CureQuest: A Digital Game for New Drug Discovery

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***Abstract*—*Cure Quest* is an educational adventure game about Clinical Translational Therapeutics, the process of discovery and development of new medical treatments, drugs, devices, and therapies. The game is being developed through collaboration between faculty and students from a game design program and those from a medical school to raise awareness and improve collaboration in the "bench to bedside" process. *Cure Quest* aims to address this gap, first with medical students and ultimately for a general audience, with a game that instills wonder and inspires players with drug discovery challenges. In addition to the game's impact when completed, the development process itself presents a novel case study of integrating the interdisciplinary fields of game development and "team science." We present the current version of the game in development, the unique design challenges presented by the project, and the evolution of our collaborative process.**

***Index Terms*—game-based learning, drug discovery, translational science, team science, serious games, medical education**

I. Introduction

Developing a new drug can take ten to fifteen years and tens of millions of dollars, with numerous unsuccessful compounds that cannot be turned into a successful drug. To make drug discovery work well requires collaboration and communication between multiple disciplines across both clinical practices of health care and basic science, as well as business, funding agencies, and regulatory processes. While the process is essential to modern medicine, the full scope is not always well understood within the medical professions, by basic researchers, or by the general public. This is partly due to the specialized nature of medical training and gaps between basic science and clinical science. Drug development also involves a complex web of stakeholders with different roles and motivations. It requires the observations of health care providers, the basic research of molecular chemists, the data-driven guidance of biostatisticians, research support from government agencies or foundations, a viable business case for investors and pharmaceutical companies, and patients willing to join clinical trials. Game-based learning presents an opportunity for improving understanding of this process. There is little additional space in the curriculum for medical students, so a game can provide a valuable informal learning mode to augment the curriculum. For the general public, a game can provide an accessible entryway to an otherwise impenetrable topic. This research collaboration between the Icahn School of Medicine at Mount Sinai (ISMMS) and Rensselaer Polytechnic Institute (RPI) was formed to investigate these possibilities. In this project, faculty and students from a games program at a technical university and a medical school form a team to address the challenge of using games to provide informal education on drug discovery.

Fig. 1: *Cure Quest* Screenshot 1.

The group, from diverse academic arenas, levels of training & disciplines (computer science, software engineer, creative writing, art, gaming, biostatistics, drug discovery, clinical trials, education, graphic design, and music), gathered around a large conference table to share domains of expertise, experience and exchange ideas. Their challenge was to develop a videogame that captured second-year medical students' imagination while raising the player's awareness, insight, and appreciation for the complexities of drug discovery and development. Learning to speak the same language, along with investments in each other's

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talents, this team is creating *Cure Quest*. This adventure videogame instills a sense of wonderment about this challenging team science process via a fun-to-play game that involves a world of magic, where a mysterious condition has affected the land. It is the player's job to find a treatment using the discovery and development methods of translational biopharmaceutical research.

II. Prior Work

A. Educational Games for Pharmaceutical Education

Board games and digital games have been used to represent different aspects of the drug discovery pipeline, both in the genre of educational games and in games more generally. However, existing games have tended to focus on specific stages, such as biochemistry or management simulation. An early example is *The Pharm* [1], a board game targeting new employees in the pharmaceutical and biotech industries. The game uses a familiar board game structure with a track, dice, and question cards, and is mechanically a competitive series of multiple-choice questions with some aleatory factors. It focuses primarily on knowledge assessment. Other applications of board games, quiz games, and card games have been used in pharmaceutical education [2]. Cain and Piascik argue for the value of serious games, both analog and digital, and outline key requirements for learning games to be successful [3].

B. Digital Games

Big Pharma [4] is a computer game in which the player manages a pharmaceutical company, building assembly lines to manufacture drugs, including refining their properties, reducing side effects, and making a profit. These are represented as high-level functional abstractions, with an underlying design based on systems simulation and management. *Pandemic* [5] is a cooperative tabletop game in which players take on different roles to combat global disease outbreaks. Actions such as discovering a cure, treating a disease, and sharing knowledge with other players are high-level abstractions. The design emphasizes collaborative planning and managing resources and risks against the time pressure of exponentially spreading diseases. Operating at a micro level, *Opus Magnum* [6] is a computer puzzle game about alchemy, challenging the player to build intricate machines to transmute elements into other forms. While it is fantastical, the puzzle design relates to the molecular chemistry involved in designing and optimizing a drug. *Elder Quest* [7] is a 3D adventure game about geriatrics. It is set in a fantasy world referencing role-playing games such as *EverQuest* [8]. *Elder Quest* is focused on fourth-year medical students on geriatrics rotation, covering topics including delirium, falls, and managing medications represented through magic spells or combat [9]. A non-game-based digital media example is the *Sketchy Medical* video series, an exam study tool for medical students that uses visual mnemonics. In each video, the narrator draws an elaborate scene with each element representing a medical concept. The *Sketchy Micro* series covers microbiology, and other video series cover pathology, pharmacology, and clinical internal medicine [10].

These examples use different approaches to represent the content, but all rely on abstractions to present the content through game mechanics rather than direct simulation.

III. The Drug Discovery and Development Pipeline

The drug discovery and development pipeline describe the full cycle from the identification of an unmet human medical need, all the way to approval of a new treatment (New Drug application: NDA). Classic Target Based Discovery, Mechanism-informed or phenotypic screen (target unknown) guided drug discovery and development involves a series of sequential stages, each guided by specific goals and requiring different collaborators. The duration of each stage and the expertise needed to be brought to bear may vary depending on the nature of the reagent being developed and the methodology being employed, but the overall pipeline process moves from laboratory discovery and candidate selection to clinical development through progressive clinical trials, and ultimate delivery to patient populations at large following regulatory approval. Discovery begins with observation. This may be a new disease or a disease without a known cure, but it may also refer to a need for an improved treatment such as reduction in side effects, reduction in cost, or improvement in patient compliance. These observations may originate from Pharma, Biotechnology, research labs, clinicians and/or allied healthcare professionals.

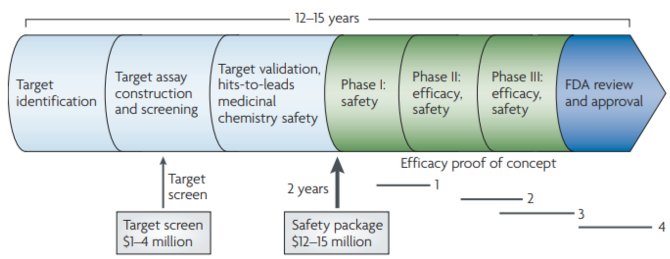

Fig. 2: Drug discovery and development pipeline. The figure is taken from [11].

In classical target-based discovery, target identification and validation are the searches for a druggable target, a cellular or molecular structure that is part of the disease process and can be effectively manipulated. This may involve working with a known target and determining that it is involved in the disease process, or it may involve discovering a previously unknown target. Once the target is validated, thousands of molecules are screened to find “hit molecules” that will interact with the target in the desired way. These candidates may come from natural sources, chemical libraries of existing known compounds, or may be guided by computational design. The hit molecules are then refined to develop “leads,” which form the basis ultimately for the new drug. Lead compounds undergo additional modifications to optimize ideal pharmacological properties and fundamental safety with the final selection of a specific Lead Candidate which is then tested for safety and in some instances efficacy in pre-clinical *in vivo* models.

Once the preclinical research is complete, the FDA must approve the start of clinical trials in humans. In Phase I clinical trials, the goal is to establish the drug's safety, pharmacokinetics, and dosing with a small group of healthy volunteer participants, or in some instances, patients with the underlying condition for which the drug might be ultimately used. In Phase II pilot and pivotal trials, the drug is studied in people with the disease or condition, in some instances in comparison to an existing treatment or a placebo. Finally, Phase III trials are performed to definitively prove the clinical efficacy of the new drug in larger populations of patients.

IV. Game design for learning outcomes

The pipeline process immediately suggested an episodic or modular structure, dividing the game into sections based on the different stages. Our initial design approach focused on first developing a complete list of learning outcomes, and then devising a unified set of core mechanics shared across all the stages. The game would be based on a case study, either from the development of a real drug or a fictionalized version. The player would work through the different stages in the pipeline, solving the challenges in each stage to move their new drug forward. Several limitations with this approach became apparent, however.

As we developed the learning outcomes for each stage, we discovered that the content areas were exceptionally diverse, with very different kinds of knowledge, processes, challenges, and modes of thinking. For example, the initial discovery phase would need to focus on individual patients and patterns of symptoms in a larger population. The lead optimization phase would focus on a small molecule's structure and behavior, while the clinical trial phases would emphasize statistical analysis, study design, and ethical issues. The team science nature of the pipeline means that multiple disciplines are involved, and furthermore, that very different kinds of questions must be posed in each stage and each discipline. A game could be designed around the abstraction of the work of molecular chemistry or biostatistics, or seeking funding and investors, or designing and running clinical trials. However, the challenge here is to incorporate all of these and many others. From a game production perspective, the ideal would be to find a reducible set of features across all of these domains to provide a core set of game mechanics.

An additional challenge is in the level of detail and scientific accuracy. For example, a faithful representation of target validation for a G-Protein Coupled Receptor (GPCR) might involve the player performing assays of hundreds of g-proteins, with increased calcium concentration indicating a potential ligand bonding [12]. In the clinical trial stage, the player might be asked to develop appropriate selection criteria for study participants, or make decisions based on changes to a participant's condition over the course of the trial. Each stage involves highly specialized knowledge, and accurate modeling of each of these processes at a granular level is daunting. In combination, these two problems reflect the real-world problem that motivates the project: a gap in high-level understanding across domains of deeply specialized expertise. Developing a game with high simulation fidelity in this context would approach Borges' famous map that must become the size of the empire it represents.

V. Game design for experiential outcomes

A. *Limits of the Learning Outcome Approach*

The emphasis on granular learning outcomes and case-study realism led to designs with an unstated goal of process competency that after completing the game, the player would be able to perform a high-throughput screening assay or correctly design an experiment with transgenic drosophila. However, the project's original goals were to increase high-level awareness of the big picture, not to provide training simulation for all (or any) of the roles involved. This was an essential realization in the design process, and opened the door to a new approach to the design problem. After reframing the learning goals, we then approached the design from the opposite direction, asking first about the player's experience.

B. *Motivation, Feeling, Experience*

While process simulation might be impractical, we could instead examine the motivations and the experience of people involved in drug discovery and development and use these to drive the design. We conducted an informal survey of medical school faculty, asking them to identify feelings and motivations as investigators in translational therapeutics. The responses to the question of motivation from the medical and scientific community fell into three categories: helping patients, the intellectual challenge, and personal accomplishment and success. Respondents were motivated by an altruistic desire to help individuals and whole communities, and by curiosity, critical thinking, and the excitement of solving a puzzle. Peer recognition, fame, and competition - the desire to be the first and the best, to "beat others," "to win the race," were consistent motivators, but so were teamwork and negotiation. When listing feelings associated with translational therapeutics, respondents focused on the challenge of the unknown such as "feeling like a detective" or an explorer, the feeling of a treasure hunt, of uncovering and keeping secrets; and also, of being an inventor, a tinkerer, and a "Math whiz." Responses also highlighted the intensity of the challenge, with terms like "persistent," "relentless," "focused," "resilient," and "decisive," as well as the need to be contemplative and thoughtful. These feelings and motivations formed design pillars for the game, with the goal of giving players an experiential relation to the translational therapeutics process.

C. *Motivations of Researchers and Corporations*

Monetary gain and power were notably absent from the list of responses. In further discussions these emerged as potential motivators from the perspective of the pharmaceutical industry, and also as motivations to guard against among researchers. This highlights a tension between the goals of a pharmaceutical company or venture capital fund to maximize return on investment for its shareholders and gain competitive advantage in the market, and the goals of researchers and doctors.

D. *Patients and Doctors*

A third perspective is the feelings and motivations of patients with respect to clinical trials. In addition to self-benefit, hope, and a feeling of retaking control, motivations may also include altruism, bravery, a desire to help others. However, patients may also feel powerless, anxious about the unknown, coerced, or taken advantage of. Randomized, double-blind assignment may create anxiety for patients since they don't know what treatment they are receiving, or resentment and anger at having potentially life-saving treatment withheld. Doctors may find themselves conflicted about whether a clinical trial is the best treatment for their patients. These are necessary tensions that ultimately emerge as an essential theme in the game: drug discovery is not driven purely by altruism or by greed, but by complex and sometimes contradictory motivations.

VI. Focus Group

A. Participants and Format

Building on these experiential pillars, we conducted conversations with students and faculty at the medical school to understand our target audience as players better. We met with a group of eight students, primarily second-year medical or Ph.D. students. The group was evenly divided between male and female, with a mix of students who described themselves as playing games frequently, playing games occasionally, and rarely playing games. All were interested in the *Cure Quest* game and thought it could be beneficial to themselves or others. The discussion and a follow-up survey collected input on game genres, art styles, play styles, and game concepts.

B. Findings

1) Game genres, features, and play styles

Students highlighted the opportunity to apply fact-based memorization in their curriculum to larger concepts and real-world situations. When discussing game genres and examples, participants gravitated towards exploration and adventure games, anchored by relatable characters and narrative. The open exploration and puzzles of games like the *Legend of Zelda* series were repeatedly highlighted for the experience of being immersed in the game world. At the same time, participants universally stressed the need for a low learning curve and ability to play in short time periods, such as "while standing in line at the cafeteria," as the intense medical school schedule leaves little room for extended game playing sessions. Games with an emphasis on characters and story were preferred over abstract games. Humor and mnemonic learning devices, as in the *Sketchy Medical* series, were also very positive.

2) Art Styles

Participants responded positively to the rich color palettes of *Ni-No-Kuni* [13], *The Legend of Zelda: Skyward Sword* [14], *Monument Valley* [15], and *Journey* [16]. Games with a palette with heavy primary colors like *Paper Mario* [17], *Yoshi's Island* [18], *The Legend of Zelda: WindWaker* [19], and *Kingdom Hearts* [20] were less preferred, and viewed as overly childlike. The pixel art style of games like *Fez* [21] and *Hyperlight Drifter* [22] had divided responses. Some participants were attracted for nostalgic or purely stylistic reasons. Others were firmly put off by this style, feeling that it signaled the game was meant for a limited gamer audience. Art style tests with a character concept design rendered in a matrix of illustration styles provided similar results. Respondents preferred designs with a naturalistic but illustrative style over detailed realistic rendering and more cartoony styles. There was strong feedback that we should avoid anime and manga styles.

3) Management Simulations and Life-and-death Scenarios

While tabletop strategy games like *Settlers of Catan* [23] were viewed positively, participants reacted negatively to *Big Pharma* and other management simulation games, citing the complexity of the systems and interface. This was a surprising finding, as these students work with far more complex systems on a daily basis. Additionally, participants were strongly negative towards games and game concept pitches that featured realistic serious diseases, such as a real or fictional aggressive viral epidemic. This included completely fantastical scenarios with life or death stakes, such as a game where the player would have to find a cure for a zombie apocalypse. *The Walking Dead* [24] was viewed positively, but more as an example of a character-based game than for its specific setting. Medical students explained that they were already coping with real-world life or death pressure in their daily life, and they had little desire for more in their gameplay. This may also explain the aversion to complex simulation games, that they were seen as layering more weight onto existing cognitive load.

4) Discussion

These were unexpected results for the design team, and caused us to further reevaluate basic assumptions that a simulation management game or a real-world case study would be the logical form for the game to take. Additionally, our initial design concepts had tended to revolve around serious real or fictional diseases, both for dramatic urgency and to communicate the importance of drug discovery. However, these discussions led us to a better understanding of our target audience as players, and to a new design direction.

VII. Design Iteration

A. CureQuest

The focus group feedback inspired the final design concept for *Cure Quest:* an adventure game across the Island of Aceso and its metaphorical lands representing the different stages in the drug discovery pipeline, such as the Forest of Compound Discovery, the Labyrinth of Target Identification and Validation, and the Desert of Funding.

B. Key Concepts and Narrative

The key high-level concepts include the motivations behind drug discovery; the principles of ethical scientific conduct; gathering evidence, forming hypotheses and interpreting experimental results; and understanding the role of the different stages and the different disciplines involved. The ultimate goal is to discover a cure for a mysterious disease, "transfeatheration", which begins with cold or allergy-like respiratory symptoms but progresses to the patient growing a thick coat of bird feathers. Along the way, the player explores unknown territory, solves puzzles, and seeks help from a cast of characters, including the Medicinal Chemist, the Librarian, the Biostatistician, the Pharmacologist, and the wise Sage of the Island. They must content with the Angel Investor and Venture Capitalist, a Rival Gang of Unscrupulous Researchers, and the High Mountain of FDA Approval.

C. Learning Approaches

This design is a combination of real-world processes within a fantasy scenario. The world of *Cure Quest* has both magic and microbiology, grounded in science but humorously fictionalized and abstracted. We employ a range of approaches to convey the learning material. Some processes are represented in a fairly direct manner. For example, in the initial stage of drug discovery, observation of unmet need, the player collects observations around a city to gain an understanding of the symptoms and epidemiology of the disease. Later in the game, the concept of phenotypic expression in transgenic animal models is presented through a game of cross-breeding to produce zebrafish with feathers. Other concepts are presented visually, metaphorically, or mnemonically. In the Labyrinth of Target Identification and Validation, the player explores a maze and solves a series of puzzles to collect Trophy Orbs representing druggable targets. The Nucleotide Orb is found by manipulating an enormous clockwork mechanism similar to a Renaissance orrery of the solar system, to move its spheres into the molecular structure of the nucleotide. Another orb is won by rolling a ball through an elaborate track in the shape of a protein kinase. The Transporter Carrier Protein Orb is found by fishing in a pond deep in the labyrinth, a metaphor for target validation as a fishing expedition.

Fig. 3. The orrery nucleotide puzzle in the labyrinth of target identification and validation.

While some key concepts can be expressed procedurally, other content is conveyed through didactic text woven into dialog. Finally, a quiz format augments the other presentation methods, in periodic Quiz Battles with the Rival Gang of Researchers. Here, the player must answer questions on topics such as Lipinski's Rule of Five, ethics and scientific integrity, and clinical trial endpoints. The purpose of these multiple modes is to engage players at different levels, foregrounding high-level concepts but still making more granular knowledge available.

VIII. Technical Implementation & Production Process

A. Development Team

The development team is composed of undergraduate and graduate students studying game development, computer science, electronic art, and graphic design. An additional goal of the project is to provide educational and professional training opportunities, including working on a large-scale educational game production project. Students have central roles in all aspects of production, from narrative design and systems design to concept art and modeling to gameplay programming, level design, music composition, playtesting, and project management.

B. Game Platform, Engine, and Tools

Based on the play session styles and time constraints described by the medical students, we focused development on mobile devices, rather than on PC or other gaming platforms. Initial design concepts focused on 2D game styles such as management simulation games, puzzle games, 2D top-down role-playing games, or interactive narratives, and we used the Phaser.io engine to develop these prototypes. However, the focus group feedback indicated a strong preference for 3D game worlds, so the team developed a small prototype as a proof of concept and to determine if the workflow would be feasible. This was successful, and we transitioned to developing using the Unity3D engine. Modeling, texturing, rigging, and animation are done in Maya, Modo, 3DCoat, and Substance Painter.

C. Collaboration Tools

When working with a team of primarily undergraduate students, students often only work on the project for one semester, leading to continuous cycles of new team members and onboarding. The team frequently has members working remotely, and since most students are taking a full course load, work tends to be asynchronous. Collaboration tools and project organization become essential. Our initial primary collaboration platform was Google Drive combined with Slack, and GitHub for source code. We encountered a common workflow challenge, a separation between programmers working in the GitHub repository with bug tracking, and artists working in a google drive folder requiring spreadsheets to track progress on assets. To improve versioning, review, and approval for artists, we began using ftrack, a cloud-based service for managing visual effects projects. However, ftrack's focus on shot approval workflow is less relevant for games, and the versioning connection from within Maya was often unpredictable. The advantages of ftrack did not outweigh the difficulty of still having different team members working in different version control systems. Over time, the organization of the google drive folder became more difficult as each new team of students would create new folders for their work. Finally, we transitioned to a new combination of platforms, using Basecamp for project management and Perforce Helix for both code and art asset version control. Perforce provided some improvements over GitHub in better adoption by non-programmers on the team, integration within the Unity3D editor, ability to resolve issues, and ability to handle large binary files. However, it does still require significant onboarding and training for new team members. Basecamp provides a somewhat better organization over the Google Drive folders, as well as task and issue tracking. Though Basecamp is designed for simplicity, it also did require onboarding for new team members. Overall, regardless of the collaboration tools, a project manager role on the team is still needed, particularly as the scale of production increases with sub-teams working on different episodes in parallel.

IX. Discussion and future work

A. *Status of Game Development*

The game is structured in episodes following a pipeline of stages. We are currently completing the first four episodes, in preparation for initial assessment with medical students. These episodes include:

1) Starting the Quest: in which the player arrives on the island, meets the Sage of Aceso, and receives their Quest and fundamental principles of ethical scientific research.

2) Discovery of Unmet Human Medical Need: the player journeys to the island's capital city, observes a progression of symptoms and discovers a new disease.

Fig. 4. *Cure Quest* Screenshot 2.

3) The Labyrinth of Target identification and Validation: the player explores a mysterious maze and solves puzzles to collect and learn about Druggable Targets.

4) Desert of Funding: before progressing with developing a new drug, the player must travel across the Desert of Funding, prepare their evidence and arguments, and choose wisely when selecting a funding source.

Future episodes will include The Forest of Compound Discovery, Hit Discovery and Lead Optimization, Preclinical Trials, Preparing for First-in-Man Trials, Phase I Clinical Trial, Phase II Clinical Trial, Phase III Clinical Trial, and the High Mountain of New Drug Application.

B. *Reflection on Multi-level Transdisciplinary Teamwork*

In addition to the expected impact of the game, the design process has illuminated new approaches to making learning games about complex transdisciplinary processes and subject matter. Transdisciplinarity here is distinguished from multidisciplinarity and interdisciplinarity [25] and requires that researchers invent new solutions by exploring research questions at the intersection of their respective fields to re-integrate and expand knowledge [26]. *Cure Quest* seeks to do this with its refreshing, experiential games approach to understanding the critical steps of drug discovery and development. Yet another level of knowledge has also emerged – that of working together, across very diverse academic arenas, levels of training and disciplines and sharing domains of expertise and experience. These include computer science, software engineering, creative writing, visual art, game design, biostatistics, drug discovery, clinical trials, medical science and research, education, graphic design, music composition and sound design amongst others.

According to the International Center for Transdisciplinary Research, "*... [transdisciplinarity] occasions the emergence of new data and new interactions from out of the encounter between disciplines. It offers us a new vision of nature and reality. Transdisciplinarity does not strive for mastery of several disciplines but aims to open all disciplines to that which they share and to that which lies beyond them*." [27]

The design process has also expanded the concept of Team Science, an approach to collaborative research across disciplines which is at the core of successful translational science. In team science, transdisciplinary research is a mode in which different disciplines not only fill different roles, but where there is fusion, interpenetration or combination of disciplinary methodologies. There is a sharing of language around a shared community of practice, such as in integrative medicine or environmental science. While this often refers to connecting disciplines of Basic Science and Clinical Science, these aspects of team science have clear parallels in the practice of game design and development. In developing *Cure Quest*, the medical experts have learned the language and processes of game design, and the game designers have immersed themselves in translational science. The result is an example of how the team science model can be further expanded, and how game design practice can incorporate subject matter as part of game design. In each case, the individuals on the *Cure Quest* team have a deep respect for each other's knowledge trajectory and have a strong shared goal.

Acknowledgments

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