Receptor-interactomics™ – a new dimension in drug development

Blue Therapeutics is an IND-stage drug discovery and development platform advancing transformative new medicines. Our proprietary R2i technology delivers novel therapeutics that overcome the side effect profiles and limited efficacy of traditional pharmacological approaches by leveraging a new dimension of disease biology. Blue's proprietary receptor-interactomics™ approach is creating deep insights to deliver superior outcomes for patients.

This concept paper is part of a series exploring the exciting world of receptor interactions. What is it? How does it disrupt drug discovery? How does it improve patient lives?

Part 2

Innate Proximity: inherent physicality of receptor interactions

by Ajay Yekkirala, CSO and Co-Founder of Blue Therapeutics

In part 1 of the concept series on receptor-interactomics, we discussed how receptor interactions are fundamental to biology and function. Before we dig into the next stage, let us quickly recap:

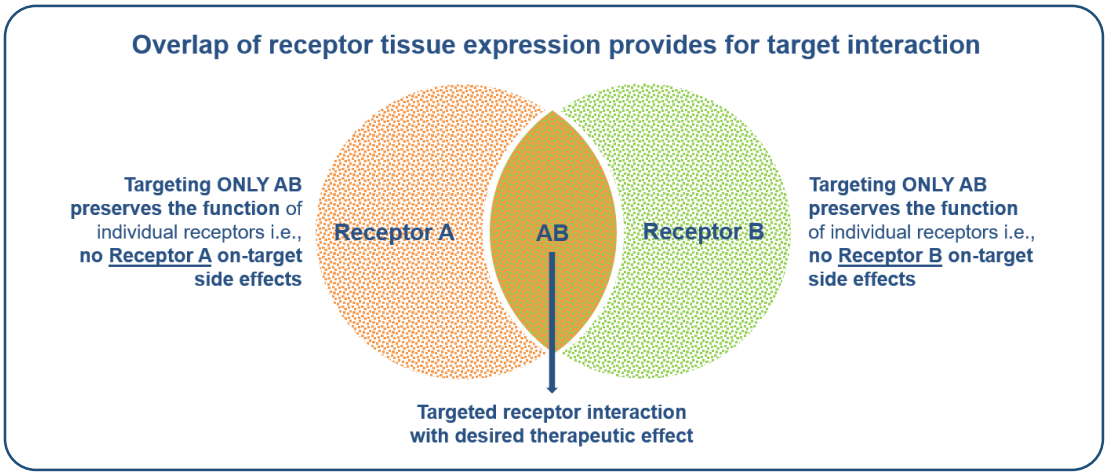
Receptors interact. Period.

This then begs some important questions: So what? And importantly, why should this matter to a drug hunter?

Let me give away the answer first before digging into the concept. When a receptor, or any protein for that matter, interacts with another receptor there is an inherent physicality to this interaction. We term this – Innate Proximity – where the interacting receptors are in natural proximity to each other while performing some function that brought them together in the first place.

Innate Proximity and spatial resolution

The physicality of the interaction due to Innate Proximity of two receptors matters immensely as we can develop better drugs if we can selectively target the interaction in the tissue of relevance while sparing the activity of the individual receptors in all other tissues. In other words, innate proximity confers spatial resolution which can be exploited for precision.

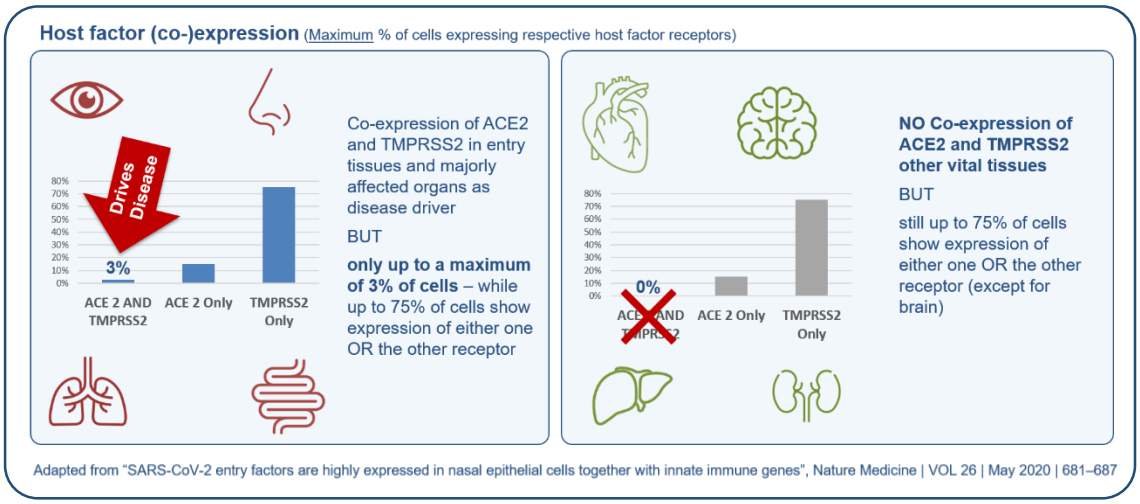


Increasing SPATIAL resolution: being able to target only the interaction between receptors preserves the function of the individual receptors WHERE (i.e., organ/tissue) both receptors are not co-expressed.

A very tangible example: we are living in a time that will be remembered throughout history for people across the globe have been cloistered in our homes, with increasing Innate Proximity of our families. And all of this in a battle of attrition with the supervirus from the dark side – SARS-Cov-2. Importantly, us drug hunters know that the virus utilizes ACE2 as the host receptor[1] to be

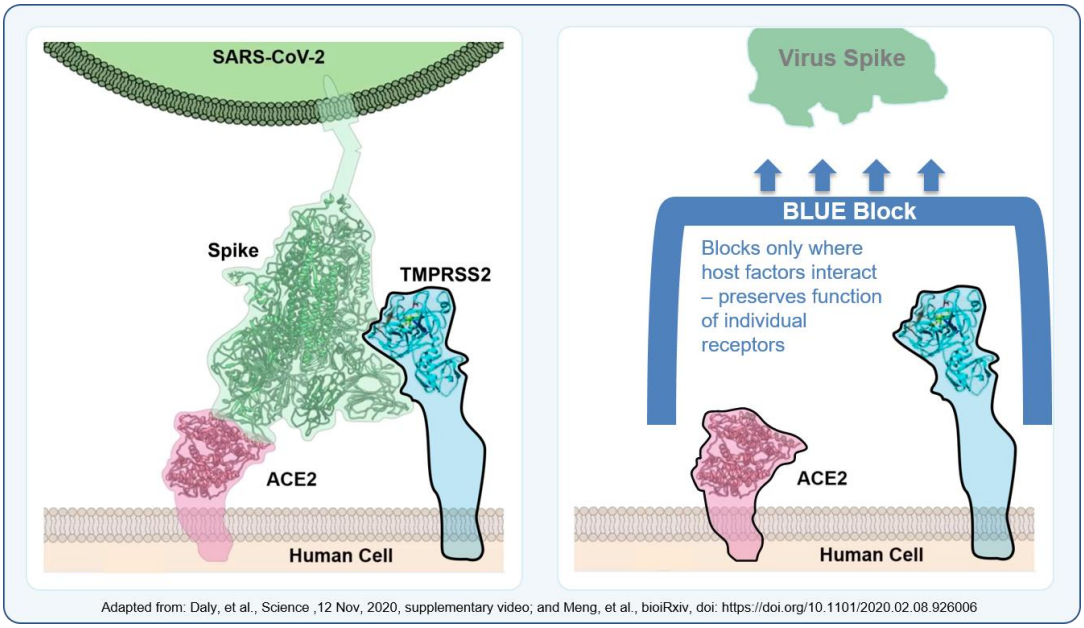
internalized and infect the host cell. I was however shocked to realize that SARS-Cov-2 is a big believer in Blue's receptor-interactomics™ platform. It utilizes the natural interaction between ACE2 and a serine protease, TMPRSS2, in lung epithelial cells where the protease cleaves the viral spike protein to activate it and also cleaves ACE2 to facilitate its internalization with the bound virion[2]. The nerve of this virus!

Normally, ACE2 and TMPRSS2 interact for a transient period in time where TMPRSS2 binds ACE2 and cleaves it so it can be internalized. You could of course try and target just ACE2 or TMPRSS2 with inhibitors and there are some early trials looking into this[3]. But there is a catch. ACE2 is expressed in several important tissues including the heart and is involved in important cardiovascular functions[4]. TMPRSS2 is also expressed in several tissues and cleaves several other receptors and proteins[4]. However, the two receptors are only co-expressed in the nasal cavity, lungs, upper airway, eyes and the gut but not co-expressed at all in CNS, heart, or other tissues. Even in the respiratory and GI tissues where they are co-expressed, they are only present together in 3% of all the cells[4] providing terrific spatial resolution to the target interaction.



With only a fraction of cells involved in virus replication, targeting single receptors would be highly inefficient and very likely result in substantial side-effects. Being able to target only the interaction will spare the physiological function of the single receptors in critical organ systems and the vast majority of cells overall!

We at Blue are however up to this challenge. We have embraced the innate proximity of the ACE2-TMPRSS2 interaction to design interaction modulators (iMods) that selectively target interacting receptors in specific tissues providing spatial resolution, sparing individual ACE2 and TMPRSS2 to go about their normal business in all other contexts. We are just trying to be as smart as the virus and evolution in the end.



Adapted from: Daly, et al., Science ,12 Nov, 2020, supplementary video; and Meng, et al., bioiRxiv, doi: https://doi.org/10.1101/2020.02.08.926006

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4. Sungnak W, et al., SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes", Nature Medicine, 26: 681–687

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