GlycoMimetics, Inc.

GLYC : NASDAQ : US$10.01

BUY

Target: US$17.00

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COMPANY STATISTICS:

Forecast Return:	70%
Shares Out (M):	18.0
Market Cap (M):	US$180.2
52-week Range:	US$8.40 - 11.99

EARNINGS SUMMARY:

FYE Dec		2013E	2014E	2015E
Revenue:		21.9	23.5	0.0
EPS:		0.61	(0.09)	(1.84)
Revenue:	Q1	1.3A	0.0	-
	Q2	1.3A	13.5	-
	Q3	1.3A	0.0	-
	Q4	18.0	10.0	-
Total		21.9	23.5	0.0
EPS:	Q1	(0.18)A	(0.29)	-
	Q2	(0.19)A	0.44	-
	Q3	(0.20)A	(0.37)	-
	Q4	0.76	0.13	-
Total		0.61	(0.09)	(1.84)

SHARE PRICE PERFORMANCE:

Source: Interactive Data Corporation

COMPANY DESCRIPTION:

GlycoMimetics is a clinical-stage biotech company focused on novel glycomimetic (carbohydrate imitating) drugs. The disease-related functions of carbohydrates can include roles in inflammation, cancer cell survival/behavior and infection. GlycoMimetics' GMI-1070 is a very promising therapy for sickle cell disease.

All amounts in US$ unless otherwise noted.

Life Sciences -- Biotechnology

SELECTIN' A GAME CHANGER FOR SICKLE CELL CRISIS; INITIATING WITH BUY, $17 PRICE TARGET

Investment recommendation

Initiating coverage with BUY, $17 target on GMI-1070's potential in sickle cell crisis. GLYC's lead candidate, Pfizer-partnered GMI-1070, is a pan-selectin inhibitor for sickle cell vaso-occlusive crisis (VOC). We expect positive data from the upcoming Ph3 trial to show reduced length of sickle cell vaso-occlusive crisis based on strong Ph2 data. We think GMI-1070 could gain significant market share and model potential US peak sales of $1.2B. Our $17.00 target is based on a pNPV analysis.

Investment highlights

- **GMI-1070 is a first-in-class pan-selectin inhibitor that could shorten sickle cell disease (SCD) VOC crisis and has the potential for ~$1.2B peak sales.** SCD is an orphan genetic disease caused by mutated hemoglobin that deforms and destroys red blood cells, causing painful VOCs. Standard of care is hydration, oxygen and opiates for pain. GMI-1070 inhibits adhesion of activated white blood cells to blood vessel walls and other surfaces by blocking selectin-mediated binding. Partner Pfizer will start a Ph3 trial in SCD H2/14. We anticipate top-line data around H2/16.
- **Strong Phase 2 GMI-1070 SCD data showed large reductions in duration of SCD VOC crisis, which bodes well for Ph3 chance of success.** Phase 2 data showed unprecedented 40- to 60-hour reductions in VOC length, and 50- to 80-hour reduction in hospital stays, with excellent safety. Despite missing statistical significance due to data variance, this data has been unanimously lauded by SCD KOLs we have spoken to. We anticipate potential approval and US market launch both in 2017 with peak US sales of $1,212M by 2023, and peak royalties to GLYC of $218M.
- **GLYC's technology platform of small molecule inhibitors to carbohydrate ligand binding has significant potential in a number of other programs and diseases, including AML.** We think 1070's Phase 2 data gives major proof of concept to the biological activity of selectin inhibition. GLYC will start a Ph1 trial of pan-selectin inhibitor GMI-1271 in AML in H1/14, and has another preclinical program targeting E-Selectin/CXCR4 for chemosensitization of blood cancers.

Figure 1: GLYC upcoming catalysts

Expected date	Drug/Program	Item	Impact
Q1/14	GMI-1271	IND filing	+
Q2/14	GMI-1271	Initiation of Ph1 trials in AML	+
Q2/14	GMI-1070	TQTc study	+
H2/14	GMI-1070	Initiation of Ph3 SCD trial	+
H2/16	GMI-1070	Data from Ph3 pivotal trial	+++

Source: Company reports and Canaccord Genuity estimates

Figure 2: GLYC pipeline

Drug/ Program	Disease	Licensing/ Partnership	Preclinical	Phase 1	Phase 2	Phase 3	Post-Marketing
GMI-1070	Vaso-occlusive crisis	Pfizer					
GMI-1271	Acute myeloid leukemia	Wholly owned					
E-selectin and CXCR4 antagonist	Cancers	Wholly owned					
Orally available E-selectin antagonist	CV indication / imflammation	Wholly owned					
GMI-1051	Pseudomonas	Wholly owned					

Source: Company website

INVESTMENT THESIS

We think GMI-1070 is a very promising therapy for sickle cell disease, a highly underserved, multifactorial and poorly understood disease. GMI-1070 is an oral small molecule pan-selectin antagonist that inhibits adhesive interactions between different types of white blood cells and other blood cells as well as blood vessel walls. The drug is partnered with Pfizer worldwide. Sickle cell disease (SCD), especially SCD vaso-occlusive (VOC) pain crises, represents a significant unmet medical need as there are no specific treatments; the only therapy is hospitalization to provide oxygen, hydration and narcotics. Hospitalizations due to the excruciating pain associated with VOC crises usually last ~4 days, driven by the length of period patients require IV opiates to manage their pain levels. There are an estimated 100,000-200,000 SCD-related hospitalizations each year in the U.S., driven by an estimated ~100,000 SCD patients. We think that the true size of the future market may be significantly underestimated by these figures due to drastically reduced childhood mortality rates starting ~20-30 years ago, age-dependent increased crises and hospitalization rates, and immigration patterns.

We believe that GMI-1070 may be able to have a very strong impact on the inflammatory component of SCD crisis. We think selectin binding contributes significantly to both to the onset and prolongation of SCD VOC by facilitating the 'sticking' of white blood cells to other blood cells as well as blood vessel walls. While the sequence of biological events during a crisis is not well understood, most experts believe selectin binding and activation increases systemic inflammation and blood viscosity, causing hypoxia, which in turns leads to sickling of SC blood cells. This leads to micro-occlusions which are then further exacerbated by selectin binding. Inhibiting selectin binding could slow multiple pathologies involved in SCD crises.

Phase 2 GMI-1070 data shows an unprecedented level of clinical benefit according in KOLs as well as excellent safety. Previous GMI-1070 Phase 2 data showed very strong signs of efficacy and excellent safety. A 76-patient Phase 2 clinical trial run at 22 US sites showed treatment with GMI-1070 in the very early stages of an SCD crisis was able to reduce length of VOC crisis by a mean of 41 hours and median of 63 hours. Other measures of crisis resolution such as time to discharge and time to transition off IV analgesics showed between a 50 and 80 improvement as well. While these measures did not reach statistical significance due to higher than expected variability in the data, the cumulative amount of opioid analgesics was reduced by a statistically significant 83%. Safety and tolerability was excellent with no signal of increased infection risk. GMI-10 KOLs we have spoken to about this data, as well as public forum comments indicate this data is unprecedented in the field of SCD drug development, and real world benefit even approaching this would represent an enormous clinical benefit to SCD patients as well potential cost-savings in their care.

We think the soon to be initiated Pfizer Phase 3 trial has a relatively high chance of success due to supportive Phase 2 data as well as intelligent trial design. We believe the expected GMI-1070 Phase 3 trial to be started by Pfizer in H2/14 is well designed, well powered and has the correct inclusion/exclusion criteria. The primary endpoint will again be time to resolution of VOC, like the Phase 2. We think this trial is well designed enough to support FDA and EMA approval by itself if it is successful, or even if it misses statistical significance by a small margin. We think Pfizer is wholly committed to the GMI-1070

program and the lag between the recent FDA end of Phase 2 meeting and Phase 3 start is entirely necessary given the complexity of trial site and enrollment logistics for any SCD VOD trial.

We think SCD represents an enormous market opportunity, given its large, yet orphan prevalence and almost non-existent treatment options: We estimate US peak sales of $1,212M. SCD clinicians and caregivers to whom we have spoken are preparing for an increase in the numbers of adult in-patient hospitalizations (well above the current 100,000 per year base estimate in the U.S.) related to SCD due to population trends. Patients and clinicians alike bemoan the complete lack of targeted therapies for the treatment of acute crises and the lack of options for prophylactic treatment (hydroxyurea is the only currently approved therapy). While many have considered the SCD market extremely challenging due to reimbursement reasons, we note that coverage (whether public or private) is widespread and will likely only grow with the Affordable Care Act.

We also think GMI-1070's role in SCD will be complementary to other non-selectin inhibitor drugs. Given the complex pathology of the SCD crisis, most experts we have spoken to believe that multiple drugs with multiple separate mechanisms will be needed to optimally control and treat the disease. We expect GMI-1070 will prove to have at least additive, if not synergistic benefit with standard of care hydroxyurea and may also work well together with Mast's Phase rheological agent MST-188, also in development for SCD.

GlycoMimetics' selectin inhibitor platform also has the potential to generate therapies for a number of other diseases whose pathologies are dependent on selectin interactions, such as AML. GlycoMimetics' technology platform is based on finding small molecule inhibitors for carbohydrate mediated interactions in the body. Lead programs have focused on selectin-based interactions, which are important in a number of white blood cell mediated disorders, including blood cancers. GLYC intends to initiate a wholly owned program Phase 1 program in Acute Myeloid Leukemia for GMI-1271. The company also has a preclinical E-selectin/CXCR4 antagonist program blood cancer chemotherapy sensitizer program. While these programs are preclinical and are not included in our valuation model, we think they can be key value creators in the future.

INVESTMENT RISKS

Clinical risk – GlycoMimetics' current Phase 3 trial may not be successful. We note that there has been relatively little drug development in SCD and no successful clinical trials that have led to the approval of drugs for the disease based on the endpoint GlycoMimetics is pursuing. Further, the Phase 2 trial of GMI-1070 did not meet its primary endpoint (the same endpoint in the Phase 3 trial design) due to data variability. However, we feel the expansion of the patient numbers in the upcoming Phase 3 trial will compensate for the data variability inherent to SCD trials.

Clinical risk – Additional clinical investigation may show GMI-1070 to have an unacceptable safety and tolerability signal. GMI-1070's selectin-based mechanism could potentially interfere with immune responses to infection, thereby increasing risk of infections, opportunistic and otherwise. This is the potential side effect of most concern to KOLs although they have noted to us that no signal of this has yet been seen, and the episodic nature of potential treatment with GMI-1070 likely mitigates this risk even further.

The only serious adverse event in the Phase 2 trial was one case that was controlled and resolved without discontinuation of treatment.

Regulatory risk – GMI-1070 may not be approved by the FDA and/or EMA despite Phase 3 success. We note the only approved drug for treatment of SCD is indicated for the prevention of the number of crises, rather than reduction of the duration of crisis (the trial design). There is no precedent for the approval of SCD drugs based on reduction of length of hospitalization. However, experts we have spoken to unanimously agree on the importance and clinical meaningfulness of the endpoint and we believe it will support approval.

Competitive risk – GlycoMimetics faces potential competition from other agents seeking to decrease the time to resolution of SCD crises, as well as indirect competition from agents being developed to prevent the onset of crises. Mast's Phase 3 rheological MST-188 and Selexys' SelG1 (partnered with Novartis) are both in mid- to late-stage development for the same indication as GMI-1070. Positive data from either of these programs could result in pressure on GLYC shares. We anticipate, however, that the heterogeneous presentation of VOCs and the multi-factorial process involved will likely require combination that includes selectin inhibitors like GMI-1070.

Commercialization risk – There is little to no precedent for the successful promotion to the sickle cell disease market. Hydroxyurea, the only currently-approved drug for the treatment of SCD, was first approved in 1967 for the treatment of blood cancers and approved for SCD in 1998. The drug has been available in multiple generic forms for SCD for a number of years, and is no longer promoted by Bristol-Myers, its original SCD sponsor. Commercial uptake has historically been extremely limited, and KOLs tell us the drug was never properly promoted. As such, we see no precedent for the successful launch and promotion of a drug for SCD.

Reimbursement risk – There is no guarantee that GlycoMimetics, or its partners, will garner reimbursement for GMI-1070. There has historically been significant skepticism regarding the market opportunity in SCD due to concerns about insurance coverage rates of the affected population. While current research estimates that 80% of SCD patients are covered by public insurance plans, there are a number of commercially successful therapies that have this coverage profile, including erythropoietins, for chronic kidney disease. We also note GMI-1070's initially pursued indication would dictate its use in the hospital setting, which will require prior approval from hospital P&T committees. P&T committees are notoriously cost-conscious and focused on the pharmacoeconomic savings afforded by new products and can represent formidable reimbursement hurdles. Failure to obtain such reimbursement, or if the use of GMI-1070 is restricted or impeded, could limit sales of the drug and have a negative impact on the company's share price.

VALUATION

We have built our valuation of GLYC using a probability-weighted NPV model of peak sales.

Potential upside to valuation

We see the following as potential drivers of upside to our model:

- **Sooner-than-expected results due to rapid enrollment.** If clinician enthusiasm is stronger than expected, it could enroll faster than currently modeled.
- **New market estimates that could indicate a larger-than-expected market opportunity.** Current market consensus suggests there are 100,000 SCD-related hospitalizations in the U.S. per year, driven mostly by ~75,000 SS mutation patients. The newest CDC estimates put the hospitalization number at closer to 200,000 annually and not growing in prevalence due to immigration patterns and an aging SCD demographic driven by greatly reduced pediatric mortality from the 1970s onward. Further, if Phase 3 data is very positive, there could be meaningful use of GMI-1070 in earlier stages of crisis, which could expand the market opportunity.
- **Revenues generated in the EU and ROW markets.** There are a considerable number of SS and SC patients in Europe (especially the UK and France) and enormous numbers in Africa and the Near East. Given recent restrictive reimbursement reform in the EU and uncertainty in the approval and reimbursement in ROW territories, we do not include them in our current market model.
- **Stronger-than-expected top-line data in 2016:** Should top-line data show that GMI-1070 has a much better-than-expected crisis resolution time reduction (16+ hours), GMI-1070's commercial prospects could be better than expected.
- **Rapid development and positive data for GLYC's preclinical programs, such as GMI-1271 for AML**. GlycoMimetics intends to start clinical development for GMI-1271 in 2014, with first potential efficacy data in H2/15. Should this program advance faster than expected, showing strong treatment effect, it could represent upside to shares from a program not included in our valuation.

Potential downside to valuation

As with all companies in commercial and clinical development, there always exists the risk of failed or inconclusive clinical trials, slower-than-expected commercial launches, or lower-than-expected peak sales, which could lead to downward pressure on the stock. For more detailed risks, see our "Investment risks" section.

Figure 3: GLYC valuation

Product Development													
Drug name	Indication	Status	Launch	Years to Launch	Years to Launch plus 6	Success	Sales (US$m)	Probability weighted Peak Sales (US$m)	Royalty	Profitability	Probability weighted Peak Profit (US$m)	Discount Factor	NPV (US$)
GMI-1070	Sickle cell disease	Phase 3	2017	3	9	60%	1212.4	727.4	18%	90%	117.84	5.99	16.81
										Total			16.81

Source: Company reports and Canaccord Genuity estimates

REVENUE MODEL AND FINANCIALS

Our forecast financial model is built on the assumption that GMI-1070 will launch in the US in 2017 for use in SCD VOC-related hospitalization. Our GMI-1070 market model assumes peak GMI-1070 market share of 80% in pediatric SCD patients and 80% in SCD patients between 18 and 30 years old. We assume peak sales will be reached in 2023, six years from launch.

We assume that GMI-1070 and potential partner, if any, will price one course of GMI-1070 around $12,000 in the US. Our discussion with GlycoMimetics management indicates its market research supports a ~1200% premium to hydroxyurea pricing if GMI-1070 proves to be able to reduce time to VOC resolution. We assume market research would support an even larger margin on improved efficacy and/or safety, but are currently modeling with a much more conservative price.

Overall, we forecast peak market share for GMI-1070 in 2023 with corresponding sales of ~$1,212M. We have not modeled potential revenue streams from EU or ROW, which could increase the peak sales figure significantly.

GlycoMimetics reported current asset of $8.7M on September 30, 2013 and received net proceeds of ~$59M post offering. We think this represents around eight quarters' worth of operating cash. We expect most of the R&D spend to be focused on bringing preclinical candidates into the clinic and advancing lead compounds such as GMI-1271 into Ph1/2 trials by H2/14.

Figure 4: GMI-1070 revenue projections

		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
Sickle cell disease market model														
US population	1.0%	321.2	324.4	327.6	330.9	334.2	337.6	340.9	344.3	347.8	351.3	354.8	358.3	361.9
Patients with sickle cell disease		115,729	120,978	126,464	132,199	138,194	144,461	151,013	157,861	165,020	172,504	180,327	188,505	197,053
SCD incidence	3.5%	*0.000360*	*0.000373*	*0.000386*	*0.000400*	*0.000413*	*0.000428*	*0.000443*	*0.000458*	*0.000474*	*0.000491*	*0.000508*	*0.000526*	*0.000544*
Patients with SCD under 18		26,912	28,034	29,203	30,420	31,688	33,009	34,386	35,819	37,313	38,868	40,489	42,177	43,935
% of US population under 18	-0.4%	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*22%*	*22%*	*22%*
Hospitalization due to VOC	50.0%	40,368	42,051	43,804	45,630	47,532	49,514	51,578	53,729	55,969	58,302	60,733	63,265	65,903
VOC attacks per year	0.0%	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*	*3.0*
Patients with SCD between 18 and 30		34,719	36,547	38,472	40,498	42,631	44,877	47,240	49,728	52,347	55,104	58,006	61,061	64,277
% of US population (18 and 30)	0.7%	*30%*	*30%*	*30%*	*31%*	*31%*	*31%*	*31%*	*32%*	*32%*	*32%*	*32%*	*32%*	*33%*
Hospitalization due to VOC	20.0%	41,663	43,857	46,167	48,598	51,158	53,852	56,688	59,674	62,817	66,125	69,608	73,274	77,133
VOC attacks per year	0.0%	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*	*6.0*
Total hospitalization		82,030	85,907	89,970	94,228	98,690	103,366	108,267	113,403	118,786	124,427	130,341	136,539	143,035
GMI-1070 penetration														
% of pediatric patients	0.0%				*10.0%*	*30.0%*	*50.0%*	*60.0%*	*70.0%*	*75.0%*	*80.0%*	*80.0%*	*80.0%*	*80.0%*
Total pediatric Tx courses					4,563	14,260	24,757	30,947	37,610	41,977	46,642	48,586	50,612	52,722
% of patients between 18 and 30	0.0%				*10.0%*	*30.0%*	*50.0%*	*60.0%*	*70.0%*	*75.0%*	*80.0%*	*80.0%*	*80.0%*	*80.0%*
Total young adult Tx courses					4,860	15,347	26,926	34,013	41,772	47,113	52,900	55,686	58,619	61,706
Number of course of GMI-1070					9,423	29,607	51,683	64,960	79,382	89,089	99,542	104,273	109,231	114,428
Gross price	3.0%				12,000.00	12,360.00	12,730.80	13,112.72	13,506.11	13,911.29	14,328.63	14,758.49	15,201.24	15,657.28
Net revenue	15.0%				10,200.00	10,506.00	10,821.18	11,145.82	11,480.19	11,824.60	12,179.33	12,544.71	12,921.05	13,308.69
GMI-1070 Revenue					96.11	311.05	559.27	724.03	911.32	1,053.44	1,212.35	1,308.07	1,411.38	1,522.89
Royalty payment to GLYC	18.0%				17.30	55.99	100.67	130.33	164.04	189.62	218.22	235.45	254.05	274.12

Source: Company reports and Canaccord Genuity estimates

RECOMMENDATION

We expect GMI-1070 to very rapidly become a key therapy for the treatment of acute sickle cell crises and part of standard of care. We believe the soon-to-be initiated Phase 3 trial run by Pfizer will be successful in showing a statistically significant improvement in duration of sickle cell VOC. Given the unmet need in sickle cell disease, we would actually view the trial as successful even if it missed statistical significance by a relatively small margin. We think any drug that showed more than 24-hour reduction in hospitalization would easily be included in hospital formularies for the treatment of SCD pain crises. Further, we expect the safety and tolerability profile of GMI-1070 to continue to be positive, with little to no evidence increased infection risk with episodic use. First data from this trial will be available in H2/16 according to our estimates.

We expect GMI-1070 to obtain full FDA and EMA approval if the trial shows the therapeutic profile described above. We also expect the process of hospital formulary inclusion in the U.S. will be manageable if the drug is priced around our current estimate of $12,000 per treatment course. We also expect EU reimbursement hurdles to be manageable given the vast unmet medical need and the small overall burden to the national healthcare systems given the genetic demographic of most EU markets. Given recent trends in EU reimbursement reform, we have chosen to conservatively exclude the EU markets from our current estimates. We also exclude potential ROW revenues given the lack of clarity on approval and reimbursement, despite noting that the African and Near Eastern patient populations are vast.

In the U.S., we expected GMI-1070 to be used in over 80% of pediatric vaso-occlusive crises and around 80% of crises in young adults. This could lead to $1,212M in peak market share-driven sales in the U.S. in 2023, assuming a 2017 U.S. approval. EU approval and launch would likely occur one to two years after the U.S.

COMPANY OVERVIEW

Novel glycomimetics platform – specialized carbohydrate chemistry

GlycoMimetics is a clinical stage biotechnology company focused on the discovery and development of novel glycomimetic (carbohydrate imitating) drugs to address unmet medical needs resulting from diseases in which carbohydrate biology plays a key role. Glycomimetics are molecules that mimic the structure of carbohydrates involved in important biological processes. GlycoMimetics has the proprietary expertise in carbohydrate chemistry and knowledge of the structure and function of carbohydrate biology to develop a pipeline of proprietary glycomimetics that specifically target the disease-related functions of carbohydrates. These can include roles in inflammation, cancer cell survival/behavior and infection. We believe this represents an innovative approach to drug discovery to treat a wide range of diseases.

BIOLOGY OF SELECTINS

Selectins are carbohydrate-binding molecules that bind to fucosylated and sialylated glycoprotein ligands. Selectins are found on endothelial cells, leukocytes and platelets, and are closely involved in trafficking of cells of the innate immune system, T lymphocytes and platelets.

An absence of selectins or selectin ligands has serious consequences in mice or humans, leading to recurrent bacterial infections and persistent disease. Selectins are involved in constitutive lymphocyte homing, and in chronic and acute inflammation processes, including post-ischemic inflammation in muscle, kidney and heart, skin inflammation, atherosclerosis, glomerulonephritis and lupus erythematosus.

Selectin-neutralizing monoclonal antibodies, recombinant soluble P-selectin glycoprotein ligand 1 and small-molecule inhibitors of selectins have been tested in clinical trials on patients with multiple trauma, cardiac indications and pediatric asthma, respectively. Anti-selectin antibodies have also been successfully used in preclinical models to deliver imaging contrast agents and therapeutics to sites of inflammation. Further improvements in the efficiency, availability, specificity and pharmacokinetics of selectin inhibitors, and specialized application routes and schedules hold promise for therapeutic indications.

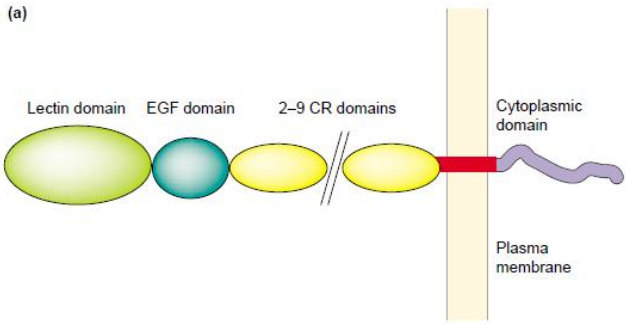
SELECTIN SUBTYPES: E, P &L

The selectins are a family of three type-I cell-surface glycoproteins: E-, L- and P-selectin:

- L-selectin is expressed on all granulocytes and monocytes and on most lymphocytes:
- P-selectin is stored in a-granules of platelets and in Weibel–Palade bodies of endothelial cells, and is translocated to the cell surface of activated endothelial cells and platelets.
- E-selectin is not expressed under baseline conditions, except in skin microvessels, but is rapidly induced by inflammatory cytokines.

Selectins show a significant degree of sequence homology among themselves (except in the transmembrane and cytoplasmic domains) and between species (Fig. 5). Analysis of this homology has revealed that the lectin domain, which binds sugars, is most conserved, suggesting that the three selectins bind similar sugar structures. Interestingly, the cytoplasmic and transmembrane domains are highly conserved between species, but not conserved across the selectins. These parts of the selectin molecules are responsible for their targeting to different compartments: P-selectin to secretory granules, E-selectin to the plasma membrane, and L-selectin to the tips of microfolds on leukocytes.

Figure 5: Selectin structure



(b) Approximate amino acid identity

Among same selectin between species	72%	60% (P > 90%)	40%	80% (L > 95%)	>75%
Among different selectins in same species	52%	47%	35%	None	None

Source: Ley, 2003

The involvement of negatively charged groups, such as sulphates and carboxylates, in the binding of L- and P-selectin has led to one of the major pitfalls in designing small molecule inhibitors for the selectins. A wide range of structurally diverse, negatively charged molecules has been reported to bind P- and L-selectins, which can result in non-specific binding and signaling. These include sulphatides, heparins, fucoidan, sulphated dextran, chondroitin sulphate, dermatan sulphate, tyrosine sulphates, sulphated hyaluronic acid and sulphogalabiose.

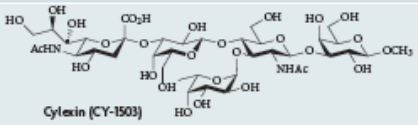
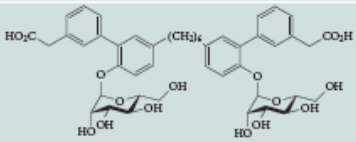
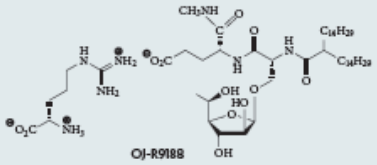
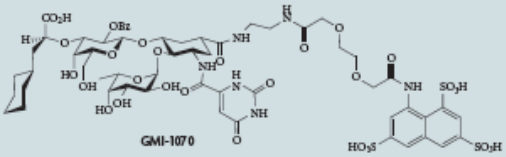
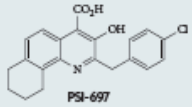
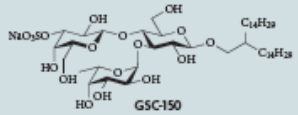
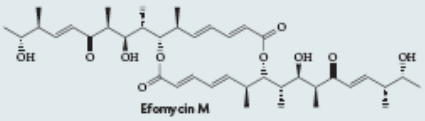
Such a promiscuous range of molecules suggests that their inhibitory activity is due to nonspecific negative charge interactions. In fact, the Kretzschmar 1997 study even described potent P-selectin activity found in trace contaminants of polyanions from ion exchange media used in preparation samples. Thus, the specificity of small molecule, highly charged selectin antagonists that inhibit P- and L- but not E-selectin must be carefully evaluated.

In diseases in which cell adhesion, extravasation of cells from the bloodstream or the migration of specific lymphocytes has been implicated in the pathology, selectins present an attractive therapeutic target. For example, E- and P-selectins have been shown to mediate the acute adhesion and aggregation of leukocytes and erythrocytes during a vasoocclusive crisis in a mouse model of sickle cell disease. Furthermore, anormal extravasation of cells from the bloodstream is the hallmark of many inflammatory diseases (such as asthma, colitis, arthritis and psoriasis) and cancer. Tumor cells that extravasate out of the bloodstream use the selectin pathway to metastasize. Many solid tumors and adenocarcinomas, such as gastrointestinal, pancreatic, breast, lung and prostate cancers, express high levels of selectin ligands. Incidentally, expression of these markers on the tumor cells of patients with gastric and colon cancers is significantly correlated with poor survival. Cimetidine (Tagamet; GSK), a histamine receptor antagonist that also suppresses vascular expression of E-selectin, markedly and specifically improved survival of high risk patients identified by tumor expression of selectin ligands, further supporting the usefulness of selectins as therapeutic targets for cancer.

SELECTINS IN BLOOD CELL TRAFFICKING

Selectins and their ligands have also been reported to play key parts in the dissemination of hematological cancers and the homing of leukemic stem cells to select areas (or microdomains) within the bone marrow. E-selectin in particular is constitutively expressed in the bone marrow and binds carbohydrate ligands that are found on leukemic stem cells. Once adherent to these microdomains in the bone marrow, leukemic cells become dormant (or quiescent) and therefore less metabolically active and less susceptible to killing by anti-proliferative chemotherapy drugs such as cytosine arabinoside. Potent selectin antagonists present new therapeutic opportunities for treating these diseases. By preventing sequestration of leukemic cells in the bone marrow and keeping them in circulation, combination therapy with selectin antagonists is likely to make the cells more susceptible to chemotherapy. Some examples of glycomimetic, small-molecule antagonists of the selectins are presented in Figure 6.

Figure 6: Small-molecule selectin antagonists in preclinical and clinical trials

Name and structure	Specificity	Disease	Institution	Status	Refs
 Cylexin (CY-1503)	E-, P- and L-selectin	Cardio-vascular injury	Cytel	Stopped	179
 Bimosiamose (TBC-1269)	E-, P- and L-selectin	Asthma and psoriasis	Revotar	Phase IIa	180
 OJ-R9188	E-, P- and L-selectin	Allergic dermatitis	Nippon Organon	Preclinical	181
 GMI-1070	E-, P- and L-selectin	Sickle cell crisis	Glyco-Mimetics	Phase I	182
 PSI-697	P-selectin	Athero-thrombotic and venous thrombotic diseases	Wyeth	Phase I	183
 GSC-150	E-, P- and L-selectin	Metastatic cancer	Kanebo	Unknown	184
 Eforycin M	E- and P-selectin	Psoriasis	Bayer	Preclinical	185

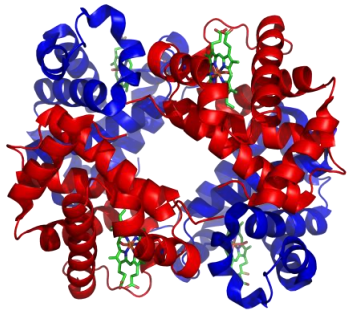
Source: Magnani, 2009

SICKLE CELL DISEASE

Background on sickle cell disease

Sickle-cell disease (SCD), or sickle-cell anemia (SCA), or drepanocytosis, is a hereditary blood disorder, characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and results in a risk of various complications. The sickling occurs because of a mutation in one of the hemoglobin genes. Hemoglobin is a tetramer of four iron-containing oxygen-transport metalloprotein subunits in the red blood cells of humans. Hemoglobin in the blood carries oxygen from the respiratory organs to the rest of the body where it releases the oxygen to burn nutrients to provide energy to power the functions of the organism, and collects the resultant carbon dioxide to bring back to the respiratory organs to be dispensed. In humans, the protein makes up about 97% of the red blood cells' dry content by weight and around 35% of the total content, including water. Hemoglobin has an oxygen binding capacity of 1.34mL O2 per gram per hemoglobin, which increases the total blood oxygen capacity seventy-fold compared to dissolved oxygen in blood. The human hemoglobin molecule can bind up to four oxygen molecules.

Figure 7: Structure of adult human hemoglobin A heterotetramer $(\alpha\beta)_2$



Source: NIH

Hemoglobin variants (with differing subunits) are a part of the normal embryonic and fetal development, but may also be pathologic mutant forms of hemoglobin in a population, caused by variations in genetics. Five hemoglobin variants are found in the embryonic and fetal body: Gower 1 (ζ2ε2), Gower 2 (α2ε2), hemoglobin Portland I (ζ2γ2), hemoglobin Portland II (ζ2β2), and hemoglobin F (α2γ2). Hemoglobin F is the main oxygen transport protein in the human fetus during the last seven months of development in the uterus and in the newborn until 6 months after birth. Functionally, fetal hemoglobin differs most from adult hemoglobin in that it is able to bind oxygen with greater affinity than the adult form, giving the developing fetus better access to oxygen from the mother's bloodstream.

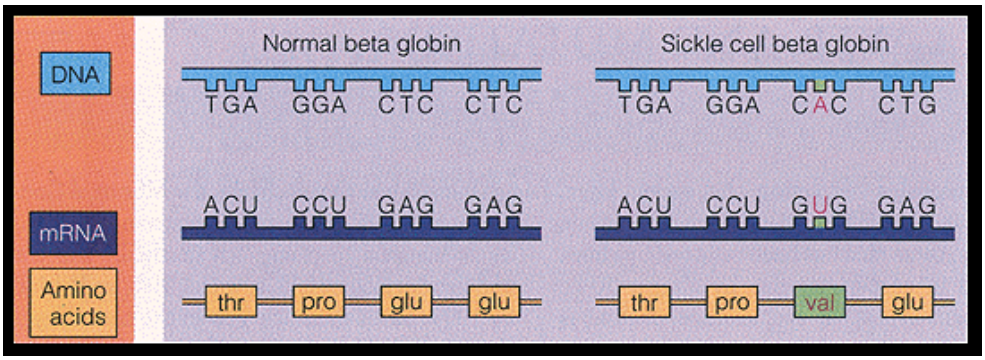
In adults, there are three major forms of hemoglobin variants: hemoglobin A (α2β2), hemoglobin A2 (α2δ2), and hemoglobin F (α2γ2). Hemoglobin A is the most common variant comprising over 97% of the total red blood cell hemoglobin in normal adults and it consists two pairs of the alpha and beta subunits (Figure 7). Hemoglobin A2 (HbA2) is a normal variant of hemoglobin A that consists of two alpha and two delta chains (α2δ2) and is found at low levels in normal human blood. HbA2 exists in small amounts in all adult humans, accounting for 1.5-3.1% of all hemoglobin molecules. In adults, hemoglobin F is

restricted to F-cells, the pancreatic polypeptide producing cells in the islets of Langerhans of the pancreas.

Hemoglobin S

Hemoglobin S (α2βS2), hemoglobin AS, and hemoglobin SC disease are the three hemoglobin variants that contribute to the sickling of red blood cells. Hemoglobin S results from the substitution of a valine for glutamic acid as the sixth amino acid of the beta globin chain, which produces a hemoglobin tetramer that is barely soluble when deoxygenated (Figure 8).

Figure 8: Single nucleotide substitution leads to the production of sickle cell beta globin



Source: Pagon, 1993.

The polymerization of deoxy-hemoglobin (Hb) S is essential to vaso-occlusive phenomena. However, polymerization alone does not account for the pathophysiology of sickle cell disease. Changes in red cell membrane structure and function, disordered cell volume control and increased adherence to vascular endothelium also play an important role. Common varieties of sickle cell disease are inherited as homozygosity for beta S globin chain, called sickle cell anemia (Hb SS) or as compound heterozygosity of the beta S globin chain with another type mutant beta globin: sickle cell – beta 0 thalassemia (Hb S-β° thal), sickle cell-Hb C disease (Hb SC disease) and sickle cell – beta + thalassemia (Hb S-β+ thal). The beta-thalassemia mutation occurs at a different point on the beta subunit gene, and renders it defective (beta+) or unreadable (beta 0). Hb S-β° thal (referred to as 'beta zero thal'). patients as a result rely only on their 'other' hemoglobin beta subunit gene for all their beta subunit production. Disease manifestations are most severe in patients with Hb SS and Hb S-β° thal.

Mutation characterization

Sickle cell anemia and Hb S-β° thal are characterized by a severe hemolytic anemia with intermittent painful vaso-occlusive crises. Other typical acute complications of sickle cell anemia include focal infarction of the spleen, kidneys, lungs, bone, retina, or brain, sudden extensive sequestration of blood in the spleen or liver or overwhelming infection with encapsulated bacteria. Hb S-β+ thal and Hb SC are characterized by rare crises and aseptic necrosis, but they can still occur and some clinicians we have spoken to have a percentage of their SC patients on hydroxyurea treatment. Sickling normally takes place when the PO2 falls below 60 mmHg.

Sickle cell trait (SCT) (Hb AS) is a benign condition where only 20-45% of hemoglobin is Hb S. Normally human blood consists of 96-98% Hb A, 2-3% Hb A2, and <1% Hb F. SCT is not associated with anemia, change in red blood cell survival, or life expectancy alteration. Though persons with SCT are generally regarded as clinically normal there has been rare association of sickle cell trait with acute medical issues. The conditions include splenic infarction at high altitude with exercise or hypoxemia, hematuria secondary to renal papillary necrosis, fatal exertional heat illness with exercise, sudden idiopathic death with exercise, glaucoma or recurrent hyphema following a first episode of hyphema, hyposthenuria (an inability to fully concentrate urine), bacteriuria in women, bacteriuria or pyelonephritis associated with pregnancy, renal medullary carcinoma in young people (ages 11 to 39 years), early onset of end stage renal disease from autosomal dominant polycystic kidney disease, and priapism.

Prevalence

National SCD population estimates ranged from 104,000 to 138,900, based on birth-cohort disease prevalence, but from 72,000 to 98,000 when corrected for early mortality. Several limitations were noted in the available data, particularly for SCD mortality in adults.

Figure 9 lists the birth-cohort prevalence estimates of SCD for African-American and Hispanic populations as reported by US Agency for Health Care Policy and Research.

Figure 9: Birth cohort-SCD prevalence estimates

	Source of prevalence estimate		
Population, type of SCD	**AHCPR[2] 1993**	**California[9] 1990–1998**	**NNSIS 2005–2007**
African-American			
All types of SCD	1:346		1:365
HbSS		1:700	1:601
HbSC		1:1,297	1:1,127
HbSβthalassemia		1:4,056	1:4,198
Hispanic			
All types of SCD	East: 1:1,114 West: 1:31,847		1:16,305
HbSS		1:45,622	1:18,642
HbSC		1:364,976	1:57,700
HbSβthalassemia		1:729,953	1:175,233

Source: US Agency for Health Care Policy and Research

The total U.S. SCD population estimates based on disease prevalence as reported by U.S. Agency for Health Care Policy and Research and as derived from the National Newborn Screening Information System are noted in Figure 10.

Figure 10: US SCD population estimates

	Population estimate based on			
SCD population	AHCPR prevalence	Hispanic	NNSIS prevalence	Hispanic
African-American	105,261		101,840	
Hispanic	10,180		2,646	
Total	115,442	9%	104,487	2.5%

Source: US Census, 2009

Pathophysiology of sickle cell disease

The fundamental pathophysiological basis of SCD is the polymerization of sickle hemoglobin in the cytoplasm of the red blood cell (RBC). The degree of sickle hemoglobin polymerization varies with microenvironmental changes, including hydration, oxygen saturation and anatomic location in the body, and varies over time. Most prominent of its consequences is diminished RBC flexibility, which impairs blood flow through the microvasculature. Unique to SCD are episodes of acute vascular occlusion that promote tissue ischemia and pain, sometimes progressing to organ infarction. Vascular occlusion may also cause a pneumonia-like condition, known as "acute chest syndrome," and bone necrosis, especially in the femoral head. Vascular occlusion due to polymerization of sickle hemoglobin remains the hallmark and virtually unique feature of SCD.

Sickle hemoglobin polymerization leads to a remarkable spectrum of biochemical, cellular and physiological pathology, which is associated with a wide array of clinical complications. Sickling appears to promote adhesion of various blood cells to the activated, adhesive vascular endothelium, which may contribute to vascular occlusion. Sickle hemoglobin polymerization robustly induces RBC oxidant stress, with linked damage to RBC metabolism, the cytoskeleton and membrane, leading to loss of membrane integrity and hemolysis. Recent evidence suggests the hemolysis induced by sickle hemoglobin polymerization promotes deficiency of nitric oxide (NO), increasing the risk of pulmonary hypertension, and cutaneous leg ulceration and priapism. It has been shown that chronic SCD crises lead to permanent damage to the brain, heart, kidneys, liver, spleen, and bones.

Normal erythrocyte proteome

RBC membrane proteome include proteins involved in membrane repair, maintaining RBC shape and deformability, regulation of cell volume, the transport of nutrients and intercell signaling and interaction. The RBC membrane consists of the phospholipid bilayer and supporting cytoskeletal network, which are attached to each other by protein 4.1, protein 3 and ankyrin. The RBC is unable to synthesize phospholipids itself, so any loss of integrity of the phospholipid membrane depends on exchange with the environment for repair – the outer layer, by incorporating free cholesterol obtained from plasma lipoproteins, and the inner layer by ATP-mediated acylation of membrane lysophospholipids.

Red blood cell shape and deformability is largely determined by the cytoskeletal network, which consists of highly coiled helical rods of spectrin tetramers, conferring flexibility and spring-like properties, and actin, which polymerizes to increase cell rigidity and *vice versa*. Dematin (protein 4.9) and α- and β-adducin heterodimers bundle the actin filaments. Adducin also acts as an actin polymer cap and, together with tropomyosin and tropomodulin, tightly controls the ratio of polymerized:depolymerized actin to affect cell

malleability. ATP-driven phosphorylation of the cytoskeletal network, calcium extrusion and various membrane-associated enzymes also mediate RBC plasticity.

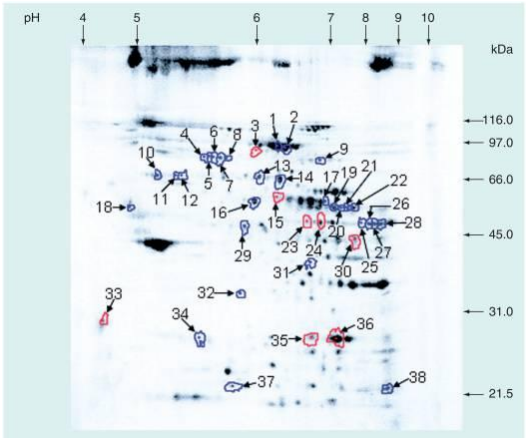
Deformability of the RBC is a crucial property to facilitate its passage through capillaries, and for successful oxygen delivery to the target tissues. Two factors that have been identified as major contributors to the deformability of the cell are the reduced surface area: volume ratio and cytoplasmic viscosity, which depends on the concentration of hemoglobin. The viscoelastic property of the membrane is also a minor factor. Owing to cell volume being an important determinant, the red cell has a number of transporters believed to have a role in volume regulation, including several different cation ATPase transporters, passive K:Cl co-transporters and calcium-dependent potassium transporters, aquaporins that respond to changes in osmolarity and amino acid transporters that are also involved in osmoregulation.

Other transporters found in the RBC membrane are responsible for RBC function (the band 3 anion exchanger facilitating proton-mediated oxygen release from hemoglobin to tissues) and nutrient influx (facilitated glucose transporters providing RBCs with their primary energy source and nucleoside transporters).

Red blood cell membrane proteomics in SCD

In 2005, Kakhniashvili *et al.* evaluated the sickle cell erythrocyte membrane proteome using 2D fluorescence difference gel electrophoresis (2D-DIGE; Figure 11), trypsin digest, HPLC and tandem MS (LC-MS/MS). A total of 22 proteins were identified (44 protein forms, including post-translational modifications) from sickle cell RBC membranes that had a 2.5-fold or greater difference from control RBC membranes, according to the threshold deemed statistically significant, based on normal variation of protein levels in normal healthy controls.

Figure 11: Representative 2D fluorescence difference gel electrophoresis



Source: J. Investig. Med. 2004;52(6):402-6

Proteins with the most pronounced increases in sickle cell RBCs included the 70-kDa heat-shock protein 8 isoform 1 and chaperonin-containing T-complex protein 1 (TCP1) – both involved in protein repair; protein 4.1; and ankyrin – both involved in cytoskeleton attachment to the phospholipid bilayer, and the α-subunit of ATP-synthase. Interestingly, protein 4.1 was both increased and decreased in differing spots on the 2D gel. The two

isoforms diverging in quantity had a notable difference in isoelectric point (pI) and molecular weight (MW). The isoform with a pI of 5.98 and MW of 89.2 kDa was decreased 3.2-fold in sickle cell RBCs, in contrast to the isoform with a pI that increased from 5.6 to 5.78 and a MW of 82.7 kDa, which was increased 3.3– to 6.6-fold. Ankyrin's MW was increased 3.9– to 4.9-fold in sickle erythrocytes (Figure 12).

Figure 12: Erythrocyte proteins altered in sickle cell disease

Category	Function	Protein (MW)	GI no.	Change in SCD
Cytoskeletal	Actin accessory	Ankyrin 1 (92 kDa)	105337	Increased 3.9–4.9-fold; increased threefold with HU
		Protein 4.1 (82 kDa); pI: 5.72	14916944	Increased 2.7–6.6-fold; increased two–threefold without HU†
		Protein 4.1 (89.2 kDa); pI: 5.98, 6-kDa larger	14916944	Decreased 3.2-fold; increased two–threefold without HU†
		Dematin protein 4.9 (44.1 kDa)	22654240	Decreased 2.6-fold
		Tropomyosin 3 (30 kDa)	24119203	Decreased 2.6-fold
		Anion exchanger band 3 (52 kDa)	4507021	Increased 2.5-fold with HU
		Tropomodulin (40 kDa)	135922	Increased two–threefold with HU
		Actin, β-actin (41 kDa)	1703156, 1419444	Increased 2- to 3.5-fold with HU
		Palmitoylated membrane protein p55 (55 kDa)	62898353	Increased two–threefold with HU
Membrane	Active transport	ATP synthase α-subunit (48.9 kDa)	4757810	Increased 2.6–5.1-fold
	Lipid raft	Flotillin-1 (49 kDa)	5031699	Decreased 2.8–3.3-fold
		Stomatin isoform a (27.4 kDa); pI: 6.5	38016911	Decreased 3.8-fold
		Stomatin isoform a (27.4 kDa); pI: 5.56	38016911	Increased 2.7-fold
	Vesicle transport	RAB-8b GTPase (22 kDa)	7706563	Increased 2.8-fold
Cytoplasmic	Protein turnover	Proteasome-β 1 subunit (22 kDa)	4506193	Increased 2.8-fold
		Proteasome 26S ATPase subunit 6 (39 kDa)	24430160	Increased 2.6-fold
		Proteasome-α 1 subunit, isoform 1 (34 kDa)	23110935	Increased 2.5-fold
	Protein folding	Chaperonin containing TCP1 subunit 7 (54 kDa)	5453607‡, 1729870‡	Increased 2.9–4.2-fold
	Protein repair	Heat-shock protein 8 (68 kDa)	5729877	Increased 7.3-fold
	Antioxidant	Peroxiredoxin 3 isoform b (22.2 kDa)	32483377	Increased 2.9-fold
		Peroxiredoxin 1 (22 kDa)	4505591	Increased 2.8-fold
	Antioxidant	Catalase (56 kDa)	4557014	Increased 3.1-fold
	Glycolysis	Glyceraldehyde-3-phosphate dehydrogenase (36 kDa)	7669492	Increased two–fourfold with HU
		Fructose bisphosphate aldolase (39 kDa)	113606	Increased twofold with HU

Source: Suffredini, 2010

Decreases in sickle cell membranes tended to be among components of the lipid raft (flotillin-1 and stomatin) and actin accessory proteins (dematin and tropomyosin 3). Flotillin-1 and stomatin are moieties that may also be involved in signal transduction as they regulate transmembrane monovalent cation flux.

Chronic treatments: hydroxyurea and penicillin prophylaxis

Hydroxyurea (HU) is the only drug approved by the US FDA expressly for SCD. Hydroxyurea was first approved in 1967 for the treatment of blood cancers and approved for SCD in 1998. This agent is known to promote elevation of fetal hemoglobin, increasing the mean corpuscular volume suggestive of improved RBC hydration and decreasing endothelial adhesion. The gene coding for hemoglobin F is distinct from that of the hemoglobin beta gene, but F can substitute for beta in the hemoglobin tetramer, forming a functional hemoglobin molecule with no risk of sickling. HU elevates the amount of Hemoglobin F expressed, and therefore non-sickling hemoglobin present, Patient responses vary greatly, and doses are titrated to optimally balance HbF levels versus neutropenic side effects. Some physicians believe that the neutropenic effects of HU are at least part of what mediates the benefit of the treatment. There is significant evidence white blood cells are critical in the precipitation and/or prolongation of SCD pain crisis. According to this theory, reducing levels of white blood cells could then reduce the potential for a SCD pain crisis.

The physicians we spoke with believe aggressive HU treatment at the early onset of crisis to be most effective. Typical dosage is around 20mg/kg, and the treating physician will titrate 5mg/kg increments every eight to 12 weeks for optimal clinical and hematological response while monitoring for toxicities manifested in GI symptoms, rash, hair loss, thrombocytopenia, neutropenia, or hemoglobin drop of over 20%. We note that some patients are concerned about leukemic transformation as see with myeloproliferative disorders and some even consider the side effects to be more severe of the SCD VOC itself. A study done by the Sickle Cell Disease Organization estimates the cost of a course of HU at $1000.

On a molecular level, ten erythrocyte membrane proteins are affected by the administration of hydroxyurea: a trend involving antioxidants (catalase, thioredoxin peroxidase, flavin reductase and peroxiredoxin-2 isoform a), an oxidoreductase (aldehyde dehydrogenase), proteins involved in protein repair (chaperonin-containing TCP1 subunits δ and ε) and protein degradation (proteasomal α2 subunit). In addition, a structural membrane component (palmitoylated membrane protein p55), carbonic anhydrase and β-globin are also involved.

The oxidative stress effect of hydroxyurea via its mechanism for induction of altered erythroid differentiation is usually followed by a compensatory rise in antioxidants. The increase in protein repair and turnover constituents was suggested as a response to oxidative protein damage. Further research assessing the post-translational modification of catalase using 2D quantitative western blotting showed a twofold increase in tyrosine phosphorylation with hydroxyurea exposure. This observation is consistent with prior studies that showed phosphorylation of catalase by tyrosine kinases in response to oxidative stress, increasing catalase activity at a post-translational level. In patients with SCD, there are large numbers of circulating reticulocytes – enucleated immature RBCs that contain abundant RNA and are translationally active – so it is possible the experiments are reflecting hydroxyurea's translational and post-translational effects.

Studies using *in vivo* administration of therapeutic doses of hydroxyurea observed significant increases in cytoskeletal components (anion exchanger band 3, ankyrin, protein 4.1, p55, actin, tropomodulin and stomatin) and glycolytic enzymes (glyceraldehydes-3-phosphate dehydrogenase and fructose bisphosphate aldolase). The increase in glycolytic

enzymes was attributed to an increased demand for ATP synthesis as a result of hydroxyurea-induced oxidative stress; however, an alternate explanation might involve activation of the hypoxia-inducible factor (HIF)-1, which is known to regulate anaerobic glycolysis. Decreases were observed in chaperonin-containing TCP1 subunit 2 (2.45-fold) and proteasome subunit-α type 4 (4.13-fold), though these decreases may be attributed to increased oxidative stress in response to hydroxyurea they may actually reflect a clinical improvement in response to treatment, considering that both of these proteins are elevated in SCD at baseline. The only hydroxyurea-induced change common to both the *in vivo* and *in vitro* studies was the increase in p55, which was confirmed by an immunoblot that demonstrated a five–tenfold increase of p55 in two representative hydroxyurea-treated patients, as compared with untreated patients.

Penicillin prophylaxis. Prophylaxis with penicillin has become standard of care for children with SCD, and is largely responsible for the sharp drop in childhood disease mortality since the 1980s. Prophylaxis is thought to prevent morbidity associated with infections related to splenic infarcts, ACS and other manifestations of disease. The Prophylactic Penicillin Study (PROPS) Group conducted the first study to assess the efficacy of penicillin prophylaxis in the prevention of severe bacterial infections in children with SCA and the reported effectiveness of penicillin prophylaxis formed the foundation of the guidelines for penicillin prophylaxis in SCD. The investigators concluded that penicillin prophylaxis would drastically reduce the risk of pneumococcal infection in children with SCA, especially those under the age of three. They also noted the earlier penicillin prophylaxis begins, the more likely it is to be effective since the risk of infection is inversely related to age. In addition, even though compliance of penicillin therapy could not be accurately assessed, Gaston and colleagues suggested that infection rates decreased since parents could administer penicillin at the first signs of febrile illness in the patient with SCA. Another outcome of the PROPS trial was the advocacy for sickle cell testing as a standard component of newborn screenings. This early diagnosis of SCD allowed practitioners to initiate penicillin prophylaxis before the age of 4 months.

Stem cell transplant is the only curative treatment for sickle cell disease. More than 200 patients with sickle cell disease have undergone stem cell transplants from a matched sibling donor. Stem cell transplant has a 5%-10% risk of death, but patients with successful transplants were completely cured of sickle cell disease, with no further episodes of pain. Stem cell transplants are performed in young patients with severe sickle cell disease who have a matched sibling donor. Stem cell transplant using umbilical cord blood from a related donor has also been curative in a small number of patients.

Acute treatment: Treatment of SCD pain crises

The mainstay of therapy for pain episodes is supportive: hydration through intravenous fluids, anti-inflammatory agents and pain medication via nonsteroidal anti-inflammatory drugs and narcotic analgesia. There are no disease-specific treatments that have been proven to reduce length of crises and even supportive care can only reduce length of crises to ~4-5 days, during which patients experience excruciating, immobilizing pain. Pain is the hallmark and major marker of these episodes: patients are admitted when they subjectively feel they are experience incapacitating pain that are not controlled by outpatient prescription oral opiates and now require IV opioids. Patients are also discharged when they feel crises- associated pain has reduced sufficiently that it can be managed at home.

Pain episodes are therapeutically managed in-patient with a multi-model approach. Life threatening or severe complications such as acute chest syndrome and stroke are often treated with transfusion to reduce the percentage of Hb S while increasing oxygen-carrying capacity. Other treatments may include joint replacement, hemodialysis, kidney transplantation, splenectomy for splenic sequestration crisis, and/or cholecystectomy for cholelithiasis. Acute treatment of stroke includes red blood cell exchange transfusion and aggressive management of increased intracranial pressure and seizures. Severe priapism may require aspiration and irrigation. Management of pulmonary hypertension can include routine treatments and specific therapies such as phosphodiesterase inhibitors or nitrous oxide. Notably, there are no disease specific treatments for SCD pain crisis.

White blood cells in sickle cell disease

There is an increasing body of evidence that suggests white blood cells, especially neutrophils, may be involved in the initiation and propagation of vasoocclusive crisis in SCD. Elevated total WBC counts are common in SCD patients and WBC counts of more than 15,000 cells/µL are associated with an increased risk of early death in SCD. Adhesion of activated neutrophils to endothelium in patients with SCD may lead to endothelial damages as descried in other vascular diseases. Because the neutrophil is larger and more difficult to deform than the red cell, its attachment to the endothelium, particularly in the microcirculation, would impede passage of RBC and WBC, which could increase the risk for VOC.

In a study by Lard et al, the activation state of neutrophils in sickle cell patients was analyzed by determining the level of expression of neutrophil antigens such as CD62L, CD11b, CD66b, CD63, and Fc-gamma receptors. Plasma levels of lactoferrin, elastase, soluble CD16 (sFc-gamma-RIII), and serum levels of soluble CD62L (sL-selectin) were analyzed as neutrophil activation markers. There was significant observed differences in the activation state of neutrophils in non-symptomatic sickle cell patients compared to healthy HbAA controls as exemplified by significant decrease in L-selectin expression, enhanced expression of CD64, and increased levels of soluble markers like sL-selectin, elastase, and sCD16. During VOC the differences were even more pronounced. These results show neutrophils to be activated in sickle cell patients, suggesting a role of importance in the pathophysiology of sickle cell disease.

Monocyte proteomics in sickle cell disease

Elevated PlGF levels correlate with the severity of vaso-occlusive manifestations in SCD. PlGF activates endothelial cell adhesion molecule expression by increasing monocyte production of IL-1β and TNF-α. Monocyte membrane proteins correlated with disease severity were glycolytic enzyme transketolase, coronin and moesin – actin binding proteins involved in motility – and cell signaling mediator guanine nucleotide-binding protein. They were all negatively correlated with vaso-occlusive manifestations. Cytosolic monocyte proteins with the positive correlation with disease severity were the upstream element-binding protein, α-actinin, the myristic acid/tri-iodobenzoic acid/albumin complex, filamin A, integrin, the apo form of human mitochondrial aldehyde dehydrogenase chain A and leukotriene A-4 hydrolase. Negatively correlated cytosolic monocyte proteins largely consisted of those involved in protein folding, repair and turnover – heat-shock proteins, TCP and chaperonin-containing TCP1. Elevated PlGF levels correlate with the severity of vaso-occlusive manifestations in SCD. PlGF activates endothelial cell adhesion molecule expression by increasing monocyte production of IL-1β and TNF-α. Monocyte membrane

proteins correlated with disease severity were glycolytic enzyme transketolase, coronin and moesin – actin binding proteins involved in motility – and cell signaling mediator guanine nucleotide-binding protein. They were all negatively correlated with vaso-occlusive manifestations. Cytosolic monocyte proteins with the positive correlation with disease severity were the upstream element-binding protein, α-actinin, the myristic acid/tri-iodobenzoic acid/albumin complex, filamin A, integrin, the apo form of human mitochondrial aldehyde dehydrogenase chain A and leukotriene A-4 hydrolase. Negatively correlated cytosolic monocyte proteins largely consisted of those involved in protein folding, repair and turnover – heat-shock proteins, TCP and chaperonin-containing TCP1 (Figure 13).

Figure 13: Significant monocyte proteins altered in sickle cell disease

Category	Function	Protein (MW)	GI no.	Change in SCD
Membrane	Glycolysis	Transketolase (75 kDa)	4507521	Negatively correlated with VOC rate
	Actin-binding; cell motility	Coronin (62 kDa)	5902134	Negatively correlated with VOC rate
	Actin-binding; cell motility	Moesin (81 kDa)	4505257	Negatively correlated with VOC rate
	Cell signaling	Guanine nucleotide-binding protein (32 kDa)	5174447	Negatively correlated with VOC rate
Cytosolic	ATP-dependent DNA helicase	Far upstream element-binding protein (96 kDa)	37078468	Positively correlated with VOC rate
	Actin accessory	α-actinin (103 kDa)	4501891, 2804273	Positively correlated with VOC rate
	Unclear	Myristic acid/tri-iodobenzoic acid/albumin complex	4389275	Positively correlated with VOC rate
	Actin accessory	Filamin A (272 kDa)	116241365	Positively correlated with VOC rate
	Intra-/extra-cellular signal transduction	Integrin (168 kDa)	64654539	Positively correlated with VOC rate
	Aldehyde oxidation	Mitochondrial aldehyde dehydrogenase (63 kDa)	28949044	Positively correlated with VOC rate
	Arachidonic acid metabolism	Leukotriene A-4 hydrolase (82 kDa)	4505029	Positively correlated with VOC rate
	Protein repair	Heat-shock protein (70 kDa)	12585261	Negatively correlated with VOC rate
	Protein repair	Mitochondrial heat-shock protein (60 kDa)	129379	Negatively correlated with VOC rate
	Protein folding	TCP1, subunit-α (73 kDa)	57863257	Negatively correlated with VOC rate
	Protein folding	Chaperonin-containing TCP1, subunit 8 (69 kDa)	48762932	Negatively correlated with VOC rate
	Mitochondial apoptotic mediator	Adenylate kinase 2 (64 kDa)	5453595	Negatively correlated with VOC rate
	Glycolysis/angiogenesis	Phosphoglycerate kinase 1 (46 kDa)	48145549	Negatively correlated with VOC rate

Source: Suffredini, 2010

Sickle cell plasma proteomics

Pulmonary hypertension (PH) is an independent risk factor for mortality in SCD. Studies suggest decreased plasma levels of apolipoprotein A-I (apoA-I) as a potential marker of PH risk in the setting of SCD. Other markers were increased apolipoprotein A-II (apoA-II) and serum amyloid A (SAA)-4 levels, and decreased levels of plasminogen dimer and haptoglobin dimer (Figure 14).

Figure 14: Significant plasma proteins altered in sickle cell disease

Function	Protein (MW)	GI no.	Change in SCD
Antioxidant/anti-inflammatory, HDL component	ApoA-I (28.1 kDa)	4960066†	Decrease in SCD vs control Decrease in SCD + PH vs SCD - PH Decreased during acute pain episodes
LDL/VLDL component	ApoB	178790†	Decrease in SCD vs control
Ratio	ApoB:ApoA-I ratio	–	Decrease in SCD vs control
HDL component	ApoA-II (8.9 kDa)	296633†, 178424†	Increase in SCD + PH vs SCD - PH
HDL component, constitutive SAA	SAA-4 (13.4 kDa)	13937846†, 119588821†	Increase in SCD + PH vs SCD - PH
Glycoprotein precursor of plasmin	89.4 kDa‡	387031†	Decrease in SCD + PH vs SCD - PH
Scavenges cell-free hemoglobin	Haptoglobin dimer (75.2 kDa)	386783†	Decrease in SCD + PH vs SCD - PH
Uncertain identity	18.4	–	Decrease in SCD + PH vs SCD - PH
Acute phase reactant, antagonizes apoA-I	SAA	40316910†	Increase in acute pain episodes
Ratio	SAA:apoA-I ratio	–	Decrease in acute pain episodes
Oxidative post-translational modification	Malondialdehyde–albumin adduct	–	Qualitative increase in SCD + PH vs SCD - PH

Source: Suffredini, 2010

In a supporting blood flow physiology study of vasomotor reactivity in SCD subjects, lower levels of apoA-I were associated with an impaired vasodilatory response to the endothelial-dependent agonist acetylcholine ($p = 0.001$), indicating association of endothelial dysfunction with lower apoA-I levels in SCD. These results taken together suggest that apolipoprotein dysregulation, manifested by low apoA-I levels, contributed to endothelial dysfunction and PH associated with SCD.

Protein function and structure alterations due to oxidative stress are thought to potentially be a contributor to the pathogenesis of PH. Albumin isolated from the plasma of sickle cell patients, with and without PH, revealed an increased presence of a malondialdehyde (MDA) adduct, localized at the K159 residue, in PH. A similar study of albumin from patients with non-SCD-related idiopathic pulmonary arterial hypertension also showed increased post-translational modification with MDA at the same site. This suggests an oxidative lesion specific to the pathogenesis of pulmonary hypertension, and that post-translational modifications may be present on other abundant, as well as potentially non-abundant, plasma proteins.

Sickle cell transcriptomics versus proteomics

A few studies have examined reticulocyte, erythrocyte, platelet and monocyte gene-expression profiles in the setting of SCD, as well as hydroxyurea treatment, and offer an additional perspective. Several findings from a high-throughput microarray mRNA genomic-profiling study of sickle cell whole blood coincide with recurring proteins in proteomic research, in particular, significant upregulation of ankyrin, erythrocyte membrane protein bands 3 and 4.1, peroxiredoxin and stomatin. Increased levels of enzyme 2,3-bisphosphoglycerate kinase mRNA supports the theory of stimulation of glycolytic pathways in SCD, suggested by proteomic data. Other differentially expressed transcripts included selenium-binding protein, exportin, spermine oxidase, chemokines, interleukin receptor and peptidyl arginine deaminase.

A similar study design assessing platelet mRNA expression identified 100 differentially expressed genes in SCD, major categories being arginine and nitrogen metabolism, redox homeostasis, cell growth, adhesion and signaling pathways. Most notably, there was a significant increase in mRNA of arginase II and ornithine decarboxylase, both enzymes being involved in converting arginine to polyamines. The absence of SCD platelet proteomic studies limits direct comparisons between this study and proteomic data, but the finding of increased redox proteins glutathione peroxidase 4, thioredoxin reductase and superoxide dismutase continues to support the recurrent SCD theme of a response to oxidative stress.

Mononuclear gene-expression profiles in patients with steady state SCD identified a highly specific leukocyte transcriptional response in SCD. A total of 112 genes were identified as being differentially expressed in SCD by global transcriptional microarray analysis, major categories involving heme metabolism, cell cycle regulation, antioxidants, inflammatory mediators and angiogenesis. Most notable were the upregulations of hemeoxygenase 1, biliverdin reductase, cyclin-dependent kinase p21, IL-15, ECGF-1 and antioxidants glutathione peroxidase, thioredoxin and thioredoxin peroxidase. Hydroxyurea, however, did not appear to have a direct effect on leukocyte gene expression, but the study appears underpowered to definitively comment on this effect. A reverse transcriptase PCR-based transcriptomic study of hydroxyurea-induced gene expression in reticulocytes found upregulation of a host of metal-ion-binding proteins and transporters, RNA binding proteins, ubiquitin-protein ligases and glycolytic enzymes.

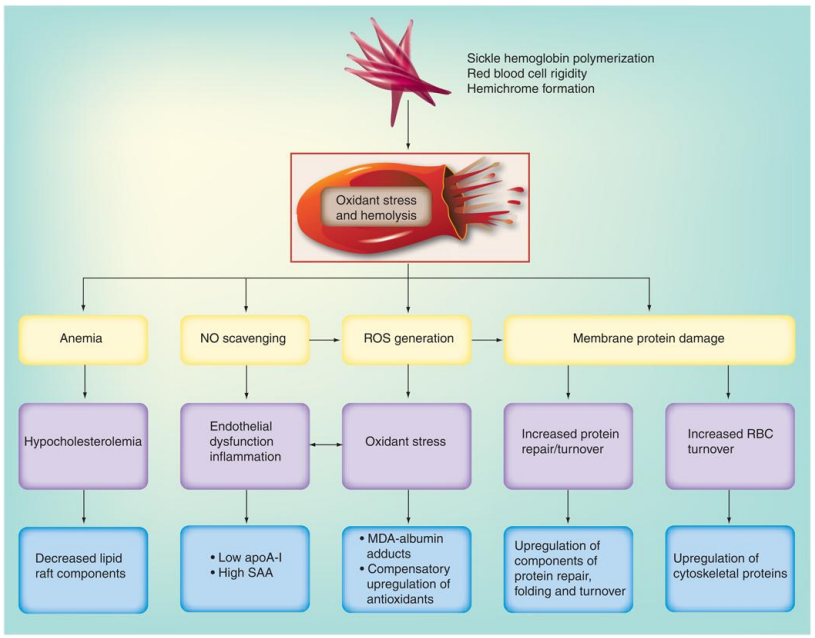
Another similar study of patients with homozygous SCD at steady state focused specifically on the hydroxyurea-induced expression of several low-affinity reticulocyte adhesion molecules suggested that hydroxyurea reduces the adhesive properties of sickle cell erythrocytes and does so at the transcriptional level.

SCD proteomic interactome

A recent interactome mapping study attempts to define sickle cell erythrocyte membrane proteome in the context of a preliminary erythrocyte interactome network constructed from a compilation of 751 erythrocyte membrane proteins. Several of the SCD-altered proteins coincided with the repair or destroy box, a categorization of closely correlated proteins that share functions responsible for protein folding, repair and degradation. Several others (ankyrin 1, dematin, protein 4.9, heat-shock protein 8, proteasome subunit-α type 1 and -β type 1, chaperonin-containing TCP1, proteasome subunit-α and 26S subunit, and ATPase 6) appeared as key articulation points on the interactome map, with

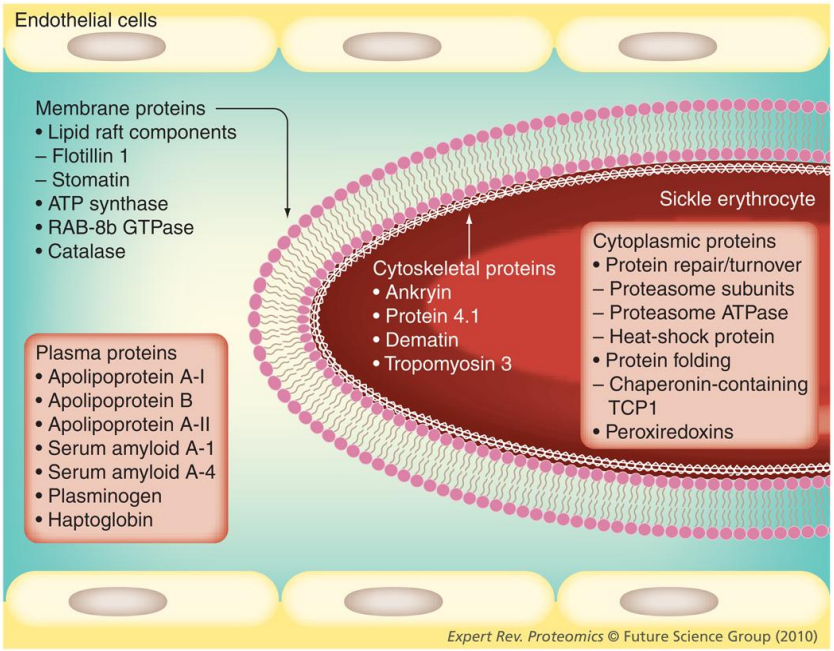
unclear significance (Figure 15 and 16). Admittedly this approach was incomplete and carried a certain degree of false discovery risk.

Figure 15: Major categories of erythrocyte and plasma proteins altered in SCD



Source: Yuditskaya, 2010.

Figure 16: Common pathways leading to protein alteration in SCD



Source: Yuditskaya, 2010.

Antioxidants in SCD

Upregulation of antioxidant proteins are widely studied in recent publications and, most notably, the increases in catalase and peroxiredoxins. A compensatory increase in antioxidants is expected in the setting of the high oxidative burden of SCD. Oxidative stress is believed to be a consequence of several mechanisms, including: hemolysis, causing NO depletion and generation of oxidant species; generation of reactive oxidative species by upregulation of NADPH oxidase and xanthine oxidase; chronic ischemic reperfusion in the setting of intermittent microvascular vaso-occlusion; and loss of catalytic antioxidants. Oxidative stress is thought to promote the formation of irreversibly sickled cells, which, in a vicious cycle, fuels further oxidative stress. Oxidative damage is manifested on RBC membranes via the lower presence of sulphydryl groups, increased lipid peroxidation and deformation of the cytoskeleton.

Cytoskeletal components in SCD RBCs

Cytoskeletal proteins are consistently found to be altered in proteomic profiling of sickle cell erythrocytes. Cytoskeletal attachment proteins 4.1 and ankyrin were both increased significantly in SCD. In addition, levels of an isoform of protein 4.1 with an altered pI and MW were decreased, suggestive of an SCD-related alteration in a post-translational modification. Such protein alterations may be consistent with previously reported oxidative forms of protein 4.1, β-actin and spectrin in sickle erythrocytes. No significant quantitative changes have been found in β-actin or spectrin in sickle cell proteomic experiments, but studies have reported disulfide bridge formation by β-actin when oxidized, as well as glutathiolation of the cysteine residues of α-spectrin, which impedes dissociation from a ternary complex with protein 4.1 and β-actin. These changes reduce cytoskeletal flexibility, which may contribute to sickled RBC rigidity. The increase of the cytoskeletal attachment proteins ankyrin and protein 4.1 may reflect a compensatory cellular response to impaired anchoring of the phospholipid bilayer to the damaged cytoskeleton. Potentiation of this response may be reflected in the relative increase in these proteins seen in patients undergoing hydroxyurea treatment versus untreated SCD patients. The function of the p55 protein is to link the plasma membrane with the cytoskeleton in a ternary complex with protein 4.1, thereby maintaining the stability of the erythrocyte membrane. Its increased expression, induced by both *in vivo* and *in vitro* hydroxyurea treatment, may hypothetically contribute to decreased RBC damage and hemolysis.

Besides protein 4.1, other actin accessory proteins show quantitative changes in the setting of SCD. Dematin and tropomyosin were both decreased by proteomic profiling, and both play a central role in RBC malleability by controlling actin bundling and the actin polymerization:depolymerization ratio. A decrease in these proteins may thus also reflect contribution to increased RBC rigidity. Proteomic analysis of RBC membranes, obtained from blood stored in blood banks by 2D-DIGE, revealed shifts in isoelectric points in cytoskeletal proteins after seven days, which is thought to represent progressive degradation of actin, dematin, and ankyrin, due to oxidation by reactive oxygen species. It is not clear why no compensatory increase in dematin expression, similar to that of ankyrin, has been observed, but it may be related to the nature of dematin's dynamic function, as opposed to the more static one of ankyrin. Tropomyosin, also with a dynamic function, has a similar response to dematin.

Protein repair, protein turnover, and protein folding components in SCD

A major consequence of oxidative stress is protein damage. Therefore several proteins involved in protein repair, folding and turnover emerged as being increased in the sickle cell erythrocyte and monocyte proteomic studies; namely components of proteasomes, chaperonin-containing TCP1 and several heat-shock proteins. Decrease of the former two proteins with *in vivo* hydroxyurea treatment could hypothetically reflect a lower net rate of protein damage, and thus a reduced demand for them. Proteasomes, heat-shock protein and the TCP1 ring complex are ATP dependent in their functions, which coincides with an increase in ATP synthase detected in sickle cell proteomic profiling. Alterations in enzymes involved in glycolysis may be speculatively related to such an increase in demand for ATP synthesis, or alternatively, to a shift from oxidative phosphorylation to anaerobic glycolysis as an adaptation to hypoxia. The ATP dependence of these protein-folding, turnover and repair processes may explain the upregulation of ATP synthase and, possibly, the increased metabolic rate seen in sickle cell patients. However, as stated previously, until many of these findings are validated by independent clinical assays, firmer mechanistic conclusions cannot be drawn.

Alternation in glycolytic enzymes in SCD

There is a clear association of upregulation of glycolytic enzymes with a favorable clinical course in SCD. In the monocyte, higher levels of phosphoglycerate kinase-1 and transketolase correlated with a lower vaso-occlusive crisis rate. *In vivo* treatment with hydroxyurea, a medication known to promote clinical improvement in SCD patients, revealed upregulation of GADPH and fructose bisphosphate aldolase, compared with untreated patients.

Glycolytic enzyme expression is known to be under the control of HIF-1, the gene-expression response to hypoxia. HIF-1 coordinates adaption to hypoxia, shifting ATP production away from oxygen-dependent mitochondrial oxidative phosphorylation, and shunting pyruvate away from the mitochondria via activation of pyruvate dehydrogenase kinase and toward anaerobic ATP production via HIF-1-induced upregulation of glucose uptake and glycolytic enzyme genes. Studies have found a three- to five-fold increase in the level of an ATP synthase subunit in SCD patients at baseline that may reflect a compensation for reduced oxidative phosphorylation synthesis of ATP. HIF-1 target genes within these pathways with proteomically identified alterations include phosphoglycerate kinase-1 and GADPH. Fructose bisphosphate aldolase, which favors gluconeogenesis, may be induced by hydroxyurea, which potentially benefits meeting the increased requirement for glucose under less-efficient anaerobic pathways.

Lipid raft proteins in SCD

A less obvious category of proteins altered in SCD by proteomic profiling are lipid raft components, namely flotillin-1 and stomatin. Both are known to be part of the stomatin prohibin flotillin Hflk/c (SPFH) domain-containing protein family, which is found in lipid raft microdomains in various cellular membranes and is, as yet, incompletely characterized. Lipid rafts are cholesterol-rich regions in the phospholipid bilayer. In a proposed “lipid shell” hypothesis, SPFH domain-containing proteins form large multimeric complexes, which bind cholesterol and form cholesterol-rich microdomains. They are thought to actively recruit other types of proteins to these domains and mediate various protein–protein interactions. Functions of SPFH proteins have not been completely

elucidated, but processes attributed to them include ion channel regulation, membrane protein chaperoning, vesicle and protein trafficking, membrane-cytoskeletal communication and mechanosensation. Flotillin-1 has specifically been cited in roles handling neuronal regeneration, adipocyte GLUT4 trafficking, cell proliferation, endocytosis, phagocytosis and signaling from the cell surface to the cytoskeleton. Stomatin has been putatively implicated in ion channel regulation. Proteasome activation and inactivation has been characterized as a lipid raft-compartmentalized event in macrophages, which suggests a possible relationship between the decrease in lipid raft components and the increase in proteasome proteins observed by proteomics in SCD.

Furthermore, in the cell membrane, the actin cortex plays a central role in organizing lipid raft sphingolipid–cholesterol assemblage potential, so the sickle cell-associated decrease in flotillin-1 and stomatin may be a consequence of impaired actin functioning. Impaired mechanosensation, along with poor communication between the cytoskeleton and plasma membrane, could cause inappropriate responses to environments calling for increased cell malleability, and thus contribute to RBC microvascular clumping and increased cell fragility. Decreases in lipid raft components could also be related to the hypocholesterolemia generally associated with SCD. Low serum cholesterol levels may be a consequence of increased cholesterol consumption by membrane synthesis during increased erythrocyte production, but are more likely to be due to equilibration with the reservoir of RBC membrane cholesterol, which is diminished owing to anemia. The depleted cholesterol levels may lead to a lower presence of lipid rafts in the RBC membrane, reflected by the proteomically identified decrease in stomatin and flotillin-1. Interestingly, stomatin levels have been documented to increase following *in vivo* hydroxyurea treatment, which hypothetically suggests reversal of one or more of these potential mechanisms.

Signaling and interactions between erythrocytes and their environment generally remains a poorly understood subject that, with further elucidation may shed more light on the contribution of lipid raft defects to SCD pathophysiology.

Apolipoprotein dysregulation associated with complications of SCD

There are studies that show intriguing roles of apolipoproteins in the pathogenesis of sickle cell-associated pulmonary hypertension and APEs. Low apolipoprotein levels were associated with each, on a chronic basis in pulmonary hypertension and more acutely in APEs. ApoA-I is known to have both antioxidant and anti-inflammatory properties, yet the increase in acute-phase SAA along with apoA-I depletion suggests involvement of a possible mechanism of apoA-I replacement by acute-phase SAA in HDL, either by direct displacement or, more likely, by competition during HDL synthesis. This replacement would render HDL a proinflammatory particle, and inhibit its ability to prevent oxidation of apoB-containing particles, such as low-density lipoprotein, particularly in the subendothelial space.

Apolipoprotein A-I is a key participant in the activation of endothelial NO synthase by HDL-mediated phosphorylation and thus plays a central role in increasing NO production in the presence of reactive oxygen species. As such, beyond reverse cholesterol transport and atherogenesis inhibition, apoA-1 protects against direct endothelial injury. HDL, in its anti-inflammatory state, also inhibits adhesion molecule expression on endothelial cells. A deficiency in apoA-I predisposes to the development of PH, and a precipitous drop in apoA-I level from steady state levels occurs during a sickle cell APE.

Apolipoprotein A-II is often elevated in the setting of PH by proteomic profiling of sickle cell plasma. ApoA-II, along with acute-phase SAA, impairs the antioxidant properties of HDL by displacing paraoxonase-1, a HDL-associated enzyme. Paraoxonase-1 enables HDL to accept and inactivate oxidized phospholipids from cell membranes. Impairment of this function might be especially problematic in a setting of severe oxidative stress such as SCD. As evidenced by the elevation of apoA-II, this mechanism might contribute to vasculopathy and the development of PH in SCD.

The significance of the elevated constitutive SAA-4 in the setting of sickle cell-associated pulmonary hypertension is less clear as its function has not been as well characterized, but it does suggest a disorder of lipoprotein metabolism.

GMI-1070 IN SICKLE CELL DISEASE

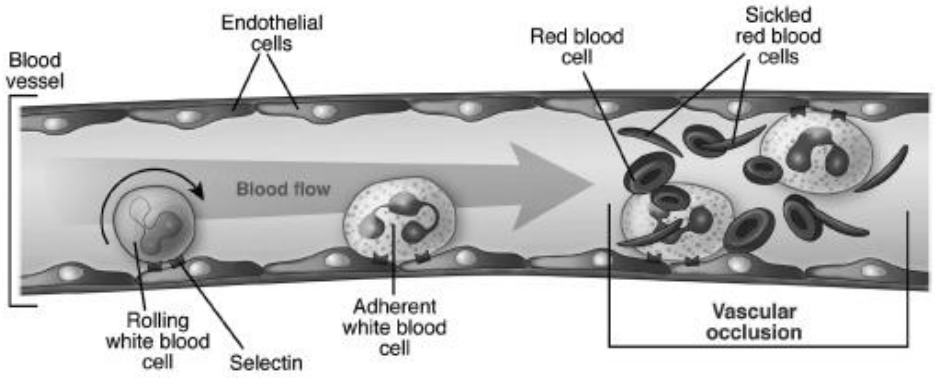
GLYC is developing the pan-selectin antagonist GMI-1070 to treat VOC with the goal of reducing duration of VOC episodes, length of hospital stay and use of opioid analgesics for pain management. In the Phase 2 clinical trial, patients treated with GMI-1070 plus the standard of care demonstrated large, unprecedented improvements in these endpoints compared to patients receiving placebo plus the standard of care. Clinicians we have spoken to believe the Phase 2 data could represent a tremendously meaningful improvement in patient care as well as significant savings in treatment costs for hospitals and payors.

We think GMI-1070 has the potential to become an effective treatment for VOC that provides significant clinical and pharmacoeconomic benefit. According to the U.S. Agency for Healthcare Research and Quality, the average hospital charges in the United States for a patient treated for VOC were approximately $20,000 in 2006. However, in states such as California the average hospital charges for a patient treated for VOC could be as high as $40,000. A reduction in the length of a hospital stay could reduce these costs. If GMI-1070 is shown to be safe and effective in reducing the duration of VOC in hospitalized patients, it should also be tested to see if hospitalization could be prevented with use of GMI-1070 in the emergency department, or if VOC could be managed safely and effectively in the home or in an outpatient setting through a self-administered dosage form, thereby avoiding costly ED visits. We think uses in each of these settings represent potentially significant market opportunities.

Potential mechanism of action of GMI-1070

The cause of SCD vascular occlusion is thought to involve both an inflammatory component and a mechanical component. In the inflammatory component, white blood cells begin to roll along and adhere to the endothelium, the thin layer of cells that lines the interior surface of blood vessels. These white blood cells then become activated and express adhesion receptors known as integrins, which bind and form aggregates with platelets, red blood cells and other white blood cells. These cell aggregates are responsible for the mechanical component of vascular occlusion, where rigid sickled red blood cells are more easily caught in the post-capillary venules, the small blood vessels connecting capillaries and veins. The resulting vascular occlusion causes slowing of blood flow in the post-capillary venules, contributing to inadequate oxygen supply in the local tissue, or ischemia, which in turn causes further tissue inflammation and pain (Figure 17).

Figure 17: Chemical composition of GMI-1070

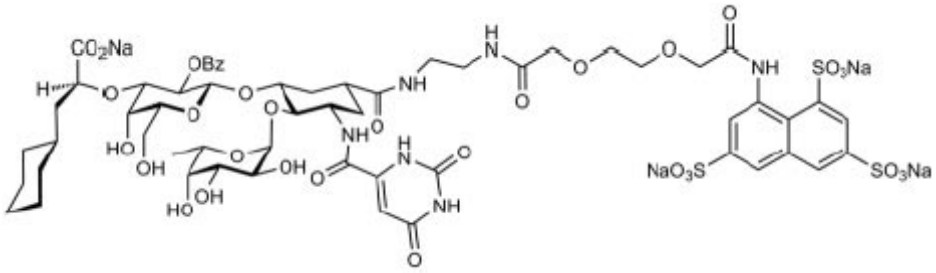


Source: Company presentation

Chemical composition and proposed mechanism of action

Selectins are important in this process because they act as adhesion molecules and play a key role in the initial recognition and binding of white blood cells to the endothelial cells, and their formation of aggregates with platelets, red blood cells and other white blood cells. White blood cells express carbohydrates on their surfaces that bind to E-selectin that is present on inflamed vascular endothelium. White blood cells bound to E-selectin on the endothelial cells then become activated and act as adhesion sites for platelets, red blood cells and other white blood cells, thereby leading to the formation of an occlusion. GMI-1070 is a glycomimetic drug candidate designed to inhibit binding of all three types of selectins and inhibit the selectin-mediated recognition and binding of white blood cells to the endothelium (Figure 18). The rationale for the development of GMI-1070 to treat VOC is that, by blocking these steps in the vaso-occlusive process, it has the potential to decrease the duration and intensity of VOC.

Figure 18: Chemical composition of GMI-1070



Source: Chang, 2010

Studies have long suggested that VOC is a complex cascade that involves multiple blood cells, adhesion, and signaling molecules. Intravital microscopy analyses carried out by Chang et al in a SCD mouse model expressing exclusively human globin genes indicate that sRBCs interact primarily with adherent leukocytes in postcapillary and collecting venules of cremasteric muscle and leading to vascular obstruction. The key role for leukocyte adhesion in sickle cell vascular occlusions has been suggested by the amelioration of flow

abnormalities in sickle transgenic mice by anti-inflammatory therapies directed at nuclear factor-kB activation, reactive oxygen species, or endothelial adhesion molecules such as vascular cell adhesion molecule 1, intercellular adhesion molecule 1 (ICAM-1), or the selectins.

The selectins comprise a family of 3 members that mediate adhesion events between blood cells and the endothelium. L-selectin is constitutively expressed on leukocytes and mediate lymphocyte recruitment in lymph nodes and secondary tethers between leukocytes in activated venules. Endothelial cells express 2 selectins, P-selectin that is stored in Weibel-Palade bodies and can be rapidly translocated to the cell surface on stimulation, and E-selectin whose expression is induced by inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha) or interleukin-1beta (IL-1beta). Selectins mediate leukocyte rolling along on the endothelium, allowing leukocytes to rapidly decelerate and to come into close contact with chemokines that leads to induction of firm adhesion.

Although mice lacking single selectin genes have relatively mild deficits in leukocyte recruitment, animals deficient in both P- and E-selectins exhibit severe defects in leukocyte adhesion and are protected from VOC. Most studies that evaluate the selectin functions in various animal models have confirmed their overlapping roles, suggesting that the greatest potential for therapy may involve the inhibition of more than 1 selectin and the need to balance anti-inflammatory activities with the risks of infections. However, recent studies of the individual function of single selectins in a mouse model of SCD have shown a key role for E-selectin, but not P-selectin, in sending activation signals leading to the up-regulation of the beta2 integrin Mac-1, specifically at the leading edge of crawling neutrophils in inflamed venules. All 3 selectins bind to sialylated and fucosylated moieties presented by glycoprotein or glycolipid ligands.

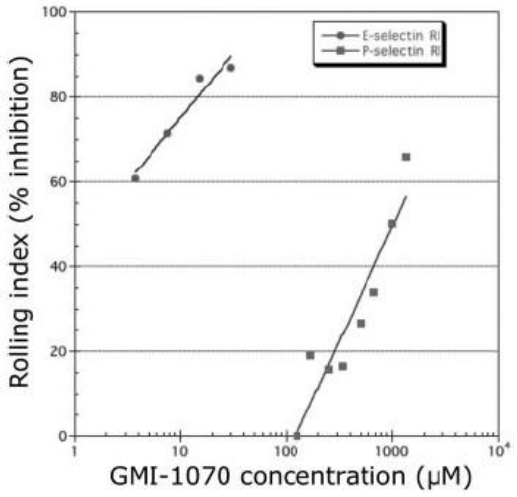
GMI-1070 was designed on the basis of the bioactive conformation of sLex in the carbohydrate-binding domain of E-selectin as determined by nuclear magnetic resonance techniques. Structural requirements for binding L- and P-selectins were also incorporated.

The ability of GMI-1070 to inhibit binding to E-, P-, and L-selectins was evaluated by Chang et al with the use of ELISA in which selectin chimeras were immobilized on microtiter plates and binding to sLea or sLex was determined. The investigators found that the IC50 of GMI-1070was 4.3uM for E-selectin, much lower than P-selectin (423uM) or L-selectin (337uM), suggesting that, although GMI-1070 inhibits binding to all 3 selectins, its activity is greatest toward E-selectin.

Compelling preclinical data

Chang further assessed the effect of GMI- 1070 on selectin-mediated cell adhesion in vitro with the use of a parallel plate flow chamber. Confluent HUVEC monolayers were stimulated with TNF-alpha to induce the expression of E-selectin or IL-4 and histamine to up-regulate P-selectin expression on the cell surface. PMNs were perfused through the chamber containing GMI-1070 under a shear stress of 0.9 dynes/cm2. Consistent with the ELISA findings, GMI-1070 inhibited the interactions of PMNs more effectively when E-selectin was induced on HUVECs than for P-selectin (Figure 19).

Figure 19: GMI-1070 inhibits selectin-mediated rolling



Source: Chang, 2010

Preclinical studies on dosing and pharmacokinetics have established that GMI-1070 administered intravenously has a serum half-life of 1.25 hours in mice and 7.4 hours in humans (Thackray, 2009). To ensure adequate dosage during the entire course of studies, a second dose of GMI-1070 was administered 70 minutes after the TNF-alpha injection (Chang, 2010). Leukocyte behavior, including rolling, adhesion, and the capture rates of sRBCs, were analyzed in 51 venules of 5 mice treated with GMI-1070 and in 58 venules of 5 mice treated with P- and E-selectin antibodies. Administration of GMI-1070 did not significantly change systemic WBC counts in SCD mice under the protocol, whereas significant increased WBC counts in mice treated with P- and E-selectin antibodies were observed (Figure 20).

Figure 20: Hemodynamic parameters of SCD mice treated

Treatments	Mice, n	Weight, g*	Venules, n	Venular diameter, μ*	Centerline velocity, mm/s*	Wall shear rate, s⁻¹*	WBC count, $10^3/\mu L$*
PBS	10	25.9 ± 0.8	42	21.3 ± 0.5	1.4 ± 0.1†	696 ± 48†	14.6 ± 3.3‡
GMI-1070	5	26.9 ± 0.3	51	20.9 ± 0.4	3.1 ± 0.2	1573 ± 117	11.7 ± 1.5§
αPsel + αEsel	5	26.3 ± 0.7	58	20.7 ± 0.4	3.1 ± 0.3	1578 ± 130	24.3 ± 1.2

SCD indicates sickle cell disease; WBC, white blood cell; and PBS, phosphate-buffered saline.
*Data are presented as mean ± SEM.
†$P < .001$ compared with GMI-1070.
‡$P < .05$ compared with αPsel + αEsel.
§$P < .01$ compared with αPsel + αEsel.

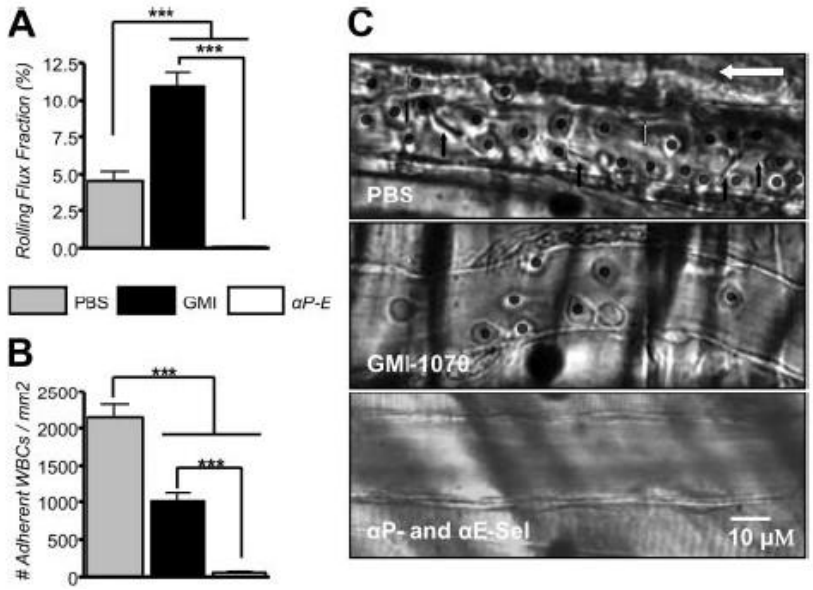
Source: Chang, 2010

Leukocyte rolling, adhesion, and RBC interaction with adherent leukocytes were monitored and analyzed in the 60-minute interval between 90 and 150 minutes after the inflammatory challenge. Leukocyte rolling was assessed as leukocyte rolling flux fraction, defined as the number of rolling leukocytes divided by the total number of leukocytes passing through the same vessel.

Under inflammatory condition induced by combined surgical exteriorization of the cremaster muscle and exposure to TNF-alpha, rolling flux fraction was approximately 4.6% in PBS-treated SCD mice. Virtually all rolling during this time interval was mediated by P-

and E-selectins because it was completely ablated by coinjection of anti-P-selectin and anti-E-selectin antibodies. Unexpectedly, the rolling fraction was increased to 11% in GMI-1070-treated mice. (Figure 21, A; ***P <.001). The increased rolling fraction is reminiscent of past experiments in which E-selectin is inactivated and confirms the in vitro studies described in the previous section, suggesting that GMI-1070 largely antagonizes E-selectin in vivo. The changes in rolling fractions were not due to alterations in leukocyte counts because similar conclusions can be drawn if the results are expressed as absolute numbers of rolling leukocytes per minute (10.9 ±1.4 for PBS control; 41.6 ± 3.5 for GMI-1070, and 0.3 ± 0.1 for the group anti-P- and -E-selectin; all groups P <.01 compared with PBS). By contrast, the average number of WBCs adherent to endothelium was reduced by approximately 53% in SCD mice treated with GMI-1070 compared with SCD controls treated with PBS (Figure 21, B-C; ***P <.001), suggesting significant blockade of P-selectin. Leukocyte adhesion was markedly reduced (by ~97%) when endothelial selectins were blocked with the use of antibodies (Figure 21,B-C).

Figure 21: GMI-1070 alters leukocyte recruitment

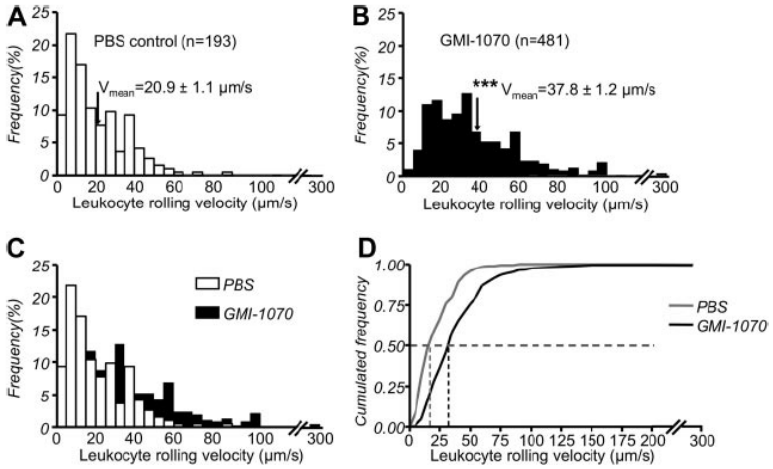


Source: Chang, 2010

In addition, Chang et el found that GMI-1070 dramatically increases leukocyte rolling velocities (Figure 22), inhibits RBC interaction with WBCs (Figure 23), inhibits leukocyte adhesion and sRBC interactions after the inflammatory trigger (Figure 24), and ultimately reverses sickle cell crisis by improving blood flow and survival of SCD mice (Figure 25).

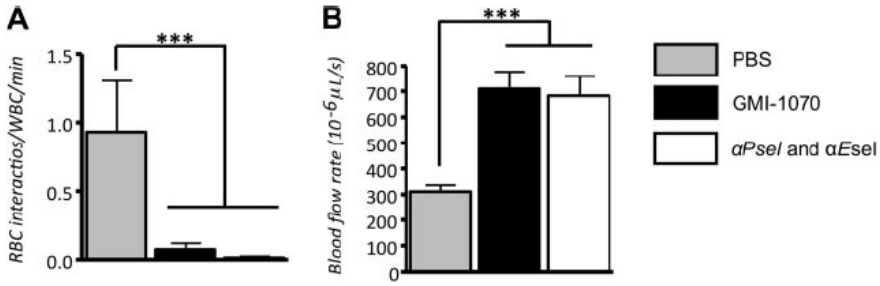
We note the mouse model of VOC is generally much more severe than the human disease in that it can lead to the death of most animals in several hours, in contrast with human sickle cell crises that are usually brought up over hours to days and are usually not lethal. As such, we believe disease reversibility in the face of such a severe model bodes well for potential clinical relevance of a specific intervention.

Figure 22: Leukocyte rolling velocity histograms



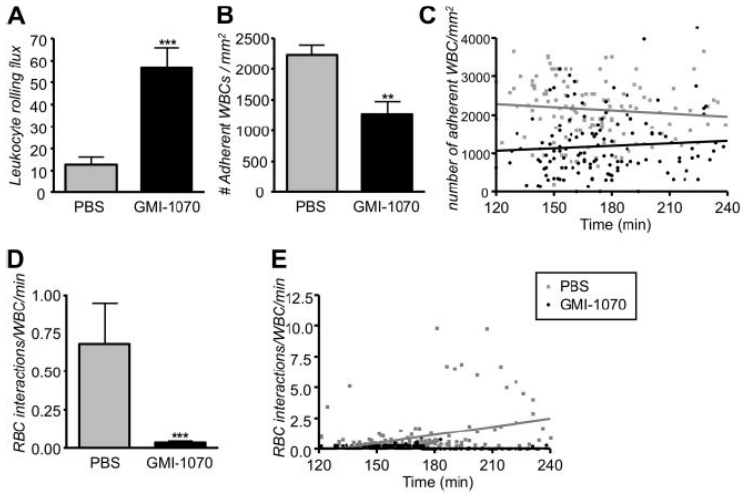
Source: Chang, 2010

Figure 23: GMI-1070 inhibits RBC captures and improves blood flow in SCD mice



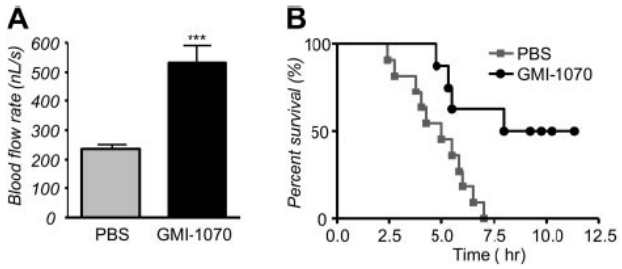
Source: Chang, 2010

Figure 24: GMI-1070 administration after inflammatory trigger shows the same biological effect



Source: Chang, 2010

Figure 25: GMI-1070 inhibits RBC captures and improves blood flow in SCD mice



Source: Chang, 2010

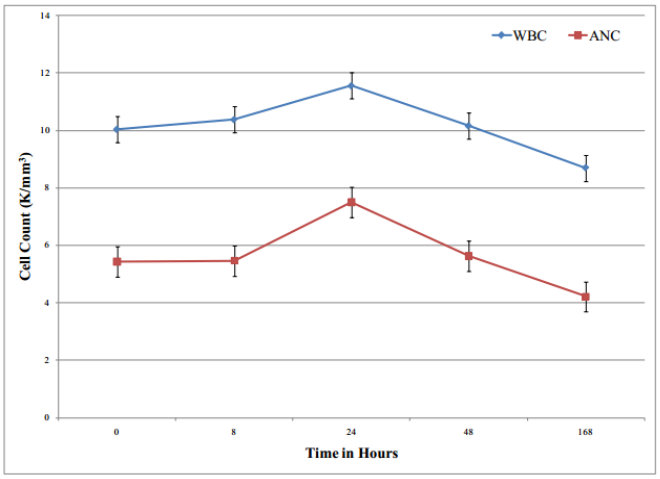
Phase 1 clinical results

Based on the compelling preclinical data, GLYC held a pre-IND meeting with the FDA in June 2007 and submitted an IND for GMI-1070 in July 2008. Upon approval of the IND, GLYC initiated a single dose Phase 1a trial of GMI-1070 in August 2008. In December 2008, GLYC completed the Phase 1a trial, in which 40 healthy volunteers were enrolled. Of these subjects, 30 were dosed once with one of five dose levels of GMI-1070, ranging from 2 to 40 mg/kg, and 10 received placebo. In addition, GLYC completed a multiple dose Phase 1b trial in February 2009, in which 32 healthy volunteers were enrolled. Of these subjects, 24 were dosed with four dose levels of GMI-1070, and eight received placebo. Three groups of six subjects each were dosed at 5, 10 or 20 mg/kg every eight hours for 13 doses. An additional group of six subjects received a loading dose of 40 mg/kg, followed by 20 mg/kg every eight hours for six doses. The results of these trials demonstrated a half-life of GMI-1070 of approximately seven hours, with the drug excreted largely intact. GMI-1070 was well tolerated in these subjects and no safety concerns were identified. Adverse events occurred at similar rates across the treatment groups in both of these trials.

In 2010, GLYC completed a Phase 1 pilot trial in 15 adults with sickle cell disease not experiencing VOC. In this trial, patients received a loading dose of 20 mg/kg of GMI-1070, followed by a dose of 10 mg/kg ten hours later. The trial focused on the evaluation of safety, pharmacokinetic, or PK, profiles and certain biomarkers. In individuals with sickle cell disease and at the dose levels intended for further evaluation, no safety concerns associated with the use of GMI-1070 were identified and the PK profile was also similar to that seen in healthy volunteers. When administered to patients with sickle cell disease, GMI-1070 was shown to affect biomarkers of inflammation and coagulation (Figure 26).

Results from these three Phase 1 clinical trials demonstrated evidence of linear PK for GMI-1070 when administered as single or multiple doses to the 72 healthy volunteers and the 15 patients with sickle cell disease. GMI-1070 was well tolerated in these subjects and no safety concerns were identified. Adverse events occurred at similar rates across the treatment groups in these trials.

Figure 26: Observed (mean/SE) absolute WBC and ANC over time



Source: ASH 2013

Phase 2 clinical results

GLYC also completed a Phase 2 clinical trial of GMI-1070 in sickle cell patients hospitalized for VOC (Figure 27). This trial, first presented at the American Society of Hematology's 2013 annual meeting in December 2013 produced data unparalleled in the history of sickle cell drug development, showing potential two or more day's reduction in hospitalization and significant reduction in need for pain killers. Clinicians we have spoken to believe that this data suggests GMI-1070 could be an incredibly powerful new potential treatment for SDC acute pain crises, with potential to shorten these episodes to a degree that would be both incredibly meaningful to patients as well as represent significant cost savings for treating hospitals and payors.

Figure 27: Ph2 GMI-1070 trial design

	Phase 2
NCT ID	NCT01119833
Design	Randomized, placebo controlled, double blind
Enrollment	76
Dosing	Intravenous GMI-1070 given twice a day during hospital stay for sickle cell pain crisis
Key inclusion criteria	• 12 to 60 years of age • Confirmed diagnosis of sickle cell disease (HbSS or HbS-β0thalassemia) • Diagnosis of VOC at the time of enrollment • Hospitalized or in process of admission at the time of enrollment • Able to receive the first dose of study drug within 24 hours of initial medical evaluation in the Emergency Department/clinic for VOC; o Subjects treated as an outpatient within the past 48 hours for the same VOC episode may be enrolled if dosing is also expected within 24 hours of their second (admitting) presentation.

Key exclusion criteria	• Infection, diagnosed or strongly suspected, as evidenced by one or more of the following:
	  • Fever >39°C (102.2°F)
	  • In the presence of fever ≥38.5°C (101.3°F), 1 of the following:
	  • Positive findings (suspicious for infection) on diagnostic tests, such as cerebral spinal fluid [CSF] evaluation, radiographs, or bacterial culture of normally sterile sites
	  • Exam findings leading to diagnosed or strongly suspected bone or joint infection
	  • Determination by physician that bacterial or serious systemic viral infection is likely (eg, influenza, mononucleosis)
	  • Subjects may be included with uncomplicated urinary tract infections (provided they do not have fever ≥38.5° C [101.3° F] or costo-vertebral angle [CVA] tenderness), and/or suspected minor viral syndromes (upper respiratory infection symptoms but no symptoms suggestive of bacterial infection other than uncomplicated otitis media or uncomplicated streptococcal pharyngitis)
	• Acute chest syndrome, diagnosed or strongly suspected, as evidenced by a new infiltrate on chest radiograph, and 1 or more of the following:
	  • Fever >39° C (102.2° F)
	  • Hypoxia (confirmed by arterial blood gases [ABG] with paO2 <70 mmHg)
	  • Chest pain
	  • Suspicious findings on exam (tachypnea, intercostal retractions, wheezing, and/or rales)
	• Sickle cell disease (SCD) pain atypical of VOC, including hepatic or splenic sequestration, cholecystitis, or pneumonia.
	• Acute stroke, acute priapism, severe avascular necrosis of the hip/shoulder when the presenting pain is only in the affected hip/shoulder
	• Serum creatinine:
	  • >1.2 mg/dL for subjects 16 to 60 years of age
	  • >1.0 mg/dL for subjects 12 to 15 years of age
	• Alanine transaminase (ALT/SGPT) >2x upper limit of normal (ULN) (based on clinic laboratory normal range)
	• Hemoglobin <5 g/dL
	• Platelets <100,000/mm3
	• Recent (within the past 30 days) major surgery, hospitalization for other than VOC, documented serious bacterial infection requiring antibiotic treatment, or significant bleeding
	• Hospitalization for uncomplicated VOC, or treated with parenteral pain medications in other medical settings such as the emergency department or day hospital for uncomplicated VOC, within past 14 days. Subjects may be included if treated as an outpatient within the past 48 hours for the same VOC episode.
	• Recent (within the past 90 days) cerebrovascular accident, transient ischemic attack, or seizure
	• pRBC transfusions in the past 14 days
	• Systemic steroid therapy within 48 hours prior to enrollment or expectation that therapy may be used during the study (inhaled or topical steroids are allowed)
	• For those on chronic or long-acting opioids, a change in dose in the past 14 days OR pain requiring medical attention in the past 14 days (change in opioid medication for acute pain in the past 48 hours and directly related to this VOC admission is allowed)
	• Greater than 5 episodes of hospitalization for VOC in the past 6 months (180 days)
	• Medical or psychiatric condition that, in the opinion of the investigator, may pose a risk to the subject for participation or interfere with the conduct or results of the study
	• Currently receiving, or has received within the previous 4 weeks, any other investigational agent
	• Previous administration of GMI-1070
	• Expectation that the subject will not be able to be followed for the duration of the study
	• Pregnant or lactating female; or female of childbearing potential or male unable or unwilling to comply with birth control methods or abstinence during the course of the study
	• Active use of illicit drugs and/or alcohol dependence, as determined by the investigator

Primary endpoint	Reduction in time to resolution of vaso-occlusive crisis
Secondary endpoint	Safety during the study / pharmacokinetics / markers of inflammation and cell stickiness in the blood
Powering	80% to see a 40% reduction in time to resolution of VOC

Source: Clinicaltrials.gov

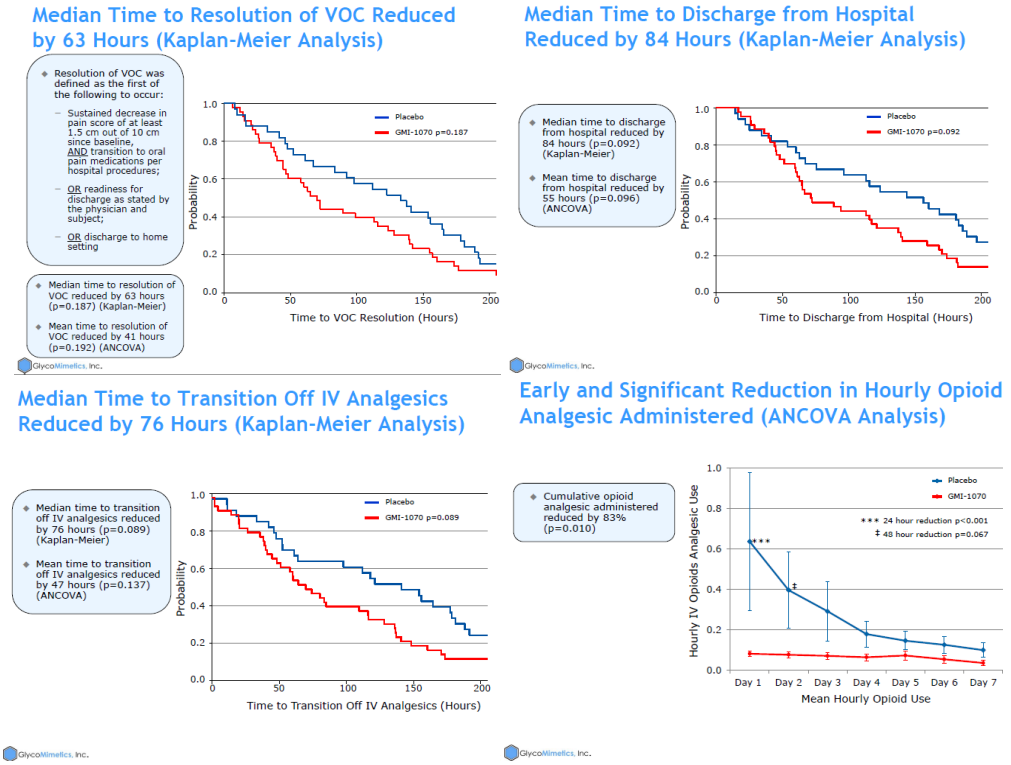
This trial was a randomized, double-blind, placebo-controlled trial at 22 sites in the US and Canada evaluating the safety, efficacy and PK of multiple IV doses of GMI-1070 or placebo in 76 patients hospitalized for VOC, ranging from 12 to 60 years old. Of these patients, 43 received GMI-1070 and 33 received placebo, in both cases in addition to the standard of care. Patients receiving GMI-1070 in the trial received one of two dose levels. Patients in the low dose group received a loading dose of 20 mg/kg, followed by a 10 mg/kg dose every 12 hours. Patients in the high dose group received a loading dose of 40 mg/kg, followed by a 20 mg/kg dose every 12 hours.

Data: In patients receiving GMI-1070 in this trial, there were reductions in multiple measures related to a VOC episode as compared to patients receiving placebo. Two widely used statistical methods, known as ANCOVA and Kaplan-Meier, were used to analyze the results of this trial. The time to reach resolution of VOC, the primary endpoint of the trial, was reduced in the patients receiving GMI-1070 by a mean of 41.0 hours, as measured by ANCOVA, with a p-value of 0.192, and reduced by a median of 63.3 hours, as measured by Kaplan-Meier, with a p-value of 0.187.

In addition, in the patients receiving GMI-1070, the time to hospital discharge was reduced by a mean of 54.7 hours, as measured by ANCOVA, with a p-value of 0.096, and a median of 83.9 hours, as measured by Kaplan-Meier, with a p-value of 0.092. The time to transition off IV analgesics was reduced by a mean of 47.0 hours, as measured by ANCOVA, with a p-value of 0.137, and a median of 75.7 hours, with a p-value of 0.089, as measured by Kaplan-Meier.

Importantly, the cumulative amount of opioid analgesic administered during hospitalization was reduced by 83%, as measured by ANCOVA, with a p-value of 0.01. This last data measure (Fig. 28) is particularly compelling given almost all clinicians believe it is the most reliable measure of patient pain burden. Opioids administration in the SCD pain crises setting is almost always patient controlled administration (PCA) morphine IV drip, and therefore a reduction in opioid use is viewed as a very meaningful measure of a patient's pain level.

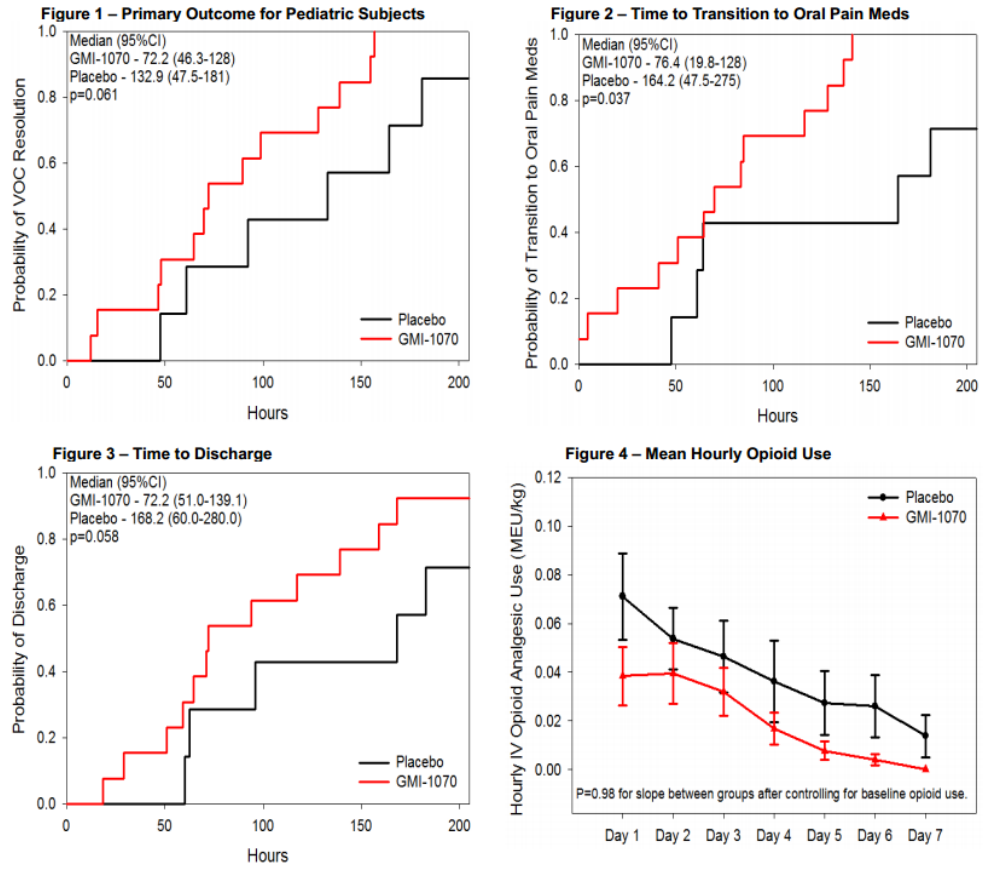
Figure 28: Clinical results from Ph2 study of GMI-1070



Source: Company presentation

Although the Phase 2 clinical trial was not large enough to detect statistically significant differences in most of these endpoints, including what will be the primary endpoint in the pivotal trials, we believe the observed reductions in these measures in patients treated with GMI-1070, and the consistency of a positive response across multiple measures, demonstrate the potential benefit of GMI-1070 . Presenting investigators at ASH indicated that the data variance in the trial was twice that expected, which was the reason the data did not reach statistical significance despite the large mean and median data figures.

Figure 29: Pediatric subgroup analysis from Ph2 study of GMI-1070



Source: ASH 2013

The types and frequency of adverse events and serious adverse events were comparable across the treatment groups in the Phase 2 clinical trial. The most common SAE was rehospitalization for VOC. Measures of organ function, respiratory and cardiac function and routine tests of medical status while in the hospital were similar between the groups. One serious rash occurred in the high dose group, which resolved with minimal medical treatment. Acute chest syndrome, a complication of sickle cell disease affecting the lungs, occurred in six subjects receiving GMI-1070 and in three subjects receiving placebo. Rehospitalization rates for VOC were similar between the groups and lower than the rehospitalization rate that is typical for VOC.

One side effect of particular concern given GMI-1070's mechanism has been opportunistic infection or increased infection risk. Phase 2 data did not suggest an increased infection risk, and clinicians we spoke with are not particularly concerned given the episodic nature of potential treatment, as the drug will likely only be used around SCD crisis. Most SS SCD patients have about one crisis a year, which would likely limit annual exposure in all but the most severe patients.

We think the favorable effects observed in GLYC's Phase 2 clinical trial are the result of mechanism-based resolution of VOC. Specifically, we think these results suggest that by inhibiting selectin-mediated adhesion of white blood cells to the endothelium, GMI-1070

prevents propagation of VOC and promotes early resolution. Results from the Phase 2 clinical trial provide the first clinical evidence of a positive effect of GMI-1070 in adult and pediatric patients experiencing VOC. No currently available therapies provide similar benefits to patients in VOC. Based on the data from GLYC's Phase 2 clinical trial for GMI-1070, we believe GMI-1070 has the potential to become the first drug approved to treat VOC in both adult and pediatric patient populations.

Design of upcoming pivotal Phase 3 Trial

Following the completion of the Phase 2 clinical trial, Pfizer is now responsible for the further clinical development, regulatory approval and potential commercialization of GMI-1070. Pfizer has advised GLYC through the joint steering committee that Pfizer intends to begin enrolling adult and pediatric patients for a Phase 3 trial of GMI-1070 in H2/14, pending approval through Pfizer's governance process. Pfizer has also informed GLYC that activities necessary to support the initiation of a Phase 3 trial in H2/14 are currently underway pending approval through Pfizer's governance process.

We believe Pfizer's Phase 3 preparation includes manufacturing the drug substance to be used in the Phase 3 trial, completion of toxicology studies that would support a Phase 3 trial and an NDA, engagement with regulatory authorities in the United States and overseas to discuss plans for the conduct of a Phase 3 trial planning and preparation for a TQTc clinical trial to evaluate cardiac safety that would support a Phase 3 trial, contracting with a CRO to provide services in the conduct of a Phase 3 trial and convening clinical investigators in the United States and overseas to discuss plans for a Phase 3 trial.

In December 2013, Pfizer, GLYC and the FDA held an End of Phase 2 Type B meeting to receive agency opinion and guidance on Pfizer's plans for the Phase 3 pivotal trial of GMI-1070, including the proposed endpoints for the trial and submission of an SPA. GlycoMimetics indicated the meeting went very well, and according to expectations. We believe Pfizer is already taking a number of steps to prepare for Phase 3 initiation in H2/14. SCD KOLs we have spoken to have indicated Pfizer's hematology have been in touch regarding opinions on trial design and feasibility, and seem very committed to the Phase 3 program. Given at least comparable trial enrollment timeline, namely Mast's EPIC, and duration of trial, we reasonable expect top-line data from the proposed Phase 3 trial by H2/16.

We expect primary endpoint of the Phase 3 trial to be shortening of VOC with the endpoint being around hospital discharge or readiness for discharge, which fits well given the observed 55- to 84-hour reduction (depending on mean or median) in the Phase 2 data. We think enrollment will be around 300 patients for the Phase 3 and will provide GLYC with a potential for an interim analysis half way in.

Collaboration with Pfizer

In October 2011, GLYC entered into a license agreement with Pfizer, under which GLYC granted Pfizer an exclusive worldwide license to develop and commercialize GMI-1070, also known as rivipansel sodium, for all fields and uses. The products licensed under the agreement also include certain backup compounds, along with modifications of and improvements to GMI-1070 that meet defined chemical properties.

Under the terms of the agreement, GLYC received a $22.5 million upfront payment and are eligible to earn up to $115.0 million upon the achievement of specified development

milestones, including the dosing of the first patients in Phase 3 clinical trials for up to two indications and the first commercial sale of a licensed product in the United States and selected European countries for up to two indications, up to $70.0 million upon the achievement of specified regulatory milestones, including the acceptance of our filings for regulatory approval by regulatory authorities in the United States and Europe for up to two indications, and up to $135.0 million upon the achievement of specified levels of annual net sales of licensed products. GLYC is also eligible to receive tiered royalties for each licensed product, with percentages ranging from the low double digits to the low teens, based on net sales of GMI-1070 worldwide, subject to reductions in specified circumstances.

COMPETITIVE DRUG CANDIDATES

Mast Therapeutics, Inc. is currently conducting a Phase 3 clinical trial of its purified poloxamer MST-188 that may be used to treat an ongoing VOC episode. MST-188 binds to damaged membranes, restoring the cell's natural, hydrated, non-adhesive surface. This aborts dysfunctional inflammation and thrombosis and directly contributes to improved blood flow and reduced tissue ischemia. GLYC noted that MST-188 is only being tested in pediatric patients ages 8 to 17 years old, unlike GMI-1070 which is being tested to treat both adult and pediatric patients experiencing VOC. However, given the multifactorial pathophysiology of SCD, we believe there exists a multimodal treatment paradigm that utilizes both GMI-1070 and MST-188.

A 255-subject, randomized, double-blind, placebo-controlled study of MST-188 in patients with sickle cell disease experiencing vaso-occlusive crisis was conducted in 1998-1999. Signs of efficacy were observed in the primary endpoint, duration of crisis, but it did not reach statistical significance (Figure 30).

Figure 30: Duration of crisis

Groups	Purified Poloxamer 188	Placebo	*P* Value
All randomized patients (n = 255)	132.62 (41.38)	141.43 (41.90)	.04
All treated patients (n = 249)	132.34 (41.42)	140.35 (42.39)	.07
Patients concurrently receiving hydroxyurea (n = 54)	141.36 (37.04)	157.19 (27.58)	.02
Patients ≤15 years old (n = 73)	127.07 (42.47)	148.58 (36.71)	.01

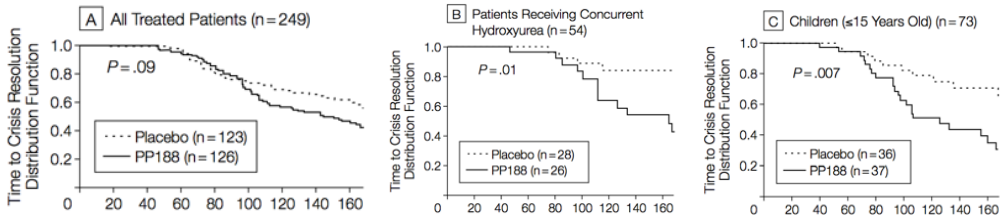
Source: Grindel, 2001.

An eight-hour decrease in the duration of crisis (p=0.072) was observed in the intent-to-treat population (n=249). Notably, post hoc analyses identified a statistically significant and greater treatment effect in patients under 16 years of age and in patients receiving hydroxyurea. Among patients under 16 years of age (n=73), there was a 21.6-hour decrease in the duration of vaso-occlusive crisis in the MST-188 group compared to the placebo group (p=0.010). Hydroxyurea patients showed a statistically significant 16-hour benefit (p=0.02). It is interesting to note that these two subgroups of patients are ones that receive more intensive background care than the average sickle cell patients. In many cases, optimized background care reduces the clinical benefit seen in a trial, although in this case it seems to be the reverse.

A potentially significant limitation of the prior Phase 3 study is that it did not follow subjects until hospital discharge; rather, subjects were followed for 168 hours from randomization and any subject whose crisis had not resolved by 168 hours was, for purposes of determining that patient's duration of crisis, attributed a duration of exactly 168 hours. This truncation had a potentially significant effect on the duration of crisis reported in the prior Phase 3 study, particularly because a substantial number of subjects did not achieve crisis resolution within 168 hours. However, a "responder's analysis," which analyzes the proportion of subjects who had achieved crisis resolution at 168 hours (without attribution), would not be affected by this truncation and may provide a more accurate picture of the MST-188 treatment effect in this setting. Figure 31 shows a post-hoc responder's analysis, in the intent-to-treat population (n=249), over 50% of subjects receiving MST-188 achieved crisis resolution within 168 hours, compared to 37% in the control group (p=0.02). Likewise, in the under-16 age group, over 60% of the MST-188 group achieved crisis resolution within 168 hours, compared to under 28% of the control group (p=0.009).

Figure 31: Crisis resolution rate and progression within 168 hours

Groups	Purified Poloxamer 188	Placebo	*P* Value
All randomized patients (n = 255)	65/127 (51.2)	45/128 (35.2)	.01
All treated patients (n = 249)	65/126 (51.6)	45/123 (36.6)	.02
Patients concurrently receiving hydroxyurea (n = 54)	12/26 (46.2)	4/28 (14.3)	.02
Children ≤15 years old (n = 73)	23/37 (59.5)	10/36 (27.8)	.009



Source: Grindel, 2001.

Selexys Pharmaceuticals is currently in Phase 2 development of SelG1 for SCD. SelG1 is a humanized antibody that binds P-selectin with high affinity and specificity and blocks its function. Studies in animal models of SCD have shown that blocking or eliminating P-selectin function has a potential therapeutic effect by preventing vasoocclusion and maintaining normal blood flow. SUSTAIN is the first clinical study to test an anti-P-selectin antibody for the reduction or prevention of vasoocclusive pain crises. If the drug successfully completes the clinical programs, we think it may also play a role in a multimodal treatment regimen for SCD. Novartis has options right to Selexys after the current Phase 2 trial data.

ACUTE MYELOID LEUKEMIA (AML)

Background on AML

Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. The symptoms of AML are caused by replacement of normal bone marrow with leukemic cells, which causes a drop in red blood cells, platelets, and normal white blood cells. These symptoms include fatigue, shortness of breath, easy bruising and bleeding, and increased risk of infection. Several risk factors and chromosomal abnormalities have been identified, but the specific cause is not clear. As an acute leukemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated.

AML is the most common acute leukemia affecting adults, and its incidence increases with age. Although AML is a relatively rare disease, it accounts for approximately 1.2% of cancer deaths in the United States. The American Cancer Society estimates that in 2013, approximately 15,000 people in the United States will be diagnosed with AML and over 10,000 people in the United States will die of the disease. AML is more commonly present in elderly patients, with a median age at diagnosis of 67 years according to the National Cancer Institute. In a review published in the Journal of Clinical Oncology, the median overall survival of patients 60 years old or older was 8.7 months. The overall five-year relative survival rate for all AML patients is 24%, and only 5% for patients over 65 years old at diagnosis. A number of published studies indicate that only some AML patients who receive chemotherapy achieve a complete response, which is defined as the disappearance of all signs of AML, and that most of those with a complete response will eventually relapse.

We believe there is a large unmet medical need for elderly AML patients as well as for those AML patients who relapse or develop refractory disease. Most AML patients with relapsed or refractory disease have no established treatment options and, accordingly, may be referred for participation in clinical studies of potential new therapies. For patients who elect not to participate or are unable to participate, treatment options typically include chemotherapy regimens, hypomethylators and supportive care. Further, many elderly AML patients are not suitable to undergo chemotherapy as a result of other medical conditions, and may only be able to tolerate pain comfort or control measures. Without treatment, however, AML is uniformly fatal.

Rationale of E-selectin in AML

E-selectin has been shown to play important roles in the progression of AML. In several studies E-selectin has been shown to mediate tumor dissemination, enable tumor trafficking to bone marrow microdomains, and facilitate tumor cell sequestering in bone marrow niche where tumor stem cells are protected from chemotherapy. Moreover, level of E-selectin has been correlated with tumor infiltration and relapse and survival rates. In addition, we see potential to combine E-selectin antagonist with any cytotoxic regimen as antagonizing E-selectin affects tumor cells and HSCs differently.

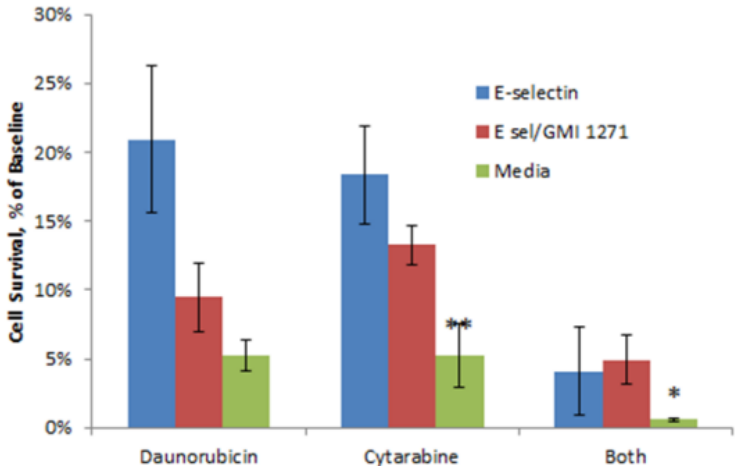
Some leukemia cells, known as blast cells, bind to E-selectin in the bone marrow where they are relatively protected from the effects of chemotherapy. This phenomenon is known as cell adhesion-mediated drug resistance, or CAMDR. We think E-selectin inhibition

disrupts the adhesion involved in CAMDR and mobilizes blast cells out of the bone marrow and into the bloodstream, making them more susceptible to chemotherapy. We believe that this mechanism of action may allow GMI-1271 to improve chemotherapy response rates, duration of remission and, ultimately, survival in patients with hematologic cancers such as AML and may at the same time protect normal HSCs from chemotoxicity by slowing cell cycling. As such, we believe GLYC's E-selectin antagonist, GMI-1271, has the potential to improve the current treatment of AML patients.

Compelling preclinical data

In one in vivo study in a mouse model of AML, combining GMI-1271 with chemotherapy mobilized AML blast cells and significantly reduced tumor burden as compared to treatment with chemotherapy alone. In an in vitro study, AML cells bound to E-selectin were more resistant to chemotherapy (Figure 32). In a related study, when treated with GMI-1271, the resistance of such cells to chemotherapy was reduced. Tumor cells of patients who have relapsed AML, when tested in the laboratory, bound significantly higher levels of E-selectin than tumor cells of patients at initial diagnosis.

Figure 32: E-selectin/GMI-1271 conferring chemotherapy drug resistance in vitro



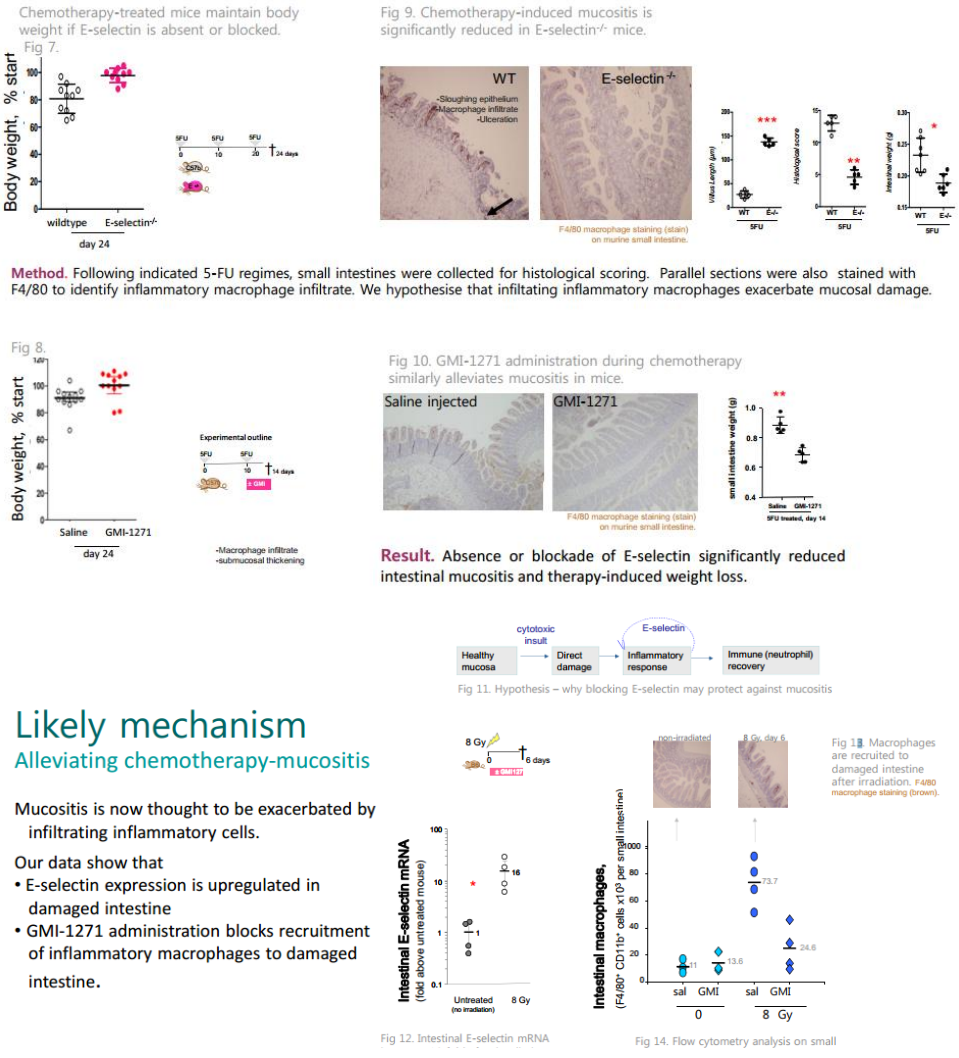
Source: ASH 2013

In another in vitro study, GMI-1271 inhibited the E-selectin-mediated activation of the Wnt and Hedgehog signaling pathways, which are known to play important roles in the development and progression of AML. These pathways are activated in tumors when they are bound to E-selectin, and activation of these pathways may enhance the survival of these tumor cells. We think these are compelling data points that support GLYC's strategy for targeting E-selectin in these patients. GMI-1271 represents a novel agent that we think could potentially be combined with many chemotherapeutic agents.

We suspect that GMI-1271, which broadly targets the interactions between cancer cells and bone marrow, may not be specific to a certain cancer type. As such, GLYC has also tested the GMI-1271 in other cancer models. In in vivo studies involving animal models of pancreatic cancer and breast cancer, GMI-1271, as a single agent, inhibited metastasis, and in the breast cancer model it also translated to improved survival. When combined with chemotherapy, in the pancreatic cancer model, GMI-1271 reduced metastasis to a more significant degree than did the chemotherapy alone.

In addition to its anti-tumor effects, GMI-1271, in animal models, has shown protection against some of the toxicities of chemotherapy. In particular, animals treated with GMI-1271 in combination with chemotherapy had less severe neutropenia and mucositis and lower bone marrow toxicity as compared to animals treated with chemotherapy alone (Figure 33).

Figure 33: GMI-1271 alleviates intestinal mucositis and therapy-related weight loss



Source: ASH 2013

We think that treatment with GMI-1271 may result in lower bone marrow toxicity due to its inhibition of E-selectin, thereby making hematopoietic stem cells divide less frequently and protecting them from chemotherapy agents that target rapidly dividing cells. GLYC is currently considering reductions in some of the toxicities of chemotherapy as secondary efficacy endpoints in future clinical studies.

Clinical path forward for GMI-1271

GLYC had a pre-IND meeting with the FDA in November 2013 and plan to file an IND for GMI-1271 in Q1/14. If the IND is accepted, GLYC intends to initiate a Phase 1 single dose-escalation clinical trial of GMI-1271 in healthy volunteers in Q2/14, to be followed by a Phase 1/2 multiple dose-escalation clinical trial in defined populations of patients with AML. Once dose-escalation is complete, GLYC plans to extend the Phase 1/2 clinical trial into specific patient populations in two or three randomized, placebo-controlled clinical trials. Each of these randomized clinical trials will evaluate a different group of patients with AML.

We think GLYC will focus the first two trials on elderly AML patients and relapsed AML patients of all ages. As more data on GMI-1271 becomes available in AML and other malignancies, a third randomized clinical trial may include an additional AML patient group, or may expand to additional hematologic cancers. In these trials, we think GLYC will combine GMI-1271 with standard of care chemotherapy. Each trial may therefore evaluate GMI-1271 in conjunction with a different chemotherapy regimen, based on the standard for that patient population. Although final trial designs are not complete, we expect that the trials to be blinded through the first or second course of GMI-1271 in combination with chemotherapy, then unblinded to allow an ongoing evaluation of patient outcomes in comparison to the standard of care. These trials will likely evaluate both short-term outcomes, including response rates and minimal residual disease, and longer-term outcomes, including duration of remission and progression-free survival.

E-selectin and CXCR4 as targets

GLYC has identified a family of drug candidates that are designed to simultaneously inhibit both E-selectin and a chemokine receptor known as CXCR4. We think GLYC will select one of these drug candidates to be developed for the treatment of cancers with significant bone marrow involvement, such as myeloma. Chemokines are signaling proteins secreted by cells that bind CXCR4. E-selectin and CXCR4 are binding targets that share important roles in cellular migration in cancer and inflammation. Therefore, a compound targeting both E-selectin and CXCR4 may also be useful in treating inflammatory components of disease.

CXCR4 has been successfully targeted by the approved drug plerixaflor, which is marketed by Sanofi as Mozobil. This drug has been shown to improve the mobilization of stem cells out of bone marrow and into the circulating blood where they can be collected in anticipation of a stem cell transplant. CXCR4 is a binding protein on the surface of stem cells that keeps them in the bone marrow and prevents them from entering the bloodstream. Mozobil works by binding to CXCR4 on stem cells, thereby blocking the bond that normally keeps them anchored to the bone marrow. Mozobil is currently in clinical trials to treat AML and myeloma in combination with chemotherapy.

Due to the similar cellular functions of E-selectin and CXCR4 as adhesion molecules that bind cancer cells in the bone marrow, we think targeting both E-selectin and CXCR4 with a single compound could meaningfully improve efficacy in the treatment of cancers that affect the bone marrow as compared to targeting CXCR4 alone.

INTELLECTUAL PROPERTY

GLYC has filed for patent protection covering compositions of matter and methods of use for its drug candidates. GLYC owns six issued U.S. patents that are expected to expire between 2023 and 2029 and that cover the compound GMI-1070 and methods of using these compounds to modulate selectin-mediated function and for the treatment of sickle cell disease or a complication associated therewith. On January 25, 2013, GLYC applied for a broadening reissue of one of these patents, U.S. Patent 7,728,117, which expires in 2029 and covers the compound GMI-1070. We think GLYC will rely on the potential seven years' orphan exclusivity in the US and potential 10 years' orphan exclusivity in the EU for SCD market protection.

GMI-1271's patent portfolio consists of one pending Patent Cooperation Treaty application and four pending U.S. provisional applications that are wholly owned by GLYC. The PCT application covers the compound GMI-1271 and methods of using these compounds to treat or prevent metastasis of cancer cells, inhibit infiltration of cancer cells into bone marrow, inhibit adhesion of a tumor cell to an endothelial cell, treat or prevent thrombosis and enhance hematopoietic stem cell survival. The PCT application is eligible for entry into the United States and non-U.S. countries. If issued, the resulting patents are expected to expire around 2032. The U.S. provisional applications are eligible for worldwide filing and may be used to establish non-provisional applications that, if issued, are expected to expire around 2033.

In addition, GLYC has patent portfolios for compounds that simultaneously inhibit both E-selectin and CXCR4 and compounds that target pseudomonas virulence factors. These patent portfolios are wholly owned by GLYC and include five issued U.S. patents that are expected to expire between 2027 and 2031, five pending U.S. non-provisional patent applications that, if issued, are expected to expire between 2027 and 2031 and four pending U.S. provisional patent applications. The U.S. provisional applications are eligible for worldwide filing and may be used to establish non-provisional applications that, if issued, are expected to expire around 2033.

Figure 34: Summary of key GlycoMimetics patents

Patent	Title	Expiration
7,517,980	Glycomimetric inhibitors of the PA-IL lectin, PA-IIL lectin or both the lectins from Pseudomonas	2026
8,039,442	Compounds and methods for treatment of sickle cell disease or complications associated therewith	2028
7,989,601	Heterobifunctional pan-selectin inhibitors	2030
8,518,896	Treatment of cancers of the blood using selected glycomimetic compounds	2029

Source: Company reports and Canaccord Genuity estimates

MANAGEMENT TEAM

The GlycoMimetics management team has a strong history of corporate leadership, development and commercialization in the biotechnology industry.

Ms. Rachel K. King is a co-founder of GlycoMimetics and has served as the president and chief executive officer and as a member of the board of directors since 2003. Previously, Ms. King was an executive in residence at New Enterprise Associates, a venture capital firm, from 2001 to 2003. From 1999 to 2001, Ms. King served as a senior vice president of Novartis Corporation, a pharmaceutical company. Before joining Novartis, Ms. King spent 10 years with Genetic Therapy, Inc., a biotechnology company, where she served in a number of roles as part of the executive team, which included the company's initial public offering and later acquisition by Novartis. After the acquisition by Novartis, she served as chief executive Officer of Genetic Therapy, which was then a wholly owned subsidiary of Novartis. Ms. King previously worked at Alza Corporation, a pharmaceutical and medical systems company that was later acquired by Johnson & Johnson, as well as at Bain and Company, a management consulting firm. She received a B.A. from Dartmouth College and an M.B.A. from Harvard Business School.

Dr. John L. Magnani is a co-founder of GlycoMimetics and has served as the vice president of research and chief scientific officer and as a member of the board of directors since 2003. Dr. Magnani is also the founder, president and owner of GlycoTech Corporation. Prior to founding GlycoTech, Dr. Magnani was the vice president of research at BioCarb, Inc., one of the first glycobiology-based companies. Earlier in his career, Dr. Magnani was a tenured research chemist at the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases, part of the National Institutes of Health. Dr. Magnani received an A.B. from Washington University in St. Louis and a Ph.D. in biology from Princeton University.

Dr. Helen M. Thackray has served as the vice president of clinical development since 2006 and as the chief medical officer since January 2012. Prior to joining GlycoMimetics, Dr. Thackray was vice president of clinical product development at Biosynexus, Inc., a biopharmaceutical company, from 2001 to 2006. From 1995 to 2011, Dr. Thackray was a practicing physician at the Children's National Medical Center in Washington, D.C., where she also completed her pediatrics residency and served as pediatric chief resident and as an adjunct instructor in pediatrics. From 1999 to 2000, she served as a medical genetics fellow at the National Human Genome Research Institute, part of the National Institutes of Health. Dr. Thackray received a B.S. from Stanford University and an M.D. from The George Washington University School of Medicine. She is a board-certified pediatrician, a fellow of the American Academy of Pediatrics and assistant clinical professor of pediatrics at The George Washington University School of Medicine. Dr. Thackray is also a member of the Institutional Review Board of Holy Cross Hospital in Silver Spring, Maryland, and recently served on the BIO PDUFA V Technical Discussions team.

Mr. Brian M. Hahn has served as the chief financial officer of GlycoMimetics since January 2012 and previously served as the director of finance and administration from February 2010 to January 2012. From 2002 to September 2009, Mr. Hahn served as executive director of finance at MiddleBrook Pharmaceuticals, Inc., formerly Advancis Pharmaceutical, a specialty pharmaceutical company, and from September 2009 to

February 2010 he served as assistant controller for OpGen, Inc., a biotechnology company. From 1998 to 2001, he was a senior accountant with Bering Truck Corporation. Mr. Hahn received a B.B.A. from Shenandoah University and an M.B.A. from the University of Maryland. Mr. Hahn currently serves as chair for the Financial Executive Committee of the Technology Council of Maryland.

Figure 35: GLYC key management members

Name	Title	Work History	Joined GLYC in:
Rachel King	President and Chief Executive Officer	New Enterprise Associates Novartis Genetic Therapy Alza (acquired by Johnson & Johnson) Bain & Company	2003
John Magnani, Ph.D.	VP of Research and Chief Scientific Officer	GlycoTech BioCarb National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases	2003
Helen Thackray, M.D.	VP of Clinical Development and Chief Medical Officer	Biosynexus Children's National Medical Center National Human Genome Research Institute	2006
Brian Hahn	Chief Financial Officer	MiddleBrook Pharmaceuticals Advancis Pharmaceutical OpGen Bering Truck Corporation	2010

Source: Company reports and Canaccord Genuity estimates

Figure 36: GLYC P&L

	2011A	2012A	Q1/13A	Q2/13A	Q3/13A	Q4/13E	2013E	Q1/14E	Q2/14E	Q3/14E	Q4/14E	2014E	2015E	2016E
GMI-1070	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Product revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Collaboration revenue	3.8	15.3	1.3	1.3	1.3	18.0	21.9	-	13.50		10.00	23.5		-
Total revenues	**3.8**	**15.3**	**1.3**	**1.3**	**1.3**	**18.0**	**21.9**	**-**	**13.5**	**-**	**10.0**	**23.5**	**-**	**-**
Cost of goods sold		-	-	-	-	-	-	-	-	-	-			
Gross Profit	**3.8**	**15.3**	**1.3**	**1.3**	**1.3**	**18.0**	**21.9**	**-**	**13.50**	**-**	**10.00**	**23.5**	**-**	**-**
R&D expense	7.8	9.4	2.7	2.8	2.9	4.0	12.4	4.5	5.0	6.0	7.0	22.5	30.0	50.0
SG&A expense	2.1	2.2	0.5	0.5	0.6	0.6	2.1	0.6	0.7	0.7	0.7	2.7	3.0	3.5
Other operating expense	-	0.0					-	-	-	-	-	-	-	-
Total operating expense	**9.9**	**11.6**	**3.2**	**3.3**	**3.5**	**4.6**	**14.5**	**5.1**	**5.7**	**6.7**	**7.7**	**25.2**	**33.0**	**53.5**
Operating income	**(6.1)**	**3.6**	**(1.8)**	**(2.0)**	**(2.1)**	**13.4**	**7.4**	**(5.1)**	**7.8**	**(6.7)**	**2.3**	**(1.7)**	**(33.0)**	**(53.5)**
Net Interest/Investment income	0.0	0.0												
(interest expense)	(0.0)	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
Other non-operating income (expense)	-	(0.0)	(0.0)	(0.0)	(0.0)		-					-	-	-
Interest and other, Net	0.0	(0.0)	-	-	-	-	-	-	-	-	-	-	-	-
Pre-tax income	**(6.1)**	**3.6**	**(1.8)**	**(2.0)**	**(2.1)**	**13.4**	**7.5**	**(5.1)**	**7.8**	**(6.7)**	**2.3**	**(1.7)**	**(33.0)**	**(53.5)**
Income tax expense (benefit)	-	-	-	-	-	-	-					-	-	-
Net income (loss)	**(6.1)**	**3.6**	**(1.8)**	**(2.0)**	**(2.1)**	**13.4**	**7.5**	**(5.1)**	**7.8**	**(6.7)**	**2.3**	**(1.7)**	**(33.0)**	**(53.5)**
Basic EPS	**(6.58)**	**3.93**	**(0.18)**	**(0.19)**	**(0.20)**	**0.76**	**0.61**	**(0.29)**	**0.44**	**(0.37)**	**0.13**	**(0.09)**	**(1.84)**	**(2.97)**
Diluted EPS	**(6.58)**	**0.33**	**(0.18)**	**(0.19)**	**(0.20)**	**0.76**	**0.61**	**(0.29)**	**0.44**	**(0.37)**	**0.13**	**(0.09)**	**(1.84)**	**(2.97)**
Basic shares outstanding	0.9	0.9	10.5	10.6	10.6	17.6	12.3	17.7	17.8	17.9	18.0	17.8	17.9	18.0
Diluted shares outstanding	0.9	11.0	10.5	10.6	10.6	17.6	12.3	17.7	17.8	17.9	18.0	17.8	17.9	18.0

Source: Company reports and Canaccord Genuity estimates

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