MDN-0090: novel chemotherapeutic to treat cancer

MEDINA

Madrid, 14 de noviembre de 2017

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3. Partnering Opportunities

The Institution

- Independent & non-profit Research Organization

- Private-public partnership between:
- Merck Sharp and Dohme de España S.A
- Government of Andalucía (Spain)
- University of Granada (Spain)

- Established in 2008 from CIBE, former Merck Research Labs in Madrid, Spain.

Our Mission

Discovery of new bioactive compounds and innovative therapies for unmet medical and industrial needs.

Health Sciences Technology Park, Granada, Spain

MEDINA: Microbial Natural Products Drug Discovery

http://www.medinadiscovery.com

- Multidisciplinary team of scientists (28 permanent staff , up to 40 employees)
- 2300 m^2 fully equipped facilities
- One of the largest microbial collections and libraries for natural products drug discovery
- High capacity center for high throughput screening
- Drug discovery research programs in infectious and tropical diseases, cancer and neurodegeneration

The Institution

MEDINA

Leveraging:

- 50 years expertise in Drug Discovery
- 5 Drugs in the market
- Collaborations with industry & academia

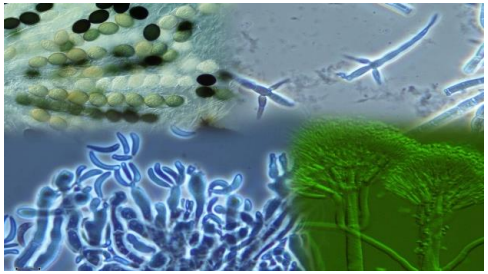
- Microbial collections (190.000 strains)
- Microbial Genome Banks
- Natural Products Libraries (135.000 extracts)

- High Throughput Screening
- Natural Products Chemistry
- Compound Structural Elucidation
- Bioanalytics
- Preclinical Safety
- Genome mining

- New Compound Discovery
- Patents
- Collaborations
- Publications

The Institution

Unique Technology Platforms & Capacities
(from discovery to early preclinical studies)

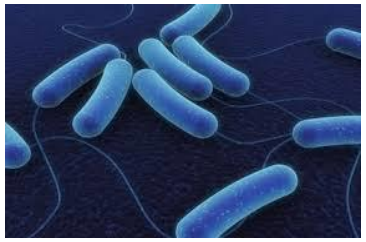


Screening	Chemistry	Microbiology	Analytics	Preclinical
• Target Validation • HTS Drug Discovery •High Content Bioimaging • Mode of Action	• **NPs libraries** •Isolation of Natural Products • Analytical Chemistry Services /Dereplication (NMR, LC_MS) • Structural Elucidation	• **Culture Collections** •Isolation and identification • Fermentation and scale-up production • Genome mining	• Bioanalysis • Metabolomics •Biomarkers discovery	• Safety/ADME platform (PK/PD, bioanalysis) •Toxicology profiling & functional screening • Translational / clinical R&D support

eu-openscreen

The Institution

- Strategic role in drug discovery and high value biotechnology products
- R&D Programs to respond to unmet medical needs

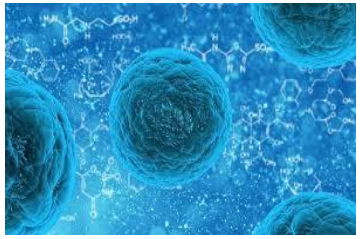


Infectious diseases

- Antibiotics
  - Gram negative
  - Tuberculosis
- Antifungals
  - Aspergillosis

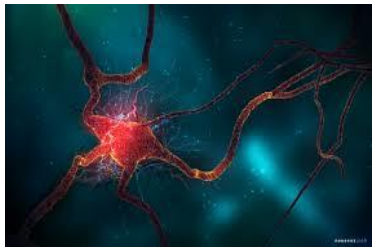
Parasitic Diseases

- Malaria
- Leishmaniasis
- Trypanosomiasis



Oncology

- Kidney
- Breast
- Pancreas
- Lung
- Biomarkers



Neuro-degeneration

- Amyothrophic Lateral Sclerosis
- Neuro-degeneration

- Programs based on collaborations and partnerships with academia and industry

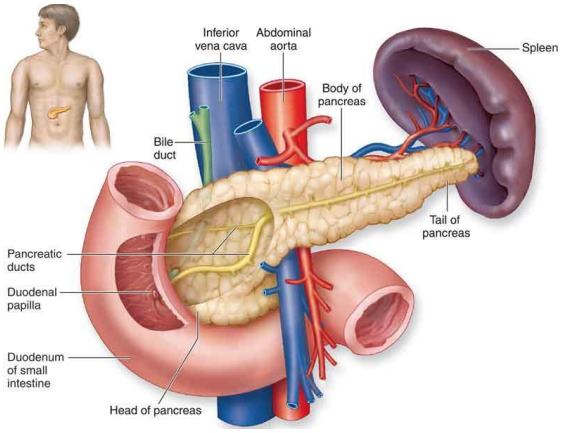
The Product: MDN-0090
Target indications

Pancreatic Cancer: *"the silent cancer"*

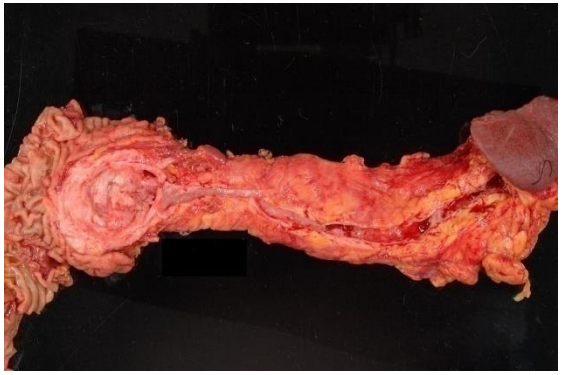
5 YEAR
SURVIVAL FOR
5% OF THE PATIENTS[2]

103 773
NEW CASES PER
YEAR IN EUROPE[3]

4TH
LEADING CAUSE
OF DEATH BY
CANCER IN EUROPE[1]



- ✓ Treatments with conventional antitumoral therapy are not effective
- ✓ New treatments are urgently needed



* *http://www.pancreaticcancereurope.eu*

The Product: MDN-0090
Target indications

Pancreatic Cancer: *"the silent cancer"*

HIT IDENTIFICATION:

MDN-0090 is:

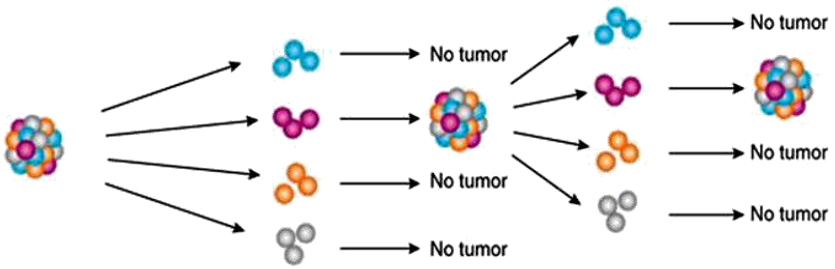
- a **small molecule of microbial origin**
- identified from a anti-tumour screening campaign
- patent protected

HIT EFFECTIVENESS:

- **MDN-0090** is a new *hit compound* with demonstrated ***in vitro*** **and** ***in vivo*** **efficacy against pancreatic cancer.**
- **MDN-0090 inhibits pancreatic adenocarcinoma** development and **reduces tumor size** of tumors developing both from pancreatic tumoral cells and **pancreatic cancer stem cells**

The Product: MDN-0090
Innovative Mechanism of Action

Inhibitor of Cancer Stem Cells (CSC) proliferation:



Cancer Stem Cells (CSC) are responsible for:

- → Drug-resistance
- → Initiate tumor growth
- → Cancer recurrence
- → Metastasis

In vitro

❑ **MDN-0090 inhibits human pancreatic CSC proliferation:**

BxPC3 (wildtype K-RAS):

Parental	ED_{50}= 4.67 µM
CSCs	ED_{50}= 10.34 µM

MiaPaca-2 (**mutated K-RAS, most PC patients**):

Parental	ED_{50}= 8.84 µM
CSCs	ED_{50}= 2.18 µM

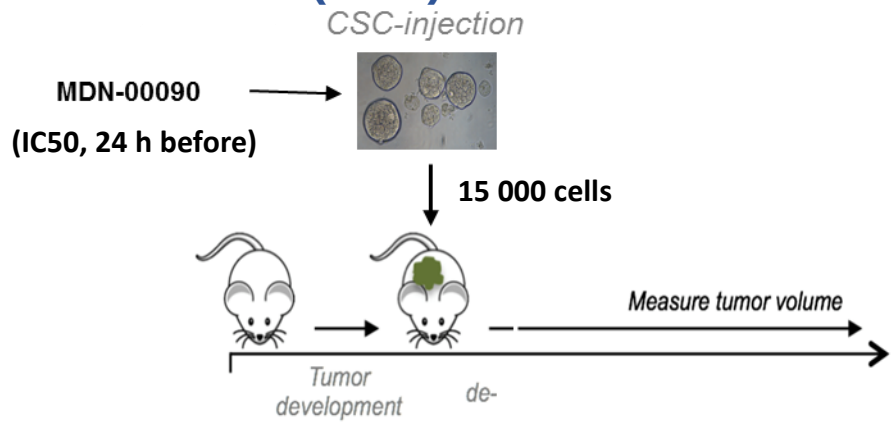
❑ **Synergistic effect with Gemcitabine and Selumetinib on cancer stem cells:**

- Anti-tumour synergistic effect of MDN-0090 and Gemcitabine (inhibition of mitosis) in BxPC3 (Combination Index, CI= 0.18) and MiaPaca-2 (CI=0.08)
- Anti-tumour synergistic effect of MDN-0090 and Selumetinib (experimental drug, inhibitor MEK1 and MEK2) in BxPC3 (CI= 0.08) and MiaPaca-2 (CI=0.12)

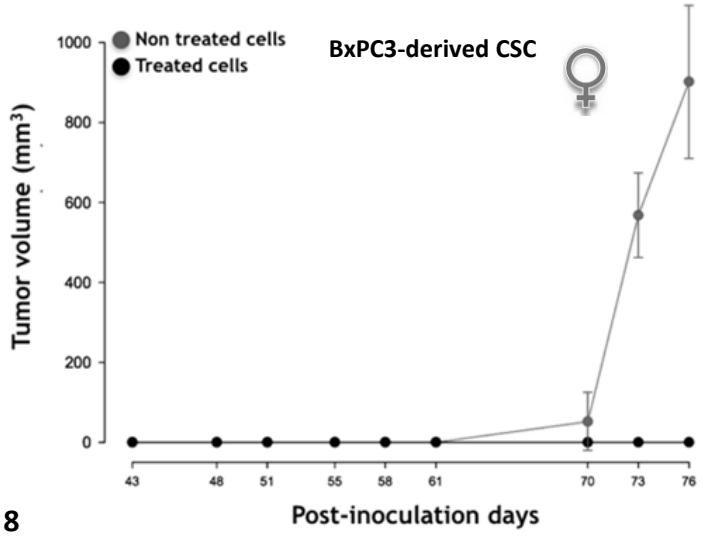
The Product:
Innovative Mechanism of Action

MDN-0090 inhibits the tumor-initiating ability by pancreatic cancer stem cells

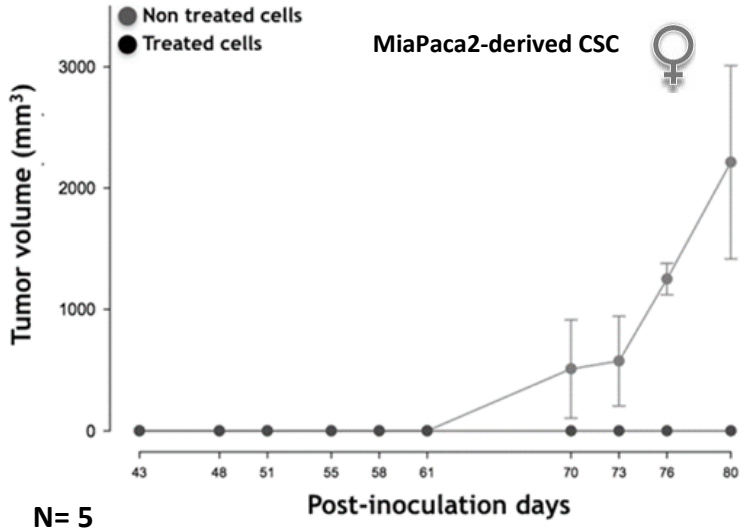
In vivo effect on Cancer Stem Cells (CSC) in CSC-derived tumor xenograft models:



In vivo



N= 8

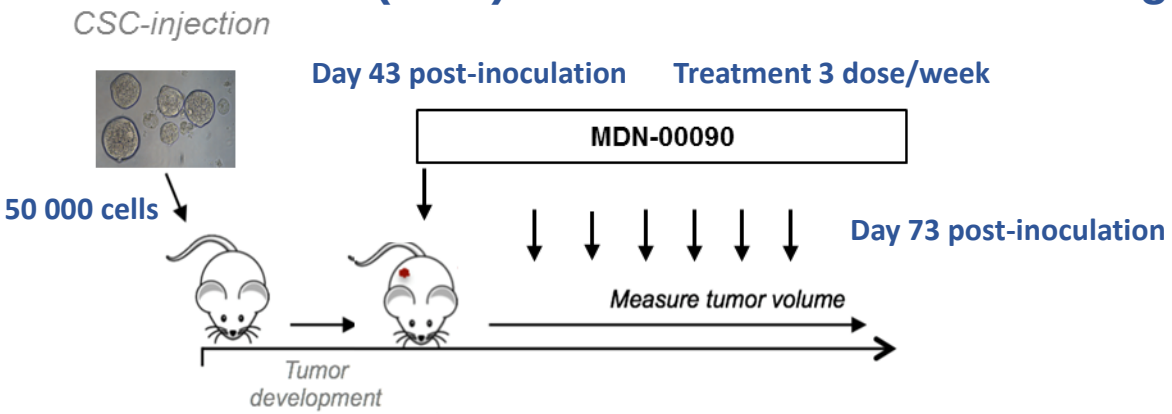


N= 5

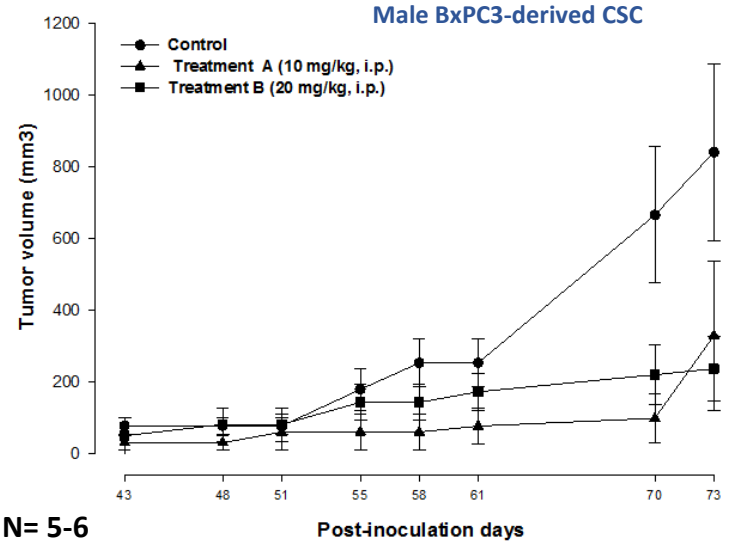
The Product:
Innovative Mechanism of Action

MDN-0090 inhibits the tumor development by pancreatic cancer stem cells:

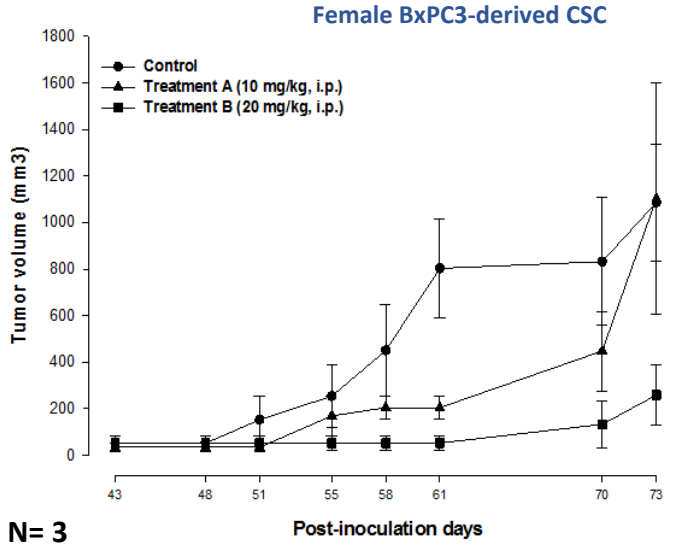
In vivo effect on Cancer Stem Cells (CSC) in CSC-derived tumor xenograft models:



In vivo



N= 5-6



N= 3

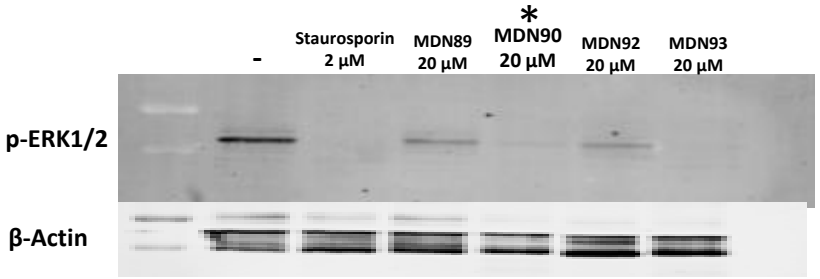
The Product:
Innovative Mechanism of Action

MoA: **MDN-0090** targets **Ras/Raf/MEK/ERK** pathway

Decreased p-ERK 1/2 levels

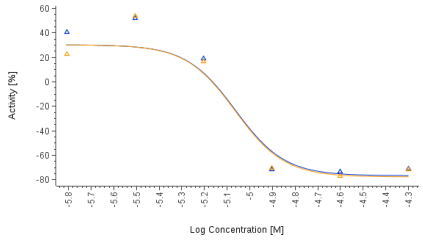
Western blot

MiaPaca-2 cell line / 24 hour incubation

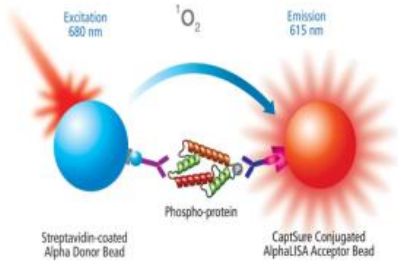


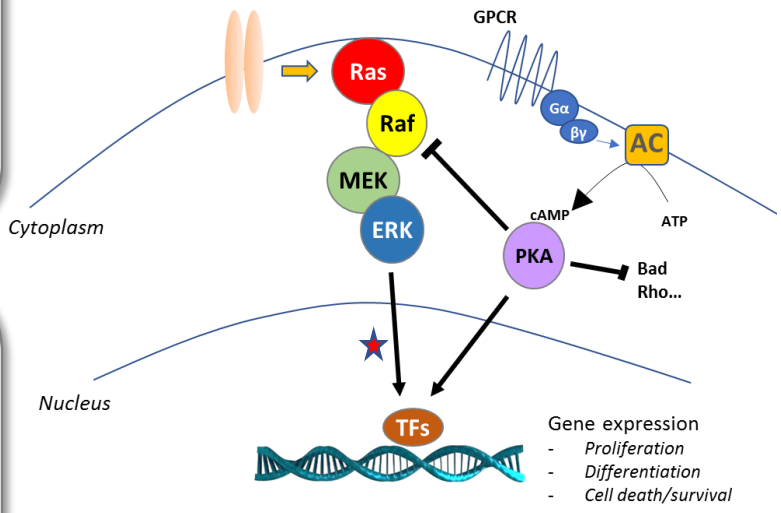
AlphaLisa SureFire pERK

MiaPaca-2 cell line/ 24 hour incubation



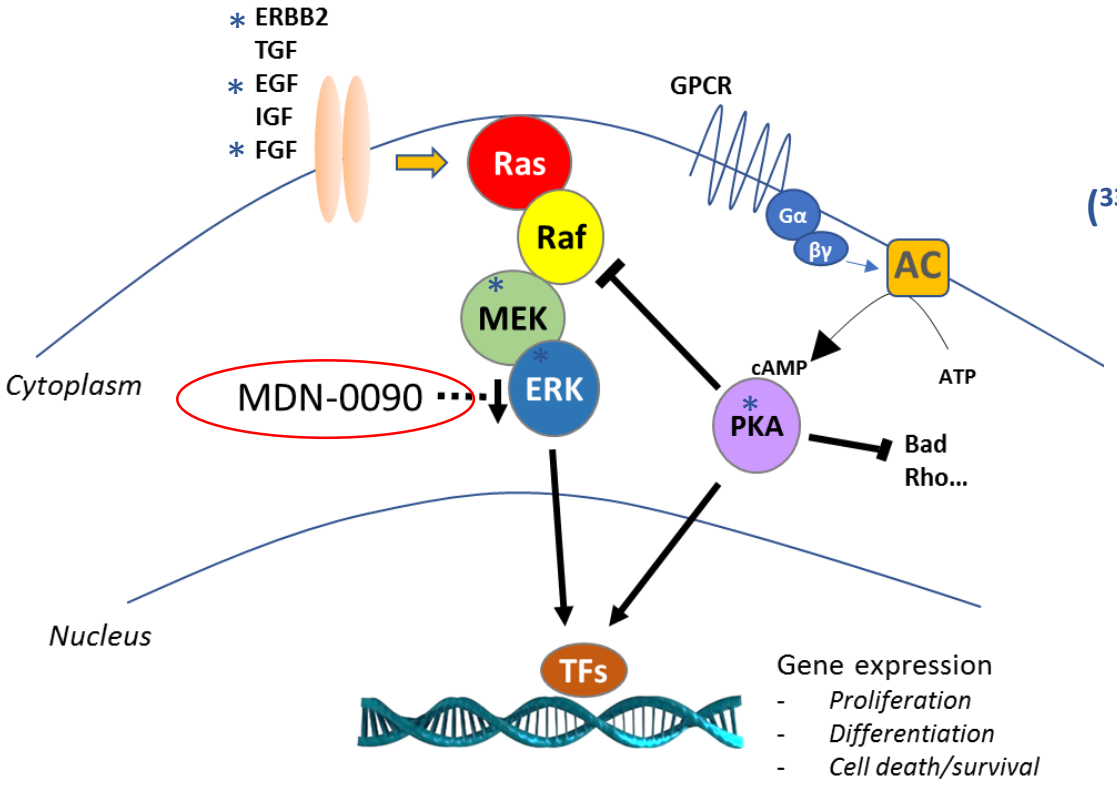
IC_{50} = 6.6 µM





The Product:
Innovative Mechanism of Action

MoA: **MDN-0090** targets **Ras/Raf/MEK/ERK** pathway



Radiometric protein kinase assay

(^{33}PanQinase® Activity Assay, ProQinase)*

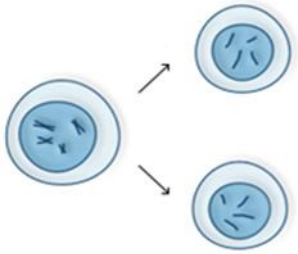
No.	Kinase	IC_{50} (µM)
1	EGF-R wt	58
2	ERBB2 wt	>100
3	ERK1	67
4	ERK2	91
5	FGF-R1 wt	48
6	MEK1 wt	>100
7	MEK2	>100
8	PKA	13

- ✓ **MDN-0090 reduces activation of ERK1/2** (western blot and AlphaLISA assays)
- ✓ **MDN-0090 inhibits PKA** (radiometric protein kinase assay)

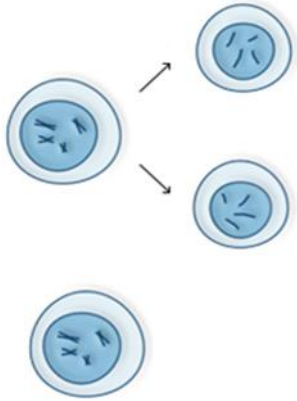
The Product:
Differential features facing the market

Cell targets

First-line chemotherapeutic drugs
(5-FU, gemcitabine)



Only target actively dividing cells



Actively dividing cells

MDN-0090

CSC, in quiescent state

MDN-0090 targets both actively dividing cancer cells and quiescent cancer stem cells

The Product:
Differential features facing the market

Current treatment options:

	Treatment	*MoA*	*Pros and cons*
	Gemcitabine (FDA 1996)	Cytidine analogue-Inhibition of mitosis	Poor effectiveness (increase OS 6 months)
Gemcitabine +	**Leucovorin**	Adjuvant (vitamer of folic acid)	Adjuvant
	Capecitabine	Prodrug of 5-FU	Side effects, treatment of breast and colon cancer
	Erlotinib (FDA 2005)	EGFR inhibitor	Increase OS 6.4 months vs 6 gem. alone
	Cisplatin/oxaliplatin	Inhibition of DNA synthesis	Severe side effects (neurotoxicity, rhabdomyolysis)
	Nab-paclitaxel (FDA 2013)	Stabilizer microtubule-Inhibition of mitosis	Increase OS to 2 years
	Irinotecan	Inhibition of DNA replication and transcription	Extreme suppression of the immune system
	FOLFIRINOX (oxaliplatin, irinotecan, 5-FU and leucovorin)		Increase OS 4.3 months more, severe side effects

OS, overall survival

- **Poor effectiveness**
- **High toxicity and severe adverse effects**

There are no drugs in the market with MoA involving the inhibition of PKA

The Product:
Differential features facing the market

Current treatment options:

	Treatment	*MoA*	*Pros and cons*
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Gemcitabine +	**Leucovorin**	Adjuvant (vitamer of folic acid)	Adjuvant
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OS, overall survival

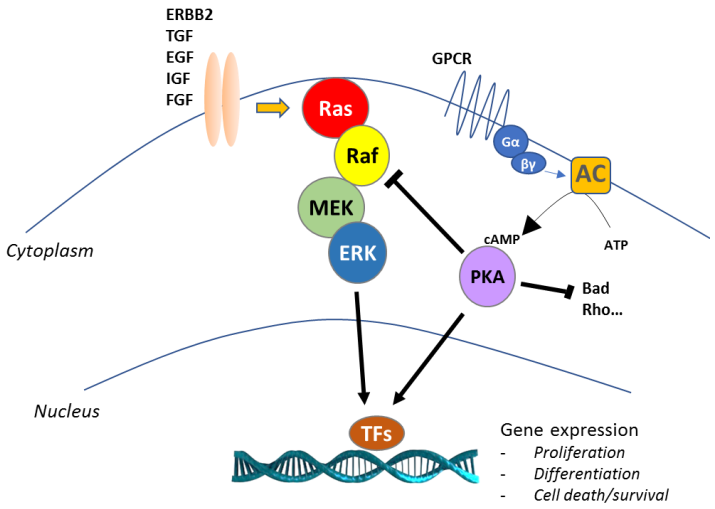
MDN-0090 opportunity:

- **High efficacy in mice models**
- **Good safety profile in mice (up to 200 mg/kg, oral)**
- **Novel target in a key pathway in pancreatic cancer**

The Product:
Differential features facing the market

Targeted Pathways in cancer drug discovery:

Pathways	Targets
K-ras	**Raf, MAPK, Erk, PI3Ks, PDK-1**
p53	p53
Growth factor	EGF, EGFR, FGF, FGFR, VEGF
Epithelial to mesenchymal transition (EMT)	Wnt, β-catenin, TNFα, Notch, Snail-1, Slug, E-cadherin



PKA in cancer

- ✓ cAMP/PKA signaling pathway is altered in different cancers [Naviglio et al. 2009]
- ✓ PKA is involved in neoplastic transformation and tumor growth [Mantovani et al., 2008]
- ✓ PKA regulates actin dynamics, controlling cytoskeleton remodeling and cell migration [McKenzie et al., 2011]
- ✓ Analogues of cAMP that inhibit PKA cause inhibition of cancer cell growth [Cho-Chung and Nesterova, 2005]

The Product:
Differential features facing the market

Targeting PKA in cancer therapy:

Clinical trials:

- ✓ *Evaluating the **Effect of ADRB2 Blockers** on PKA/BAD/CREB Signaling in Patients Undergoing Prostatectomy.* 2017-. Participant recruitment.
- ✓ ***Pentoxifylline Treatment in Acute Pancreatitis**.* 2015-. **Pentoxifylline** is a competitive nonselective phosphodiesterase inhibitor which raises intracellular cAMP, activates PKA, … Ongoing study.
- ✓ ***Phase II Midostaurin** in Aggressive Systemic Mastocytosis and Mast Cell Leukemia.* **Midostaurin** is a broad-spectrum protein kinase inhibitor (PKC, PKA, etc…). 2005-2011. Results posted: serious adverse effects.

Targeting **Protein Kinase A** in cancer therapy: an update [Sapio et al 2014]:

- PKA is largely known to control cell growth in many cancer types in vitro and in vivo
- Targeting PKA by either site-selective cAMP analogs or antisense approaches has clearly shown antitumor activity in cancer patients.
- However**, discovering further PKA inhibitors** is desirable

The Product:
Current status of development

MDN-0090

Molecular features, physicochemical properties and PK

- **New Family of 6 aromatic compounds** (MW: 354 to 405 Da)
- HBD/HBA: 4/6 ; clogP: 5.54 ± 0.87
- **Chemical stability** at 1 and 2 µM: stable up to 5 hours at pH 1.2, 4.7 and 7.4.
- **Metabolic stability** (microsomes**): $T_{1/2}$ =** 4.98 min
- **Plasma stability** (% of parent compound remaining): 8.9% (5 min), 7.0% (15 min), 5.7% (30 min), 3.9% (60 min), 4.7% (120 min)
- **Plasma Protein binding** (Fraction bound in %): 95.1 ± 2.4 %
- **Metabolomic profiling**: ketone and oxidation metabolites
- **PAMPA (parallel artificial membrane permeability assay):** moderate membrane permeability (Pe= $3.1 \pm 1.4 \times 10^{-6}$ cm s^{-1})
- **Mouse PK** (ip, formulation 20 mg/Kg in PBS): Cmax (initial) (ng/mL)= 1638.63; Cl (clearance) (mL/min*Kg)= 23; AUC (ng*min/mL)= 840208.2; **t1/2 (h) = 11** ; Vd (L/Kg)=12.2.

The Product:
Current status of development

MDN-0090

Liability and ADME: no cardiotoxic, mild CYP inhibition and no reactivity

- **No Cardiotoxicity:** hERG, Nav 1.5 and Cav1.2 IC_{50} > 50 µM
- **CYP inhibition:** CYP3A4 (IC_{50}=13.41 µM); CYP2C9 (IC_{50}=6.14 µM); CYP2D6 (IC_{50} >34.5 mM)
- **Non-mutagenic**: Ames test negative
- **No reactivity observed**: not potential reactive metabolites was found in glutathione-trapped reactive metabolites *in vitro* assay in human liver microsomes by LCMS.

New *in vitro* results in other cancer stem cells: prostatic cancer

MDN-0090 inhibits* primary prostatic cancer stem cells proliferation *in vitro:

PR318 (Gleason 4+5):

ED_{50}= 6.9 µM, androgen sensitive

ED_{50}= 9.7 µM, androgen resistant

PR285 (Gleason 3+4):

ED_{50}= 2.6 µM, androgen sensitive

The Product:
Current status of development

Ongoing studies:

- ✓ **Full synthetic route determination**
- ✓ **Full MoA determination**
- ✓ **Medicinal chemistry**: initial development of analogues based in structure-activity relationship (**SAR**). Family compounds development.

Future development:

- ✓ Complete SAR development. **Hit-to-lead**
- ✓ *in vitro* and *in vivo* lead efficacy
- ✓ **Lead to Candidate optimization:** improvement compound PK/PD; **improvement of administration pattern** (tumor directed-nanoparticles);
- ✓ **Candidate nomination and preclinical regulatory package (IND)**

The Product:
IPR protection

Patent protected: WO2016174226 (PCT/EP2016/059650)

Priority date: 30/04/2015

PCT Regional Patent extension:
US, Europe, Canada, China, Japan and Korea

Family compounds:

Compound	ED_{50} (µM)*
MDN-0089	7.6
MDN-0090	4.7
MDN-0092	9.1
MDN-0093	8.7

* Citotoxicity in BxPC3 (human pancreatic cell line)

Claims:
- ✓ For use in medicine
- ✓ For use in the treatment and/or prophylaxis of cancer

Examples included:
- ✓ Effect on pancreatic and pancreatic CSC cells *in vitro* and *in vivo*
- ✓ Synergistic effect with gemcitabine *in vitro*

The Product:
Pitfalls and Risks to be considered

Strengths

Hit compound

- ✓ ***In vitro*** **and** ***in vivo*** **anti-tumoral effect on pancreatic parental and CSCs**
- ✓ **No cardiotoxicity, non-mutagenic**
- ✓ **Good safety** ***in vivo***

Pitfalls

MedChem Development required:

- ✓ **Full synthetic route determination**
- ✓ **Full MoA determination**
- ✓ **Primary pancreatic cancer studies**
- ✓ **SAR development**
- ✓ **Hit-to-Lead and Lead to Candidate**

Opportunities

Hit compound:

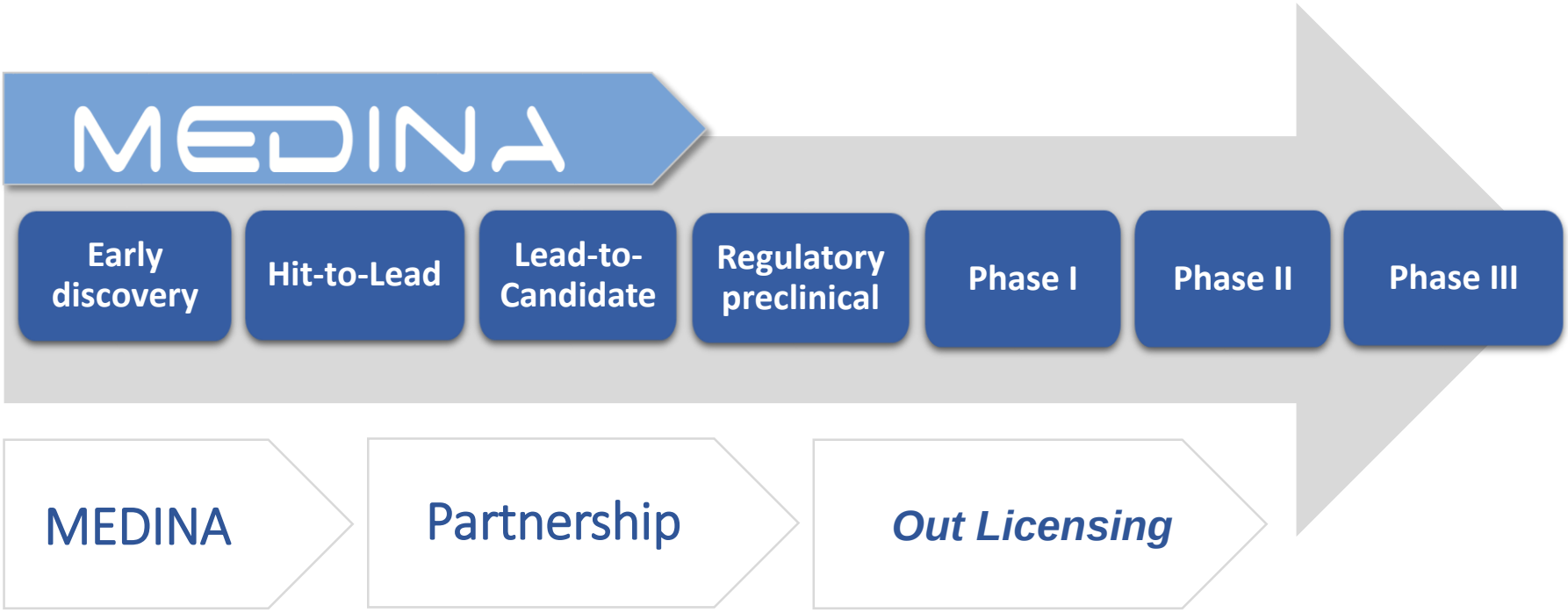
- ✓ **Novel compound, patent filed**
- ✓ **Interesting target and not very exploited**
- ✓ **Family of active compounds**

Risks

Risks of future *Hit-to-Lead development:*

- ✓ **Poor improvement of compound efficacy**
- ✓ **Improved efficacy implies increased toxicity**
- ✓ **Poor bioavailability of lead compound**

Partnering Opportunities



Looking for industrial partners interested in:

- Establishing a collaboration to ensure **Hit-to-lead development and Lead-to-Candidate optimization programs**
- **In-licensing option of a potential future pre-clinical candidate**

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