Register Today!

September 24 - 25, 2013

Eighth Annual
GPCR-Based Drug Discovery

Inaugural
Antibodies Against Membrane Protein Targets - Part 1

September 25 - 26, 2013

Inaugural
GPCR-Targeted Therapeutics

Inaugural
Antibodies Against Membrane Protein Targets - Part 2

Discovery on Target Event Features:

- 12 Conferences
- 150+ Scientific Presentations
- 10 Interactive Short Courses
- 35+ Breakout Discussion Groups
- Exhibit Hall, Poster Viewings & Networking Opportunities

PLENARY KEYNOTE SPEAKERS

Towards a Patient-Based Drug Discovery
Stuart L. Schreiber, Ph.D., Director, Chemical Biology, Founding Member, Broad Institute of Harvard and MIT; Howard Hughes Medical Institute Investigator; Morris Loeb Professor of Chemistry and Chemical Biology, Harvard University

Enteroeendocrine Drug Discovery for Treatment of Metabolic Diseases
Paul L. Feldman, Ph.D., Senior Vice President, GlaxoSmithKline

PREMIER SPONSORS

CELLECTA
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FEATURED SPEAKERS:

Dano Doller, Ph.D., Director, Discovery Chemistry & DMPK, Lundbeck Research USA
Thomas P. Sakmar, M.D., Professor, Laboratory of Chemical Biology & Signal Transduction, The Rockefeller University
William R. Strohl, Ph.D., Vice President, Biologics Research, Janssen Research & Development, LLC
Roger K. Sunahara, Ph.D., Associate Professor, Pharmacology, University of Michigan Medical School
Christopher Tate, Ph.D., Professor, Laboratory of Molecular Biology, MRC, United Kingdom

Organized by Cambridge Healthtech Institute
About the ‘GPCR’ and ‘Antibodies Against Membrane Protein Targets’ Meeting:

If you work with membrane proteins or GPCRs, you have several meetings tracks relevant to your work to choose from at this year’s Discovery on Target. And though you will register for one track or two, you are free to ‘track-hop’ to customize your own program.

The event includes two GPCR-focused conferences – covering allosteric modulators, the allosteric-intertwined issues of finding ligands that bias the receptor towards coupling with specific G proteins (or b-arrestin) and recently-solved crystal structures of GPCRs.

New for this year is the two-part “Antibodies Against Membrane Protein Targets,” providing a forum in which discovery biologists and protein engineers can come together to discuss next generation strategies and technologies that will allow antibody therapeutics directed against membrane proteins, particularly GPCRs, ion channels and transporters, to advance into the clinic and beyond.

Plenary Keynote Speakers

Towards a Patient-Based Drug Discovery
Stuart L. Schreiber, Ph.D., Director, Chemical Biology, Founding Member, Broad Institute of Harvard and MIT; Howard Hughes Medical Institute Investigator; Morris Loeb Professor of Chemistry and Chemical Biology, Harvard University

Enteroendocrine Drug Discovery for Treatment of Metabolic Diseases
Paul L. Feldman, Ph.D., Senior Vice President, GlaxoSmithKline

Conference-at-a-Glance

<table>
<thead>
<tr>
<th>Mon., Sept. 23</th>
<th>Pre-Conference Short Courses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC2: Practical Aspects of Structure-Based Drug Discovery with GPCRs</td>
<td></td>
</tr>
<tr>
<td>SC4: Allosteric Modulators of GPCRs</td>
<td></td>
</tr>
<tr>
<td>SC5: Advancing Tools and Technologies for Fragment-Based Design</td>
<td></td>
</tr>
<tr>
<td>SC7: Production and Presentation of Integral Membrane Proteins for Antibody Discovery</td>
<td></td>
</tr>
</tbody>
</table>

*Separate Registration Required for Short Courses

Recommended Short Courses*

MONDAY, SEPTEMBER 23 | 12:00 – 3:00 PM
SC2: Practical Aspects of Structure-Based Drug Discovery with GPCRs
Instructors:
Michael Hanson, Ph.D., Director, Structural Biology, Receptos
Christopher Tate, Ph.D., Professor, Laboratory of Molecular Biology, MRC, United Kingdom

MONDAY, SEPTEMBER 23 | 3:30 – 6:30 PM
SC4: Allosteric Modulators of GPCRs
Instructors:
Corey Hopkins, Ph.D., Research Assistant Professor, Pharmacology, Vanderbilt University
Debra Kendall, Ph.D., Distinguished Professor & Department Head, Pharmaceutical Sciences, University of Connecticut
Stephan Schann, Ph.D., Head, Research, Domain Therapeutics SA

SC5: Advancing Tools and Technologies for Fragment-Based Design
Instructors:
Daniel A. Erlanson, Ph.D., Co-Founder, Carmot Therapeutics, Inc.
Edward R. Zartler, Ph.D., President & CSO, Quantum Tussera Consulting

SC7: Production and Presentation of Integral Membrane Proteins for Antibody Discovery
Instructor:
David Bramhill, Ph.D., Principal, Bramhill Biological Consulting, LLC

*Separate Registration Required for Short Courses

Present a poster and save $50!
Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by August 16, 2013. Please see registration page for details.
SPONSORSHIP, EXHIBIT, AND LEAD GENERATION

CHI offers comprehensive sponsorship packages which include presentation opportunities, exhibit space and branding, as well as the use of the pre and post-show delegate lists. Customizable sponsorship packages allow you to achieve your objectives before, during, and long after the event. Signing on early will allow you to maximize your exposure to hard-to-reach decision makers!

**Agenda Presentations**
Showcase your solutions to a guaranteed, highly-targeted audience. Package includes a 15 or 30-minute podium presentation within the scientific agenda, exhibit space, on-site branding and access to cooperative marketing efforts by CHI.

**Lunchenon Presentations**
Opportunity includes a 30-minute podium presentation. Boxed lunches are delivered directly into the main session room, which guarantees audience attendance and participation. A limited number of presentations are available for sponsorship and they will sell out quickly. Sign on early to secure your talk!

Looking for additional ways to drive leads to your sales team? CHI can help through:

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- Targeted campaign promotion to unparalleled database of 800,000+ individuals in the life sciences
- Experienced marketing team promotes campaign, increasing awareness and leads

**Live Webinars:**
- Assistance in procuring speakers
- Experienced moderators
- Dedicated operations team to coordinate all efforts

**Invitation-Only VIP Dinner/Hospitality Suite**
Sponsors will select their top prospects from the conference pre-registration list for an evening of networking at the hotel or at a choice local venue. CHI will extend invitations and deliver prospects. Evening will be customized according to sponsor’s objectives (i.e. purely social, focus group, reception style or plated dinner with specific conversation focus).

**Exhibit**
Exhibitors will enjoy facilitated networking opportunities with 700+ high-level delegates, making it the perfect opportunity to speak face-to-face with prospective clients and showcase your latest product, service, or solution.

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**Whitepapers:**
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DiscoveryOnTarget.com
The exponential growth in crystallography of G protein-coupled receptors (GPCRs) in recent years has led to the structure determination of more than 23 unique GPCRs, most recently expanding coverage to non-Class A receptors. This talk will review how the flow of high-resolution data combined with molecular modeling tools redefines our understanding of structural diversity, molecular interactions, functional mechanisms of GPCRs, and enables structure-based drug discovery.

The recent explosion in the number of GPCR structures determined by X-ray crystallography has transformed our understanding of the mechanism of receptor activation. I will discuss the results of a network analysis of inactive-state structures that clearly defines conserved interactions within the receptors and the interactions that affect basal activity. Factors that affect drug efficacy at the A2A1-adrenoceptor and adenosine A2A receptor will then be compared based on high-resolution structure.

We generated Nanobodies that stabilize transient functional conformations of the human 2 adrenergic receptor. Nanobodies that faithfully mimic G protein binding were used to crystallize active agonist-bound states of this GPCR. Other nanobodies that stabilize the 2AR-Gs complex were instrumental to obtain the crystal structure of this complex, providing the first view of transmembrane signaling by a GPCR.

The growing body of GPCR structural knowledge is facilitating a new approach to cancer immunotherapy. Treg recruitment and suppressive function can provide a successful cancer immunotherapy. A humanized anti-CCR4 antibody has been developed to investigate if inhibition of the chemokine receptor CCR4. They are involved in immune system homeostasis through their ability to suppress proliferation of effector T cells. However, tumor-induced recruitment and expansion of Tregs and resulting immunosuppression represent major obstacles for successful cancer immunotherapy. A humanized anti-CCR4 antibody has been developed to investigate if inhibition of Treg recruitment and suppressive function can provide a new approach to cancer immunotherapy.

11:15 Antibodies against Difficult Targets: How to Tackle G-Protein Coupled Receptors
Stefanie Urlinger, Ph.D., Director, Research & Development, MorphoSys AG

GPCRs comprise a huge class of proteins, many of which are considered relevant targets for drug discovery. Due to their membrane embedded structure only 25-30% of the protein is accessible for antibodies, making GPCRs notoriously difficult targets. We have generated fully human antibodies against GPCRs of therapeutic interest using phage display in combination with sophisticated antibody libraries, a broad range of selection methods and various antigen variants. Different strategies for successful antibody generation will be presented.

12:15 A Novel Regulatory Role of a Humanized Antibodies against Endothelin A and B Human GPCR Subtypes
Frederic Ducancel, Ph.D., Head, Laboratory, Institute of Biology and Technology, Saclay, Atomic Energy Commission, France

Overactivation or overexpression of human EDNRB and/or EDNRA are associated with the development of various diseases, and both receptors appear highly relevant targets for therapy or diagnosis. Using electroporation-aided DNA immunization, we have raised 27 monoclonal antibodies highly specific for hEDNBR and 4 antibodies for hEDNAR. These antibodies appear as very attractive molecular tools not only for fundamental studies of the molecular structure and function of both receptors in normal and immunomaging.
12:45 LUNCHEON PRESENTATION: 
Sponsored by DiscoverRx
New Era of GPCR Drug Discovery: Multi-Pathway Screening Technologies
Elizabeth R. Quinn, Ph.D., Director, LeadHunter Discovery Services, DiscoverRx Corporation
Discovery of Arrestin-mediated signaling has revolutionized GPCR drug discovery and led to the pursuit of biased ligands that selectively target different aspects of receptor activation resulting in drugs with greater therapeutic benefit. Through case studies, attendees will gain an understanding of how Arrestin signaling relates to in vivo compound activity and how PathHunter® technology can be used to triage hits, determine compound mode of action, identify off-target liabilities and monitor neutralizing antibodies in patient samples.

LIGAND-BIASED SIGNALING

2:15 Chairperson’s Opening Remarks
Dave Unett, Ph.D., Vice President, Receptor Pharmacology, Arena Pharmaceuticals

2:20 FEATURED PRESENTATION: Allosteric Regulation of G Protein-Coupled Receptors: Implications to Functionally Selective Ligand Pharmacology
Roger K. Sunahara, Ph.D., Associate Professor, Pharmacology, University of Michigan Medical School
G protein-coupled receptors exist in an ensemble of conformational states, ranging from active and inactive forms with some states stabilized by agonists and inverse agonists. Indeed agonist binding facilitates recruitment and activation of G proteins or arrestins. Here we investigate the capacity of G proteins to allosterically enhance agonist binding through decreasing the ligand dissociation rate. Crystallographic evidence provides a structural rationale for the altered off-rate and provides insight into functionally selective, or biased ligands.

2:50 Discovery of β-Arrestin-Biased Agonists of Dopamine D2 Receptors
Kyle Butler, Ph.D., Post-Doctoral Fellow, Laboratory of Jian Jin, Division of Chemical Biology and Medicinal Chemistry, The University of North Carolina at Chapel Hill
Activation of noncanonical dopamine D2 receptor signaling through β-arrestins may be a significant contributor to the therapeutic action of antipsychotic drugs. Through comprehensive structure-functional selectivity relationship studies of the aripiprazole scaffold, we discovered the first β-arrestin-biased D2R agonists. These functionally selective ligands display potent in vivo antipsychotic activity without inducing the motoric side effects.

3:20 Panel Discussion: Applying it All with a focus on Biased Signaling
Andrew Alt, Ph.D., Senior Research Investigator II, Lead Discovery, Bristol Myers Squibb and Co.
How will emerging topics in GPCR biology (GPCR structural biology, allosterism, signaling bias, hetero-oligomerization) change the way we do drug discovery?

3:50 Refreshment Break in the Exhibit Hall with Poster Viewing
4:30 Directed Evolution of Conformationally-Selective GPCR Antibodies and Applications to Discovered Biased Ligands
Aaron Ring, MD/PhD candidate, Laboratory of K. Christopher Garcia, Department of Structural Biology, Stanford University School of Medicine
Antibodies stabilizing specific GPCR conformations have proven to be valuable research tools in understanding how receptor conformation affects signaling. Moreover, there is considerable interest in developing antibodies that can induce desired receptor states and operate as GPCR ligands. I will discuss new techniques to rapidly identify conformationally-specific GPCR binders. These techniques can be used to discover ligands of a defined efficacy, as well as ligands biased for particular signaling pathways.

5:00 GPCR-Biased Ligands as Improved Therapeutics: Promise and Progress
Jonathan Violin, Ph.D., Director, Biology, Trevena, Inc.
GPCR biased ligands selectively engage subsets of the intracellular signals entrained by full agonists, and in some cases are agonists for one set of receptor responses but antagonists for another set of receptor responses. This concept has been demonstrated in vitro and in vivo with TRV027 targeting the angiotensin II type 1 receptor, and several molecules targeting opioid receptors, including TRV130. These examples, now in clinical development, show the potential utility of biased ligands for solving on-target adverse effects.

5:30 Interactive Breakout Discussion Groups
6:30 Welcome Reception in the Exhibit Hall with Poster Viewing
7:30 Close of Day

WEDNESDAY, SEPTEMBER 25

7:30 am Registration and Morning Coffee

NEW APPROACHES FOR ALLOSTERICS, INTERNALIZATION AND OTHER PHARMACOLOGIC CHALLENGES

8:00 Chairperson’s Opening Remarks
Dario Doller, Ph.D., Director, Discovery Chemistry & DMPK, Lundbeck Research USA

8:05 Functional Evaluation of 5-HT2C Receptor Agonists for Obesity
Dave Unett, Ph.D., Vice President, Receptor Pharmacology, Arena Pharmaceuticals
In evaluating the functional selectivity of 5-HT2C agonists we systematically assessed the influence of receptor reserve and receptor-agonist association kinetics on functional readouts in a number of assay platforms. We find that some assays greatly underestimate the potencies of agonists with slow receptor-association kinetics. Furthermore, some agonists produce persistent receptor signaling that likely originates from internalized receptors.

8:35 Label-free Assays to Probe Ligand-Biased Signaling
Hong Xin, Ph.D., Principal Scientist, CREATE Core technologies, Janssen R&D

9:05 Structure of FSH and Receptor Ectodomain Complex: Relevance to the Discovery of Small Molecule Allosteric Modulators
Xuliang Jiang, Ph.D., Associate Director, Structural Biology and Computational Chemistry, EMDDerisomo
We have solved the crystal structure of FSH in complex with its receptor. The complexes exist as a trimer in crystal, an unprecedented GPCR oligomerization form. FSH receptor is a proven drug target. Yet the mechanism how FSH activates FSHR is still poorly understood, and small molecule FSHR agonists are still unavailable. My talk addresses some of...
these issues by proving the biologically relevance of the trimer using various approaches, including employment of small molecule allosteric modulators.

9:35 Report-Back from Breakout Discussion Moderators

10:05 Coffee Break in the Exhibit Hall with Poster Viewing

10:50 The “No Ligand Depletion” Assumption Is Unnecessary and Can Be Misleading

Gilles Gncadja, Ph.D., Principal Analyst, System Informatics, Amgen

Binding equilibrium concentrations in receptor-ligand interactions are routinely calculated with formulas that assume the non-depletion of ligands. This can result in discrepancies and is unnecessary, as we demonstrate for the allosteric ternary complex model. The method can be used within curve-fitting algorithms to estimate binding parameters, e.g. Kd and alpha, without concerns as to whether it is legitimate to assume that each ligand has equal total and equilibrium concentrations.

11:20 Discovery of Positive Allosteric Modulators of the Mu-Opioid Receptor

Neil Burford, Ph.D., Senior Research Investigator II, Lead Discovery & Profiling, Molecular Sciences and Candidate Optimization, Bristol-Myers Squibb Company

Here we describe the characterization of two mu opioid receptor positive allosteric modulators (PAMs) resulting from a high-throughput screen using a β-arrestin recruitment assay in cells expressing opioid receptors. These PAMs were shown to enhance both the efficacy and binding affinity of mu-opioid receptor agonists. To our knowledge these are the first mu-opioid receptor PAMs described in the literature, implicating positive allostery as a potential novel avenue for the discovery of tightly regulated pain therapeutics.

11:50 Lunch on Your Own

1:40 pm PLENARY KEYNOTE PRESENTATIONS

See Page 2 for information

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing

3:50 Close of Conference
Identification and characterization of GPCR allosteric modulators using standard functional assays remain elusive due to the ‘context-dependent phenomena’. Novel technological approaches such as combining a Fluorescence Resonance Energy Transfer (FRET)-based library filtering with a bioluminescence resonance energy transfer (BRET)-based multiparametric compound profiling can circumvent the limitations of current GPCR screening processes and simplify the discovery of biased AMs.

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2:30 EBI2 – A Moving Target – A Recently De-Orphanized GPCR
Mette Rosenkilde, Ph.D., Professor, Neuroscience and Pharmacology, University of Copenhagen

EBI2 (GPR183) was recently deorphanized as an oxysterol directed 7TM class A receptors. It is involved in B cell-migration within the lymph nodes, and is induced by Epstein-Barr virus infection. We have shown the receptor signals through Gai in leukocytes (2006, JBC) and have described small molecule inverse agonists and antagonists and their molecular mechanisms (JBC 2011, FEBS 2013) in addition to the molecular interaction of oxysterols with EBI2 (JBC, 2012). In this talk we describe animal models for the in vivo function of EBI2 during virus infection, immune suppression and enhanced EBI2 expression conditions.

3:00 TGR5 in Metabolic Diseases
Michael Orsini, Ph.D., Principal Scientist, Diabetes Drug Discovery, Bristol-Myers Squibb

TGR5 is a G protein-coupled receptor for bile acid. This talk will discuss the receptor’s role in metabolic diseases and our efforts in developing potential therapies targeting TGR5.

3:30 Ice Cream Refreshment Break in the Exhibit Hall with Poster Viewing

4:00 Lactate Receptor, GPR81/HCA1, as a Novel Target for Metabolic Disorders
Changlu Liu, Ph.D., Scientific Director, Janssen Fellow, Head of Molecular Innovation, Neuroscience, Janssen Research & Development, LLC

We identified L-lactate as the endogenous ligand for GPR81, predominantly expressed in adipocytes. The EC50 value of L-lactate for GPR81 is 4 mM, which is in the middle of the physiological L-lactate concentration range in the body (1-20 mM), allowing the receptor to best sense the change of lactate concentration under the physiological conditions. Administration of GPR81 agonists inhibits lipolysis, suggesting GPR81 is an attractive target for metabolic disorders.

4:30 Targeting GPR55 in Cancer and Diabetes
Marco Falasca, Ph.D., Professor of Molecular Pharmacology, Queen Mary University of London

Several studies, including work from our own laboratory, have revealed a role for the orphan G protein-coupled receptor 55 (GPR55) and its main agonist, lysophosphatidylinositol (LPI) in cancer and diabetes. Our work aims at validating GPR55, and GPR55-dependent signaling pathways, as a novel potential therapeutic target and LPI as a novel potential biomarker. Recent results have shown that GPR55 is expressed in the endocrine pancreas and revealed its function at stimulus-secretion coupling of insulin secretion, suggesting a role in glucose homeostasis.

5:00 Close of Conference
TUESDAY, SEPTEMBER 24

7:00 am Registration and Morning Coffee

BIOLoGY OF GPCR ANTIbODY TARGETS

8:10 Chairperson’s Opening Remarks
Christopher Koth, Ph.D., Senior Scientist, Structural Biology, Genentech

8:15 FEATURED PRESENTATION: Probing GPCR Dynamics Using Genetically-Encoded Unnatural Amino Acids
Thomas P. Sakmar, M.D., Richard M. & Isabel P. Furlaud Professor, Laboratory of Chemical Biology & Signal Transduction, The Rockefeller University
Recent advances in molecular and structural studies of GPCRs have revolutionized drug discovery. Our aim is to elucidate the principles that underlie ligand recognition in GPCRs and to understand with chemical precision how receptors change conformation in the membrane bilayer when ligands bind. This lecture will describe new interdisciplinary technologies to study receptor dynamics and allosteric mechanisms.

8:45 Conformationally Sensitive Camelid Antibodies to Stabilize GPCR-G Protein Complexes
Roger Sunahara, Ph.D., Assistant Professor of Pharmacology, University of Michigan
Elucidating the structure of membrane proteins, a notoriously challenging endeavor, has taken advantage of antibodies and fusion proteins to stabilize and facilitate crystallogenesis. The application of these technologies to the GPCR field has been instrumental in the recent stream of high resolution crystal structures. In particular, our laboratory and those of our collaborators have taken advantage of conformationally sensitive single chain camelid antibodies for these purposes.

9:15 LY2951742, an Antibody to Calcitonin Gene-Related Peptide (CGRP) for Prevention of Migraine Headaches
David S. Grayzel, M.D., CEO, Arteaus Therapeutics
LY2951742 is a humanized monoclonal antibody that potently and selectively binds to Calcitonin Gene Related Peptide (CGRP). The CGRP pathway has been shown to play a key role in neurogenic inflammation and the pathophysiology of migraine. In Phase 1 clinical testing, LY2951742 was well-tolerated and demonstrated potent, durable suppression of the CGRP pathway. The antibody is currently in Phase 2 clinical trials for migraine prevention.

9:45 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:45 Nanobodies for the Structural and Functional Characterization of GPCR Transmembrane Signaling: From Structure to Function to Drugs
Jan Steyaert, Ph.D., Head of Department, Structural Biology, Vrije University Brussels, Belgium
We generated Nanobodies that stabilize transient functional conformations of the human b2 adrenergic receptor. Nanobodies that faithfully mimic G protein binding were used to crystallize active agonist-bound states of this GPCR. Other nanobodies that stabilize the b2AR-Gs complex were instrumental to obtain the crystal structure of this complex, providing the first view of transmembrane signaling by a GPCR.

11:15 Antibodies Against Difficult Targets: How to Tackle G-Protein Coupled Receptors
Stefanie Urlinger, Ph.D., Director, Research & Development, MorphoSys AG
GPCRs comprise a huge class of proteins, many of which are considered relevant targets for drug discovery. Due to their membrane embedded structure only 25-30% of the protein is accessible for antibodies, making GPCRs notoriously difficult targets. We have generated fully human antibodies against GPCRs of therapeutic interest using phage display in combination with sophisticated antibody libraries, a broad range of selection methods and various antigen variants. Different strategies for successful antibody generation will be presented.

11:45 Monoclonal Antibodies Against Endothelin A and B Human GPCR Subtypes
Frederic Ducancel, Ph.D., Head of Laboratory, Institute of Biology and Technology, Saclay, Atomic Energy Commission, France
Overactivation or overexpression of human EDNRB and/or EDNRA are associated with the development of various diseases. Using electroporation-aided DNA immunization, we have raised 27 monoclonal antibodies highly specific for hEDNBR and 4 antibodies for hEDNAR. These antibodies appear as very attractive molecular tools not only for fundamental studies of the molecular structure and function of both receptors in normal and cancer cells, but also for immunotherapy and immunoimaging.

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els to assess its potential as a prophylactic agent.
12:15 A Novel Regulatory Role of a Humanized Anti-CCR4 Antibody in Cancer Immunotherapy
DeKuan Chang, Ph.D., Research Fellow, Cancer Immunology & AIDS, Dana-Farber Cancer Institute
Tregs express high levels of the chemokine receptor CCR4. They are involved in immune system homeostasis via their ability to suppress proliferation of effector T cells. But, tumor-induced recruitment and expansion of Tregs and resulting immunosuppression represent major obstacles for successful cancer immunotherapy. A humanized anti-CCR4 antibody has been developed to investigate if inhibition of Treg recruitment and suppressive function can provide a new approach to cancer immunotherapy.

12:45 LUNCHEON PRESENTATION: Sponsored by
New Era of GPCR Drug Discovery: Multi-Pathway Screening Technologies
Elizabeth R. Quinn, Ph.D., Director, LeadHunter Discovery Services, DiscoverRx Corporation
Discovery of Arrestin-mediated signaling has revolutionized GPCR drug discovery and led to the pursuit of biased ligands that selectively target different aspects of receptor activation resulting in drugs with greater therapeutic benefit. Through case studies, attendees will gain an understanding of how Arrestin signaling relates to in vivo compound activity and how PathHunter® technology can be used to triage hits, determine compound mode of action, identify off-target liabilities and monitor neutralizing antibodies in patient samples.

TARGETING MEMBRANE PROTEINS WITH ANTIBODY FRAGMENTS AND NOVEL PROTEIN SCAFFOLDS

2:15 Chairperson’s Opening Remarks
Kristen M. Picha, Ph.D., Director, Biology, Centyrex, Johnson & Johnson Ventures, Janssen Pharmaceuticals

2:20 Antibody Fragments and Alternative Scaffolds from In Vivo and In Vitro Sources Against Membrane Protein Targets
Hilmar Ebersbach, Ph.D., Lab Head Antibody Generation, NIBR Biologics Center, Novartis Institutes for BioMedical Research, Switzerland
There is a high interest to tackle complex multi-domain membrane proteins as antigen in different indications. The identification of functional binding molecules, regardless whether agonistic or antagonistic, requires expression and purification or specific presentation of targets in a functional state. Often multi-parallel approaches, e.g. classical or DNA immunization or in vitro panning like phage or yeast display are applied to increase chances of success to provide potent drug candidates.

2:50 Rapid Identification and Characterization of Fabs for Structural Analysis of Membrane Proteins
Charles S. Craik, Ph.D., Professor of Pharmaceutical Chemistry, Pharmacology, Biochemistry and Biophysics, University of California, San Francisco
Structural studies with antibody fragments have emerged as a promising solution to obtain subnanometer resolution three-dimensional structures of small proteins (<100 kDa) using single particle cryoEM. Antibody binding to the target membrane protein can yield a homogenous population of the protein. Antibody interactions can also form stable and rigid complexes and the Fab provides a defined feature for accurate image alignment. Rapid identification of antibody fragments that can recognize native protein structure makes phage display a valuable method for these studies of membrane proteins. Methods that speed the reliable characterization of phage display selected antibody fragments are needed to make the technology more generally applicable and will be presented.

3:20 Discovery of MAbs against Difficult GPCRs, Ion Channels, and Transporters
Benjamin Doranz, Ph.D., President and CSO, Integral Molecular, Inc.
To enable the isolation, characterization, and engineering of MAbs against challenging membrane protein targets, Integral Molecular has developed the MPS Discovery Engine platform, encompassing Lipoparticles for concentrating native membrane proteins and Shotgun Mutagenesis for membrane protein engineering and epitope mapping. We have generated inhibitory MAbs against the ion channel P2X3 for treating neuropathic and inflammatory pain, and will also be discussing additional MAbs we have isolated against GPCRs, ion channels, and transporters.

3:50 Refreshment Break in the Exhibit Hall with Poster Viewing

4:30 A Bi-Specific Centyrin Targeting EGFR and c-Met Inhibits Cellular Signaling through Avidity
Kristen M. Picha, Ph.D., Director, Biology, Centyrex, Johnson & Johnson Ventures, Janssen Pharmaceuticals
Centyrins bind their target with high affinity and specificity and can be linked together so one molecule inhibits multiple targets. Anti-EGFR and c-Met Centyrins were selected and bi-specific Centyrins were generated. Clinical data have demonstrated additivity when inhibiting these targets. Our data demonstrates that in addition to inhibiting two targets simultaneously, a single bispecific molecule allows for significant avidity at the cellular level.

5:00 Nanobodies as Highly Specific Antagonists and Agonists of the P2X7 Ion Channel
Friedrich Koch-Nolte, Ph.D., Professor, Immunology, Molecular Biology, University Medical Center Hamburg, Germany
Nanobodies display a strong propensity to bind hidden, functional epitopes that are not accessible to conventional antibodies. P2X7, an ion channel gated by ATP released from injured cells, plays a key role in inflammation. We have generated Nanobodies from immunized llamas that effectively block or potentiate P2X7 on monocytes and regulatory T cells in vitro and in vivo. The P2X7-blocking Nanobodies show therapeutic benefit in an experimentally induced inflammatory disease.
5:30 Interactive Breakout Discussion Groups
6:30 Welcome Reception in the Exhibit Hall with Poster Viewing
7:30 Close of Day

WEDNESDAY, SEPTEMBER 25

7:30 am Registration and Morning Coffee
ION CHANNELS AND OTHER TARGETS

8:00 Chairperson’s Opening Remarks
Matthew Gardener, Ph.D., Senior Scientist, ADPE, MedImmune, United Kingdom

8:05 FEATURED PRESENTATION: Protease-Resistant IgG Platform Targeting Cell Surface Proteins for Anti-Tumor and Anti-Bacterial Therapy
William R. Strohl, Ph.D., Vice President, Biologics Research, Janssen Research & Development, LLC
Human IgG1 antibodies are cleaved by bacterial proteases as well as matrix metalloproteases produced in the tumor microenvironment. Single-cleaved IgG1s are devoid of Fc effector function but still retain antigen binding and FcRn recycling like an intact IgG1. While human IgG2 antibodies are more protease-resistant, they do not possess optimal effector function for killing target cells. We have engineered protease-resistant antibodies with strong Fc effector activity and killing capacity.

8:35 Antibody Therapeutics Targeting Ion Channels: Are We There Yet?
Han Sun, Researcher, The Solomon H. Snyder Department of Neuroscience, Johns Hopkins Ion Channel Center, High Throughput Biology Center, School of Medicine, Johns Hopkins University
The combination of technological advances, genomic sequences and market success is driving rapid development of antibody-based therapeutics. Cell surface receptors and ion channel transporter proteins are well known drug targets, but the latter has seen less success. The availability of crystal structures, better understanding of gating biophysics and validation of physiological roles now form an excellent foundation to pursue antibody-based therapeutics targeting ion channels.

9:05 Ion Channels as Targets for Monoclonal Antibodies
Matthew Gardener, Ph.D., Senior Scientist, ADPE, MedImmune, United Kingdom
Ion channels represent attractive drug targets for a wide variety of disease states. Modulatory monoclonal antibodies would allow specific targeting of ion channel subtypes, whilst avoiding structurally similar family members and thus avoiding potential off-target effects. The key requirements for the generation of modulating antibodies will be discussed, with the primary focus on early stage lead generation and optimization.

9:35 Novel Strategies for Identification and Characterization of Human Antibodies against Nav1.7 Ion Channel Target
Hans de Haard, Ph.D., Professor, University of Utrecht, CSO, arGEN-X BV
hNav1.7 is notoriously complex as a monoclonal antibody target, with potent antagonists selective for the desired isoform proving elusive. We have used outbred llama immunization and phage display to generate large, highly diverse panels of hNav1.7 specific antibodies. hNav1.7 loop-llama Fc fusion proteins as immunogens generated multiple loop-specific antibodies for functional analysis. Moreover, DNA-based primary immunization boosted by hNav1.7-expressing cells yielded antibodies recognizing hNav1.7 in the context of the cell membrane.

10:05 Coffee Break in the Exhibit Hall with Poster Viewing

10:50 XMetS, an Allosteric Modulator Antibody to the Insulin Receptor (INSR) that Enhances Insulin Binding to INSR and Restores Glycemic Control in Mouse Models of Diabetes
Hassan Issafras, Ph.D., Senior Scientist, Molecular Interactions & Biophysics, Preclinical Research, XOMA Corp.
The ModulXTM platform was used to develop XMetS, a human antibody that allosterically sensitizes insulin receptor activation. XMetS induced a 20-fold increase in the binding affinity of insulin to the INSR, potentiating insulin-mediated receptor activation and signaling. In diabetic mice, XMetS enhanced insulin sensitivity and normalized fasting glucose levels without causing hypoglycemia. INSR antibodies are potentially novel therapeutics for insulin resistance states such as type-2 diabetes.

11:20 Engineering Novel Therapeutics Targeting the Ion Channel Kv1.3
Ronald V. Swanson, Ph.D., Senior Director, Biologics Research, Janssen Pharmaceuticals
Kv1.3 is a homotetrameric voltage-gated K+ channel expressed on T cells. To explore the potential of inhibition of Kv1.3 activity for the treatment of T cell mediated immune disorders, we have applied our in-house gene synthesis capabilities and robust semi-automated mammalian expression platform to peptides active against Kv1.3 to engineer potent, selective long-acting tools.

11:50 Lunch on Your Own

3:10-3:50 Refreshment Break in the Exhibit Hall with Poster Viewing
3:50 Close of Conference
11:50 am Registration
1:30 pm Chairperson’s Opening Remarks
1:40 PLENARY KEYNOTE PRESENTATIONS
See Page 2 for information
3:10-3:50 Refreshment Break in the Exhibit Hall with Poster Viewing

STRUCTURAL BIOLOGY AND CHARACTERIZATION OF ANTIBODY-MEMBRANE PROTEIN INTERACTIONS

3:50 Chairperson’s Remarks
Hassan Issafras, Ph.D., Senior Scientist, Molecular Interactions & Biophysics, Preclinical Research, XOMA Corp.

4:00 Synthetic Antibodies to Probe the Structural and Conformational Diversity of GPCRs and Their Signaling Complexes
Arun Shukla, Ph.D., Assistant Professor, Medicine, Duke University Medical Center
Recent discovery of biased GPCR signaling has changed the classical two-state model of receptor activation and necessitates structural investigation of distinct conformational states of GPCRs and their signaling complexes. Synthetic antibody fragments to stabilize and capture distinct functional conformations of selected GPCRs and GPCR signaling complexes have been identified and characterized. Crystal structure of activated ?-arrestin-1 bound to the carboxy-terminal of the human vasopressin receptor in complex with a conformationally selective synthetic antibody fragment will be presented.

4:30 Sponsored Presentations (Opportunities Available)

5:00 Antibody Inhibition of Bacterial Manganese Transport
Christopher Koth, Ph.D., Senior Scientist, Structural Biology, Genentech
The bacterial MntABC membrane transporter aids in the acquisition of the essential co-factor manganese. Mechanisms that antagonize this pathway have implications for antibiotic development. We have developed an inhibitory antibody that targets the Staphylococcus aureus MntABC pathway. A structural and mechanistic analysis of this antibody will be presented.

5:30 On-Cell, Solution Binding Affinity Measurements for Membrane Targets
Palaniswami Rathanaswami, Ph.D., Senior Scientist, Amgen, Canada
The need for generation of therapeutic antibodies for targets expressed on the membrane, either as single span or multi-span, is growing enormously in oncology, inflammation, neurology and other therapeutic areas. While antibody generation itself is a challenge for multi-span membrane targets, screening and characterization of the antibodies for their specific binding is also not trivial. For affinity measurements of membrane proteins, using a soluble counterpart or immobilizing the purified membrane protein to a solid surface may not fully reproduce the solution binding characterization of the target as it is expressed on cell. We have developed a simple method that allows affinity measurements of antibodies to integral membrane proteins in their native state. This method uses the Kinetic Exclusion Assay (KinExA) technology that eliminated the requirement for soluble antigen or modifications of the antibody with radio- or fluorescent-labeling. The successes and limitations of this method will be discussed.

6:00 Therapeutic Targeting of Homeostatic Chemokine Receptors with Antibodies
Eldar Kim, Ph.D., Chief Scientific Officer, MSM Protein Technologies, Inc.
Homeostatic chemokine receptors play a critical role in developing and maintaining the state of the adaptive immune system in normal and pathological conditions. We developed a panel of therapeutic quality antibodies against several chemokine receptors. Characteristics of the antibody interactions with the receptors imply that chemokine receptors have a substantial conformational plasticity. Data on the physiological importance and therapeutic implications of the phenomenon will be presented.

6:30 Close of Day
9:10 Evolution of Stable and High Expressing GPCRs for Structure Determination and as Screening Targets
Pascal Egloff, Ph.D., Scientist, Plückthun Laboratories, Biochemistry Institute, University of Zürich, Switzerland

Drug screening and antibody selection on GPCRs in vitro and structure determination attempts are hampered by the inherent instability of these targets when solubilized in detergent micelles. We developed directed evolution technologies that allow generation of GPCR variants with up to 60-fold improved functional expression levels in E. coli and superior stability in detergent solution. We determined x-ray structures of evolved neotensin receptor 1 variants using signaling-competent constructs.

9:40 Application of Tetrahymena Thermophila as an Alternative Platform for Difficult to Express Immunogens
Gregory Carven, Ph.D., Associate Research Fellow, Head of Hybridoma Research, Pfizer

Traditional approaches for generating antibodies against integral membrane proteins have had limited success. The alternative expression host Tetrahymena thermophila can enable high-density display of recombintant human ion channels on surface membranes of Tetrahymena for immunogen preparation and screening. A case study is presented.

10:10 Coffee Break in the Exhibit Hall with Poster Viewing

10:55 Immunization Strategy for Multiplex Target Validation and Therapeutic Antibody Generation
Partha Chowdhury, Ph.D., Principal Scientist, MedImmune

11:25 Casting a Wide Net: Strategies to Meet the Challenges of Multi-Transmembrane Targets
Meredith Hazen, Senior Research Associate, Genentech

I will describe an immunization and screening strategy that successfully resulted in the identification of monoclonal antibodies that bind specifically to extracellular epitopes of a 12 transmembrane protein, multi-drug resistant protein 4 (MRP4), developed following hydrodynamic tail vein (HTV) immunization and were characterized by flow cytometry. Use of the immune modulators positively enhanced the immune response against MRP4. We also describe a comparison of plasmids used for immunizations, containing different promoters.

11:55 Expression and Purification of Ligand Gated Ion Channels and Applications in Drug Discovery
Arjan Snijder, Ph.D., Associate Principal Scientist, Discovery Sciences, AstraZeneca, Sweden

We describe the expression and purification of ligand gated ion channels to help facilitate drug discovery. We have used fluorescent size exclusion chromatography (FSEC) to monitor expression level, stability and monodispersity of a range of constructs of the target ion channel. We used a novel, peptide-based fluorescent multivalent nitrilotriacetic acid probe for the detection of the his-tagged target protein. We successfully purified mg quantities of human ion channels. Application of the novel FSEC approach can improve the efficiency of the expression and purification of membrane proteins.

12:25 pm Chicken Monoclonal Antibodies to Native Conformation GPCRs and Ion Channels
Bill Harriman, Ph.D., MBA, Chief Science Officer, Crystal Bioscience

Chickens are known to mount a vigorous immune response to many conserved mammalian proteins. Crystal Bioscience leverages the chicken immune repertoire using its proprietary GEM screening technology to recover exceptional antibodies to elusive targets.

1:10 Native & Full Length Membrane Protein Isolation for Antibody Development and Drug Anass Jawhari, Ph.D., CSO, Membrane Protein Alliance

The membrane protein alliance offers a patented technological platform allowing to express, solubilize, purify and stabilize in solution and/or liposomes (cell free) full length GPCRs, Ion Channels, Transporters, Receptors and Viral Proteins, while keeping their structural and functional integrity (without refolding and mutagenesis) for better antibody production.

TECHNOLOGIES TO ENABLE ANTIBODY MEMBRANE TARGET DISCOVERY

2:25 Chairperson’s Opening Remarks
Susan Lacy, Ph.D., Associate Director, AbbVie Bioresearch Center

2:30 User Perspective on Commercial Technologies for Antibody Generation to Multi-Spanning Membrane Proteins
Susan Lacy, Ph.D., Associate Director, AbbVie Bioresearch Center

Generation of antibodies to multi-spanning membrane proteins often requires technologies and strategies different from those used to generate antibodies to more conventional targets. Platform technologies and screening assays may need to be re-evaluated and/or re-established to allow successful generation of antibodies to targets like ion channels and GPCRs. The available commercial technologies that are uniquely suited to support antibody isolation to complex membrane proteins will be reviewed.

3:00 Biacore Assay Development for GPCR Antibody Targets
Rick Chu, Ph.D., Principal Investigator, Genzyme

Recent development utilizing stabilized forms of GPCRs has enabled measurement of receptor binding constants of small-molecule antagonists. In an effort to develop reliable Biacore assays for characterizing mAbs targeting GPCRs, we have successfully expressed and purified native forms of GPCRs. A unique coupling method was employed for preparing stable Biacore chip surfaces. Biacore assays have been successfully applied to multiple anti-GPCR mAb projects.

3:30 Ice Cream Refreshment Break in the Exhibit Hall with Poster Viewing

4:00 Generating Therapeutic Antibodies against Complex Membrane Targets: Case Studies Using the XenoMouse Discovery Platform
Chadwick T. King, Ph.D., Principal Scientist, Amgen, Canada
I will review immunogen/immunization and screening strategies we have used to raise therapeutic antibodies against GPCR and/or transporters and/or ion channels. Specific examples will be described closer to the presentation time after legal review. The focus will be on the generation and characterization of lead antibodies and not the preclinical or clinical development of candidates.

4:30 Using Stabilized Receptors to Generate Therapeutic Antibodies to GPCR Targets
Cath Hutchings, Ph.D., Antibody Project Manager, Heptares Therapeutics Ltd., United Kingdom

The opportunities for targeting GPCRs with antibodies will be outlined along with the challenges encountered. Here we present a novel approach using stabilized receptors, where GPCRs have been engineered to include a small number of point mutations that greatly increases the stability of the receptors. Data will be presented that exemplify approaches to demonstrate the potential of this emerging technology to generate therapeutic antibodies.

5:00 Isolation of High-Content Single-Domain Antibodies from a Synthetic Library
Ario de Marco, Ph.D., Director, Tab-IP Platform, Institut Curie, France

A large synthetic nanobody library allows for the rapid identification of antibodies that recognize the native conformation of membrane-bound antigens in their natural lipid environment. The data demonstrate the advantage of using pre-immune libraries for isolating antibodies with specific features, such as binders interfering with a biological activity, recognizing epitopes exclusively expressed in a cell sub-population, or cross-reacting among different species.

5:30 Ligand and Antibody Binding Studies on Immobilized Cannabinoid Receptor Type II (CB2)
Silvia Locatelli-Hoops, Ph.D., Scientist, National Institute on Alcohol Abuse & Alcoholism, Laboratory of Membrane Biochemistry and Biophysics, National Institutes of Health

Human cannabinoid receptor type II (CB2), a G protein-coupled receptor (GPCR), is involved in regulating inflammation. We developed procedures for purification and immobilization of functional CB2 for structural and functional studies by SPR. Specific capture of receptor on a resin and biosensor surface using C-terminal Rhod- tag was developed allowing characterization of ligand binding and interaction with a monoclonal antibody raised against CB2.

6:00 Close of Conference
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**Monday, September 23**

- SC1: New Classes of Kinase Inhibitors: Covalent Modifiers
- SC2: Practical Aspects of Structure-Based Drug Discovery with GPCRs
- SC3: Biochemical and Structure-Based Approaches to Epigenetic Drug Discovery
- SC4: Allosteric Modulators of GPCRs
- SC5: Advancing Tools and Technologies for Fragment-Based Design
- SC6: Setting Up Effective RNAi Screens: Getting From Design to Data
- SC7: Production/Presentation of Integral Membrane Proteins for Antibody Discovery
- SC8: Characterization and Quantification of Histone Modifications

**Wednesday, September 25**

- SC9: Setting Up Effective Functional Screens Using 3D Cell Cultures
- SC10: Tools for Epigenetic Biomarker Discovery

If you are unable to attend but would like to purchase the Discovery On Target CD for $750 (plus shipping), please visit DiscoveryOnTarget.com. Massachusetts delivery will include sales tax.

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**September 24 - 25**

- Track 1: Targeting Epigenetic Readers
- Track 2: Targeting Histone Methyltransferases
- Track 3: GPCR-Based Drug Discovery
- Track 4: Functional Genomics Screening Strategies - Part 1
- Track 5: Novel Strategies for Kinase Inhibitors
- Track 6: Antibodies Against Membrane Protein Targets - Part 1

**September 25 - 26**

- Track 7: Next-Generation Histone Deacetylase Inhibitors
- Track 8: Targeting Histone Demethylases
- Track 9: GPCR-Targeted Therapeutics
- Track 10: Functional Genomics Screening Strategies - Part 2
- Track 11: Cardio-Metabolic Drug Targets
- Track 12: Antibodies Against Membrane Protein Targets - Part 2

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