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Web-based ecosystem software for virtual crossmatching in transplant programs

Keylla S.U. Aita [a,*], Semiramis J.H. Monte [b,e], Adalberto S. Silva [c,d], Mário S.C. Marroquim [b], Antônio Gilberto B. Coelho [b], Luiz Claudio D.M. Sousa [b,c]

[a] Distance Education Centre, Federal University of Piaui, Rua Olavo Bilac – Bairro Centro, CEP: 64280001 Teresina, Piaui, Brazil
[b] Immunogenetics and Molecular Biology Laboratory, Federal University of Piaui, Teresina, Piaui, Brazil
[c] Computation Department, Federal University of Piaui, Teresina, Piaui, Brazil
[d] Department of Biology, Federal University of Piaui, Teresina, Piaui, Brazil
[e] Health Sciences Centre, Federal University of Piaui, Teresina, Piaui, Brazil

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ABSTRACT

Background: The compatibilities between donors and recipients are extremely important for evaluating the immunological risks of transplants. One challenge faced by data analysis tools is the transformation of complex data into simple, intuitive, and important information that can be used to resolve contemporary problems. To address this challenge, we developed the EpViX software to perform epitope reactivity analyses and automated epitope virtual crossmatching. EpViX is a facilitator of medical decision-making regarding the identification of the best donor for a high-immunologic risk recipient. The objective of this work is to describe the computational architecture of the EpViX ecosystem (http://www.epvix.com.br).

Materials and methods: EpViX is a freeware on the web that was developed in the Ruby language. EpViX can be accessed from different platforms, e.g., PCs, tablets, and smartphones. It consists of an ecosystem of tools that are capable of integrating all of the stakeholders who are involved in a transplant process with a deceased donor.

Results: We successfully developed a program that allows people to work collaboratively and effectively during the donation process by accurately predicting negative crossmatches, saving time and other resources.

Conclusions: EpViX represents a significant breakthrough for the organ transplant process and may meet the current needs of transplant programs because it increases the chances of the allocation of low-immunologic risk donors to highly sensitized recipients and assures greater equity among the recipients on a waiting list. EpViX was duly verified and tested in terms of data security. Moreover, usability tests demonstrated that EpViX is an intuitive and easy-to-use tool.

1. Introduction

The compatibilities between donors and recipients are extremely important for evaluating the immunological risks of transplants. Anti-HLA antibodies recognize specific amino acid sequences in HLA antigens that are called epitopes [1,2]. The determination of the specificities of anti-HLA antibodies implies the identification of a donor with HLA (Human Leukocyte Antigens) molecules for which the recipient does not have preformed antibodies. Recipients who are highly sensitized to HLA molecules have greater quantities of preformed antibodies and thus have a smaller chance of receiving a transplant due to their high immunological risk, which reduces the quantity of compatible donors. Consequently, the waiting list grows, and the mortality is high. One challenge faced by data analysis tools is the transformation of complex data into simple, intuitive, and important information that can be used to resolve contemporary problems. To address this challenge, we developed the EpViX software to perform epitope reactivity analyses of anti-HLA antibodies before and after transplantation. EpViX is a facilitator of medical decision-making regarding the identification of the best donor for a high-immunologic risk recipient.

From the historic perspective, two important elements stand out in regard to epitope-based reactivity analysis. The first element is the theoretical description of epitopes by René Duquesnoy [1,2] and the epitopes identified by Terasaki [3,4] in experimental

* Corresponding author.
E-mail address: keyllaurtiga@ufpi.edu.br (K.S.U. Aita).

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models. The second element is the universalization of Luminex Single-Antigen Bead (LSAB) tests that involve isolated HLA molecules on the surfaces of synthetic particles that, when placed in contact with the recipients' sera, allow the identification of sera with anti-HLA antibodies that recognize the HLA molecules. This process enables the identification of the specificity of the preformed antibody and indicates not only that a particular antibody recognizes a specific HLA molecule but also the specific part of the HLA molecule or epitope that is recognized.

To further this type of analysis, René Duquesnoy proposed the HLAMatchmaker algorithm [5], which was developed in a set of Excel spreadsheets that contain a list of predicted HLA epitopes constructed by the author himself and the potential targets of the preformed anti-HLA antibodies in the sera of patients on the transplant waiting list. The results of this epitope analysis enable the identification of the specificity of the preformed anti-HLA antibody in the recipient's serum at the epitopic level. However, the HLAMatchmaker was not able to universalize the use of epitope reactivity analyses because the donor-recipient compatibility analyses were difficult and slow to perform using the existing spreadsheets. Thus, in 2008, our group developed the EpHLA program [6], which expanded the functionality of the HLAMatchmaker algorithm. The EpHLA eased the epitope analysis because it provided a graphical interface and a centralized database in which the recipients' and donors' examination results are stored in a safe and structured manner in an Access database. In 2012, the EpHLA program was validated and demonstrated an accuracy equal to that of the HLAMatchmaker while being up to eight times faster [7]. Nevertheless, the EpHLA did not predict the epitopic virtual crossmatches (EvXM) between a donor and the potential recipients or between a recipient and diverse donors. Therefore, we sought to develop this functionality, and the resulting program was named EpViX [8]. In addition to predicting EvXM, EpViX integrates and follows up all of the phases of the process from pre- to post-transplant.

2. Objective

Our objective was to develop a system that integrated all of the stakeholders involved in the epitope reactivity analysis process for solid organ transplant programs involving deceased donors across the different transplant phases, through a single interface [8]. Normally, diverse tools and isolated databases would be necessary to achieve this objective. In this work, we present the EpViX Ecosystem and the methods that we developed to integrate the multiple components of this system and make them accessible to all types of users, including those with little experience with the underlying tools, through the single EpViX interface.

3. Materials and methods

3.1. Internal architecture

EpViX is a freeware that was developed in the Ruby language. EpViX can be accessed from different platforms, e.g. PCs, tablets, and smartphones, because it works entirely on the Web environment. The Ruby-on-Rails framework was used to support its layered model-view-controller (MVC) architecture. These technologies were chosen because they are open-source and are secure, robust, and easy to learn and use [9,10]. Various Ruby libraries (gems) were used on EpViX to perform different tasks. These gems included the following: Authlogic for authentication, Cancan for resource authorization, Nokogiri and HTTPClient for integration with external web services, and Spawn for the asynchronous processing of specific requests [11]. All of the source code was versioned with Git (http://www.git-scm.com), through Bitbucket (http://www.bitbucket.org). The operating environment used on the developing and production machines was based on Linux (Debian), and the application server and database management system were Apache and MySQL, respectively.

3.2. Project development process

All of the source code was created by a team of seven developers and coordinated by four researchers. Meetings were arranged for the software requirement specifications and the presentation of newly coded functionalities and formed short planning cycles that allowed for constant evaluation by the researchers. In this context, other good practices of the Extreme Programming (XP) methodology were adopted during the development of the EpViX, e.g. incremental design, short cycles, pair programming, refactoring, and continuous integration [12].

To protect the patients' clinical data, the system was developed to avoid human failures and unauthorized access through redundant filters to check the data provided to users and the extensive use of techniques to identify and prevent attack attempts, such as cross-site scripting (XSS) and SQL injection. Currently, all accesses are monitored, and all data traffic is accomplished in an encrypted manner through Secure Software Layer (SSL) certificates.

3.3. EpViX ecosystem

EpViX is integrated into a set of other Web tools to form a software ecosystem that provides various services that are necessary to evaluate the immunological risks associated with solid organs transplants. The functionalities of the integrated services may be used in consonance due to the powerful interface of EpViX. The major integrated tools of EpViX are illustrated and explained below (Fig. 1).

3.4. EpLoader

The EpLoader software was developed in Ruby by our group and imports all of the reactivity panels contained in the database of the HLA Fusion® program, which is installed at the laboratories, into EpViX in real time. The importation is accomplished via a Web service and uses the Hypertext Transfer Protocol Secure (HTTPS) to increase the security of the patients' information traffic. The EpLoader is connected directly to the HLA Fusion® database and therefore must be installed on the same machine. Because it is an environment that is not controlled by our research group, the EpLoader uses a simplified checkpoint-based algorithm to maintain a sending log and recover from eventual failures. Although it is not strictly necessary for the use of EpViX, the EpLoader precludes the requirement that the user manually import the reactivity panels.

3.5. HLA Epitope Registry (EpRegistry)

EpViX makes use of the International Registry of Antibody-Defined HLA Epitopes (Epitope Registry or EpRegistry) available at http://www.epregistry.com.br. The EpRegistry was developed in PHP by our group and contains the entire repertoire of HLA epitopes predicted by René Duquesnoy. These data are the basis of the epitope reactivity analyses of the waiting list patients' sera in the EpViX program and have been tested with the LSAB panels. This website provides access to the following five separate epitope databases: HLA-ABC; -DRB; -DQ; -DP and MICA. Each of the layouts for the five epitope databases has the following displays: