

From primary microcephaly-associated CPAP as centriole size/number regulator to microtubules-targeting novel chemotype

A Thesis submitted by

Sonal Jaiswal

in partial fulfillment of the requirements for the award of the degree of

Doctor of Philosophy

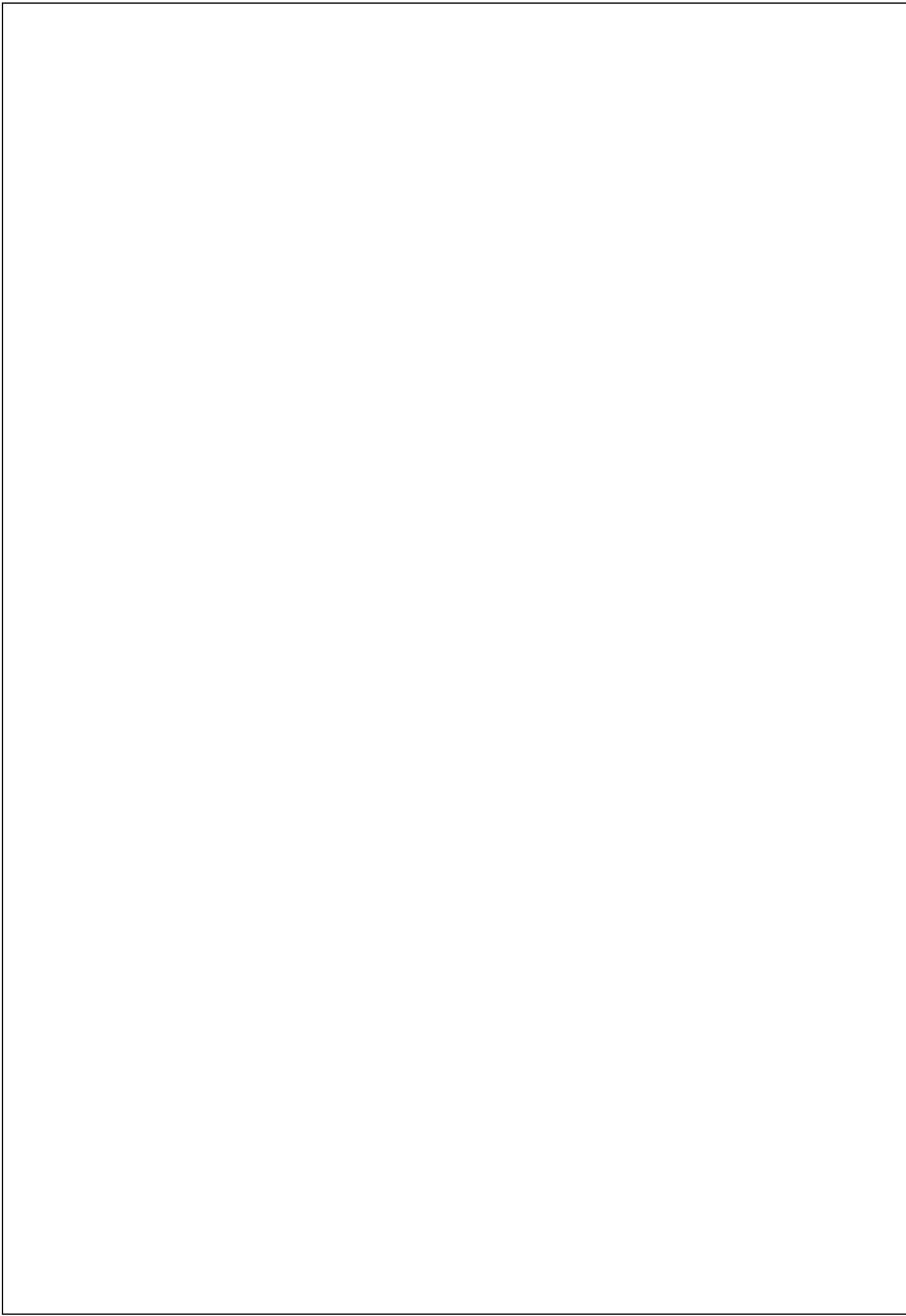


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Bioscience and Bioengineering

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Declaration

I hereby declare that the work presented in this thesis titled “**From primary microcephaly-associated CPAP as centriole size/number regulator to microtubules-targeting novel chemotype**” submitted to Indian Institute of Technology Jodhpur in partial fulfilment of the requirements for the award of the degree of Doctor of Philosophy, is a bonafide record of the research work carried out under the supervision of Dr. Priyanka Singh. The contents of this thesis in full or in parts, have not been submitted to, and will not be submitted by me to any other Institute or University in India or abroad for the award of any degree or diploma.

Sonal Jaiswal
P18BB006

Certificate

This is to certify that the thesis titled **“From primary microcephaly-associated CPAP as centriole size/number regulator to microtubules-targeting novel chemotype”** submitted by Sonal Jaiswal (P18BB006) to Indian Institute of Technology Jodhpur for the award of the degree of Doctor of Philosophy, is a bonafide record of the research work done by her under my supervision. To the best of my knowledge, the contents of this report, in full or in parts, have not been submitted to any other Institute or University in India or abroad for the award of any degree or diploma.

Dr. Priyanka Singh
Ph.D. Thesis Supervisor

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List of Symbols

α	=	Alpha
β	=	Beta
γ	=	Gamma
nm	=	Nano-Meter
μM	=	Micro-Meter
nM	=	Nano-Molar
mM	=	Milli-Molar
MDa	=	Milli-Dalton
KDa	=	Kilo-Dalton
IC₅₀	=	Half-maximal inhibitory concentration
$^{\circ}\text{C}$	=	Degree Celsius
RPM	=	Rotation per minute
p	=	Probability
μm	=	Micro-Meter
$\Delta\Delta\text{G}$	=	Gibb's free energy
μl	=	Micro-Liter
μg	=	Micro-Gram
CH₂	=	Methylene
OH	=	Hydroxide
O	=	Oxygen
SD	=	Standard Deviation

List of Abbreviations

PCM	=	Pericentriolar Material
CPAP	=	Centrosomal-P 4.1 associated protein
MT	=	Microtubule
MCPH6	=	Autosomal recessive primary microcephaly
γ-TuRC	=	Gamma-tubulin ring complex
γ-TuSC	=	Gamma-tubulin small complex
STIL	=	SCL-interrupting locus protein
CEP	=	Centrosomal Protein
MTT	=	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
KIF2	=	Kinesin family member 2
MTOC	=	Microtubule organizing center
<i>C. elegans</i>	=	<i>Caenorhabditis elegans</i>
SCLT1	=	Sodium channel and clathrin linker 1
FBF1	=	Fas binding factor 1
ODF2	=	Outer dense fibre protein 2
Spc	=	Spindle body component
GCP2/3	=	Gamma tubulin complex component
CDK5RAP2	=	CDK5 regulatory subunit associated protein 2
Sgo1	=	Shugoshin1
SCF^β-	=	Stem cell factor Beta transducing repeat containing protein
TrCP		
cNap1	=	Centrosomal Nek-2 associated protein 1
LRRC45A	=	Leucine rich repeat containing protein 45A
PLK4	=	Polo-like kinase 4
PP1R35	=	Protein phosphatase 1 regulatory subunit 35
SAS6	=	Spindle assembly abnormal protein 6
CP110	=	Centriolar coiled coil protein
Nek2A	=	NIMA related kinase 2A
Eg5	=	Kinesin spindle protein 5
Kif25	=	Kinesin like protein 25
NDE1	=	Nuclear distribution protein nude homolog 1
OMIM	=	Online mendelian inheritance in man
SCKL	=	Seckel syndrome
NIN	=	Nodule inception protein
Nlp	=	Nucleoplasmin like protein
GTP	=	Guanosine triphosphate
DHA	=	Dihydroartemisinin
LSD1	=	Lysine specific demethylase 1
SAR	=	Structure activity relationship
HDAC	=	Histone deacetylases
FAK	=	Focal adhesion kinase
EV	=	E1235V
DN	=	D1196N
SPD-2	=	Spindle defective protein 2
SAK	=	Staphylokinase

ANA2	=	Anastral spindle 2
CEA	=	Centriole elongation activator
CEI	=	Centriole elongation inhibitor
EGFP	=	Enhanced green fluorescent protein
GST	=	Glutathione-S-transferase
His-MBP	=	Histidine-Maltose binding protein
Ni-NTA	=	Nickel-Nitrilotriacetic acid
NaCl	=	Sodium chloride
RNAi	=	RNA interference
PBST	=	Phosphate buffered saline with Tween 20
TRITC	=	Tetramethylrhodamine
FITC	=	Fluorescein isothiocyanate
IgG	=	Immunoglobulin G
DTT	=	Dithiothreitol
PMSF	=	Phenylmethylsulfonyl fluoride
SDS-PAGE	=	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
RMSD	=	Root Mean Square Deviation
RMSF	=	Root Mean Square Fluctuation
SD	=	Standard Deviation
SEM	=	Standard Error of mean
wt	=	Wild-type
DAPI	=	4,6-Diamidino-2-phenylindole
WHO	=	World Health Organization
P-gp	=	Phospho-glycoproteins
Bcl2	=	B-cell leukemia 2 protein
PDK1	=	Phosphoinositide dependent kinase 1
DMEM	=	Dulbecco's Modified Eagle Medium
DMSO	=	Dimethyl sulfoxide
PI	=	Propidium Iodide
v	=	Version
BSA	=	Bovine serum albumin
SMILES	=	Simplified Molecular Input Line Entry System
ADMET	=	Chemical absorption, distribution, metabolism, excretion, and toxicity
Cmpd	=	Compound
ACE	=	Atomic Contact Energy
ROS	=	Reactive Oxygen Species
PI3K	=	Phosphoinositide 3-kinase
mTOR	=	Mammalian target of rapamycin
S6K1	=	S6 kinase beta1
PDB	=	Protein data bank
CDK	=	Cyclin dependent kinase
MK-2	=	Mitogen activated protein kinase 2
bp	=	Base pair

