Atlantic Cancer Research Institute

Overview to MLA breakfast

Fredericton
March 21th 2019

ATLANTIC
CANCER RESEARCH
INSTITUTE

ACRI Snapshot

- Created in 1998
- Not-for-profit research organization
- Operating budget $5M

Vision

- Contribute to the global efforts to finding solutions against cancer:
  - Attract best possible talent
  - Research with translational focus on bench to bedside and unmet needs in health
  - Researchers working in a team environment as well as with partners from academia and private sector.
  - Allow research and health care sectors access to our expertise and technology.

ACRI recruits globally

- Over 70 employees, primarily HQP: PhD research scientists and laboratory technicians and graduate students
- Two thirds of our team have come to NB. We have highly qualified people representing 5 continents.

The Team

Researchers
Dr. David Barnett
Dr. Jacqueline Bélanger
Dr. Anirban Ghosh,
Dr. Stephen Lewis
Dr. Rodney Ouellette
Dr. Jocelyn Paré
Dr. Gilles Robichaud
Dr. Jeremy Roy
Dr. Sandra Turcotte

PostDoc Fellow
Dr. Craig Ayre
Dr. Amit Bera
Dr. Charles Bullerwell
Dr. Nichole Cumby
Dr. Rostyslav Horbay
Dr. Awanit Kumar

Bioinformatitians
Ilyass Hajji
Daniel Léger
Dina Soliman
Dr. Gabriel Wajnberg

Platform Managers
Simi Chacko
Dr. Pierre Deprez
Andrew Joy
Mark MacDonald

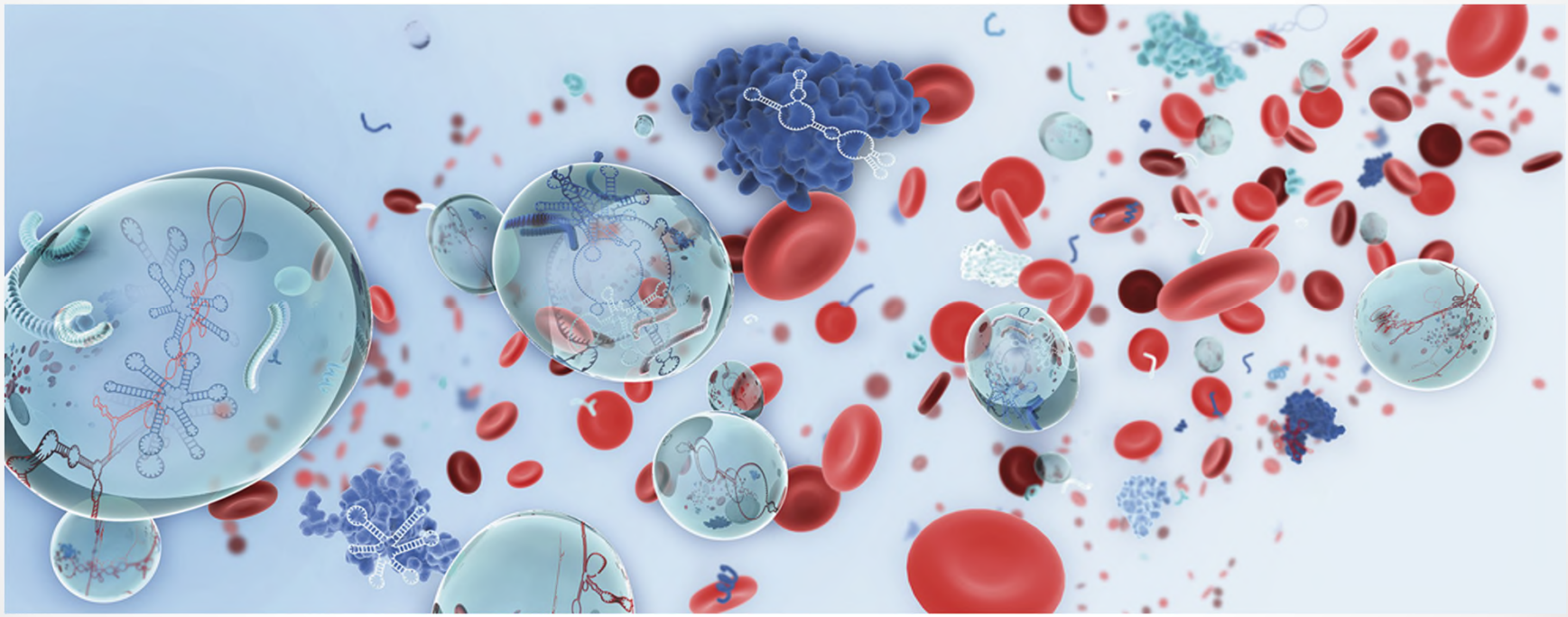
Research Assistants
Biji Anish Kumar
Laura Ayre
Dr. Amrita Basu
Sonia D'Astous
Sébastien Fournier
Sheena Fry
Jacynthe Lacroix
Max Merilovich
Mai Ngoc-Nu
Surendar Reddy Dhadi
Catherine Taylor
Dr. Eric Merzetti

Students
Ioanna Armata
Alexandre Arseneau
Nadia Bouhamdani
Kathryn Carrier
Kristine Dugas
Britney Dupuis,
Naoufal El Bekkouri
Roxann Guerrette
Brandon Hannay
Mathieu Johnson
Justin LeBlanc
Julie Lewis,
Alexander MacPherson
Danick Martin
Amélie Ouellet
Caleb Ouellette
Patric Page
Lauren Pitre
Caleb James Reynolds,
Marc-André Richard
Mathieu Sanschagrin
Vanessa Veilleux

Projects

- Cancer Biology projects (individual PIs)
- Extra-cellular vesicle capture technologies for liquid biopsy (Team)
- New treatment target identification using CRISPR knock-out (Team)
- Microwave ablation technology (J. Paré/J. Belanger)

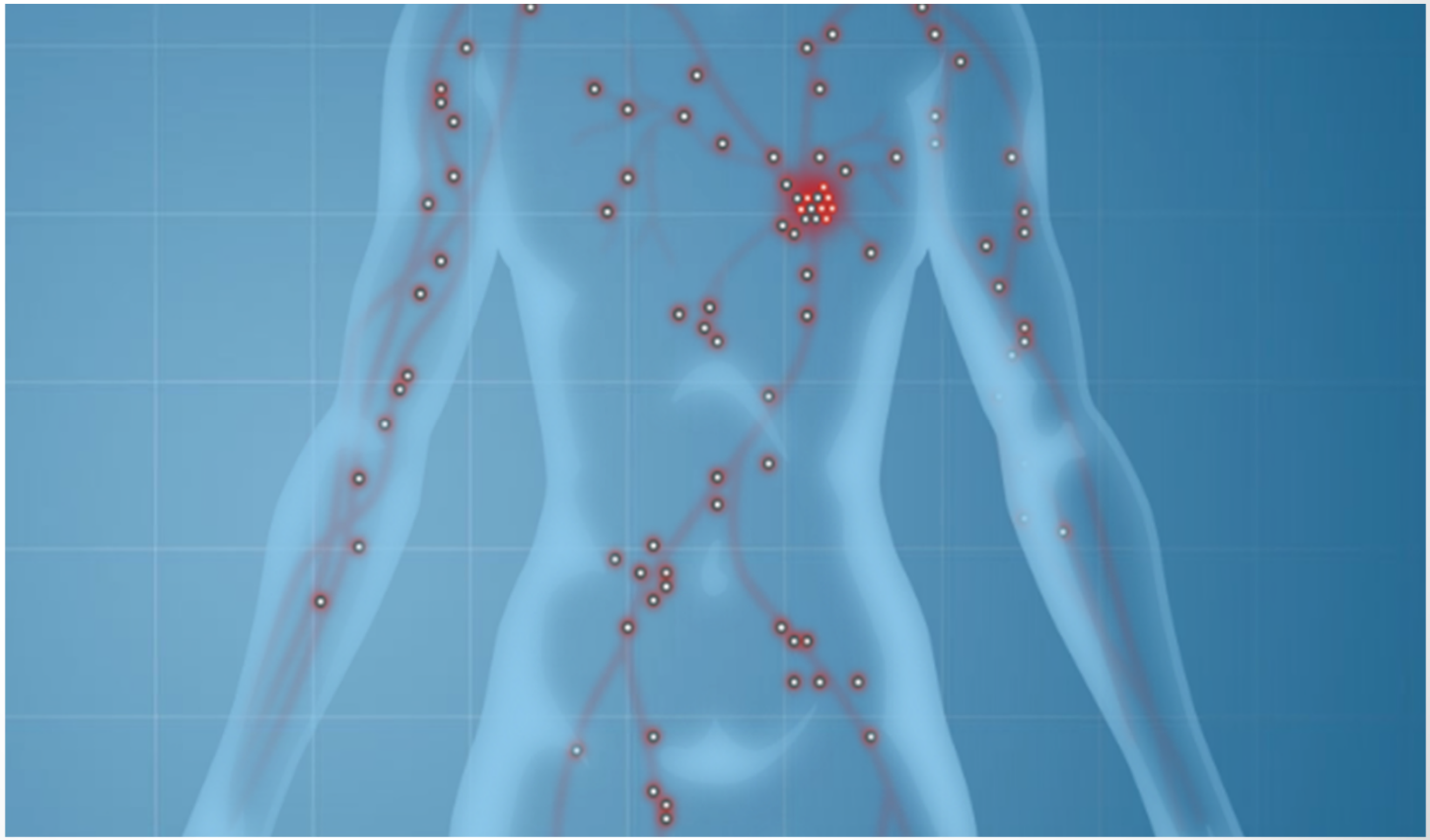
Liquid biopsy enabling technologies



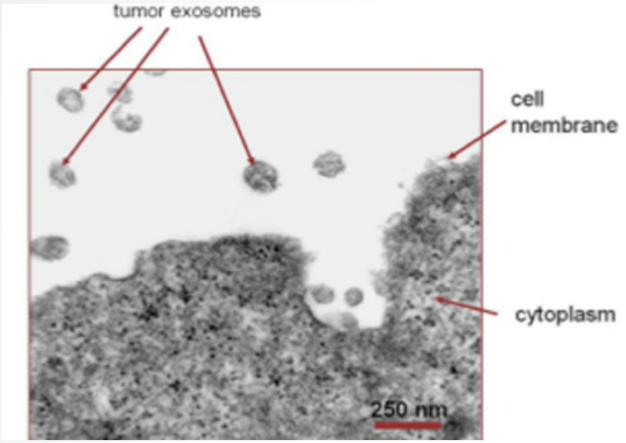
Liquid Biopsy: Definition

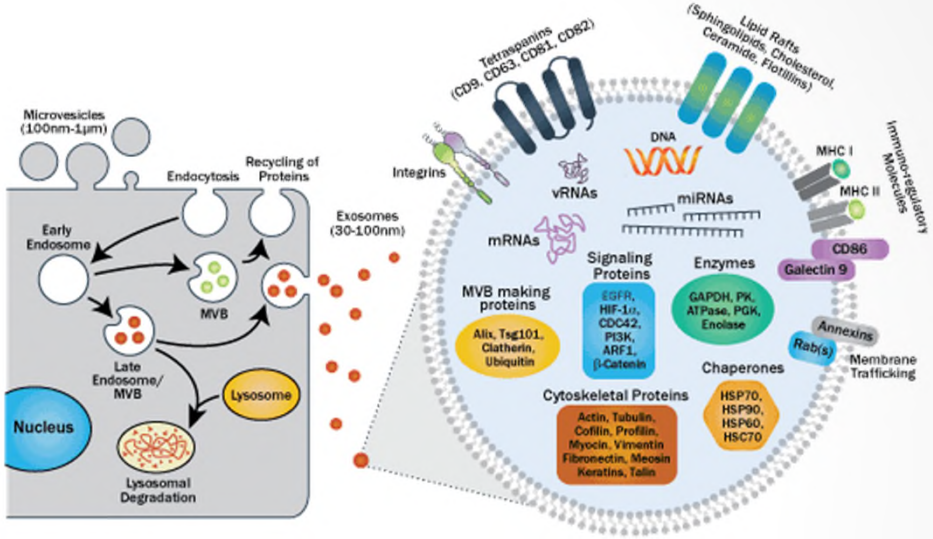
Liquid biopsy is a minimally invasive sampling of a biological fluid that can detect cell derived material that indicates the presence of an underlying pathology such as cancer.

The cell derived material may be actual cells, nucleic acids, proteins, metabolites or any other biomarker.



Exosomes and microvesicles: The Twitter of the cell

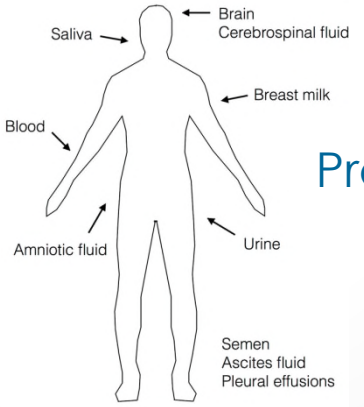




Exosomes and microvesicles contain biological information, ie:

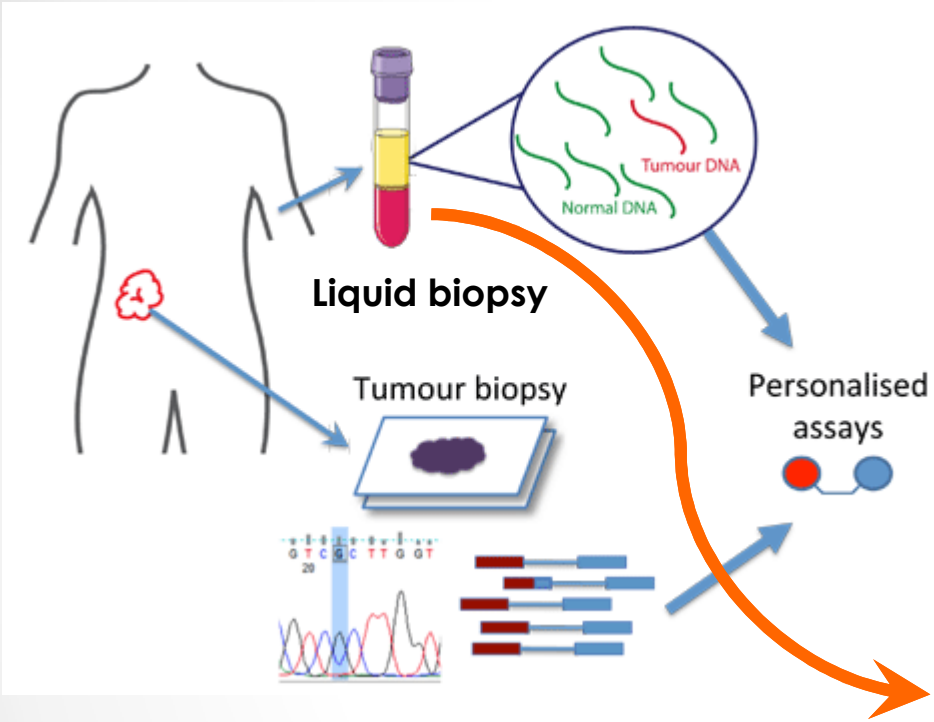
- DNA
- RNA
- Proteins
- Etc…

Provides insight on the activity of the parent cell



Present in all body fluids

Liquid Biopsy as a better source of information

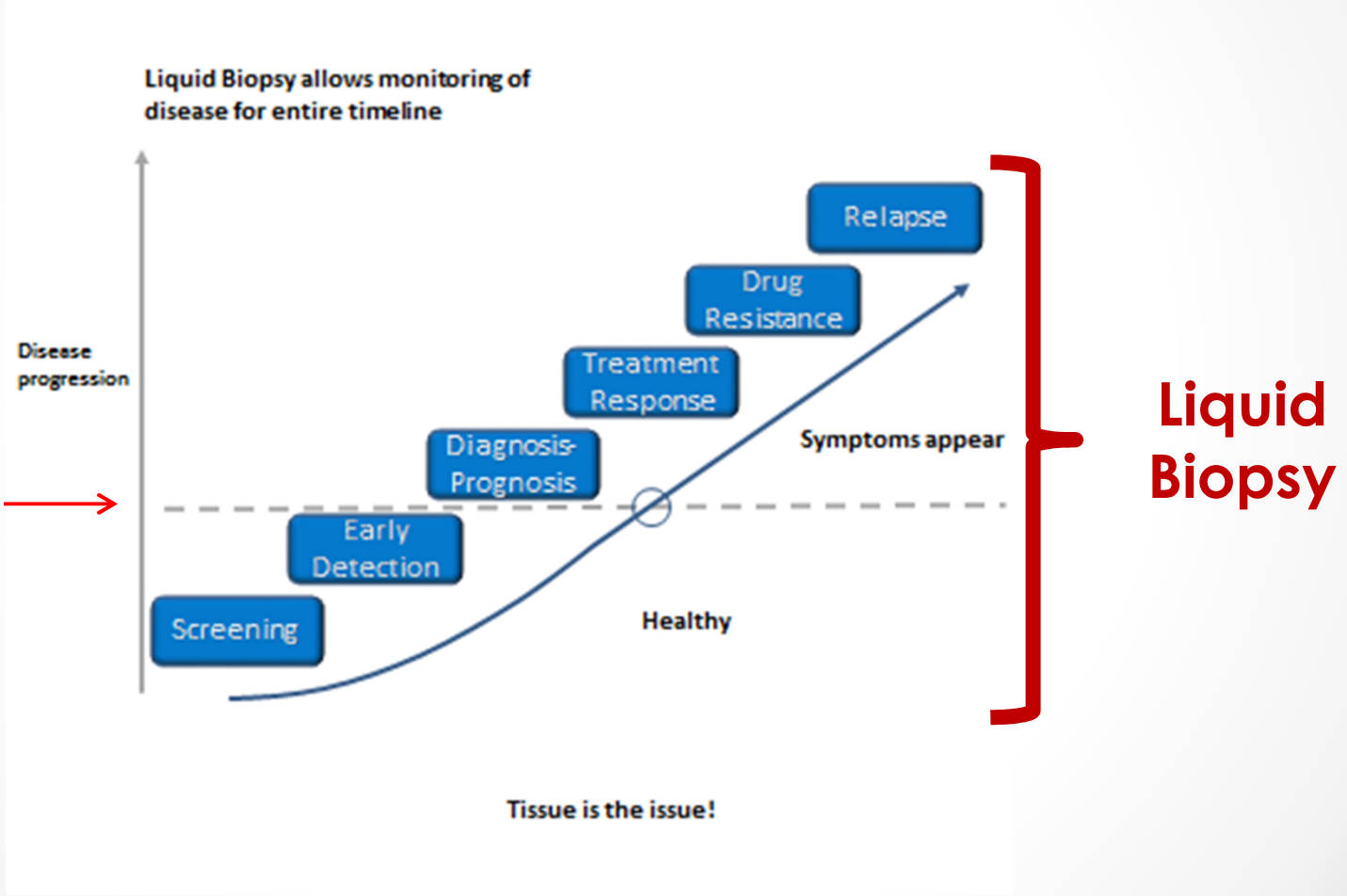


Liquid biopsy is a real-time dynamic view into a patient's cancer

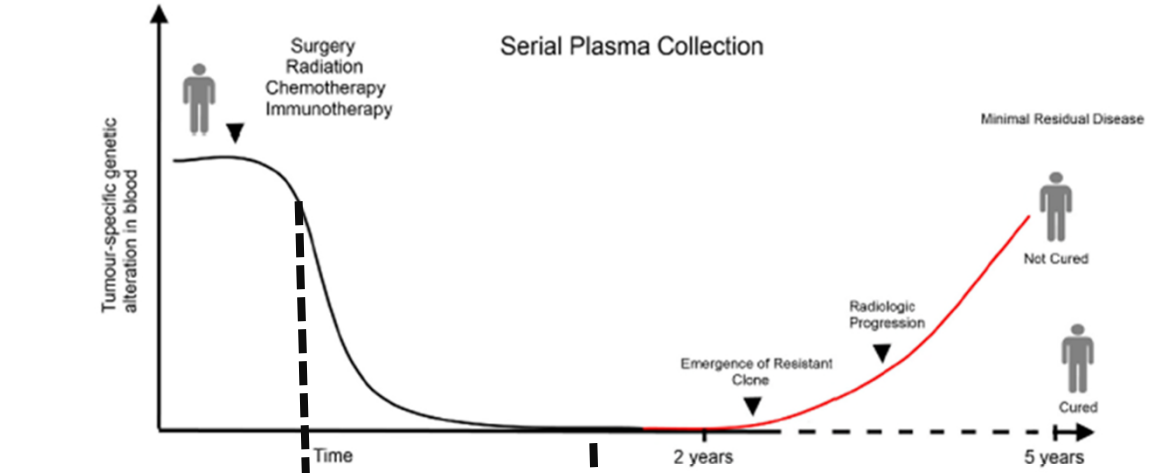
Using exosomes we can detect changes in real time that inform on

- Early Diagnosis
- Early Response to treatment
- Treatment resistance
- Disease relapse

Liquid Biopsy: enabling real time picture of disease



Monitoring cancer in real-time



Liquid biopsy

Radiology

1-2 weeks

4-6 months

Metastatic lesions in the lungs of a Head and Neck cancer patient post-treatment

Why is real-time data important?

- Patient
  - Reduces the uncertainty of knowing if treatment working or not
  - Unnecessary exposure to ineffective treatment
- Medical team
  - Monitor and adapt treatments situation before cancer evolves into more aggressive form
- Health System
  - Real-time information of efficacy of costly Rx
- Pharma Industry
  - Transforms cost structure of clinical trials

Leaders in Liquid Biopsy Field

- Exosome Diagnostics-Boston, USA
- Exosomics-Siena, Italy
- ACRI

FierceBiotech

MedTech

Bio-Techne to pay up to $575M for liquid biopsy maker Exosome Diagnostics

by Joseph Keenan | Jun 27, 2018 9:35am

Bio-Techne agreed to pay up to $575 million to acquire liquid biopsy player Exosome Diagnostics, boosting the company's position in the noninvasive liquid biopsy market. (Pixabay)

Lonza Acquires HansaBioMed, Invests in Exosomics

May 16, 2017 | staff reporter

NEW YORK (GenomeWeb) – Lonza announced today that it has acquired HansaBioMed Life Sciences, an Estonian exosome research tool developer, and made an investment in Exosomics, an Italian molecular diagnostics startup.

Financial and other terms of the agreements were not discussed.

Breaking News

- Rhabdomyosarcoma Genes Revealed by Statistical Analysis of Gene Expression, CNV Data
- Loneliness, Participation in Social Activities Linked to Dozens of Genomic Loci

New England Peptide Announces License Agreement

New England Peptide acquires next generation exosome and microvesicle affinity technology for potential detection of cancer and other diseases.

New England Peptide, Inc, (NEP) today announced that it has entered into a licensing agreement with the Atlantic Cancer Research Institute (ACRI). Under the terms of the agreement NEP has acquired the worldwide exclusive rights for Vn96 and a portfolio if other peptide compounds to be used for the research grade enrichment of microparticles, microvesicles, and exosomes. NEP will be releasing a research grade affinity enrichment kit next quarter. ACRI and NEP, co-inventors of Vn96, are actively seeking collaborators for the clinical use of Vn96.

ME -Microvesicle Enrichment Kit®

Product licensed for research applications and sold by NEP

nep
new england peptide

exosomics

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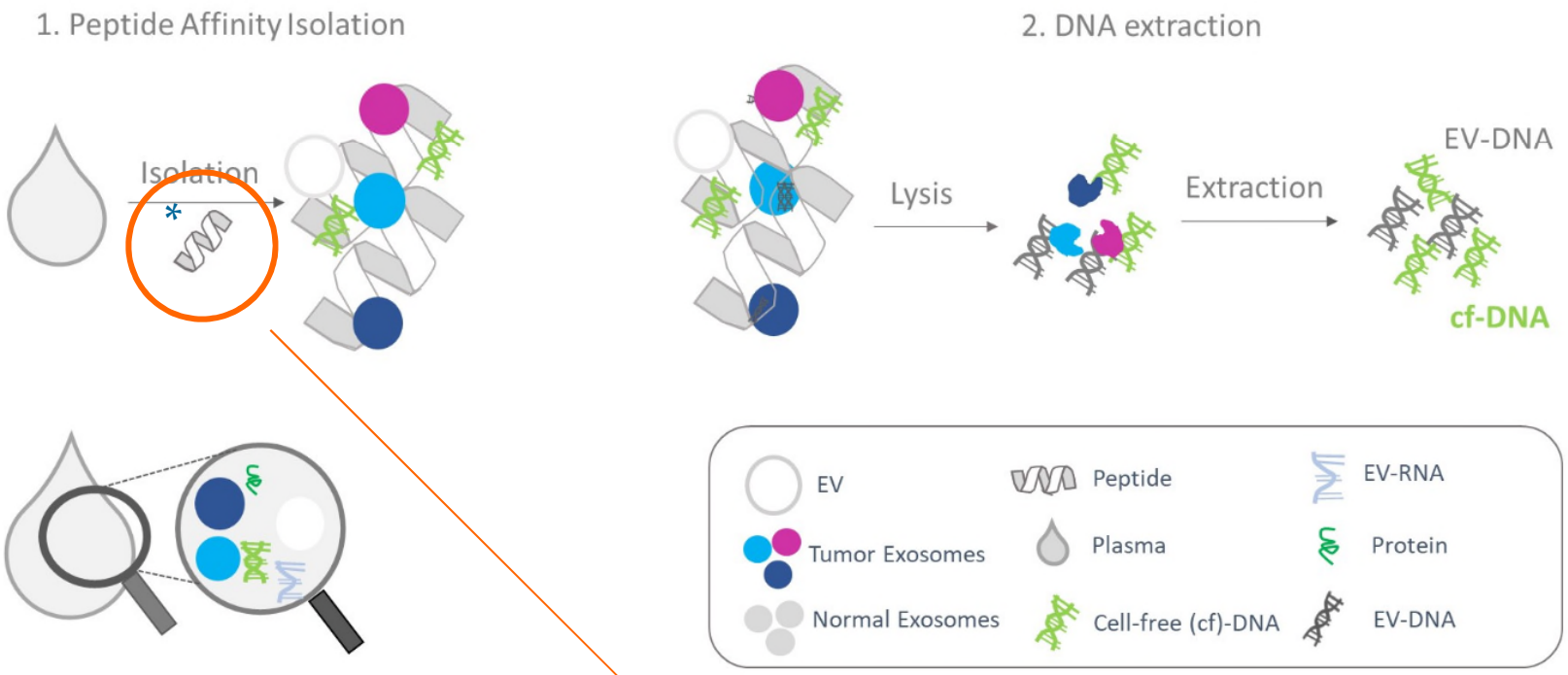
SeleCTEV™ DNA ENRICHMENT KIT (RUO)

SeleCTEV™ DNA Enrichment kits co-isolate exosome-derived nucleic acids (EV-DNA) and a fraction of circulating-free DNA (cfDNA).

SeleCTEV™ DNA Enrichment kits allow maximum recovery of genetic material from biofluids by combining circulating and tumor-specific nucleic acids from tumor-derived exosomes.

The isolation is based on Exosomics proprietary peptide-affinity technology.



*ACRI licensed product (yet to be announced)

Fast growing market

Exosomes Market Size to Reach $2.28 Billion by 2030 | CAGR: 18.8%: Grand View Research, Inc.

NEWS PROVIDED BY
Grand View Research, Inc.→
Feb 07, 2018, 04:20 EST

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SAN FRANCISCO, February 7, 2018 /PRNewswire/ --

The global **exosomes market** size is expected to reach USD 2.28 billion by 2030, according to a new report by Grand View Research, Inc., exhibiting a CAGR of 18.8% during the forecast period. Nanovesicles, which play a major role in intercellular communication, are anticipated to witness a significant rise in R&D, thus leading to revenue growth in the coming years.

Research Insights

Exosome Diagnostic and Therapeutics Market Expand at the Fastest CAGR of 23.1% by 2027

June 14, 2018 Vaidehi 0 Comments

Partner companies and organizations

- Atlantic
  - Dalhousie University
  - Memorial University
  - Université de Moncton
  - Organigram
  - Soricimed
  - Vitalité Health Network
  - Horizon Health Network
  - True North Clinical Research
  - Cooke Aquaculture
  - Fisheries and Oceans
  - Mycodev Group
  - St-Laurent Golf Products
- National
  - Stem Cell Technologies
  - Romich Holdings
  - Gamma-Dynacare
  - CHUQ/Université Laval
  - McGill University
  - Terry Fox Research Institutes
  - Exactis Network
- International
  - Merck
  - Harvard University
  - Cynvenio Biosystems
  - BioVendor
  - **Exosomics -Siena**
  - **Lonza**
  - SiMPore
  - IZON Science
  - Epigenomics
  - MIMA-PRO (Vison Medical)

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Research is not a black hole

ACRI Economic Facts

- Has attracted over $100 Million to NB since 2000
- Provincial support to ACRI: $8 Million (direct, NBHRF, NBIF)
- Return on investment ration >10:1
- For every $1 dollar invested by NB….ACRI returns $0.95 dollar in income, property and consumption taxes back to Treasury
- The rest of the >$90 Million would not have come to NB
- ACRI's 70 jobs @ $50k average has a bigger economic footprint than 200 jobs at minimum wage
- Our inventions have reached market and generating revenues
- Little known fact: ACRI operates NB's only fertility clinic and assists 100 new births to province every year.

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ACRI's Challenges

- Lack of core funding
  - Research grants do not cover all costs
  - Other provinces support 20-40% of budget for core funding
- Province ceased support in 2014 and negotiated temporary deal with ACOA for 5 years
- Agreement ends on March 31st 2019
- No funding for ACRI in either provincial or federal budget
- Future uncertainty

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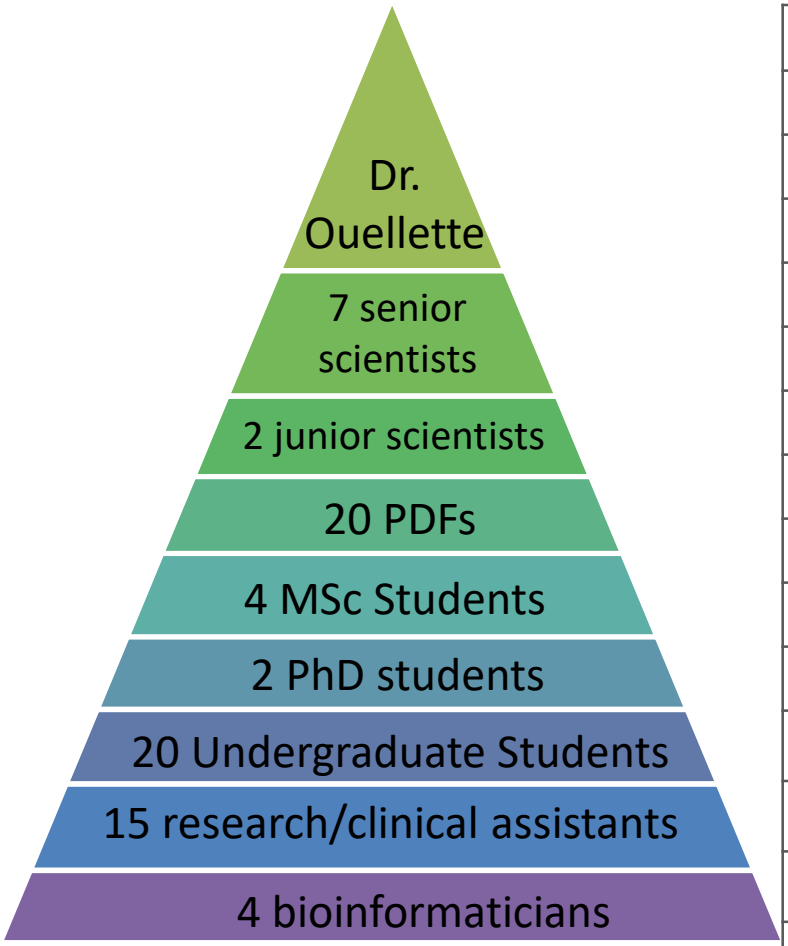

+ instigated two Canadian Cancer Society Research Chairs for UNB and UdeM (Dr Reiman and Dr Turcotte)
+member of core group that lobbied and created NBHRF

Funding held last 5 years

AIF Cancer Liquid Biopsy Project I (2012-2016)	$5,900,000
AIF Cancer Liquid Biopsy Project II(2016-2020)	$5,700,000
AIF Synthetic Lethality Project (2014-2018)	$5,900,000
REGI Innovation Grant (2019-2022)	$3,500,000
Cancer Research Society	$120,000
Merck/Exactis/CRS/NBHRF	$2,000,000
Exactis Innovation	$250,000
NBIF Concept Validation Grant	$120,000
Colon Cancer Canada	$120,000
Prostate Cancer Fight Foundation	$50,000
Philanthropic Funding	$3,000,000
TOTAL as PI (last 5 years)	**$26,750,000**
Co-PI-NB Center for Precision Medicine	$24,000,000
ACOA Equipment Grant NBCPM	$3,100,000
TOTAL as PI and Co-PI	**$53,850,000**

* Does not include funding received by individual trainees or students supervised

Thank you


Centre de recherche
sur la médecine de précision
du Nouveau-Brunswick
Stantec

Provincial Support History

- **2009**: Provincial support commitment for $1M/year for 5 years initiated
  - Funds leverageable for other funding including AIF
- **2011**: Sudden and premature elimination of annual funding
  - Created uncertainty for ACRI
- **2011**: RDC allocates remaining of funds to honour commitments until 2014 and invest in research and innovative capacity
- **2014**: Provincial financial support ends
- **2014**: Agreement for ACOA to take over operational support to ACRI from the province
  - Funds un-leverageable for other large scale ACOA initiatives
- **2019**: End of ACOA BDP Support

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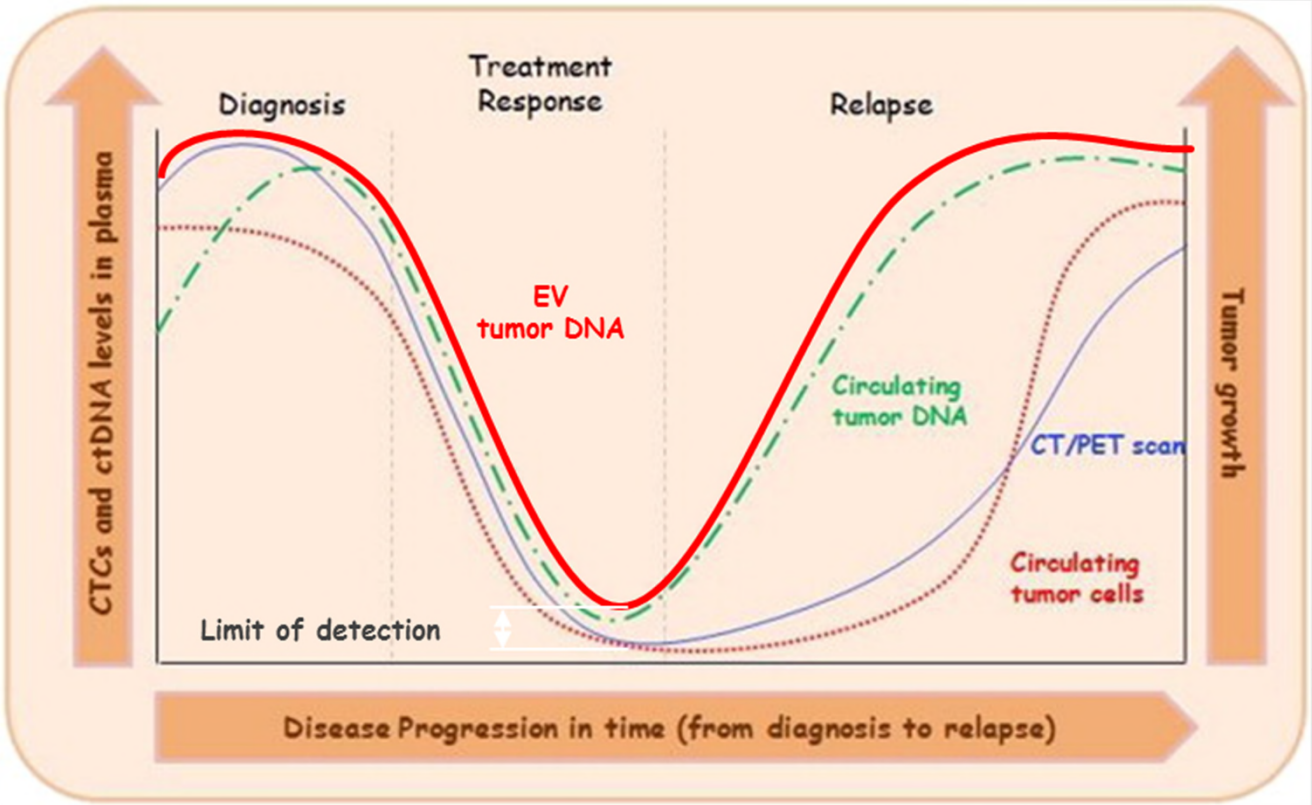
Liquid Biopsy: real time monitor of disease

- From diagnosis to relapse
  - A more accurate and timely indicator of the current status



ACRI Signs Non-Exclusive License Agreement with BioVendor for liquid biopsy enabling technology

(Moncton, Canada) - March 15th, 2017 – The Atlantic Cancer Research Institute (ACRI) is pleased to announce an agreement with BioVendor – Laboratorni medicina a.s. to license its patented intellectual property for the use of the Vn96 synthetic peptide in liquid biopsy applications. The agreement gives BioVendor non-exclusive rights to use the Vn96 peptide for the isolation of extracellular vesicles for the diagnosis of diseases, such as cancer.

exosomics

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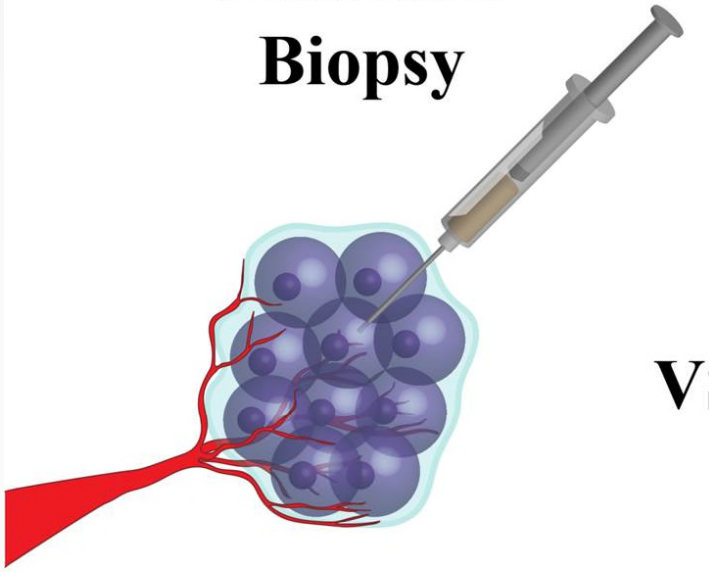
Our mission is to develop and commercialize a new generation of tests for cancer screening and liquid biopsy, based on analysis of circulating extracellular vesicles and exosomes.

The company offers a wide range of proprietary solutions for cancer screening and liquid biopsy, suitable for research use and clinical diagnostics.

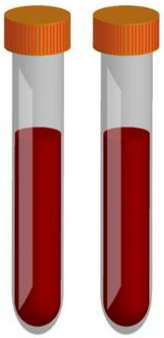
Exosomics envisions a world in which a simple blood draw will be sufficient for early diagnosis, easier monitoring and ultimately better patient outcomes.

Standard Biopsy



VS.

Liquid Biopsy



Time-Intensive Procedure
Localized Sampling of Tissue
Not Easily Obtained
Some Pain/Risk
Invasive

Quick
Comprehensive Tissue Profile
Easily Obtained
Minimal Pain/Risk
Minimally Invasive

Case for Provincial Support

- Support R&D and Innovation
- Build and attract research excellence
  - Pioneers 20 years ago
  - From virtually nothing to over 85 Million in R&D funding to NB
- Goal:
  - Leverage for additional federal and private research funding
  - Grow this knowledge sector of economy

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- **Press Release** • **Jun 28, 2018 03:09 EDT**

Exosome Diagnostic and Therapeutic Market

Exosome Diagnostic and Therapeutic Market is required to collect $367 million by 2022, enlisting a CAGR of 37.8% amid the period 2016-2022. Analytic application section ruled the market in 2015 and anticipated that would proceed with its predominance all through the estimate time frame. North America represented the greater part of the world exosome indicative and helpful piece of the overall industry in 2015.

Highly Qualified Personnel (HQP)

- ACRI is highly attractive for HQPs
  - HQPs often bring their spouses and families with their own skills and potential – Economic development
  - High wages, fast growing industry, foster innovation – economic ripple effect
  - Helps create a critical mass in biomedical research
- ACRI currently supports 69 HQPs
  - Over $1Million reinvested into NB treasury via taxes
- Research team is one of the most culturally diverse in the region
  - Five Continents represented
  - Creation of a vibrant local community

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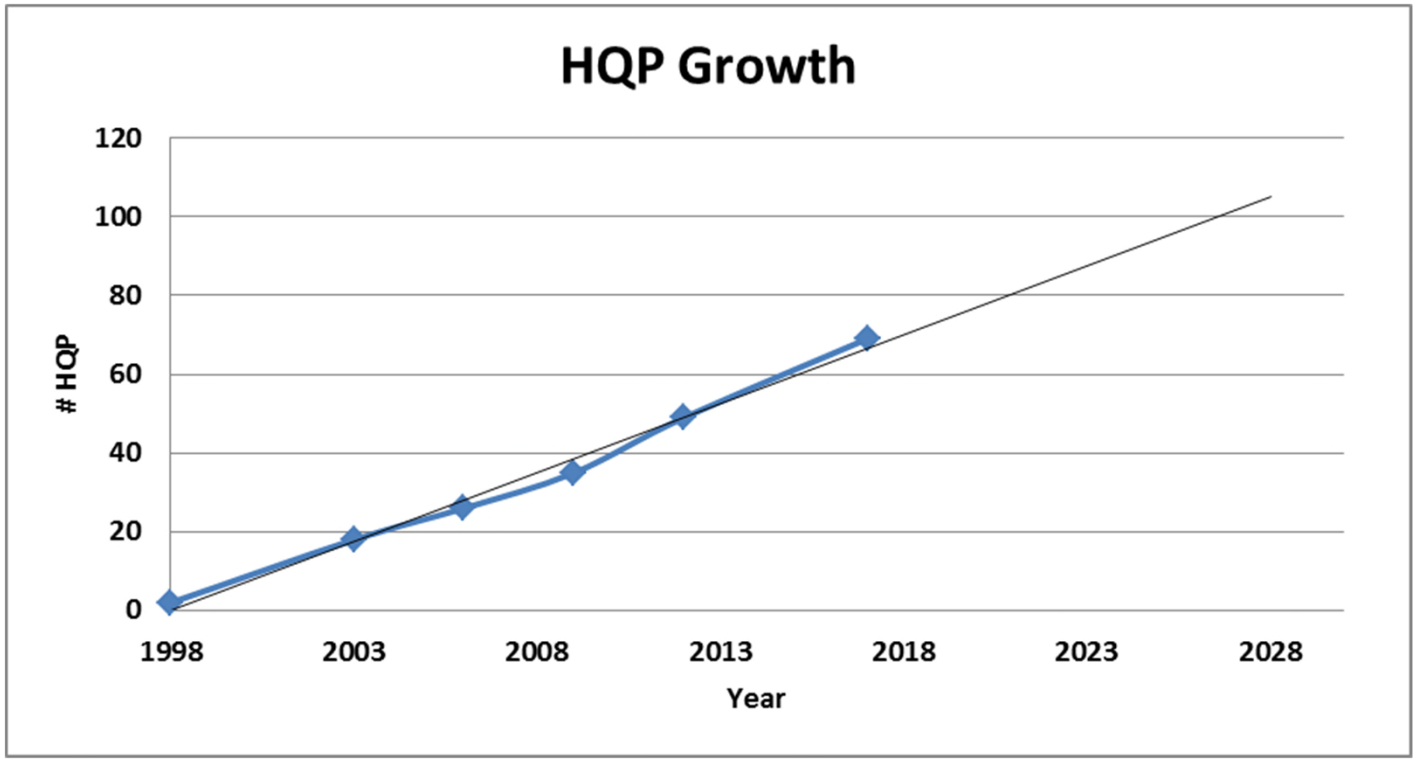
ACRI HQP Growth

- Since inception, ACRI has sustained a robust growth rate



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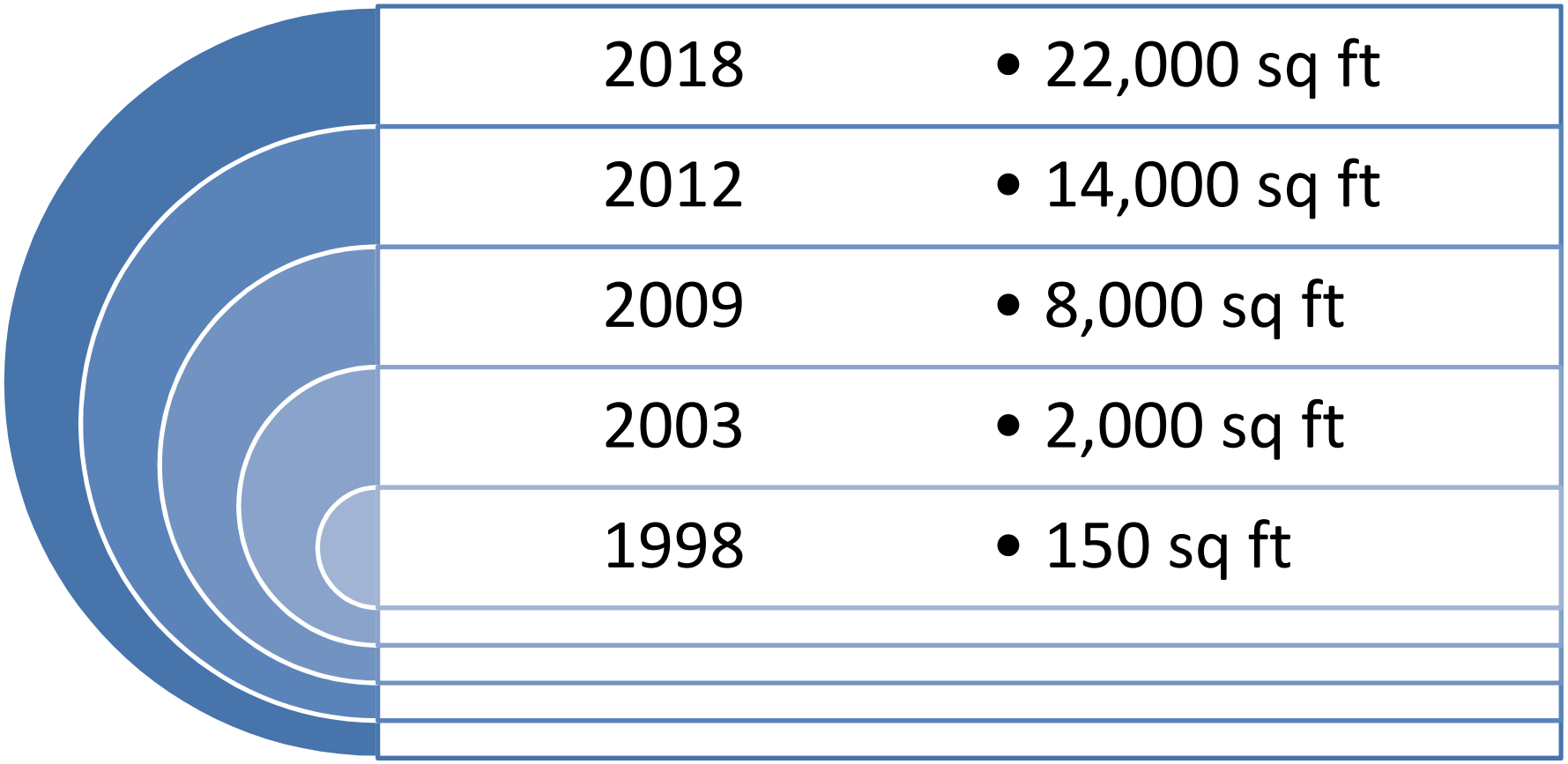
ACRI Footprint



2018	• 22,000 sq ft
2012	• 14,000 sq ft
2009	• 8,000 sq ft
2003	• 2,000 sq ft
1998	• 150 sq ft

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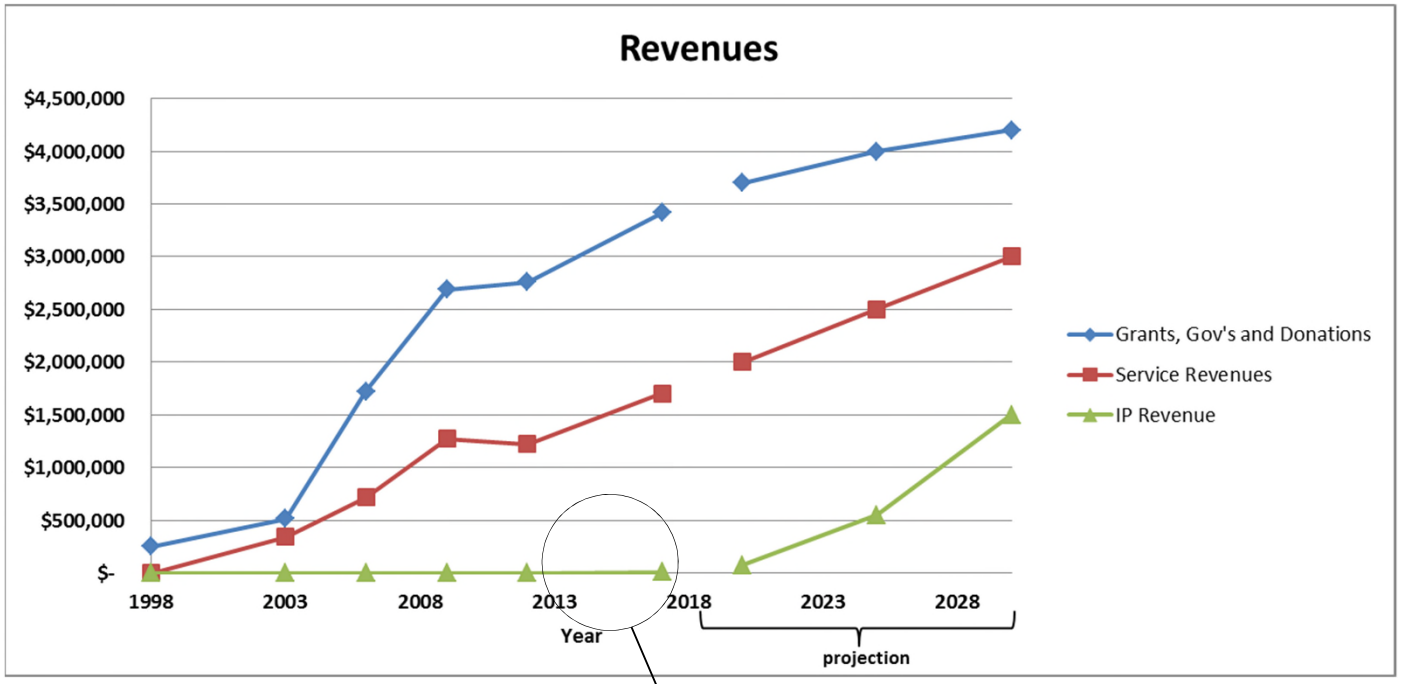
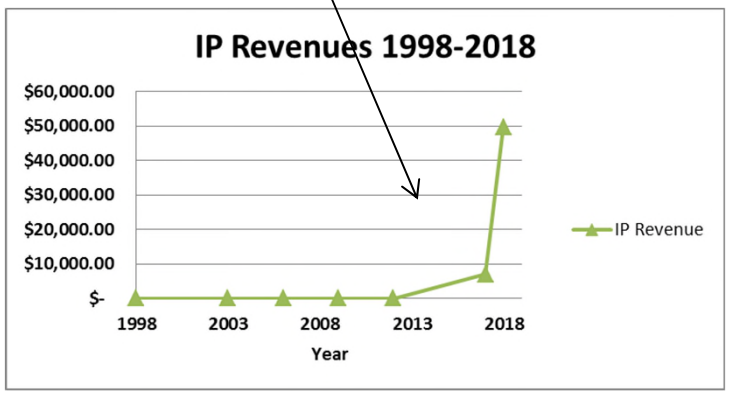
Revenues





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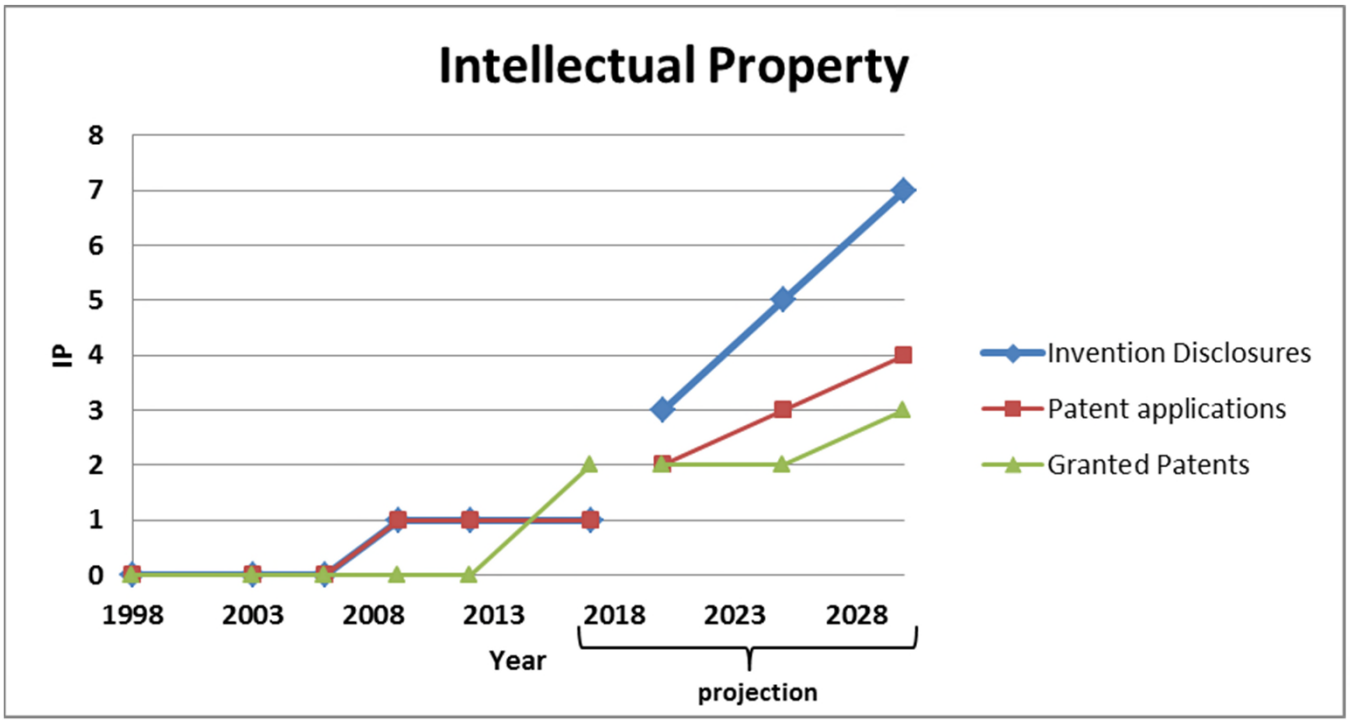
Intellectual Property (IP)

- All IP generated at ACRI facilities is institution-owned and has the potential to be commercialized



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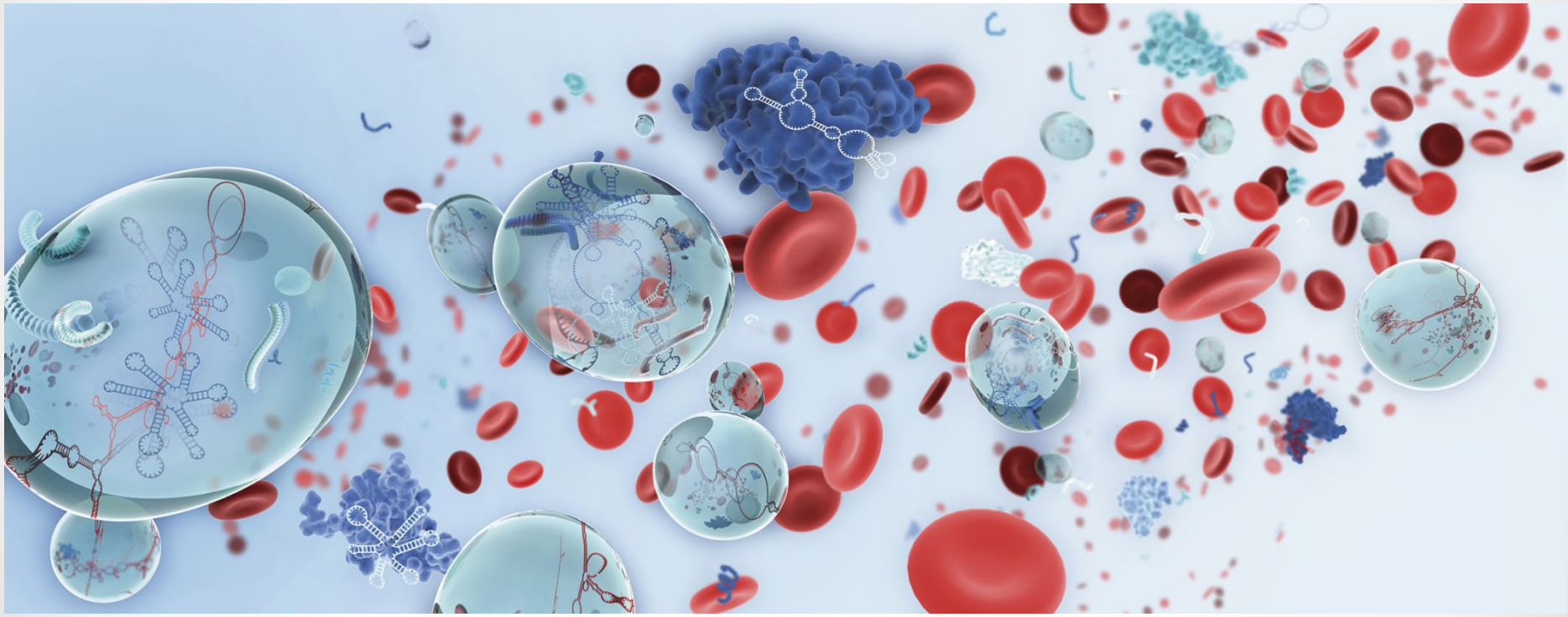
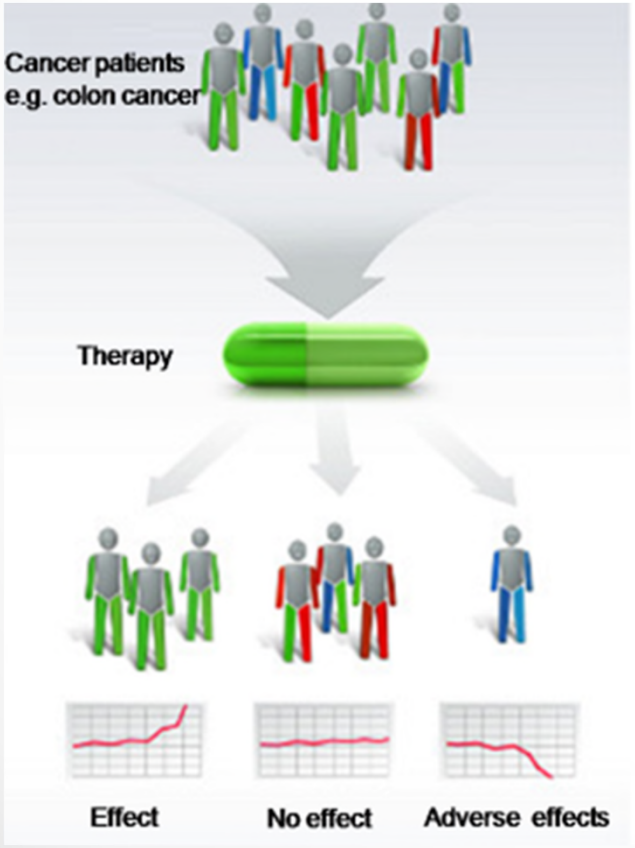
Thank you…

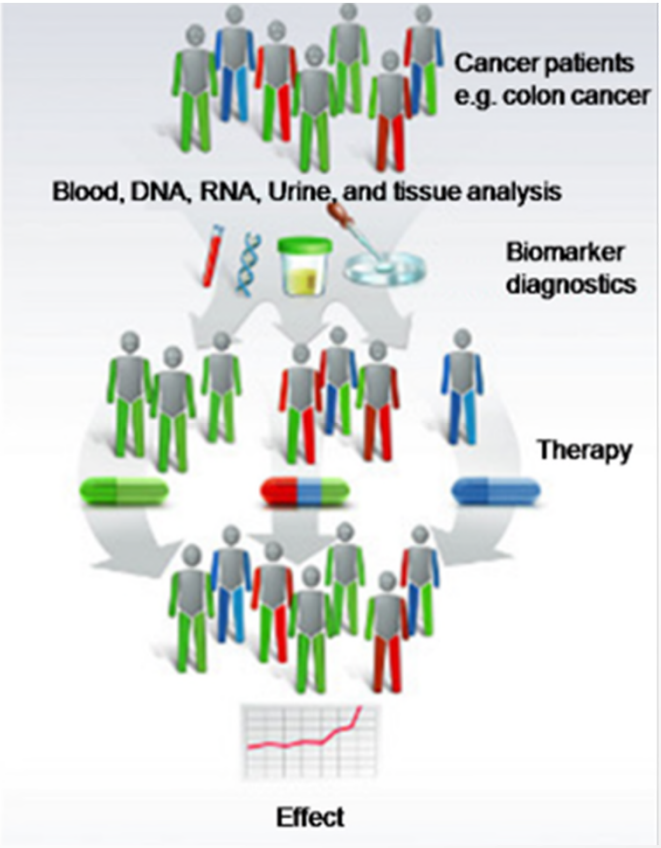


Precision Medicine

- Moving away from one size fits all to better treatments for optimal patient response

Without Precision Medicine **With Precision Medicine**





Merck effect…

Atlantic Canada Opportunities Agency | Agence de promotion économique du Canada atlantique

Canada

- Merck $1M investment helped leverage additional $3M funding from the province of NB and Cancer Research Society
- With Merck investments, ACRI was able to obtain a 4 year $5.9M research grant to develop liquid biopsy and personalised patient assays such as TMB
- Funding success convinced provincial government to prioritize NB Center for Precision Medicine a $20M infrastructure project!
- Next…???
- Thank you!!

Funding partners

Cancer Research Society | Société de recherche sur le cancer

100% research since 1945 - 100 % recherche depuis 1945

New Brunswick Health Research Foundation

Fondation de la recherche en santé du Nouveau-Brunswick

Atlantic Canada Opportunities Agency

Agence de promotion économique du Canada atlantique

Canada

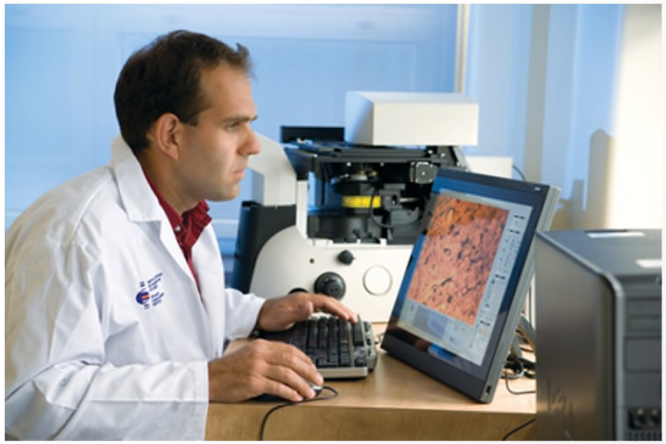
MERCK

CANADA MOTORCYCLE RIDE FOR DAD

FINBIF INNOVATION

CRAIG'S CAUSE PANCREATIC CANCER SOCIETY

Team at work



Current progress

Step 1 – Synthetic lethal target discovery

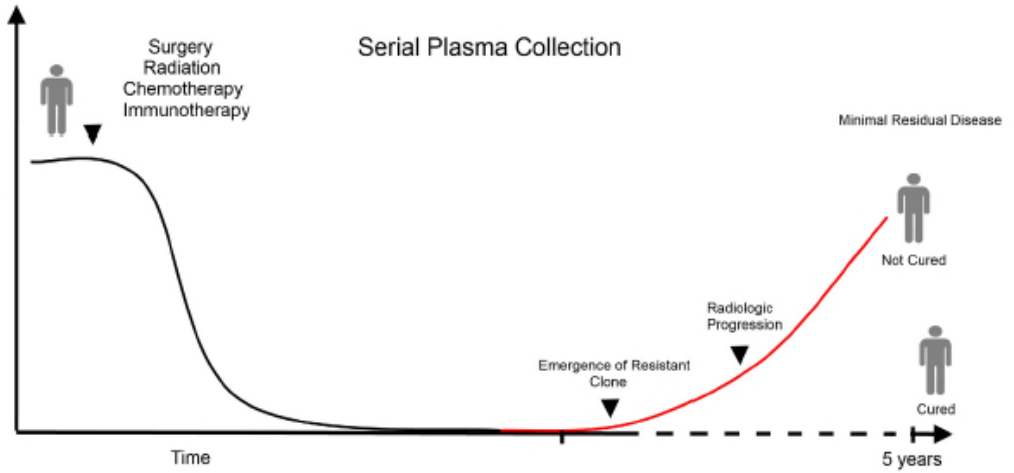
1. Target discovery
2. Target verification
3. gRNAs validation
4. Target validation

Step 2 – Drug discovery

a. Surface/EC	Peptide-based Exosome coating
b. Intracellular	Inhibitor Exosome loading

Liquid Biopsy as a real-time monitor of cancer status

Exosome Liquid Biopsy

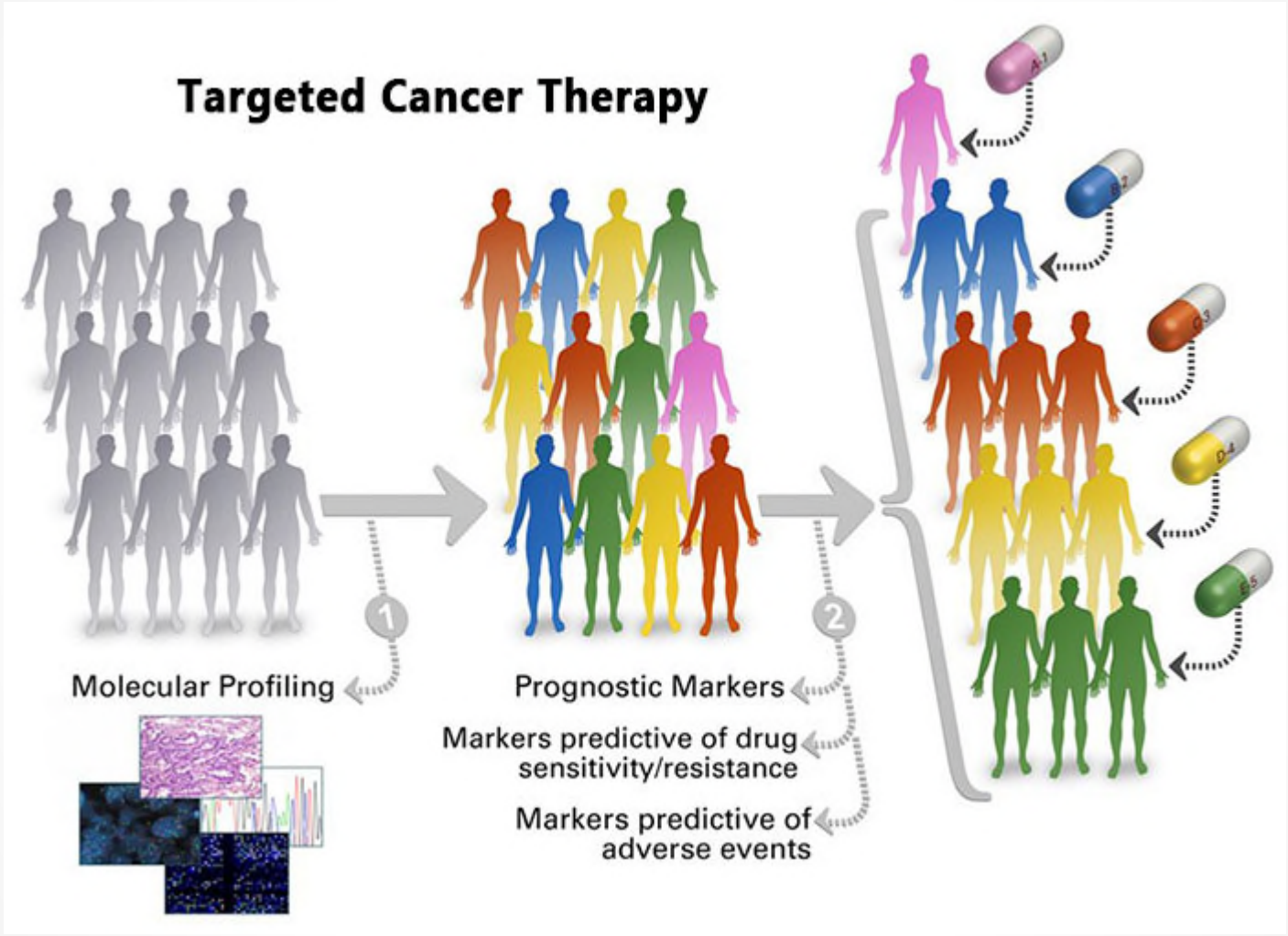


- CD63+ EV events by FC
- Tumor mutation profile
  - Decrease indicative of initial effectiveness of treatment
  - No change or increase points to ineffective therapy

- RNA profile may reveal response signatures

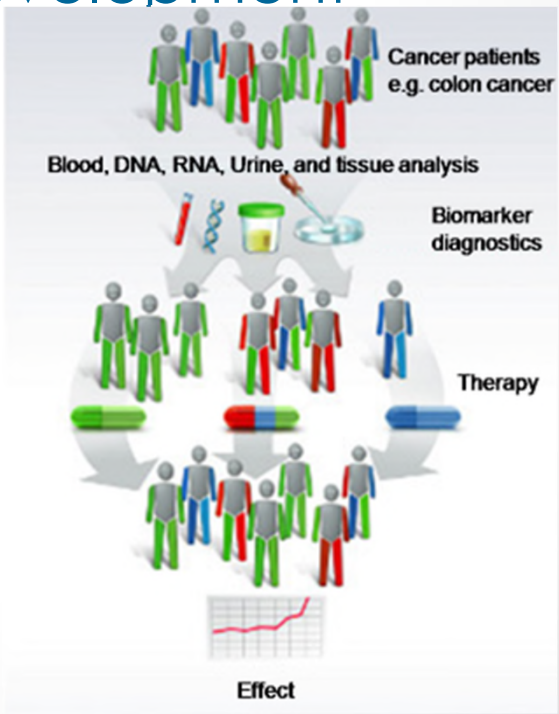
Future Objectives

- Develop liquid biopsy-based assays that will provide clinically-actionable information for cancer and other diseases.
- Use captured extracellular vesicles as a delivery system for therapeutics in cancer and other diseases.
- Use Crispr technology to identify vulnerability in patient derived cancer to inform therapy choices


Targeted Cancer Therapy
Molecular Profiling
Prognostic Markers
Markers predictive of drug sensitivity/resistance
Markers predictive of adverse events
1
2

The right treatment to the right patient

- Identifies companion biomarker
- Re-profiling of existing therapies to other indications
- Identifies new targers for drug development
- Overcome resistance
- Optimal combination therapy

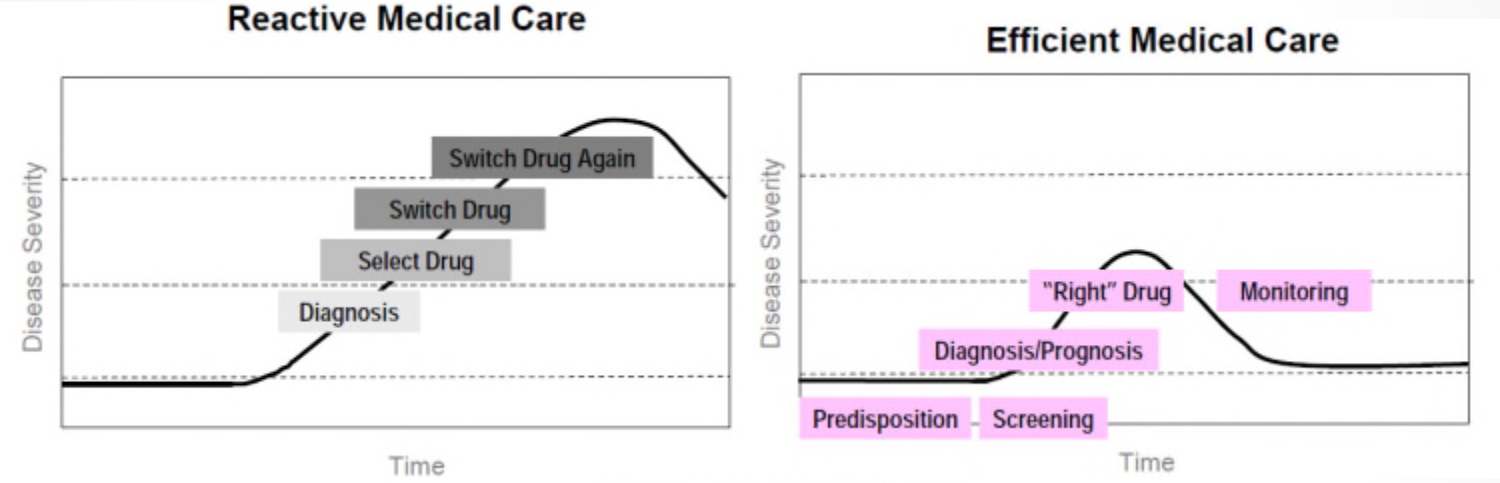


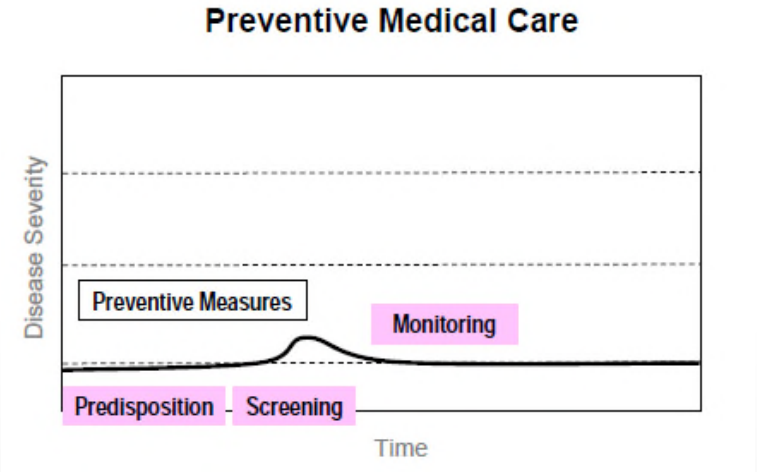
ACRI Focus

Research Objectives:

- Investigator -initiated Cancer Biology research
- Team Translation research
  - Liquid Biopsy Project
    - Patented Exosome capture technologies
    - Applications in cancer care spectrum
  - Synthetic lethal genome screens using CRISPR-Cas9 to identify new therapies for cancer

Precision Medicine: A Shift from Reactive to Efficient and Preventive





Oncomine Comprehensive Assay Gene List

Hotspot genes, n=73

ABL1	GNA11	MYD88
AKT1	GNAQ	NFE2L2
ALK	GNAS	NPM1
AR	HNF1A	NRAS
ARAF	HRAS	PAX5
BRAF	IDH1	PDGFRA
BTK	IDH2	PIK3CA
CBL	IFITM1	PPP2R1A
CDK4	IFITM3	PTPN11
CHEK2	JAK1	RAC1
CSF1R	JAK2	RAF1
CTNNB1	JAK3	RET
DDR2	KDR	RHEB
DNMT3A	KIT	RHOA
EGFR	KNSTRN	SF3B1
ERBB2	KRAS	SMO
ERBB3	MAGOH	SPOP
ERBB4	MAP2K1	SRC
ESR1	MAP2K2	STAT3
EZH2	MAPK1	U2AF1
FGFR1	MAX	XPO1
FGFR2	MED12	
FGFR3	MET	
FLT3	MLH1	
FOXL2	MPL	
GATA2	MTOR	

Full-gene coverage, n=26

APC
ATM
BAP1
BRCA1
BRCA2
CDH1
CDKN2A
FBXW7
GATA3
MSH2
NF1
NF2
NOTCH1
PIK3R1
PTCH1
PTEN
RB1
SMAD4
SMARCB1
STK11
TET2
TP53
TSC1
TSC2
VHL
WT1

Copy Number Variants, n=49

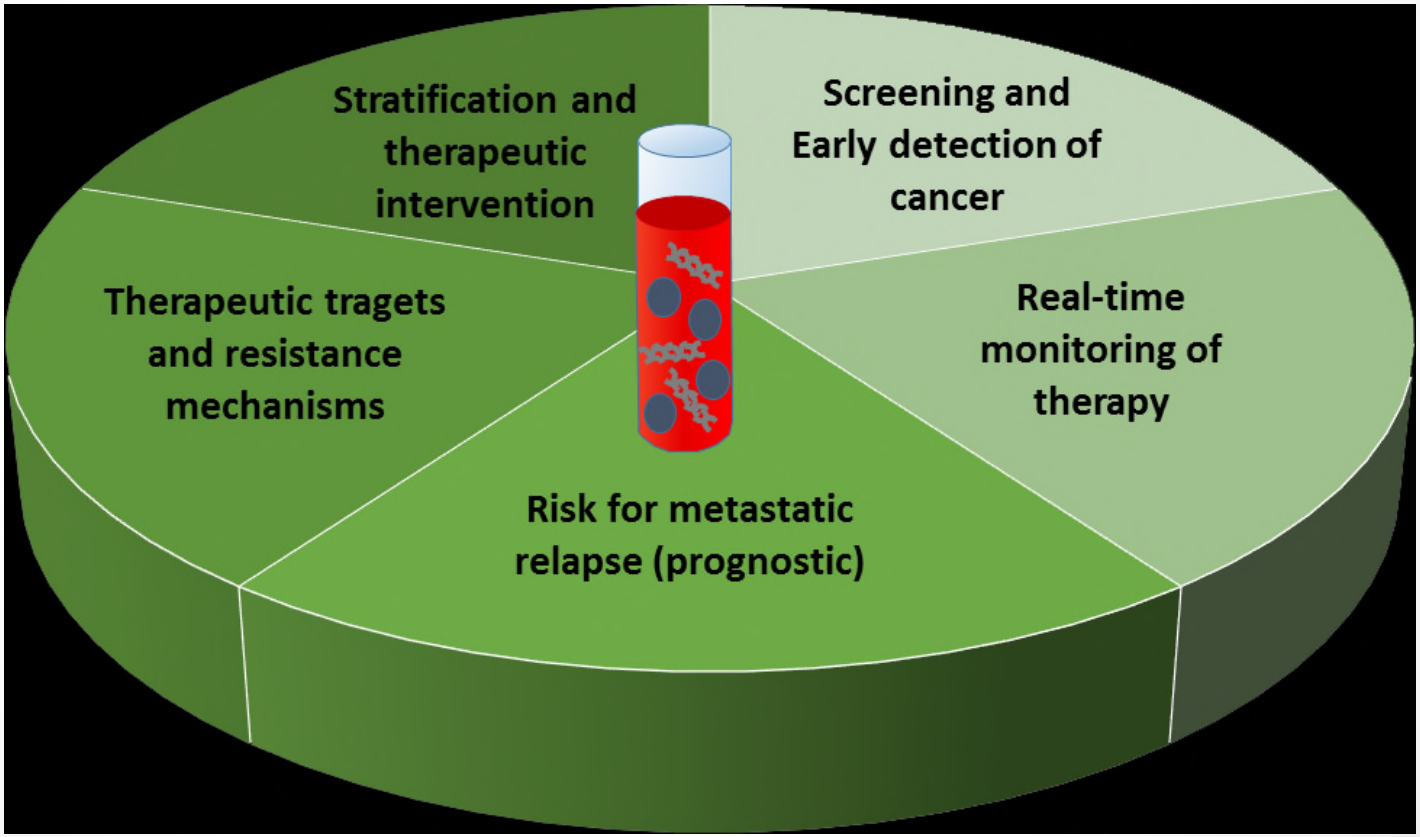
ACVRL1	IGF1R
AKT1	IL6
APEX1	KIT
AR	KRAS
ATP11B	MCL1
BCL2L1	MDM2
BCL9	MDM4
BIRC2	MET
BIRC3	MYC
CCND1	MYCL
CCNE1	MYCN
CD274	MYO18A
CD44	NKX2-1
CDK4	NKX2-8
CDK6	PDCD1LG2
CSNK2A1	PDGFRA
DCUN1D1	PIK3CA
EGFR	PNP
ERBB2	PPARG
FGFR1	RPS6KB1
FGFR2	SOX2
FGFR3	TERT
FGFR4	TIAF1
FLT3	ZNF217
GAS6	

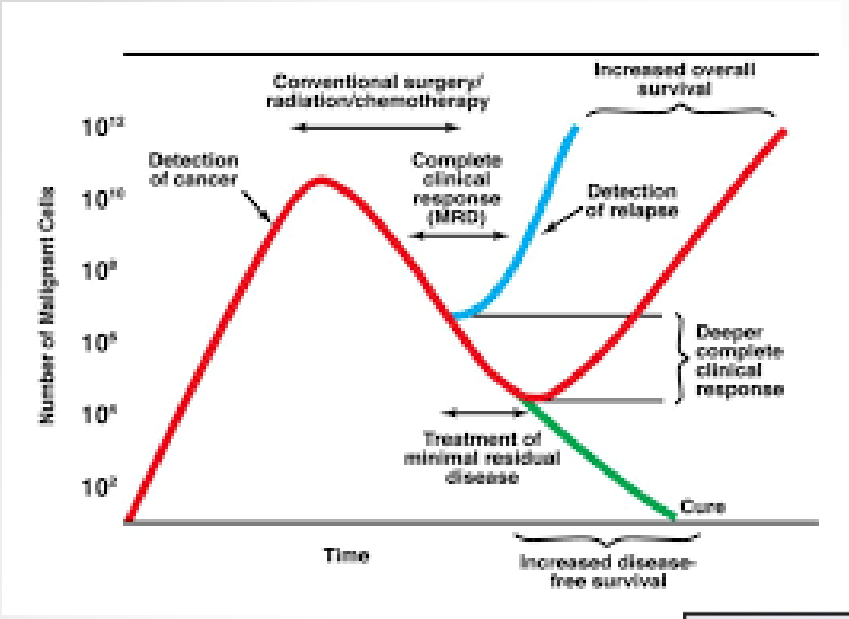
Fusion drivers, n=22

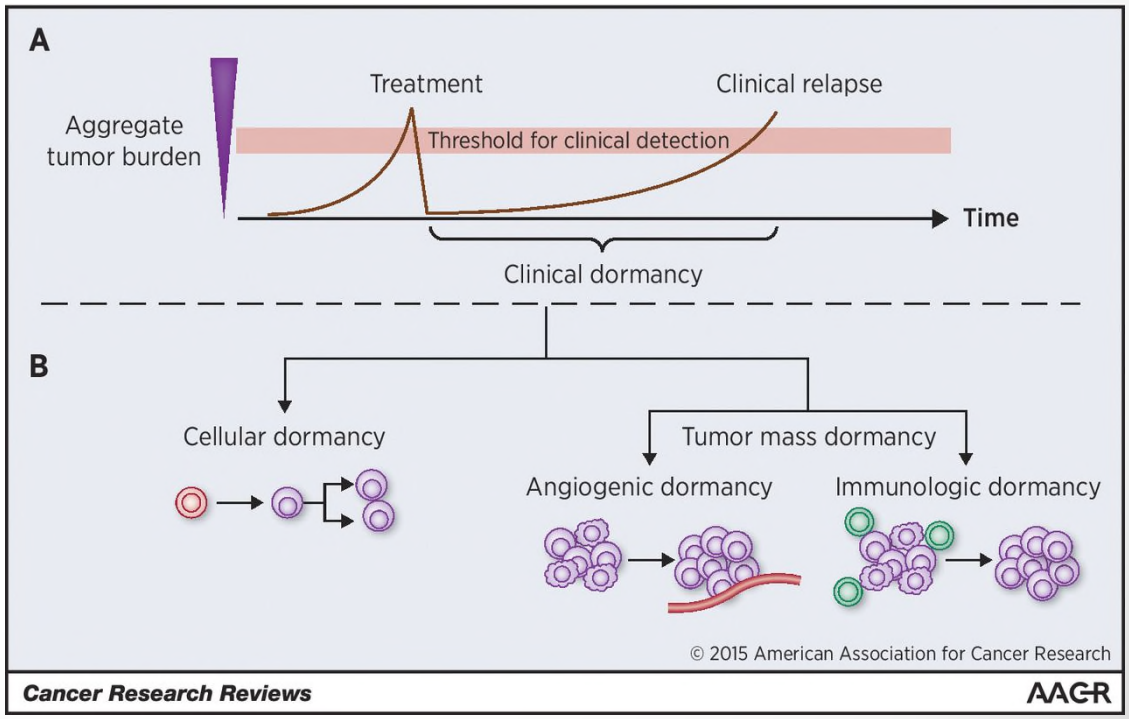
ALK
RET
ROS1
NTRK1
NTRK3
FGFR1
FGFR2
FGFR3
BRAF
RAF1
ERG
ETV1
ETV4
ETV5
ABL1
AKT3
AXL
EGFR
ERBB2
PDGFRA
PPARG

- **143 unique genes**
- **2530 amplicons in DNA panel**
- **207 amplicons in RNA panel**

ECOG-ACRIN cancer research group | NIH NATIONAL CANCER INSTITUTE


Stratification and therapeutic intervention
Screening and Early detection of cancer
Therapeutic tragets and resistance mechanisms
Real-time monitoring of therapy
Risk for metastatic relapse (prognostic)


Conventional surgery/
radiation/chemotherapy
Increased overall
survival
Detection
of cancer
Complete
clinical
response
(MRD)
Detection
of relapse
Deeper
complete
clinical
response
Treatment of
minimal residual
disease
Cure
Number of Malignant Cells
Time
Increased disease-
free survival


A
Treatment
Clinical relapse
Aggregate
tumor burden
Threshold for clinical detection
Time
Clinical dormancy
B
Cellular dormancy
Tumor mass dormancy
Angiogenic dormancy
Immunologic dormancy
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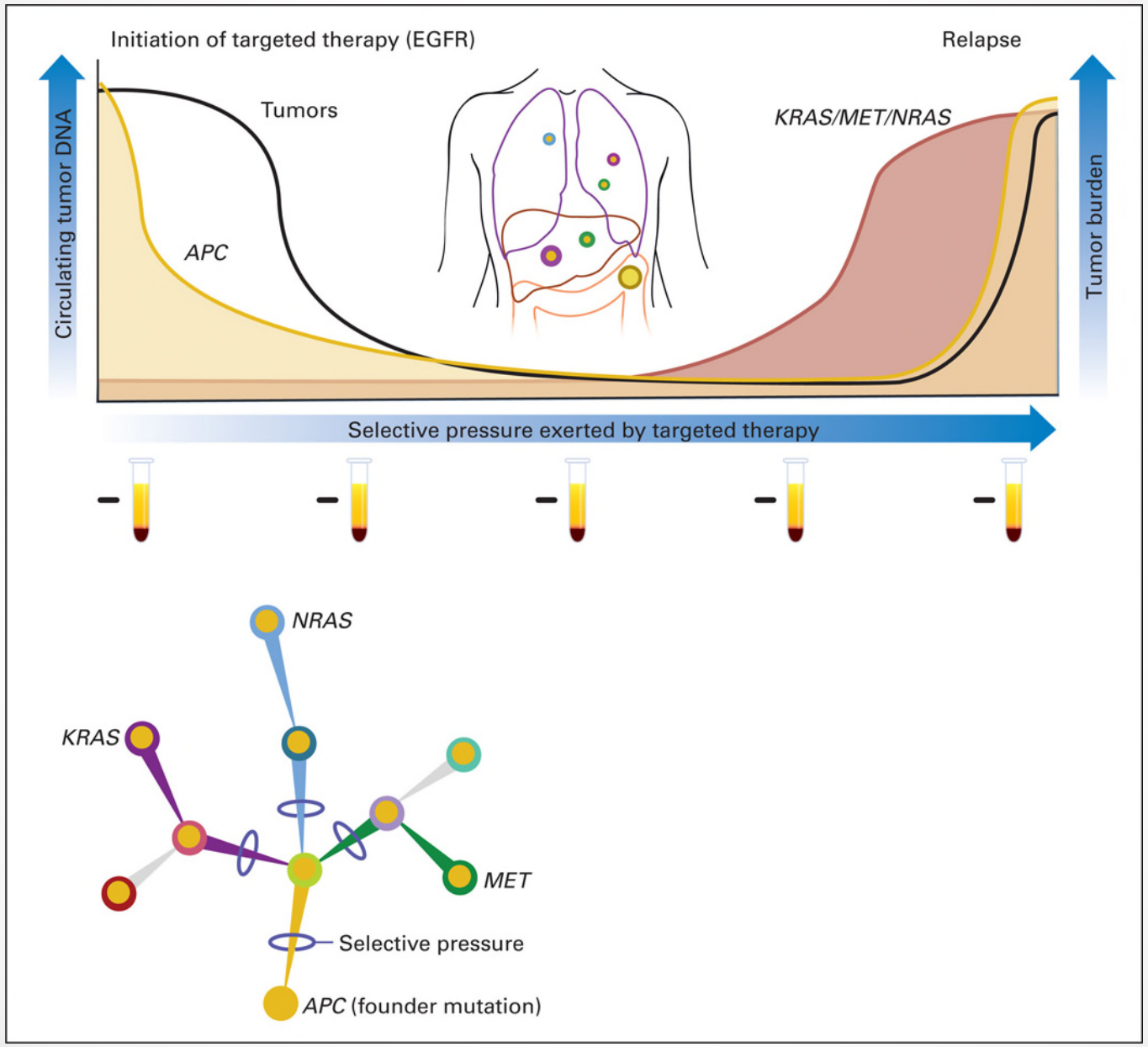
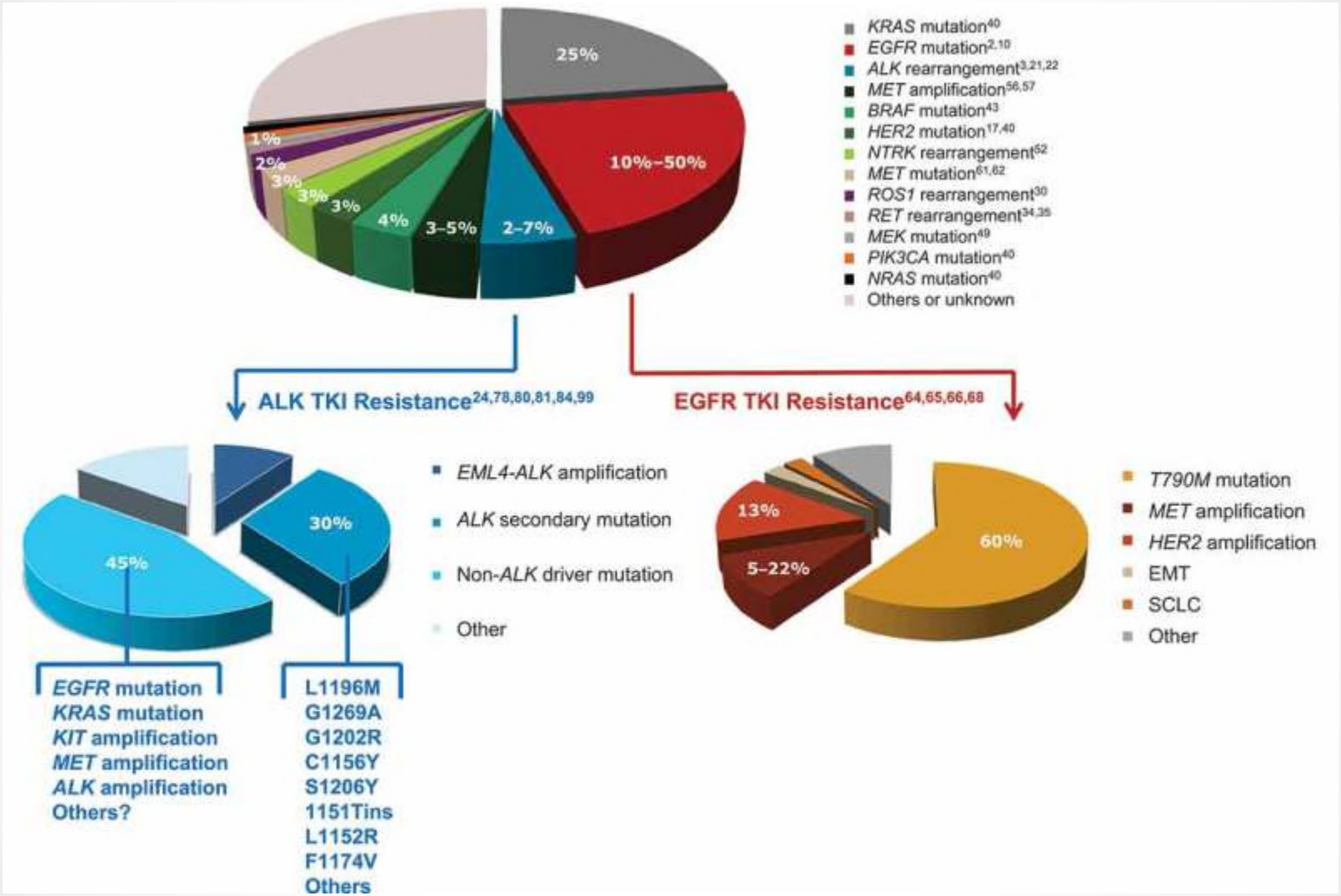
Cancer Research Reviews
AACR


Initiation of targeted therapy (EGFR)
Relapse
Circulating tumor DNA
Tumors
APC
KRAS/MET/NRAS
Tumor burden
Selective pressure exerted by targeted therapy
NRAS
KRAS
MET
Selective pressure
APC (founder mutation)

Current knowledge and expertise contribution

- **Local**
  - Fisheries and Oceans
  - Mycodev Group
  - St-Laurent Golf Products
  - Dalhousie University
  - Memorial University
  - Université de Moncton
  - Organigram
  - Soricimed
  - Vitalité Health Network
  - Horizon Health Network
- **National**
  - STEMCELL
  - Romich Holdings
  - Dynacare
  - CHUQ – Université Laval
  - McGill University
- **International**
  - Cynvenio Biosystems
  - BioVendor
  - Exosomics Siena
  - Lonza
  - SiMPore
  - IZON Science
  - Epigenomics
  - MIMA-PRO (Vison Medical)
  - SAIREM
  - Harvard Medical


25%
10%–50%
2–7%
3–5%
4%
3%
3%
2%
1%
KRAS mutation[40]
EGFR mutation[2,10]
ALK rearrangement[3,21,22]
MET amplification[56,57]
BRAF mutation[43]
HER2 mutation[17,40]
NTRK rearrangement[52]
MET mutation[61,62]
ROS1 rearrangement[30]
RET rearrangement[34,35]
MEK mutation[49]
PIK3CA mutation[40]
NRAS mutation[40]
Others or unknown
ALK TKI Resistance[24,78,80,81,84,99]
EGFR TKI Resistance[64,65,66,68]
45%
30%
EML4-ALK amplification
ALK secondary mutation
Non-ALK driver mutation
Other
EGFR mutation
KRAS mutation
KIT amplification
MET amplification
ALK amplification
Others?
L1196M
G1269A
G1202R
C1156Y
S1206Y
1151Tins
L1152R
F1174V
Others
13%
5–22%
60%
T790M mutation
MET amplification
HER2 amplification
EMT
SCLC
Other

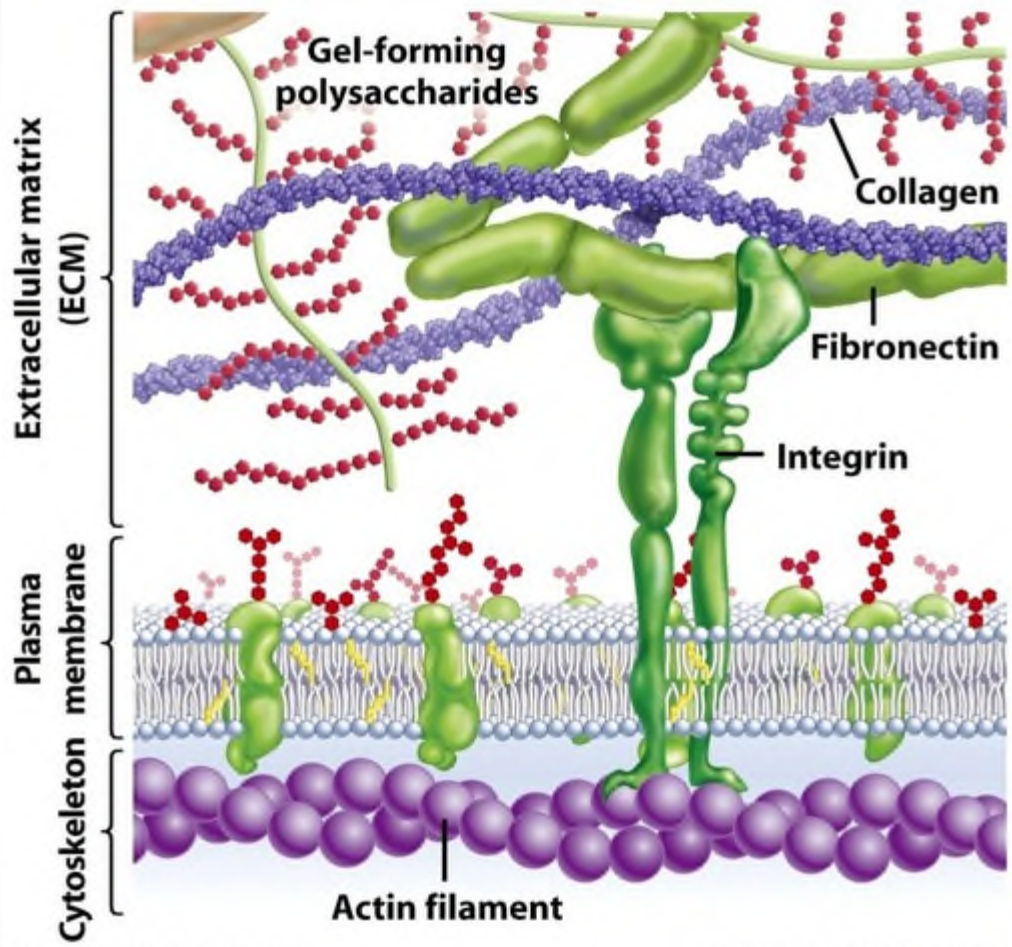
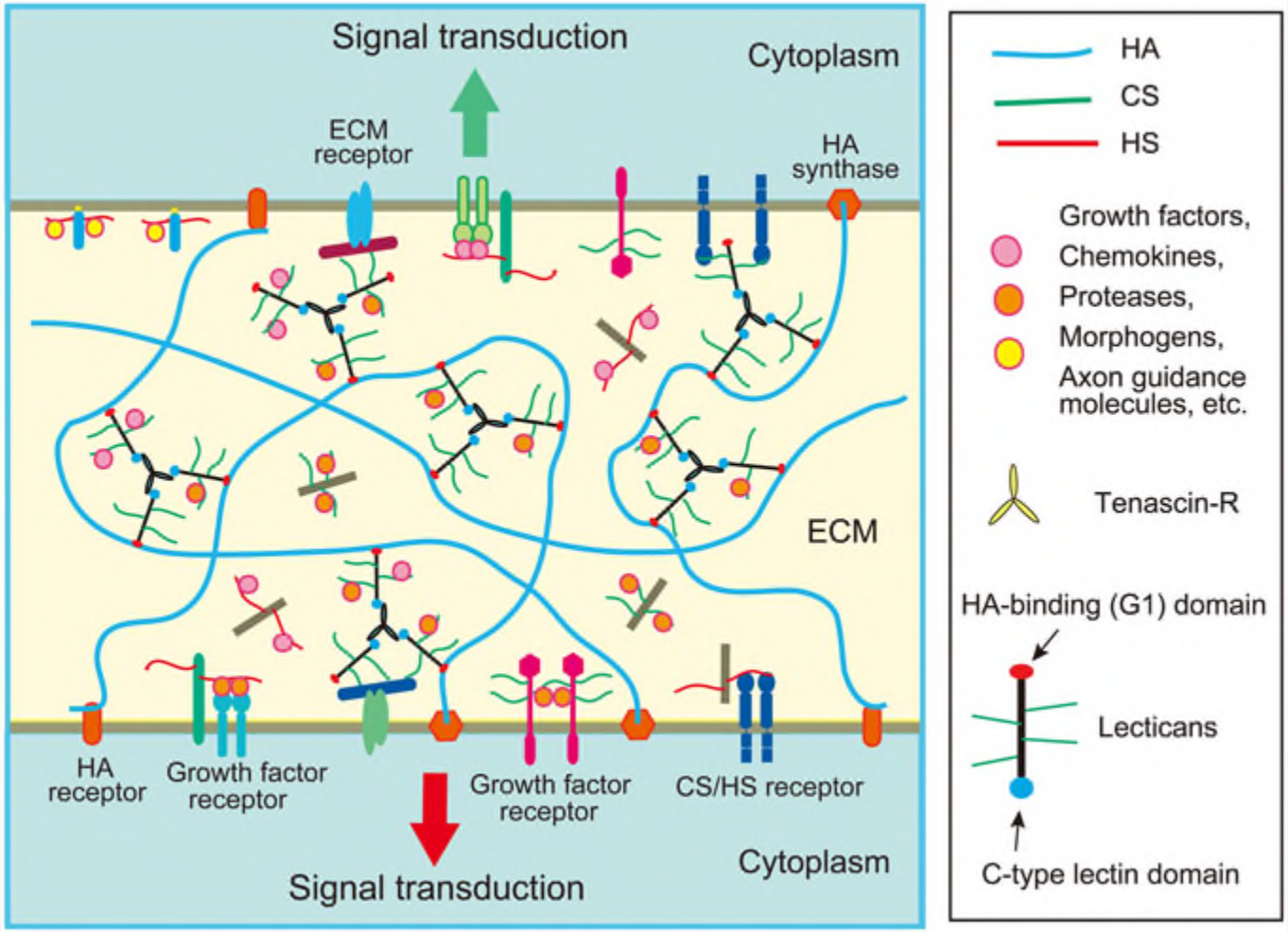
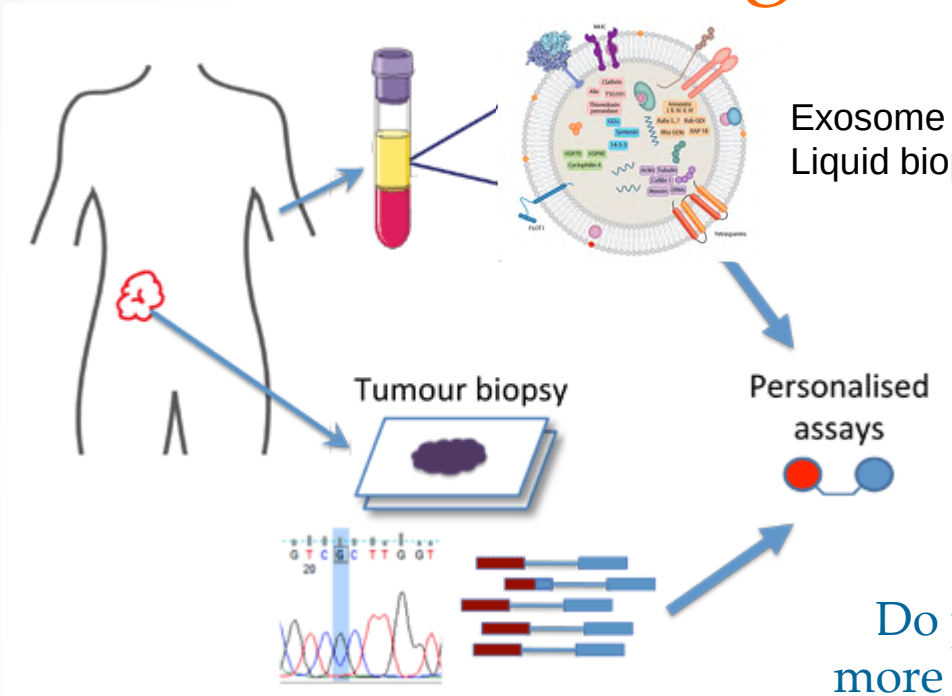
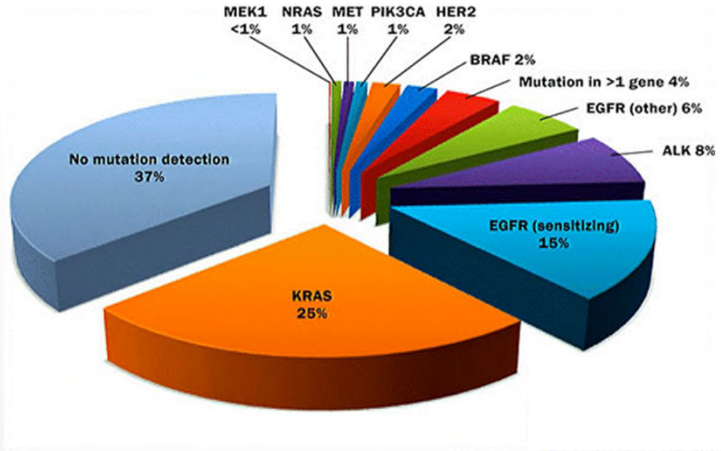


Figure 8-4 Biological Science, 2/e


Signal transduction
Cytoplasm
ECM receptor
HA synthase
ECM
HA receptor
Growth factor receptor
Growth factor receptor
CS/HS receptor
Cytoplasm
Signal transduction
HA
CS
HS
Growth factors,
Chemokines,
Proteases,
Morphogens,
Axon guidance molecules, etc.
Tenascin-R
HA-binding (G1) domain
Lecticans
C-type lectin domain

Exosome Liquid biopsy to monitor current state of a given cancer



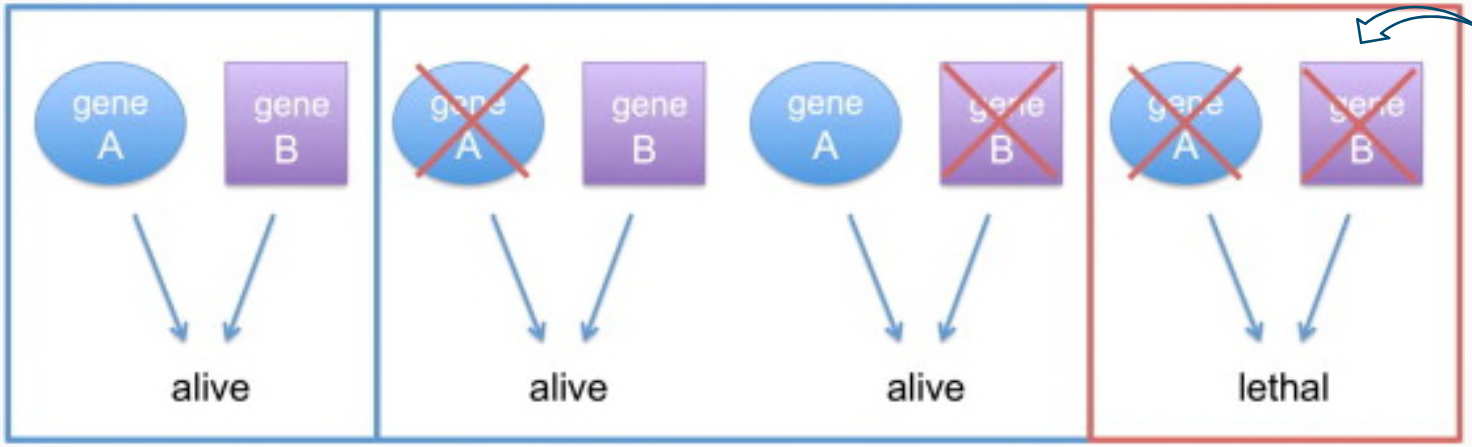


Do plasma exosomes provide a more representative snapshot of all tumour sub-clones?

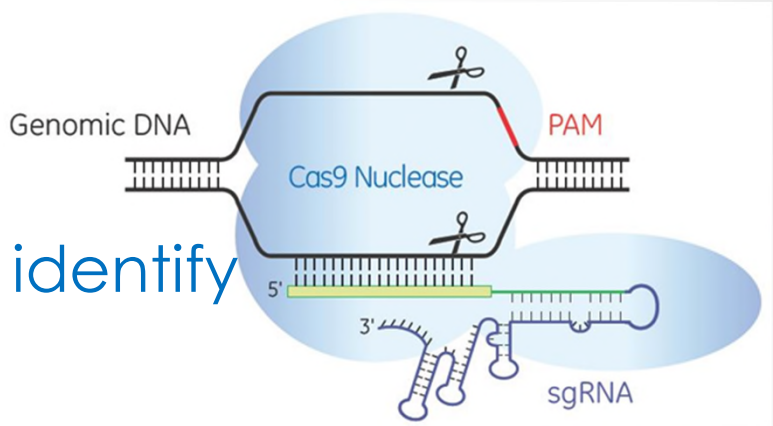
Detect changes in real time

- Tumor heterogeneity
- Treatment response
- Treatment resistance
- Disease relapse

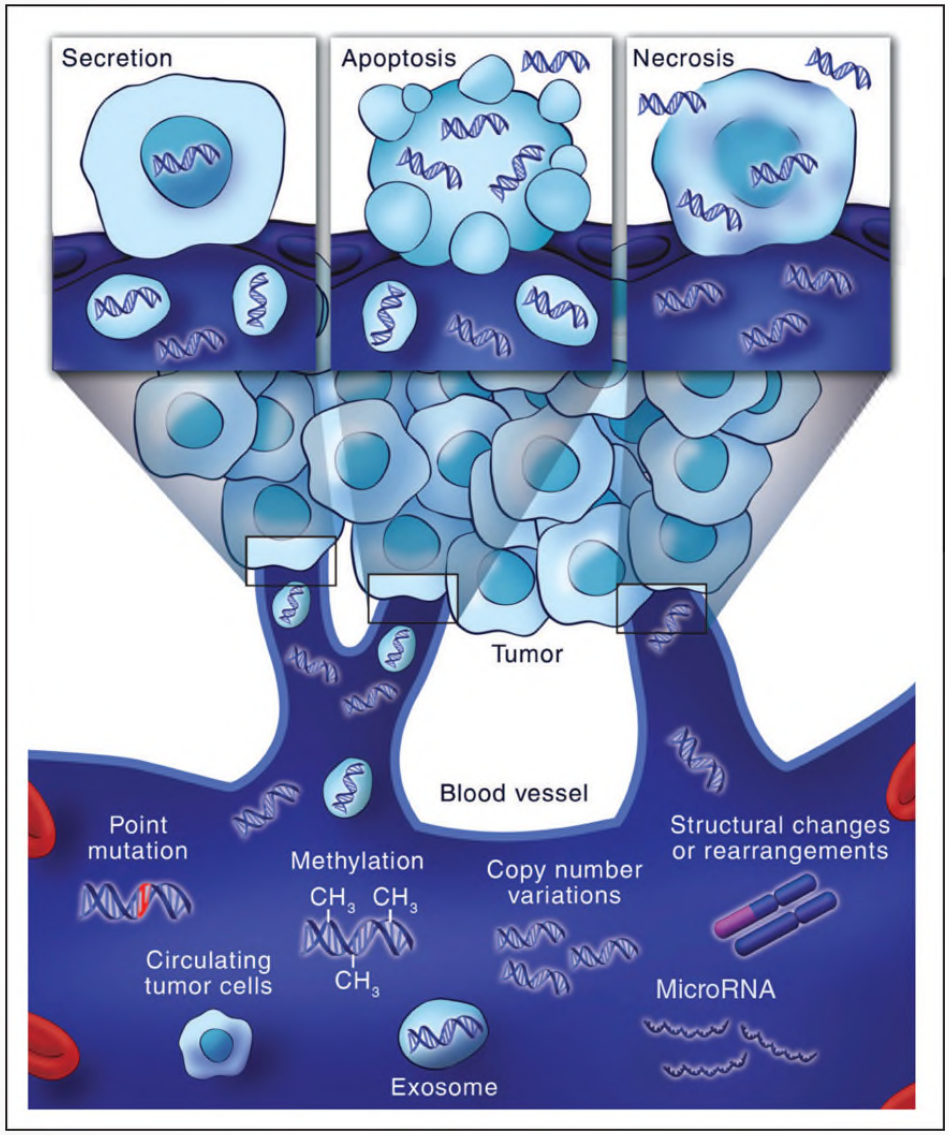
Synthetic Lethality Project



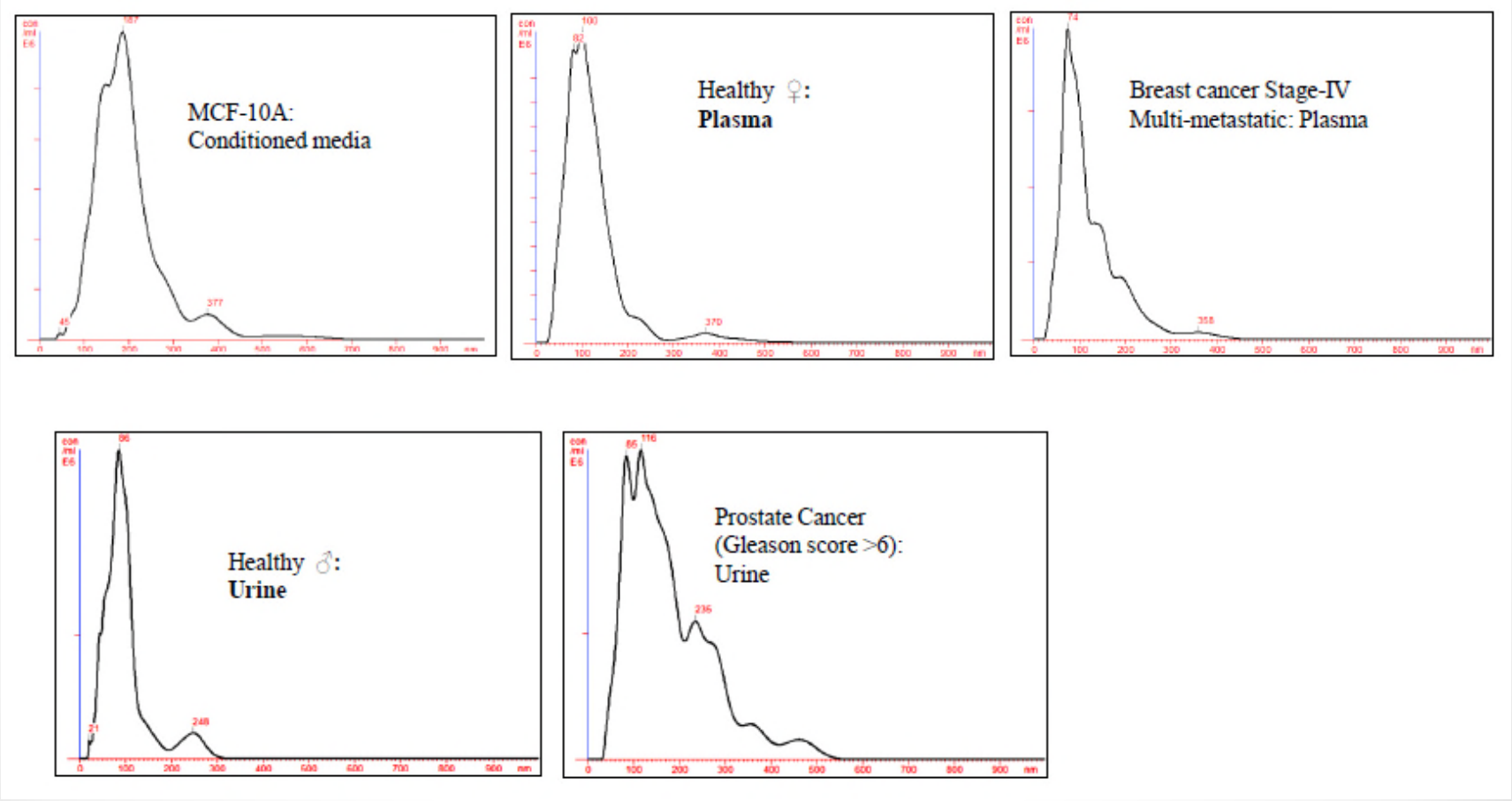
CRISPR-Cas9 genomic screens



- Screen cancer genomes to identify vulnerability targets
  - Synthetic Lethality
- Screened cancer sub-types
  - Lung, pancreatic, breast, kidney cancers and glioblastoma multiform
- Identification of vulnerable pathways and specific gene targets
  - Validation stage


Secretion
Apoptosis
Necrosis
Tumor
Blood vessel
Point mutation
Methylation
CH_3 CH_3
CH_3
Copy number variations
Structural changes or rearrangements
Circulating tumor cells
MicroRNA
Exosome

Particle size distribution in human samples by NTA



Expertise

- Collectively, ACRI has leading-edge expert in various areas including:
  - Biology and Chemistry
  - Genomics and Proteomics
  - Bioinformatics and Complex Data
  - Microwave Technology (Extraction)
  - Human Research and Clinical Trials
  - Partnerships, Licensing and IP Protection

Possible areas of collaboration

- Pharmacogenomics
  - determine individual's likelihood of benefiting or having adverse response to product.
- Microwave-assisted extraction
  - Rapid, controled process to achieve desired result
  - Avoid use of solvents
- Clinical trials