



## **TDN Compound Evaluation Process**

### **Assessment of Candidate Anti-Inflammatory Agents for Cystic Fibrosis**

Although much excitement surrounds the development of CFTR modulators, it is unclear how much impact these drugs will have on downstream consequences like airway obstruction, chronic infection and excessive inflammation in the long term.

As lung disease is the primary cause of morbidity and mortality in individuals with cystic fibrosis, research into therapies aimed at downstream pathologic consequences must continue until a cure is found.

The strong development pipeline for CFTR modulators has created tremendous opportunities for new CF therapies, but it has also led to real concerns that the availability of individuals with CF to participate in clinical trials may soon become a limiting factor in CF drug development, especially for downstream therapies.

Many anti-inflammatory drugs in development target various aspects of the host inflammatory response, which might be applicable to CF. Patient and financial resources are limited, and not all of these candidate anti-inflammatory drugs will make it into clinical trials.

To utilize patient resources optimally, the Therapeutics Development Network's Clinical Research Executive Committee and Protocol Review Committee are implementing an early step in clinical protocol evaluation that will apply to agents specifically designed to modulate the inflammatory response.

The goal of this evaluation is to independently assess the preclinical biological characteristics to better predict the likelihood of success of each compound within the class of compounds designated as anti-inflammatory agents.

Several factors will be considered when assessing a compound's likelihood of clinical benefit including, but not necessarily limited to, the following:

1. Mechanism of action and its novelty relative to other anti-inflammatory agents.
2. Relevance of the proposed target of the anti-inflammatory drug to the inflammatory response in the CF airway.
3. Whether the anti-inflammatory drug acts broadly or inhibits a single mediator and therefore might have to be given with other anti-inflammatory drugs.
4. Extent to which compounds have been evaluated for efficacy in appropriate in vitro model

systems including, but not limited to, immortalized cell lines, primary human bronchial epithelial cells, primary nasal epithelial cells, CF sputum or BAL, and circulating cells under defined culture and assay conditions.

5. Extent to which compounds have been evaluated for safety in CF-relevant pulmonary infection animal models.
6. Definition of toxicity profile in animal models.
7. Potential biomarkers of efficacy that have been identified in pre-clinical models that could be used in phase II studies.
8. Drug delivery method and whether the method under consideration delivers the anti-inflammatory drug to the correct space.

Please note that compound evaluation will take into account the overall profile of multiple criteria, recognizing difficulties in direct translation to clinical benefit. We also recognize that the mechanism of action of a given compound may influence the relative importance of certain criteria listed above.

The goal, therefore, is to assess overall data that supports the biological basis for anti-inflammatory effect. For this purpose, evaluations will be performed by multiple independent experts under conditions of confidentiality.

The content of these evaluations along with other aspects of the protocol review process will be used by the Clinical Research Executive Committee and Protocol Review Committee to score each protocol.

These scores will be provided to TDN sites to allow them to make educated decisions about which studies to select for participation. The ultimate goal is to achieve the most efficient use of TDN centers and resources.

For more information, please write to the TDN Coordinating Center at [TDNCC@seattlechildrens.org](mailto:TDNCC@seattlechildrens.org).