BUSINESS DEVELOPMENT & LICENSING

THE ENABLING TECHNOLOGIES TEAM
APRIL, 2018

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The Enabling Technologies Search & Evaluation Team

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We have a bi-directional relationship with the areas we support

Opportunity Landscape

Targeted Search & Evaluate

Unsolicited/Opportunistic Prospecting

BD&L-Enabling Technologies

Needs

Scientific Review

Functional and Therapeutic Areas

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Why consider MSD?

- Your work inspires us
  - Through the talent and tenacity of extraordinary researchers and entrepreneurs like you, MSD is pursuing many of the most innovative areas in biomedical research emerging today.
- Working together is essential
  - Building partnerships is the most important job we have and we are among the most active dealmakers in the biopharma industry.
- We have a flexible partnering model
  - Evaluation
  - Research Collaboration
  - License
  - Technology Transfer
  - Co-Development

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Notes regarding the following information

- The MSD Enabling Technologies Team are interested in any science that can enable or accelerate the drug discovery and development process
  - Science can mean reagents, assays, methods, software, technologies, platforms, etc.
  - The degree of enablement can be incremental or game-changing
- The following slides capture the key functional areas that collaborate presently with the Enabling Technologies Team. This can change from time to time depending on MSD's R&D strategy.
- The following information is for guidance only and does NOT represent an exhaustive list of MSD's technology needs.
- The following information is subject to change and often does as science continues to advance throughout the world

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Science of Interest to MSD

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Biomarker Groups

- Genetics
- Target & Pathway Biology
- Genomic & Proteomic Sciences
- Discovery Pharmacogenomics
- Clinical Pharmacogenomics
- Translational Biomarkers
- Translational Pharmacology
- Imaging

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- Quantitation/detection/enrichment of low abundant analytes/cells/microvesicles
- High quality biospecimens, including sample preparation technologies that preserve sample integrity (e.g. using FFPE tissue for both RNA and DNA extraction)
- Microscale and multiplexed biomarker analysis
- Inflammation & inflammatory models/biomarkers
- Novel technologies for molecular analyses, including high-throughput genomic technologies for gene expression and genotyping, improved PCR methods. rare sequence detection and advances in next generation sequencing that improve sensitivity and/or throughput
- Novel protein arrays technologies
- Low cost, instrument free disposable biomarker assays
- Real-time, in vivo biomarker sensor devices
- Well-annotated patient cohorts with the capability of patient recall

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- Improved flow cytometry techniques, including microparticle quantification
- Gene editing technology with direct editing of *in vivo* tissues, improvements in the efficiency of editing (indel, not KO) and direct base editing.
- Imaging agents:
  - high throughput cellular imaging capabilities
  - in vivo imaging of small animals
  - central (neuro) pharmacodynamics markers
  - immune cell/ inflammation imaging, assessment of leukocyte trafficking to organs of interest
  - targeting platforms (i.e. mAb, nanobodies, aptamers) for imaging
  - oncology targeted imaging agents.
  - for pathologies in neurodegenerative diseases, including neuro inflammation
  - for drug induced vascular injury
  - for liver transporter dysfunction
  - Single- step radiolabeling strategies for labeling peptides/proteins with fluorine-18

Pharmacology Groups

- In Vitro Pharmacology
- In Vivo Pharmacology
- Safety Assessment & Toxicology
- Pharmacokinetics, Pharmacodynamics & Drug Metabolism

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- **In Vitro Pharmacology**
  - Nanodiscs
  - Bioluminescence resonance energy transfer (BRET)
  - High throughput binding assays for solubilized membrane proteins
  - Improved hosts for protein expression
  - Tools & techniques that facilitate more reliable in vitro/in vivo correlations
  - Technology for low volume custom dispensing (High throughput)
  - High content high throughput cell imaging
- **In Vivo Pharmacology**
  - Genetic animal models of disease beyond mice
  - Genetic tools to interrogate targets in a tissue specific manner
  - Disease-relevant in vivo models of disease (e.g., cognition)
  - In vivo, essential virulence factor evaluations and inhibitors in infectious disease models
  - Novel methods of CNS drug delivery
  - Tools & techniques that facilitate more reliable in vitro/in vivo correlations
  - Tools and techniques for pharmaco-EEG

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- **Safety Assessment & Toxicology**
  - Highly active in vitro human liver model, with applicability for toxicity investigations & de-risking
  - Microfluidic-enabled human-on-a-chip & 3D organ in vitro models
  - 3D bio-printed tissue
  - Mature, stable, and fully functional in vitro human and rat kidney proximal tubule cell co-culture models
  - Mature, stable, and fully functional complex in vitro testicular co-culture model
  - Mature, stable, and fully functional complex in vitro skin, neuro, ocular or GI tissues
  - Capability to enrich and specifically isolate progenitor cell population from rat liver and other rat organs
  - Capability to quantify epigenetic alterations to germ line cells in vivo in animals following drug treatments that are heritable
  - Test system for evaluating HLA haplotype dependent drug hypersensitivity potential
  - New toxicity biomarker technologies

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Pharmacokinetics, Pharmacodynamics & Drug Metabolism Bioanalytical

Function

- Microsampling or less invasive/non-invasive sampling technologies for pre- clinical and clinical studies
- Assay miniaturization technologies, including lost cost quantitative nano/picoliter dispensing
- Novel approaches to assessing immunogenicity

Absorption, Distribution, Metabolism and Excretion, ADME Function

- Microfluidic-enabled human-on-a-chip & 3D organ in vitro models
- Mixed-cell cultures for applications in drug metabolism and toxicology
- Humanized in vivo models

Quantitative Pharmacology and Pharmacometrics Function

- Disease-related aggregated datasets – combining clinical response data, baseline demographic, treatment, and clinical factors, diagnostic and other biomarker data. Ideally would capture longitudinal (variation with time) to inform timecourse of natural disease progression and response to interventions
- Systems biology and pharmacology models of disease

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Chemistry Groups

- Discovery Chemistry
  - Discovery Chemistry
  - Discovery Chemistry Modalities
  - Chemistry Capabilities & Screening
  - Chemical Biology
- Process Research & Development

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- **Target Identification and Hit Finding**
  - Knowledge-based algorithms for identifying novel therapeutic targets and pathways
  - Phenotypic Screening and Quantitative Chemoproteomics
  - Linker Technology (new methods to connect payloads/probes and targets in biological systems)
  - Chemical probes
  - Screening compound libraries (focused libraries: Protein-Protein Interactions, Epigenetics, Natural Product-Like etc.)
  - Innovative computational methods for identifying novel hit classes

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- **Screening**
  - High throughput binding assays for solubilized membrane proteins
  - Improved hosts for protein expression
  - Label-free techniques
  - Cell-based assay automation/multiplexation
  - Automated data analysis tools (not just for Flow and MS-cytometry)
  - High throughput screening techniques, especially for receptor binding
  - Disease relevant and translatable cellular models that are amenable for screening
  - Higher throughput label free technologies for binding
  - Selection/enrichment platforms enable identifying cell permeable peptides
  - Nano discs (repeated)
  - Tools & techniques that facilitate more reliable in vitro/in vivo correlations (repeated)

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- **Synthetic**
  - Automation and parallel preparative and analytical methods particularly focusing on high throughput chemistry and high throughput reaction screening
  - Microscale parallel purification
  - Flow chemistry and in-line assay feedback loops
  - Chemocatalysis & biocatalysis
  - Novel chemical building blocks
  - Emerging technologies such as template guided and knowledge-based iterative systems
  - Computational algorithms able to predict successful reactions (reagents, conditions) and process impurities
  - PET tracer generation methods
- **Computational**
  - Methods that offer quantitative prediction of activity and other drug development parameters
  - Quantitative capabilities and SAR analysis for Peptide ligands
  - Methods for quantitative prediction in protein design
  - Solid state property predictions for solubility, polymorph, stability

- **Cheminformatics**
  - Methods to assess and visualize ADME and PKPD potential of multiple chemical series after an HTS
  - A mathematical framework to understand biological knowledge and gaps of networks (including disease)
  - Visualization approaches that present data or models in a form of a hypothesis so project teams can independently interpret it and make decisions.
  - Methods to form assertions from complex biological data (compounds, targets, phenotypes)
- **Biochemical Engineering and Structural Sciences**
  - Cryo-EM
  - Protein construct design and selection of stabilized/optimized proteins
  - Automation and scoring for protein crystallization
  - Membrane Protein structural biology
  - BioNMR and HDX for protein analysis and MOA determination

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- **Peptide Design & Chemical Space**
  - Enabling peptide synthetic chemistry
    - Methods that accelerate peptide synthesis beyond current platforms
  - Macrocyclic peptides computational chemistry
    - Virtual docking/screening of macrocyclic peptides (high resolution 3D structures of targets)
- **Peptide Cell Permeability & Exposure**
  - Biophysical and computational methods for peptide cell permeability
    - MS-based methods, fluorescent labeling, membrane model systems
    - Predictive *in silico* methods for passive diffusion (correlation to experimental data)
  - Cell-based systems for peptide cell permeability
    - Intracellular delivery; oral delivery
- **Peptide Target Space and Druggability**
  - Novel peptide lead finding approaches
    - Extracellular (*e.g.*, GPCR, ion channel)
    - Intracellular (e.g., enzymes, protein-protein interactions)

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- **Oligonucleotides**
  - Novel oligonucleotide chemistry
    - Designs that improve stability, potency and trafficking
  - Delivery
    - Novel delivery methods superior to current state
- **Bioconjugates**
  - Novel site-specific modification of biomolecules
  - Targeted delivery – Tissue specificity
- **Targeted Protein Degradation**
  - Capabilities and expertize that enable targeting of the ubiquitin proteasome system for protein degradation
    - Endogenous E3 Ligase Modulators – Activators, Inhibitors
    - Recruited E3 Ligase Modulators – PROTACs, Molecular Glues (e.g. imides)
    - DUB Modulators – Allosteric, Orthosteric

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Vaccine R&D Groups

- Vaccine platforms and discovery
- Upstream process
- Downstream process
- Drug product and new technologies
- Analytical development

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- **Vaccine discovery and platforms**
  - Delivery systems for nucleic acids
  - LNP formulations demonstrating improved therapeutic index
  - Adjuvantization
- **Upstream process development of vaccines**
  - Chemical modifications to increase vaccine production
  - Cell engineering to improve vaccine production
  - Gene editing to yield better cell lines
- **Downstream process development of vaccines**
  - Bulk freezing technology
  - Conjugate vaccine technology to increase immunogenicity and/or stability of product
  - Nanoparticulate delivery systems as carriers for conjugate vaccines
  - Innovations in sterile processing of live viruses
  - Novel downstream purification technologies
  - Oral vaccine delivery

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- **Drug product and new technologies**
  - Innovations for improved thermostability for vaccines such as lyosphere- like technologies, novel stabilizers, and sterile vacuum drying technologies such as microwave assisted drying
  - Technologies to lower cost of goods through novel delivery (e.g. ID, needle-free and patch-formulations, sustained release etc.) and novel adjuvants
  - Closed vial filling (i.e. sterile and sealed vial filling using laser).

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Microbiome Research

- Advance data analysis platform for metagenomics, metabolomics, human metadata and their integration
- Novel/cheap sequencing technologies (metagenomics, viromics)
- Platform for discovery of bioactives from microbiome
- Microbiome manipulation tools: non-lytic phages, genetic systems, exogenous expression of biosynthetic gene clusters

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Drug Delivery Stakeholders

- Pharmaceutical Sciences
  - Analytical Sciences
  - Biopharmaceutics
  - Formulation Sciences
- Device Development
- Clinical Supply

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- **Oral Delivery**
  - Controlled release technologies capable of QD delivery for compounds with poor aqueous solubility and QW/Q2W delivery of compounds agnostic of compound solubility
  - High drug-load technologies compatible with amorphous formulations
  - Novel preservative-free liquid or solid formulation approaches for children under age 2 to enable dosing flexibility (pediatric dosage forms)
  - Novel formulations and devices to meet the specific needs of geriatric patients
  - Novel taste modification technologies (beyond encapsulation, complexation)
  - Novel approaches to enable rapid, safe intraoral delivery of absorption limited drugs
  - Novel oral protein / peptide delivery systems (e.g. insulin, GLP-1 analogues) with human clinical data (systemic delivery and also local GI targeting of macromolecules)
  - Novel solubilizing excipients.

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- **Injection Delivery and Devices**
  - Novel solubilizing and stabilizing excipients and technologies for poorly soluble compounds, with supporting safety/tolerability data
  - Novel drying technologies (e.g. increased process efficiency, better molecule stability) with demonstrated pharmaceutical application (vaccines/biologics/small molecules)
  - Novel, safe biomaterials or technologies for injectable or implantable sustained release dosage forms that enable doses > 500 mg and duration
    > 6 mo
  - Easy to use self-injection systems with proof of concept prototypes available
  - Improved “liquid / dry” or “liquid /dry / dry” reconstitution technologies with single or multiple dosing options
  - Devices for delivery of large injection volumes and/or high viscosity formulations

- **Injection Delivery and Devices**
  - Technologies (devices and excipients) enabling shift from IV to subcutaneous delivery
  - Organ / tissue specific targeted and/or intracellular delivery technologies / devices
  - Liquid formulations and novel excipients that enable room temperature storage and transportation of labile molecules
  - Single-use, disposable devices with connection (e.g. Bluetooth) technology
  - Viscosity-reducing excipients for high concentration parenteral solutions

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- **Ophthalmics**
  - Non-invasive (topical) and minimally invasive delivery to the posterior eye and retina
  - Long-acting intravitreal injections
  - Long-acting implants (intravitreal, scleral)
- **Miscellaneous**
  - Tissue-specific or local delivery for GI, dermal and ocular applications
  - Technologies to improve patient adherence/compliance (all dosage forms)
  - Intelligent delivery systems capable of modulating delivery with user feedback and personalized control
  - Novel half-life extension or novel pro-drug technologies with clinical data (genetic fusion or chemical conjugation)
  - New approaches for co-dosing and/or co-administration of incompatible compounds that cannot be co-formulated via conventional methods
  - Transdermal delivery:
    - High drug load intra-dermal delivery of small molecules and peptides (e.g. microneedles)
    - Intradermal delivery of vaccines to reduce cost of goods due to dose-sparing and/or improved immunogenicity

- **Miscellaneous**
  - Innovative modality-agnostic technologies that enhance CNS delivery of drugs
  - Predictive models for taste assessment
  - Predictive computational tools and in vitro or preclinical models
    - Approaches to enable mechanistic understanding of how various drug species quantitatively contribute to insoluble drug absorption
    - in vitro or in silico modeling drug release from controlled/sustained release oral or parenteral dosage forms
- **Inhalation**
  - Devices for pediatric respiratory delivery
  - Novel nasal devices and formulation platforms for insoluble drugs
  - Soft mist inhalers/nebulizers

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Biologics Technology Groups

- Discovery Biology
- Assay Development
- Downstream Bioprocess
- Pharmacology
- Upstream Bioprocess

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- Novel mAb discovery and screening platforms
- Novel expression systems
- Technologies to improve cell culture expression such as media & feed enhancers
- Primary recovery tools
  - Improve efficiency of cell removal and enable continuous processing
- Novel purification tools for lower cost and continuous processing
- Process analytic tools; Single use sensor technologies for bioprocess monitoring that also enable continuous processing
- Primary cell-based binding/screening assays applicable to antibodies
- Cell-based models for combination studies
- More predictive models for cytokine storm

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THANK YOU!