Target candidates for TPD platform

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## Date: Monday, January 21, 2022 at 09:27

**From**: John Ross <jross@degradetx.com>

**To**: ZS | Intomics <contact@intomics.com>

**Subject**: Target candidates for TPD platform

Hi ZS | Intomics,

I work at DEgrade Tx - a small-size pharma company in Boston - that's developing first-in-class therapeutics using targeted protein degradation (TPD) to treat diseases with unmet needs. Our unique edge is the Lysosome-Targeting Chimeras (LYTACs) platform we've patented. If you're not familiar with LYTACs, this recent review article will **help you understand the basis of the technology**: <https://chemistry-europe.onlinelibrary.wiley.com/doi/full/10.1002/cmdc.202100393>

We need help identifying target candidates for our platform. For the first part of the project, we want to find target candidates using RNA co-expression analysis.

From a quick look at your website, I think you might be able to help here. If so, please let me know if you can.

- John

Senior biological scientist, Ph.d.

## **Date**: Monday, January 21, 2022 at 15:21

**From**: Pascal <pnt@intomics.com>

**To**: John Ross <jross@degradetx.com>

Hi John,

Thanks for reaching out! Based on your description, we will definitely be able to help you out. Our target discovery projects usually span 6 calendar months. It would be great if you can explain what you consider good target candidates and ideal outcomes for the project. And while you share that information, I'll fix up a CDA so we can talk freely.

- Pascal

## **Date**: Tuesday, January 22, 2022 at 09:02

**From**: John Ross <jross@degradetx.com>

**To**: Pascal <pnt@intomics.com>

Hi Pascal,

Glad to hear I've come to the right place! And thanks for providing and signing the CDA.

We would like to collaborate with you on a 6-months project, starting the project as soon as possible.

Our LYTAC platform is based on [IGF2R](https://www.uniprot.org/uniprot/P11717) (CI-M6PR) to degrade extracellular proteins. (We've shown that IGF2R can degrade secreted proteins and also transmembrane proteins produced by the same cell as IGF2R.) To generate the *initial* target candidate list, we will consider proteins co-expressed with IGF2R at tissue-level.

We need the list of target candidates to show our investors that our platform is feasible. This will unlock our next funding milestone so we can continue the development of the platform. Our next board meeting with investors is approaching fast, so we need a quick and efficient solution to our problem. In fact, we need the list of target candidates in one month.

I hope this is not too big a challenge for you. It would be very unfortunate if the development of this ground-breaking technology - with the potential to treat diseases with unmet needs - stops here.

- John

## **Date**: Wednesday, January 23, 2022 at 11:21

**From**: Pascal <pnt@intomics.com>

**To**: You <[you@intomics.com](mailto:gwh@intomics.com)>

Great talking to you earlier today about this project. For this project, we should focus on their immediate needs (due in 1 month) and then scope the remaining 5 months. I think you brought up some really good ideas for identifying target candidates using RNA co-expression analysis, and I’m excited about having you as project lead. You’ve got this!

- Pascal

## **Date**: Thursday, January 24, 2022 at 13:57

**From**: You <you@intomics.com>

**To**: John Ross <jross@degradetx.com>

Hi John,

I’ve consulted with my team and we’ve come up with a crude strategy for generating the initial target candidate list. We can deliver an initial target candidate list to you in one month.

We will use tissue-level expression data from the [Human Protein Atlas](https://www.proteinatlas.org/humanproteome/tissue). We will use mRNA expression levels from the [RNA consensus tissue gene data](https://www.proteinatlas.org/about/download) (rna\_tissue\_consensus.tsv.zip). This dataset summarizes gene expression levels across 55 tissues.

One of the benefits of using HPA is that it is a [well-documented](https://www.proteinatlas.org/about/assays+annotation#normalization_rna) resource, so it's easy for you and me to know the data origin, processing and normalization.

We will write **Python or R code** to parse this dataset and **output (one or more) data tables that show co-expression between IGF2R and the genes/proteins in the dataset across tissues**. We haven’t planned the specifics for defining co-expression and may come up with multiple solutions.

We will schedule a meeting with you in one month where we will **present our solution(s) to your problem using a few slides**. Here’s a **tentative**\* **agenda** for the **meeting** (“**DEgrade Targets - project month 1**”):

1. Executive summary: problem and solution (5 min)
2. Approach: how we approached the problem
3. Quality control: how we performed quality control (or plan to do it in the next part of the project)
4. Output: data tables (and visualizations)
5. Results: our suggestion for best target candidates
6. Shortcomings: assumptions, limitations and risks of our approach
7. Code: walk-through of the code we wrote to solve your problem
8. (Questions: we might want to ask you some questions)
9. Improvements: suggestions for an improved approach to be implemented in a later phase of the project (better data / method)

*\* we might deviate substantially from this agenda. We don’t expect to go into details with all points on the agenda. We will focus on what we find most relevant.*

We expect that **we will present our key points for *about* 45 min**. We will **book your calendars for at least 1 hour**, so we have enough time for Q&A. (Sometimes these meetings end up with long discussions, so 1.5 hours for this meeting is not unheard of.)

We will share our code and commit history (preferably via **GitHub**) with you **no later than the day before the meeting** (“**DEgrade Targets - project month 1**”).

The project scope for the first month is clear to us, so we don’t expect we need further inputs from you until after the meeting. (At ZS | Intomics, we work closely with our clients, so if something is not clear to us, or we think the project could benefit from your inputs, we will not hesitate to reach out.)

## **Date**: Friday, January 25, 2022 at 10:44

**From**: John Ross <jross@degradetx.com>

**To**: You <you@intomics.com>

This is great, we like your initial crude strategy. We will get in touch with Pascal to setup the Work Order for a 6-months project, so you can begin the work immediately. We look forward to seeing you and your team’s skills in action!

As you are working on a serious time constraint for this first month of the project **we understand if your output and results are not perfect**. What’s important to us is that you can explain the limitations, so we can communicate this at the broad meeting.

For the meeting next month, I will invite one or two from management to take part in the executive summary. They are busy people, so please stay on time. My team and I have a background in molecular biology but have worked with bioinformatic approaches for several years, so we should be able to follow some of the technical details. For the code review - if we have time to cover it - it’s only our geeky bioinformatics experts that will participate. (They can be a bit tough - don’t take it personally.)

We are very interested in hearing your suggestions for improving the initial crude solution, so we can start scoping the remaining 5 project months. As inspiration, we’ve come up with some **bonus questions that you might be able to address at the meeting** (“**DEgrade Targets - project month 1**”).

**Bonus question 1**

We hope to be able to degrade clinically relevant targets. Our list of targets include:

* PCSK9
* TARDBP
* UCP2
* DCN
* APOD

Does your analysis give any evidence to whether or not we can expect to degrade any of these proteins?

**Bonus question 2**

Can you provide us with any data visualizations for the board meeting? Perhaps related to Bonus question 1.

**Bonus question 3**

For the remaining part of the project, we need to refine the target candidate list and prioritize it, to identify the most **relevant targets** and **therapeutic areas** (i.e. disease indications) for our platform. We imagine you could build a target discovery data foundation for our LYTAC platform, by gathering additional relevant data. What data and resources do you suggest could be relevant for the ‘target discovery data foundation’? (We are particularly interested in target candidates known to play a role in disease - ideally with some level of clinical validation)

**Bonus question 4**

As a follow-up to bonus question 3: we haven’t decided on what therapeutic areas (i.e. disease indications) for our platform. Do you have any suggestions?

- John

## **Date**: Friday, January 25, 2022 at 12:44

**From**: You <you@intomics.com>

**To**: John Ross <jross@degradetx.com>

Thanks John, I’m glad you like the overall approach.

I will do my best to help you out with those extra questions, so we can scope the remaining part of the project.

Talk to you next month!