

THERAPEUTIC AREAS AND RESEARCH TECHNOLOGIES

Areas of Interest



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Dear Colleagues,

I am delighted to invite you to discover more about Merck and our partnership interests. We are actively seeking collaborations that will accelerate the medicine and vaccine discovery process, improve research productivity, and increase the probability of our shared success. Whether you are working for a biotechnology company, an academic institution, or a financial organization, we are constantly and proactively seeking new external partnerships.

The exciting biomedical research you're conducting and the discoveries you've made are important to us. In fact, we've formed an External Basic Research group — composed of a team of our senior scientists — whose sole focus is on expanding Merck's pipeline through partnerships. Our goal is that within the next 5 years, 25 percent of our early clinical pipeline will be generated through our collaborations with external partners.

Inside this book you will find a complete list of our 6 therapeutic areas of interest, including new research technologies and biologics. We welcome:

- Novel patented compounds in development
- Targets with proof of concept
- Molecules with a defined mechanism of action or testable hypothesis
- Technologies with patent protection that provide a competitive advantage

We are particularly interested in compounds that have a large market potential for unmet medical needs. Late-stage clinical compounds with proven therapeutic value (phase IIb or beyond) are of interest in any therapeutic area.

We encourage you to use this resource to gauge our level of interest in your specific discovery. To begin a discussion about partnering with Merck, contact our scientific licensing expert in your region. Contact information for our licensing experts can be found in the back of this book. Or, if you prefer, please visit our Web site at **www.merck.com**.

I'm confident that, together, we can combine our strengths and translate cutting-edge science into breakthrough medicines.

Sincerely,



Mervyn Turner, PhD

Chief Strategy Officer, Merck & Co., Inc., and Senior Vice President,
Worldwide Licensing and External Research, Merck Research Laboratories

Therapeutic Areas and Research Technologies

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- We have aligned our areas of interest with our 6 franchises... plus new technologies and biologics.
- Additionally, Merck will continue to pursue external licensing opportunities in other disease areas where clinical proof of concept exists.
- Merck will also pursue niche acquisitions and partnerships in diagnostics and devices where it complements our pipeline, and not as a stand-alone business.



EMBRACING PARTNERSHIPS



Atherosclerosis and Cardiovascular Diseases

LIPIDS / METABOLIC SYNDROME

Areas of Interest:

- Novel LDL- and triglyceride-lowering (apoB-lowering) therapies
 - eg, cholesterol absorption inhibitors and agents that target PCSK9
 - Agents with additional effect on glucose, body weight, and / or HDL
- HDL-raising therapies
 - Acute HDL-mimetic (or apoA-I mimetics) therapy for high-risk patients
 - Oral compounds, with known mechanism of action, that increase HDL-C or apoA-I levels

Technology / Methods:

- Cell-based screening assays for new target identification in hepatocytes, adipocytes and enterocytes
- Methods, biomarkers, or platforms to assess antiatherogenic properties of HDL or other lipoproteins
- Acute methods to assess cholesterol transport in humans (especially reverse cholesterol transport), including imaging and kinetic models
- Acute methods to assess gut lipoprotein production in animals and / or humans
- Platform technologies for identifying novel lipid targets
- GWAS and other genomic datasets from cohorts with well-phenotyped lipid and metabolic end points
- Biomarkers of patient subtypes

Not Interested in:

- Non-selective ACAT inhibitors
- Triglyceride-lowering therapies with no other benefit
- Fibrates or other PPAR-alpha agonists
- Early-stage PPAR-delta agonists
- Fish oil
- Nutraceuticals
- In vitro reverse cholesterol transport assays

VASCULAR WALL

Areas of Interest:

- Agents for reduction of vascular inflammation with strong mechanistic validation and clinical proof of concept
 - An agent that favorably affects vascular wall elements
 - Acute therapy to lower vascular inflammation in high-risk patients (biologic or small molecule)
- Anti-inflammatory agents with benefits on vascular as well as adipocyte and / or hepatic inflammation

Technology / Methods:

- Platform technologies for identifying novel targets for atherosclerosis
- Animal models of 2 or more components of metabolic syndrome, atherosclerosis, or plaque vulnerability
- Alliances / consortia around vulnerable / high-risk plaque
- GWAS and other genomic datasets from cohorts with coronary artery disease and lipid / metabolic end points
- Multiplex and / or genetic markers of CV risk and / or patient stratification

Not Interested in:

- Pre-proof of concept
 - Acute treatments for MI
 - Post-MI therapeutics for myocardial preservation or perfusion-reperfusion injury
- Treatment of restenosis
- Nutraceuticals

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

HYPERTENSION / CARDIOVASCULAR

Areas of Interest:

- Antihypertensive agents, with at least preclinical proof of concept for improved lowering of pulse pressure (or SBP / DBP) as compared to current therapies
- Diuretics for treating hypertension with improved efficacy and / or safety / tolerability as compared to thiazides
- Long-acting vasorelaxants with improved efficacy and / or safety / tolerability as compared to amlodipine
- Agents that inhibit aldosterone synthesis and / or action
- Novel RAAS pathway modulators
- Agents with more than one antihypertensive MOA
- Agents that lower BP and have pleiotropic benefits on end-organ protection (especially cardiac and renal)
- Agents with additional benefits on other components of metabolic syndrome and other cardiovascular risk factors
- Heart failure agents
 - Agents that demonstrate end-organ protection, especially cardiac protection or efficacy in acute HF
 - CHF agents that can be registered on their anti-hypertensive effectiveness or on length of hospitalization for acute HF
 - Adenosine A₁ receptor antagonists

Technology / Methods:

- Cell-based screening assays for new target identification (vascular SMC, endothelial cells, renal cells, liver adipose)
- Technologies for measuring vascular dynamics (eg, flow, shear stress, vascular compliance) and intravascular pressure beyond tonometry
- Platform technologies for identifying novel targets for hypertension
- Platform technologies for matching the right patient to the right antihypertensive treatment regimen
- Animal models of hypertension
- GWAS and other genomic data from cohorts with blood pressure, metabolic and / or hypertensive end points
- Markers that link HTN to other metabolic syndrome phenotypes and / or atherosclerosis
- Markers for renal sequelae of HTN, including renal perfusion
- Markers for metabolic effects of diuretics

Late-Stage (Agents with clinical proof of concept ready for phase IIb / III):

- Late-stage, best-in-market, patent-protected combinations of 2 drugs or 3 drugs
- An ARB with clear and promotable advantage over the existing ones
- Antithrombotic agents
- Antiarrhythmic agents for atrial fibrillation

Not Interested in:

- Existing classes: ACE inhibitors, ARBs, CCBs, beta-blockers, adrenergic agents, renin inhibitors
- Beta-blocker combinations; ACE-inhibitor combinations
- Nutraceuticals
- Early-stage endothelin antagonists
- Chronic heart failure agents
- Blood substitutes
- Myocardial imaging platforms
- Drug-eluting stents
- Agents that target pulmonary artery hypertension

EMBRACING PARTNERSHIPS



BIOLOGICS

Areas of Interest:

- Follow-on-biologics with high quality and high POS, including biosimilars and biobetters
- Novel biologics that fit franchise strategies

Technologies of Interest:

- Fc engineering to enhance / improve effector functions and half-life
- Targeted delivery technologies that:
 - Address / overcome the blood brain barrier
 - Glycan-mediated targeting
 - Address and provide for multi-specificity, including bi-specifics
- Non-antibody scaffolds with preliminary in vivo data
- Technologies that enhance expression, production, formulation, stability, and bioavailability (via SQ admin) of proteins
- Platforms for the identification, generation, and modification of monoclonal antibodies (MAbs, FAbs, scFVs) and engineered proteins displaying pharmaceutical properties

Not Interested in:

- Transgenic animal-based or plant-based production systems for therapeutics
- Inhaled delivery of biologics

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

EMBRACING PARTNERSHIPS



Bone, Respiratory, Immunology, and Endocrine

ANEMIA

Areas of Interest:

- New pathways involved in anemia of chronic disease
 - Human genetic studies
 - Preclinical knock-in or knockdown animals that mimic anemia
- New pathways that may be EPO-sparing
- Novel clinical biomarkers associated with:
 - Anemia of chronic disease
 - Defects in iron absorption and metabolism
 - Heparin (exists in different cleavage forms), ferroportin, others
 - Anemia of aging
- New targets
 - Small molecules, biologics, or RNAi-mediated knockdown that increase hemoglobin / hematocrit in at least one animal model of:
 - Anemia of chronic disease (also called anemia of inflammation)
 - Acute anemia
 - Chemotherapy-induced anemia
 - Normal animals
 - Mechanism should be independent of treatment for inflammation
- Diagnostics
 - Noninvasive devices for monitoring Hb
 - Must have good test-retest reliability
 - Must be accurate to ≤ 0.5 g / dL Hb in the 7 to 14 g / dL range
 - Must be usable by patients in the home setting
 - Improved methods for hepcidin detection in biological fluids

Not Interested in:

- Erythropoietin

ARTHRITIS AND IMMUNE-BASED DISEASES

Areas of Interest:

- Disease-modifying antirheumatic drugs or mechanisms with clinical proof of concept
 - Biologics superior to TNF sequestrants
 - Novel oral DMARDs with equivalent or superior efficacy to TNF sequestrants
 - Selective glucocorticoid modulators
 - Syk or JAK inhibitors
 - Th17 pathway modulators
- Disease-modifying osteoarthritis drugs with clinical proof of concept
- Cartilage / joint imaging technologies
- Immunomodulators for psoriasis or IBD in phase IIb or later

Not Interested in:

- Broadly immunosuppressant mechanisms
- TNF sequestrants
- Calcineurin inhibitors

ASTHMA / COPD

Areas of Interest:

- Compounds / biologics for asthma
 - Anti-inflammatory agent with novel mechanism
 - Anti-inflammatory agent additive or differentiated from a glucocorticoid
 - Selective glucocorticoid receptor modulators
 - Novel and / or differentiated bronchodilator mechanisms
 - Novel targets with known mechanism of action
- Compounds / biologics for COPD with clinical proof of concept
- Technologies
 - Biomarkers
 - Predictive animal models of asthma pathophysiology
 - Translational medicine platforms

Not Interested in:

- Acute lung injury
- Sinusitis
- Antioxidants (ie, direct scavengers)
- Adenosine antagonists (A_1 , A_2 , and A_3)
- CCR3 and CCR4 antagonists
- Antihistamine antagonists (H_1 , H_2)
- IL5 antagonists
- Leukotriene antagonists
- PDE inhibitors
- VLA4 antagonists

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

BONE

Areas of Interest:

- Osteoanabolic agents
 - Novel mechanisms with known molecular target
- Biomarkers
 - Surrogate biomarkers of bone strength and / or fracture risk
 - More sensitive and faster biomarkers of bone anabolism
 - Selective markers for cortical and trabecular bone anabolism
 - Markers for specific bone loss / fracture risk in:
 - Postmenopausal and male osteoporosis
 - Glucocorticoid osteoporosis
 - Cancer-related bone loss
- Novel bone imaging technologies and measures of bone quality
- Osteoporosis diagnostics
 - Self-assessment tools
 - Inexpensive BMD / BMx and fracture risk measures

Not Interested in:

- Growth hormone or derivatives by any route
- ER alpha agents
- Classic “antiresorptive agents,” including bisphosphonates, with improved formulations that allow less-frequent dosing or better tolerability
- Cat K inhibitors

SARCOPENIA

Areas of Interest:

- Mechanisms that preserve / restore fibers (both biologics and small molecule)
 - Myoanabolic agents (anti-myostatin)
 - Satellite cell maintenance / proliferation
 - Anti-catabolic agents
- Mechanisms that improve fiber function (both biologics and small molecule)
 - Neuromuscular junction / alpha motor unit maintenance
 - Fiber recruitment
 - Fiber type switching
 - Fiber metabolism
 - Sarcomere dysfunction
- Biomarkers and diagnostics
 - Biochemical markers of muscle functional state (remodeling, metabolism)
 - Imaging markers of muscle function
 - Physical tests

Not Interested in:

- Growth hormone (GH), growth hormone- releasing hormone (GHRH), or derivatives by any route
- Growth hormone secretagogues

UROLOGY

Areas of Interest:

- Novel therapies for OAB (phase I or later)
- Novel therapies for stress urinary incontinence (phase I or later)
- Novel therapies for BPH (phase I or later)
- Biomarkers
 - Surrogate biomarkers of bladder dysfunction
 - Imaging approaches for indices of bladder function, including control of bladder function
- Diagnostics to improve specificity of diagnosing OAB from stress incontinence
- Diagnostics to predict response or non-response to therapy, including anticholinergics or other mechanisms of action

Not Interested in:

- Sexual dysfunction (male or female)
- Hormonal therapies for BPH

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

EMBRACING PARTNERSHIPS



Diabetes and Obesity

DIABETES

Areas of Interest:

- Oral therapies
 - “Best-in-class” compounds
 - Novel targets (need to meet internal preclinical and / or clinical validation / proof-of-concept criteria)
 - Additive / synergistic in combination with existing therapies
 - Non-PPAR insulin sensitizers
 - Beta-cell protection or regeneration if also affects GDIS
 - Glucose-dependent insulin secretagogues
 - Treatments for glucose and comorbidities (eg, dyslipidemia, hypertension)
 - Novel mechanisms for insulin resistance
- Non-oral therapies
 - Novel or best-in-class protein / peptide therapeutics; consider strategic alliance
 - Novel insulins with unique PK or relative tissue effects (liver / muscle)
- Transforming or disruptive technologies
 - Imaging, oral delivery of peptides, RNAi
- Microvascular complication treatments with phase IIa data
 - Agents that halt / reverse complications in preferably >1 target (diabetic nephropathy, neuropathy, retinopathy)
- Pharmacogenetics /-genomics, proteomics, or other for prediction of diabetes, drug response, and sub-phenotyping disease
- Platform technologies for the identification and validation of novel targets

Not Interested in:

- Nutraceuticals
- Glycogen phosphorylase inhibitors
- Non-glucose-dependent insulin secretagogues
- Aldose reductase inhibitors
- Cell-based insulin replacement for type 1 diabetes
- Inhaled insulin (short acting)
- Compounds with unknown molecular target unless clinical proof of concept exists

OBESITY

Areas of Interest:

- “Best-in-class” compounds
- Novel mechanisms for weight loss or both weight loss and prevention of weight gain
 - Meet registration criteria for obesity indication with better safety and tolerability vs current agents
 - Any effective mechanism, eg, those acting centrally or peripherally on appetite, satiety, or metabolic rate, and nutrient absorption inhibitors
 - Peptide, protein, or oral small molecule
 - Independent effects on comorbidities desirable
- Mechanisms that are additive or synergistic as combination therapy
- Mechanisms for weight loss / prevention of weight regain with positive effects on cardiometabolic risk factors (blood pressure, glucose, lipids)
- Early-stage opportunities with robust animal mechanism-based proof of concept and preclinical safety data
- Platform technologies for the identification and validation of novel targets to complement existing efforts
- Peptide delivery platforms (particularly oral platforms)
- Pharmacogenetics /-genomics, proteomics, or other for prediction of diabetes, drug response, and sub-phenotyping obesity
- Clinical methods for early prediction of long-term weight loss

Not Interested in:

- Nutraceuticals, botanicals
- Compounds with unknown molecular target unless clinical proof of concept exists

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

EMBRACING PARTNERSHIPS



Infectious Diseases and Vaccines

ANTIBACTERIALS

Areas of Interest:

Preclinical:

- Compounds with compelling preclinical documentation to treat bacterial disease, including efficacy in validated animal models of infection and preliminary toxicology data

Phase I or later:

- Gram-negative or gram-positive agents (narrow and broad spectrum) that cover problematic pathogens with either intrinsic or acquired resistance to existing agents, particularly MRSA, *Pseudomonas*, and *Acinetobacter* (IV with oral step-down a plus)
- Novel approaches to *C. difficile* that address the recrudescence rate
- Combinations that address bacterial resistance
 - Beta lactamase (A / C / D) inhibitor
 - Carbapenem potentiator (adds MRSA coverage to carbapenem class)

Phase IIb or beyond:

- Gram-positive (w / MRSA) oral agent only
- Community RTI oral agents
- Sepsis

Not Interested in:

- Topical antibacterials
- Quinolones (mechanism of action for quinolones is of interest, but not the structural class)
- New targets without validation in animal models

ANTIFUNGALS

Areas of Interest:

Preclinical or later in development:

- Agents directed at validated novel targets (other than ergosterol biosynthesis and glucan synthase)

Phase I or later in development:

- IV / oral broad-spectrum agent with improved activity over azoles and echinocandins against *Candida*, *Aspergillus*, and rare moulds for hospital use
- *Aspergillus*-specific small molecule or MAb (therapeutic and / or prophylactic)

Phase IIb or later in development:

- Oral agents for community use active against *Candida* and dermatophytes, including azole-resistant strains, with superior adverse event rates compared with terbinafine

Not Interested in:

- Incremental improvements upon inhibitors of ergosterol biosynthesis and glucan synthase

ANTIVIRALS – HIV

Areas of Interest:

Preclinical or later in development:

- RNase H inhibitors
- Inhibitors of viral budding and / or maturation
- Latency targets
- Other new mechanisms, eg, host targets (NOT chemokine receptors)

Phase I or later in development:

- Integrase inhibitors with new MOA or novel structural scaffold with QD dosing; would consider BID dosing with differentiated resistance profile
- Protease inhibitors that do not require ritonavir-boosted QD dosing; would consider BID dosing with differentiated resistance profile
- Non-nucleoside reverse transcriptase inhibitors dosed QD with a high barrier to resistance / efficacy against efavirenz-resistant virus

Phase IIb or later in development:

- Nucleoside reverse transcriptase inhibitors with differentiated resistance profile to existing agents, QD dosing

Not Interested in:

- Chemokine receptor (CCR5, CXCR4) antagonists
- PK enhancers
- Agents administered parenterally

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

ANTIVIRALS – HCV

Areas of Interest:

Preclinical or later in development:

- Nucleoside inhibitors
- Small-molecule inhibitors of HCV helicase
- NS5A inhibitors with proven mechanism of action
- HCV viral entry inhibitors
- Cyclophilin or cyclosporin analogues
- Novel mechanism agents

Phase Ib or later in development:

- Non-nucleoside inhibitors
- Second-generation protease inhibitor with activity against genotypes 1, 2, and 3, and key mutants with preclinical safety data and PK suggestive of QD or BID dosing suitable for development as fixed-dose combinations

Phase IIb or later in development:

- First-generation protease inhibitors

ANTIVIRALS – OTHER INTERESTS

Areas of Interest:

Preclinical or later in development:

- Curative approaches to HBV

Phase IIb or later in development:

- HBV oral agents
- RSV, CMV, or EBV oral agents with pristine safety profiles

Phase III or later in development:

- Influenza with pristine safety profile

Not Interested in:

- Interferon parenterally administered
- TLR agonists or activators

Not Interested in:

- Agents administered parenterally

ANTIVIRAL AND ANTI-INFECTIVE TECHNOLOGIES

Antiviral:

- Animal or cellular models of latency
- In vitro tissue models for HCV
- Robust cell culture systems for HCV replication
- Biomarkers / noninvasive assay technology for HIV and HCV with enhanced sensitivity and / or lower cost; particularly interested in prognostics
- Genotyping and phenotyping technologies for HCV polymerase and HCV protease
- HCV-infected human liver tissue samples

Antifungal and Antibacterial:

- Rapid (<2 hours), point-of-care, pathogen-specific, and host response diagnostic tests

VACCINES

Areas of Interest:

- Novel technologies for antigen selection, discovery, and identification
- Viral, bacterial, and fungal vaccine candidates in areas of high medical need / high incidence
 - Preclinical efficacy or clinical proof of concept achieved, an advantage but not required
- HIV
 - Novel immunogens that elicit broadly cross-neutralizing immunity
- Novel adjuvants and immunomodulators
 - Highly desirable if preclinical efficacy or clinical proof of concept achieved, but not necessarily required
- Novel viral vector approaches
- Novel delivery mechanisms of vaccine target antigens
- Multiplexed clinical assay platforms
- Novel approaches to production of virus-like particles
- Improvements on existing Merck vaccines, which would allow for reduced dosing or increased cross-strain protection

Not Interested in:

- Biodefense targets
- Products containing thimerosal or unmodified animal / human components
- Seasonal vaccines (eg, influenza)
- DNA-based vaccines for infectious diseases
- Viral vectors based on pox viruses, retroviruses, and adeno-associated viruses

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

EMBRACING PARTNERSHIPS



Neurosciences and Ophthalmology

ALZHEIMER'S DISEASE

Areas of Interest:

- Agents in late phase I or later with potential disease-modifying activity
 - Specific interest in BACE inhibitors and γ -secretase modulators
- Agents with the potential to modulate the formation of toxic A β or tau species
 - Should preferably be validated in vivo
 - For tau, includes kinase inhibitors, tau aggregation inhibitors, microtubule stabilizing agents
- Agents with the potential to influence brain cholesterol homeostasis
 - Examples include LXR agonists
- Novel mechanism symptomatic improvement agents with at least comparable characteristics to existing approved medications
 - May be used as monotherapy or in combination with current therapies
 - Brain penetrant HDAC inhibitors selective for members of Class 1 / 2, or acetylation activators selective for members of Class 3

CIRCADIAN DISORDERS

Areas of Interest:

Novel therapeutic agents, chemical leads, or targets for:

- **Sleep enhancement:** Beyond improving sleep onset and maintenance, novel mechanisms with potential to:
 - Enhance next-day mood / cognitive performance
 - Allow full restoration of waking state upon arousal
 - Promote sleep and facilitate improved metabolic performance resulting in weight loss for the obese, and glucose control

Tools and Technologies:

- Prognostic, diagnostic, and progression biomarkers of disease and disease state (electrophys-, fluid-, or imaging-based)
 - Tau imaging agent (eg, PET ligand)
 - Fluid-based assays for A β and tau oligomeric species
- Novel animal models for target evaluation
 - Models that develop both plaques and tangles
 - Must have clear IP status
- Novel genetic / RNA-based approaches to target validation or therapeutics

Not Interested in:

- Acetylcholinesterase inhibitors without additional pharmacological activity
- The following agents:
 - A β -based vaccines
 - Antioxidants
 - Metal chelators

- **Depression:** Novel mechanisms with potential to:
 - Work within 1 week
 - Substantially improve remission rates
 - Do not have any meaningful side effects

- **Alerting:** Novel mechanisms with potential to:
 - Work in sleepiness *and* all forms of malaise and fatigue
 - Improve cognitive performance
 - Improve measures of mood in patients with MDD with atypical features

CIRCADIAN DISORDERS

Areas of Interest:

- **Sleep apnea**
 - Increase respiratory efficiency in apnea patients
 - Promote sleep and facilitate improved metabolic performance
 - Eliminate next-day excessive sleepiness
- **Circadian rhythm**
 - Shifts in central circadian activity and are not melatonin modulators

Tools and Technologies:

- Novel biomarkers of sleep debt, mood
 - Circulating, etc, predictors of sleep debt, depressive mood, etc, that show responsiveness to recovery sleep
- Novel technologies to measure sleep debt, altered physiology related to insufficient sleep, circadian dysrhythmia, etc

MIGRAINE

Areas of Interest:

- Novel therapeutic agents that, alone or in combination, address unmet needs in migraine or migraine prophylaxis
- Biologics for prophylaxis
- Mechanisms that complement CGRP antagonists for acute migraine
- Synergistic combination approaches

Tools and Technologies:

- Novel and patented delivery systems
 - For novel or existing molecules

Not Interested in:

- GABA modulators
- Any sleep agent without both sleep onset and maintenance
- Sleep or wake modulators that impair cognitive performance
- Sleep, wake, or circadian therapies that are directed at targets that would be highly likely to be scheduled mechanisms of action
- SSRI / SNRI

Not Interested in:

- Triptans
- New formulations of existing antimigraine drugs
- COX-2 inhibitors and NSAIDs

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

OPHTHALMOLOGY

Disease Areas of Interest (all opportunities require clinical proof of concept):

- **Retinal diseases**
 - **Diabetic retinopathy / diabetic macular edema**
 - Mechanisms to reduce progression of NPDR in moderately to severely affected patients
 - Anti-angiogenics with superior dosing to VEGF-Trap to treat or prevent PDR
 - Mechanisms with dosing / AE profile compatible with treating DME patients without existing vision loss (eg, topical, periocular, or ≥ 6 months' duration intravitreal; non-cataractogenic and / or non-IOP elevating)
 - Mechanisms to treat patients with existing vision loss with superior efficacy and favorable AE profile vs laser and steroids
 - **AMD**
 - Wet AMD therapies showing less-invasive dosing than Lucentis™ / VEGF-Trap (topical, periocular) and / or additional efficacy
 - Dry AMD therapies to reduce geographic atrophy progression
- **Glaucoma**
 - Non-prostanoid MOAs with efficacy \geq Xalatan™
 - Additional properties of interest: trabecular outflow enhancers, non-topical delivery formulations, neuroprotective activity
- **Anterior segment disease**
 - **Dry eye**
 - Efficacy / tolerability \geq Restasis™
 - **Allergic conjunctivitis**
 - Efficacy \geq Elestat™ and Patanol™
 - **Uveitis**
 - Superior efficacy and safety profile compared to steroids and cyclosporin-based therapies

Tools and Technologies:

- Retinal delivery technologies with preclinical data demonstrating:
 - Favorable dosing regimen (intravitreal or periocular delivery with 6-month or longer dosing interval; topical delivery with preclinical proof of concept in large-eyed animal)
 - Compatible with in-office procedure
 - Technologies compatible with siRNA and proteins

Not Interested in:

- Anti-infectives
- Cataract therapies
- Glaucoma IOP lowering therapies without clinical proof of concept
- Steroids for DME

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PAIN

Areas of Interest:

- Novel therapeutic agents or chemical leads for neuropathic or inflammatory pain
 - NGF / TrkA antagonists and antibody approaches
 - Subtype selective sodium channel blockers
 - Endocannabinoid pathway modulators
 - But no interest in CB1 or CB2 agonists
 - P2X antagonists
 - Trp channel modulators
 - KCC2 chloride transporter modulators
 - K-channel modulators
 - Anticonvulsant MOA for pain
 - Disease-modifying or nerve-regeneration approaches to NP
 - Novel proprietary targets for neuropathic and OA pain
 - Includes collaborations with key opinion leaders
 - ASIC3 blockers
 - Novel nicotinic receptor modulators
- Late-stage abuse-deterrent opioids
- Synergistic combination approaches
 - Therapies providing improved efficacy or safety as add-on or part of novel combination therapy

PARKINSON'S DISEASE

Areas of Interest:

- Non-dopaminergic agents with clinical proof of concept in palliative therapy for Parkinson's disease
- Non-dopaminergic agents that modify L-dopa-induced dyskinesias
- Agents and approaches to prevent disease progression
 - LRRK2 inhibitors and LRRK2 animal models

Tools and Technologies:

- New models for chronic pain
- Biomarkers and genetic markers for chronic pain
- Imaging agents and sensors
- Alternate formulation (eg, topical) technology

Not Interested in:

- New formulations of marketed drugs
 - Unless novel formulation technology (see above)
- NSAIDs and COX-2 inhibitors
- iNOS inhibitors
- Serotonergics

Tools and Technologies:

- Animal models of Parkinson's disease progression

Not Interested in:

- Metal chelators
- Antioxidants

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

SCHIZOPHRENIA

Areas of Interest:

Novel compounds and chemical leads

- Monotherapy or add-on therapy for positive, negative, and / or cognitive Sx
- Any mechanism that shows efficacy in preclinical models of antipsychotic activity or cognition, or with clinical proof of concept
- Add-on mechanisms for reducing weight gain induced by atypical antipsychotics
- Specific mechanisms of particular interest
 - Orthosteric mechanisms
 - NDEL inhibitor
 - PDE 1, 9 inhibitor
 - Compounds that increase synaptogenesis
 - Asc-1 inhibitor
 - GlyT1 inhibitor
 - Nicotine $\alpha 6$ antagonist
 - Somatostatin 2 antagonist
 - Erb4 / Neuregulin modulator
 - D aspartic acid oxidase inhibitor
 - Adenylate cyclase 1 activator
 - Trace amine 1 antagonist
 - Allosteric mechanisms
 - D1 receptor PAM
 - M4 PAM
 - NT1 PAM
 - EAAT2 PAM
 - Glutamate antiporter modulator

Not Interested in:

- Monoamine-based atypical antipsychotics
 - Desmethyl clozapine
 - D3 antagonists
- CB1 antagonists / CB1 inverse agonist
- PDE 3 / 4 / 5

EMBRACING PARTNERSHIPS



Oncology

ONCOLOGY

Areas of Interest:

- Late-stage clinical
 - Must have a differentiated profile based on completed phase IIb proof of concept through marketed agents
 - Clinical data in large market solid tumor indications or established hematological tumors
 - Global or regional deals (US, EU, and / or Asia Pacific)
- Early-stage (up to and including clinical proof of concept)
 - Signal transduction and proliferation / survival
 - PI3K and Ras / Raf / MEK pathways, RTKs
 - DNA damage / checkpoint
 - p53 pathway modulators, agents selective for MMR- or HR-defective tumors

Not Interested in (applies to Early and Late Stage):

- Preventive care
- Personalized immunotherapy / autologous therapies
- Gene therapy
- Intra-tumoral delivery (except for RNAi delivery)

CAPABILITIES – TECHNOLOGIES TO EVALUATE

- Biomarkers and diagnostics
 - Diagnostic platforms that are ready for clinical application, including imaging, cell-based, blood, nucleic acid, and IVD capabilities with WW distribution
 - Pharmacodynamic and response biomarkers for PI3K and DNA damage / checkpoint pathways
 - Minimally invasive platforms for measuring tumor biology: circulating tumor cells, circulating nucleic acids, novel imaging tracers
- RNAi
 - Tumor-targeted delivery systems for systemic administration of small molecules, RNAi, and microRNA
 - Tools for development of therapeutic microRNA and antagomirs
 - Relevant preclinical models of HCC for the evaluation and validation of siRNA / microRNA / antagomir targets
- Kinases
 - Platforms for discovery of allosteric kinase inhibitors
 - Bioinformatic tools to integrate protein structure, compound structure, and SAR analysis of kinase inhibitors
 - Capabilities for identification of kinase mutations in solid tumors
- Other
 - Robust technology that could predict in vitro therapeutic index of combinatorial library

Merck will continue to pursue licensing opportunities in all disease areas where clinical proof of concept exists.

EMBRACING PARTNERSHIPS



Research Technologies

DRUG DELIVERY

Areas of Interest:

- Tissue-specific targeting (eg, siRNA,^a chemotherapeutics)
- Novel technologies for delivery of high concentration antibody formulations
- Novel vaccine and adjuvant delivery technologies
- CNS delivery (across or around blood brain barrier)
- Oral-controlled release technologies
 - For poorly soluble compounds (<0.1 mg / mL)
 - For narrow absorption windows compounds (eg, those with poor colonic absorption)
- Back-of-the-eye delivery systems
 - Retinal delivery systems – clinically proven gene tx vectors – retinal delivery of siRNA^a and trophic factors
 - Retinal drug delivery device with greater than 3 months' dosing
- Inhalation / nasal delivery systems for small and large molecules
- Technologies for delivery of water insoluble compounds:
 - Injectable delivery (eg, IV small molecules and peptides)
 - Oral delivery: mitigation of food effect
- Implantable delivery systems for extended release over 1 to several months
- “Intelligent” delivery systems – modulated delivery (eg, signal or drug concentration); personalized / feedback control
- Technology with potential to improve compliance with any dosage form
- Novel passive and active transdermal and topical technologies for small molecule and peptide delivery
- Sublingual delivery for fast onset
- Orally disintegrating tablet (ODT) technology or film technology with robust in vivo performance and simple packaging
- Pediatric / geriatric delivery technologies (other than ODT)
- Novel technologies for formulation and delivery of adenovirus and DNA
- Novel oral protein / peptide delivery systems (eg, insulin)^b
- Injection devices

^aSee RNA Therapeutics section for complete listing of interests related to delivery of nucleic acids.

^bSee Peptide Therapeutics section for complete listing of interests in peptide delivery.

INFORMATION / INFORMATICS TECHNOLOGY

Areas of Interest:

- Experimental data management and mining
 - Applications to assemble and make broader use of target data in internal databases
 - **Analyze ADME data:** Large, diverse datasets for less-common metabolic pathways (eg, aldehyde oxidase, sulfotransferases, transporters) and data on surrogate markers (eg, cardiac cell line surrogate for Q-T prolongation as an assay between hERG binding and CV dog model)
 - **Predict ADME:** In silico systems that more accurately predict drug behavior, safety / toxicity outcomes in preclinical species and patient safety outcomes
 - **Protein modeling:** High-throughput capabilities for protein library design, including multiple templates and flexible backbone design – Prediction of antibody structure, protein loop conformation, protein-protein complexes, aggregation spots; folding and expression optimization
- Knowledge management, data mining, modeling, and predictive analysis capabilities that **integrate external and internal data sets**
 - **Improve connectivity** within MRL as well as ability to share information with external partners
 - Improved software tools for convenient **analysis and visualization** of large amount of experimental results from various high-throughput analysis tools

METHODS (PROTOCOLS, REAGENTS, ETC)

Areas of Interest:

- Development, optimization and control of **protein expression, vaccine production, and purification processes**
- Improved **production-scale RNA purification** technologies
- **Profiling of compound / sample effects** on molecular targets in vitro, in/ex vivo using biochemical, whole cell and / or tissue-based assays
- **Protein multiplex assay technologies** for biomarker discovery / development for clinical applications (target engagement, patient stratification, dose finding)
- General **catalytic methodologies** with a **broad substrate** scope and **functional group** compatibility, especially **C-H activation**

PEPTIDE THERAPEUTICS

Areas of Interest:

- Peptide chemistry
 - Novel chemistries for improving resistance to enzymatic degradation
 - Novel chemistries for improving cell penetration
 - Novel chemistries for reducing immunogenicity
 - Improved processes for increased quality and efficiency, and reduced COG
- Technologies that extend the half-life through fusion / chemical conjugation
 - Polymers (different from PEG)
 - Protein moieties for fusion / conjugation (Ab and Ab fragments, serum proteins, designed proteins, etc)
 - Carbohydrates
- Delivery technologies (see Drug Delivery section)
 - Controlled release (IV and sc applications)
 - Inhalation and nasal delivery systems
 - Transdermal delivery systems
 - Oral delivery systems
 - Technologies for targeted delivery that address / overcome the blood brain barrier

PLATFORMS (IN VIVO, ASSAY, OTHERS)

Areas of Interest:

- **Animal platforms** to validate **targets** and / or qualify for PK / PD
- Semi-, non-invasive clinical instrumentation for **molecular optical imaging** in preclinical / clinical applications
- **New biologics analysis tools:** quantitative tools for analysis of peptides (and conjugates like PEG), siRNA, and proteins at low levels in biological fluids, and quantitative and sensitive tools for in situ analysis of polymer and lipid-based delivery vehicles for siRNA and small molecules
- **Technologies to generate kinase data:** a dataset where >100 compounds are tested on >100 kinases. IC₅₀ data is preferred over % inhibition, but most important gap is bigger dataset

Not Interested in:

- Transgenic animal-based or plant-based production systems for peptide therapeutics
- recDNA processes for peptide production lacking the possibility to introduce non-coded amino acids

RNA THERAPEUTICS

Areas of Interest:

- siRNA sequence, structure, and modification
 - Novel chemistries for:
 - Improving resistance to enzymatic degradation
 - Reducing immunostimulation
 - Enhancing Ago2 / RISC incorporation and potency
 - Increasing chemical stability
 - Improving target specificity
 - Improving unaided cellular delivery
- siRNA Delivery vehicles
 - Systemic administration
 - Novel polymers and lipids for encapsulation that exhibit:
 - Low toxicity
 - Biodegradability
 - Efficient cellular uptake
 - Efficient endosomal escape
 - Molecular targeting
 - Targeting agents (antibodies, peptides, or small molecules) that are suitable for direct siRNA conjugation or for nanoparticle / liposome delivery
 - Local delivery
 - Systems exhibiting direct siRNA delivery to eye, lung, CNS, and muscle tissue
- Assays for siRNA and delivery vehicles
 - Techniques for tethered polymer complex evaluation (quantitative and qualitative)
 - Biochemical assays for strand selection, RISC incorporation, and catalytic efficiency
 - Cell-based assays to measure toll-like receptor binding and activation
 - Medium- and high-throughput screening techniques for siRNA quantitation
 - Techniques for evaluation of siRNA trafficking, endosomal escape, and distribution (high- and medium-resolution approaches)
 - Assays for clinical biodistribution
 - Assays for pharmacodynamic evaluation of miRNA activity
 - Molecular modeling tools for oligonucleotides and for lipid / polymer delivery systems

- Delivery vehicle screening strategies
 - Microassembly techniques
 - High-throughput in vivo screening technologies for determining mRNA silencing
- miRNA
 - Novel chemistries to create miRNA mimics and / or antagonists
 - Therapeutic agents that:
 - Demonstrate reduction of miRNA levels in animals, with evidence that reductions have expected effects on mRNA levels and / or disease phenotype
 - Demonstrate delivery of miRNA in animals, with evidence that increases in miRNA have expected effects on mRNA levels and / or disease phenotype
- RNA Manufacturing
 - Advancements in large-scale production of modified siRNA
 - Improved processes for increased quality, efficiency, and reduced COG
 - Novel chemistries
 - Universal linker-based solid support for production of siRNAs
 - Robust LC-MS method for determination of impurity profile of phosphoramidite raw materials and oligonucleotides (siRNAs)
 - Alternative methods to produce siRNA clinical supplies

Not Interested in:

- Plasmid DNA-based methods for RNA therapies
- Viral delivery methods for RNA therapies
- Aptamers as therapeutics

WORLDWIDE LICENSING CONTACTS

CENTRAL SCIENTIFIC LICENSING CONTACT



Greg Wiederrecht, PhD, CLP

Vice President and Head, External Scientific Affairs
Licensing and External Research
Merck Research Laboratories
Merck & Co., Inc.
PO Box 2000/RV70-200
Rahway, NJ USA 07065-0900
Email: greg_wiederrecht@merck.com
Phone: +1 732 594 6576



Pamela Demain, MBA, CLP

Executive Director, Corporate Licensing
Merck & Co., Inc.
PO Box 100
Whitehouse Station, NJ USA 08889-0100
Email: pamela_demain@merck.com
Phone: +1 908 423 6940



Reid J. Leonard, PhD

Executive Director, Licensing and External Research
Merck Research Laboratories, Boston
Merck & Co., Inc.
33 Avenue Louis Pasteur, BMB 2-410
Boston, MA USA 02115
Email: reid_leonard@merck.com
Phone: +1 617 992 2321

WESTERN UNITED STATES



James M. Schaeffer, PhD

Executive Director, Licensing and External Research
Merck Research Laboratories, West Coast
Merck & Co., Inc.
7825 Fay Avenue, Suite 320
La Jolla, CA USA 92037
Email: jim_schaeffer@merck.com
Phone: +1 858 454 6502 ext. 102



CANADA

Steven Xanthoudakis, PhD

Director, Licensing and External Research
Merck Frosst Canada, Ltd.
9-2-446A, Research Bldg 9
16711 Trans Canada Highway
Kirkland, Quebec
H9H 3L1, Canada
Email: steven_xanthoudakis@merck.com
Phone: +1 514 428 3461



WESTERN UNITED STATES

Yael Weiss, MD, PhD

Director, Licensing and External Research
Merck Research Laboratories, West Coast
Merck & Co., Inc.
1700 Owens Street, Suite 400
San Francisco, CA USA 94158
Email: yael_weiss@merck.com
Phone: +1 415 627 8781

HEAD, EUROPEAN GROUP, ITALY, SWITZERLAND, AND ISRAEL



Margaret Beer, MSc, PhD

Senior Director and Head
Licensing and External Research, Europe
Merck Sharp & Dohme
Hertford Road
Hoddesdon, Herts
EN 11 9BU, United Kingdom
Email: margaret_beer@merck.com
Phone: +44 1992 452639



FRANCE, SPAIN, PORTUGAL, GERMANY, RUSSIA, AND EASTERN EUROPE

Manfred Horst, MD, PhD, MBA

Director, Licensing and External Research, Europe
Merck Sharp & Dohme
Avenue Hoche 3
75114 Paris, France
Email: manfred_horst@merck.com
Phone: +33 1 4754 8858



SCANDINAVIA, THE BALTIC COUNTRIES, AND THE BENELUX

Hans Boström, MSc, PhD

Director, Licensing and External Research, Europe
Merck Sharp & Dohme (Sweden) AB
Rotebergsvägen 3, Box 7125
192 07 Sollentuna, Sweden
Email: hans_bostrom@merck.com
Phone: +46 8 626 15 24

UNITED KINGDOM, REPUBLIC OF IRELAND, AND SOUTH AFRICA



Rob Pinnock, BSc, PhD

Director, Licensing and External Research, Europe
Merck Sharp & Dohme
Hertford Road
Hoddesdon, Herts
EN 11 9BU, United Kingdom
Email: rob_pinnock@merck.com
Phone: +44 1992 452850



JAPAN, SINGAPORE

Koichi Kato, PhD

Senior Director, External Scientific Affairs
Licensing and External Research
Banyu Pharmaceutical Co., Ltd.
Kitanomaru Square, 1-13-12, Kudan-kita, Chiyoda-ku
Tokyo 102-8667, Japan
Email: koichi_kato2@merck.com
Phone: +81 3 6272 2209



JAPAN

Masayuki Kinoshita, MSc

Director, Corporate Licensing
Banyu Pharmaceutical Co., Ltd.
Kitanomaru Square, 1-13-12, Kudan-kita, Chiyoda-ku
Tokyo 102-8667, Japan
Email: masayuki_kinoshita@merck.com
Phone: +81 3 6272 1792

KOREA



Kuchan Kimm, MD, PhD

Science Ambassador
168 Gongduk-dong Mapo-gu
12F Mirae Asset Life Insurance Building
Seoul 121-705, Korea
Email: kuchan_kimm@merck.com
Phone: +82 2 6363 0012 (Direct)
Mobile: +82 10 7534 0012



CHINA, HONG KONG, AND TAIWAN

Jing-Shan (Jennifer) Hu, PhD

Director, Licensing and External Research
Merck Sharp & Dohme (China) Ltd.
20F Park Place, 1601 Nanjing Road (West)
Shanghai 200040, China
Email: jing_shan_hu@merck.com
Phone: +86 21 2211 8535



AUSTRALIA, NEW ZEALAND

Phil Kearney, PhD, MBA

Director, External Scientific Affairs
Merck Sharp & Dohme
54-68 Ferndell Street
South Granville, New South Wales
Australia, 2142
Email: phil_ Kearney@merck.com
Phone: +61 2 9795 9500

INDIA



Swami Subramaniam, MD, PhD

Director, Licensing and External Research
Merck Sharp & Dohme
6th and 7th Floors, Tower B
Gurgaon 122002, India
Email: swami_subramaniam@merck.com
Phone: +91 98455 44147