AOP ID and Title:

AOP 460: Antagonist binding to smoothened causes disruption of shh signaling resulting in orofacial clefting
Short Title: Antagonist binding to smoothened causes orofacial clefting

Authors

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Status

Author status	OECD status	OECD project	SAAOP status
Under development: Not open for comment. Do not cite			

Summary of the AOP

Events

Molecular Initiating Events (MIE), Key Events (KE), Adverse Outcomes (AO)

Sequence	Type	Event ID	Title	Short name
1	MIE	2027	Antagonism, Smoothened receptor	Antagonism Smoothened
2	KE	2028	Decrease, GLI1/2 translocation to nucleus	Decrease, GLI1/2 translocation

Key Event Relationships

There are no Relationships associated with this AOP

Stressors

Name	Evidence
Vismodegib	High

Vismodegib

Vismodegib (GDC-0449) is small molecule modulator of the sonic hedgehog (shh) pathway. It functions as an antagonist by binding to Smoothened (SMO) blockings its' activation and subsequent downstream signalling cascade. Vismodegib became the first agent approved to target the shh pathway in Jan. 2012 by the US FDA. It was approved by the European Medicines Agency (EMA) in July 2012 (Meiss, Andrlová et al. 2018). It has been used to identify critical periods of development for the shh pathway. Pregnant C57BL/6J mice dosed with 40mg/kg of Vismodegib between E7 and E10.0 had a peak incidence of CPO (34.38%) at E9.5(Heyne, Melberg et al. 2015). Pregnant C57/BL6J mice treated with 100mg/kg vismodegib via oral gavage at E10.5 and E12.5 displayed a 100% penetrance of complete cleft palate (Zhang, Wang et al. 2017). In a HWJSC/HPEKp spheroid fusion model 10µm vismodegib did not affect HPEKp viability or migration, did not affect *in vitro* fusion (Belair, Wolf et al. 2018).

Overall Assessment of the AOP

References

Appendix 1

List of MIEs in this AOP

Event: 2027: Antagonism, Smoothened receptor

Short Name: Antagonism Smoothened

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:460 - Antagonist binding to smoothened causes disruption of shh signaling resulting in orofacial clefting	MolecularInitiatingEvent

Biological Context

Level of Biological Organization
Molecular

List of Key Events in the AOP

Event: 2028: Decrease, GLI1/2 translocation to nucleus

Short Name: Decrease, GLI1/2 translocation

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:460 - Antagonist binding to smoothened causes disruption of shh signaling resulting in orofacial clefting	KeyEvent

Biological Context

Level of Biological Organization
Molecular

Appendix 2

List of Key Event Relationships in the AOP

There are no Relationships associated with this AOP