EUROPEAN UREMIC TOXIN WORK GROUP (EUTox)

SUMMARY OF ACTIVITIES 2000-2004

R Vanholder

ESAO Meeting in Warsaw, 8-11 September 2004

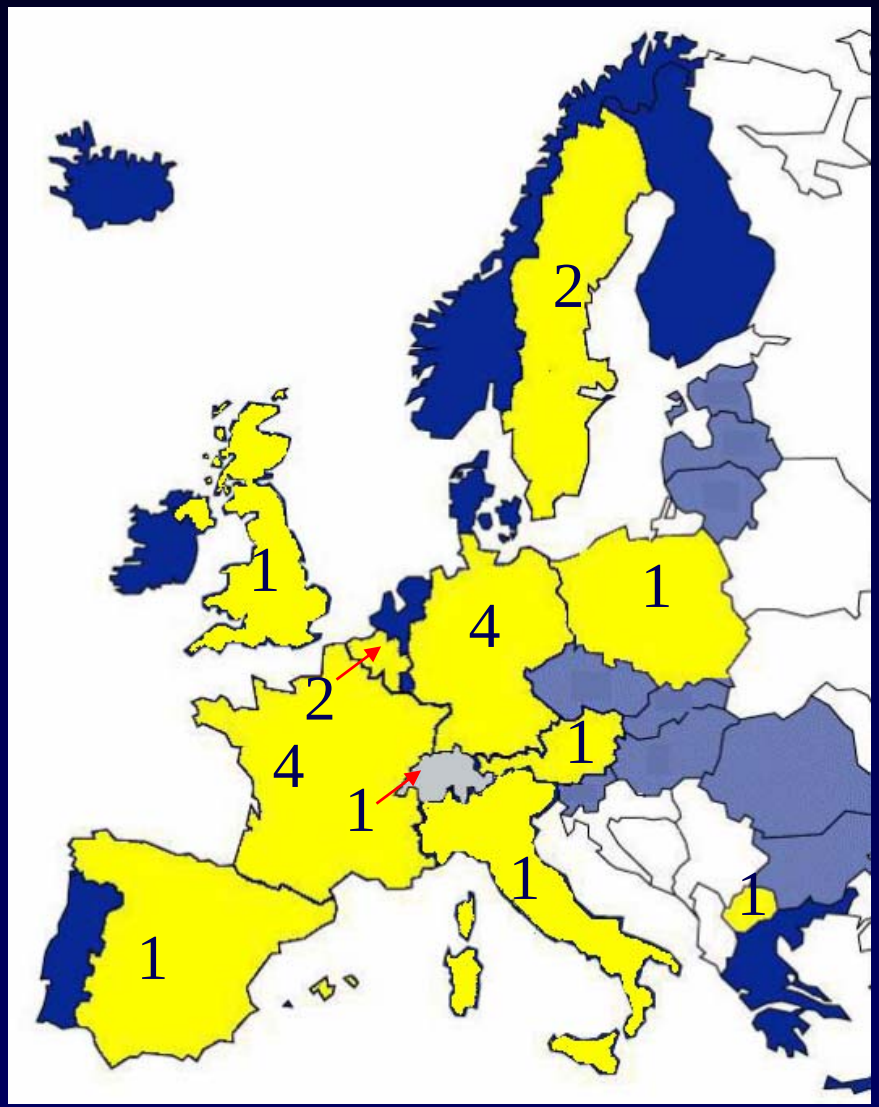
MEMBERS OF THE EUTox GROUP

- A Argiles
- J Beige
- P Brunet
- G Cohen
- PP De Deyn
- B Descamps-Latscha
- T Henle
- S Herget-Rosenthal
- J Jankowski
- A Jörres
- ZA Massy
- M Rodriguez
- G Spasovski
- B Stegmayr
- P Stenvinkel
- R Vanholder
- C Wanner
- A Wiecek
- W Zidek

- Amgen
- Baxter Healthcare
- Fresenius Medical Care
- Gambro
- Genzyme
- Membrana
- Nipro Europe
- Roche

MEMBERS OF THE EUTox GROUP

Number of members from differnt countries



Industrial partners

1. **Development of extracorporeal treatment systems and their improvement**
   - **Baxter Healthcare**
   - **Gambro**
   - **Membrana**
   - **Nipro Europe**
2. **Extracorporeal treatment systems; bioartificial reactors; regenerative medicine**
   - **Fresenius Medical Care**

Industrial partners

3. Treatment with erythropietin and analogues; calcimimetics
   - Amgen
4. Treatment with erythropoietin; diagnostics and markers; vitamin D treatment; medical treatment
   - Roche
5. Peroral adsorption; enzymatic treatment
   - Genzyme

Academic institutes

1. **Production and preparation of the molecules**

   Vanholder (Belgium); Brunet (France); Descamps-Latscha (France); Cohen/Hörl (Austria); Henle (Germany); Jörres (Germany); Jankowski (Germany);Massy (France); Rodriguez (Spain)

Academic institutes

2. **Study patho-physiologic mechanisms and elements**

   Vanholder (Belgium);Argiles (France); Brunet (France); De Deyn (Belgium); Descamps-Latscha (France); Henle (Germany); Hörl (Austria); Jörres (Germany); Massy (France); Rodriguez (Spain); Herget-Rosenthal (Germany); Spasovski (Macedonia); Stenvinkel (Sweden); Wiecek (Poland); Jankowski (Germany);

Academic institutes

3. Clinical evaluation

Vanholder (Belgium);Argiles (France); Brunet (France); Descamps-Latscha (France); Hörl (Austria); Jörres (Germany); Massy (France); Rodriguez (Spain); Spasovski (Macedonia); Stenvinkel (Sweden); Wiecek (Poland);

PREVIOUS MEETINGS OF THE EUTox GROUP

Place (Date)	Main purposes
Lausanne, Switzerland (2000)	• General work plan • Planning common review publication
Paris, France (2001)	• Writing common review publication • Planning common research • Set-up e-communication system
Cologne, Germany (2001)	• Finalisation common review publication • Further elaboration e-communication • Development website

PREVIOUS MEETINGS OF THE EUTox GROUP

Place (Date)	Main purposes
Gent, Belgium (2001)	• Planning common research • Molecules and concentrations • Development website
Montpellier, France (2002)	• Planning strategic research standardisation • Preparation Expression of Interest FP-6 • Development concept clinical study
Vicenza, Italy (2002)	• Planning strategic research standardisation • Finalisation Expression of Interest FP-6

PREVIOUS MEETINGS OF THE EUTox GROUP

Place (Date)	Main purposes
Würzburg, Germany (2002)	• Planning *in vitro* research • Planning FP-6 • Extension protocol clinical study
Gent, Belgium (2002)	• Preparation writing FP-6-project
Cordoba, Spain (2002)	• Finalisation FP-6 project • Elaboration protocol clinical study • Standardisation of preparation of solutes

PREVIOUS MEETINGS OF THE EUTox GROUP

Place (Date)	Main purposes
Vienna, Austria (2003)	• First *in vitro* results • Results of „Master of molecule concept“
Niedernberg, Germany (2003)	• Finalisation concept interactive web-based database • Finalisation of „Master of molecule concept“
Marseille, France (2004)	• *In vitro* results • Preparation of review publication

FINALIZED PUBLICATIONS I

Vanholder et al.

Uremic toxicity: present state of the art

Int J Artif Org, 24, 695-725, 2001

Vanholder et al.

Uraemic toxins and cardiovascular disease

Nephrol Dial Transplant, 18, 463-466, 2003

UREMIC TOXINS WITH VASCULAR IMPACT

Polymorphnuclear Neutrophils

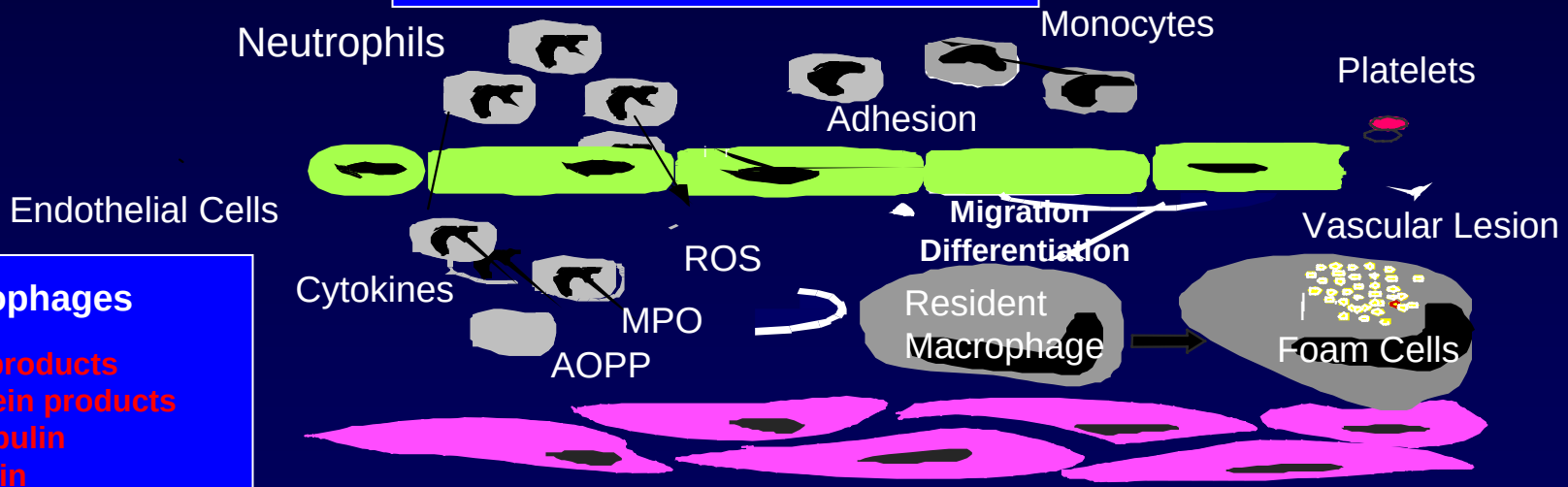
Advanced glycation products
Advanced oxidation protein products
Angiogenin (DIP I)
Complement factor D (DIP II)
Cytokines
Ig Light chains
Leptin

Endothelial Cells

Advanced glycation products
Advanced oxidation protein products
ß2-microglobulin
Cytokines
Homocysteine
Leptin
Oxalic Acid
Oxidized LDL

Platelets

Cytokines
Leptin



Monophages/Macrophages

Advanced glycation products
Advanced oxidation protein products
AGE-ß2-microglobulin
ß2-microglobulin
Cytokines
Homocysteine
Leptin

Smooth muscle cells

ß2-microglobulin
Homocysteine

Vanholder et al, IJAO, 24, 695-725, 2001

FINALIZED PUBLICATIONS II

Vanholder et al.

New insights in uremic toxins

Kidney Int, 63 (Suppl 84), S6-S10, 2003

Vanholder et al.

Review on uremic toxins: classification, concentration and interindividual variablility

Kidney Int, 63, 1934-1943, 2003

Table 1. Free water-soluble low-molecular-weight solutes (N = 45)

Solute	C_N	C_U	C_{MAX}	MW	Ref	Group
1-methyladenosine *μg/L*	17.1 ± 5.1/10	104.0 ± 56.2/17	216.4	281	[12]	Ribonucleosides
1-methylguanosine *μg/L*	13.7 ± 16.9/10	41.6 ± 23.8/17	89.2	297	[12]	Ribonucleosides
1-methylinosine *μg/L*	13.5 ± 3.9/10	620.4 ± 203.4/14	1027.2	282	[12]	Ribonucleosides
ADMA *mg/L*	0.2 ± 0.06/6	1.6 ± 1.2/10	7.3[a]	202	[13, 14]	Guanidines
α-keto-δ-guanidinovaleric acid *μg/L*	<30.2/66	—	140.4[a]	151	[15]	Guanidines
α-*N*-acetylarginine *μg/L*	18.1 ± 24.8/16	328.3 ± 142.6/13	4580.0[a]	216	[16, 17]	Guanidines
Arab(in)itol *mg/L*	<0.6/33	15.0 ± 9.0/12	33.0	152	[18, 19]	Polyols
Argininic acid *μg/L*	<77.0/66	80.5 ± 56.0/11	197.8[a]	175	[15, 16]	Guanidines
Benzylalcohol *mg/L*	—	27.0 ± 50.7/17	187.9[a]	108	[20]	
β-guanidinopropionic acid *μg/L*	<3.3/24	28.8 ± 18.3/29	65.4	131	[21]	Guanidines
β-lipotropin *ng/L*	<55.3/10	62.7/22	108.8[a]	461	[22]	Peptides
Creatine *mg/L*	9.7 ± 3.3/24	134.0 ± 30.3/29	235.8[a]	131	[21]	Guanidines
Creatinine *mg/L*	<12.0/23	136.0 ± 46.0/19746	240.0[a]	113	[23, 24]	Guanidines
Cytidine *μg/L*	<468.0	683.3 ± 287.8/7	1263.6[a]	234	[25]	Purines
Dimethylglycine *μg/L*	<381.1/33	576.8/18	1040.3[a]	103	[26]	
Erythritol *mg/L*	<0.7/33	9.8 ± 14.0/12	37.0[a]	122	[18, 19]	Polyols
γ-guanidinobutyric acid *μg/L*	<3.6/24	33.3 ± 16.0/30	1750.0[a]	145	[27, 17]	Guanidines
Guanidine *μg/L*	<11.8/16	172.9 ± 83.8/13	800.0[a]	59	[16, 17]	Guanidines
Guanidinoacetic acid *μg/L*	222.3 ± 79.6/24	383.8 ± 143.9/29	693.8[a]	117	[21]	Guanidines
Guanidonosuccinic acid *mg/L*	0.03 ± 0.01/16	6.5 ± 3.4/13	47.0[a]	175	[16, 17]	Guanidines
Hypoxanthine *mg/L*	1.5 ± 0.5/145	2.0 ± 1.6/65	5.3	136	[28, 29]	Purines
Malondialdehyde *μg/L*	257.7 ± 81.7/30	428.8 ± 170.4/16	769.6	71	[30]	
Mannitol *mg/L*	<1.3/33	26.0 ± 25.0/12	76.0	182	[18, 19]	Polyols
Methylguanidine *μg/L*	<7.3/24	773.8 ± 508.8/5	1820.0[a]	73	[21, 17]	Guanidines
Myoinositol *mg/L*	<10.0/8	94.0 ± 69.0/12	232.0	180	[18]	Polyols
N^2,N^2-dimethylguanosine *μg/L*	9.0 ± 4.7/10	236.4 ± 89.7/14	415.8	311	[12]	Ribonucleosides
N^4-acetylcytidine *μg/L*	57.0 ± 17.1/10	159.6 ± 30.8/14	221.2	285	[12]	Ribonucleosides
N^6-methyladenosine *μg/L*	18.5 ± 8.4/10	70.3 ± 53.3/17	176.9	281	[12]	Ribonucleosides
N^6-threonylcarbamoyladenosine *μg/L*	35.5 ± 27.2/10	378.0 ± 151.2/17	680.4	378	[12]	Ribonucleosides
Orotic acid *mg/L*	0.5 ± 1.4/30	6.7 ± 16.0/22	38.7	174	[31]	Pyrimidines
Orotidine *mg/L*	1.2 ± 1.6/30	20.2 ± 13.5/22	47.2	288	[31]	Pyrimidines
Oxalate *mg/L*	0.3 ± 0.1/8	4.9 ± 1.4/8	7.6	90	[32]	
Phenylacetylglutamine *mg/L*	<4.7	53.3 ± 44.7/6	120.6[a]	264	[33]	
Pseudouridine *mg/L*	0.5 ± 5.8/30	13.1 ± 21.4/7	86.6[a]	244	[25, 31]	Ribonucleosides
SDMA *μg/L*	76.1 ± 21.0/66	640.3 ± 212.1/38	1232.2[a]	202	[15]	Guanidines
Sorbitol *mg/L*	<0.4/33	3.1 ± 2.1/12	7.3	182	[18, 19]	Polyols
Taurocyamine *μg/L*	<52.2/24	—	121.8[a]	174	[17]	Guanidines
Threitol *μg/L*	<319.6/33	990.0 ± 920.0/12	5697.4[a]	122	[18, 19]	Polyols
Thymine *mg/L*	—	2.8 ± 4.2/22	11.2	126	[31]	Pyrimidines
Uracil *μg/L*	<224.0	252.0 ± 154.6/7	448.0[a]	112	[25]	Purines
Urea *g/L*	<0.4/23	2.3 ± 1.1/16	4.6[a]	60	[24]	
Uric acid *mg/L*	<67.2	83.4 ± 44.5/7	146.7[a]	168	[25]	Purines
Uridine *mg/L*	1.5 ± 1.3/30	9.8 ± 11.4/22	32.6	244	[31]	Pyrimidines
Xanthine *mg/L*	0.5 ± 1.4/180	1.5 ± 0.8/65	3.0	152	[28, 29]	Purines
Xanthosine *μg/L*	23.9 ± 12.8/10	96.6 ± 62.9/11	222.4	284	[12]	Ribonucleosides

Abbreviations are: C_N, normal concentration; C_U, mean/median uremic concentration; C_{MAX}, maximal uremic concentration; MW, molecular weight; ref, reference; ADMA, asymmetrical dimethylarginine; SDMA, symmetrical dimethylarginine. The underlined numbers behind the slash point to the number of data on which the means or medians have been obtained. No underlined number indicates that no data about the number of samples were available. Normal values are reported as means ± SD, or in the case of a single value as a maximum (accompanied by <); uremic values are reported as means ± SD or, in the case of a single value, as a median.

[a] C_{MAX} values are original data (all other values were calculated as mean + 2 SD based on C_U)

Vanholder et al, KI, 63, 1934-1943, 2003

Table 1. Free water-soluble low-molecular-weight solutes (N = 45)

Solute	C_N	C_U	C_{MAX}	MW	Ref	Group
1-methyladenosine *μg/L*	17.1 ± 5.1/10	104.0 ± 56.2/17	216.4	281	[12]	Ribonucleosides
1-methylguanosine *μg/L*	13.7 ± 16.9/10	41.6 ± 23.8/17	89.2	297	[12]	Ribonucleosides
1-methylinos						
ADMA *mg/*						
α-keto-δ-gua						
α-*N*-acetylar						
Arab(in)itol						
Argininic ac						
Benzylalcoh						
β-guanidinop						
β-lipotropin						
Creatine *mg*						
Creatinine *m*						
Cytidine *μg/*						
Dimethylgly						
Erythritol *m*						
γ-guanidinot						
Guanidine *μ*						
Guanidinoac						
Guanidonos						
Hypoxanthi						
Malondialde						
Mannitol *mg*						
Methylguani						
Myoinositol						
N^2,N^2-dimeth						
N^6-acetylcyti						
N^6-methylad						
N^6-threonylc						
Orotic acid						
Orotidine *m*						
Oxalate *mg/*						
Phenylacetyl						
Pseudouridi						
SDMA *μg/L*						
Sorbitol *mg/*						
Taurocyami						
Threitol *μg/*						
Thymine *mg*						
Uracil *μg/L*						
Urea *g/L*						
Uric acid *mg*						
Uridine *mg/*						
Xanthine *mg*						
Xanthosine						

Abbreviatio
ADMA, asym
means or med
means ± SD,
median.
[a]C_{MAX} value

Table 2. Protein-bound solutes (N = 25)

Solute	C_N	C_U	C_{MAX}	MW	Ref	Group
2-methoxyresorcinol *μg/L*	—	19.6 ± 81.2/17	322.0[a]	140	[20]	Phenols
3-deoxyglucosone *mg/L*	0.3 ± 0.1/30	1.7 ± 1.0/27	3.5	162	[34]	AGE
CMPF *mg/L*	7.7 ± 3.3/7	61.0 ± 16.5/15	94.0[a]	240	[35]	
Fructoselysine *mg/L*	—	58.1 ± 10.8/10	79.7	308	[10]	AGE
Glyoxal *μg/L*	67.0 ± 20.0	221.0 ± 28.0/20	277.0	58	[36]	AGE
Hippuric acid *mg/L*	<5.0	247.0 ± 112.0/7	471.0	179	[37]	Hippurates
Homocysteine *mg/L*	<1.7/24	8.1 ± 1.6/7	26.4[a]	135	[38–40]	
Hydroquinone *μg/L*	—	50.6 ± 84.7/17	286.0[a]	110	[20]	Phenols
Indole-3-acetic acid *μg/L*	17.5 ± 17.5/7	875.0 ± 560.0/42	9076.9[a]	175	[41,42]	Indoles
Indoxyl sulfate *mg/L*	0.6 ± 5.4/40	53.0 ± 91.5/20	236.0	251	[35]	Indoles
Kinurenine *μg/L*	<391/7	686.4 ± 178.9/21	952.6	208	[43]	Indoles
Kynurenic acid *mg/L*	<1.0	—	9.5[a]	189	[44]	Indoles
Leptin *μg/L*	8.4 ± 6.7/56	72.0 ± 60.6/8	490.0[a]	16000	[45, 46]	Peptides
Melatonin *ng/L*	26.5 ± 7.1/35	175.8 ± 130.2/13	436.2	126	[47]	Indoles
Methylglyoxal *μg/L*	47.0 ± 12.0/15	110.0 ± 18.0/20	146.0	72	[36]	AGE
N^{ε}–(carboxymethyl)lysine *mg/L*	1.1 ± 0.3/24	4.3 ± 1.3/44	6.9	204	[11]	AGE
p-cresol *mg/L*	0.6 ± 1.0/12	20.1 ± 10.3/20	40.7	108	[48]	Phenols
Pentosidine *μg/L*	51.6 ± 18.8/19	896.0 ± 448.0/24	2964.0[a]	342	[49]	AGE
Phenol *mg/L*	0.6 ± 0.2/12	2.7 ± 3.9/10	10.5	94	[48]	Phenols
P-OHhippuric axid *mg/L*	—	18.3 ± 6.6/13	31.5	195	[50]	Hippurates
Putrescine *μg/L*	21.1 ± 7.9/10	77.4 ± 27.3/25	132.0	88	[51]	Polyamines
Quinolinic acid *mg/L*	0.1 ± 0.05/10	1.5 ± 0.9/54	3.3	167	[52]	Indoles
Retinol-binding protein *mg/L*	<80	192.0 ± 78.0/112	369.2[a]	21200	[53]	Peptides
Spermidine *μg/L*	—	97.2 ± 45.0/25	187.2	145	[51]	Polyamines
Spermine *μg/L*	—	18.2 ± 16.2/25	66.7[a]	202	[51]	Polyamines

Abbreviations are: C_N, normal concentration; C_U, mean/median uremic concentration; C_{MAX}, maximal uremic concentration; MW, molecular weight; ref, reference; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid; AGE, advanced glycation end products. The underlined numbers behind the slash point to the number of data on which the means or medians have been obtained. No underlined number indicates that no data about the number of samples were available. Normal values are reported as means ± SD, or in the case of a single value as a maximum (accompanied by <); uremic values are reported as means ± SD.

[a]C_{MAX} values are original data (all other values were calculated as mean + 2 SD based on C_U).

Vanholder et al, KI, 63, 1934-1943, 2003

Table 1. Free water-soluble low-molecular-weight solutes (N = 45)

Solute	C_N	C_U	C_{MAX}	MW	Ref	Group
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1-methylguanosine *μg/L*	13.7 ± 16.9/10	41.6 ± 23.8/17	89.2	297	[12]	Ribonucleosides
1-methylinos						
ADMA *mg/*						
α-keto-δ-gua						
α-*N*-acetylar						
Arab(in)itol						
Argininic ac						
Benzylalcoh						
β-guanidinop						
β-lipotropin						
Creatine *mg*						
Creatinine *m*						
Cytidine *μg/*						
Dimethylgly						
Erythritol *m*						
γ-guanidinot						
Guanidine *μ*						
Guanidinoac						
Guanidonos						
Hypoxanthi						
Malondialde						
Mannitol *mg*						
Methylguani						
Myoinositol						
N^2,N^2-dimeth						
N^4-acetylcyti						
N^6-methylad						
N^6-threonylc						
Orotic acid						
Orotidine *m*						
Oxalate *mg/*						
Phenylacetyl						
Pseudouridi						
SDMA *μg/L*						
Sorbitol *mg/*						
Taurocyami						
Threitol *μg/*						
Thymine *mg*						
Uracil *μg/L*						
Urea *g/L*						
Uric acid *mg*						
Uridine *mg/*						
Xanthine *mg*						
Xanthosine						

Abbreviatio
ADMA, asym
means or med
means ± SD,
median.
[a]$C_{\_\_}$ value

Table 2. Protein-bound solutes (N = 25)

Solute	C_N	C_U	C_{MAX}	MW	Ref	Group
2-methoxyresorcinol						
3-deoxyglucosone *mg*						
CMPF *mg/L*						
Fructoselysine *mg/L*						
Glyoxal *μg/L*						
Hippuric acid *mg/L*						
Homocysteine *mg/L*						
Hydroquinone *μg/L*						
Indole-3-acetic acid *μ*						
Indoxyl sulfate *mg/L*						
Kinurenine *μg/L*						
Kynurenic acid *mg/L*						
Leptin *μg/L*						
Melatonin *ng/L*						
Methylglyoxal *μg/L*						
N^2–(carboxymethyl)ly						
p-cresol *mg/L*						
Pentosidine *μg/L*						
Phenol *mg/L*						
P-OHhippuric axid *m*						
Putrescine *μg/L*						
Quinolinic acid *mg/L*						
Retinol-binding prote						
Spermidine *μg/L*						
Spermine *μg/L*						

Abbreviations are: $C_{\_\_}$
CMPF, 3-carboxy-4-meth
of data on which the me
values are reported as m
[a]$C_{\_\_}$ values are origi

Table 3. Middle molecules (N = 22)

Solute	C_N	C_U	C_{MAX}	MW	Ref	Group
Adrenomedullin *ng/L*	13.2 ± 4.6/17	41.8 ± 19.7/29	81.2	5729	[54]	Peptides
Atrial natriuretic peptide *ng/L*	28.0 ± 12.2/23	202.0 ± 117.3/27	436.6	3080	[55]	Peptides
β_2-microglobulin *mg/L*	<2.0	55.0 ± 7.9/10	100.0[a]	11818	[53, 56]	Peptides
β-endorphin *ng/L*	<173.3/10	301.5/22	492.0[a]	3465	[22]	Peptides
Cholecystokinin *ng/L*	<20.0	45.9 ± 32.3/38	131.5[a]	3866	[57]	Peptides
Clara cell protein (CC16) *mg/L*	<0.1	3.3 ± 2.0/112	12.5[a]	15800	[53]	Peptides
Complement factor D *mg/L*	1.9 ± 0.5/5	19.8 ± 4.1/5	26.0[a]	23750	[58]	
Cystatin C *mg/L*	<1.6	11.8 ± 3.0/112	20.0[a]	13300	[53]	Peptides
Degranulation inhibiting protein I[c] *μg/L*	321.7 ± 59.7/23	713.7 ± 390.0/125	1631.4[a]	14100	[59][b]	Peptides
Delta-sleep inducing peptide *μg/L*	—	1.5 ± 0.9/7	3.3	848	[60]	Peptides
Endothelin *ng/L*	20.8 ± 3.8/23	63.0 ± 33.2/12	129.4	4283	[55]	Peptides
Hyaluronic acid *μg/L*	<124.0/86	215.0 ± 257.0/184	1843.0[a]	25000	[61]	Peptides
Interleukin-1β *ng/L*	<160.0/15	428.0 ± 134.0/29	1700.0	32000	[62]	Cytokines
Interleukin-6 *ng/L*	13.3 ± 3.1/28	92.3 ± 117.9/230	328.1	24500	[63]	Cytokines
κ-Ig light chain *mg/L*	34.0 ± 15.0/15	70.0 ± 60.9/104	287.0[a]	25000	[64]	Peptides
λ-Ig light chain *mg/L*	31.0 ± 11.2/15	87.0 ± 60.9/104	328.0[a]	25000	[64]	Peptides
Leptin *μg/L*	8.4 ± 6.7/56	72.0 ± 60.6/8	490.0[a]	16000	[45, 46]	Peptides
Methionine-enkephalin *ng/L*	<18.3/10	32.2/22	75.5[a]	555	[22]	Peptides
Neuropeptide Y *ng/L*	<80.0	64.9 ± 25.5/19	115.9	4272	[57]	Peptides
Parathyroid hormone *μg/L*	<0.06	1.2 ± 0.6/10	2.4	9225	[65]	Peptides
Retinol-binding protein *mg/L*	<80	192.0 ± 78.0/112	369.2[a]	21200	[53]	Peptides
Tumor necrosis factor-α *ng/L*	13.3 ± 3.0/28	114.0 ± 147.0/230	408.0	26000	[63, 66]	Cytokines

Abbreviations are: C_N, normal concentration; C_U, mean/median uremic concentration; C_{MAX}, maximal uremic concentration; MW, molecular weight; ref, reference. The underlined numbers behind the slash point to the number of data on which the means or medians have been obtained. No underlined number indicates that no data about the number of samples were available. No number indicates that no n value was given. Normal values are reported as mean ± SD, or in the case of a single value as a maximum (accompanied by <); uremic values are reported as mean ± SD or, in the case of a single value, as a median.

[a] C_{MAX} values are original data (all other values were calculated as mean + 2 SD based on C_U)

[b] S Schmaldienst, Vienna: personal communication

[c] Degranulation inhibiting protein I corresponds to angiogenin

Vanholder et al, KI, 63, 1934-1943, 2003

UREMIC SOLUTES LISTED

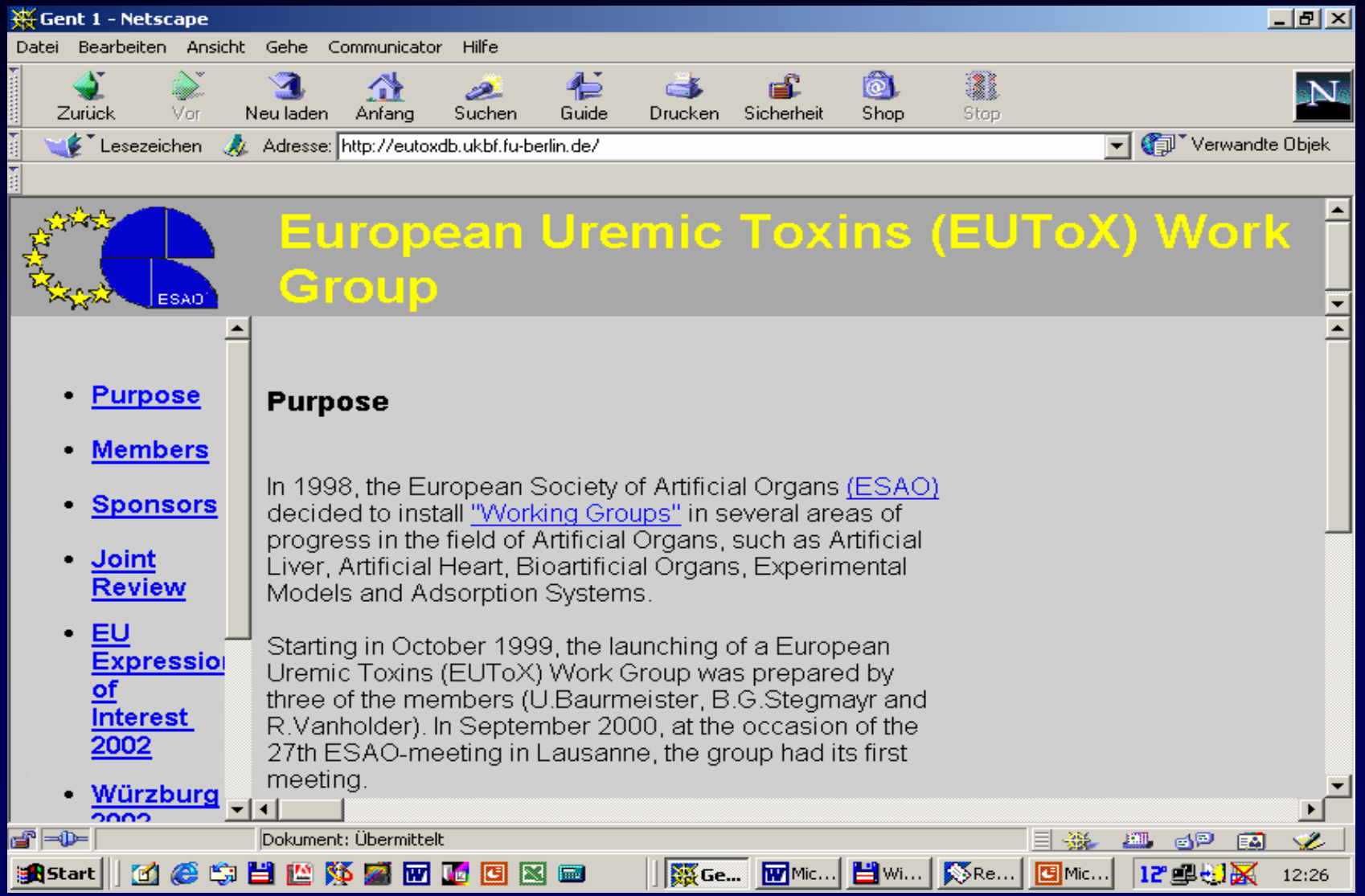
Small water soluble compounds (<500D): 1-Methyladenosine, 1-Methylguanosine, 1-Methylinosine, ADMA, γ-Keto-guanidinovaleric acid, α-N-acetylarginine, Arab(in)itol, Argininic acid, Benzylalcohol, ß-guanidinopropionic acid, Creatine, Creatinine, Cytidine, Dimethylglycine, Erythritol, γ-guanidinobutyric acid, Guanidine, Guanidinoacetic acid, Guanidonosuccinic acid, Hypoxanthine, Mannitol, Methylguanidine, Myoinositol, N4-acetylcytidine, N6-methyladenosine, Orotic acid, Orotidine, Oxalate, Phenylacetylglutamine, Pseudouridine, SDMA, Sorbitol, Taurocyamine, Threitol, Thymine, Uracil, Urea, Uric acid, Uridine, Xanthine, Xanthosine

Protein-bound molecules: 2-Methoxyresorcinol, 3-deoxyglucosone, CMPF, Dimethylguanosine, Fructoselysine, Glyoxal, Hippuric acid, Homocysteine, Hydroquinone, Indole-3-acetic acid, Indoxyl sulfate, Interleukin 1ß, Interleukin 6, Kinurenine, Kynurenic acid, Leptin, Melatonin, Methylglyoxal, N–(carboxymethyl)lysine, P-cresol, Pentosidine, Phenol, Phenylacetic acid, Phenylethylamine, P-OHhippuric acid, Putrescine, Quinolinic acid, Retinol binding protein, S-nitrosothiol, Spermidine, Spermine, Thiocyanate, Tumor Necrosis Factor α

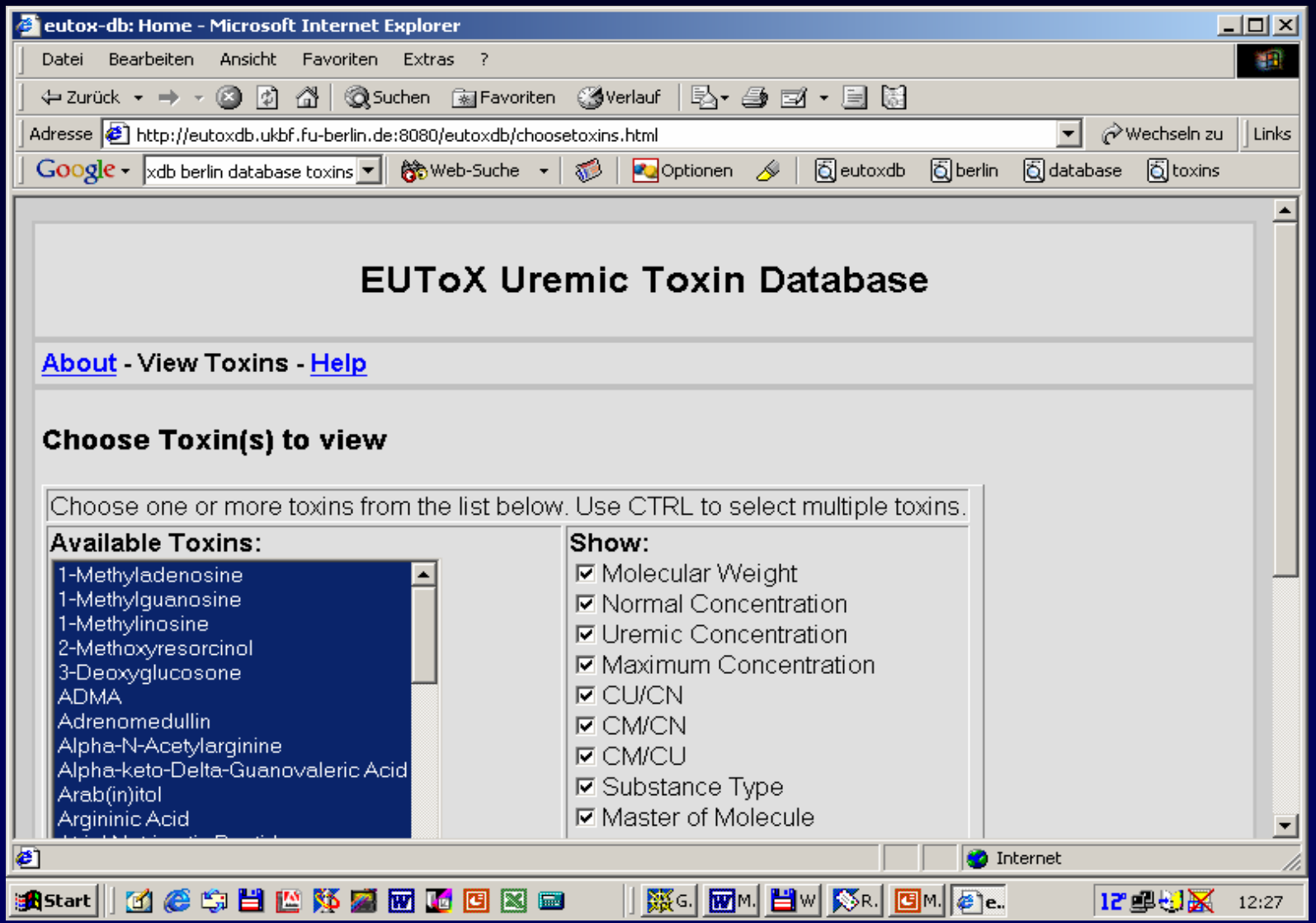
Middle molecules (>500D): Adrenomedullin, Atrial natriuretic peptide, β2-microglobulin, β-endorphin, Cholecystokinin, Clara cell protein, Complement factor D, Cystatin C, Degranulation inhibiting protein I, Delta-sleep inducing peptide, Endothelin (ng/L),Ghrelin, Hyaluronic acid, Interleukin 1ß, Interleukin 6, Interleukin-18, κ-Ig light chain, λ-Ig light chain, Leptin, MC-SF, Methionine-enkephalin, Neuropeptide Y, Orexin A, Parathyroid hormone, Retinol binding protein, Tumor Necrosis Factor α

Vanholder et al, KI, 63, 1934-1943, 2003

www.Uremic-Toxins.org



www.Uremic-Toxins.org > Uremic Toxins Database



PUBLICATIONS BEING PREPARED

1. **Review of publications stressing enhanced cardio-vascular risk in renal disease.**

2. **Review of potential, “less traditional” risk factors at play in this process.**

3. **Review of therapeutic/preventive approach.**

PUBLICATIONS BEING PREPARED

4. **Review of clinical modifications in patients with renal disease**

5. **Review of different reported concentrations of uremic solutes**

6. **Review of biological/biochemical effects of uremic solutes**

AIMS RESEARCH

1. ***In vitro* studies**

   Identification of uremic toxins responsible for vascular damage (effect on the 4 major cell systems involved: endothelium, leukocytes, thrombocytes, smooth muscle cells)

2. ***In vivo* *studies***

   Identification of mechanisms leading to vascular damage in CRF

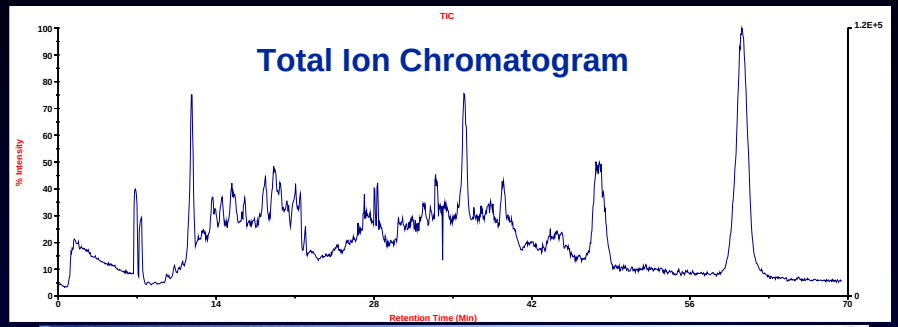
AIMS RESEARCH

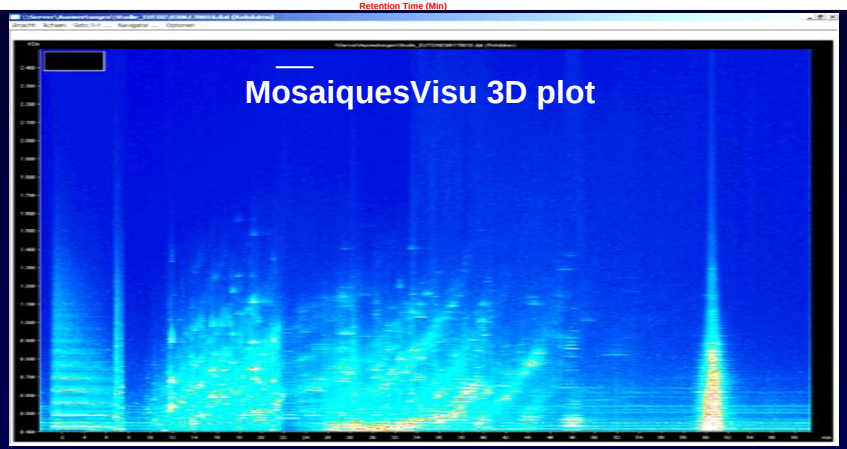
3. **Genome analysis and proteome analysis**

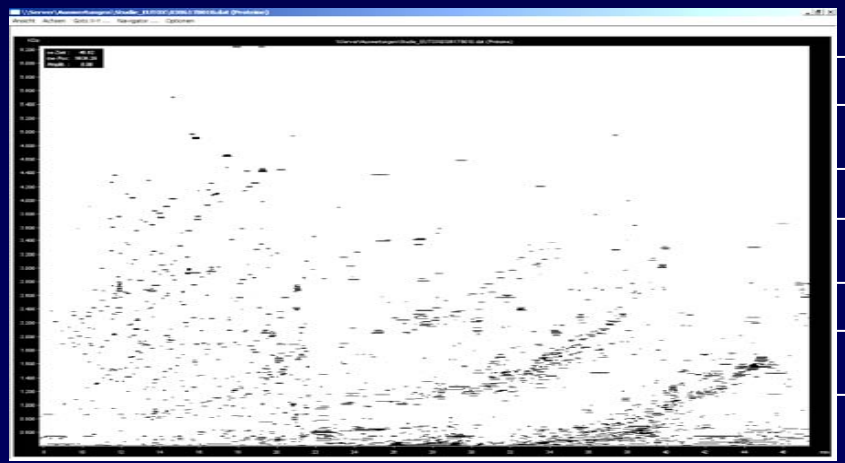
   - Identification of unknown uraemic toxins

   - Identification of unknown pathophysiologic mechanisms

Sample 1: DC dialysate with F10 membrane

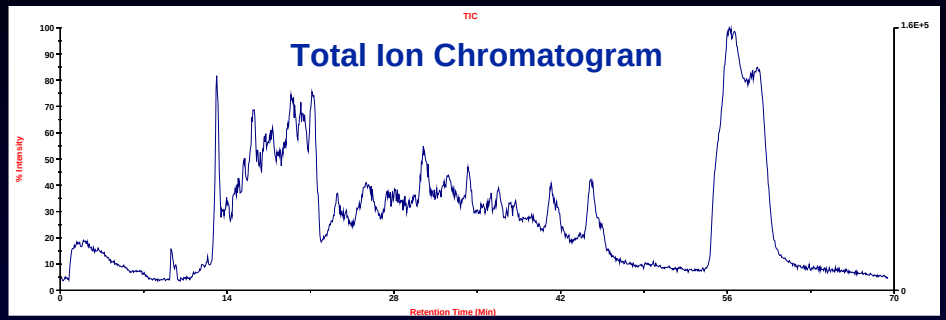


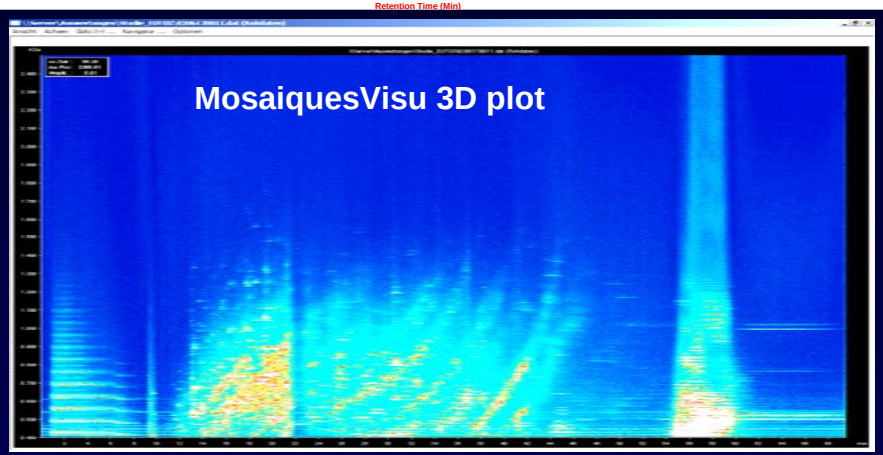


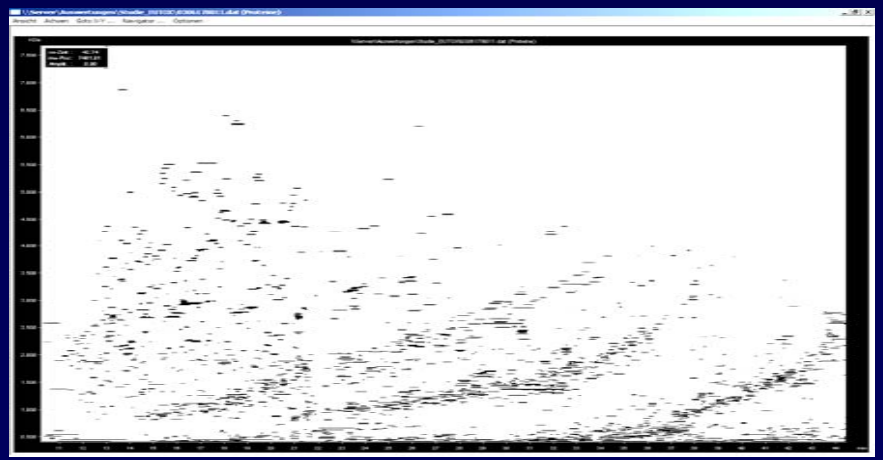


CE-retention time (min)

Sample 2: DC dialysate with F70 membrane







CE-retention time (min)

mass/charge(KD/z

7 kD
6 kD
5 kD
4 kD
3 kD
2 kD
1 kD

CURRENT RESEARCH ACTIVITIES

Investigation of effects of uremic toxins on:

- **Endothelial cell function**
- **Thrombocyte aggregation**
- **NADPH oxidase activity, leukocyte free radical production**
- **Vascular smooth muscle cell reactivity**
- **Tubular cells**
- **Fibroblasts**

CURRENT RESEARCH ACTIVITIES

Preparation of the clinical study:

- **collection of plasma samples of CRF patients**
- **analytical, proteomic and genomic research to elucidate differences in retention and genome pattern between affected and non-affected patients**