Granada Health Technology Park & AcexHealth:

Translating Discovery into Innovation

Lourdes Núñez Müller, MBA, PhD
Director of Knowledge Transfer, Internationalization and Entrepreneurship
www.acexhealth.com in **lnunezmuller**

Dublin, November 21 2023

Universidad de Granada

CSIC

master diagnóstica

AcexHealth Investment

Developing a community of investors in Andalusia for early stage health technology investing (pre-seed, seed).

Abbott
A Promise for Life

Pfizer

MSD

ROVI

CONFIDENTIALAND TRADESECRETS

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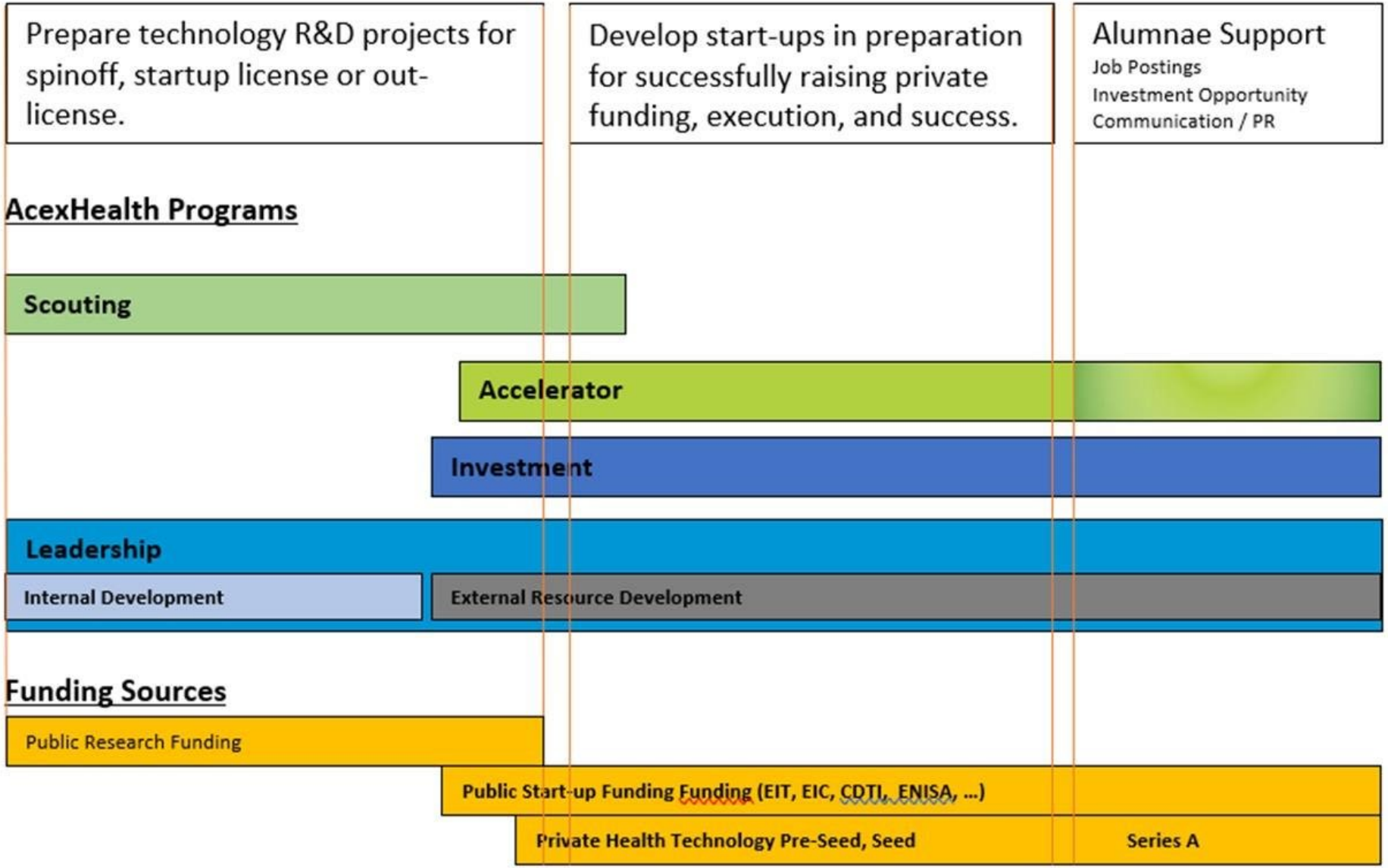
AcexHealth Verticals Brainstorming



AcexHealth
Health Accelerator of Andalucía

AcexHealth Mission

- AcexHealth helps start-ups avoid making critical errors in the early stages of development from which it could be difficult or impossible to recover.

- AcexHealth focuses on making start-ups more investable through a thorough assessment and development of strategies in areas critical to success in the health technology space (business model, regulatory, development strategy, indication for use, ...

- Mentors from the US and across the EU are selected whose experience and expertise match the start-up's technology (Biotech, Medtech, digital Health, ..) and business area to be addressed (Strategy, Development, Regulatory, IP, ..).

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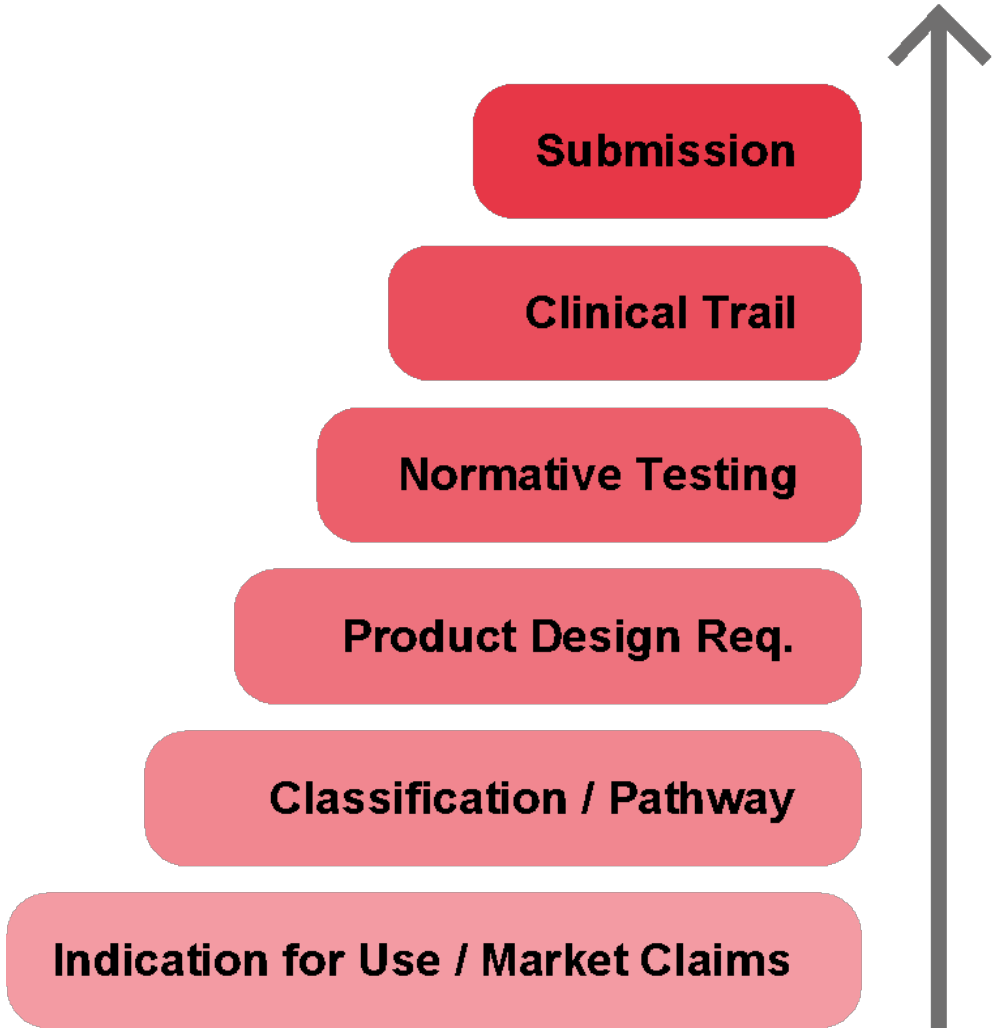
Module 3 -Regulatory

COMMERCIALIZATION



Regulatory,
a barrier
to the market?
or
Pathway
to success?

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CHECKLIST

Checklist – make sure you have covered the following key information:

1. Have you assessed targeted regions? Global? US & EU? China? ...
2. Have you determined your indication for use statement and your market claims?
3. Have you determined your classification?
4. Have your identified similarly classified technologies or products?
5. Have you identified regulatory pathway in targeted regions based on classification?
6. Have you developed initial plan for executing regulatory strategy?
7. Have you developed a projected timeline and projected costs associated with regulatory?
8. Have you understood that a sound and thoughtful strategic regulatory plan is tightly coupled with the competitive positioning of a new technology, and it informs the sales and marketing approach, clinical strategy, quality processes, and risk management policies the company puts in place?
9. Have you understood that the strategic regulatory plan should be considered early on and not be considered by itself?

Some of our 10+ SMEs

Transforming Andalusian Startups into successful enterprises

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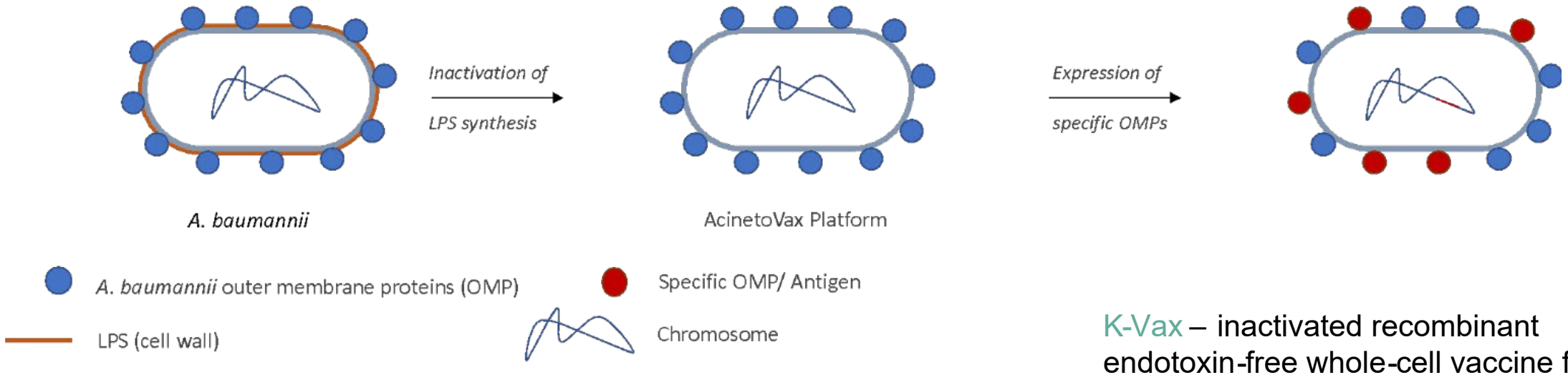
K-VAX

Vaccine against invasive infections by *K. pneumoniae*

Vaxdyn is developing a new drug entity within the vaccines class, for global distribution beginning with EMA approval

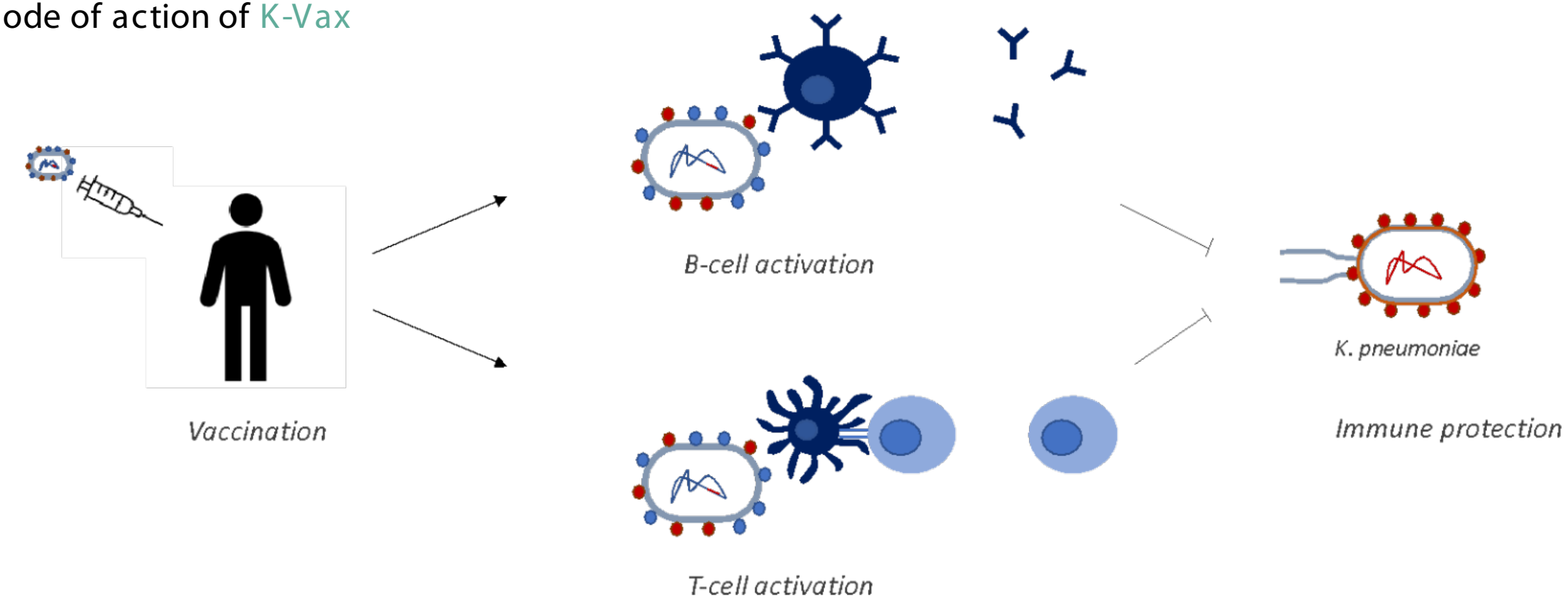


K-Vax – inactivated recombinant endotoxin-free whole-cell vaccine for prevention of invasive infections by *Klebsiella pneumoniae*

Research reported in this presentation is supported by CARB-X. CARB-X's funding for this project is sponsored by the Cooperative Agreement Number IDSEP160030 from ASPR/BARDA and by awards from Wellcome Trust, Germany's Federal Ministry of Education and Research (BMBF), the UK Global Antimicrobial Resistance Innovation Fund (GAMRIF) and the Bill & Melinda Gates Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of CARB-X or any of its funders.

1. INTRODUCTION OF VAXDYN'S TECHNOLOGY & K-VAX

Mode of action of K-Vax



Clinical strategy: vaccination of high-risk groups for raising immunity preventing invasive *K. pneumoniae* infections

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2. REGULATORY ACTIONS

Current stage of the project: preclinical stage

Initiation First in Human trial

Regulatory actions:

- Vaxdyn & CARB-X had a regulatory (pre-scientific advice) meeting with the Paul-Erlich Institute (PEI) o

  PEI team led by Volker Öppling (QC & Assessment of Human Vaccines at EMA, Senior Expert at PEI)

  Vaxdyn exposition assisted by Biopharma Excellence by Pharmalex (Munich, GER)

- The meeting provided endorsement of Vaxdyn's strategy and valuable input from regulators

  Topis discussed: Non-clinical PoC; CMC-manufacturing plan; Clinical plan

  The PEI acknowledged the novel and innovative character of the Acinetobacter platform technology. It further encouraged Vaxdyn to request a formal Scientific Advice

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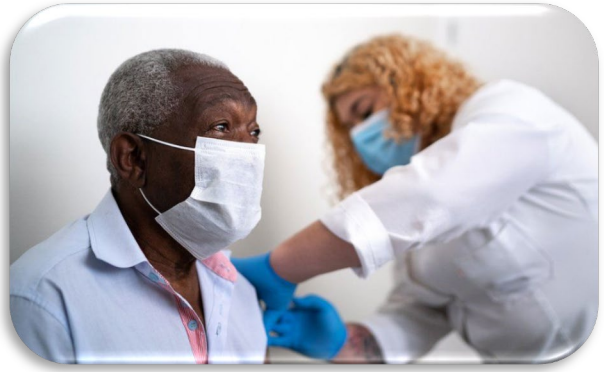
The solution : Klebsiella vaccine

K-Vax : 1 vaccine for the 2 profiles demanded by the WHO

1. **Prevention of neonatal sepsis by *Klebsiella pneumoniae***

Prevention of 80K neonatal deaths & 400K neonatal sepsis[1]



2. **Prevention of disease by *Klebsiella pneumoniae in adult population at risk***

Prevention of 320K deaths & 14M DALYs[2]

Global Market *$6 billion* by 2035[3,4]

1. Kumar et al. 2023 Global, regional, and national estimates of the impact of a maternal Klebsiella pneumoniae vaccine: A Bayesian modeling analysis. PLoS Med 20(5): e1004239.
2. Kim et al. 2023 (Global and regional burden of attributable and associated bacterial antimicrobial resistance avertable by vaccination: modelling study" BMJ Glob Health 2023;8:e011341.
3. Spellberg & Rex 2013. The value of single-pathogen antibacterial agents. Nat Rev Drug Discov. 12(12):963
4. Globaldata & Avance Market analyses 2023

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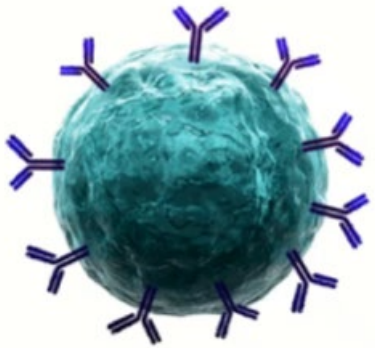
1. INTRODUCTION OF LENTISTEM'S TECHNOLOGIES

LentiStem is R&D company focused on immunogenetherapy to provide the optimal activity control of living drugs such as CAR-T cells

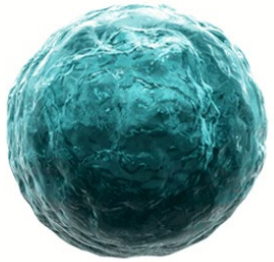
TCR-*like* technology



CAR-T cell

The product: AWARI CAR-T cells against R/R CD19+ tumors whose CAR expression mimics a more physiological behavior in order to provide a more controlled and less exhausted product.

Lent-On-Plus technology



The product: iTRUCKs19.18 that are CAR-T cells generated by the co-transduction of two different Lentiviral vectors: one LV for expressing the CAR against CD19 antigen and a second for externally control of the expression of IL18.

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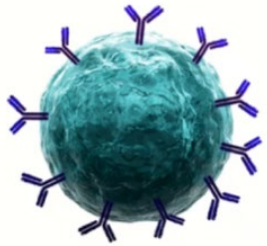
2. REGULATORY ACTIONS

TCR-like platform: AWARI CAR-T cells for R/R CD19+ tumors

*This product will be evaluated in an independent **PUBLIC CLINICAL TRIAL** by the Instituto de Salud Carlos III (ICI22/00015). Principal Investigator: Dra. Concha Herrera, Hospital Universitario Reina Sofía (Córdoba)*



CAR-T cell

Regulatory preclinical phase (on -going)

- Production of 3 batches of AWARI CAR-T cells under GMP conditions
- Manufactured GMP-grade LVs.
- Current in vitro evaluation of the best type of CD19+ tumor (density, LLC, LL-B, NHL, Burkitt's) as candidate for AWARI treatment vs ARI-0001 treatment.

Evaluation of safety/efficacy on a Phase I/II Clinical Trial

- Patients that do not fulfil commercial CAR -T criteria under Refractory/relapse CD19+ disease.
- Evaluation over 20 patients with dose scalation in a cohort of 3+3 patients.
- Data comparison with published data from ARI -0001 clinical trial.

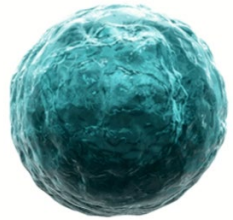
If data comparison is positive (equal efficacy and lower side effects or superior efficacy and equal side effects)

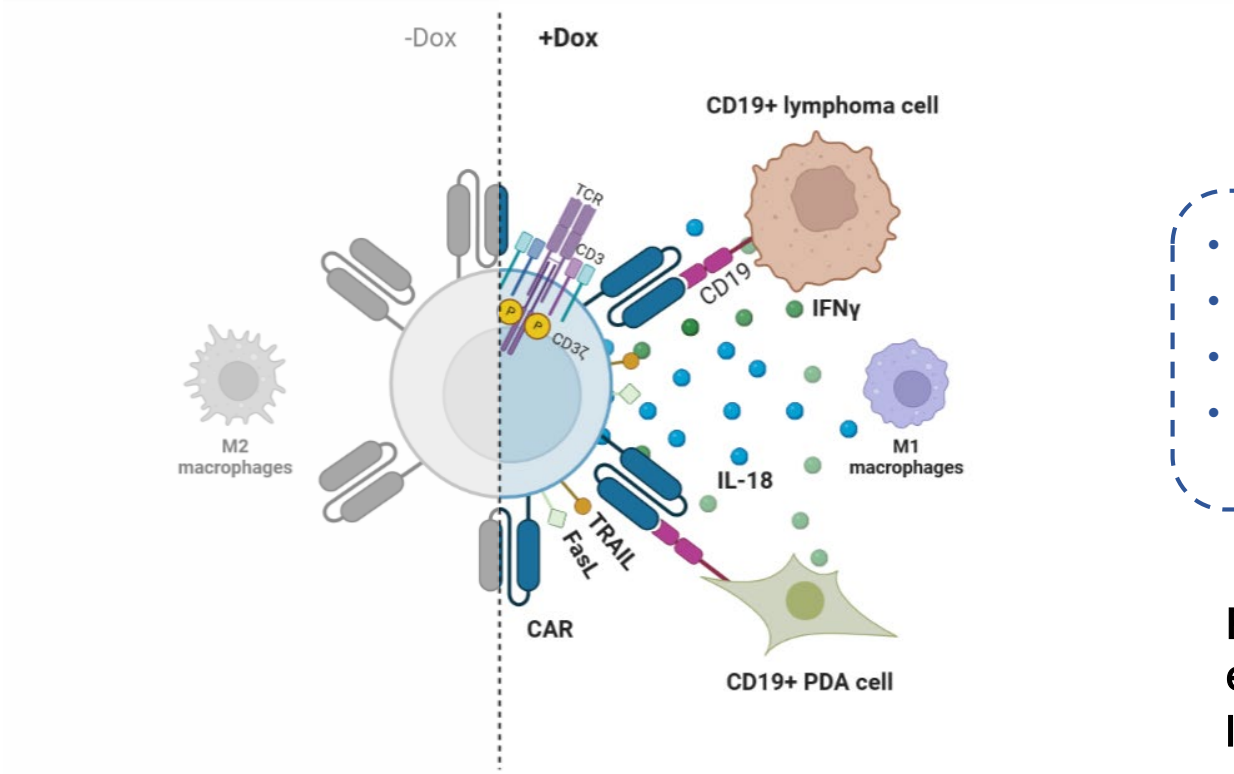
- We would like to propose a in human comparison of ARI-0001 vs AWARI

- Q: Is it OK to compare ARI-0001 (hospital exemption) vs AWARI?

2. REGULATORY ACTIONS

Lent-On-Plus® for controlled TRUCKs releasing IL-18



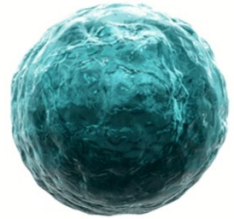


- IL-18 regulation *in vitro* and *in vivo*
- Controlled activation state on T cells
- IL-18-dependent macrophages polarization
- Controlled cytotoxicity in aggressive tumor cells

Ready to start with regulatory preclinical evaluation against aggressive R/R CD19+ lymphomas with tumor microenviroment .

3. Regulatory questions intro-Lent-On-Plus® platform: iTRUCKS19.18

The product: these iTRUCKs19.18 are CAR-T cells generated by the co-transduction of two different Lentiviral vectors: one LV for expressing the CAR against CD19 antigen and a second for externally control of the expression of IL18 after minimal dose of antibiotic under clinician criteria.



Selection criteria of patients: R/R patients low expression of CD19 and aggressive lymphoma.

ADVANTAGES OF LOP

- **Minimal dosis of antibiotic** (*in vitro*: picogram/ml, lower to exert an effect as antibiotic; *in vivo*: 100 ng/ml dissolved in orally water).
- **Absence of transactivators** (current ab systems use transactivators and exert severe cellular toxicity)

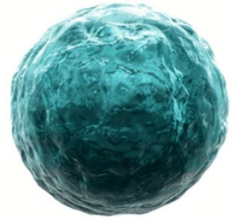
Experimental design for Ab-inducible TRUCKs19.18 dose in humans

-Anti-CD19-CAR is going to be expressed always in the membrane ➡ **Loss of CD19+ cells in blood**

-Effect as antibiotic? ➡ **Evaluation of microbiota in fecal material.**

-Effect as an inductor? ➡ **Detection of secreted IL18 in blood.**

3. Regulatory questions for Lent-On-Plus® platform in clinical trials:



- **Possible Problem I:** the CAR-T cell product is generated with two LVs.
  - **BUT**: IL-18 exert its effect independently of the CAR **BENEFITIAL bystander effect .**
  - Q: Is it OK to use two lentivirus to generate the CAR-T?

- **Possible Problem II:** the inductor is antibiotic
  - **BUT the system is extremely sensitive to AB.**
  - **Which is the best administration route in humans?**
    - *We have determined that the minimal amount of Ab provided orally was 100ng/ml in mice, sufficient to achieve expression.*
  - Q: Does the EMA agrees that our phase I/II trial design is aligned with EMA's evidence generation standards? Should we ask at academia@ema.Europe.eu? A Scientific Advice Meeting for SME?

limnopharma

Novel topical treatments for degenerative retinal diseases

The Problem:

Retinitis Pigmentosa (RP)

- A rare disease (Pursuing Orphan Designation)
- First Targeted Indication (Facilitated Regulatory and Exclusivity Protection)

Orphan designation

Academic sponsors can apply for orphan designation and benefit from incentives such as protocol assistance, fee and regulatory incentives at time of marketing authorisation.

Disease Prevalence

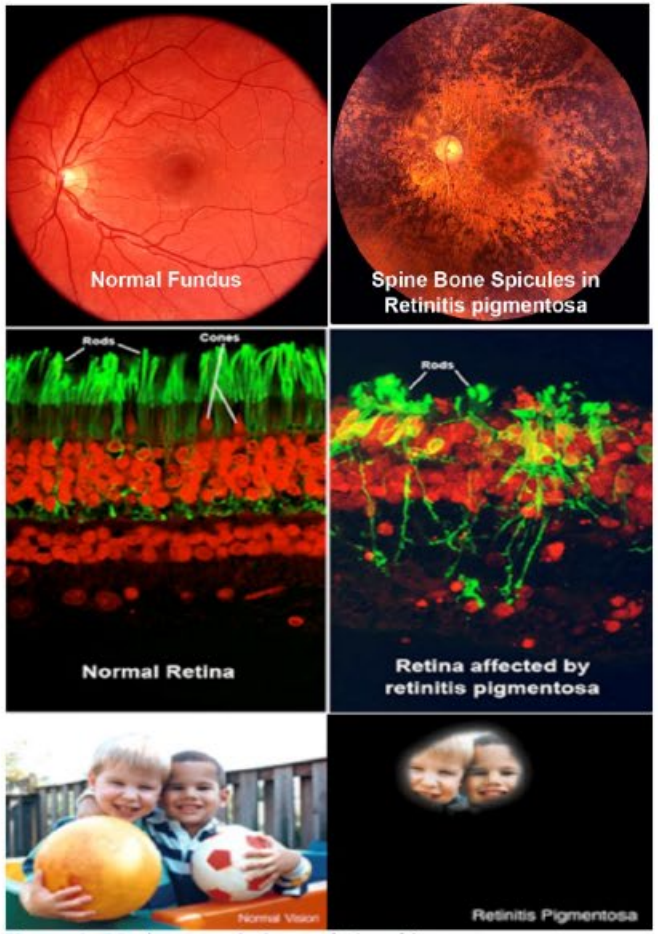


Figure 1. RP characteristics and visual impact

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- Natural product as HIT
  - Resveratrol based lead compound
- Rational design of derivatives & chemical synthesis

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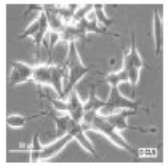
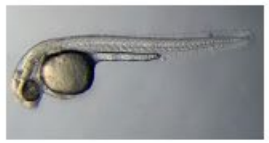
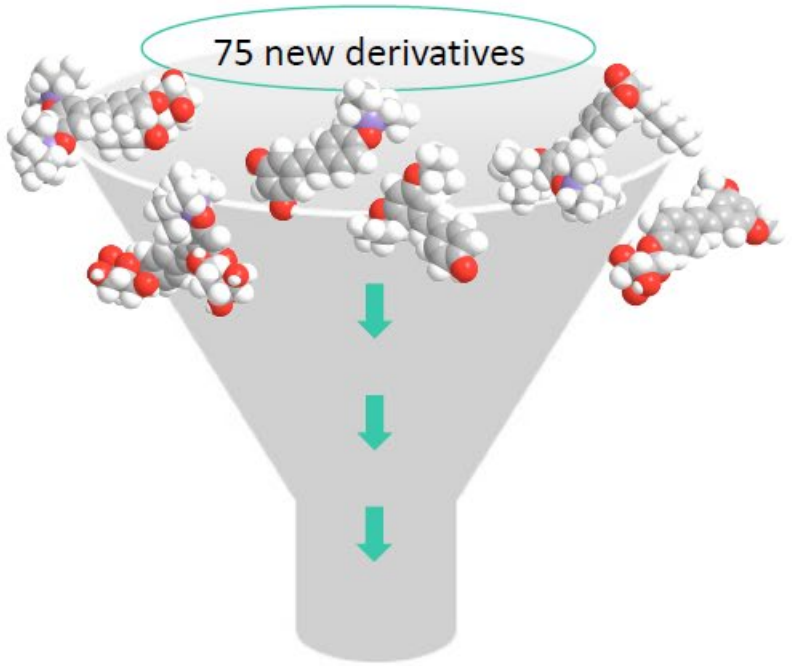
Fundación Progreso y Salud
CONSEJERÍA DE SALUD







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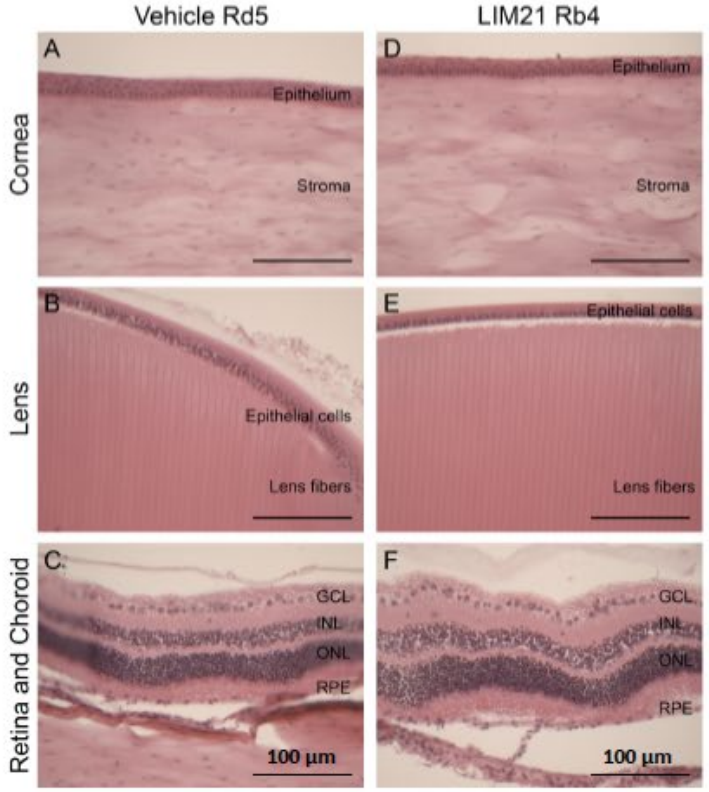
LIM21 shows ocular tolerability

- Rabbits. Administration of LIM21 or vehicle. Eye drops 15 days, three times per day
- Outcomes: Clinical observations (mortality/morbidity and general clinical observations), Ocular observations (Draize score; McDonald-Shadducks score (corneal damage) and Schimer strips (tear secretion)



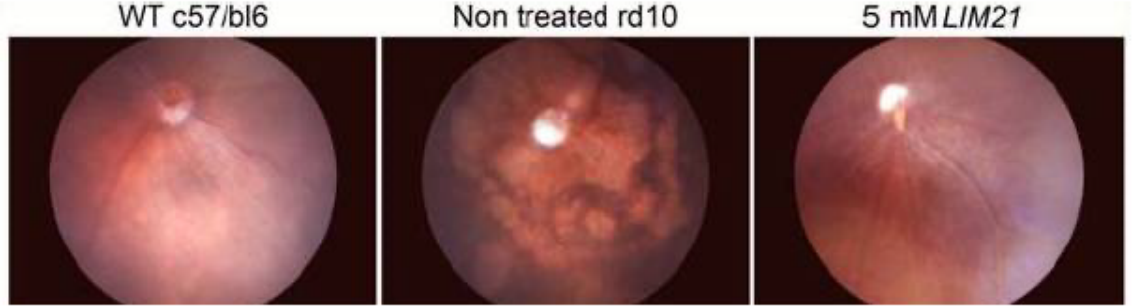
iris PHARMA

Under these experimental conditions, LIM21 is well tolerated

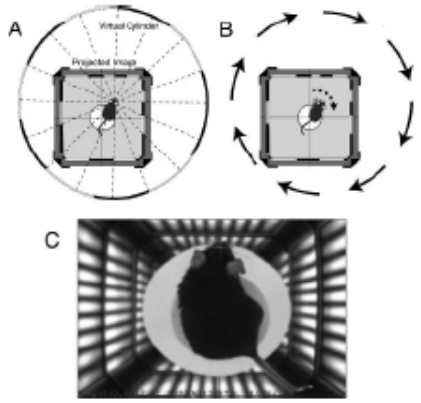
No toxicity signals were observed.

LIM21 shows high efficacy

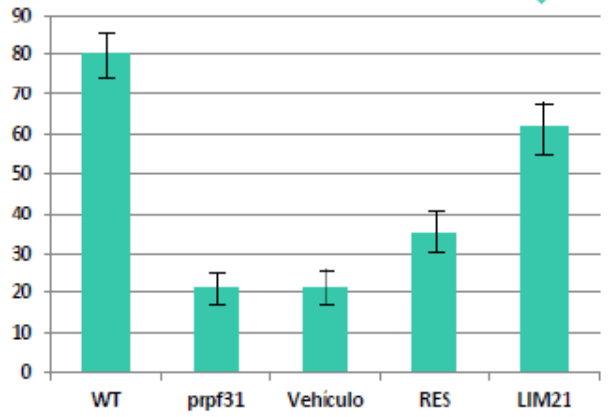
- Demonstrated in mouse models of different retinal degenerative diseases



Retinitis pigmentosa



optomotor test

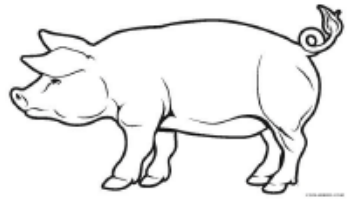


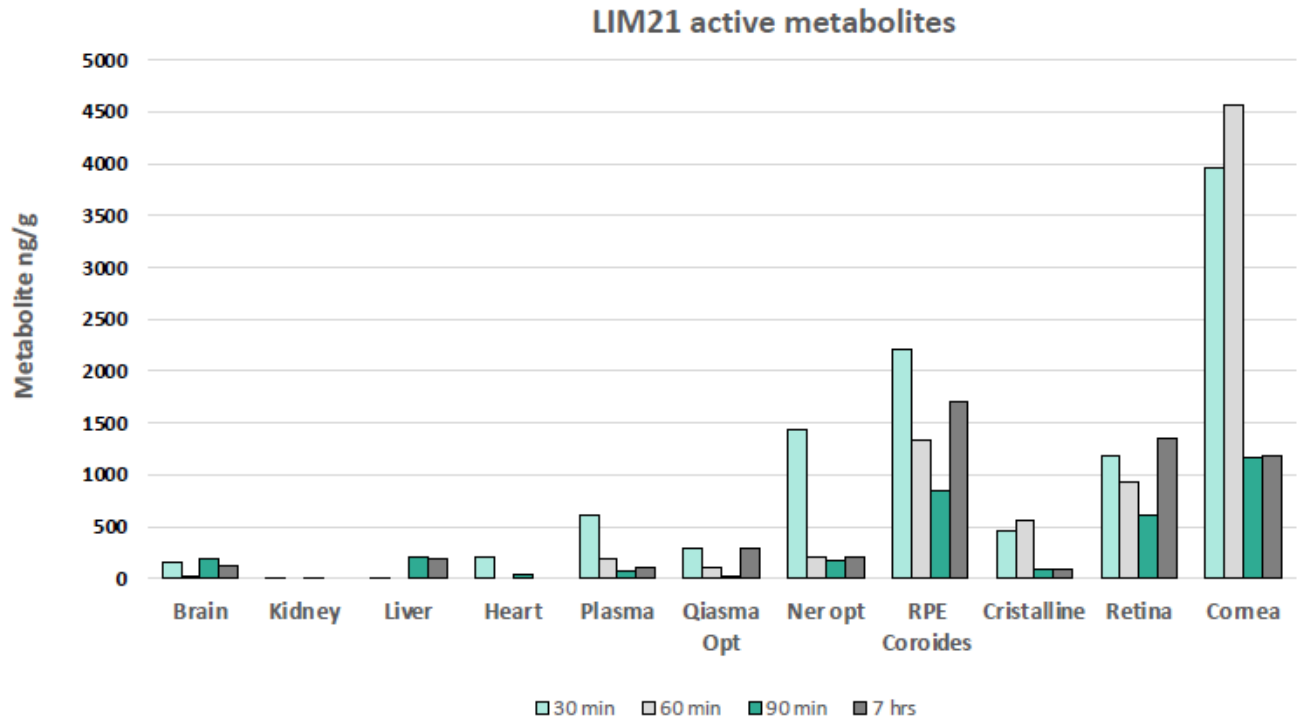
% Response to light stimulus

Dry Age-related Macular Degeneration

LIM21 biodistribution

- Formulation as that used on mice studies (**13% HP-β-Cyclodextrin, 2% tyloxapol** in water)
- Experimental conditions: **Pigs**, * eye drops (50 µL, 20 mM LIM21; 3 times, 5 minutes apart)
  * sample collection at 30, 60, 90 minutes or 7 hrs
  * UPLC-MS-MS (mass detection for LIM21 and metabolites)





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➢ **LIM21 metabolites** detected in the retina are 600-1400 ng/g. Also confirmed in rabbits and rats.

Corroborated by companies that recently have also shown the ability to deliver medications using eye drops to the back of the eye for other diseases.

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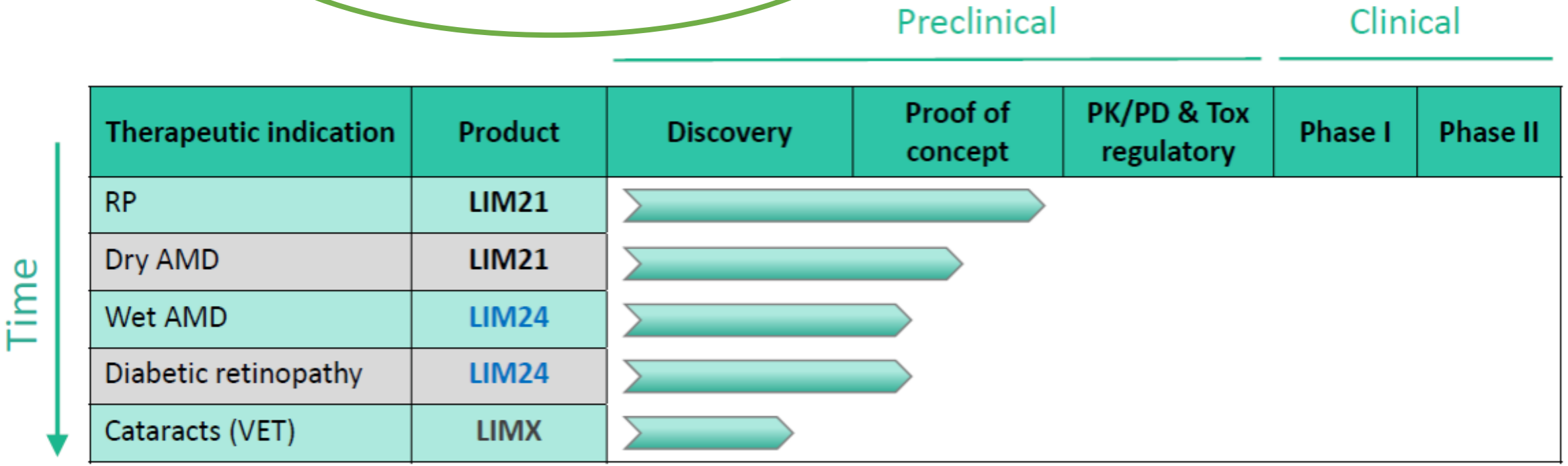
Scientific advice & Protocol assistance for orphans

EMA can provide scientific advice on quality, non-clinical and clinical development to generate robust evidence for regulatory submissions. Protocol assistance is a special form of scientific advice available for developers of designated orphan medicines to discuss compliance criteria such as demonstration of 'significant benefit' or 'clinical superiority'.

AEMPS vs EMA?
Phase I in Spain



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1. INTRODUCTION OF OLAVIDE NEURON TX & ONESTX

Biotechnology company dedicated to the development of drugs that delay aging and cognitive decline for patients affected by neurodegenerative diseases

ONESTX-1 is a steroid sulfatase inhibitor that was tested as investigational product (Phase II) for oncological indications in the past by Pharma, showing an excellent safety profile in daily administration for 6 months protocols.

Relevant preclinical and CMC development has been transferred to ONESTX from previous sponsor

The IVD company Biomedal SL became Seed Capital investor in 2022 to boost the project to clinical development.

ONESTX-1: A Novel mechanism of action, first-in-class drug for Neurodegenerative Diseases

- ✔ Anti-aging effect in *C. elegans* (increases lifespan).
- ✔ Anti-aging effect in mice (improves memory in old mice).
- ✔ Prevents protein aggregation in brain in both models (mice and C. elegans)
- ✔ Ameliorates cognitive symptoms (passive avoidance test) and plaque formation in a mammalian model of AD.
- ✔ Induces neurogenic activity in old brains.

Available in their publication at Nature Communications:

Perez-Jiménez et al. (2021) and unpublished results

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1. INTRODUCTION OF ONESTX PROJECT

Proposed intended use:

ONESTX-1, 667-Coumate. Other names: irosustat, STX64

API: Inhibitor of steroid sulfatase. An orally active investigational medicinal product that blocks sulfatase of steroids (STS), promoting an increase in the sulfated form of some neurosteroids, commonly known as neurohormones.

The main indication is **age-related neurodegeneration**, such as Alzheimer's, Parkinson's or Huntington's diseases.

ONESTX-1 is a compound with **extensive safety and toxicology reports** regarding a different indication and sponsor. The drug reached Phase II Clinical trials and was withdrawn due to slightly differences of efficacy compared to standard of care in oncological patients.

Market claim:

- Delay of aging brain processes as the cognitive decline due to Alzheimer's disease and other neurodegenerative diseases.

1. INTRODUCTION OF ONESTX PROJECT

Previous sponsor provided a letter granting a right of reference to the IMPD associated with any clinical trials, marketing authorisathion applications and/or certificate of pharmaceutical product related to the compound

ONESTX1 TPP version 1.0 summary

	Minimum	Base Case	Optimum
Indication	Alzheimer's disease	Cognitive decline due to neurodegenerative diseases	AD, Huntington's and Parkinson's disease
Patient Population	Mild Cognitive Decline	Moderate, Severe	Mild, Moderate, Severe
Therapeutic Modality	Small molecule		
Efficacy	>30% response rate	>50% response rate	>80% response rate
Safety	<50% Dry skin and <4% Asthenia	<25% Dry skin	<10% Dry skin
Dosing/Admin	Tablets for oral administration		
Storage	RT 24 months	5ºC 36 months	RT 36 months
Approach	Disease Modifying	Disease Modifying	Cure
MoA	Inhibitor of steroid sulfatase (STS), regulator of neurosteroids		

2. REGULATORY ACTIONS PHASE Ib/IIa PREPARATION, INITIAL SITUATION:

Safety and Toxicology
Assessment by a previous sponsor of the molecule for oncological indications

CMC
GMP manufacturing was succesfully performed in the past and development steps are available

CLINICAL
Up to 6 previous clinical trials for different indications
(Phase I and Phase II studies)

Regulatory roadmap

Q: Requirements for a new indication phase II product?

1. Transfer and assessment of previous data and results to CNS diseases

- New indication: CNS diseases and cognitive impairment
- Target population: Men and >60 years were under represented in previous clinical studies
- Dose: Administered dose in previous studies is under the maximum tolerated dose and optimal dose for new indication is unknown
- Treatment: > 6 months of treatment, longer than pre-clinical studies and patients treated in clinical trials (máx 6 months so far)

2. Applying for Scientific Advice to EMA, main subjects:

- Planned strategy to develop a comprehensive and exhaustive protocol to explore efficacy of the molecule in humans
- Planned strategy to address point 1, regarding differences between the New Protocol and previous clinical trials with the same IMP

Q:EMA vs AEMPS?

3. Documentation preparation
(IMPD, IB, protocol, informed consent forms)

4. Application for approval of the Clinical Trial

3. ONESTX-1 Safe treatement in humans:

- Pre-clinical dossier supported non-toxic and safety profile of ONESTX-1 – all relevant information from previous sponsor is provided to **ONESTX**
- In the past, 7 previous clinical trials showed the high safety profile of this small molecule in oral treatment at daily doses from 1 mg to 80 mg
- The investigational drug for these indications was withdrawn by the previous sponsor due to slight insufficient improvement over the currently approved standard treatment.

References: *Stanway et al. 2006; Coombes et al. 2013; Parra-Guillén et al. 2014; Pautier et al. 2017; Palmieri et al 2017(a); Palmieri et al. 2017(b).*

Identifier	Phase	Condition	Time frame	Dose	Enrollment	Status
NCT00790374	I	Prostate cancer	28 d / daily / o.a.	20 mg, 40 mg, 60 mg	17	Completed
NCT01840488	I	Breast cancer	≥ 7 d / daily / o.a.	1 mg, 5 mg, 20 mg, 40 mg, 80 mg	50	Completed
NCT01785992	II	Breast cancer	~ 6 m / daily / o.a.	40 mg	27	Completed
NCT01230970	II	Breast cancer	14 d / daily / o.a.	40 mg	2	Terminated
NCT01662726	II	Breast neoplasms	≥ 2 w / daily / o.a.	40 mg	13	Terminated
NCT00910091	II	Endometrial cancer	26 w / daily / o.a	40 mg	73	Completed
NCT01251354	II	Endometrial cancer	≥ 12 w / daily / o.a	40 mg	6	Terminated

A representative group of TReatment Adverse Events (TRAEs) are indicated in the table aside, in this study (NCT00910091) compared to the clinical pre-studied dose 40 mg.

The most common event in oncological patients were mild/moderate dry skin and asthenia

Results from NCT00910091 (Pautier et al. 2017)

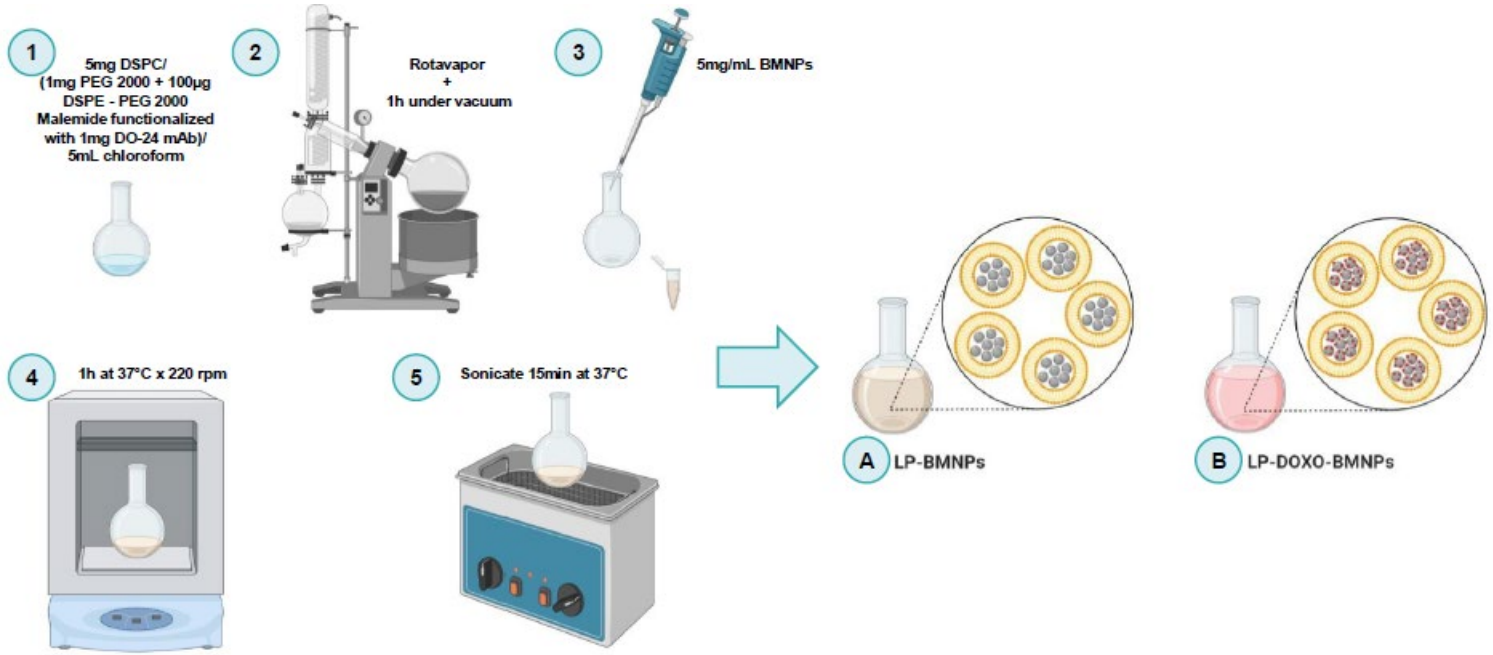
TABLE 3. Summary of TRAEs occurring in more than 1 patient by treatment group (safety population)*

	Irosustat 40 mg (N = 36) n (%)			Megestrol Acetate 160 mg (N = 35) n (%)		
	Total	Mild/Moderate†	Severe†	Total	Mild/Moderate†	Severe†
Patients experiencing any TRAEs	20 (55.6)	17 (47.2)	3 (8.3)	13 (37.1)	10 (28.6)	3 (8.6)
Dry skin	14 (38.9)	13 (36.1)	1 (2.8)	3 (8.6)	3 (8.6)	0
Asthenia	4 (11.1)	3 (8.3)	1 (2.8)	2 (5.7)	1 (2.9)	0
Fatigue	3 (8.3)	3 (8.3)	0	1 (2.9)	1 (2.9)	0
Constipation	3 (8.3)‡	2 (5.6)	0	0	0	0
Nausea	2 (5.6)	2 (5.6)	0	1 (2.9)	1 (2.9)	0
Vomiting	2 (5.6)	2 (5.6)	0	0	0	0
Muscle spasms	2 (5.6)	2 (5.6)	0	0	0	0
Headache	2 (5.6)	2 (5.6)	0	0	0	0
Hyponatremia	1 (2.8)	0	1 (2.8)	0	0	0
Hypertension	1 (2.8)	0	1 (2.8)	0	0	0
Hot flush	0	0	0	2 (5.7)	2 (5.7)	0
Dyspnea	0	0	0	2 (5.7)	2 (5.7)	0
Pulmonary embolism	0	0	0	2 (5.7)	0	2 (5.7)
Hyperglycemia	0	0	0	1 (2.9)	0	1 (2.9)

*All severe TRAEs reported.
†Mild/moderate defined as grade 1 or 2, severe defined as grade 3 or higher.
‡Severity of 1 result missing.

1. INTRODUCTION OF BIOMIMETIC MAGNETOLIPOSOMES

Synthesis of doxorubicin-functionalized biomimetic -magnetoliposomes as drug delivery systems *in vitro* and *in vivo*



Investigated the properties of a system based on BMNPs enveloped in liposomes, the so called magnetoliposomes (LP-BMNPs), functionalized with the chemotherapeutic drug doxorubicin (DOXO) and the ability to respond to a gradient magnetic field (GMF) in vitro and in vivo.

Suitability of the LP-BMNPs as magnetic nanocarriers for local targeted chemotherapy and for future agents for hyperthermia and photothermia paving the way for the development of powerful promising approaches for cancer therapy suggesting a tumour multiple attack by different combined strategies.

Scientific Guidelines on nanomedicines
Scientific Guidelines on liposomal products

Q: These guidelines?
Q: Something specific for magnetics?

academia@ema.europa.es

3. Regulatory petitions:

1. Intermediate advice service between SME and ITF

2. More integration (whenever is possible) between EMA and FDA in early phase clinical trials (Pre -IND meetings & EMA Scientific Advice) because parallel Scientific Advice meetings are more appropriate when the product is more advance.

3. More trainings in You Tube.

4. Need Small and Medium Size Enterprise Status at EMA for IVD/MDR https://www.ema.europa.eu/en/human -regulatory/overview/support -smes

5. Q-sub MDR (similar to FDA)