

The Amyloid Beta-42/40-Ratio:

The Tool for *In Vitro* Diagnosis of Alzheimer's Disease, Patient Stratification and Drug Monitoring

Overview and Clinical Validation

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the **GENETICS** company, inc.

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Introduction

In the cortex of Alzheimer's disease patients, senile plaques consisting of aggregated Amyloid beta (Abeta) appear as a characteristic pathological hallmark. Abeta, which is nowadays widely accepted as the main culprit in the generation of Alzheimer's disease, is a short peptide of about 40 amino acids. While Abeta40 is the most prominent peptide, Abeta42 is the neurotoxic form and the main component of senile plaques.

The Genetics Company has developed Amyloid beta ELISA kits enabling the highly specific and most sensitive detection of human Amyloid beta 40 and 42 levels in cerebrospinal fluid and many other matrices, including plasma.

The Company's assays for the analysis of cerebrospinal fluid (CSF) are CE-certified and approved as IVD in Europe (**CSF-ELISA kit**). In addition, the Company offers high sensitive research kits (**hs-ELISA kits**) for the analysis of cell culture supernatants or plasma as well as ELISA kits for the analysis of brain tissue samples (**brain-ELISA kits**). Finally, we offer highly sensitive and selective monoclonal Abeta antibodies which are applied to our ELISA kits.

Our assays are used in clinical studies for the monitoring of the efficacy of Amyloid beta-modulating drugs (e.g. by Neurochem and JSW-Research), for the reliable and early *in vitro* diagnosis of Alzheimer's disease (e.g. in diagnostics labs, hospitals, and by the German Competence Network Dementia), and for many applications in the fields of Alzheimer's drug discovery and exploratory research (more than 200 customers worldwide from both industry and Academia).

Our products enable the reliable determination of the Abeta42/40-ratio (or Abeta-ratio) in patients. As summarized herein, several clinical studies have not only validated **the diagnostic accuracy of the Abeta-ratio** but also demonstrate that **the Abeta-ratio is superior to the analysis of Abeta42 alone** as Abeta40 taken into account as an internal reference.

The clinical data with our products also suggest an additional potential of our products with regard to the **stratification of patient groups and drug monitoring tool for clinical studies using Abeta-modulating drugs**. As an example, Study 1 demonstrates how the Abeta-ratio is not only able to identify those MCI patients that will develop AD four years prior inception of the disease but also correctly stratifies patients and controls which would be otherwise wrongly classified by classical neuropsychological tests.

Overview of the Studies

Study number	Authors	Patient groups analyzed	Total number of patients analyzed	Sensitivity	Specificity
1	Hansson et al.	137 MCI	137	MCI developing to AD: 91%	MCI developing to nAD: 91%
2	Wiltfang et al.	74 AD, 28 nAD, 141 MCI to AD, 69 MCI to nAD	312	Abeta-ratio but not Abeta42 alone is able to correctly classify high (potential wrong negatives) and low (potential wrong positives) Abeta load patients	
3	NN	31 AD, 27 MCI, 10 MC, 15 CON	83	AD vs. MC/CON: 83.9%	AD vs. MC/CON: 88%
4	Beyreuther et al.	24 AD, 3 LB, 5 FTLD, 3 SC, 2 VD, 5 AFD, 36 CON	102	AD vs. nAD: 96% AD vs. CON: 92%	AD vs. nAD: 86% AD vs. CON: 91%
5	Lewczuk et al.	22 AD, 11 nAD, 35 CON	68	AD vs. nAD: 95.2% AD vs. CON: 95.2%	AD vs. nAD: 91% AD vs. CON: 80%
6	Lewczuk et al.	9 nAD, 8 MCI, 1 DEP, 1 BP, 1 EM	20	Abeta-ratio is more stable towards influence of pre-analytical factors than Abeta42 alone.	

AD: Alzheimer's disease; AFD: Affective disorders; BP: Bipolar disorders; CON: Controls; DEP: recurrent Depression; EM: Emotionally unstable personality; FTLD: Frontotemporal lobar dementia; LB: Lewy body dementia; MC: Memory complaints; MCI: Mild cognitive impairment; nAD: other dementia/non-healthy controls; SC: Schizophrenia; VD: Vascular dementia.

Study 1

Prediction of Alzheimer's disease using CSF A β 42 and A β 42/A β 40 ratio in patients with mild cognitive impairment

Oskar Hansson, Henrik Zetterberg, Peder Buchhave, Ulf Andreasson, Lennart Minthon, and Kaj Blennow

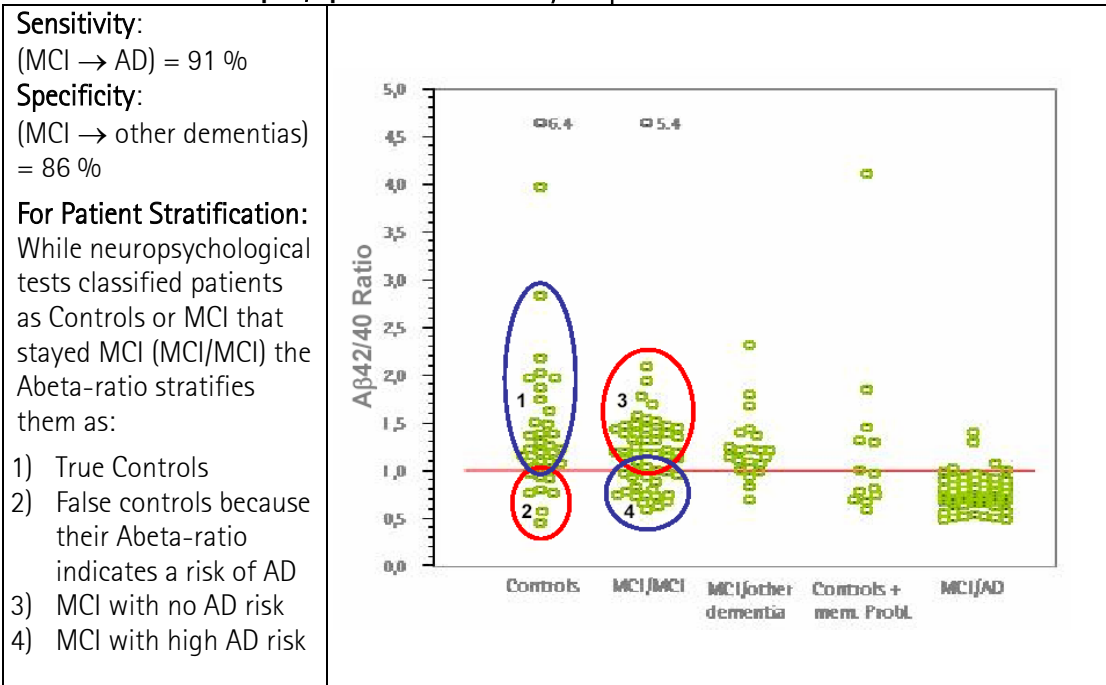
Dement Geriatr Cogn Disord. 2007 Mar; 23: 316-320.

Abstract

Abundant evidence supports an important role for β -amyloid (A β) and its conversion from soluble to insoluble forms in the pathogenesis of Alzheimer's disease (AD). Here, we investigate baseline levels of the 40 and 42 amino acid long A β peptides (A β 40 and -42) in CSF from a cohort of patients with mild cognitive impairment (MCI, n=137) in relation to final diagnosis after 4-6 years follow-up time. CSF A β 42 concentration at baseline and the A β 42/ A β 40 ratio were significantly decreased in the MCI patients who developed AD as compared to cognitively stable MCI patients, and MCI patients who developed other forms of dementia (P<0.001). The baseline levels of A β 40 were similar in all MCI groups but correlated to change in mini mental state examination (MMSE) scores in converters to AD, so that individuals with the lowest A β 40 concentration had the greatest annual decline in MMSE.

The A β 42/A β 40 ratio was superior to A β 42 concentration with regards to identifying incipient AD in MCI (P<0.05). Altogether, the data provide further support for the view that amyloid precursor protein metabolism is disturbed in early sporadic AD and points to the usefulness of the A β 42/A β 40 ratio as a predictive biomarker for AD.

Performance of CSF A β 42/A β 40 ratio to identify incipient AD



Study 2

Amyloid beta peptide ratio 42/40 but not A β 42 correlates with phospho-Tau in patients with low- and high-CSF A β 40 load

Wiltfang J, Esselmann H, Bibl M, Hull M, Hampel H, Kessler H, Frolich L, Schroder J, Peters O, Jessen F, Luckhaus C, Pernecky R, Jahn H, Fiszer M, Maler JM, Zimmermann R, Bruckmoser R, Kornhuber J, Lewczuk P.

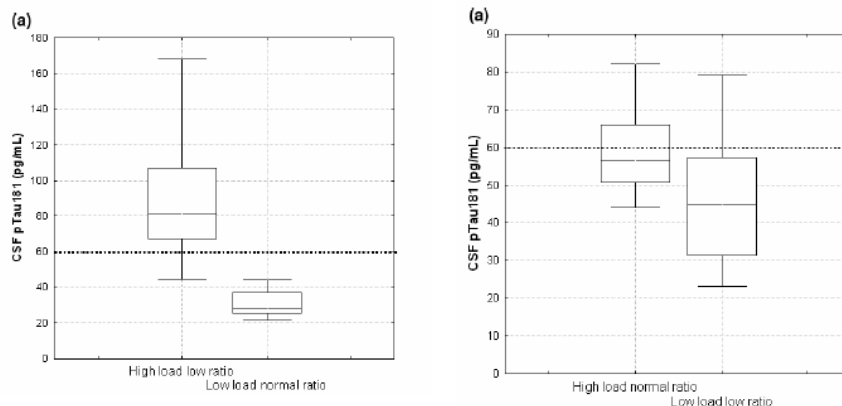
J Neurochem. 2007 May; 101(4): 1053-1059

Abstract

Neurochemical dementia diagnostics (NDD) can significantly improve the clinically based categorization of patients with early dementia disorders, and the cerebrospinal fluid (CSF) concentrations of amyloid beta peptides ending at the amino acid position of 42 (Abeta₄₂ and Abeta₁₋₄₂) are widely accepted biomarkers of Alzheimer's disease (AD). However, in subjects with constitutively high- or low-CSF concentrations of total Abeta peptides (tAbeta), the NDD interpretation might lead to erroneous conclusions as these biomarkers seem to correlate better with the total Abeta load than with the pathological status of a given patient in such cases. In this multicenter study, we found significantly increased CSF concentrations of phosphorylated Tau (pTau₁₈₁) and total Tau in the group of subjects with high CSF Abeta₄₀ concentrations and decreased Abeta₄₂/x-40 concentration ratio compared with the group of subjects with low CSF Abeta₄₀ and normal Abeta ratio ($p < 0.001$ in both cases). Furthermore, we observed significantly decreased Abeta ratio ($p < 0.01$) in the group of subjects with APOE epsilon4 allele compared with the group of subjects without this allele. Surprisingly, patients with low-Abeta₄₀ and the decreased Abeta ratio characterized with decreased pTau¹⁸¹ ($p < 0.05$), and unaltered total Tau compared with the subjects with high Abeta₄₀ and the Abeta ratio in the normal range.

We conclude that the amyloid beta concentration ratio should replace the 'raw' concentrations of corresponding Abeta peptides to improve reliability of the neurochemical dementia diagnosis.

Correlation of p-tau and the A β 42/A β 40 ratio in high and low load A β patients



Study 3

Plasma and cerebrospinal fluid levels of A β 42, A β 40 and A β 42/40 ratio in Alzheimer's disease, mild cognitive impairment and healthy controls

Manuscript in preparation, authors to be announced

The CSF A β 42/A β 40 ratio was the only marker significantly distinguishing MCI from AD patients and the best marker to distinguish AD from healthy (HC) or mental (MC) controls:

AD vs. HC/MC	Sensitivity [%]	Specificity [%]	Overall correct classification [%]
CSF A β 42	87.1	76.0	82.1
CSF A β Ratio	83.9	88.0	85.7
Plasma A β 42	83.9	72.0	78.6
Plasma A β Ratio	80.6	72.0	76.8

Sensitivity, specificity and overall correct classification rates (number of correctly allocated cases divided by number of all cases) are derived from binary logistic regression analyses including CSF and blood marker controlled for age to discriminate between AD patients and comparison subjects.

Furthermore, in this study, plasma A β 42 analyzed by the Company's hs-ELISA kits was significantly changed in MCI vs. controls:

MCI vs. HC/MC	Sensitivity [%]	Specificity [%]	Overall correct classification [%]
CSF A β 42	77.8	56.0	67.3
CSF A β Ratio	66.7	72.0	69.2
Plasma A β 42	77.8	76.0	76.9
Plasma A β Ratio	77.8	60.0	69.2

Sensitivity, specificity and overall correct classification rates (number of correctly allocated cases divided by number of all cases) are derived from binary logistic regression analyses including CSF and blood marker controlled for age to discriminate between AD patients and comparison subjects.

Patient groups:

AD (N = 31) MCI (N = 27)
 MC (N = 10) HC (N = 15)

Study 4

Implementing A β -Ratios into the neurochemical diagnosis of early Alzheimer's disease

Beyreuther et al., manuscript in preparation

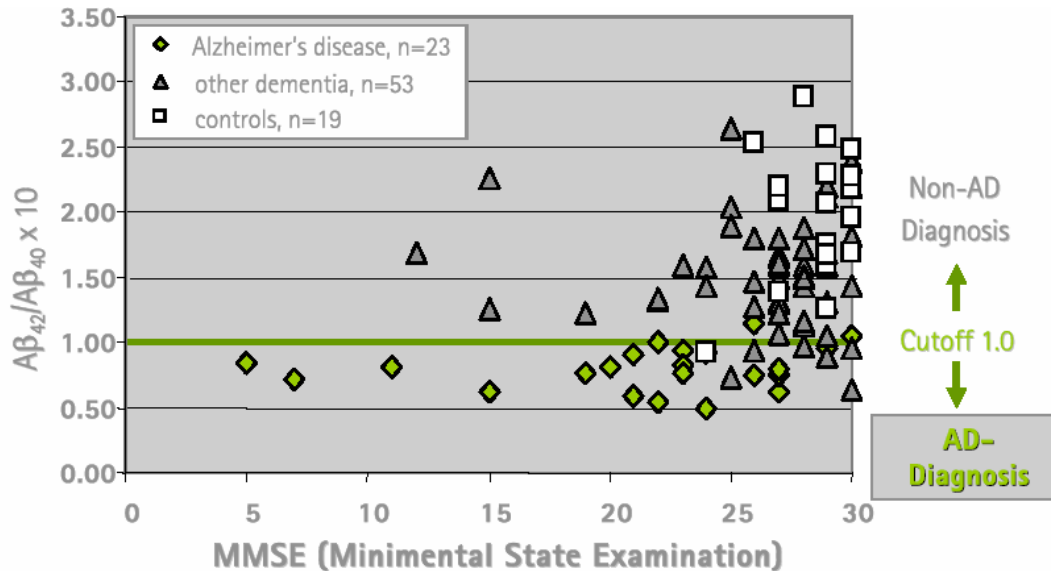
Abstract

Several cerebrospinal fluid amyloid β peptides (A β) and tau proteins have been introduced as biomarkers for Alzheimer's disease (AD). However, insufficient data exist whether building ratios of these markers would implicate additional diagnostic benefit.

We measured cerebrospinal fluid (CSF) concentrations of A β 42, A β 40 and tau by commercially available ELISA in 102 patient samples with AD, healthy and non-healthy control subjects - the latter comprising of heterogeneous psychiatric diagnostic entities. Single markers and calculated ratios thereof were compared. As expected, A β 42-levels decreased in AD subjects.

Although A β 40-levels were similar in patients and controls, a significantly increased diagnostic specificity for the A β 42/40-ratio as compared to single markers and other ratios like the Alzheimer's-Index was achieved. Our conclusion is that the A β 42/40-ratio could substantially support the clinical diagnosis of AD as a routine marker in the laboratory diagnostics.

Comparison of A β 42/A β 40 ratio to MMSE scores:



Diagnostic Accuracy:

AD (N=23) vs	Sensitivity	Specificity
Non-Healthy Controls (N=53)	96%	86%
Healthy Controls (N=19)	92%	91%

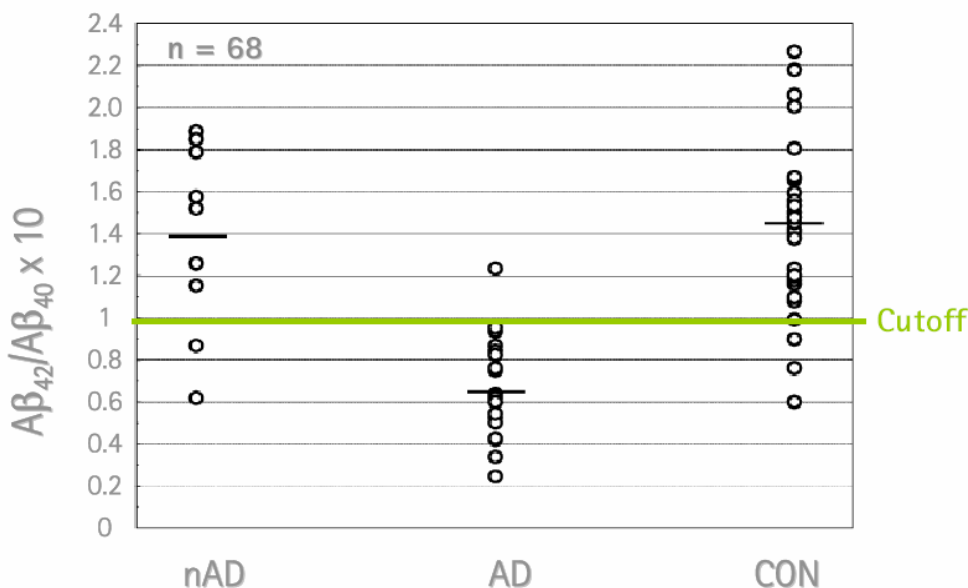
Study 5

Neurochemical diagnosis of Alzheimer's dementia by CSF Abeta42, Abeta42/Abeta40 ratio and total tau

Lewczuk P, Esselmann H, Otto M, Maler JM, Henkel AW, Henkel MK, Eikenberg O, Antz C, Krause WR, Reulbach U, Kornhuber J, Wiltfang J.

Neurobiol Aging. 2004 Mar;25(3):273-81

Cerebrospinal fluid (CSF) concentrations of amyloid beta peptides ending at positions 42 and 40 (Abeta42 and Abeta40, respectively), and total tau (tTau) protein were measured by ELISA in order to compare their accuracy in discriminating patients with Alzheimer's disease (AD, n = 22), non-Alzheimer dementia (nAD, n = 11) and control subjects (CON, n=35). As compared to the other groups, the concentrations of Abeta42 and tTau were decreased (P<0.001) and increased (P<0.001) in AD, respectively, while Abeta40 did not differ significantly among the groups. Receiver operating characteristic (ROC) analysis was performed to define cut-off values for maximized sensitivity and specificity. **For all groups compared the Abeta peptide ratio 42/40 classified more patients correctly, as compared to the concentration of Abeta42 alone: AD versus controls, 94 and 86.7%; AD versus nAD, 90 and 85% and AD versus nAD plus controls, 90.8 and 87%, respectively.** The percentage of correctly classified patients was further improved when the Abeta ratio was combined with the analysis of the tTau concentration. Presence of the apolipoprotein E 4 allele, age or degree of mental disability did not significantly influence the parameters studied.



Diagnostic Accuracy:

AD (N=22) vs	Sensitivity	Specificity
Non-Healthy Controls (nAD, N=11)	95.2%	91%
Healthy Controls (CON, N=35)	95.2%	80%

Study 6

Effect of sample collection tubes on cerebrospinal fluid concentrations of tau proteins and Amyloid β peptides

Lewczuk P, Beck G, Esselmann H, Bruckmoser R, Zimmermann R, Fiszer M, Bibl M, Maler JM, Kornhuber J, Wiltfang J.

Clinical Chemistry. 2006. 52; 2:332-334.

The effect of different tubing materials regarding their interference with A β and tau was analyzed to assess the influence of pre analytical factors on the biomarker analysis.

It is suggested that the A β 42/A β 40 ratio is a more reliable biomarker than pure A β peptide concentrations as A β 42/A β 40 ratios are not altered by interaction with the surface of collection tubes.

Characteristics of TGC's Abeta ELISA Tests

	CSF ELISA	hs ELISA	Brain ELISA
Concept:	Quantitative detection of human A β 40 and A β 42 peptides using highly selective and specific monoclonal antibodies		
Detection limit:	100 pg/ml	25 pg/ml	
Test range:	100 – 2000 pg/ml	25 - 500 pg/ml	
Sample type:	Cerebrospinal fluid (CSF)	Cell culture supernatants (e.g. transfected SH-SY5Y, COS7), plasma or primary neurons	Neuronal tissue homogenates
Sample volume:	50 μ l per sample		
Calculation of results:	Linear calibration with 8 peptide standards in the test range		
Measurements:	40 samples in duplicate + 8 standards		
Time to result:	Approx. 20 hours, with overnight incubation for samples/antibodies and analysis the next day		
Working time:	Approx. 2 hours for 40 samples in duplicate (=1 plate)		
Selectivity of A 40-test-kit:	No cross-reactivity with A β 1-38, A β 1-39, A β 1-42, A β 1-43 or A β 1-44		
Selectivity of A 42-test-kit:	No cross-reactivity with A β 1-38, A β 1-39 or A β 1-40 Very weak cross reactivity for A β 1-43 (13 %), A β 1-44 (10 %)		
Supplies required:	Pipettes, microtiter plate reader (multichannel pipettes, plate washer)		
Delivery time:	<p>Delivery is usually within a few working days but may be up to a week depending on the destination in question. Please contact us for availability and detailed ordering information.</p> <p>Please note that orders are usually sent out on Mondays except for Germany and Switzerland where Tuesday and Wednesday can be arranged</p>		
Price:	Upon request		

Further information can be found on <http://www.the-genetics.com>.

Selected Scientific Publications

Buée L, Hamdane M, Delobel P, Sambo AV, Begard S, Ghestem A, Sergeant N, Delacourte A.

Tau story: from frontotemporal dementia to other tauopathies.

J Soc Biol. 2002; 96 (1): 103-8.

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Sczufca M; Alzheimer's Disease International.

Global prevalence of dementia: a Delphi consensus study.

Lancet. 2005 Dec 17; 366 (9503): 2112-7.

Hansson O, Zetterberg H, Buchhave P, Andreasson U, Londos E, Minthon L, Blennow K.

Prediction of Alzheimer's disease using the CSF Aβ ratio in patients with mild cognitive impairment.

Dement Geriatr Cogn. 2007 Mar; 23:316-320.

Ida N, Hartmann T, Pantel J, Schroder J, Zerfass R, Forstl H, Sandbrink R, Masters CL, Beyreuther K.

Analysis of heterogeneous βA4 Peptides in human cerebrospinal fluid and blood by a newly developed sensitive Western Blot Assay.

J Biol Chem. 1996 Sep 13; 271 (37): 22908-14.

Jensen M, Hartmann T, Engvall B, Wang R, Uljon SN, Sennvik K, Naslund J, Muehlhauser F, Nordstedt C, Beyreuther K, Lannfelt L.

Quantification of Alzheimer Amyloid β peptides ending at residues 40 and 42 by novel ELISA systems.

Mol Med. 2000 Apr; 6 (4): 291-302.

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Cerebrospinal fluid Aβ42 is increased early in sporadic Alzheimer's disease and declines with disease progression. Ann Neurol. 1999 Apr; 45 (4): 504-11.

Lewczuk P, Beck G, Esselmann H, Bruckmoser R, Zimmermann R, Fiszer M, Bibl M, Maler JM, Kornhuber J, Wiltfang J.

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Neurochemical diagnosis of Alzheimer's dementia by CSF Aβ42, Aβ42/Aβ40 ratio and total tau.

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Incidence and risk of dementia. The Rotterdam Study.

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Shoji M.

Cerebrospinal fluid Abeta40 and Abeta42: natural course and clinical usefulness
Front Biosci. 2002 Apr 1; 7: d997-1006.

Sinha G.

European Scientists push spinal taps for Alzheimer diagnosis
Nat Med 2006 Feb, 12 (2): 156.

Tolnay M, Probst A.

The neuropathological spectrum of neurodegenerative tauopathies.
IUBMB Life. 2003 Jun; 55 (6): 299-305.

Wiltfang J, Esselmann H, Bibl M, Hüll M, Hampel H, Kessler H, Frölich L, Schröder J, Peters O, Jessen F, Luckhaus C, Perneczky R, Jahn H, Fiszer M, Maler JM, Zimmermann R, Bruckmoser R, Kornhuber J, Lewczuk P.

Amyloid beta ratio 42/40 but not A β 42 correlates with phospho-Tau in patients with low- and high-CSF A β 40 load.

Journal of Neurochemistry 2007 May; 101 (4): 1053-1059

References

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About The Genetics Company

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COMPANY PROFILE

The Genetics Company is a dedicated team of entrepreneurs and scientists focusing on the research, development and commercialization of innovative products for the diagnosis, therapy and treatment monitoring of patients suffering from neurodegenerative disease or from cancer.

In 2002, the Company acquired key assets from CallistoGen AG, Berlin, Germany in order to substantially strengthen its in-house chemistry capabilities and to expand its product pipeline. This transaction was complemented by the acquisition of German Alzheimer's disease specialist, Abeta GmbH, core business in 2003, which fortified the Company's Alzheimer's program and established a platform for the development and marketing of world leading products for the diagnosis of Alzheimer's disease.

These diagnostics products have already attracted a wide range of customers including major international pharmaceutical and biotech companies as well as renowned academic laboratories.

Located at the Biotech Center Zurich (Schlieren), Switzerland, the Company currently employs a total staff of 8.

FINANCIAL SUMMARY

The Company became operational following the closure of its Series A financing round in May 2000, which raised a total of CHF 10.5 Mio in equity. In November 2003 the Company completed a CHF 14 Mio Series B financing round, co-led by existing shareholders Nextech Venture and Novartis Venture Fund. New investors included Najeti Capital, a leading Spanish venture capital firm from Madrid, Heidelberg Innovation of Heidelberg, Germany and several high net worth individuals.

In February 2005 a Series C financing round was closed with a volume of CHF 25 Mio. While a total of CHF 17 Mio has been committed upfront, an additional installment of CHF 8 Mio is associated with the achievement of certain clinical milestones in 2007. This round was co-led by Nextech Venture, Novartis Venture Fund and a major new investor, Varuma AG of Basel.

EXECUTIVE MANAGEMENT

Dr. Mátyás Végh
Chief Executive Officer
vegh@the-genetics.com

PRODUCT OPPORTUNITIES & TECHNOLOGIES

- A unique set of diagnostic kits and tools for the diagnosis and monitoring of patients suffering from Alzheimer's disease (AD) and for use in pre-clinical Alzheimer's disease research.
- Small molecule inhibitors of Bcl-9, an essential protein for Wnt-signaling, a physiological process found to be aberrantly overactive in more than 85% of colorectal and 65% of liver cancers. Lead compounds could enter IND-enabling studies in year 2008 and clinical trials are expected to start in 2009.
- Small molecule inhibitors of hPygopus, a second proprietary drug target in Wnt-signaling / cancer, have been generated. These compounds are being profiled for potential therapeutic use.

BOARD OF DIRECTORS

Mr. Hans-Beat Gürtler	Partner, Varuma AG, Switzerland
Dr. Rudolf Gyga	Vice Chairman; Managing Director, Novartis Venture Fund, Switzerland
Dr. Peter Rickli	Partner, Christen Rickli Partners, Switzerland
Dr. Alfred Scheidegger	Chairman; Founder of Nextech Venture AG, Switzerland

KEY SCIENTIFIC ADVISORS

Prof. Michel Aguet	Director, Swiss Institute for Experimental Cancer Research (ISREC), Switzerland; Co-Founder
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