Metabolomics: Open Access
ISSN: 2153-0769

Cacabelos, Metabolomics 2016, 6:2
DOI: 10.4172/2153-0769.1000e145

Editorial Open Access

The Complexity of Alzheimer's Disease Pharmacogenomics and Metabolomics in Drug Development

Ramon Cacabelos*

EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, Corunna, Spain

***Corresponding author:** Ramón Cacabelos, EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, Camilo Jose Cela University, 15165-Bergondo, Corunna, Spain, Tel: 34981780505; E-mail: rcacabelos@euroespes.com

Received date: April 22, 2016; **Accepted date:** April 25, 2016; **Published date:** April 29, 2016

Editorial

Alzheimer's Disease (AD) is the most prevalent form of dementia and the 6th cause of death in the USA with an age-adjusted death rate of 25.4 per 100,000. For the past 25 years, 5 drugs (Tacrine, Donepezil, Rivastigmine, Galantamine, Memantine) have been approved by the FDA for the treatment of AD. However, these drugs are not cost-effective and no new drugs for AD have been introduced in the market since 2005. About 10-20% of the total cost of AD in the USA ($226 billion/year) and in Europe (€160 billion/year) is dedicated to pharmacological treatment. It is estimated that by the year 2050 in the USA alone the direct cost of AD could be over $1.1 trillion in people older than 65 years of age, with a global cost of $20.8 trillion for the 2015-2050 period [1].

During the past 10 years, over 1,000 different compounds have been screened as candidate drugs for AD [2], and over 400 unsuccessful formal attempts to develop anti-AD drugs have been reported for the past 15 years [3]. At present, 74 clinical trials with AD-related drugs (for diagnosis or treatment) are under way [1].

This historical failure in the pharmacotherapy of AD could be explained on the basis of various scenarios: (i) ignorance of the pathogenetic mechanisms responsible for the premature death of neurons in AD; (ii) the development of inappropriate drugs or the erroneous identification of therapeutic targets; (iii) inertia of developing symptomatic medications to improve memory, but not to protect neurons against a programmed cell death; (iv) a very limited understanding of genomic and epigenomic defects underlying the risks of suffering from dementia; and (v) the absence of a precise knowledge on drug-genome interactions [2].

Therefore, there is an urgent need to change this impoverished tendency, since the approval of a new disease-modifying drug by 2025, capable of delaying AD onset by 3-5 years, would reduce the prevalence of AD by 30% and, consequently, reduce the cost of AD in the USA at an estimated rate of $300-$400 billion/year by 2050 [1].

AD is a heterogeneous disorder with, at least, a tetravalent phenotype: (i) neuropathological component (classic hallmarks: senile plaques, neurofibrillary tangles, neuritic desarborization, neuronal loss); (ii) neurobehavioral component: cognitive deterioration, behavioral changes, functional decline; (iii) age-related biological component (direct, indirect, and un-related biochemical, hematological and metabolic phenotypes); and (iv) gender-related phenotypes. Consequently, the therapeutic intervention in dementia is polymodal, to modify the expression of all these complex phenotypes. From a biomedical perspective, AD patients present concomitant disorders including hypertension (20-30%), overweightness or obesity (20-40%), diabetes (20-25%), hypercholesterolemia (>40%), hypertriglyceridemia (20%); excess of urea (>80%), creatinine (6%) and uric acid (5%); alterations in transaminases (ASAT, ALAT, GGT) (>15%), alkaline phosphatase (14%), bilirubin (17%), and ions (>10%); deficit of iron (5%), ferritin (3%), folate (5%), and vitamin B12 (4%); thyroid dysfunction (5-7%), and reduced levels of RBC (3%), HCT (33%), and Hb (35%). Cardiovascular disorders (>40%), atherosclerosis (>60%), and different modalities of cerebrovascular damage (>60%) are also frequent among patients with AD. Most of these biochemical, hematological and metabolic anomalies exhibit gender differences and may contribute to accelerate the dementia process. The pharmacological treatment of these concomitant pathologies adds complexity and risks to the multifactorial therapeutic intervention in patients with dementia. Of major relevance is the treatment of diabetes, hypertension, dyslipidemia, and cardiovascular, cerebrovascular and neuropsychiatric disorders (psychosis, depression, anxiety, insomnia, parkinsonism, myoclonic jerks, epilepsy). In this context, the incorporation of pharmacogenetic protocols into clinical practice is fundamental to minimize drug-drug interactions and ADRs, and to optimize the global therapeutic outcome, avoiding deleterious effects on mental function and cognition [2,4-6].

Pharmacogenomics accounts for over 60-90% variability in the pharmacodynamics and pharmacokinetics of drugs. The genes involved in the pharmacogenomic response to drugs in dementia fall into five major categories: (i) genes associated with disease pathogenesis (APP, PSEN1, PSEN2, MTAU, APOE, and over 600 susceptibility variants distributed across the genome); (ii) genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers); (iii) genes associated with drug metabolism: (a) phase I reaction enzymes: Alcohol Dehydrogenases (ADH1-7), Aldehyde Dehydrogenases (ALDH1-9), Aldo-Keto Reductases (AKR1A-D), Amine Oxidases (MAOA, MAOB, SMOX), Carbonyl Reductases (CBR1-4), Cytidine Deaminase (CDA), Cytochrome P450 family (CYP1-51, POR, TBXAS1), Cytochrome b5 Reductase (CYB5R3), Dihydroprimidine Dehydrogenase (DPYD), esterases (AADAC, CEL, CES1, CES1P1, CES2, CES3, CES5A, ESD, GZMA, GZMB, PON1, PON2, PON3, UCHL1, UCHL3), Epoxidases (EPHX1-2), Flavin-containing Monooxygenases (FMO1-6), Glutathione Reductase/Peroxidases (GPX1-7, GSR), short-chain Dehydrogenases/Reductases (DHRS1-13, DHRSX, HSD11B1, HSD17B10, HSD17B11, HSD17B14), Superoxide Dismutases (SOD1-2), and Xanthine Dehydrogenase (XDH); and (b): phase II reaction enzymes: amino acid transferases (AGXT, BAAT, CCBL1), dehydrogenases (NQO1-2, XDH), Esterases (CES1-5), Glucuronosyl Transferases (UGT1-8), Glutathione Transferases (GSTA1-5, GSTK1, GSTM1-5, GSTO1-2, GSTP1, GSTT1-2, GSTZ1, GSTCD, MGST1-3, PTGES), Methyl Transferases (AS3MT, ASMT, COMT, GNMT, GAMT, HNMT, INMT, NNMT, PNMT, TPMT), N-Acetyl Transferases

(ACSL1-4, ACSM1, ACSM2B, ACSM3, AANAT, GLYAT, NAA20, NAT1-2, SAT1), Thioltransferase (GLRX), and Sulfotransferases (CHST2-13, GAL3ST1, SULT1A1-3, SULT1B1, SULT1C1-4, SULT1E1, SULT2A1, SULT2B1, SULT4A1, SULT6B1, CHST1); (iv) genes associated with drug transporters: In humans there are 49 ABC transporter genes and the Multidrug Resistance associated Proteins (MRP1/ABCC1, MRP2/ABCC2, MRP3/ABCC3, MRP4/ABCC4, MRP5/ABCC5, MRP6/ABCC6, MRP7/ABCC10, MRP8/ABCC11 and MRP9/ABCC12) which belong to the ABCC family integrated by 13 members. Other genes encoding transporter proteins are genes of the Solute Carrier Superfamily (SLC) and Solute Carrier Organic (SLCO) transporter family, responsible for the transport of multiple endogenous and exogenous compounds, including folate (SLC19A1), urea (SLC14A1, SLC14A2), monoamines (SLC29A4, SLC22A3), aminoacids (SLC1A5, SLC3A1, SLC7A3, SLC7A9, SLC38A1, SLC38A4, SLC38A5, SLC38A7, SLC43A2, SLC45A1), nucleotides (SLC29A2, SLC29A3), fatty acids (SLC27A1-6), neurotransmitters (SLC6A2 (noradrenaline transporter), SLC6A3 (dopamine transporter), SLC6A4 (serotonin transporter, SERT), SLC6A5, SLC6A6, SLC6A9, SLC6A11, SLC6A12, SLC6A14, SLC6A15, SLC6A16, SLC6A17, SLC6A18, SLC6A19), glutamate (SLC1A6, SLC1A7), and others; and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions [2].

Epigenetic aberrations (DNA methylation, histone modifications, microRNA dysregulation) can also affect the expression of genes involved in the pharmacogenetic cascade leading to abnormal processing of drugs with negative consequences on drug efficacy and safety [7,8]. Alterations in the epigenetic machinery are responsible for defective tissue-specific expression of genes associated with pharmacogenetics; and epigenetic changes in pathogenic, metabolic and transporter genes are determinant for the development of drug resistance. miRNAs target ABC transporters and are influential epigenetic regulators of drug metabolism, resistance and toxicity [7-9].

The development of new compounds by using pharmacogenetic strategies encompasses a series of steps in a multidisciplinary fashion: (i) genetic screening (genotyping) of single genes to identify major gene targets; (ii) analysis of genetic variation to differentiate populations; (iii) structural and functional genomic analyses including genetic clusters and haplotypes; (iv) analysis of genotype-phenotype correlations to characterize major phenotypes as therapeutic targets associated with a particular gene or a cluster of genes involved in a metabolic pathway; and (v) implementation of basic and clinical pharmacogenomic procedures for drug development [10].

With regard to the future of pharmacogenomics as a practical discipline to efficiently optimize therapeutics in dementia and other neuropsychiatric disorders, several issues should be addressed: (i) the education of physicians in medical genomics and pharmacogenomics is fundamental (less than 2% of the members of the medical community are familiar with genomic science); (ii) genomic screening of gene clusters involved in pharmacogenomic outcomes must become a clinical routine; (iii) each patient must be a carrier of a pharmacogenetic card indicating what kind of drugs he/she can take and which medications he/she should avoid; (iv) Regulatory Agencies should request pharmacogenetic data from the pharmaceutical industry when applying for drug approval; (v) pharmacogenetic data must be included in the patient information leaflet and the pharmaceutical vade mecum; and (vi) new guidelines for daily praxis, such as that of the first World Guide for Drug Use and Pharmacogenomics [11], will facilitate the understanding of the relationship between drugs and genes (and vice versa) to make drug prescription a genuinely personalized procedure [1,2,7-9].

References

1. Cacabelos R, Teijido O, Carril JC (2016) Can cloud-based tools accelerate Alzheimer's disease drug discovery? Expert Opin Drug Discov 11: 215-223.
2. Cacabelos R, Cacabelos P, Torrellas C, Tellado I, Carril JC (2014) Pharmacogenomics of Alzheimer's disease: novel therapeutic strategies for drug development. Methods Mol Biol 1175: 323-556.
3. Cummings JL, Morstorf T, Zhong K (2014) Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Res Ther 6: 1-7.
4. Cacabelos R, Goldgaber D, Vostrov A, Matsuki H, Torrellas C, et al. (2014) APOE-TOMM40 in the Pharmacogenomics of demetia. J Pharmacogenomics Pharmacoproteomics 5: 1-12.
5. Cacabelos R, Torrellas C, Carrera I (2015) Opportunities in Pharmacogenomics for the treatment of Alzheimer's Disease. Future Neurology 10: 229-252.
6. Cacabelos R, Goldgaber D, Roses AD, Vostrov A, Matsuki H, et al. (2015) Gene interactions in the Pharmacogenomics of Alzheimer's Disease. Sciforschen Genetics and Gene Therapy 1: 1-22
7. Cacabelos R, Torrellas C (2015) Epigenetics of aging and Alzheimer's disease: Implications for pharmacogenomics and drug response. International Journal of Molecular Sciences 16: 30483-30543.
8. Cacabelos R, Torrellas C, Aliev G (2016) Epigenetics-related drug efficacy and safety: The path to pharmacoepigenomics. Current Genomics.
9. Cacabelos R, Torrellas C (2014) Epigenetic drug discovery for Alzheimer's disease. Expert Opin Drug Discov 9:1059-1086.
10. Cacabelos R (2015) Impact of genomic medicine on the future of Neuropsychopharmacology. J Neuropsychopharmacol Mental Health 1:1.
11. Cacabelos R (2012) World Guide for Drug Use and Pharmacogenomics. EuroEspes Publishing, Corunna, Spain.