Programa Cooperación Farma-Biotech

Jornada presentación de resultados 2011 - 2014

LIPOPHARMA

Lipid Science for life

Next generation medicines!

La oportunidad de participar en el programa

Vicenç Tur. CEO, Co-founder

Barcelona, 2 de julio de 2015

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

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Next generation medicines!

Lipopharma, a pioneering clinical-stage biopharmaceutical company based in Palma de Mallorca (Spain) focusing on the discovery, design and development of next-generation medicines associated with a novel breakthrough therapeutic approach: the Membrane-Lipid Therapy (MLT)

Programa Cooperación Farma-Biotech Jornada II: Oncología

Minerval®:
Treatment of glioma and other types of cancer

LIPOPHARMA
Lipid Science for life

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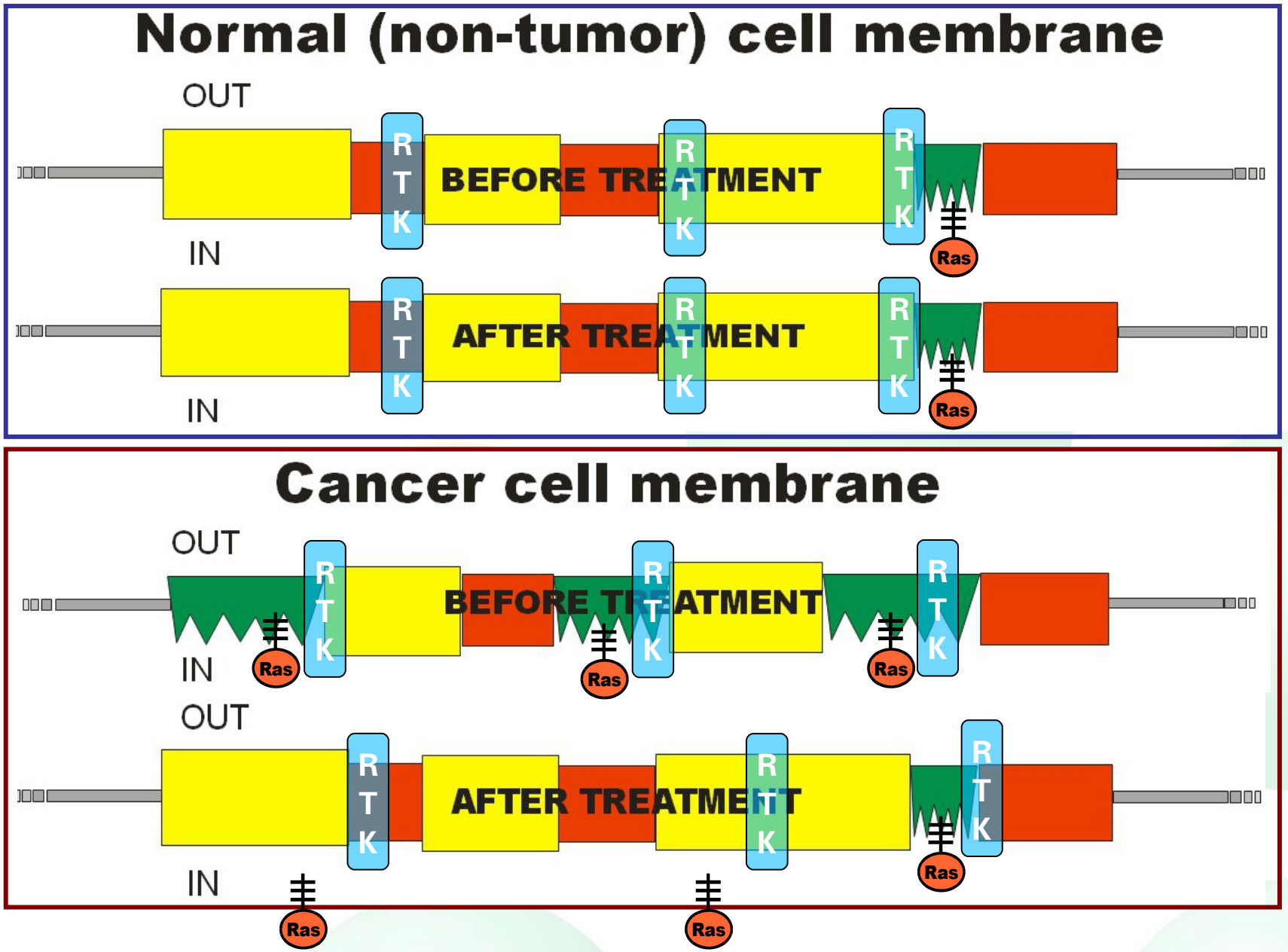
Barcelona, 13 de abril de 2011

Minerval: MLT in Action



High SM (raft) membrane domains

High DAG membrane domains

High PE & PC membrane domains

MLT drugs are designed to influence and **regulate lipid organization in cell membranes** based on **structure–function principles**, inducing a concomitant modulation of **membrane protein localization and activity**, which finally induces changes in cell signaling and gene expression.

Minerval® in Cancer: novel MOA

Regulation of Membrane Lipids structure & composition (1)

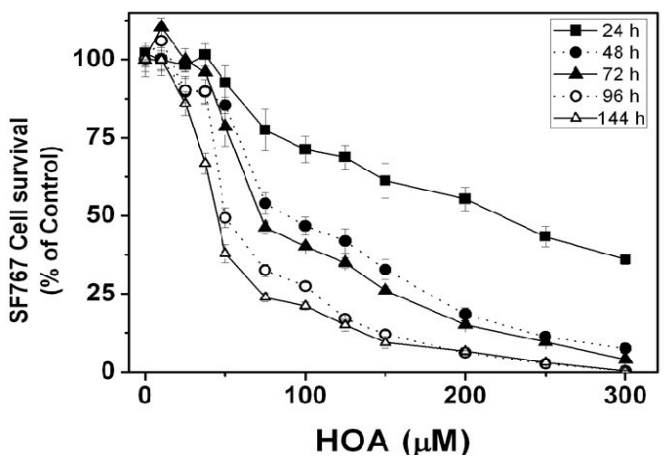
Ras / MAP kinase pathway inhibition (2)

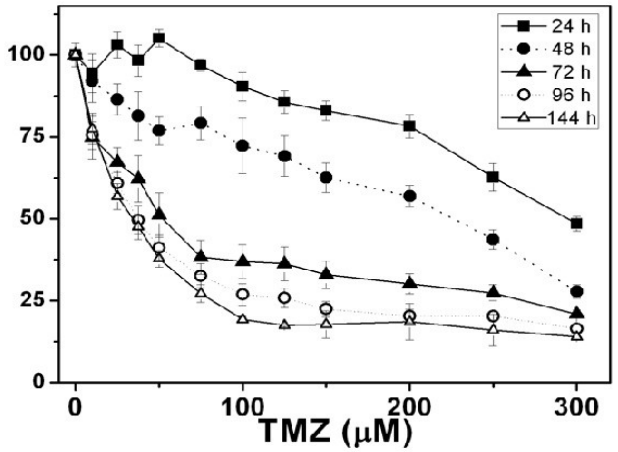
Cell cycle arrest (3)
(DNA synthesis inhibition)

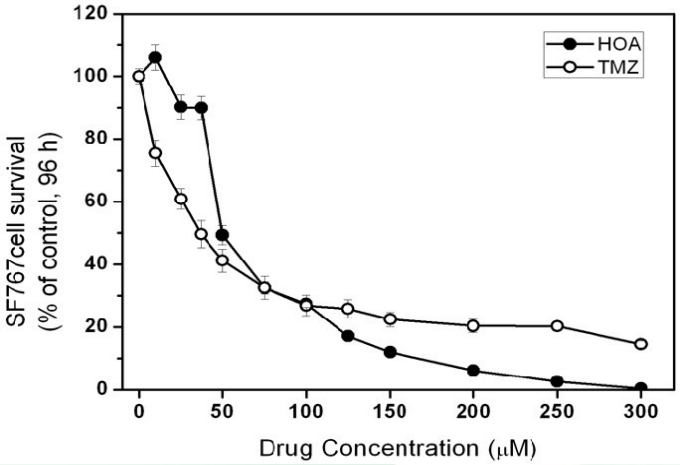
cell differentiation (4)

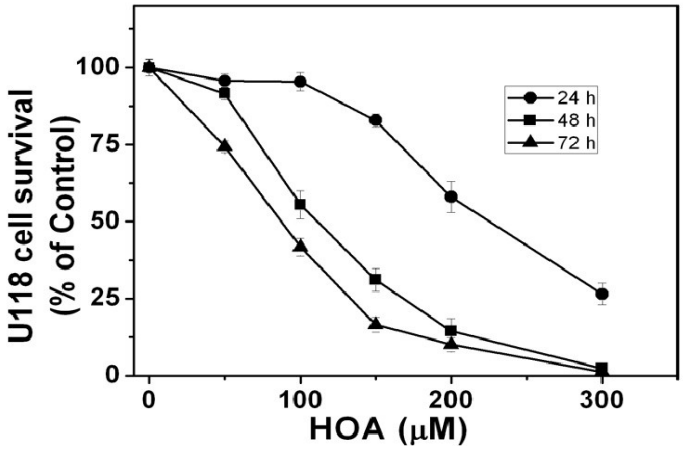
p27/RB associated Autophagy (5)

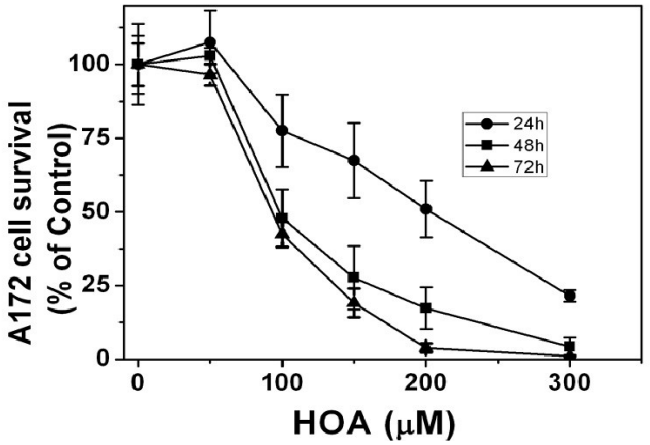
Efficacy of Minerval in cellular models

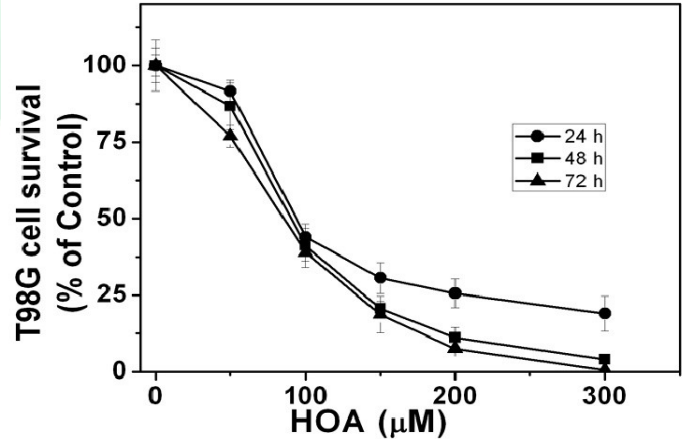






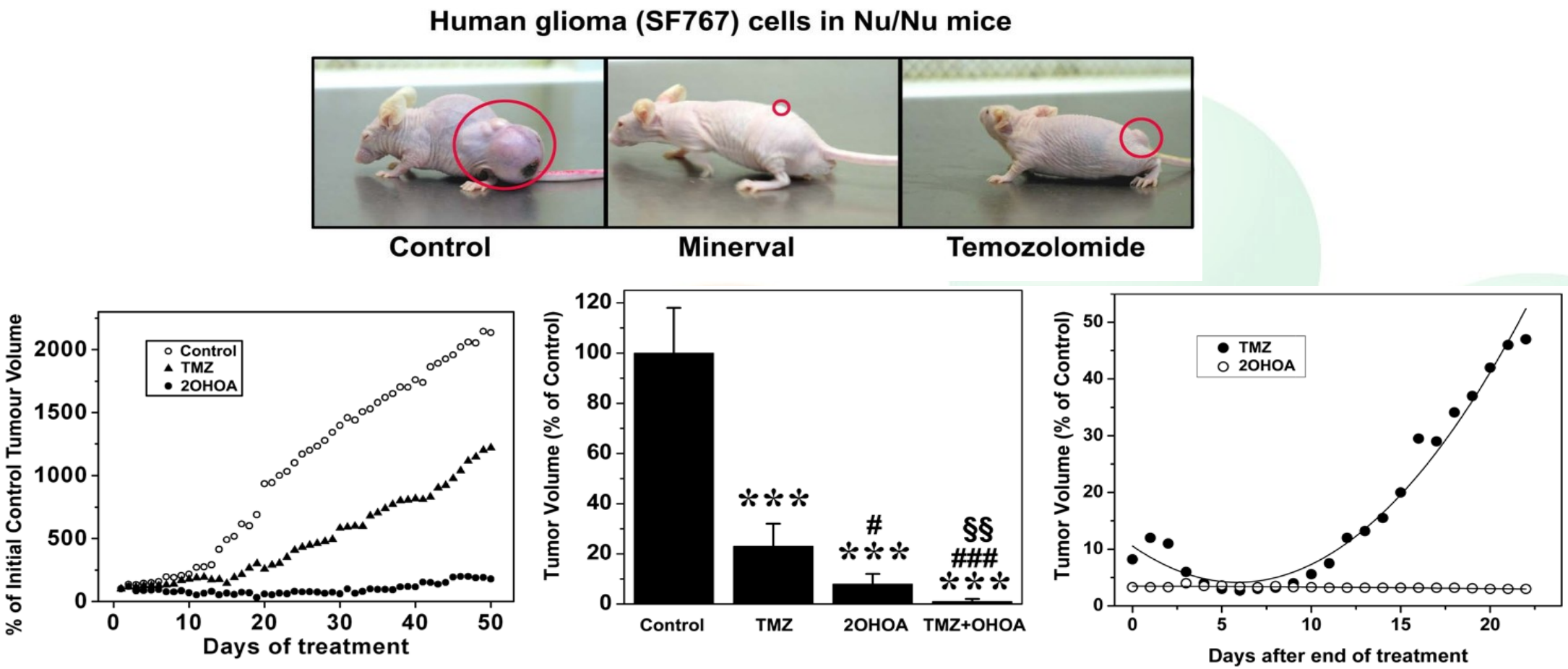






Minerval (HOA) is able to inhibit, in a time and concentration dependent manner, the growth of several human glioma cell lines (SF767, U118, A172, T98G). In SF767 cell line, Minerval clearly demonstrates a superior efficacy than temozolomide, which is not able to kill all cancer cells at 300 microM

Effect of Minerval in animal models of human brain tumours (GLIOMA) compared with temozolomide



Minerval (2OHOA, OHOA) has demonstrated a potent anticancer effect in xenograft animal models, clearly outperforming temozolomide (TMZ) in 50 days treatment (bottom left). Combinatory regime with TMZ showed strong synergistic results after 60 days treatment (bottom middle). Moreover, animals treated with Minerval do not show tumour relapse after treatment termination, as it happens with animals administered with TMZ (bottom right)

MINERVAL®

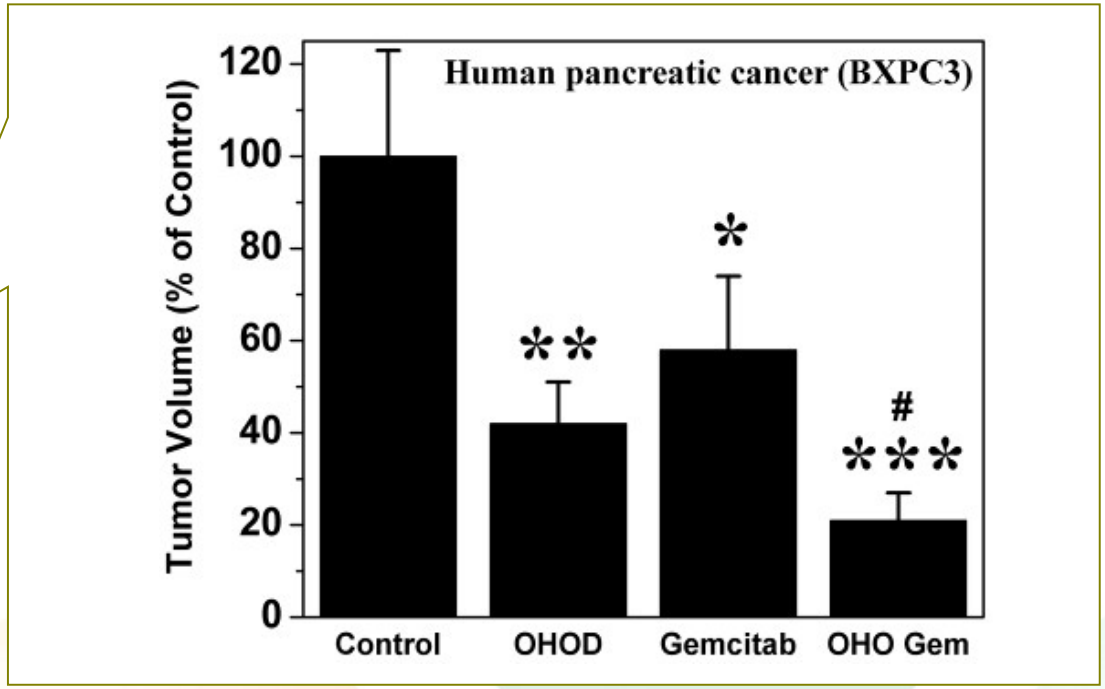
High Efficacy

+

Absence of Toxicity

+

Oral Administration



Minimum Lethal Dose not determined!

> 3.000 Mg/Kg

Very promising profile in Cancer treatment !

Programa Cooperación Farma-Biotech

8º encuentro (7 de mayo de 2013)

Minerval for the treatment of glioma and other solid tumors

LIPOPHARMA

Lipid Science for life

Vicenç Tur. CEO, Co-founder

Madrid, 7 de mayo de 2013

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Minerval, a new class of lipid regulator, multi-pathway anticancer drug

for tumors with **sphingomyelin metabolism alterations**

Specific activator of sphingomyelin synthase (SMS) [1]

Selective** regulation of **lipid composition** in cancer cell **membranes:

▲SM; ▲DAG; ▼PE; ▼PC [2]

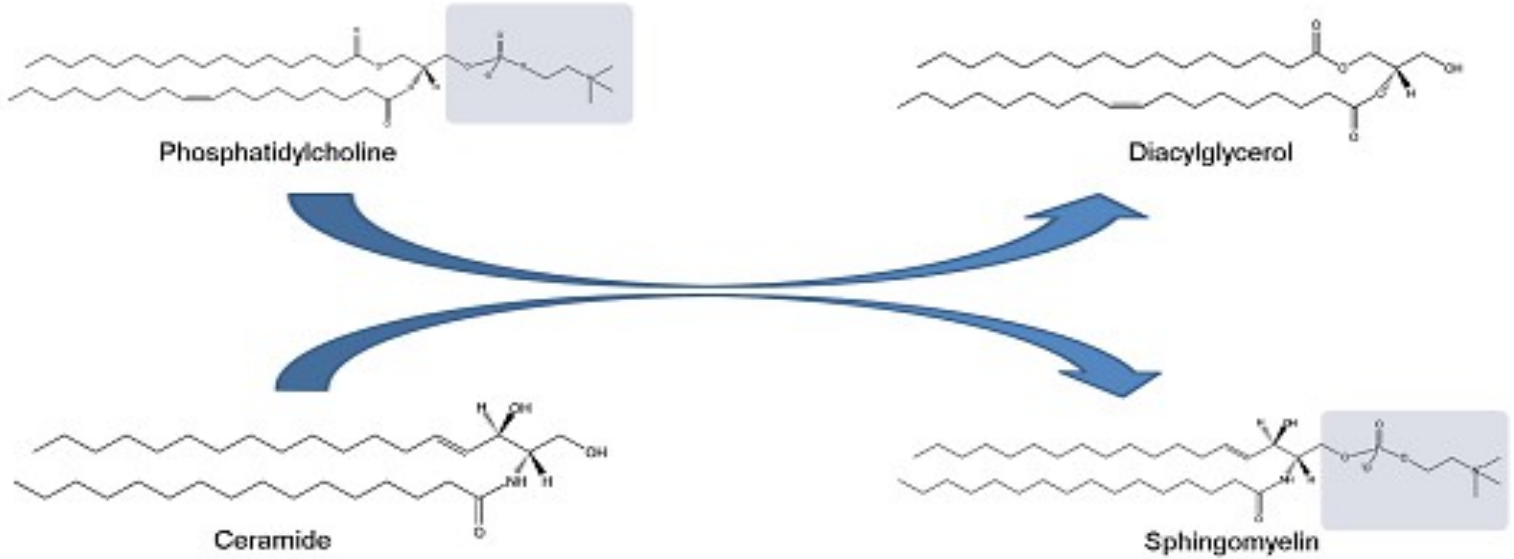
PKC/Cyclin CDK
Regulation [4]

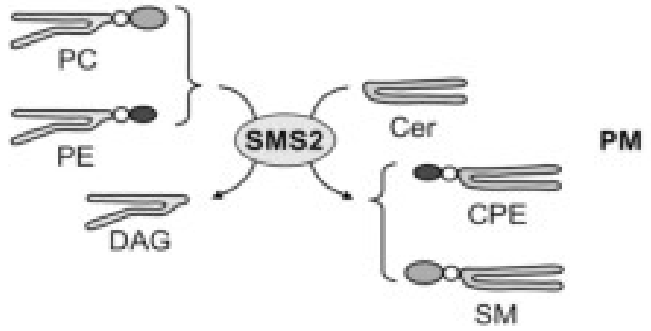
Ras traslocation
↓
MAPK – PI3K/Akt
pathway normalization [3]

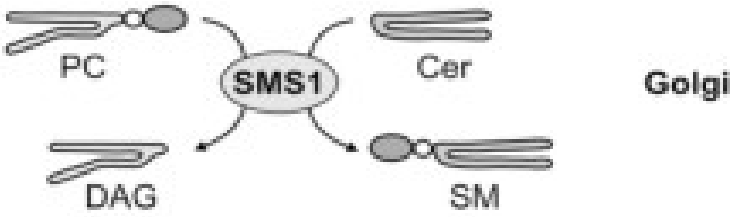
Cell cycle arrest [▼DHFR]
& **differentiation** [4]

selective **Autophagy**
[5]

Sphingomyelin synthase (SMS) catalyzes SM synthesis

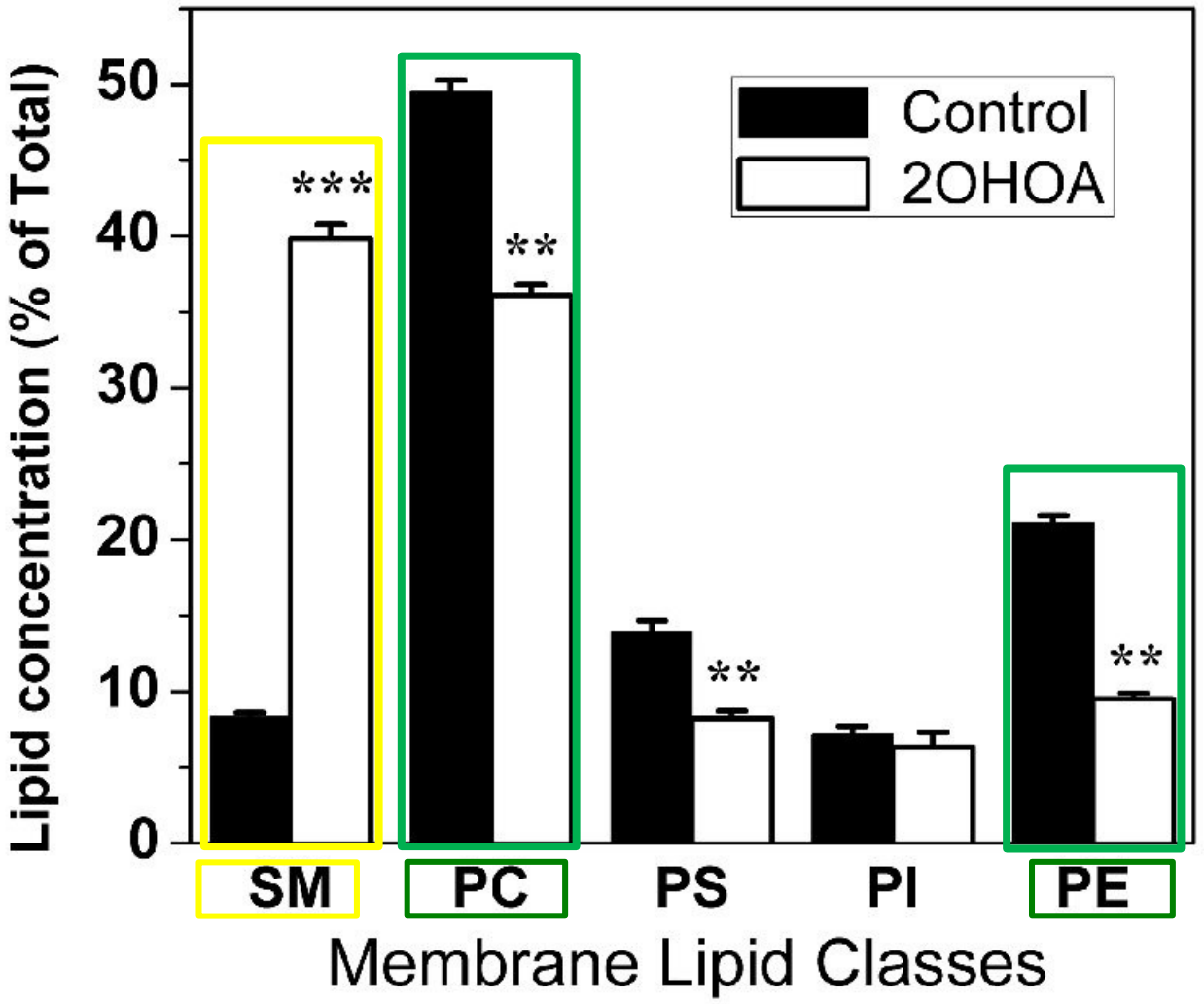






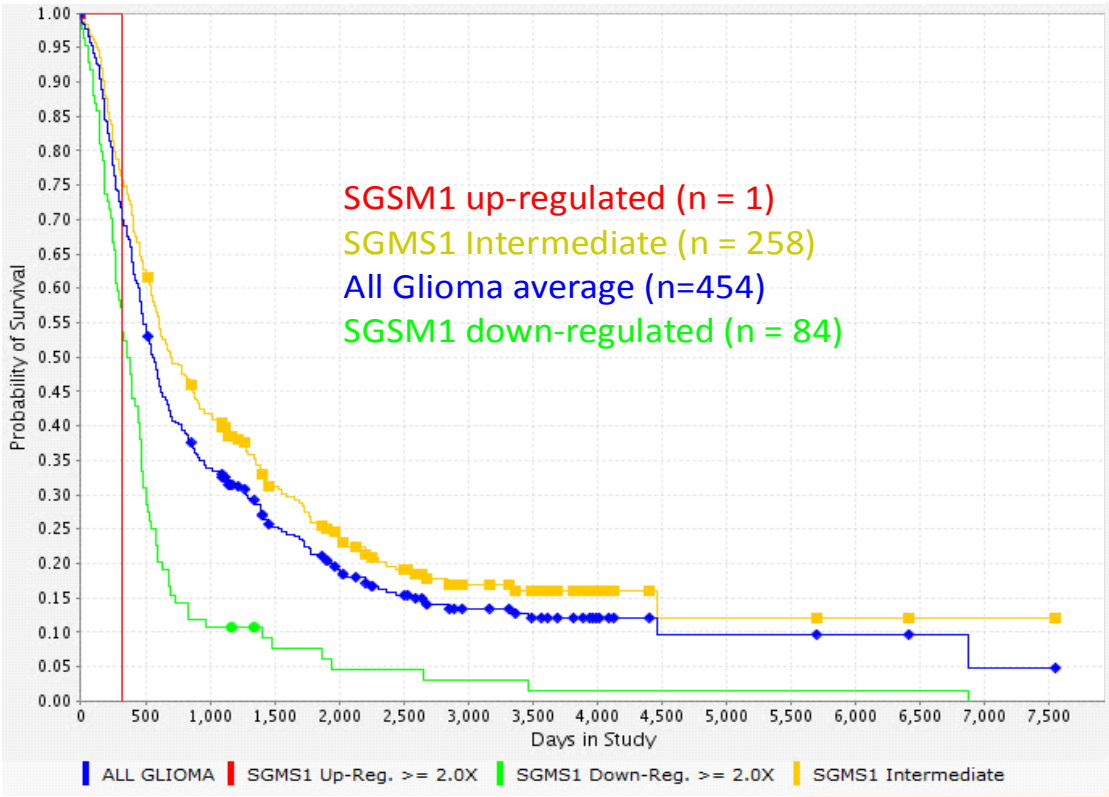
SMS mediates the synthesis of sphingomyelin (SM) and DAG using ceramide and phosphatidylcholine (PC) or phosphatidyl-ethanolamine (PE) as substrates. Because this enzyme can work forth and back, in cells where the levels of substrate (e.g., PE) are high and product (e.g., SM) low, 2OHOA activates SMS (e.g., cancer cells). By contrast, when membrane levels of PE are low and SM are high, SMS cannot be activated by 2OHOA (e.g., normal cells and tissues).

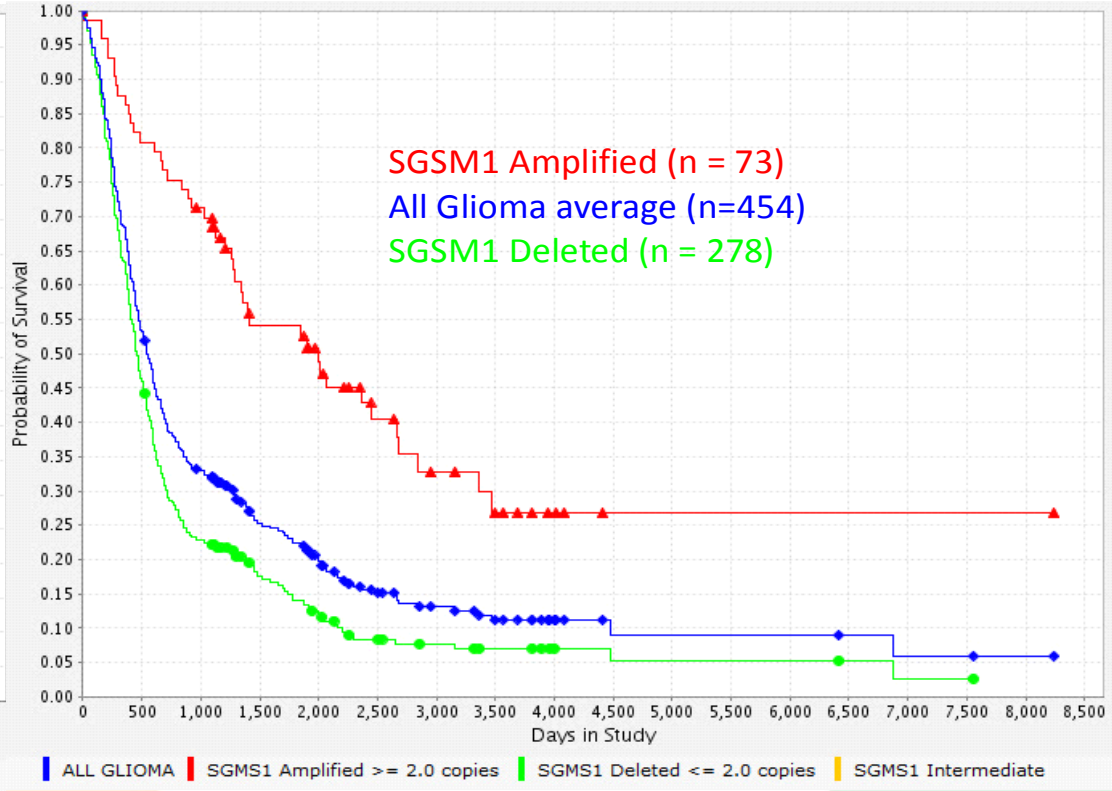
Minerval on membrane lipids in human glioma cells (U118)



Levels of SM, phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylinositol (PI) and phosphatidylethanolamine (PE) after 72-h treatments with Minerval (2OHOA)

Effect of SMS1 genetic alterations on glioma patients' survival
(Differential SGMS1 Gene Expression & Copy Number Analysis for SGMS1)





Kaplan-Meier survival plot for patients with glioma (n=454) *vs* sphingomyelin synthase 1 (SGMS1) expression (**left**) or gene copy number (**right**). Human glioma cells have low sphingomyelin (SM) levels (Barcelo-Coblijn et al., PNAS 2011; 108:19569-19574) and Minerval-induced normalization of SM levels causes glioma cell death. The left panel shows that down-regulation of SGMS1 is associated with a marked and significant ($P = 2 \times 10^{-10}$) reduction in the life-span of glioma patients. The right panel shows that deletion of the SGMS1 gene occurs in about 61% of all glioma patients and is associated with a significant reduction in their life-span, whereas patients with more than 2 copies of the SGMS1 gene have an increased life span and ca. 25% probability to live over 20 years.

National Cancer Institute. 2005. REMBRANDT <http://rembrandt.nci.nih.gov>. October 2012

Current status: PI/II Clinical Study with Minerval

MIN-001-1203: "*A phase I/IIa open-label dose escalation study of Minerval in subjects with advanced solid tumors including malignant glioma*".

Top leading European KOL and **investigational sites** involved: **Johann de Bono** (Royal Marsden Hospital, London), **Roger Stupp** (University Hospital, Zurich), **Jordi Rodon** (Vall d'Hebron Institute of Oncology, Barcelona), **Herbie Newell** and **Ruth Plummer** (Northern Institute for Cancer Research, Newcastle)

Part A. Dose escalating study. Up to 30 patients. 21-day treatments. Glioma and other solid tumors (lung, pancreas…)

Part B. Exploratory study. Up to 20 patients in two groups. 21-day treatments. 1st group with glioma patients. 2nd group with biopsiable solid-tumors patients for biomarker evaluation.

Biomarkers: **SM**, **DHFR** and **GFAP** (glioma only) + **Imaging** (FLT/PET, MRS), miRNA,...

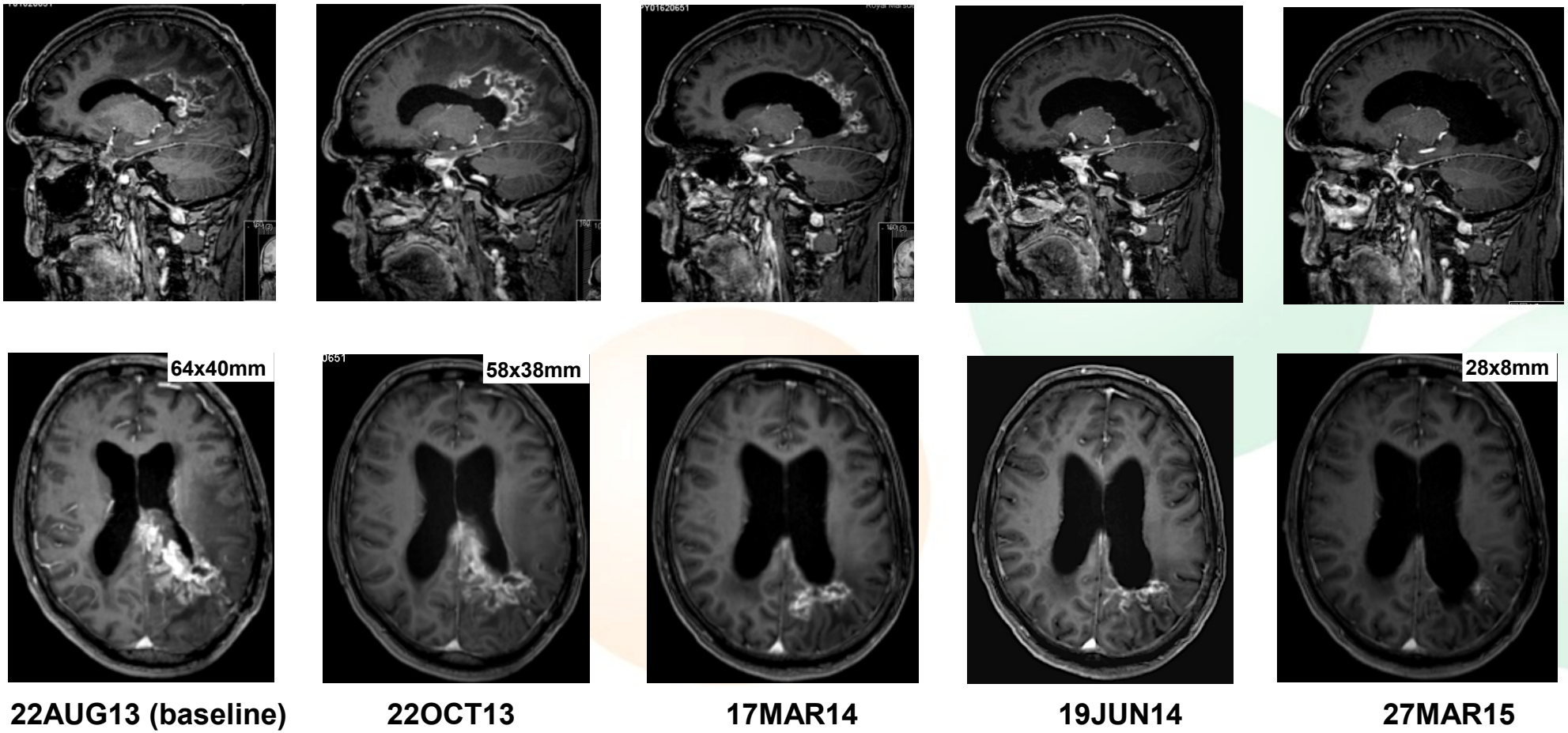
CTA approved in Dec. 2012 by the MHRA (UK) & by the AEMPS (Spain) in Apr. 2013. First patients enrolled expected in May 2013

MIN-001-1203. Main results summarized [as of 02Jul15]

	Cohort #01	Cohort #02	Cohort #03	Cohort #04	Cohort #05	Cohort #06	*Cohort #07 (on-going)*	TOTAL (first 6 cohorts)
Dose (g/day)	**0.5 (BID)**	**1 (BID)**	**2 (BID)**	**4 (BID)**	**8 (BID)**	**12 (TDS)**	***16 (BID)***	
# patients eligible for safety assessment	**3**	**4**	**3**	**3**	**3**	**6**	***2***	**22**
… of which GBM pts	*1*	*3*	*2*	*1*	*0*	*3*	*1*	*10*
Drug related SAEs	**0**	**0**	**0**	**0**	**0**	**0**	***0***	**0**
DLTs	**0**	**0**	**0**	**0**	**0**	**1** (G3 diarrhoea)	***0***	**1**
Drug-related G1 AE	**0**	**5** (all GI effects)	**4** (all GI effects)	**7** (all GI effects)	**15** (all GI effects)	**27** (all GI effects)	***?***	**58**
Drug-related G2 AE	**0**	**1**	**0**	**0**	**3** (all GI effects)	**4** (all GI effects)	***?***	**8**
Drug-related G3 AE	**0**	**0**	**0**	**0**	**1** (diarrhoea)	**1** (diarrhoea)	***?***	**2**
# pts with response	**1** SD (mesothelioma)	**1** PR (GBM)	**0**	**0**	**0**	**2** 2 SD (all GBM)	***?***	**4**

ANTI-CANCER CLINICAL ACTIVITY CONFIRMED IN 4 PATIENTS (3 GBM)

Minerval in humans. MIN-001-1203 pt 010202 (GBM) 1g/day BID



Patient on treatment since 02SEP13. Partial Response on RANO criteria confirmed in last scan in 27MAR15 (**91% tumour shrinkage over baseline assessment**)

Minerval in glioma: next steps

Preparing **PIIb study** in **newly-diagnosed glioblastoma** to evaluate **significant benefit** Vs SoC.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Scientific Advice & **Protocol Assistance** with **EMA** completed in Dec. 2014. If results are positive Lipopharma will seek **conditional approval** in Europe after PIIb study in glioma.

Orphan Drug status granted in EU (glioma) in Oct. 2011

Formal interactions on-going with **FDA** to conduct a **paediatric trial** with Minerval in the US in collaboration with **Dana-Farber Cancer Institute** (Boston, MA)

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA
FDA

DANA-FARBER CANCER INSTITUTE
HARVARD MEDICAL SCHOOL

National Cancer Institute

Discussions with NCI on-going to evaluate a collaboration in the clinical development of Minerval in USA.

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Minerval: current partnering / investment status

- >12M€ raised in grants & equity since project start-up
- Partnered with Praxis Pharmaceutical for Spain, Portugal, Switzerland, Turkey, Israel and Colombia. Negotiating an extension of the collaboration to partnering rights in the rest of Europe and other latam markets
- In active negotiations with potential partners in Japan, South Korea, China, …
- “In touch” with most large Pharma Companies

Why participating in "Pharma-Biotech programs" is of interest to Lipopharma?

- Create **awareness** and improve **understanding** of **MLT** technology
- Rise **interest** for **Minerval** program in oncology
- Understand **needs** and **priorities** of Pharma companies
- Show **progress** of **Lipopharma project** to biopharmaceutical community
- Build and strengthen a **network** of global **collaborators**…
- …
- Identify & bring in potential **partners** for development and commercialization of **Minerval** worldwide!

Opportunities can arise anywhere!!

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