

Quote Expires in 30 days.

QUOTATION and Statement of Work for Aptamer R&D Services:

Thank you for contacting Aptagen regarding your aptamer development needs. Aptagen has over 25 years of experience and a number of testimonials attributing to our exceptional customer service and quality for success. Please see the FAQs section in this document for *Frequently Asked Questions*.


Unlike antibodies, aptamers (known as “synthetic antibodies”) are single-stranded DNA, RNA, modified nucleic acids, or peptides (i.e. peptimers™) capable of binding to a unique target or analyte with HIGH Affinity and HIGH Specificity. The types of targets include small molecules, proteins, biomarkers, cells, and tissues.

Intellectual Property (IP): Aptagen owns its proprietary processes of aptamer development; however, ***the Client will own 100% of the rights to the aptamers Aptagen develops for the Client.*** Client contracts Aptagen to perform the R&D, the Client owns the IP. No royalties.

Introductory



Demo Kit
\$199
(< 1 month)

		Basic	Standard	PREMIUM	PREMIUM Plus
Phase I	Library Enrichment (SELEX)	✓	✓	✓	✓
Phase II	Polyclonal Sequencing & Bioinformatic Analysis	✓	✓	✓	✓
Phase III	High-throughput Screen (monoclonal candidates)		✓	✓	✓
Phase IV	Candidate Synthesis & Qualitative Assessment		✓	✓	✓
Phase V	Quantitative Assessment (affinity & specificity)			✓	✓
Phase VI	Assay Development				✓
	TOTAL Cost* Contact Us for special pricing on multiple projects.	\$25,000 (2 - 3 months)	\$50,000 (3 - 4 months)	\$75,000 (4 - 6 months)	\$100,000 (6 - 8 months)

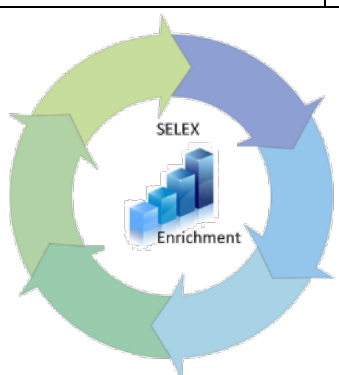
* Cost is Per Project against any target or analyte for ssDNA aptamer chemistry *only*.

The above Package Deals are not available for DELUXE Chemistries (i.e. non-DNA such as RNA, 2'-F-RNA, peptimers).
For DELUXE Chemistries, refer to a la carte pricing model.

DISCOUNTS are available. See FAQs below for details.

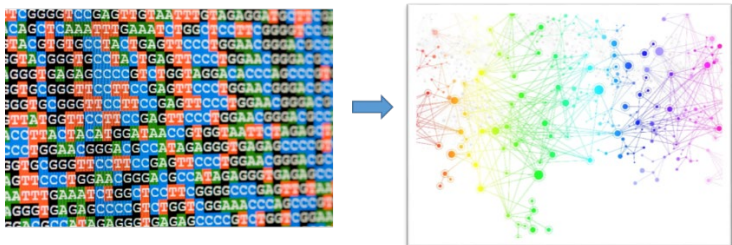
60% (non-refundable) Set-Up Fee shall be due prior to project start date.

STATEMENT OF WORK (A la carte pricing model):

PHASE	Description (illustrations on website)	Target Type	Upfront Payment	Time	Milestone Payment*	Subtotal
I: Screening/Selection (SELEX)	Iterative rounds of screening an initial random library against a target for positive selection, and counter-selection against a counter-target or sample matrix for specificity. Client Materials: Please note that the Client will need to provide the target samples and matrix material for Aptagen. <i>An additional convenience fee will be applied if Aptagen is responsible for sourcing materials.</i> It is highly recommended that counter-target(s) is also provided for enrichment of highly specific aptamers. A Material Acquisition Form must be completed for background information on the target, any associated hazards, and handling requirements.	Small Targets: Small Molecules or Peptides	\$12,000	1-2 months	\$8,000 Enrichment > 5%	\$20,000
		Large Targets: Proteins, Biomarkers, Cells, Tissues	\$12,000	1-2 months	\$8,000 Enrichment > 5%	\$20,000
				<p>* Enrichment > 5% is more than sufficient for subsequent phase II analysis based on a library size of 10¹³ to 10¹⁴. A lower enrichment value is not necessarily a cause for concern since NextGen sequencing is employed in Phase II.</p> <p>Biweekly updates on progress.</p> <p>Deliverables: Full Progress Report (including enrichment chart and qualitative assessment of polyclonal response to positive, counter, and negative matrix conditions).</p>		

(Please see **FAQs** in this document for Frequently Asked Questions)

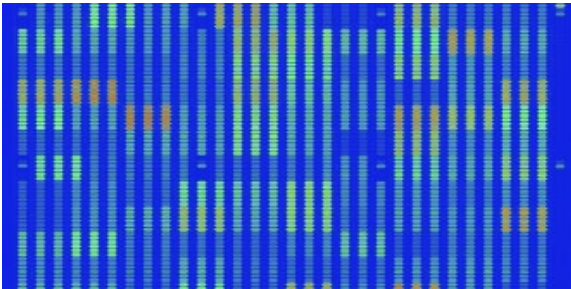
STATEMENT OF WORK (A la carte pricing model):

PHASE	Description	Upfront Payment	Time	Milestone Payment	Subtotal
<p>II: NextGen Sequencing & Bioinformatics</p>	<p>The enriched polyclonal pool is sequenced and thousands of aptamer sequences are provided. Client will have access to all the data generated from the polyclonal aptamer pool in Phase I (millions of sequences).</p> <p>Candidates are grouped into families on the basis of sequence homology, then ranked according to the ratio of their representation in the positive population as compared to control population(s). The stability of a sequence as predicted by secondary structure analysis is also considered for choosing the best candidates.</p>	<p>\$7,500</p>	<p>2-3 weeks</p>	<p>\$5,000 At least 5 Families with more than 15 members</p>	<p>\$12,500</p>
		<p>Deliverable: The most promising aptamer candidates are identified using proprietary bioinformatics. A full Progress/Analysis Report on a handful of the most likely candidates based on sequence homology, frequency, and motif analysis. Client will have access to all of the aptamer sequence information and data. <i>Client owns patent rights to all the sequence information.</i></p>			

(Please see **FAQs** in this document for *Frequently Asked Questions*)




STATEMENT OF WORK (A la carte pricing model):

PHASE	Description	Upfront Payment	Time	Milestone	Subtotal
III: High-throughput Screening Assessment [†]	At least 200 aptamer candidates are synthesized on microarray for semi-quantitative assessment against positive and counter targets to determine the top 5 candidates for further characterization . [†] Not available for cell-based targets or peptimer libraries. Under these circumstances, refer to next phase for assessment.	\$13,800	2-3 weeks	\$9,200	\$23,000
					

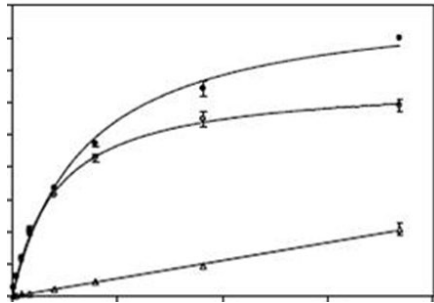

(Please see **FAQs** in this document for *Frequently Asked Questions*)

STATEMENT OF WORK (A la carte pricing model):


PHASE	Description	Upfront Payment		Time	Milestone Payment	Subtotal
IV: Monoclonal Synthesis & Qualitative Pre-Validation of Candidates	Monoclonal aptamer oligo candidate(s) are synthesized, purified, and QC'd. Project costs and time are based on <u>unmodified</u> aptamers, e.g. without fluorescent labelling. The top 5 candidates are qualitatively assessed in “pre-validation” before the next Phase for characterization and validation. *RNA aptamers/apta-switches are transcribed from DNA template. If synthesis is required, then \$800 extra cost. Assay Choices: Gel-shift assay, Microscopy, Flow Cytometry, CD spectra for conformation changes, or Imaging, etc.	Chemistry	Upfront Payment	Time	Milestone	Subtotal
		ssDNA	\$500 per candidate	1 week	Mass spec verified	\$2,500
		RNA*	\$1,300 per candidate	3-4 weeks	Mass spec verified	\$6,500
						
		Deliverable: At least 20 nmoles (~0.5 mg) of each purified ssDNA aptamer, sufficient material for the next phase of the project. Unused material will be provided to Client upon project completion. If more material is needed, a separate quote will be issued. Inquire for non-ssDNA aptamer guaranteed yields.				

(Please see **FAQs** in this document for *Frequently Asked Questions*)

STATEMENT OF WORK (A la carte pricing model):

PHASE	Description	Upfront Payment	Time	Milestone Payment*	Subtotal (5 candidates)
<p>V: Validation (Quantitative Characterization)</p>	<p>Each candidate is <i>quantitatively</i> tested for Kd affinities, signal-to-background, LOD, targeting, or EC50/IC50, etc..</p>	<p>\$1,200 set-up fee \$3,000 per candidate (per trial)</p>	<p>1 month</p>	<p>\$2,000 per candidate†</p>	<p>\$26,200</p>
	<p>Assay Choices: SPR, BLI (ForteBio), Isothermal Titration Calorimetry (ITC), Microscale Thermophoresis (MST), CD spectra for conformation changes, Dot Blot, Gel-shift assay, ELONA (ELISA), Microscopy, Flow Cytometry, or Imaging, etc.</p>		<p>Anticipated Outcome*</p>	<div data-bbox="1528 654 1959 954" data-label="Figure">  </div> <p>Deliverable: Full Report on Kd Affinities and Specificities. Aptagen validates monoclonal candidates.</p> <p>At least one (1) aptamer candidate must meet Anticipated Milestone Outcome.</p>	
	<p>For Biomarker Discovery, Binding characterization can be substituted with Pull-Down Assays and Mass Spec Analysis for target identification.</p> <div data-bbox="396 1078 783 1256" data-label="Image">  </div>		<p>Small Targets: Small Molecules or Peptides Affinity: < 2 μM OR Specificity: > 10X</p> <p>Large Targets: Protein Biomarkers Affinity: < 200 nM OR Specificity: > 100X</p> <p>Cells & Tissues >50% response above background using Fluorescent Microscopy/ Imaging, or Flow Cytometry.</p>		
		<p>* Aptamers routinely exhibit micromolar affinity for smaller targets and low nanomolar affinity for larger targets.</p> <p>Peptimers™, i.e. peptide aptamers, should have at least a 10-fold improvement in affinity/specificity from values listed above.</p> <p>For lower limits of detection, see Phase VI. † Restrictions apply for Premium Service (pg. 1)</p>			

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PHASE	Description	Upfront Payment	Time	Milestone Payment	Subtotal
<p>VI: (optional) Optimization -- OR -- Apta-sensor Development (Assay Sensitivity & LOD)</p>	<p><u>Aptamer Optimization:</u> This phase may not be necessary. At the Client’s discretion, Aptagen can test additional candidates under a variety of conditions, reselect using a “biased” library based on the best-performing aptamer candidate, truncate aptamer oligos to reduce production costs for commercialization, or “multimerize” aptamers to further increase affinity/avidity. Aptagen’s proprietary <i>in silico</i> maturation algorithm searches and explores sequence space for achieving >10-fold improvement. This Phase may trigger only if Client believes Optimization a) is cost effective to minimize production costs while maximizing activity for large-scale commercial use and/or, b) widens the claims in Client’s IP to strengthen the coverage of all possible aptamer sequence variants.</p> <p><u>Apta-sensor Feasibility Study & Prototype Development:</u> Inquire about re-selection to develop an Aptamer ‘Sandwich’ Assay (ASA), or Apta-sensor Development including Lateral Flow Assays (LFAs), apta-switches, or the apta-beacon™ technology to eliminate antibody-based ELISAs with the advantage of:</p> <p>“No Capturing, No Washing, Just READ”™</p>	<p>\$18,000</p>	<p>1-2 months</p>	<p>\$12,000</p>	<p>\$30,000</p>
					



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FAQs (Frequently Asked Questions):

Why Aptagen? We Guarantee our Services. No final payment until benchmarks and milestones are met. Aptagen has over 25 years of experience and a number of testimonials attributing to our exceptional customer service and quality for success. We have the highest success rate in the industry, >80% for small molecule targets and >90% for large protein and cell targets. We are known for “...*taking on Challenging Projects where others have failed, and Delivering Positive Results.*” Several former clients did go another route with disappointing results and ended up spending more capital to get the job done right by us. Ask for our References/Testimonials.

Our business model is straightforward and simple: You pay us to do the work, you own 100% of the aptamers we develop for you. No royalties. No negotiations needed. You will own exclusive rights to all the aptamer sequences we discover against your target, and you'll have the freedom to file for patent rights to those aptamers.

What chemistries can be used for aptamer discovery (i.e. Deluxe chemistries)? In addition to ssDNA, RNA, 2'F-RNA, and 2'OMe-RNA (under special circumstances), Aptagen can use alternative chemistries such as peptimers™ (peptide aptamers), aptabodies™ (next-gen aptamers), and HMAs (see below). Inquire for pricing.

Can you discover Unknown or Unique biomarkers using aptamers? Yes. Aptamers can be developed to respond to a set of positive patient samples over negative patient samples (both determined by clinical means). These aptamers will then be used in a pull-down assay followed by mass-spec analysis to identify the biomarker(s) of interest. Contact Us for more details.

Can Aptagen source my target samples and matrix material for me to start a project? We prefer the Client provide the materials for Aptagen, i.e. drop-ship to our laboratory facility. However, *for an additional convenience fee, Aptagen can source the project materials.* It is highly recommended that counter-target(s) is also provided for enrichment of highly specific aptamers. A Material Acquisition Form must be completed for background information on the target, any associated hazards, and handling requirements.

How much target and counter-target are needed to start a project? At least 10 nanomoles (e.g. 1 ml of 100 μM solution), 1 mg of solid material, or 1×10^8 cells.

Purity of sample target? The target sample may be crude in purity; however, an equivalent crude sample without the presence of the target is needed to perform a counter-selection before positive selection. These consecutive strategy steps effectively subtracts the influence of other endogenous components in the sample milieu and enriches for apta-sensor(s) against only the target in the crude sample specifically.

My target is hydrophobic; any special considerations to be aware of? Aptagen has experience with hydrophobic targets using traditional chemistries. However, in certain circumstances, Aptagen would recommend using Hydrophobically-Modified Aptamers (HMAs), a unique set of proprietary nucleotides that enhance binding to hydrophobic epitopes.



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Affinity (K_d) vs. Limit of Detection (LOD)? Low affinity (i.e. high K_d) is not necessarily an issue for many downstream applications. Although high-affinity aptamers serve as better starting points for assay development, low to moderate affinity aptamers may exhibit high sensitivity in a particular platform. As a rule of thumb for many platforms, LOD is typically 1 to 2 orders of magnitude lower than the K_d . Contact us for details.

Can Aptagen synthesize additional material at larger scales of manufacturing? Aptagen has established close relationships with Original Equipment Manufacturers (OEMs). For all R&D customer projects, Aptagen can facilitate arrangements for the production of milligram- to gram-scale deliverables of aptamers.

Sandwich-based vs. Split-Aptamers? Sandwich aptamers are aptamer pairs that bind to different epitopes on the same target. They individually have the ability to bind to the target in question, and can be used independently from each other. A split aptamer is generated from an aptamer that binds to a single epitope on a given target. The aptamer is divided into 2 segments such that the aptamer re-assembles in the proximity of the target epitope.

Apta-beacons™ vs. Apta-switches? Apta-beacons™ are aptamers that produce an output signal for detection of analytes free in solution (either fluorescent or colorimetric output). They exhibit low limits of detection and can be easily implemented in a 96-well plate assay with No Capturing, No Washing, Just READ™. Multistep approaches like ELISA always requires optimization and is time consuming. The single-step apta-beacon approach does not require optimization and is fast. Apta-switches are aptamers with a structural and/or catalytic response to aptamers, but do not incorporate a readable output signal. Contact Us for more details.

Are there Discounts for multiple projects? For multiple projects initiated simultaneously, a 10% discount will be applied per additional target.

Are there any Academic or Additional Discounts? Yes, an additional 10% discount is available under the following conditions: 1) Royalty Agreement and/or Client and Aptagen share Joint IP, and 2) Aptagen has the right to publish the research in a peer-reviewed journal with Client as co-authors.

Can Aptagen honor a payment plan? Aptagen is flexible to Client R&D needs. Each phase is at the Client's discretion whether Aptagen performs the work or is performed by another provider. Executing the 'a la carte' pricing for each phase allows a Client to implement 'go/no-go' decision points throughout the project. This is the payment plan we will honor; however, note that the total combined cost of all phases is greater than the listed Package Rates (refer to table on the first page).

Are there additional ways to save costs to meet budget constraints? For a 25% discount, a mixture of antigens may be considered as one target, and therefore, substantially discounted from the cost of multiple targets in parallel projects (i.e. 'pooled-split' strategy). During later rounds of library enrichment, the pool is split to sort through and identify target-specific binders which will result in additional cost and development time in Phase V (Validation). However, the cost of sorting through validation (or characterization) is nominal compared to the significant savings gained from pooling the targets in Phase I for screening.

If budget is still a concern, we can collaborate on a grant application for funding or provide technical consultation under the Do-It-Yourself (DIY) option (see below). *Alternatively, a reduced quote may be issued in exchange for royalty payment terms.* Contact Us for details.



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Does Aptagen offer a Do-It-Yourself (DIY) option and Consultation Services? If Client desires to perform the research and development work themselves in whole or in part, Aptagen is able to provide consultation services at rate of \$500/hr. Email and phone support included. To initiate Aptagen's mentoring relationship during the course of DIY, an upfront \$5,000 non-refundable deposit is required.

Additional Notes & Disclaimers:

- 1) The Quote expires in 30 days, after which, the prices are subject to change.
- 2) The Client will need to provide the target(s) for Aptagen. *An additional fee may be applied if Aptagen is responsible for sourcing materials.*
- 3) The Up-front (*Non-Refundable*) payment is required before Project initiation. However, any special promotions or discounts may require special terms.
- 4) Aptagen reserves the right to use the Client's name for public relations or marketing purposes. We also would like to ask for feedback and testimonials regarding our quality of services.
- 5) Aptagen maintains a strict policy of confidentiality with all Clients, which includes identity of Client's target(s). However, Client may elect to sign a separate Confidentiality Agreement with Aptagen. Aptagen does not publicize the Client's aptamer sequence(s) in The Apta-Index™.
- 6) Aptamers routinely exhibit nanomolar affinity; however, there is no guarantee of a successful research effort since each target is unique and may present unforeseen difficulties during aptamer development. Aptagen has over 25 years of experience in this field.
- 7) The service Aptagen provides is a research and development effort, and may be canceled by the customer at any time for any reason; however, paid invoices are non-refundable for work rendered and all current invoices will become due immediately.
- 8) Exclusivity Option: The Client will own 100% of the rights to the aptamers Aptagen develops for the Client. Aptagen maintains a strict policy not to engage in Research and Development projects against client target(s) using the identical aptamer chemistry (e.g. DNA) employed for prior projects. Aptagen reserves the right to engage in future projects against any target(s) using alternative aptamer chemistries (e.g. RNA, 2'-F-RNA, Peptimer™, Aptabody™, etc.). A Client, at any time up until 120 days after receipt of final Deliverables, may arrange to purchase the Exclusivity Option as well as the 'right of first refusal' to exclude others from procuring Aptagen's Research and Development efforts against the Client's specific target(s) for any and all aptamer chemistries. Inquire for price.



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Contract Service Provider:

G. Thomas Caltagirone, Ph.D.,
Aptagen, LLC
President & CEO

Please complete for the terms and conditions:

Client Name (print): _____

Title: _____

Organization: _____

Mailing Address: _____

Project (or Target) Name: _____

Signature: _____ Date: _____