

Chronothérapie des cancers

Francis Lévi

« Chronothérapeutique des Cancers »

INSERM E 0118 et Service de Cancérologie

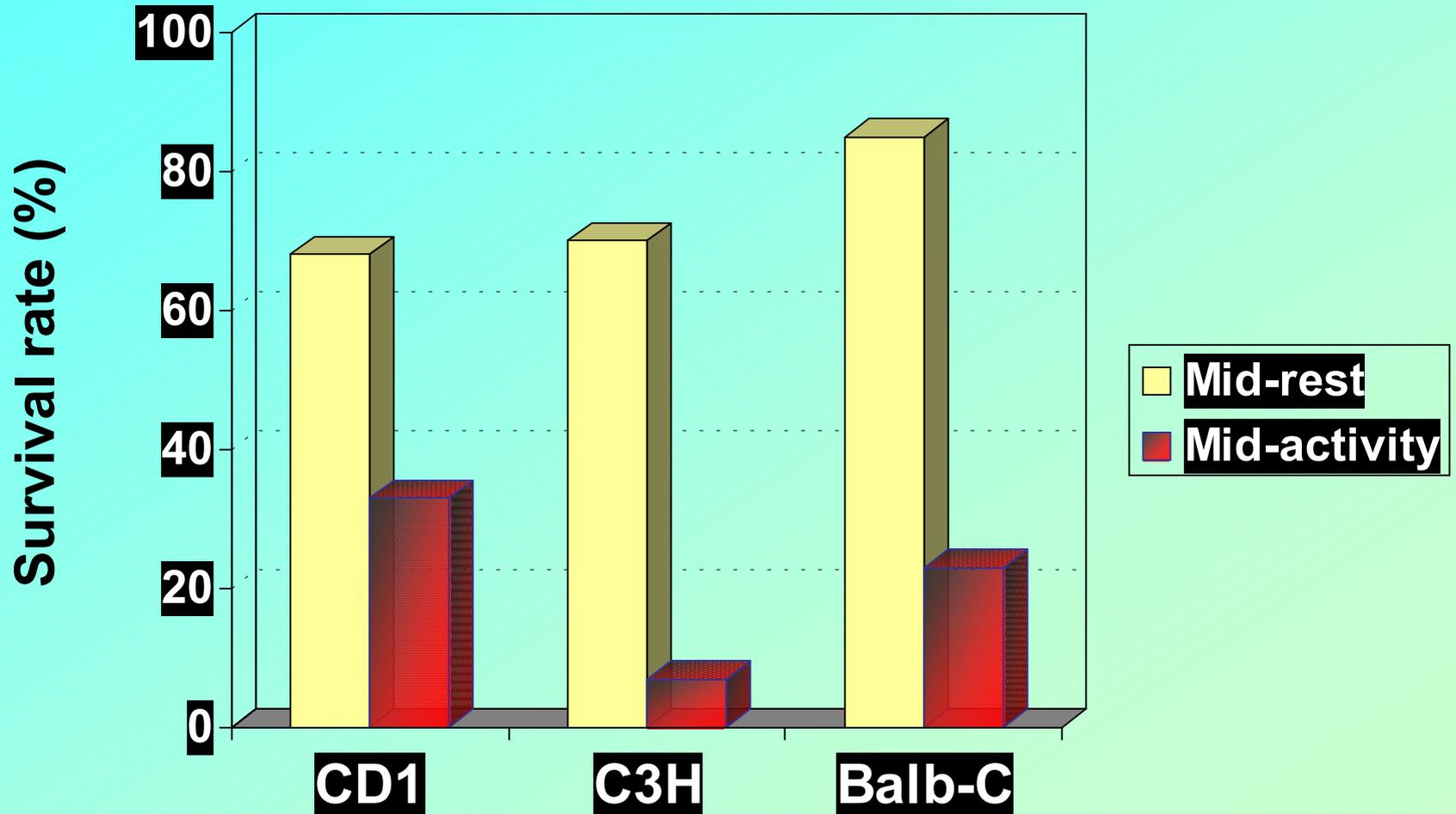
Hôpital Paul Brousse, 94800 - Villejuif

Développement chronothérapeutique

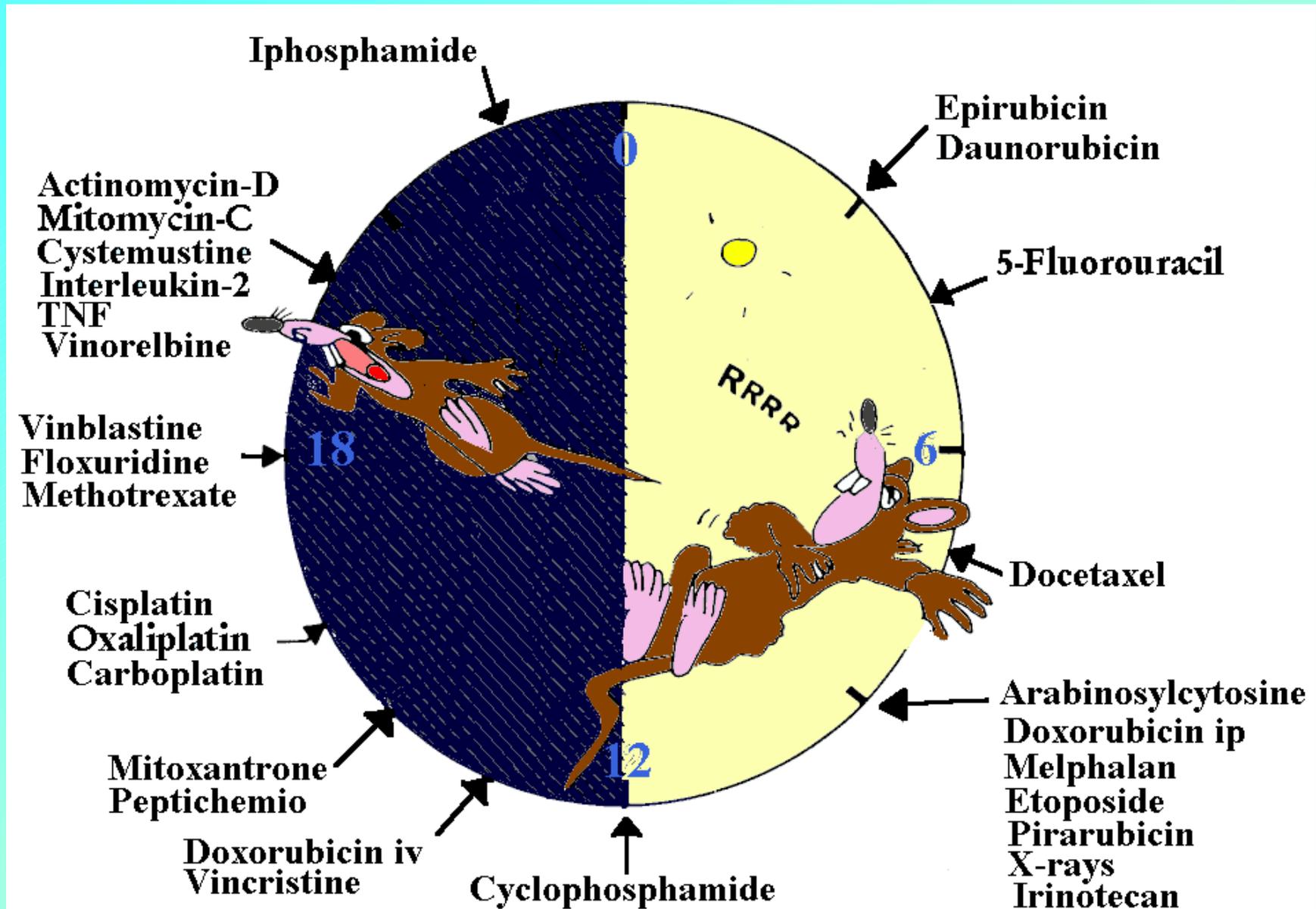
• Prérequis	chronopharmacologie rythmes en pathologie	expérimentaux cliniques
• Phase I	toxicité, pharmacocinétique dose recommandée	< 30 sujets
• Phase II	efficacité	30-100 patients
• Phase III <i>(randomisé, multicentrique)</i>	pertinence clinique	200–1000 patients

Rhythms in anticancer drug metabolism and disposition.

5-FU tolerability in mice

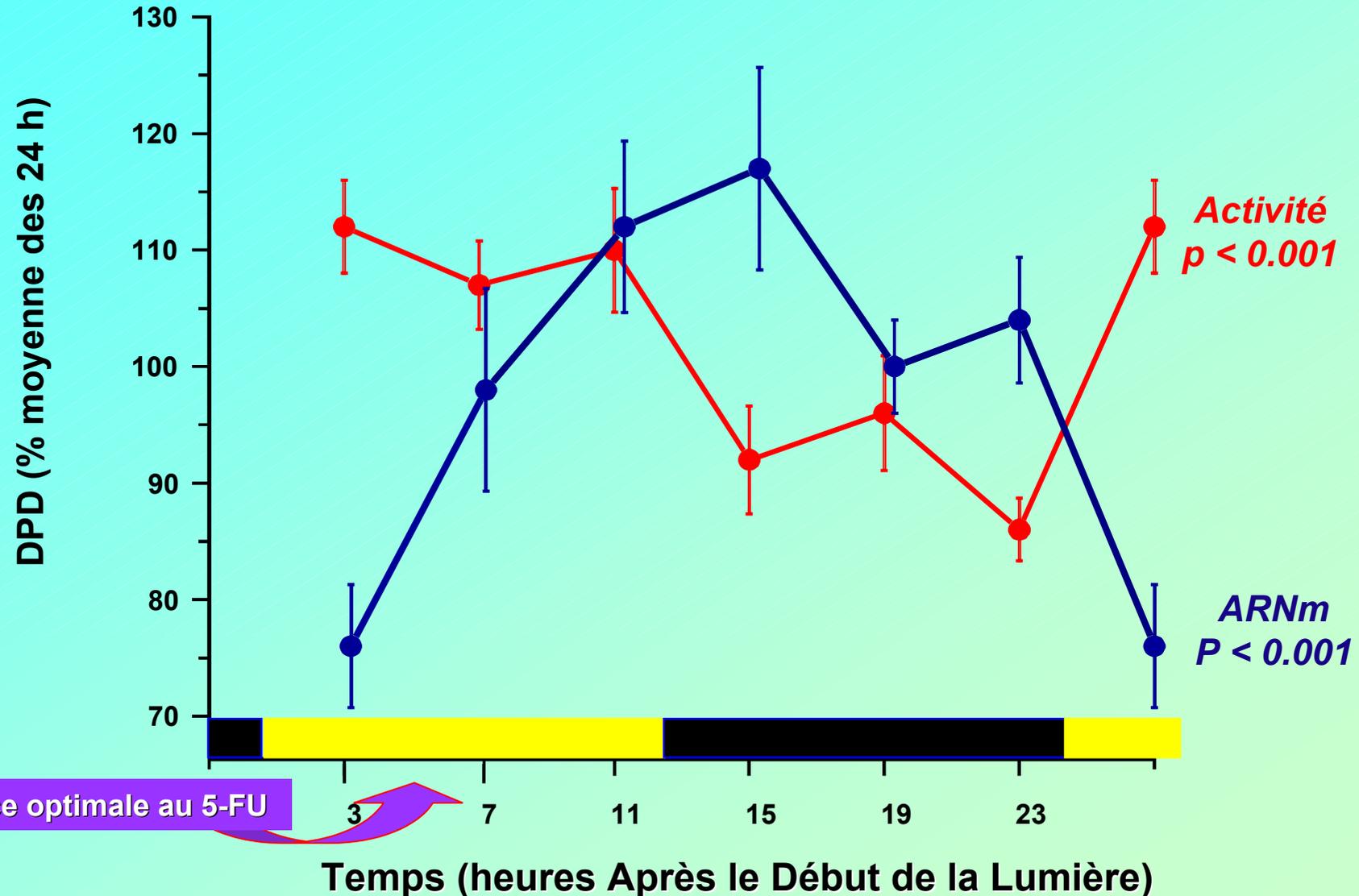


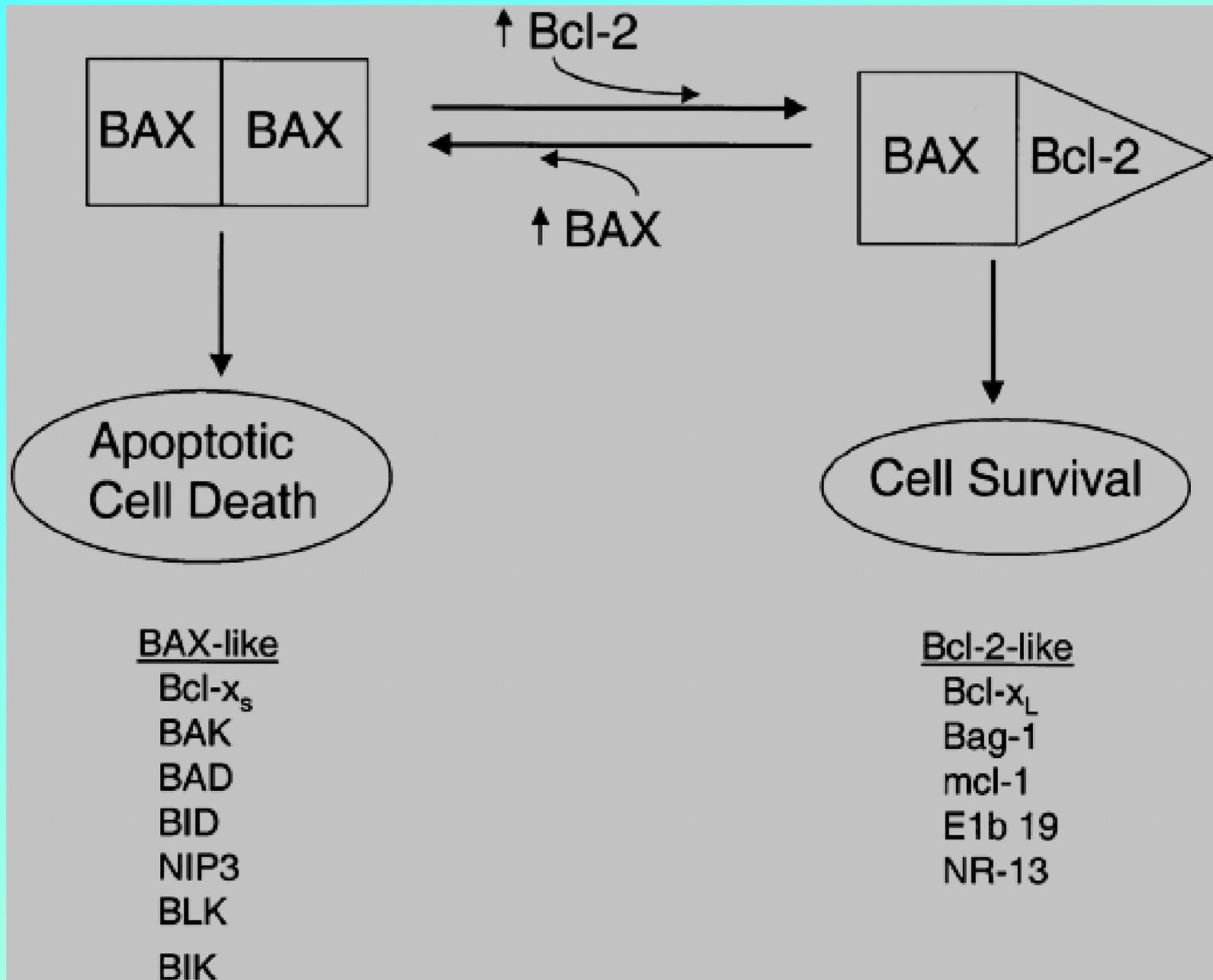
Circadian rhythm in anticancer drug tolerability



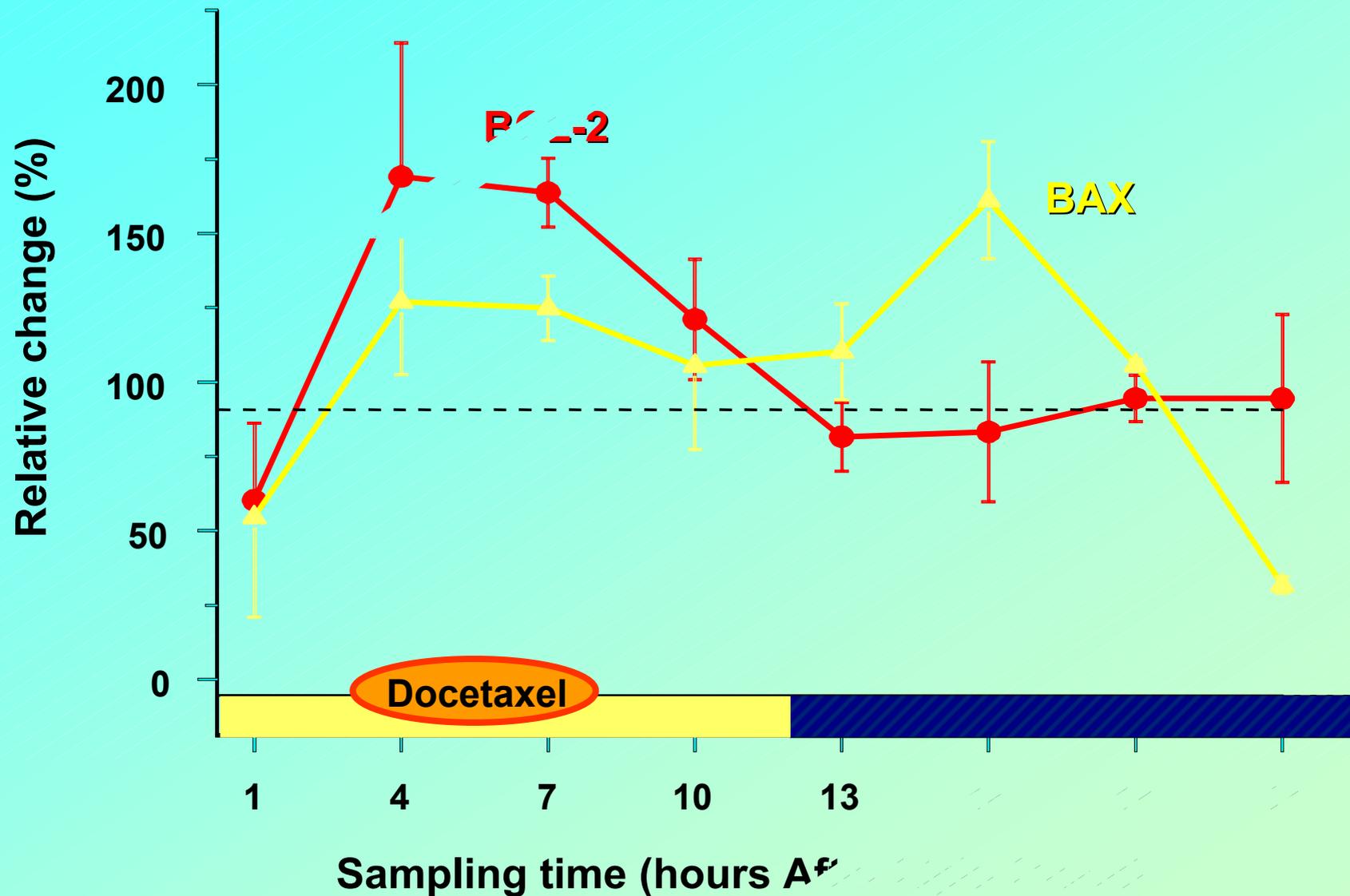
Développement chronothérapeutique

Déshydroypyrimidine déshydrogénase (DPD) hépatique



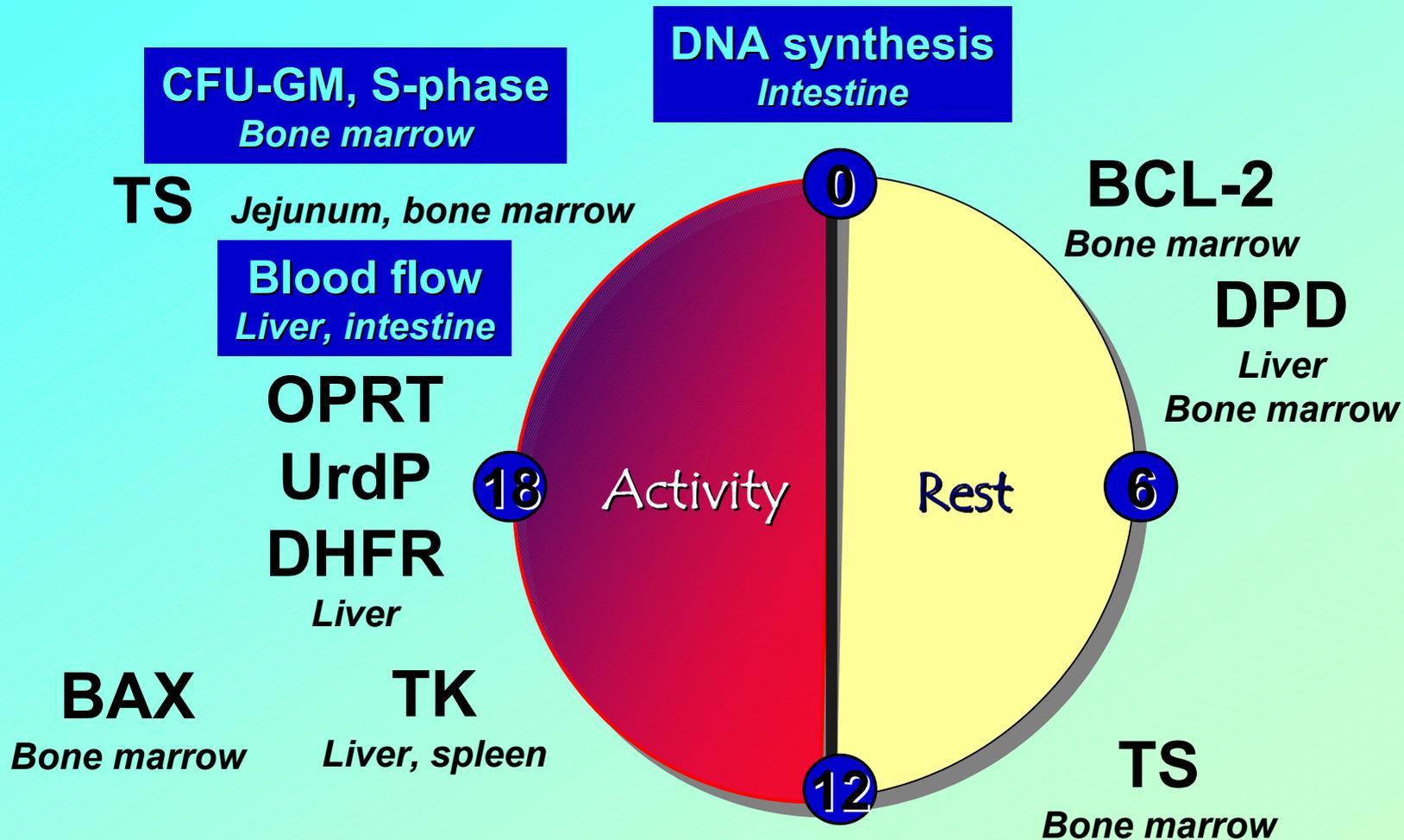


BCL-2/BAX rhythms in mouse bone marrow



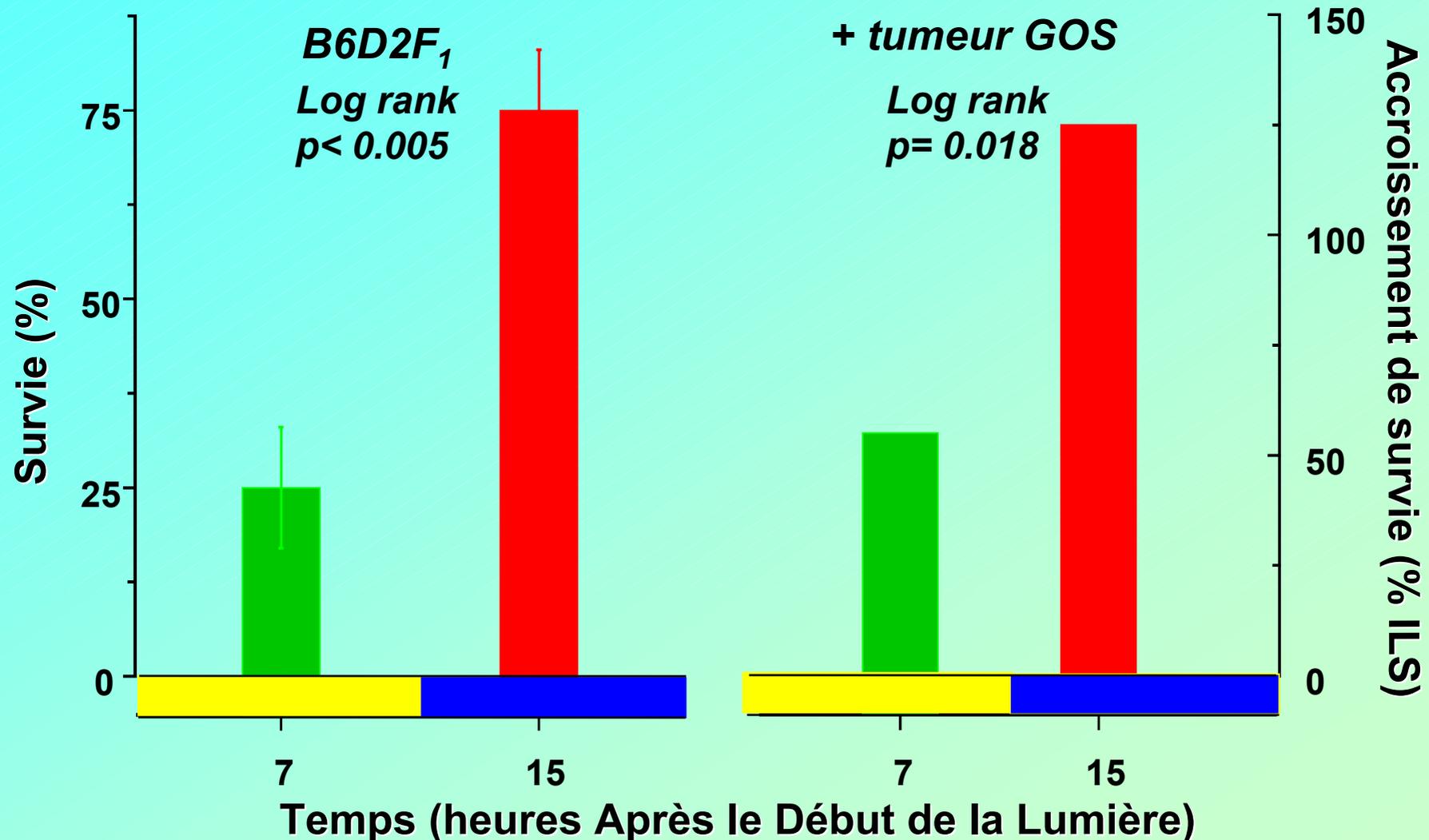
Rhythms in anticancer drug metabolism and disposition.

Rhythms in target host tissues (mice or rats)



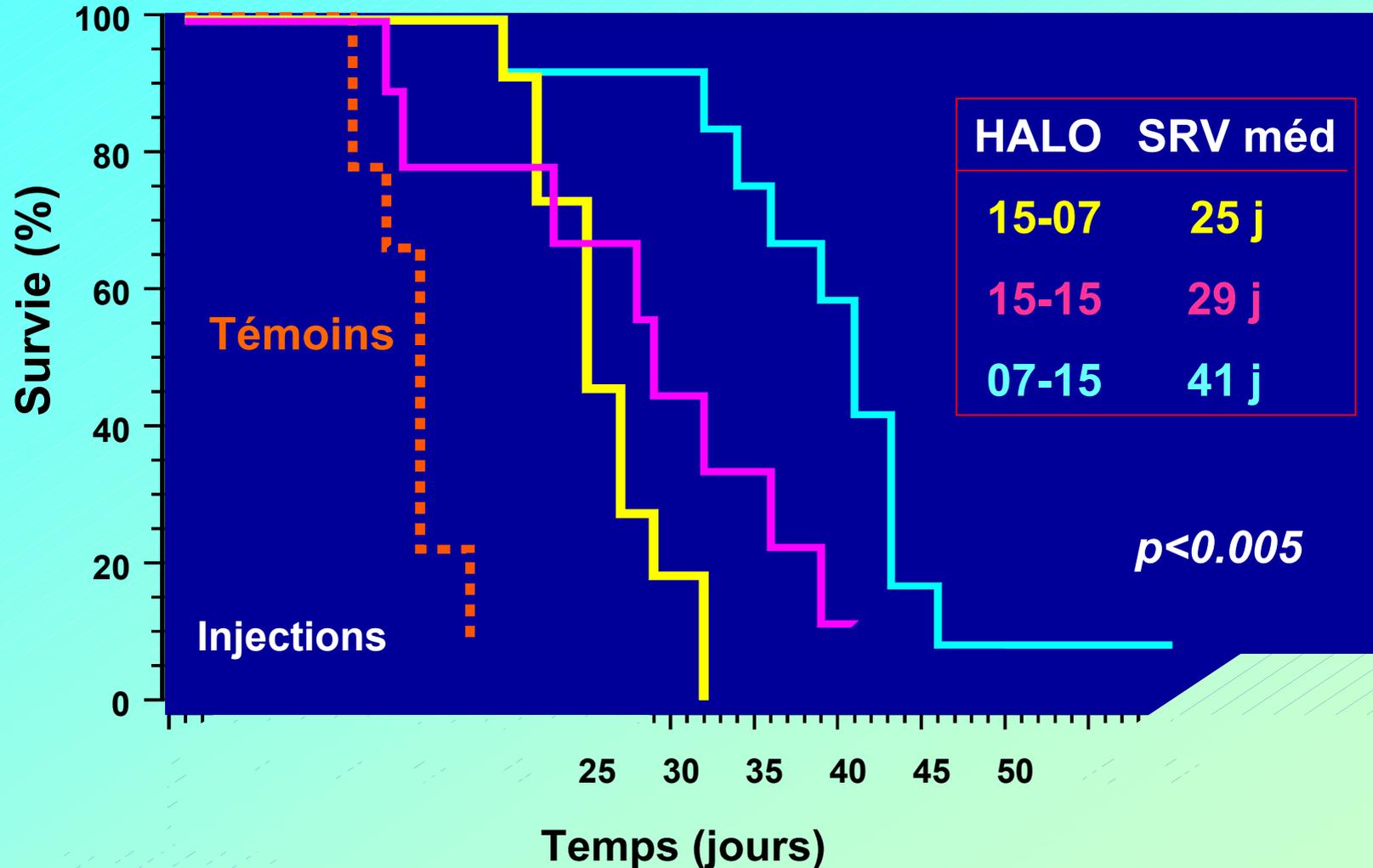
Développement chronothérapeutique

Tolérance et d'efficacité de l'oxaliplatine



Développement chronothérapeutique

Efficacité de l'association irinotécan-oxaliplatine



Développement chronothérapeutique

Principes établis dans le modèle expérimental

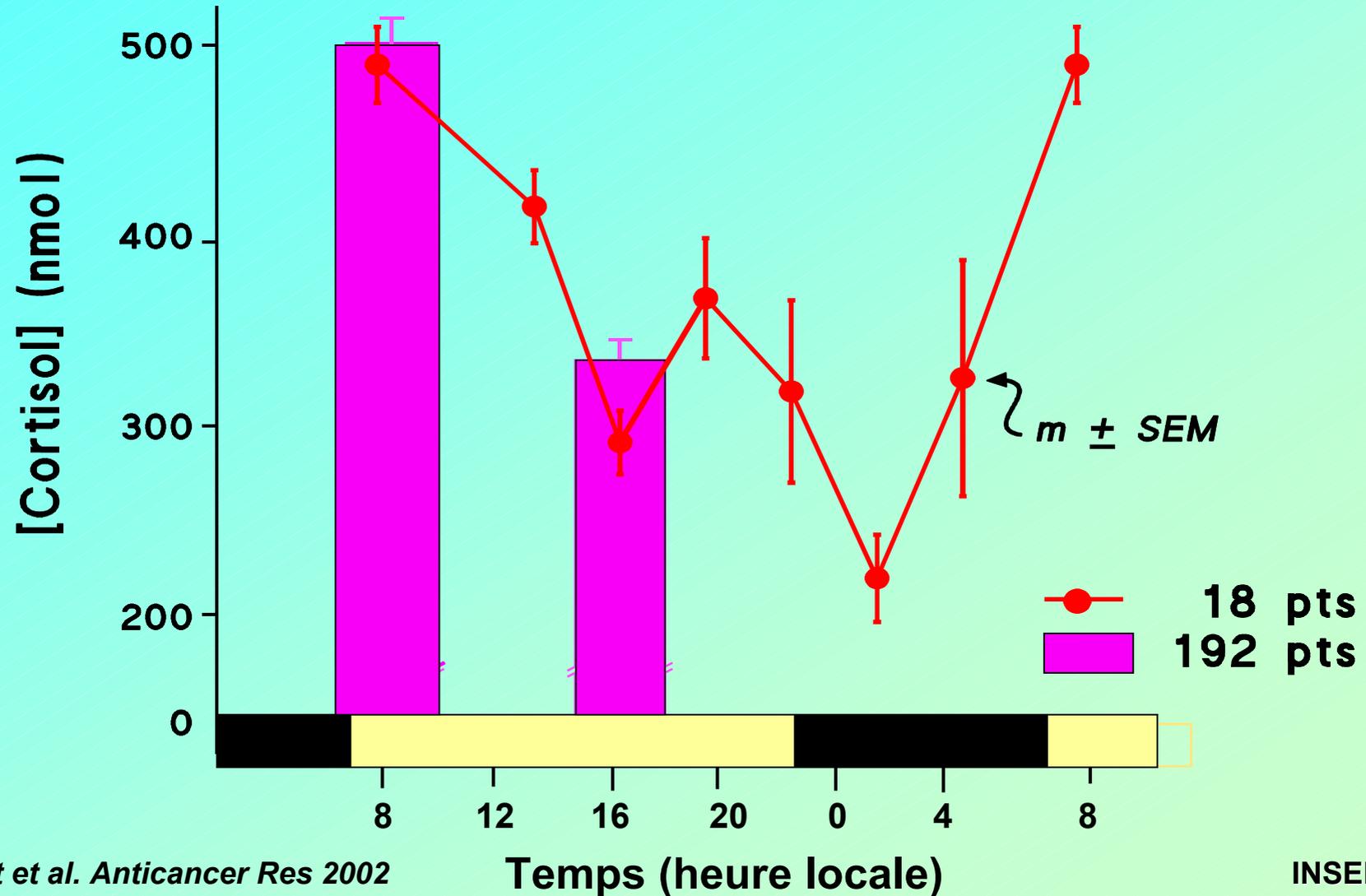
- Tolérance aux agents anticancéreux :
variation > 50% selon le moment d'administration
- Déterminants :
rythmes de métabolisme, prolifération, apoptose,
réparation
- Activité antitumorale
supérieure près de l'heure de meilleure tolérance
- Associations de cytotoxiques
plus efficaces lorsque chaque agent est donné
à l'heure de meilleure tolérance



Pertinence clinique?

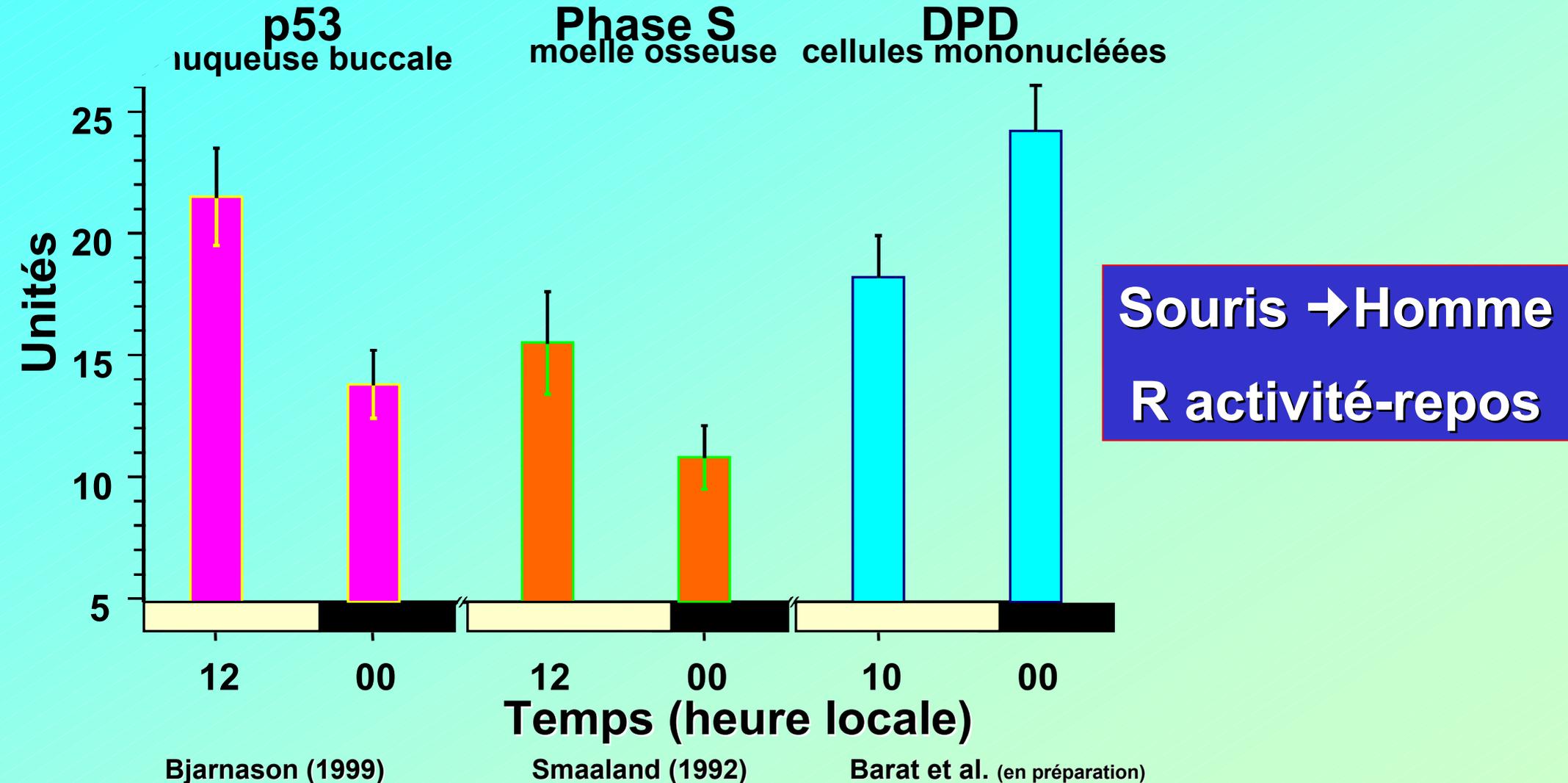
Développement chronothérapeutique

Rythme du cortisol chez des patients atteints de cancer colorectal métastatique

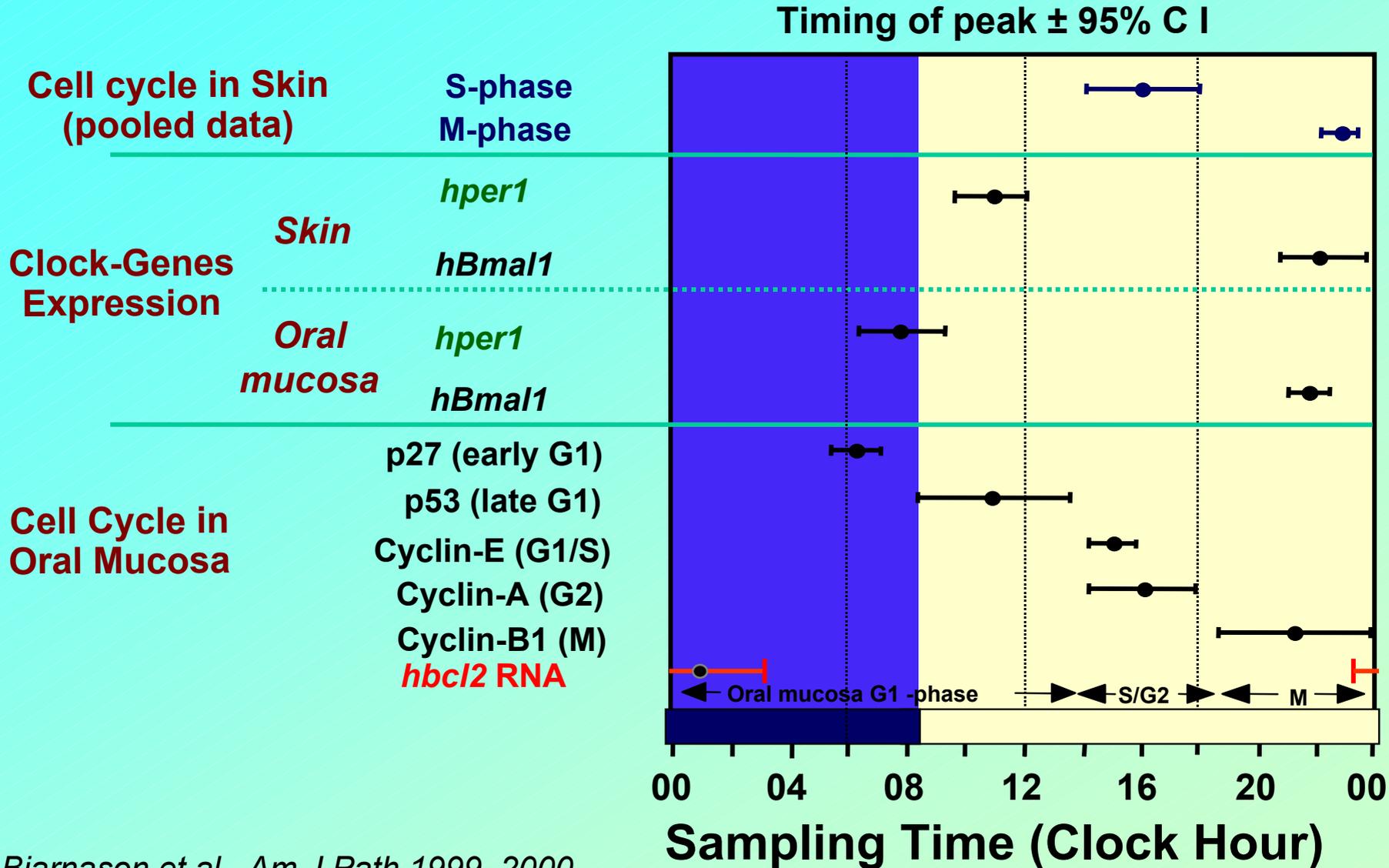


Développement chronothérapeutique

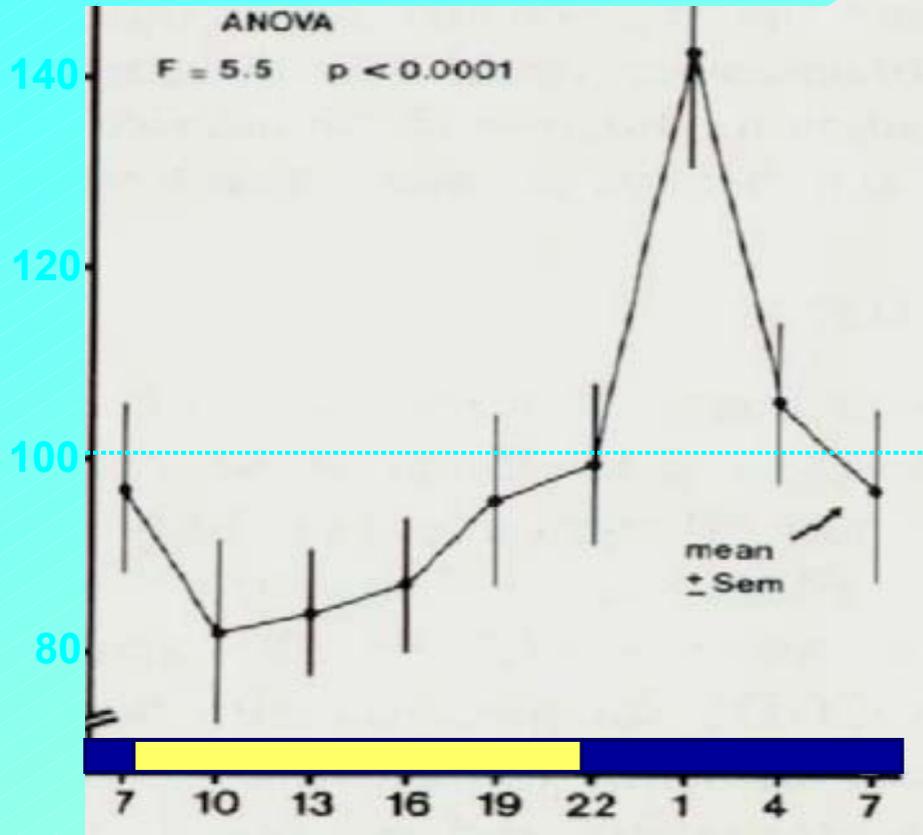
Rythmes pertinents chez l'Homme



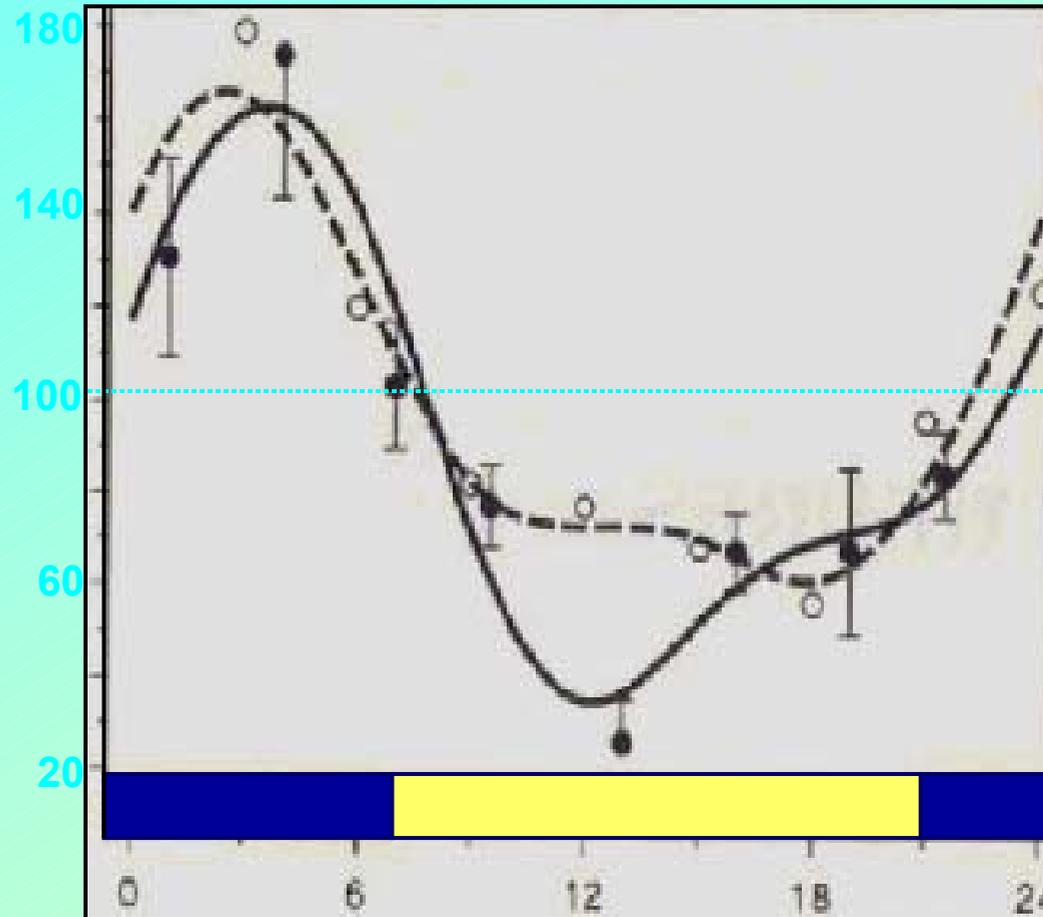
Circadian organisation of cell cycle in humans



Rhythm in [5-FU] disposition despite constant rate infusion



Petit et al., 1988

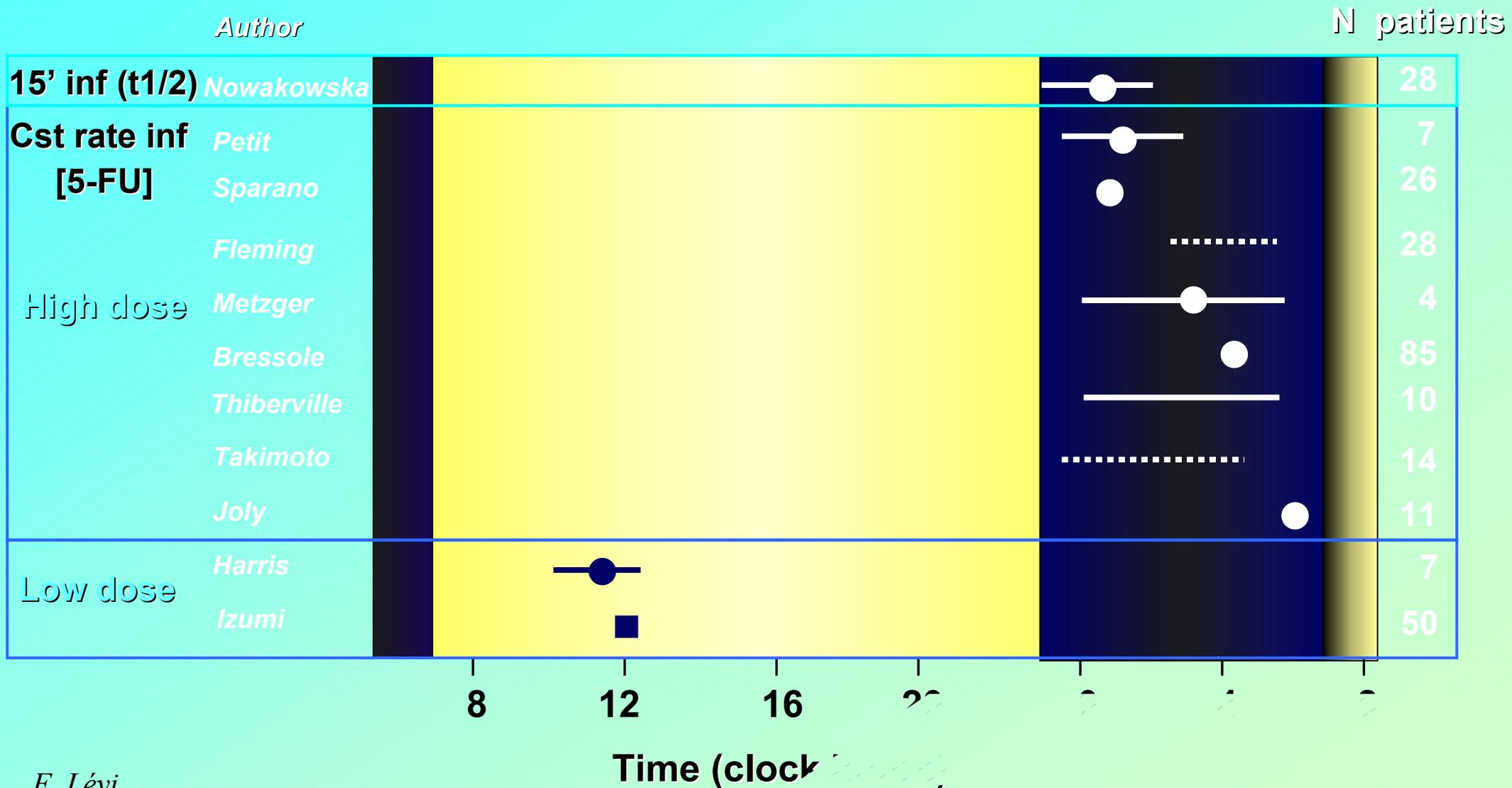


Metzger et al., 1994
Fleming et al., 1994

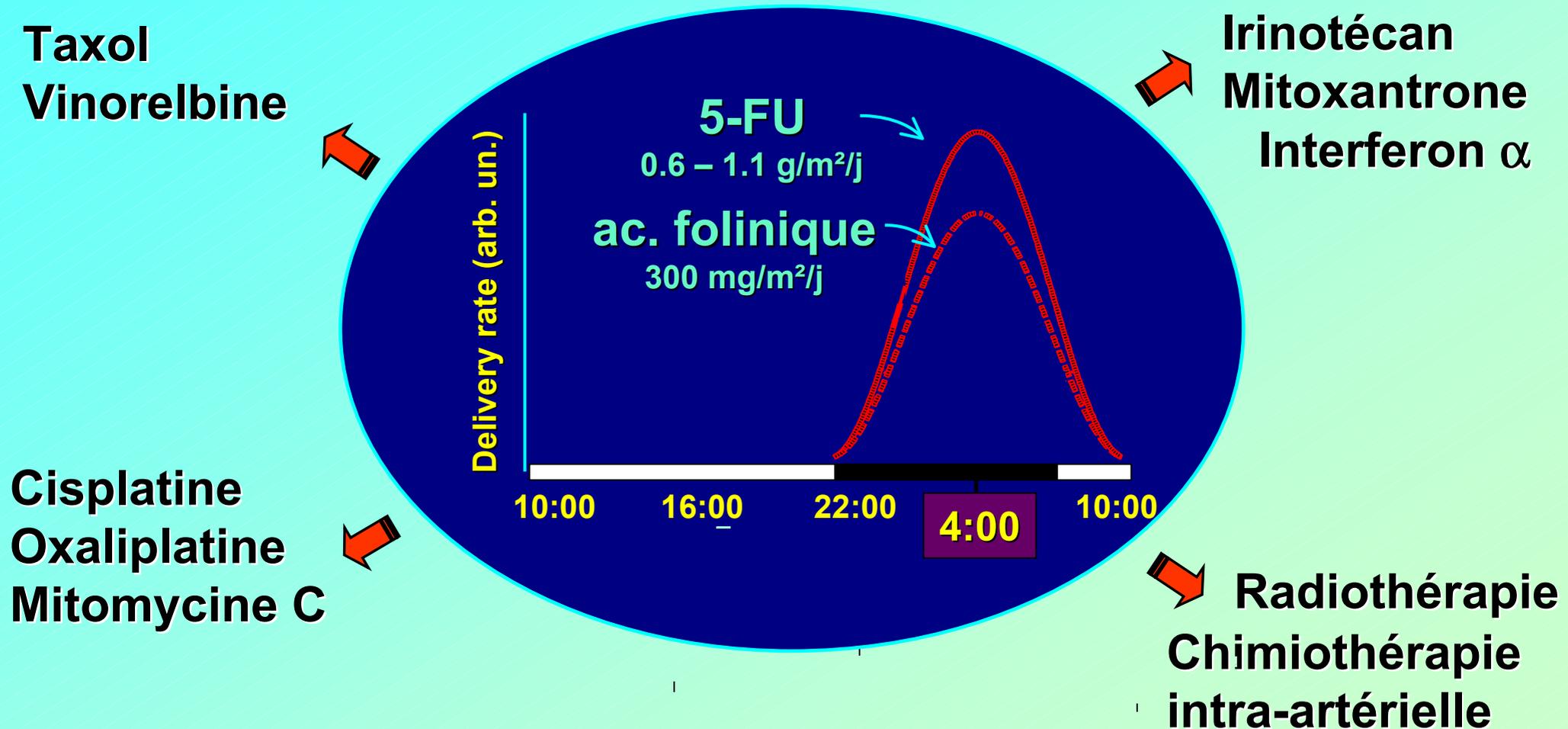
Time (clock hours)

Rhythms in anticancer drug metabolism and disposition.

Rhythm in [5-FU] disposition (270 patients)



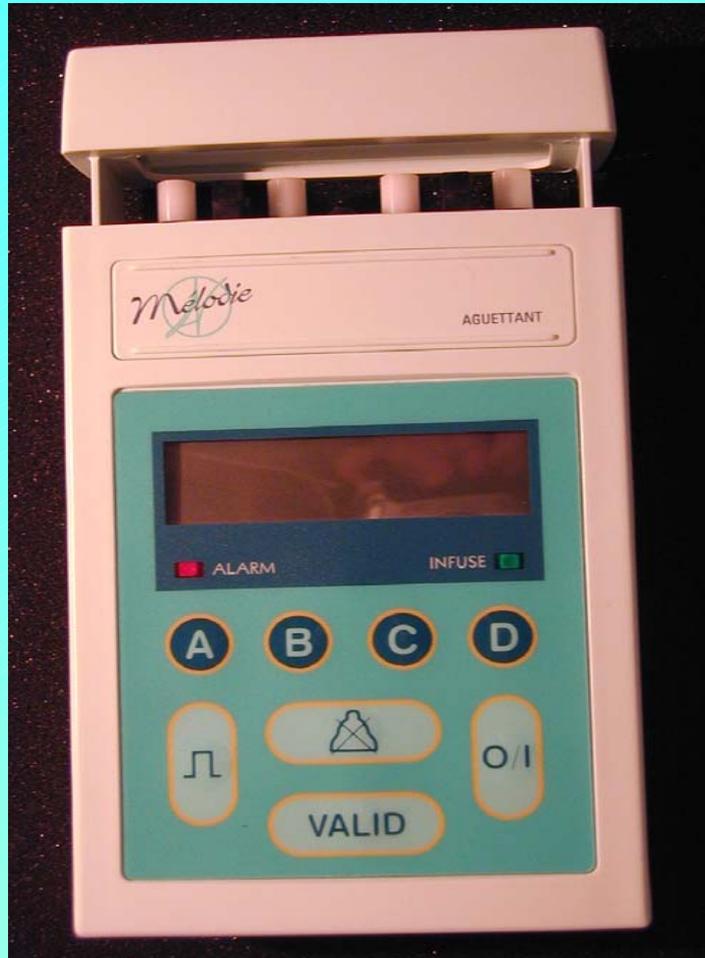
Développement chronothérapeutique du 5-fluorouracile



Phase I, II & III chez >

Développement chronothérapeutique

Injecteur multivoies pour chronothérapie



- Programmation centralisée
- Modulation de débit
- 4 réservoirs (100-2000 ml)
- 2 voies indépendantes
- Débits de 1 à 3000 ml/h

- Sécurité
- Alarmes
- Rapports de perfusion
- Traçabilité

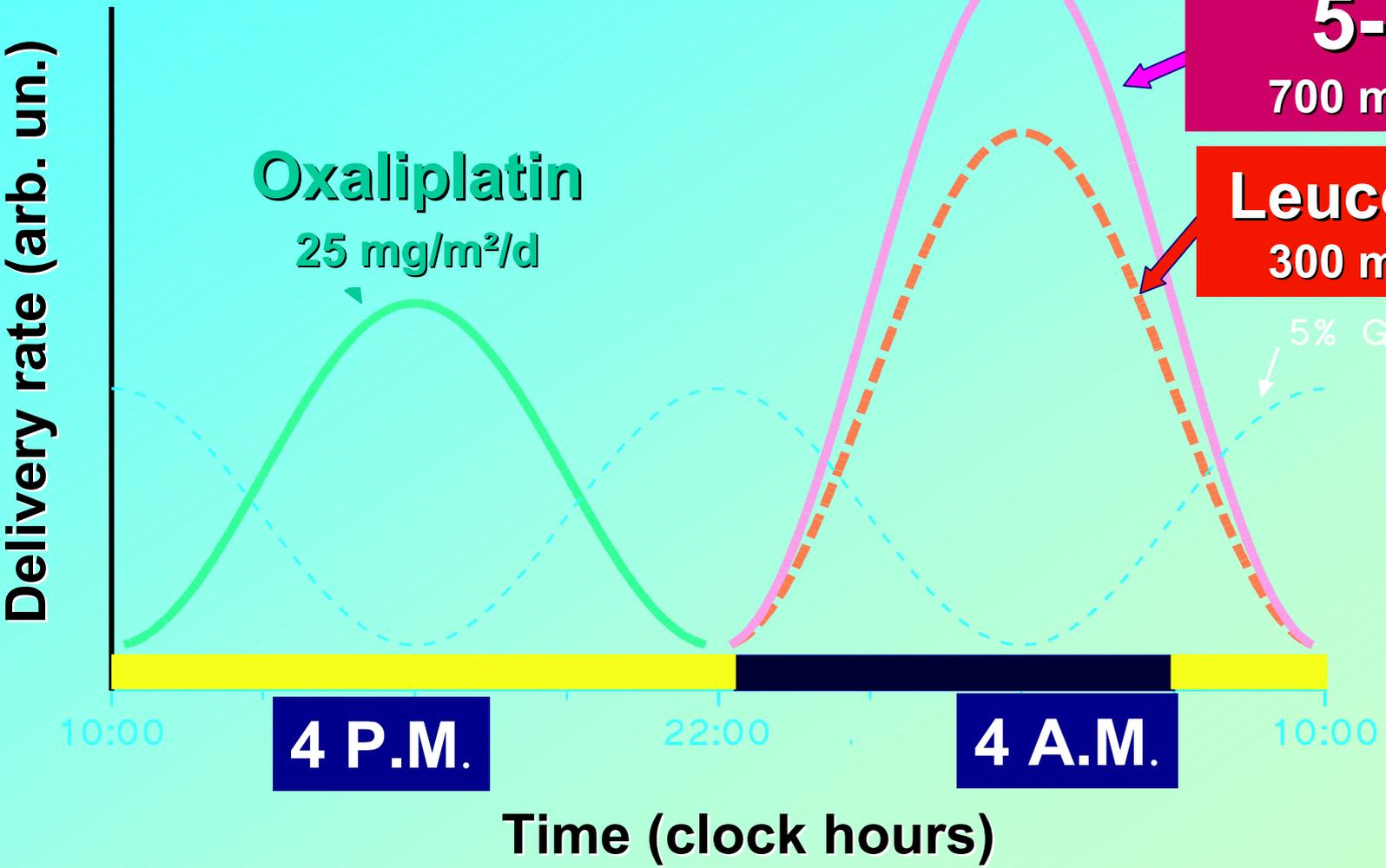
Chonotherapy of gastrointestinal malignancies



Chemotherapy of gastrointestinal malignancies

Fluorouracil modulated 5-FU-LV-I-OHP
in patients with metastatic colorectal cancer

12 weeks (FFL5-16)



5-FU
700 mg/m²/d

Leucovorin
300 mg/m²/d

Oxaliplatin
25 mg/m²/d

Phase II
ORR :
58%
*Lévi et al.,
Cancer 1992*

Développement chronothérapeutique

Association 5-FU-AF-I-OHP (79 patients)

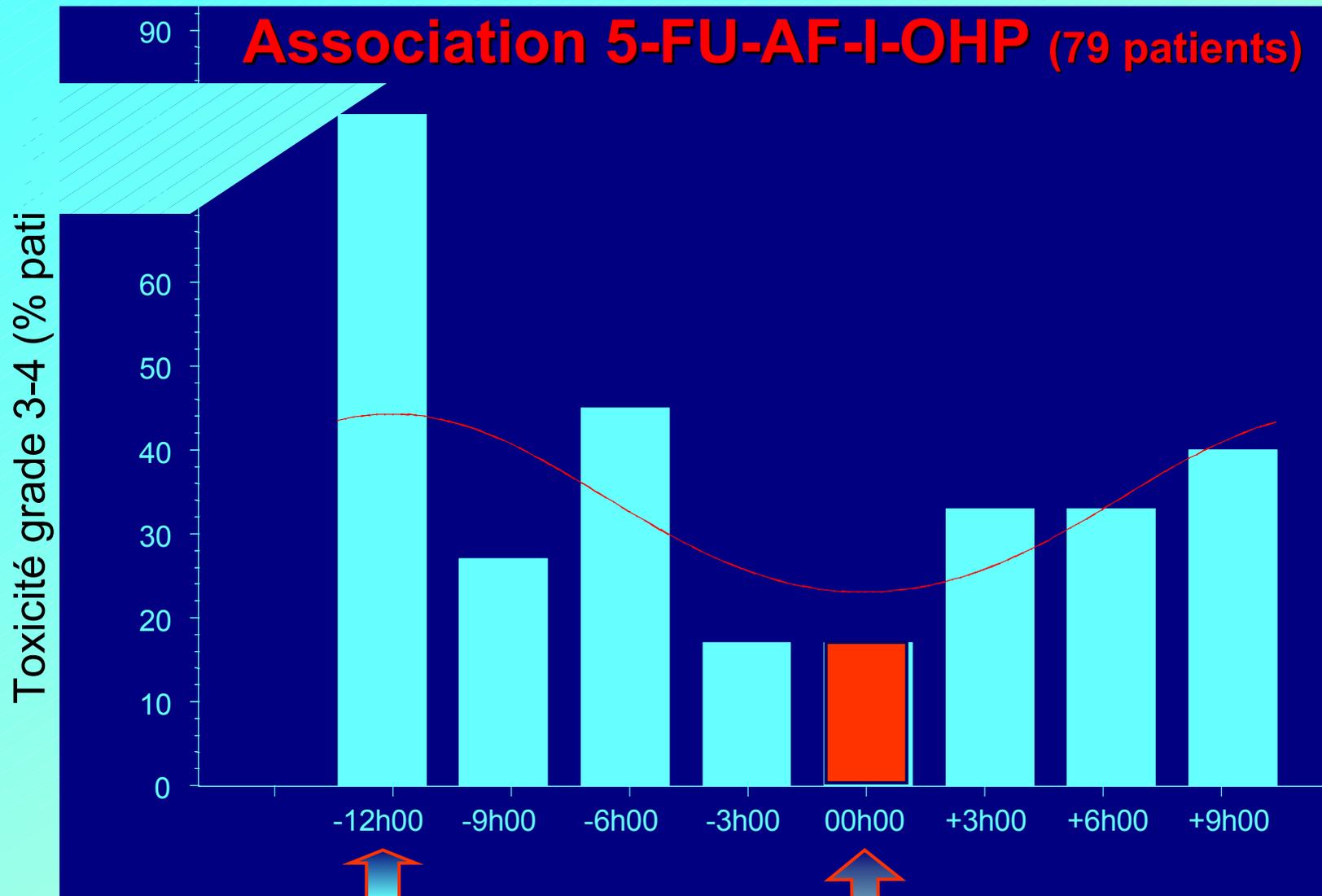
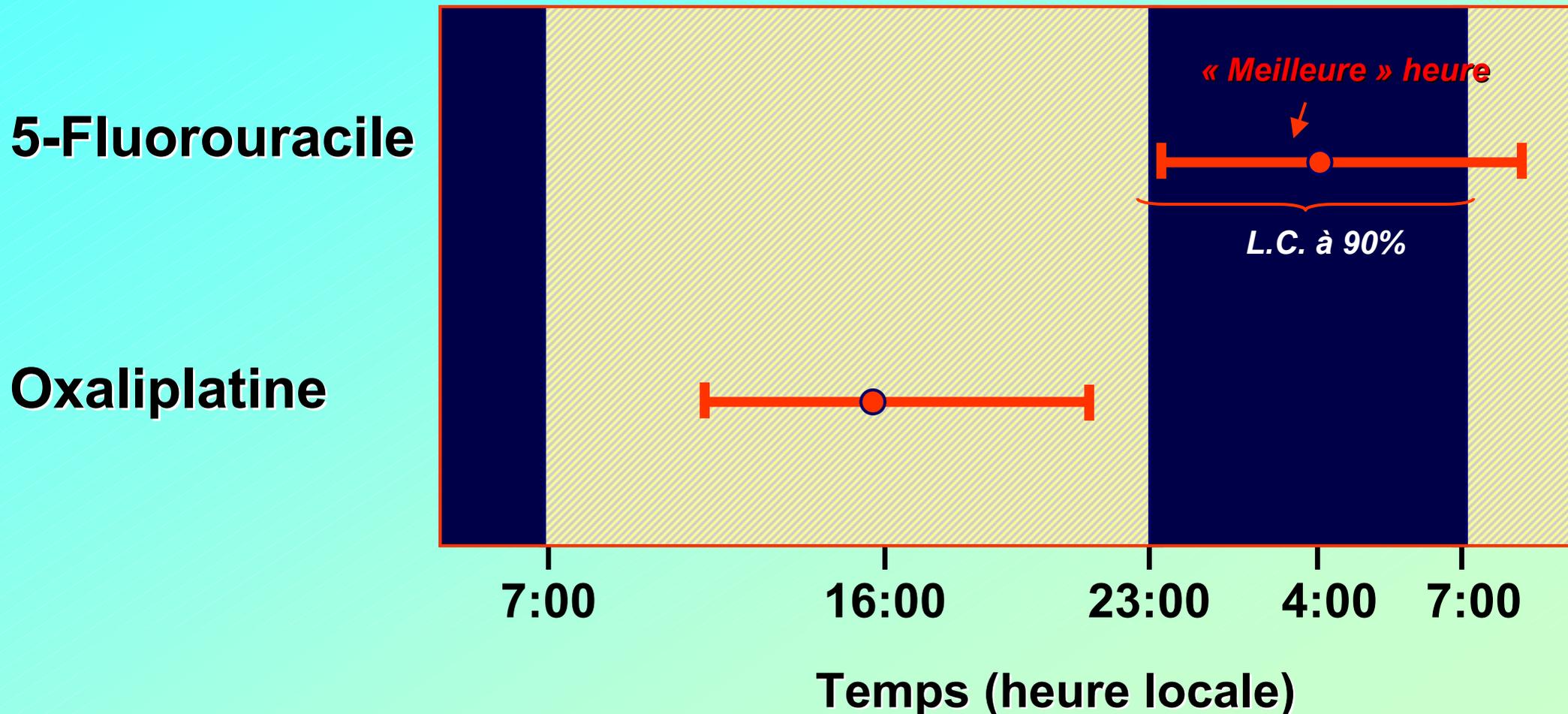


Schéma chrono opposé

Schéma chrono de référence

Développement chronothérapeutique

Emplacement du pic de débit chronomodulé pour une tolérance optimale (méthode du bootstrap)



Développement chronothérapeutique

Association 5-FU-AF-I-OHP

278 patients avec métastases de cancer colorectal

R

Débit constant

5-FU : 600 - 700 mg/m²/j

Ac Fol : 300 mg/m²/j

Oxaliplatine : 20-25 mg/m²/j

Chronothérapie

Cycle de 5 jours, puis 16 j de repos

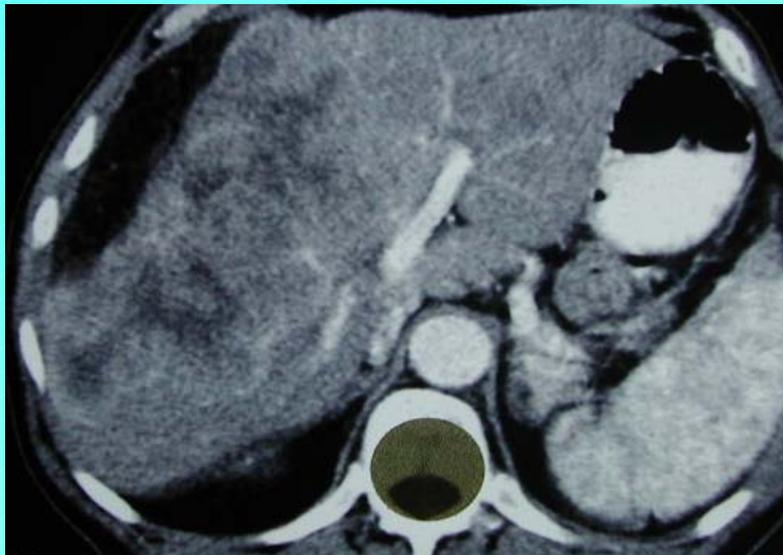
16:00

04:00

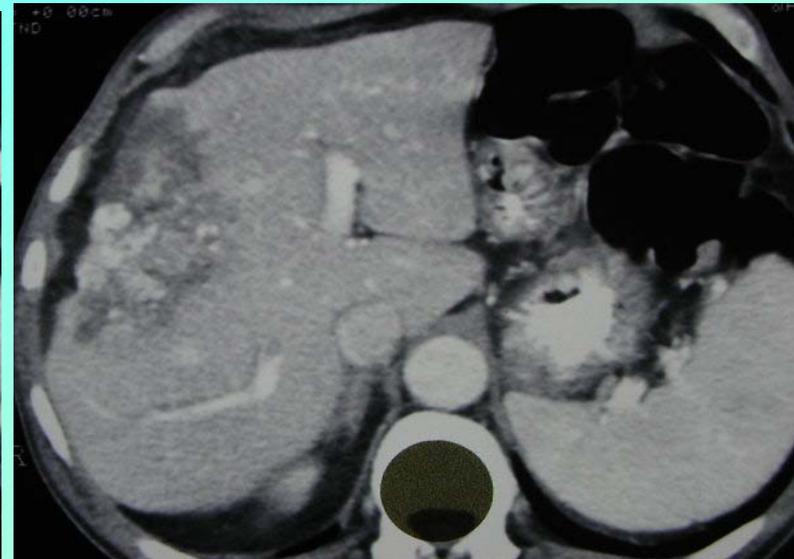
Temps (heure locale)

Développement chronothérapeutique

Association 5-FU-AF-I-OHP



ACE = 301 ng/ml
Avant 1er cycle



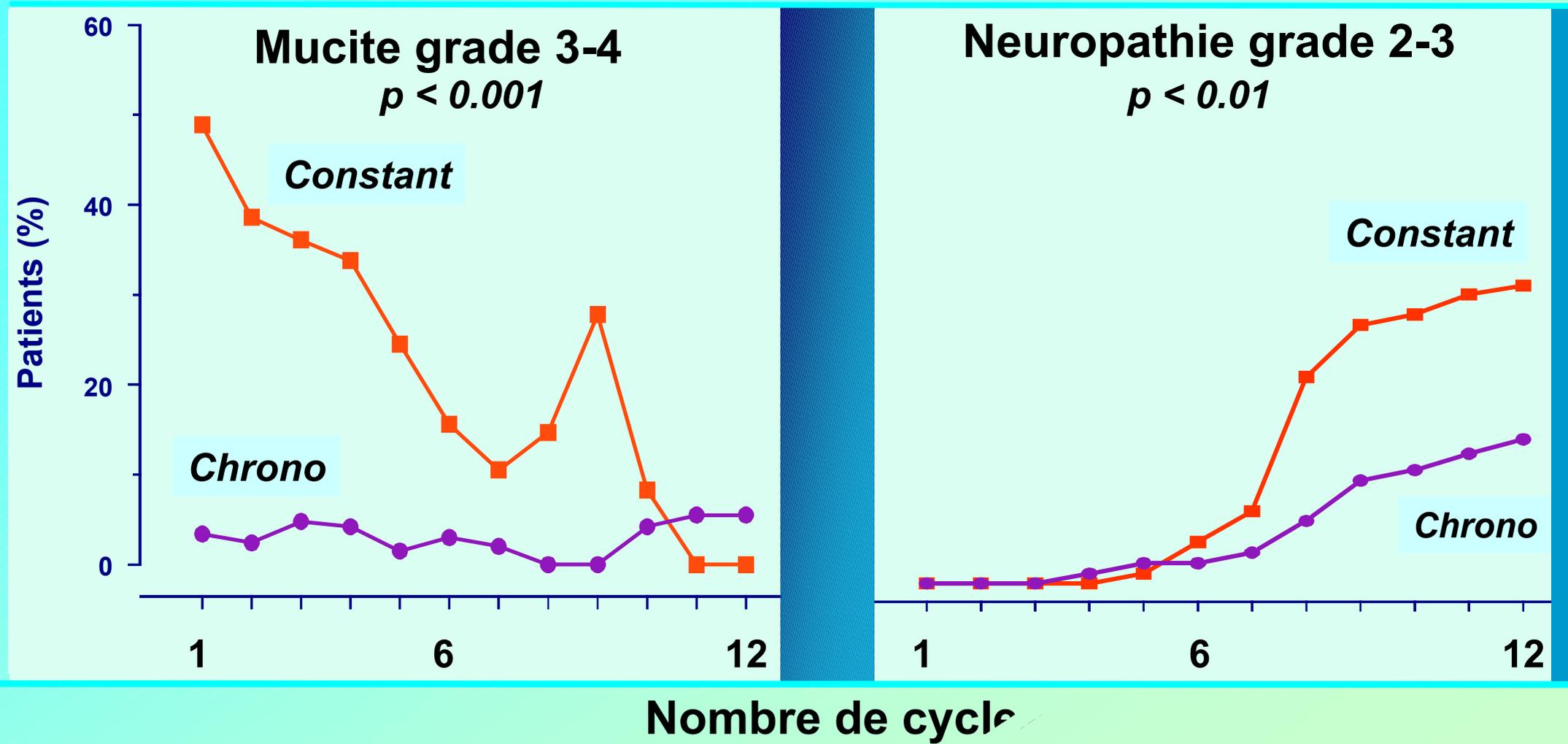
ACE = 27 ng/ml
Après 7 cycles

Critère principal : taux de réponses objectives

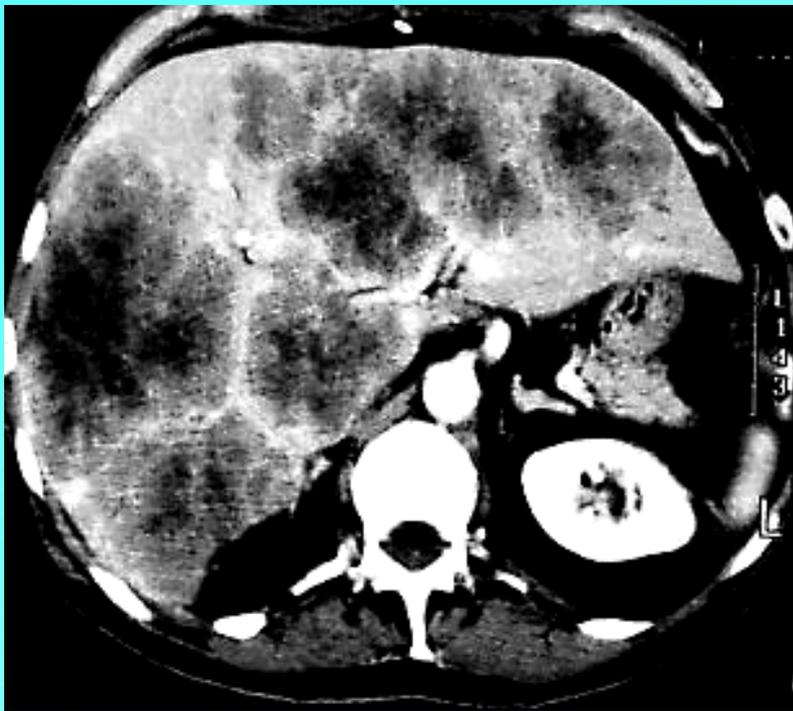
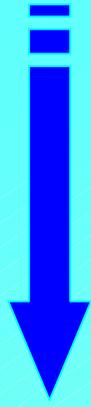
Perfusion constante	30%	p < 0.001
Chronothérapie	51%	

Développement chronothérapeutique

Association 5-FU-AF-I-OHP

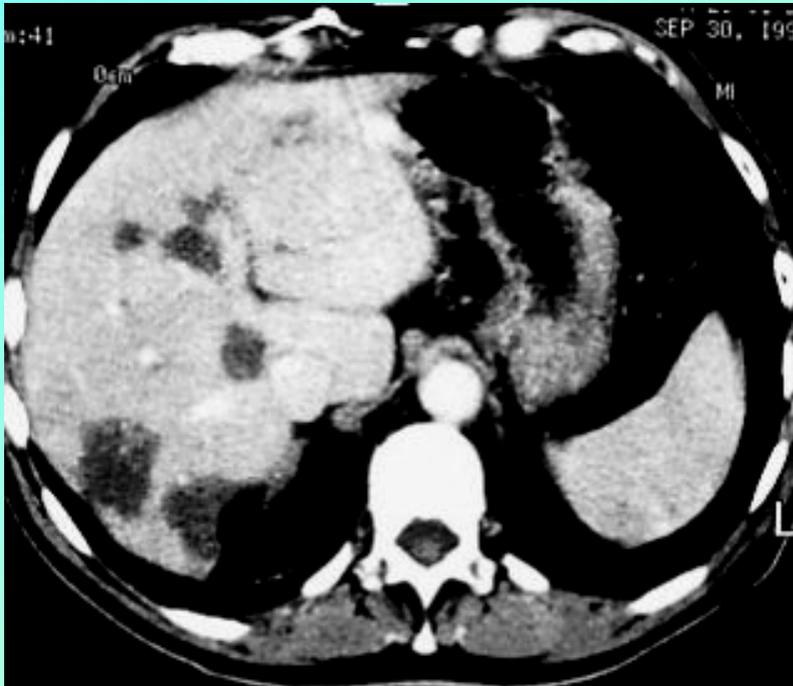


Inclusion



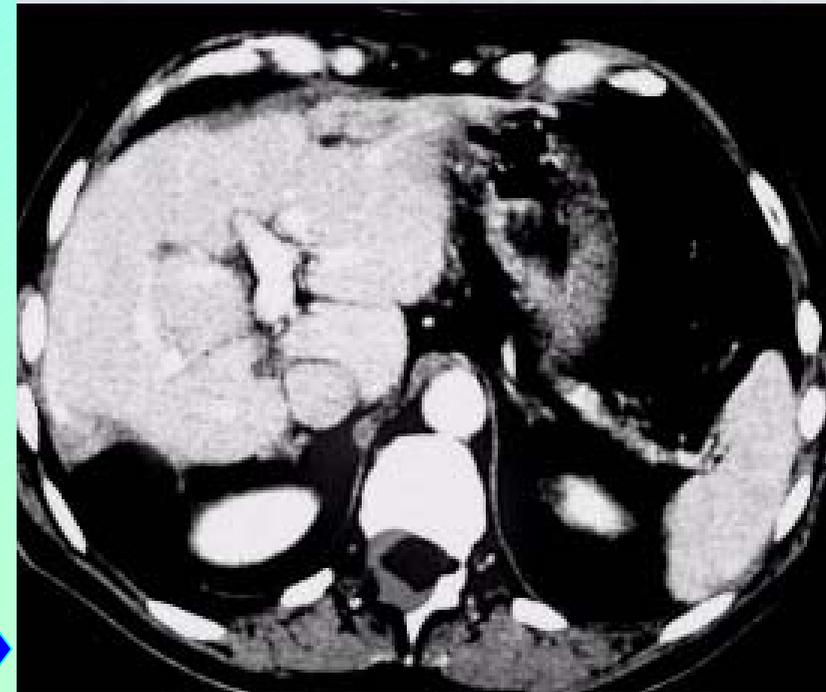
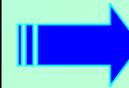
After 10 courses

PR



Partial hepatectomy

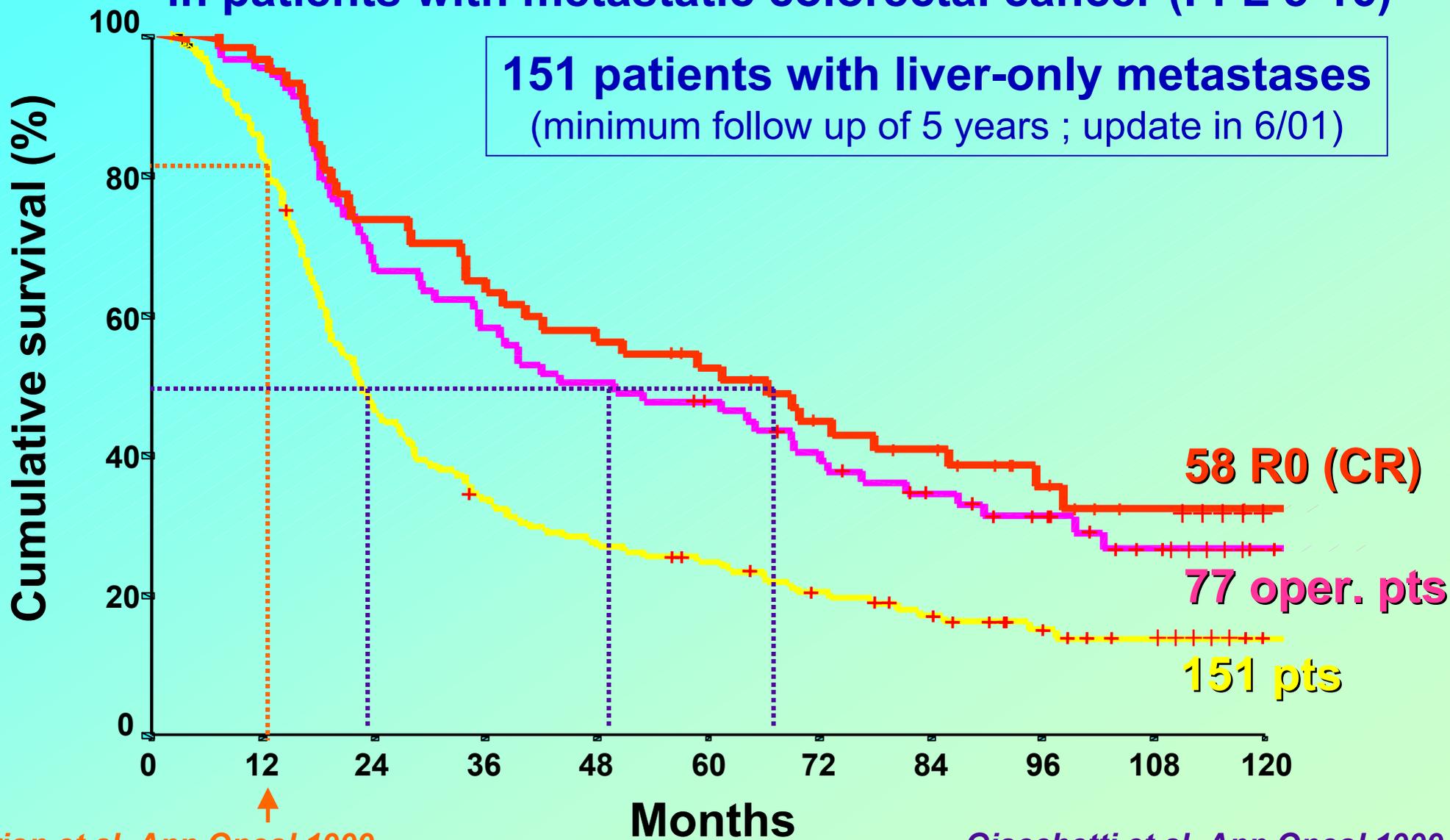
**Complete
macroscopic resection**



Alive at 5 years

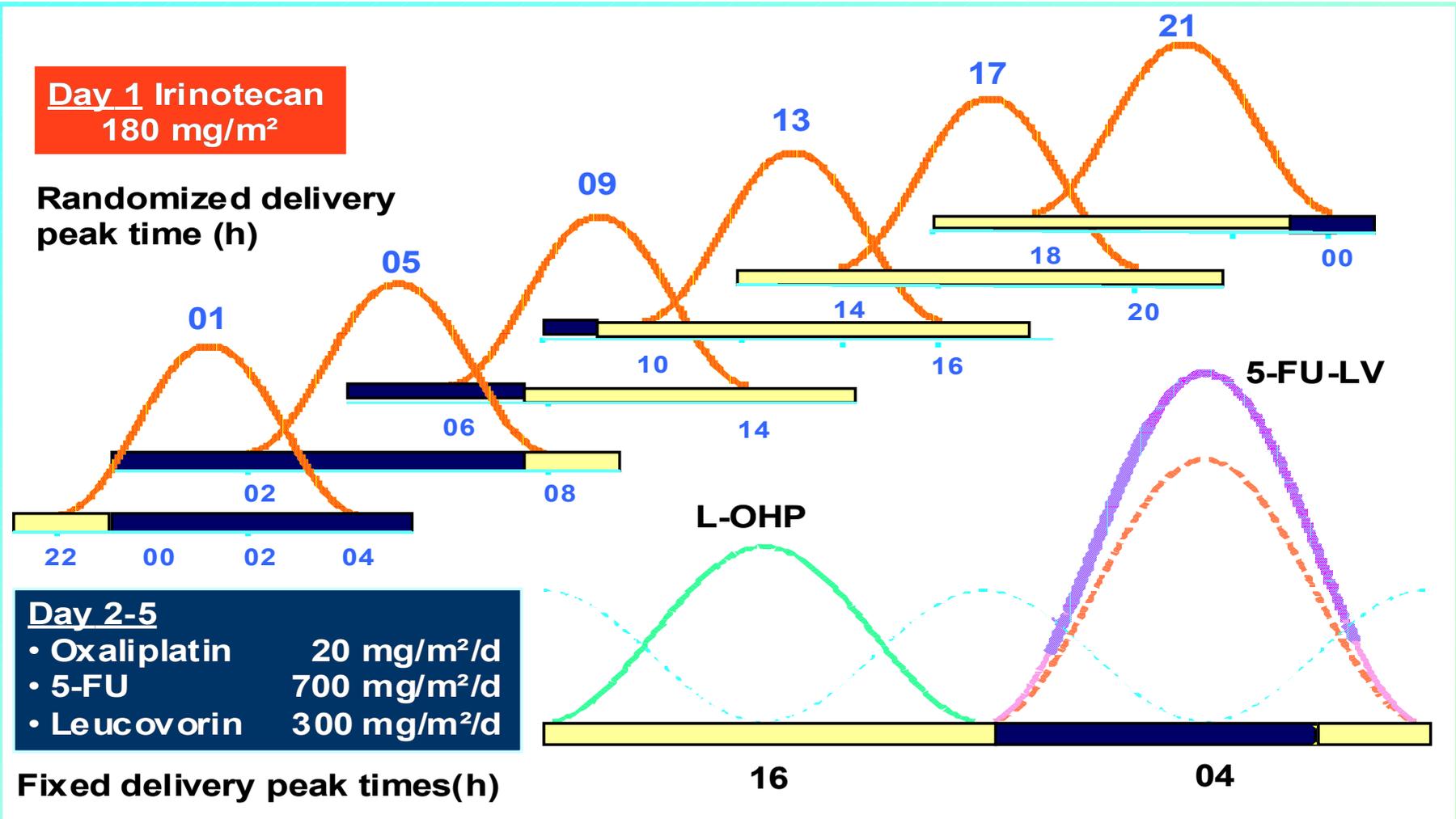
First to third line chronomodulated 5-FU-LV-I-OHP in patients with metastatic colorectal cancer (FFL 5-16)

151 patients with liver-only metastases
(minimum follow up of 5 years ; update in 6/01)



Trial Design: Optimal Time Finding Design

First or 2nd line chemotherapy for colorectal cancer metastases



EORTC 05011 (C. Garufi, Rome) : 200 patients planned

Concepts developed with chronotherapy for patients with metastatic colorectal cancer

- ① Introduction of a new agent in the standard treatment of MCC : oxaliplatin (L-OHP)**
- ② Role of treatment intensification on tumor response rate**
- ③ New medico-surgical strategy : resection of metastases (R0) after effective chemotherapy**
- ④ Circadian rhythms as prognostic factors**

Performance status (WHO), Main prognostic factor of survival

0 Able to carry out normal activity without restriction

I Restricted in physically strenuous activity
but ambulatory and able to do light work.

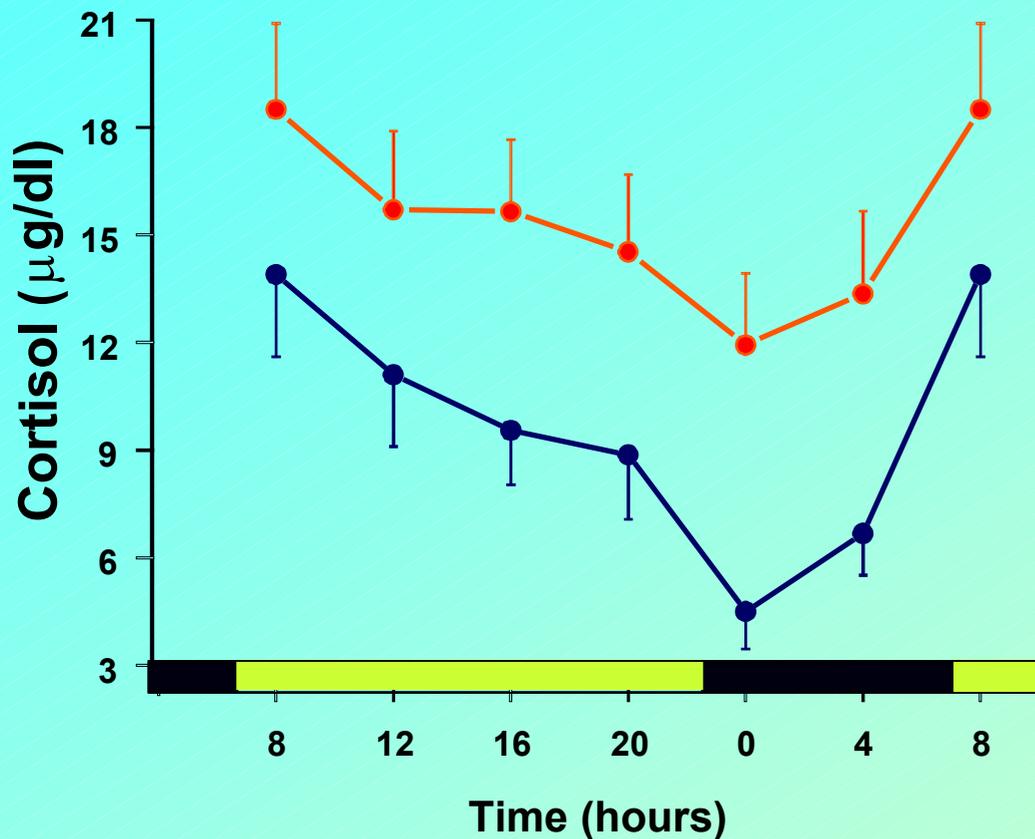
II Ambulatory and capable of self-care
but unable to carry out any work.
Up and about >50% of waking hours

III Capable of only limited self-care,
confined to bed or chair > 50% of waking hours

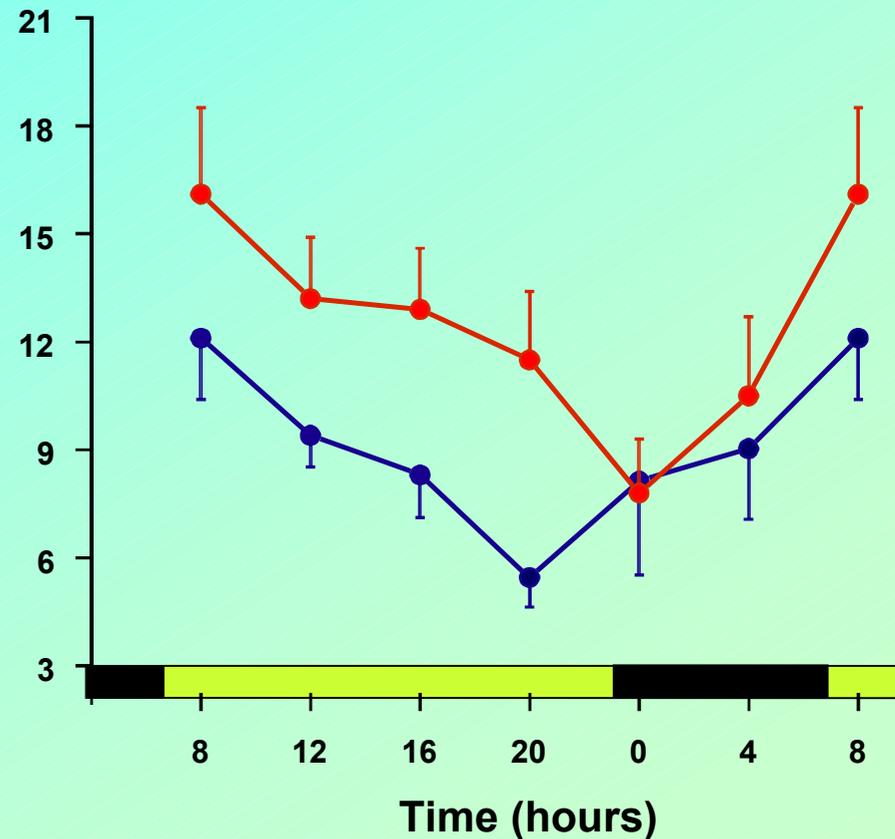
IV Completely disabled. Cannot carry on any self-care.
Totally confined to bed or chair

Plasma cortisol according to performance status

Stage III-IV ovarian cancer
(20 patients)



Stage IV breast cancer
(13 patients)



Performance status

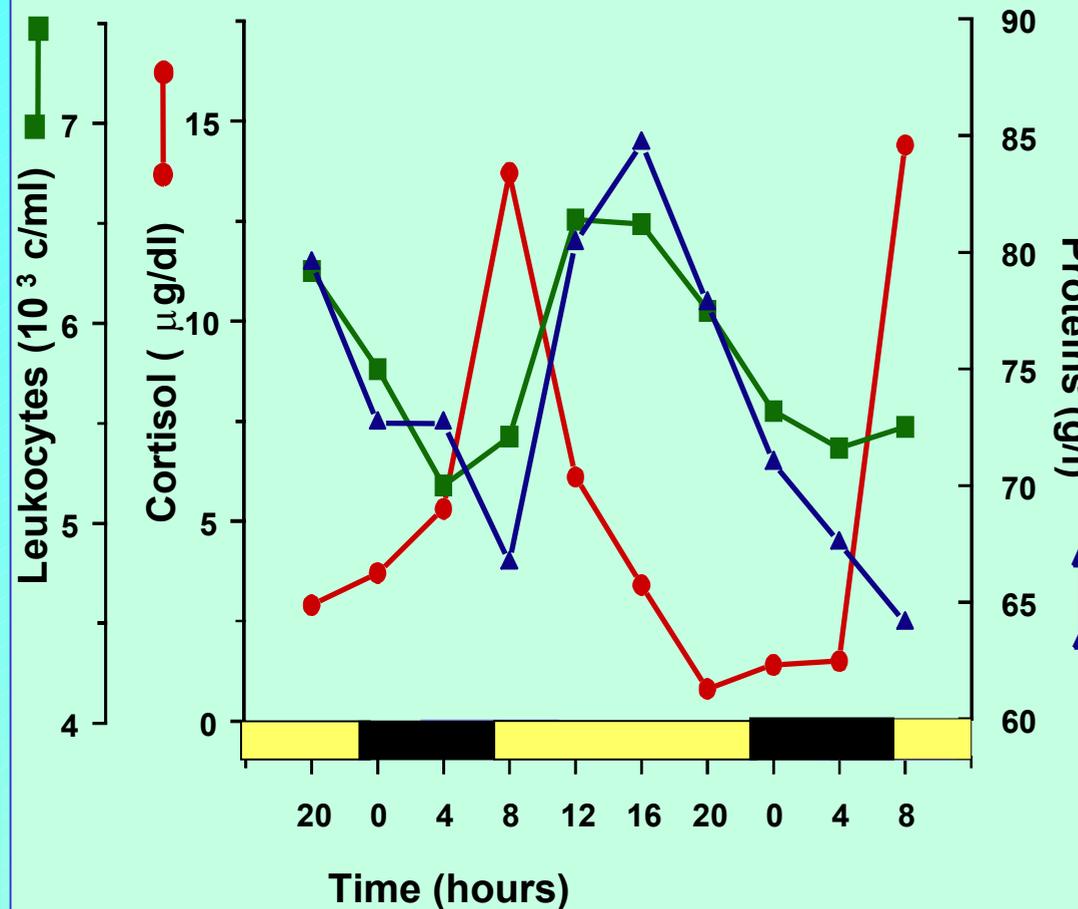
●—● 0-I

●—● II-IV

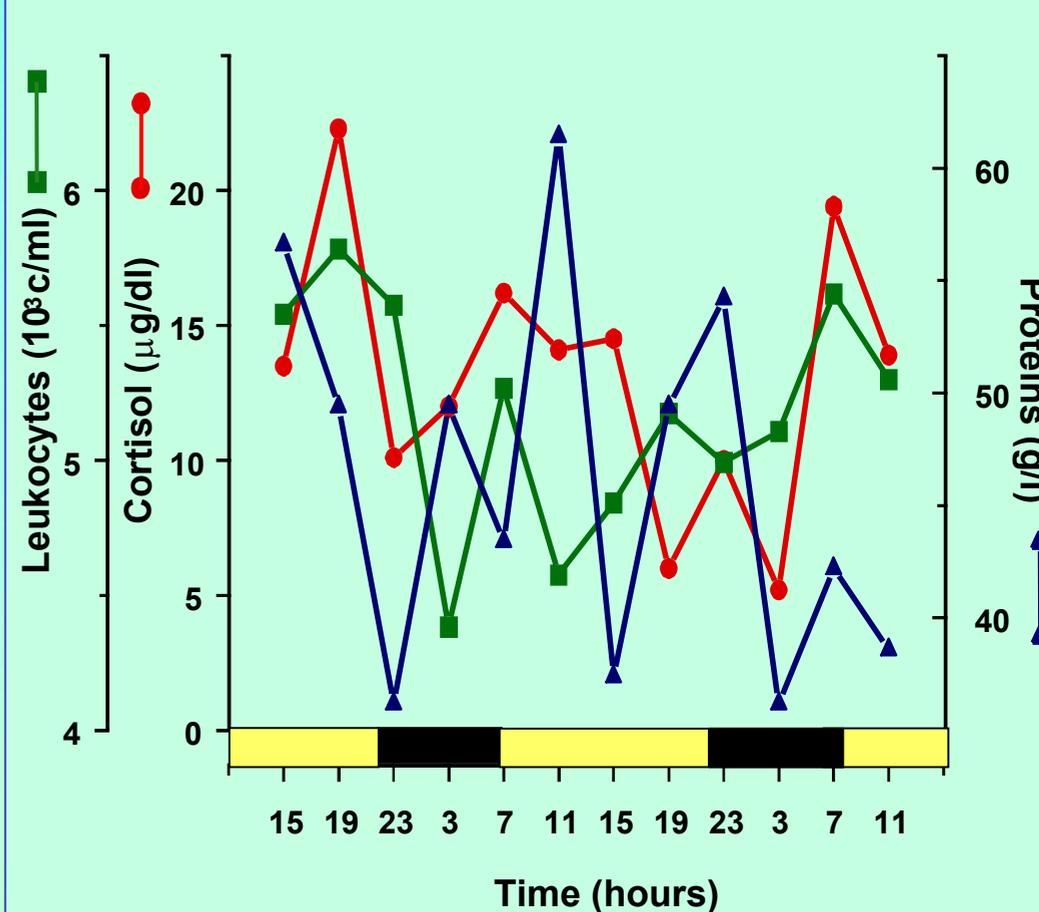
Rhythms as a function of disease status

Stage IV breast cancer

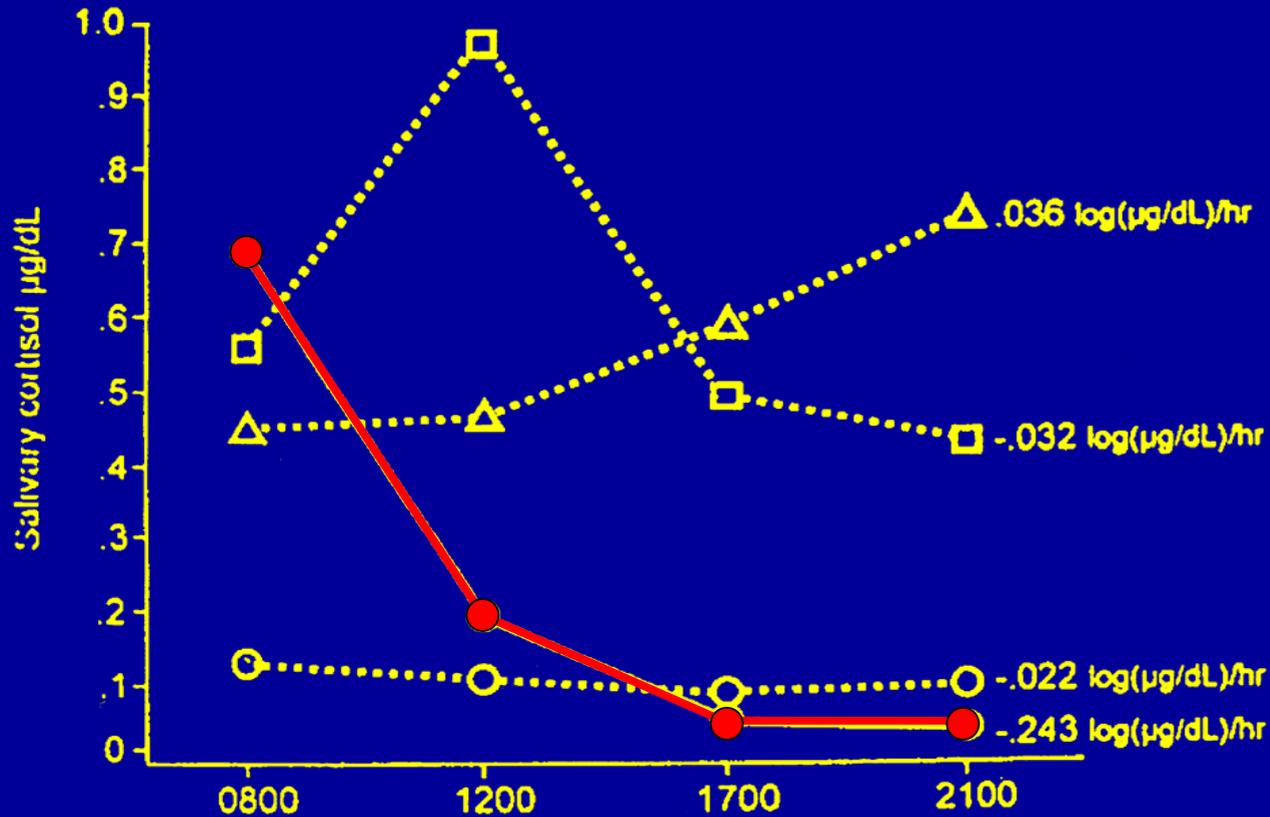
N.C. : 48 y.; PS=I; BONE METASTASES.



JL : 50 y.; PS=III; LIVER, SKIN & LYMPH NODES METASTASES

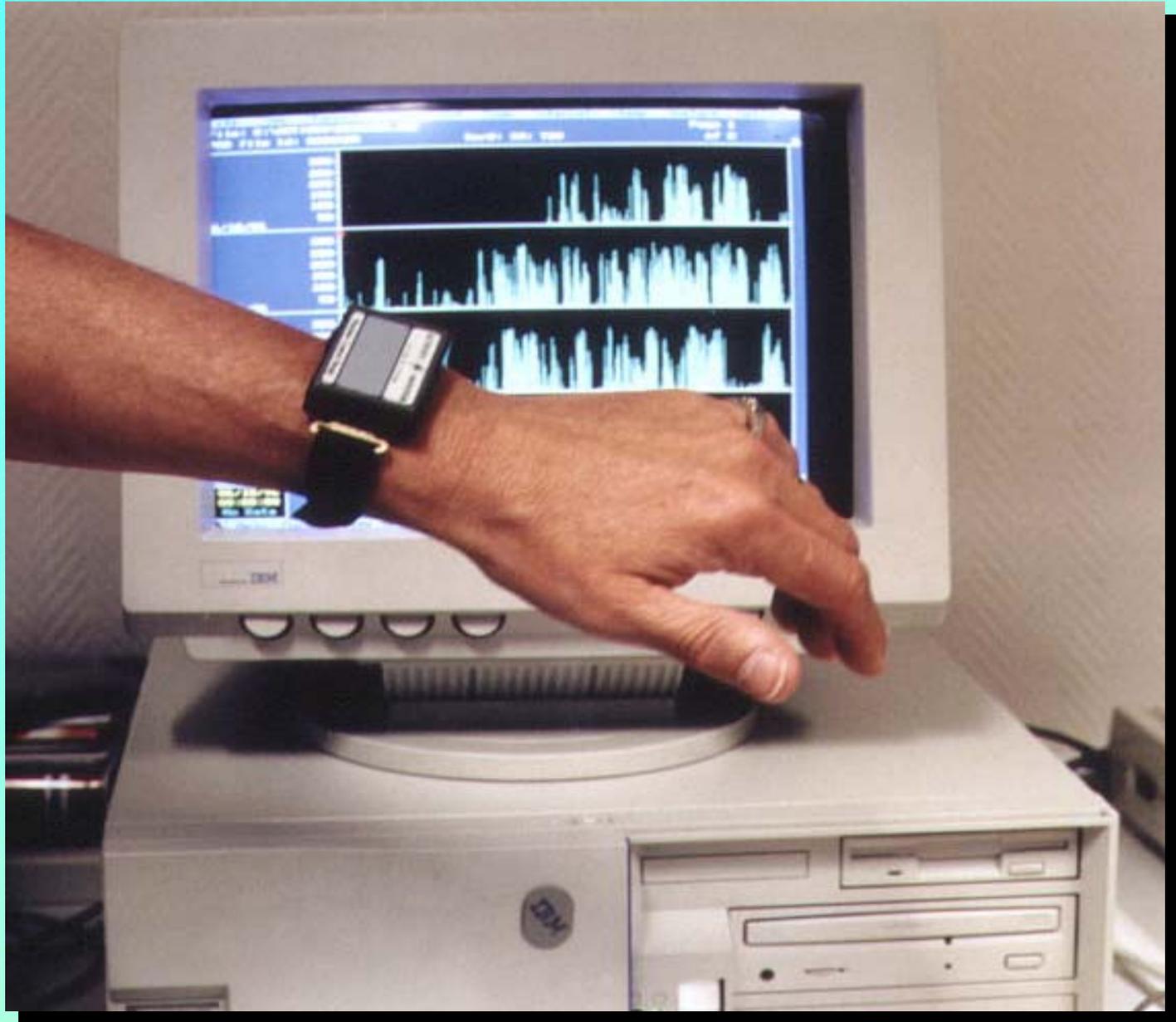


Cortisol circadian pattern prognostic of patient outcome ?



Sampling Time

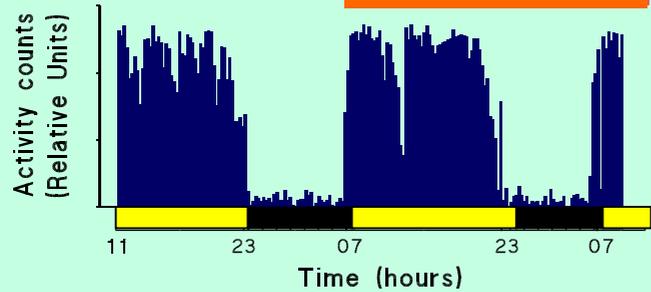
- Sephton et al, 2000
JNCI, 92, 994
- 104 pts with
metastatic breast
cancer
- Salivary cortisol
(diurnal slope)



Altérations du système circadien chez les patients cancéreux

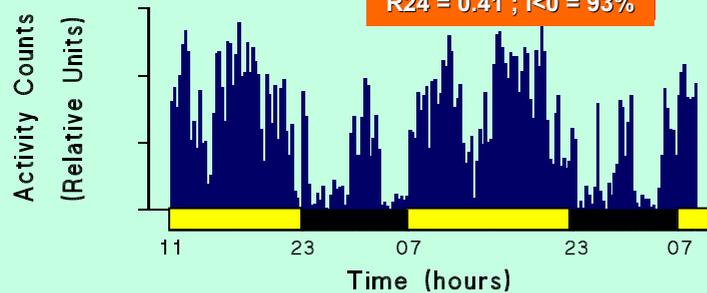
56 y.o. man, PS = 1, colon cancer
3 metastatic sites (liver < 25%)

$R_{24} = 0.71$; $I < 0 = 99\%$



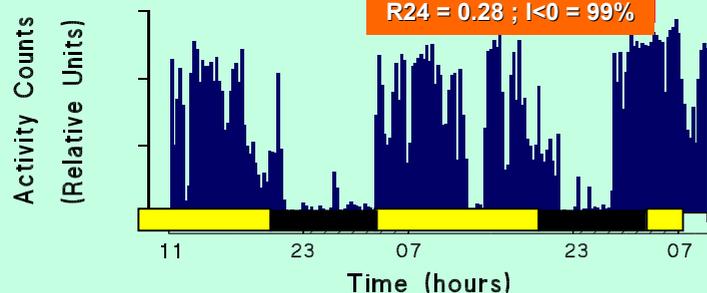
50 y.o. man, PS = 1, rectal cancer
Liver-only metastases (>25%)

$R_{24} = 0.41$; $I < 0 = 93\%$



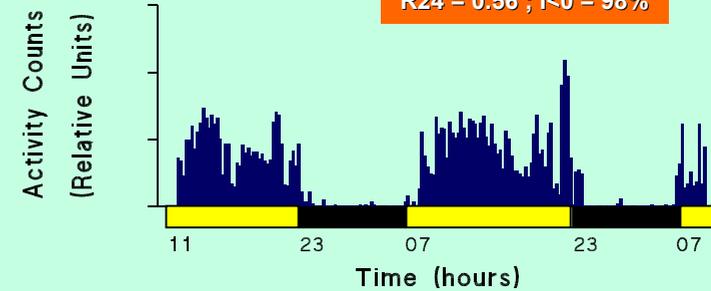
63 y.o. man, PS = 1, colon cancer
1 metastatic site (not liver)

$R_{24} = 0.28$; $I < 0 = 99\%$



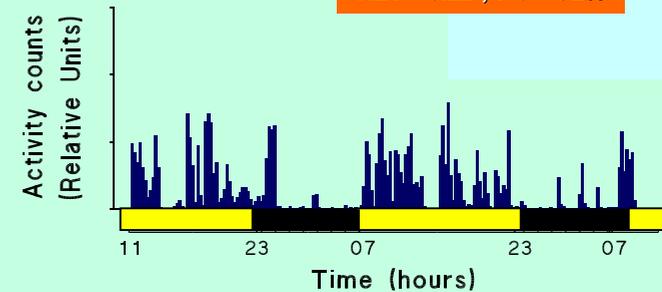
48 y.o. man, PS = 0, rectal cancer
Liver-only metastases (> 25%)

$R_{24} = 0.56$; $I < 0 = 98\%$



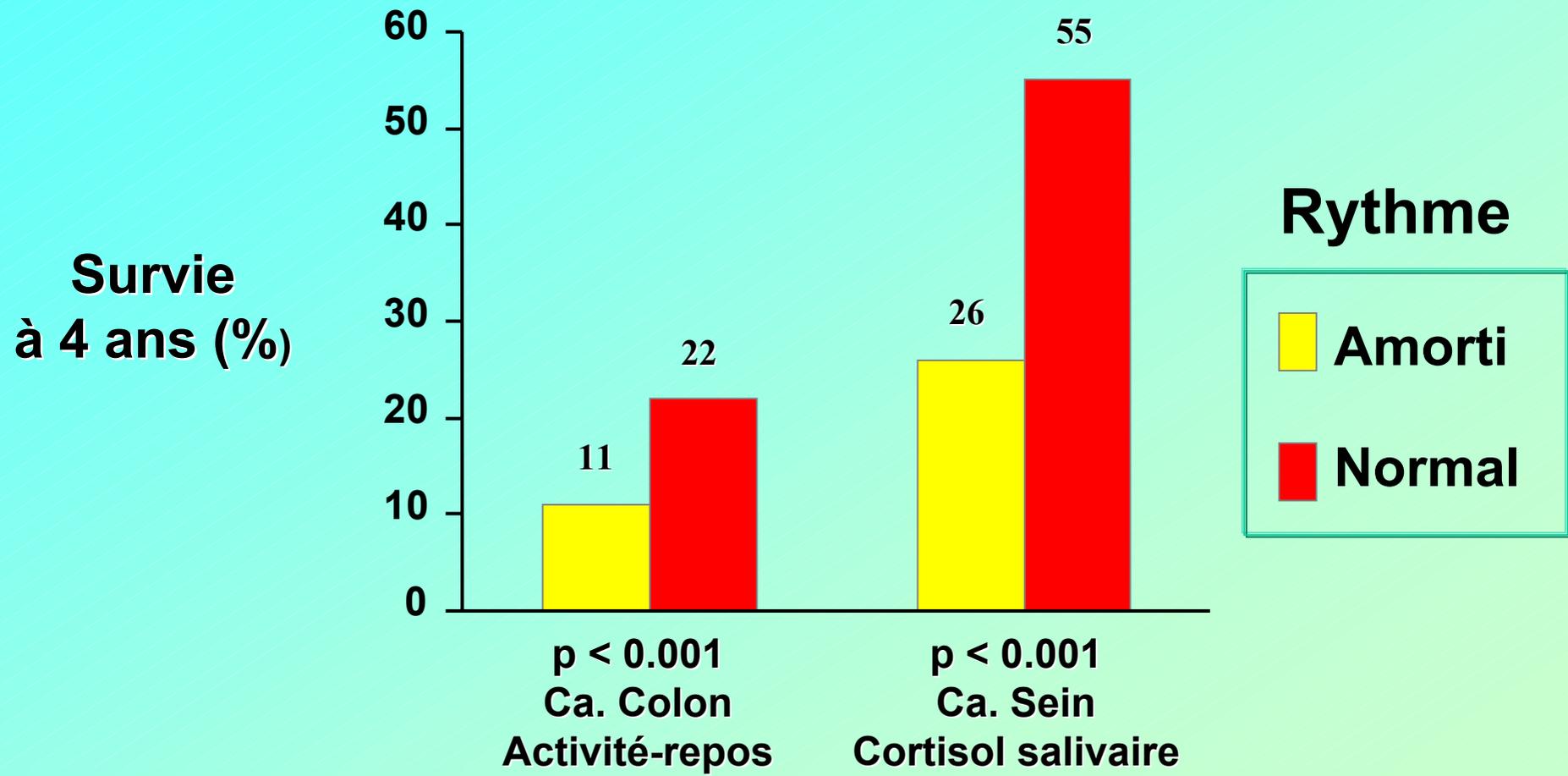
72 y.o. man, PS = 0, rectal cancer
2 metastatic sites (liver < 25%)

$R_{24} = 0.22$; $I < 0 = 92\%$



200 patients avec
Cancer colorectal métastatique

L'horloge circadienne comme cible thérapeutique en cancérologie



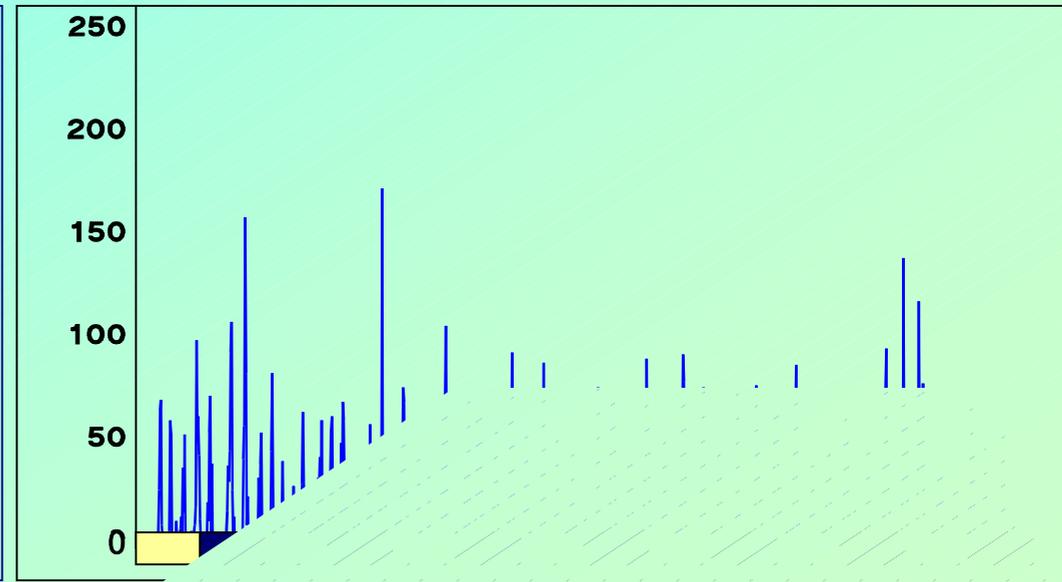
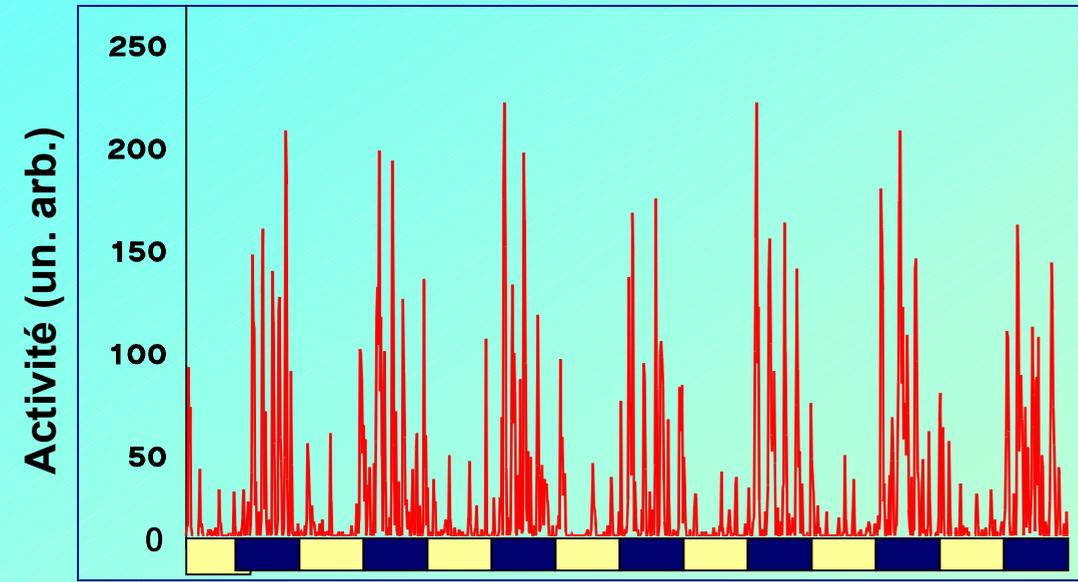
Mormont et al. Clin Cancer Res 2000 ; Sephton et al. JNCI 2000

L'horloge circadienne comme cible thérapeutique

Témoin



NSC*

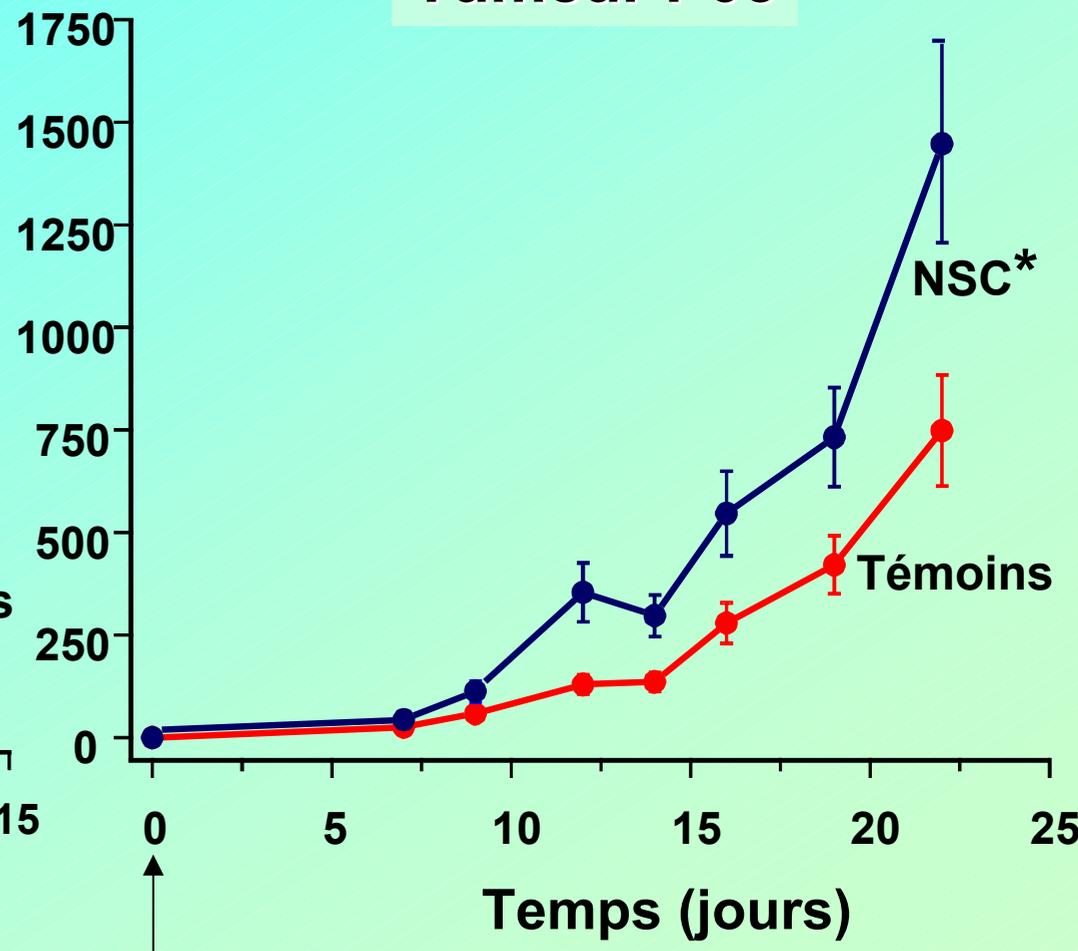
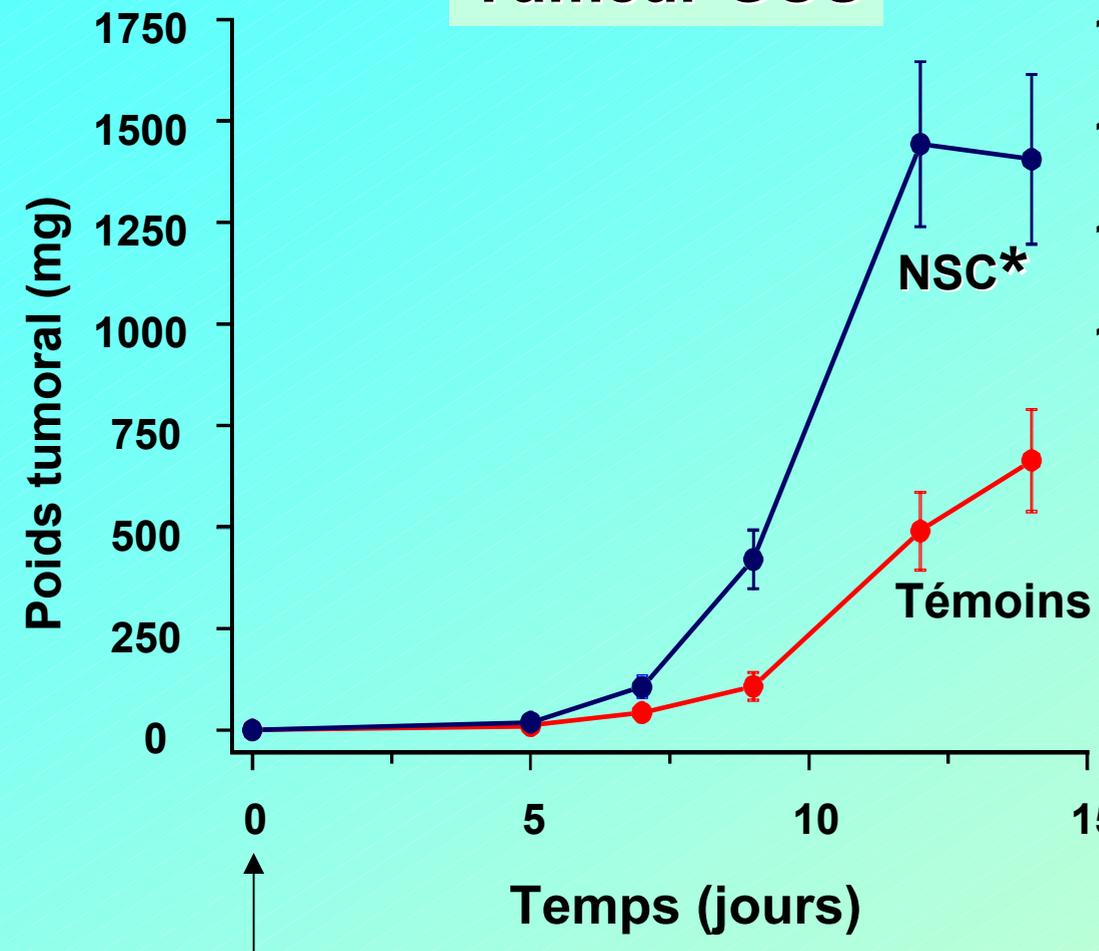


Temps (jours)

L'horloge circadienne comme cible thérapeutique

Tumeur GOS

Tumeur P03



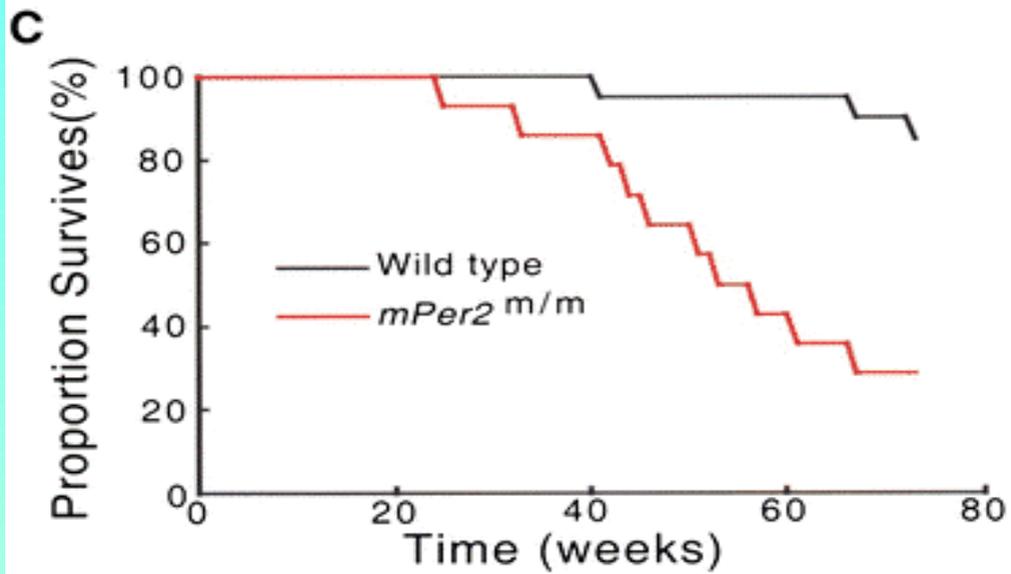
ANOVA, $p = 0.004$

ANOVA, $p = 0.001$

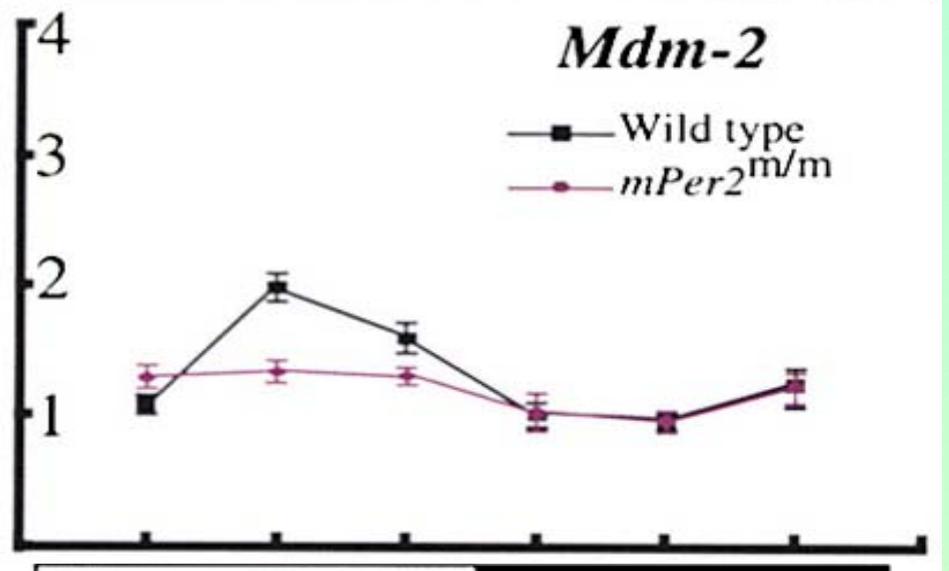
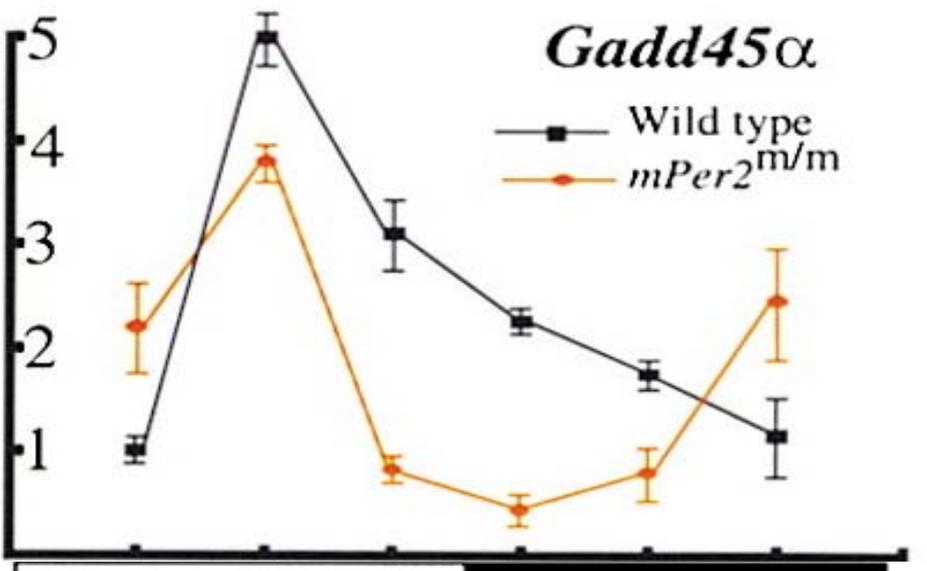
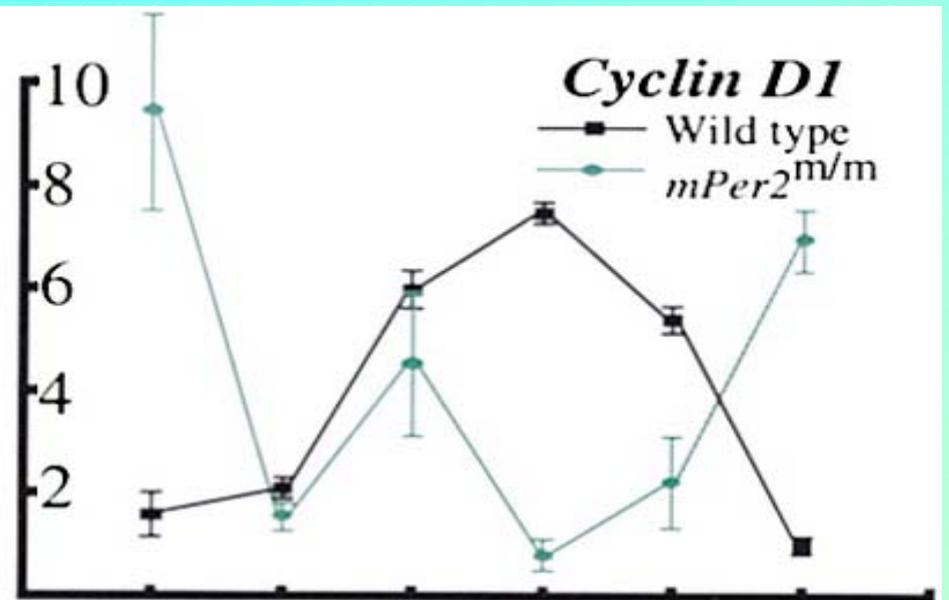
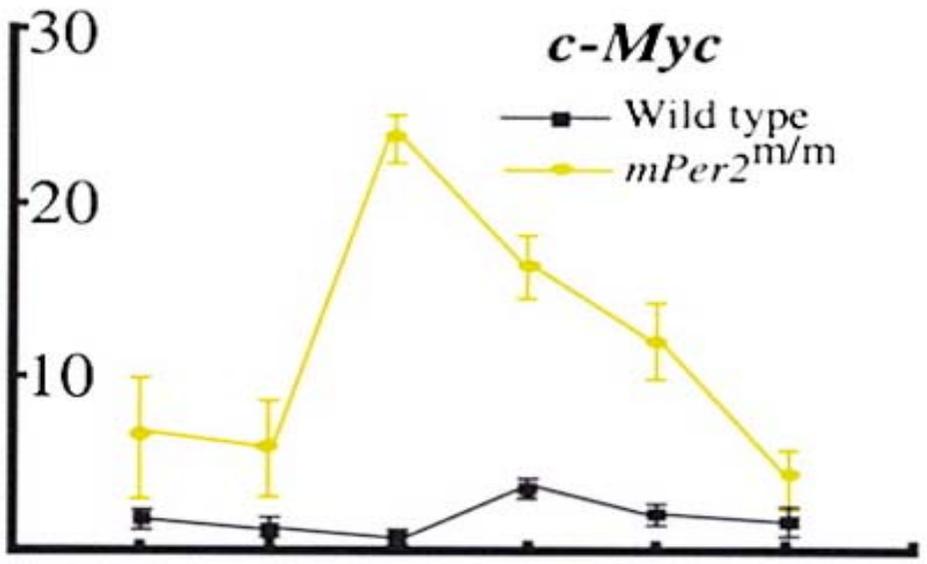
**Copyright © 2002 Cell Press.
Cell, Vol 111, 41-50, October 2002**

**The Circadian Gene *Period2* Plays an
Important Role in Tumor
Suppression and DNA Damage
Response In Vivo**

**Loning Fu¹, Helene Pelicano², Jinsong
Liu³, Peng Huang², and Cheng Chi
Lee¹**

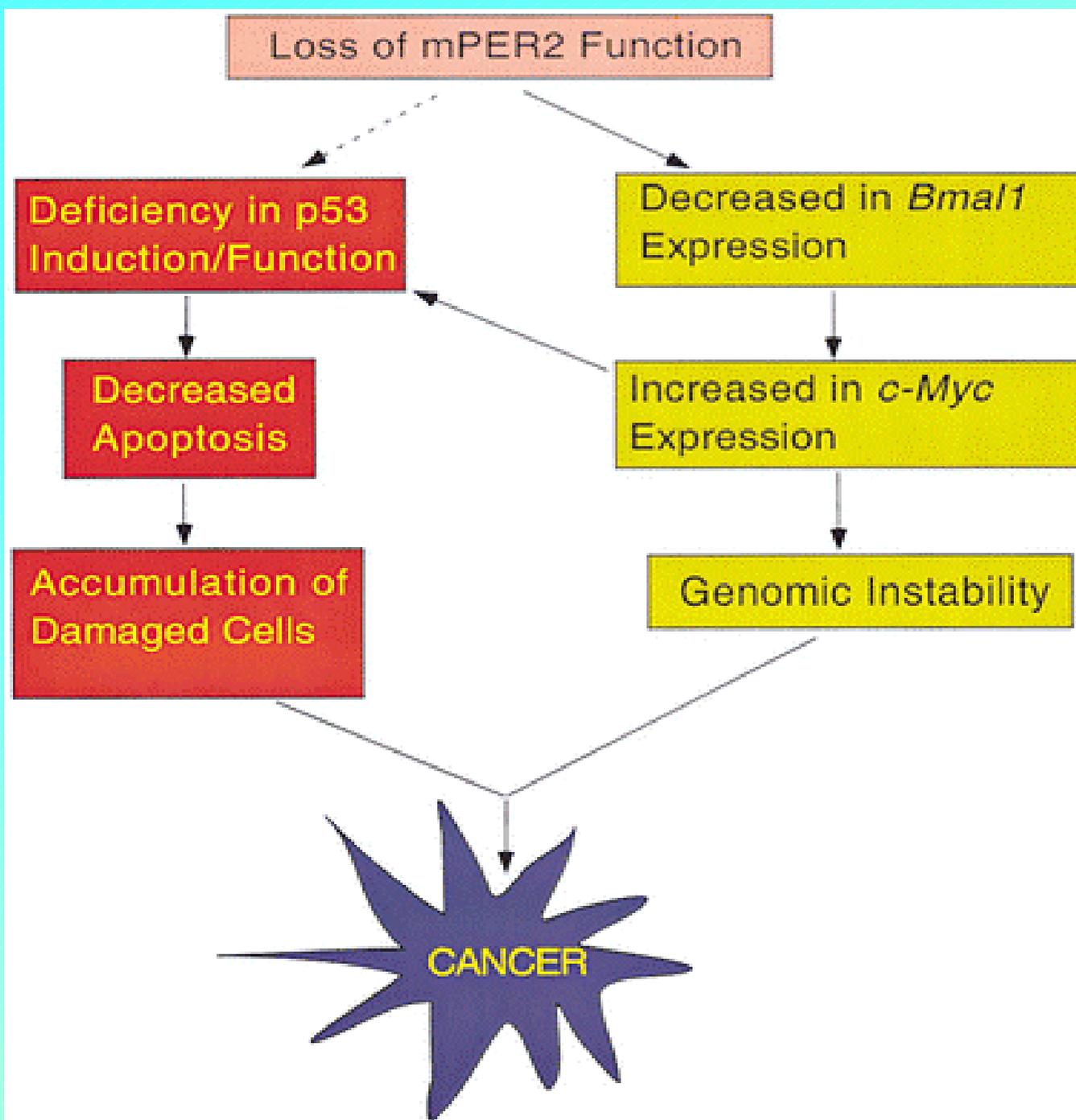


Relative level of mRNA (# of fold)



Zeitgeber Time (ZT)

Zeitgeber Time (ZT)



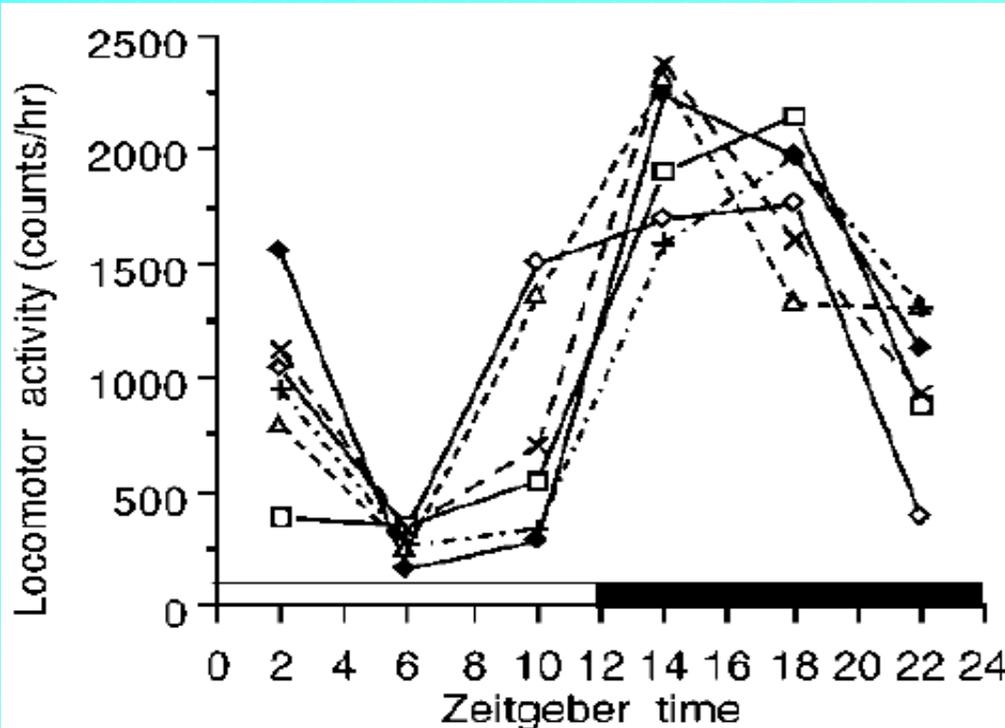
*Fu et al.,
Cell 2002, 111, 41-50*

**Changing the dosing schedule
minimizes the disruptive effects
of interferon on clock function**

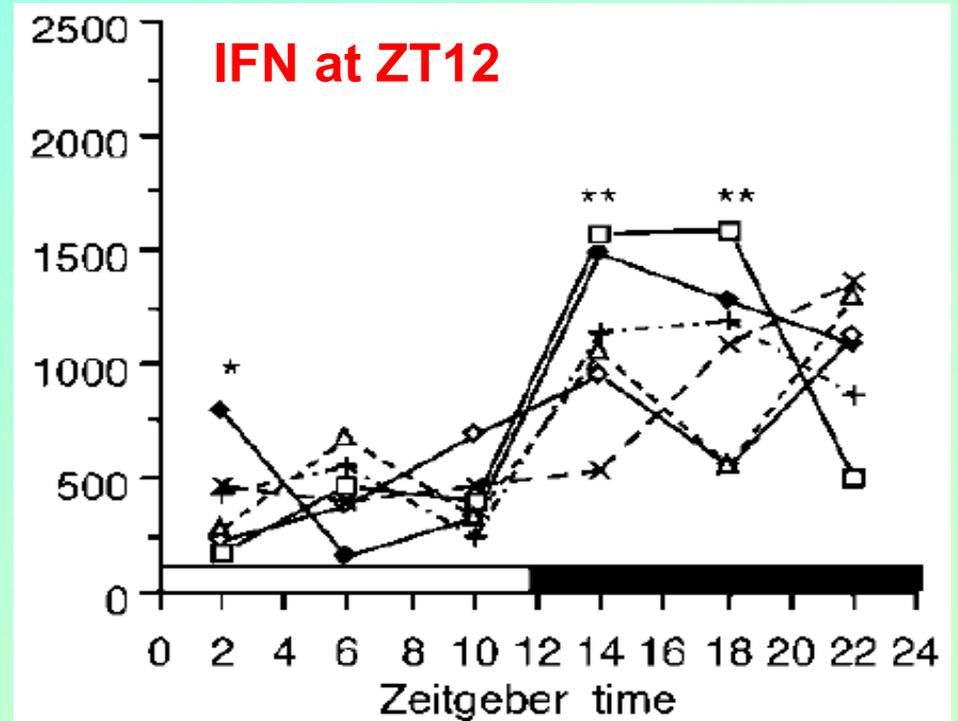
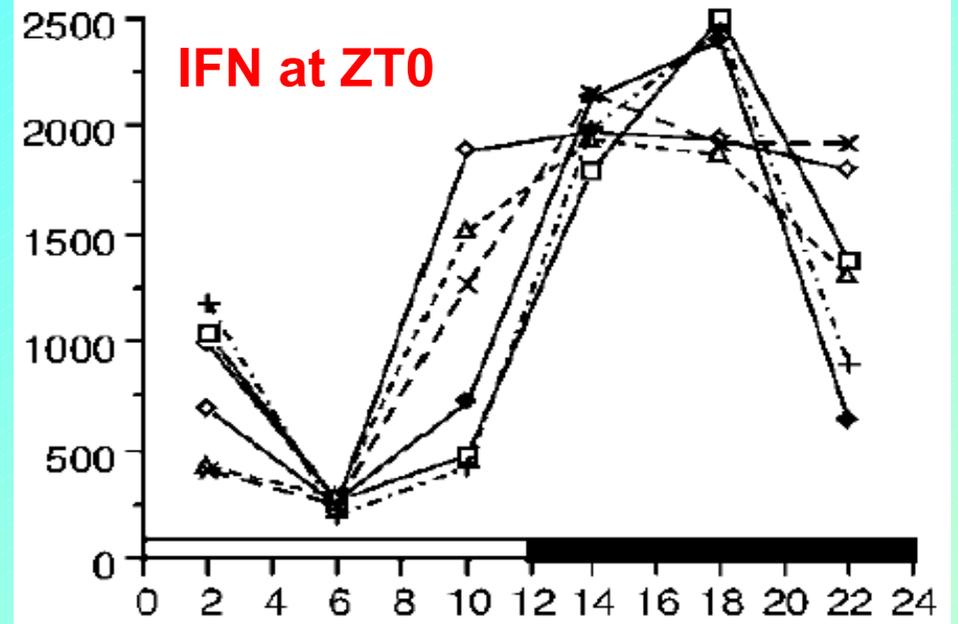
Ohdo et al.

Nature Med 2001, 7, 356-360

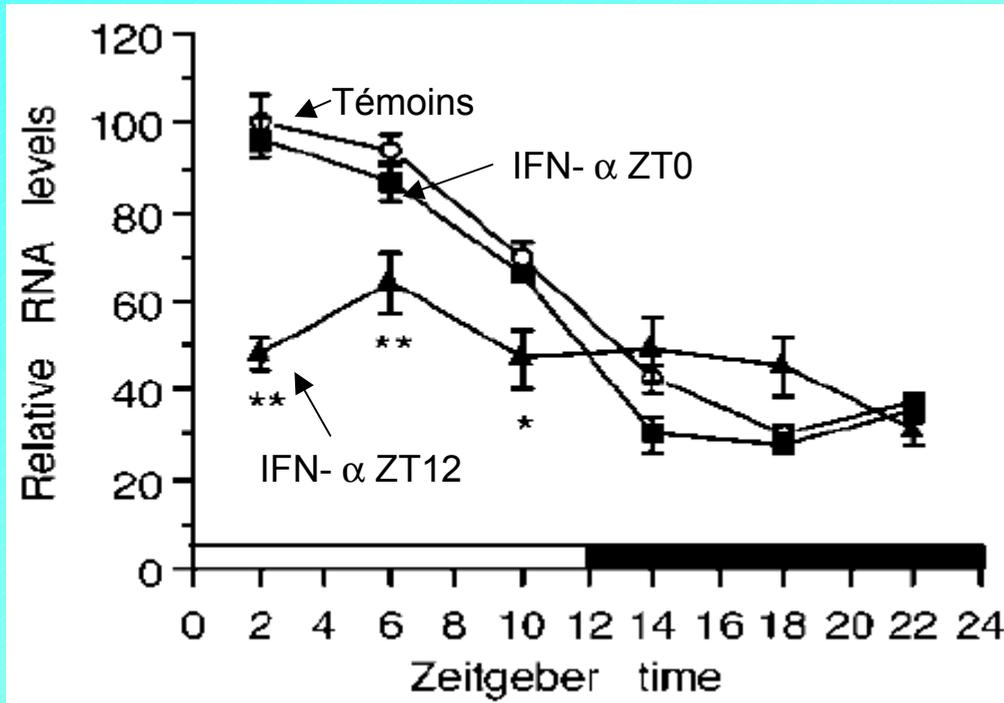
Rest-activity cycle after interféron- α (2 MIU/kg/d x 6d)



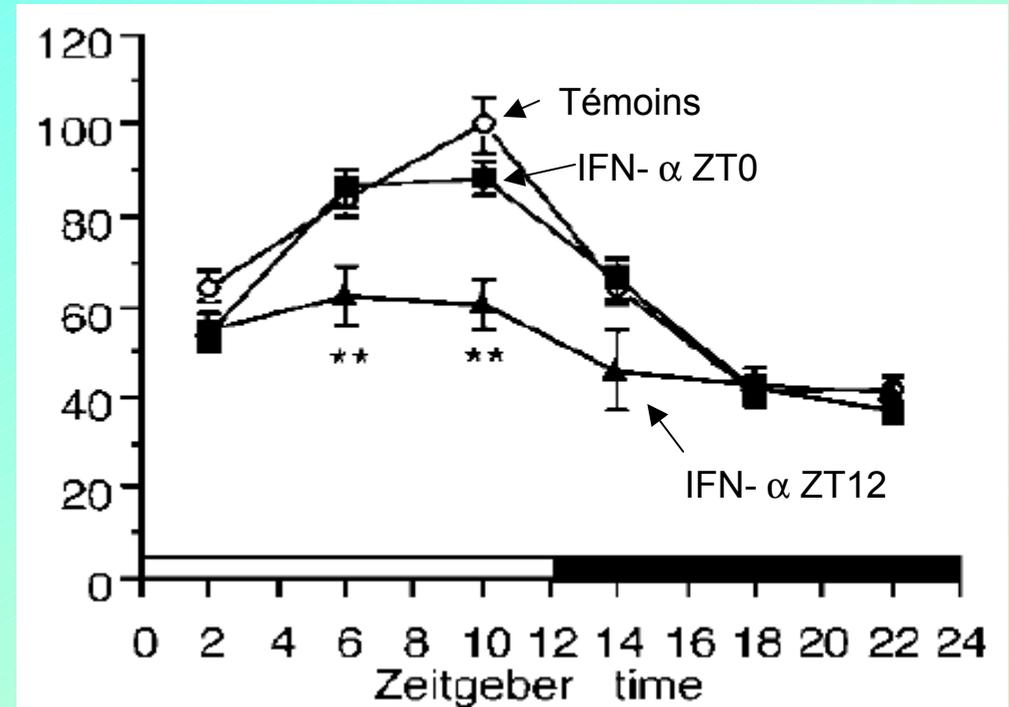
Témoins (NaCl 0.9%)



Interféron- α on clock genes in SCN

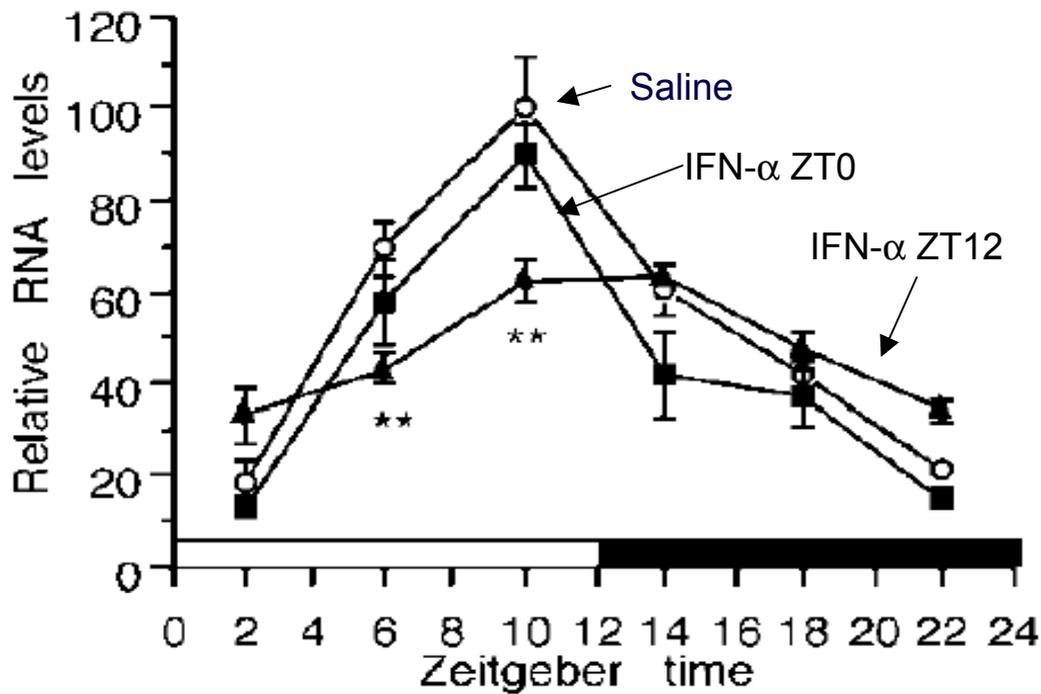


mPer1

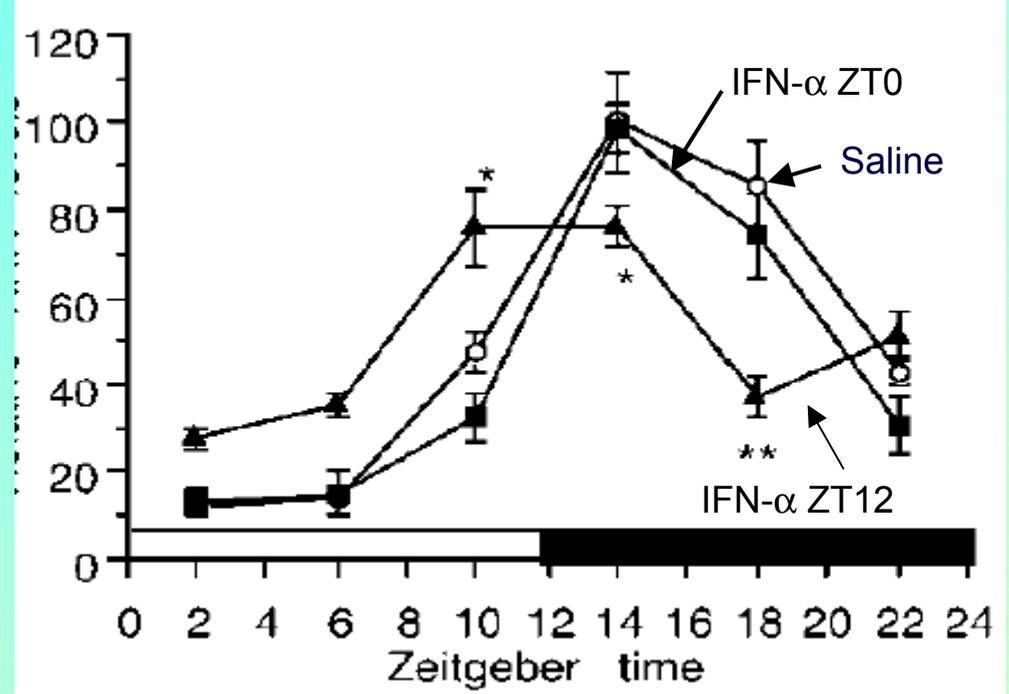


mPer2

Interféron- α on clock genes in peripheral oscillators

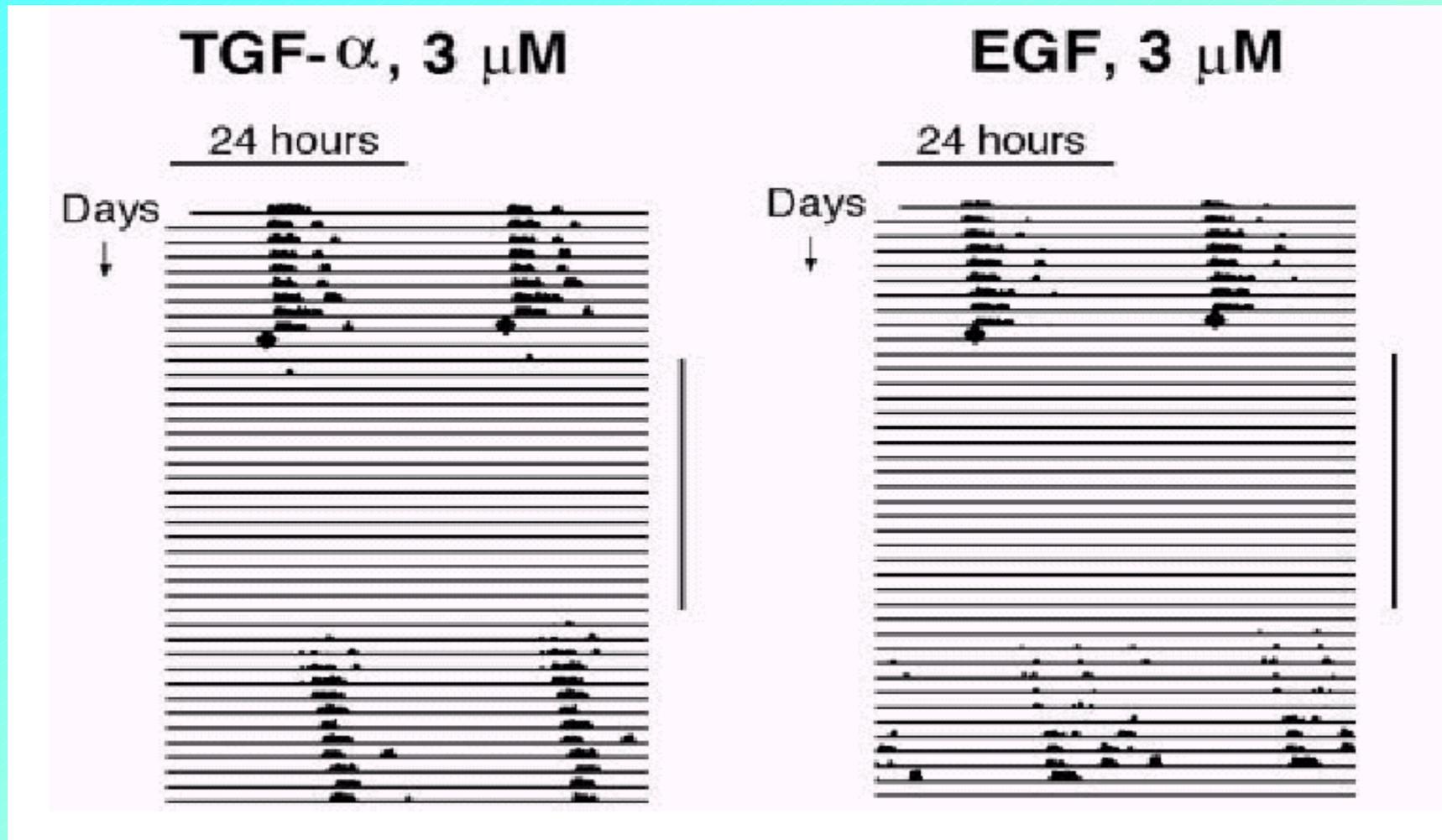


Adrenals



Liver

Regulation of Daily Locomotor Activity and Sleep by Hypothalamic EGF Receptor Signaling



Kramer et al. SCIENCE VOL 294 21 DECEMBER 2001

Suppression physique, génétique ou fonctionnelle de la coordination circadienne

→ **Accroissement du risque de cancer**

→ **Accélération de croissance tumorale**



**L'horloge circadienne :
cible thérapeutique potentielle en cancérologie**

Chronothérapie des cancers

Hypothèse chronothérapeutique en cancérologie

- Développement chronothérapeutique
- Thérapeutique ciblée sur l'horloge circadienne

Expérimental ↔ Modélisation ↔ Technologie ↔ Clinique

Critères : Tolérance, efficacité, qualité de vie, survie