



A success in Toxinology translational research in Brazil: Bridging the gap



Ana Silvia S.B.S. Ferreira^{a,b,c}, Benedito Barraviera^{a,c},
Silvia Regina C.S. Barraviera^{a,c}, Luciana P.F. Abbade^{c,d},
Carlos Antonio Caramori^{a,b,c}, Rui Seabra Ferreira Jr.^{a,c,*}

^a Department of Tropical Diseases and Image Diagnosis, Botucatu Medical School, São Paulo State University (UNESP – Univ. Estadual Paulista), Brazil

^b Clinical Research Unit (UPECLIN), Botucatu Medical School, UNESP – Univ. Estadual Paulista, Brazil

^c Centre for the Study of Venoms and Venomous Animals (CEVAP), UNESP – Univ. Estadual Paulista, Brazil

^d Department of Dermatology and Radiotherapy, Botucatu Medical School, São Paulo State University, Brazil

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ABSTRACT

Basic research is fundamental for discovering potential diagnostic and therapeutic tools, including drugs, vaccines and new diagnostic techniques. On this basis, diagnosis and treatment methods for many diseases have been developed. Presently, discovering new candidate molecules and testing them in animals are relatively easy tasks that require modest resources and responsibility. However, crossing the animal-to-human barrier is still a great challenge that most researchers tend to avoid. Thus, bridging this current gap between clinical and basic research must be encouraged and elucidated in training programmes for health professionals. This project clearly shows the challenges faced by a group of Brazilian researchers who, after discovering a new fibrin sealant through 20 years of painstaking basic work, insisted on having the product applied clinically. The Brazilian government has recently become aware of this challenge and has accordingly defined the product as strategic to the public health of the country. Thus, in addition to financing research and development laboratories, resources were invested in clinical trials and in the development of a virtual platform termed the Virtual System to Support Clinical Research (SAVPC); this platform imparts speed, reliability and visibility to advances in product development, fostering interactions among sponsors, physicians, students and, ultimately, the research subjects themselves. This pioneering project may become a future model for other public institutions in Brazil, principally in overcoming neglected diseases, which unfortunately continue to afflict this tropical country.

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1. Introduction

Translational research refers to the work involved in translating research into practice, ensuring that new treatments and research knowledge actually reach the patients or populations for whom they are intended and that these treatments and knowledge are implemented correctly. The production of a new drug, a common end-point for “bench-to-bedside” translational research, is only the starting point for this area of research. Such

* Corresponding author. Centro de Estudos de Venenos e Animais Peçonhentos da UNESP – CEVAP, Univ. Estadual Paulista – UNESP, Rua José Barbosa de Barros 1780, Fazenda Experimental Lageado, CEP: 18610-307 Botucatu, São Paulo, Brazil. Tel.: +55 (14) 3814 5555; fax: +55 (14) 3814 5446.

E-mail addresses: rseabra@cevap.org.br, rui.ead@gmail.com (R.S. Ferreira).

translational research seeks to close that gap and enhance quality by improving access, reorganising and coordinating care delivery systems, helping clinicians and patients to change behaviours and make more informed choices, providing reminders and point-of-care decision support tools and strengthening the patient–clinician relationship (Woolf, 2008). The toxins produced by animals, plants and microorganisms are rich in molecules that could serve as potential candidates for treating diseases that afflict humans and animals.

Among the substances used for the treatment of venous ulcers are fibrin sealants composed of human fibrinogen and bovine/human thrombin (Vanscheidt et al., 2007). These sealants promote the reduction of bacterial colonisation and oedema, control haemorrhaging, alter the pain threshold by protecting nerve endings, ensure hydration of the wound and stimulate the formation of granulation tissue, thereby favouring the healing process. The disadvantages of commercial fibrin sealants include their high cost and the fact that human fibrinogen can transmit infectious diseases such as hepatitis, human immunodeficiency virus, syphilis and Chagas disease, among others. To overcome these problems, researchers at the Centre for the Study of Venoms and Venomous Animals of UNESP – CEVAP have developed a new sealant consisting of fibrinogen extracted from large animals and an enzyme derived from snake venom, both of which have been used experimentally since 1989 (Barros et al., 2009). The fibrin sealant produced by CEVAP does not contain human blood, while its low production cost will permit its routine use in hospitals and facilitate its accessibility for poorer segments of the population.

To date, various experiments on fibrin sealants have been performed on both animals and humans (Barros et al., 2009). In 2009, researchers treated 25 patients suffering from chronic ulcers and concluded that the sealant is suitable for treating leg ulcers and is more economical than currently available options on the market. Fibrin sealants also present the following advantages: easy application, amenable bed preparation and reduced pain. Furthermore, it has been suggested that weekly application, for at least eight weeks, improves the healing process and raises cure indices (Gatti et al., 2011).

However, it is known that the discovery and development of new medicaments are based on the discovery of therapeutic targets, the design and selection of a molecule directed toward the intended target, optimisation of the leading molecule, development of the candidate and, finally, the discovery of the medicament (Calixto and Siqueira Jr., 2008). Venkatesh and Lipper (2000) indicate that the main factors responsible for failures in the development of new medicaments are low bioavailability (39%), a lack of efficacy (29%), the detection of toxic effects (21%) and market-related reasons (6%). In this context, toxins appear to be excellent candidates with worldwide bioavailability, but bridging the gap between basic and applied research is not a simple task.

This apparent gap between discovery and transformation into commercial products has been attributed to animal models that are poorly representative and to a lack of scientific rigour, a profile that results in insufficient beneficial effects in subsequent clinical trials (Morgan et al.,

2011). A “translational” investigation aims to bridge these gaps, and, as described by Cooksey (2006), provides a “process for taking discoveries from basic or clinical research and using them to produce innovations in healthcare environments.” Nevertheless, the realisation of a more efficacious translational process is currently achieved by “re-engineering” research companies to overcome the barriers between basic and applied research, principally due to the cost and time of execution.

To bridge this gap in Brazil, the Ministry of Health has supported “From Bench to Bedside” projects. With the Ministry’s approval of the fibrin sealant project, which supports the construction of a pilot factory as well as clinical trials, the present work aims to reveal both the difficulties faced during the process of developing a new pharmaceutical product derived from animal toxin as well as the alternatives available when facing these challenges.

2. Methods

2.1. Hits to lead: translational potential

In deciding upon a new product or drug to develop from basic research to clinical practice, researchers generally consider one main factor: does the candidate molecule have translational potential? This question was evaluated by means of six key dimensions on the translational potential of a product (Morgan et al., 2011). After establishing whether the product or translational medicine has significant potential, one must define the necessary staff for its development.

2.2. Bridging the gap

2.2.1. Team

The research team must be comprised of professionals dedicated to prospecting, product development and clinical trials. The members must be multidisciplinary professionals from different fields of scientific knowledge. The team must be focused on developing products with pre-set targets and attending frequent scientific–academic meetings, where ideas from different viewpoints on the same scenario are discussed. In this case, decisions were reached with the overall purpose of developing an effective fibrin sealant.

2.2.2. Senior researcher

How is a potential application for a particular molecule discovered? At this stage, creative and experienced researchers, who know the research and development laboratory at their institution and have extensive knowledge and keen physician–pharmacist intuition for clinical applications, must integrate and coordinate prospecting teams. These researchers are individuals who can envision promising clinical applications for specific molecules.

2.3. Virtual System to Support Clinical Research (SAVPC)

After identifying several barriers to performing clinical studies in Brazil, the authors proposed the creation of a Virtual System to Support Clinical Research (SAVPC), called SAVPC, to manage the activities of research subjects, investigators, sponsors and research centres. SAVPC was

developed to overcome the barriers described by Beckett et al. (2011) for physician/community participation in clinical research. This context afforded five major actions.

SAVPC and all website content followed the ethical principles of the HON Code and were approved by the ERB (Ethics Research Board) – CEP of the Botucatu Medical School, UNESP. Some of the content was obtained from the National Ethics Council of Brazil, the World Health Organization and the National Institutes of Health.

3. Results

3.1. Fibrin sealant and its translational potential

Six main dimensions (Morgan et al., 2011) were crucial for determining the translational potential of fibrin sealant; these are described in Table 1.

3.2. Bridging the gap

The final development of the product was accomplished by a research translator (Morgan et al., 2011), an individual responsible for pre-clinical trials and formulation. Thereafter, integration of the research translator with the clinical trial team became crucial to trial design.

In this study, the research translator acted as a physician-veterinary toxinologist and, for the clinical trial, as a physician-dermatologist who was responsible both for the coordination and realisation of the research and for the integrity and well-being of the research subjects. The following formational tasks were performed: clinical evaluations and consultations, clinical evolution of patient charts, medical prescriptions, evaluations of adverse events, assessment of eligibility (criteria for inclusion and exclusion), and delegation of tasks within the team.

Therefore, the two research translators, together with the senior researcher, designed a phase I/II clinical trial that relied on the aid of sub-investigators, physicians, nurses and eight clinical research units located in Brazil. However,

several barriers to the development of a clinical trial were noted, as described by Beckett et al. (2011), including the human resources policies and the infrastructure of the research centres. To overcome these barriers, the authors proposed the creation of the SAVPC, containing information, databases and interactive systems not only to support researchers, sponsors and research subjects, but also to support healthy laypeople and the general public in relation to clinical research.

3.3. Virtual System to Support Clinical Research (SAVPC)

The SAVPC was developed to overcome the barriers described by Beckett et al. (2011). Five major actions were taken to achieve this goal:

- 1) Develop and customise a virtual environment that contains information on clinical research for investigators, sponsors, research subjects and the general public.

Project materials have been developed both to support researchers (information on good clinical practice, regulatory documents and steps for developing research projects) and research subjects (ethical and bioethical aspects) involved in clinical research and to provide information to the general public. This information is available at the website <http://www.savpc.com.br>, and the approach is tailored based on the different audiences involved. Research subjects and the general public are addressed in clear and simple language, whereas researchers and sponsors are offered detailed scientific information.

- 2) Develop a database for registering research subjects and researchers.

A registry of individuals interested in participating in clinical research was compiled. To ensure the security of these data and to avoid revealing the identities of research subjects, all personal information was duly encrypted.

Table 1

Six main dimensions crucial for deciding on the translational potential of fibrin sealant.

Translational potential	Questions	Fibrin sealant
Quality of Science	Whether the design and proposed methodology represent 'Good science'.	Diverse academic studies conducted over the last 20 years have evidenced the importance of the product (Barros et al., 2009).
Appropriateness	Whether the methods are precise enough to discover an intervention that would work in humans (e.g. deciding if an animal model is sufficiently transferable).	Studies on different tissues, in different animal species, as well as humans, were completed.
Stage	Whether the research was too early, close to basic research or too hypothesis driven.	The application timeline of fibrin sealant and its components were tested <i>in vitro</i> and <i>in vivo</i> .
Time-span	Whether production of a useable end product can be achieved in a reasonable time-span e.g. 5 years was a cut-off point mentioned.	The development time was long due to the low commercial importance given by pharmaceutical companies to the treatment of neglected diseases.
Commercialization potential	The likelihood of the project being taken-up and developed by an industrial partner, with this being more likely if there is a perceived market need for a distinct product advantage, lack of competitors, and likelihood of a particular company taking it on.	The product today is understood to be strategic by the Single Health System of Brazil due to its potential for treatment of a neglected disease, besides being produced through domestic technology.
Clarity of path ahead	Clarity of a forward path: How clear, feasible, and achievable is the path ahead in terms of being able to enumerate and detail future of research required.	After the registry of the product, via a public-private partnership, the technology will be transferred to a Public Producer Laboratory.

A registry was also developed for researchers interested in participation, which contained a field for sending one's curriculum vitae to facilitate the filtering of information.

The above-mentioned databases can be accessed through a system that provides straightforward data filtration and information retrieval, indicating (by the use of different colours) research subjects and researchers that have already been recruited for participation in other research studies.

3) Develop databases for Brazilian National Clinical Research Network (RNP) research studies.

The system integrates the central components of RNP, with information on research studies at each network centre that are either complete, underway, in recruitment or in the planning phase. These databases will facilitate the recruitment of research subjects and researchers in the areas of interest.

4) Design “Research Methodology” teaching modules to enable the online recruitment and training of health professionals.

To contribute to the preparation of research projects, 12 teaching modules on applied scientific research methodology and evaluation in the health sciences were developed (Ferreira Junior et al., 2008) for professionals involved in basic research and clinical research. These modules are available free of cost on the SAVPC website and include video lessons, text, online assessments and directed study.

5) Customise and deploy tools for tele-education and tele-care to facilitate interactions among the RNP centres.

Multi-centre studies such as “Treatment of venous ulcers with fibrin sealant derived from snake venom” are available in two interactive forms:

1. Asynchronous interaction in the virtual learning environment, Moodle®.

This environment contains specific information on the study, such as a brochure provided by the researcher, the study protocol and good clinical practices for the researchers involved in the trial. Moreover, this information can only be accessed using a login and password.

2. Synchronise interactions via internet tele-conferencing tools.

Tele-conferencing tools were made available, via the internet, that can be used at pre-scheduled times to integrate research centres, researchers and sponsors and to empower each of these participants during the clinical trials.

4. Discussion

It is widely claimed that the discovery and development of new pharmaceutical products entail high costs and risks

in a decidedly competitive market, with few advantages for the companies that act in this scenario. However, Light and Warburton (2011) have suggested that with public funding, companies can develop and produce clinically superior medicines at low prices with minimal risk.

Due to the indifference of the pharmaceutical market for developing new, strategic bioproducts for the Brazilian health system, a public–public partnership (PuP) was established for developing our fibrin sealant. The fibrin sealant developed by CEVAP-UNESP demonstrated a huge translational potential based on the large number of academic studies conducted over the last 20 years (Barros et al., 2009). According to Morgan et al. (2011), evaluating the translational potential of a product requires one to consider the quality of the related research and the product's appropriateness, stage, timespan and commercialisation potential as well as the clarity of the path ahead. The fibrin sealant was deemed a strong contender in each of these areas, thus warranting further investment in the subsequent development stages. However, there were two major challenges inhibiting the product's advancement from the lab to technological development: investment in research and development (R&D) and the implementation of clinical trials in Brazil.

Calixto and Siqueira Jr. (2008) have indicated several difficulties in relation to the development of R&D by the Brazilian pharmaceutical industry: high costs and risks associated with the development of new traditional drugs, high financial costs (interest rates) and a low supply of risk capital, the long maturation time of R&D projects, a lack of formal R&D divisions in the industry, a reduction in the number of domestic companies due to mergers with or acquisitions by multinational/transnational corporations, a lack of experience in technological innovation, the absence of researchers in companies, and a lack of programmes that include the participation of the national government and its agencies.

By understanding the role of the Brazilian Ministry of Health in Neglected Diseases R&D, the Department of Science and Technology (DECIT) has supported several projects in this area, through the Secretariat of Science, Technology and Strategic Inputs (SCTIE). Thus, our fibrin sealant has obtained the necessary R&D funding. This scenario was only possible due to the advanced-stage development and translational capacity of the fibrin sealant and because the Brazilian government is committed to investing in technology and the development of new drugs targeting public health.

At the website <http://www.clinicaltrials.gov>, a total of 119,470 clinical studies were registered between 01/01/1990 and 31/12/2011. Over the same period, Brazil was responsible for only 2720 records on this platform. Regarding the ability to conduct clinical trials in Brazil, it is observed that only 19.9% of trials were recorded as phase 0, phase I, phase II or phase I + II, while 62.1% of the trials were recorded as phase II + III, phase III or phase IV (ClinicalTrials.gov, 2012). This finding demonstrates that most of the clinical trials conducted in Brazil, representing a small proportion of the studies performed worldwide, involve protocols that reflect the priorities of foreign laboratories. The participation of Brazilian researchers in these studies has been limited to

executing protocols developed in other countries. Furthermore, both the analysis and ownership of the data are entirely within the scope of the contracting companies.

In this context, there is a great disincentive for the academic community to participate in clinical research. Without financial incentive, physicians often feel undervalued or indifferent to the benefits of performing clinical research for their patients (Kahn et al., 2011). According to Morgan et al. (2011), researchers describe translational research as “high risk” and are seldom viewed by their peers as contributing “authentic” knowledge that would bestow symbolic capital in their field. The general impression of these professionals is that they are wasting their time and grant money by performing translational research because researchers are rewarded for publications, not patents.

To bridge this gap during the final development of a translational product, research translators are of great importance due to their vital integration with the pre-clinical and clinical teams. Thus, small adjustments can still occur in product formulation at the end of phase I/II clinical trials. In addition, Morgan et al. (2011) suggested the importance of a website portal that provides a confidential venue for registering queries, complaints and concerns about current and future protocols. This pioneering experience in the near future may contribute to solving problems related to neglected diseases, either by discovering new treatments or standardising new vaccines.

Thus, SAVPC presents an important alternative that provides a detailed description of the features, benefits and requirements of clinical research that clinicians can access at their own convenience. In addition to providing information regarding investigators, research subjects, sponsors and on-going and future trials, this system will supply training for stakeholders and identify local infrastructure and skilled labour for each research study.

The present case shows that clinical research and basic science cannot (and should not) be separated. To bridge the gap between basic science and the clinical development of drugs, governmental and financial agencies should continue to encourage clinical researchers and basic investigators to work closely to frame important questions directed toward solving neglected health problems.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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