

# HiTrap MabSelect SuRe

## HiTrap MabSelect

## HiTrap MabSelect Xtra

HiTrap™ MabSelect SuRe™ (Superior Resistance), HiTrap MabSelect™, and HiTrap MabSelect Xtra™ (Fig 1) are members of the HiTrap family of prepacked columns for purification of monoclonal antibodies (MAbs).

Key performance characteristics of HiTrap MabSelect products include:

- Increased binding capacity compared with other protein A media
- High purity in one step
- Convenient, prepacked 1-ml and 5-ml columns
- Excellent for process development and screening of purification conditions
- Convenient operation with a syringe, a laboratory pump, or a chromatography system, such as ÄKTAdesign™

The protein-A ligand used in all three MabSelect media is produced by validated fermentation and downstream processes. The entire production process is free of components of mammalian origin. The resulting highly purified ligand is immobilized to the agarose matrix through a chemically stable thio-ether linkage.

### HiTrap MabSelect SuRe

MabSelect SuRe is composed of a rigid, high-flow agarose matrix and alkali-stabilized protein A-derived ligand that allows the usage of up to 0.5 M NaOH for cleaning-in-place (CIP). This ligand provides greater stability than conventional protein A-based media in the alkaline conditions used in CIP protocols. This is important when the same column is



**Fig 1.** HiTrap MabSelect SuRe, HiTrap MabSelect, and HiTrap MabSelect Xtra 1 and 5 ml for purification of monoclonal antibodies with optimized binding capacities at high flow rates.

used for purification of different antibodies, as performing CIP will prevent cross-contamination between the different purifications. The enhanced alkali stability of MabSelect SuRe also improves purification economy; cleaning can be performed with cost-effective reagents such as 0.1 to 0.5 M sodium hydroxide.

The MabSelect SuRe ligand was developed by protein engineering of one of the IgG-binding domains of protein A. Amino acids particularly sensitive to alkali were identified and substituted with more stable ones. The final construct is a tetramer of the engineered domain with a C-terminal cysteine, which enables single-point attachment to the matrix. The combination of low ligand leakage and high dynamic binding capacity together with the high-flow matrix makes MabSelect SuRe well suited for the purification of MAbs when scaling up. Characteristics of HiTrap MabSelect SuRe are listed in Table 1.



## HiTrap MabSelect

MabSelect features a highly cross-linked agarose, produced using a manufacturing process that gives a very rigid matrix that is optimal for high-throughput affinity chromatography of IgG. The matrix of MabSelect allows at least five-times higher flow rates to be used in process scale compared with conventional cross-linked agarose of similar porosity. The epoxy-based coupling chemistry ensures low ligand leakage. The high capacity, low ligand leakage, and specially developed base matrix make MabSelect ideal for purification of monoclonal antibodies at process scale. See Table 2 for a summary of characteristics.

## HiTrap MabSelect Xtra

MabSelect Xtra has been developed to meet the demands of ever-increasing levels of expression in monoclonal antibody feedstocks. MabSelect Xtra uses the same recombinant protein A ligand as MabSelect, but has a smaller particle size and greater porosity, which ensures increased dynamic binding capacity. The medium provides a lower overall production cost due to the possibility of processing concentrated feedstocks in fewer batches. The characteristics of HiTrap MabSelect Xtra are listed in Table 3.

## Column characteristics

HiTrap columns are made of biocompatible polypropylene and they have porous top and bottom frits. Columns are delivered with a stopper on the inlet and a snap-off end on the outlet. Note that HiTrap columns cannot be opened or repacked.

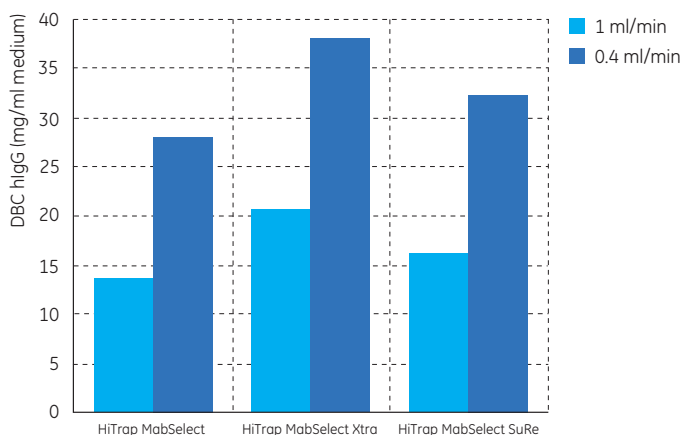
## Low ligand leakage

All three MabSelect media exhibit only a low level of ligand leakage during elution. Leakage is affected by chromatographic running conditions and the composition of the sample. For detailed information, please refer to the instructions for each media.

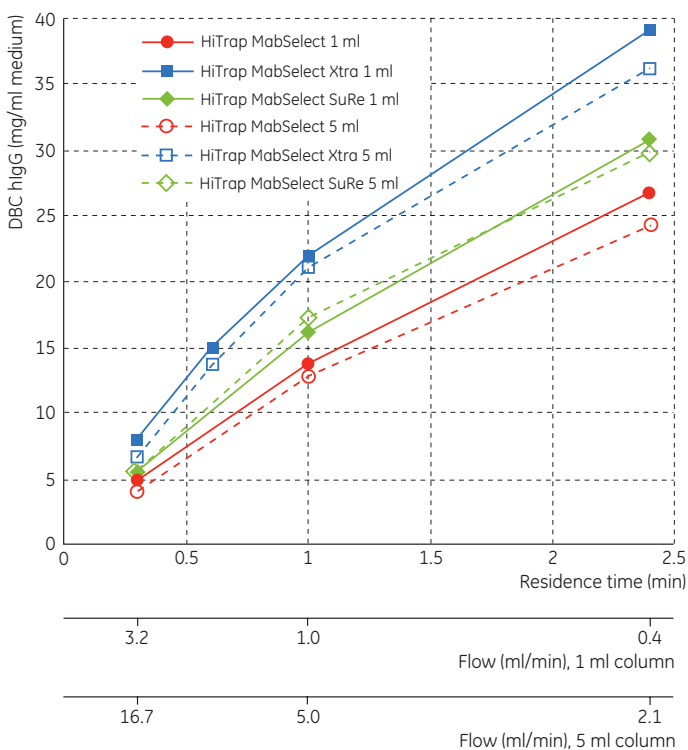
## High dynamic binding capacities

The recombinant protein A in MabSelect media has been engineered to include a C-terminal cysteine. The coupling conditions are controlled to favor a thioether coupling providing single point attachment of the protein A. The oriented coupling also enhances the binding of IgG.

The dynamic binding capacity (DBC) of MabSelect media is affected by the flow rate, or residence time. The lower the flow rate (or the higher the residence time), the higher the DBC (Figs 2 and 3). A residence time of 2.4 min yields the specified binding capacities for the media, as stated in Tables 1 to 3. The dynamic binding capacity may decrease for columns with a bed height of 2.5 cm at the recommended flow rates (1 ml/min for 1-ml column or 5 ml/min for 5-ml column) because the residence time will be too short to ensure optimal binding.



**Fig 2.** Comparison of dynamic binding capacities (DBC) of HiTrap MabSelect, HiTrap MabSelect Xtra, and HiTrap MabSelect SuRe 1 ml columns at two different flow rates. Sample: 1 mg/ml human IgG (hlgG) Gammanorm™ (Octapharma); Binding buffer: 0.02 M phosphate, 0.15 M NaCl, pH 7.4; Elution buffer: 0.1 M sodium citrate, pH 3.0. Samples were run on an ÄKTAexplorer™ 10 system.



**Fig 3.** Dynamic binding capacity (DBC) as a function of residence time and flow rates for HiTrap MabSelect, HiTrap MabSelect Xtra, and HiTrap MabSelect SuRe 1 ml and 5 ml columns. Sample: 1 mg/ml human IgG (hlgG) Gammanorm (Octapharma); Binding buffer: 0.02 M phosphate, 0.15 M NaCl, pH 7.4; Elution buffer: 0.1 M sodium citrate, pH 3.0. Samples were run on either an ÄKTAexplorer 10 or ÄKTAexplorer 100 system.

**Table 1.** Characteristics of HiTrap MabSelect SuRe

|                                       |   |
|---------------------------------------|---|
| Medium                                | MabSelect SuRe  |
| Matrix                                | Rigid, highly cross-linked agarose                                      |
| Average particle size                 | 85 µm   |
| Ligand                                | Alkali-tolerant, protein A-derived ( <i>E. coli</i> )                   |
| Coupling chemistry                    | Epoxy   |
| Dynamic binding capacity <sup>1</sup> | Approx. 30 mg human IgG/ml medium                                       |
| Column volumes                        | 1 ml or 5 ml  |
| Column dimensions                     | 0.7 × 2.5 cm (1 ml)<br>1.6 × 2.5 cm (5 ml)                              |
| Recommended flow rate                 | 1 and 5 ml/min for 1- and 5-ml column respectively                      |
| Maximum flow rates                    | 4 and 20 ml/min for 1- and 5-ml column respectively                     |
| Maximum back pressure <sup>2</sup>    | 0.3 MPa, 3 bar  |
| Chemical stability                    | Stable in all aqueous buffers commonly used in protein A chromatography |
| pH, working range                     | 3 to 12   |
| Cleaning-in-place stability           | 0.1 to 0.5 M NaOH   |
| Storage                               | 4°C to 8°C in 20% ethanol   |

<sup>1</sup> Determined at 10% breakthrough by frontal analysis at 250 cm/h in a column with a bed height of 10 cm. Residence time is 2.4 min. Residence time is equal to bed height (cm) divided by nominal flow velocity (cm/h) during sample loading. Flow velocity is equal to flow rate (ml/h) divided by column cross-sectional area (cm<sup>2</sup>).

**Note:** The dynamic binding capacity may decrease for columns with a bed height of 2.5 cm at the recommended flow rate (1 ml/min for 1-ml column and 5 ml/min for 5-ml column), as residence time may be too short for optimal binding.

<sup>2</sup> H<sub>2</sub>O at room temperature

**Table 2.** Characteristics of HiTrap MabSelect

|                                       |   |
|---------------------------------------|---|
| Medium                                | MabSelect   |
| Matrix                                | Rigid, highly cross-linked agarose  |
| Average particle size                 | 85 µm   |
| Ligand                                | Recombinant protein A ( <i>E. coli</i> )  |
| Coupling chemistry                    | Epoxy   |
| Dynamic binding capacity <sup>1</sup> | Approx. 30 mg human IgG/ml medium   |
| Column volumes                        | 1 ml or 5 ml  |
| Column dimensions                     | 0.7 × 2.5 cm (1 ml)<br>1.6 × 2.5 cm (5 ml)  |
| Recommended flow rate                 | 1 and 5 ml/min for 1- and 5-ml columns, respectively  |
| Maximum flow rates                    | 4 and 20 ml/min for 1- and 5-ml columns, respectively   |
| Maximum back pressure <sup>2</sup>    | 0.3 MPa, 3 bar  |
| Chemical stability <sup>3</sup>       | Stable in all aqueous buffers commonly used in protein A chromatography: 10 mM HCl (pH 2), 10 mM NaOH (pH 12), 0.1 M sodium citrate/HCl (pH 3), 6 M guanidine HCl, 20% ethanol, 2% benzyl alcohol |
| pH stability, working short term      | 3 to 10<br>2 to 12  |
| Storage                               | 4°C to 8°C in 20% ethanol   |

<sup>1</sup> Determined at 10% breakthrough by frontal analysis at 500 cm/h in a column with a bed height of 20 cm, i.e. residence time is 2.4 min. Residence time is equal to bed height (cm) divided by flow velocity (cm/h) during sample loading. Flow velocity (cm/h) is equal to flow rate (ml/h) divided by column cross-sectional area (cm<sup>2</sup>).

**Note:** The dynamic binding capacity may decrease for columns with bed height of 2.5 cm at the recommended flow rate (1 ml/min for 1-ml column or 5 ml/min for 5-ml column), due to too short residence time for optimal binding.

<sup>2</sup> H<sub>2</sub>O at room temperature.

<sup>3</sup> No significant change in chromatographic performance after 1 week storage, or 100 cycles normal use at room temperature, which corresponds to a total contact time of 16.7 h (10 mM NaOH).

**Table 3.** Main characteristics of HiTrap MabSelect Xtra

|                                       |   |
|---------------------------------------|---|
| Medium                                | MabSelect Xtra  |
| Matrix                                | Rigid, highly cross-linked agarose  |
| Average particle size                 | 75 µm   |
| Ligand                                | Recombinant protein A ( <i>E. coli</i> )  |
| Coupling chemistry                    | Epoxy   |
| Dynamic binding capacity <sup>1</sup> | Approx. 40 mg human IgG/ml medium   |
| Column volumes                        | 1 ml or 5 ml  |
| Column dimensions                     | 0.7 × 2.5 cm (1 ml)<br>1.6 × 2.5 cm (5 ml)  |
| Recommended flow rate                 | 1 and 5 ml/min for 1- and 5-ml columns, respectively  |
| Maximum flow rates                    | 4 and 20 ml/min for 1- and 5-ml columns, respectively   |
| Maximum back pressure <sup>2</sup>    | 0.3 MPa, 3 bar  |
| Chemical stability <sup>3</sup>       | Stable in all aqueous buffers commonly used in protein A chromatography: 10 mM HCl (pH 2), 10 mM NaOH (pH 12), 0.1 M sodium citrate/HCl (pH 3), 6 M guanidine HCl, 20% ethanol, 2% benzyl alcohol |
| pH stability, working short term      | 3 to 10<br>2 to 12  |
| Storage                               | 4°C to 8°C in 20% ethanol   |

<sup>1</sup> Determined at 10% breakthrough by frontal analysis at 250 cm/h in a column with a bed height of 10 cm, i.e. residence time is 2.4 min. Residence time is equal to bed height (cm) divided by flow velocity (cm/h) during sample loading. Flow velocity (cm/h) is equal to flow rate (ml/h) divided by column cross-sectional area (cm<sup>2</sup>).

**Note:** The dynamic binding capacity may decrease for columns with bed height of 2.5 cm at the recommended flow rate (1 ml/min for 1-ml column or 5 ml/min for 5-ml column), due to too short residence time for optimal binding.

<sup>2</sup> H<sub>2</sub>O at room temperature.

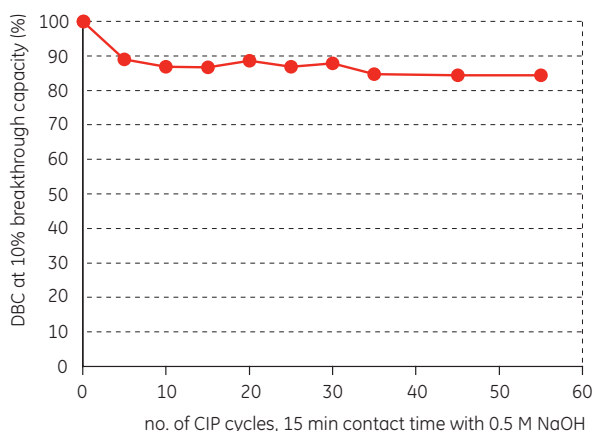
<sup>3</sup> No significant change in chromatographic performance after 1 week storage, or 100 cycles normal use at room temperature, which corresponds to a total contact time of 16.7 h (10 mM NaOH).

## Cleaning-in-place using HiTrap MabSelect SuRe

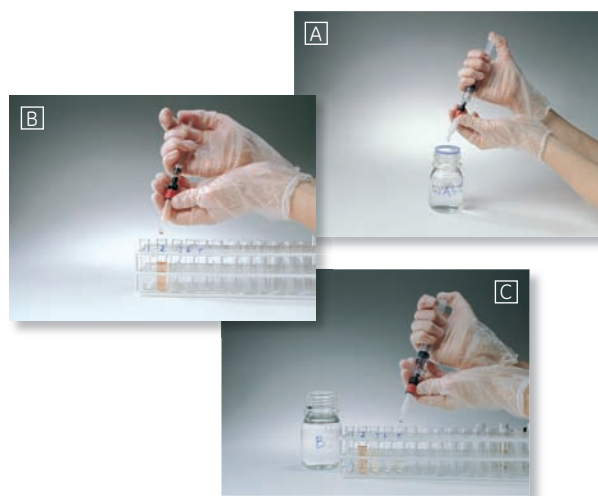
CIP is an essential step in the purification of MAbs. The main drawback with using sodium hydroxide for CIP of conventional protein A-based media is the sensitivity of native and recombinant Protein A to alkaline conditions. MabSelect SuRe, however, retains dynamic binding capacity after repeated CIP cycles with 0.5 M NaOH.

Approximately 85% to 90% of the initial dynamic binding capacity of MabSelect SuRe is retained after numerous CIP cycles with 0.5 M sodium hydroxide (Fig 4).

Rigorous CIP with sodium hydroxide reduces the risk of both contamination from host cell proteins and microbial growth in the prepacked column, as well as carry-over in the purified antibody.



**Fig 4.** Dynamic binding capacity for HiTrap MabSelect SuRe 1 ml for polyclonal human IgG after more than 50 CIP cycles with 0.5 M NaOH.



**Fig 5.** Using HiTrap MabSelect products 1 ml with a syringe. **A)** Prepare buffers and sample. Remove the stop-plug from the top of the column and snap-off the end. Wash and equilibrate. **B)** Load the sample and begin collecting fractions. **C)** Wash and elute, continue collecting fractions.

## Operation and method optimization

HiTrap MabSelect, HiTrap MabSelect SuRe, and HiTrap MabSelect Xtra 1-ml and 5-ml columns bring added time-savings, convenience, and reliability to the purification of antibodies. The columns can be easily used with a pump or a chromatography system such as ÄKTAdesign systems or FPLC™ System. The columns are also simple to operate with a syringe and the supplied Luer connector (Fig 5). Note that ÄKTAdesign includes preset method templates for these columns, which further enhances operation, especially reproducibility. In addition, multiple HiTrap columns can be easily connected in series for increased purification capacity.

**Table 4.** Relative binding strengths of protein A and protein G

| Species         | Subclass          | Protein A binding | Protein G binding |
|-----------------|-------------------|-------------------|-------------------|
| Human           | IgA               | variable          | -                 |
|                 | IgD               | -                 | -                 |
|                 | IgE               | -                 | -                 |
|                 | IgG <sub>1</sub>  | ++++              | ++++              |
|                 | IgG <sub>2</sub>  | ++++              | ++++              |
|                 | IgG <sub>3</sub>  | -                 | ++++              |
|                 | IgG <sub>4</sub>  | ++++              | ++++              |
|                 | IgM*              | variable          | -                 |
| Avian egg yolk  | IgY†              | -                 | -                 |
| Cow             |                   | ++                | ++++              |
| Dog             |                   | ++                | +                 |
| Goat            |                   | -                 | ++                |
| Guinea pig      | IgG <sub>1</sub>  | ++++              | ++                |
|                 | IgG <sub>2</sub>  | ++++              | ++                |
| Hamster         |                   | +                 | ++                |
| Horse           |                   | ++                | ++++              |
| Koala           |                   | -                 | +                 |
| Llama           |                   | -                 | +                 |
| Monkey (rhesus) |                   | ++++              | ++++              |
| Mouse           | IgG <sub>1</sub>  | +                 | ++++              |
|                 | IgG <sub>2a</sub> | ++++              | ++++              |
|                 | IgG <sub>2b</sub> | +++               | +++               |
|                 | IgG <sub>3</sub>  | ++                | +++               |
|                 | IgM*              | variable          | -                 |
| Pig             |                   | +++               | +++               |
| Rabbit          | no distinction    | ++++              | +++               |
| Rat             | IgG <sub>1</sub>  | -                 | +                 |
|                 | IgG <sub>2a</sub> | -                 | ++++              |
|                 | IgG <sub>2b</sub> | -                 | ++                |
|                 | IgG <sub>3</sub>  | +                 | ++                |
| Sheep           |                   | +/-               | ++                |

\* Purify using HiTrap IgM Purification HP columns.

† Purify using HiTrap IgY Purification HP columns.

++++ = strong binding

++ = medium binding

- = weak or no binding

The primary aim of method optimization is to establish the conditions that will bind the highest amount of target molecule, in the shortest time, and with the highest product recovery. The degree to which IgG binds to protein A varies with respect to both origin and antibody subclass (Table 4). Typically, the clarified feedstock is loaded onto the column directly.

After optimizing the antibody purification at laboratory scale, the process can be scaled up by keeping the residence time constant in order to maintain capacity. This can be achieved by increasing the column diameter, and keeping the mobile phase velocity and sample-to-bed volume ratio constant.

## Cleaning

It is important to clean a column between samples when the same column is used for the purification of different antibodies. Proper cleaning will prevent cross-contamination between the different samples. For detailed information, please refer to the instructions for each media.

## Scale-up

The easiest way to scale-up is to go from a 1-ml HiTrap column to a 5-ml column. Alternatively, scale-up of small scale purifications can be done by coupling the columns in series. The different MabSelect media are also available in bulk packages for further scale-up.

## Storage

Recommended storage conditions for HiTrap MabSelect SuRe, HiTrap MabSelect, and HiTrap MabSelect Xtra are in 20% ethanol at 4°C to 8°C.

## Applications

### Single-step purification

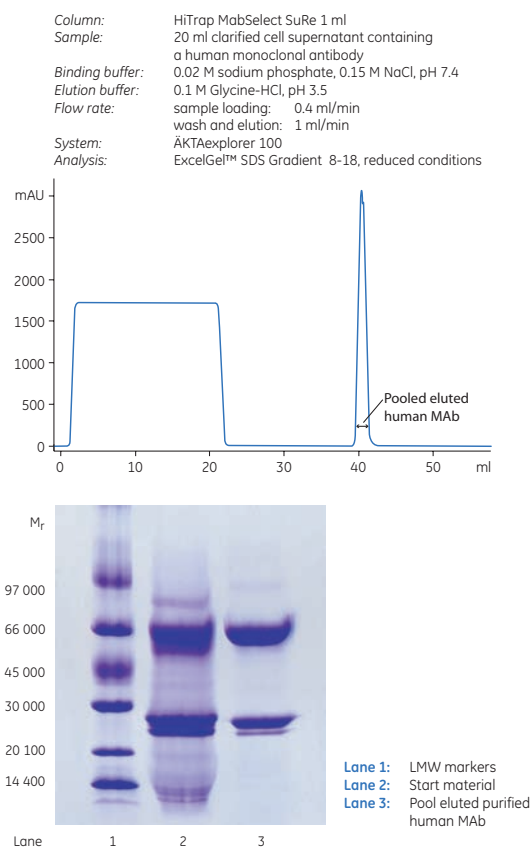
Different samples of human IgG were purified on HiTrap MabSelect SuRe 1 ml (Fig 6), and HiTrap MabSelect Xtra 1 ml (Fig 7). Both media yielded highly pure antibody, as shown by SDS-PAGE, in a single purification step.

### Automatic two-step purification

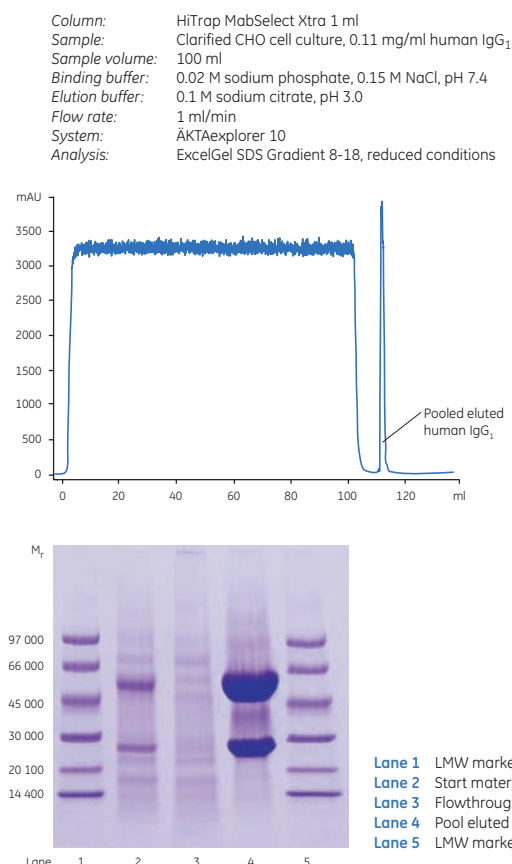
HiTrap MabSelect, HiTrap MabSelect SuRe, and HiTrap MabSelect Xtra are easy to use with ÄKTExpress™ MAB, which offers automated, multistep, high-throughput purification of monoclonal antibodies. Examples of two-step purifications (affinity followed by gel filtration) for each column are shown in Figures 8 to 10.

### Acknowledgement

Samples of mouse IgG<sub>2a</sub> and IgG<sub>1</sub> were supplied by kind courtesy of Phadia AB, Uppsala, Sweden. Human IgG<sub>1</sub> was supplied in collaboration with Polymun Scientific, Vienna, Austria.

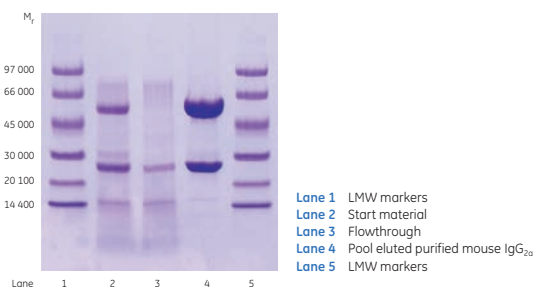
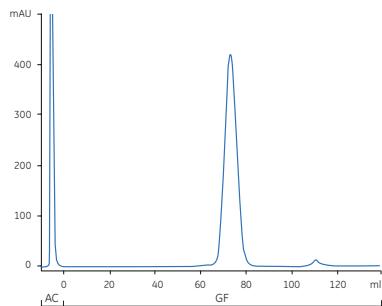


**Fig 6.** Purification of a human monoclonal antibody (MAB) on HiTrap MabSelect SuRe 1 ml on ÄKTExplorer 100. For quick neutralization of eluted antibodies, 1 M Tris, pH 9, was added to the tubes.



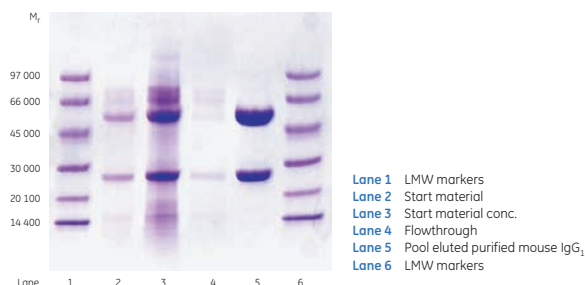
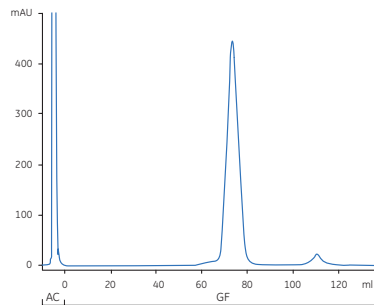
**Fig 7.** Purification of human IgG<sub>1</sub> on HiTrap MabSelect Xtra 1 ml on ÄKTExplorer 10. For quick neutralization of eluted antibodies, 1 M Tris, pH 9, was added to the tubes.

Affinity column: HiTrap MabSelect 1 ml  
 Gel filtration column: HiLoad™ 16/60 Superdex™ 200 pg  
 Sample: Filtered mouse myeloma cell culture, 165 mg/l IgG<sub>2b</sub>  
 Sample volume: 75 ml  
 Binding buffer (affinity): 0.02 M sodium phosphate, 0.15 M NaCl, pH 7.4  
 Elution buffer (affinity): 0.1 M sodium citrate, pH 3.0  
 Buffer (gel filtration): 0.15 M NaCl  
 Flow rate:  
 affinity: 1 ml/min  
 gel filtration: 1.5 ml/min  
 System: ÄKTApur MAb  
 Analysis: ExcelGel SDS Gradient 8-18, reduced conditions



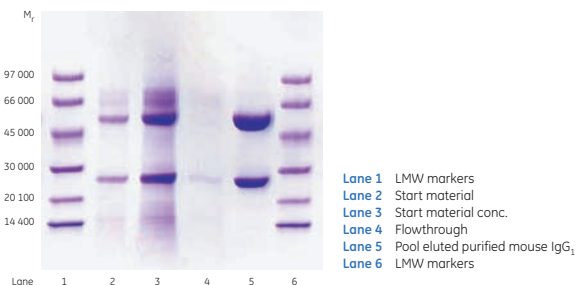
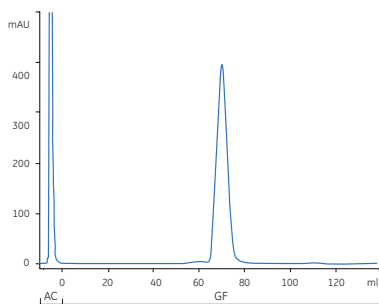
**Fig 8.** Purification of IgG<sub>2b</sub> using HiTrap MabSelect 1 ml in an automated two-step purification on ÄKTApur MAb. Yield of purified antibody was 9.2 mg at a concentration of 0.75 mg/ml.

Affinity column: HiTrap MabSelect SuRe 1 ml  
 Gel filtration column: HiLoad 16/60 Superdex 200 pg  
 Sample: Filtered mouse myeloma cell culture, 54 mg/l IgG<sub>1</sub>  
 Sample volume: 200 ml  
 Binding buffer (affinity): 0.1 M sodium phosphate, 2.5 M NaCl, pH 7.0  
 Elution buffer (affinity): 0.1 M sodium citrate, pH 3.0  
 Buffer (gel filtration): 0.15 M NaCl  
 Flow rate:  
 affinity: 1 ml/min  
 gel filtration: 1.5 ml/min  
 System: ÄKTApur MAb  
 Analysis: ExcelGel SDS Gradient 8-18, reduced conditions



**Fig 10.** Purification of IgG<sub>1</sub> using HiTrap MabSelect SuRe 1 ml in an automated two-step purification on ÄKTApur MAb. Yield of purified antibody was 9.6 mg at a concentration of 0.78 mg/ml.

Affinity column: HiTrap MabSelect Xtra 1 ml  
 Gel filtration column: HiLoad 16/60 Superdex 200 pg  
 Sample: Filtered mouse myeloma cell culture, 54 mg/l IgG<sub>1</sub>  
 Sample volume: 150 ml  
 Binding buffer (affinity): 0.1 M sodium phosphate, 2.5 M NaCl, pH 7.0  
 Elution buffer (affinity): 0.1 M sodium citrate, pH 3.0  
 Buffer (gel filtration): 0.15 M NaCl  
 Flow rate:  
 affinity: 1 ml/min  
 gel filtration: 1.5 ml/min  
 System: ÄKTApur MAb  
 Analysis: ExcelGel SDS Gradient 8-18, reduced conditions



**Fig 9.** Purification of IgG<sub>1</sub> using HiTrap MabSelect Xtra 1 ml in an automated two-step purification on ÄKTApur MAb. Yield of purified antibody was 7.6 mg at a concentration of 0.72 mg/ml.

## Ordering Information

| Products              | Quantity | Code No.   |
|-----------------------|----------|------------|
| HiTrap MabSelect SuRe | 5 x 1 ml | 11-0034-93 |
|                       | 1 x 5 ml | 11-0034-94 |
|                       | 5 x 5 ml | 11-0034-95 |
| HiTrap MabSelect      | 5 x 1 ml | 28-4082-53 |
|                       | 1 x 5 ml | 28-4082-55 |
|                       | 5 x 5 ml | 28-4082-56 |
| HiTrap MabSelect Xtra | 5 x 1 ml | 28-4082-58 |
|                       | 1 x 5 ml | 28-4082-60 |
|                       | 5 x 5 ml | 28-4082-61 |

### Related products

|                         |             |            |
|-------------------------|-------------|------------|
| MabSelect SuRe          | 25 ml       | 17-5438-01 |
|                         | 200 ml*     | 17-5438-02 |
| MabSelect               | 25 ml       | 17-5199-01 |
|                         | 200 ml*     | 17-5199-02 |
| MabSelect Xtra          | 25 ml       | 17-5269-07 |
|                         | 200 ml*     | 17-5269-02 |
| HiTrap Desalting        | 5 x 5 ml    | 17-1408-01 |
|                         | 100 x 5 ml† | 11-0003-29 |
| HiPrep™ 26/10 Desalting | 1 x 53 ml   | 17-5087-01 |
|                         | 4 x 53 ml   | 17-5087-02 |

\* Larger pack sizes are available

† Pack size available by special order

### Accessories

|  |   |            |
|--|---|------------|
| 1/16" male/Luer female*                            | 2 | 18-1112-51 |
| Tubing connector flangeless/M6 female*             | 2 | 18-1003-68 |
| Tubing connector flangeless/M6 male*               | 2 | 18-1017-98 |
| Union 1/16" female/M6 male*                        | 6 | 18-1112-57 |
| Union M6 female /1/16" male                        | 5 | 18-3858-01 |
| Union Luerlock female/M6 female                    | 2 | 18-1027-12 |
| HiTrap/HiPrep, 1/16" male connector for ÄKTAdesign | 8 | 28-4010-81 |
| Stop plug female, 1/16"†                           | 5 | 11-0004-64 |
| Fingertight stop plug, 1/16"‡                      | 5 | 11-0003-55 |

\* One connector included in each HiTrap package

† Two, five, or seven female stop plugs included in HiTrap packages, depending on products

‡ One fingertight stop plug is connected to the top of each HiTrap column

### Related literature

|   |            |
|---|------------|
| Antibody Purification Handbook                            | 18-1037-46 |
| Affinity Chromatography Handbook, Principle and Methods   | 18-1022-29 |
| Affinity Chromatography Columns and Media Product Profile | 18-1121-86 |
| Convenient Protein Purification, HiTrap Column Guide      | 18-1129-81 |

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