You Have Research Questions, We Have Some Answers

Questions posed by registered patient families, and answered by members of our Medical Advisory Board.

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What are the challenges to developing therapies and treatment for CFC syndrome?

CFC Syndrome arises from gene changes that alter a fundamental biological process called the RAS/MAP kinase signaling pathway (RAS pathway for short). In CFC Syndrome, there is too much signaling through this pathway. The challenge is to find medicines that will decrease the RASpathway signaling without turning it off. If RAS signaling is turned down too low, then many normal bodily functions could be altered, leading to unacceptable side effects. So, finding a medication that appropriately reduces RAS signaling is very challenging. It is also possible that a stronger RAS pathway inhibitor could be used at lower doses, but it remains unproven whether that approach will result in reducing the CFC Syndrome symptom of interest.

Another challenge is the developmental changes that occur in utero because of disruption of RAS/MAPK signaling pathway.

What types of therapies or treatments are possible options for CFC Syndrome? Please briefly explain each and how they might work in CFC Syndrome.

The primary goal of potential therapies for CFC syndrome would be to develop new medication/s that could decrease signaling through the RAS/MAP kinase pathway, which is overactive in CFC Syndrome. Because adult cancers frequently have acquired gene changes that also lead to overactive RAS pathway signaling, pharmaceutical companies have already developed some medications and continue to put substantial effort into developing additional medications that reduce signaling in this pathway. A few of those medications have already gained FDA approval for specific cancers, and many others are in or approaching clinical trials for cancer.

In order to be considered as potentially useful for individuals with CFC Syndrome, certain criteria must be met. First, we have to know that the medication is safe for children, particularly if it is to be given for a long time. A medication can have relatively severe side effects and still be acceptable as a treatment for cancer, which is life-threatening. The standard for CFC Syndrome clearly is different. Second, we need to have some evidence from cell and/or animal models showing that the medication is successful in improving one or more aspects of CFC Syndrome. Third, we need to know what would occur in a child with CFC Syndrome who was NOT treated. In other words, in order to show that a new medication improves an aspect of CFC Syndrome, we need to be clear on what to expect in the first place. We have good information on some issues of CFC Syndrome but weaker data about others.

At the current time, the lead classes of medications being discussed as possible treatments for CFC Syndrome include MEK inhibitors, of which some are already FDA approved, and farnesyltransferase inhibitors (FTIs). Inhibitors at other steps in the pathway such as at RAS and at the RAF proteins are in clinical trials, so might soon be worth considering as well. There is one BRAF-specific treatment for melanoma that has FDA approval; because this medication targets BRAF proteins with a change commonly seen in melanoma, but not in CFC syndrome, it is not viewed as useful for children with CFC syndrome.

Previously, there was consideration of using cholesterol-lowering medications called statins. However, clinical trials with children with a different RASopathy, Neurofibromatosis Type I, failed to show improvement in intellectual functioning. This has diminished the enthusiasm for this group of medications.

What is the likelihood that these therapies would be effective in treating the symptoms of CFC Syndrome?

At this time, we do not know how effective any treatment would be in treating the symptoms of CFC Syndrome over time. It is very unlikely that one medicine would be highly effective against all clinical aspects. Some aspects of CFC Syndrome are probably going to be more treatable in infants and toddlers than in older children or teenagers. To give examples, a treatment that prevented heart valve abnormalities from progressing in babies would not likely cause a very abnormal valve to revert to normal in an older child; a treatment that improves brain function would probably lead to better outcomes if started in a young child rather than in a teenager.

What is the status of some of these therapies in clinical trials?

As noted in the answer to Question 2, medications are at various stages in the drug development path. Some, such as Sorafenib and Trametinib, have already achieved FDA approval for specific cancer indications. A number of other drugs are in trials varying from the earliest stage (Phase 1) through the last one (Phase 3). While most of the clinical trials are with adults with cancers, there is some clinical trial activity for pediatric cancers as well. One farnesyl transferase inhibitor, Lonafarnib, was used in a successful clinical trial with children for a different severe genetic disorder, Progeria, providing potentially useful information about dosing and side effects for pediatric patients generally.

In what areas (developmental, neurological, cardiac, etc.) could we expect to see some improvement (if at all) in symptoms with these therapies?

The current best targets for treatment are cardiac (hypertrophic cardiomyopathy) and neurologic (development/learning). We do not know if a medicine that would work well against those aspects of CFC Syndrome might also help with other challenges such as growth, skin issues, seizures and gastrointestinal function. We also have no way of knowing how an effective treatment might affect behavior.

What can families and our organization do to facilitate clinical trials and research into therapeutic options?

Here are some suggestions:
(1) Get to know your state representatives, consider meeting with your senator, perhaps together with another CFC family, to inquire about their support of funding for rare disease research.
(2) Continue involvement with CFC International and RASopathies Network.
(3) Fundraise for CFC syndrome research.
(4) Approach researchers actively publishing about CFC for ideas/guidance/perceived barriers to progress.
(5) Actively participate in CFC research studies including longitudinal natural history studies.

Are there other treatments/therapies that have been used in other RASopathies that might work in CFC syndrome?

To date, there is no medication that has achieved FDA approval for a RASopathy indication specifically. A MEK inhibitor, Selumetinib, had a successful Phase 2 clinical trial for reducing tumors in patients with Neurofibromatosis Type 1. Subsequently, the FDA granted Selumetinib orphan drug status, further incentivizing the pharmaceutical companies developing it, AstraZeneca and Merck, to undertake further studies in order to achieve FDA approval for this drug. A few years ago, another MEK inhibitor, Trametinib, was used to treat two infants with Noonan Syndrome and severe hypertrophic cardiomyopathy and appeared to show positive effects. It has been used since then in several sick babies and children; a scientific paper describing those larger experiences is expected soon. None of these usages was a clinical research study so more information is needed about the usefulness of Trametinib for RASopathies.

What can we hope to learn from a CFC mouse (or other animal) model(s)?

Although humans and animals (technically “non-human animals”) may look different, at a physiological and anatomical level they are remarkably similar. Animals, from mice to monkeys, have the same organs (heart, lungs, brain, etc.) and organ systems (respiratory, cardiovascular, nervous systems, etc.) which perform the same functions in pretty much the same way. While the fundamentals of life are the same – there is a 67 percent similarity between the DNA of humans and earthworms – there are differences in species and even in individual animals. Some animals are good human-like models for one thing and some for another.

Rodents are the most common type of mammal employed in experimental studies, and extensive research has been conducted using rats, mice, gerbils, guinea pigs, and hamsters. Among these rodents, the majority of genetic studies, especially those involving single gene disorders, have employed mice, not only because their genomes are so similar to that of humans, but also because of their availability, ease of handling, high reproductive rates, and relatively low cost of use. Other common experimental organisms include fruit flies, zebrafish, and baker's yeast.

To study novel therapies in a human disease, we can't, for ethical reasons, perform the initial work in humans; we have to develop an animal model for treatment and testing. Any potential drug therapy must first be tested for safety and evidence of efficacy first in animal models before it can be offered to humans. Some models may be in vitro – literally, in glass tubes – but as we learn more and more, eventually we can test ideas in vivo– in living animals. That means, we have to have a way of producing the disease that allows us to study it. Animal models allow closer approximation to a human response. They are not perfect, of course; animals host different diseases and different responses.

Animal models can also be used to screen large numbers of drugs, this is an area where fruit flies and zebrafish are particularly useful because of their short life cycle.

DISCLAIMER: Above indications of use of therapies to treat cancers does not imply that the risk of cancer is elevated in CFC Syndrome. Individuals with CFC Syndrome are not at increased risk of cancer compared to the general population.

The questions in this document were submitted by registered patient family members of individuals with CFC Syndrome. All answers were provided by one or more members of CFC International's Medical Advisory board and reviewed by members of the Board of Directors. To see a comprehensive list of Medical Advisory Board members, please visit our website at www.cfcsyndrome.org.

If you would like to submit a question for future review, please email your question to info@cfcsyndrome.org.

Questions are reviewed by members of CFC International's Medical Advisory Board annually. This document is updated to reflect changes in research annually.

Last update: July 1, 2021.