# Addex Pharmaceuticals

Vincent Mutel, CEO

BIO CEO & Investor Conference

15 February 2011

# Disclaimer

These materials do not constitute or form part, or all, of any offer or invitation to sell or issue, neither in the United States of America nor elsewhere, or any solicitation of any offer to purchase or subscribe for, any securities, nor shall part, or all, of these materials or their distribution form the basis of, or be relied on in connection with, any contract or investment decision in relation to any securities.

These materials contain forward-looking statements based on the currently held beliefs and assumptions of the management of Addex Pharmaceuticals Ltd, which are expressed in good faith and, in their opinion, reasonable. Forward-looking statements involve known and unknown risks, uncertainties and other factors, which may cause the actual results, financial condition, performance, or achievements of Addex Pharmaceuticals Ltd, or industry results, to differ materially from the results, financial condition, performance or achievements expressed or implied by such forward-looking statements. Given these risks, uncertainties and other factors, recipients of this document are cautioned not to place undue reliance on these forward-looking statements. Addex Pharmaceuticals Ltd disclaims any obligation to update these forward-looking statements to reflect future events or developments.

These materials are strictly confidential and must not be disclosed or distributed to third parties.

# Vision

Goal: allosteric modulators for human health

How: proprietary discovery platform

Focus: CNS, metabolic disorders & inflammation

# Financials & Stock

- Cash through early 2013
  - CHF56.7 (US$54/€42) million in cash as of June 30
  - CHF20 ($20) million raised on Sep 14 from BVF
  - $900,000 grant from The Michael J. Fox Foundation on Sep 8
- Market cap (10 Feb): CHF66 (€50 / US$69) million
- Symbol on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)
- 6,464,809 shares outstanding plus
  - Zero coupon mandatory convertible notes (MCN) held by BVF
    - MCN represent 1,371,069 shares
    - conversion occurs on March 14, 2011
  - Equity incentive plan: 735,175 shares
- Five analysts covering:

| | |
|---|---|
| Jefferies | Peter Welford & Philippa Gardner |
| Helvea | Olav Zilian |
| Bank Vontobel | Andrew C. Weiss & Silvia Schanz |
| Bank am Bellevue | Bob Pooler |
| Edison | Robin Davison |

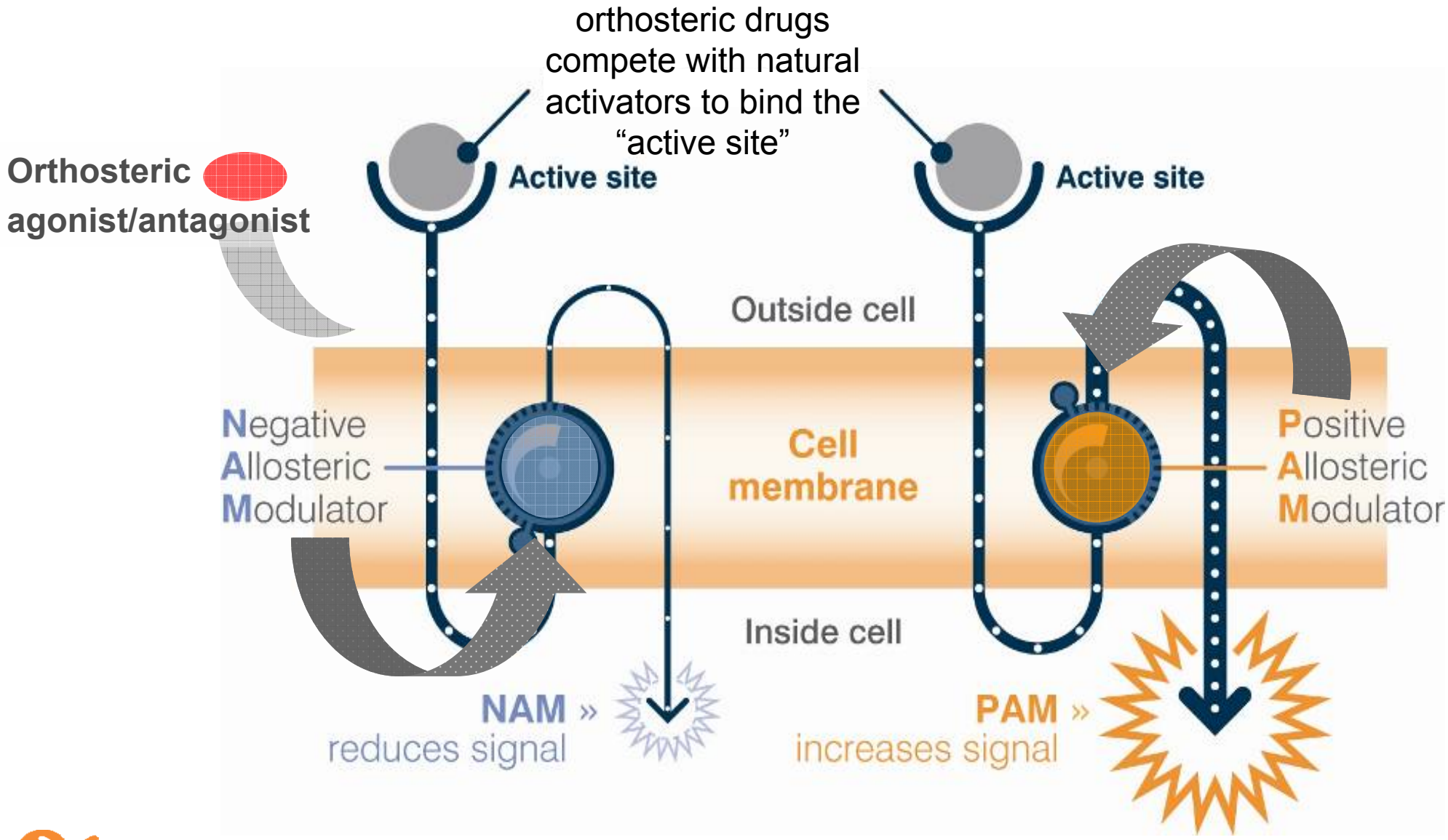
# Small molecule drug discovery is an important bottleneck

- Industry does not have all the discovery tools it needs
  - There is no shortage of exciting targets
  - Incremental innovations help but have largely failed to open the bottleneck
- Allosteric discovery tools represent a paradigm shift
  - Standard techniques are most efficient for finding molecules that bind the “active site” (or “binding pocket”)
    - The active site is a relatively small part of the target receptor
    - The active site can be highly conserved within a receptor family (e.g. mGluR & cytokine receptors), making subtype selectivity via the active site challenging
  - Addex tools identify molecules that bind anywhere on the target
  - Our tools are more sensitive because they can detect molecules that modify receptor activity without fully activating/blocking it

# Allosteric modulators (AM) are an emerging new therapeutic class

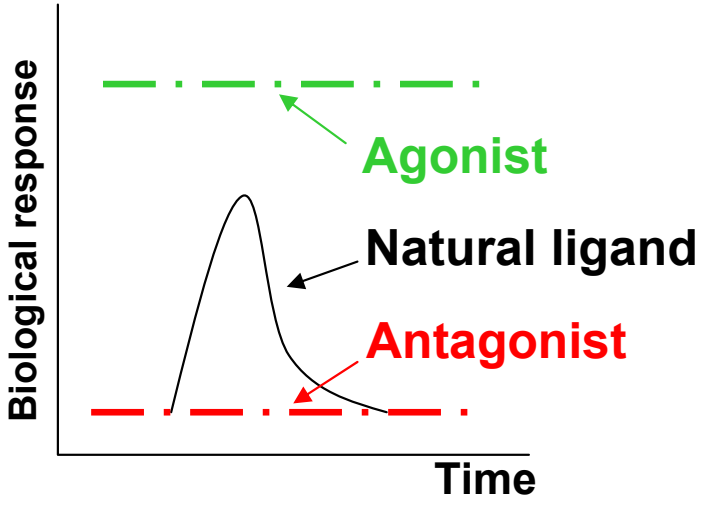
- AM are different from traditional “orthosteric” drugs
  - AM bind to different sites on cell surface receptors
  - AM have structurally different characteristics
- Modulatory not binary
  - Like a dimmer switch not an on/off switch
  - Positive allosteric modulators (PAM) increase activity of receptors
  - Negative allosteric modulators (NAM) inhibit receptor activity
- AM are proven drugs
  - Sensipar/Mimpra cinacalcet (Amgen/NPS) is a PAM of CaSR
  - Selzentry/Celsentri maraviroc (Pfizer) is a NAM of CCR5
- But AM are hard to find with classical tools!

# Allosteric Modulation

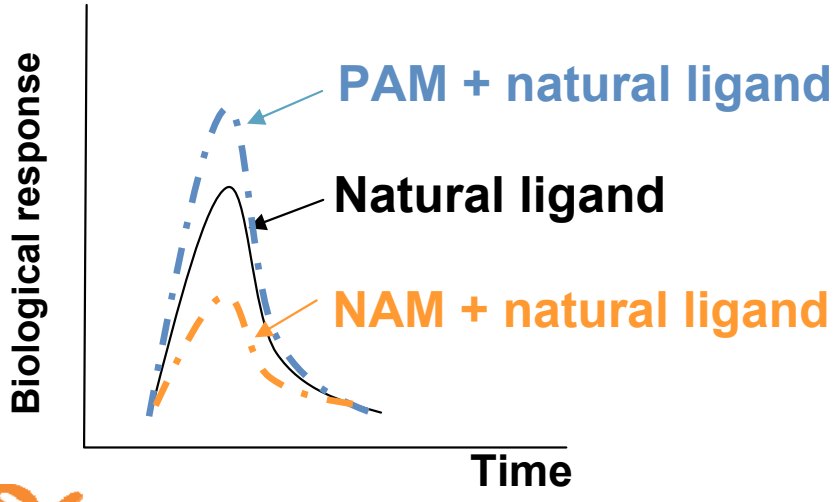


# Allosteric Advantages

**Orthosterics are steady state**




**Allostery preserves natural rhythm**

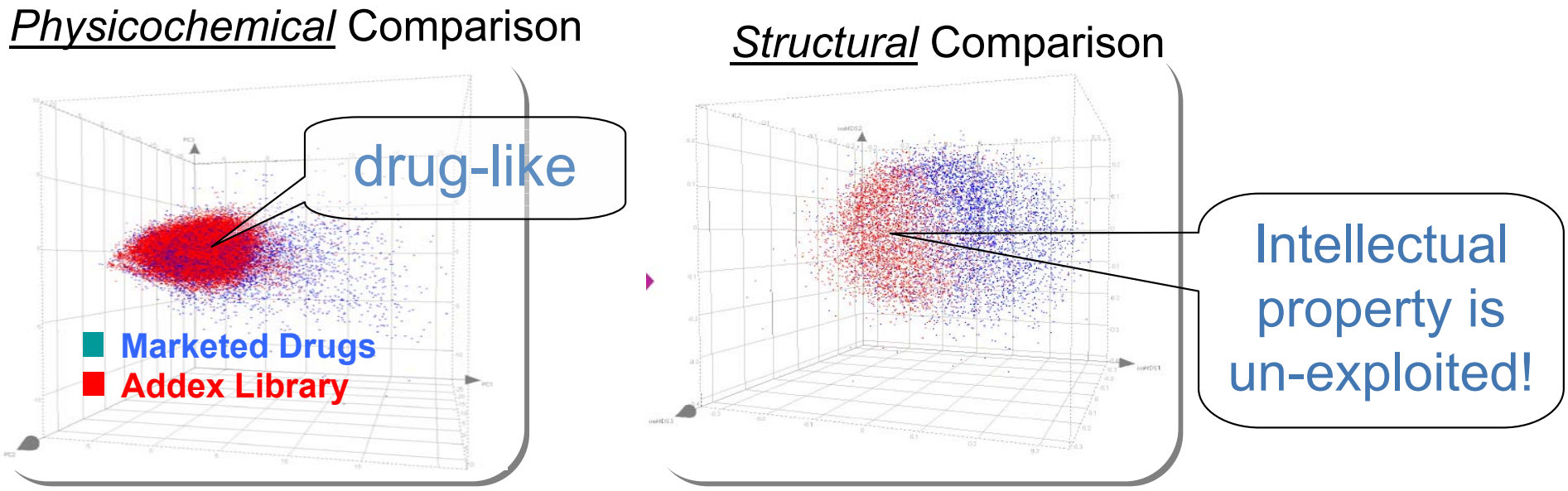



- Better specificity/selectivity for target
  - e.g. mGluRs
- Can target receptors considered intractable for small molecules
  - e.g. GLP-1 and TNF
- Acts like a dimmer not “on/off” switch
  - better control = better drugs

addex Pharmaceuticals

# Platform

- 70,000+ compound allostery-biased library




- Proprietary high throughput screening tools
  - ProxyLite
  - Phoenyx
  - AddeLite

# PIPELINE

| Partner | Molecule / Mechanism | Assay Development & Screening | Hit-to-Lead | Lead Optimization | Preclinical | Phase I | Phase II | Milestone |
|---|---|---|---|---|---|---|---|---|
| | **ADX48621** mGluR5 NAM | Parkinson's Disease Levodopa Induced Dyskinesia (PD-LID) partially funded by The Michael J. Fox Foundation | | | | | | Start PhII 1Q11 |
| | | Dystonia | | | | | | Start PhIIa 2H11 |
| Ortho-McNeil-Janssen | **ADX71149** mGluR2 PAM | Schizophrenia funded & developed by OMJPI* | | | | | | Start PhIIa 1Q11 |
| | | Anxiety funded & developed by OMJPI* | | | | | | |
| | **ADX68692** FSHR NAM | Endometriosis | | | | | | |
| | **ADX71943** GABA-B PAM | Osteoarthritic Pain | | | | | | |
| Merck & Co. | **ADX63365** mGluR5 PAM | Schizophrenia ‡ funded & developed by Merck | | | | | | |

**NAM** = negative allosteric modulator (an inhibitor)
**PAM** = positive allosteric modulator (an activator)

‡ and undisclosed additional indications
* Ortho-McNeil-Janssen Pharmaceuticals, Inc., a Johnson & Johnson subsidiary

addex Pharmaceuticals

# DISCOVERY

| Partner | Molecule / Mechanism | Assay Development & Screening | Hit-to-Lead | Lead Optimization | Preclinical | Phase I | Phase II | Milestone |
|---|---|---|---|---|---|---|---|---|
| | mGluR2 NAM | Alzheimer's / Depression | | | | | | |
| Merck & Co. | mGluR4 PAM | Parkinson's Disease ‡ funded by Merck | | | | | | CNS |
| | mGluR7 NAM | Depression<br>Post Traumatic Stress Disorder | | | | | | |
| | Orexin 2R NAM | Sleep Disorders | | | | | | |
| | GLP1 PAM | Type II Diabetes | | | | | | Metabolic Disorders |
| | GIPR PAM | Type II Diabetes | | | | | | |
| | TNFR1 NAM (CD120a) | Rheumatoid Arthritis, Psoriasis, Inflammatory Bowel Disease<br>Alzheimer's, Multiple Sclerosis | | | | | | |
| | A2A PAM | Psoriasis, Osteoarthritis | | | | | | Inflammation |
| | IL1R1 NAM (CD121a) | Gout, Type II Diabetes | | | | | | |

**NAM** = negative allosteric modulator (an inhibitor)
**PAM** = positive allosteric modulator (an activator)

‡ and undisclosed additional indications

addex Pharmaceuticals

# Platform Performance

- Addex has received partnering revenue every year since 2004
- Cash inflows generated to date: CHF44 (US$45) million
- All three partnerships are fully funded by our partners
- Addex is eligible for up to about $1 billion in milestones plus royalties

| Summary of Partnerships | | | | | | | |
|---|---|---|---|---|---|---|---|
| Partner | Product | Indication(s) | Status at signing | Upfront Cash | Revenues to date | Total Milestones | Royalty |
| Ortho-McNeil-Janssen | mGluR2 PAM ADX71149 | Anxiety & schizophrenia* | Hit-to-Lead (Dec 2004) | €3 | €5.2 | €112 | low double-digit |
| Merck & Co., Inc. | mGluR4 PAM | Parkinson's disease* | Hit-to-Lead (Dec 2007) | $3 | $2.5 | $167.5 | ND |
| Merck & Co., Inc. | mGluR5 PAM ADX63365 | Schizophrenia* | Clinical Candidate (Jan 2008) | $22 | - | $680 | ND |

*** and undisclosed indications**

# Partnering Priorities

- mGluR5 NAM (ADX48621 & backups)
  - PD-LID / dystonia
  - fragile X / autism
  - anxiety
  - depression
  - GERD
  - pain
- FSH receptor NAM (ADX68692)
  - endometriosis
  - prostate cancer
- mGluR2 NAM
  - Alzheimer's disease
  - depression

# ADX48621 Overview

- Metabotropic glutamate receptors (mGluR)
  - Like dopamine & serotonin, glutamate is a major neurotransmitter and has similar commercial/therapeutic potential
    - Blockbuster antipsychotics work via dopamine receptors
    - Blockbuster antidepressants (SSRIs) work via serotonin receptors
  - ADX48621 inhibits mGluR5 via negative allosteric modulation
  - mGluR5 inhibition is clinically validated in multiple indications including
    - Parkinson's disease levodopa-induced dyskinesia (PD-LID)
    - Gastroesophageal reflux disease (GERD)
    - Generalized anxiety disorder (GAD)
- Initial Phase I program of ADX48621 completed sucessfully
  - Three studies: SAD, MAD, gender & food effects
  - 132 subjects studied to date, including 30 older subjects
  - Safety & tolerability support further clinical study
- Exceptional preclinical data in PD-LID model

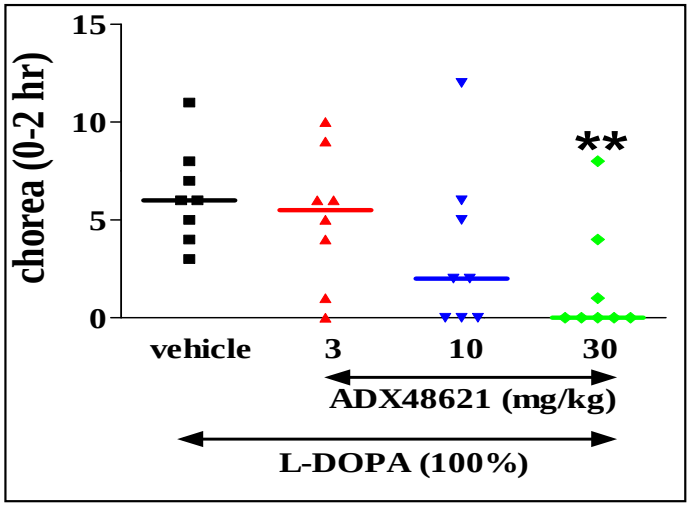
# Why PD-LID & Dystonia?

- PD-LID
  - Clinically validated by another mGluR5 NAM (AFQ056 from Novartis*)
  - Attractive specialty pharma commercial opportunity
- Dystonia (abnormal sustained muscle contractions)
  - Third most common movement disorder (following PD and essential tremor)
  - ADX48621 is the first drug-candidate to report efficacy for dystonia in LID models
- The Michael J. Fox Foundation grant
  - MJFF advisors, PD key opinion leaders (KOLs), reviewed the ADX48621 preclinical data and Ph IIa trial design
  - Publicity & KOL familiarity (via grant review) with ADX48621 could facilitate enrollment

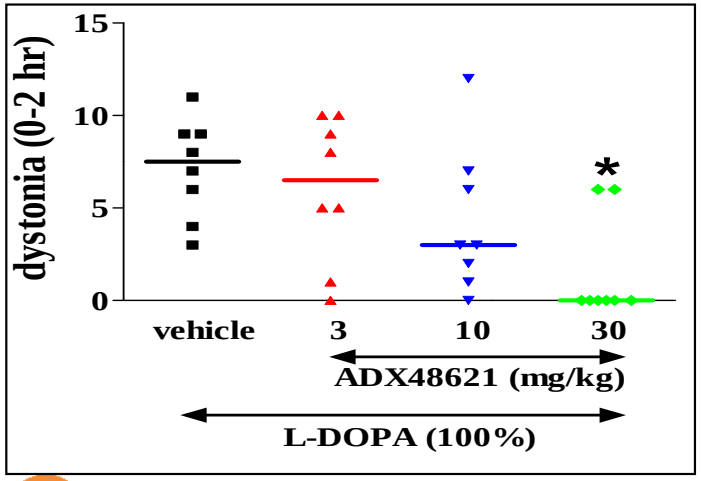
*for data: http://bit.ly/dgEVbH

# ADX48621 in the MPTP model

Chorea
(rapid uncontrolled movements)




Dystonia
(sustained muscle contractions)




- Parkinsonian macaques with levodopa induced dyskinesia (LID) received
  - ADX48621 or vehicle (e.g. placebo)
  - levodopa
- Behavioral assessment began upon levodopa administration
  - trained observers performed video review
  - dyskinesia & PD scoring (10 min every 30 min for 4hrs)
    - lower scores (left axis) indicate fewer symptoms/disability
    - dyskinesia symptoms are side effects from levodopa
- ADX48621 is the first compound reported to show statistically significant efficacy for dystonia

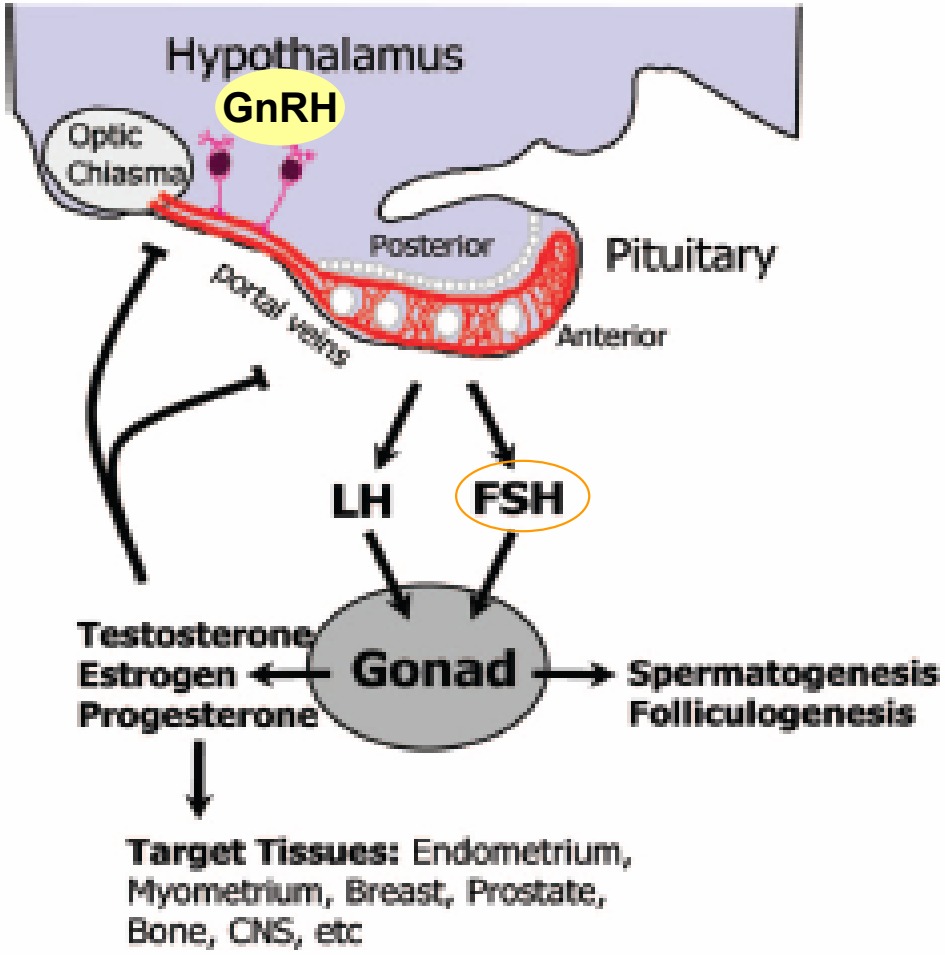
addex Pharmaceuticals

# ADX48621 PD-LID Trial

Study ADX48621-201 (n=90)

- Phase IIa trial in the EU and US
  - Randomised, double-blind, placebo-controlled, muliticenter
  - Patients with moderate to severe LID
  - Treatment duration 4 weeks
- Placebo or ADX48621
  - Taken with 3 of the patients' daily levodopa doses
  - Dose titration for 50mg o.d. to 100mg t.d.s over the 4 weeks
- Primary objective: safety & tolerability
- Secondary objective: exploratory efficacy
  - Objective evaluation in the clinic
    - Before starting treatment and at weeks 2 and 4
    - Trained observer scores LID severity
    - Abnormal Involuntary Movement Score (AIMS)
  - Patient diaries
    - PD rating scales (including dystonia)
    - Evaluation of mood

# FSHR NAM




**GnRH, FSH & Endometriosis**

- FSH NAM offer a more specific approach to estradiol control compared to GnRH antagonists
- Endometriosis is linked to excess estradiol
- GnRH antagonists have been shown to reduce estradiol & endometriosis symptoms
- FSH is downstream from GnRh and is more directly responsible for production of estrogen/estradiol

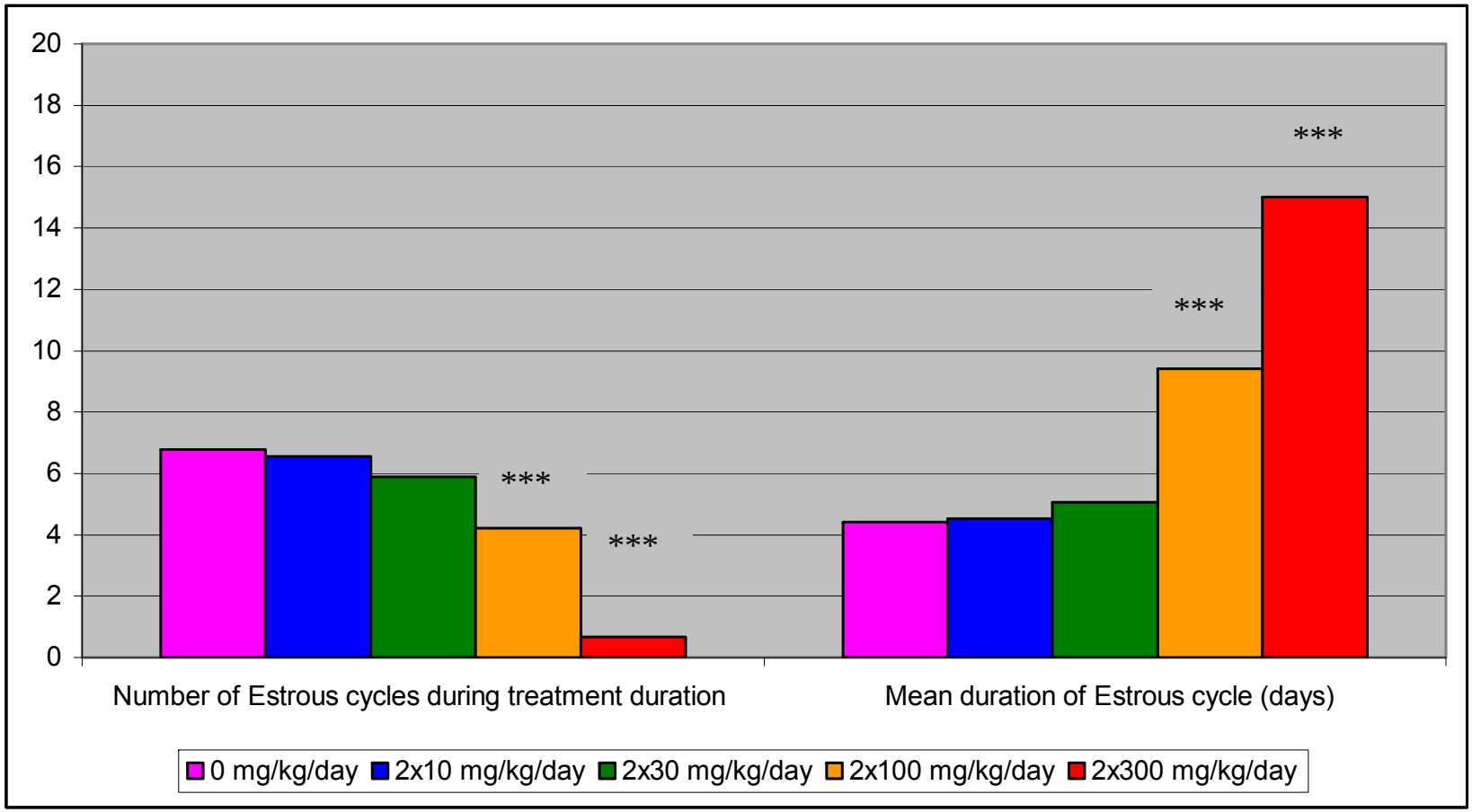
**ADX68692**

- ADX68692 is a follicle stimulating hormone receptor (FSHR) NAM
- Orally available non-steroid molecule with drug-like characteristics
- In late preclinical development
- ADX68692 is available for partnering

addex Pharmaceuticals

# FSHR NAM efficacy in rats

## 4 weeks treatment - effect on estrus cycle duration




ADX68692 disrupts the estrus cycle leading to complete blockade at high dose

addex Pharmaceuticals

# mGluR2 NAM

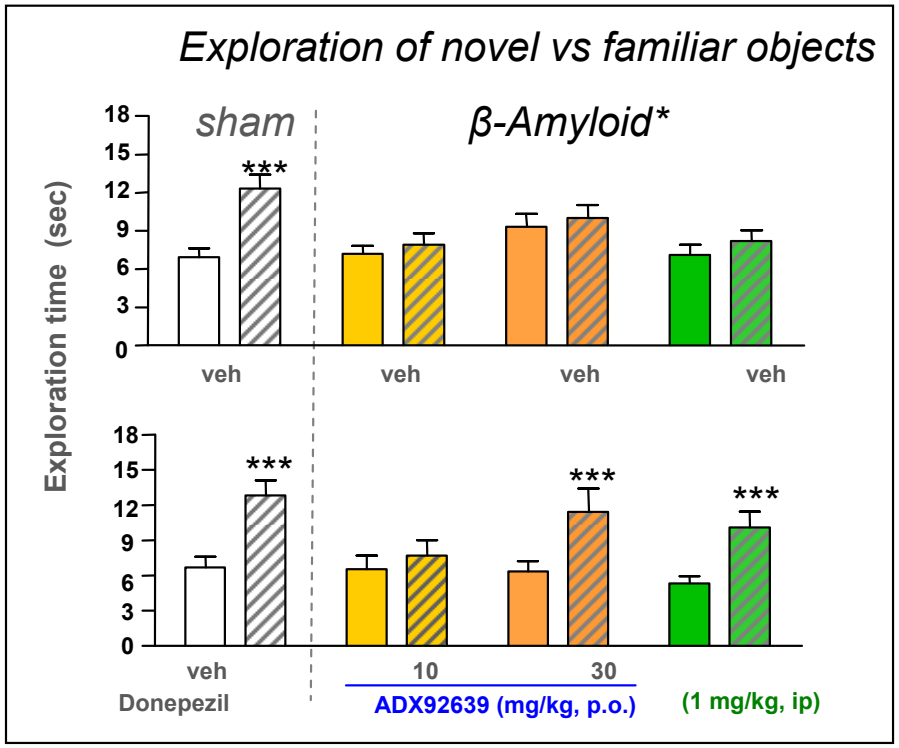
- Data from Addex and others show that mGluR2 inhibition can reverse cognitive deficit in preclinical models
  - in models of cognitive deficit
  - in physiologically relevant models of AD
  - mechanism may be complementary to marketed drugs
- Published data suggest that mGluR2 inhibition may reduce generation of beta-amyloid* and may be synergistic with donepezil**
  - mGluR2 NAM may be disease modifying
  - greater magnitude of effect possible via combination therapy

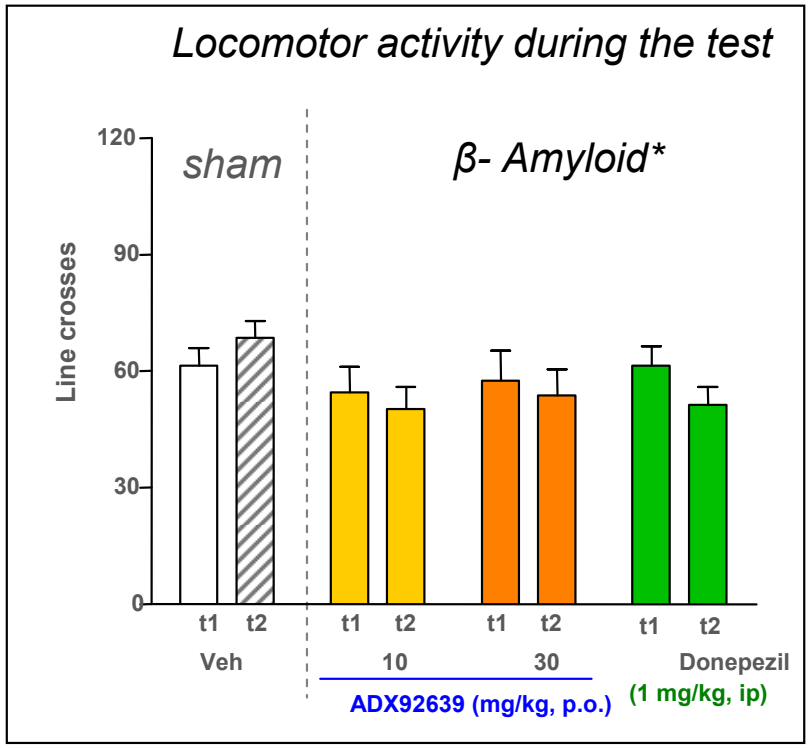
*_The Journal of Neuroscience_, March 17, 2010; 30(11):3870-3875

**_Bioorganic & Medicinal Chemistry Letters,_ Dec 1, 2010; 20(23):6969-6974

# ADX92639 reverses β amyloid-induced deficit

Rat novel object recognition (NOR) test




*Single administration into the lateral ventricle of 8 µl solution
Final concentration of β amyloid = 2 mg/ml

Familiar object

Novel object

**ADX92639 reverses cognitive impairment induced by intracebroventricular (icv) β-amyloid in the rat NOR test after oral administration:**

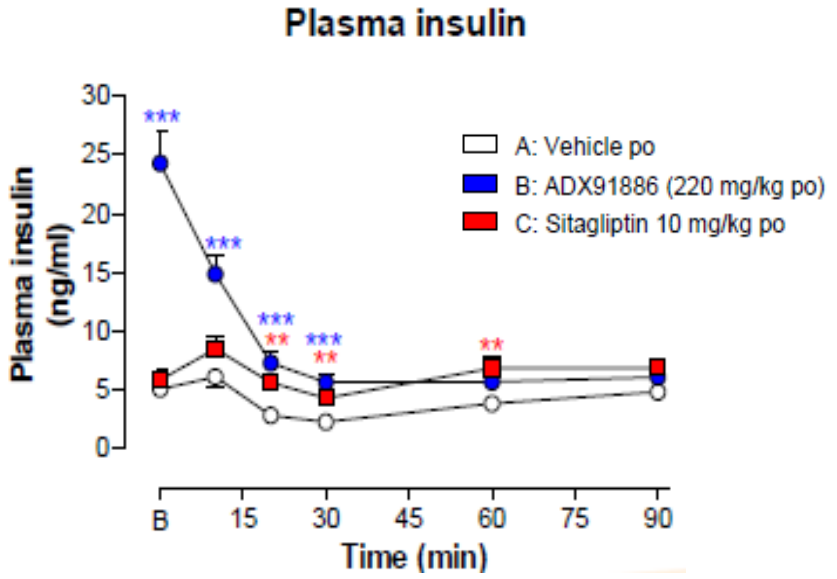
- **Full and donepezil-like reversal of the memory deficit at 30 mg/kg**
- **No effect on locomotor activity observed during the test**

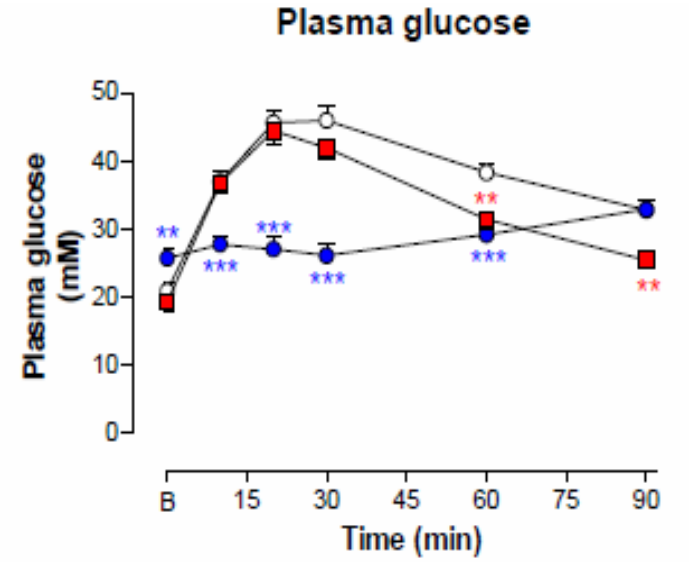
addex Pharmaceuticals

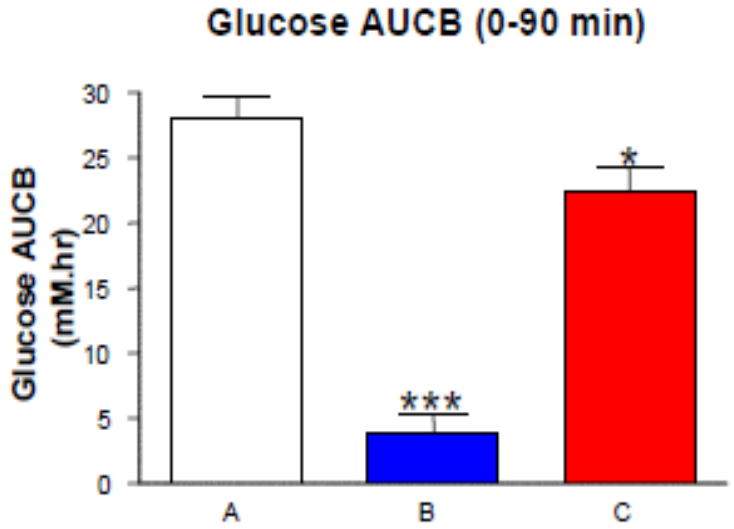
# Oral GLP1R PAM in ogtt test in diabetic db/db mouse model

- db/db knockout mice have no leptin receptors
  - develop human Type II diabetes mellitus
  - develop hypertension and obesity
  - have disrupted circadian blood pressure (BP) rhythm
- Oral Glucose Tolerance Test (ogtt)
  - Diabetic db/db KO mice received orally
    - ADX91886 GLP1R PAM
    - sitagliptin (Januvia) DPP IV inhibitor
    - or vehicle
  - 15 min later oral glucose (2 g/kg) was administered
  - Blood glucose + insulin levels were measured: 10; 20; 30; 60; 90 min after glucose administration

# GPL1R PAM vs. sitagliptin in ogtt test in diabetic db/db mice



# Management & Boards

## *Executive Management*

Vincent Mutel, *Chief Executive Officer*
Tim Dyer, *Chief Financial Officer*
Charlotte Keywood, *Chief Medical Officer*
Sonia Poli, *Head of Non-Clinical Development*
Laurent Galibert, *Head of Inflammation & Metabolic Disorders*
Jean-Philippe Rocher, *Head of Core Chemistry*
Robert Lütjens, *Head of Core Biology*
Tatiana Carteret, *Head of Human Resources*
Chris Maggos, *Business Development & Communication*

## *Board of Directors*

André J. Mueller, *Chairman*
Vincent Mutel, *Vice Chairman & CEO of Addex*
Andrew Galazka, *SVP Scientific Affairs, Merck-Serono*
Ray Hill, *former Head of EU Licensing, Merck & Co., Inc.*
Vincent Lawton, *former MD of Merck Sharp & Dohme U.K.*
Beat E. Lüthi, *CEO of CTC Analytics*
Antoine Papiernik, *Sofinnova Partners*

## *Scientific Advisory Board*

George F. Koob, *Ph.D., Chairman*
Bernhard Bettler, *Ph.D.*
Mark A. Geyer, *Ph.D.*
Barbara J. Mason, *Ph.D.*

*allosteric modulators for human health*

www.addexpharma.com

addex
Pharmaceuticals