

# Nlife, the future of siRNAs

Guillem Laporta

## Nlife, the company



nLife is a Spanish start-up that is currently developing a small interfering RNA (siRNA) platform for the treatment of Central Nervous System (CNS) diseases by intranasal delivery. Its business model is based on early R&D collaborations, co-development and licensing of its own compounds. It is an interesting and paradigmatic case of a small and yet ambitious company which avoided shutdown in 2010 and is now moving its main compound towards Phase I in humans.

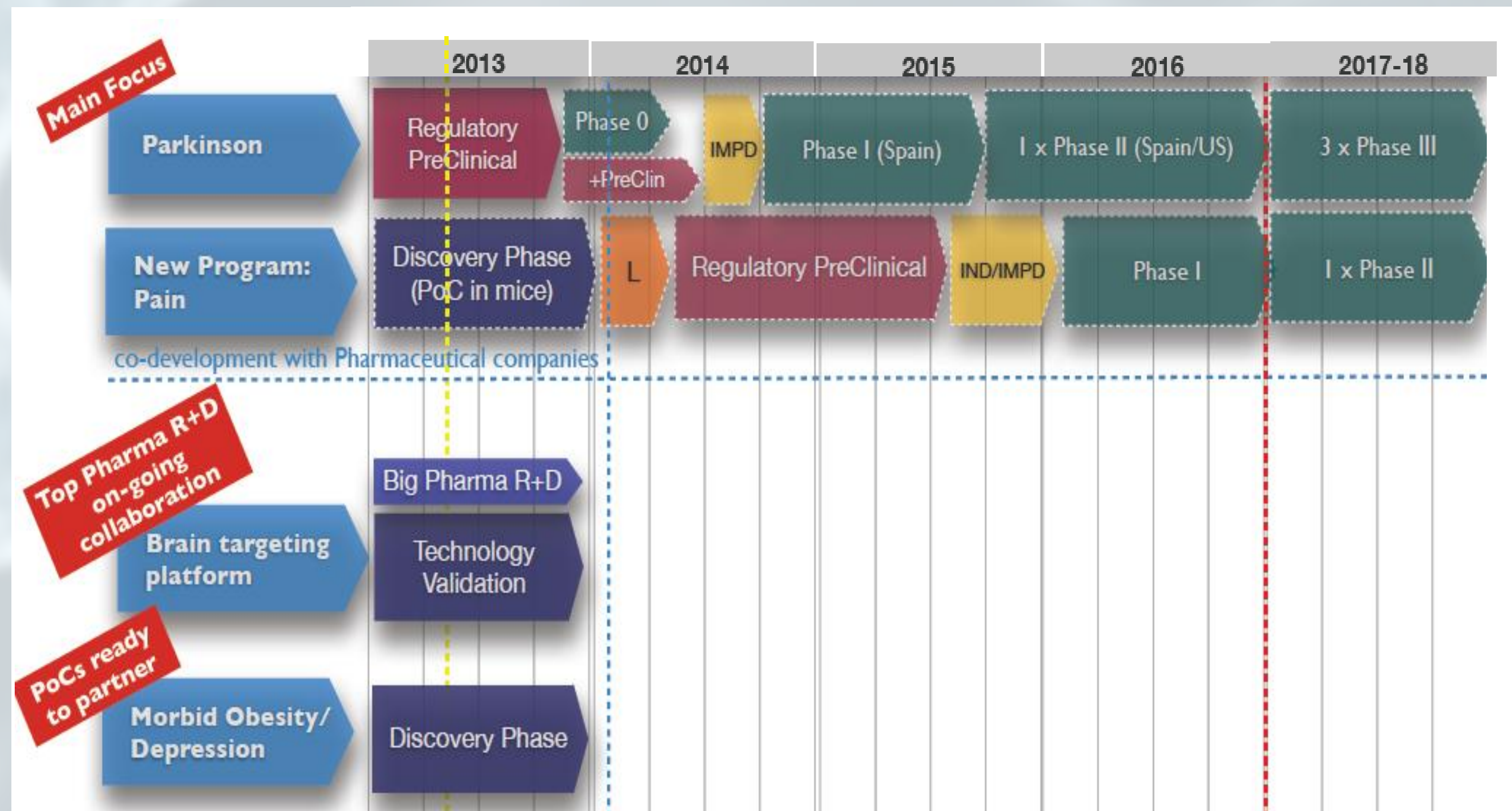


Figure 1. Nlife Pipeline as of April 2013.

## Industry outlook

### CNS market

By 2018 the CNS market will reach \$133Bn, primarily driven by increase in aging population. However, as branded drugs continue to expire, big pharmas are experiencing generic erosion. This is an opportunity for nLife since pharmaceutical corporations are seeking novel CNS drugs to overcome revenue loss.

| Brand name | Indication             | Company     | Expiry date (product patent) | Revenue (M) |
|------------|------------------------|-------------|------------------------------|-------------|
| Abilify    | Schizophrenia          | Otsuka      | 2015                         | \$ 7.254    |
| Seroquel   | Schizophrenia          | AstraZeneca | 2012                         | \$ 6.175    |
| Zyprexa    | Schizophrenia          | Eli Lilly   | 2011                         | \$ 4.622    |
| Ciprexal   | Depression             | Lundbeck    | 2012                         | \$ 3.577    |
| Aricept    | Alzheimer              | Eisai       | 2010                         | \$ 2.557    |
| Risperdal  | Schizophrenia          | Janssen     | 2008                         | \$ 1.583    |
| Exelon     | Alzheimer              | Novartis    | 2014                         | \$ 1.067    |
| Geodon     | Schizophrenia          | Pfizer      | 2012                         | \$ 1.022    |
| Comtan     | Parkinson              | Novartis    | 2013                         | \$ 968      |
| Vyvanse    | Hyperactivity disorder | Shire       | 2023                         | \$ 805      |

Figure 2. Expiry date for blockbuster CNS drugs.

### Oligo industry

In 2010 the iRNA industry collapsed as drug giants exited internal oligo R&D. However, recent deals, an increasing pipeline and new oligo game-changing innovations have prompted a renewed interest in the oligo platform. Pharmas see oligo companies as a way to capitalize the money invested in their own compounds.

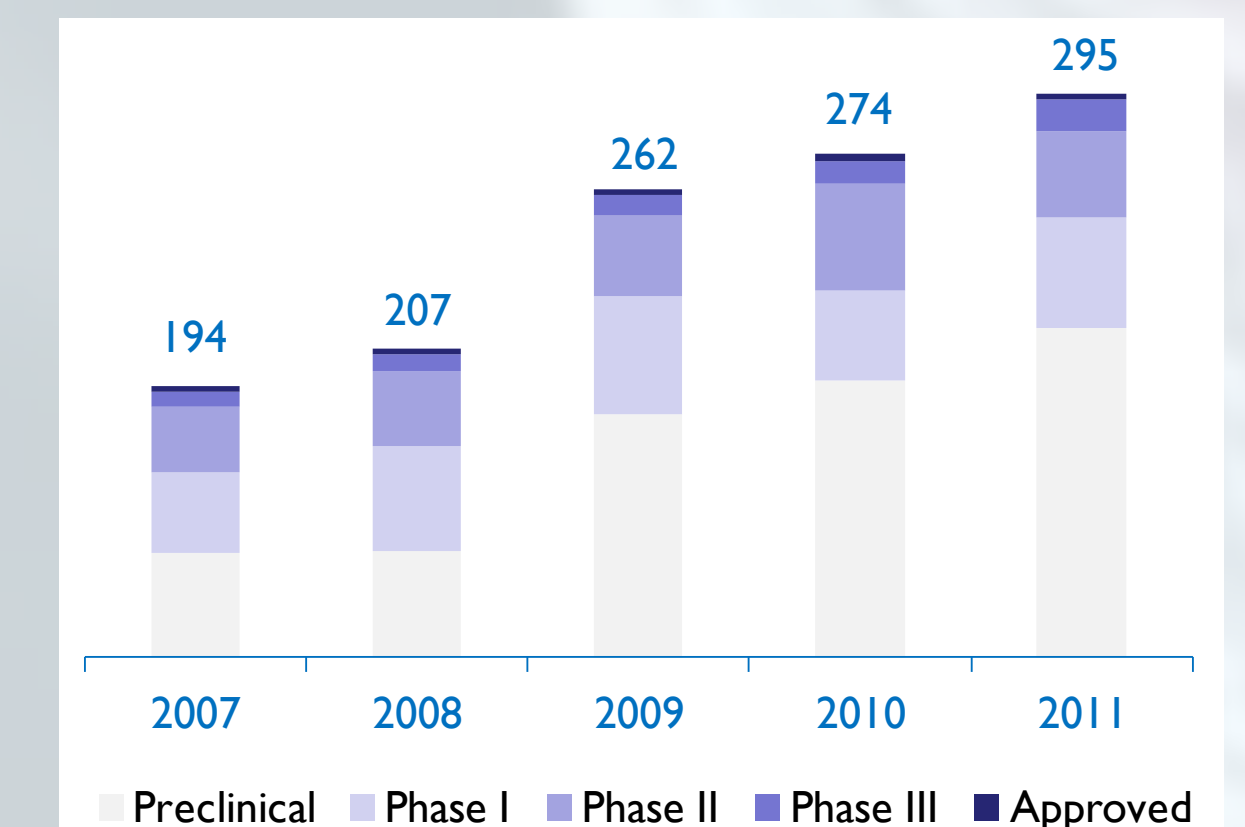


Figure 3. World pipeline of the oligo industry.

### Intranasal delivery

Nasal delivery seems to be a favorable way to circumvent the BBB allowing the direct drug delivery in the biophase of the CNS. Some other advantages include rapid drug absorption, quick onset of action, avoidance of the gastrointestinal and hepatic metabolism, non-invasiveness and painlessness.

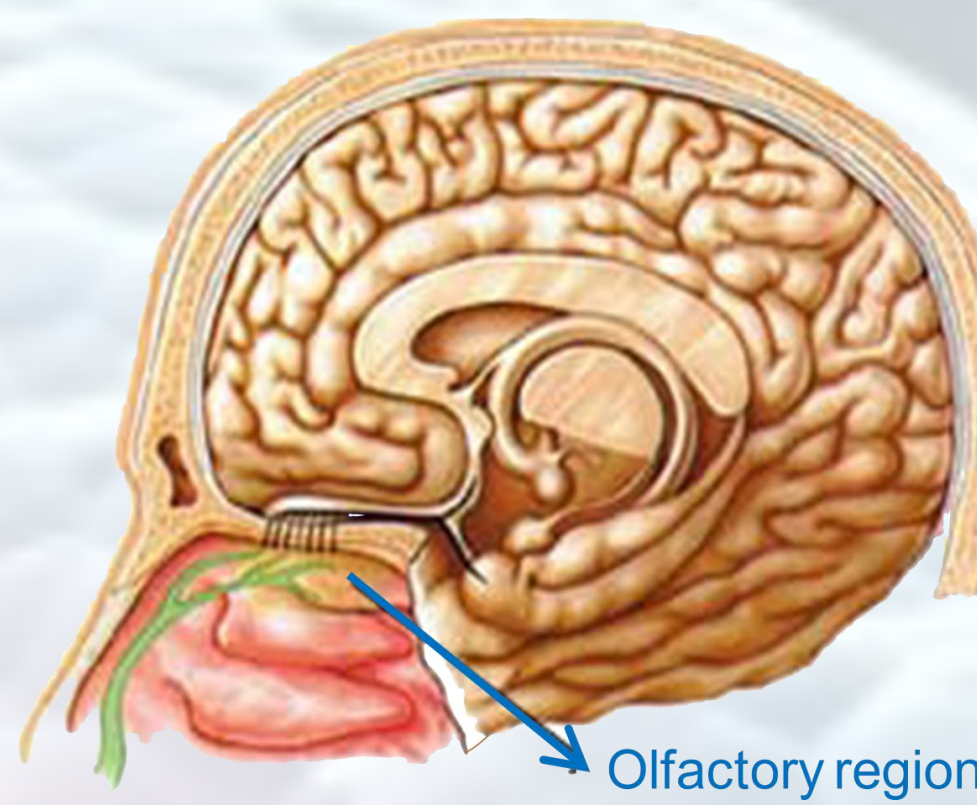


Figure 4. Drug absorption from the nasal cavity to the brain takes place along the olfactory region.

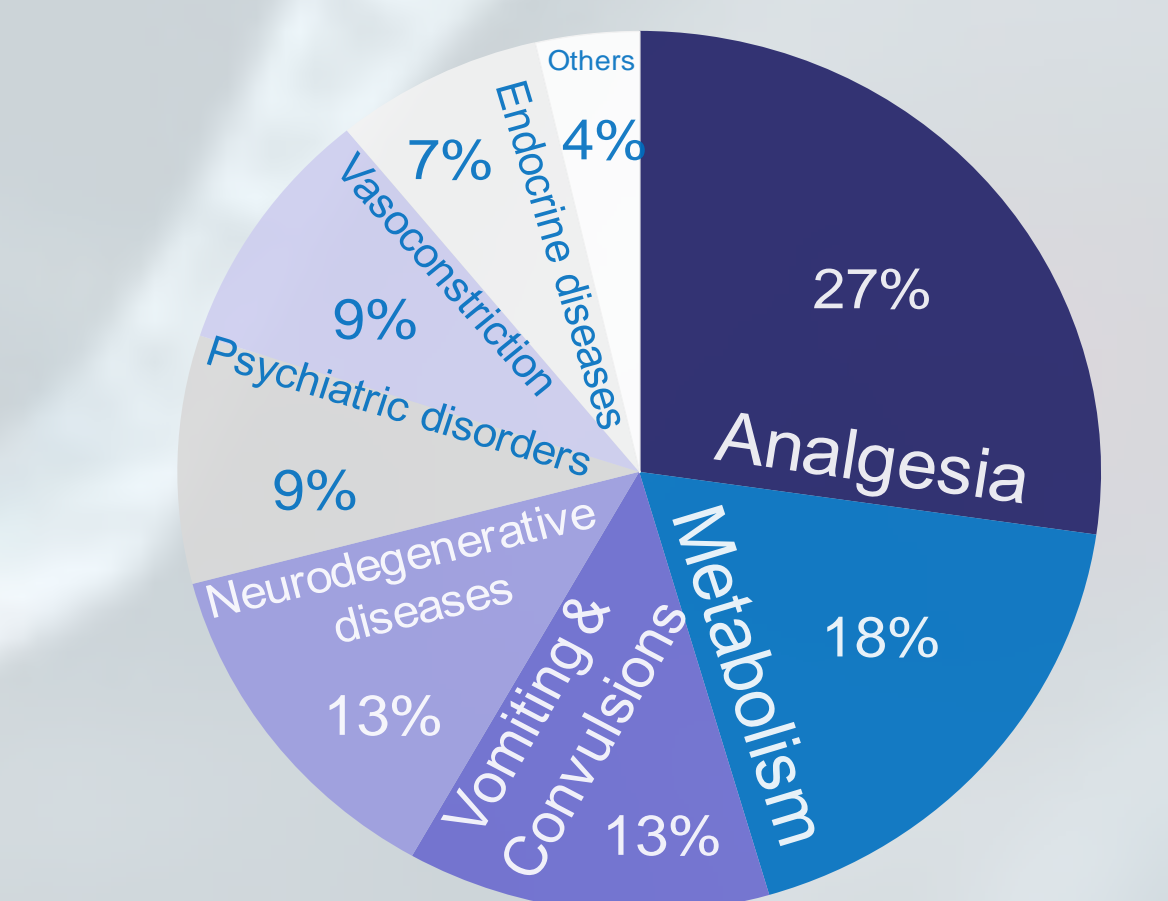


Figure 5. Intranasal world pipeline for CNS diseases by indication.

## Technological platform

The main variables that need to be defined when developing a therapeutic compound through this platform are:

- The neurotransmitter transporter used for targeting
- The ligand acting as a selectivity agent for the neurotransmitter transporter.
- The target mRNA to be silenced.

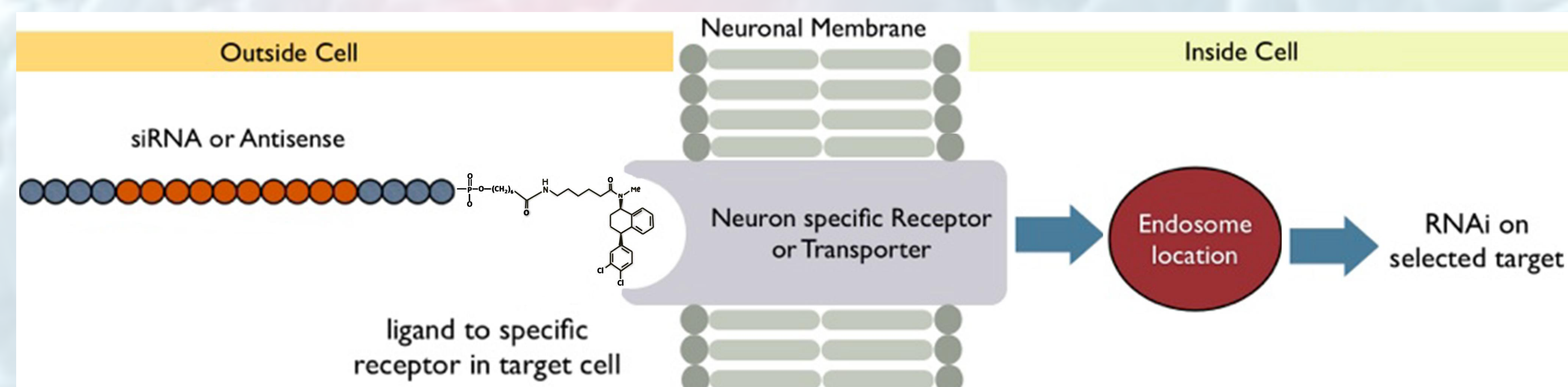


Figure 6. The siRNA conjugate interacts with the neuronal receptor and is endocytosed. Inside the cell, the siRNA vesicle fuses with the endosome. After endosomal escape, silencing takes place.

## Scientific evidence in Major Depressive Disorder

MDD is believed to be caused by serotonin deficiency. nLife's antidepressant strategy is based on the use of siRNAs to reduce the expression of presynaptic 5-HT<sub>1A</sub> receptors. These receptors trigger a negative feedback on the production of serotonin. The siRNAs are coupled to molecules of sertraline, which act as a SERT ligand and allow for the selective accumulation of the siRNAs in presynaptic serotonergic neurons.

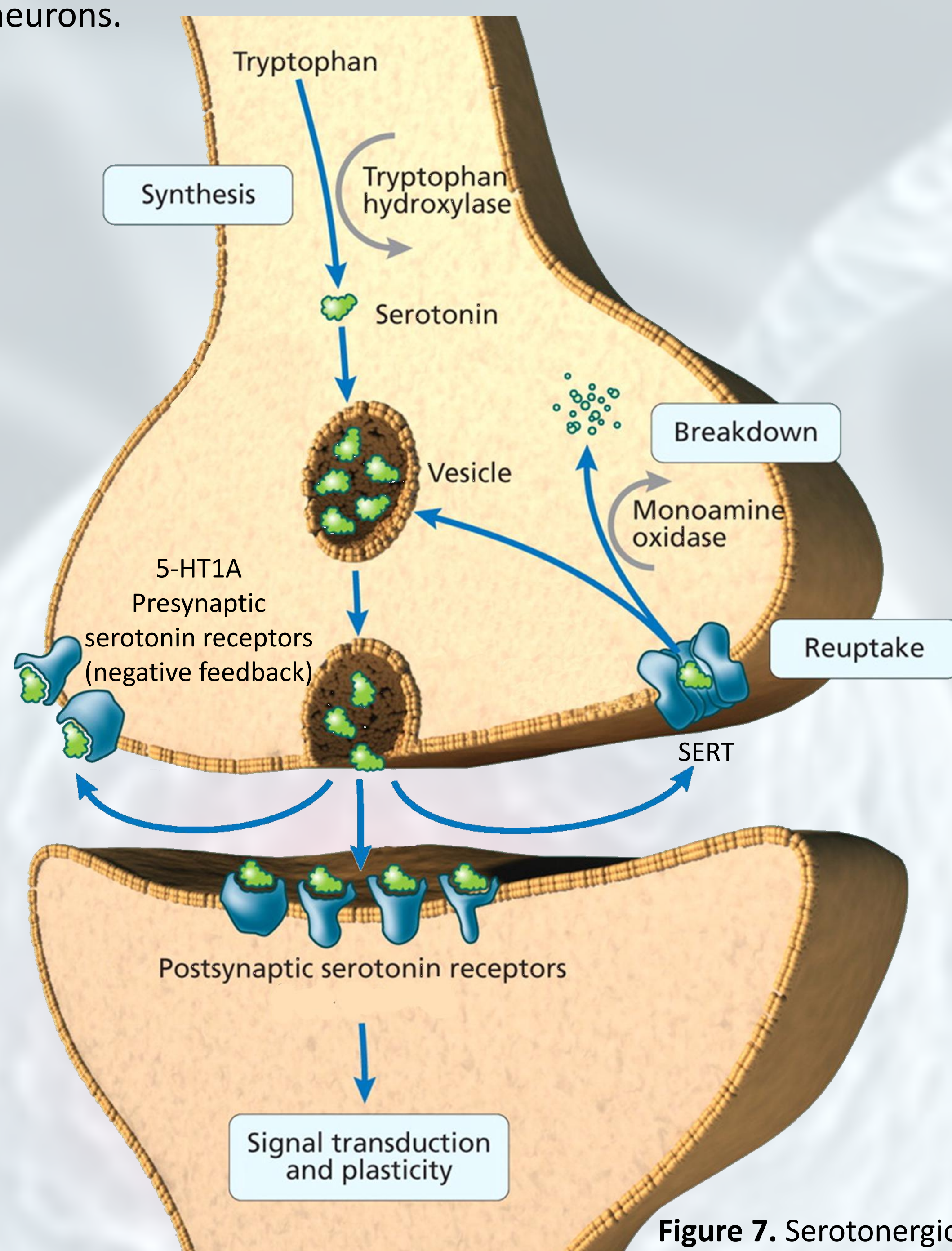


Figure 7. Serotonergic system.

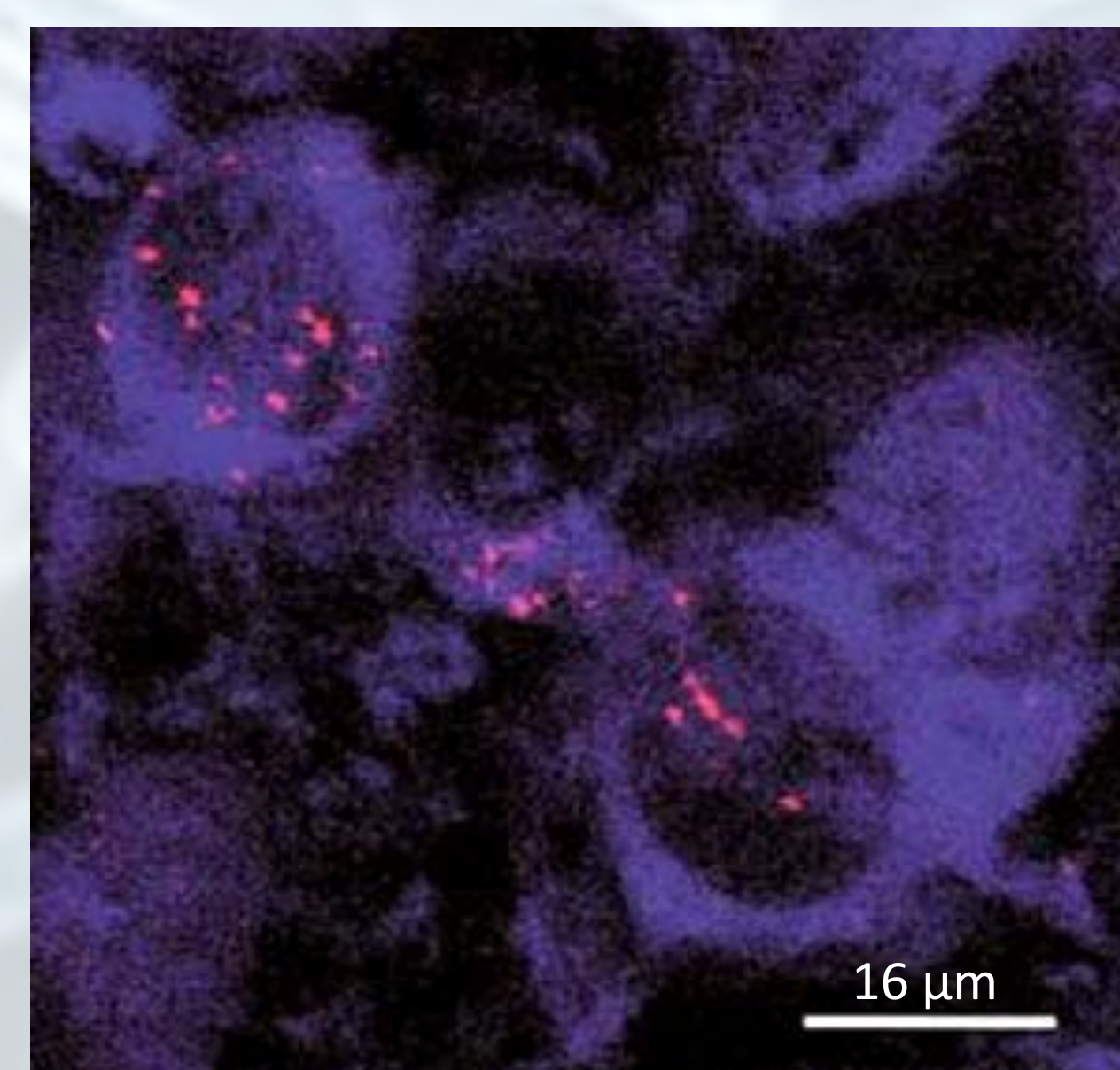


Figure 8. Serotonin neurons (blue) showing immune-localized biotin-labeled siRNA conjugates (red). Control not shown.

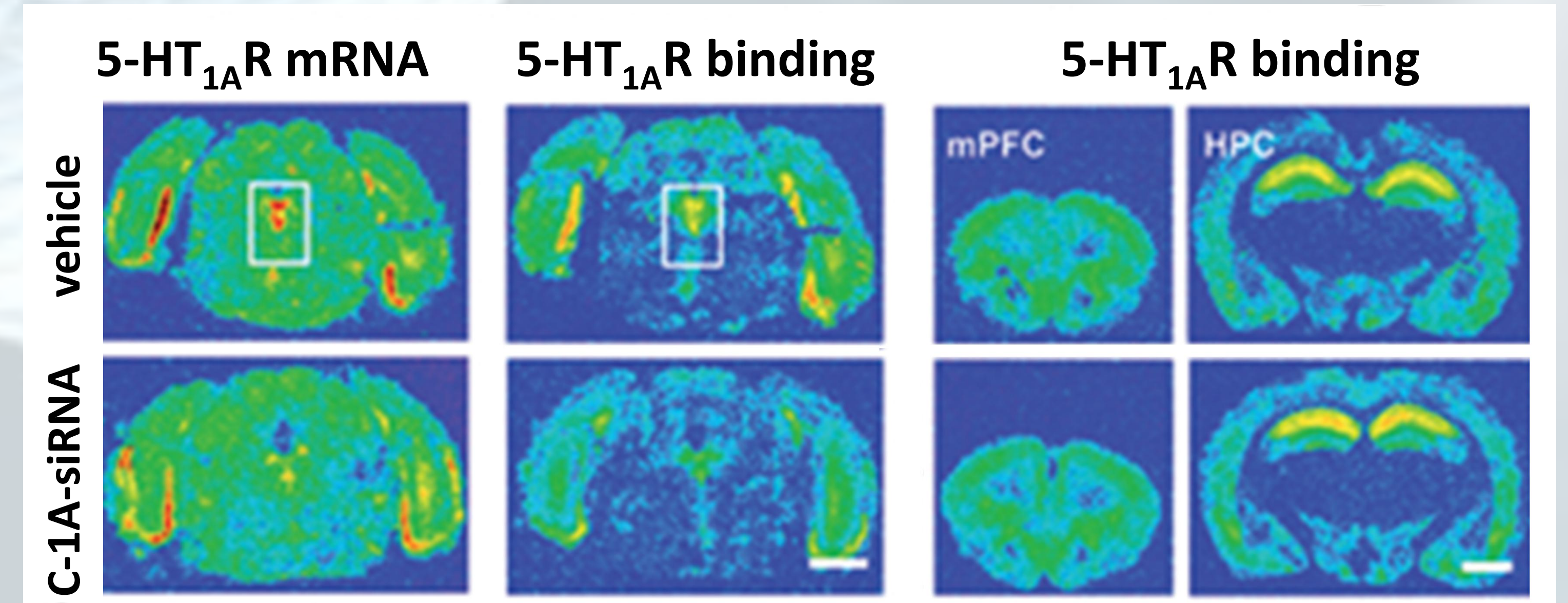


Figure 9. Selective 5-HT<sub>1A</sub> presynaptic receptor silencing by intracerebroventricular infusion of siRNA conjugates in mice. 5-HT<sub>1A</sub> postsynaptic receptors are not silenced as seen in mPFC and HPC images. Other controls and intranasal delivery not shown.

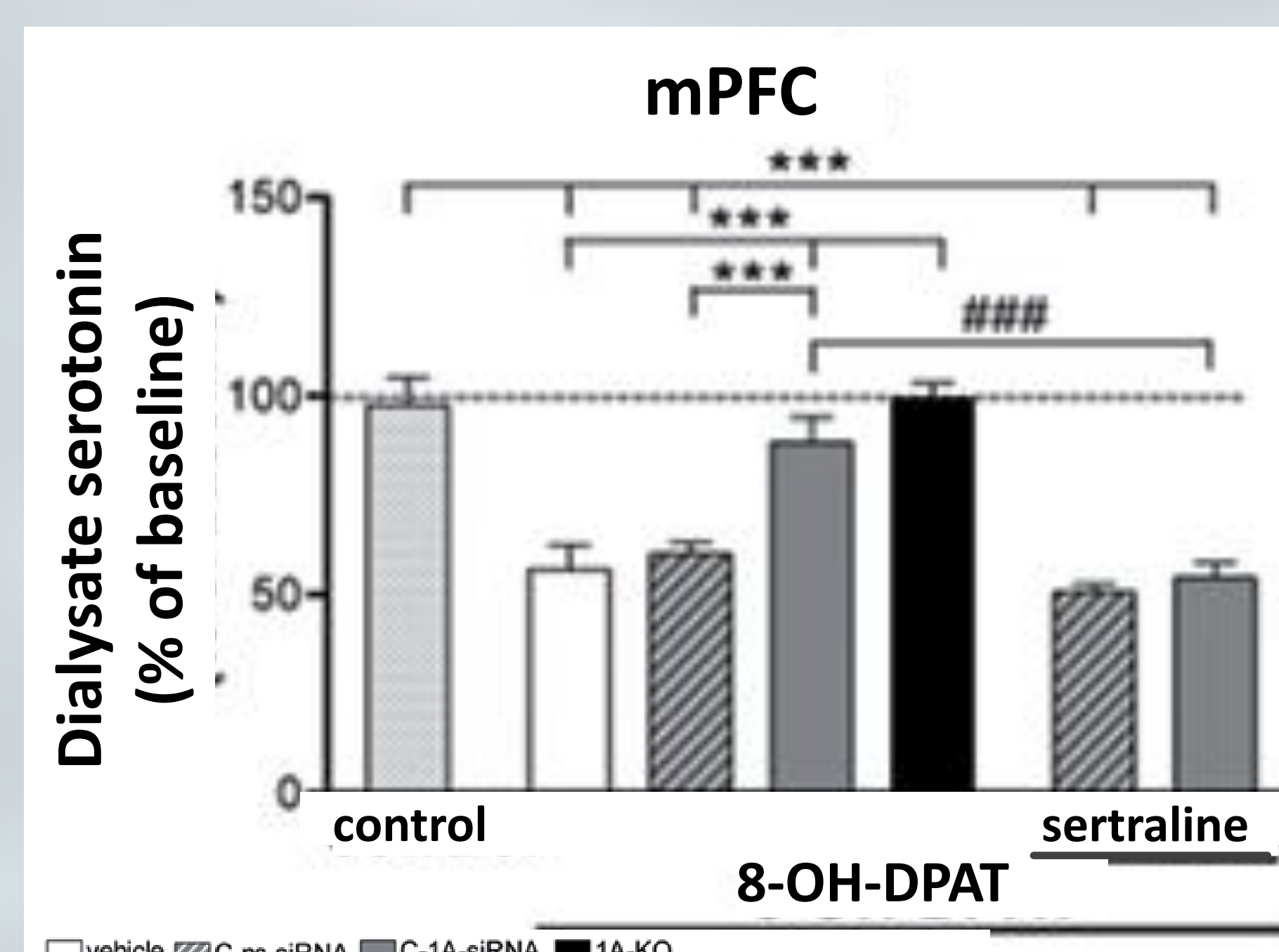


Figure 10. Competitive assay demonstrating siRNA internalization by SERT transporters. The siRNA conjugate cannot reverse 8-OH-DPAT effects when coadministered with sertraline, indicating competition for SERT transporters.

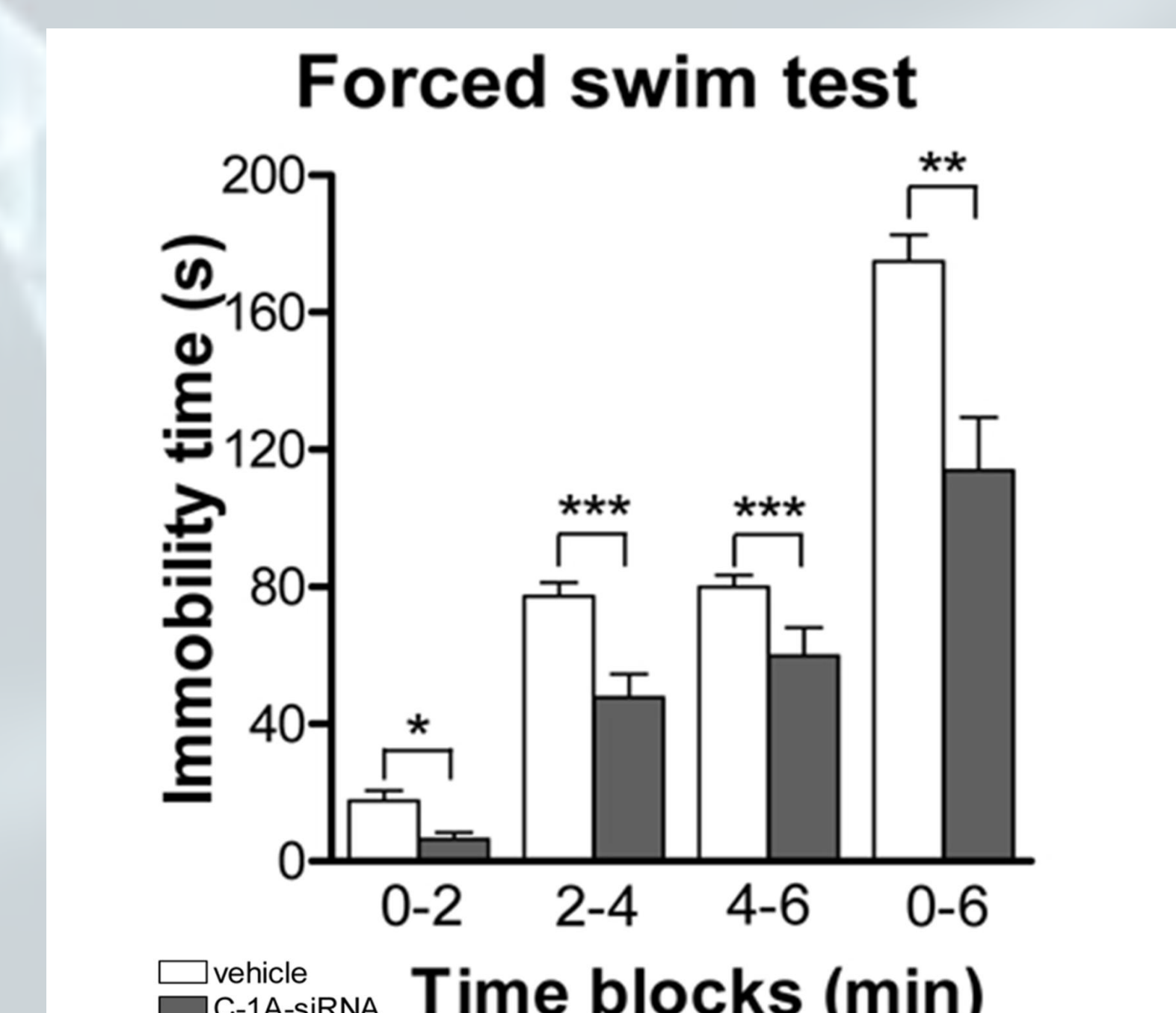


Figure 11. Antidepressant-like effects produced by the siRNA conjugate in the Forced Swim Test. Similar results are achieved in the Tail Suspension Test (not shown).

Figures 8-11 have been taken from the following paper: Bortolozzi, A. et al. Selective siRNA-mediated suppression of 5-HT<sub>1A</sub> autoreceptors evokes strong anti-depressant-like effects. Mol Psychiatry (2012) 17, 612-62.

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Universitat Autònoma de Barcelona