NUVISAN

INTEGRATED THERAPEUTIC SOLUTIONS

Innovative Oncology R&D programs

Oncology services from target discovery to the clinic

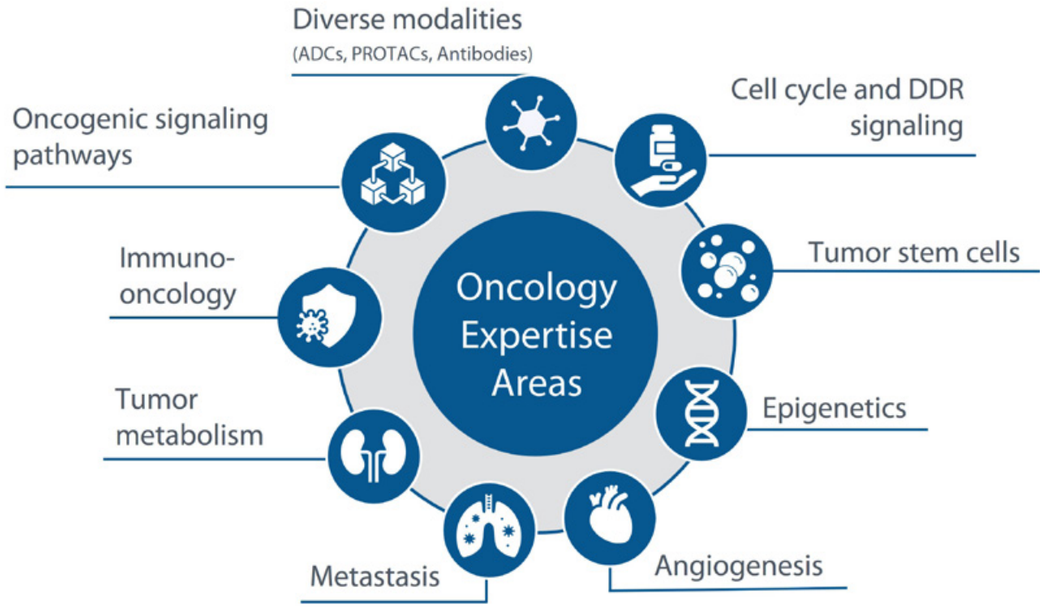
Cancer is the second leading cause of death globally after cardiovascular diseases. The cancer burden continues to grow, exerting tremendous physical, emotional, and financial strain on individuals, families, communities, and health systems. Developing new and effective therapeutic approaches for this diverse and complex disease remains a challenge.

At NUVISAN, our oncology team of specialists offers high quality pharmacology services from pre-clinical and translational science to clinical development to help our customers.

Through our long-standing industry experience with different drug targets and modalities, we know how to establish and implement novel target-specific mechanistic cellular and *in vivo* assays. Building on our existing repertoire of different models, we can deeply explore the biology of drug development programs to unravel molecular drivers of efficacy.

Our team will work closely with you to support, design, and deliver pharmacology studies which will be tailored to your specific needs.

ONCOLOGY SERVICES AT **NUVISAN**



Integrated oncology services covering the entire drug discovery and development value chain to Phase 2 from target discovery & validation, robust assay development for *in vitro* and *in vivo* characterization, in-depth biology exploration to support positioning into a specific disease, biomarker exploration and analysis of clinical samples, drug metabolism and pharmacokinetics, toxicology, GMP API synthesis, and Phase 1 clinical studies in healthy volunteers.

- Holistic assessment and validation of targets to enable data-driven decisions, including tailored model generation and target deconvolution studies
- Development of project-tailored novel cellular mechanistic assays or tumor models
- Support of drug discovery programs by generating data on on-target activity *in vitro* to proof-of-principle experiments *in vivo*
- Identification and validation of pharmacodynamic and predictive biomarkers through combined *in silico*, *in vitro*, and *in vivo* studies
- *In vivo* PK / PD studies correlating drug exposure to efficacy (e.g. identification of PK-driver of efficacy, biologically active dose range) for mechanistic modeling being the basis for dose selection for toxicological studies & human dose prediction
- Biomarker studies (*in vitro*, *in vivo* and *ex vivo*) correlating PK-PD relationship, with PD biomarker modulation for the identification of corresponding PD biomarker for clinical development
- *In-house* biobank of human normal and cancer tissues to support profiling of the drug target or predictive biomarker expression using clinically relevant assays
- DMPK compound profiling during discovery
- DMPK lead compound characterization towards IND and beyond according to the ICH S6 or ICH M3 guidelines
- *In vitro* and *in vivo* GLP toxicology
- Small GMP API batch synthesis
- Phase 1 clinical studies in healthy volunteers for oncology compounds that are not directly genotoxic

OUR ONCOLOGY SERVICES AT A GLANCE

Experienced scientists and staff with decade-long pharmaceutical industry background

Extensive knowledge in a wide range of oncology areas and modalities

Proven track record of successfully translating drug discovery programs into the clinic

State-of-the-art *in vitro* and *in vivo* facilities fully equipped to support all aspects of drug discovery and development

Platforms and capabilities:

- Comprehensive cancer model collection
- Target validation
- CRISPR / Cas9
- Customized model and assay generation
- Gene & protein expression
- Histology / IHC / RNAscope™
- NGS / Single cell sequencing
- Multiplex flow cytometry
- *In vivo* facility: tolerability, exposure, DMPK, efficacy, PK/PD & biomarker studies
- Small animal imaging and radiation capabilities
- Tissue biobank

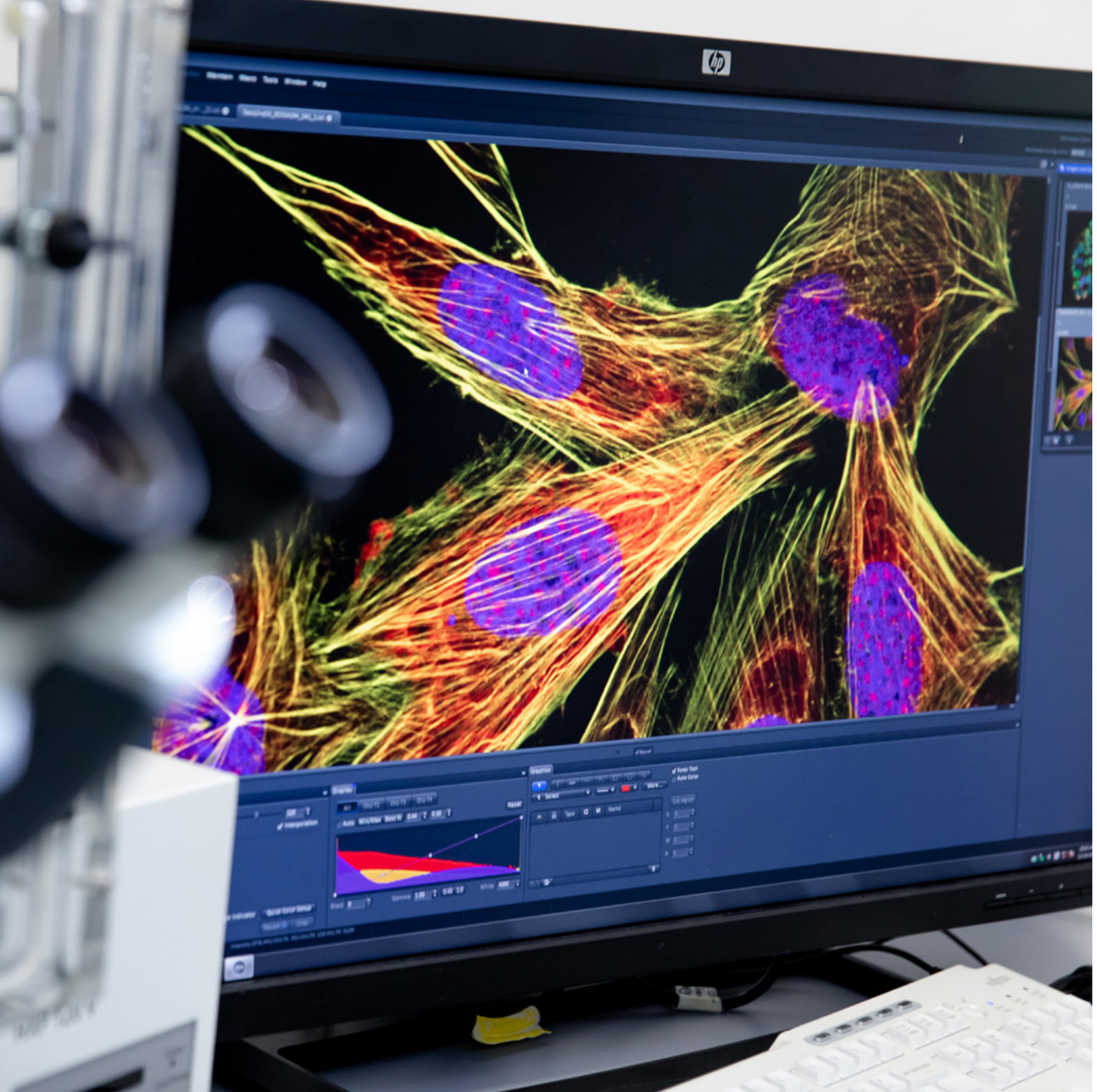
IN VITRO PHARMACOLOGY SERVICES

Our oncology services consist of different complementary technologies to develop all kinds of cellular mechanistic assays to characterize a variety of modalities (e.g. compounds, antibodies, PROTACs) or novel potential therapeutic targets. Our scientists can support you in selecting the most suitable model systems, performing robust target validation experiments using state-of-the-art functional genomics analyses, and setting up of novel mechanistic assays.

- Comprehensive cancer cell line collection (human, mouse, rat)
- Bioinformatic support for the choice of relevant model systems
- Primary cells
- Co-culture systems
- Access to human blood donor panel

Cell line generation

- Variety of delivery options for genetic modifications
- CRISPR knockout, knockin, RNAi, overexpression
- Generation of drug resistant sub-lines
- Different reporter and tag options (e.g. HiBiT, Nanoluc, Luciferase)
- Isogenic cell pair generation



Technologies / assay / examples

- Cell viability and proliferation assays (Life cell / 2D / 3D / drug combinations)
- Apoptosis assays
- Cell cycle assays
- Cell migration and chemotaxis assays
- Multiplex flow cytometry
- Live-cell metabolic assay
- Cancer cell differentiation assays
- Gene expression profiling (NGS, qRT-PCR)
- Single cell sequencing
- Chromatin immunoprecipitation (ChIP)
- High content analysis (HCA)
- Immunohistochemistry (IHC) and immunofluorescence (IF) readouts
- Protein detection (Simple western / in cell / classical)
- ELISA, MSD
- G-Lisa, HTRF, peptide arrays
- DNA damage repair assays
- Cytotoxic T cell killing
- Antibody-dependent cell-mediated cytotoxicity (ADCC)

IN VIVO PHARMACOLOGY SERVICES

Different studies in tumor bearing animals allow for in-depth characterization of novel test substances, answering many crucial questions for further development. We have hands-on experience with a broad range of over 200 pre-clinical oncology models in mice and rats. Our scientists can help you design and conduct *in vivo* pharmacology studies tailored to your specific needs.

Study types

- Tolerability
- Exposure
- Anti-tumor efficacy studies
- Studies describing pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of your drug
- Therapeutic index / drug-drug interactions
- Model establishment

Cell line-based syngeneic and xenogeneic models

- Subcutaneous models
- Orthotopic models
  - Brain, pancreas, liver, colon, kidney, other organs
  - Haematological (liquid) & bone marrow (intrafemural) tumor models
- Metastasis models
- Colonization models
- Lung colonization models
- Intracardiac injection models

Treatments

- SMOLs, biologics, standard of care (SoC), radiation, combination therapies
- Assessment of different formulations
- Various routes (sc, ip, im, po, iv) and timelines (bolus, infusion) of application possible
- Various treatment schedules

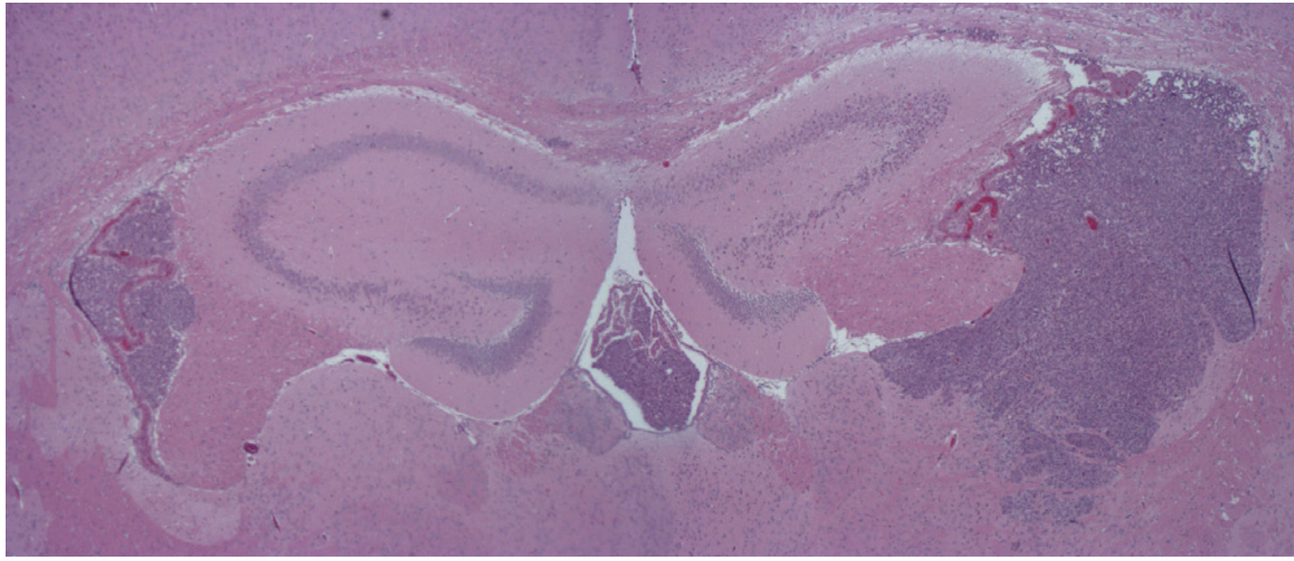
Analysis / readout

- Tumor growth kinetics, tumor weights, human endpoint survival
- Regrowth assessment after treatment stop
- Small animal imaging and radiation capabilities (bioluminescence, µCT, US)
- Profiling of tumor immune status
- Early investigation of potential organs of side effects (e.g. histopathology, target expression, analysis of mode-of-action in these organs)

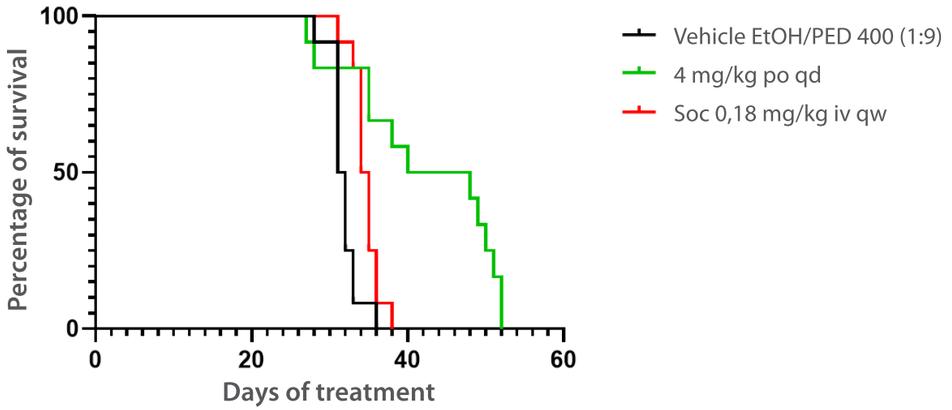
Possibility to combine with PK / PD (biomarker) *ex vivo* analysis in organs / tissues, and tumors

- IHC, sequencing, RNA / DNA analyses, multicolor flow cytometry
- *Ex vivo* analysis of bodily fluids (cytokine profiling, multicolor flow cytometry)
- Immune cell profiling
- Immune cell infiltration by IHC / RNAscope / multicolor flow cytometry

Cell line derived xenograft (CDX) intracranial in mouse



H&E staining of brain section of cell line derived brain tumor in mouse (100 µm)



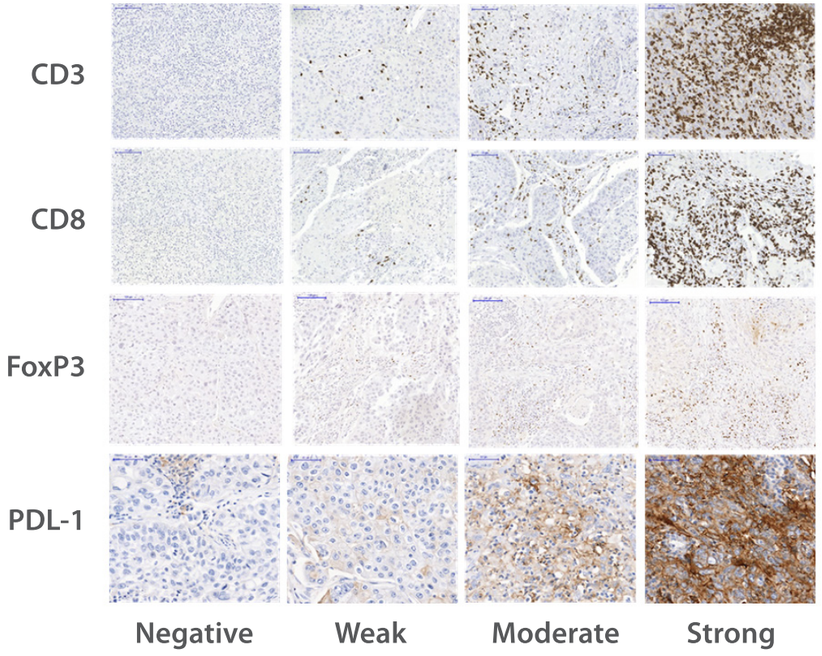
Immuno-Oncology

Research and development in the field of Immuno-Oncology (I-O) has changed fundamentally since its inception. Numerous potential new I-O therapies and combinations are currently being evaluated pre-clinically and in clinical trials. These efforts require appropriate tools and technologies to enable an efficient and successful transition to the next critical milestone.

At NUVISAN, we support our clients in the pre-clinical development of I-O projects by providing state-of-the-art *in vitro* and *in vivo* models and utilizing biomarkers with pharmacodynamic, predictive, and surveillance utility.

Comprehensive profiling of tumor infiltrating immune cells can shed light on mechanisms of cancer-immune evasion, thus providing opportunities for the development of novel therapeutic strategies. We offer comprehensive panels to characterize immune cell populations for pre-clinical models and clinical samples for I-O.

T cell infiltration in human NSCLC



Models and platform techniques for Immuno-Oncology projects include:

- Access to blood donor panel
- Chemotaxis assay
- Cytokine release assay
- Immune cell functional assays
- Cytotoxic T cell killing
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- *Ex vivo* immune cell assays
- CRISPR-based screening in primary cells (e.g. T cells)
- *In vivo* characterization in syngeneic tumor models
- Immune cell infiltration by IHC / RNAscope/flow cytometry
- Immune cell phenotyping
- Single cell sequencing for immune cell profiling
- Blood-based biomarker assay development including transfer to clinical trial assay format

Assays for all major immune cell populations established & extensively validated

Cell type	Target	Human & mouse
Leukocytes	CD45	✓
T-cells	CD3	✓
T-helpers	CD4	✓
T-cytotoxic	CD8	✓
Tregs	Foxp3	✓
Activated Tregs	CD25	✓
B-cells	CD19	✓
B-cells	CD20	✓
B-cells	CD22	✓
pDCs	CD123	✓
Macrophages	CD68	✓
Macrophages (M1)	CD86	✓
Macrophages (M2)	CD206	✓
NK-cells	CD56	✓
NK-cells	NCR1	✓
Activation / Exhaustion	PD-1	✓
Immunosuppression	PD-L1	✓
Immunosuppression	ICOS	✓
Immunosuppression	TIM-3	✓

Biomarker services

Integrated biomarker services covering the entire drug discovery value chain from pre-clinical biomarker discovery & validation, robust assay development, target patient population refinement all the way to biomarker analysis of clinical samples.

- Identification and validation of pharmacodynamic biomarkers in target organs and surrogate tissues
- *In vivo* PK / PD & biomarker studies for subsequent *ex vivo* validation of PD biomarker candidates, correlation of drug exposure to efficacy, and PD biomarker modulation for mechanistic modeling
- Identification of predictive biomarkers guiding target patient population refinement through combined *in silico*, *in vitro*, and *in vivo* studies
- In-house biobank of human normal and disease (e.g., cancer) tissues to support profiling of the drug target or predictive biomarker expression using clinically relevant assays
- Reverse translation and refinement of biomarker candidates through biomarker analysis of clinical trial samples

Single cell sequencing & NGS technologies

The NGS platform offers the full spectrum of different techniques to support oncology projects. Possible applications include RNA, exome, ATAC, ChIP, bisulfite, Sanger, and single cell sequencing. Single cell sequencing enables whole genome expression profiling of thousands of individual cells in parallel.

At NUVISAN, we use single cell sequencing to identify novel targets as well as biomarkers and can analyze the mode-of-action of development compounds at unprecedented resolution.

Our NGS and single cell sequencing platforms offer integrated services to customers including:

- Experimental design
- Professional execution in the lab
- In-house NGS sequencing
- State-of-the-art bioinformatic analysis

NUVISAN single cell sequencing is a certified service provider for 10x Genomics.

DMPK compound profiling during discovery and development

During the early stage of oncology compound synthesis, pharmacology testing, and structure optimization, the compounds will go through a standard battery of DMPK studies such as:

- PK and absolute bioavailability in rodents
- Plasma protein binding
- *In vitro* CLint, in combination with early metabolite profiling as needed
- Pgp and MDCK transporter inhibition
- CYP inhibition
- CYP induction, small CYP panel
- Tailored DMPK assays as needed

When your compound moves forward in development, we can support you with tailored DMPK studies towards and beyond IND. These efforts go all in line with the oncology indication for your molecule and the respective ICH guidance's S9 or M3, respectively: compounds for advanced disease with limited therapeutic options (ICH S9) or for all other cancers (ICH M3). The panel of DMPK studies towards IND in a registration format may include the studies listed below. Moreover, we will perform tailored assays to fit your needs.

- Plasma protein binding with binding partner
- Whole blood plasma distribution ratio
- CYP inhibition
- CYP phenotyping
- CYP induction
- Cross species comparison (non-radio-labeled)
- Pgp and MDCK transporter studies
- Other transporter studies as required
- Bioanalytical assay development and validation for toxicology, DMPK, and human studies
- In support of the bioanalytical assay, we can synthesize stable labeled internal standards with [^{13}C] or [^{2}H]

DMPK services post IND

Following a successful IND and completion of first clinical studies, NUVISAN can support you with the establishment of a custom-tailored pre-clinical development plan to specifically answer those questions you need for submission. We have numerous DMPK studies in our portfolio to characterize your molecule even further.

In case we do not have the necessary assays immediately available, we will develop them to fit your needs. If studies with radio-labeled API at the post IND stage are required, we cover this service as well, both for the use in animals and employing [^{14}C]-labeled API under GMP for the application to the human mass balance study.

Toxicology and API synthesis

During the IND phase, NUVISAN can also support the development of your compound with *in vitro* and in vivo toxicology studies including full clinical chemistry and pathological evaluation.

- Ames (OECD 471)
- hERG (ICH S7B)
- Micronucleus testing *in vitro* (OECD 487) and *in vivo* (OECD 474 / 407)
- Phototoxicity (OECD 432, ICH S10)
- Skin irritation (OECD 439 / 431) test
- 2 week DRF in rodents
- 4 week GLP toxicology in rodents
- 13 week GLP toxicology in rodents
- Studies in the second tox species in collaboration with one of our partners

API synthesis

Furthermore, we offer API synthesis for DMPK and toxicology studies, research batch, and GMP quality, respectively, with a batch size for the GMP API of up to 5 kg.

Phase 1-4 clinical studies

Following IND, your compound is ready to be tested in the first clinical trials. NUVISAN has its own Phase 1 clinical unit, located in Neu-Ulm and equipped with 80 overnight and 40 intensive care beds.

We have performed clinical Phase 1 studies with oncology drugs in healthy volunteers. Study designs used were SAD, MAD, FE, DDI, and BE studies. Oncology drugs tested in these trials include angiogenesis inhibitors, GnRH agonists, tamoxifen, c-Met inhibitors, and drugs affecting the PI3-Kinase/Akt pathway. Trials in HVs require compounds that are not genotoxic and administered with low starting doses (e.g. 1/10 of HED based on NOAEL).

The advantages of trials in HVs include timely recruitment, absence of confounding factors when assessing pharmacokinetics (although these will have to be considered at a later time) and not having to expose patients to subtherapeutic doses. Limited assessment of PD using surrogate markers may be possible.

Other services related to clinical studies include:

- Bioanalytical lab
- Safety lab
- Central lab
- Project management
- Regulatory affairs
- Medical monitoring and pharmacovigilance
- Biostatistics
- Clinical monitoring
- Data management
- Medical writing

OUR ONCOLOGY SERVICES IN DETAIL

Moreover, NUVISAN´s clinical team in Latin America provides dedicated operational resources from single monitoring assignments to global large full-service trials. Patient safety, compliance, and data quality are our top priorities.

Our operational staff has two decades of experience in a variety of therapeutic areas and study types, with a particular focus on Phase 2 and 3 oncology trials since the organisation's inception as a specialized oncology CRO. We have proven deep regulatory expertise in managing and accelerating trial start-up in this region.

These efforts include regulatory submissions, particularly in key countries of Argentina, Brazil, and Peru, both for other CROs as well as clients.

With our central LATAM office based in Buenos Aires, Argentina, a highly experienced team, and local offices and representation in Peru and Brazil, we are happy to cover almost all Latin American countries.

We can offer regulatory start-up activities and monitoring services in countries including, but not limited to, Chile and Colombia.

NUVISAN´s clinical team in LATAM has performed more than 20 oncology trials (Phase 2 / 3 / 4).

NUVISAN

YOUR PARTNER OF CHOICE

All relevant technologies and competences combined in one team

ONE TEAM

Seamless transition of projects along the drug discovery value chain
Quick turnaround times through close co-localization
Unified data and compound handling standards

ONE PARTNER

Fully integrated drug discovery and development team along the value chain and beyond
Programs or part of programs to be handled by one partner
Integrated or selected services out of one hand

ONE SOLUTION

High caliber drug discovery and development team available to drive challenging programs
Long-term drug discovery experience and knowledge in one integrated team
High-end technology and competence portfolio to deliver on challenging tasks

NUVISAN

YOUR SCIENTIFIC CRO / CDMO PARTNER

NUVISAN is a fully integrated CRO / CDMO offering all solutions from drug discovery to proof of concept in patients including: target identification, high-throughput screening, compound profiling, pre-clinical DMPK, toxicology, API synthesis, formulation development, pharmaceutical analysis, and clinical trials in healthy volunteers and patient populations.

With capabilities distributed over 6 locations in Europe, a presence in Latin America, and more than 40 years of experience, we deliver high-quality solutions certified by various accreditations and inspections (e.g. BfArM, EMA, FDA, ANVISA, ANSES, AAALAC, GLP, GMP, CIR).

40 **A trusted scientific partner**
With a 40-year track record of customer satisfaction

A wide range of expertise
A unique, comprehensive and, integrated offer from target identification to clinical trials

A data-focused expert
Our top priority is to ensure accurate, reliable, and consistent data quality

A flexible service provider
Fast turnaround ability and strong responsiveness to change

Enquire now

Whether you need support in specific areas only or need a more comprehensive offer, NUVISAN can tailor a solution to fit your specific requirements.

If you have any questions or need more information, please reach out to us:

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