Rare Disease Day
Tea Party 2015

Rare and severe – how one might help

Timothy M Cox
University of Cambridge
Addenbrooke’s hospital

British Paediatric Surveillance Unit
RCPH Youth Advisory Panel

Royal College of Paediatrics & Child Health
Thursday 5th March
"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change."

Charles Darwin
The Human Gene Lexicon
The International Human Genome Sequencing Consortium*

Completing the inherited disease catalogue

Ensembl genome-annotation system estimate 23,299

Single-gene disorders (Mendelian traits)

Total: 8207 (Online Mendelian Inheritance in Man)

You might not remember this one...
Course of Infantile Tay-Sachs Disease
(aged 10-23 months)
Anglo-Jewish Community in 19th century East London

Jewish East London (1900)
Symmetrical changes in the Region of the Yellow-spot in each Eye in an Infant
Survival in Modern Times

Hitherto - disease prevention
Clinical diversity in this single disease
WHY?
Ultra-orphan – just a drop in the ocean...
Facing up...
# Lysosomal diseases (>80)

<table>
<thead>
<tr>
<th>MPS</th>
<th>Sphingolipidoses</th>
<th>Glycoproteinoses</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurler, Scheie Hunter&lt;br&gt;Sanfillipo A-D&lt;br&gt;Marquio A, B&lt;br&gt;Maroteaux-Lamy&lt;br&gt;Sly&lt;br&gt;Kanzaki disease&lt;br&gt;Hyaluronidase deficiency (X)</td>
<td>Tay-Sachs&lt;br&gt;Gaucher&lt;br&gt;Krabbe&lt;br&gt;Anderson-Fabry&lt;br&gt;Farber&lt;br&gt;Metachromatic Leuko-dystrophy&lt;br&gt;Niemann-Pick A &amp; B&lt;br&gt;GM1 Gangliosidosis&lt;br&gt;Sandhoff&lt;br&gt;GM2 activator deficiency</td>
<td>Fucosidosis&lt;br&gt;Aspartylglucosaminuria&lt;br&gt;Mannosidosis-α&lt;br&gt;Mannosidosis-β&lt;br&gt;Sialidosis&lt;br&gt;Galactosialidosis</td>
<td>Cathepsins C, D &amp; K&lt;br&gt;Pompe (GSD type II)&lt;br&gt;Niemann-Pick C types I,II&lt;br&gt;Neuronal Ceroid&lt;br&gt;Lipofuscinoses (CLN 1-14)&lt;br&gt;Wolman /CESD&lt;br&gt;Hermansky-Pudlak (1-9)&lt;br&gt;Chédiak-Higashi&lt;br&gt;Griscelli (1-3)&lt;br&gt;Cystinosis (cystine)&lt;br&gt;Danon (glycogen &amp; debris)&lt;br&gt;Salla (sialic acid)&lt;br&gt;Mucolipidosis II/III&lt;br&gt;Mucolipidosis IV&lt;br&gt;Multiple sulphatase def&lt;br&gt;LIMP-2/SCARB deficiency&lt;br&gt;Sphingolipid activator protein deficiencies (A-D)&lt;br&gt;T2-family acidic endoribonuclease (RNASET2)</td>
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- **n=1164**

<table>
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<tr>
<th>Condition</th>
<th>Number</th>
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<tr>
<td>GM2 gangliosidosis</td>
<td>73</td>
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<tr>
<td>Lysosomal disease</td>
<td>45%</td>
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<tr>
<td>Other</td>
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<tr>
<td>Total</td>
<td>73</td>
</tr>
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</table>

**Tay-Sachs** 40
**Sandhoff** 31
**Activator** 2

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Parkinson Disease and the Lysosome

Glucocerebrosidase is present in α-synuclein inclusions in Lewy body disorders

Medication for Orphan Diseases

EMPTY BOTTLE
Homozygous patient with familial hypercholesterolemia who first received compactin in 1978.

Her treatment paved the way to development of statins.

Statins are being administered daily to more than 30 million patients to prevent coronary heart disease and stroke.

Treasuring Exceptions – Statins
Dr Akira Endo – Lasker award winner
Tay-Sachs disease – its paradigms

- First Lysosomal disease
- Relentless disease of infancy
- Effective screening
- Comparative pathophysiology
- Emerging molecular therapeutics of the brain
How?
Functional Complementation

Correction of lysosomal enzyme deficiency by secretion-recapture
Christian de Duve

Biochemist who won the Nobel Prize for a breakthrough in the study of cells

De Duve: he said that he was motivated by a desire to cure such rare but fatal genetic disorders as Tay-Sachs disease

Ingrid Grütter
Authentic living models of Tay-Sachs disease
## Gene Therapy for Tay-Sachs and Related Diseases

### ‘Gene Therapy for Tay-Sachs and Sandhoff diseases’

**MR/K025570/1**

[www.controlled-trials.com/ISRCTN57061190](http://www.controlled-trials.com/ISRCTN57061190)

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<table>
<thead>
<tr>
<th>Tasks</th>
<th>Month</th>
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<tbody>
<tr>
<td><strong>Patient organisation communication</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IMP authorisation</strong></td>
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<td>Milestone 1</td>
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<td>Pre clinical work with IMP vector</td>
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<td><strong>Regulatory approval</strong></td>
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<td>Milestone 2</td>
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<td>Regulatory submission</td>
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<td>Protocol, IB, IMPD</td>
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<td>MHRA, GTAC, SSA</td>
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<td>R&amp;D, study initiation</td>
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<tr>
<td><strong>Recruitment</strong></td>
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<td>Milestone 3</td>
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<tr>
<td>Clinical assessment &amp; recruitment (up to 12 patients)</td>
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<tr>
<td>Screening/evaluation</td>
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<tr>
<td>Enrollment</td>
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<td>Treatment Phase</td>
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<tr>
<td><strong>Clinical follow-up and evaluation</strong></td>
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<td>National, global communication</td>
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<tr>
<td><strong>Collate data</strong></td>
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<tr>
<td>Evaluation</td>
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<td>Clinical summary report</td>
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Approved: 17th May 2013

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**MRC Medical Research Council**

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[www.controlled-trials.com/ISRCTN57061190](http://www.controlled-trials.com/ISRCTN57061190)
Good Doctors....

Hunt in packs!

Cure sometimes;
relieve often,
and comfort - always
Massive ‘unmet need’: currently expressed as lobbying, fundraising, agitating for research, understanding, treatment, recognition, supportive care, respite...

Families with MLD – www.elizaswish.org

Also courtesy of Dr Patrick B Deegan (Cambridge, UK)
Obviously clinical medicine presents immense fields of scientific research and those who cultivate them have the added satisfaction of knowing that every advance of medical science will, sooner or later, bring in its train some forward movement of the healing art.

‘Treasure your exceptions’
William Bateson

The Debt of Science to Medicine
A.E.Garrod (1924)
Treasuring Exceptions - humanitarian choice

Fabryka Schindlera
Schindler Factory
ביה גורש שינדלר
1939-1944

Kto ratuje jedno życie,
jakby świat cały ratował.

Whoever saves one life,
saves the world entire.

cحل המקים מעשה אחד כא힐 קים עלום מלא

—Talmud Yerushalmi, Sanhedrin 4:12

Oskar Schindler
1908-1974
The Extreme Case

Rare and unusual patients with rare and unusual diseases

need rare and unusual people to look after them

- Physicians and Nurses
- Diagnostic biochemists and Geneticists
- Genetic counsellors
- Professionals allied to medicine
- Other specialists – in shared care
- Transitional care specialists

The diseases may be rare but suitable people to help are even rarer
Politics is the Art of Preventing
People from Minding their own Business

Paul Valery
Role of Patient Organizations

- Supporting cases of urgent need
- Providing independent information
- Education & engagement of healthcare professionals
- Negotiating with industry
- Supporting independent research
- Political advocacy—at all levels
- Be prepared to unite and work as one
Next Generation for Rare Disorders

Treatments – experiments becoming a reality

Research is done in buildings and with equipment

- not by buildings or equipment

Discovery comes from people

Progress depends upon people

Special people...
Facing up ...

Why should you?
Providing Treatment

Do the work....

- Build up knowledge, experience & expertise
- Provide each patient with an understanding of their condition
- Develop agreed protocols for treatment - set goals for therapy
- Work closely with all stakeholders - especially patient groups

Good Doctors....