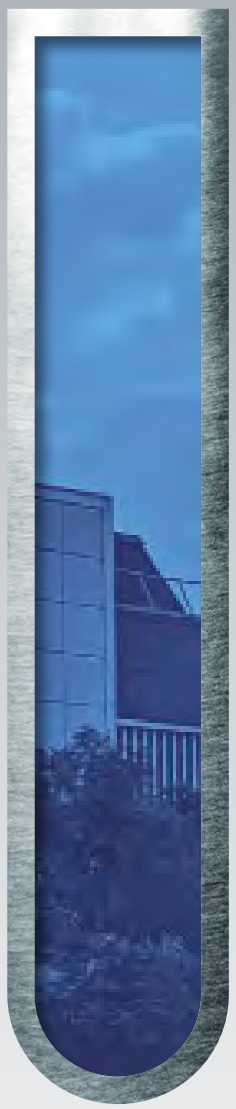
WORLD-CLASS DRUG DISCOVERY EXPERTISE



IRBM
passionate about science

PASSIONATE ABOUT SCIENCE

CONTENTS

MEET IRBM

WE HAVE BEEN INSTRUMENTAL IN THE DISCOVERY OF FOUR DRUGS NOW ON THE MARKET

WE LEVERAGE OUR ACCOMPLISHMENTS IN DRUG DISCOVERY WITH OUR DETERMINATION TO REMAIN AT THE CUTTING EDGE OF RESEARCH TO DELIVER INNOVATION FOR INDUSTRY AND ACADEMIA. AS YOUR PARTNER, WE PROVIDE YOU WITH ROBUST AND CUTTING EDGE SCIENTIFIC EXPERTISE, HONED IN GLOBAL PHARMA, ALONG WITH THE STEADFAST SUPPORT REQUIRED IN A FAST-PACED AND CHALLENGING INDUSTRY.

[WE ARE DRIVEN BY]

PASSION

Science is our cornerstone. Our unprecedented track record in discovering drugs demonstrates this. We capitalize on our shared enthusiasm for innovative R&D, spurred on by our dedication to deliver excellence at every opportunity.

EXPERTISE

Our expertise spans different modalities including small molecule, peptide and biologic therapeutics. With a passionate, interdisciplinary and accomplished team, and capabilities ranging from target validation to clinical candidate nomination, we bring great science to your project.

COLLABORATION

Our partners are of the utmost importance. We always strive to go above and beyond your expectations, treating your projects as our highest priority.

IRBM IN NUMBERS

4
DRUGS ON THE MARKET THAT IRBM HELPED DISCOVER

25+
CLINICAL CANDIDATES DELIVERED, INCLUDING 2 PEPTIDE CANDIDATES

100+
PATENTS ATTRIBUTED TO OUR SCIENTISTS

200+
EXPERIENCED CHEMISTS AND BIOLOGISTS

800+
PUBLICATIONS PRODUCED BY IRBM SCIENTISTS

OUR EXPERTISE COVERS MULTIPLE RESEARCH AREAS, SPANNING DIFFERENT MODALITIES AND THERAPEUTIC AREAS, WITH CAPABILITIES RANGING FROM TARGET VALIDATION THROUGH TO CLINICAL CANDIDATE NOMINATION.

OUR JOURNEY

WE ARE A FORWARD-LOOKING INNOVATIVE RESEARCH ORGANIZATION THAT IS GROUNDED IN GLOBAL PHARMA HERITAGE. OUR DRUG HUNTERS UTILIZE THEIR DECADES OF EXPERIENCE WORKING ON BEST-IN-CLASS PROCESSES.

2023
IRBM selected for participation in the **National Chemical Biology Consortium**

2022
EIB provides €15 million to fund coronavirus research at IRBM

2021
IRBM out licenses **best in class HBV asset**

2020
IRBM **collaborates with MSD** to develop peptides against coronavirus

2019
Our first two non-proprietary peptide drug candidates **enter the clinic**

2016
We develop an **ultrasensitive mutant Huntingtin quantification assay**, which is widely used to detect levels of the mutant protein in samples from Huntington's disease patients

2014
The first non-proprietary small molecule drug developed at IRBM since the reorganization **enters the clinic**

2010
We began trading as an **Independent Research Organization**

2006
Our peptide group is designated **The Merck Peptide Centre of Excellence** for the development of peptide therapeutics

2000
We become a fully owned **Merck Research Laboratory**

1990
We are **established** as a molecular biology institute, a joint venture between Merck & Co. and Sigma Tau

OUR PROVEN TRACK RECORD

OUR CORE TEAM HAS INVENTED MULTIPLE THERAPEUTICS THAT ARE CURRENTLY ON THE MARKET. THESE INCLUDE:

ZEJULA®
The first and only once-daily, oral PARP inhibitor used in the treatment of ovarian cancer

ZOLINZA®
We contributed to the development of this therapeutic which is used in patients with T cell lymphoma

ONCOLOGY

ISENTRESS®
The first-in-class HIV integrase inhibitor

GRAZOPREVIR
This is a component of HCV ZEPATIER® combination therapy

INFECTIOUS DISEASES

THE IRBM WAY

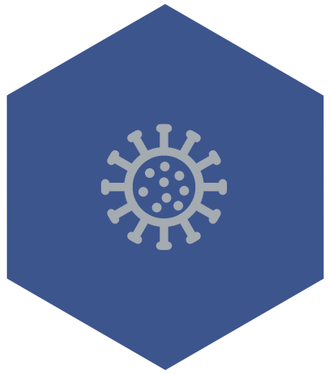
WHAT DRIVES SUCCESSFUL DRUG DISCOVERY? WE BELIEVE THAT CREATING STRONG, LONG-TERM AND HIGHLY COLLABORATIVE PARTNERSHIPS IS KEY IN THIS DYNAMIC FIELD. CENTRAL TO THIS IS OUR FLEXIBLE BUSINESS MODEL THAT CATERS TO OUR PARTNERS' EVOLVING NEEDS.

Whether you need fully integrated support on a project spanning the discovery pipeline or a standalone service, our interdisciplinary team - located under one roof - is here for you. From target validation through to candidate nomination, our passion and expertise help create a seamless approach for drug discovery.

Integrated projects spanning discovery to early stage preclinical development typically use an FTE-based approach. For partners with different business needs, we are also happy to tailor our solutions to your unique projects. Examples of this include addressing smaller projects and standalone services on a fee-for-service basis; adopting risk-sharing R&D contract agreements to share costs; or linking downstream payments to agreed-upon milestones.

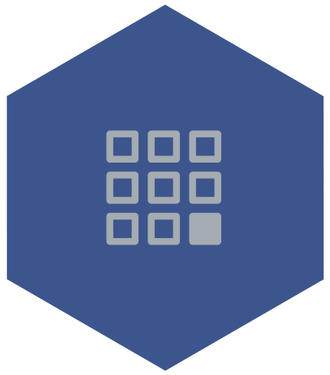
[WE PARTNER WITH]

NEUROSCIENCE



INFECTIOUS DISEASES

ONCOLOGY



RARE AND NEGLECTED DISEASES

THERAPEUTIC AREAS

OUR DEDICATED SCIENTISTS ARE COMMITTED TO FINDING TAILORED PHARMACOTHERAPEUTIC SOLUTIONS FOR A WIDE RANGE OF HIGH-IMPACT DISEASES. WE HAVE ESTABLISHED FOUR DEDICATED THERAPEUTIC UNITS:

NEUROSCIENCE

The gulf between available effective therapies and patient need is increasingly apparent as our understanding of central nervous system (CNS) disorders improves. We have developed specific platforms to support therapeutic discovery and advancement in this complex area:

- Tools to evaluate the molecular effect of protein misfolding for Alzheimer's, Parkinson's and Huntington's disease
- Human iPSC blood brain barrier (BBB) model to evaluate CNS-targeted molecules
- Established and validated methods to detect and modulate toxic protein aggregate conformations, and relevant pathophysiological pathway identification
- Biomarker assays for patient stratification and determination of efficacy

ONCOLOGY

We have significant experience in creating translational Oncology drug research and development has advanced dramatically in recent times, and IRBM is proud to have played its part. Two medicines which we helped to develop are now licensed: ZEJULA®, for ovarian cancer, and ZOLINZA®, for a skin-affecting lymphoma.

At IRBM, we cover the whole range of oncology drug discovery phases from target validation through to candidate nomination and apply a toolbox of assays which include cytokine release, T Cell activation/proliferation, Th polarization, Immuno-checkpoint modulation (SEB-driven T cell Exhaustion), Treg suppression, iTreg differentiation, CD8 T Cells or NK Cells-mediated tumor killing, MDSC (Myeloid-Derived Suppressor Cells) suppression, Macrophage differentiation and polarization (M1/M2).

We are honoured to collaborate with leading oncology focussed organisations such as MD Anderson Cancer Centre, and, to have been selected as a member of the NCI Experimental Program's Chemical Biology Consortium to help address unmet needs in therapeutic oncology.

INFECTIOUS DISEASES

Global healthcare providers need to respond to some of the world's most devastating infectious diseases. Currently, we are faced with the COVID-19 pandemic and our scientists have been contributing to fighting this devastating disease in several areas including a collaboration with MSD to identify and develop novel peptide therapeutics active against different strains of coronavirus, and the manufacture and testing of the Oxford SARS-CoV-2 vaccine known as AZD1222. Over the years, we have made substantial contributions to patient quality of life for other key infectious diseases, through the discovery of the marketed drugs ISENTRESS® and Grazoprevir (ZEPATIER®). Our Infectious Disease Unit continues to develop capabilities in this field and includes:

- Viral replicon high-throughput screening (HTS) assays
- cccDNA assay

RARE AND NEGLECTED DISEASES

We are particularly proud of the work that we have done in rare, neglected and poverty-related diseases. A large part of our work in this field has been as a member of a public/private consortium – The National Consortium and Collection of Chemical Compounds (CNCCS) - identifying compounds acting on innovative biological targets. We have also worked with rare disease foundations including the Grace Foundation in the area of DMD and Autism, and the CHDI Foundation for Huntington's disease. In addition, we have experience in adenoviral vector-based vaccine manufacture for diseases such as Rift Valley Fever, Leishmania and MERS. Our advantages in this area include:

- A unique collection of compounds and screening capabilities
- High sensitivity biomarkers
- Development of Isentress for treatment of HIV
- Development of Zepatieris for treatment of Hepatitis C

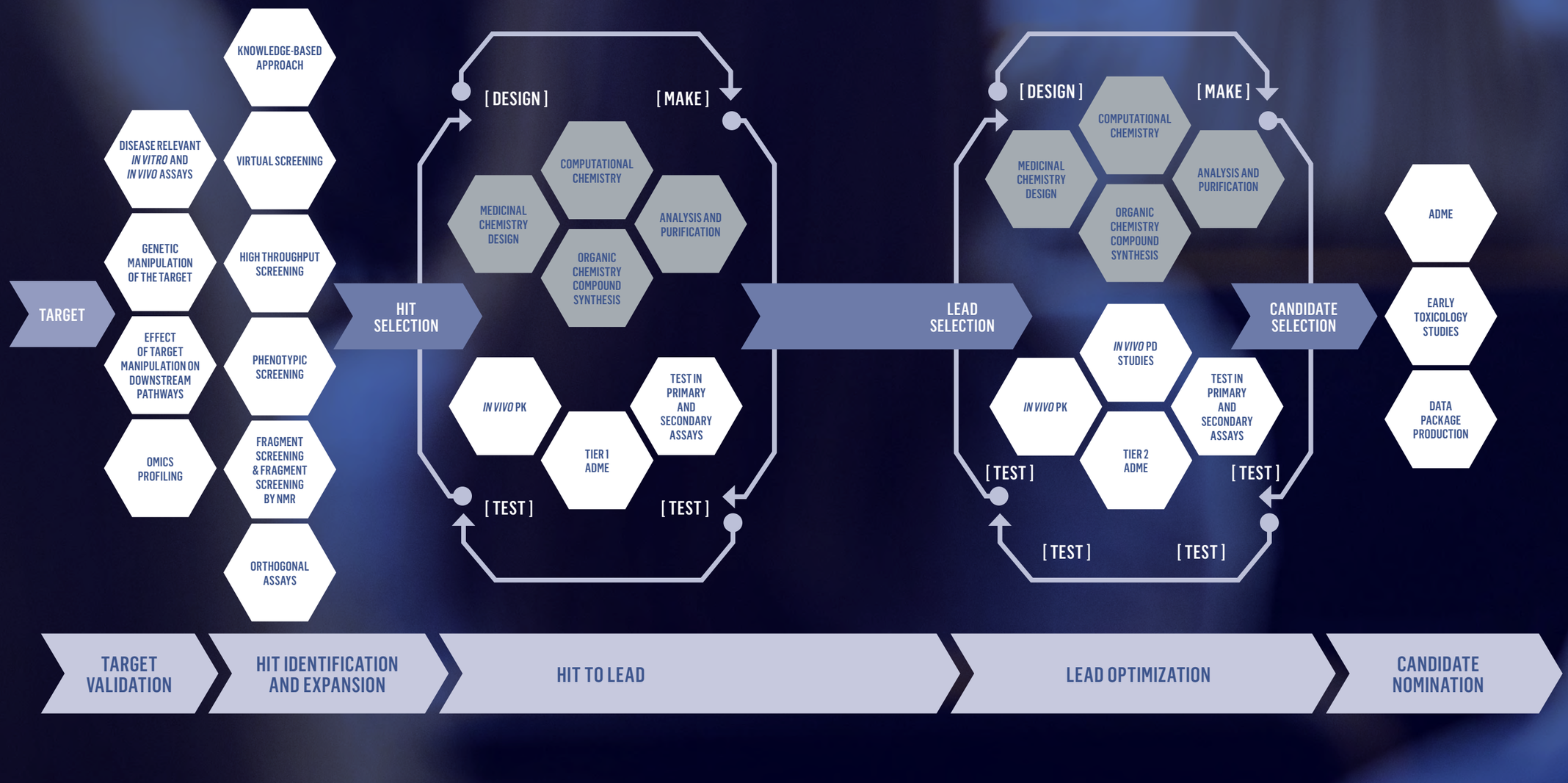
OUR R&D ENGINE

WE USE OUR POWERFUL, INTEGRATED R&D ENGINE TO VALIDATE YOUR TARGET AND IDENTIFY HITS. WE THEN PROGRESS THESE THROUGH A SPECIFICALLY DESIGNED AND EVOLVING SCREENING CASCADE TO GENERATE AND OPTIMIZE LEADS AND FINALLY SELECT A CANDIDATE.

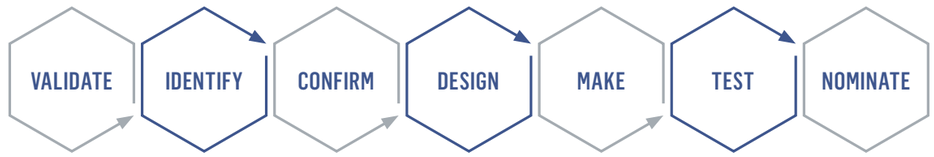
Key to driving each venture forward is an assigned Project Leader with the relevant background and experience. They lead the dynamic team of biologists and chemists working on your project and ensure that you are supported at every step of your drug discovery journey.

At the heart of our R&D engine you will find our state-of-the-art facilities in Pomezia, near Rome, Italy. Discovery projects are carried out under one roof, allowing faster cycle times and facilitating close internal collaboration. In addition to our Small Molecule and Peptide Chemistry, Translational and High-Content Biology departments, we have an automated high-throughput screening unit and a Nuclear Magnetic Resonance (NMR) laboratory. This is as well as our exceptional Absorption, Distribution, Metabolism, and Excretion (ADME) and pharmacokinetic capabilities.

THE RIGHT SCIENTIFIC TEAM SIGNIFICANTLY INCREASES THE CHANCES OF SUCCESSFULLY DISCOVERING AND DEVELOPING HIGH-QUALITY DRUG CANDIDATES



DRUG DISCOVERY



PARTNER WITH US TO HELP PUSH THE BOUNDARIES OF DRUG DISCOVERY IN THIS HIGHLY COMPETITIVE INDUSTRY. OUR INTEGRATED DRUG DISCOVERY SERVICES PROVIDE AN INTERDISCIPLINARY APPROACH THAT IS ROBUST, AGILE AND EFFICIENT.

We combine our passion for innovation and extensive expertise to deliver exceptional services from target validation through to candidate nomination.

TARGET VALIDATION

WE WORK WITH YOU TO DEMONSTRATE THE DISEASE RELEVANCE OF YOUR TARGET AND TO ELUCIDATE ITS DRUGGABLE ATTRIBUTES. APPROACHES WE USE INCLUDE:

- **Genetic manipulation** of the target
- Investigating the consequences of **target manipulation** on downstream pathways
- **Omics profiling** in relevant cell systems
- **In vivo model development** to perform early proof of concept studies
- Identification of appropriate **biomarkers**

HIT IDENTIFICATION AND EXPANSION

WE ARE DEDICATED TO IDENTIFYING HIGH-QUALITY HITS AND HIT SERIES. WE CAN EMPLOY ONE OR MORE HIT FINDING STRATEGIES UTILISING A VARIED RANGE OF ASSAYS INCLUDING BIOCHEMICAL AND CELL BASED. APPROACHES WE USE INCLUDE:

- **High-throughput** screening using our customers' or our own diverse library of over 320,000 compounds
- **Virtual** screening
- **Fragment-based** screening
- **Phenotypic** screening
- **NMR** screening
- **Phage** display

HIT TO LEAD

THE GOAL OF THIS STAGE IS TO SELECT THE MOST PROMISING SERIES THROUGH LIMITED STRUCTURE–ACTIVITY RELATIONSHIP (SAR) STUDIES. APPROACHES WE USE INCLUDE:

- Computational chemistry to **cluster the active hits** into families
- Medicinal chemistry and synthetic chemistry to **design and synthesize new compounds** based on the active hits and their chemotypes
- Implementation of an **efficient screening cascade**, bringing together an interdisciplinary team for **rigorous primary and secondary testing** to assess potency, selectivity, on and off target activity and early ADME

LEAD OPTIMIZATION

HERE WE EXTENSIVELY OPTIMIZE, IN PARALLEL, BOTH THE BIOLOGICAL ACTIVITY AND THE PROPERTIES OF THE LEAD SERIES, AGAIN UTILISING A DEDICATED SCREENING CASCADE BUT WITH A BROADER SUITE OF ASSAYS AND SCREENS AND CLEAR GO/NO GO DECISIONS. APPROACHES WE USE INCLUDE:

- **Multi-parametric optimization** of promising series
- Primary and secondary screenings to **assess potency and selectivity** both in enzymatic and cell based assays
- Medicinal chemistry SAR, design, synthesis and **optimization of the lead series**
- Pharmacokinetic (PK) and Pharmacokinetic / Pharmacodynamic (PK/PD) animal studies, including **metabolite ID**
- *In vitro* and *in vivo* **assessment of metabolism and off-target activities**
- An *in vitro* blood-brain barrier model generated from human induced pluripotent stem cells to **predict brain penetration**
- NMR support for **structural biology evaluations** (structural characterization, aggregation state, target/ligand interaction)
- **Metabolomics and biomarker ID** in animal and human biofluids
- **Formulation support**
- **Scale-up synthesis** for small molecule compounds (up to 1kg scale)
- Chemistry support and route scouting for **synthesis optimization**
- **Separation of chiral compounds** at the preparative scale
- Crystalline **salt selection**
- Parallel and **rapid analog synthesis** supported by automated purification systems

CANDIDATE NOMINATION

IN THIS PHASE WE CHARACTERIZE THE MOST PROMISING LEADS FROM THE LEAD OPTIMIZATION PHASE WITH THE AIM OF PRODUCING A DATA PACKAGE READY TO SUBMIT FOR INVESTIGATIONAL NEW DRUG (IND). APPROACHES WE USE INCLUDE:

- **Full characterization of compounds** for promotion to development
- **Focused ADME** around a specific dosage form
- **Early toxicity** studies including genotoxicity and carcinogenicity

DISPLAY TECHNOLOGIES

WE CAN SCREEN PROPRIETARY PHAGE LIBRARIES DISPLAYING:

PEPTIDE
Complexity: 1 x 10^9)

ANTIBODY LIBRARIES
(complexity: 5 x 10^{10})

We can also design and generate **custom libraries** that are best suited for the target of interest.

In the field of macromolecule discovery, the **possibility to explore combinations** of amino acid and/or binding determinants by rational design is often hampered by the lack of previous knowledge or by limitation in synthetic technologies.

The availability of the above mentioned libraries and the generation of target-specific libraries allows the identification of hit molecules to be further developed as **therapeutics, diagnostics or tools for biology discovery.** We can apply display technologies to the discovery of biologically relevant compounds, such as:

Identification of peptides with improved receptor affinity for therapeutics development in IP free areas

Identification of **peptides** with improved target affinity for PPI disruption for further development (e.g. through peptidomimetic approaches)

Identification of **antibodies** for use in immuno-oncology.

The interplay between molecular biology, display technologies, testing and synthetic biology is key for the discovery of novel entities able to open innovative avenues toward **unprecedented therapeutic** approaches. At IRBM, we offer all these **capabilities available under one roof.**

PHAGE DISPLAY TECHNOLOGY

PROPRIETARY M13 PHAGE DISPLAY LIBRARIES FOR BIOLOGICS DISCOVERY PROGRAMS:

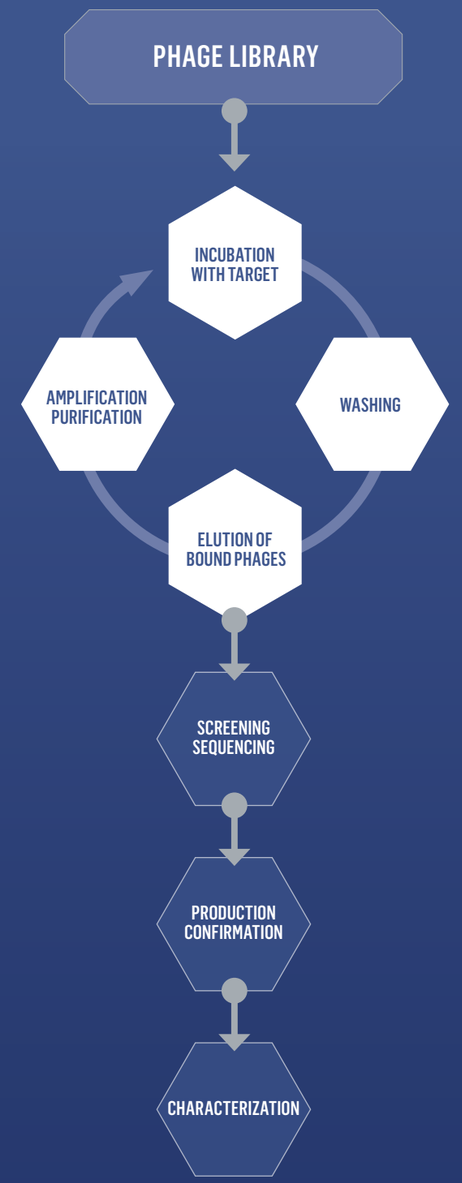
- Linear dodecamers
- Loop-constrained dodecamers and ninemers
- CDR3-based dodecamers
- Antibodies
- Custom-built phage display libraries

SCREENING

- Lead identification on phage display library
- Selection on recombinant proteins/ target-expressing cell lines
- Screening by binding/activity assays
- Specific activity assay development

CLONE CHARACTERIZATION

- Peptide synthesis
- Sequence analysis
- Antibody, antibody-like fragments production
- Biochemical characterization
  - ELISA, Western Blot , FACS, IF, IHC
  - Binding kinetics by SPR or BLI
  - Activity assays
  - Pharmacokinetic assays



ANTIBODY DISCOVERY

PHAGE DISPLAY SINGLE CHAIN ANTIBODY LIBRARY RAPIDLY DELIVERS HUMAN ANTIBODY HITS AND PROVIDES THERAPEUTIC LEADS FASTER THAN ANY OTHER METHOD

IRBM Antibody Library (IAL) is a f**ully human** phage display library comprised of over 50 billion unique fully human antibodies, with the diversity and design to deliver therapeutic leads against all types of antigen, including difficult targets.

IAL is a fully human **single chain fragment variable (scFv) display** library of high complexity (> 5x1010) and with more than 90% of clones correctly expressing the scFv variants. The library was designed to include diversity into the H-CDR3 and variations were carefully selected among those comprised in the human natural immune repertoire. The frameworks have been chosen among those most common in the human population to ensure ease of production in terms of expression levels, thermal stability and aggregation state. The fully human design and the absence of somatic mutations in the chosen frameworks act as safeguard for ensuring non-immunogenicity.

In addition to H-CDR3 that represents the primary interaction site with the target, variations in other H-CDRs, as well as L-CDRs, play a crucial role in determining the overall affinity of an antibody. The IRBM **Affinity Maturation Library** (IAML) includes variations naturally occurring in the H- and L-CDRs of the germlines defining the scFv scaffold of IAL to generate human antibody sequences that represent fully human affinity-matured versions of each variant selected from the naive IAL.

FROM PHAGES TO ANTIBODIES

Selection and **screening strategy** based on the specific project requirement

- Recombinant proteins, on cells, in vivo
- Screening by single clone analysis
  - automated process for analyzing thousands of individual phage clones
- **HTP IgG conversion, production and specificity**
- **Affinity maturation**

ANTIBODY CHARACTERIZATION AND DEVELOPMENT

- Binding kinetics parameters by SPR or BLI
- Epitope mapping
- Epitope binning
- Binding and affinity on target cells: Cell-Based ELISA, FACS analysis, IF
- Cell-based functional assays: internalization by FACS or IF, ADC, ADCC, CDC, cell toxicity, receptor agonism/ antagonism
- Tissue specificity by IHC
- *In vivo* studies: MTD, efficacy in Xenograft models, IHC

PEPTIDE DISCOVERY

IRBM IS ONE OF THE LEADING EXPERTS IN THE FIELD OF PEPTIDE THERAPEUTIC DISCOVERY, STEMMING FROM OUR HERITAGE AS THE MERCK "PEPTIDE CENTRE OF EXCELLENCE". OUR EXPERIENCE SPANS THE ENTIRE PROCESS OF PEPTIDE DRUG DISCOVERY AND EARLY DEVELOPMENT, FROM THE SYNTHESIS OF PUTATIVE PEPTIDE LEADS TO THE DELIVERY OF A PRECLINICAL CANDIDATE. WE HAVE DEVELOPED MULTIPLE DRUG CANDIDATES, INCLUDING MACROCYCLES INCORPORATING MULTIPLE CONSTRAINTS AND PEPTIDES CONJUGATED TO FATTY ACIDS, CHOLESTEROL AND POLYMERS.

PEPTIDE DRUGS

We have a proven track record in the clinic with ten patent applications and two clinical candidates approved since 2010, one of which entered the clinic in 2019.

An integrated platform of multidisciplinary expertise underlies our peptide discovery efforts. Critical tools include our phage display libraries, structural studies through NMR and the bioanalysis of peptides for *in vivo* studies supported by state-of-the-art mass spectrometry instrumentation.

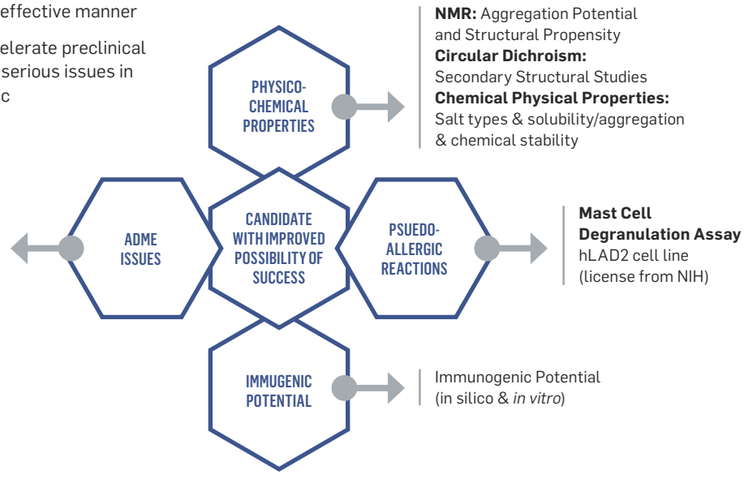
WE SUPPORT YOUR PEPTIDE PROJECTS WITH:

- Multi-parametric optimization for activity, efficacy and selectivity
- Optimization of ADME properties
- Identification of metabolites
- Aggregation/oligomerization studies
- Studies for pseudo-allergic reactions due to mast cell activation and histamine release
- Immunogenicity assessments

PEPTIDE DISCOVERY STRATEGY

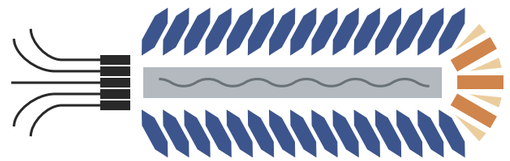
AN INTEGRATED PLATFORM TO SUPPORT PEPTIDE DISCOVERY WITH INCREASED POSSIBILITY OF SUCCESS.

- An appropriate screening funnel essential to drive peptide discovery in a time and cost-effective manner
- Addressing specific issues helps accelerate preclinical development, preventing potentially serious issues in higher animal species and in the clinic



PHAGE DISPLAY

Phage display is a powerful tool that can be used to select binding partners from complex libraries. This technology takes advantage of the direct link between phage-displayed peptides or proteins and the nucleic acids that encode them. Building on over 20 years of established expertise in the field, we can advance your project using our in-house peptide and antibody libraries, or build custom libraries that suit the unique needs of your project.



OUR TOOLKIT INCLUDES:

- In-house libraries:
  - **Linear** and **Cys-constrained random peptide libraries** in M13 pVIII- and pIII-display formats
  - **Linear** and **Cys-constrained conformational HC-CDR3-based peptide libraries** in M13 pVIII- and pIII-display formats
- **Selection** and **screening design** based on specific project requirements:
  - Recombinant proteins, on/in cells, *in vivo*
  - Screening by single clone analysis and/or next-generation sequencing (NGS)
  - Binding and/or functional assays
- **Peptide synthesis** and characterization of **affinity, specificity and activity**
- Chemical SAR and modification to gain ***in vivo* stability**
- **Drug metabolism and pharmacokinetics (DMPK)** and ***in vivo*** studies

DISCOVERY AND TRANSLATIONAL BIOLOGY

IDENTIFYING STRONG AND MEANINGFUL CONNECTIONS BETWEEN DRUG TARGETS AND PHENOTYPES IS THE FOUNDATION OF A SUCCESSFUL DRUG DISCOVERY PROGRAM. OUR DISCOVERY PROGRAMS FOCUS ON UNDERSTANDING THE UNDERLYING BIOLOGY, GIVING US KEY INSIGHTS INTO MOLECULAR MECHANISMS. START YOUR JOURNEY WITH IRBM USING OUR THREE-STEP APPROACH:

1. DEFINE

2. DESIGN

3. DECIPHER

1. DEFINE YOUR PROJECT'S CHALLENGES

We work collaboratively with customers in co-creating a clear definition of project goals, decision criteria and timings after considering some or all of the following parameters:

- Cell model/target definition and identity check using genome-wide association study (GWAS) and omics
- Phenotypic, on-target and off-target knowledge using genome editing and pharmacogenomics
- Screening cascade and target product profile

2. DESIGN THE BIOLOGICAL TOOLKIT THAT WILL ENABLE YOUR SUCCESS

- Target-based readouts such as strategies for targeted modes of action, specificity and selectivity
- Target engagement in cells and pharmacodynamic assays such as reporter-based and orthogonal assays
- Cell interrogation via phenotypic/functional readout using primary cells, induced pluripotent stem cells (iPSC) and embryonic stem cells (ESCs)
- *In vivo* readouts such as transcriptional profiling, circulating protein biomarkers and efficacy endpoints

3. DECIPHER ALL RESULTS

Gain the momentum required for success through the identification of key molecular interactions and networks, together with the establishment of criteria for target engagement and disease-relevant inclusion criteria.

HIGH-THROUGHPUT BIOLOGY AND SCREENING

WE COMBINE COMPOUND LIBRARIES AND BIOLOGICALLY RELEVANT ASSAYS TO IDENTIFY THE MOST PROMISING HIT MOLECULES FOR FUTURE OPTIMIZATION. WE MAXIMIZE THE PROBABILITY OF YOUR SUCCESS THROUGH OUR:

COMPOUND COLLECTION

Our screening libraries of small molecules, peptides and antibodies focus heavily on diversity and quality. We have a highly curated small molecule collection of over 320,000 compounds with focused sub-collections which include:

- Post-Translational Modification (PTM) and Kinase subsets
- Safe-in-Man subset
- RNA binding subset
- Cancer compound subset
- Natural product subset
- Fragment-Based Lead Discovery (FBLD) collection
- Brain penetrant compounds

In addition, we have peptide and antibody libraries that we can screen using phage display. Our team, who have over two decades of experience in this field, can also build custom libraries for the target of interest.

ROBUST ASSAYS

We develop and optimize assays tailored to your project's evolving needs. These include biochemical (enzymatic and binding assays), cellular (reporter-based, target-engagement, functional/phenotypic, disease-relevant cells) and biophysical assays.

HIGH-CONTENT BIOLOGY AND SCREENING

WE APPLY HIGH-CONTENT BIOLOGY ACROSS THE DRUG DISCOVERY AND EARLY DEVELOPMENT PIPELINE. WITH THIS WE CAN EVALUATE DRUG EFFICIENCY IN RELEVANT CELL MODELS, INVESTIGATE DRUG-DRUG INTERACTIONS, SELECT COMPOUNDS FOR ANIMAL STUDIES AND PREDICT HUMAN *IN VIVO* PROPERTIES.

WE OFFER:

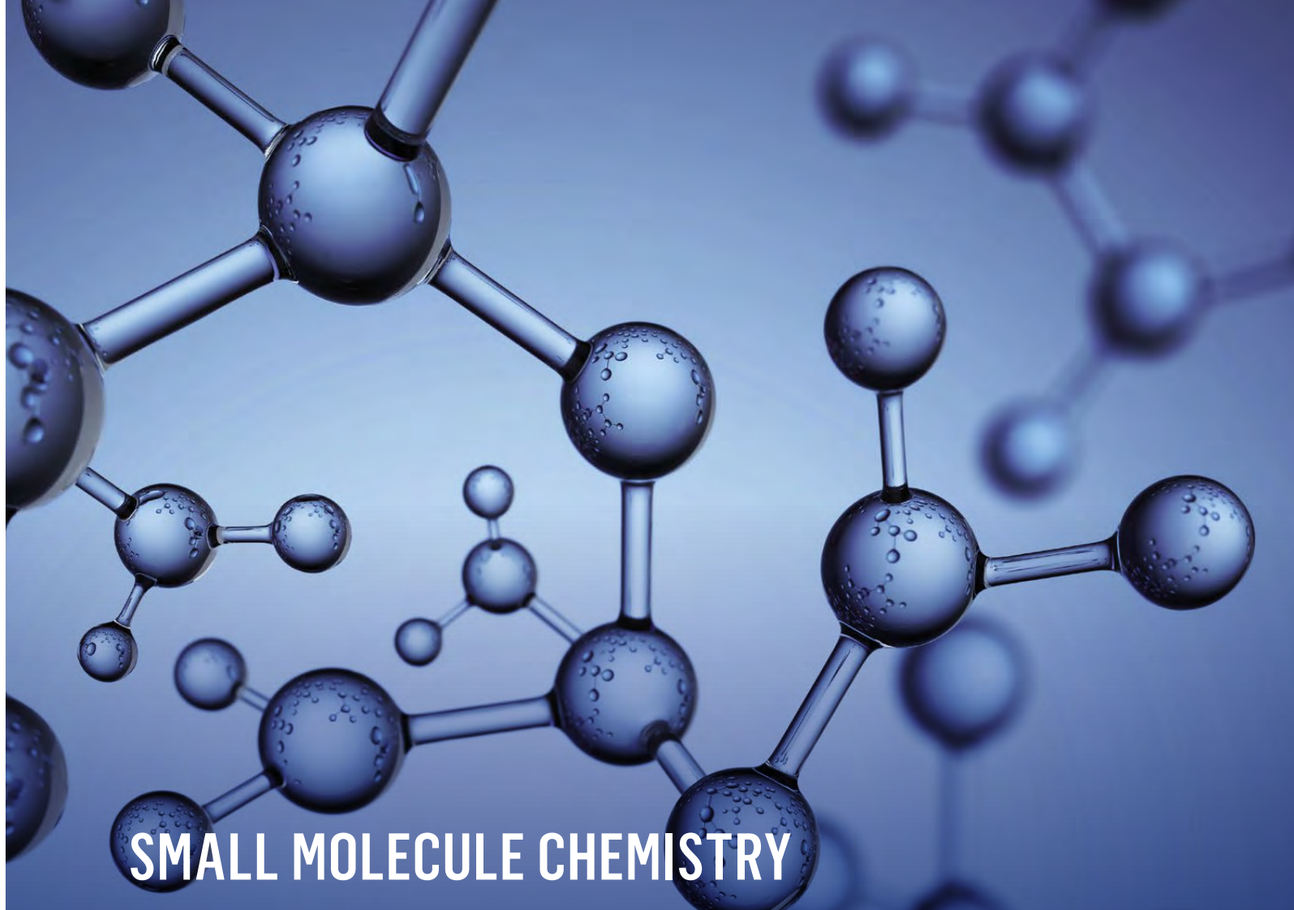
- Primary compound screening
- Qualitative secondary assays evaluating structure-activity relationships
- Early evaluation of toxicity potential
- Multi-dimensional drug profiling

WE CAN EVALUATE THESE PARAMETERS USING:

- Stem cells and neuronal cultures by utilizing IRBM's *in vitro* Blood-Brain Barrier Model
- Quantitative high-content, high-throughput assays - based on multiplexing and imaging readouts. Our experience with automated fluorescence microscopy spans more than two decades, and we can use additional state-of-the-art technologies such as:
  - ▸ Confocal automated microscopy for screening
  - ▸ Live cell acquisition
  - ▸ Real-time injection of modulators for fast kinetic readout
  - ▸ Image analysis and multivariate set mining

THE IRBM *IN VITRO* BLOOD-BRAIN BARRIER (BBB) MODEL

Comprehensively understanding the BBB is particularly critical for the discovery and development of a central nervous system (CNS) targeted drug. We investigate the BBB permeation of new compounds with our physiologically relevant human BBB screen. The model is based on endothelial cells derived from human iPSCs, has been validated with different pharmacological classes of molecules that vary in size and, more importantly, use various mechanisms of brain entry.



SMALL MOLECULE CHEMISTRY

OUR UNPRECEDENTED TRACK RECORD IN SUCCESSFULLY EXECUTING MEDICINAL CHEMISTRY PROGRAMS MEANS YOU CAN BE SURE THAT YOUR PROJECTS ARE IN SAFE HANDS - AND THAT OUR FOCUS WILL BE ON ANSWERING THE KEY QUESTIONS NEEDED TO ADVANCE YOUR SCIENCE, SWIFTLY AND COST EFFECTIVELY.

Our in-house capabilities provide all the tools needed to drive efficient design-synthesis-testing cycles. Through a flexible and results-oriented approach, we aim to maximize results and minimize the generation of superfluous compounds and studies.

MEDICINAL CHEMISTRY

Our medicinal chemistry team has a vast publication record with some of the leading peer-reviewed journals.

SYNTHETIC CHEMISTRY

Our industry-honed synthetic chemistry skills provide the foundation for all of our medicinal chemistry work. We utilize our state-of-the-art infrastructure and practical expertise to implement “fit-for-purpose” solutions. On a practical level, our synthesis-purification-analysis workflows are tailored to streamline productivity, helping our chemists realize their enthusiasm and creativity on your drug discovery project.

COMPUTATIONAL CHEMISTRY

Our full range of ligand- and structure-based approaches can either support your integrated project or provide independent in silico services. We also use our proven cheminformatics expertise to produce tailored models for physicochemical descriptors and Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) parameter predictions, reagent selection for chemistry libraries and generation of virtual libraries.

COMPOUND COLLECTIONS AND ANALYSIS

IRBM's diverse library of over 320,000 high-quality compounds has been curated to focus on structural diversity and molecular properties. We are dedicated to minimizing the number of reactive, promiscuous or undesirable compounds. The library can be used in a range of challenging screening campaigns, including protein-protein interactions, phosphatases and cell-based phenotypic screens.

ADME/DMPK

BEHIND EVERY EFFECTIVE AND SAFE DRUG CANDIDATE LIES A COMPREHENSIVE UNDERSTANDING OF ITS DRUG METABOLISM AND PHARMACOKINETICS (DMPK). EVALUATING KEY PROPERTIES OF A POTENTIAL THERAPEUTIC, SUCH AS ITS ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (ADME), IS CRITICAL TO THE ADVANCEMENT OF COMPOUNDS ALONG THE DRUG DISCOVERY CONTINUUM.

We customize the screening cascade for each chemical series, avoiding "box ticking" but ensuring a smooth transition to *in vivo* studies in preclinical species. Physicochemical properties are evaluated using kinetic solubility, log D and parallel artificial membrane permeability assay (PAMPA) assays. Once this is complete, and accounting for the chemical structure of drug candidates, stability assays are established. Initial stability testing is conducted using SGF (simulated gastric fluid), SIF (simulated intestinal fluid), plasma, and blood. Metabolic stability is assessed using microsomes from selected species or other subcellular fractions, if appropriate.

For profiling radiolabeled metabolites in different tissues, we use ultra-high performance liquid-chromatography coupled to high resolution mass spectroscopy (HRMS) and fast fraction collection (FC) (≤ 1 s/fraction) followed by microplate scintillation counting (MSC). Distribution assays such as plasma protein binding (PPB), binding to microsomes or tissue homogenates and blood/plasma partition are also available, with a variety of protocols for different throughputs.

IN VIVO PHARMACOLOGY

OUR PK STUDIES ARE FAST AND REPRODUCIBLE. WE USE AUTOMATED SAMPLE PREPARATION TAKEN DIRECTLY FROM THE BIOFLUID COLLECTION TUBE TO AVOID TUBE TRANSFER. ALL OPERATIONS, FROM DESIGN TO REPORTING, ARE COORDINATED BY WATSON LIMS.

We set up "dilute-and-shoot" methods that enable quick analysis of very small volumes of plasma (5 µL) to obtain pharmacokinetics parameters, together with metabolite identification. The turnaround time for a PK study can be as quick as a week from beginning to end and we can conduct PK studies in mice and rats using micro sampling and micro dosing.

All major routes of administration can be assessed in our PK studies. Automatic blood sampling (AccuSampler®) in freely moving laboratory rats is routinely employed. Samples can be collected for metabolite profiling and mass balance. Distribution of compounds is studied using cold or radiolabeled material and the team is extremely experienced in analysing tissue distribution to organs and tumors.

STRUCTURAL BIOLOGY AND VIRTUAL SCREENING

OUR PASSION FOR SCIENCE DRIVES INNOVATION IN...

VIRTUAL SCREENING

Our structure- and ligand-based virtual screening can optimize your workflow to maximize your project's efficiency. Moreover, we provide an automated benchmark assessment to select the best structure-based docking procedures. Statistical and graphical analysis of your results is also available through our extended integration of commercial/open-source software.

NMR

NMR spectroscopy is a powerful tool in drug discovery. We utilize several 600 MHz Avance Bruker spectrometers to support your project with:

- Structural, purity and stability checks
- Aggregation state analysis
- Determination of macromolecule 3D structure
- Protein/ligand interaction studies
- Chemical shift mapping
- Saturation-transfer difference (STD)
- 2D or 3D triple-resonance NMR

Our NMR team has perfected the use of this technology across a range of applications. We can study the 3D structure of biomolecules ranging from small peptides to large proteins and protein complexes. Moreover, we use structure-activity relationship analysis and Fragment-Based Drug Discovery (FBDD) to identify and develop hits in the early phases of drug discovery.

BIOMARKER IDENTIFICATION AND DEVELOPMENT

THE EARLY GENERATION AND VALIDATION OF A BIOMARKER ASSAY DURING THE DEVELOPMENT OF A PHARMACEUTICAL PRODUCT HAS PROVEN TO BE INSTRUMENTAL IN REDUCING ATTRITION RATES.

We develop and validate biomarker assays according to FDA/EMA guidelines in order to minimize the technical variability and ensure maximal reproducibility. To ensure that we include a wide variety of biomarker molecules, we employ different technologies for detection including:

- Mass spectrometry for high-sensitivity metabolite detection
- NMR for metabolite profiling as a biomarker technique
- Immunoassays for protein and biologics detection (including anti-drug antibodies)

One of our strengths is the development and validation of assays for the detection of low abundance protein biomarkers. We have developed immunoassays by using ultrasensitive platforms like SMC (formerly Singulex, now SMCxPRO), Quanterix and MesoScale Discovery. In addition, we have experience in running several aspects of an assay to GCP/GLP compliance:

- Production, qualification and handling of in-house produced reagents (e.g. standard proteins and derivatized antibodies)
- Fully electronic traceability of samples and data analysis
- Stand Operating Procedure (SOP) regulated environment

We carry out the following tests according to validation guidelines, which are then provided in the form of a validation report:

- Performance of the standard curve
- Accuracy and precision
- Stability
- Linearity
- Parallelism
- Spike recovery
- Selectivity and specificity
- Reproducibility

THE IRBM GROUP

**OUR EXTENSIVE RANGE OF CAPABILITIES GOES BEYOND OUR PARENT COMPANY.
WE HAVE TWO SUBSIDIARIES THAT ARE PART OF OUR IRBM FAMILY.**

1

ADVAXIA BIOLOGICS

Fully owned by IRBM, ADVAXIA is a cGMP Contract Development and Manufacturing Organization geared towards the production of novel investigational biologics, such as adenovirus-based vaccines and gene therapy products. The facility is fully GMP accredited by regulatory authorities (AIFA). ADVAXIA's mission is to maximize quality and cost effectiveness of clinical lot production and testing on behalf of its customers. This is achieved by the outstanding scientific support the team can provide in such areas as analytical method development, process development/validation, in-process assay release setup and qualification, and cell banking.

2

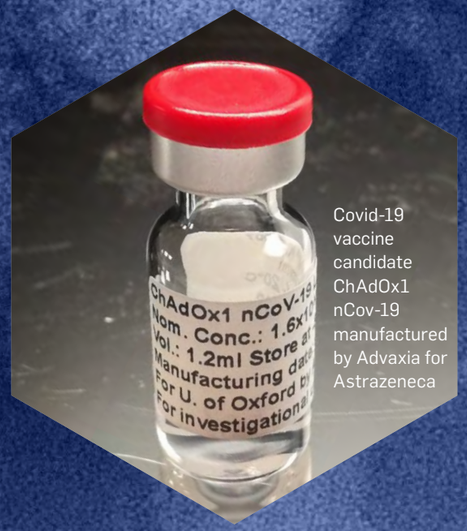
CNCCS

The National Collection of Chemical Compounds and Screening Center is a public-private consortium created in 2010 by IRBM in collaboration with the Italian National Research Council (CNR) and the Italian National Institute of Health (ISS). It acts as a "lead factory", identifying compounds acting on innovative biological targets in addition to being a center for translational research in the areas of rare, neglected and poverty-related diseases. IRBM's activities for the consortium include creating and managing chemical collections containing hundreds of thousands of compounds, and designing and performing high-throughput screening assays.

ADVAXIA BIOLOGICS

ADVAXIA BIOLOGICS IS A CGMP CONTRACT DEVELOPMENT AND MANUFACTURING ORGANIZATION THAT IS DEDICATED TO THE PRODUCTION OF BIOLOGICAL CLINICAL LOTS. THE FACILITY HAS BEEN GRANTED THE AUTHORIZATION TO PRODUCE INVESTIGATIONAL MEDICINAL PRODUCTS BY THE ITALIAN NATIONAL REGULATORY AUTHORITY (AIFA) AND IT COMPLIES WITH THE REGULATORY GUIDELINES OF BOTH THE FDA AND EMA. THE SITE IS CURRENTLY FOCUSING ON ADENOVIRUS-BASED VIRAL VECTORS, FOR VACCINE AND GENE THERAPY APPLICATIONS.

Since our establishment in 2012, we have worked closely with authorities and government entities spanning the globe. We have significant experience in preparing regulatory dossiers, having prepared dossiers for over 50 products. Our track record is unprecedented, with 100% of our clinical lots successfully released due to our robust GMP quality system and experienced team.



Covid-19 vaccine candidate ChAdOx1 nCov-19 manufactured by Advaxia for Astrazeneca

cGMP MANUFACTURING

We are fully GMP compliant to ensure that there are no contaminants and that the purity level of the vaccine is the highest possible. Our stringent strategies include plant and facility design, selection of the appropriate equipment, maintenance and re-validation plans, and the accurate selection of raw materials. Moreover, we maintain a continuous improvement policy to better comply with current regulatory guidance on products and operations.

ANALYTICAL DEVELOPMENT

We combine a skilled team and state-of-the-art facilities to design fast and reliable analytical methods. Our breadth of capabilities include characterization, identification, safety testing, impurities, potency, stability and cell and molecular biology assays. The analytical development team works hand in hand with the process development team, in order to proceed quickly from a pre-GMP phase to the production of clinical batches in the GMP environment.

QUALITY ASSURANCE

Medicines need to meet the requirements of authorized quality standards. Quality assurance plays an important role in achieving this aim. Our team has developed detailed protocols and practices designed to improve and streamline the process of quality assurance, while maintaining transparency and complying with all regulatory guidelines from major agencies such as the EMA, AIFA and the FDA.

EXPRESSION SYSTEMS

We have extensive experience in the generation of high-quality research materials such as cell lines, pre-GMP virus seed stocks and research batches. This includes the development of different mammalian expression systems, starting from the gene of interest. Moreover, we are proficient in using many different adenoviral vectors from human and non-human sources to generate prophylactic and therapeutic vaccines for Phase I and II clinical studies.

QUALITY CONTROL

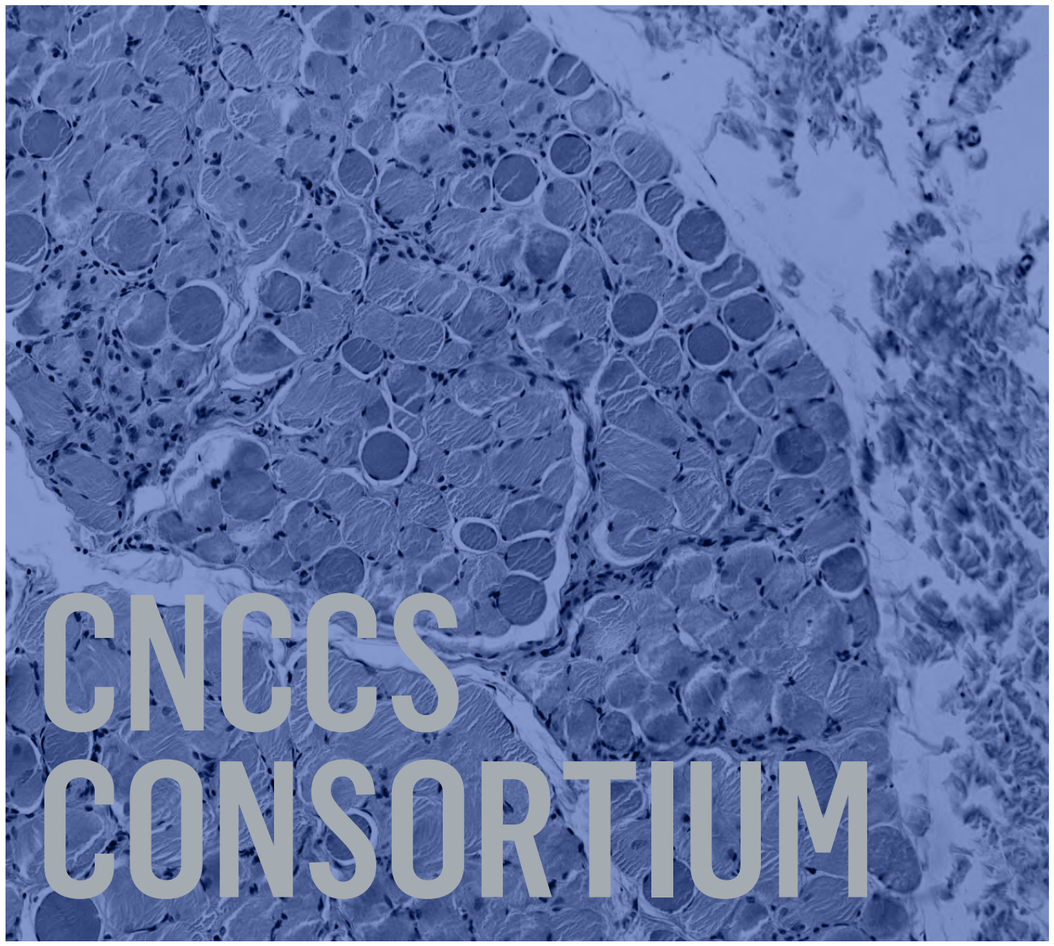
Vaccines must adhere to stringent quality standards. To ensure compliance, quality control is a crucial facet of the work we do at ADVAXIA. A dedicated quality control team supports production and covers important areas that include environmental monitoring, trend analysis, raw materials management, in-process control sample analysis and finished product analysis, to name just a few.

PROCESS DEVELOPMENT

We have designed and developed robust and reproducible processes required for safe adenoviral vector delivery. Every step has been analyzed to ensure a high level of quality and safety for vaccine production, as requested by GMP regulations. The steps have then been translated into Standard Operating Procedures (SOP), tested and refined to improve the overall process yield. A particular effort has been made to ensure these procedures maintain the highest quality level, guaranteed by continuously trained production staff and by an extensive in-process and release test matrix.

REGULATORY SUPPORT

In order to ensure that our clients can confidently use their products in clinical trials, we provide regulatory support and expertise for the submission and maintenance of regulatory filings. We can assist you with compiling the Investigational Medicinal Product Dossier (IMPD), Investigator's Brochure and CMC section of the Investigational New Drug (IND) application.



WE ARE PROUD OF THE VITAL WORK THAT WE UNDERTAKE AS A MEMBER OF THE PRIVATE-PUBLIC NATIONAL CONSORTIUM AND COLLECTION OF CHEMICAL COMPOUNDS (CNCCS). THIS ORGANIZATION ENDEAVORS TO IDENTIFY COMPOUNDS ACTING ON INNOVATIVE BIOLOGICAL TARGETS AS A "LEAD FACTORY". MOREOVER, IT FORMS PART OF AN INTERNATIONAL NETWORK FOR TRANSLATIONAL RESEARCH INTO RARE, NEGLECTED AND POVERTY-RELATED DISEASES.

The consortium aims to make a significant contribution to the research of such diseases. It does this through engaging and collaborating with leading international partners to encourage the development of new approaches to diagnosis and treatment. Furthermore, it seeks to identify risk, evaluate disease severity and affect clinical outcome.

As a core facility within this organization, we provide a state-of-the-art central repository for organic compounds. Our key contributing activities include creating and managing chemical collections containing hundreds of thousands of compounds, and designing and performing high-throughput screening assays.

We partner with the Italian National Research Centre (CNR) and National Institute of Health (ISS) in this consortium. CNR is one of the largest public research organizations in Italy, as a principal center of excellence in biomedical research. ISS is the leading technical-scientific body of the Italian National Health Service, and performs public health research, trials, control, counseling, documentation and training.

The CNCCS successfully unites the public and private sectors, along with investors and stakeholders, to maximize the unique collection of compounds and screening capabilities.

NOTES

passionate about science

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