Cilastatin, a safe nephroprotector to prevent Acute Kidney Injury

spherium biomed®

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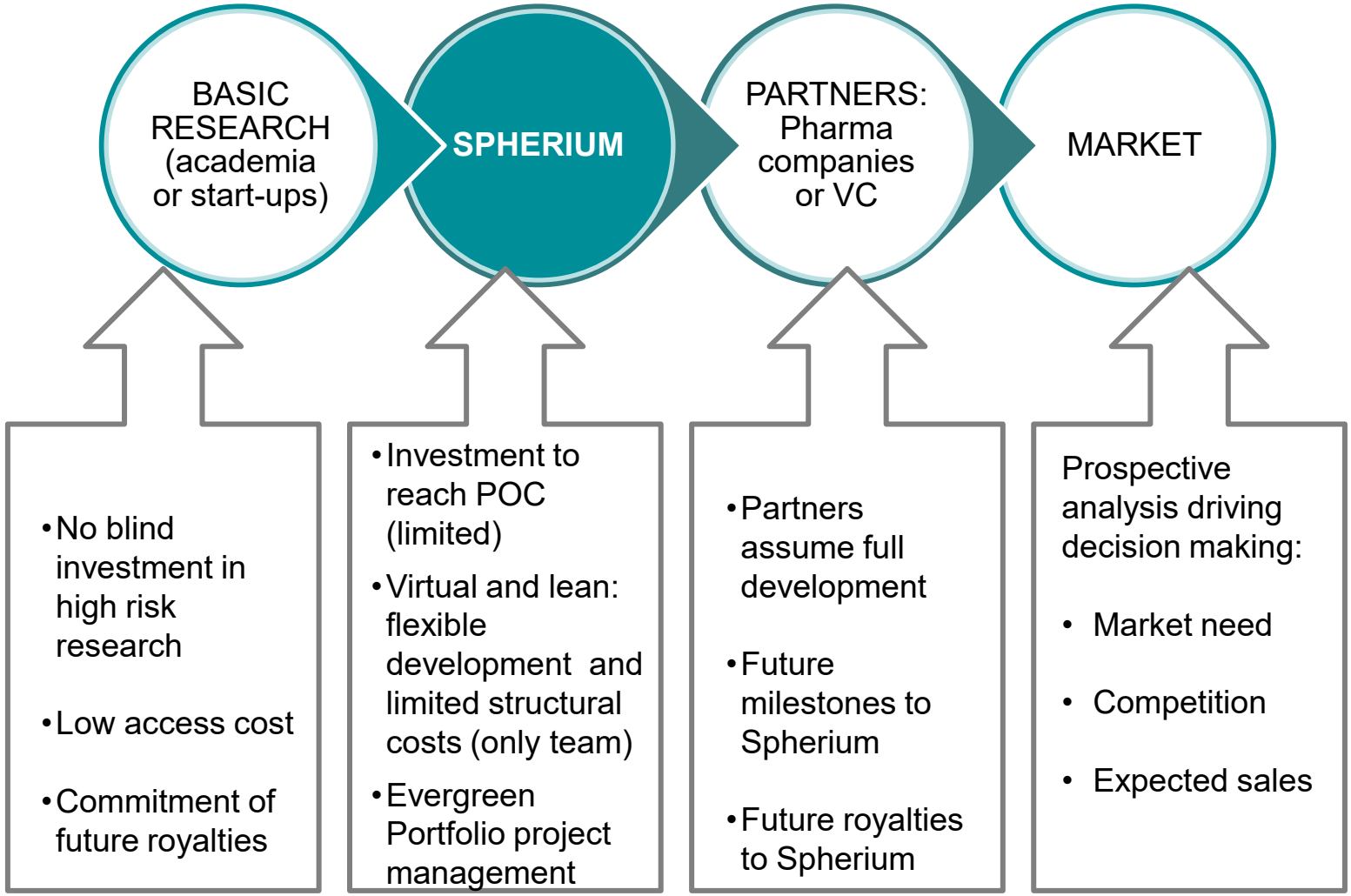
1. The Institution

- Spherium is a private, independent portfolio development company of the Ferrer Group
- focused in adding value in early stage to Proof of Concept
- continuously sourcing new innovations from academic research
- a lean virtual company
- with an experienced team with a diversified background specialized in Project Management
- developing a wide range of therapeutic opportunities with high unmet medical need (indication agnostic)

1. In the value chain…



1. Pipeline as of March 2018

		Development milestone achieved March 2018	Commercialization strategy
SP14008	*Mucomel, oral mucositis*	Clinical Phase IIa results (POC)	Partner after clinical POC (2018)
SP14019	*Cyclatop, atopic dermatitis/psoriasis*	Clinical Phase IIa results (POC)	Partner after clinical POC (2018)
SP12008	*Comboprofen, Mild Muscular Pain*	Clinical Phase IIa results (POC)	Local distributors after NDA (2021)
SP15016	*Cilastatin, AKI*	Authorized IND	Partner after clinical POC (2020)
SP12008	*Autoimmune Diseases (RA, Lupus, IBD)*	Preclinical candidate selected	License out (2018)
SP14040	*Cognitive deficit, negative symptoms schizophrenia*	Preclinical candidate selected	License out (2018)
SP15028	*Muscle lesions (local treatment)*	Preclinical candidate selected	Develop to clinical POC (2020)
SP15008	*IBD & amyloid diseases*	Preclinical candidate selected	License out (2019)

2. The Product

- SP15016 is Cilastatin, a fully developed drug approved in a fixed combination with the beta-lactamic antibiotic Imipemen (Primaxin®) administered intravenously. The role of Cilastatin in the combination is to increase Imipenem's bioavailability inhibiting a fast acting kidney degradation route.
- Cilastatin has never been developed as a stand-alone drug, however there is a broad and public record of human use, safety and pharmacokinetic data for the combination.
- There is extensive preclinical, clinical and mechanistic data supporting the use of Cilastatin to prevent **Drug related nephrotoxicity** by a general MoA.

OPPORTUNITY: Fast development of Cilastatin as a stand-alone IV drug to prevent AKI caused by medical treatment and procedures

2.a The Product: Target Indications

Acute Kidney Injury (AKI) is an abrupt loss of kidney function that develops within 7 days after injury aggression. No proven effective pharmacologic therapies are currently available for the prevention or treatment of AKI.

The causes…

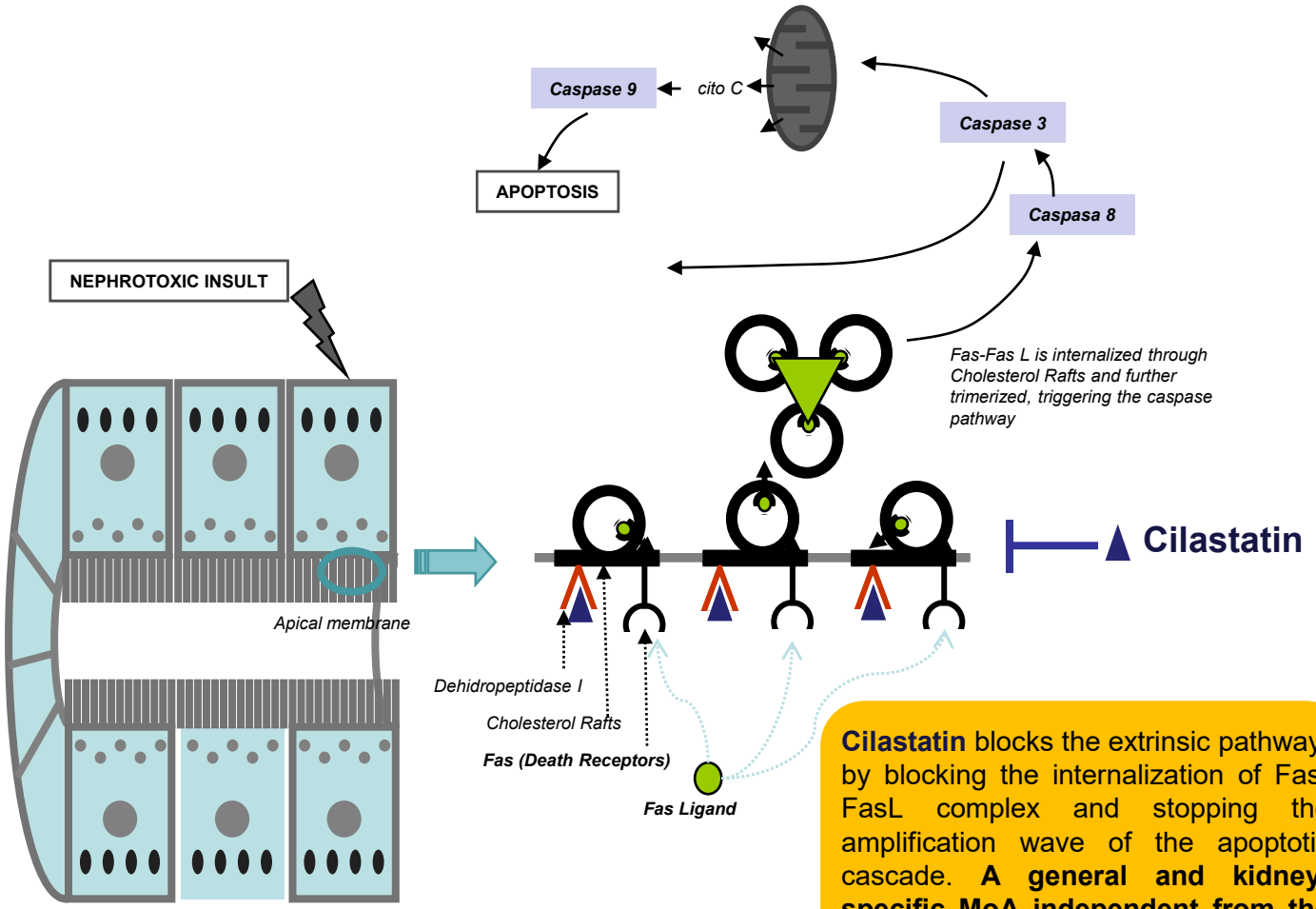
1. Drug induced AKI: cisplatin, vancomycin, gentamycin, cyclosporine, tacrolimus...
2. Contrast medium induced AKI (CIN): Coronary angioplasty and cath lab interventions
3. Ischemia-reperfusion AKI: subsequent to cardiac surgery.
4. Sepsis
5. Rhabdomyolysis

…and the effects

1. Mortality: Patients surviving AKI have increased long-term mortality
2. CKD: AKI increases significantly the risk of developing CKD
3. Marked increased risk of ESRD (End Stage Renal Disease)
4. Increased in-hospital morbidity and mortality
5. Increased short and long term costs

POC and prospective entry indication: **Prevention of contrast Induced Nephrotoxicity (CIN)** in angioplasty in Myocardial Infarction. Incidence of AKI may be up to 35% of interventions (even up to 50% in case of patients suffering diabetes). Up to 700.000 patients are at risk every year in the US.

2.b The Product: mechanism of action

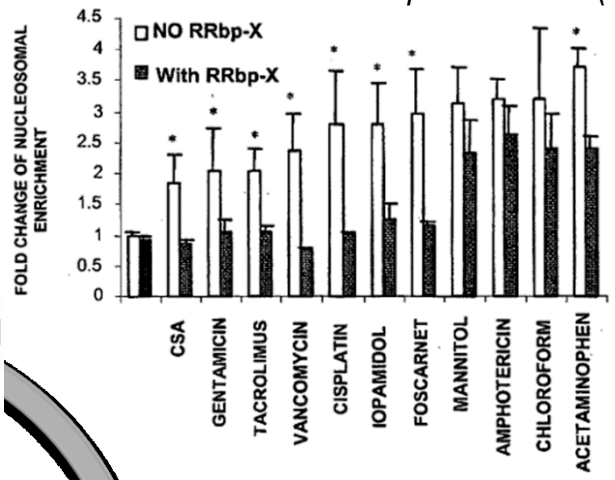


Cilastatin blocks the extrinsic pathway, by blocking the internalization of Fas-FasL complex and stopping the amplification wave of the apoptotic cascade. **A general and kidney-specific MoA independent from the primary insult.**

2.b The Product: experimental evidence

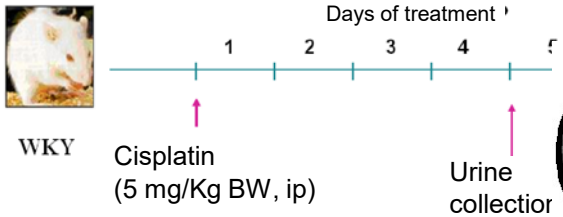
All the initial preclinical experimentation, the understanding of the MoA and related IP, have been developed by Dr Tejedor group (HG Marañón)

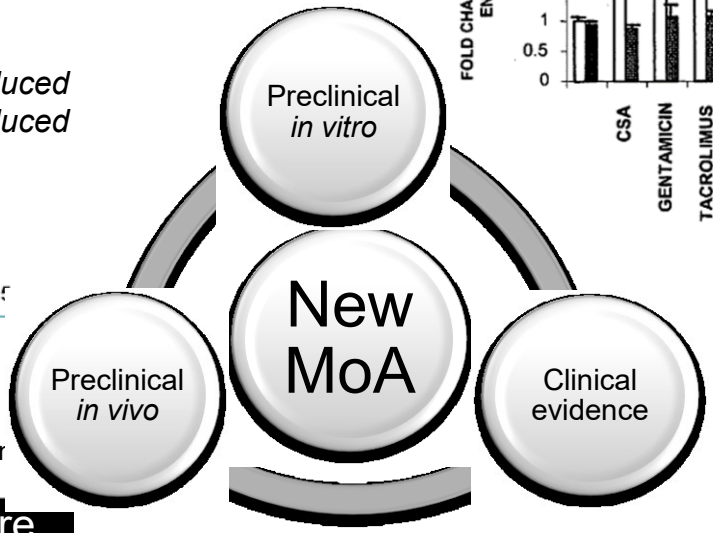
Primary cultures of pig kidney proximal tubule epithelial cells (PTECs)

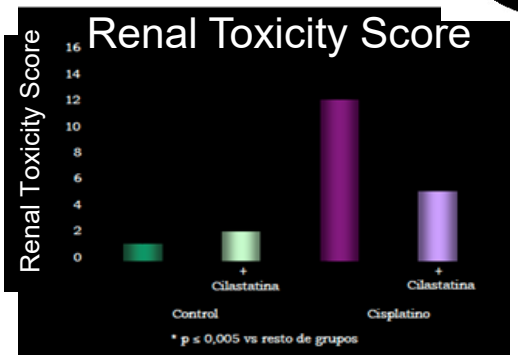


*Rat model of **cisplatin**-induced nephrotoxicity and **gentamycin**-induced nephrotoxicity*

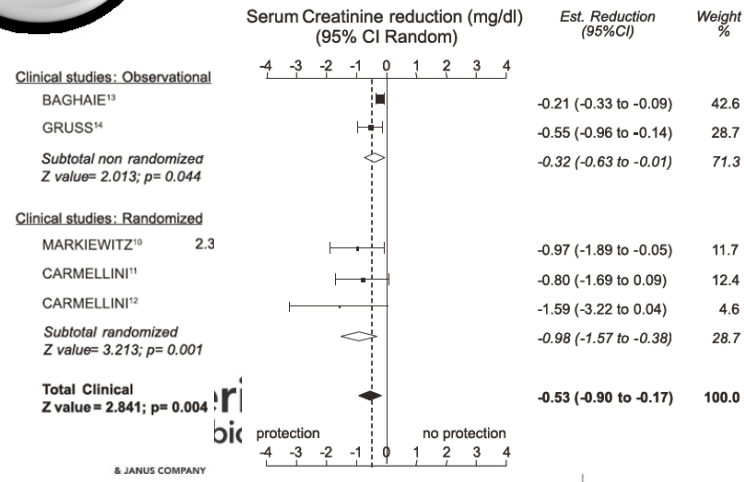
Cilastatin (75 mg/Kg/12h, ip)







Patients treated with cyclosporine alone versus cyclosporine plus cilastatin/imipenem



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2.c The Product: Differential features facing the market

1. Cilastatin may be used to prevent AKI in a number of clinical situations with NO PHARMACOLOGICAL alternatives (management of patients based on hydration protocols and risk assesment)
   - Drug induced AKI: cisplatin, vancomycin, gentamycin, cyclosporine, tacrolimus, colistine...
   - Contrast medium induced AKI (CIN): Coronary angioplasty and cath lab interventions
   - Ischemia-reperfusion AKI: subsequent to cardiac surgery.
   - Sepsis
   - Rhabdomyolysis

2. As the entry indication Spherium has chosen CIN. We consider this is the best indication to run a PoC Phase II clinical trial. The market for this particular condition is in the range of 100 M€ based in Covance Market Acces report

3. The total potential market is much bigger. A relevant example is sepsis derived AKI: AM Pharma (https://www.am-pharma.com/) is a company developing Alkaline Phosphatase for the treatment of this condition.In 2015 Pfizer acquired a minority equity interest in AM-Pharma and secured an exclusive option to acquire the remaining equity in the company. The option will become exercisable upon completion of a Phase II trial of recAP in the treatment of Acute Kidney Injury (AKI) related to sepsis. Pfizer made an upfront payment of $87.5 million for the minority equity interest and exclusive option, with additional potential payments of up to $512.5 million upon option exercise and potential launch of any product that may result from this agreement. Other terms of the transaction were not disclosed.

2.d The Product: current status of development

CMC and Pharmaceutical development

Development of single dose vials of solid sterile cilastatin to prepare an extemporaneous solution for infusion. Analytical methods already validated. First technical batch available in September.

Phase I Clinical Trial

Safety and pharmacokinetics dose-range study for a single administration of Cilastatin in an intravenous 3h-infusion regimen. PK simulation, bioanalytical methods and trial design on going. The trial aims to demonstrate cardiovascular safety upon high dose and prolonged cilastatin exposure, to define prospective dosing and regime within the potential therapeutic window during phase II.

Proof of Concept Phase II Clinical Trial

Use of Cilastatin in a randomized, prospective, placebo-controlled and double blind study, to prevent **Contrast Induced Nephrotoxicity** in non-STEMI angioplasty patients. Trial design ready, built jointly with our clinical advisory team of relevant cardiologists and nephrologists KOLs from Spain (Drs. M. Sabater, A. Cequier, JM Griñó, A. Garcia-Touchard and A. Tejedor).

Regulatory strategy and prospective calendar

Submission of IND to Spanish Agency by December. Prospected authorization 1Q2018. Results available June 2018. The results of this phase I will be used to support starting phase II in Spain (4Q 2018). They can also be used to prepare a scientific advice with FDA to adjust the design for phase II strategy in the US.

2.e The Product: IPR protection

PCT/ES2008/070137 — **Granted in EP and US**

Priority date	Valid til	Application Num	Coverage	Status
11-07-2008	2028 + extensions	EP 2 143 429 B1	Iopamidol and foscarnet	Granted
11-07-2008	13-Jan-2030	US 12/442,249	Gentamycin, cisplatin, foscarnet, iopamidol, mannitol, amphotericin B, chloroform	Granted
11-07-2008	2028 + extensions	US 14/940,669	Dose range and administration schedule for cisplatin	Granted
11-07-2008	2028 + extensions	US 15/223,665	gentamycin, cisplatin, an **iodinated contrast agent**, foscarnet, mannitol, amphotericin B, acetaminophen and chloroform agents	Granted

PCT/EP2017/065609 (priority June 2016, submitted June 23 2017)	**Cilastatin for Sepsis.** Priority date June 2016 2017.10.05 ISR: all claims (claims 1-15) are **new and inventive**.
Other uses, formulation, dosing and regime	**Patents planned, based on clinical results and final product profile** **Data protection in the EU (8+years), US and Canada (3 or 8 years), Korea (4 years)**

2.f Risk assessment

Above average for the development stage:

- Commercial: relatively undefined and underestimated market
- Technical (efficacy): difficult to design clinical trials + historical failures, tough indication

Below average for the development stage:

- Technical (safety): known drug with safe profile
- Industrial (CMC): fully developed API

3. Partnering Opportunities

- Future value share in exchange to investment
- Option to license after phase II
- Co-development
- Straight licensing