BACKGROUND

Chirality and Chiral Switching

Chemical compounds and drugs can exist as non-superimposable mirror-images of each other (enantioomers). Some drugs have been successfully 'switched' from a mixture of two enantiomers to the single, preferred enantiomer based on its superior properties resulting in an improved therapeutic profile.

Example of a chiral switch: From a racemate to the single, preferred enantiomer

METHODS

• Stability (2,3) was determined by incubation in phosphate-buffered saline (PBS), human or mouse plasma at 37°C and analysis by LC/MS-MS. Rate constants were obtained by numerical nonlinear regression of the LC/MS-MS data against differential kinetic equations (Excel solver). T9A inhibition (2,3) IC50s were obtained by analysis of quantitative T9A data from 18 incubation of human peripheral blood mononuclear cells (PBMCs) stimulated with lipopolysaccharide (LPS) in the presence of increasing concentrations of test compounds (HL equation with variable slope). Cereblon binding data were obtained in a fluorescent polarization probe displacement assay as described before (5) with the exception that the Cys-5-thalidomide probe was replaced by an Atto565-thalidomide probe.

• Pharmacokinetics (PK) studies were run in male rats (lenalidomide) or female SCID mice (CC-122) dosed orally with test compounds with quantitation of drug in plasma by chiral LC/MS-MS. PK parameters were derived using non-compartmental analysis.

• Xenograft studies [3] were performed in female SCID mice administered 106 RPMI-8226 or H929 tumor cells in Matrigel. When tumors reached 100-150 mm3, animals were treated by daily oral gavage with test compounds. Body weights were measured periodically and tumor size was determined biweekly until study termination (42 days, respectively).

IN VITRO EFFECTS OF DEUTERIUM-STABILIZED ENANTIOMERS...

• Improved in vitro stability

Thalidomide Analogs

Immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide have demonstrated anti-tumigogenic and anti-inflammatory activity in human clinical trials and are approved for the treatment of hematological cancers. Their mechanism of action has been linked to their cereblon-binding activity. Recently, these compounds have also demonstrated strong synergistic effects for immuno-oncology applications when combined with immunomodulatory compounds (e.g. rituximab, pembrolizumab), and other cancer agents. Compounds CC-122 and CC-220 are examples of a new series of cereblon (Cereblon) ligands that are in clinical development. CC-122 is being studied as a monotherapy and in combinations with rituximab, obinutuzumab, lurbintrl, nivolumab, sorafenib, the mTOR inhibitor CC-223, and the BTK inhibitor CC-292 for hematological cancers and solid tumors. CC-122 is more potent than lenalidomide and is being studied in clinical trials without dexamethasone.

DEUTERIUM STABILIZATION OF THALIDOMIDE ANALOGS

Some thalidomide analogs contain a rapidly interconverting chiral center. This has prevented a classical ‘chiral switch’ approach. We have used DECS to stabilize and characterize the enantiomers of candidate drugs [2] and several additional thalidomide analogs including CC-11006 [3], CC-122 [3], and CC-220 [4]. The stabilized (S)-enantiomer of CC-122 is DRX-164.

• Only the (S)-enantiomer of CC-122 binds to cereblon (displacement of a lenalidomide-based fluorescent probe) with similar potency to lenalidomide and thalidomide

CONCLUSIONS

• Deuterium stabilizes enantiomers of thalidomide analogs against interconversion

Stabilization enables characterization of the properties of (S)- and (R)-enantiomers.

• Cereblon-binding propensity to (S)-enantiomer (CC-122)

• Anti-inflammatory activity consistently stronger for (S)-enantiomers

• Pharmacokinetics: stereoselective exposure for undesired (R)-enantiomer

• (S)-Anti-tumigogenic activity in xenograft models of multiple myeloma

• Efficacy due exclusively to (S)-enantiomers: similar or improved vs. racemate

Potential tumor-promoting effects due to (R)-enantiomers in these particular models

(Note: The SCID mouse model does not account for the known immunomodulatory effects of drugs such as lenalidomide and does not, therefore, replicate all of the therapeutic effects observed in humans.)

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REFERENCES

1. Deuteria Pharmaceuticals, Inc. was acquired and became a subsidiary of Celgene (2012 Form 10-K).

2. Deuteria Pharmaceuticals, Inc. U.S. Patents #8,288,414, #8,669,276, and #9,023,868.


4. CC-220 is being developed as the (S)-enantiomer. It undergoes rapid interconversion to the (R)-enantiomer in vitro but minimal interconversion in vivo.


6. Data for racem CC-11006 from pharmacology and toxicology review of lenalidomide NDA 021880.