PSU McNair Scholars Online Journal

Volume 11
Issue 1 *Without Borders: Original Contributions
in Undergraduate Research*

Article 6

2017

Wings Outstretched: New Contributions in Undergraduate Research

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(2017) "Wings Outstretched: New Contributions in Undergraduate Research," *PSU McNair Scholars Online Journal*: Vol. 11: Iss. 1, Article 6.

<https://doi.org/10.15760/mcnair.2017.01>

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Without Borders: Original Contributions in Undergraduate Research

2017

Ronald E. McNair Scholars Journal

Portland State University

About the Program

The Portland State University (PSU) Ronald E. McNair Scholars Program at Portland State University works with motivated and talented undergraduates who want to pursue PhDs. It introduces juniors and seniors who are first-generation and low income, and/or members of under-represented groups to academic research and to effective strategies for getting into and graduating from PhD programs.

The McNair Scholars Program has academic-year activities and a full-time summer research internship. Scholars take academic and skills-building seminars and workshops during the year, and each scholar works closely with a faculty mentor on original research in the summer. Scholars present their research findings at the McNair Summer Symposium and at other conferences, and are encouraged to publish their papers in the McNair Journal and other scholarly publications.

The Ronald E. McNair Post-baccalaureate Achievement Program was established in 1986 by the U.S. Department of Education and named in honor of Challenger Space Shuttle astronaut Dr. Ronald E. McNair. The program, which has been on campus since 2003, is funded by a \$1,155,000 grant from the U.S. Department of Education and institutional costshare funds.

The McNair Scholars Program's student-centered approach relies heavily on faculty and university commitment. Activities and opportunities provided by the program focus on building a positive academic community for the scholars while they are undergraduates at PSU.

About Ronald E. McNair

Ronald Erwin McNair was born October 21, 1950 in Lake City, South Carolina. While in junior high school, Dr. McNair was inspired to work hard and persevere in his studies by his family and by a teacher who recognized his scientific potential and believed in him. Dr. McNair graduated as valedictorian from Carver High School in 1967. In 1971, he graduated magna cum laude and received a Bachelor of Science degree in Physics from North Carolina A&T State University (Greensboro). Dr. McNair then enrolled in the prestigious Massachusetts Institute of Technology. In 1976, at the age of 26, he earned his Ph.D. in laser physics. His dissertation was titled, "Energy Absorption and Vibrational Heating in Molecules Following Intense Laser Excitation." Dr. McNair was presented an honorary doctorate of Laws from North Carolina A&T State University in 1978, an honorary doctorate of Science from Morris College in 1980, and an honorary doctorate of science from the University of South Carolina in 1984.

While working as a staff physicist with Hughes Research Laboratory, Dr. McNair soon became a recognized expert in laser physics. His many distinctions include being a Presidential Scholar (1971-74), a Ford Foundation Fellow (1971-74), a National Fellowship Fund Fellow (1974-75), and a NATO Fellow (1975). He was also a sixth degree black belt in karate and an accomplished saxophonist. Because of his many accomplishments, he was selected by NASA for the space shuttle program in 1978.

His first space shuttle mission launched successfully from Kennedy Space Center on February 3, 1984. Dr. Ronald E. McNair was the second African American to fly in space. Two years later he was selected to serve as mission specialist aboard the illfated U.S. Challenger space shuttle. He was killed instantly when the Challenger exploded one minute, thirteen seconds after it was launched. Dr. McNair was posthumously awarded the Congressional Space Medal of Honor. After his death in the Challenger Space Shuttle accident on January 28, 1986, members of Congress provided funding for the Ronald E. McNair Post-Baccalaureate Achievement Program. Their goal was to encourage low-income and first-generation college students, and students from historically underrepresented ethnic groups to expand their educational opportunities by enrolling in a Ph.D. program and ultimately pursue an academic career. This program is dedicated to the high standards of achievement inspired by Dr. McNair's life.

Source: mcnairscholars.com

Table of Contents

List of 2017 PSU McNair Scholars

PSU McNair Scholars Program Staff

Citizens United v The Federal Election Commission, Inverted Totalitarianism and Contemporary Fiction

By: Cory R. Chambers

Faculty Mentor: Jennifer Ruth, Ph.D.

Chemical Modulation of Cancer Cells to Enhance Tumor Immunity

By: Florisela Herrejon Chavez

Faculty Mentor: Jason E. Podrabsky, Ph.D.

Toward a Critical Philosophy for Children

By: James Funston

Faculty Mentor: Alex Sager, Ph.D.

Prevalence and Use of Guns in Perpetration of Intimate Partner Violence By: Caroline

Cummings

Faculty Mentor: Eric Mankowski, PhD

Sulfolobus Spindle-Shaped Virus 1 Growth Kinetics

By: Setarah Mohammad Nader

Faculty Mentors: Kenneth Stedman, Ph.D.

List of 2016 PSU McNair Scholars & Mentors

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Sarah Akin
Luz Alvarez
Yesenia L. Carrillo
Cory R. Chambers
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Florisela Herrejon Chavez
Kerry Hooton
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Ashleigh Mustain
Setarah Mohammad Nader
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Pablo Saldana
Jaime A. Schwoch
Kalera Stratton
Marta Szabatin
Michele Torland
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Dr. Jennifer Ruth

Dr. Susan Masta
Dr. Monica Mueller
Dr. Miriam Abelson
Dr. Alex Sager
Dr. Jennifer Tappan
Dr. Angela Coventry
Dr. Jason Podrabsky
Dr. Barry S. Oken

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Dr. Suzanne Estes
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**Citizens United v The Federal Election Commission, Inverted
Totalitarianism and Contemporary Fiction**

By

Cory Chambers

Faculty Mentor: Dr. Jennifer Ruth

Citation: Chambers, C. and Ruth, J. *Citizens United v The Federal Election Commission, Inverted Totalitarianism and Contemporary Fiction*. Portland State University McNair Scholars Online Journal, Vol. 11, Year: 2017

Abstract

In this paper I will explore the results of the 2010 Supreme Court *Citizens United vs The Federal Election Commission* as reflected in the contemporary literature. I will look at the role the corporation plays in American politics post *Citizens United*. My primary texts is the novel *Super Sad True Love Story*. My research question is: did the *Citizens United* decision open the door for 'inverted totalitarianism' to seep through the cracks of American society Using the allegorical novel *Super Sad True Love Story* by Gary Shteyngart, I will show how *Citizens United*, the political theory of Hannah Arendt, and the novel parallel and reflect the reality of our culture; where the weight of corporate oppression squashes the individual leaving that person simultaneously exposed and in complete loneliness.

Keywords: Super Sad True Love Story, Gary Shteyngart, Citizens United, Inverted Totalitarianism

Introduction

American democracy in the mid twenty-first century is being threatened by a corporate backed autocracy. "Democracy is a difficult concept to tie down...Its meaning is slippery and allusive," says Peter Murphy in his essay *Socialism and Democracy*. Murphy continues, "We can probably agree upon a minimal content for the idea of democracy viz. that it means that all persons have a share in government; that no class or party or group monopolizes the state" (12). While the Supreme Court's decision on the *Citizens United v. The Federal Election Commission* seems innocuous, it allows for inverted totalitarianism to seep into democracy. As with traditional forms of totalitarianism the individual is deprived of her ability to participate in the democratic process, leaving the individual powerless. Only inverted totalitarianism puts the corporation at the helm instead of a traditional governmental regime. In her essay, *On the Nature of Totalitarianism*, Hannah Arendt states, "The dependence and interdependence which we need in order to realize our power (the amount of strength which is strictly our own) becomes a source of despair whenever, in complete loneliness, we realize that one man alone has no power at all but is always overwhelmed and defeated by superior power" (336). Was Arendt's statement a prediction? Using the allegorical novel *Super Sad True Love Story* by Gary Shteyngart, I will show how *Citizens United*, the political theory of Hannah Arendt, and the novel parallel and reflect the reality of our culture; where the weight of corporate oppression squashes the individual leaving that person simultaneously exposed and in complete loneliness.

Citizens United v. The Federal Election Commission

January 21, 2010, is the date that dramatically changed the American political system, a change that threatens the foundation of our democracy. On this date the United States Supreme Court announced their decision on the *Citizens United v. The Federal Election Commission* case. The 5-4 decision undermines and in some cases voids decades of campaign finance legislation, the very legislation that protects the political system from blatant corruption and domination. In essence the decision grants corporations the status of an individual citizen, without seeming to consider the extreme disparity of power that money buys. The ruling not only gives the corporation unprecedented status, but it shifts priority to their shareholders, including foreign investors. The ruling awards the corporation superior power over the singular American citizen and our political system.

One of the most powerful forces in American politics and business are the Koch brothers. In her book *Dark Money*, author Jane Mayer exhaustively explores the impact corporations, especially Koch Industries, has on our political system. Here is how Mayer introduces the brothers when they took charge of Koch Industries in 1967:

Charles and David – often referred to as the Koch brothers – owned virtually all of what had become under their leadership the second largest private company in America. They owned four thousand miles of pipelines, oil refineries in Alaska, Texas, and Minnesota, The Georgia-Pacific lumber and paper company, coal, and chemicals, and they were huge traders in commodity futures, and other businesses. The company's consistent profitability had made the two brothers the sixth- and seventh-wealthiest men in the world. Each was worth an estimated \$14 billion in 2009 (2).

In addition to being two wealthy men who own multinational corporations they have an intense dislike for our system of government. Here Mayer describes the hatred the brothers have for anything not libertarian in nature, "the Kochs waged a long and remarkable battle of ideas. They subsidized networks of seemingly unconnected think tanks and academic programs and spawned advocacy groups to make their arguments in the national political debate" (3). More relevant to my argument than their political platform, the brothers spent monies to challenge voter protection

laws and set new precedent in the courts, as Mayer goes on to say, “[The Koch Brothers] financed legal groups and judicial junkets to press their cases in the courts. Eventually, they added to this private political machine that rivaled and threatened to subsume the Republican Party” (3). In fact, the Koch brothers are not just threatened by the Republican Party, they succeeded in sowing seeds of discord, creating gridlock in congress and in fighting amongst the Republican Party. The party is now tearing itself apart, as is apparent in the 2016 Presidential election. The dissension amongst the Republican Party made way for the extreme candidacy of President Donald Trump. Although President Trump did not receive money from the Koch brothers, he did run his campaign on the Koch Brothers platform of xenophobia, anti-regulation, and hatred of all things related to sitting President Barack Obama, the Democratic Party and the Republican party. However, President Trump’s extremism terrifies the entities that created space for him to run, and the Republican establishment and the Koch Brothers were quick to distance themselves from Trump. Author Stephen King speaks to the Donald Trump candidacy, “Conservatives who for eight years have sowed the dragon’s teeth of partisan politics are horrified to discover they have actually grown a dragon.”

The Koch Brothers are by no means the only wealthy heads of multinational corporations working in secrecy to subvert our democratic system and disempower the citizenry. In his *New York Times* article, “Club of the Most Powerful Gathers in Strictest Privacy,” author David Kilpatrick states, “Three times a year for 23 years, a little-known club of a few hundred of the most powerful conservatives in the country have met behind closed doors at undisclosed locations for a confidential conference, the Council for National Policy, to strategize about how to turn the country to the right” (1). Now that *Citizens United* is in place, these powerful people, in secret meetings are strategizing how to spend billions of dollars electioneering races that range from Presidential to the State. This new system of politics is what Sheldon Wolin calls “Inverted Totalitarianism” and he describes inverted totalitarianism as this, “Inverted totalitarianism is only in part a state-centered phenomenon. Primarily it represents the political coming-of-age of corporate power and the political demobilization of the citizenry” (x).

American Restorations Authority

Seven months after *Citizens United* Gary Shteyngart’s totalitarian novel *Super Sad True Love Story* was released. Shteyngart presents an inept vaguely familiar American government in the midst of collapse. Comprised of caustic consumers, filled with anxiety regarding their jobs and credit rating, they are overwhelmed by the surveillance state; Shteyngart’s citizens are prostrate to the Bipartisan party, the American Restoration Authority (ARA), and all corporations. This version of America is not dissimilar to Twenty-first century America, where as economist Annie McClanahan states, “Real median family income failed to rise for the first time in post-war history while everything from housing to health care to education was becoming more and more unaffordable. Households were thus increasingly dependent on the availability of ready consumer credit” (83). The consumer centric ARA leadership displays a person’s credit score on poles — not unlike telephone poles — as said person passes by. Shteyngart includes government approved instructions to the consumer, “The Boat is Full, Avoid Deportation, Latinos Save, Chinese Spend, ALWAYS Keep Your Credit Ranking Within Limits,” (54) along side projected credit scores. These slogans imply that the citizen can be deported for poor credit and the instructions are divided along lines of race. Shteyngart further divides the population into High Net-Worth Individuals (HNWIs) and Low Net-Worth Individuals (LNWIs). Shteyngart’s early focus on credit and the financialization of the citizen sets the stage for the great gulf between those with all the money and those with none.

Once the financial hierarchy is established, — the business of reducing the rights of LNWIs — dehumanizing and justified killing of citizens begins. In the “Decline of Nation-State and the End of Rights of Man” section of *The Origins of Totalitarianism*, Hannah Arendt asserts, “For the nation-

state cannot exist once its principle of equality before the law has broken down" (290). As the ARA embraces the breakdown of "equality" they increase the use of violence. Lenny Abramov, the protagonist of *Super Sad True Love Story* describes learning of a "riot" in Central Park: "This black dude is getting his ass kicked by the Guard and all these LNWI's are getting seriously whaled on" (156). This scene is poignant because it is the point where violent, physical domination of LNWI's begins. It is as Arendt predicted "the principle of equality before the law," that has completely broken down. Lenny and his friends — who financially are protected by their credit ratings and employment — view the riot from a place of safety: "News of the Central Park slaughter was spreading through the bar. No one was streaming live yet, but there were Images coming up on our *äppäräti* and on the bar's big screens" (156). The images seem to be ghosts from Nazi Germany that have come back to haunt Lenny and his friends, "The bodies of three men and a woman (a family?) lying on their backs, their naked black arms thrown wildly across their bodies, as if haphazardly hugging themselves" (156). Shteyngart uses this terrifying image to make his point; the image of dead bodies slung on top one another is ingrained in the world's collective memory. With just a few sentences, Shteyngart solidifies the fate of LNWI's and simultaneously warns the rest of his fictional population of the urgent need to conform. The riots end with this message from the ARA, "NOW IS THE TIME FOR SPENDING, SAVING, AND UNITY. ONE PARTY, ONE NATION, ONE GOD" (161).

Lenny, still shaken by the events in Central Park, returns to work at Post-Human Services, a subsidiary of Staatling-Wapachung Corporation. Lenny listens intently to a speech given by his boss Joshie Goldman, a powerful figure within the Wapachung corporation. "Pointless loss of life," Joshie says, and "loss of prestige for the country. Loss of tourist yuan. Loss of face for our leadership, as if they had any face to lose. And for what? Nothing has been achieved in Central Park. When will the Bipartisans realize that killing Low Net Worth Individual will not reverse this country's trade deficit or cure our balance-of-payment problems?" (180). Joshie continues to pontificate about the damages caused by the ARA: "We are finally no longer critically relevant to the world economy. The rest of the globe is strong enough to decouple from us. We, our country, our city, our infrastructure, are in a state of freefall" (181). While accounting for the failing state, Joshie also protects his position amongst the elite with this statement, "We must remind ourselves of the Fallacy of Merely Existing, which restricts what we can do for a whole sector of people. Yet, even though we may absolve ourselves of responsibility, we, as a technological elite can set a good example" (181). Joshie is not concerned with humanity and is willing to dismiss an entire group of people solely because they only exist and in his views do not contribute to the new regime.

Staatling-Wapachung Corporation: Assumes Control

In *Origins of Totalitarianism*, Arendt states, "Nothing is more characteristic of the totalitarian movements in general and of the quality of fame of their leaders in particular than the startling swiftness with which they can be replaced" (306). This statement rings true in the fact that shortly after Joshie Goldman's "state of the things" speech, the Bipartisan Party and the ARA fall and are "swiftly" replaced by the Staatling-Wapachung Corporation.

The Wapachung Corporation quickly assumes ultimate power and control of the United States — the type of power only obtained by the corrupting forces of the elite, the corporation the very entity the United States Supreme Court made a citizen on that fateful January day.

The Wapachung Contingency begins their reign by assuaging the fears of their shareholders and executives with this statement, "We at Staatling-Wapachung are reaching out to other nations' sovereign wealth funds looking for investment and alliance. We anticipate social changes that will benefit all shareholders and top-level personnel" (240). Following the reassurance that the shareholder's money is safe, Wapachung then asserts its power of protection with an

announcement: "Wapachung Contingency personnel have been instructed to protect you from rioting Low Net Worth Individuals and Rogue National Guard elements" (240). Shteyngart's corporation assumes control. First, by protecting the share holders as well as looking to foreign monies to prop up the government. Second, the Wapachung personal military supplants the American National Guard thus depriving the individual of a security force put in place by elected officials.

One campaign finance law that, in theory, survived *Citizens United* is that no foreign entity or government can directly contribute to American election campaigns. The knowledge that foreign entities invest in American corporations did not escape the attention of the Supreme Court. Justice Ruth Bader Ginsburg asked, "Would that include today's mega corporations, where many of the investors may be foreign? A week later, in his 2010 *State of the Union* speech, President Barak Obama echoed Justice Ginsburg's fears saying, "I don't think American elections should be bankrolled by America's most powerful interests, or worse, by foreign entities." Justice Ginsburg and President Obama are referring to the *Citizens* argument that the shareholder, and by extension the corporation, has a right to free speech, that the corporation should have unrestricted access to the political system as a function of Constitutional Rights.

Wherever there is a political collapse there is also a military force or secret police at the ready. In *Super Sad True Love Story* that force belongs to the aforementioned Staatling-Wapachung corporation. The message sent to employees and shareholders assures protection. As an employee, Lenny is given a Wapachung escort to visit his family in Long Island. The leader of the escort tries to comfort Lenny on the journey by saying, "Anyway, we are armed to the teeth, so no worries, We've got a heavy .50 caliber M2 Browning machine gun on the lead vehicle and AT4 anti-armor on both" (285). Here it becomes clear that the Staatling-Wapachung Contingency is the dominant military force. There is evidence, outside of fiction, that powerful American corporations have undue political power and military might. One of Meyer's most frightening examples of a corporation corrupting the system is in the story of the DeVos family, better known as the Amway Corporation. The DeVos family and Amway have strong foreign ties, "By 2006, fully a third of Amway's revenue came from the [Chinese] communist state" (234). This alone justifies Justice Ginsburg's fear of foreign interests playing out in the American Political system.

However, the most disturbing power of the DeVos family is its access to a para military. Richard (Dick) DeVos married Betsy Prince. While a marriage of power might be harmless, this one is treacherous as Betsy Prince (Devos) is not only President Trump's Secretary of Education, but the sister of Erik Prince the founder of Blackwater, a paramilitary force. Here is what Meyer says about the marriage: "Her brother Erik Prince, meanwhile, founded the global security firm Blackwater, which reporter Jeremy Scahill described as 'the world's most powerful mercenary army'" (234). Amway and Blackwater are the real life version of the Staatling-Wapachung and their ties prove a point that Hannah Arendt makes in her essay, *On the Nature of Totalitarianism*: "In totalitarian states, neither army nor church nor bureaucracy was ever in a position to wield or to restrain power; all executive power is in the hands of the secret police" (347).

The Americans

"A person who has been seduced by the consumer values system, whose identity is dissolved in an amalgam of the accoutrements of mass civilization, and who has no roots in the order of being, no sense of responsibility for anything higher than his own personal survival, is a demoralized person," states Václav Havel in his essay *The Power of the Powerless*; "The system depends on this demoralization, deepens, is in fact a projection of it into society" (45) The culture of *Super Sad True Love Story* is in the throes of seduction by the consumer value system. The citizens have attached themselves to their technology, the *äppäräti*, through which they purchase commodities,

monitor and judge each other. Each person has access to another's most personal information through technology without speaking a single word to another. Shteyngart calls this process "FAC...it means 'Form a Community'" (88). This process reveals not only Lenny's ZIP code, but his blood pressure, aggregated wealth, liabilities and assets. It also shockingly exposes Lenny's sexual preferences for women who have been sexually abused and have low self-esteem. Citizens (both real and fictional) participate in the dissemination of demoralizing information.

What Shteyngart calls FAC, technologist Maciej Ceglowski calls "surveillance capitalism". Ceglowski explains surveillance capitalism in his June 2016 speech to The Society for the Social Advancement of Socio-Economics, "Surveillance capitalism has some of the features of a zero sum game. The actual value of data collected is not clear, but it is definitely an advantage to collect more than your rivals do. Because human beings develop an immune response to new forms of tracking and manipulation, the only way to stay successful is to keep finding new and novel ways to peer into people's private lives." While Ceglowski is not speaking of Shteyngart's novel, he also concludes that technology leads to an isolated yet trackable citizen. Ceglowski also speaks to the idea of not using invasive technology, "opting out of surveillance capitalism like opting out of electricity, or cooked foods – you are free to do it in theory. In practice, it will up end your life." In an early scene of *Super Sad True Love Story* Lenny observes the uncomfortable results of a person choosing to opt out, Lenny notes that: "He didn't have an äppärät, or it wasn't set on 'social' mode." Lenny later continues the narrative of this non-social man being pulled off an airplane as the man yells, "What did I do? Look at my wallet. I'm Bipartisan" (40). Lenny, quiet and afraid, sneaks a glance at the military men removing the offender from the plane, "standing evenly around him, fingers on triggers" (40). Technology is a key player in *Super Sad True Love Story*. It is the way in which people communicate and are tracked by the ARA and the Staatling-Wapachung.

Technology as it exists in modern societies gives the illusion of connection. Facebook, Instagram, Snapchat and a host of other platforms allow citizens to feel as if they are participating in each others' lives. While the opposite is true, we have become self-absorbed voyeurs. We pass through mountains of data without interacting in an honest face to face fashion. Shteyngart accurately captures this phenomenon in this scene: "All you could hear were the whirs and clicks of our äppäräti downloaded and the competing chirping of the cicadas emerged from their seven-year slumber. And the looks on the faces of our countrymen—passive heads bent, arms at their trousers, everyone guilty of not being their best, of not earning their daily bread, the kind of docility I never expected from Americans, even after so many years of decline" (130). Even as Lenny and his friends walk through dehumanized, soon to be dead soldiers, they do not verbally interact, instead they let the äppäräti 'whir and click' and collect data to be viewed at an emotionally safe distance. Technology changes people, for example, Lenny's friend Noah, using his äppärät broadcasts a constant stream of his daily actions and meetings and the Noah Weinberg Show is sponsored by "a former Bipartisan politician who now ran security consulting for the Wapachung Contingency, the well-armed security division of [Lenny's] employer" (85). Lenny notes that Noah has changed: "Noah, hadn't always been this angry and caustic, but there was something disproportionate about his efforts these days, as if he could no longer keep track of how his personal decline paralleled that of our culture" (85). This early description of Noah is particularly telling as Shteyngart continues to illustrate decline throughout the rest of the novel as it parallels modern American culture.

The most poignant example of the demoralization of a population in *Super Sad True Love Story* is presented in the form of an art opening, or what Lenny refers to as a "Chinese welcoming party" sponsored by Wapachung Contingency. The exhibit "purposely zoomed in on the living, or, to be more accurate, the forced-to-be-living and the soon-to-be dead" (318). Lenny describes the art, or proof of humanities demise, in great detail, "An old man from Wichita without eyes, with the eyes physically removed, with one of the eyeholes being forced open by a laughing young man"

(318). Lenny is seeing this art from the safe distance of an art gallery complete with refreshments. Again, in his June 2016 speech Maciej Ceglowski describes the current state of affairs in a wealthy, tech and corporate driven society saying, "Take a stroll through downtown San Francisco and try to persuade yourself you're in the heart of a boom that lasted for forty years. You'll see a residential theme park for tech workers, surrounded by areas of poverty and misery that have seen no benefit and ample harm from our presence." While this statement lacks the gravity presented at Shteyngart's "art opening" it is an echo of the past and future where humanities depravity is always on display.

Conclusion

The future of modern America rests on the precipice between a failing democracy and inverted totalitarianism. Sheldon Wolin's timely definition of inverted totalitarianism is: Inverted totalitarianism works differently. It reflects the belief that the world can be changed to accord with a limited range of objectives, such as ensuring that its own energy needs will be met, that 'free markets' will be established, that military supremacy will be maintained, and 'friendly regimes' will be in place in those parts of the world considered vital to its own security and economic needs (47) *Super Sad True Love Story* successfully supports Wolin's definition, wherein Wapachung maintains the free market, a military force, and relations with China that benefit its 'own economic needs'. The Koch brothers and their ilk maintain the same beliefs and needs described by Wolin. Just as a modern corporation benefits from *Citizens United* so would the fictional Staatling-Wapachung corporation. Our society continues to cede power and information to the corporation, be it Apple, Facebook, Twitter or Instagram, with surveillance capitalism and the political power derived from the *Citizens United* decision. Wolin explains, "The acceptance of restraints on personal freedom and being resigned to political impotence: such possibilities are not wildly implausible for a society that is accustomed to exchanging new habits for old, to adapting to rapid change, uncertainty, and social dislocation, to having one's fate determined by distant powers" (42). The more freedoms we give up as citizens, the more reliant upon technology we are then the more isolated we become, leaving us in a disempowered state. In *Origins of Totalitarianism*, Arendt describes our future by reflecting on France, "she had no more true Dreyfusards, no more who believed that democracy and freedom, equality and justice could any longer be realized under the Republic" (93). The Dreyfusards that Arendt refers to are a group of French citizens who pushed against an unjust court ruling. The result is they lost faith in their government, they became hopeless, and left adrift in loneliness. If the ruling of *Citizens United* stands and the power of the corporation continues to increase exponentially, then the American citizens will no longer believe in the republic and will be "consumed by a 'superior power' and we will fall to inverted totalitarianism. All of these texts demonstrate that to fail to restrain the power of corporations will lead to the disempowered and alone individual of the state, resulting in a power vacuum that will consume us all in totalitarianism.

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Chemical Modulation of Cancer Cells to Enhance Tumor Immunity

By

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Citation: Herrejon Chavez, F and Podrabsky, J. E. Chemical Modulation of Cancer Cells to Enhance Tumor Immunity. Portland State University McNair Scholars Online Journal, Vol. 11, 2017

Abstract

Breakthroughs in immunotherapy have led to cancer therapeutics that activate the immune system by blocking inhibitory mechanisms. This class of therapeutics has resulted in longer survival rates for cancer patients, some living over 10 years after being diagnosed as terminally ill. However, only a small fraction of patients who receive immunotherapy drugs respond favorably. Recent studies suggest that certain anticancer agents (both cytotoxic chemotherapeutics and targeted drugs) stimulate immune recognition of cancers. Identification of such immunomodulatory anticancer agents would make ideal partners for current immunotherapy treatments, thus increasing the proportion of the treated patients who benefit from immunotherapy. This study aimed to identify the immunomodulatory effects of several anticancer agents by using a novel cell co-culture assay that modeled recognition of breast cancer cells by natural killer cells (NK cells). This physiologically relevant assay was used to systematically characterize effects of anticancer drugs on NK cell function. This assay successfully identified four types of immunomodulatory effects: antagonistic (suppressive), synergistic (enhancing), additive, and no effect on NK cell function. Further investigation confirmed the modulatory effects of those compounds that had been identified as antagonistic or synergistic.

Introduction

Cancer immunotherapy is an emerging field of cancer research, which focuses on developing therapeutics that target the immune system instead of cancer cells. Tumor cells develop immune resistance by taking advantage of inhibitory checkpoint mechanisms. Normally these inhibitory mechanisms are used to prevent the immune system from attacking healthy tissue (autoimmunity). However, cancer cells can cause dysregulation in the expression of inhibitory 'checkpoint' proteins and this can lead to immune resistance. These types of checkpoint mechanisms rely on ligand-receptor interactions and can be blocked by therapeutic antibodies.¹ Among the first such inhibitory receptors to be identified were the Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and Programmed Death 1 (PD-1) receptors. Development of therapeutic antibodies to block these receptors essentially removes the brakes on the immune system and allows the immune system to mount an attack on cancer cells.

A large focus in this field is identifying checkpoint receptors and developing antibody treatments that help activate tumor-cancer recognition, such as Bristol Myers Squibb's anti-CTLA-4 antibody treatment, ipilimumab, for metastatic melanoma.² Treatment with immunotherapy therapeutics has produced impressive long term survival of some cancer patients, some living several years after being diagnosed with advanced stages of cancer. However only about 15-20% of treated patients benefit from immunotherapy treatment.^{3,4,5,6} For example, ipilimumab only produced long term survival beyond two years in 18% of patients in one clinical trial.¹ A promising solution to increasing the proportion of patients who benefit from treatment is to use immunotherapy in combination with other anti-cancer agents.⁷ A study on 502 previously untreated metastatic melanoma patients found that long term survival beyond 3 years was occurring in 20.8% of patients who were assigned to take ipilimumab along with dacarbazine (chemotherapy drug) versus only 12.2% long term survival in patients only receiving dacarbazine.⁴

The goal of this study is to identify potential anti-cancer agents that enhance cancer-immune recognition and could be prioritized for used in combination with current cancer immunotherapy treatments. Another goal is to identify which anti-cancer agents suppress cancer-immune recognition, in order to deprioritize them as potential combination partners. Immune-cancer interactions will be modeled using a novel cell co-culture assay that models recognition of breast cancer cells (MDA-MB-231) by natural killer cells (NK cells; a type of effector immune cells). It is predicted that treatment of cancer cells with anti-cancer agents can alter their destruction by natural killer cells *in vitro*. NK cell activity can be extrapolated from growth inhibition of GFP+ MDA cells when compared to GFP+ MDA cells grown alone. This will allow a better understanding of what immunomodulatory effects anti-cancer agents have on the innate immune system.

Methods

Tissue Culture

Breast Cancer Cells

The MDA-MB-231 cell line that overexpresses a green fluorescent protein (GFP) construct was cultured in Dulbecco's modified Eagle medium enriched with 10% fetal bovine serum and 1% pen strep. Cells were incubated at 37°C and 5% CO₂.

Natural Killer Cells

Peripheral Blood CD56+ CD16+ Natural Killer Cells, Negative Selection (Lonza, Walkersville, MD) were cultured in LGM-3™ Lymphocyte Growth Medium (Lonza, Walkersville MD) supplemented with 10% Fetal Bovine Serum. Interleukin-2 (IL-2) (PeproTech, Rocky Hill, NJ) was added to NK cell culture at a concentration of 100 units per mL.

High Throughput Screening of Anti-Cancer Agents on MDA NK Cell Co-Culture

Breast cancer cells from cell line MDA-MB-231 were plated in Corning black with clear flat bottom 384 well assay plates (Corning Inc., Corning, NY) at a density of 1000 cells per well with a total volume of 50 μ L, and incubated overnight at 37°C and 5% CO₂. The next day compounds were added to the plates using a CyBi-Well Bario 384/60 μ L Head (CyBio, Woburn, MA) and 100 nL of common anti-cancer agent was added to each well. Anti-cancer agents were obtained from the compound set previously used for the NCI-CTD² project (<http://www.broadinstitute.org/ctdp.v2/>); see Table 3 (in supplemental material) for compounds. The stock concentration for the compounds varied, see Table 3 (in supplemental material) for concentration details. Plates were incubated at 37°C and 5% CO₂ overnight. The following day, compound-containing media was removed and natural killer cells (experimental) or LGM3 + IL2 media alone (control) were added at a ratio of 12.5 to 1, NK cells to MDA cells. Assay plates were then incubated for the next 6 days at 37°C and 5% CO₂ and imaged daily.

Dose Response Series

Forty selected compounds were serially diluted to 0.333X, 0.111X and 0.0370X the initial concentration (see Table 5 in supplemental material for compounds and detailed concentrations). Breast cancer cells (MDA-MB-231) were plated in 384 well assay plates the same as previously described. After cells adhered overnight, the compounds were added using the same protocol as before. After a 24-hour compound treatment, compound media was removed and natural killer cells (experimental) or LGM3 + IL2 (control) were added at a ratio of 12.04 to 1, NK cells to MDA cells. Assay plates were then incubated as described previously.

Testing ABT-737's Synergistic Mechanism

Compounds ABT-737, ABT-199 and SZ4TA2 were obtained from the same CTD² collection as before. Initial stock concentration of ABT-737 was 10 mM, and was diluted to 5 mM in DMSO. Initial stock concentrations of ABT-199 and SZ4TA2 were both 20 mM and both compounds were diluted to 2.5 mM in DMSO. Cancer cells were plated in 384 well assay plates the same as previously described. After an overnight incubation period, compounds were added as previously described. After a 24 h compound treatment, compound media was removed and NK cells (experimental) or LGM3 + IL2 (control) were added at a ratio of 12 to 1, NK cells to MDA cells. Assay plates were then incubated the same as described before.

Microscopy Imaging

High content microscopy (IXMicro, Molecular Devices) was used to image 384 well plates. Cells were imaged under GFP wavelengths and bright field illumination in order to track MDA cell growth (GFP+ cells) and NK cell activity. Microscope magnification was set at 4X. For the GFP wavelength, exposure was set at 200 ms and target max intensity at 50000. For the bright field (transmitted light) wavelength, exposure was set at 200 ms, target max intensity at 3000 and Z-offset from GFP was -50 μ m. Cells were imaged for 6 days (one-time point per day) starting on the day compounds were added. Cells were quantified using MetaXpress software, using a 'Count Nuclei' algorithm. Parameters for this analysis were set at approximate min width 10 μ m = 6 pixels, approximate max width 20 μ m = 12 pixels and set to an intensity above local background of 300 graylevels.

Results

Global overview of Compounds Screened in MDA-NK Cell Co-Culture Assay

The immunomodulatory effects of many of the compounds tested in this study have already been identified (see Table 1-3). Importantly, this study further confirms their immunomodulatory effects and validates this co-culture assay as a tool that can correctly predict immunomodulatory effects. As proof of concept, this study was successfully able to identify the immunomodulatory effects of 320 anti-cancer agents (Table 4). Of the 320 compounds screened in the MDA-NK cell culture assay more than half (51.56%) of the compounds were manually identified to be additive, which can be seen in Figure 1. Under this condition the compounds caused a partial reduction in cancer

cell growth and this effect combined with the natural killer cells abilities created an additive effect that was the sum of the combined effects. Another observed effect was antagonism which accounted for 12.81% of the compounds screened. Compounds in this group exhibited an immunosuppressive effect i.e. the combined cancer inhibitory effect of the compound and NK cells was less than the cancer inhibitory effect of NK cells alone. The synergistic group of compounds which consisted of 4.69% of the tested compounds, displayed immune enhancing effects, i.e. the combined cancer inhibitory effect of compound and NK cells was far greater than the effects of compound or NK cells alone. The last category to be observed was the group of compounds that had no effect on natural killer cell function and consisted of 30.94% of the compounds screened.

Total 320 Compounds

Figure 1. Global Overview of Immunomodulatory Effects on 320 Screened Compounds.

Compounds were categorized by manual inspection into four groups: antagonistic, additive, synergistic and having no effect on NK cell activity. Antagonistic compounds exhibited an immunosuppressive effect, while synergistic compounds exhibited immune enhancing effects. Additive compounds demonstrated a combined effect from the compound and NK cells that resulted in a total effect that equaled the sum of the two effects. No effect compounds matched the controls indicating no effect on NK cell activity.

Figure 2. Effects of NK cells on GFP+ Breast Cancer Cells. Two controls were tracked across 6 days, one with only cancer cells (control) and one with cancer cells and NK cells (NK cells alone). These represent the effects of NK cells on breast cancer cells in a single assay without the presence of compounds. (A) Cancer cell growth was normalized to Day 0 (indicating initial density at 100%) and means were graphed. (B) Bright-field illumination (top row) and GFP fluorescent illumination illustrate the effects of NK cells on cancer cell proliferation.

2B). In the control condition's GFP images, there's an increase in GFP+ cells with each day, which is also reflected in the bright field images. Meanwhile, in the NK cells alone condition's GFP images, there is a reduction of GFP+ cells, indicating cancer cell growth inhibition. In the bright field there is a visible formation of clumps of cancer cells that are surrounded and attacked by NK cells.

Identifying the Immunomodulatory Effects Anti-Cancer Agents Have on NK Cell Activity

When pre-treated with compound and co-cultured with NK cells, four effects on cancer cell growth were observed (Figure 3). Pifithrin-alpha (Figure 3A) is an example of a compound with no effect on natural killer cell function. In this figure the condition with compound only matches up closely with the control line, and the NK cell + compound combination condition also matches up with the NK cell only condition, indicating that this compound had no effect on Natural killer cell activity. MK-2206 (Figure 3B) is an example of an antagonistic immune suppressive compound. While the compound alone doesn't decrease cancer cell growth, in combination with NK cells cancer growth is greater compared to the NK only condition. This suggests that MK-2206 is immune suppressive. Erlotinib (Figure 3C) is an example of an additive compound. In combination with NK cells, erlotinib causes a greater growth suppression of cancer cells compared to the NK cell alone condition. This indicates that Erlotinib combined with NK cells produces an additive effect, which is the sum of the effects of the compound and NK cells on cancer cells. ABT-737 (Figure 3D) exhibits effects that are synergistic and immune enhancing. When the compound alone condition is compared to the control condition, there is a similar amount of cancer growth. However, in combination with NK cells there

Figure 3. Immunomodulatory Effects of Anti-Cancer Agents on Natural Killer Cells. Breast cancer cells were pre-treated with compounds for 24 hours (Day 0) before introducing natural killer cells. The four types of observed immunomodulatory effects are illustrated by (A) Pifithrin-Alpha – no effect, (B) MK-2206 – antagonistic effect, (C) Erlotinib – additive effect, and (D) ABT-737 – synergistic effect. Each line represents the mean growth of MDA-MB-231 breast cancer cells normalized to Day 0. Each compound was tested under four conditions: a control with no NK cells and no compound, a compound only condition with no NK cells, a NK cells only condition with no compound, and a combination condition with both NK cells and compound.

is a dramatic decrease in cancer cell growth when compared to the NK cell alone condition. This suggests that this compound was synergistic with immune cells in mediating cancer cell suppression.

Microscopy Images Confirm Immunomodulatory Effects

Daily images (GFP and brightfield) were taken for 5 days after 24 h compound pre-treatment at each time interval for each compound. Figure 4 shows the images that correspond to treatments presented in Figure 3. Figure 4 compares the NK cells only condition with the NK + compound combination condition. Treatment with pifithrin-alpha leads to a similar decrease of GFP+ cells when compared to treatment with NK cells only. This supports the conclusion that pifithrin-alpha had no effect on the ability of NK cells to kill cancer cells (Figure 4A). Figure 4B verifies the immunosuppressive effects of MK-2206, where it can be seen that NK cells + MK-2206 leads to an increase of GFP+ cells compared to treatment with NK cells alone. Erlotinib's additive effects on cancer cell growth are illustrated in Figure 4C, where the combination of erlotinib with NK cells leads to a reduction in cancer cell growth compared to NK cells alone. Note that in the bright field images for this drug a pronounced clumping of cancer cells that is absent in the NK cell only treatment. A strong synergistic effect is illustrated for ABT-737 in combination with NK cells on inhibition of cancer cell growth (Figure 4D). There was a striking decrease in GFP+ cancer cells in this treatment that is far more pronounced than in any other treatments presented, indicating that ABT-737 is highly immune enhancing.

A **B** **C** **D**

Figure 4. Imaging Visually Confirms Immunomodulatory Effects of Screened Compounds. All compound conditions were imaged under bright-field (top row) and GFP (bottom row) wavelengths. Each compound (A) Pifithrin-Alpha, (B) MK-2206, (C) Erlotinib and (D) ABT-737 visually displayed what was observed in the cancer growth graphs: (A) no effect, (B) antagonistic, (C) additive and (D) synergistic. All compounds are compared to NK alone control condition.

Dose Response Series Verifies Immune Enhancing and Immune Suppressive Effects

Select compounds were tested in a dose response series, where their modulatory effects were observed at different concentrations. Cells were pre-treated with compound and imaged the same as in the initial drug screen. Figure 5 shows the dose response for two compounds that had been previously seen to be either enhancing or suppressing immune activity. MK-2206 (Figure 5A), which was immunosuppressive in the initial drug screen, was found to be immunosuppressive at all concentrations when compared to the DMSO control with no compound (0 μ M concentration condition). This confirms MK-2206's immunosuppressive effects towards NK cell activity. ABT-737 (Figure 5B) was previously seen to be immune enhancing and synergistic in the initial drug screen, and this effect was confirmed across various concentrations when compared to the DMSO control. Although these compounds were able to demonstrate their modulatory effects at all concentrations, they were most effective at higher concentrations.

Figure 5. Dose Response Series Confirms Immunomodulatory Effects. The modulatory effect of (A) MK-2206 – immunosuppressive, and (B) ABT-737 – immune enhancing, were confirmed across a variety of concentrations. The concentration of 0.000 μ M is the DMSO control. Red bars represent growth of cancer cells in the presence of the compound, while blue bars represent the combined effects of NK cells and the compounds.

Exploring Synergistic Mechanism of ABT-737

ABT-737 is an inhibitor of several proteins in the BCL family, including BCL-2, BCL-xL and BCL-w. In order to investigate the potential mechanism by which ABT-737 is synergistic, ABT-199 and SZ4TA2 (BCL selective compounds) were tested alongside ABT-737. ABT-199 is a selective inhibitor of BCL-2, and SZ4TA2 is a selective inhibitor of BCL-xL. While the effects of ABT-737 in this trial were similar to previous experiments (compare Figure 3D, 6A), neither of the other BCL family inhibitors exhibited this synergistic effect (Figure 6B, C). This indicates that both ABT-199 and SZ4TA2 have no effect on natural killer cell activity.

Figure 6. Investigating ABT-737's Synergistic Mechanism. Cells were pre-treated for 24 hours before adding NK cells. (A) ABT-737 (10 μ M) which inhibits BCL-2, BCL-xL and BCL-W was compared to two compounds that selectively inhibit certain proteins in the BCL-2 family. (B) ABT-199 (5 μ M) is selectively inhibits BCL-2, while (C) SZ4TA2 (5 μ M) selectively inhibits BCL-xL. Synergistic effects of ABT-737 were confirmed, while both ABT-199 and SZ4AT2 showed no effect.

Discussion

We were successfully able to determine that treatment of cancer cells with anti-cancer agents does alter their destruction by natural killer cells *in vitro*. Some of these compounds such as erlotinib are already in clinical trials as combination partners with current immunotherapy treatments (www.clinicaltrials.gov, identifier NCT02013219). In addition to identifying known immunomodulatory effects, this study was able to identify many unknown immunomodulatory effects. Compounds identified as synergistic or immune enhancing (4.69%) should be given priority when considering potential immunotherapy combination partners. While compounds that were identified as antagonistic or immune suppressive (12.81%) should be deprioritized when considering potential immunotherapy combination partners. This study also identified most of the

compounds as additive (51.56%). However, further investigation into these compounds is required to determine if they would make good combination partners with immunotherapy. Another important aspect that this study uncovered was successfully modeling cancer immune interactions *in vitro*. This study confirmed that NK cells are able to destroy breast cancer cells *in vitro*. As a result of this ability, we were able to use this assay to determine the immunomodulatory effects of anti-cancer agents. This study was successfully able to identify four types of immunomodulatory effects: antagonistic, synergistic, additive, and no effect on NK cell activity. Examples of such identified compounds include MK-2206 (antagonistic), ABT-737 (synergistic), erlotinib (additive), and pifithrin-alpha (no effect). And a dose response series of select compounds was able to confirm their immunomodulatory effects. For example, the effect of MK-2206 as immunosuppressive was confirmed at all tested concentrations, and the immune enhancing effect of ABT-737 was also confirmed. Despite demonstrating immunomodulatory effects at low concentrations, the compounds all seemed to be most effective at higher concentrations. Some additional aspects that need to be considered in future studies are the effects of the tumor microenvironment; specifically, the immunosuppressive effects of the tumor microenvironment. In order to make this assay more physiologically relevant, immunosuppressive cells (such as stromal cells) would need to be introduced, and the effects of the compounds would need to be monitored. Other types of cancer cells would also need to be tested in order to see if these immunomodulatory effects are specific to breast cancer or if they can be generalized to other types of cancer. By identifying immunomodulatory effects, we can make new hypotheses on mechanisms that make compounds immunosuppressive or immune enhancing. One such mechanism that we further investigated was the mechanism that made ABT-737 synergistic. ABT-737 is a compound that inhibits BCL-2, BCL-xL and BCL-W, and the BCL-2 protein family is associated with regulating cell death. Dysregulation or overexpression of the BCL-2 family can inhibit cell death pathways and lead to malignancies.⁸ Therefore inhibiting BCL-2 family proteins has the potential to stimulate apoptosis under certain conditions and thus prevent potential cancerous or pre-cancerous cells from becoming malignant. In order to determine which member of the BCL-2 family was causing synergism, two selective compounds were tested side by side to ABT-737. ABT-199 is a selective inhibitor of BCL-2 and SZ4TA2 is a selective inhibitor of BCL-xL. It was found that neither of these compounds had any immunomodulatory effects, indicating that BCL-2 and BCL-xL alone do not cause synergistic effects. This suggests that synergism may either be caused by BCL-W or by combining the inhibitory effects of two or all three of these BCL-2 family proteins. Further studies would need to combine compounds and introduce a BCL-W selective inhibitor in order to fully determine the mechanism that makes ABT-737 synergistic.

Conclusion

This study confirms the usefulness of a co-culture assay of NK cells and cancer cells as an *in vitro* method to screen potential anti-cancer agents. We successfully identified certain compounds as suppressive or enhancing which will be useful for prioritizing and deprioritizing immunotherapy combination partners. The usefulness of this *in vitro* assay was illustrated by confirming previously known modulatory effects such as erlotinib's additive effect that resulted in greater reduction of cancer cell growth or survival. In addition, the assay identified previously unknown effects such as MK-2206's suppressive effects and ABT-737's enhancing effects on NK cell activity. Despite these promising findings, further research is needed to finish testing all the known anti-cancer agents, to see the effects that the tumor microenvironment has on anti-cancer agent's immunomodulatory effects and to see if these effects are specific to breast cancer cells or if they can be generalized to more cancers.

Acknowledgements

We'd like to thank the Howard Hughes Medical Institute (HHMI) for funding this project, as well as the HHMI EXROP and Capstone programs for providing the opportunity for this project to be

conducted. We'd also like to thank Cherrie Huang for her contributions and support during this project. We also thank the McNair program for their support.

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Supplemental Material

Table 1. Common Immune Enhancing Anti-Cancer Agents		
Compound	Effects	Source
Etoposide*	Enhances NK cell activity	Nars et al., 2013 Markasz et al., 2007
Axitinib*	Enhances activation and recruitment of CD8 ⁺ T cells	Bose et al., 2012
Topotecan*	Enhances immune tumor recognition via Fas signaling	Wei et al., 2009
Dacarbazine	Improves overall survival when combined with immune checkpoint therapy	Drake et al., 2012
Doxorubicin*	Increases IL-12 expression by Dendritic cells	Nars et al., 2013
	Enhances T cell activity	Ramakrishnan et al., 2010 Hannesdóttir et al., 2013
	Enhances NK cell activity	Markasz et al., 2007
Cisplatin	In clinical trials for combination therapy with immune checkpoint inhibitor	Morrissey et al., 2016
Cyclophosphamide	Shown to sensitize tumors to Fas mediated cytotoxicity	Micheau et al., 1997
	Augments antitumor immune response of Dendritic Cells	Liu et al., 2007
	Suppressive to immune system at high doses (augments immune response at low doses)	Brittenden et al., 1996
Trametinib	In clinical trials with BRAF inhibitor and PD1 inhibitor combination therapy	Morrissey et al., 2016
Temsirolimus	Increases interferon- γ and T-cell response when used in combination with cancer vaccines	Wang et al., 2011
Lapatinib	Enhances interferon- γ secreting T-cells present at tumor site when used in combination with Doxorubicin	Hannesdóttir et al., 2013
Vincristine*	Enhances NK cell activity	De Vecchis et al., 1981
Pazopanib*	In clinical trials for combination therapy with immune checkpoint inhibitor	Morrissey et al., 2016
Gemcitabine*	Inhibits myeloid suppressor cells but doesn't reduce CD4 ⁺ T cells, CD8 ⁺ T cells,	Koido et al., 2011

	NK cells, macrophages, or B cells	
Erlotinib*	In clinical trials for combination therapy with immune checkpoint inhibitor	Morrissey et al., 2016
Thalidomide*	Enhances NK cell numbers and activity	Davies et al., 2001
Gefitinib*	Enhances NK cell Activity	He et al., 2013
Vorinostat*	Enhances expansion of IFNg-producing T-cells	West et al., 2013
Ibrutinib*	Immune response enhanced when used in combination with a TLR9 ligand	Sagiv-Barfi et al., 2015

* Assay identified known immune modulatory effects

Table 2. Common Immune Suppressive Anti-Cancer Agents

Compound	Effects	Source
Dasatinib	Has been seen to be immune enhancing	Lowe et al., 2014
	However, it is suppressive to NK cell activity	Salih et al., 2010 Heine et al., 2011
Bortezomib	Shown to enhance antitumor properties	Boccadoro et al., 2011
	However, it is suppressive to NK cell activity	Markasz et al., 2007
Methotrexate	Suppressive to NK cell activity	Brittenden et al., 1996
	Inhibits macrophage activation	Nelson et al., 2003
Paclitaxel	Shown to inhibit tumor growth, and recruit CD4+ and CD8+ T cell	Nars et al., 2013
	However, it is suppressive to T-cell and NK cell activity	Ramakrishnan et al., 2010 Markasz et al., 2007
Dexamethasone*	Inhibits dendritic cell maturation	Matsue et al., 2002
Docetaxel	Enhances T-cell activity	Kodumudi et al., 2010
	However it is suppresses NK cell activity	Markasz et al., 2007

* Assay identified known immune modulatory effects

Table 3. Common Anti-Cancer Agents with No Immunomodulatory Effects

Compound	Effects	Source
Mitomycin	NK cell activity is not affected when used in combination with other chemotherapy agents	Brittenden et al., 1996

Nilotinib*	NK cell cytotoxicity is not altered, but NK cytokine production is decreased at high concentrations	Salih et al., 2010
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* Assay identified known immune modulatory effects

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
CAY10576	0.1	0.2	No Effect
UNC0638	5	10	Additive
Bafilomycin A1	0.1	0.2	Additive
Etoposide	5	10	Additive
Narciclasine	0.1	0.2	Additive
SRT-1720	5	10	No Effect
SB-743921	0.1	0.2	Additive
JW-480	5	10	No Effect
Dasatinib	5	10	No Effect
BRD-K34485477	5	10	No Effect
SN-38	0.1	0.2	Additive
BRD-K01737880	5	10	Additive
Bortezomib	0.1	0.2	No Effect
BRD-K44224150	5	10	No Effect
Brefeldin A	0.1	0.2	Additive
Axitinib	5	10	Additive
BRD-A96645632	5	10	No Effect
Triazolothiadiazine	5	10	Additive
SGX-523	0.1	0.2	Additive
GW-843682X	5	10	No Effect
Barasertib	5	10	Additive
ML239	5	10	Additive
SU11274	5	10	No Effect
PF-573228	5	10	Additive
SCH-79797	5.5	11	No Effect
Afatinib	5	10	Additive
AZD8055	5	10	Additive
Doramapimod	5	10	Additive
BRD-K34222889	5	10	Additive
GDC-0941	5	10	Antagonistic
Itraconazole	5	10	No Effect
CAL-101	5	10	Antagonistic
Topotecan	5	10	Additive
CHIR-99021	5	10	No Effect

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
Methotrexate	5	10	No Effect
XL765	5	10	Synergistic
Compound 7d-cis	5	10	Additive
Spautin-1	5	10	Synergistic
PD318088	5	10	Antagonistic
Dacarbazine	5	10	Antagonistic
SR8278	0.1	0.2	No Effect
Paclitaxel	5	10	Additive
Mitomycin	5	10	Additive
Neratinib	5	10	Additive
BRD4132	25	50	Additive
Vorapaxar	5	10	Additive
ML006	25	50	Synergistic
Tipifarnib	5	10	Additive
RAF265	5	10	Antagonistic
Veliparib	5	10	No Effect
Serdemetan	5	10	No Effect
AT13387	5	10	Additive
MST-312	5	10	Additive
AZD7762	5	10	Additive
KU 0060648	5	10	Antagonistic
Doxorubicin	5	10	Additive
BRD-K63431240	5	10	Additive
ML029	5	10	No Effect
BRD-K04800985	0.1	0.2	Additive
Tamatinib	5	10	Additive
Teniposide	5	10	No Effect
Semagacestat	5	10	Additive
CAY10618	5	10	Antagonistic
NSC19630	5	10	Additive
Pifithrin-mu	5	10	Additive
Lenvatinib	5	10	Additive
WZ4002	5	10	Additive
BRD-K66453893	5	10	Additive
QS-11	5	10	No Effect
BRD-K96970199	5	10	No Effect
Tanespimycin	5	10	Additive
BRD-K33199242	5	10	Synergistic
Cediranib	5	10	Synergistic

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
BRD-K41597374	5	10	No Effect
Trifluoperazine	5	10	No Effect
BRD-K50799972	5	10	No Effect
Alvocidib	5	10	No Effect
GSK-J4	5	10	Additive
Cytarabine Hydrochloride	5	10	Additive
Masitinib	5	10	No Effect
BRD-K27224038	0.1	0.2	Antagonistic
Manumycin A	5	10	Additive
ISOX	5	10	Additive
PD 153035	5	10	Additive
AT7867	5	10	Additive
ML162	5	10	No Effect
Repligen 136	5	10	Additive
BRD-K92856060	5	10	Additive
Cisplatin	5	10	Antagonistic
SJ-172550	5	10	Antagonistic
SZ4TA2	5	10	No Effect
AC55649	5	10	Synergistic
Tozasertib	5	10	Additive
BRD-K09344309	5	10	No Effect
PF-3758309	5	10	Additive
CCT036477	5	10	Synergistic
Methazolastone	5	10	Additive
HLI 373	5	10	Additive
ML258	0.1	0.2	No Effect
PF-184	5	10	Additive
Clofarabine	5	10	Additive
Necrosulfonamide	5	10	No Effect
WZ8040	5	10	No Effect
NSC48300	5	10	Additive
Nintedanib	5	10	No Effect
BRD-K19103580	5	10	Additive
Compound 1541A	5.5	11	Additive
BRD-K41334119	5	10	Synergistic
PI-103	5.5	11	No Effect
MI-2	5	10	No Effect
CHM-1	4.8	9.6	Additive

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
JW-55	5	10	No Effect
PAC-1	5	10	No Effect
BRD-K13999467	5	10	No Effect
Apicidin	5	10	Additive
BRD-K17060750	5	10	Antagonistic
WP1130	5	10	No Effect
Bexarotene	5	10	Antagonistic
GSK-3 inhibitor IX	5	10	Additive
SMER-3	5	10	No Effect
Dinaciclib	0.1	0.2	Additive
Daporinad	5	10	No Effect
BRD-K34099515	5	10	Additive
VER-155008	5	10	Additive
Salermide	25	50	Additive
BMS-536924	5	10	Additive
Cyclophosphamide	0.1	0.2	No Effect
MK-2206	5	10	Antagonistic
BCL-LZH-4	0.1	0.2	No Effect
BIX-01294	5	10	Additive
Navitoclax	5	10	Additive
AZD1775	5	10	Additive
ML203	5	10	Additive
Ciclosporin	5	10	No Effect
Indisulam	5	10	No Effect
CD-437	5	10	Additive
Vandetanib	5	10	No Effect
Tivozanib	5	10	Additive
Dexamethasone	0.1	0.2	Antagonistic
Obatoclax	5	10	Antagonistic
LY-2183240	5	10	Additive
MGCD-265	5	10	Additive
NVP-BSK805	5	10	Additive
Importazole	25	50	No Effect
Nilotinib	5	10	No Effect
Tamoxifen	25	50	No Effect
Vorinostat	5	10	Additive
N9-isopropylolomoucine	25	50	Additive
Oligomycin A	5	10	Antagonistic

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
Fumonisin B1	25	50	Antagonistic
Belinostat	5	10	Additive
AM-580	25	50	Antagonistic
BRD-K33514849	5	10	Antagonistic
Necrostatin-1	25	50	No Effect
Cyanoquinoline 11	5	10	Antagonistic
Zebularine	25	50	Antagonistic
Cytochalasin B	5	10	Additive
Valdecoxib	25	50	Antagonistic
TW-37	5	10	No Effect
BRD8958	5	10	No Effect
Panobinostat	0.1	0.2	Additive
Gefitinib	5	10	Additive
QW-BI-011	5	10	Additive
NVP-ADW742	5	10	No Effect
BRD-K42260513	5	10	Additive
Alisertib	5	10	Additive
BRD6340	5	10	Additive
Parbendazole	5	10	Additive
SCH-529074	5	10	Additive
AZ-3146	5	10	Additive
PLX-4720	5	10	No Effect
FGIN-1-27	5	10	No Effect
ML210	5	10	Additive
Erastin	5	10	Additive
YK 4-279	5	10	Additive
MLN2238	5	10	Additive
Bax channel blocker	5	10	Antagonistic
BRD-K02251932	5	10	Synergistic
Omacetaxine Mepesuccinate	0.1	0.2	Additive
STF-31	5	10	No Effect
ABT-737	5	10	Synergistic
Mdivi-1	5	10	Additive
Bardoxolone Methyl	5	10	No Effect
Neuronal Differentiation Inducer III	25	50	Additive
Crizotinib	5	10	Additive
BIBR-1532	25	50	Synergistic

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
Foretinib	5	10	No Effect
PF-750	25	50	Additive
Trametinib	5	10	No Effect
CI-976	25	50	Synergistic
Tacedinaline	5	10	Antagonistic
Cimetidine	25	50	Antagonistic
Bosutinib	5	10	Additive
Etomoxir	25	50	No Effect
Piperlongumine	5	10	Additive
Sildenafil	25	50	Synergistic
KX2-391	5	10	Additive
Phloretin	25	50	No Effect
Silmitasertib	5	10	Additive
COL-3	5	10	No Effect
Leptomycin B	0.1	0.2	Additive
PF-543	5	10	Additive
Epigallocatechin-3-monogallate	25	50	Additive
Temsirolimus	5	10	Antagonistic
BI-2536	0.1	0.2	Additive
NSC632839	5	10	No Effect
Myriocin	0.1	0.2	Additive
R428	5	10	Antagonistic
ABT-199	5	10	No Effect
Lapatinib	5	10	Antagonistic
Canertinib	5	10	Additive
Erismodegib	5	10	Additive
BRD-K04574331	5	10	Synergistic
PRIMA-1-Met	5	10	No Effect
I-BET151	5	10	No Effect
NSC95397	5	10	No Effect
WAY-362450	5	10	No Effect
GMX-1778	5	10	Additive
Sepantronium Bromide	0.1	0.2	No Effect
BRD-K37390332	5	10	Antagonistic
Merck60	5	10	Additive
Regorafenib	5	10	Additive
Pluripotin	5	10	Additive
NSC23766	25	50	Additive

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
AZD4547	5	10	Additive
ATRA	25	50	Additive
GSK1059615	5	10	Additive
SKI-II	25	50	Additive
Cabozantinib	5	10	Additive
Purmorphamine	25	50	Antagonistic
Fedratinib	5	10	No Effect
PDMP	25	50	Additive
Niclosamide	5	10	Additive
Pifithrin-alpha	25	50	No Effect
NVP-TAE684	5	10	Additive
MI-1	0.1	0.2	Antagonistic
BRD9647	5	10	No Effect
UNC0321	0.1	0.2	No Effect
Fingolimod	5	10	No Effect
BMS-195614	5	10	No Effect
Dactolisib	0.1	0.2	Additive
Tubastatin A	5	10	Additive
BEC	5	10	Additive
Isoliquiritigenin	5	10	Additive
9-dihydropipltartine	5	10	Additive
Istradefylline	5	10	Synergistic
AA-COCF3	5	10	Additive
AGK-2	5	10	Additive
Curcumin	5	10	No Effect
Tipifarnib-P1	5	10	Antagonistic
GW-405833	5	10	No Effect
Ko-143	25	50	Additive
PRIMA-1	5	10	Additive
Isoevodiamine	5	10	Additive
Olaparib	5	10	Additive
SNX-2112	5	10	Additive
Lovastatin	5	10	Additive
Abiraterone	5	10	No Effect
SM-406	0.1	0.2	Additive
CD-1530	25	50	Additive
GDC-0879	5	10	No Effect
KU-60019	5	10	Additive
Lomeguatrib	5	10	Additive

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
Docetaxel	0.1	0.2	Additive
CID-5951923	5	10	Additive
BRD-K14844214	0.1	0.2	Additive
Betulinic acid	5	10	Additive
Vincristine	0.1	0.2	Additive
Hyperforin	5	10	Additive
Ouabain	0.1	0.2	No Effect
Pazopanib	5	10	Additive
Blebbistatin	0.1	0.2	Additive
NVP-231	5	10	Additive
BRD-K96431673	0.1	0.2	No Effect
KU-0063794	5	10	Additive
LY-2157299	0.1	0.2	No Effect
Sirolimus	5	10	Antagonistic
ML312	0.1	0.2	Antagonistic
1S	5	10	No Effect
OSI-027	5	10	No Effect
Avicin D	5	10	No Effect
HMN-214	5	10	Additive
AZD7545	5	10	Additive
Rigosertib	5	10	Additive
BRD-K88742110	5	10	Additive
SID 26681509	25	50	Additive
ML320	5	10	Additive
BMS-270394	5	10	No Effect
SR1001	5	10	No Effect
PRL-3 inhibitor I	25	50	Antagonistic
Darinaparsin	5	10	No Effect
Nutlin-3	5	10	No Effect
PF-4800567	5	10	Antagonistic
Simvastatin	5	10	No Effect
KW-2449	5	10	Additive
TGX-221	5	10	No Effect
Ruxolitinib	5	10	Antagonistic
BMS-345541	5	10	Additive
Gemcitabine	0.1	0.2	Additive
SNS-032	5	10	Additive
Ch-55	5	10	No Effect
ML204	5	10	No Effect

Table 4. Immunomodulatory Effects of CTD² Compound Collection Subset			
Compound Name	Stock Concentration mM	Final Concentration μM	Modulatory Effect
Nelarabine	5	10	Additive
Ifosfamide	0.1	0.2	No Effect
Sotrastaurin	5	10	Antagonistic
BRD-K09587429	0.1	0.2	Additive
Erlotinib	5	10	Additive
Thalidomide	0.1	0.2	Additive
Ibrutinib	5	10	Additive
BRD-K29086754	0.1	0.2	No Effect
Ki8751	5	10	Additive
BRD-K49290616	0.1	0.2	Antagonistic
BRD1812	5	10	Additive
Fulvestrant	0.1	0.2	No Effect
AZD1480	5	10	Antagonistic
CBB-1007	0.1	0.2	No Effect
Necrostatin-7	5	10	No Effect
O-6-benzylguanine	0.1	0.2	No Effect
Isonicotinohydroxamic acid	5	10	Additive
Azacitidine	5	10	Antagonistic

Table 5. Immunomodulatory Effects of Compounds Screened in Dose Response Series			
Compound	Stock Concentrations	Final Concentrations	Modulatory Effect
Erlotinib	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00 μ M, 3.334 μ M, 1.112 μ M, 0.370 μ M	No Effect
I-BET151*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00 μ M, 3.334 μ M, 1.112 μ M, 0.370 μ M	Additive
Olaparib*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00 μ M, 3.334 μ M, 1.112 μ M, 0.370 μ M	Additive
KU-0063794	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00 μ M, 3.334 μ M, 1.112 μ M, 0.370 μ M	No Effect
Lovastatin	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00 μ M, 3.334 μ M, 1.112 μ M, 0.370 μ M	Synergistic
Panobinostat*	0.10mM, 0.033mM, 0.011mM, 0.0037mM	0.20 μ M, 0.066 μ M, 0.022 μ M, 0.0074 μ M	Additive
Neuronal Differentiation Inducer III*	25.00mM, 8.333mM, 2.778mM, 0.926mM	50.00 μ M, 16.666 μ M, 5.556 μ M, 1.852 μ M	Additive
Vorapaxar	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00 μ M, 3.334 μ M, 1.112 μ M, 0.370 μ M	No Effect
NVP-BSK805	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00 μ M, 3.334 μ M, 1.112 μ M, 0.370 μ M	Antagonistic

Table 5. Immunomodulatory Effects of Compounds Screened in Dose Response Series			
Compound	Stock Concentrations	Final Concentrations	Modulatory Effect
Doramapimod	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
Tipifarnib	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Antagonistic
BRD-K66453893*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Additive
PF-750	25.00mM, 8.333mM, 2.778mM, 0.926mM	50.00µM, 16.666µM, 5.556µM, 1.852µM	Synergistic
Navitoclax	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Synergistic
GSK-3 Inhibitor IX*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Additive
Compound 1541A*	5.50mM, 1.833mM, 0.611mM, 0.204mM	11.00µM, 3.666µM, 1.222µM, 0.408µM	Additive
SCH-529074	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
Temsirolimus*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Antagonistic
Trametinib*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Antagonistic
Oligomycin A	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
BRD-K27224038	0.10mM, 0.033mM, 0.011mM, 0.0037mM	0.20µM, 0.066µM, 0.022µM, 0.0074µM	No Effect
ABT-737*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Synergistic
ML006	25.00mM, 8.333mM, 2.778mM, 0.926mM	50.00µM, 16.666µM, 5.556µM, 1.852µM	No Effect
BRD-K41334119	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
BRD-K66453893	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
BRD-K04574331*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Synergistic
Spautin-1	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
Istradefylline	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
Sildenafil	25.00mM, 8.333mM, 2.778mM, 0.926mM	50.00µM, 16.666µM, 5.556µM, 1.852µM	No Effect
KU 0060648*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Antagonistic
BRD-K37390332	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
MK-2206*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Antagonistic
R428*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Antagonistic

Table 5. Immunomodulatory Effects of Compounds Screened in Dose Response Series			
Compound	Stock Concentrations	Final Concentrations	Modulatory Effect
AM-580*	25.00mM, 8.333mM, 2.778mM, 0.926mM	50.00µM, 16.666µM, 5.556µM, 1.852µM	Antagonistic
Cyanoquinoline	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	No Effect
MI-1	0.10mM, 0.033mM, 0.011mM, 0.0037mM	0.20µM, 0.066µM, 0.022µM, 0.0074µM	No Effect
Bexarotene*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Antagonistic
Dexamethasone*	0.10mM, 0.033mM, 0.011mM, 0.0037mM	0.20µM, 0.066µM, 0.022µM, 0.0074µM	Antagonistic
Ruxolitinib*	5.00mM, 1.667mM, 0.556mM, 0.185mM	10.00µM, 3.334µM, 1.112µM, 0.370µM	Antagonistic
PRL-3 Inhibitor I	25.00mM, 8.333mM, 2.778mM, 0.926mM	50.00µM, 16.666µM, 5.556µM, 1.852µM	No Effect

**Serial dose response verified modulatory effect*

Toward a Critical Philosophy for Children

By

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Citation: Funston, J. and Sager, A. Toward a Critical Philosophy for Children. Portland State University McNair Scholars Online Journal, Vol. 11, Year: 2017.

Abstract

I explore the role of Philosophy for Children (P4C) and critical pedagogy in pre-college education--what is the purpose of engaging with children on philosophical questions and how ought teachers ask such questions? This paper examines the current and past approaches of P4C through the work Brazilian educator Paulo Freire, and attempts to situate P4C within the framework of critical pedagogy, resulting in a synthesis I call "critical P4C." Implementing critical P4C has the capacity to create communities of inquiry around questions of agency and freedom that are central to critical pedagogy. Critical P4C offers strategies for engaging students in discussions relevant to social issues and breaks the boundaries between "school life" and the students' everyday life outside the classroom.

Keywords: critical pedagogy, philosophy for children, education

Introduction

Philosophy for Children (P4C), an effort by philosophers and educators to bring philosophy young people, was initiated in part to address concerns about the state of the mainstream education that they felt did not meet the demands of modern democratic society. P4C pioneers such as Matthew Lipman (1973) decided to introduce critical education into the curriculum by having students experience the process of reasoning about philosophical problems, providing them with a tool set that they could apply to new problems (Brandt, 1988; Beyer, 1990). Students would thus be more equipped to make rational choices that take into account the interests of others and themselves. P4C had the goal of introducing more voices of the community in conversation, because this has a greater chance of bringing about “a general and appropriately representative consensus” (Vansieleghem, 2005, p. 20). Children’s voices were particularly important to include in this conversation, in part for their natural capacity for questioning (Vansieleghem, 2005, p. 20) and because they often ask questions that might not occur to adults.

This paper argues for an approach to doing philosophy with young people that combines aspects of the American P4C movement with the tradition of critical pedagogy in the work of Brazilian educator Paulo Freire. Situating P4C within the framework of critical pedagogy can both increase the potential for P4C to improve young people’s reasoning skills and serve as a way to inject critical pedagogy into schools. P4C and critical pedagogy have overlapping goals of enabling students to understand the world around them and similar assumptions about the capacities for reasoning, questioning, and understanding they possess.

One of the justifications of public education is that it provides students with the tools they need to participate in civil society. Along with this, students are socialized into accepting the norms of society. Very rarely is any time spent with students engaging in a dialogue with their peers about the social world they will eventually join. Students aren’t given the chance to engage in social and political conversations in the classroom where an increasing amount of time is devoted to teaching for standardized tests (Kohn, 2000; McNeil, 2000, ch. 7; Aronowitz, 2008).

Furthermore, music, art, literature, and other components of a humanities education are taking a backseat to technical and vocational education (McNeil, 2000, ch. 4). The humanities can help students understand others through their language, culture, and history and how people have attempted to make sense of the world. Learning how to evaluate competing sense-making attempts and how to respond reasonably are paramount if society is to be predicated on a rational consensus arising out of a plurality of ideas (Vansieleghem & Kennedy, 2011, p. 176). Lipman (1973) felt that subjects such as mathematics and reading are crucial to good thinking, though they are not sufficient to develop the kind of thinking students need (p. 2).

The question for Lipman, and critical pedagogists, is not which subjects should or should not be taught but *how* they are taught that is primary; for Lipman the problem is that children are taught to think about a variety of subjects, but not to think about thinking, nor are students stimulated to think independently (p. 7). Correspondingly, educators in the tradition of critical pedagogy have applied their principles to a variety of topics, such as mathematics, attempting to teach the subject “for social justice” (Stinson et al., 2012, p. 79) or to “read the world” using that subject (Gutstein, 2003, p. 44).

In this paper, I will first provide a brief discussion of the P4C movement in the United States, beginning with the work of Matthew Lipman. That will be followed by an examination of critical pedagogy emerging from Freire’s *Pedagogy of the Oppressed*. Then I will discuss the similarities and differences between the two pedagogical traditions. I next argue that for P4C to be part a truly

emancipatory education, the principles of critical pedagogy need to be taken seriously. However philosophy lessons can provide an entry point for discussing the political and social issues that are central to critical pedagogy with students. What emerges is a synthesis of these pedagogy traditions that I label "critical P4C." Finally, I develop suggestions for teaching Critical P4C and speculate on possible implications of its practice in the classroom. Implementing critical P4C has the capacity to create communities of inquiry around questions of agency and freedom that are central to critical pedagogy. Critical P4C offers strategies for engaging students in discussions relevant to social issues and breaks the boundaries between "school life" and the students' everyday life outside the classroom.

This paper is meant to be accessible to primary and secondary teachers, particularly those who wish to engage their students in discussions of philosophy, particularly political and social philosophy. Specific background knowledge isn't necessary to facilitate these discussions, rather I will address the orientation the teacher should have toward her students, toward what counts as knowledge, and toward the goals of education. I will be focusing on the early thinkers in both P4C and critical pedagogy--for the former that is mainly Matthew Lipman and Gareth Matthews, for the latter, I will discuss the work of Paulo Freire--to show the principles and goals they share and how their differences can compliment each other.

Philosophy for Children

Proponents of P4C have generally agree on the premise of the movement--bringing philosophy lessons to pre-college students--however, they differ on what these lessons should look like in practice (Vansieleghem, 2005). Nancy Vansieleghem and David Kennedy (2011) divide the history of P4C in the US into two generations that differ both in their methodologies but also their understandings of what it is to be a child and the role that education plays in development. Matthew Lipman and the Institute for the Advancement of the Philosophy of Children spearheaded the first generation, emerging around the late 1960s, followed by the work of Gareth Matthews and others in the 1970s.

The second generation of P4C is marked by the use of philosophy as a "means of reconstructing relations of power and agency in the classroom, and for communicating and reflecting upon personal meanings, with a goal of facilitating the self-actualisation of conscious moral actors" (p. 173). Representatives of this generation, such as David Kennedy, Karin Murris, Karel Van der Leeuw, and Ann Margaret Sharp, tend to reject many of the assumptions of what counts as "philosophy." In "Can Children Do Philosophy?" Karin Murris (2000) writes that P4C is partly a criticism of the way of doing philosophy that Lipman compared to "memorising the inscriptions in a graveyard; the memorising of a collection of names and dates" (p. 274).¹ Murris argues that doing philosophy with children could lead to philosophy becoming more relevant and raises questions about the ideal philosopher; with solitary, independent rationality, P4C adds "dialogue, embodiment and the imagination" (p. 276).

The drive to bring philosophy into the educational curriculum in the United States began with the work of Matthew Lipman. Lipman's (1974) book, *Harry Stottlemeier's Discovery*, sought to develop methods for creating philosophical dialogues with young people. Soon after, the Institute for the Advancement of the Philosophy of Children (IAPC) was established at Montclair State University; its mission is to develop educational content, create affiliations with organizations whose work is related to P4C, and support research in teaching philosophy ("Institute for the Advancement of

¹ Murris (2000) makes a point to use the abbreviation *PwC* instead of *P4C*, the latter she associates with Lipman and the IAPC's work. *PwC*, for her is a broader term, inclusive of educators who do not agree that Lipman's method and the materials of the IAPC are best for doing philosophy with young people (p. 27).

Philosophy for Children (IAPC),”). P4C has been largely situated in a liberal education framework, one that promotes democratic values with the aim of preparing the students for their future citizenship (Bleazby, 2006) through the creation of a community of inquiry (COI) (Cevallos-Estarellas & Sigurdardottir, 2000) Lipman’s understanding of education was influenced largely by the philosophy of American pragmatist John Dewey and psychologists Lev Vygotsky and Jean Piaget (Juuso, 2007).

Juuso (2007) writes, “Matthew Lipman has constructed P4C based on the thinking of the best known advocates of early American pragmatism, Charles Sanders Peirce, John Dewey and George Herbert Mead. Especially the last two of them are the direct pivotal figures behind P4C” (p. 221). In fact, Lipman became fascinated with Dewey’s work while serving in the military and enrolled in Columbia University, where Dewey himself taught, to study philosophy. Lipman was impressed with the ‘practicality’ of Dewey’s thinking which convinced him to study philosophy (p. 16).

For Dewey, students excel when they are allowed to experience and interact with their education. In *Experience and Education*, Dewey (1938) makes a distinction between traditional and progressive education. Traditional education, like Lipman’s standard paradigm and Freire’s banking method, contains a body of information and skills that have been found to be correct, and the work of the teacher is transmitting this to students. Education is also responsible for the moral training of students by promoting habits that conform to previously-develop standards and rules of conduct (p. 17).

Dewey advocated for a new education that reflects the primacy of the role of experience in learning. Education arises through experience but not all experiences have the same educational value. Some experiences, including those that occur in traditional education, can be mis-educative. Dewey judges the quality of experience in two ways. One is the feeling of agreeableness or disagreeableness associated with that experience, but more importantly, is the effect that experience has on fostering or inhibiting future experiences (p. 23-25). Thus new education is “a development within, by, and for experience” (p. 28).

Lipman promoted using stories and narratives with philosophically-interesting content that were appealing to students as a catalyst for discussion. The students are then asked open-ended questions and invited to reflect on the text. The text is not necessary for a P4C discussion; many begin with a group activity, thought experiment, or just introducing a concept, such as *fairness* or *friendship*, that children are familiar with. However Lipman understood that parents and teachers who don’t have advanced degrees in philosophy would need some help in engaging philosophical discussions. He wrote *Harry Stottlemeier’s Discovery*, and number of other works, intended to stimulate critical thinking and moral judgment but also to show the importance of reasoning, questioning, and conceptual exploration.

Lipman incorporated the community of inquiry concept from Peirce and Dewey. Peirce intended the community of inquiry as a model of scientific inquiry; Dewey expanded the concept and applied it to education. In a community of inquiry, knowledge is within a social context and agreement between the inquirers is necessary for legitimization of that knowledge, unlike traditional models of inquiry that tend to be individual and solitary quests to know a static, unchanging world. Peirce (1992/1998), and other pragmatist philosophers, questioned the individualist idea of inquiry, that the solitary thinker can begin with doubt and end with only certainty. Peirce questioned this account for a number, instead modeling inquiry on science in which no individual is the ultimate judge of certainty. In science the question of certainty is put aside once scientists come to agree on a theory (vol.1 p. 29). Dewey (1897) believed that the challenges of social spaces were necessary for learning. The demands of social life cause children to conceive of themselves as a

member of a group, and to understand what their actions mean in social terms (p. 77). To Dewey the individual educational inquiry was necessarily situated in a community.

For Lipman (2003), a community of inquiry occurs in what he termed a *reflective paradigm* where teachers guide students in a reasonable and judicious manner with education as the goal. He contrasts this with the *standard paradigm*. In the standard paradigm, knowledge is transmitted to the student in discrete, unambiguous units from the teacher who stands as authority on what is or isn't legitimate knowledge (p. 18-19). By giving students the chance to think about the world, the reflective paradigm creates a space for a community of inquiry to form.

In the community of inquiry, students are provided a stimulus, such as a story, picture book, or a philosophical paradox, and are then asked to develop questions about aspects of the stimulus they find puzzling, problematic, false, or ambiguous. Following that, the students engage in discussion with each other to put forth ideas, respond to others' ideas, and ask new questions based on the ideas of their co-inquirers. Over the course of the discussion, the questions become more thoughtful and reflective, and ideally, the discussion would continue until all participants are satisfied with the answer. The role of the teacher is to ask guided questions and work to inspire students to think about the world in a way that builds on their ideas and those of their peers (Fisher, 2001, p. 71; Lipman, 2003, ch. 4).

Following Lipman, other philosophers and educators took philosophy with young people in new directions. Questions about the developmental process as it relates to philosophy were explored, and this led to different views children and philosophy. For Lipman, the child is a young philosopher who can benefit from doing philosophy. Lipman's approach was controversial in the sense that many think that subjects like philosophy should be avoided until students are a certain age.

In *Philosophy and the Young Child*, Gareth Matthews (1980) questions assumptions about children's cognitive capacity and development, particularly view that children master concepts progressively. The idea Matthews rejects is that children, as they develop, become more mature in their thinking process and that at certain ages children are unable to grasp certain concepts until their thinking has sufficiently progressed. The standard account of childhood development as understood by psychologists raises problems for doing philosophy with children. Psychologists might be skeptical about the capacity for children to understand philosophical ideas. Matthews responds by arguing that this misconstrues the activity of philosophy--it is hard to say what counts as "progress" in philosophy. Also, philosophical progress is not normally part of the standard development of people of any age group. Furthermore, when doing philosophy, children engage in conceptual explorations that many psychologists would deem childish or irrational since the goal is not to have more concrete views on the world that are consistent with one's peers, but rather to question the standard "conviction." Matthews writes, "... it is the deviant response that is most likely to be philosophically interesting" (p. 38).

Matthews, instead of doing philosophy *with* or *for* children, developed what he called "dialogues with children." Matthews and those of the P4C movement following Lipman, broke from earlier thinking by emphasizing the difference in the way children think and philosophize rather than working for analytic uniformity in reasoning. Children's philosophy, for Matthews, was "a form of desire--of the opportunity for children to explore and articulate what they have not said or even thought before," not an opportunity to engage in strictly logical thinking (Vansieleghem & Kennedy, 2011, p.176). In *Dialogues with Children*, Matthews (1984) has two aims in mind. One is providing adults with philosophical questions to ask children. Each chapter covers a particular topic from the canon of philosophy using anecdotal conversations between young people, generally aged eight to eleven, with Matthews' reflections. His second aim is to show an example of a relationship with children that is not based on condescension (p. 3).

Matthews (1994) saw children as capable philosophers due to their inherent sense of wonder, and that what they are doing is legitimately philosophy. When children have philosophical dialogues, what they are doing is not "proto-philosophical, or quasi-philosophical, or semi-philosophical, it is the real thing ..." (p. 34). Matthews writes that it is difficult to categorize philosophical thinking as cognitively 'mature' or 'immature.'

In the first generation of P4C, children are capable of thinking philosophically in a way that resembles adults, and bringing philosophy into the classroom gives them a chance to practice reasoning and develop moral judgment. After Lipman, philosophers working with children began to value children's thinking because it differs from adult thinking. Matthews (1984) was interested in the ways children think that are not captured by developmental psychology, because they are "primarily concerned with the normal and the standard" (p. 116). There is little agreement on counts as normal and standard thinking in philosophy, so Matthews argues that developmental psychology might have nothing to say about the philosophical capacities of young people (p. 118). It is the unique ways in which children understand and take part in philosophical questioning, that differed from those of adults, that became the crucial factor. Children, because they think differently than adults, have contributions to add to philosophical discussion that "may be quite as valuable as any we adults have to offer" (p. 3).

Philosophy in the second generation, Vansieleghem and Kennedy write, "appears as a form of communal deliberation that stimulates critical reflection on existing power relations, these being envisaged as historical constructions that are or should be open to reconstruction" (p. 176). Dialogue becomes the core of the educational process with the goal of creating "a free space in which all persons involved in the inquiry have an equal chance to bring their arguments forward in the interest of a an emergent, rationally founded consensus" (p. 176). Instead of being presented with the idea of what the philosopher *is* and taught to emulate that, children in dialogues are shown and given a chance to participate in what philosophers *do*. In this generation, children are encouraged to question even the norms of human thinking and action--the dialogue is a space where children are able to ask "why?" such and such is the case.

For example, Matthews (1984) compares a story that he presented to a class of twenty adults to a group of seven children. The story centers on whether or not plants can have desires or wants. One difference between the responses from the two groups is the commitment to a divide between thinking literally and figuratively. Adults could concede that plants figuratively have a desire for water, but not literally. Children, on the other hand, were more free in their use of imagination to believe that plants *could* have desires. Adults might know more about the actual life of plants, such as the biochemistry of photosynthesis, which is important for the question of whether they can desire; but children excel in dialogue by more readily thinking beyond the actual to the possible life of plants (p. 18). With Matthews, children's insights are valuable in relation to the gap between how they think and how adults think.

The second generation emphasizes the importance of critically engaging with the concept of *thinking* and on the relations of power that underlie these norms (Vansieleghem and Kennedy, 2011, p. 176). Accepting the idea of objective truth that is true for anyone and for all time is not the goal for the new generation of P4C. Instead there is a focus on the varieties of thinking done by people in different contexts. A rational exchange of opinions is still the goal, but, as Vansieleghem and Kennedy (2011) point out, "[t]here is, however, no longer understood to be one best way of reasoning, for collective reason, it is held, is shaped and articulated by the social community in which it operates" (p. 178). So rather than be taught there is one particular method of thinking about a problem, philosophy helps children to reflect on their own views and relate them to others.

Educators in this generation of P4C stress the importance of children's participation in a common reality that is increasingly interconnected and rapidly changing (Van der Leeuw, 2009, p. 113).

This generation of P4C has much in common with the tradition of critical pedagogy, particularly in promoting dialogue and the resistance to an epistemology that sees knowledge as concrete, static, and unambiguous. In the new P4C, children philosophize about different ways of conceptualizing the common reality that we all share. No one perspective necessarily has the privilege of "truth."

With critical pedagogy the assumption of a stable common reality is questioned, and students and teachers are encouraged to think about how we shape the common social reality. Society is not just a thing that is there, waiting for children to become adults and take part in preordained roles; critical pedagogists draw attention to the subjectivity of people within the public sphere and the forces of oppression and domination that silence some voices but not others. Freirean critical pedagogy has unique contributions to add to the project of P4C but also raises questions about the role of teacher and student in a philosophical dialogue. Using Freire as a "starting point" to move beyond the current generation, critical P4C intends to go further, not just questioning the distinction between *adult* and *child* in philosophical inquiry but also the between *teacher* and *student* in education.

Critical Pedagogy

Critical pedagogy stems from Paulo Freire's efforts teaching *campesinos* in Brazil. Freire's theory of education is very intricate and touches on nearly every aspect of human existence in the world. Here I will limit myself to considering aspects that are relevant to contemporary educators, and not on, say, issues pertinent to activists, progressives, and others not engaged in teaching-related activities. Freire examined the connection between education and poverty and was led to believe that education held the potential for promoting social justice and transforming society. Education could not be separated from political considerations nor could it be considered neutral.

For Freire, the purpose of education is human liberation and begins from experience. Education has the capacity to reinforce the passivity of students or challenge social forces that limit human liberation (Wallerstein, 1987, p. 33). He calls the dominant non-dialogic style the "banking method" of education. The teacher is the store of knowledge which is "deposited" into the students' minds. The students later show they have learned by repeating that information back to the teacher (Freire, 2005, ch. 2).

This, Freire argues, maintains hierarchical systems of domination and oppression. He advocates for a liberatory teaching that he calls "problem-posing" education that rejects deposit-making. Instead the focus of education is "the posing of the problems of human beings in their relations with the world" (p. 79). Problem-posing education sees the essence of thinking as *intentional*, that is about things or pointing to things in the world, and *relational*, connected to others via communication.

The principles of critical pedagogy establish relationships between student-teachers and teacher-students. Knowledge is constructed in the educational interaction, rather than transmitted to students from teachers. Teachers who wish to be progressive ought to be concerned with pedagogy, or their method of teaching. The teacher, to avoid becoming reactionary and reinforcing authoritarian practices, must be aware of how she is teaching.

For Freire (1987), there is no neutral position; the progressive teacher must have a political and pedagogical understanding of teaching (p. 212). When the goal is to teach students how to learn,

instead of just transmitting information that is to be memorized, progressive educators should work toward eroding the dichotomy between teacher and student. This is because the students must "enter into the discourse of the teacher, appropriating for themselves the deepest significance of the subject being taught (p. 213). The teacher has to give up the exclusive authority to name the world," and not think of her student as an "empty vessel to be filled," but as an active participant in learning how to learn (Freire, 2005, p. 79).

Freire's major work, *Pedagogy of the Oppressed*, does not provide a simple plan for teaching, rather the attitude the teacher, or *facilitator*, adopts toward her students and the educational process is the main concern. The role of teacher changes from an authoritative source of truth to a facilitator of learning. The pedagogical roles change in a Freirean project; the teacher-of-the-students and the students-of-the-teacher become teacher-students and student teachers. For Freire, critical pedagogy cannot be imported but must be reinvented anew each time it is practiced. The content of the discussions is based on the world the students find themselves in. The facilitator of the critical pedagogical project doesn't employ prepackaged lesson plans but must investigate her students' environments and lived situations prior to the class session.

Without knowing something about the students' lives, we risk further alienating them from an educator that from their point of view seems disconnected from the real world. Patricia Reynolds (2007) argues that teachers should go even further than this and work to alleviate problems that students face in their lives. The No Child Left Behind Act has caused schools to focus on teaching for standardized tests which tends to exclude certain topics, such as the distribution of power in society, from the curriculum (p. 53). The problems posed in problem-posing education are those that teachers have just as much to learn as students, and, in Freire's view, teachers need to abandon some of their epistemological authority so they can learn along with students in a dialogue.

Dialogue, in Freire's view, is the situation when people come together to name the world they are in. Naming the world is a continuous process--the named world appears again and requires a new name. In a dialogue this process of action and reflection works toward finding the authentic word. Freire calls this work *praxis*. For this dialogue to occur, however, certain conditions must be in place. Dialogue fails when some are denied their right to speak, to do so is to dehumanize them, since Freire views the act of speaking to be fundamental to human beings. Dialogue is impossible when only some members have ability to speak with authority about the world and when others' voices are ignored (p. 88).

Freire also emphasizes the importance of love as a component of dialogue. Love is the courage to be committed to others whose voices have been denied. For the person attempting a dialogue, love of life, the world, and people is essential--"[l]ove is at the same time the foundation of dialogue and dialogue itself" (p. 89). Love, in this context, means listening to and valuing the voice of the oppressed. Dialogue also requires humility, as in the absence of arrogance. The educator who places herself above others or who is worried about being displaced from her position of privilege closes herself off from the dialogue. A lack of humility creates a distance from the people, and prevents her from taking part in the naming of the world. Freire warns against thinking in terms of "utter ignoramuses" and "perfect sages" rather "there are only people who are attempting, together, to learn more than they now know" (p. 90). Humility is letting go of the arrogance of being the teacher and the wish to direct the dialogue in directions that silence some voices.

Faith is another requirement for dialogue, however what Freire writes of is a faith in the power of humans to engage in the naming and renaming of the world and faith in the work of all humans to free themselves from oppression, that is "to be more fully human" (p. 90). Freire's work is inspired by his Catholic faith, though the faith in a dialogue is a trust in people, and is not connected to any

specific religious tradition. It is a faith in the idea that people want to be free and the way to become so is through dialogue. Love, humility, and faith in others together create trust, another necessary component of dialogue. What the speaker says should match her true intentions; words should not be taken lightly (p. 91). The participants in the dialogue need to trust each other to be speaking honestly in order to create a space that welcomes all voices.

Dialogue cannot occur without hope. There must be a sense that something will come out of the dialogue. Without hope, the dialogue will be "empty and sterile, bureaucratic and tedious (p. 92). Hope prevents people from falling into despair due to their incompleteness. For Freire (1998), hope causes humans to be seekers and explorers as it is "necessary impetus" of the project of becoming more fully human (p. 69). Lastly, a dialogue needs critical thinking; however, Freire's sense of critical thinking differs from the common use of the term as implying the use of logic and analytical thinking to evaluate evidence. For Freire (2005), critical thinking is the reflecting component of praxis but is never separate from action. To think critically is to see the "indivisible solidarity" that connects people to the world (p. 92). Humans are not outside of a world of static essences, rather reality is dynamic, transforming through the action of people.

Freire reinforced these requirements for dialogue when addressing the coordinators of "cultural circles" in rural Chile. Freire (1971) wrote, "In order to be a good coordinator for a 'cultural circle,' you need, above all, to have faith in man, to believe in his possibility to create, to change things. You need to love. You must be convinced that the fundamental effort of education is the liberation of man, and never his 'domestication'" (p. 61). The cultural circle shouldn't be thought of like a traditional school. The teacher is not a provider of absolute knowledge to passive ignorant students. In a cultural circle, discussion is lively and creative, where participants have varying levels of knowledge but everyone works together to know more.

Critical pedagogy, and the methods developed within its framework, can help us examine the structure of educational practice and correct for what Freire (2005) calls dehumanization, which "is a distortion of the vocation of becoming more fully human" (p. 44); critical pedagogy is intended to be a tool for both the oppressors and the oppressed to become aware of their common dehumanization (p. 48). Freire notes that there are many well-meaning educators who use in the banking method of education but must abandon this method to fully engage in the struggle for liberation.

Education is a key part of this struggle since liberation cannot be given to the oppressed, instead it comes as a result of their own 'critical consciousness.' (p. 67). This consciousness, which is normally left untranslated as *conscientização*, is a deep "attitude of awareness" (p. 109). *Conscientização* is the process of learning to see dehumanizing and oppressive elements in the political, social, and economic world and to take action against them (p. 33fn). The first step to a critical consciousness is literacy. Learning to read can be understood in the sense of grasping of letters and symbols, but there is a deeper level of literacy Freire is concerned with. There are those who are "illiterate" in the sense that they can read the words on a page, but do not fully understand the meanings of what they read, such as someone reading about worker layoffs and corporations relocating their factories overseas and not connect these two points. Literacy here means not just reading the newspapers but not being taken in by biases and propaganda. *Conscientização* involves a recognition of how the oppressed have been silenced and taught to internalize a negative image of themselves.

There are a number of conceptual links between Freire's work and each of the generations of P4C in the United States. Below I will examine these links in an effort to push the P4C movement in a more critical direction; following that, I will point out the major differences of the traditions.

Freire and Lipman

Freire and those within the P4C movement share an antipathy towards the traditional structure of the classroom and its method of knowledge transmission--what Lipman calls *the standard paradigm* and Freire *the banking method*. This classroom is dominated by the teacher who is the source of legitimate knowledge and the judge of what counts as an acceptable topic of study. The ideal student in this classroom is a passive receptacle of information, skills, and values. Lipman and Freire reject the view of knowledge as static, instead, stressing the importance of dialogue in the construction of knowledge; however, Lipman's critique of schooling is concerned with the authoritarian structure of the teacher-student relationship, and Freire, though he is also a critic of hierarchy in educational projects, emphasizes the importance of including the voices of marginalized and dehumanized people in dialogue.

There are, however, differences between the community of inquiry and Freire's vision of the cultural circle. In a community of inquiry, the teacher plays a role in steering the discussion and in deciding the topic to discuss. The teacher stands apart from the other participants and retains a level of epistemic authority. The coordinator of a cultural circle has a diminishing role; in the dialogue, the hierarchy breaks down and her status as an authority over her students fades--"the teacher-of-the-students and the students-of-the-teacher cease to exist and a new term emerges: teacher-student with students-teacher" (Freire, 2005, p. 80).

The idea of critical thinking has different meanings for critical pedagogy and P4C. The latter is firmly within the Western tradition of critical thinking that focuses on a specific set of reasoning skills that are the foundation of the entire curriculum. Students with these skills are able to apply them to the study of any subject. A critical thinking educational project would focus on teaching students to be rational thinkers who are capable of using the reasoning skills they learned to evaluate new evidence. Burbules and Berk (1999) write that the critical thinker "is something like a critical consumer of information; he or she is driven to seek reasons and evidence" (p. 47). The critical thinker in this tradition is ultimately concerned with minimizing false beliefs.

In critical pedagogy, critical thinking goes beyond changing the individual to thinking about relations between teachers and students and power inequalities within institutional structures--"the endeavor to teach others to think critically is less a matter of fostering individual skills and dispositions, and more a consequence of the pedagogical relations, between teachers and students and among students, which promote it; furthermore, the object of thinking critically is not only against demonstrably false beliefs, but also those that are misleading, partisan, or implicated in the preservation of an unjust status quo" (Burbules & Berk, 1999, p. 49). For critical pedagogy, thinking critically means thinking politically as well.

Critical P4C develops critical thinking in both these senses, to provide a set of reasoning skills and dispositions that aid in uncovering injustice within the status quo. We must reject, however, the idea of a static world; the critical thinker is not a detached observer and evaluator. The analysis of evidence in critical thinking happens in the world that is being read. Freire's work was concerned with teaching literacy, both as reading words but also "reading the world" as a first step in naming and renaming the world. Western critical thinking, on the other hand, is most commonly applied to scientific and technical education.

There have been attempts to apply critical pedagogy to other fields, for example mathematics; these question the supposed "value-free" nature of mathematical knowledge and increase mathematical literacy (Frankenstein, 1983; Cohen, 1997; Stinson et al. 2012). Teaching a critical mathematics looks at the ways mathematics and statistics are employed, especially in politics and

the media--*what claims are they being used to support, who gets to decide what counts as legitimate mathematical knowledge, and who is excluded from the field mathematical study.* Frankenstein writes that critical mathematics rejects both the "common sense" view that mathematical truths is discovered and not created, and the cynical view that sees statistics as "self-serving lies" (p. 10). Instead a Freirean approach reflects on the roles of subjectivity and objectivity in the creation of mathematical knowledge. In her critical mathematics course she uses examples such as the government making military spending appear less through the manipulation of statistics or how significance tests can be used to make differences, for example between the intelligence of ethnic groups, appear significant and meaningful, when there is not a strong correlation (p. 10). Critical P4C takes the opposite route of incorporating elements of critical thinking in the Western sense into a critical pedagogy project, that is adopting 'value-free' reasoning skills for a value-laden dialogue.

Lipman's P4C finds itself within a liberal framework of thinking about education, heavily informed by Deweyan principles. Education, in the liberal view, can fix problems by making students that are more rational and more equipped to evaluate evidence. However the demands of the modern school have forced some aspects of Dewey's pedagogy to be sidelined. The school, for Dewey, should be teaching through experiences which beget other experiences, having a transformative effect on the world. Freire's work is a part of the radical tradition of education that examines oppressive structures in the world and seeks a way to change them. Liberal education changes individuals to better navigate their social environment; radical education questions why the environment is structured in a way that dehumanizes some and thinks of alternative ways of organizing people.

Critical Philosophy for Children

Teachers intending to coordinate a dialogue would need to do their research beforehand. Critical P4C should explore questions that face the young people in their day-to-day experience. However the facilitator should not refer only to development psychology research to construct a view of the child, as we saw with Matthews, such accounts miss what makes children's philosophical insights valuable. Also Freire would argue that the "standard and normal" accounts of developmental psychology denies the voices of children who have been silenced by oppression. Freire advises facilitators and coordinators to integrate with the community prior to any educational activity. So prior to beginning the pedagogical process, facilitators must research the students' lives.

There are multiple levels of research that can be done. First is speaking directly to the students. What philosophical questions do they have? How much do they know about philosophy and philosophers? What media do they consume? How aware of politics and social issues are they? What do they want to learn? Second, meet with parents and teachers. What is the social environment of the classroom? What are the social dynamics of the students? What are they talking about? Third, study the community and larger cultural context the students are situated within. To what social classes do the students belong? What are the dynamics of race and class in the students' environment?

Once this has been satisfactorily completed, facilitators and students can begin the lesson, usually sitting together in a circle to emphasize the break from traditional hierarchic roles. The lesson can begin a number of ways, with a reading from text, using art or a picture book as the catalyst, or a warm-up activity. The facilitator should first direct questions to the group as a whole, then to individual participants who may be in need of motivation. These questions should build upon the answers given in the discussion. The facilitator should limit this unless it is absolutely necessary; the goal is to incite enough for the dialogue to sustain itself. At some point, the facilitator is no longer the primary figure in the dialogue, and she becomes a member of the group (Freire, 1971).

This is in many ways an ideal situation. It is unlikely that a dialogue will reach the point where everyone is completely equal; the dialogue exists within a society where adults have authority over children and where people are treated differently based on race, gender, and class. A critical P4C dialogue might never overcome these influences, but this should be the discursive goal that participants are working for. Some might argue that the adult-child relationship adds another complication, that children need positive authority figures in their lives. For critical P4C, adults should model the kind of thinking the dialogue aims at, that is, retaining the mindset of love, faith, humility, trust, and critical thinking that Freire stressed.

When dealing with children, the adult should see a difference between correcting a child for being wrong about some factual claim and engaging in wrong behavior. The former should be discussed; the latter implies a limit to what dialogue with children can achieve. There are points when the teacher-of-the-students must reappear as a figure of authority, for example, if a student physically assaults another. A dialogue seeks to find a balance between the goals of ideal discussion and the reality of childhood. The point when the adult should step in as an authority figure is unclear. Physical violence or self-destructive acts should be prevented but is there a line of thinking that children shouldn't engage in? There is no easy answer to this question. Freire would urge us to consider why some topics are not up for discussion by children and what effects this might have on silencing children's opinions or questions.

Knowledge, in critical P4C, is socially constructed and legitimized. A dialogue thus should lead to questions of not only the hierarchical structure of the classroom but the larger society as well. Social norms should be a subject of discussion and students should question these norms to uncover their hidden meanings. The dialogue must be a safe space for students to engage with the peers about controversial topics, and, in the spirit of a community of inquiry, build upon each other's ideas.

Remember that *conscientização* is the goal for all participants in the dialogue. The teacher's goal should be to become a student-teacher with teacher-students. Letting go of the authority that comes with the role of teacher can be daunting, and many educators fear that they would lose control of the classroom in the process. Lipman, Matthews, and Freire would respond with an appeal to an inherent desire of students to engage in dialogue, that children and, for Freire, the oppressed want to be respected intellectually. An important consideration is that the shift from authoritarian teacher to co-inquirer doesn't happen immediately; the teacher's authority wanes as the students become used to the new dynamics of their relationship to the teacher.

Freire writes that a component of banking education is the teacher's confusion between their intellectual authority with professional authority (2005, p. 73). In modern public education, students have been socialized to accept this same confusion. Thus students may resist the dismantling of intellectual hierarchy or assume that this also means the end of professional authority of the teacher. Both of these cases pose a problem to creating a dynamic community of inquiry. In the former, students may refuse to contribute to the discussion opinions or arguments that haven't been justified through the banking education that have experienced. In the latter, students may engage in disruptive behavior (cf. Giroux, 1983).

This issue is discussed by Freire and other theorists; however, when working specifically with younger children, it takes more prominence. Future work in this area is important for critical P4C. Freire notes that in a dialogue arguments based on authority are invalid and that for it to function, "authority must be *on the side of freedom*" (2005, p. 80). Perhaps adult learners are more apt to accept the distinction between professional and intellectual authority, hence the reason that there is little attention paid to how to convey this to adults. For Freire, 'reading the word and the world'

is the human vocation; so people have an innate desire to engage in dialogue and the facilitator's role is to break them out of the banking model. This process is likely to take a different shape when working with children who have a closer engagement with banking education, assuming most of their education thus far has fit that model. How can educators explain this distinction to children to accept authority in some situations--when a parent says not to run with scissors--but not others, such as when a banking-model classroom? Do children need positive authority figures and how can critical P4C facilitators fulfill that role? What are the limits of inquiry with children? Should children be forced to accept certain ideas without dialogue or debate? Critical P4C practitioners and theorists should carefully consider these questions.

As an example of a P4C course with critical pedagogy in mind, working with Portland State University's Philosophy Department, my colleagues and I engaged 12- to 15-year-old students in a number of philosophy lessons centered on life in a city. For their final project, groups of students designed their own ideal cities. The students' utopias showed a wide range of creativity. Instead of thinking how to take the pre-existing concept of *city* and build on that to make it more efficient, students rethought the the goals and principles of a city. One city was focused on maximizing human enjoyment and combatting boredom, while another attempted to create an egalitarian society without sacrificing productivity. The students demonstrated both lateral and critical thinking. The cities showed the students' capacity to, on one hand, think unconventionally about problems and, on the other, apply rigorous thinking to that problem.

Conclusion

Why implement a critical philosophy for children? For P4C practitioners and theorists, incorporating critical pedagogies can be helpful for advancing the movement in a direction that is specifically concerned with human freedom. Critical pedagogy is controversial because of its unabashed political nature. Freire and his followers are heavily influenced by thinkers in the Marxist tradition. However, educating is not a politically-neutral occupation; Freire (1987) believed that the neutral teacher, in not being literate of the political nature of her actions, serves the interests of power (p. 212). Applying a Freirean reading to P4C can show us the hidden contradictions that may be present, in a sense being *critical of critical thinking*. Educators that are committed to helping their students become more liberated need to be vigilant to the ways that they might be inadvertently reinforcing dominance and oppression.

Working with children adds some complications to a critical education project. Completely eliminating the teacher-student hierarchy in the classroom is an unachievable ideal. There might even be a necessary distinction that has to be in place. The teacher can play a role in modeling positive types of intellectual behavior. The student sees that the teacher is not equal in some respects. When inequality is seen as essential, that is, there is something internal to the student that makes her less than the teacher, the motivation to want to learn suffers; if the student believes there is some unchangeable flaw in her character, she'll be cynical about the use of education to better herself. In a dialogue the goal should be to question hierarchies based on race, gender, class, and status in society. P4C begins from an authoritarian, top-down model of education and works toward a less hierarchical model. Using a critical pedagogy with children requires us to decide how egalitarian the classroom can be. In public schools, the demands of the curriculum will be more extreme, particularly regarding standardized tests, though alternative schools, particularly those that are student-centered, provide more opportunity to expand education beyond the standard paradigm and the banking method.

Lipman questioned the dichotomy between child and adult; he claimed that children could do philosophy and could employ reasoning if given the chance. Children are able to think like adults think, albeit with less complexity and depth. In Matthews, we see childhood as a state of wonder.

The insight is not that children can follow the same line of reasoning as adults, but that children sometimes think in terms that are outside of what normally counts as reasoning. Through dialogue with children, insights develop that can provide philosophically-interesting pathways for adults to explore and “results in a profound critique of the normative adult view of the child and of its expression in the ‘science as usual’ of developmental psychology” (Vansieleghem & Kennedy, 2011, p. 176).

The second generation of P4C turns to questions of power relations within the context of education, personal meaning, and self-actualization. This generation builds upon the work of its predecessors, adapting their ideas to the new socio-political environment; in a sense advocates of this generation are updating the work of Lipman and Matthews for the contemporary world. However they also criticize aspect of earlier generations, particularly Lipman’s emphasis on analytical reasoning which seems to have little connection to the goal of seeking personal meaning. For theorists and educators of the second generation, philosophy can’t be confined to the classroom. Reasoned deliberation is necessary in many aspects of life in an information-rich, increasingly-complex world (Van der Leeuw, 2009, p. 111-113). P4C from this approach attempts to provide children with the skills to be rational actors in the world. Critical P4C shares much in common with the second generation, and uses its predecessors as a foundation to rethink prior assumptions about teacher and student.

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Sulfolobus Spindle-Shaped Virus 1 Growth Kinetics

By

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Citation: Nader, S.M., Stedman, K. Sulfolobus Spindle-Shaped Virus 1 Growth Kinetics. Portland State University McNair Scholars Online Journal, Vol. 11, Year: 2017

Abstract

Geothermal and hypersaline environments are rich in viral particles, among which spindle-shaped morphologies predominate. Currently, viruses with spindle- or lemon-shaped virions are unique to Archaea and belong to two distinct viral families. The larger of the two families, the *Fuselloviridae*, encompasses spindle-shaped viruses with very short tails, which infect *Sulfolobus solfataricus* and close relatives. Sulfolobus spindle-shaped virus 1 (SSV1) is the best-known member of the family and was one of the first hyperthermophilic archaeal viruses to be isolated. However, our knowledge of fuselloviral life cycles and the relationships between these viruses and their hosts is still limited. As a result, to establish one-step growth curves to study virus replication kinetics and to investigate the mechanism of host binding, the adsorption kinetics of wild-type SSV1 to its Sulfolobus host needed to be determined.

Keywords: SSV1, adsorption kinetics, binding assay

Introduction

Prokaryotic-infecting viruses are the most predominant biological entities on Earth. Like all viruses, they are not able to replicate on their own, but require a host cell to release their genome and reprogram that host to produce more viruses. Viruses are thus intracellular parasites that have symbiotic relationship with all three domains of life (*Archaea*, *Bacteria* and *Eukarya*). Moreover, viruses often imply a co-evolution with their host and exert natural control of the dominant populations (Lobo et al., 2009; Sharp & Simmonds, 2011; Best & Kerr, 2000). In some ecosystems, viruses are known to serve as organic matter to lower parts of the food web and they are able to modify the fixation and cycling of key elements, such as carbon, phosphorus and nitrogen globally (Wilhelm & Suttle, 1999). Thus, viruses can have important ecological impacts. Fundamental studies of viruses are crucial in a broad range of biological sciences, such as biotechnology and molecular biology, health and medicine, ecology and evolution.

The viruses of *Archaea* in particular exhibit completely novel and unique morphologies and forms (Prangishvili and Garrett, 2005). Shortly after the recognition of the *Archaea*, research focused on isolation of viruses and viral particles from extremely hot, low pH or hyper saline ecosystems (Woese et al. 1978; Albers et al. 2013). In many geothermal hot springs around the world, members of the *Fuselloviridae* family of viruses are found to be most abundant. The archetype, *Sulfolobus* spindle-shaped virus 1 (SSV1), was isolated from a geothermal hot spring in Beppu, Japan and found to contain a 15.465 kb circular double-stranded DNA (dsDNA) genome, containing 35 open reading frames (ORFs), of which the products of only five have been assigned functions (Iverson and Stedman 2012; Queminn et al., 2015). The genomes can be found as episomes, integrated into the host genome, or packaged as enveloped virions. SSV virions are generally lemon or spindle-shaped, about 60nm by 90nm in size, with sticky tail-fibers at one end (Ceballos et al., 2012; Stedman et al., 2015).

The hosts for most *Fuselloviruses* are members of the *Sulfolobales*, a widespread genus of archaea. Brock et al. first described this hyperthermophilic and acidophilic sulfur-oxidizing Creanarchaeote in 1972. They isolated several *Sulfolobus* strains from thermic and acidic habitats in the Yellowstone National Park (USA), El Salvador, Italy and Dominica (Brock et al., 1972). The genome of *Sulfolobus solfataricus* from Pisciarelli, Italy, the main host for SSV1, is completely sequenced and its growth is optimal between 70°C and 80°C and at pH 2 to 3 (She et al., 2001). *Sulfolobus* have a proteinaceous Surface layer or S-layer with hexagonal symmetry which is strikingly similar to the geometry of the putative tail structure of SSV1 (Stedman et al., 2015).

Although spindle-shaped viruses represent one of the most prominent viral groups in *Archaea*, very little is known about the life cycle of SSV1 and its relationship with its host. The gold-standard for examining virus replication cycles is the so-called one-step growth curve, whereby host cells are simultaneously infected with virus, washed to remove free virus, and then virus production followed over time to determine the average kinetics of virus replication. The first step of such a one-step growth curve, and the very first step of infection is when viruses bind to cells. It is this step, the virus adsorption period, which is the focus of this study.

Knowledge of host-cell binding will allow one-step growth curve experiments to determine the kinetics of SSV1 replication. Moreover, how SSV1 interacts with its *Sulfolobus* host at high temperature (80°C) and low pH (3) is unknown. Determining binding kinetics will also allow imaging experiments where SSV bound to *Sulfolobus* at the very first step of the infection process can be imaged with transmission electron microscopy. The mechanism by which the positively supercoiled SSV1 genome is released into the host cell is also not known. Being able to isolate freshly bound SSV1 may allow insight into this critical step in virus infection.

Once wild-type (WT) SSV1 has been characterized, this will allow us to work with different SSV mutants and identify the growth characteristics of these mutant viruses. Optimization of binding may also allow the production of large numbers of SSV1 virus particles, which will be critical for the determination of a higher resolution structure than currently available and allow testing of the hypothesis that the capsid of the SSV1 virus is similar in overall morphology to that of the nucleocapsid of HIV-1 (Stedman et al., 2015).

Methods

Growth of Sulfolobus cultures:

Sulfolobus cultures were grown from small amounts of frozen cell stocks (~50 µL) and inoculated into 5 mL of Yeast-Sucrose (YS) medium at pH 3.0-3.2, then incubated in a 75° C shaking incubator (Gyrotory water bath shaker G76, Speed 4.2, New Brunswick Scientific) until turbid (48 – 96 hr) (Iverson & Stedman, 2012). Generally, cells were then transferred to a larger volume of YS medium (50 – 100 mL) in long-neck Erlenmeyer flasks and incubated until the desired OD_{600nm} was reached.

SSV1 production in stably-infected S441 cells:

S524 (*Sulfolobus* strain S441 infected with wild-type SSV1) was cultured from frozen stock in 5 mL of YS medium at 75° C until turbid (~72 hr) (Iverson and Stedman, 2012). This culture was transferred to 50 mL fresh YS medium in a long neck flask and grown for 120 hours. The cell density (OD_{600nm}) of S524 was 0.854 when cultures were removed from high temperature. Cultures were centrifuged for 10 min at 6,000 x g (Eppendorf 5810R) at room temperature. The supernatant was collected and split into two aliquots of equal volume, and viral titer (PFU/mL) was measured (Schleper et al., 1996). The average viral titer at each time point was calculated from plaque assays done with cell-free supernatants.

Viral binding to host:

A culture of S441 was diluted with YS medium to OD_{600nm} of ~0.13 and allowed to recover at 75° C for 2 – 4 hours until the optical density reached 0.16, a value experimentally determined to equal 10⁸ *Sulfolobus* cells/mL (Iverson & Stedman, 2012; Prangishvili et al., 1999). 40 mL of the S441 culture was added to 4 mL of SSV1 to yield the desired MOI of 0.1. Negative controls were prepared using an equal volume of YS medium in place of the host cells. Following addition of virus, cultures were incubated at 75° C and the viral titers were measured at various time points throughout the experiment. Samples (1 mL) were prepared for plaque assay by pelleting the cells via centrifugation (5 min) at 6,000 x g room temperature and carefully collecting the virus supernatant (~500 µL) by pipet.

Plaque Assays

Virus titers were measured via plaque assay as in Schleper et al. (1992) and Stedman et al. (1999). Briefly, an S441 culture was diluted with fresh YS medium to OD_{600nm} 0.35 – 0.38 and allowed to recover at 75° C until the cell density reached ~0.40 (2 – 4 hours). Cells were centrifuged at 3,000 rpm (Eppendorf 5810R) for 5 minutes and pellets were re-suspended in a volume of YS resulting in ten-fold concentration of the cells. Purified virus suspensions were serially-diluted in YS liquid medium. Virus dilutions were prepared by ten-fold serial dilution of a virus stock or the collected samples at different time points in YS medium. 100µL of each SSV1 dilution were added to 500 µL of 10X concentrated *Sulfolobus* cells and 5 mL of soft-layer was added and the mixture was quickly poured and evenly distributed on a warm YS Gel-rite plate. So-called “Soft-layers” were allowed to solidify at room temperature for 20 min and were then placed in a sealed plastic box with a moist paper towel and incubated for 48 hours at 27° C. Plaques began to appear after 24 hours but were most visible after 48 hours of incubation. Plaque Forming Units (PFUs) were counted and the titer of the original purified virus suspension (PFUs/mL) was calculated as follows:

$$\text{Virus titer} = \frac{\text{Plaques observed}}{\text{Volume added} * \text{Dilution Factor}}$$

Results and Discussion

Infection of S441 cells with SSV1 at a low MOI was performed to measure the kinetics of viral adsorption. Briefly, 4 mL of SSV1 with a titer of 2.0×10^8 PFU/mL was isolated from the virus preparation made from culture of S524 (as above) and was mixed with 40 mL of S441 cells ($OD_{600nm} = 0.16 = 10^8$ CFU/mL) for an MOI of 0.2. An uninfected control was also prepared using an equal volume of YS in place of virus supernatant. The infected SSV1 cultures and the uninfected control were simultaneously grown at 75° C for 4 hours with shaking in long-neck flasks and samples (1 mL) were taken after every 30 minutes. The samples were centrifuged at high speed ($6,000 \times g$; Eppendorf 5810R) to pellet cells and the virus-containing supernatant was collected to measure the SSV1 titer via plaque assay (typical plaques are shown in Figure 1). The initial titer of the infected sample (immediately after dilution) was low ($\sim 10^1$ PFU/mL) and reached a maximum of 10^5 PFU/mL within 30 minutes of incubation. In stably infected cultures after several hours the titer significantly decreased (Figure 2). Repetitions of this experiment routinely resulted in viral titers in this range ($10^5 - 10^7$ PFU/mL) (Table 1). Ideally, a decline in virus titer would be expected upon virus adsorption, however since the contamination of the *Sulfolobus* cultures, it resulted in unusual titers between points 0 and 0.5 and between 1.5 and 2 (Figure 2). Also, the majority of the uninfected cells produced good lawns mostly in the early time points indicating that the host cells were in good condition for the first half hour, after which cell debris were observed in the both infected and uninfected cultures. This correlated with the plaque results showing debris on the lawns after time point 1 (Figure 1B). Similar results were obtained for infected cultures, in which dramatic decrease in titer were observed after 30 minutes (Figure 2). Ideally it was expected that for infected cultures viral titer would decrease after incubation for longer than 1 hour. Data for the SSV1 adsorption constant has not been published, however, data from an undergraduate honors thesis reported that SSV1 at an initial titer of 10^5 HFU/mL (halo-forming units/mL) became undetectable within 5 hours following incubation with *S. solfataricus* G-theta at 23° C. The MOI of this incubation was 0.01 (Drummond thesis 2010). In our case, it is probable that the viral adsorption did not occur properly because the viral titers before infection were within a reasonable range ($10^5 - 10^8$ PFU/mL), however, after incubation of the host with SSV1 for several hours, there was a noticeable decrease in titers with visible cell debris. The presence of cell debris implies cell death, but it is unclear if this is due to external contamination or lysis by SSV1. In addition, incubating SSV1 with YS media did not result in cell debris after several hours of incubation, this indicates that the debris comes from S441 cells.

Another potential factor affecting rates of adsorption is motion within the adsorption medium, where too little motion (i.e., lack of mixing or agitation) or too much motion could have resulted in reduced rates of virus adsorption (Delbrück et al., 1940; Koch et al., 1960; Anderson, T.F. 1949). Thus, it would be worthwhile to further investigate this phenomenon, as the collected data is not sufficient to make an accurate determination of the true kinetics of viral infection. Multiple trials need to be conducted to eliminate plating and/or culture preparation errors that might have limited the precision of measurements, as sufficient data will help improve the accuracy of one-step growth curves and the information about SSV1 infections that they provide.

A.

B

Figure 1: **A.** Plaque assay results for infected S441 with SSV1 immediately after mixing with SSV1 (10^{-1} dilution), after 1 and 2 hours of incubation at (10^{-1} dilution), respectively. **B.** Plaque assay results for uninfected control immediately after incubation (10^{-1} dilution), after 1 and 2 hours of incubation (10^{-1} dilution) respectively.

Figure 2: Titer of SSV1-infected S441 cells

Sulfolobus cells of strain S441 stably infected with SSV1 (diamonds) were diluted to 75 mL with fresh YS medium and incubated for 4 hours at 75° C. Samples (1 mL) were taken every half hour to measure the viral titer by plaque assay. The viral titer was measured in triplicate at each time point and the average viral titer (PFU/mL) of two independent cultures are presented with standard deviations.

Table 1: Titers from serial dilutions of the prepared SSV1 supernatant with 0.01 MOI for 3 replicates.

SSV1 dilutions	Viral Titers for Trial 1 (PFU/mL)	Viral Titers for Trial 2 (PFU/mL)	Viral Titers for Trial 3 (PFU/mL)
10^{-1}	1.32×10^7	2.05×10^8	1.28×10^5
10^{-2}	1.73×10^5	6.75×10^5	3.04×10^6
10^{-3}	1.71×10^5	1.70×10^5	4.00×10^5
10^{-4}	3.04×10^5	0	0
10^{-5}	2.00×10^6	0	0
Average	$2.81 \pm 5.81 \times 10^6$	$4.12 \pm 9.16 \times 10^7$	$7.14 \pm 1.31 \times 10^6$

Conclusion

This work focused on the hyperthermophilic virus from the family *Fuselloviridae*: SSV1. While in the process of establishing a platform for performing a one-step growth curves to study virus replication kinetics and to investigate the mechanism of host binding, we were unable to gather viable data to be able to draw conclusions about the adsorption kinetics of wild-type SSV1 to its *Sulfolobus* host. However, through this experiment we learned how to better handle and work with hyperthermophilic viruses. For instance, we were able to infer from the results that to better understand how the binding of the virus to its host occurs, infection protocols should be optimized in order to obtain high titers. In addition, it was found that titer values should be reported to the cell concentration, in order to obtain more comparable data and be able to perform one-step growth curve that would be equated to those performed in the past (Iverson thesis 2015). Thus, more work needs to be done to clarify and expand upon these ambiguous results and optimize the binding assay. In the future, this would also permit to observe how SSV bound to *Sulofobus* at the very first step of the infection process by transmission electron microscopy (TEM). In addition, being able to isolate freshly bound SSV1 may allow insight into this critical step in virus infection.

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