

Bioengineering

Count on GeneArt synthetic DNA and protein services

Your partner in utilizing synthetic biology to help you scale and expedite discovery

For Research Use Only. Not for use in diagnostic procedures.

invitrogen



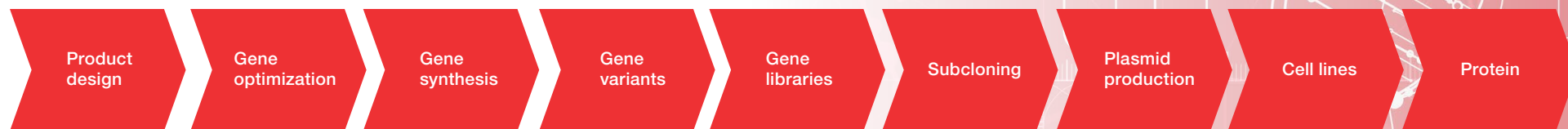
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Why choose GeneArt services?

We are your partner for gene synthesis all the way through to protein production.

Invitrogen™ GeneArt™ services provide gene synthesis support from DNA design to protein production. DNA synthesis is the driving force behind new and emerging synthetic biology technologies, including those contributing to the fight against infectious diseases. GeneArt services offer a comprehensive set of tools and solutions to accelerate discovery (Figure 1).



Custom DNA for research in many cutting-edge application areas

Target optimization and target interaction analysis	Discovery
Antibodies and biologics Expression optimization Quality improvement Documented source	Therapeutics development and biologics optimization
mRNA-based applications Neoantigens	New therapies development
Genome editing—knock-in genes, CAR T cell receptors	Cell and gene therapy development
Biomarkers and antibodies Positive controls	Diagnostics development
dsDNA RNA templates Virus-based constructs	Vaccine development
DNA tools for basic research	Basic research

Discovery and development

- Transient expression in mammalian cells
- Early candidate expression—small scale up to 1 L
- Lead candidate expression—laboratory mid-scale up to 50 L

Figure 1. GeneArt services accelerate discovery by starting with an electronic sequence that can be taken all the way to protein production.

GeneArt DNA and protein services

Whether you're looking to save time or improve existing processes, GeneArt services provide a single resource for all of your outsourcing needs.

GeneArt gene synthesis and cloned genes

Using the Invitrogen™ GeneArt™ gene synthesis service is a reliable and cost-effective way to obtain customized DNA constructs with 100% sequence accuracy. The GeneArt gene synthesis service offers a variety of options, including accelerated production, cloning into your vector of choice, and plasmid preparation.

- Industry leader for reliable delivery and performance
- Proprietary, peer-reviewed, and proven Invitrogen™ GeneArt™ GeneOptimizer™ algorithm optimizes genes at no additional cost for maximum protein expression
- High-quality production with ISO 9001:2015 certification
- Delivery in tube format with a minimum of 5 µg DNA

GeneArt Strings DNA fragments

Invitrogen™ GeneArt™ Strings™ DNA fragments are an economical and time-saving alternative to PCR. They are made by the same high-quality process used for gene synthesis, and they can be prepared quickly for cloning.

- Up to 3 kb available with fast production
- Can be optimized with the GeneArt GeneOptimizer algorithm
- Delivered dried, ready for resuspension and cloning with any method

GeneArt directed evolution

The Invitrogen™ GeneArt™ directed evolution service utilizes DNA libraries for protein engineering, which overcomes many of the limitations of conventional gene variant library construction. *De novo* gene synthesis enables construction of virtually any gene variant, so your library can encode maximum variability. The GeneArt directed evolution service includes combinatorial library construction and site-directed mutagenesis.

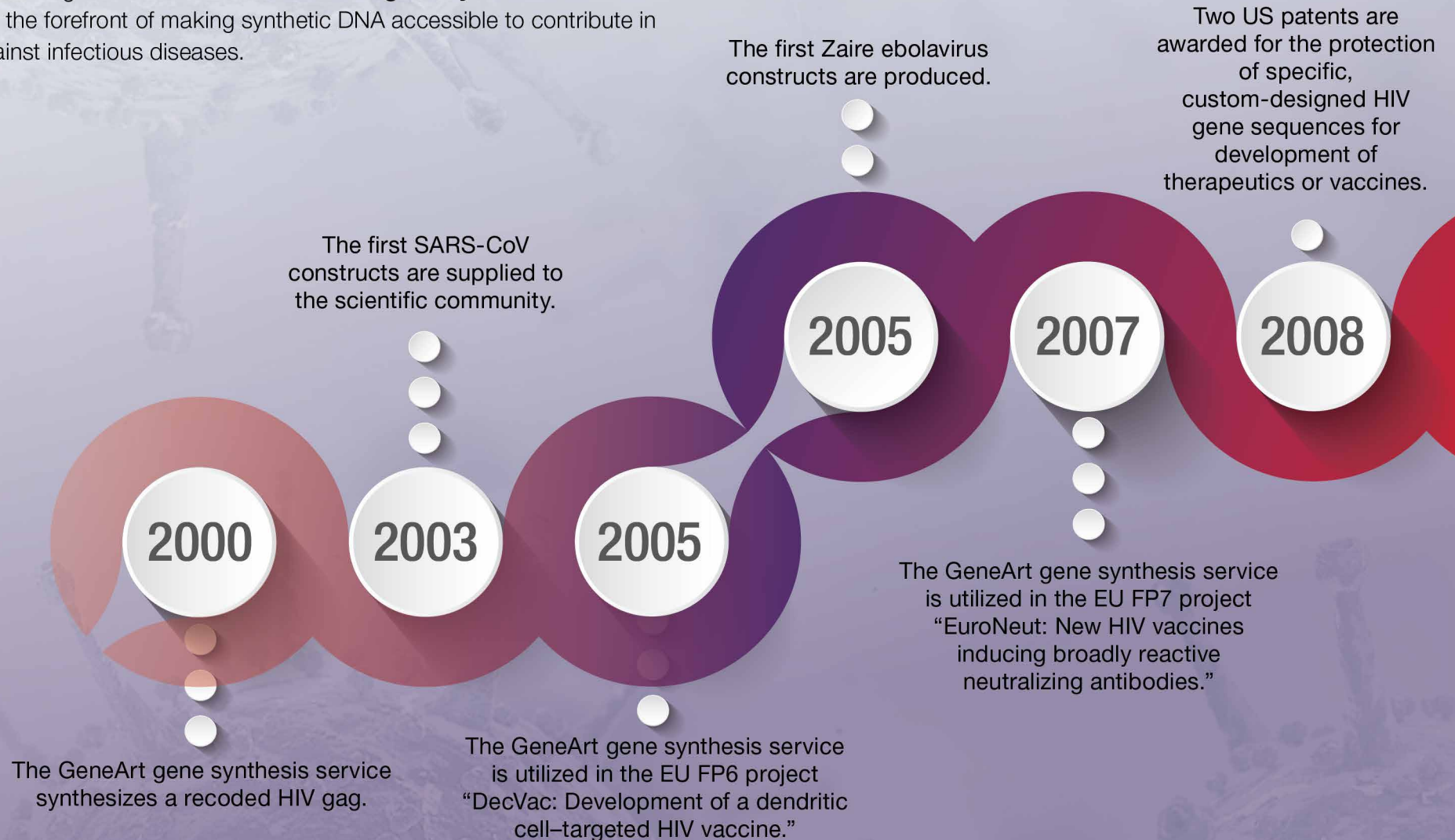
GeneArt protein expression and purification services

The Invitrogen™ GeneArt™ gene-to-protein workflow provides a rapid and dependable way to obtain correctly folded native protein from transiently transfected mammalian cells. Start your discovery projects with a transient protein expression pilot and utilize *de novo* gene synthesis and optimization to obtain error-free clones for rapid production scale-up.

The ongoing fight against infectious diseases

Understanding the mechanism of SARS-CoV-2 infection has been critical for vaccine development at unprecedented rates.

Many successful approaches for vaccine development rely on recombinant DNA technologies, and synthetic DNA provides researchers with fast and highly reliable access to genetic material. **The GeneArt gene synthesis service** has been at the forefront of making synthetic DNA accessible to contribute in the fight against infectious diseases.



The Middle East respiratory syndrome coronavirus (MERS-CoV) is identified, and hundreds of related constructs are produced using the GeneArt gene synthesis service.

To support the fight against Zika fever, thousands of Flavivirus constructs are produced using the GeneArt gene synthesis service.

2012

2014

2015

2020

2021

2009

In response to the Ebola crisis in West Africa, thousands of constructs of Ebolavirus are produced using the GeneArt gene synthesis service.

GeneArt gene synthesis service becomes part of Thermo Fisher Scientific as a crucial scientific offering.

Synthetic H1N1 genes are created for a top pharmaceutical company, and the GeneArt gene synthesis service is utilized in the EU FP7 project “CUT’HIVAC: Cutaneous and mucosal HIV vaccination”.

January 2020—The GeneArt gene synthesis service produces genes based on SARS-CoV-2. The constructs are prioritized and delivered with the GeneArt Express delivery service.

March 2020—Synthesis of all constructs related to SARS-CoV-2 are prioritized for express delivery to the scientific community at no additional charge.

December 2020—The first SARS-CoV-2 variants are received, prioritized, and produced with the GeneArt Express delivery service.

January 2021—An ultrafast manufacturing process for SARS-CoV-2 spike variants is launched for timely development of new SARS-CoV-2 vaccines.

February 2021—The GeneArt gene synthesis service reaches the milestone of producing 10,000+ SARS-CoV-2 gene constructs.

The GeneArt gene synthesis site

Our Global Centers of Excellence for gene synthesis are located in Regensburg, Germany

GeneArt products and services are superior gene synthesis solutions for researchers around the globe. Our Regensburg site produces millions of base pairs on a monthly basis and conforms to the International Organization for Standardization (ISO) 9001:2015 standard. We're constantly expanding site capacity to meet growing market demands for synthetic genes. More than 300 employees are working worldwide to provide you with the best products and services possible.

A new way to synthesize genes

The Regensburg site is also the birthplace of our chip-based platform*—our highly innovative, proprietary technology for gene synthesis that combines miniaturization, automation, and next-generation sequencing (NGS) to provide exceptional accuracy, reliability, and performance (Figure 2).

* Kuhn P et al. (2016) Next generation gene synthesis: from microarrays to genomes. *Eng Life Sci* 17(1):6–13.

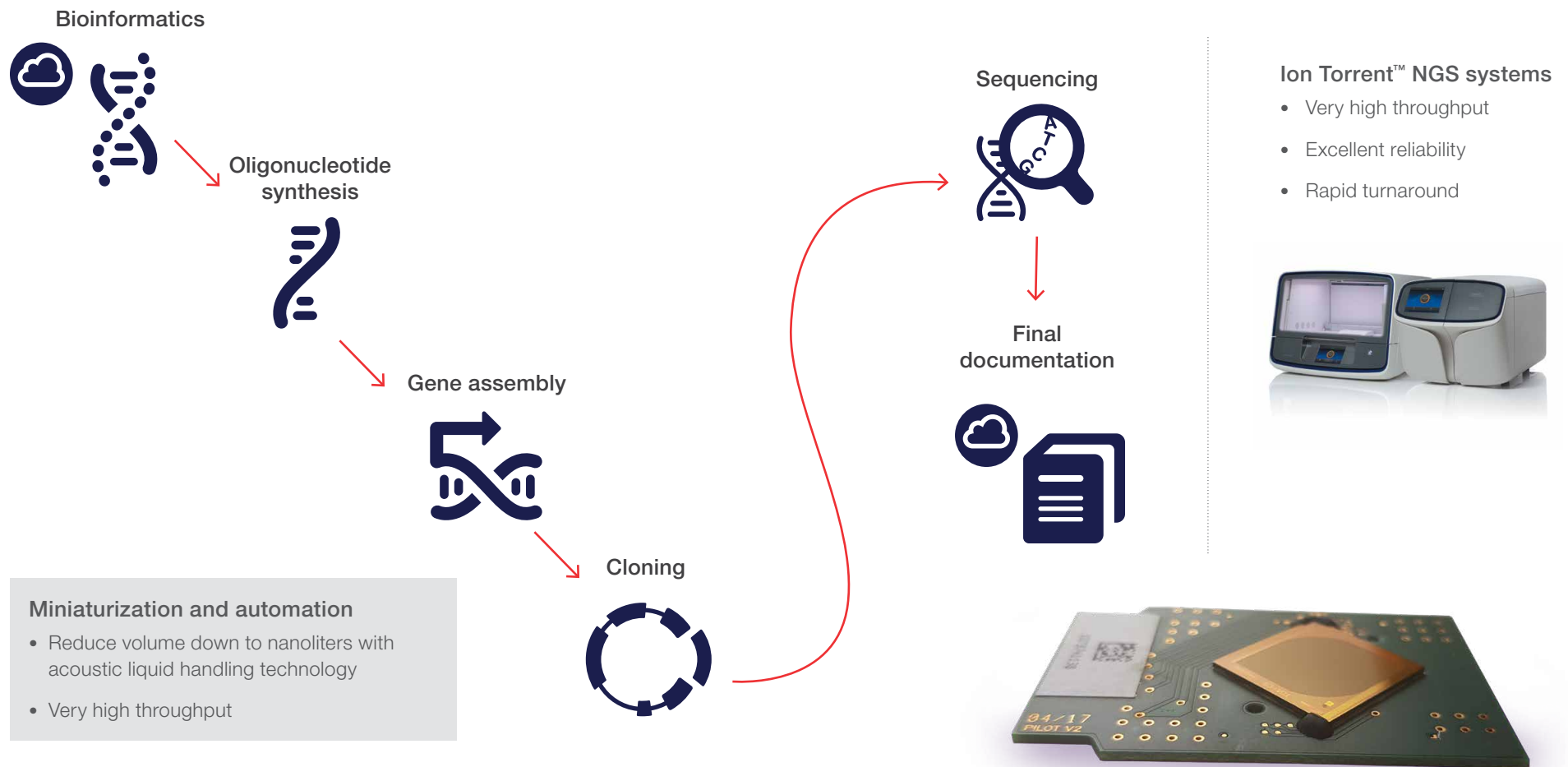


Figure 2. Overview of the chip-based platform.



GeneArt gene synthesis

High-quality, 100% accurate custom synthesis

Synthetic biology is a powerful tool for quickly and precisely creating the DNA you wish to study and optimizing your sequence for protein expression (Figure 3). It is a viable alternative to conventional molecular biology techniques, and it can enable you to achieve more reliable protein expression and higher quality. GeneArt gene synthesis tools go beyond traditional gene synthesis by allowing expression to be optimized for maximum performance. By optimizing your sequence with our proprietary Invitrogen™ GeneArt™ GeneOptimizer™ software, you can realize substantially more protein expression than you would with a wild-type sequence at no extra cost.*

- Industry-leading optimization
- Easy and intuitive Invitrogen™ GeneArt™ Instant Designer online ordering tool
- Nearly unlimited flexibility for gene and vector design
- Ready-to-use constructs for expression and transfection
- Maximum production speed and worldwide delivery; capacity and reliability supported by a fully automated, industrial-scale gene processing platform

* See page 14 for more about how gene optimization works.

GeneArt gene synthesis



Classic cloning

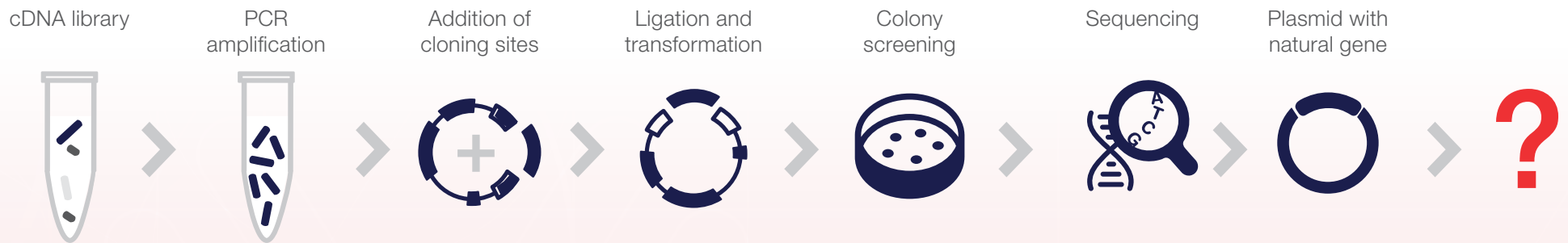


Figure 3. GeneArt gene synthesis and optimization are faster than classic cloning methods and can yield better results.

Find out more at thermofisher.com/genesynthesis



GeneArt gene synthesis production times

Thermo Fisher’s service record of more than 20 years in gene synthesis and our relentless pursuit of continual process improvements help ensure excellent predictability and reliability. With our expertise in manufacturing design, our manufacturing fulfillment metrics for gene synthesis exceed 99.7% regardless of gene length.

Express service is available for any sequence to reduce the production time by 1–2 business days. For non-complex sequences up to 1.2 kb, the SuperSPEED option is also available to further reduce production time. For the fastest service, access these options when ordering online in the GeneArt Services Dashboard.

Insert length (bp)	Production time (business days)	
	Non-complex sequence	Complex sequence
100–1,000	5–8	5–14
1,001–3,000	5–10	9–19
3,001–5,000	7–17	Starts from 16
5,001–7,000	Starts from 12	Starts from 19
7,001–12,000	NA	Starts from 19

Note: On rare occasions, requested sequences are found to be toxic or genetically unstable. Production times are only valid for nontoxic sequences that are genetically stable in *E. coli*.

Visit thermofisher.com/genesyntesis for the latest updates on our services

GeneArt Strings DNA fragments

GeneArt Strings DNA fragments are custom-made, uncloned, double-stranded linear DNA fragments assembled from synthetic oligonucleotides using the same high-quality process developed for GeneArt gene synthesis (Figure 4), making them ideal for multi-fragment assembly with our Invitrogen™ GeneArt™ Gibson Assembly™ cloning kits. A sequence optimized using our proprietary GeneArt GeneOptimizer algorithm can help you realize significantly more downstream protein expression than a wild-type sequence.

GeneArt Strings DNA fragments are delivered dried and ready for resuspension, cloning, and screening to identify the correct clone. They are delivered in tube format and are a fast and smart alternative for getting your synthetic gene cloned into an expression plasmid.

-  **High quality**—GeneArt Strings DNA fragments are built using the same high-quality process as our cloned genes, and there are no adapters to remove
-  **Fast**—produced in as little as 3 days
-  **Flexible**—compatible with any cloning method
-  **Easy to order**—simply load your sequence, optimize, and order
-  **Industry-leading optimization**—with proprietary GeneArt GeneOptimizer software, you can realize substantial gains in protein expression levels at **no extra cost**

Production times based on sequence length

Sequence range	Production time (business days)*
DNA fragments 200–1,000 bp	3–5
DNA fragments 1,001–3,000 bp	4–6
DNA libraries: IUPAC mixed bases	10–15

* Production time is the number of business days required to synthesize GeneArt Strings DNA products in our manufacturing facility. Delivery time is in addition to production time and depends on the shipping destination.

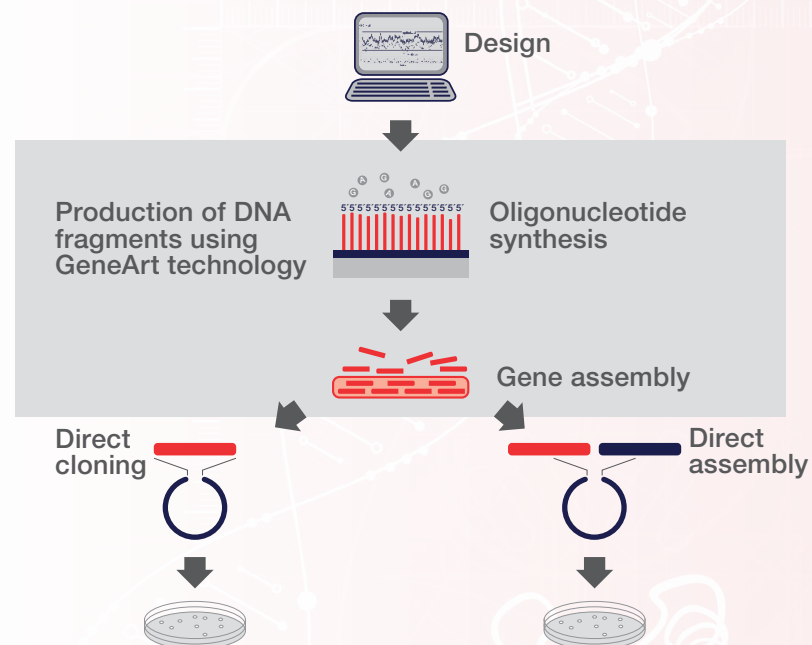


Figure 4. Synthesis of a gene with GeneArt Strings DNA fragments, which can then be easily cloned.

Gene optimization

Maximize protein expression at no additional cost

Protein expression involves several key steps (Figure 5), and a high expression level can be difficult to achieve. Gene optimization is the solution for overcoming the limitations of traditional protein expression. Using data published in the literature together with proprietary data, the GeneArt GeneOptimizer algorithm determines the optimal gene sequence for your expression experiments [1]. Common pain points associated with protein expression, such as low yield, can now be addressed in a rational and systematic way.

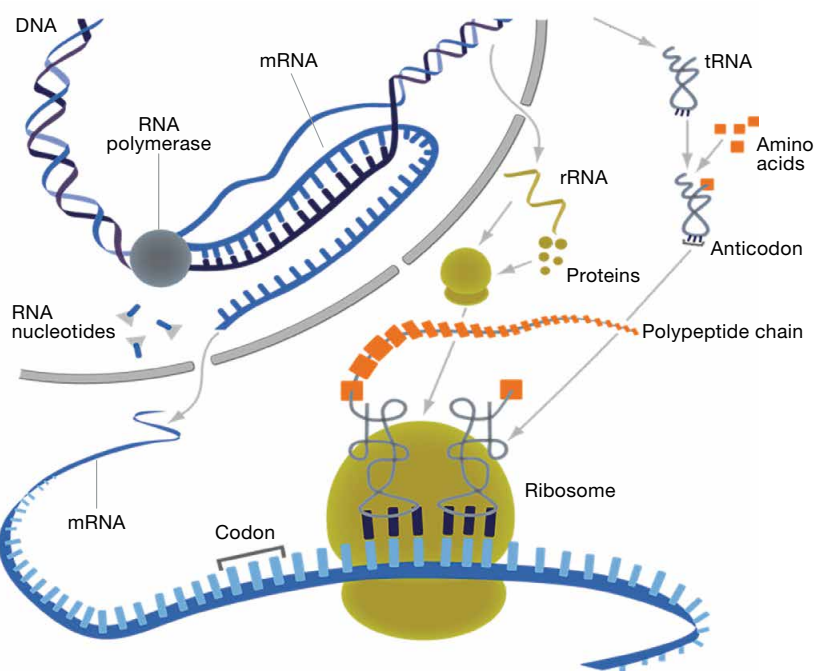


Figure 5. Key steps in protein expression.

GeneArt GeneOptimizer sequence processing

- Identifies the best way to incorporate your requested sequence elements
- Eliminates cryptic splice sites and mRNA-destabilizing sequence elements for more stable mRNA
- Optimizes codon usage and adapts GC content to your expression system
- Prevents undesirable mRNA secondary structures
- Eliminates repetitive sequences

Many synthetic gene providers offer some form of gene optimization, but it is quite often limited to codon optimization with a few additional parameters. Our GeneArt GeneOptimizer algorithm enables true multiparameter optimization. It takes into account many sequence-related parameters that affect different aspects of gene expression, such as transcription, splicing, translation, and mRNA degradation. It considers all relevant parameters in a single operation and delivers an optimized DNA sequence configured to your specifications for maximum performance (Table 1).

Table 1. Parameters that influence protein expression.

Transcription level	mRNA level	Translation level
• GC content • Consensus splice sites • Cryptic splice sites • SD sequences • TATA boxes • Termination signals • Artificial recombination sites	• RNA instability motifs • Ribosomal entry sites • Repetitive sequences	• Codon usage • Premature poly(A) sites • Ribosomal entry sites • Secondary structures

Comparison of wild-type sequences and sequences optimized with GeneArt GeneOptimizer software

We compared expression of optimized mammalian kinase sequences from different suppliers. GeneArt GeneOptimizer software consistently produced sequences with higher expression levels than the wild-type sequences (3-fold, 1.25-fold, and 27-fold increases) and provided excellent reliability (Figure 6).

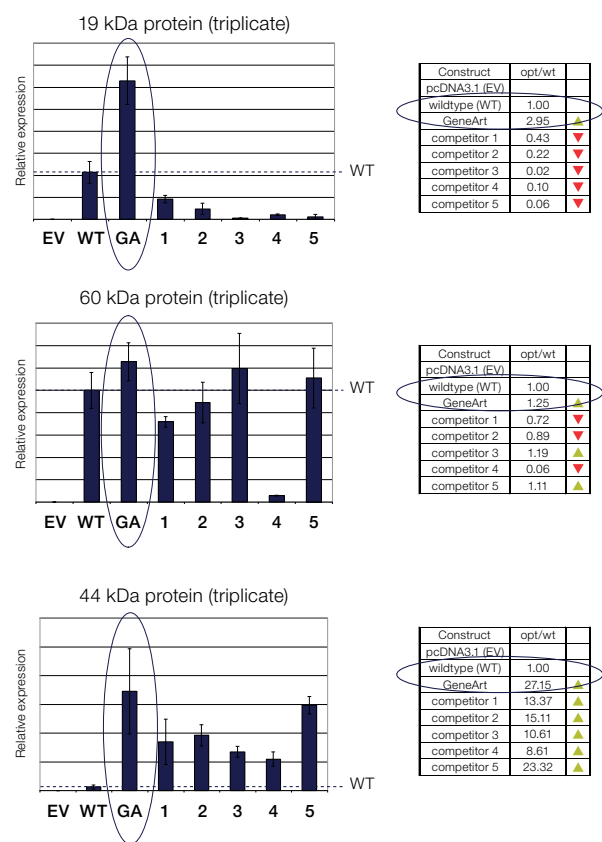


Figure 6. Comparison of mammalian kinase protein expression.

Find out more at thermofisher.com/geneoptimization

GeneArt subcloning service

After synthesis of your gene, the Invitrogen™ GeneArt™ subcloning service can deliver your sequence in virtually any vector of your choice. Choose from over 150 Invitrogen™ vectors, or onboard your own favorite vector. We even support complex cloning projects involving multiple open reading frames, such as monoclonal antibody expression with large double-gene vectors, and we'll store the plasmid for future subcloning projects.

Benefits of the GeneArt subcloning service

- **Convenient**—tell us what you need and receive your ready-to-use clone quickly
- **Reliable**—inserts are 100% sequence-verified and documented
- **Versatile**—get access to a wide selection of Invitrogen vectors
- **Confidential**—no data or materials are made available to third parties
- **Ready**—we'll store your vector for future use

Get your gene subcloned directly into the Gateway cloning system

As the sole provider of Invitrogen™ Gateway™ recombination cloning technology, we can subclone your gene into one of our many Gateway™ vectors. This proven and highly cited cloning system is ideal for shuttling genes of interest between vectors with site-specific, recombination-based cloning (Figure 7). With Gateway vectors, the proper insert orientation and reading frame are maintained during shuttling for cloning in multiple expression systems.

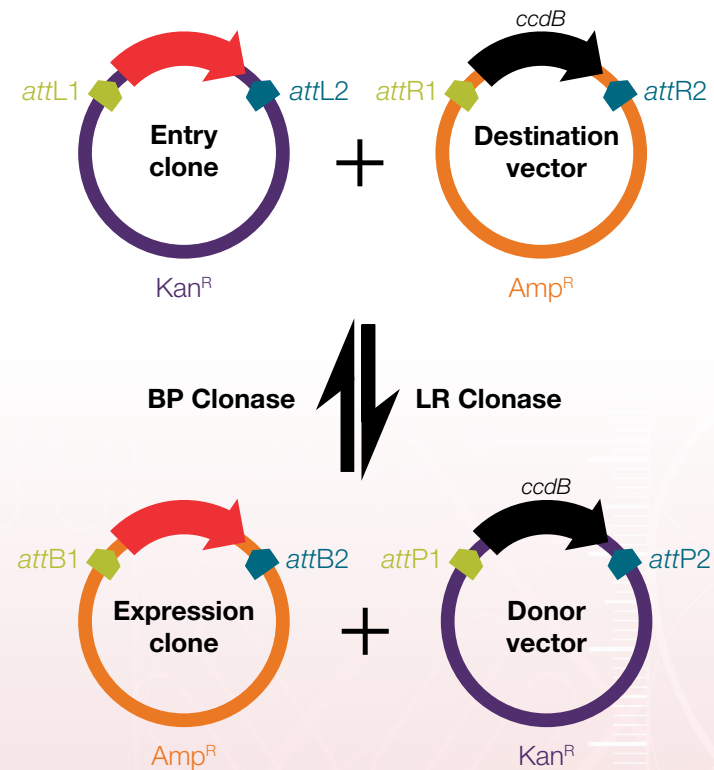


Figure 7. Gateway cloning reactions. The schematic shows four types of plasmids and enzyme mixes involved in Gateway cloning reactions. The red arrows represent fragments of interest. Adapted from Katzen F (2007), *Expert Opin Drug Discov* 2(4):571–589.

Learn more about the Gateway cloning system at thermofisher.com/gateway

GeneArt direct cloning service

With our Invitrogen™ GeneArt™ direct cloning service, you can save 4–5 days of turnaround time compared to subcloning and receive expression-ready genes faster in selected Invitrogen vectors. Simply choose one of our direct cloning vectors when building your clone in the GeneArt Instant Designer ordering portal to assess compatibility of your sequence. You will receive your synthesized gene in the chosen expression vector. The express gene synthesis service option (page 12) saves an additional 1–2 days.

Invitrogen™ direct expression-ready vectors	Application
• pcDNA™3.1(+)	Constitutive expression in a variety of mammalian cell lines
• pcDNA™3.4-TOPO™	Constitutive mammalian expression vector designed to deliver exceptionally high levels of transgene expression
• pFastBac™1	Production of recombinant baculovirus for expression in insect cells
• pDONR™221	Access to the Gateway cloning system
• pET100/D-TOPO™	Bacterial expression in <i>E. coli</i>
• pET151/D-TOPO™	Bacterial expression in <i>E. coli</i>
• pRSET A	Prokaryotic expression
• pYes2.1/V5-His-TOPO™	<i>Saccharomyces cerevisiae</i> expression

Find out more about our direct cloning services at thermofisher.com/expressgenes

GeneArt plasmid DNA purification service

The Invitrogen™ GeneArt™ plasmid service can prepare research-grade plasmid DNA (pDNA) and preclinical-grade pDNA with quality-controlled systems and reagents using proven protocols. GeneArt facilities are ISO 9001:2015–certified and consistently provide products and services that satisfy customer requirements. Preclinical-grade pDNA comes with outstanding quality control, and documentation upon request. Endotoxin and bioburden testing is available for plasmid prep yields over 1 mg (Table 2).

GMP-grade plasmid preparation services are also available through Patheon™ Pharma Services. For more information, visit thermofisher.com/patheon.



Our highly pure, homogeneous plasmid DNA is ready for transfection and transformation:

- Extremely low endotoxin levels (<0.1 EU/μg pDNA at selected scales); generally considered endotoxin-free
- Microgram- to milligram-scale production
- Flexible delivery options—liquid or frozen on dry ice
- Custom aliquoting and tube labeling



Learn more at thermofisher.com/geneartplasmid

Table 2. Plasmid preparation and testing options.

Plasmid prep scale	Communicated yields	Concentration	Endotoxin testing	Restriction analysis	Bioburden testing (gDNA and RNA assays)
Midiprep (50 mL)	10–100 µg pDNA (~100 µg high-performance plasmid**)	Standard: 1 mg/mL On request: 0.1, 0.5, 2.0, and 4.0 mg/mL	NA	NA	NA
Maxiprep* (250 mL)	50–500 µg pDNA (~500 µg high-performance** plasmid)		NA	NA	NA
Megaprep*	Guaranteed 1 mg pDNA (high-performance plasmid,** >3 mg/L prep in LB culture)		Optional	Optional	NA
Gigaprep* (2.5 L)	1–5 mg pDNA (~5 mg high-performance plasmid**)		Yes	Optional	Optional
2x Gigaprep* (5 L)	2–10 mg DNA (~10 mg high-performance plasmid**)		Yes	Optional	Optional

* Prepared with endotoxin-free plasmid prep technology.

** High-performance plasmids typically have high copy numbers and are production-friendly, nontoxic plasmids that routinely provide >3 mg/L in LB culture.

Quality control and documentation

- Appearance based on visual inspection
- Purity assessed by measuring A_{260}/A_{280}
- >85% closed circular construct (visual inspection)
- Transmissible spongiform encephalopathy (TSE)-free option available
- Gene sequence verification
- Restriction analysis available for larger scales
- Low endotoxin (larger scales): <100 EU/mL
- Buffer options: TE, H₂O, and PBS

Further documentation available upon request

Material documentation—Gene construction documentation includes gene design; cloning strategy; oligo design; chemicals and enzymes (provider and Cat. No.); releasing scientist; shipping provider; and tracking number. Additional documents can include a working SOP list and documentation by the releasing scientist.

Data storage for material documentation—All relevant data and material documentation are stored for 10 years. A material documentation report can be requested at any time during the 10-year storage period.

Project design and tracking with the GeneArt Services Dashboard

Easy online project management

The Invitrogen™ GeneArt™ Services Dashboard is a browser-based online resource for all your gene synthesis projects. Powered by the GeneArt Instant Designer application, it makes designing custom DNA clones and linear DNA fragments easy.

Beyond design, the GeneArt Services Dashboard also offers:

- **Personal templates**—save time entering projects with frequently used vector and sequence configurations
- **Pricing**—get quick estimates without uploading a sequence, or download a detailed instant quote for completed designs
- **Daily updates on project status**—track progress of the whole order or a single line-item
- **Courier tracking**—enables seamless monitoring of your project from order to delivery
- **Quality assurance documents**—download data for completed projects

Customer communication care and project support

For immediate needs, our customer communication care (CCC) team provides dedicated global telephone support. CCC team members are experienced specialists located in primary geographic locations and provide support 18 hours per day. Most project orders are placed through our online channels, but offline orders can be placed with the CCC team. If necessary, the CCC team will organize communication with internal functions and connect you to them.

Experienced PhD-level professionals from customer project management, R&D, and our manufacturing teams are available for complex scientific questions or troubleshooting, and they have in-depth knowledge to discuss your results. Depending on the collaboration, a dedicated communications partner can be assigned to handle project setup, general questions, and project updates.

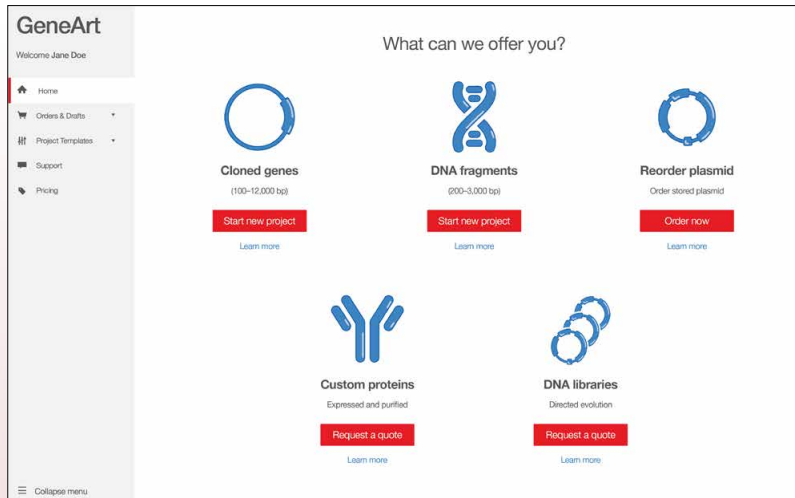


Figure 8. The GeneArt Services Dashboard is the hub for all gene synthesis service projects.

The GeneArt Services Dashboard is designed to enable independent customer-directed gene synthesis and is backed by dedicated support teams to assist with more customized solutions when needed.

Learn more at thermofisher.com/geneartdashboard

GeneArt directed evolution service

Custom mutations and libraries for faster discovery

The Invitrogen™ GeneArt™ directed evolution service employs a variety of approaches to create genetic variants with maximum control and efficiency, including rational protein design and engineering. From a single base pair exchange to full synthetic libraries, we offer custom solutions to provide the genetic diversity and protein characteristics you need. Examples of protein adaptation for specific requirements using GeneArt directed evolution include:

- **Affinity**—increasing the affinity of an antibody for its target via affinity maturation
- **Enantioselectivity**—creating enzymes that only catalyze production of one stereoisomer
- **Specific activity**—increasing the activity of an industrial enzyme to help generate product faster
- **Stability**—increasing the stability of protein drugs in serum

Combinatorial libraries

True rational design allows defined randomization of selected sites only while providing maximum framework integrity.

Benefits: low ancillary mutation rates and high diversity; quality control with NGS available

Applications: construction of recombinant antibody libraries and promoter libraries; combining substitutions identified via site-directed mutagenesis

	50	60	70	
wild type	G	V	P	I
peer A01	G	V	P	I
peer A02	G	V	P	I
peer A03	G	V	P	I
peer A04	G	V	P	I
- - -	-	-	-	-

Controlled randomization libraries

Substitute any amino acid in a gene with a defined probability.

Benefits: accurate fine-tuning of the mutation rate and randomization of the entire open reading frame

Applications: antibody affinity maturation; industrial enzyme improvement; and modification of enzyme enantioselectivity

	50	60	70	
wild type	G	V	P	I
peer A01	G	V	P	I
peer A02	G	V	P	I
peer A03	G	V	P	I
peer A04	G	V	P	I
- - -	-	-	-	-

Site-saturation mutagenesis

Scanning a protein region by site-saturation mutagenesis identifies all beneficial substitutions for enhanced function.

Benefits: cost-effective; no structural data needed for protein improvement

Applications: industrial protein improvement; alienation of proteins from patented sequences

	50	60	70	
wild type	G	V	P	I
F58A	G	V	P	I
F58C	G	V	P	I
F58D	G	V	P	I
F58E	G	V	P	I
- - -	-	-	-	-

Site-directed mutagenesis

Introduce single or multiple substitutions, insertions, or deletions into an existing DNA sequence.

Benefits: fully sequence-verified clones; no unwanted backbone mutants; rapid turnaround

Applications: Construction of fusion proteins, tagged proteins, alternative splice forms, and alanine scans

	50	60	70	
wild type	G	V	P	I
F58A	G	V	P	I
S59A	G	V	P	I
V60A	G	V	P	I
S61A	G	V	P	I
- - -	-	-	-	-

GeneArt Strings DNA libraries and GeneArt combinatorial DNA libraries

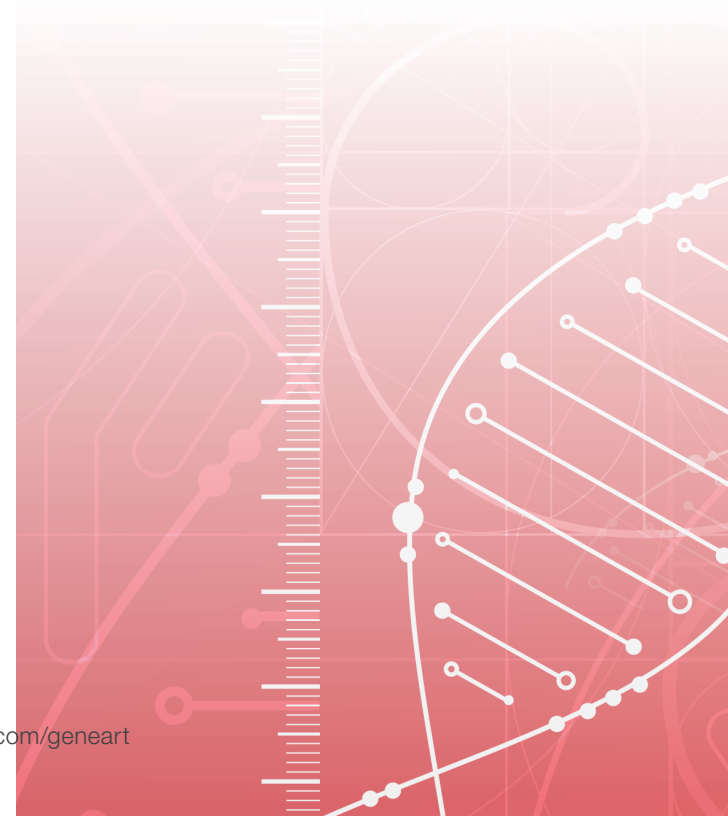
Multiple nucleotide positions can be mutated within a sequence in a combinatorial DNA library, and mutations at different positions can be combined. Based on true rational design, combinatorial DNA libraries can provide maximum diversity to screen for and identify synergistic beneficial mutations (e.g., affinity maturation via phage display libraries). We offer both Invitrogen™ GeneArt™ Strings™ DNA libraries and GeneArt™ combinatorial DNA libraries.

	GeneArt Strings DNA libraries	GeneArt combinatorial DNA libraries	GeneArt combinatorial DNA libraries with NGS
Design flexibility	+ Full IUPAC code available; however, control over frequently occurring amino acids is limited.	+++ TRIM technology allows accurate determination of occurring amino acids and ratios.	+++ TRIM technology allows accurate determination of occurring amino acids and ratios.
Correctness	+ More unintended mutations occur with gene synthesis process.	+++ Error-free template provides best possible correctness.	+++ Error-free template provides best possible correctness.
Cost	+	++	+++
Production time	+++ 10–15 business days	+ 4–6 weeks	+ 4–6 weeks

Combinatorial TRIM technology

In addition to randomization via degenerate codons, such as NNS degenerate codons, sequences in GeneArt combinatorial DNA libraries can be diversified using preassembled trinucleotide building blocks. Utilizing trinucleotide mutagenesis (TRIM) technology in the chemical synthetic process provides significantly better quality than conventional technologies. This enables complete customization of the amino acid composition at randomized sites and prevents the occurrence of unwanted stop codons or amino acids. You can achieve an extra level of quality control for your combinatorial DNA libraries with optional next-generation sequencing (NGS) on the Ion Torrent™ sequencing platform.

Learn more at thermofisher.com/directedevolution



DNA library delivery formats

GeneArt Ready-to-Clone Combinatorial Library	• 2–5 µg linear DNA ready to clone via 5′ and 3′ restriction sites • Non-amplified library; 17–170 fmol (10^{10}–10^{11} specimen variant diversity) depending on library diversity • Amplification primers
GeneArt Cloned Combinatorial Library	• >30 µg plasmid DNA cloned into the vector of your choice • 12 aliquots of 0.5 mL glycerol stocks • Non-amplified library; 17–170 fmol (10^{10}–10^{11} specimen variant diversity) depending on library diversity • Amplification primers



Determining the right library for your research

The GeneArt directed evolution service offers libraries that can be tailored for your needs. Use Figure 9 as an introductory guide to library selection.

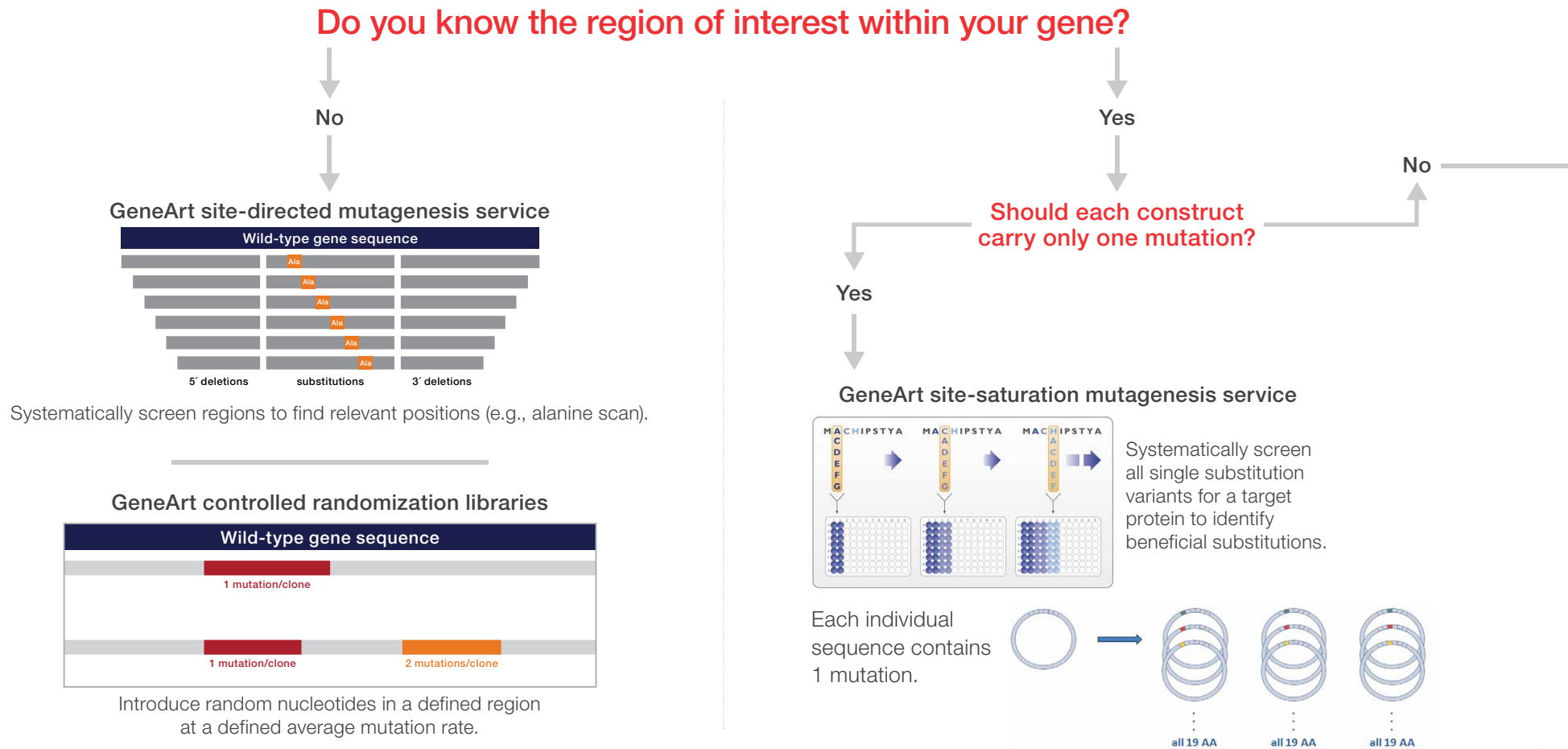


Figure 9. Decision tree for determining which type of library will meet your needs.

GeneArt protein expression and purification services

The gene-to-protein advantage

Make your protein and antibody research more efficient from discovery to commercialization with our complete gene-to-protein workflows. By partnering with us, you can speed up your discovery process and rapidly express and purify protein from transiently transfected mammalian cells.

With a unique combination of our patented GeneArt GeneOptimizer sequence design tool, industry-leading synthetic DNA expertise, and advanced Gibco™ expression systems, our gene-to-protein workflows have been shown to increase protein yields more than 10-fold (Figure 10).

We're here to support all or part of your protein expression and purification needs—from gene synthesis and optimization to early pilot-scale studies and production runs with up to 25 L. Move from idea to purified and documented protein in as few as 5 weeks with GeneArt gene-to-protein services.

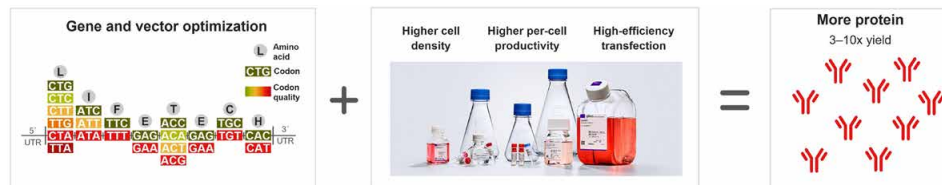


Figure 10. Schematic showing how GeneArt gene synthesis services and advanced Gibco expression systems can increase transient protein yields.

Gibco Expi293 and ExpiCHO Expression Systems

Advantages of using Gibco™ Expi293™ and ExpiCHO™ Expression Systems include:

- Culture medium allows 3-fold higher cell density
- More protein expression per cell
- Transfection reagent effectively delivers DNA in high-density cell cultures
- Protocol fits directly into a 5–7 day workflow

Expression scale

- Highly flexible and extendable
- Allows small-scale 24-well expression
- Production scales from >25 L down to 30 mL



Partnering with GeneArt services to expedite antibody and drug discovery and development

Outsourced protein production and purification in recent years has served many needs of biotech and pharmaceutical companies around the world. These services have become critical for SARS-CoV-2 vaccine and biotherapeutic development.

The primary question is often “How can I move from discovery to commercial scale-up as fast as possible?” By starting with a transient protein production and purification pilot project, researchers can quickly obtain critical data early in the discovery process. This involves 2 key steps:

- 1. Antibody production with GeneArt services begins with *de novo* gene synthesis. Use the GeneArt GeneOptimizer tool (page 14) to optimize recombinant protein expression. Starting with gene synthesis is a fast and efficient way to screen for error-free clones and quickly identify the most promising candidates for production scale-up.
- 2. Select an expression vector and production volume to run a pilot protein expression and purification study. Our protein production and purification pilot studies encompass a wide range of formats from 24-well plates to 1 L volumes. While we offer production volumes all the way up to 100 L, we always recommend starting with a pilot study and analyzing the results before scaling up to 1 L and beyond.

GeneArt services have more than 20 years of experience in the bioproduction of genes and transient proteins. The most successful recombinant protein and antibody production projects start with DNA and pilot studies. Our integrated bioproduction services will expedite the discovery process from pilot studies to commercial production.

Screening antibody candidates with high-throughput ExpiCHO expression and purification

GeneArt services also include a small-scale ExpiCHO transient protein expression and purification service to support partners interested in screening antibody candidates as quickly as possible. These small-scale protein pilots are offered in 24-well plate format with standardized purification approaches to rapidly deliver results.

Size	Culture volume	Samples per plate	Controls per plate	Quantity after purification	Final volume	Control minimum*
24-well	2.5 mL	20	4	1.8 mg to 10 g	350 µL	200 µg

* Controls included across each plate (+ rIgG, – mock). Customer-specific controls (e.g., GM controls) can be substituted in mock wells.





Purification methods

- Highly flexible—capacity depends on product mix
- >5,000 proteins produced per year (various scales)
- Multiple ÄKTA™ Pure, Purifier, and Xpress devices
 - ≥300 antibody purifications per week at <250 mL scale
 - ≥60 antibody purifications per week at 1 L scale
 - ≥10 antibody purifications per month at 25 L scale
- ÄKTA™ Flux system for diafiltration
- Multiple tangential flow filtration devices

Service	Standard specifications
Purification	• Affinity chromatography • Size-exclusion (SEC) chromatography • Ion-exchange (IEX) chromatography
Affinity tags	• His-tag • Fc-tag (protein A/G/L) • Strep-tag™ tag • FLAG™ tag • C-tag • HSA-tag • Other tags available on request, including Fabs, fusion proteins, and bi-specifics
Additional options	• Polishing (additional column purification) • Epitope tag removal via protease cleavage • Customized protocols, resins, buffers, and reports • Aliquoting service • Protein concentration adjustment • Others upon request

Driving performance through collaboration

Expression plasmid	Expression	Purification	Purification
• GeneOptimizer algorithm increases yield • Full design flexibility • Invitrogen™ vector suite • High-quality plasmid preparation • In-house gene-to-protein process provides full control	• Flexible scale • Parallel workflows for high throughput • Expi293 and ExpiCHO expression systems	• Parallel purification (ÄKTA™ system) • Crossflow filtration system • Rapid pre-purification titer detection • >5,000 Ab purifications per year • >500 non-Ab purifications per year	Standard: • SDS-PAGE or western blot • A₂₈₀ (Thermo Scientific™ NanoDrop™ spectrophotometer) • Capillary gel electrophoresis (Caliper LabChip™ GXII system) • Analytical size-exclusion HPLC • Endotoxin detection (PTS cartridge or MW)

Request a quote for a project at thermofisher.com/g2pservice



Biosafety and biosecurity

Our commitment to protection

Biosafety protocols protect laboratory staff, the environment, and the public from exposure to microorganisms. Biosecurity protocols are public health safeguards that protect against domestic or international terrorism and warfare involving the use of dangerous biological agents or toxins like *Bacillus anthracis* and *Yersinia pestis*. Biosafety and biosecurity are strictly regulated under national and international law. It is a Thermo Fisher policy to be fully compliant with such regulations, and Thermo Fisher is one of the founding members of the International Gene Synthesis Consortium (IGSC). Every sequence is screened using several pathogen databases (Figure 11) according to national and international laws regulating the export of dual-use goods and the nonproliferation of potential biological warfare agents. This database screening process is subject to continual improvement and updates.



Figure 11. Sequence review process for biosafety and biosecurity compliance.

What happens in the case of a hit?

Biosafety

- Level one and level two sequences can be produced under the respective production conditions.
- Sequences that reach level three or higher will not be synthesized.

Biosecurity

- Customers will be notified, and specific production and export requirements will be discussed.
- Sequences can be shipped after signing an end-use declaration. In some cases, special export and import licenses will be required by the respective export control office.
- No additional costs will be incurred.



ISO certification

Our Regensburg manufacturing site is ISO 9001:2015–certified and adheres to specific ISO quality management standards that help ensure reliable, reproducible, and timely production of your gene sequence (Figure 12).

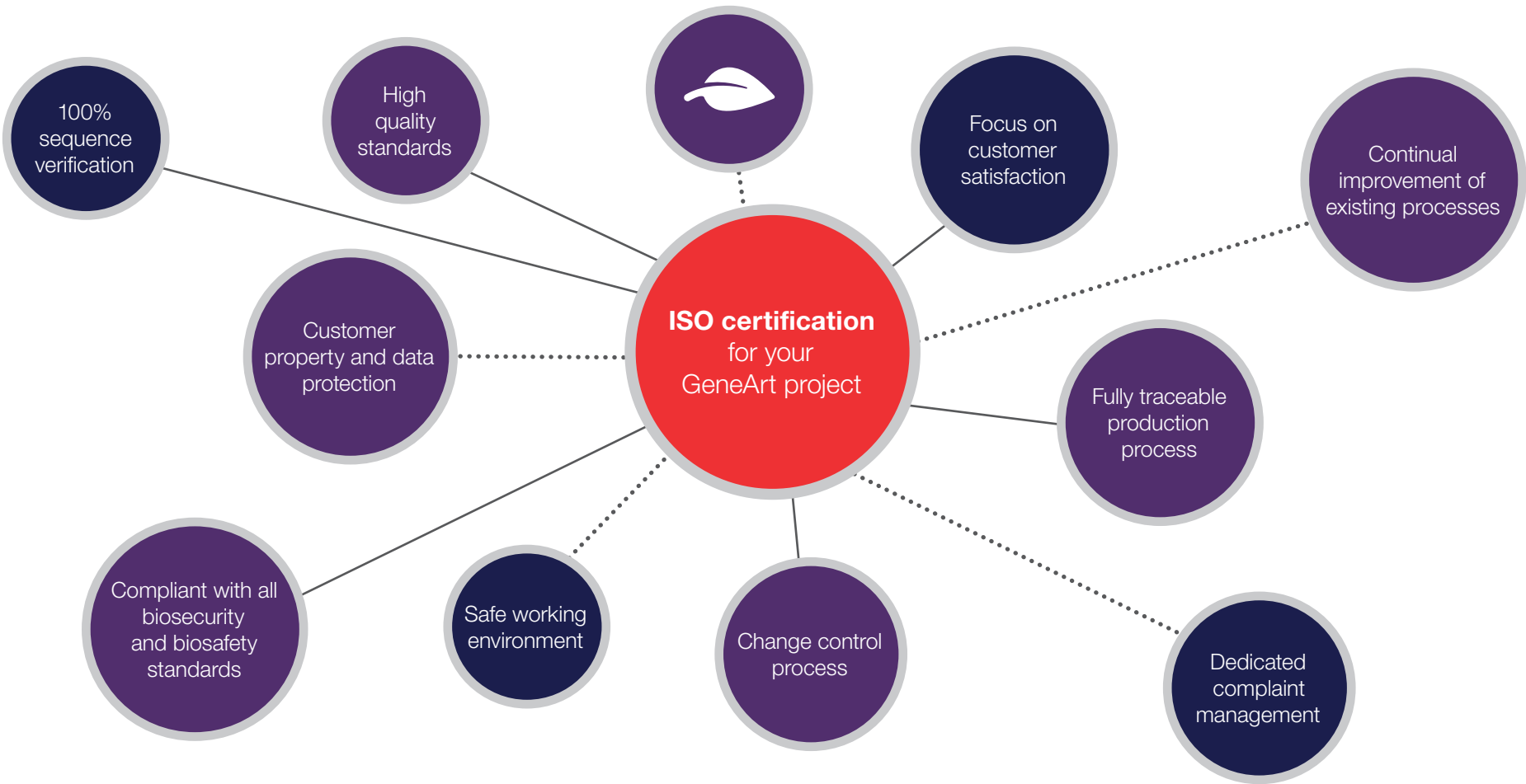


Figure 12. Important ISO certification and day-to-day benchmarking criteria.

Our commitment to you and the environment

Sustainability matters to us

At Thermo Fisher, we take responsibility for our environmental impact. More waste is generated by humans every year. Greater self-awareness on the part of consumers is encouraging, but individuals are only part of a complex waste-reduction equation. Businesses must take stock, too. We have 16 externally certified zero-waste sites around the world as of 2021, including our Regensburg production site for GeneArt projects.

It's paper. It's cool.

Some of our biggest environmental impact has been due to cold shipping. Traditional expanded polystyrene (EPS) foam coolers are good for protecting products but are difficult to recycle, which creates disposal issues for our customers. Our 100% paper cooler is an environmentally preferable alternative to EPS coolers, and it meets the thermal requirements necessary to uphold our stringent product quality standards.



Here are some examples of how we've reduced waste

Redesigned GeneArt product packaging

- We replaced the original 20-tube rack with an 8-tube rack for a 54% reduction in weight and a 1,100 kg reduction of cardboard.
- We use fully recyclable cardboard.
- The redesigned packaging improves functionality for our customers.



Developed an automated reagent transfer system for oligo synthesis

- Makes manual handling of hazardous substances unnecessary.
- Reduces labor time.
- Reduces glass waste by approximately 20 tons per year and cardboard waste by 4.5 tons per year.
- Reduces reagent and waste disposal costs.



Enabled data transfer for quality assurance documentation (QAD) via the Thermo Fisher™ Connect Platform

- Download QAD from the Thermo Fisher Connect Platform instead of receiving a CD with your shipment—look for the GQ icon.
- Eliminates printed manuals and product information and the need to store QAD on CDs.





Customer support

Whether you interact with us indirectly online or directly via our customer support team, we strive to provide the best customer experience. Nearly all GeneArt services can be ordered with our online tools, and we have a dedicated support team for your peace of mind.

GeneArt gene synthesis customer care group

Our GeneArt gene synthesis customer care group is a single point of contact to serve you from initial inquiries about our products, technology, and on-line ordering through the manufacturing process and delivery of your gene construct. All of our customers worldwide have access to individualized project consulting, because we care about your projects.



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Learn more at thermofisher.com/geneart

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