3e Rencontre Patients de l'Association A.R.T.U.R - Jeudi 2 Avril 2009
Theatre du Rond Point. Champs Elysees. Paris

Vers un traitement personnalise du cancer du rein?



Evaluation des rythmes biologiques de la relation hote-tumeur: validation de cibles cliniques, genomiques et pharmaco-therapeutiques

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" Le savant n'est pas l'homme

qui fournit les vraies réponses,

c'est celui qui pose les vraies questions."

Claude Levi Strauss

Le Cancer n'est pas seulement une maladie d'un tissu ou de cellules.

C'est aussi une maladie de l'hote (le patient), interactive et evolutive (localisee, recidivante, ou metastatique).

Si souvent le diagnostic de cancer s'arrete au niveau du diagnostic pathologique,

- La maladie ne s'arrete ni le jour ou la nuit, ni les samedis dimanches et jours feries…

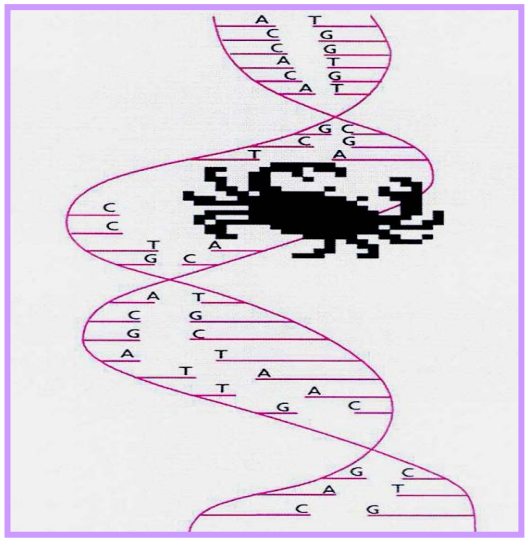
- Un individu sain ou un patient atteint de cancer possedent une horloge biologique et la tumeur cree ses propres rythmes!

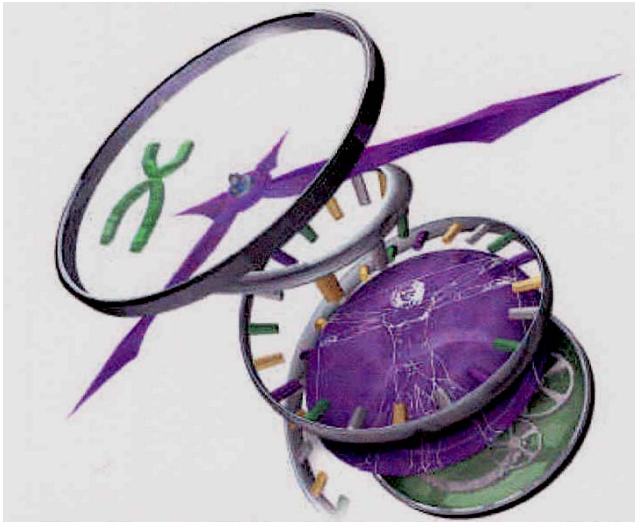
…..Il est donc temps de reconsiderer la temporalite clinique, genomique et pharmacologique de la relation hote-tumeur

Que signifie traitement personnalise du cancer en 2009?

- Pourquoi personnaliser ?
- Qui (genetique ?)
- Quand ?
- Comment ?
- Criteres de vulnerabilite epigenomique (vie societale de 24h)
-

“RENAL CANCER CLOCK-MEDICINE”





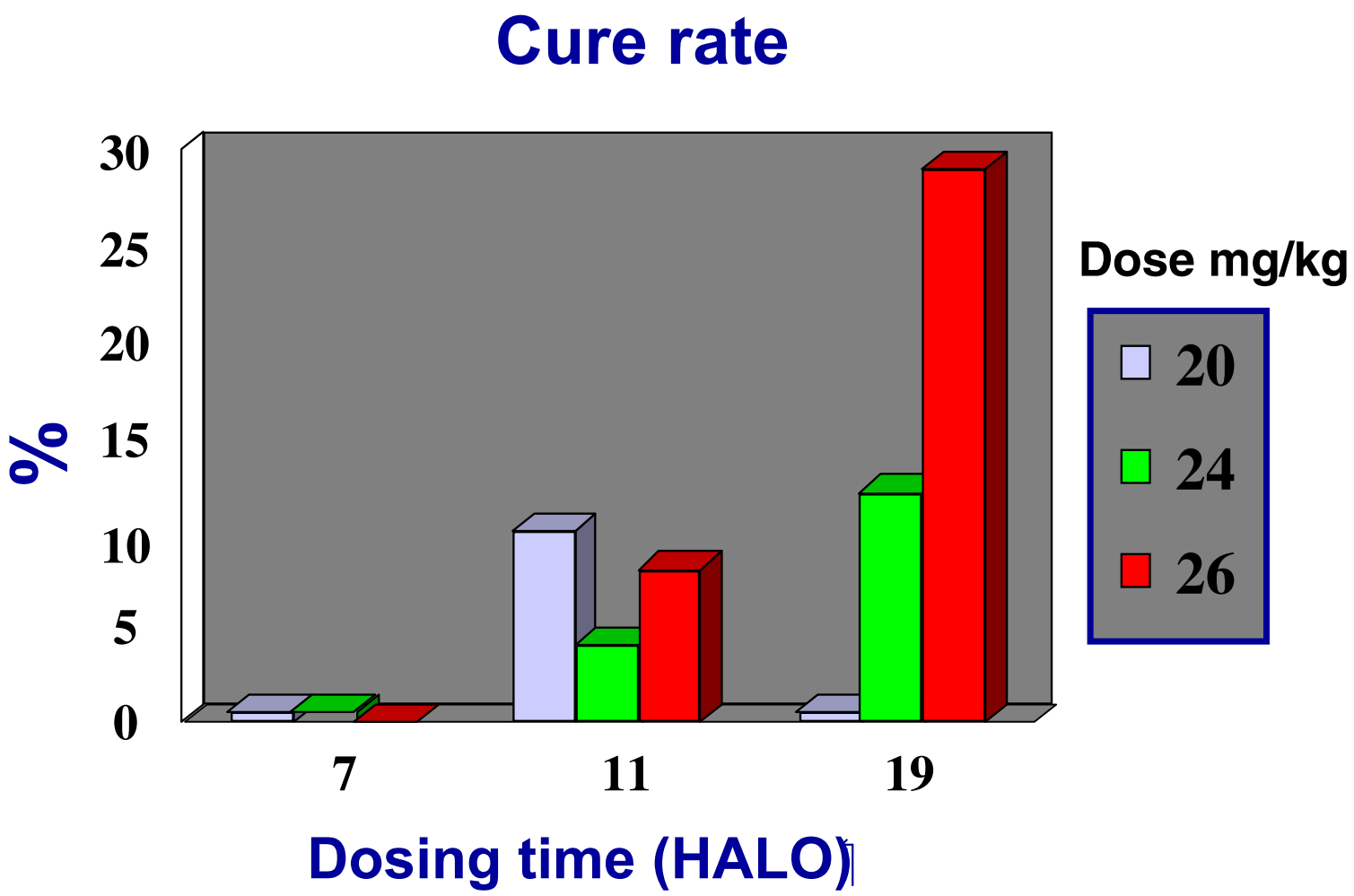
FROM GENOME CLOCK-NETWORK

TO

TIMED and MAPPED

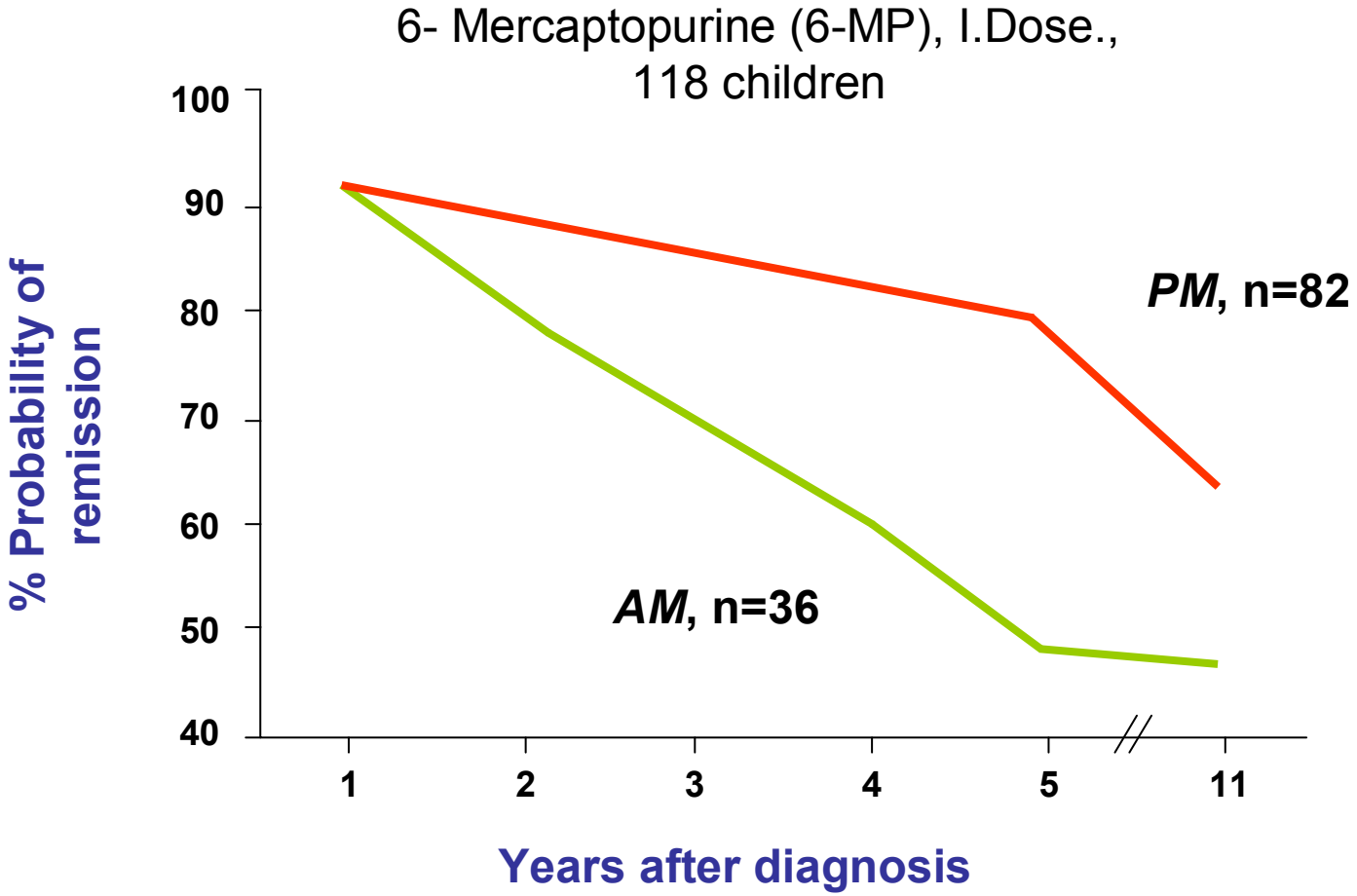
GENDER INDIVIDUALIZED CHRONOTHERAPIES

Cure rate of weekly Vinorelbine in B6D2F1 mice with P388 Leukemia depending on dosing time



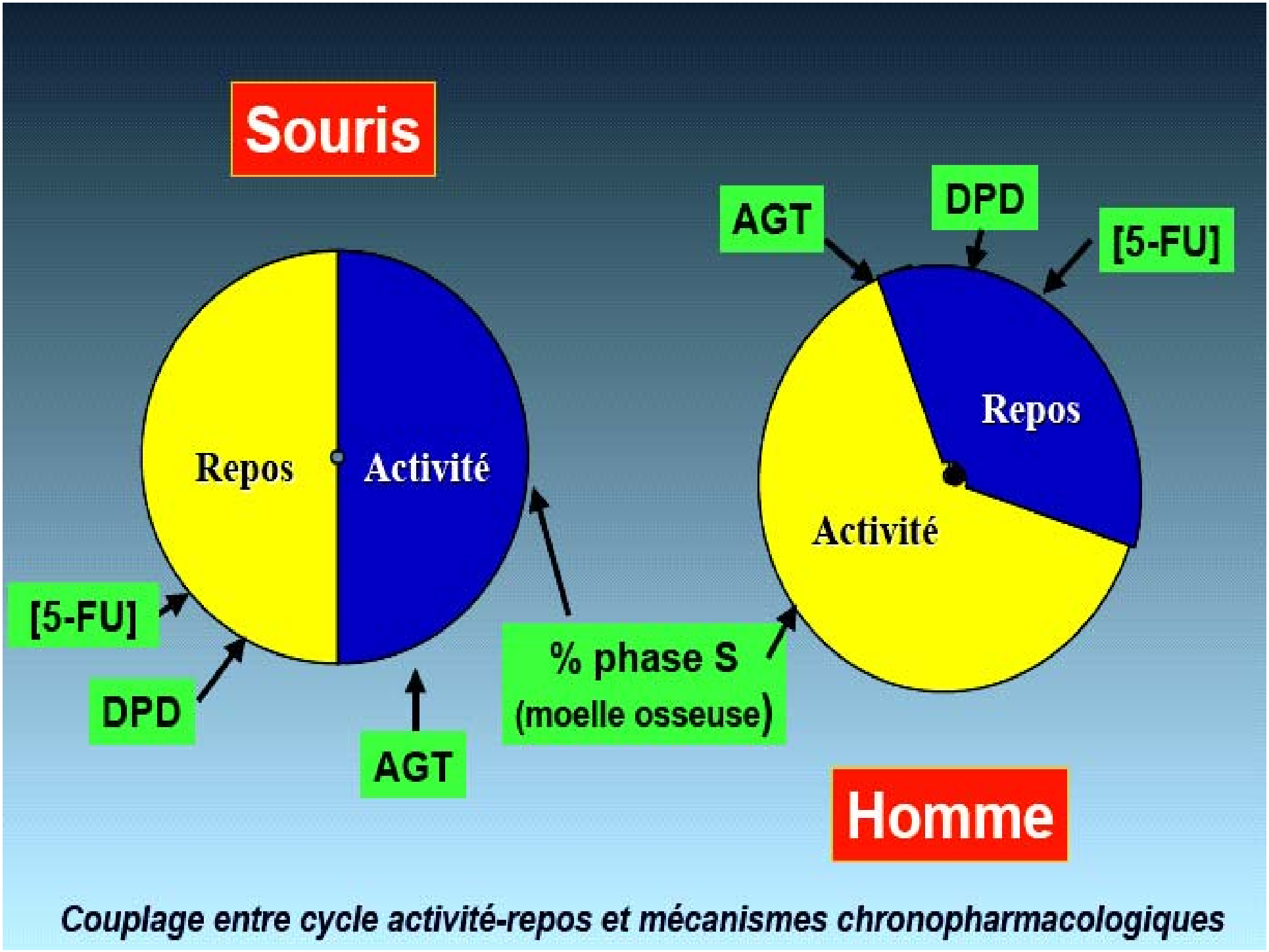
Pediatric Acute Lymphoblastic Leukemia

Effect of Drug Timing (AM / PM)



Rivard et al. : Lancet ii : 1264 - 1266, 1985

Rivard et al : Chronobiol. Int. 10 : 201 - 204, 1993



Couplage entre cycle activité-repos et mécanismes chronopharmacologiques

Personnaliser
le traitement du cancer du rein:

Une place pour valider
les parametres
cliniques, genomiques et therapeutiques
de l' Horloge Biologique
dans la relation Hote-tumeur

Genomic Circadian Time Structure

Altered Maintained

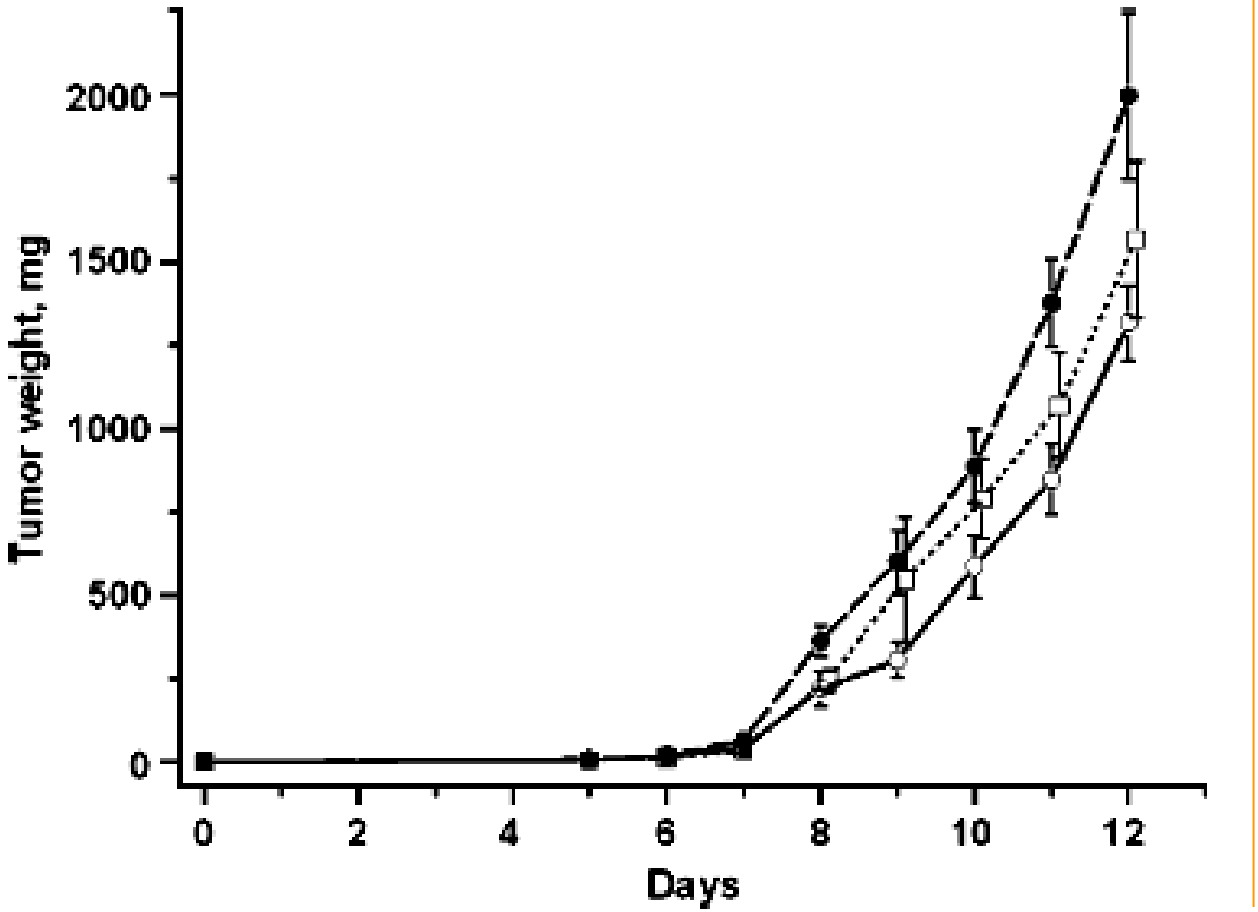
RUNS

1- The cancer drug pharmacogenomic Disposition & metabolism

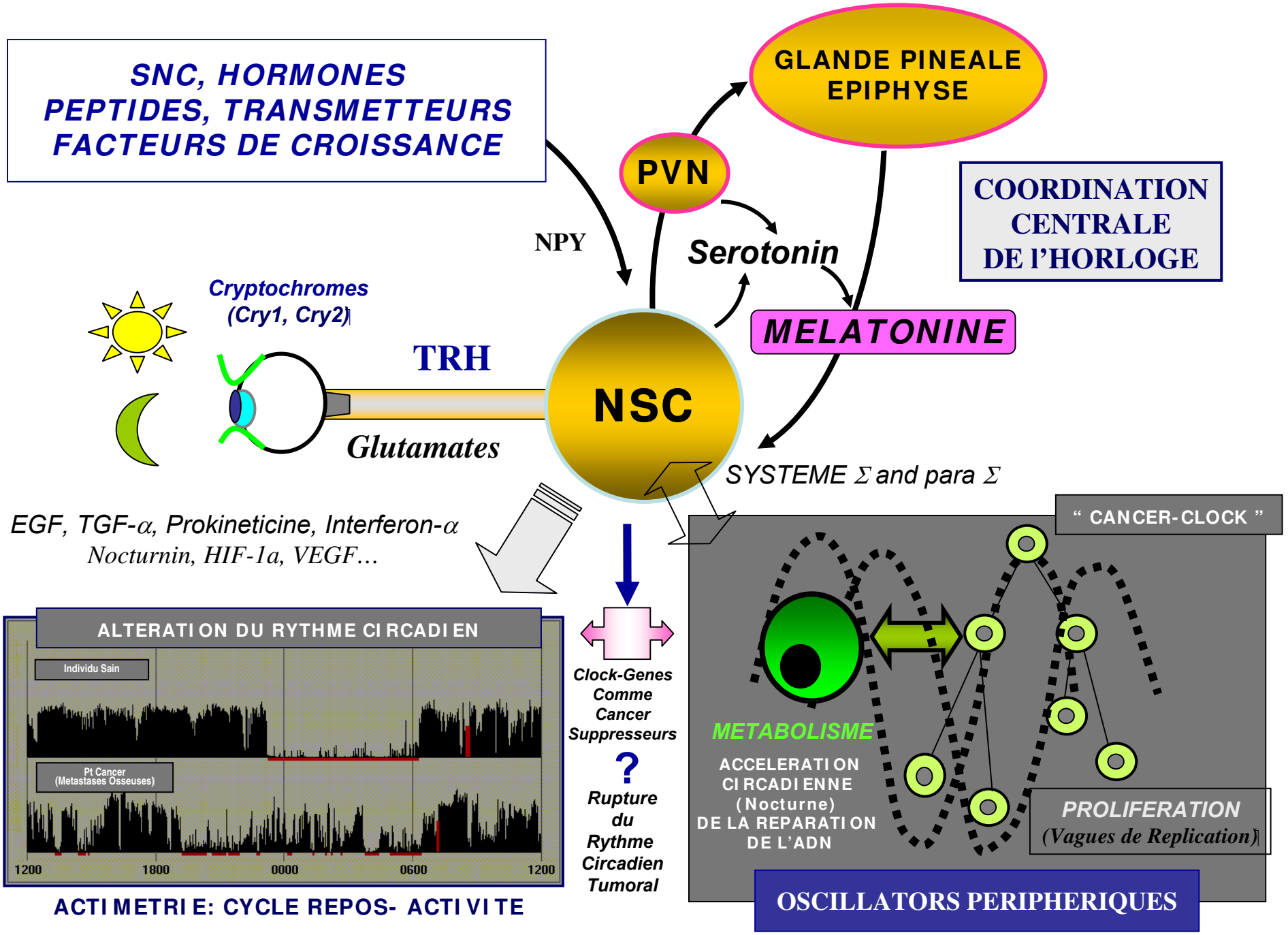
2- The host delivery schedules

Perturbations de l'horloge circadienne et croissance tumorale

Observation : une perturbation du rythme circadien par DHC (décalage horaire chronique) stimule la prolifération tumorale



(d'après Filipski et al., JNCI 2005)



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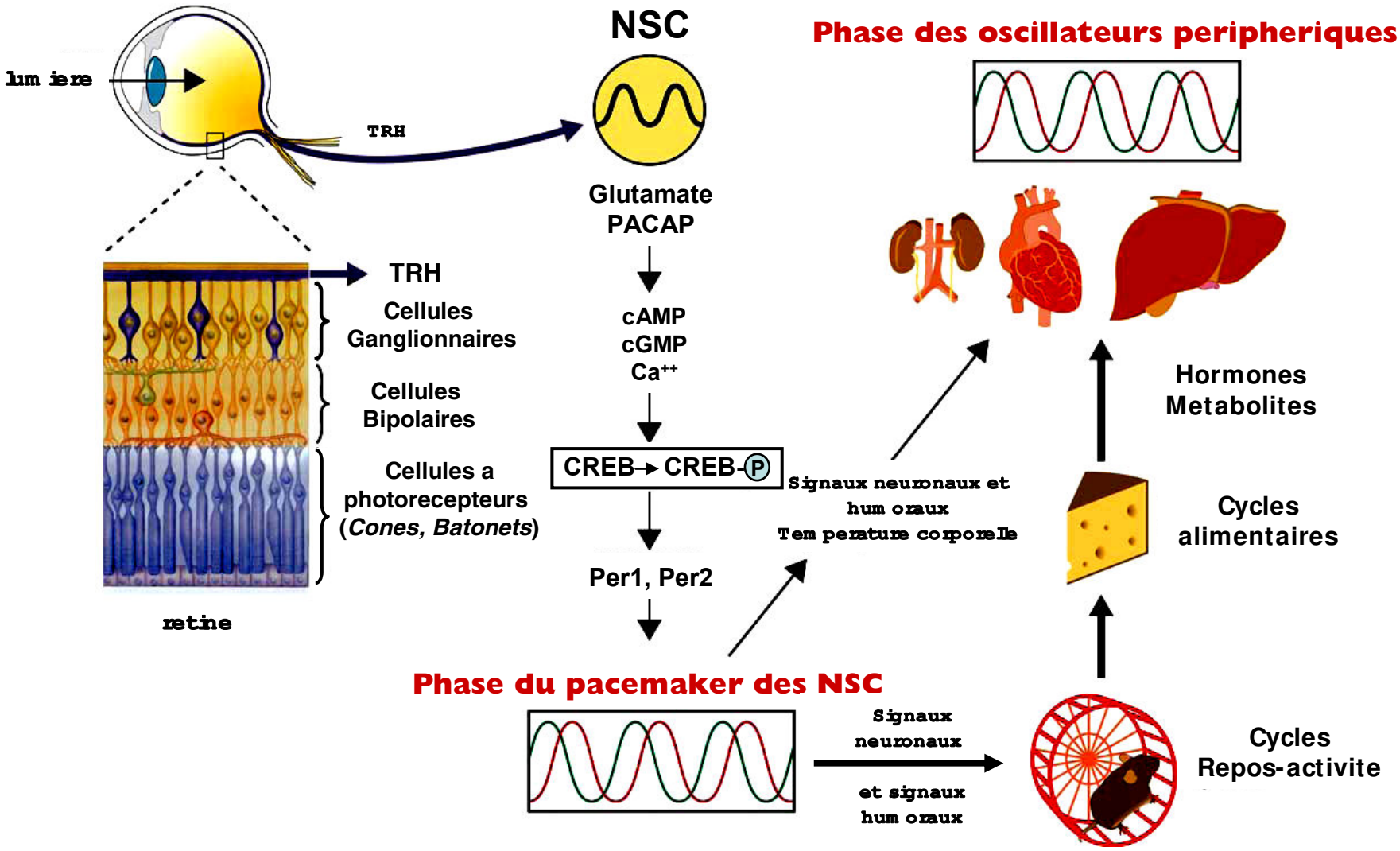
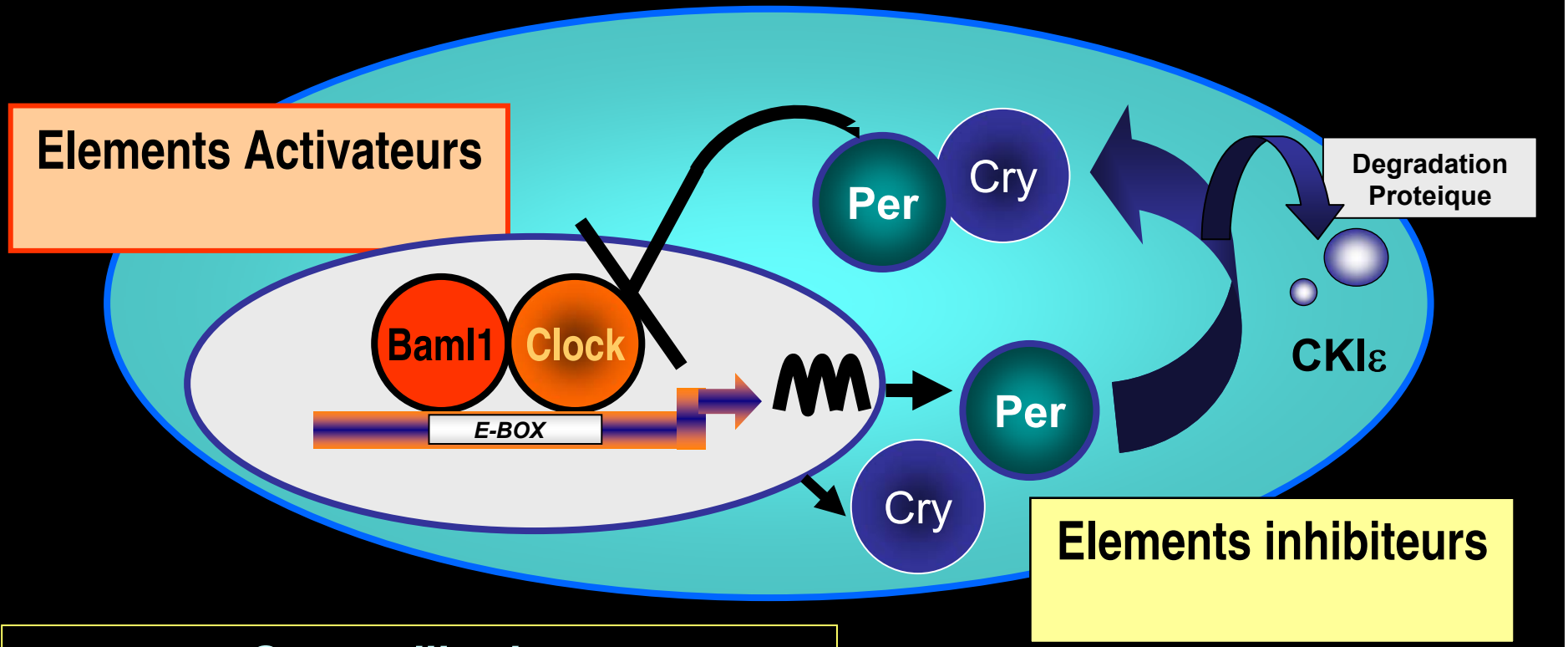
Synchronisation de l'horloge centrale et des horloges peripheriques.



Le pacemaker central de l'horloge biologique dans les NSC est synchronise par les cycles de lumiere et d'obscurite generes par la photoperiode.
Ceci synchronise par la suite les oscillateurs peripheriques a partir des rythmes comportementaux de la vie societale (comme le cycle repos-activite engendrant les cycles circadiens d'alimentation)
Les signaux de transmission chimique neuronaux et humoraux associes avec les rythmes de nutrition ou de starvation et la nature precise de ces signaux est en cours d'identification.

Coordination moleculaire de l'horloge circadienne



Genes d'horloge

Per1, Per2, Per3, Cry1, Cry2, Tim, Ror
Baml1, Clock, CKIε, Rev-erbα, Dec1, Dec2

Genes controlles par l'horloge

~ 10% du genome humain

Suppression Tumorale ?

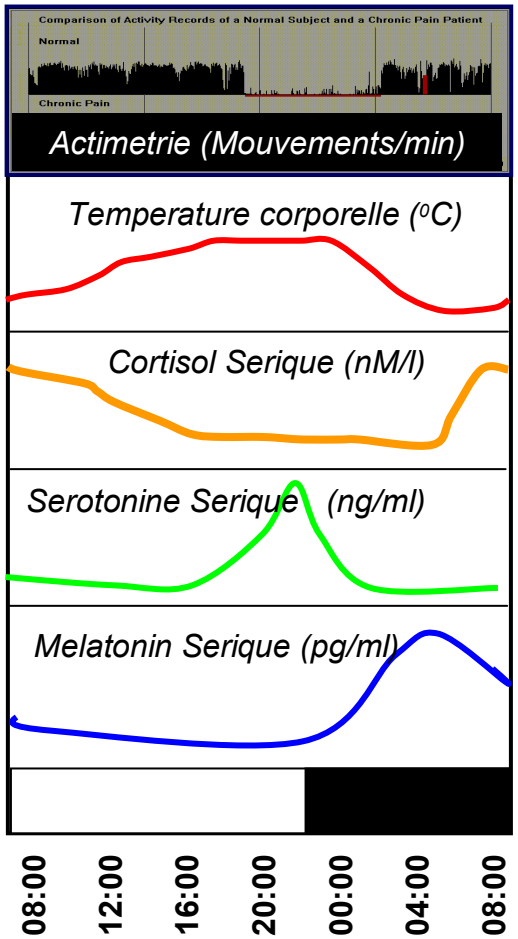
FONCTIONS BIOLOGIQUES

- ***Cycles de Repos/Activite***
- ***Rythmes Metaboliques***
- ***Rythme de Division Cellulaire***
- ***Rythme de reparation de l'ADN***
- ***Rythme d'apoptose***

Synchroniseurs externes

Cycle jour-nuit
Heure des repas
Habitudes socio-professionelles

Physiologie Circadienne



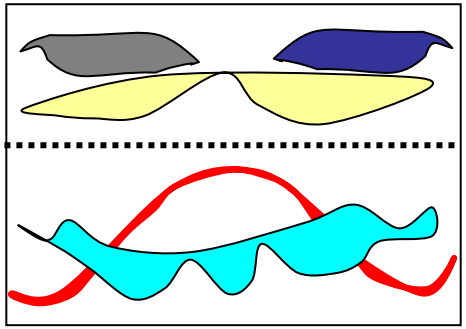
Noyaux Suprachiasmatiques

Systemes Sympathique / Parasympathique

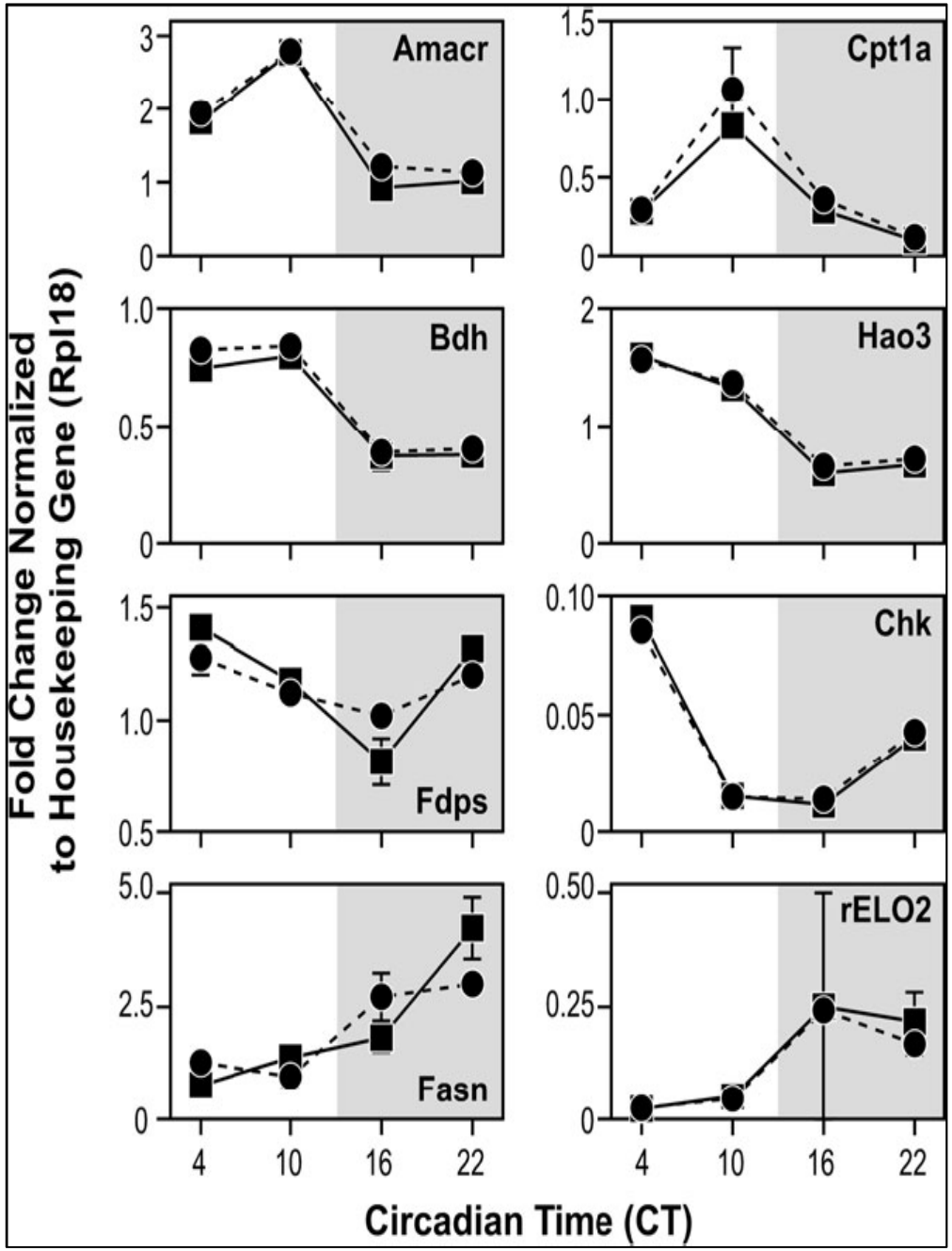
Hormones et Cytokines

Tissus peripheriques Horloges moleculaires

Transcriptome Circadien
Timesome
(specificite proteomique et domaines tissulaires)

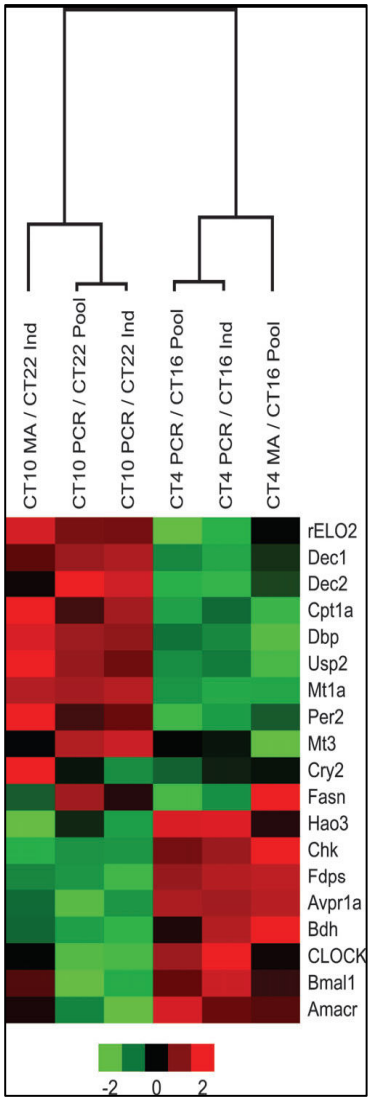


Temps (24 heures)

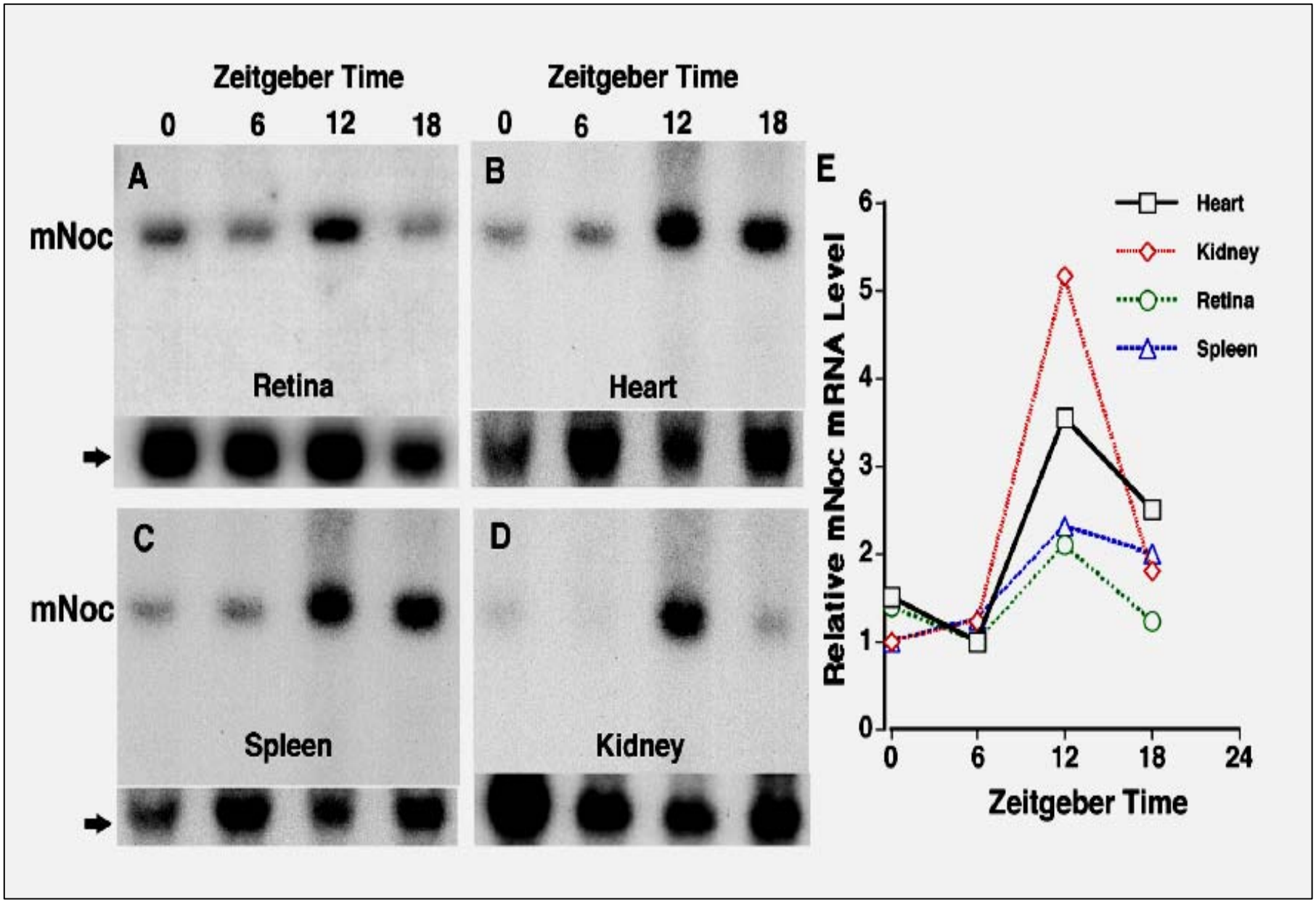


Variation circadienne des Genes de maison

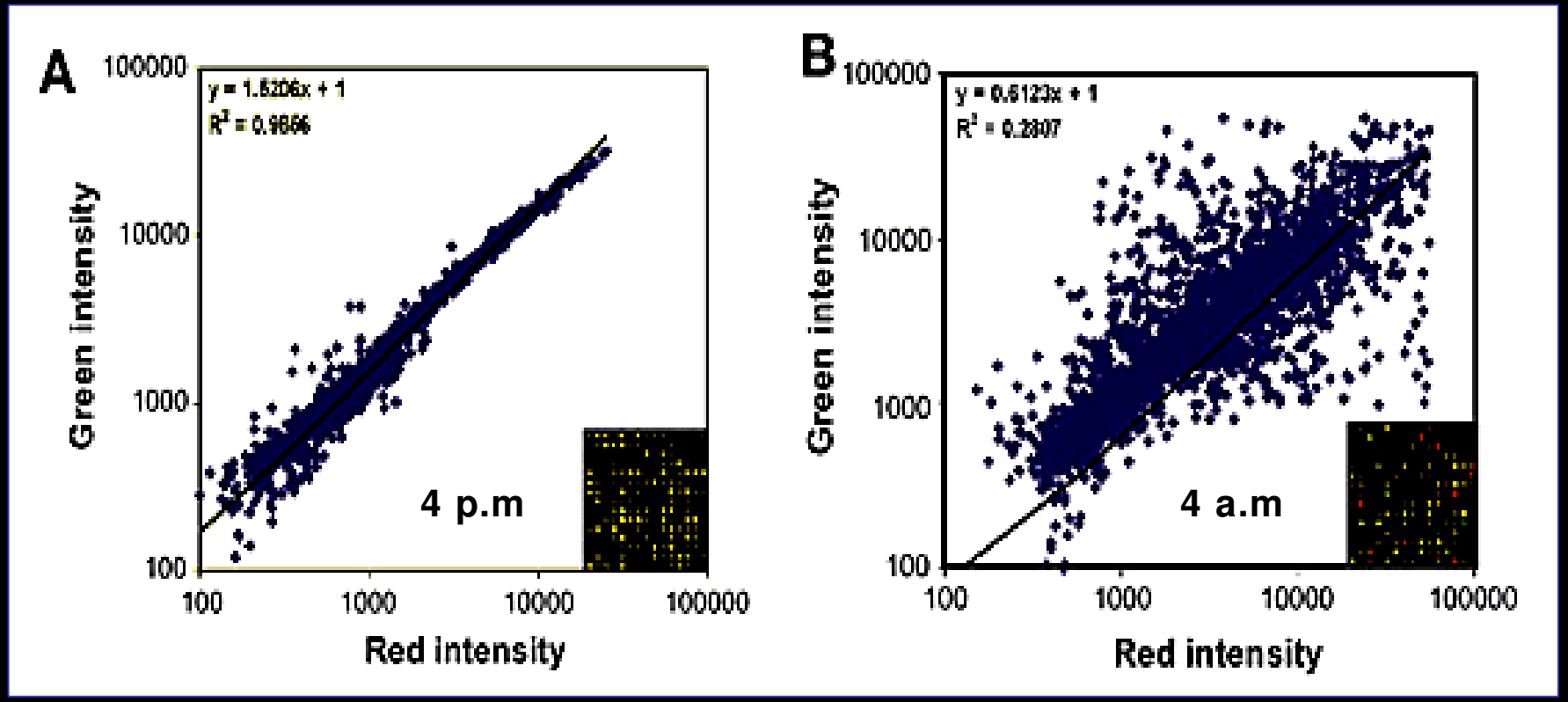
(expression genomique circadienne chez des rats Fisher)



Nocturnin dans les Tissus Peripheriques



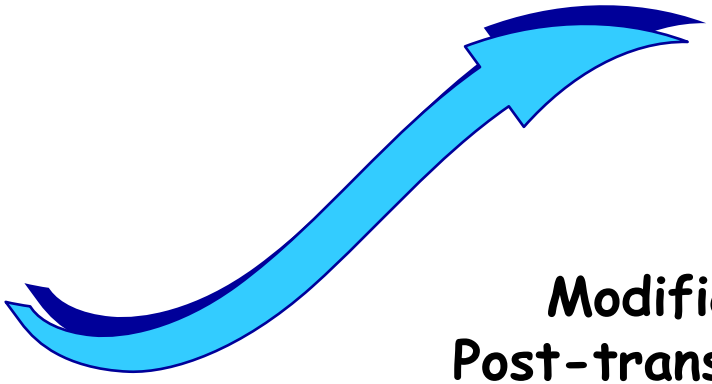
Genomique Fonctionelle Temporelle:
Expression circadienne de transcripts de genes
(mRNA array)



Dr Haim J. Bendayan. Theraclock.02/2002

Genome

~ 25'000 genes humains (avec polymorphismes)



Proteome

~ 1'000'000 proteines humaines

Modifications Post-translationelles (PTMs)

alternative promoter usage
alternative splicing
mRNA editing
etc.

Transcriptome

~ 100'000 transcripts humains

Complexite accrue avec:

- Signatures genomiques selon le genre
- Expression circadienne des genes

LE CONCEPT DE TIMESOME:

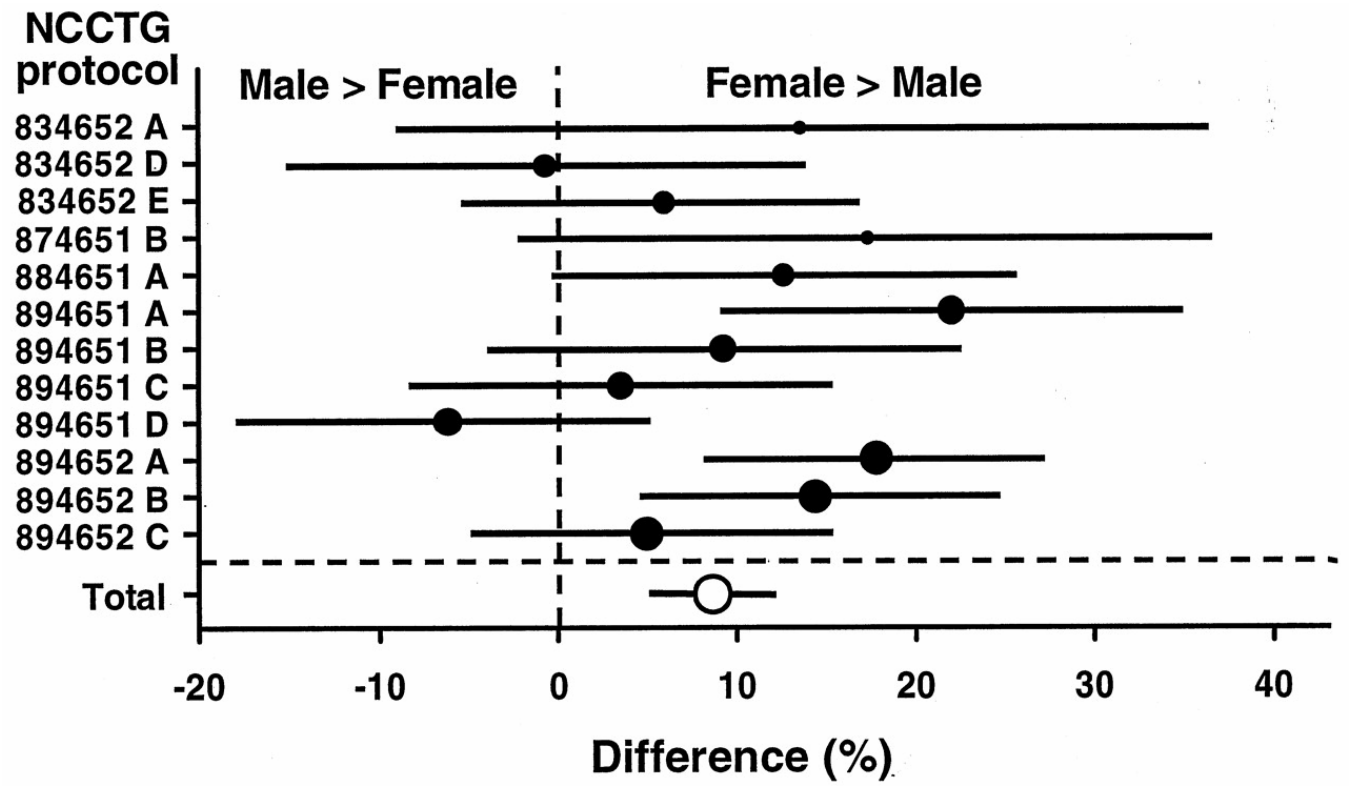
(Interactome male et femelle du temps biologique humain)

Il est temps maintenant, de commencer à
revoir le Genome Humain
non comme un maillage ou un calque,
mais comme une
dynamique oscillatoire circadienne à 3 dimensions
de protéines à structures mouvantes (3-DP),
produits de gènes gardiens
de la temporalité biologique,
à partir de laquelle
se dessinent des signatures
selon le genre male ou femelle
desquels émergent la vie humaine.

(Dr Haim J. Bendayan. 2005. Berlin.1rst World Congress Gender Medicine)

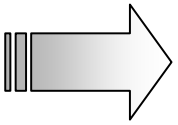
5FU Gender Toxicity (overall)

Meta-analysis review from 5FU based Treatment of Colon Cancer [NCCTG protocols]



BASIS OF CLINICAL CANCER GENDER CHRONONO-PHARMACOGENOMICS

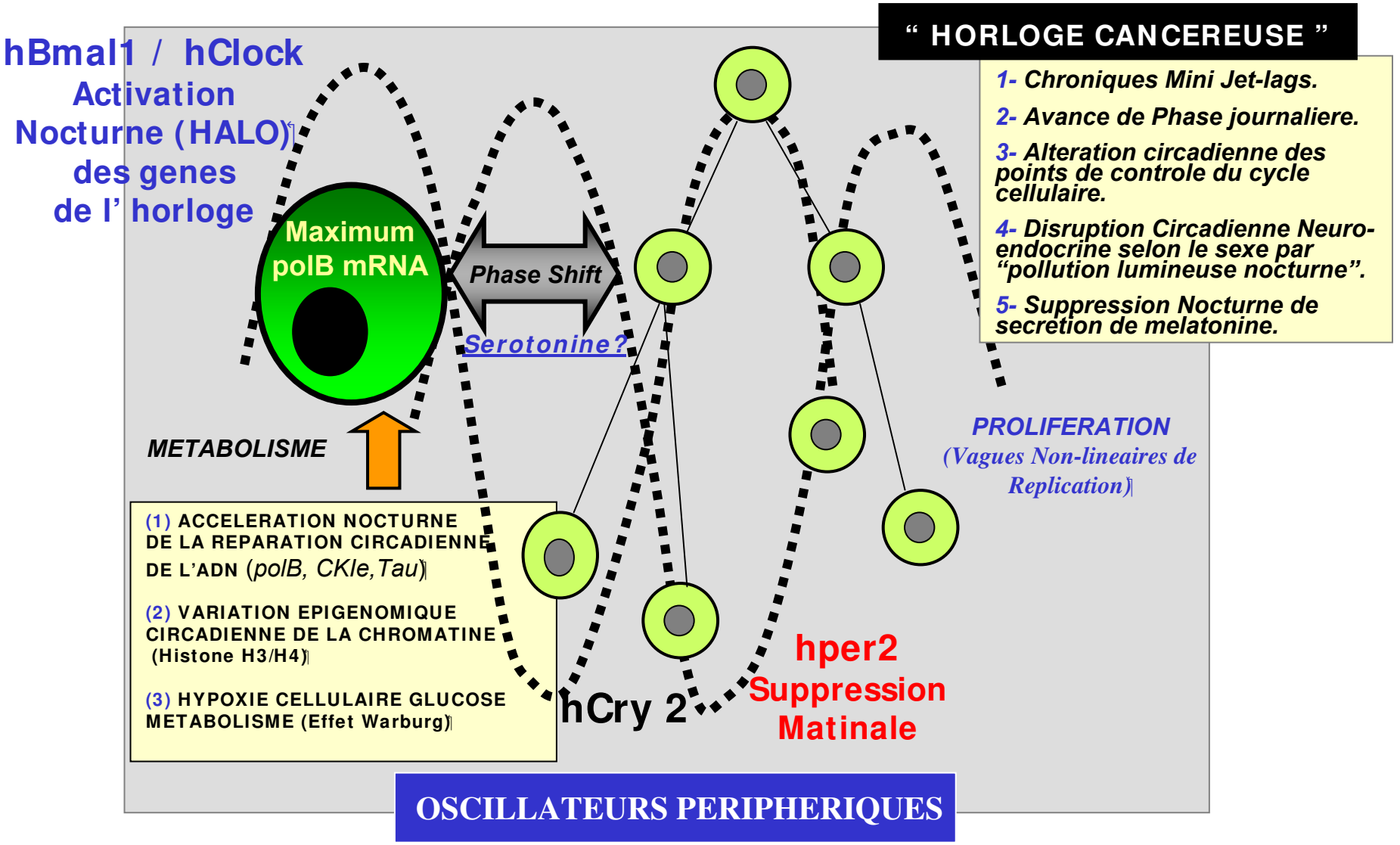
- *Known circadian pattern of 5-FU*
- *Known circadian of 5-FU related enzymes (mRNA DPD expression)*



Gender "Clock-Medicine" in Clinical Oncology

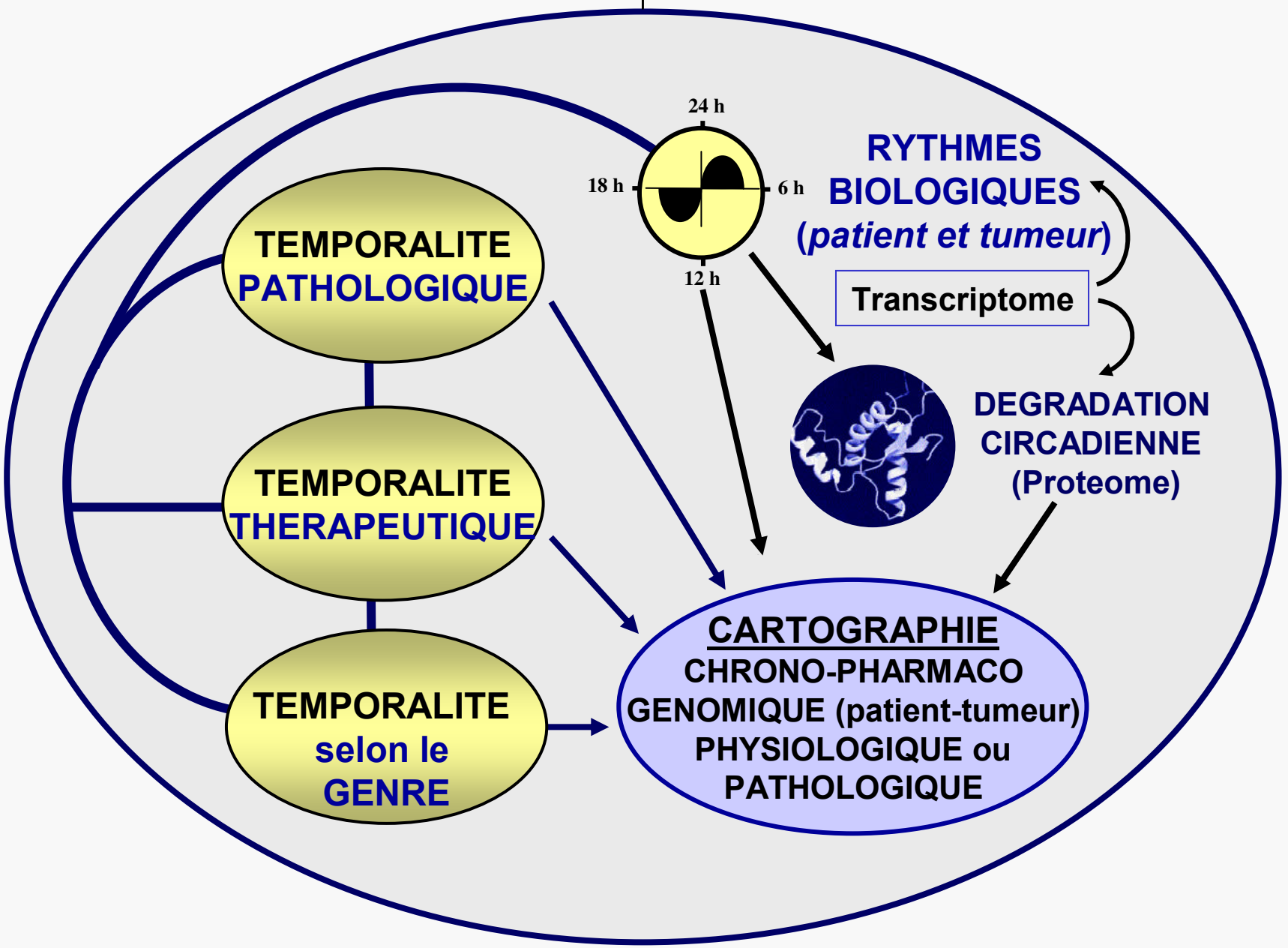
Nouvelle Hypothese en Carcinogenese Renale Humaine:

Proliferation tumorale par reduction temporelle épigenomique du rythme circadien



Dr Haim J. Bendayan (2007)

“Cancer Clock-Medecine” et therapies personnalisees ?

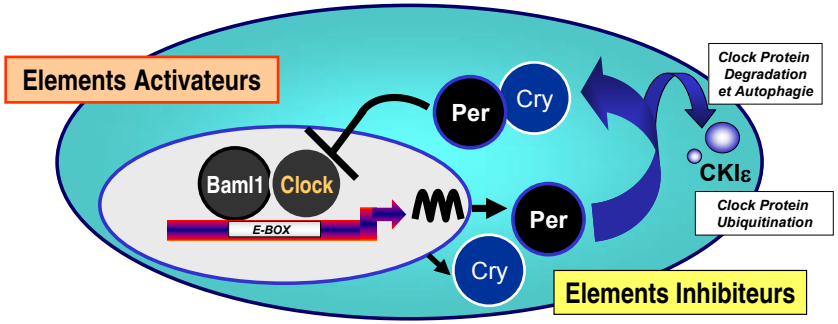


THERACLOCK GENOMICS INTERNATIONAL PROJECT

HORLOGE MOLECULAIRE COMME VALIDATION DE CIBLE EN CARCINOGENESE ET POUR LE TRAITEMENT DU CANCER RENAL

Organisation Moleculaire de l'Horloge Biologique

Boucles de Translation/ Transcription (Feed-back)



Genes de l'Horloge

Per1, Per2, Per3 Cry1, Cry2, Tim, Rore
Baml1, Clock, CKIε, Rev-erbα, Dec1, Dec2

Genes Controlles par l'horloge

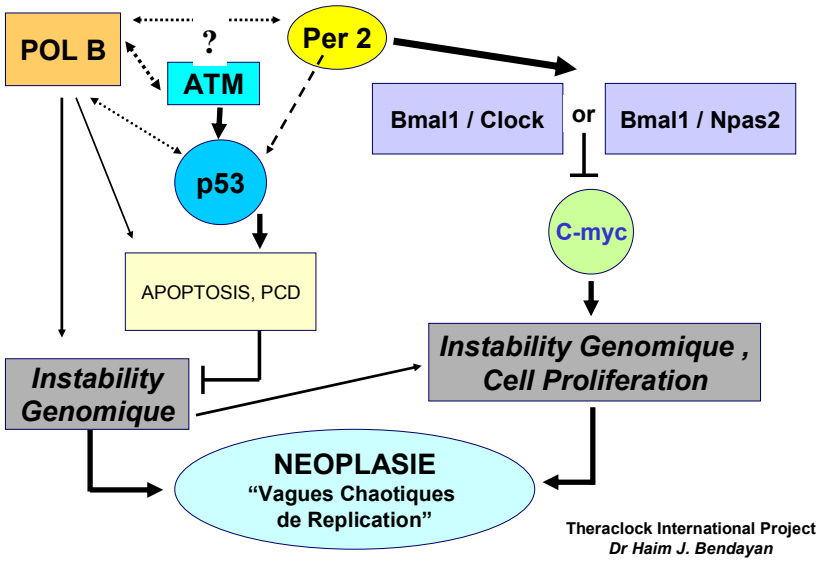
~ 10% of the genome

Suppression Tumorale ?

FUNCTIONS BIOLOGIQUES

- *Cycle Repos/Activite*
- *Rythmes Metaboliques*
- *Rythmes de Division Cellulaire*
- *DNA Repair Capacity*

CHRONO-MUTATEURS MOLECULAIRES



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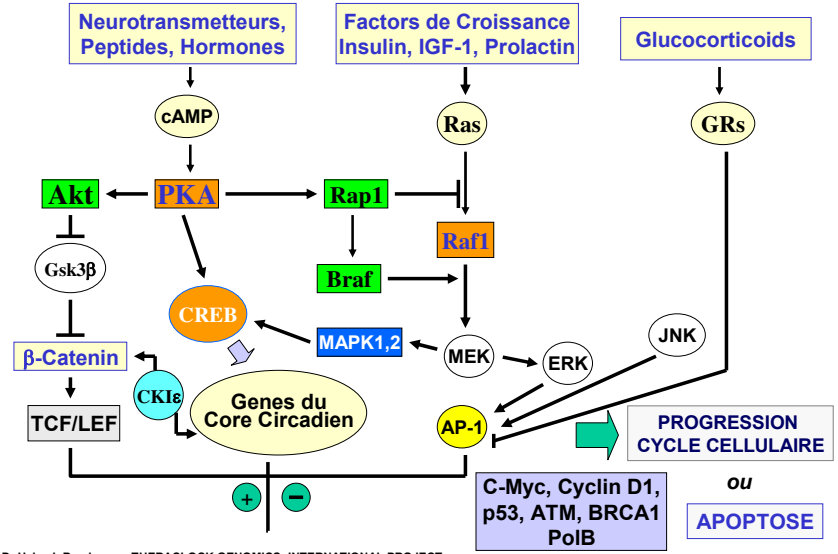
Determinants Pharmacogenomiques de Chrono-Carcinogenese



Dr Haim J. Bendayan – THERACLOCK GENOMICS INTERNATIONAL PROJECT

Rythms Circadiens et Traitement du cancer

Prediction Potentielle
Rythmes Genomique des Cibles

(Profils circadiens et kinetiques de RNA messagers. "fit curve")

- **DPD, TK, TS**
- **GSH**
- **Erb-2, IGF-1/2, VEGF, TGFβ, EGF, mTOR, HIF1α**
- **Cell cycle –related cyclins,**
  (P53, BCL-2, BAX)
- **Reparation de l'ADN (POLB, XPG, AGT, ATM, BRCA1)**

CHONOTHERAPY BASEE SUR
DES PROTOCOLES CIRCADIENS PHARMACOGENOMIQUES

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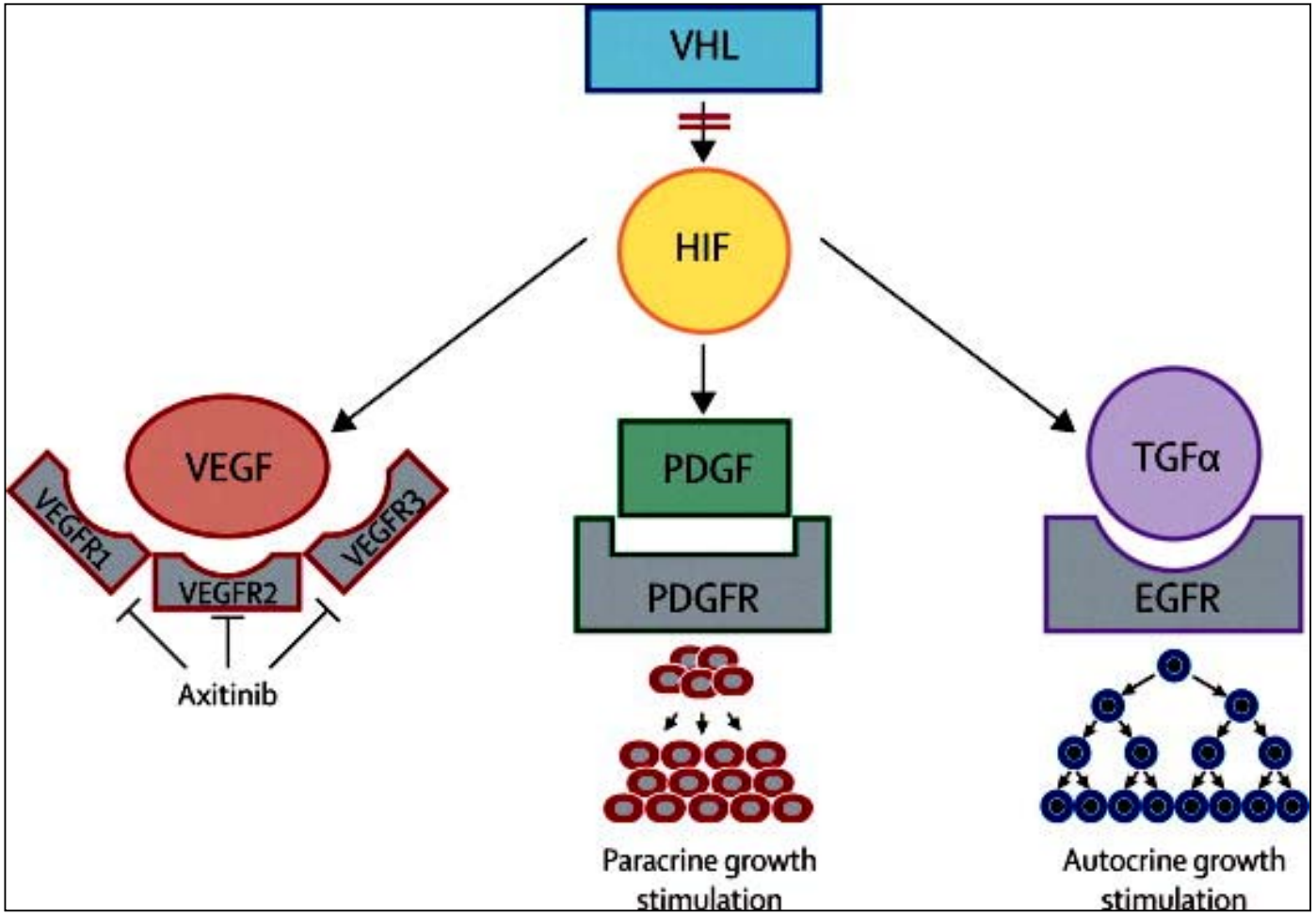
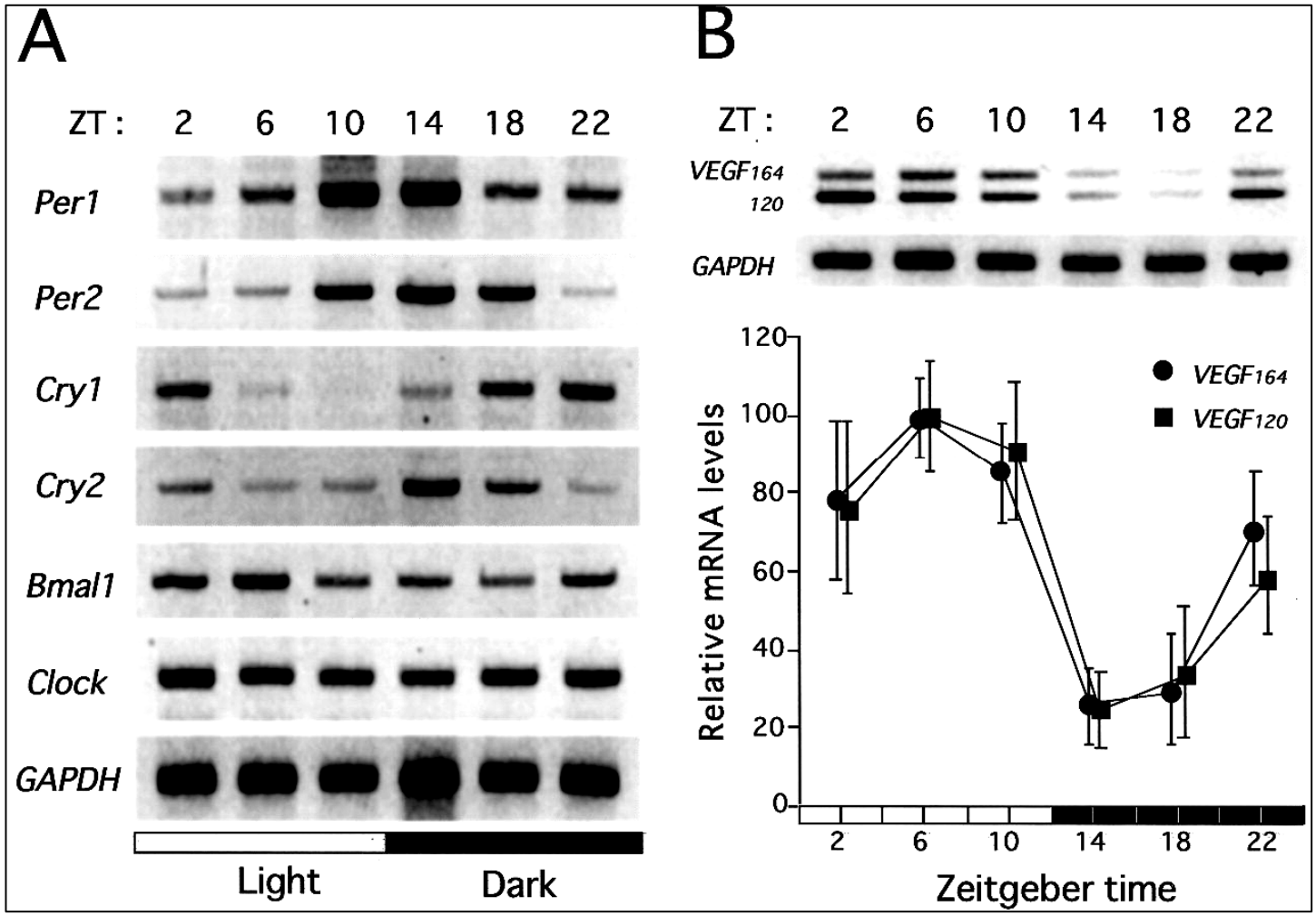
traitement personnalise du cancer du rein

VEGF



Targeting VEGF receptors in clear-cell kidney cancer
The VHL protein targets the transcription factor, HIF, for ubiquitin-mediated degradation. In clear-cell kidney cancer, mutation of *VHL* leads to increased HIF, which results in increased transcription of a number of HIF target genes, including *VEGF, PDGF, TGF*α. Axitinib targets a part of the VHL/HIF pathway and is directed at inhibiting the VEGF receptors 1, 2 and 3. *Modified from Sosman and co-workers.*

Circadian expression of clock genes and *VEGF* in implanted tumor cells.

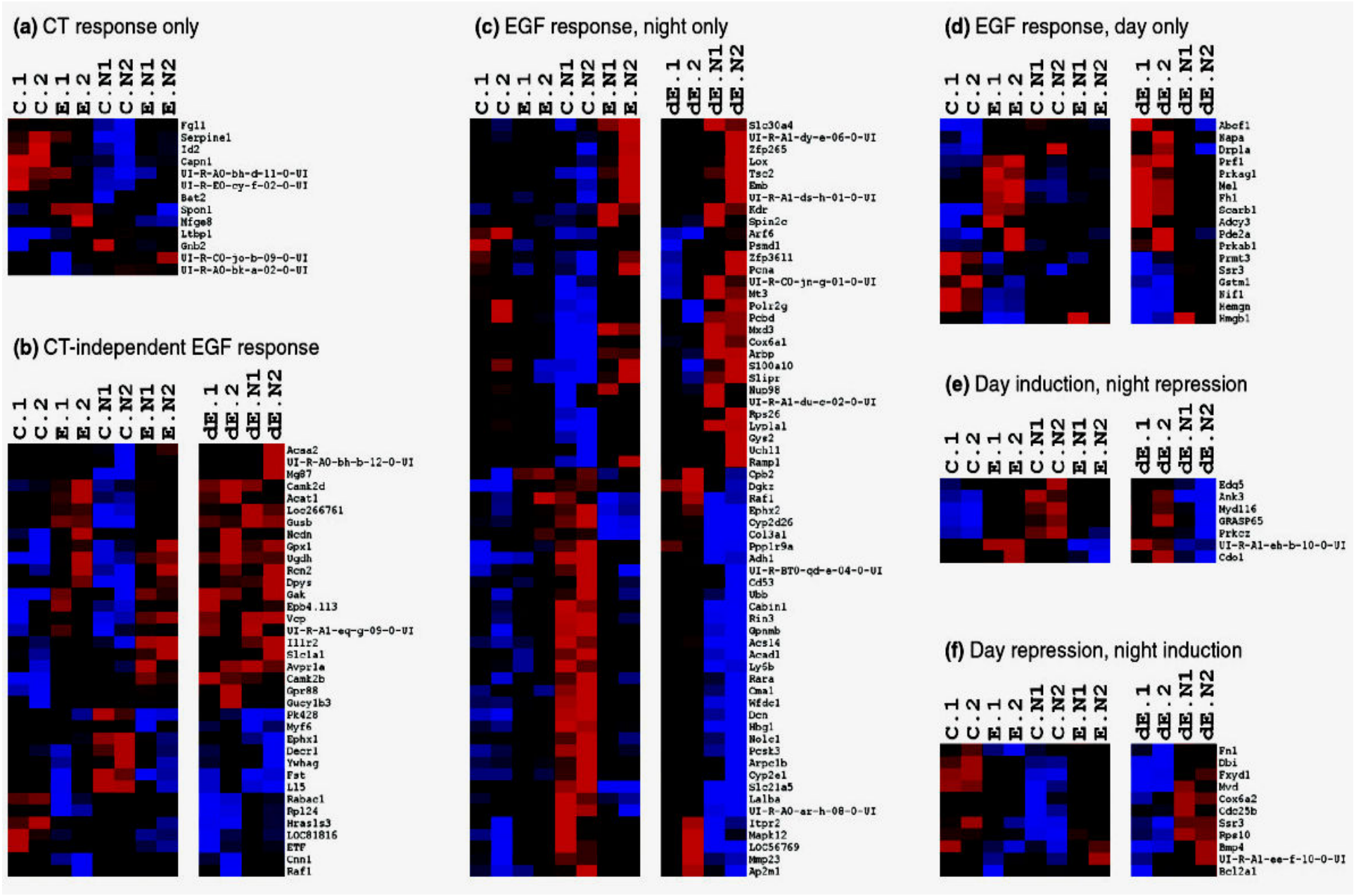


A, representative electrophoretic image of RT-PCR products of clock genes in tumor masses. GAPDH mRNA was used as an internal control for transcripts whose expression was constant throughout the day. The *horizontal bar* at the *bottom* indicates light and dark cycles.

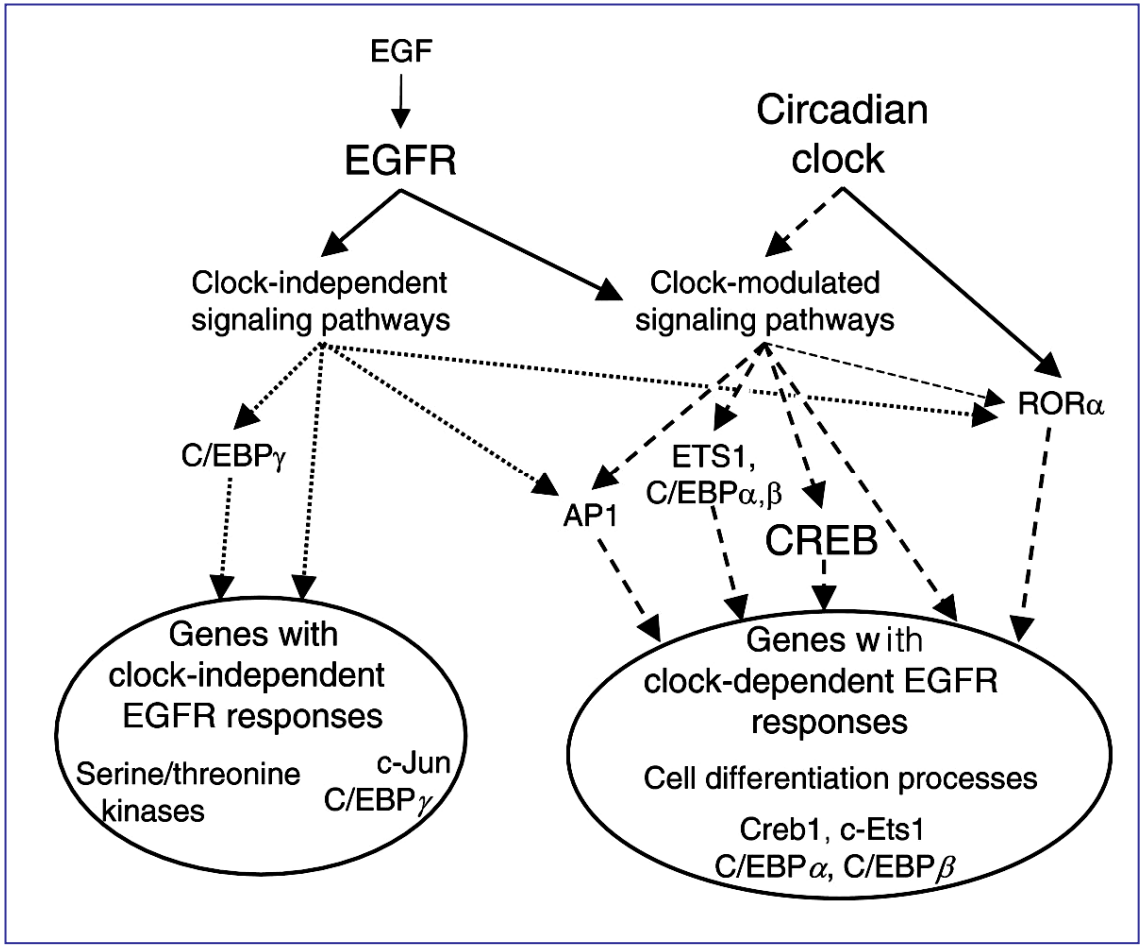
B, temporal profiles of mRNA expression of VEGF164 and VEGF120 in tumor masses. For plots of RNA, the mean peak values for VEGF164 and VEGF120 are set at 100. Each point represents the mean ± SE (*bars*; $n = 4–6$). The mRNA levels for both VEGF164 and VEGF120 exhibit significant circadian variations ($P < 0.01$, respectively; ANOVA). The *upper panel* shows a representative electrophoretic image of RT-PCR products of the *VEGF* gene. The *horizontal bar* at the *bottom* indicates light and dark cycles.

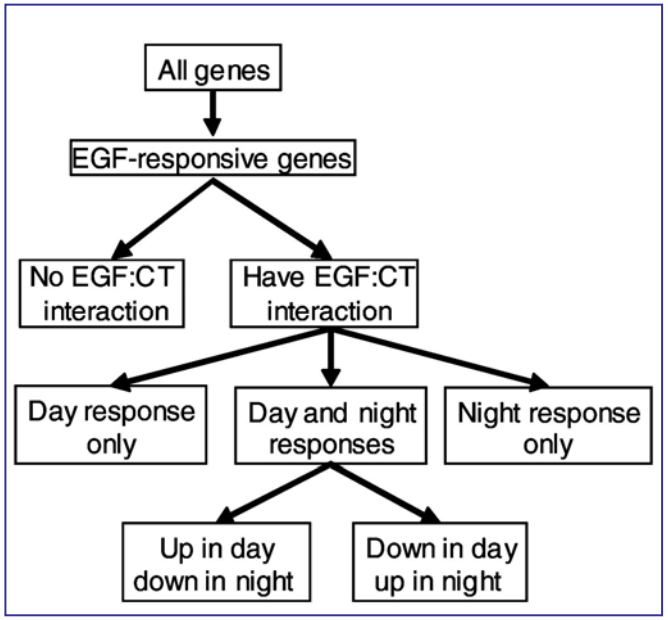
Vers un traitement personnalise du cancer du rein

EGFR


(a) CT response only
C.1 C.2 E.1 E.2 C.N1 C.N2 E.N1 E.N2
Fgl1
Serpine1
Id2
Capn1
UI-R-A0-bh-d-11-0-UI
UI-R-E0-cy-f-02-0-UI
Bat2
Spon1
Mfge8
Ltbp1
Gnb2
UI-R-C0-jo-b-09-0-UI
UI-R-A0-bk-a-02-0-UI
(b) CT-independent EGF response
C.1 C.2 E.1 E.2 C.N1 C.N2 E.N1 E.N2
dE.1 dE.2 dE.N1 dE.N2
Acsa2
UI-R-A0-bh-b-12-0-UI
Mg87
Camk2d
Acat1
Loc266761
Gusb
Ncdn
Gpx1
Ugdh
Rcn2
Dpys
Gak
Epb4.113
Vcp
UI-R-A1-eq-g-09-0-UI
Il1r2
Slc1a1
Avpr1a
Camk2b
Gpr88
Gucy1b3
Pk428
Myf6
Ephx1
Decr1
Ywhag
Fst
Ll5
Rabac1
Rpl24
Hras1s3
LOC81816
ETF
Cnn1
Raf1
(c) EGF response, night only
C.1 C.2 E.1 E.2 C.N1 C.N2 E.N1 E.N2
dE.1 dE.2 dE.N1 dE.N2
Slc30a4
UI-R-A1-dy-e-06-0-UI
Zfp265
Lox
Tsc2
Emb
UI-R-A1-ds-h-01-0-UI
Kdr
Spin2c
Arf6
Psmd1
Zfp3611
Pcna
UI-R-C0-jn-g-01-0-UI
Mt3
Polr2g
Pcbd
Mxd3
Cox6a1
Arbp
S100a10
Slipr
Nup98
UI-R-A1-du-c-02-0-UI
Rps26
Lypla1
Gys2
Uchl1
Ramp1
Cpb2
Dgkz
Raf1
Ephx2
Cyp2d26
Col3a1
Ppp1r9a
Adh1
UI-R-BT0-qd-e-04-0-UI
Cd53
Ubb
Cabin1
Rin3
Gpnmb
Acsl4
Acad1
Ly5b
Rara
Cma1
Wfdc1
Dcn
Hbg1
Nole1
Pcsk3
Arpc1b
Cyp2e1
Slc21a5
Lalba
UI-R-A0-ar-h-08-0-UI
Itpr2
Mapk12
LOC56769
Mmp23
Ap2m1
(d) EGF response, day only
C.1 C.2 E.1 E.2 C.N1 C.N2 E.N1 E.N2
dE.1 dE.2 dE.N1 dE.N2
Abcf1
Napa
Drpla
Prf1
Prkag1
Mel
Fh1
Scarb1
Adcy3
Pde2a
Prkab1
Prmt3
Ssr3
Gstm1
Nif1
Hemgn
Hmgb1
(e) Day induction, night repression
C.1 C.2 E.1 E.2 C.N1 C.N2 E.N1 E.N2
dE.1 dE.2 dE.N1 dE.N2
Edq5
Ank3
Myd116
GRASP65
Prkcz
UI-R-A1-eh-b-10-0-UI
Cdo1
(f) Day repression, night induction
C.1 C.2 E.1 E.2 C.N1 C.N2 E.N1 E.N2
dE.1 dE.2 dE.N1 dE.N2
Fn1
Dbi
Fxyd1
Mvd
Cox6a2
Cdc25b
Ssr3
Rps10
Bmp4
UI-R-A1-ee-f-10-0-UI
Bcl2a1

CIRCADIAN SIGNALLING PAHWAYS: A CASE FOR EGF

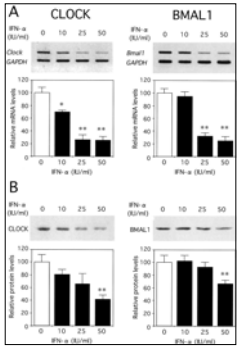




Bendayan H.J (2007)

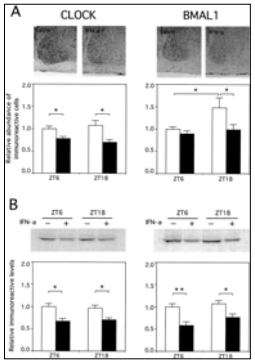
Interferon and Clock-controlled Genes: Circadian Expression

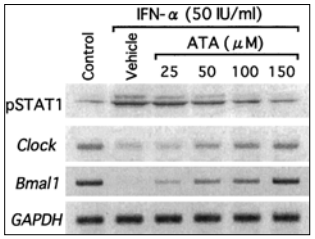
Modulation of the Vasculature Clock?



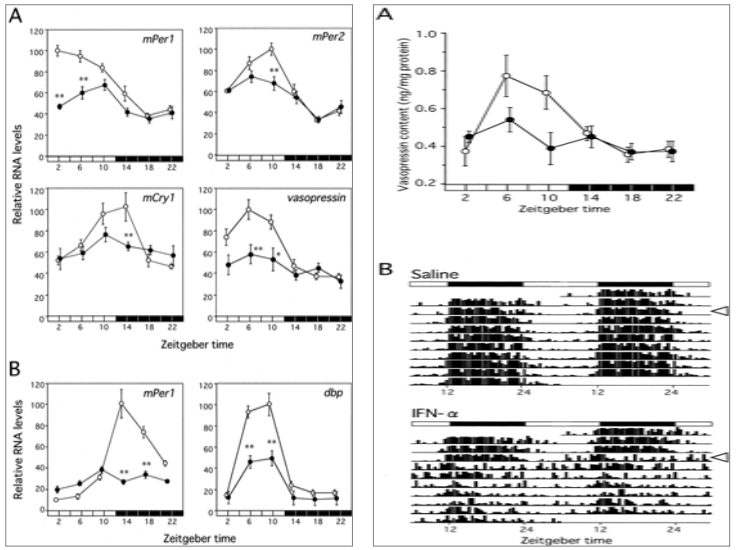
Interferon-α:

Circadian expression on Clock-genes



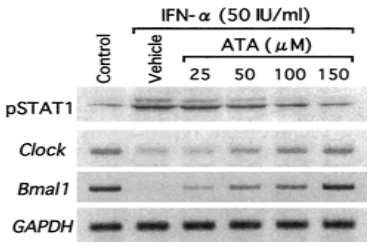


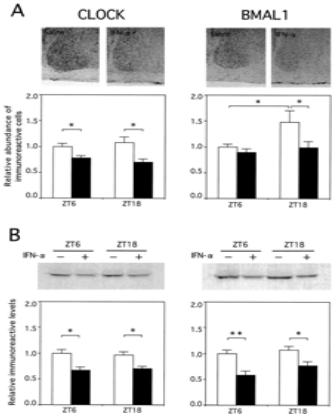
Vasopressin and Interferon-α: Effect on Clock-genes and Behavior



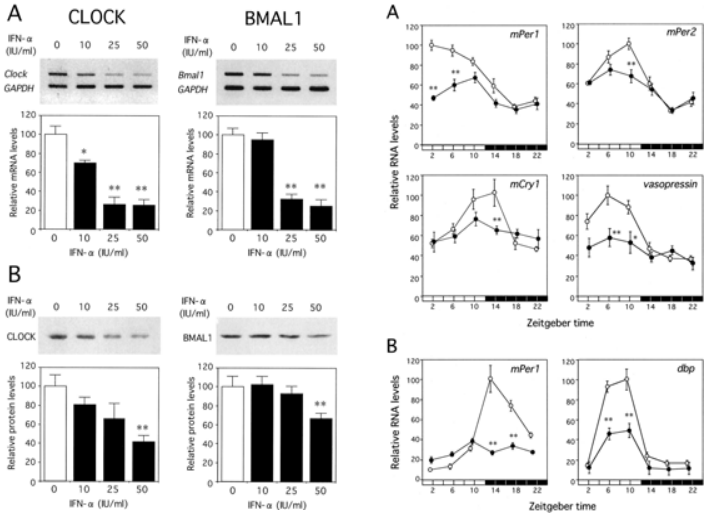
Interferon-a modulation:

Circadian pattern on Clock-Genes



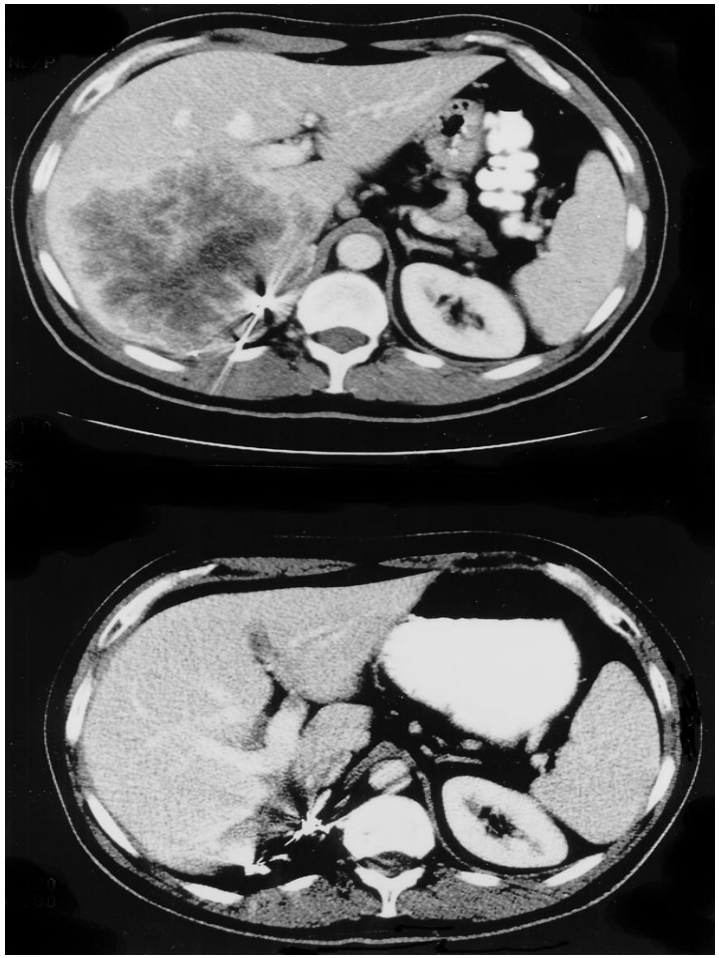


Clock-Genes Modulation: IFN-α and Vasopressin Pattern



Cancer Renal: IL-2 Chronomodulee

SSRI and Interleukin-2 (IL-2)



Regression complete de metastase hepatique d'un cancer du rein

traite par

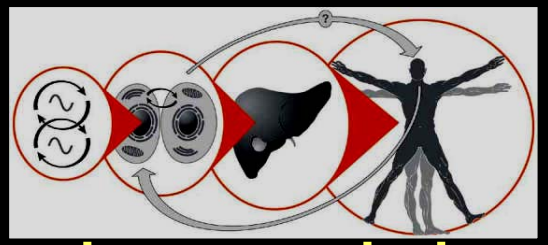
chronomodulation d'IL-2 + SSRI

7 ans de survie sans recidive

traitement personnalise du cancer du rein….2010?

Biologie de systemes ?
Biologie des fonctions ?
Bioinformatique ?
Genomique fonctionelle ?
Proteomique ?

Timekeeping for Systems Biology



- The circadian system in higher organisms and humans temporally orchestrates fall and rise rhythmic changes in a vast number of genes and gene products in different organs.
- Complex interactions between these components, both within and among cells, ultimately lead to rhythmic behavior and physiology.
- Identifying the plethora of circadian targets and mapping their interactions with one another is therefore essential to comprehend the molecular mechanisms of circadian regulation.
- The emergence of new technology for unbiased identification of biomolecules and for mapping interactions at the genome-wide scale is offering powerful tools to decipher the regulatory networks underpinning circadian rhythms.
- Potential application of these genome-wide approaches in the study of circadian rhythms.

CARTOGRAPHIE ET TEMPORALITE POUR UN TRAITEMENT CHRONO-PHARMACOGENOMIQUE DU CANCER DU REIN (Hote-tumeur interactions)

CIRCADIAN CANCER DRUGS

CIBLES CHRONO-GENOMIQUES

Cancer Chrono-Genotypes

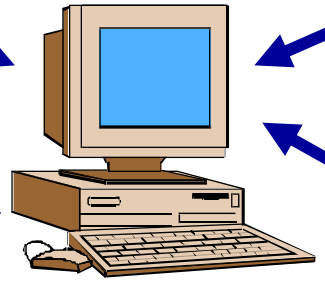
Cancer Chrono-Pharmacologie and Profile du Patient

Profile Chrono-Genotype

Disruption du Rythme Circadien Tumoral

Reparation Circadienne de l'ADN et Sensitivite Cycle Cellulaire

Cancer Time-keeping Genotypes Resistants?



CHRONO-METABOLISME du RYTHME DES AGENTS ANTICANCEREUX

Profils Endocriniens de Repos/Activite

Profil Proteomique (et ARN Circadien)

Chrono-Genotypes Individuels

Toxicite Tumorale Circadienne
Toxicite Cliique Circadienne

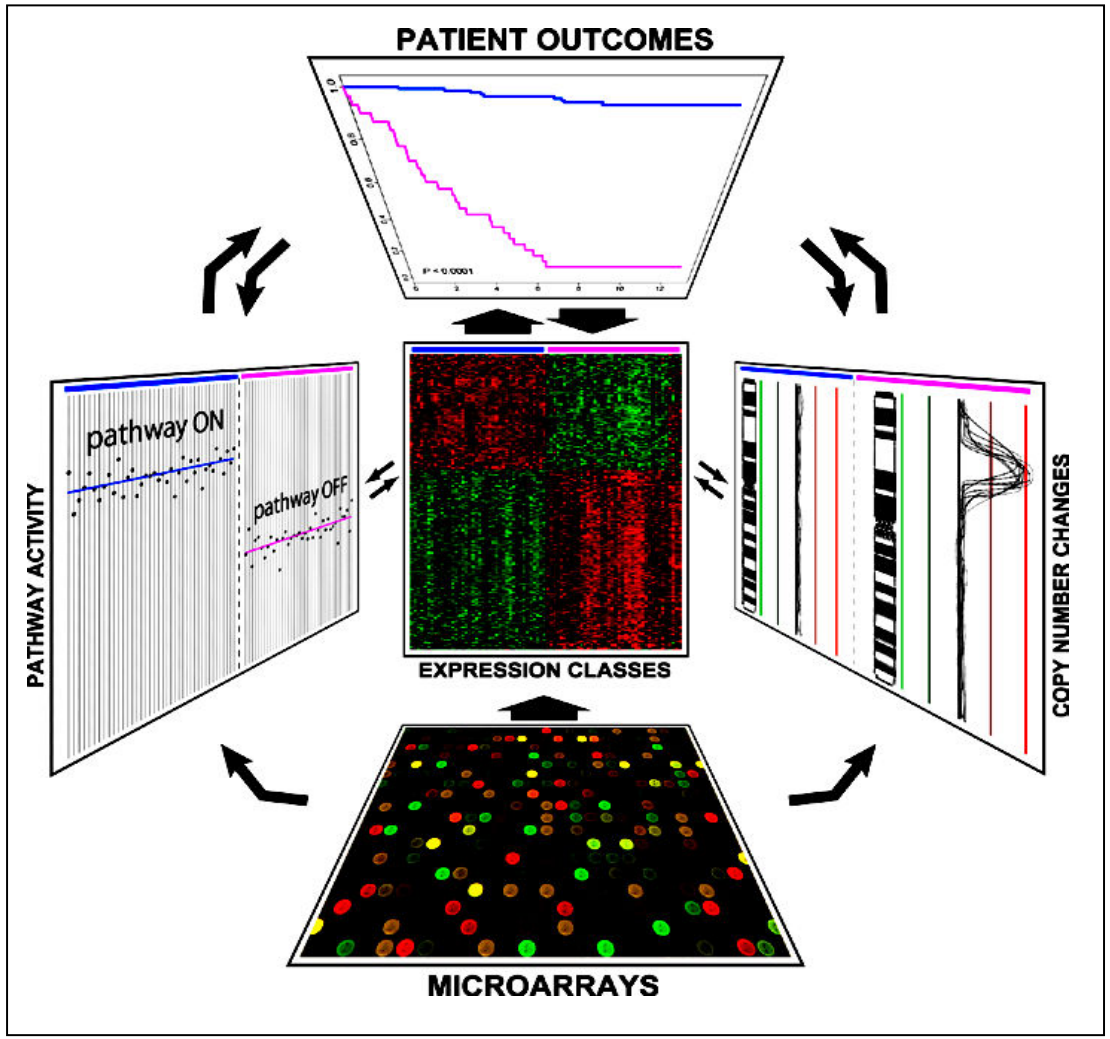
Chrono-respondeurs Patient/Tumeur Genotypes?

Genre, Timing et Doses

TRAITEMENT TEMPORALISE CIBLE, INDIVIDUALISE

Dr Bendayan Haim J. Theraclock Genomics International Project

RENAL CANCER SYSTEMS BIOLOGY IN REAL TIME: NEW SOLUTIONS FOR THERAPY



PARAMETERS:

- **Relation Hote (patient)/ Tumeur**
  (rein, sites metastatiques..)
- **Signatures molec selon le genre**
- **Rythmes circadiens genomiques:**
  . Du patient (WGA, Monocytes)
  . De biopsies
- **Variations saisonnieres**
- **Alterations epigenomiques**
- **Vie Societale de 24h**
  (Luminosite, Alimentation,Environnement)

Bio-informatique ***Modeles Mathematiques***

SIGNAUX INTEGRATIFS DU PATIENT ET DE LA TUMEUR

Genomic Cancer Timesome Database

Bendayan JH 2008

Theraclock Genomics International Project

CHRONO-PHARMACOGENOMICS

Genre et Genome du Temps Biologique Humain

Pour definir

le meilleur traitement a son meilleur temps

Pour traiter votre tumeur

Et adapter

les doses appropriees selon

la connaissance

De votre profile personnel, votre sexe et les signatures moleculaires tumorales associees

(PaT-ID-Clock)

“Research is to see
what everybody else has seen

and

to think
what nobody else has thought.”

— ALBERT SZENT-GYÖRGYI

Progress demands that the inestimable "force" of inertia be underestimated.

Thinking "new" thoughts:

- impossible for most,
- difficult for all,
- frightening for many

...and... irresistible for a few.
...dangerous in Science...
...deadly in Medicine...

“ The Voyage of Discovery

Does Not Consist In

Seeking New Landscapes

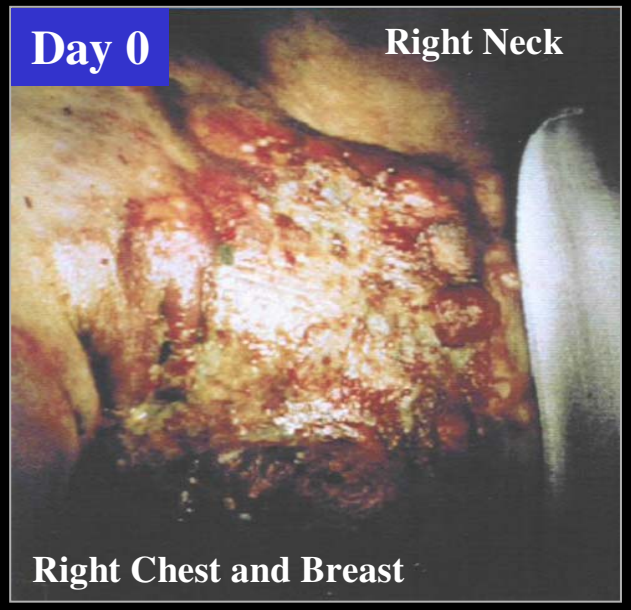
But

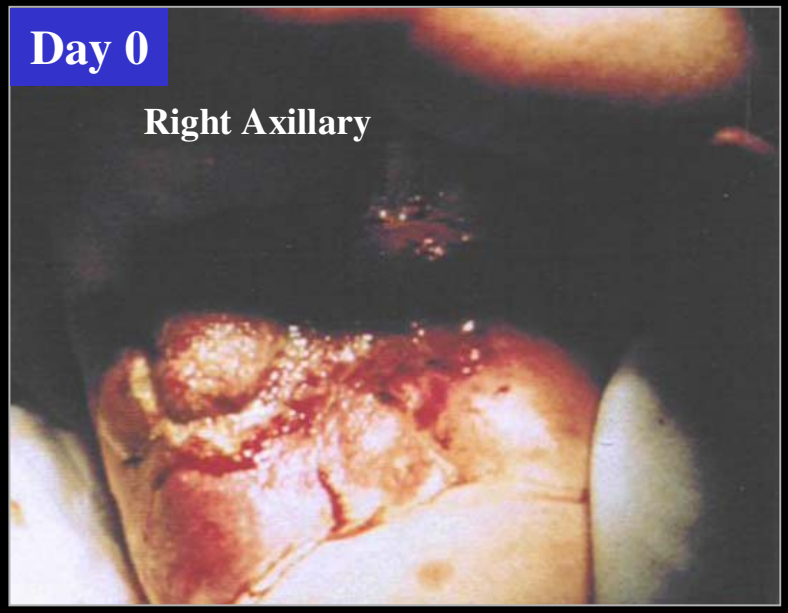
In Having New Eyes “

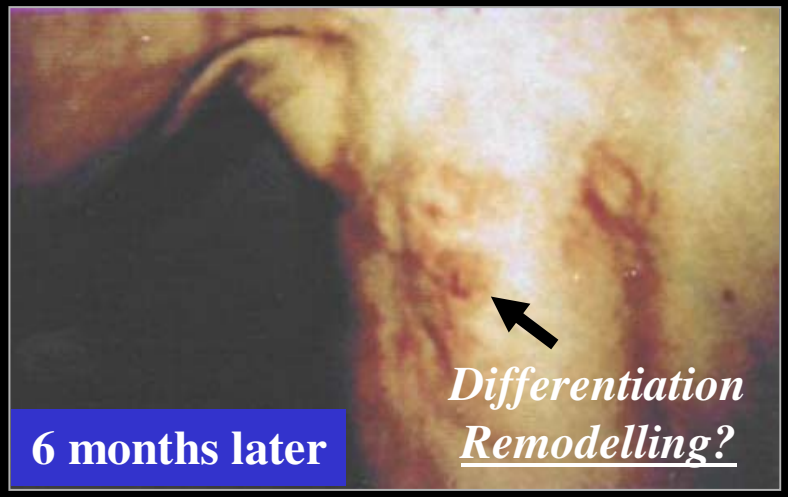
Dr Haim J. Bendayan (1995)

TRIP CONCEPT: Chronotherapy for Advanced Breast Cancer

Chrono-Endocrine Modulation of Kinetic DNA Repair Inhibition (polB) and Chrono-Pharmacogenomic Enhancement of Low-dose (CMF) Drug Uptake



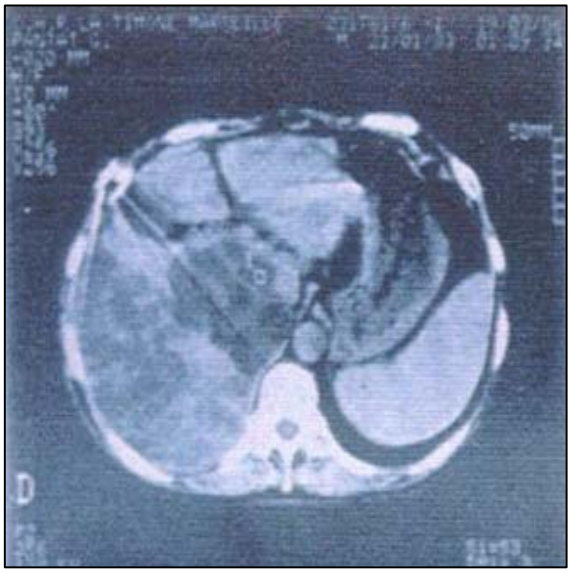


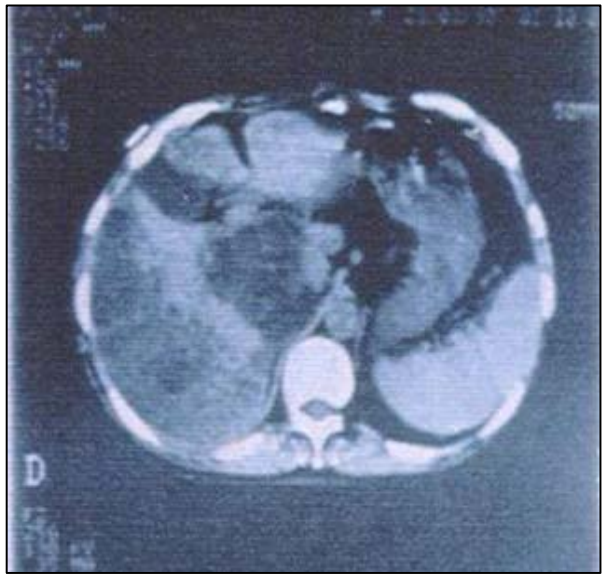


Dr Haim J. Bendayan

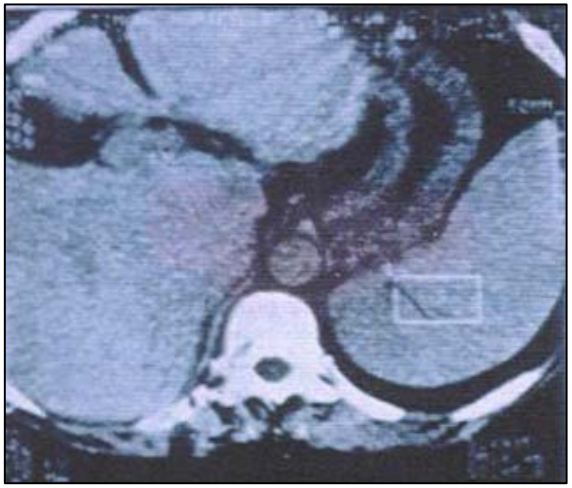
TRIP CONCEPT: Hepatic Intra-Arterial Chronotherapy of Liver Metastasis

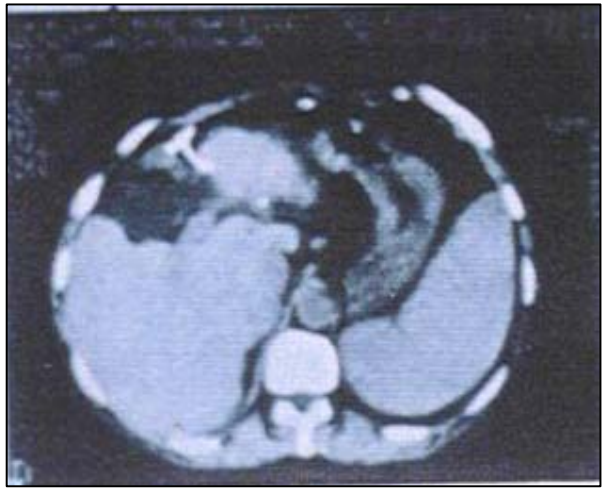
Circadian endocrine kinetic Inhibition of DNA Repair (PolB) and Pharmacogenomic enhancement of low-doses FuDr (IA) + MTX (IV)





Before Treatment (Intra-arterial Hepatic Artery Catheter Insertion)





After Surgical Removal of Hepatic Intra-arterial Artery Catheter

Differentiation/ Tissue Remodelling?

Dr Haim J. Bendayan