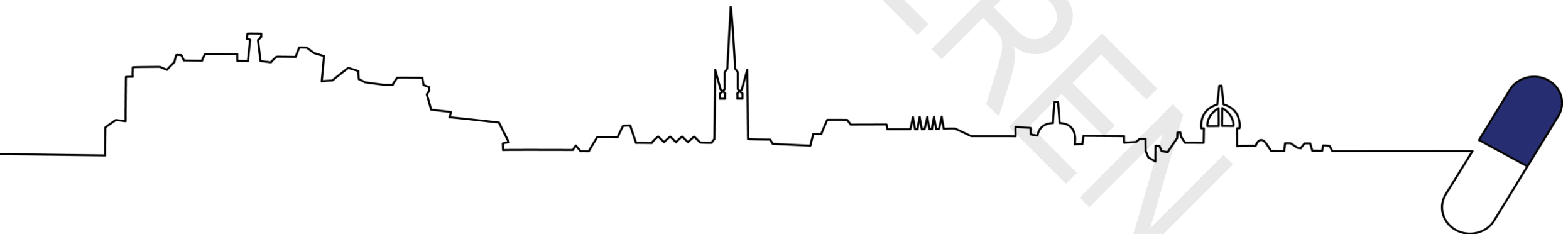


NIHR PREVENTING DEATHS FROM
RIGHT4 ACUTE POISONING IN LOW AND
MIDDLE INCOME COUNTRIES



Current and future management of paracetamol poisoning

Michael Eddleston & James Dear
University of Edinburgh



Edinburgh in the 1970s



Laurie Prescott & Alex Proudfoot
(2nd physician director
1975-99)



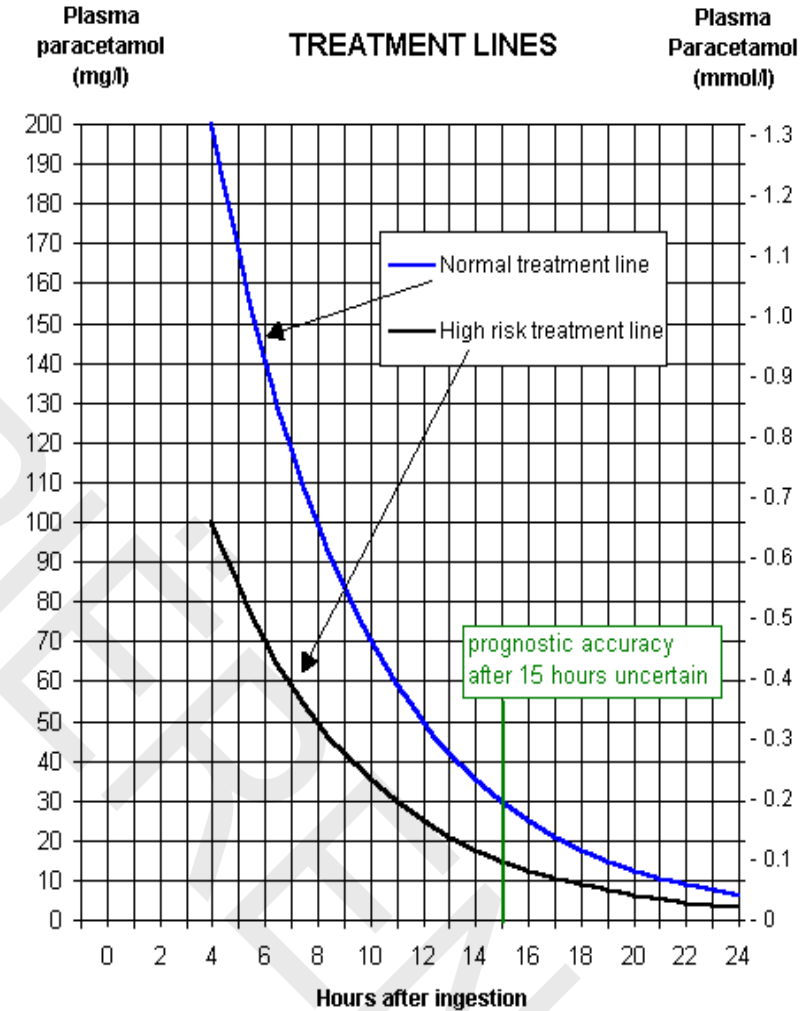
Henry Matthew
(1st physician director
1965-74)



Barry Rumack
1973

First cases & nomogram

- Davidson and Eastham.
Acute liver necrosis following
overdose of paracetamol
BMJ 1966, 2: 497-9
- Thomson and Prescott.
Liver damage and impaired glucose
tolerance after paracetamol
overdosage
BMJ 1966, 2: 506-7



THE LANCET, APRIL 6, 1974

**SUCCESSFUL TREATMENT OF SEVERE
PARACETAMOL OVERDOSAGE WITH
CYSTEAMINE**

L. F. PRESCOTT

R. W. NEWTON

C. P. SWAINSON

N. WRIGHT

A. R. W. FORREST

H. MATTHEW

*Regional Poisoning Treatment Centre, and University
Department of Therapeutics, Royal Infirmary,
Edinburgh EH3 9YW*

Initial dose of cysteamine 2g was given IV over 10 min followed by 3x 400mg doses in 500 mL of 5% dextrose infused over 4, 8, and 8 hrs.

Total dose of cysteamine 3.2 g over 20 h

**TREATMENT OF PARACETAMOL
(ACETAMINOPHEN) POISONING WITH
N-ACETYLCYSTEINE**

L. F. PRESCOTT

J. PARK

A. BALLANTYNE

P. ADRIAENSSENS

A. T. PROUDFOOT

*Regional Poisoning Treatment Centre, and University
Department of Therapeutics, Royal Infirmary, Edinburgh
EH3 9YW*

Summary Fifteen patients with paracetamol (acetaminophen) poisoning were treated with intravenous N-acetylcysteine (300 mg/kg given over 20 h). Mean admission and 4 h plasma-paracetamol concentrations were 262 and 369 $\mu\text{g/ml}$, respectively. Liver-function tests remained normal or were only slightly disturbed in 11 of 12 patients treated within 10 h of paracetamol ingestion. Severe liver damage developed in the other patient and in the three in whom treatment was started more than 10 h after paracetamol ingestion. In contrast to cysteamine, N-acetylcysteine was

PAPERS AND ORIGINALS

Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning

L F PRESCOTT, R N ILLINGWORTH, J A J H CRITCHLEY, M J STEWART, R D ADAM, A T PROUDFOOT

British Medical Journal, 1979, **2**, 1097-1100**Summary and conclusions**

One hundred cases of severe paracetamol poisoning were treated with intravenous N-acetylcysteine (acetylcysteine). There was virtually complete protection against liver damage in 40 patients treated within eight hours after ingestion (mean maximum serum alanine transaminase activity 27 IU/l). Only one out of 62 patients treated within 10 hours developed severe liver damage compared with 33 out of 57 patients (58%) studied retrospectively who received supportive treatment alone. Early treatment with acetylcysteine also prevented renal impairment and death. The critical ingestion-treatment interval for complete protection against severe liver damage was eight hours. Efficacy diminished progressively thereafter, and treatment after 15 hours was completely ineffective.

Intravenous acetylcysteine was more effective than cysteamine and methionine and noticeably free of adverse effects. It is the treatment of choice for paracetamol poisoning.

Regional Poisoning Treatment Centre and University Departments of Therapeutics and Clinical Pharmacology and Clinical Chemistry, Royal Infirmary, Edinburgh EH3 9TW

L F PRESCOTT, MD, FRCPD, consultant physician and reader in clinical pharmacology

R N ILLINGWORTH, RM, MRCP, medical registrar (now senior registrar, Accident and Emergency Department, General Infirmary, Leeds)

J A J H CRITCHLEY, MB, FRD, senior house officer

M J STEWART, PhD, MRCPATH, senior lecturer in clinical chemistry (now top-grade biochemist, Department of Pathological Biochemistry, Royal Infirmary, Glasgow)

R D ADAM, MRCP, senior house officer (now registrar, Monklands District Hospital, Airdrie)

A T PROUDFOOT, BSC, FRCPD, consultant physician

Introduction

Now that the biochemical mechanisms of paracetamol hepatotoxicity are understood¹ sulphhydryl compounds such as cysteamine, L-methionine, and N-acetylcysteine (acetylcysteine) may be used successfully to treat severe paracetamol poisoning.²⁻¹² Nevertheless, the relative efficacy of these agents in protecting against liver damage, renal impairment, and death is uncertain and doubts have been raised about the safety of cysteamine and methionine.³⁻⁵ Furthermore, cysteamine and methionine are not available commercially for intravenous administration. Our initial findings with intravenous acetylcysteine were encouraging,⁶⁻⁸ and we describe here the results of treating 100 cases.

Patients and methods

Patients—Eighty-seven patients admitted on 100 occasions with severe paracetamol poisoning between December 1976 and May 1979 were treated with intravenous acetylcysteine. Their mean age was 33 years (range 13-82), and 33 were male. Those admitted on more than one occasion were considered as separate patients for each admission. Forty-eight patients claimed to have taken only paracetamol, 31 took it in combination with dextropropoxyphene as Distalgesc, and the remainder also took one or more other drugs, usually benzodiazepines or aspirin. All patients were admitted within 24 hours after ingestion and had plasma paracetamol concentrations above a treatment line joining plots of 200 mg/l at four hours and 30 mg/l at 15 hours on a semilogarithmic graph. More severely poisoned patients with plasma paracetamol concentrations above a similar line joining 300 mg/l at four hours and 45 mg/l at 15 hours were defined as "high-risk" cases. Patients with values between these two lines were designated as an "intermediate-risk" group. When necessary the lines were extrapolated to 24 hours.

General management—Gastric aspiration and lavage were performed on patients admitted within four hours of ingestion and those in coma. Patients with persistent nausea and vomiting were given intravenous fluid replacement and antiemetics. Impending or established hepatic failure was treated conventionally. Twenty-one patients who took Distalgesc required naloxone—20 were in deep coma, and respiratory arrest had occurred in 10.

Treatment with acetylcysteine—Intravenous acetylcysteine was given in an initial dose of 150 mg/kg in 200 ml 5% dextrose over 15 minutes

**Acetylcysteine
"Prescott Regimen"****150mg/kg over 15 min****50mg/kg over 4 hr:****100mg/kg over 16 hr:****BMJ 1979**



Nick Bateman
Edinburgh



James Dear
Edinburgh

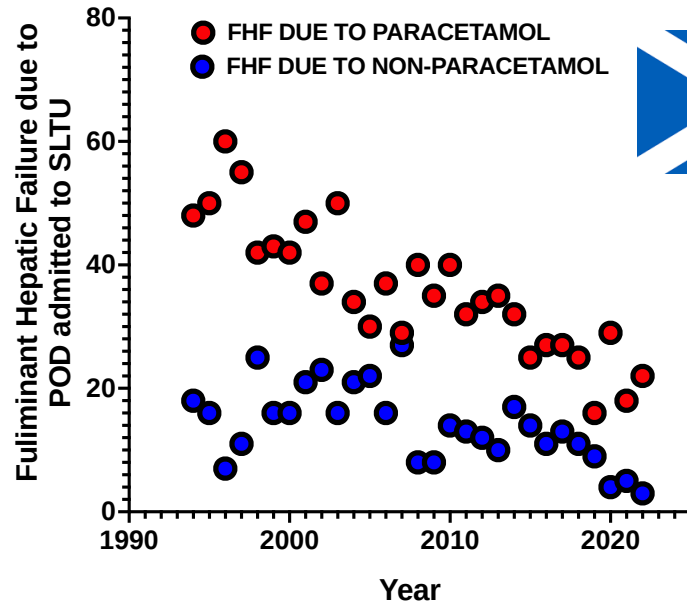


Simon Thomas
Newcastle

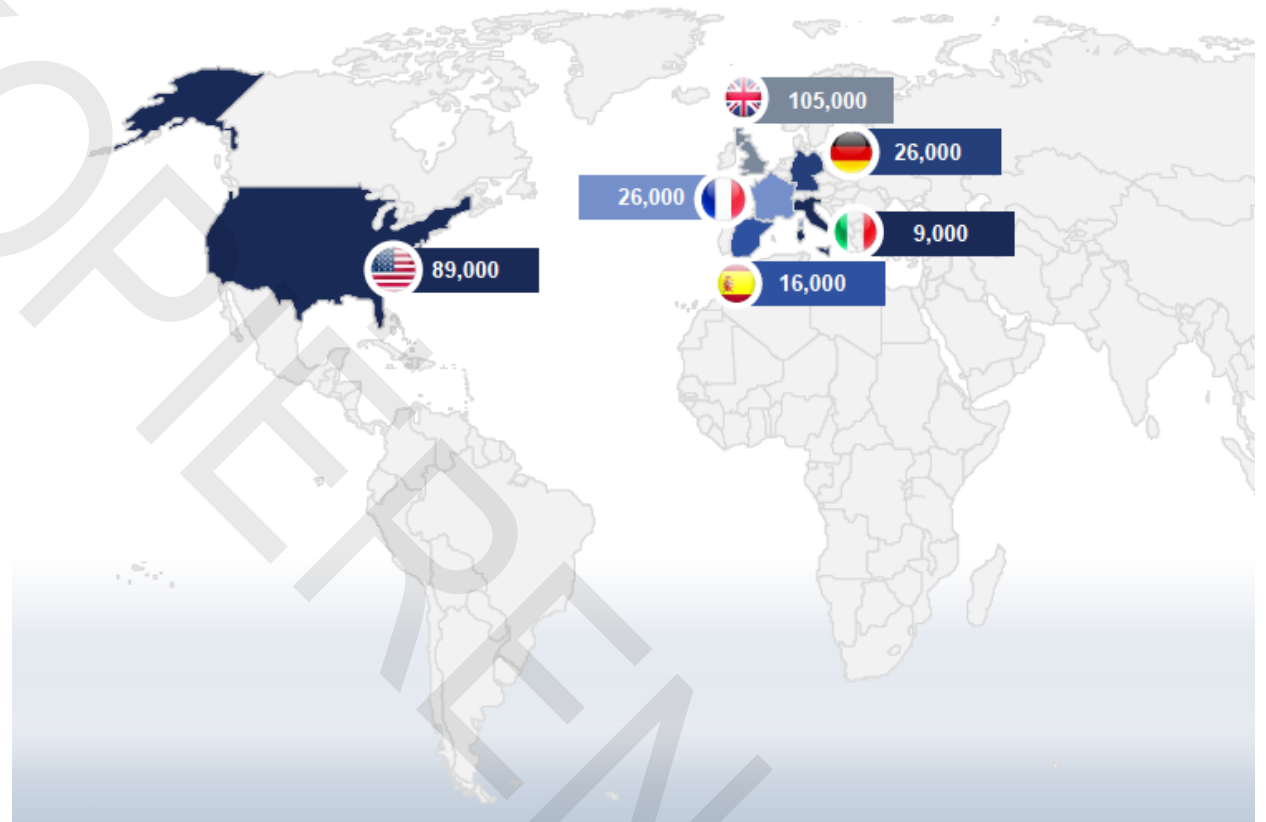
Background:

Clinical situation: Paracetamol overdose epidemiology in UK

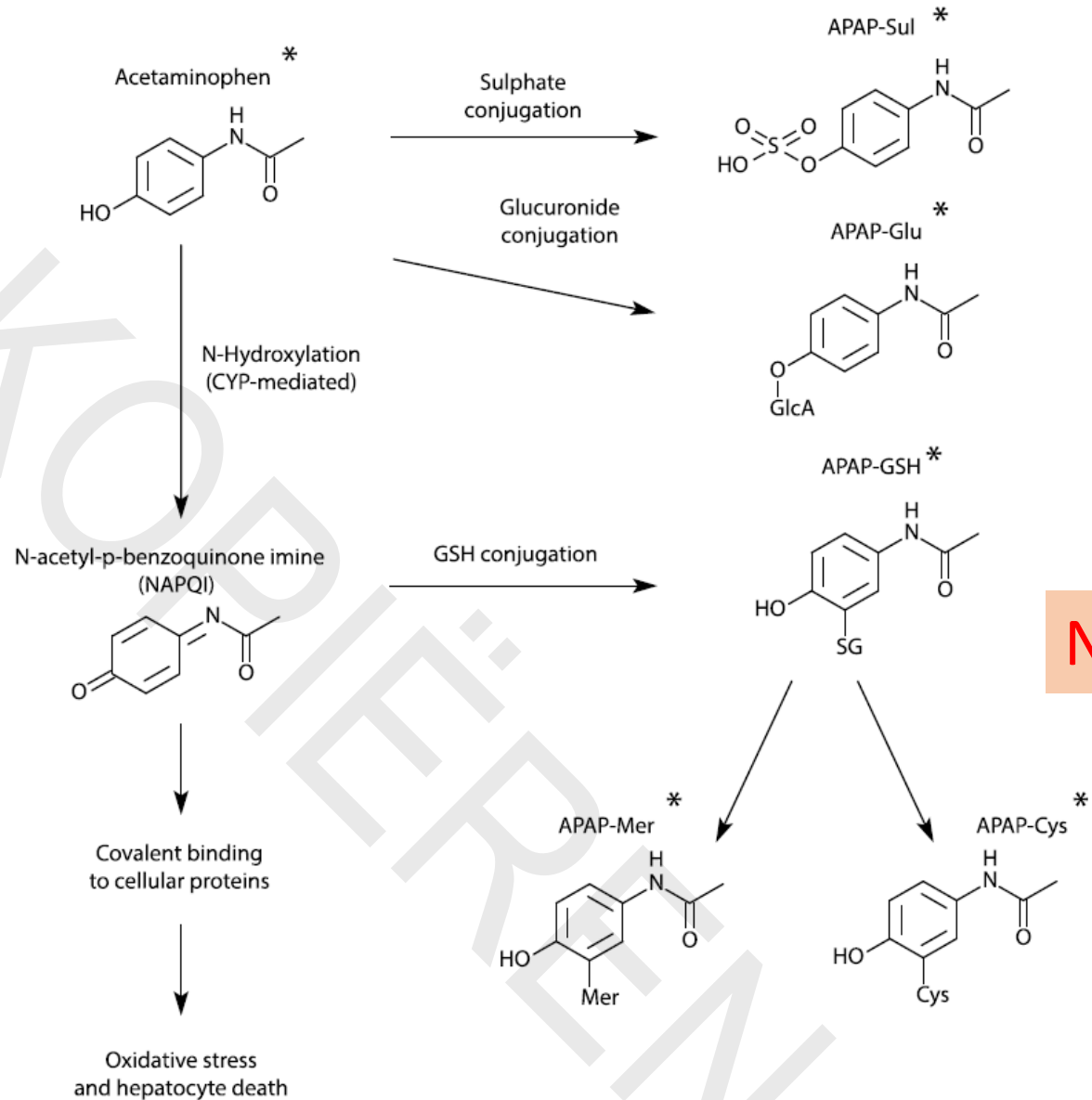
Someone presents to hospital following a paracetamol overdose every 5 minutes in UK
– **same as myocardial infarction**



POD incidence in EU5 and US – Hospital visits 2018



Precision medicine approach to acute liver failure



Precision medicine approach to acute liver failure

Clinical
Features

High APAP ++
Normal ALT
Within 8h

Disease
Phenotype

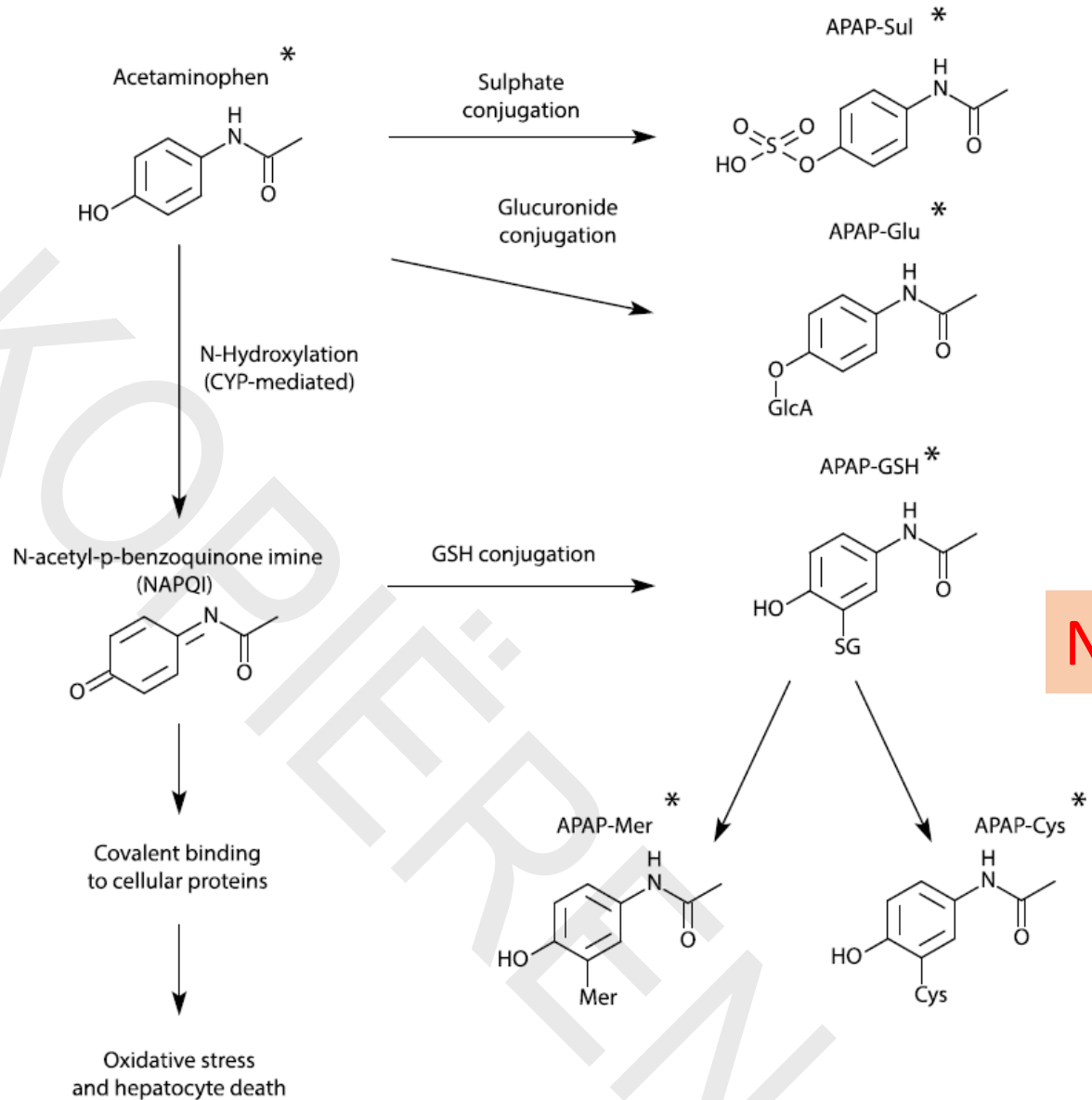
EARLY
PRESENTER

Mechanism

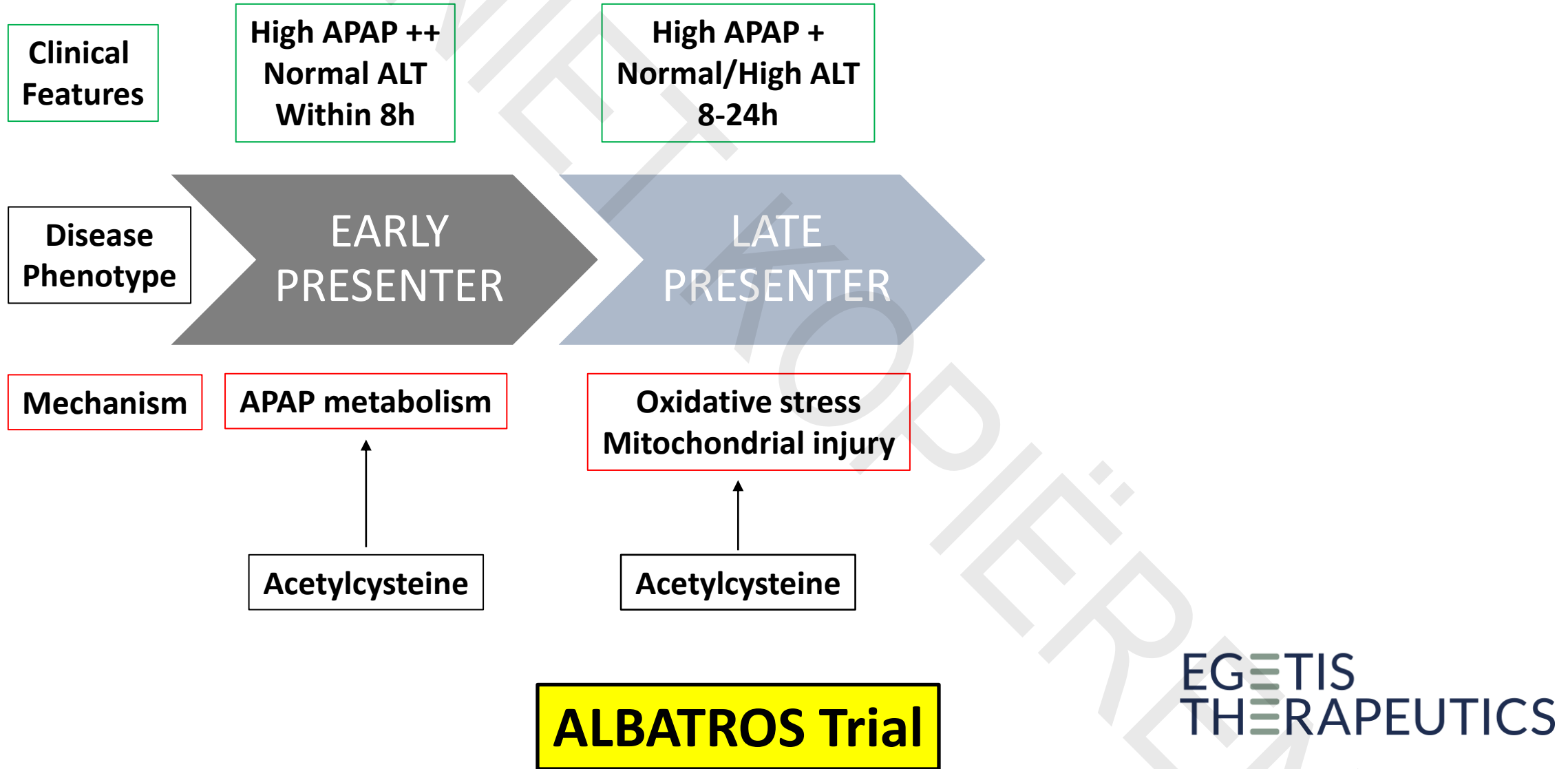
APAP metabolism

Acetylcysteine

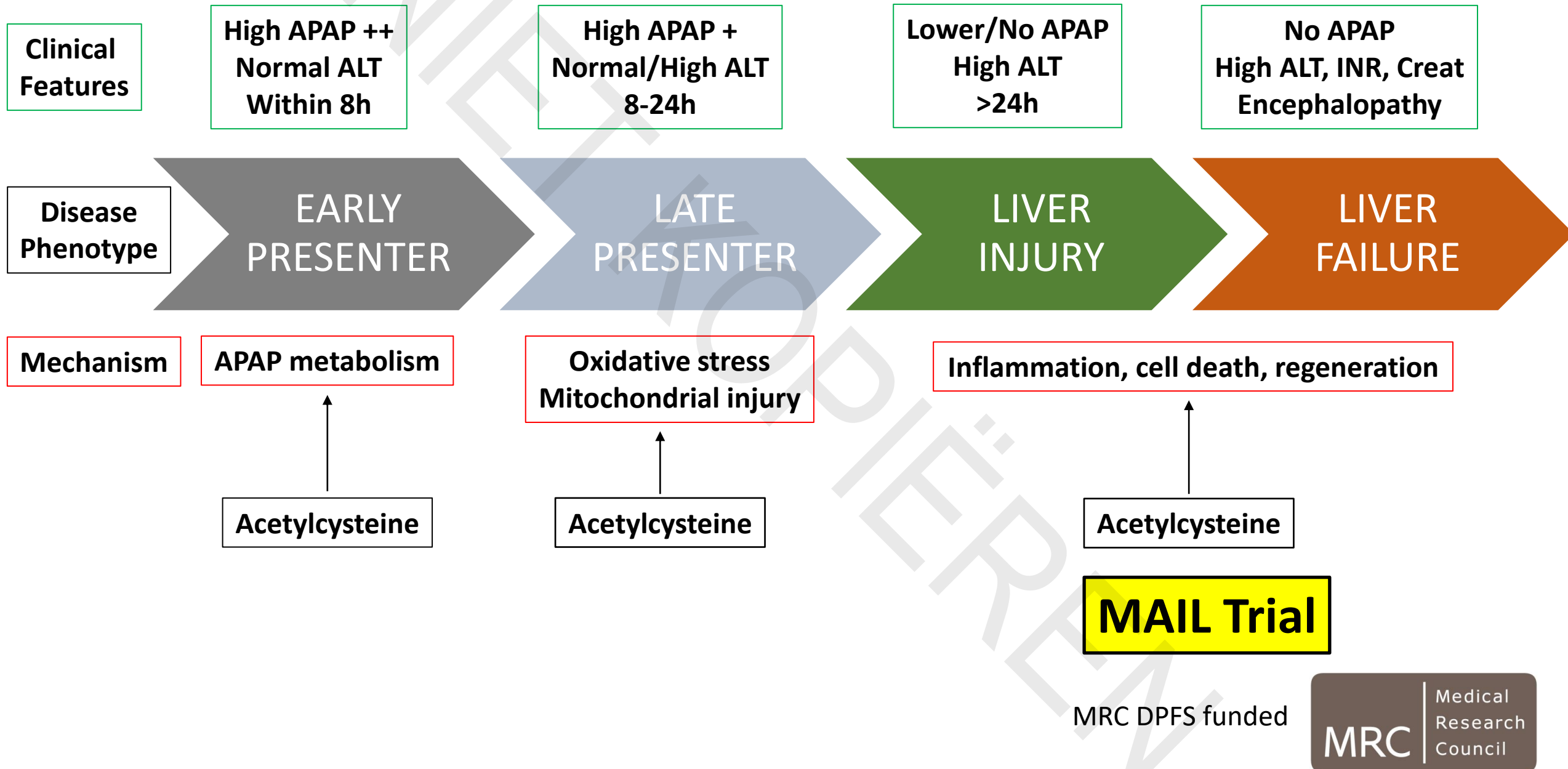
HiSNAP Trial



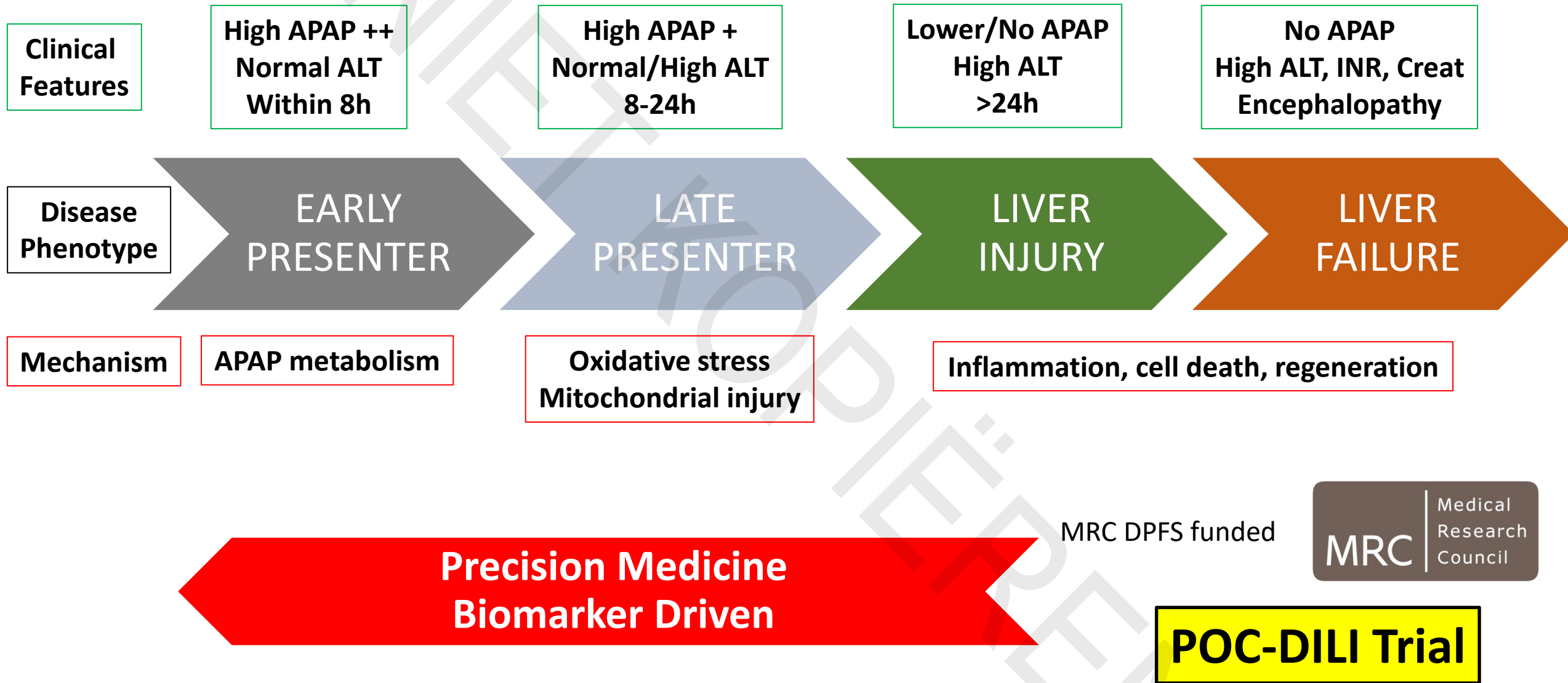
Precision medicine approach to acute liver failure



Precision medicine approach to acute liver failure



Precision medicine approach to acute liver failure



SNAP regimen

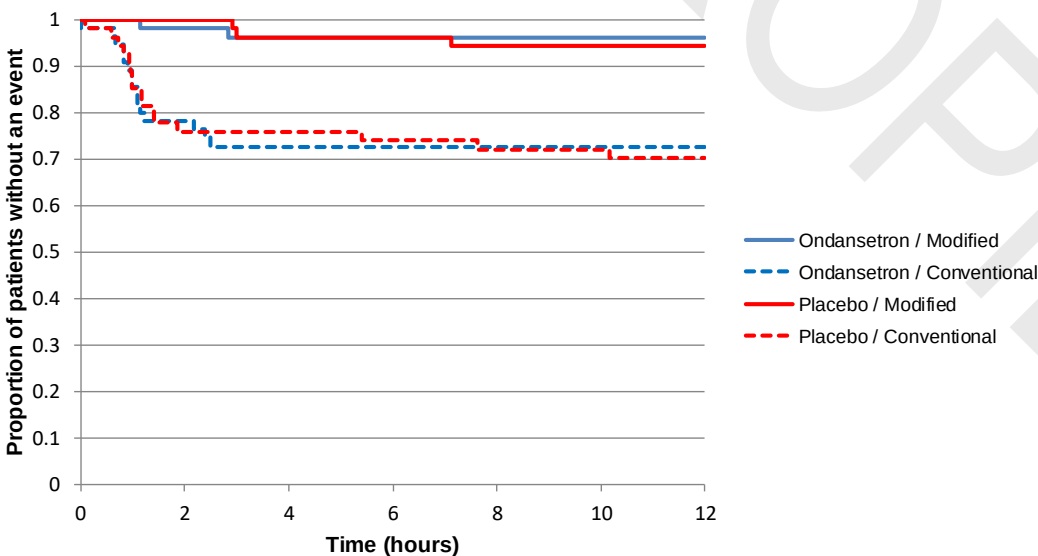
EARLY PRESENTER

Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial

Lancet 2014

D Nicholas Bateman, James W Dear, H K Ruben Thanacoody, Simon H L Thomas, Michael Eddleston, Euan A Sandilands, Judy Coyle, Jamie G Cooper, Aryelly Rodriguez, Isabella Butcher, Steff C Lewis, A D Bastiaan Vliegenthart, Aravindan Veiraiah, David J Webb, Alasdair Gray

100 mg/kg NAC over 2 hrs
Then
200 mg/kg NAC over 10 hrs
Then blood tests



Patients at risk

Ondansetron/Modified	54	53	50	50	50	50	50
Ondansetron/Conventional	55	43	40	40	40	40	40
Placebo/Modified	55	55	51	51	50	50	50
Placebo/Conventional	54	41	41	39	38	38	37

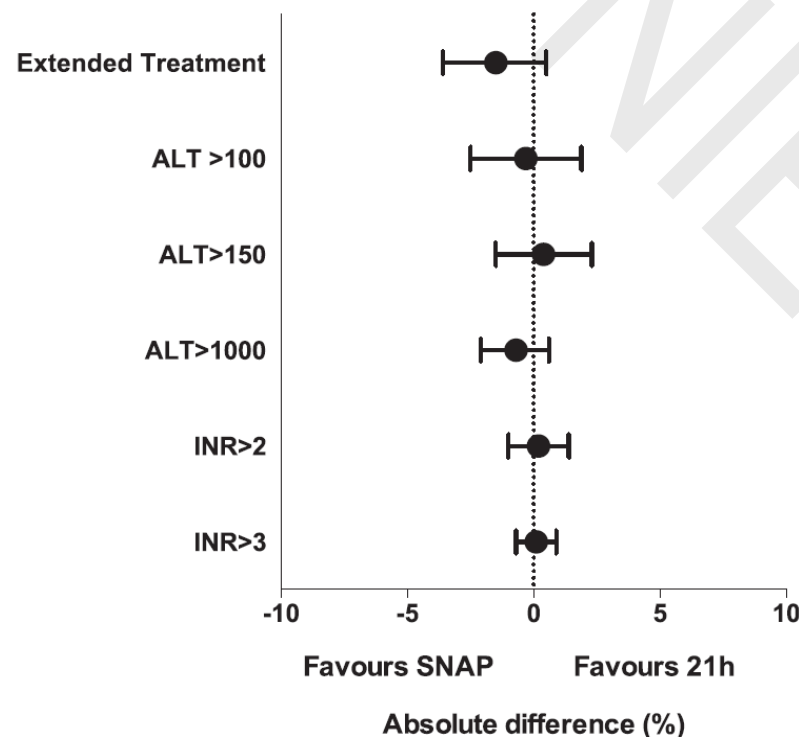




Research Paper

Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Overdose

Janice M. Pettie^a, Thomas M. Caparrotta^b, Robert W. Hunter^b, Emma E. Morrison^b, David M. Wood^{c,d}, Paul I. Dargan^{c,d}, Ruben H. Thanacoody^e, Simon H.L. Thomas^e, Muhammad E.M.O. Elamin^e, Ben Francis^f, David J. Webb^b, Euan A. Sandilands^a, Michael Eddleston^b, James W. Dear^{b,*}

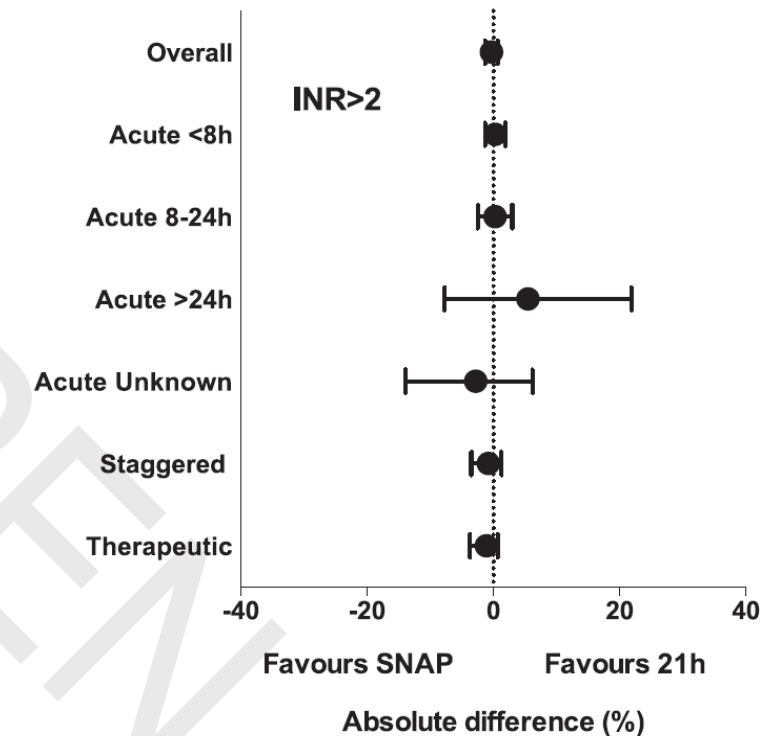
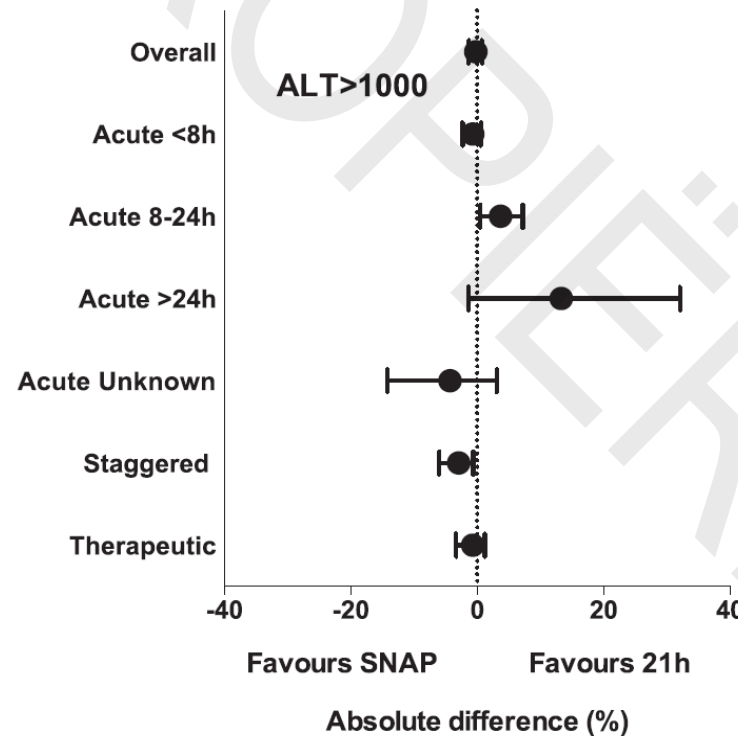
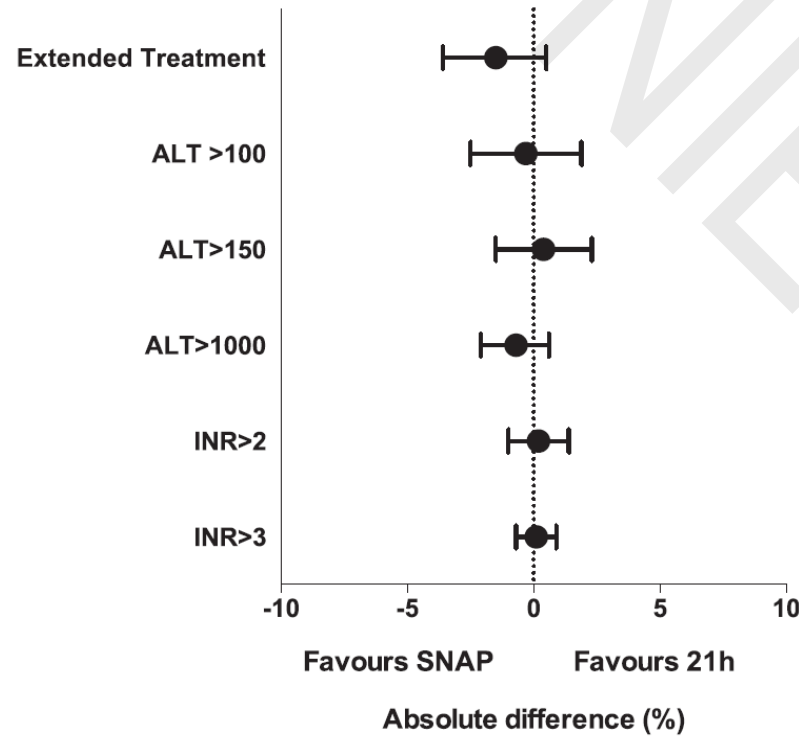




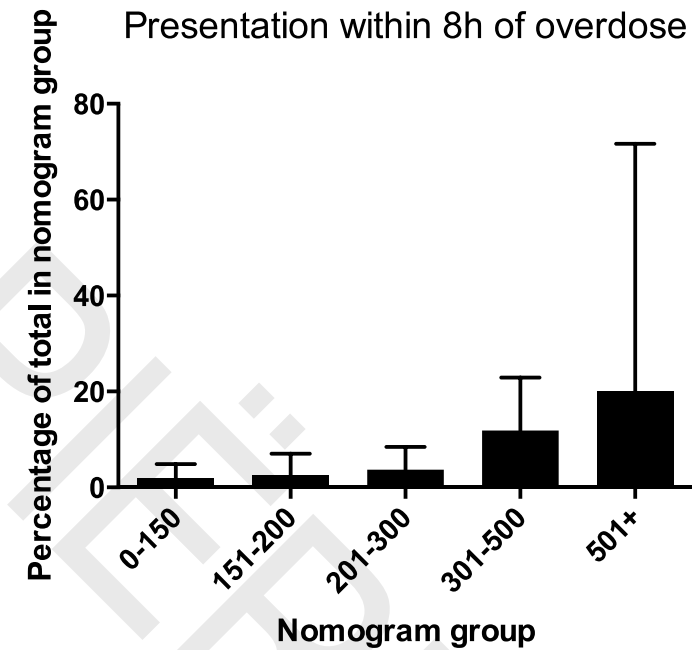
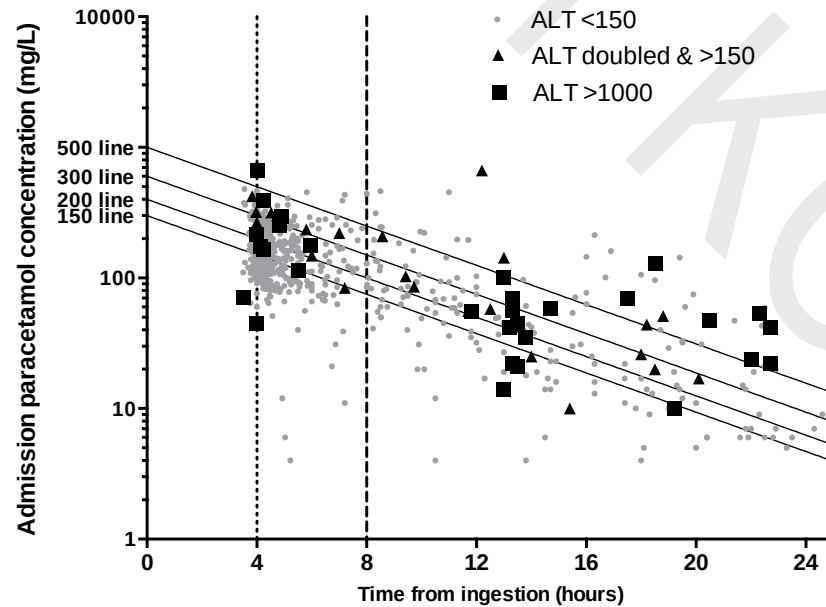
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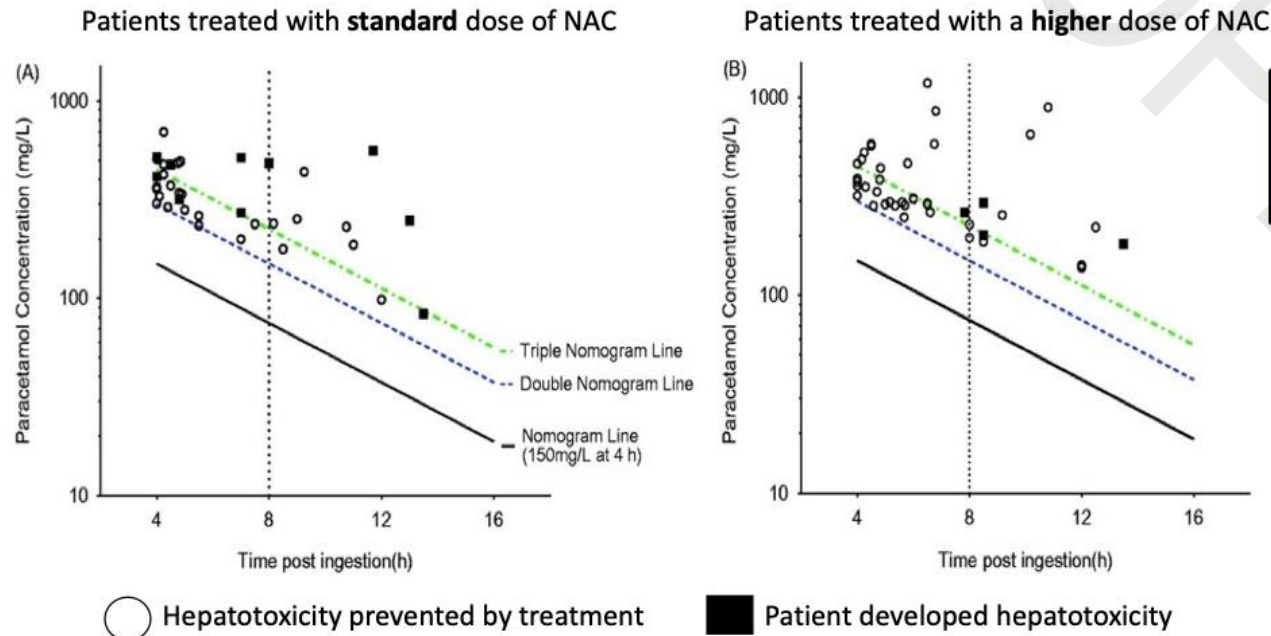
Paracetamol concentration vs liver injury despite NAC



Risk of liver injury increases with higher paracetamol load

Should we give a higher dose of NAC?

- No robust evidence
- SNAP will give more NAC in first 21h (500 mg/kg vs 300 mg/kg)
- Theoretical modelling supports higher NAC in larger OD
- Observational data suggest benefit
- Need RCT to assess efficacy and safety



Increased NAC had a decreased risk of hepatotoxicity [OR:0.27 (95% CI: 0.08-0.94)]

Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2)

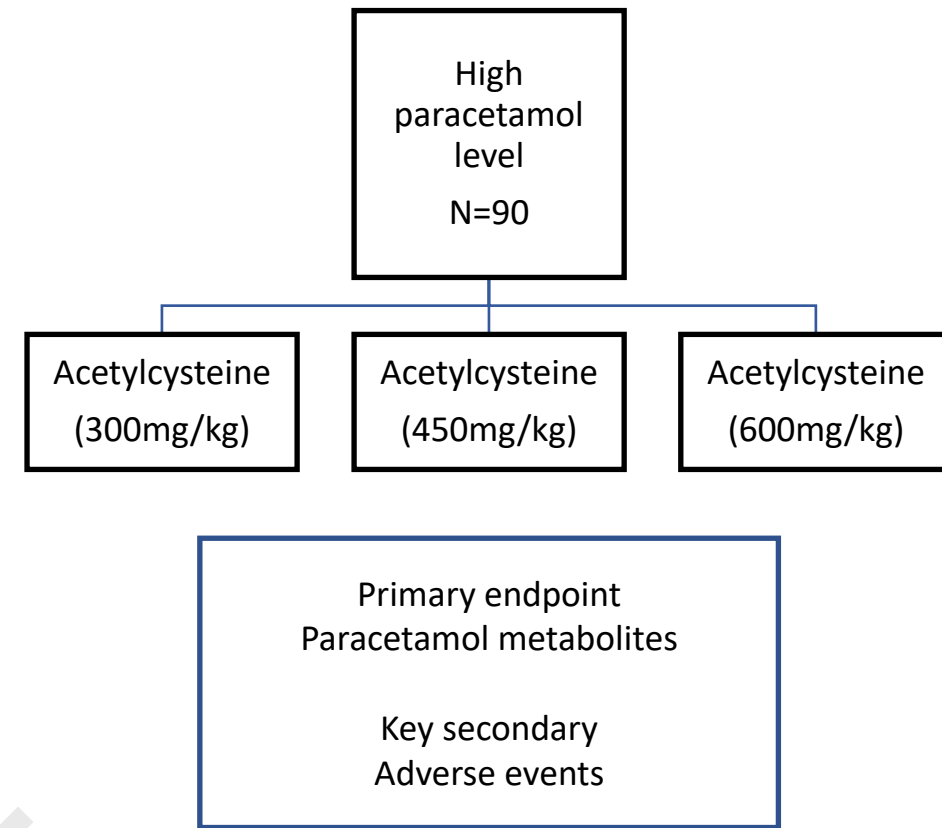
Angela L. Chiew, Geoffrey K. Isbister, Katharine A. Kirby, Colin B. Page, Betty S. H. Chan & Nicholas A. Buckley

Pages 1055-1065 | Received 14 Mar 2017, Accepted 19 May 2017, Published online: 23 Jun 2017

Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial

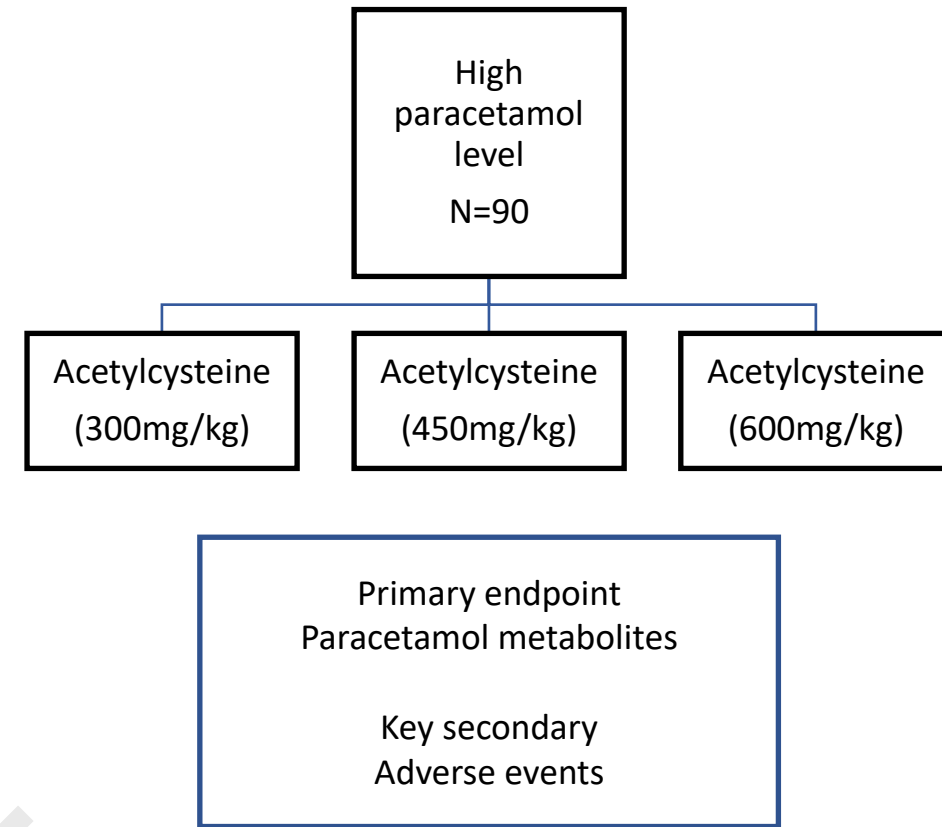
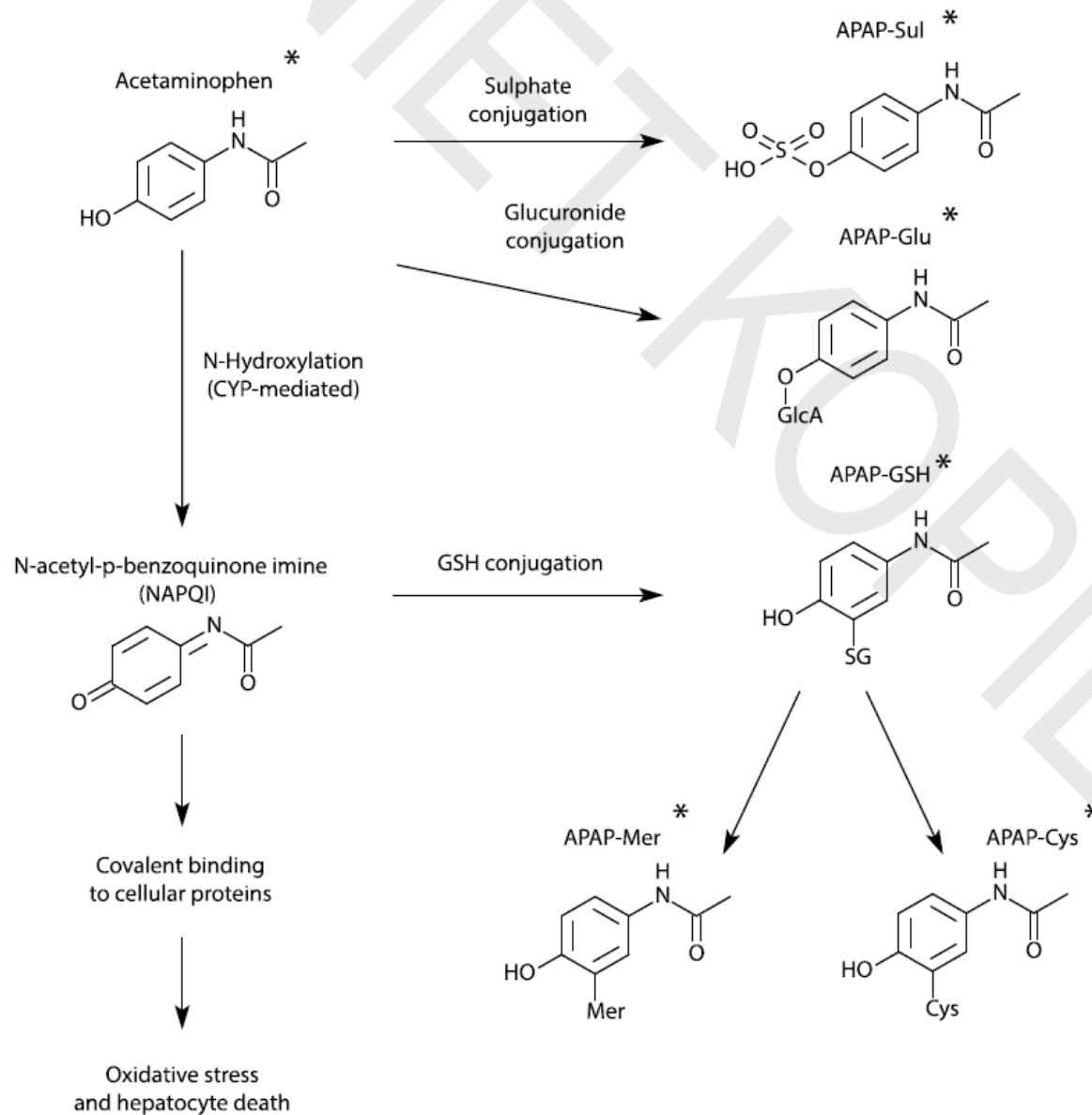
Lancet 2014

D Nicholas Bateman, James W Dear, H K Ruben Thanacoody, Simon H L Thomas, Michael Eddleston, Euan A Sandilands, Judy Coyle, Jamie G Cooper, Aryelly Rodriguez, Isabella Butcher, Steff C Lewis, A D Bastiaan Vliegthart, Aravindan Veiraiiah, David J Webb, Alasdair Gray



HiSNAP Trial

EARLY PRESENTER

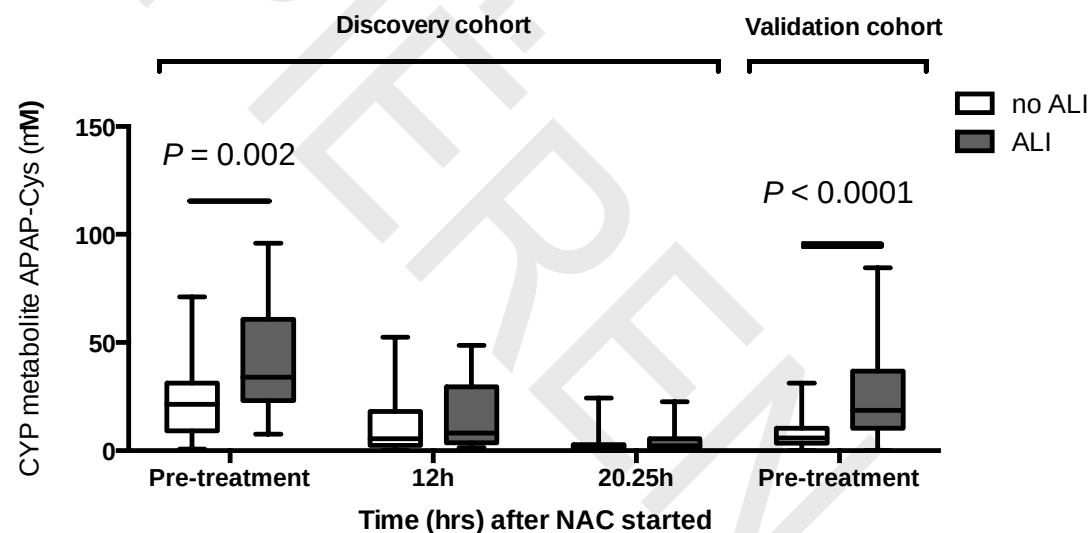
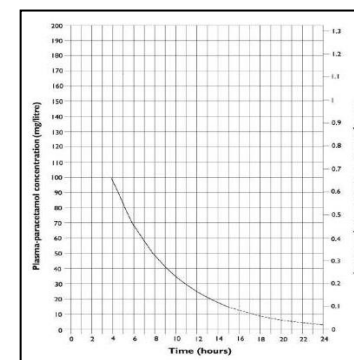
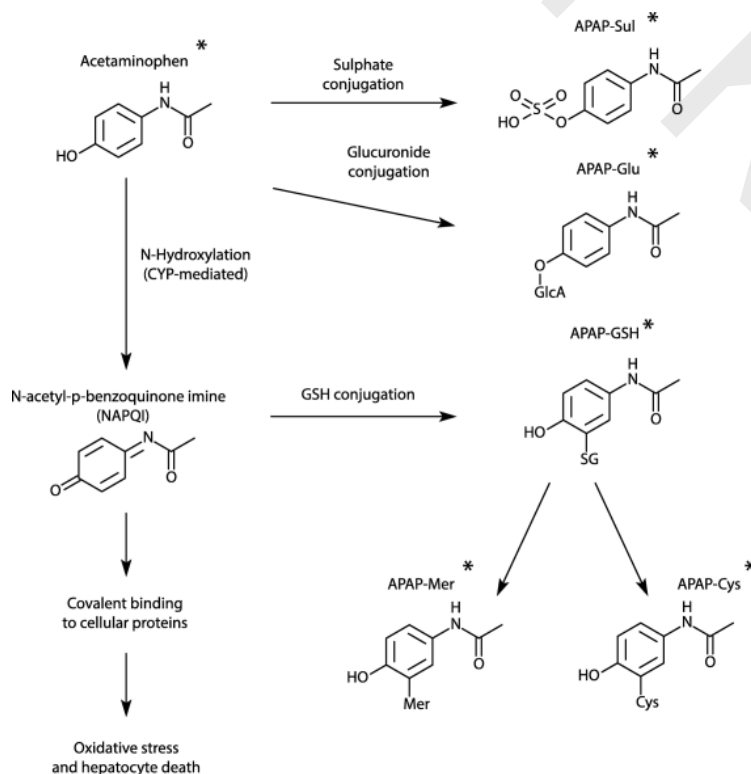




Bastiaan Vliegthart

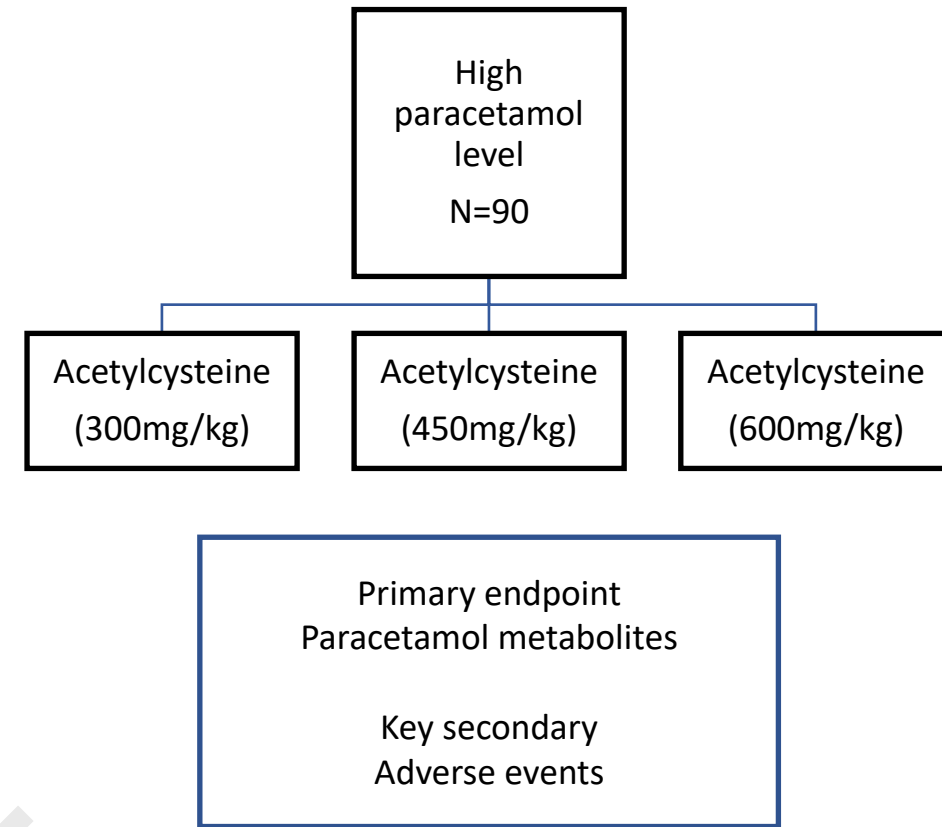
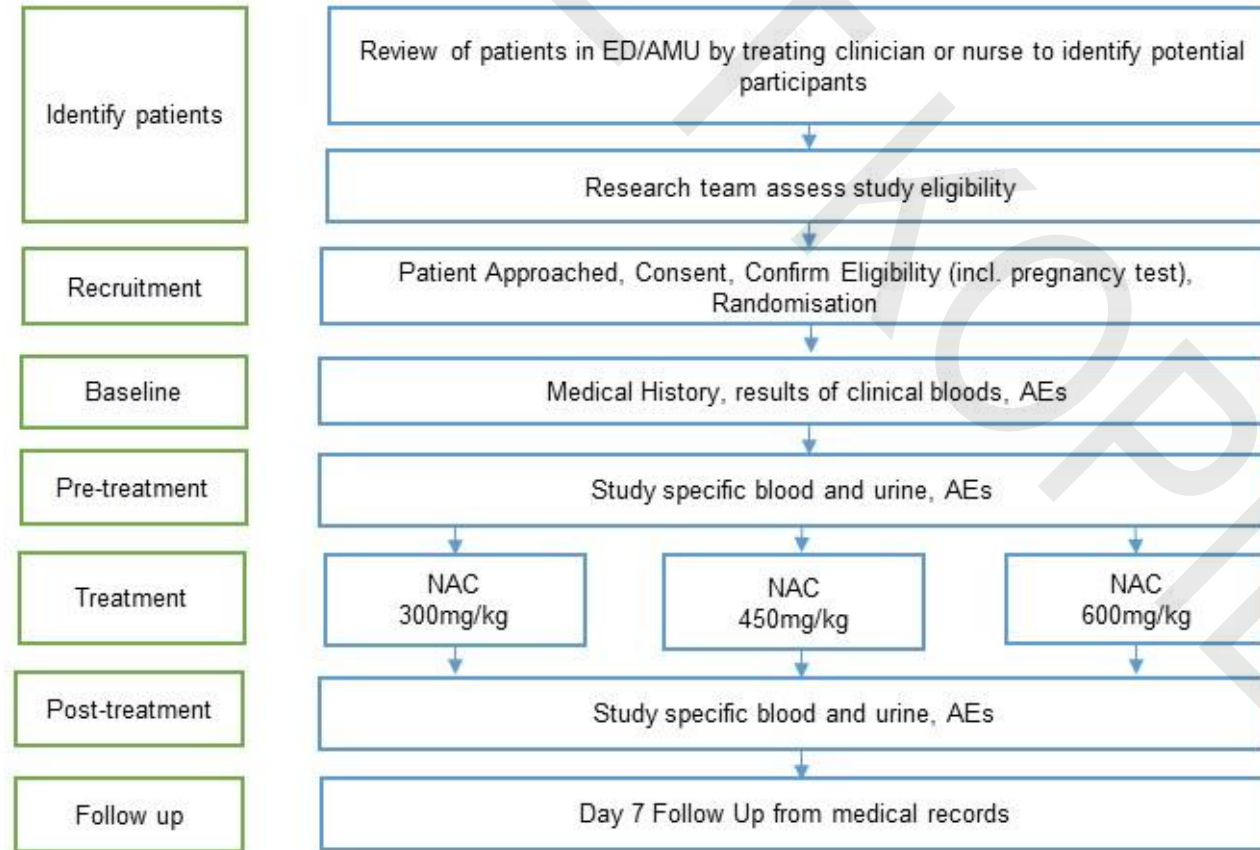
Circulating Acetaminophen Metabolites Are Toxicokinetic Biomarkers of Acute Liver Injury

ADB Vliegthart¹, RA Kimmitt¹, JH Seymour¹, NZ Homer¹, JI Clarke², M Eddleston¹, A Gray³, DM Wood^{4,5}, PI Dargan^{4,5}, JG Cooper⁶, DJ Antoine², DJ Webb¹, SC Lewis⁷, DN Bateman¹ and JW Dear¹



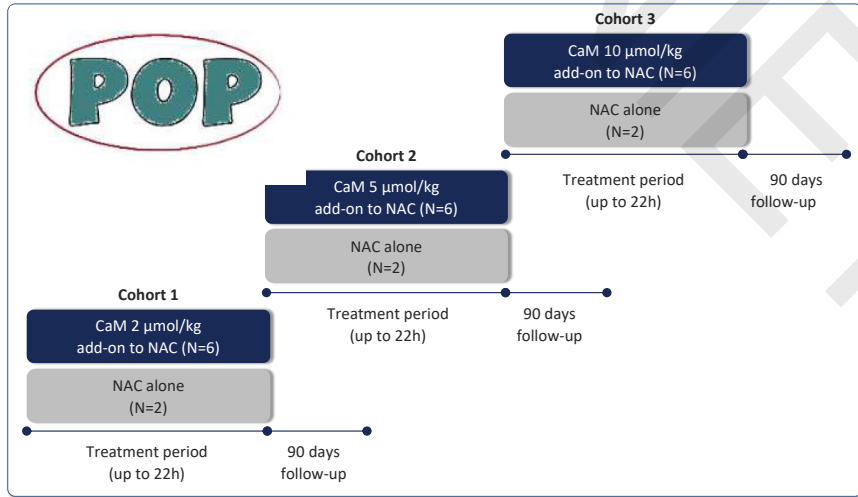
HiSNAP Trial

EARLY PRESENTER

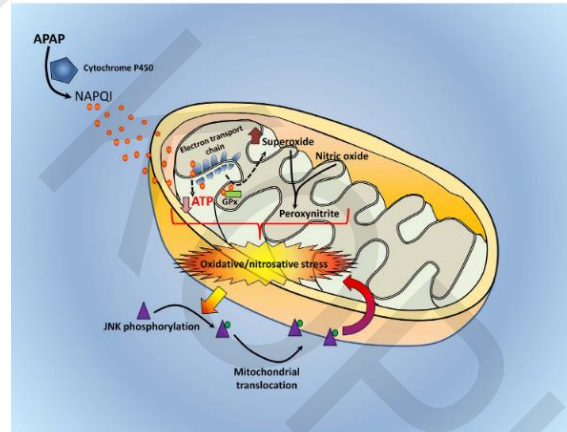


ALBATROS Trial

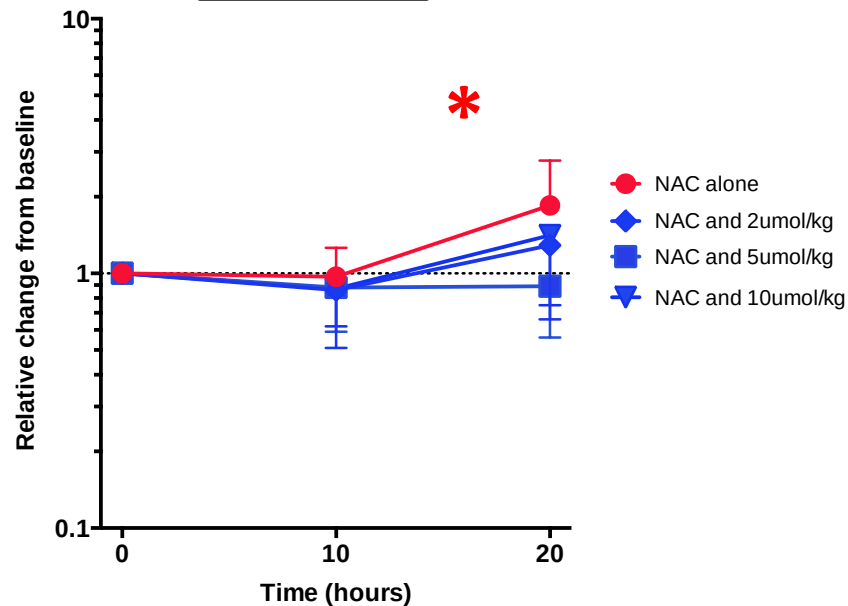
LATE PRESENTER



Pivotal Phase II/III study for US/EU regulatory submission



K1 Keratin-18



Late presenting patients
N=250

Double blind, Randomised

Placebo and
acetylcysteine

Calmangafodipir
(1µmol/kg) and
acetylcysteine

Calmangafodipir
(5µmol/kg) and
acetylcysteine

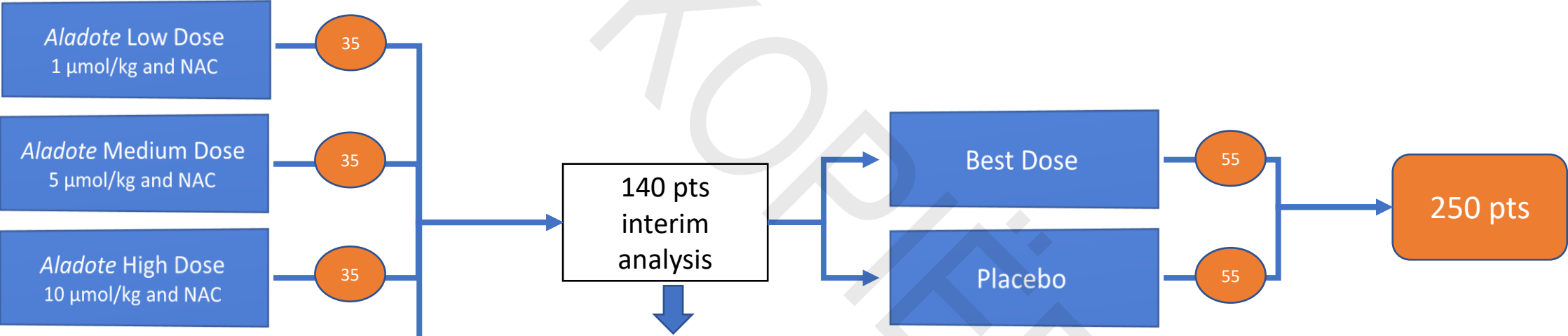
Calmangafodipir
(10µmol/kg) and
acetylcysteine

Primary endpoint
Prevention of liver injury

Seamless Phase IIb/III design

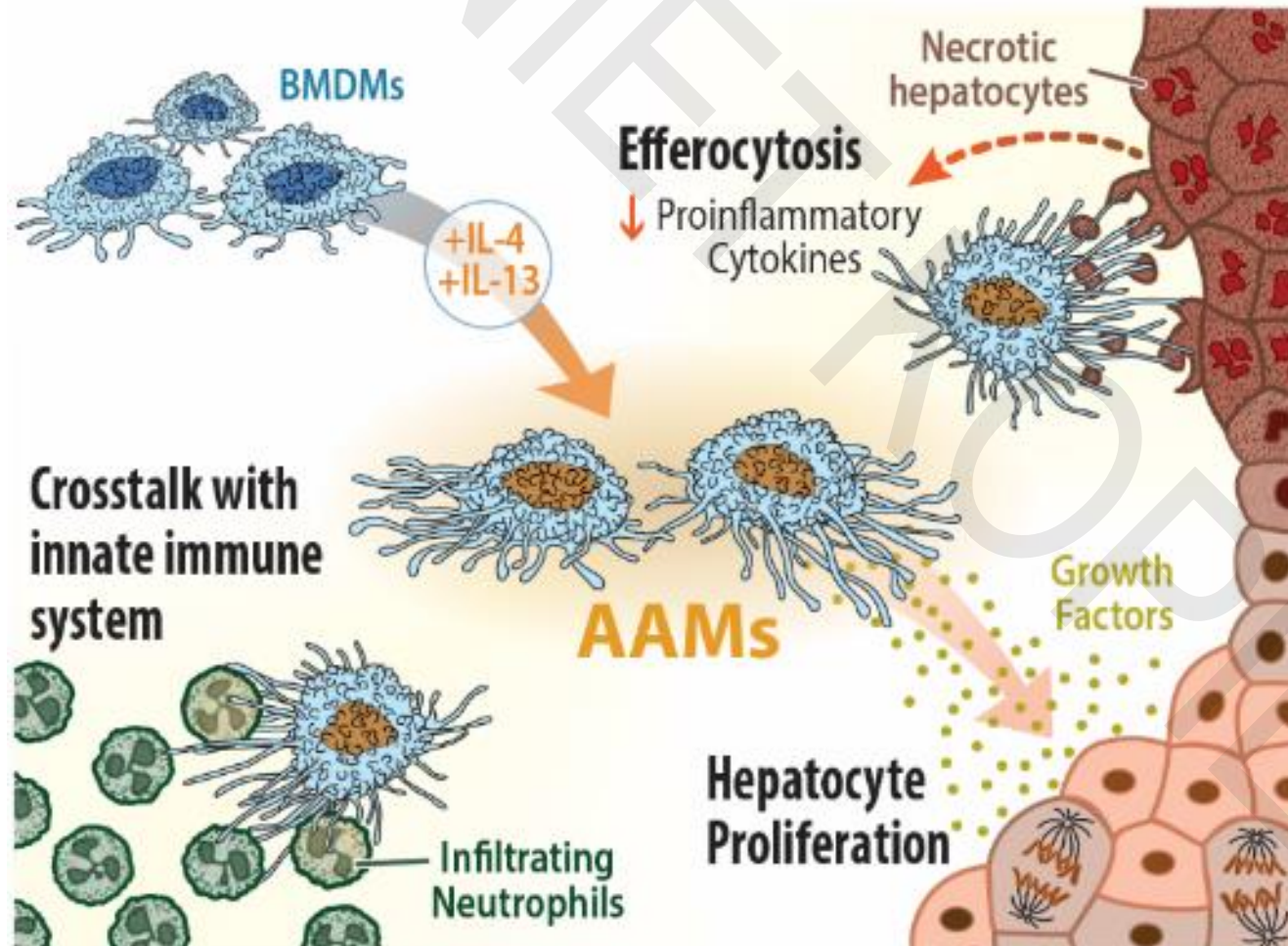


Based on the acetaminophen/paracetamol levels eligible patients will be randomised in a 1:1:1:1 ratio to one of the 4 treatment arms in combination with NAC:



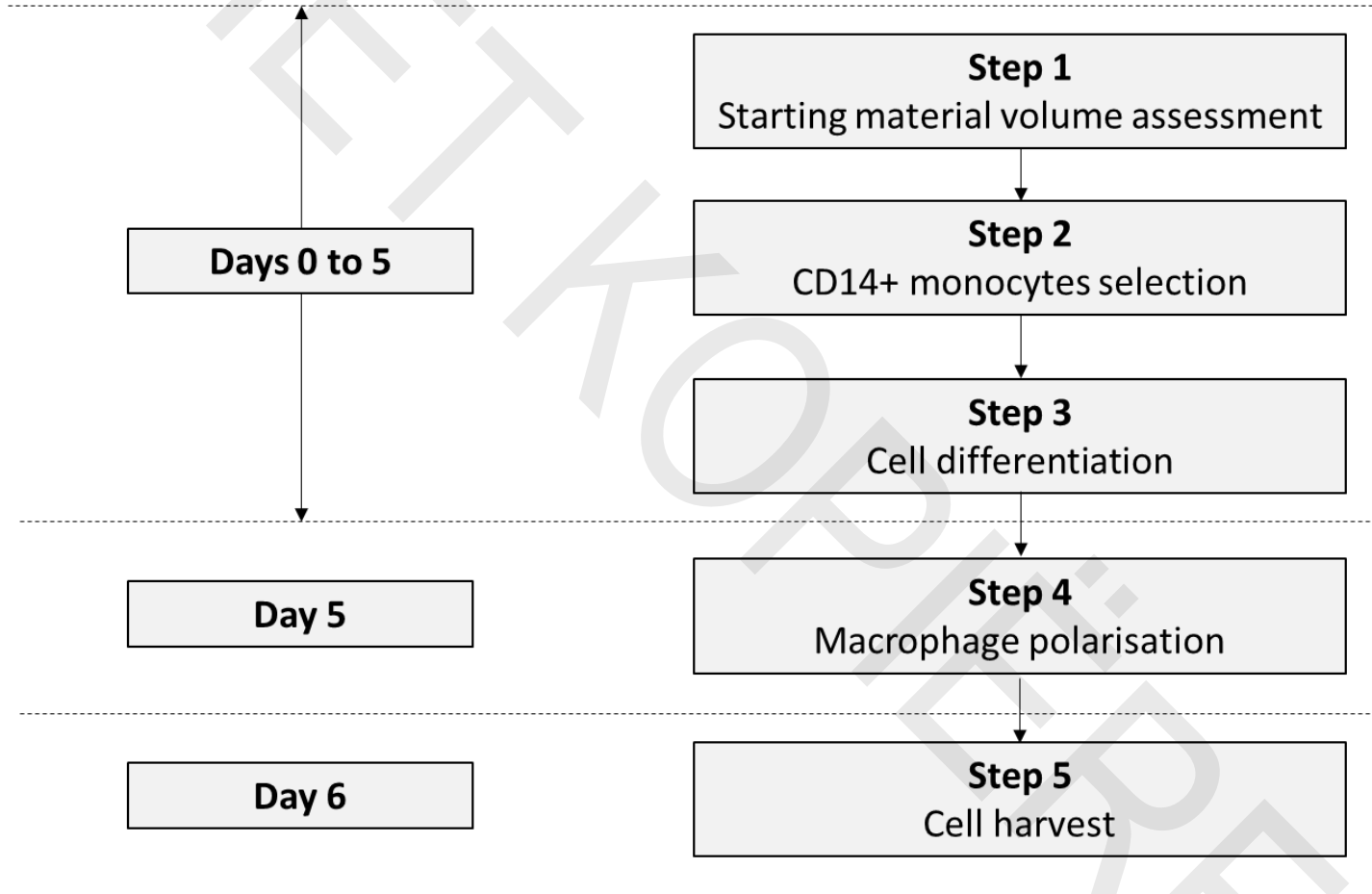
- Stop the study for futility; or
- Continue the study with the most effective of the 3 doses and placebo up to the preplanned sample size; or
- Increase the sample size in the arm with the most effective dose and the placebo arm to boost the power

Primary endpoint:
Patients w/o hepatic injury
INR ≤ 1.3 and ALT ≤ 50 or
INR ≤ 1.3 and ALT > 50 but not
increased by >10% up to 20h



Allogenic alternatively activated macrophages (AAMs)

- resolves hepatic necrosis
- promotes hepatocellular proliferation
- reduces systemic inflammation
- retains anti-inflammatory phenotype in vivo



MAIL Trial

LIVER INJURY



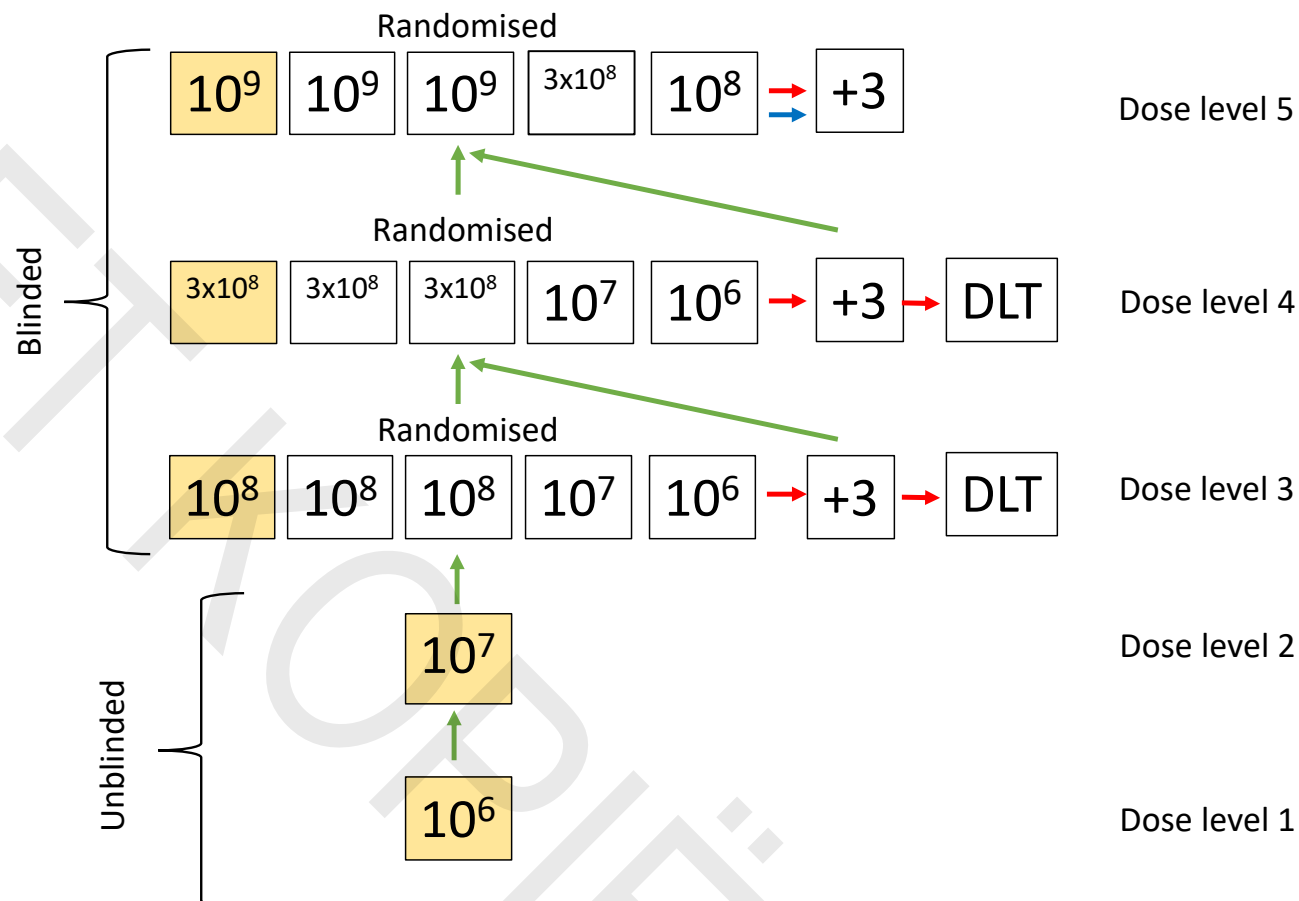
Stuart Forbes



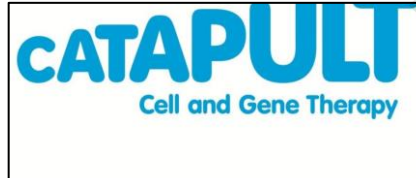
John Campbell



Chris Weir



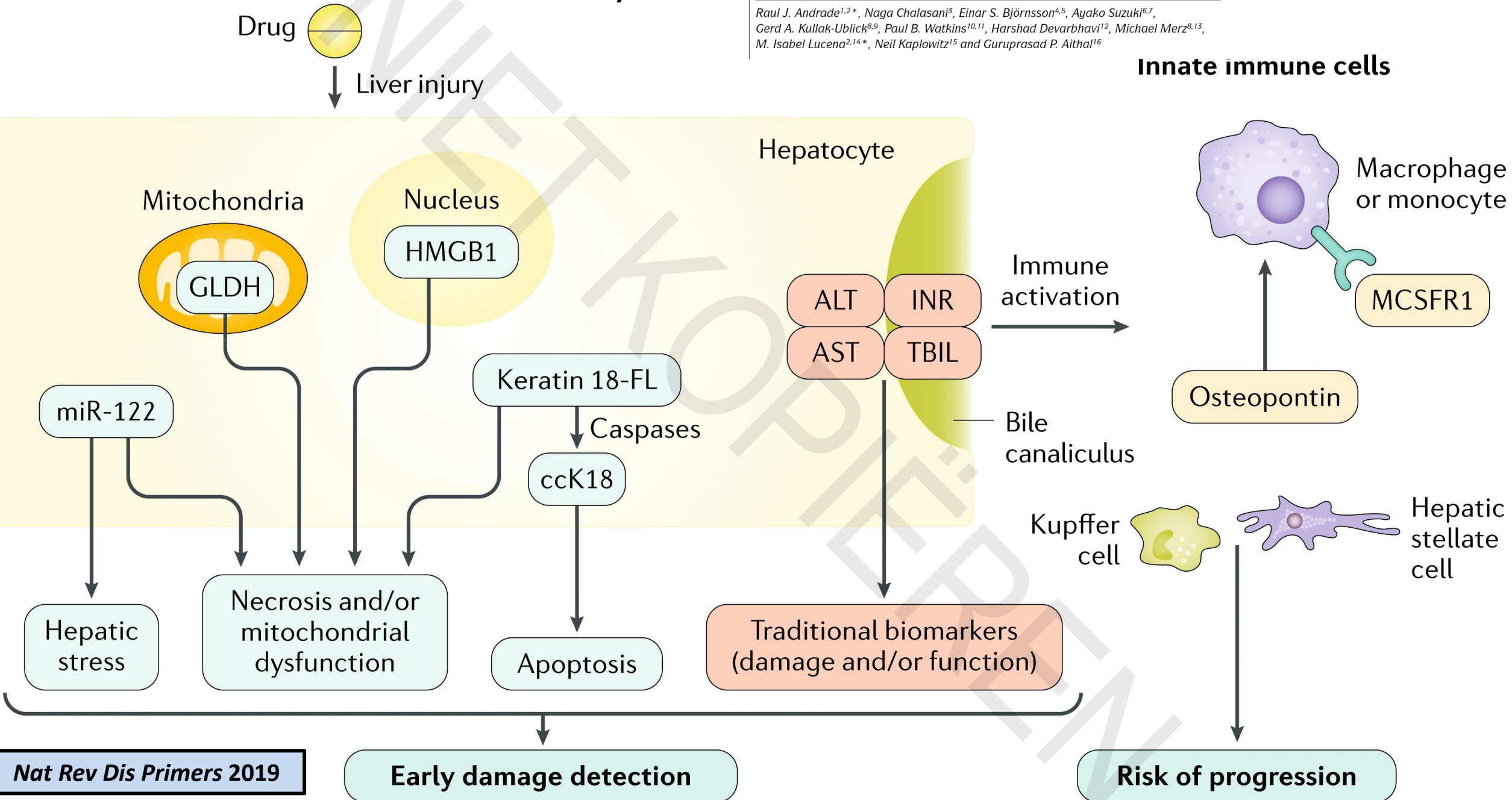
Patients with established liver toxicity
 $ALT > 1000$

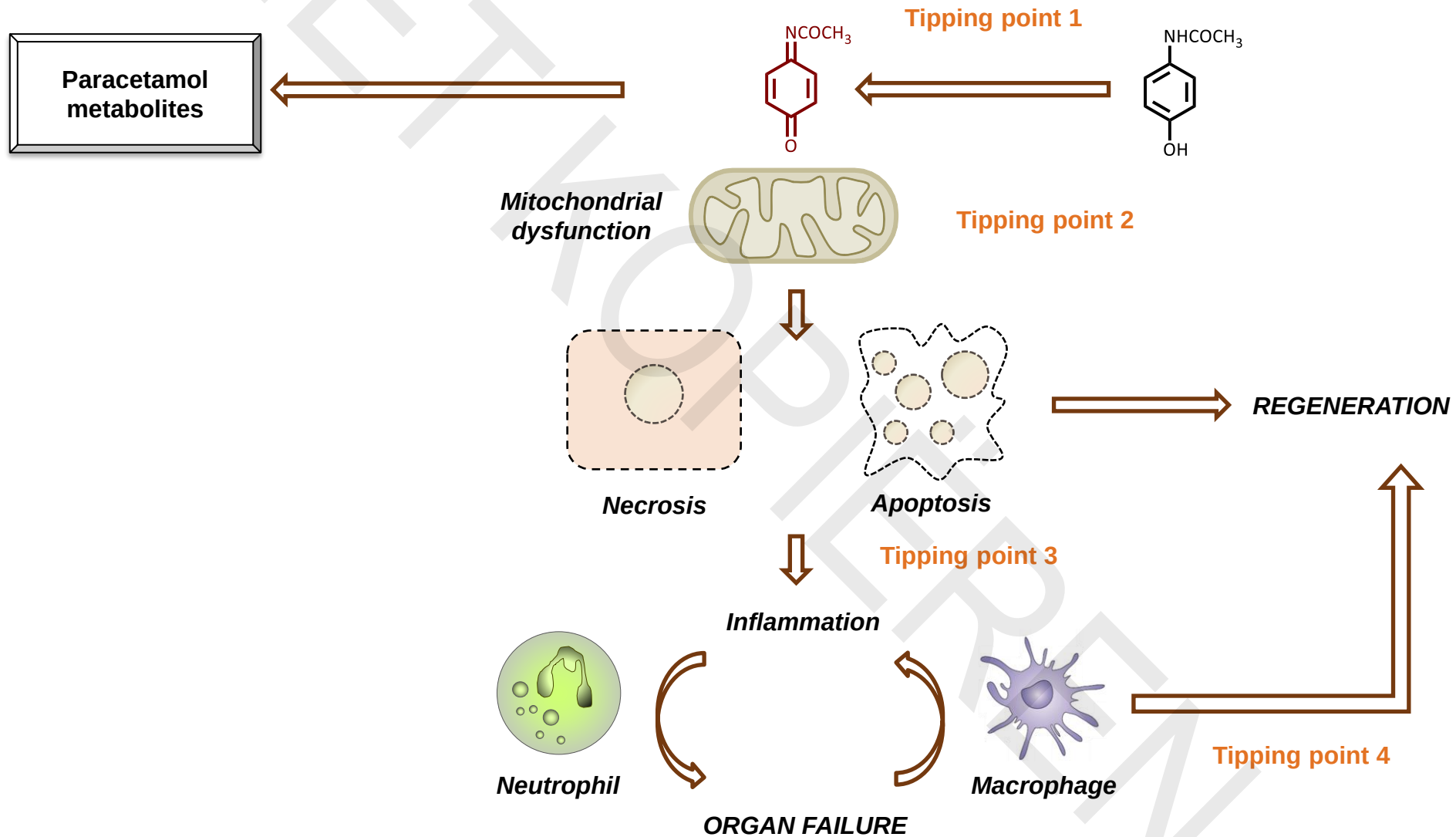


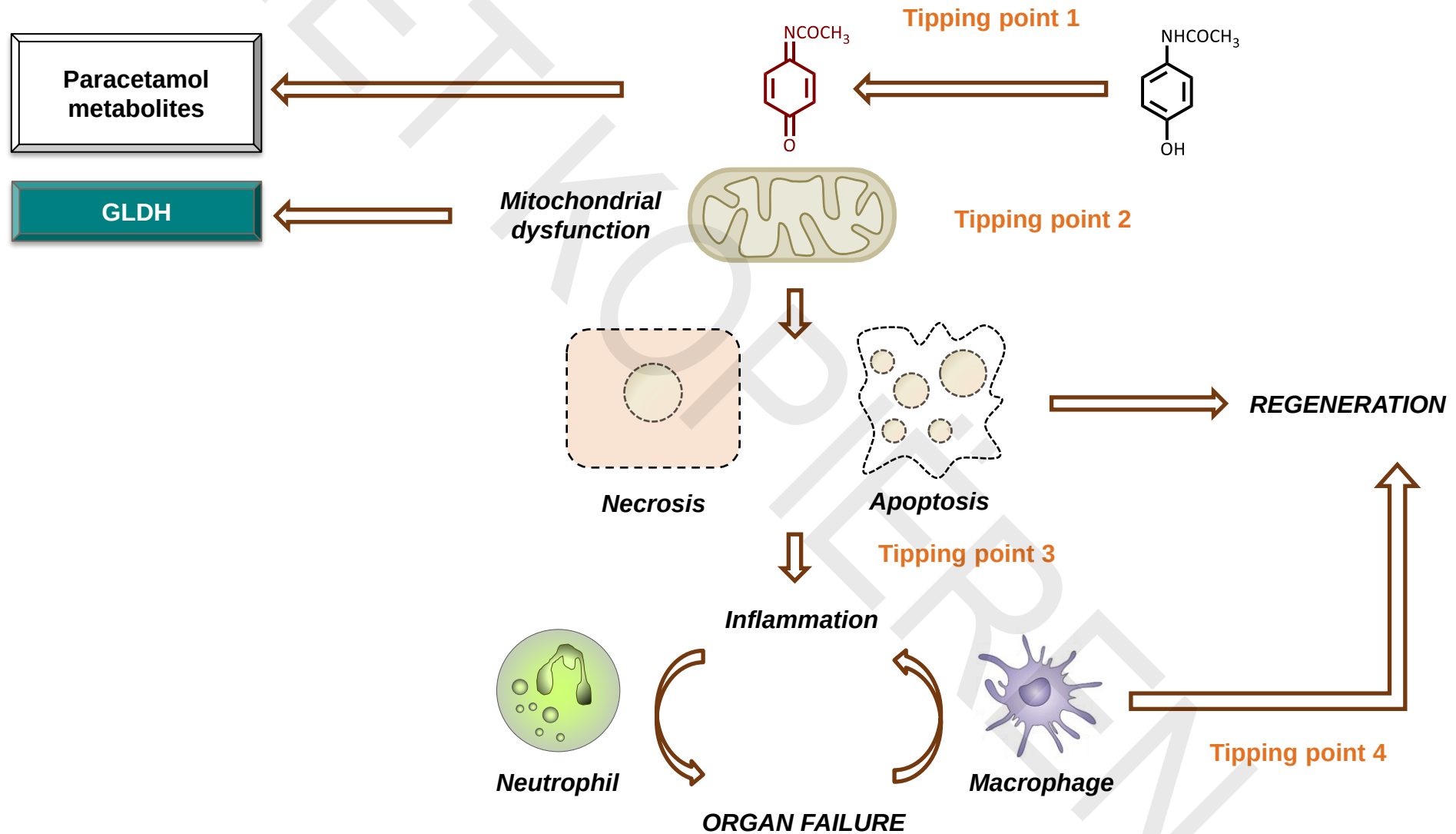
Biomarkers of liver toxicity

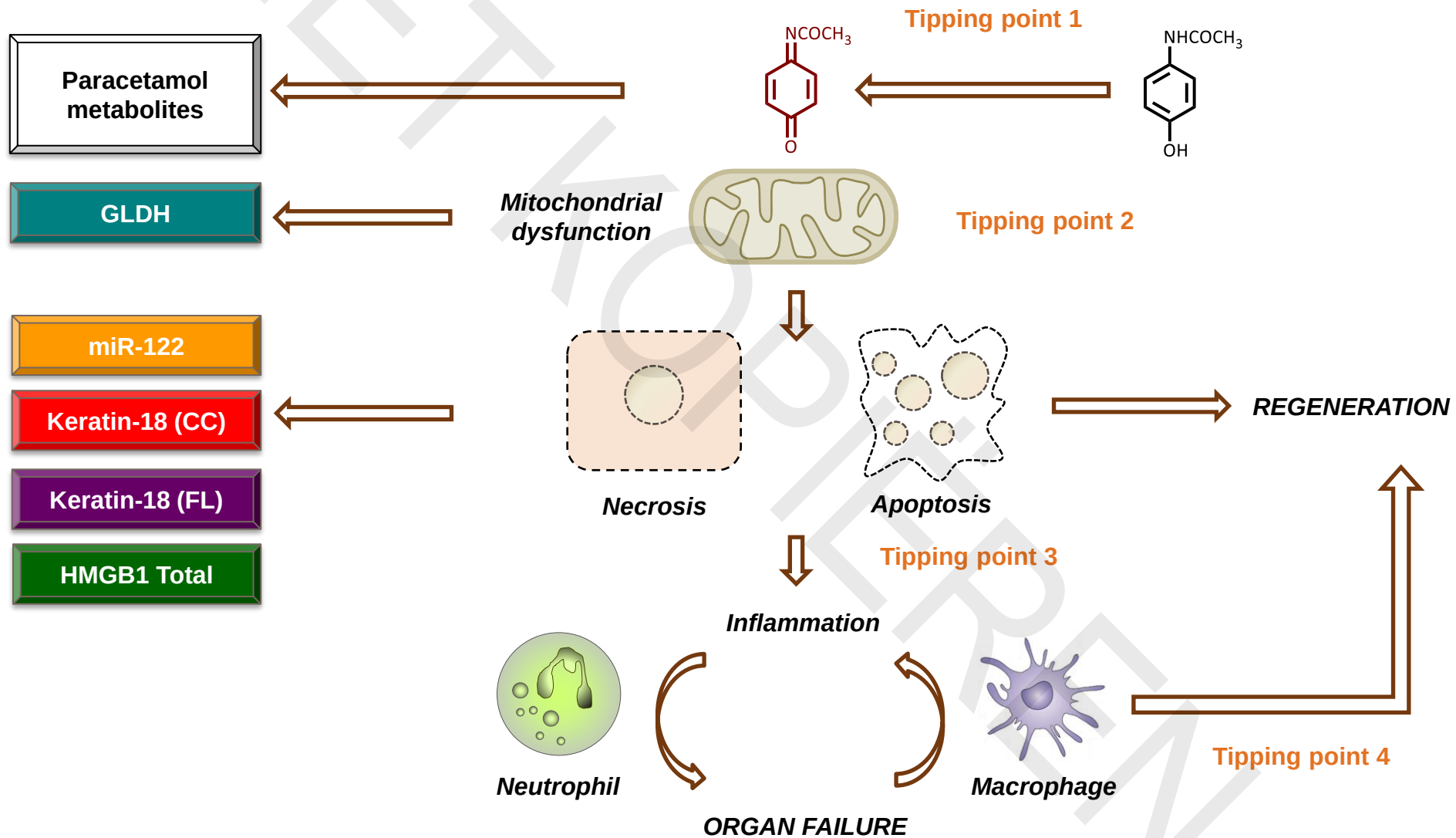
Drug-induced liver injury

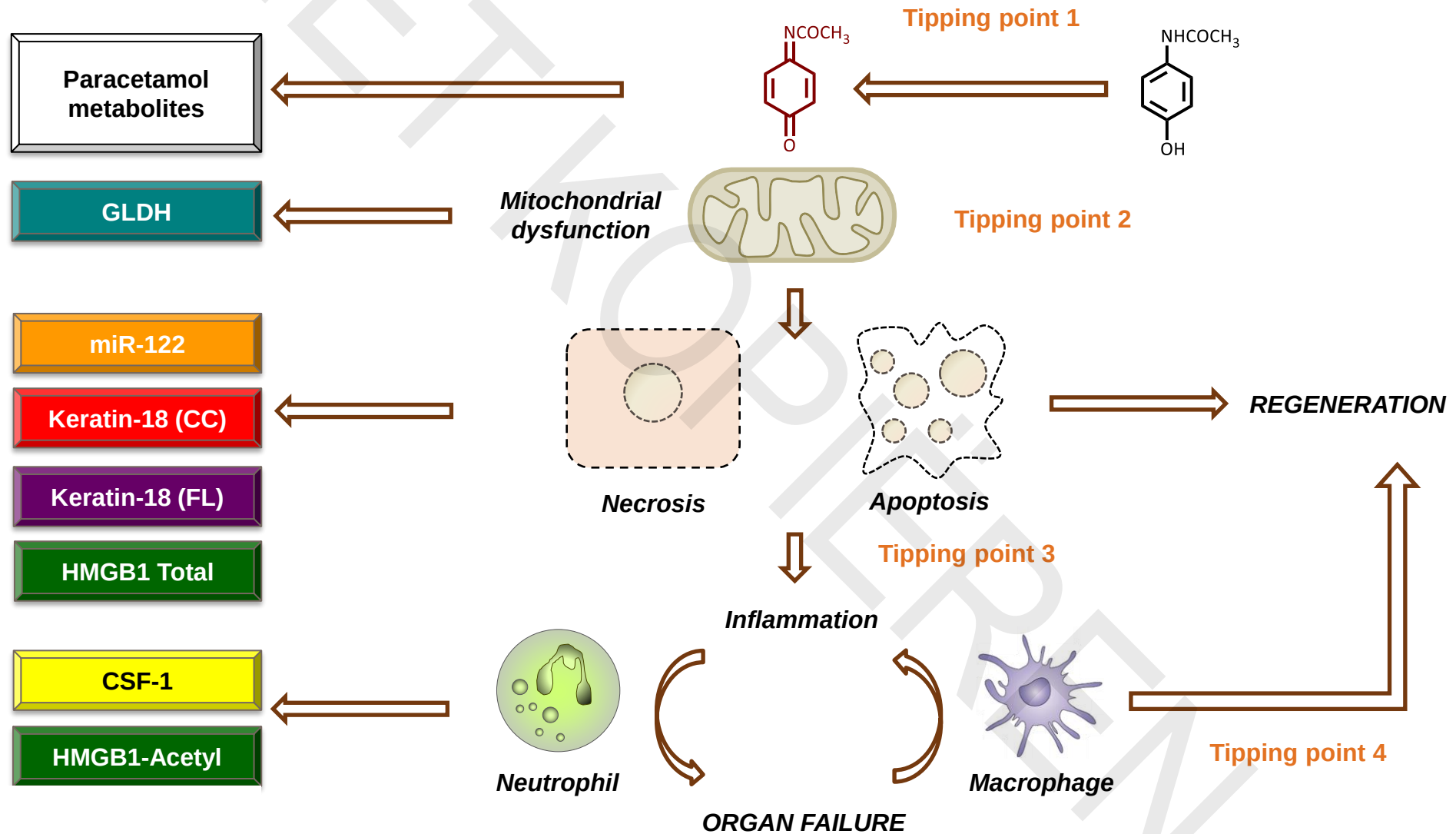
Raul J. Andrade^{1,2}, Naga Chalasani³, Einar S. Björnsson^{4,5}, Ayako Suzuki^{6,7}, Gerd A. Kullak-Ublick^{8,9}, Paul B. Watkins^{10,11}, Harshad Devarbhavi¹², Michael Merz^{8,13}, M. Isabel Lucena^{2,14*}, Neil Kaplowitz¹⁵ and Guruprasad P. Aithal¹⁶*











CASE REPORT:

25 year old male

Single overdose of 35g paracetamol at 02:30 (timing supported by Facebook message)

Assessed 4.5h after OD

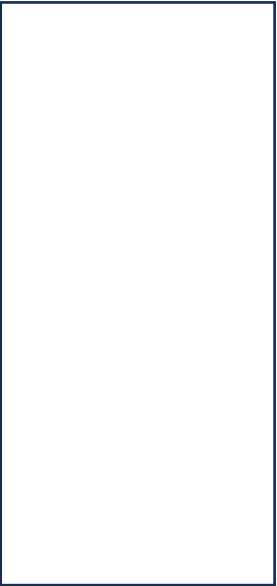
No risk factors for hepatotoxicity. Paracetamol level 107 mg/L (below nomogram)

Normal biochemical evidence of liver injury

Assessed by senior doctor and not treated

Discharged after psychiatry review

Time from OD (h)	4.5
Paracetamol (mg/L)	107
ALT (U/L) (ULN 50)	34
INR	1.0



BJCP

British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12214

Letter to the Editors

Early detection of paracetamol toxicity using circulating liver microRNA and markers of cell necrosis

James W. Dear,^{1,2} Daniel J. Antoine,³ Philip Starkey-Lewis,³ Christopher E. Goldring³ & B. Kevin Park³

¹National Poisons Information Service Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, ²University of Edinburgh/British Heart Foundation Centre for Cardiovascular Science, Edinburgh and ³MRC Centre for Drug Safety Science, Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK

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No risk factors for hepatotoxicity. Paracetamol level 107 mg/L (below nomogram)

Normal biochemical evidence of liver injury

Assessed by senior doctor and not treated

Discharged after psychiatry review

Represented to hospital 43h after OD

Lethargic and vomiting

Tender abdomen

Time from OD (h)	4.5	43
Paracetamol (mg/L)	107	9
ALT (U/L) (ULN 50)	34	11314
INR	1.0	2.1

Letter to the Editors

Early detection of paracetamol toxicity using
circulating liver microRNA and markers of
cell necrosis

James W. Dear,^{1,2} Daniel J. Antoine,³ Philip Starkey-Lewis,³ Christopher E. Goldring³ &
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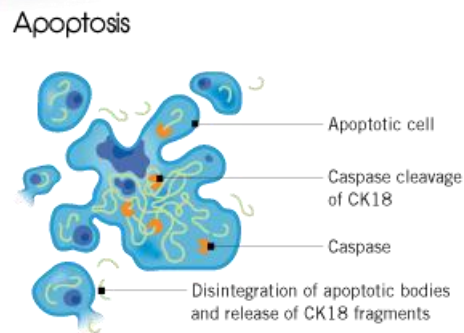
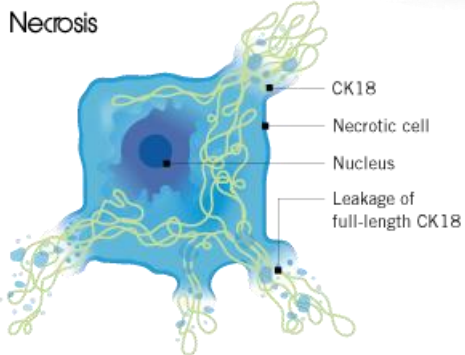
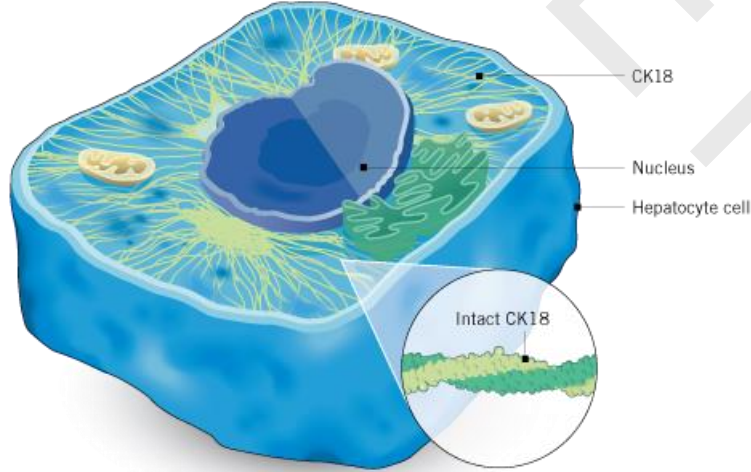
**NEW MARKERS CORRECTLY
IDENTIFIED
LIFE THREATENING
HEPATOTOXICITY MISSED
BY CURRENT TESTS**

Time from OD (h)	4.5	43
Paracetamol (mg/L)	107	9
ALT (U/L) (ULN 50)	34	11314
INR	1.0	2.1
miR-122 (/ let-7d) (ULN 5.2*)	261 (x50)	
Necrosis K18 (U/L) (ULN 480*)	4018 (x8)	

*95% prediction interval – no liver injury after overdose
n=82 *Hepatology* 2013

POC-DILI Trial

Mechanism of Cell Death – cytokeratin-18



Study	Cause of liver injury	N	ROC-AUC (95%CI)	Spec at 95% Sens	Reference
Hepatology 2013	Paracetamol	129	0.94 (0.87-1.0)	0.90	Hepatology 2013. PMID 23390034
MAPP	Paracetamol	985	0.94 (0.89-0.99)	0.91	Lancet Gastro 2018. PMID 29146439
BIOPAR	Paracetamol	202	0.93 (0.81-1.00)	0.90	Lancet Gastro 2018. PMID 29146439
Hepatology 2019	Non paracetamol DILI	689	0.95 (0.93-0.97)	Not reported	Hepatology 2019. PMID 29357190
Edinburgh/Pfizer 2020	Paracetamol	198	0.98 (0.95-0.99)	0.94	Toxicol Sci 2021 PMID 33483742
Nature Comms	Non paracetamol DILI	142	0.96 (0.92-0.99)	Not reported	Nature Comms 2023 PMID 36869085
Nature Comms	Non paracetamol DILI	75	0.97 (0.94-1)	Not reported	Nature Comms 2023 PMID 36869085
Spanish DILI Registry	Non paracetamol DILI	109	0.96 (0.91-1)	Not reported	Brit Journal of Clinical Pharmacology 2023 PMID 36965054
POC-DILI	Paracetamol DILI	100	?	?	MRC DPFS



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University of
Strathclyde
Glasgow

Wasatch Photonics

- Dr Sian Sloan-Dennison
- Prof Duncan Graham
- Prof Karen Faulds
- Bionano Team

- Dr David Creasey
- Cicely Rathmell
- Dr Dieter Bingemann
- Jonathan Faircloth
- Mark Zieg
- Samie Bee
- Wasatch Team



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- Dr Kathleen Scullion
- Prof James Dear
- Dr Paul Fineran
- Joanne Mair
- Dr Christopher Weir

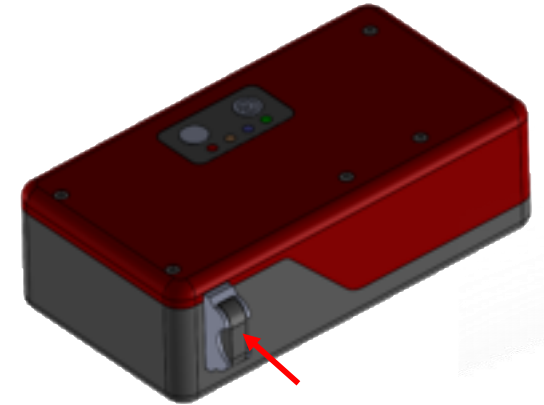
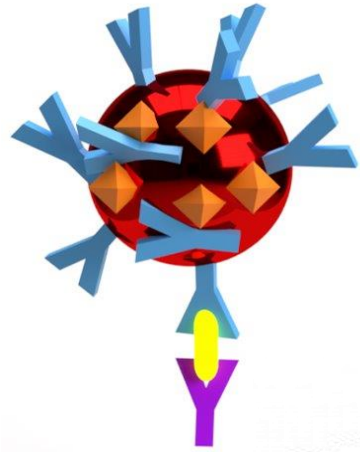
IRDG
Infrared & Raman Discussion Group



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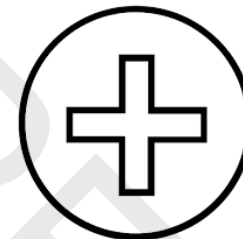
SERS-LFIA Device for Emergency Department



Quantitative
Reproducible SERS
results for clinically
relevant K18
concentration in serum

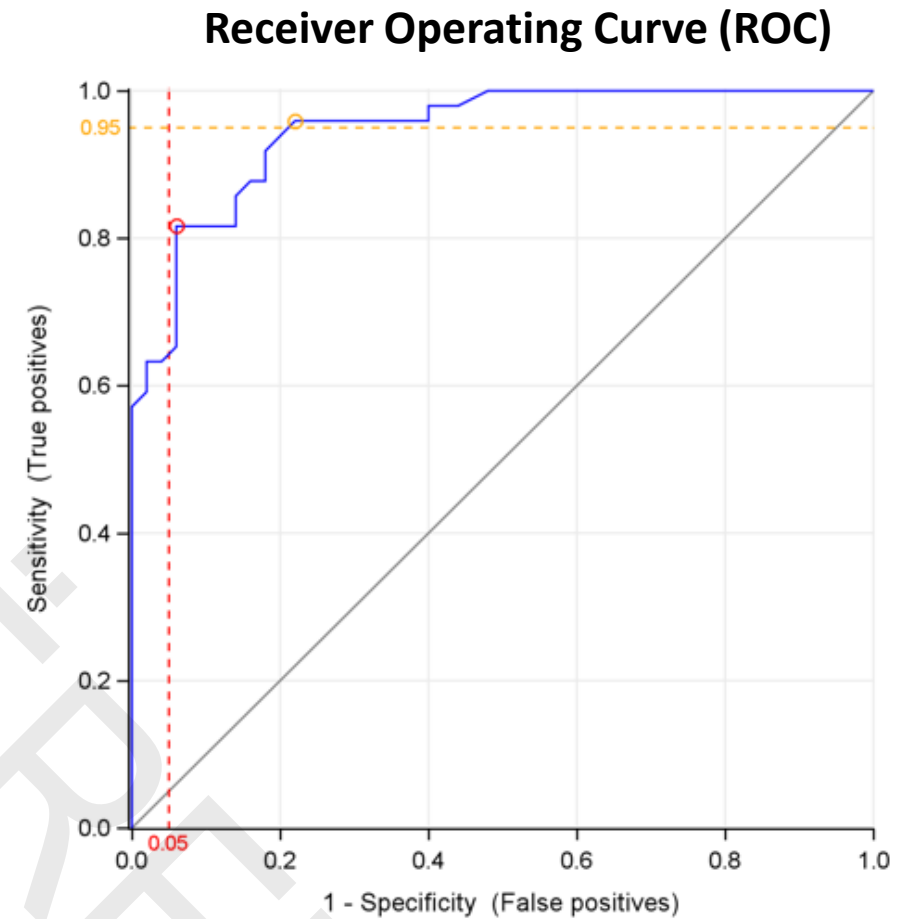
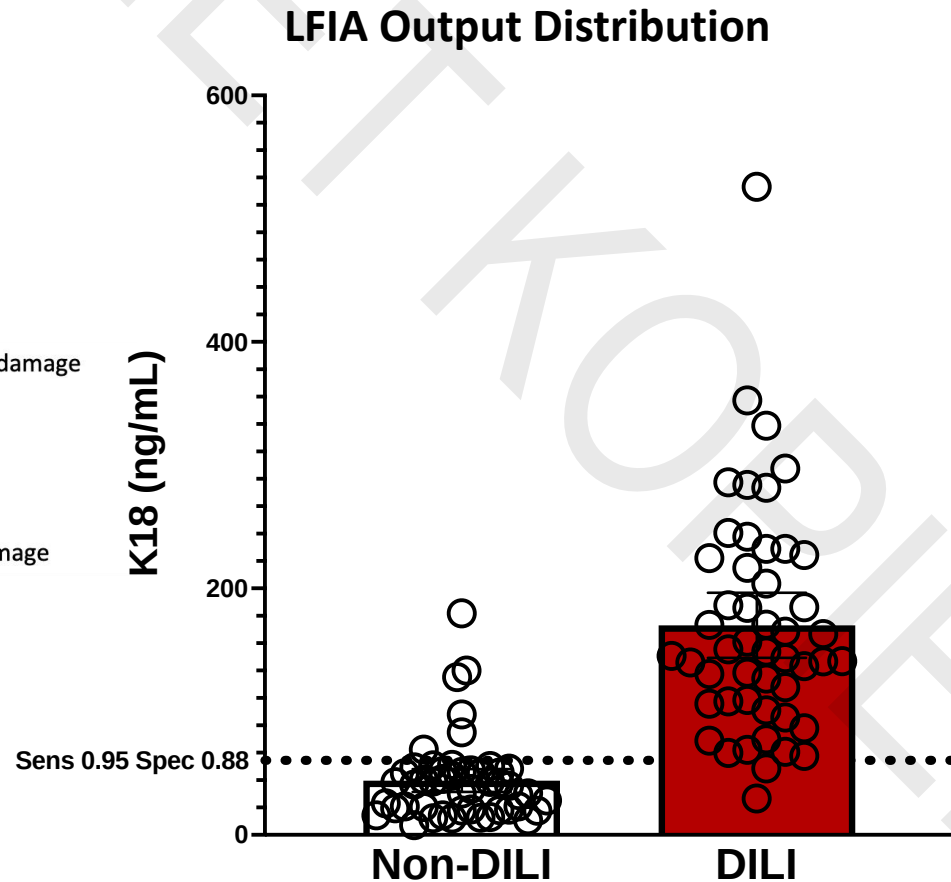
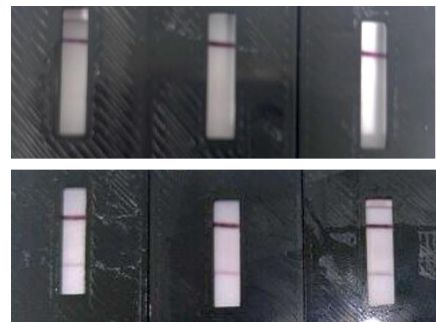


Rapid
Provide 20 minutes
after sample taken
from patient



Point of care
Run test and
deliver results
next to patient

Blinded Clinical Study



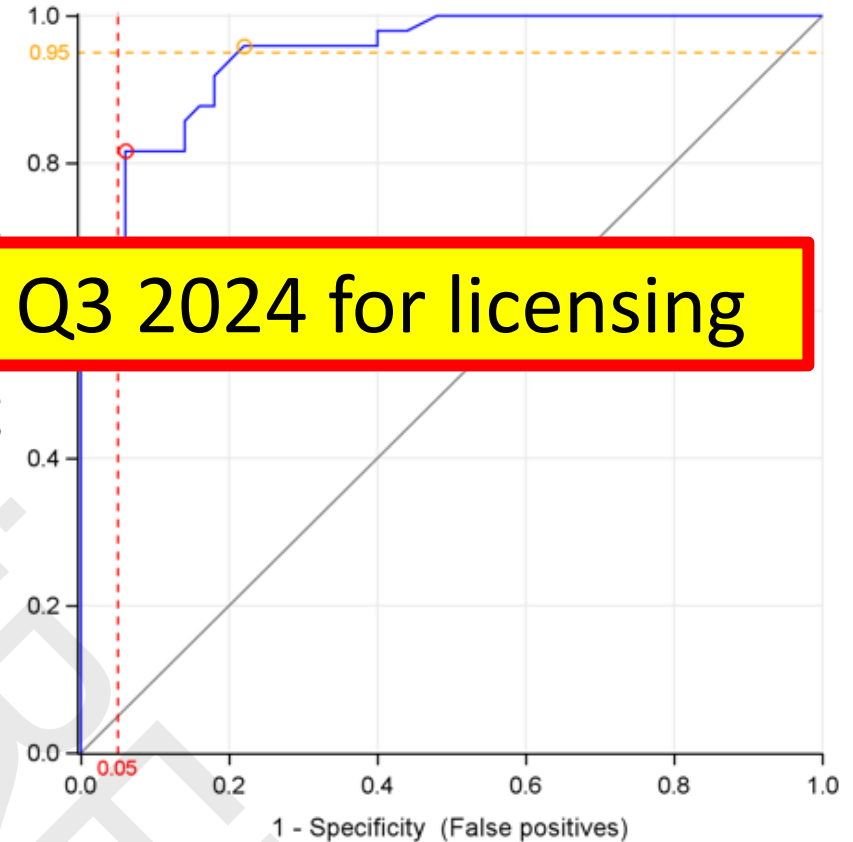
- High combination of sensitivity (95%) and specificity (88%) was achieved.
- Receiver operating characteristic (ROC) curve gives an area under the curve **(AUC) of 0.946.**

Blinded Clinical Study

LFIA Output Distribution



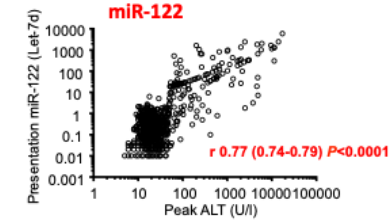
Receiver Operating Curve (ROC)



Prospective performance evaluation to start Q3 2024 for licensing

- High combination of sensitivity (95%) and specificity (88%) was achieved.
- Receiver operating characteristic (ROC) curve gives an area under the curve **(AUC) of 0.946.**

Biomarker Developmental Pathway



Paracetamol poisoning as model of acute organ injury

Clinical adoption in UK

Biomarker discovery in model systems

Biomarker qualification in animal models

Proof of concept in humans

Biomarker qualification in humans

Clinical adoption in Africa



Completed

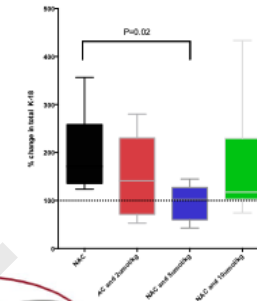
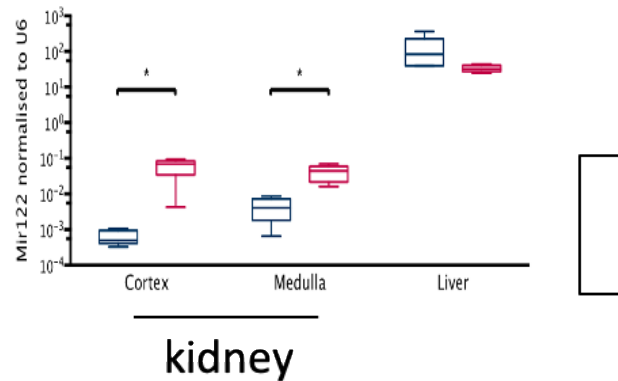
Completed

Completed

Qualification as tool in drug development

Vet Medicine

Mechanistic science



University of Edinburgh

Kathleen Scullion
Robert Hunter
Susan Armstrong
Stuart Forbes
Bastiaan Vliegthart
Wilna Oosthuyzen
Emma Morrison
Olivia Matthews
Bean Dhaun
John Tranter
Sarah Stedman
Nathalie Brilliant
Ken Simpson
David J Webb
Nick Bateman
Matthew Bailey
Till Bachmann
Holger Schulze

University of Strathclyde

Duncan Graham
Karen Faulds
Sian Sloan-Dennison
Ben Clark

Translation Healthcare Technologies

Paul Fineran
Jo Mair
Kevin Dhaliwal

ECTU

Chris Weir
Anna Heye

EMERGE

Rachel O'Brien
Julia Grahamslaw
Miranda Odam

SNBTS

John Campbell

AstraZeneca

Dominic Williams

