MINISTRY OF NATIONAL EDUCATION

NATIONAL INSTITUTE FOR CHEMICAL-PHARMACEUTICAL R&D - ICCF BUCHAREST

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The mission of our institute (founded in 1949) is to perform high quality research activities to support the development of new technologies, products and services for the pharmaceutical industry and therapeutics, as well as for other domains requiring similar expertise (food industry-nutraceuticals, food supplements; ecological agriculture - biofertilizers, biostimulators; environment protection - biofuels).

Its core competence consists in the capability, unique in Romania, of accomplishing the discovery and development cycle of a new pharmaceutical or related product, including the non-clinical phase.

Working in health improvement, with renewable raw materials and using environmental friendly technologies (biotechnologies, green/clean chemistry), the institute contributes to a knowledge based, sustainable development of pharmaceutical, food, biotechnology or chemical companies as well as to the Romanian participation to the scientific and technology progress.

According to this mission, NICPRD - ICCF Bucharest offers new products and technologies, methods, studies, specific services (analytical and pharmacological) in the above mentioned domains, for technology transfer in industry or in its own production capacities and for products to be launched on market.

Main research directions:

Biotechnologies (microbial and plant extractive). Fine organic synthesis of bioactive substances. Pharmaceutical technologies. Analytical Chemistry. Pharmacology

Strategic objectives

To keep and enhance our competences leading to a sustainable new leadership position in the Romanian medicines R&D

To consolidate the competitive advantage in some domains of large and actual interest (e.g., non-pharm bio-products: biopesticides, biofertilizers).

To enlarge our recognition as a trustworthy partner in the European and international research

Main general objectives of R&D activities

- To achieve a major qualitative improvement in methodology and techniques, *creating and developing a laboratory of molecular biology and drug discovery* (functional genomics, proteomics, drug design, performant screening) to insure the experimental and bioinformatic data base for R&D activities.
- *To follow the trends and contribute to the development* of those topics in which the institute has got a long-term expertise;
- *To develop innovative products* and corresponding technologies which *turn into good account renewable resources of Romania*

Specific objectives and outcomes of each R&D direction

Microbial biotechnology implies a very complex set of activities, starting from selection, preservation and improving producing microorganisms and going on to bioprocesses on increasing working volume (sometimes up to 1000 L fermentation broths), bioproduct isolation and purification through specific post-biosynthesis processing.

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Objectives

- Development of bioprocesses with highly producing microorganisms, applying modern bioengineering methods, for the obtainment of bioactive products and biomaterials
- Drawing up some unconventional procedures and products for the sustainable development and pollution reducing, including required biocatalysts.

Outcomes

- New biopolymers (polysaccharides and derivatives, polyesters) of microbial origin, with immunomodulatory action or as biomedical materials;
- Yeasts enriched in essential microelements (Se, Zn, Cr), other microbial preparations as food supplements or nutraceuticals
- Biopeparations for sustainable agriculture (bio-stimulating and bio-fertilizing products)
- Valorisation of plant or animal waste as well as of byproducts as renewable resources in polymer biosynthesis and unconventional energy (biogas)

Plant biotechnologies. It is a traditional area of the institute activity, turning to account plant renewable resources of the rich Romanian flora by developing new drugs and herbal-based products and technologies using the following main *competences:* plant extractive technologies, phytocompounds isolation, phytochemical screening, antioxidant screening.

Objectives

- New products and technologies based on structure – activity relationship in natural compounds classes
- Obtaining selective extracts and formulations thereof, well characterized and standardized (biorefinery)

Outcomes

- New phyto-therapeutically active products containing selective concentrated extracts with active ingredient set by studying the cellular mechanism of illness; their registration as medicines or food supplements adjuvants in therapy
- Product development and technology transfer at industrial beneficiaries
- Participation at 3 projects financed by European Funds (2 from FP 7 – Programs „Cooperation" and „Marie Curie", and 1 from RO-BG Crossborder Cooperation Program;
- Initiating a partnership of technology transfer with a start-up company and a project of a spin-off.

Synthesis of bioactive substances. Developing new technologies of generic medicines and new active entities discovery has been a traditional activity in chemical synthesis R&D.

Objectives

- Discovery and development of active substances for medicines addressing prioritary therapeutic domains (chronic degenerative diseases, cancer, resistant infections)
- Performant technologies for generic active substances using „clean" chemistry techniques (biocatalysis, non-volatile and non-toxic – ionic liquids)

Outcomes

- About 250 original compounds (structures), potentially active, some of them with promising *in vitro* action or with reduced toxicity, for severe diseases with poor therapeutic solutions
- Memantine synthesis technology, anti-Alzheimer generic medicine;
- Complex, competitive technologies for stereo-controlled synthesis of drug substances: antiglaucoma (prostaglandins) and for breast cancer and osteoporosis treatment (steroids).
- Technologies and innovative products (active ingredients for nutraceuticals and cosmetics) based on oils enriched in omega 3/6 fatty acids by transesterification, resulted from ostrich fat

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complex processing (project funded from FEDR, POS-CCE, prioritary axis 2, O.2.1.1 "Research projects in partnerships between universities/R&D institutes/ and companies")

Pharmaceutical technology. This research area is oriented to liposomes as drug delivery systems with multiple applications, planning also other types of nanoformulations as therapeutic systems for controlled drug release, many of them based on biodegradable and biocompatible natural polymers obtained in the institute.

Objectives

- Obtaining new formulations for controlled/directed release of active ingredient based on micro/nano particles

Outcomes

- Transdermal pharmaceutical products with liposome nanoparticles
- Original transdermic system with elastic nanovesicles for steroids administration.

Analytical research is supporting the preparative research, as well as Romanian and even foreign pharmaceutical companies by performing analytical studies for characterization and control of substances/medicines and similar products, raw materials and packages, GLP certified as reference laboratory.

Objectives

- Using high performance analytical techniques for characterization of structure and purity of substances/products results from preparative research;
- Setting up validated analytical methods for quality control, *in vitro* dissolution, stability of pharmaceutical products according to European Pharmacopoeia and to other international regulations.

Outcomes

More than 300 analytical methods drawn up and validated, using a broad range of modern techniques and equipments: high performance liquid chromatography coupled with mass spectrometry (LC-MS), UV-VIS and FTIR spectrometry, elemental analysis, gas chromatography (GC), inductively coupled plasma atomic emission spectrometry (ICP-MS).

Pharmacological research is achieved on two levels: biopharmacology, for *in vitro* methods, at cellular and molecular level (unconventional, alternatives to animal tests) and non-clinical/pre-clinical pharmacology, for *in vivo* studies (on experimental animals).

Objectives

- Implementation and development of *in vitro* testing methods in toxicological and pharmacodynamic screening, thus contributing to the reduction, replacement and refinement of animal tests
- Microbiological (GLP certified) and preclinical pharmaco-toxicological and characterization of active substances, medicines and other products requiring similar testing, applying European regulation in this domain (on animals and microbiological tests)

Outcomes

- *In vitro* testing methods for: antidiabetic activity and antihypertensive activity
- Cell culture models for: anti-atherosclerotic effects, cytotoxicity, biocompatibility
- More than 80 *in vivo* pharmacological studies for preparative research products
- Pharmacokinetics studies for nano-pharmaceuticals
- Microbiological studies for antimicrobials
- *In vivo* and *ex vivo* pharmaco-toxicological studies for acute and chronic toxicity, local tolerance, mutagenic potential, immunological response.

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Important achievements (projects)

1. **NPRDI-Partnerships /** ***New microorganisms able to enzymatic synthesis of therapeutically active polymers using glycerol as substrate (Glicerobiopol)***

The project aimed at turning into good account of glycerol obtained as byproduct in the biodiesel industry, by identifying and genetically modifying some microorganisms able to produce from glycerol glucan type biopolymers, potentially pharmaceutical substances. By obtaining biosynthesis products and a large area of their semi-synthetic derivatives, having high added value, the perspective of increasing the economical efficiency of this biofuel production and the development of substances with immunostimulatory/ anti-inflammatory/ antitumor activity is being created.

Preparative, analytical and pharmacological research led to results with a high degree of novelty: new microorganisms (isolated from nature and mutants) have been exploited as biopolymer producers. 2 biotechnologies for the obtaining of a *new curdlan type biopolymer and original pseudozan* were elaborated. Derivatives of these products showed anti-inflammatory and/or antitumor activity; formulated as micro and nano-structures, they were tested as adjuvants for new generations of vaccines (original results published in international journals and patent awarded with Silver Medal at International Exhibition of Geneva, 2009).

2. **Eye-drops technology from truffles**

A R&D project, directly financed by a private company, led to the obtaining of an original potential ophthalmic medicine (eye drops) of natural origin (brown desert truffles). Starting from the Arab folk medicine, we succeeded the preparation, by an original technology, of a new active product consisting of a selective extract containing a peptide complex with antimicrobial activity. Formulated as eye drops, this innovative medicine proved to be efficient on pets, in the experimental treatment of ophthalmic diseases (cornea lesions, secondary glaucoma).

The product and its preparation procedure were the subject of a patent application on national (RO) and international (PCT) level.

At present, the new medicine is turned to account by small scale production of the eye drops (in collaboration with the Romanian pharmaceutical producing company Rompharm) to finalize the pre-clinical study and to start the clinical trial on humans to be put firstly on the market in Orient countries (India and Mid-East).

Meanwhile, we perform intense research studies of preparative chromatography, mass spectrometry and microbiology to identify the active compound/compounds of the extract composition, with the aim to publish the results in a widely recognized international journal with a high impact factor.

3. **FP7-KBBE-2008-2B-Coordination and Support Action "Crops2Industry"/** ***Non-Food Crops-to-Industry schemes in EU27***

The general objective of this project was to identify whether and under which terms Europe has the potential and the technical competence to develop a competitive bio-industry fed by a sustainable agriculture. NICPRD was responsible for the evaluation of the potential use of medicinal and aromatic crops in various sectors of industry, in order to optimize raw material-product flow and increase economical efficiency and durability in Europe. As task leader of "Medicinal and aromatic plant crops", NICPRD-ICCF team work resulted in:

-a screening on wild and cultivated medicinal and aromatic plants in EU 27

-a study regarding the quality characteristics that the herbal substances/preparations/ medicinal products/ traditional herbal medicinal products should meet

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-a screening on the pharmaceutical and other specialty crops based on MAP that are/ could be manufactured in Europe: essential oils, human and veterinary drugs, colorants and dyes, perfumes, beauty products, plant protection products, other intermediate products from which the above are manufactured.

-recommendation of the most promising medicinal crops emphasizing the importance of climate change and its impact on crops development; three case studies were performed, due to the multi-purpose potential of the selected plants

4. FP7-PEOPLE-IRSES-2008 Marie Curie Action "International Research Staff Exchange Scheme" / *Natural Antidiabetic and Antihypertensive Drugs (NAAN)*

This project objectives consist in performing detailed scientific research in order to define the most active fractions of extracts from two Egyptian plants *Balanites egyptiaca* and *Solanum distichum* and determine their mechanism of action as anti-hypertensive and antidiabetic drugs respectively. Such studies are considered as the first step to the development of safe and effective natural drugs.

NICPRD-ICCF contribution, as project partner, is related to the following items: development and use of experimental models for selection of biologically active fractions; development of experimental models for the elucidation and demonstration of mechanisms of action; education and training of specialists from the Egyptian partner for the application of the research methodology; exchange of personnel; implementing the selected methods to the Egyptian partner, Sekem Development Foundation.

As specific outcomes of NICPRD-ICCF, we can point out methods and assays for:

- antidiabetic activity, using multiple test systems, that comprise modulation of aldehyde dehydrogenase assay and sorbitol dehydrogenase assay;
- antihypertensive activity based on the angiotensinogen conversion enzyme (ACE2) assay (human blood as biological system)
- classification of extracts and fractions based on their pharmacodynamic efficacy
- 6 stages of training for a total of 9 specialists form SEKEM-SDF

5. Core programme “Biotechnologies and bioactive molecules for health and life quality (BIOINOV) / Structural analogues of local prostaglandin and prostamide hormones of therapeutic interest

The objective of this project was to perform stereo-controlled synthesis of receptor selective analogs of PGF2α prostaglandin local hormone and their 1-isopropylester prodrugs, as active pharmaceutical ingredients for last generation antiglaucoma drugs or luteolytic drugs for veterinary use. Prostaglandins, especially their esterified prodrugs, represent a new class of ocular antihypertensive agents, useful in the therapeutic control of glaucoma in humans, as well as in company animals.

As results, a foreign financed R&D contract was achieved for some drug substance technologies of 3 medicines and their intermediaries used in glaucoma long term management. *Cloprostenol-1-isopropyl ester*, other PGF2α receptor-selective structural analogs or derivatives with higher lipophilicity, were also obtained. Based on these results, *an international patent was granted* with the Italian pharmaceutical company Industriale Chimica, belonging to transnational group Chemo.