Syngene

Putting Science to Work

Science that

ANNUAL REPORT 2022

Science that Solves, Scales and Sustains

Scientific research is in Syngene's DNA, from the earliest stages of discovery through the development process into scale-up and commercial manufacturing. Every project brings a new opportunity to examine a target, molecule, compound or process, scrutinise the results and draw conclusions that take the project to the next milestone. Great science involves creativity, problem-solving, accuracy, resilience and persistence. To this, Syngene scientists add a unique wealth of experience gained from working on many projects in different domains, for a wide range of customers.

Solving problems for clients

Much of research is founded on solving problems: for example, the discovery of an oral agent for treatment of chronic liver disease (see showcase page 73) or the development of oligonucleotides as adjuvants for COVID vaccines (see showcase page 7). Working together with each partner, dedicated teams generated outcomes that moved promising molecules to the next stage.

Problem-solving can also mean delivering more with less. In a project with a major food company, the cost of production was significantly reduced by using artificial intelligence to predict outcomes using parameters proven in prior research (see showcase on page 47). In a project related to Parkinsons Disease, the research project delivered a less invasive and costly intervention for the patient while improving outcomes (see showcase page 35).

Scaling science for people and patients

The journey from discovery research to manufacturing involves taking a production process from very small scale to one that can be delivered reliably, cost-effectively and rapidly at a commercial scale. Here, years of experience and manufacturing know-how are invaluable. Manufacturing remdesivir was one example. With a pressing need for the product in India and abroad, the development team reduced a complex manufacturing process to fewer steps, thus simplifying the manufacturing process and making drug available to patients more quickly.

Sustaining science for clients and the community

Above all, the focus on quality and continuous improvement sustains every project. With fully digitized quality processes, Syngene is routinely audited by the major global regulatory bodies, as well as clients themselves. Sustaining science also means leveraging new technology to improve processes, make them faster and reduce costs. Improving manufacturing processes is equally important and a project focused on viral clearance through a continuous flow reactor offered new thinking for the biologics industry (see showcase page 16 & 17).

For more than 25 years, Syngene has delivered solutions rooted in research. Today, as ever, it remains committed to offering **science that solves, scales and sustains** - to help our partners and clients make the next generation of materials and medicines.

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To view this report online, please visit:
www.syngeneintl.com/investors/

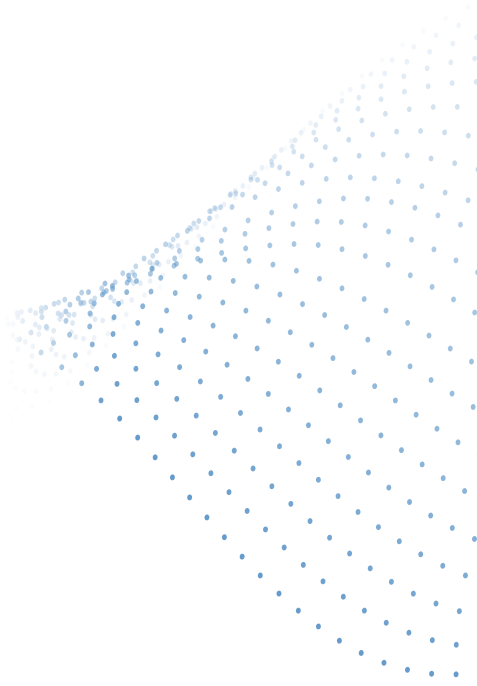
About Syngene

Dedicated to science

Syngene is an integrated research, development and manufacturing services organization. Working for clients around the globe, the Company delivers innovation that will benefit human and animal health and shape next-generation materials to improve people's lives in the years to come.

For more than twenty-five years, the Company has partnered with clients to find solutions through science. Every project has specific requirements and the solutions and services provided range from specialist, stand-alone activities to longer term, integrated programs spanning the discovery, development and manufacturing value chain. While the Company focus is primarily on human and animal health, the same research and development capabilities are applied to a range of industry sectors including nutrition, consumer goods and specialty chemicals. Many of our clients are world leaders in their fields ranging from leading global multinationals to small and medium-sized start-ups, non-profit institutions, academic institutes and government organizations.

Headquartered in India and listed on the Indian stock exchanges, our research, development and manufacturing operations are based at our original 90-acre campus in Bangalore, supported by two satellite campuses which house enabling functions and the clinical development facility. A new, state-of-the-art discovery research campus in Hyderabad, India located in the government-sponsored biotech zone, currently accommodates 600 scientists with further phases of expansion planned. The large-scale active pharmaceutical ingredient (API) manufacturing site is located on a dedicated campus in Mangalore, India. US clients are supported by Syngene USA Inc., a US-based subsidiary.



OUR VISION

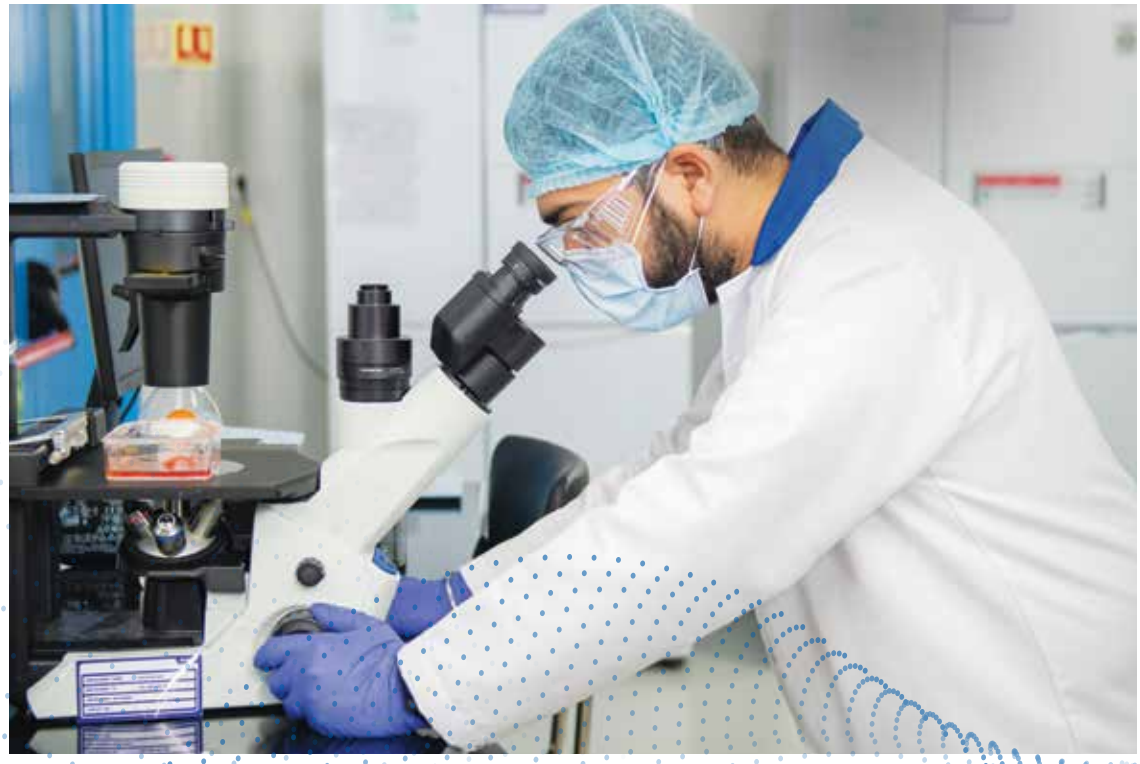
To be a world-class partner delivering innovative scientific solutions.

OUR VALUES

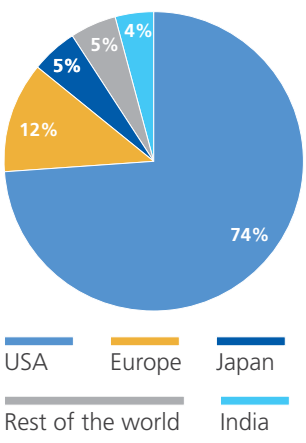
Integrity

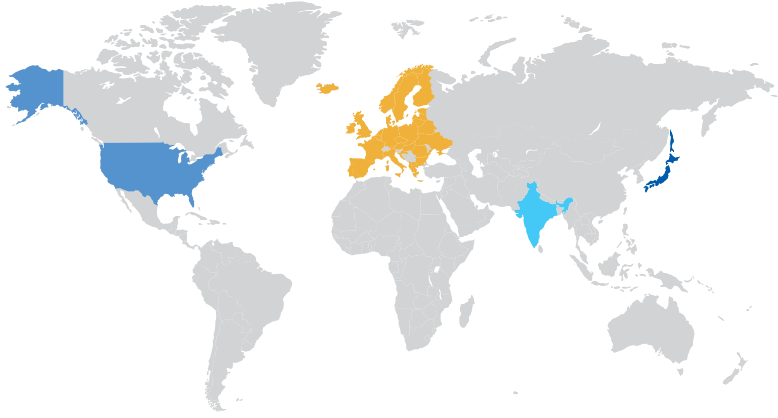
Excellence

Professionalism



Client footprint by number of clients





BUSINESS DIVISIONS

Discovery Services

Discovery Services undertakes early-stage research from target identification to delivery of drug candidates for further development. Capabilities include chemistry, biology, safety assessment and research informatics for small molecules; recombinant DNA engineering, cell line development, next-generation sequencing and protein sciences for large molecules. Discovery Services also lies at the heart of the SynVent platform which offers clients an end-to-end project delivery capability leveraging the breadth of technology and expertise available across the Company.

Development Services

Development Services takes drug candidates and offers services ranging from pre-clinical to clinical trials, including drug substance, drug product development and associated services to demonstrate safety, tolerability and efficacy. Using advanced technology platforms, the Company offers a comprehensive set of oligonucleotide synthesis services ranging from development to the manufacture of chemically synthesized oligonucleotides. The Chemical Development team is responsible for cGMP[1]-compliant manufacturing of clinical supplies and registration batches for large and small molecules. The Performance and Specialty Materials team focuses on the science and engineering aspects of polymeric materials and small molecules working in areas such as biopolymers, specialty polymers, highly active monomers and performance chemicals.

Manufacturing Services

Manufacturing Services offers commercial scale manufacturing of small and large molecules from a cGMP-compliant API manufacturing campus in Mangalore, India and a biologics manufacturing facility in Bangalore, India.

Dedicated R&D Centers

Dedicated R&D Centers encompass teams of multi-disciplinary scientists, operating from ring-fenced infrastructure plus access to our entire ecosystem for research and development operations on an exclusive, dedicated basis for an individual client.

[1] *cGMP compliant – compliance with current Good Manufacturing Practice*

COLLABORATION MODELS

Recognizing that each client has different needs, our range of collaboration models offer flexibility and customization to meet those individual requirements. Clients can select a single model or a combination to suit their business needs.

Fee for Service (FFS)

Agreed services delivered within a defined scope. Flexible, on-demand personnel and research infrastructure deployed to achieve the project objectives. Engagements may be short or long-term.

Full-time Equivalent (FTE)

Pre-defined numbers of scientific personnel from pre-determined disciplines work full-time on client projects. Deliverables and team composition evolve as the project advances. Agreements are typically renewed annually.

Dedicated R&D Centers

Clients are provided with customized and ring-fenced infrastructure. Dedicated scientific and support teams work exclusively on the client's projects. Long-term strategic alliances that last usually five years or more.

Risk/ Reward

Implementing a stage-gate model across a portfolio of research projects. Clients benefit from reduced upfront payments in exchange for milestone payments based on pre-agreed success criteria.

Outcome based model with Service Level Agreement (SLA)

The contract is based on achievement of a defined outcome and linked to productivity goals.

Industry presence - over 400+ active customers

Large & Mid-sized BioPharma	abbvie, AMGEN, gsk, MERCK, Albireo, Bristol Myers Squibb, Johnson & Johnson, SANOFI
Emerging BioPharma	ASCENEURON, PharmAust, rodin THERAPEUTICS, sosei HEPTARES, Genmab
Animal Health	BAYER, MERCK, zoetis
AgroChem	FMC
Consumer Products	Unilever

Glycan profile prediction tool for monoclonal antibody

Solves Scales Sustains

Sustaining solutions with science

Engineered monoclonal antibodies offer new ways of treating a wide range of diseases. However, ensuring that the monoclonal antibodies have the profile needed to be effective has historically been the result of complicated and repeated experimentation. Syngene scientists introduced mathematical modelling to create virtual experiments and reduce the physical research program. This solution added speed and efficiency to the development program while reducing costs and improving the results.

Scientific Challenge: Engineered proteins and glycosylation

Modern engineered monoclonal antibodies (mAbs) are developed for numerous therapeutic applications ranging from cancer to COVID-19. An important aspect during mAbs manufacturing is to confer the right patterns of glycosylation at the right locations of the protein. Glycosylation is a post-translational modification critical for protein function, folding and activity. Finding the right set of factors to deliver the required glycosylation profile is complex. Currently, this is done by complicated and repeated experiments in the laboratory where the proteins are cultured with the addition of different sugars over a period of two weeks.

Using systems modelling, a mathematical modelling approach where processes and reaction kinetics are depicted in a set of coupled differential equations, simulations of complex processes can be used to run virtual experiments that can optimize processes and save resources. With the benefit of the simulations, a smaller number of experiments in the laboratory are required and more meaningful results are obtained.

Using technology to find a solution

The Research Informatics team has developed two models that replicate the glycosylation processes (N-glycosylation and O-glycosylation models). These models are an AI (data-driven) approach to reduce the number of experiments required to produce generic (biosimilar) versions of therapeutic medicines (mAbs) that are comparable to the ones that are already approved by global regulatory bodies.

The N-glycosylation model, which captures the relevant enzyme kinetics in the cells to achieve the required glycosylation profile (fucosylation and/or sialylation). This technology will speed up mAb manufacture for the treatment of communicable diseases and non-communicable diseases.

The O-glycosylation model helps achieve the best adhesion properties for lymphocytes/ immune cells and enhances the properties of chimeric antigen receptor (CAR) T-cells for cancer immunotherapy.

Why is this important?

Building mathematical models such as these bring speed and efficiency to the development process of glycoprotein therapeutics while reducing the need for conducting many experiments, offering cost benefits and reducing timelines for product development.

Advances in COVID research

Solves Scales Sustains

COVID-19

Syngene scientists applied their knowledge and skills to aid diagnosis, increase understanding of immune responses and find long-term solutions to COVID-19. They generated reagents and assays for monitoring COVID-19 infection and vaccine efficacy and partnered with clients to discover novel vaccines.

Partnering in diagnostics

Throughout the year, the Company supplied gram quantities of purified viral proteins (S1 subunit; receptor-binding domain, RBD; nucleocapsid) for use in diagnostic kits for clients including US-based Diabetomics Inc.[1] and Himedia Ltd. Reagents were also supplied to Bharat Biotech as part of monitoring the clinical efficacy of COVAXIN.

The scientists rapidly developed two assays to monitor immune response to natural infection or following vaccination: a surrogate neutralizing antibody assay (sNAb assay) and a COVID-specific T cell assay.

While the immune system mounts many specific antibodies against the virus, the antibodies that 'neutralize' or inactivate the virus are the most relevant. Conventional neutralizing antibody assays (NAb) use the virulent form of the wild-type virus in a plaque reduction neutralization (PRNT) assay. These assays require very stringent containment possible through the use of labs. They also take time and are tedious to perform. Syngene researchers developed a novel ELISA-based format for detecting host-cell ACE2 receptors binding to viral RBD protein in the presence and absence of patient sera.

The data from these studies showed a very high correlation (>95%) to the conventional PRNT assay–both in sensitivity and specificity. The assays have the potential to be configured to detect NAbs to all the viral variants, including against the Omicron strain, as required.

While antibodies to COVID-19 offer protection, another arm of the immune system involves T cells which impart memory and long-lasting protection against re-infection. Our scientists developed assays to examine COVID-specific T cell responses using white blood cells from human blood in which cells are incubated with a cocktail of viral peptides. Samples obtained from donors who have been exposed to COVID infection or vaccination would result in release of mediators (IFN-gamma and IL-2) in response to peptide stimulation. These T cell assays have been used to monitor community surveillance of infection and vaccine effectiveness.

Science that sustains

Looking to the longer term, scientists have partnered with clients to evaluate the immunogenicity of novel vaccine candidates in preclinical settings. Some of these include a measles virosome based vaccine, mRNA vaccines and protein vaccines on novel scaffolds to improve immune response. Cell-based and animal-based studies are in progress.

[1] *https://www.prnewswire.com/news-releases/fda-issues-emergency-use-authorization-for-covab-sars-cov-2-ab-test-the-oral-fluid-rapid-test-for-sars-cov-2-antibodies-301318887.html*

Services are delivered by four business divisions

With the skills and technology to solve, scale and sustain scientific innovation, the four divisions work seamlessly to offer an end-to-end capability as well as offering individual specialist services.

Discovery Services

	Target identification and Validation	Hit Validation	Hit to lead	Lead optimization	IND enabling	IND/Ph1 DE
Biology translation	**Target ID** 1. Pathway analysis 2. Omics 3. Knock-in / knock-out	***In vitro* assays:** 1. Biochemical 2. Orthogonal 3. HTS Formats	***In vitro* assays:** 1. Cellular mechanistic 2. Cellular functional 3. Relevant off-target(s) ***In vitro* ADME assays:** 1. Protein binding 2. Metabolism 3. CYP inhib/induct	***In vivo* assays/studies:** 1. PK (R/NR) 2. PD, PK/PD 3. Efficacy	**Later translational:** 1. PK/PD/efficacy 2. Refinement of patient selection hypothesis 3. Biomarkers	**Ph1-HV or patient (as appropriate):** 1. Exposure 2. PD
	Hypotheses: 1. Therapeutic 2. Mechanistic 3. Target engagement		**Research Operating Plan:** 1. Assay priority 2. Key studies 3. Critical path	**Hypothesis:** 1. Patient selection		
Chemistry development, Formulation, clinical development	**HTS/DEL/fragments/virtual screening** 1. Library design/synthesis/ maintenance 2. Hit validation, resynthesis 3. Series qualification, prioritization		**Optimization:** 1. Biochem/cell potency 2. Selectivity 3. Phys/chem properties 4. *In vitro/vivo* tool cmpds	**Optimization:** 1. Tgt optimal h-profile 2. Candidate selection 3. Backup strategy	**Drug Substance (DS, aka API)** 1. Route scouting (define specs) 2. Scale up 3. Manufacture/stability	**Drug Product (DP)** 1. Pre-formulation studies 2. Ph1 suitable formulation 3. Prototype/stability 4. Manufacture/stability 5. IND, BA/BE, DDI and Phase 1 clinical trials 6. GCP bioanalysis
Safety assessment			***In vitro* Safety:** 1.hERG 2.Ion channels	**Tax-suitable Formulation (maximize exposure)**	DRF tox (R/NR) Bioanalysis GLP tox (R/NR) GLP bioanalysis	MTD or RP2D (as appropriate)

Iterative data analysis and interpretation, models, hypothesis generation

SynVent - fully integrated therapeutic discovery

Dedicated R&D Centres

Each research and development centre includes exclusive research infrastructure and dedicated research teams to support client requirements.

Amgen

Baxter

Bristol Myers Squibb