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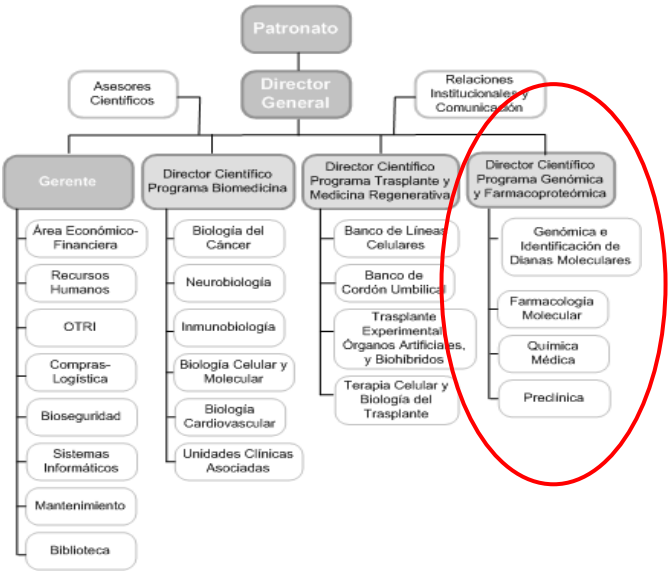
CENTRO DE INVESTIGACION

# Genómica y farmacoproteómica

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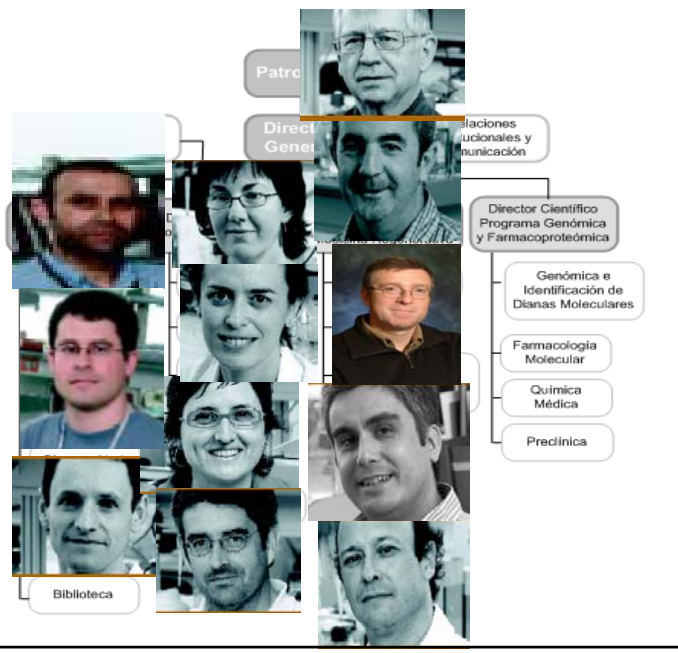

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# Genómica y farmacoproteómica

## DD-2005

MONTH 0-2 | 3- 6 | 4- 7 | 5- 8 | 6- 12

SAMPLES → TARGETS → SCREENING → CHEMISTRY → DD-LEAD

- Pharmacophores
- Structural diversity
- PN / Synthesis
- Available Weight
- Feasiblity Synth.
- Repository.
- Storage.
- Pre-Plating

- 1-50 mcM /well

- 4-6 Screens 4Q05:

A.- Transcription Factors:
B.- mRNA Transport
C.- Self-Renewal
D.- Differentiation.
E- Apoptosis.
F.- Matastasis.
G.- ZF-Pathway screening

- dB Searching
- D/R. Potency.
- Selectivity.
- Cell Cycle.
- Signalling.
- HPLC- AnalyticalProfile.
- In vitro TOX
- Tissue Selectivity.

- Structure- Novelty
- Amenable for Synthesis?
- S.A.R..
- Weigth
- MTD
- Efficaccy _Animal Model.
- IP- recomendation

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# Genómica y farmacoproteómica

## farmacología molecular

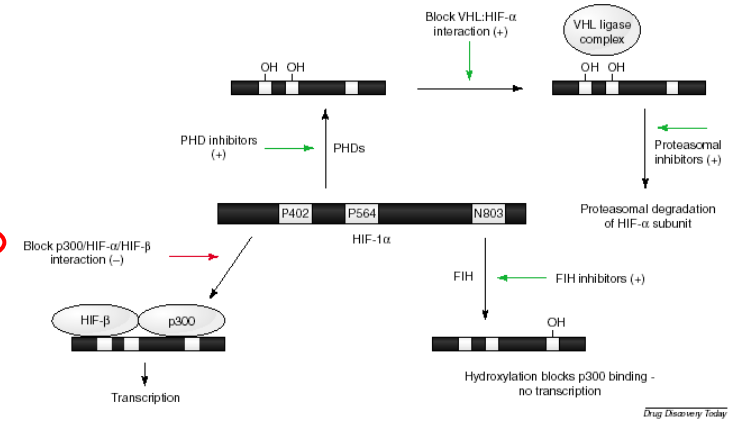


Figure 1. The HIF pathway. The coloured arrows indicate possible points of therapeutic intervention by small molecules, either to increase (green; +) or decrease (red; –) HIF levels or activity.

*Hewitson KS and Schofield CJ, Drug Discov Today. 2004 Aug 15;9(16):704-11. Review.*

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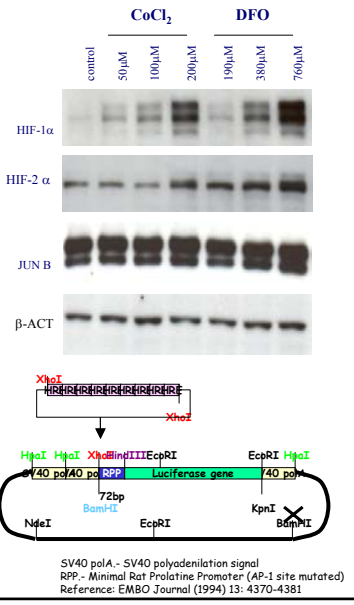
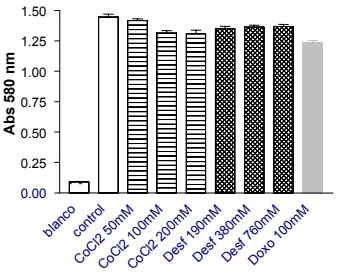
*Genómica y farmacoproteómica*

## HeLa / 6h hipoxia química

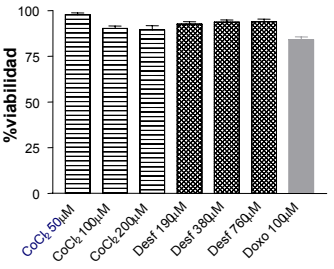



SV40 polA.- SV40 polyadenilation signal
RPP.- Minimal Rat Prolatine Promoter (AP-1 site mutated)
Reference: EMBO Journal (1994) 13: 4370-4381

### HeLa 6 h hipoxia química
### VIABILIDAD valores absolutos




### Hela 6 h hipoxia química

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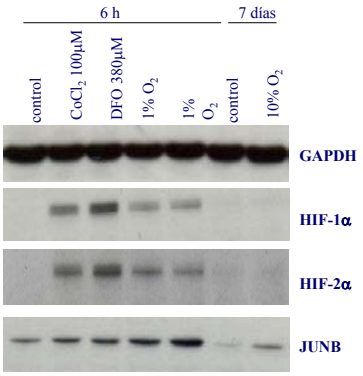
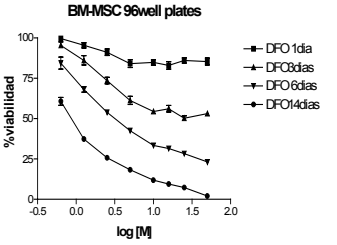
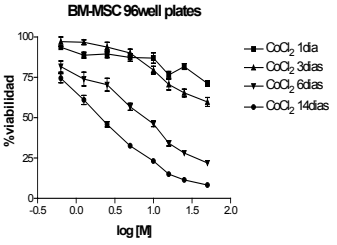
*Genómica y farmacoproteómica*

## BONE MARROW-MESENQUIMAL STEM CELLS



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# Genómica y farmacoproteómica

## farmacología molecular

HIFα JunB

### Proteómica

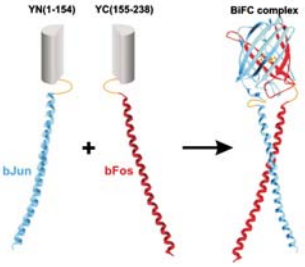
Identificación de los complejos proteicos implicados en la modulación y homeostasis de las dianas

### Genómica

Mapa transcripcional en presencia /ausencia de moduladores.

### Laboratorio de Peptidos

BiFC YFP




### Citómica

Inmunocitoquímica de marcadores regulados directa o indirectamente por las dianas.

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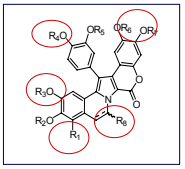
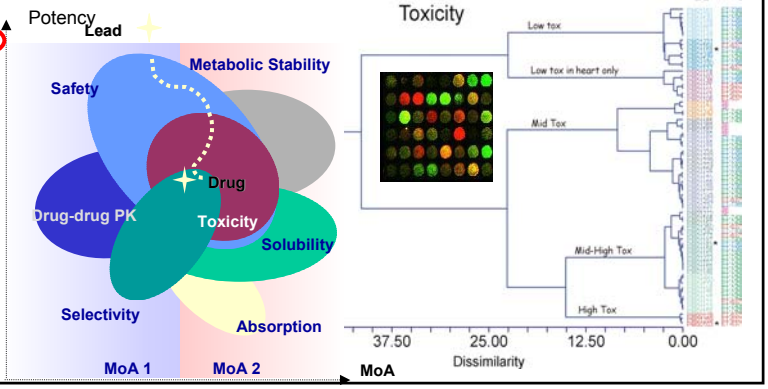
Genómica y farmacoproteómica

farmacología molecular





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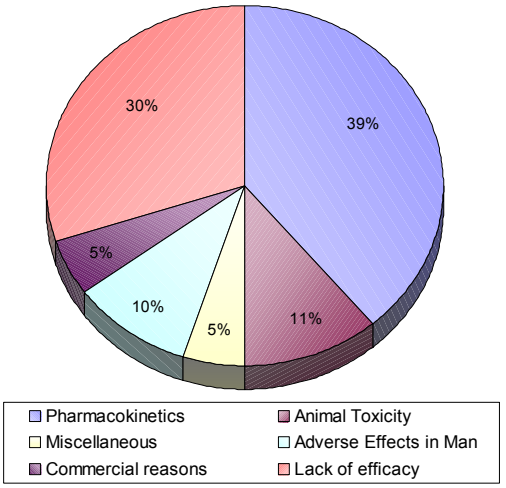
# Genómica y farmacoproteómica

## Análisis de las principales causas de terminación de fármacos en desarrollo en los 90




*Nature Reviews / Drug Discovery*

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# Genómica y farmacoproteómica

## farmacología molecular

## diferenciación de células troncales

J.L. Mullor

**Zebrafish-Based Small Molecule Discovery**

Calum A. MacRae and Randall T. Peterson*
Developmental Biology Laboratory and Cardiovascular Research Center
Massachusetts General Hospital
Charlestown, Massachusetts 02129

*IN VIVO* DRUG DISCOVERY IN THE ZEBRAFISH

*Leonard I. Zon* and Randall T. Peterson†*

Aquaria Fish Models of Human Disease: Reports and Recommendations from the Working Groups

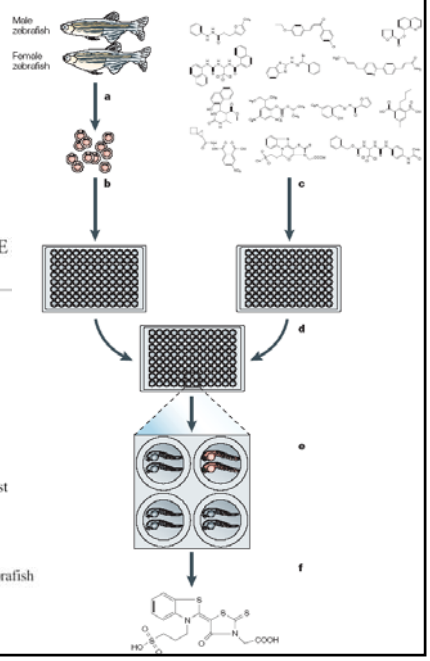
Rodney S. Nairn,[1] Michael C. Schmale,[2] John Stegman,[3] Richard N. Winn,[4] and Ronald B. Walter[5,6]

Exposure of Japanese medaka (*Oryzias latipes*) to benzo[a]pyrene suppresses immune function and host resistance against bacterial challenge

E.A. Carlson, Y. Li, J.T. Zelikoff *

Induction of reversible hemolytic anemia in living zebrafish using a novel small molecule☆

Ebrahim Shafizadeh[a,1], Randall T. Peterson[b], Shuo Lin[a,*]



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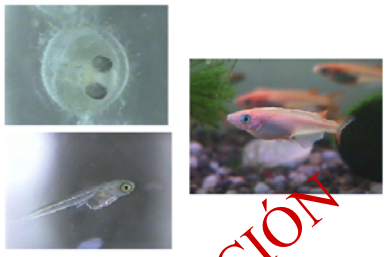
# M E D A K A

Oryzias latipes

Development of Test Methods and Suitability of Medaka as Test Organism
for Detection of Endocrine Disrupting Chemicals





February 2003

Ministry of the Environment, Japan
Chemicals Evaluation and Research Institute, Japan

Genómica y farmacoproteómica

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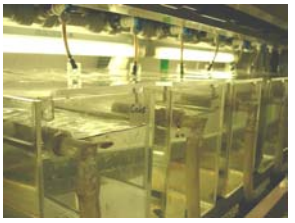
## Desarrollo de plataformas para HTS sobre embriones de Medaka y Xenopus



Ranas (*Xenopus tropicalis*)

Peces medaka (*Oryzias latipes*)

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## *Genómica y farmacoproteómica*

**Pros**:

- Desarrollo ex útero
- Gran número de embriones
- Fácil manipulación genética
- in vivo
- Correlación Preclínica positiva.

***Xenopus tropicalis***

**Cons**:

- Infraestructura.
- Gran número de embriones.
- Aceptación regulatoria.

***Medaka (Oryzias latipes)***

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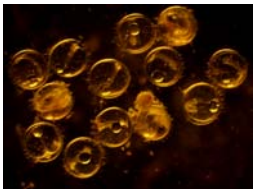
## *Genómica y farmacoproteómica*

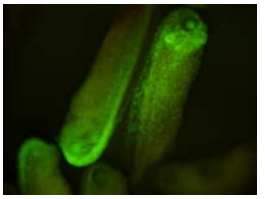
## *Generación de transgénicos*

[ *Pathway-based Screening*]

- ❑ **BMP**
- ❑ **WNT**
- ❑ **p53**
- ❑ **Shh**
- ❑ **HIF1**
- ❑ **JUN B**



***Medaka (Oryzias latipes)***



***Xenopus tropicalis***

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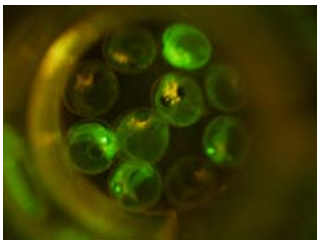
## Genómica y farmacoproteómica

**CIPF**: *"Medium Throughput Screening"*

- 96-pocillos.
- Fluorescencia (Victor$^3$)
- Dosis-Respuesta.
- 300-2000 embriones/día (60-400 ensayos/día)

***Medaka (Oryzias latipes)***

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## Genómica y farmacoproteómica

### *Modelos de Tumorogénesis en el CIPF*