Programa Cooperación Farma-Biotech
8º encuentro (7 de mayo de 2013)

ABTL0812: an oral, safe mTORC1/C2 and DHFR inhibitor in phase I/Ib in lung and pancreatic cancer

Ability Pharma
real medicine for real life

Madrid, 7 de mayo de 2013

Carles Domènech, PhD - CEO
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GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española
farmaindustria

Ability Pharma
real medicine for real life

Eureka Building - Research Park
Bellaterra - Barcelona

- → Biopharmaceutical company based in Barcelona
- → Founded in November 2009
- → US Development offices in 2014
- → € 3.4 M raised (2010-2012)
- → Investors: Inveready Capital Company (Venture Capital)
  Founders and Private Investors

- → **High efficacy**
- → **Low toxicity**
- → **Few adverse events**
- → **Oral administration**
- → **Once daily**
- → **Chronic treatment**
- → **Patent Protection (2030)**
- → **Potential sales > €1.6 B**

New drug class:

LIPID ANALOGUE THERAPEUTICS

Building a development pipeline

ABTL0812:

FIRST IN CLASS: **- mTORC1/C2 inhibitor**

- DHFR gene expression inh.

Phase I/Ib in July 2013 – CTA presented in April 2013

→ Non-small cell lung carcinoma (1st indication)

→ Pancreatic cancer (2nd indication)

TEAM

EXECUTIVE TEAM

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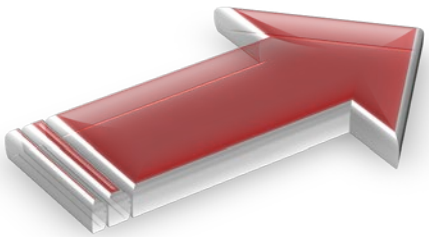
MARKET

- **Lung cancer** causes 30% of all cancer deaths.
  - 42% of patients survive after one year, but only 15% survive after 5 years.
  - Non-Small Cell Lung Carcinoma (NSCLC) accounts for the 25% of all drugs sales for cancer treatment.
  - NSCLC sales **from $4 billion in 2009 to > $6.5 billion in 2019** (USA, France, Germany, Italy, Spain, UK and Japan).
- **Pancreatic cancer** has a very low survival (**less than 5% after 2 years**).
  - The US pancreatic cancer drug **market will grow to $1.1 billion by 2013**.



UNMET MEDICAL NEEDS

OPPORTUNITY TO IMPROVE HUMAN HEALTH

MARKET OPPORTUNITY (Sales of ABTL0812 > €1.6 B)

LIPID ANALOGUE THERAPEUTICS

Proprietary new drug class called Lipid Analogue Therapeutics

- → **New chemical entities**
- → **Chemically synthesized analogues of naturally occurring lipids**

NOVEL MECHANISM OF ACTION

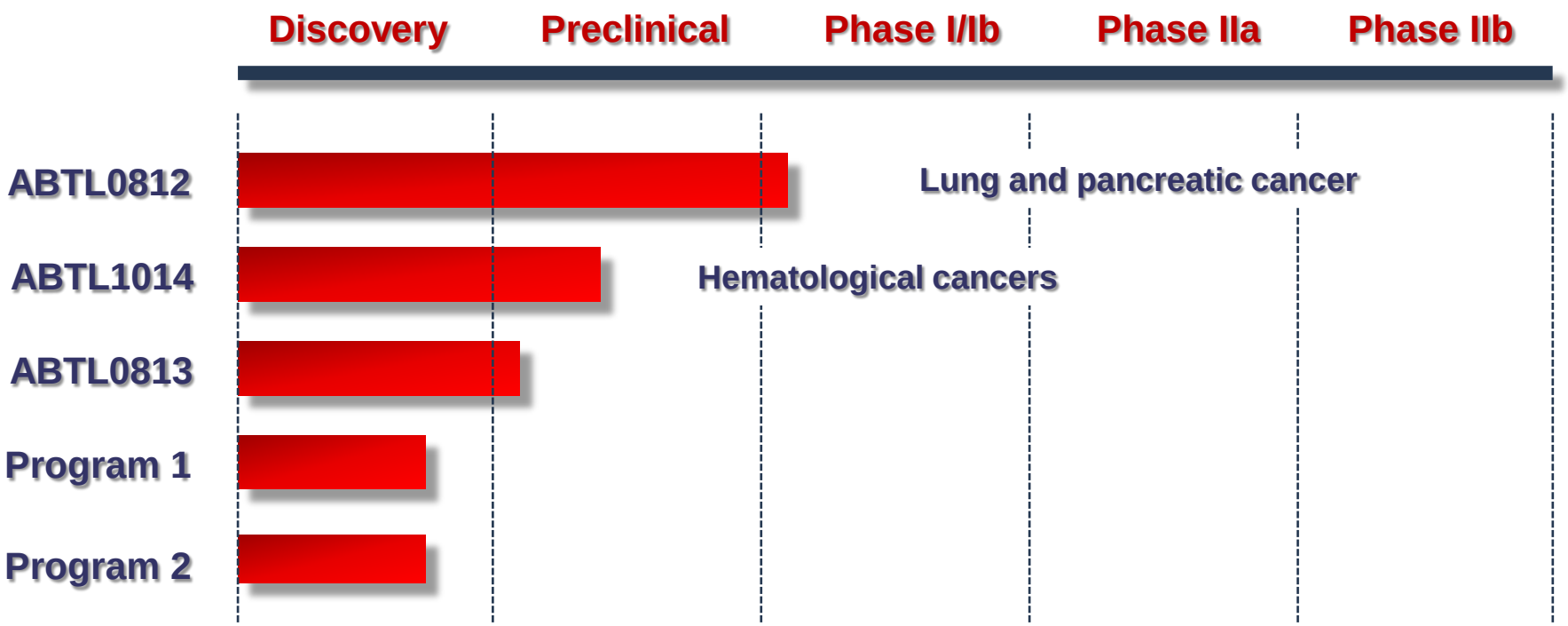
- → **Influence the activity of proteins which are central to cellular replication and oncogenesis**
- → **Alter the signaling of specific pathways**

PATENT PROTECTION UNTIL MARCH, 15, 2030

- → **Patent filed in 2009**
- → **PCT initiated in March 2010**
- → **Published in October 2010**

- → **National phases: AU, BR, CA, CH, CN, EP, IN, IL, JP, KR, MX, RU, ES, US.**

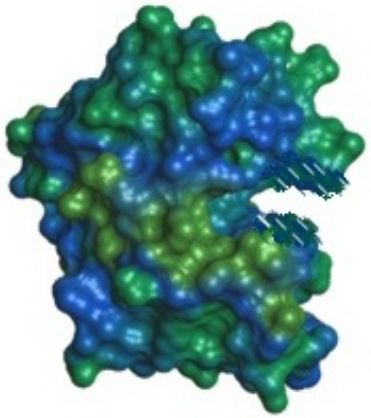
DEVELOPMENT PIPELINE



ABTL0812 – MECHANISM OF ACTION

Simultaneous action on 2 clinically validated targets for cancer chemotherapy:

- Dihydrofolate reductase (DHFR)
- Mammalian Target Of Rapamycin (mTORC1/C2) →AUTOPHAGY



ABTL0812

Inhibition of DHFR expression → **inhibition of DNA synthesis**

Inhibition of mTOR-C1 mTOR-C2 → **AUTOPHAGY**

TUMOR CELL DEATH

NOVEL MECHANISM OF ACTION

ABTL0812 – MECHANISM OF ACTION

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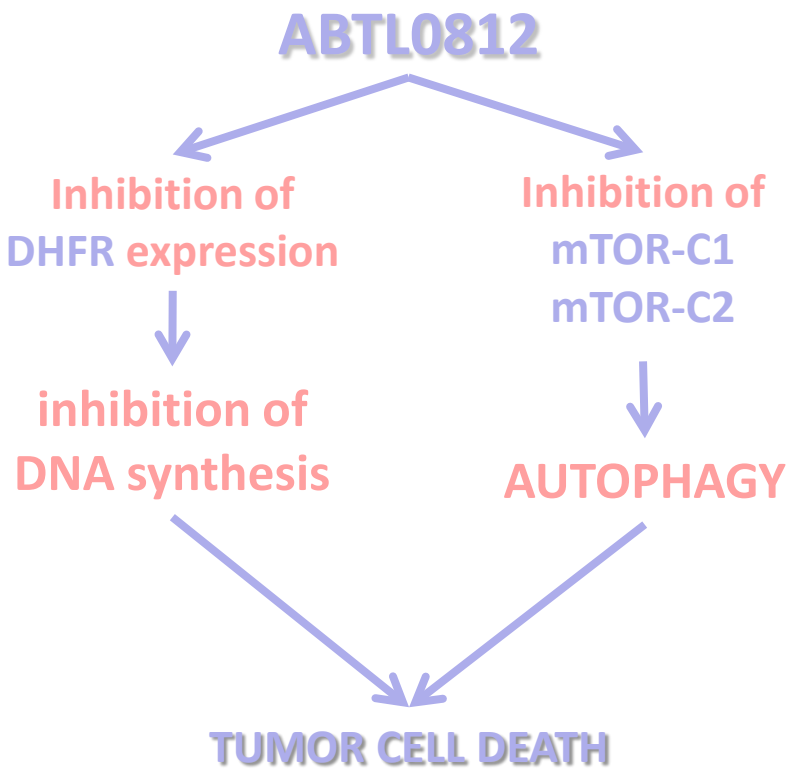


DHFR is the target of:

- **Methotrexate**
- **Pemetrexed (i.v)**

(Alimta, Lilly)

2011 SALES > 1,5 B €

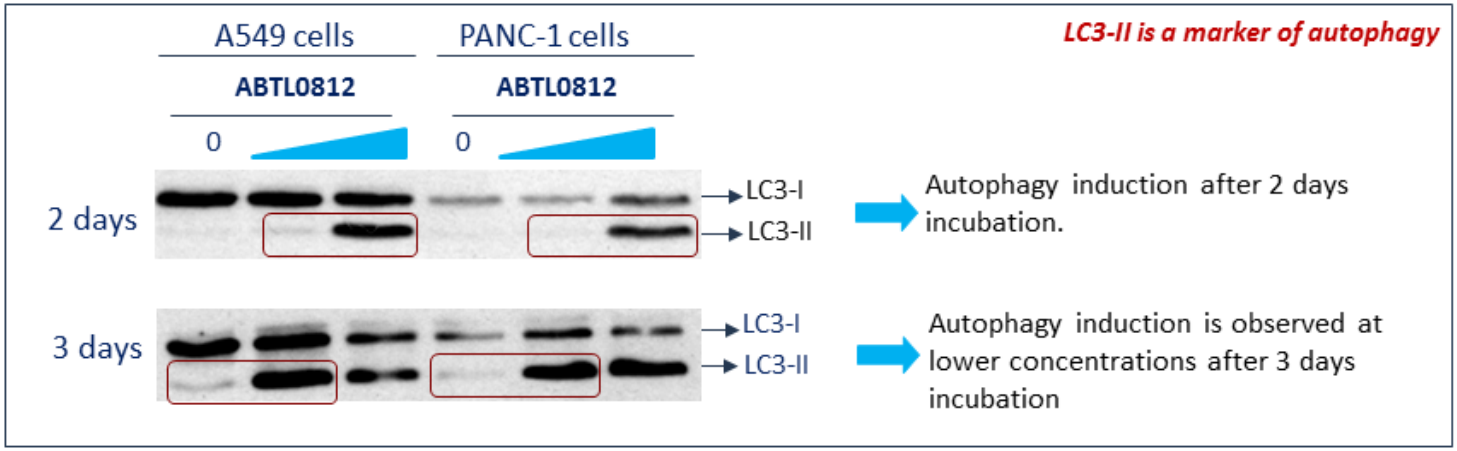
mTOR-C1 (and not mTOR C2) is the target of:

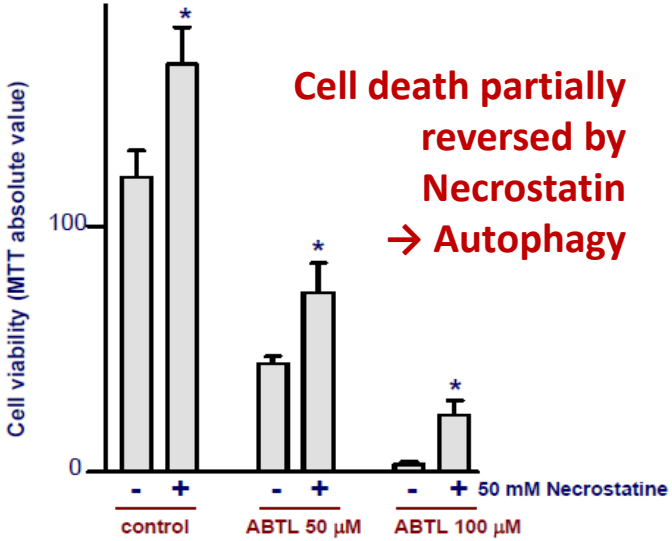
- **Temsirolimus (i.v)** (Torisel, Pfizer)
- **Everolimus (p.o)** (Afinitor, Novartis)
- **Deforolimus (p.o)** (ARIAD / Merck &Co PhIII)

2017 SALES > 2 B €

ABTL0812 - AUTOPHAGY

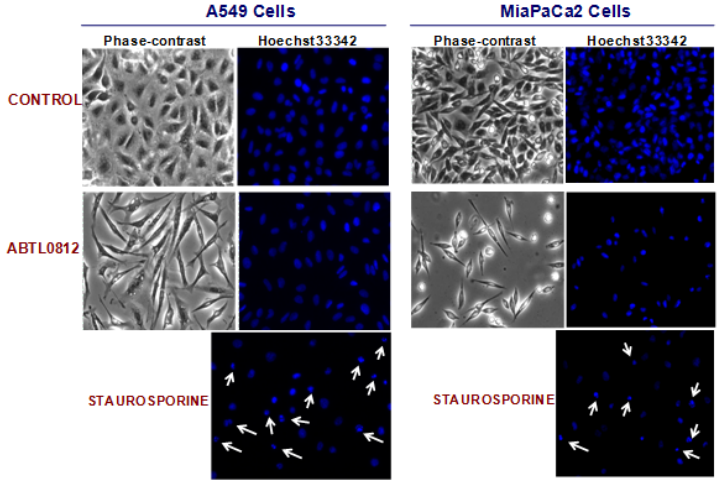
ABTL0812 induces tumor cell death by autophagy





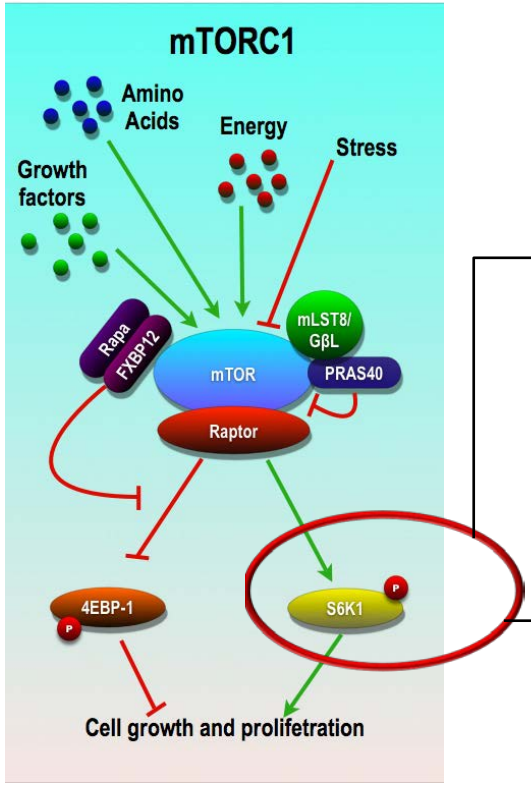
Cell death partially reversed by Necrostatin → Autophagy

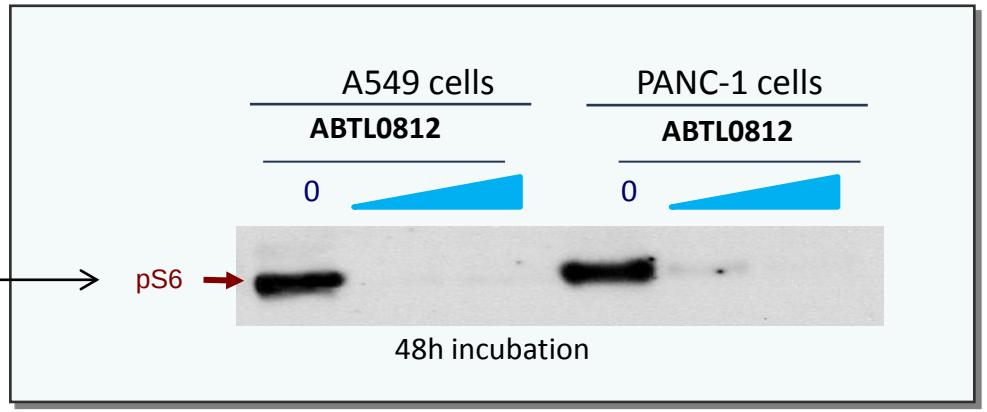
Absence of Apoptosis

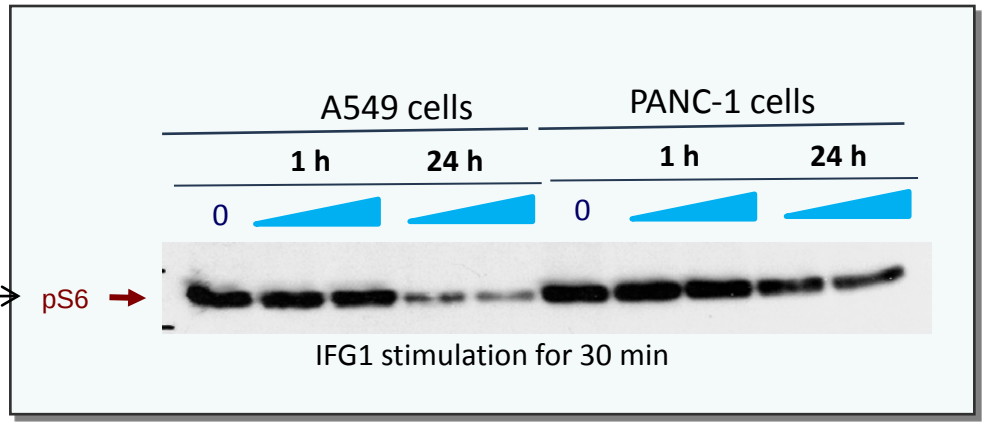


ABTL0812 – mTORC1 inhibition

ABTL0812 inhibits mTORC1 and prevents phosphorylation of S6 ribosomal protein

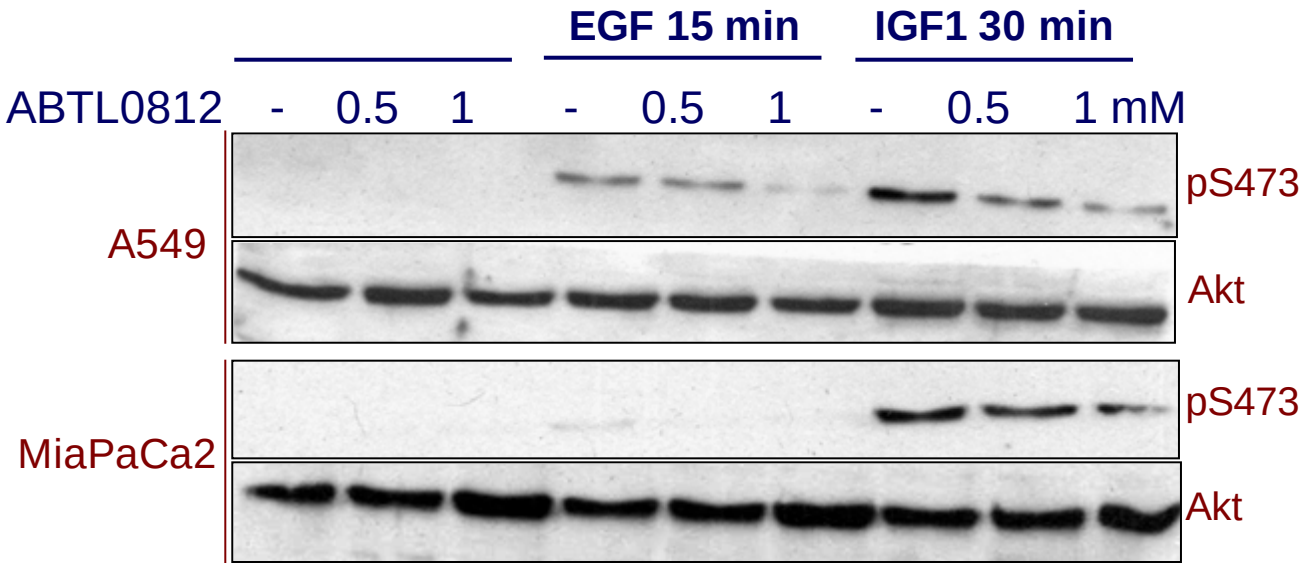






ABTL0812 – mTORC2 inhibition

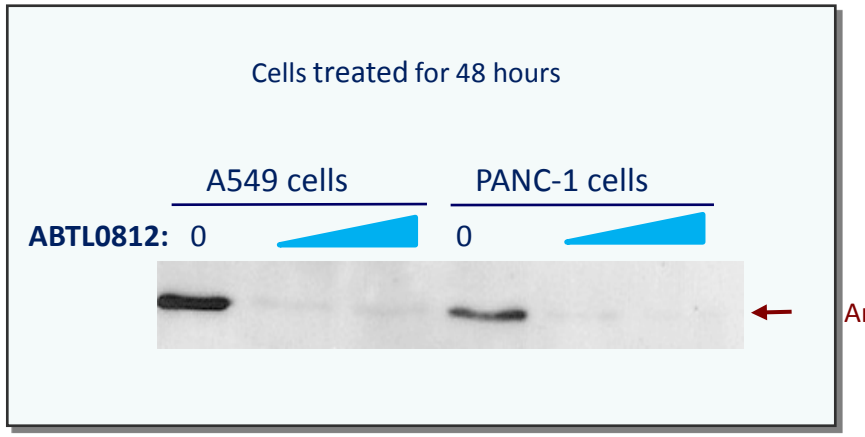
ABTL0812 inhibits mTOR2 pathway and prevents phosphorylation of Akt

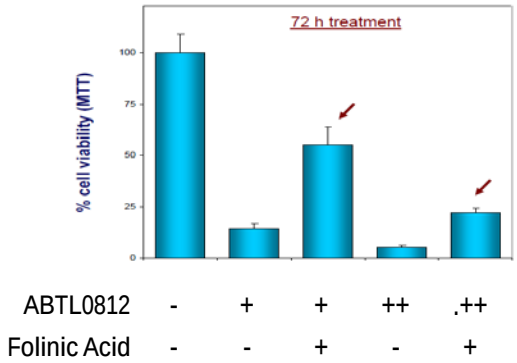


ABTL0812 prevented EGF and IGF-1 mediated mTORC2 activation, monitored by Akt phosphorylation at Ser473 (mTORC2 substrate). As loading control, Akt protein expression levels are shown.

ABTL0812 – inhibition of DHFR expression

DHFR expression is inhibited in cells treated with ABTL0812



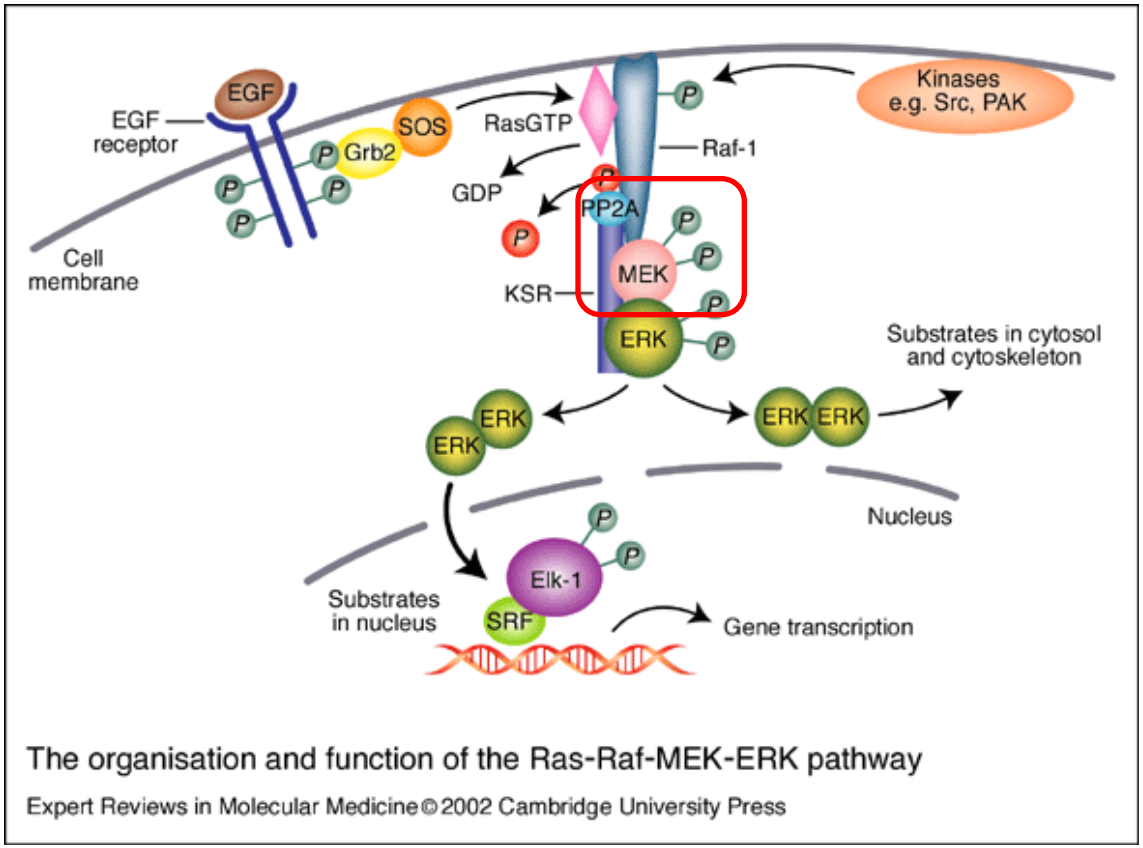


ABTL0812-induced cell death was partially reversed by folinic acid → DHFR inhibition is involved in cytotoxicty.

Working Hypothesis

ABTL0812 → **mTORC2 (Akt-P)** → **GSK3β phosphorylation** → **c-myc expression** → **E2F1 expression** → **DHFR expression**

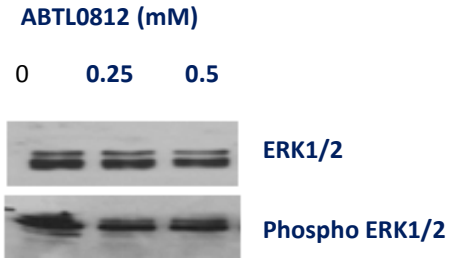
MAPK PATHWAY NOT AFFECTED



The organisation and function of the Ras-Raf-MEK-ERK pathway

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press

ABTL0812 does not inhibit MAPK pathway



ABTL0812 - HIGH EFFICACY IN LUNG CANCER

Active in a wide range of human cancer cell lines:

→ Lung cancer, pancreatic cancer, hepatoma, melanoma and glioblastoma

→ High efficacy in animals models of human lung cancer, ORAL:

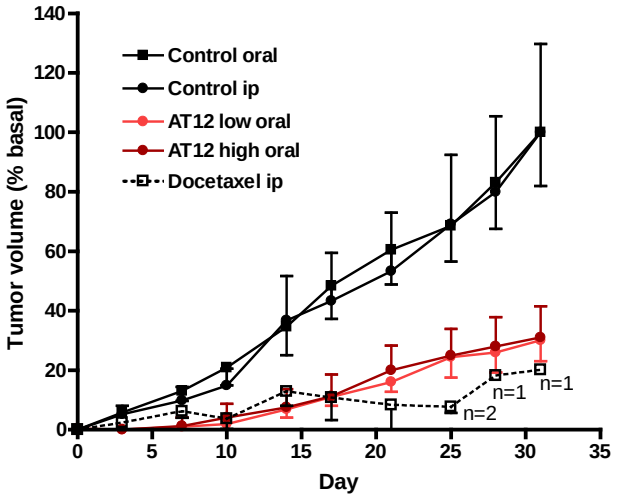
→ As potent as docetaxel (TaxotereTM) → ABTL0812 is much safer

→ Superiority to erlotinib (TarcevaTM) → ABTL0812 is active in broader populations

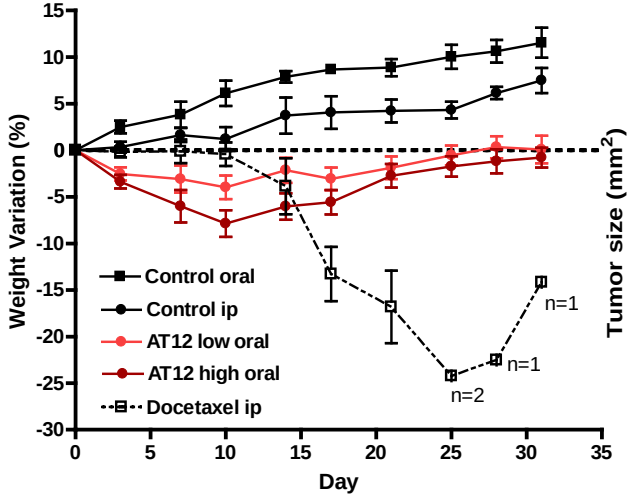
PK/PD correlation:

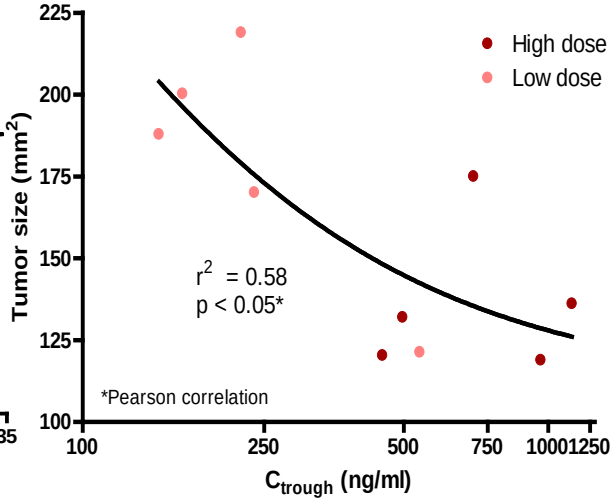
→ Steady state plasma levels of ABTL0812 in mice correlate with tumor volume

AT12 vs. docetaxel, tumor volume



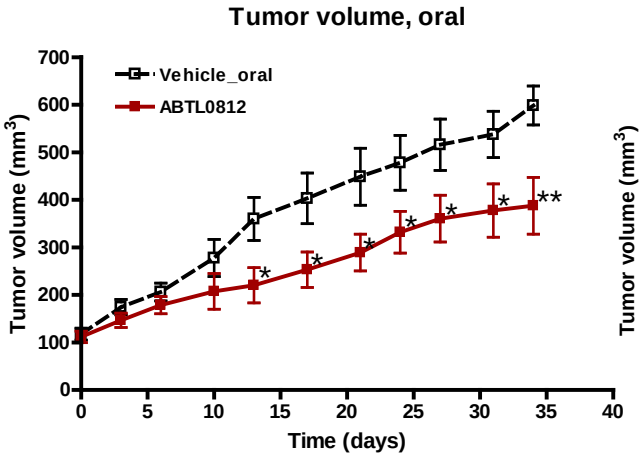
AT12 vs. docetaxel, body weight



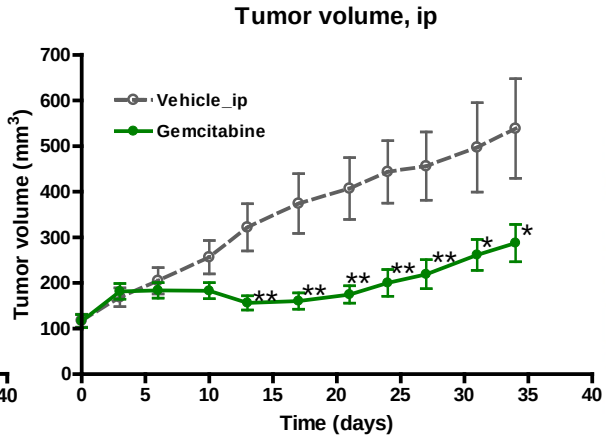


ABTL0812 -HIGH EFFICACY IN PANCREATIC CANCER

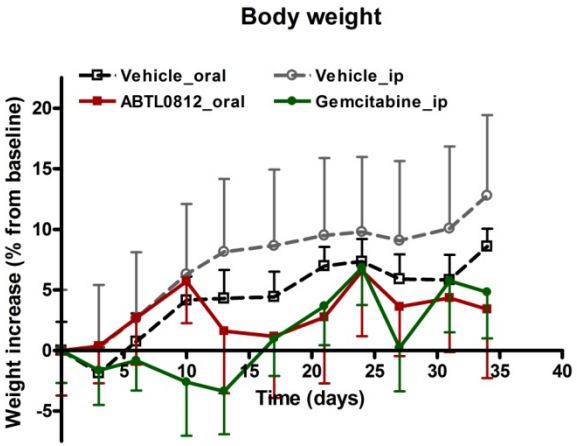
High efficacy in animals models of HUMAN PANCREATIC CANCER



* p<0.05 vs. vehicle by t-test
**p<0.01 vs. vehicle by t-test
n=5



* p<0.05 vs. vehicle by t-test
**p<0.01 vs. vehicle by t-test
n=5 all groups (n=4 in gemcitabine group on days 31 and 34)



n=5 all groups (n=4 in gemcitabine group on days 31 and 34)

Efficacy equal to gemcitabine, but oral

Category: Experimental and Molecular Therapeutics 7

Session Title: Pharmacology, Pharmacogenetics, and Pharmacogenomics 1

#922 ABTL0812: A new drug class with oral antitumor action inhibiting mTOR activity and DHFR expression. Jose Alfon[1], Jordi Espadaler[1], Jose A. García-Martínez[1], Jose Miguel Lizcano[2], Carles Domènech[1]. [1]AB-Therapeutics, SL, Bellaterra (Barcelona), Catalonia, Spain; [2]Institut de Neurociències, Departament de Bioquímica i Biologia Molecular, Universitat Autònoma de Barcelona, Bellaterra (Barcelona), Catalonia, Spain.

ABTL0812* is a lipid analogue that has shown high efficacy by the oral route in mouse models of cancer. Here we show that two clinically validated targets are responsible for the cytotoxic effect of ABTL0812: mTOR (mammalian target of rapamycin), as shown by the dramatic reduction in S6 phosphorylation, and dihydrofolate reductase (DHFR), as shown by its reduced expression, resulting in autophagic cell death. Moreover, the compound's cellular potency increases with incubation time, and it has a long lasting cytotoxic effect after removing the compound from the incubation medium.

In vivo efficacy was determined in a human lung cancer xenograft model by subcutaneously injecting A549 human lung adenococarcinoma cells into nu/nu mice. ABT0812 was administered daily at two dose levels and its impact on tumor volume was measured. ABT0812 showed a similar efficacy to docetaxel but with much lower toxicity, and better efficacy than erlotinib. Histological analysis of the tumors revealed increased necrotic area, more inflammatory cells and fewer cells undergoing mitosis. Additionally, plasma levels of ABTL0812 were inversely correlated with tumor volume, reinforcing the concentration-effect relationship. A parallel study was performed to evaluate ABTL0812 efficacy in a pancreatic cancer model. Nu/nu mice were subcutaneously injected with MiaPaCa-2 cells and the volume of xenograft was used as a measurement of efficacy. Again, ABTL0812 showed a statistically significant reduction of tumor volume, increased tumor cell death, and better tolerance than gemcitabine in the mice.

DMPK properties in rats and dogs showed very low *in vitro* hepatic metabolism, ~50% bioavailability and half lives that calculate to single daily oral administration. Safety pharmacology studies with very high doses of the compound showed no impact on the central nervous system. Ongoing toxicological studies show that the margin between efficacy and toxicity is broad.

In conclusion, ABTL0812 is a lipid analogue that hits two clinically validated targets: mTOR and DHFR. This multitarget property increases antitumor efficacy and reduces drug resistance. In addition, preliminary *in vivo* results indicate that the potential therapeutic margin will be high.

* Protected by PCT WO 2010/106211, by Escribá Ruiz PV, et al., licensed to AB-Therapeutics, SL.

Citation Format

Alfon J, Espadaler J, García-Martínez J, Lizcano J, Domènech C. ABTL0812: A new drug class with oral antitumor action inhibiting mTOR activity and DHFR expression [abstract]. Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, Illinois. Philadelphia (PA): AACR; 2012. Abstract nr 922.

1042 ABTL0812, a Dual Inhibitor of mTOR and Dihydrofolate Reductase With High Oral Efficacy and Safety Margin in Human Lung and Pancreatic Cancer Xenograft in Mice

J. Espadaler[1], J. Alfón[1], J.A. García-Martínez[1], C. Domènech[1], J.M. Lizcano[2]. *[1]AB-Therapeutics, Bellaterra (Barcelona), Spain, [2]Institut de Neurociències, Departament de Bioquímica i Biologia Molecular UAB, Bellaterra (Barcelona), Spain*

Introduction: Most cancer types are the result of multiple gene mutations and/or impairment of several pathways that control cell proliferation and viability. A compound targeting several key pathways may have enhanced efficacy. We describe ABTL0812, which has oral anticancer properties through a novel mechanism of action involving mTOR (mammalian target of rapamycin) pathway and dihydrofolate reductase (DHFR).

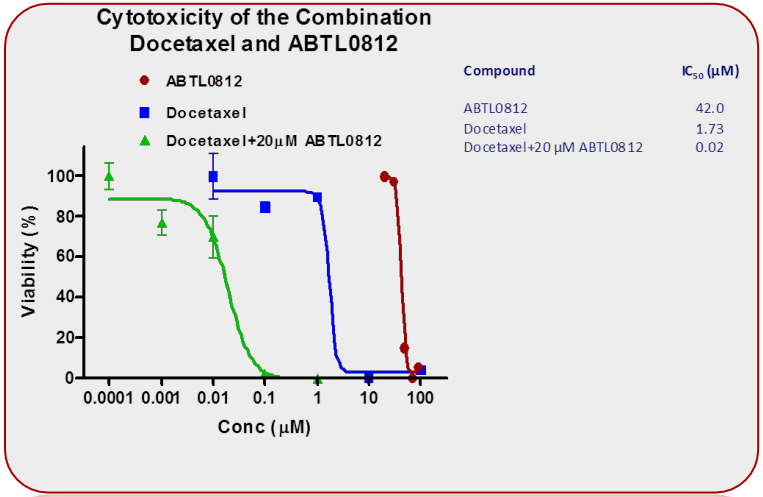
Material and Methods: Cellular assays were performed in the A549 lung adenocarcinoma, and Panc-1 and MiaPaca2 pancreatic carcinoma cell lines. Cell proliferation assays were carried out by monitoring bromodeoxyuridine (BrdU) incorporation, cell viability by MTT assay, and protein expression by immunoblotting. Cellular apoptosis was assessed by nuclear staining; and autophagy by LC3-II lipidation assay. In vivo efficacy was studied in nu/nu mice bearing A549 and MiaPaca2 xenografts, in which ABTL0812 was orally administered daily. Body weight and tumor volume were regularly measured. At sacrifice, histopathological analysis of tumors was performed by H/E staining. ABTL0812 plasma levels were determined by LC-MS followed by a PK/PD analysis.

Results and Discussion: ABTL0812 showed antiproliferative (cell count and BrdU incorporation) and cytotoxic (MTT) effects. ABTL0812 abolished DHFR expression, and cell viability was partially rescued by folinic acid. ABTL0812 inhibited both mTOR complex 1 and 2 activities, as shown by pS6 (mTORC1) and pS473-Akt (mTORC2) phosphorylation. ABTL0812 did not induce apoptosis (caspase 3 activity and PARP immunoblotting). Furthermore, ABTL0812 cell death was not reverted by pretreatment with caspase inhibitor Z-VAD, and no nuclear staining indicative of apoptosis was observed. By contrast, ABTL0812 treatment induced LC3-II, and necrostatin partially reversed ABTL0812-induced cell death, suggesting a major role for autophagy. ABTL0812 significantly reduced tumor volumes similarly to reference compounds such as docetaxel, erlotinib or gemcitabine. However its impact on body weight was marginal without systemic toxicity. Histopathological analysis of the tumors showed less mitotic cells, increased necrotic area, fibrotic cap and inflammatory cells which could contribute to the anticancer effect. Plasma concentrations correlated with tumor volume and in vivo EC90 = 955 ng/ml.

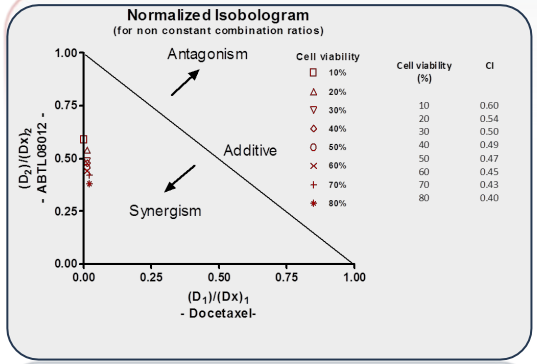
Conclusion: ABTL0812 shows a high anticancer efficacy and safety in human lung and pancreatic cancer xenografts in mice. ABTL0812 induces autophagic cell death by inhibiting mTOR activity and DHFR expression, which makes it a very unique compound. ABTL0812 is currently in preclinical development for lung and pancreatic cancer.

ABTL0812 SYNERGY : DOCETAXEL AND GEMCITABINE

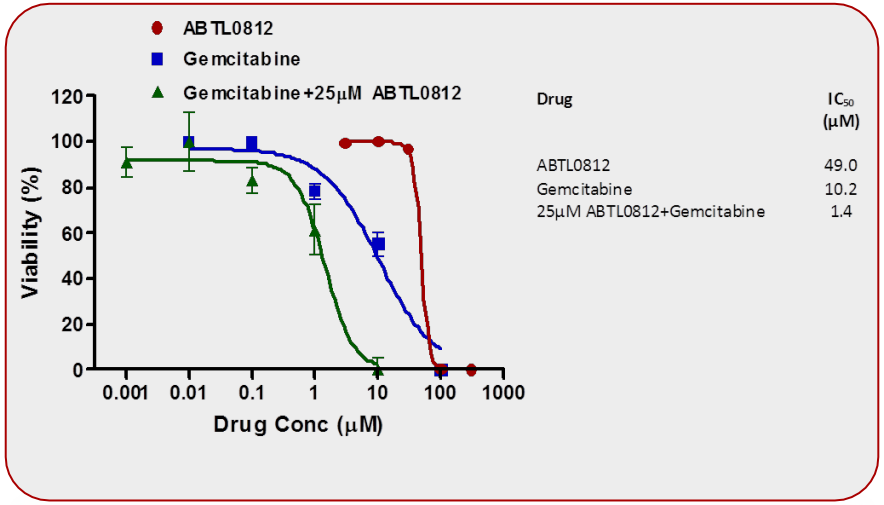
Potentiation of docetaxel: 87x



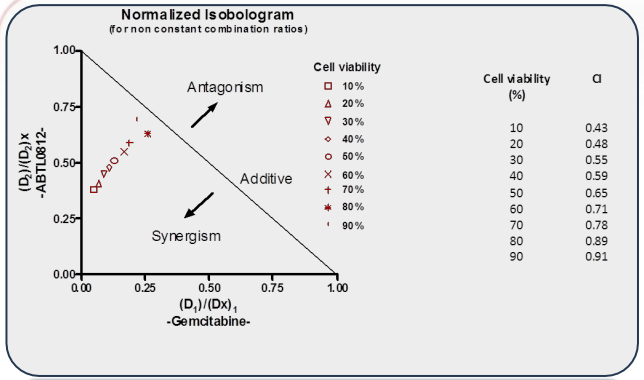
Compound	IC_{50} (µM)
ABTL0812	42.0
Docetaxel	1.73
Docetaxel+20 µM ABTL0812	0.02



Potentiation of gemcitabine: 8x



Drug	IC_{50} (µM)
ABTL0812	49.0
Gemcitabine	10.2
25µM ABTL0812+Gemcitabine	1.4



ABTL0812 – DEVELOPMENT – KEY FINDINGS

Regulatory preclinical development: pharmacokinetic facts

In vitro

- Stable in human hepatocytes of relevant species and humans
- Similar protein binding in relevant species and humans
- ABTL0812 does not inhibit most relevant cytochromes

In vivo

- Pharmacokinetic in vivo profile studied in mice and rats
- ca. 50% bioavailability in rats and dogs at therapeutic doses
- Half life: 2h (rat) and 6h (dog)
- Anticipated once daily dosing in humans

Regulatory preclinical development: safety and toxicological facts

Safety
(core battery studies)

- Central Nervous System: No effects up to very high oral doses
- Cardiovascular and Respiratory: Included in pivotal 28d tox studies. No effects up to very high doses

Toxicology

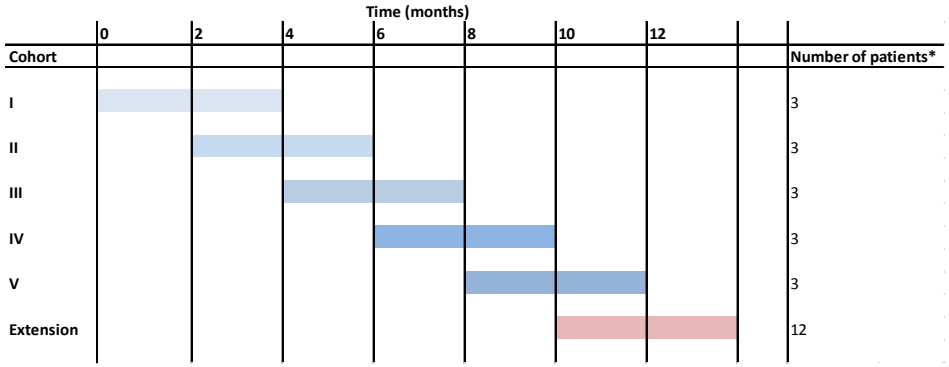
- Rats:
  - Acute: No effects up to very high oral doses
  - DRF: No effects up to high oral doses after 14d oral dosing
  - 28d GLP Tox. Completed
- Dogs:
  - DRF: No effects up to high oral doses after 14d oral dosing
  - 28d GLP Tox Completed

ABTL0812 – FIRST IN HUMANS TRIAL

PHASE I/Ib IN ADVANCED CANCER PATIENTS WITH SOLID TUMORS

- → Multiple ascending dose trial. Multicenter
- → Phase I/Ib: dose-limiting toxicity in 27 patients with advanced cancer
- → Phase IIa: dose, schedule and response rate in 40 patients
- → **HOSPITAL CLINIC BARCELONA (University of Barcelona)**

Phase Ib trial design



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Hospital Clínic

Dr. Laura Vidal
Head Cancer Trials
Hospital Clínic

Dr. Toni Pérez
Chairman Advisory Board
Ability Pharma

Dr. Marc Cortal
Director Clinical Research
Ability Pharma

Dr. José M. Lizcano
Head Kinases and Signal Transduction Biomarkers – UAB

Dr. Mercè Brunet
Head Biomedical Diagnosis Pharmacokinetics
Hospital Clínic

CLÍNIC BARCELONA Hospital Universitari

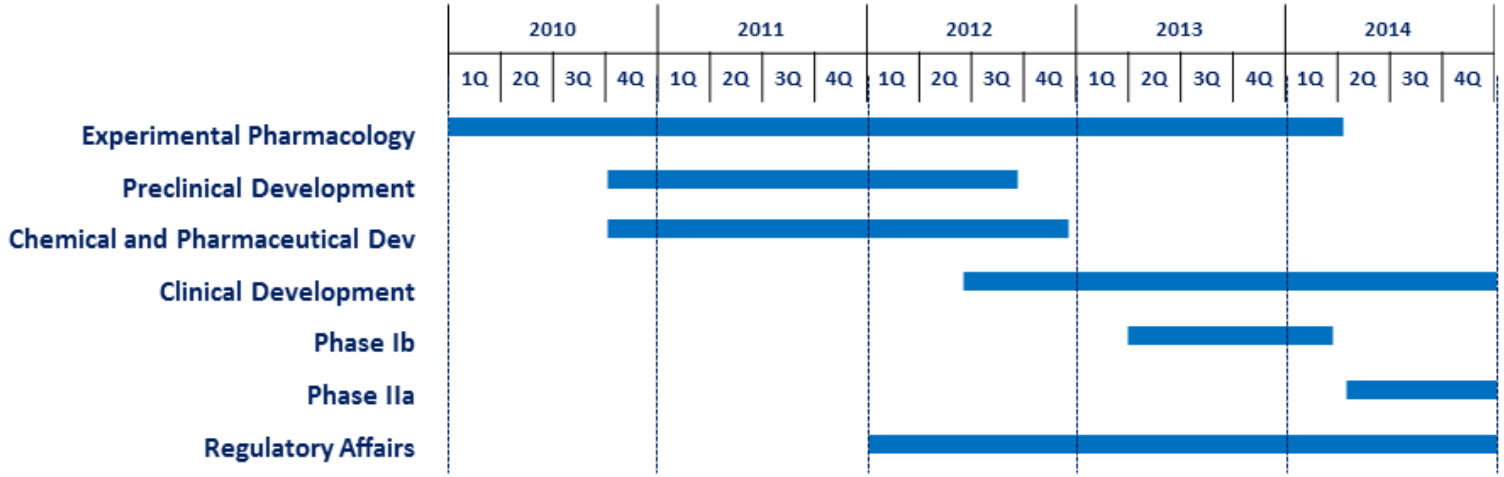
IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

Universitat de Barcelona

UAB Universitat Autònoma de Barcelona

ANTICIPATED MILESTONES

- → March 2013. Scientific Advisory Board Meeting.
- → April 2012. CTA/IND filing. First in Man clinical trial. phase Ib.
- → June 2013. CTA approval
- → July 2013. First patient in. First in Man clinical trial, phase Ib.
- → March 2014. MTD determination. First in Humans clinical trial, phase Ib.
- → May 2014. End First in Man clinical trial, phase Ib.
- → May 2013. Series A financing round > € 5 million.
- → End of 2014. Licensing-out Agreement



Thank you !

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Special thanks to: