

Correspondence

Statement of Principles for Health Care Journalists

Gary Schwitzer

In “The Commercialisation of Medical and Scientific Reporting” [1], Caulfield calls on journalists to ask researchers about the nature of their funding and the financial relationship of the researchers to the sponsor. This is just one principle addressed in a much broader “Statement of Principles” I wrote this past year for the Association of Health Care Journalists (<http://www.ahcj.umn.edu>). The statement is available online [2]. ■

Gary Schwitzer

University of Minnesota School of Journalism and Mass Communication
Minneapolis, Minnesota, United States of America
E-mail: schwitz@umn.edu

References

1. Caulfield T (2004) The commercialisation of medical and scientific reporting. *PLoS Med* 1: e38.
2. (2004) Statement of principles. Minneapolis (Minnesota): Association of Health Care Journalists. Available: http://www.ahcj.umn.edu/files/AHCJ_principles.pdf. Accessed 9 February 2005.

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Accounting for Individual Differences in Risk of Alzheimer Disease

William Grant

Gatz’s statement, “At least half of the explanation for individual differences in susceptibility to Alzheimer disease is genetic” [1], is, in my opinion, incorrect. As the one who led the team debating Ashford and Mortimer, whose 2002 article [2] supports this statement, at the 2001 conference on Alzheimer disease (AD) in Cincinnati (“Challenging Views of Alzheimer’s Disease”) [3], I think that the evidence that dietary and lifestyle factors explain the majority of the individual risk for AD in the US is very strong. My original paper in 1997 [4] found that total dietary fat and energy intake were the most important dietary risk factors, while fish and cereal intake were the most important risk reduction factors. These findings have been generally confirmed by Drs. Luchsinger and Morris and others. The reason I did my study was that the Honolulu Heart Study reported that Japanese American men in Hawaii had 2.5 times the risk of AD of native Japanese. African-Americans have about four times the risk of AD of native Nigerians. If genetics were the primary risk factor, those living in the US would have a risk of developing AD very similar to that of individuals living in their ancestral home. The reason this is not the case is that the American diet provides too much food, which is a particular problem for those genetically predisposed to AD. ■

William Grant

Sunlight, Nutrition and Health Research Center (SUNARC)
San Francisco, California, United States of America
E-mail: wgrant@sunarc.org

References

1. Gatz M (2005) Educating the brain to avoid dementia: Can mental exercise prevent Alzheimer disease? *PLoS Med* 2: e7.
2. Ashford JW, Mortimer JA (2002) Non-familial Alzheimer’s disease is mainly due to genetic factors. *J Alzheimers Dis* 4: 169–177.
3. Grant WB, Campbell A, Itzhaki RF, Savory J (2002) The significance of environmental factors in the etiology of Alzheimer’s disease. *J Alz Dis* 4: 179–189.
4. Grant WB (1997) Dietary links to Alzheimer’s disease. *Alz Dis Rev* 2: 42–55. Available: <http://www.sunarc.org/JAD97.pdf>. Accessed 10 February 2005.

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Author’s Reply

Grant [1] describes as incorrect the statement that at least half of the explanation for individual differences in risk for Alzheimer disease is genetic. He suggests instead that dietary and lifestyle factors explain the majority of individual susceptibility to Alzheimer disease.

The basis for asserting a 50% or greater role for genetics in Alzheimer disease risk comes from family studies and from twin studies. In family studies, first-degree relatives of individuals with Alzheimer disease are at more than double the risk of Alzheimer disease compared to those with no affected relatives [2,3]. In twin studies, across different Scandinavian twin registries, estimates of heritability of Alzheimer disease range from 55% to over 70% [4].

Genetic risk undoubtedly represents the cumulative influence of many genes, including apolipoprotein E (APOE) and other genes not yet identified. In particular, it appears that the magnitude of the genetic component of Alzheimer disease risk is similar across ethnic communities, but that different genetic factors may contribute differently to that risk in white, Latino, and African American families [5].

Further, there are interactions between genetic and environmental risks, for example, between the APOE e4 allele and high cholesterol [6] or head injury [7].

Clearly Alzheimer disease is the outcome of multiple genetic and multiple environmental influences, operating additively and interactively. If genetic effects account for half of individual differences in liability, then environmental influences also account for half of the variation in susceptibility. From a public health viewpoint, it is vital to identify those influences that are modifiable. Controlling blood pressure and avoiding head trauma are examples. However, it is also important to appreciate that individuals bring differences in genetic risk to the table. ■

Margaret Gatz

University of Southern California
Los Angeles, California, United States of America
E-mail: gatz@usc.edu

References

1. Grant W (2005) Diet and lifestyle are important risk-modifying factors for Alzheimer disease. *PLoS Med* 2: e82.
2. Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, et al. (2004) Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: The REVEAL study. *Genet Med* 6: 192–196.
3. Breitner JC (1991) Clinical genetics and genetic counseling in Alzheimer disease. *Ann Intern Med* 115: 601–606.
4. Pedersen NL, Posner SF, Gatz M. (2001) Multiple threshold models for genetic influences on age of onset for Alzheimer's disease: Findings in Swedish twins. *Am J Med Genet* 105: 724–728.
5. Devi G, Ottman R, Tang MX, Marder K, Stern Y, et al. (2000) Familial aggregation of Alzheimer disease among whites, African Americans, and Caribbean Hispanics in Northern Manhattan. *Arch Neurol* 57: 72–77.
6. Jarvik GP, Wijisman EM, Kukull WA, Schellenberg GD, Yu C, et al (1995) Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: A case-control study. *Neurology* 45: 1092–1096.
7. Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, et al. (1995) Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. *Neurology* 45: 555–557.

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Tumor Cell Recognition Efficiency by T Cells

Daniel E. Speiser, Jean-Charles Cerottini, Pedro Romero

Stuge et al. report a detailed analysis of the fine specificity of CD8+ T cells against tumor-associated antigen in melanoma patients [1]. They compared peptide-vaccination-driven with naturally arising T cell responses against the HLA-A*0201 restricted melanoma peptide antigens M26 (derived from Melan-A/MART-1) and G209-2M (derived from gp100 protein). A major endpoint of this study was in vitro tumor cell recognition by T cells. Fortunately, this is increasingly used as a “golden” standard in the assessment of tumor-specific T cells. The authors suggest that spontaneously arising antigen-specific T cell populations are qualitatively different from those induced by vaccination with heteroclitic peptides (which are altered for increased HLA binding): tumor cell recognition was found in nearly all T cells from the former, but only in a minority from the latter. As reported previously, these results correlated with recognition efficiency of antigenic peptides. We agree that this has considerable implications for immunotherapy and congratulate the authors for analyzing T cell recognition in great detail. However, in one point our own studies lead to different results: we repetitively found that the majority of T cells generated with the heteroclitic Melan-A M26 peptide were tumor reactive. This was the case for Melan-A-specific T cell populations generated in HLA-A*0201 transgenic mice [2], in vitro [3], and in melanoma patients [4]. The latter studies also assessed T cells from vaccination-site sentinel lymph nodes, containing T cells that are very likely selected and activated by vaccination and not by the tumor.

The authors point out correctly that tetramer+ T cells comprise many cells unable to recognize and kill tumor cells in an antigen-specific manner, presumably owing to low T cell receptor avidity to cognate antigen. An extreme case is

naïve T cell populations, of which the majority are unable to recognize tumor cells, despite their specific binding to MHC/peptide tetramers [5]. Therefore, it is crucial to exclude naïve T cells from studies analyzing tumor recognition. HLA-A*0201+ humans (healthy individuals and melanoma patients) have 0.07% ± 0.05% naïve Melan-A tetramer+ cells within peripheral blood CD8+ T cells [5,6]. The three patients studied by Stuge et al. had 0.23%, 0.12%, and 0.50% Melan-A tetramer+ cells. Thus, one can estimate that the studied populations from the three patients contained approximately 30%, 60%, and 15% naïve Melan-A-specific T cells, respectively. This is only a rough estimate—tetramer analysis before vaccination and assessment of CD45RA/CCR7 expression would give more insight. Nevertheless, it remains likely that the first two patients had considerably more naïve cells than the third patient (i.e., the one without immunotherapy). In addition, naïve-derived CD8+ T cells have a higher clonogenic potential than activated Melan-A-specific T cells from melanoma patients (unpublished data). This means that overrepresentation of clones derived from naïve CD8+ T cells is likely to occur when both naïve and activated antigen-specific CD8+ T cells co-exist in a given lymphocyte population. As mentioned, Stuge et al. found unexpected high frequencies of T cell clones not recognizing tumor cells in the two vaccinated patients. It is conceivable that this was due to the presumably high percentages of naïve Melan-A-specific cells present in the populations used for generating the clones, which would provide an explanation for the discrepancy with the results of our studies [2,3,4].

Ethical considerations limit vaccination studies in healthy humans. In patients, candidate antigens should therefore be tested with strong adjuvants [7], to increase the likelihood that the studied responses are predominantly vaccination-driven, with only minor contribution of spontaneous T cell activation [8]. It would be desirable to directly compare vaccination with heteroclitic peptide versus vaccination with natural peptide. However, this is hampered by the lack of ex vivo detectable responses to native peptides owing to their low immunogenicity. Another option is to analyze clonal distributions (T cell receptors) of responding T cells extensively: Further support for the notion that spontaneous (tumor driven) responses have increased potential for tumor recognition would be obtained if mono/oligoclonal T cell repertoires are indeed significantly more often found in spontaneous than vaccination-induced responses.

We certainly agree that vaccines must be optimized. Thus, more such studies are desirable, since they have high potential to lead to better understanding of the differences between clinically irrelevant and relevant T cell responses, and to rapidly identify the most promising vaccine formulations that can subsequently be tested in large-scale clinical trials. ■

Daniel E. Speiser (daniel.speiser@hospvd.ch)

Jean-Charles Cerottini

Pedro Romero

Ludwig Institute for Cancer Research
Lausanne, Switzerland

References

1. Stuge TB, Holmes SP, Saharan S, Tuettenberg A, Roederer M, et al. (2004) Diversity and recognition efficiency of T cell responses to cancer. *PLoS Med* 1: e28.

2. Men Y, Miconnet I, Valmori D, Rimoldi D, Cerottini JC, et al. (1999) Assessment of immunogenicity of human Melan-A peptide analogues in HLA-A*0201/Kb transgenic mice. *J Immunol* 162: 3566–3573.
3. Valmori D, Fonteneau JF, Marañón Lizana C, Gervois N, Liénard D, et al. (1998) Enhanced generation of specific tumor-reactive CTL in vitro by selected Melan-A/MART-1 immunodominant peptide analogs. *J Immunol* 160: 1750–1758.
4. Ayyoub M, Zippelius A, Pittet MJ, Rimoldi D, Valmori D, et al. (2003) Activation of human melanoma reactive CD8+ T cells by vaccination with an immunogenic peptide analog derived from Melan-A/MART-1. *Clin Cancer Res* 9: 669–677.
5. Zippelius A, Batard P, Rubio-Godoy V, Bioley G, Lienard D, et al. (2004) Effector function of human tumor-specific CD8 T cells in melanoma lesions: A state of local functional tolerance. *Cancer Res* 64: 2865–2873.
6. Romero P, Valmori D, Pittet MJ, Zippelius A, Rimoldi D, et al. (2002) Antigenicity and immunogenicity of Melan-A/MART-1 derived peptides as targets for tumor reactive CTL in human melanoma. *Immunol Rev* 188: 81–96.
7. Speiser DE, Liénard D, Rufer N, Rubio-Godoy V, Rimoldi D, et al. (2005) Rapid and strong human CD8+ T cell responses to vaccination with peptide, IFA and CpG oligodeoxynucleotide 7909. *J Clin Invest*. In press.
8. Speiser DE, Rimoldi D, Batard P, Liénard D, Lejeune F, et al. (2003) Disease-driven T cell activation predicts immune responses to vaccination against melanoma. *Cancer Immunity* 3: 12.

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Authors' Reply

Drs. Speiser, Cerottini, and Romero [1] correctly point out that CD8+ T cells from HLA-A*0201 melanoma patients and healthy donors may contain small populations (on average, $0.07\% \pm 0.05\%$ in their publications [2,3]) that bind tetramers made with the heteroclitic Melan-A M26 peptide, and that such cells express a naïve phenotype (CD45RA+). We too observe this phenomenon in a portion of HLA-A*0201 healthy donors and patients with melanoma that we analyze with M26 tetramers. Importantly, this is not seen in all subjects. These cells do not recognize the native M27 peptide, and represent cross-reactive subsets of naïve CD8+ T cells of multiple specificities [4]. We routinely analyze all subjects pre-vaccination, and the four post-vaccination responses analyzed in our report [5] did not contain M26 or gp100 tetramer-binding cells pre-vaccination (data not shown). Thus, it was unlikely that M26-cross-reactive cells spontaneously developed post-vaccination (not due to peptide vaccination) and were the basis of some of the low-recognition-efficiency MART-specific clones we analyzed. Furthermore, such a phenomenon has been seen only with M26 and not with the heteroclitic gp100 (G209-2M) peptide, so would not be a factor in the gp100-specific responses we analyzed.

The authors also point out that in their experience, they found that the majority of T cells generated with the heteroclitic Melan-A M26 peptide were tumor reactive, citing their studies in vitro [6], in mice [7], and in patients with melanoma [8]. We focus on their publication on patients with melanoma, as this is most directly relevant to our study. This report [8] focused on three patients with melanoma immunized with M26, and analyzed T cells from lymph nodes draining the vaccination site (vaccine-site sentinel nodes [VSSNs]). VSSNs from these three patients contained 0.11% (0.08%–0.15%) MART-specific T cells by tetramer staining.

Importantly, contralateral lymph nodes in these subjects (distant from the vaccination site) also contained 0.06% (0.05%–0.09%) MART-specific T cells. With their reported background of less than 0.01%, this suggests the possibility of endogenous MART-specific T cells within lymph nodes in these subjects. These authors have shown in previous studies that endogenous MART-specific T cell responses frequently exist within lymph nodes, even in the absence of such cells in peripheral blood mononuclear cells [9]. Furthermore, these VSSN responses were analyzed only after two vaccinations, while the authors could not detect circulating MART-specific T cells in any of these three patients even after six vaccinations. MART-specific T cell lines were generated via tetramer-guided sorting of VSSN cells from patients 2 and 3, then individual clones generated via limiting dilution. They reported 16 of 17 clones killed A2+ MART+ melanoma targets. Without knowing the Vbeta usage of these clones and the Vbeta diversity of the parental MART-specific populations, it is difficult to know what fraction of each response these clones accounted for in the two subjects, as we have done in our study. More importantly, these tumor-reactive clones analyzed may be derived from endogenous T cell responses, possibly amplified by vaccination, rather than from de novo vaccine-elicited T cell responses. If so, these data would in fact fit well with our findings that endogenous responses consist mainly of cells with tumor-cytolytic potential that recognize the native peptide with high recognition efficiency.

In our study [5], we analyzed in detail four vaccine-elicited T cell responses (two to M26 and two to G209-2M) via the generation of more than 200 cytotoxic T lymphocyte clones, and assessed the fraction of each response that these clones accounted for collectively by analyzing the Vbeta usage of each clone and the parental peptide-specific populations. From this, we showed that the vaccine-elicited T cells were diverse in their tumor-cytolytic potential, which correlated with their recognition efficiency for the native peptides. It is important to point out that tumor-cytolytic T cells were present in these four subjects, but represented a significantly lower fraction than those derived from endogenous responses. These data are consistent with those we recently reported using a different experimental approach—assessing the fraction of T cells in a tetramer+ population that degranulate (via CD107 mobilization) to tumor stimulation [10]. While generating individual cytotoxic T lymphocyte clones and analyzing each for tumor killing and recognition efficiency, as we have done in this study, is the most definitive approach to analyze individual cells within an antigen-specific T cell response, this approach is extremely labor-intensive, and thus not feasible for large numbers of patients. As such, more rapid flow-cytometry-based methods, such as the CD107 mobilization assay and a new method to rapidly assess recognition efficiency of a T cell population via differential TCR downregulation (H. E. Kohrt, C. T. Shu, S. P. Holmes, J. S. Weber, P. P. L., et al., unpublished data), will allow analysis of many more patients to various vaccine formulations and strategies. This knowledge will be vital to the improvement of future cancer immunotherapies. ■

Tor B. Stuge

Peter P. Lee (ppl@stanford.edu)

Stanford University
Stanford, California, United States of America

References

1. Speiser DE, Cerottini JC, Romero P (2005) Tumor cell recognition efficiency by T cells. *PLoS Med* 2: e77.
2. Zippelius A, Batard P, Rubio-Godoy V, Bioley G, Lienard D, et al. (2004) Effector function of human tumor-specific CD8 T cells in melanoma lesions: A state of local functional tolerance. *Cancer Res* 64: 2865–2873.
3. Romero P, Valmori D, Pittet MJ, Zippelius A, Rimoldi D, et al. (2002) Antigenicity and immunogenicity of Melan-A/MART-1 derived peptides as targets for tumor reactive CTL in human melanoma. *Immunol Rev* 188: 81–96.
4. Dutoit V, Rubio-Godoy V, Pittet MJ, Zippelius A, Dietrich PY, et al. (2002) Degeneracy of antigen recognition as the molecular basis for the high frequency of naive A2/Melan-a peptide multimer(+) CD8(+) T cells in humans. *J Exp Med* 196: 207–216.
5. Stuge TB, Holmes SP, Saharan S, Tuettenberg A, Roederer M, et al. (2004) Diversity and recognition efficiency of T cell responses to cancer. *PLoS Med* 1: e28.
6. Valmori D, Fonteneau JF, Lizana CM, Gervois N, Lienard D, et al. (1998) Enhanced generation of specific tumor-reactive CTL in vitro by selected Melan-A/MART-1 immunodominant peptide analogues. *J Immunol* 160: 1750–1758.
7. Men Y, Miconnet I, Valmori D, Rimoldi D, Cerottini JC, et al. (1999) Assessment of immunogenicity of human Melan-A peptide analogues in HLA-A*0201/Kb transgenic mice. *J Immunol* 162: 3566–3573.
8. Ayyoub M, Zippelius A, Pittet MJ, Rimoldi D, Valmori D, et al. (2003) Activation of human melanoma reactive CD8+ T cells by vaccination with an immunogenic peptide analog derived from Melan-A/melanoma antigen recognized by T cells-1. *Clin Cancer Res* 9: 669–677.
9. Romero P, Dunbar PR, Valmori D, Pittet M, Ogg GS, et al. (1998) Ex vivo staining of metastatic lymph nodes by class I major histocompatibility complex tetramers reveals high numbers of antigen-experienced tumor-specific cytolytic T lymphocytes. *J Exp Med* 188: 1641–1650.
10. Rubio V, Stuge TB, Singh N, Betts MR, Weber JS, et al. (2003) Ex vivo identification, isolation and analysis of tumor-cytolytic T cells. *Nat Med* 9: 1377–1382.

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Cholesterol, Statins, and Alzheimer Disease

Alexei R. Koudinov, Temirbolat T. Berezov

After reading the excellent research article by Pedrini et al. [1] and the associated synopsis [2], one may conclude that the only pathway of statins' effect on Alzheimer disease (AD) is the regulation of amyloid precursor protein (APP) processing and amyloid- β protein (A β) generation. The moderation is provided in the research article's patient summary, reminding that "statins are likely to influence the risk for Alzheimer disease by several different pathways." What are these other pathways? It is essential to note that in addition to APP processing and A β chemistry being modulated by statins, fine tuning of cholesterol homeostasis also affects cholinergic function, ionotropic and metabotropic receptors, tau phosphorylation, neural oxidative stress reactions, and other features of neurodegeneration (reviewed in [3]). Moreover, precise regulation of neural cholesterol dynamics and supply is itself essential for synapse function, plasticity, and behaviour [3]. These data suggest that in addition to its role in sporadic AD, cholesterol homeostasis break is the unifying primary cause of neuromuscular diseases, Niemann-Pick type C disease, and Down syndrome, and explains why rare cases of familial AD (associated with mutations in APP and presenilin genes)

are translated into Alzheimer's via membrane cholesterol sensitivity of APP processing by secretases and A β generation. Also important, is the synopsis's [2] apparently outdated dividing of APP processing into "harmful" (A β -generating) and "healthy" (non-amyloidogenic). One should be cautious in calling A β a harmful molecule. This is because several recent studies have illuminated an essential function for amyloidogenic processing of APP and A β in neurons [4] and synapses [5]. In this context, the reciprocal effect of A β on cholesterol synthesis, cellular uptake, efflux, and esterification, and its relation to the experimental restoration of long-term potentiation (LTP, a synaptic plasticity measure) may represent one of the poorly comprehended physiological functions of A β [6,7]. ■

Alexei R. Koudinov (koudinov@neurobiologyofflipids.org)

Temirbolat T. Berezov

Russian Academy of Medical Sciences
Moscow, Russia

References

1. Pedrini S, Carter TL, Prendergast G, Petanceska S, Ehrlich ME, et al. (2005) Modulation of statin-activated shedding of Alzheimer APP ectodomain by ROCK. *PLoS Med* 2: e18.
2. (2005) How statins may protect against Alzheimer disease. *PLoS Med* 2: e22.
3. Koudinov AR, Koudinova NV (2004) Cholesterol homeostasis failure as a unifying cause of synaptic degeneration. *J Neurol Sci*. doi:10.1016/j.jns.2004.11.036
4. Plant LD, Boyle JP, Smith IF, Peers C, Pearson HA (2003) The production of amyloid beta peptide is a critical requirement for the viability of central neurons. *J Neurosci* 23: 5531–5535.
5. Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, et al. (2003) APP processing and synaptic function. *Neuron* 27: 925–937.
6. Koudinov AR, Koudinova NV (2003) Amyloid beta protein restores hippocampal long term potentiation: A central role for cholesterol? *Neurobiol Lipids* 1: 8. Available at: <http://neurobiologyofflipids.org/content/1/8/>. Accessed 10 February 2005.
7. Koudinov AR, Berezov TT (2004) Alzheimer's amyloid beta (A β) is an essential synaptic protein, not neurotoxic junk. *Acta Neurobiol Exp* 64: 71–79. Available at: <http://www.nencki.gov.pl/pdf/an/vol64/koudin.pdf>. Accessed 10 February 2005.

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Authors' Reply

We appreciate the note from Drs. Koudinov and Berezov [1]. In our opinion, no model has yet been presented that plausibly accounts for all the data on statins, cholesterol, amyloid- β protein (A β), and Alzheimer disease. In our paper [2], we present evidence that the isoprenoid pathway contributes to statin-activated shedding of the APP ectodomain in cultured cells. We do not yet know which (if any) other "cholesterol-related" Alzheimer phenomena are also attributable to modulation of isoprenoids, Rho, or ROCK.

Previously, conventional wisdom held that A β load and hypercholesterolemia were directly related, based on observations that high-fat diet aggravated amyloid pathology in plaque-forming mice [3,4,5]. More recently, however, the formulation that statins act simply via cholesterol-

lowering fails to account for several observations that cannot immediately be reconciled, either with the original “dogma” or with each other.

First, Fagan et al. [6] questioned the role of cholesterol as the final common pathway in A β load specification, since, in their experiments, low cholesterol per se apparently had no impact on brain A β load in plaque-forming transgenic mice. Then, equally puzzling pharmacological data emerged. Atorvastatin was shown to lower brain amyloid load and A β levels, but brain cholesterol levels were unaffected by the drug [7]. In an apparent complete contradiction with the original observations, now, some investigators have been able to devise circumstances under which there is an inverse relationship between cholesterol and A β , with low neuronal cholesterol increasing A β generation [8], and vice versa [9]. These newer observations are unexpected and extremely puzzling, and no comprehensive explanation has yet emerged.

For those readers seeking an update on this challenging area, we would direct your attention to the Alzheimer Research Forum Web page (<http://www.alzforum.org/new/detailprint.asp?id=1135>), where you will find an excellent review of the literature as well as a series of evaluations of how our data fit into existing scenarios and models regarding cholesterol, statins, cerebral amyloidosis, and the cognitive failure of Alzheimer disease. ■

Sam Gandy (samgandy@earthlink.net)

Farber Institute for Neurosciences, Thomas Jefferson University
Philadelphia, Pennsylvania, United States of America

Suzana Petanceska

Nathan Kline Institute at New York University
Orangeburg, New York, United States of America

References

1. Koudinov AR, Berezov TT (2005) Cholesterol, statins, and Alzheimer disease. *PLoS Med* 2(3): e81.
2. Pedrini S, Carter TL, Prendergast G, Petanceska S, Ehrlich ME, et al. (2005) Modulation of statin-activated shedding of Alzheimer APP ectodomain by ROCK. *PLoS Med* 2: e18.
3. Refolo LM, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, et al. (2000) Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. *Neurobiol Dis* 7: 321–331.
4. Levin-Allerhand JA, Lominska CE, Smith JD (2002) Increased amyloid-levels in APPSWE transgenic mice treated chronically with a physiological high-fat high-cholesterol diet. *J Nutr Health Aging* 6: 315–319.
5. Shie FS, Jin LW, Cook DG, Leverenz JB, LeBoeuf RC (2002) Diet-induced hypercholesterolemia enhances brain A beta accumulation in transgenic mice. *Neuroreport* 13: 455–459.
6. Fagan AM, Christopher E, Taylor JW, Parsadanian M, Spinner M, et al. (2004) ApoAI deficiency results in marked reductions in plasma cholesterol but no alterations in amyloid-beta pathology in a mouse model of Alzheimer's disease-like cerebral amyloidosis. *Am J Pathol* 165: 1413–1422.
7. Petanceska SS, DeRosa S, Olm V, Diaz N, Sharma A, et al. (2002) Statin therapy for Alzheimer's disease: Will it work? *J Mol Neurosci* 19: 155–161.
8. Abad-Rodriguez J, Ledesma MD, Craessaerts K, Perga S, Medina M, et al. (2004) Neuronal membrane cholesterol loss enhances amyloid peptide generation. *J Cell Biol* 167: 953–960.
9. George AJ, Holsinger RM, McLean CA, Laughton KM, Beyreuther K, et al. (2004) APP intracellular domain is increased and soluble Abeta is reduced with diet-induced hypercholesterolemia in a transgenic mouse model of Alzheimer disease. *Neurobiol Dis* 16: 124–132.

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A Canadian Perspective

James E. Till

Erick H. Turner [1] notes that “ClinicalTrials.gov, a registry authorized by the Food and Drug Modernization Act of 1997, appears not to be comprehensive.” While we await the creation of clinical trials registry and results databases that are truly comprehensive, innovative efforts to provide convenient access to credible information about known existing clinical trials need to continue. A Canadian example is provided by OntarioCancerTrials.ca, a consumer-oriented site developed by the Ontario Cancer Research Network (OCRN), with funding from the Ontario government. ■

James E. Till

University of Toronto
Toronto, Ontario, Canada
E-mail: till@uhnres.utoronto.ca

References

1. Turner EH (2004) A taxpayer-funded clinical trials registry and results database. *PLoS Med* 1: e60.

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