

CHALLENGES IN DRUG-DISCOVERY

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Over 200 years have passed since 1806, when a young German pharmacist, Friedrich Wilhelm Adam Sertürner, isolated morphine from the opium poppy. Not only was morphine the first example of a pure substance obtained from a plant, it was also the first single component drug ever obtained.

The ability to administer pure compounds led to the development of tight dose-effect relationships maintaining control over the efficacy of the therapy. Improvements in medicine such as these generated great enthusiasm among scientists and led to the discovery of strychnine (1817), colchicine (1819), quinine and caffeine (1820), nicotine (1828) and cocaine (1855).

With the advance of synthetic chemistry in the Fifties however, the isolation of drugs from Nature was progressively neglected. Isolating active ingredients from living organisms has always been, and still is, challenging to chemists not only because of the technological issues related to large scale processes, but also because of the general low abundance of active principles in the biomass.

Paclitaxel, a drug used widely for ovarian and breast cancer, is a notable example of how technological issues and the low abundance in the Yew tree impacted on the development and manufacture of the drug. Paclitaxel is only 0.01% by weight of the dried Yew tree bark, and the process for its purification required years. Despite its promising anticancer activity, the scarcity of the compound put its development as a drug at risk.

Furthermore the progress made in medicinal chemistry, especially with the advent of drug-design and combinatorial chemistry, made scientists less and less interested in natural substances and more inclined towards the apparently more accessible synthetic products.

In the last decade, however, we have witnessed the progressive return to drug discovery from Nature since it has been recognised that combinatorial chemistry has severe limitations in generating novel classes of biologically active compounds. We support the theory that Mother Nature already evolved her own combinatorial chemistry as living bodies were adapted to the environment. Combinatorial chemistry, on the other hand, remains a powerful force in the optimisation of compounds.

The importance of natural products can be seen in the statistical analysis of registered drugs. According to a recent review by Newman *et al.*¹ not only 28% of the new chemical entities (NCE) discovered in the last 25 years are natural products, or natural derivatives, but this rate increases to 47% in the area of cancer for small molecules discovered over the last 60 years.

In terms of overall sales, Butler² showed how 25% of the 35 top selling ethical drugs in 2002 were natural or naturally derived substances. These figures appear even more impressive if one considers that to end up with this 40% of commercialised "natural pharmaceutical products" only 90,000 of them have been screened, against the 2,000,000 screened for the remaining 60% of compounds of non-natural inspiration. All this has laid new emphasis on research in Phytomedicine. Knowledge of the healing properties of plants existed long before medicinal and food plants were domesticated, and long before dr. Sertürner made his crucial discovery. Since then, only a limited number of molecules present in the botanical kingdom have been studied, while it is believed that the number of secondary metabolites will continue to constitute a huge resource in drug discovery.



INDENA, A TORCH BEARER FOR THE CHEMICAL GAMES



"Chemical Games 2007" Regional Award

The "Chemical Games", a national initiative dedicated to High School students, are organised by the Italian Chemistry Society (SCI). The purpose of the event is two-fold: to stimulate the interest and help young people understand the educational, cultural and practical significance of the chemical sciences; and to select the Italian team to participate in the International Chemical Olympics. The intention behind the "Chemical Games", which took place under the patronage of the Italian Ministry of Education, was to promote cultural exchanges between teachers and co-ordinate the level of student preparation nation-wide.

INDENA LICENSES ANTI-CANCER MOLECULE

Indena research which aspires to discover new chemical entities (NCE) in oncology has chalked up a new success. Last summer Indena and Spectrum Pharmaceuticals (Irvine, Ca, USA) signed an international licensing agreement for ortataxel, a new generation taxane which in Phase 2 experimentation, has proved to be active on taxane-resistant tumours.

The American company will take forward the clinical development of the molecule which is expected to become a treatment of choice in the taxane market.

The international finals were held in Moscow. Winners of the regional final in this year's games were awarded their prizes at the "Teulié" Military Academy in Milan on 12 May.

Indena was one of the event's sponsors, confirming the commitment of the company to supporting the chemists of tomorrow. In his address, Indena researcher Gabriele Fontana referred to the historic coincidence which associates the company with this occasion and indeed to the place in which it was taking place. At the time when Indena was created, co-founder Biagio Alberto Della Beffa after honourable war service, was given the rank of Colonel in the Italian Army and appointed by General Cadorna Commanding Officer of the Vincenzo Monti Barracks in Milan.

There are many common values to be found in the military spirit and the study of chemistry: rigour and discipline above all, since chemistry is a science and science is rigour and method. Then passion and enterprise, since "playing about" with formulae and test tubes, and the pursuit of one's instincts requires curiosity and determination. And finally the great attention paid to human values since it is fundamental for a winning company to foster harmony and group spirit amongst all those who are part of it. It was no mere coincidence therefore, that the earliest colleagues of Colonel Della Beffa in the infant company were men he had met during his military career.

Portland Building, home to the international conference "Diet and Cancer: susceptibility, prevention and therapy", Nottingham (U.K.)



INDENA IS COMMITTED TO PREVENTION

Proof which confirms that botanical extracts can act as chemopreventive agents is now legion. Considered strategic by the entire scientific community, pharmacological prevention lies at a half-way point between antineoplastic therapy and primary prevention, which itself involves lifestyle issues, nutrition and lowering risk factors. Indena has long been engaged in oncological research and naturally contributed to the workshop on "Pharmacological Prevention in Oncology", which took place as part of the international convention held in June at the MultiMedica auditorium in Sesto San Giovanni, near Milan. In the words of Indena Scientific Director dr. Morazzoni, who spoke at the meeting: *"we begin to have sound experimental and clinical evidence that the administration of low toxicity drugs, derived from the extracts of edible plants such as green tea and bilberry, is proving effective with patients at risk in the prevention of primary or secondary tumours. An interesting study published last year in the journal "Cancer Research" illustrated how extract of green tea prevented the outbreak of prostate cancer in patients affected by the initial form of intraepithelial tumours."* Indena participated in another international conference with a similar theme, "Diet and Cancer: susceptibility, prevention and therapy". This was also held in June in the English city of Nottingham, organised by the British Association for Cancer Research. This was an opportunity for Indena to raise its profile in the United Kingdom at a conference which saw the participation of an extremely select group of researchers. It was also a valuable opportunity to review and debate the experimental, clinical and epidemiological evidence regarding the extent to which a healthy lifestyle and good well-supplemented nutrition can prevent the onset of tumours.

WELCOME PROFESSOR APPENDINO



Prof. Giovanni Appendino

After more than two decades of highly valued collaboration with the company, Indena is proud to welcome Prof. Giovanni Appendino, who officially took up his post as Director of Research and Development in November 2006. His vast knowledge, unique in the fields of research into natural products and organic chemistry, together with his experience as a member of the most prestigious chemical associations in the world, will be fundamental in taking Indena research even further forward. Prof. Appendino's own research has drawn inspiration from natural products to resolve issues in organic chemistry with new methods

of synthesis, new activity mechanisms in cellular biology and exploring new medicinal drugs. Prof. Appendino has been a joint signatory to more than 250 learned articles and 10 chapters as well as lecturing widely in European and American institutes. In 1991 he was awarded the Rhône-Poulenc-Rore Award of the Phytochemical Society of Europe for his work on terpenoids. During his professional career he has held various chairs in prestigious universities in Italy and abroad and has been local co-ordinator of research projects into natural products for the EU and for numerous national programmes on natural bioactive products.

ANOTHER PLACE AT THE TABLE 2006

Once again last year as part of the solidarity project, which for some time has linked its Italian plant with the one in Madagascar, Indena was proud to be able to support the event "Another place at the table". Initiatives in favour of the children of Fianarantsoa culminated in a huge lunch on 9th December in which 1,200 children with their families feasted at the Don Bosco Church School. The personal commitment of Andrea Borsari in Milan and Vittorio D'Adago in Madagascar and the participation of numerous Indena colleagues ensured the event was the success it deserved. Through the generosity of those who contributed to the collection, this year the children have received basic school equipment

such as exercise books, pens, sketchpads and footballs. Specialist support shoes have also been provided for all the young patients in the orthopaedic ward of the local hospital. This year, our colleagues Borsari and D'Adago have set themselves the objective of laying the foundations of a new school building in Fianarantsoa: the present construction is dilapidated and insufficient for the ever growing number of children it needs to accommodate. It is our belief that education is a most effective weapon in the fight against poverty and forms the very basis for a more dignified life. It is an ambitious target, though by no means unattainable; one of those challenges that can be overcome when everyone pulls together and makes a contribution.



The Fianarantsoa children's names

OPENING UP THE FACTORY GATES

Indena took part in the "Open Factory" operation, held in Settala on 11th November 2006. Promoted by the town council, this annual initiative involves local manufacturers who throw open their gates to allow members of the public to visit their production facilities. Indena participated in this initiative with the spirit of creating a further opportunity for increasing awareness, transparent dialogue and fostering the atmosphere of good neighbourliness with the local community in which Indena has made its home. Visitors were greeted with light refreshments as the factory gates in Settala opened

at 9.30 on this November Saturday. After the initial welcome, our guests were accompanied by Indena personnel on a complete visit of the plant where they could observe a standard



Indena personnel welcoming visitors

production cycle, from the drug warehouse to the packaging of the finished product. The visitors were also able to see the state-of-the-art laboratories where scientists apply world-renowned analytical methods to phytotherapy. The following Saturday the factory gates were opened up yet again. This time in response to many requests, the company had decided to extend the invitation also to employees and their families. The results were more than satisfactory with a total number of 345 visitors expressing their sincere appreciation for this unusual day discovering science and nature.

INDENA SUPPORTS PARTNERS THE WORLD OVER

Indena attaches the highest importance to relations with partners and distributors. The 2nd Asia Pacific Regional Meeting, organised by the company in Sidney from 19th to 21st February 2007 is testimony to this commitment. As on a similar previous occasion, objectives of this meeting were to explore knowledge of Indena products from a scientific standpoint, to share and compare commercial and regulatory information and to set out a common strategy in the area. There was a fruitful exchange of information and ideas during the three-day meeting, in which our partners who had travelled from as far afield as Australia, India, Taiwan, China, South Korea, Malaysia, Japan, Indonesia, Thailand and the Philippines took turns in making their presentations. It was also a great chance to socialise and a genuine team spirit was created in the enjoyable moments of leisure time.

Back home in Italy, a day of training for doctors was held at the Catholic University of "Sacro Cuore" of Piacenza on 31st March. The officially accredited session entitled "Prospects and clinical uses of natural antioxidants in the prevention and treatment of chronic-degenerative pathologies" was organised by the Italian Phytotherapy Society in conjunction with Omeopiacenza and PharmExtracta, both pharmaceutical firms which use raw materials of botanical origin in their products. Indena, which was a pioneer in this area and remains amongst the major experts in antioxidants, contributed to the day of study with two lectures: "Standardisation and titration of vegetal extracts", given by dr. Enrico Mercalli and "Treatment of venous pathologies with Leucocianidins from *Vitis vinifera* L."



Group photo call at the 2nd Asia Pacific Regional Meeting

by dr. Aldo Cristoni. The course, which generated lively interest amongst the 200 participating doctors and chemists, was

particularly successful, in the light of the attention being shown for some time in the whole antioxidant area.

WHAT'S COOKING IN THE INDENA LAB?



Medicine in the kitchen? The belief that nutrition plays a vital role in maintaining health is ever more prevalent. Edible as well as medicinal plants, can in fact represent an important focus of research in order any active substances with protective actions contained in them. If we consider that medicine and nutrition are two sides of the same coin, that a recipe

can be seen as a protocol common to both gastronomy and medical science, it comes as no surprise that gastronomy, especially at high level, is being "chemistrified". Cooking is in fact, in the last analysis, a chemical experiment in which the constituents of one ingredient are combined with those of others in the masterful art of the chef or the rigour of the chemist. These are then modified by physical agents such as heat or microbiological processes such as fermentation. The fascinating themes of comparison and affinity between gastronomy and chemistry were recently explored by Professor Giovanni Appendino, Indena's Director of Research and Development in a lecture at the University of Gastronomic Science in the Piemontese village of Pollenzo (CN, Italy).

AT SCHOOL WITH INDENA

Fruitful collaboration between Indena and the academic world proceeds apace. For some time, the company has promoted and sustained training in fields which are at the heart of its own research, investing in new generations of graduates and ensuring they have the wherewithal to become the researchers and scientists of the future. Indena professionals regularly give lectures and attend seminars and conferences in numerous

seats of learning. The company also sponsors an array of Master's and specialist schools at a number of Italian Universities: a post-graduate course in Phytotherapy at the University of Trieste; Master's courses in Phytotherapy at the University of Siena, and in Drug Design and Development at the University Faculty of Pharmacy in Pavia; and a Level II Master's in Innovative Synthesis Methodology in Organic Chemistry in Florence.

In addition, more and more teachers and classes include a visit to the Settala plant as a valuable feature of their training programmes. In the first half of 2007 alone, more than 200 university students visited the modern laboratories and production facilities, enriching their classroom learning with direct experience. Indena offers a vote of thanks to teachers who each year strive to pass on their passion and knowledge to the researchers of tomorrow.

ALL SYSTEMS GO FOR SEMI-SYNTHETIC PACLITAXEL



New facility dedicated to the production of semi-synthetic Paclitaxel

A brand new facility for the manufacture of high-power cytotoxic active principles and dedicated to the production of semi-synthetic Paclitaxel was inaugurated by Indena at its main factory in Settala, near Milan. With this new high-containment plant, Indena has strengthened its position as world leader in the production of Paclitaxel, one of the world's most widely sold anti-tumour agents. The semi-synthetic active principle will be marketed

alongside the natural extract. The company's target is to capture an increasing share in a market where finished products have exceeded an annual turnover of some € 2.5 billion. Semi-synthetic Paclitaxel is obtained using a specific process patented by Indena based on the 10-Deacetylbaccatin, a molecule extracted from yew trees (*Taxus baccata*) cultivated in the company's-own plantations. The 10-Deacetylbaccatin acts as an

intermediate for the production of various anti-tumour molecules such as Paclitaxel, Docetaxel and others on which the company is still experimenting. The aim of the company is to respond to market demands by moving over to a more competitive semi-synthetic active principle. In this case, Indena can exercise direct control over the entire supply chain from initial plantation to the end product.

INDENA EMBRACES RESPONSIBLE CARE®

People and the environment are at the heart of the Indena philosophy. Naturally therefore the company has signed up to Responsible Care®, the voluntary programme of the Chemical Industry world-wide which includes over 10,000 companies in 52 countries, managed in Italy by Federchimica. Businesses following this programme commit themselves to the continuous improvement of products and processes, health and safety issues for



employees and environmental protection. All these make a significant contribution to sustainable development of the industry, local communities and society. This objective of constant and significant improvement becomes tangible also through communication of the

results achieved. Actions will involve the adoption of specific Guidelines, the definition and evaluation of indicators to measure improvements in the company, communication regarding environmental and personnel safety, and the use of the "Responsible Care®" logo. Indena is putting itself to the test to ensure the health and safety of its people and the environment in which they work.

QUALITY ANALYSIS FOR A QUALITY PRODUCT

Mirtoselect® is the bilberry extract most widely used in food supplements, for the prevention of vascular diseases and in ophthalmics. The bilberry contains in fact anthocyanins, which play an important role in protecting and reinforcing vasal walls. Indena has always been committed to the quest for constant, excellent repeatable quality in all its extracts, and the bilberry is no exception. Recently the European Pharmacopoeia accepted an HPLC method developed and validated by Indena for the analysis of bilberry extract. This surpasses the limits of previous methods, which were seldom able to cope with the task of separating and adequately identifying the characteristic active

principles of the bilberry. The Indena method may also be applied to the finished product, and is in fact able to evaluate the quality of the bilberry extract even within complex formulations. After two decades of research in the field, this method has made it easier for Indena to respect the GMP procedure for integrators (DS-GMP) approved in the US in August 2007: not only is the conformity of the ingredient analysed therefore, but the stability of active principles found in the formulation and declared on the label can also be assessed. Bilberry extracts coming from many countries and particularly from the USA have been analysed using this new method. Over 30% of



the samples examined did not have the content of active principles stated on the label and around 15% were even revealed to have a zero content of anthocyanins. It is the constant commitment of Indena and its researchers to provide, in addition to top quality raw materials, equipment and methodology able to certify the quality, effectiveness and the safety of its products right up to their release onto the market.

INDENA AND MUSIC: COMBINING TRADITION WITH INNOVATION



"Joy" by Giovanni Allevi for Indena

The exciting music of young internationally acclaimed Italian composer Giovanni Allevi was Indena's choice of Christmas gift in 2006. Allevi's pianoforte is his chosen means of expressing his own brand of contemporary music, which opens up the classic tradition to the sounds of our own times. His quest for modern keys to classic melodies is the essence of his artistry, just as Indena's own quest for innovation is rooted in the ancient science of nature. This was the inspiration behind the special Indena edition of the composer's latest album "Joy". To accompany the CD in its elegant gift box Indena chose a collection of creative images of plants captured by another of nature's artists, Italian photographer Mario de Biasi.

COSMETICS BY INDENA

The innovative olive extract Opextan™ is the fruit of Italo-Japanese collaboration between Indena and one of the world's major cosmetic companies.

Its new logo is a guarantee of Indena quality in the world of topical and oral cosmetics today.



LESSONS FROM AFAR

Rituals and traditional medicine have often proved to be an exciting treasure-trove for Indena: over numerous years of experience in the cosmetic and pharmaceutical sector, the study of tribal and native traditions has many times provided the background for the isolation of new and effective active principles.

Traditional masks, such as the one shown here, fashioned from the pulp of plants such as *Santalum album*, for example, led to the development of Ximilene®, a cosmetic ingredient active on microcirculation. Numerous important active principles have similarly been developed in collaboration with some of the world's greatest cosmetic manufacturers, demonstrating how the science of today can still be inspired by knowledge rooted in the annals of time.



Macua woman, Ian Michler/Images of Africa



At Indena we believe that an in-depth knowledge in active ingredients derived from medicinal plants and the search for excellence at all times are crucial commitments to serving our customers in pharmaceuticals, health foods and cosmetics.

INDENA EVENTS CALENDAR

- **CPhI 2007** - Milan, Italy
2-4 October, 2007
Fieramilano Rho Exhibition Centre
- **Supply Side West 2007** - Las Vegas, USA
6-8 November, 2007
Sands Expo
- **HI Japan 2007** - Tokyo, Japan
20-22 November, 2007
Big Sight Exhibition Centre
- **CphI Japan 2008** - Tokyo, Japan
9-11 April, 2008
Big Sight Exhibition Centre
- **In-Cosmetics 2008** - Amsterdam, The Netherlands
15-17 April, 2008
The Rai
- **CphI China 2008** - Shanghai, China
20-24 June, 2008
SNIEC
- **HI Europe 2008** - Paris, France
11-13 November, 2008
Paris Nord Villepint

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