

The background of the slide is a dark blue, semi-transparent image of neural tissue, showing a complex network of branching fibers and cell bodies, likely representing a brain or spinal cord section.

Laboratory for Drug Discovery in Neurodegeneration - A Model for Lead Discovery in Academia

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*Drug Discovery, Development, and Delivery for
Neurodegenerative Diseases -*

A Course for Academic & Industry Scientists

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LDDN - One Model for Academia-Based Lead Discovery

- General Concepts of Academia-Based Lead Discovery
 - Role, Goals, and Measures of Success
 - Models for Achieving Goals

- Features of the LDDN Model

Academia-Based Lead Discovery - Role

Compliment, not compete with, activities of pharma.

- Work in diseases areas neglected by pharma.
 - Rare cancers
 - Infectious disease
 - Parasitic diseases
 - Neurodegenerative diseases

- Work on targets too risky for pharma.
 - Cell-based assays with phenotype end-points.
 - Protein-protein interaction
 - Enzyme activation

Academia-Based Lead Discovery - Role

Compliment, not compete with, activities of pharma.

Except in cases where the academic lab has special expertise or insights.

- Inhibitor design
- Assay methodology
- Cell-lines

Academia-Based Lead Discovery - Goals and Success

Given its role, goals of an academic center need not be the goals of a pharmaceutical company.

- Assay development
- Hit discovery
- Lead optimization
- Animal model efficacy
- Publications
- Training

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Given its role, goals of an academic center need not be the goals of a pharmaceutical company.

- Assay development
- Hit discovery
- Lead optimization
- Animal model efficacy
- Publications
- Training
- Partnering with pharma

Academia-Based Lead Discovery - Models

Pluses

Minuses

Core, Service Facility

“Do-It-Yourself” Shop

Collaborative Model

Academia-Based Lead Discovery - Models

Pluses

Minuses

Core, Service Facility

- Great for PI
- Simple IP

- Assay development
- Med chem support

“Do-It-Yourself” Shop

Collaborative Model

Academia-Based Lead Discovery - Models

Pluses

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Core, Service Facility

- Great for PI
- Simple IP

- Assay development
- Med chem support

“Do-It-Yourself” Shop

- Great for center
- Simple IP

- Time commitment
- Operator error
- No med chem

Collaborative Model

Laboratory for Drug Discovery in Neurodegeneration

Mission of the LDDN is to ...

Create a new model for drug discovery that integrates the best of industry and academics.



Discover chemical agents that can be used as lead structures in the development of drugs to treat neurodegenerative diseases.

Laboratory for Drug Discovery in Neurodegeneration

Features of the LDDN model ...

- Hypothesis-driven, screening-based approach.

Laboratory for Drug Discovery in Neurodegeneration

Features of the LDDN model ...

- Hypothesis-driven, screening-based approach.
- Management and staff from pharma and biotech.

Laboratory for Drug Discovery in Neurodegeneration

Leads Discovery

Marcie Glicksman, Director

April Case

Mickey Huang

Min Liu

Sudeepa Sanyal

Eli Schuman

David Wilson

Medicinal Chemistry

Greg Cuny, Director

Sungwoon Choi

Lixin Qiao

Xin Teng

Xuechao Xing

Informatics

Ken Auerbach

Administration

Eiblis Goldings

Business Development

Frances Toneguzzo ^a

John Montana ^a

Craig Kennedy ^b

IP Manager

Connie Caron ^a

(a) Partners Healthcare (b) Harvard Med School

*Laboratory for Drug Discovery in
Neurodegeneration*

Laboratory for Drug Discovery in Neurodegeneration

Features of the LDDN model ...

- Hypothesis-driven, screening-based approach.
- Management and staff from pharma and biotech.
- Programs based on tight collaborations.

Collaborative Interactions Drive Discovery at LDDN

Unique staffing reflects a commitment to collaboration and team-work.

Permanent Staff

Leads Discovery

- assay development -
- high throughput screening -
- mechanism -

Informatics

- data base management -

Medicinal Chemistry

- lead optimization -
- inhibitor design -

Post-Doctoral Fellows

Bring novel opportunities for drug discovery to the LDDN.

Provide access to resources of neuroscience labs.

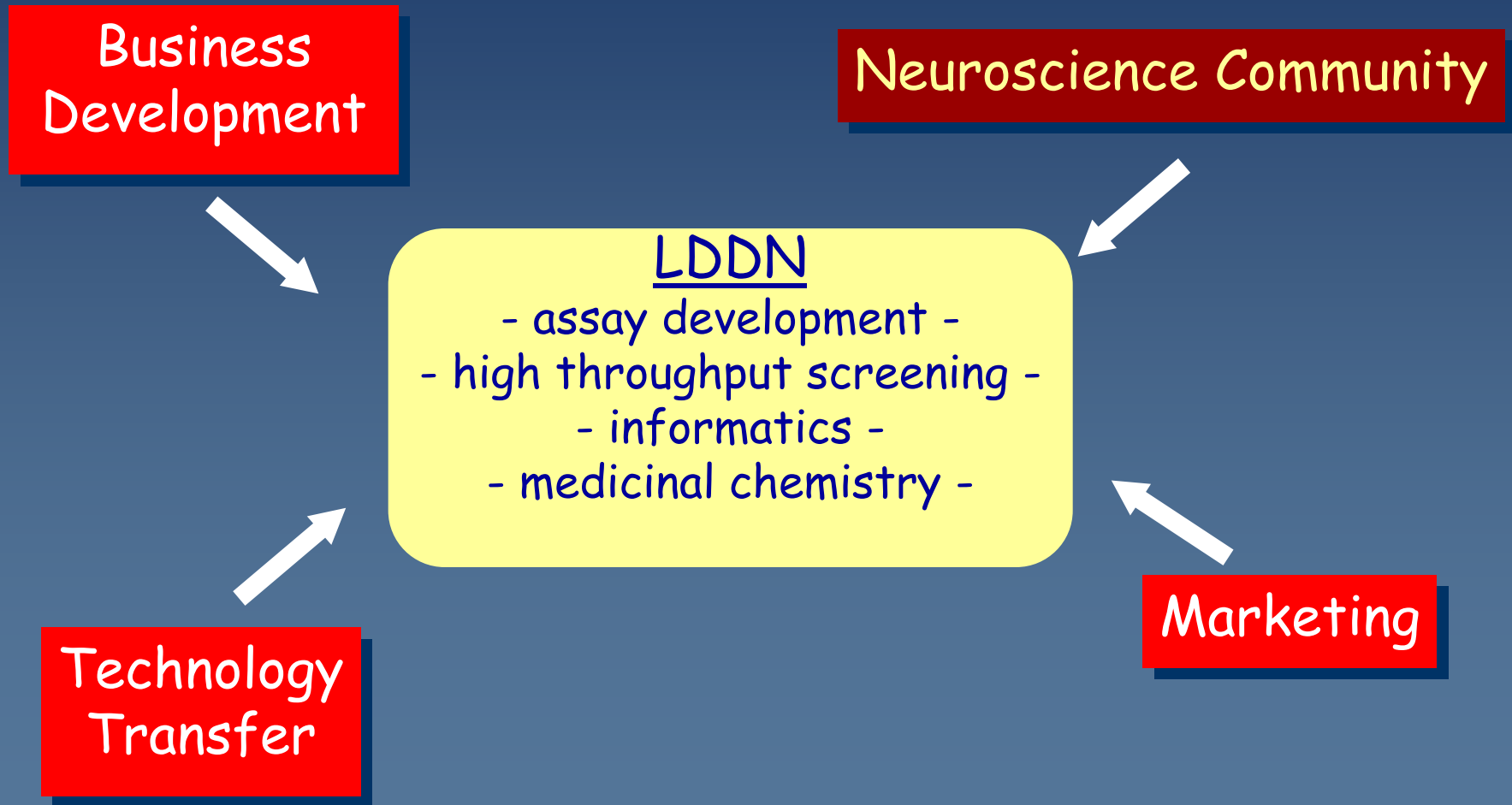
Laboratory for Drug Discovery in Neurodegeneration

Features of the LDDN model ...

- Hypothesis-driven, screening-based approach.
- Management and staff from pharma and biotech.
- Programs based on tight collaborations.
- Virtual structure motivated by the goal of partnering.

Resources of the LDDN - Intellectual Resources

LDDN has the resources to move drug discovery projects from conception through animal modeling to out-licensing.



Laboratory for Drug Discovery in Neurodegeneration

Features of the LDDN model ...

- Hypothesis-driven, screening-based approach.
- Management and staff from pharma and biotech.
- Programs based on tight collaborations.
- Virtual structure motivated by the goal of partnering.
- **Cover a broad range of targets in neurodegeneration.**

Projects of the LDDN

Assay Development HTS Med Chem *In vivo*

Project Name	Assay Development	HTS	Med Chem	<i>In vivo</i>
Necrosis Inhibitors			██████████	
Modulators of Processing of Amyloid- β Precursor	██████████	██████████	██████████	██████████
Inhibitors of Tau Phosphorylation	██████████	██████████	██████████	██████████
Modulators of Peptide-Exchange on MHC II	██████████	██████████	██████████	
Inhibitors of polyGln Polymerization	██████████	██████████	██████████	
Inhibitors of APP mRNA 5'-Untranslated Region	██████████	██████████	██████████	
Inhibition of Botulinum Proteases	██████████	██████████	██████████	
Modulators of SOD Gene Regulation	██████████	██████████	██████████	
Expression of Survival Motor Neuron (SMN)	██████████	██████████	██████████	
Inhibitors of A β -Induced Calpain Activation	██████████	██████████	██████████	
Inhibition of Toxic Conformational Isomerization of polyQ	██████████	██████████	██████████	
Inhibition of EphB3 Kinase	██████████	██████████	██████████	
Modulators of G-Protein-Coupled Receptor for Diabetes	██████████	██████████	██████████	
Modulators of G-Protein-Coupled Receptor for CNS	██████████	██████████	██████████	
Modulators of G-Protein-Coupled Receptor 54	██████████	██████████	██████████	
Modulators of the Expression of β -Synuclein	██████████	██████████	██████████	
Activation of Akt Kinase	██████████			
Modulators of Glu Transport in the CNS	██████████			
Activators of Atoh1	██████████			
Translational Inhibition of Mutant Htt	██████████			
Activation Glial Glu Transporter EAAT2 Expression	██████████			
Activation of the PERK Pathway	██████████			
Functional Inhibition of LRK2	██████████			

Laboratory for Drug Discovery in Neurodegeneration

High-Throughput Screening

Assays/screens under development	15
Screens underway	6
Screens in the database	27

Medicinal Chemistry

Programs underway	4
Programs complete	12

Efficacy Studies in Anima Models

Studies being plan	3
Studies with preliminary data	3

Medicinal Chemistry Programs at LDDN (2001 - 2006)

	Active	Dormant	No. of Series
Necrosis Inhibitors ¹	X		3
Modulators of APP Processing	X		3
Inhibitors of Tau Phosphorylation	X		1
		X	2
Modulators of Peptide-Exchange on MHC II		X	2
Inhibitors of APP mRNA 5'-Untranslated Region	X		1
SOD Dimerization Stabilizers ²		X	1
Inhibitors of A β -Induced Calpain Activation	X		1
Inhibition of EphB3 Kinase	X		1
Inhibitors of Tissue Transglutaminase		X	2
Modulators of Insulin Degrading Enzyme	X		2
Modulators of UCH-L1		X	2
Neuroprotection		X	1
Modulators of G-Protein-Coupled Receptor 54	X		2
BMP Receptor Kinase	X		1
Axonal Outgrowth	X		2
ER Stress		X	1

1. Optioned

2. Licensed