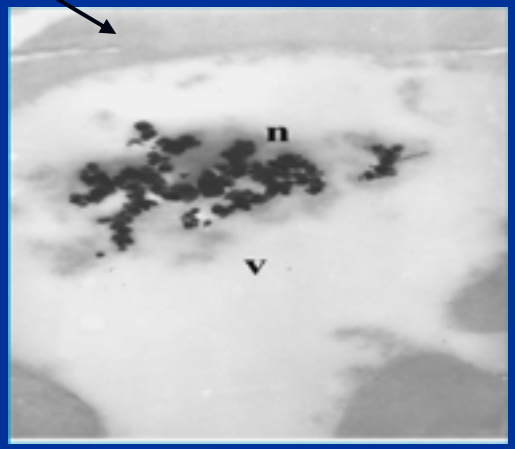
ICG può uscire dai neovasi

Perchè non usare un carrier?

Carriers di nanoparticelle magnetiche

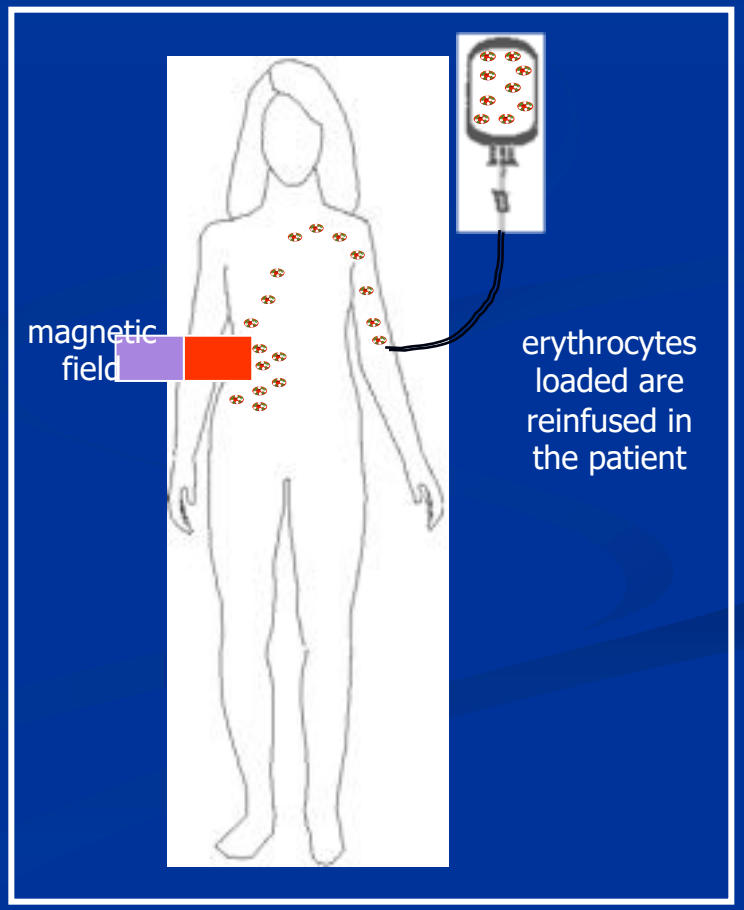






TEM analysis

RBC-SiMagn6D-Loaded



- UK Patent Application GBP95309 of 03 July 2006
- **Delivery of Contrasting Agents for Magnetic Resonance Imaging**

  "Erytrocytes exposed to dialysis with an hypotonic buffer stably take up superparamagnetic iron oxide particles and may be used MRI contrast agents. Such erythrocytes may also be used as drug delivery vehicles"
- Università degli Studi di Urbino "Carlo Bo"

Tutto ciò ha permesso la nascita di una nuova

START UP

EryDel s.r.l. Viale F. Brandani, 18 Urbino (PU)
info@erydel.com – www.erydel.com

FEBBRAIO 2007