FUNDACIÓN MEDINA

www.medinadiscovery.com

SPAIN

high-capacity screening site

GRANADA

an official partner site of eu openscreen

THE PEOPLE

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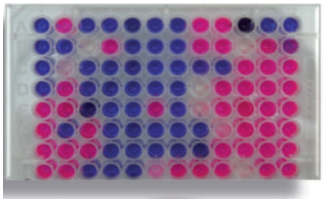
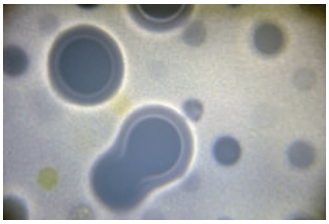
THE PROJECTS

Novel Anti-infectives

Antibacterial and antifungals discovery programs are focused on the phenotypic screening of our Natural Products libraries against panels of Gram positive and Gram negative bacteria and fungal human pathogens. Validation of hit compounds on clinical MDR strains, preliminar MOA studies and preclinical safety and ADME evaluation has allowed to identify 20 novel families of molecules, including a new chemical class of broad spectrum antibiotics against Gram negative pathogens (MDN-0057/-0060), the new glycolanthipeptide MDN-0270 active on *C.difficile* or the new spirotetronates active on *M.tuberculosis*.

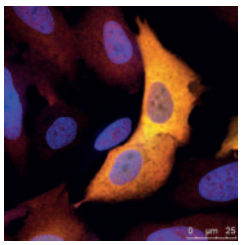


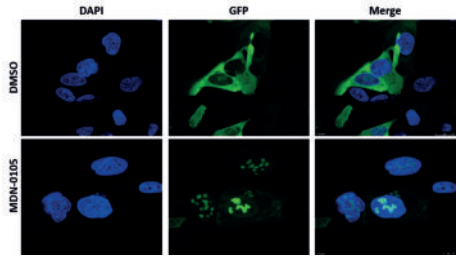


Discovery of novel anticancer compounds

Natural products research in cancer involves: 1) a combination of phenotypic assays targeting tumor specific compounds on a panel of human solid tumor cancer cell lines (liver, breast, pancreas, colon, and melanoma cancer), and 2) whole-cell target-based HTS assays looking for novel inhibitors with specific mode of action in the VHL/HIF pathway and the FOXO nuclear-cytoplasmic translocation.

Two families of compounds including the novel chemical class of PDK1 inhibitors MDN-0088 for cancers overexpressing PI3K (breast, colon, etc..) and the pancreatic cancer specific compound MDN-0090 targeting the MAPK pathway and with efficacy in in vivo animal models (including pancreas cancer stem cells) are in preclinical development.





THE HARDWARE

HTS screening systems

HTS Liquid Handlers and workstations (96/384/1536 wells): **Acoustic nanodispensing Echo 550** Labcyte; Tecan **Aquarius**; **Thermo Multidrop**; FlexDrop; **Beckman Biomek FX** (Beckman; microdispensing; 96/384 wells; Stackers); **Packard EP3**.

Compound libraries

- MEDINA Natural Products libraries: 200.000 extracts and fractions derived from microbial sources
- Future allocation of one copy of EU-OPENSCREEN compound library

Readouts/ Screening technologies

Readers: **High Content BD Pathway**; Perkin Elmer **EnVision; FLIPR**; Perkin Elmer **Victor II**; Tecan **Ultra**; Tecan **Spectrafluor; Typhoon; Image analyzers; Odyssey**

Screening technologies: fluorescence, colorimetry, luminescence, polarisation, HTRF, FRET, FLIPR, ELISA, AlphaLISA, Alphascreen, Thermofluor, High Content Screening, cellular reporter assays, cytometry, WB, PCR, agar-diffusion, LC-HRMS, LC-MS/MS

Phenotypic and target-based screens:

- **Human targets:** cell viability, cell cycle, NO levels, ATP levels, nuclear translocation, antioxidant, ROS, genotoxicity, PPi, immunomodulation, ion channels, mitochondrial membrane depolarization, kinases, caspases, CYP450 inhibition and induction
- **Antimicrobial targets:** bacterial and fungal pathogen viability, synergism, biofilm inhibition, essential viability genes; tropical parasites (kinetoplastids and P. falciparum)

THE SOFTWARE

Software tools:

Commercial Software: Genedata Screener 14.0.0, Dotmatics 5.0 Studies/Browser, IDBS XLfit; EnVisison Tools 1.13; Odyssey 3.0

In-house developments: Image Analyser, Data Browser 1.0; Activity Browser 1.0, Patterns-Matching 1.2; Regression v1.0; WIFF Converter; NucleusFinder

Compound logistics software: Nautilus LIMS 9.0 (Thermo); Inventory (Dotmatics)

Bioinformatics software tools: Bionumerics 6.6 (Applied Maths); FermInfo 1.0 (Internal)

In silico screening and rational drug discovery tools: Open Babel, Vina & Tools (AutoDock), Pymol v0.99, HyperChem 8.0

Chemoinformatics & metabolomics:

Commercial Software: ACD Labs ChemSketch and Suite; DNP (Dictionary of Natural Products); Chem Office Ultra 12.0 Suite; NIST 14; Metabolite Pilot 2.0; Alpha Markerview 1.2.1.1; Peak view 1.2.0.3

In House developments: HPLC Studio 2.0; MASS Studio 1.0

Screening informatics & data analysis:

- **Input and processing tools:** a) QC statistical parameters (signal to noise ratio, Z Factor); b) noise reduction procedures; c) outlier automated detection; d) systematic non-random patterns automated detection (side-edge effects and gradients).
- **Data Management tools** for data integrity and consistency, traceability procedures, and data redundancy and archiving.
- **Oracle Data Base tools**. Data referential integrity and consistency; data archiving and backup procedures.
- **Hardware tools**. Redundant units (RAID). Backup and archiving procedures. Virtualization of servers and equipment computers; centralized maintenance.

THE OUTPUT

1. *Pérez-Bonilla et al. (2018). Phocoenamicins B and C, New Antibacterial Spirotetronates Isolated from a Marine Micromonospora sp. Mar Drugs.16(3). pii: E95. doi: 10.3390/md16030095*
2. *Pérez-del Palacio et al. (2017). Exploring the Role of CYP3A4 Mediated Drug Metabolism in the Pharmacological Modulation of Nitric Oxide Production. Front. Pharmacol. 8: 1-14.*
3. *Cautain et al. (2016). Discovery of a Novel Isothiazolonaphthoquinone-Based Small Molecule Activator of FOXO Nuclear-Cytoplasmic Shuttling. PLoS ONE 11: e0167491.*
4. *de Pedro et al. (2016) Protective Effects of Isolecanoric Acid Neurodegenerative Diseases. Neuropharmacology, 101, 538-548.*
5. *Cautain et al., (2013). HCS Strategy Targeting Dysregulation Of The VHL/HIF Pathway For Drug Discovery. Adv Biosci and Biotechnol, 4: 398-405*

- Key Collaborations: CMerck Sharp & Dohme • CUBIST Pharmaceuticals • MICROBIOPHARM • WarpDrive Bio • Cyclenium Pharma • CrossBeta • DTU Biosustain • SYNBIOCHEM • Natural Products Discovery Institute • CSIC • CNM – Institute of Health Carlos III • Vall d'Hebron Institute of Oncology • CNIO • CNB • University of Granada • Complutense University • IBIS •
- Patents: 5 (ES2433142 A1, 2012; WPO2014/170295 A1., 2013; WO 2015/000825 A1., 2013; WO 2016/128401 A1., 2015; EP11559EP00, 2015)

- Training capacities: EU Innovative Training Networks (ITN) Marie Curie actions; University Granada Master Programs: Regenerative Medicine, Molecular Biology Applied to Biotechnological Bioenterprises, Biotechnology; Mobility European Projects: Leonardo Da Vinci Projects
- Networks: EU-OPENSCREEN; ORPHANET; BEAM ALLIANCE; EUROPEAN BIOTECHNOLOGY NETWORK; SPANISH DRUG DISCOVERY NETWORK; REDEFAR (RED DESCUBRIMIENTO TEMPRANO DE FARMACOS); RICET (RED DE INVESTIGACION COLABORATIVA EN ENFERMEDADES TROPICALES)

THE FUTURE

Future plans: expand core capacities plans to include 1) 3D cell based assays; 2) medicinal chemistry and chemical synthesis capacities.

Added value: Access to a world reference multidisciplinary HTS platform with core expertise in natural products drug discovery , enabling the full integration of discovery programs from the target validation to the preclinical evaluation of early drug candidates.

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