Domainex

Driving discovery • Delivering leads

PureDisc™

Membrane Protein Solutions for Drug Discovery



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The Membrane Protein Challenge

Membrane proteins sit at the heart of drug discovery, but they remain among the most technically demanding target classes to work with. GPCRs, ion channels, transporters and other integral membrane proteins depend on their native lipid environment for correct folding, stability and function. Once removed from the cell membrane, these proteins rapidly lose structural integrity, aggregate, or become unsuitable for downstream assays.

Traditional detergent-based purification is effective for some targets, but detergents can disrupt critical lipid-protein interactions and reduce biological relevance. Detergent-free approaches, including SMALPs and other co-polymer nanodiscs, help preserve a lipid-associated state; however, instability and aggregation can still limit performance. For challenging targets, this can compromise biophysical data quality, weaken screening robustness and make structural biology programmes slower and less predictable.

The result is a common discovery bottleneck: high-value membrane protein targets are biologically compelling, but difficult to produce in a format suitable for biophysics and structural biology.

Key challenges include:

- Preserving native-like conformation and lipid interactions
- Generating stable, monodisperse preparations
- Producing sufficient quality material for biophysics, screening and structural biology
- Reducing downstream troubleshooting caused by unstable or poorly behaved protein

Introducing PureDisc™

PureDisc™ builds on established polymer nanodisc approaches to generate near-native, SEC-purified membrane protein preparations suitable for downstream discovery applications. Combined with Domainex's in-house expertise in membrane protein production, biophysics and structural biology, PureDisc™ provides a streamlined route from target selection to assay-ready material for binding studies and structural characterisation. This supports faster project decisions, improves data confidence and reduces experimental uncertainty.

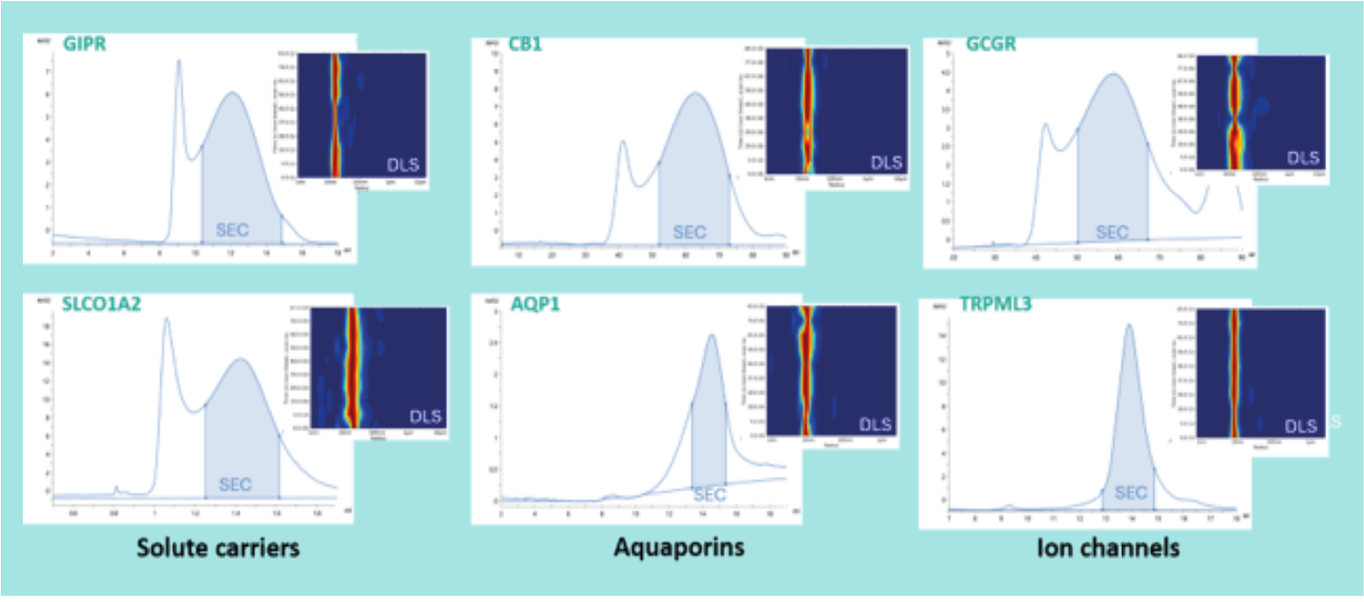
PureDisc™ is more than a nanodisc preparation method; it is an integrated membrane protein workflow combining commercial co-polymer screening, purification optimisation, quality control, biophysics and cryo-EM readiness.

What PureDisc™ Enables

- Detergent-free solubilisation and purification, removing the need for harsh surfactants
- Native-like lipid environment, preserving conformation, stability and function
- Stable, monodisperse, SEC-purified preparations, characterised by DLS
- Compatibility with biophysics, screening and structural biology workflows
- Broad applicability to challenging targets, including GPCRs, ion channels and transporters

The solution: Domainex's PureDisc™ platform uses commercial polymers to generate high-quality, membrane protein preparations, achieving high protein concentrations, fully supported by in-house biophysics and cryo-EM

Size-Exclusion Chromatography Panel



From Construct to Discovery-Ready Protein

Every membrane protein target is different. Domainex applies a tailored protein production strategy that brings together construct design, expression system selection, solubilisation conditions and rigorous quality control to define the most suitable route for each programme.
Our scientists generate fit-for-purpose protein preparations for downstream applications including antibody generation, biophysical and biochemical screening, and structural biology.

Membrane Protein Production Workflow:

1. Construct design & review tailored to downstream applications
2. Expression system selection & optimisation to obtain soluble expression
3. Co-polymer screen to improve solubilisation efficiency
4. Purification optimisation involving affinity purification & SEC to improve sample homogeneity
5. Extensive QC & characterisation (DLS, nanoDSF)
6. Downstream application readiness

Outcome: A well-characterised membrane protein target, matched to the scientific question and ready to support confident decision-making in discovery.

In-house Biophysical Assays

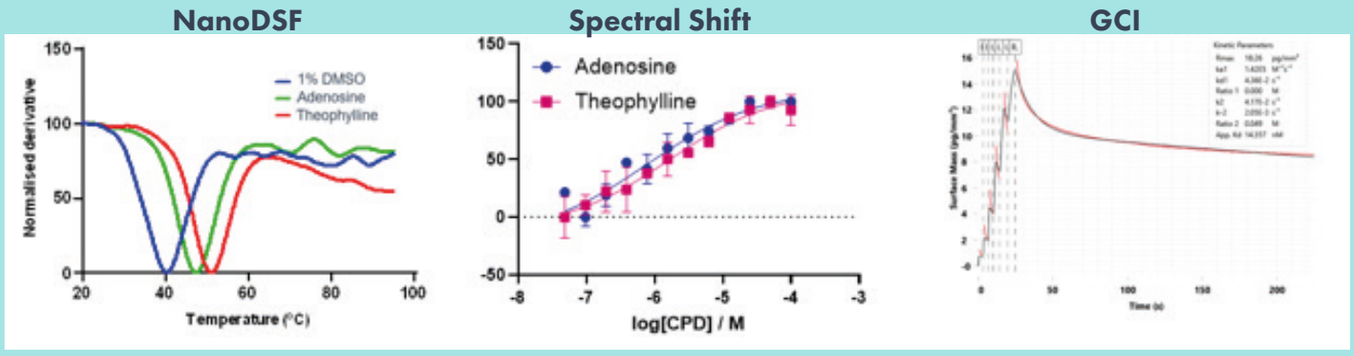
From affinity and binding kinetics to bespoke assay development, Domainex biophysicists have extensive experience working with challenging membrane protein targets. Whether supporting screening campaigns, hit identification, hit validation or detailed mechanistic characterisation, our team applies complementary biophysical approaches to generate robust data that informs programme decisions.

PureDisc™-purified proteins are designed to support downstream biophysical assays by providing stable, assay-ready material for binding, screening and mechanistic studies.

Biophysical capabilities include:

- Grating-Coupled Interferometry (GCI), affinity and kinetic measurements for biologics
- Spectral Shift, small molecule, peptide or antibody equilibrium binding data
- NanoDSF, thermal stability assessment, formulation support and binding confirmation

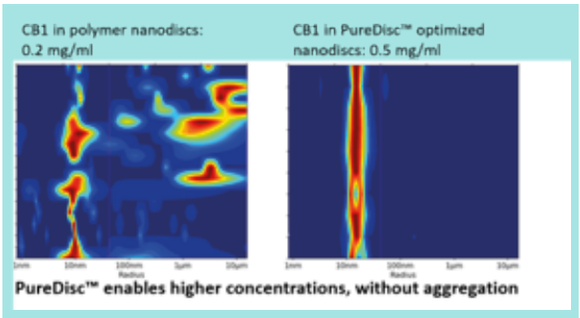
Illustrative data: Thermal stability (DSF) and affinity measurements (Spectral Shift) for the wild-type Adenosine A2a Receptor (small molecules). Affinity and kinetic measurements for antibody binding to the CB1 receptor (Grating-Coupled Interferometry).



Structural Biology

Structure-enabled drug discovery depends on membrane protein samples that are stable, homogeneous and biologically relevant. For many membrane targets, detergent purification can disrupt key lipid–protein interactions, while conventional nanodisc approaches may still suffer from aggregation at the concentrations needed for cryo-EM.

PureDisc™ is designed to address these challenges by generating SEC-purified, nanodisc-embedded membrane proteins stable at high concentrations required for Cryo-EM that maintain a biologically relevant lipid context and remain suitable for downstream structural studies. By combining membrane protein production, biophysical quality control, cryo-EM and computational chemistry, Domainex helps clients progress difficult targets from purified protein to structurally enabled discovery.



Structural biology support includes:

- Generation of monodisperse, nanodisc-embedded protein at concentrations suitable for cryo-EM
- Cryo-EM sample preparation, data collection and structure determination
- In-house CADD support for structure interpretation, ligand design and optimisation
- Integration with downstream structure-guided drug discovery programmes

Cryo-EM Workflow:

Cryo-EM Workflow for PureDisc™ Membrane Protein Targets				
1. Cryo-EM-ready protein SEC-purified, monodisperse PureDisc™ material at concentration suitable for grid	**2. Quality Control** DLS, nanoDSF and biophysical validation to confirm stability, and homogeneity	**3. Grid Optimisation** Screen grid type, sample concentration, vitrification conditions	**4. Data Collection** Acquire cryo-EM datasets from optimised grids, with iterative assessment	**5. Structure Determination** Image processing, map generation, model building and interpretation to support
Output: high-quality structural insight from native-like, nanodisc-embedded membrane protein preparations, integrated with CADD and downstream drug discovery decisions.				

Case Study: TRPML3 Ion Channel

Target and Challenge

TRPML3 is a heteromeric ion channel associated with endolysosomal trafficking, autophagy and disease pathways including neurodegeneration and cancer. Producing stable, functional TRPML3 in a nanodisc format suitable for biophysical analysis and cryo-EM is challenging due to a pronounced tendency of the polymer nanodiscs to aggregate at higher concentrations.

Key results at a glance

- Monodisperse, SEC-purified TRPML3 generated in polymer nanodiscs
- Ligand binding measured for known TRPML3 activators using Spectral Shift
- Binding affinities consistent with literature potency values
- 2.8 Å cryo-EM structure determined from PureDisc™-purified material
- Improved regional coverage compared with detergent-prepared protein

Domainex Approach

Domainex applied PureDisc™ to generate monodisperse, SEC-purified TRPML3 in polymer nanodiscs and determined the first cryo-EM structure of TRPML3 using polymer nanodiscs.

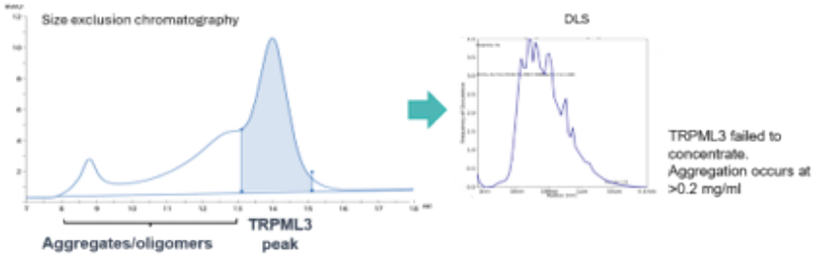
Production workflow:

- Full-length wild-type TRPML3 overexpressed in Expi293™ cells
- 96-well solubilisation screen identified Ultrasolute Amphipol, AASTY and Cubipol as effective polymers
- PureDisc™-optimised affinity purification (Co-IMAC/Talon) followed by SEC
- TRPML3 eluted as a single peak consistent with tetrameric nanodiscs

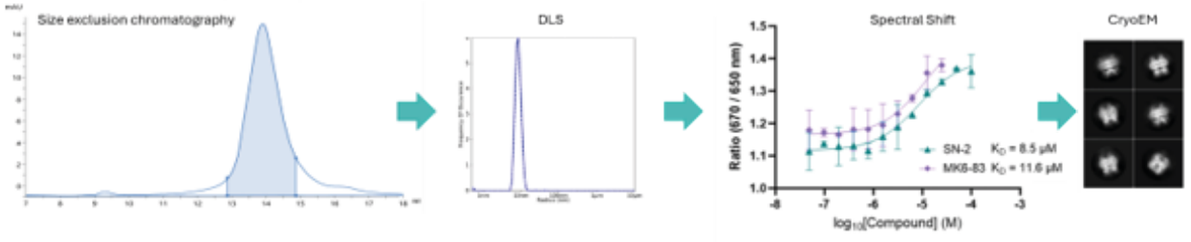
Biophysical characterisation:

- Spectral Shift used to determine binding affinities for TRPML3 activators SN-2 and MK6-83
- Measured affinities consistent with literature potency values, confirming native-like functional presentation

TRPML3 in polymer nanodiscs- failed due to aggregation



TRPML3 in PureDisc™ optimised nanodiscs - Biophysics and Cryo-EM compatible



Structural biology:

- Cryo-EM grid preparation from PureDisc™-purified material
- Overnight data collection (10,002 micrographs)
- Structure determination yielding a detailed 2.8 Å resolution map
- Structural stabilisation of a key region previously unresolved in detergent-prepared maps
- Insight into two key regulatory residues (H283 and E361) between the luminal/extracytosolic domain and transmembrane helix S2

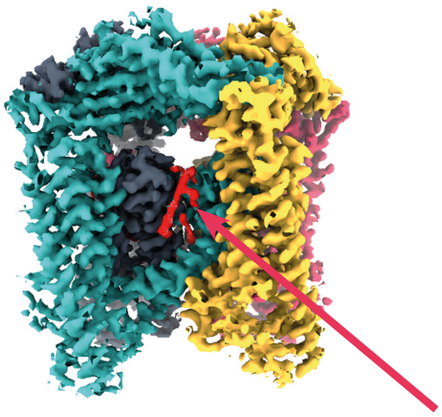
Outcome

PureDisc™ enabled TRPML3 to be progressed from an aggregation-prone membrane protein target to a stable, functionally validated preparation suitable for high-resolution structural analysis. By integrating polymer screening, purification optimisation, biophysical validation and cryo-EM, Domainex generated material that supported both ligand-binding analysis and structure determination.

Discovery impact: This case study demonstrates how PureDisc™ can de-risk challenging membrane protein targets and provide a clearer route from protein production to interpretable binding and structural data.

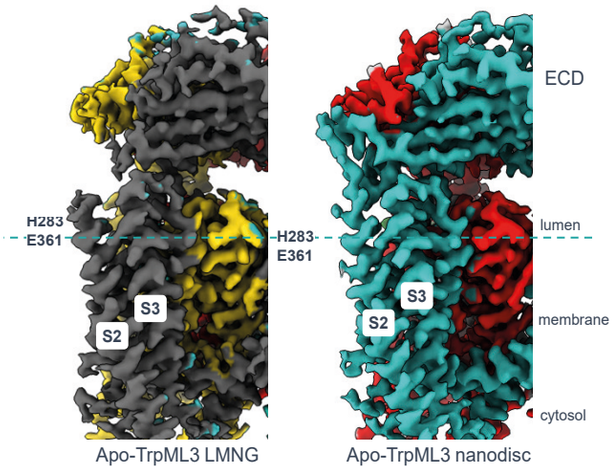
Domainex Approach

2.8 Å Cryo-EM Map of Apo TRPML3



Resolved lipid within the agonist binding pocket

Additional Structure Revealed using PureDisc™



Start Your Membrane Protein Project with Domainex

Whether you need purified membrane protein, assay-ready material, biophysical characterisation or structural biology support, Domainex can help define the right strategy for your target.

Our multidisciplinary team brings together protein science, assay biology, biophysics, structural biology and drug discovery expertise to help overcome membrane protein bottlenecks and generate data that advances your programme.

Talk to Domainex if you are looking to:

- Produce a challenging GPCR, ion channel, transporter or receptor
- Compare detergent-based and polymer-based purification strategies
- Generate native-like membrane protein for binding assays
- Support fragment screening, hit validation or antibody discovery
- Prepare membrane protein samples for cryo-EM or structure-guided discovery

PureDisc™: Turning Challenging Membrane Proteins into Actionable Data

Contact Domainex to discuss how PureDisc™ and our integrated expertise can support your next membrane protein programme.

www.Domainex.co.uk **Enquiries@Domainex.co.uk**

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About Domainex

Domainex is a fully integrated drug discovery service company based in Cambridge, UK. We serve a wide range of pharmaceutical, biotechnology, and academic organisations and patient foundations globally. We have ambitious growth plans and currently have over 80 scientists. We provide integrated services, from disease target selection to candidate drug nomination. We have a very strong reputation for contributing innovative ideas, undertaking high-quality experiments and for generating intellectual property on behalf of our clients. We strive to build strong, dynamic relationships and work with our clients to provide customised services.

How Can Domainex Help Your Drug Discovery Project?

Our highly experienced, multi-disciplined scientists – molecular biologists, protein biochemists, assay biologists, structural biologists, medicinal, computational and bio/analytical chemists, in vitro pharmacologists and ADME scientists – will support you to advance your drug discovery projects towards drug development effectively and efficiently. We provide customised programmes to address your specific needs at each stage of the pre-clinical drug discovery process. We draw from a wealth of expertise built up over the last 25 years across a wide range of drug targets and therapeutic areas. From our site within Europe's leading bioscience hub at Cambridge, UK and with access to the very latest cutting-edge technologies, we are able to help you realise your goals and enrich your discovery pipeline.

Contact

If you would like to know more about Domainex's discovery services, or speak to us regarding your own drug discovery needs, please contact us at enquiries@domainex.co.uk

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