The CEAMED's STEMINIB Program:

CM-363 & CM-728:
Fused natural quinones for treatment of triple negative breast cancer

CEAMED

Madrid, 17 de noviembre de 2015

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española
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Agenda

1. The Company

2. The Products
   - Target indications
   - innovative mechanism of action
   - Differential features facing the market
   - Current status of development
   - IPR protection
   - Pitfalls & Risks to be considered

3. Partnering opportunities

CEAMED SA

CEAMED SA is a private company founded in 2006 by a group of professors from the universities of Las Palmas de GC and of La Laguna, and the Fundación Instituto Canario de Investigación del Cáncer (FICIC).

Mission:

Identification and development of new drugs to treat oncologic diseases.

CEAMED SA

Location:

Parque Científico y Tecnológico de Tenerife

(PCTT, La Laguna, Tenerife, Canary Islands, Spain)

Facilities:

- Laboratories and office: 240 m2.
- 1 chemistry laboratory
- 1 molecular and cellular biology laboratory
- 1 cell culture room
- Access to support research facilities of the ULL

Founding resources:

- 60.000 € seeding money from founders
- 1,100.000 € from private investors
- 500,000 € loan from the CDTI
- 530.000 € public founding (Canary Gov. and MINECO)

Parque Tecnológico de Tenerife
Avda. La Trinidad s/n
Torre Prof. Agustín Arévalo
CP 38204 La Laguna

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Employees:

- 5 doctors, 1 technician, 1 administrator (Total: 7)
- External help: legal and accounting advisers

Collaborations:

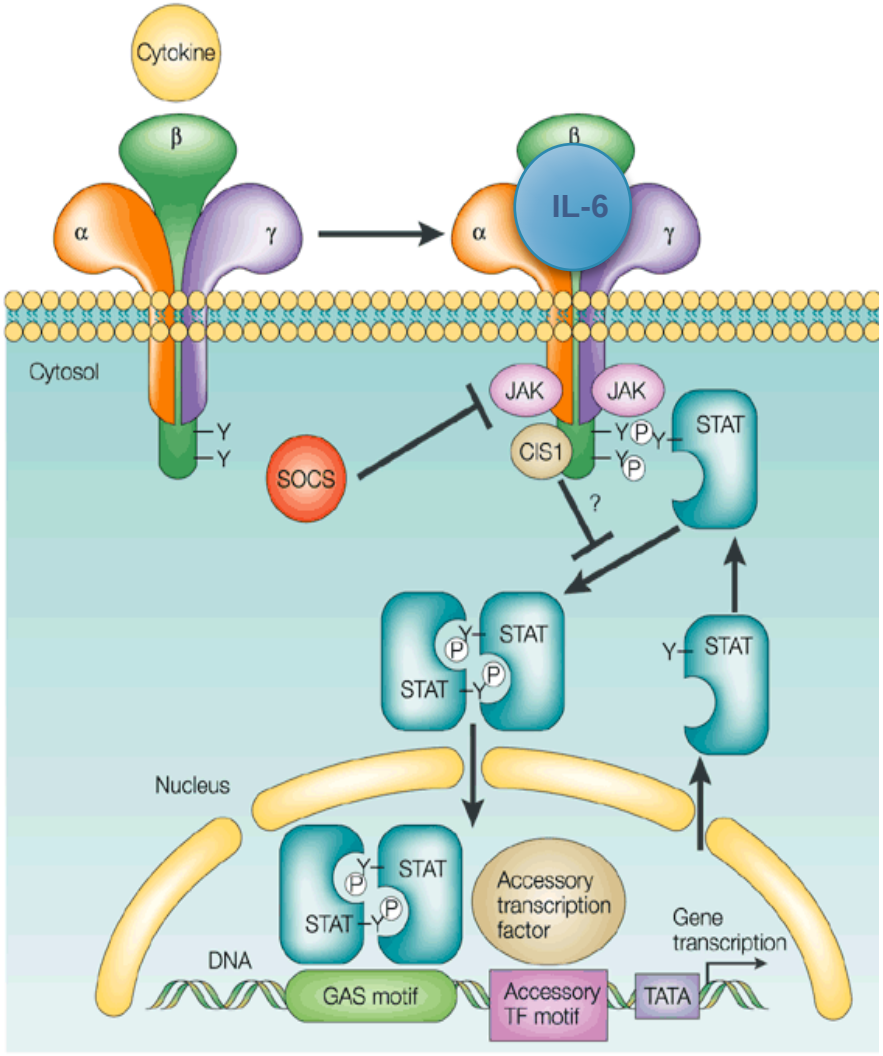
- Las Palmas de GC and La Laguna universities (Spain)
- Cancer Research Center, Salamanca (Spain)
- Erasmus Medical Center (Rotterdam, The Netherlands)
- The National Cancer Institute (USA)
- CRO's: ENVIGO, CEREP

Patents:

- Issued Patents: ES2365231; ES2338193; ES2326355; ES2352491
- Patents pending: EP2690094; WO2014016314

Target: STAT's

Signal Transducers and Activators of Transcription



STATs (1, 2, 3, 4, 5a, 5b, and 6) are:

- gene transcription factors activated by non-receptor tyrosine kinases,
- recruited to membrane receptors by hormones, cytokines and growth factors,
- involved in many physiological functions.

STATs are considered as escape pathways in chemo-resistant cancers:

- STAT5: **Bcr/Abl+ leukemias**.
- STAT3: **Basal-like breast cancer.**

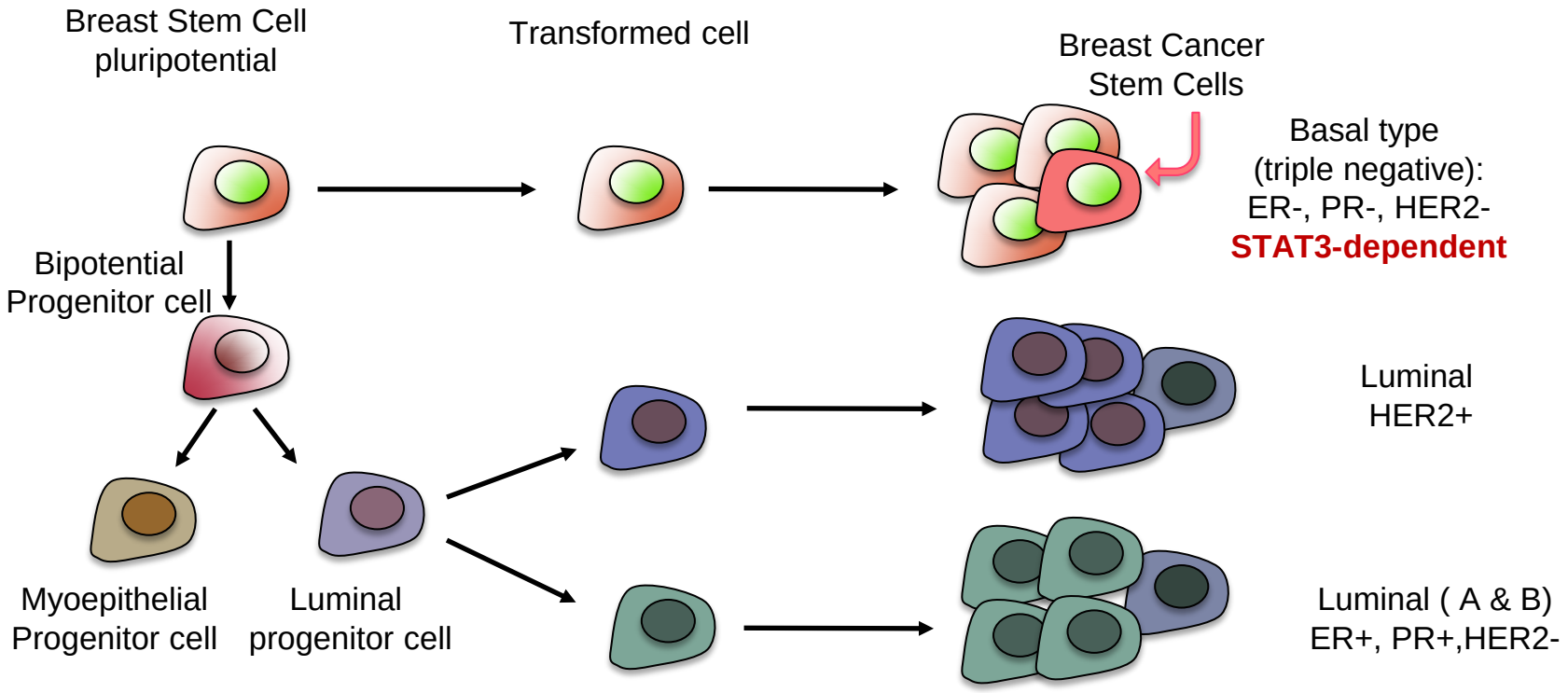
Target:
Triple Negative Breast Cancer

- Triple negative breast cancers (TNBC) are those that do not express ER, PR or hER2 receptors.
  - Approximately 15% of all breast cancers are classified as TNBC.
  - In addition, 10-15% of ER+ and/or HER2+ become resistant to specific treatments and behave as TNBC.
- TNBC are mostly resistant to treatment with standardized therapies used for other breast cancers:
  - A non-specific chemotherapy is their only therapeutic option.
- Woman with TNBC have a higher mortality rate (42.2% vs 28.0% in non-TNBC) due to higher rates of recurrence and metastasis.

No specific therapy for TNBCs has been approved yet.

140.000.000 patients worldwide are waiting for effective drugs

Rationale and Indications:
STAT3 and Triple Negative Breast Cancer



CEAMED's inhibitors are potentially important agents to treat basal type, triple negative forms of breast cancer overexpressing activated STAT3.

Rationale and Indications:
STAT3 and "Stemness" phenotype

- Many TNBC present high levels cancer stem cell cellularity ("stemness") which are inherently more difficult to eradicate, and are the source for further recurrence and metastasis.

- Recent studies have shown that inhibiting STAT3 can reduce the cancer stem cell load, tumorigenic potential and metastasis in these types of breast cancers.

Inhibitors of STAT3 activation are potentially important agents to treat triple negative forms of breast cancer cancers and those with "stemness" phenotype, either in primary or metastatic disease.

The CEAMED'S STEMINIB program

- Activated STAT3 is present in approximately 65% of drug resistant multiple myeloma, pancreatic, prostate, liver and breast cancers.
  - Recent studies indicate that supressing STAT3 signalling reverses resistance to the first-in-file chemotherapies in 9 cancer types.
- **Activated STAT3 and the STAT3-dependent oncogene cMyc are overexpressed in many solid tumors with a STEM PHENOTYPE.**

The CEAMED´s STEMINIB Program:

Aimed at development of inhibitors of STAT3 activation as potentially important agents for the treatment of metastatic, drug resistant cancers and those with stem phenotypes.

CM-363 & CM-728
Lead compounds of fused natural quinones

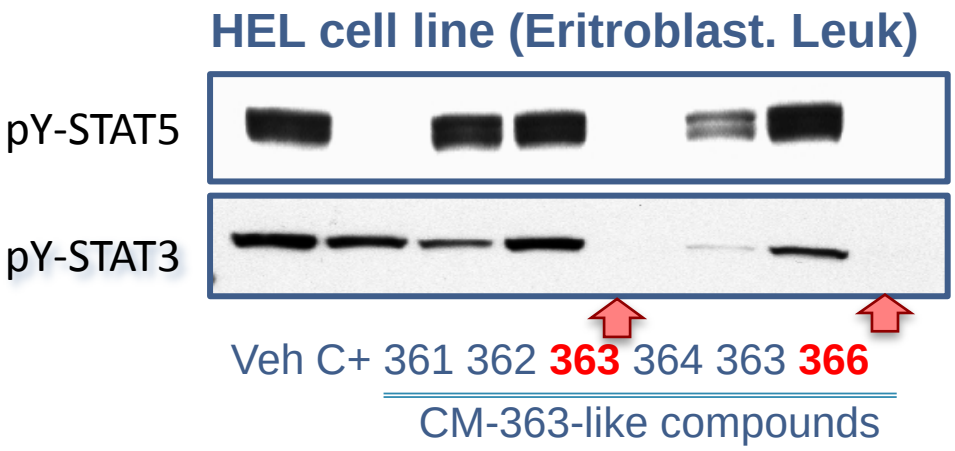
- Natural quinones have been found from algae and filtering animals to superior plants.
- A few “small quinones” (Plumbagin, Shikonin…):
  - possess antitumoral activity
  - are inhibitors of STAT’s activation.
  - display poor pharmacokintetics and toxicity.
- Modified quinones like Doxorubicin are clinically useful agents.

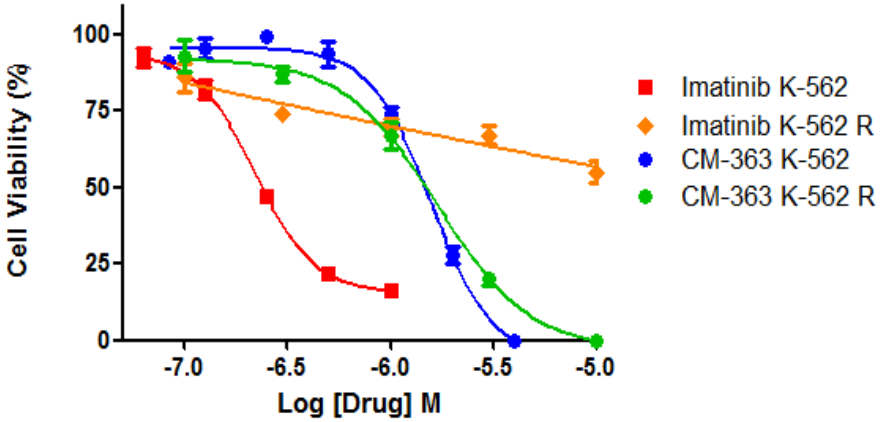
CEAMED presents two new fused quinones:

CM-363, to treat STAT-dependent solid tumors and leukemias.

CM-728, to treat STAT3-depending tumors, including Triple Negative Breast Cancers.

Product: CM-363
A STAT5 and STAT3 inhibitor



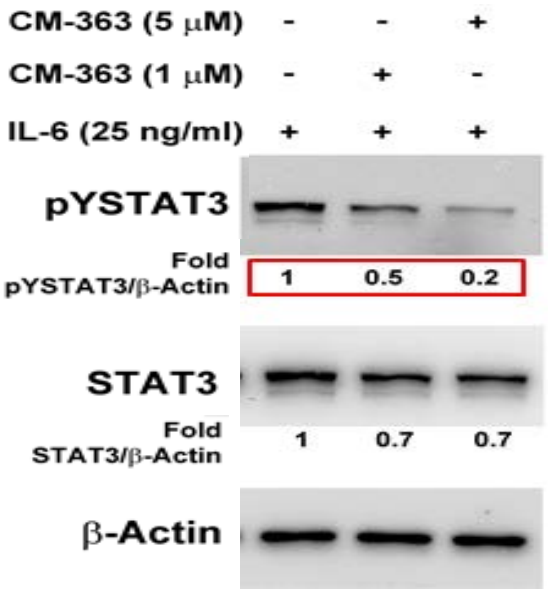


- CM-363-like compounds were initially identified as inhibitors of STAT5-dependent transcription.
- CM-363 inhibits both STAT3 and STAT5 phosphorylation in HEL cells (mutated JAK2, with consitutive activity that keeps active STAT5 and STAT3)
- CM-363 was developed primarily for the treatment Bcr/Abl+ leukemias, with constitutive pY-STAT5.

CM-363 proved to be very active on tyrosine kinase inhibitors (TKI)-resistant forms of CML (K562R)

Product: CM-363
Inhibitor of STAT5 and STAT3 activation

T47D ER+ Breast Cancer cell line



	Lung	Prostate	Pancreas	Colon
	NCI-H1299	DU-145	PANC-1	HT-29
	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
CM-363	1.1	1.6	1.5	5.0
DOXO	nd	>1	1.5	1.3

CM-363 inhibits all tested physiological ways for STAT3 and/or STAT5 activation by cytokines (IL-6, GM-CSF) or hormones (EPO, GH) “in vitro” and “ex vivo”

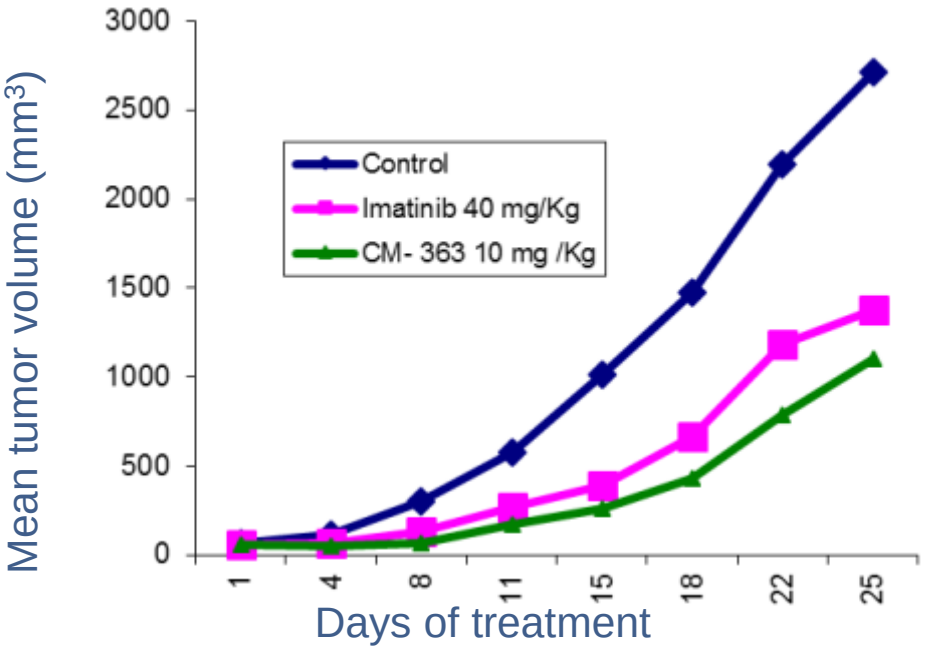
CM-363 in breast cancer cell lines revealed that it could inhibit:

- STAT3 activation (T47D, a BC ER+PR+) induced by the cytokine IL-6.
- Constitutive activation of STAT3 (MDA-MB-231, TNBC)

CM-363 was also found to reduce the cell viability of tumor cell lines from other tissue types that have STAT3 constitutively activated.

Proof of concept
CM-363 inhibits CML xenograft growth

K562 human CML xenografts
In nude mice



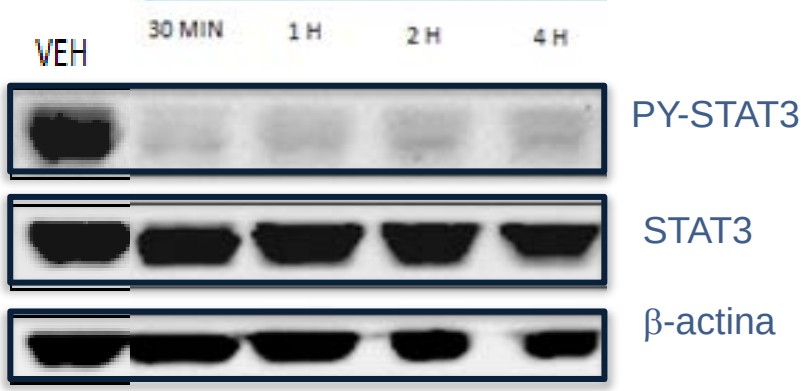
CM-363 was shown to be as effective *in vivo* as Imatinib (the first-in-line treatment for CML) in mice.

CM-363 is orally bioavailable

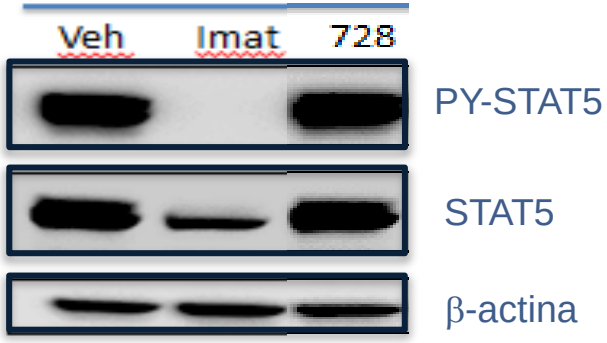
Innovative mechanism of action
CM-728: A STAT3 inhibitor

MDA-MB-231 (TNBC)

CM-728 @ 1μM



K562 (CML)



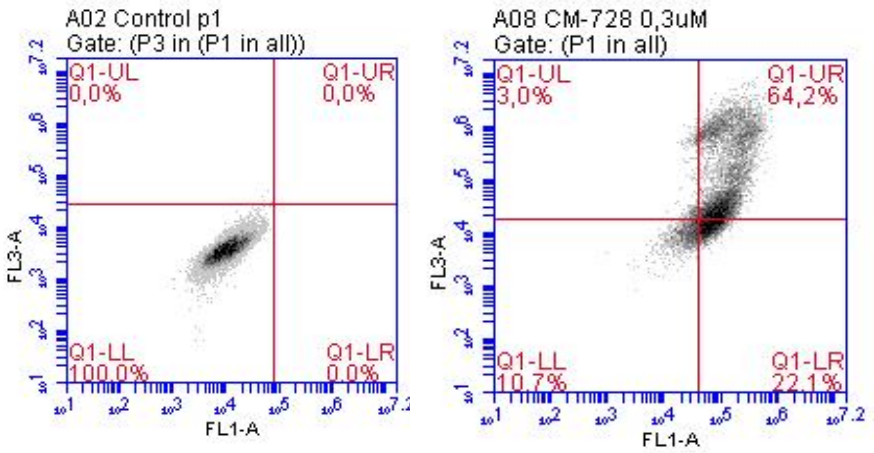
Structural modifications to CM-363 have led to a new lead compound that is more potent and selective.

CM-728 causes:

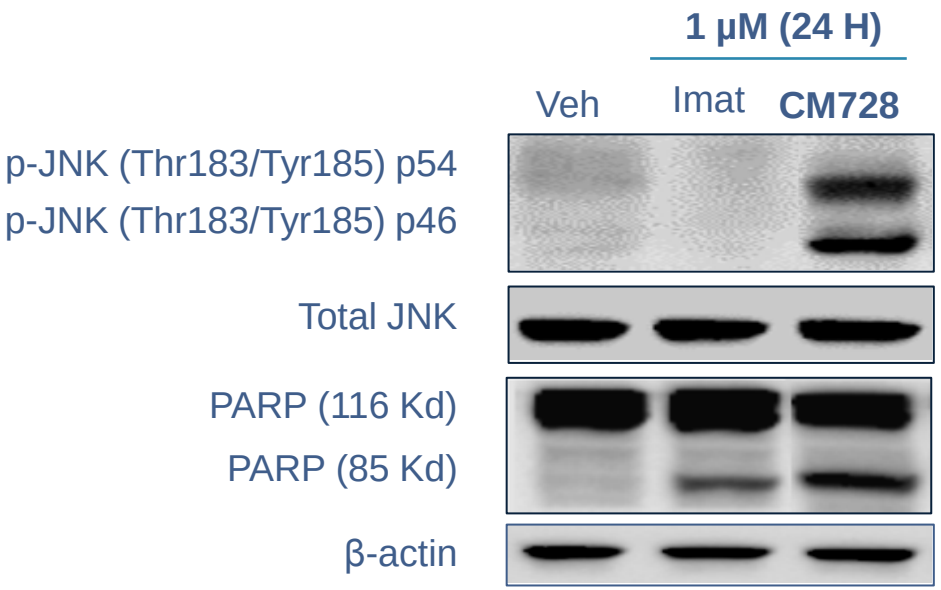
- a rapid, time and concentration dependent, de-activation of PY-STAT3 in the TNBC cell line MDA-MB-231,
- but does not affect PY-STAT5 or STAT5 levels in K562 cells.

Innovative mechanism of action

CM-728 induces JNK and PARP mediated apoptosis



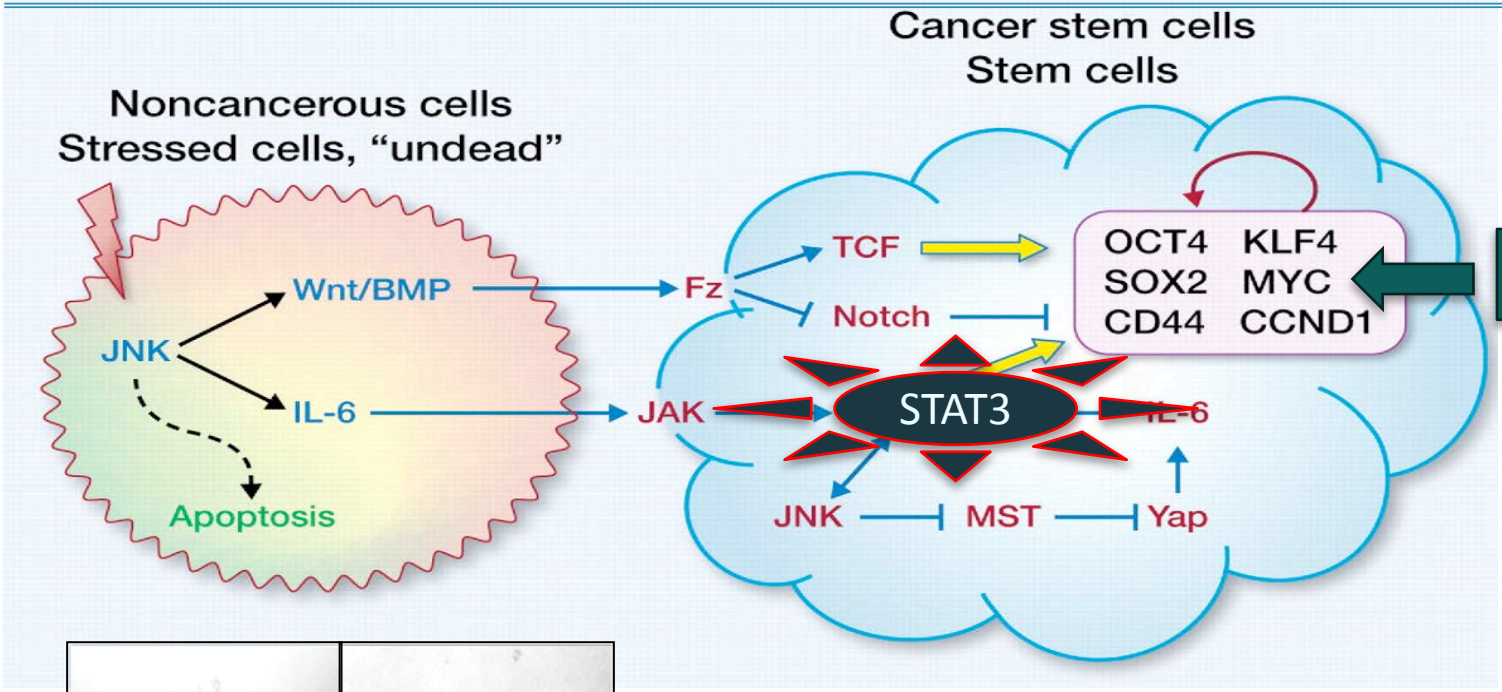
CM-728 at 0,3 µM induces 65% apoptosis in MDA-MB-231 cells after 24 h.

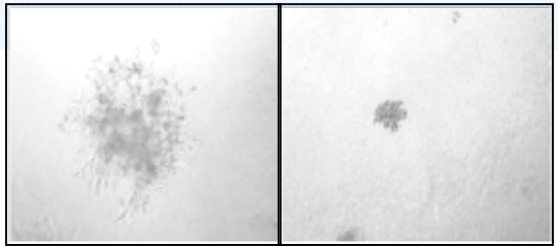


CM-728 at 1 µM induces a potent activation of p-JNK, and PARP-mediated apoptosis after 24h.

Innovative mechanism of action

CM-728 blocks key targets in cancer stem cells



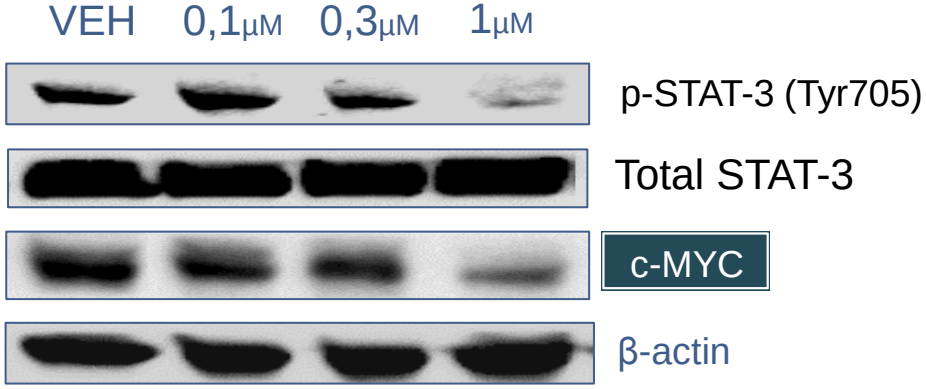


Vehicle CM-728

MICROSPHERE STEMNESS ASSAY

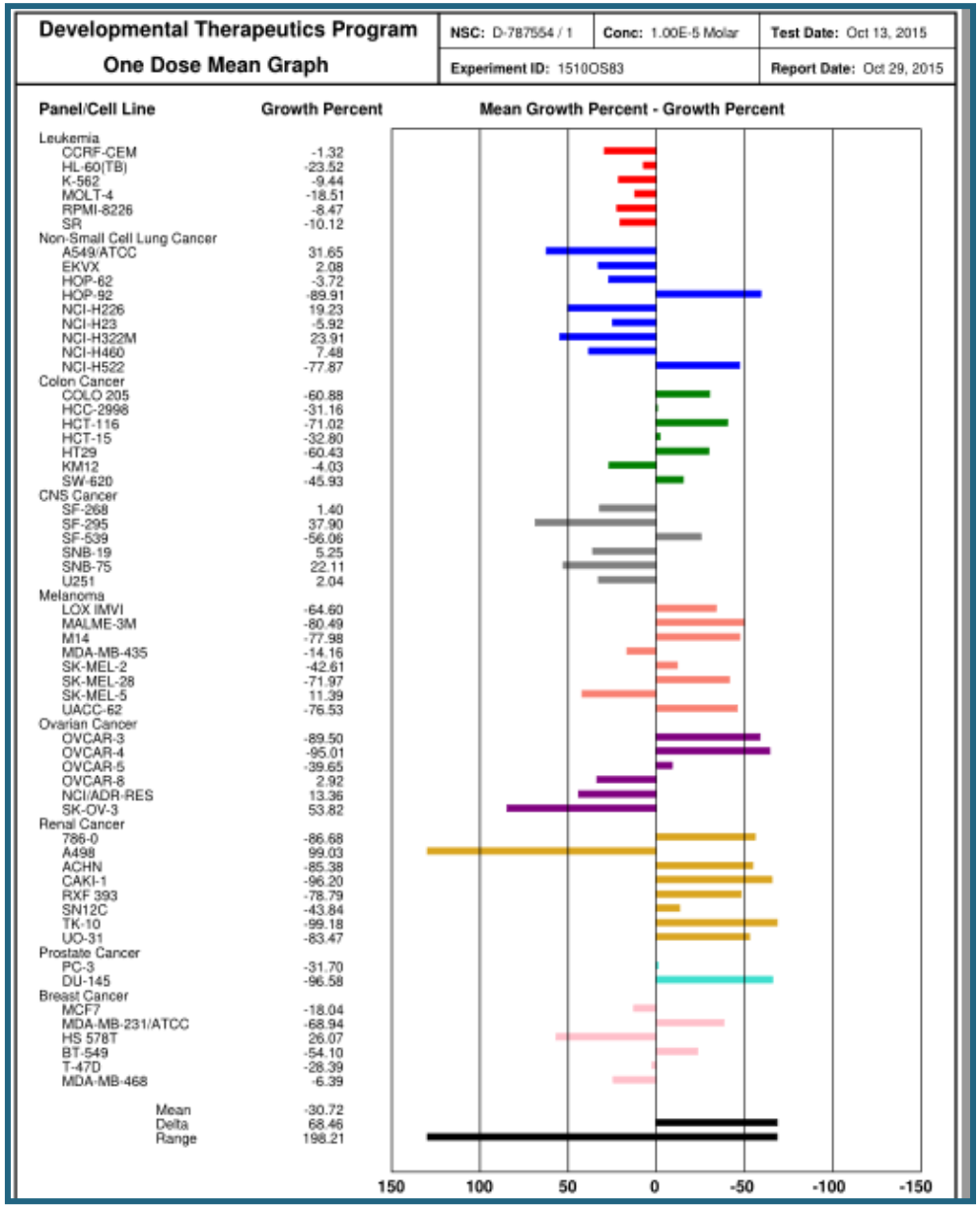
CM-728 at 1 µM inhibits microsphere of MDA-MB-231 cells (85% stem cells)

CM-728 (30 MIN)



Innovative mechanism of action

CM-728: NCI 60 panel



Data from the NCI 60-cell line panel (@10μM) revealed that CM-728

- can differentiate between types of cancers;
- can differentiate between cell lines from the same type of cancer.

Studies aimed at finding a correlation between cell line response to CM728 and the presence of activated STAT3 are in progress.

Innovative mechanism of action

CM-728: In house cell line panel

Cell line	Tissue	CM-728 IC_{50} (MTT, 48h)
HT-29	Colon	2.4 μM
NCI-H1229	Lung	0.6 μM
DU-145	Prostate	0.7 μM
PANC-1	Pancreas	0.4 μM

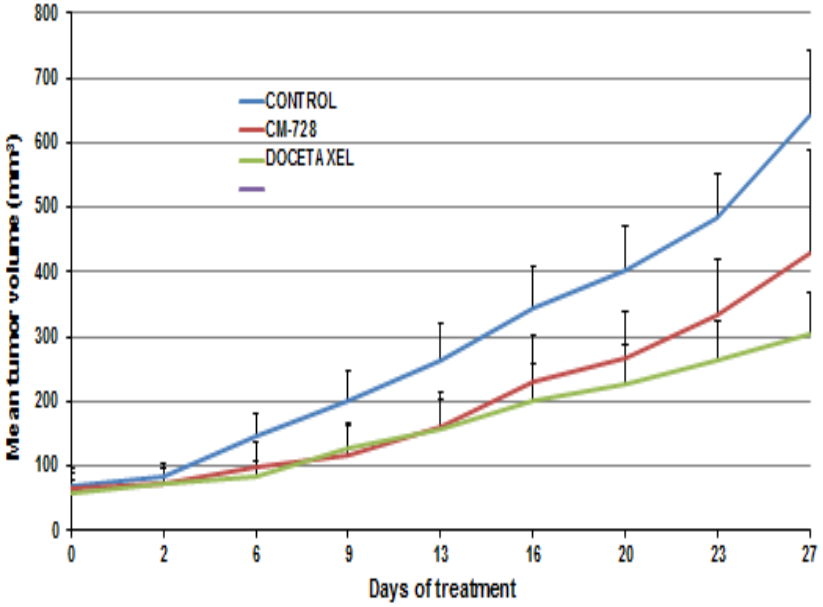
Breast cancer Cell line	Sub-type	CM-728 IC_{50} (MTT, 48h)
SK-BR-3	$HER2^+$	0.7 μM
MCF7	ER^+	1.6 μM
MDA-MB-231	TNBC	0.3 μM
MDA-MB-468	TNBC	1.7 μM

Chronic myeloid leukemia	Imatinib	CM-728 IC_{50} (MTT, 48h)
K562	Sensitive	0.05 μM
K562R	Resistant	0.06 μM

In-house screening showed that CM-728 possesses:

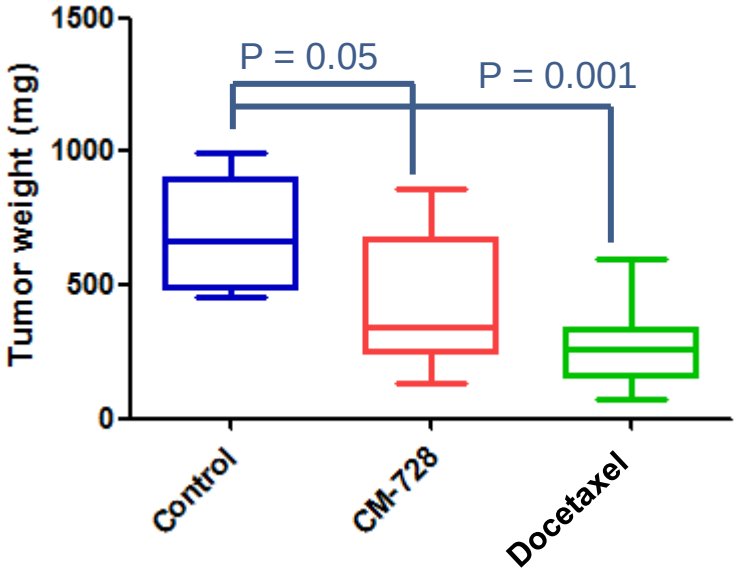
- sub-micromolar IC_{50} values in several tumor cell lines,
- an interesting profile against a panel of breast cancer sub-types.
- Nanomolar activity on Imatinib resistant chronic myeloid leukemia cell line.

Proof of concept
CM-728 inhibits TNBC xenograft tumor growth



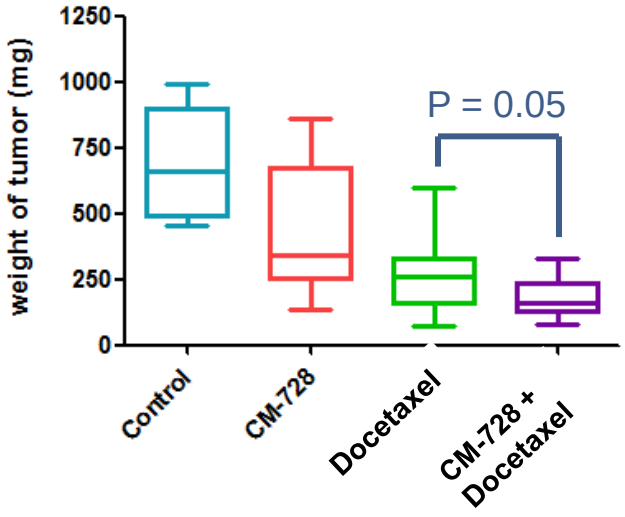
Oral administration of a suspension of CM-728 (5-10mg/kg) produced a statistically significant reduction in the growth of orthotopic tumors, induced by a very aggresive subclone of MDA-MB-231 cells (85% stem cellularity).

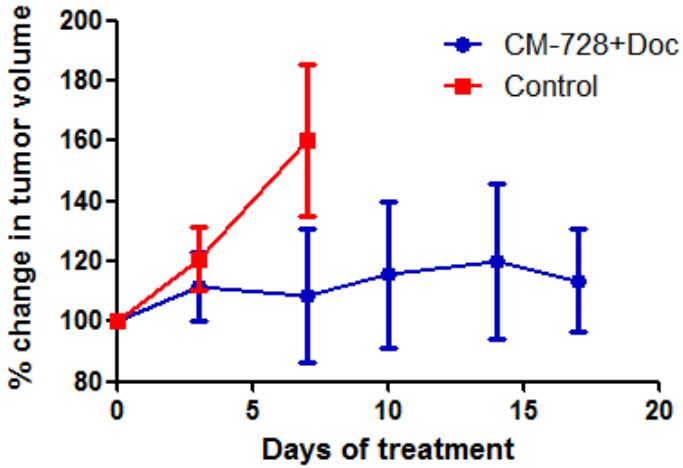
CM-728 as a single agent



The mean of tumor weigth reduction with CM-728 was not significantly different to that produced by the gold standard docetaxel (10 mg/kg, IP).

Proof of concept
CM-728 + Docetaxel inhibts TNBC xenograft tumor growth





CM-728 + Docetaxel
as a combined therapy

Administration of a combination of oral CM-728 and Docetaxcel (IP) to recently induced tumors (60-70 mm^3) with the subclone of MDA-MB-231 was more effective than either treatment alone.

The combined treatment of CM-728 + Docetaxel was also able to inhibit the growth of large, established (350-450 mm^3) tumors.

Differential features facing the market
CM-728 *vs.* common first-in-line TNBC treatments

	MDA-MB-231 (SRB)		
Test agent	**GI_{50}**	**TGI**	**LC_{50}**
CM-728	**0.1**	**0.3**	**0.8**
Doxorubicin	**0.1**	**2.2**	**>10**
Docetaxcel	**0.001**	**>10**	**>10**

Values are in micromolar (μM)

Significantly, CM-728 can reduce and block cell growth at nanomolar concentrations (GI_{50} = 100nM; TGI = 300nM).

- Doxorubicin requires micromolar concentrations to block cell growth (TGI),
- Docetaxel is incapable of blocking cell growth even at 10 micromolar.

CM-728 is an order of magnitude more potent against a TNBC cell line than a surrogate “normal” cell line (MRC-5).

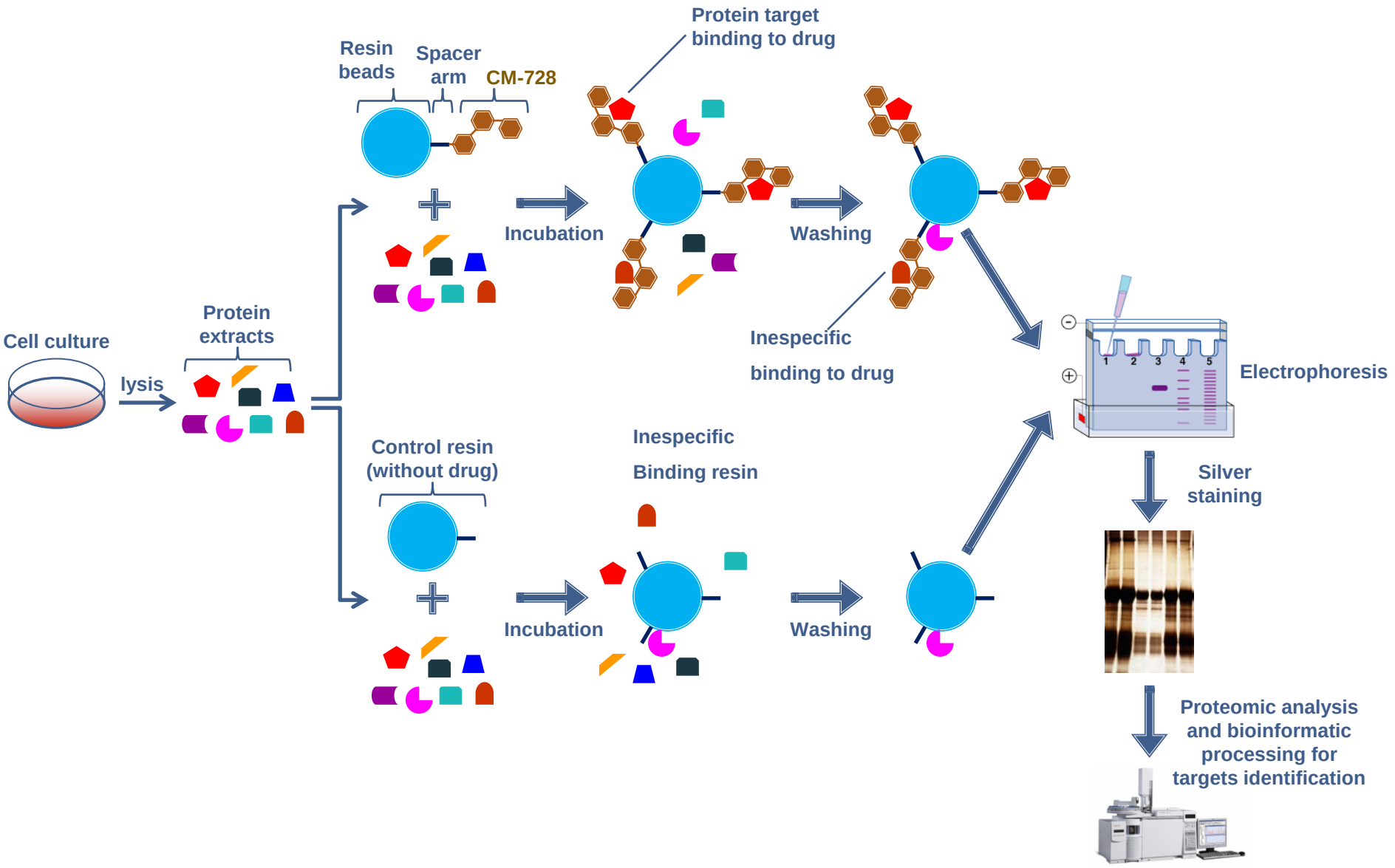
- Docetaxel and Doxorubicin have poor selectivity indices (tumor cells vs non-tumor cells)

Current status development
CM-363 & CM-728

- Current investigations are focused on the pre-clinical ADME, PK and toxicology studies required for an IND filling.

- Manufacturing of the current lead compounds is not envisioned to be a problem. The synthesis uses a three step, convergent sequence, using four commercially available, inexpensive reagents.

Looking for biomarkers: CM-728 target identification by proteomics



Intellectual protection status
CM-363 & CM-728

- CM-363 is described in the following published patent applications:

Application type	Publication #	Publication Date	Priority Date
European	EP2690094	29.01.2014	24.07.2012
World/PCT	WO2014016314	30.01.2014	24.07.2012

- CM-728 is described in an application currently waiting to be filed.

Competitors and Risk Assesment
CM-363 & CM-728

- No specific inhibitors of STAT3 are currently in the market.
- There are several patent applications from small companies and universities that describe small molecules, peptidomimetics or anti-sense oligonucleotides as potential STAT3 inhibitors.

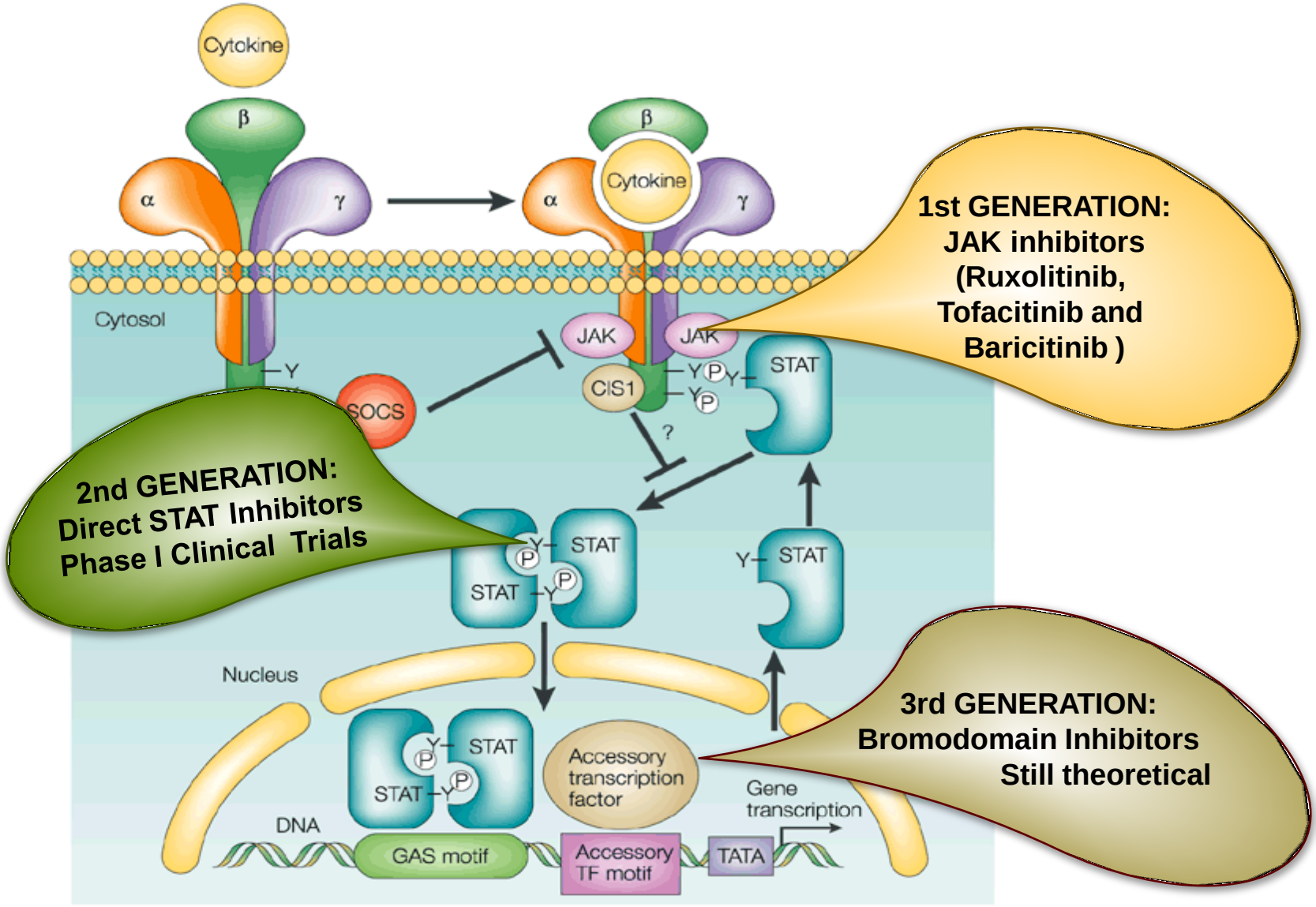
CURRENT STATUS OF STAT3 INHIBITORS IN CLINICAL TRIALS

Clinical trials.gov ID	Sponsor	Agent	Study	Cancer type
NCT01563302	Isis Pharmaceuticals	ISIS 481464 (Antisense Oligonucleotide)	Phase I/II	DLBCL or other advanced lymphomas
NCT02417753	National Cancer Institute (NCI)	AZD9150 (ISIS 481464) (Antisense Oligonucleotide)	Phase I/Ib	Advanced/Metastatic Hepatocellular Carcinoma
NCT01423903	Otsuka Pharmaceutical	OPB-51602	Phase I	Advanced Cancer
NCT01066663	Dana-Farber Cancer Institute	Pyrimethamine	Phase I/II	Treatment of Relapsed CLL/SLL

Risk assessment
CM-363 & CM-728

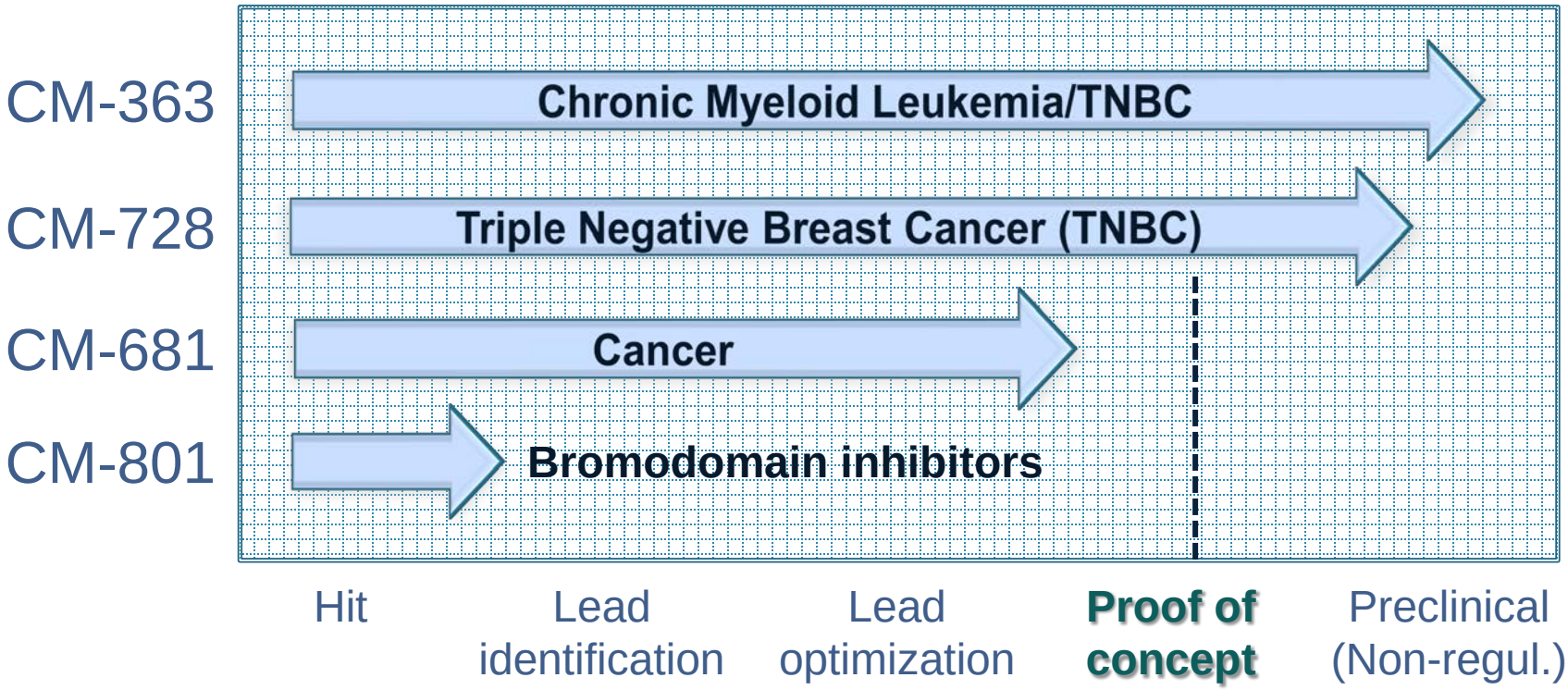
- There is compelling evidence, both *in vitro* and *in vivo*, that inhibiting the activation of STAT3 is a validated oncology target for tumors of different tissues, in particular those displaying a stem cell phenotype.
- To date three inhibitors (ruxolitinib, tofacitinib and baricitinib), of ONE OUT OF AT LEAST SIX upstream activators of STAT3 (JAK2), have been approved by the FDA, indicating that an in-direct inhibition of STAT3 activation appears to be well tolerated.
- CM-728 is a small molecule with a novel structure, and as such will have a unique pharmacological/toxicological profile, which is as yet undefined in humans.
- However, in initial acute toxicity studies in mice, CM-728 was well tolerated when administered as an oral suspension (>100 mg/Kg single dose and >20 mg/Kg for 8 days; 5-10 mg/Kg 45 days).

Partnering oportunities
STATs as clinical targets



Partnering oportunities

CEAMED's STEMINIB Program Pipeline



CM-363 & CM-728:

Ready to start the regulatory preclinical phase in 2016.

Partnering oportunities

CEAMED is open to an agreement with a pharmaceutical company in order to advance our lead compounds of the STEMINIB Program through preclinical regulatory development and beyond.

CEAMED prefers a long term association,

but will also consider signing a joint venture agreement.

CEAMED