



Samoa Mamala & Prostratin Recommendations: Pharmaceutical Plant Proposal

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**Prepared for:
The Government of Samoa
The Family of Paela Lilo**

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Table of Contents

Executive Summary	3
Samoa and Prostratin	4
Details of Samoan pharmaceutical plant project.....	14
Appendix 1: Prostratin-related Patents and Recommended Adjustments	19
Appendix 2: Patent Coverage for US5599838.....	20
Appendix 3: Original Field Observation Report	21

EXECUTIVE SUMMARY

Although there has been a diligent effort by the Government of Samoa to comply with all aspects of the Convention on Biological Diversity and the agreement on Trade-Related Aspects of Intellectual Property Rights, Samoa has not received the economic benefit promised it when it agreed to allow international development of Prostratin. Prostratin is a compound based on traditional knowledge from healers in Samoa that shows promise in treating HIV/AIDS, Hepatitis and possibly certain forms of cancer. It is an extract from the bark of the Mamala tree that grows in Samoa. The anti-viral uses of Prostratin were first identified by Samoan traditional healers. These healers were incorrectly not listed on the filed patents for Prostratin. In addition, patent protection for Prostratin will end in 2014, well before clinical trials for the drug can be completed. This leaves Samoa with little benefit for its significant contribution to fighting AIDS on a worldwide scale.

In light of this information, M-CAM suggests that Samoa could build a pharmaceutical plant to produce Prostratin or other Mamala derivative compounds within the country or in partnership interests where Samoans have direct creative contribution to the production and distribution process. Samoa would use its rights as original knowledge source of Prostratin under international agreements to become the sole producer of this medication, selling it at cost to least developed countries and at small markups to wealthier countries. The profits from sales to the developed world can be used to pay startup and licensing costs and reinvest in local production capabilities, biodiversity, and compensation for the traditional healers who developed the product. Finally, Samoa must take action to have the original Prostratin patent corrected to list the traditional healers, form partnerships with researchers innovating based on Prostratin, and file opposition to any Prostratin-related patents that do not properly refer back to Samoa's role in Prostratin development.

On March 14, 2008, Dr. Martin promised the family of Paela Lilo that he would insure that the world knew of, and honored her gift to humanity. This document is presented by M-CAM to the Government of Samoa and her family in Falealupo, Savai'i in her honor and in honor of all those who have given their healing knowledge to humanity in anonymity.

SAMOA AND PROSTRATIN

For years, traditional healers in Samoa have known about the healing effects of the bark of the native Mamala tree on patients who are suffering from viral infections. In 1984, an American ethnobotanist named Paul Cox went to Samoa and talked to these traditional healers. They shared their knowledge with him and he sent samples of the Mamala tree back to the United States for testing. The National Cancer Institute isolated the Prostratin compound from the Mamala tree and confirmed that it had the potential to help fight AIDS more effectively. They quickly obtained a patent listing Cox and not the traditional healers among the inventors. Based on the patent, the National Institute of Health (NIH) gave an exclusive license to the non-profit group AIDS Research Alliance (ARA) to research Prostratin and turn it into a drug. ARA negotiated an agreement to share some of the eventual licensing revenue from the drug with Samoa. Over the next 7 years, ARA worked on the preclinical trials of Prostratin. As of June 2008, Prostratin had still not entered full-scale therapeutic clinical trials, which typically take several years to complete. The patent on Prostratin will expire on February 3, 2014, leaving little to no protection for sales, even with a Hatch-Waxman term extension. Since high profits and large license revenues depend on patent protection, the current situation means that Samoa will be unable to gain any significant economic compensation for its role in originating this knowledge.

This report suggests that Samoa could build a pharmaceutical plant to produce the Prostratin-based medication for world-wide consumption (detailed below). Since the patent will likely have expired, the revenues from this production would be modest but would provide jobs and tax revenue for Samoa. Samoa's international claims to ownership and low profit margins would discourage other countries from entering the market. In addition, Samoa may be able to continue negotiations with researchers to gain exclusive or beneficial access to produce new or modified forms of Prostratin that do have patent protection.

International legal overview

There are several different agreements that cover Prostratin: the Convention on Biological Diversity (CBD), the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement of the WTO, and direct agreements between Samoa and other parties.

Convention on Biological Diversity (CBD)

The CBD is a widely accepted international treaty that aims at conservation and sustainable use of biodiversity. The treaty encourages all parties to protect and seek benefits from their biodiversity. Countries agree to share in their discoveries in ways that maintain protection for intellectual property, with preferential access for less developed countries. The CBD also establishes a fund to help countries maintain biodiversity.

Samoa joined the CBD in 2004 and has since been working steadily toward significant improvements in forest and marine protection. In a 2006 report on their CBD progress, they explained that preserving traditional knowledge was an area for improvement: “The recent National Capacity Self Assessment project has identified ‘preserving indigenous and local knowledge, innovations and practices’ as one of the country’s ‘neglected requirements’ and education, training, human resource development and stakeholder capacity building are targeted.”¹ Innovative projects such as the one proposed in this report are crucial for helping countries meet CBD objectives. By actively sharing Prostratin worldwide while recognizing the role of traditional healers in its development, Samoa will be able to honor traditional healers, improving this aspect of CBD compliance. In addition, Samoa will have funds to reinvest in the appropriate protection of traditional knowledge.

There are many sections of the CBD that encourage the active participation of all countries that have signed the treaty.² In the case of Prostratin, while other countries certainly have the capacity to produce this drug, the CBD calls on parties to “carry out scientific research based on genetic resources provided by other Contracting Parties with the full participation of, and where possible in, such Contracting Parties.’ (Article 15.6) Investment in local production would allow Samoa to fully participate in this and future research. Section 7 of article 15 requires countries to take measures “with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources.” In this

¹ Convention on Biological Diversity: Samoa’s Third National Report 2006. Available from <http://www.cbd.int/information/nr-nbsap/search/>

² <http://www.cbd.int/convention/convention.shtml>

case, Samoa is the contracting party providing the genetic resources, so it is entitled to share in a fair and equitable way the results and benefits of the development of Prostratin and other compounds based off of Prostratin. Since monetary benefits are not likely forthcoming from the original patent, Samoa deserves instead to have priority access to Prostratin-related production within the country.

Article 16 of the CBD deals more fully with how to deal with intellectual property related to genetic material. Section 1 calls on countries to share biodiversity related technologies with other nations. Samoa fulfilled this requirement when it shared genetic materials with United States researchers. Section 2 requires that resulting technologies be shared with developing countries on favorable terms, which in this plan means that Prostratin-based medicines could be provided at cost for least-developed countries and at low markups to other countries. If other countries choose to produce Prostratin, they would be under the same obligations to provide similar discounted rates to the poorest countries. Section 2 also requires that the transfer of technologies “shall be provided on terms which recognize and are consistent with the adequate and effective protection of intellectual property rights.” In Samoa’s case this did not happen. While Prostratin was patented, the property rights were not actually protected since the reduction to practice will likely end up using much or all of the patent duration. Samoa therefore met its CBD obligations but was denied the expected benefits from that compliance.

Despite this loss, Samoa can still benefit under sections 3 and 4 of Article 16. Section 3 requires that countries that have provided genetic resources “are provided access to and transfer of technology which makes use of those resources, on mutually agreed terms, including technology protected by patents and other intellectual property rights.” Since Samoa provided the genetic resources for Prostratin, it is entitled to use the resulting technology, in this case for low-cost production. Since this benefit accrues only to Samoa, this would give the country a competitive advantage in producing Prostratin compared to other countries. Samoa could choose to use this benefit to achieve higher profits and invite international competition but this report recommends maintaining ethically low pricing. Section 4 of Article 16 states that Parties must enable the private sector to jointly develop or transfer genetic-based technologies “for the benefit of both governmental institutions and the private sector of developing countries.”

Since local Prostratin production benefits both the government and private sector of Samoa, there is ample encouragement for continuing development and transfer of technologies to Samoa in exchange for their work in Prostratin origination.

These principles of the CBD have been upheld in subsequent debates and decisions. Decision VII/29 about the CBD encourages innovative approaches for meeting CBD obligations.³ It cites past declarations that states should “strengthen endogenous capacity-building for sustainable development” and finance “access to and the development, transfer and diffusion of environmentally sound technologies and corresponding know-how.” The decision requests proposals that include “incentives to private-sector actors ... to encourage cooperation and transfer of technologies to developing countries ... and promote the effective participation in related technological research by those Parties.” Further, countries should “develop innovative approaches and means of technology transfer” and “identify mechanisms for financial support of capacity development.” Prostratin production in Samoa would meet these objectives through innovative technology transfer to a developing country to enhance its sustainable development of biodiversity-derived materials and further promote access to that technology to other states.

The CBD Program of Work is the implementation of the CBD; it also contains language to support this proposal since this plan would “ensure participation in biotechnological research by Parties that provide the genetic resources for such research” and would help with “building or enhancing human and institutional capacity at all levels, in particular in ... small island developing states.” The Program of Work calls for the “strengthening of national research institutions for the adaptation and further development of imported technologies.” By starting a pharmaceuticals program, Samoa would be able to enhance production and knowledge capacity, eventually leading to full participation in biotechnological innovation. In sum, all aspects of the Convention on Biological Diversity support Samoa’s efforts to make use of these biological materials in a way that provides worldwide benefits. If successful, this plan would become a model for other states to follow in furthering the goals of the CBD.

³ <http://www.cbd.int/convention/cop-7-dec.shtml?m=COP-07&id=7766&lg=0>

Trade Related Aspects of International Property Rights (TRIPS)

The CBD deals with biodiversity and has provisions that mandate that technology sharing follow international agreements for protecting intellectual property rights. One of the key international intellectual property agreements is the agreement on Trade Related Aspects of International Property Rights (TRIPS). TRIPS is an agreement originating from the World Trade Organization that seeks ways to promote innovation through the protection of intellectual property rights. Samoa will become a full TRIPS signatory on accession to the WTO. In terms of existing intellectual property protection, Samoa supplemented its existing patent protection legislation by joining the World Intellectual Property Organization (WIPO) in 1997.

TRIPS overlaps with the CBD when the innovation in question involves biodiverse material. There have been significant debates about the interaction of these treaties, eventually leading to calls for a full re-examination of TRIPS. This review is still ongoing, with dialog occurring between countries as to the best methods for protection of innovations in applied genetic and biological areas. Even with these debates, Samoa can move forward with confidence based on the intent of the TRIPS agreement, as detailed below.

Two key objectives of TRIPS are laid out in Articles 7 and 8 of the agreement. Article 7 states that “The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.” Article 8 states that members may “protect public health ... and promote the public interest in sectors of vital importance to their socio-economic and technological development” and “prevent the abuse of intellectual property rights by right holders” as long as those measures are in line with other TRIPS requirements.⁴

In examining the situation, we find that Samoa’s intellectual property rights under TRIPS were not upheld because the traditional healers were not included as inventors and the reduction to practice has extended through most of the term of patent protection. This qualifies as an

⁴ http://www.wto.org/english/docs_e/legal_e/27-trips_01_e.htm

“abuse of intellectual property rights by right holders.” To rectify this failing, the original patent should be corrected to include the original healers: Epenessa Mauigoa, Paela Lilo, and Lemau Seumanutafa. Under current patent regulations (MPEP 1412.04), if all current parties agree and the only change is to add inventors, this can be accomplished using a certificate of correction. Otherwise, a patent reissue is required. In addition to correcting the original patent, current and future patent applications based on that original work need to reference the important contribution made by Samoan citizens to this line of innovation.

To achieve this goal, Samoa should consider immediately implementing a process to review patents related to Prostratin, Mamala extracts, and all derivatives or modifications. All patents that do not explicitly acknowledge the rights of Samoa would receive opposition filings in the requisite patent offices. Samoa should also continue to negotiate revenue-sharing agreements or preferential production rights for all Prostratin-related patents.

Although the original patent did not follow TRIPS guidelines, Samoa can still work within the framework of TRIPS to find benefits from biodiversity. Per TRIPS, continuing work on Prostratin should foster technological innovation while balancing rights and obligations. In this case, foreign patent holders have rights to benefit from their contributions and would receive appropriate license payments from Samoa. Those same foreign patent holders also have obligations to allow Samoa preferential access to their innovations and recognition for their originating contributions. Overall, while there are continuing disagreements about TRIPS and CBD, this proposal finds a way to satisfy both agreements in a win-win situation for everyone involved.

Direct agreements

Samoa has direct agreements in place with both the Aids Research Alliance (ARA) and with the University of California Berkley that theoretically allow Samoa to benefit from eventual revenue from Prostratin-based patents. This plan honors the intent of these agreements. In this plan, Samoa would seek permission from ARA to produce Prostratin-based drugs in Samoa at low or zero license costs. Since the patent protection on Prostratin will likely expire before clinical trials are complete, this agreement could supplement or replace the original license-sharing

agreement that will never be realized. Both parties would benefit: ARA would have a low-cost manufacturing partner to maximize AIDS treatment medication and Samoa would benefit from the ability to produce both Prostratin and further derivatives developed by ARA. One of ARA's partners has already found a formulation that minimizes side-effects; a continuing relationship with ARA could allow Samoa to produce these formulations.⁵ In a similar vein, Samoa can continue discussions with UC Berkley about Prostratin production to replace or supplement the original agreement in the case that they create a different form of Prostratin. Samoa would benefit from access to a high-volume production method for Prostratin while UC Berkley could benefit from new research materials from Samoa. Both ARA and UC Berkley would gain significant positive press for their role in bringing low-cost AIDS drugs to the world.

In addition to existing agreements, Samoa should negotiate with other patent-holders who are developing Prostratin-inspired technologies. Their patents need to reference the original Prostratin patent (which should in turn be amended to list the Samoan healers as inventors). This is required under current US law as part of citing existing prior art on the subject so that the limits of the patent can be correctly bounded. If mandatory disclosure of country of origin for genetic material is implemented under TRIPS, referencing the original patent would be supplemented by referencing Samoa as a direct source of the genetic material.⁶ Second, Samoa should seek agreements with these parties to allow Samoa to make use of their innovations in pharmaceutical production. Samoa has a strong negotiating position due to its claims under the CBD, TRIPS, and sovereign interest in promoting affordable, high-quality public health advancements. A partial list of Prostratin-related patents is provided in Appendix I.

Alternative strategies for redress

Samoa could pursue several other strategies to recover some of the benefits originally promised when antiviral traditional knowledge and materials were taken from the country. The government could argue that the original Prostratin patent should be invalidated and that the anti-viral uses of Prostratin should lead to remuneration as a misappropriated Samoan trade secret. However, invalidating the original patent does not honor subsequent agreements and a significant favorable ruling based on Prostratin trade secret status is unlikely. Instead, Samoa can

⁵ http://www.aidsresearch.org/scientific_research/ARA_Prostratin_nwsltr.pdf

⁶ http://www.wto.org/english/news_e/news08_e/trips_6june08_e.htm

and should push for the original and subsequent patents to reference the original Samoan traditional healers and their patent respectively. A second option would be for Samoa to try to extend its sovereign claim to complete ownership of everything related to Prostratin, essentially nationalizing the drug and derivatives. However, this would harm WTO accession goals and Samoa's international reputation. A third option would be for Samoa to encourage ARA to use standard biopharmaceutical techniques to extend the life of the patent protection by seeking protection on other forms, formulations, and combinations of the drug. While plausible, we discourage this option since these practices are generally harmful to the public good. This report concludes that enforcing, altering, or destroying the original patent claims is unlikely to produce financial benefits to outweigh the costs of doing so. The best way forward is a strategy that relies on new work and innovation rather than focusing on prior wrongs.

Assumptions

In examining how Samoa should handle revenue generation from Prostratin activities, it is useful to examine a few underlying assumptions. At the time Prostratin was first isolated from the Mamala tree, multinational corporations assumed that extracting biological material from a country without consent or recompense was acceptable. There was little protection for genetic materials and even less for traditional knowledge. The situation has changed slightly in the intervening years, leading to the CBD and TRIPS (explained above) and to a somewhat greater understanding that the contributions of developing states and traditional knowledge should be recognized and should lead to benefits. Even with these advances, the current prevailing school of thought continues to assume that patents and related IP protection mechanism are the best way to extract financial returns from traditional knowledge and innovation rather than the adoption of *sui generis* systems. This assumption has not always led to ideal outcomes for the originators of the knowledge, as is the case with the Prostratin patent. While progress has been made, countries need to continue to develop better methods for protecting and producing benefits from traditional knowledge sharing.

In some cases, sharing traditional knowledge leads to its use in ways that are not in harmony with the original intent. This can occur when religious aspects of the knowledge are ignored or exploited. This can also occur when a multi-faceted healing technique is reduced to a single

isolated and purified chemical extract. This frequently ends up addressing only symptoms and often lacks the complex synergy found in the original natural formulation. It is noteworthy that while Prostratin as an isolated compound has shown great promise, prolonged high doses show indications of toxicity⁷. This is an example of how a traditional formulation can be used for years with no side effects but may demonstrate them in an isolated form. *M•CAM proposes a new IP-integrated strategy to reconsider the in situ traditional processes, methods of preparation, and modes of delivery and build a proprietary platform on the dosimetry and sequelae management that is indigenous and the exclusive domain of Samoa's control.*

Traditional knowledge can also be improperly used when the contribution of traditional healers is forgotten. The years of dedication and work from traditional healers is seldom mentioned after the commercialization process occurs. As part of this plan, Samoa's recognition of the role played by traditional healers can help incrementally raise awareness of both their role and their methodologies for treatment. Wider change will require the concerted efforts of many international partners.

The last set of assumptions relate to the likely success of this project. We project that Samoa is capable of undertaking this project, improving capacity as it diversifies its production into a new sector. This would require that Samoa be willing to take part in Western-style commercialization of a traditional remedy. If this is feasible, we assume that costs could be controlled enough that producing beneficial drugs at cost to developing countries and at small markups to wealthier countries could be sustainably profitable. In order to protect these profits and prevent foreign entry, we assume that Samoa would leverage or extend existing agreements giving it greater rights over Prostratin production. We also expect that Samoa could build the plant in an environmentally sustainable manner. Finally, we assume that other interested parties will see the benefits from this project and not stop it from going forward. Specifically, this proposal relies on favorable negotiations with ARA, NIH, and other researchers for production rights and relies on non-interference by large pharmaceutical companies that could feel threatened by this type of project. Overall, we are confident that the

⁷ <http://www.jbc.org/cgi/content/full/279/40/42008>

government and people of Samoa are amply capable of meeting these assumptions and making this project successful.

DETAILS OF SAMOAN PHARMACEUTICAL PLANT PROJECT

A new pharmaceutical production plant in Samoa would allow Samoa to gain some revenue from its role in bringing Prostratin to the world. Since the treatment has already been identified, Samoa could step into the role typically played by large pharmaceutical companies. In this role, Samoa would ethically gain benefit from Prostratin without use of exploitative methods sometimes used to achieve extremely high pharmaceutical profits. In this plan, Samoa would produce significant amounts of Prostratin at low cost for poor countries and at slightly higher cost for developing and developed countries.

The following sections provide basic details useful for understanding one possible implementation of this plan. It should be understood that these serve as a starting point for discussion rather than as a proposal since much more detail is required. This plan attempts to simultaneously meet the objectives of the CBD, TRIPS, Samoan policy (including the Joint Samoa Program Strategy or JSPS), and the general welfare needs of those who suffer from HIV/AIDS but receive limited benefit due to economic constraints.

Prostratin production and licensing

There are three general sources of the chemicals used in Prostratin. The natural source comes from the Mamala tree that grows in Samoa. Unfortunately, yields of Prostratin from the bark and trunk are low and widespread production might be unsustainable on the scales needed to combat AIDS globally. A second source of Prostratin is to have genetically-modified bacteria produce the drug directly. A team of scientists at UC Berkley is working on this and have had success using this process with a related drug. The government of Samoa has a revenue sharing agreement with UC Berkley for any profits derived from this process. This lowers Samoa's relative cost of using this process compared to other producers since it would not have to pay itself for the rights to use the technology. The third method of Prostratin creation is to chemically process existing substances into Prostratin. Stanford researchers have successfully made use of this method using the Croton seed as a base. Understanding other licensing agreements is also important. The AIDS Research Alliance (ARA) has an exclusive license from

the National Institute of Health “to develop Prostratin as an anti-HIV drug.”⁸ ARA and Samoa already have a profit-sharing agreement in place concerning Prostratin; part of the negotiations for this production facility would require ARA to allow Samoa to produce the final approved product. Given Samoa’s possible goal to distribute the medicine widely at low cost and ARA’s nonprofit goal to eliminate AIDS, favorable negotiation seems likely.

Pharmaceutical plant in Samoa

Adding pharmaceutical production capabilities to Samoa would meet the JSPS goal of “building up the narrow export base, ... providing income generation and employment opportunities and reducing vulnerability to external economic shocks and natural disasters.”⁹ Samoa currently has no pharmaceutical production capacity and imports all of its medicine from other countries. In addition to creating a small number of jobs, this sort of capacity would significantly reduce Samoa’s vulnerability to internal and external economic shocks since the demand for HIV pharmaceuticals is largely independent of climate, season, and commodity market swings.

Location

If possible, this plant may be ideally built in the Vaisigano district of Samoa. This would help provide “formal employment opportunities for the rural-based population,” which are currently “very limited” according to the JSPS. A location in this district on the island of Savai’i could provide some employment opportunities for villagers from Falealupo where Prostratin was first identified. Asau Harbor could provide nearby port access to the plant. If infrastructure improvements are needed, these would also fall in line with Samoa’s goal to reduce urban-rural inequalities in “electricity and water services.” From a regional standpoint, because pharmaceuticals are more compact than other Samoan export industries, the country’s remoteness would not be a barrier to production. Also, because the Croton seed required for one method of synthetic Prostratin production is grown in Asia, Samoa’s location could actually be beneficial.¹⁰ Samoa as a whole is an environmentally friendly location since it uses local

⁸ http://www.aidsresearch.org/scientific_research/ARA_Prostratin_nwsltr.pdf

⁹ <http://www.nzaid.govt.nz/library/docs/samoa-jsps-prog-strategy-2006-2010.pdf>

¹⁰ <http://news-service.stanford.edu/news/2008/may7/samoahiv-050708.html>

hydropower for all of its electricity generation.¹¹ Finally, Samoa has a good business and investment environment, key qualities for allowing a new project of this sort to succeed.¹²

Initial costs

Pharmaceutical plant construction costs vary widely and depend primarily on the type of plant and the square footage. These can be identified once a production technology and dosing scheme are determined. Pharmaceutical plant construction costs vary between \$10 and \$60 million for bulk manufacturing plants that can produce the hundreds of millions of doses that would be needed yearly for wide-spread Prostratin treatment.¹³ Besides facility costs, the project would also require staff for fund-raising and agreement negotiation, possible infrastructure improvements to the selected site, and recruiting and training plant workers and managers.

A Prostratin production plant could start to see significant demand for Prostratin as early as the start of Phase III trials. If approved, the planning and construction times would likely occupy a significant portion of the time spent doing Phase I and Phase II trials. If the plant were ready before Prostratin has final approval, it could be used to produce generic antibiotics for domestic consumption. Samoa currently imports all of its medication, with antibiotics making up a significant portion. Pharmaceuticals make up 20% of Samoa's annual health budget: a total of approximately \$19 per person per year on pharmaceuticals. By producing some of these locally, Samoa could save on those imports. Even if domestically consumed antibiotics are never produced, eventually the project could expand to cover other widely needed pharmaceuticals that are derived from biological diversity.

Startup funding

Because this project benefits many people, there are a number of potential sources for funds. Nationally, the government of Samoa could fund part of the project in advance of job creation

¹¹<http://inweb18.worldbank.org/servlet/OEDSearchServlet?SearchType=byField&PerPage=20&DbURL=oed/oeddoclib.nsf&Form=OEDSearch&&Series=Country%20Evaluation&Language=English&Title=Pacific%20Member>

¹² <http://www.doingbusiness.org/ExploreEconomies/?economyid=161>

¹³ Multiple examples at: http://cr.pennnet.com/articles/enlarge_image.cfm?IMAGE_ID=155968&SITE_ID=CR,
<http://www.pharmaceutical-technology.com/projects/daiichi/>,
http://www.pharmaceutical-technology.com/projects/ic_asia/,
http://cr.pennnet.com/display_article/210423/15/ARTCL/none/none/1/Approximating-facilities-costs/

(10-20 jobs) and some additional tax revenue. In the region, Australia and New Zealand could donate some funds to the project; they are long-term partners in Samoan development and co-authored the JSPS. Internationally, Samoa could request funds from CBD in order to fund the project since it qualifies as a small island state. Funds could also be procured from AIDS program budgets through the World Health Organization. Even the US government might be willing to contribute since Medicare currently pays for the bulk of continuing anti-retroviral costs that Prostratin could help alleviate.¹⁴ To complement government funds, significant donations are likely to be procurable from charities and NGOs dedicated to eliminating AIDS such as the AIDS Healthcare Foundation or the Bill and Melinda Gates Foundation. If for some reason these funding sources are inadequate, loans could be procured from private sources or from the International Development Agency at the World Bank. If no other funding is obtainable, a split-license where Samoa produces Prostratin internationally and a large pharmaceutical company produces it for US markets might be negotiated.

Project goals

In addition to meeting a global demand for anti-retroviral medication, this plan would also have the following financial goals.

- Provide sustainable employment for local workers, resulting in economic benefits for the region.
- Repay the initial startup costs quickly so that the project isn't hampered by long-term debt servicing.
- Direct some proceeds to protecting biodiversity in the region that produced Prostratin. If the project expands to other drugs, part of the proceeds from those drugs would go toward protecting biodiversity in the contributing region.
- Recompense the villages and families that helped originate knowledge of Prostratin. If the project expands to other drugs, part of the proceeds from those drugs would go to the individuals and country that contributed knowledge or materials.
- Pay applicable license fees to companies that have helped develop the process. Ideally, these license fees will be discounted but will still provide an incentive for continuing partnerships in innovation.

¹⁴ <http://www.worldbank.org/aids-econ/arv/floyd/whoarv-webp9.htm>

- Expand production capacity to allow project expansion. This would include training for additional Samoan workers, managers, and researchers. An eventual goal would be to increase local research to allow end-to-end pharmaceutical research and development based on Samoan and regional biodiversity.

Rough revenue projection example

- Assume that the cost to produce or distribute Prostratin is \$0.50 per daily dose.
- Note that the total incidence of AIDS worldwide is over 33 million.
- Further note that the number infected individuals in non-LDC countries is greater than 7 million (2 million in US/Western Europe¹⁵ + 5.5 million in South Africa¹⁶). These are some of the doses that would produce revenue above cost.
- Assume that Samoa can provide medication for at least 10% of the market in a given year.
- Assume average markup for non-LDC countries of at least \$0.50 per dose (equal to the production cost). One cost structure option is to produce Prostratin at cost for LDCs and charge 2x cost to developing countries and 3-4x cost to developed countries. This would be comparable to current discounting schemes.^{17 18}
- Assume a minimum of 1 month of treatment to help flush out HIV reservoirs (at least 30 doses)
- Total year profits = 700,000 people * 30 doses * \$0.50 = \$10.5M
- If 25% of this goes to repay startup costs on a small plant, it would take ~5 years to pay off the initial startup costs. After that, the additional funds could be used for expanding capacity.

¹⁵ <http://www.avert.org/safricastats.htm>

¹⁶ <http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007/default.asp>

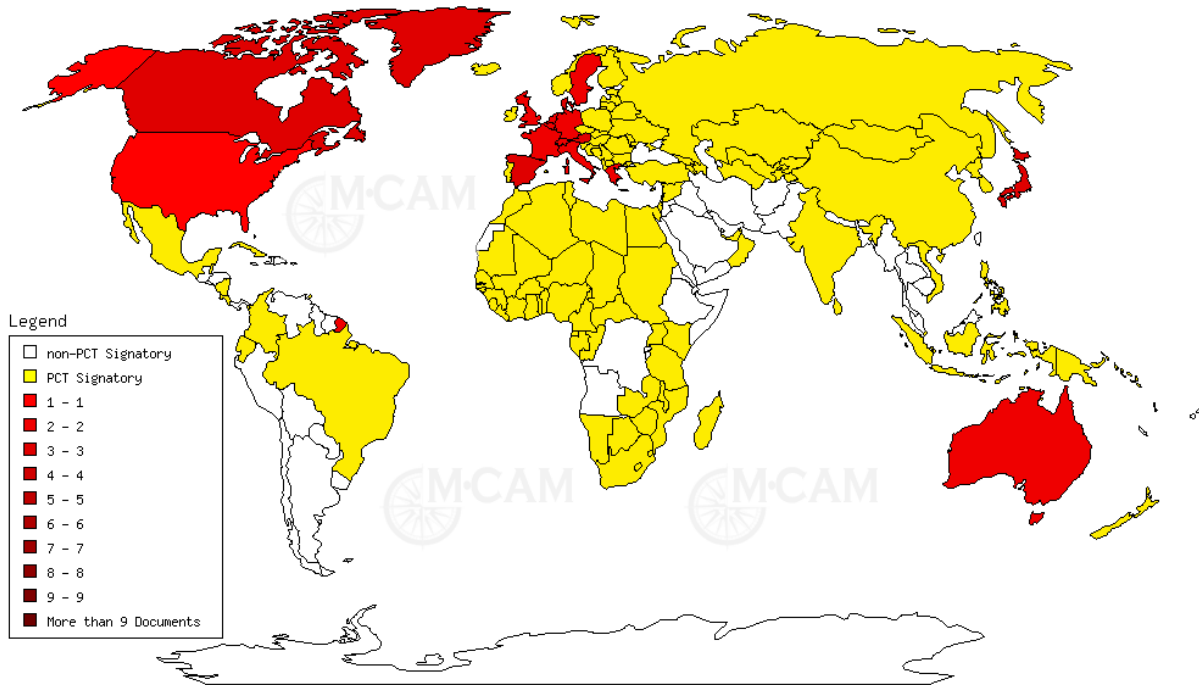
¹⁷ <http://news.bbc.co.uk/1/hi/health/1158637.stm>

¹⁸ <http://www.un.org/ecosocdev/geninfo/afrec/vol15no1/151aids1.htm>

APPENDIX I: PROSTRATIN-RELATED PATENTS AND RECOMMENDED ADJUSTMENTS

Number	Title (Assignee)	Edit this patent to cite original?	Partner with this patent?
US7199151	DHA-pharma agent conjugates (Lutipold)	No	Possible
US7183089	Method for enhancing production of isoprenoid compounds (UC)	Yes	Yes (done)
US6602902	DHA-pharma to improve tissue selectivity (Protarga)	No	Possible
US6576636	Treating liver disorder with fatty acid conjugates (Protarga)	No	Possible
US5795909	DHA-pharma agent conjugates (Neuromedica)	No	Possible
US5767095	Anti-inflammatory compositions (Roger Winget)	No	No
US5674902	Inhibiting hyperplasia (USDoH)	Yes	No
US5620962	Anti-inflammatory compositions (Roger Winget)	No	No
US5599839	Antiviral composition (USDoH)	Original	Original
US5420162	Phorbol ester for treating inflammation (USDoH)	Yes	No
US5405875	Method of inhibiting neoplasia and tumor promotion (USDoH)	Yes	No
US20080118494	Compositions For Detection Of Latent Hiv Reactivation And Methods Of Using The Same	Yes	Yes
US20070269379	Penetration enhancer combos for delivery (Mitragotri Samir)	No	Possible
US20070212756	Methods for treating lentivirus infections (UC)	Yes	No
US20070134653	Methods for treating lentivirus infections (UC)	Yes	No
US20070093462	Ionic compositions for overcoming polymorphism (Swatloski Richard)	No	Yes
US20060216251	Topical formulations (Tracie Martyn Intl, LLC)	No	Possible
US20060079476	Enhancing isoprenoid compounds (Keasling, Jay)	Yes	Yes
US20060024365	Novel dosage form (Vaya Navin)	No	Possible
US20060018934	Novel delivery system (Vaya Navin)	No	Possible
US20060018933	Novel delivery system (Vaya Navin)	No	Possible
US20050053977	Method for treating lentivirus infections (Greene Warner)	Yes	No
US20040180949	DHA-pharma conjugates of taxanes (Protarga, Inc.)	No	Possible
US20030059471	Oral delivery formulation (Compton Bruce)	No	Possible
US20020010208	DHA-pharma agent conjugate of taxanes (Shashoua Victor)	No	Possible
EP0531413B1	An Antiviral Composition Containing Prostratin	Family	Family

APPENDIX 2: PATENT COVERAGE FOR US5599838



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APPENDIX 3: ORIGINAL FIELD OBSERVATION REPORT

Technical Briefing on Prostratin and the Mamala Tree Remedies

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March 20, 2008

Executive Summary:

Dr. Paul Alan Cox reported having been involved in a series of interviews with traditional healers in Savai'i learning about the potential and actual therapeutic benefits of the use of material from the mamala tree. Upon reflection, Dr. Cox elected to pursue a strategy of both testing material for the characterization of therapeutic agent(s) and clinical indications for potential use.

Heralded as a "Samoa's Rainforest Savior" and a "Hero of Medicine", Dr. Paul Alan Cox's reported misgivings about signing a patent application may have been warnings from the spirits of the ancestors that rest eternally off the coast of Falealupo. Just beyond the Lilo family home of the traditional healer from whom Dr. Cox received critical information leading to the identification of a potential AIDS-fighting drug are the rocks where the chiefs' spirits go after their death. Sitting under their thatch roof and hearing that the family of the late Paela Lilo is prohibited from talking to anyone without written permission from Dr. Cox seems a dissonant chord contrasted to his stated position of being the steward of a knowledge that belongs to Samoa. When approached, the patriarch of the family honored his agreement with Dr. Cox to tell us nothing about the traditional medicine but provided a considerable window into a process that has seriously impaired the long-term commercial prospects for a promise that was misappropriated. So maybe, the foreboding he reported during a November 2005 interview was a warning from the ancestors just beyond the forest - something that he could have heeded rather than potentially removing most, if not all, of the rights that could have served as a means to develop Samoa's economy by other means.

U.S. Patent 5,599,839 was filed by as a continuation of application number 530,562 claiming an invention priority date to May 30, 1990. The inventors listed on the patent include: Michael R. Boyd (US); Paul A. Cox (US); Gordon M. Cragg (US); Peter M. Blumberg (US); Nancy A. Sharkey (US); Junichi Ishitoya (US); James B. McMahon (US); John A. Beutler (US); Owen S. Weislow (US); John H. Cardellina II (US); and Kirk R. Gustafson (US) with **no inventor attribution** to either of the traditional healers who supplied the knowledge. The U.S. patent was issued on February 4, 1997 with an assignment to The United States of America's Department of Health and Human Services and Brigham Young University. According to published news articles, the rights have been assigned to the AIDS Research Alliance. National phase filings have been made in Japan, Spain, the European Union, Canada, Australia, Austria, Germany and Denmark. Based on a 2005 report stating that Phase I Clinical Trials were being initiated, it is likely that the Samoan "invention" claimed by the U.S. researchers will be in public domain at least three years before a Phase II/Phase III completion and product introduction. The University of California Berkeley's Jay D. Keasling has initiated (and filed for his own patent

on) research to clone the genes of the mamala tree to manufacture potential drugs derived from this work “more cheaply”. While there is a reported license agreement in which UC Berkeley has agreed to share 50-50 in their proceeds, what is missing from the published reports of this agreement are any of the mandatory licensing or material supply agreements assuring Samoa of anything beyond 1/2 of UC Berkeley's ultimate royalty. In the best case possible, Samoa might expect to gain far less than 5% of the value for knowledge that it provided the world. In fact, over 20 patents and patent applications are now improving upon or expanding from the work done by Dr. Cox. As a result, the ability for this knowledge to provide the economic benefit that was supposed to come to Samoa (12.5% to the government, 6.7% to the village; and 0.4% each to the two families that provide ALL the original knowledge) was most assuredly impaired and, given the prematurity of patent filing long before a commercialization pathway could be initiated, means that the patent filed by the original team will not function to control the market for the mamala derivatives. The facts of this case demonstrate that the patenting of derivative works from traditional knowledge without a clear path for commercialization actually permanently bar a nation like Samoa from developing its own proprietary distribution platform. In short, by filing a patent which, on its face can be legally challenged as two known “inventors” are not included (a violation of patent law), and which, due to its long period of non-commercial reduction to practice will do little to protect a market, Samoa has now not only lost an economic option but has been given another example of knowledge exploitation.

I believe that, based on my readings of Dr. Cox’s interviews, lectures, and publications, that this was by no means an intentional outcome or resulting from any malice whatsoever. As in other cases of botanical and biological expropriation, intellectual property mis-information (and possible malpractice) creates unintended consequences which serve as a statutory bar from future international commercial optionality. I am certain that an indigenous designation should be sought to protect the *formulation* and all derivatives thereof so that economic value options might exist for this unfortunate series of events.

Without an extension for clinical trials time, the patent and the knowledge disclosed therein will enter into perpetual public domain (and thereby lose all proprietary economic value) on May 29, 2010. Assuming that there is interest in Samoa, M·CAM will work with the family of Paela Lilo, the other traditional healers, and the government of Samoa to identify the appropriate strategy to limit the downstream damage which could arise from this situation and will work with all parties to develop a comprehensive plan for the preservation of this and future knowledge contributions to the global community. We propose the development of the “Paela Law” which should set forth a model for prohibiting the exploitation of traditional knowledge and healing which can be exported to the world. This should be done as part of the IP discussions currently happening in anticipation of the 2010 target for WTO accession.

Analysis:

The people and government of Samoa operate under the assumption that the knowledge that was shared regarding the use of the mamala tree (and other potential traditional remedies) could allow them to, “share in the windfall, thanks to royalty agreements Cox set up.”¹⁹

¹⁹ http://findarticles.com/p/articles/mi_m0820/is_n255/ai_21224855

However, for royalty agreements to generate income, one must control the commercial distribution of a drug, material or related product and, given the prosecution history of the patents that have been issued, neither the term, nor the international scope of protection is likely to be sufficient to render this possible. In addition, while the University of California, Berkeley signed an agreement acknowledging Samoa's national sovereignty over the gene sequence for Prostratin²⁰, the ability to generate meaningful income from future income on the resulting patents may be far less valuable than proposed. The reasons for these are numerous.

First, the UN Convention on Biodiversity claim, based on an agreement ratified in 1992, post-dates the U.S. patent filing by two years. Given that Article 16 of the CBD details a requirement for Contracting Parties to provide access to patents and other intellectual property rights around claimed subject matter²¹, one has to ponder how Samoa can have jurisdiction over a patent filed in the U.S. without any sovereign or civil participation of Samoa and that contains no statutory assignment to Samoa or Samoan interests. In short, the rush to file an overly broad patent application by the U.S. "inventors" may have adversely impacted the ability of Samoa to defend an argument of CBD designation.

Second, since National Institutes of Health and National Cancer Institutes have licensed the AIDS Research Alliance (a non-profit) with the AIDS research initiative²², the "windfall" expectations are assuredly limited due to the nature of the licensing structure. While M·CAM applauds the ARA and has done significant amount of work to extend generic drugs world-wide for the treatment of HIV-AIDS related disease, we must acknowledge that this ethical use is antithetical to profit-driven pharmaceutical company participation. In fact, due to this strategy, the likelihood that one can generate value apart from controlling manufacturing in Samoa or in a Samoan-held interest, is attenuated at best. For Samoa to stand a chance at an economic consequence of benefit, a strategy to own or manage the production (not share in a fractional license) is essential.

Finally, if one carefully reviews the promised "royalty sharing" agreements with ARA, UC Berkeley and others, a key fact that is lacking is any commitment to insuring that all relevant haste is applied to accessing the commercial market. In point of fact, each year that lapsed between the issuance of the patent and the launching of formal clinical trials significantly limited the potential economic value of the patent and the proprietary contract interest to a point of being of little to no value. While the percentages sound substantial, there is no agreement published that states what minimum royalty expectations are and, as a result, Samoa has no negotiating power in the face of third party transactions for commercialization beyond the tenacity of their partners.

The following table sets forth the patents, patent applications, assignees, classification codes and filing dates of intellectual property claims explicitly surrounding prostratin.

²⁰ http://www.berkeley.edu/news/media/releases/2004/09/29_samoa.shtml

²¹ <http://www.cbd.int/convention/articles.shtml?a=cbd-16>

²² http://www.aidsresearch.org/scientific_research/prostratin_press.html

Document number	Title	Assignee name	Primary classification	Priority date File date Issue date
US7199151	DHA-pharmaceutical agent conjugates of taxanes	Luitpold Pharmaceuticals, Inc.	514/449 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	22-May-96 14-Jul-03 3-Apr-07
US7183089	Method for enhancing production of isoprenoid compounds	The Regents of the University of California	435/167 - CHEMISTRY MOLECULAR BIOLOGY AND MICROBIOLOGY	21-May-04 20-May-05 27-Feb-07
US6602902	Dha-pharmaceutical agent conjugates to improve tissue selectivity	Protarga, Inc.	514/449 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	22-May-96 1-May-01 5-Aug-03
US6576636	Method of treating a liver disorder with fatty acid-antiviral agent conjugates	Protarga, Inc.	514/261 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	22-May-96 5-Dec-00 10-Jun-03
US5795909	DHA-pharmaceutical agent conjugates of taxanes	Neuromedica, Inc.	514/449 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	22-May-96 22-May-96 18-Aug-98
US5767095	Anti-inflammatory compositions containing monogalactosyl dieicosapentaenoyl glycerol and methods relating thereto	Rodner R. Winget	514/25 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	30-Apr-93 7-Jan-97 16-Jun-98
US5674902	Method of inhibiting hyperplasia to a mammal in need thereof	The United States of America as represented by the Department of Health	514/570 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	8-Apr-91 26-May-95 7-Oct-97
US5620962	Anti-inflammatory compositions containing monogalactosyl dieicosapentaenoyl glycerol and methods of relating thereto	Rodner R. Winget	514/25 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	30-Apr-93 7-Jun-95 15-Apr-97
US5599839	Antiviral composition	The United States of America as represented by the Department of Health	514/546 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	30-May-90 17-Apr-95 4-Feb-97
US5420162	Phorbol ester pharmaceutical compositions and their use for treating inflammation	The United States of America as represented by the Department of Health	514/570 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	8-Apr-91 31-Jul-92 30-May-95
US5405875	Method of inhibiting neoplasia and tumor promotion	The United States of America as represented by the Department of Health	514/546 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	8-Apr-91 20-May-93 11-Apr-95
US20070269379	Penetration Enhancer Combinations for Transdermal Delivery	MITRAGOTRI SAMIR	424/009.200 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	23-Jul-03 21-Jul-04 22-Nov-07
US20070212756	METHODS FOR TREATING LENTIVIRUS INFECTIONS	The Regents of the University of California	435/069.100 - CHEMISTRY MOLECULAR BIOLOGY AND MICROBIOLOGY	10-Jun-03 6-Feb-07 13-Sep-07
US20070134653	METHODS FOR TREATING LENTIVIRUS INFECTIONS	The Regents of the University of California	435/005.000 - CHEMISTRY MOLECULAR BIOLOGY AND MICROBIOLOGY	10-Jun-03 6-Feb-07 14-Jun-07
US20070093462	Multi-functional ionic liquid compositions for	SWATLOSKI RICHARD P	514/184.000 - DRUG, BIO-AFFECTING AND	7-Oct-05 10-Oct-06

	overcoming polymorphism and imparting improved properties for active pharmaceutical, biological, nutritional, and energetic ingredients		BODY TREATING COMPOSITIONS	26-Apr-07
US20060216251	Topical formulations and methods of use	Tracie Martyn International, LLC	424/059.000 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	24-Mar-05 24-Mar-06 28-Sep-06
US20060079476	Method for enhancing production of isoprenoid compounds	KEASLING JAY D	514/044.000 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	21-May-04 20-May-05 13-Apr-06
US20060024365	Novel dosage form	VAYA NAVIN	424/468.000 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	29-Jul-03 19-May-05 2-Feb-06
US20060018934	Novel drug delivery system	VAYA NAVIN	424/400.000 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	29-Jul-03 19-May-05 26-Jan-06
US20060018933	Novel drug delivery system	VAYA NAVIN	424/400.000 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	29-Jul-03 19-May-05 26-Jan-06
US20050053977	Methods for treating lentivirus infections	GREENE WARNER C.	435/6 - CHEMISTRY MOLECULAR BIOLOGY AND MICROBIOLOGY	9-Jun-04 9-Jun-04 10-Mar-05
US20040180949	DHA-pharmaceutical agent conjugates of taxanes	Protarga, Inc.	514/449 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	14-Jul-03 14-Jul-03 16-Sep-04
US20030059471	Oral delivery formulation	COMPTON BRUCE JON	424/489 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	29-Nov-01 29-Nov-01 27-Mar-03
US20020010208	Dha-pharmaceutical agent conjugates of taxanes	SHASHOUA VICTOR	514/449 - DRUG, BIO-AFFECTING AND BODY TREATING COMPOSITIONS	1-May-01 1-May-01 24-Jan-02
EPI466628A1	DHApharmazeutische Produkt Konjugate	Luitpold Pharmaceuticals, Inc.	A61K 47/48 - SECTION A HUMAN NECESSITIES	13-Oct-04 22-May-97 13-Oct-04

As is evident above, there are a number of patents and patent applications that are issued and pending that have built on the knowledge disseminated by Dr. Cox's team which have little or no relation to, or obligation under, the agreements that have been promoted as defending the interest of Samoa. The country of Samoa and the assignees of the patent would need to vigorously defend, oppose or otherwise limit these actions if they wish to preserve the future value of the knowledge for the Samoan economy. Regrettably, many of the intended uses that are under patent have not been commercially evaluated or defended and run the risk of entering the public domain with NO economic value to Samoa whatsoever. Effective immediately, the government or its designee should formalize opposition filings or invalidation efforts to repatriate as much of the rights as possible or, at a minimum, not cede them to 3rd parties.

It is clearly the case that the patent statutory validity, the patent filing priority, the CBD designation and all subsequent licensing contracts have considerable impediments to creating an

equitable return to the people of Samoa. The absence of an active vigilance and surveillance program not only has adversely impacted this situation but has been detected in many other areas in which Samoan interests have been patented without the knowledge or beneficial interest of the country. M·CAM would recommend the following explicit steps:

1. Immediately consider a remedy for the failure to include Samoan individuals or interests on the patent and seek to have assignment repatriated (if the inventorship issue can be remedied).
2. Consider filing alternative rights under a Geographic Indication for the material in formulated use for a class or classes of therapeutic indications.
3. Immediately activate a surveillance and interdiction program managed by a government agency to review this and other IP obstacles where Samoa either has suffered unauthorized expropriation or where Samoan exports will encounter IP barriers to value-added business initiatives.
4. Immediate initiate opposition or invalidation activities surrounding issued and pending patents which have failed to acknowledge the Samoan prior art.
5. Finally, we restate our proposal for the development of the “Paela Law” which should set forth a model for prohibiting the exploitation of traditional knowledge and healing which can be exported to the world. This law should set forth conditions which guarantee production and distribution control extending beyond royalty-sharing under current exploitative paradigms. This should be done as part of the IP discussions currently happening in anticipation of the 2010 target for WTO accession.

Appendix A:

Pre-clinical study of prostratin; a potential adjunct therapy targeting HIV viral reservoirs.

Brown SJ, Hezareh M, Moukil M, Pondarzewski M, Cherix N, Carpentier JL, Foti M.

Int Conf AIDS. 2004 Jul 11-16; 15: abstract no. TuPeB4490.

AIDS Research Alliance, West Hollywood, California, United States

Background: The persistence of latent HIV-1 reservoirs represents a major barrier to virus eradication in patients on HAART. Prostratin, the active compound in a Samoan herbal remedy, is a phorbol ester with potent anti-tumor activity. It activates viral expression from latently infected cells and inhibits viral infection. Thus, prostratin may be a potential adjunctive therapy to activate latently infected cells in patient on HAART. Here we present a condensed drug development plan including data on the investigation of intracellular mechanism of prostratin as well as our preliminary toxicology results. **Method:** Cell surface expression and trafficking of receptors was investigated by FACS-based analyses. PKC translocations were assessed by western analysis or immunofluorescence. **Results:** 1. Intracellular signaling pathway: Prostratin induces downregulation of CD4 and CXCR4, but not CCR5, through receptor mediated internalization in lymphocytic cell lines, and both receptor-mediated endocytosis and macropinocytosis in monocytic cell lines. The use of specific PKC inhibitors revealed this downregulation is mediated by activating conventional and novel PKCs. 2. **Preliminary toxicology:** Single dose range finding studies in rats and monkeys indicates a dose dependent reversible hepatotoxicity with a MTD between 0.2 and 0.4 mg/kg in rat and 0.4 and 0.6 mg/kg in monkeys. Human microsomal experiments indicate time dependent loss of parent compound with a single metabolite (less than 17% of total). PK experiments show rapid drug elimination. Urinary excretion was less than 5%. Oral bioavailability is estimated at 28%. Additional dosing to determine if toxicity is related to a 'Cmax' effect or total exposure (i.e., AUC) is planned. **Conclusion** The initial clinical trial design will attempt to determine the MTD of prostratin, and the time to return to baseline of any toxicities seen. Initial endpoints will be determinations of activation markers, 'blips' in plasma and tissue (gut mucosal) viral RNA and changes in proviral DNA.

Prostratin: activation of latent HIV-1 expression suggests a potential inductive adjuvant therapy for HAART

Joseph Kulkosky, Derek M. Culnan, Jeanette Roman, Geethanjali Dornadula, Matthias Schnell, Michael R. Boyd, and Roger J. Pomerantz

From the Dorrance H. Hamilton Laboratories, Center for Human Virology, Division of Infectious Diseases, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA; and the Molecular Targets Drug Discovery Program and Development, Center for Cancer Research, National Cancer Institute, Frederick, MD.

Prostratin is a unique phorbol ester that stimulates protein kinase C activity but is nontumor promoting. Remarkably, prostratin is also able to inhibit de novo human immunodeficiency virus type 1 (HIV-1) infection yet up-regulate viral expression from latent proviruses. Prostratin's lack of tumor promotion, coupled with its ability to block viral spread yet induce latent proviral expression, prompted studies to determine whether this compound could serve as an inductive adjuvant therapy for patients treated with highly active antiretroviral therapy (HAART). The current experiments indicate that prostratin is a potent mitogen for mononuclear phagocytes

possessing many of the activities of phorbol myristate acetate (PMA) with notable functional differences. Prostratin, like PMA, accelerates differentiation of the myeloid cell-lines, HL-60 and THP-1, as well as mononuclear phagocytes from bone marrow and peripheral blood. Enzyme-linked immunosorbent assay and gene array analyses indicate significant changes in the expression of proteins and messenger RNA after treatment of cells with prostratin, consistent with phagocyte activation and differentiation. Prostratin blocks HIV-1 infection relating to down-regulation of CD4 receptor expression. The array analysis indicates a similar down-regulation of the HIV-1 coreceptors, CXCR4 and CCR5, and this may also reduce viral infectivity of treated host cells. Finally, prostratin is capable of up-regulating HIV-1 expression from CD8⁺ T lymphocyte-depleted peripheral blood mononuclear cells of patients undergoing HAART. This novel observation suggests the agent may be an excellent candidate to augment HAART by inducing expression of latent HIV-1 with the ultimate goal of eliminating persistent viral reservoirs in certain individuals infected with HIV-1. (Blood. 2001;98:3006-3015)

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Note: The preceding report is prepared by M·CAM and contains information and recommendations that are for the benefit of the people of Samoa and the family of Paela Lilo. M·CAM undertook this report as an independent interested party and nothing about this report, its observations, recommendations, or conclusions are assigned to any party by virtue of its transmission in any form. All use of this document or any derivative activity hereby inspired, in part or in whole, requires the prior written authorization of M·CAM. M·CAM has relied on public information for the compilation of this report and does not represent or warrant the accuracy of such information beyond that which it has independently verified vis-à-vis the intellectual property claims.