Ataxia telangiectasia: drug repositioning for pediatric treatment of a rare genetic neurological disease

Cinzia Cimino[1,2,*]; Teresa Musumeci[1,2]; Claudia Carbone[1,2]; Angela Bonaccorso[1,2]; Agata G. Copani[1]; Rosario Pignatello[1,2]

[1] Department of Drug and Health Sciences, University of Catania, Via Valdisavoia 5, 95123 Catania, Italy;
[2] NANOMED, Research Centre for Nanomedicine and Pharmaceutical Nanotechnology, University of Catania, Via Valdisavoia 5, 95123 Catania, Italy.
[*] cinzia.cimino@unict.it

Introduction

Ataxia telangiectasia
(A-T, Louis-Bar syndrome)
is a rare genetic condition which involves a mutation in the ataxia-telangiectasia mutated (ATM) gene, resulting in[1]:

- Neurological disorders
- Telangiectasias
- Immunological impairment
- Tumor appearance
- Radiosensitivity
- Diabetes

- The incidence is 1:40.000 to 1:300.000[1].
- The median survival is 18-25 years.
- The mechanism of occurrence is still unknown.
- The therapeutic approach is mainly focused on the treatment of symptoms and the monitoring for the prevention of complications[2].

Pharma-HUB project

It is financed by the Italian Minister for Health, and it is aimed to the development of a biomedical and pharmaceutical national Hub for pediatric repositioning of active drug compounds for the treatment of A-T disease, focusing mainly on the central nervous system (CNS).

Methods

- identification of the pharmacological targets and of the pathways involved
- *in silico* drug repositioning studies
- selection of potentially active molecules
- verification of neuroprotective activity through 2D-3D *in vitro* biological models
- development of technological platforms using two approaches:

Galenic approach
focused on the reformulation of commercially available drug products to meet pediatric needs, basing on European Pharmacopoeia requirements.

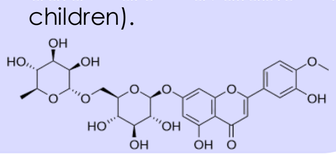
Innovative approach
focused on the development of new drug delivery system platforms for nose-to-brain (N2B) administration.

Results

A-T was modeled by COPASI (complex pathway simulator), and SAveRUNNER (Searching off-lAbel dRUg aNd NEtwoRk) was used to predict off-label drugs to be repositioned against A-T.

Through *in silico* studies, different molecules resulted to interact with the target, belonging to the following pharmacological classes: cyclin-dependent kinase 4/6 inhibitors; mTOR inhibitors; Nrf2 pathway modulators; HDAC 4 inhibitors; casein kinase 2 activators.

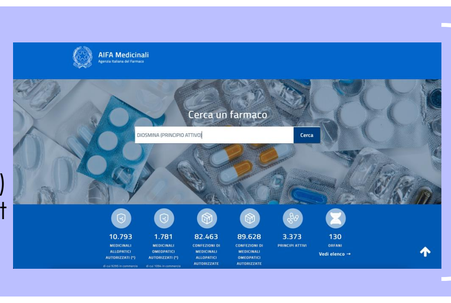
Among them, as a first model drug, **diosmin** was selected for its safety in adults[3] (no toxicological data are available in children).



The studies aimed to verify the neuroprotective activity of diosmin through 2D-3D *in vitro* biological models are still ongoing.

Galenic approach

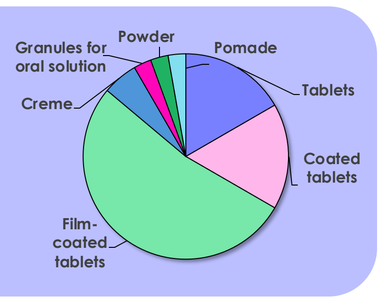
Commercialized medicines containing diosmin as active pharmaceutical ingredient (API) were searched on the official list of AIFA approved medicines.



36 medicines resulted to be approved:

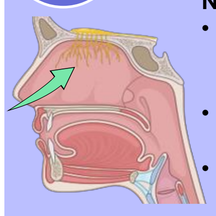
- mainly used for the treatment of venous insufficiency and capillary fragility;
- generally formulated as tablets or cream;
- 21 of them were co-formulated with hesperidin.

The galenic development is still ongoing. LOADING...



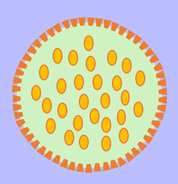
Innovative approach

Nose-to-brain route[4]



- Allows the achievement of the CNS bypassing the blood brain barrier (BBB);
- Avoids gastrointestinal and systemic metabolisms;
- Reduces side effects.

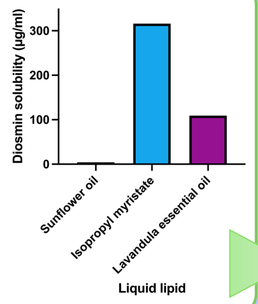
Nanostructured lipid carriers (NLC)
Composed of a core of solid and liquid lipids, and a shell of surfactants.



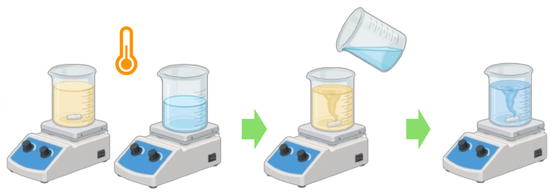
Advantages:
- Biocompatible and biodegradable;
- High encapsulation efficiency;
- Controlled release of the drug.

Selection of the liquid lipid basing on diosmin solubility

Isopropyl myristate was selected for the development of NLC, having the highest diosmin solubility (~316 µg/ml) among the considered oils.



Development of the NLC platform using Phase Inversion Temperature (PIT) method



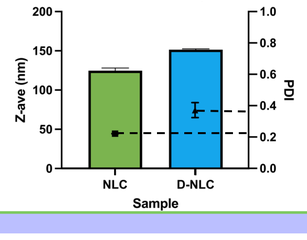
Lipid and aqueous phases are separately heated.

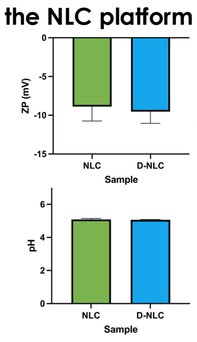
Aqueous phase is added dropwise to lipid phase, under constant stirring.

Sample is stirred to allow the formation of the nanoparticles.

Characterization of the NLC platform

Particles are homogeneous (PDI <0.4) and with size (Z-ave) lower than 200 nm, thus are suitable for N2B delivery. The increase in both Z-ave and PDI of D-NLC compared to NLC is related to the steric hindrance of the encapsulated diosmin.

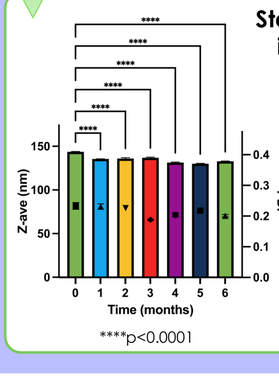




Superficial charge (zeta potential, ZP) being slightly negative allows a slight retainment on the mucin layer of the nasal mucosa.

pH of the sample is within the nasal tolerated pH range (4.5-6.5).

Stability of the NLC in accelerated conditions



****p<0.0001

Stability study was performed in constant climate chamber, following ICH guidelines Q1A (R2) (40±2°C; 75±5%RH). The analysis, which is predictive of 1 year storage at room temperature, demonstrated the long-term stability of the NLC platform.

Conclusions and future perspectives

Considering the difficulty of overcoming the BBB, the encapsulation of diosmin into nanocarriers could represent a valid alternative to the traditional dosage forms to reach the CNS.
The developed NLC platform results suitable for the N2B administration route in terms of size, ZP and pH; moreover, the formulation is long-term stable up to 1 year at room temperature.

- Further characterization studies of the NLC formulation.
- Development of the galenic product.
- *In vivo* validations in mouse A-T models.
- Set of clinical trials in comparison with the currently available not-specific therapy.

Acknowledgments

References

(1) McGrath-Morrow et al., 2021; doi: 10.2147/JMDH.S295486.
(2) Rothblum-Oviatt et al., 2016; doi: 10.1186/s13023-016-0543-7.
(3) Srinivasan et al., 2019; doi: 10.1016/B978-0-12-813822-9.00022-9.
(4) Bonaccorso et al., 2024; doi: 10.2147/IJN.S452316.