DIACC2010, Sole-in-Class Selective Inhibitor of Kinesin KIF20A, Has Potent Preclinical Efficacy in Acute Myeloid Leukemia

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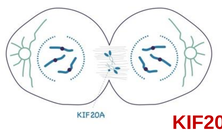
INTRODUCTION

Mitotic kinesins are essential regulators of cancer cell replication and migration.
The microtubule associated motor protein KIF20A (also called MKlp2), a member of the kinesin-6 family, plays an essential role during cytokinesis and is also involved in the fission of RAB6-positive vesicles from Golgi membrane, therefore contributing to intracellular vesicular trafficking (1).

KIF20A plays a critical role in the development and progression of many cancers, and its high expression is associated with disease progression and poor survival outcome (2). More specifically, immature hematopoietic cells, exhibit high KIF20A expression, whereas mature peripheral blood cells do not (3).

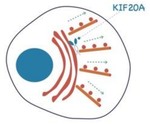
KIF20A: microtubule-associated motor protein, Kinesin-6 family member

- Involved in cell division (cytokinesis)
- and intracellular transport (fission and exit of Rab6 vesicles at Golgi hotspots)



Cytostatic agent
Cytokinesis defect leading to mitotic arrest (multinucleated cells)

KIF20A inhibitor
DIACC2010



Cytotoxic agent
Golgi disruption leading to cell death (apoptosis)

B. Goud, C. Bougeret et al, Nature Com (2017)

DIACC2010: first small molecule targeting KIF20A

- Discovered in collaboration with ICSN/CNRS
- Novel targeted chemotherapy with dual mode of action
- High selective activity against tumor cells

AIM

Herein we describe the preclinical anti-leukemic efficacy of DIACC2010, sole-in-class selective KIF20A inhibitor

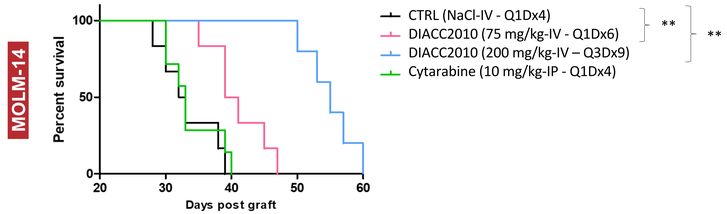
RESULTS

DIACC2010 efficacy: high potency in AML cell lines & PDX-amplified primary AML

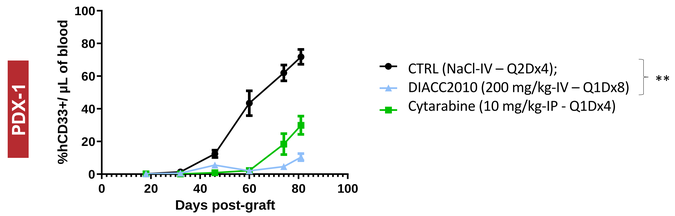
***In-vitro* cytotoxic activity**
(IC_{50} at 96h) on AML human cells

AML cell lines	Cytarabine (nM)	DIACC2010 (nM)	Primary cells	Cytarabine (nM)	DIACC2010 (nM)
KG1	6	20	Hepatocytes	nt	>50 µM
CEM	13	47	PBMC	nt	>50µM
U937	64	14			
KASUMI	70	40	AML PDX-1	**131**	**56**
SKM1	207	65	AML PDX-2	151	165
MOLM-14	**325**	**27**	AML PDX-3	270	777
HL60	700	76	AML PDX-4	768	499
MV4-11	900	40	AML PDX-5	1127	13780
THP1	1550	44	AML PDX-6	4588	909

***In-vivo* anti-tumoral efficacy in AML xenograft model**
NSG mice (n=8/group), IV injection of MOLM14 cells at D0, treatment from D1

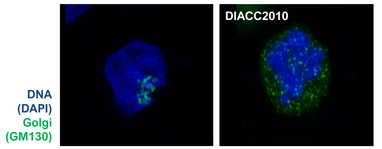


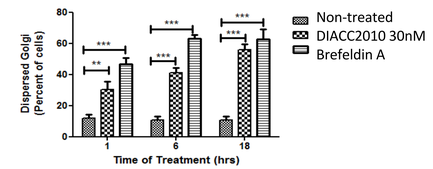
NSG mice (n=6/group), IV injection of PDX-1 cells at D0, treatment from D19



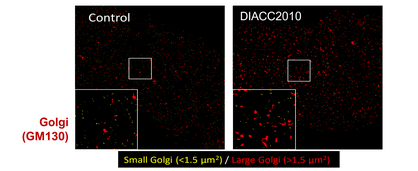
DIACC2010 alters Golgi apparatus

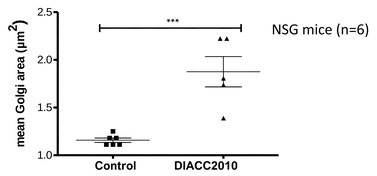
***In-vitro* impact on Golgi** in MOLM14 cells
(18h treatment, confocal microscopy analysis)





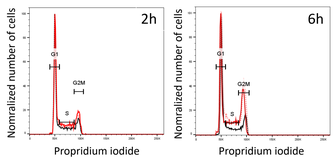
***In-vivo* impact on Golgi** in MOLM14 model
(confocal microscopy analysis in spleen sections, D24)





DIACC2010 blocks cell cycle in G2/M

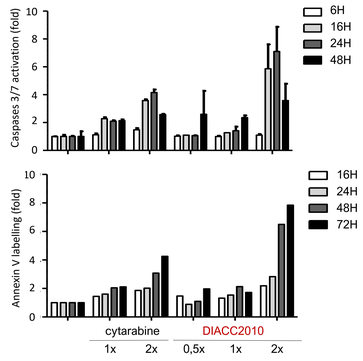
***In-vitro* cell cycle analysis** in MOLM14 cells
(Propidium iodide & flow cytometry)



kinetic	Stages	CTRL	DIACC2010 0,1µM	DIACC2010 1µM
2h	G2/M	16,8	20	21,7
	S	20,5	22,5	24,1
	G1	62,4	57,1	53,8
	total	100	100	100
6h	G2/M	22,1	34,1	31,3
	S	17,9	23,1	23,4
	G1	60,1	42,9	45,6
	total	100	100	100

DIACC2010 induces apoptosis

***In-vitro* induction of apoptosis** in MOLM14 cells
(caspases activation and annexin V labelling)



CONCLUSIONS

- DIACC2010 demonstrated **potent and consistent cytotoxic activity *in-vitro*** against a panel of human AML cell lines and PDX-amplified primary AML
- DIACC2010 was **also efficient in vivo** in CDX and PDX AML models
- DIACC2010-exposed AML cells displayed characteristic **Golgi scattering and cycle arrest leading to cell death**
- Altogether, these results confirm the relevance of KIF20A-directed therapeutic approaches and **support the development of DIACC2010 for the treatment of AML**

REFERENCES

1.Coupling fission and exit of RAB6 vesicles at Golgi hotspots though kinesin-myosin interactions, S. Miserey-Lenkei et al, Nature com, 2017, 104:300

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