PCM EVW ES

Grant Baxalta

Molecular and clinical profile of VWD in Spain (pcm-evw.es)

recruitment extension, further data analysis, improvement of registry platform, diagnosis and management of VWD application development

March 31, 2016

PRINCIPAL INVESTIGATORS

Dr. Francisco Javier Batlle Fonrodona
Indtituto de Investigación Biomédica (INIBIC)
Complexo Hospitalario Universitario, A Coruña

Dr. Francisco Vidal Pérez
Unitat de Diagnòstic i Teràpia Molecular
Ed Dr. Frederic Duran i Jordà, Barcelona

1. Project information

1.1. Principal investigators

Dr. Francisco Javier Batlle Fonrodona

INIBIC-Complexo Hospitalario Universitario A Coruña (Edificio Materno Infantil)
Carretera del Pasaje s/n; 15006-A Coruña, Spain.

Dr. Francisco Vidal Pérez

Unitat de Diagnòstic i Teràpia Molecular
Ed Dr. Frederic Duran i Jordà
Passeig Taulat 106-116
08005 Barcelona, Spain.

1.2. Co-investigator name, title & Institution

Dr. María Fernanda López-Fernandez / Dr. Almudena Pérez-Rodríguez

Complexo Hospitalario Universitario A Coruña (Edificio Materno Infantil)
Servicio de Hematología y Hemoterapia
Carretera dcel Pasaje s/n; 15006-A Coruña, Spain.

Dr. Almudena Pérez Rodríguez

Complexo Hospitalario Universitario A Coruña (Edificio Materno Infantil)
Servicio de Hematología y Hemoterapia
Carretera dcel Pasaje s/n; 15006-A Coruña, Spain.

Dr. Irene Corrales Insa

Unitat de Diagnòstic i Teràpia Molecular
Ed Dr. Frederic Duran i Jordà
Passeig Taulat 106-116
08005 Barcelona, Spain.

Dr. Ana Rosa Cid Haro

Hospital Universitari i Politecnic La Fe
Bulevar s/n
46026-Valencia (Spain)

1.3. Duration

3 years.

1.4. Keywords

von Willebrand disease, von Willebrand factor, diagnosis, genetic testing, diagnostic platform, registry database, LOPD, NGS, custom panel, Data encryption and security, Cloud computing, Software usability, API, IaaS, e-Learning, BPM, Translational research, Software usability, Software scalability, Data modeling, Iterative and Incremental Development, e-Training, Web 2.0, Machine Learning.

1.5. Correspondence to

Dr. María Fernanda López Fernández

Chairman Servicio de Hematología.
Complexo Hospitalario Universitario A Coruña (Edificio Materno Infantil)
Servicio de Hematología y Hemoterapia
Carretera del Pasaje s/n; 15006-A Coruña (Spain)
E mail: Francisco.Javier.Batlle.Fonrodona@sergas.es

2. Summary of grant request

The present Project is a third phase of the previous **PCM-EVW-ES** Project (*Batlle et al. Thromb & Haemost 2015*) with the aim of its extension, further analysis with an innovation development in the field of VWD based in the newer recently available methodologies. The aim of this project is to help the physician in a **more uniform characterization and therapy of VWD** in clinical practice, at an international level. **A reduction of the expenses in the diagnosis process** by using the new methodologies is pursued.

The ***specific objectives*** and corresponding ***tasks*** of the present project are as follows:

Main objective is:

1. Extension of the central phenotypic and NGS genotypic characterization of the VWD in Spain, through the prospective recruitment in the Spanish VWD cohort of approximately 500 new patients with local historical VWD diagnosis (from approximately 38 centres).

Secondary objective is:

1. Development of an electronic platform using this proposed algorithm. In a second step, some other mutation-oriented tests or investigations could be carried out for confirmation.

This project involves leading innovation and translational research with a direct impact on the quality of clinical care (applicability). To our knowledge there is no similar project in this field. Potential patents may derive from this project. It involves also development of e-learning and new information technologies (debate forum, ads, google search engine). This project may promote international collaboration. Development of an algorithmic platform that facilitates diagnosis and therapy orientation of VWD in clinical practice using the selected data from the overwhelming amount of information that new technologies, such as NGS, are producing.

3. State of art/study background

VWD overview in Spain

A previous published multicenter study on the situation of VWD in Spain showed a frequency of this disease and distribution of the different types similar to that observed in some other European countries. The results of a concise survey on the diagnosis of VWD showed a frequency fivefold greater in Spain than that expected from epidemiological studies in other European countries; this may result from overdiagnosis and/or a higher prevalence of VWD. These results clearly reinforce the need for the Spanish VWD registry. The rate of response to our questionnaire was 66.6% (36 centers, including the 5 Hemophilia Treating Centers), which is very similar to the mean responses indicated in the study of Rodeghiero et al (65%) [30]. From an epidemiological point of view, the entire population analyzed, corresponding to the responding centers, was 22.8 million inhabitants; this represents 49% of the global Spain population. When also taking the wide geographic distribution of the participating centers into account, we believe it is possible to extrapolate our findings to the entire country.

It is particularly noteworthy that in classified patients the distribution of VWD types is quite similar to that observed by Rodeghiero et al [30], especially for types 1 and 2.

Globally, participant investigators experienced difficulty in characterizing about a third of the patients with a definite diagnosis of VWD.

Diagnostic strategy

The data obtained in that survey for diagnostic parameters indicated that the more widely used tests are FVIII activity (FVIII:C), VWF:RCo, and VWF:Ag, and, to a lesser extent, VWF:CB. The RIPA at low ristocetin concentration (that allow identified the type 2B), the plasma VWF capacity to bind exogenous FVIII (VWF:FVIIIB) (that can distinguish between hemophilia and type 2N VWD) and the multimeric analysis were test very little used due to their complexity. The limited use of these methods may lead to underdiagnosis of some patients. Also, the complexity, high cost, and experience required to perform a molecular study constitute the main reasons for that only five centers carried out this study by Sanger and the 50% of participants never request this study its low use. One of the conclusions of ~~this~~ the Spanish study was that because of the complexity and/or difficulty in performing some of the tests used in the diagnosis of VWD, supporting the centralization of these tests in laboratories that have the experience necessary to achieve a more uniform characterization.

The Molecular and Clinical Profile of von Willebrand Disease in Spain (PCM-EVW-ES) Project. Spanish Registry

Motivated by the success and experience of the European Project MCMDM-1VWD, a Spanish Registry on VWD has been initiated. Several European countries already have their own registry. In order to achieve a better comprehension of this complex pathology, it is necessary to rely on a patient database that must be as much extensive and detailed as possible [31].

A main feature of the PCM-EVW-ES is that the analysis of the samples has been centralized in three laboratories that have the experience necessary to achieve a more uniform characterization. It should be emphasized that this study was not intended as a prevalence study or as a quality assessment of the participant laboratories. The main goals of the study are:

i. An assessment of the real diagnosis and therapeutic situation of VWD in Spain in normal clinical practice;
ii. The achievement of a platform of recruited patients with the best possible characterization;
iii. The development of a Spanish Working Group on VWD (recently created);
iv. Participation in international projects on VWD (European Union VWD Group, Zimmerman Project, Type 3 VWD International “Registry Inhibitor Prospective Study (3WINTERS-IPS)”;
v. Elaboration of practical guidelines on diagnosis and therapy of VWD in Spain.

There are several additional aims to the study, summarized as follows:

1. To ascertain the clinical profile of those patients diagnosed with VWD who had been referred to the Spanish centers and were in active follow-up in 2011. The bleeding score is used to establish the bleeding history.
2. To characterize the diagnosis of types and subtypes up to the most complete hierarchical level, based on the revised and updated classification of the ISTH-SSC VWF.
3. To know the modality of therapy used.
4. To register and analyze any genetic abnormality.
5. To register patients with bloodborne diseases, such as human immunodeficiency virus, hepatitis B, and hepatitis C infected patients, and under retroviral therapy.
6. To develop knowledge on alloantibodies against VWF and to evaluate any corresponding treatments.
7. To record the history of major surgeries and types of treatment.

Study Cohort

Patients of any age previously diagnosed locally with VWD or referred from any hospital department or from family care that fulfill one or more of the following inclusion criteria: 1) VWF:Ag, VWF:RCo and/or VWF:CB ≤30 UI/dL (%), observed on two or more occasions; 2)detection of multimeric abnormalities; 3) in case of isolated FVIII deficiency it will be necessary to provide demonstration of a decreased VWF:FVIIIB; 4) presence of VWF mutations; 5) presence of RIPA at a low ristocetin concentration.

Exclusion criteria: Presence of any data suggesting acquired Von Willebrand syndrome. The definitive diagnosis will be performed centrally.

Genetic analysis: Initially it was planned to analyze by using the expensive Sanger method either some exons or the whole *VWF* in some patients with types 2 and 3 VWD. However, thanks to the availability of the new methodology based on NGS, much less expensive, the genetic analysis was extended to all the recruited patients.

3.1. Previous results from the PCM-EVW-ES Project.

A cohort of 556 patients from 330 families previously diagnosed as VWD at the local centres were analyzed centrally. VWD was confirmed in 480 [31]. NGS of the whole coding *VWF* was carried out in all recruited patients, compared with the phenotype, and a final diagnosis was established. A total of 238 different VWF mutations were found, 154 were not included in the Leiden Open Variation Database (LOVD). Of these patients, 463 were found to have *VWF* mutation/s. A good phenotypic/genotypic association was estimated in 96.5% of the patients. One hundred and seventy-four patients had two or more mutations. Occasionally a predominant phenotype masked the presence of a second abnormality. One hundred and sixteen patients presented with mutations that had previously been associated with increased VWF clearance. RIPA unavailability, central phenotypic results disagreement and difficult distinction between severe type 1 and type 3 VWD prevented a clear diagnosis in 70 patients. The NGS study facilitated an appropriate classification in 63 of them. The remaining seven patients presented a *VWF* novel mutation pending further investigation. In five patients with a type 3 and two with a type 2A or 2B phenotype with no mutation, an acquired von Willebrand syndrome (AVWS) was suspected/confirmed.

A 42.3% local/central phenotypic diagnosis discrepancy was observed indicating the practical difficulties/drawbacks of VWD diagnosis. A 96.5% phenotypic/NGS genotypic association was observed, suggesting the possibility of incorporating the NGS in the initial VWD work-up. Comparative analysis of sensitivity and specificity with traditional gold standard sequencing method showed values of nearly 99% and 98% respectively.

These data seem to support the NGS as a first line efficient and faster paradigm in VWD diagnosis. Anew algorithm for the initial study of VWD was proposed. It includes family history, bleeding score, VWF:Ag, VWF:RCo/VWF:GPIbα assay, platelet count and peripheral blood smear, and *VWF* molecular study by NGS, using a cut-off for VWF:Ag of ≤ 30 IU/dL in type 1 VWD, considering all of them as essential information to predict and manage the severity of the clinical bleeding phenotype. In a second step, some other mutation-oriented tests or investigations could be carried out for confirmation.

Thus, this does not intend at all to transmit the message of molecular analysis as a surrogate approach of a phenotypic study. We are now developing an algorithm platform as a software based on these parameters that will help in the diagnostic process in the clinical setting. It includes a *VWF* mutations database that will be updated regularly, taking into account the *VWF* sequence variants that are known not to influence VWF levels or cause a clinical disease.

Recently a similar study in a Portuguese cohort has been published [32] confirming the NGS value in VWD diagnosis.

4. Hypothesis

i. Homogeneous characterization of patients with VWD is not generally accomplished in Spain and also in many countries. There is considerable confusion between variant and non-variants forms. The methods, which would allow us a better characterization of the patients, are not available in all centers due to the fact that they lack the necessary infrastructure to carry them out.
ii. The possibility to enlarge the number of patients by the reopening of the project will allow the validation of the proposed algorithm (phenotype study and NGS of the *VWF* as a first line diagnostic approach) enriching our knowledge of VWD spectrum in our population.
iii. The feasibility to develop linkage analysis and expression studies of certain mutations can help to establish their possible common origin and explain how the mutation affect the protein synthesis or secretion deeping in the molecular basis of VWD at the population or individual level
iv. Currently the new diagnostic methodologies are very helpful but generating overwhelming amount of information impossible to manage at clinical setting. The creation of an algorithmic platform with a regularly updated database that includes processed information in regard to mutations and approved international criteria, to guide the physician in the VWD diagnostic process and recommended therapy should be extremely helpful in facilitating a more uniform characterization and therapy of VWD patients in clinical practice at an international level. Also another main point might be a reduction of the cost (work effort and expenses) in the diagnosis process by using the new methodologies as it is the NGS.

5. Specific objectives description, rationale, methodology and corresponding tasks

The present project was already approved by the Galicia Ethical Committee (CEIC) (***Annex I***).

5.1. Specific main objective

Extension of the central phenotypic and NGS genotypic characterization of the VWD in Spain, through the prospective recruitment in the Spanish VWD cohort of approximately 500 new patients with local historical VWD diagnosis (from approximately 38 centres)

5.2. Secondary objective

Development of an electronic platform using this proposed algorithm. In a second step, some other mutation-oriented tests or investigations could be carried out for confirmation.

Overwhelming information provided from VWD phenotypical and genetic data requires the help of electronic applications.

6. Limitations of the study

i. A higher number of cases for simulation than that available at this moment desirable ▸ the future inclusion of newer cases will facilitate the platform improvement.

ii. Existence of some complex cases that fail in the algorithm process (such as complex genetic changes) ▸ they are not frequent and, again, with their better knowledge will help to improve and refine the platform.
iii. Potential legal problems with the corresponding foreign LOPDs in regard to the possibility of collaborative platform use ▸ an authorization from each particular country should be obtained by the collaborator research team in its country.
iv. Nomenclature of the mutations and diagnostic assignment not always uniformly followed according the international standards and recommendations (for instance from ISTH-SSC VWF) ▸ the present project includes a regular revision of the international information and the adaptation in case of controversy or non-uniform report.
v. The utility of the machine learning approach will require the future participation of cohorts of patients from other countries to achieve solid information in regard to the meaning of some VWF genetic variations.

7. Expected achievements

I. To improve the database for the Spanish Registry on VWD to save the already available data from the records of PCM-VWD-ES project, that allows interconnection with newer future electronic applications, facilitating further studies.
II. Enlargement of the Spanish VWD patients cohort uniformly well characterized at the phenotypic and genetic levels. Future incorporation of new patients potentiating the development of this registry.
III. Achievement of a platform maintainable, potentially scalable, extensible, usable in clinical practice, validated and accepted at an international level that allows a more accurate and uniform diagnosis and therapy of the VWD patients.
IV. Potential ISTH acceptance of this platform to be used internationally.

8. References

1. Lillicrap D. von Willebrand disease: advances in pathogenetic understanding, diagnosis, and therapy. Hematology 2013; 254-60.

2. Mancuso DJ, Tuley EA, Westfield LA, Worrall NK, Shelton-Inloes BB, Socace JM, et al. Structure of the gene for human von Willebrand factor. J Biol Chem 1989; 264: 19514-19527.

3. Bowman M, Hopman WM, Rapson D, Lillicrap D, James P. The prevalence of symptomatic von Willebrand disease in primary care practice. J Thromb Haemost.2010;8:213-6.

4. Sadler JE, Budde U, Eikenboom JC, Favaloro EJ, Hill FG, Holmberg L, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost. 2006; 4:2103-2114.

5. Costa-Pinto J, Pérez-Rodríguez A, Goméz-del-Castillo MC, Lourés E, Rodríguez-Trillo A, Batlle J, et al. Diagnosis of inherited von Willebrand disease: Comparison of two methodologies and analysis of the discrepancies. Haemophilia 2014; 20:559-567.

6. Othman M. Platelet-type von Willebrand disease and type 2B von Willebrand disease: a story of nonidentical twins when two different genetic abnormalities evolve into similar phenotypes. Semin Thromb Hemost. 2007; 33:780-6.

7. Castaman G, Goodeve A, Eikenboom J; European Group on von Willebrand Disease. Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica. 2013; 98:667-74.

8. Hamilton A, Ozelo M, Leggo J, Notley C, Brown H, Frontroth JP, et al. Frequency of platelet type versus type 2B von Willebrand disease. An international registry-based study. Thromb Haemost. 2011; 105:501-8.

9. Ahmad S, Ptashkin B, DiGiovanni C, Cines DB, Konkle BA, Cuker A. False normal von Willebrand factor activity by monoclonal antibody-based ELISA in a patient with type 2A(IID) von Willebrand disease. Thromb Haemost 2011; 106:1224-5.

10. Flood V, Gill J, Haberichter S, Bellissimo D, Christopherson P, Friedman K, et al. Binding Of VWF To Type IV Collagen: An Additional Collagen Binding Mechanism Beyond Types I, III, and VI Collagen?. Blood (Suppl) 2013. Abstract 333.

11. Flood V, Schlauderaff A, Jacobi P, Slobodianuk T, Montgomery R, Haberichter S et al. VWF Interaction With Type IV Collagen Is Mediated Through Critical VWF A1 Domain Residues. Blood (Suppl) 2013. Abstract 29.

12. Flood VH, Gill JC, Christopherson PA, Bellissimo DB, Friedman KD, Haberichter SL, et al. Critical von Willebrand factor A1 domain residues influence type VI collagen binding. J Thromb Haemost. 2012; 10:1417-24.

13. Corrales I, Catarino S, Ayats J, Arteta D, Altisent C, Parra R, et al. High-throughput molecular diagnosis of von Willebrand disease by next generation sequencing methods. Haematologica. 2012; 97:1003-7.

14. Peake I, Goodeve A. Type 1 von Willebrand disease. J Thromb Haemost. 2007; Suppl 1:7-11. Review.

15. Goodeve A, Eikenboom J, Castaman G, Rodeghiero F, Federici AB, Batlle J, et al. Phenotype and genotype of a cohort of families historically diagnosed with type 1 von Willebrand disease in the European study, Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (MCMDM-1VWD). Blood. 2007; 109:112-21.

16. Rodeghiero F, Castaman G. Von Willebrand disease: epidemiology. En “Textbook of hemophilia”. CA Lee, EE Berntorp, WK Hoots. Blackwell Publishing. 2005, pp265-272.

17. Castaman G, Goodeve A, Eikenboom J; European Group on von Willebrand Disease. Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica. 2013 May;98(5):667-74. Eikenboom J, Federici AB, Dirven RJ, Castaman G, Rodeghiero F, Budde U, Schneppenheim R, Batlle J, Canciani MT, Goudemand J, Peake I, Goodeve A; MCMDM-1VWD Study Group. VWF propeptide and ratios between VWF, VWF propeptide, and FVIII in the characterization of type 1 von Willebrand disease. Blood. 2013 Mar 21;121(12):2336-9.

18.Tosetto A, Rodeghiero F, Castaman G, Goodeve A, Federici AB, Batlle J, Meyer D, Goudemand J, Eikenboom J, Schneppenheim R, Budde U, Ingerslev J, Lethagen S, Hill FG, Peake I. A comparison between two semi-quantitative bleeding scales for the diagnosis and assessment of bleeding severity in type 1 von Willebrand disease. Haemophilia. 2011 ;17(1):165-6.

19. Castaman G, Tosetto A, Goodeve A, Federici AB, Lethagen S, Budde U, Batlle J, Meyer D, Mazurier C, Goudemand J, Eikenboom J, Schneppenheim R, Ingerslev J, Habart D, Hill F, Peake I, Rodeghiero F. The impact of bleeding history, von Willebrand factor and PFA-100(®) on the diagnosis of type 1 von Willebrand disease: results from the European study MCMDM-1VWD. Br J Haematol. 2010;151(3):245-51.

20. Castaman G, Tosetto A, Cappelletti A, Goodeve A, Federici AB, Batlle J, Meyer D, Goudemand J, Eikenboom JC, Schneppenheim R, Budde U, Ingerslev J, Lethagen S, Hill F, Peake IR, Rodeghiero F. Validation of a rapid test (VWF-LIA) for the quantitative determination of von Willebrand factor antigen in type 1 von Willebrand disease diagnosis within the European multicenter study MCMDM-1VWD. Thromb Res. 2010;126(3):227-31.

21. Eikenboom J, Hilbert L, Ribba AS, Hommais A, Habart D, Messenger S, Al-Buhairan A, Guilliatt A, Lester W, Mazurier C, Meyer D, Fressinaud E, Budde U, Will K, Schneppenheim R, Obser T, Marggraf O, Eckert E, Castaman G, Rodeghiero F, Federici AB, Batlle J, Goudemand J, Ingerslev J, Lethagen S, Hill F, Peake I, Goodeve A. Expression of 14 von Willebrand factor mutations identified in patients with type 1 von Willebrand disease from the MCMDM-1VWD study. J Thromb Haemost. 2009 Aug;7(8):1304-12.

22. Batlle J, López-Fernández MF, Fraga EL, Trillo AR, Pérez-Rodríguez MA. Von Willebrand factor/factor VIII concentrates in the treatment of von Willebrand disease. Blood Coagul Fibrinolysis. 2009;20(2):89-100.

23. Haberichter SL, Castaman G, Budde U, Peake I, Goodeve A, Rodeghiero F, Federici AB, Batlle J, Meyer D, Mazurier C, Goudemand J, Eikenboom J, Schneppenheim R, Ingerslev J, Vorlova Z, Habart D, Holmberg L, Lethagen S, Pasi J, Hill FG, Montgomery RR. Identification of type 1 von Willebrand disease patients with reduced von Willebrand factor survival by assay of the VWF propeptide in the European study: molecular and clinical markers for the diagnosis and management of type 1 VWD (MCMDM-1VWD). Blood. 2008; 111(10): 4979-85.

24. Castaman G, Lethagen S, Federici AB, Tosetto A, Goodeve A, Budde U, Batlle J, Meyer D, Mazurier C, Fressinaud E, Goudemand J, Eikenboom J, Schneppenheim R, Ingerslev J, Vorlova Z, Habart D, Holmberg L, Pasi J, Hill F, Peake I, Rodeghiero F. Response to desmopressin is influenced by the genotype and phenotype in type 1 von Willebrand disease (VWD): results from the European Study MCMDM-1VWD. Blood. 2008; 111(7): 3531-9.

25. Budde U, Schneppenheim R, Eikenboom J, Goodeve A, Will K, Drewke E, Castaman G, Rodeghiero F, Federici AB, Batlle J, Perez A, Meyer D, Mazurier C, Goudemand J, Ingerslev J, Habart D, Vorlova Z, Holmberg L, Lethagen S, Pasi J, Hill F, Peake I. Detailed von Willebrand factor multimer analysis in patients with von Willebrand disease in the European study, molecular and clinical markers for the diagnosis and management of type 1 von Willebrand disease (MCMDM-1VWD). J Thromb Haemost. 2008; 6(5): 762-71.

26. Hashemi Soteh M, Peake IR, Marsden L, Anson J, Batlle J, Meyer D, Fressinaud E, Mazurier C, Goudemand J, Eikenboom J, Goodeve A. Mutational analysis of the von Willebrand factor gene in type 1 von Willebrand disease using conformation sensitive gel electrophoresis: a comparison of fluorescent and manual techniques. Haematologica. 2007; 92(4): 550-3.

27. Goodeve A, Eikenboom J, Castaman G, Rodeghiero F, Federici AB, Batlle J, Meyer D, Mazurier C, Goudemand J, Schneppenheim R, Budde U, Ingerslev J, Habart D, Vorlova Z, Holmberg L, Lethagen S, Pasi J, Hill F, Hashemi Soteh M, Baronciani L, Hallden C, Guilliatt A, Lester W, Peake I. Phenotype and genotype of a cohort of families historically diagnosed with type 1 von Willebrand disease in the European study, Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (MCMDM-1VWD). Blood. 2007; 109(1): 112-21.

28. Tosetto A, Rodeghiero F, Castaman G, Goodeve A, Federici AB, Batlle J, Meyer D, Fressinaud E, Mazurier C, Goudemand J, Eikenboom J, Schneppenheim R, Budde U, Ingerslev J, Vorlova Z, Habart D, Holmberg L, Lethagen S, Pasi J, Hill F, Peake I. A quantitative analysis of bleeding symptoms in type 1 von

Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). J Thromb Haemost. 2006; 4(4): 766-73.

29. Eikenboom J, Van Marion V, Putter H, Goodeve A, Rodeghiero F, Castaman G, Federici AB, Batlle J, Meyer D, Mazurier C, Goudemand J, Schneppenheim R, Budde U, Ingerslev J, Vorlova Z, Habart D, Holmberg L, Lethagen S, Pasi J, Hill F, Peake I. Linkage analysis in families diagnosed with type 1 von Willebrand disease in the European study, molecular and clinical markers for the diagnosis and management of type 1 VWD. J Thromb Haemost. 2006; 4(4): 774-82.

30. Batlle J, Perez-Rodriguez A, Pinto JC, Fraga EL, Rodriguez-Trillo A, Fernanda Lopez-Fernandez M. Diagnosis and management of von Willebrand disease in Spain. Semin Thromb Hemost. 2011; 37:503-10.

31. Batlle J, Pérez-Rodríguez A, Corrales I, López-Fernández MF, Rodríguez-Trillo Á, Lourés E, Cid AR, Bonanad S, Cabrera N, Moret A, Parra R, Mingot-Castellano ME, Balda I, Altisent C, Pérez-Montes R, Fisac RM, Iruín G, Herrero S, Soto I, de Rueda B, Jiménez-Yuste V, Alonso N, Vilariño D, Arija O, Campos R, Paloma MJ, Bermejo N, Toll T, Mateo J, Arribalzaga K, Marco P, Palomo Á, Sarmiento L, Iñigo B, Nieto Mdel M, Vidal R, Martínez MP, Aguinaco R, César JM, Ferreiro M, García-Frade J, Rodríguez-Huerta AM, Cuesta J, Rodríguez-González R, García-Candel F, Cornudella R, Aguilar C, Borràs N, Vidal F. Molecular and clinical profile of von Willebrand disease in Spain (PCM-EVW-ES): Proposal for a new diagnostic paradigm. Thromb Haemost. 2015 Dec 22;115(1):40-50.

32. Fidalgo T, Silva Pinto C, Corrales I, Borràs N, Oliveira A, Almeida H, Marques D, Oliveira C, Tavares A, Diniz MJ, Antunes M, Caetano G, Kjöllerström P, Maia R, Martinho P, Gonçalves E, Sevivas T, Vidal F, Ribeiro L. Genotype–phenotype correlation in a cohort of Portuguese patients comprising the entire spectrum of VWD types: meaningful contribution of NGS Thromb Haemost 2016; (In press).

33. Corrales I, Ramirez L, Altisent C, Parra R, Vidal F. Rapid molecular diagnosis of von Willebrand disease by direct sequencing. Detection of 12 novel putative mutations in VWF gene. Thrombosis And Haemostasis. 2009;101:570-576.

34. Corrales I, Ramirez L, Altisent C, Parra R, Vidal F. The study of the effect of splicing mutations in von Willebrand factor using RNA isolated from patients' platelets and leukocytes. J Thromb Haemost. 2011;9:679-688.

35. Houdayer C. In silico prediction of splice-affecting nucleotide variants. Methods Mol Biol. 2011;760:269-281.

9. Experience and suitability of the proposed investigator team

9.1. Medical Team 1

This Team is deeply involved in the Medical Institute of Research A Coruña (INIBIC) and Foundation Professor Novoa Santos of Xerencia de Xestion Integrada Area de A Coruña (XXIAC), Spain.

Composition

1. Dr. Francisco Javier Batlle Fonrodona (Chairman of Service Hematology and Hemotherapy).
2. Dr. María Fernanda López Fernández (Head of Unit in Hemostasia and Thrombosis, Hematology Department).
3. Dr. Almudena Pérez Rodríguez (Post-doctoral Investigator,Hematology Department).
4. María Joana Costa Pinto Prego de Faria (Pre-doctoral Investigator, Hematology Department. Doctoral Thesis ongoing in the PCM-EVW-ES Project).
5. Ángela Rodríguez Trillo (Pre-doctoral Investigator, Hematology Department. Doctoral Thesis ongoing in the PCM-EVW-ES Project).
6. Dr. María del Carmen Gómez del Castillo Solano (Assistant Physician and Pre-doctoral Investigator, Hematology Department. Doctoral Thesis ongoing in the PCM-EVW-ES Project).
7. Dr. Marta Fernández Docampo (Assistant Physician and Pre-doctoral Investigator, Hematology Department. Doctoral Thesis ongoing in the PCM-EVW-ES Project)

Experience

1. Continuous development of a line of research on VWF and VWD started in the Department of Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla, California, USA (Dr. Theodore S. Zimmerman). It was funded by different institutions such as FIS (Instituto Carlos III, Spain), European Union (project MCMDM-1VWD), Xunta de Galicia and North American Committee for Scientific and Technological Collaboration.
2. Our group participated as expert group in the project of standardization and evaluation of patients with VWD sponsored by the Subcommittee on von Willebrand Factor of the ISTH-SSC VWF. The objective was to assess the minimum required methodology for the study of the VWD in clinical practice. Thirty-two laboratories from around the world participated.
3. Since the year 2000, the Team is part of the European Group of VWD, participating in several projects such as:
    i. European Project **"MCMDM-1VWD"**. It is a European Union (EU)–funded survey on type 1 VWD. Fourteen VWD treatment centers in 9 European countries participated. The study aimed at recruiting the full spectrum of type 1 VWD families, including milder cases to mimic the clinical situation as much as possible and not to have bias toward the more severe, highly penetrant type 1 VWD. Also, affected and unaffected family members were recruited. (2000-2003).
    ii. Member of the **European Group on VWD.**

iii. International Project **"3WINTERS-IPS"**. It is an European-Iranian study based in the study of the type 3 von Willebrand disease (a total of 16 investigational sites are involved in this project in 8 European countries). (2012-to the present).

iv. Coordinator center for the project **"PCM-VWD-ES".** Thirty-eight Spanish hospitals are participating in this project. Currently, a total of 557 have recruited and studied in a centralized way.

v. Coordinating center for the initial analysis of VWD in Spain that was published in Seminars in Thrombosis and Hemostasis.

4. Six **Doctoral Thesis,** two of them currently under development, related to the field of VWD.
5. Reference Laboratory for the study of many patients with VWD from Spain including their phenotypic and genetic characterization.
6. Initiation of **Translational Research and Innovation and Development** by cooperation with the enterprise LapiSoft in the field of VWD.

Recent publications related to the field of the present proposal

1. Pérez-Rodríguez A, Batlle-López A, Blanco R, Varela I, León J, Delgado MD, et al. *A novel mutation in the ADAMTS13 of a child with Upshaw-Schulman Syndrome*. Thromb Haemost, 2014 [ahead of print].
2. Costa-Pinto J, Pérez-Rodríguez A, Gómez-del-Castillo M del C, Lourés E, Ródríguez-Trillo A, Batlle J, López-Fernández MF. Diagnosis of inherited von Willebrand disease: comparison of two methodologies and analysis of the discrepancies. Haemophilia 2014;20:559–567.
3. Castaman G, Goodeve A, Eikenboom J; European Group on von Willebrand Disease. Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica. 2013;98:667-74.
4. Eikenboom J, Federici AB, Dirven RJ, Castaman G, Rodeghiero F, Budde U,et al. VWF propeptide and ratios between VWF, VWF propeptide, and FVIII in the characterization of type 1 von Willebrand disease. Blood. 2013;121(12):2336-9.
5. Batlle J, Perez-Rodriguez A, Pinto JC, Fraga EL, Rodriguez-Trillo A, Lopez-Fernandez MF. Diagnosis and management of von Willebrand disease in Spain. Semin Thromb Hemost. 2011;37:503-10.
6. Pérez-Rodríguez A, Pinto JC, Lourés E, Rodríguez-Trillo A, Cuenca JJ, Batlle J, López-Fernández MF. Acquired von Willebrand syndrome and mitral valve prosthesis leakage. A pilot study. Eur J Haematol. 2011;87:448-56.
7. Tosetto A, Rodeghiero F, Castaman G, Goodeve A, Federici AB, Batlle J, et al. A comparison between two semi-quantitative bleeding scales for the diagnosis and assessment of bleeding severity in type 1 von Willebrand disease. Haemophilia. 2011;17:165-6.
8. Castaman G, Tosetto A, Goodeve A, Federici AB, Lethagen S, Budde U, et al. The impact of bleeding history, von Willebrand factor and PFA-100(®) on the diagnosis of type 1 von Willebrand disease: results from the European study MCMDM-1VWD. Br J Haematol. 2010;151:245-51.
9. Castaman G, Tosetto A, Cappelletti A, Goodeve A, Federici AB, Batlle J, et al. Validation of a rapid test (VWF-LIA) for the quantitative determination of von Willebrand factor antigen in type 1 von

Willebrand disease diagnosis within the European multicenter study MCMDM-1VWD. Thromb Res. 2010;126:227-31.

10. Batlle J, López-Fernández MF, Fraga EL, Trillo AR, Pérez-Rodríguez MA. Von Willebrand factor/factor VIII concentrates in the treatment of von Willebrand disease. Blood Coagul Fibrinolysis. 2009;20:89-100.

11. Eikenboom J, Hilbert L, Ribba AS, Hommais A, Habart D, Messenger S, et al A. Expression of 14 von Willebrand factor mutations identified in patients with type 1 von Willebrand disease from the MCMDM-1VWD study. J Thromb Haemost. 2009;7:1304-12.

12. Hermans C, Batlle J. Autosomal dominant von Willebrand disease type 2M. Acta Haematol. 2009;121:139-44.

13. Pérez-Rodríguez A, García-Rivero A, Lourés E, López-Fernández MF, Rodríguez-Trillo A, Batlle J. Autosomal dominant C1149R von Willebrand disease: phenotypic findings and their implications. Haematologica. 2009;94:679-86.

14. Haberichter SL, Castaman G, Budde U, Peake I, Goodeve A, Rodeghiero F, et al. Identification of type 1 von Willebrand disease patients with reduced von Willebrand factor survival by assay of the VWF propeptide in the European study: molecular and clinical markers for the diagnosis and management of type 1 VWD (MCMDM-1VWD). Blood. 2008;111:4979-85.

15. Budde U, Schneppenheim R, Eikenboom J, Goodeve A, Will K, Drewke E, et al. Detailed von Willebrand factor multimer analysis in patients with von Willebrand disease in the European study, molecular and clinical markers for the diagnosis and management of type 1 von Willebrand disease (MCMDM-1VWD). J Thromb Haemost. 2008;6:762-71.

16. Castaman G, Lethagen S, Federici AB, Tosetto A, Goodeve A, Budde U, et al. Response to desmopressin is influenced by the genotype and phenotype in type 1 von Willebrand disease (VWD): results from the European Study MCMDM-1VWD. Blood. 2008;111:3531-9.

17. Batlle J, Pérez-Rodríguez A, Franqueira MD, López-Fernández MF. Type 2M von Willebrand disease: a variant of type 2A? J Thromb Haemost. 2008;6:388-90.

18. Hashemi Soteh M, Peake IR, Marsden L, Anson J, Batlle J, et al. Mutational analysis of the von Willebrand factor gene in type 1 von Willebrand disease using conformation sensitive gel electrophoresis: a comparison of fluorescent and manual techniques. Haematologica. 2007;92:550-3.

19. Tosetto A, Rodeghiero F, Castaman G, Bernardi M, Bertoncello K, Goodeve A, et al. Impact of plasma von Willebrand factor levels in the diagnosis of type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1VWD). J Thromb Haemost 2007;5:715-21.

20. Goodeve A, Eikenboom J, Castaman G, Rodeghiero F, Federici AB, Batlle J, et al. Phenotype and genotype of a cohort of families historically diagnosed with type 1 von Willebrand disease in the European study, Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (MCMDM-1VWD). Blood. 2007;109:112-21.

21. Eikenboom J, Van Marion V, Putter H, Goodeve A, Rodeghiero F, Castaman G, et al. Linkage analysis in families diagnosed with type 1 von Willebrand disease in the European study, molecular and clinical markers for the diagnosis and management of type 1 VWD. J Thromb Haemost. 2006;4:774-82.

22. Tosetto A, Rodeghiero F, Castaman G, Goodeve A, Federici AB, Batlle J, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). J Thromb Haemost. 2006;4:766-73.

23. Rodeghiero F, Castaman G, Tosetto A, Batlle J, Baudo F, Cappelletti A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. J Thromb Haemost. 2005;3:2619-26. Erratum in: J Thromb Haemost. 2006;4:925

24. Penas N, Pérez-Rodríguez A, Torea JH, Lourés E, Noya MS, López-Fernández MF, et al. von Willebrand disease R1374C: type 2A or 2M? A challenge to the revised classification. High frequency in the northwest of Spain (Galicia). Am J Hematol. 2005;80:188-96.

25. Penas N, Pérez A, González-Boullosa R, Batlle J. C1272S: a new candidate mutation in type 2A von Willebrand disease that disrupts the disulfide loop responsible for the interaction of VWF with platelet GP Ib-IX. Am J Hematol. 2004;75:73-7.

26. Batlle J, Pérez-Rodríguez A, Corrales I, López-Fernández MF, Rodríguez-Trillo Á, Lourés E, Cid AR, Bonanad S, Cabrera N, Moret A, Parra R, Mingot-Castellano ME, Balda I, Altisent C, Pérez-Montes R, Fisac RM, Iruín G, Herrero S, Soto I, de Rueda B, Jiménez-Yuste V, Alonso N, Vilariño D, Arija O, Campos R, Paloma MJ, Bermejo N, Toll T, Mateo J, Arribalzaga K, Marco P, Palomo Á, Sarmiento L, Iñigo B, Nieto Mdel M, Vidal R, Martínez MP, Aguinaco R, César JM, Ferreiro M, García-Frade J, Rodríguez-Huerta AM, Cuesta J, Rodríguez-González R, García-Candel F, Cornudella R, Aguilar C, Borràs N, Vidal F. Molecular and clinical profile of von Willebrand disease in Spain (PCM-EVW-ES): Proposal for a new diagnostic paradigm. Thromb Haemost. 2015 Dec 22;115(1):40-50.

9.2. Medical Team 2. Banc de Sang I Teixits, Barcelona.

Composition

Molecular Diagnosis and Therapy Unit (UDTM) of the Blood and Tissue Bank (BST).

1. Dr. Francisco Vidal, UDTM coordinator.
2. Dr. Irene Corrales.
3. Dr. Nina Borràs.
4. Mrs. Lorena Ramírez, lab technician
5. Ms. Natalia Comes (Lab technician, UDTM department)

Hemophilia Unit of the Vall d'Hebron University Hospital

1. Dr. Rafael Parra (Head of Unit of Hematology, Hematology department).
2. Dr. Carme Altisent (Doctor of Unit of Hematology, Hematology department).

Experience

The research team involved in the project comprised a balance of basic, applied and clinical researchers, as well as attending physicians. The research team members conducted basic and applied studies of high quality, all having complementary expertise optimally covers the different objectives of the proposed project.

They have a broad expertise in clinical diagnosis and therapy of patients with VWD since the unit is the Congenital Coagulopathies Comprehensive Care Centre in Catalonia and is one of the largest in Spain, taking care of more that and none thousand patients and relatives. The Hemophilia Unit has an experienced multidisciplinary team comprised for a total of 12 professionals who perform their work exclusively on this service, developing comprehensive care of the patients and relatives. The continuous monitoring of the quality of care through clinical sessions, has converted the unit into a worldwide reference center for the congenital coagulation disorders. Equally significant, is the participation of the Unit in multicenter international clinical trials, as well as in phase III & IV trials for new drugs. Hemophilia Unit has the human and material resources necessary for diagnosis, patient selection and sample extraction. Specific coagulation studies are performed routinely in the Coagulation Laboratory of the Hospital Universitari Vall d'Hebron.

This Unit has a dual character since their foundation in 1998: diagnostic support in congenital coagulation disorders as well as other hereditary diseases; research and development of new approaches in the field of medical diagnostics and therapeutics. In-depth studies of molecular events present in some affected individuals and the relation genotype-phenotype constitute the most basic area of the team objectives. The UDTM is comprised of a talented staff of scientists with a broad range of expertise to support clinical needs. Among the primary tasks of the lab there is the applied research in the molecular diagnosis of congenital blood coagulation disorders, genetic counseling and prenatal diagnosis. Also, an important part of the current research objectives is the innovation in technological tools and their transfer to the routine laboratory. The protocols designed and optimized in our laboratory for the molecular diagnosis of HA (Vidal et al. 2001. Thromb Haemost 85: 580-3) and HB (Vidal et al. 2000. Br J Haematol 111: 549-51) that are currently used to provide routine care service (certified according to the ISO 9001 standard), includes identification of the molecular defect in patients and offered genetic counseling and prenatal diagnosis. Also, the developed technology has been transferred to other national centers involved in diagnosis of hemophilia. These protocols were recognized as an outstanding technological contribution among international experts in the field. The UDTM counts with a molecular biology laboratory with three full-equipped independent work areas: pre-PCR, post-PCR and cell culture.

Dr. Irene Corrales, part of the UDTM staff since July 2006 and contracted by a grant awarded by the Catalan Private Foundation of Hemophilia and intramural funding from the BST, reached the PhD degree with the highest qualification. Her doctoral project has been focused on the development of optimized procedures for amplification and sequencing of the *VWF* by traditional and NGS sequencing, validation of this technique in patients with VWD with very satisfactory results. With above 10 years of experience in molecular biology she also has a broad experience in the in silico and in vivo analysis of the identified mutations. Since her incorporation to the UDTM, she performed the routinely molecular and prenatal diagnosis of congenital coagulopathies. Moreover, she also participates very effectively in research projects contributing with large technical and creative skills.

Dr. Francisco Vidal, IP of this project and UDTM coordinator, has extensive experience in molecular biology, cell biology and molecular diagnosis of genetic diseases. Specifically, due to both the development of his current job as the projects in which he has been involved in his career, is closely familiar with theoretical and practical level with the genetic basis of hereditary diseases as well as with the methodology used to detect them. Also, an important part of his duties include the research and process innovation in the field of human genetics for their translation to the routine laboratory. The work on the characterization of genes involved in these coagulopathies allows epidemiological studies of the relationship between the type of mutation and clinical aspects of the disease and also offers the possibility of further study of specific mutations that provide information about some of the basic mechanisms

associated to disease. Besides research activity also plays a care activity through molecular diagnosis of hereditary diseases, genetic counseling and prenatal diagnosis.

Recent publications related to the field of the present proposal

1. Corrales I, Catarino S, Ayats J, Arteta D, Altisent C, Parra R, Vidal F.High-throughput molecular diagnosis of von Willebrand disease by next generation sequencing methods. Haematologica. 2012 Jul;97(7):1003-7.
2. Corrales I, Ramírez L, Altisent C, Parra R, Vidal F. The study of the effect of splicing mutations in von Willebrand factor using RNA isolated from patients' platelets and leukocytes. J Thromb Haemost. 2011 Apr;9(4):679-88.
3. Corrales I, Ramírez L, Ayats J, Altisent C, Parra R, Vidal F. Integration of molecular and clinical data of 40 unrelated von Willebrand Disease families in a Spanish locus-specific mutation database: first release including 58 mutations.Haematologica. 2010 Nov;95(11):1982-4.
4. Fidalgo T, Silva Pinto C, Corrales I, Borràs N, Oliveira A, Almeida H, Marques D, Oliveira C, Tavares A, Diniz MJ, Antunes M, Caetano G, Kjöllerström P, Maia R, Martinho P, Gonçalves E, Sevivas T, Vidal F, Ribeiro L. Genotype–phenotype correlation in a cohort of Portuguese patients comprising the entire spectrum of VWD types: meaningful contribution of NGS Thromb Haemost 2016; (In press).
5. Corrales I, Ramírez L, Altisent C, Parra R, Vidal F. Rapid molecular diagnosis of von Willebrand disease by direct sequencing. Detection of 12 novel putative mutations in VWF gene. Thromb Haemost. 2009 Mar;101(3):570-6.
6. Batlle J, Pérez-Rodríguez A, Corrales I, López-Fernández MF, Rodríguez-Trillo Á, Lourés E, Cid AR, Bonanad S, Cabrera N, Moret A, Parra R, Mingot-Castellano ME, Balda I, Altisent C, Pérez-Montes R, Fisac RM, Iruín G, Herrero S, Soto I, de Rueda B, Jiménez-Yuste V, Alonso N, Vilariño D, Arija O, Campos R, Paloma MJ, Bermejo N, Toll T, Mateo J, Arribalzaga K, Marco P, Palomo Á, Sarmiento L, Iñigo B, Nieto Mdel M, Vidal R, Martínez MP, Aguinaco R, César JM, Ferreiro M, García-Frade J, Rodríguez-Huerta AM, Cuesta J, Rodríguez-González R, García-Candel F, Cornudella R, Aguilar C, Borràs N, Vidal F. Molecular and clinical profile of von Willebrand disease in Spain (PCM-EVW-ES): Proposal for a new diagnostic paradigm. Thromb Haemost. 2015 Dec 22;115(1):40-50.

9.3. Medical Team 3. Hospital Universitario Politécnico La Fe. Valencia.

1. Dr. Ana Rosa Cid Haro.

Experience

Dr. Cid has participated in applied studies of high quality, all having complementary expertise optimally covers the different objectives of the proposed project. She has a broad expertise in clinical diagnosis and therapy of patients with VWD since the unit is the Congenital Coagulopathies Comprehensive of Valencia and is also one of the largest in Spain, taking care of patients and relatives. This Unit has participated in multicenter international clinical trials and has the human and material resources necessary for diagnosis, patient selection and sample extraction, as well as for specific coagulation studies.

Recent publications related to the field of the present proposal

1. Batlle J, Pérez-Rodríguez A, Corrales I, López-Fernández MF, Rodríguez-Trillo Á, Lourés E, Cid AR, Bonanad S, Cabrera N, Moret A, Parra R, Mingot-Castellano ME, Balda I, Altisent C, Pérez-Montes R, Fisac RM, Iruín G, Herrero S, Soto I, de Rueda B, Jiménez-Yuste V, Alonso N, Vilariño D, Arija O, Campos R, Paloma MJ, Bermejo N, Toll T, Mateo J, Arribalzaga K, Marco P, Palomo Á, Sarmiento

L, Iñigo B, Nieto Mdel M, Vidal R, Martínez MP, Aguinaco R, César JM, Ferreiro M, García-Frade J, Rodríguez-Huerta AM, Cuesta J, Rodríguez-González R, García-Candel F, Cornudella R, Aguilar C, Borràs N, Vidal F. Molecular and clinical profile of von Willebrand disease in Spain (PCM-EVW-ES): Proposal for a new diagnostic paradigm. Thromb Haemost. 2015 Dec 22;115(1):40-50.

9.4. Engineer Informatics Team

LapiSoft Projects S.L A Coruña. NIF: B70442140 contact@lapisoft.es

In order to cope with the main objectives of the project it will be necessary to rely on a researchers group with technical expertise and experience on the field of Information Technologies. An important aspect of relying on professionals with the mentioned expertise, obeys not only to the need of engineering and developing both patient register and diagnosis platforms but also to the fact of the necessary cooperation with the medical team, creating a space of mutual collaboration and interaction, needed to develop the main platform through the specified iterative process. Lapisoft Projects S.L. has been chosen for this project because their experience in all of the required informatics and technological aspects.

The technical team will contribute with the technological knowledge and thus helping to find solutions to the possible problems and guide the medical team in their main objectives. One of the main concept will consist on translate the diagnosis algorithms into software (by using BPM and flow-design) which will support the digital representation of the medical algorithmic. Some other aspects of the projects can be enhanced positively by informing and teaching the medical team about options that new technologies offer.

The members of the technical team count with professional expertise on different fields of IT including experience on research and implementation of computer science applications in the field of biomedicine, including the data collection and analysis of biomedical datasets. In these projects, multi-modal data was collected (from different sources) and machine learning techniques were applied to find patterns to characterize the data. These projects were mainly developed in the Human Sensing Lab (Robotics Institute, Carnegie Mellon University). The adviser for these projects was the Prof. Fernando de la Torre. The experience acquired on the mentioned previous work in the university helped to lead several projects in PHRQL Inc., and innovative startup company dedicated to the field of biomedicine. As a briefly description of the technologies used, we can mention data encryption, secure data accessing, compliance of data protecting laws and a user-friendly design.

Other team members on the tech team are specialists on business intelligence, data mining, big data processing and BMP modelling with huge experience across several IT projects. The team also counts with a former designer (Advertisement and Multimedia Communication) who has experience as leader of a designing team which cover all the phases of the design process, for instance, ideation, contents architecture, graphical interface design and usability tests. The objective was to create multi-devices applications (tv, portable devices, pc browsers) prioritizing the friendly user experience on the graphical interfaces as a key design concept.

The already proved capabilities of the Tech Team to adapt the technological concepts to specific fields of work, particularly the biomedical one, will be crucial to bind both worlds, technological and medical to create a necessary synergy to cope with the objectives of the project. At the same time with the potential that the new technologies offer it is very important to apply the user friendly designs, which result into a better experience to the final user of the platform.

As an external adviser, the Professor Fernando de la Torre, from the Robotics Institute in the Carnegie Mellon University will provide his expertise to engineer and run machine learning techniques over the

datasets and the diagnosis algorithms to try to find behavioral and trend patterns which can lead to a better general comprehension of the VWD in general and diagnosis in particular. The collaboration with the mentioned CMU department (world leading institution) would eventually provide international visibility to the main project and specifically to the techniques applied on the data. Expenses for this collaboration are considered on the final budget. A letter of Prof. de la Torre accepting to collaborate in the project is included at the end of this proposal.

Publications and awards of the team members.

1. Fernando Batlle, Alberto Gil, Fernando de la Torre, Jessica Hodgins. Grand Challenge Data Collection: System Engineering & Technical Challenges. *Quality of life workshop at Robotics Institute (Carnegie Mellon University) 2011.*
2. Fernando Batlle. Caremedia: creating a system to improve the knowledge of the elderly people behavior. *Cum laude in Master thesis (Carnegie Mellon University – University of Vigo) 2011.*
3. Breogán Amoedo, Manuel López, Francisco Vicente, Fernando de la Torre, Alexander Hauptmann, Dona Curti. Monitoring elderly in independent living and in nursing homes. *Quality of life workshop at Robotics Institute (Carnegie Mellon University) 2012.*
4. Samarjit Das, Breogan Amoedo, Fernando De la Torre, Jessica Hodgins. Detecting Parkinsons' Symptoms in Uncontrolled Home Environments: A Multiple Instance Learning Approach. Engineering in Medicine and Biology Conference Management System (EMBC) 2012.
5. Sanofi US Innovation Challenge Award 2013. Won by the startup PHRQL Inc. counting with two members of the tech team as tech lead designers.

10. Study duration, timelines and milestones

The estimated duration of the whole proposed project is three years.

11. Relevance of the project in terms of clinical care and/or technological development

All the advances generated during this project will have beneficial repercussions for the patients.

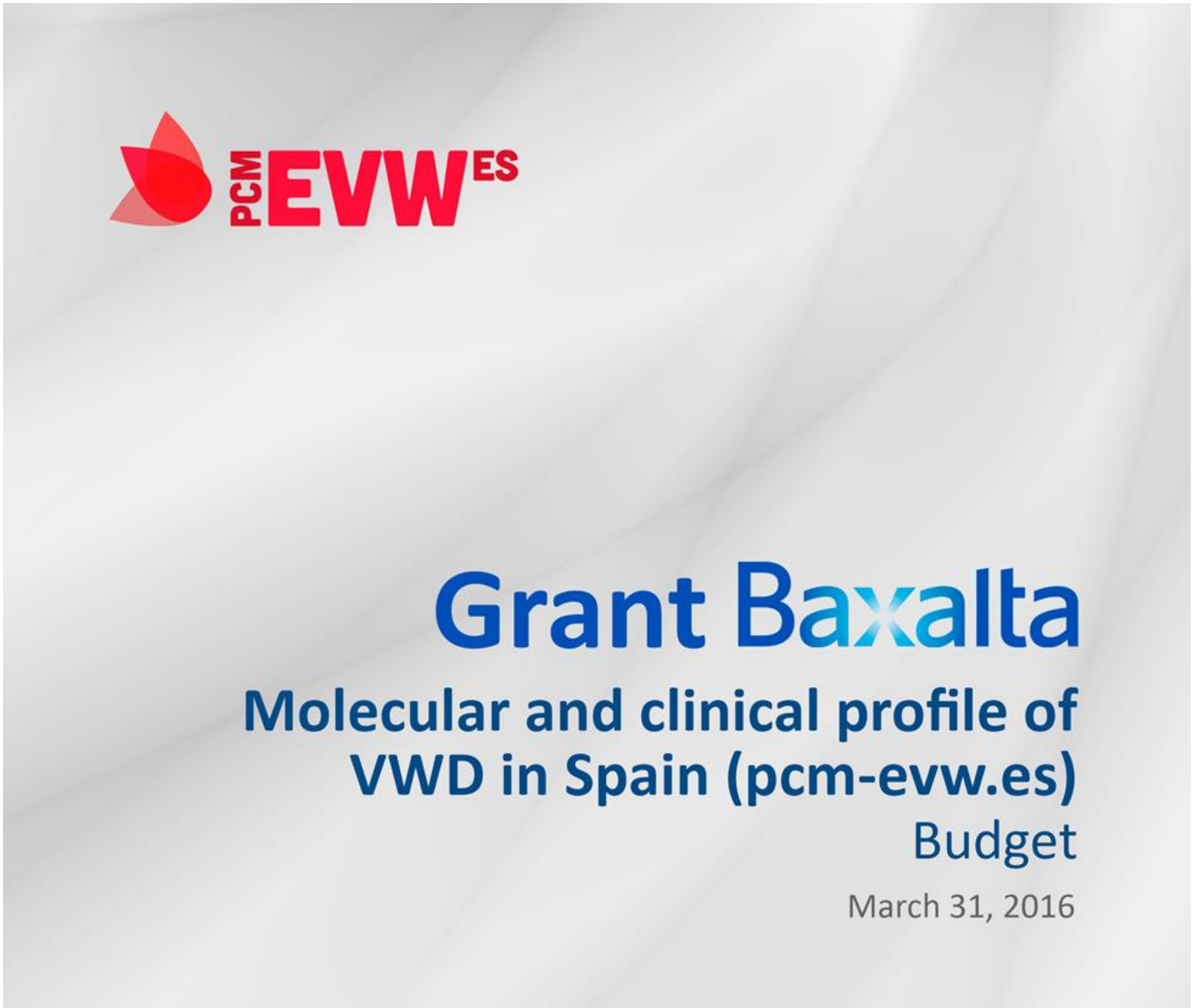
1. Improvement of therapeutic strategies.
2. Greater preventive capacity in patients to face up to risk situations of thrombosis or bleeding.
3. To increase the cost-effectiveness of diagnostic methods and select the most appropriate therapeutic strategies.
4. Adequate characterization of patients.
5. Better knowledge of the actual state of the disease in Spain.
6. Provide a platform of Spanish patients the best characterized possible and homogeneously which allows us to develop our own projects and participate in international projects such as the European project "3WINTERS-IPS" ("Type 3 VWD and international registries inhibitors prospective study") in which we are currently participating, or American project GWAS (Genome Wide Association Study).
7. Create a registry into the Spanish Society of Thrombosis and Haemostasis (SETH).
8. Develop consensus guidelines for diagnosis and treatment of the VWD (Methodology GRADE).
9. This project will contribute to the clinical diagnosis of VWD at international level, especially in patients with particularly complex symptoms and diagnostic. This project is otherwise essential to establish international partnerships, participate in international studies and to access to additional funding resources.
10. An aim of this project is the accomplishment of doctoral theses.

12. Relevance of the project in terms of scientific impact and technological development

1. **Dissemination of results:** Target conferences to present the results of the project will be the 2017-19 meetings and congresses of ISTH, World Federation of Haemophilia, ASH, EAHAD, SETH, aside from partial results will be presented in other minor workshops or meetings. It is expected to publish some articles with the results of this project in international journals (e.g., Journal Thrombosis and Haemostasis, Blood, Haemostasis and Thrombosis, Haematologica, American

Journal of Haematology). The initial expected publications from the present Project are shown in **Annex VIII**

2. Ellaboration of a website similar to that carried out in the European project MCMDM-1VWD.
3. The partnership between LapiSoft and PCM workgroup has, among their aims, to participate and leading **innovation** and **research** projects with a **markedly translational** nature and with a direct impact on the quality of clinical care (**applicability**). To our knowledge there is no similar project in this field.
4. **Potential patents** may derive from this project.
5. Development of **e-learning** and **new information technologies (forum discussion, ads, google search engine)**.
6. Eventually, there will be a study of all the data gathered, and will consult to experts on pattern recognition and **machine learning** in order to achieve more knowledge of the disease. New computer science algorithms will be defined, and the results of applying them, will be submitted for their publication in either medical or technical international journals.
7. We believe that this project will contribute to the clinical diagnosis of VWD at international level, especially in patients with particularly complex symptoms and diagnostic. This project is otherwise essential to establish international partnerships, participate in international studies and to access to additional funding resources.


PCM EVW ES
Grant Baxalta
Molecular and clinical profile of VWD in Spain (pcm-evw.es)
Budget
March 31, 2016

13. Summary of the whole budget

CONCEPT	DESCRIPTION
Consumables	Central phenotipic study
	Central genotipic assay
Staff	Postdoctoral Investigator Fellowship
Services	Local patients sampling collection and transfer to central Laboratories
	Engineer Technical Teem budget contacted as a technical external service
Whole requested budget	US$ 374,473.00

13.1. Postdoctoral Investigator Fellowship Research Medical Team.

For the accomplishment of this project it is needed to contract a post-doctoral investigator (at half time) with a deep knowledge in VWF and VWD. His/her activity will include:

1. Central phenotipic analysis of the 500 samples.
2. Update of the database (monthly). Exhaustive bibliographical search will be realized as well as also there will be checked different database that already exist in order to incorporate all those mutations and polymorphisms that have been described recently, providing the most detailed information possible about them.
3. Analysis of controversy. To help to adopt a position in those cases in which exist controversy.
4. In collaboration with LapiSoft, will conduct some basic testing on each new feature developed and report any discrepancy with the initial specification.
5. Elaboration of reports and modifications according new requirements and features of the algorithm.
6. Validation of the platform.

13.2. Sampling collection and transfer to central laboratories

This budget has been calculated estimating a recruitment of 400 patients from approximately 35 different centres from Spain with recollection of the samples from de local centres and transfer to Central Laboratory of La Coruña, Spain assuring to keep them permanently and adequately frozen. In order to make efficient this transfer, it will be carefully planned together with the enterprise chosen grouping as much as possible different centres form close geographical areas. Once received the samples, aliquot fractions will be sent to Central Laboratory of Barcelona for molecular analysis.

13.3. Engineer Technical Team (Lapisoft Projects S.L) contacted as a technical external service.

Based on Software engineer paradigms, Lapisoft will break down the implementation of the technical part of the project. These activities include the detailed design of the system by a System Analyst and a UX designer, the implementation by a software developer and the validation by a betatester. These will be considered for the full duration of the project:

- **Legal LOPD advising:** To assure the compliance of the Spanish data privacy law. Professional expert consulting will be required.
- **Cloud resources and support**: this includes the cost of the infrastructure plus the support plan for both systems.
- **Machine learning consulting:** As it was mentioned, since machine learning techniques will be applied to the dataset, external advising will provide guides to follow.

We wish to emphasized that the present project will be funded by the grant requested to Baxalta and it will not suppose additional costs to the FETH.