

ORAL PRESENTATION

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# Development of a pharmacophore model for pharmacological chaperones targeting mutant trafficking-deficient CNG channels

Charlotta PI Schärfe<sup>1\*</sup>, Joachim Taeger<sup>2</sup>, Peggy Reuter<sup>2</sup>, Nina M Fischer<sup>1</sup>, Jens Krüger<sup>1</sup>, Bernd Wissinger<sup>2</sup>, Oliver Kohlbacher<sup>1</sup>

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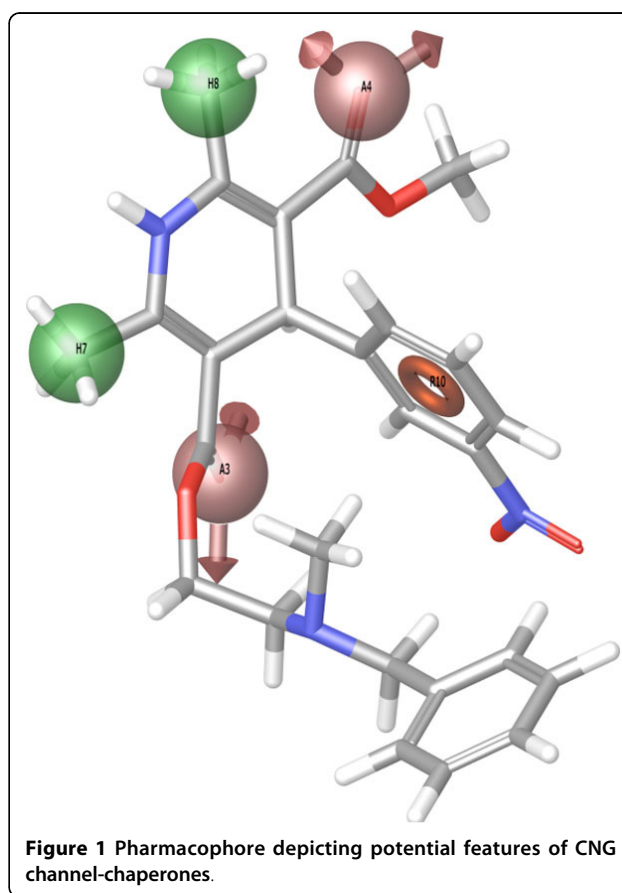
Complete colorblindness (achromatopsia) is caused by autosomal recessively inherited mutations in the retinal phototransduction pathway, predominantly in the CNGA3- and CNGB3-subunit of the cyclic nucleotide-gated (CNG) channels in cone photoreceptors. CNGA3, which is mutated in about 25% of the achromatopsia patients, mainly harbors missense mutations which frequently impair the folding and/or trafficking of the mutant CNGA3-channels [1].

Pharmacological chaperones stabilizing the folding of the mutant protein may be used to overcome this folding-/trafficking-deficiency. More than 50 compounds were evaluated in their ability to restore signal transduction using a calcium imaging-based bioassay utilizing the CNGA3-mutant E228K [2]. With this data we created several pharmacophore models using Schrödinger Phase [3], which describe the chemical features of potential pharmacological chaperones targeting achromatopsia.

We used several approaches leading to different pharmacophore hypotheses:

- Training with the complete set of experimental data (see Figure 1)
- Training with only dihydropyridines since this group showed the highest experimental activity, and
- Training with a data set excluding dihydropyridines.

Our in-house database TueScreen, which includes ZINC12 [4], was screened to identify potentially active compounds. As a result, several potential molecule classes could be found that may be useful as pharmacological



chaperones to improve folding/trafficking of mutant CNG-channels. We will experimentally validate these predictions in a calcium imaging-based bioassay.

\* Correspondence: charlotta.schaerfe@uni-tuebingen.de

<sup>1</sup>Applied Bioinformatics, Center for Bioinformatics, Quantitative Biology Center and Department of Computer Science, University of Tübingen, Tübingen, 72076, Germany

Full list of author information is available at the end of the article

#### Author details

<sup>1</sup>Applied Bioinformatics, Center for Bioinformatics, Quantitative Biology Center and Department of Computer Science, University of Tübingen, Tübingen, 72076, Germany. <sup>2</sup>Molecular Genetics Laboratory, Institute for Ophthalmic Research, Center for Ophthalmology, Tübingen, 72076, Germany.

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