SAPIEN BIOSCIENCES

Advancing Science, Personalizing Medicine

SAARUM SCIENCES

Drug Discovery Platforms & Services

Bio-Bank & Personalized Medicine
Primary cell models – phenotypic assays
Research & Clinical Support Services

A joint venture with

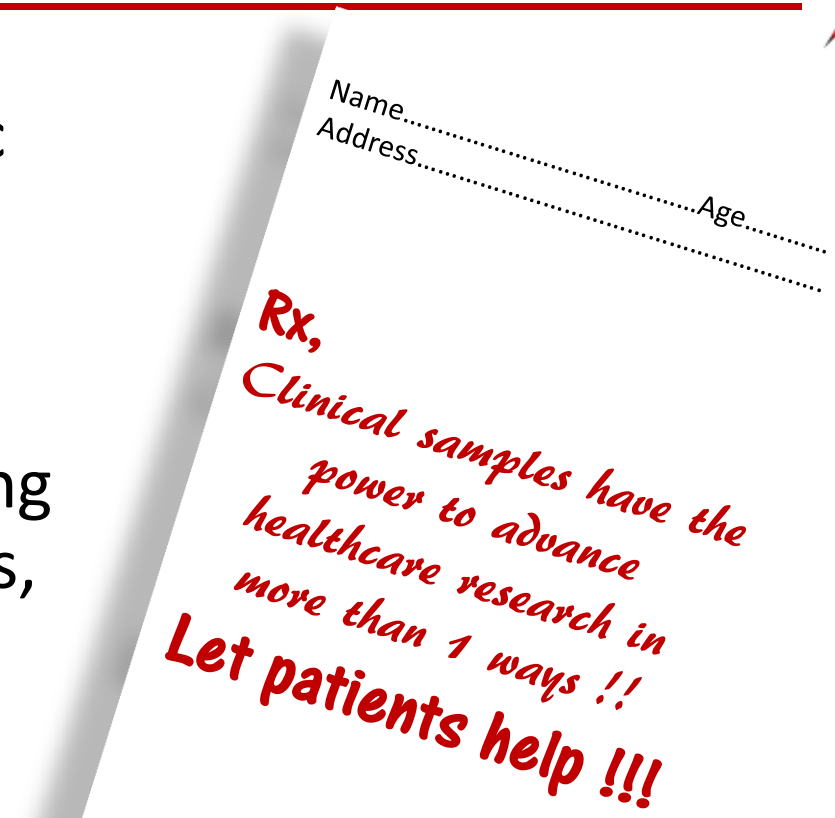
Apollo HOSPITALS

The ‘Essence’ of Saarum-Sapien

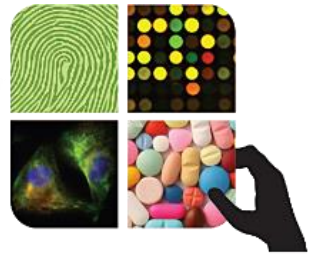
India’s 1st commercial **Bio-bank** with systematic archive of ethically consented, anonymized patient samples & associated data

With a mandate to utilize these samples to revolutionize healthcare scenario by contributing to drug discovery, novel diagnostics, biomarkers, personalized medicine alike…

To ensure effective clinical outcome !!



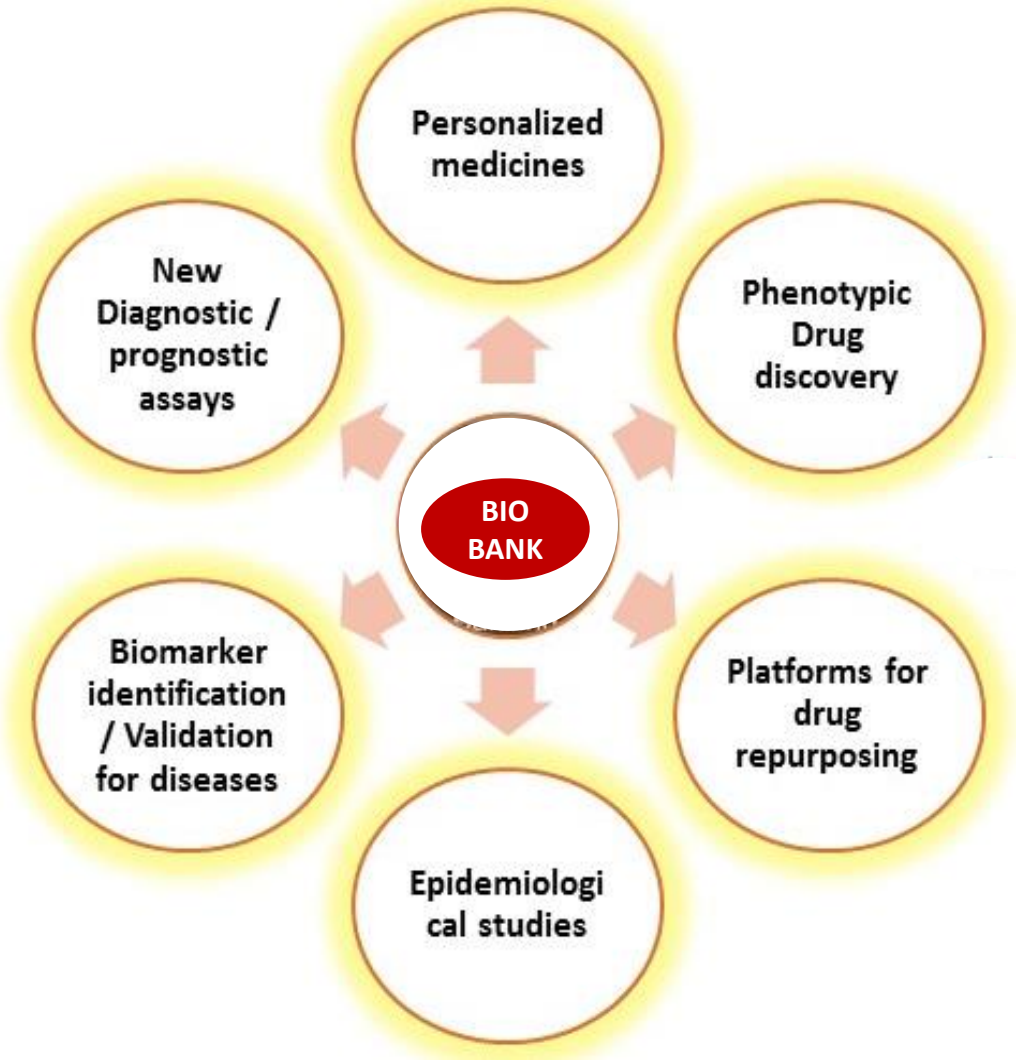
Sapien is not a vendor of samples.
Banked samples are used only for R&D
NOT FOR regenerative medicine or transplantation

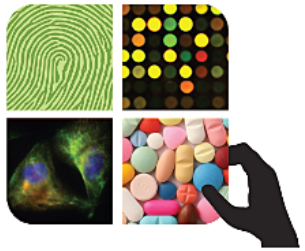


Our win-win set-up to revolutionize healthcare

SAPIEN BIOSCIENCES

Advancing Science, Personalizing Medicine





SAARUM SCIENCES

Drug Discovery Platforms & Services

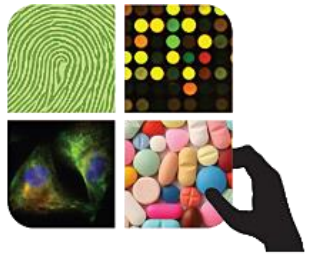
Leadership team

Sreevatsa Natarajan
CEO

- Experienced business professional with over 16 yrs of global pharma experience in drug discovery, clinical research, portfolio mgt, licensing & bus. dev.
- Extensive experience in constructing & negotiating several collaboration & licensing deals and managing global alliances.
- Proven track record of leadership roles across several global drug discovery organizations & business models
- Participated in and managed teams that have developed and registered several NCEs (Oxycontin, Telaprevir etc)

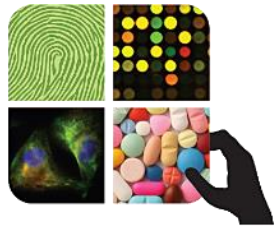
Jugnu Jain, Ph.D.
CSO

- Molecular and cell biologist experienced in the use of primary human samples & related cellular paradigms for drug discovery & target validation
- PhD in Genetics (Cambridge), post-doc in immunology (Harvard) with 25 years of post-PhD experience in autoimmune, inflammation & neuro-inflammation, cancer & diabetes therapeutic areas.
- Led biology teams on novel drug discovery targets & contributed to IND filing for many molecules.
- Extensive R&D leadership experience and proven track record of forging several successful R&D collaborations



Leadership team

- **Dr Lakshmipathi Khandrika** – Senior Scientist - Over 14 years of experience in Molecular Biology and ~8 years in Cancer Cell Biology (India, US, Europe).
- **Dr Mukesh Gandhari** – Principal Scientist – over 9 years of experience in drug discovery and biopharmaceuticals at Sun Pharmaceuticals, GVK Biosciences
- **Dr. Prasanna Kumar** – Associate director – Strategic marketing Clinical diagnostics - Physician with about 7 years of ICU and ER experience, MBA + 4 Yrs of Pharma diagnostics experience in Elli Lilly , MedGenome.
- **Dr. Rachna Goyal** – Associate Director – Business and project management – Trained cell Biologist with over 9 years of customer facing project management experience at Millipore, Vimta, Lonza
- **Dr. Soma Chatterjee** – Associate director – Biobank operations – Trained cancer biologist with over 9 years of experience in ethical tissue sourcing and cell biology applications at Lonza
- **Dr. Sumeda Dange** – Quality Assurance – Trained Pharmacist with PhD in Electro-physiology. Decade of Industrial exposure in the field of Quality Assurance at Dr. Reddy's and Nektar Therapeutics



The Apollo advantage

The Apollo set-up – Asia's largest hospital network

Owned	Managed	Total		Owned	Managed	Total
6,684	1,933	8,617	across	39	11	50

Tertiary, Super Specialty & Secondary Care

JCI accreditation 8 | NABH accreditation 10

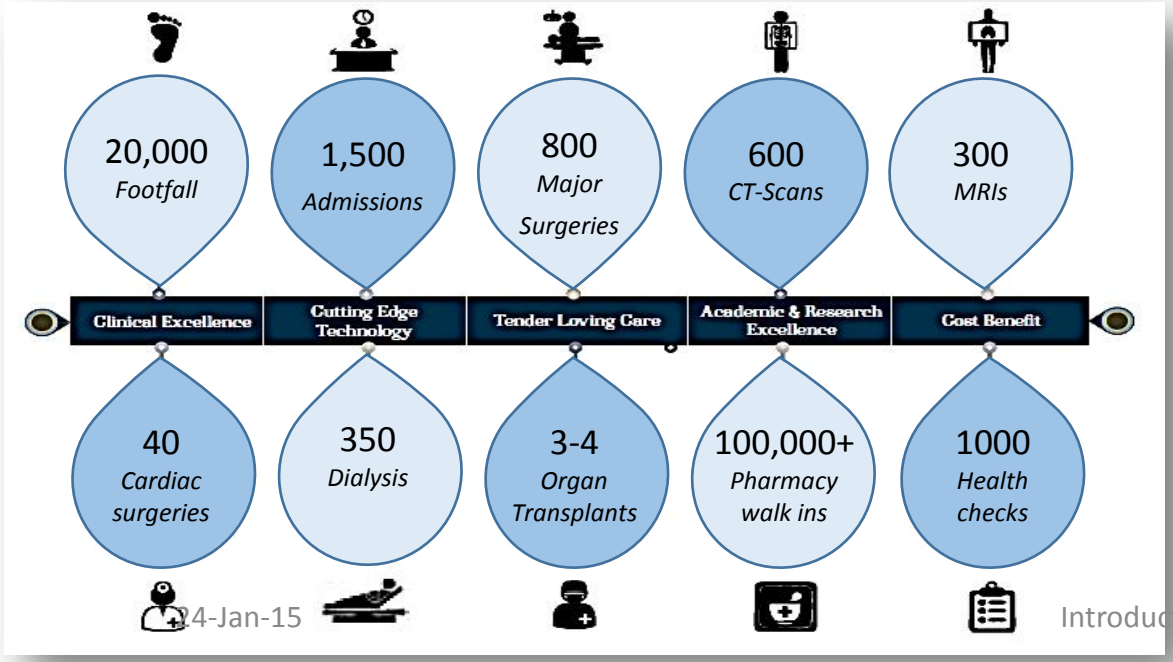
Employed + "fee for service" Doctors	Nurses	Paramedics
5,870	9,469	3,141

67% of Consolidated Revenues

FY14 at Apollo hospitals

325,000+ Admissions	3,000,000 Out-Patients	250,000+ Preventive Health Checks
10,000 Heart Surgeries	5,000+ Joint Replacements	13,000 Neuro Surgical Operations
500 Robotic Surgeries	1,000+ Kidney Transplants	375 Liver Transplants
120 Countries Medical Value Travel	150 Bone Marrow Transplants	150,000+ Radiotherapy Sessions 42,000+ Chemotherapy Sittings

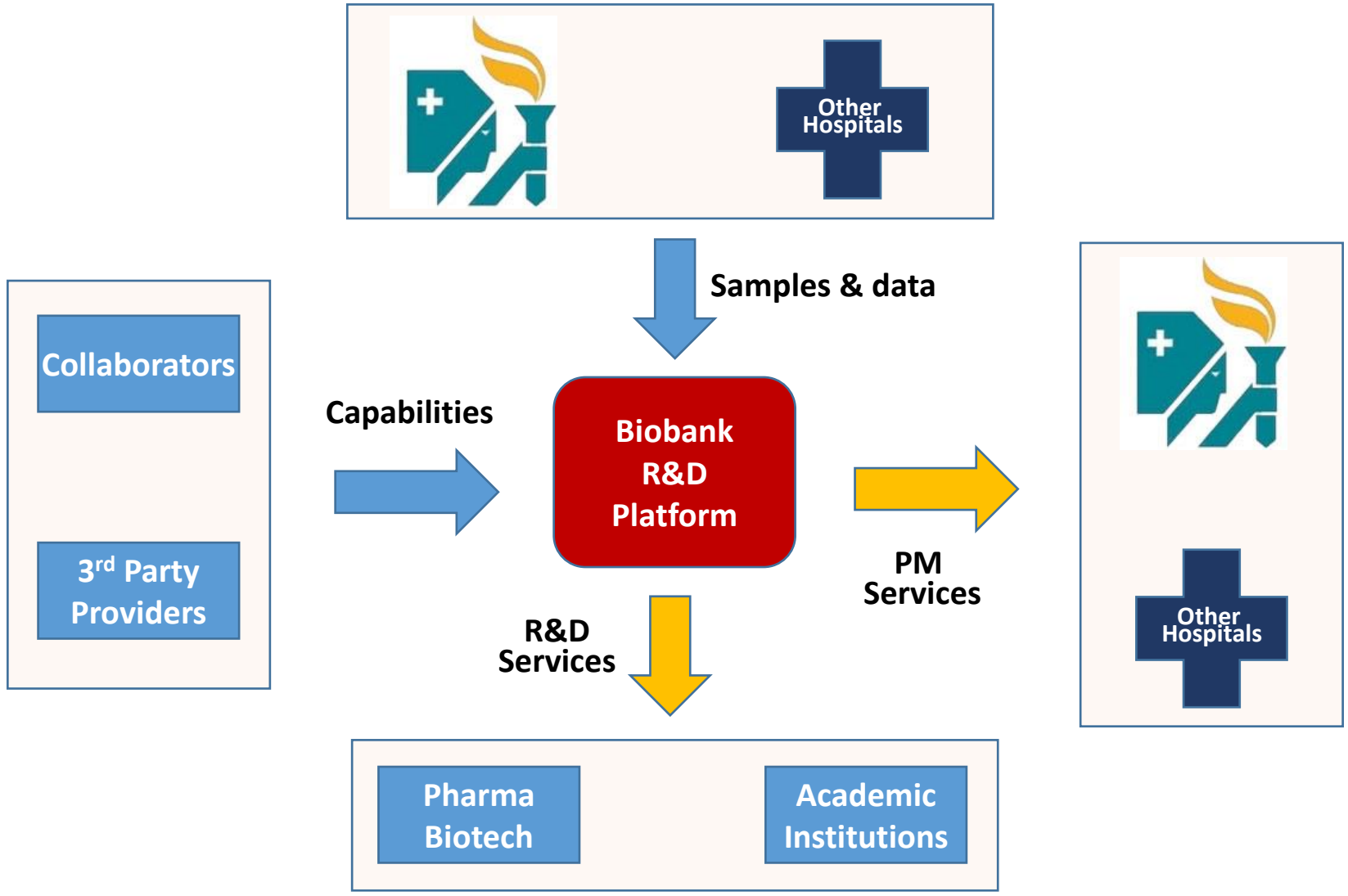
A typical weekday in the world of Apollo



An abundant resource of diseased tissue samples and an honest will to use them for betterment of mankind

- contributing to diagnostics and drug development
- offering these new drugs / diagnostics for their patients

Our Networked Business Model



Impact of Biobank @ Drug discovery

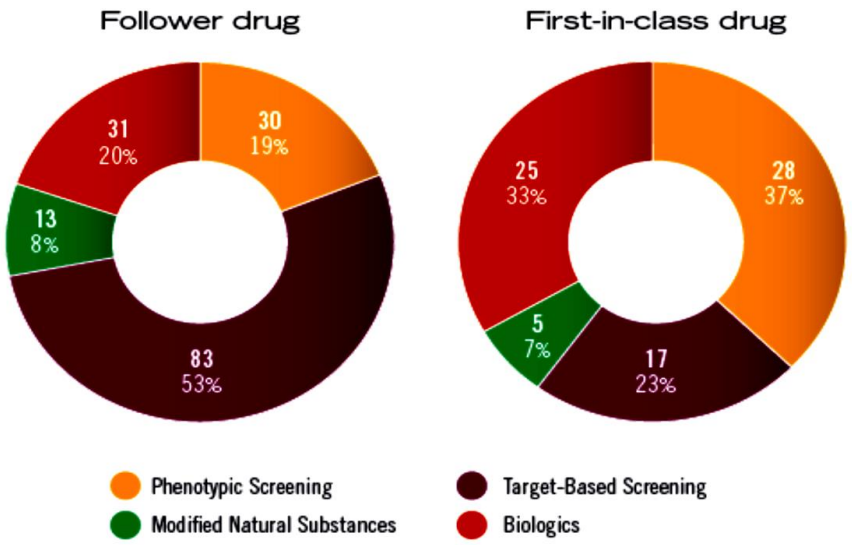
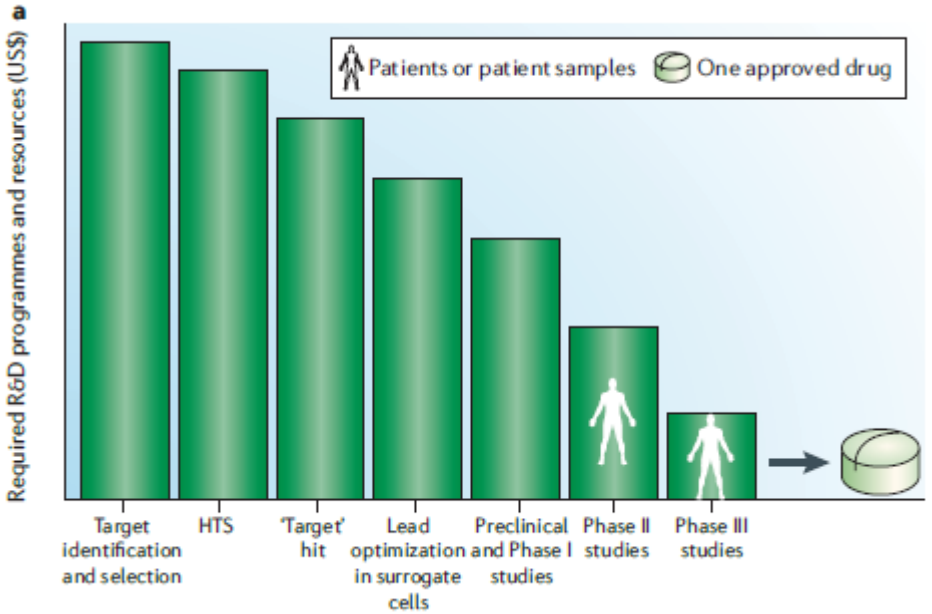
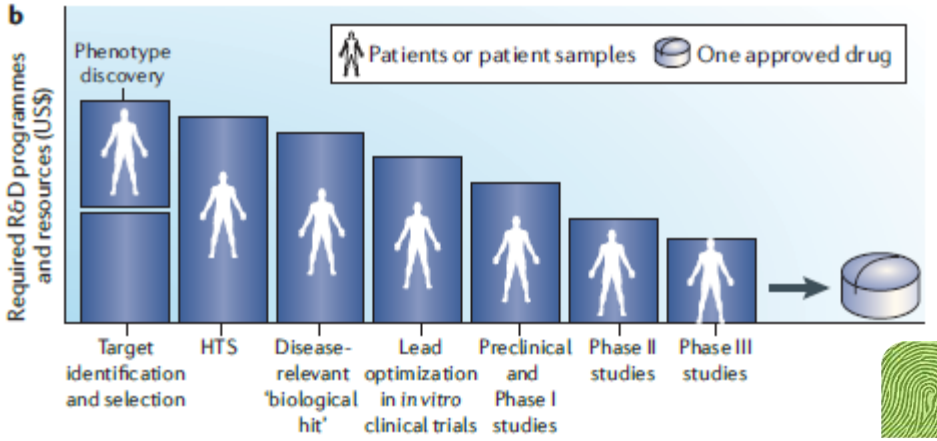


Figure 1. The distribution of new drugs discovered between 1999 and 2008, according to the discovery strategy. Adapted from Swinney and Anthony 2011. The graph illustrates the number of NMEs in each category. Phenotypic screening was the most successful approach for first-in-class drugs, whereas target-based screening was the most successful for follower drugs.

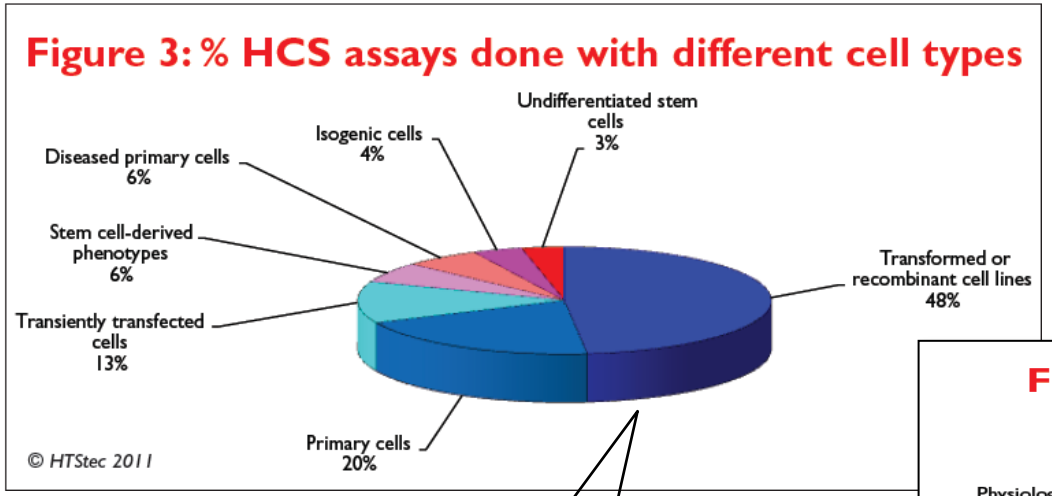




Grskovic et al., Nat Rev Drug Disc 2011

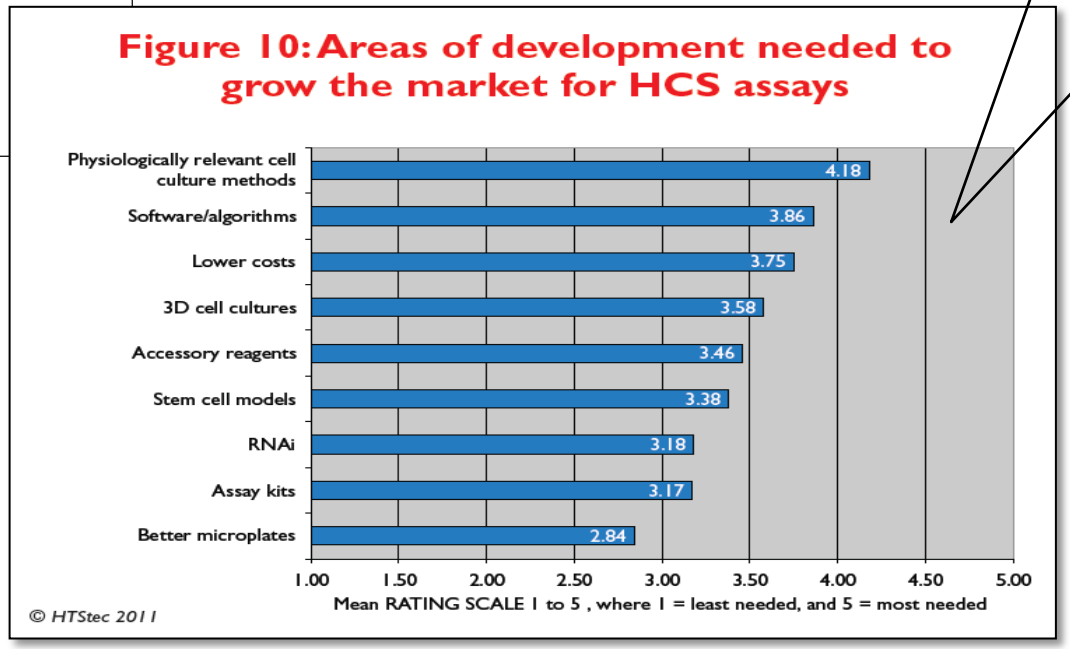
Phenotypic screening using tissues / primary cells for a direct desired effect in a living system, possibly a broad range of effects simultaneously, independent of any defined target - increases the mechanistic understanding of the underlying biology and can **reduce cost of discovery by 50-80%**

Physiological assay systems are need of the hour



26% of High content screening assays are being performed using primary cells (Diseased or healthy)

Most researchers feel that Physiologically relevant cell culture methods (imply primary cells / co-cultures / tissue models etc.) needs the most development to make screening assays more effective

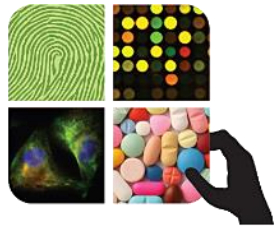


Courtesy : HTSec Survey on Diseased primary cells 2010 and HTStec HCS assay trend 2011

Sample types banked at Sapien

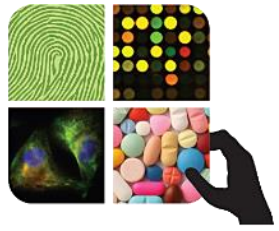
- **Retrospective – after anonymization.**
  - FFPE blocks – Tumor as well as adjacent non-tumor
- **Prospective samples - with informed consent**
  - Fresh tumor and adjacent non-tumor samples
  - Hematological tumors: Cell types (PBMCs, T/B cells, platelets etc.)
  - Blood, Plasma, Serum
  - Saliva, Urine, BAL, Pleural fluid, synovial fluid etc.
  - *Non-diseased specimens*
- **Health Check-up left over samples - with informed consent**
  - Serum / Blood / Urine - With extremely rich associated data

~50,000 patients' blocks & data are being retrieved at Hyd. Expect ~500,000 samples in 5 years across Apollo network



Ethics of Bio-banking – Peace of mind for researchers

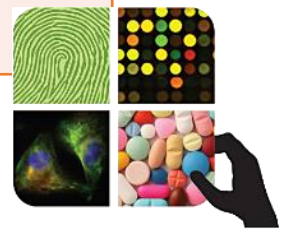
- Sapien works within ICMR and international guidelines, and follows high ethical norms with respect to transparency and patient privacy
- Sapien banks samples after Hospital EC approval & with Informed Consent
  - Informed consent form language follows ICMR guidelines
  - Retrospective samples (FFPE blocks) after anonymization
  - Prospective samples with ICF
- Sapien's Repository Ethics Committee (REC) also being constituted to review projects internally



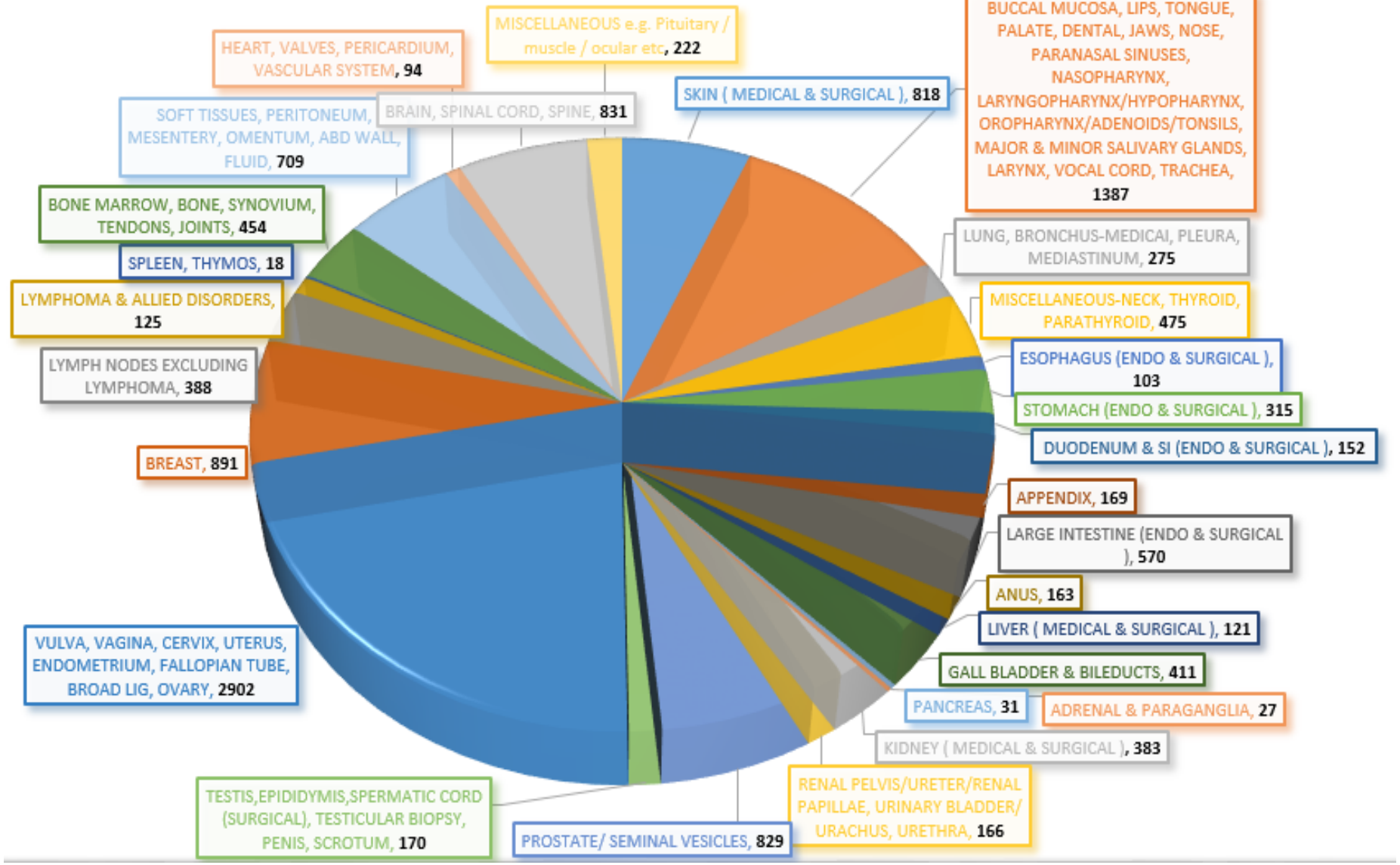
Access to fresh tissues

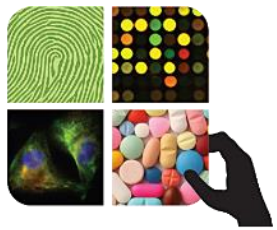
- Accessibility across Apollo network - Possible to source many more sample types based on requirement !!
- **Many of these have been cultured to derive primary cancer cells e.g. breast / prostate/ Glioma**

Fresh tissues @ Sapien - Currently banked / feasible to source				
Abdominal cavity	Tonsil	Parathyroid	Malignant Lymph nodes	Surgical resection of Adenoids
Bladder	Glossectomy	Parotid	Laryngectomy	Surgical resection of the spleen
Brain	Thyroid	Pancreas	Uterus	Surgical resection of Tonsils
Breast	Testis	Ovary	Prostate	Fibroids from uterus
Kidney	Stomach	Omentum	Penis	Spinal Tumor
Colon	Spleen	Oesophagus	Normal Lymph nodes	Liposuction
Buccal Mucosa	Spinal Cord	Lung	Male normal breast reduction	Vitreous gel from eye
Gluteal Region	Rectum	Liver	Female normal Breast reduction	Synovial fluid
Cervix			Non malignant hysterectomy sample	Cord Blood



Current inventory of FFPE Blocks – source tissue wise

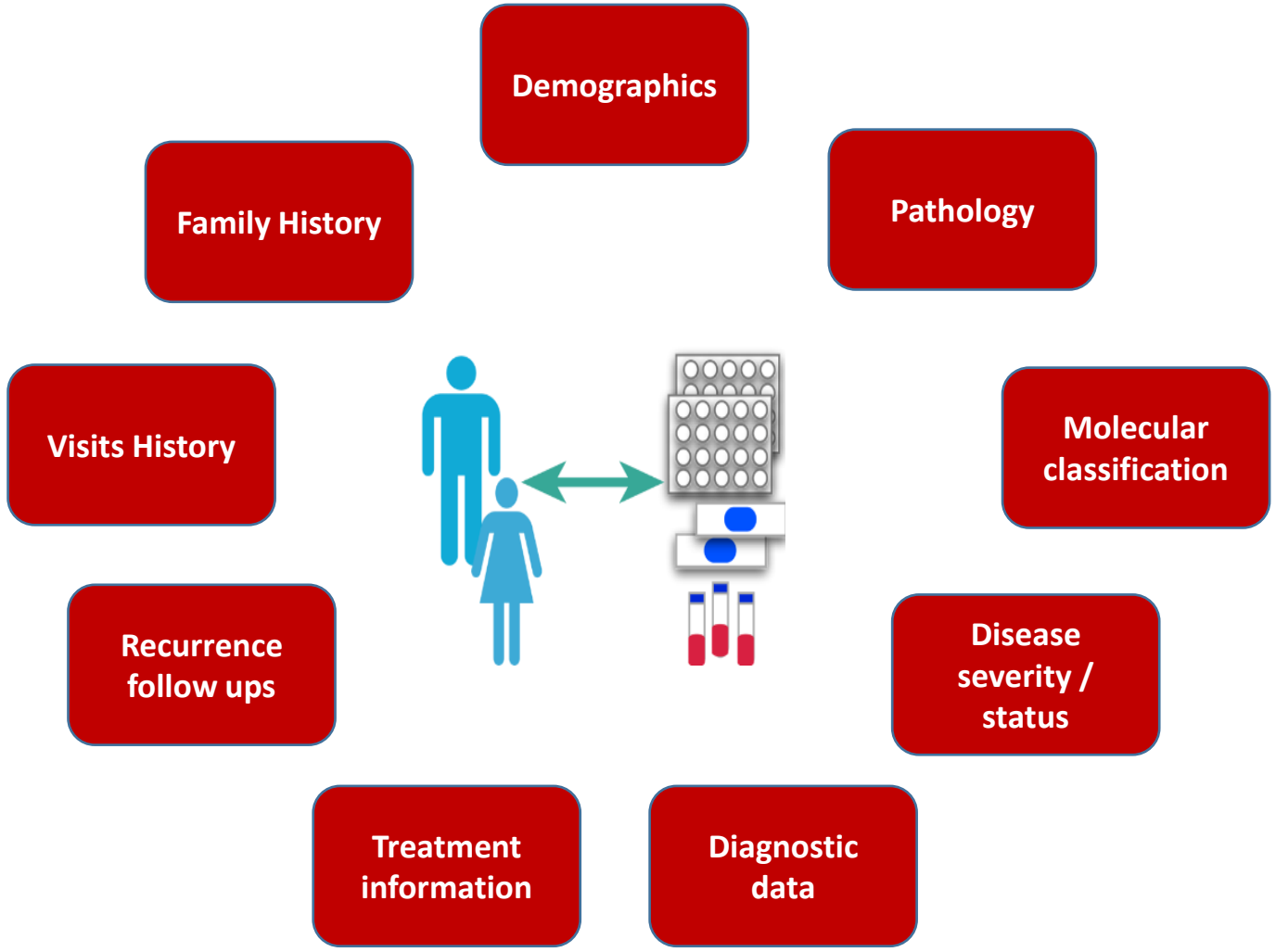




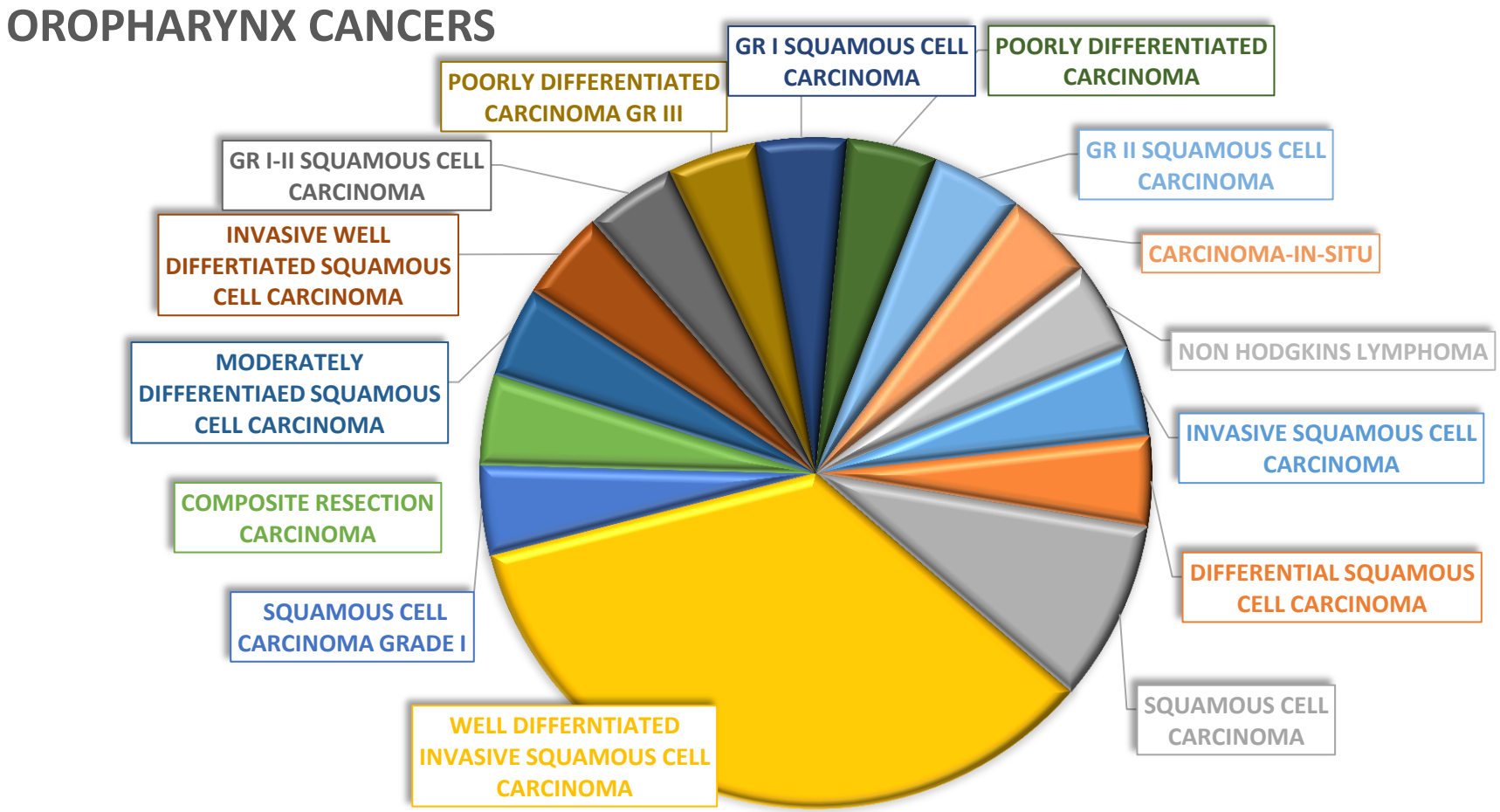
* Data from single location - Apollo Hyderabad for 3 yrs. Sapien is working on systematically archiving samples from across Apollo network over several years

Associated information: holds promise for future

Any specific inclusion / exclusion criteria can be set as per need of study



Sneak peek into the diversity of banked samples



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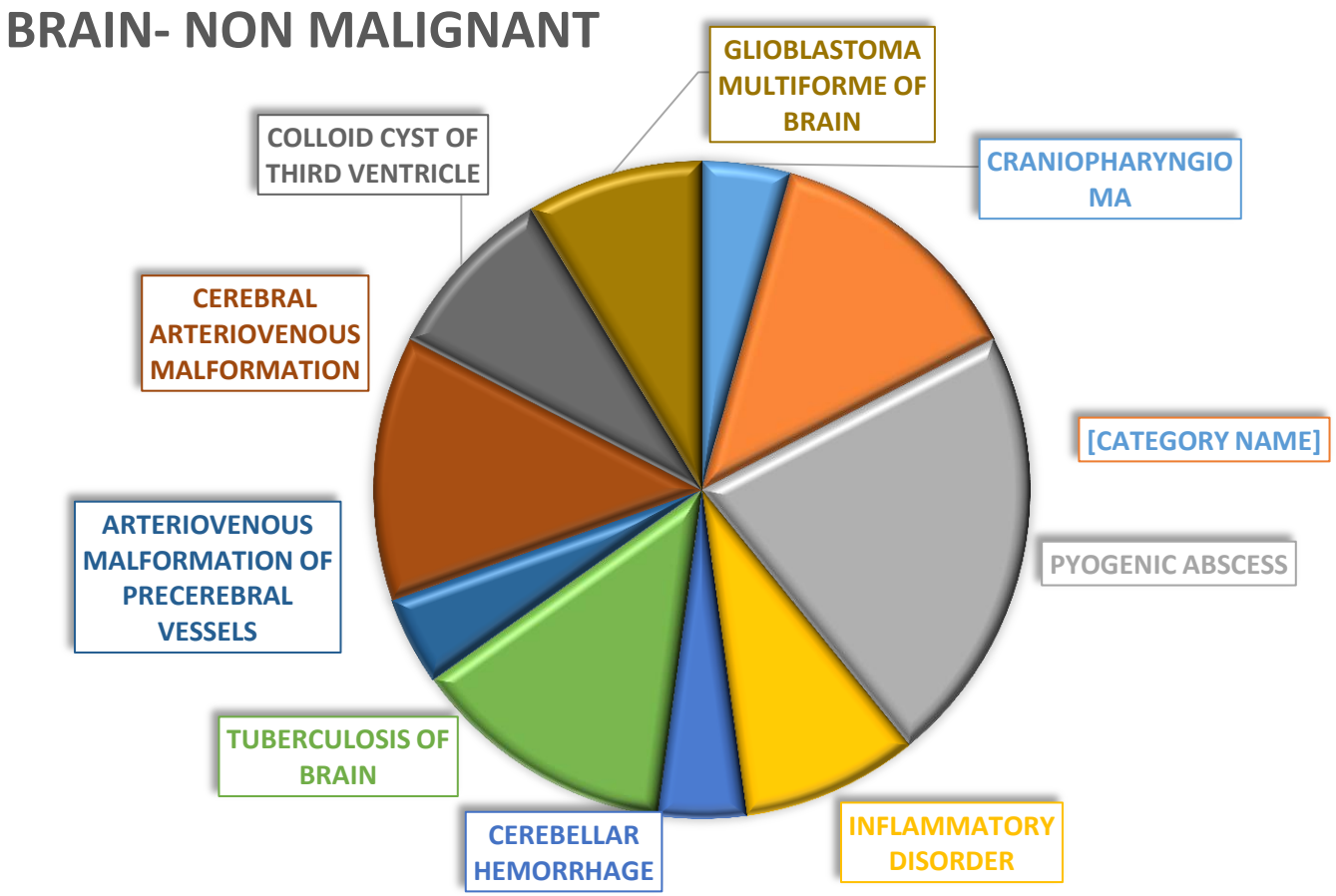
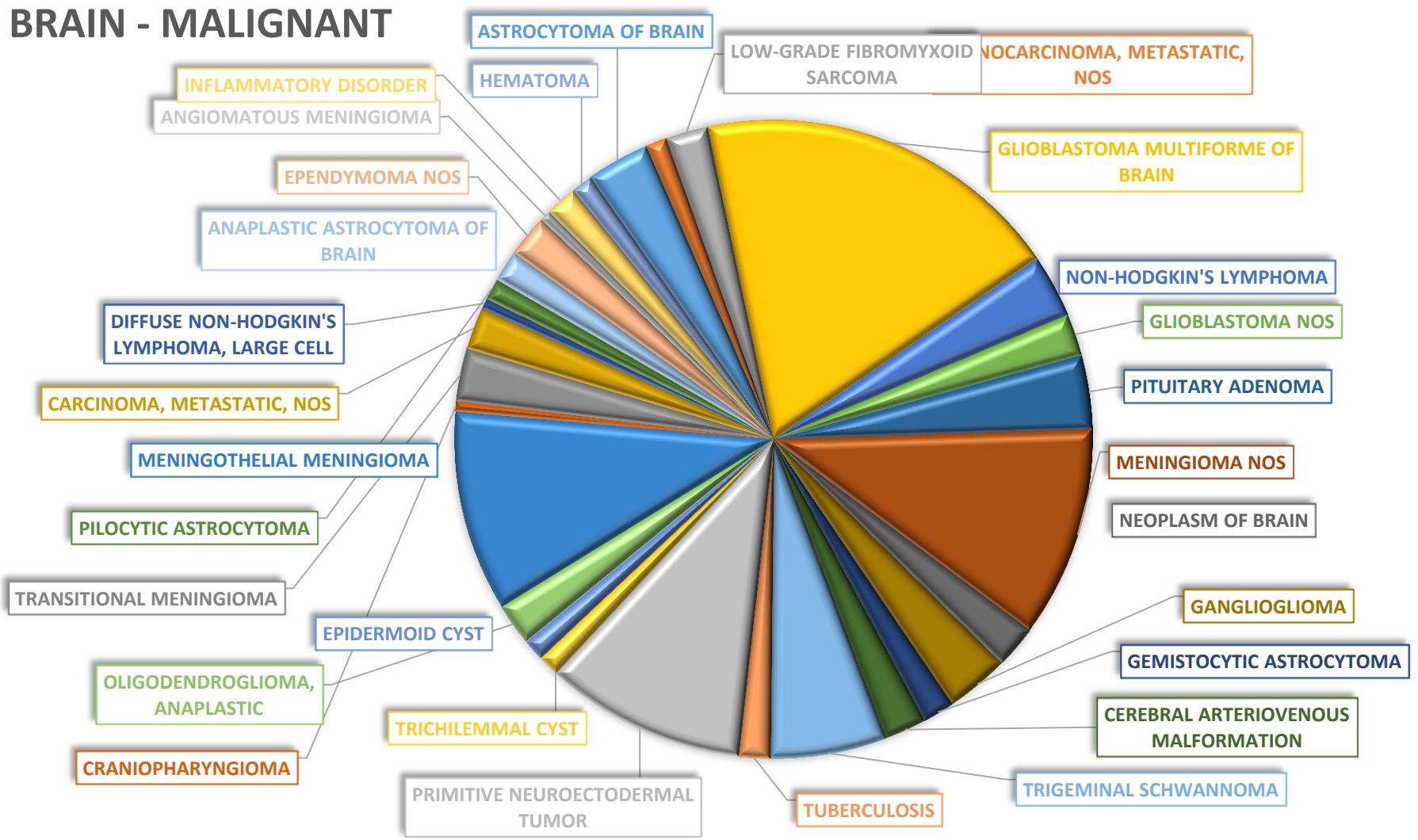
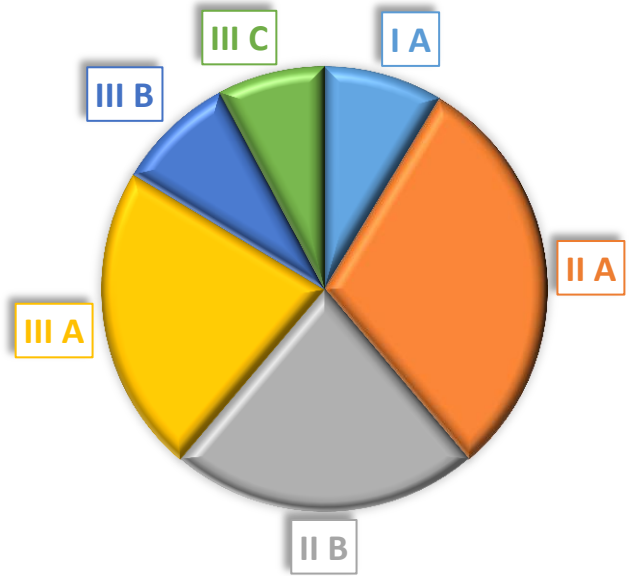


Sneak peek into the diversity of banked samples

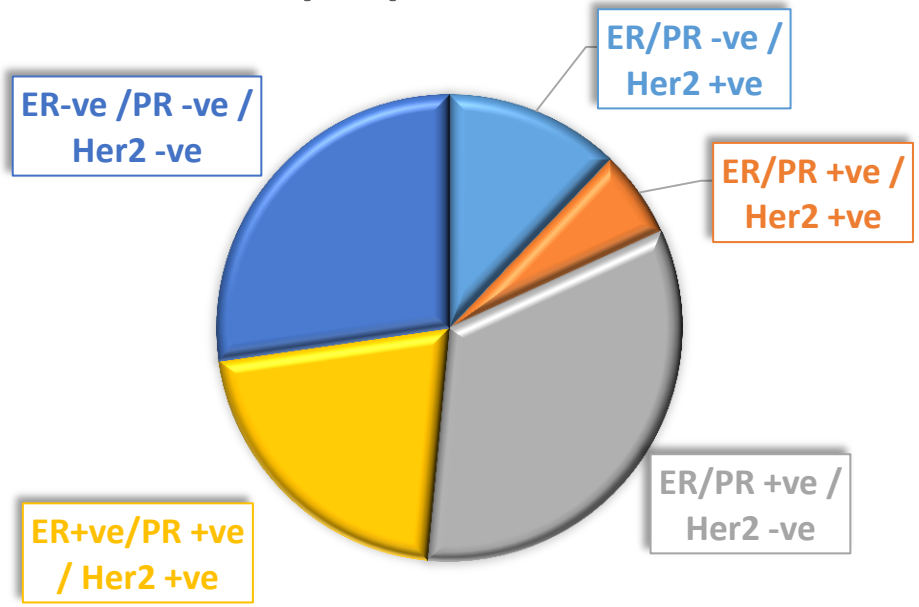


Sneak peek into the diversity of banked samples

BREAST CANCER - STAGES



BREAST CANCER - ER/PR/Her2 STATUS*



* Information only for a subset of the entire sample inventory

Sneak peek into the associated information*

Sample Information				
Serial No.	Date & method of diagnosis	Date of birth, Age at diagnosis, Sex	Registration / hospital #	Pathology block #/ Slide #
ABC001	14th July 2005, lumpectomy	01-12-1960; 45/F	XYZ1234	5124/05

Pathological information				
Specimen type: MRM/BCS surgery with date	DCIS/IDC/ILC /Papillary carcinoma & Grade	TNM & stage, Metastasis at detection	ER/PR/Her-2 /Ki67/P53	Miscelleneous:, FISH for Her-2/neu Oncotype Dx score
BCS; 21st July 2005	IDC-3 with DCIS focus	pT2N2M0, Stage 2	70%P/45%P/ 1+/60%/Not done	FISH: negative; ODx score: 18

Chemotherapy information		
Neo-adjuvant/ Adjuvant, Drugs/Regimen and # of cycles	Dates of CT	Repeat CT with drugs and dates
Adjuvant, FACx4 + Paclitaxelx12 ;	September 2005-March 2006	Capecitabine x6 in January 2007-March 2007

Radiotherapy information		
RT: Type, Dose and fractions	Dates of RT given	Miscelleneous: Booster dose ?
EBRT; 58 Gy/28 Fractions	April 2006-May 2006	10Gy/5 Fractions June 2006

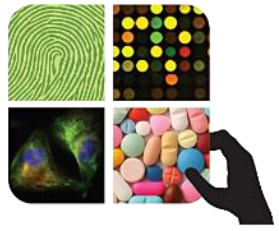
Hormonal therapy		
Neo-adjuvant/ Adjuvant & Drug name	Dose & dates of HT taken	If HT changed, new drug name & date
Adjuvant, Tamoxifen 20mg/day	Started July 2006 for 5 yrs	Chaged to AI July 2011

Recurrence information	
Date & site of recurrence	How was recurrence detected?
December 2006, Liver and Bone	PET-CT and Bone scan

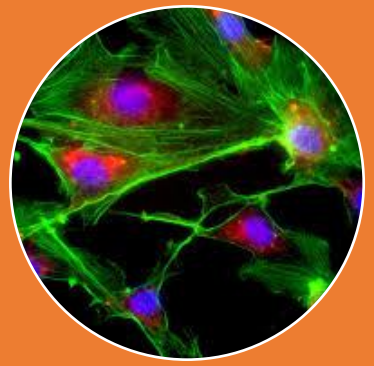
Current Status			
Last F/up date	Alive: Date & With mets or not	Passed away: Cause of death & date	Miscelleneous:
12th Sept 2013	Alive with liver & bone mets	N/A	On regular f/up, every 3 months; no more new mets as assessed by CxR, US(A+P), PET-CT,

Example of associated data for Breast cancer samples

* that can be collated and provided based on requirement.



R&D Infrastructure available to Saarum-Sapien



Flow cytometry

Cell sorting

Fluorescent microscopy

Laser scanning confocal

SNPs, SNP arrays

Sequencing

Bioinformatics including pathway/ systems biology

Biacore

HPLC

GCMS

LC-MALDI-TOF

X-Ray diffraction

CD

Karyotyping

FISH

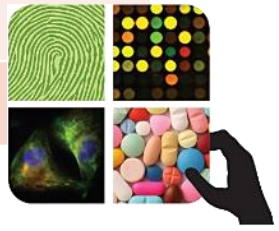
ISH

ELISAs

In-house @ Saarum- Sapien or at strategic collaborators

Capabilities @ Sapien

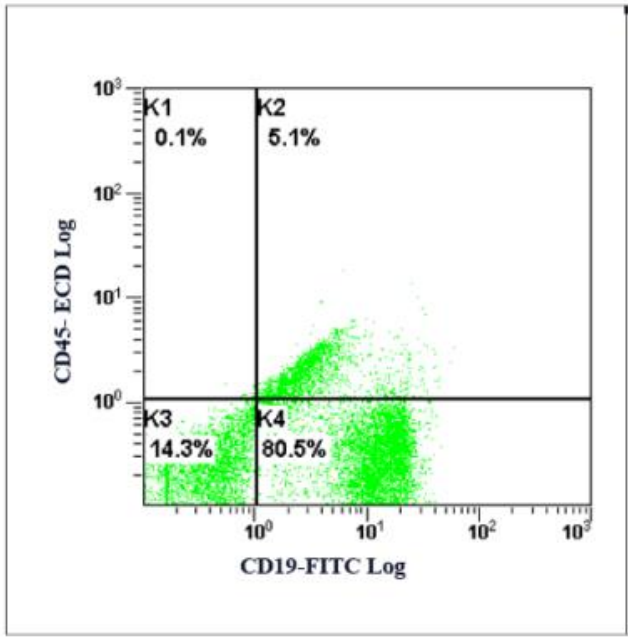
Capability	Source
Cell enrichment using FACS, MACS	Fresh tissues / blood
Isolation and culture of primary cells	Fresh tissues / Blood
Primary cell immortalization	Primary human cells
Cell survival/ cytotoxicity assays/ Apoptosis	Fresh cells
Delineating cellular pathways of interest	Fresh cells using FACS, Western blot analysis
Target identification/ validation	IHC using FFPE slides Western blot analysis using flash frozen tissue
Phenotypic assays for cancer metastasis	Primary and immortalized cells isolated from patients
Assays for pro- and anti-inflammatory cytokines	PBMCs / other cell types isolated from healthy or diseased individuals
Reporter assays for target genes	Primary and immortalized cells from patients
Biochemical assays for specific molecules of interest	Serum, Plasma, Urine, and Saliva
DNA / RNA extraction, PCR, qPCR	Blood, Fresh frozen tissues, FFPE, Saliva

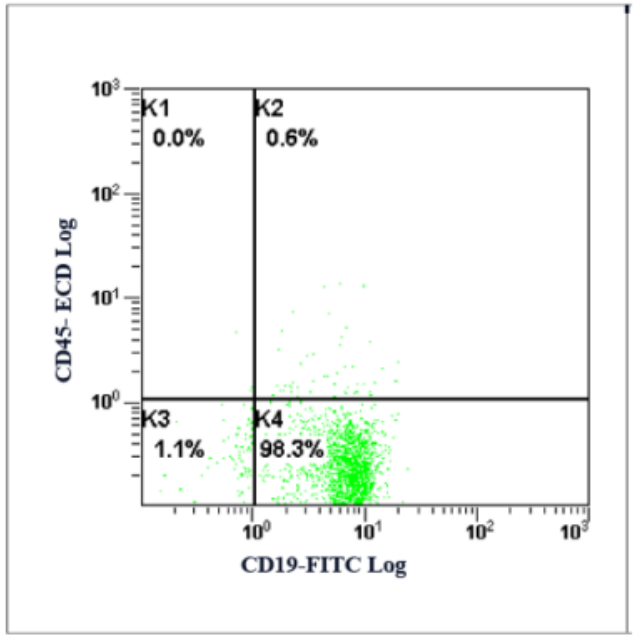


Some case studies

1. Cytotoxicity of Cytarabine on NHL patient samples

Patient with NHL: B cells enriched using MACS based negative selection from 20 ml blood





Concentration of Cytarabine (µM)	Apoptotic cells (%)
DMSO control	4.5
0.1	6.8
1	11.0
10	15.3

Cell populations before enrichment

Cell populations after enrichment

- Cells enriched using FACS
- Primary cultures of B cells exposed to various concentrations of Cytarabine
- Induction of apoptosis assessed using Annexin V/ PI staining after 48 hours measured using FACS

2. Panel of Annotated primary Cancer Cultures

Objective : Evaluate drugs in cancer cells isolated from fresh cancer tissue to :

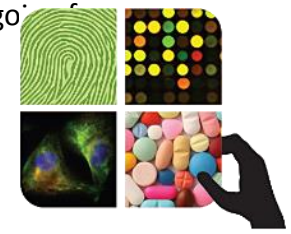
- Screen new chemical or biological entities for companies
- Generate Indian cancer patient response data by combining *in vitro* assays with outcomes
- Systematically screen Indian cancers against a 'pill box'
- Can repurpose drugs / combinations to benefit patients
- Conduct gene profiling of Indian cancers

ADVANTAGE !! mimics clinical variability in terms of:

- **Genetic diversity**
- **Disease state based variations**

Cancer Types being cultured presently*
Hematological
Brain
Breast
Colon
Endometrium
Oesophagus
Prostate
Renal

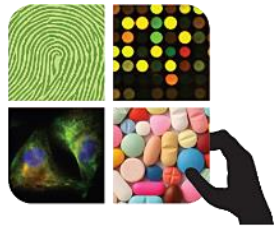
* Acquisition and culturing ongoing for more sample types



e.g. Breast cancer panel

- ~27 breast cancers as well as normal breast tissue

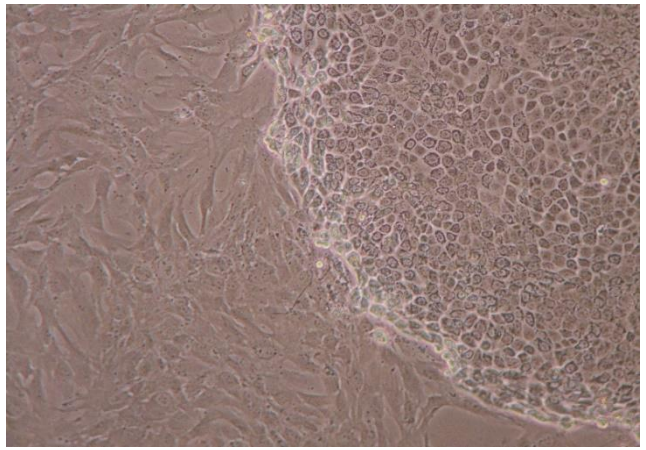
Sample ID	Age	Pathology	ER Status	PR Status	Her2 Status
SB-Br-146	73	Invasive Duct carcinoma Gr III (3+2+3)	-ve	-ve	02/03 +ve
SB-Br-175	63	Infiltrating lobular carcinoma, grade 1	+ve	-ve	-ve
SB-Br-178	37	Cystosarcoma phylloides	NA	NA	NA
SB-Br-193	69	Grade II, IDC	+ve	+ve	ND
SB-Br-286	46	Grade II, IDC	+ve	+ve	ND
SB-Br-287	72	Grade III, IDC	-ve	-ve	02/03 +ve
SB-Br-302	57	Grade III, IDC	+ve	-ve	01/03 -ve
SB-Br-320	53	Grade III, IDC	+ve	+ve	-ve
SB-Br-324		Grade II, IDC	+ve	+ve	ND
SB-Br-353	58	Adenocarcinoma	+ve	+ve	-ve
SB-Br-356	46	Grade II, IDC	+ve	+ve	Weak or moderate
SB-Br-357	40	Cystosarcoma phylloides	NA	NA	NA
SB-Br-359	39	Ductal carcinoma, NOS, grade – III	-ve	-ve	-ve
SB-Br-390	79	Grade I, IDC	+ve	+ve	-ve (01/03)
SB-Br-406	54	Grade II, IDC	+ve	+ve	-ve
SB-Br-407	47	Grade II, IDC	+ve	+ve	-ve
SB-Br-408	44	Grade III, IDC	+ve	-ve	03/03
SB-Br-434	56	Grade III, IDC	+ve	-ve	-ve
SB-Br-438	44	Grade III, IDC	-ve	-ve	-ve



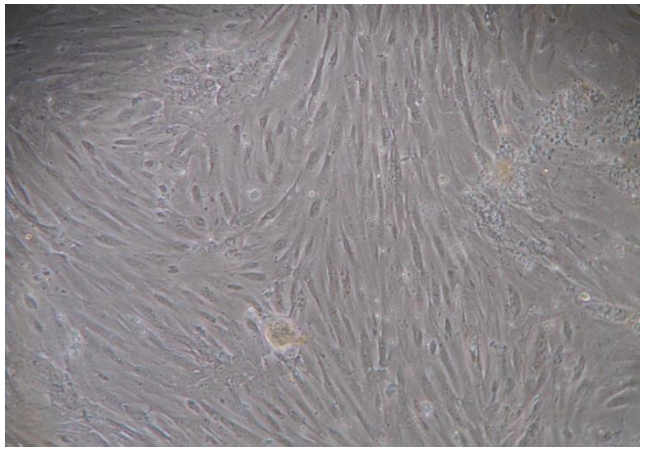
e.g. Breast cancer panel (cont.)

- Cells being characterized for rate of proliferation, expression of molecular & histological markers, response to chemo drugs, generation of CSC, mutation profiling

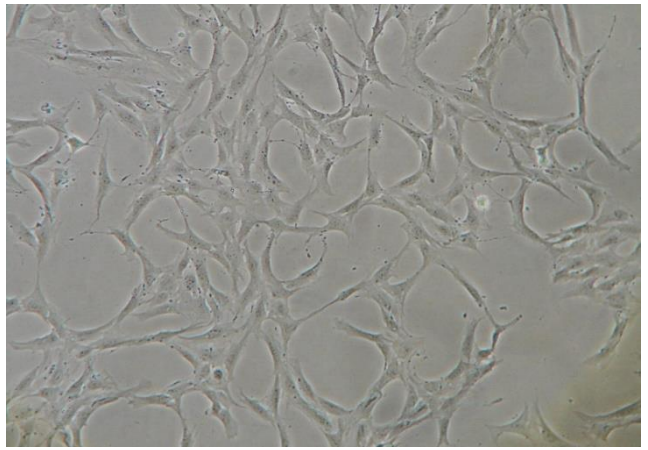
SB-Br-408



P0 Day 15

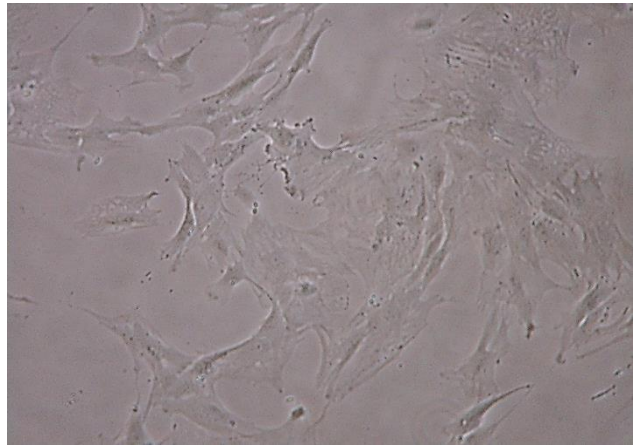


P1 Day 5

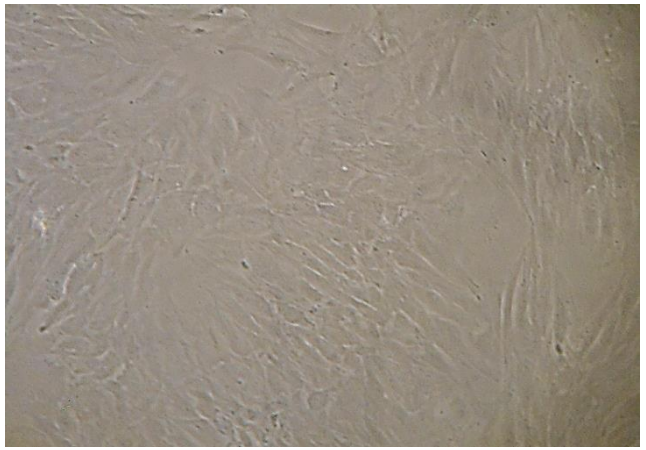


P2 Day 4

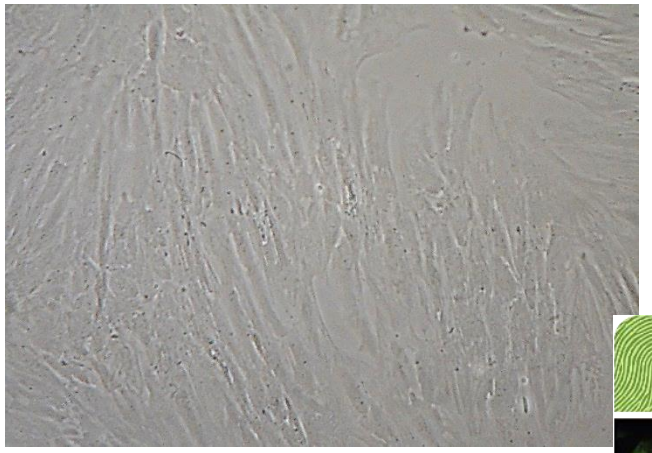
SB-Br-6045



P1 Day 7



P2 Day 7

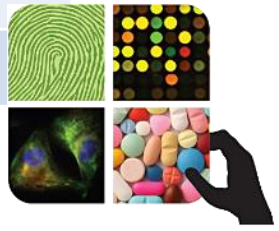


P3 Day 7

More e.g. Prostrate cancer panel, Glioma panel

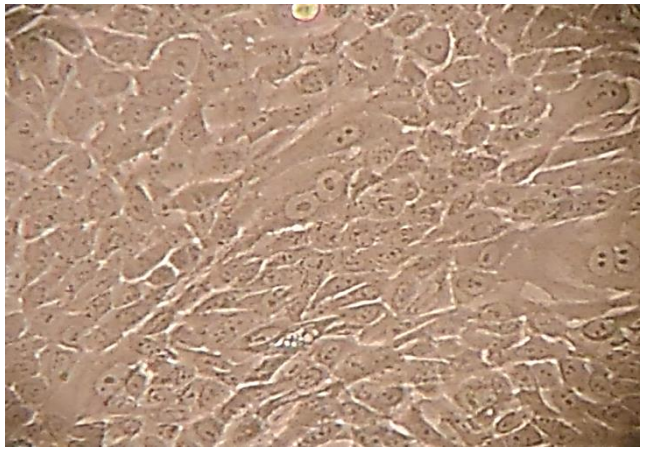
Sample ID	Age	Pathology
SB-Pr-472	52	BPH
SB-Pr-501	58	PCa Grade II
SB-Pr-544	56	PCa Grade III
SB-Pr-559	54	PCa Grade I
SB-Pr-6086	76	PCa Grade
SB-Pr-6092	76	BPH

Sample ID	Age	Sex	Pathology
SB-Gm-038	58	M	Glioblastoma Multiforme Gr IV
SB-Gm-085	54	F	Glioblastoma Multiforme Gr IV
SB-Gm-144	38	F	High Grade Glioma
SB-Gm-295	36	F	Anaplastic Astrocytoma Gr III
SB-Gm-298	35	F	Glioblastoma Multiforme Gr IV
SB-Gm-305	58	M	Gemistocytic Astrocytoma Gr II
SB-Gm-474	49	M	Anaplastic Oligodendroglioma Gr III
SB-Gm-5972	44	F	Anaplastic Astrocytoma Gr III
SB-Gm-5980	56	M	Awaiting report
SB-Gm-6077	35	F	Awaiting report
SB-Gm-6129	32	M	Awaiting report
SB-Gm-8528	53	F	Awaiting report
SB-Gm-8530	40	F	Awaiting report

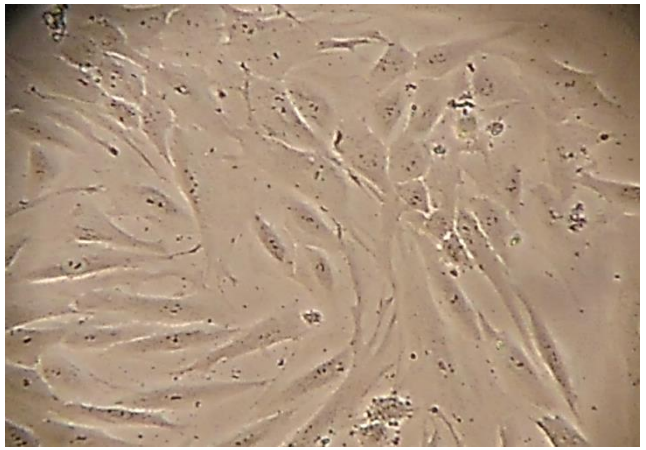


More e.g. Prostrate cancer panel, Glioma panel

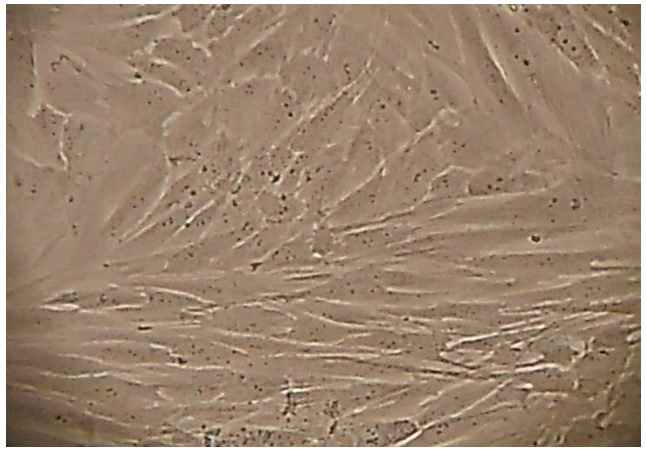
Prostrate
SB-Pr-544



P0 explants 11 day

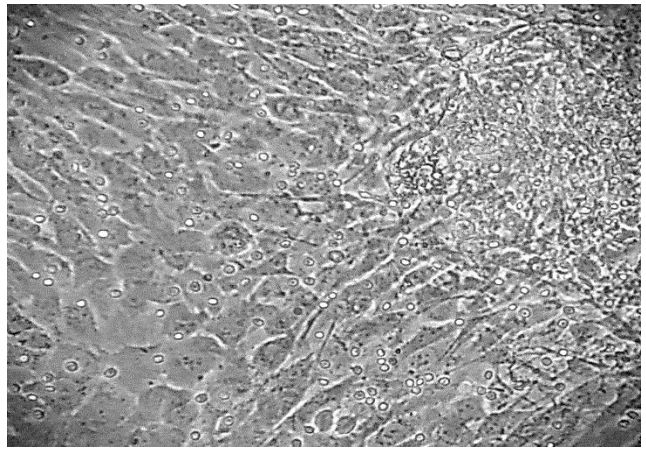


P1 5 day

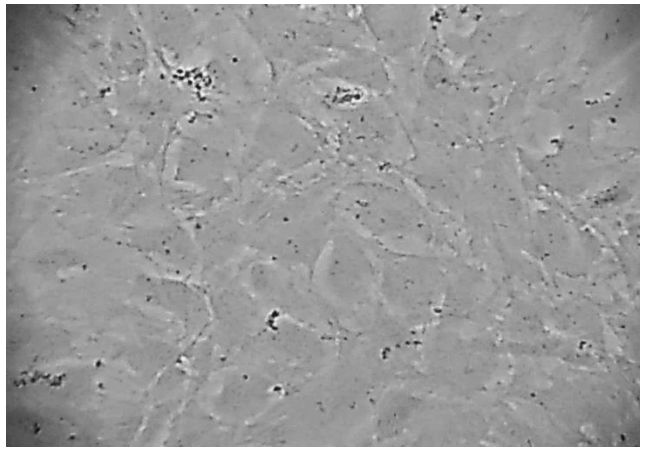


P2 4 day

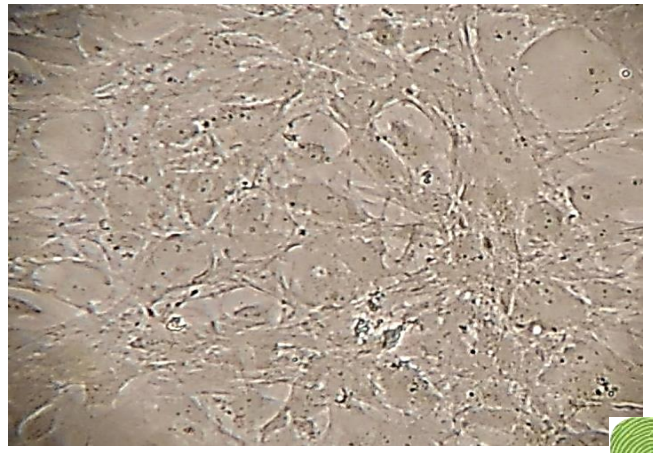
Glioma
SB-Gm-295



P0 explant 8 day

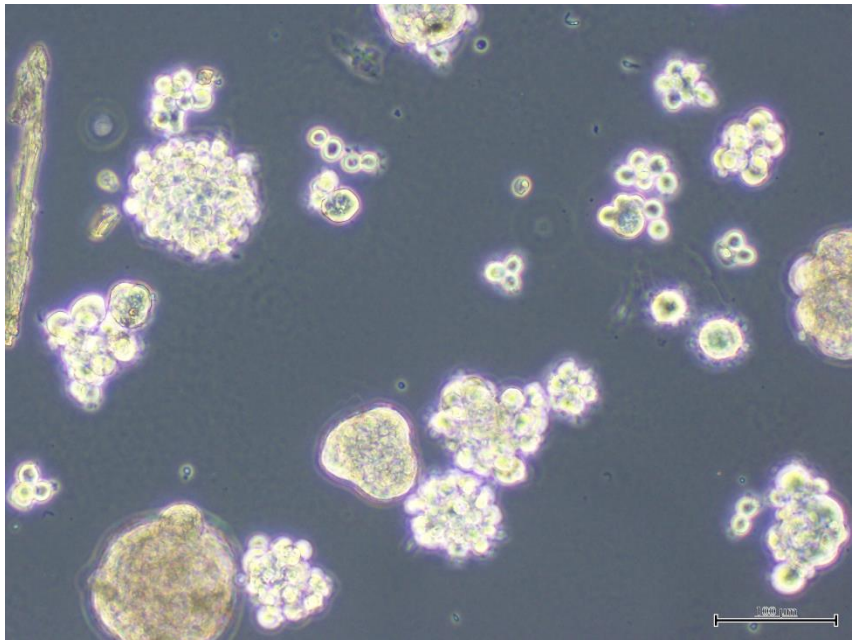


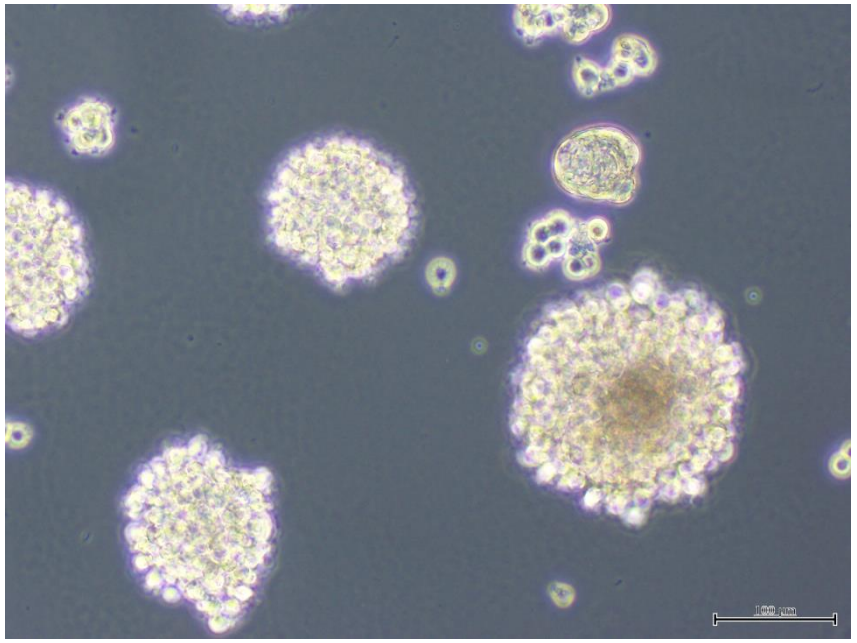
P2 5 day



P4 5 day

More e.g. Glioma panel – Neurospheres





SB-Gm-144

High grade Glioma Neurospheres

Glioma cells growing as Neurospheres

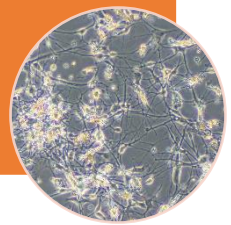
- Optimizing SOC treatment for IC50 readouts

Characterization plan for primary cell platform

In progress

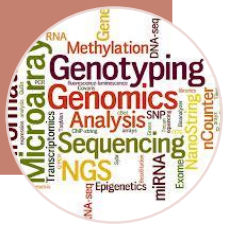
- Morphological evaluation at each passage
- Cell surface markers – common and specific
- Including sterility and Mycoplasma testing

Morphology



- **Breast cancer -** BRCA1/2, EGFR, B-RAF, K-Ras, HER-2/Neu, TP53, C-Met, C-myc, PI-3K, MEK, FLT-3, PDGFR, TERT1,2
- **Glioma -** IDH1, TP53, PTEN, CDK4, NF1, EGFR, PDGFR, TERT1,2

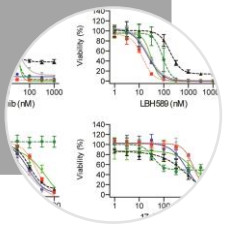
Mutation and Epigenetic profiling



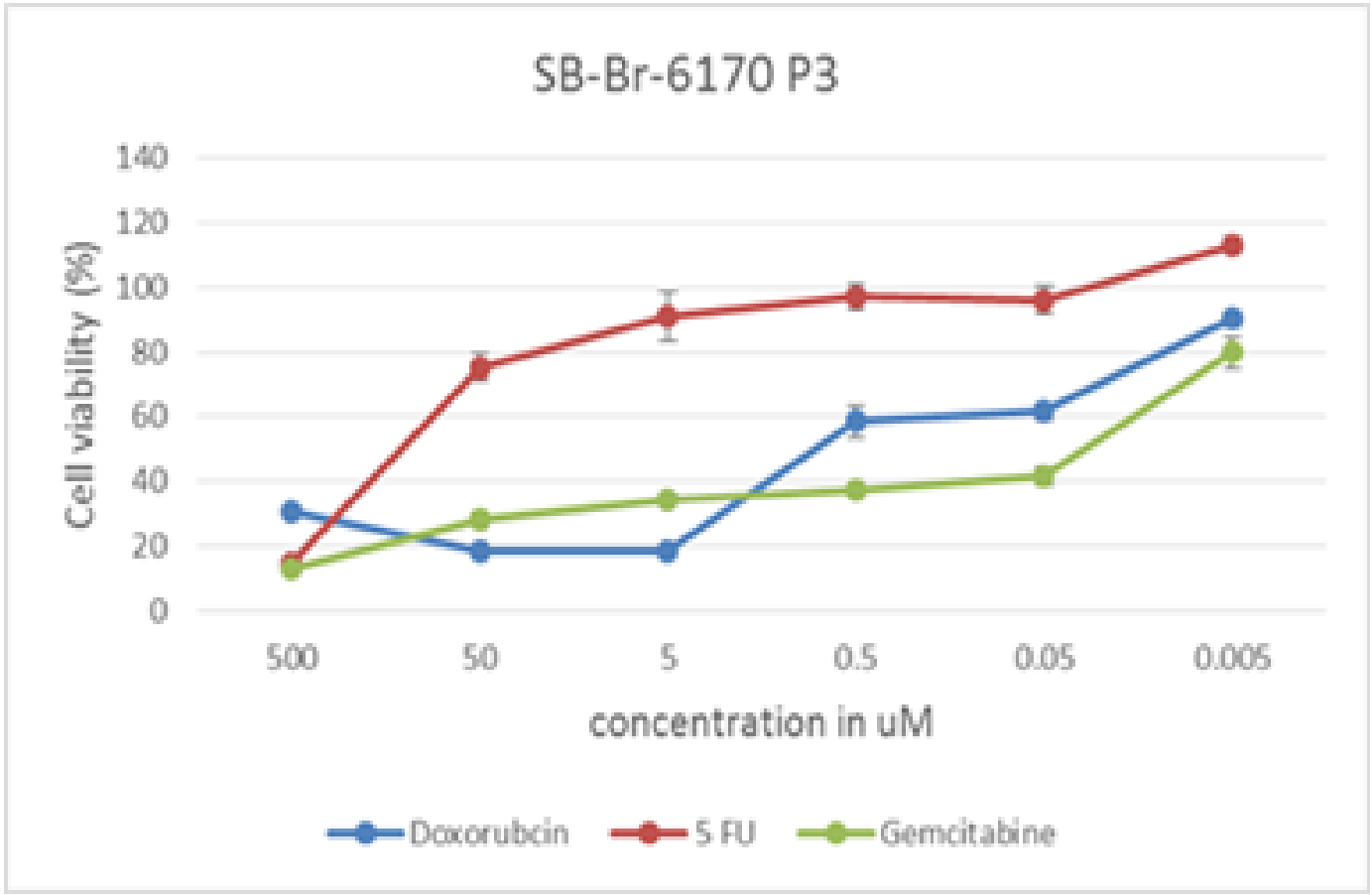
- Migration
- Invasion
- Colony formation
- Sphere formation
- Standard of care data for drug screening

Functional assays

Reference drug data



Some early results on drug screening – with SOCs



- Primary breast cancer cells derived from patient sample were treated with Standard of care compounds like Doxorubicin, 5FU and Gemcitabine.
- Can be used as a drug screening model for new molecules / combination therapies in different patient samples offering genetic diversity.

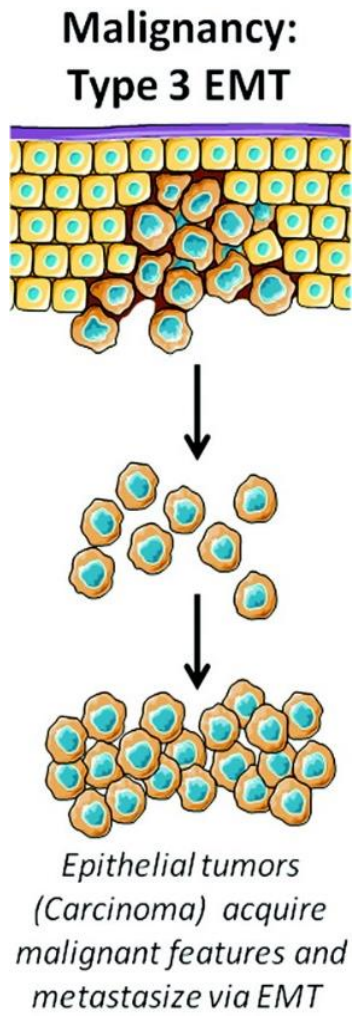
3. Regulated model of Epithelial Mesenchymal Transition

- Natural phenomenon occurring during early development. In cancer, EMT is involved in:
  - the initial steps of metastasis
  - Potentially involved in the formation of cancer stem cells

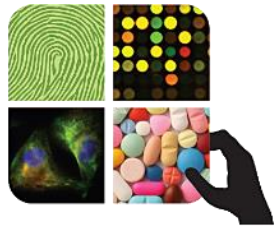
- Therapeutics targeting EMT will target the crucial step of metastasis and the formation of secondary sites of cancer.

- **We have engineered regulated model of human EMT* currently being characterized for phenotypic screens thus allowing us to perform unbiased screens!**

- The EMT model generated will be useful for
  - target discovery or validation,
  - ID & screening of new drugs/combinations
  - ID novel EMT/Metastasis biomarkers

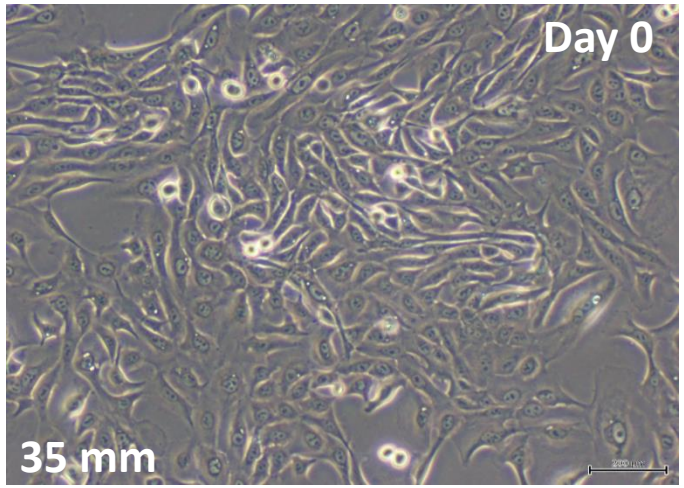


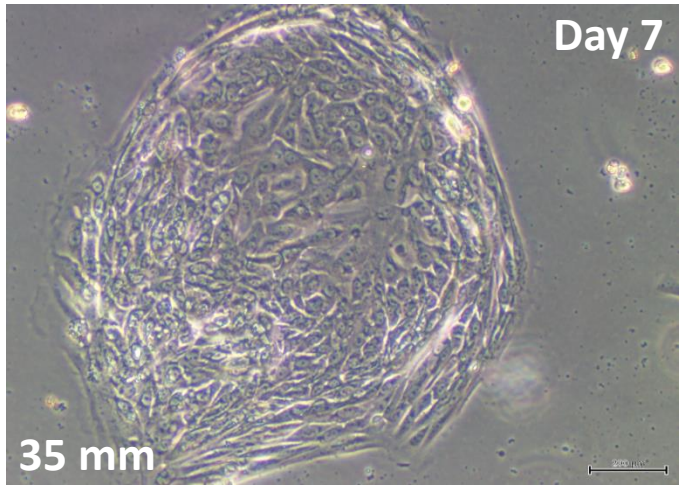
Epithelial tumors (Carcinoma) acquire malignant features and metastasize via EMT

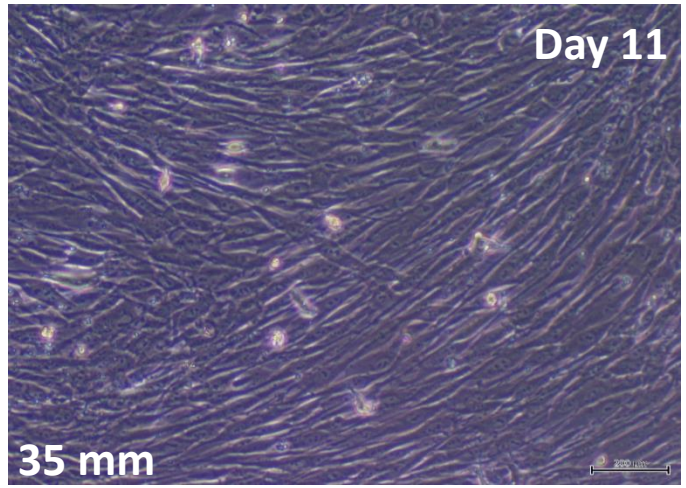


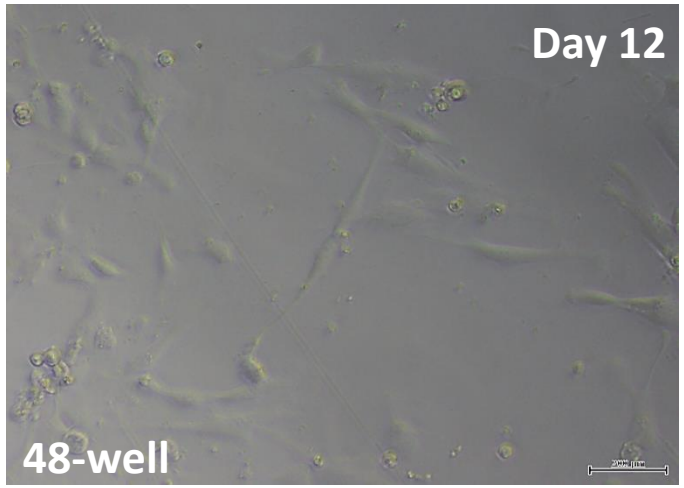
* Applied for provisional Patent

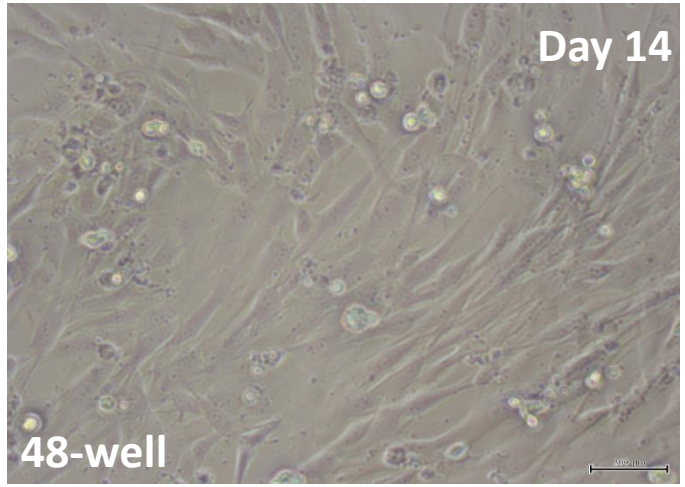
Some early Evidence - Epithelial to Mesenchymal Transition

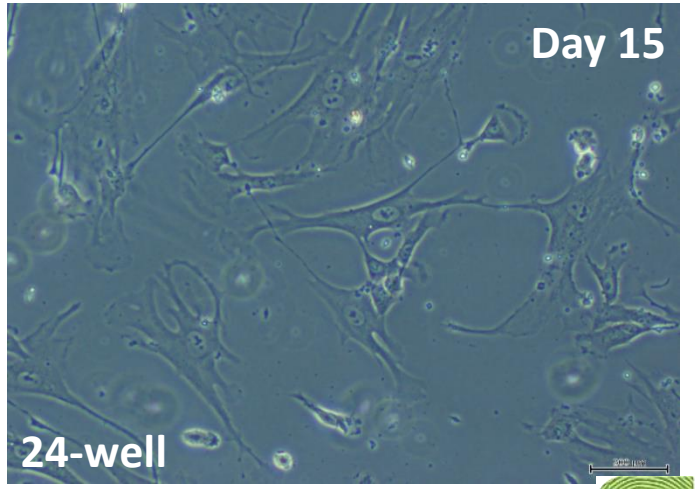










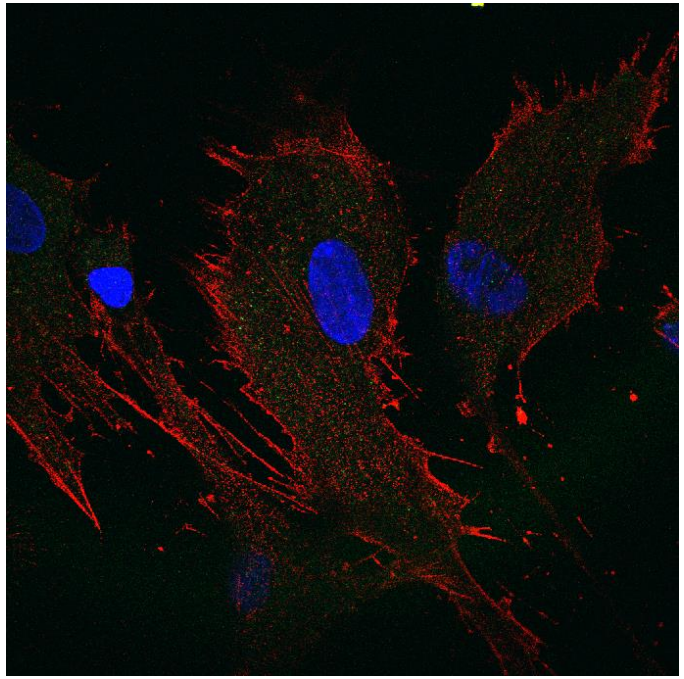


Epithelial to mesenchymal transition after transfection of primary normal breast epithelial cells with our provisional patented constructs.

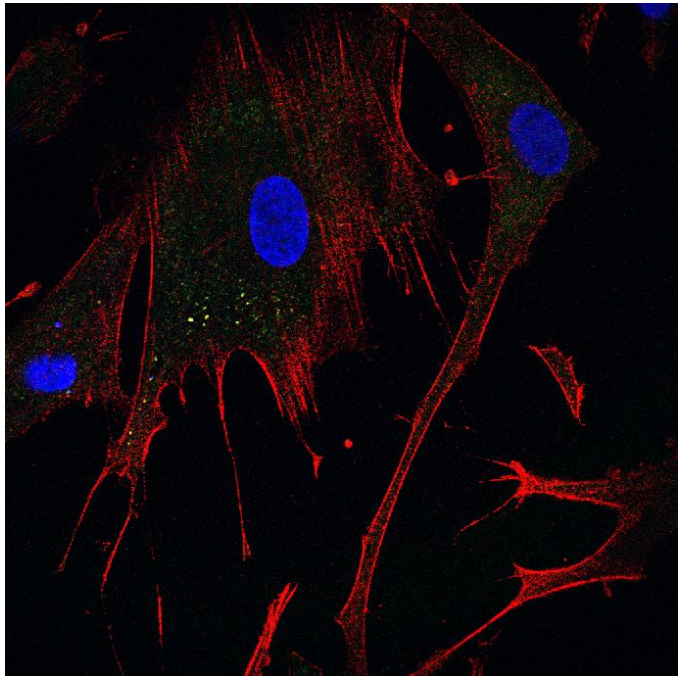
Some early Evidence - Epithelial to Mesenchymal Transition

Epithelial markers	Mesenchymal markers
EPCAM	N-Cadherin
E-Cadherin	Vimentin
Cytokeratin 8/18	Smooth muscle actin

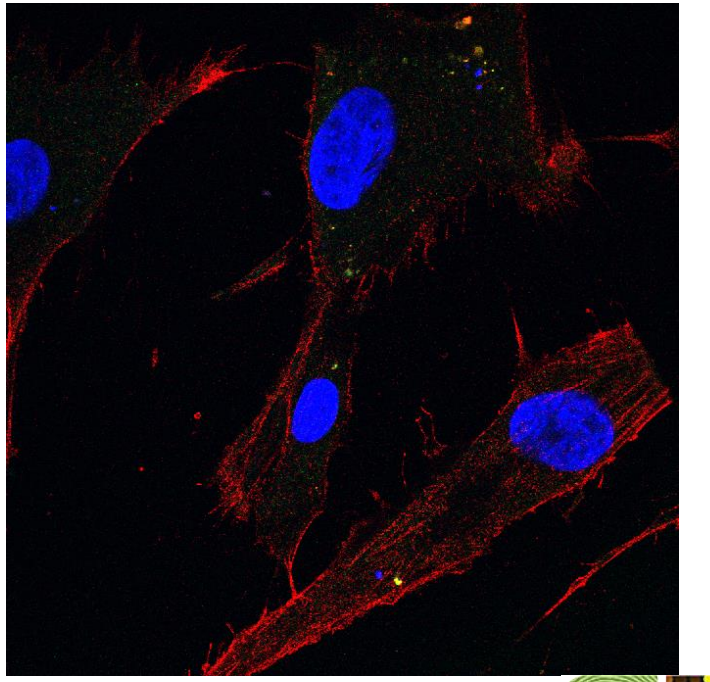
DAPI, CK 8/18 & Smooth Muscle Actin



DAPI, CK 8/18 & Smooth Muscle Actin



DAPI, CK 8/18 & Smooth Muscle Actin

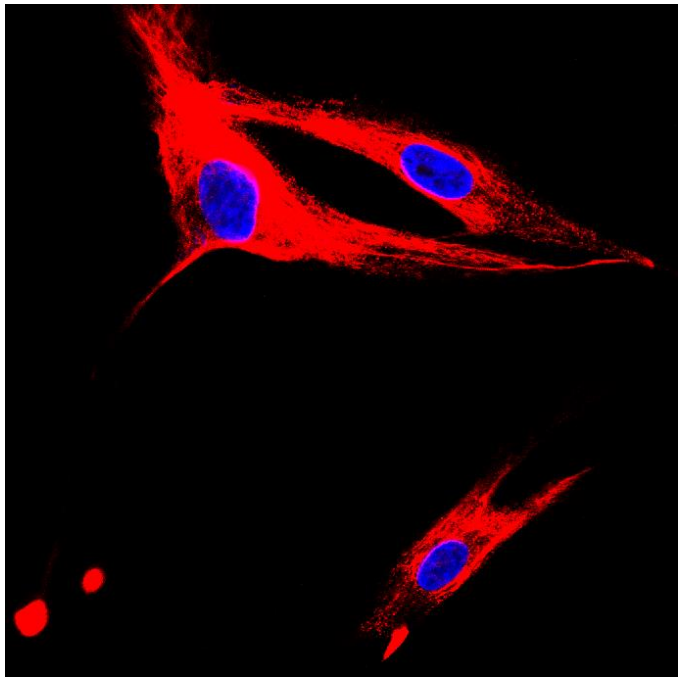


At P# 1, induced cells show positive staining (+++) for mesenchymal markers and minimal (+) staining for epithelial marker

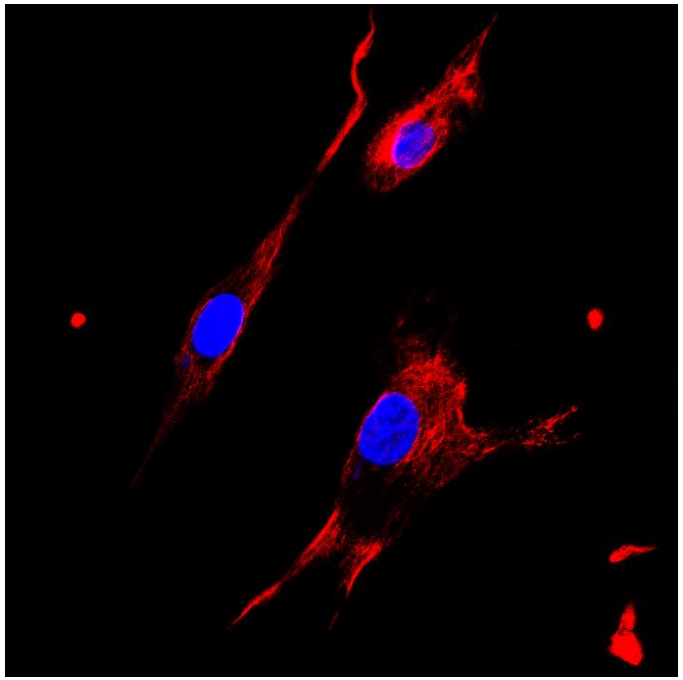
Some early Evidence - Epithelial to Mesenchymal Transition

Epithelial markers	Mesenchymal markers
EPCAM	N-Cadherin
E-Cadherin	Vimentin
Cytokeratin 8/18	Smooth muscle actin

DAPI, EPCAM Vimentin



DAPI, EPCAM Vimentin



DAPI, EPCAM Vimentin

At P# 2, induced cells show positive staining (+++) for mesenchymal markers and negative (-) staining for epithelial marker- Further characterization also using PCR for quantification is ongoing

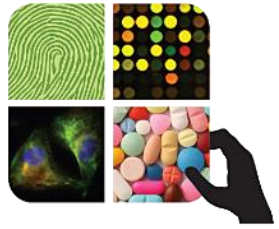
Our capabilities in clinical diagnotics

- *my*PLATELET™ : India's 1st & only novel combination (genotype + phenotype) to identify non-responders to anti-platelet therapy and personalize/optimize treatment for such patients
  - Successfully launched at Apollo-Jubilee Hills, Apollo-Bhubaneswar, Apollo Bangalore
  - Roll-out underway across other Apollo sites nation-wide
  - ~180 test performed so far; 2 of every 3 patients (~66%) benefited from the test

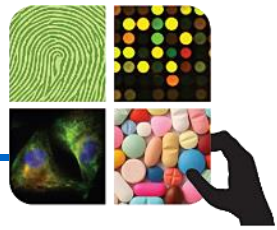
- *my*CarDiO™ : Genetic screening test for CVD, diabetes and obesity based on an assessment of a small panel of genes/SNPs correlated with risk of developing such diseases
  - Also incudes some metabolic/nutritional components related to these disease
  - Being rolled-out within the context of preventive health checks at Apollo nation-wide shortly
  - Enables development of a large database (~50,000 nos) of genotype-phenotype correlation data

- **Collaborations** : with a niche Indian & a US biotech, structured around validation of novel biomarker approaches for assessment of recurrence
  - Working on providing highly curated FFPE samples for validation of recurrence Biomarker(s)

- Other tests in the pipeline:
  - Assay for differential diagnosis of genetic disorders – Eye panel, cardiac panel etc
  - Cancer genomics assays - germline & somatic mutations



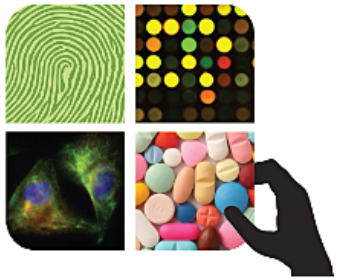
Potential Synergies & Collaborative Opportunities



Collaboration Objectives	Collaboration Modes	
	Short-Term (Quick wins in service mode)	**Mid/Long-Term (Shared-risk Mode)**
Screening opportunities	• Screening & profiling of Pharma NCE hits/leads in primary cells & co-cultures (2D, 3D etc.,)	• Generation of customized libraries of 'phenotypically active' molecules/fragments using primary cell-based models
Translational Paradigms	• Mechanistic profiling of hits/leads in primary cells & co-cultures • Derivation/optimization of primary tumors for mouse xenograft studies	• Profiling leads/hits in Saarum's EMT model & derivatives • Co-development of other phenotypic models • Generation of CSCs/CTC paradigms for screening & profiling hits/leads
Target/Biomarker ID & Validation	• Biomarker/Target ID & validation in FFPE & Fresh samples	• Development of novel/custom paradigms using primary cells for biomarker/Target ID & validation • Collaboratively mine Sapien's sample sets for diagnostic markers
Toxicology Platforms	• Safety screening of hits/leads in specific primary cell types (ES/MSCs, PBMCs etc.)	• Co-development & integration of ES/iPS-derived liver/cardiac/neuro tox paradigms into the NCE/NBE discovery workflow.

SAPIEN BIOSCIENCES

Advancing Science, Personalizing Medicine



SAARUM SCIENCES

Drug Discovery Platforms & Services

Thank you

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