RARE DISEASES AND ORPHAN DRUGS

SILVIO GARATTINI

Bologna 7th March 2018
WHY RARE DISEASES SHOULD BE STUDIED?

• All the patients independently from the type of their disease have the right to be cured

• They furnish information useful also for common diseases

• They represent the future: an example of personalized medicine
1983

U.S.A. GOVERNMENT APPROVES

“ORPHAN DRUGS ACT”

TO BOOST THERAPIES FOR

RARE DISEASE

PREVALENCE < 200,000 PEOPLE
1992
THE MARIO NEGRI INSTITUTE ESTABLISHES A CLINICAL RESEARCH CENTER FOR RARE DISEASES
THE CLINICAL RESEARCH CENTRE FOR RARE DISEASES

Since 1992

Since 2001

http://malattierare.marionegri.it

COORDINATING CENTRE OF THE LOMBARDY NETWORK FOR RARE DISEASES
EXPERTISE AND ORGANIZATIONAL SUPPORT IMPLEMENTED AT THE CENTER

IMPROVE KNOWLEDGE AND POSSIBILITY OF TREATMENT IN RARE DISEASES

RESULTS DIFFUSION

STATISTICAL ANALYSIS

STUDY MONITORING

STUDY DEVELOPMENT

REGULATORY ASPECTS

STUDY DESIGN

RESEARCH AIM DEFINITION

- **11,419** rare disease cases submitted to multidisciplinary team evaluation
  - 34% Lombardy
  - 66% other Italian regions

- **1,468 (13%)** undiagnosed cases addressed to revaluation at reference centres

- **127** monitored cases (undiagnosed following careful periodic revaluations)

- **27*** cases selected for genomic and functional analyses

* 1 patient enrolled in NIH Undiagnosed diseases program
**Rete Regionale Malattie Rare**

- **46 Hospital**
- **642 Rare disease**
- **60000 Patients**

Diagram:
- Registry
  - Center
  - Center
  - Center
- Coordinating center
  - Analisi dei dati
    - Reports periodical
  - Data Set
    - ISS
      - Istituto Superiore di Sanità
      - National registry
Registro Lombardo Malattie Rare
Distribuzione dei pazienti in Lombardia al 31/12/2015 (Età e Genere)

Population 10.008.349*
Prevalence 58.509
Rare Diseases / Coded graphs 294
Prevalence 5,8/1000 People

* ISTAT Censimento popolazione italiana – 01/01/2016
EXPERIMENTAL AND CLINICAL STUDIES
AT THE MARIO NEGRI INSTITUTE

- HUS
- MEMBRANOUS GLOMERULONEPHRYSIS
- SYSTEMIC AMYLOIDOSIS
- FABRY DISEASE
- CEREBRAL CAVERNOUS MALFORMATIONS
- PRIONS DISEASES
- ALS
- RETT SYNDROME
- SMA
- EFI
- LIPOFUSCINOSI
- MOLIBDO DEFICIENCY
- APL
- MYXOID LIPOSARCOMAS
- MESOTHELIOMAS
- THYMOMAS
- B-LYMPHOMAS
- UTERINE LEIOMYOSARCOMAS
- OVARIAN CANCER
Transgenic SOD1 mutant mouse, the first animal model of fALS

Tg SOD1G93A mouse

Similarities and differences with human fALS

- Loss of lower MN
- Reactive gliosis
- Ubiquitinated inclusions
- Loss of glutamate transporter
- Oxidative damage
- Neuroinflammation

- Lack of upper MN loss
- Hyper-vacuolization
- Overexpression of mutant SOD1

Adapted from Bendotti and Carri, TRENDS Mol. Med. 2004
Variable disease course in ALS patients


<table>
<thead>
<tr>
<th>G93C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, mean ± SD, y</td>
<td>45.9 ± 10.6*</td>
</tr>
<tr>
<td></td>
<td>(n = 20)</td>
</tr>
<tr>
<td>Diagnostic delay, mean ± SD, mo</td>
<td>15.3 ± 16.1</td>
</tr>
<tr>
<td></td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Survival, median ± SE, mo (95% CI)§</td>
<td>153.0 ± 46.1</td>
</tr>
<tr>
<td></td>
<td>(62.7-243.3)</td>
</tr>
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<td></td>
<td>(n = 20)</td>
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</tbody>
</table>

Disease modifiers - Therapeutic Targets

Variable disease course in two mouse models of ALS: a useful paradigm to identify potential disease modifiers

Fast progressor at onset
- Reduced protein catabolism
- Massive mitochondrial dysfunction
- Impaired nerve regeneration
- Massive NMJs denervation

Slow progressor at onset
- Prompt immune response in PNS
- Increase motor axons regeneration
- Early activation of neurotrophic factor

Nardo et al. Brain 2013
Marino et al. Neurobiol Aging 2015
Caron et al. PLoS One 2015
Nardo et al. Brain Pathol 2016
Variable disease course in two mouse models of ALS: a useful paradigm to identify potential disease modifiers, prognostic disease biomarkers, therapeutic targets.

Potential mechanisms for slowing down the disease course:

- Increase the protein quality
- Protection of mitochondria
- Activation of immune response in peripheral motor axons
- Increase of neurotrophic factor
RNS60 delays neuromuscular impairment and prolong survival in SOD1G93A mouse model

**Motor Deficit Onset**

- NS: 121.3 ± 1.1
- RNS60: 128.8 ± 1.2
- **P value < 0.0001**

**Paralysis**

- NS: 155.3 ± 2.5
- RNS60: 163.4 ± 1.4
- **P value = 0.0095**

**Survival**

- NS: 164.7 ± 4.6
- RNS60: 175.1 ± 2.8
- **P value = 0.087**

- 6/13
- 12/14 (85.7%)

**Disease duration**

- NS: 59.7 ± 4.6
- RNS60: 70.1 ± 2.9
- **P value = 0.0312**

**+17%**
A new agent with anti-inflammatory properties

Mechanism of action

- Activation of protective glial cells
- Immune system modulation
  - Increase of Tregs
  - Reduction of Th17 cytokines
- Reduction of demyelination
- Mitochondrial protection and increased biogenesis
- Activation of antioxidant response
Clinical Trial with RNS60 Study Design

- Multicenter, randomized, double-blind, placebo-controlled, parallel group, add-on trial.
- Eligible patients (total 142) have definite or probable ALS (revised El Escorial criteria), disease duration 6 to 24 months, self sufficiency (measured by the ALS-FRS-R scale) and satisfactory bulbar function.
- Subjects will be randomly assigned to receive treatment with either RNS60 or placebo while concomitantly taking riluzole (50-mg tablet twice a day).
- Eligible patients currently treated with edaravone will not be included.
ONLY AFTER 17 YEARS
EUROPE FOLLOWS U.S.A.
OFF J.Eur.Communieities
2000; L18:1
EC Regulation 141/2000

Orphan medicinal products
designation by the Comp at the Ema

Criteria for designation

• That it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that affects not more than 5 in 10,000 people in the Community when the application is made (‘prevalence criterion’)

or

• That it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment (‘insufficient return on investment criterion’)

and, in addition,

• That there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community (‘no satisfactory method criterion’)

or

• If such a method exists, that the medicinal product will be of significant benefit to those affected by that condition (‘significant benefit criterion’)
EC Regulation 141/2000

**Incentives**

**Protocol assistance:** access to free-of-charge protocol assistance at the EMA.

**The centralized procedure** is compulsory (as of 20 November 2005) for all orphan medicinal products to be authorized via a centralized procedure, which gives access to 29 countries in Europe (27 EU member states, including Norway and Iceland). Marketing authorization applications for orphan medicinal products in Europe currently also benefit from a reduction in the regular fee.

**Market exclusivity** (10-year) protects against a ‘similar’ drug being authorized in the EU for the same therapeutic indication. Three derogations from this rule exist: first, the sponsor’s consent; second, a lack of supply; third, if a new product, although similar, could be demonstrated to be ‘clinically superior’ - that is, “safer, more effective or otherwise clinically superior” to the product already on the market.

**National incentives**

**Community research programmes** support Europe-wide studies of the natural history of a rare disease and its pathophysiology, and the development of preventive, diagnostic and therapeutic interventions.
1/2.000  UE
1/1.250  US
1/2.500  JAPAN
1/15.000 Australia
ACCORDING TO THE EU LAW A RARE DISEASE IS REPRESENTED BY THE PREVALENCE OF 

<5/10,000

(<250,000 PATIENTS)

IT IS SUGGESTED TO MODIFY THE PREVALENCE 

<5/100,000

(<25,000 PATIENTS)
5,000 - 8,000 RARE DISEASES

27 - 36 MILLION PATIENTS

1900 ORPHAN DESIGNATIONS

141 ORPHAN DRUGS APPROVED AFTER 17 YEARS
142 Market authorisations

- 36 End of market exclusivity
- 13 withdrawals
Over 1900 medicines with orphan designation

EMA's Committee for Orphan Medicines

The Committee for Orphan Medicinal Products (COMP) is in charge of reviewing applications for orphan designation.

Over 140 orphan medicines authorised in the EU

How orphan medicines reach patients
The chart illustrates the number of medicines recommended for authorisation and authorised orphan medicines from 2001 to 2017. The bar graph shows a significant increase in the number of medicines recommended for authorisation in 2009, reaching a peak of 117. The number of authorised orphan medicines has remained relatively stable, with a peak of 15 in 2015. While the number of medicines recommended for authorisation has fluctuated, the number of authorised orphan medicines has not varied much over the years.
142 initial orphan marketing authorisations and 20 extension of indication granted to date

- A Alimentary tract and metabolism
- B Haematology
- C Cardiovascular system
- H Systemic hormonal
- J Anti-infectives for systemic use
- L Immunology
- L Antineoplastic
- M Musculo-skeletal system
- N Nervous system
- R Respiratory system
- S Sensory organs
- V Various

Number of conditions: 111
Active orphan MA: 94
Active extension of indication: 13

Chart includes:
- 13 authorised extensions of indication
- 13 withdrawals from the register of orphan medicinal products (including 6 ext. of indication)
- 5 withdrawals from register medicinal products human use
- 36 removals of initial MAA from register after expire of the market exclusivity period & 1 ext of indication
### Characteristics of Pivotal Preapproval Trials of Orphan and Nonorphan Cancer Drugs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Orphan Drug Pivotal Trials (n = 23)</th>
<th>Nonorphan Drug Pivotal Trials (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary trial end point reported&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease response&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17 (68)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Disease progression&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 (16)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>2 (8)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (8)</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

Kesselheim et al., 2017
## Characteristics of Pivotal Preapproval Trials of Orphan and Nonorphan Cancer Drugs

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<tbody>
<tr>
<td></td>
<td>No. (%)^a</td>
<td></td>
</tr>
<tr>
<td>Blinding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-blind</td>
<td>1 (4)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Single-blind</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Open-label</td>
<td>21 (91)</td>
<td>10 (67)</td>
</tr>
</tbody>
</table>

Kesselheim et al., 2017
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</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>No. (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>4 (17)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Supportive care</td>
<td>2 (9)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1 (4)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>None</td>
<td>16 (70)</td>
<td>3 (20)</td>
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</table>

<sup>a</sup> Calculated as percentage of each group.

Kesselheim et al., 2017
<table>
<thead>
<tr>
<th>Active principle</th>
<th>Rare disease</th>
<th>Patients studied</th>
<th>Potential cases in EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>miglustat</td>
<td>Type 1 Gaucher disease and Niemann-Pick type C disease</td>
<td>28</td>
<td>10,000</td>
</tr>
<tr>
<td>velaglucerase</td>
<td>Gaucher disease</td>
<td>35</td>
<td>15,000</td>
</tr>
<tr>
<td>algasidase alpha</td>
<td>Fabry disease</td>
<td>41</td>
<td>10,000</td>
</tr>
<tr>
<td>algasidase beta</td>
<td>Fabry disease</td>
<td>56</td>
<td>10,000</td>
</tr>
<tr>
<td>clofarabine</td>
<td>Acute lymphoblastic leukaemia in paediatric patients</td>
<td>61</td>
<td>10,000</td>
</tr>
<tr>
<td>neralabine</td>
<td>T-cell acute lymphoblastic leukaemia or T-cell lymphoblastic lymphoma</td>
<td>100</td>
<td>50,000</td>
</tr>
<tr>
<td>eltrombopag</td>
<td>thrombocytopenic purpura</td>
<td>150</td>
<td>50,000</td>
</tr>
<tr>
<td>romiplostim</td>
<td>thrombocytopenic purpura</td>
<td>150</td>
<td>50,000</td>
</tr>
<tr>
<td>icatibant</td>
<td>hereditary angioedema</td>
<td>150</td>
<td>50,000</td>
</tr>
<tr>
<td>sapropterin</td>
<td>hyperphenylalaninemia</td>
<td>150</td>
<td>50,000</td>
</tr>
<tr>
<td>Drug</td>
<td>Repeated dosetoxicology</td>
<td>Exposure</td>
<td>Genotoxicity</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------------</td>
<td>---------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Agalsidase alpha</td>
<td>Rabbits, rats, monkeys</td>
<td>2–26 weeks</td>
<td>NA</td>
</tr>
<tr>
<td>Agalsidase beta</td>
<td>Rats</td>
<td>27 weeks</td>
<td>NA</td>
</tr>
<tr>
<td>Anagrelide</td>
<td>Rats, monkeys, dogs</td>
<td>12–52 weeks</td>
<td>Yes (negative)</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>Mice, rats, dogs, monkeys</td>
<td>Not specified</td>
<td>Yes (positive)</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Rats, dogs, marmosets</td>
<td>1–4 weeks</td>
<td>Yes (negative)</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Dogs</td>
<td>4 days</td>
<td>NA</td>
</tr>
<tr>
<td>Carglumic acid</td>
<td>Rats</td>
<td>2–18 weeks</td>
<td>Yes (positive)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Rats, dogs</td>
<td>24–52 weeks</td>
<td>Yes (negative)</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Mice</td>
<td>4 weeks</td>
<td>Yes (positive)</td>
</tr>
</tbody>
</table>

Joppi et al, 2006
<table>
<thead>
<tr>
<th>Drug</th>
<th>Repeated dosetoxicology</th>
<th>Exposure</th>
<th>Genotoxicity</th>
<th>Carcinogenicity</th>
<th>Reproduction toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>NR</td>
<td>NR</td>
<td>Yes (negative)</td>
<td>Yes (negative)</td>
<td>Yes (negative)</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Rats, dogs</td>
<td>24–52 weeks</td>
<td>Yes (negative)</td>
<td>Yes (negative)</td>
<td>Yes (positive)</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Monkeys</td>
<td>39 weeks</td>
<td>Yes (+ in vitro and –in vivo)</td>
<td>Ongoing</td>
<td>Yes (positive)</td>
</tr>
<tr>
<td>Laronidase</td>
<td>Dogs, monkeys</td>
<td>8–26 weeks</td>
<td>NA</td>
<td>NA</td>
<td>Yes (not conclusive)</td>
</tr>
<tr>
<td>Miglustat</td>
<td>Rats, monkeys</td>
<td>4–52 weeks</td>
<td>Yes (negative)</td>
<td>Yes (negative)</td>
<td>Yes (positive)</td>
</tr>
<tr>
<td>Mitotane</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pegvisomant</td>
<td>Rats, monkeys</td>
<td>24 weeks</td>
<td>Yes (negative)</td>
<td>NA</td>
<td>Yes (negative)</td>
</tr>
<tr>
<td>Porfimer</td>
<td>Rats, dogs</td>
<td>13 weeks</td>
<td>Yes (positive)</td>
<td>NA</td>
<td>Yes (negative)</td>
</tr>
<tr>
<td>Zinc acetate</td>
<td>Rats</td>
<td>53 weeks</td>
<td>Yes (not conclusive)</td>
<td>Yes (not conclusive)</td>
<td>Yes (negative)</td>
</tr>
</tbody>
</table>

Joppi et al, 2006
# European Reference Networks (ERNs)

| ERN BOND - European Reference Network on bone disorders | 7 | 1 |
| ERN CRANIO - European Reference Network on craniofacial anomalies and ENT disorders | 6 | 3 |
| Endo-ERN - European Reference Network on endocrine conditions | 9 | 2 |
| ERN EpiCARE - European Reference Network on epilepsies | 5 | 2 |
| ERNKnet - European Reference Network on kidney diseases | 11 | 2 |
| ERNICA - European Reference Network on inherited and congenital anomalies | 1 | |
| ERN EURACAN - European Reference Network on adult cancers (solid tumors) | 17 | 4 |
| ERN EuroBloodNet - European Reference Network on haematological diseases | 21 | 5 |
| ERN eUROGEN - European Reference Network on urogenital diseases and condition | 4 | 1 |
| ERN EYE - European Reference Network on eye diseases | 6 | |
| ERN GENTURIS - European Reference Network on genetic tumor risk syndromes | |
| ERN GUARD-HEART - European Reference Network on diseases of the heart | 6 | 3 |
| ERN ITHACA - European Reference Network on congenital malformations and rare intellectual disability | 8 | 1 |
| ERN RARE-LIVER - European Reference Network on hepatological diseases | 3 | 2 |
| ERN LUNG - European Reference Network on respiratory diseases | 15 | 2 |
| MetabERN - European Reference Network on hereditary metabolic disorders | 11 | 2 |
| ERN EURO-NMD - European Reference Network on neuromuscular diseases | 15 | 5 |
| ERN PaedCan - European Reference Network on pediatric cancer (haemato-oncology) | 9 | 2 |
| ERN ReCONNET - European Reference Network on connective tissue and musculoskeletal diseases | 8 | 3 |
| ERN RITA - European Reference Network on immunodeficiency, autoinflammatory and autoimmune diseases | 5 | 3 |
| ERN RND - European Reference Network on neurological diseases | 4 | 2 |
| ERN Skin - European Reference Network on skin disorders | 6 | 1 |
| ERN TRANSPLANT-CHILD - European Reference Network on transplantation in children | 3 | 1 |
| VASCERN - European Reference Network on multisystemic vascular diseases | 6 | 3 |
The present system does not allow an efficient conduct of clinical trials

➢ There is a need to carry out clinical trials

- timely
- rapidly
- with no deadlines (no restriction to 3-5 years)
- with adequate financial support
- addressing patients and public health needs
- addressing comparative effectiveness
- independent from pharma companies
A SPECIAL AREA SHOULD BE MADE AVAILABLE WITHIN FP9 OR OTHER KIND OF EU RESEARCH PROGRAMS ONLY FOR INDEPENDENT TRIALS.

THE FUND SHOULD NOT HAVE DEADLINES.

PROPOSALS SHOULD BE EVALUATED BY AN INDEPENDENT COMMITTEE MADE UP BY CLINICIANS AND METHODOLOGISTS EXPERT IN RCTs.
NEED FOR INDEPENDENT CLINICAL RESEARCH

THE AMOUNT OF AT LEAST 1 BILLION EURO (<0.3% OF EU PHARMACEUTICAL MARKET) DEVOTED TO NON–PROFIT INDEPENDENT RESEARCH ON RANDOMIZED CONTROLLED CLINICAL TRIALS OF ORPHAN DRUGS
IMPRENDITORIAL NON-PROFIT COMPANIES MADE UP BY DIFFERENT INSTITUTIONS SUPPORTED BY PUBLIC AND CHARITY FUNDS TO PRODUCE NEW ORPHAN DRUGS AT LOW PRICES