

Discovering drugs for and with patients

Lessons from the DevelopAKUre clinical trials for
AKU

Dr Nicolas Sireau, Chairman and CEO, AKU Society

1902: Sir Archibald Garrod



THE LANCET, JULY 11, 1908.

The Croonian Lectures

ON

INBORN ERRORS OF METABOLISM.

*Delivered before the Royal College of Physicians of London
on June 18th, 23rd, 25th, and 30th, 1908,*

By ARCHIBALD E. GARROD, M.A., M.D.
OXON., F.R.C.P. LOND.,

ASSISTANT PHYSICIAN TO, AND LECTURER ON CHEMICAL PATHOLOGY
AT, ST. BARTHOLOMEW'S HOSPITAL; SENIOR PHYSICIAN, HOSPITAL
FOR SICK CHILDREN, GREAT ORMOND STREET.

LECTURE II.¹

Delivered on June 23rd.

ALKAPTONURIA.

MR. PRESIDENT AND FELLOWS,—Of inborn errors of metabolism, alkaptonuria is that of which we know most, and from the study of which most has been learnt. In itself it is a trifling matter, inconvenient rather than harmful, which only attracts attention because an infant stains its clothing, or because an adult fails to effect an insurance of his life. The medical man merely needs to be aware of its existence and to be acquainted with the methods for its recognition in order that he may not mistake it for troubles of graver kinds; but for the chemical physiologist and pathologist it is one of the most interesting of metabolic

the early years of the nineteenth century was drawn in medical writings: black when passed and such as but it is difficult to suggest an alkaptonuria for some cases: sixteenth and seventeenth century G. A. Scribonius⁴ (in 1584) of enjoyed good health, continuous that cited by Schenck⁵ (in 1606) similar peculiarity and stated life. The most interesting record in the work of Zacutus Lusitanus patient was a boy who passed age of 14 years, was submitted to a treatment which had for its aim the removal of his viscera, which was supposed to be in question by charring and the measures prescribed were a cold and watery diet, and drug treatment had any obvious effect, and eventually the patient died. The result was the futile and superfluous therapy of their natural course. None of the patients married, begat a large family, and lived a long life, always passing urine black.

That alkaptonuria is a very rare question, and many medical men have never met with it. Of its occurrence in a family and of its mode of inheritance has been spoken at sufficient length in the literature. In the majority of instances it is present throughout life, but has been seen

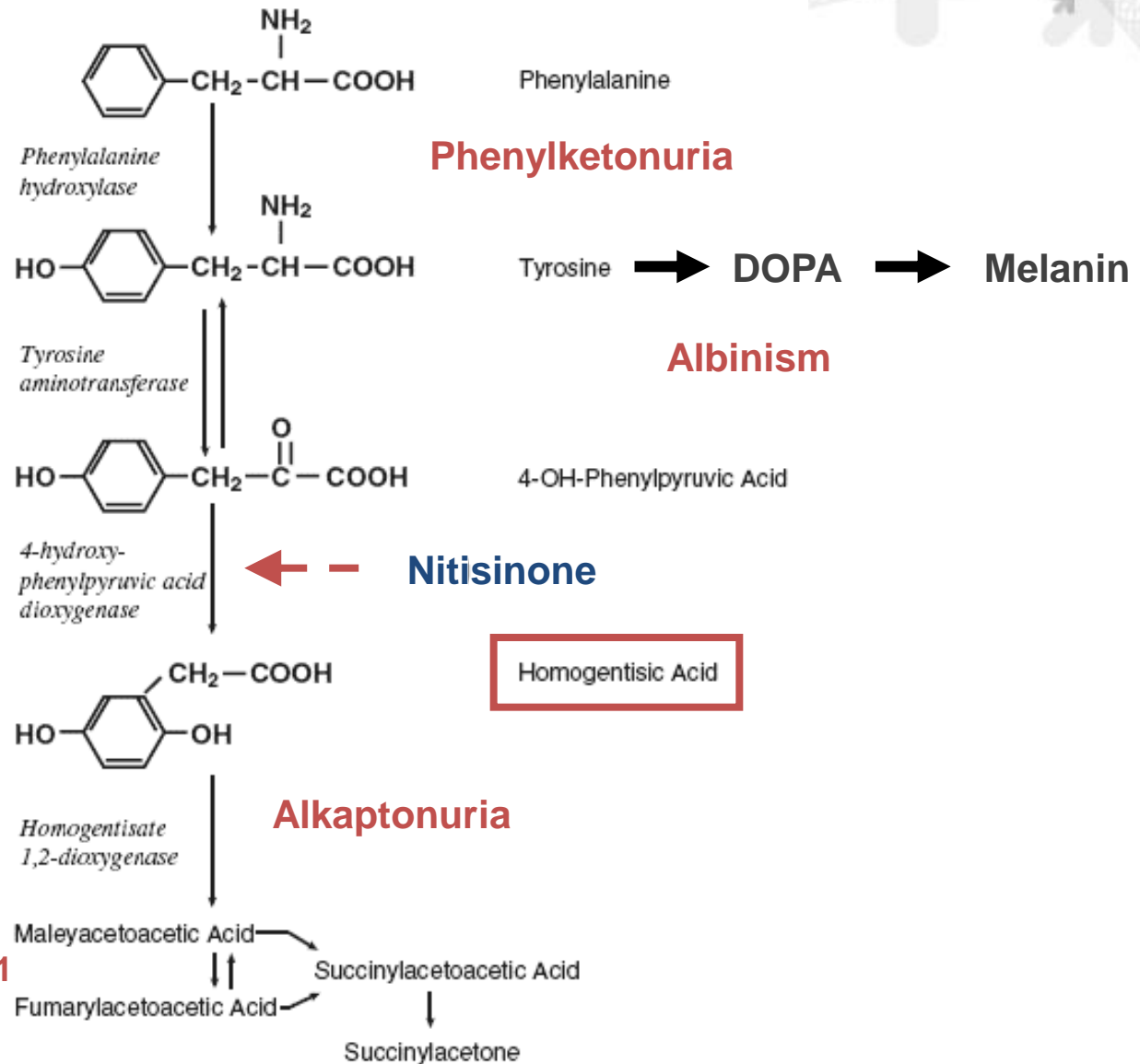
Harwa

Oldest AKU Patient
1500BC



Stenn et al 1977

Metabolic pathway

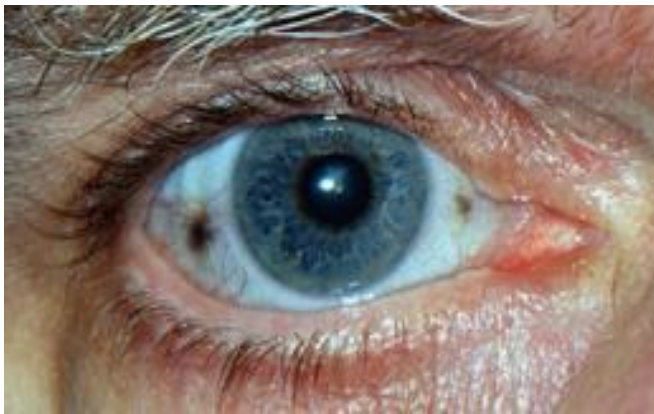




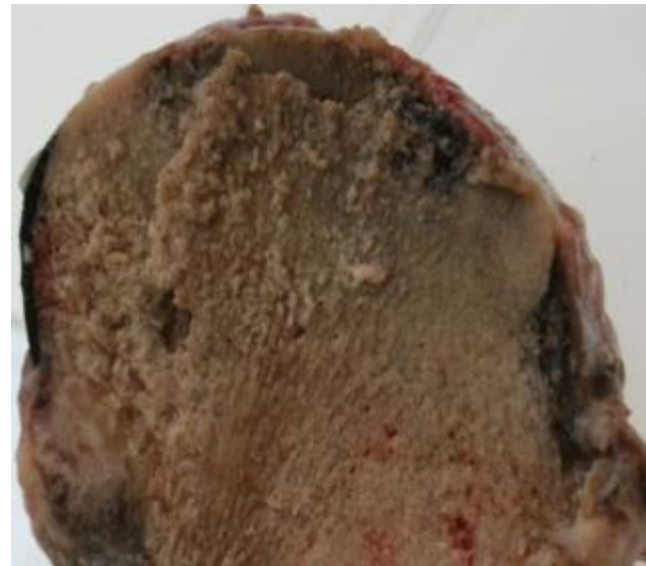
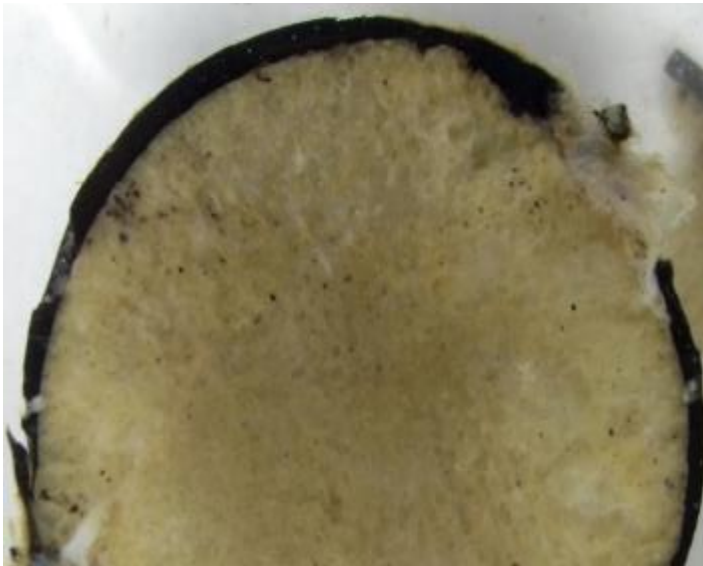
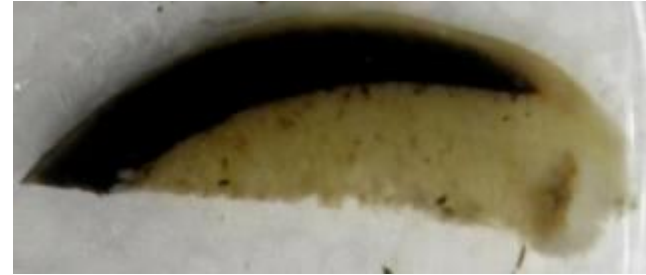
Step 1:

Understanding the disease

The AKU tetrad



Black Bone Disease

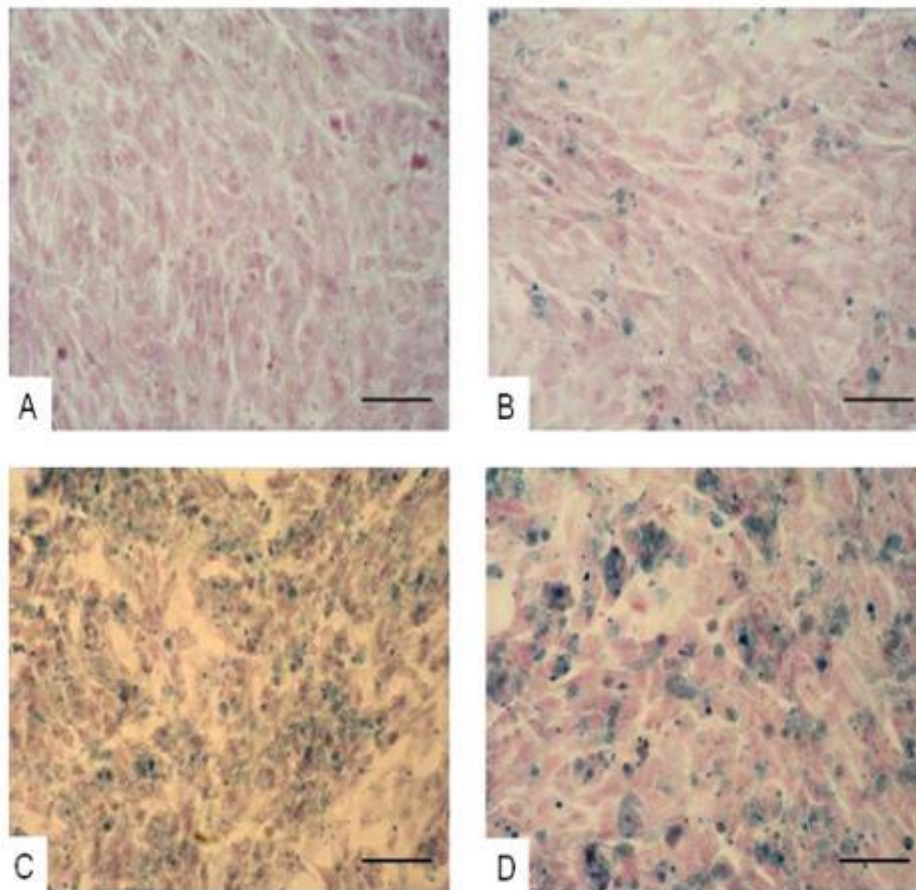


Effects on spine



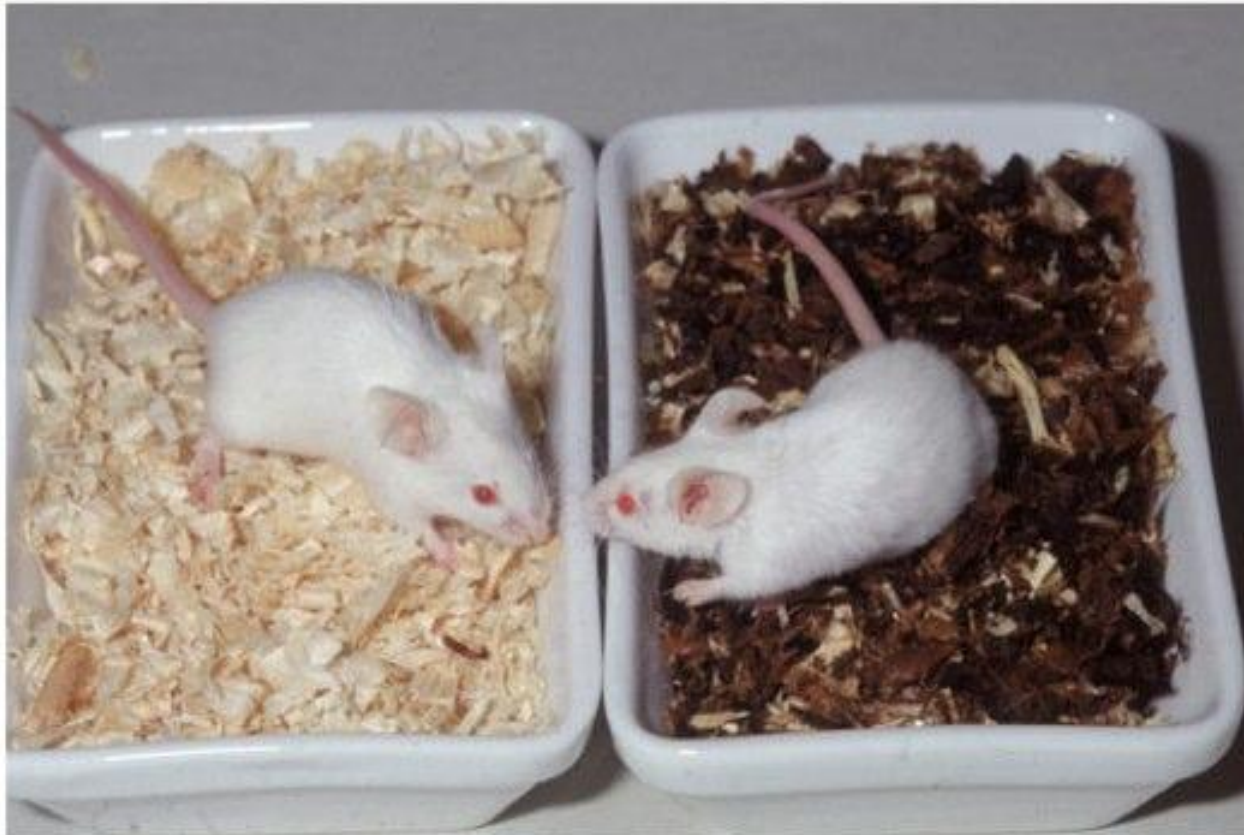
Sofia Michopoulou & Andrew Todd Pokropek

A cell model



AKU Research Team

AKU mouse model



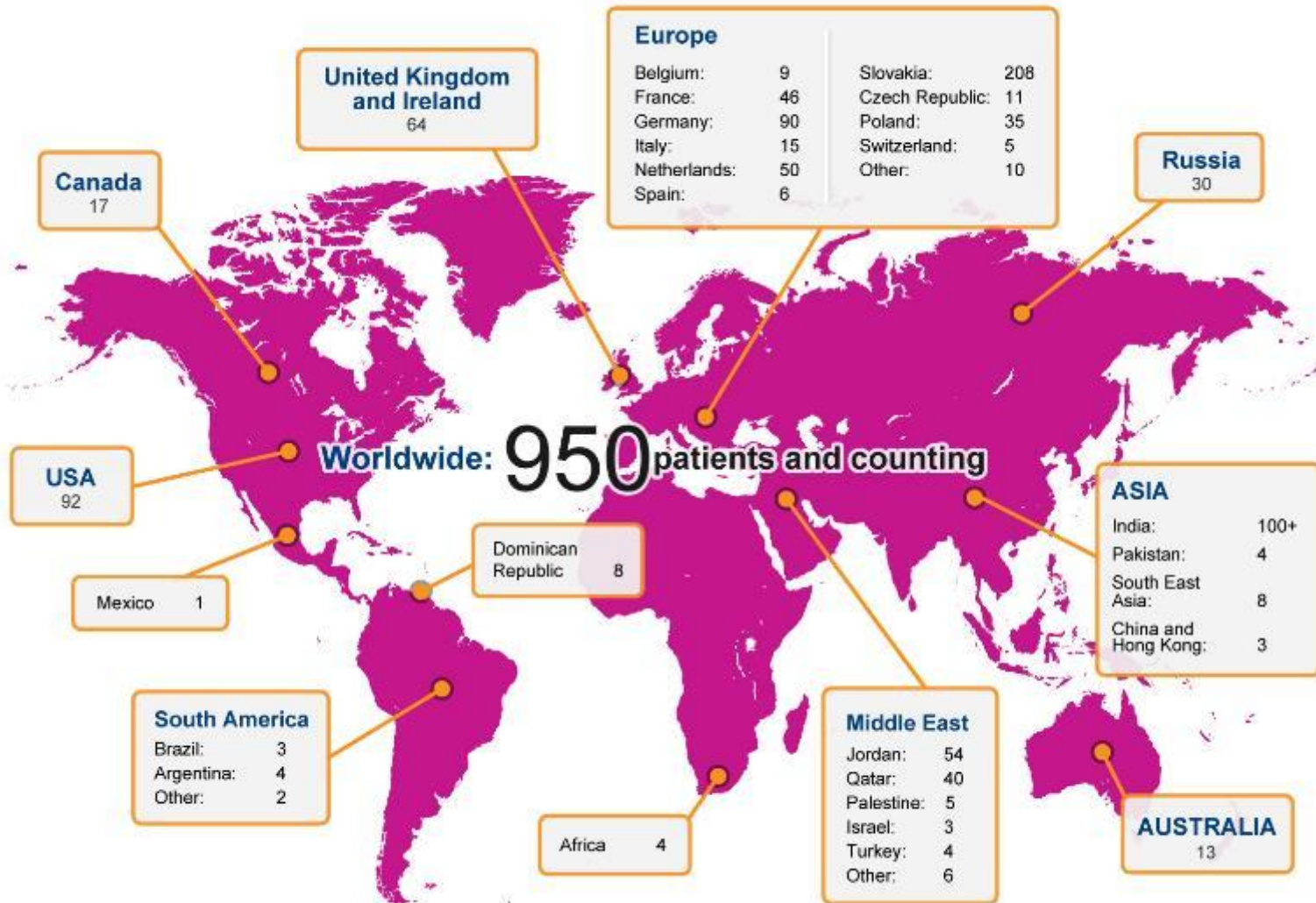
Springer-Verlag



Step 2:

Building a global patient movement

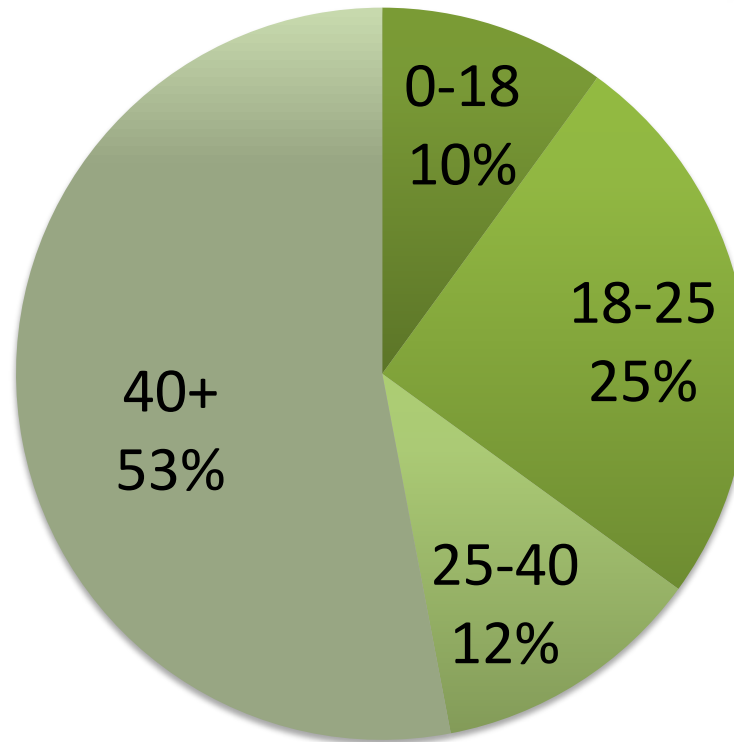
A global patient movement



AKU Societies in EU, Asia, Middle East and North America

- AKU Society UK
- ALCAP (France)
- AIMAKU (Italy)
- AKU Society Germany
- AKU Society Netherlands
- AKU Society Jordan
- AKU Society India
- AKU Society Slovakia
- AKU Society North America (USA and Canada)
- AKU Society Belgium (in progress)

Age of diagnosis of AKU patients



How many misdiagnoses are there?

Average cost of an AKU patient

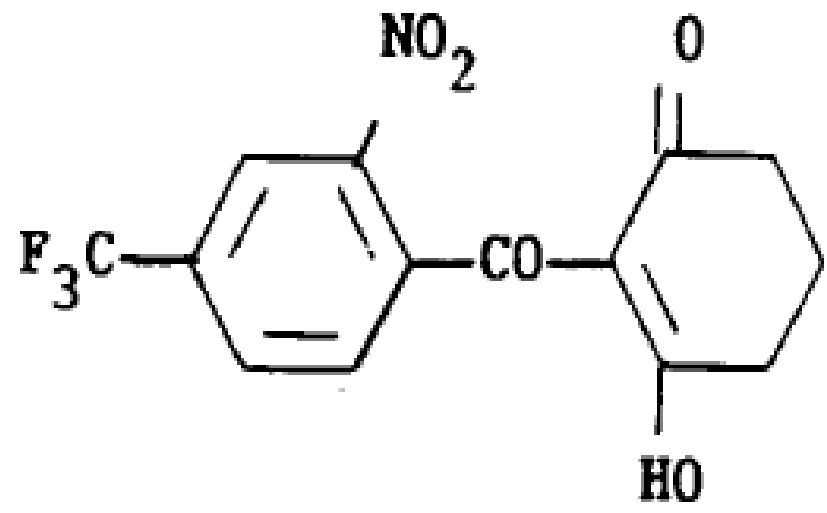
- Direct costs from one AKU patient for one year can be in excess of £100,000
- A weighted average of all scenarios shows total direct health care costs of approximately £1m may be a reasonable conservative estimate
- A conservative approximation of total costs of AKU in UK including indirect costs (lost wage and production) is £1.4m - £2m per year, with the upper limit as high as £7m



Step 3:

**Setting up a strong clinical
development programme**

Nitisinone



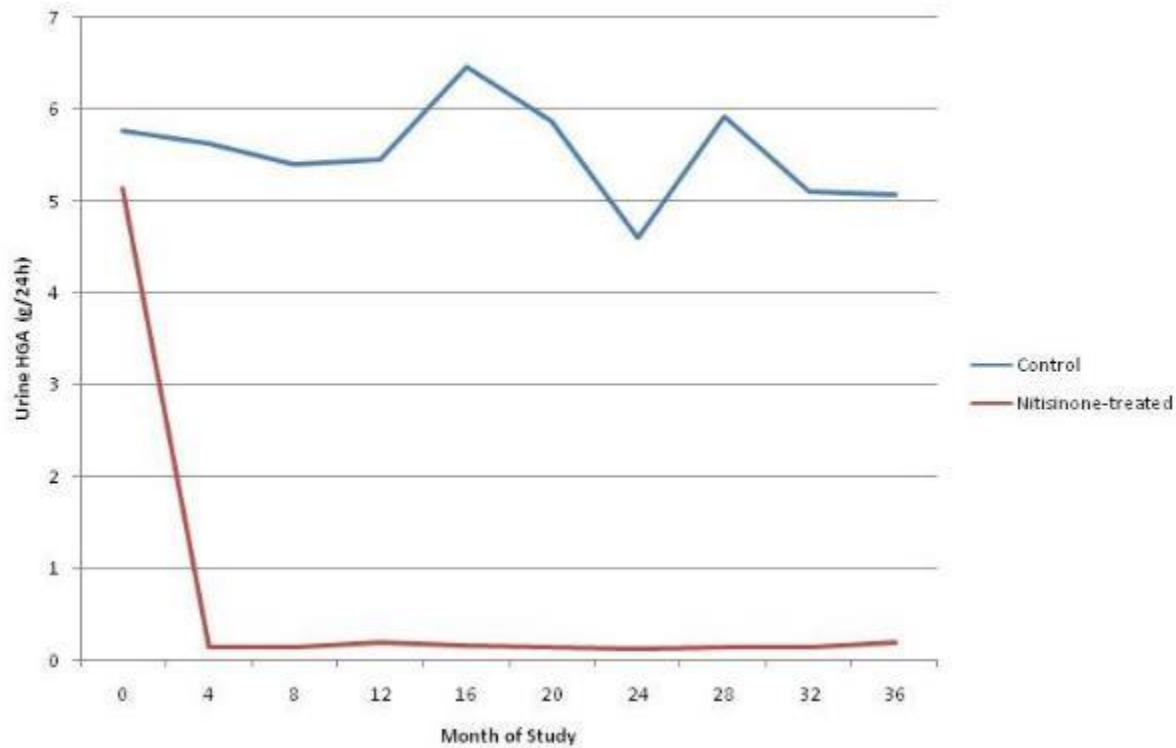


**Nitisinone reduces
homogentisic acid by**

95%

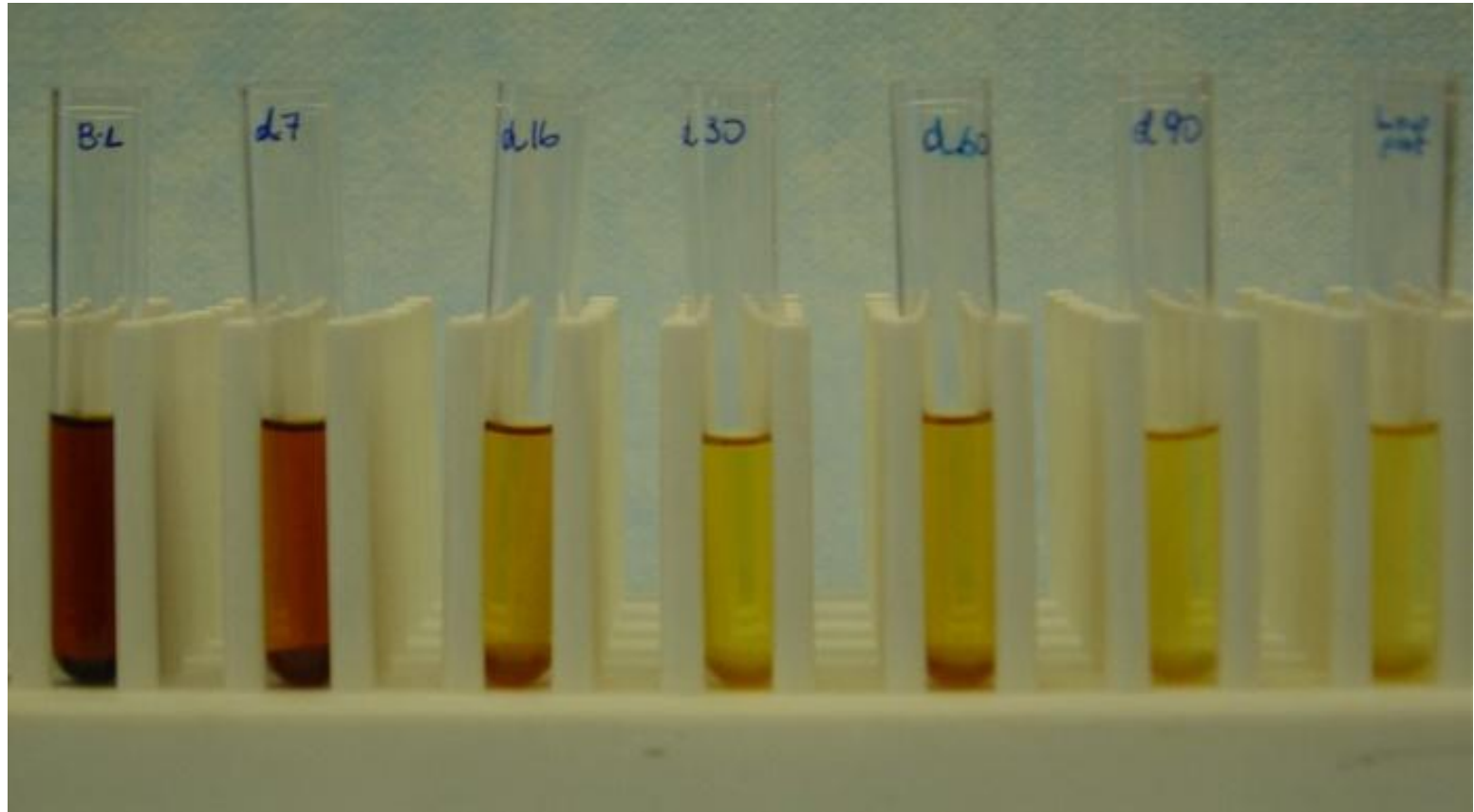
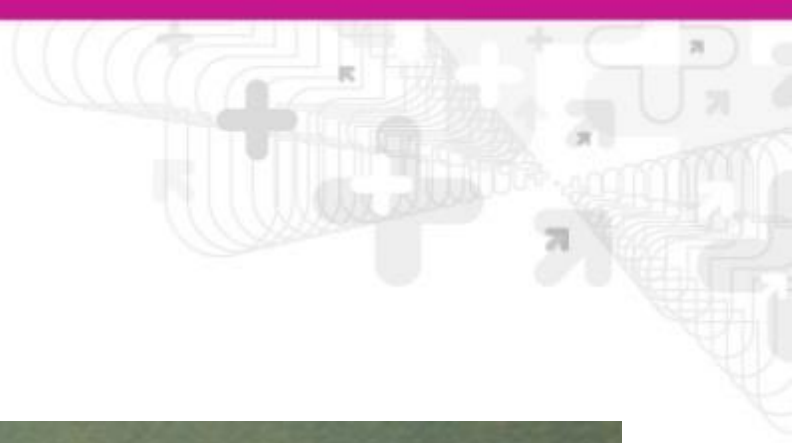
Urinary HGA

Figure 1.



National Institutes of Health

Urinary HGA



Pre-Ochronotic

Ochronotic phase

Slower

Rapid

100

Asymptomatic

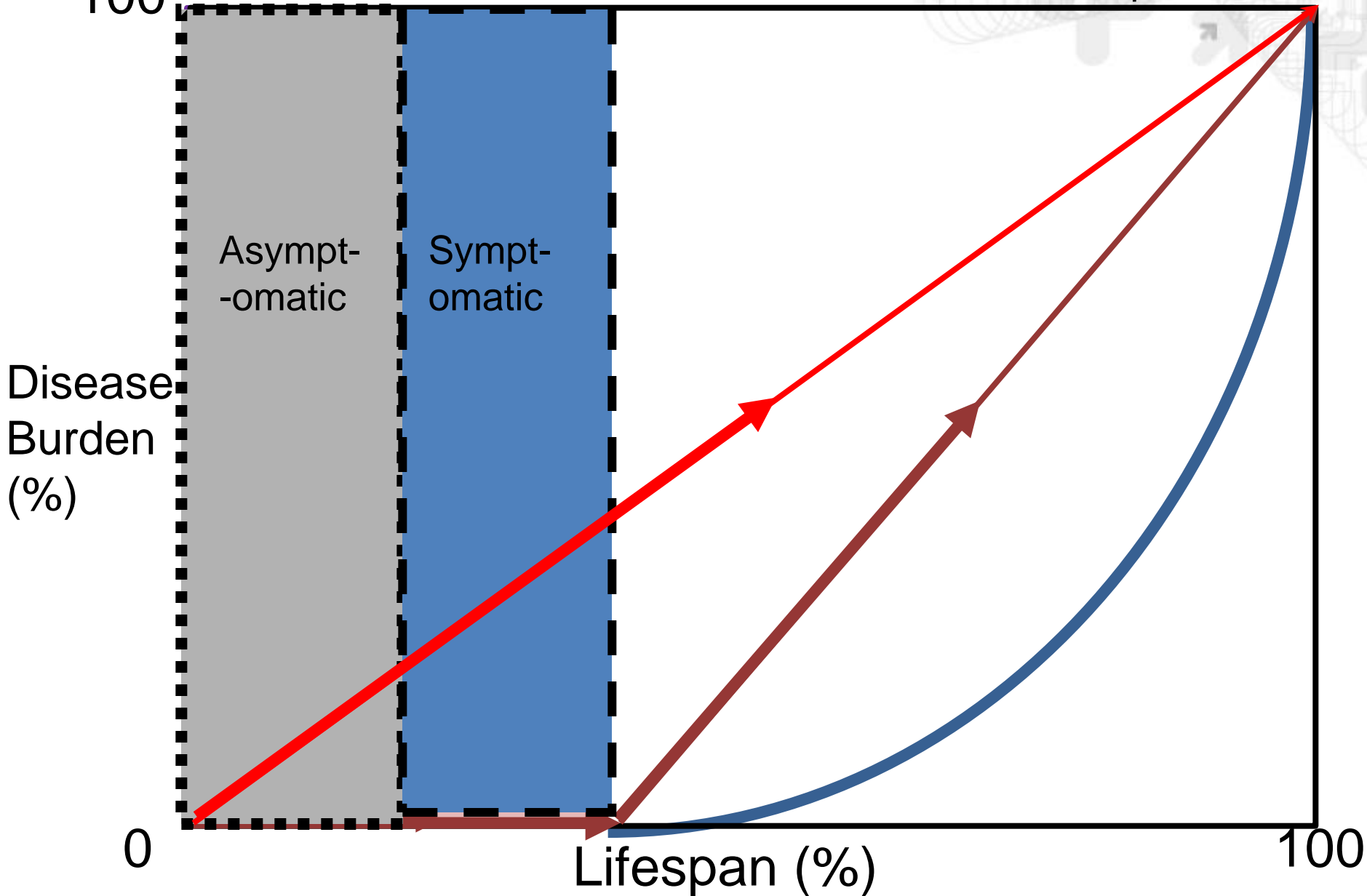
Symptomatic

Disease Burden (%)

0

Lifespan (%)

100



Three stage development plan



- Drug response study
- Clinical efficacy phase 3 trial
- Cross-sectional study to determine age of treatment



Step 4:

**Putting together a solid EU
consortium**

The DevelopAKUre partners

The Royal Liverpool and
Broadgreen University Hospitals
NHS Trust



UNIVERSITY OF
LIVERPOOL



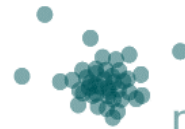
Hôpital Necker
Enfants Malades



INSTITUT NECKER



UNIVERSITY OF SIENA



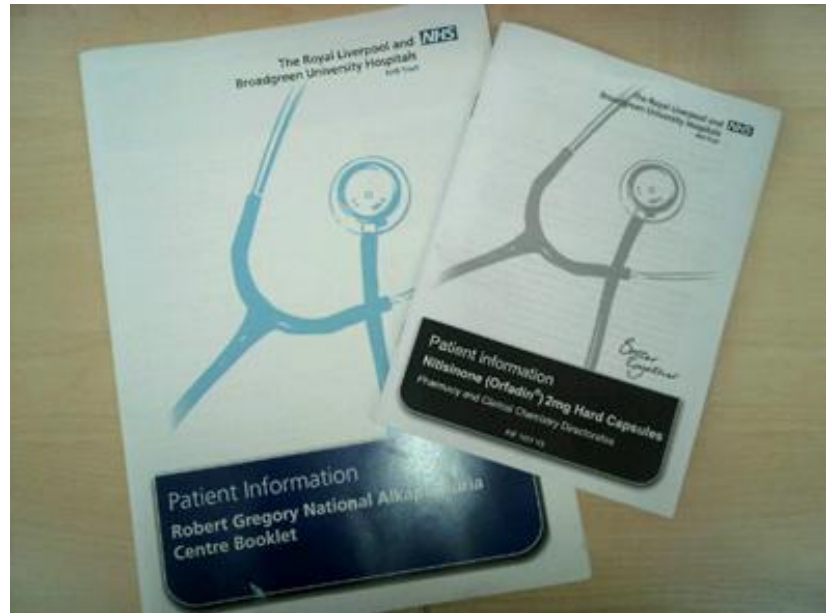
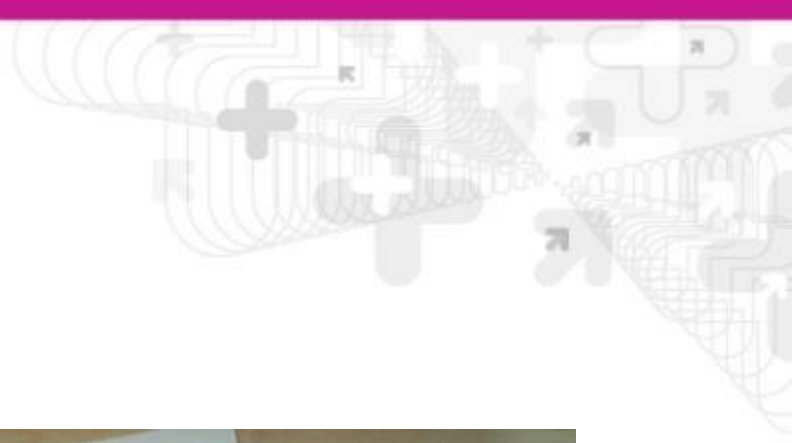
nordicbioscience





Step 5:

Setting up a clinical reference centre



The Robert Gregory National Alkaptonuria Centre



Funded by NHS England



Step 6:

Launching DevelopAKUre





Step 7:

**Our global campaign to raise awareness
and funds for DevelopAKUre**

**HELP US
CURE BLACK
BONE DISEASE**



HELP US
CURE BLACK
BONE DISEAS

Cure Black Bone Disease

Three years ago, Nick gave up his job to devote himself to find a cure for Black Bone Disease, which affects his boys. Please help him by donating now!

Health – Cambridge, United Kingdom

Campaign Home

Updates / 28

Comments / 202

Funders / 1469

Gallery / 43



\$98,685

Raised of \$98,000 Goal

🕒 0 time left

Flexible Funding

This campaign has ended and will receive all funds raised. Funding duration: August 31, 2013 - October 20, 2013 (11:59pm PT).

Select a Perk *for your contribution*

\$11

Your name on our website!

For an \$11 donation, you will get your name on

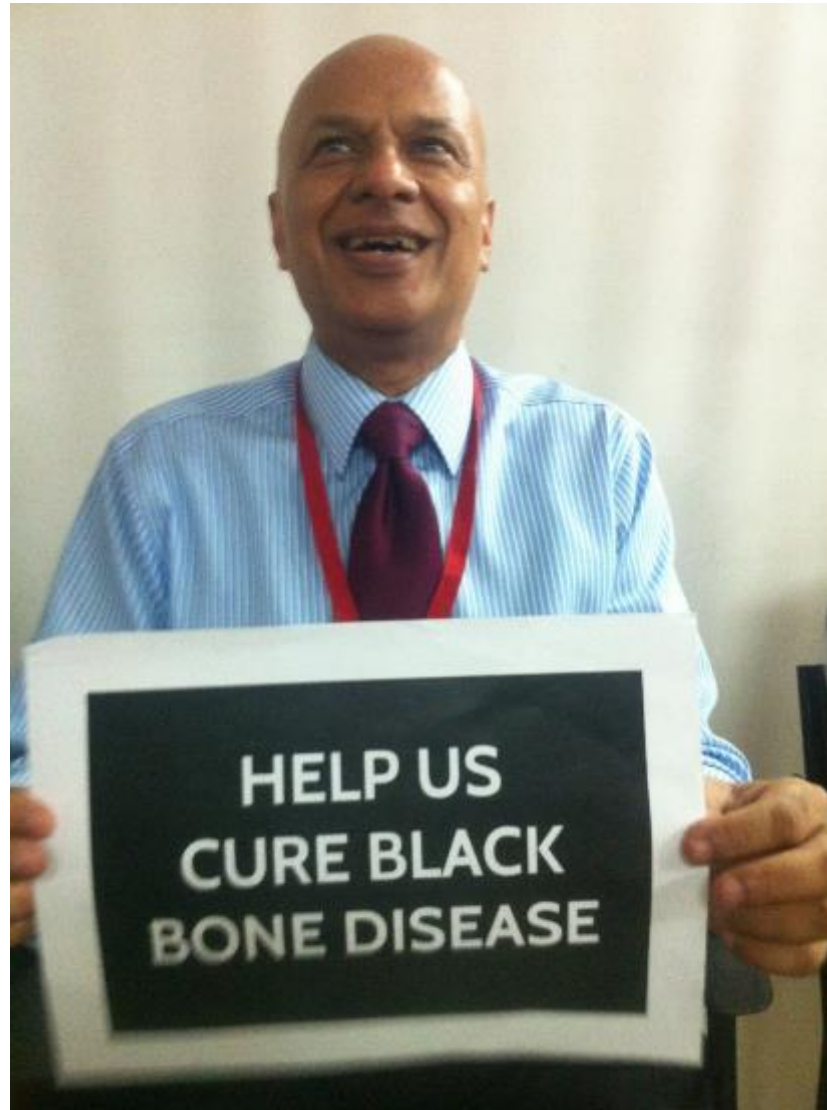
AKU patient Ann Kerrigan



B M John Rajkumar, AKU patient and head of the 500,000-strong Tamil Nadu Gypsy Society



Prof Ranganath, Coordinator of DevelopAKUre



The AKU Society team



We made it!

Our campaign had **28,598** visits over

50 days which led to **1469** donors

from **40** countries donating a total of

\$98,685 on Indiegogo.

\$6123 was also donated offline taking us to a

grand total of **\$104,808**

We couldn't have done it without your help. Every dollar donated and every email, tweet or facebook post sent has helped us reach our goal.

So we would like to say a great big



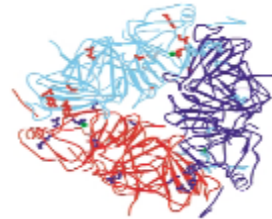
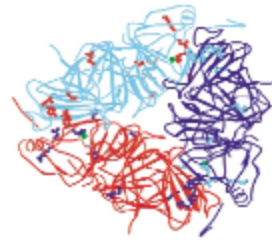


Step 8:

Working on other therapies

Gene and enzyme therapies

Imperial College
London

The logo for Protein Technologies, featuring a stylized orange molecular structure above the word "PROTEIN" in orange and "TECHNOLOGIES" in black below it.

PROTEIN
TECHNOLOGIES



www.akusociety.org
www.developakure.eu