Technological Trends on Dengue Virus Diagnosis through Patent and Literature Analysis

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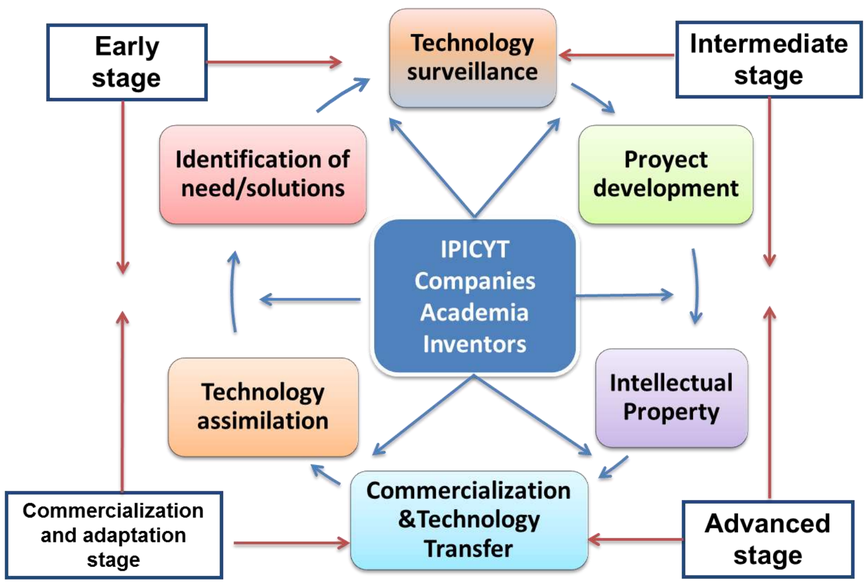
Technology Management Model



Tech trends for R&D efficiency

Novel Tech Surveillance method is proposed for increasing efficiency in R&D, patent grants and Technology transference from Research centers, companies or inventors. Tech surveillance is a source of vital information for deciding on investing in certain R&D pathways according to business/tech/IP strategy of the user.

Arising from an adapted Tech management model which requires to receive projects at different stages of development, Tech surveillance has become into a important tool for decision making.

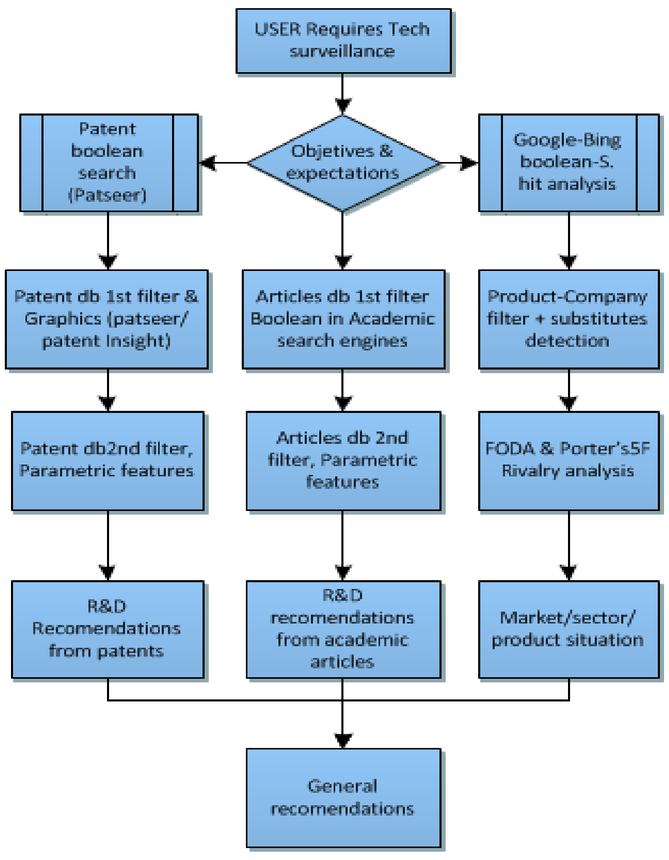
For those early-intermediate stage projects, the R&D team (research/IP/investor) should have information about prior art (patents, articles, web & products) to visualize the past and also could visualize what has not been done. Then, they could evaluate

how to set an strategy of R&D with clear goals and risks (technical & IP) related to a market opportunity window or scenarios.

In an advanced stage of R&D and commercialization, Tech surveillance becomes into a tool for securing IP according to sectorial trends, is useful in Tech transference negotiations and could point out which are the tech trends for adapting a product.

R&D efficiency increases when decision makers have the most complete information about the tech, legal and market trends and could evaluate potential scenarios and choose the best R&D route.

Tech Surveillance Procedure



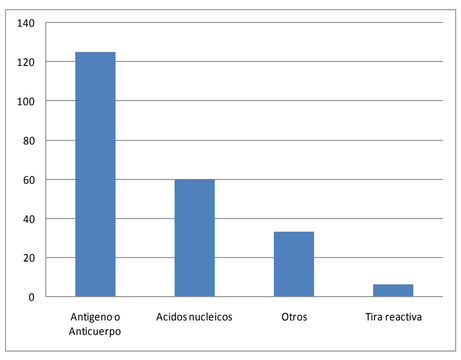
Dengue Virus Diagnosis

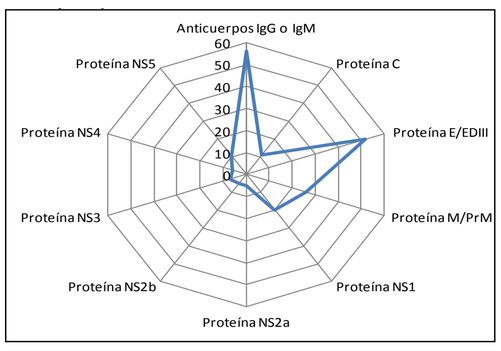
Dengue is a viral disease that, according to WHO, occurs in about 50 million cases worldwide yearly, increasing over 30 times in the last 50 years. Nowadays affects 110 countries in the world's intertropical region and spreading in a pandemic way. From those millions officially diagnosed about 500,000 cases require hospitalization and about 12,500 die, implying high socio-economical costs. Meanwhile, more aggressive serotypes of Dengue virus are emerging, more cost effective, specific and rapid diagnosis is urgently needed.

This work is focused on the study of technological trends on dengue virus diagnosis. Patent and literature databases were developed using different Boolean keyword search approaches, for selecting those patent and scientific articles specifically related to detection and diagnosis methods on dengue virus. Said documents were filtered and classified according to the type of diagnosis strategy (immunologic, molecular, etc.) and upon time. Afterwards, specific kinds of methodologies (culture media, ELISA, PCR, RT-PCR, etc.) were pointed out, including specific protein or nucleotide sequences related to each document. Our analysis allowed us to detect which methods, proteins or genes are the most protected and studied and the different actors (universities, companies, inventors, researchers) upon time, involved in the development of this technology. By analyzing both patent and scientific literature documents, the technological trend over diagnosis and detection of dengue virus is provided, which may be helpful for deciding new research projects based on detecting potential research opportunities over highly protected or disclosed areas.

Patent Trends

184 patent documents from US, Europe, Japan and Espacenet System documents, were found. Furthermore, additional 21 patents not captured on Espacenet system from China, India, Brazil and Mexico directly related with diagnosis





From these 184 patent documents, 125 are directed antigen/antibody detection, 66 are directed to nucleic acid detection, 6 point of care systems and 33 to other detection methodologies.

The target viral antigen was also classified, finding that antibody detection IgG/IgM was preferred, followed by proteins E/EDIII, M/prM, NS1 and NS3.

However, since Dengue virus ARN genome comprises only 11 Kb, detection strategies are limited, in view of the fact that it has been extensively studied.

Protein E is located in the exterior membrane of the virus and also recognizes target cell receptors. It is easy to detect in plasma serum and easy to correlate with virus presence, thus it has been claimed in at least 29 detection method patents. Furthermore, Panbio kit is related with this protein.

Protein prM/M belongs to the virus membrane and is coupled to protein E, thus, it can also been detected on plasma and is an indicator of virus presence.

Protein NS1 is excreted from infected cells, and is involved on ARN replication, and is in high proportions outside cells. It has been protected in at least 15 patents. Biorad's kits Platelia are based on this protein detection.

Proteins NS2, NS3, NS4 and NS5 are inside the infected cells or within the viruses, thus they are in low quantities in serum and are not natural targets for patient's antibodies. Thus, patent protection over these proteins is low.

Literature Trends

274 relevant scientific articles were found. Said articles were classified into several categories (table)

Subject	Publication No.*
ELISA	131
Antibody	174
Immunochromatography	38
Molecular assays	101
Antigens	56
IgG	60
IgM	100
IgA	8
NS1	54
Protein E	14
NS3	4
NS5	4
Protein C	3
Biosensors	18
Detection method comparisons	133
Commercial kit evaluations	78
Other techniques	40

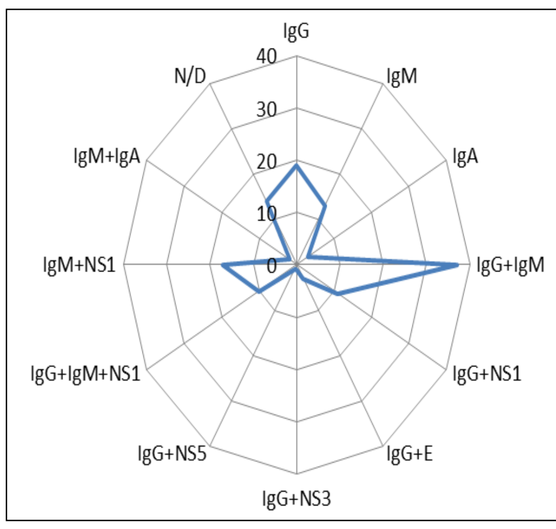
Since the main question for this research was focused on immunological/point of care detection methods, only those documents related with ELISA, antibodies, antigens were analyzed.

It can be deduced that the main issue is the comparison among diagnosis/ detection kits, mainly by IgG/IgM, since, according to the papers, having a trustful dengue diagnosis, without cross-reactions with other flavivirus with high specificity and sensitivity and quick is fundamental.

The fundamental subjects of said articles are on IgG, IgM, IgA immunoglobulins, antigens and viral proteins (left figure)

From the above documents, it's worthy to mention that results vary depending on the standard referenced, the kind of test or the compared kit. Also, only IgG, IgM or IgA kits or test were compared, wherein the latter has been extensively reported during the last 2 years for point-of-care tests.

Furthermore, NS1 and its combination with IgG, IgM or IgG+IgM is particularly relevant, since although NS1 alone has good sensibility and sensitivity, its synergistic effect with said immunoglobulins increases maximum values on serological tests.



Type of protein	
IgG	19
IgM	13
IgA	3
IgG+IgM	37
IgG+NS1	11
IgG+E	3
IgG+NS3	1
IgG+NS5	1
IgG+IgM+NS1	10
IgM+NS1	17
IgM+IgA	2
N/D	14

CONCLUSIONS

From the above analysis, in order to focus R&D efforts on Dengue Virus Detection Methods, the following recommendations were made:

1. Do not look for detection on NS2, NS3, NS4 and NS5, because of the low amount of antigens/antibodies on clinical samples.
2. It is not recommended to detect protein E, since it has been protected extensively and with broad scope, unless a new epitope is designed.
3. Protein NS1 detection should be avoided in its hexameric form by designing mono or polyclonal antibodies or associated to IgG, IgM or IgA immunoglobulins.
4. In spite of the above, it is recommended to focus efforts on in silico and/or experiments directed on changes in pH, temperature or chemical reaction can brake the NS1 hexamer or make a difference on external NS1 epitopes. This could help to generate novel antibodies or detection methods, based on said putative novel epitopes.
5. Chimeric or multivalent protein development/design over main surface or serum proteins (E, M and NS1) is encouraged, provided that said sequences are not already protected or disclosed.

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