AKU International Patient Workshop 2024

AKU

Alkaptonuria Society

Housekeeping

Please note, there is no fire drill planned at the hotel today. If the fire alarm sounds, please walk out to the coffee area and take the stairs left of the coffee stations.

If you would need assistance, please fill out the fire procedure from - we will collect these and give these to the hotel team.

UNIVERSITY OF LIVERPOOL

Department of Musculoskeletal and Ageing Science

OVERVIEW OF AKU RESEARCH

AT THE UNIVERSITY OF LIVERPOOL

Dr Juliette Hughes
Lecturer in Anatomy

14th November 2024
AKU International Patient Workshop 2024

Who am I?

Lecturer of Anatomy | AKU researcher | Cat owner

Background

- BSc Human Anatomy and Biology (2012
- Master of Biological Science (2015-16)

- PhD Musculoskeletal Biology (2016-2

- Lecturer of Anatomy (teaching only) (2021-2
- Lecturer of Anatomy (teaching & research) (2023-pres
  - Research into AKU continues

Phenotyping of a new conditional mouse model of alkaptonuria and investigation of nitisinone-induced tyrosinaemia

- Characterised our newest mouse model of AKU
- The liver is the crucial for HGD activity and HGA breakdown
- Dietary restriction is effective at reducing serum tyrosine

University of Liverpool AKU research team Nov 2024

Principal Investigators

Prof George Bou-Gharios

- Gene therapy
- Expert in mouse models
- Expert in cartilage and osteoarthritis

Dr Juliette Hughes

- AKU and osteoarthritis mouse models
- Pigmentation of tissues

Dr Brendan Norman

- Metabolomics
- Tyrosinaemia

Prof Roy Goodacre

- Biological chemist
- Spectroscopy techniques

Prof L. Ranganath

NAC/Royal

Many collaborator

Patient samples

Post-doc researchers

Dr Peter Wilson

Dr Hazel Sutherland

PhD students

Rebecca Brown 2nd year

- Gene therapy for AKU

Dominic Rutland (just finished)

- Role of the kidney in AKU

Daisy Quinn 1st year

- Role of the calcified cartilage in AKU and OA

Fran Congues 1st year

- Tyrosine metabolism and oxidative stress

Harriet Willett 3rd year

- Analytical techniques to study pigmentation

Prof Jim Gallagher

Summary of work in AKU

https://akusociety.org/information-and-support/history-of-aku/

Lots of success in AKU research over the years

- Nitisinone was shown to be effective at reducing serum HGA in mice and preventing pigmentation
- SONIA-1, SONIA-1, SOFIA studies
- Started to understand pigmentation of cartilage

1500 BC – Earliest evidence of AKU in Harwa the Egyptian mummy

1584 AD – A German doctor, Dr Scribonius, describes the urine of a patient turning black when left in air

1859 – Dr Boedeker names the chemical that darkens urine as an "alkapton", and therefore calls the associated disease: "alkaptonuria"

1866 – Dr Virchow describes the pigmentations seen in the cartilage of AKU patients and calls the process: "ochronosis"

1902 – Sir Archibald Garrod describes alkaptonuria as an inherited disease

1908 – Sir Archibald Garrod defines an inborn of metabolism, using AKU as an example

1958 – Dr La Du shows that AKU is caused by a lack of an enzyme, homogentisate dioxygenase (HGD)

1993 – Dr Pollak maps the AKU mutation to chromosome 3

1994 – Dr Montagutelli shows that some mice naturally develop AKU

2003 – AKU Society founded by Bob Gregory and Prof Ranganath

2008 – The US National Institute of Health conclude their unsuccessful clinical trial testing nitisinone in AKU patients (results were published in 2011)

2011 – Results of the first coordinated identification campaign of AKU patients in the UK

2011 – Dr Taylor and colleagues show the progression of pigmentation in AKU patient cartilages

2012 – Launch of the National AKU Centre (NAC)

2012 – Launch of the DevelopAKUre clinical trials, which aimed to reassess the effects of nitisinone in AKU patients

2012 – Dr Taylor shows AKU in mice is the same disease as in humans

2013 – Dr Preston shows AKU in mice can be treated by nitisinone

2013 – SONIA 1 (the first study in DevelopAKUre) ends, with results confirming that nitisinone does lower HGA and setting the correct dose for future study (results were published in 2015)

2014 – SONIA 2 (the second study in DevelopAKUre) begins, aiming to compare the effects of nitisinone against no treatment

2019 – End of the SONIA 2 clinical trial and notification that nitisinone does effectively lower HGA by 99%. Sobi submit the findings to the European Medicines Agency (EMA).

2020 – Based on the success of DevelopAKUre and SONIA 2, the European Medicines Agency (EMA) recommend that nitisinone be extended as a treatment for AKU.

2020 – The European Commission (EC) extends the existing marketing authorisation for nitisinone use in AKU. Nitisinone receives a licence for its use in the treatment of AKU.

Research plans as a group

Brendan Norman will speak about this next

Short-term

Nitisinone-induced tyrosinaemia

Role of oxidative stress in AKU

New project

Effect of HGA, Tyrosine and Pigment on the body

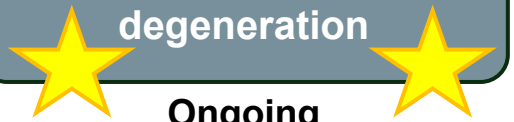
Long-term

Gene therapies for AKU

Chemical reaction of HGA to pigment

Ongoing

Ochronosis and tissue degeneration



Ongoing

AKU mouse models

- Use this for understanding biology of AKU
- Pre-clinical studies of treatment/drugs/interventions

AKU mouse

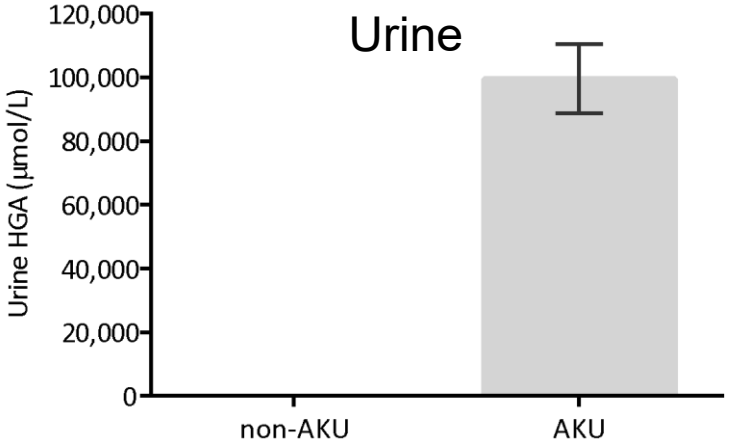
- **Have dark urine**

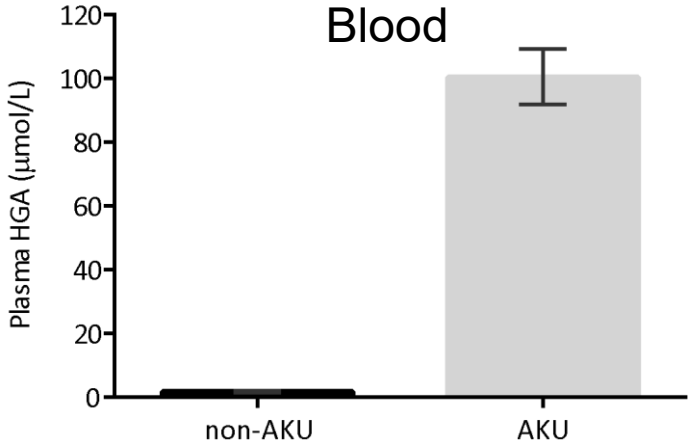
Fresh bedding

AKU mouse bedding

AKU mouse

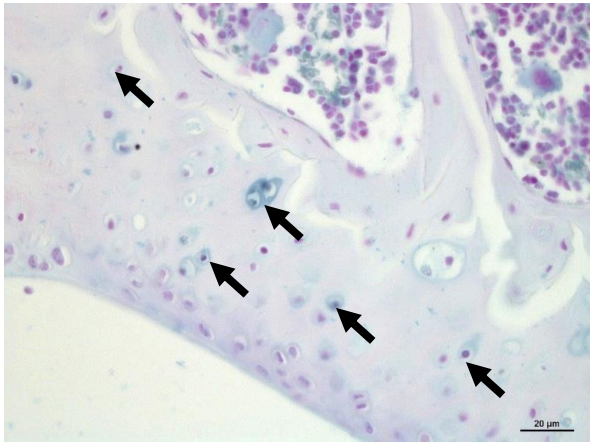
- Have dark urine
- **Have elevated urine HGA**
- **Have elevated plasma HGA**



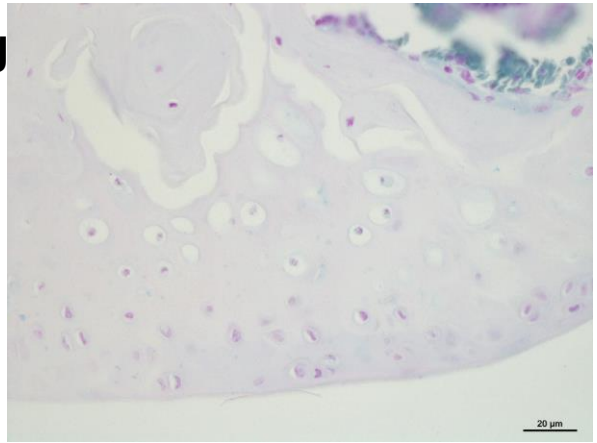


AKU mouse

- Have dark urine
- Have elevated urine HGA
- Have elevated plasma HGA
- **Have pigmentation of cartilag**
  - **Very mild**



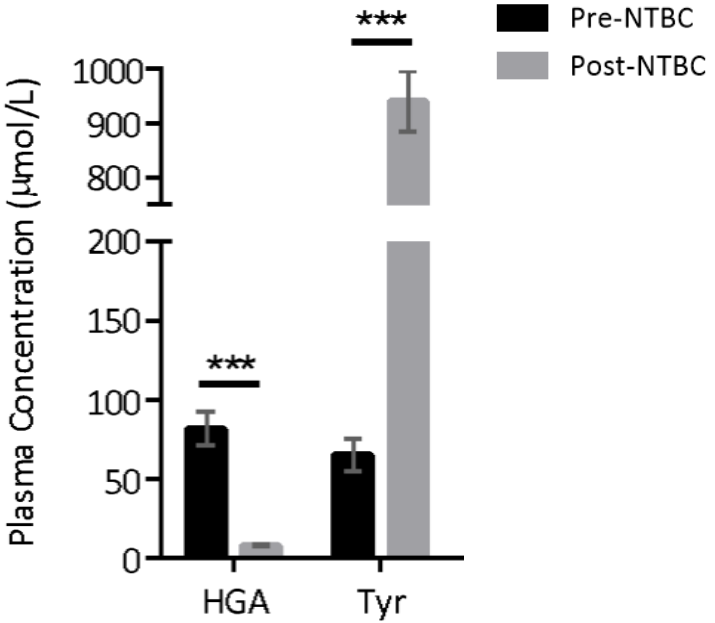
AKU mouse knee
- pigment



Non-AKU mouse knee
- no pigment

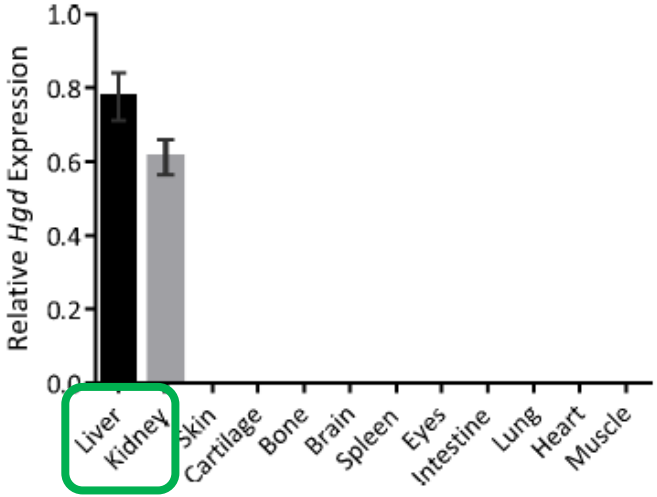
AKU mouse and nitisinone

- Have dark urine
- Have elevated urine HGA
- Have elevated plasma HGA
- Have ochronosis of cartilage
- **Responds to nitisinone treatment**
  - **HGA decreases**
  - **Tyrosine increases**



AKU mouse and HGD location

- Used the new AKU mouse to show where the HGD enzyme is located
- Liver and kidney



- Need to target the liver for future **gene**

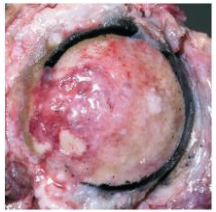
Tissue pigmentation

Overview of major findings from studying AKU tissues

What do we know?

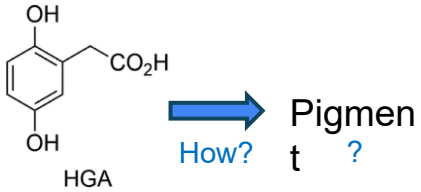
- Despite nitisinone, ochronosis and tissue degeneration is still an issue for many people with AKU.

- Ochronosis affects cartilage more than any other tissue (do not know why..
- Ligaments, tendons and heart valves are also affected.



Questions

- What is the chemical composition of HGA-derived pigment?
- Where does pigment bind to in the tissues specifically?



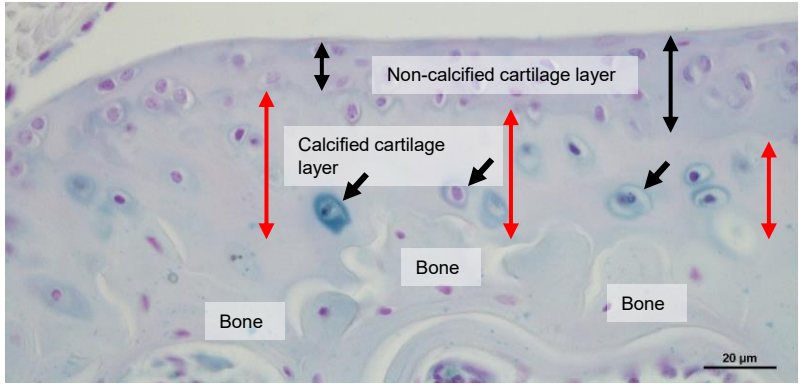
- Why and how does pigmentation lead to tissue degeneration?
  - Joint osteoarthritis
  - Tendon and ligament rupture
  - Heart valve stenosis

Can pigment be removed from tissues?
May help us to understand common degenerative disorders such as osteoarthritis.

How can we investigate tissue pigmentation?

- **AKU mice**
  - ✓ Have high HGA in the blood (like human AKU)
  - ✓ Show mild pigment of cartilage – early stage
  - ✗ Do not get osteoarthritis

- **STR/Ort mice**
  - ✓ Gets osteoarthritis naturally
  - Early changes in cartilage in similar place to AKU



Use a stain in mice tissue to make HGA-pigment turn blue in tissue slices

- **AKU + oxidative stress mice**
  - Does extra oxidative stress make the AKU condition worse? How?

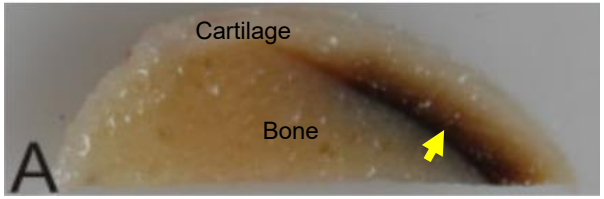
- **Establishing cartilage cell models of AKU**
  - Can add the HGA chemical to the cells (makes them AKU) and induce them to pigment

- **Study of human AKU tissues**

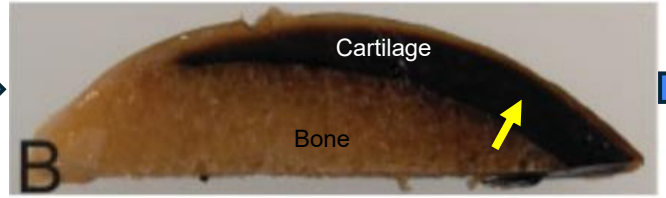
Research highlights from AKU tissue

Pigment begins in the deep cartilage and spreads upwards

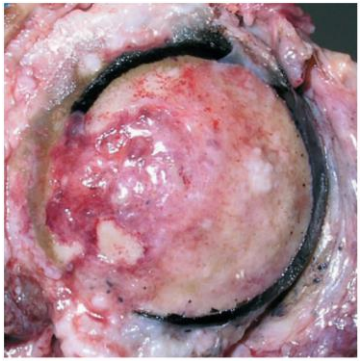
Dark pigment begins in deep calcified cartilage



Pigment progresses towards surface, encompassing the full thickness of the cartilage

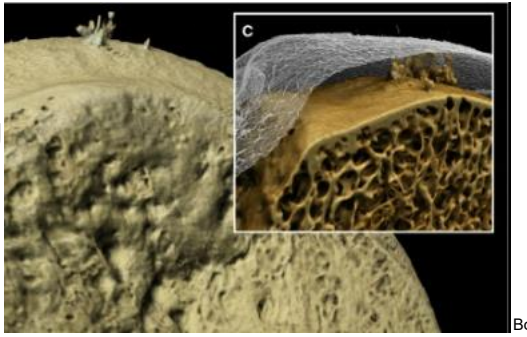


Taylor et al, 2011



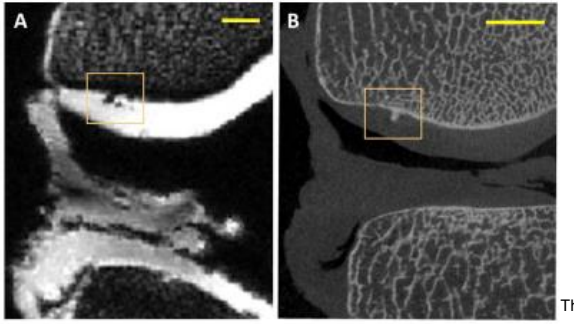
High density mineralised protrusions identified in AKU and then in common OA

AKU



Boyde et al, 2014

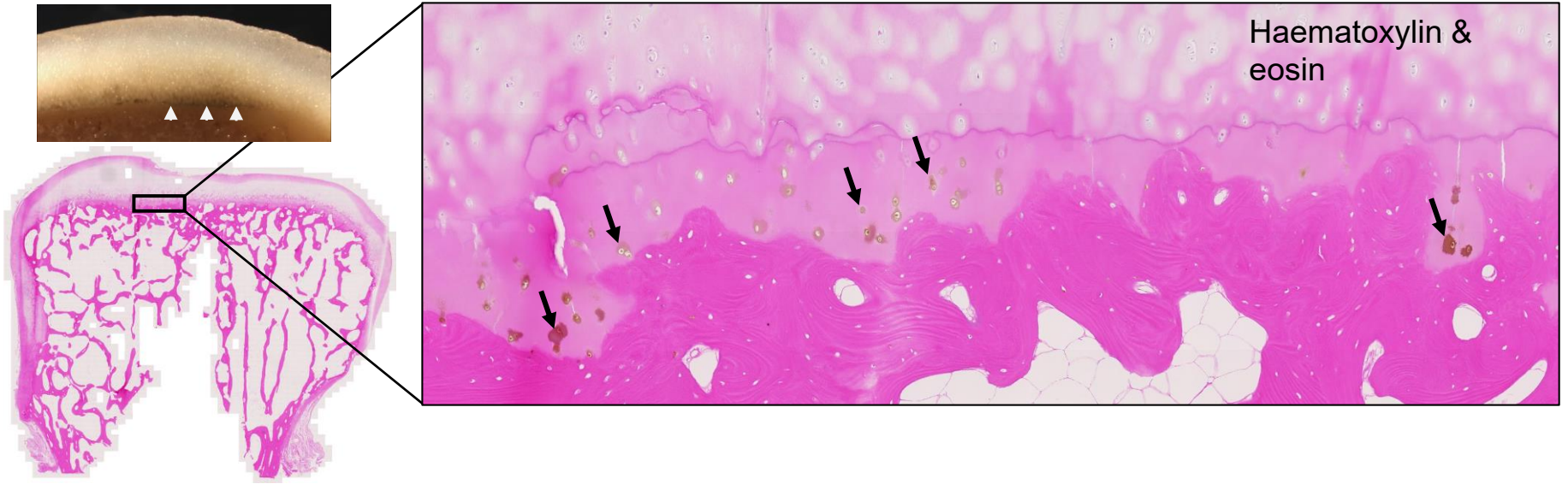
OA



Thomas et al, 2017

Research highlights from AKU tissue

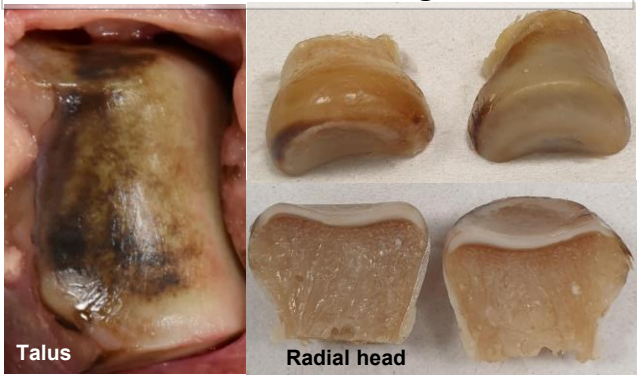
Pigment begins in the deepest cartilage near the bone



Research highlights from AKU tissue

Cartilage pigmentation is not uniform across the body

Articular cartilage

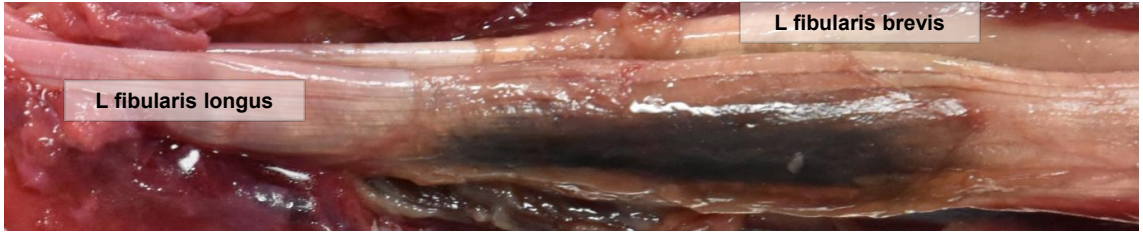


Costal cartilage

All these tissue are from one person with AKU

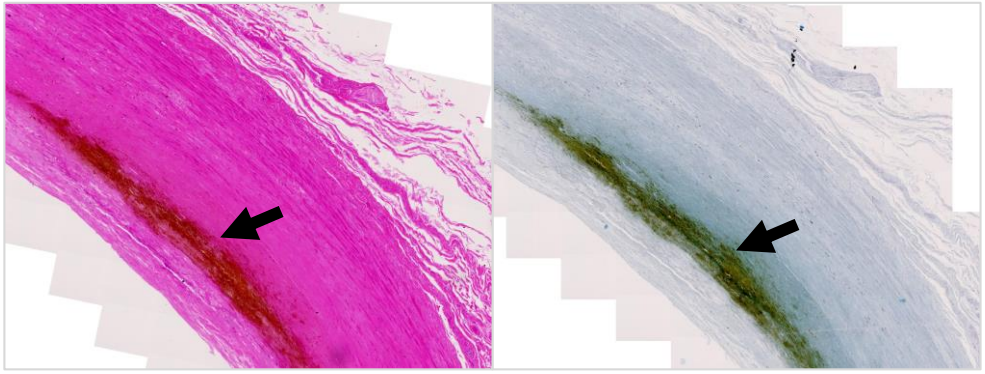
Thank you to the donor and the family

Tendons and ligaments pigment at different rates



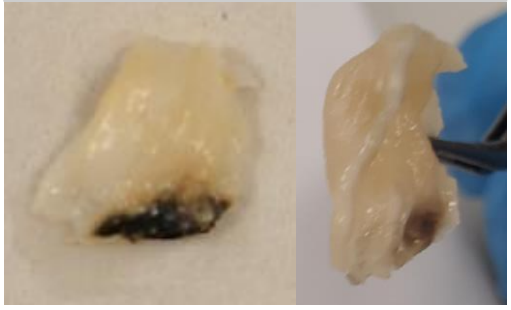
Research highlights from AKU tissue

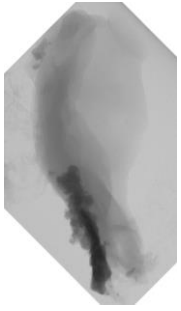
Arteries can become pigmented, but veins do not



Heart valves can pigment, and become calcified

Aortic valve cusp





We still have a lot to learn and understand about HGA and pigmentation across the body

- Cartilage is a major focus

- Tissues that require more investigation include tendon and ligaments, heart valves and the spine

- New targeted treatments require more understanding of the disease mechanisms

- Opportunity to apply knowledge from AKU to other conditions such as osteoarthritis

Thank you

Any questions?

Brendan Slides

Controlling tyrosine without dietary restriction: transporting us to future therapies

Dr Brendan Norman

Research Fellow

Institute of Life Course & Medical Sciences
University of Liverpool

Email: bnorman@liv.ac.uk

UNIVERSITY OF LIVERPOOL

AKU Alkaptonuria Society

My research into AKU

- 2009-2012 **BSc Psychology**
- 2014-2015 **MSc Clinical Neuroscience**
- 2015-2019 **PhD**
- 2019-2022 **Post-doc**
- 2022-present **Sireau Fellowship**

AKU
Alkaptonuria Society

Otsuka jnana Therapeutics

UNIVERSITY OF LIVERPOOL

Australian National University

THE UNIVERSITY OF ALABAMA IN HUNTSVILLE

NHS
Liverpool University Hospitals
NHS Foundation Trust

Tyrosinemi

CONCEPT LIFE SCIENCES

sanofi

Ochronotic pigment chemistry

Harriet Willett

MANCHESTER 1824
The University of Manchester

WARWICK
THE UNIVERSITY OF WARWICK

Understanding tyrosine metabolism

Metabolite biomarker discovery

University of Sheffield

NHS
The Clatterbridge Cancer Centre
NHS Foundation Trust

Liverpool Women's
NHS Foundation Trust

Analytical chemistry

Agilent Technologies

HGA & oxidative stress

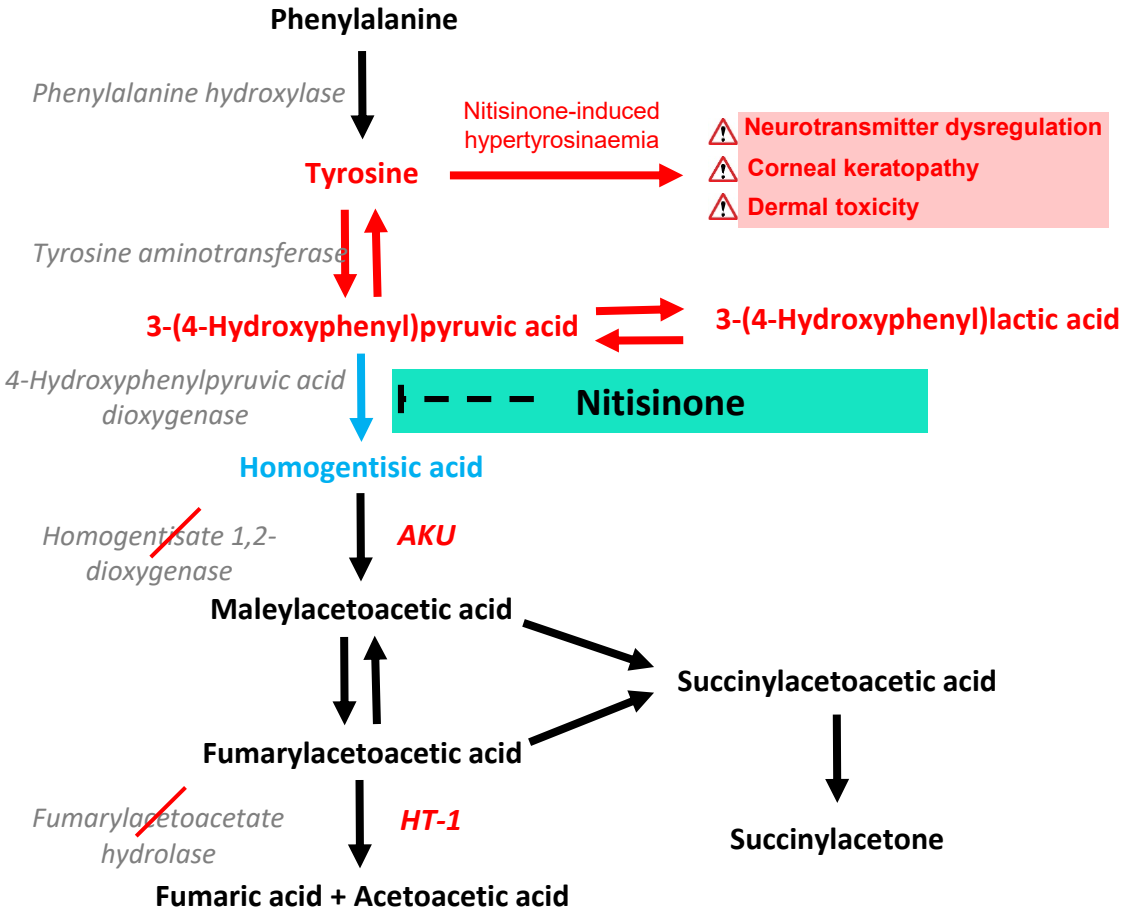
Fran Congues

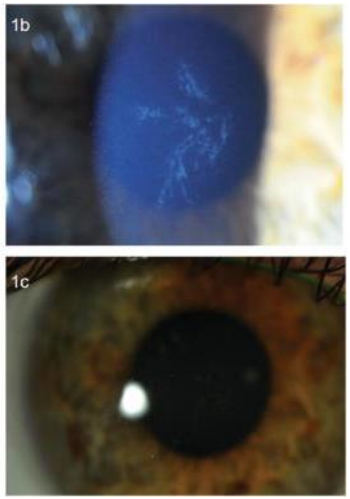
UCL

Future therapies in AKU: gene & mRNA

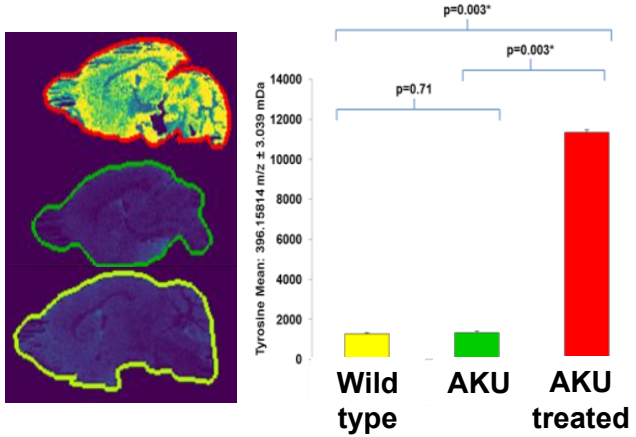
Rebecca Brown

Nitisinone: an effective treatment but not a cure



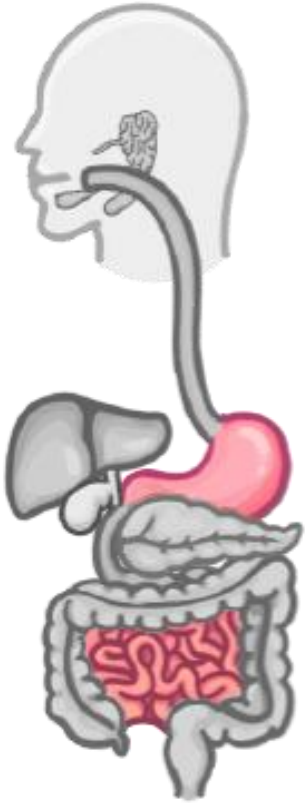


Stewart RM. *JIMD reports*. 2014;*17*:1–6.

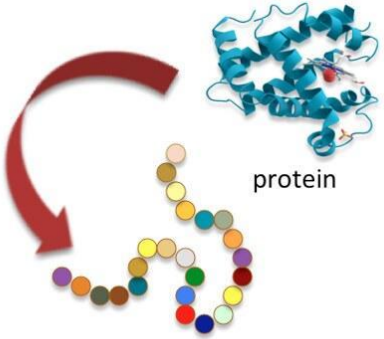


Davison AS et al. *Metabolomics. 2019;15*(5):68.

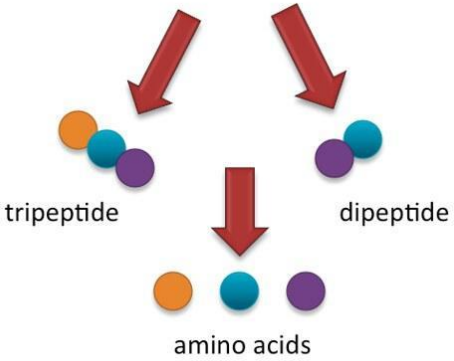
Dietary protein to blood tyrosine: how does it work?



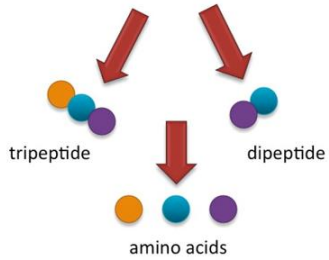
PROTEIN
(POLYMER)



AMINO ACIDS
(MONOMERS)

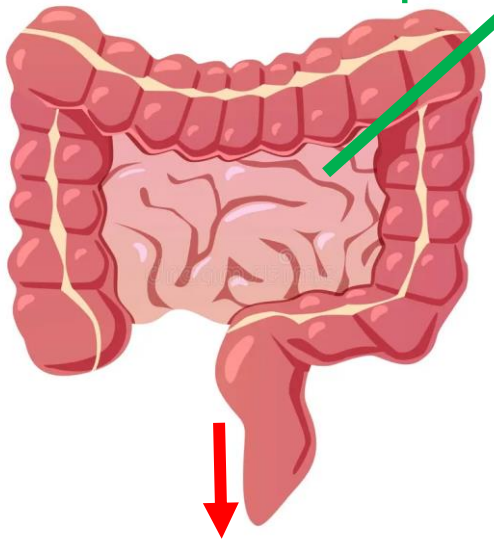


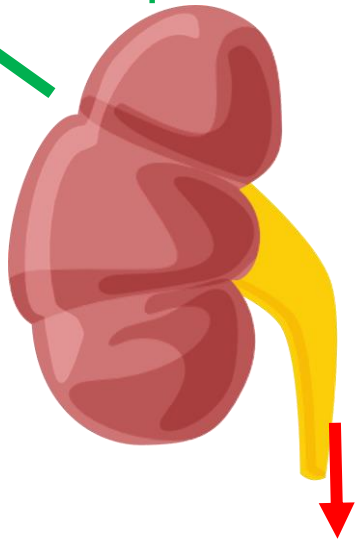
Blood tyrosine concentration – transport is key!



Absorption

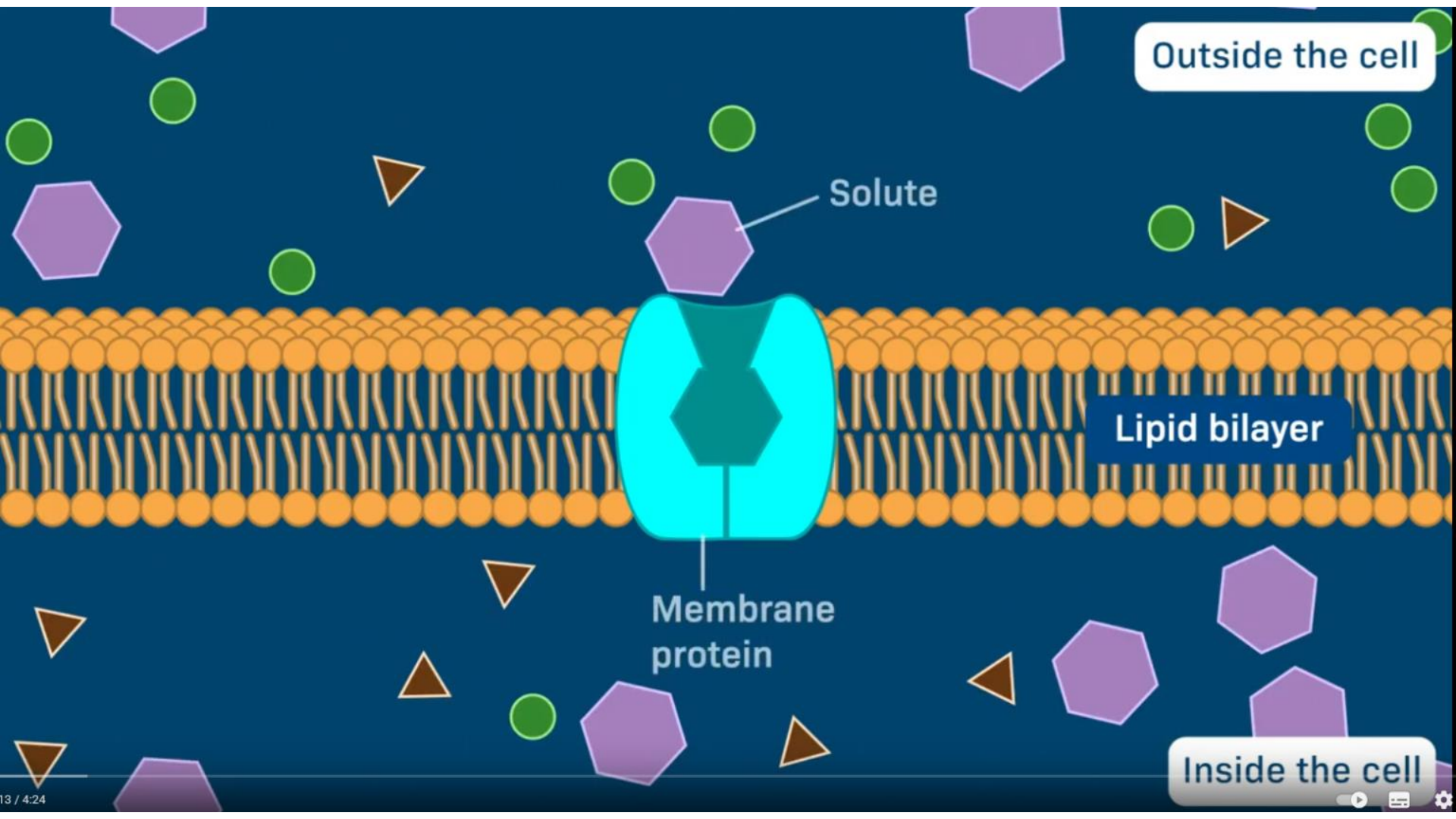
Reabsorption

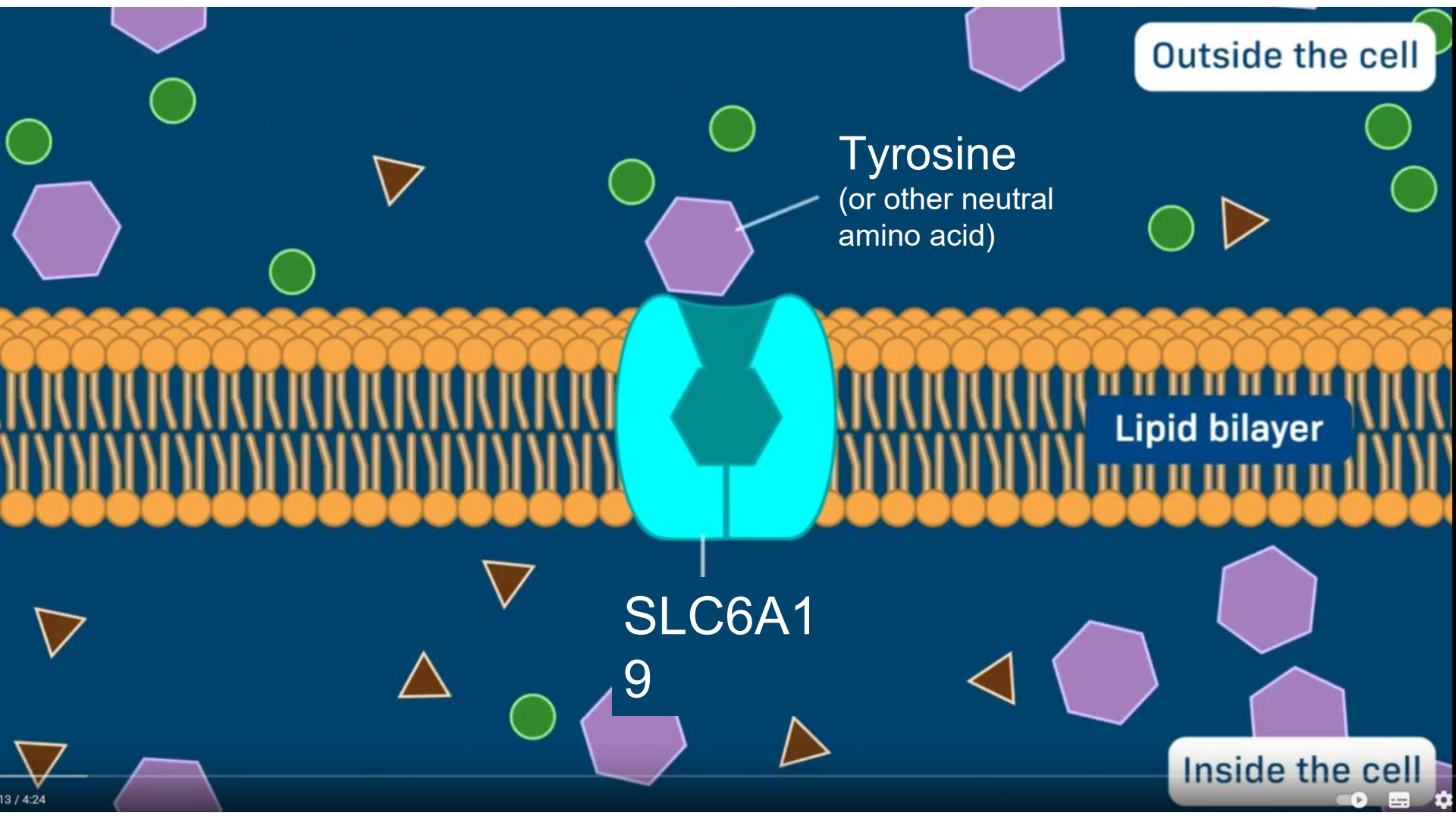


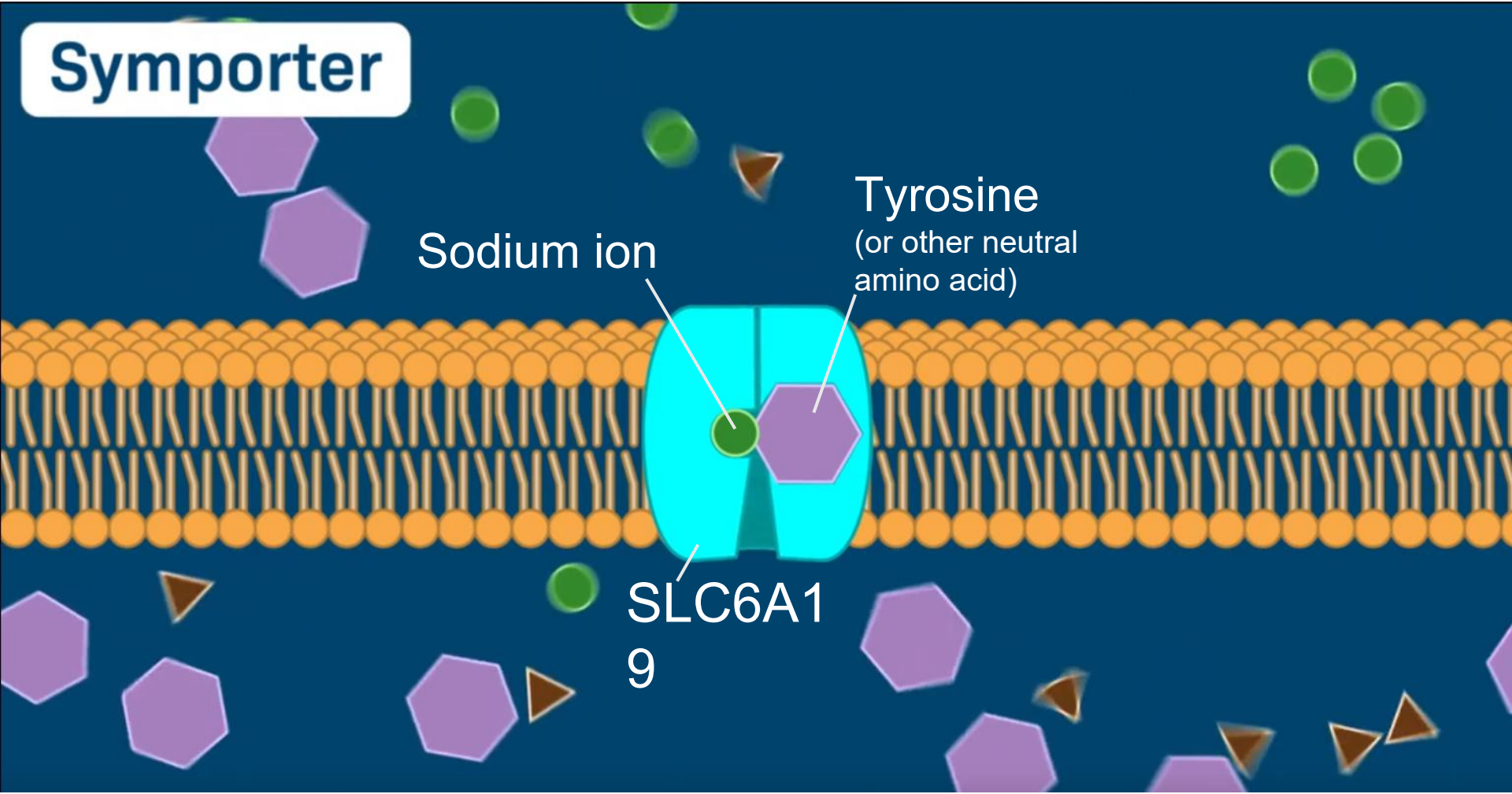


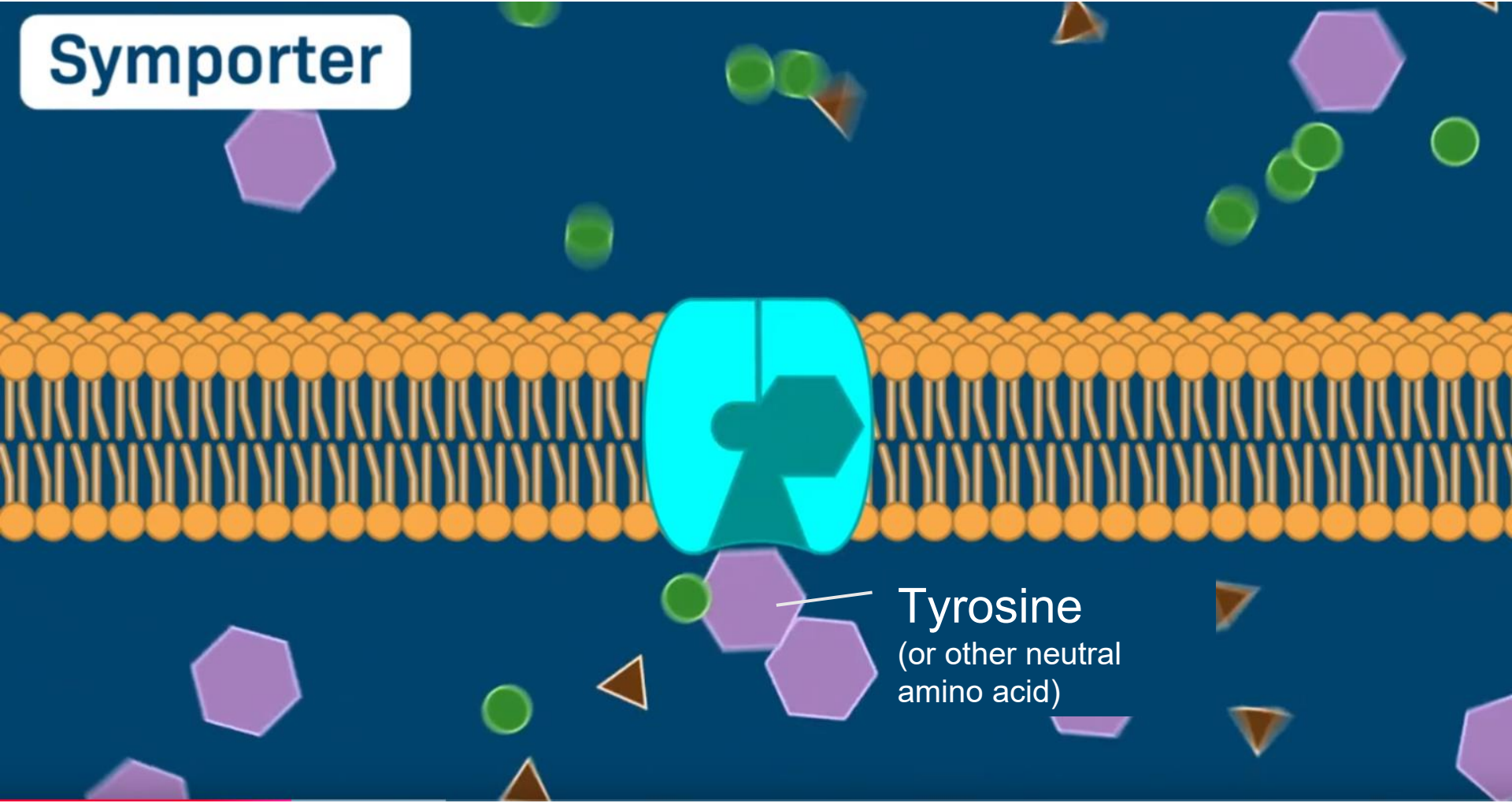
Elimination

Elimination

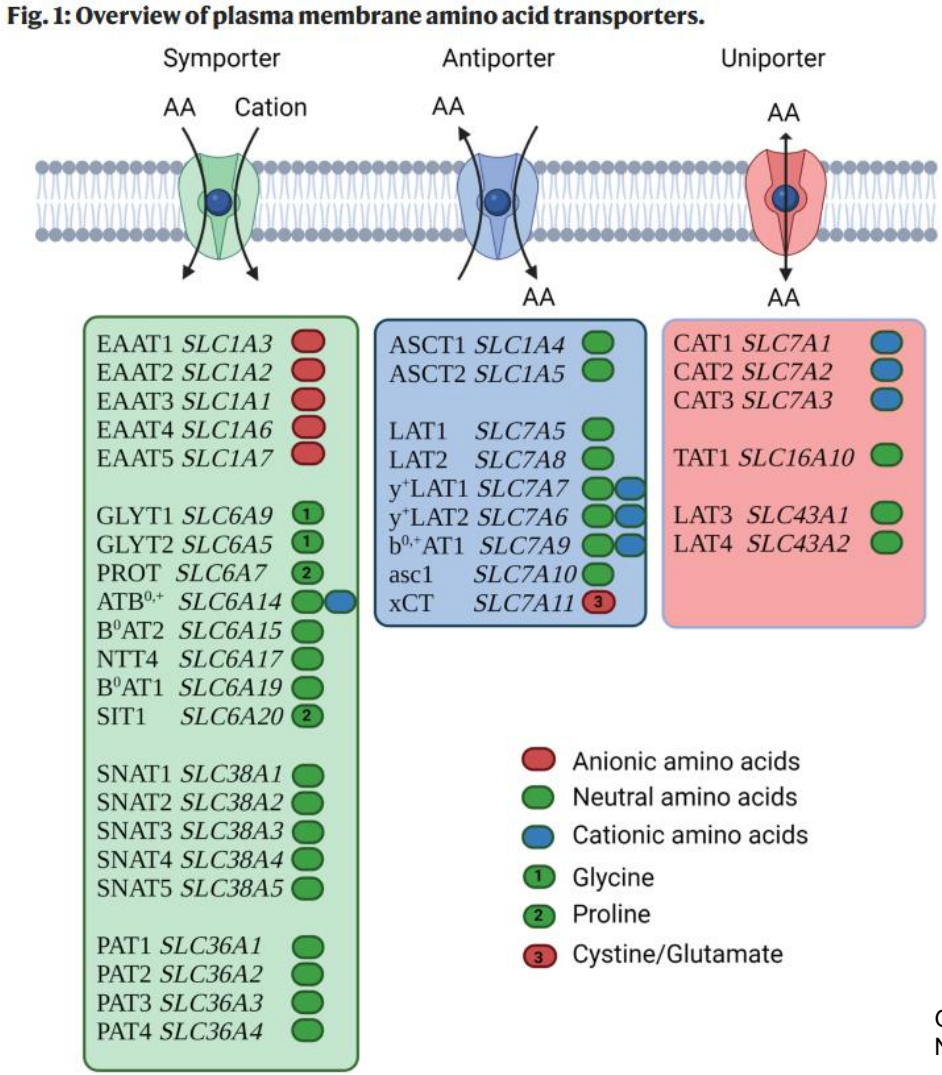

Outside the cell
Solute
Lipid bilayer
Membrane protein
Inside the cell


Outside the cell
Tyrosine
(or other neutral amino acid)
Lipid bilayer
SLC6A1
9
Inside the cell
13 / 4:24


Symporter
Sodium ion
Tyrosine
(or other neutral
amino acid)
SLC6A1
9


Symporter
Tyrosine
(or other neutral
amino acid)

Transporting amino acids:
biology is rarely simple!



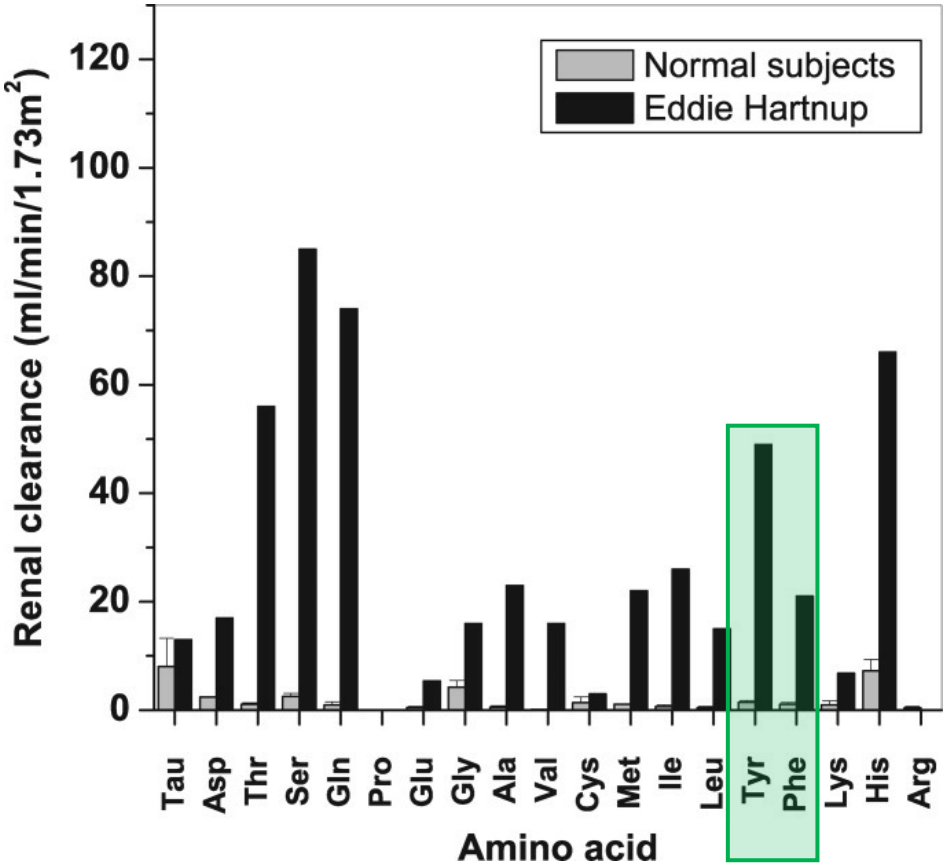
Gauthier-Coles et al.
Nat Comm, 12, 5282.

Amino acid transport in biology

Chaos

Hartnup's disorder: inspiration for new tyrosinemia treatments?

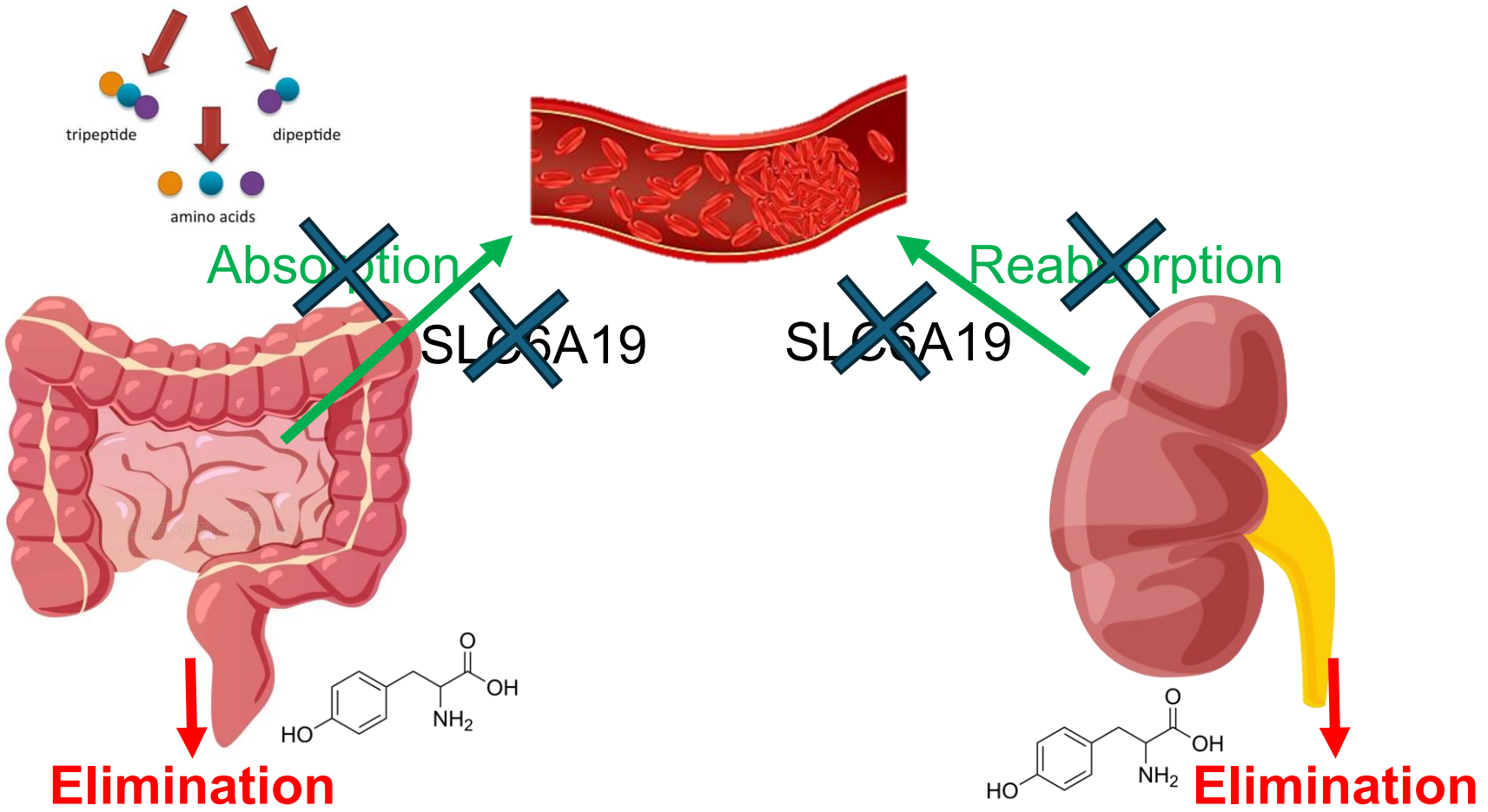
- Specific solute carrier gene mutation causes neutral amino aciduria: **SLC6A19**
- Symptoms: pallegra-like skin rash, cerebellar ataxia (tryptophan deficiency)
- **Can mimicking Hartnup's phenotype be advantageous in some conditions?**



Cusworth & Dent. (1960) *Biochem. J.* 74, 550–561.

Looking beyond dietary protein restriction:
can we reduce tyrosine absorption/reabsorption by selectively blocking the SLC6A19 transporter?

Selective SLC6A19 transport inhibitors exist!



JNT-517, a first-in-class SLC6A19 inhibitor, reduces plasma phenylalanine levels in subjects with phenylketonuria in a phase 1/2 study

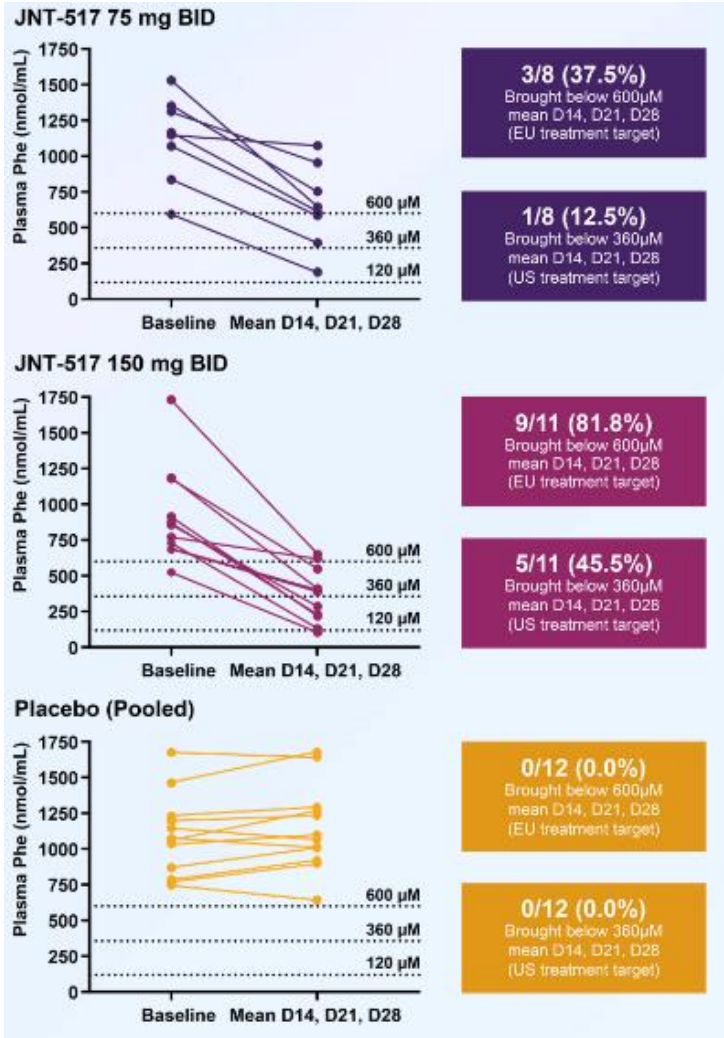
Cary O. Harding[1], Andreu Viader[2], Toby Vaughn[2], Elaina Jurecki[2,3], Nicola Longo[4], Markey McNutt[5], Ania C. Muntau[6], Rani Singh[7], Joel Barrish[2], George Vratsanos[2], Haoling H. Weng[2], John Throup[2]

[1]Department of Molecular and Medical Genetics, Oregon Health & Science University, Portland, OR; [2]Jnana Therapeutics, Boston, MA; [3]National PKU Alliance, San Ramon, CA; [4]Division of Medical Genetics, University of Utah School of Medicine, Salt Lake City, UT; [5]University of Texas Southwestern Medical Center, Dallas, TX; [6]University Children's Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 7Department of Human Genetics, Emory University, Atlanta, GA

Comparison using Mean of D14, D21, and D28 Pre-dose

	75 mg BID cohort (n=8)	150 mg BID cohort (n=11)
Mean percent Phe change vs. pre-dose baseline	44%	60%
≥30% reduction plasma Phe	6/8 (75.0%)	10/11 (90.1%)
≥50% reduction plasma Phe	3/8 (37.5%)	8/11 (72.7%)

"Pee the phe"



Inhibiting <u>SLC6A19</u>: does it work for tyrosine reduction?

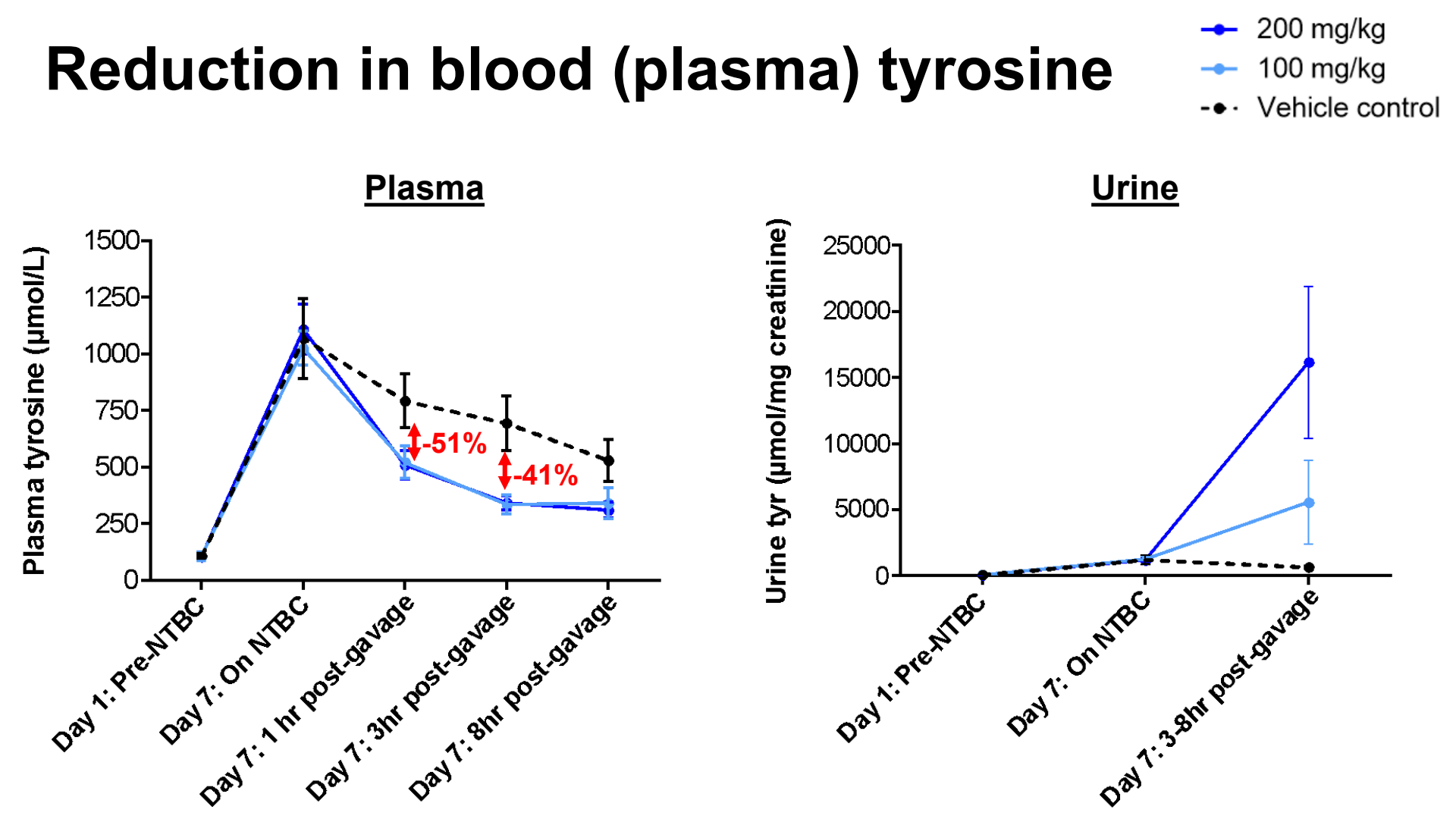
Peter Wilson

Hazel Sutherland

Juliette Hughes

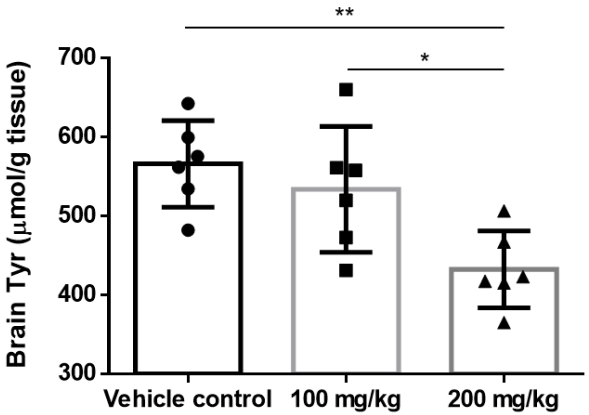
Rebecca Brown

Reduction in blood (plasma) tyrosine

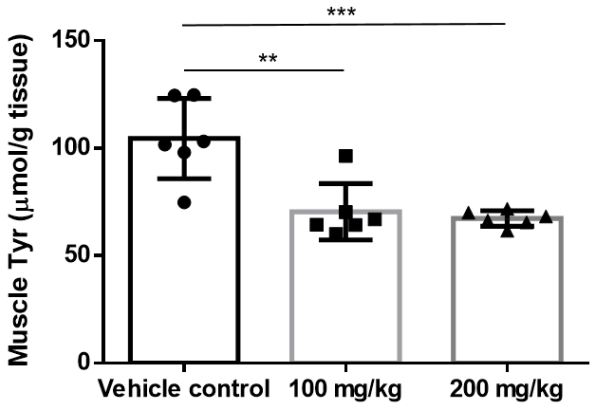


Reduction in tissue tyrosine

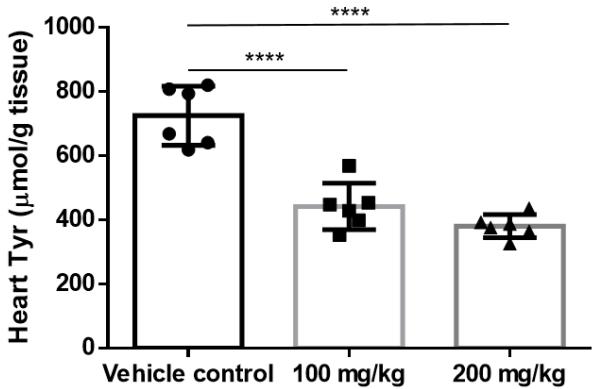
Brain



Quadricep muscle



Heart



* P <0.05
** P <0.01
*** P <0.001
**** P <0.0001

Longer-term study, tool compound #2

NTBC

SLC6A19i diet
(500 or 250 mg/kg)

Week 0 -1 | Weeks 1-3 | Weeks 3-6 | Weeks 6-9 | Weeks 9-12

Pre-NTBC

Pre-diet

3 weeks on diet

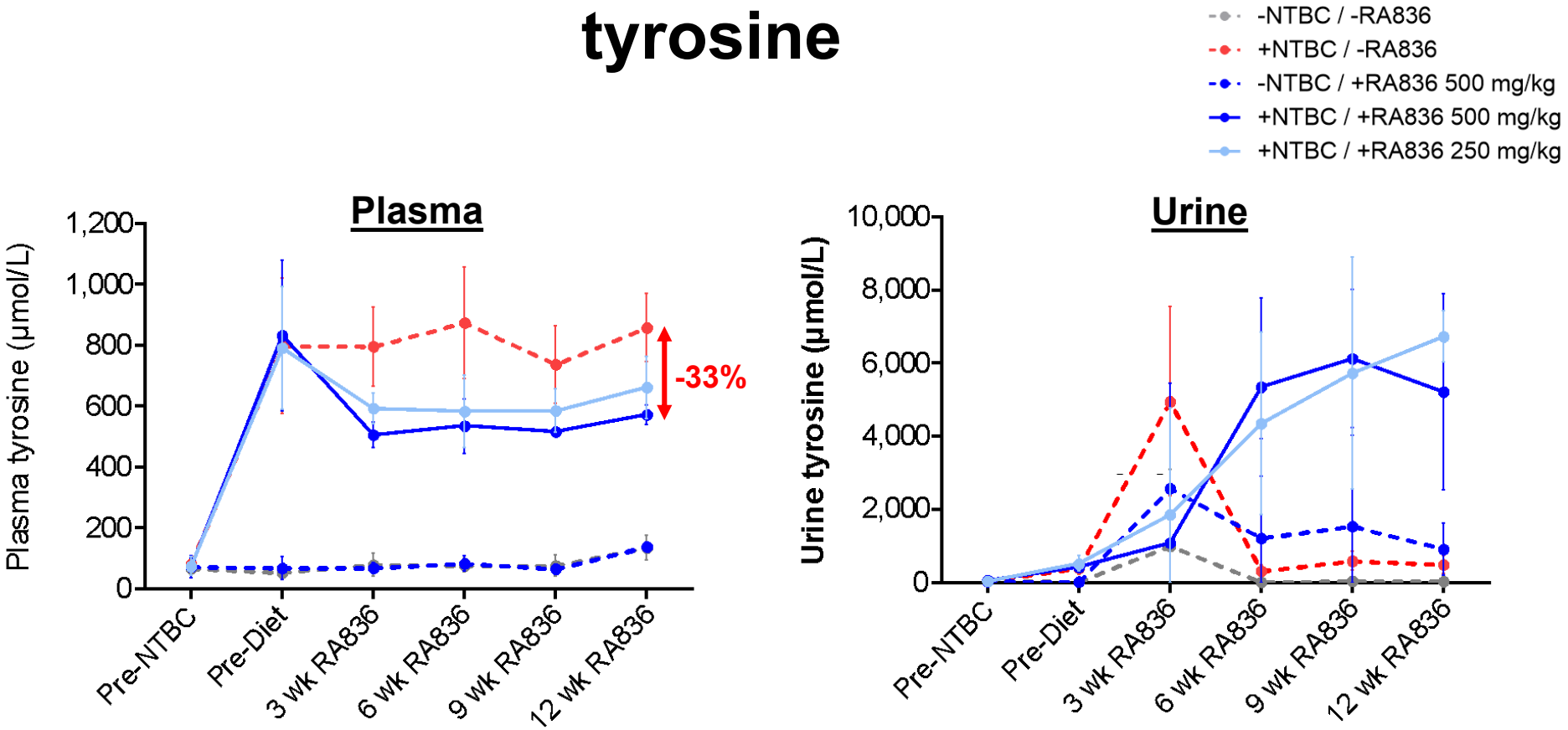
6 weeks on diet

9 weeks on diet

12 weeks on diet

Sampling (plasma & urine)

Sustained reduction in blood (plasma) tyrosine

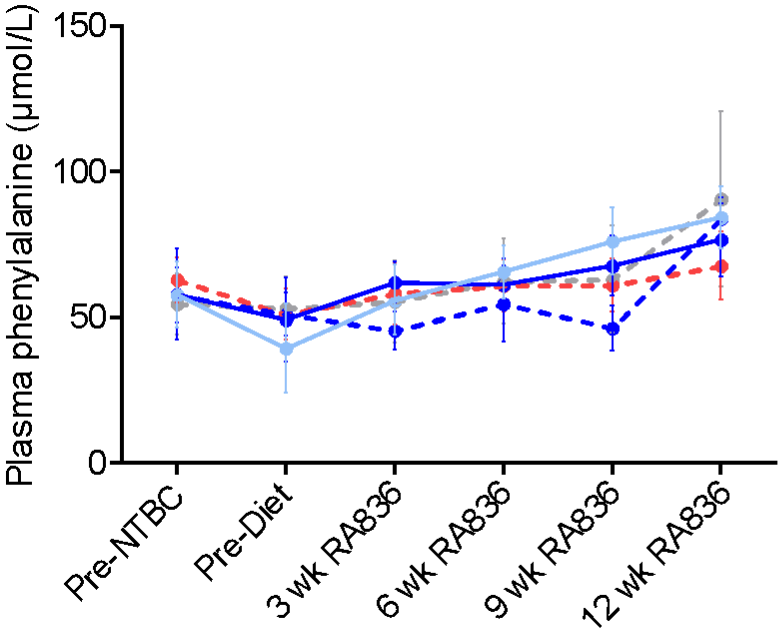


Missing data: 5 missing samples across dataset. Imputation performed by replacement with group mean value (per timepoint, per treatment group).

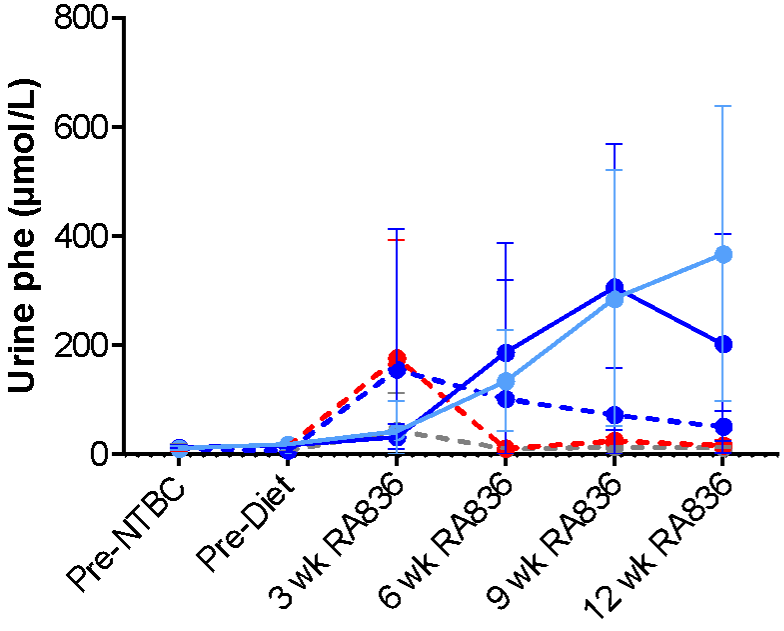
Minimal effect on blood (plasma) phe

-NTBC / -RA836
+NTBC / -RA836
-NTBC / +RA836 500 mg/kg
+NTBC / +RA836 500 mg/kg
+NTBC / +RA836 250 mg/kg

Plasma



Urine



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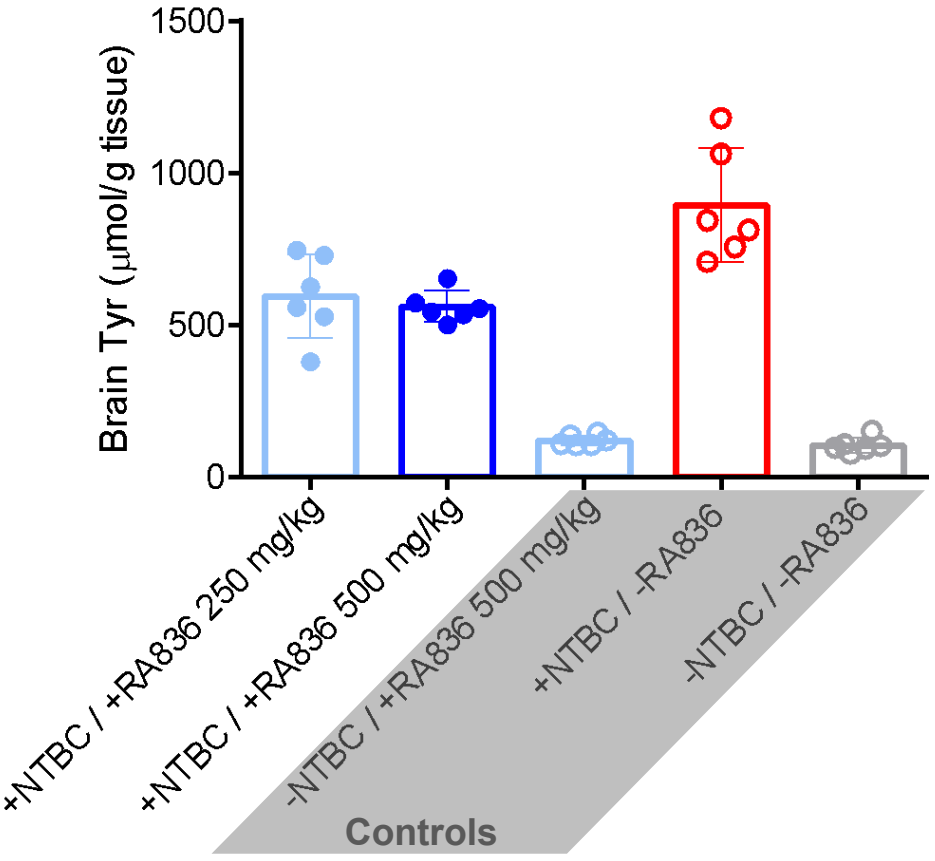
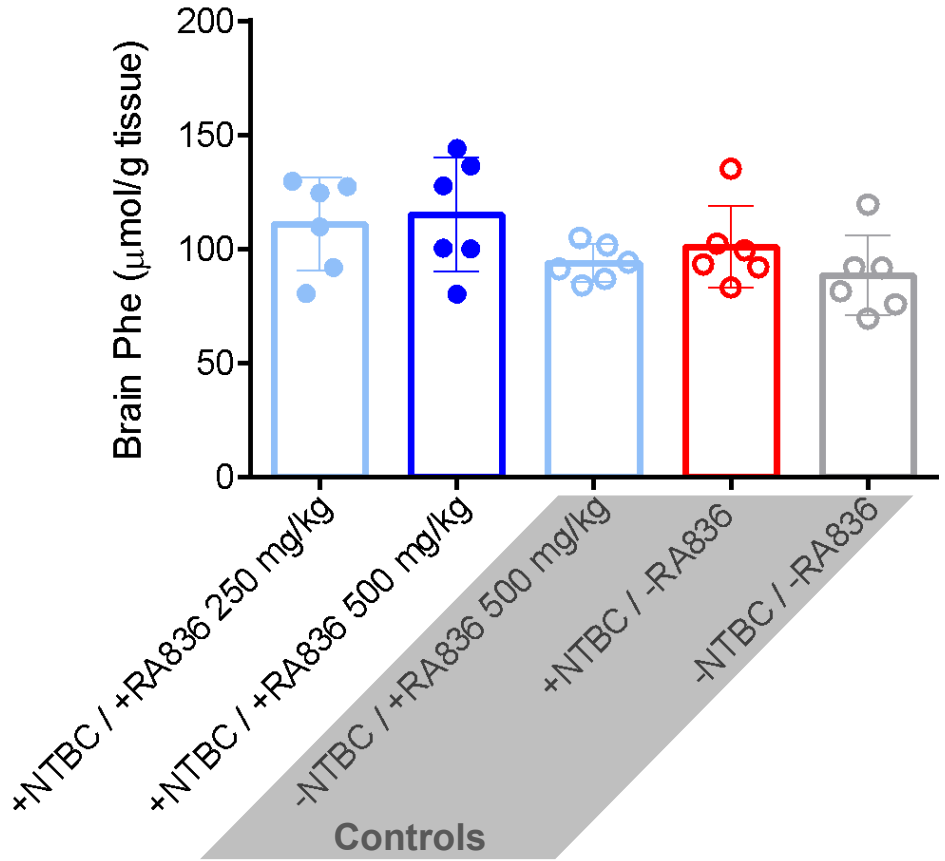
Sustained reduction in brain tyrosine





Acknowledgements

Sireau Fellowship Award: 2022-2025

AKU Research Group

Hazel Sutherland
Peter Wilson
Juliette Hughes
Dominic Rutland
Rebecca Brown
George Bou-Gharios
Lakshminarayan Ranganath
Jim Gallagher

Anna Milan
Andrew Hughes
Andrew Davison

NUTRICIA METABOLICS
LIFE TRANSFORMING NUTRITION

This information is intended for or patients, and carers, who have been prescribed Foods for Special Medical Purposes by a Healthcare Professional.

All products mentioned here are Foods for Special Medical Purposes for the dietary management of Inherited Metabolic Disorders (IMD) and must be used under medical supervision.

Accurate at time of publication: November2024.

A RICH HISTORY OF INNOVATIVE SCIENCE AND CARE

1896

The patent: a breakthrough in infant milk formula

Professor Backhaus filed a patent for his innovation in infant milk formula: a more easily digestible formula inspired by breast milk, saving the lives of thousands of babies all around the world.

N° 16,016 A.D. 1896

Date of Application, 30th July, 1896

Complete Specification Left, 30th Apr., 1897—Accepted, 5th June, 1897

Backhaus's Improved Treatment of the Milk of Cows or other Domesticated Animals.

An Improved Treatment of the Milk of Cows, or other Domesticated Animals, to Render it Suitable as Food for Infants and Children.

claim is :—

1. The treatment of the milk of cows or other domesticated animals resulting in separating the said milk into cream and skim-milk, subjecting the skim-milk to the combined action of a ferment capable of converting caseine into soluble albumose, and a ferment capable of precipitating caseine, rendering the said ferments ineffective after due action, and adding cream and milk-sugar after separation of the precipitated remainder of caseine from the liquor, substantially as and for the purpose described.

1901

The name Nutricia

Our founders named their enterprise 'Nutricia' after Professor Backhaus' laboratory, the 'Nutricia Zentrale', which derived its name from the latin word 'nutrire' ('to feed').

The expertise Professor Backhaus brought to the Nutricia company, together with the easily identifiable name (meaning something close to 'wet nurse'), enabled the company to quickly build trust as it supported mothers and their infants across the Netherlands, Belgium and Luxembourg.

1946

First Research facilities

Nutricia sets up its first research team with laboratories for baby and medical nutrition in Zoetermeer, The Netherlands.

1986

Introducing a consumer care line

Dedicated to going the extra mile for the people who use its products and for those who care for them, Nutricia's consumer Care Line opened in 1986, managed by qualified dieticians.

This free Care Line support that Nutricia offers, is still an important service for consumers, carers and healthcare professionals today, helping those who have a question to ask or a problem to share - however big or small - in The Netherlands as well as in many countries around the world.

Breastfeeding is best for babies and provides many benefits. It is important that, in preparation for and during breastfeeding, you eat a varied, balanced diet. Combined breast and bottle feeding in the first weeks of life may reduce the supply of your own breastmilk, and reversing the decision not to breastfeed is difficult. The social and financial implications of using an infant formula should be considered. Improper use of an infant formula or inappropriate foods or feeding methods may present a health hazard. If you use an infant formula, you should follow manufacturer's instructions for use carefully – failure to follow the instructions may make your baby ill. Always consult your doctor, midwife or health visitor for advice about feeding your baby.

2021

Nutricia celebrates 125th anniversary

2021 marks Nutricia's 125th anniversary. For 125 years Nutricia has positively impacted the lives of millions of people around the world. Nutricia is a partner to HCPs with decades of experience anchored in credible science, to help address some of the world's biggest health challenges.

NUTRICIA METABOLICS - SUPPORTING 54 IMDS

Over the years, we continued to **innovate** and **extend** our global portfolio to support nutritional management in over **54 different IMDs***, focusing on:

DISORDERS OF **PROTEIN** METABOLISM

- **PKU** – Phenylketonuria
- **MMA / PA** – Methylmalonic Acidemia / Propionic Acidemia
- **HCU** – Homocystinuria
- **MSUD** – Maple Syrup Urine Disease
- **GA1** – Glutaric Acidemia - Type 1
- **SOD** – Sulfite Oxidase Deficiency
- **TYR** – Tyrosinemia
- **IVA** – Isovaleric Acidemia
- **NKH** – Non-Ketotic Hyperglycinemia

DISORDERS OF **FAT** METABOLISM

- **FAOD** – Fatty Acid Oxidation Disorders

DISORDERS OF **CABOHYDRATE** METABOLISM

- **GALACTOSAEMIA**
- **GLUT 1****

NUTRICIA METABOLICS
LIFE-TRANSFORMING NUTRITION

*Data in file, 2024.
** Glucose Transporter Deficiency Syndrome

PRODUCTS

NUTRICIA
LIFE-TRANSFORMING NUTRITION
METABOLICS

PRODUCTS THAT MAY BE USED IN AKU* PATIENTS

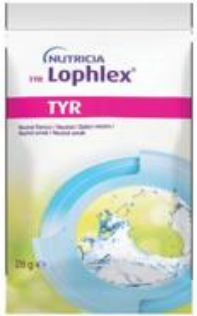
TYR GMPro Mix-In

Unflavoured
3+ years
12.5g sachet

TYR Lophlex LQ 10 & 20

Juicy Berries
4+ years
10g PE 62.5ml
20g PE 125ml pouch

TYR Lophlex Powder



Neutral
3+ years
20g PE 28g sachet

*Alcaptonuria

NUTRICIA

TYR GMPro Mix-In®

Make your protein substitute your own with TYR GMPro Mix-In!

A ready to mix, unflavoured and odourless substitute to meet your protein needs

My Mix. My Way!

TYR GMPro Mix-In is a Food for Special Medical Purposes for the dietary management of proven tyrosinaemia (TYR) and must be used under medical supervision.

What is TYR GMPro Mix-In?

- TYR GMPro Mix-In is a glycomacropeptide (GMP) based protein substitute
- GMP protein substitutes are from a natural, whole protein source
- It is unflavoured and odourless
- Each sachet contains 10 g protein equivalent (PE)
- 40 kcal per sachet
- No added vitamins and minerals to give the flexibility to add to your usual protein substitutes
- Suitable for ages 3+ years old

TYR GMPro Mix-In contains 18 mg phenylalanine (PHE) and 3.5 mg tyrosine (TYR) per 12.5 g serving. Do not heat, bake or add to hot foods or drinks (above 55°C). When mixing with food it is important to ensure that all food is consumed to ensure the full dose of protein substitute is delivered.

Why try TYR GMPro Mix-In?

- TYR GMPro Mix-In comes in pre-measured **sachets which are lightweight and easy to carry for everyday use**
- Unflavoured and odourless so you can add it to your favourite **low protein food or drink* – making it easier to adhere to your diet**
- Low in calories at 40 kcal per sachet / 10g PE
- **No added vitamins and minerals** giving you flexibility to add TYR GMPro Mix-In to your usual protein substitute without increasing micronutrients or combine with a separate vitamin and mineral supplement to meet your individual requirements

Our Phlexy-Vits Powder**
and Paediatric Seravit* can be used with TYR GMPro Mix-In to provide you with your needed vitamins and minerals!**

*Do not heat, bake or add to hot foods or drinks (above 55°C). When mixing with food it is important to ensure that all food is consumed to ensure the full dose of protein substitute is delivered.

**Phlexy Vitamin Powder is a Food for Special Medical Purposes for use under medical supervision, may be used as the vitamin, mineral and trace element component of restricted therapeutic diets and has been designed to meet the micronutrient requirements of older children (from approximately 11 years) and adults.

***Paediatric Seravit is a Food for Special Medical Purposes for use under medical supervision. For the dietary management of infants and children on restricted therapeutic diets requiring vitamin, mineral and trace element supplementation. Powdered product is not sterile. Do not boil and do not use a microwave oven to heat. TYR GMPro Mix-In can only be added to Paediatric Seravit when the patient is over 3 years old.

How to prepare TYR GMPro Mix-In?

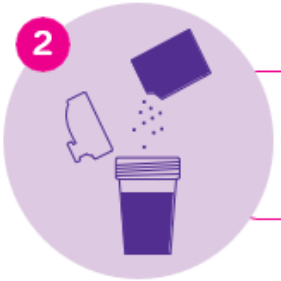
TYR GMPro Mix-In is unflavoured and odourless! It can be mixed with protein substitutes, a variety of foods low in protein, water or any flavoured drink of choice.*

The possibilities are endless!

Preparing TYR GMPro Mix-In

1. 

   Add approx. 180-240 ml of water/flavoured drink into a shaker

2. 

   Pour in a TYR GMPro Mix-In sachet

3. 

   Shake well, until the powder has dissolved completely

4. 

   Drink immediately

*Do not heat, bake or add to hot foods or drinks (above 55°C). When mixing with food it is important to ensure that all food is consumed to ensure the full dose of protein substitute is delivered.

Mix-in to...
Sports drinks, water or flavoured drinks*

NUTRICIA GMPro Mix-In®

As an unflavoured, odourless substitute, TYR GMPro Mix-In can be added to a variety of foods low in protein, water or any flavoured drink of choice, giving your patients the opportunity to make their protein substitute their own!

Into protein substitutes

Increase protein intake by adding to current protein substitute

Into foods*

Blends easily into foods low in protein for those seeking a spoonable option

- Low protein desserts / coconut-based yoghurt alternatives
- Fruit or vegetable purees
- Smoothies
- Low protein milk substitutes (for cereal)

Into drinks*

Mixes easily with water or flavoured drinks (approx. 180-240ml) to help prevent taste fatigue

- Water
- Fruit-flavoured drinks
- Sports drinks
- Iced coffee or iced tea

Serving suggestions

*Do not heat, bake or add to hot foods or drinks (above 55°C). When mixing with food it is important to ensure that all food is consumed to ensure the full dose of protein substitute is delivered.

TYR LOPHLEX LQ

TYR protein substitutes designed to fit busy lifestyles

Contains **43%** fruit juices***

- **Low volume*** and ready to drink
- **Contains DHA**** (150g per 20g PE), as intake of this essential fatty acid may be low in protein restricted diets
- Contains **vitamins** and **minerals**
- **4+** Suitable for 4+ years old

Available in Juicy Berries flavour in 10g PE† and 20g PE

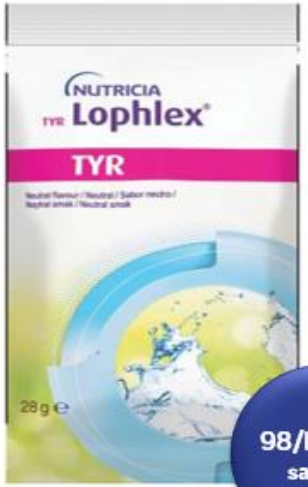
*TYR Lophlex LQ is a low volume ready to drink protein substitute available for use for people with TYR from 4 years of age and adults, containing 10g PE in 62.5ml and 20g PE in 125ml.
**Docosahexaenoic acid is an omega-3 fatty acid to address specific dietary requirements. ***TYR Lophlex LQ Juicy Product information. Intended for use in children from 4 years of age and adults (including pregnant women).
TYR Lophlex® LQ Juicy flavours may contain traces of phenylalanine from mixed fruit juices at a level of <5mg per 100mL.

TYR LOPHLEX POWDER

Interchangeable with the other products in the Lophlex® range

NUTRICIA Lophlex®

- The **lowest volume** product.† An alternative to liquids, ideal for travelling!
- **Contains DHA** as intake of this essential fatty acid may be low in protein restricted diets
- Contains **vitamins** and **minerals**
- 3+ Suitable for 3+ years old



98/kcal per sachet*

The **low-calorie*** content is ideal for those interested in calorie management.

To aid variety and adherence, use in combination with

Flavour Sachets

Available in Cherry-Vanilla, Lemon & Lime and Grapefruit flavours

Modjul flavours

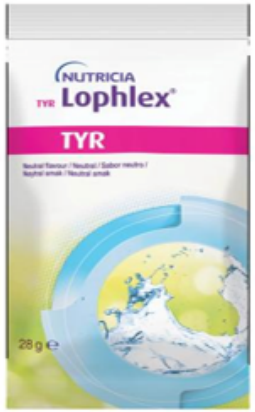
Available in Blackcurrant & Orange flavours

† TYR Lophlex Powder is the lowest volume powdered protein substitute available for use in the UK market for people with TYR from 3 years of age and adults. Only 65mls of water per sachet is required to make a low volume drink containing 20g PE. Accurate in MIMS UK (November 2024).

*For those interested in reducing calorie intake, TYR Lophlex® Powder contains 98 calories per 20g PE, which is lower than Nutricia's equivalent protein substitutes.

TYR LOPHLEX POWDER

As an alternative to liquids, it's suited to patients who are travelling as its low volume makes it easy to take anywhere.



PASTE IT

Add **5ml of water** to make a paste

SHOOT IT

Add **10-20ml of water** to make a shot

DRINK IT

Add **65ml of water** to make a drink

Lophlex Squiz pouches allow you to take Lophlex Powder on the go - convenient way to get ready for your lunch box.

Find out more: Squiz Pouch Video


NUTRICIA
Loprofin
Rice
NUTRICIA
Loprofin
Fusilli
500 g
NUTRICIA
Loprofin
Flakes
NUTRICIA
Loprofin
Sno-Pro
200 ml
NUTRICIA
Loprofin
Herb Crackers
150 g

THE LOPROFIN RANGE

Explore the Loprofin range and recipes to open up a world of opportunities

NUTRICIA Loprofin

Pasta

Loprofin Fusilli
Loprofin Penne
Loprofin Tagliatelle
Loprofin Macaroni
Loprofin Lasagne
Loprofin Spaghetti
Loprofin Animal Pasta

Egg Replacer

Egg Replacer
Egg White Replacer

Drinks

Loprofin Sno-Pro
Loprofin Drink LQ

Cereals

Loprofin Flakes Chocolate
Loprofin Flakes Strawberry
Loprofin Loops

Cake Mix

Loprofin Cake Mix

Snacks

Loprofin Crackers
Loprofin Herb Crackers

All Purpose Mix

Loprofin Mix

Rice

Loprofin Rice

FOR RECIPES AND TIPS
on how to use Nutricia's Loprofin Products

Check out our recipe cards. Request a copy from your Nutricia representative.

NUTRICIA Loprofin

The Loprofin Range are Foods for Special Medical Purposes, for the dietary management of inherited metabolic disorders and other conditions requiring a low protein diet and must be used under medical supervision.

HOMEWARD

NUTRICIA HOMEWARD METABOLICS AND KETOGENICS SPECIALIST SERVICE

NUTRICIA LIFE-TRANSFORMING NUTRITION HOMEWARD

25 Providing support for 25 years

With Nutricia Homeward Metabolics and Specialist, every delivery is a special delivery. We are dedicated to going the extra mile to help take a load off for our customers:

- NO CONTRACT, NO TIE-INS
- A DEDICATED NAMED COORDINATOR
- PEACE OF MIND AT ALL TIMES
- TRANSLATION SERVICE
- REDUCED WASTE, MORE SPACE
- IN-HOUSE PHARMACY
- FRIENDLY DELIVERY DRIVERS
- KEEPING YOU UPDATED ON HOME DELIVERIES

Visit nutricia.co.uk to learn more

WE'RE HERE TO HELP

We want to help make staying on diet a little simpler and proudly offer a range of helpful services, including:

Nutricia Homeward

FREE home delivery in UK & NI.
We can bring your products directly to your door, for free.

FREE home delivery in UK & NI. Call: **0800 093 3675**
Visit **www.nutriciahomeward.co.uk** to learn more or ask your metabolic team.

Social Media

Follow **@lowproteinconnect** to access helpful low protein tips, recipes, educational articles/resources and patients' testimonials.

Online Resources

From videos to blog posts, we've developed a range of educational materials to help you stay informed.

Visit **www.nutricia.co.uk** to learn more.

Nutricia.co.uk
Giving you the support and tools to stay on track with your controlled protein diet.


THANK
YOU!

Coffee break + exhibition 10:15am - 11:00am

Breakout sessions at 11:00am

Pilates session, please go to Liverpool Suite 2+ 3

Parents and Children’s Workshop, please return to this room

Parents and Children's Workshop

AKU
Alkaptonuria Society

- **Welcome** – Jess Barnes

- **Progress in Alkaptonuria – Focus on Children**

  - Prof Lakshminarayan Ranganath - Consultant in Clinical Biochemistry and Metabolic Medicine

- **Diet and AKU** – Clare Soulsby - Senior Dietitian: National Alkaptonuria Centre

- **Questionnaire**

Alkaptonuria in Children

Disclaimer

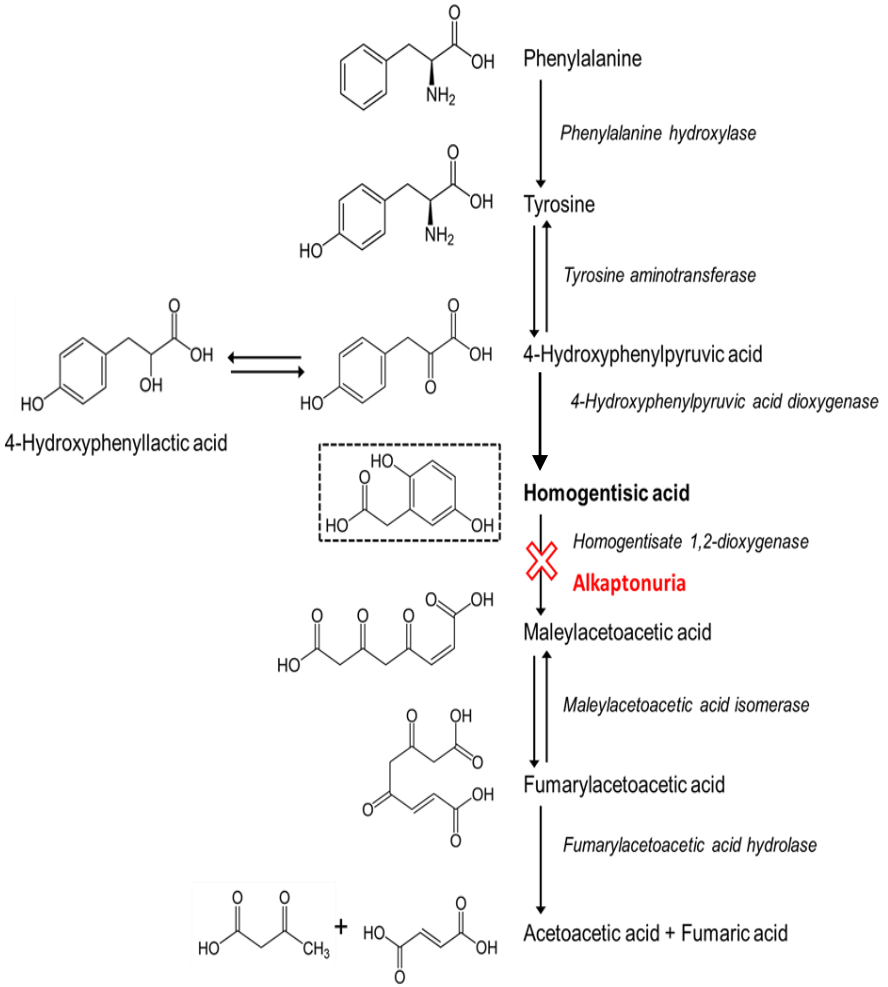
- All opinions expressed and implied in this presentation are solely those of the presenter
- This presentation is intended to support the scientific and medical education of scientists and clinicians on clinical management of alkaptonuria

Disclosures

- Served on advisory boards for Astra Zeneca, MSD, Sanofi, Servier, Genzyme, Pfizer
- Received fees for consultation and lectures from Sobi, Astra Zeneca, MSD, Sanofi, Servier, Pfizer, Merck

Alkaptonuria (AKU)

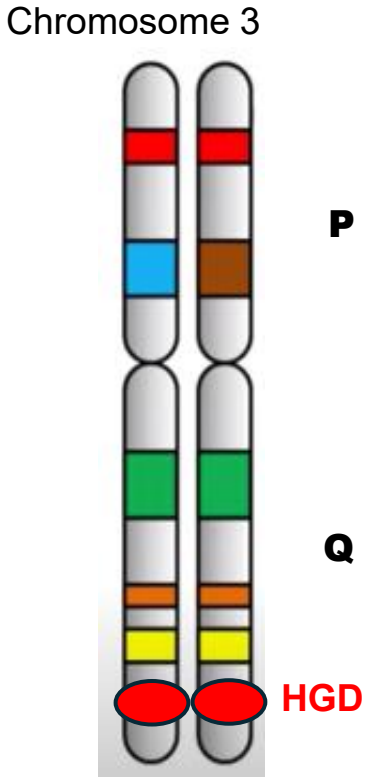
- Rare autosomal recessive disorder - 1 in 250,000 (Carriers 1 in 500)
- Lack of Homogentisate dioxygenase (HGD) activity
- Homogentisic acid (HGA) accumulates



AKU is present at birth

AKU gene

Chromosone 3Q – long arm of chromosome

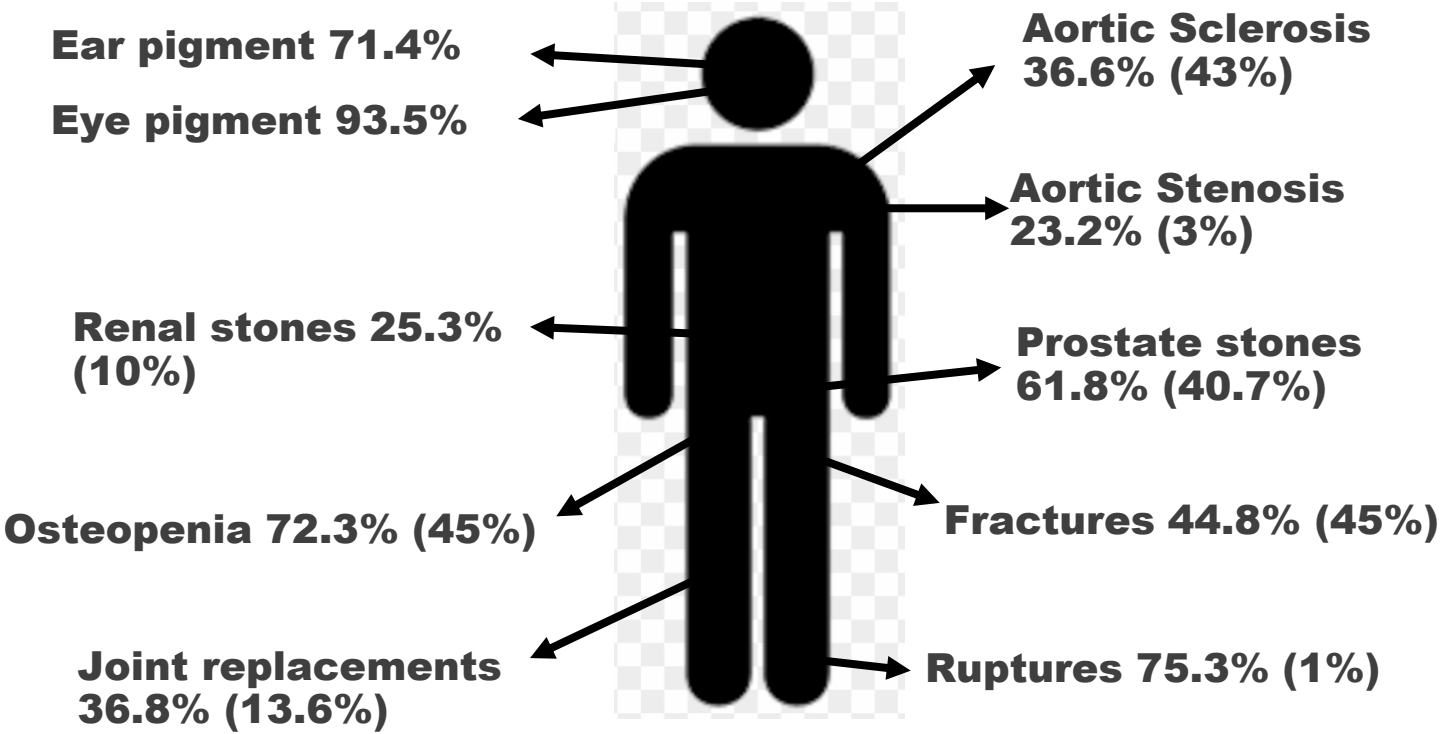


Pathogenesis (AKU)

COLORIZED URINE

- Delayed darkening due to HGA

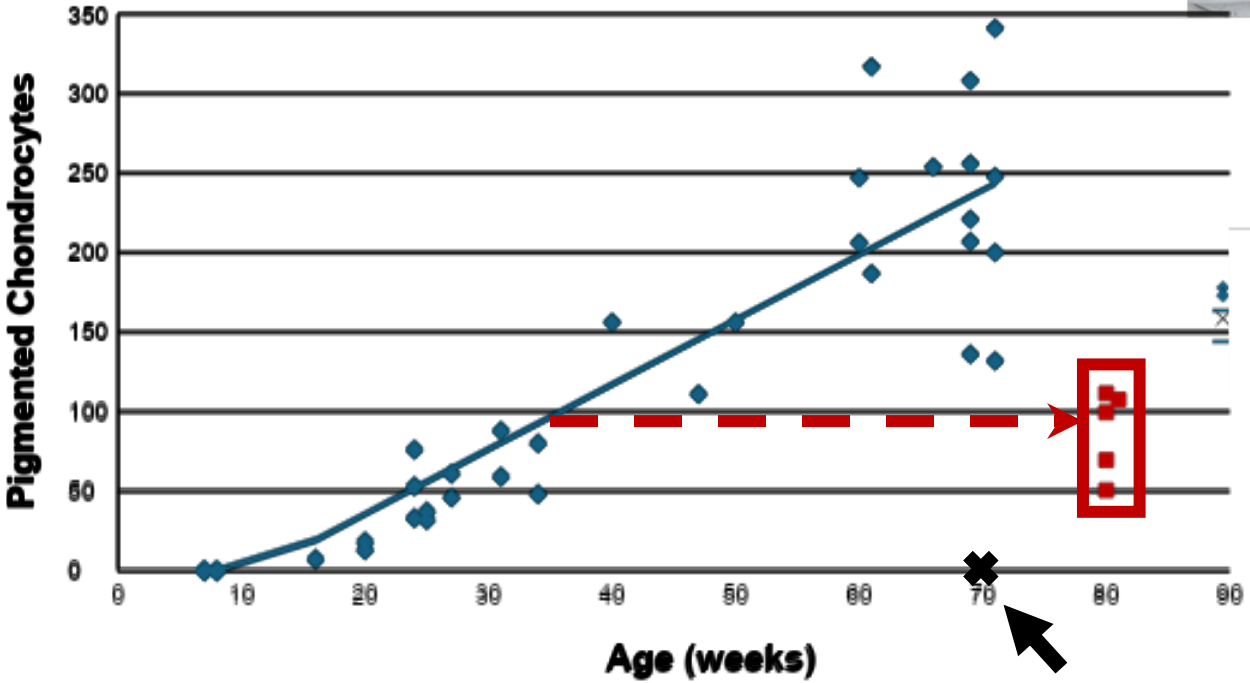
Prevalence of traditional AKU features (NAC)



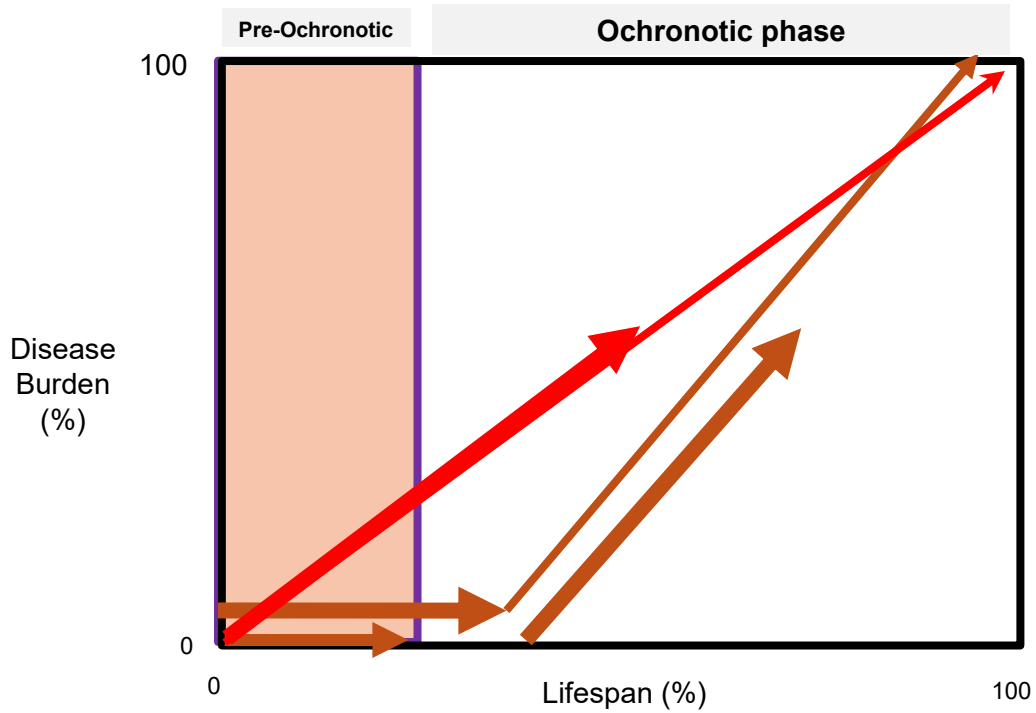
Ranganath LR et al. *JIMD*. 2011;34:1141–51; Rudebeck et al. *JIMD Rep.* 2020:53:71-9; Ranganath et al Mol Genet Metab 2018;125:127-134

Is AKU reversible

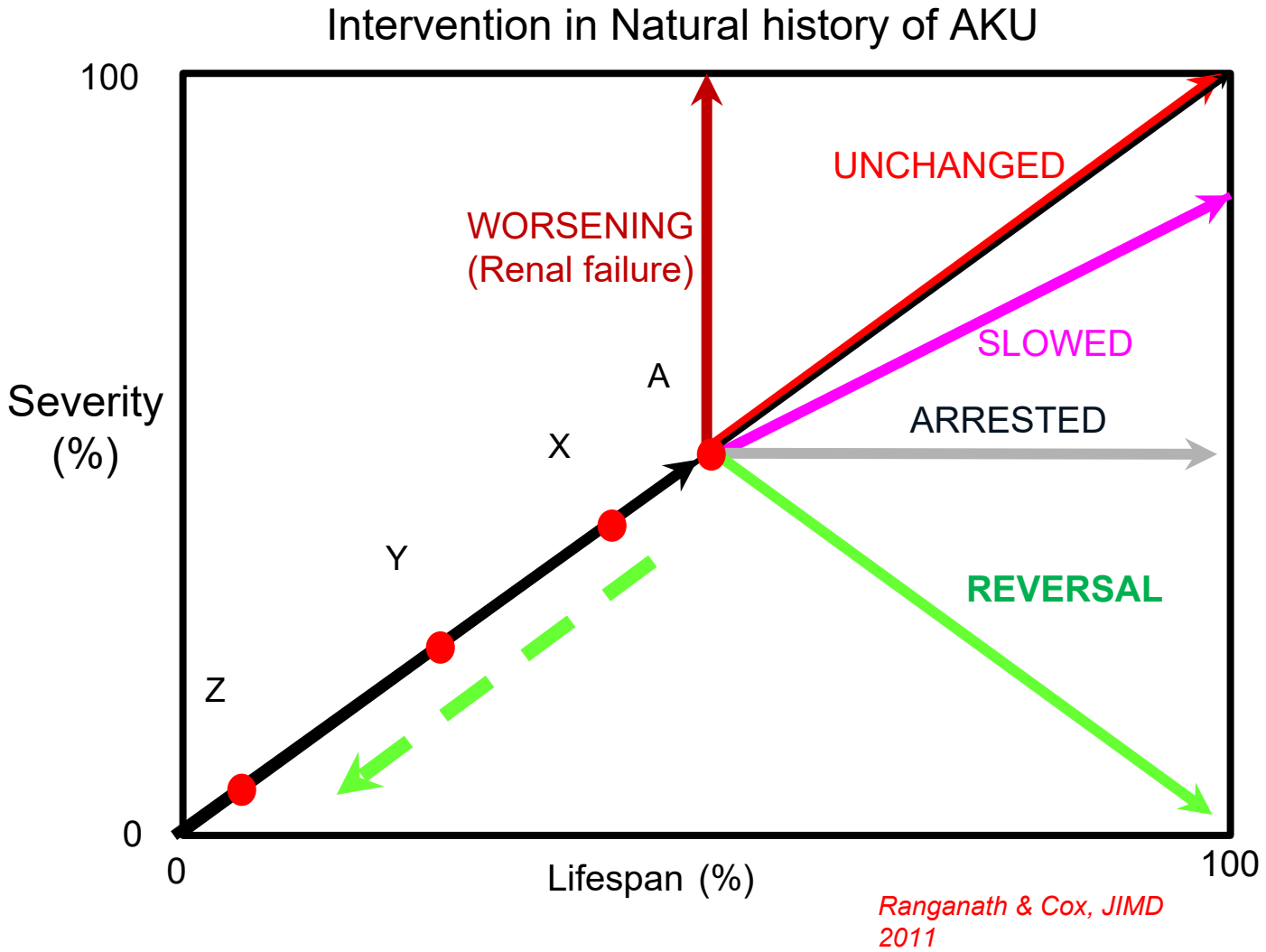
Natural history of ochronosis in AKU mouse model



Natural History of AKU



Ranganath & Cox, JIMD 2011


Intervention in Natural history of AKU
100
Severity
(%)
0
0
Lifespan (%)
100
WORSENING
(Renal failure)
UNCHANGED
SLOWED
ARRESTED
REVERSAL
A
X
Y
Z
Ranganath & Cox, JIMD
2011

Published cases of childhood AKU

49 cases with available details, there were 9 cases under 1 year of age, 14 cases between 2 and 5 years, 19 cases between 6 and 10 years and 7 cases over the age of 11 and less than 18 years.

12% of children with AKU had pigmentation (eye, ear, skin, buccal, teeth), while 4% had joint pain.

There were two publications from Turkey containing data on groups of patients describing ochronosis and joint pain without providing individual patient details

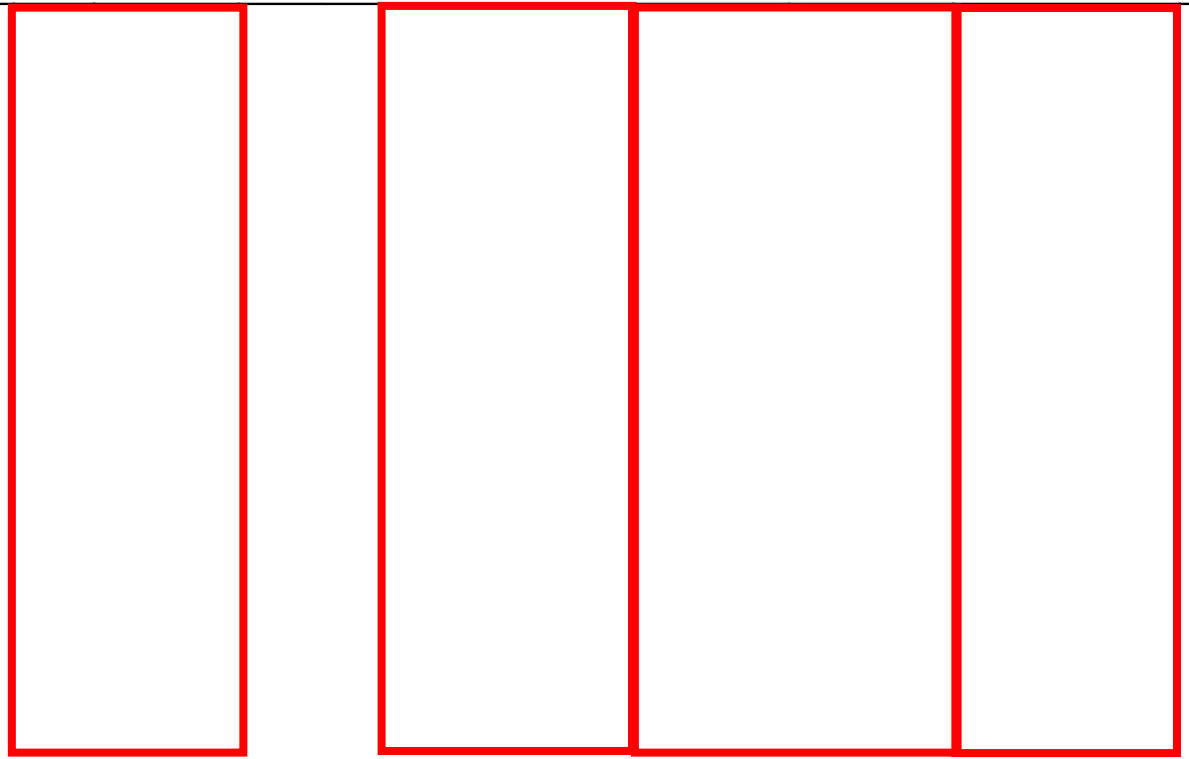
A Dutch series of 12 cases did not provide information on individual patients although described joint pain as a feature in children

These reports suggest that the irreversible disease process of AKU such as ochronotic pigmentation and joint/spine features may take hold in childhood.

SLOVAK NATURAL HISTORY

Clinical manifestation of AKU in relation to age (n=149)									
	Age (years)								
	≤ 1	>1-5	>5-10	>10-15	>15-20	>20-30	>30-40	>40-50	>50
Dark urine	+++	+++	+++	+++	+++	+++	+++	+++	+++
Dark ear wax	+++	+++	+++	+++	+++	+++	+++	+++	+++
Axillary pigmentation	-	-	±	+	++	+++	+++	+++	+++
Ear cartilage changes				±	±	+	++	+++	+++
Scleral pigmentation				±	±	+	++	+++	+++
Ochronotic arthropathy						±	+	++	+++
Crosses indicate the frequency of occurrence and intensity of the symptom									
From Srseň S, Srseňova K, Lanyi A. Clinical manifestation of alkaptonuria in relation to Age. Bratisl. lek. Leaves, 1982;77:641-76 (REF 52).									

Demographic and clinical data of the study patients (Polish study)



Psychological assessment results in the Polish study

General adaptation, to everyday challenges, assessed by the ABAS III in Polish, five of 13 were found to need more support regarding the psychological fields of functioning.

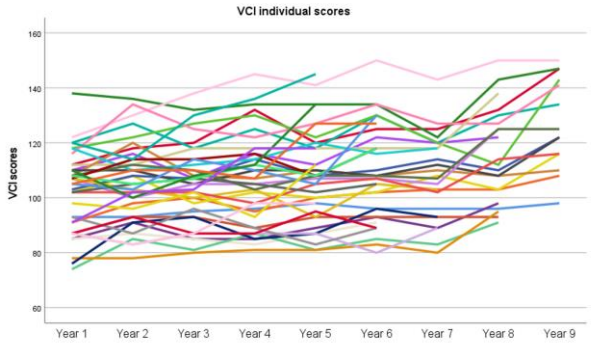
NAC Young group (demographic, metabolic & clinical data)

NAC – Young group (Clinical Gait Analysis)

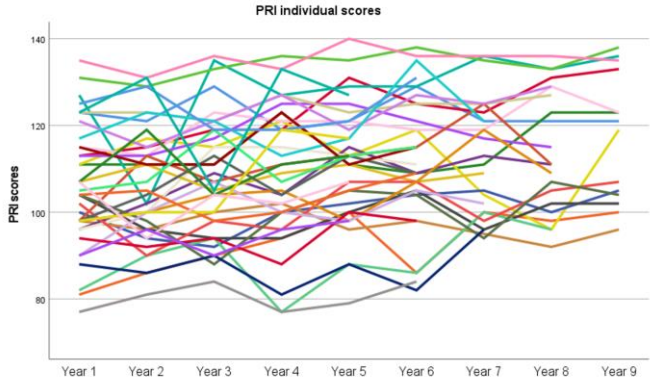
NAC – Young Group - Psychometry (WAIS-IV)

Index scores increased during nitisinone in the NAC

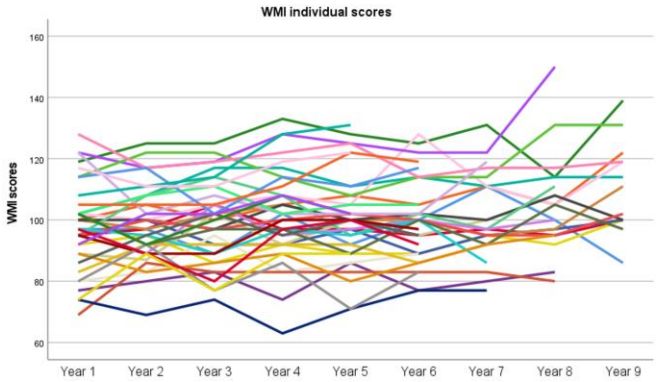
VCI



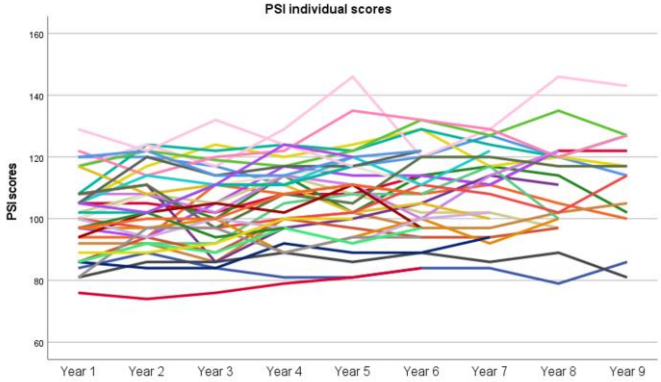
PRI



WMI



PSI



Does homogentisic acid cause cognitive impairment?

AKU itself may cause brain effects -

Morris water-maze testing of the HGD-/-

mice and wild-type mice showed

significant differences in spatial learning

and memory with impairment in the

HGD-/- mice compared to wild type

mice

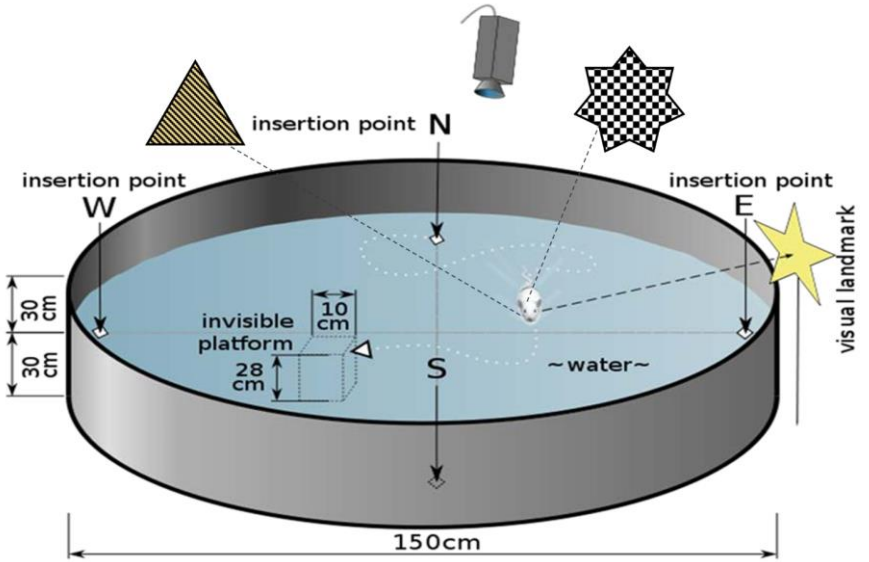
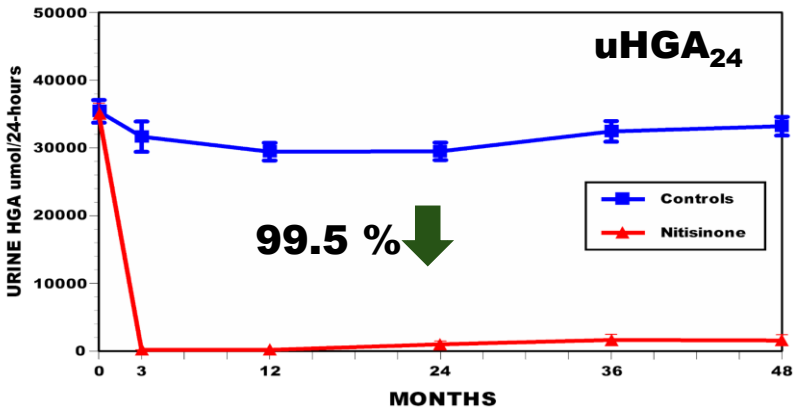


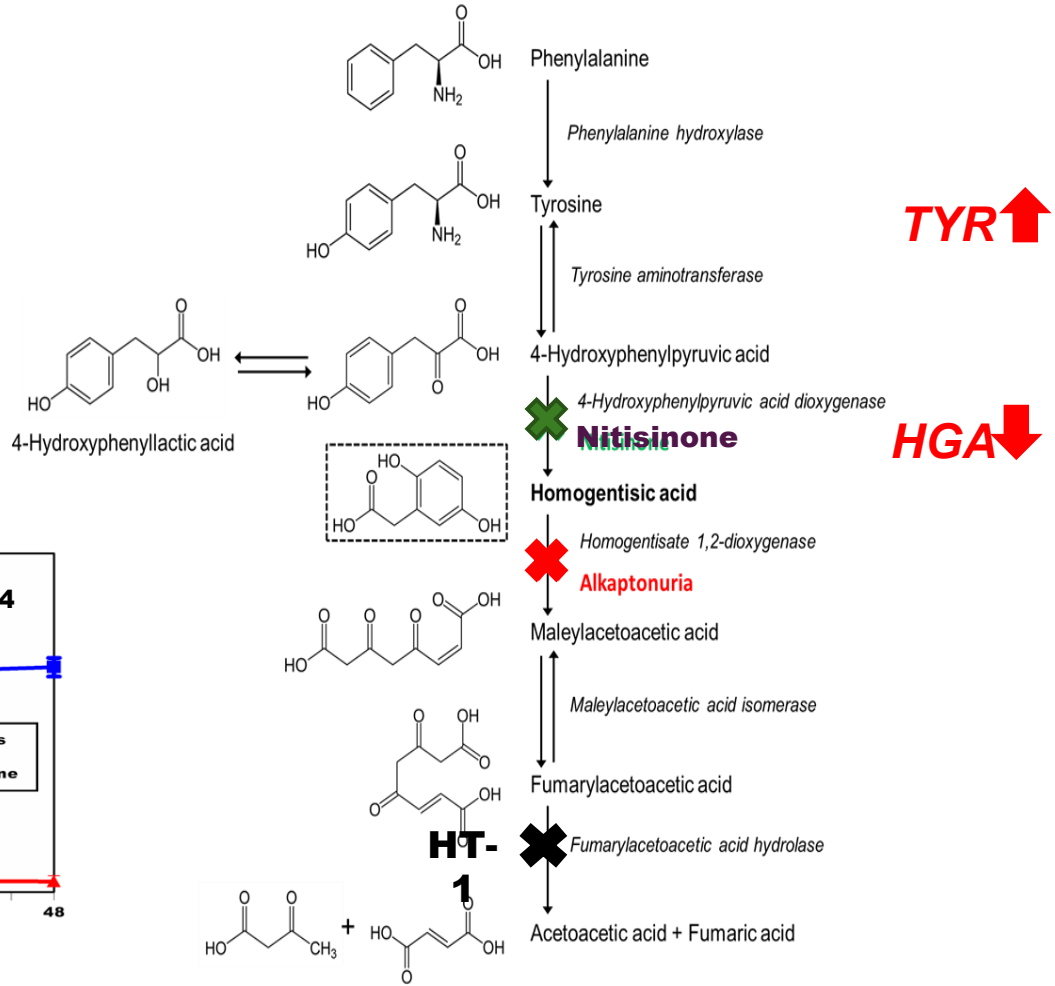
Figure 2.4 – Morris water maze equipment set up. High contrast 3D spatial cues are mounted around the pool during hidden platform trials to aid with spatial navigation to the submerged platform. Image edited and reused from Wikimedia commons [87].

Lewis R (March 2018), PhD thesis, LJMU

Nitisinone in AKU

Nitisinone – efficacy as an HGA-lowering therapy in AKU established





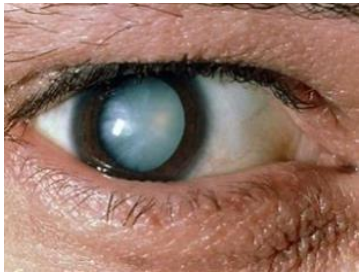
New knowledge of relevance (non-ochronotic effects)

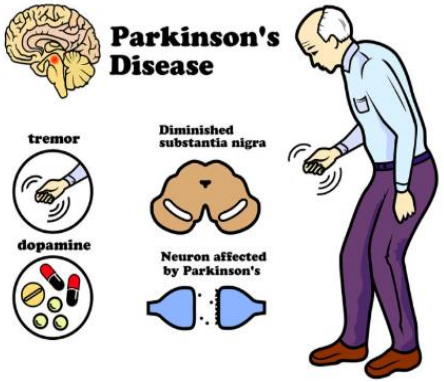
Cataract prevalence is increased in untreated AKU

Increased frequency of Parkinson’s disease has been seen in untreated AKU

Increased oxidative stress due to HGA appears to be the common denominator between cataract & Parkinson’s disease

Life-long HGA-exposure might be important in these settings.





Pragmatic reasons for earlier treatment of children with AKU (nitisinone)

Case-finding has improved due to availability of nitisinone

Late presentations of the disease are still commonplace - lack of registration following diagnosis, lack of interest in the disease in the paediatric field, where it is seen as a benign condition

Earlier treatment would prevent the main disease process ochronosis

Earlier treatment would minimise residual disease

Earlier treatment would also decrease long-term oxidative damage features such as cataract and Parkinson’s disease.

Cognition in HT-1 children

Life-saving nitisinone therapy in HT-1 has been associated with cognitive impairment.

Careful survey of the current literature in this area does not support the hypothesis that tyrosinaemia during nitisinone treatment causes cognitive deficit in children

The toxic metabolites of the HT-1 disease, the molecule nitisinone itself, the resultant tyrosinaemia as well as the protein restriction leading to amino acid deficiencies (phenylalanine in particular) have all been debated

Age-critical brain development could be influenced by the nitisinone therapy

Because of the aggressive nature of HT-1, there are, however, no cognition data on untreated patients.

Brain growth and considerations for nitisinone therapy in children

Human brain development is most rapid in the first few years of life but continues until around age 25 years

While the evidence for early nitisinone treatment of AKU is mounting, not only because irreversible ochronosis begins in childhood but also to decrease HGA-related oxidant damage, **safety needs to be paramount**

Psychometry testing should be carried out before and during possible nitisinone therapy of AKU in childhood.

Changing calculus in children with AKU

Supportive and preventative approaches in childhood

Diet/Vitamin C

Hydration

Physical activity

Hobbies

Vocation

Occupation

Surveillance for disease progression

National Registration

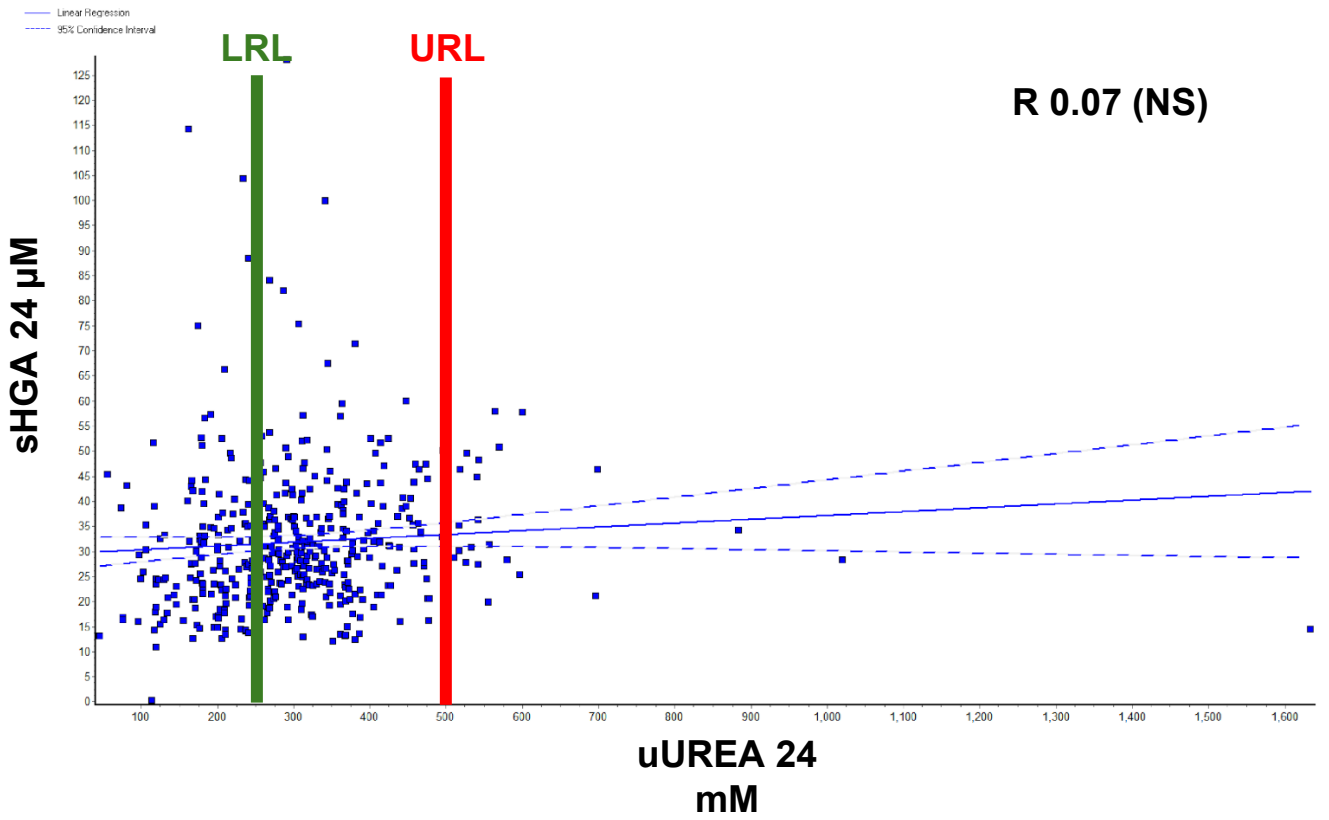
Regular follow-up

French AKU patients have more dietary restriction of protein?

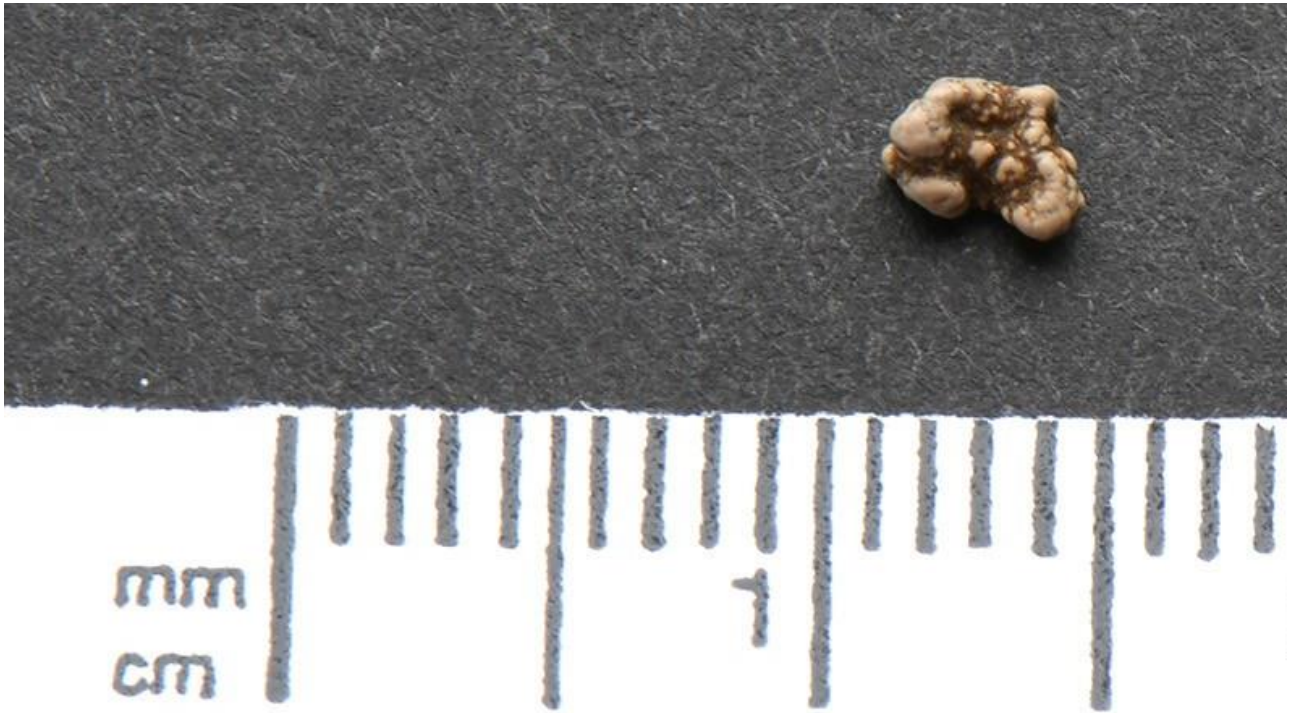
SONIA 2 clinical study sites			
	Liverpool (n=41)	Piešťany (n=65)	Paris (n=32)
Age (y)	50 ±10.8	46.2 ±11.5	50.3 ±7.9
sHGA (uM)	35.6 ± 13.7	27.8 ± 11	34 ± 19.1
uHGA24 uM	35245 ± 10203	39706 ± 16123	29733 ± 8857
AKUSSI	98.4 ± 37.9	72.6 ± 31.2	87.8 ± 23.9

Does more dietary protein cause higher circulating HGA – data from NAC at baseline

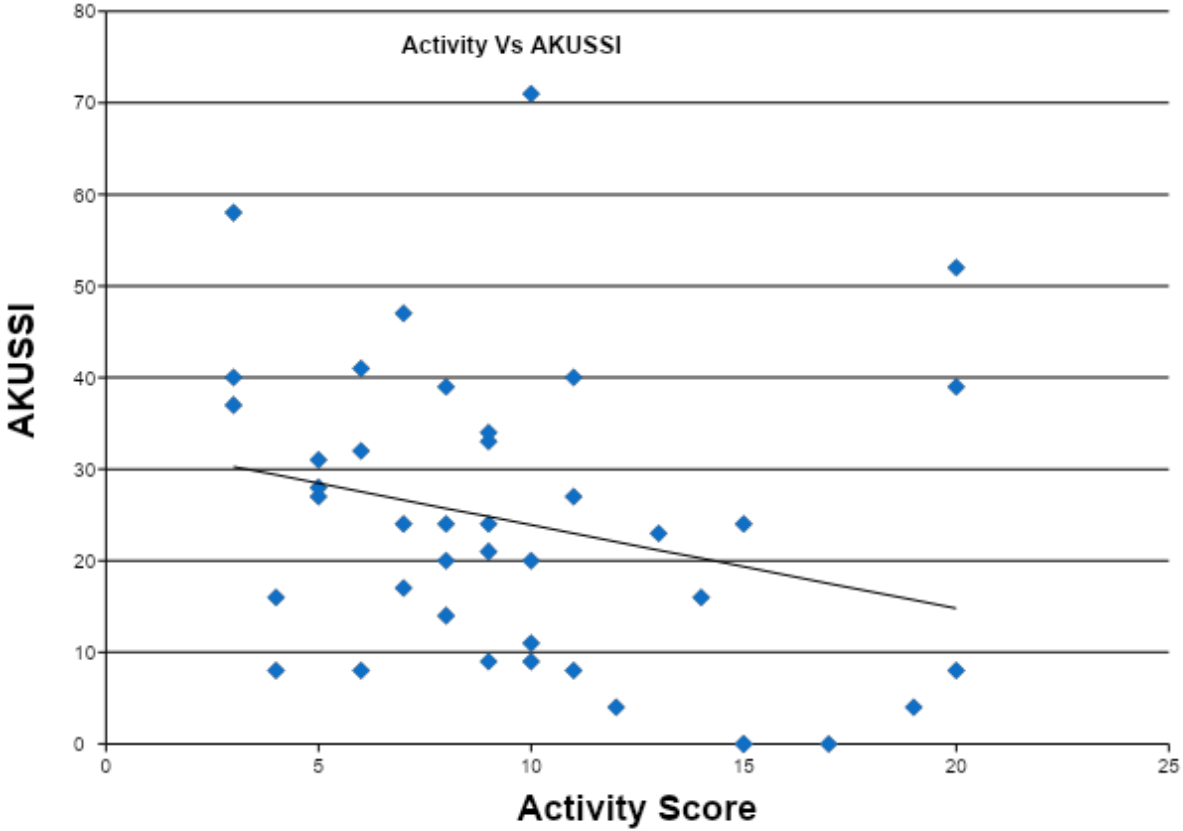
(**LRL = lower reference limit**; **URL = upper reference limit**)



Kidney stone (25.3% vs 10%) – hydration important



Those with greater disease burden have lower current physical activity



Summary

- Features of AKU including pain and pigment is present in later childhood
- Pigment features are not fully reversible and earlier treatment is better
- New features relevant here include cognitive impairment in children (Possibly due to HGA)
- Features such as cataract and Parkinson's disease presenting later in adulthood is due to life-long exposure to HGA (early lowering of HGA beneficial)
- Increasingly, nitisinone may not be associated with cognitive decline and this not a reason to withhold nitisinone in children
- Timing of nitisinone is childhood should be debated possibly by age 10 years
- Safety of nitisinone in children should be monitored (regular psychometry)

Challenges - developing nitisinone in children

Nitisinone generics

Pharma ‘buy-in’

Funding for nitisinone childhood studies

End points in studies of childhood AKU should be metabolic

Numbers for clinical trial (multinational)

Time for questions
&
Discussion

Children's workshop

Clare Soulsby
AKU Dietitian
The Robert Gregory National AKU Centre (NAC)

The Robert Gregory
National AKU Centre

NHS
Liverpool University Hospitals
NHS Foundation Trust

DIETARY MANAGEMENT OF AKU IN CHILDREN

Dietary management of children with AKU in the UK

- Aim for a “normal” protein intake
- Nitisinone when referred to adult services
- Joint friendly exercise

HOW MUCH PROTEIN DO CHILDREN?

Table 4 *Dietary Reference Values for Protein*

Age	EAR – g/d	RNI – g/d
0–3 mo	—	12.5[a]
4–6 mo	10.6	12.7
7–9 mo	11.0	13.7
10–12 mo	11.2	14.9
1–3 yr	11.7	14.5
4–6 yr	14.8	19.7
7–10 yr	22.8	28.3

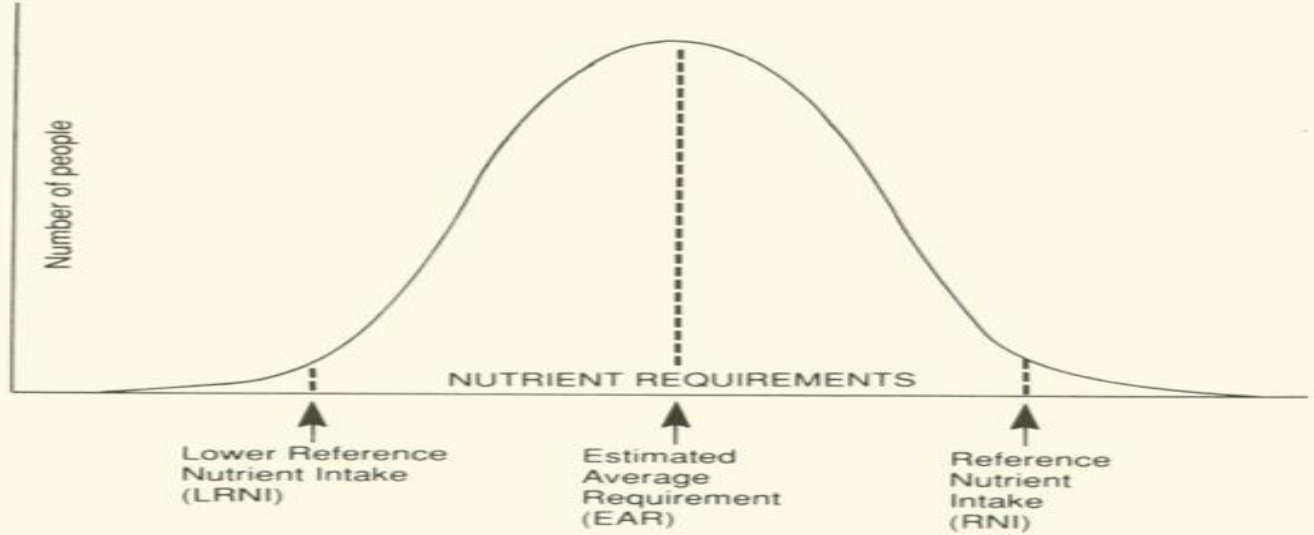
Continued

Table 4 *continued*

Age	EAR – g/d		RNI – g/d	
	Males	Females	Males	Females
11–14 yr	33.8	33.1	42.1	41.2
15–18 yr	46.1	37.1	55.2	45.4
19–49 yr	44.4	36.0	55.5	45.0
50+ yr	42.6	37.2	53.3	46.5
Additional amounts to be added to pre-pregnancy DRVs				
Pregnant women		+6		+6
Lactating women up to 6 mo		+11		+11
6+ mo		+8		+8

[a] No figures given by WHO. RNI calculated from recommendations of COMA 1980. (DHSS 1980)

Figure 1 Relationship between various reference values



The Lower Reference Nutrient Intake is enough for only a small number of people (about 3% of the population who have low needs). It is not enough for most people.

The Estimated Average Requirement for energy or a nutrient is the amount which any stated group of people will, on average, need.

The Reference Nutrient Intake is the amount of a nutrient which is enough for at least 97% of the population.

STRATEGIES TO HELP TRANSITION TO A CONTROLLED PROTEIN DIET

How to prepare a teenager for adult AKU management

1. Physiological vs psychological “right time”
2. Gain an understanding of protein in food
3. Moving away from “meat-veg-potato”
4. Debunk the “high protein” message

How to prepare a teenager for adult AKU management

1. Physiological vs psychological “right time to start”

Gaining an understanding of protein content of food

- **7g PROTEIN SWAPS**
  - 25g meat/chicken
  - 40g fish
  - 25g cheese
  - 200ml milk
  - 125mls yoghurt
  - 1 egg
  - 100-110g legumes
- **2g PROTEIN SWAPS**
  - ½ slice bread
  - 30g cooked pasta
  - 125g boiled potatoes
  - 60g chips
  - 75g cooked rice
  - 20g oats

Moving away from “meat-veg-potato”

- 4 slices (150g) roast beef
- 160g roast potatoes
- 180g broccoli

- 200g sweet and sour chickpeas
- 160g boiled rice

Moving away from “meat-veg-potato”

- 4 slices (150g) roast beef 45g
- 160g roast potatoes 4g
- 180g broccoli not counted
- Gravy (minimal protein)

- 200g sweet & sour chickpeas 14g
- 160g boiled rice 6g

TOTAL PROTEIN 20g

Plant based/ vegan foods

Useful

- Plant based milk
- Plant based cheese (high kcal)
- Beans, pulses, chickpeas
- Vegetable based sausages and burgers

- ***NB dairy is a good source of dietary calcium***

Less Useful

- “Mock meats” from soy based products

What are plant-based meat made of?

- soybeans, peas, legumes,
- wheat and other grains,
- fungus, such as mycoprotein,
- vegetables.

Sausages		
Thick sausage (meat)	21g protein (3 x 7g swaps per 2sausages)	~2x regular pork sausages (2 x 57g sausages)
Soy-based	14-18g protein (2 – 2½ x 7g swaps per two sausages)	-Tesco Plant Chef Herby Bangers -Morrisons Plant Revolution Meat Free Sausages
Pea-based	10-18g protein (1½ - 2½ x 7g swaps per two sausages)	-Beyond Meat Plant Based Sausage -Birds Eye Green Cuisine Vegan Sausages
Vegetable-based (veggie sausage)	3-7g protein (1-3 x 2g swap per two sausages)	-Plant Based by ASDA Leek, Carrot & Sweet Potato Sausages

Type	Protein (g) per 200ml*
Soya	7g protein (1 x 7g swap)
Oat	2g protein (1 x 2g swap)
Almond	2g protein (1 x 2g swap)
Hazelnut	1g protein (½ x 2g swap)
Cashew	1g protein (½ x 2g swap)
Rice	free food
Hemp	free food
Coconut	free food
Dairy (full) (semi) (skimmed)	7g protein (1 x 7g swap)

Plant based: summary

Wholefood plant-based (beans, pulses, nuts, tofu):

- less protein than meat
- low in saturated fat, kcal, salt and contain other vital nutrients

Plant-based meat alternatives

- may have less protein than meat
- can be high in protein.
- often high in salt, fat and kcal

Plant-based alternatives to dairy milk:

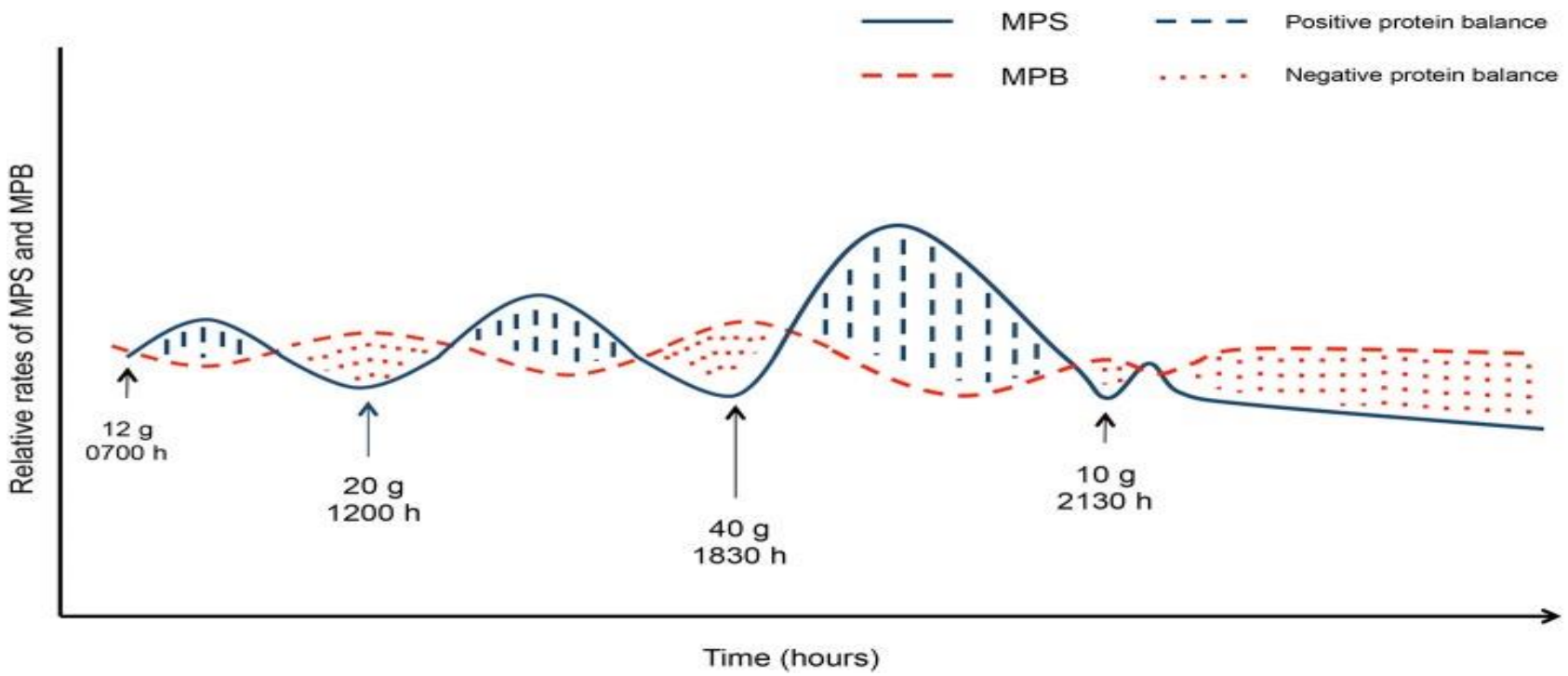
- contain much less protein (except soya).

Coconut-oil-based plant-based cheese:

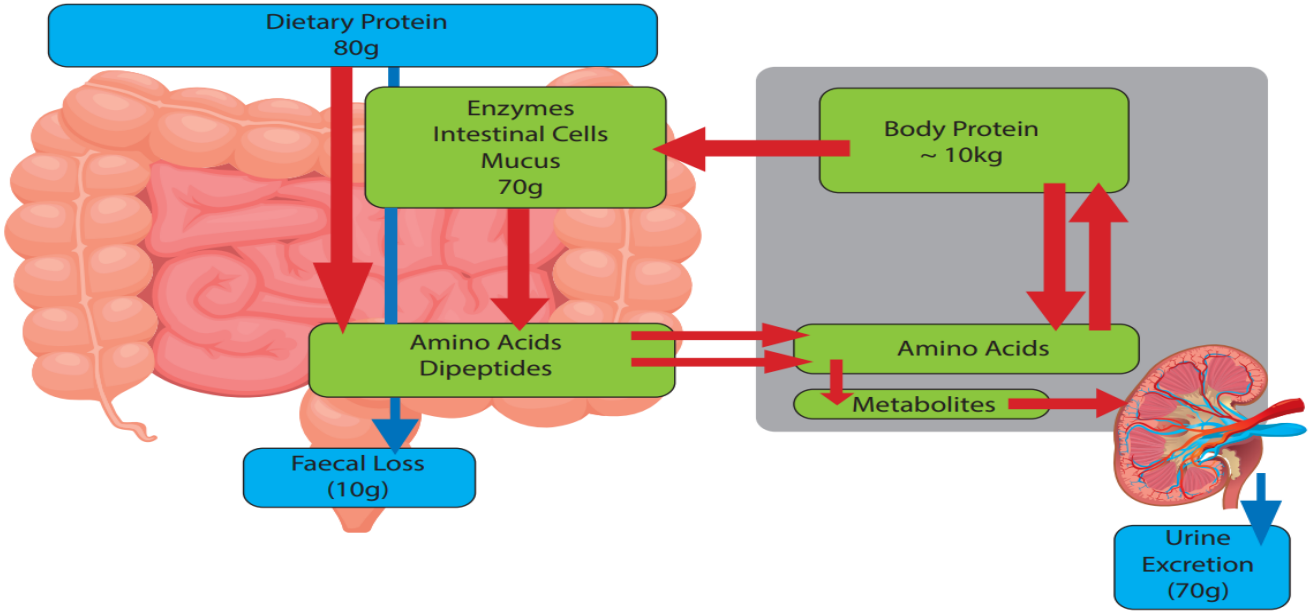
- virtually protein free.

I GO TO THE GYM -
DO I NEED PROTEIN SHAKES?

Protein utilisation by muscles



Nitrogen Balance



Exercise and muscle protein synthesis

- Timing
- Quantity
- Quality
  - Branch chain amino acids (BCAA)
  - Leucine, isoleucine, valine
  - Dairy, meat, fish, egg and legumes are rich sources
  - Especially dairy and whey protein

Really good podcast

- https://zoe.com
- ZOE Podcast: Should I eat more protein
- Professor Christopher Gardner
- Stanford University

Questions

Alkaptonuria Society

Lunch in the restaurant 12:30pm - 1:30pm

Aquatic Fitness for Arthritic Joints

Hot Tub Yoga

Jim Fish

November 14, 2024

Acknowledgments

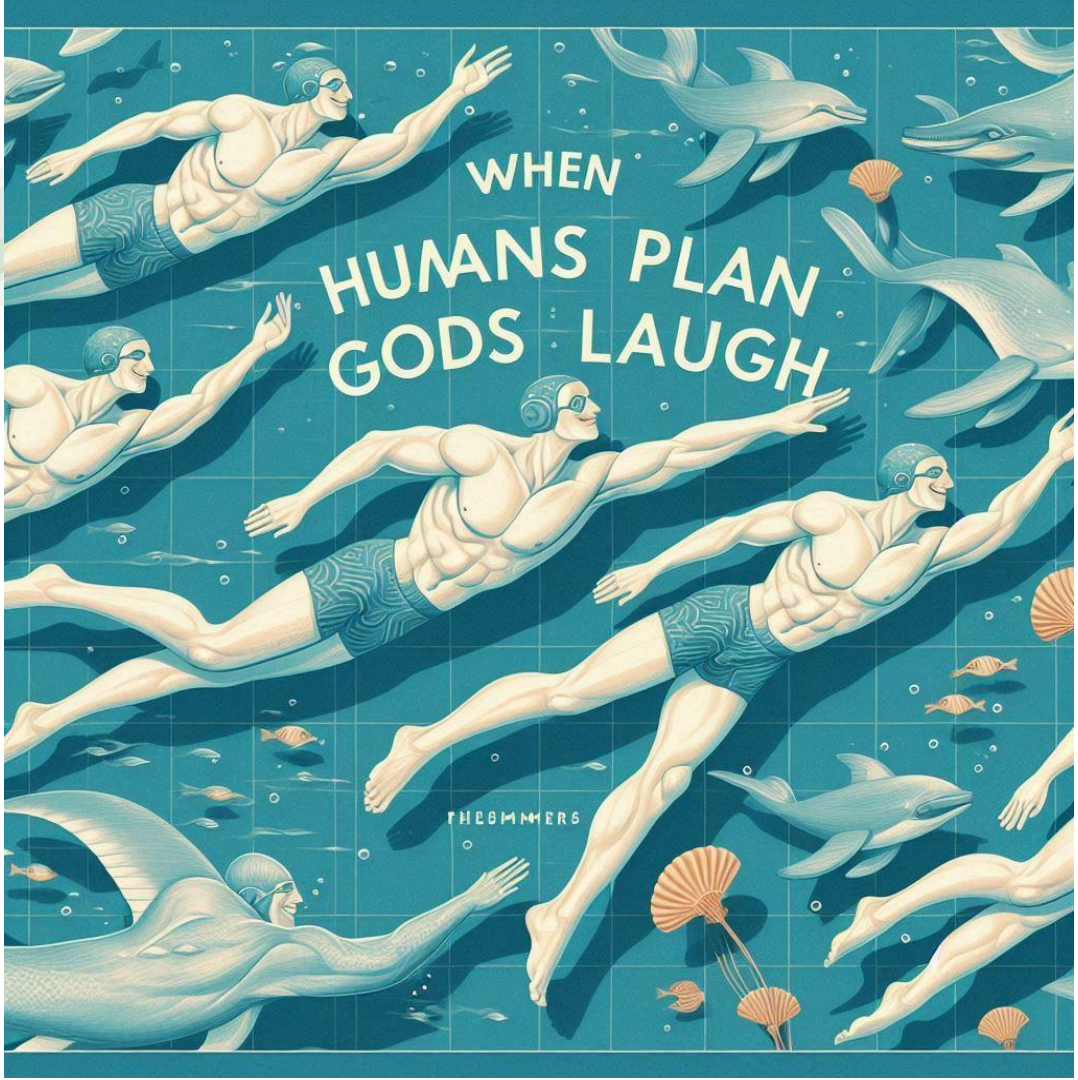
- AKU Society
- Platoon of caring medical providers including a tram of nine specialists
- Incredible Family support
- Past and present chair yoga instructor Sian Williams

Looking Back to 2018…

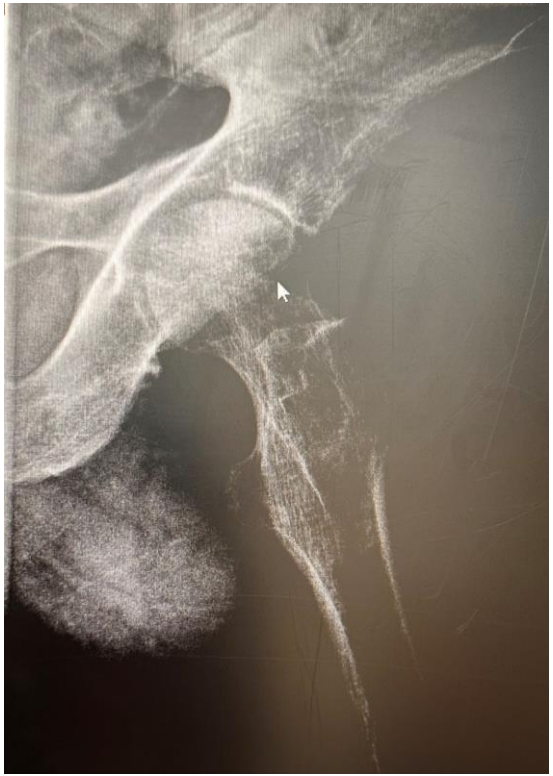
- At 53, I was going strong without any orthopedic surgery on the horizon…

- **Supportive Factors:**
  - Good diet
  - Low BMI
  - Good conditioning BASELINE
  - Positive Visualizer

"Be the Oldest Person In the World with AKU to Never have a Joint Replaced"


WHEN
HUMANS PLAN
GODS LAUGH
THESWIMMERS

Six Year Later:



- 5 Joints replaced, with a #6 on the Horizon
- Lost four inches of spine height
- Reduced to only teaching one ‘in-water’ aquafit classes.
- Became deeply familiar with Amazon Prime and Disney+ TV

"So. Maybe this Hot Tub Yoga Isn't the Thing for You?

This can be YOU Four Weeks After Starting Aquafit!

Results May Vary…

Recent Status: October 2024

- Teaching Two Aquafit Classes/week
- Golfing of some sort 3-4 times/week
- Active Gardener and Landscaper
- Walking 20km+ on any given day
- Active up to the day of surgery, and had a quick return to normal activity

COVID and Catalysts

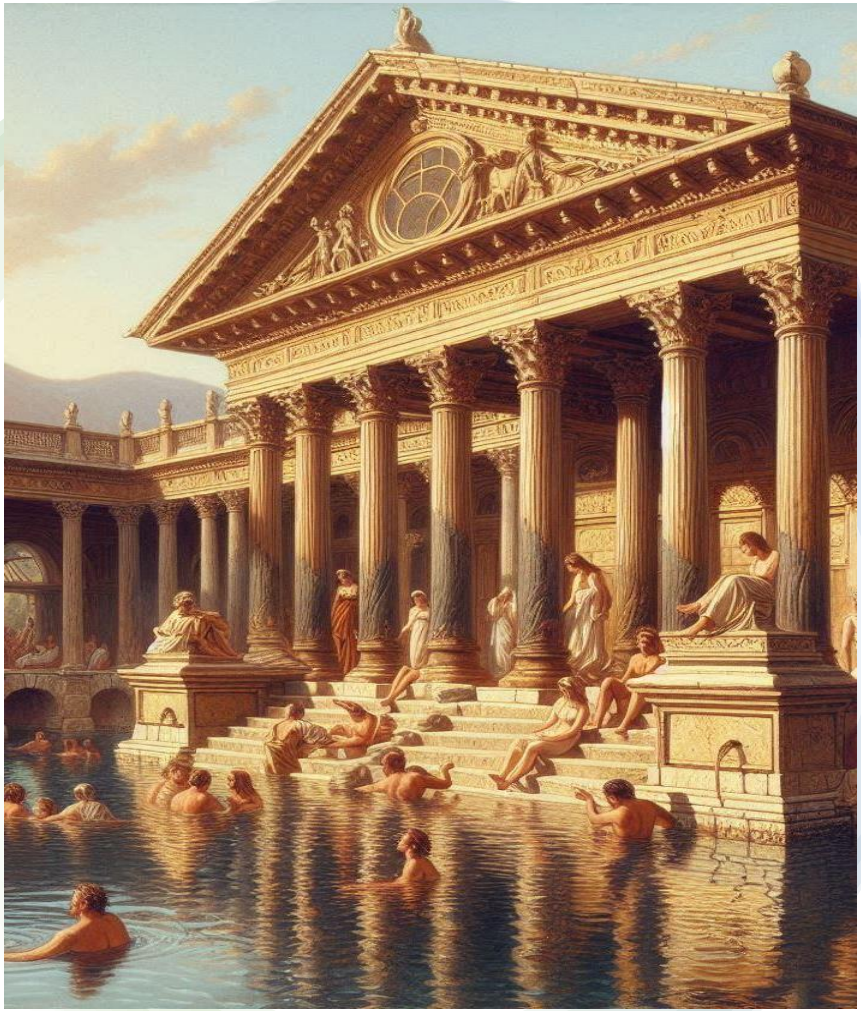
- Due to multiple joint issues, I had been prescribed HOURS of daily Physical Therapy!
- Worked with a local kinesiologist and Dr. Monique Perry at the NIH to consolidate my PT into a water-based program (I was going to the pool anyways...)
- Finished Netflix after my fourth joint replacement

Warm Water Therapy Through The Ages:

Bath, England

Dr. William Oliver said in 1707:

"If it can't be cured by drinking and bathing, it can't be cured"



The Roman Baths

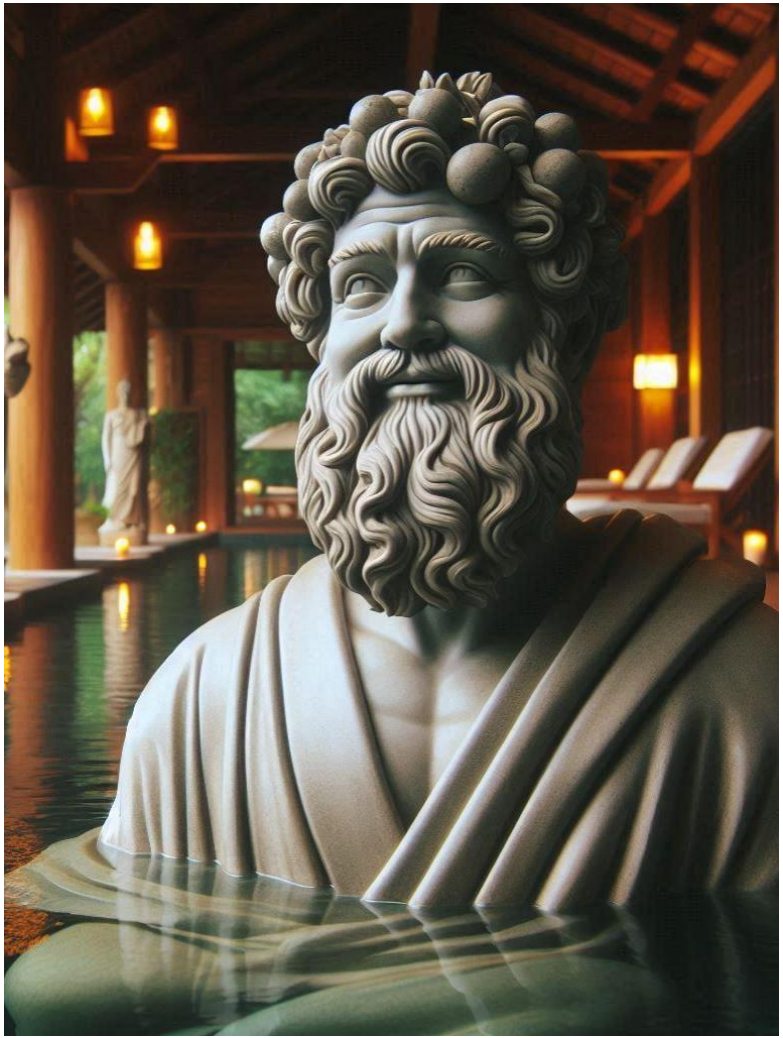
Invented the word “SPA” (Sanus Per Aquam - meaning “health by or through water)

Hydrotherapy became synonymous with Socialization

Hippocrates ~390 BC

- Greek Father of Modern Medicine

"The way to health is to have an aromatic bath and scented massage every day"



Traditional Asian Therapy

Around 400 BC, Asian medicine began to prescribe warm water to align a patients Qi flow

Ancient Egypt

In 600 BC, the King of Media, constructed the first known hot tub, which used red-hot stones to heat water in a cauldron-like container

Key Points Before Starting Any Fitness Program

- ALWAYS Seek Medical advice before beginning any new exercise program
- Determine the lowest barrier to allow you to *get started and keep going!*
- It takes four weeks to affect a change in habits, so start easy to allow you to build into the next month
- Effective routines can be created for any situation:
  - Walking
  - Gardening
  - Watching TV
  - Lying in Bed

Let’s Jump Right In!

Pick a Location that best suits YOU

- Local Pool
- Health Club
- Outdoor Spa
- The Beach

Local Pools and Health Clubs

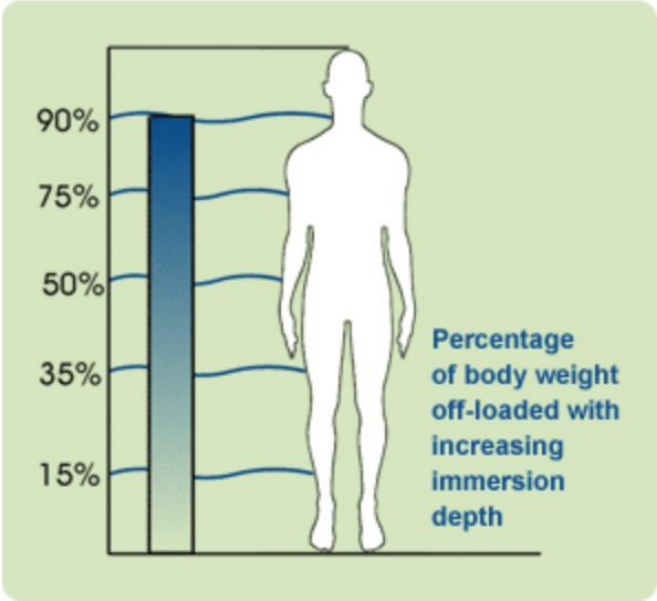
Provide Instant access to group classes and qualified instructors

AKU Pro-Tip:

You will always have the best stories relating to joint replacement surgery!

Buoyancy Reduces the Effect of Gravity

North Coast Physical Therapy Blog on WordPress.com



Our AKU Joints Love The 360° Support!

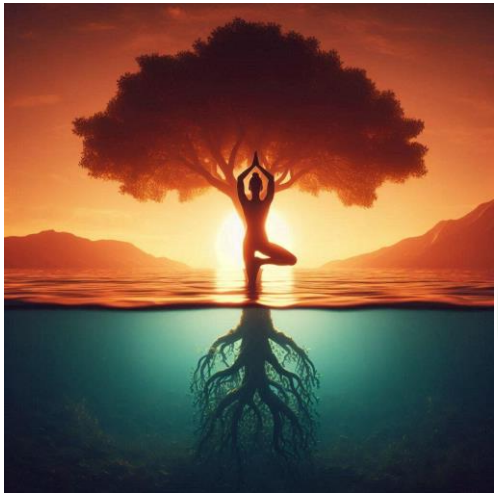
Water is a Safe Environment to Practice BALANCE

AKU Pro Tip:

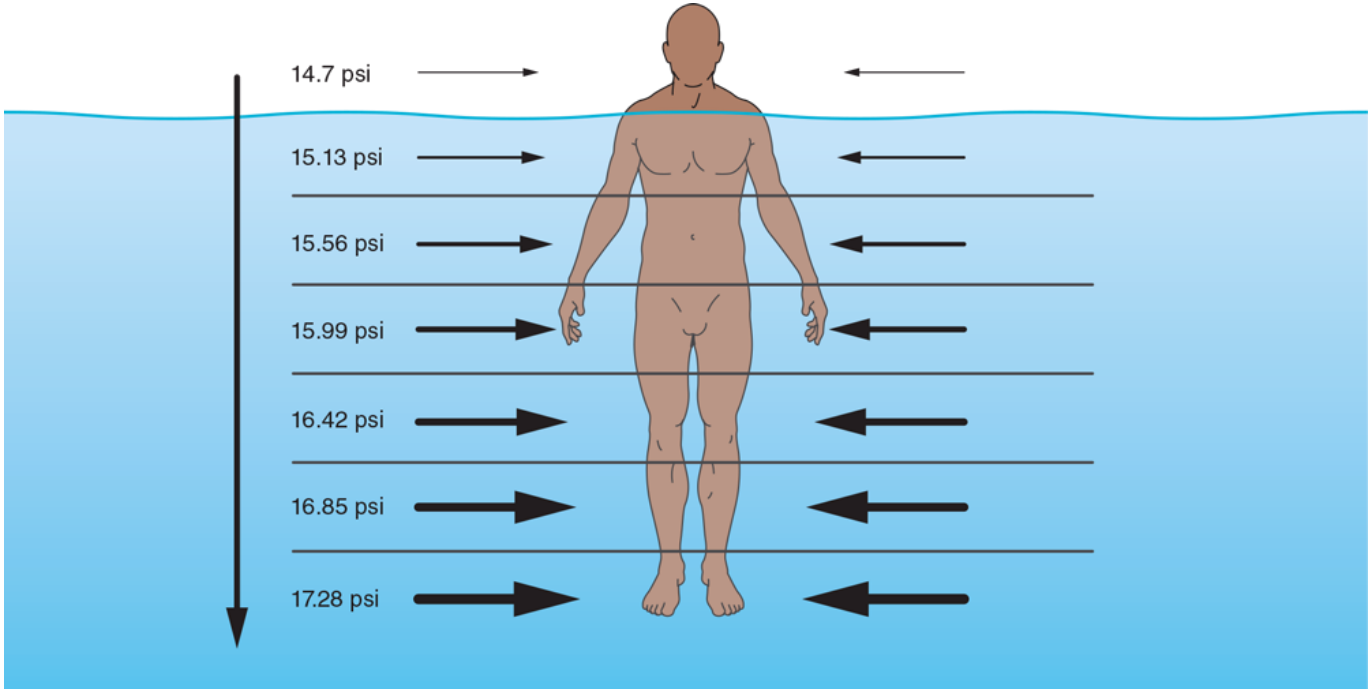
Your ability to recover from stumbles in order to avoid serious falls is directly related to your level of conditioning

Physical Balance Basics

- Involves delicate coordination by our brain using inputs from our eyes, ears, nervous and musculoskeletal systems
- Needs to be practiced! All these senses get lazy as we age…
- Water is the ideal place to practice as the risk and severity of falling is greatly reduced!
- Sample In-Water Exercises:
  - Leg Lifts (to avoid stair stumbles)
  - Walking "Like a Model"
  - Soccer Style Leg Swings
  - Ballet Style Arabesque



Cardio Friendly: Boost Your Circulation



AKU can become a Cardiac Disease with a Skeletal Component…

- Prioritize ANY activity which raises your heart rate in a controlled fashion
- Everyone benefits from improving Mental Health, Lowering General Disease Risks, and Increased Longevity if we exercise regularly
- AKU Patients need to BREATH a Little Deeper!
  - Mild Cardiac Activity helps maintain the capacity of our rib cage
  - Regular cardiac activity MAY BE beneficial to AKU Heart Valves
  - Endurance type exercises lead to the increase of synovial fluid in the joints (Very complicated process…)

Key Exercises for Any Aquatic Environment

Anything that Targets "The Big Muscles"

- Glutes
  - Squats / Donkey Kicks
- Quad's
  - Single Leg Squats train legs independently
- Lats
  - Any swimming or rowing motion

- Spine
  - Sitting on the "Bum Bone" recruits spinal extensors and lumbar flexors
- Abdominals
  - Bring The Belly Button IN
- Shoulder Blades
  - Down and In

Form is Critical!

Remember the Five B's:

- Blades
- Belly
- Butt
- Balance
- Breathe

Where’s the best place to start?

The Sumo Squat (Shinko)

A Cascade of Benefits from Doing Squats in Water!

- Holding the position at the bottom of the squat is incredible for *increasing* knee and hip flexibility
- Wider stance *targets* spine and hip stabilizers and balance
- Move to shallower water as you *build* strength and increase range of motion
- Arms can be added in for additional resistance
- In the water, Aqua Squats are an excellent base for performing other routines

What about our Shoulders?

- From the Sumo Squat, it's easy to perform internal and external shoulder rotation as well as targeted isometrics
- Pushing up from a seat built into a pool or hot tub targets the arm muscles used to assist in rising from a chair
- AKU Pro Tip:

No matter if it's spine, hip, knees or shoulders that bothering you the most, you will need strong arms and shoulders to maintain mobility

Our Goal is "Functional Fitness"

- Moving the laundry from the washer to the dryer
- Picking up a child
- Entering a vehicle or restaurant booth
- Raking a garden
- Starting a lawnmower
- "Stair and Chairs"

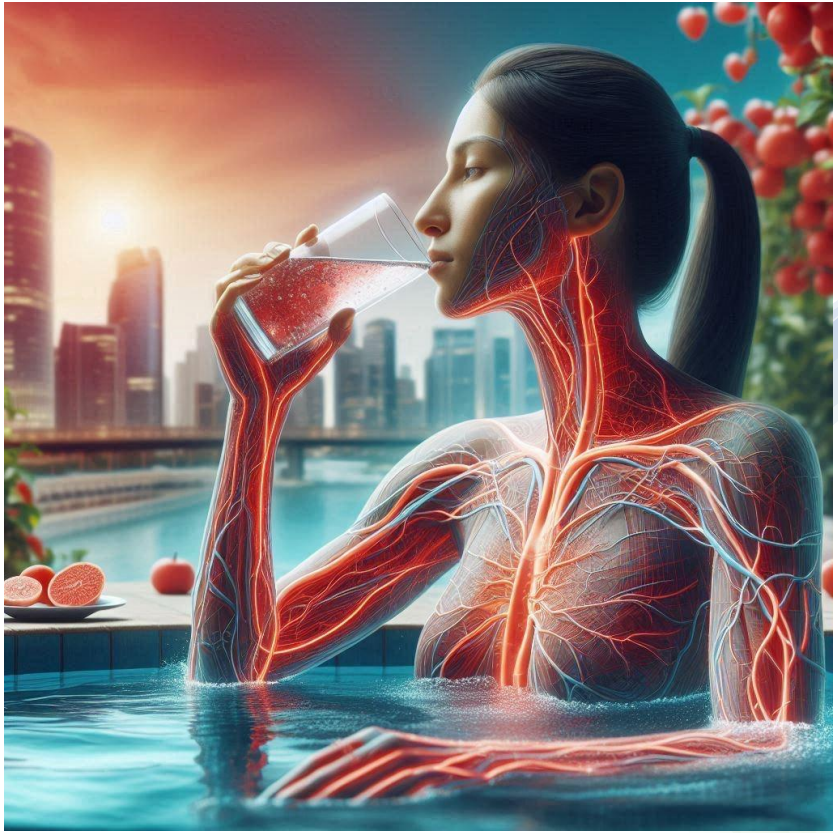
But what happens when things Heat Up?

Musculoskeletal

- Aches and Pains Reduces
- Inflammation Reduces
- Flexibility Increases

Cardiovascular

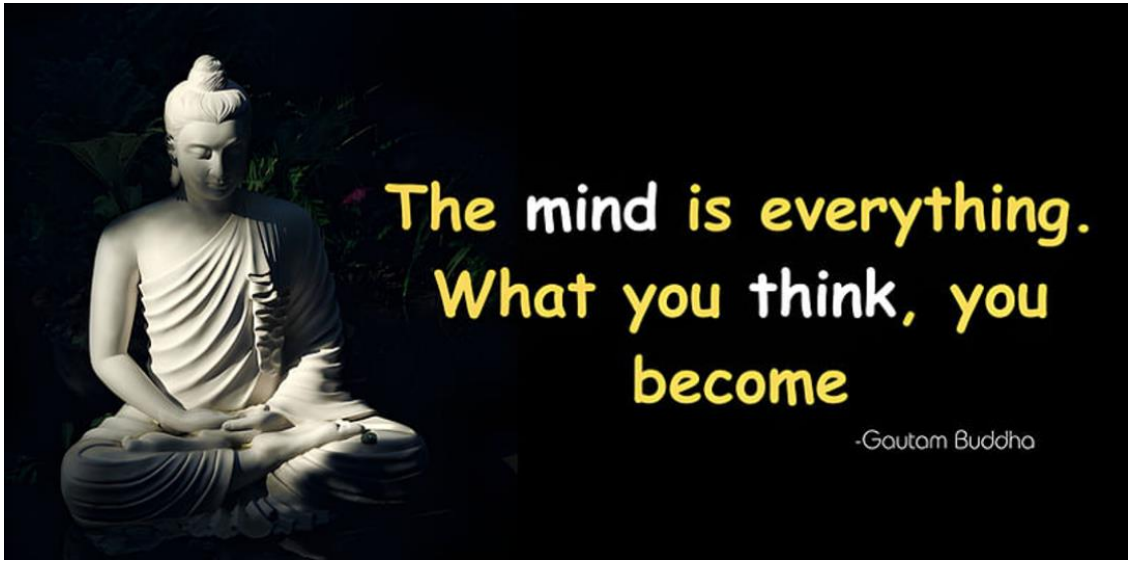
- Heart Rate Increases
- General Vasodilation
- Blood pressure decrease
- Blood Flow Diverted to Periphery



Metabolic

- Energy burned equivalent to a light walk
- Stimulation of Heat Shock Protein 70 “The Protein Chaperone” (HSP70)
- Better control of blood sugar (McKee Medical Center Colorado / University of Loughborough)
- General Vasodilation enhances Amino acid and cytokine distribution

Mental Health and Relaxation



Final Thoughts:

Discipline is a Promise to Our Future Selves

Everything in Moderation

Become the “Favorite Patient” of all your Doctors

Thanks For Listening!

AKU
Alkaptonuria Society

History of Alkaptonuria

A Timeline

Lakshminarayan Ranganath
Inaugural Clinical Director
National Alkaptonuria Centre
University of Liverpool

AKU history

1500 BC

Harwa – "the oldest AKU patient"

Harwa – died age early 30's cause unknown

Custodian of a granary in Egypt 1500 BC

X-Rays revealed extensive calcification in spinal intervertebral discs

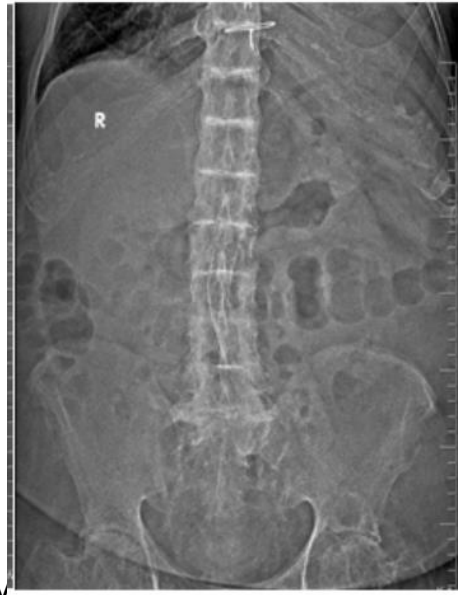
Hip and in both knee joints disease seen

Needle biopsy of the hip was carried out for suspected AKU

Infrared studies of hip biopsy showed HGA-pigment

How common was AKU is ancient Egypt - was there consanguinity in those day

AKU may have been present even earlier in antiquity



Ref - Stenn FF, Milgram JW, Lee SL, Weigand RJ, Veis A, Rogers F. Biochemical Discovery of Homogentisic Acid Pigment in an Ochronotic Egyptian Mummy. Henry Ford Hosp Med Journal. Vol 27, No 1, 1979
Simon G and Zorab PA: The radiographic changes in alkaptonuric arthritis: A report on three cases (one an Egyptian mummy). Br J Radiol 34:384-386, 1961
Wells C and Maxwell BM: Alkaptonuria in an Egyptian mummy, Br J Radiol 35:679-682, 1962
Gray PHK: Radiography of ancient Eygptian mummies. Med Radiogr Photogr 43:34-44, 1967.

Consanguinity rates in Middle-East countries	
Country	**Consanguinity rate (%)**
Algeria	22-34
Bahrain	39-46
Egypt	21-80
Iraq	47-60
Jordan	49-64
Kuwait	38-64
Lebanon	25-42
Libya	48
Mauritania	47
Morocco	19-25
Oman	56
Palestine	17-45

Temaj et al. Journal of Rare Diseases (2022) 1:2https://doi.org/10.1007/s44162-022-00004-5

AKU history

Scribonius publishes a case of a healthy schoolboy who excreted urine as black as ink

1500 BC

1584

Harwa – "the oldest AKU patient"[4]

G. A. Scribonius (in 1584) described a healthy schoolboy who continuously excreted black urine
Schenck (in 1609) described a monk who exhibited a black urine

Zacutus Lusitanus, published in 1649 that a 14-year-old boy passed black urine

Lusitanus writes ‘At the age 14 years, he was submitted bleedings, purgation, baths, a cold and watery diet, and drugs galore

None of these had any obvious effect - the patient resolved to let things take their natural course

None of the predicted evils ensued - he married - begat a large family, and lived a long and healthy life, always passing urine black as ink’

Lifespan in those times

Scribonius GA: De Inspectione Urinarum. Lemgo, Germany, 1584, p.50.

Schenck: Urine nigra in sanis quibusdam. Observationes Medicae. Lib. III. Frankfort, 1609, p. 558
Lusitanus: Praxis Medica Admiranda. Lib, III, 1649, cap. 134

AKU history

Scribonius publishes a case of a healthy schoolboy who excreted urine as black as ink

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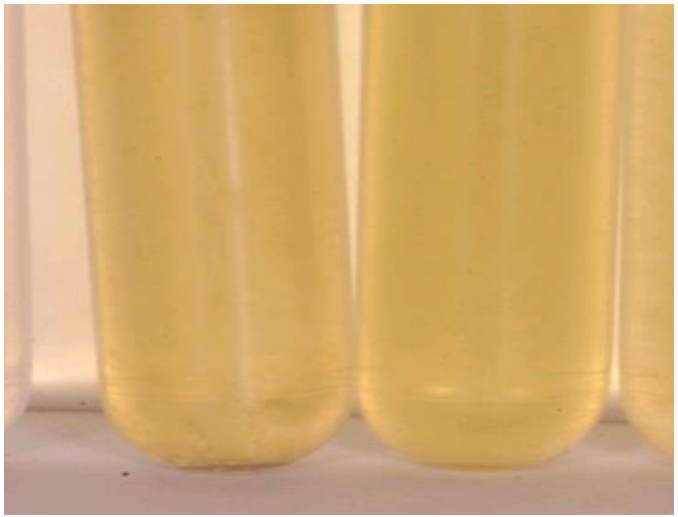
Bödeker first named the new substance "alkapton"



Urines which were black when passed and became black on exposure to air

As the urine darkened from 'the surface', "it took up oxygen gas," and this gave the substance its name

He called it for this reason 'Alkapton' (Greek word ‘to suck oxygen up greedily’, and the Arabic alkali), after its behaviour toward oxygen in alkaline solution

Before he could chemically identify the alkapton the patient discharged himself!

(Boedecker: Ueber das Alcapton; ein neuer Beitrag zur Frage. Z Rat Med 7:130, 1859)

AKU history

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1866

Virchow names ochronosis at necropsy

Virchow reported the first case as a pathological curiosity

Autopsy of a sixty-seven-year-old man

Subject also had arthritis deformans

Cartilages and tendon insertions in the bones all over the body were stained black to light grey

Under the microscope the tissues showed yellow (ochre) pigment, from which the name was derived

HE DID **NOT** KNOW ALKAPTONURIA & OCHRONOSIS WERE THE SAME CONDITION

(Virchow R: Ein Fall von allgemeiner Ochronose der Knorpel und knorplahnlichen Theiie. Virch Arch Path Anat 1866;37:212-219)

AKU history

1500 BC

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1891

Wolkow & Baumann: identified homogentisic acid (HGA)

Identified alkapton as a compound unknown till then, 2,5-dihydroxyphenylacetic acid and named it homogentisic acid

Showed that HGA came from tyrosine

The series of reactions leading to homogentisic acid was determined

BUT - stated that homogentisic acid was formed by the putrefaction of protein in the gut and not by the tissue metabolism

i.e. AKU was due to a gut infection with a bacterium

Adamant that only plants and not animals could make aromatic compounds from non-benzene structures

Wolkow M and Baumann E: Ueber das Wesen der Alkaptonurie. Hoppe-Seyler Z Physiol Chem 15:228, 1891

Koch's postulates, Covid, and misinformation rabbit holes

16 November 2020 | Coronavirus, Faculty of Medical and Health Sciences

Opinion: Take a 19th century German scientist, a 21st

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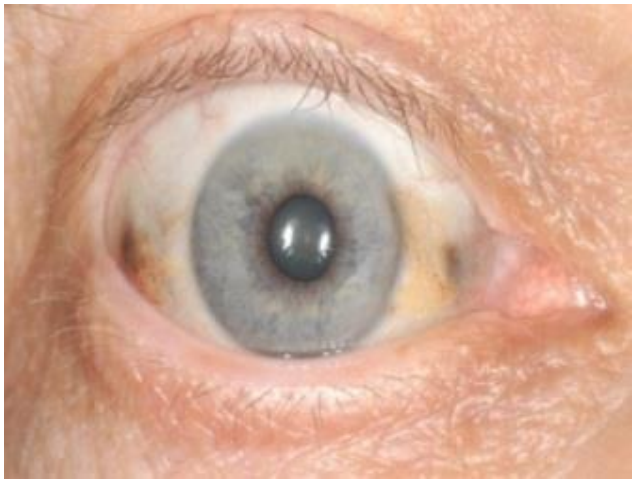

Ochronosis was recognised externally for the first time

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1902

Garrod's publicati on AKU is considered the start of human genetics and he introduce the term 'inborn error of metabolism'[8]

28 cases of AKU (Great Ormond Street Hosp. Barts)

Uncovered mode of transmission of this first hereditary human disease

Introduced a link between a specific enzyme and a specific Mendelian factor (now called genes)

Also studied albinism, pentosuria and cystinuria

Coined the term Inborn Error of Metabolism when studying alkaptonuria

CHROMOSOMES

Blogging the Human Genome: How genetics nearly killed off Darwinism.

How genetics—and a very dirty diaper—nearly killed off Darwinism.

BY SAM KEAN JULY 09, 2012 • 6:00 AM

Darwinism also had something else working against it: emotion. People hated the idea. Starvation and death seemed to be of paramount importance, with superior types always crushing the weak. Darwinism violated the progressive ethos of the young century, and even by 1904, one German biologist could cackle, "We are standing at the deathbed of Darwinism, and making ready to send the friends of the patient a little money, to ensure a decent burial."

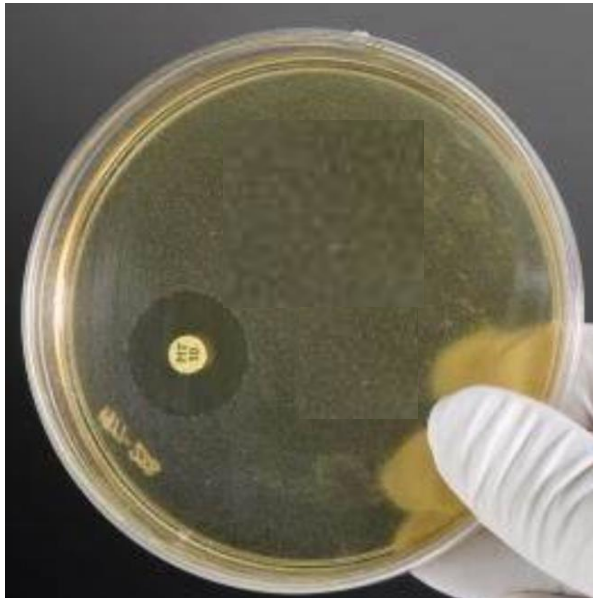
Illustration by Andrew Morgan

TWEET

Human genetics started with a black diaper. Around 1900, the English doctor Archibald Garrod

Garrod/Mendel/Bateson

Darwin



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1902

Garrod's publication on AKU is considered the start of human genetics and he introduce the term 'inborn error of metabolism'[8]

1902

Albrecht confirms alkaptonuria and ochronisis – same disease

Albrecht Autopsy and review

Connected **black urine and ochronosis as one and the same disease**

Also noted deforming arthritis

Albrecht H: Ueber Ochronose, Z Hez/k 23(2);366-378, 1902

AKU history

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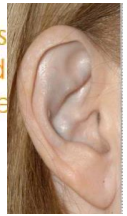


1904

Osler – ears and skin ochronosis[12]

Ochronosis was recognised externally in ear & skin for the first time

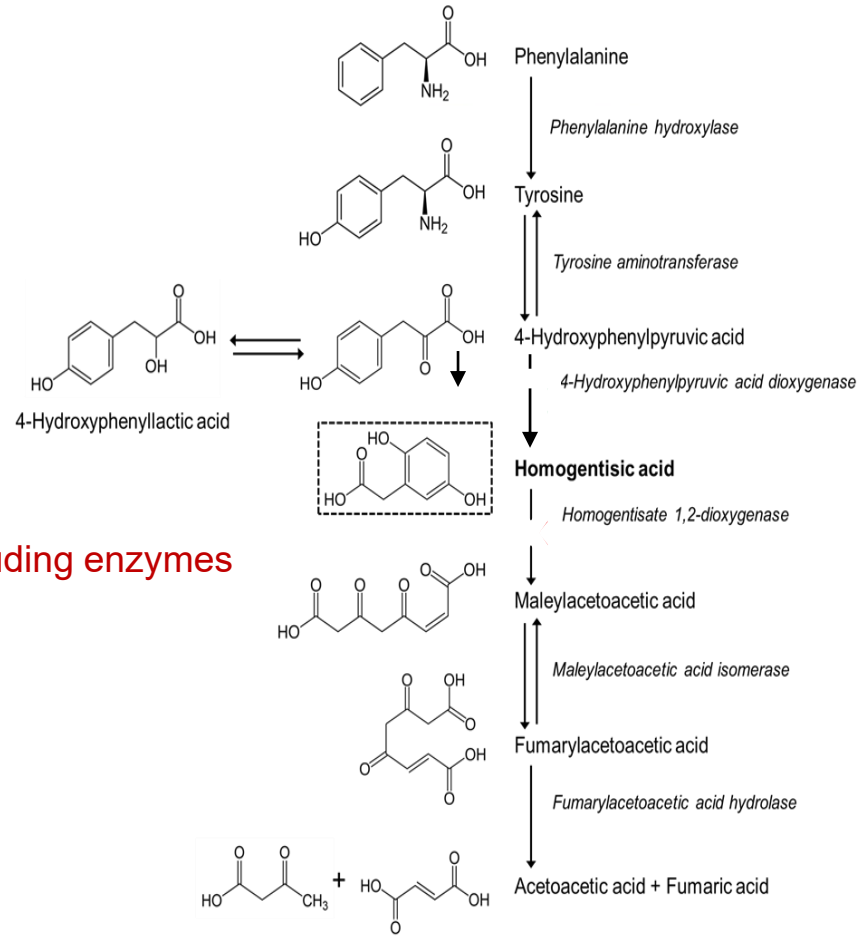
Osler W: Ochronosis: The pigmentation of cartilages, sclerotics, and skin in alkaptonuria. Lancet 1:10, 1904

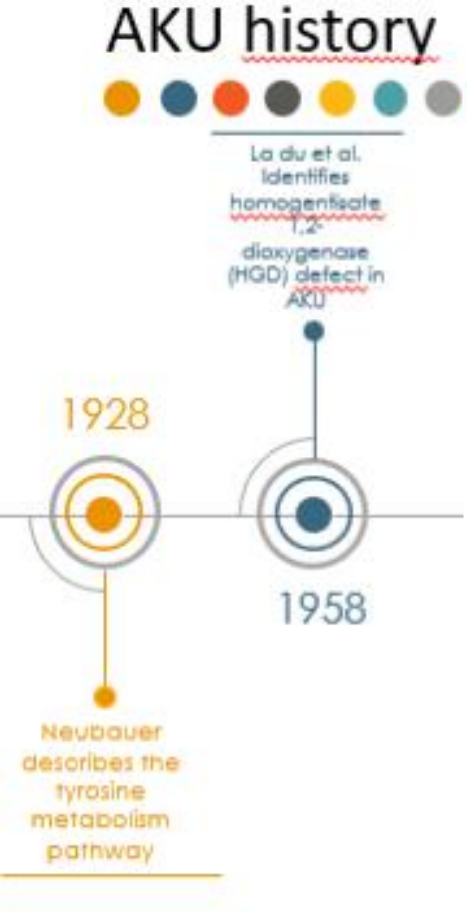
AKU history

1928

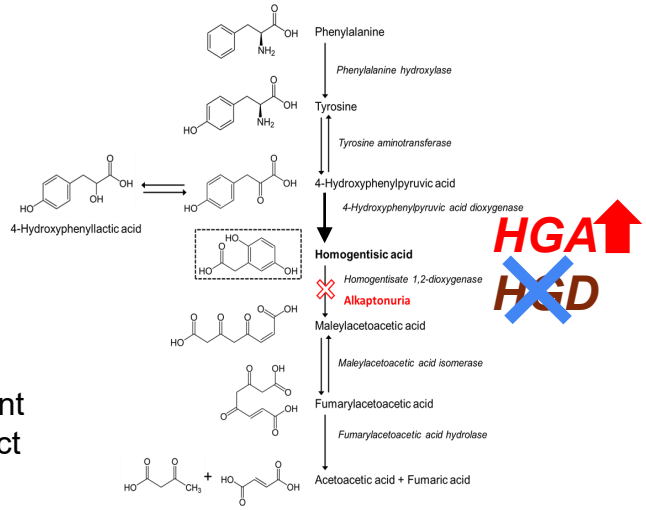
Neubauer describes the tyrosine metabolism pathway

Neubauer O. Intermediarer Eiweisstoffwechsel. Handb. Norm. Path. Physiol. 1928;5: 671-981 – reviewed and deduced the pathway to HGA including enzymes





La Du, Zannoni, Laster and Seegmuller report that all of the enzymes of tyrosine metabolism were present in a biopsy sample of liver from an alkaptonuric subject but that the *homogentisate oxidase was inactive*



THE NATURE OF THE DEFECT IN TYROSINE METABOLISM IN ALCAPTONURIA

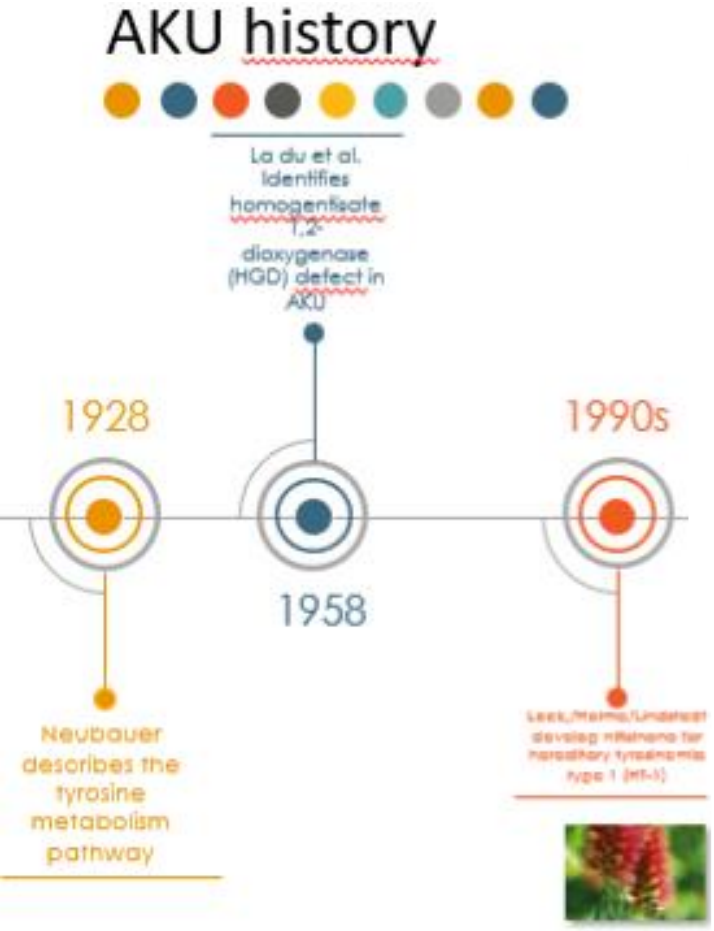
By BERT N. LA DU, VINCENT G. ZANNONI, LEONARD LASTER, AND J. E. SEEGMILLER

(*From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, United States Public Health Service, Bethesda, Maryland*)

(Received for publication, July 29, 1957)

Alcaptonuria is a rare, hereditary, metabolic disorder characterized by a defect in the oxidation of tyrosine (1–3). In this condition homogentisic acid, an intermediary product of tyrosine degradation in mammalian

LA Du, B. N., ZANNONI, V. C., LASTER, L., & SEEGMULLER, J. E. The Nature of the Defect in Tyrosine Metabolism in Alcaptonuria. J Biol Chem 1958; 230: 251–260

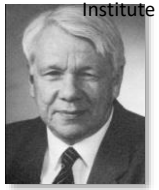


Lindstedt et al. *Lancet* 1992; 340: 813–17

Liverpool John Moores University

Prof Edward Lock
ICI & Syngenta

Karolinska Institute



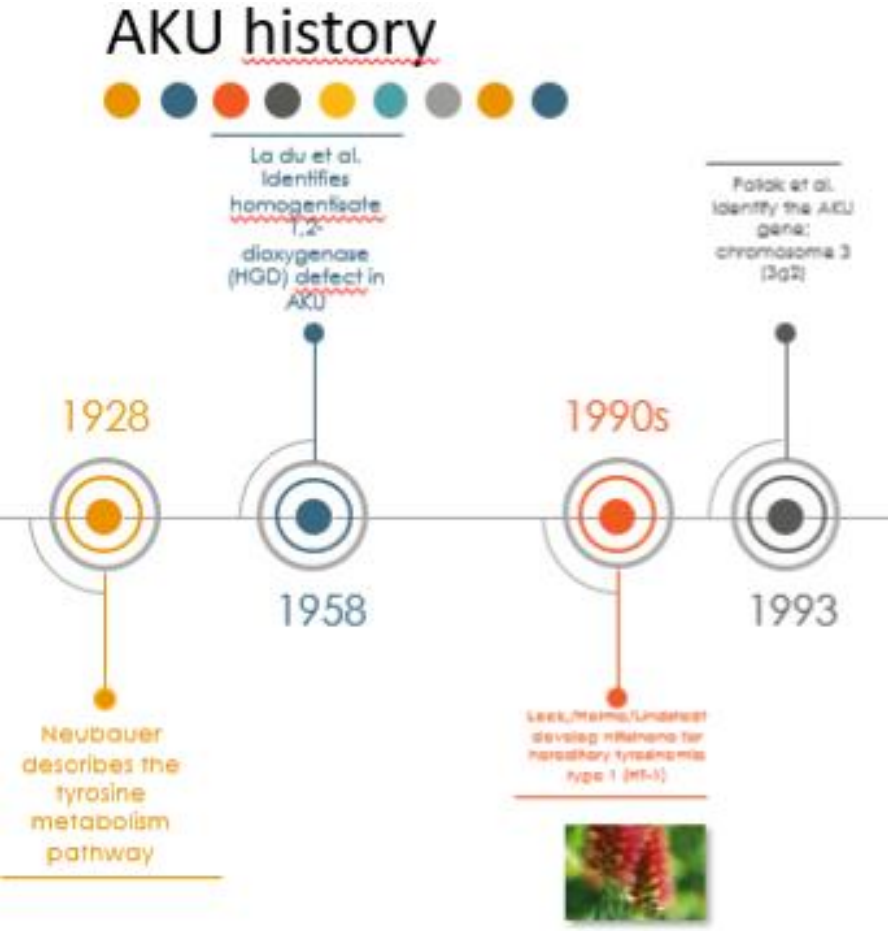
Prof Sven Lindstedt

Prof Elisabeth Holme

Edward Lock (ICI) and colleagues developed nitisinone from leptospermone from the Australian bottlebrush plant

Lindstedt, Holme & Lock et al pioneered nitisinone use as life-saving therapy in children with HT-1

Treatment for HT-1 was liver transplantation until then

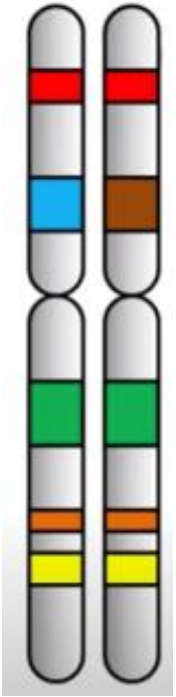


AKU gene identified

Chromosone 3Q – long arm of chromosome 3

Heterozygosity mapping – genes that are close together on a chromosome are inherited

Boston in USA



The molecular basis of alkaptonuria

José M. Fernández-Cañón*,[1], Begoña Granadino*,[2],
Daniel Beltrán-Valero de Bernabé[2], Mónica Renedo[3], Elena Fernández-Ruiz[3],
Miguel A. Peñalva[1] & Santiago Rodríguez de Córdoba[2]

Alkaptonuria (AKU) occupies a unique place in the history of human genetics because it was the first disease to be interpreted as a mendelian recessive trait by Garrod in 1902. Alkaptonuria is a rare metabolic disorder resulting from loss of homogentisate 1,2 dioxygenase (HGO) activity. Affected individuals accumulate large quantities of homogentisic acid, an intermediary product of the catabolism of tyrosine and phenylalanine, which darkens the urine and deposits in connective tissues causing a debilitating arthritis. Here we report the cloning of the human *HGO* gene and establish that it is the *AKU* gene. We show that *HGO* maps to the same location described for AKU, illustrate that *HGO* harbours missense mutations that cosegregate with the disease, and provide biochemical evidence that at least one of these missense mutations is a loss-of-function mutation.

Nature Genetics 1996:14:19-24

AKU history

1928

Neubauer describes the tyrosine metabolism pathway

1958

La du et al. Identifies homogentisate 1,2-dioxygenase (HGD) defect in AKU

1990s

Lock,/Holme/Lindstedt develop nitisinone for hereditary tyrosinemia type 1 (HT-1)

1993

Pollak et al. identify the AKU gene; chromosome 3 (3q2)

1998

Japanese study of NTBC in mouse AKU

NIH investigators propose NTBC as possible treatment for AKU

Am. J. Hum. Genet. 63:920–921, 1998

Anikster, Nyhan,& Gahl

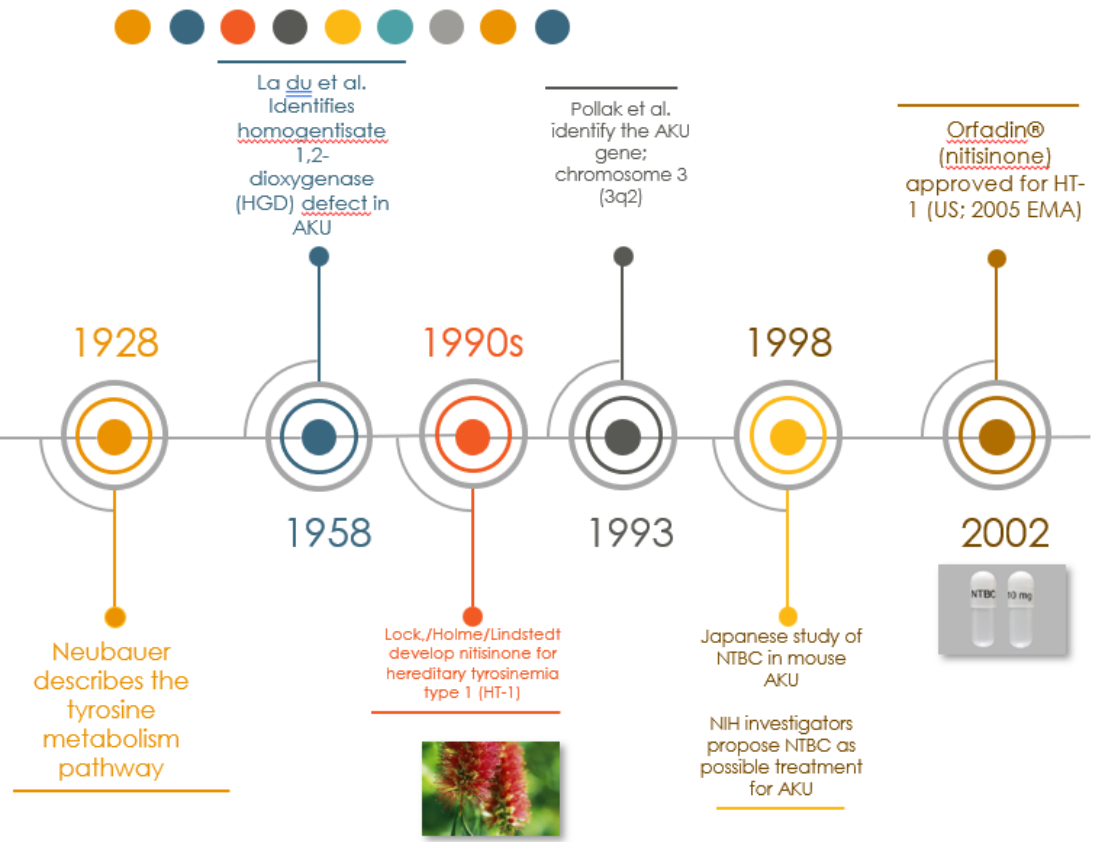
NTBC and Alkaptonuria

To the Editor:

La Du (1998) sounds an appropriate note of caution in posing the editorial question, "Are we ready to try to cure alkaptonuria?" (i.e., with homogentisate 1,2-dioxygenase [HGO] gene-replacement therapy). He suggests that localization of recombinant HGO to certain tissues might lead to accumulation of reactive intermediates of the tyrosine catabolic pathway. We would like to point out an alternative therapy for alkaptonuria (La Du 1995; MIM 203500) that obviates the problem of gene localization.

The potential treatment consists of oral administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, or NTBC, in combination with some dietary restriction of phenylalanine and tyrosine. NTBC is a member of the triketone class of herbicides, which cause plants to bleach. The triketone herbicides are inhibitors of 4-hydroxyphenylpyruvate dioxygenase

AKU history



Orfadin (nitisinone, NTBC) was approved for HT-1 in the USA in 2002 and in Europe in 2005

Swedish Orphan Biovitrum (Sobi) had market exclusivity

AKU history

1928 — Neubauer describes the tyrosine metabolism pathway

1958 — La du et al. Identifies homogentisate 1,2-dioxygenase (HGD) defect in AKU

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NIH investigators propose NTBC as possible treatment for AKU

2002 — Orfadin® (nitisinone) approved for HT-1 (US; 2005 EMA)

2003 — AKU Society formed in UK

Lakshminarayan Ranganath

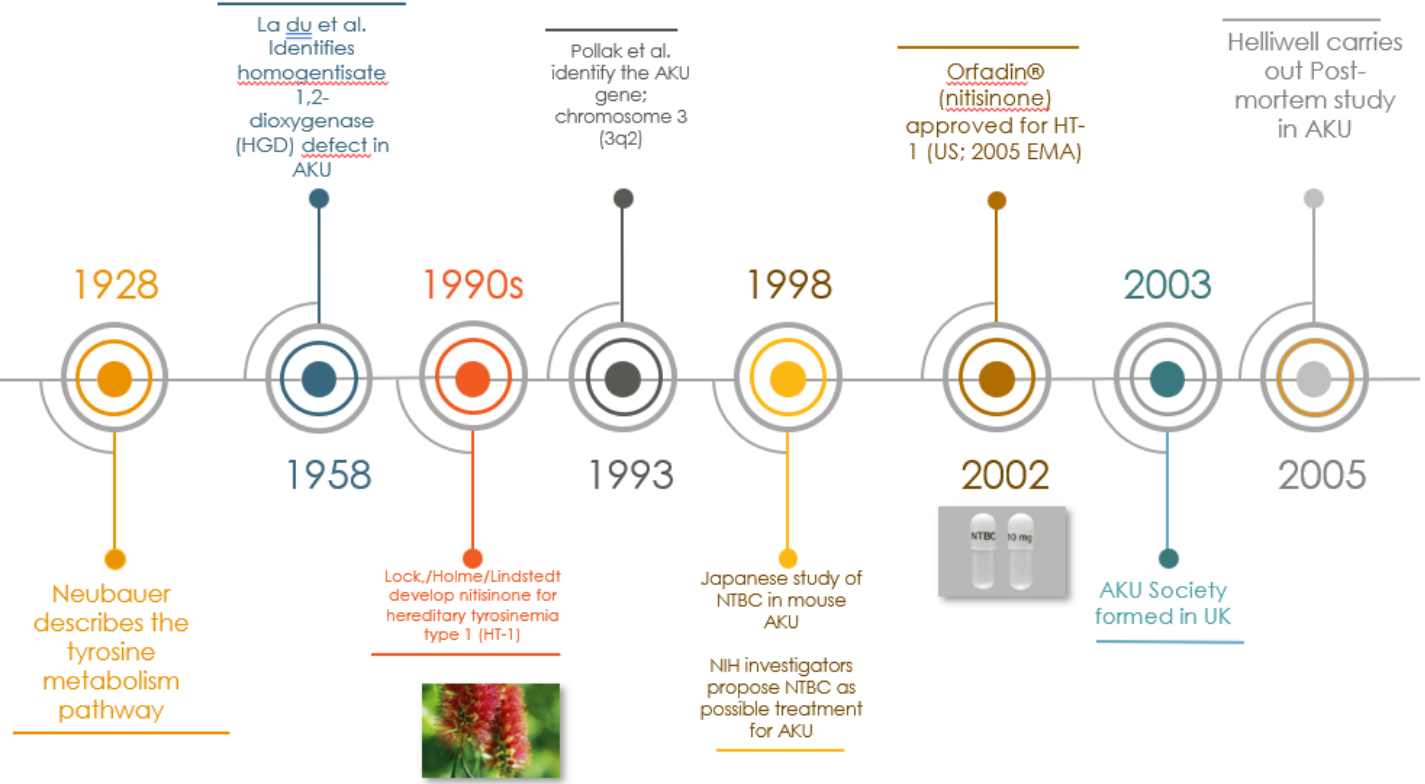
Robert Gregory

Nicolas Sireau

An AKU patient in Liverpool along with a doctor founded the AKU Society in 2003 with Nicolas Sireau as the CEO

This created an opportunity for AKU patients in the UK for the first time

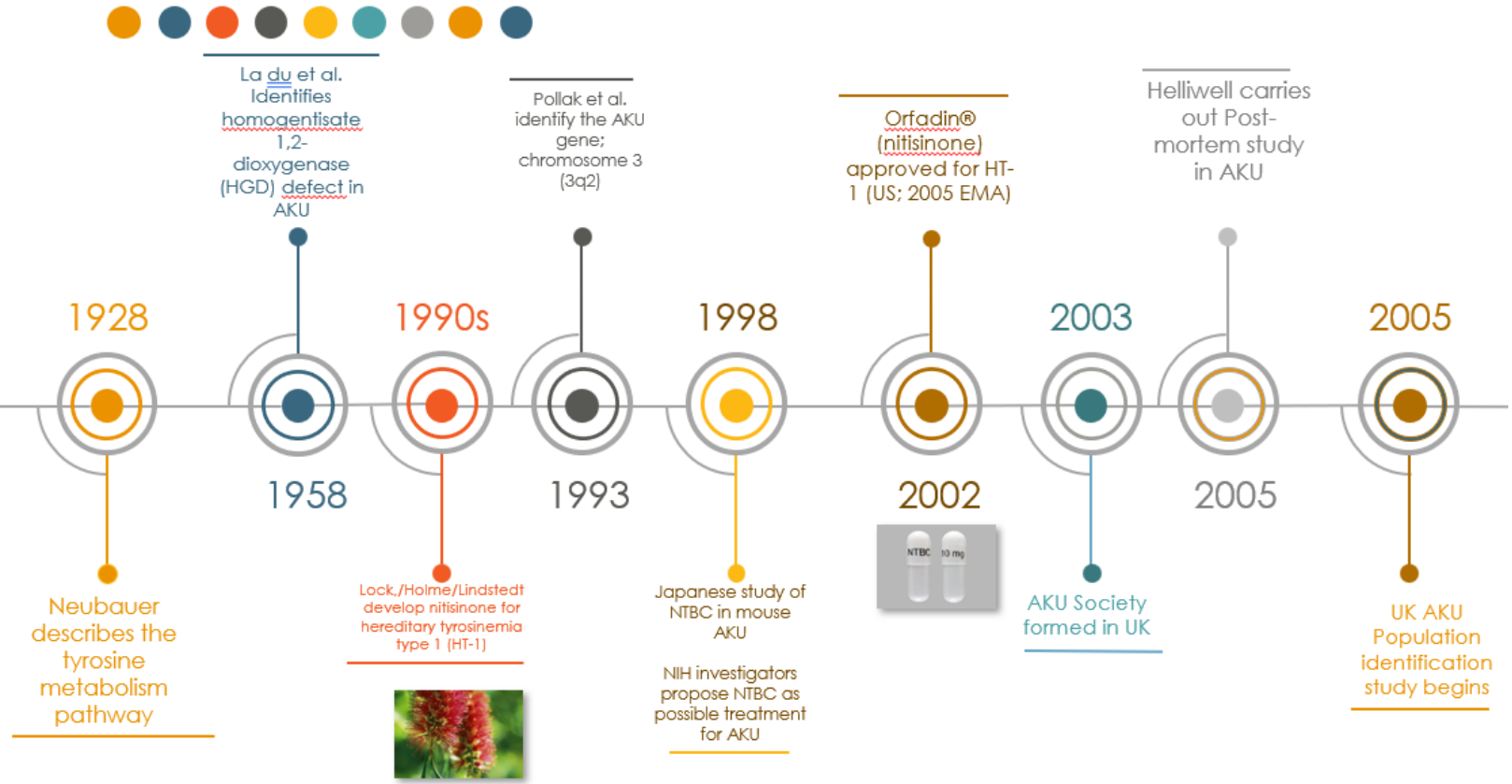
AKU history



The postmortem study was due to a donation from an AKU patient

Gave our research the needed direction

AKU history



We wanted to be ready to administer Nitisinone to our UK patients when it became available.

So, we began a population identification program between 2005 and 2009.

16,000 GP questionnaires posted

Patient numbers increased from 4 to 79

AKU history

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Neubauer describes the tyrosine metabolism pathway

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2003
AKU Society formed in UK

2005
Helliwell carries out Post-mortem study in AKU

2005
UK AKU Population identification study begins

2008
AKU Cell model of ochronosis established

Cell model of ochronosis was developed to study ochronosis better

AKU history

NIH 3-y Nitisinone Trial In AKU Reports inconclusive

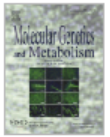
2008

UK Natural history study of AKU begins

ELSEVIER

Molecular Genetics and Metabolism

Volume 103, Issue 4, August 2011, Pages 307-314



A 3-year randomized therapeutic trial of nitisinone in alkaptonuria

Wendy J. Introne [a], Monique B. Perry [b], James Troendle [c], Ekaterini Tsilou [d], Michael A. Kayser [e 1], Pim Suwannarat [e 2], Kevin E. O'Brien [a f], Joy Bryant [a], Vandana Sachdev [g], James C. Reynolds [h], Elizabeth Moylan [b], Isa Bernardini [e], William A. Gahl [a e]

Show more

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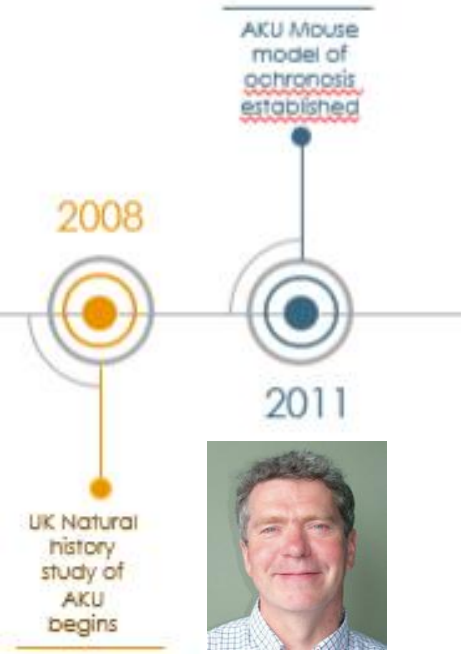
https://doi.org/10.1016/j.ymgme.2011.04.016 Get rights and content

Abstract

Alkaptonuria is a rare, autosomal recessive disorder of tyrosine degradation due to deficiency of the third enzyme in the catabolic pathway. As a result, homogentisic acid

AKU history



Prof Jim Gallagher
Scientist

NIH 3-y Trial Reports inconclusive

Basic and translational research
Extended report

Ochronotic osteoarthropathy in a mouse model of alkaptonuria, and its inhibition by nitisinone

Andrew J Preston [1], Craig M Keenan [1], Hazel Sutherland [1], Peter J Wilson [1], Brenda Wlodarski [1], Adam M Taylor [1, 2], Dominic P Williams [3], Lakshminarayan R Ranganath [1, 4], James A Gallagher [1], Jonathan C Jarvis [1]

Correspondence to Professor James A Gallagher and Professor Jonathan C Jarvis, Department of Musculoskeletal Biology, Institute of Ageing and Chronic Disease, Bone and Joint Research Group, University of Liverpool, Sherrington Building, Ashton Street, Liverpool L69 3GE, UK; jag1@liverpool.ac.uk and J.C.Jarvis@ljmu.ac.uk

Abstract

Background Alkaptonuria (AKU) is a rare metabolic disease caused by deficiency of homogentisate 1,2 dioxygenase, an enzyme involved in tyrosine catabolism, resulting in increased circulating homogentisic acid (HGA). Over time HGA is progressively deposited as a polymer (termed ochronotic pigment) in collagenous tissues, especially the cartilages of weight bearing joints,

In AKU mice, nitisinone was effective not just in lowering the HGA
but could also modify the disease process ochronosis.

AKU history

NIH 3-y Trial Reports inconclusive

NHS

Specialised Services

Advisory Group for National Specialised Services

2nd Floor Southside
105 Victoria Street
London
SW1E 6QT

Tel: 020 7932 3821
Fax: 020 7932 3800
Website: www.specialisedservices.nhs.uk
Email: Teresa.Moss@nsct.nhs.uk

Off-label use of nitisinone in AKU

NAC operational in June 2012

Lakshminarayan Ranganath
Clinical Director National Alkaptonuria Service
Department of Clinical Biochemistry and Metabolic Medicine
Royal Liverpool University Hospital
Prescot Street
Liverpool, L7 8XP
By email: lrang@liv.ac.uk; lakshminarayan.ranganath@rlbuht.nhs.uk

5 March 2012

Dear Dr Ranganath,

Application for National Commissioning and designation from April 2012: National Alkaptonuria Service

Thank you for submitting a full application for national commissioning and designation.

The Advisory Group for National Specialised Services – which advises Department of Health Ministers on which services are best commissioned nationally and which centres should be designated to provide them – considered eight full applications at its meetings in December 2011. I am pleased to say that Ministers agreed the recommendation that the National Alkaptonuria Service for patients should be nationally commissioned from April 2012.

I know that Mark Scott, NSCT Senior Commissioning Manager has already been in touch with you and that you have begun work on the detailed arrangements and implementation of

AKU history

NIH 3-y Trial Reports inconclusive

From: Thomas.Jussen@ec.europa.eu <Thomas.Jussen@ec.europa.eu>
Sent: 20 April 2012 08:54
To: Ranganath, Lakshminarayan <lrang@liverpool.ac.uk>
Subject: FP7-HEALTH-2012-INNOVATION-1 : Initial information on the outcome of the evaluation of Stage 2

EUROPEAN COMMISSION
DIRECTORATE GENERAL FOR RESEARCH & INNOVATION
Directorate F – Health
The Director

Clinical trials of nitisinone in AKU
DevelopAKUre
Regulatory approval of nitisinone in AKU

Brussels, 20/04/2012
rtd.ddg3.f.1(2012) 486800

€6 million + €4 million co-financing

Sent by E-mail only by Thomas Jussen on behalf of Ruxandra Draghia-Akli

Dr. Lakshminarayan Ranganath
Royal Liverpool and Broadgreens University Hospitals Trust
lrang@liverpool.ac.uk

Specific Programme "Cooperation" – Theme "Health"
Call identifier: FP7-HEALTH-2012-INNOVATION-1
Proposal No: 304985-2
Acronym: DevelopAKUre

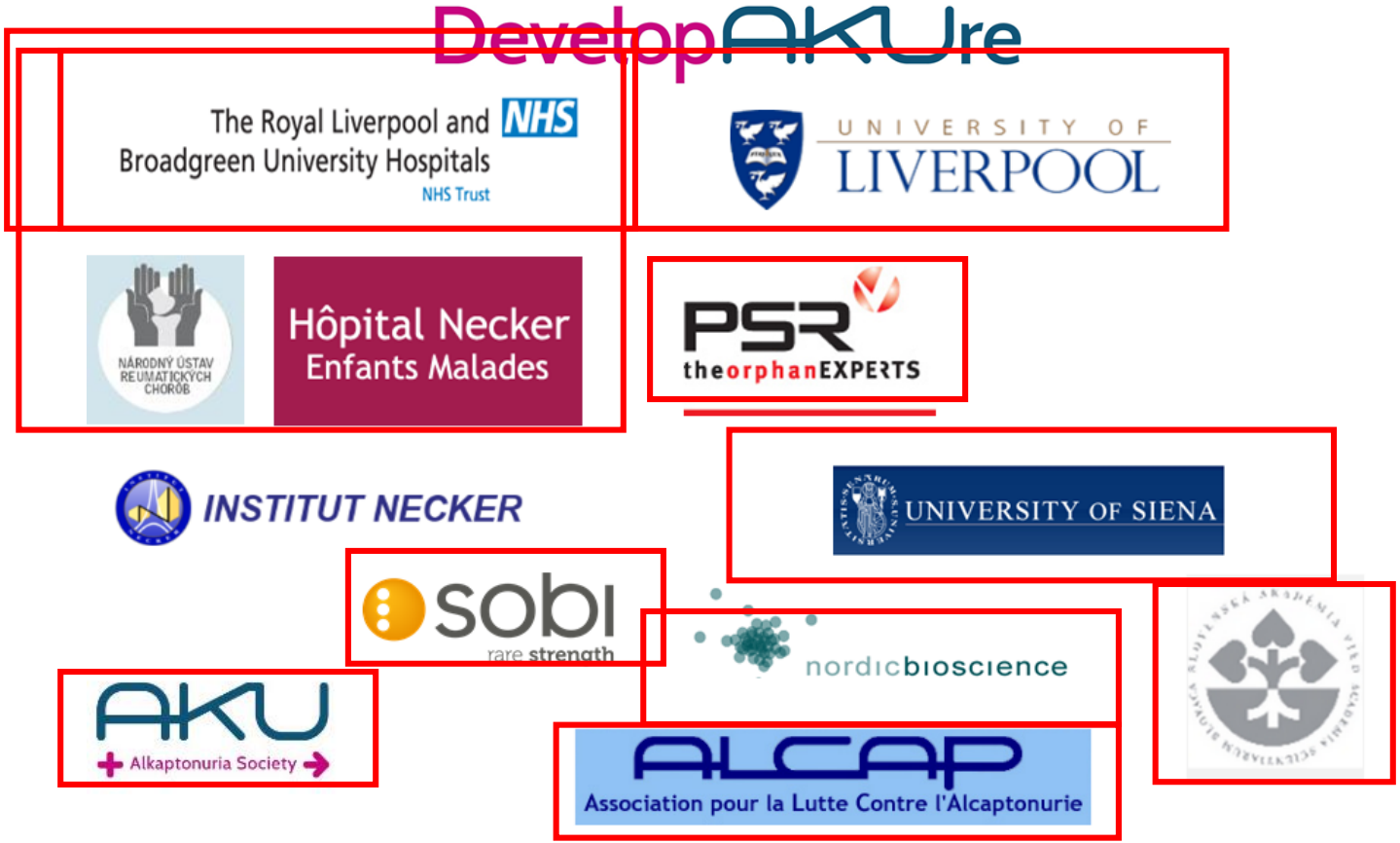
Dear Dr. Lakshminarayan Ranganath,

I am pleased to inform you that the proposal entitled: Clinical Development of Nitisinone for Alkaptonuria, has been favourably evaluated by the Commission services with the help of independent experts. Accordingly, the Commission services wish to proceed to negotiations for a Grant Agreement on your proposal.

In Annex A to this letter, you will find attached a copy of the Evaluation Summary Report (ESR) on your proposal. The ESR reflects the comments of the independent experts and their advice to the Commission on the proposal. It does not necessarily reflect the views of the Commission or its services. In the case where an ethical review raises substantive issues, you will receive within the next

The Research Consortium

Suitability of nitisinone in alkaptonuria (SONIA) 1 & 2
Subclinical ochronosis features in alkaptonuria (SOFIA)



AKU history

NIH 3-y Trial Reports inconclusive

Clinical and epidemiological research

EXTENDED REPORT

Suitability Of Nitisinone In Alkaptonuria 1 (SONIA 1): an international, multicentre, randomised, open-label, no-treatment controlled, parallel-group, dose-response study to investigate the effect of once daily nitisinone on 24-h urinary homogentisic acid excretion in patients with alkaptonuria after 4 weeks of treatment

Lakshminarayan R Ranganath,[1,2] Anna M Milan,[1,2] Andrew T Hughes,[1,2] John J Dutton,[1] Richard Fitzgerald,[3] Michael C Briggs,[4] Helen Bygott,[1] Eftychia E Psarelli,[5] Trevor F Cox,[5] James A Gallagher,[2] Jonathan C Jarvis,[6] Christa van Kan,[7] Anthony K Hall,[8] Dinny Laan,[7] Birgitta Olsson,[9] Johan Szamosi,[9] Mattias Rudebeck,[9] Torbjörn Kullenberg,[9] Arvid Cronlund,[9] Lennart Svensson,[9] Carin Junestrand,[9] Hana Ayoob,[10] Oliver G Timmis,[10] Nicolas Sireau,[10] Kim-Hanh Le Quan Sang,[11] Federica Genovese,[12] Daniela Braconi,[13] Annalisa Santucci,[13] Martina Nemethova,[14] Andrea Zatkova,[14] Judith McCaffrey,[15] Peter Christensen,[16] Gordon Ross,[16] Richard Imrich,[17] Jozef Rovensky[18]

Ranganath LR, Milan AM, Hughes AT, et al. Ann Rheum Dis 2016;75:362–367

8 mg dose of nitisinone was very effective with no safety issues

AKU history

NIH 3-y Trial Reports inconclusive

4-y clinical trial called SONIA 2 which began in 2014

10 mg dose nitisinone used

138 patients – 69 on nitisinone and 69 untreated

Largest clinical trial in the inherited metabolic disorder field ever

AKU history

NIH 3-y Trial Reports inconclusive

SOFIA (Subclinical Ochronosis Features in Alkaptonuria) study

Ochronosis could be present earlier than age 20 years

Early treatment of AKU is therefore needed since ochronosis is not fully reversible

AKU history

NIH 3-y Trial Reports inconclusive

SONIA 2 trial was completed

HGA was lowered

Ochronosis was not just arrested but partially reversed

Most importantly that there was significant slowing of disease

Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): an international, multicentre, open-label, randomised controlled trial

Lakshminarayan R Ranganath, Eftychia Eirini Psarelli, Jean-Baptiste Arnoux, Daniela Braconi, Michael Briggs, Anders Bröijersén, Nadia Loftus, Helen Bygott, Trevor F Cox, Andrew S Davison, Jane P Dillon, Michael Fisher, Richard FitzGerald, Federica Genovese, Helena Glasova, Anthony K Hall, Andrew T Hughes, Juliette H Hughes, Richard Imrich, Jonathan C Jarvis, Milad Khedr, Dinny Laan, Kim-Hanh Le Quan Sang, Emily Luangrath, Olga Lukáčová, Anna M Milan, Alpesh Mistry, Vanda Mlynáriková, Brendan P Norman, Birgitta Olsson, Nicholas P Rhodes, Jozef Rovenský, Mattias Rudebeck, Annalisa Santucci, Ella Shweihdi, Ciarán Scott, Jana Sedláková, Nicolas Sireau, Roman Stančík, Johan Szamosi, Sophie Taylor, Christa van Kan, Sobhan Vinjamuri, Eva Vrtíková, Chris Webb, Elizabeth West, Elizabeth Záňová, Andrea Zatkova, James A Gallagher

Lancet Diabetes Endocrinol 2020; 8: 762–72

See Comment page 732

Department of Clinical Biochemistry and Metabolic Medicine (Prof L R Ranganath MD, H Bygott BN, A S Davison MSc,

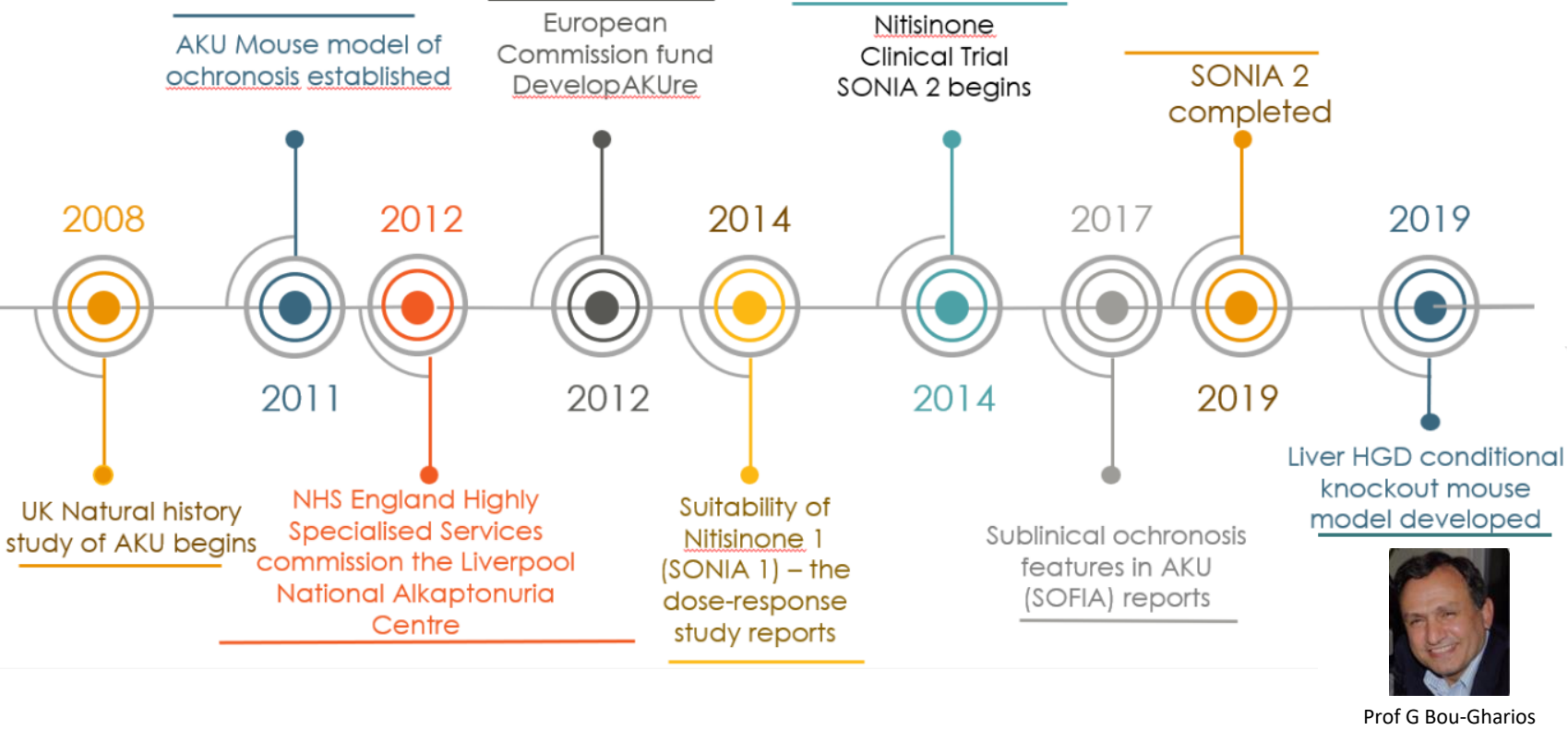
Summary

Background Alkaptonuria is a rare, genetic, multisystem disease characterised by the accumulation of homogentisic acid (HGA). No HGA-lowering therapy has been approved to date. The aim of SONIA 2 was to investigate the efficacy and safety of once-daily nitisinone for reducing HGA excretion in patients with alkaptonuria and to evaluate whether nitisinone has a clinical benefit.

Methods SONIA 2 was a 4-year, open-label, evaluator-blind, randomised, no treatment controlled, parallel-group study done at three sites in the UK, France, and Slovakia. Patients aged 25 years or older with confirmed alkaptonuria

Ranganath et al. Lancet Diab Endocrinol. 2020;8:762-772

AKU history



Nitisinone causes high tyrosine

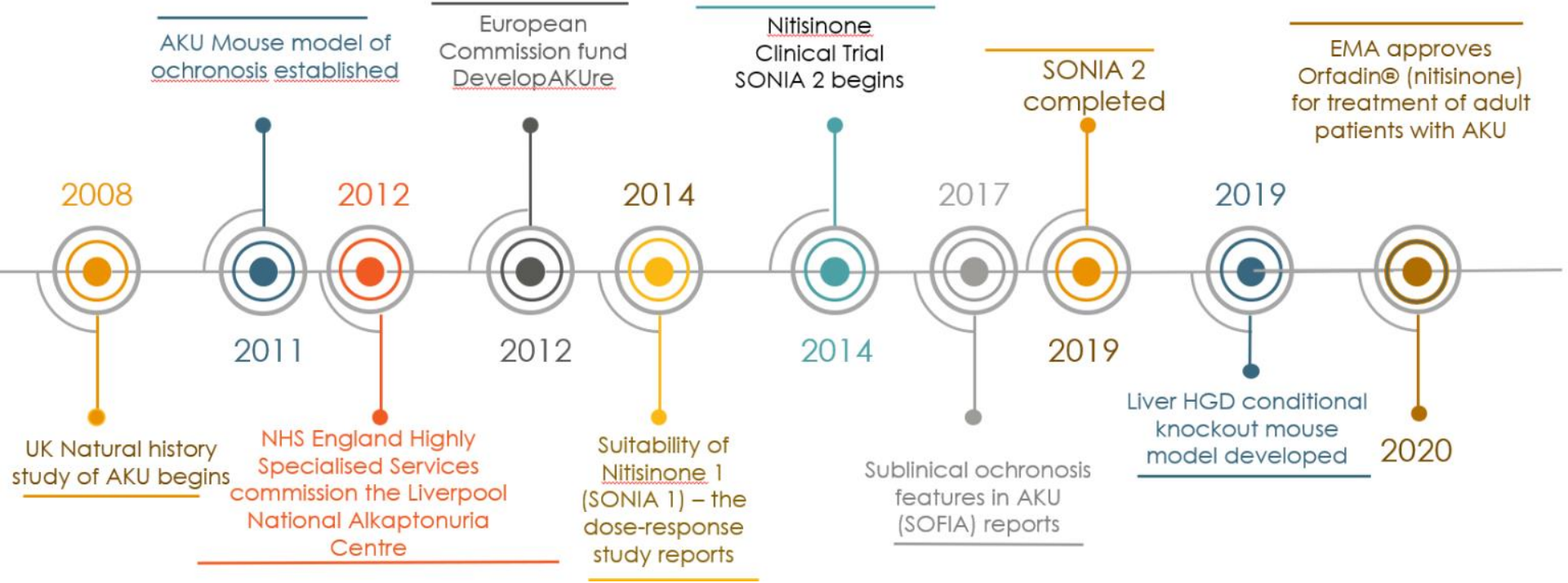
?HGD replacement therapy

Do liver and kidney HGD need to be corrected

Liver knockout of HGD produces AKU

Prof G Bou-Gharios

AKU history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2020
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First treatment for rare metabolic disorder alkaptonuria

Share

News 18/09/2020

EMA has recommended granting an extension of indication to Orfadin (nitisinone) to include the treatment of alkaptonuria in adult patients.

Nitisinone development for Children key

This rare disorder affects one in every 250,000 to 1 million people and is more common in certain areas of Slovakia. It is characterised by the inability of the body to metabolize homogentisic acid (HGA) due to the lack of an enzyme. People with alkaptonuria typically develop arthritis, particularly in the spine and large joints. 50 percent of patients require at least one joint replacement by the time they are 55. Affected individuals can also suffer from heart problems and kidney stones. There are currently no approved medicines for alkaptonuria and treatment options are limited to dealing with the outcomes of the disease as they arise. Therefore, there is an unmet medical need for patients with this rare disorder.

2023

The future of AKU research in Liverpool

Tyrosinaemia – unwanted consequences	
Corneal keratopathy (TYR)	Stewart RM, et al. *JIMD Rep*. 2014;17:1-6
Vitiligo (TYR)	Ranganath LR, et al. *JIMD Rep*. 2021;1-9
Cataract (HGA+TYR)	Ahmad MSZ, et al. *JIMD Rep*. 2022;63:351-360
Parkinsonism (HGA+TYR)	Ranganath et al. JIMD Rep. 2023;64:282-292
Low-protein diet	Inconvenience and social consequences
Low protein diet	Muscle mass and malnutrition

Co-therapies & New therapy development	
Tyrosine absorption inhibitors	Sanofi, JNANA
HGD mRNA therapy	Explorna, Philanthropy
HGD Gene therapy	Vrije Universiteit Brussels, UCL

AKU history

1500 BC

Harwa – "the oldest AKU patient"[4]

1584

Scribonius publishes a case of a healthy schoolboy who excreted urine as black as ink

1859

Bödeker first named the new substance "alkapton"

1866

Virchow names ochronosis at necropsy

1891

Wolkow & Baumann: identified homogentisic acid (HGA)

1899

Hecker and Wolf publish eye ochronosis findings

1902

Garrod's publication on AKU is considered the start of human genetics and he introduce the term 'inborn error of metabolism'[8]

1902

Albrecht confirms alkaptonuria and ochronosis – same disease

1904

Osler – ears and skin ochronosis[12]

AKU history

1928

Neubauer describes the tyrosine metabolism pathway

1958

La du et al. Identifies homogentisate 1,2-dioxygenase (HGD) defect in AKU

1990s

Lock,/Holme/Lindstedt develop nitisinone for hereditary tyrosinemia type 1 (HT-1)

1993

Pollak et al. identify the AKU gene; chromosome 3 (3q2)

1998

Japanese study of NTBC in mouse AKU

NIH investigators propose NTBC as possible treatment for AKU

2002

Orfadin® (nitisinone) approved for HT-1 (US; 2005 EMA)

2003

AKU Society formed in UK

2005

Helliwell carries out Post-mortem study in AKU

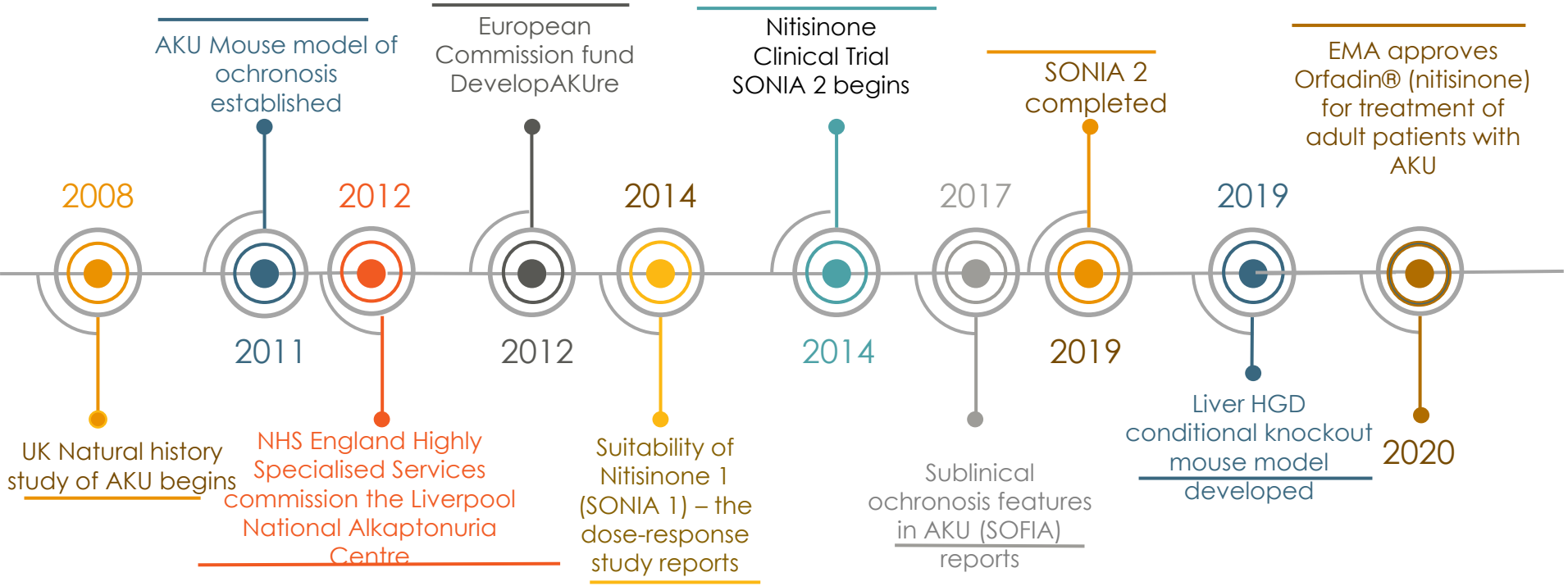
2005

UK AKU Population identification study begins

2008

AKU Cell model of ochronosis established

AKU history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AKU
Alkaptonuria Society

Thank you for attending the
AKU International Workshop 2024 !