Current IMTM research programs

1. The program Molecular Basis of Diseases and Molecular Targets aims to identify, describe and understand the metabolic and signaling pathways, and genetic and epigenetic causes of human disease with special focus on cancer, inflammatory and infectious diseases. The outcome of this program is the identification of target molecules for which drug or biomarker can be designed to influence the disease outcome.

2. The Medicinal Chemistry program concentrates on synthesis, isolation and/or optimization of novel organic compounds with potential biological activity with focus on specific classes of new compounds, their derivatization, and structure modification in response to biological activity. In-solution and solid-phase synthesis combinatorial chemistry plays a crucial role in establishment of scaffolds modification collections. The outcomes of this program are new hits and new optimized lead compounds.

3. The Chemical Biology and Experimental Therapeutics program provides high throughput (HTS) screening on a broad diversity of assays and detection platforms. The program is responsible for, and provides feedback information to, all the stages in the lead generation pipeline. Our HTS platform is industry strong, modular and flexible, and allows testing in BSL3 and BSL2+ environment, screening in combination with ionizing radiation, mass spectrometry, high content analysis and others. The outcomes of this program are preclinical and clinical candidate molecules for further proof-of-concept clinical trials.

4. The main focus of the Biomarkers – Identification and Validation research program is identification, validation and implementation of new biomarkers for diagnostic, prognostic and predictive purposes. Unique tissue bank collections in combination with complex genomic, metabolomic and proteomic analyses, and complex analysis of biomolecules modulating signal and regulation pathways in normal and diseased cells, form the base of our biomarker discovery engine. The outcomes of this program are new validated biomarkers and certified diagnostics.

5. The main goal of the Pharmacology and Toxicology program is to elucidate toxicity, the modes of absorption and transformation of active substances by the experimental organisms and in clinical trials. The outcomes of this program are optimized administration routes, basic preclinical ADME/Tox data and pharmacokinetics in clinical trials.

6. The Translational Medicine program removes barriers to multi-disciplinary collaboration by pointing out clinically relevant problems on one hand, while on the other validating discoveries from molecular targets, biomarker and drug discovery pipelines in proof-of-concept clinical trials. In addition to facilitating the exchange of information, the program collects and comparatively analyzes clinical information and provides support for clinical trials phase I – III. The outcome of this program are drugs and biomarker validated in proof-of-concept clinical trials.

The research programs are supported by nine core facilities that provide their expertise and technical support in their respective fields to all the research programs. These core facilities are: Bioinformatics and Biostatistics, Animal Models and Imaging, Genomics, Proteomics, Metabolomics, Cell Biology, Combinatorial Chemistry, Radiochemistry and uHTS/HCA screening platform.

Collaboration

IMTM can accommodate almost any type of collaboration: out-licensing of the intellectual property, collaborative or sponsored research, joined research programs, students / researchers exchanges, providing an open-access, public-private partnerships, spin-offs, etc.
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Biologically active triterpenoid derivatives I

Introduction:
Triterpenoids are naturally occurring substances showing a large range of biological activities, including strong cytotoxic activity. This would make them suitable for use as pharmaceuticals.

Description of the invention:
The present invention relates to the use of a compound of formula (I), or a pharmaceutically acceptable salt, crystal form, complex, hydrate, or hydrolysable ester thereof, in the preparation of a medicament for treating a patient suffering from leukaemia, cancer or other proliferative disorder. A further embodiment relates to the use a compound of formula (I) in an assay for detecting the phosphorylation state of cellular substrates. The present invention also relates to novel compounds of formula (I), and the chemical synthesis thereof.

Advantages:
The invention provides a novel class of compounds possessing a cytotoxic activity to a wide range of tumor cell lines. Our recent data demonstrate that selected compounds covered by these patents are hedge-hog inhibitors, pro-apoptotic compounds inducing selective release of cytochrome c from tumor cells, tubulin polymerization inhibitors, hemoxygenase I inducers, HIV maturation inhibitors, etc. These compounds will be useful as medicaments for the treatment of cancer and other diseases connected with abnormal proliferation and/or HIV infection.

Development status:
Laboratory scale, data on cell lines, limited ADME/Tox data, in vivo pharmacology and pharmacodynamics.

Papers:

Patent protection:
US 7858606 US2004087561

Commercial offer:
Exclusive/non-exclusive licence to the patents, related know-how and data

Ownership:
Palacky University Olomouc, Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry
Charles University Prague
Cyclacel Ltd.

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
Biologically active triterpenoid derivatives III

Introduction:
Triterpenoids are naturally occurring substances showing a large range of biological activities, including strong cytotoxic activity. This would make them suitable for use as pharmaceuticals.

Description of the invention:
The present invention relates to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in therapy. Preferably, the compound may be used for treating a patient suffering from leukaemia, cancer or other proliferative disorder. A further embodiment relates to the use of a compound of formula (I) in an assay for detecting the phosphorylation and acetylation state of cellular substrates. The present invention also relates to novel compounds of formula (Ia).

Advantages:
The invention provides a novel class of compounds possessing a cytotoxic activity to a wide range of tumor cell lines. Our recent data demonstrate that selected compounds covered by these patents are hedge-hog inhibitors, pro-apoptotic compounds inducing selective release of cytochrome c from tumor cells, tubulin polymerization inhibitors, hemoxygenase I inducers, HIV maturation inhibitors, etc. These compounds will be useful as medicaments for the treatment of cancer and other diseases connected with abnormal proliferation and/or HIV infection.

Development status:
Laboratory scale, data on cell lines, limited ADME/Tox data, in vivo pharmacology and pharmacodynamics.

Papers:

Patent protection:
WO 00190136
DE 60113838.4
EP 1294370
AU 6044501
US 7041701, US 7749988
AT 305776
ES 2250406

Commercial offer:
Exclusive/non-exclusive licence to the patents, related know-how and data

Ownership:
Palacky University Olomouc - Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry
Charles University Prague
Cyclacel Ltd.

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
Ultrasonograph PSF meter

Introduction:
The ultrasound scanners manufactured or refurbished must be checked for imaging quality before their expedition to customers. A measurement system to evaluate a comprehensive group of qualitative parameters with high objectivity and accuracy for the whole imaging system quality assessment is needed.

Description of the invention:
The Point Spread Function (PSF) tester is based on imaging a spherical high reflective target of specified diameter by an evaluated scanner. The scanning is performed in a tank filled with water. The target position in the scanned plane is computer controlled during the scanning. The PSF tester analyses an output video – signal (composite PAL, DVD-I-D, HDMI or VGA) of the scanner – the sonogram for nine different qualitative parameters of the picture.

Advantages:
The PSF tester accesses complete imaging system from transducer to the imaging display. The system is computer assisted, independent of the type of the scanner measured. All the types of transducers can be evaluated including the matrix one. An input of the tester allows measurements of any scanner system commercially available. The tester measures and numerically expresses 9 important qualitative parameters with good reproducibility in any specified region of the imaged area by single measurement process. The parameters are: received signal amplitude uniformity, lateral resolution, transverse resolution, axial resolution, transverse scan slice profile of the scanned plane, number and position of the foci of the dynamic focussing in the both lateral and transverse planes, ultrasound scan line density and distribution in the scan plane, Time Gain Compensation profile in the scan plane and sonogram geometric accuracy.

Development status:
Prototype. Studies on reproducibility and validation in practice have been successfully completed.

Patent protection:
CZ 300799
GB 2434206 B

Commercial offer:
Exclusive/non-exclusive license to the patents, related know-how and data.

Ownership:
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry, Faculty of Science

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (tto@imtm.upol.cz).
Technologies Available for Licensing

Derivatives of 2-phenyl-3-hydroxyquinoline-4(1H)-one and methods of their preparation and utilization

Introduction:
2-Phenyl-3-hydroxy-4(1H)-quinolinones can be considered as aza-analogues of flavones, compounds which are known for the wide-range of their biological activities. These quinolinones were studied as inhibitors of topoisomerase, gyrase and IMPDH. They were tested for anticancer activity in vitro and were also shown to possess immunosuppressive properties.

Description of the invention:
Derivatives of 2-phenyl-3-hydroxyquinoline-4(1H)-one of the general formula (II) where X represents a nitro group, amino group, and Y represents an atom of halogen, oxygen or sulphur substituted by C1 to C6 alkyl or phenyl group, whereby both the alkyl and phenyl group may be further substituted and the substituents may be identical or different, or by nitrogen substituted independently by hydrogen, C1 to C6 alkyl, C1 to C6 alkyl, which may be substituted among others by halogen, hydroxy, C1 to C4 alkoxy or C1 to C4 alkylamino group, or may form a saturated or unsaturated heterocyclic ring with 5 to 7 atoms, where the individual ring atoms comprise atoms of carbon, and any of the carbon atoms may be substituted by an atom of nitrogen, sulphur or oxygen, X and Y together form an imidazo group, or imidazo group substituted by C1 to C6 alkyl, which may be substituted among others by halogen, hydroxy, C1 to C4 alkoxy or C1 to C4 alkylamino group, CHO or acetyl group, or a heterocyclic ring with 5 to 6 atoms, where the ring atoms may be further substituted. Methods of preparation of these compounds are described. In addition, their cytostatic, cytoxic, antiproliferation and immunosuppressive activity is described including examples of their potential pharmacological and pharmaceutical utilization.

Advantages:
The invention provides a novel class of compounds possessing a cytotoxic activity to a wide range of tumor cell lines. Our recent data demonstrate that selected compounds covered by these patents modulate protein-protein interactions of EF1A1. These compounds will be useful as medicaments for the treatment of cancer and other diseases connected with abnormal proliferation of cells/tissues.

Development status:
Laboratory scale, data on cell lines, limited ADME/Tox data, in vivo pharmacology and pharmacodynamics.

Papers:

Patent protection:
CZ 300589
WO 2008/028427
EP 2064200
US 8299092

Commercial offer:
Non-exclusive licence to the patents, related know-how and data

Ownership:
Palacky University Olomouc - Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
Light source with uniform energy density for in vitro induction of photodynamic effect in cells

Introduction:
Photodynamic therapy (PDT) is besides chemotherapy, radiotherapy and immunotherapy other option for treatment of tumor diseases. It is a kind of photochemistry that is characterized by a harmful effect of photodynamically active drug and light in the presence of oxygen molecules. The therapeutic principle is based on whole-body or local administration of the sensitizers followed by UVA or VIS irradiation. Light emitting diodes (LEDs) nowadays more often are used as a source of radiation. The efficiency of PDT significantly depends on the type of sensitizer, its concentration and irradiation dose. Therefore, we have developed a source with an uniform arrangement of LEDs to homogenize such irradiation.

Description of the invention:
Light source with uniform energy density for in vitro induction of photodynamic effect in cells is assembled from a field of neighboring superficially emitting LED diodes arranged into hexagonal form, where triplet of neighboring LED diodes forms equilateral triangle. LED diodes are fixed to a board opposite sample place arranged on distance elements, where six neighboring LED diodes is everywhere arranged in constant distance from randomly selected LED diodes lying out of the field edge.

Advantages:
Light source with uniform energy density for in vitro induction of photodynamic effect in cells comprises a field of neighboring superficially emitting LED diodes, where the distance between 2 individual diodes is constant from 1 to 9 mm. Led diodes fixed into a pad are exchangeable. The light field is height adjustable. The source comprises a controlled cooling device.

Development status:
Prototype.

Papers:

Patents:
CZ 302829

Commercial offer:
Exclusive/non-exclusive licence to the patents, related know-how and data.

Ownership:
Palacky University Olomouc - Institution of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry.

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
Method for determining the sensitivity of patients towards the cancer treatment by HER family (namely EGFR and HER-2) inhibitors

Introduction:
The human genome revolution brings with it large quantities of new molecular information and has spawned impressive high-throughput analytical technologies. This knowledge provides new research tools and raises the possibility of developing novel therapeutics and disease biomarkers that diagnose and treat each patient as an individual. Such an opportunity has profound implications for those charged with delivering them into a clinical setting. The future medicinal product development changes fundamentally through the involvement of pharmacogenetics and develops increasingly towards an individualized (personalized) medicine. Predictive biomarkers are particularly important, since they help clinicians to stratify patient population into groups with highest/lowest therapeutic benefit. Application of predictive biomarkers in early clinical development of new drugs helps to better design clinical trials and to increase response rates.

Description of the invention:
A method for determining the sensitivity of patients towards the cancer treatment by HER family (namely EGFR and HER-2) inhibitors is provided, using a new biomarker, the expression of which highly correlates with progression-free survival and overall survival in HER positive tumors, particularly of breast, colorectal, lung, pancreatic, head and neck, brain, prostate or skin. The method is based on analysis of posttranslational modifications of S6 ribosomal protein and can be carried out on a tumor bioptic sample or on a sample of body liquid using immunochemistry, mass spectrometry and/or other analytical tools.

Advantages:
The biomarker is frequently expressed in patient population and allows for a quick and reliable distinction between the patients benefitting from the HER targeted therapies and the patients for whom this medication would not bring a positive effect and which can then be indicated for other, more effective therapies.

Development status:
Laboratory scale, extensive validation study on patient tissues.

Patent protection:
CZ 302709
US 8,465,936
JP 5295268
EP 2 241 890

Commercial offer:
Exclusive/non-exclusive license to the patents, related know-how and data

Ownership:
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry
Masaryk Memorial Cancer Institute in Brno

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (tt@imtm.upol.cz).
Anti-tumor triterpenoids substituted with nitrogen substituents

Introduction:
Triterpenoids are natural compounds with a number of biological activities including anticancer. Most of the triterpenoids are not sufficiently water soluble, which makes the biological tests difficult and also is a reason for low bioavailability. Therefore it is important to improve the solubility by modifying the compounds with polar functional groups such as quaternary ammonium salts.

Description of the invention:
The invention is based on the introduction of quaternary ammonium salts into the triterpenic structure of active compounds. Those ammonium salts are connected to the 18-carboxylic acid via alkyl-ester linker. Compounds containing both aliphatic and aromatic quaternary ammonium salts were studied and patented and they showed high in vitro cytotoxic activities.

Advantages:
The invention provides a large group of novel compounds active on broad spectrum of cancer cell lines. New anti-cancer pharmaceuticals can be based on the invention as well as abnormal proliferation therapeutics.

Development status:
Laboratory scale, data on cell lines, primarily human tumors, orientational pharmacology/toxicology on rodents.

Papers:

Patent protection:
CZ 301158

Commercial offer:
Exclusive/non-exclusive licence to the patents, related know-how and data

Ownership:
Palacky University Olomouc - Institution of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry
Charles University Prague

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
Laboratory device for ultrasound specimen irradiation

Introduction:
Several significant demands are placed on devices analyzing effect of ultrasound energy on various live and nonlive samples. They involve effective energy transfer, uniform distribution of ultrasound intensity with its precise value in the sample, sample manipulation, and monitoring of physical conditions, such as position, temperature, pressure, etc. Usually, a tank filled with suitably treated water forming a good acoustic contact is used to sample irradiation by ultrasound. General problem of all devices is an interference of the emitted ultrasound waves with the waves reflected primarily from the tank walls resulting in nonhomogeneity of the ultrasound field with difficult definition of the energy distribution.

Description of the invention:
Ultrasound irradiating system composed of tank filled by immersion liquid and ultrasound source positioned inside the tank. Irradiated sample is fixed by a holder in the ultrasound beam axis. The principle effect is based on barring unwanted ultrasound wave interference by nonparallel configuration of the tank walls to the ultrasound beam axis and efficiency may be increased by use of shielding diaphragm(s).

Advantages:
Device for specimen irradiation by ultrasound consists of tank, ultrasound source placed inside, and a sample holder in the axis of the ultrasound beam. At least one side tank wall is nonparallel with the axis of the ultrasound beam and at least one special shielding aperture is placed between source and sample. This part is in a shape of truncated cone, and arranged with its smaller base towards the source.

Development status:
Prototype. Validation studies.

Papers:

Patent protection:
CZ 19375

Commercial offer:
Exclusive/non-exclusive licence, related know-how and data

Ownership:
Palacky University Olomouc - Institution of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry.

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM's director (director@imtm.upol.cz) or the technology transfer office (ttt@imtm.upol.cz).
Cell growth synchronizer

Introduction:
The presented technology relates to a new method of production of synchronized adherently growing cell lines that can be used especially in laboratories for basic and applied research, and provide also a complete technological solution for carrying out said method. Cell line growing techniques are an integral part of work for many biological, biotechnological and medical laboratories. One of the integral aspects of the cell population growth is the asynchronicity, which means that the cells go through the stages of the cell cycle at different pace. This heterogeneity of the cell population represents a serious problem for many experimental procedures because cells in different phases of the cell cycle vary in physical, physiological, biochemical and genetic properties. Achieving homogeneous synchronous cell population of a sufficient size is a complicated technological process. It can be achieved by either separation of the cells (using sorters or counter-flow elutriators) or by chemical synchronization of the cell growth (manipulation of growth factors, inhibitors of replication, inhibitors of mitosis, permanent checkpoint activators). Among disadvantages of standard methods belongs stress which induces biochemical, transcriptional and even irreversible genomic changes and/or high demands on special equipment and laboratory personal.

Our invention aims at eliminating the negative effects of the commonly used synchronization methods and at the same time decreasing the financial, time and operational intensity of this important laboratory procedure. The method explores natural principle of anchorage dependence of the cellular growth which is shared by most adherently growing cell lines cultivated in-vitro.

Description of the invention:
Reversible proliferation block of adherently growing cells in a specific phase of cell cycle based on anchorage dependence mechanism is achieved by using a specialized device. The conception of the device equipped by its own high-power battery allows the usage in standard cell incubators and is fully compatible with standard tissue culture plastic. The device consists of a special vibration unit which causes a defined vibration deflection of a freely suspended platform. This vibration causes a movement of the culture medium in a standard culture bottle which is firmly attached to the platform with elastic straps. Such defined mechanical forces are causing a release of mitotic cells into suspension because they are physiologically incapable of full adhesion. Released cells are prevented from adhering again by the constant vibrations. Such induced change of anchorage during mitosis stops in multiple cell lines further proliferation in late telophase and/or early G1 phase. This inhibition of proliferation is non-toxic and fully reversible within the subsequent 24 hours. Once the inhibited cells are allowed to adhere to the bottom of the culture bottle they continue to grow. Thus prolonged cultivation of a normal exponentially growing adherent cell population on the device creates rich suspension of proliferation-inhibited cells which is an ideal basis for a new cell population which for experimental reasons needs to be homogeneously synchronous in the terms of the cell cycle phase.

Advantages:
Our product offers a unique way for obtaining synchronized cell population reversibly arrested in late telophase with minimum stress affecting the cells fitness. Moreover it is cheap for production and is compatible with standard laboratory equipment and consumables. It is also very easy to use and its primary purpose of usage can be extended to a programmable self-powered shaker usable for other lab-techniques.

Development status:
Prototype. Validation studies on different cell lines.

Patent protection:
CZ 302682
EP 2 419 503

Commercial offer:
Exclusive/non-exclusive license to the patents, related know-how and data

Ownership:
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (tt@imtm.upol.cz).
Light source with homogeneity of light field, primarily for induction and monitoring of photodynamic effect in vitro

Introduction:
Photodynamic therapy (PDT) is besides chemotherapy, radiotherapy and immunotherapy other option for treatment of tumor diseases. It is a kind of photochemotherapy that is characterized by a harmful effect of photodynamically active drug and light in the presence of oxygen molecules. The physical principle of PDT is energy or electron transfer from excited sensitizer onto oxygen molecule or other substrate. This transfer accompanies reactive oxygen species (ROS) or free radicals formation. Due to fast photophysical and chemical reactions related to ROS production, it is necessary to monitor these processes continuously. Our light source was proposed to provide homogenous light sample irradiation with continuous monitoring of products formation during PDT by means of common spectrophotometers or readers.

Description of the invention:
The invention is in an arrangement of a light source with homogeneity of light field, primarily for induction and monitoring of photodynamic effect in vitro, intended primarily for treatment tumor diseases via photodynamic therapy.

Advantages:
Light source with homogeneity of light field, primarily for induction and monitoring of photodynamic effect in vitro consists of a body adapted for sample placing and a set of LED diodes. LEDs are mounted inside of the body and arranged in a circle around the sample minimally in one horizontal plane so that their light beams are focused on the sample. LED diodes are exchangeable.

Development status:
Prototype. Validation protocols.

Papers:

Patent protection:
CZ 302084
SK 288148

Commercial offer:
Exclusive/non-exclusive licence to the patents, related know-how and data.

Ownership:
Palacky University Olomouc - Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (tt@imtm.upol.cz).
Biologically active derivatives of N6-benzyladenosine-5’-monophosphate

Introduction:
Cytokinin ribosides are phytohormones with anticancer activities against a range of cancer cell lines including leukemia stem cells. Their activity was confirmed in several xenograft models.

Description of the invention:
The present invention relates to the use of a compound of formula (I) for treatment of patients suffering from cancers or other proliferative disorders. Cytokinin ribosides, N6-substituted derivatives of adenosine, have only a limited water solubility which complicates preparation of pharmaceutically acceptable formulations. Introduction of 5’-phosphate moiety increases polarity and allows much higher solubility. Parent compound is released by the activity of serum/tissues esterases.

Advantages:
The invention provides a novel class of cytokinin prodrugs with improved solubility profile.

Papers:


Development status:
Laboratory scale, data on cell lines, limited ADME/Tox data.

Patent protection:
CZ 303327
EP 2 563 801
US 2013/0040908
ZA 2012/07173

Commercial offer:
Exclusive/non-exclusive license to the patent, related know-how and data

Ownership:
BioApex, s.r.o., Olomouc
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry, Faculty of Science

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
Pyrimidine based receptor for advanced glycation endproducts (RAGE) inhibitors as an anti-inflammatory compounds

Introduction:
The interaction between RAGE and its ligands is thought to result in pro-inflammatory gene activation. RAGE has been linked to several chronic diseases, which are thought to result from vascular damage. The pathogenesis is hypothesized to include ligand binding upon which RAGE signals activation of the nuclear factor kappa B (NF-kB). NF-kB controls several genes which are involved in inflammation. Interestingly, RAGE itself will also be up-regulated by NF-kB. Given a condition in which there is a large amount of RAGE ligands (e.g. AGE in diabetes or Amyloid-β-protein in Alzheimer’s Disease) this establishes a positive feed-back cycle, which leads to chronic inflammation. This chronic condition is then believed to alter the micro- and macrovasculature in a fatal way which ends in organ damage or even organ failure. Diseases that have been linked to RAGE are: atherosclerosis, peripheral vascular disease, myocardial infarction, congestive heart failure, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, Alzheimer’s disease, psoriasis.

Description of the invention:
Receptor for advanced glycation endproducts plays an important role in many pathological processes and thus represents potential for research and development of diagnostic and therapeutic strategies. Although there were several small molecular RAGE inhibitors described in the literature, they mostly do not showed proof-of-concept therapeutic potential, and thus, there is still potential for future developments in the field.

Advantages:
We have discovered a group of pyrimidine derivatives with proprietary structure and ability to inhibit RAGE receptor (low micromolar concentrations). The effects were described under in vitro conditions using RAGE ligand (β-amyloid, S-100 protein and glycated albumin) dependent activation of NFkB, MAPK/JNK (AP-1) and JAK/STAT (STATJ) signaling. The binding was further confirmed and SAR elucidated by docking against the crystal structure of the RAGE. In vitro validation experiments have also demonstrated inhibition of RAGE ligand dependent activation of NO production in macrophages cells co-stimulated with IFN-γ. The compounds have reasonable toxicity, regiments with 50 mg/kg (2-3x daily) orally were well tolerated in rat model of rheumatoid arthritis and inflammatory bowel diseases (IBDs). The model compound was significantly active in IBD (comparable efficacy to sulfasalazine), but not in RA, which seems to be in agreement with published data on RAGE role in IBD versus RA.

Development status:
Laboratory scale, data on cell lines, structural data from receptor docking, limited ADME/Tox data, in vivo pharmacology and pharmacodynamics.

Patent protection:
Patent protection is scheduled for 2016. For more details a CDA/NDA is required.

Commercial offer:
Exclusive/non-exclusive licence to the patents, related know-how and data

Ownership:
Palacky University Olomouc - Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry
Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences
Institute of Experimental Medicine, Czech Academy of Sciences

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
Carborane derivatives as inhibitors of human carbonic anhydrase isoenzymes

Introduction:
Human carbonic anhydrases (CAs) play important roles in many pathological processes and several CA isoenzymes thus represent diagnostic and therapeutic targets. The development of certain isoform-specific sulfonamide inhibitor is still an important task in current medicine.

Description of the invention:
We have developed unique selective CAIX inhibitors with anticancer properties based on carborane scaffold to structure-assisted design of novel and original inhibitors targeting therapeutically relevant isoenzymes of human carbonic anhydrase.

Advantages:
Novelty, in brief, is represented by the intended elaboration of carborane, heteroborane and metallaborane compounds as active-site inhibitors of CA isoenzymes. All currently used inhibitors anhydrase inhibitors contain a sulfonamide or a sulfamate moiety connected to so called ‘ring structure’ which is usually a 5- or 6-membered aromatic ring or conjugated ring system containing nitrogen, oxygen, and/or sulfur heteroatoms. The ‘ring structure’ bears characteristics or functionality which modulates the affinity toward certain CA isoform. The use of three-dimensional boron cluster is a novel approach in development of isoform-specific CA inhibitors. Selected sulfamides incorporating cluster with inhibitory effects toward CAs (IC50 values in low micromolar and submicromolar range, some of the inhibitors being more than 50-times more selective toward the tumor specific CAIX than for CAII abundantly present in normal tissues).

Development status:
Laboratory scale, data on cell lines, crystal structure, limited ADME/Tox data, in vivo pharmacology and pharmacodynamics.

Patent protection:
EP 2 771 015
US 9,290,529

Commercial offer:
Exclusive/non-exclusive licence to the patents, related know-how and data

Ownership:
Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences
Institute of Molecular Genetics, Czech Academy of Sciences
Institute of Inorganic Chemistry, Czech Academy of Sciences
Palacky University Olomouc - Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttb@imtm.upol.cz).
Method of determination of cancer cell drug sensitivity towards Aurora kinase inhibitors and overcoming their resistance

Introduction:

Recently, Aurora kinases (A, B, and C/serine threonine kinases) gained much attention due to their implication in several types of cancers. Aurora kinases are involved in multiple functions in mitosis. Aurora A is involved in mitotic entry, separation of centriole pairs, accurate bipolar spindle assembly, alignment of metaphase chromosomes and completion of cytokinesis. Aurora B is a chromosomal passenger protein involved in the regulation of chromosomal orientation, and regulating the association between kinetochores and microtubules, and cytokinesis. Aurora C exhibits similar functions to those assigned to Aurora B and is required for cytokinesis. The above mentioned functions are directly involved in maintaining genomic stability. The relation between Aurora kinases overexpression and transformation has been reported in many cancers. Aurora A was shown to overexpress in colorectal, renal, melanoma, and breast cancers. Mainly Aurora B was shown to overexpress in colorectal cancer. Aurora B was also implicated in thyroid anaplastic carcinoma and glioblastoma. Apart from this, Aurora kinases were shown to overexpress in many other advanced solid carcinomas. Aurora kinases overexpression in many solid cancers is the basis of strong rational to discover and develop several Aurora kinase inhibitors. Some Aurora kinase inhibitors are already in the clinical trials and have shown promising antitumor activity in advanced solid cancers. AZD1152 (AstraZeneca) is currently in phase II studies and have proven effective in colon and melanoma cancers. It achieved stable diseases in progressive cancers. Similarly AT-9283 (Astex), PHA-739358 (Pfizer), and MLN8237 (Millennium), MLN8054 (Millennium), VX-680 (Vertex) were proven to be very promising in the clinical trials. CYC116 (4-methyl-5-(2-(4-morpholinophenylamino)pyrimidin-4-yl)thiazol-2-amine), discovered and developed by Cyclacel pharmaceuticals (Dundee, UK) is a novel pan-Aurora kinase inhibitor. It showed promising antitumor activity in both preclinical and early clinical studies. Apart from Aurora kinases, (Aurora A - 44 nM, Aurora B - 19 nM, Aurora C- 65 nM) CYC116 also inhibits other oncogenic kinases including VEGFR2 and Flt-3. ZM447439 (N-[4-[6-Methoxy-7-3-(4-morpholinyl)propoxy]4quinazolinyl]amino)phenyl-benzamide), is a first generation Aurora kinase inhibitor.

Description of the invention:

The present invention provides a group of genes the expression of which or the level of proteins coded by the genes changes with the resistance towards Aurora kinase inhibitors. Therefore, the present invention provides a method for determining the sensitivity of a patient suffering from a cancer disease to Aurora kinase inhibitor therapy and therapeutic approaches to overcome these drug resistance mechanisms.

Advantages:

The genes and proteins identified in the present invention can be used to monitor response to Aurora kinase inhibitors in clinical setting, to monitor the efficacy of Aurora kinase inhibitors therapy, to stratify patients according to the expression of these genes, etc. AstraZeneca’s AZD1152 (Aurora B specific) is currently in phase II clinical trials. Both ZM44739 and AZD1152 have nearly identical mode of actions in cancer cells. ZM447439 and CYC116 resistant clones were highly cross-resistant to AZD1152 (AstraZeneca’s Aurora B specific inhibitor), MLN8054 (Millennium’s Aurora A specific inhibitor), and VX-680 (Vertex’s pan-Aurora inhibitor). This strongly indicates similar mechanisms of tumor cell resistance towards these compounds. Hence the ZM44739 gene expression data and proteomics data is suitable to use in predicting AZD1152 long-term response. CYC116 data can also be used to predict AZD1152 and other Aurora kinase inhibitors response based on the fact that CYC116 clones are highly cross-resistant to AZD1152, VX-680, and MLN8054. By the use of the prediction of sensitivity of patients to Aurora kinase inhibitors, the therapy can be administered only to those patients for whom it is beneficial, thereby decreasing the overall costs of cancer therapy and side effects. Those patients for whom the Aurora kinase inhibitors therapy would not bring any benefit, can be quickly selected for another therapy with medications which are more suitable for them and do not need to undergo an unnecessary and ineffective treatment. Moreover, the genes and their pathways identified in this invention as hallmarks of Aurora kinase drug resistance can be used as future therapeutic targets to develop novel strategies for overcoming the drug resistance. Also, the present invention provides for the use of a Bcl-2 family of inhibitors in combination with an Aurora kinase inhibitors for use in the treatment of Aurora kinase inhibitor-resistant tumors in order to overcome the resistance.

Development status:

Laboratory scale, validation study on patients’ tissues.

Patent protection:

EP 12816228.6
JP 2014-545094
CA 2.855.921
US 14/361087

Commercial offer:

Exclusive/non-exclusive license to the patents, related know-how and data

Ownership:

Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:

More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
Method for obtaining follicular cells and a device for carrying out this method

Introduction:
We developed a specialized device dedicated to a simple, fast and non-invasive withdrawal of follicular cells. Follicular cells can be used for different medicinal or veterinary examinations including pharmacokinetic and biomarkers studies, alopecia studies and for experiments and research on life cells with persisting proliferation capacity. A method of follicular cells withdrawal is, from the medicinal point of view, a form of skin biopsy. Compared to the classical biopsy (skin excision or thin needle biopsy) or blood collection it is less invasive, brings minimum discomfort to the patient and it is also faster and cheaper. Moreover, a set of unique proliferating cells can be obtained by this method.

Description of the invention:
Our technological solution is based on a special withdrawal-gun which is connected to a source of vacuum on one end (e.g. standard vacuum cleaner) and to a removable disposable one-shot grip made of inert sterilizable material, which specifically captures hair including significant portion of its nesting matrix rich for follicular cells allowing its withdrawal and further processing. A prototype of this device has been successfully tested practically and thus a patent application has been registered by the end of 2012.

Advantages:
Presented product is aimed mainly on market covering human alternatively veterinary health care in the category of biological samples collection for diagnostics. This includes:
- Non-invasive testing of biomarkers
- Pharmacokinetic studies
- Bio-equivalence studies on generic drugs
- Basic and applied research specializing on primary live tissues with persisting proliferative capacity

This product also covers specific field of self-made sample collection in home environment. Moreover, it collects unique biological material (rich for proliferating cells) and thus opens new commercially attractive possibilities.

Development status:
Prototype. Validation studies on patients and volunteers.

Patent protection:
CZ 304255
WO 2014/086324
EP 13802526.7
US 14/649785

Commercial offer:
Exclusive/non-exclusive license to the patents, related know-how and data

Ownership:
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttb@imtm.upol.cz).
Substituted 7-deazapurine ribonucleosides for cancer treatment

Introduction:
Several purine nucleosides are clinically used in cancer therapy but their use is limited to treatment of hematological malignancies. The mechanism of action of these nucleosides is based in their incorporation into cellular DNA and subsequent inhibition of DNA synthesis. However, purine nucleosides and nucleotides are participating on many other cellular processes including e.g. de novo synthesis of nucleic acid components, RNA synthesis, protein synthesis, cell signaling and regulation. Targeting of these processes by purine nucleoside analogues can provide cytotoxic nucleosides with new mechanisms of action in treatment of solid tumors and drug-resistant malignancies.

Description of the invention:
A library of novel hetaryl 7-deazapurine nucleosides was prepared and tested for cytotoxic activity against cancer cell lines and normal fibroblasts. The compounds showed strong cytotoxic activities (low nanomolar range) against cancer cell lines derived both from solid tumors and leukemia, including p53-mutated cell lines and cell lines resistant to taxol and daunorubicin. On the other hand the compounds possessed low cytoxicities (> 10 μM) towards normal fibroblasts. Selected compounds have been tested in a P388D1 leukemic syngeneic mouse model and in ovarian (SK-OV-3), colorectal (HT-29) and breast (BT-549) tumor xenografts. The tested compounds significantly prolonged survival of treated animals and reduced tumor volumes. Further studies showed that hetaryl 7-deazapurine nucleosides are effectively phosphorylated in cells to the corresponding nucleoside triphosphates. Fast inhibition cellular RNA synthesis and induction of apoptosis were observed in vitro, whereas DNA synthesis was barely affected. Furthermore, rapid inhibition of protein expression after treatment with hetaryl 7-deazapurine nucleoside was shown in mice bearing 4T1-luc2 tumors. These indicates that hetaryl 7-deazapurine nucleosides possess different mechanism of action than conventional purine nucleoside cytostatics and therefore they could provide broader application range in cancer therapy.

Hetaryl 7-deazapurine nucleosides are phosphorylated in cells to nucleoside triphosphates and inhibit cellular RNA synthesis which leads to induction of apoptosis. In vivo antitumor activity of selected hetaryl 7-deazapurine nucleoside in P388D1 syngeneic tumor model is demonstrated by prolonged mean survival time and significant increase of overall survival in mice. Lines indicate administration of active molecule or vehicle in control animals. Selected compound showed inhibition of luciferase activity (i.e. protein expression) in mice bearing 4T1-luc2 tumors after 4h treatment with tested compound (B) which was not observed in mice treated by vehicle (A).

Development status:
Early preclinical stage, in vitro and in vivo testing, xenografts, toxicology, pharmacokinetics.

Patent protection:
CZ 305 466, US 2014/562,090, AU 2009204568, JP 5485172, AU 2014277740

Commercial offer:
The project is offered for co-development and licensing.

Ownership:
Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences
Palacky University Olomouc - Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm).
Method of predicting the tumor response to DNA methylation inhibitors and alternative therapeutic regimens for overcoming resistance

Introduction:
Aberrant DNA methylation remains the consistent hallmark due to its frequent involvement in all types of cancer including myelodysplastic syndromes (MDS). Cytosine analogues currently one of the most effective epigenetic drugs inhibiting the expression of de novo DNA methyltransferases and have shown substantial potency in reactivating tumor suppressor genes. Few prototypical drugs have been approved in USA and EU for the treatment of MDS. However, like other anti-cancer drugs, resistance to these hypomethylating agents is the major barrier, reversing the effective epigenetic therapy. Molecular mechanisms dilating the cause of resistance to these drugs in vitro are diverse but they fail to explain the acquired resistance in patients.
In congruency with the fact that the gene silencing mechanisms (DNA hypermethylation, mutations in chromatin remodeling complexes and multiple post-translational histone modifications) are not isolated from each other but interlinked, bromodomains (BRDs), chromatin effector modules that recognize and bind to ε-N-acetyl lysine motifs have rapidly emerged as exciting new targets in the quest for clinical progress in cancer. The present invention exposes such bromodomain containing genes and/or proteins coded by the genes, the expression of which was differentially regulated during the development of resistance, and targeting of which may sensitize the patients suffering from resistance towards DNA methylation inhibitors.

Description of the invention:
The present invention provides a method for determining the response of the patients (i.e. sensitive or resistant) towards DNA methylation inhibitors and also provides the alternative therapeutic regimens to resolve the resistance.

Advantages:
Bromodomain containing genes and/or proteins disclosed in the present invention can be used as the biomarkers for predicting the clinical response towards the epigenetic therapy, targeting aberrant DNA methylation. The varying level of expression of the genes and/or proteins and the mutations involving non-synonymous change in amino acid sequence can be used as a fundament to differentiate between the responders and the non-responders. This provides the accessibility of the method of prediction, and personalization of the therapy. The patients who do not respond to the DNA methylation inhibitors and suffer from the primary resistance can be quickly eliminated from the ineffective treatment. This will provide the benefit to such patients by escape from the relative side effects that might associate with the drug, redundant cost of therapy, and suggests for other possible treatment protocol in time. The patients who initially respond to the drug but during prolonged treatment develop the sign of disease progression by acquiring secondary resistance to the drug can be re-sensitized by the use of a bromodomain inhibitor in combination with a DNA methylation inhibitor. This provides the alternative therapeutic regimen to overcome the resistance and may reduce the incidence of developing resistance to a particular DNA methylation inhibitor.

Development status:
Laboratory scale, validation study on patient samples.

Patent protection:
EP 16158309.1

Commercial offer:
Exclusive/non-exclusive license to the patents, related know-how and data

Ownership:
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (tt@imtm.upol.cz).
Method of determining the activity of enzymes converting cytosine derivatives to uracil derivatives in cells and tissues

Introduction:
Nucleoside analogs are widely used drugs in the chemotherapy of malignant and viral diseases. Their application and effectiveness is considerably influenced by a wide range of mechanisms involving transport, phosphorylation, catabolism and as well mutual competition with natural nucleosides. Cytosine specific enzymes participate in the deamination of analogues of deoxycytidine and their monophosphates into uracil derivatives. Important examples of such analogues are some medicaments, e.g. ara-C (1-β-arabinofuranosylcytosine), dFdC (2’,2’-difluoro-2’-deoxyuridine), PSI-6130 (β-D-2’-deoxy-2’-C-methylcytidine), L-dC (β-L-2’-deoxycytidine) or 5-aza-dC (5-aza-2’-deoxycytidine). In this respect, it is expected that their deamination could influence the results of a treatment. Currently, however, there is a lack of quick and reliable procedures for determining the activity of cytosine deaminases. The most common approach for determining the activity of cytosine deaminases in cells is the analysis of the products of deamination after the disintegration of the cells, or tissues. However, when using current techniques, it is a relatively long process, often with the usage of radioactive markers and special equipment, which allows the acquisition of data on the average activity in a relatively large population of cells, but not in small cell populations, or in individual cells.

Description of the invention:
The developed method allows a quick determination of the activity of enzymes transforming cytosine derivatives into uracil derivatives in a sample of tissues, or cells using analogues of cytosine nucleosides. These substances are transformed into uracil derivatives by deamination, and are subsequently detected in DNA or RNA. The amount of the uracil nucleoside analogue is then determined and the signal can be analyzed by i.e. classical microscopic techniques or by flow cytometers or plate readers.

Advantages:
The main benefit of the developed method is quick and reliable identification of the activity of enzymes converting cytosine derivatives to uracil derivatives and can help in research focused on the seeking of new inhibitors of deaminases or testing various cell lines from the perspective of deaminase activities or in testing the effect of DNA or RNA oligonucleotides (antisense oligonucleotides and siRNA) targeted at the inhibition of the expression of deaminases. In the diagnostics, it can help with the application of medicaments based on cytosine analogues of nucleosides.

Development status:
The method has been developing for the use in solutions to allow detection of deaminase activities e.g. in sera or cell suspensions.

Patent Protection:
PV 2014-579
PCT/CZ2015/000097

Commercial offer:
Exclusive/non-exclusive license to the patents, related know-how and data

Ownership:
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry
Institute of Organic Chemistry and Biochemistry, The Czech Academy of the Sciences, v.v.i.
Institute of Applied Biotechnologies a.s.

Figure 1
Schema of the conversion of EdC into EdUMP. As EdCTP is not the effective substrate of the replication machinery in human cells, the detection can be performed by the click chemistry approach.

Figure 2
The simplified schema of the determination of the cytidine deaminase activity in cells
Environmental microhyperbaric chamber for biological studies at high pressure

Introduction:
A hyperbaric chamber is a pressure vessel, which can be hermetically sealed and create the overpressure of several bar. Depending on the size is used for therapeutic methods or testing e.g. diving equipment. On the market there is no easily transportable device that allows cell experiments at higher pressures and at specific composition of the atmosphere.

Description of the invention:
The invention is essentially a overpressure container that allows to create specific climate in the interior space, i.e., to set various pressures up to 10 bar, to create a different composition of the atmosphere of the compressed gas (for instance hypoxic, hyperoxic etc.), to set the temperature of the internal environment, and due to the unique design it can be installed and to use of with specific combinations of light sources. It is also structurally adapted for use of a sufficient number of sensors.

Advantages:
Microhyperbaric Chamber for biological studies at high pressure is not currently available on the market. Some of the features can be found in other devices, but not combined. The main difference is in the possibility of increasing the pressure in combination with the creation of a specific atmosphere, also in combination with temperature control and the possibility of interior illumination by specific light source.

Development status:
Prototype.

Patent protection:
CZ 27799
PCT/CZ2014/000153

Commercial offer:
Exclusive/non-exclusive license to the know-how and data.

Ownership:
Palacký University Olomouc - Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttb@imtm.upol.cz).
Small portable CO₂ incubator for cell cultures

Introduction:
Cell lines grown in-vitro in specialized CO₂ incubators are kept in standard conditions involving constant temperature, CO₂ level (sometimes also O₂) and 100% humidity. However some experimental procedures demand a transport of live cell cultures leading to an exposition of the cells to the environmental conditions for pro-longed time period. Such exposition can cause indefinable cellular stress potentially interfering with the experimental procedures. To solve such specific situations we developed portable incubator which keeps constant conditions during the transport.

Description of the invention:
We developed and successfully tested a small portable cell culture incubator which integrates systems for temperature and CO₂ concentration control and keeps 100% humidity. It can be used as a standard cell culture incubator connected to the external 220V power and CO₂ source. In case it is needed the incubator can be switched into the transport regime involving its own high-power battery and internal CO₂ source (it has embedded 2L cylinder with liquid CO₂). Disconnected it can keep constant conditions for many hours (depending on environmental conditions and frequency of doors opening). Practical handle, low weight and small size allow one-person transport of the incubator. In case of transport inside a car it can be connected to the standard 12V plugin to save the internal battery. The refiling of internal CO₂ cylinder is done by the user from standard CO₂ cylinders with liquid CO₂.

Typical application:
► Inter-laboratory transport of live cell cultures
► Transport of live cell cultures towards specialized non-portable machines (ionizing radiation sources, accelerators, NMR etc.)

Advantages:
► High-power LiFePO₄ battery powered
► Its own source of CO₂
► Holds 100% humidity
► Disconnected keeps constant cell culturing conditions for many hours
► Can be connected to external power sources (220V AC and 12V DC car plugin)
► Can be connected to external source of CO₂
► Small size, low weight and practical handle – one person can carry it
► Allows easy refilling of internal CO₂ cylinder from standard CO₂ cylinders

Development status:
Prototype.

Patent protection:
CZ 28 195

Commercial offer:
Exclusive/non-exclusive license to the patent, know-how and data.

Ownership:
Palacky University Olomouc - Institute of Molecular and Translational Medicine (IMTM),
Faculty of Medicine and Dentistry
Brno University of Technology

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz),
the technology transfer office (ttol@imtm.upol.cz).
Magnetic Unitrap

Introduction:
The popularity of separation techniques based on magnetic particles has increased due to their proven benefits. The example is e.g. separation by means of ferromagnetic particles associated with extravidin used for isolation of substances containing biotin. Another example are the ferromagnetic particles associated with protein A or particles used for isolation of nucleic acids. These particles are also usable for separations of complexes associated with antibodies. For magnetic separations special magnetic separators are usually used. The most often way of use is the placement of the vial with the samples with the ferromagnetic particles in the separator equipped with the vial holder and magnet. These separators are in most cases made only for one dimension of the vials. Some disadvantage is also the fact that the ferromagnetic particles are generally trapped on the large part of the vial wall including the part tightly neighboring with the bottom of the vial or the vial bottom itself.

Description of invention:
The new sort of magnetic separators based on the patented technology of the mutual orientation of magnet and separation vials. A magnet to test tube orientation in the UniTrap Separators enables a stronger magnetic force to act upon magnetic particles and therefore enables very fast concentration of isolated particles. As the special orientation is used, the particles are concentrated in the narrow area of the vial wall and the same device can be used for at least two different sizes of vials. The patented orientation can be used in a large variety of layouts.

We offer two tested and optimized products (laboratory separators) with modern designs, which can be directly and immediately marketed. One of these layout enables the use of multichannel pipettes and is designed for tubes with nominal volume 0.2 ml, 0.5/0.6 ml, 1.5 ml and 2 ml. Moreover, it is possible to use 2 different removable plates and therefore, proceeds separation in 2 different sizes of tubes simultaneously. The maximum number of simultaneously used tubes for 0.2 ml, 0.5/0.6 ml, 1.5 ml and 2 ml is 24, 18, 16 and 16 tubes, respectively. The second layout enables separation either in 50 ml tubes or in 15 ml tubes.

We also have manufacturing potential in cooperation with our own 3D printing unit and can adjust designs according to the needs of the licensee.

Development stage:
Four prototypes.

Patent protection:
PCT/CZ2016/050006, CZ 306187

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttt@imtm.upol.cz).

www.imtm.cz/magneticunitrap
Method of HER2 gene copy number quantification in samples with indeterminate ISH

Introduction:
Current oncology is focused towards the search and use of predictive biomarkers that could determine suitable patients for targeted therapy. One of the well-known predictive biomarker is HER2 gene, localized on 17q, which is amplified in 15-20% breast cancer patients. HER2 amplification is poor prognostic factor but predictor of good response to anti-HER2 therapy (trastuzumab, pertuzumab and lapatinib) which significantly increase survival rates in both palliative and adjuvant settings. Anti-HER2 agents are approved for treatment of HER2-positive breast cancer patients usually determined by immunohistochemistry and in situ hybridization (ISH). The proper determination of HER2 status is therefore fundamentally important.

Description of the invention:
The HER2 DNA quantification kit was developed as a complementary test method for the quantification of HER2 gene in breast cancer patient samples which cannot be reliably evaluated by ISH. The kit works on the basis of the three duplex quantitative real-time polymerase chain reactions (qPCR) and is applicable for DNA from formalin-fixed, paraffin-embedded (FFPE) tissue samples. The HER2 gene copy number status is compared with three reference genes – GCS1 (chromosome 2), DCK (chromosome 4) and EPN2 (chromosome 17). The kit reliably detects HER2 gene amplification in samples containing at least 5% of strongly positive cells (approximately 20 HER2 gene copies per cell). High sensitivity and specificity levels were validated using 223 breast cancer patient samples.

Advantages:
Presented product is able to determine HER2 gene status in breast cancer FFPE samples with indeterminate ISH result. This kit allows quick and reliable identification of patients who could benefit from targeted anti-HER2 therapy and is useful in clinical practice as an alternative DNA-based method when ISH fail.

Papers:

Patent protection:
CZ 28 596

Commercial offer:
Laboratory scale, validation study on patient samples.

Ownership:
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttt@imtm.upol.cz).
A tissue culture dish engineered for the preparation of microscopic examination slides

Introduction
The preparation of slides for microscopic examination of adherent cultures is a common practice in cellular and molecular biology laboratories. Briefly, multiple glass slides are placed alongside one another lengthwise, and the dish is seeded with cells. Once the seeded cells adhere and multiply, the slides are removed, processed and examined under a microscope. There are however flaws in the design of culture dishes currently in use that make this procedure less than optimal. For one, the slides may move sideways over one another during a medium change, or during transport. This damages the cells on the slides and renders the slides unusable. For another, the slides may stick to the dish bed because of capillary forces. This is a problem as it complicates their removal with forceps. If they are tightly bound they may break in the process, again rendering them useless. The culture dish prototype designed at IMTM addresses these issues.

Description of the invention
The prototype culture dish is made of glass or plastic, and has an engineered dish bed for eliminating the described issues. Tiny projections called “Limit stops” engineered into the dish bed/bottom delineate the space for each slide and restrict its motion to this space. The limit stops are spaced at intervals which allow to accommodate four to six slides in the dish. Additionally, a rasterized surface in the said spaces elevates the slides above the dish bed by 0.05 – 5 mm above the dish bed. The elevation prevents them from sticking to the bed and facilitates their removal with forceps. These spacer elements have a height of 0.05 – 5 mm above the dish bed. It is important to note that the elevated glass slides still grow the cultivating cells and do not interrupt cell-culture in the dish.

Advantages
In conventional tissue culture dishes, a shifted slide or a slide that breaks during removal necessitates a repetition of the experiment. This results in wastage of labour, time and material resources and impedes discovery. The prototype culture dish effectively eliminates such wastage and is an improvement on the conventional dish.

Developmental status
Prototype

Papers

Patent protection
Utility Model CZ 28 806
Design CZ 36 622
Registered Community design RCD/003039577-0001
Registered Community design RCD/003039577-0002

Ownership
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

Contact
More information is available upon signing a CDA/NDA. Please contact IMTM’s director (director@imtm.upol.cz) or the technology transfer office (ttto@imtm.upol.cz).
An *in-vitro* sensor for early-stage neoplastic disease

**Introduction**
Blood has been shown to contain trace quantities of proteins secreted or leaked by the tissues that it irrigates. These substances are indicative of their tissues of origin and of their physiological state. The invention leverages this property for detecting the presence of neoplastic and preneoplastic disease in a person’s blood, for a timely and correct diagnosis. The invention should aid the detection and diagnosis of cancers that are typically detectable only in advanced stages (e.g. GI cancers).

**Description of the Invention**
The invention is an *in vitro* method for the sensitive detection of neoplastic or preneoplastic disease in human blood. It is based on mass spectrometry and makes use of a 9-amino acid peptide from the Immunoglobulin superfamily 5 (IGSF5) protein. The peptide is unique to the IGSF5 protein and proteotypic, and as such, confers specificity to the method. For the same reasons, a targeted proteomic technique can measure its levels in blood with precision. The said peptide also constitutes an antigen or an antigenic epitope that can enable antibody-based assays or IVDs.

**Advantages**
Sensitive and specific method of detection and diagnosis, can be performed at speed, level of peptide marker in blood can be measured by targeted mass spectrometry for the development of a classifier, peptide is a candidate antigen for antibody development for antibody-based assays

**Development Status**
Patent filed for, quantitation in patient plasma in progress

**Patent protection**
EP16153221.3

**Commercial offer**
Exclusive/non-exclusive license to the patent, know-how and data

**Ownership**
Palacky University Olomouc- Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

**Contact**
More information is available upon signing a CDA/NDA. Please contact the director’s office at IMTM (director@imtm.upol.cz) or the technology transfer office (tt@imtm.upol.cz)
Diagnostic kit for the detection of human papilloma virus (HPV) integration status (iHPV kit).

Introduction:
Cervical cancer is the seventh most common malignancy with mortality rate of 6.8 per 100,000 people. It is caused by the presence of aggressive forms of HPV (human papilloma virus). More than 2.6 billion woman are at the risk of the cancer and about 500,000 cases are annually detected worldwide. The technology allows the sensitive detection of the most abundant high-risk HPV presence in a sample with additional information about integration status, where episomal (not-integrated) forms of the HPV are less pathogenic than the integrated HPV forms. It expands the information and helps to provide the patients effective treatment. The procedure is simple to perform, rapid and reliable.

Description of the invention:
The principle of the technology is based on a quantitative fluorescent detection of amplification of HPV genes E2, E6 using the polymerase chain reaction (PCR) in real time using specific TaqMan probes. The technology detects 3 genes (HPV E2, E6, and human GAPDH) in one PCR reaction and contains 3 different fluorescent dyes compatible with mainstream real-time thermocyclers. The GAPDH detection serves as an internal control of amplification and/or DNA presence in the PCR reaction. The technology is currently able to detect these high-risk genotypes of HPV: 16, 18, 31, 56. Could be adapted for further genotypes detection.

Advantages:
The main benefit of the technology over existing diagnostic kit features resolution form of the virus (a form of free - episomal and integrated form). Integration of HPV has been associated with disease (cancer) progression. The technology is capable of absolute quantification of HPV load in the sample. Able to detect only 4 copies in HPV genome in analyzed sample per PCR reaction.

Development status:
Prototype of a diagnostic kit, stability tests, performance tests, primer design, optimized standard operation protocol, documentation for manufacturing, related know how.

Know-how protection:
Subject to confidentiality

Ownership:
Palacky University Olomouc - Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

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Iodinated radio labelable ChT ligands for diagnostics and therapy

INTRODUCTION:
Choline transporter (ChT) is strongly overexpressed in certain types of cancer cells, e.g. prostate carcinoma, glioma, and small-cell carcinoma. Moreover, alterations in ChT function have been linked to various neurological and psychiatric disorders. Thus, ChT represents a valuable target for diagnostic and therapeutic radiopharmaceuticals.

TECHNOLOGY DESCRIPTION:
Current medicine and the field of cancer management in particular greatly and increasingly profits from radionuclide imaging methods such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and planar scintigraphy (PS). We have developed a novel series of iodinated small-molecule ligands, which are applicable in diagnostics and therapy of diseases related to pathological expression/function of choline transporter. Labeling of these compounds with different radioactive isotopes of iodine enables their use not only in all of the aforementioned imaging modalities - PET (124-I), SPECT (123-I, 131-I), PS (123-I, 131-I) - but also in therapy (131-I). Our labeling procedure optimized for mild conditions would allow manufacture of radiopharmaceutical kits.

ADVANTAGES OVER EXISTING SOLUTIONS:
The two radiopharmaceuticals [11-C]choline and [18-F]fluorocholine presently used in clinical practice suffer from serious drawbacks. These drawbacks are stemming mainly from the short half-lives of applied nuclides (20 min and 110 min, respectively). The short nuclide half-lives in combination with rapid renal excretion and high organ uptake of the mentioned drugs results in a high image background and unfavourable lesion detection sensitivity. Iodine radioisotopes possess more favourable half-lives and unlike [11-C]Ch and [18-F] FCh allow combining diagnostics with therapy. Use of iodinated radiopharm. does not require an on-site cyclotron, which significantly reduces the cost of examination.

DEVELOPMENT STATUS:
Data on cancer cell lines and ADME/Tox, in vivo bio-distribution data.

IP PROTECTION STATUS:
PCT/CZ2017/050010
PV 2016-117

TECHNOLOGY/IP OWNERS:
Institute of Macromolecular Chemistry AS CR, v.v.i.; Palacky University Olomouc, Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry
Software for identification of mutant proteins, splicing variants and SNPs in MS/MS data

Introduction:
Mutations cause a wide spectrum of diseases including cancers. Knowledge of mutation profiles allows us to understand which processes are altered and select therapies accordingly. Modern high-throughput methods like SNP chips and NGS are used for alteration screening; however, the mass spectrometry of proteome is not used for this purpose yet.

Description of the invention:
Software for the identification of mutant, polymorphic and/or alternatively spliced genes on protein level using MS spectra/fragmentation data. It uses a dedicated mutation/SNPs/splice variant database with a unique coverage (number of both mutation and integrated information sources). The search space can be optionally extended beyond the known disease-associated mutations by including in silico generated sets of mutants with predicted impact on protein function (e.g. changes in active sites of enzymes, sites of post-translational modification). A database for the detection of non-canonical splicing variants is also available.

Advantages:
The software allows to software upgrade mass-spectrometer into a tool for reading of mutations, polymorphisms and protein splicing variants spectra in addition to reference sequence. This type of information is critical in cancer research and diagnostics of somatic mutations, but can be used also in other genetics/proteomics applications. The advantage of the MS over the standard nucleic acid-based approaches is the possibility to directly observe the effect of mutation on posttranslational modifications.

Development status:
Beta-version of the software, access through the web interface

Commercial offer:
Exclusive or non-exclusive license to the software

Ownership:
Palacky University Olomouc – Institute of Molecular and Translational Medicine (IMTM), Faculty of Medicine and Dentistry

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Evaluation of drug interactions and their metabolism by cytochromes P450

**Introduction:**
Almost one half of prospective drugs, including new chemical entities are not suitable for clinical use because of their metabolic unstability and for danger of drug interactions. This type of toxicity has been underlying several drug withdrawals in recent years and hence it is needed now to bring with any new compound proposed an information on its metabolism and on its interactions with major drug metabolizing enzyme systems namely with liver microsomal cytochromes P450 (CYP). Then, possibility of drug interactions with other drugs taken by the patient on the basis of drug metabolism may be evaluated to prevent significant losses in time, effort and money in drug development.


**How can we support your (research) projects?**
Presence of drug-microsomal CYP interactions is first checked with human liver microsomal fraction. Then, possible influence of a drug on established CYP activities is studied in vitro. Possible formation of metabolite(s) and the role of individual CYP enzymes in this metabolism is then analyzed using the human liver microsomal fraction and human hepatocytes. Finally, systems expressing single CYP form (e.g. bactosomes, supersomes) are used to confirm the role of the specific CYP form in the respective metabolic process. Induction of CYP is achieved using human hepatocytes; in specific cases, a preliminary study on CYP induction may be performed with experimental animals (rats). Expression of the individual genes, protein expression and changes in the respective enzyme activities are evaluated by RT-PCR, Western blotting and by evaluating the enzyme activities. Wherever possible, high-throughput analytical technologies are applied.

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Biostatistics & Bioinformatics – searching for information inside and small datasets

Introduction:
The Biostatistics & Bioinformatics Core of IMTM provides expertise and infrastructure for various types of analysis as well as for acquisition, storage and distribution of complex datasets. The Biostatistics & Bioinformatics Core staff members with an overlapping expertise in IT infrastructure, programming, web/database management, data mining, statistics and bio/chemoinformatics can consult and assist in study design, implementation, and analysis, and develop new software tools to support your research activities.

In addition to standard equipment and common software resources, computing infrastructure of the Biostatistics & Bioinformatics Core includes two high performance computing clusters:

1) IBM BladeCenter H (276 cores, 39 TB):
   ► 23x BladeCenter HS22 (48 GB, 2x Intel Xeon CPU X5650, 2.67 GHz, 6 cores),
   ► 38 TB SATA + 1 TB SAS

2) IBM Flex System (1008 cores, 835 TB):
   ► 42x CPU Node (2x Intel Xeon E5-2650 8C, 2.0 GHz),
   ► 18x GPU Node 48 GB (2x Intel Xeon E5-2650 8C, 2.0 GHz, NVidia Tesla M2090),
   ► 1x Backup Node (2x Intel Xeon E5-2650 8C, 2.0 GHz)
   ► 24x 300 GB + 276x 3TB

How can your research be improved with biostatistics?
   ► Preparation of design of clinical trials and laboratory experiments (determine sample size, specify analysis plan)
   ► Conduct statistical analyses and provide statistical support to researchers in appropriate reporting of results

How can we help you to understand your big data?
   ► Provision of expertise on the collection, organization, analysis and interpretation of genomic, proteomic and other biological data
   ► Provision of chemoinformatics support for high-throughput screening program including annotation of compounds in the library, analysis of structure-activity relationships and identification of mechanism of mechanism of action

Which unique software tools and databases do we use and develop?
   ► Dymka — high-performance, multi-engine, system for identification of peptides from MS/MS data
   ► Decryptor — web-accessible software for identification of mutant and polymorphic proteins from standard MS/MS data (see http://decryptor.imtm.cz/)
   ► MedChemBio portal of medicinal and biological chemistry (see http://medchembio.cz/)

Papers:


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Proteomics core facility

Introduction:
The IMTM proteomic core facility features a comprehensive set of analytical instruments to cover a broad range of proteomic analyses: Orbitrap based mass spectrometers Elite and Fusion (Thermo Scientific) for discovery proteomics, QToF5600 (ABSciex) for intact protein and SWATH analyses, QTrap 5500 (ABSciex) for protein quantitation and validation by single/multiple reaction monitoring (SRM/MRM). The facility also has HCTultra PTM Discovery System (Bruker Daltonics) for PTM analyses and two MALDI-TOF UltrafleXtreme (Bruker Daltonics) systems.

Except of mass spectrometers, proteomic core facility is also equipped with Quadra3 liquid handling workstation (TOMTEC Life Sciences) for solid phase extraction, PROTEINEER dp (Bruker Daltonics) in-gel digestion and MALDI sample preparation station, 1D, 2D, DIGE scanner Typhoon (GE), recombinant protein production and purification instrumentation NGC-Discover Chromatography system (Bio-Rad) available to expedite a high-volume sample preparation and analysis.

The instrumentation is supported by data management and complex analyses systems that are administered by bioinformatics & IT support staff. The IMTM proteomic core facility is able to perform a broad scale of experiments including protein identification and quantification in samples ranging from single gel bands to whole cell lysates, serum or other biological fluids. Quality control of your samples and LC/MS method development can be done as well.

How can the proteomic core facility help with your research project?
► Protein identification, discovery, quantitation (labelled, label-free), SILAC, FASP
► Biomarker discovery, validation, SWATH, SRM, MRM, glycoproteomics
► Identification of protein post-translational modifications
► Immunoaffinity pull-down experiments, molecular targets identification
► Mass spectrometry data analyses
► Consultations, trainings

Regulatory/QA aspects of the proteomic core facility
► Access to a broad scale of high-end proteomic equipment including orbitrap, MALDI-TOF, Q-TOF and other mass spectrometers connected with nano-LC
► Isotope labeling of proteins doesn’t affect their function and behavior
► Seamless transition from cell-culture to tissue or serum experiments
► Precise targeted quantification with isotope labeled internal standards
► Robotic liquid handling reduces variability
► Both discovery and validation phase can be performed
► We offer a scientific environment with advanced knowledge and methodic support

List of references:


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Introduction:
Small, medium, and medium-large sequencing and genotyping

Despite the buzz about the low price of getting genetic information, starting a sequencing or genotyping project requires initial investment in millions of Euros, continuous education of staff not only in the wet part of laboratory work but also in bioinformatics, and uninterrupted stream of samples to keep instruments running. In many cases, outsourcing may be the most reasonable solution.

The genomics core facility at IMTM provides services using dozen of real time thermocyclers including 1536-wells format. Moreover, Affymetrix microarray device (Human Gene- and Exon-level expression, miRNA profiling, FFPE OncoScan, HD Cytoscan) and two different next-generation sequencing platforms from Illumina (MiSeq and HiSeq) are installed there.

How can we help you with your research?
The supported genomics core facility applications include:
► SNP genotyping
► Amplicon sequencing for metagenomic studies
► Targeted sequencing of formalin fixed paraffin embedded (FFPE) samples
► Transcriptome sequencing of humans
► Whole genome sequencing of non-model organisms

How can we support your research?
Analysis from high throughput technologies is provided in cooperation with IT core facility. In addition, the facility continues to offer a variety of traditional genetic services, including:
► Comparative genomic hybridization (aCGH)
► Constructing of DNA FISH probes for designated genes/chromosomal areas
► Fluorescent in situ hybridisation (FISH)
► Fragment analysis
► Genotyping, SNPs
► High Resolution Melting Analysis (HRM)
► Karyotyping
► Microarray analysis
► Reverse transcription Real-Time quantitative PCR
► Real-Time quantitative PCR
► Cancer aggressivity testing (Endopredict)
► Circulating tumor cells detection

List of references (2015)


Quotes/ pop-out boxes:
“Correctly assessed genotype is milestone of precision medicine”
“Outsourcing of massive parallel sequencing can be the most reasonable solution for your project”
Biobanking facility - Finding a defined set of samples

Finding a defined set of samples

Introduction:
The Biobank at the Institute of Molecular and Translational Medicine is a part of European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI). The process of sample collection is marked with close collaboration between patients, surgeons, pathologists, researchers, and biobank personnel. Thus, obtaining coherent cohort of clinically characterised samples may be behind reach of academic centres without direct contact to teaching hospitals.

How can we help you to find appropriate samples?
The IMTM biobanking core facility provides samples from tumour collection that include:

- DNAs (more than 10000)
- RNAs (more than 2000)
- FFPE slices (more than 5000)
- Cryosamples (about 1000 tissue samples from lung, brain, colorectal, breast, lymphatic node, ovary, testicle, prostate, and bone marrow)
- Tissue samples fixed in RNA later (parallelly collected with tissue cryosamples)
- Other tissues samples through appropriate material transfer agreements.

How can the biobanking help your research projects?
Patient samples are essential to understanding the diversity of human diseases. Biobanking constitute a basis for disease prevention programmes and improvement of public health.

Core facility also provides infrastructure for storing frozen and deep-frozen samples, mostly from cancer patients. The facility houses liquid nitrogen cryosystems from Lineq equipped with Kesai alarm systems. Mowden -80°C cryosystems are also available, and are equipped with CryoData2, Innova U725, and COMET software.

How can the biobanking support your research programmes?
Biological samples and accompanying patient data are necessary for the development of any new drug or a diagnostic assay and consequently for advancing biomedical research in the context of personalised medicine.

List of references:


Quotes/ pop-out boxes:
“Preanalytical phase can ruin or raise your research”
“Well characterized, high quality samples are prerequisites for –omics research”

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High throughput screening and high content analysis (HTS/HCA) platform

Introduction:
IMTM's high throughput screening and high content analysis platform is one of the largest academic installations worldwide and provides screening and high volume biology data on a broad diversity of assays and detection systems. Our HTS platform is industry strong, modular and flexible, and allows testing in BSL3 and BSL2+ environment, screening in combination with ionizing radiation (X-rays), mass spectrometry, high content analysis and others. The screening assays provide leads for downstream drug research and development. The HTS/HCA screening platform is based on a state-of-art robotic system provided by HighResBiosolutions Ltd. The system consists of three robotic arms, automatic incubators, liquid handlers for microliter and nanoliter volumes, sealers, de-sealers, centrifuges and readers for fluorescence, luminescence, absorbance and ionizing radiation. Also integrated with the system are wide-field or spinning disc confocal microscopes (Operetta, Yokogawa CV7000) equipped with software tools for image analysis and data evaluation. A critical part of the robotic system is the automatized chemical library, which contains more than 110,000 compounds.

Our tests focus on:

- Cytotoxicity (non/cancer, resistant cell lines)
- Primary human normal and diseased cells
- Cell cycle analysis (fixed and live cells)
- Phenotypic screens using HCA
- Cytoskeleton modulation/integrity
- DNA, RNA, protein synthesis
- DNA damage/repair activity, screening in combination with X-ray radiation
- Protein-protein and protein-nucleic acids interactions
- Adenosine receptor activity
- Mapping the most significant signaling pathways (e.g., Hedgehog, Wnt, p53, KRAS, RAGE) via phosphorylation and reporter assays
- Custom made biochemical tests
- Antimicrobial activity in G+/G- strains including drug resistant bacteria, mycobacterium strains, yeasts, filamentous fungi, viruses and parasites under BSL2 and BSL3 conditions
- Cellular 3D culture models (cytotoxicity, reporter studies, etc.)

Academic and commercial offer:
Collaborative and contractual R&D projects in the field of uHTS/HCA and chemical biology/genetics.
Tests of biological activities of small molecules.

How can the "SERVICE" help potential customers in their (research) projects?
- Development and validation of homogenous mix-and-measure assay (384-well and 1536-well format) in tight collaboration with customer for:
  - Absorbance
  - Luminescence
  - Fluorescence polarization
  - Fluorescence intensity
  - Fluorescence resonance energy transfer (FRET), ALPHA-Screen, LANCE
  - Time resolved Fluorescence (TRF)
  - High Content Screening
- Identification of new molecular target or new assay approach
- Validation of assay on provided by customer or commercial chemical libraries (Lopac1280, Prestwick, Enzo)

How can the "SERVICE" support their (research) projects?
- Support in analysis of HCS data
  - Custom scripts for image analysis on Columbus, Acapella, Matlab and ImageJ
- Availability of broad spectrum of reporter cell lines
- Hit and Lead profiling and preclinical development of selected drug candidates

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Animal facility

Introduction
The facility provides preclinical in vivo efficacy models for numerous diseases, including neurology, oncology, pharmacokinetic, toxicology and metabolic studies. Facility is also poised to customize preclinical pharmacology and consulting services to speed up a development of your drugs. Preclinical studies at IMTM’s Animal facility have utilized species of laboratory animal models (including GMO animal models) in SPF conditions. The employees of the Animal facility can administer test agents into rodent via any route and perform surgical techniques or procedures with special imaging and analysis capabilities for all specialized and/or custom programmes. Animal facility has been accredited under the applicable laws of the Czech Republic.

How can we help in your research/drug development projects?
Facility in Vivo Department can guide you through this stage of the development process by selecting appropriate animal models, designing research practices, conducting high-quality in vivo studies, and generating study reports custom-built to your needs.

How can we support your research/drug development projects?

Pharm / Biopharm
In vivo toxicology studies are intended to assess the onset, severity, and duration of toxic effects, their dose dependency and degree of reversibility (or irreversibility). At IMTM, in vivo toxicology studies can encompass dosing regimens from acute (single dose) to chronic (multiple doses). Several routes of exposure (e.g. oral, intravenous, intramuscular, topical, etc.) can be accommodated and multiple species of rodents are available. The full complement of toxicology evaluations is available, either through in-house resources or through strategic partnerships with external vendors. These evaluations include Biochemistry (Clinical chemistry), Hematology, urinanalysis, histopathology, bioanalysis and toxicokinetics. Pharmacokinetic (PK) and toxicokinetic (TK) analyses are key activities of early drug development. PK and TK studies provide useful and required information which informs no effect levels (NOEL), human equivalent doses (HED), and pharmacokinetic/pharmacodynamic (PKPD) drivers. Carrying out pharmacokinetic studies enables the determination of PK parameters such as AUC, clearance, volume of distribution, half-life, Cmax, and Cmin.

In Vivo Cancer Studies
The preclinical oncology studies provide highly customizable in vivo compound evaluation to help evaluate novel anticancer therapies. Studies are conducted from traditional xenografts to advanced humanized mouse models of cancer. This area includes subcutaneous human tumor xenografts, syngeneic tumor grafts, orthotopic engraftment, patient-derived xenograft resource, tumor cell lines in Implant Membrane (Hollow Fiber).

Irradiation Studies
The irradiation is a treatment approach for many types of cancer, researchers seeking compounds which selectively enhance a tumor’s irradiation sensitivity, protect healthy tissues or allow increased doses to the affected areas. The IMTM’s irradiation department includes RS Research Cabinet X-Ray source.

Antimicrobial Studies
The employees of the Animal facility have experience and expertise in testing an efficacy of novel antimicrobials in bacterial infectious animal models (e.g. rat model of infected skin ulcer, murine model of bacterial keratitis, mouse peritonitis/sepsis model, murine model of bronchopulmonary aspergillosis).

Neuroscience services
The animal facility is equipped for behavioral neuroscience tests (e.g. locomotor activity, anxiety, and habituation, cognition).

Other Services
The general aims of a division of Hematology and Clinical chemistry are to obtain a detailed knowledge on mechanisms of the effect of tested substances which determine a hematopoietic stem cell self-renewal and differentiation as well as the effect on functions of organs, with an ultimate goal to deepen our insights in a development of drugs.

Histopathology
It is an investigative method which involves right treatment and microscopic examination of animal tissue. The investigation of animal tissues after sampling provides deep freezing in a liquid nitrogen and storage in -80°C or a fixation in a suitable fixative solution (e.g. buffered aqueous formaldehyde or paraformaldehyde). The paraffin embedded tissues are prepared from a well-fixed sample. The Tissue-Tek® VPTM 5 Jr Vacuum Infiltration Processor (Sakura) is used for dehydration, clearing, and paraffin infiltration of a variety of animal tissue specimens. The embedding of tissue is processed in Tissue-Tek® TECTM 5 (Sakura). Prepared samples are cut into thin slices and placed on a glass slide and stained. For the staining, the most common stain in histopathology combination of hematoxylin and eosin (H&E) or diver’s immunohistochemical staining are used. Based on customers’ needs we can provide the special staining and immunohistochemical methods.

Surgery
The surgical equipment provides a technical expertise and creation of sophisticated models of diseases. The animals are operated on according to the principles of a good surgical practice under the guidance of our animal welfare officer, which include an aseptic working method, minimal surgical trauma, anesthesia (injection or inhalation) and analgesia, if necessary, peri- and post-operative care and detailed reporting. The employees of the Animal facility have experience, expertise and equipment for Microsurgery and Stereotaxy.

Endoscopy
Endoscopy is an examination method of body cavities and hollow organs. The flexible endoscope is used (videendoscope).

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Multimodal imaging in drug discovery: tracing of the biological destiny of compounds

Introduction:
Multimodal imaging comprises advanced non-invasive techniques (e.g. PET, SPECT, CT, US, optical) for studying of dynamic biological processes within living animals. To better understand the progression and treatment of diseases multimodal imaging uses cutting edge technologies allowing quantitative 3D imaging of tracers. It provides data on the kinetics and biodistribution of studied compounds in various animal models. Precise information on the biodistribution profile of the drug is one of the crucial requirements for the future success in the drug development. The state-of-art multimodal imaging systems allows imaging of various kinds of tracers in all types of small animal models (e.g. rat, mouse) and even in models of isolated organs.

How can multimodal in vivo imaging help in your drug development projects?
► Multimodal imaging of tracers in given time points
► Evaluation of disease progression or treatment response over time
► Very high resolution and sensitivity resulting in superior image quality
► Rapid multimodal acquisition and reconstruction
► Powerful quantification and dynamic analysis option
► 3D output images combining the data from several imaging modalities
► Longitudinal studies on the same animal
► Possibility of 3D animations
► Biodistribution data output as continuous record in given time period
► Detection of compounds labeled by a wide range of radionuclides

How can multimodal in vivo imaging support your drug development projects?
► Assessing the efficacy of your novel drug candidate
► Tracking of physiologic and structural changes together in vivo
► Monitoring of disease progress and drug distribution, delivery and therapeutic response
► Enhancing the efficiency and accuracy of preclinical studies
► Reducing time and costs for the translation
► Powerful approach for characterizing your drug candidate in vivo in preclinical studies

List of references:
Haas, H., Petrik, M., Decristoforo, C. An iron-mimicking Trojan horse entering fungi - has the time come for molecular imaging of fungal infections? PLOS Pathogens. 2015, 11(1), 1-7.

Quotes/ pop-out boxes:
„Cutting-edge in vivo imaging technologies help to decrease the number of animals thus enabling significant cost reduction in the drug development“
„In vivo imaging visualize the biodistribution of the compound in a straightforward and clear way so such self-explanatory images can greatly increase value of your publications“

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