

Custom Affinity Adsorbents

- Maximize process yield with minimal steps
- Custom design of ligands for specific targets
- Complete adsorbent development, scale-up and manufacturing program
- Proven structured ligand screening and development approach
- Close collaboration with end user at all stages
- Quality assured process for supply of validated adsorbent



Custom ligand/adsorbent development: A creative purification solution

Downstream process development is critical in getting your biopharmaceutical product into clinical trials and out to the market quickly. Now you can leverage the tremendous power of affinity chromatography for any target protein, right from the start of your process development. ProMetic Biosciences, with our vast expertise in biomolecular chromatographic separations, can develop an adsorbent specifically tailored to your needs.

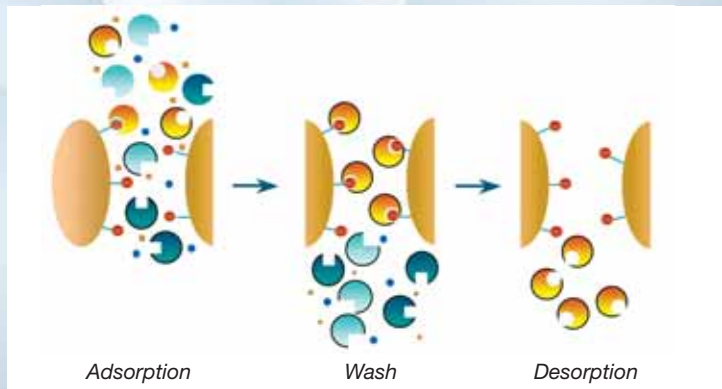
The goal of our complete ligand/adsorbent discovery and development program is to provide you with a fully validated affinity adsorbent and all associated process parameters for your target biomolecule resulting in maximum yield and purity while employing a minimum number of steps.

Depending upon the target molecule you seek to isolate, we can deliver your custom adsorbent and process in as few as nine months, or fast-track a ligand development program in less than half the time – within a very reasonable budget.

About Affinity Chromatography

Affinity chromatography is used principally for the separation and isolation of proteins. The technique relies upon the ability of proteins to recognize and bind to other molecules (ligands) in a specific and reversible manner. The ligand is normally bound by the protein at a "specific" site often within a fold of the protein.

Affinity chromatography uses an adsorbent comprising a porous support matrix to which the ligand is attached. The attachment or bonding is performed so that the immobilized ligand is still able to interact with the protein. If the ligand is relatively small a spacer arm is often incorporated between ligand and matrix, allowing the immobilized ligand to interact more effectively with the protein.



Schematic Diagram of Affinity Chromatography

An affinity separation is then performed by passing the starting protein solution over the adsorbent, incorporating the ligand, so that the target protein is adsorbed while allowing contaminants (other proteins, lipids, carbohydrates, DNA, pigments, etc.) to pass through without hindrance. The adsorbent is normally contained within a chromatography column, though the adsorption stage can be performed equally well by using the adsorbent as a stirred slurry in batch binding mode. Following adsorption, the adsorbent is washed with buffer to remove residual contaminants and then the bound protein is eluted in pure form. Elution is normally achieved by changing the buffer composition so the protein can no longer interact with the immobilized ligand.

Why Use Affinity Chromatography?

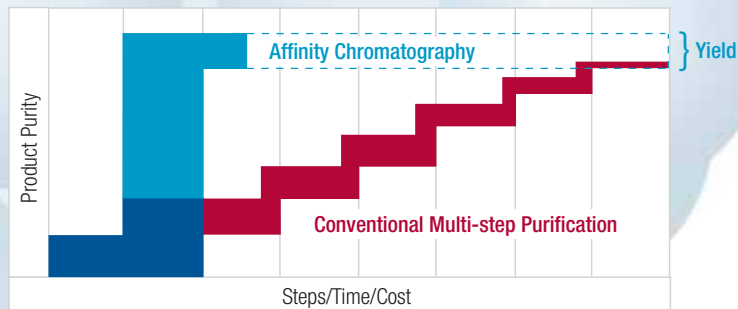
Affinity chromatography offers the user several major advantages compared to other protein purification techniques:

Selective Binding and Elution

- results in very pure product in a single unit operation
- provides high yields of purified product
- greatly reduced processing time
- cost reduction with economical affinity adsorbents
- high concentrations of material leave the column

Protein adsorption and concentration of purified protein make affinity chromatography ideal for

- large scale use
- stabilization of bound protein



Mimetic Ligand benefits: Fewer steps, faster process, higher purity, higher yields

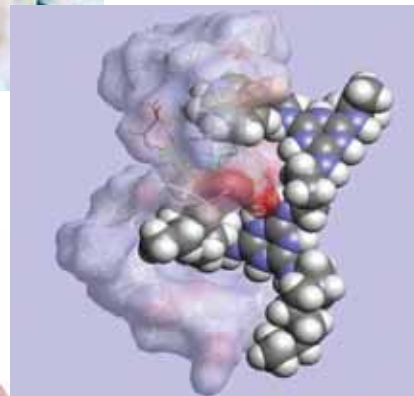
Custom Ligand/Adsorbent Development Program

Our Custom Adsorbent Development Service program employs ProMetic's intelligent Chemical Combinatorial Libraries™ of affinity ligands and our proprietary technology and know-how for screening, optimization, synthesis and manufacture of the affinity adsorbent. These programs also encompass the end user's technology and know-how for process development and engineering to successfully integrate the affinity adsorbent into the desired manufacturing process for the target biomolecule.

The illustration at far right outlines the progression of a typical development program work plan. The progression toward



delivery of a completely validated adsorbent with appropriate documentation and in sufficient quantity is driven by end user review and consent at each stage of the process.



Dedicated to ISO9001 quality and increased production efficiency

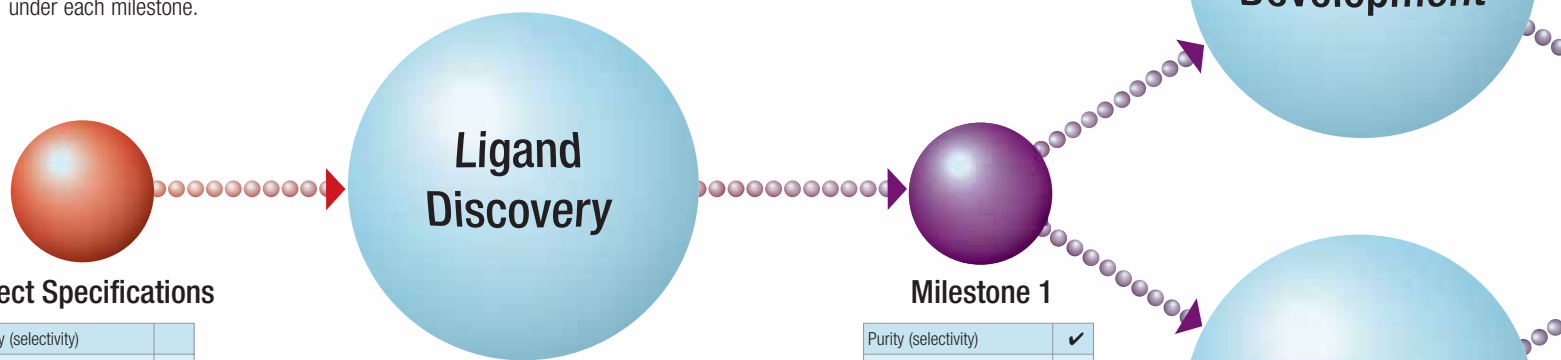
Quality and innovation go hand in hand, that's why we work hard to maintain and even exceed ISO9001:2000 standards. By staying close to our customers and their unique requirements, we enhance our ability to provide innovative solutions to meet the needs of the biopharmaceutical market.

We collaborate with pharmaceutical and biotech companies to optimize bioseparation and purification processes. Our patented separation technology and expansive Chemical Combinatorial Library™ of synthetic ligand media increases production efficiency, reduces manufacturing costs and enables companies to strengthen market positions through continuous improvements in product purity and yield.

Custom Ligand/Adsorbent Development Program

Project Definition

Upon entering into a development program a list of the attributes and properties that are required of the affinity adsorbent for use in an integrated manufacturing process for the target biomolecule will be defined. These criteria will serve as the basis of acceptance of the affinity adsorbent by the end user, and are listed in the tables shown under each milestone.



Project Specifications

| | |
|--------------------------------|--|
| Purity (selectivity) | |
| Capacity | |
| Recovery | |
| Alkali resistance/cleanability | |
| Binding & elution conditions | |
| Adsorbent scale-up | |
| Stability | |
| Ligand loss | |
| Safety | |
| DMF | |

Ligand Discovery

This first step includes screening of combinatorial ligand libraries against the starting material, for ligand selection. Both rational design and combinatorial chemistry approaches will be used to identify suitable ligands for further adsorbent development. ProMetic's Mimetic Ligands (Chemical Combinatorial Libraries™) will be screened against the actual material to be purified using automated screening techniques. The screening is carried out with ligands presented in the solid phase, therefore ensuring that any ligand interaction closely mimics actual processing conditions. Assays will be implemented to enable the identification of specific ligands with required binding activity. Based on information obtained from initial screening rounds, additional ligand libraries might be constructed and screened to facilitate the identification of ligands possessing the desired properties and capable of achieving target specifications.

Milestone 1

| | |
|--------------------------------|---|
| Purity (selectivity) | ✓ |
| Capacity | |
| Recovery | |
| Alkali resistance/cleanability | |
| Binding & elution conditions | |
| Adsorbent scale-up | |
| Stability | |
| Ligand loss | |
| Safety | |
| DMF | |

Adsorbent Development

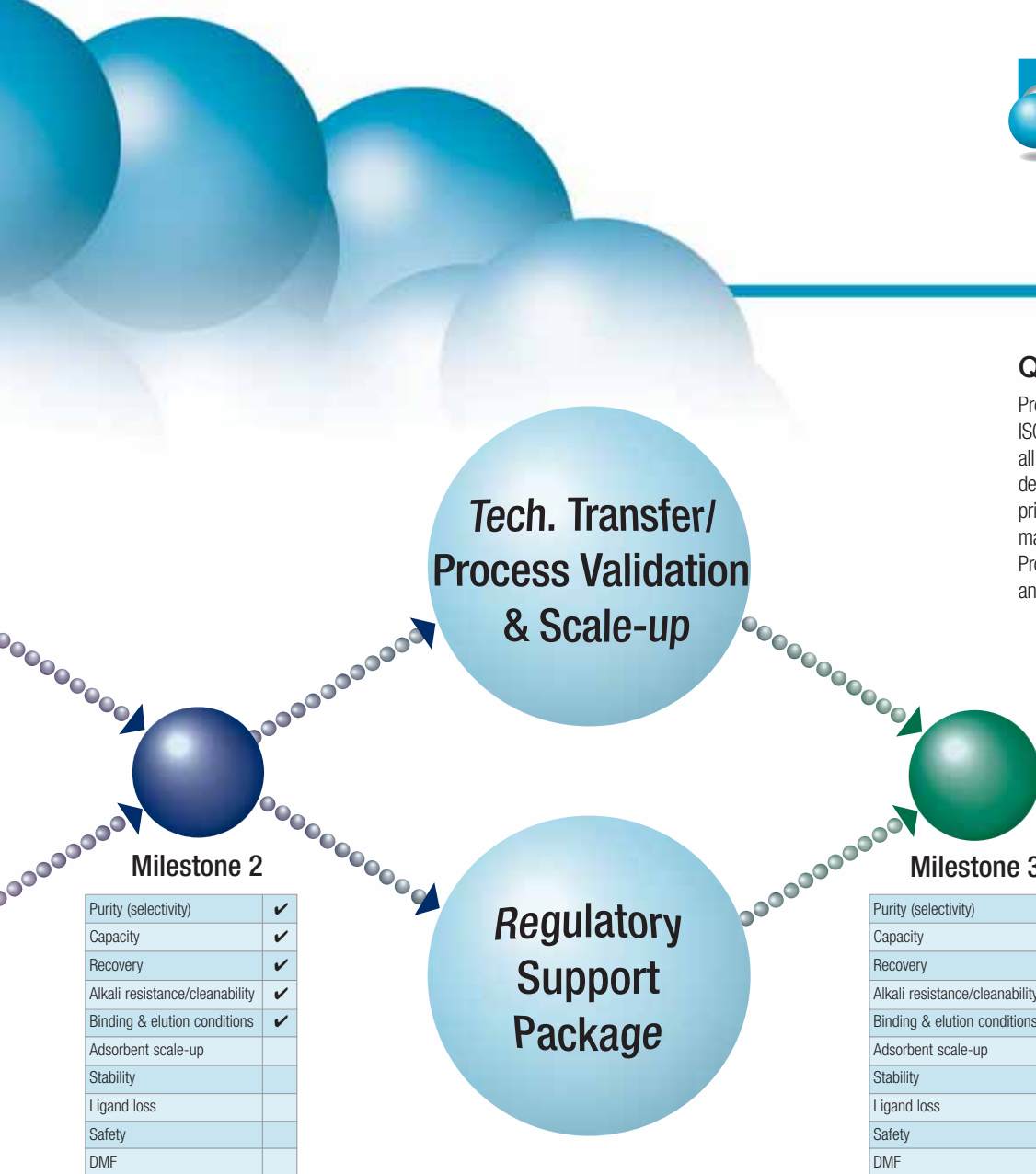
Specific binding ligands identified at the ligand discovery stage will be further developed and, if necessary, studies performed to identify methods of ligand attachment to support particles to provide an affinity adsorbent which meets the defined specifications. Procedures for adsorbent manufacture will also be investigated at this stage, including procedures for washing the adsorbent to remove any soluble components which remain following ligand attachment. ProMetic's Purabead® support matrix (rigid near monodisperse high performance agarose beads) will be used for the construction of the affinity adsorbent. A single ligand Mimetic structure will be selected for scale-up.

Batch sizes of up to 1 liter will be produced as a part of the Adsorbent Development phase and will be made available to the end user for process development work or small batch manufacture. On conclusion of the Adsorbent Development phase, written methods describing the manufacture of the affinity adsorbent (including raw materials, in-process and finished product controls) will be produced in readiness for transfer to ProMetic's manufacturing facility located on the Isle of Man, UK.

Quality Systems



ProMetic BioSciences is ISO 9001:2000 accredited, all work for a custom ligand/adsorbent development program follows GLP/cGMP principles, and completed adsorbents are manufactured in clean room conditions. ProMetic welcomes audits of its manufacturing and research & development facilities.



Milestone 2

| | |
|--------------------------------|---|
| Purity (selectivity) | ✓ |
| Capacity | ✓ |
| Recovery | ✓ |
| Alkali resistance/cleanability | ✓ |
| Binding & elution conditions | ✓ |
| Adsorbent scale-up | |
| Stability | |
| Ligand loss | |
| Safety | |
| DMF | |

Milestone 3

| | |
|--------------------------------|---|
| Purity (selectivity) | ✓ |
| Capacity | ✓ |
| Recovery | ✓ |
| Alkali resistance/cleanability | ✓ |
| Binding & elution conditions | ✓ |
| Adsorbent scale-up | ✓ |
| Stability | ✓ |
| Ligand loss | ✓ |
| Safety | ✓ |
| DMF | ✓ |

Chromatography Development

This phase comprises method development for optimizing use of the completed adsorbent and defines the conditions necessary to utilize the adsorbent in the most efficient way. This is performed in parallel with the Adsorbent Development phase. Conditions for use of the identified affinity adsorbent will be developed (including binding, wash, elution, sanitization and regeneration procedures). The objective for this phase is achievement of the process performance criteria identified in the target specifications. An adsorbent re-use study may be performed as part of this work.

Validation and Scale-Up

Procedures for manufacture of the affinity adsorbent will be transferred to ProMetic's Isle of Man, UK, facility. Trial lot(s) are usually made at the 1 liter scale prior to validation of the manufacturing process by production of three conformance batches of affinity adsorbent at production scale. Manufactured batches will be tested for their ability to achieve the process performance defined specifications. Batches of affinity adsorbent produced during the validation process will be supplied to the end user. A validation plan and associated summary report will be produced as a part of this activity. Ongoing supply and support of custom adsorbent is assured with a formal manufacturing and supply agreement.

Regulatory Package

A comprehensive supporting package of information will be developed and supplied to the end user to assist registration of the purification process with regulatory authorities. The regulatory package will include information derived from the following studies (additional testing and documentation can be included on request):

- a) Ligand Leakage Study
(Including a forced degradation study under extreme conditions)
- b) Stability Trials
(Under a range of normal and extreme conditions, up to one year duration)
- c) Toxicology Studies
(MTD *in vivo*, and Standard WHO AMES tests)

Custom Affinity Adsorbents

Get started on the road to better protein purification

We offer you a choice between off-the-shelf affinity chromatography products and our highly modular, customized affinity adsorbent development programs.

Depending on your target protein you may choose to explore our line of Mimetic Ligand™ Adsorbents which are available from stock. A convenient screening kit, containing ten packed adsorbents, allows for easy identification of the right ligand for your purpose.

For more information visit us at www.ligands.discoverprometic.com where you can download our brochures and application notes.

However, if you need to purify specific proteins from complex mixtures you should also consider a custom ligand/adsorbent development program as described in detail in this brochure. These programs allow you to access the power of affinity chromatography for any process and protein. Our programs have the flexibility to work within your timelines to fulfill your specific needs and process requirements.

Contact us with details of your protein of interest, and a list of desired process attributes and adsorbent properties, and we will supply you with project specifications and a quotation along with an estimated timeline tailored to your needs.

Since 1987

ProMetic has been pioneering design, development, manufacture and distribution of affinity purification technology for research and development at lab-scale as well as large-scale bioprocessing in the biotechnology industry. Our patented Mimetic™ technology synthetically “mimics” and enhances the natural molecular affinity of targeted biomolecules. The result: Optimized binding and yields for all your biomolecular purification needs.

- Recovery and purification of biologicals
- Antibody purification
- Proteomics and genomics applications
- Plasma protein purification
- Biocontaminant removal

Core technologies

The key to our success in biomolecule purification lies in the development of an extensive Chemical Combinatorial Library. Through years of dedication, research and development we've systematically screened countless ligand arrays and utilized our patented computer modeling processes to design new ligand structures.

Our expertise

ProMetic's experience in polymer chemistry has led to the development and manufacture of proprietary matrices such as PuraBead® agarose beads and Perfluorosorb® S highly fluorinated adsorbent as platforms for our purification technologies. Finally we bring it all together with our application know-how, resulting in high-performance products that are ideally suited to meeting the purification challenges of biotechnological research, development, and manufacturing.

Global support

With sales and support offices in North America and Europe, and R&D facilities in Cambridge, UK and Montreal, Canada we are able to meet your needs and support your applications wherever you are. Our manufacturing facilities are located on the Isle of Man, UK and in Joliette, PQ, Canada.

We invite you to visit or call any of our facilities to discuss how we can help you get more of what you want from your process and less of what you don't.

International Sales and Technical Support:

ProMetic BioSciences (USA) Inc.
155 Willowbrook Boulevard,
Suite 460
Wayne, NJ 07470, USA
Tel: +1.973.812.9880
Fax: +1.973.812.9881
E-mail: sales@prometic.com
techsupport@prometic.com

www.prometic.com