General Business Terms (GBT) about Molecular Biodesigns, Gene Syntheses and Related Additional Services like Highest Quality Vectors or Expression of Gene Products.

1. General Business Terms

This **GBTs** are regulating the contractual relations and agreements between the molecular *biodesign*s made executed on the responsibility of ATG and the provision of gene syntheses and expression systems for the customers of the genes, gene fragments or multiple genes organized in integrated gene constructions like combinatorial vector constructs or individual gene clusters and its *biodesign*.

1.1 General remarks on pricing, warranty and project requirements

Products: For products like expression vector kits the actual price list is binding. The customer can get the actual price list upon request or he will find it in the internet on *www.atg-biosynthetics.com*.

Standard gene related services: The customer can get the actual listed pricing upon request or can find it in the internet.

For gene syntheses the pricing determined in the QUOTES inquired for is binding. The pricing and delivery time is substantially dependent on the length of the gene [bp], the GC-content [%], the length and quality of direct repeats and inverted repeats, repetitive structures as well as homo-poly-nucleotide stretches and the degree of homology with sequence motives like Chi – recombination sequences with a clear impact in the stability of the DNA sequences.

Warranty issues for gene syntheses: For synthetic genes ordered at ATG the company is responsible to deliver the sequence identity of the target sequence and the amount as well as the quality of DNA which was requested by the customer.

The basic standard unit and minimum standard quality of delivery of the DNA ordered is a mini preparation of plasmid DNA by use of a *Col*EI ori high copy number pUC-derivative vector. Please note that the choice of the type of vector has a substantial impact on the amount of DNA delivered. This is the case by using a low copy type of vector for sub-cloning. The amount of DNA required by the customer can differ in low and medium copy number vectors and the amount of DNA needed for experiments must be provided by an additional service.

Special DNA-services: For other quality levels like GMP like quality e.g. animal free, protein free, RNA free, low or no LPS/pyrogen degree further documentation about the requirement specification in detail are needed which are determining the quality expected to be delivered from ATG. For projects covering specific high quality levels of DNA and big amounts or many variant DNA-constructs of high quality specific agreements are necessary in order to define the project planning time lines, milestone and objectives.

1.2 General terms of delivery time

For gene syntheses individual terms are indicated in the individual OFFER/ QUOTE. The delivery time is dependent on the length of the gene [bp], the GC-content [%], the length and quality of repeats and inverted repeats as well as homo-poly-nucleotide stretches, repetitive structures and the degree of homology towards sequence motives like Chi – recombination sequences with a clear impact in the stability of the DNA sequences.

In case of gene toxicity problems the delivery time can be severely be influenced until a stable construct can be selected. Please read in more detail below.

1.3 General terms of payment

(1) Date of Delivery has the same date of the INVOICE/ BILL OF DELIVERY/ PACKING LIST

(2) Date of payment is expected to be not longer than the date of the INVOICE plus max. 10 working days (two weeks)
(3) After five days the first REMINDER is sent without any charge of interest but instant payment is expected
(4) With default of payment ATG can require interests on arrears at the rate of 8% about the respective base interest rate sentence of the European central bank p.a. The assertion of a proved higher damage is left.

General terms for molecular *biodesign*s and warranty of molecular function

General definition and remarks: An artificial gene construction comprises several functionally interrelated and inter-dependent collaborating genes which can be clustered in operons but are always acting in a predetermined, desired concerted fashion.

A *biodesign* is basically an intended man made, mostly computer aided molecular construction plan which can determining sequential, structural and formal-functional molecular information like genetic or genomic sequences, artificial sequence compositions or sequence motives like control elements or the explicit as well as implicit (en-)coding of information in the sequence of informative molecules. Most if not all *biodesign* are ideally basically dependent on ideally iterative experimental designs or multiple constructive variants for testing the functionally relevant assumptions made in the construction plans.

It can include arbitrary, (semi-)rational or predetermined specific sequences of formal-functional verified DNA - templates but also experimentally verified individual phenotypic functions of verified genotypes as well as arrangements and combinations thereof.

1.1.1. Regarding a pure service mode for custom gene syntheses in a direct or sub-contracting situation with ATG the customer agrees that in case the sequence design of a DNA/gene construction was performed by the customer or his co-workers himself or in his project responsibility with collaborating parties (like this is the case with funded projects); the customer himself is in full responsibility for the functionality of the gene sequences he provided for to be delivered by ATG in form of physical DNA-molecules.

This applies in all those cases where the sequence ordered by the customer was provided correctly and with documented sequence identity by sequencing QC by ATG like it was ordered by the customer.

1.1.2. In another (sub-)contracting custom service mode where ATG is involved in sequence calculations and the *biodesign* a mutual agreement with the customer needs to be set up. The intension in this agreement is creating the legal basis for the project. It provides a realistic and clear objective and is regulating the expectations to the project about what parameters can be realized, the time lines, milestones as well as all technical and quality requirement specifications.

For the *biodesign* of DNA sequences ATG is responsible for providing the most plausible rational data basis available for the *biodesign* process and to provide these to the customer as well as successively implementing this information in *de novo biodesigns* into the target molecules of interest in the best mode possible according to the state of the art of the algorithms.

In the agreement most plausible decisions relevant for the final outcome of molecular *biodesign*s are made. The genes of interest (e.g. the coding sequences, CDS, needed), the different sequence motives needed (e.g. regulatory) the number of different parameters to be processed, the degree of sequence parameter calculations *in parallel*, the number and quality of variants to be tested for analysing the outcome of the predicted gene function is to be determined in advance. In this project mode ATG serves as qualifies consultant *biodesign*er provides algorithma and calculation time and based on the status quo knowledge is in charge for to find the best plausible mode for realizing the

customer's requirements for the biological or other like technical functionality of the DNAs or its gene products of interest.

The results for this assessment of the best mode for the *biodesign* of gene variants are presented to the customer in a detailed report and discussed before starting the realization of the *biodesigns*.

If compliance with the customer is achieved on the contractual basis and the fair treatment of the complexity of the tasks to be realized as well as on the documented *status quo* of available and best reliable knowledge the realization of the *biodesigns* according to the assumptions made and accepted are realized with the appropriate highly *in parallel* calculations *in silico.*

Finally the mode of realizing results physically by gene syntheses can be further realized in collaboration with ATG. Proprietary databases and software for the handling variant DNA libraries is another expertise of ATG.

Obvious errors during the process documented made by ATG are clearly in the responsibility of ATG. Issues on DNA identity and quality are dealt with according to paragraph § 1 and 2.

Although the risk for functional failure is deemed to be low the general functional outcome of the molecular *biodesign* approaches can finally not be guaranteed by ATG and therefore for the general risk of functional failure no warranty can be provided. This is because even the best basis of most plausible knowledge is extracted from publications of third parties and published gene and genome sequences. This published knowledge might be erroneous and lacking the decisive points or was misinterpreted by third parties.

However the documentation of the highest degree of plausibility for a successful outcome is a duty of ATG.

1.1.3. In a project mode activities of *biodesign*ers can be organized as a collaborative group. Individual group members may have mutual agreements. These GBTs here are to be applied on the whole group of collaborative members in relation to a given customer. The GTBs require that collaborative *biodesign* projects despite the service agreement with the client includes the non-disclosure agreement with ATG which is in compliance with the needs of the ATG client. This includes all collaborative group members and reflects all the provisions made in the GBTs. The GBTs here are valid in particular also if the collaborative group and/or the customer uses „general terms" of business being conflicting and which contains divergent conditions compared to the regulations of the GBTs here.

1.1.4. In another (sub-)contracting situation ATG despite being molecular *biodesign*er acts in addition responsible for experimentation in iterative functional improvements or for verifying the functional outcome of sequence variants. In this case ATG is managing the custom project directly based on the detailed agreement with the customer. For the realization of such projects a project plan with all time lines, duties, cost, tasks, payment schemes and milestones is set up with all technical and quality requirement specifications documented in detail. In this case ATG governs the project organization, realization and controlling according to the project plans agreed with the customer.

1.1.5. Additional frame conditions for molecular *biodesigns* and service gene syntheses agreements

1.1.5.1. Provided that the molecular construction in part or as a whole are related to and potentially are affected with biosecurity and biosafety issues the rule applies:

In obvious conflicts with the existing legislation with issues of biosecurity and safety ATG refuses to provide any services. Gene syntheses which are not obviously and visibly associated with biosecurity and safety relevant regulations of the genes itself and in addition its primary and/ or secondary synthesis products are in the sole responsibility of the customer. For malicious deceit about hidden harmful but real objectives of the client ATG does not take any responsibility.

1.1.5.2. Provided that the molecular construction as a whole or in part is NOT toxic to E. coli but the function of the genes and clusters are not the desired ones the customer expected, the rules apply:

In the case the individual *biodesign*s of given sequence constructions are performed exclusively by the customer and ATG delivers the DNA/ gene sequence/ molecular construction just like ordered ATG does **NOT at all** take the responsibility for the *biodesign* of the customer and its final molecular functionality of the molecular constructs which was created without any expertise of ATG.

This also applies if the customer just ordered a basic formal codon adaption of the gene mostly termed "gene optimization" in the standard mode. In this most simple mode generally accepted computer based algorithms are adapting the general codon use according to the genomic codon frequencies of generally accepted genomic codon tables or statistically selected subgroups of genes in a statistical fashion.

1.1.5.3. Provided that the molecular construction as a whole or in part is toxic to E. coli the rules apply:

In the case the *biodesign* construction demonstratively - after three rounds of final assembly - shows to be toxic to ***E. coli*** during the assembly process ATG does **NOT** take the responsibility for the *biodesign* of the customer's choice of the gene which was selected by the customer without the expertise of ATG.

A gene construction is regarded not to be synthesizable in the case of **(1)** toxicity for ***E. coli*** on the basis of the proven gene syntheses processes. In case intermediate assembly products are repeatedly coming not together by standard methodology or the final two fragments of the assembly process do not go together either by ligation or by recombination. These rules are to be applied provided that the last two fragments of the assembly process are sequence verified and show 100% sequence identity **(2)** The **full length gene** fails in an appropriate expression vector and cannot established in the *E. coli* cell - even finally by use of low or single copy vector systems and with the regulatory elements the customer used for his individual *biodesign*s **(3)** genetic instability - the full length construct can repeatedly only isolated from *E. coli* with sequence errors and not be completely sequence verified because of continued sequence defects of prior sequence verified sequences in part. Sequence defects can be identified as silent or non-silent point mutations or micro-deletions as well as sequence rearrangements either in coding sequences of a gene or in regulatory sequence regions by the sequencing QC of fragments or finally the whole gene construct.

The molecular constructions are to be fully paid by the customer if the final assembly of the last two fragments showing 100% sequence identity was repeated three times under standard conditions but finally failed under proved standard assembly process conditions and in addition the outcome of the final sequences are described like in **(1), (2)** and/ or in **(3)**.

1.2 The GBTs listed here are also applied if the *biodesign*er ATG in knowledge of conflicting or divergent conditions of the customer realizes the contract **according to the customers' instructions** without reservation.

1.3 Diverging conditions to these listed here are valid only if the *biodesign*er agrees to it expressly in writing.

2. Subject matter of the contract; copyright and rights of use

2.1 Contracts with the *biodesign*er deal with the achievements of a single originator or a team. These are subjected to the granting of rights for the use of the work's achievements. The contracts do not cover monitoring of conflicting protection rights which are infringing with the admissibility of the

biodesigner's work to the object. It also does not include the monitoring of relevant features or registration of industrial or other protection rights or usability of the work of the *biodesigner*.

The customer himself is responsible for research on these topics in-depth.

2.2 All drafts and molecular construction plans including formal-functionally verified DNA - templates and all amendments thereof in order to improve constructive features or biological function or for molecular prototyping in terms of achieving technical requirement specifications for the realization by syntheses are covered by the copyright protection law and all laws protecting accomplishments in design. The regulations covered by this law are valid between the parties even if a threshold for originality should not be given in particular cases e.g. like basic protection conditions needed for patenting. With this in particular the rules for originator protection §§31 are applied in such a case following UrhG (German law); in addition, in particular the copyright claims from §§97 are entitled to the parties in such a case following UrhG.

2.3 The conceptual designs and construction plans for sequence compositions especially in formal-functional verified forms which are intended for its realization by syntheses and left to the customer are not allowed to be amended without explicit compliance with the *biodesigner* (ATG) neither in the original form nor during its reproduction or via transmission to third parties.

2.4 Every imitation – also from parts – is inadmissible. Any offence against this paragraph 2.3 and 2.4 entitles the *biodesigner* for a contract punishment of compensation and pricing at an adequate rate compared to the economical damage or an adequate participation on revenues achieved e.g. in form of royalties. The economical damage caused is to be assessed by arbitration of an independent panel of referees nominated in equal parts by the disputing parties.

2.5 The *biodesigner* (ATG) grants the necessary right of use for the individual contractual purpose to the customer. In case nothing else is agreed, only the simple right of use is granted case by case. Any transfer of exploitation rights to third parties needs the written consent.

2.6 The rights for exploitation of the achievements of the *biodesigner* are only transferred to the customer after completion of contractual payments.

2.7 On any publications of results the *biodesigner* needs to be referred to as the originator. An offence against this regulation entitles the *biodesigner* for demanding a fine at the rate of 100% according to the invoice amount as the regular and agreed compensation.

2.8 Molecular design proposals and cooperative influence of the customer and/or his employees do not have any impact on the value of the price agreed and do not establish co-copyright or originator rights.

2.9 For use of its *biodesigns* ATG raises no claims on the ideas of individual applications formulated by customers and the applicability to be achieved as well as the right for its exclusive utilization. But the *biodesigner* (ATG) claims originator rights on the improvement of molecular biological function in terms of improvements for construction or functional purposes like high yield expression or other technical requirement specifications aimed on as well as economical desired features of functional improvements e.g. traits in production strains). Every application beyond the extent of utilization for gaining experimental knowledge (temporal, spatially and with regards to contents) like in particular any not expressly agreed commercial use of functionally improved biological design results is permitted.

3. Compensation

3.1 Conceptual sequence designs or molecular construction plans and/or formal-functional verified sequence features for the realization by syntheses together with granting of rights for its use form a uniform achievement. The calculations for the value of an individual offer is performed on the basis of the an agreement determining the quality and scope of molecular biological design achievements expressed in a quote provided that no other arrangements were met. The prices are net amounts which are to be paid plus the legal value added tax.

3.2 If no rights for use in applications are granted for molecular construction plans and functional sequence designs no compensation is due for the final outcome of the functional realization of the design or for experimental – scientific progress in knowledge.

3.3 The manufacture of conceptual designs and all other activities which the *biodesign*er (ATG) produces for the customer are liable to pay costs, provided that there is not expressly agreed something else.

4. Achievements in offers maturity of the price, decrease of compensation, delay of delivery

4.1 For setting up complex offers e.g. where an orientation towards the specific features of the customer s' project is necessary, collaborative work is necessary to figure out the scope of an offer and or it is necessary to perform research in publications, data mining in data bases etc. complex offers a milestone payment for the planning phase of a project can be individually negotiated and separated from the realization phase for independent invoicing.

4.2 Alternatively for setting up an appropriate offer 10% of the final amount of the contractual value can be charged if the offer is not finished yet. In case the customer received the offer in its final stage 20% of the final value of the quote are charged even if the quote is not accepted. The setup fee is calculated as part of the final value and is to be credited and not charged extra.

4.3 The price is due by delivery of the work. It is payable without deduction. If the ordered sequence *biodesigns* are taken in parts, a suitable price in part is due in each case for each part provided that there is no other agreement. If an order takes longer time or requires high financial payments of the *biodesign*er in advance, adequate payments in advance, for progress and final payments are to be performed. For *biodesign* projects upfront in advance payments are basically 30% to the whole price with placing of order; 40% after completion of 80% of the works upon the delivery of the biodesigned molecular construction plans, 30% after final delivery and the finalized and accepted reporting. Exceptions can be agreed.

With notice before the start of uptake of syntheses work and its realization **40%** of the agreed price will be paid as upfront payment in advance and **60%** upon the delivery of the quality control (QC) sequencing data of the gene/ DNA-constructs.

The DNA-molecules resulting from *biodesigns* are delivered in time in standard quality. In case of delay due to problems during the syntheses, e.g. gene toxicity the customer is informed immediately.

The standard quality requirements are vector bound DNA delivered in the known miniprep format and the quality specifications are according to standard procedures.

Additional services like the provision of DNA-sequences (mostly based on the related *biodesigns*) in a higher quality like the basic service requires or for the production of gene products *in vitro* or *in vivo* additional agreements are required which formally are related to the modes described here.

The acceptance of the work by the customer may not be refused for irrational or specialized ignorant reasons, especially not against features of the *biodesign* which were agreed before. Within the scope of the accepted agreement freedom of creation exists.

5. Special achievements, additional costs and travel expenses

5.1 Special achievements like the re-writing or change of molecular constructional designs and formal- functional verified sequences for the realization by syntheses, study of scientific literature manuscripts, data mining, supervision of processes are calculated after the time involved and required to gain biology design achievements separately.

5.2 The *biodesign*er (ATG) is entitled after previous consultation with the customer to order subcontractor achievements necessary for the fulfilment of the order in the name of and on account of the customer. The customer undertakes the commitment to give suitable authority to the molecular *biodesign*er. Third party or subcontractor achievements by purchase on own account for the fulfilment of orders are not needed to be disclosed to the customer.

5.3 As far as in particular cases contracts about foreign achievements are concluded in the name of and on account of ATG, the customer undertakes to release ATG in the inside relation from all obligations which arise from the completion of the contract.

5.4 Expenses for additional technical costs, in particular for special materials, chemicals, kits and fees for the manufacture of prototypes and functional variations, reproductions, agreed realizations are to be refunded by the customer.

5.5 Travel expenses and expenses for travelling, to undertake in connection with the order and are arranged with the customer, are to be refunded by the customer according to the previous arrangement.

6. Property in conceptual designs and data

6.1 In conceptual designs and molecular construction plans or designs only rights of use are transferred but no property rights.

6.2 ATG remains its ownership to the plans, texts, images, sequences and already realized molecules in sequence and structure. If there is no other agreement in writing all relevant materials are to be returned after an adequate time back to ATG. By damage or loss the customer has to substitute for the costs which are necessary to the restoration of the originals. The assertion of further damage remains untouched.

6.3 Also in fulfilment of the contract to originating data and files remain in the property of ATG. He is not obliged to provide, generated or researched data and any files to the customer. If the customer wishes their publication, this is to be agreed separately and to compensate.

6.4 If the molecular *biodesign*er has made available data and files to the customer, these may be changed only with previous approval of ATG. Rights of recourse on unauthorized changes of molecular designs construction plans by the customer or other persons on behalf of the customer are not legal.

6.5 Shipping of all in paragraph 6.1 to 6.4 listed objects occurs on own risk and on the account of the customer.

7. Correction, production control, specimen copies and self-advertising

7.1 Before the sequence realizations are subjected to syntheses the templates used for this are to be provided to the customer for final control (e.g. together with the *biodesigners*) and if applicable for to unravel mistakes and to find final corrections.

7.2 The production control of the *biodesign*er by the customer/ client occurs only on account of special arrangements. In case of the production control by the customer he is entitled to meet necessary decisions at its own discretion and to give suitable instructions. This is preferably the case

when ATG is calculating and realizing sequence designs which are based on the ideas of the customer.

7.3 In case of a project success in terms of a veritable positive scientific outcome or commercially exploitable relevant results during the realization of the project on the markets the customer discloses and refers this to ATG.

If not agreed otherwise in writing ATG is entitled to claim for royalty payments as a vital contribution to the customer's/ client's success. The royalty payments are to be determined in the range of commonly accepted percentages to the revenue.

If not agreed otherwise in writing ATG is entitled to use the results of the projects as well as the functional descriptions and all information exchanged for the fulfilment of the contract for the purpose of self-advertising in all media and to inform about the contractual relation to and the work for the customer. This provided that there is no conflicting situation with the NDA/CDA agreement.

8. Liability

8.1 The *biodesigner/originator* (ATG) is liable for resulted damages or loss of data and materials like templates, data media left to him but also for issues of confidentiality related to project aims and results only in case of intention and coarse carelessness. For the rest he is liable only for light carelessness, provided that a duty is neglected whose compliance is of particular importance for reaching the contract purpose (cardinal's duty).

For damages from the injury of the life, the body or the health resulting from the instructed work of *the biodesigner/ originator* (ATG) the customer is liable for such damages also on the basis of light carelessness in case of its use.

8.2 For any orders which are given in the name of and on count of the customer to third parties the *biodesigne*r (ATG) takes no liability towards the customer, unless, fault meets solely with the choice of *the biodesigner/ originator*. In these cases *the biodesigner/ originator* (ATG) appears merely as a mediator.

8.3 With the approval of rationally reasonable and plausible conceptual designs or formal-functionally verified molecular construction plans and designs for the realization by syntheses the customer takes the responsibility for the all over technical correctness according to the specific function of the results especially for its applicability (e.g. instability or toxicity of a construct in a certain environment which is predetermined by the customer). For such conceptual designs created in collaboration and approved by the customer *the biodesigner/ originator* (ATG) is free of liability for the functional outcome. *The biodesigner/ originator* (ATG) takes the responsibility for the biological function (natural, synthetic, artificial) of molecular constructions only if it was expressively agreed on and contractually fixed (e.g. in a milestone plan) especially in iterative modes of continuous functional improvemens but not in general.

8.4 Objections of evident defects are to be asserted within 30 days after delivery of the work in writing with *the biodesigner/ originator (ATG)*. For the protection of the term the timely sending of the rebuke is sufficient.

9. Creation freedom, realization of the order and presentations

9.1 Within the scope of the order creative freedom exists. After approval complaints concerning the Creation by *biodesign*s are excluded. If the customer wishes changes during or after the agreed scope of the design or after start of realization or reproduction, he has to take over any of the add-on costs caused thereby.

9.2 If the realization of the order is delayed for reasons of which the customer has to represent, the *biodesigne*r (ATG) can require an adequate increase of the price. With intention or coarse carelessness he also can assert compensation claims. The assertion of a further delay damage remains untouched of it.

9.3 The customer assures that he is entitled to the use of all sequences, originals, pattern, templates, models etc. handed over to *the biodesigner/ originator* (ATG). In case he is not entitled to the use it against this assurance, the customer releases *the biodesigner/ originator* (ATG) from all claims for damages of third parties.

10. Termination of contracts

In case of a premature contract termination by the customer ATG retains the right on full compensation. In addition ATG receives the agreed price nevertheless saved expenditures or not carried out or wilful omitted substituting contracts (§649 Civil Code, Germany) need to be accounted. Part working achievements are to be paid by the customer according to the progress of the work realized if explicitly agreed.

11. Final clauses

11.1 Provided that the customer is a businessman, place of fulfilment and legal venue is the main operation of ATG. For solving conflicts all efforts shall be made for to find an acceptable solution for both parties without the involvement of third parties. Self-organized arbitration committees deploying suitable and experienced experts shall be intentionally preferred to institutional courts. Courts of arbitration shall be preferred to the public courts in case the cost for both parties can be substantially reduced by arbitration. The most cost effective solution shall be applied for finding appropriate solutions.

11.2 The laws of the Federal Republic of Germany are to be applied.

State 1-2007/revision 5-2016/ revision 01-2017

ATG:biosynthetics GmbH
Responsible for the content: Dr. rer. nat. Hubert S. Bernauer
Molecular *biodesigne*r (Molecular Genticist)
Weberstr. 40, 79249 Merzhausen (close to Freiburg i.Br.)
hubert.bernauer@atg-biosynthetics.de