Drug Discovery and Development from Natural Products: The Way Forward

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Abstract

It is well established that natural products have been a source of leads for the development of many of the most effective drugs currently available for the treatment of a variety of human diseases. Biodiversity will continue to provide novel leads for drug development, but major obstacles limit efficient progress and result in decreased interest in the pharmaceutical sector. These include problems with the large-scale procurement of sufficient source material for bulk production, the potency and inherent toxicity of many natural products resulting in narrow therapeutic indices, as well as significant problems associated with the development of suitable vehicles and dosing schedules for the administration of the drugs to patients. The development of the anticancer drug, taxol® and related analogs, provides a good example of how these problems can effectively be overcome. Efficient lead optimization can also be achieved through the application of methodologies such combinatorial or parallel synthesis and biosynthesis, as well as total synthesis. It is clear that optimizing the value of natural products as drug leads requires multidisciplinary and international collaboration. Aspects of these issues will be discussed.

Keywords: Biodiversity, drug development, supply, formulation, collaboration

Introduction

Throughout the ages humans have relied on Nature to cater for such basic needs as the production of foodstuffs, shelters, clothing, means of transportation, fertilizers, flavors and fragrances, and not least, medicines. Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years, and their uses by many cultures have been extensively documented (1). These plant-based systems continue to play an essential role in healthcare, and it has been estimated by the World Health Organization that approximately 80% of the world's inhabitants rely mainly on traditional medicines for their primary health care (2).

Plant products also play an important role in the health care systems of the remaining 20% of the population, mainly residing in developed countries. A recent study using US-based prescription data from 1993, demonstrated that natural products play a major role in drug treatment, as over 50% of the most-prescribed drugs in the US had a natural product either as the drug, or as a "forebear" in the synthesis or design of the agent (3).

The continuing valuable contributions of nature as a source of potential chemotherapeutic agents has been reviewed by Newman et al. (4). An analysis of natural products as sources of new drugs over the period 1981-2002 indicates that 67% of the 877 small molecule, new chemical entities (NCEs) are formally synthetic, but 16.4% correspond to synthetic molecules containing pharmacophores derived directly from natural products (S* and S*/NM, Fig. 1) (5). Furthermore, 12% are actually modeled on a natural product inhibitor of the molecular

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target of interest, or mimic (i.e., competitively inhibit) the endogenous substrate of the active site, such as ATP (S/NM, Fig. 1). Thus, only 39% of the 877 NCEs can be classified as truly synthetic in origin. (S, Fig.1). In the area of anti-infectives (anti-bacterial, -fungal, -parasitic and –viral), close to 70% are naturally derived or inspired, while in the cancer treatment area 67% are in this category.

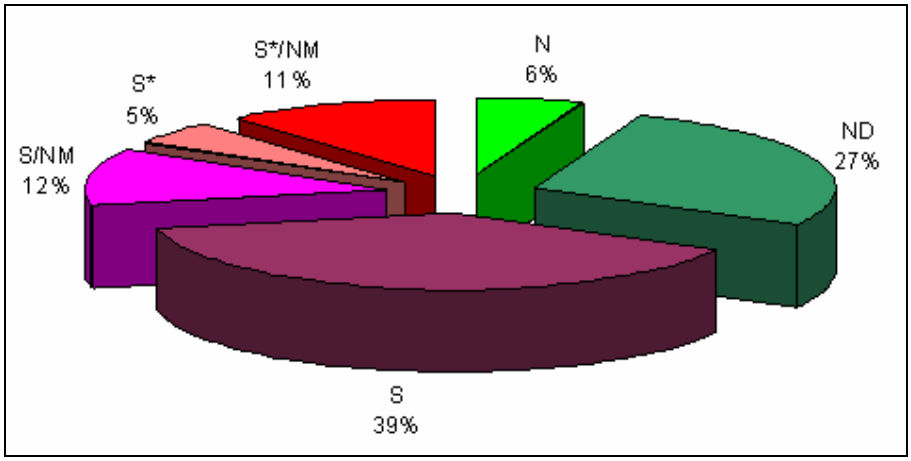


Figure 1. Breakdown of New Chemical Entities 1981-2002 (see reference 5 for description of codes)

Preclinical and Clinical Drug Development

The natural product drug discovery process generally involves the testing of extracts of source organisms of plant, marine or microbial origin in appropriate *in vitro* assays (cell or enzyme/target based), followed by bioassay-guided fractionation of the active extracts and isolation and purification of active constituents. Those constituents showing significant *in vivo* activity in appropriate animal models are considered as lead molecules which may be selected as candidates for preclinical development. Initially, such leads may be structurally modified through use of medicinal or combinatorial chemistry techniques to provide agents having superior activity or decreased toxicity (optimization of the therapeutic index) and acceptable pharmacological properties.

The key steps in the preclinical development of a potential drug involve:

- The development of an adequate supply of the agent to permit preclinical and clinical development.

- Formulation studies to develop a suitable vehicle to solubilize the drug for administration to patients, generally by intravenous injection or infusion in the case of cancer.

- Pharmacological evaluation to determine the best route and schedule of administration to achieve optimal activity of the drug in animal models, the half-lives and bio-availability of the drug in blood and plasma, the rates of clearance and the routes of excretion, and the identity and rates of formation of possible metabolites.

- IND-directed [directed toward application to the appropriate regulatory agency (the Food and Drug Administration in the United States) for Investigational New Drug

status] toxicological studies to determine the type and degree of major toxicities in rodent and dog models. These studies help to establish the safe starting doses for administration to human patients in clinical trials.

Once an agent has been granted IND status, it then advances to the clinical development stage which involves the following process:

- Phase I studies conducted to determine the maximum tolerated dose (MTD) of a drug in humans, and to observe the sites and reversibility of any toxic effects. In contrast to trials with agents directed at other diseases, all patients in Phase I cancer trials have some form of the disease.

- Once the MTD has been determined and the clinicians are satisfied that no insurmountable problems exist with toxicities, the drug advances to Phase II clinical trials. Phase II trials generally are conducted to test the efficacy of the drug against a range of different cancer disease types.

- In those cancers where significant responses are observed, Phase III trials are conducted to compare the activity of the drug with that of the best chemo-therapeutic agents currently available for the treatment of those cancers. In addition, the new drug may be tried in combination with other effective agents to determine if the efficacy of the combined regimen exceeds that of the individual drugs used alone.

Development of Natural Product-Derived Drugs

The development of natural product-derived drugs poses significant challenges in several areas. Of prime concern is the supply of the drug in sufficient quantities to permit preclinical, and hopefully clinical, development, and ultimately, if given a successful, clinical outcome, commercial production. Another major challenge is that of formulation. Natural products generally are highly insoluble in aqueous media, and such solubility is a prime requirement for administration of the drug to human patients, particularly through the intravenous route commonly used in the treatment of cancer patients.

Development of Paclitaxel (Taxol®). Long-Term Commitment Yields a Successful Drug

Discovery and Preclinical Development

The development of the successful anticancer drug, paclitaxel (Taxol®; **1**)[2] provides an excellent example of how these challenges can be overcome, but not without considerable ingenuity, patience and persistence. The chronology for the discovery and preclinical development of taxol is given in Table 1. It should be noted that 15 years elapsed from the time of the initial collection of the source plant material, the bark of *Taxus brevifolia*, to the approval for preclinical development. Most of the testing in the early days of the NCI drug discovery program (1955-1982) was performed using *in vivo* models, mainly mouse leukemias, and a major reason for the considerable time lapse was the fact that the activity of taxol in these systems was in no way superior to that observed for many other potential drug leads. It was only when significant activity in the more resistant B16 mouse melanoma was

[2] Because this account is historical in nature, the name taxol is used subsequently in the text when referring to Taxol®. No infringement of the Bristol-Myers Squibb trademark is implied.

observed, that taxol was considered of special interest, and selected for preclinical development. The first stage in the process was testing against a panel of human solid tumor xenograft models, and strong activity against the MX-1 mammary and CX-1 colon models confirmed the initial promise. The crowning moment, however, was the seminal discovery by Horwitz et al. that taxol possessed a unique mechanism of action, whereby the polymerization of tubulin to form microtubules was promoted, and the resultant microtubules were stabilized, leading to inhibition of mitotic spindle formation (6). This was in direct contrast to other tubulin-interactive agents, such as vinblastine and vincristine, which inhibit mitosis by inhibition of the tubulin polymerization process.

The formulation of taxol in a suitable aqueous vehicle posed considerable challenges. Like most complex natural products, taxol is soluble in most organic solvents, but highly insoluble in water and aqueous-organic solvent mixtures. Extensive research led to the development of a formulation vehicle comprised of a 1:1 mixture of the emulsifying agent, Cremophor, and ethanol at a concentration of 6 mg/mL. For clinical purposes, 5 mL ampoules were stored at 2-8^{0}C and diluted with either 50 mL 0.9% NaCl which was stable for 3 hr, or with 1,000 mL 5% dextrose which was stable for 24 hr. As will be mentioned later, there were serious, initial clinical problems with these formulations. Toxicology studies in rodents and dogs showed reversible toxicities in high turnover cells (hematopoietic, lymphatic, gastrointestinal), and sensitivity of dogs to the Cremophor in

TABLE 1: CHRONOLOGY OF THE DISCOVERY AND PRECLINICAL DEVELOPMENT OF TAXOL®

- 1962: First collection of Taxus brevifolia by USDA botanists
- 1964: Confirmed KB activity
- 1965: Recollection of bark and assignment to Dr. Monroe Wall, RTI
- 1966: Confirmed in vivo activity – mainly mouse leukemia models
- 1969: Taxol first isolated in pure form (0.01% yield from bark)
- 1969: Survey of plant parts and abundance by USDA
- 1971: Isolation and structure first reported by Wall, Wani, et al.
- 1974: Good in vivo activity against B16 mouse melanoma
- 1975: B16 activity confirmed. Increased interest
- 1977: Accepted as a candidate for preclinical development Tumor panel testing started
- 1977: Strong activity observed against human solid tumors, the MX-1 mammary and CX-1 colon xenograft models
- 1978: Recognized as a mitotic spindle poison
- 1979: Unique mechanism of action determined.
- 1980: Formulation completed. Supplies adequate for toxicology studies
- 1982: Toxicology studies completed.
- 1982: Approved for INDA filing with FDA the formulation vehicle was observed. Application for IND status with the FDA was approved in 1982, 20 years after the first collection of the source plant material, and taxol was advanced into clinical trials in 1983.

Clinical Development

The chronology of the clinical development of taxol is given in Table 2. Problems were soon encountered in Phase I trials with severe allergic reactions, resulting in the death of some patients. This led to a dramatic drop in clinician interest, but the observation of some positive patient responses by one clinician led to the development of a slow intravenous infusion as opposed to original bolus injection, which, combined with pre-medication using steroids, overcame the allergic reactions. These reactions were determined to be caused by the large amounts of Cremophor present in the formulation vehicle, and the development of more water-soluble taxol analogs is an ongoing area of research. The toxicities observed in the Phase I trials, mainly leukopenia, neuropathy, alopecia, and nausea, were found to be reversible, and the drug was advanced to Phase II trials in 1985. The progression of the Phase II trials was restricted by the limited quantities of drug available, but the observation of significant activity against refractory ovarian cancer in 1989 highlighted the urgent need to develop more abundant and reliable sources of the drug.

The Supply Issue

The supply issue related to use of drug isolated from the bark of *Taxus brevifolia* is

TABLE 2: CHRONOLOGY OF THE CLINICAL DEVELOPMENT OF TAXOL®

- 1983: Phase I clinical trials begin.
- 1985: Phase II trials begin
- 1986-1989 - Trials limited by drug supply issues
- 1989: Activity observed against refractory ovarian cancer
- 1989: Bristol-Myers Squibb (BMS) selected as Cooperative Research and Development Agreement (CRADA) partner.
- 1989: Seven year exclusivity granted to BMS for investment in development
- 1991: Activity observed against metastatic breast cancer
- 1992: NDA approved by FDA for treatment of refractory ovarian cancer
- 1994: FDA approval for treatment of refractory breast cancer

illustrated by the following facts (7). The yields of pure drug isolated from the bark were generally about 1 gm per 14 Kg of dried bark, amounting to a yield of approximately 0.01% with a 73% recovery rate; this was equivalent to harvesting about 1.5 trees per 1 gm. Patient requirements of 500 mg/patient/course and 4 courses of treatment for ovarian cancer equated to 2 gm/patient, and with some 12,000 patients suffering from ovarian cancer, the annual requirements for treating this patient population alone were 24 Kg or 36,000 trees. While the sustainable harvest of bark is theoretically possible by avoiding stripping of the bark around the complete circumference of the trunk and not disturbing the life-preserving cambium layer (a difficult and tedious process requiring great care), in practice the bark was collected by felling the tree and completely stripping the bark, thereby destroying the tree. *Taxus* (yew) species are notoriously slow growing, and generally trees being harvested were 100 or more years old! The increased demand for the bark led to concerns about the continued viability of *T. brevifolia* populations in the western United States and Canada, and resulted in confrontations between environmental groups and patient advocacy groups which even reached the halls of the U. S. Congress.

Through grants and contracts, the NCI sponsored the performance of worldwide surveys and assessments of alternative *Taxus* species, including *T. baccata* (Europe/Caucasus/Himalayas), *T. canadensis* (eastern Canada), *T. cuspidata* (Japan), *T. globosa* (Mexico), and *T. yunnanensis* (China). In addition, alternative sources were considered, including: the cultivation of *T. brevifolia*, *T. baccata* and other species, varieties and cultivars, with the selective propagation of best producers; hydroponics, with selective breeding of the best producers, and optimization of the growth medium and the addition of precursors and elicitors; plant cell suspension culture, with the cloning of the most productive cell lines, the establishment of stable cell lines, and the optimization of growth conditions and use of elicitors (e.g., methyl jasmonate); cultivation of endophytes which have been shown to yield taxol in extremely low yields (8); genetic engineering, through identification of the key enzymes involved in rate limiting biosynthetic steps, isolation of the encoding genes, and overexpression of the genes in *Taxus* species or relevant endophyic fungi; semi-synthesis of taxol and analogs from more abundant natural precursors; and total synthesis.

The cultivation of *T. baccata*, in particular, has been a key factor in solving the supply problem (vide infra), while plant cell culture methodology recently has been optimized to yield multi-Kg quantities of the commercial drug (9).

A key breakthrough in solving the supply problem came with the pioneering development of a semi-synthetic conversion of the precursor, 10-deacetylbaccatin III (**2)**, to taxol by Potier et al. (10). This and other baccatins are isolated in good yields from *T. baccata*, and taxol and other taxane analogs, such as the clinically-active docetaxel (Taxotere®; **3**) (11), are now produced commercially by a variety of efficient semi-synthetic procedures.

Taxol: A Continuing Development Process

The development of taxol from the first collection of the source plant material to its approval for commercial use spanned some 30 years, and it would never have reached the global cancer population without the considerable commitment of funds and resources by the NCI. It has been estimated that the NCI, funded by the U. S. Congress and the U. S. taxpayers, invested over $400 million, and investment continues in the support of ongoing clinical trials.

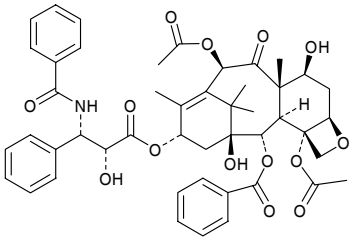
Paclitaxel (taxol) has proven to be efficacious in the treatment of breast, ovarian and non small cell lung cancers, as well as the AIDS-related malignancy, Kaposi's sarcoma. Docetaxel (taxotere) has a similar treatment profile to paclitaxel, but is easier to formulate and administer due to its greater aqueous solubility. Recently, it has also been found to be effective in the treatment of metastatic, hormone-refractory prostate cancer (12). In addition, 10 other taxanes are in Phase II or Phase I clinical trials, while 23 taxanes are in preclinical development. Taxol has also shown potential for the treatment of multiple sclerosis, psoriasis, and rheumatoid arthritis (http://www.phrma.org/newmedicines/newmedsdb/drugs.cfm).

For more detailed discussions of taxol and analogs the reader is referred to the reviews by Kingston (13), Cragg and Newman (14), and the book edited by Suffness (15).

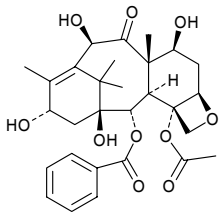
Halichondrin B. The Importance of Organic Synthesis

The first report of the isolation of halichondrin B (**4)**, together with other congeners from the Japanese sponge, *Halichondria okadai* was by Hirata and Uemura in 1986. This was

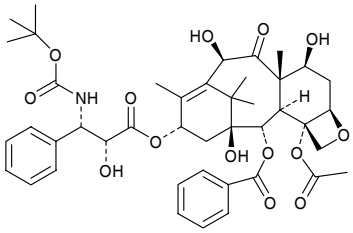
followed by a report by Pettit et al. in 1991 of the isolation of halichondrin B from the Palauan sponge, *Axinella* sp. Testing in the NCI 60 human cancer cell line screen and analysis of the data using the COMPARE program indicated that it was a tubulin binder (at the Vinca site) (16), and, in 1992, the NCI approved halichondrin B for preclinical development. In the same year, NCI grantee, Kishi, published the total synthesis, a multistep process with low overall yields (17).



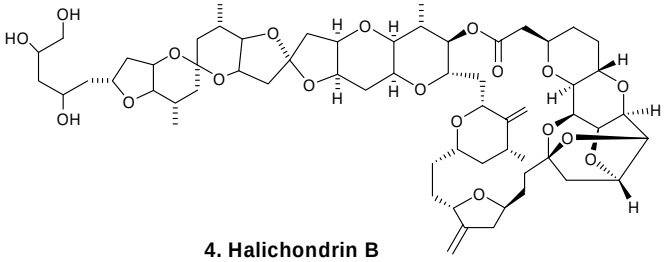
1. Taxol



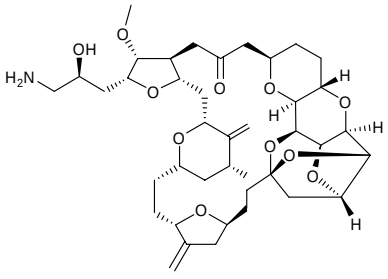
2. 10-deacetylbaccatin III



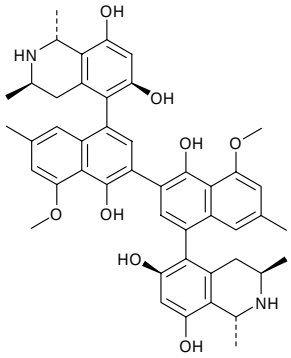
3. Taxotere



4. Halichondrin B



5. E7389



6. Michellamine B

Structures 1-6

Entry into preclinical development required the large-scale production of the compound. In April, 1992, NCI requested help from the natural products chemistry community in order to obtain large quantities of various natural product materials, including Halichondrin B. The New Zealand group of Blunt and Munro contacted the NCI reporting that they had discovered a family of halichondrin B analogs in a sponge, *Lissodendoryx* sp., collected from deep water off the Kaikoura Peninsula on the east coast of South Island. Over the next 5-6

years, the NCI worked closely with the New Zealand Halichondrin Joint Venture, led by Blunt and Munro from the University of Canterbury and Battershill from National Institute for Water and Atmospheric Research (NIWA), and, by 1998, 300 mg of Halichondrin B was available (18). The NCI provided close to US$300K in direct funding, with an estimated US$250K provided in kind by the New Zealand government.

Although the process seemed simple, it actually involved interlocking stages encompassing an environmental assessment of the sponge bed (at 200 m. depths and lower), bathyspheric investigations as to the actual source of the sponge, and low, medium and large-scale collections (10 kg to 1000 kg), with permits being issued by the NZ government, and permission granted by the local Iwi population. In addition, aquaculture experiments were performed over multiple seasons and under a variety of water conditions, temperatures, and times, leading to the successful aquaculture of the sponge in the Marlborough Sound between North and South Islands. The large-scale chemical isolation of the compound, and subsequent purification to >98% purity, proved challenging since no chromophore is present in the molecule to aid ready detection. Nevertheless, the process was considered as economically feasible.

Meanwhile, the total synthetic work performed by Kishi et al. had led to the synthesis of two macrocyclic ketones which were designed to simplify the parent structure of halichondrin B, and to overcome the lactone instability found with the single macrocyclic ring in the right half of the molecule. Eisai Research Institute, working with Kishi, performed *in vivo* testing using late stage tumors, and showed that one of these ketones, E7389 (**5)**, had superior activity compared to halichondrin B. Toxicological testing using myelosuppression assays showed slight differences between the two synthetic ketones, and the therapeutic indices observed were much better for the ketones than for halichondrin B.

Three options were now available for the development of a halichondrin B candidate for preclinical and clinical studies. Firstly, the collection or aquaculture of the source sponge could be undertaken to enable isolation of sufficient quantities of halichondrin B. Secondly, halichondrin B could be prepared by total synthesis, or thirdly, the development of the synthetic ketone analogs of the right hand portion of the halichondrin B molecule could be considered. Based on the results mentioned above, E7389 (**5**) was selected for development, and, in July, 2001, E7389 was approved for Phase I clinical trials under NCI aegis, Eisai provided 6 grams of cGMP product for the early trials, and in May, 2005, at the meeting of the American Society of Clinical Oncology (ASCO), the authors of abstract 3036 reported that Phase II trials are ongoing. The details of the discovery and development of E7389 are provided in a review by Yu, Kishi and Littlefield (19) which illustrates the power of organic total synthesis in optimizing an important drug discovery lead from natural sources.

Michellamine B. A Promising Lead but Problems with Toxicity

Michellamine B (**6**) was isolated as the main *in vitro* active anti-HIV agent from the leaves of the liana, *Ancistrocladus korupensis*, collected in the Korup region of southwest Cameroon through an NCI contract with Missouri Botanical Garden (MBG) (20). This new species (21) is found only in and around the Korup National Park, and vine densities are very low, on the order of one large vine per hectare. While fallen leaves do contain michellamine B, and their collection provided sufficient biomass for the isolation of enough drug to complete preclinical development, it was clear that extensive collections of fresh leaves could pose a possible threat to the limited and sparse wild population.

Thus far, no other *Ancistrocladus* species has been found to contain michellamine B, and investigation of the feasibility of cultivation of the plant as a reliable biomass source was initiated in 1993 through a contract with the Center for New Crops and Plant Products of Purdue University working in close collaboration with the University of Yaounde 1, the World Wide Fund for Nature Korup Project, MBG, Oregon State University and the NCI-Frederick contractor, Science Applications International Corporation (SAIC). An extensive botanical survey was undertaken, and the range and distribution of the species were mapped, and dried leaves were analyzed for michellamine B content. Promising plants were re-sampled for confirmatory analysis, and those showing repeated high concentrations were targeted for vegetative propagation. A medicinal plant nursery was established for the *A. korupensis* collection near Korup Park Headquarters in Mundemba, and through selection of promising plants from the wild and their subsequent propagation and growth in the nursery, it was demonstrated that michellamine B content well above the wild average could be produced routinely. In keeping with the NCI policies of collaboration with source countries, all the cultivation studies were performed in Cameroon, and involved the local population, particularly those in the Korup region where the plant was originally discovered.

Based on the observed activity and the efficient formulation of the diacetate salt, the NCI committed michellamine B to advanced preclinical development, but continuous infusion studies in dogs indicated that *in vivo* effective anti-HIV concentrations could only be achieved close to neurotoxic dose levels. Thus, despite *in vitro* activity against an impressive range of HIV-1 and HIV-2 strains, the difference between the toxic dose level and the anticipated level required for effective antiviral activity was small, and NCI decided to discontinue further studies aimed at clinical development. However, the discovery of novel antimalarial agents, the korupensamines, from the same species (22), adds further promise for this species.

Natural Product Drug Development and International Collaboration

The drug discovery and development cases discussed above clearly demonstrate that the preclinical and clinical development processes are costly and lengthy undertakings which require considerable international and multi-disciplinary collaboration. The discovery and development must be carried out with the prior informed consent and the necessary collection and export permits from the relevant Source Country Government and stakeholders, and working in close collaboration with Source Country Organizations. Appropriate agreements must be negotiated encompassing terms of training and technology transfer, protection of environment and sustainable development, and plans for benefit-sharing. In the case of the NCI, these agreements are based on the NCI Letter of Collection (LOC; http://ttb.nci.nih.gov/nploc.html) and Memorandum of Understanding (MOU; http://dtp.nci.nih.gov/branches/npb/agreements.html) (23).

The Need for Realistic Expectations

From 1960 to 1982, some 35,000 plant samples (representing about 12,000 to 13,000 species) were processed by the NCI to yield 114,000 extracts. Though a significant number of interesting active chemotypes were discovered, only two compounds advanced to the stage of development into commercial products. These were the taxol® (e. g., paclitaxel and it's analog, docetaxel) and camptothecin, which, though it proved to be too toxic in clinical trials to become a commercial drug, has yielded commercial analogs, such as topotecan

(Hycamptine®) and irinotecan (Camptosar®). One other product, homoharringtonine, remains in advanced clinical trials for treatment of refractory leukemias. Thus, 114,000 extracts derived from approximately 12,000 species only gave two compounds yielding products of commercial value. As noted above, further derivatives and analogs of taxol are being developed which may become commercial products, and the same applies to camptothecin.

The above observations are based only on screening for antitumor activity, and exposure of extracts and compounds to a greater number of assays representing a wider range of diseases would undoubtedly raise the level of success. The undeniable message, however, is that the chances of developing a commercially viable drug from drug lead discoveries from any source are extremely small, and source countries should not pin their hopes on deriving significant royalties from the sales of drugs derived from drug leads discovered from their natural resources.

Recommended Collaborative Process

Based on the NCI experience, a two phase approach to the exploration of source country genetic resources as a source of potential novel drugs and other bioactive agents is recommended.

Phase I of the process should involve negotiation of a Basic Research Agreement between the research organization (e.g., representing pharmaceutical, agrochemical or cosmetics/flavoring interests in "developed" countries) and the relevant Source Country government department or agency, or with a qualified source country organization (SCO) selected by the government to represent its interests. The involvement of a suitably qualified local organization, if available, should be an essential requirement, and the Basic Research Agreement should incorporate terms of collaboration covering exchange of data, training, and technology transfer as spelled out in DTP/DCTD/NCI role, terms 1-6, of the NCI Letter of Collection (see LOC; http://ttb.nci.nih.gov/nploc.html). In addition, there should be requirements for adequate protection of the environment and endangered species.

Obtaining the Prior Informed Consent of relevant local stakeholders (e. g., indigenous peoples, local communities, and healers, where appropriate) should be the responsibility of the local collaborating organization, or, if an SCO is not identified, the relevant Source Country government agency should assist in this process. Most importantly, the Basic Research Agreement should clearly require the negotiation of separate agreements (Phase II agreements) covering any agents which are selected for preclinical or equivalent advanced development.

Selection of an agent for advanced (e.g., preclinical) development will probably trigger submission of an application for patent coverage, but it is most important to note that issue of a patent is far removed from the possibility of commercialization. In fact, very few patented agents ever reach the stage of commercialization. Generally, from available data we estimate that less than four percent of patented pharmaceutical drug candidates actually become commercial drugs (24).

Selection of a drug lead candidate for preclinical or equivalent development should trigger negotiations of a new Phase II Commercial Development Agreement (CDA) covering the specific issues related to the development and possible commercialization of the candidate.

The CDA should address terms of collaboration in the large-scale procurement of supplies of raw material for production of sufficient quantities of the drug candidate for preclinical and possible clinical development in the case of pharmaceutical agents. Such terms should address environmental impact studies, the possibility of sustainable harvest, and the possible need for cultivation the source organism. Local scientists and communities should be involved in these processes, as far as possible. The CDA should also include terms of collaboration in the production of the development candidate (extraction, isolation, analysis, etc.) depending on the facilities and expertise existent in the source country, and training and technology transfer where appropriate, as well as training in the preclinical aspects of a drug candidate (e. g., formulation, pharmacology). In the above two points it must be noted that conditions of current Good Manufacturing Practice (cGMP) (e. g., approved facilities) have to be met to satisfy the requirements of the US Food and Drug Administration (FDA) and equivalent regulatory bodies in other countries. These are extremely expensive conditions to fulfill, and generally these processes will be best performed by the collaborating research organization.

Finally, terms should be included covering milestone payments when certain stages of development are achieved (e. g., FDA approval for entry into Phase I clinical trials, completion of Phase I trials, etc.), and payment of a percentage royalties on the sales of the drug, should it become commercialized. An attractive alternative to royalties that may be considered by a source country may be the provision of supplies of the drug free of charge for treatment of the local population, and/or provision of other drugs (e.g., antimalarial, anti-HIV) more useful to the source country, or the granting of a royalty free license for production of the drug for use in the source country only.

Given the very low success rate in actually developing a product through to commercial use, it is strongly recommended that agreements should focus on short term benefits such as training, technology transfer and milestone payments, rather than attempting to maximize royalty payments which in all likelihood will never materialize! There are decided advantages to maximizing short term benefits in terms of improving the capacity of source country organizations and personnel to perform the drug discovery and early development steps in-country, thereby optimizing the value of their resources. In addition, discovery of promising drug leads entirely in-country creates the opportunity for source country organizations to gain complete control of their inventions through application for appropriate sole source country inventorship patent coverage (composition of matter patents in the case of novel chemical entities, or use patents in the case of novel uses for known chemical entities).

Regional Collaborative Networks – Coordination of Regional Strengths

Even with large organizations such as the NCI, experience has clearly demonstrated that the development of effective new drugs depends on multi-institutional and international collaboration. The developments of taxol and the halichondrin analog discussed above are clear examples of the need for such collaboration. Source countries rich in genetic resources (plant, marine, microbial) can optimize the opportunities for effective use of their resources through establishing regional collaborative networks in which the skills and capacities/facilities of different countries in the region are shared, rather than each country trying to develop it's own multiplicity of capabilities. Thus, different assays (e.g., antimalarial, anti-HIV, anti-TB, antitumor, etc.) and different instrumentation facilities (e. g., NMR, MS, HPLC-MS, etc.) can be established in different countries selected by mutual

agreement between countries in the region. Research organizations in different countries can submit extracts to their collaborating partner organizations in other countries for testing in a variety of assays, with results returned on a confidential basis, and active compounds isolated by source country organizations can be submitted to partner organizations for spectroscopic and spectrometric examination to aid in structural elucidation.

The establishment of a close collaborative regional network requires a high level of mutual trust and commitment to true partnership, as well as the negotiation of regional agreements ensuring appropriate confidentiality of results and the fair sharing of benefits, including coauthorship on papers and coinventorship of involved parties on patent applications for promising discoveries. The NCI and NIH have promoted multi-institutional and international research collaboration through their National Cooperative Drug Discovery Group (NCDDG) (25) and International Cooperative Biodiversity Group (ICBG) (26) programs which have been very effective in advancing drug discovery and development, and in many cases, involving beneficial collaborations with source country organizations.

In the case of sub-Saharan Africa, an organization such as NAPRECA has the attributes for successfully establishing an effective collaborative regional network incorporating already existent strengths, and applying for international support for the establishment of centers of excellence in various screening and structural elucidation technologies, as well as for strengthening the natural products chemistry capacity (isolation and synthesis) of selected organizations in all member countries. It is only through the demonstration of the will to establish such regional collaboration that progress will be made in obtaining the support necessary for optimizing the use and sustainable development of the regions undoubtedly rich natural resources.

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