

TRANSLATIONAL RESEARCH

By: Mr. Mehul Shah, Executive Vice President and COO

Ms. Nicki Shah, Technical Interface & Research Programs Manager, CTIS

Ms. Sharon Gaheen, NCICB/SAIC Program Manager Contractor, SAIC

The most important objectives when managing research for purposes of improving healthcare are ensuring the integrity of data, improving both the responsiveness of data and the efficiency by which it can be shared with others, and expediting the amount of time it takes to get from concept to delivery.

CTIS recognizes that there is a widening gap between researchers and information evaluated through clinical trials, largely because many of these trials exist independently, in what could be called “isolated silos” throughout the medical community. This results in the duplication of data because researchers are unaware and do not have access to previously compiled data and information. Scientists and doctors are continually performing the same tasks and trials as well as documenting the same information. These processes are clearly not an efficient way of conducting research.

In addition to this inefficiency, a valuable opportunity to evaluate and utilize coexisting health conditions in large groups of patients is lost. This limits the possibilities of sharing intelligence and the benefits of clinical research data convergence, as well as the possible benefits of mining intelligence out of basic and clinical research data.

The objective of translational research is to fundamentally improve human health. In order to do this, scientific discoveries must be translated into practical applications as quickly and efficiently as possible. Such discoveries typically begin at “the bench” with basic research — in which scientists study diseases at a molecular or cellular level — then progress to the clinical level, or the patient’s “bedside.” NIH’s three broad initiatives are going to be responsible for closing the gaps between researchers and scientists, allowing them to work from a common bench with a collective database of information. This will dramatically increase the effectiveness and efficiency throughout and across specific research areas. The ability to share conclusions, data, and information allows for broader, more informed views and more complete evaluations of developing and potential therapies. The key to enabling the NIH Roadmap, is understanding the full lifecycle for therapeutic discovery and development, and mapping existing tools to this life cycle, and performing a gap analysis of the essential tools needed to successfully translate bench-side research, to the bedside, and importantly to the public.

There has been various barriers growing between clinical and basic research, along with the ever increasing complexities involved in conducting clinical research, that is making it more difficult to translate new knowledge from the bench to the clinic. These challenges are unfortunately hampering clinical research at a time when it should be expanding. It is because of this that the NIH has made translational research a priority, forming centers of translational research at its institutes and launching the Clinical and Translational Science Award (CTSA) Consortium in October 2006.

The Critical Path initiative includes many of the same goals as NIH's Roadmap including the recognition for technological advances which can be used to expedite the process by which a new drug or therapy goes from the discovery stage to the delivery stage.

There is a concern that fewer drugs are being submitted to the FDA for approval, and of those that are being submitted, it is taking longer to complete the approval process and get the drug into the hands of patients who need them.

This initiative was launched due to the gradual decrease in the number of innovative medical products being submitted to the FDA for approval, a puzzling fact considering the recent advances that have been made in biomedical sciences. The concern was that the difficulty and unpredictability of medical product development was now beginning to require a serious effort to modernize the scientific tools (e.g. in vitro tests, computer models, qualified biomarkers, and innovative study designs) and also harness the potential of bioinformation to evaluate and predict safety, effectiveness, and manufacturability of potential medical products.

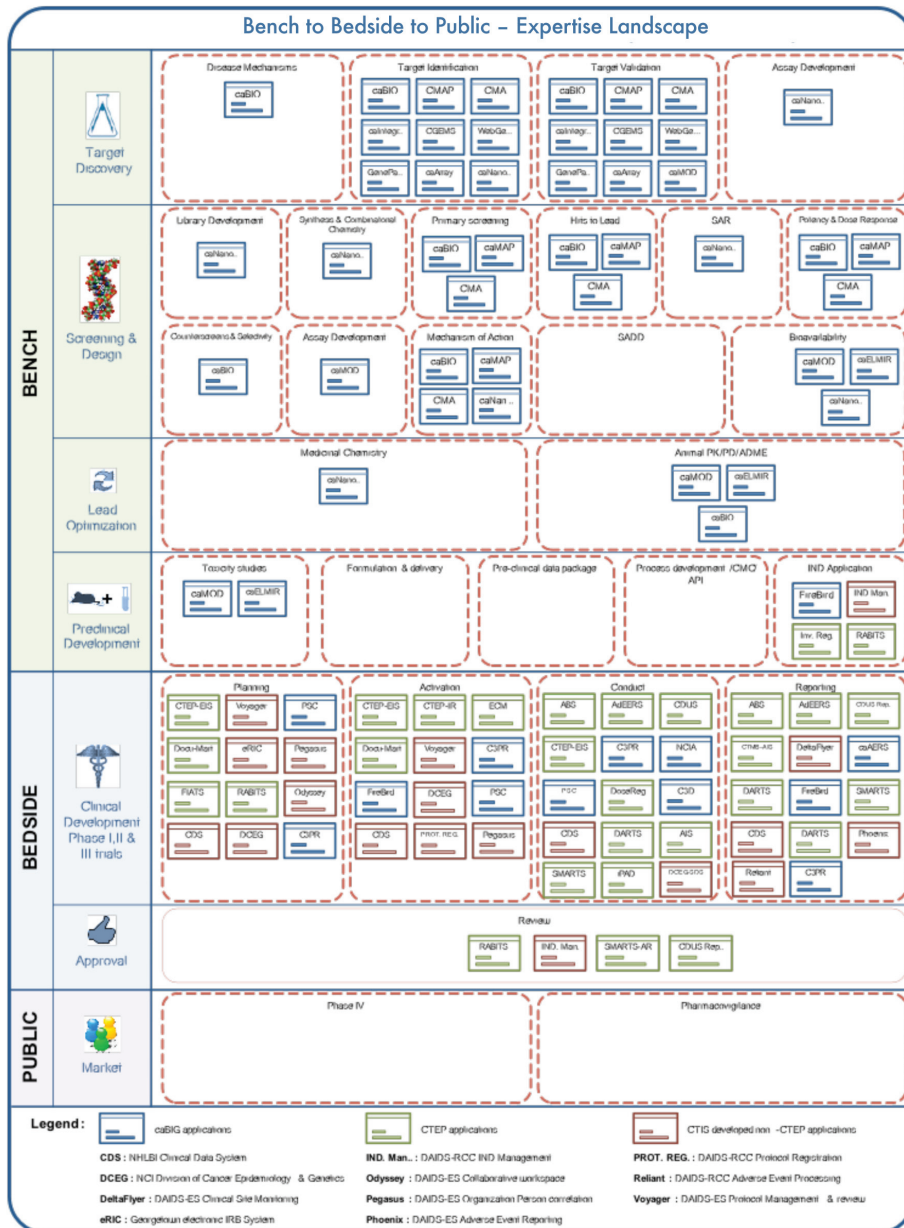
In addition to the decline in innovation, the sciences used to predict and evaluate the performance of therapies already in the evaluation stage also have not advanced at the same pace as basic science. We are continuing to use the same tools from the 19th and 20th centuries to evaluate 21st century technologies. This has become the bottleneck in the critical progress of clinical trials and drug development. It is thus necessary to devise a plan to manage the rate limiting factors and to balance the capacity with the workload at a given stage. There is huge opportunity to improve product development with new science, but it requires a major paradigm shift.

Cutting out unnecessary steps and improving technology to quickly get through the process is more than desired, it is essential. This can be done with the use of many "critical path tools" including biomarker qualifications which would utilize advanced imaging technology to quickly take quantitative markers of effects and influences experienced by the participants during trials. "Biomarkers" are quantitative measures of the effects of such influences as physiology, pathophysiology, pharmacological, physical, etc... (e.g. liver function tests, ECGs, radiographs, psychological tests). Biomarker discovery is fast, but understanding the

clinical relevance of the marker develops very slowly. Using these biomarkers, however, is the key to personalized health care and medicine. Advanced imaging technologies are useful in distinguishing disease subgroups for therapy while also rapidly evaluating responses to treatment on an individual basis.

These biomarkers can and are being used as targets in the development of novel therapeutics that enable personalized medicine so that patients can be treated based on their molecular signature. With these tools that can also predict which product candidates do not hold promise early in the development process, product sponsors can redirect resources to more promising products. We are in a revolutionary time in disease research, a renaissance, where discoveries of these new Critical Path tools will help product sponsors devote those resources to new and better candidates, thus facilitating the availability of more new medical products for patients.

In addition to using biomarkers to create novel therapeutics, using this modern evaluation



tool to assess the potential success of therapies, other modern evaluation tools will be more informative, and we will learn more about products before they are approved. This will give doctors and patients the best information available about how to use the product to maximize its benefit and minimize side effects. In fact, many of the tools being considered would help individualize therapy, by identifying who is likely to respond well to a treatment and who should avoid it.

If these critical path initiatives are incorporated in the development process, the payoff will include having a much more predictable process with higher success rates and lower development costs. There will be more available information about product performances and the continuous improvement of development science and processes will occur. On an individual patient basis, the payoff will include having much more personalized treatment with better effects due to having a more targeted therapy. The ability to stop ineffective therapies faster, avoidance of side effects and injury through prevention, and lastly having better/earlier product availability will all lead to an overall higher quality of healthcare.

The following table provides details of the existing plethora of CTEP and caBIG™ tools and their role in the life cycle:

Process	Program	Tool	Role in Process
Target Discovery and Validation: <ul style="list-style-type: none"> • Identification and validation of the function of a therapeutic target and role in disease • Understanding the mechanisms of disease (e.g. genetic disorders, etc.) • Discovering disease genes including genetic defects or mutations • identifying target types (e.g. receptors, proteins, etc.) and whether a therapy can be engineered to access the target type • Understanding the biological systems as a whole through analysis of biochemical pathways • Use of in vitro and in vivo studies to validate identified targets; Includes use of animal models to determine the function of targets • Validation of a target through clinical efficacy and safety data • Use of compound and chemical libraries to study the chemical effects of a compound on the biological system 	caBIG™	caBIO	<ul style="list-style-type: none"> • API that provides access to information on genes, anomalies, agents, protocols, cellular pathways
	caBIG™	caIntegrator	<ul style="list-style-type: none"> • Framework that provides access to clinical, genomic, and epidemiological findings from diverse cancer studies • Framework is leveraged by NCI translational research studies including Rembrandt brain cancer study, the Cancer Molecular Analysis (CMA) portal, and the ISPY breast cancer trial • Provides access to Kaplan-Meier Survival Plots, gene expression and copy number histograms, and advanced high order analysis plots
	caBIG™	CGEMS	<ul style="list-style-type: none"> • Portal and repository that provides access to cancer genetic markers of susceptibility including SNPs
	caBIG™	caArray	<ul style="list-style-type: none"> • Repository of gene expression (MicroArray) data from cancer studies
	caBIG™	GenePattern	<ul style="list-style-type: none"> • Computational and visualization tools supporting the analysis of genomic data including gene expression analysis, proteomics, and SNP analysis
	caBIG™	WebGenome	<ul style="list-style-type: none"> • Application for creating genomic plots for copy number data, fold change, LOH, and gene expression data
	caBIG™	caMOD	<ul style="list-style-type: none"> • Portal and repository of cancer animal models including knockouts, transgenic models, and xenografts

Process	Program	Tool	Role in Process
Assay Development: <ul style="list-style-type: none"> • Use of in-vitro and cell based assays to test cytotoxicity • Use of in vivo and whole animals to assess biological and pre-clinical efficacy • Use of High-Throughput-Screening (HTS) to assess the activity of compounds on a target to assist in assay development 	caBIG™	caMOD	<ul style="list-style-type: none"> • Portal and repository of cancer animal models including knockouts, transgenic models, and xenografts
	caBIG™	caNanolab	<ul style="list-style-type: none"> • Portal and repository of nanoparticle characterizations and protocols. Provides access to in vitro assays supporting nanoparticle characterizations including cytotoxicity
Screening & Hits to Lead and Lead Optimization: <ul style="list-style-type: none"> • Screening compound libraries to identify leads and hits • Involves characterization of compounds and use of compound libraries • Involves use of CAD tools to identify structure-activity-relationships in support of structure based drug design • Use of in-silico screening to filter through compounds and compound physical and chemical properties • Involves synthesis and compounds • Includes testing for dose-response • Involves profiling an identified hit to reduce target side-effects • Involves refining the structure of a confirmed hit and improving drug characteristics to optimize pharmacological properties • Includes assessment of PK/PD/ADME and toxicity properties in animals • Includes assays to assist in drug formulation and delivery 	caBIG™	caNanolab	<ul style="list-style-type: none"> • Portal and repository of nanoparticle characterizations and protocols. Includes initial design of an in vivo model capturing nanoparticle efficacy, PK/ADME, and toxicity properties
	caBIG™	caMOD	<ul style="list-style-type: none"> • Portal and repository of cancer animal models including knockouts, transgenic models, and xenografts. Includes interface to DTP for retrieval of drug screening data
Development: <ul style="list-style-type: none"> • Involves preparation of the preclinical data package for submission to the FDA • Includes evaluation of the drugs toxic and pharmacological effects that occurred through in vitro and in vivo testing • Involves submission of the IND application 	caBIG™ and CTEP	Firebird	<ul style="list-style-type: none"> • Application that automates the form 1572 registration process and provides a secure global investigator registry
Clinical Trials: <ul style="list-style-type: none"> • Includes Phase 1, Phase 2, and Phase 3 trials • Involves planning, activation, conduct, and reporting throughout all trial phases 	caBIG™	C3PR	<ul style="list-style-type: none"> • Portal and central repository of clinical participants • Assists in managing clinical trial data across multiple cancer clinical trials

Process	Program	Tool	Role in Process
Clinical Trials: Planning	CTEP	SMARTS	
	CTEP	PARTS	
	CTEP	CIBISCIT	
	CTEP	EIS	
	CTEP	Docu-Mart	
	caBIG™	PSC	<ul style="list-style-type: none"> Application that provides the ability to create and edit study calendar templates, generate and view prospective calendars of patient activities, track activities as they occur, and manage patient calendars as they change during a study
Clinical Trials: Activation	CTEP	ECM	
	caBIG™	PSC	<ul style="list-style-type: none"> Application that provides the ability to create and edit study calendar templates, generate and view prospective calendars of patient activities, track activities as they occur, and manage patient calendars as they change during a study
Clinical Trials: Conduct	caBIG™	NCIA	<ul style="list-style-type: none"> Portal and repository of in vivo images; Provides image visualization tools for collaborative evaluation
	caBIG™	C3D	<ul style="list-style-type: none"> Clinical trials data management system that collects clinical trial data using standard case report forms (CRFs) based on common data elements (CDEs)
	CTEP	DARTS	
	CTEP	OSC	
Clinical Trials: Reporting	caBIG™	caAERS	
	CTEP	adEERS	
	CTEP	CDUS	
	CTEP	FIATS	
	CTEP	RABITS	
NDA Market <ul style="list-style-type: none"> Involves the submission of New Drug Applications to the FDA 	caBIG™	caAdapter	<ul style="list-style-type: none"> Tool that provides model mapping services and transformation among different kinds of data sources including HL7 v2 messages, HL7 v3 messages, and Regulatory Data Sets including the SDTM

Table A-1. CTEP and caBIG mapping Therapeutic drug discovery and development life cycle. Both CTEP and caBIG™ tools can be leveraged throughout each phase of the life cycle. Use of informatics throughout the life cycle the impetus for enabling personalized medicine and improving patient outcomes.

In this initial mapping, gaps in existing informatics platforms supporting the therapeutic drug discovery and development life cycle become realized. These gaps include:

Lack of tool integration between CTEP and caBIG™ tools –Integration between CTEP and caBIG™ tools has already been initiated via the standard interface developed between Adeers and caAERS. This integration will continue to occur in this proposal effort via the creation of CTEP grid services and other interfaces with caBIG™ tools. Example interfaces are the creation of CTEP grid services enabling the sharing of protocols, agents, and diseases

and sharing of adverse events data across the caBIG™ community and cooperative groups.

Other interfaces can be developed based on use cases identified during detailed analysis. For example, CTEP's tools supporting the conduct of clinical trials can be integrated with the caBIG™ NCIA image repository for the storage and retrieval of MRI and CT images obtained from the study.

- **Lack of an integrative view of available tools supporting the therapeutic life cycle** – The CTEP organization and caBIG™ program have produced numerous tools supporting clinical and translational research. Providing access to these tools in an integrative view by leveraging portal software will allow all stakeholders in the therapeutic discovery and development life cycle have at their fingertips, customizable views of information they need. Use of portal software with portlets generated for both CTEP and caBIG™ applications can assist in creating a “MyCTEP” customized portal for all CTEP stakeholders. Portlets can be developed leveraging Portlet standards for interchange with the caBIG™ grid portal (caGrid Portal).
- **Lack of access to clinical outcomes data to support the bench-to-bedside paradigm** – Key to the development of personalized medicine is access to clinical outcomes data. Clinical outcomes data can include patient survival data, data values associated with RECIST criteria (existing and enhanced) including changes in tumor dimensions and volume, genetic response data (change in gene/protein expression), and prognostic factors. This data can be used to generate new guidelines and decision support tools enabling personalized medicine. CTEP can work with cooperative groups to develop and leverage standards for clinical outcome data and work with the caBIG™ program to develop standard Case Report Forms to capture clinical outcomes throughout each therapeutic timepoint and at the end of the trial. The capture of clinical outcomes throughout the trial will be essential in support of upcoming adaptive trials in which just-in-time access to data is imperative and can result in dramatic impacts on patient outcomes.
- **Lack of user driven tools customized for each user groups** – Diverse user groups often have different needs and may have different and similar questions to ask from clinical and research data. Below are some example questions that may be of interest to diverse CTEP stakeholders:

Researchers:

- What are the biomarkers (SNPs, chromosome abnormalities, etc.) for each type of cancer?
- What therapies can be developed to target known biomarkers of cancer? What is the best delivery mechanism for these therapies?
- What groups of patients respond best to what treatments?

Oncologist View:

- What is the best therapy for my patient based on their molecular signature?
- What is the probability of survival for my patient?
- Are there any new treatments or experimental therapies available for my patient?
- Who are the experts that I can collaborate with?

Patient View:

- Who are the expert oncologists in my cancer area?
- What is the optimal therapy for my type of cancer? Are there any adverse events associated with the optimal therapy? What is the optimal therapy that also exhibits the best quality of life?
- Is there any other patient with similar characteristics that I can collaborate with?

The key to developing tools for diverse user's groups is to work with them to identify needs, and demonstrate existing and new technology platforms. The formulation of a consortium of Cooperative Groups in CTEP, interaction with caBIG™, and discussions with Patient Advocates can assist in engineering user driven tools that assist all stakeholders throughout the life cycle. These tools may leverage the same underlying data services but be presented differently for each stakeholder.

The above mapping of existing CTEP and caBIG™ tools to the therapeutic development and discovery process along with the identification of potential areas of expansion is based on a cursory analysis of a select group of available CTEP and caBIG™ tools. In this analysis, it is evident that that tools that both CTEP and caBIG™ have already developed are working towards the achievement of the NIH Roadmap. It is also evident that both CTEP and caBIG™ are key organizations that can lead the NCI into the identification and utilization of targeted therapies making a significant impact on our Nation's war against cancer and our personal commitment to each and every cancer victim.

We are at a time where the availability of information on disease research has created a well informed patient population who are not only demanding but expecting that information be shared for the good of the public to save lives. It is our obligation to work together to continue to break through the institutional barriers of information sharing through programs like caBIG™, create the infrastructure and tools that provide the clinical and research communities with the information needed to improve patient outcome, and meet the demands of our ever growing patient population.

Translational research has proven to be a powerful process that drives the clinical research engine. However, a stronger research infrastructure could strengthen and accelerate this critical part of the clinical research enterprise. The NIH Roadmap and FDA's Critical Path attempt to catalyze translational research in various ways, therefore streamlining the way in which clinical trials are conducted, and drug therapies are produced.

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