EC-8042 - first in class agent for pediatric and adult tumors with transcriptional deregulation

Madrid, 29 de Octubre de 2018

1. The Institution: EntreChem at a glance

Spanish biotech focused on optimizing natural anticancer products by improving efficacy and reducing toxicity.

EntreChem applies bacterial genetic engineering to open up new, otherwise unexplored, chemical space.

Founded in 2006, raised >9M EUR public and private funding.

Two oncology candidates about to enter the clinic:

EC-8042, first in class transcription reprogramming agent for tumors with altered transcription.

EC-70124, first in class triple Flt3-Pim-Syk inhibitor for AML with superior metabolic and PPB profile.

We have both an in-house R&D team and an international panel of academic oncology research advisors, same examples:

Francisco Morís, Ph.D.
Managing Director & Co-founder

Jesús Cortés, Ph.D.
Genetic Engineering, Microbiology

Paula Costales, Ph.D.
Cell Biology, Pharmacology

Alberto Ocaña, M.D., Ph.D.
Hospital Clínico San Carlos, Spain

Carlo Catapano, M.D., Ph.D.
Institute of Oncology Research, Bellinzona, Switzerland

Patrick Grohar, M.D., Ph.D.
CHOP, Philadelphia, USA

KOL: Chair of Ewing Biology and VICE-chair for bone tumors in the COG

Atanasio Pandiella, M.D., Ph.D.
Centro de Investigación del Cancer, Salamanca, Spain

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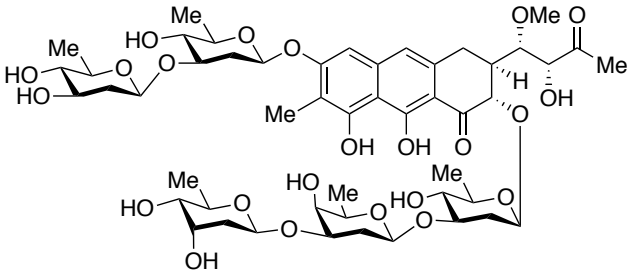
1. The Institution: Pipeline

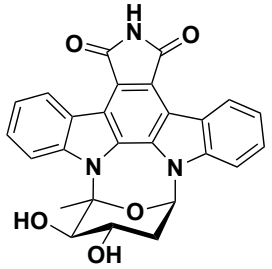
- Currently developing two lead compounds with **highly favorable preclinical data** :

- **EC-8042**, novel in class transcription reprogramming agent for tumors with genomic instability.



EC-8042

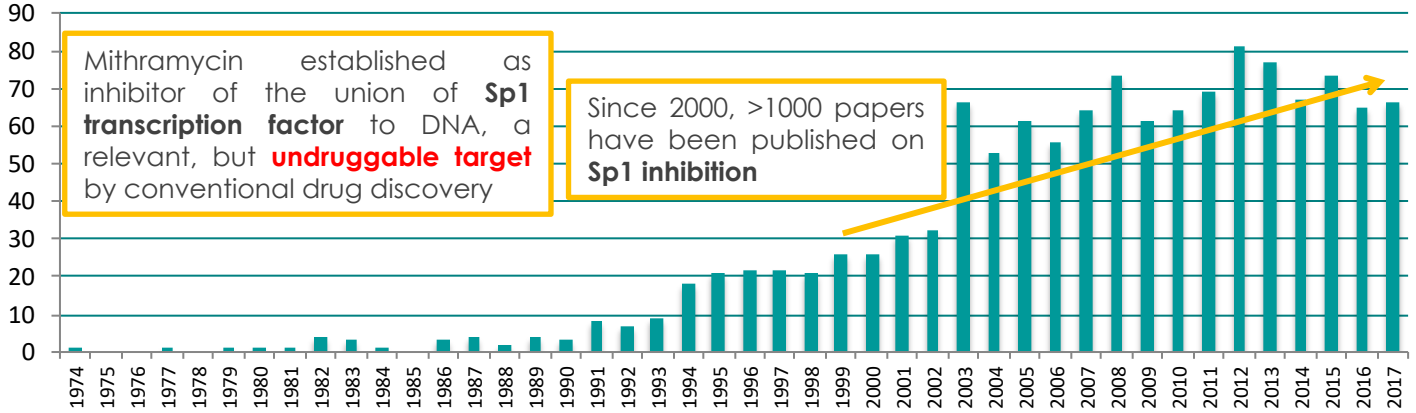
- **EC-70124**, next-generation Midostaurin for AML with superior metabolic and PPB profile.



EC-70124

Mithramycin & Sp1 inhibition are subjects of intense research

Sp1 inhibition PubMed papers / year



Mithramycin established as inhibitor of the union of **Sp1 transcription factor** to DNA, a relevant, but **undruggable target** by conventional drug discovery

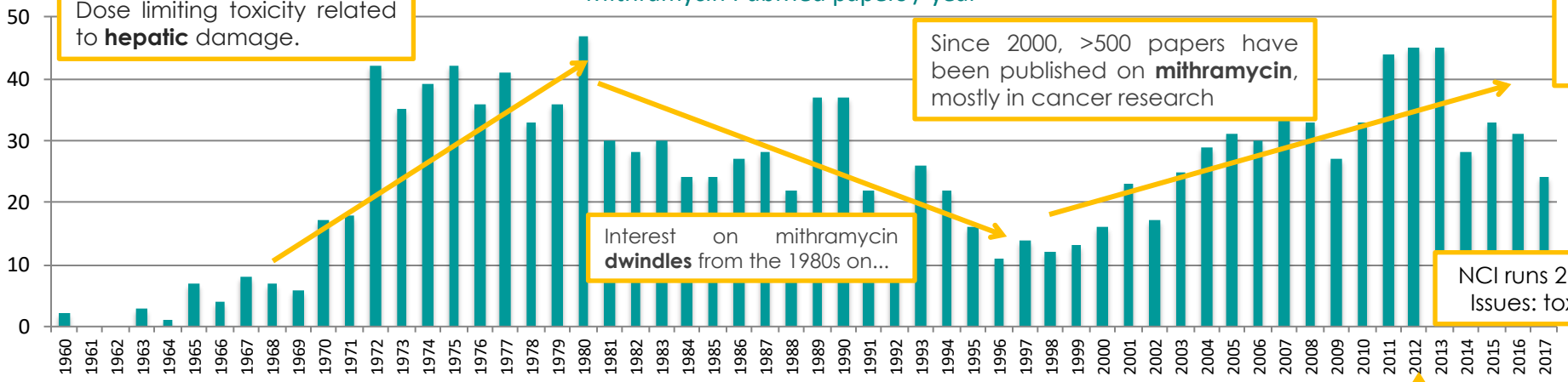
Since 2000, >1000 papers have been published on **Sp1 inhibition**

More recently, transcription of **other modulated targets** also modulated by MTM:

- Fusion genes: **EWS-FLI1** (Ewing sarcoma)
- Transporters: **ABCG2** (NSCLC)
- CSC genes: **SOX2** (medulloblastoma, sarcoma)
- Epigenetics: **HDAC**, **DNMT**, **H3K9Me3**

Mithramycin FDA approved in 1970 for cancer.
Dose limiting toxicity related to **hepatic** damage.

Mithramycin PubMed papers / year



Since 2000, >500 papers have been published on **mithramycin**, mostly in cancer research

Interest on mithramycin **dwindles** from the 1980s on...

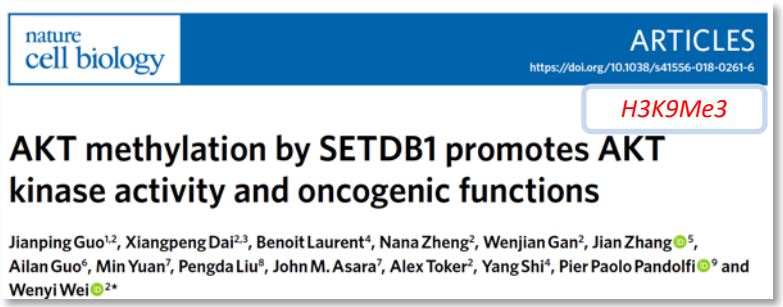
EC-8042, a mithralog with an **improved efficacy/safety ratio**

NCI runs 2 clinical trials in EWS and NSCLC
Issues: toxicity, **insufficient plasma** levels

2. The Product a) target indications

Mithramycin traslational efforts by top tier academia

Highlighted recent papers describing effect on relevant targets, including in vivo proof of concept


nature cell biology

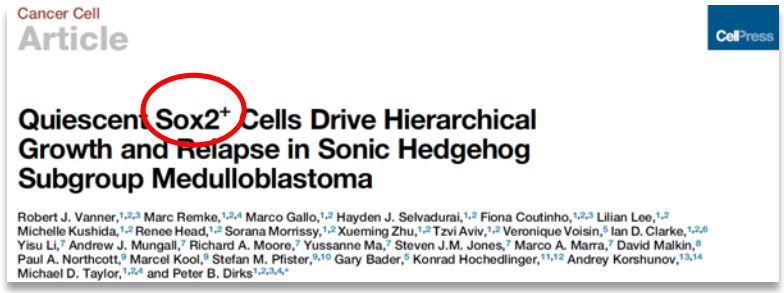
ARTICLES

https://doi.org/10.1038/s41556-018-0261-6

H3K9Me3

AKT methylation by SETDB1 promotes AKT kinase activity and oncogenic functions

Jianping Guo[1,2], Xiangpeng Dai[2,3], Benoit Laurent[4], Nana Zheng[2], Wenjian Gan[2], Jian Zhang[5], Ailan Guo[6], Min Yuan[7], Pengda Liu[8], John M. Asara[7], Alex Toker[2], Yang Shi[4], Pier Paolo Pandolfi[9] and Wenyi Wei[2]*

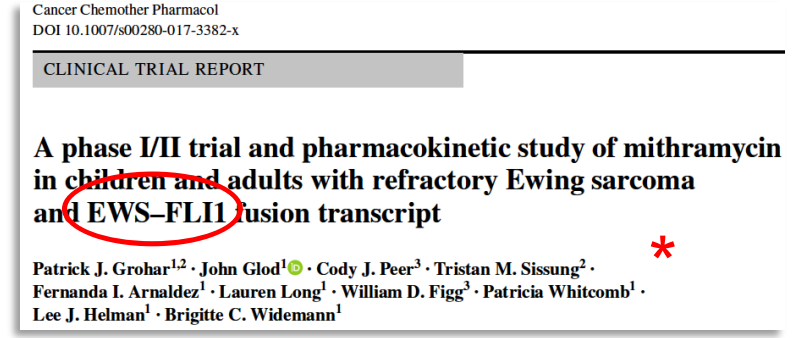

Cancer Cell

Article

CellPress

Quiescent Sox2+ Cells Drive Hierarchical Growth and Relapse in Sonic Hedgehog Subgroup Medulloblastoma

Robert J. Vanner[1,2,3] Marc Remke[1,2,4] Marco Gallo[1,2] Hayden J. Selvadurai[1,2] Fiona Coutinho[1,2,3] Lilian Lee[1,2] Michelle Kushida[1,2] Renee Head[1,2] Sorana Morrissy[1,2] Xueming Zhu[1,2] Tzvi Aviv[1,2] Veronique Voisin[5] Ian D. Clarke[1,2,6] Yisu Li[7] Andrew J. Mungall[7] Richard A. Moore[7] Yussanne Ma[7] Steven J.M. Jones[7] Marco A. Marra[7] David Malkin[8] Paul A. Northcott[9] Marcel Kool[9] Stefan M. Pfister[9,10] Gary Bader[5] Konrad Hochedlinger[11,12] Andrey Korshunov[13,14] Michael D. Taylor[1,2,4] and Peter B. Dirks[1,2,3,4,*]


Cancer Chemother Pharmacol

DOI 10.1007/s00280-017-3382-x

CLINICAL TRIAL REPORT

A phase I/II trial and pharmacokinetic study of mithramycin in children and adults with refractory Ewing sarcoma and EWS–FLI1 fusion transcript

*

Patrick J. Grohar[1,2] · John Glod[1] · Cody J. Peer[3] · Tristan M. Sissung[2] · Fernanda I. Arnaldez[1] · Lauren Long[1] · William D. Figg[3] · Patricia Whitcomb[1] · Lee J. Helman[1] · Brigitte C. Widemann[1]


Cell Reports

Article

SOX2

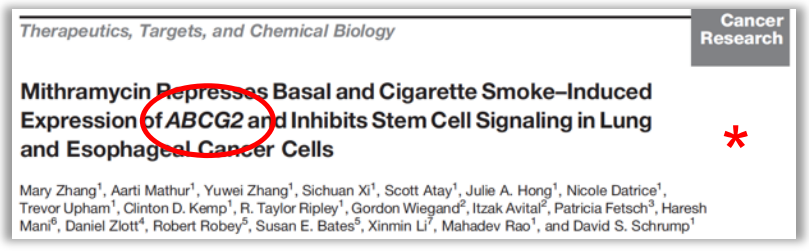
OPEN ACCESS

CellPress

Oncogenes Activate an Autonomous Transcriptional Regulatory Circuit That Drives Glioblastoma

*

Dinesh K. Singh,[1,2,3,12,13] Rahul K. Kollipara,[3,12] Vamsidara Vemireddy,[1,2] Xiao-Li Yang,[1,2] Yuxiao Sun,[1,2] Nanda Regmi,[1,2] Stefan Klingler,[4] Kimmo J. Hatanpaa,[2,5] Jack Raisanen,[2,5] Steve K. Cho,[1,2] Shyam Sirasanagandla,[2,6] Suraj Nannepaga,[1,2] Sara Piccirillo,[1] Tomoyuki Mashimo,[2,6] Shan Wang,[3] Caroline G. Humphries,[3] Bruce Mickey,[2,7] Elizabeth A. Maher,[1,2,6,8] Hongwu Zheng,[4] Ryung S. Kim,[9] Ralf Kittler,[3,8,10,11,14,*] and Robert M. Bachoo[1,2,8,8,*]

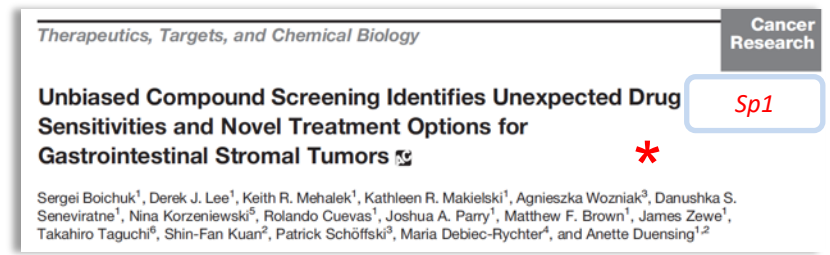

Therapeutics, Targets, and Chemical Biology

Cancer Research

Mithramycin Represses Basal and Cigarette Smoke–Induced Expression of *ABCG2* and Inhibits Stem Cell Signaling in Lung and Esophageal Cancer Cells

*

Mary Zhang[1], Aarti Mathur[1], Yuwei Zhang[1], Sichuan Xi[1], Scott Atay[1], Julie A. Hong[1], Nicole Datrice[1], Trevor Upham[1], Clinton D. Kemp[1], R. Taylor Ripley[1], Gordon Wiegand[2], Itzak Avital[2], Patricia Fetsch[3], Haresh Mani[6], Daniel Zlott[4], Robert Robey[5], Susan E. Bates[5], Xinmin Li[7], Mahadev Rao[1], and David S. Schrump[1]


Therapeutics, Targets, and Chemical Biology

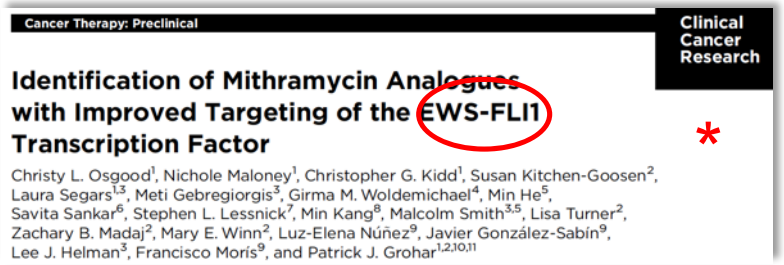
Cancer Research

Unbiased Compound Screening Identifies Unexpected Drug Sensitivities and Novel Treatment Options for Gastrointestinal Stromal Tumors

Sp1

*

Sergei Boichuk[1], Derek J. Lee[1], Keith R. Mehalek[1], Kathleen R. Makielski[1], Agnieszka Wozniak[3], Danushka S. Seneviratne[1], Nina Korzeniewski[5], Rolando Cuevas[1], Joshua A. Parry[1], Matthew F. Brown[1], James Zewe[1], Takahiro Taguchi[6], Shin-Fan Kuan[2], Patrick Schöffski[3], Maria Debiec-Rychter[4], and Anette Duensing[1,2]

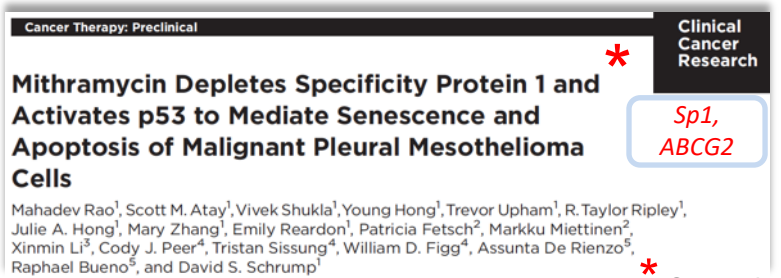

Cancer Therapy: Preclinical

Clinical Cancer Research

Identification of Mithramycin Analogues with Improved Targeting of the EWS-FLI1 Transcription Factor

*

Christy L. Osgood[1], Nichole Maloney[1], Christopher G. Kidd[1], Susan Kitchen-Goosen[2], Laura Segars[1,3], Meti Gebregiorgis[3], Girma M. Woldemichael[4], Min He[5], Savita Sankar[6], Stephen L. Lessnick[7], Min Kang[8], Malcolm Smith[3,5], Lisa Turner[2], Zachary B. Madaj[2], Mary E. Winn[2], Luz-Elena Núñez[9], Javier González-Sabín[9], Lee J. Helman[3], Francisco Morís[9], and Patrick J. Grohar[1,2,10,11]


Cancer Therapy: Preclinical

Clinical Cancer Research

Mithramycin Depletes Specificity Protein 1 and Activates p53 to Mediate Senescence and Apoptosis of Malignant Pleural Mesothelioma Cells

*

Sp1, ABCG2

Mahadev Rao[1], Scott M. Atay[1], Vivek Shukla[1], Young Hong[1], Trevor Upham[1], R. Taylor Ripley[1], Julie A. Hong[1], Mary Zhang[1], Emily Reardon[1], Patricia Fetsch[2], Markku Miettinen[2], Xinmin Li[3], Cody J. Peer[4], Tristan Sissung[4], William D. Figg[4], Assunta De Rienzo[5], Raphael Bueno[5], and David S. Schrump[1]

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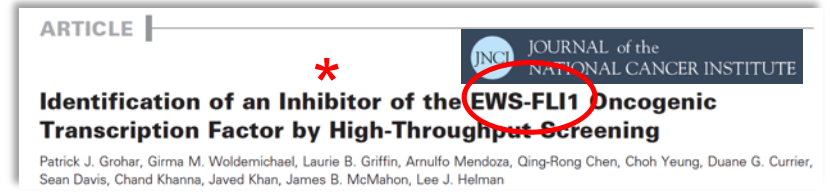
ARTICLE

JNCI JOURNAL of the NATIONAL CANCER INSTITUTE

*

Identification of an Inhibitor of the EWS-FLI1 Oncogenic Transcription Factor by High-Throughput Screening

Patrick J. Grohar, Girma M. Woldemichael, Laurie B. Griffin, Arnulfo Mendoza, Qing-Rong Chen, Choh Yeung, Duane G. Currier, Sean Davis, Chand Khanna, Javed Khan, James B. McMahon, Lee J. Helman

Currently collaborating with EntreChem for development of mithralog EC-8042

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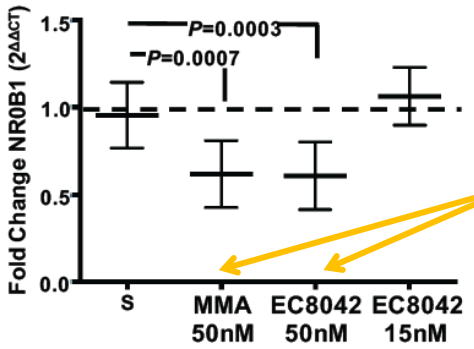
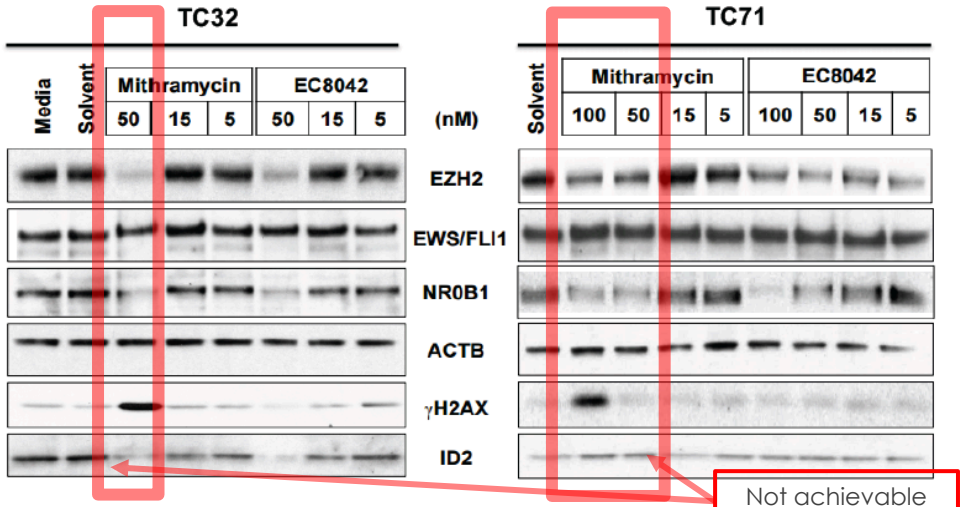
EC-8042 hits EWS-FLI1 targets in Ewing sarcoma

Mithramycin inhibits downstream targets of EWS-FLI1 *J. Natl. Cancer Inst.* **2011**, 103,962-78

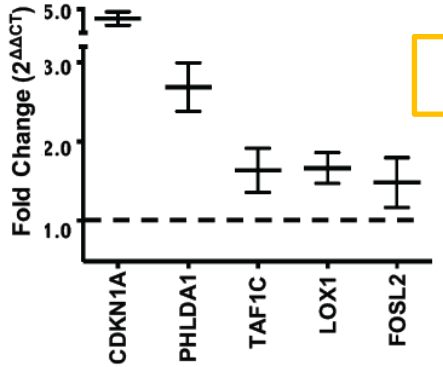
EC-8042 also hits EWS-FLI1-induced and –repressed targets at gene ***AND*** protein level at same concentration as MTM (50nM for 3h)



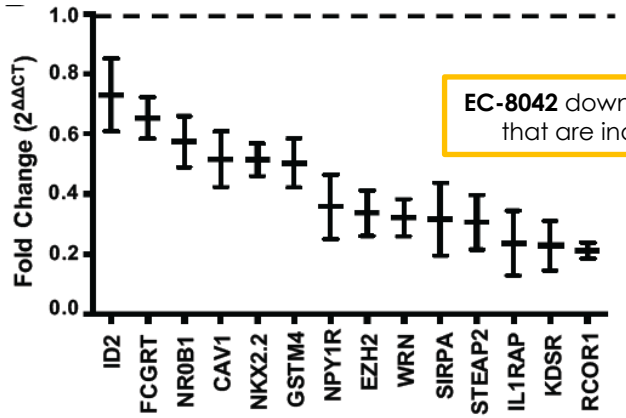
Same response at concentrations achievable *in vivo* for **EC-8042** , not for MTM



Not achievable in vivo for MTM



EC-8042 upregulates genes that are repressed in EWS



EC-8042 downregulates genes that are induced in EWS

Osgood et at. *Clinical Cancer Res.* **2016**, 22(16):4105-18

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2. The Product b) Innovative mechanisms of action

EC-8042 is efficacious in vivo and superior to MTM in EWS

experimental set up

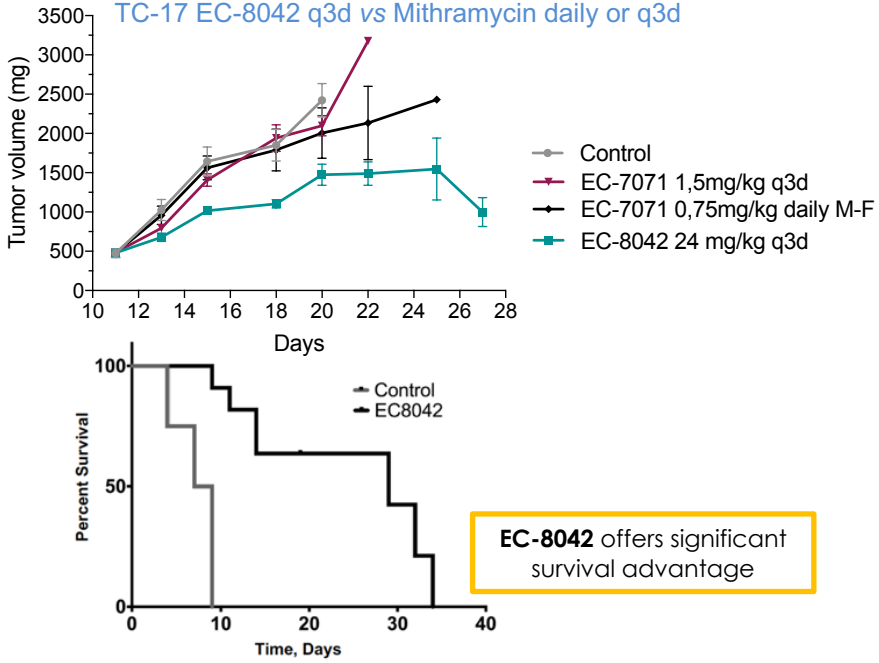
Orthotopic TC-71 line in nude mice, dosing starts at 500mm^3: **very aggressive** setting

Drugs administered **i.v. bolus** at the respective MTDs.

MTM i.v. shows **no effect**

EC-8042 responds better, with best prolonged survival

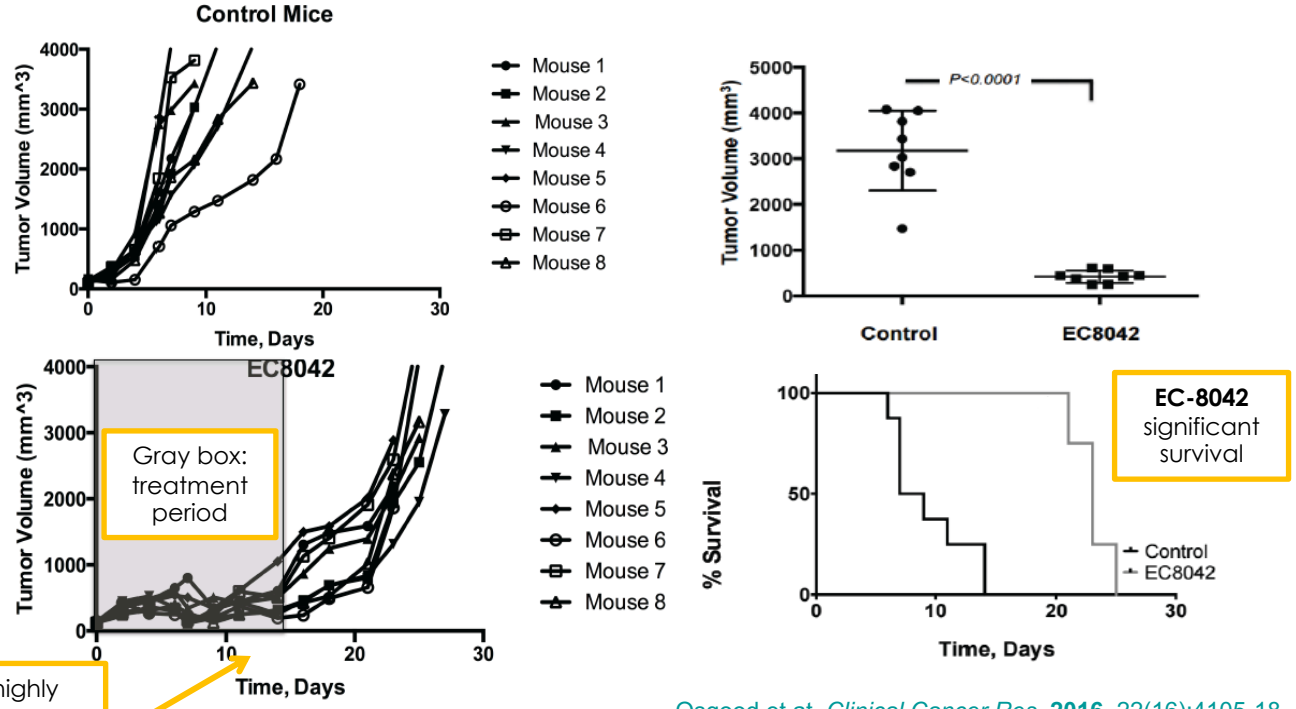
Daily dosing is not superior to **spaced, q3d dosing**



EC-8042 offers significant survival advantage

Tested i.p. M-F-W schedule at 24mg/kg (**10% of i.p. MTD**)

Spaghetti plots for individual mouse response: **better tumor volume response** by day 11



EC-8042 highly efficacious during treatment window

Osgood et at. *Clinical Cancer Res.* **2016**, 22(16):4105-18

Ewing sarcoma (EWS), mostly a pediatric tumor

Ewing sarcoma epidemiology, treatment and survival

Epidemiology

2nd most common **childhood** bone tumor

Annual incidence in the US around 250 cases (25% **metastatic**)

Most commonly in **teenagers**

Treatment

Five drug, aggressive chemotherapy, surgery and/or radiation

Chemo: cyclophosphamide, doxorubicin, etoposide, ifosfamide, and/or vincristine ...

...plus dactinomycin (if metastatic)

Survival

55% overall survival

25% for metastatic disease

<20% for relapsed disease

Need for new targeted therapies

Ewing sarcoma (EWS) treatment landscape

Promising new approaches for EWS

Drug/Target Class	Example drugs
EWSR1-FLI1 Target agents: Splicing inhibitors Minor groove-binding agents	TK-216 Mithramycin, Trabectedin and Lurbinectidin
Epigenetic therapies	Lysine-specific demethylase 1A (LSD1) inhibitors (seclidemstat and IMG-7289) Histone deacetylase inhibitors (vorinostat, entinostat, and panobinostat) Bromodomain inhibitors
CD99 targeting agents	Clofarabine/Cladribine and CD99 antibody
Novel cytotoxic agents	**Eribulin**, aldoxorubicin and palifosfamide
Multi-targeted tyrosine Kinase Inhibitors	**Pazopanib, regorafenib** and **cabozantinib**
Mammalian target of rapamycin (mTOR) inhibitors	**Nab-Rapamycin**, temsirolimus
DNA damage/Repair	Poly-ADP-ribose polymerase (PARP) inhibitors **(niraparib, olaparib, talazoparib)** Wee1 inhibitors (AZD1775) CHK1 inhibitors (prexasertib)
Cell cycle cyclin-dependent kinase (CDK) inhibitors	CDK4/6 Inhibitors **(palbociclib, ribociclib, abemaciclib)**
Transcriptional CDK Inhibitors	CDK7 inhibitor (SY-1365) CDK12 inhibitor
MDM2 Inhibitor	AMG-232, DS-3032b, ALRN-6924 and idasanutlin
Insulin-like growth factor 1 receptor (IGF-1R) inhibitors	**Ganitumab**
Platelet-derived growth factor receptor (PDGFR) antibodies	Olaratumab
Other monoclonal antibodies	MORab-004
Metabolic modulators	Nicotinamide phosphoribosyltransferase (NAMPT) inhibitors and Metformin
Immunotherapy	GD2 antibody **(dinutuximab)** VIGIL/FANG Chimeric antigen receptor (CAR) T cells

Within the target class, EC-8042 is the only one that hits the EWS-FLI1 validated target in Ewing sarcoma

Most new approaches do not directly address the EWS-FLI1 target

Bailey K *et al. F1000Research* **2019**, 8: 493

2. The Product c) differential features facing the market

Business opportunities in Ewing sarcoma for EC-8042

Orphan disease (EU, US & Japan) and eligible for the Rare Pediatric Disease Priority Review Voucher Program in the US

Orphan disease

EC-8042 is eligible for market exclusivity:

10 years in Europe and Japan

7 years in the US

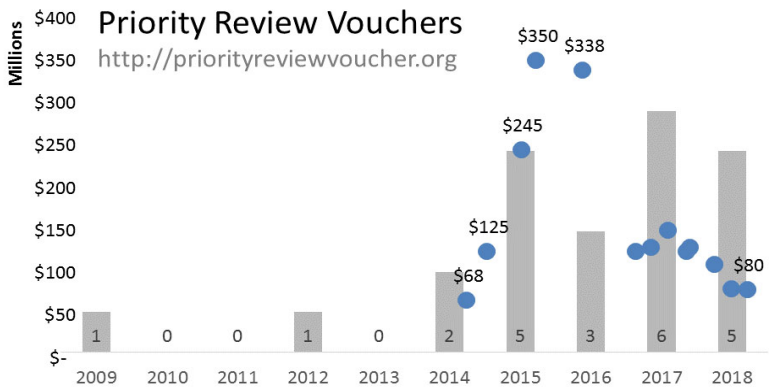
EntreChem plans to file for **Orphan Drug Designation** (ODD) once IND is accepted

Priority Review Voucher

Established in **2012** in the US as part of the **FDA** Safety and Innovation Act.

Since 2014, 13 drugs have been awarded the PRV

EC-8042 would get the voucher ($70M-$350M) once **clinical trials are completed** and obtain FDA approval



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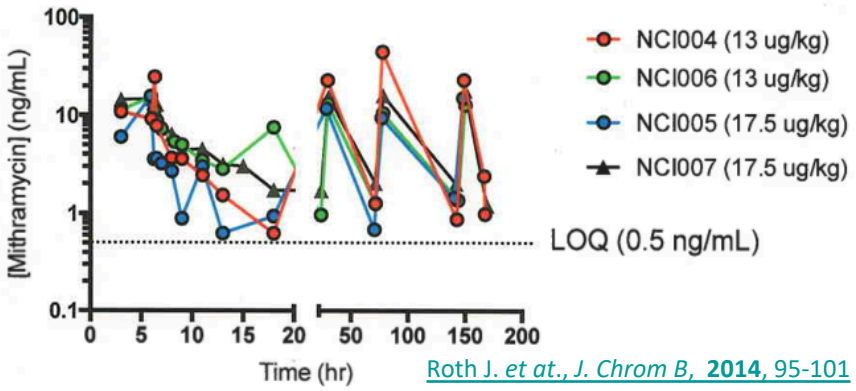
Phase I Strategy for EC-8042: value inflexion point

- **EC-8042 FIH** trial will determine:
  - ✓ the Recommended Dose for a Phase 2 trial.
  - ✓ plasma levels (PK) for early assessment of treatment potential: **spaced bolus** anticipated as superior
- Unlike most drug development programs, **the value inflexion** point for EC-8042 resides in the Phase I data
  - ✓ Intrinsic potential to capture Mithramycin potential **without its dose-limiting toxicity**



Roth J. *et at., J. Chrom B,* **2014**, 95-101

	13 ug/kg (n=2)	17 ug/kg (n=2)
C_{MAX}[1] (ug/L)	20.03* ± 6.72	15.64 ± 0.12
C_{MAX}/D (ug/L/ug)	0.0368 ± 0.0223	0.0183 ± 0.0038
AUC_{INF} (hr*ug/L)	1,878 ± 1,064	1,210 ± 356.2
AUC_{INF}/D (hr*ug/L/ug)	3.57 ± 2.85	1.37 ± 0.13
$T_{1/2}$ (hr)	6.11 ± 3.58	7.58 ± 1.13
CL (L/hr)	1.42 ± 0.70	2.56 ± 0.15
Vss (L)	217 ± 11.6	369 ± 6.50

Grohar *et al., Cancer Chemother Pharmacol* **2017,** 645-652

- NCI 2012 trials used the historical **6h infusion** daily regimen (0.0175 mg/Kg)
- Very low plasma levels detected
- Cmax **peaks** at 20nM (lower than IC_{50})…
- … but **AUC is high** due to the infusion half-life
- No signs of activity

2. The Product e) IPR Protection

Strong IP position - Composition of Matter until 2028

Topic	Priority Date	Status
1st generation mithralogs *In-licensed from UniOvi, Uni Kentucky*	Mar 1st, 2004	Granted on Sept 9, 2008: **US 7,423,008** (in force)
2nd generation mithralogs *In-licensed from UniOvi, Uni Kentucky*	Feb 6th, 2007	Granted on April 23, 2013: **US 8,426,169** (in force) Granted on April 23, 2014, **EP2151448** Validated in DE, FR, GB, IT, ES, CH, SE, NL and DK (All in force)
3rd generation mithralogs *100% EntreChem* *EC-8042*	July 23rd , 2009	Granted on Feb 28, 2014: **US 8,772,253** (in force) Granted on March 19, 2014: **EP2457921** Validated in ES, DE, FR, GB, IT, BE, DK, SE, NL, CH and IE (All in force)
EC-8042 combinations in triple negative breast cancer *100% EntreChem*	Sept 17th, 2015	EP Grant of patent expected USA Examination in progress

- In addition to patent protection, EC-8042 is eligible for Orphan Drug Status and Pedatric Orphan Drug Designation in its lead indication EWS, which confers a **market exclusivity of 10 years in Europe and Japan, and of 7 years in the US, as well as access to the Pediatric Voucher Program in the USA**.

- An additional layer of protection is provided by EntreChem's **exclusive access** to the proprietary bacterial strain which is required for producing EC-8042.

Potential Pitfalls and Risks

1) *Biomarkers for adult tumors not yet available*

2) *Unexpected toxicity not foreseen in preclinical studies*

3. Partnering Opportunities

Prefered scenario

- *Co-development until PoC in humans. Unmet disease, fast regulatory approval.*
  - *upfront fee + milestones*
- *From PoC until approval : EntreChem to provide CMC expertise + production*
  - *Royalties based on PoC results*

3. Partnering Opportunities

Final Summary

- **EC-8042** is a first in class **reprogramming agent** for tumors with **transcriptional deregulation**, including ***pediatric*** indications (Ewing, rhabdoid).
- **EC-8042** is a mithralog that captures Mithramycin potential **without** its dose-limiting toxicity.
- Based on strong in vitro and in vivo data, EntreChem has selected EC-8042 **as clinical development candidate** with FIH scheduled for 2020.
- Comparative *in vivo* studies demonstrate **marked improvements over the parent compound** and **Standard of Care agents** in commercially relevant **adult tumor** indications.
- EC-8042 **production is straightforward** through fermentation of a proprietary bacterial strain.

We are seeking for a partner to advance EC-8042 into the clinic, gain regulatory approval, and to commercialize the product on a regional or worldwide level.

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