Good morning everyone.
I am delighted to be here today to demonstrate to you the Power of StaR Technology in GPCR drug discovery.
Turning to slide 2
My name is Stacey Southall and I am the head of the biophysics team at Sosei Heptares.
I’m of British and Irish heritage and am based in the UK.
I studied at Sheffield and Cambridge where I developed a passion for understanding protein structure.
I followed my studies with postdoctoral Fellowships at UEA, the Institute of Cancer Research and EMBL where I developed this into a desire to use protein structure information to combat disease.
I’ve been at Sosei Heptares for 5 years and as lead a team of passionate and talented scientists focussed on using biophysical and structural data for drug discovery.
• Turning to slide 3
• Biophysics is part of our Platform Technology area along with Protein Engineering and integrated with Biomolecular Structure.
• Here we operate at the very start of drug discovery process.
Agenda

1. StaR® Technology and its Benefits
2. StaR® Technology in Action
3. StaR® Technology Driving Collaborations
4. Future Directions

• Turning to slide 4
• I’ll start by explaining to you what G protein coupled receptors are, why we target them and how we harness the power of our StaR technology to give us a unique advantage in GPCR drug design
• I will then give you some specific examples of how we have employed our technology.
• I’ll expose how this has driven some exciting major collaborations.
• I’ll finish by looking to the future, showing how StaR receptors are at the heart of exploiting new technologies.
Turning to slide 5
StaR Technology and Its Benefits
What are G protein-coupled receptors (GPCRs)?

**WHAT THEY DO**

- Integral membrane proteins that span the lipidic bilayer of cell membranes
- Primary function is to transduce external stimuli into intracellular signals
- Respond to a variety of different ligands

**HOW THEY LOOK**

- 7 transmembrane helices (TM)
- 3 intracellular loops (ICL)
- 3 extracellular loops (ECL)
- Interact with guanine nucleotide binding proteins (G proteins) to transmit signal

Largest super-family of transmembrane proteins in the human genome with ~800 members

- Turning to slide 6
- So what is a G protein coupled receptor, or as they are commonly known a GPCR?
- They are integral membrane proteins, spanning the lipid bilayer of our cells and are responsible for translating extracellular stimuli such as hormones, neurotransmitters, lipids and even light, into intracellular signals to elicit cellular responses.
- GPCRs share a common architecture of 7 transmembrane helices connected by 3 intra cellular loops and 3 extracellular loop and undergo major conformational rearrangements in these helices upon activation, allowing interaction inside the cell with the heterotrimeric G proteins that give them their name, to propagate the signal.
- There are over 800 different GPCRs in the human genome making them the largest family of integral membrane proteins.
Turning to slide 7

This large number of GPCRs makes for a very diverse family of drug targets. Although they share a common fold, they differ drastically in sequence and in the domains present on the extracellular side of the receptor. They are typically classified into sub families based on functional similarities.

Family A is by far the largest and best studied family, containing the rhodopsins and olfactory receptors, and typically have a compact structure with activating molecules binding in a pocket on the extracellular side of the receptor.

Family B receptors are further subdivided into B1 and B2. B1 contains the secretin receptors which have a characteristic peptide hormone binding domain, and B2 are the adhesion GPCRs.

The extracellular region of adhesion GPCRs can be exceptionally long and contain a variety of structural domains facilitating cell and matrix interactions. The mature GPCR exists as noncovalently associated complexes between the extracellular domains and the transmembrane region.

Family C receptors such as the glutamate receptors typically exist as dimers.
in the membrane and interact via their ligand-binding Venus fly trap domains.

- Family F or Frizzled receptors have a cysteine rich extracellular domain and are activated by binding to WNT proteins, which are proteins with fundamental functions in cell proliferation.
Why do we target G Protein-Coupled Receptors (GPCRs)?

- Turning to slide 8
- So now that I have introduced GPCRs, the question I want to answer is why do we target them? Quite simply, almost half of all GPCRs have been shown to be involved in disease, with diverse indications including neurological diseases, gastro-intestinal disorders, metabolic disorders, oncology, cardiovascular and respiratory disease and many more.
- Targeting GPCRs has long been and continues to be a major focus in drug discovery. Over 30% of all FDA approved drugs target them and around 27% of global drug sales are for GPCR drugs.
- Despite this, only 27% of those 400 disease relevant GPCRs are currently being drugged with another 17% in clinical trials.
- This leaves huge opportunities to target the remaining undrugged GPCRome with first-in-class therapies and by using StaR technology and taking a structure-based drug design approach, we have opportunities to generate best in class therapies for long-standing targets.

The Stabilized Receptor (StaR®) is at the core of our SBDD platform

- GPCR drug discovery remains challenging
  - Low expression levels – often with complicated expression and secretion pathways
  - Difficult purification – lose structural integrity outside the membrane
  - Heterogeneity – inherently flexible; changing conformation depending on the bound ligand
- We introduce point mutations into a GPCR which leads to increased thermostability
  - The receptor is trapped in a relevant conformation to match the drug product profile
  - Finally, the Stabilized receptor (StaR®) can be extracted from the membrane, purified and function retained
- 60+ Stabilized Receptors generated in agonist and/or antagonist conformations

Turning to slide 9
- StaR technology underpins our success and lies at the core of our structure-based drug design platform.
- So what is a StaR? StaR stands for stabilised receptor and describes the process of selecting a desired drug modality for a receptor and introducing a small number of individual mutations into the sequence looking for increases in thermostability.
- These are iteratively combined monitoring the pharmacology and characterising their properties until a sufficiently stable receptor is generated – a StaR.
- These StaRs are then suitable for downstream applications such as screening, biophysics and structure determination, facilitating structure based drug design and optimisation for Hit ID.
- Why is this process necessary? GPCR drug discovery is very challenging. GPCRs are poorly expressed in the cell and often require complicated expression and secretion pathways to generate active protein in the membrane. They are inherently instable, making it very difficult to extract them from the membrane for further study. Finally, they naturally exist in a
range of conformations depending on the molecule bound to it making modelling drug interactions without a structure more challenging.

The StaR process of introducing thermostabilising mutations typically improves expression and stability. By targeting a particular state, we can trap the receptor in a drug-relevant conformation for study and crucially it allows the extraction and purification of large quantities of functional, stable receptor from the membrane environment for downstream activities.

At Sosei Heptares we have generated over 60 stabilised receptors in the active (that is the agonist) or the inactive (or antagonist) conformations.
Turning to slide 10

Thanks to the increased thermostability and expression levels, a StaR lends itself to many biochemical, biophysical and structural techniques.

Biochemical assays are used to screen molecules and conditions for additional thermostability, identifying those optimal for protein purification.

Surface Plasmon Resonance (SPR) is a powerful technique that allows us to analyse the kinetic components of a receptor-drug interaction; an important consideration in drug product profile.

It can be used for biophysical mapping of ligand-receptor interactions by characterizing the impact of designed mutations in the predicted binding site on drug binding.

SPR is also used for screening libraries for example of low molecular weight fragments that offer starting points for new chemical series against a target.

Mass spectroscopy is classically used for protein quality control but additionally techniques such as hydrogen-deuterium exchange or HDX and Native MS offer insights into binding interactions and dynamics.

Structure determination is at heart of our drug design cascade and can be more readily achieved with StaR receptors. This can be by X-ray.
crystallography or emerging techniques such as XFEL and Cryoelectron microscopy.
We have solved **260+ molecular structures** from **25+ different GPCRs**

- Turning to slide 11
- Sosei Heptares has generated StaRs and crystal structures in all 4 major GPCR classes as represented here. This validates the transferability of our platform across the GPCR phylogenetic tree.
- In the protein data bank or PDB there are over 60 GPCR structures and over 200 unique GPCR-ligand complexes
- At Sosei Heptares we have generated over 260 structures of which 30 are available in the PDB. Additionally, we have determined the highest resolution GPCR structure to date.
StaR® technology: revolutionary for GPCR structure-based drug design

- Improved physiochemical properties (more polar, more selective, lower dosage)
- Better safety and efficacy
- Reduced clinical attrition
- Small molecule, peptide or antibody discovery

Our StaR®/SBDD platform capabilities allow us to develop better, differentiated drug candidates against emerging novel GPCR target mechanisms

- Turning to slide 12
- Our StaR technology, feeding our structure pipeline, uniquely positions us to perform structure-based drug design SBDD – a strategy that leads to better, differentiated drugs.
- It has been demonstrated that drugs designed in this way often have better physiochemical properties such as being more polar, with an improved selectivity profile, ultimately allowing lower dosage for patients.
- These drugs are likely exhibit better safety and efficacy in turn leading to reduced rates of clinical attrition.
- StaRs are not only ideally suited for small molecule drug discovery but are valuable tools in peptide and antibody discovery too.
- Our integrated StaR and SBDD platform positions us to be able to develop better, differentiated drug candidates against a wealth of GPCR target mechanisms.
• Turning to slide 13
• Now I’d like to demonstrate to power of StaR technology with some examples of how it has been successfully employed.
Multiple different ways to target the PAR2 receptor using StaRs

- Identification of potent cyclic peptide antagonists
- Optimisation of small molecule antagonists
- Antibody discovery
- Identification of functional PAR2 antagonists

Turning to slide 14

PAR2 is a Family A GPCR and a member of the protease-activated receptor family. PAR2 modulates inflammatory responses, obesity, metabolism, and acts as a sensor for proteolytic enzymes generated during infection and so is an important drug target. Many ways of targeting PAR2 have been and are being explored in the pharmaceutical industry. Here I will describe some of those where StaR technology has played a critical role in collaborations aimed at generating a PAR2 antagonist. I will describe two small molecule projects in collaboration with AstraZeneca and using XChem technology, an ongoing peptide antagonist project in collaboration with Peptidream and our current therapeutic antibody project with Morphosys.
The PAR2 receptor, as with most GPCRs, is very poorly expressed in cells and is very unstable when extracted making screening for inhibitors or this receptor very difficult.

Indeed at the start of the project, no suitable PAR2 antagonist ligands were available for StaR generation, so we performed a ligand free stabilisation of the receptor.

The PAR2 antagonist StaR we generated has vastly improved expression and thermostability and could be readily purified making it suitable for a range of screening approaches.

In the search for any new chemical matter or tool compounds we collaborated with Astrazeneca to perform HTS and a fragment screen on the StaR
This campaign identified a small molecule AZ8838 which could inhibit activation of PAR2.

However, it was difficult to understand the mechanism of this antagonism and to optimise the molecule without structural data.

Challenging protein engineering was required to obtain a high resolution structure by X-ray crystallography of the PAR2 StaR bound to AZ8838, viewed here from both parallel to the membrane and from the extracellular side. We could observe unambiguously in the structure, that the binding site for the ligand was not in the conventional binding pocket where it had been modelled, but adjacent to it, thus explaining the difficulty of optimising the compound based on the original modelled position. The structure also allowed us to propose a mode of action for this molecule. It is likely to be competition with the binding site of the natural peptide ligand.
• Turning to slide 16
• In order to try and find a new and improved starting point we engaged in collaborative hit finding with Astra Zeneca using the DNA encoded library technology from XChem.
• This uses a diverse library of small molecules displayed on a DNA barcode for screening.

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• Binding hits to the PAR2 StaR were identified that showed function as PAR2 antagonists in cells. Again, these were hard to optimise away from their poor drug-like properties without structural understanding.

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• Our Platform was able to offer structural support once more and a structure of the PAR2 StaR was determined bound to the small molecule AZ3451.

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• Once again, the binding site came as a surprise; it sits in novel extra-helical
pocket formed between transmembrane helices 2, 3 & 4. Interaction with PAR2 is predominately hydrophobic in nature as this is a very lipophilic compound.

- The compound likely acts as a kind of molecular glue, preventing the outward movement of TM3, a requirement for receptor activation.
Turning to slide 17

Our collaboration with Peptidream has allowed us to further exploit the PAR2 StaR to screen for peptide antagonists using Peptidream’s proprietary DNA-encoded peptide display library.

This has generated several potent cyclic peptide antagonists of PAR2.

We were able to determine a structure of one of these high affinity cyclic peptides by X-ray crystallography, which has demonstrated that the mode of action is most likely to be competition for PAR2 with the native peptide agonist shown modelled here in yellow.

Efforts are ongoing, and progressing well, to improve potency and optimise peptide stability supported by Sosei Heptares biophysics and SBDD platforms.
platforms.
AstraZeneca and Morphosys | PAR 2 antibody discovery

1. StaR generation allowed structure determination with the Fab portion (AstraZeneca) of a non-pharmaceutical antibody
2. StaR structure highlighted possibility of targeting PAR2 using an antibody to the extracellular side of the receptor
3. StaR receptor allowed Sosei Heptares to screen using Morphosys human antibody library technology
4. Hits optimized to generate a proprietary novel, efficacious pharmaceutical antibody


- Turning to slide 18
- Antibodies targeting GPCRs have been desirable for many years.
- However, because they are difficult to prepare and isolate in solution, often having only a small exposed area on the extracellular side of the receptor, GPCRs are notoriously difficult targets to generate antibodies against.
- Indeed, only two FDA approved GPCR-targeting antibodies exist to date, despite a wealth of programs in existence.
- As part of our collaboration with AstraZeneca we exploited the PAR2 StaR to determine the structure in complex with a Fab fragment from a high-affinity non-pharmaceutical antibody.

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- This structure highlighted the possibility of using the PAR2 StaR as an antigen for generation of a specific therapeutic antibody against PAR2.

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- We engaged with Morphosys to screen their library based on specialised
human antibody technology using the PAR2 StaR.

- We identified a number of hits and these have been iteratively optimised and characterised to generate a proprietary novel, efficacious pharmaceutical antibody.
Turning to slide 19

As I mentioned previously, typical GPCR ligands exert their action from within a binding site on the top of the receptor.

In the absence of a structure and with sometimes limited pharmacological and mutation data available, we tend to model ligands in the orthosteric site.

StaR structures have helped to reveal a substantial number of surprising additional sites of receptor modulation, distal from the orthosteric binding site, known as allosteric binding sites. Some examples of these are shown here.

The possibility of multiple target sites on a receptor opens even more opportunities for drug development.
For some well-established projects such as the A2A receptor, we routinely achieve very high resolution structures which is typically very challenging for GPCRs.

This high resolution allows us to see extra levels of detail including water molecules, shown here in the binding site as red spheres.

This dramatically aids our understanding of the atomic basis of the mode of action of compounds and adds value to structure based drug design.

The StaR process does not introduce any conformational artefacts to the structure as seen by the very good correlation between the A2A StaR structure and the wild type structure bound to the same ligand, even down to the position of the water molecules.

High resolution structures allow detailed atomic understanding of ligand mechanism of action.
• Turning to slide 21
• Typical GPCR structures are obtained with high affinity ligands that add additional stability to the protein.
• For some StaRs we can purify and crystallise the receptor with a low affinity ligand such as A2A which binds the caffeine-related molecule theophylline weakly with fast kinetics.

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• We were still able to purify and crystallise the protein in the presence of this ligand due to the inherent StaR stability and obtained a high resolution structure.

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• We have subsequently been able to soak higher affinity ligands into crystals bound to theophylline, exchanging the ligand. This has allowed us to generate multiple co-structures.

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Indeed up to 96 new structures could be generated from one crystallisation plate.
Turning to slide 22
I hope I have been able to demonstrate to you the power of Sosei Heptares StaR technology.
It is confidence in this that has led to a large number of collaborations and partnerships.
Turning to slide 23

We are considered the preferred partners for GPCR drug discovery driven by the strength of our Platform.
Multi-target collaborations with innovative leaders in the industry

- Collaboration to discover and develop novel small molecules and/or biologics
  - Directed at up to 10 GPCR targets across multiple therapeutic areas

- Collaboration to discover and develop novel small molecules and/or biologics
  - Directed at multiple targets across multiple therapeutic areas

- Collaboration to discover, develop and commercialize novel small molecules and/or biologics
  - Directed at multiple targets across multiple therapeutic areas, with initial focus on high-priority gastrointestinal targets

Sosei Heptares delivered multiple StaR® proteins, X-ray structures and biophysical protocols

Pfizer nominated two clinical candidates to advance into development in 2019

Signed Nov 2015

- Turning to slide 24
- As well as numerous individual target collaborations we have negotiated 3 multi-target collaborations with industry leaders Pfizer, Genentech and Takeda.
- These are aimed at discovering new small molecules or biologics against targets in multiple therapeutic areas.

- The first of these to be initiated was with Pfizer in 2015 with the possibility of up to 10 targets.
- This has been a resounding success with multiple StaRs, biophysical data and structures being generated.
- This has led to the nomination of two clinical candidates to take forward this year triggering milestone payments to Sosei Heptares.
- The power of our PLATFORM and what we have achieved with our platform has been a key driver of multiple partnerships with world leading pharma companies.
Our R&D team is recognized for challenging the frontiers of science.

With scientific breakthroughs in many areas driven by our Platform.

- Turning to slide 25
- Our R&D team is recognized for challenging the frontiers of science.
- With scientific breakthroughs in many areas driven by our Platform.

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- We have published over 180 peer reviewed articles including 7 prestigious Nature Papers
- We have and continue to be recognized for scientific breakthroughs in the field of GPCRs
• Turning to slide 26
• Looking to the future, how can we build on what we have achieved and exploit our platform in emerging technologies?
Embracing technological advances in GPCR structure determination

- **SMX / SFX (XFEL)** makes use of protein crystals too small and fragile for conventional X-ray crystallography - “Diffraction before destruction”
- Protein crystals injected through high energy X-ray or X-ray free-electron laser, continuously collecting diffraction patterns
- Allows for time resolved experiments introducing an interaction dynamics dimension in addition to the classical static picture

Turning to slide 27

At Sosei Heptares we are embracing new methods for GPCR structure determination to complement and fortify our structure based drug design approach.

- Serial millisecond crystallography and serial femtosecond crystallography using Xray Free Electron Laser or XFEL makes use of protein crystals too small and fragile for conventional X-ray crystallography, applying a “Diffraction before destruction” approach.
- Protein crystals injected through high energy X-ray or X-ray free-electron laser, continuously collecting diffraction patterns on each tiny crystal, integrating all the data and solving the structure.
- This allows for time resolved experiments introducing an interaction dynamics dimension in addition to the classical static picture obtained from a crystal structure.
Cryo-EM is revolutionizing structural biology

- GPCR structures have now been reported with resolutions comparable to X-ray crystallography and for increasingly difficult targets
- Sosei Heptares has developed in-house sample vitrification and screening facilities (Glacios, 200 keV) in a purpose-built extension
- High resolution data collection at Cambridge Pharmaceutical Cryo-EM Consortium (2 x Krios, 300 keV)
  - Sosei Heptares, Astex Pharmaceuticals, AstraZeneca, GSK, UCB, MRC-LMB and the University of Cambridge

- Turning to slide 28
- For many years cryo-EM reconstructions of proteins were limited to resolutions too low to be useful in SBDD and were typically of large proteins/complexes
- Technical advances making use of direct electron detectors (DED) and new image processing techniques have revolutionised the field allowing dramatic improvements in the resolutions obtainable as is nicely illustrated in this figure from Subramaniam.
- It is now possible to determine structures of GPCRs by cryo-electron microscopy with resolutions comparable to X-ray crystallography.
- To take advantage of this, we expanded our facility with a purpose-built extension housing a cryoEM sample preparation lab and a ThermoFisher Glacios microscope.
- This allows more streamlined screening of samples before selecting the best for high resolution data collection on the two Krios microscopes housed at the University of Cambridge that we share with other companies as part of the Cambridge Pharmaceutical CryoEM Consortium.
- In summary we are taking our powerful StaR technology and using it to
drive new technologies that will open further avenues in GPCR drug discovery.
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Thank you for your attention

I hope this has shown you the Power of StaR technology and I thank you for your attention