SIMULTANEOUS TARGET-INDICATION SCREENING: A GAME OF 3D CHESS

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Selecting a suitable target and lead indication is one of the most critical decisions for an early-stage biotech company. An objective prioritization framework should be used to avoid detrimental consequences of a wrong choice. The task at hand is complex and requires consideration of multiple relevant scientific and non-scientific dimensions across a vast option space of potential indications.

At Scitaris, we utilize a flexible, science-driven methodology to provide the best recommendations for our clients. Our approach is universally applicable and can handle even the immense option spaces encountered by platform companies trying to identify a suitable target-indication pair.

Lead indication selection is a critical, yet non-trivial task

Pioneering biotech companies are often founded with a potential solution (i.e., novel targets or platforms) that can be applied to a multitude of problems (i.e., indication, target-indication pair). The selection of a suitable lead indication is central to the company's fate, both for ongoing capital raising as well as because regaining investor support after a failed lead proof of concept is often difficult. While the lack of strict external restrictions, such as a therapeutic area focus, in this early stage of the biotech's lifetime can be regarded as a blessing, it is also a curse given the resulting extremely large option spaces.

Even though science may point towards an obvious, specific indication, a sole focus on the technical probability of success is often insufficient for prioritization. Other dimensions, such as differentiation, unmet need, number of addressable patients, and development feasibility, must also be considered to bring a well-differentiated product to patients and attract sufficient funding. For the practical integration of these non-scientific dimensions, it is crucial to have an accurate understanding of the current regulatory and payor environment as well as an appreciation for the underlying principles driving potential future changes (usually cost-efficient improvement of patients' health). A prominent example is gene therapy, which not only fought to overcome technical challenges but also faced additional hurdles as investors became increasingly concerned that development for ultra-rare target populations could not be conducted in a commercially feasible manner given the historical regulatory and pricing framework. Recent record prices, as seen for CSL's Hemgenix (LINK) indicate payors' willingness to now sufficiently consider long-term health benefits even for one-off treatments, which has the potential to bring previously discarded, smaller patient populations back into focus.

With the numerous scientific and non-scientific dimensions impacting the choice of a suitable lead indication, it is unsurprising that an indication with

optimal characteristics across all dimensions often does not exist. Furthermore, it is not uncommon that relevant dimensions act against each other (e.g., breadth of target population vs technical probability of success), further hampering a compromise-free selection of the lead indication. These challenges are even more evident for platform companies (e.g., siRNA, degraders, drug delivery technologies), which, in addition to a lead indication, also must prioritize a suitable target. For these companies, the combined search for a high probability of success lead target-indication pair results in an exponentially increased option space, which requires careful consideration and pressure testing (Fig. 1).

Here, we discuss the best practices and methodologies to navigate the challenges and identify the most suitable and promising lead indications (or lead target-indication pairs) for early-stage companies. We briefly outline such an approach for companies developing drugs for a specific target and then focus on platform companies in greater detail.

Lead indication searches for a target-focused biotech are comparably straightforward

For biotech companies developing an asset for a specific target, selecting a suitable lead indication is a comparably straightforward task. The respective target's biology is one of the main drivers of the prioritization process. This scientific dimension is further complemented by relevant non-scientific dimensions (e.g., unmet need, competition, potential for differentiation). Selection and weighting of the relative dimensions is asset-specific and requires a thorough understanding of the relevant biology and current clinical, regulatory, and economic landscape. Specifically, a proof of mechanism, such as a measurable biomarker, can greatly facilitate development in a certain indication. A meaningful proof of concept for a target in a disease gives confidence but must always be supported by a strong differentiation hypothesis. Otherwise, the developmental path and subsequent commercialization of an asset might become an uphill battle. Once those dimensions are defined, iterative rounds of validation with increasing depth and manual curation are used to refine the initial option space and derive the highest probability of success indications.

In the beginning, semi-automated, high-throughput screening rounds serve as coarse filters to identify and exclude the low probability of success hits out of the ~10 thousand initial indications. The resulting refined option space (Fig. 2) is subsequently analyzed in iterative rounds of manual expert analysis with increasing analysis depth,

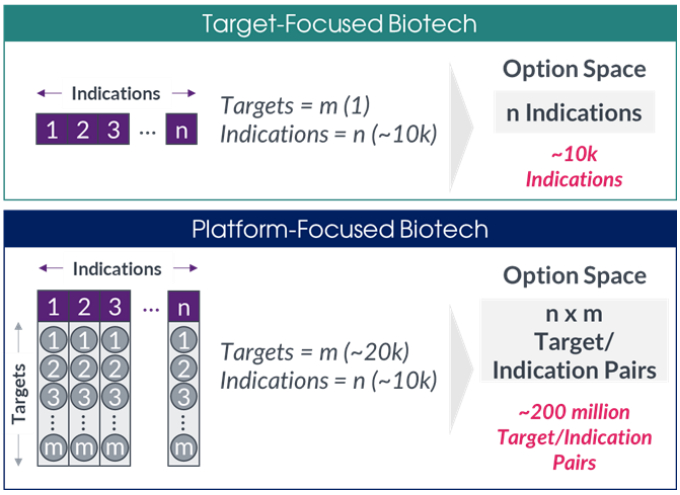

Figure 1. Comparison of the raw option spaces for target - and platform-focused biotech companies. For platform companies, the exponentially larger option spaces complicate lead target-indication selection.

Identifying a lead target-indication pairs is a combinatorial challenge

For platform companies, prioritization is a multi-dimensional challenge with combinatorial complexity. In the absence of a clear target, these companies must prioritize a suitable target-indication-pair for their respective technology (e.g., siRNA, degrader, delivery platforms). Since the suitability of a target is indication-dependent, only the combined prioritization of target-indication pairs can yield the highest probability of success. Unfortunately, this requirement leads to an exponentially larger option space. While the raw option space for a novel drug targeting a single target equals approximately ~10 thousand indications and sub-settings, the option space for a platform company is the product of all indications and targets included in the screen, resulting in multiple millions of combinations (Fig 1.). Faced with this immense option space, traditional approaches (e.g., manual literature reviews and experimental validation) are unsuitable given time and money constraints. Only strategic and analytical frameworks tailored to this task can efficiently cope with the complexity.

Here, the first and central conceptual question is how the technology/platform at hand differentiates from existing technologies or modalities. Translation of the differentiation into searchable filters is the foundation of a custom database for subsequent prioritization.

These core differentiation filters are further complemented by relevant platform-agnostic dimensions (e.g., unmet need in indication). After the relevant dimensions have been

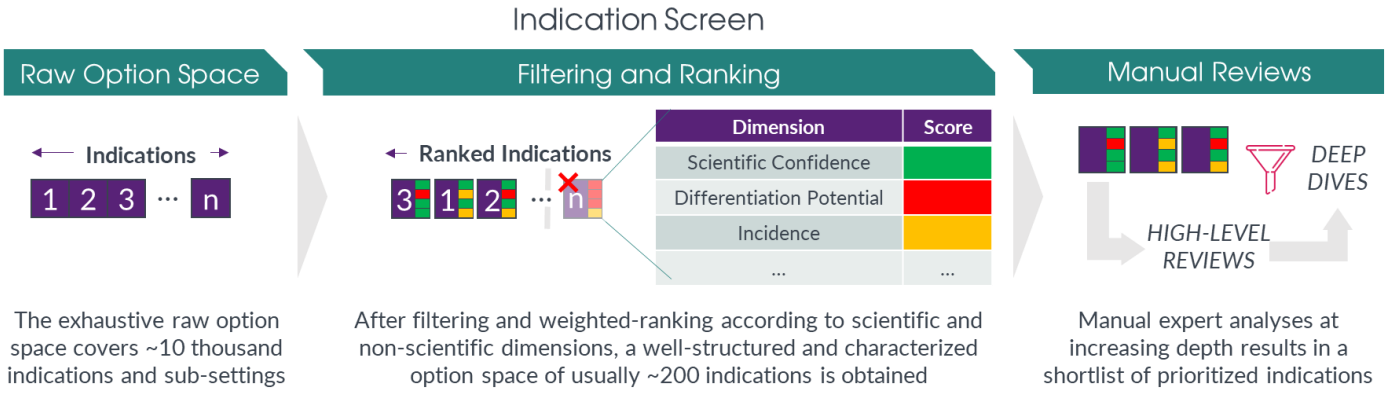

Figure 2. Schematic overview of lead indication prioritization process for a specific target. A custom-made database narrows the raw option space before multiple rounds of manual expert analyses.

defined, the custom database must be populated with the required data. Here, scientific and commercial databases provide a rich resource for various kinds of data and can be used as a primary resource. Still, a vast amount of additional information is only available in the primary literature, and systematic screening of full-text databases, for which we at Scitaris employ a proprietary search algorithm, can yield insights and associations otherwise not accessible.

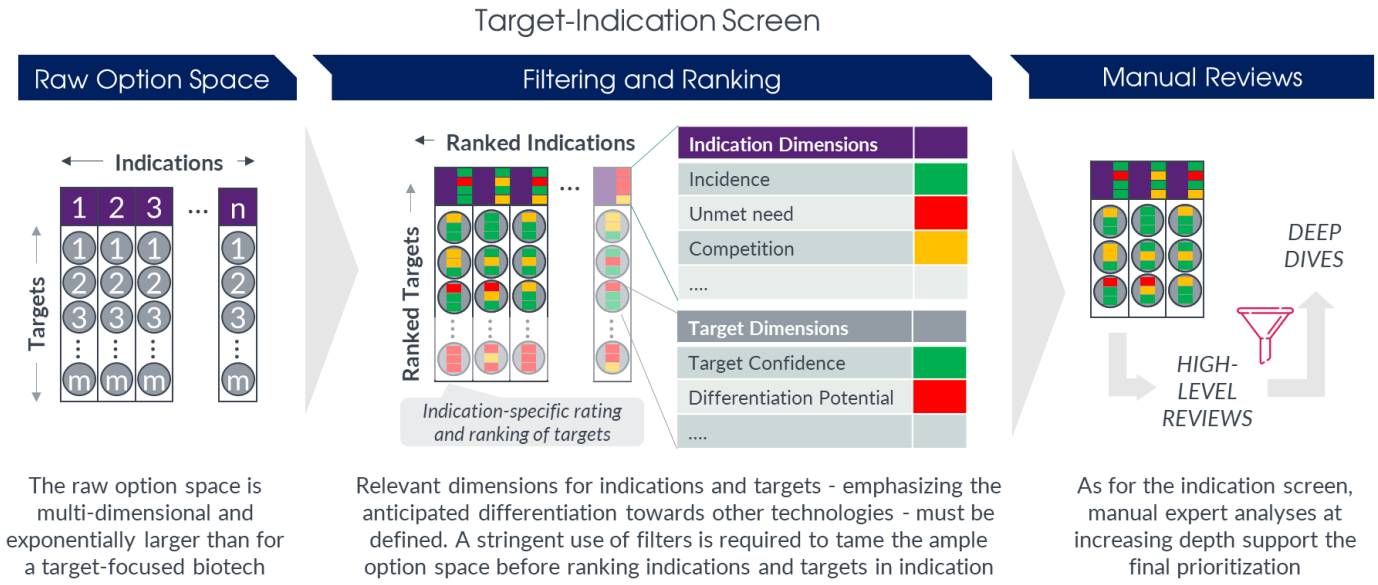

Figure 3. Schematic overview of lead indication-target pair prioritization for platform companies. Stringent indication- and target-specific filters are required to narrow the exponential option space before manual analyses.

In summary, lead indication or target-indication pair prioritization is an essential, yet daunting task most biotech companies must face. Irrespective of whether to prioritize a single indication or a target-indication pair, the underlying science should always be a major driver for any decision. No matter how alluring the commercial potential or unmet need is, without a proper scientific foundation, the probability of success is meager. But despite that, even the most promising scientific rationale does not guarantee success if the non-scientific dimensions are ignored.

Traditionally, prioritization of indications (or target-indication pairs) has been largely done via manual literature reviews. Especially for platform companies, it is highly unlikely to identify the highest probability of success target-indication pair out of millions using this labor-intensive method. With the growing availability of databases, they offer a rich source of pertinent data. Compiling, transforming, and analyzing this data provides a cost-effective and efficient means to accelerate and de-risk drug development.

If you are interested in learning more about how we at Scitaris can assist your company in delivering a 'checkmate' for this complex endeavor, please don't hesitate to contact us at any time.