environmental microbiology

Environmental Microbiology (2014) 16(1), 9–18 doi:10.1111/1462-2920.12337

Opinion

Pipelines for New Chemicals: a strategy to create new value chains and stimulate innovation-based economic revival in Southern European countries

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Summary

Countries of Southern Europe are currently suffering from severe socio-economic pain resulting from high debt levels and austerity measures which constrain investment in innovation-based recovery strategies that are essential for entry into a long-term sustainable period of increasing employment and wealth creation. Young university-educated people are particularly innovative, and hence vital to the development of such strategies, but employment opportunities are poor and many are forced to seek employment that neither profits from their training nor satisfies their justified career expectations, or to emigrate. They are the 'lost generation'. A strategy is proposed here for the creation of *Pipelines for New Chemicals*, national centre-network partnerships for the discovery-synthesis of new chemicals obtained though harvesting new biological diversity, and their exploitation to develop new medicines, agrochemicals, materials, and other products and applications. The goal is to create new regional motors of economic growth and development, by harnessing the knowledge, motivation and innovation potential of the excellently educated young people of Europe to catalyse the development of new small, medium and large enterprises centred around novel chemicals, and the value chains that will evolve with them, and thereby develop a powerful sector of sustainable growth in employment and social and economic prosperity in Southern Europe.

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The problems

The global economy, that of Europe, and in particular that of Southern Europe, is facing serious long-term problems of degradation of prosperity and social well-being. Unsustainable debt and intolerably high levels of unemployment, especially among the young, constitute a chronic sociopolitical disaster. Given the lower labour costs of developing economies, and the globalization of current technologies and manufacturing processes, the exit of Southern Europe from the current crisis, and minimization of crisis repeats, requires imaginative, selective, substantial and sustained investment in those inherent human capital strengths that can give countries of Southern Europe an edge in the competitive market of today and tomorrow, namely innovation, innovators and the entrepreneurs that take innovations to market. Fundamental research in academic centres is a major source of new discoveries and a key driver of innovation. Austerity measures in debt-laden European countries, especially Spain, Portugal, Italy and Greece, are however obliging the best educated and trained young innovators of tomorrow to emigrate to economically healthier countries, thus frustrating the societal purpose of substantial economic investment in their education. A major political goal of Europe must therefore be to create a more optimal environment in such countries for the innovation-based pathway of academic discovery, to transfer of new know-how and intellectual property (IP) to spin-offs and small and medium enterprises (SMEs), and thence to the healthy growth of spin-offs into SMEs, and SMEs into major enterprises, and thereby to retain and effectively exploit the rich intellectual talent of the young in rebuilding the economy. This will ultimately establish a solid foundation for higher employment, economic recovery and prosperity, and will sustainably change and enrich the business and economic landscape. It will also help reduce the developmental and economic divide between countries of Southern and Northern Europe.

In addition to general concerns about economic competitivity, unemployment and the degradation of prosperity, the effective treatment of life-threatening and quality of life-compromising diseases, the feeding of a growing world population, increasing the quality and safety of water and food supplies, reducing environmental pollution, reducing dependence on fossil fuels, are *inter alia* all imperatives currently of great concern to society, constitute some of the 'grand challenges' and are high priorities on the political agenda. BUT: these are also issues of innovation, as advances necessitate new discoveries, technologies and commercial products. It is therefore self-evident that investments to exit from our current economic and social crisis, to lay the foundation for sustainable growth and increased employment and prosperity, and to mitigate some of the major problems facing society today, must include new strategic measures to accelerate development of a more innovation-based economy. Here, a proposal is presented that could constitute one of a number of central pieces in the landscape of priority measures currently needed.

Biochemicals can contribute to solutions

One major area of endeavour that is almost unique in being both highly innovative, and able to make major contributions to the solution of a wide range of very different problems, is chemistry: new chemicals mean new medicines, new products for plant protection, new fuels, new materials for diverse needs including the rapidly evolving digital world, new products to make food production safer and more efficient, improved nutrition, new personal care products, new environmentally friendlier products and so on. Chemists have been making chemicals for about a century, and have developed a diverse structural range of compounds having disparate properties and applications. Practically everything we use in the home and workplace either contains or is packaged in products of the chemical industry, or has been manufactured using chemicals. Much of what we eat every day is the result of food production-processing-distribution chains whose efficiency and quality is vitally dependent on the application of chemical-biochemical products. The colours our eyes feast on all day are mostly the result of chemical dyes. The chemical industry in its various forms is one of the economically most significant in current society with an exceptional range of products and markets. Its pervasiveness and importance in the evolution of modern society, and our future development is, to use an overused and trivialized term, awesome!

Much of traditional chemistry, however, is based on petrochemicals, and is thus biased in terms of limited feedstock structures, is heavily dependent on non-renewable feedstocks, and generates some products that are poorly biodegradable and environmentally unfriendly. That said, it must be emphasized that in recent years it has made enormous progress in diversifying its feedstocks, embracing renewable sources of feedstocks, and becoming more environmentally friendly. However, in contrast to the 100 years of chemical factories, *microbial cell factories* – biological systems consisting of cells and organisms – have been making *bio*chemicals for the 4 billion years life has existed on Earth, and in this time have evolved a much wider spectrum of chemical structure diversity that has enormous, as yet largely untapped potential for an exceptionally diverse spectrum of applications. Such chemicals are generally biodegradable, environmentally friendly and most are non-toxic, as they are produced by cellular systems, and many can be produced from renewable resources. The fact that they are natural also endows them with greater public acceptability. Moreover, many biochemicals are 'bioactive': they influence biological processes (e.g. they may have antibiotic activity) and hence have become the basis of many products developed to treat disease in humans, animals or plants. 'Bioactives' have also evolved over billions of years and optimized such activities, and hence have developed optimal molecular 'shapes' for their cellular interactions. As a result, some 40% of all drugs in use in clinical medicine are based on natural products, and this is predicted to rise as the search for new chemical classes of drugs continues.

Despite this, natural products have been relatively neglected because their very characteristics which make them so attractive, namely the diversity and complexity of their chemical structures, means that they are less familiar to the chemist, and hence less easy to synthesize than the generally simpler classical industrial chemicals. Nevertheless, synthetic chemistry has advanced rapidly in recent years so that the structures of natural products can now be deconstructed and reconstructed by the synthetic chemist. Another reason for the neglect is that natural product discovery requires biologists versed in the skills of accessing and characterizing biological diversity, and hence effective cooperation between biologists and chemists, which has not always been straightforward. A further reason has been the wide spectrum of skills needed to prospect biodiversity for new chemicals with new applications – the screening, and the cost of assembling effectively integrated collaborative structures and networks for this purpose. However, the rewards of such cooperations are enormous, namely the discovery of entirely new chemicals with novel applications.

Thus: investment in efforts to discover new chemicals, especially those based on natural products or created using biological systems, and especially compounds with biological activities, will be a particularly effective long-term investment in innovation, with major consequences both for employment, the economy and European competitivity, and for a wide range of current societal problems and commercial opportunities.

New chemicals are desperately needed

Whereas innovation and novelty of products often lead to creation of new markets, so the generation of new business opportunities depends significantly upon discovery and innovation, there are also major immediate needs for new chemicals for existing markets. The sector of drugs/bioactives for treatment of humans, animals and plants is an example of this, where the growing problem of resistance to existing chemicals is inexorably eroding their efficacy. Bacterial resistance to antibiotics, parasite resistance to antimalarial drugs, resistance to anti-cancer drugs, are examples of major problems in clinical treatment of human disease that urgently require the discovery and development of new drugs. However, the supply of new drug candidates in the pipelines of established chemical industries is rather sparse and largely focused on 'blockbusters'. Moreover, commercial priorities do not always perfectly match medical priorities. Drugs desperately needed in medicine that are not strategically important for industry can at present only be sought by drug discovery-early development programmes in academic research institutions and public : private partnerships. There is at present, however, far too little investment in drug discovery research in public institutions to adequately respond to urgent needs.

Southern European countries have a wealth of untapped potential for harnessing biodiversity for the discovery and production of new chemicals

Is the human capital required to lay the foundation for the birth of new Roches/BASFs/Sanofis/etc. in Southern Europe available? It is a truism that best performance is given by individuals under modest stress. Among the universities and research institutes of Southern Europe are some of the best in the world and are home to some of the most talented scholars. They have historically, however, been modestly funded (= stressed) and had to work at maximum efficiencies to advance knowledge and compete with more generously-funded centres. Students graduating from these institutions are generally exceptionally motivated and high achievers, when offered opportunities, as amply testified by many happy principal investigators from Northern European countries. Thus: a key requirement – enthusiastic, dynamic, well-trained young scientists in abundance is satisfied. Secondly, expertise in biodiversity – microbial, animal, plant – and access to poorly explored biodiversity are also strengths, not least because of some fascinating environments present in Southern European countries, and because of their colonial pasts and close scientific and cultural links with countries of Central and South America, Africa and Asia. Moreover, this high level of expertise relates to different types of biodiversity in the different countries, thus providing, on one hand, collective expertise in a wide range of biodiversity and, on the other hand, the basis for different trajectories of specialization in distinct classes of chemicals and applications. Thirdly, the discovery of bioactives requires cell and developmental biologists who can provide expertise to detect and characterize biological activities of new chemicals, and all countries have vibrant communities of such people. And finally, all countries have multiple culture collections and impressive expertise in the classification, management and archiving of biodiversity. Other necessary skills, such as basic microbiology, (meta)genomics, fermentation, compound purification, structure analysis, synthetic chemistry, etc., are more generic and hence widely available.

Thus: collectively, there is all the expertise needed to create successful chemical discovery programmes, though at present it is largely directed towards unconnected, divergent goals, and hence rather fragmented. Most importantly, the research of cell and developmental biologists is almost never directed towards screen development and bioactives discovery. However, with relatively modest extra funding, these unconnected groups could be induced to combine to develop and make available new or better screens, *without being substantively diverted from their primary research* *interests, and hence without significant changes in existing national strategic programmes of research*. There is thus a unique wealth of talent in Southern Europe for the discovery of new chemicals, but it currently is largely untapped and cries out to be harnessed for the common good.

An initiative to provide solutions: harnessing European strengths for new chemical discovery and development through creation of integrated core centres and networks to form *Pipelines for New Chemicals*

We propose here a concept to harness available research talent for the purpose of discovering and synthesizing new chemicals, of channelling them into new or better applications, and of developing associated value chains.

The funnel-pipeline concept

The concept is that of a funnel and pipeline. The *funnel* consists of activities to collect and characterize biodiversity – particularly microbial diversity – from disparate sources, to obtain extracts from the organisms/samples, and to screen the extracts for new chemicals, especially desired activities and characteristics influencing a wide range of biological processes. Positive reactions – 'hits' – identify the sources of these activities, which then enter the *pipeline*. The pipeline consists of a sequence of technology platforms to characterize the compounds responsible for these 'hits' and involves compound isolation, chemical structure elucidation and, for new chemicals, detailed biological activity characterization and evaluation for applications. Chemical variants of interesting compounds are generated by chemical and biochemical modification, and their qualities compared with those of the parent chemical. New chemicals, and known chemicals with newly discovered activities, and their variants, are patented, as are their cellular targets, and preliminary safety assessment is made. Promising compounds are transferred to interested industries and start-ups for development and commercialization.

The Core Centre-National Network Partnership organizational structure

The systematic and effective accessing of biodiversity, and the screening of biodiversity samples for a wide range of activities and applications, requires a wide and diverse range of biological expertise and facilities that are impossible to assemble in a single centre, vary over time as new discoveries are made and new opportunities arise, and are difficult to effectively integrate and harness to work together. Without this, however, a major part of diversity available is not accessed and, more important, a large part of the spectrum of possible activities present in the accessed biodiversity is not detected, because relevant screening is not carried out. To recruit and coordinate the enormous existing potential in Southern Europe, and to channel it for new chemicals discovery, it is proposed to create in each country a *National Network* of the most competent biodiversity groups to access new biodiversity, and cell/developmental biology groups to devise new or better screens and build comprehensive national screening networks. These networks of decentralized groups form the funnels of the discovery pipelines. The technology platforms for chemical characterization would largely, though not exclusively, be established in national *Core Centres*, that would also act as both cooperation catalyst, coordinator and funder of the disparate work loads in the network needed for an effective discovery pipeline. The *Core Centres* would also create in-house *Technology Transfer Units* or effective alliances with external Technology Transfer operations, which would regularly evaluate IP, secure patents, seek appropriate industrial partnerships, and manage industrial cooperations and licensing agreements. In the *Core Centre-Network Partnership*, the *Core Centre* would be a constant (though dynamically developing) element of the partnership, whereas the individual laboratories of the *Network* would vary over time, according to the needs and priorities of the coordinating *Core Centre*. The inducements for *Network* partners to participate in the programme in a highly effective and integrated fashion will be: (i) the attraction of working with other top researchers in a high-priority national programme, (ii) additional funding from the *Core Centre* for the specific work they would do for the pipeline, and (iii) the possibility to obtain from the programme new tools, reagents (including bioactives functioning on their own biological study system), expertise and platform services that would be extremely beneficial for their own research.

The Commercial Context: Industrial Partnerships, rapid product transfer to market, and promotion of relevant economic policies

Nothing generates as much cross-disciplinary and long-lasting enthusiasm as the development of products and processes that serve societal needs. Seeking solutions to societal needs will thus be a major guiding principle of the *Pipelines*, and a major motivating factor for its members. Thus, for each *Pipeline*, an experienced and dedicated *Business Development Network* must be assembled that continually seeks to identify new consumer needs and markets, on one hand, and new discovery/development potentials of the pipeline with potential to satisfy such needs, on the other hand. This Network will consist of the *Pipeline Technology Transfer Unit* and a group of experts from diverse interested businesses. Each of the *Pipeline:Network* scientists will be encouraged to interact directly with the *Business Development Network*, in order to identify opportunities for new applications, and therefore be motivated by both the opportunity to make new discoveries and to create new value chains that contribute to the national economy. This will also create a new generation of more 'business savvy' young scientists, better equipped to go independent and create start-ups.

Once promising new chemicals are identified, prompt IP protection and commercial evaluation is critical to exploitation. This requires industrial know-how and commercial expertise, so effective industry partnerships built on mutual trust and respect will be vital. Southern Europe, while presently lacking 'big pharma' and 'big chemistry', has vibrant energy and petrochemical industries, in addition to having many thriving smaller businesses in chemicals-relevant activities, so the required business expertise and partnership potential needed for project support, product assessment and product commercialization, is available. Industrial expertise is also vital for the creation and success of spin-offs, and ultimately for their development into profitable independent companies or take-over candidates. Crucially, established industries play a key role in job creation, because they both hire people with specialized training directly from spin-offs, and stabilize those in companies they take over. And, last but not least, industry support will be crucial for obtaining political support for the *Pipelines for New Chemicals* concept and the vital funding decisions necessary to its implementation and successful development. But clearly a healthy balance is needed between industry-focused projects determined on the basis of current markets and short and medium-term strategic plans, one hand, and the overarching goal of discovery of new chemicals with highly diverse applications leading to a long term innovation pathway, on the other.

Scope and budget (see Annex for details)

It must be explicitly stated at the outset that the funding of the Pipelines for New Chemicals should under no circumstances come from existing highly stretched national research budgets, as this would reduce effectiveness of the national research efforts in general, and work and infrastructure necessary for the Pipelines for New Chemicals in particular. Rather, funding for Pipelines for New Chemicals, which are to serve as part of the national and European strategy to strengthen economic development, sustainably increase employment, and improve infrastructure, must be financed from budgets earmarked for economic development, and not through a re-direction of existing education-research funds.

It is proposed that the Core Centre-Network Partnerships be supported from public funds to the extent of ca. €120 million in total, spread over 10 years, after which they should become self-financing. *It is vital that they develop a research and development environment characterized by excellence and success in obtaining external funding*. The *Core Centres* would have in-house research facilities for 300 persons (100 core staff, 50–100 externally funded graduate students and 50–100 bachelor and master project students), and coordinate and fund bioprospecting and screening operations in a structured network of 50+ de-central academic laboratories. A €60 million contribution each from the national governments and the European Commission would seem a reasonable sharing of the costs of these new initiatives to stimulate innovation-based economic revival in Southern Europe. Further financing should come from the private sector, both in terms of 'no strings attached' support, to strengthen regional innovation, increase capacity in cutting edge skills and know-how, reduce the brain drain, and gain time-privileged access to new findings of strategic relevance before publication, and in terms of targeted investment through support and steering of specific projects to acquire IP of strategic importance, protected by appropriate confidentiality arrangements.

The issue of serendipity

Many important discoveries are serendipitous: they are neither anticipated nor explicitly sought. They often happen when two or more different trajectories of knowledge acquisition that ordinarily do not relate to one another approach a common knowledge deficit where they can both contribute in a unique manner to the solution of an existing problem. Of course, the breakthrough requires some bright and receptive individual(s) able to make contact with both strands, to have the insight to recognize the opportunity and to take the action needed to realize the potential discovery. By its very nature, serendipity cannot be scheduled or orchestrated. However, it can be favoured by bringing together enthusiastic communicative young people expert in different branches of knowledge that ordinarily would never meet professionally. The network proposed here, and the regular contacts of the network partners necessary for its functioning, will achieve just this, and thereby encourage serendipitous developments and discoveries.

Benefits of Pipelines for New Chemicals

Young people are our future: they are capable of the high levels of energy, enthusiasm, motivation, dynamism, creativity, inspiration and innovation needed for successes in a competitive climate and environment. The best will become national leaders in academia, industry and politics. But in many parts of the world, and Southern Europe in particular, their potential cannot presently be realized because austerity measures severely limit employment opportunities in occupations appropriate to their qualifications, and hence their creative and professional development. Measures are urgently needed to create expanding and sustainable high-tech, socially needed commercial activities that allow the innovation potential of the young to be realized, to flourish and to be harnessed. The proposed creation of *Pipelines for New Chemicals* should catalyze the development of a stable and sustainable chemical-based and innovation-led economy in Southern Europe, regional motors of growth powered by the young, which in turn should provide a favourable attractor environment for the further establishment of new high-tech industries, as was the case for information technology in Silicon Valley. The resulting significant strengthening of the innovation base and competitive edge of countries of Southern Europe would clearly have substantive long-term economic and social benefits for all of Europe.

It is also evident that *Pipelines for New Chemicals* will have additional benefits that include

i. Stimulation of the national research efforts.
ii. Underpinning of the national research effort, by providing new resources: libraries of new bioactives, metabolites, enzymes, materials, etc., for prospecting and use in basic and applied research; access to *Pipelines for New Chemicals* platforms, latest technology and expertise.
iii. Marked increase in networking, new intellectual exchanges and partnerships for new research projects and grant applications.
iv. New courses and training schemes in natural product-related topics and methods.
v. Creation of a powerful skilled workforce with cutting edge skills and know-how in natural product discovery, production, chemistry and biological activity characterization.

Concluding remarks

We present here a concept for harnessing disparate activities of research excellence in Southern Europe to create powerful synergistic structures that will forge partnerships and alliances with industry to discover new chemicals and apply them to new or better applications, and create new value chains. This will involve recruiting and effectively utilizing the creative talents and enthusiasm of the best young scientists of the region to build *Pipelines for New Chemicals* that will both fulfil a central political justification for national investment in university education and research training, and solve societal needs in a range of sectors, including health care, agriculture, food supply, energy and environment protection. The goal of the concept is to contribute to measures to stimulate sustainable innovation-led economic growth in Southern Europe, and to minimize the loss of its talented young scientists, by creating a pathway and favourable environment for the birth of new industries created and populated by the best of such scientists. Our wish is that this Opinion stimulates discussion of its ideas and merits among regional, national and European policy makers, representatives of industry, economists and influential scientists, and triggers the creation of chemical discovery pipeline structures.

Although we have focused on Southern Europe, it is clear that the concept could be applied to other countries that have historically invested heavily in tertiaryeducation, established a strong research base, and have a vibrant industrial base that would be a fertile environment for the growth of new chemical industries.

Acknowledgements

We greatly appreciate the support and helpful input of Felipe Cabello.

Dedication

Kenneth Timmis dedicates his contribution to this Opinion to (i) the memory of Ivano Bertini, the larger-than-life florentine chemist par excellence and friend who was both an inspiring innovator, networker and entrepreneur, and an enthusiastic catalyst for collaborative research at the interface of biology and chemistry, and (2) the succession of highly personable and motivated talented young scholars from Southern Europe and Latin America who passed through his laboratory, establishing in the process new benchmarks for quality and originality, forming creative and supportive collaborative networks, and demonstrating to all and sundry the pleasures of discovery.

Annex

[NB: while there are different sources of new chemicals, natural products retrieved from new biodiversity are some of the most promising, so this concept emphasizes natural product discovery. However, other sources, such as variants of known chemicals obtained by biocatalysis, using existing or newly discovered enzymes and whole cell catalysts (which may also be retrieved from new biodiversity), or by chemical methods, are also important and readily incorporated into the basic concept, according to national priorities and available expertise.]

The network-funnel for discovery and development of new chemicals

Accessing new natural products

The principal, though not exclusive, sources of natural products of the *Pipelines for New Chemicals* will be microbes. The reasons are that: (i) microbes have the greatest metabolic and evolutionary diversity of all forms of life and hence the greatest diversity of metabolites produced by cellular systems; (ii) the microbial world is a known rich source of new natural products and has provided, for example, many powerful antibiotics and other therapeutics in clinical use; (iii) most microbial diversity is currently unknown and is waiting to be discovered; and (iv) microbial diversity research is currently enjoying a renaissance, driven by important technical advances in genomics, culturing, culture-independent physiological methods. The increasing appreciation that microbial activities control or have a pervasive influence on biosphere functions, including human/animal and plant health and nutrition, pollutant mitigation and environmental health, and global processes, like the production and consumption of greenhouse gases, to mention just a few examples, has also brought microbes squarely into the spotlight. Microbes, being simple biological entities, are also amenable to systems and synthetic biology approaches to delineate relevant metabolic routes, regulatory controls and bottlenecks for the purposes of optimizing yields of interesting products.

Microbial diversity will be harvested from environmental samples through three procedures:

i. The isolation and cultivation of individual strains and microbial communities, and
ii. the creation of metagenomic libraries, which contain all of the genomic resources of the sample archived in a laboratory bacterium, such as *Escherichia coli* and *Pseudomonas putida*.
   The isolates, communities and individual clones of the metagenomic libraries will be cultivated in small scale, and natural products released from the organisms will be harvested, concentrated and used to produce extract libraries for screening (ng-μg quantities).
iii. Furthermore, the genomes of novel species, and species with unusual physiology and/or metabolic characteristics, will be sequenced and the genome sequences inspected for the genetic determinants of natural products. Those that are not recovered from the isolate themselves – so-called orphan metabolites – will then be subjected to expression from a controllable expression system, and isolated in the same way as the from new isolates.

As indicated already, although emphasis will be on microbial diversity and microbial natural products, the pipeline can and would be used for natural product discovery from essentially any biological source, and would be available to the entire national community for this purpose.

Screens

The *Pipelines for New Chemicals* networks would differ from industrial chemical discovery programmes, whose screens are directed at products for markets in which companies have a current commercial interest (or have a strategic plan to enter), and hence are highly focused, and from current publically funded research programmes, which are generally principal investigator-driven and thus reflect the expertise and interest of a few leading scientists. The *Pipelines for New Chemicals* would harness the diverse spectrum of scientific expertise within countries to develop an individual palette of screens that would both be characteristic of each country and reflect its spectrum of expertise. This in turn will favour divergence in product and market interests between countries and the development of different commercial trajectories (though overlaps in activities, and thus healthy competition, will always exist to some extent).

A battery of diverse screens, from whole organism responses to individual cellular and molecular reactions, exploiting the latest expertise of the national research communities, would be established. To the extent that the screens should not be for everything in all countries, some degree of focus would need to be imposed that reflects national strengths and interests, and to some extent potential synergies with existing industries (though a programme established with the goal of creating new industries should not be tightly coupled to existing traditional industries), for example screens for activities relevant to agriculture, to aquaculture, to human health, to human and animal nutrition, to personal care products, etc., or for natural products that can serve as the basis of new materials.

In parallel to the screens for biochemicals exhibiting new activities or properties, screens for new enzymes with desired catalytic activities would be set up. Libraries of cell factories expressing novel catalytic activities, as well as isolated enzymes, would be created as sources of unique biotransformation reagents for creating specific chemicals and combinatorial libraries of chemicals centred on specific core structures and scaffolds.

Where the possibility of recruiting a specific screen necessary to complete a strategic programme does not exist, it would be established in the Core Centre, as would any necessary scale-up of a screen that could not be accomplished in a network laboratory.

New activities – new targets

The exploitation of bioactive compounds, such as those leading to clinical drugs and agrobiocides, involves two elements: the bioactive compound itself, and the cellular process it inhibits (or stimulates) – its target. At present, compared with the number of known biochemical reactions, and hence potential targets of bioactives, only relatively few targets are known and used in applications. The discovery of new targets will substantially increase the number of new applications, so the hunt for new targets is a critical component of bioactives research. New targets also provide opportunity for patent protection of an important IP component of a bioactivity pipeline, and thus added value.

The identification of new bioactives is important not only because they open up new opportunities and serve as the focal point for the development of related compounds that are often better, but also because they often have new targets which can then be identified and characterized. This, in turn, enables the specific screening for new bioactives against the new target, which may also be better than the original bioactive.

There are, however, other means of identification of new targets of bioactives. One highly promising one is the new approach of 'interactomics', which reveals new protein interaction partnerships in cellular processes which may serve as targets of compounds that act on such processes. These interaction partnerships are validated by mutational analyses, and genomic : bioinformatic analyses of these across species reveal how universal such interactions are and hence how useful the new targets may be. Whereas new target identification by means of a new bioactive is an empirical procedure – it can identify any cellular process – interactomics is a more directed approach, as new targets are normally by definition within the cellular process selected for study.

The pipeline-core centre

Identification of bioactive molecules in extracts giving hits in screens

Microbial strains whose extracts have given positive readouts in a screen – hits – will be cultivated in larger scale, extracts prepared and the mixtures fractionated into their individual components. Active components will be checked for purity, further purified if necessary, analysed spectroscopically, and their spectra compared with spectra in databases to determine whether or not the compound purified (μg-mg quantities) is known or so far unknown. If unknown, the structure of the compound will be elucidated by nuclear magnetic resonance spectroscopy. Though the most interesting natural products are those exhibiting new chemicals structures, those with known structures having new activities are also interesting, as they may have new applications.

Larger-scale production

New compounds need to be characterized in detail, biologically, chemically, physically and, for those showing application promise, toxicologically and environmentally. This requires the isolation of substantial amounts of the natural product in high purity, generally in milligram/gram quantities. If an industrial partner is already involved at this stage, it will generally also require pure material, often in larger quantities (10–100 g). This requires larger-scale fermentation, with appropriate facilities and attendant expertise, and downstream processing to isolate the compound. Sometimes, however, yields are too low and strain and cultivation optimization are necessary prior to larger-scale fermentation. This can involve random mutation, followed by screening higher yielding mutants, and variation of cultivation parameters to identify optimal culture conditions.

Characterization of new compounds and known compounds with new activities

New compounds in high purity are characterized in terms of their type of gross activity (lethality, inhibition, stimulation of growth, etc.), cellular target and mode of action, the range of affected cells/organs/species and selectivity of action (e.g. the range of plants inhibited by a herbicide), specific affinity for target, target differences in non-affected cells/organisms, frequency of mutation to resistance/tolerance, and physico-chemical properties, location and nature of double bonds, chiral centers, solubility and so on.

Generation of structural variants

The most promising candidates will be structurally 'tuned' to optimize activity and characteristics (e.g. hydrophobicity). There are various procedures for this, including chemical modification or replacement of specific moieties, but the most straightforward is to chemically synthesize the compound and derive variants during the synthesis. Combinatorial chemistry may be employed in some instances to create libraries of variants. In some cases, variants and combinatorial libraries will be created by biocatalysis, using enzymes and whole cell biocatalysts also obtained through the pipeline. These will constitute 'non-natural' natural products. The creation of new structural variants of known chemicals will also, where appropriate, be conducted.

Non-bioactive natural products

In addition to bioactives, natural products embrace small molecules whose applications do not involve thus far detectable biological activities, i.e. interference with a biological process, but rather other useful properties. Compatible solutes, for example, provide protection against osmotic stress and desiccation, and stabilize macromolecules, so find applications in personal care products that protect the skin from dryness, in stabilization of enzymes in biocatalytic processes to produce chemicals, etc. Amino acids and vitamins have applications in human and domestic animal nutrition. Organic acids modify intestinal physiology, increase resistance of fish to intestinal pathogens and hence have applications in aquaculture. Natural products also include large molecule biopolymers, such as enzymes which are used in biocatalytic processes, and carbon storage products like polyhydroxyalkanoates, which are being developed as biodegradable bioplastics to replace environmentally problematic petrochemical-based plastics. Other biopolymers are being developed as new materials and additives for a range of products. Microbially-generated nanoparticles and materials constitute another important sector with diverse applications. While the main emphasis of *Pipelines for New Chemicals* will be bioactives, they will be able to accommodate both small and large molecule natural products and hence deal with all types of natural and engineered products having potential applications.

Metabolic engineering

For the most promising products, a more detailed analysis of their biological properties will be undertaken, as will a genomics-based analysis of their biosynthetic routes, regulation and integration in cellular networks. Bioinformatic analyses and modelling, followed by experimental testing of model predictions, will be carried out as a prelude to biochemical engineering of the producer strain to channel carbon into the products and thereby obtain substantive increases in product yield, and/or production through different routes and from different starting points. Systems and synthetic biological approaches may be employed to understand metabolic routes and optimize yields of products of significant commercial value.

Patent protection of IP, commercial assessment and commercialization

In order to maximize the value and commercial utility of new natural products, new enzymes, new screens, new targets, new variants, new processes and new applications, as well as new technical developments that are made in the course of developing and exploiting the pipeline, their patentability will be assessed at regular intervals and patent protection sought as early as possible. Ideally, some discoveries will be supported by industry from the outset and taken over at an early stage for commercial development. In other instances, industrial interest will need to be attracted by evidence of commercial value, so preliminary commercial assessment will need to be done in the *Core Centre*. Where a *Core Centre* considers that a particular new chemical has strong application potential, but there is at the time no commercial interest, it may carry out preliminary proof of principle (PoP)/proof of concept studies to explore the application. This may, for example, be a limited field trial of a candidate herbicide. The information gained, if the PoP experiment is successful, will make the application more attractive to industry and the added patent protection will make the product more valuable.

In any case, the support of a small, equity-participating *Technology Transfer Unit* associated with the *Core Centre*, will be essential to establish and cultivate contacts with potentially interested industries, evaluate commercial value, draw up cooperation contracts with industry, advise on patenting, etc.

Publications, knowledge dissemination and confidentiality

Commercial interest in the activities of the *Pipelines for New Chemicals* will be of utmost importance, and commercialization of their products will be a key goal, so building mutual confidence with industry involving confidentiality agreements will be an essential characteristic of *Core Centre* policy. At the same time, its overarching goal to strengthen national capacities in new chemical discovery and characterization, makes it equally important to disseminate new findings and technology to the network and other national groups, through presentations at national workshops, publications, etc. To achieve these sometimes opposing goals, a policy of rapid information transfer of discoveries after patent filing will be practiced, in parallel with confidential interactions with industry, where industry directly contributes financial support to project development.

The budget

The budget is based on the following assumptions:

i. The nature of the *Pipelines for New Chemicals* necessitates a sustained, long-term financial commitment: a 10-year period of financial support would seem appropriate.
ii. Important new scientific discoveries should emerge after 5 years and some will attract increasing independent public funding.

iii. New discoveries of commercial interest should emerge after 5 years and will attract increasing commercial financing.
iv. New discoveries of commercial interest will be patented and some will be licensed and result in royalty income.
v. New technologies will be developed by the platforms that become established, and some of these, and some of the platform services, may become commercial services, either through the spinning off of appropriate components or through the centres offering commercial services. In both cases, licenses/royalties may emerge as income streams.
vi. These income streams, plus others, should cover the *Pipelines for New Chemicals* annual budgets after 10 years, and allow organic growth of the *Pipelines for New Chemicals* thereafter; in other words, they should become self-financing after 10 years. Any *Pipeline for New Chemicals* that did not succeed could, if desired, be terminated at this point.
vii. Obviously, personnel and construction costs differ from country to country, as are available infrastructures, but it is assumed that a typical *Pipeline for New Chemicals* will need a construction budget of €20 million and a recurrent budget of €10 million per year. Of the €120 million needed over 10 years, €60 million could be provided through EC funds and the remaining €60 million would come from the national budget.
viii. Whereas the *Network* would rely principally upon the existing academic research and infrastructure landscape, it will be necessary to create the *Core Centres de novo*, preferably as entirely new structures, on campuses of academic centres of excellence. Despite the need for intellectual synergies between *Core Centres* and their campus partners, it is crucial that they should be entirely independent of existing research and administrative structures, and self-sufficient. They will therefore need their own buildings and staff, and should remunerate other institutions on campus for any significant services requested.
ix. To create the dynamic and enthusiastic environment needed for the long-term success of the *Pipelines for New Chemicals* concept, it is crucial to integrate students and student teaching and training in the disparate aspects of the biology and chemistry of natural products and in their development as potential commercial opportunities. For this, *Core Centres* need either to be effectively integrated in a university campus structure, or officially affiliated with a nearby university. Where possible and appropriate, *Core Centre* staff might participate in selected postgraduate/final year undergraduate teaching, so long as this does not negatively impinge on research responsibilities.
x. The complexity and scale of the task requires that the *Core Centres* have approximately 10 scientific Departments and an adequate personnel contingent, say 300 people, consisting of 100 core staff (the Scientific Head, a 2-person Secretariat, a 3-person Administrative Unit, 10 Department heads, 10 senior scientists, 30 postdocs, 40 Technical Assistants and 4 general support staff, 100 externally funded graduate students, and 100 undergraduate students carrying out Bachelor and Master degree projects. Obviously, the details of personnel needs, and the distribution of personnel among departments, will differ from *Core Centre* to *Core Centre* and reflect perceived priorities and available talent.

These considerations and assumptions lead to the following estimates:

i. Building(s) and physical infrastructure, €20 million
ii. Equipment, €10 million
iii. Personnel, €40 million
iv. Consumables, €20 million
v. Funding of external labs of the network (mostly for sampling, isolation, and setting up and conducting screening) €20 million (€100 thousand/year/lab for 20 labs, in general 1 Technical Assistant plus equipment and supplies, each on average for an initial 2-year period). At the end of the 10 year period, perhaps 60–80 national groups would have participated.
vi. Technology transfer, patenting, teaching, workshops, information transfer, public outreach, € 5 million
vii. Building running costs, € 5 million

Grand total ca. €120 million