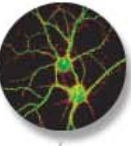


# Jefferies Global Healthcare Conference

Dr. Bharatt Chowrira, CEO

09.27.2011



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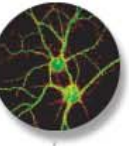


# key value drivers

Leading allosteric drug discovery	<ul style="list-style-type: none"><li>• Proprietary 70,000 allostery-biased small molecule library</li><li>• Proprietary HTS systems</li><li>• Deep allosteric know-how &amp; expertise</li></ul>
Validated emerging therapeutic class	<ul style="list-style-type: none"><li>• Proven mechanism, that has led to marketed products</li><li>• Significant investment from all major pharma</li><li>• Growing pipeline of allosteric modulators in the clinic</li></ul>
Robust pipeline	<ul style="list-style-type: none"><li>• 2 Phase II programs</li><li>• 8 preclinical programs</li><li>• Unmatched track record advancing allosteric modulators</li></ul>
Partnership with leading pharma	<ul style="list-style-type: none"><li>• Janssen Pharmaceuticals Inc. (JPI) for mGluR2 PAM in Phase II testing for schizophrenia</li></ul>
Dominant IP portfolio	<ul style="list-style-type: none"><li>• 13 issued patents</li><li>• 45 pending patents</li></ul>
Strong balance sheet	<ul style="list-style-type: none"><li>• CHF50 (US\$62 / €43) million at June 30, 2011</li><li>• No debt</li></ul>

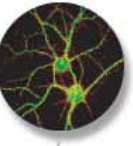
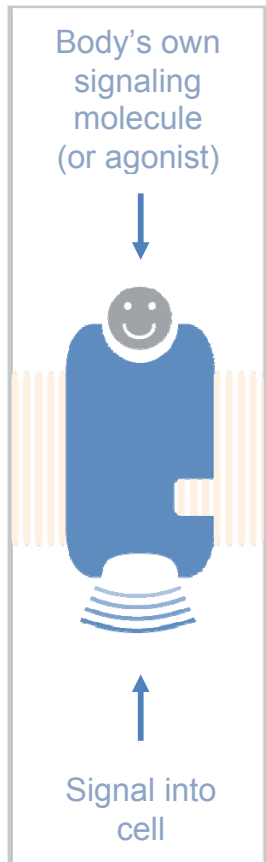


# allosteric drug discovery



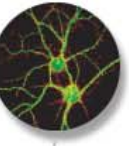
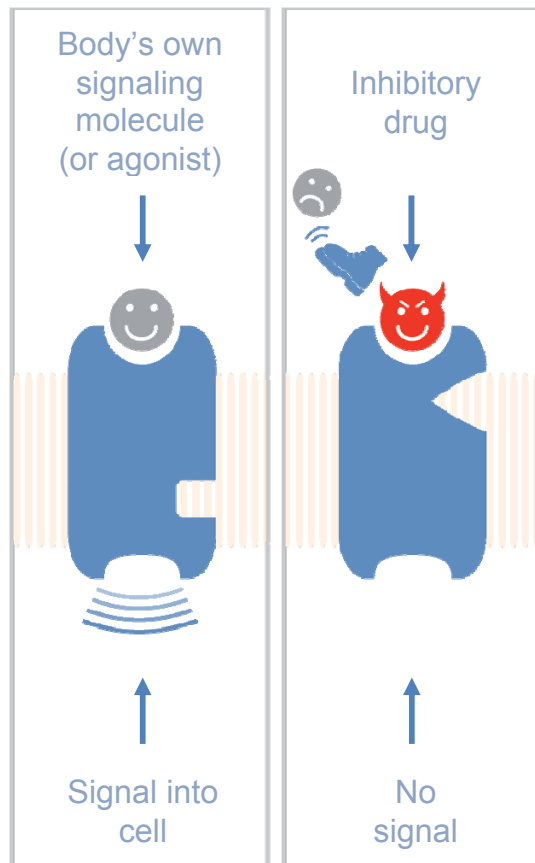
# allosteric modulators (AMs) are different from conventional drugs

## allosteric modulation explained



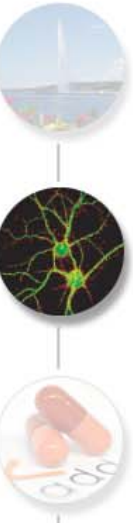
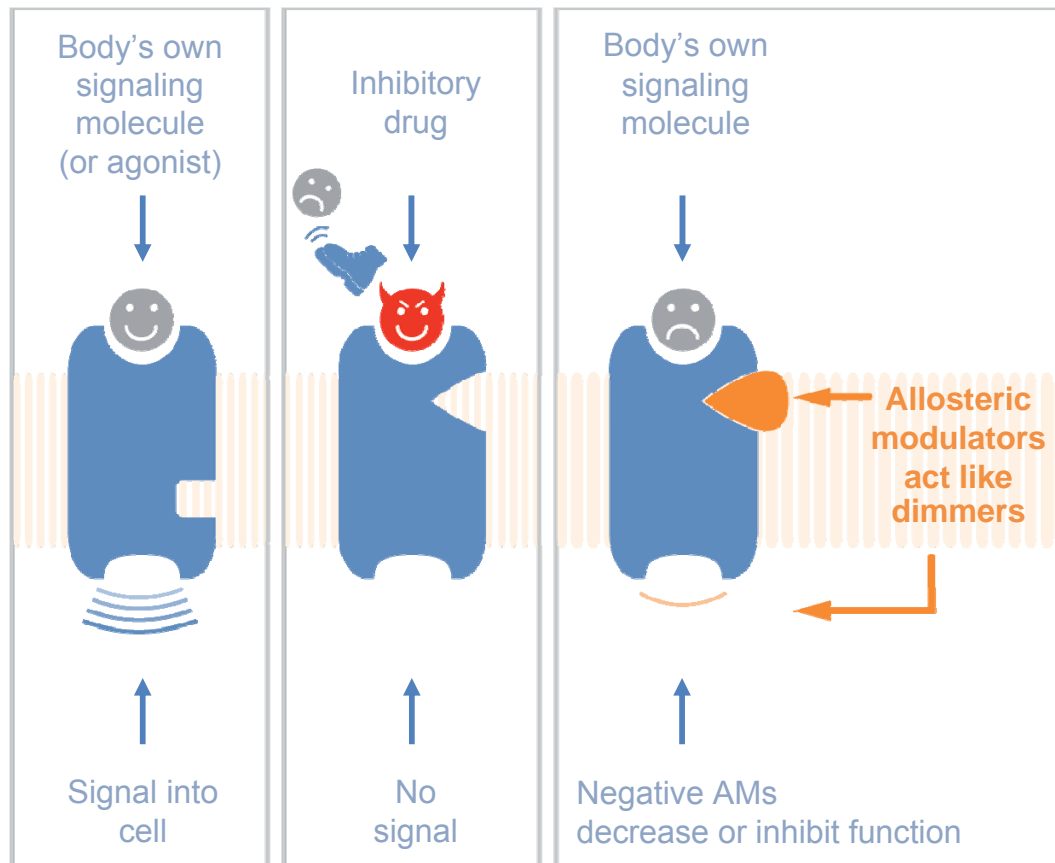
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## allosteric modulation explained



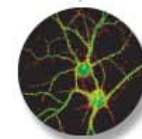
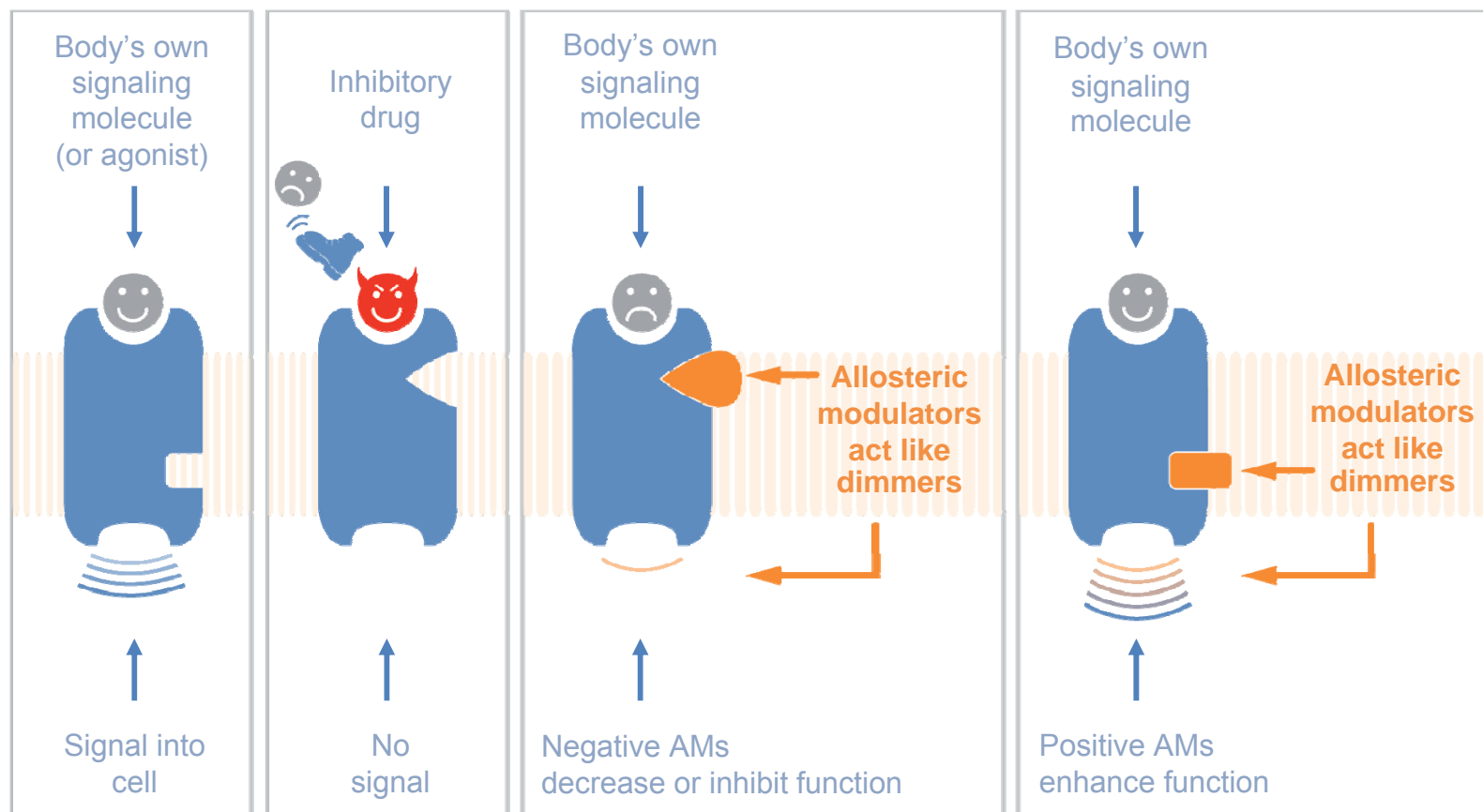
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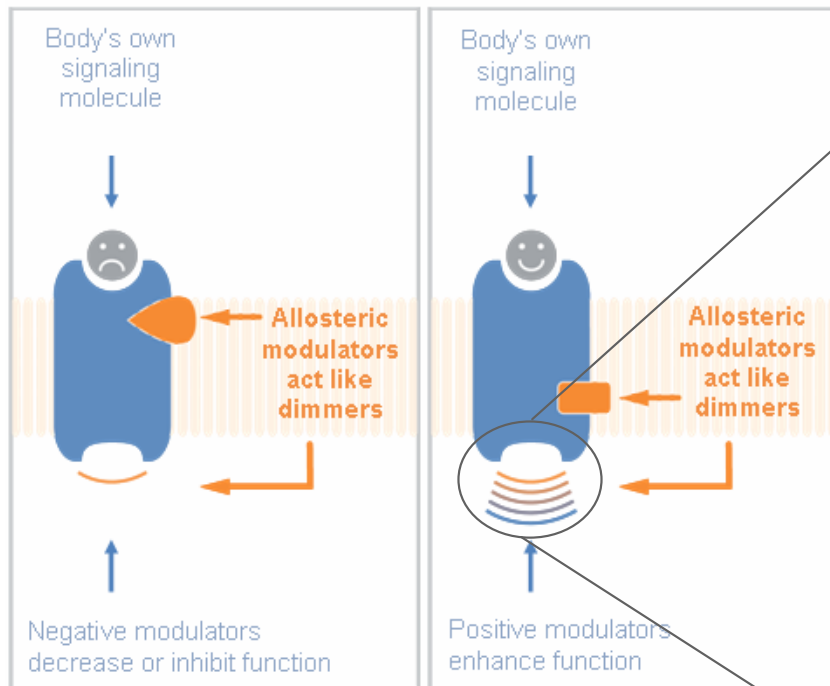
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## allosteric modulation explained

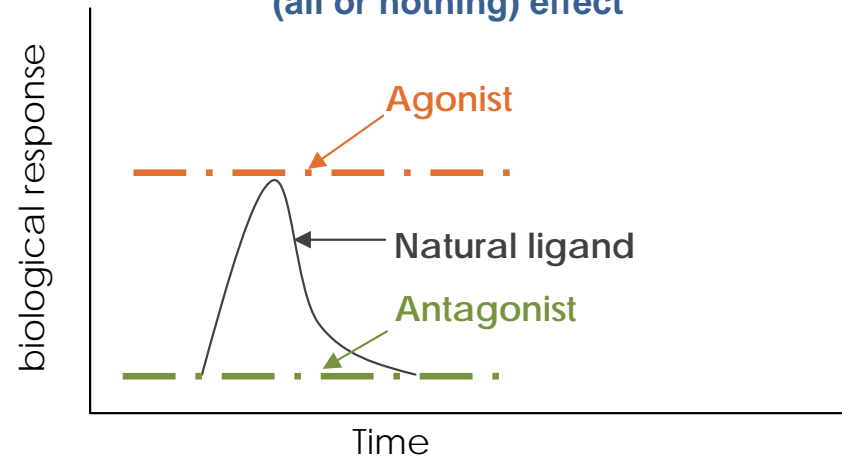




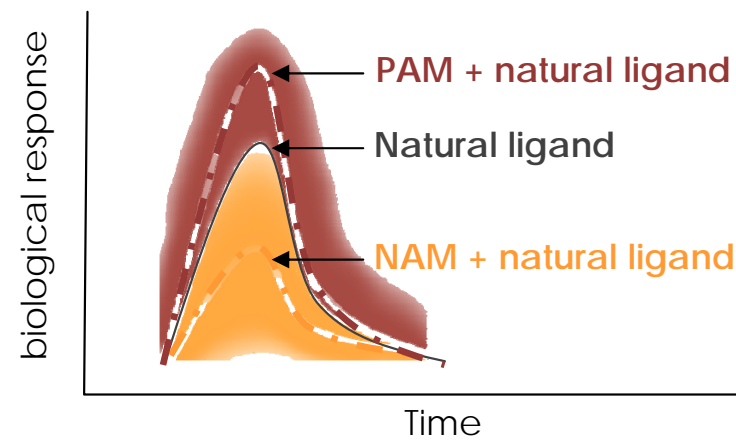
# allosteric modulators (AMs) are different from conventional drugs



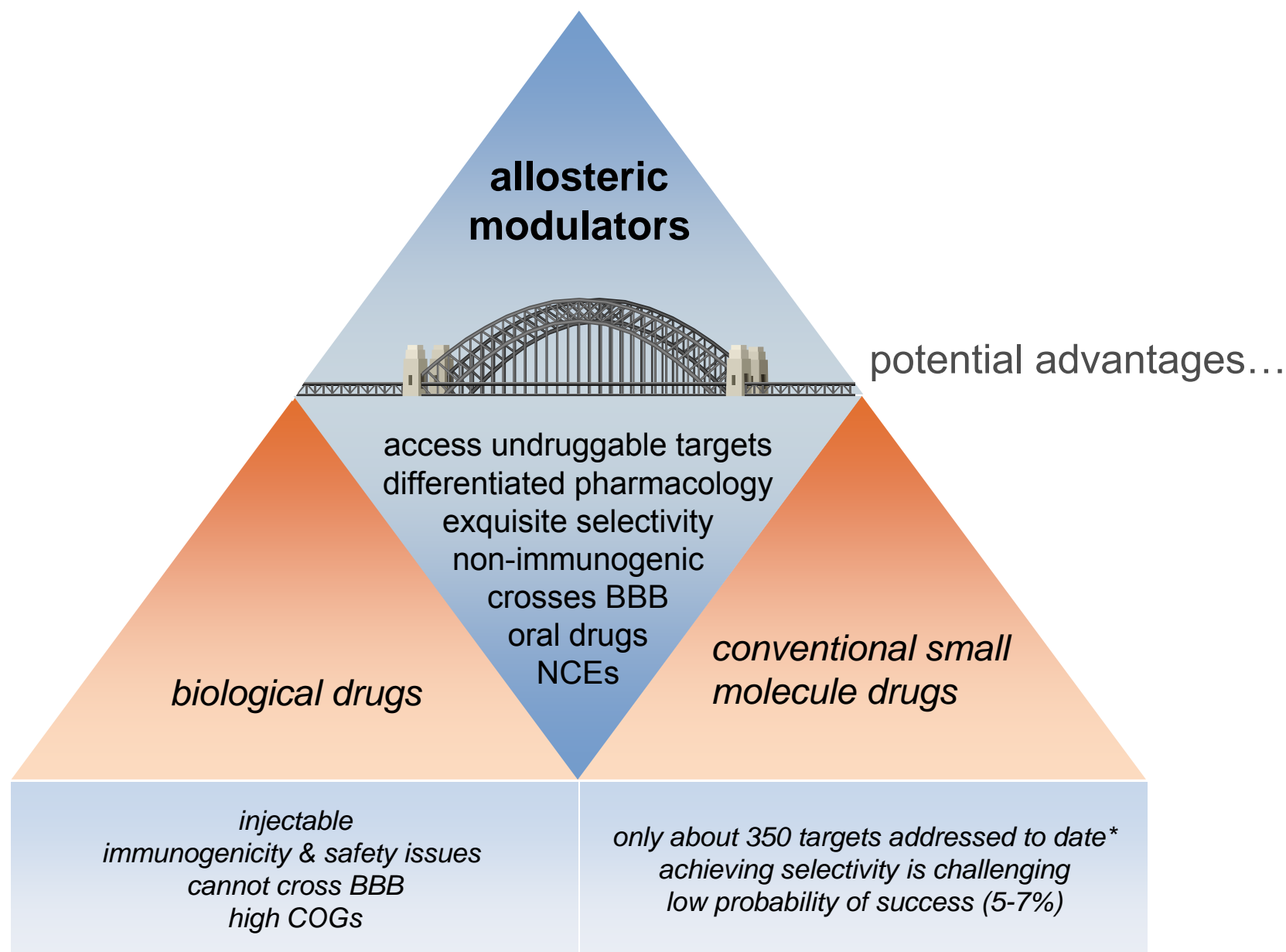
conventional drugs have binary (all or nothing) effect



allostery preserves natural rhythm (dimmer effect)



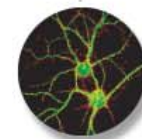
# allostery bridges the divide, offers best of both worlds



# the road less traveled



- Most pharma pursue conventional small molecule approaches
  - A road well-paved by past successes
  - Huge past investments in state of the art HTS and libraries make it hard to leave the well-beaten path
  - Innovation in small molecule discovery required to address undruggable targets
- Potential of AMs to reinvigorate small molecule discovery is generally well recognized BUT AMs are hard to find using conventional routes
  - Traditional screening tools have yielded rare successes
    - More sensitivity required
  - Conventional libraries are biased towards orthosteric (“active site”) drugs
- High barrier to entry
  - Addex is the leader in allosteric discovery and development
    - Specific dedicated expertise & broad experience
    - Proprietary & unique chemistry and screening capabilities
  - Initial investment is significant
    - Addex infrastructure well-established



# the Addex advantage

## allostery-specific screening systems

- High-throughput
- Greater sensitivity
- Greater fidelity
- Fewer false +’s
- Fewer false –’s

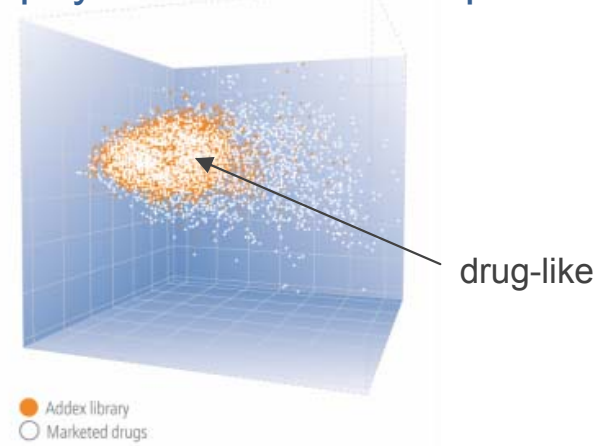


### Addex advantages

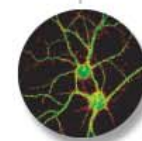
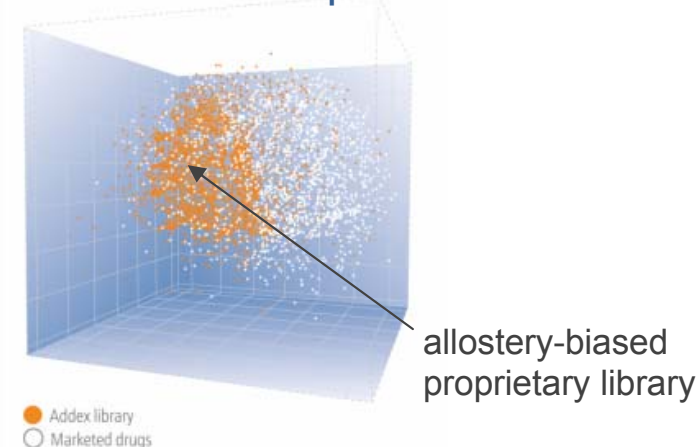
- Addex hit confirmation rate: 70-95%
- Industry hit confirmation rate: 10-30%
- Seamless integration with development
- Strong IP protection

## allostery-biased library

### physicochemical comparison

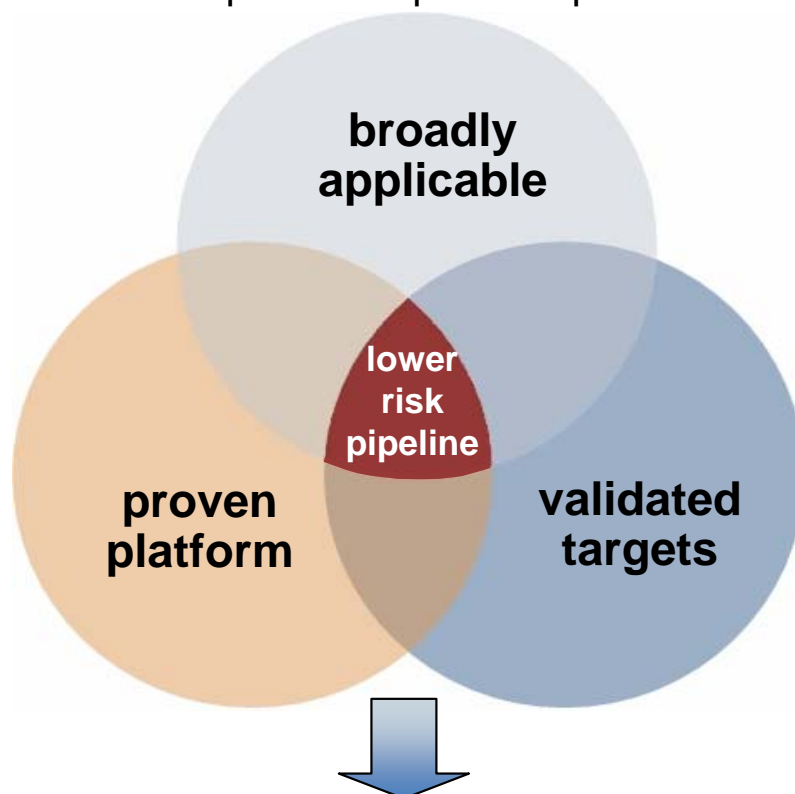


### structural comparison



# Addex is uniquely positioned in the biopharma world

- NCEs on validated targets
  - GPCRs
  - Cytokine receptors & RTKs
  - Enzymes
- Spans multiple therapeutic areas

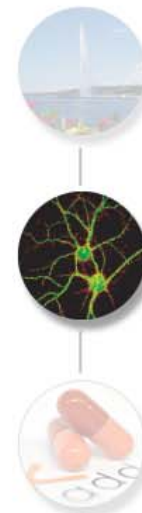


- Proven mechanism
- Clinical validation
- JPI partnership

- Novel NCEs for clinically validated targets (e.g. GLP1)
- First-in-class drugs for well-characterized undruggable targets (e.g. mGluR)
- Lower target risk

## Pipeline – robust and lower risk

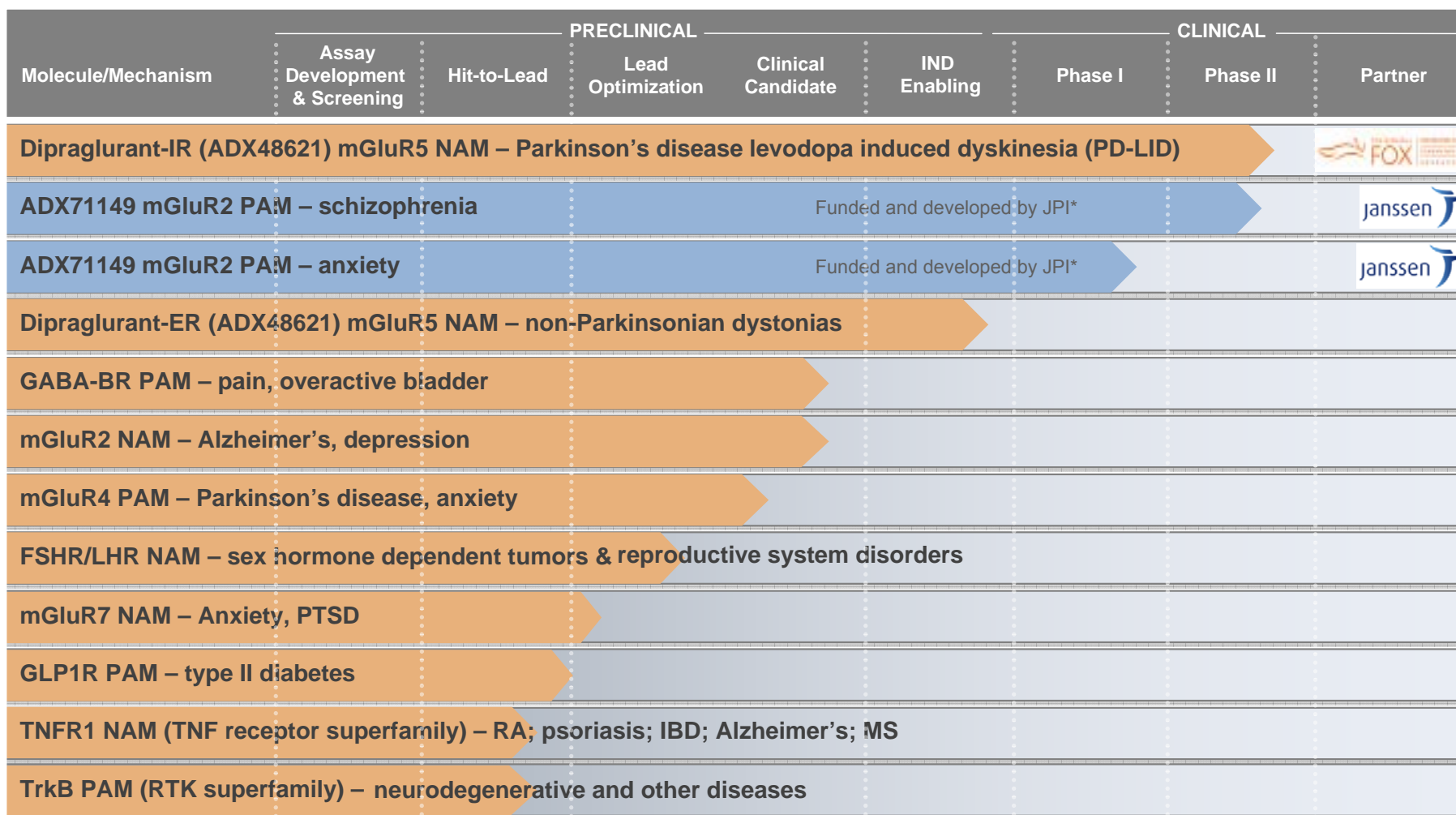
- 2 clinical product candidates
- 8 preclinical programs



# products in development



# pipeline



NAM = negative allosteric modulator (inhibitor)

PAM = positive allosteric modulator (activator)

\*Janssen Pharmaceuticals Inc., formerly Ortho-McNeil-Janssen Pharmaceuticals Inc.

Wholly-owned by Addex

Partnered



# programs





# schizophrenia

- Worldwide antipsychotic drug sales >\$16 billion
  - Antipsychotics are off patent
  - Atypical antipsychotics are going off patent now
- Typical and atypical antipsychotics inhibit dopamine D2 receptor
  - Address positive symptoms
- Significant unmet medical need in Schizophrenia
  - Negative symptoms like depression/anxiety & cognitive dysfunction are inadequately addressed
  - Non-dopaminergic drugs that do not cause prolactinemia (lactation); weight gain; extrapyramidal symptoms are needed
- mGluR2 activation is the first non-dopaminergic mechanism to show clinical efficacy in decades\*
  - Potential to provide a more desirable profile compared to D2 antagonists



\*Source: *Nature Reviews Drug Discovery* 7, 471-472 (2008) & *Nature Med.* **13**, 1102–1107 (2007).

# ADX71149 ongoing EU Phase IIa schizophrenia study

## Part A

- Open label monotherapy for 12 weeks
- 15 subjects with (sub)acute positive symptoms
- 50mg ADX71149 b.i.d increasing to up to 150mg b.i.d

105  
patients

## Part B

- Double-blind placebo-controlled for 10 weeks
- Subjects with stable but symptomatic schizophrenia
- Patients continue on their currently prescribed antipsychotic
- 50mg ADX71149 b.i.d increasing to up to 150mg b.i.d



- Primary outcome measures
  - Safety
  - Tolerability
- Secondary outcome measures
  - Positive and negative syndrome scale (**PANSS**)
  - Clinical Global Impression Schizophrenia (**CGI-SCH**)
  - Subjective well-being under neuroleptics scale (**SWN**)



# dipraglurant (ADX48621) overview

- Dipraglurant inhibits metabotropic glutamate receptor 5 (mGluR5) via negative allosteric modulation (NAM)
- mGluR5 inhibition has clinical or preclinical validation in multiple indications
  - Clinical
    - Parkinson's disease levodopa-induced dyskinesia (PD-LID)
    - Generalized anxiety disorder (GAD)
    - Acute treatment of migraine pain
    - Gastroesophageal reflux disease (GERD)
  - Preclinical
    - Pain
    - Addiction
- Initial Phase I program of dipraglurant-IR successful
  - Three studies: single & multiple ascending doses, gender/food effects
  - 132 subjects studied to date, including 30 older subjects
  - Safety & tolerability support further clinical study
- Dipraglurant-IR is being studied in a Phase IIa trial in 72 PD-LID patients
  - Top-line data 1H12
- Dipraglurant-ER formulation development is complete
  - Preclinical testing indicate it has potential to be twice- or once-daily
  - ER form has potential for non-Parkinsonian dystonias and validated indications above
  - Phase I testing will be initiated in 2012

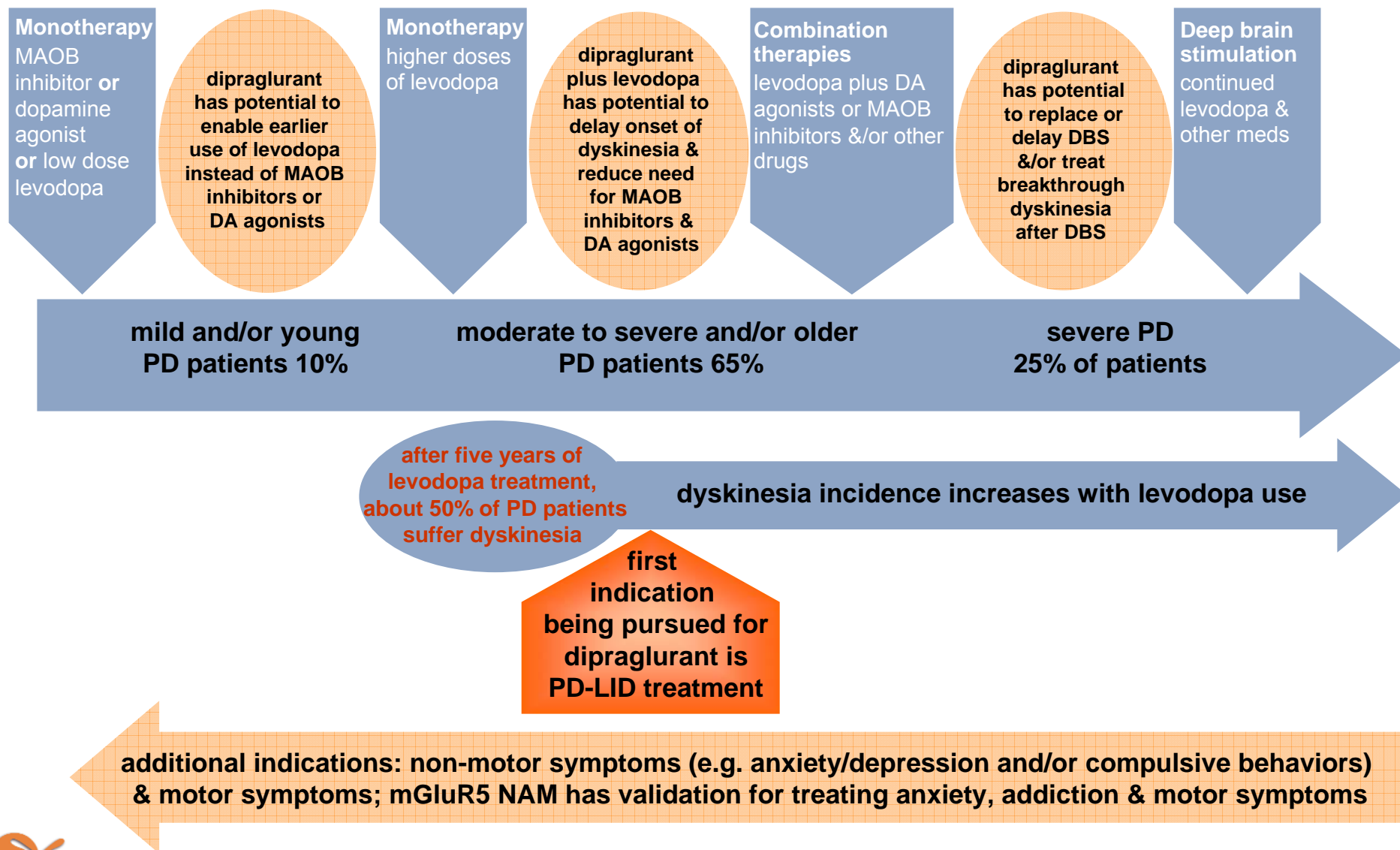


# why PD-LID?

- PD-LID is a growing unmet medical need with no approved treatment
  - 50% of PD patients suffer from LID after five years of levodopa treatment
    - Incidence & severity of LID increases with use of levodopa
  - Clear path to market for this mechanism
    - PD-LID is an FDA - recognized distinct indication with unmet medical need
    - Potential for rapid path to market (fewer patients, shorter trials than in PD)
  - Potential market size of over \$1 billion\*
- Dipraglurant has potential to change PD treatment paradigm
  - Could be used in combination with levodopa earlier in the disease process
  - Could be used to treat non-motor symptoms (anxiety/depression, pain, addiction/compulsive behaviors) – as well as motor symptoms
  - Has potential to reduce use of MAO-B inhibitors and dopamine agonists, which are associated with side effects such as compulsive behavior disorders
- Exceptional preclinical data in PD-LID models
- PK profile of IR formulation similar to that of levodopa
  - Therefore well-suited for acute treatment of LID

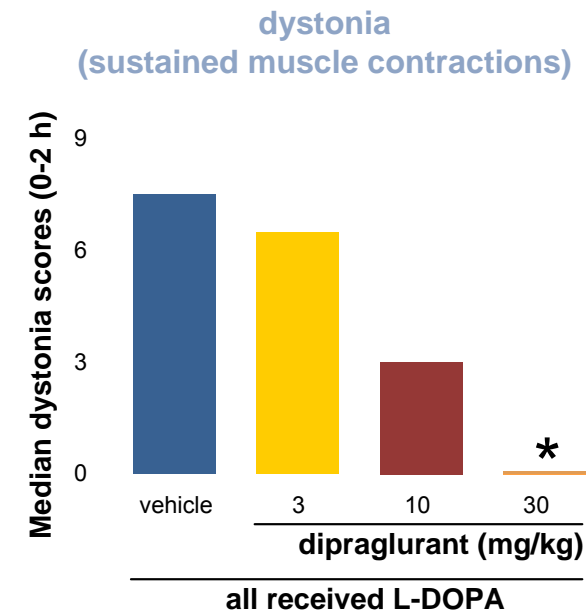
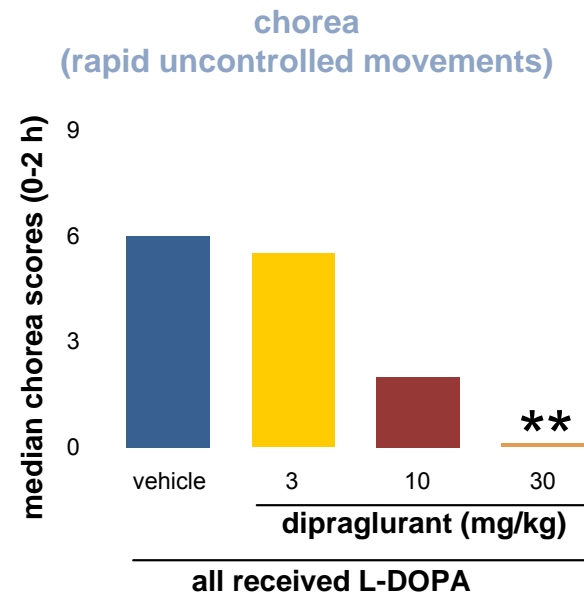


# dipraglurant has potential to change PD treatment paradigm



# dipraglurant (ADX48621) in PD-LID model

- Both components of dyskinesia, chorea and dystonia are exhibited in the Parkinsonian (MPTP-treated) macaques model of levodopa-induced dyskinesia (LID)
- Behavioral assessment began upon levodopa administration
  - trained observers performed video review
  - dyskinesia & PD scoring (10 min every 30 min for 4hrs)
- In this model of PD-LID, dipraglurant effectively reduced the severity of both components of dyskinesia, chorea and dystonia, without affecting the anti-Parkinson's efficacy of levodopa
- Dipraglurant is the first compound ever reported to show efficacy for dystonia in this model**



# EU and US Phase IIa dipraglurant trial for PD-LID

72  
patients

- Randomized, double-blind, placebo-controlled, multi-center trial
- Patients with moderate to severe LID

- Dipraglurant taken with levodopa
- Dipraglurant titration from 50mg q.d. to 100mg t.i.d over 4 weeks
- Individual levodopa regimens remain constant for duration of study (300 -1500mg/day)

- Primary objective: safety & tolerability
- Secondary objective: exploratory efficacy
- Objective evaluation in the clinic on day 1 and 14 & 28
  - Trained observer scores LID severity using **mAIMS** - modified Abnormal Involuntary Movement Scale
- Patient diaries of on & off time
- Unified Parkinson's Disease Rating Scale (**UPDRS**)
- Patient and clinician global impression of change (**PGIC** & **CGIC**)
- Evaluation of mood using Hospital Anxiety & Depression Scale (**HADS**)

top-line data 1H12



# oral GABA-B receptor PAM

- Activation of gamma-aminobutyric acid subtype B (GABA-B) receptor is clinically & commercially validated
  - Generic GABA-B receptor agonist, baclofen, is marketed for spasticity & some spinal cord injuries and used for overactive bladder (OAB)
  - Orthosteric GABA-B receptor agonists showed clinical validation in gastroesophageal reflux disease (GERD)
- GABA-B receptor PAMs are differentiated from baclofen
  - Allosterism may reduce/eliminate development of tolerance
  - Allosterism may reduce other tolerability issues, like somnolence
- Addex GABA-B receptor PAMs have shown efficacy in multiple preclinical models including: pain, osteoarthritis pain and anxiety
- Target indications
  - Pain
  - Overactive bladder (OAB)
- Clinical candidate selection 4Q11
- Regulatory filing for clinical testing 4Q12





## oral mGluR4 PAM

- mGluR4 PAM is one of the most exciting approaches for PD
  - Disease-modifying potential\*
  - Non-dopaminergic
  - Potential for treatment of symptoms
- Addex has **first-in-class brain penetrant oral** small molecule mGluR4 PAM candidates
  - First oral nanomolar mGluR4 PAM to achieve preclinical PoC
  - Clinical candidate selection expected in 1H12



## oral GLP1R PAM

- GLP-1 peptide drugs are marketed for diabetes
  - Marketed drugs are injectable and have been reported to have side effects (immunogenicity, pancreatitis and injection site reactions)
  - Oral PAM mechanism has potential to offer superior product profile
- Addex has identified oral small molecule GLP1R PAM candidates
  - Addex lead series have drug-like properties
  - Addex GLP1R PAMs have demonstrated functional activity in relevant *in vitro* & *in vivo* models, including “diabetic” (db/db) mice oral glucose tolerance test



## oral TNFR1 NAM

- TNF pathway is targeted by five marketed biological drugs generating over \$16 billion in annual revenues
  - Marketed drugs are injectable and have been reported to have side effects (immunogenicity and injection site reactions)
  - Oral selective TNFR1 NAMs have potential to offer a superior product profile
- Addex is optimizing oral small molecule TNFR1 NAMs
  - Addex has developed proprietary, highly sensitive HTS screening & validation systems to identify small molecule allosteric modulators selectively targeting individual members of the **TNF receptor superfamily**
  - TNFR1 NAMs are likely to be brain penetrant – opening the possibility for development of additional indications, including neurological inflammation (Alzheimer's, multiple sclerosis, depression, etc)



## oral TrkB PAM

- Pharmacology of BDNF is well characterized
  - The natural ligands for TrkB receptor are BDNF and NT-4
  - TrkB (an RTK) has been intractable using conventional small molecule approaches & biologicals
  - Allosteric modulation offers a novel way to address this **undruggable** target
- TrkB PAM has broad potential for treating neurodegenerative diseases
  - Parkinson's, Alzheimer's & Huntington's diseases
- Addex has identified oral small molecule TrkB PAM candidates
  - Addex has developed proprietary, highly sensitive HTS screening & validation systems to identify small molecule allosteric modulators selectively targeting individual members of the **receptor tyrosine kinase (RTK) superfamily**
  - Potentially the first small molecules selective for TrkB
  - Lead optimization to begin in 1Q12



## major milestones



Milestones	Timing
Clinical candidate selection for at least one program	1Q12
Dipraglurant-IR mGluR5 NAM Phase IIa PD-LID data	1H12
ADX71149 mGluR2 PAM Phase IIa Schizophrenia data	ND
Start dipraglurant-ER Phase I testing	2012
Regulatory filing for clinical testing of at least one compound	4Q12

# three-pronged strategy for building value



## Focused Execution

- Dipraglurant – Phase II
- GABA-BR PAM
- mGluR4 PAM
- GLP1R PAM
- TrkB PAM
- TNFR1 NAM

## Partnering

- Priorities:
  - dipraglurant
  - mGluR4 PAM
  - mGluR2 NAM/PAM
  - mGluR7 NAM/PAM
- High-value partnerships - single/multi -target & product deals
- Flexible deal structures to balance near-term cash with future product revenues

## Investor Outreach

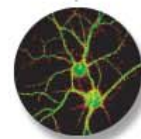
- Increase liquidity
- Broaden shareholder base
- Non-deal roadshows
- Expand analyst coverage
- Media relations

Increasing Shareholder Value

# financials and stock

- Cash through Q3 2013
  - CHF50.2 (US\$63 / €44) million in cash as of June 30, 2011
  - 2011 burn guidance CHF28-32 million
- Traded on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)
- 7,835,878 shares outstanding
  - Biotechnology Value Fund holds 30%
- Five analysts covering:
  - Jefferies: Peter Welford and Philippa Gardner
  - Ladenburg Thalmann: Juan Sanchez
  - Helvea: Olav Zilian
  - Bank am Bellevue: Bruno Eschli
  - Edison: Robin Davison





*allosteric modulators for human health*

*[www.addexpharma.com](http://www.addexpharma.com)*

