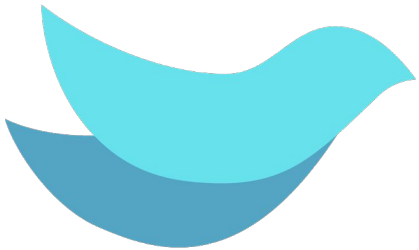
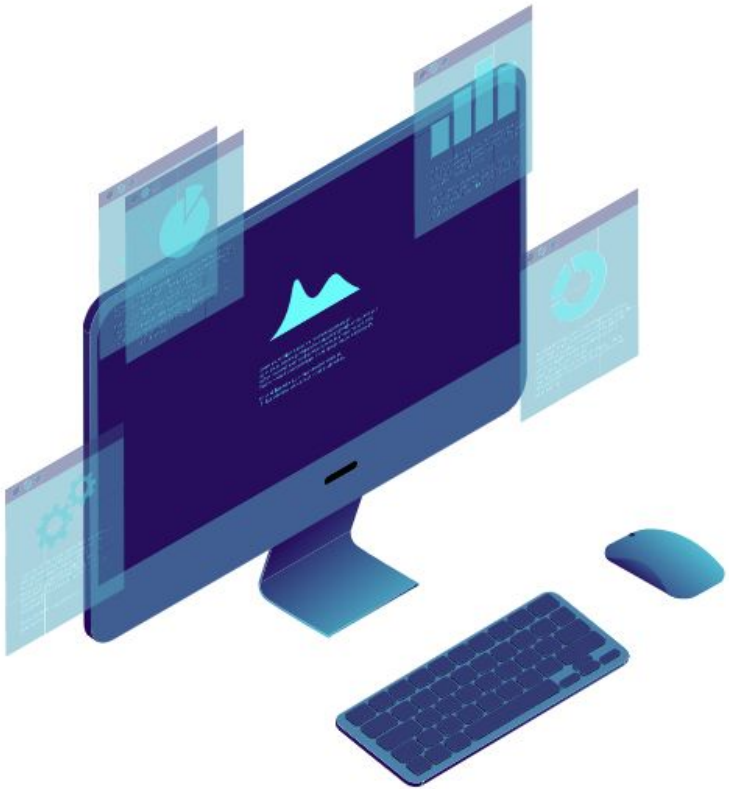


Poloma

Powerful logic for M&A

The problem.



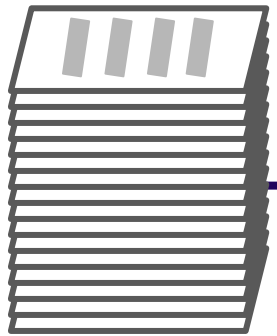
Biotech M&A deals totaled $64.8B in 2018. **$1.95B** of this was spent on due diligence.

We want to help companies get value for money spent on diligence.

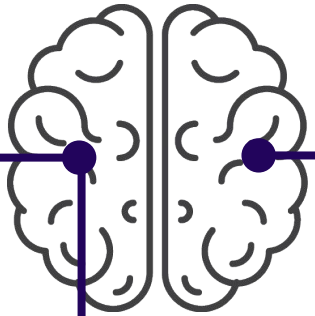
This includes using AI to gauge **IP strength** by finding related patents, finding **inconsistencies** relative to public knowledge, and comparing the **novelty of the science** to other research.

Our solution for biotech.

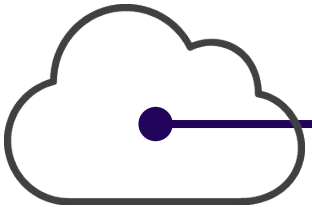
Our **IP Strength metric** takes into consideration proprietary information that has been previously patented.



Data Room



Poloma Analytics



Online Documents

- IP Strength
- Novelty of Science
- Inconsistent Claims

Our goal is to **increase efficiency**, and **reduce risk** in strategic transactions. We point out omissions and inconsistencies in public preclinical and clinical data by comparing with documents from the data room. We also compare the science to pre-existing information to deduce its novelty.

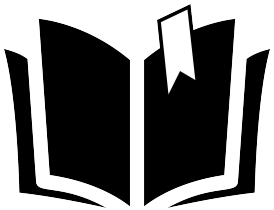
Our Tech

Bidirectional LSTM Language Model

Poloma reads documents and uses Bidirectional LSTM to **learn** how to understand language.

Vector Space Indexing

Poloma breaks down any document and indexes each sentence into vector space, allowing for scalable lookup when deciding which sentences to compare.



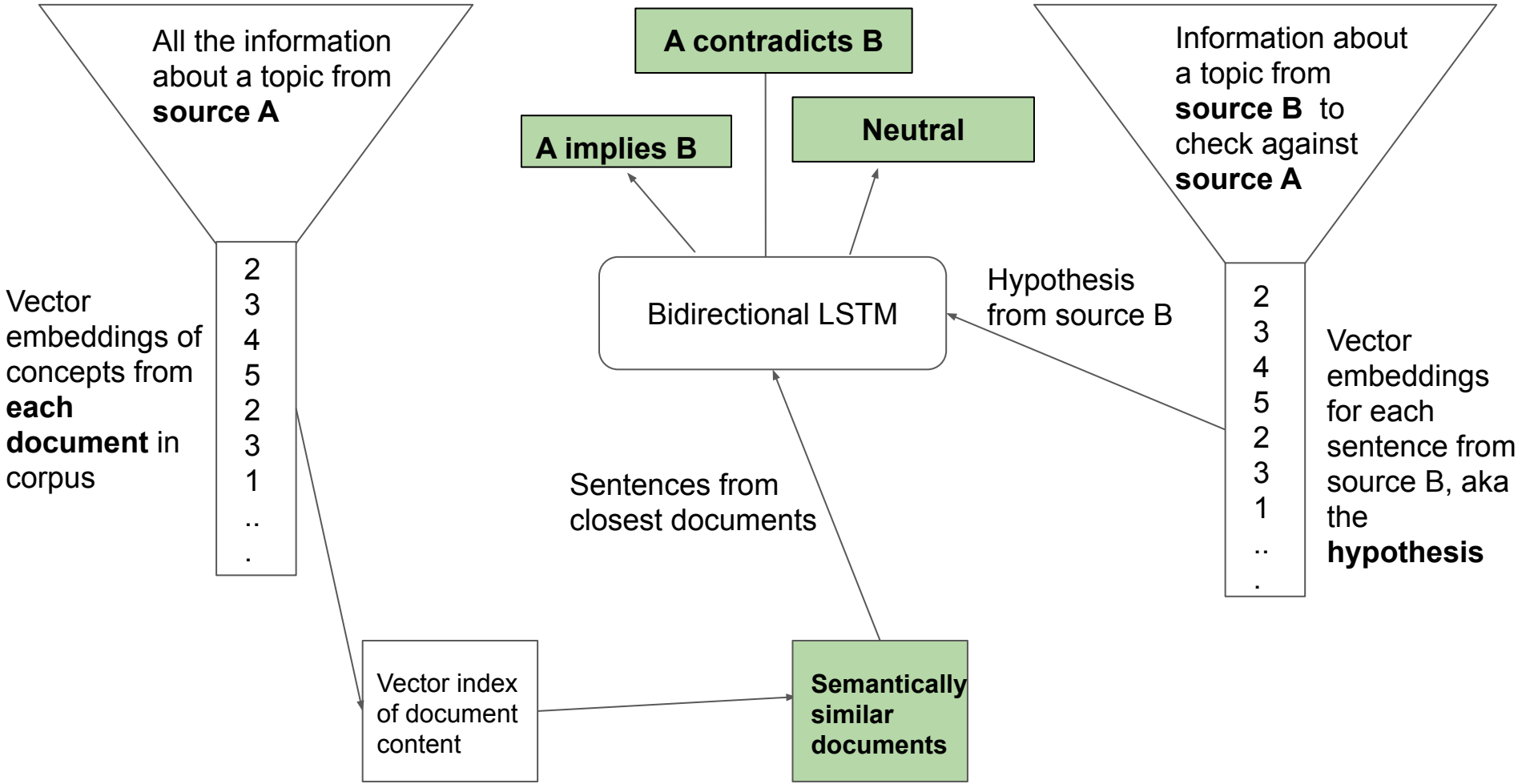
Entailment Classification

Poloma **learns** how to check consistency between any two sentences.

Inputs | Output

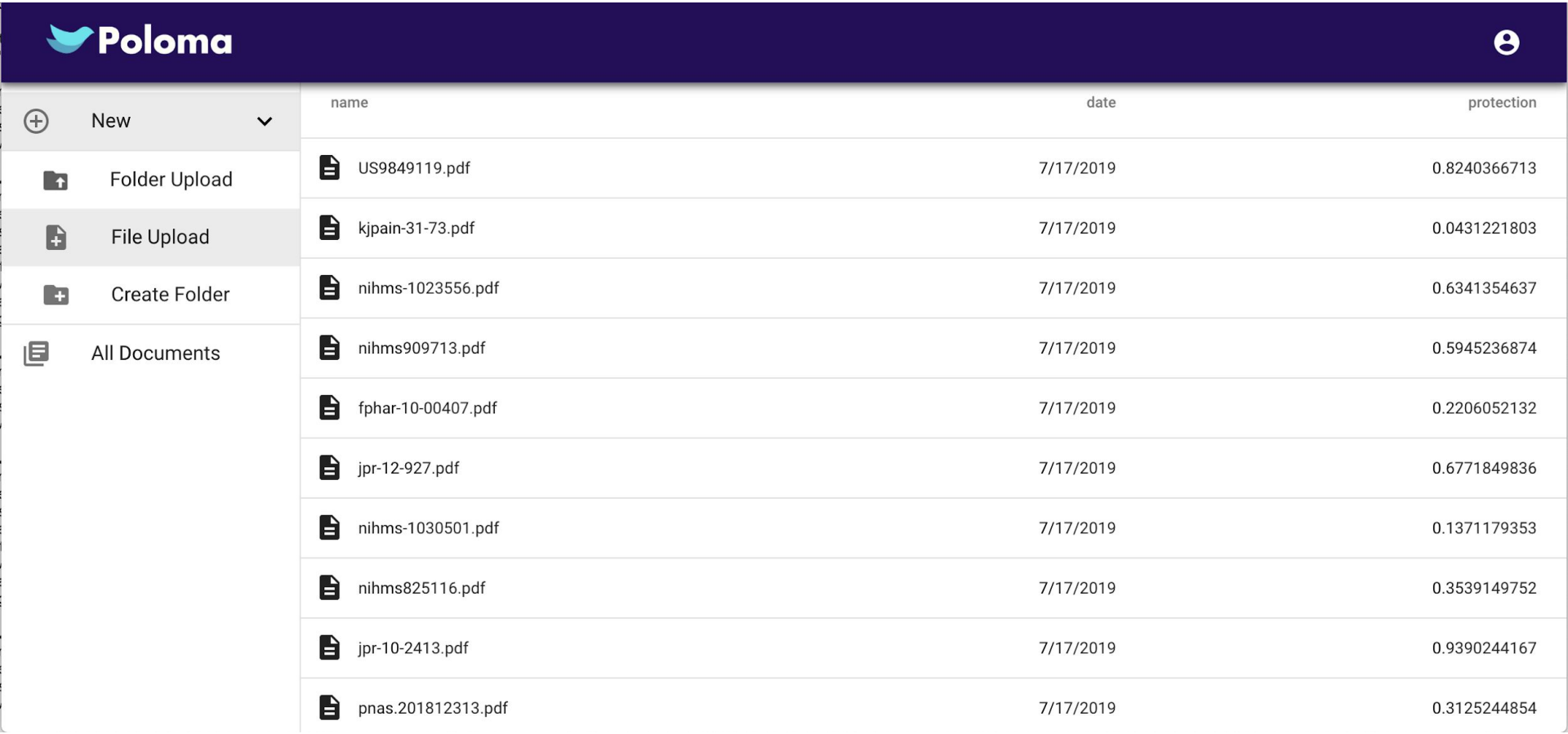
Sentence 1	Sentence 2	Result
An older and younger man smiling.	Two men are smiling and laughing at the cats playing on the floor.	Neutral
A black race car starts up in front of a crowd of people.	A man is driving down a lonely road.	Contradiction
A soccer game with multiple males playing.	Some men are playing a sport.	Entailment

Poloma streamlines the due diligence process by organizing the data room, revealing inconsistencies between private data and public data, and highlighting novel information that isn't available in the public domain.


All the information about a topic from **source A**
Vector embeddings of concepts from **each document** in corpus
2
3
4
5
2
3
1
..
.
Vector index of document content
Sentences from closest documents
A contradicts B
A implies B
Neutral
Bidirectional LSTM
Hypothesis from source B
Information about a topic from **source B** to check against **source A**
2
3
4
5
2
3
1
..
.
Vector embeddings for each sentence from source B, aka the **hypothesis**
Semantically similar documents

Is it accurate?

- Entailment classifier **85% accurate** (on NYU's MNLI benchmark)
  - Problem: not domain specific benchmark.
  - Biotech documents are very context-heavy
- Data is still not clean enough
  - Need to improve our pdf extractors and language models
- Semantic Search should be more accurate, Support OOV words better
  - Multi-level document vector space index? To improve context awareness



DEVELOPMENT OF SIGNAL-BIASED OPIOIDS IN SEARCH OF ENHANCED THERAPEUTIC WINDOWS

The majority of clinically used opioids selectively target the μ opioid receptor (μOR). Their use however, particularly in patients with chronic pain disorders, is complicated by side effects including opioid dependence, tolerance, constipation, itch and respiratory depression (Chou et al., 2009). The beginning of the 21st century saw the emergence of the hypothesis that the side effect profile of μOR based drugs may be attributed to β-arrestin 2 signaling, as preclinical studies showed that mice lacking this protein displayed reduced morphine tolerance and respiratory depression (Bohn et al., 1999, 2000; Raehal et al., 2005). Despite morphine being already a relatively low efficacious β-arrestin 2 recruiter (Whistler and von Zastrow, 1998), the β-arrestin 2 KO mice studies were the driving factor for the development of so-called G protein-biased μOR agonists that preferentially signaled via the canonical G protein pathway, while further minimizing β-arrestin 2 recruitment and signaling. Such signal-biased opioids like TRV130 (Chen et al., 2013) and PZM21 indeed appeared to have improved therapeutic windows (Soergel et al., 2014; Manglik et al., 2016), and TRV130 advanced through all three clinical trial phases under the brand-name Olinvo ϕ(oliceridine) for the treatment of moderate-to-severe pain via intravenous injection for example following abdominoplasty (Singla et al., 2017). However, recent preclinical studies have sowed doubt regarding the potential for these G protein-biased μOR agonists to reduce side effects like constipation, respiratory depression and dependence (Altarifi et al., 2017; Austin Zamarripa et al., 2018; Hill et al., 2018; Kliewer et al., 2019). Moreover, in October of 2018, the Food and Drug Administration (FDA) decided on a 8– 7 vote not to approve Olinvoϕ, as the committee still had doubts as to whether the benefits associated with the drug outweighed the risks.

CLINICAL UTILITY OF KAPPA OPIOID RECEPTOR (κOR) SELECTIVE DRUGS

The μOR is not the only opioid receptor modulating nociceptive

cocaine use (Butelman et al., 2012; Walker et al., 2012; Karkhanis et al., 2017). Negative affect is an important factor in chronic pain management and the amygdala plays an important role in the circuitry associated with negative affect (Corder et al., 2019). Like μOR, activation of κOR produces analgesia, however the κOR/dynorphin system is heavily present in the amygdala (Land et al., 2008; Knoll et al., 2011; Kissler et al., 2014; Crowley et al., 2016). Thus there is a therapeutic promise for utilizing κORs in chronic pain settings, yet this requires producing κOR agonists with optimized pharmacological properties to ensure the drug produces analgesia, but are capable of mitigating the negative affect. Currently, the therapeutic potential of κOR agonists is limited by negative side effects they can produce, which include sedation, motor incoordination and dysphoria (or aversion in rodents) and psychotomimesis, the latter two effects being specific to κOR (Pfeiffer et al., 1986; Dykstra et al., 1987; Roth et al., 2002; Land et al., 2009) (**Figure 1**). The FDA has approved several non-selective opioids that target both the μOR and the κOR. However, these drugs act either as partial agonists (nalbuphine, nalmefene, pentazocine, butorphanol) or antagonists (buprenorphine) at the κOR, thus largely avoiding the side effects associated with strong κOR activation. Yet beyond partial agonism, an additional strategy may include biasing the κOR agonists signaling to a specific downstream pathway.

CAN SPECIFICALLY TARGETING G PROTEIN-BIASED SIGNALING LEAD TO THE DEVELOPMENT OF CLINICALLY EFFECTIVE, κOR-SELECTIVE, FULL AGONISTS?

Similar to studies of μOR signaling bias, studies investigating κOR signaling have indicated that some of the negative side effects, such as aversion, could be mediated by β-arrestin 2 (Bruchas and Chavkin, 2010). Specifically, Bruchas et al. (2007), first revealed that U50,488 induced aversion requires p38 activation, which largely depends on G protein receptor kinase 3, which has been linked to β-arrestin 2 recruitment (Bruchas et al., 2006). In a follow up study, mice virally expressing the S369A κOR mutant, which does not get phosphorylated by G protein

Patent Coverage

This application relates to a family of compounds acting as opioid receptor ligands.

Title: A G protein-biased ligand at the Âμ-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared to morphine.

The compounds of the present invention are potentially useful in the treatment of a range of disorders where a TrkA antagonist is indicated, particularly pain indications.

Click to view patent

initially tested at 20 μM and was incubated with ^{3}H-DPN at a concentration equal to the Kd (0.4 nM) of the radioligand in μOR containing Sf9 insect cell membranes. The reaction contained 40 fmol of μOR and was incubated in a buffer of 20 mM HEPES pH 7.5, 100 mM sodium chloride, and 0.1% bovine serum albumin for 1 h at 25 °C. To separate free from bound radioligand, reactions were rapidly filtered over Whatman GF/B filters with the aid of a Brandel harvester and ^{3}H-DPN counts were measured by liquid scintillation. Compounds with more than 25% of ^{3}H-DPN radioactivity were further tested in full dose–response to determine the affinity (Ki) in HEK293 membranes. Subsequently, the 15 analogues were tested in full dose–response for affinity at the μOR and the κOR by the National Institutes of Mental Health Psychoactive Drug Screen Program (PDSP)[45], as were the affinities of compounds **12**, PZM21, and their stereoisomers at the μOR, δOR, κOR and nociception receptor.

Radioligand depletion assays to test the irreversible binding of compound PZM29 were performed as described previously[46]. Human embryonic kidney 293 (HEK 293) cells were transiently transfected with μOR or the cysteine mutant μOR:N127C using the Mirus TransIT-293 transfection reagent (MoBiTec, Goettingen, Germany), grown for 48 h, harvested, and homogenates were prepared as described[47]. For radioligand depletion experiments, homogenates were preincubated in TRIS buffer (50 mM Tris at pH 7.4) at a protein concentration of 50–100 μg/ml or 70–120 μg/ml for μOR and μOR:N127C, respectively and the covalent ligand (at 5 μM) for different time intervals. Incubation was stopped by centrifugation and reversibly bound ligand was washed three times (resuspension in buffer for 30 min and subsequent centrifugation). Membranes were then used for radioligand binding experiments with ^{3}H-diprenorphine (final concentration: 0.7 nM, specific activity: 30 Ci/mmol, purchased from Biotrend, Cologne, Germany) to determine specific binding at the μOR (B_{max} = 4,000–6,500 fmol/mg protein, K_D = 0.25–0.45 nM) and the μOR:N127C receptor (B_{max} = 1,300–6,000 fmol/mg protein, K_D = 0.18–0.25 nM), respectively as described[48]. Non-specific binding was determined in the presence of 10 μM naloxone. For data analysis, the radioactivity counts were normalized to values where 100% represents effect of buffer and 0% represents non-specific binding. Five independent experiments, each done in quadruplicate, were performed and the resulting values were calculated and pooled to a mean curve which is displayed.

Author Manuscript

GTP-γS Binding Experiments

Inconsistent Information

The reaction was cooled, diluted with EtOAc, filtered through celite and concentrated in vacuo.

The reaction was placed on a preheated hot plate (110° C.) for 16 hours.

The filtrate was washed with water (200 mL), dried over magnesium sulfate and concentrated in vacuo.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The reaction was filtered through celite and concentrated in vacuo.

The assay was carried out in 96 well plates; testing compounds using a 10 point semi-log dilution range from 19 uM top concentration.

The cold pain test, has been shown to be a reproducible and sensitive measure of the effect of opiates and other centrally acting drugs (Van F

Right Now

- Working with a large pharma company to determine if our tool would be helpful for their IP lawyers

- Talking to potential partners who invest in biotech and are interested in improving therapy discovery / evaluation and diligence

- **Political fact checking on speeches in real time as proof-of-concept for our tech and to generate leads. Live stream fact-check 2nd democratic debate on July 30th.**

What did it take to get here?

- 6 weeks
- $6,000
- AWS Credits
- Great board of advisors

What would it take to get to the next level?

- 1-2 months
- Resources to continue paying interns/ engineers
- Partner(s) who are passionate about the tech and/ or have interesting uses for it

Why us?

- Co-founders and team chemistry
- Spent the past year working together building semantic bidirectional LSTM language models and applying them creatively to different problems
- Mentorship from professors and incredible Cornell CS community

Method	Accuracy
Illinois-LH (Lai and Hockenmaier 2014)	**84.6**
ECNU (Zhao, Zhu, and Lan 2014)	83.6
UNAL-NLP (Jimenez et al. 2014)	83.1
Meaning Factory (Bjerva et al. 2014)	81.6
Reasoning-based n-best (Lien and Kouylekov 2015)	80.4
LangPro Hybrid-800 (Abzianidze 2015)	81.4
SNLI-transfer 3-class LSTM (Bowman et al. 2015)	80.8
MaLSTM features + SVM	84.2

Table 4: Test set accuracy for the SICK semantic entailment classification. The first group of results are top SemEval 2014 submissions and the second are more recently proposed methods.

Entailment classification is often glossed over as a statistical evaluation test rather than an end unto itself

Our competitors (in the Legal AI market)

	Semantic Search	Bidirectional LSTM ML	Contradiction and Entailment Analysis	Revenue / Funding ($)
Poloma	⊙	⊙	⊙	-
Deepset.ai	⊙	⊙		5M /50M
Cortical.io	⊙			5M/10M
NEC Labs, Inc		⊙	⊙	100M/500M

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