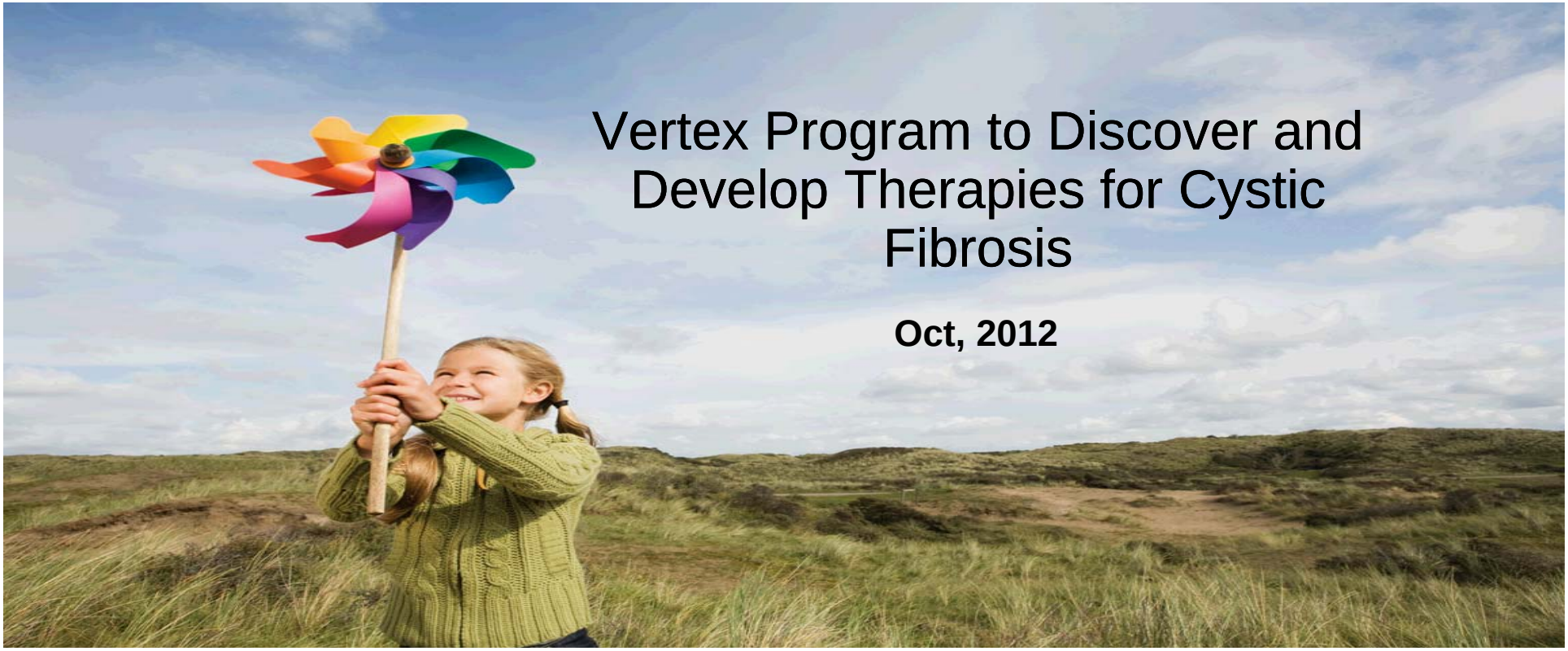

Vertex Program to Discover and Develop Therapies for Cystic Fibrosis

Oct, 2012

Eric Olson, Ph.D.
VP, Cystic Fibrosis
Vertex Pharmaceuticals, Inc.
Cambridge, MA

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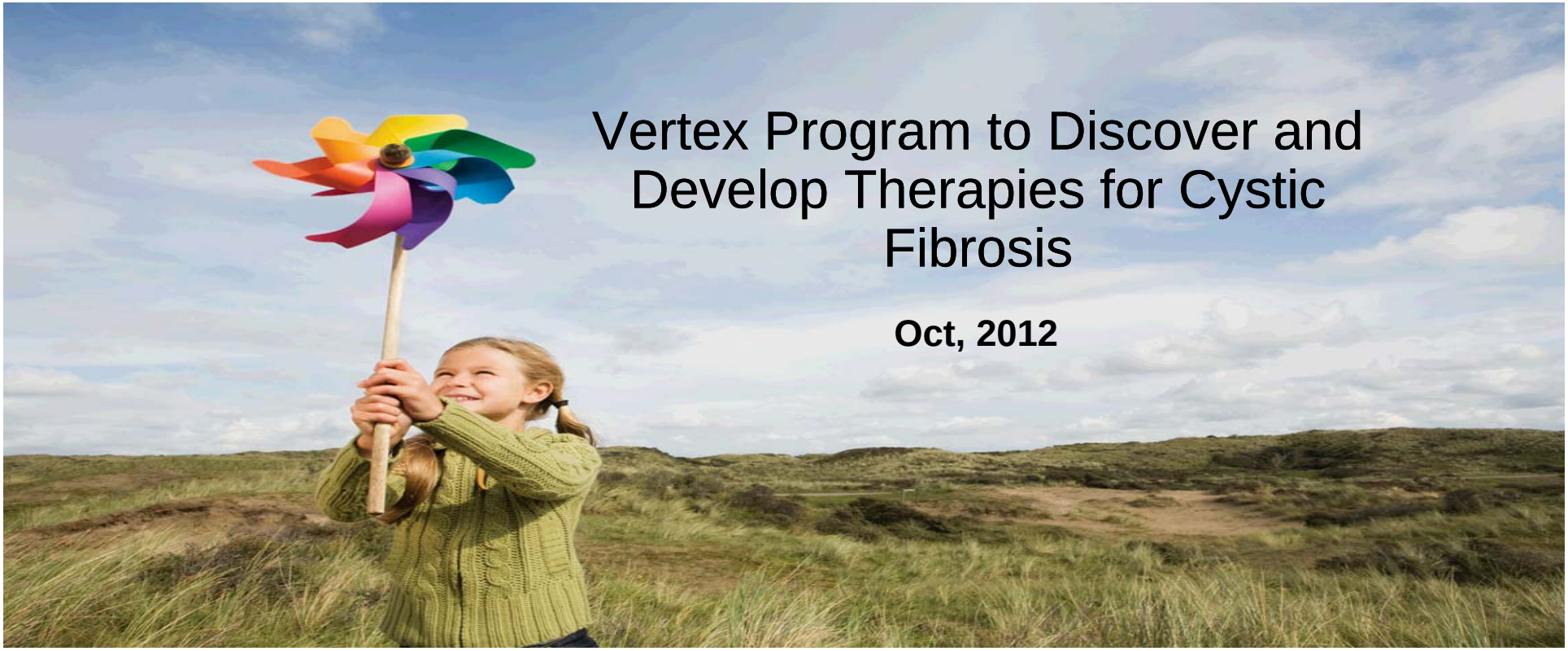

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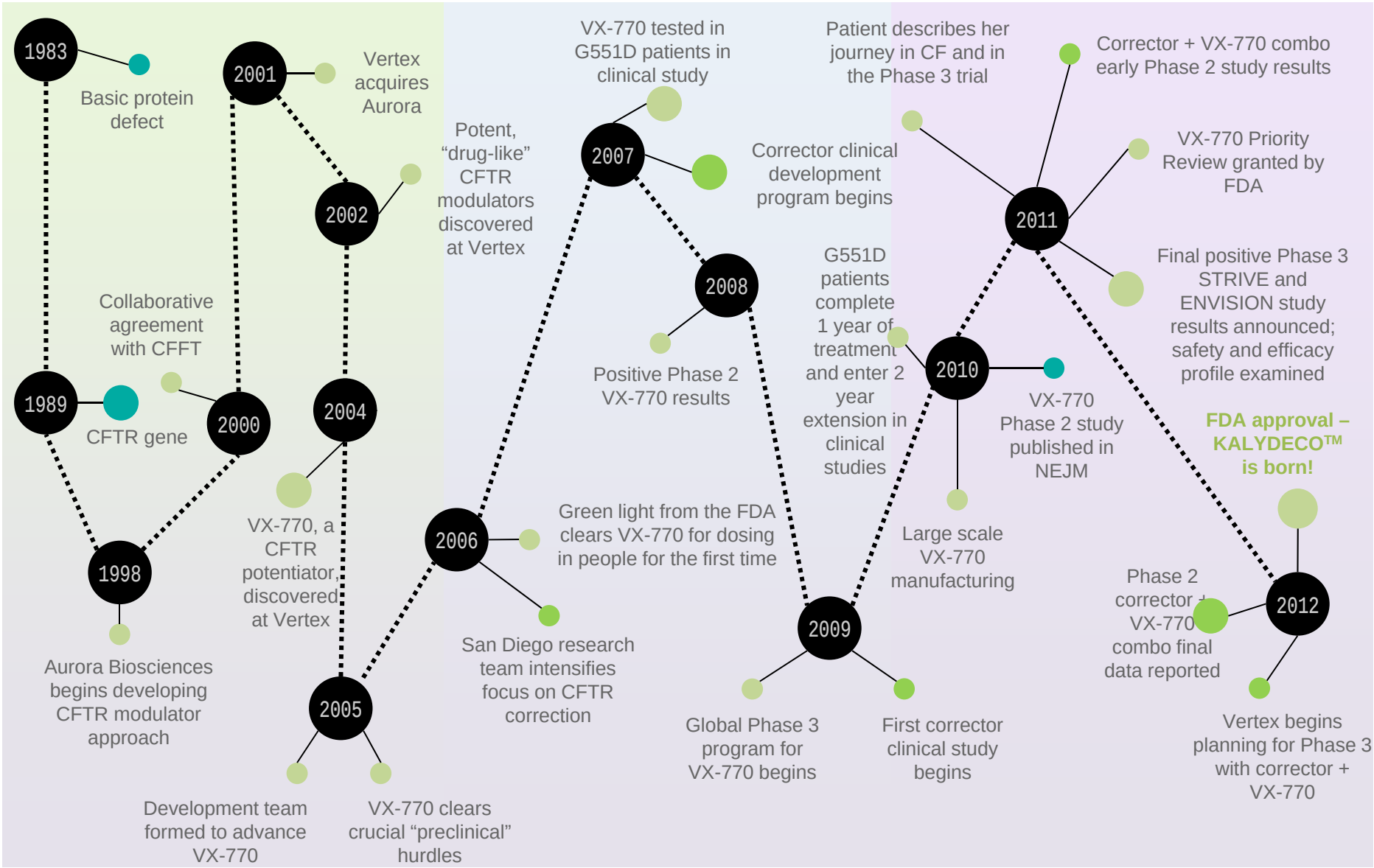
Outline

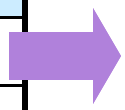
1. **The strategy**
2. **Why CF made sense for Vertex**
3. **Our relationship with academic centers and the CF Foundation**
4. **Role of orphan drug status**
5. **Discovery and Development challenges**
6. **The US indication statement**
7. **General lessons**

Milestones



1. The strategy

Mutation	Percent of Patients
F508del	**88.5**
G542X	**4.6**
G551D	**4.4**
R117H	**2.7**
N1303K	**2.5**
W1282X	**2.4**
R553X	**1.8**
621+1G->T	**1.8**
1717-1G->A	**1.7**
3849+10kbC->T	**1.6**
2789+5G->A	**1.3**
3120+1G->A	**1.0**



50% F508/F508

40% F508/Other

Discovery and Develop a regimen that can restore CFTR function to the largest number of patients

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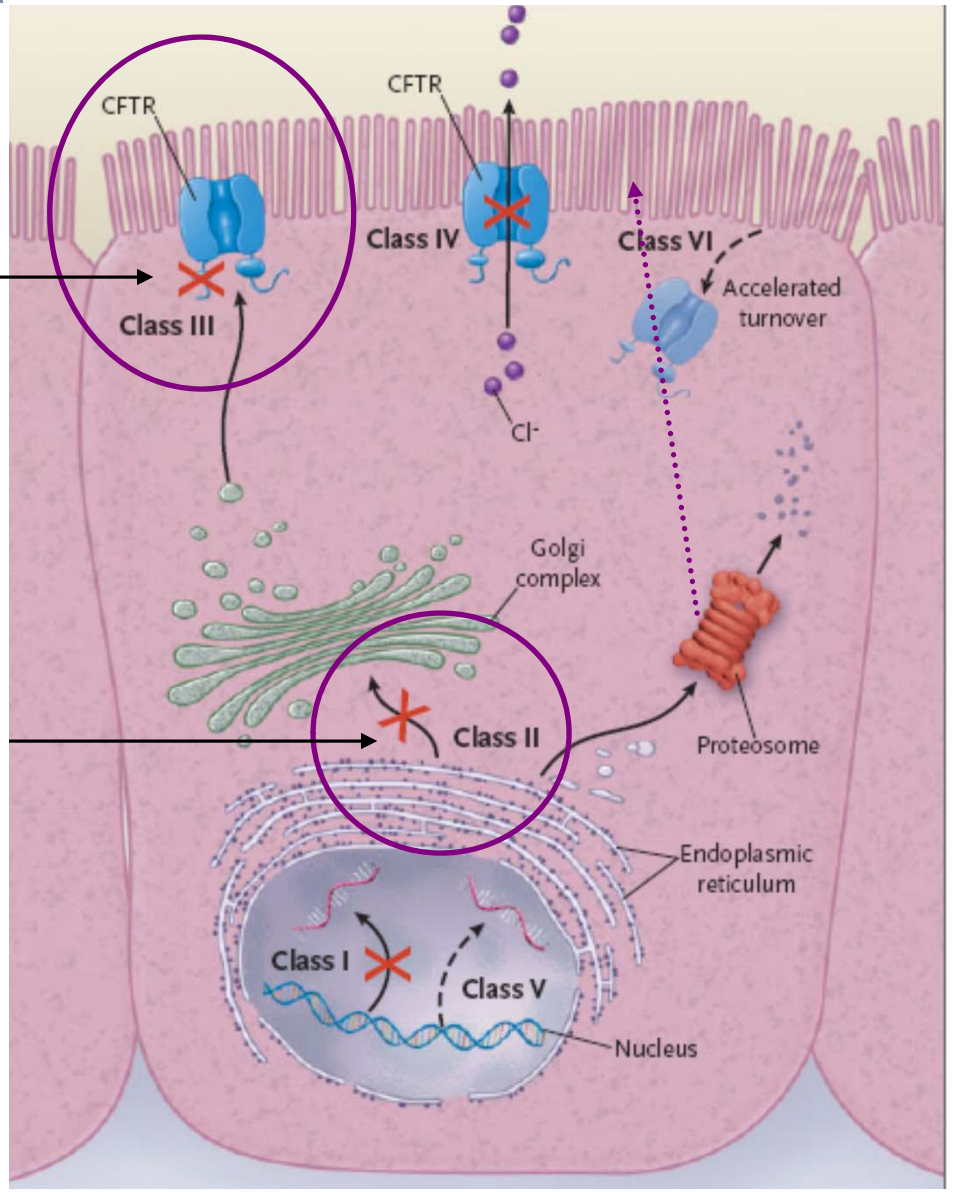
Two classes of CFTR modulators

Potentiators:
Increase the function of F508del-CFTR

Correctors:
Restore trafficking of F508del-CFTR



Adapted from Rowe et al. NEJM 2005

A potentiator could be developed for G551D patients

Mutation	Percent of Patients
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In vitro studies suggested that this form may only need a potentiator….

…and there might be enough patients for a development program

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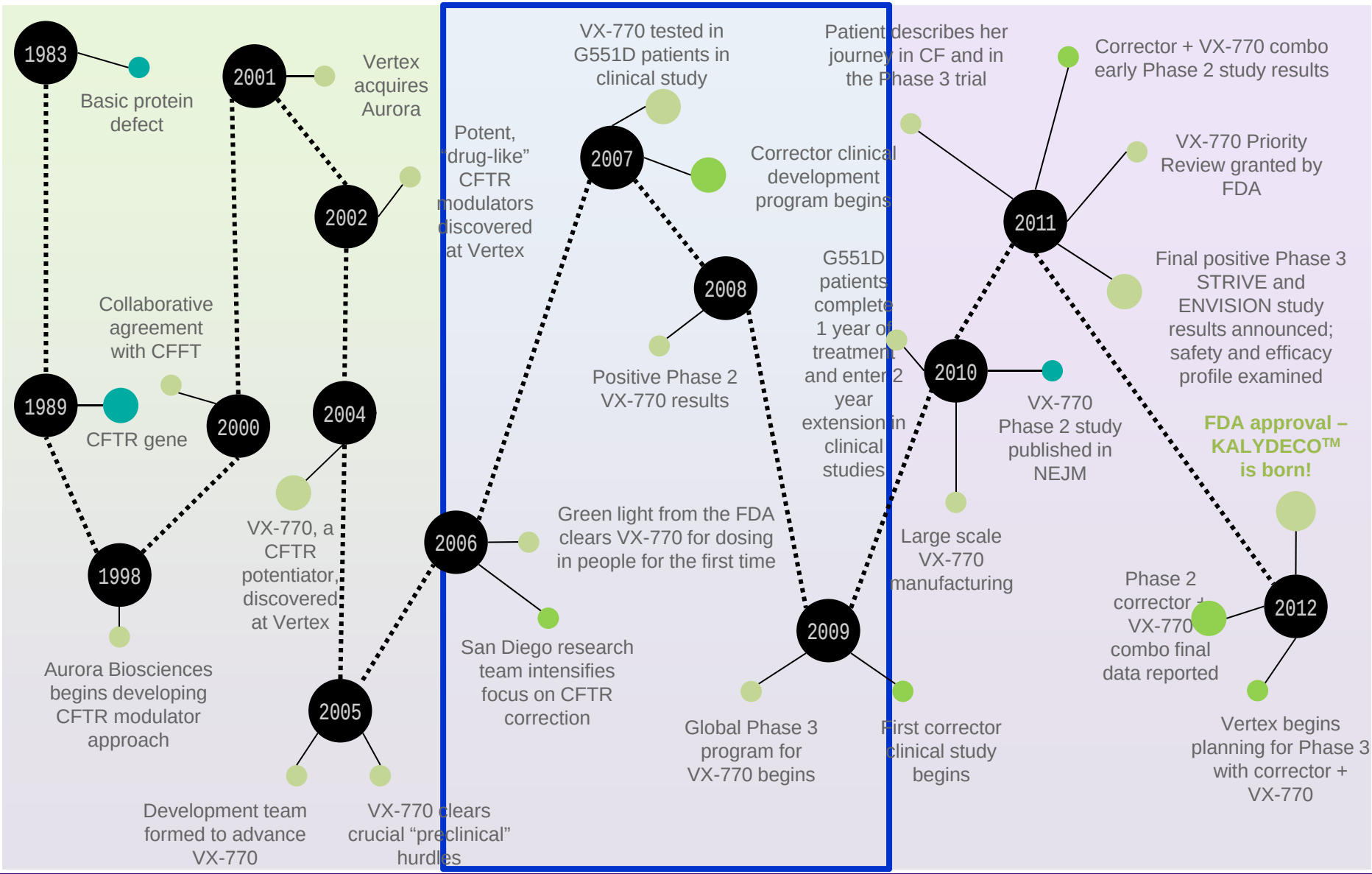
Milestones



2. Why CF made sense for Vertex

- Aligned with the corporate objective of focusing on potential transformational therapies
- Solid scientific foundation to build a drug discovery program upon, both external and internal
- Access to leading experts and knowledge through CF Foundation and clinical trial network (TDN)
- Risk reduced through CFF investment
- Dedicated patients and families
- Good commercial match, including ex-US

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3. Our relationship with the CFF

- Formal collaborative agreement and governance
- Amended several times over the past 12 years
- Joint Research and Joint Development Committees
- Both organizations remained focused on the end game
- Flexibility was needed given different pressures on each organization
- Close communication and alignment across the different functions

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4. Role of US orphan drug designation

- Visibility to the program
- PDUFA user fee waived
- Tax break for certain development expenses
- Exclusivity beyond that awarded for a new NCE
- Grant to help defray clinical study costs

5. Discovery and development challenges

- Little CF expertise at Vertex
- No defined preclinical, clinical path, regulatory or commercial paths
- Limited patient population
- Desire to progress to Phase 3 from a single, small Phase 2 study
- Outcomes for proof-of-concept and Phase 3

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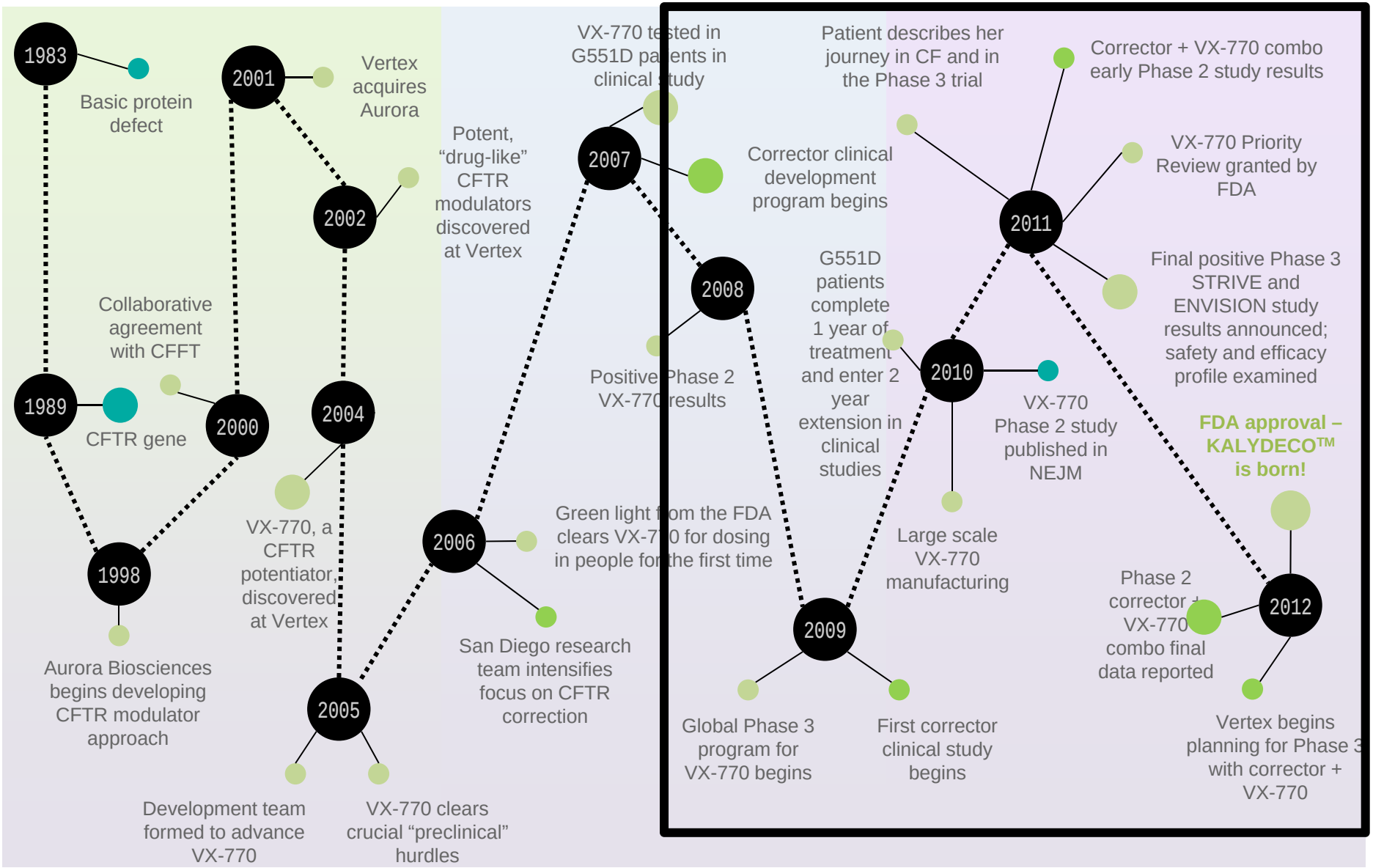
Milestones



6. The US Indication

KALYDECOTM (ivacaftor) Tablets
Initial U.S. Approval: 2012
----------INDICATIONS AND USAGE----------

KALYDECO is classified as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *G551D* mutation. (1)

Limitations of Use:

- Not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene. (1, 14)
- KALYDECO has not been studied in other populations of patients with CF.

Full prescribing information is available at www.kalydeco.com

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7. General lessons

- Understanding genotype-phenotype relationships provided insights into the level of modulation to target with a drug
- The strategic importance of proof-of-concept outcome measures can not be overestimated
- Global studies may be needed to find enough patients and support regulatory requirements in multiple regions
- Be prepared to move to pivotal studies following a small PoC study
- New clinical and regulatory paradigms are needed for addressing those with the very rare mutations

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Acknowledgements

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Patients and families

Collaborators