# Extracorporeal photopheresis: clinical aspects and quality issues

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**NATIONAL JACIE MEETING DAY**
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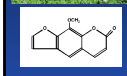
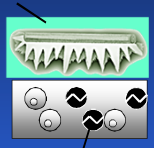
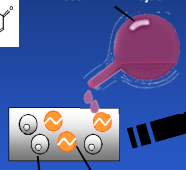
## Photodynamic Therapy

**Photosensitizer**
**Is a Psoralen – a group of Chemical compounds found naturally in Bishop weed: Ammi-Majus**



**Light source: visible light (512 nm)**



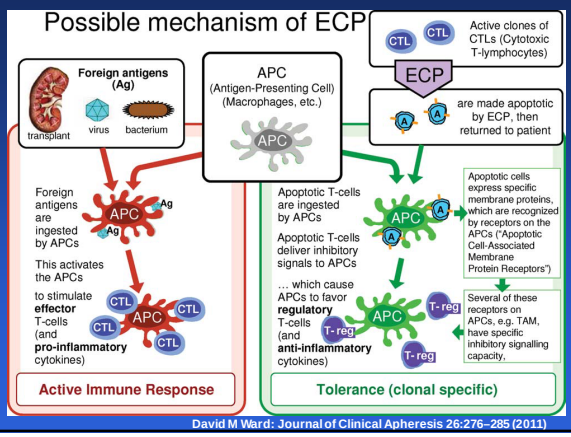


Activated T cells saturated by dye
Inert until activated by UVA.

Non-activated cells spared by photosensitizer

Results in DNA damage due to cross-linking between the DNA strands.
Apoptosis of activated T lymphocytes
Remains active for 24hours after exposure to UVA

## The purpose of the procedure is to induce in vivo immunomodulation




David M Ward: Journal of Clinical Apheresis 26:276–285 (2011)

Therakos PHOTOPHERESIS

The UVAR XTS® and CELLEX®

Photopheresis closed systems integrated, automated systems allowing for a one step procedure during which the patient remains constantly connected to the system.

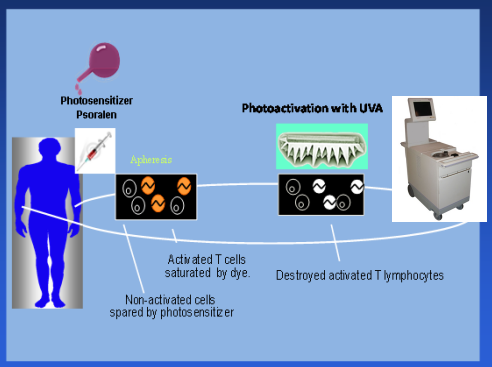
Eliminating the need for a cell manipulation facility.

These systems are CE-marked

The CELLEX® system is the new generation online system.
Unlike the UVAR XTS® system, the CELLEX® system includes continuous-flow separation technology and the ability to treat in double-needle mode.

Therakos PHOTOPHERESIS

JACIE : Sector C procedures only

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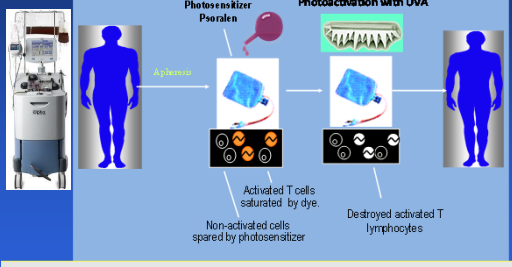
JACIE : Sector C + D procedures




**The CE marked MACOGENIC ensures a GMP-compliant illumination, with PC monitored traceability of illumination. Extremely low dose of methoxypsoralen is used in bags compared to the dose directly injected into the patient in the closed system.**

## Step 1 Aepheresis (sector C)

BIOTHERAPY

### 3- Main steps of EPC procedure (French Technique)

Cochin Hospital (Paris)

Step 1

A unit of mononuclear cells is harvested by aphaeresis with a COBE SPECTRA cells separator.

**100 to 150 ml mononuclear cells**
**Anticoagulation: no heparin, ACDA (ratio 1/12 to 1/14)**
**Hematocrit: max 5 %**



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## In a cell manipulation facility. (sector D)

Weight the apheresis bag
Connect apheresis bag with physiological serum bag and dilute to obtain 300 ml in total
Transfer the cells in the irradiation bag

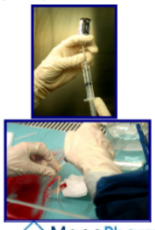
BIOTHERAPY

### 3- Main steps of EPC procedure (French Technique)

Cochin Hospital (Paris)

Step 8

3 mL of 8-MOP are collected with a syringe provided with a needle, to be then injected in the XUV8501Q bag via the injection site, this step is followed by a phase of homogenisation.





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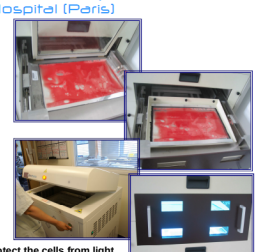
BIOTHERAPY

### 3- Main steps of EPC procedure (French Technique)

Cochin Hospital (Paris)

Step 10

The XUV8501Q bag containing the mixture = mononuclear cells + sodium chloride solution + 8MOP is placed on the plate of the MacoGenic UVA irradiator. Then, the glass pane is closed, the device is then closed by pushing the two red buttons.



**Irradiate (around 12 minutes, the time is determined by the device according to the wear of the lamps) at 2 J/cm².**

**Transfer the cells to a new cellular bag in a closed box to protect the cells from light.**
**Injection of the cells into the patient in 10 to 15 minutes.**
**The bag is wrapped in a paper to protect the cells from light.**



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## For FAGG / AFMPS

- Not a drug
- Not a device

**As registered and approved in other European Community countries**

**Can be used in Belgian with Ethics Comities approval but no need for CTA form**

## Currently:

Belgian multicentric protocol in chronic GVHD with the MACOPHARMA device (adult and children)

## Cost of PCE

| | Therakos Cellex | | | Therakos XTS | | | Local Offline System | | |
|---|---|---|---|---|---|---|---|---|---|
| Unit Resource | Unit Price | Quantity | Cost | Unit Price | Quantity | Cost | Unit Price | Quantity | Cost |
| Apheresis Kit | 945,00 | 1 | 945,00 | 945 | 1 | 945,00 | 280,00 | 1 | 280,00 |
| Light set | 1.800,00 | 0,008 | 14,40 | 1.800 | 0,008 | 14,40 | 1.800,00 | 0 | 0,00 |
| consumables | | | 50,00 | | | 50,00 | | | 135,48 |
| UVADEX (1 bottle = 2 treatments)/drug | 46,13 | 1 | 46,13 | 46,13 | 1 | 46,13 | 46,13 | 0 | 0,00 |
| Nurse hours | 35,00 | 2 | 70,00 | 35 | 4 | 140,00 | 35,00 | 4 | 140,00 |
| Doctor hours | 70,00 | 0,30 | 21,00 | 70 | 0,30 | 21,00 | 70,00 | 1 | 70,00 |
| UVA bag including Psoralène | 400 | 0 | 0,00 | 400 | 0 | 0,00 | 400,00 | 1 | 400,00 |
| Subtotal | | | 1.146,53 | | | 1.216,53 | | | 1025,48 |
| Apheresis : Depreciation over Life (10 years) | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 27.750 | 0,10 | 27,75 |
| Depreciation over Life (10 years) | 110.670 | 0,10 | 110,67 | 74.370 | 0,10 | 74,37 | 60.500 | 0,10 | 60,50 |
| Warranty | 12.100 | 0,05 | 60,50 | 11.495 | 0,05 | 57,47 | 6.050 | 0,05 | 30,25 |
| Subtotal | | | 171,17 | | | 131,84 | | | 90,75 |
| | | | | | | | | | |
| Total | | | 1.317,77 | | | 1.348,44 | | | 1.116,23 |

In the future with Offline system, if one aphaeresis for a cycle of two days treatment is validated . Cost: 803.49 (apheresis time will be divided by two)

## ECP INDICATION

Strength of recommendation

A There is Good evidence to support the use of the procedure.
B There is Fair evidence to support the use of the procedure.
C There is Poor evidence to support the use of the procedure.

D There is fair evidence to support the rejection of the use of the procedure.
E There is good evidence to support the rejection of the use of the procedure.

Quality of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial.

II-i Evidence obtained from well-designed controlled trials without randomization.
II-ii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group.
II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts of evidence).

J.J. Scarisbrick, British Journal of Dermatology 2008 158, pp659–678

| | Strength of Recommendation/ Quality of evidence |
|---|---|
| **Cutaneous T-cell lymphoma** | |
| Nonerythrodermic (stage IA–IIB) | E I |
| Erythrodermic (stage III /IVA,/B1,/0) | A I |
| **Cutaneous T-cell lymphoma (ECP and combination therapy)** | |
| **ECP + interferon alfa** | |
| Nonerythrodermic (stage IA–IIB) | C/B II-ii |
| Erythrodermic (stage III /IVA,/B1,/0) | C II-ii |
| **ECP + total skin electron beam therapy** | B II-ii |
| **ECP + psoralen–ultraviolet A** (Erythrodermic) | C II-i |
| **ECP + fludarabine** (Erythrodermic) | C II-i |
| **Graft-versus-host disease** | |
| **Chronic graft-versus-host disease** | |
| Cutaneous /mucous membrane | A II-ii |
| Hepatic | B II-iii |
| Gastrointestinal /pulmonary | D II-ii |
| **Acute graft-versus-host disease** | |
| Cutaneous | B II-iii |
| Hepatic | B II-iii |
| Gastrointestinal /pulmonary | C II-iii |
| **Transplantation rejection** | |
| Cardiac | A I |
| Renal | C II-iii |
| Lung | C II-iii |
| Liver | C II-iii |

OTHER

| | Strength of Recommendation/ Quality of evidence |
|---|---|
| Systemic sclerosis | D/C I |
| Multiple sclerosis | D/C I |
| Type 1 diabetes mellitus | C I |
| Rheumatoid arthritis | C II-iii |
| Psoriasis | C II-iii |
| Psoriatic arthritis | C II-iii |
| Systemic sclerosis + type 1 diabetes mellitus | D II-iii |
| Atopic dermatitis | C II-iii |
| Atopic eczema | C III |
| Blistering disease | C III |
| Systemic lupus erythematosus | C III |
| Lichen planus | C III |
| AIDS-related complex | C III |
| Chronic hepatitis C infection | D III |
| B-cell chronic lymphocytic Leukaemia | D III |

J.J. Scarisbrick, British Journal of Dermatology 2008 158, pp659–67

## BHS INDICATIONS FOR ECP THERAPY

**Cutaneous T cell lymphoma (mycosis fungoides, Sezary syndrome)**

*The following 2 conditions must be fulfilled*

- Mycosis fungoides/Sezary syndrome in erythrodermic stage IIIA-IIIB or stage IVA1-IVA2.
- One of the following minor criteria
  - Circulating clonal disease (circulating T cell clone by PCR or Southern blot analysis)
  - Evidence of circulating Sezary cells (>10% of circulating lymphocytes)
  - CD4+/CD8+ ratio >10

**Chronic GVHD**

*The following 3 conditions must be fulfilled*

- Moderate or severe chronic GVHD (NIH criteria).
- Second or further line of therapy because either :
  - refractory to steroids (minimal or no response to prednisolone 1mg/kg or equivalent after a minimum of 4 weeks of treatment)
  - steroid-dependent (inability to reduce steroids to prednisolone < 0.5 mg/kg/d or equivalent daily without flare of GVHD)
  - intolerant to steroids
- Chronic GVHD primarily affecting at least one of the following organs : skin; mucosal membranes (mouth and/or eye and/or genital organs); gastrointestinal tract; liver; lung.

**Acute GVHD**

*The following 3 conditions must be fulfilled*

- Grade II to IV acute GVHD
- Second line therapy because either :
  - refractory to corticosteroids (2 mg/kg/d) and calcineurin inhibitors
  - steroid-dependent (inability to reduce steroids to prednisolone < 0.5 mg/kg/d or equivalent daily without flare of GVHD)
  - intolerant to steroids
- Acute GVHD primarily affecting at least one of the following organs : skin; mucosal membranes (mouth and/or eye and/or genital organs); gastrointestinal tract; liver; lung.

**Lung transplantation**

*The following 2 conditions must be fulfilled*

- Lung transplantation within the first 3 years post-transplant
- Chronic allograft dysfunction (BOS)

## TREATMENT SCHEDULE REVIEW

**Photopheresis is performed on two consecutive days every 1-4 weeks, depending on disease treated .**
**- aGVHD every week**
**- cGVHD every 2 weeks.**
**- CTCL every 3-4 weeks .**

**Depending on patient response will determine frequency of further treatments**

**3 MONTHS:**
**- Complete or partial response: treatment 4 weekly.**
**- Minimal /or no response but reduction of other treatments by 50%: continue 2 weekly.**
**When neither of above stop treatment**

**6 MONTHS:**
**- Complete response: Taper and stop.**
**- Partial response or if > 50% reduction of other treatment but less then partial response: Continue 4 weekly and reduce other treatment as tolerated**
**- When no further response after 3 months or progression of disease: Stop**

## Response Rates for ECP in the treatment of Chronic GvHD in Adults (CR and OR )

| Lead Author | Type | | Year | No. studies | N= | % CR | % OR |
|---|---|---|---|---|---|---|---|
| Abu Dalle | Meta-analysis | | 2014 | 5 | 87 | 26 | 64 |
| Malik* | Meta-analysis | | 2014 | 18 | 595 | 29 (19-42) | 64 (65-82) |
| McKenna | Meta-analysis | | 2006 | 23 | 521 | | 68 |
| Douglas | Meta-analysis | | 2008 | 9 | 206 | 68 | 66.2 |
| Berger | Single arm prospective | | 2007 | N/A | 10 | 30 | 40 |
| Greinix | Cross over prospective | | 1998 | N/A | 29 | 50 | 88 |
| Foss | Single arm prospective | | 2005 | N/A | 25 | | 64 |

*Included children and adults. No statistical difference in CR an OR between children and adults. Adults CR 26%; OR 78%. Pediatric CR 39%; OR 69%.

### Survival Data in Adults with Acute GvHD second line treatment

| Lead Author | Year | N= | Years F/Up | Overall Survival |
|---|---|---|---|---|
| Malik | 2014 | 595 | 1 | 49% |
| Greinix | 2006 | 59 | 4 | 59%* |
| Perfetti | 2008 | 23 | Up to 81 months** | 38% |

* complete responders only
** Retrospective review 1996-2006

### Response Rates for ECP in the Treatment of Paediatric acute GvHD: *Overall Response (OR) and Steroid tapering (second line treatment)*

| Lead Author | Year | N= | % OR | % Discontinuation of steroids | % Tapering of steroids |
|---|---|---|---|---|---|
| Salvaneschi | 2001 | 9 | 78 | 43* | |
| Messina | 2003 | 33 | 76 | 42* | 36 |
| Berger | 2007 | 15 | 100 II;75 III; 0 IV | | |
| Kanold | 2005 | 41 | 73 | | |
| Kanold | 2007 | 12 | 83 | 30 | 33 |
| Perseghin | 2007 | 10 | 70 | | |
| Gonzalez-Vicent | 2008 | 8 | 100 | | |
| Calore | 2008 | 15 | 100 | 67 | |
| Merlin | 2010 | 12 | 83 | | |
| Gonzalez-Vicent | 2010 | 21 | 90 | | |
| Perotti | 2010 | 50 | 68 | 16 @ 30 days | |
| Witt | 2012 | 15 | 73 | | |

### Survival Data for Children with Acute GvHD on ECP

| Lead Author | Year | N= | Years F/Up | Overall Survival | Progression Free Survival | Disease free Survival |
|---|---|---|---|---|---|---|
| Salvaneschi | 2001 | 9 | 0.75 | 55% | | |
| Messina | 2003 | 33 | 5 | 69%* | | |
| Burger | 2007 | 15 | | 100% Grade II; 30% Grade II-IV | | |
| Kanold | 2007 | 12 | | 67% | | |
| Calore | 2008 | 15 | 2 | 85% | 87% | |
| Gonzalez-Vicent | 2010 | 21 | | | | 43% |
| Perotti | 2010 | 50 | 5 | 46% | | |
| Merlin | 2010 | 12 | 5 | 57% | | |
| Witt | 2012 | 15 | 10 | 89%* | | |
| * Responders | | | | | | |

## Summary of published response rates CTCL

| Author | Year | Total Patients | Overall Response | Partial Response | Complete Response |
|---|---|---|---|---|---|
| Edleson et al | 1987 | 37 | 27 (73%) | 18 | 9 (24%) |
| Heald | 1989 | 32 | 17 (53%) | 12 | 5 (14%) |
| Armus | 1990 | 8 | 7 (87.5%) | n.d | 2 (25%) |
| Dall' Amico et al | 1991 | 37 | 27 (73%) | n.d | 9 (24%) |
| Koh | 1994 | 34 | 18 (53%) | 13 | 5 (15%) |
| Prinz | 1995 | 17 | 12 (71%) | 6 | 0 |
| Zic et al | 1996 | 20 | 10 (50%) | 5 | 5 (25%) |
| Gottlieb et al | 1996 | 31 | 20 (65%) | 13 | 7 (23%) |
| Duvic et al | 1996 | 34 | 17 (50%) | 11 | 6 (18%) |
| Owsianowski et al | 1996 | 16 | 11 (69%) | 7 | 4 (25%) |
| Konstantinow et al | 1997 | 12 | 8 (67%) | 5 | 1 (8%) |
| Russel-Jones | 1997 | 19 | 10 (53%) | 7 | 3 (16%) |
| Dippel | 1997 | 19 | 7 (36%) | n.d | 5 (26.3%) |
| Vonderheid | 1998 | 32 | 10 (31%) | 6 | 4 (13%) |
| Zouboulis et al | 1998 | 20 | 13 (65%) | n.d | n.d |
| Jiang et al | 1999 | 25 | 20 (80%) | 15 | 5 (20%) |
| Crovetti et al | 2000 | 30 | 22 (73%) | 12 | 10 (33%) |
| Bissacia et al | 2000 | 37 | 20 (54%) | 15 | 5 (14%) |
| Wollina et al | 2001 | 15 | 10 (67%) | 3 | 5 (33%) |
| Stevens et al | 2002 | 13 | 7 (54%) | 0 | 7 (54%) |
| Knobler et al | 2002 | 20 | 10 (50% | 7 | 3 (15%) |
| Bouwhuis et al | 2002 | 55 | 34 (62%) | 33 | 1 (2%) |
| Duvic et al | 2003 | 54 | 23 (43%) | 16 | 7 (13%) |
| **Total** | | **617** | **360 (58%)** | | **108 (17%)** |

## Take Home Message

- ECP is a therapeutic approach based on the combined effect of ultraviolet light (UV-A) and a photosensitising agent (Psoralen derived) on peripheral blood mononuclear cells
- ECP has emerged as a safe and efficacious approach for the management of the resistant to the 1st line treatment graft versus host disease (GvHD) and cutaneous T cell lymphoma (CTCL).
- Few cure but a high overall response rate, implying long term treatment.
- It is being increasingly used around the world
- Access to ECP : Is now Part of the Jacie standard
- The Therakos approached involved only sector C.
  The Macopharma approached involved sector C and D.
- In Belgium: ECP is not yet reimbursed by RIZIV/INAMI, procedure is in progress
- ECP can be performed with Ethics Comities approval only, for diseases for which it is approved in other European community countries.