CASE WESTERN RESERVE UNIVERSITY

CASE COMPREHENSIVE CANCER CENTER

NCI Comprehensive Cancer Center

A Cancer Center Designated by the National Cancer Institute

Case Comprehensive Cancer Center

Strategic Plan 2017-2023

University Hospitals

Case Western Reserve University Est. 1826

Cleveland Clinic

Case Comprehensive Cancer Center Strategic Plan 2017-2023

Mission: Apply scientific discoveries in human cancers to improve lives through cancer prevention, detection, treatment, cure, and survivorship

Objective	Action
Multi-investigator initiatives incorporating paradigm shifting discoveries	-GI SPORE -Cancer immunology -Brain, Breast, Ovarian, Prostate,AML / MDS, AYA Imaging and therapeutics -Cancer disparities
Underserved populations and disparities research	-Tobacco exposure -Lung cancer screening -Disparities research in colon, breast ovarian, prostate, AML/MDS
Immune cancer biology & therapeutics	-Cancer - immuno biology & therapy -Cell therapy - Microbiome, -VLP immune activation
Preclinical therapeutic investigation and early phase trials	-Drug screening -Medicinal chemistry - Nano Rx, VLP drug resistance -imaging -Genomics -Early phase clinical trials
Diagnostics, therapeutics, prevention and health policy	-Early detection -MRF imaging, -Genomic prognostics -Population validation -Policy efforts to improve detection
Big data, Genomics, other omics & EMR studies of catchment area samples	-EMR warehouse Universal Informed consent -Genomics: discovery, clinical, risk, lifestyle diagnostics -Prevention & health policy diagnostics
PDX and organoid human tumor models and cancer atlas	-PDX & organoid human tumor research in: -Pathways -Drug development and resistance -Omics
Integrated cancer research, training, and career enhancement	Mentoring at all levels Trainee Membership Diversity R25s T32s: Cancer biology, Nanomed, Stem cells K12 Scholars

Leadership goals: Focus on our catchment. Expand Case CCC recognition through NCI, NCCN, AACI, societies and collaborations across centers. Increase philanthropic support of cancer research.

2017 update

CASE COMPREHENSIVE CANCER CENTER

CASE CCC CURRENT INITIATIVES and STRATEGIC PLAN 2017-2023

The Case CCC Strategic Plan serves as a roadmap to focus scientific initiatives and investments of the Case CCC. The strategic planning process is dynamic and updated annually. As noted above, our processes encourage active review through our various planning and evaluation committees and retreats. The Executive Committee, with input from Program Leaders and members, maintains an ongoing planning process at each meeting to review and prioritize new scientific initiatives. Over the current grant period, the EC has reviewed and approved the following major new program initiatives, which are now incorporated into our strategic plan. While the Center has instituted a longitudinal plan that evolves regularly, the plan is facile and includes current links to the Moonshot initiatives as outlined by the NCI Cancer Moonshot Blue Ribbon Panel. Our Center conducted discussions linking a number of the Blue Ribbon Panel's recommendations to Center initiatives and Dr. **Gerson** is a co-author of a review in Lancet Oncology 2017. While this has informed the center's approach, many new efforts come from our program and executive committee leadership. As the Center's strategic priorities emerge, each is discussed and vetted with the PLC and presented to the IAC and EAC. Some initiatives will evolve into new research programs. For this reason, criteria were established for full research program status:

- Alignment with the Center's strategic plan
- Sufficient depth and breadth of research to catalyze interdisciplinary and cross-consortium research efforts, including a translational and disease-based focus
- Funding to sustain the initiative, including > 8 R01 level funded projects from a minimum of 5 PIs
- Evidence of minimal impact on existing programs or development of a plan to reorganize impacted programs

The new initiatives aligned with the Strategic Plan 2017-2023 include the following areas that feed back to our current research programs.:

Drug Discovery and Drug Development: Drew Adams was recruited jointly by the Center and the Department of Genetics and Genome Sciences from the Broad Institute to initiate a campus-wide drug screening and medicinal chemistry effort. These efforts reflect a Moonshot recommendation for new drug development. Support for this initiative has been through pilot RFAs issued by CaseCCC and supported by VeloSano funds. Research Programs involved include MO, CI, GICG, HICB, DT.

- The Small Molecule Drug Development Shared Resource has supported 13 drug screens that complement 18 other ongoing Center member-initiated discovery and development efforts that cut across all scientific programs.
- The new Research Center in Targeted Medicinal Chemistry (RCTMC) at Taussig Cancer Institute (TCI), led by James Phillips provides medicinal chemistry support for development of lead compounds.
- The CWRU CAHH has provided $1.4M in support, leading to license agreements and further grant support; Cleveland Clinic has supported drug development efforts based on identified mutated genes in hematological malignancies and facilitated sponsored research; and the UH Harrington Discovery Institute has supported four center members (>$100K each) for lead compound optimization.
- The Committee on Cancer Drug Development and Resistance (CDDR, DT) evaluates and provides input on development of all new lead compounds as well as approaches to combat resistance to current therapies.
- Nicole Steinmetz has received CWRU support to initiate a new Center for Nanotherapeutics to support cancer oriented development of LVPs.

Cancer Genomics: Expansion of cancer genomics capabilities into each research program has been a priority and is reinforced by a Moonshot Blue Ribbon Panel recommendation. The Center enables many genomic and epigenomic studies across Programs. Case CCC RFAs for human cancer genomics have been issued by CaseCCC in 2015, 2016, 2017. Research Programs involved include MO, CI, GICG, GU, CPC, HICB, DT.

- **Alex Miron (GICG)** was recruited from the Dana-Farber Cancer Institute to co-direct the Genomics SR equipped with three HiSEQ and a planned CLIA laboratory. The SR offers full sequencing and analytics capabilities.

- A clinical tumor gene panel of 52 genes and the NCI MATCH gene list are available for targeted sequencing. Both UH and CC participate in Foundation Medicine testing and the PMEC consortium. All AML/MDS patients undergo genomic analysis and about 40% of solid tumors are now undergoing panel NGS.
- With Tempus Inc., we are conducting whole exome, whole genome, and RNA sequencing. Projects focus on ovarian and TNBC cancers (including PDX), brain tumor exome and RNA sequencing for glioma recurrence , and 100 clinical samples to be analyzed in four disease areas.
- A single cell sequencer has been added to the genomics SR through an S10 award to facilitate tumor complex heterogeneity studies.
- A high-risk assessment effort by **Drs. Eng (CPC)**, **Narla (DT)**, and **Vinayak (HICB)** for familial cancer clusters has been developed at both hospitals. High risk families that lack known mutations undergo WES to identify private mutations that may be drivers within the family and may implicate a common pathway for cancer etiology.
- Multi-disciplinary genomics tumor boards facilitate clinical trials accrual and serve as a consultative service across the cancer networks of both hospitals. Individual boards review hematological malignancies, lung cancer, breast cancer, and other solid tumor malignancies.
- Epigenetic signatures are being developed for colon and breast cancers as well as osteogenic sarcomas with the goal of identifying key drivers of these diseases. In addition, the efficacy of combining the epigenetic targeting drug, decitabine, a DNMT1 inhibitor, with cytidine deaminase inhibitors is being evaluated in pancreatic, lung, and lymphoid malignancies.

Brain Tumor Program in Development: Justin Lathia (MO) and **Jill Barnholtz-Sloan (CPC, GICG)** co-lead this initiative in brain tumors. An RFA from VeloSano and from other philanthropic efforts (Cristal awards) were issued in 2016. Research Programs involved include MO, CPC, CI, HICB, DT.

- The 40 members across the CaseCCC institutions are engaged in brain cancer research that integrates basic biology, imaging, use of tissues and genomics, and novel therapeutics, to inform marker-driven therapeutics for these recalcitrant malignancies.
- The discoveries of hypoxia signaling, alterations in Connexins and novel MR imaging analysis for diagnosis and monitoring are powerful tools in the effort to better understand and treat adult gliomas and pediatric medulloblastomas, linked to the AYA group.
- The cross CaseCCC efforts have also allowed for establishment of a large resource of experimental models available for use within the CaseCCC, including animal models (PDX, GEM, syngeneic) and organoids.
- **Drs. Lathia (MO)** and **Barnholtz-Sloan (CPC, GICG)** are leading a multi-institutional effort towards a NCI Program Porject submission for 2018 focused on sex specific differences in glioma.
- The CaseCCC brain tumor biobank has been leveraged for multiple funded multi-institutional, international efforts in gliomas including The Cancer Genome Atlas and the Glioma International Case-Control Study and newly funded efforts from Brain Tumor Charity UK focused on meningioma (PI: **Barnholtz-Sloan (CPC, GICG)**).
- R01s focused on brain tumors have been awarded in the past 2 years to **Drs. Lathia (MO), Basilion (CI), Yu (MO)**, **Brady-Kalnay/Sloan (MO, DT), Bar (MO)**, and **Bao (MO).** Investigator-initiated clinical trials (IITs) are led by **Drs. Andrew Sloan (CI), Jennifer Yu (CI), Michael Vogelbaum (DT)** and **Manmeet Ahluwalia (DT).**

Cancer Immunotherapy: The Center undertook a strategic assessment of its efforts in cancer immunology and elected, with advice of the EAC, to consolidate immunotherapeutics into two groups: one that was cell-based in HICB under **Alex Huang** as co-leader of HICB and one that focused on small molecules under the direction of co-leader **John Letterio** in DT. These studies will continue to expand over the next grant cycle, impact clinical investigation across programs, and align with Moonshot recommendations. A Case CCC RFA was issued by CaseCCC. Research Programs involved include MO, CI, GU, HICB, DT.

- The Center has a cell production facility that includes 6 clean rooms.
- The Center recruited young investigators, expanded cell-based and small molecule IITs, and has increased DC, NK, and T-cell based studies using cells produced in the Hematopoietic SR with trials led by **Drs. Hill, Yi, Wald, and de Lima (**all **HICB)**.

- Preclinical studies with plant virus-like particles (VLP, **Nicole Steinmetz (CI)**), TGFbeta, cdk5 inhibitors (**Drs. Letterio and Huang)** and MDSCs (**Drs. Finke (GU) and Lathia**) provide novel therapeutic approaches to immunotherapy.

Women's Cancers Program in Development: William Schiemann (MO) and **Ruth Keri (MO)** lead this effort of 43 members, 23 of whom are basic breast or ovarian cancer biologists, and 20 are physician scientists/clinical researchers from the MO, CI, DT, HICB, and CPC programs.

- This interprogrammatic effort reflects transdisciplinary research approaches to breast and ovarian cancer etiology, genomics, detection, and treatment.
- Members have remarkable interactions across signaling, cell biology, genetic screening, epigenetics, genetically engineered animal and human PDX models, nanoparticle therapeutics, cancer immunology and microenvironment, and drug development. PDX support has come from an RFA issued by CaseCCC.
- A breast cancer biorepository, high-risk assessment program (led by **Charis Eng [CPC] and Goutham Narla (DT)**), and clinical trials program (led by **Jame Abraham [DT]**) provide human samples for research, including effofrts to understand the role of the microbiome in breast cancer etiology and progression (with Steven Gorbmeyer).
- A gynecological tumor biorepository (developed by **Analisa DiFeo [DT]**) has been used to generate a large array of endometrial and ovarian PDX models for preclinical testing of novel therapies.
- Discoveries include the role of TGFβ and integrin-β3 in breast cancer epithelial/mesenchymal transition (**Dr. Schiemann [MO]**), the role of mir181 in ovarian cancer (**Analisa DiFeo [DT]**), mechanisms of action of Bromodomain protein inhibitors in triple negative breast cancer (**Ruth Keri [MO]**), the predictive value of first dose changes in gene expression in pathological CR after anti-Her2 therapy (**Vinay Varadan [GICG]**), and the marked immune cell infiltrate in TNBC (**Shaveta Vinayak [MO**]), suggesting a potential for immune checkpoint therapeutics.
- Studies of breast cancer detection using optoacustic, digital and MRI digitization (Drs Grobmeyer, **Plecha and Matabhushi**)
- UH is currently recruiting a director for breast cancer clinical research.

Adolescent and Young Adult (AYA) Cancer Research Initiative: Supported by a $6.7M philanthropic gift and endowment to Case CCC, the Center established the AYA (15 to 30 year olds) cancer research initiative, led by **John Letterio (DT)** (chief of Pediatric Heme-Onc). This program directly addresses the AYA research recommendation by the Moonshot panel. Research Programs involved include MO, CI, HICB, DT, CPC.

- A 4-year pilot grant program is building a cohort of collaborating investigators focused on the etiology and treatment of AYA cancers, expanding a biorepository, and managing late effects.
- Projects include MR fingerprint imaging of AYA brain tumors and late effects of irradiation (**Mark Griswold [CI]**); development of NK cell therapy for AYA ALL and AML (**Drs. Wald, Dallas, Parameswaran, Otegbeye, and de Lima**, all **[HICB]**); targeting CDK5 to block PDL1 expression in medulloblastoma (**Drs. Huang and Agne Petrosiute [HICB]**); studies of osteogenic sarcoma variable enhancer loci (**Peter Scacheri [GICG]**), and melanoma progression (**Dr. Letterio [DT]**).
- Multi-investigator pilot award RFA was issued by CaseCCC in August 2017.
- The ACS IRG issued by CaseCCC has an earmarked pilot each year for a junior faculty member to develop an AYA project.

Community Outreach and Cancer Health Disparity Initiative: Monica Webb Hooper (CPC), Director for the Office of Cancer Disparities Research, is establishing oversight and coordination of Center-based community outreach and interaction with the hospital-based programs of CCTCI and UHSCC. The goal of this office is to reduce cancer disparities through research, education, and outreach and its efforts are specifically recommended by the Moonshot panel to improve research of underserved populations. Research Programs involved include CPC, MO, CI, GU, GICG, HICB, DT.

- This effort is supported by the Preventive Research Center led by **Elaine Borawski (CPC)**, the Cancer Prevention and Control Research Network led by **Susan Flocke (**co-leader**, CPC)** and a number of community-oriented research efforts in CPC.
- New research efforts led by **Fred Schumacher (CPC)** include developing analytics to better understand the catchment area [*eg.*, graphic information systems (GIS) geo-mmapping], effectively

translate basic discoveries for community benefit, and disseminate findings into communities with high need.
- Annual pilot grants across programs to stimulate disparities focused research.
- In the next grant period, community-focused and disparities research involving the catchment area community will be developed and supported from pilot fund RFAs issued by CaseCCC across all research programs.

LONG-TERM STRATEGIC INITIATIVES 2017-2023

In addition to these current initiatives, the Center, through its Center-wide strategic planning, has committed to the following new strategic efforts.

- *Develop multi-investigator initiatives responsive to the new SPORE guidelines for translational excellence awards in disease-focused efforts* (GI, brain, lung, prostate, breast and ovarian cancers, and AML) *and pathways* (metastasis, metabolomics, immunology, drug resistance) (Programs involved include: GICG, MO, CI, GU, DT, HICB, CPC).

- *Conduct genomics and pan-omics (systems biology analytics) that identifies cancer causes and progression.* We will build and contribute to an expanded human tumor atlas that includes catchment area population samples (normal, premalignant and tumor) for genomics, other omics, and samples for early detection screening (CPC, MO, GICG, GU, DT, HICB).

- *Support drug discovery and development for clinical utility.* We will coordinate preclinical therapeutic investigation focused on pathways and targets of drug, radiation and immune checkpoint resistance, nanotherapeutics, and developing agents to overcome this resistance. We are also identifying small molecule therapeutics that will lead to clinical trials based on our expanding pathway-targeted pipeline of lead compounds. This will require expanding our PDX and organoid human tumor models, use of bioinformatics and database systems to drive and support discoveries in disease etiology; prognosis, drug resistance and treatment response; monitoring drug activity using quantitative imaging modalities, and population based screening and prevention research across populations and cancer types (MO, GU, DT, GICG, HICB, CI, CPC).

- *Expand the spectrum of research areas based on emerging Center strengths.* Efforts are focusing on immune therapeutics in cell-based therapy (HSC, T cell, DC, NK cells) and cytokine-mediated immunomodulation (*eg*, TGFβ, CDK5, IL-15) and viral like particles (GU, CI, HICB, DT); building an AYA research program that includes a focus on immunotherapy as well as other areas of research (DT, CI, HICB, GICG); and enhancing basic science discoveries regarding mechanisms of tumor initiation, progression, and therapeutic response (GICG, MO, GU, HICB, DT).

- *Link basic and disease-based cancer research to key issues in our catchment area by including underserved populations and disparities research in most initiatives.* We will focus both on mechanisms and treatment of cancers prevalent within our catchment area as well as screening and exposures research (GICG, MO, CI, GU, DT, HICB, CPC).

- *Pursue population and intervention studies.* We will lead practice-changing studies in diagnostics, therapeutics, prevention and health policy to improve the lives of the catchment area population (GICG, CI, GU, DT, HICB, CPC).

- *Promote clinical research emerging from our discoveries in screening, therapeutics, and genomics.* We will initiate novel therapeutic and marker-based investigator-initiated and other early phase trials that extend access throughout the regional clinical networks with increased overall accrual (GU, HICB, DT, CI, GICG, CPC).

- *Create an environment for integrated cancer research training and program leadership.* We are developing programs for transdisciplinary mentoring and training that spans programs and career levels and is inclusive of underrepresented groups (GICG, MO, CI, GU, DT, HICB, CPC).

Implementation strategy for the long-term initiatives

The center will use its planning and evaluation processes to direct developmental funds and institutionally committed resources to all aspects of the long-term initiatives. Likewise, current initiatives have a clear

developmental path and will report progress to Program Leaders and the Executive Committee. All major investments and commitments will be vetted by the EC and the Case Cancer Cabinet to ensure scientific and programmatic alignment of the initiatives and to maximize return on investment. Realization of these efforts will evolve through the membership, Program Leaders, specific responses to pilot RFAs by the Center members, and through proactive engagement by the EC. Each initiative will be monitored by setting metrics and monitoring of expectations and endpoints. Program leaders will be responsible for close scrutiny through metric reporting of major initiatives and presentations to the EC. Institutional support for cancer research, developmental funds through the CCSG, philanthropic support for cancer research and the direct support to the Center from the institutions will focus on these initiatives. In essence, the Center's EC approval of funding is required before any investments are made in these priorities.

Examples of implementation approaches are as follows:

1 Multi-investigator initiatives

These will be promoted by the program leaders and will most often be interprogrammatic. Awards made in response to RFAs will occur only after review and presentation to the EC with an expectation that multi-investigator grant submissions are made within 2 years of pilot award funding. Sustained funding required review of regular progress reports by the EC. Each area identified has a leader and working groups are ongoing.

2 Contribute samples to a human tumor atlas that includes catchment area population samples for genomics, and other omics

Our Center has contributed extensively to the NCI TCGA and has cohort samples (normal, premalignant and tumor) available for use across our research programs in brain tumors, colon cancer, Barrett's Esophagus, familial cancers, AML/MDS, TNBC, kidney cancer, lung, ovarian, endometrial, and prostate cancer. Ongoing efforts include expansion of biorepositories, links to samples analyzed by digital imaging, links to medical information through the CLEARPATH data warehouse initiative, and open access to data for investigators through the Center's LABMATRIX and Oncore databases for shared resources using biospecimens. We will conduct research in our disease and pathway targeted areas and utilize systems biology integration analytics.

3 Preclinical therapeutic investigation focused on pathways and targets of drug, radiation and immune checkpoint resistance, nanotherapeutics, and developing agents to overcome resistance using relevant preclinical models

The Center has considerable strength in drug discovery and development and further investments are supported through coordinated efforts of multiple programs and the Committee for Cancer Drug Development and Resistance (CDDR). Further, the institutional track record favoring commercialization strategies, support for toxicology and pre-IND studies, and an active IIT program reinforces drug development from concept to early phase clinical trials. These will continue through ongoing RFAs to advance drug pathway progression. To ensure Center member access to accurate preclinical models, we have expanded tissue sample processing and consenting efforts and increased genomic analysis as part of routine clinical evaluation. All PDX and organoids are catalogued by the Athymic and Preclinical Model SR and data is shared by investigators to facilitate discovery and link the use of PDX for pathway discovery, drug sensitivity, and preclinical drug combination efficacy.

4 Immune therapeutics

The center recently awarded $150,000 for three pilot projects for immune therapeutics supported by a philanthropic gift. We recently recruited Lewis Shi from Jim Allison's group at MD Anderson and we have established a working group in immune cancer biology and therapeutics. We will continue to issue RFAs and expect to add additional recruits in therapeutics and lab-based investigation to the Molecular Oncology, GU Malignancies, Developmental Therapeutics and Hematopoietic and Immune Cancer Biology Programs.

5 Underserved populations, disparities research, prevention, and health policy

The center will continue to annually award RFAs specifically in disparities research, noting the importance of including underserved populations in research supported through the pilot award program of the Center. Targeted tobacco cessation research focused on high risk groups from underserved populations and cancer patients will expand through studies of intervention strategies to optimize efficacy. Implementation science

initiatives in tobacco cessation, health care access and involvement in the ongoing NCI Cancer Moonshot initiative and the Biden Cancer Initiative complement these efforts. Progress will be monitored through the Office of Disparities Cancer Research.

6 Innovative diagnostics and therapeutics

Current initiatives will be expanded to study detection rates, prognostic impact, and decision making for colon cancer screening using the DNA stool test, use of the Barrett's Esophagus detection balloon to assess genetic markers indicative of conversion towards esophageal carcinoma, genomic testing for prostate and kidney cancer using gene sets developed here in collaboration with Genomic Health, and MRF for prostate cancer detection and staging. Novel detection science is evaluating circulating miRNA for ovarian cancer, a novel PMSA detection method for prostate cancer and digital imaging analysis for breast cancer and recurrence of brain tumors.

7 Novel therapeutic investigator-initiated early phase trials

Both hospitals continue to expand investigator initiated clinical trials and are utilizing compounds emanating from Center member efforts in drug discovery and pathway target identification. These are supported through conventional R, S and U grants, philanthropy, sponsored research agreements and pharmaceutical partnerships. We will expand our participation in CTEP sponsored early phase clinical trials including career development efforts and initiating nd supporting multi-site early phase clinical trials. We will also link new compounds to our pathways research efforts and to genomic and protein expression based biomarker selection of study participants. We wll contribute by developing and testing novel biomarkers that are pathway delimited.

8 Mentor and train across disciplines

Our many educational programs, institutional training grants, and trainee research lab experiences provide the workforce backbone for our research programs. We will continue a robust effort to expand grant supported training in nanopharmacology, functional genomics, and translational oncology (K-12). New training in hematologic malignancies, stem cell transplant and cell therapy and cancer pharmacology are planned. The Case CCC sponsored K-12 Clinical Translational Oncology Research Program provides rigorous training for junior clinical investigators, most of whom become members of the Center's clinical research leadership. All trainees conducting cancer research have appointments in the cancer center as Training Associate members. Training and mentoring occurs at all levels of career development, including mentoring programs for junior faculty and leadership training for Program Leaders and Associate Directors. Career enhancement in cancer research is coordinated through the Center's training office.

Resource allocation for these and evolving initiatives

Proposed use of development funds for the next grant cycle

The Case CCC will use awarded funds to support recruitments, new SR initiatives, and pilot grant awards to stimulate strategic projects and encourage multi-investigator and transdisciplinary research, provide protected time for clinical investigators, and sponsor early phase investigator-initiated clinical trials. The balance of support required for these initiatives will be coordinated with the consortium institutions through their itemized commitments to cancer research as outlined in the MOU and institutional leader letters to the NCI. These will be managed by the director and deputy directors and presented for discussion and approval by the EC.

Recruitments The institutions have committed to recruiting 24 cancer investigators with competitive packages to their departments over the next grant period. Based on the past grant cycle when recruitments of cancer investigators extended well beyond the formal MOU commitments to include an additional 11 cancer investigators at Case Western Reserve University (CWRU) and University Hospitals and 8 to Cleveland Clinic (CC) Lerner Research Institute (LRI), the Center expects the institutions will likely recruit an additional 15 scientists with a cancer research interest and focus. Thus, we anticipate that we will recruit a total of 39 new cancer-oriented recruits. It will be invaluable to have developmental funds from the Case CCC to augment those recruitments. Such support would facilitate recruitment of key program-relevant individuals that are aligned with the Center's Strategic Plan 2017-2023. Requests for this support will be made by the Program Leaders and department chairs and approved by the EC; they will be limited to **$100,000** over 2 years with 2

recruits per year. As appropriate, the Center will use up to $150,000/year in funds available from the Center's institutional commitment as a match to this support and in this way enhance up to 25 of the projected 39 recruits over the grant period.

New Shared Resource Initiatives The Center has made strategic commitments and investments in Genomics, Drug Discovery, and Bioinformatics in the last grant cycle, mostly through institutional funds and strategically through CCSG developmental funds. In the next grant cycle, the Center anticipates committing up to **$100,000** per year for initiation of new SRs. Specific needs will be defined over the next 2-3 years, and will be aligned with the strategic plan. Possible areas will be development of an Immunomonitoring SR for advances in immunotherapy in both preclinical and clinical studies, single cell analysis in tumors that extend beyond sequencing, genetic screening (using CRSPR, siRNA, shRNA etc), digital pathology or MRF imaging - areas of strength within the CI Program that could become SRs, or support for developing the CLEARPATH EMR data warehouse that was generated by the Institute for Computational Biology, into an SR.

Pilot Grant Awards The use of developmental funds for Program-oriented pilot awards that initiate strategic projects and encourage multi-investigator and transdisciplinary research has been very successful. Enabling new ideas to flourish and to build collaborations is the mainstay of a successful Center. The Case CCC proposes to apply $**300,000 per year,** with $190,000 per year in matching institutional funds committed to the Case CCC to award approximately $70,000 annually to each of the 7 Research Programs (1 award per Program). This will support high-impact initiatives that enhance or extend each program. The Center also continues to invest in new strategic initiatives in women's cancers, brain tumors, renal and bladder cancers, adolescent and young adult (AYA) cancer research, drug discovery, and genomics-based research. These initiatives will be augmented by the Center with philanthropic funds.

Protected Time for Clinical Investigators and Support of Early-Phase Investigator-Initiated Clinical Trials This new CCSG support initiative correctly identifies the difficulty in gaining protected time for most clinical investigators for conducting investigator-initiated clinical trials (IITs). The Center's leadership also appreciates that although the Center's track record is quite good, national surveys indicate that many IIT are never completed or published. In contrast, the Case CCC's focus on translational efforts that have successfully led concepts and new drugs from the Center's labs to clinical trials. Thus, we propose to use these funds preferentially for trials that emerge from the Center's pipeline from lab to clinical trial. The Case CCC will use developmental funds to support clinical investigators conducting early-phase trials and for the clinical trials themselves. By linking support to these Program-initiated priority trials, it is far more likely that they will be coordinated through a scientific and clinical team, and will be completed. Examples from the current grant cycle include: studies of DNMT1 depleting agents, decitabine and 5-azacytidine, combined with the Center-discovered CDA-inhibitor (tetrahydrouridine) in AML/MDS that are now being applied to solid tumors (Hematopoietic and Immune Cancer Biology [HICB] and Developmental Therapeutics [DT] Programs); moving the Center-discovered base excision repair inhibitor (methoxyamine, TRC102) that augments therapeutic response to DNA damage through phase I to multiple phase II combination clinical trials (DT); and the initiation of a trial adding CB-839, a potent small-molecule glutaminase inhibitor from Calithera that blocks the first step of glutamine metabolism (based on CWRU IP), with 5FU in colon cancers that harbor a PIK3CA mutation. This last trial is now part of both the GI SPORE and an SU2C award (GI Cancer Genetics [GICG], DT Programs). In addition, CTEP- aligned early phase drug development (led by Drs. **Dowlati and Shepard [DT]**) will be supported through cancer center funds for translational correlates and for protected time. The Center requests support for 20% effort for up to three clinical investigators involved in such trials with a limit of 2 years of support for each (**$105,000** per year). The Center also requests **$60,000** per year to support the clinical trial costs of these IITs such as data management, research nurses, and correlative studies. Investigator applications and all trial requests will undergo review by the EC and require research program prioritization to encourage timely completion. Case CCC resources will provide a 1.5:1 match for the clinical trials support while the institutions will match the investigator support from operations and philanthropic sources.

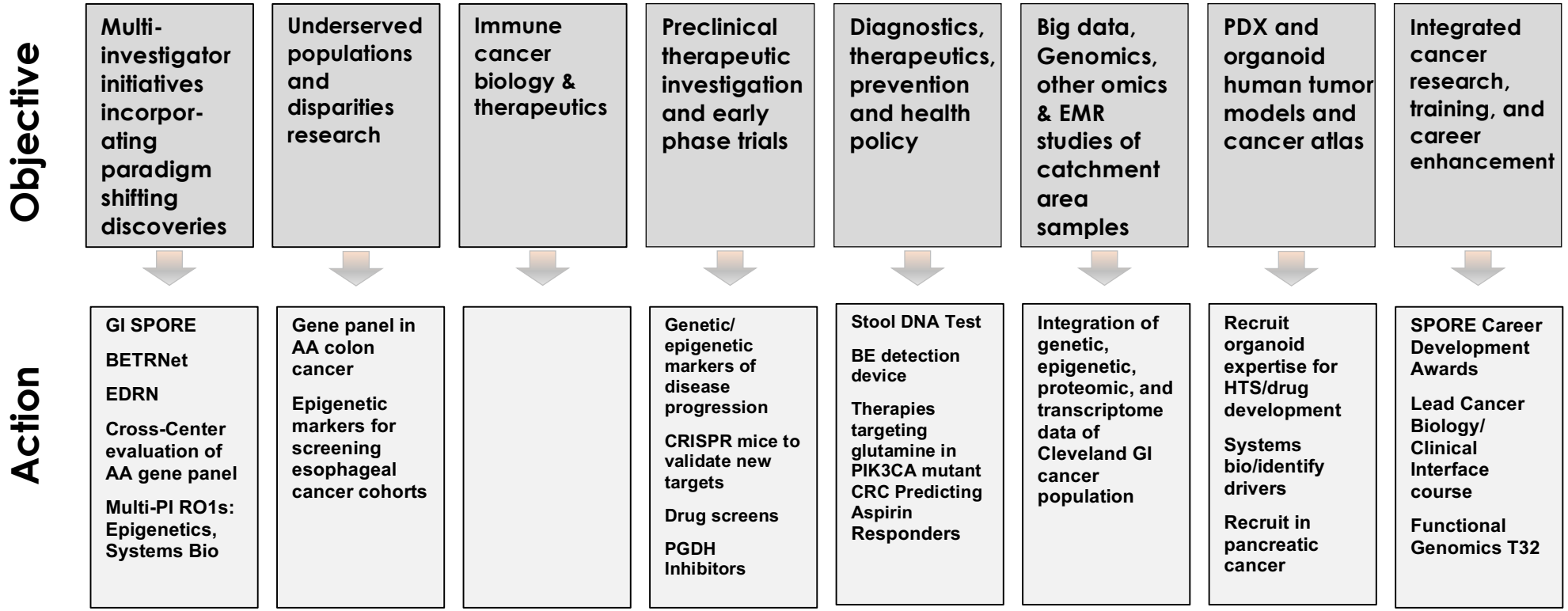
Case Comprehensive Cancer Center

Program Specific Strategic Plan

GI Cancer Genetics

Case Comprehensive Cancer Center Strategic Plan 2017-2023

Mission: Apply scientific discoveries in human cancers to improve lives through cancer prevention, detection, treatment, cure, and survivorship



GICG Strategic Plan

Aim 1 Discover and clinically translate genetic alterations in GI cancers:

1.1 Implement Systems Biology Approaches to Identifying Driver Pathways and Therapeutic Targets for GI Cancers including Esophageal Cancer and Signet Ring Colon Cancers

The incidence of esophageal cancer in the US has risen 7-fold over in recent years and has only a 15% 5-year survival. Signet ring colon cancer is a pathologically distinct colon cancer subtype with particularly worse prognosis. To elucidate the biological basis of both these diseases, the GICG CRC and Esophageal Cancer Working Groups will explore systems biology approaches to mining genetic, epigenetic, and transcriptomic datasets to identify driver pathways and therapeutic targets in these 2 cancers. This will be pursued through intra-programmatic interactions of wet lab GICG members with experts in systems biology (eg, **Varadan, Chance and Koyuturk**).

1.2 Implement Phase II Clinical Trials of Novel Targeted Therapeutics for Genetic Subsets of Colon Cancers As described above, the investigator-initiated phase I clinical trial of the combination of CB-839 with capacitabine is open. An immediate future goal of the GICG Program is to perform a phase II clinical trial to assess the efficacy of this drug combination in PIK3CA-mutant CRC patients. This will be pursued via enhanced partnering with **Drs. Meropol (DT, CPC), Eads (DT)** and **Khorana (DT)**. To the Center's knowledge, this trial will be first clinical assessment of drugs targeting glutamine metabolism in GI cancers.

1.3 Identify Gene Environment Interactions Contributing to Racial Disparities in GI Cancers GICG investigators made the seminal discovery of mutations in 15 genes that typify colon cancers arising in African Americans and that additionally are associated with adverse outcomes. A key future direction will be testing the hypothesis that this 15-gene panel reflects gene-environment interactions in the genesis of African American CRC. This hypothesis will be interrogated by inter-cancer center collaboration with University of North Carolina, Vanderbilt, UT Southwestern, and University of Chicago to investigate African American CRC epidemiology cohorts at these centers, and by forging new collaborations with the Institute of Computational Biology led by Jonathan Haines at CWRU.

Aim 2 Discover and clinically translate epigenetic changes in GI cancers,

2.1 Bring Epigenetic Markers for Early Detection of Esophageal Neoplasia to Clinical Trial in Screening Cohorts In addition to methylated vimentin DNA, GICG members discovered several other epigenetic makers that when combined with vimentin increase sensitivity of detection of esophageal neoplasia, while preserving specificity. An exciting future direction will be bringing this panel of epigenetic markers to clinical trials for early detection of esophageal neoplasia, and extending the current trial of a convenience cohort to testing this approach in a true screening cohorts.

2.2 Determine the Role of Epigenetic Alterations in Progression of GI Cancers Initial results from whole genome methylome analysis supports a key role of epigenetic alterations in driving progression of Barrett's esophagus to dysplasia and cancer. Pursuing and validating this novel progression pathway, and translating it to biomarkers for disease monitoring and potential therapeutic targets, is an exciting new direction of GICG emphasis. Similarly, enhancer profiling has implicated epigenetic chromatin modifications as playing a key role in colon cancer. Using the bromodomain inhibitor JQ1 as a functional probe, GICG investigators have commenced work on identifying superenhancers that the Program Leaders hypothesize play a key role in driving progression of colon neoplasias.

Aim 3 . Development of novel methods and models to facilitate GI cancers research

3.1 Develop Novel *In Vivo* Models of GI Cancers Using Cutting Edge Genome Editing Technologies The advent of CRISPR/Cas 9 genome-editing technology enables quick and easy generate of gene knockout and knockin mice. Taking advantage of this technology revolution, GICG members will develop novel *in vivo* GI cancer models to interrogate functions of oncogenes and tumor suppressors and to exploit them as preclinical models for cancer drug development.

Programmatic Plans:

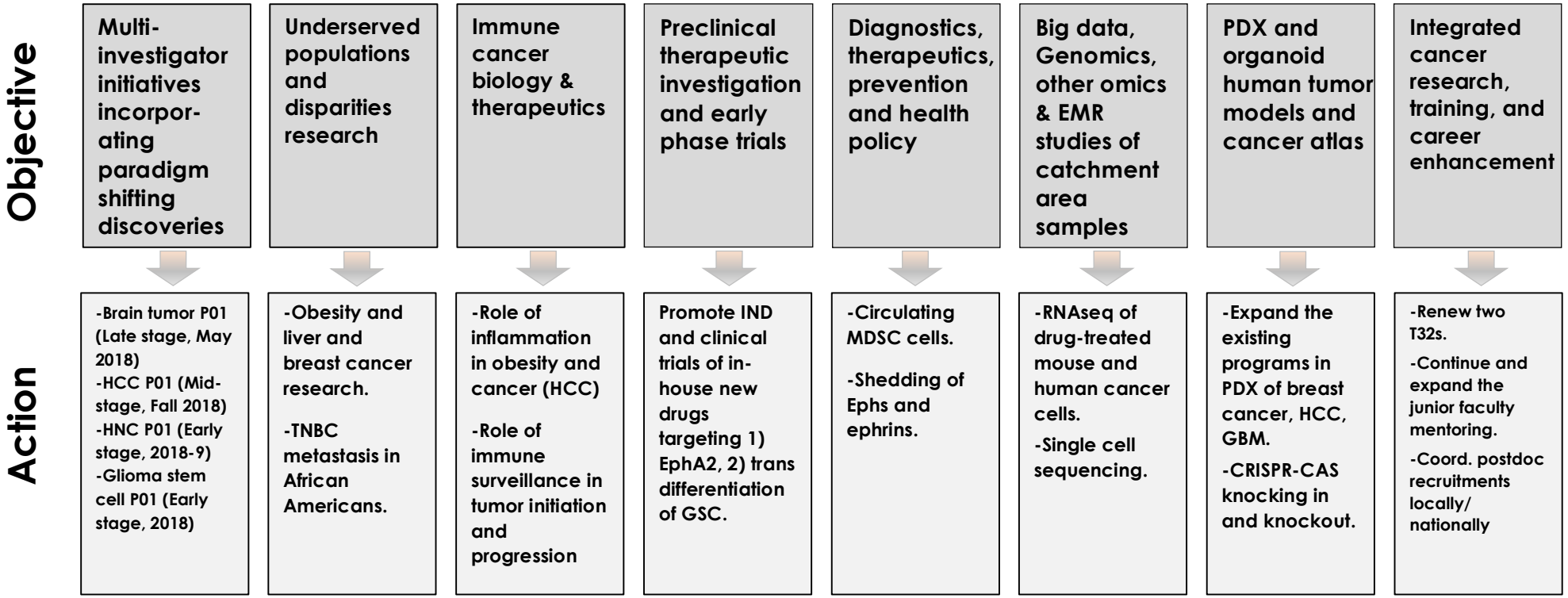
Recruit New GICG Faculty with Interest and Expertise in Organoid-Based Models of GI Cancers Colon and intestinal organoids have emerged as exciting models for interrogating cancer biology and for high throughput assessment of new therapeutics. As a programmatic development, the GICG Program plans to recruit faculty with interest and expertise in this new and enabling technology.

Recruit New GICG Faculty with Interest and Expertise in Pancreatic Cancer The Program's new name of GI Cancer Genetics reflects our evolution toward and strong focus on GI malignancies. To broaden the current focus on colorectal and esophageal cancers, the Program will recruit new basic science and translational faculty with interest and expertise in pancreatic cancer. The new recruit(s) will partner with clinical Cancer Center faculty members (eg, **Dr. Eads [DT]**) with strong clinical trials interest and expertise in pancreatic cancer.

Molecular Oncology

Case Comprehensive Cancer Center Strategic Plan 2017-2023

Mission: Apply scientific discoveries in human cancers to improve lives through cancer prevention, detection, treatment, cure, and survivorship



MO Program Strategic Plan

As the basic science program of the Cancer Center, MO provides central experimental and intellectual catalysis for the Case CCC. During the next funding period, MO will continue to foster innovative research into the basic mechanisms of cancer initiation, progression, and metastasis. To accomplish this goal, the Program Leaders will identify and promote highly collaborative activities both within the program and through coordination with other programs within the Case CCC. Specific examples of on-going and new initiatives are the following:

Aim 1 Discover mechanisms of cancer stem cell regulation for cancer prevention and treatment. MO members have exceptional depth of expertise in both basic and translational research on glioma stem cells (GSCs). Approaches and questions being addresses by the GSC investigators will be expanded to include additional members of MO who have expertise in breast cancer (**Keri**, **Jackson,** and **Schiemann**), HCC (**Brown**), and head and neck cancer (**Jin, Pan**). In the new funding cycle, Program Leaders will leverage the exquisite expertise in GSCs and expand it to breast cancer (**Schiemann**), HCC (**Brown**) and HNC (**Jin**, **Pan,** a new recruit to MO) serving as leaders in these initiatives. An example of such activities includes identification of mechanisms controlling dormancy of triple negative breast cancer, and CSC in drug resistance for HNC.

The MO Program will leverage the considerable strengths in cancer cell signaling to reveal pathway intersections to unveil compensatory activation of alternative growth promoting and stem cell expansion pathways following inhibition of key kinases. This includes assessments of the role of focal adhesion in mTOR feedback signaling and the functions of the FACT (Facilitates Chromatin Transcription) complex in mediating resistance to EGFR inhibitors.

Multi-PI Applications MO is the home of multiple brain tumor investigators. Program Leader **Wang** has actively engaged in planning two multi-PI projects involving Cancer Center-wide participation as part of the Brain tumor initiative of the Cancer Center. With the recruitment of **Pan**, there has already been active discussion of HNC P01 initiative on HNSCC stem cells and therapeutic resistance.

Aim 2 Identify how defective DNA damage repair promotes genomic instability and alters therapeutic response. DNA damage and repair has been historically an area of significant strength in the Cancer Center's basic science program. A focus for MO in the new funding cycle in therapeutic resistance will be uncovering synthetic lethal combinations in which DNA repair defects can be targeted for personalized medicine. Among the studies being developed are: 1) targeting autophagy and DNA repair abnormalities of cancer; 2) expand upon novel links between regulators of apoptosis and DNA repair discovered by Program members to target pathway cross-talk in developing new cancer treatments, 3) targeting mechanisms that alters HR and NHEJ pathway choices to promote sensitivities to therapy with radiation or PARP inhibitors. The Program will also utilize a viral insertion-based screening system that was developed within the Case CCC to uncover novel mechanisms of resistance to inhibitors that target PARP, DNMT, or EGFR. In collaboration with DT, MO is building an interdisciplinary team effort to discover innovative approaches that will be more effective and prevent resistance to current therapeutic agents.

Aim 3 Reveal key host-tumor interactions that promote tumor progression and therapeutic resistance The MO Program is building significant expertise in the tumorigenic impact of metabolic disruptions such as obesity and diabetes. For example, **Dr. Brown,** who was recruited in 2013, focuses on the interrelationship between lipid metabolism and development of chronic diseases including cancer. The MO Program Leaders helped **Dr. Brown** transit part of his research portfolio into cancer. His collaborative project with **Dr. Lathia** on lipid metabolism in glioma was selected for MO pilot funding. He also has a project on high fat diet-induced HCC and another collaborative HCC project with **Dr. Wang**. The emerging strong interests in HCC has led to the establishment of a Liver Cancer Center of Excellence (LTCOE) in early 2017 with $300,000/year initial institutional support that is renewable for two additional years. Obesity and liver cancer (**Brown** and **Wang**) represent two potential P01 projects as part of the P01 initiative originating from the LTCOE.

Last but not the least, **Drs. Fox** and **Brown** and their team have found a major downstream effector molecule EPRS for mTORC1-S6K1 that influences adiposity in mice (Arif, Nature 2017*)*. The team is now looking at the roles of mTORC1-S6K1-EPRS signaling pathway in breast cancer. Together with the obesity and HCC team

above as well as the Cancer Population Program, the Program Leaders foresee obesity and cancer as a focal area of growth in the next funding cycle.

Cultivate and/or Identify Emerging New Multi-PI Grant Ideas and Promote their Maturation Among the multi-PI initiatives on the horizon are 1) HCC P01 led by Dr. Brown that has received $300,000 institutional support and is at advanced stage of planning, 2) a P01 initiative on gender differences in GBM led by Lathia and Barnholtz-Sloan, and 3) breast cancer multi-PI R01s led by Keri and Schiemann and ultimately breast cancer P01. Toward this end, Program Leaders will continue to make effective use of the pilot grant mechanisms, among other approaches.

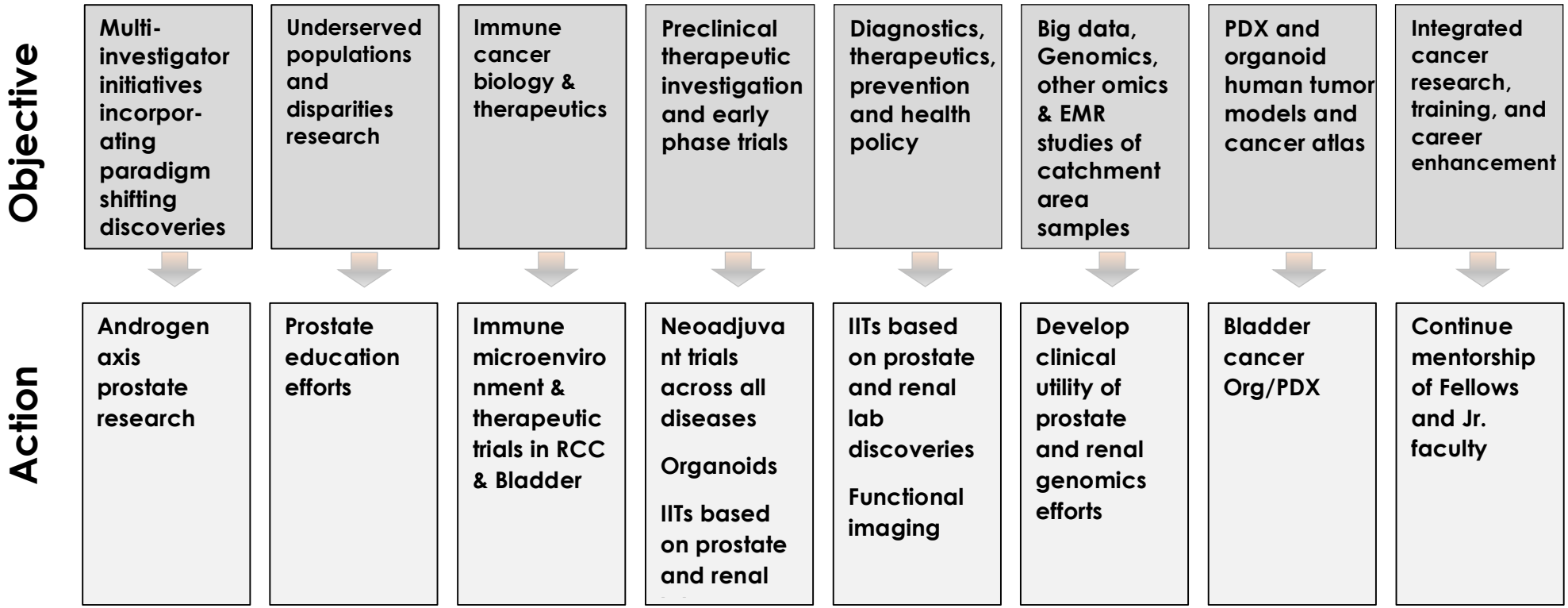
Programmatic Plans:

By executing the three Aims, the MO Program will continue promoting the exceptional strengths in cutting edge basic cancer research. Complementing these strengths, we will work with the associate directors and leaders of other programs, notably DT Program, for handoffs of translational research projects or collaborations ready for the preclinical and early clinical evaluations. MO Program will continue to serve as an incubator for developing research programs, which includes Breast Cancer Program, Brain Tumor Initiative and LTCOE. MO will promote collaborative research interactions at the local, national, and international levels through: a) continued organization of, and participation in, national and regional theme-based conferences or symposia; b) Program-wide mini-retreats that draw the entire MO membership; and c) regularly scheduled groups meetings among members with complementary interests. MO Leaders will also work with CC leadership to recruit exceptional talents to further solidify existing strengths, and to expand into new areas of cutting edge research.

GU Malignancies

Case Comprehensive Cancer Center Strategic Plan 2017-2023

Mission: Apply scientific discoveries in human cancers to improve lives through cancer prevention, detection, treatment, cure, and survivorship



GU Program Strategic Plan
Ongoing and future research efforts of GU Program members continue to build upon our significant accomplishments in the basic science of prostate cancer and exceptional ability to conduct clinical trials in prostate, renal, and bladder cancers.

Aim 1 Delineate the Pharmacogenetic Impact of the *HSD3B1* Variant in Prostate Cancer Therapy
The E3805 CHAARTED study, with major contributions by **Drs. Garcia** and **Cooney**, demonstrated a profound survival benefit for patients with metastatic prostate cancer who were treated upfront with docetaxel chemotherapy along with ADT, *versus* with ADT alone (Sweeney, N Engl J Med, 2015). This finding changed both practice and standard of care. The GU Program will now leverage this study to a) validate the impact of the *HSD3B1* variant in ADT responses using samples from this prospective clinical trial (ADT alone arm) and b) determine if patients who harbor the *HSD3B1* variant and progress more rapidly on ADT alone experience a disproportional benefit from upfront docetaxel treatment. Genotyping of germline DNA from patients in this clinical trial is currently underway (approved by ECOG-ACRIN and CTEP). Leaders anticipate that these studies will guide selection of effective treatments for patients with prostate cancer based on their individual genetic characteristics.

Program members will also determine whether the adverse influence of *HSD3B1* variant inheritance is pharmacologically reversible, in an investigator-initiated, IRB-approved neoadjuvant prostatectomy study (CASE5815; PI: **Garcia**; co-PI: **Sharifi; Klein, Rini, Stephenson, Magi-Galluzzi**). Patients with all 3 germline genotypes who are candidates for radical prostatectomy will be enrolled, treated with 1 month of medical castration (Lupron) plus the potent AR antagonist apalutamide (formerly ARN-509), followed by radical prostatectomy (Figure 5). Two hypotheses will be tested: 1) that inheritance of the *HSD3B1* variant is associated with higher sustained prostate tissue DHT concentrations; and 2) that higher DHT concentrations will be reversed by concomitant treatment with apalutamide. If the data are consistent with these hypotheses, this will justify initiation of a new randomized trial with clinical endpoints to test the ability of more intensive upfront hormonal therapy to reverse the earlier progression that is observed in patients expressing the *HSD3B1* variant.

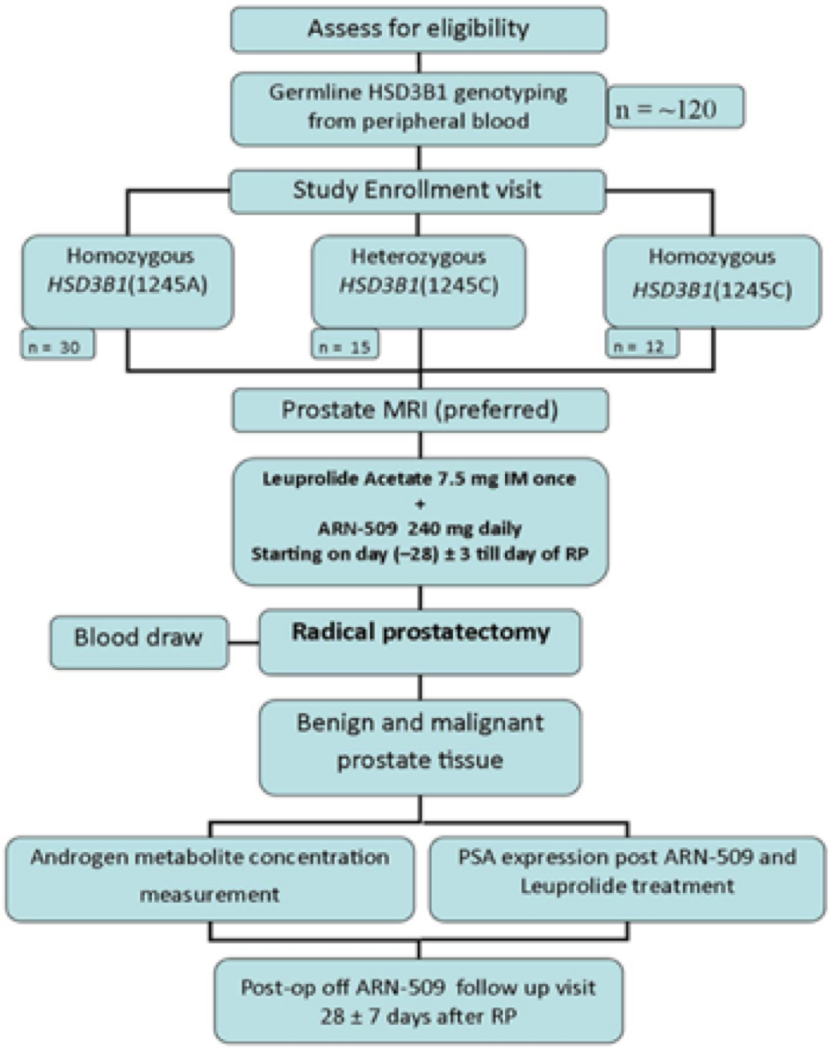


Figure 5: Schema for neoadjuvant clinical trial to test for reversibility of the adverse influence of the HSD3B1(1245C) variant in prostate cancer.

Build Organoid Models for Mechanistic and Therapeutic Studies of Metastatic Prostate Cancer
A major challenge in prostate cancer research is to develop models that closely recapitulate the human

disease. Members of the GU Program have adapted the technology for "organoid" culture of metastatic castration-resistant prostate cancer (CRPC) tissues as part of an internally- and Prostate Cancer Center of Excellence (supported by funds from CC LRI) co-led by **Drs. Sharifi** and **Klein**, in which investigators will use these *in vitro* tools to evaluate mechanisms of tumor progression and drug response, and serve as a translational seedbed for initial testing of new therapies.

Aim 2 Generate and Apply Novel Functional Imaging Approaches for Cancer Detection and Assessment of Therapeutic Responses

Drs. **Zhenghong Lee** (Co-Leader of **CI**) and **Sharifi** are investigating the utility of PET radionuclides that may signal the status of steroid metabolic signaling, thereby reflecting sensitivity or resistance to hormonal therapies for prostate cancer.

Lee Ponsky is collaborating with CI Program members (**Drs. Gulani** and **Griswold [CI]**) to apply a very novel MR fingerprint (MRF) technology to detect prostate cancer. This approach has yielded near-perfect quantitative separation between normal-tissue peripheral zone and prostate cancer, and to extremely promising discrimination (AUC=0.83) between Gleason (3+3=6) low-risk disease and intermediate- or high-risk disease. This analytic tool will be developed as a prospective screen that may ultimately provide a noninvasive alternative to biopsy. Active collaborations are also underway between **Drs. Ponsky, Madabhushi (CI),** and **Gregory MacLennan** to develop radiomics approaches to better stratify risk by using MRF, and also to discriminate prostatitis from prostate cancer, supported by an R01 (R01CA208236, PI: **Gulani [CI]**).

Develop Genetic and Metabolic Biomarkers of Therapeutic Response in GU Cancers

The novel RCC prognostic gene signature panel developed within the GU Program will be evaluated using additional samples from other completed multi-center adjuvant trials (SOURCE and ASSURE), and also incorporated into a prospective investigator-initiated phase III trial of adjuvant checkpoint inhibitors (RAMPART, conducted through the UK-based MRC cooperative group) to assess its predictive potential. Additional biomarker studies will include assessment of immune mediator markers such as PD-L1 in tumor resections linked to clinical risk factors and gene expression. In addition, an investigator-initiated neoadjuvant trial of anti-PD-L1/anti-CTLA4 therapy prior to nephrectomy (CASE12815) with correlative endpoints evaluates gene expression signature-based prediction of response/resistance.

Aim 3 Define the Cancer Immune Microenvironment and its Role in Dictating Therapeutic Outcomes in GU Malignancies with the Goal of Using Precision Therapy for Durable Responses

GU Program members are active participants in emerging plans to develop an immune-monitoring SR with members of HICB. This new SR will be used for the expanding effort in immune-based translational clinical trials. It will include assessment of the immunomodulatory microenvironment in GU cancers – both bladder, kidney and prostate, and the use of additional peptide and cell-based vaccines. Program members' studies have already identified roles of MDSCs, specific cytokines, and PD-1/PD-L1 expression in the tumor bed. These will be used both as targets and as correlative endpoints in future immune checkpoint studies, leading to predictive markers of therapeutic efficacy. The urothelium penetrating nanoparticle, developed by **Dr. Hoimes** may yield results that can be moved into early-phase clinical assessment in locally-advanced bladder cancer.

Programmatic plans:

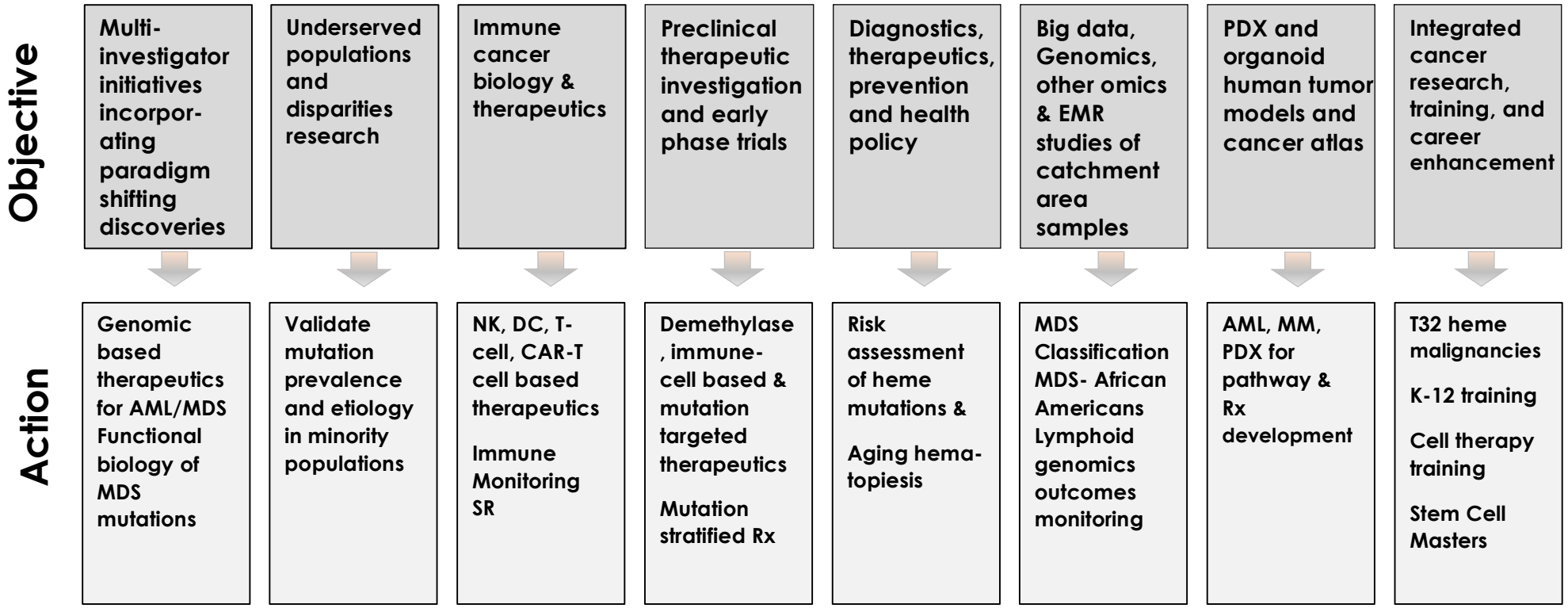
Recruit New Investigators with Expertise in Basic Mechanisms of Renal and Bladder Cancer Initiation, Progression, and Therapy

Program Leaders will capitalize on significant clinical strengths in prostate, renal and bladder cancers to recruit basic scientists to the GU Program to expand the Program's translational efforts and to continue to link basic cancer biology and immune microenvironment studies with therapeutic targets for improve treatment regimens for these diseases. As is evident in this Program, Leaders will focus on the ability to discover new mechanisms of disease progression to translate such findings into clinical trials that test new diagnostic tools and therapies, validating efficacy with pathway analysis using patient samples.

Hematopoietic and Immune Cancer Biology

Case Comprehensive Cancer Center Strategic Plan 2017-2023

Mission: Apply scientific discoveries in human cancers to improve lives through cancer prevention, detection, treatment, cure, and survivorship



HICB Program Strategic Plan

Aims 1,3 Implement a clinically-applicable molecular mutational screen for hematologic malignancy patients to select best treatment options

Use genetic mutational and pathway assessments in MDS and AML to develop new therapeutic approaches including a leukemia drug discovery effort with Drug Development SR, and with DT.

Apply genomic and protein expression assessment of lymphoid malignancies to design targeted therapies by developing a comprehensive biobank and genomic analysis including fusion, translocations and deletions to inform classification and therapeutic decisions and new combinations.

Continue discovery of germ line genetic factors in seemingly sporadic adult lymphoid and myeloid neoplasms.

Aim 2 Pursue basic and clinical research into mechanisms of tumor surveillance, tumor immune privilege, tumor evasion, and new accessory molecules

Apply deep T cell receptor sequencing to monitor anti-tumor responses, immune reconstitution during immune or immunosuppressive therapies including HSCT, and GVHD.

Expand investigations of lymphoid neoplasms using genotypic features to design targeted therapies and clinical trials.

Aim 3 Develop cellular therapies and graft engineering including antigen-primed and selected T-cells, dendritic cell vaccines, and activated NK cells for AML, myeloma, lymphomas and solid tumors

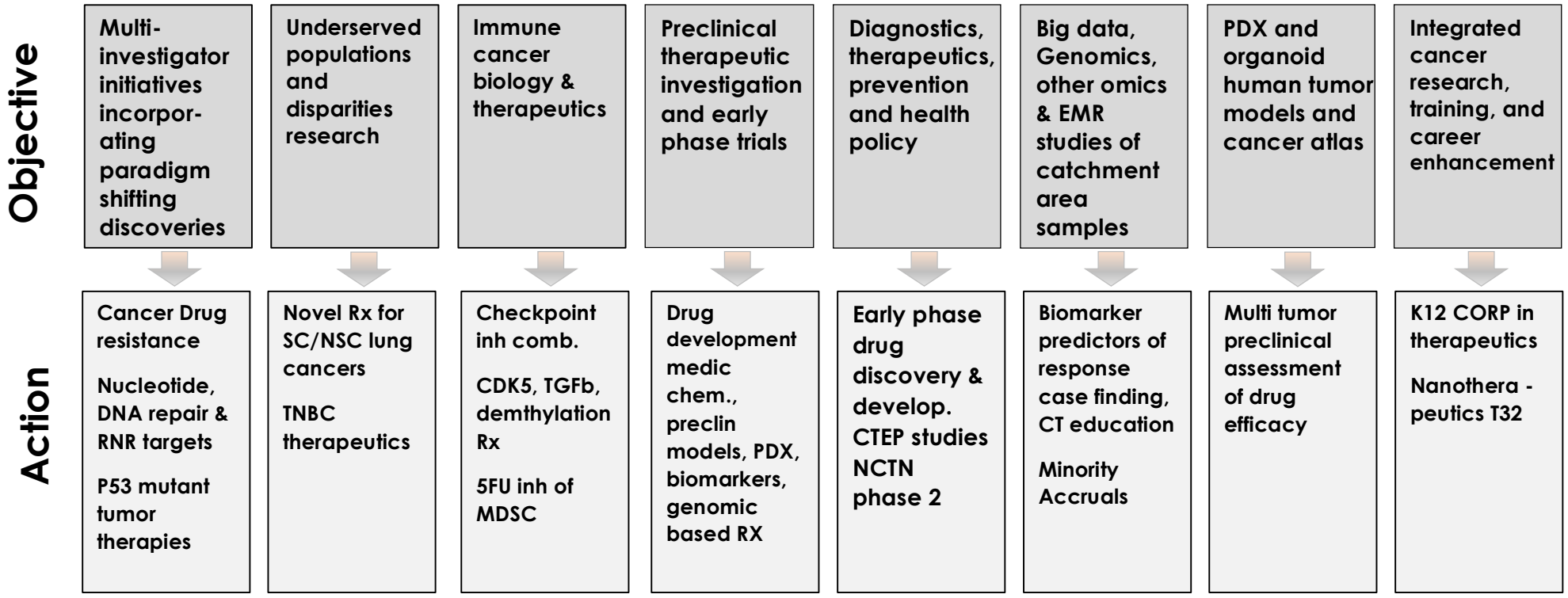
Programmatic plans:

Strengthen training infrastructure, including a T32 submission in hematopoietic malignancies and marrow failure.
Maintain active junior faculty training in hematopoietic and immune based cancer biology and therapeutics through the K12 Scholars program.
Expand cell therapy based efforts through the Stem Cell SR and the Cell Production Facility.
Recruit new clinical/laboratory investigators in lymphoma/myeloma (1 at UH, 1 at LRI).
Create a Center for Aging Hematopoiesis and Elderly Hematopoietic Disorders.

Developmental Therapeutics

Case Comprehensive Cancer Center Strategic Plan 2017-2023

Mission: Apply scientific discoveries in human cancers to improve lives through cancer prevention, detection, treatment, cure, and survivorship



DT Program Strategic Plan

Aim 1: Overcome apoptosis resistance of cancer cells
Complete phase II combination clinical trials of TRC102 (methoxyamine) with temozolomide, pemetrexed, decitabine and floxuridine, to address DNA repair related resistance of cancer cells.

Complete pilot and phase II clinical trials of the optimized non-cytotoxic epigenetic drug oral THU-decitabine in pancreatic and lung and lymphoid cancers.

Extend clinical trials of this agent to other p53-null cancers with poor outcomes, including bladder cancer, GBM and ovarian cancer.

Complete development of the companion predictive functional imaging biomarker TFAC-PET, used to select between oral THU-decitabine and oral THU-5-azacytidine therapy.

Secure IND and initiate early phase clinical trials with first-in-class SWI/SNF-ATPase, GSK3B inhibitors and non-natural nucleoside analogues.

Aim 2: Therapeutics towards signaling targets
Initiate early-phase clinical trials with the first-in-class PP2A activator.

Complete phase II clinical trial of RET inhibition to treat genetically defined subset of SCLC.

Complete phase II clinical trials of FACT inhibition.

Initiate mTOR inhibitor clinical trials in SCLC with RICTOR amplification.

Aim 3: Improve efficacy of cancer immunotherapies
Complete phase II evaluation of oral THU-decitabine in combination with nivolumab in NSCLC.

Complete proof of concept clinical trial evaluations of gemcitabine or 5-FU to reduce MDSC in combination with checkpoint inhibitors and/or vaccines.

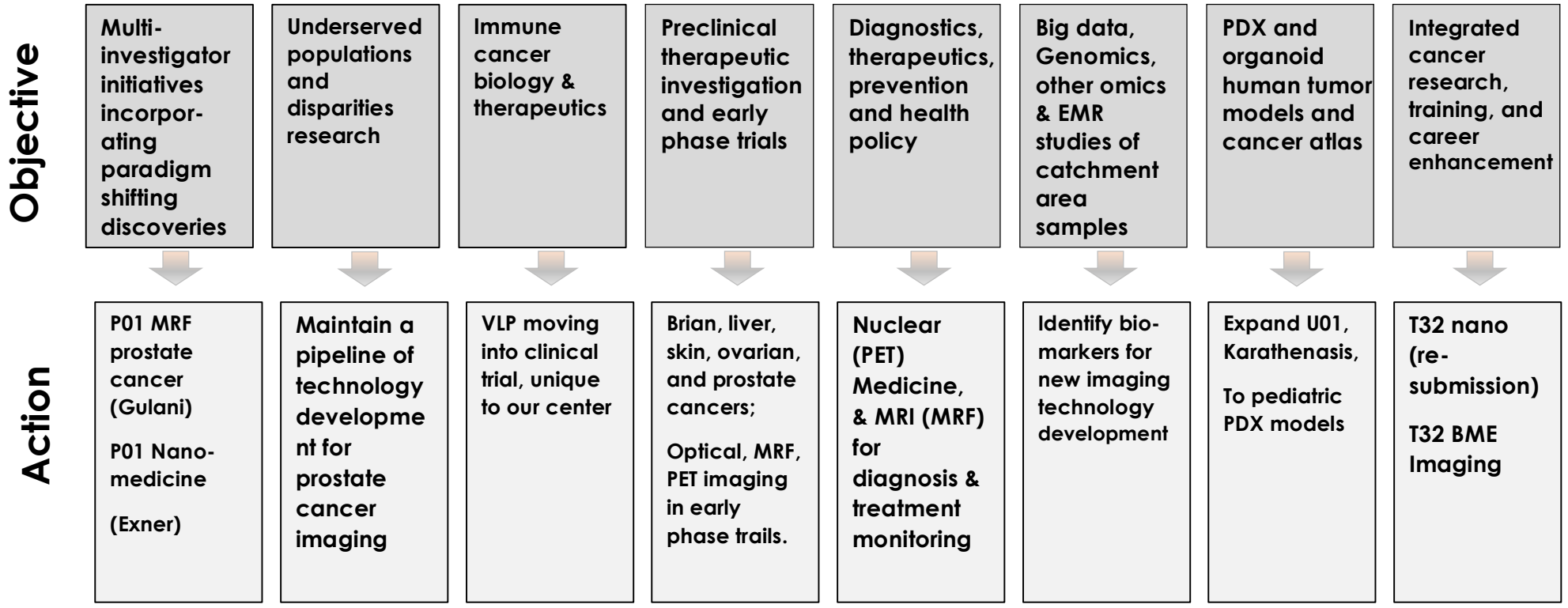
Define signaling modulators appropriate for combination with checkpoint inhibitors.

Programmatic plans:
Recruit additional clinical investigators in disease specific areas, early phase clinical trials and junior faculty for the K12 CORPS training program. Train in nanotherapeutics.
Continue CTEP protocol development for novel early phase clinical trials.

Cancer Imaging

Case Comprehensive Cancer Center Strategic Plan 2017-2023

Mission: Apply scientific discoveries in human cancers to improve lives through cancer prevention, detection, treatment, cure, and survivorship



CI Program Strategic Plan

Program members will pursue clinical validation of the utility of their newly developed technologies in clinical investigations and broaden applications for theranostics and precision image-based detection. Future programmatic goals are to 1) increase the clinical applications of developing technologies and 2) foster a high-degree of interaction within the interest/working groups, including expanding nanotechnology and radionuclide imaging inter-programmatically with DT, GU and HICB.

Aim 1: Utilize Imaging Agents to Study Cancer and Develop Cancer-Targeting Therapeutics The Program will develop new technologies that will enter the developmental pathway (pipeline) for eventual use as validated imaging research or clinical tools for all imaging modalities (ie, MRI, PET, US, Optical). This will include the newly approved clinical radiopharmacy capabilities. The goal is to demonstrate utility of the approach for detection and monitoring therapy in this model and then exploit GMP radiopharmacy to develop a clinical IND, and translate this important discovery with clinical PET imaging. Second is the development of targeted nanobubbles. The synthesis of these agents was developed by CI members at CWRU. They allow utilization of US contrast agents to target cancer cells directly. US contrast agents can also molecularly probe biomarkers for cancer and aid in the work up of prostate cancer (biopsy and staging) as well as other cancers (brain and ovarian cancers are currently under study).

Aim 2: Expand and Validate Quantifiable Imaging Tools to Study Cancer Biology The Program will use precision imaging diagnostics, staging, and cancer treatment response, including a new R01 (R01CA208236) to combine several different imaging and biomarker data sets to allow for non-invasive assessment and staging of prostate cancers. The goal is to identify cancers that are candidates for “watchful waiting” versus those that should immediately undergo surgery and/or other treatment. Rapid MRI acquisition and data reconstruction has been adapted by **Dr. Seiberlich** to characterize liver cancer lesions. She has an NSF career award to utilize MRF for quantitative tissue characterization of brain tumors. Program Leaders are also collaborating with investigators at University of California Berkeley (Steve Connelly) to develop the novel magnetic particle imaging (MPI), which allows PET-like imaging of cancer biomarkers without the burden of radiation exposure.

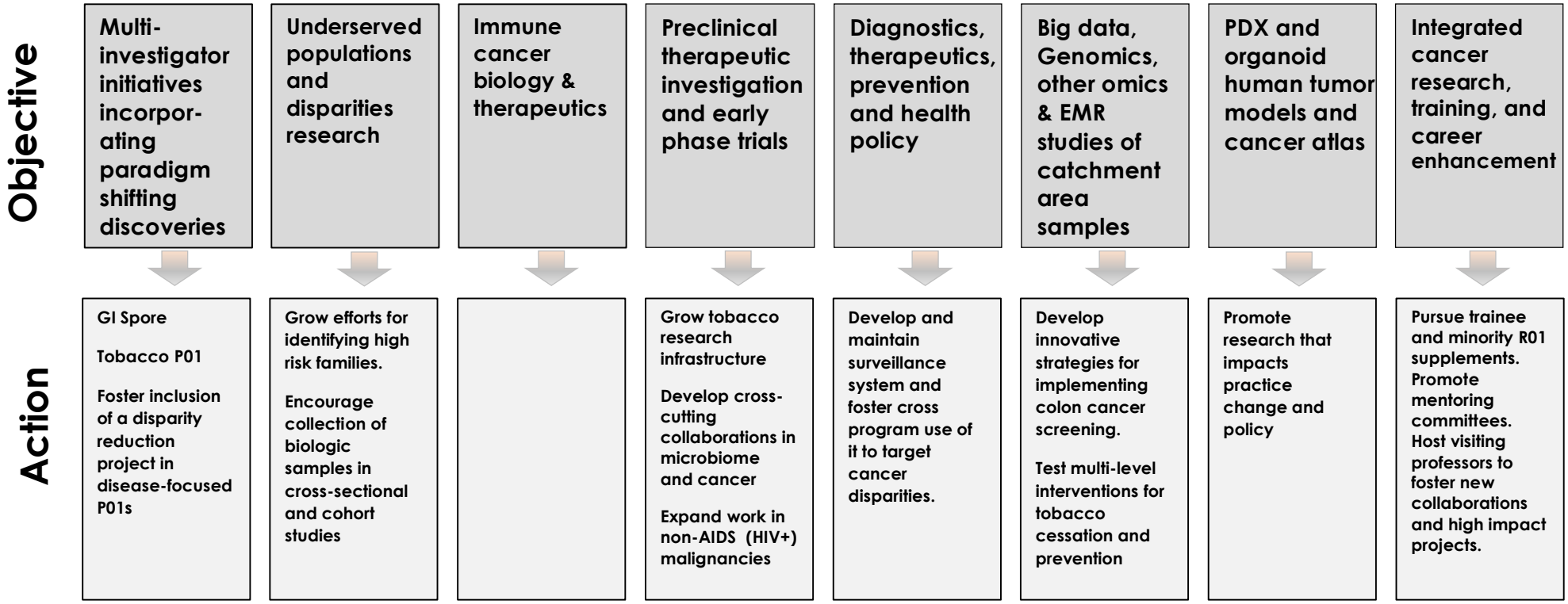
Aim 3: Translation of Novel Imaging Technologies The Program will move validated technologies to clinical trials applications in cooperation with DT, GU, and HICB. Quantitative imaging developments such as MRF for tissue and tumor differentiation are ready for prospective clinical trials. Radiomics methods will likely enter clinical application by 2022. INDs will be submitted for assessing the utility of novel non-FDA approved PET radiotracers for evaluating treatment response and will include determining the utility of MRI/PET. The Dana Farber-developed RECIST program to standardize response assessment is now available and will be used for all clinical trials requiring imaging-generated RECIST evaluation.

Programmatic plans:
The Program will recruit a new physician investigator with interests in brain cancer imaging to work with the strong MRF effort, and a new faculty member focused on ultrasound research. The recruitment in ultrasound (US)/optacoustic imaging will include endogenous fluorophores *or* targeted optical probes for deep tissue imaging. UH will purchase a new research MRI and expand radionuclide clinical investigation production for PET imaging for both hospitals, with colleagues in DT

Cancer Prevention, Control and Population Research

Case Comprehensive Cancer Center Strategic Plan 2017-2023

Mission: Apply scientific discoveries in human cancers to improve lives through cancer prevention, detection, treatment, cure, and survivorship



CPC Program Strategic Plan

Aim 1: Broaden the multidisciplinary engagement in the tobacco working group to accelerate research that has the potential to reduce the harms from tobacco.
The group will build on current grants to fund research in smoking cessation (PCORI, PI: **Flocke**; ODH, PI: Trapl) and measuring nicotine dependence among cigarillo users and interest in collection of biomarkers to characterize nicotine dependence and variations (NCI, PI: Flocke, Co-I: Trapl, Cavallo), as well as Dr. Mazzone's clinical lung screening program and a focus on disparities and culturally tailored tobacco cessation interventions (ACS, PI: Webb Hooper).

Aim 2: Foster cross-cutting disease-specific disparities research
The program will expand efforts such as the Prostate Cancer working group led by **Drs. Simon Kim (GU)** and **Schumacher** with a focus on prostate cancer aggressiveness and screening among African Americans.
Expand Genomic High Risk initiative with epidemiologic and genomic assessment of high risk populations.
Pursue the role of microbiome and mycobiome with model-based mechanistic studies and to promote cancer prevention research modulating the human microbiome.

Aim 3: Promote big data population-based cancer prevention and control research
Program members will capitalize on 2 valuable resources: 1) The CLEveland Area Research Platform for Advancing Translational Healthcare (CLEARPATH) database that is being developed by a Center-wide team led by **Dr. Barnholtz-Sloan.** CLEARPATH is a scalable platform using a Limited Data Set (LDS) of electronic health record (EHR) data linked to a biorepository of blood and tissues; and 2) The Northeast Ohio Cancer Risk Assessment and Surveillance Engine (NEO-CASE) that integrates multiple databases containing spatial information, including data from Ohio's state cancer registry, the state death certificate file, an ongoing survey of Ohio residents with emphasis on insurance status and Medicaid expansion, and a social and economic database for Northeast Ohio neighborhoods. Understand premature aging and cancer risk in HIV positive patients.

Programmatic Plans:

Recruit in cancer epidemiology to expand research in this area through an ongoing recruit in the Department of Population and Quantitative Health Sciences.

Continue to offer RFAs in disparities research.

Work with all research programs to develop disparities focused research initiatives.

Continue to emphasize research that can be used for health policy impact in areas of access, reduction of cancer risk behavior including obesity, smoking cessation, and screening.