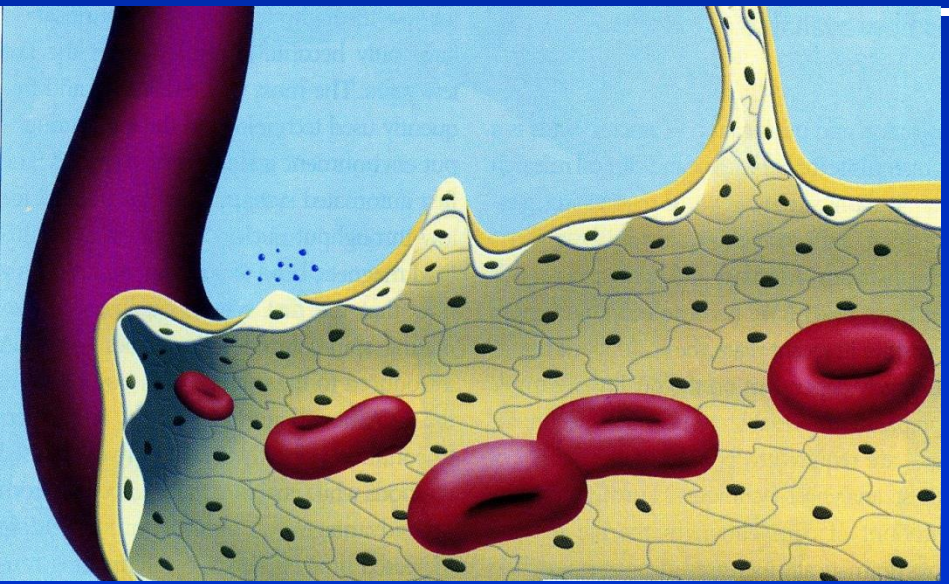
UNIVERSITY OF CALGARY

5th International Conference on Environmental Toxicology and Risk Assessment, Phoenix/AZ September 12-13, 2016

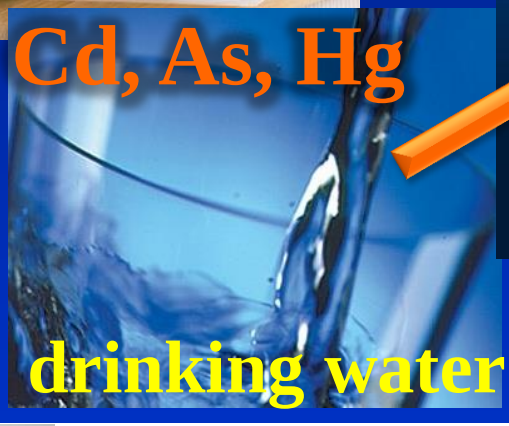
Probing toxicologically relevant interactions of inorganic pollutants in the bloodstream



Matthew A. Gibson, Peter Sagmeister, Sophia Sarpong-Kumankomah and Jürgen Gailer
Department of Chemistry, Calgary, Alberta











metal-based drugs



toxic metals in blood ?↔

Cadmium



2010: recall of 12 million drinking glasses by McDonald's





~1.7 µg Cd/cigarette

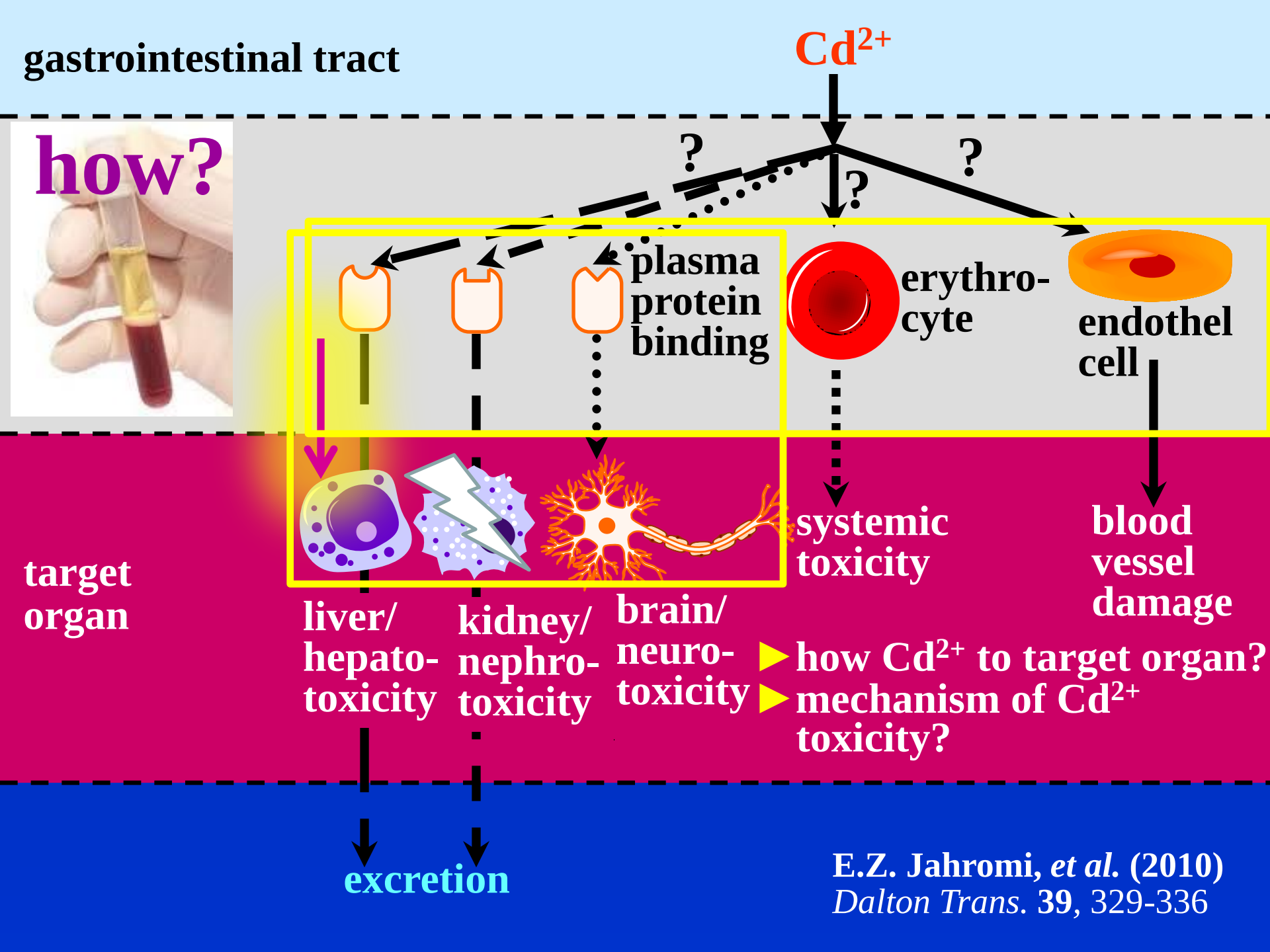


0.1-4.7 mg Cd/kg

5% of US population urinary Cd ≈ kidney injury

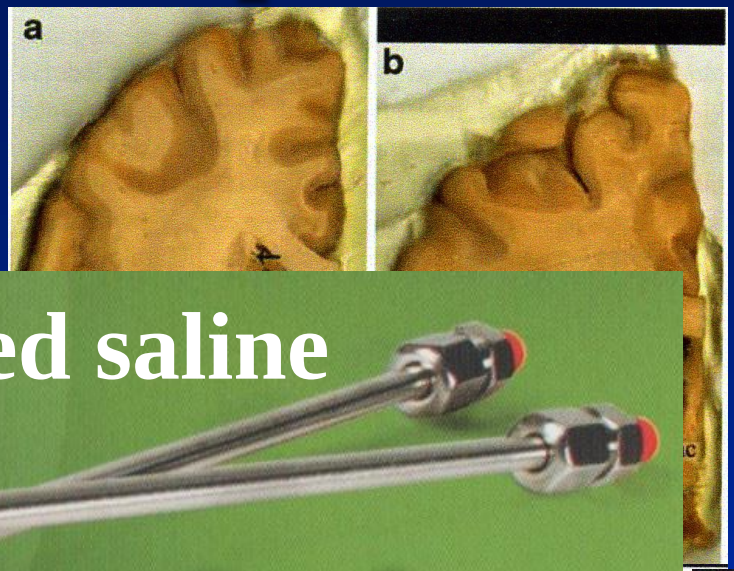
exposure-disease associations ill defined

?


gastrointestinal tract
Cd2+
how?
?
?
?
plasma protein binding
erythro-cyte
endothel cell
target organ
systemic toxicity
blood vessel damage
liver/ hepato-toxicity
kidney/ nephro-toxicity
brain/ neuro-toxicity
how Cd2+ to target organ?
mechanism of Cd2+ toxicity?
excretion
E.Z. Jahromi, et al. (2010)
Dalton Trans. 39, 329-336

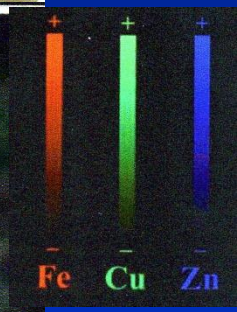
deadly dose:
0.5 mg

top down

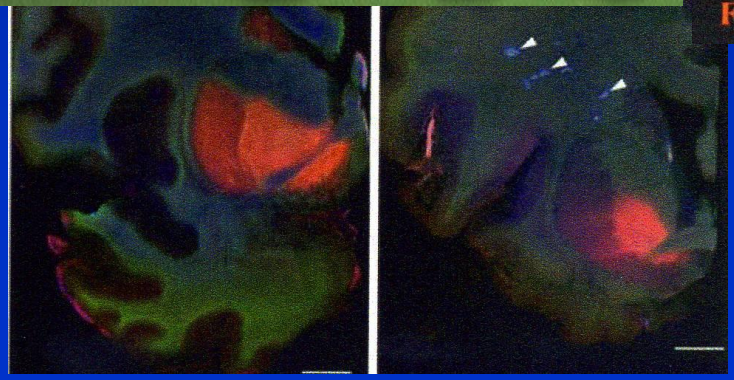


ate buffered saline
nobile phase

size-exclusion
chromatography

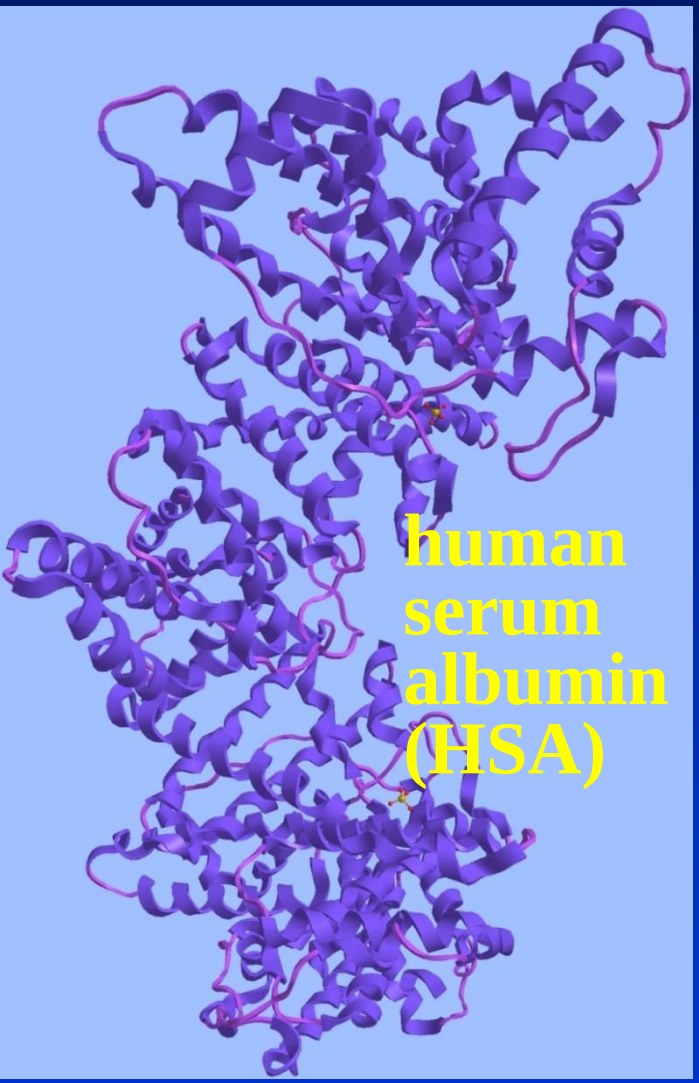




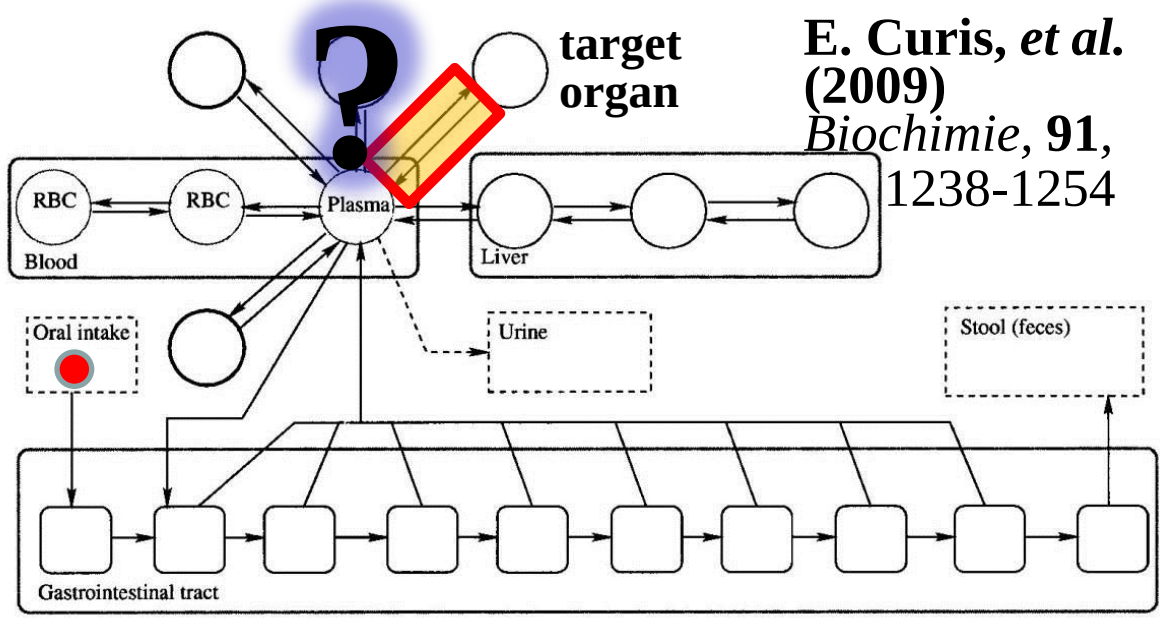


bottom up

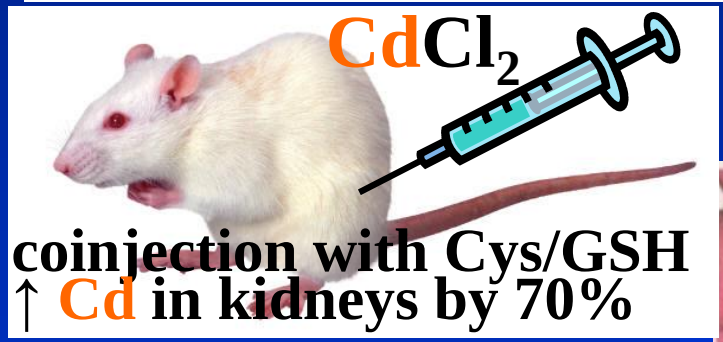
B.F. Popescu *et al.* (2009)
Cerebellum, **8**, 340-351



human serum albumin (HSA)



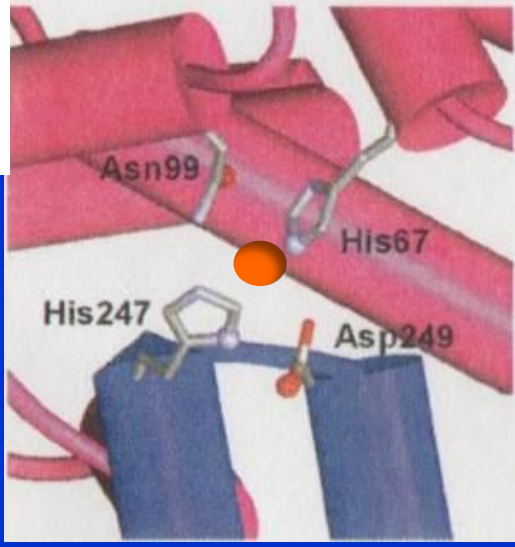
E. Curis, *et al.* (2009) *Biochimie*, **91**, 1238-1254



coinjection with Cys/GSH ↑ Cd in kidneys by 70%

C.A. Blindauer, *et al.* *J. Biol. Chem.* 2009, 284, 23116-23124

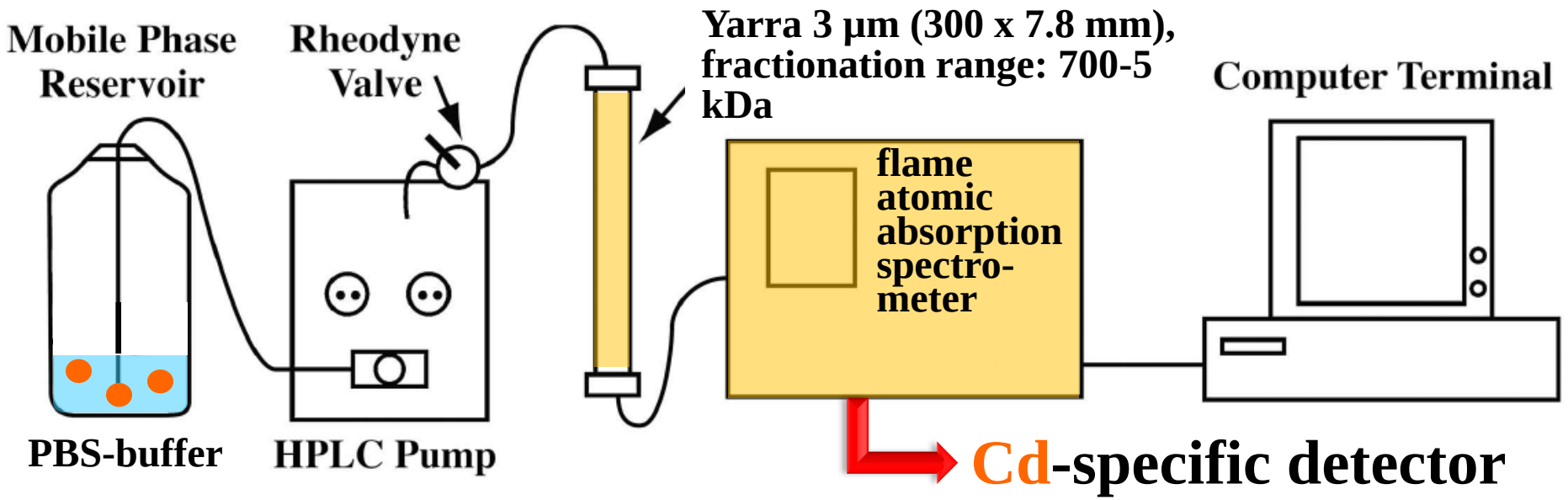
R.K. Zalups *Toxicol. Appl. Pharmacol.* 2000, 164, 15-23



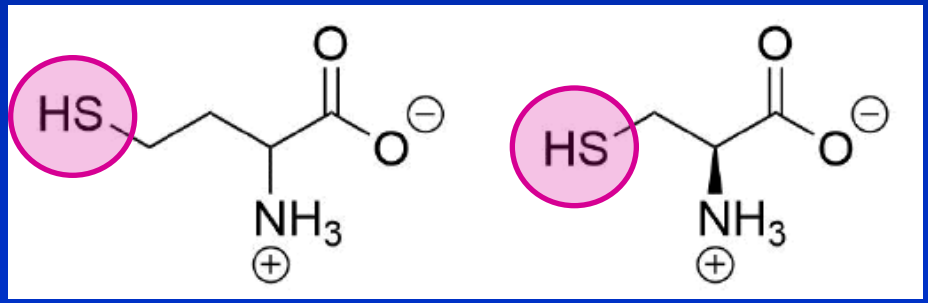
HSA-Cd 1:1 complex

are small MW thiols involved in trans-location?

instrumental set-up:



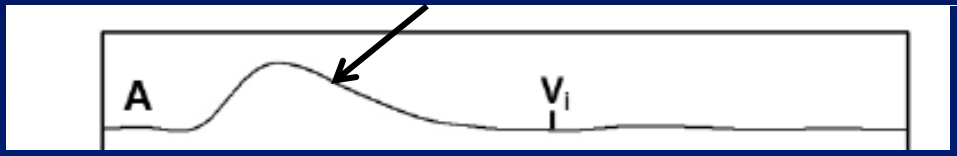
add up to 1.5 mM SMW thiols to PBS-buffer



L-cysteine L-homocysteine

→ study their effect on stability of HSA-Cd 1:1 complex

HSA-Cd 1:1 complex



P. Sagmeister, *et al.* *J. Chromatogr. B*, 2016, 1027, 181-186

Cys/hCysCd complexes → target organ?

Biochem. Pharmacol. 1984, 33,199-203
Toxicol. Appl. Pharmacol. 1999, 154, 59-66

hyperhomocysteinemia

Annu. Rev. Med. 1998, 49, 31-62

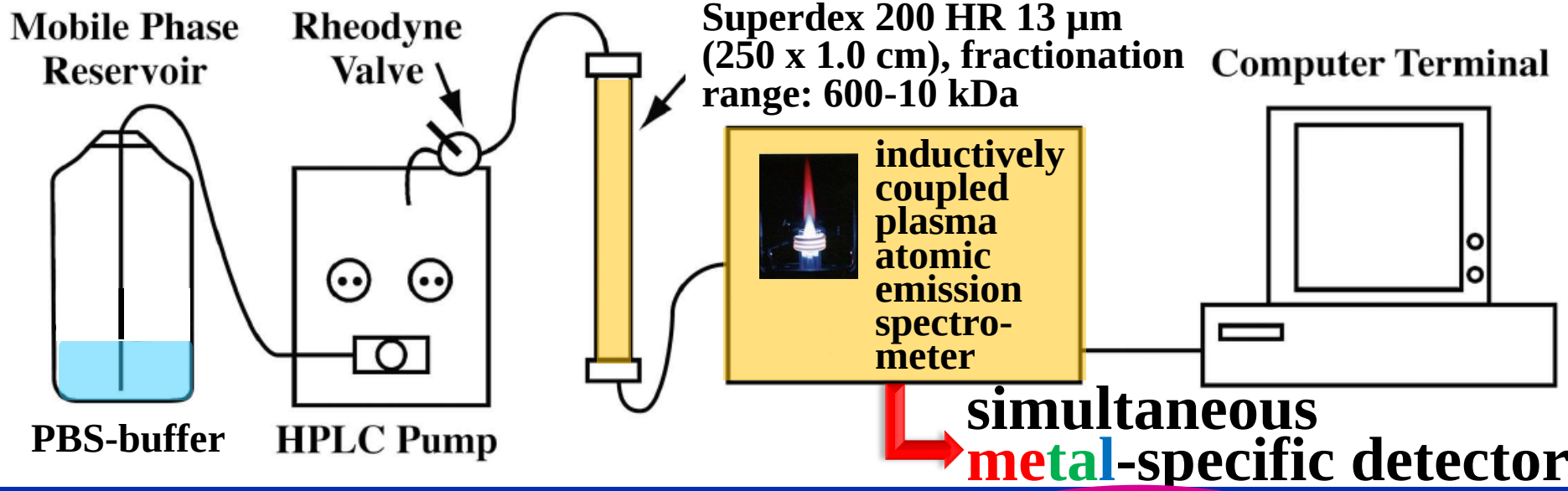


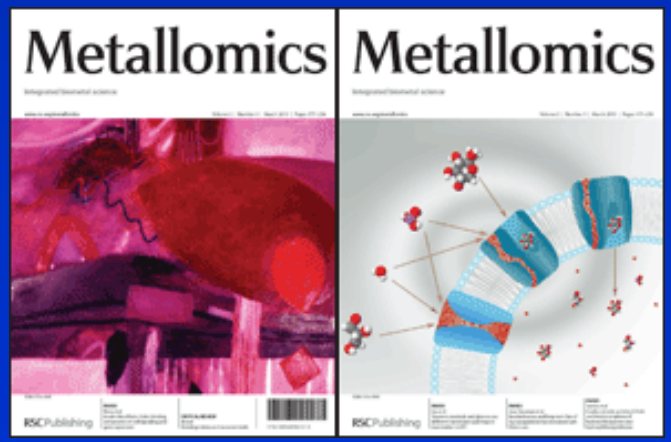
top down

analyze  directly → difficult > 3700 proteins

simplify if we analyze for metalloproteins

instrumental set-up:



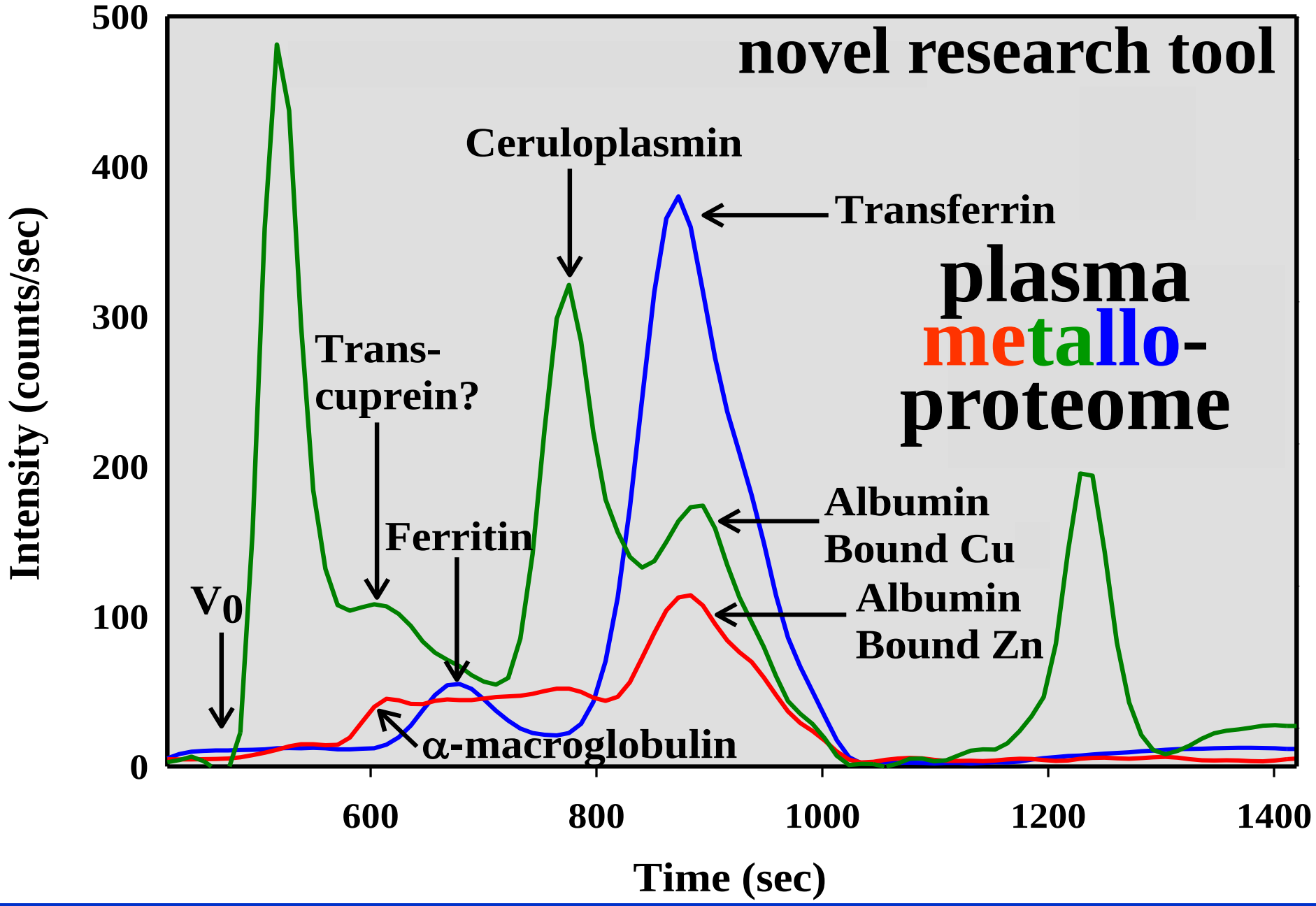


…the study of a metallome

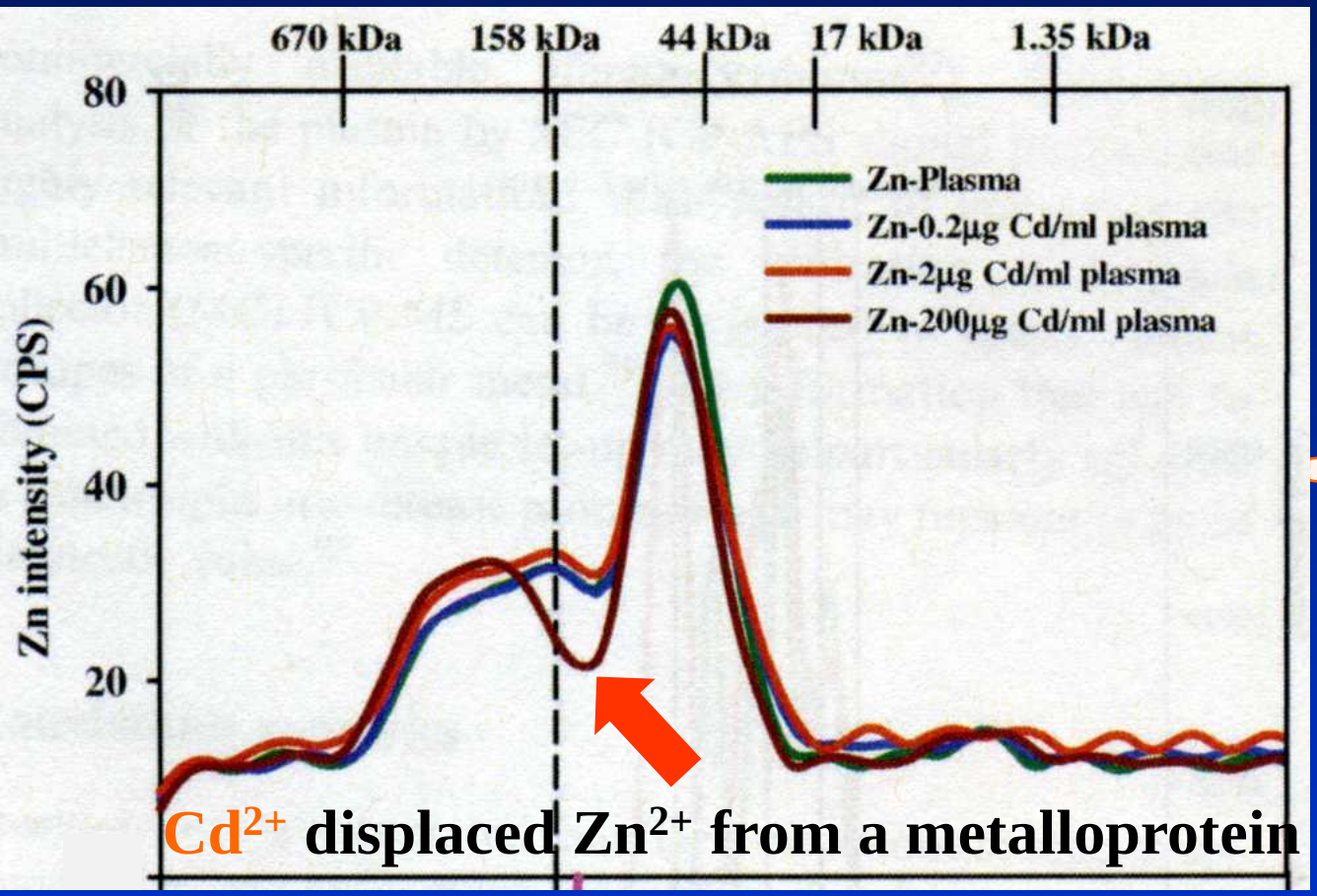
S. Mounicou, *et al.*

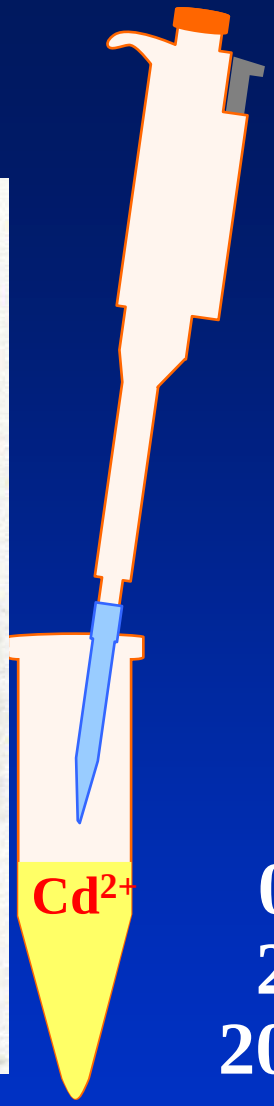
Chem. Soc. Rev. 2009, 38, 1119-38





S.A. Manley, *et al.* *J. Biol. Inorg. Chem.* 2009, 14, 61-74





0.2 µg/mL
2.0 µg/mL
200 µg/mL

metallomics tool

J.L. Goméz-Ariza, *et al.* *Metallomics* 2011, 3, 566-577
Y.H. Huang, *et al.* *J. Cell. Biochem.* 2006, 98, 577-589

conclusion



emerges as a versatile tool to study interactions of:

toxic metals with proteins and SMW compounds bottom up

toxic metals in whole plasma using a metallomics approach top down

- **fundamentally new insight to advance the toxicology of metals in the bloodstream**
- **modulate the metabolism of toxic metal species by dietary additives to increase their excretion**

acknowledgements

- **students:**

  past:
  A.J. Percy, MSc 2006
  S.A. Manley, MSc 2008
  K.L. Pei, MSc 2009
  E.Z. Jahromi, PhD 2013
  T.T. Morris, MSc 2014
  M. Sooriyaarachchi, PhD 2015

  present:
  M.A. Gibson, MSc
  S. Sarpong-Kumankomah, PhD
  A.E. North, CHEM 502



- **collaborators:**
  G.N. George & I.J. Pickering, University of Saskatchewan, SK, Canada

- **funding:**

NSERC CRSNG Canada

Grand Challenges Canada
Grands Défis Canada
BOLD IDEAS FOR HUMANITY.
DES IDÉES COURAGEUSES POUR L'HUMANITÉ.

CIHR - THRUST
CIHR Training grant in Health Research Using Synchrotron Techniques

RUH FOUNDATION


thank you
merci
danke
謝謝
gracias
teşekkür ederim
ngiyabonga
obrigado
dziękuję
bedankt
go raibh maith agat
sukriya
kop khun krap
terima kasih
grazie
arigatô
dakujem
tapadh leat
mochchakkeram
mauruuru
hvala
sagolun
takk
tack
merci
спасибо
рахмат
Баярлалаа
faafetai lava
kiitos
dankie
dhanyavad
köszönöm
dank je
misaotra
matondo
paldies
grazzi
mahalo
хвала
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obrigada
murakoze
tenki
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akun
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chnorakaloutioun
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gràcies
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nandri
bayarlalaa
grâçie
enkosi