REPORT OF THE 8th EVALUATION

OF THE BIOTA-FAPESP PROGRAM

BY THE SCIENTIFIC ADVISORY COMMITTEE

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1. Introduction

As part of its review and quality assurance policy, the BIOTA-FAPESP Program periodically has its achievements evaluated by a committee of independent experts. This report is the eighth evaluation by such a committee.

The evaluation took place in conjunction with the VIII. Biota Program Assessment meeting in São Pedro, São Paulo, attended by a large number of students. The meeting included short courses for attending students.

The projects were presented to the Committee in a thematic way with summaries of projects provided in each thematic group along with a summary of gaps, shortcomings, linkages and future goals. This approach was helpful in the evaluation, and it appeared to also be worthwhile in bringing related projects together to examine as a theme; shortfalls, gaps, conclusions, etc.

2. Methodology followed by the Committee

The evaluation committee examined the BIOTA Program between December 8 and 12 during the VIII Symposium of BIOTA and the associated Evaluation meeting. It established its opinion through:

- attending oral presentations and poster sessions;

- interviews held with BIOTA Program coordinators, as well as with project leaders, students and presenters at the symposium
- presentations on the BIOTA Program
- document material, including a brief description of the current thematic projects
- the document - Science Plan and Strategies for the Next Decade
- previous evaluations of the Biota-FAPESP Program including the 7th Program Evaluation (2011), and the BIOprospecTA sub-program evaluation (2011)
- Studying information offered via the Internet, especially the BIOTA website, Biota Neotropica, SinBIOTA, and associated web sites.

The Scientific Advisory Committee focused on the program as a whole rather than on individual Projects. Our focus was on the goals of BIOTA, and the gaps and how to improve BIOTA.

The Scientific Advisory Committee endorses the reports of the previous evaluations as they represent a comprehensive analysis of both BIOTA and BIO*prospec*TA programs. We do not wish to repeat much of what is stated therein. We endorse the comments and recommendations they provide. We have reiterated some points, however, that we regard as continuing to be critical to the successful continuance of the BIOTA program.

In previous evaluations, the BIOTA program and the BIOTA/BIO*prospec*TA subprogram were evaluated independently. This strategy was justified because the latter subprogram had a different history and originated from a different scientific community. This is also

reflected in the composition of the Scientific Assessment Committee. For the 8th evaluation, the committee has decided to prepare a single report but separated into two clearly identifiable sections. Importantly, the final recommendations apply to the entire BIOTA/FAPESP program, inclusive of the BIO*prospec*TA sub-program.

3. The BIOTA/FAPESP program

In this section, we evaluate the BIOTA program, exclusive of the BIOTA/BIO*prospec*TA subprogram.

Objectives and priorities in the 2010 science document

In June 2009, as reported in the 2010 strategic document (Joly et al. Science 2010), the BIOTA+10 program funded by FAPESP established the following five objectives

- To inventory and characterize the biodiversity of the State of São Paulo, by defining the mechanisms for its conservation and sustainable use;
- To understand the processes that generate and maintain biodiversity, as well as those that can result in its deleterious reduction;
- To produce estimates about biodiversity loss in different spatial and time scales.
- To evaluate the effectiveness of conservation initiatives within the State of São Paulo, identifying priority areas and components for conservation.
- To increase the ability of the State of São Paulo and public and private organizations in managing, monitoring and using biodiversity in a sustainable way

In addition, the following priorities were discussed for the 2010-2019 period:

- Including native biodiversity restoration as one main objective of the BIOTA/FAPESP Program

- Development and implementation of a new information system for the BIOTA/FAPESP Program
- Biodiversity Inventories & DNA Barcoding
- Marine biodiversity
- Phylogeography
- Invasive species & GMOs
- Landscape Ecology & Ecosystem functioning and services
- Applied ecology and human dimensions in biological conservation
- Modelling & Climate Change
- Short, medium and long term plans for the BIO*prospec*TA sub-program
- Education & Public Outreach
- BIOTA NEOTROPICA
- National & International Partnerships

With regard to these priorities, the 7th Evaluation recommended that (see Appendix 1): the BIOTA biodiversity conservation goals and BIO*prospec*TA discovery goals be linked through the concept of sustainable use, marine themes be reinforced, a center in SP be developed for high-throughput DNA sequencing, the SinBIOTA 2.1 database be complemented with modelling tools, the objectives of BIOTA serve the needs of the CBD targets, public policy links be further developed, the issue of biodiversity representativeness be addressed in both the terrestrial and marine realms, spatial biodiversity surrogates be developed, performance indicators for restoration be developed, restoration be integrated in conservation planning, off-reserve land be assessed for its biodiversity value, BIOTA project

be developed to be linked to the IPBES process, databasing effort be continued, databases be adapted to the big data era, the BIOTA databases be interlinked, BIOTA participants incorporate their data in BIOTA databases, citizen science be promoted, training and education material be made available online, cooperation between FAPESP and the NSF Dimensions program be explored. For the sake of clarity, we have copied the recommendations of the 7th report in full, as an Appendix 1 of the present report.

Strengths and achievements of the BIOTA/FAPESP program

The Committee continues to be impressed by the BIOTA Program and by advances that continue to be made. The BIOTA program continues to provide an example, and sets standards, that many countries and other states within Brazil would be happy to follow. Overall, the Program has excellent breadth spatially, taxonomically and thematically.

Specifically, the Committee was given access to two summary tables on the publication output for the 2011-2014 and human resources trained. Overall, the publication record was impressive, with more than 400 publications listed (including the BIO*prospec*TA subprogram) testifying of the breadth of research addressing the objectives of BIOTA. The training was equally impressive, with 51 FAPESP-funded PhDs, 22 FAPESP-funded post-doctoral research associates, all associated with specific BIOTA projects.

Over the evaluated period, all five objectives of the BIOTA/FAPESP program have been addressed to some extent, within thematic projects or shorter-term projects. The issues of biodiversity characterization, sustainable use, processes of generation and maintenance of

biodiversity, biodiversity loss estimation, conservation initiatives, and linkage with public and private sector initiatives for biodiversity management, have all been considered in at least some of the projects presented during the meeting. The strongest contribution was on the biodiversity characterization and understanding of key processes.

There has been progress for all priorities of the BIOTA+10 program. This notably includes significant progress made in the areas of: biodiversity restoration, DNA barcoding, marine biodiversity, phylogeography, education, integration with BIO*prospec*TA, and development of the BIOTA NEOTROPICA journal.

The Scientific Advisory Committee was especially impressed by the ability of the BIOTA program to develop for the first time international programs in collaboration with the USA and the UK. These projects not only dramatically increase the visibility of the BIOTA/FAPESP program at the international scale, but also stimulate a culture of excellence and hypothesis-driven science that will be an asset for Brazilian science in the future.

The Scientific Advisory Committee found that the new strategy of launching more targeted calls for proposals has created the opportunity to truly develop areas of research heretofore missing in the BIOTA program, such as microbiology and marine science. This strategy has permitted to accelerate the integration of these sub-disciplines.

The Scientific Advisory Committee highly values the efforts invested by the BIOTA/FAPESP program to support research on the discovery and documentation of biodiversity in the

State of São Paulo and beyond. This was one of the original motivations for the BIOTA program, but such an effort can only pay off if it is continued over decades.

Perceived weaknesses in the light of the 2011 recommendations

The 7th evaluation recommended that several topics be examined by the BIOTA/FAPESP program, so as to improve its performance and outreach (see Appendix 1). Some of them were taken home, as discussed above, but not all. Here we are highlighting 2011 recommendations that, according to this Scientific Advisory Committee, still appear relevant today. It is useful to highlight which recommendations still deserve attention, although we acknowledge that not all recommendations can be followed up during such a short period.

Recommendation 1 was that the BIOTA biodiversity conservation goals and BIO*prospec*TA discovery goals be linked through the concept of sustainable use. This clearly is a challenging recommendation, and one that has not been fully followed, although some of the work on bioprospecting does makes reference to "sustainable use of biodiversity". This work argued that mapping the species from which natural products can be extracted may promote the protection of those areas where the species are found.

Recommendations 5 to 10 and 13 were related to key international initiatives including the convention on biological diversity (CBD). The issues were to address the CBD 2020 targets, the need to address key IPBES (the Inter-governmental Platform for Biodiversity and Ecosystem Services) processes including regional assessments, and collaboration with the

emerging global biodiversity monitoring program GEO BON. The Scientific Advisory Committee is of the view that more progress can be made on these recommendations.

Recommendation 8 called for a work to assess biodiversity representativeness. Conservation planning, policy-making, and assessments all depend upon having the capacity to quantify how much biodiversity is represented in protected areas. This also provides the basis for the assessment of biodiversity loss and effectiveness of conservation (cf BIOTA objectives). Again the Scientific Advisory Committee is of the view that less progress was made on this recommendation. We will return to this point under 'recommendations for the future' (see below).

The Scientific Advisory Committee also evaluated the progress of the BIOTA/FAPESP program in the light of priorities listed in 2010. One issue relates to biodiversity modelling, which seems to be less advanced than the other priorities. Biodiversity modelling cuts across many of the projects, and this point will be covered under 'recommendations for the future' (see below). Also, the Committee was not aware of projects specifically targeted at the study of invasive species or GMOs.

Recommendations for the future

1) International BIOTA projects have created a unique opportunity for conducting frontier research within BIOTA. The Scientific Advisory Committee recommends that this approach be pursued, and continue collaborations with other countries.

2) Discussions highlighted the need for predictive models of biodiversity. The need for modelling across different projects suggests an opportunity for integrative work towards a common toolbox. The Scientific Advisory Committee recommends that specific effort should be paid to developing such predictive models of biodiversity within the BIOTA/FAPESP program. These models will extend beyond conventional models for single species to allow inferences to be made about overall biodiversity patterns. Such models can better serve the objectives related to estimates about biodiversity loss and evaluation of the effectiveness of conservation initiatives. This action could be stimulated through a thematic call for proposals.
3) Conservation planning critically depends on the availability of maps that facilitate the work of prioritization. The Scientific Advisory Committee recommends that methods to create biodiversity maps be implemented at the state scale, perhaps in relation with the SinBIOTA plateform.
4) The State of São Paulo remains understudied. The Scientific Advisory Committee recommends that spatial gaps for surveying be prioritized (e.g. based on "Survey gaps analysis"). This could include biome gaps, such as the deep sea, or habitat gaps such as the microbiome of non-model organisms. We note that such mapping will be expected to integrate with mapped information on ecosystem services and opportunity costs of conservation.
5) The Scientific Advisory Committee recommends that steps be taken to enhance the awareness of BIOTA as playing an essential role in any initiative that FAPESP may take towards a green economy. The essential role of BIOTA in this context is the provision of a framework for biodiversity assessment and conservation. This

provides the foundation for ensuring the well being of future generations, and so will be an essential ingredient of a green economy.

6) High-throughput DNA sequencing is both an opportunity and a concern within the existing organization of BIOTA. Such data are orders of magnitude larger in size than before, yielding novel challenges. Also, analysing these data requires new techniques (bioinformatics). The Scientific Advisory Committee recommends attracting expertise in bioinformatics within the BIOTA program.
7) Taxonomy and field surveys have been a major drive for the BIOTA program and much of its success is associated with this vision. The Scientific Advisory Committee recommends developing a specific line of funding dedicated to conducting taxonomic research, with a thematic call for proposals.
8) The integration of both microbiology and marine science within the BIOTA program are perceived as a clear success. These subprograms should continue to be supported by FAPESP within the BIOTA program; BIOTA should also examine the pertinence of collaborating with the health sciences through a subprogram in epidemiology. The mapping of the spread of diseases particularly those "mediated" by insect vectors such as malaria and leishmaniasis may well provide an early-warning system of changes in the environment that are permitting the invasion by insects into areas where the diseases were not previously reported; conversely, the absence of such reports in previously "infected areas" may also indicate changes.
9) An increased focus could be placed on significant publications in international journals. The Scientific Advisory Committee suggests for BIOTA/FAPESP to create a synthesis and analysis centres (see e.g. the NSF-funded National Center for

Ecological Analysis and Synthesis), so as to generate integrative science and gather among projects and with international scientists. The requirement would be to publish syntheses or meta-analysis papers. This would reinforce the synergies across BIOTA projects and also with the international research community.

4. The BIO*prospec*TA subprogram

Objectives and priorities in the 2010 science document

The BIO*prospec*TA sub-program of BIOTA organizes a network of researchers and laboratories with the following objectives:

1) Standardized collection of biological samples (plants, microorganisms, marine species, insects, etc.) and pre-processing of raw materials for the subsequent preparation of extracts;
2) Establishment of a bank of extracts and pure compounds from plants, microorganisms, marine organisms and other natural sources, with the required automation and data management facilities;
3) Establish a flow between complementary research groups from standardized extracts, fractionation and purification; screening of extracts (ideally High-Throughput Screening using small sample volumes); identification and characterization (NMR, Crystallography, LC/GC-MS, ect …) of promising extracts/compounds; pharmacology and toxicology of promising bioactive extracts/compounds; synthesis of bioactive natural products and their derivatives; medicinal chemistry and drug design applied to the development of promising compounds, whenever possible with private sector partners.

4) Development of new in-vitro and in-vivo bioassays;
5) Development of a database structure for the data processing tasks of the program. It is important to emphasize that beside the bioprospecting goal, the program focused also on advances in natural product chemistry (phytochemistry, molecular biology, and pharmacology).

BIO*prospec*TA consists of 11 different projects considering different aspects of searching for valuable products from Brazilian biodiversity. That means to use the basic science for applied science. BIO*prospec*TA activities are enabled by the excellent efforts made in mapping the biodiversity in the State of São Paulo. The projects use different organisms, like plants, microorganisms including endophytes, marine organisms, and venoms from various organisms. The approach for biologically active compounds follows the classical approach of bioassay-guided fractionation, which leads to hits which needs to be further developed into leads for drug, cosmetic or agrochemical development. This latter step requires further in-depth analysis of the activity as well as studies on the toxicology at a minimum. There is one project that contributes to this lead development. In that project particularly, the pharmacokinetics are studied of promising compounds coming out of other BIOprospecTA projects. So far, 40 model compounds were studied in this project and four novel compounds from the program were tested in this preclinical project. Structures of novel compounds found will be deposited in the Royal Society of Chemistry data bank Chemspider.

Strengths and achievements of the BIOTA/FAPESP program

The BIOprospecTA group brings together international-class natural products researchers in projects where their ample experience in the isolation and structure elucidation of natural products is combined with the access to the Brazilian biodiversity, as mapped by the BIOTA project.

This is a clear applied line of research that valorises the basic biodiversity research. BIO*prospec*TA includes: well-organized individual projects, with in most cases, significant output measured in the current metrics; viz publications, undergraduate to postdoctoral fellows being trained as participants in the individual programs and outreach efforts.

The project groups are publishing in the top journals for the field, reaching out to their colleagues all over the world. The dissemination of their work also included active participation in a number of international meetings as invited lecturers, oral presentations and posters.

The individual groups have established both formal and informal networks between PIs with complementary skill sets. This is shown in areas as diverse as ecological studies at both macro and microorganism level and in the bioprospecting area where knowledge in one specific methodology is shared among PIs who need to utilize that skill set.

Strong national and international collaborations have been established.

In terms of education, the students learn to work in multidisciplinary teams bridging between biology, chemistry and pharmacy, opening the way to valorisation of the national biodiversity.

A good infrastructure has been created for the research by FAPESP, and the participating groups have shown to be able to share the availability of the equipment in the projects.

All kinds of sources of chemodiversity are being explored.

Perceived weaknesses in the light of the 2011 recommendations

Though a large number of compounds have been isolated and identified, only a few have resulted in patents. What are the criteria used to decide when to file a patent application? Is there a clear list of considerations concerning activity, toxicity, etc., based on which a patent is applied for? How strong are the patents mentioned in the output, and are they promising in terms of protection and for commercial value?

In previous reports, the importance of building a sustainable platform for routine screening of biological activity has been stressed. Such a platform could also be offered as a service to others, including commercial clients. By organizing this as a service, it would also take away the burden of the academic staff to run on a routine basis samples from others. From the presentations it was not clear if any steps in this direction have been made.

The road from a hit to a lead in drug development is long. It requires the possibility to isolate/synthesize larger number of analogues and more advanced in depth pharmacology, as well as toxicology. In fact, for the latter there should be primary screens in the early phase, to be able to focus on the most promising hits for further studies.

For the further development of a hit, a considerable amount of material is needed. In weighing the value of any hit, the sourcing thus should play a role, and if necessary the project should have the expertise for synthesis or biosynthesis by agri-/horticulture or fermentation.

Some of the activities targeted are rather complex (antitumor and anti-inflammatory) and chances of finding real leads are not high. On the other hand, a number of typical tropical diseases really ask for good medications, and big pharma does not do much on drug development for these diseases. In fact, some of these diseases are already on the list of assays. Further focus on these would be of interest.

Now, all compounds isolated are published in journals, including their activity. Extra value can be added by having an on-line library with names structures, spectral data and activities for all pure compounds and extracts. That would open the way for commercial selling of compounds and extracts, as e.g. done in Korea and China.

For developing products from any bioprospecting activity, a company must eventually take responsibility for this. This requires young entrepreneurs with a scientific background for

making spin-off companies. An educational program and an incubator infrastructure are required.

Metagenomics is able to generate huge amounts of data. To be able to have any use of these data, a solid expertise in bioinformatics is needed, and clear goals should be set for the use of the information. Metagenomics for finding novel polyketide genes requires extensive research in expressing the gene(s) in appropriate host cells, this enters the world of synthetic biology. Ethical and safety issues concerning synthetic biology should be anticipated.

Bioprospecting for enzymes is interesting, but requires clear goals and golden standards for what at present is the standard for the enzymes used, e.g. enzymes for food processing, washing, bio-breakdown, and biofuel production. A market analysis should make clear what the most promising targets are for Brazil, and what would be the minimum specifications for these target enzymes.

Recommendations for the future

The Scientific Advisory Committee wishes to provide some context on the recommendations, before listing them.

Drug discovery

One of the major aspirations of BIO*prospec*TA is to develop the most promising natural product hits discovered in the various natural products labs into clinical trials candidates

that attract the interest of pharmaceutical companies. It is unrealistic to expect academic natural products chemists to carry out the full preclinical evaluation required to advance a compound along the development pathway. It is also unrealistic to expect that the pharmaceutical industry will license a compound that has been isolated in small amounts and has only been shown to be active in an enzyme or cell based assay, regardless of its potency or the novelty of its structure. In the current drug development environment, pharmaceutical companies expect at a minimum positive phase I, but more likely, positive phase II clinical trials data before licensing a drug candidate. Therefore, Biota and BIOprospecTA need to implement realistic strategies to move compounds towards clinical trials.

Considering the large number of hits found in the program the next step should be a rigid evaluation of these compounds to set priorities and make a road map for coming from hit to lead. To make such a road map BIO*prospec*TA should convene a panel of world-class experts in natural product drug discovery to evaluate the BIO*prospec*TA portfolio for compounds that have genuine drug development potential. We would suggest Craig Crews from Yale, Carmen Cuevas from PharmaMar, Bruce Littlefield or Frank Fang from Eisai Pharmaceuticals and Georges Massiot (CNRS, Pierre Fabre, France) as the core of this panel. Each of these individuals have taken a natural product lead compound and developed it into a drug approved for clinical use. All the development pathways were challenging, so these individuals will not be pessimistic about the prospects of developing complex natural products into drugs, in contrast to most large pharma medicinal chemistry groups. The expert panel could be supplemented with additional members as Biota and BIO*prospec*TA

saw fit. This panel should meet annually in some sort of workshop with BIO*prospec*TA PIs to evaluate the portfolio.

The development of most natural products into drugs depends critically on being able to solve the supply problem. It is essential to have a sustainable and reliable source of 10s of grams to kilograms (depending upon potency) of the API for preclinical evaluation and ultimately clinical use. The common sources of natural product drugs are usually plantation grown trees, shrubs or flowering plants, fermentation of microorganisms, or laboratory synthesis. We feel that implementing solutions to solving the supply problem for BIO*prospec*TA hits would be an important and value-added next step in their evaluation and development. It would provide the material required for animal model studies of ADME, toxicology, and efficacy that are essential for making go/no go decisions about further development. If the supply problem is solved via synthesis, it would also provide methodology for making analogues for SAR and improving the drug-like properties of the hit compound. Generating new active synthetic analogues with novel compositions of matter would generate new IP that may circumvent Brazilian laws against patenting natural products. Solving the supply problem would also remove a major barrier to generating interest in a pharmaceutical partner.

Synthetic natural products or analogues with strong IP, in vivo efficacy, a good therapeutic index, good ADME, with known mechanism(s) of action (target) and a reliable and scalable source, that address an unmet medical need, should be in a strong position to attract interest from venture capital markets looking to invest in a start-up company as a vehicle to

move a compound towards clinical trials. We would encourage Biota and BIO*prospec*TA to consider taking on an entrepreneurial leadership role in building "small" companies to develop their most promising drug candidates and other products.

Recommendations

1) A regular evaluation of the hits produced by the program by experienced drug developers in the form of a workshop with the PIs is recommended to select the priority compounds and make a roadmap for further development to the level of a lead.
2) BIOTA/ BIO*prospec*TA should consider establishing a central lab facility that has the capability to synthesize natural product hit compounds and active analogues on a minimum of a 10 gram scale. This facility would be funded directly by FAPESP and it would serve the needs of all of the natural product groups in BIOprospecTA (or even in all of Brazil).
3) The central production lab might include a common bioassay lab for all of the BIO*prospec*TA groups, and as compounds moved forward, it might also make sense to add an animal facility and some analytical chemistry resources to support PK, toxicology, and efficacy studies.
4) FAPESP should consider measures to help spin-off-up companies to be started from the BIO*prospec*TA projects. This might include also educational programs for biobased business.
5) Good Practices training will be indispensable for every scientist that intend to work in partnership with pharmaceutical industry in the process of drug development

6) The practice of long-term grants of 5 to 10 years should be continued as it creates a proper environment for high-risk innovative projects.

Microbiology

Within the overall BIOTA program and distinct from the BIO*prospec*TA series of investigations, there are significant studies reporting on the properties of microbial secondary metabolites (and enzymes) from a variety of sources. Upfront, these studies can feed in to the BIO*prospec*TA program even though they are performed under the BIOTA umbrella. Below follow examples (not exhaustive, merely representative):

- The work on microbes, their genomic identification and metabolomics described by Dr. Setubal. Although each of these projects was designed as a "standalone" topic, the results obtained can provide excellent starting points.
- Studies on the secondary metabolites from toxigenic *Aspergillus* species. In particular, the discovery that the metabolome of certain species stop producing aflatoxin-like molecules at different stages of their growth cycles. This implies differential control of production under the conditions used. Thus a full genome study could identify control points of value in producing secondary metabolites.
- Studies at the São Paulo Zoo on the "moderate thermophiles" from composting. This program demonstrated that they contain degradative enzymes with potential biotechnological uses. Since they are from identifiable microbes, fermentation production is a strong possibility.
- Work on marine macroalgae has shown that marine-derived fungi can be isolated from the alga. These fungi have biological activity. Similar work with the microbial

contents of termites, other arthropods and ternary systems involving attine ants and their fungal foods/protective actinobacteria and fungal attackers have the potential to produce leads to antimicrobial and perhaps antiviral agents (arguing from external knowledge).

- Studies on the microbial flora of Amazonian Dark Earth (terra preta). The number of different microbial species and their identification of the alpha-ARDH gene cluster, plus their insecticide degradation potential, and the antibiotic activity demonstrated by selected isolates bodes well for these microbes as another source of bioactive natural products. Moreover the knowledge maybe used to develop methods to improve the rhizosphere for major crops.

Genes, enzymes, organisms

Opportunities are many, but most efforts are now focused on small molecules. The field of enzymes, genes, organisms and designs for example could be further explored. For that, some target areas must be defined, e.g. by looking at the world market for enzymes. Genes are of value for highly specific products (e.g. the green fluorescent protein encoding gene), genes encoding enzymes that have a commercial use, genes that are part of biosynthetic pathways leading to useful products, e.g. vitamins or medicines.

Bioinformatics

With the sequencing capacities available and the metagenomics approaches to study complex biological systems, there is a need for advanced bioinformatics expertise and infrastructure to be able to deal with big data. To avoid the problems of the past in setting

up appropriate databases, it is recommended to consider how the required bioinformatics should and can be covered in the near future.

Good Practices

For patents and registration dossier, the data presented should preferably be coming from a GLP-qualified laboratory. The BIO*prospec*TA groups and FAPESP itself would be greatly beneficiate if FAPESP could organize specific courses about Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) that are indispensable for every scientist intending to work in partnership with pharmaceutical industries in the process of drug development.

Recommendations

7) The microbial sources should be considered as part of the BIOTA/BIO*prospec*TA portfolio, and thus the products evaluated for their potential as both biotechnological and drug leads.
8) It may be worth performing comparison analyses (at the genomic level) of the microbes identified in the projects where there is a component of metabolomic / genomic investigation in order to see how closely linked these microbes are.
9) A market survey for industrial enzymes including food, washing, fine chemical production and research tools should be made, setting the standards for the discovery proteins of interest.
10) For handling the big data sets that are and will be produced, proper storage and data analysis methods are required. Bioinformaticians should be included in the program.

5. Conclusions and overall recommendations

A. The Scientific Advisory Committee strongly emphasizes that conserving biodiversity is the best bet-hedging or insurance strategy for maximizing our chances of finding new benefits, including new uses and products, from nature. Biodiversity assures benefits for future generations.

B. In that respect, the Scientific Advisory Committee recognizes that the BIOTA/FAPESP program has turned itself into an internationally recognized brand. It can now count on several international collaborations with prestigious institutions. In addition, the BIOTA/FAPESP program has permitted to make significant progress in education and training on biodiversity.

C. Overall, the members of the BIOTA/FAPESP program see membership in the program as a very prestigious and productive transdisciplinary association. This demonstrates that the program is working extremely well.

D. Long-term funding horizon (including some 5 yr and 10 yr grants) is a very important component of the stability and visibility of the BIOTA/FAPESP program. The Scientific Advisory Committee hopes this effort will be sustained in the future, as there is every reason to believe that it is a excellent investment for FAPESP and, beyond, for Brazilian science.

E. The Scientific Advisory Committee appreciates that the BIOTA/FAPESP program puts fundamental biodiversity research and bioprospecting (natural products research, etc.) under one umbrella. Bioprospecting is one important application of

biodiversity, and it often is used as one justification for preserving biodiversity as a storehouse of future benefits. Within the BIOTA/FAPESP program, these scientists now talk with each other and work together – perhaps a unique and visionary situation in the world.

F. The Scientific Advisory Committee made a number of critical recommendations on both BIOTA and the BIO*prospec*TA sub-program. The intention was to provide a constructive feedback and some guidance to the BIOTA research community. Noting the issues with the recommendations of the 2011 report, we recommend that the BIOTA/FAPESP program produce a point-by-point reply to this report, to be distributed to and used by the 9th evaluation panel.

G. The Scientific Advisory Committee emphasizes the opportunities to integrate, conceptually and practically, BIOTA and BIO*prospec*TA. One possible conceptual link is through the concept of "sustainable use of biodiversity". One recent BIOTA publication (the book, *Applied Ecology and Human Dimensions in Biological Conservation, eds. Luciano M. Verdade et al.*), suggested that the sustainable use of biodiversity requires the preservation of known useful species in an integrated way with the preservation of broader biodiversity. This provides a useful integrative perspective for the BIOTA/FAPESP program. The Scientific Advisory Committee recommends that the Science Plan further investigate these links and use them as a possible guideline in developing more integrated projects.

Appendix 1 – Recommendations from the BIOTA 7th Evaluation Report (2011).

1) The Committee recommends that the BIOTA biodiversity conservation goals and BIOprospecTA discovery goals be linked through the concept of sustainable use. The Committee recommends that the Science Plan make these links explicit and use this as a possible guideline in developing more integrated projects.
2) We encourage FAPESP to ensure that the new BIOTA marine Themes and other biodiversity projects are ensured equal access to its new ship, Alpha Crucis. There are many potentially serious societal side-effects associated with marine impacts on biodiversity. We also emphasize that real-time ocean monitoring can contribute to mitigation of biodiversity loss in marine systems.
3) We encourage FAPESP to invest in a center in SP for high-throughput DNA sequencing, recognizing its importance for many new ways of documenting and recording biodiversity. Such a center could also facilitate various types of commercial bioprospecting as discussed above.
4) That once the SinBIOTA database redevelopment has reached a mature state that the BIOTA Coordinating Committee consider conducting Gap Analyses (both taxonomically and environmentally) and use the results to help determine priority areas for future targeted calls for projects.
5) The Committee recommends that Target 19 of the CBD be used as a rationale for future increased efforts to extend the knowledge base of species and their

geographic distributions within the State of São Paulo.

6) The Committee recommends that future BIOTA projects further develop public policy links, and suggests that one pathway can be through a focus on CBD and other biodiversity policy contexts. These policy links also could help provide integration of various BIOTA projects.
7) The Committee recommends consideration of the challenges posed by these targets; they suggest guidelines for future projects and point to opportunities for BIOTA to provide world-leading biodiversity conservation outputs.
8) That future BIOTA projects address representativeness. Strategies will include the effective use of existing (and new) data to build robust biodiversity surrogates for the marine realm.
9) The Committee recommends that BIOTA explores the use of biodiversity surrogate models for implementing the "lens" approach of GEO BON to quantify ongoing biodiversity loss.
10) The Committee recommends development and application of indicators of degree of improvement in ecosystem services and biodiversity representation and persistence, as a consequence of restoration activities. The Committee further suggests that a future project could design and implement a critical test of the hypothesis that increased connectivity will benefit one or more species and/or ecosystem services.
11) The Committee recommends that BIOTA continue to integrate restoration planning into broader conservation and development planning within the State of São Paulo.
12) The Committee suggests that future projects attempt to quantify the biodiversity

values retained in human-altered landscapes, and integrate these contributions into the overall regional biodiversity "report card".

13) The Committee recommends that future BIOTA project planning consider opportunities to feed into the IPBES process, both through the capacity building theme and regional assessment.

14) The Committee recommends that the BIOTA Coordination Committee ensure that current linkages between the SinBIOTA 2.1 and speciesLINK databases be maintained on transfer of the SinBIOTA 2.1 database and where possible be enhanced, and that linkages between the SinBIOTA 2.1 database and the BIO*prospec*TA database be developed.

15) That the SinBIOTA 2.1 database be designed in a way that it can accept what are likely to be very large numbers of sequences, especially from microbes.

16) That enhanced integration between SinBIOTA 2.1 and external databases such as GBIF, OBIS, etc. be given a high priority.

17) That FAPESP projects that have a biotic component but that are funded other than through the BIOTA Program, be encouraged to incorporate the data and outputs of their research into the SinBIOTA 2.1 database to streamline state, national and global linkages.

18) That the Coordination Committee examine the opportunities available for enhancing the project through the use of Citizen Science, Creative Commons Licensing and Flickr. This may best be done in conjunction with the redevelopment of the SinBIOTA database.

19) That the BIOTA Coordination Committee give consideration to establishing an outlet

for the education and outreach parts of the Program in the form of linked set of publications that may be both electronic and available through the World Wide Web and in hard copy where appropriate.

20) That the BIOTA Coordination Committee examine the opportunities for collaborations with the U.S. National Science Foundation's Dimensions of Biodiversity campaign, for example, by building on the phylogenetic themes that underlie sustainable use.

Appendix 2 – Recommendations from the BIO*prospec*TA 7th Evaluation Report (2011).

1) Build up a central platform for bioactivity testing, with a clear strategy for a well defined area of diseases (e.g. antibiotics, CNS, antiinflammatory, or anticancer) or other targets (biocides, dyes, cosmetics). This platform should also include preliminary toxicity tests (e.g. mutagenesis, cytotoxicity) for rapid identification of potential harmful compounds that have small changes for developing into a medicine.
2) Add in-vivo tests for advanced pharmacological testing of activities. This could include zebrafish and *C. elegans* as step in between in-vitro and animal tests. This would also be of interest to discover things like synergy in case of studying medicinal plants by using a systems biology approach.
3) A strategy for valorization must be developed, with many groups involved, the best would be a centralized office, which could be FAPESP or a private company that does the valorization on contract basis.

4) There is an urgent need to improve the system for getting access to material for bioprospecting. The (international) legislation for working with transgenic organisms might serve as a model showing how to allow rapid progress in molecular biology and getting novel transgenic plants in the field.
5) Start to build up central libraries of microorganisms, extracts, gene sequences, enzymes, and compounds. The sinBIOTA database should have modules to search for this information in combination with the BIOTA database to be able to explore the biological space for interesting "chemical hotspots". This includes further development of the phylogenetic framework to facilitate exploration and assessments, in order to provide a solid basis of sustainable use of the biodiversity, and at the same time enhancing links between BIOTA and BIO*prospec*TA.
6) Concerning publications it would be good to show which groups participated in each paper to show to the outside world on the website how the program supports the collaboration between groups, to thus adding extra value.
7) One should consider the possibility make all output open access to increase the global visibility of the BIOTA project. It would require extra financial support to the groups when publishing in the open access mode, which is now offered by many journals.
8) Technical support personnel is needed for optimal use of equipment, both the granting organizations and universities should consider how to optimize the full time use of expensive equipment like NMR by enabling hiring qualified technicians. This is also important in connection with proper maintenance of equipment.

9) Organize at least once a year a (international) workshop on a novel technology or development that is of interest for bioprospecting, e.g. recombinatorial biochemistry, novel models for screening biological activity, metabolomics, metagenomics, toxicological testing. Such meetings will also lead to more interactions of the groups.

10) Dereplication is the keyword in the reductionist search for novel biological compounds. This requires libraries of physical data (e.g. MS, NMR or chromatography data) of known compounds and actives. This should be a central facility of the BIO*prospec*TA.

11) For central facilities (e.g. biological activity, libraries, NMR, MS) in the BIO*prospec*TA, the project should appoint responsible platform leaders that have the task to bring together the methods, collect/write SOPs for all users, and develop plans for further improvements and extensions of the platform. The platform leaders should advise the program coordinators about the plans and progess. With other words a clear management system of the BIO*prospec*TA program is required to further improve the performance and make optimal use of all the complementary expertise and equipment.

12) A central state-of-the-art sequencing center would be of interest for many BIOTA projects. The organization of such a facility in SP State where any project can pay for the costs of getting a gene or genomes sequenced with the latest method, would be of great use, and in fact an absolute requirement in the near future with the costs of sequencing decreasing rapidly. The sinBIOTA should be prepared for that in the near

future the amount of information per species entry may dramatically increase with genomic, transcriptomic, proteomic and metabolomic data.