

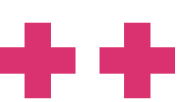


# Chemi@re<sup>++</sup>

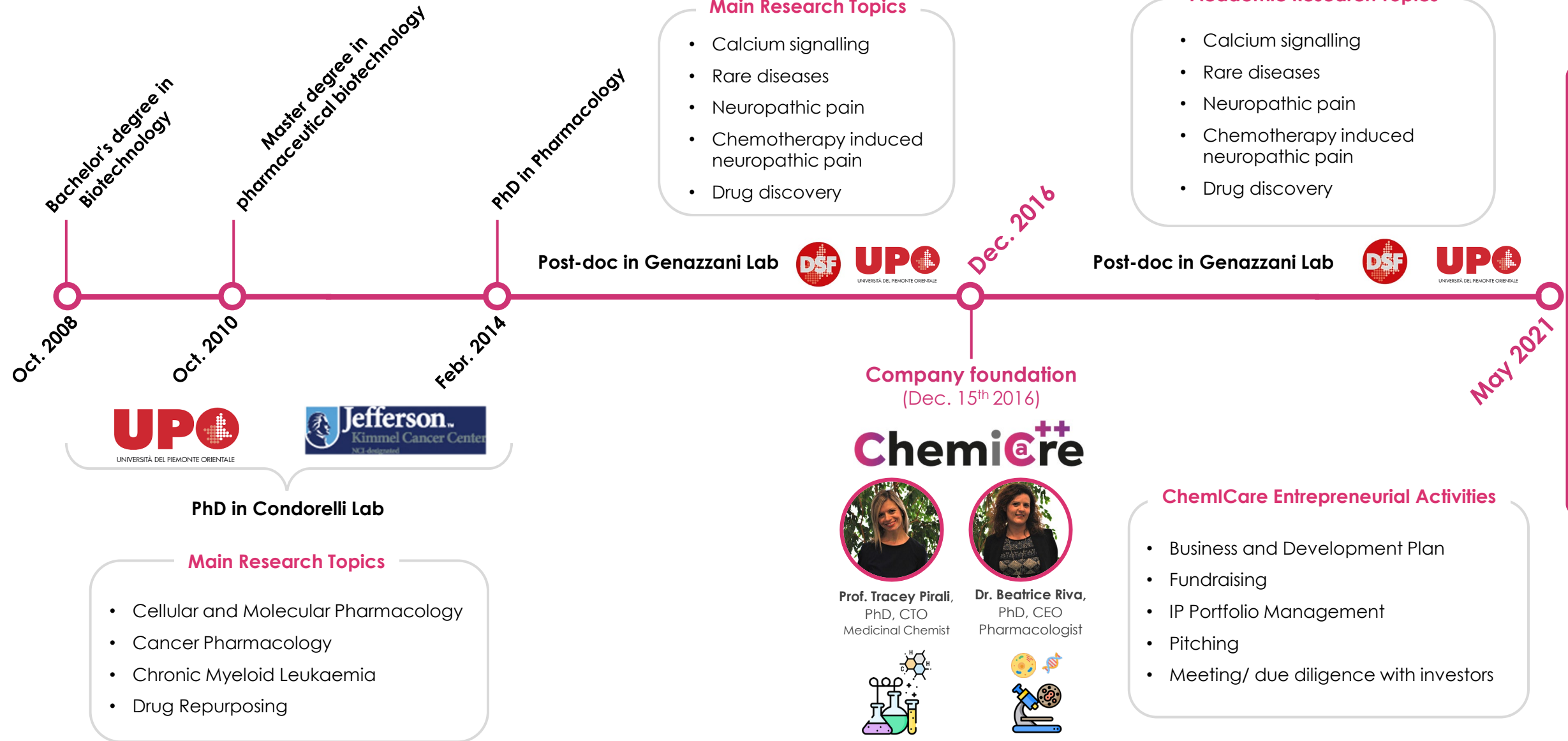
It's a rare thing to care

**Cutting-edge drugs for calcium-related diseases**

**Beatrice Riva**, PhD  
beatrice.riva@chemicare.it



# From UPO to ChemiCare



Full commitment in ChemiCare



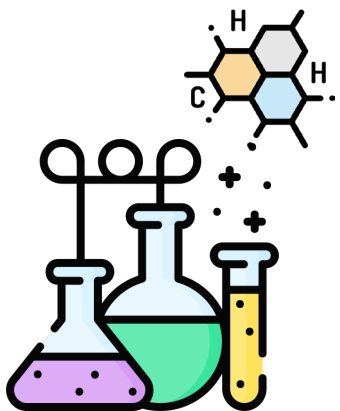
UNIVERSITÀ DEL PIEMONTE ORIENTALE



Dr. Tracey Pirali, PhD  
Medicinal Chemist



Dr. Beatrice Riva, PhD  
Pharmacologist



## ChemiCare++

- **Innovative Start-up**

Founded on December 15, 2016



- **Spin-off DSF, UPO**



- **Recognised SME from EMA**

EMA/SME/228/19/R3

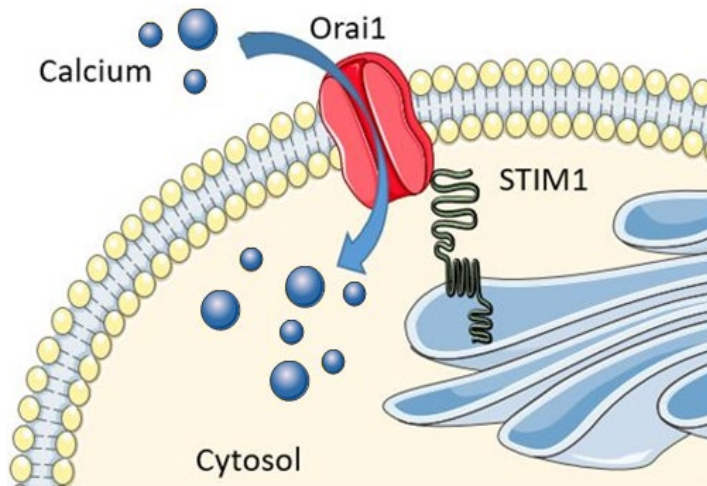


EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

### Mission

**New pharmacological therapies for  
calcium-related diseases**

## Store-operated Calcium entry (SOCE)



- **Ca<sup>2+</sup> influx mechanism** activated by depletion of **intracellular stores**
- Important mechanism in the **Ca<sup>2+</sup> homeostasis maintenance**

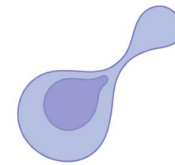
## Physiological Role of SOCE



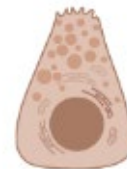
**Skeletal muscle:** Regulation of fiber formation



**Platelet activation**

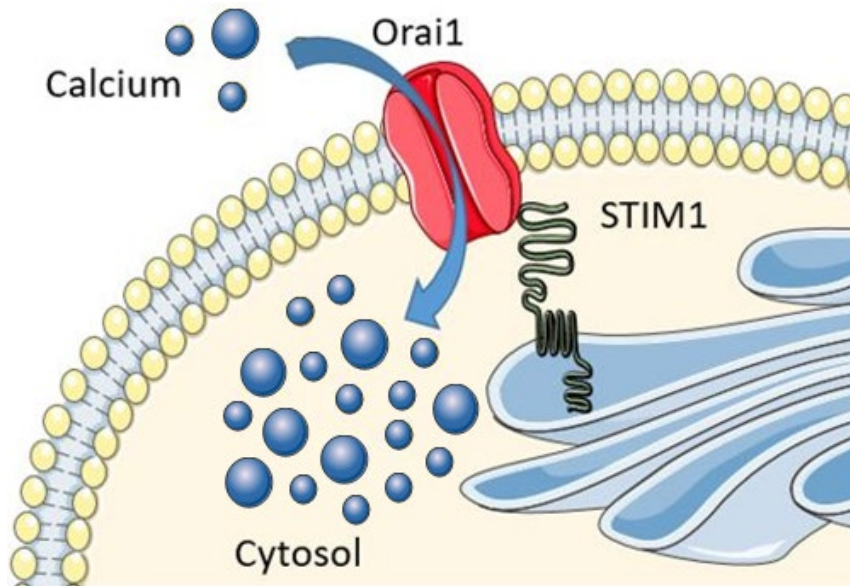


**Immune cells:** T cell differentiation



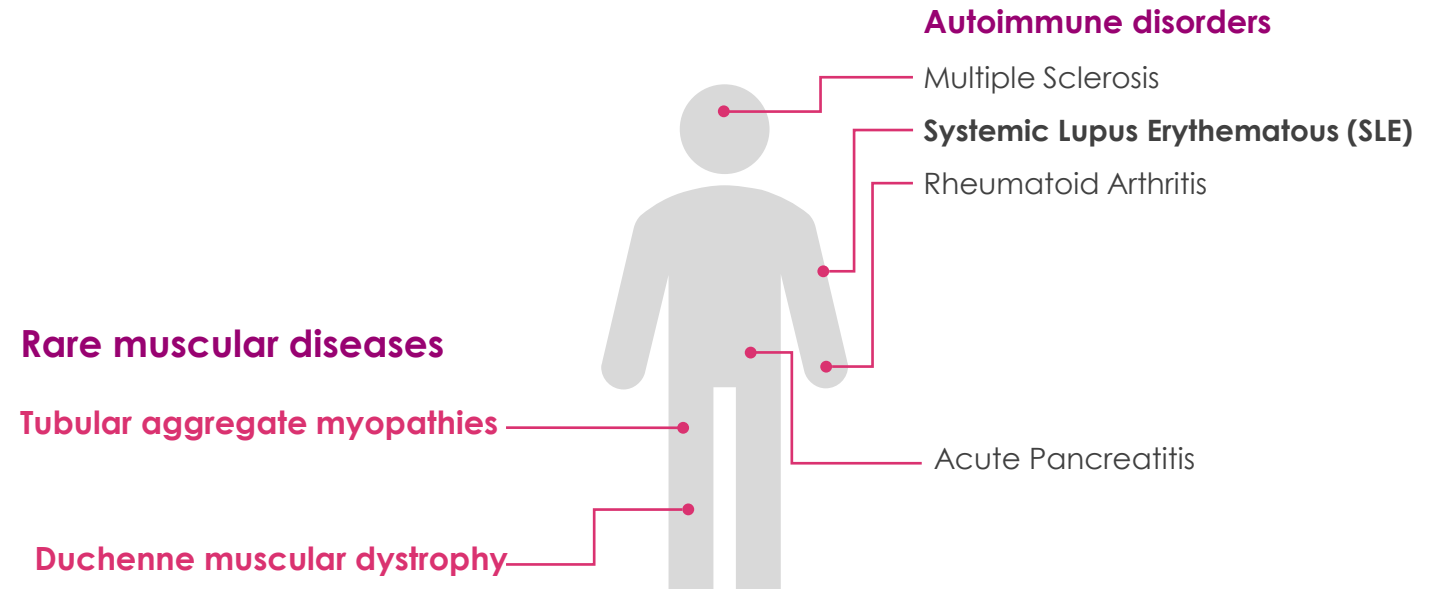
**Pancreatic acinar cells:** control of digestive enzyme secretion

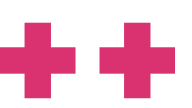
## SOCE over-activation



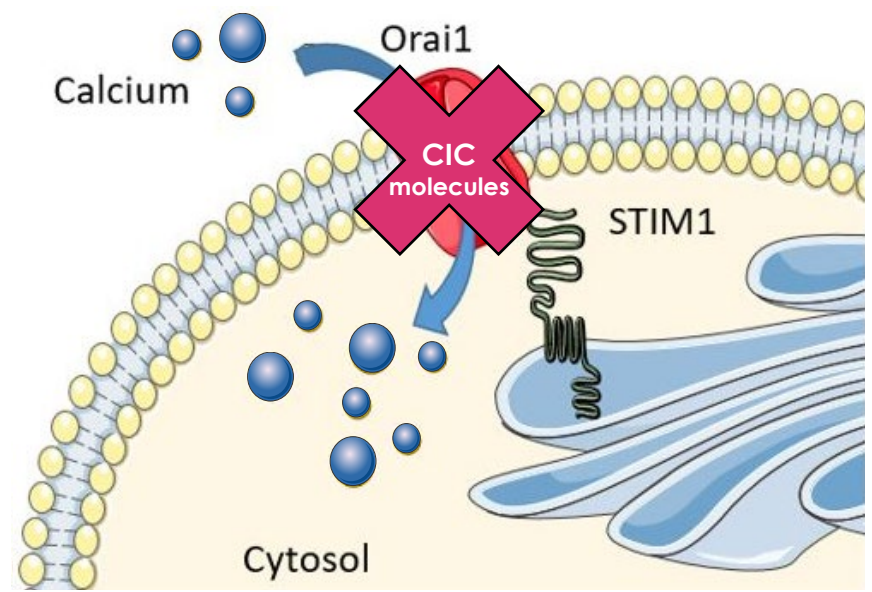
- **Ca<sup>2+</sup> influx mechanism** activated by depletion of **intracellular stores**
- Important mechanism in the **Ca<sup>2+</sup> homeostasis maintenance**

## Transversal mechanism in many disease contexts



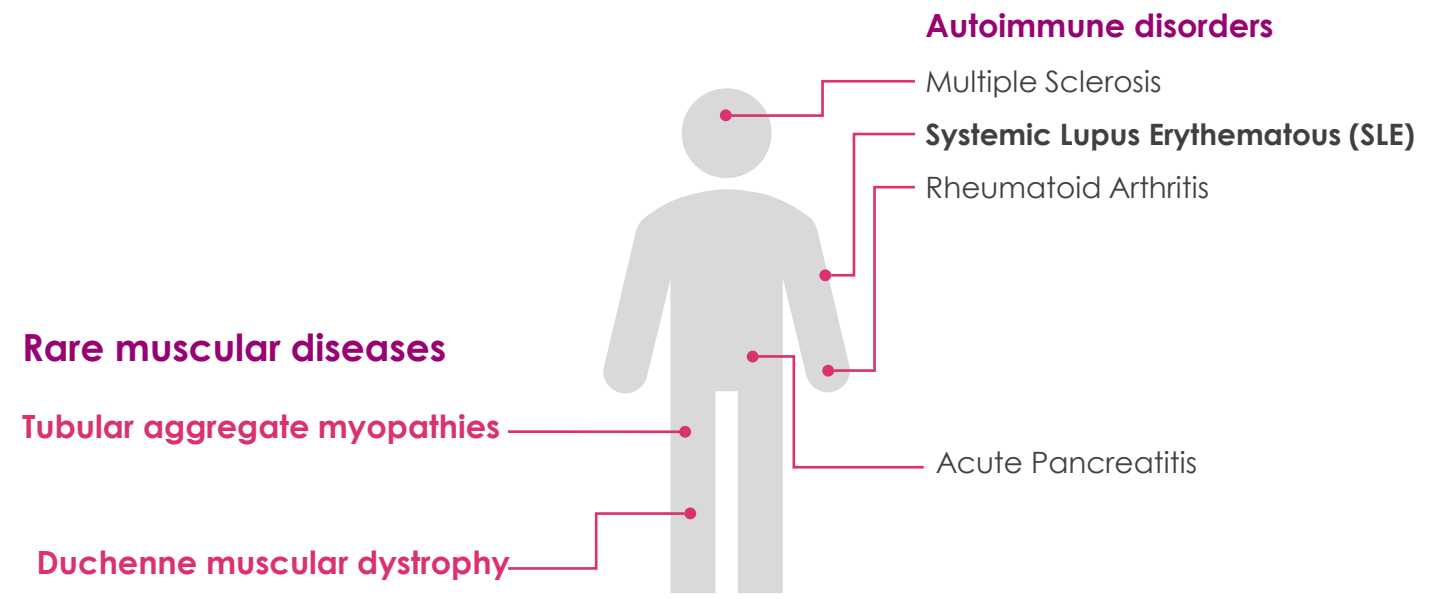


## Innovative mechanism of action



- Inhibition of overactivated SOCE
- Ca<sup>2+</sup> restored to physiological levels

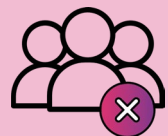
## Transversal mechanism in many disease contexts



- Novel target in pharmacology**
- Few SOCE modulators are in clinical trials
  - No SOCE modulator has reached regulatory approval

## Duchenne Muscular Dystrophy (DMD)

- **Rare disease**  
*Global prevalence 5/100,000 males.*
- **Lethal progressive** X-linked muscle disorder.
- Due to several mutation in the **dystrophin gene**.
- Characterized by progressive **muscle weakness, contractures, degeneration and wasting**.
- **Premature death** due to respiratory complications and heart failure.



### What's the Problem?

**NO absolute cure** currently available

- Severe adverse events (e.g., bone fragility)
- Small segment of patients

## Tubular Aggregate Myopathies (TAM)

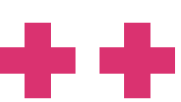
- **Cluster of rare genetic diseases**  
*Tubular aggregate myopathy, York & Stormorken syndromes*  
*Global prevalence 1/100,000.*
- Multi-organ, **progressive and chronic disorders** that mainly affect **muscle and platelet**.
- Due to several gain-of-function mutations in **STIM1** and **ORAI1** genes.
- Characterized by:
  - Painful **contractures** & **muscle degeneration**,
  - **Thrombocytopenia** & **abnormal bleeding**.



### What's the Problem?

**NO approved therapy** currently available

- No target therapies
- No real clinical benefit



> Hum Mol Genet. 2014 Jul 15;23(14):3706-15. doi: 10.1093/hmg/ddu079. Epub 2014 Feb 20.

## Enhanced Ca<sup>2+</sup> influx from STIM1-Orai1 induces muscle pathology in mouse models of muscular dystrophy

Sanjeeva A Goonasekera<sup>1</sup>, Jennifer Davis<sup>1</sup>, Jennifer Q Kwong<sup>1</sup>, Federica Accornero<sup>1</sup>, Lan Wei-LaPierre<sup>2</sup>, Michelle A Sargent<sup>1</sup>, Robert T Dirksen<sup>2</sup>, Jeffery D Molkentin<sup>3</sup>

> Arch Biochem Biophys. 2015 Mar 1;569:1-9. doi: 10.1016/j.abb.2015.01.025. Epub 2015 Feb 4.

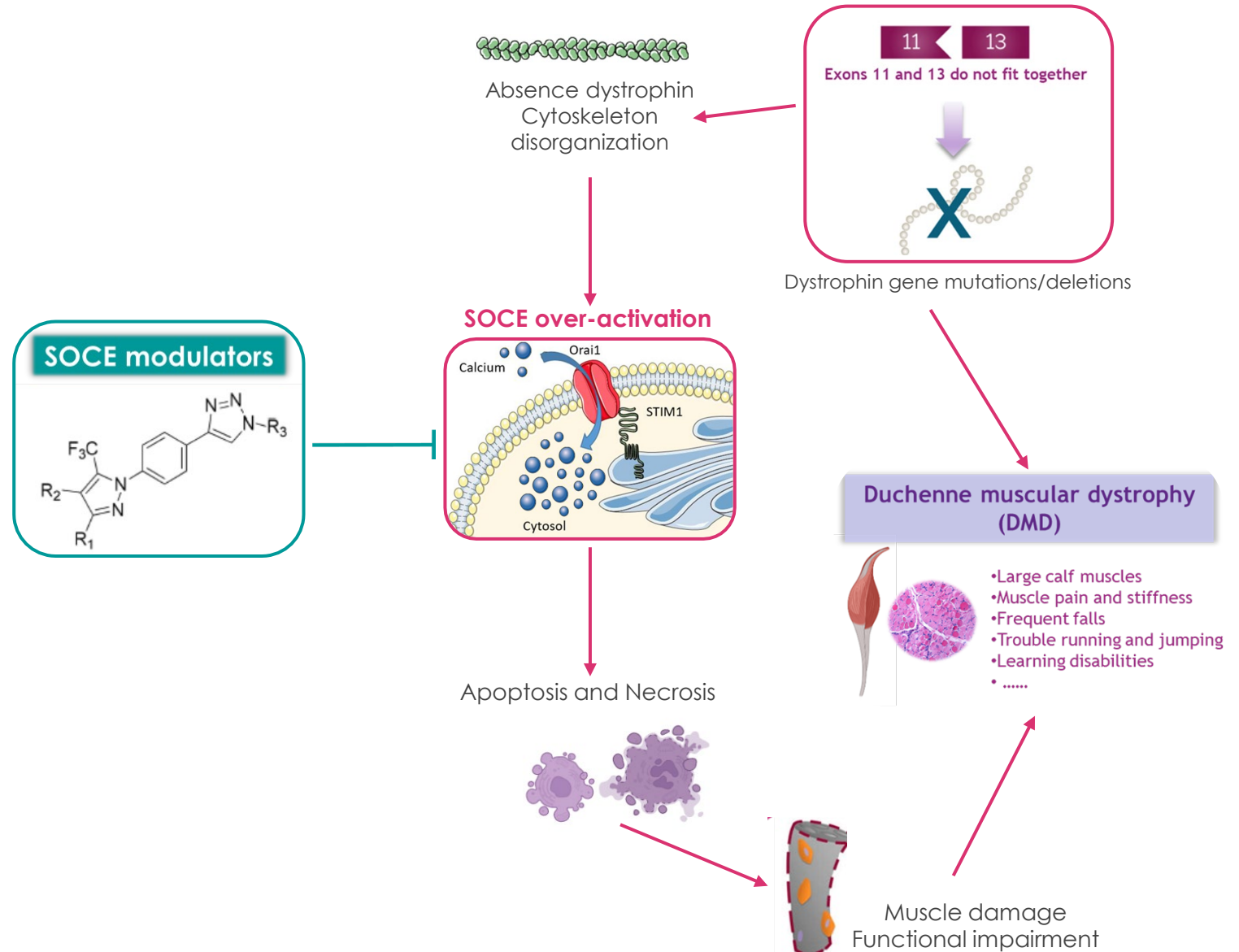
## Store-operated calcium entry contributes to abnormal Ca<sup>2+</sup> signalling in dystrophic mdx mouse myoblasts

Marta Onopiuk<sup>1</sup>, Wojciech Brutkowski<sup>2</sup>, Christopher Young<sup>3</sup>, Elżbieta Krasowska<sup>2</sup>, Justyna Róg<sup>4</sup>, Morten Ritso<sup>5</sup>, Sylwia Wojciechowska<sup>4</sup>, Stephen Arkle<sup>3</sup>, Krzysztof Zabłocki<sup>6</sup>, Dariusz C Górecki<sup>3</sup>

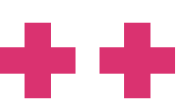
> J Gen Physiol. 2022 Sep 5;154(9):e202213081. doi: 10.1085/jgp.202213081. Epub 2022 Aug 8.

## Postdevelopmental knockout of Orai1 improves muscle pathology in a mouse model of Duchenne muscular dystrophy

Maricela García-Castañeda<sup>1</sup>, Antonio Michelucci<sup>1,2</sup>, Nan Zhao<sup>1</sup>, Sundeep Malik<sup>1</sup>, Robert T Dirksen<sup>1</sup>







# SOCE: Novel Target for TAM Treatment

Review > Ann N Y Acad Sci. 2015 Nov;1356(1):45-79. doi: 10.1111/nyas.12938. Epub 2015 Oct 15.

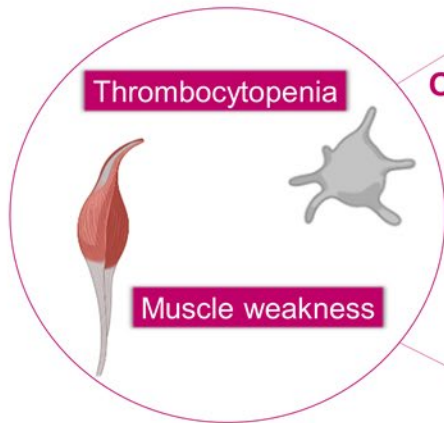
## Diseases caused by mutations in ORAI1 and STIM1

Rodrigo S Lacruz<sup>1</sup>, Stefan Feske<sup>2</sup>

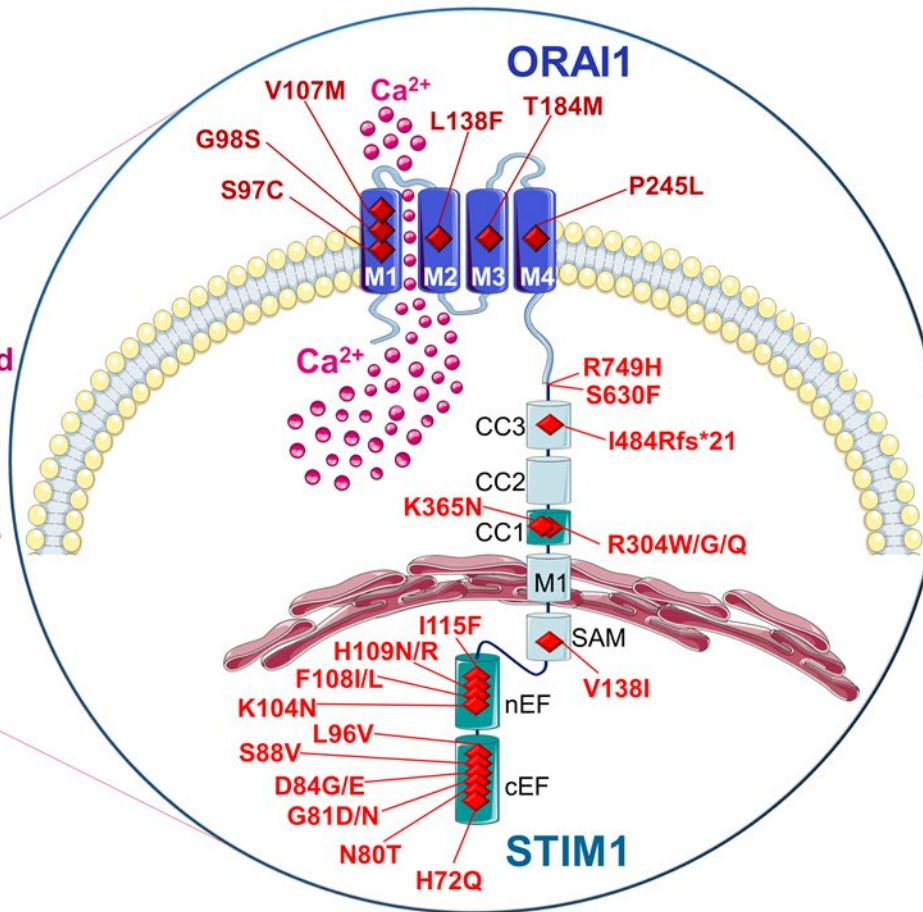
### STIM1/ORAI1 gain-of-function mutations

#### Tubular aggregate myopathies

Tubular aggregate myopathy  
York platelet syndrome  
Stormorken syndrome



Overactivated SOCE  
Ca<sup>2+</sup>

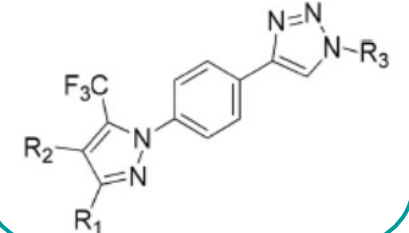


Review > Hum Mutat. 2020 Jan;41(1):17-37. doi: 10.1002/humu.23899. Epub 2019 Sep 15.

## Tubular aggregate myopathy and Stormorken syndrome: Mutation spectrum and genotype/phenotype correlation

Gilles Morin<sup>1 2 3</sup>, Valérie Biancalana<sup>3 4 5 6 7</sup>, Andoni Echaniz-Laguna<sup>8 9 10</sup>, Jean-Baptiste Noury<sup>11</sup>, Xavière Lornage<sup>3 4 5 6</sup>, Maurizio Moggio<sup>12</sup>, Michela Ripolone<sup>12</sup>, Raffaella Violano<sup>12</sup>, Pascale Marcocelles<sup>13</sup>, Denis Maréchal<sup>11</sup>, Florence Renaud<sup>14</sup>, Claude-Alain Maurage<sup>14</sup>, Céline Tard<sup>15</sup>, Jean-Marie Cuisset<sup>16</sup>, Jocelyn Laporte<sup>3 4 5 6</sup>, Johann Böhm<sup>3 4 5 6</sup>

#### SOCE modulators



Ca<sup>2+</sup>

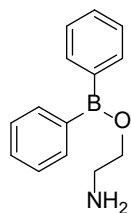


# ChemiCare Solution: Novel SOCE Modulators

## Known SOCE Modulators

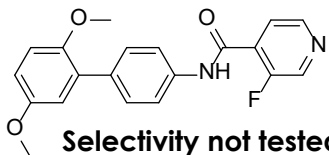
Lanthanides ( $Gd^{3+}$ ,  $La^{3+}$ ) → Multiple mechanisms

2-APB

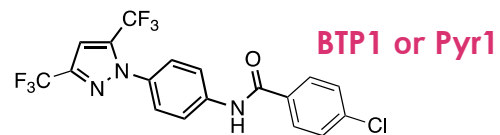


- Complex mechanism
- Not very selective

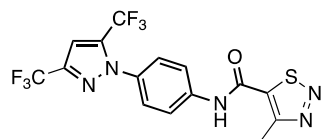
Synta66



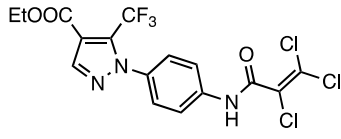
Selectivity not tested



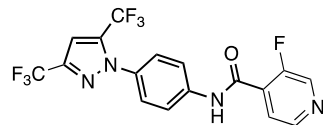
BTP2 or Pyr2



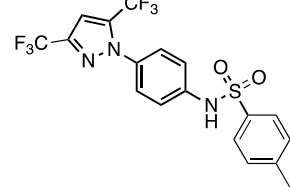
Pyr3



Pyr6



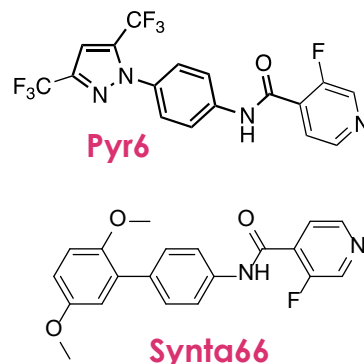
Pyr10



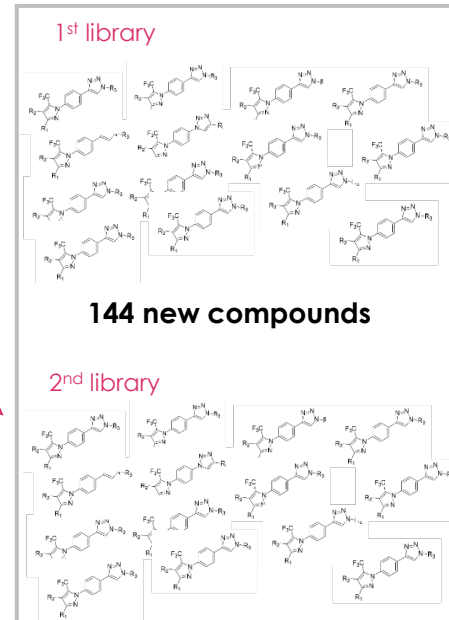
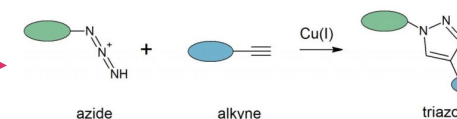
Cytotoxic

Not very selective

## Novel SOCE Modulators



Click Chemistry



ChemiCare<sup>++</sup>

First Patent\*

«Modulators of SOCE, compositions and use thereof»

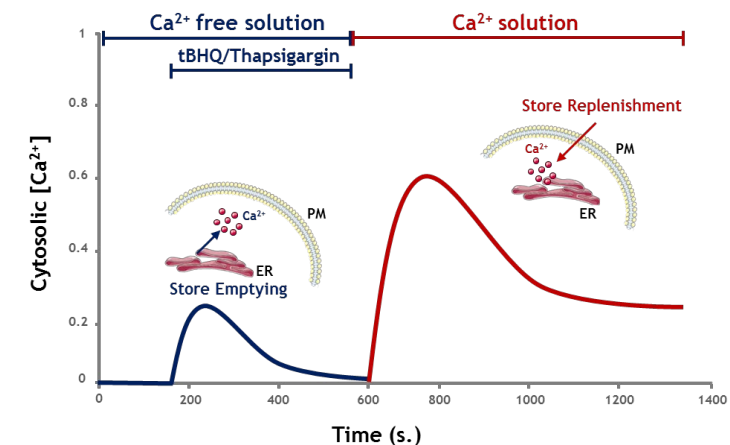
WO 2017/212414 A1

ChemiCare<sup>++</sup>

Second Patent\*

«Biphenyl compounds as SOCE modulators, compositions and uses thereof»

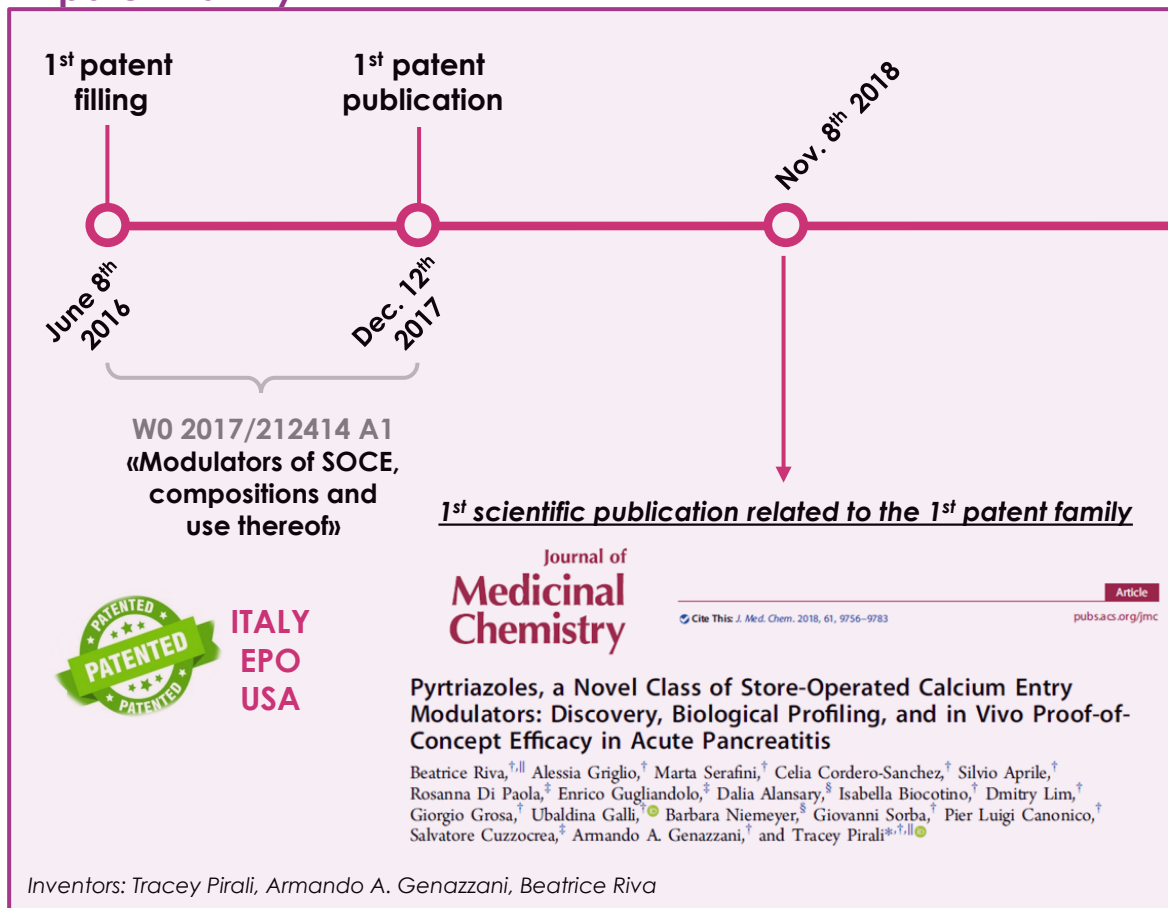
WO2021/165735 A1



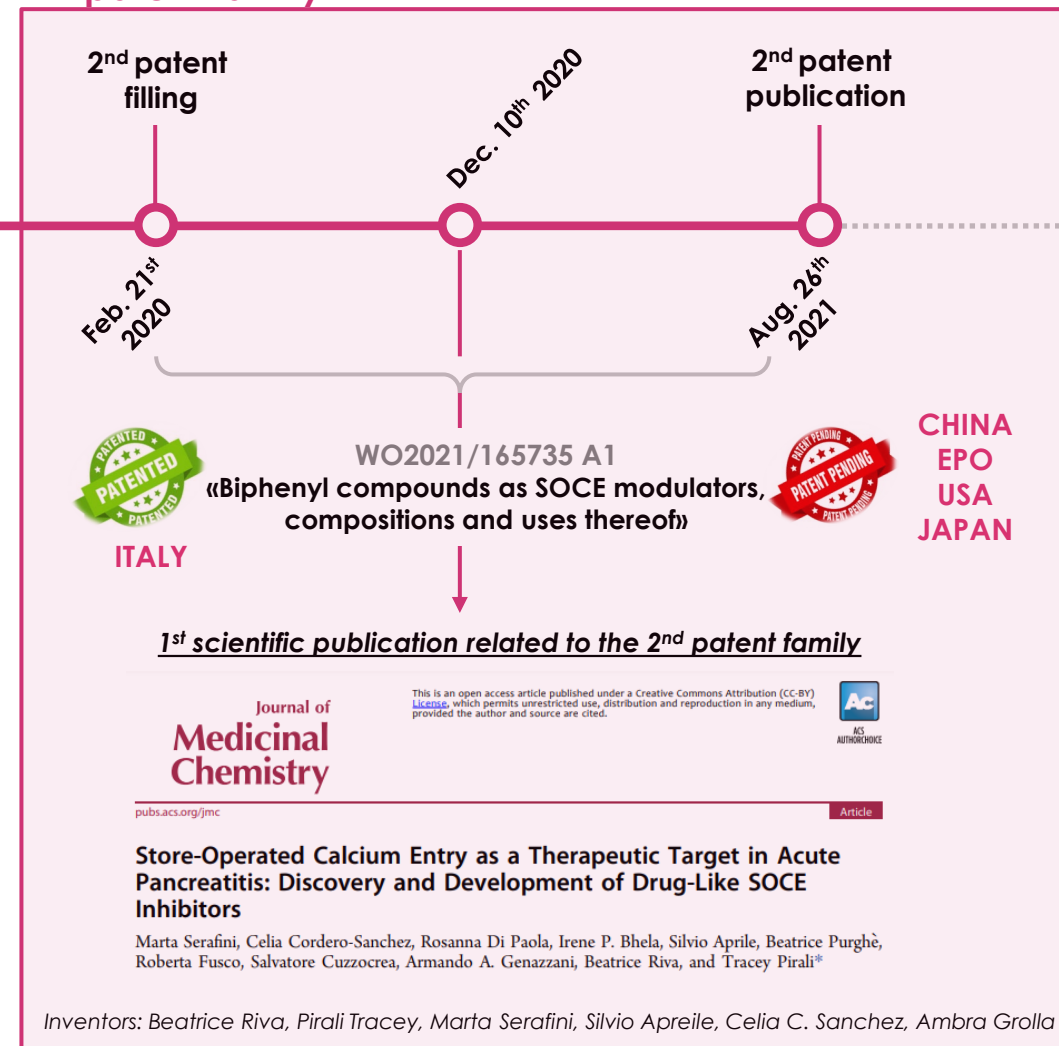
# Patents & Scientific Publications: UPO – ChemiCare Agreements

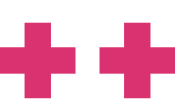
- Patents were filed by the University of Piemonte Orientale (UPO)
- **ChemiCare holds exclusive, patent life-long exploitation license** rights on filed patents

## 1<sup>st</sup> patent family



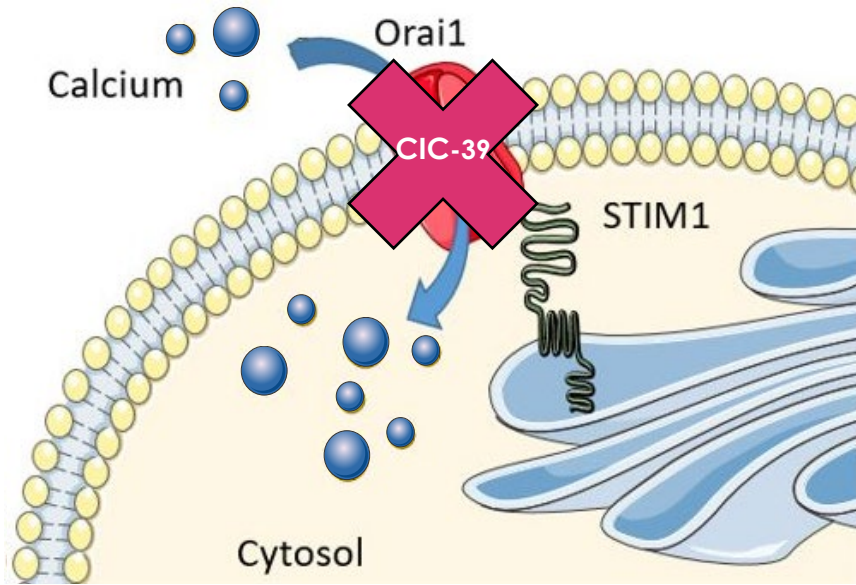
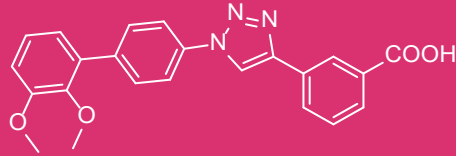
## 2<sup>nd</sup> patent family





# Our Lead Compound CIC-39

CIC-39



- Inhibition of overactivated SOCE
- Ca<sup>2+</sup> restored to physiological levels

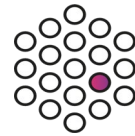
## Lead Compound CIC-39

High potency (nM) range



IC<sub>50</sub> 800 nM  
SOCE inhibition 96.5%±2.4% at 3 µM

High selectivity for SOCE channels



e.g., No inhibition of  
VOCCs, TRPM8, TRPV1

Good pharmacokinetic profile  
and metabolic stability



t<sub>1/2</sub> = 10.3 h  
C<sub>max</sub> = 16248.79 µg/L  
H<sub>2</sub>O solubility = 3550.5 mg/L  
MTD > 300 mg/Kg  
(100x predicted human dosage)

Good safety profile

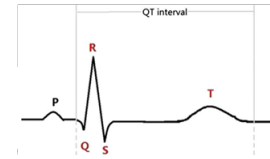
No genotoxic and mutagenic



- No micronuclei induction in human lymphocytes
- No induction of reverse mutation by Ames test



No cardiotoxic (hERG channel test)



No significant inhibition of hERG channel  
(only 2% at 1 µM)



Good bioavailability

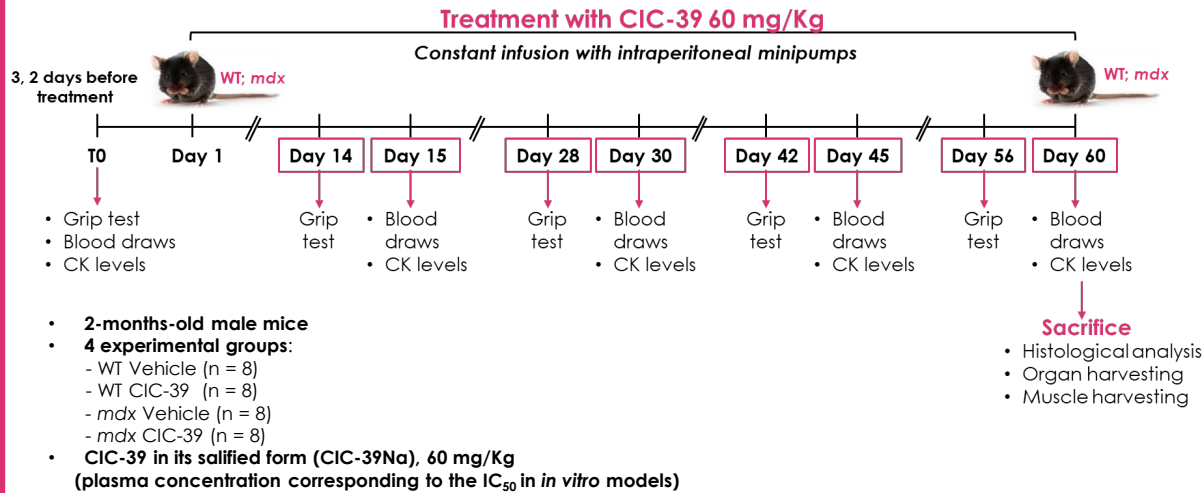
(comparative pharmacokinetic studies in rats and minipigs)



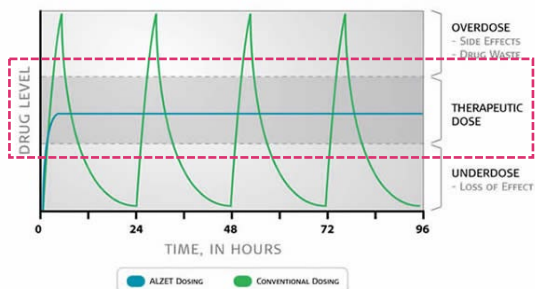
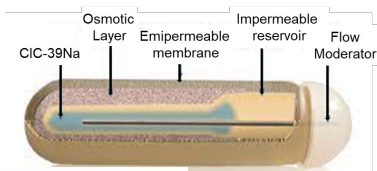
Oral Bioavailability of about 80.8%

Comparative pharmacokinetic analysis based on intravenous and oral administration

## *in vivo* Study Design

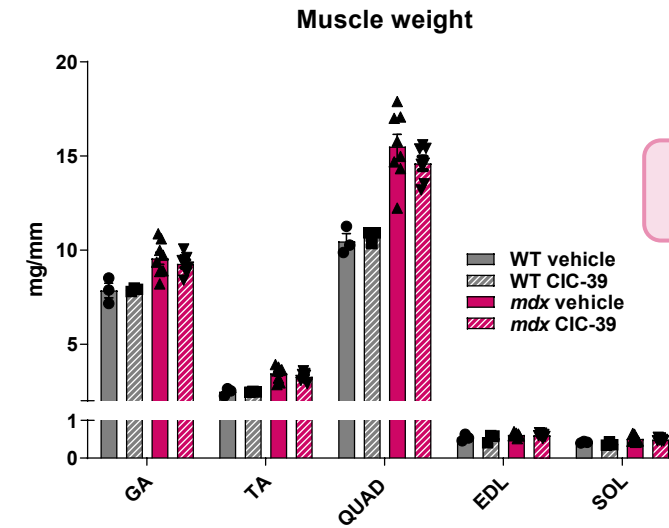


## Micropump drug delivery

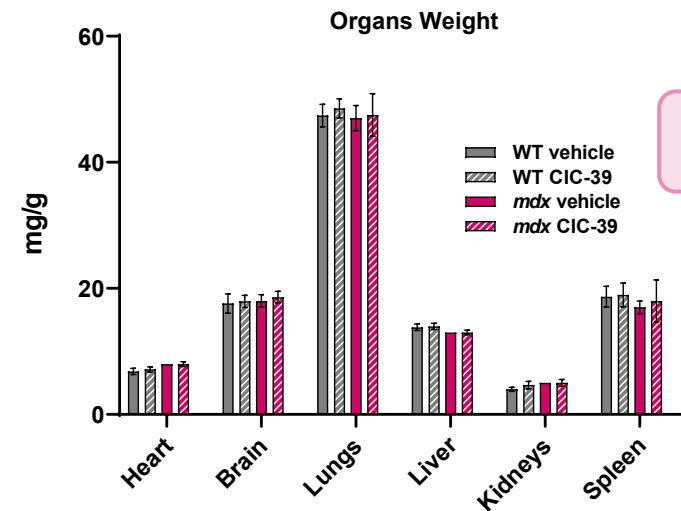


- **Continuous and controlled delivery**
- **Constant dosage** (no overdose/ underdose)
- **No external connections**
- **No frequent animal handling**

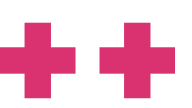
## CIC-39 tolerability



CIC-39 does not affect muscle weight

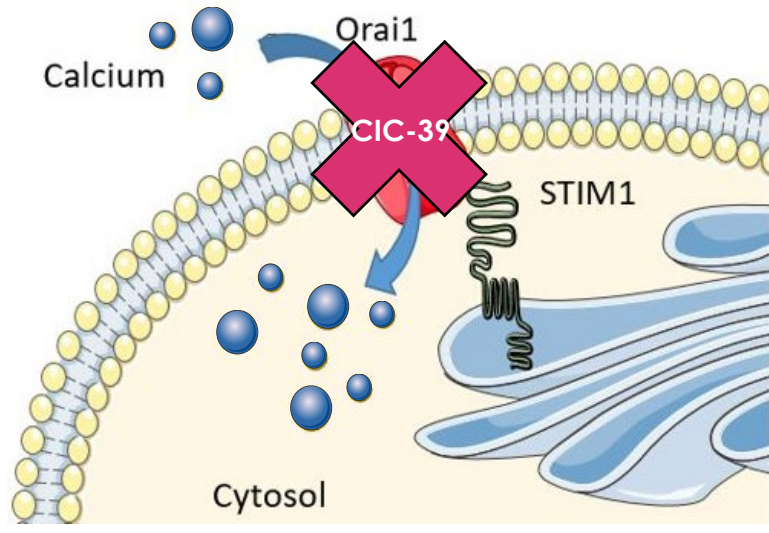


CIC-39 does not affect organ weight



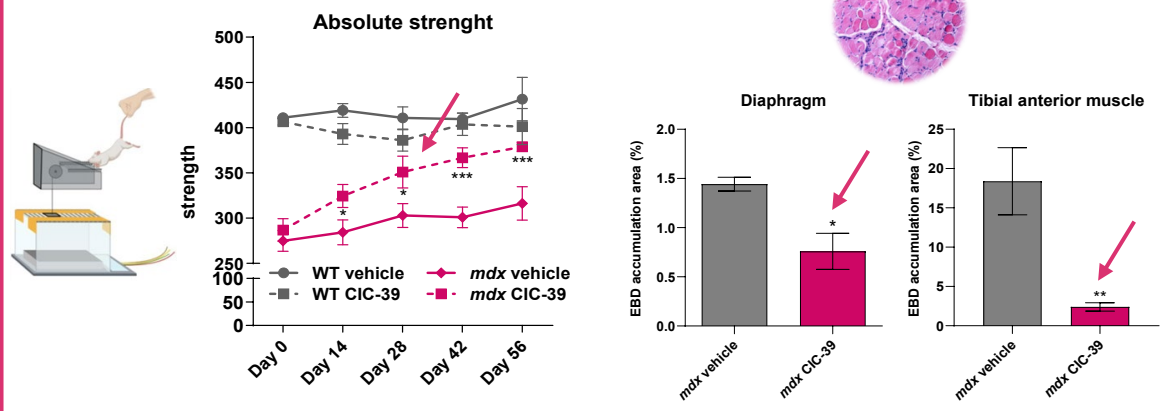
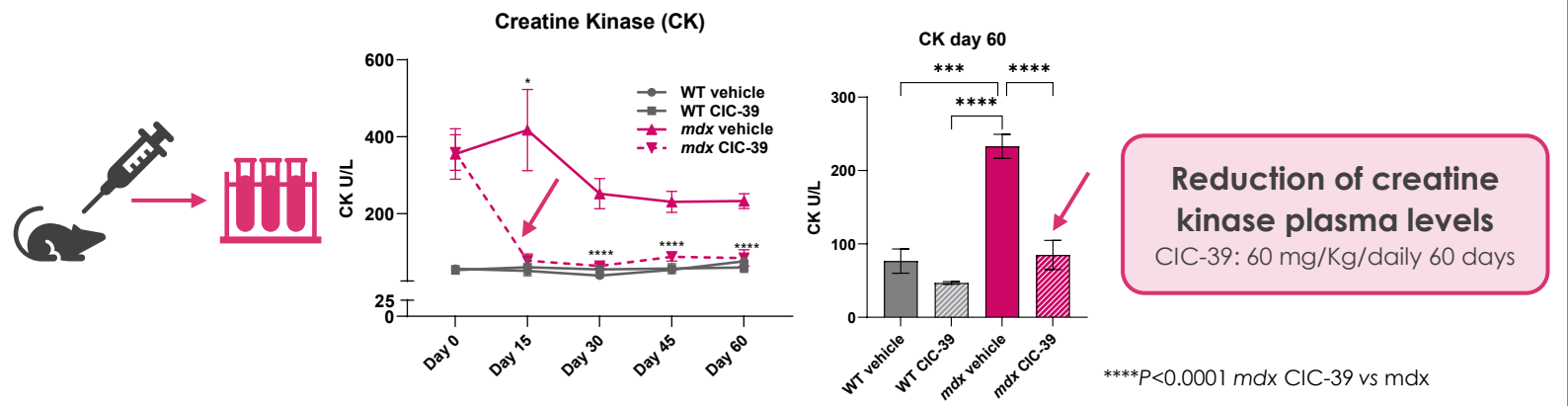
# CIC-39: Efficacy in DMD – *in vivo* Experiments

## Mechanism of action



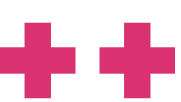
- Inhibits over-activated SOCE
- Restores Ca<sup>2+</sup> to physiological levels

## CIC-39 *in vivo* efficacy



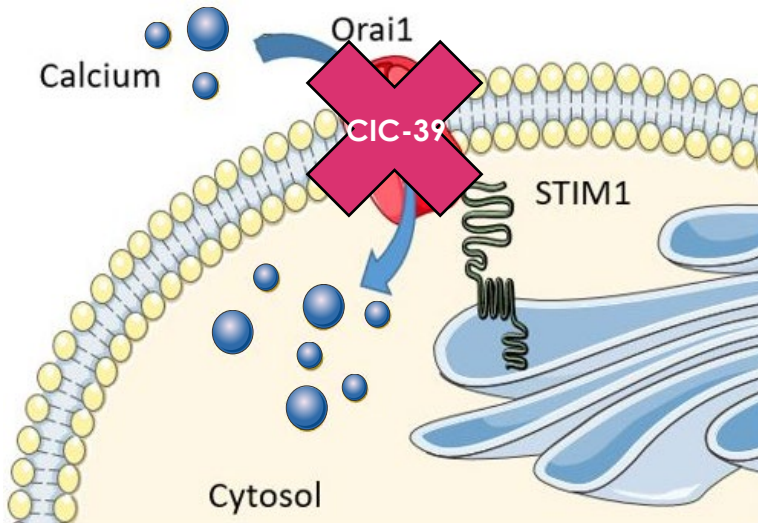
\*P=0.0027; \*\*\*P=0.0001 mdx CIC-39 vs mdx



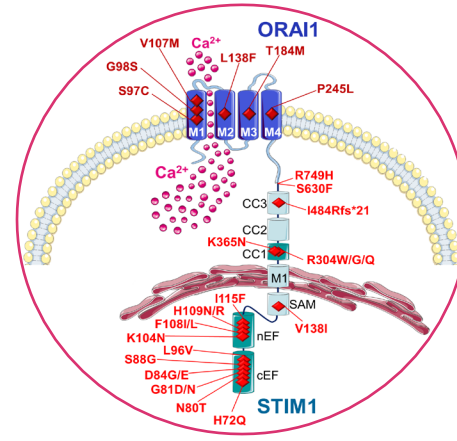


# CIC-39: Efficacy in TAM – *in vivo* Experiments

## Mechanism of action



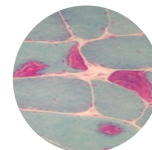
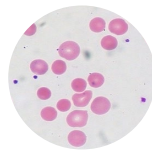
- Inhibits over-activated SOCE
- Restores  $Ca^{2+}$  to physiological levels



SOCE overactivation

Thrombocytopenia  
Abnormal Bleeding

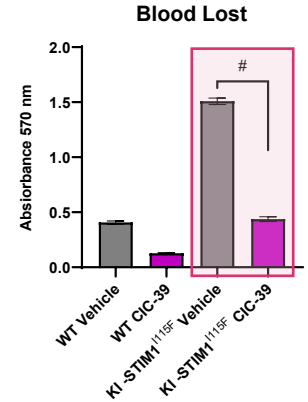
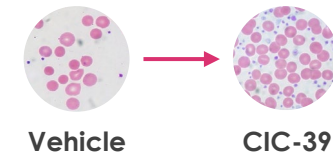
Muscle stiffness  
Painful Cramps



## Tubular Aggregate Myopathies

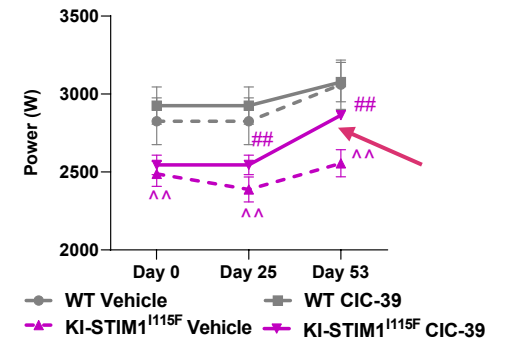
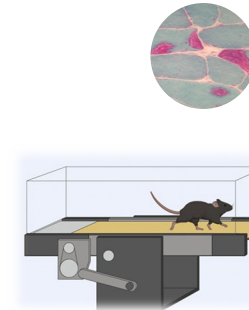
### Reduction of blood loss

CIC-39: 60 mg/Kg/daily 15 days



### Decrease of muscle damage

CIC-39: 60 mg/Kg/daily 56 days



Case Reports > Clin Genet. 2017 May;91(5):780-786. doi: 10.1111/cge.12888. Epub 2016 Nov 23.

## A novel gain-of-function mutation in ORAI1 causes late-onset tubular aggregate myopathy and congenital miosis

M Garibaldi<sup>1,2</sup>, F Fattori<sup>3</sup>, B Riva<sup>4</sup>, C Labasse<sup>5</sup>, G Brochier<sup>5</sup>, P Ottaviani<sup>6</sup>, S Sacconi<sup>2</sup>, E Vizzaccaro<sup>1</sup>, F Laschena<sup>6</sup>, N B Romero<sup>5</sup>, A Genazzani<sup>4</sup>, E Bertini<sup>3</sup>, G Antonini<sup>1</sup>

> Muscle Nerve. 2021 Nov;64(5):567-575. doi: 10.1002/mus.27391. Epub 2021 Aug 26.

## Expanding the clinical and genetic spectrum of pathogenic variants in STIM1

Chiara Ticci<sup>1,2</sup>, Denise Cassandrini<sup>1</sup>, Anna Rubegni<sup>1</sup>, Beatrice Riva<sup>3</sup>, Gaetano Vattermi<sup>4</sup>, Sabrina Matà<sup>5</sup>, Giulia Ricci<sup>6</sup>, Jacopo Baldacci<sup>1,7</sup>, Valeria Guglielmi<sup>4</sup>, Antonio Di Muzio<sup>8</sup>, Alessandro Malandrini<sup>9</sup>, Paola Tonin<sup>4</sup>, Gabriele Siciliano<sup>6</sup>, Antonio Federico<sup>9</sup>, Armando A Genazzani<sup>3</sup>, Filippo M Santorelli<sup>1</sup>, Luciano Merlini<sup>10</sup>

> Cell Calcium. 2022 Jul;105:102605. doi: 10.1016/j.ceca.2022.102605. Epub 2022 May 18.

## STIM1 and ORAI1 mutations leading to tubular aggregate myopathies are sensitive to the Store-operated Ca<sup>2+</sup>-entry modulators CIC-37 and CIC-39

Beatrice Riva<sup>1</sup>, Emanuela Pessolano<sup>1</sup>, Edoardo Quaglia<sup>1</sup>, Celia Cordero-Sanchez<sup>1</sup>, Irene P Bhela<sup>1</sup>, Ana Topf<sup>2</sup>, Marta Serafini<sup>1</sup>, Daniel Cox<sup>2</sup>, Elizabeth Harris<sup>2</sup>, Matteo Garibaldi<sup>3</sup>, Rita Barresi<sup>4</sup>, Tracey Piralì<sup>1</sup>, Armando A Genazzani<sup>5</sup>

> Dis Model Mech. 2019 Dec 3;13(2):dmm041111. doi: 10.1242/dmm.041111.

## A luminal EF-hand mutation in STIM1 in mice causes the clinical hallmarks of tubular aggregate myopathy

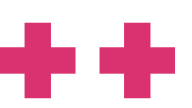
Celia Cordero-Sanchez<sup>1</sup>, Beatrice Riva<sup>1</sup>, Simone Reano<sup>2</sup>, Nausicaa Clemente<sup>2</sup>, Ivan Zaggia<sup>2</sup>, Federico A Ruffinatti<sup>1</sup>, Alberto Potenzieri<sup>1</sup>, Tracey Piralì<sup>1</sup>, Salvatore Raffa<sup>3</sup>, Sabina Sangaletti<sup>4</sup>, Mario P Colombo<sup>4</sup>, Alessandra Bertoni<sup>2</sup>, Matteo Garibaldi<sup>5</sup>, Nicoletta Filigheddu<sup>6</sup>, Armando A Genazzani<sup>7</sup>

> Blood Adv. 2022 Aug 9;6(15):4471-4484. doi: 10.1182/bloodadvances.2021006378.

## CIC-39Na reverses the thrombocytopenia that characterizes tubular aggregate myopathy

Celia Cordero-Sanchez<sup>1</sup>, Emanuela Pessolano<sup>1</sup>, Beatrice Riva<sup>1</sup>, Mauro Vismara<sup>2</sup>, Silvia Maria Grazia Trivigno<sup>2,3</sup>, Nausicaa Clemente<sup>4</sup>, Silvio Aprile<sup>1</sup>, Federico Alessandro Ruffinatti<sup>1</sup>, Paola Portararo<sup>5</sup>, Nicoletta Filigheddu<sup>4</sup>, Ivan Zaggia<sup>4</sup>, Irene P Bhela<sup>1</sup>, Marta Serafini<sup>1</sup>, Tracey Piralì<sup>1</sup>, Mario P Colombo<sup>5</sup>, Mauro Torti<sup>2</sup>, Sabina Sangaletti<sup>5</sup>, Alessandra Bertoni<sup>4</sup>, Armando A Genazzani<sup>1</sup>





# Market Figures and Entry Advantage

## Orphan Drug Designation



### Duchenne Muscular Dystrophy

December 8<sup>th</sup>, 2022 from EMA

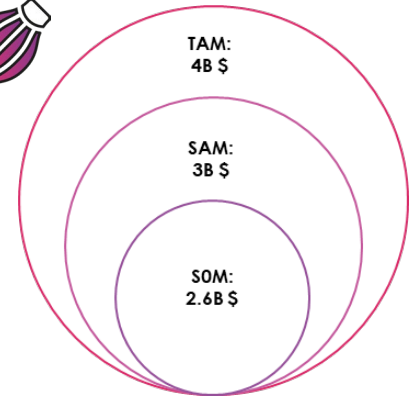


### Tubular Aggregate Myopathies

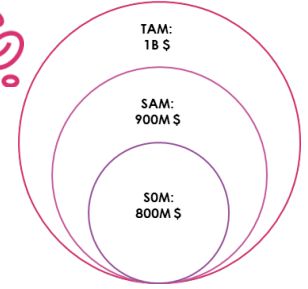
May 22<sup>th</sup>, 2022 from EMA

## Rare Muscular Diseases

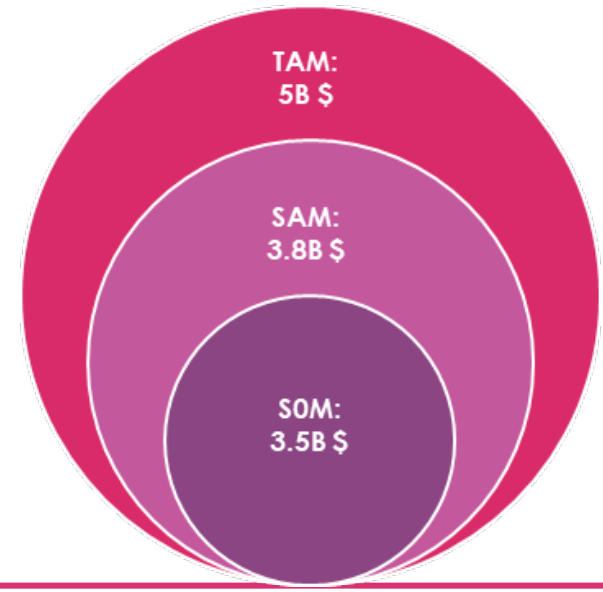
### Duchenne Muscular Dystrophy

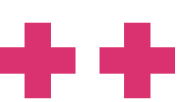


### Tubular Aggregate Myopathies



### Total Values





# Competitive Assessment in DMD and TAM



## Duchenne muscular dystrophy

### State of the Art

Corticosteroids (*off-label*)  
 Antisense oligonucleotides  
 Translarna (ataluren)  
 Gene therapy (Elevidys)

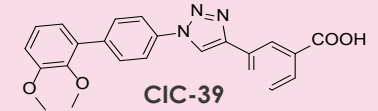
Gene therapy  
 Small molecules (givinostat)  
 Cell therapy  
 Monoclonal antibody

### Drug Weakness

**Severe Side-effects**  
**Small** segment of **patients**  
**Compromised compliance**

**Long term safety risk**  
**Small** segment of **patients**  
**Route of administration**  
**Compromised compliance**

### Chemi@re<sup>++</sup> Strength



**Safe** with moderate or none side-effects

**Effective for all patients**

**Oral administration**



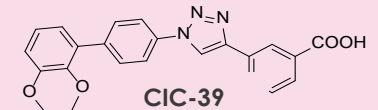
## Tubular aggregate myopathies

Corticosteroids  
 Pregabalin  
 Duloxetine  
 Amitriptyline

None

**Symptomatic** treatments  
**Not effective therapies**  
**No approved therapy**  
**No drugs** in clinical trial

None

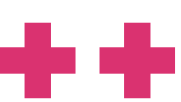


**First disease modifying therapy**

Counteracts **the cause**

**Effective** for all patients

 On Market     In Clinical Trials



# Potential Competitors – SOCE inhibitors

Drug	Company	Therapeutic indication	Phase	Status	Reference
CM4620 (Auxora)	CalciMedica	Acute pancreatitis	II	Completed	NCT03709342 NCT03401190
CM4620 (Auxora)	CalciMedica	Acute pancreatitis and systemic inflammatory response syndrome (SIRS)	I II	Recruiting	NCT04195347 NCT04681066 Bruen C., et al. 2021
CM4620 (Auxora)	CalciMedica	Severe COVID-19 Pneumonia	II	Completed	NCT04345614 Miller J., et al. 2020
RP3128	Rizhen Pharmaceuticals	Asthma	II	Terminated (Significant recruitment delay in POC part)	NCT02958982 Barde J., et al. 2021
RP4010	Rizhen Pharmaceuticals	Relapsed or refractory lymphomas	I/Ib	Terminated (Study stopped after reviewing PK and safety results)	NCT03119467
PRCL-02	PRCL Research Inc.	Plaque psoriasis	I/IIa	Completed	NCT03062618 NCT03614078

## CIC-39 vs CM4620



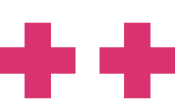
**> Selectivity**  
for SOCE channels



**< Cytotoxicity**  
in acute and chronic conditions



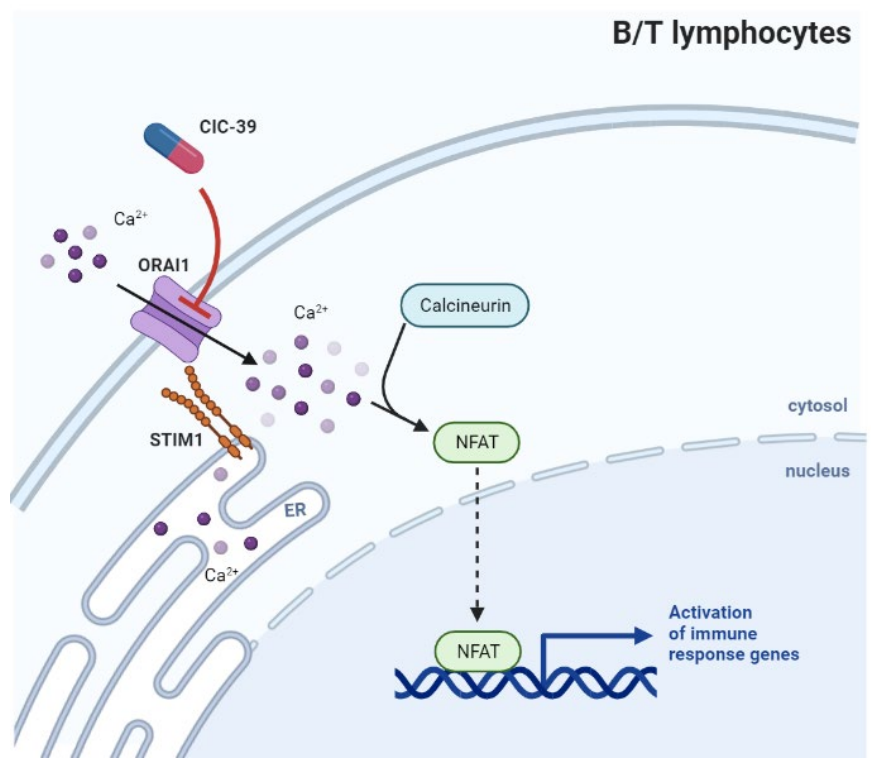
**> Solubility**  
in physiological solution



# Future Pipeline Extension: Autoimmune and Inflammatory Disorders

## The same target...

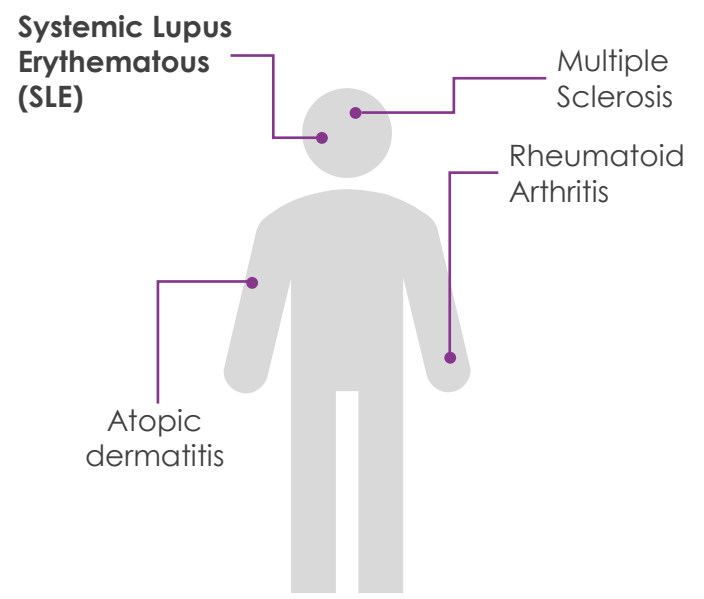
Store operated calcium entry (SOCE)



- Inhibits over-activated SOCE
- Blocks lymphocytes activation

## ...for multiple indications

Autoimmune and Inflammatory Disorders

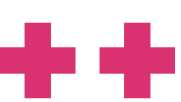


- Disease modifying therapy (DMT)
- New pharmacological target

Disease	Incidence	Addressable market
<b>Lupus*</b>	6.25/100,000 (global)	<b>1.8 B€</b>
SM*	35.9/100,000 (global)	7 B€
RA*	66.9/100,000 (women, 8MM)	4 B€
AD*	84.51/100,000 (global)	7.8 B€

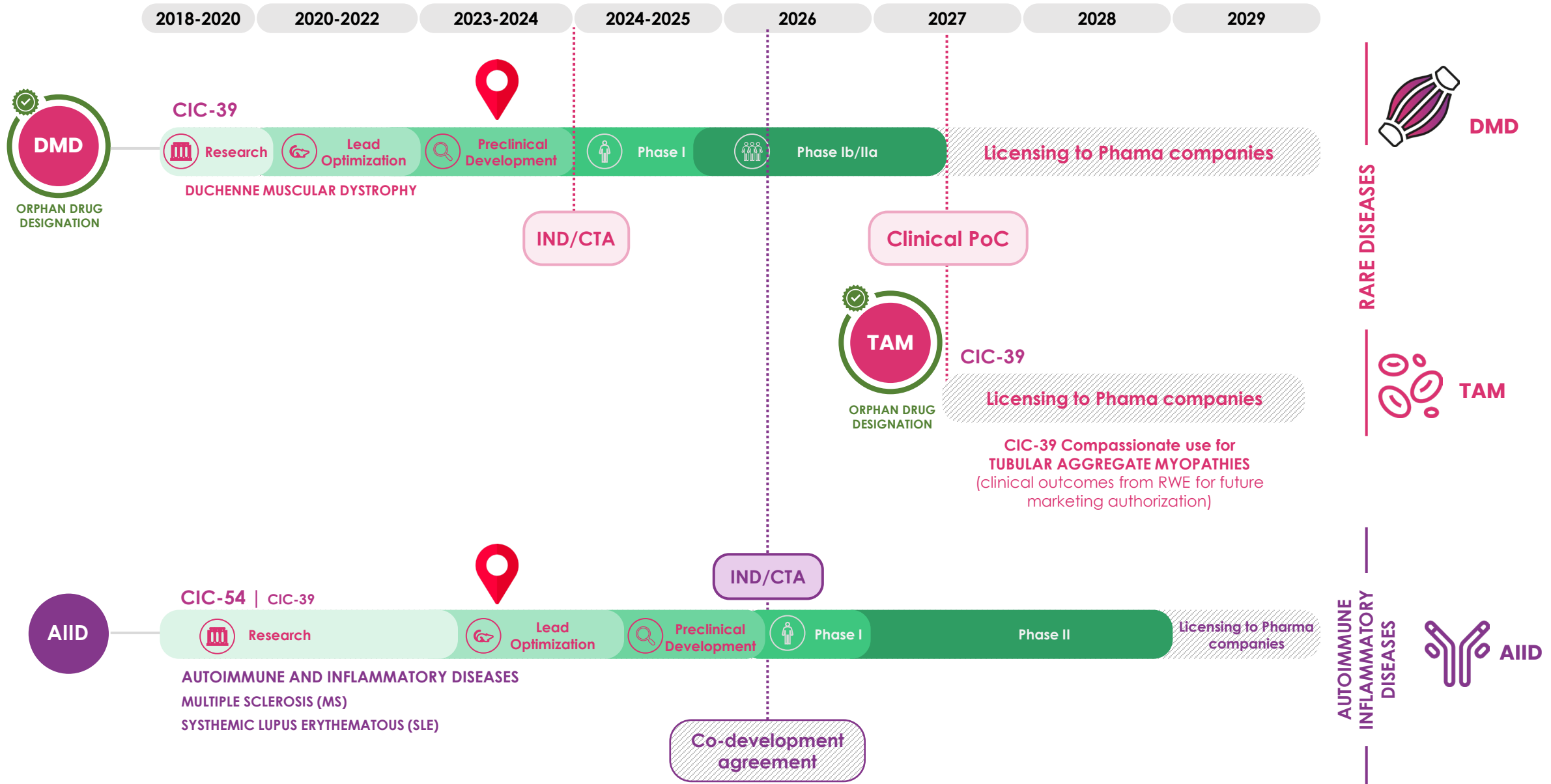
\*SM: calculated on 50% of current oral drug market; RA: calculated on 21% of total drug market; Lupus calculated on 70% of totale drug market; AD: calculated on 50% of current oral drug market. Source: GlobalData

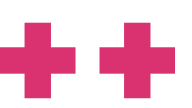
- No secondary-immunodeficiency
- Cellular recovery (e.g., synoviocytes)



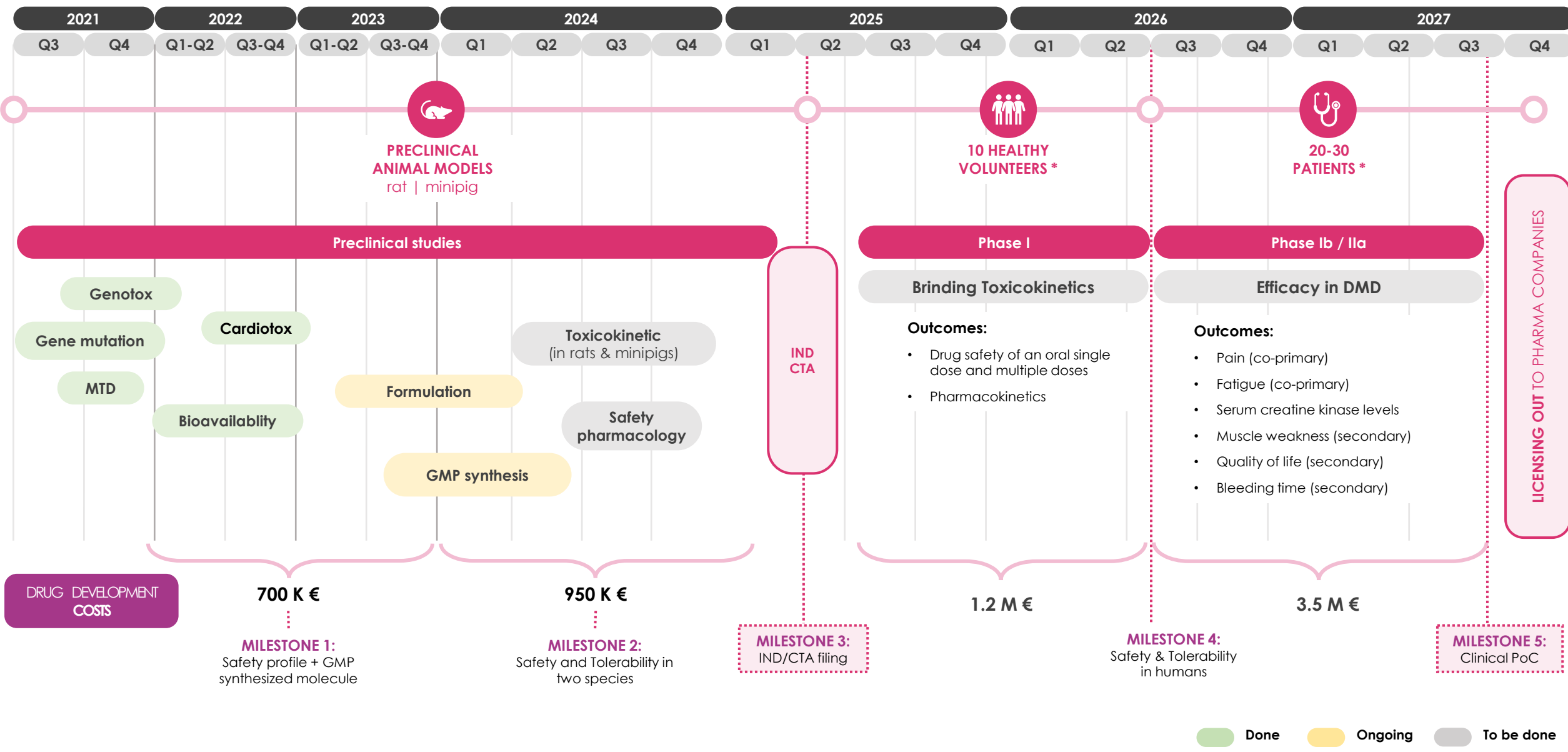
# R&D Pipeline

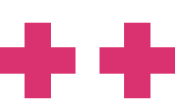
PATHOLOGIES





# Development Plan for DMD

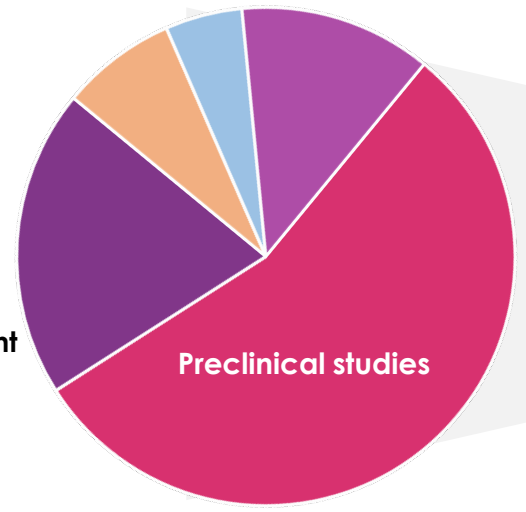




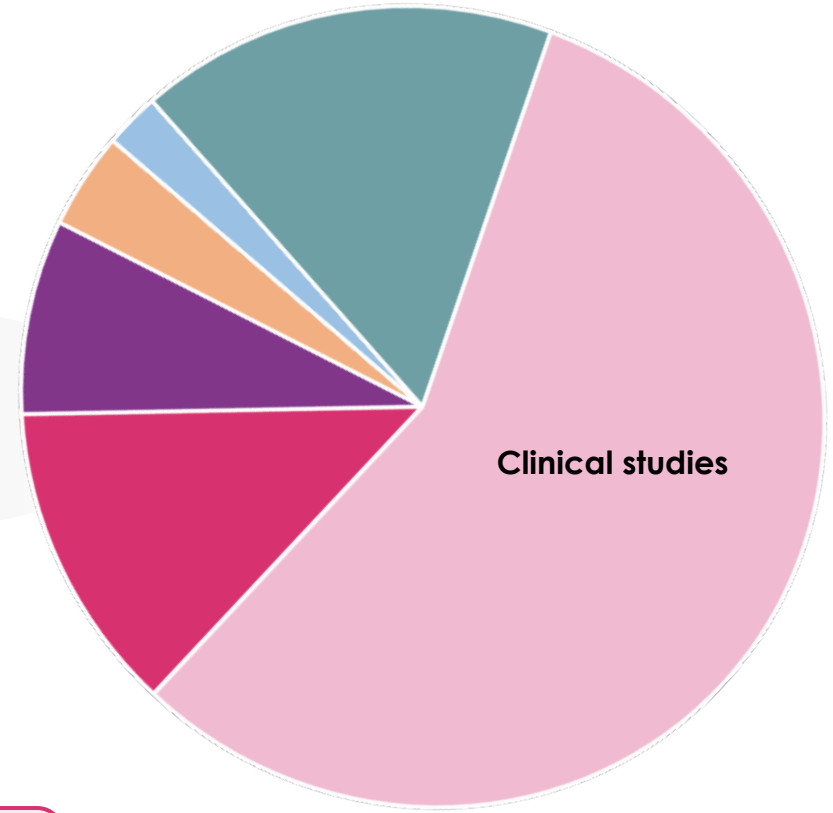
# Financial Need and Equity Fundraising

Overall Financial Need 9 M €

- Preclinical studies DMD
- Manufacturing
- R&D activities autoimmune disorders
- Business & Management
- IPR & Legal



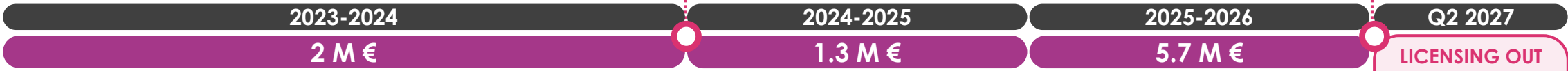
- Preclinical studies DMD
- Manufacturing
- Preclinical studies autoimmune disorders
- Clinical studies DMD
- IPR & Legal
- Business & Management



IND/CTA

Clinical PoC

EQUITY FUNDRAISING



LICENSING OUT TO PHARMA COMPANIES



**Beatrice Riva**  
PhD, Pharmacologist  
*President & CEO*  
*Founder*



**Tracey Pirali**  
PhD, Medicinal Chemist  
*CTO*  
*Founder*



**Luigi Azzarone**  
Neuroscientist  
*Research Assistant and*  
*Regulatory Affairs*



**Carlotta Muschitiello**  
Pharmacy  
*Internship Student*



**Maurizio Mariani**  
MD, PhD Pharmacology  
*Scientific Advisor*



**Daniel Chicco**  
PhD Pharmacy  
*Scientific Advisor*



**Demetra Pelos**  
Biomedical engineer  
*IP Portfolio Manager*



**Nicola Pastori**  
Economist  
*CFO*



**Simona Somaini**  
Biologist  
*Regulatory / QC*



**Marco Gili**  
Legal expert  
*Legal & General*  
*Affairs*



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

**Recognized as SME by EMA** (EMA/SME/228/19/R5)

- **Share capital:** 24,029.07 €
- **Cap table:** B. Riva(46.43%), T. Pirali (18.74%), A. Serrao (8.86%), Bio4Dreams (20.98%), M. Mariani (4.48%), Bridge4Pharma (0.5%).





UNIVERSITÀ DEL PIEMONTE ORIENTALE



- Prof. Armando Genazzani
- Dr. Emanuela Pessolano
- Prof. Dmitry Lim

- Prof. Tracey Pirali
- Dr. Marta Serafini
- Dr. Irene Preet Bhela
- Dr. Silvio Aprile



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- Dr. Luigi Azzarone
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It's a rare thing to care

**Beatrice Riva**, PhD  
beatrice.riva@chemicare.it

[www.chemicare.it](http://www.chemicare.it)

