Nielix: New antitumoural drug for leukaemia, melanoma, colon and ovarian cancer

FAES FARMA
www.faes.es

Madrid, 7 de mayo de 2013

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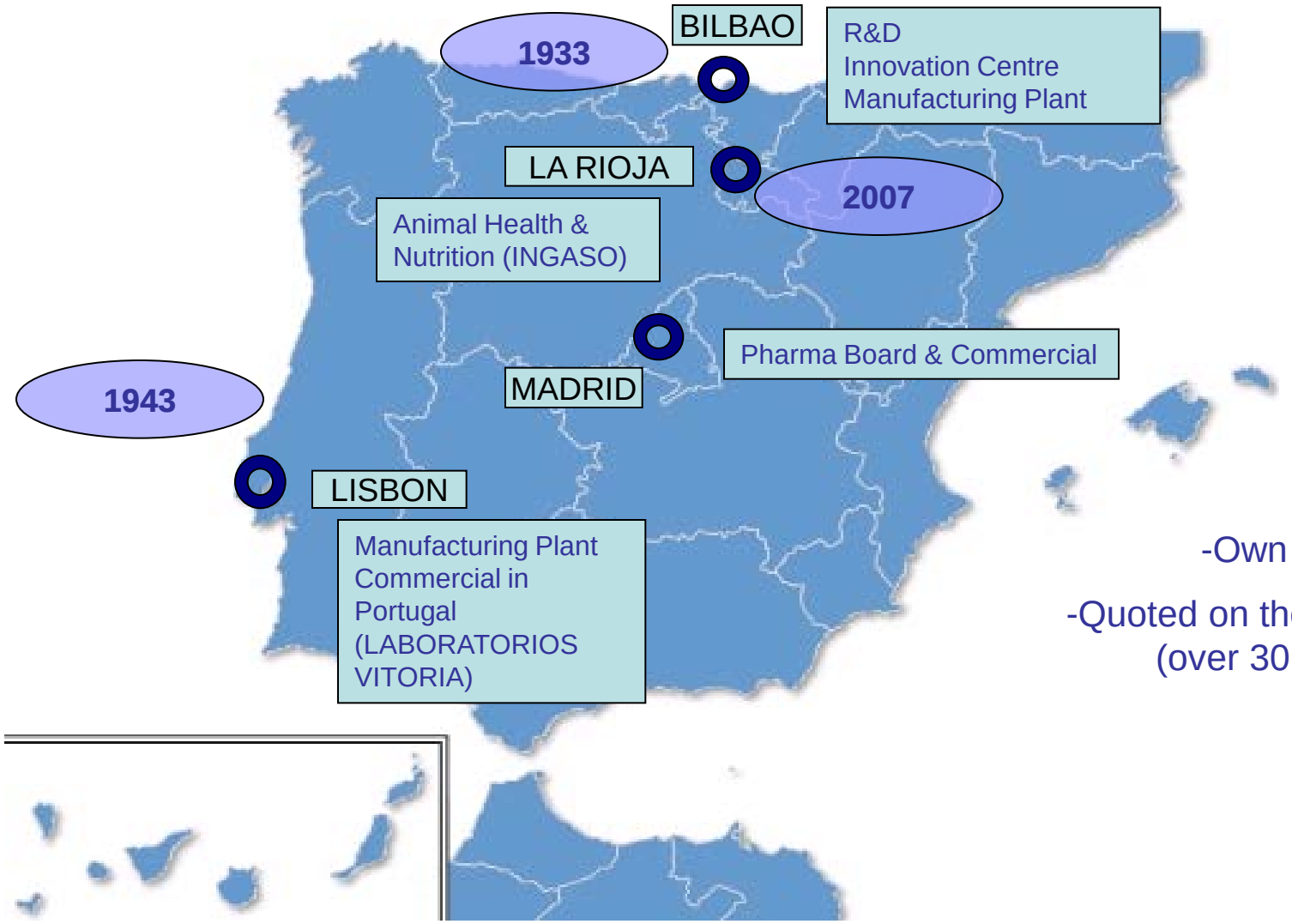
1.THE COMPANY



-Own R&D since 1935

-Quoted on the Stock Exchange, (over 30,000 shareholders)

FAES FARMA ON THE ROAD TO INTERNATIONALIZATION

2009

FAES FARMA, SAS

2011

FAES FARMA DEL ECUADOR, S.A.

2009

FAES CHILE SALUD Y NUTRICION LIMITADA

Export of drug products and raw materials to **more than 60 countries** in **Europe, Latin America, Africa and Asia**

Product portfolio and commercial activity is strengthened through a strategy of acquisitions, licensing and distribution agreements

COMARKETING

Bayer Schering Pharma

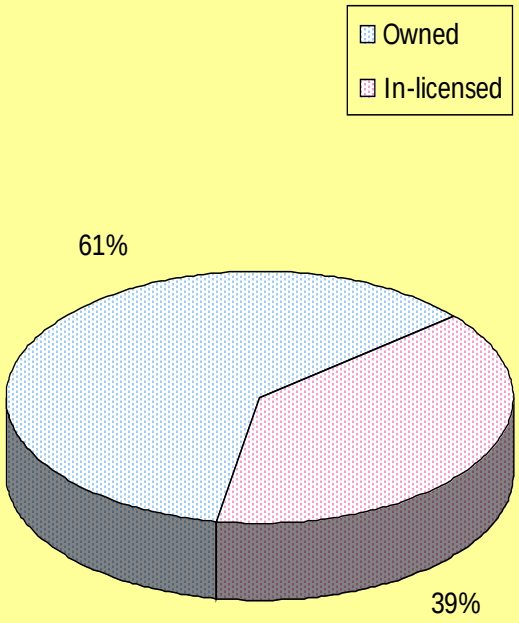
GRÜNENTHAL · Roche · sanofi aventis · MERCK Human Health · ITALFARMACO S.A. · gsk GlaxoSmithKline · Tillotts · Lilly

OTHER COMMERCIAL AGREEMENTS

IPSEN Innovation for patient care · AstraZeneca España · cinfa Nos mueve la vida · hhc human health care · Eisai · IROKO PHARMACEUTICALS, LLC · ProStrakan

BILASTINE

GRUPO MENARINI · MERCK SERONO · KALBE · INVIDA · yuhan CORPORATION · Takeda · NYCOMED · Nycomed: a Takeda Company · YIANEX · ЈИКИМА ХИМИЈА ФАРМАЦЕВТСКИ ПРОИЗВОДИ · Pfizer · TAIHO TAIHO PHARMACEUTICAL CO., LTD.



Net sales 2011
190M€

Net Sales 2012
176M€

2.TARGET INDICATIONS

Cancer is the second leading cause of death the Western world (after cardiovascular diseases). **Traditional treatments show high toxicity levels and most patients relapse.** Moreover, and haematological cancer, colon or melanoma, are still considered incurable diseases.

The investigation of novel treatments for cancer and the subsequent clinical approval of some of them with demonstrated anticancer activity, such as **biological compounds, antibodies, stimulators of immune system, have changed the outcome of cancer patients in the latest years. Unfortunately, this is a very expensive treatment and for a limited spectrum of patients.**

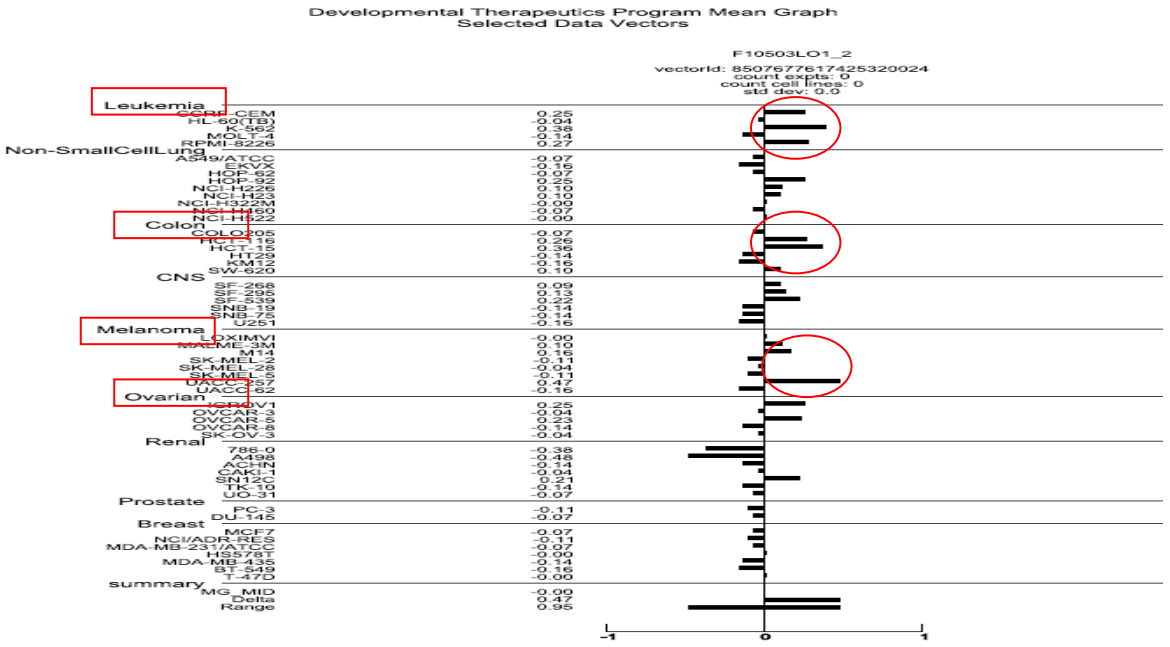
FAES FARMA is about to complete the preclinical development of a **small molecules family of its own R&D portfolio (nielix), which has demonstrated an excellent *in vitro* and *in vivo* activity on haematological and solid tumour cell lines as well as in animal models** of several tumours such as **chronic lymphatic leukaemia, multiple myeloma, melanoma, colon cancer and ovarian tumours.**

The European patent application was submitted In November 2010.

2.1. NCI 60 cell lines Panel and "Compare" Data Integration

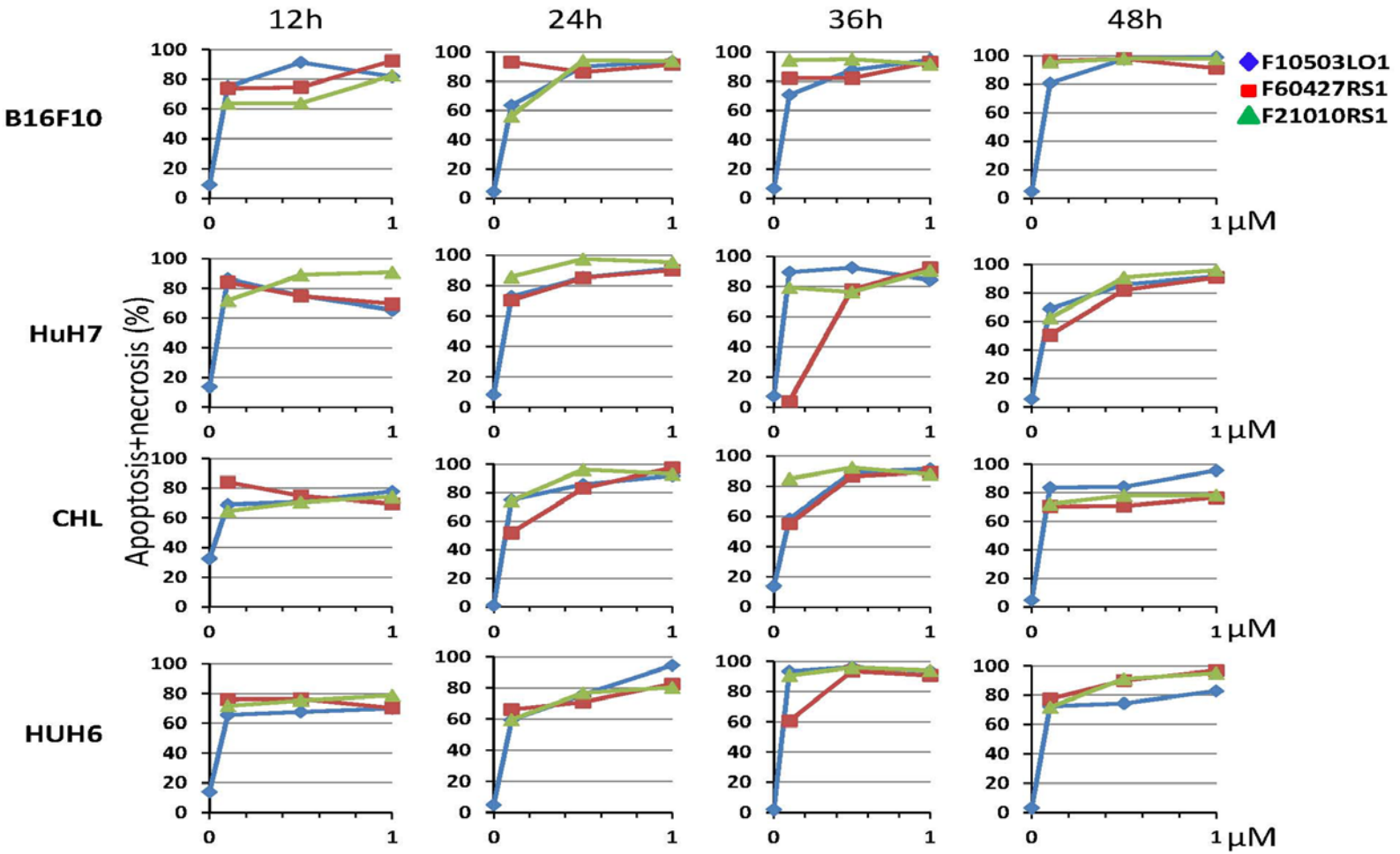
Cell lines reflect diverse cell lineages. Since 1990, data on drug-related cytotoxicity for 100,000 compounds have been collected. In addition, many genes that have been causally investigated or frankly implicated in tumorigenesis and cancer progression (molecular targets) have been studied, at the DNA, RNA, and protein level (p53, mismatch repair –MMR- status, cell cycle checkpoints, and so forth), and expression analysis of near of 8000 genes performed.

F10503LO1 resulted an active compound within a wide variety of human tumour cell lines and suggest a relative higher sensitivity of blood malignancies, melanoma and colon cancer.



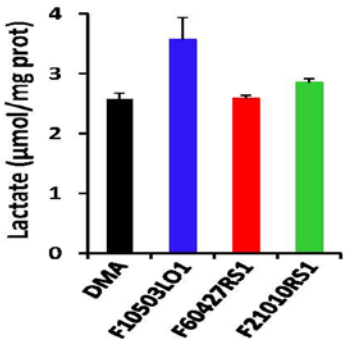
Programa Cooperación Farma-Biotech

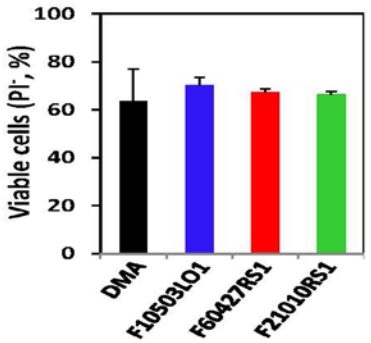
8º encuentro (7 de mayo de 2013)

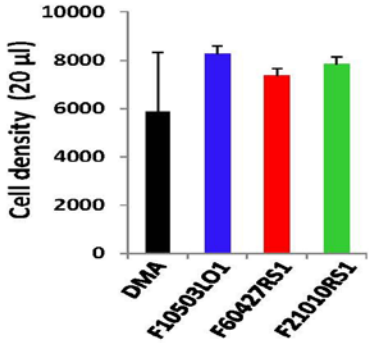


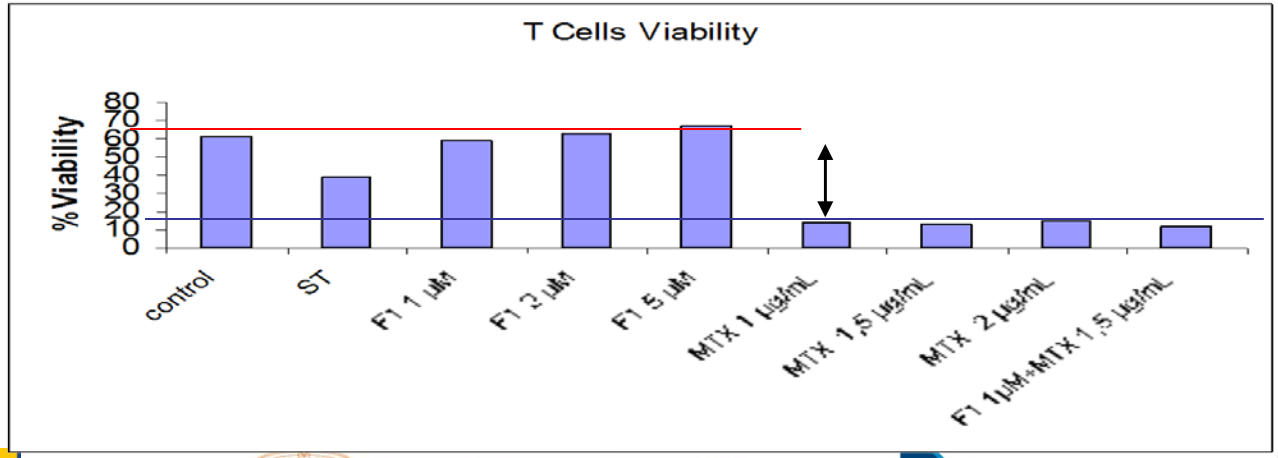
2.2. Toxicity over non tumour human cells

Human Mo differentitated into resting macrophages
200 nM FAES compounds for 18 h (per triplicate)



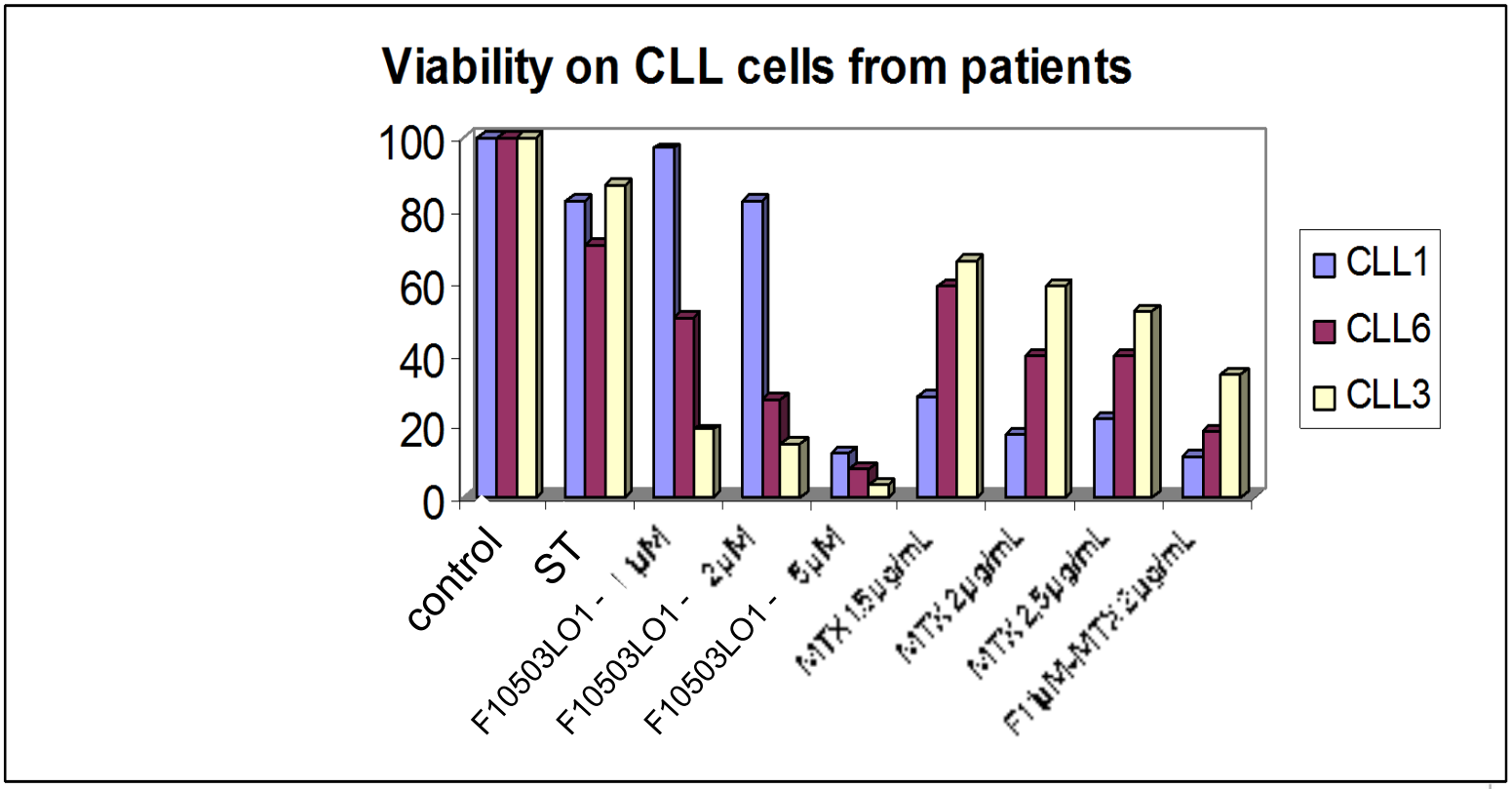






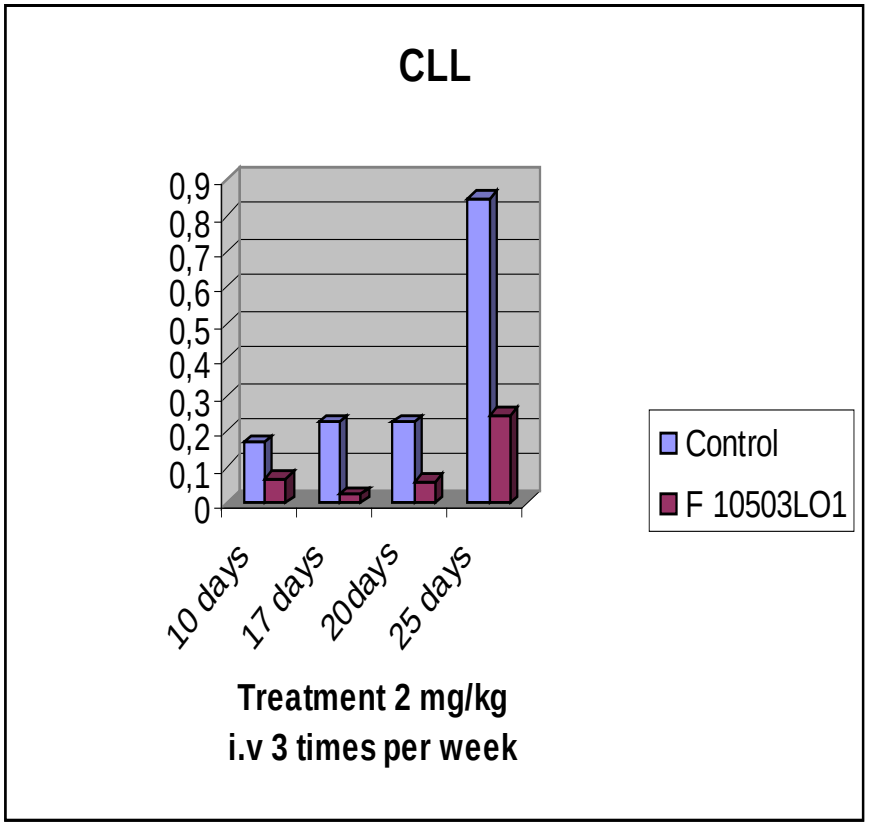
2.3. Haematological cells in vitro from patients CLL

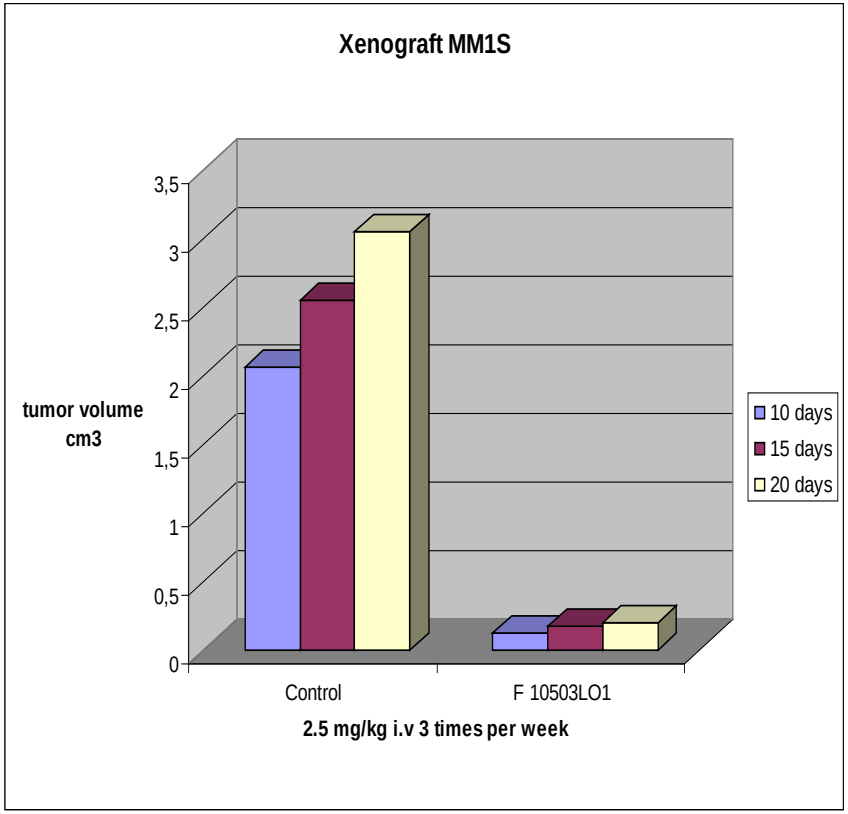
Preliminary results on *in vitro* experiment using CLL cells from patients (different levels of ZAP70 biomarker) have demonstrated a similar effect to mitoxantrone.



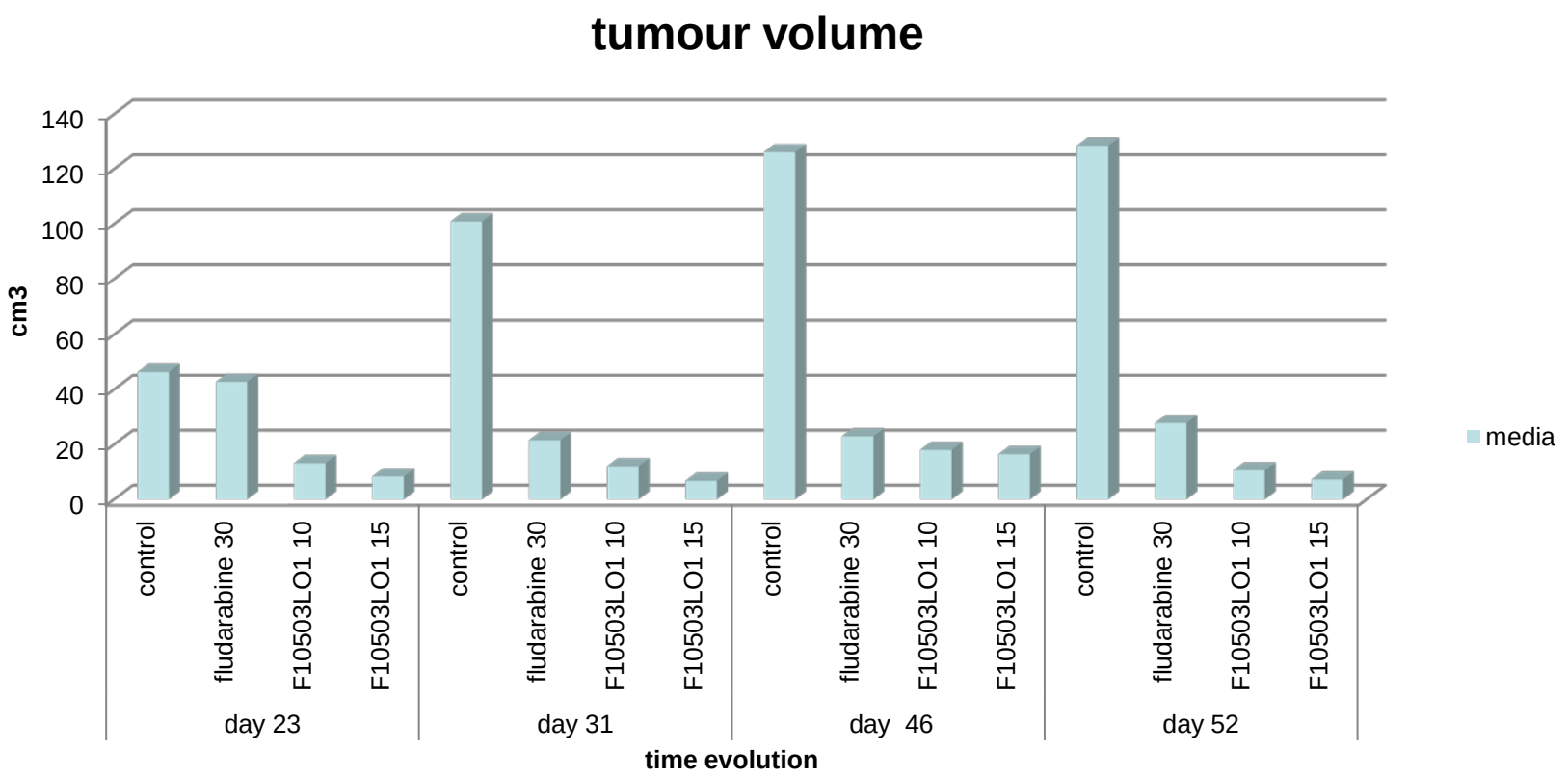
3. *IN VIVO* ASSAYS

3.1. In vivo antitumoural activity on hematological cancers





In vivo antitumoral activity in Chronic lymphocytic leukaemia F10503LO1 vs. FLUDARABINE



COLON CANCER

3.3. In vivo antitumour activity of compound F10503LO1 in a cancer colon mutated Kras orthotopic animal model

Lung cancer was also the most common cause of cancer death (341.800 deaths), followed by colorectal (203,700), stomach (137,900) and breast (129,900).

Patients with Stage IV tumour have only a 10 percent chance of a cure.

Metastasis
KRAS oncogen mutation

Control

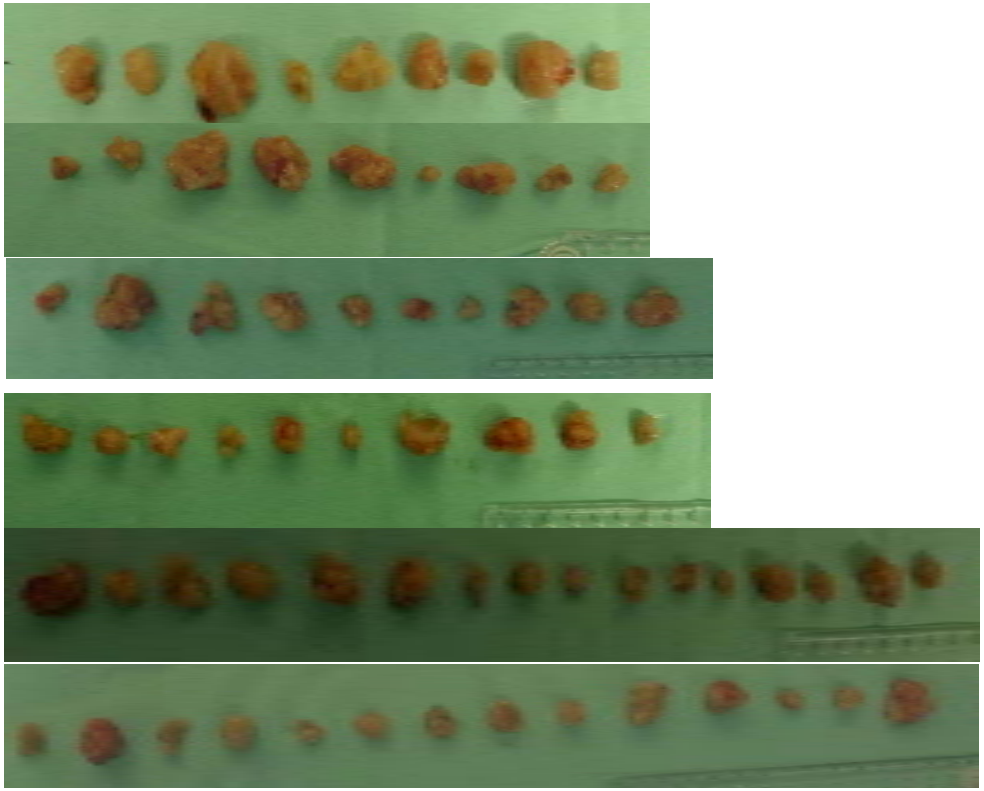
5FU

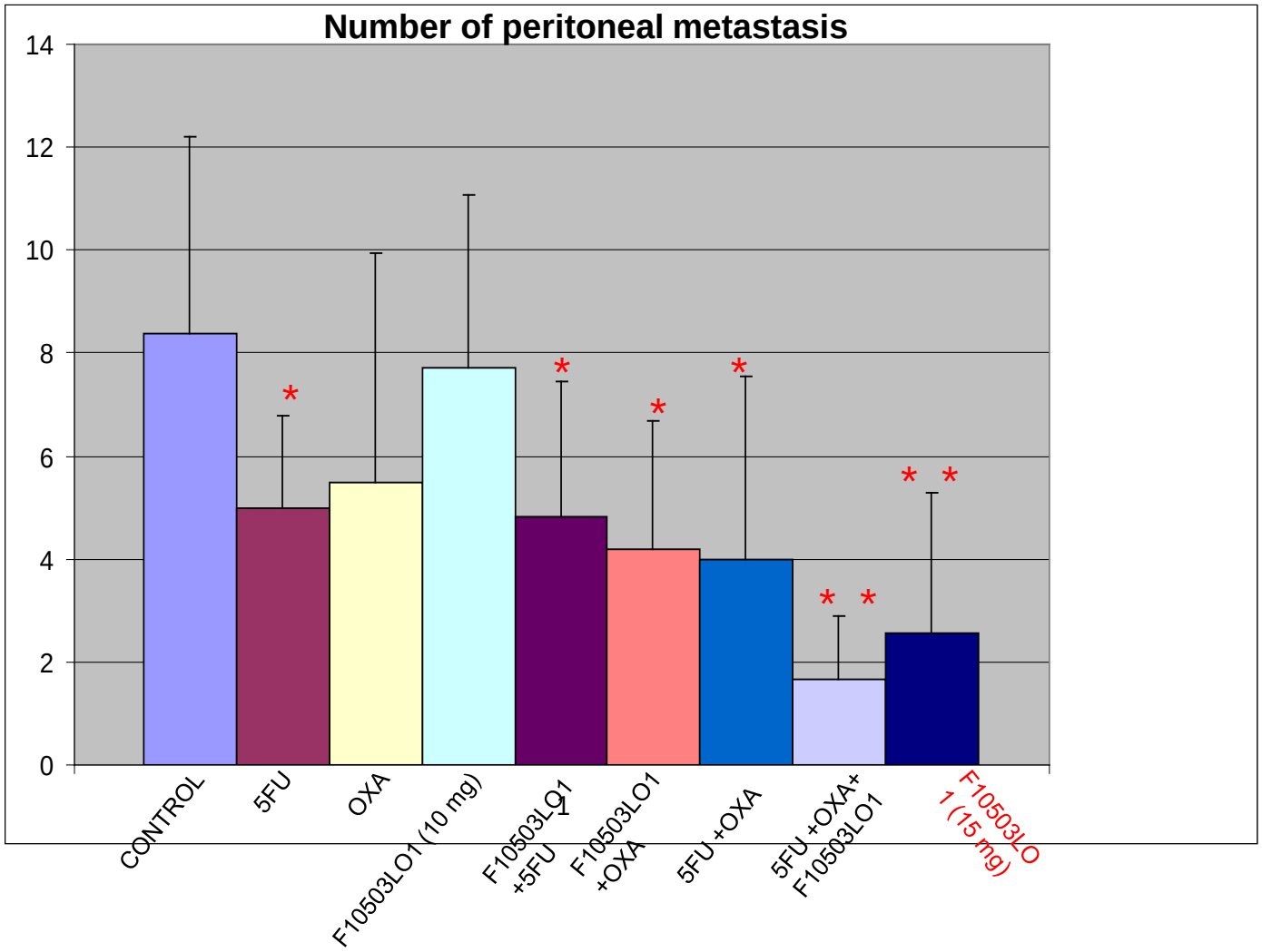
OXA

F10503LO1

5FU+OXA

5FU+OXA+F10503LO1




Number of peritoneal metastasis
14
12
10
8
6
4
2
0
CONTROL
5FU
OXA
F10503LO1 (10 mg)
F10503LO1 +5FU
F10503LO1 +OXA
5FU +OXA
5FU +OXA+ F10503LO1
F10503LO 1 (15 mg)

MELANOMA

Melanoma is one of the most aggressive tumours, with a great ability to metastasis and worse prognostic for patients. This cancer originates in the melanocytes.

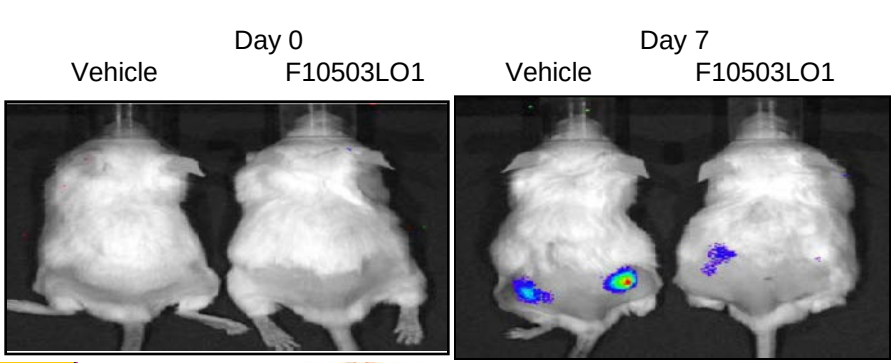
Approximately 47,700 cases per year are currently diagnosed in the United States alone, and incidence is increasing at the rate of 4.3% per year, one of the fastest increases in occurrence rates of all cancers.

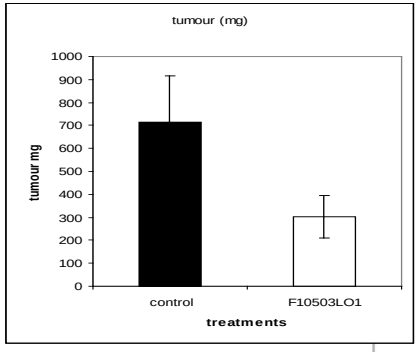
The American Cancer Society estimates there are currently 480,000 cases of melanoma in America and that there are 7,700 deaths per year because of this disease. Every year, 90,000 new cases are diagnosed in the U.S., Europe and Australia; 15,000 people die annually.

3.4. In vivo antitumour activity of the compound F10503LO1 in a melanoma orthotopic animal model

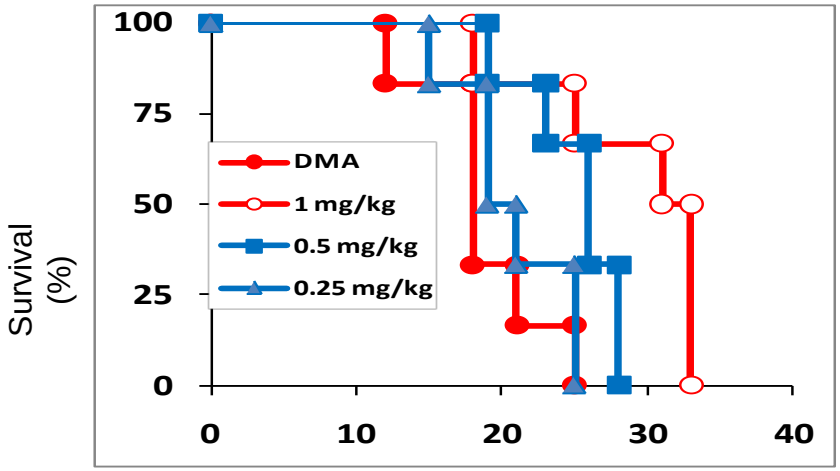
B16 mouse melanoma cells exhibit an aggressive progress and is a widely used and reproducible model to study many aspects of cancer biology and therapeutics in a solid tumour. In addition, using bioluminescent B16 melanoma allows for serial, real-time analyses of tumour burden in live mice. On this model, compound F10503LO1 exhibits a potent *in vivo* antitumour activity in the melanoma orthotopic mouse model.

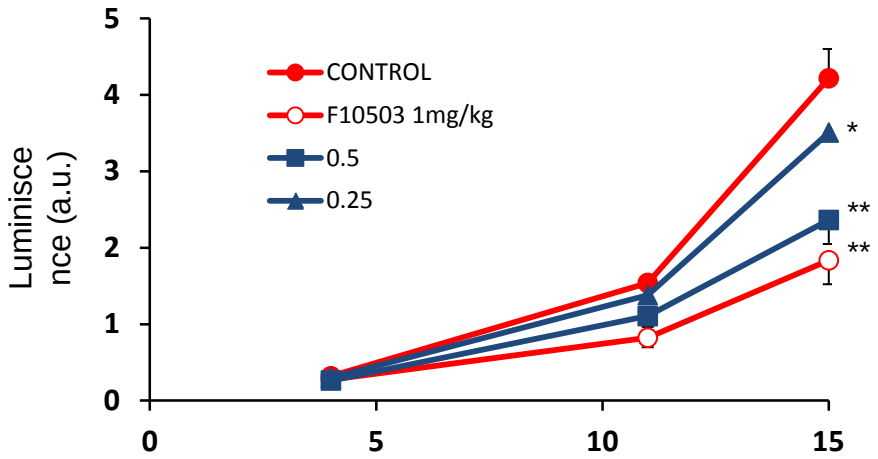
Effect of F10503LO1, 30 mg/kg/gay for 7 days, i.p. (inoculation of B16F10-luc on day 0). SCID/NOD mice



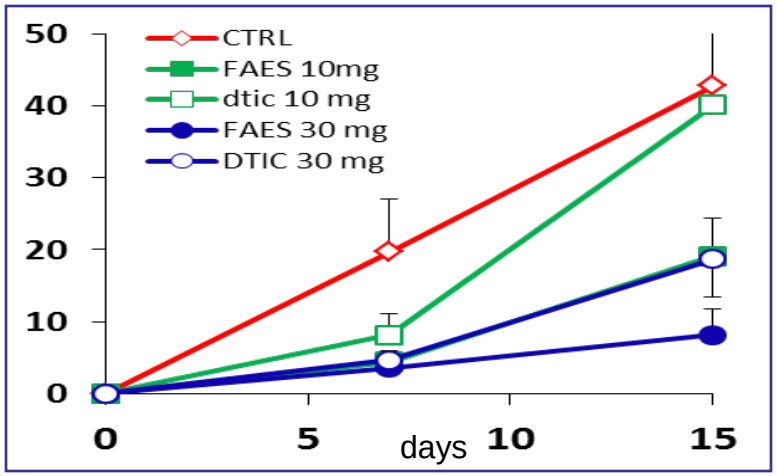


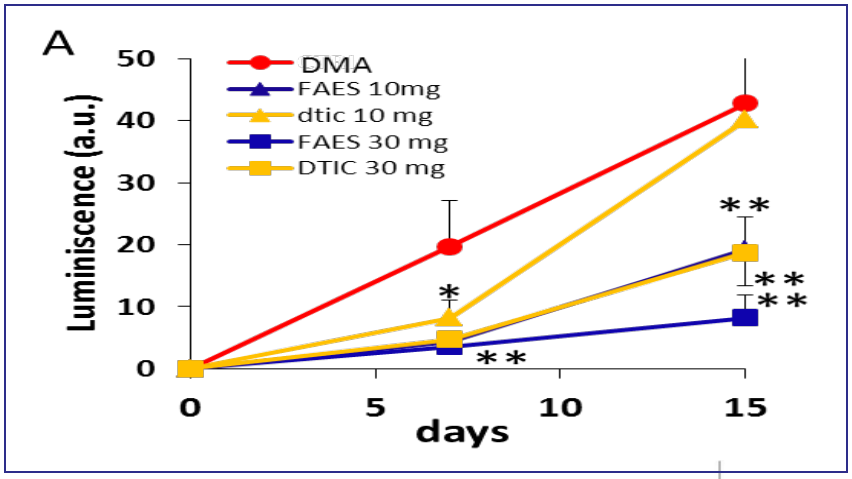
I.v. administration

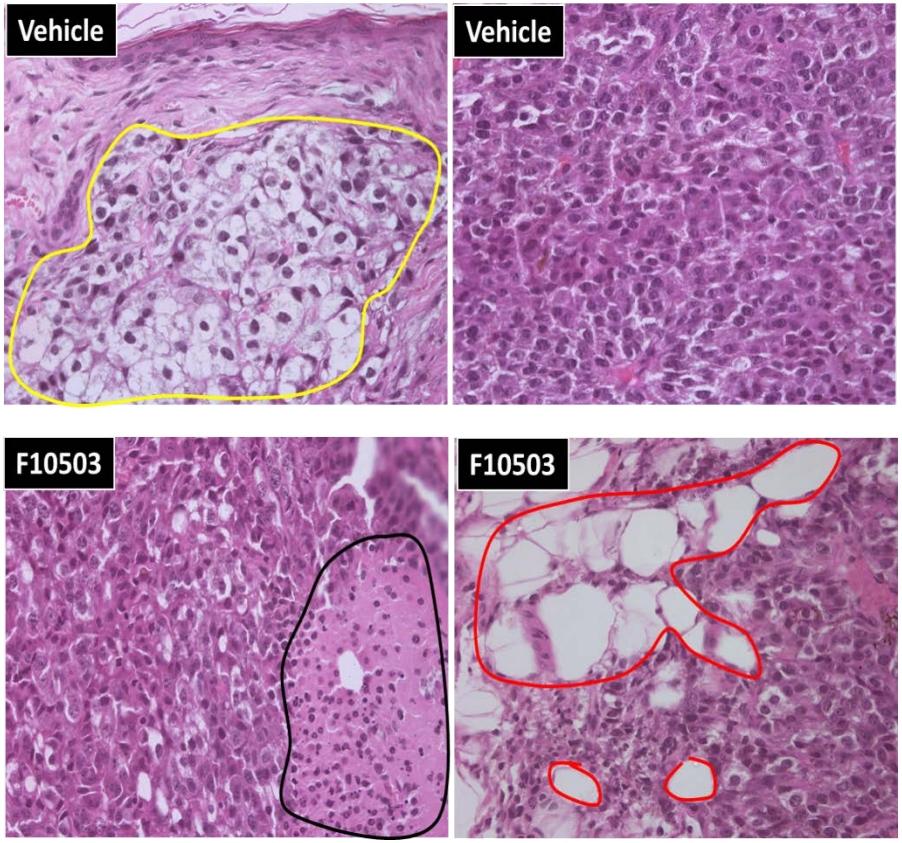




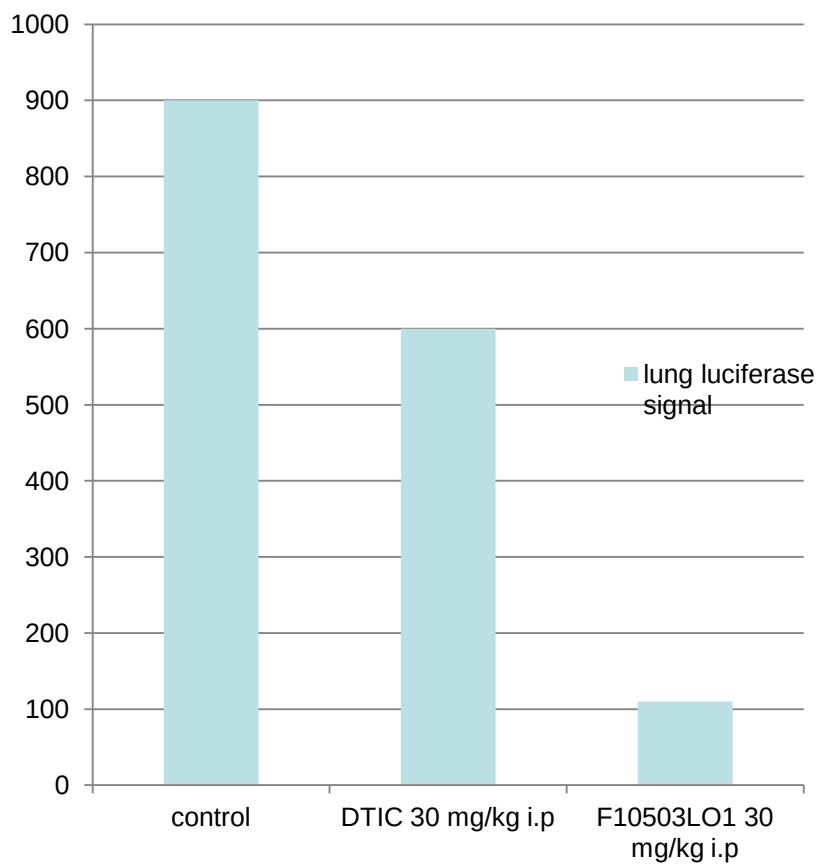
F10503LO1 Vs DTIC







(x40). Representative sections of the tumors. Black regions correspond to areas with cytolysis. Red areas, apoptotic/necrotic removal of the tumor. Yellow area, tumor invading adipose tissue. The good organization of the tumor (upper, right) contrasts with the disorganization upon treatment with F10503LO (lower panels).



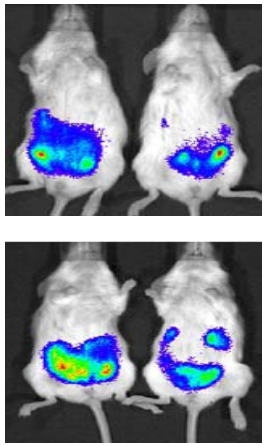
OVARIAN CANCER

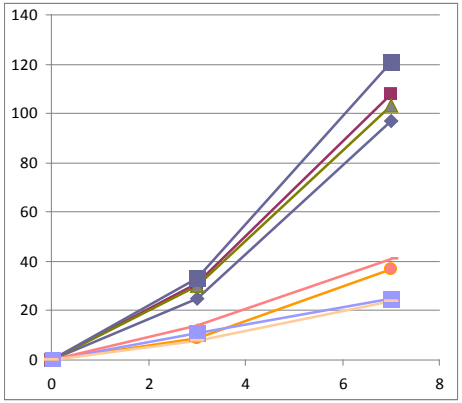
Ovarian cancer is a cancerous growth arising from the ovary. Symptoms are frequently very subtle early on and may include: bloating, pelvic pain, eating difficulty an frequent urination, and are easily confused with other illnesses.
Most (more than 90%) ovarian cancers are classified as "epithelial" and are believed to arise From the surface (epithelium) of the ovary. However, some evidence suggests that the fallopian Tube could also be the source of some ovarian cancers

3.5. In vivo antitumoural activity in ovarian cancer

In the preliminary results, F10503LO1 exhibits a potent *in vivo* antitumour activity reducing the tumour area. Several experiments were performed using MOSEC ID8 cells (Mouse ovarian surface epithelial cells) with cloned luceferase reporter, and cells implanted on mice ovarian region.

These results instigate future experiments versus clinical competitors and potential synergic effects on this model.

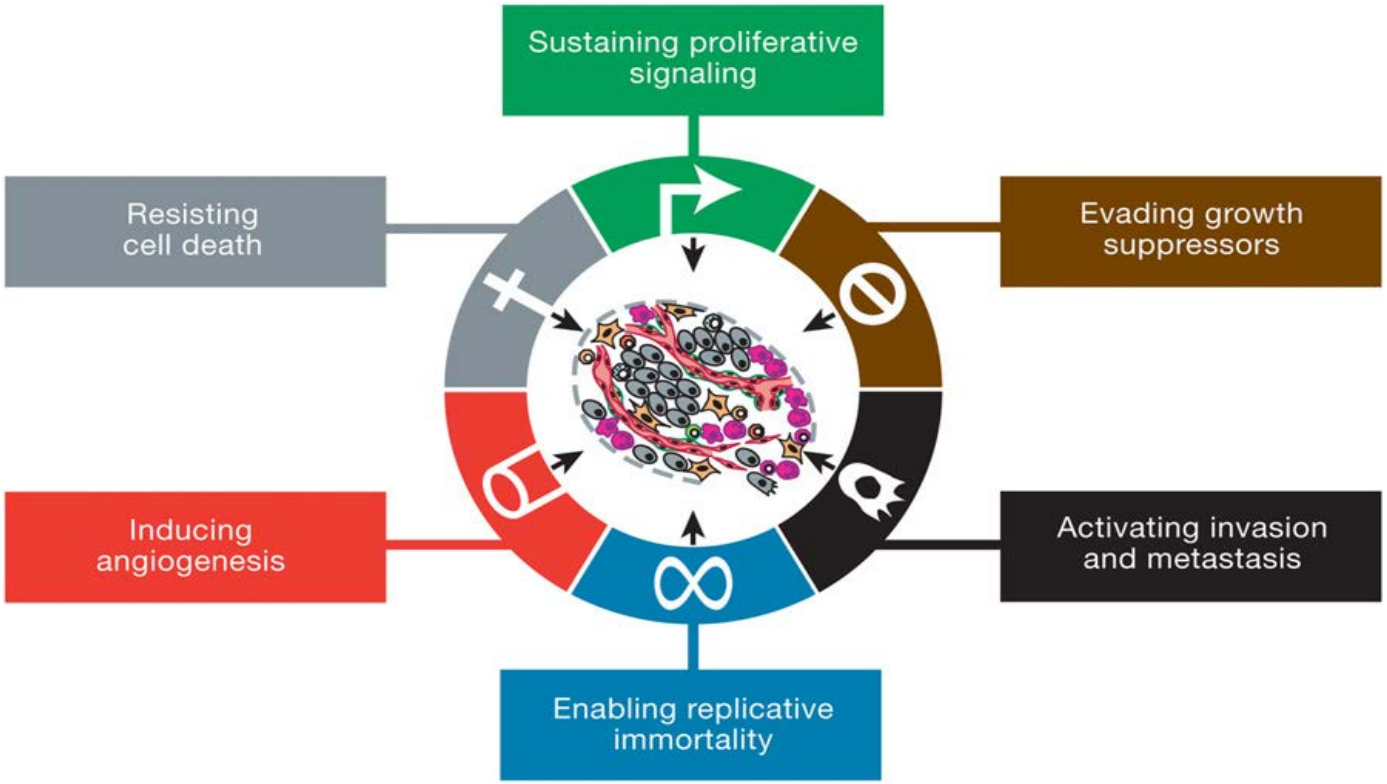




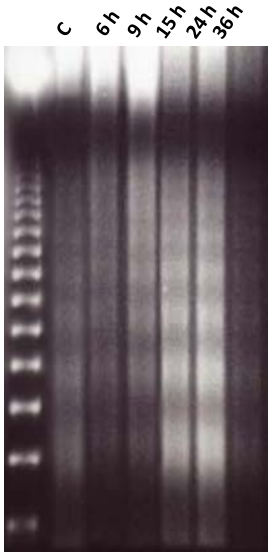
A Pet picture from lucerferase activity in vivo tumour.
B Quantification of luciferase signal from the same animals.

4. MECHANISM OF ACTION

Hallmarks of Cancer: The Next Generation Douglas Hanahan and Robert A. Weinberg. Cell 144, March 4, 2011 Elsevier Inc.

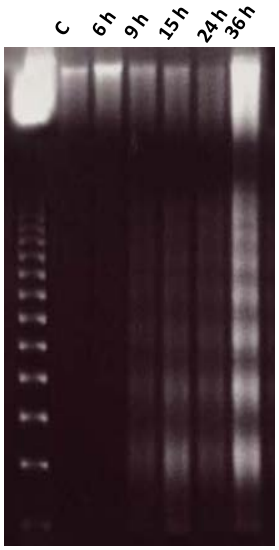


4.1. DNA degradation



EHEBB

(B-cell chronic Lymphocytic Leukemia)



Jurkat

(T cell leukemia)

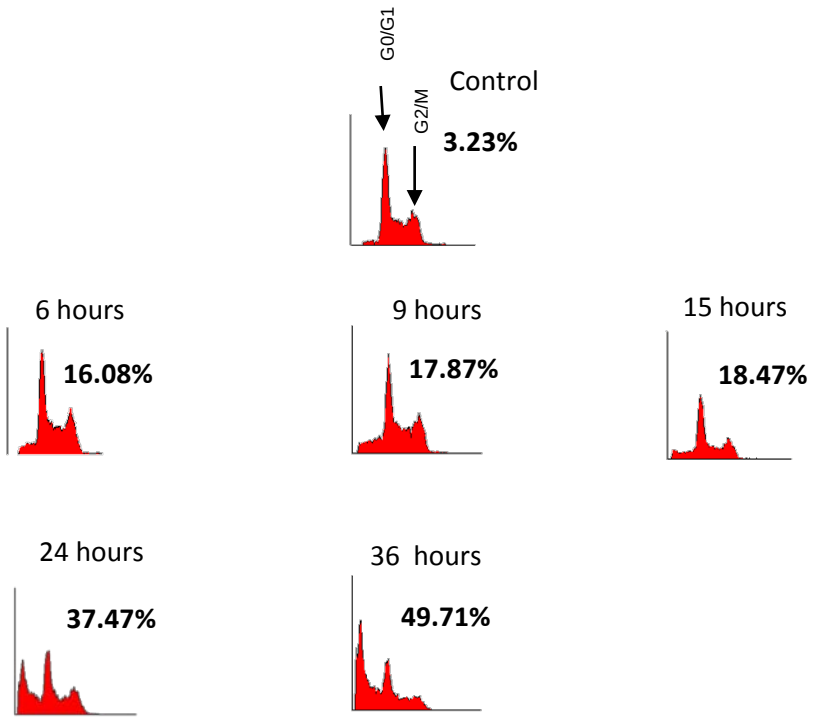
HL-60
(myeolid cells)

4.2. Cell Cycle Block

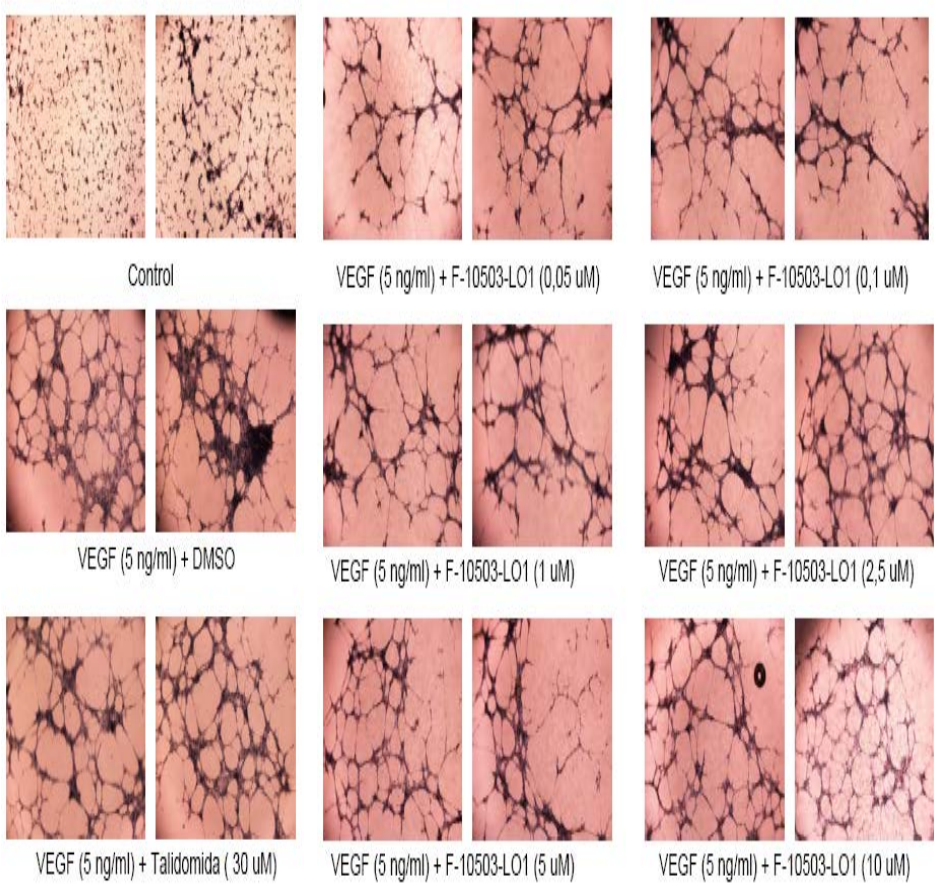
RPMI 8226

(Multiple myeloma)

F 10503 LO1 10µM



4.3 Angiogenesis

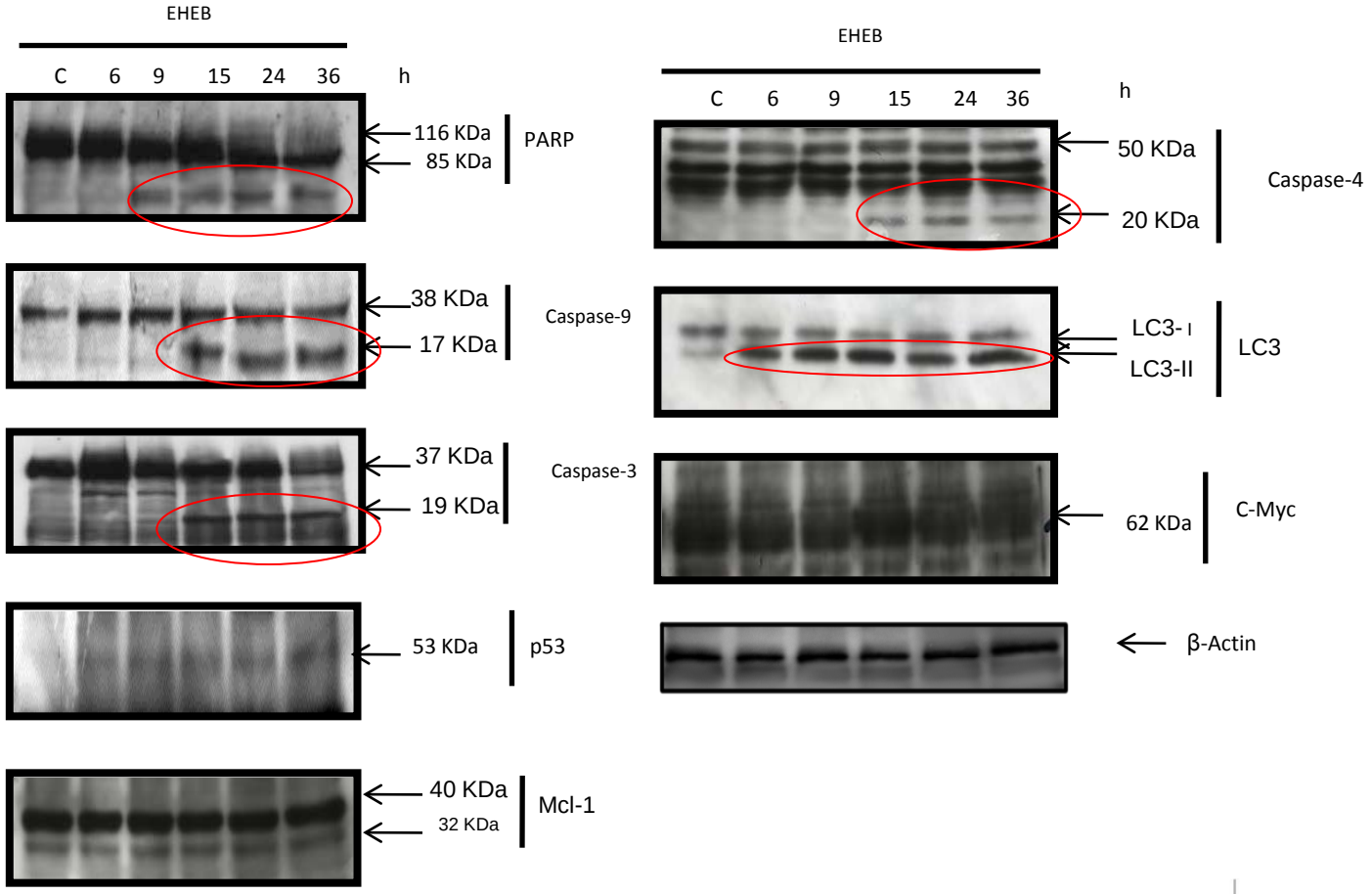


4.4. Apoptosis markers

4.5. Oncogenes expression

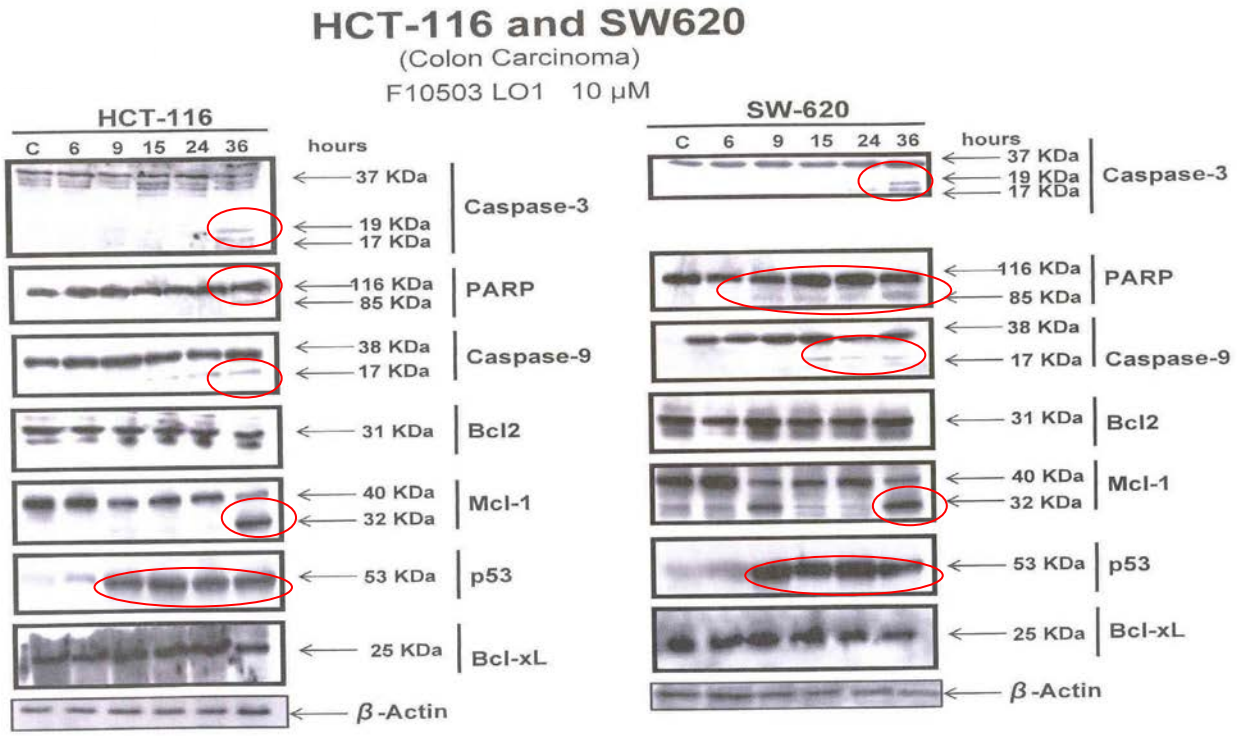
EHEBB

F10503LO1 10 µM

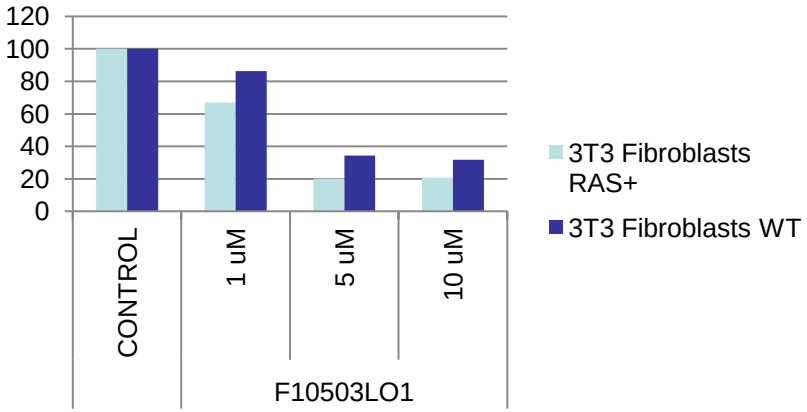


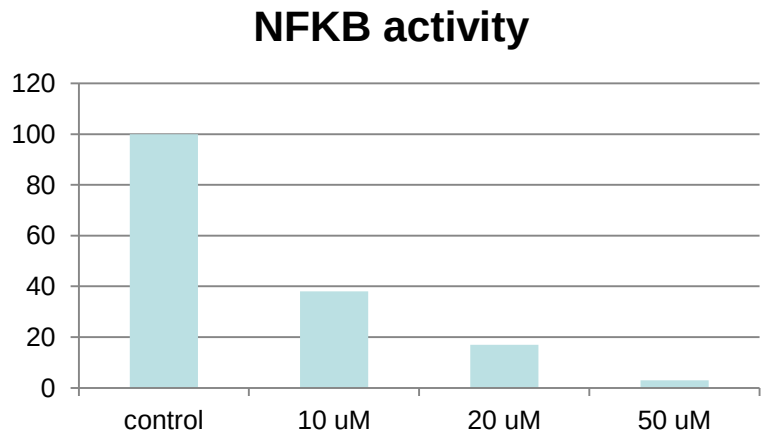
4.4. Apoptosis markers

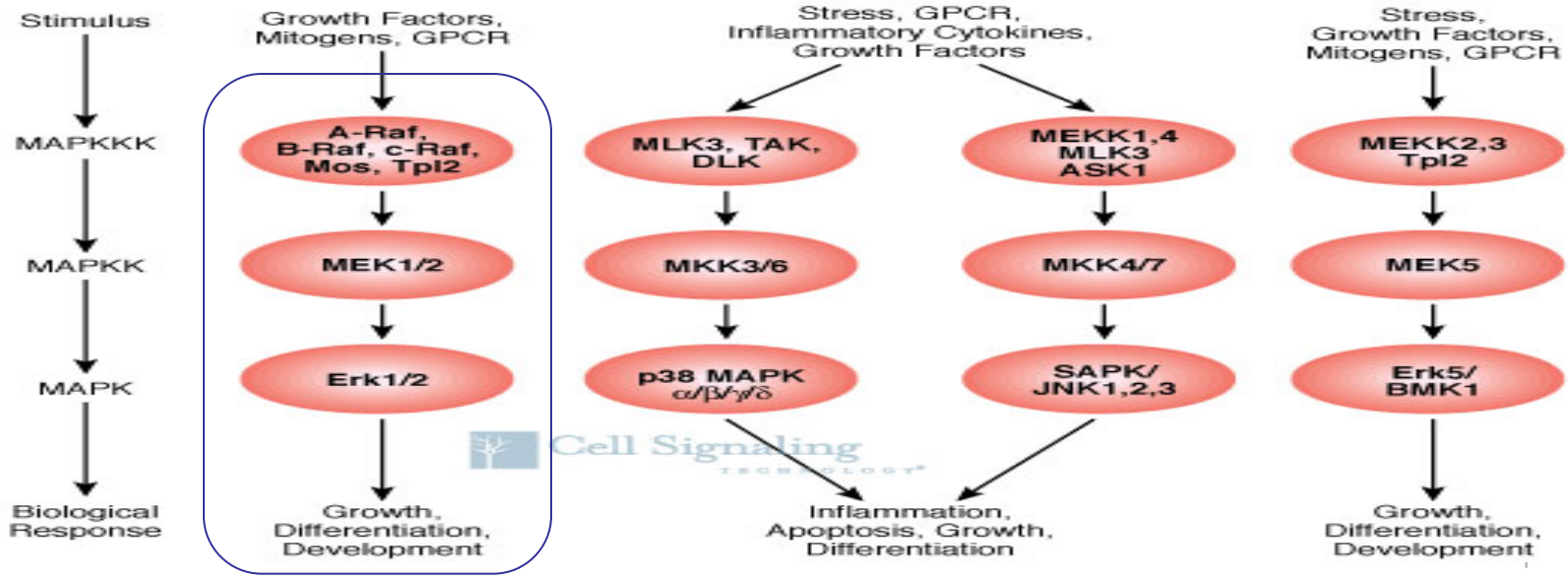
4.5. Oncogenes expression



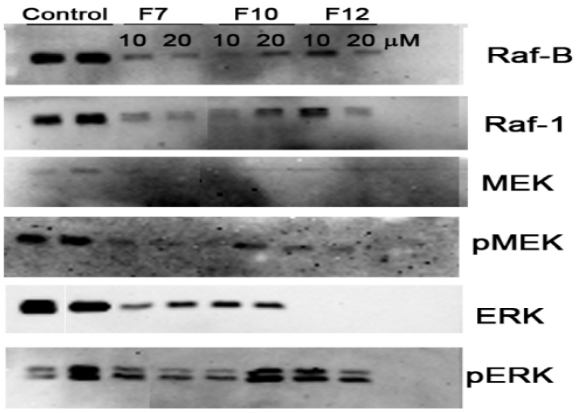
5. INNOVATIVE MECHANISMS OF ACTION

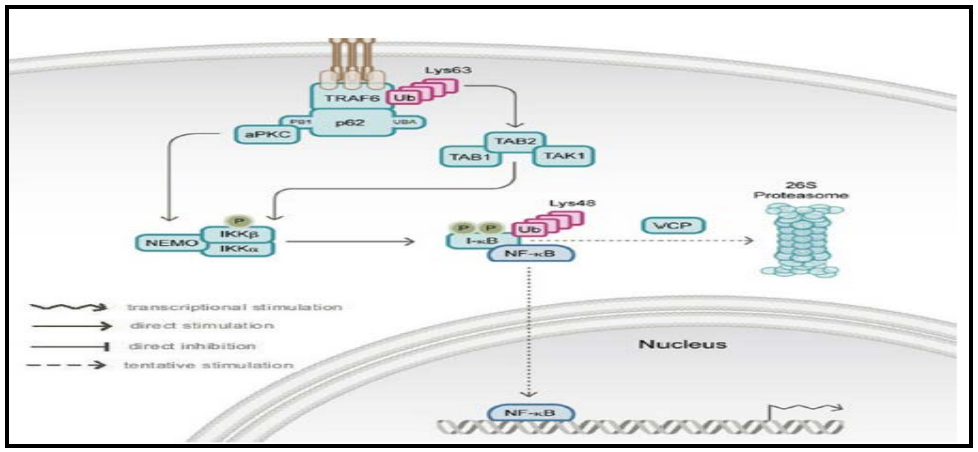




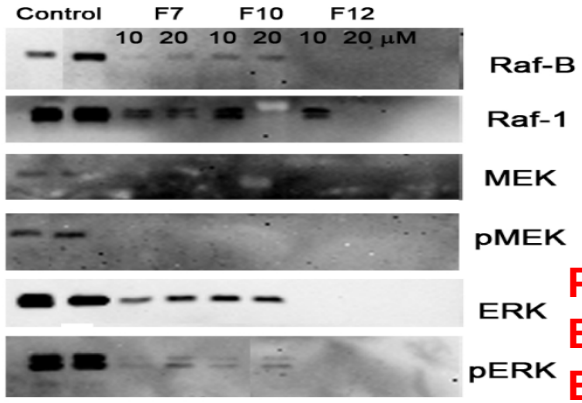


6 horas





9 horas



First small molecule inhibitor of p62-traf6 interaction
Blocking cancer progression without inmune supression
Effect over autophagia in solid and hematological cancers

F12 = F10503LO1, / F7 and F10 = other members of the family

6. STATUS OF DEVELOPMENT. PRECLINICAL TOXICOLOGY

Acute Intravenous Toxicity Study in Mice: Determination of the "Maximum Non-lethal Dose and Minimum Lethal Dose" (GLPs Study S33177)
Acute Intravenous Toxicity Study in Rats: Determination of "Maximum Non-lethal Dose and Minimum Lethal Dose" (GLPs Study S33188)
Sub-acute Intravenous (Bolus) Toxicity Study in the Wistar Rat (Non GLPs Study S33076)
Binding to human ERG channel (Non GLPs Report FT75109)
Spontaneous locomotor activity (SLA) in mice.
Effect on motor coordination (Rotarod test) in mice
Currents HERG
IRWIN test mouse
14 days. Sub-acute Intravenous (Bolus) Toxicity Study in dog
AMES TEST

7. DIFFERENTIAL FEATURES FACING THE MARKET (I)

***In vitro*:**

• F10503LO1 is a cytotoxic compound in vitro over leukaemias, colon, melanoma and ovarian cancer cells.

• **Cytotoxicity on non-tumoural cells offers enough therapeutical window on endothelial cells, fibroblasts, PBLs, B and T cells, better than other antitumoural compounds.**

• Synergist effect (taxol, doxorrubicine, revlimid, dexamethasone)

***In vivo*: Effect over solid and hematological cancers**

• CLL.- F10503LO1 reduces tumour volume/mass in xenograft animal model. *Dose-Effect range better for F10503LO1 than Fludarabine. Synergism on going.*

• Multiple myeloma.- F10503LO1 reduces tumour volume/mass in xenograft Animal model.

• Colon Cancer (K-ras mutated).- **F10503LO1 HAS POTENT EFFECT OVER METASTASIS.**

7. DIFFERENTIAL FEATURES FACING THE MARKET (II)

Melanoma:

• F10503LO1 **reduces tumour development better than DTIC. Minimal active dose might be around 10-15 folds lower than toxical dose.**

•Potent effect over lung metastasis from melanoma cancer.

Ovarian cancer:

• Preliminar results show F10503LO1 reduces tumour development.

Mechanism of action:

•F10503LO1 induces apoptotic oncogenes (MCL-1 and P53) on colon cancer cells.

• **Autophagia proteins might be modified by F10503LO1 treatment** (LC3/TRAF6)

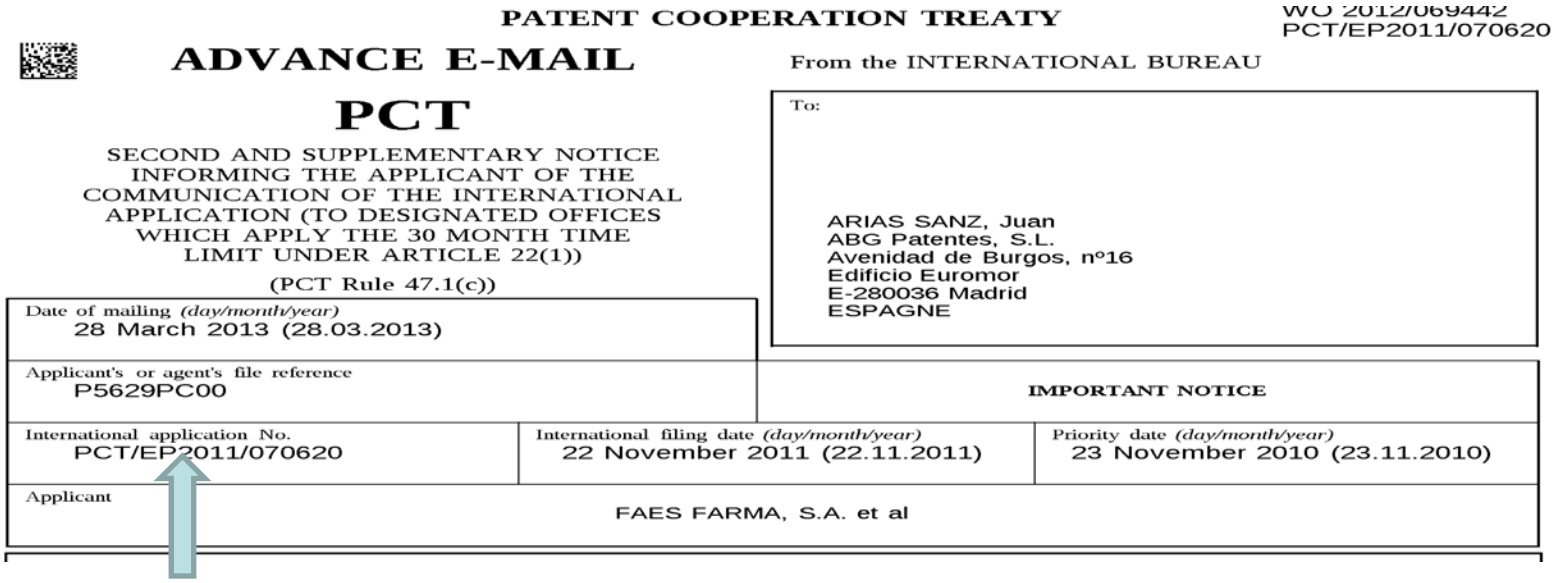
• **F10503LO1 reduces angiogenesis** (in vitro) at lower concentration than cytotoxic IC50.

-First small molecule inhibitor of p62-traf6 interaction

-Blocking cancer progression without inmune supression

Results from **in vivo toxicology** show a maximal non-toxic dose around 5-10 mg/kg i.v. 3 times per week. The minimal active dose might be around 1-2.5 mg/kg 2 times per week. Therefore, **the therapeutical window might be within the range of 5-15 folds.**

8. IPR PROTECTION



PATENT COOPERATION TREATY

WO 2012/069442
PCT/EP2011/070620

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

ARIAS SANZ, Juan
ABG Patentes, S.L.
Avenidad de Burgos, nº16
Edificio Euromor
E-280036 Madrid
ESPAGNE

Date of mailing *(day/month/year)*
28 March 2013 (28.03.2013)

Applicant's or agent's file reference
P5629PC00

IMPORTANT NOTICE

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2011/070620	22 November 2011 (22.11.2011)	23 November 2010 (23.11.2010)

Applicant: FAES FARMA, S.A. et al

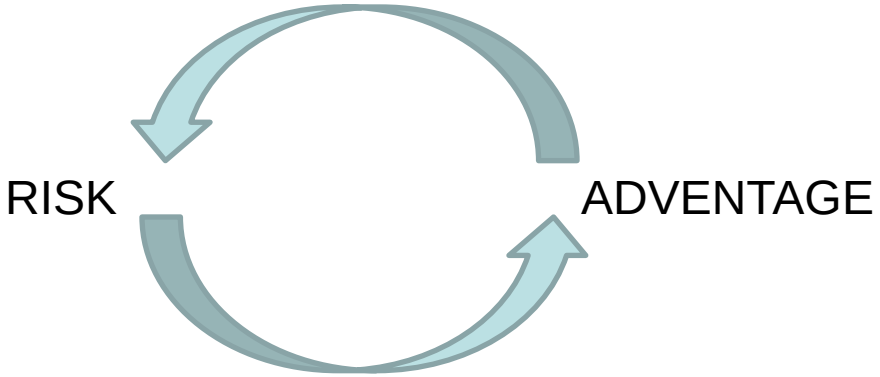
European Patent 2010 → PCT 2011 → Exclusive 2030+SPC 2035

Phase I 2014 → Clinical Development → Marketing Authorization 2020 → 15 years exclusively operating

8. Pitfalls and risk to be considered

Clinical risk : non detected on preclinical studies

Target on central role for cancer/inflammation/inmune response



WAY OUT OF LEUKAEMIA
FOCUSED ON AGRESSIVE METASTASIS

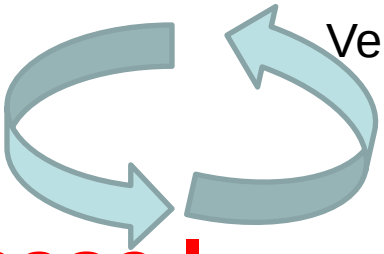
Partnering Opportunities

Codevelopment

Big pharma

Medium pharma

Venture Capital

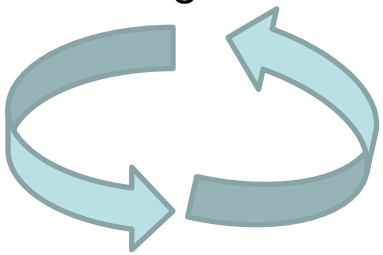


Phase I

Phase II

Phase III

Sales agreement



Future conditions

Thank you !

Dr. Francisco Ledo
New Products Research Manager
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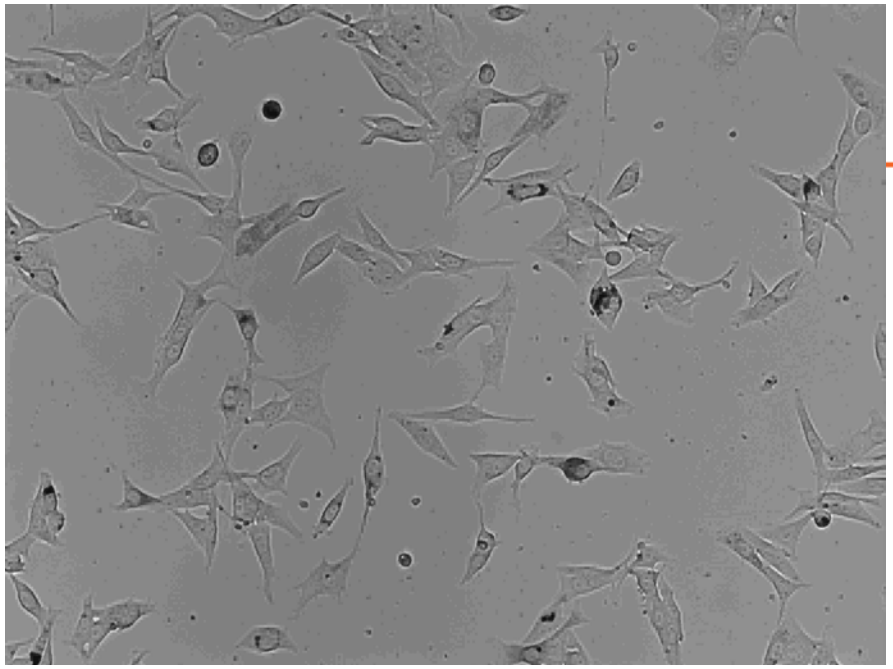
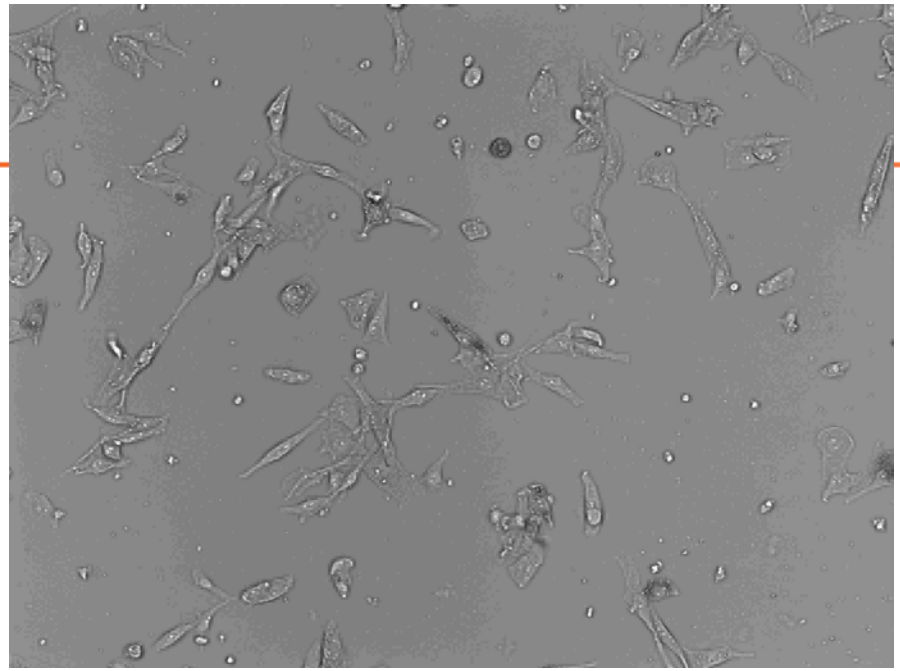
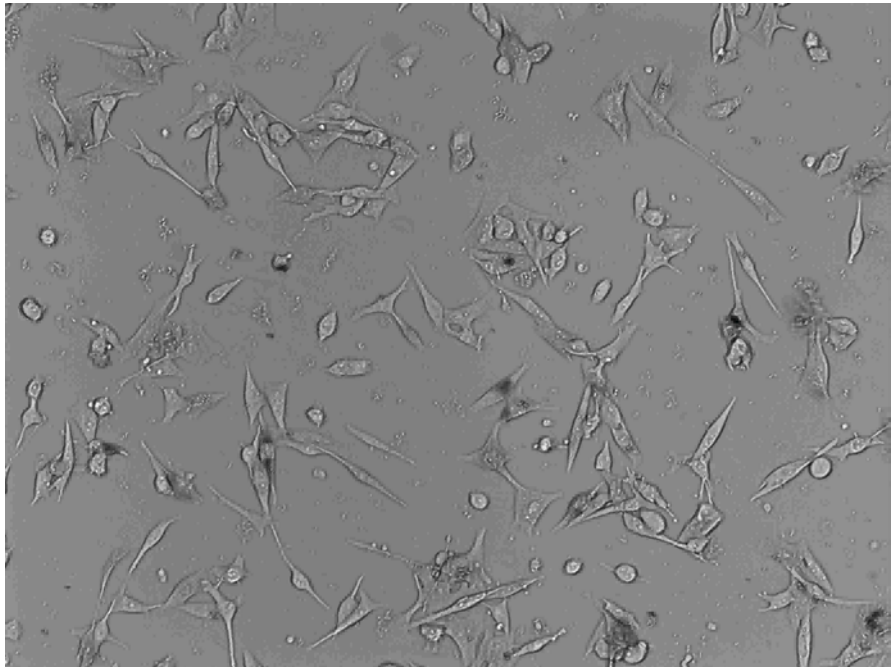


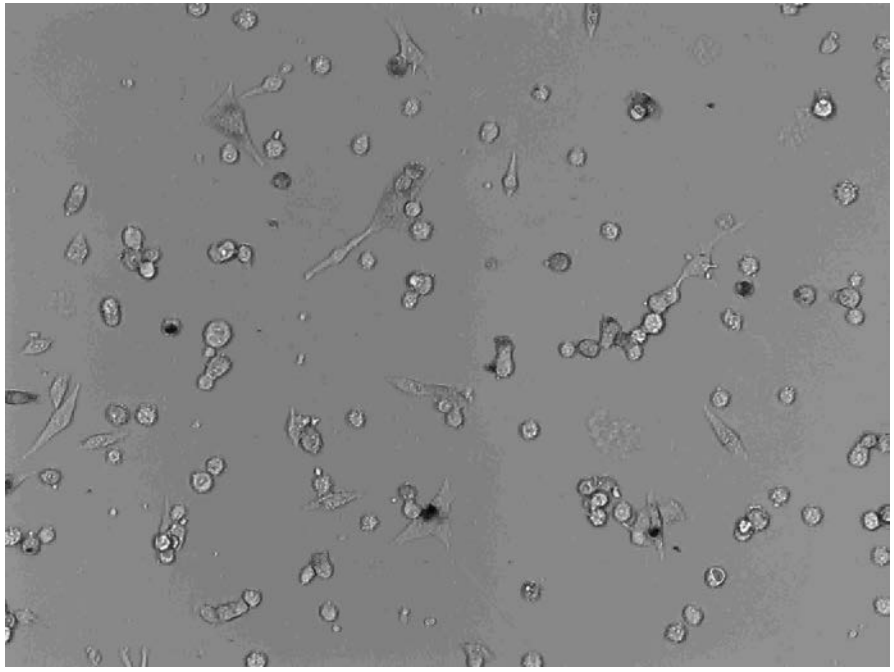
100 nM



500 nM



1000 nM



Human Mo differentitated into resting macrophages
Pretreatement (2h) with 200 nM FAES compounds for 22 h (per triplicate)
200 ng/ml LPS; TNFa/IL1b/hIFNg (20ng each)/inh PFK2 (3PO,200 nM); inh HIF1a/HIF2a (F19G11,500 nM)